Nurse navigation is helpful for cancer patients, but with some restrictions

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The 2013 European Multidiciplinary Cancer Congress
Educational Programme

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1. **Introduction**

It is my pleasure to present, on behalf of the European Cancer Organisation, the education book for the 2013 European Multidisciplinary Cancer Conference.

The comprehensive educational programme for the conference has been developed as a result of the collaborative work of both the scientific and educational committees of ECCO.

Readers will note that the book covers a number of important topics relating to common solid malignancies with the overall theme of achieving an optimal approach and therefore optimal results for our patients.

The topics covered are localised rectal cancer, early breast cancer, resectable non-small-cell lung cancer, renal cancer and melanoma. We have also included an extremely important section on the mood disorders in cancer patients.

In each chapter relating to specific solid tumours, an approach to achieving optimal outcomes is discussed by consideration of the basic biological characteristics of the tumour and its clinical management, as well as the integration of the two. It is remarkable how similar the basic principles of management for each of the tumours are. For example, the importance of careful preoperative staging with modern imaging and good, careful and fastidious surgical resection is crucial and strongly emphasised. For this to be achieved, specialised understanding of the biology of the tumour and its anatomical confines is essential. Accordingly surgical specialisation is now a mandatory requisite since outcome correlates with volume of patients treated.

The importance of a careful pathological examination is emphasised, not only to determine prognosis but also to determine the most effective adjuvant and in some cases, neoadjuvant treatment that is required.

There is increasing emphasis on personalised treatment determined by biological variables, and this is also emphasised in each chapter. In addition, the morbidity and indeed mortality associated with the specific modalities of treatment are documented so that risk–benefit analyses can be assessed.

As clinicians, we must not ignore the importance of economic consequences and resource implications of treatments, and this societal concern is also discussed. Finally, the importance of an integrated multidisciplinary approach to the management of these tumours is emphasised by all authors.

The authors of each chapter are to be congratulated for providing excellent up-to-date reviews backed by detailed and comprehensive lists of key references which include all the major randomised clinical trials and meta-analyses for the particular malignancy. Readers will find this particularly useful in determining their decision-making.

I would like to thank all our authors and Chairs for their hard work in providing chapters for this educational book, and I hope our readers find their efforts worthwhile. I am particularly grateful to Samira Essiaf for her invaluable expertise in preparing the book and dealing with all the administration.

I do hope you find the chapters helpful and of educational benefit and enjoy reading them as much as I enjoyed editing them.
Introduction

The optimal approach to early breast cancer

Lynda Wyld *

University of Sheffield, Academic Unit of Surgical Oncology, Royal Hallamshire Hospital, UK

Breast cancer outcomes continue to improve, with 5-year survival rates having increased from 50% in the 1970s to nearly 80% today. The reasons for the improvement are multifactorial, with major contributions made by the advent of screening and improved systemic therapies such as anti-oestrogens, chemotherapy and trastuzumab. Running alongside this improvement in breast-cancer-specific survival has been an increasing realisation that preservation of the breast, without compromise on rates of local control, is important for quality of life. This has led to progress in techniques of breast reconstruction and breast conservation, with oncoplastic techniques to reshape the breast, minimising distortion and asymmetry and increasing the use of primary systemic therapy to enhance rates of conservation. Whilst surgery to the breast itself is becoming more complex, surgery to the axilla is becoming less extensive as there is an increasing realisation that the main value of identifying axillary disease is not to enhance survival, or even local control, but to give prognostic information to guide adjuvant therapies. This drive has seen a move away from axillary clearance to sentinel-node biopsy, and perhaps eventually only axillary imaging assessment, with the development of increasingly sensitive tests such as magnetic resonance imaging (MRI) and positron emission tomography (PET) [1].

The changes to practice have been driven by research evidence, and the overarching theme is that of individualised therapy. This is true of all the disciplines in the breast care team. Surgery is now tailored to the woman’s disease, breast shape and size and personal preferences, and in most cases women may be offered surgery that will retain, restore or even enhance her breasts should she so wish. Radiotherapy is increasingly targeted to maximise the dose to the breast whilst reducing the dose to the surrounding tissues using highly complex computed-tomography-guided planning (tomotherapy and intensity-modulated radiation therapy, IMRT). Perhaps the most complex area of all is the interplay between the molecular pathology of the tumour and the systemic therapy which is offered. Tumour stage, grade and oestrogen receptor status have now been supplemented with Her2 status, and increasingly the proliferation index, Ki67, resulting in a new classification (luminal A, B, Her2+ and basal-like) [2] which guides prognosis and predicts treatment response. More detailed recurrence risk assessments may be provided by multigene arrays such as Oncotype Dx™ (Genomic Health, United States of America (USA)) [3] and Mammaprint™ (Agendia BV, The Netherlands) [4] which may further aid decisions about chemotherapy benefits.

The future for breast cancer treatment will hold even more individualised treatment plans than the complex schedules on offer today. Next-generation sequencing opens up the possibilities for identification of even more complex gene signatures [5], which may permit customised therapies with some of the bewildering array of targeted molecular therapies under development. Increasing rates of complete pathological responses to primary systemic therapy may lead to ‘no surgery’ options: something which is currently being trialled in respect of both the axilla and the breast.

Central to all of the above is the close working relationship of the breast multidisciplinary team. Each must have not only expertise in their own discipline but awareness of what their colleagues can (and cannot) achieve, so that every patient receives an individualised treatment plan that fits together like a perfect jigsaw, with every piece complementing the others.

The following articles have been written by some of the world leaders in the field of breast care, and exemplify these principles of individualised care and multidisciplinarity.

Conflict of interest statement

None declared.
REFERENCES


Optimal approach in early breast cancer: Adjuvant and neoadjuvant treatment

J. Ribeiro, B. Sousa, F. Cardoso *

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1. Introduction

The treatment of early breast cancer (EBC) is becoming increasingly complex, but also more effective as a better understanding of cancer biology is achieved with evolving research. Longer follow-up of prospective trials is crucial to evaluate the impact of current standard treatments in long-term outcome and safety. In this review we will summarise the current evidence for optimal treatment of EBC.

2. Which EBC patients can safely avoid adjuvant chemotherapy?

In the 1980s there were substantial advances in the treatment of breast cancer (BC), and the results of several large randomised trials indicated that adjuvant systemic therapy could decrease breast-cancer mortality by about 20%. In fact, the widespread application of adjuvant systemic therapy is considered the main cause for the declining breast cancer mortality observed in the Western world.

Treatment decisions are based on clinical (biological age, comorbidities, performance status) and pathological variables – tumour size, lymph-node status, histological grade, oestrogen receptor (ER), progesterone receptor (PR), HER2 and proliferation – that can be combined in the form of algorithms (e.g. Adjuvant!Online, Nottingham prognostic index) and form the basis of treatment for guidelines such as the ones from the European Society for Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN), and St Gallen. However, it is clear that still too many patients receive this therapy with little likelihood of benefit and substantial toxicity.

In this section, available data on biomarkers and molecular tests related to prognostication will be reviewed. In the first part we will address the evidence and utility for adjuvant treatment decisions of biomarkers of proliferation (namely Ki67) and urokinase plasminogen activator (uPA)/plasminogen activator inhibitor (PAI-1). In the second part we will assess the practical contribution of gene expression profiling in breast cancer.

2.1. Biomarkers

2.1.1. Markers of proliferation – Ki67

Uncontrolled proliferation is a driver for cancer and is one of the hallmarks of this disease. In general, markers of an elevated proliferative rate correlate with a worse prognosis in untreated patients and may add predictive information regarding benefit from chemotherapy (CT) [1]. The most commonly used method to measure proliferation involves immunohistochemical (IHC) detection of the nuclear non-histone protein ki67, which is detected only in proliferating cells. Ki67 expression is commonly assessed using the mindbomb E3 ubiquitin protein ligase 1 antibody (MIB1) and reported as a percentage of cells positive for Ki67.

2.1.2. Prognostic marker

Various studies have investigated the role of Ki67 as a prognostic marker. In a meta-analysis of 40 studies, involving over 11,000 patients, baseline Ki67 was found to have a modest prognostic value in multivariable analysis, which was more evident in lymph-node-negative patients [2]. In another meta-analysis of 46 studies including over 12,000 patients, Ki67 positivity (using cut-offs defined by individual authors) was associated with a higher risk of relapse and a worse survival in patients with EBC [3]. One must highlight several limitations of these data: namely the facts that these are retrospective studies, many include heterogeneous groups of patients who were treated and followed in various ways that are often incompletely documented, and ki67 methodology and cutoff varied widely.

The clinical utility of Ki67 as a prognostic marker is more apparent when it is considered within more narrowly defined tumour subgroups and/or as part of a multiparameter panel of biomarkers, as for example in the IHC4 [4]. Other investigators have reported that Ki67 is an important part of a prognostic
algorithm for residual risk in EBC patients treated with letrozole or tamoxifen [5].

2.1.3. Predictive marker
Studies have focused on the predictive value of this biomarker regarding benefit from CT or even from specific CT agents. In the ER-positive BC the results are contradictory. In the recently reported PACS 001 and BCIRG 001, high levels of Ki67 were predictive of benefit from adding docetaxel to fluorouracil, epirubicin and cyclophosphamide (FEC) CT as adjuvant treatment [6]. However, these results contrast with those from the International Breast Cancer Study Group Trials (IBCSG) VIII and IX that found no predictive value of Ki67 levels for the addition of cyclophosphamide, methotrexate and fluorouracil (CMF) to endocrine therapy (ET) in endocrine-responsive node-negative disease [7]. For ER-negative BC data to suggest that Ki67 predicts adjuvant chemotherapy response are scarce. However, taking into account all the available evidence that these tumours as a group are more responsive to chemotherapy than ER-positive tumours [8,9], one can hypothesise that higher chemotherapy sensitivity observed in patients with ER-negative tumours is at least partially due to the consistently higher rates of proliferation of these tumours. If so, Ki67 levels may be helpful in identifying those patients most likely to benefit from chemotherapy [10].

In spite of consistent data on Ki67 as a prognostic marker in early breast cancer, its role in breast cancer management remains uncertain [11], mainly because of the lack of standardisation. In 2007 the ASCO Tumour Marker Guidelines stated that evidence supporting the clinical utility of Ki67 was insufficient to recommend its routine use for prognostic purposes in patients with newly diagnosed breast cancer [12]. However, in the St Gallen Consensus guidelines from 2011 [13] and 2013 most panelists recommend the use of Ki67 for BC subtyping classification, prognostication and prediction of response to CT, although there is no consensus on the best cut-off to be used.

The limitations of this assay are largely related to the difficulty in interpreting the literature due to lack of standardisation of assay reagents, procedures and scoring. To overcome these constraints in 2011 the International Ki67 in Breast Cancer Working Group published recommendations for Ki67 assessment in breast cancer [14]. These guidelines aim to minimise pre-analytical and analytical variables in Ki67 assessment and harmonise scoring methodology and data handling, facilitating its routine use in clinical practice.

2.1.4. Urokinase plasminogen activator/plasminogen activator inhibitor
uPA and PAI-1 biomarkers are invasion biomarkers analysed by a protein-based enzyme-linked immunosorbent assay (ELISA). They can be used to determine the recurrence risk in patients with node-negative EBC with the aim of better refining the decision to recommend CT in this patient population.

uPA is a serine protease with an important role in cancer invasion and metastases [15]. When bound to its receptor (uPAR), uPA converts plasminogen into plasmin and mediates degradation of the ECM during tumour-cell invasion. PAI-1 levels are high in tumour tissue and plasma, and PAI-1 is inactivated when bound to uPA.

Several retrospective studies [16,17] and a large pooled analysis of individual patient data from 8377 women treated in clinical trials by the European Organisation for the Research and Treatment of Cancer (EORTC) [18], in which tumour uPA and PAI-1 levels were determined in primary tumour tissue extracts, proved that high levels of uPA, uPAR, and PAI-1 are associated with shorter survival in women with both node-negative and node-positive disease.

The Chemo N0 is a prospective, multicentre randomised trial in which researchers stratified patients with node-negative BC into two groups according to the presence of low or high uPA/PAI-1 values. Those with low values of both uPA and PAI-1 received observation only, whereas those with high uPA and/or PAI-1 values were randomised to receive either CMF or observation. The 10-year follow-up updated analysis showed that: low-risk N0 patients according to the uPA/PAI-1, thus without any systemic therapy, had an excellent prognosis, with a 10-year survival rate of almost 90% [19], while the high-risk patients according to the uPA/PAI-1 had a 1.84-fold higher disease recurrence risk (P = 0.017) than the low-uPA/PAI-1. Additionally, the assay predicted, in the high-risk population, the benefit from CT [20]. These results provide for the first time long-term follow-up from a prospective biomarker-driven clinical trial in cancer.

The Node-Negative Breast Cancer (NNBC)-3 study is a prospective multicentre phase III therapy trial, with the aim of comparing risk assessment and clinical outcome on the basis of tumour-biological factors uPA/PAI-1 with those based on established, clinical and pathomorphological factors in high-risk node-negative BC patients. It enrolled more than 4000 patients, stratified into low-risk and high-risk groups according to the uPA/PAI-1 value or according to the clinical pathological algorithm. Those classified as low risk did not receive CT, whereas those classified as high risk received either six cycles of FEC or three cycles of FEC and three cycles of docetaxel [21]. In the West German Study Group Plan B trial, a prospective comparison of recurrence score (RS) – Onco-typeDx – and independent central pathology assessment of prognostic tools was performed. The study randomised 2361 patients; 18% had a recurrence score of 0–11 (low risk), 61% had a recurrence score of 12–25 (intermediate risk), and 21% had a recurrence score of >25 (high risk). A weak correlation was found between uPA/PAI-1 and RS. These data showed that high-risk status according to RS is well correlated with high risk by uPA/PAI-1; however, there was substantial heterogeneity in risk assessment in the low- and intermediate-risk RS groups in which some patients are still considered to be high risk according to uPA/PAI-1 [22].

2.2. Gene-expression-based assays
Gene expression profiling has identified several molecular signatures that mostly have prognostic value and some prediction value.

2.2.1. First-generation prognostic signatures – MammaPrint™
MammaPrint™ is a microarray-based gene-expression-profiling assay that measures the levels of expression of 70 genes related to proliferation, invasion and angiogenesis. The assay accurately categorises patients in poor and good prognosis...
groups on the basis of the development or not of distant metastases within 5 years. Initially requiring fresh or frozen samples, it can now be effectively performed in formalin-fixed paraffin-embedded specimens (FFPE).

The initial data were derived from 78 patients with node-negative BC, ≤5 cm, the vast majority of whom had ER-positive tumours and did not receive adjuvant systemic treatment [23]. The validation cohort included 295 node-negative patients, of whom 61 were from the initial study, and confirmed MammaPrint™ independent prognostic value beyond standard clinicopathological variables in this patient population [24]. The TRANSBIG consortium carried out an independent retrospective validation of MammaPrint™ using samples from nine European countries, which further confirmed the prognostic value of this tool [25]. Additional validation studies were performed in node-positive EBC patients [26] and in HER2+ EBC patients [27].

MammaPrint™ is the first FDA-approved gene-expression-based assay to be used as a prognostic test in EBC patients. The clinical utility of this assay is being prospectively evaluated in the large, randomised MINDACT trial that enrolled 6690 EBC N0–N3 patients [28].

2.2.2. Oncotype Dx™ recurrence score
Oncotype Dx™ is a quantitative reverse transcriptase–polymerase chain reaction- (qRT–PCR-) based signature that measures the expression of 21 genes (16 cancer-related and five reference genes), performed using RNA from FFPE tumour tissues. With this multigene predictor assay a mathematical function (named recurrence score, RS) aiming at predicting the risk of distant relapse for patients with ER-positive, lymph-node-negative breast cancer treated with tamoxifen was developed based on the analysis of clinical samples from the NSABP B-20 clinical trial [29]. The RS is a continuous variable, ranging from 0 to 100, which translates into three risk-group categories: low (RS < 18), intermediate (RS from 18 to <31) and high (RS < 31).

OncotypeDx™ was then validated in a large cohort of ER-positive, node-negative, tamoxifen-treated BC patients from the NSABP-B14 trial [30]. The assay was able to stratify a generally good prognosis population into distinct subgroups (low, intermediate, or high score) with different rates of distant recurrence at 10 years (7%, 14% and 31% respectively. OncotypeDx™ RS was shown to be strongly associated with survival from breast cancer and independent from standard clinicopathological variables [30,31]. Subsequent analysis revealed that RS also seems to correlate with benefit from chemotherapy in ER-positive BC [32]. The optimal management of the intermediate-risk group is being addressed in the TAILORx trial (NCT00310180) in which 11,248 patients with ER-positive, node-negative breast cancer and intermediate risk (RS 11–25) were randomly assigned to hormone treatment either alone or in combination with chemotherapy.

Additional validation studies evaluated OncotypeDx™ in EBC patients with ER-positive disease treated with AI [33] and ER-positive node-positive BC patients [34].

The RxPONDER trial will randomise 4000 women with N1 disease and an RS of ≤25 to endocrine therapy with or without chemotherapy [35].

While waiting for MINDACT and TAILORx results, international recommendations support the selected use of MammaPrint™ and OncotypeDx™ in the ER + EBC patients in whom standard clinical/pathological factors are considered insufficient for adjuvant CT decisions.

2.2.3. PAM50
PAM50 assay provides a risk-of-relapse (ROR) score prognostic of relapse-free survival for patients with node-negative BC who did not receive adjuvant systemic therapy [36]. This assay is composed of 50 genes (derived from tumour samples of 220 patients in the training set who had ER-positive or ER-negative tumours and HER2+ or HER2-negative tumours) related to proliferation, ER-regulated genes, HER2, and basal and myoepithelial characteristics. It is compatible with FFPE-derived RNA or qRT-PCR using FF tissue.

The prognostic ability of the PAM50 has been validated in an independent test set of 786 patients with ER-positive disease treated only with adjuvant tamoxifen [37]. An ROR model containing a proliferation component (derived using 11 genes associated with cell-cycle function) was recently added to the original model.

2.2.4. Genomic grade index
The genomic grade index (GGI) is a gene expression signature developed to better define histological grade assessment with the ability to divide classic histological grade into low and high risk. It was developed to overcome the limitation issues, namely reproducibility, associated with the histological grade assessment and was developed using a “bottom-up” approach whereby 97 genes associated with histological grade were identified and subsequently related to clinical outcome [38].

The intrinsic prognostic information of proliferation genes seems to be better evaluated with the GGI than with classic histological grade as shown in a population of 570 patients for which complete recurrence-free survival (RFS) and histological grade was available [24,39,40]. The GGI was able to further stratify the subset of histological grade 2 patients into two subgroups: a grade 1 gene-like profile and a grade 3 gene-like profile with clearly different rates of relapse. Patients falling in the HG2-GGI3 category revealed a significantly higher rate of relapse than the HG2-GGI2 (HR = 3.61; confidence interval (CI) 2.25–5.78; P < 0.001). In the overall population the GGI was also able to stratify patients into two risk categories with significant differences in RFS rates (high versus low risk; HR = 2.83; CI 2.13–3.77; P < 0.001)

In addition to prognostic prediction, the GGI ability to predict response neoadjuvant CT has also been evaluated [41]. In a study with 229 tumour samples collected before the beginning of CT with docetaxel and to fluorouracil, doxorubicin and cyclophosphamide (FAC) a high GGI was associated with greater response than low-risk GGI (40% versus 12%; P < 0.001).

2.2.5. Second generation prognostic signatures – genes related to immune response
Several studies have recently analysed the prognostic role of tumour-associated lymphocytes (TIL) in breast cancer, mainly in the triple-negative subtype [42,43]. A link between increased
lymphocytic infiltrate and reduced relapse rate and improved survival has been suggested. The expression of genes related to immune response has also been shown to provide important prognostic information in ER-negative and in highly proliferative ER-positive BC [44–47]. Jointly there is evidence to suggest that both the concentration of inflammatory infiltrate defined by IHC and expression of B-cell or plasma-cell metagene defined by microarray-based gene-expression profiling are likely to provide important prognostic information.

2.2.6. Stroma-related prognostic gene signatures
The development of stroma-related prognostic gene signatures is an evolving field of great scientific interest; however, independent validation of their prognostic accuracy is still needed before clinical application.

3. Which are the current major challenges regarding neoadjuvant systemic therapy?

3.1. Advantages of neoadjuvant systemic treatment and endpoints for clinical trials

Neoadjuvant therapy (NT) is the standard of care for women with locally advanced, inflammatory or inoperable primary breast cancer (BC) [48–51]. Currently, based on the results of landmark trials NSABP B-18 and NSABP B-27, NT is mainly used in operable disease to improve the surgical options, to determine the response to chemotherapy and to obtain long-term DFS [52–56].

Pathological complete response (pCR) has been considered predictive of long-term outcome in several neoadjuvant trials [57], and this finding has been confirmed in two recent studies [58,59]. The meta-analysis from the Collaborative Trials in Neoadjuvant Breast Cancer [58] included 12 randomised neoadjuvant trials (n = 13,125) and results have shown that individual patients who achieved a pCR (ypT0ypN0 or ypT0isypN0) had a more favourable long-term outcome. This effect was only seen in HR+/grade 3, triple-negative and HER2+ tumours and not in low-grade hormone-receptor-positive tumours. Similarly, in the pooled analysis of seven prospective trials (n = 6000) published by the German Group [59] pCR was associated with improved DFS in tumours luminal B/HER2-negative, HER2+/nonluminal, and triple-negative. These recent data establish pCR as a surrogate marker for survival but emphasise that it is not an adequate endpoint for slow proliferative tumours (grade 1 or 2, HR−). Additionally, it was not possible to determine the magnitude of increase in pCR rates predictive of superior long-term outcome of a specific therapy of a clinically meaningful improvement in survival [60]. These findings led the FDA to support certain drug development programmes throughout NT trials using pCR for accelerated approval [61]. Neoadjuvant trials are also recognised as important research tools, particularly in the field of biomarkers.

3.2. Which chemotherapy and targeted therapy regimens in the neoadjuvant setting. Are there predictive markers?

Anthraccline/taxane-based CT regimens have been the most extensively studied in the neoadjuvant setting, but so far no specific regimen has been found to be clearly superior. Incorporation of taxanes has increased the response rates [54,62,63] with large phase III trials reporting pCR rates of 15–20% [57,64,65]. The studies that have accessed tailoring treatment to response [63,65–67] have not confirmed a clear benefit from changing to a non-cross-resistant regimen.

In this regard efforts have been made to study biological markers predictive of pCR. The integrated meta-analysis [68] on individual data from the German Breast Group and the AGO Breast Group, on 6402 patients enrolled in neoadjuvant trials has shown that a greater chance of pCR was seen in ER-negative patients (OR 3.2; P < 0.0001), HER2+ disease (OR 2.2; P < 0.0001), higher grade (OR 1.8; P < 0.0001), younger age (OR 1.3; P = 0.0001), non-lobular type tumours (OR 1.7; P = 0.001) and smaller tumour size (OR 1.5; P = 0.0006). Furthermore, this group recently published a pooled analysis assessing the prognostic impact of different definitions of pCR and the outcome regarding the biological intrinsic breast cancer subtypes [59]. It was found that pCR was associated with improved DFS in tumours luminal B/HER2-negative (P < 0.005), HER2+/nonluminal (P < 0.001) and triple-negative tumours (P < 0.001) but not in luminal A (P = 0.39) or in luminal B/HER2+ (P = 0.45) tumours. Despite the fact that tumours lacking expression of ER have higher pCR, exceeding 40% in some studies, overall patient survival with this phenotype is still shorter than in patients with hormone-receptor-positive disease [9]. However, recent data show that patients with HER2+/nonluminal and triple-negative disease who achieved pCR have an excellent prognosis [58,59].

Mutations in p53 were shown not to be predictive of response to taxanes in the large randomised multicentric neoadjuvant trial EORTC 10994/BIG 1-00 [69]. Some studies have generated preliminary gene signatures with potential predictive value for docetaxel and paclitaxel plus FAC [70,71] but these signatures have not yet been validated in subsequent studies and are not ready for use in clinical practice. More recent studies suggest that prediction of response to a specific CT agent is different among the different BC subtypes and is more likely to be achieved by using multifactorial tools [59,72–75]. HER2 over-expression/amplification predicts response to treatment with the monoclonal antibody trastuzumab [76], and has also been associated with a better response to anthracyclines [77,78]. It is uncertain whether the latter effect is linked to the co-amplification of topoisomerase IIα as mixed results have been obtained [78,79]. The association between HER2+ and response to taxanes suggested in some studies [80] needs to be confirmed with further research. In HER2+ disease the incorporation of trastuzumab (H) into NT chemotherapy regimens is considered standard of care [57]. The first reported randomised trial from the MDACC showed a very high pCR rate of 65.2% in patients treated with trastuzumab (versus 26%) [81,82] which led to a premature closure of the study. Data from two randomised phase III studies were subsequently available, the NOAH trial [83] and the GeparQuattro trial [65,84]. The addition of trastuzumab to an anthracycline/taxane-based regimen led to an improvement in event-free survival at 3 years (HR 0.59; 95%CI: 0.38–0.90) in the NOAH trial and a significant increase in pCR rate in the GeparQuattro trial (31.7% in HER-2-positive disease versus 15.7% in HER-2-negative disease).
Lapatinib (L) has been tested in the NT setting, both as single agent and in combination with trastuzumab in two phase III studies. In the NeoALTTO study [85], 455 patients were randomly assigned to L, H, or L plus H, given alone initially and then combined with weekly paclitaxel before surgery. Combination of L and H yielded a significantly higher pCR rate than the monotherapy arms. The dual combination was associated with higher toxicity, mainly diarrhoea and a transient reversible rise in transaminases. In the Geparquinto trial [84] 620 HER2+ patients with operable or locally advanced BC were randomised to four cycles of epirubicin plus cyclophosphamide and four cycles of docetaxel 3 weeks, with either concurrent H or L. The H arm had a significantly higher pCR (30.3%) compared with L (22.7%). Taken together, the results of these two studies have led to the recommendation that lapatinib should not be used as a single (neo)adjuvant anti-HER2 target outside clinical trials. Furthermore, the lapatinib monotherapy arm in the large adjuvant ALTTO trial has been STOPPED and patients in that arm were informed and proposed to receive adjuvant trastuzumab.

Dual-HER2 blockade has also been tested in the NeoSphere trial [86], a phase II randomised trial designed to test the antitumour activity and tolerability of the combination of docetaxel, trastuzumab and pertuzumab (THP), compared with trastuzumab plus pertuzumab (HP), docetaxel and pertuzumab (TP) and docetaxel and trastuzumab (TH). The pCR was significantly higher (P = 0.014) for the combination of docetaxel with both anti-HER2 target agents (THP), with good tolerability, namely cardiac safety. These studies plus two trials in the metastatic setting [87,88] represent growing evidence that the dual blockade of the HER2 receptor has superior efficacy and may soon become standard of care. Still, it is not known which is the optimal combination of anti-HER2 agents; the best chemotherapy regimen to use with these agents, the role of dual HER2 blockade in combination with endocrine therapy for HER2+ and HR+ BC are among other questions.

Triple-negative phenotype (TNBC) has higher response rates to NT compared to non-triple-negative tumours in several studies [59,72,89–91], but only if pCR is obtained can it be translated into a better prognosis. At the present time, CT is the only proven therapy for TNBC and international guidelines recommend the use of the same regimens as for non-TNBC, i.e. an anthracycline/taxane-based regimen. Small studies have suggested that platinums may be particularly effective in this subset. The rationale and support for adjuvant CT for patients with BC are derived from many large, randomised trials and from the Early Breast Cancer Trials’ Collaborative Group (EBCTCG) meta-analysis. In the last update analysis [96] the use of adjuvant CT, with either an anthracycline-based or a CMF regimen, was shown to be superior to no treatment in terms of risk of recurrence, breast cancer, or overall mortality (Table 1). The application of adjuvant CT translated to an absolute benefit of 5.0%.

There is no single standard adjuvant chemotherapy regimen in the treatment of EBC.

When choosing a particular regimen various factors must be taken in account: namely the recurrence risk, co-morbid illness and patient preference. The following discussion is organised along the lines of debate concerning CT regimens: anthracyclines versus CMF and anthracyclines versus taxanes.

### 4. What is the optimal adjuvant chemotherapy regimen?

#### 4.1. State-of-art regimens according to breast cancer subtype

So far available data do not allow for different regimen recommendations according to BC subtype. Therefore, the considerations below apply to all subtypes of BC when CT is deemed necessary, with some specific points for HER2+ EBC.

The rationale and support for adjuvant CT for patients with BC are derived from many large, randomised trials and from the Early Breast Cancer Trials’ Collaborative Group (EBCTCG) meta-analysis. In the last update analysis [96] the use of adjuvant CT, with either an anthracycline-based or a CMF regimen, was shown to be superior to no treatment in terms of risk of recurrence, breast cancer, or overall mortality (Table 1). The application of adjuvant CT translated to an absolute benefit of 5.0%.

There is no single standard adjuvant chemotherapy regimen in the treatment of EBC.

When choosing a particular regimen various factors must be taken in account: namely the recurrence risk, co-morbid illness and patient preference. The following discussion is organised along the lines of debate concerning CT regimens: anthracyclines versus CMF and anthracyclines versus taxanes.

#### 4.2. Anthracyclines versus CMF

Several randomised trials and the EBCTCG overview (Table 2) support the superior efficacy of anthracycline-based regimens over CMF with level I based evidence. However, some caveats must be highlighted. In the 2011 Oxford Overview anthracycline-based regimens were divided into standard doses (e.g. cumulative doses of 240 mg/m² of doxorubicin) or higher doses (i.e. cumulative doses > 240 mg/m² of doxorubicin or 360 mg/m² of epirubicin) [96]. The improvement in the risk of recurrence, breast cancer or overall mortality was present only with the use of higher cumulative doses of anthracyclines (Table 2). This suggests that a real difference between these regimens exists but is limited to anthracycline regi-

### Table 1 – Early Breast Cancer Trials’ Collaborative Group (EBCTCG) overview results comparing adjuvant chemotherapy (CT) with no CT in early breast cancer (EBC).

<table>
<thead>
<tr>
<th>Risk of recurrence</th>
<th>Breast cancer mortality</th>
<th>Overall mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracycline-based regimen versus no CT</td>
<td>RR: 0.79, 95%CI</td>
<td>RR: 0.84, 95%CI</td>
</tr>
<tr>
<td>RR: 0.73, 95% confidence interval (CI)</td>
<td>Absolute gain: 6.5%</td>
<td>Absolute gain: 5%</td>
</tr>
<tr>
<td>Absolute gain: 8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide, methotrexate and fluorouracil (CMF) regimen versus no CT</td>
<td>RR: 0.76, 95%CI</td>
<td>RR: 0.84, 95%CI</td>
</tr>
<tr>
<td>RR: 0.70, 95%CI</td>
<td>Absolute gain: 6.2%</td>
<td>Absolute gain: 4.7%</td>
</tr>
<tr>
<td>Absolute gain: 10.2%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.2.1. Anthracyclines versus Anthracylines + taxane based therapy

The role of taxane base CT as adjuvant treatment of EBC is an extensively studied but still controversial issue. We currently have 21 clinical trials of first-generation taxanes, several pooled analyses, meta-analyses, and since 2012 the role of these agents is also evaluated in the analysis of the EBCTCG overview.

Some of the key first-generation taxane trials are presented in Table 3. When analysing the 12 first-generation trials using low-strength anthracycline reference regimens, eight suggest a benefit in terms of DFS for the taxane regimen (CALGB 9344; NSABP B-28; the MD Anderson Neoadjuvant Trial; FinHER; BCIRG 001; HORG; GEICAM 9805; US Oncology Group 9735) and only three of the 10 trials that reported survival showed a benefit in OS (CALGB 9344, BCIRG 001, and US Oncology 9735).

Several pooled analyses and meta-analyses have been undertaken aiming to clarify the benefit of taxane-based therapy (Table 3). Overall they support a modest improvement in DFS and overall survival (5% and 3% absolute benefit, respectively) when taxane-based regimens are compared with standard anthracycline polychemotherapy, irrespective of the type of taxane, schedule of administration, extent of nodal involvement and hormone-receptor expression status [97].

In the EBCTCG 2012 meta-analysis, the incorporation of a taxane into an anthracycline CT regimen resulted in reduction in the recurrence risk, risk of breast cancer and overall mortality (Table 3) independently of age, nodal status, tumour size, tumour grade or ER status.

However, we must underscore that treatment comparisons varied greatly, which complicates the analysis. In this regard, the effect of taxanes was analysed taking into account how the CT regimen in the control group compared with the non-taxane CT in the taxane group (same, doubled or intermediate). The major effect of these agents was seen in the trials where the same control regimen was used in both arms (n = 11,167 women) with a reduction in the risk of recurrence, breast cancer and overall mortality that translated into an absolute gain of 4.6%, 2.8% and 3.2%, respectively [96]. When considering this benefit we must acknowledge that in these trials a ‘week’ anthracycline-based regimen was used and greater treatment duration was obtained with the additional four cycles of a taxane to the anthracycline regimen. As a matter of fact, when the number of cycles in the control anthracycline regimen was doubled (to mirror the addition of four cycles of taxanes to anthracyclines in the experimental arm) there was little difference in recurrence, breast cancer or overall mortality (Table 3).

4.2.2. HER2 positive breast cancer

The optimal anti-HER2 adjuvant treatment will be addressed below.

**Table 2 – Adjuvant anthracycline versus cyclophosphamide, methotrexate and fluorouracil (CMF) trials in early breast cancer (EBC).**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population (n)</th>
<th>Median follow-up</th>
<th>Treatment</th>
<th>Disease-free survival (DFS) (P-value)</th>
<th>Overall survival (OS) (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INT 0102</td>
<td>Node-negative high risk EBC (n = 2691)</td>
<td>60</td>
<td>CAF × 6</td>
<td>85% versus 82%, P = 0.03</td>
<td>92% versus 90%, P = 0.03</td>
</tr>
<tr>
<td>NSABP B-23</td>
<td>Node-negative, ER-negative EBC (n = 2008)</td>
<td>60</td>
<td>AC × 4</td>
<td>87% versus 87%, P = 0.9</td>
<td>90% versus 89%, P = 0.4</td>
</tr>
<tr>
<td>Belgian study</td>
<td>Node-positive EBC (n = 777)</td>
<td>50</td>
<td>CMF × 6</td>
<td>82% versus 75%, P &lt; 0.001</td>
<td>HR: 0.79, P = 0.31</td>
</tr>
<tr>
<td>Mam-1 GOCSI</td>
<td>Node-positive premenopausal EBC (n = 466)</td>
<td>60</td>
<td>A → CMF</td>
<td>82% versus 75%, P &lt; 0.001</td>
<td>82% versus 75%, P &lt; 0.001</td>
</tr>
<tr>
<td>NEAT/BR969</td>
<td>Node-negative and node-positive EBC (n = 2391)</td>
<td>48</td>
<td>versus CMF × 6/8</td>
<td>82% versus 75%, P &lt; 0.001</td>
<td>Overall mortality RR: 0.97 (P = 0.55)</td>
</tr>
</tbody>
</table>

EBCTCG Overview: anthracyclines versus CMF

| Standard-strength anthracycline-based regimen versus standard or near-standard CMF | Recurrence RR: 0.89 (P = 0.003) | BC mortality RR: 0.80 (P = 0.00001) | Overall mortality RR: 0.84 (P = 0.0002) |
| Low-strength anthracycline-based regimen versus standard or near-standard CMF | Recurrence RR: 0.99 (P = 0.76) | BC mortality RR: 0.98 (P = 0.67) | Overall mortality RR: 0.97 (P = 0.55) |

AC, doxorubicin and cyclophosphamide; CAF, cyclophosphamide, doxorubicin, and fluorouracil; EC, epirubicin and cyclophosphamide; A, doxorubicin; E, epirubicin.
Anthracyclines are amongst the most active chemotherapy agents for the treatment of breast cancer. Multiple trials in the past two decades demonstrated that anthracycline-based chemotherapy was associated with lower rates of breast cancer recurrence and improved survival when compared with non-anthracycline chemotherapy regimens, such as CMF [96]. However, these agents are associated with increased risk of cardiovascular complications, dependent on cumulative dose and schedule, and are often irreversible.

The benefit of taxanes when incorporated into the adjuvant setting for women with newly diagnosed breast cancer was analysed in several trials and has been discussed above. It is, however, unknown whether the benefit seen from add-

4.3. Should anthracyclines be avoided in the adjuvant setting?

Anthracyclines are amongst the most active chemotherapeutic agents for the treatment of breast cancer. Multiple trials in the past two decades demonstrated that anthracycline-based chemotherapy was associated with lower rates of breast cancer recurrence and improved survival when compared with non-anthracycline chemotherapy regimens, such as CMF [96]. However, these agents are associated with increased risk of cardiovascular complications, dependent on cumulative dose and schedule, and are often irreversible.

The benefit of taxanes when incorporated into the adjuvant setting for women with newly diagnosed breast cancer was analysed in several trials and has been discussed above. It is, however, unknown whether the benefit seen from add-

Table 3 – Adjuvant taxane trials in early breast cancer (EBC).

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Median follow-up (months)</th>
<th>Treatment</th>
<th>DFS (P-value)</th>
<th>OS (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Low-strength” sequential anthracycline</td>
<td>CALGB 9344 (n = 3170)</td>
<td>69</td>
<td>AC × 4 versus AC × 4 – Pac × 4</td>
<td>7 years: 64% versus 58% (HR: 0.83; P = 0.001)</td>
<td>7 years: 74% versus 68% (HR: 0.82; P = 0.01)</td>
</tr>
<tr>
<td></td>
<td>NSABP B-28 (n = 3060)</td>
<td>34</td>
<td>AC × 4 versus AC × 4 – Pac × 4</td>
<td>5 years: 76% versus 72% (HR: 0.83; P = 0.002)</td>
<td>5 years: 85% versus 85% (HR: 0.93; P = 0.46)</td>
</tr>
<tr>
<td></td>
<td>MDACC EBC (n = 524)</td>
<td>60</td>
<td>FAC × 8</td>
<td>86% versus 83% (HR: 0.70; P = 0.009)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>NSABP B-27 T1–T3 operable BC (n = 2411)</td>
<td>102</td>
<td>S → AC → Doc versus S → AC</td>
<td>71% versus 68% (HR: 0.92; P = 0.29)</td>
<td>83% versus 82% (HR: 0.93; P = 0.46)</td>
</tr>
</tbody>
</table>

“Low-strength” concurrent anthracycline

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Median follow-up (months)</th>
<th>Treatment</th>
<th>DFS (P-value)</th>
<th>OS (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCIRG-001 Node-positive EBC (n = 1491)</td>
<td>124</td>
<td>DAC × 6</td>
<td>62% versus 55%, P = 0.0043</td>
<td>76% versus 69%, P = 0.002</td>
<td></td>
</tr>
<tr>
<td>GEICAM 9805 Node-negative EBC (n = 1060)</td>
<td>77</td>
<td>FAC × 6</td>
<td>87.8% versus 81.8% (HR: 0.68, 95%CI; P = 0.01)</td>
<td>95.2% versus 93.5% (HR: 0.76; 95%; P = NS)</td>
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</tbody>
</table>

“Standard strength” sequential anthracycline

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Median follow-up (months)</th>
<th>Treatment</th>
<th>DFS (P-value)</th>
<th>OS (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEICAM 9906 Node-positive EBC (n = 1246)</td>
<td>66</td>
<td>FEQ3w × 6</td>
<td>78% versus 72% (HR: 0.74; P = 0.006)</td>
<td>90% versus 87% (NR; P = 0.11)</td>
<td></td>
</tr>
<tr>
<td>PACS 01 Node-negative EBC (n = 1999)</td>
<td>60</td>
<td>FEQ × 3 – Pac × 8w</td>
<td>78% versus 73% (HR: 0.82; P = 0.034)</td>
<td>91% versus 87% (HR: 0.73; P = 0.014)</td>
<td></td>
</tr>
<tr>
<td>WGSG/AGO EC-Doc Trial 1–3 Positive lymph node (n = 2011)</td>
<td>41</td>
<td>4 × EC – 4 × Doc 6 × FEC100 6 × CMF3</td>
<td>Estimated 5 years EFS 91% versus 85% (HR: 0.58, P = 0.004)</td>
<td>Estimated 5 years OS 95% versus 91% (P = 0.03)</td>
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</tbody>
</table>

Meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Median follow-up (months)</th>
<th>Treatment</th>
<th>DFS (P-value)</th>
<th>OS (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis 13 Studies EBC (n = 22,903)</td>
<td>–</td>
<td>–</td>
<td>HR: 0.83 (95%CI, 0.79–0.87; P &lt; 0.00001)</td>
<td>HR: 0.85 (95%CI, 0.79–0.91; P &lt; 0.00001)</td>
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</table>

EBCTCG overview – taxane-plus-anthracycline versus anthracycline-based regimen

Results for all trials that test taxane effect (n = 44,000)

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Median follow-up (months)</th>
<th>Treatment</th>
<th>DFS (P-value)</th>
<th>OS (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unconfounded trials</td>
<td></td>
<td></td>
<td>Distant recurrence RR: 0.87</td>
<td>BC mortality RR: 0.87 (P = 0.00001)</td>
<td>Overall mortality RR: 0.89 (P = 0.0001)</td>
</tr>
<tr>
<td>(taxane versus control group)</td>
<td></td>
<td></td>
<td>Any recurrence RR: 0.86 (P = 0.00001)</td>
<td>Other mortality RR: 0.99</td>
<td></td>
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<tr>
<td>Confounded trials</td>
<td></td>
<td></td>
<td>8-year recurrence: 30.2% versus 34.8% (absolute gain 4.6%)</td>
<td>8-year BC mortality: 21.1% versus 23.9% (absolute gain 2.8%)</td>
<td>8-year overall mortality: 23.5% versus 26.7% (absolute gain 3.2%)</td>
</tr>
<tr>
<td>(taxane versus control group)</td>
<td></td>
<td></td>
<td>8-year recurrence: 19.2% versus 22% (absolute gain 2.9%)</td>
<td>8-year BC mortality: 10.1% versus 11.5% (absolute gain 1.4%)</td>
<td>8-year overall mortality: 11.2% versus 12.4% (absolute gain 1.2%)</td>
</tr>
</tbody>
</table>

FEC, cyclophosphamide, epirubicin, and fluorouracil; AC, doxorubicin and cyclophosphamide; Pac, paclitaxel; FAC, fluorouracil, doxorubicin and cyclophosphamide; Doc, docetaxel; S, surgery; DAC, doxorubicin, cyclophosphamide; EC, epirubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and fluorouracil.

a Anthracycline-based adjuvant breast cancer regimens are categorized into ‘standard-strength’ and ‘low-strength’ regimens based on cumulative doses of doxorubicin >240 mg/m² and epirubicin >360 mg/m². Example: standard strength: FEC100; FEC300; CEF; CAF:A75 or E100 followed by CMF; reduced strength: FEC75; FEC60; FEC50; FAC; AC; EC.
ing a taxane in the adjuvant setting will obviate the need for anthracyclines in a subset of patients, since the great majority of studies evaluated the addition of a taxane to an anthracycline regimen and not its replacement. A phase III randomised trial, the US Oncology Research Trial 9735 [98], enrolled 1016 women with stages I–III HER2-negative breast cancer and randomly assigned therapy with four cycles of AC or four cycles of docetaxel plus cyclophosphamide (TC). With a median follow-up of 7 years, TC resulted in a significantly higher DFS (81% versus 75%) and OS (87% versus 82%). However, how the TC regimen compares with stronger anthracycline-based regimens such as FEC/FAC and with third-generation regimens, which incorporate both an anthracycline and taxane, is still unknown. Therefore, most international guidelines continue to recommend an anthracycline- and taxane-containing regimen for most women, particularly those with higher-stage tumours, and for those with triple-negative or HER2+ BC, unless there are clear contraindications for the use of anthracyclines [13].

The role of anthracycline regimens in the HER2+BC is also a matter of intense research. Several CT regimens used with trastuzumab have been evaluated in large prospective studies, and historically anthracyclines have been considered critical for the management of HER2+ BC. A number of studies from the pre-trastuzumab era support this concept. Retrospective subset analyses of anthracycline-based adjuvant CT studies have suggested that the major benefit for these regimens is seen in HER2-over-expressing tumours [99]. The value of HER2 and TOP2A as predictive markers of response to anthracycline-based therapy has been extensively studied. In the meta-analysis by Di Leo et al., although HER2 amplification and combined TOP2A amplification and deletion had some value in prediction of responsiveness to anthracycline-based therapy, the overall findings did not support the routine use of TOP2A to select the adjuvant CT regimen in this patient population [78].

With the advent of trastuzumab, concerns have been raised regarding the use of anthracycline-based regimens in HER2+ early BC due to potential cardiotoxicity. Previous or concurrent anthracyclines are a risk factor for trastuzumab-related cardiotoxicity. Notwithstanding the increased incidence of cardiac events, these still remain in very acceptable ranges for all types of CT regimens used in the adjuvant setting. Rates of severe congestive heart failure in adjuvant trials ranged between 0.4% and 3.5%, depending on the regimen and schedule used.

Combining trastuzumab with a non-anthracycline-containing CT regimen was evaluated in the BCIRG 006 trial with the aim of investigating whether the association of trastuzumab, carboplatin and docetaxel could be better tolerated and superior in terms of efficacy compared with an anthracycline-based schedule [79]. At a median follow-up of 65 months, the differences in DFS and OS between ACTH and TCH, although not statistically significant, were numerically different, with a trend favouring the anthracycline-containing regimen. The trial hypothesis that TCH was superior to ACTH was not proven and, since the study was not powered to detect equivalence between ACTH and TCH, this conclusion cannot be drawn. With respect to adverse events, the differences were significantly lower rates of severe (grade )

neutropenia (66% versus 63%) and leucopaenia (48% versus 60%) but significantly higher rates of anaemia (6% versus 3%) and thrombocytopenia (6% versus 2%) for TCH and a higher incidence of congestive heart failure (2% versus 0.4%), subclinical and sustained loss of mean left ventricular ejection fraction (18.6% versus 9.4%) for ACTH. Based on this trial alone, TCH can only be considered an alternative treatment for patients with contraindications to anthracyclines (pre-existing cardiac conditions, borderline ejection fraction at baseline, or prior anthracycline exposure) while anthracycline-based regimens remain the standard of care.

Findings suggest that the more dramatic risk reduction when adding trastuzumab to CT is observed when using some concurrent CT and trastuzumab, and employing both anthracycline and a taxane.

4.4. Dose-dense adjuvant chemotherapy

The introduction of granulocyte-colony-stimulating factors has allowed the administration of CT in the dose-dense approach, thought to have higher efficacy based on mathematical models of human breast cancer growth [100]. The pivotal trial CALGB9741 [101] has shown significant improvement in DFS and OS with dose-dense concurrent AC followed by paclitaxel in women with node-positive EBC. Several trials with dose-dense regimens have shown similar results, as shown in a systematic review and meta-analysis of these studies [102] with HR of death 0.85 (95%CI = 0.77–0.93) and HR of relapse or death 0.81 (95%CI = 0.75–0.88). Another important finding was that the benefit was seen only in hormonal-receptor-negative disease. There was no statistically significant increase in adverse events. The concern about these results is related to the design of these trials that did not evaluate the same agents and doses in the conventional arm as in the investigational arm. Further prospective data will help to clarify which patients should be selected for this approach. At the moment these regimens have been mainly used in high-risk disease with features of aggressive biology.

4.5. Sequential versus combination regimens

Sequential single-agent doxorubicin and cyclophosphamide did not improve outcome compared with combination AC [103]. Sequential versus concurrent use of anthracyclines and taxanes in EBC has been evaluated in three studies: CALGB 9741, BIG 2-98 and NSABP B-38.

The first study, CALGB 9741 [101], randomised 2005 female patients, with node-positive disease, to sequential A × 4 → T × 4 → C × 4, every 3 weeks; A × 4 → 3 T × 4 → C × 4, every 2 weeks with filgrastim; concurrent AC × 4 → T × 4, every 3 weeks or AC × 4 → T × 4, every 2 weeks with filgrastim. Dose-dense treatment was associated with improved DFS and OS, with no increase in toxicity.

In the BIG-2-98 [104] study 2887 patients, also with node-positive disease, were randomised to sequential A × 4 → CMF × 3 (sequential control); concurrent AC × 4 → CMF × 3 (concurrent control); sequential A → T × 4 → CMF × 3 (sequential experimental); concurrent AT × 4 → CMF × 3 (concurrent experimental). The updated analysis [105] revealed that sequential docetaxel was associated with significant
improvement of DFS compared with control arms and with concurrent AT.

Preliminary results of NSABP B-38 were recently presented [106]. The trial randomised 4894 women (65% node-positive) to dose-dense ACT, dose-dense AC followed by the combination of paclitaxel and gemcitabine (ACTG), or TAC. Five-year DFS and OS were similar between groups, but the TAC regimen was associated with more grade 3/4 toxicity, namely febrile neutropenia and diarrhoea. Based on the tolerability profile, and on the possible higher efficacy, sequential anthracycline–taxane-based regimens are preferred to combination regimens.

4.6. Are there predictive biomarkers to help select the optimal regimen?

Identification of markers that predict chemosensitivity in BC is a research priority. Several approaches and technologies have been used to identify these predictive markers. The aim is to answer two questions: (a) can we use gene signatures to identify tumours, which are more likely to respond to chemotherapy? and (b) when chemotherapy is indicated, what is the optimal chemotherapy regimen for a specific tumour or group of tumours?

4.6.1. Markers predicting general chemosensitivity

Since patients with poor prognosis disease defined by first-generation signatures have tumours with high expression of proliferation–related genes, and cytotoxic agents target the proliferating fraction of tumours, the finding that first-generation prognostic signatures also predict benefit from conventional multidrug CT regimens is not surprising [45,107–110].

With respect to OncotypeDx, two retrospective studies have reported its predictive value for chemosensitivity [32,111]. In the NSABP trial B-20, 651 patients with node-negative, hormone-receptor-positive tumours were randomised to tamoxifen alone (n = 227) or tamoxifen plus CT (methotrexate–fluorouracil or CMF) (n = 424) [32]. A high recurrence score predicted benefit from CT [hazard ratio (HR) = 0.26; 95% CI = 0.13–0.53], with little or no benefit from CT in the low and intermediate recurrence score groups. The predictive value of the OncotypeDx was also assessed in a subset of patients more than 50 years old with node-positive hormone-receptor-positive tumours included in the SWOG 8814 trial [111]. In this trial, patients were randomised to receive either tamoxifen alone (n = 361); CAF followed by tamoxifen for 5 years (n = 566); or concurrent CAF and tamoxifen (n = 550). The 21-gene recurrence score was assessed in 367 of these patients. The addition of CT to tamoxifen resulted in no difference in DFS or OS in the low recurrence score group, but a clear benefit in DFS and OS in the high recurrence score group. There appeared also to be a benefit for patients in the intermediate recurrence score group, but the confidence intervals were wide due to the small sample size.

This signature was assessed in a series of 167 patients with tumours >5 cm or clinically positive nodes and has also been suggested to predict the response to neoadjuvant CT [112]. Pathological complete response (pCR) after neoadjuvant CT was used as a surrogate for chemosensitivity and in this trial only patients with a bad signature achieved a pCR of 20% (29/144). None of the patients with a good signature (n = 144) achieved a pCR (0/23). The authors concluded that patients with a good signature would be unlikely to respond to CT.

4.6.2. Markers predicting drug-specific chemosensitivity

There are currently no biomarker predictors of response to specific cytotoxic agents. There are several reasons for the apparent inability to develop these predictive factors, namely: (a) resistance or response to therapies may be caused by a functional alteration in only a few genes and this may not manifest itself as a detectable signal in the complex transcriptomic landscape of a tumour; (b) tumours are often composed of a mosaic of genetically heterogeneous clonal subpopulations harbouring numerous private genetic aberrations (that is, aberrations found in a single clone of a tumour [31,113]). These private genetic aberrations may be the drivers of resistance to therapy in a subpopulation and would not be detected by microarrays that survey the average expression profile of the entire tumour.

The Topoisomerase II Alpha Gene Amplification and Protein Overexpression Predicting Efficacy of Epirubicin (TOP) trial (NCT00162812) led to the development of the anthracycline-based score (A-score), which combines three predictive signatures: a TOP2A gene signature and signatures related to tumour invasion and immune response [74]. Analysis of the predictive power of the A-score was performed in the EORTC 10994/BIG (Breast International Group) 00-01 (NCT00017095) trial and from ER-negative patients from the Randomised Clinical Trial to Evaluate the Predictive Accuracy of a Gene Expression for Stage I-II Breast Cancer (NCT00336791). Both studies revealed its high negative predictive value (0.98, 95%CI 0.90–1.00) [74] suggesting, if validated, its potential clinical use for identification of patients who are unlikely to benefit from anthracyclines.

5. What is the optimal adjuvant endocrine treatment?

5.1. Tamoxifen 5 years

Endocrine therapy (ET) is one of the most effective treatments in women with endocrine responsive breast cancer. Tamoxifen has been the mainstay endocrine agent for both pre- and postmenopausal women. Updated analyses [114] of the EBCTCTG overview assessed long-term outcomes among 21,475 women with EBC in trials of 5 years of tamoxifen compared with observation or placebo. In oestrogen-receptor (ER)-positive disease, 5 years of tamoxifen significantly reduced recurrence rates throughout the first 10 years, independently of progesterone receptor status, nodal status, or use of CT: relative risk (RR) 0.53 during years 0–4 and RR 0.68 during years 5–9 [both 2P < 0.00001]. For marginally ER-positive disease there was also an important risk reduction (RR 0.67). More importantly there was a reduction in breast cancer mortality by about a third throughout the first 15 years (RR 0.71 during years 0–4, 0.66 during years 5–9, and 0.68 during years 10–14; P < 0.0001).
5.2. Ovarian suppression and aromatase inhibitors for premenopausal patients

The standard adjuvant hormonal therapy in premenopausal women with ER-positive disease remains tamoxifen alone for 5 years, but benefit has also been shown with the use of luteinising-hormone-releasing (LHRH) agonists specifically in the absence of CT. Several studies have been conducted testing LHRH agonists alone, combined with tamoxifen, chemotherapy or both. In the EBCTCG overview [115] 8000 patients randomised to ovarian function suppression (OFS) or ablation by surgery/radiation had reduced recurrence and breast cancer mortality, but the benefit was seen mainly in the absence of other systemic treatments. An individual patient data meta-analysis [116] of 16 trials using LHRH identified 9022 women with ER+ disease and assessed recurrence rate, breast cancer mortality and overall mortality. While LHRH agonists alone did not have a significant effect, adding these agents to CT, to tamoxifen or both, significantly reduced recurrence by 12.7% (P = 0.02) and death after recurrence by 15.1% (P = 0.03). Furthermore, the benefit of LHRH agonists after CT was seen in women younger than 40 years, but not in older premenopausal women. However, the data do not answer the question of whether LHRH agonist is useful only when amenorrhea is not achieved with CT, an event that has been associated with worse outcome in some trials [117,118].

Recently a guideline from Cancer Care Ontario was published and endorsed by ASCO [119] conducting a systematic review of available literature. The guideline does not recommend the routine use of OFS added to chemotherapy, tamoxifen or a combination of both. It does acknowledge as a major difficulty in assessing its efficacy the fact that ovarian suppression has not been compared with current CT regimens (e.g. anthracyclines or anthracyclines/taxanes), which deems the benefit of these agents unclear. For chemical suppression the guideline does suggest the use of monthly injections.

The role of aromatase inhibitors (AIs) in premenopausal women was assessed in the ABCSG-12 trial [120] which randomised 1803 patients to receive goserelin monthly plus tamoxifen or anastrozole, with or without zoledronic acid for 3 years. There was no significant difference in DFS between the anastrozole and tamoxifen groups (HR = 1.10; CI 0.78–1.53), but the trial was relatively small to answer this secondary objective. Till now AIs combined with OFS are only recommended in premenopausal patients if tamoxifen is contraindicated. To better understand the role of aromatase inhibitors, as well as OFS in this setting, results from the studies TEXT, SOFT and PROMISE are eagerly awaited.

5.2.1. Aromatase inhibitors

For postmenopausal patients the aromatase inhibitors anastrozole, letrozole and exemestane have been extensively studied in adjuvant setting as upfront therapy for 5 years, “switch” strategy of initial tamoxifen for 2–3 years followed by an AI 2–3 years, the reverse sequence, or as an extended treatment after 5 years of tamoxifen (see Table 4) [121–129]. The meta-analysis of the adjuvant trials [130] analysed a cohort of 9856 patients where AI upfront therapy was compared with standard tamoxifen treatment, showing a significant 2.9% absolute decrease in recurrence and a non-significant absolute 1.1% decrease in breast cancer mortality. A second cohort comprising 9015 patients compared the switch strategy with standard tamoxifen treatment and showed a significant absolute decrease in recurrence and in breast cancer mortality of 3.1% and 0.7%, respectively. Current ASCO [131] and European Guidelines [132] recommend the incorporation of AIs in the endocrine treatment plan as switch (2–3 years) or upfront therapy strategy (5 years). For patients who have completed 5 years of tamoxifen the addition of an AI for a further period of 2–5 years is recommended, especially for patients with node-positive disease. On the other hand, 5 years of tamoxifen alone is still a viable option for certain patients at very low risk of recurrence.

The choice of endocrine treatment and the timing for AI treatment is nowadays based on the toxicity profile of these drugs compared with tamoxifen, general health issues of each individual and the risk of relapse. A recent meta-analysis [133] on safety reports from major adjuvant trials found that AI therapy was associated with a higher risk for cardiovascular disease (HR, 1.2) and bone fracture (HR, 1.48) than tamoxifen, but a lower risk for venous thromboembolism (HR, 0.53) and uterine cancer (HR, 0.32). Overall these risks were low, around 2% of patients, and fractures only occurred in fewer than 10% of all patients. Additional data from a population-based study [134] evaluating 44,000 women with breast cancer and age-matched women without breast cancer, have shown that breast cancer patients on ET had a lower risk for both myocardial infarction and ischaemic stroke than those who did not have breast cancer. No differences were seen between AI therapy and tamoxifen therapy in the risk for myocardial infarction or stroke, but AI therapy was associated with a higher risk for any fracture (mainly hip fractures). Guidelines [131,132] recommend surveillance of bone mineral density during AI treatment, and calcium and vitamin D supplementation or a bisphosphonate depending on the result.

5.3. Extended ET treatment

Because the risk of recurrence in hormone-receptor-positive disease still remains after the first decade [135], clinicians and researchers have been questioning the benefit of extended tamoxifen treatment beyond 5 years. Three prospective trials addressed this question, randomising patients after 5 years of tamoxifen treatment to additional 5 years of treatment or placebo (NSABP-B14 [136], aTTom trial [137] and ATLAS trial [138]). Except for the NSABP B14 trial, these studies together with EBCCTG [114] have shown benefit for extended tamoxifen. However, balance with side effects has to be considered as extended treatment is associated with increased incidence of endometrial cancer, which is 2.3-fold with 5 years of tamoxifen and 4-fold with 10 years [114]. On the other hand, there is some evidence that tamoxifen has a favourable effect in lipid profile [139–141]. ATLAS results suggest some protection against ischaemic heart disease and certainly no increase in stroke deaths. In the EBCCTG overview the non-significant excess of stroke deaths was balanced by a non-significant shortfall in cardiac deaths with lit-
<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment arms/population (n)</th>
<th>Median follow-up</th>
<th>Recurrence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tamoxifen 5 years</strong></td>
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<tr>
<td>Overview 2011 (W164)</td>
<td>TAM 5 years versus no TAM 10,645 ER⁺</td>
<td>15 years</td>
<td>RR = 0.53 [SE 0.03] years 0–4</td>
<td>RR = 0.71 [SE 0.05] years 0–4</td>
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<td></td>
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<td></td>
<td>RR = 0.68 [SE 0.06] years 5–9</td>
<td>RR = 0.66 [SE 0.05] years 5–9</td>
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<td></td>
<td></td>
<td></td>
<td>2P &lt; 0.00001 RR = 0.97 [SE 0.10] years 10–14</td>
<td>RR = 0.68 [SE 0.08] years 10–14</td>
</tr>
<tr>
<td>OFS Overview 2005 [115]</td>
<td>8000 ER⁺/ER unknown, &lt;50 years, OFS LHRH– 3408</td>
<td>5 years</td>
<td>15 years gain 4.3% (SE 1.9)</td>
<td>15 years gain 3.2% (SE 2.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2P &lt; 0.00001</td>
<td>P = 0.04</td>
</tr>
<tr>
<td>Meta-analysis [164]</td>
<td>11,906 Premenopausal</td>
<td>6.8 years</td>
<td>No systemic treatment versus LHRH: HR 0.72 (95%CI 0.49–1.04), P = 0.08</td>
<td>No systemic treatment versus LHRH: HR 0.82 (95%CI 0.47–1.43), P = 0.49</td>
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<td></td>
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<td>CT versus LHRH: HR 1.04 (95%CI 0.92–1.17), P = 0.52</td>
<td>CT versus LHRH: HR 0.93 (95%CI 0.79–1.10), P = 0.40</td>
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<td></td>
<td></td>
<td></td>
<td>Addition to TAM: HR 0.85 (95%CI 0.67–1.09), P = 0.20</td>
<td>Addition to TAM: HR 0.84 (95%CI 0.59–1.19), P = 0.33</td>
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<td></td>
<td></td>
<td></td>
<td>Addition to CT ± TAM: HR 0.88 (95%CI 0.77–0.99), P = 0.04</td>
<td>Addition to CT ± TAM: HR 0.85 (95%CI 0.73–0.99), P = 0.04</td>
</tr>
<tr>
<td><strong>AIs 5 years</strong></td>
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<tr>
<td>ATAC [164]</td>
<td>TAM 5 years versus ANA 5 years 3116/3125</td>
<td>120 months</td>
<td>HR = 0.91 (95%CI 0.83–0.99) P = 0.04</td>
<td>0.97 (95%CI 0.88–1.08) P = 0.6</td>
</tr>
<tr>
<td>BIG 1.98 [164]</td>
<td>TAM 5 years versus LET 5 years 2459/2463</td>
<td>76 months</td>
<td>HR = 0.88 (95%CI 0.78–0.99) P = 0.03</td>
<td>HR = 0.87 (95%CI 0.75–1.02) P = 0.08</td>
</tr>
<tr>
<td>TEAM [164]</td>
<td>EXE 5 years versus TAM 2–3 years followed EXE 2–3 years 4868/4898</td>
<td>5.1 years</td>
<td>HR = 0.97 (0.88–1.08) P = 0.60</td>
<td>HR = 1.00 (0.89–1.14) P &gt; 0.9</td>
</tr>
<tr>
<td>Meta-analysis [164]</td>
<td>Cohort 1 AIs initial monotherapy versus TAM 9856</td>
<td>5.8 years</td>
<td>9.6% AI versus 12.6% TAM 2P &lt; .00001 2.9% absolute decrease (SE 0.7%)</td>
<td>4.8% AI versus 5.9% TAM 1.1% (SE 0.5%) absolute decrease 2P = 0.1</td>
</tr>
<tr>
<td>MA.27 [6]</td>
<td>EXE 5 years versus ANA 5 years 7576</td>
<td>4.1 years</td>
<td>HR = 1.02 (95%CI 0.87–1.18) P = 0.85</td>
<td>HR = 0.93 (95%CI 0.77–1.13) P = 0.46</td>
</tr>
<tr>
<td><strong>AIs and tamoxifen in switching strategies</strong></td>
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<td></td>
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<tr>
<td>BIG 1.98 [129]</td>
<td>LET 5 years TAM 2 years followed by LET 3 years 1546/1548/1540</td>
<td>71 months</td>
<td>HR = 1.05 (95%CI 0.84–1.32) P = 0.85</td>
<td>HR = 1.13 (95%CI 0.83–1.53)</td>
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<td></td>
<td></td>
<td></td>
<td>HR = 0.96 (95%CI 0.76–1.21)</td>
<td>HR = 0.90 (95%CI 0.65–1.24)</td>
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<tr>
<td>ABCSG-8/ARNO 95 [125]</td>
<td>TAM 5 years versus Tam f 2 years followed by ANA for 3 years 28 months</td>
<td>HR = 0.60 (0.44–0.81) P = 0.0009</td>
<td>P = 0.16</td>
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tle net effect on overall vascular mortality. Interestingly, a recent study [142], with a median follow up of 10.1 years, assessed the long-term benefits of 5 years versus 2 years of tamoxifen use in a large randomised trial of EBC women more than 50 years of age. Follow-up strategies included matching trial subjects with death data from the British National Health Service Information Center. Besides the well-known positive efficacy of tamoxifen, this study revealed a nearly statistically significant reduction in cardiovascular deaths (HR, 0.79; \( P = 0.08 \)) with longer tamoxifen, and in women of 50–59 years there was an even greater reduction in cardiovascular events (HR, 0.65; \( P = 0.005 \); \( P = 0.046 \) for interaction between age and treatment groups).

In postmenopausal women extended use of AIs after 5 years of tamoxifen has shown improvement in DFS (see Table 4), and in one study, the MA-17 trial [143], an improvement in OS was also seen in node-positive patients. It is not known if longer use of AIs (more than 5 years) will increase outcomes without compromising safety, and it is not recommended until mature data from MA.17R and NSABP B-42 trials are available. The best regimen of ET for postmenopausal patients and the duration of ET treatment are still unanswered questions.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment arms/ population (n)</th>
<th>Median follow-up</th>
<th>Recurrence</th>
<th>Mortality</th>
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<tbody>
<tr>
<td>ITA [122]</td>
<td>TAM 5 years versus Tam 2 years followed by ANA</td>
<td>128 months</td>
<td>HR = 0.64 (0.44–0.94) ( P = 0.023 )</td>
<td>HR = 0.72 (0.44–1.17) ( P = 0.3 )</td>
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<td>IES <a href="164">124</a>(164)</td>
<td>TAM 5 years versus TAM 2–3 years followed by EXE 2–3 years</td>
<td>55.7 months</td>
<td>HR = 0.76 (95% CI 0.66–0.88) ( P = 0.0001 )</td>
<td>HR = 0.85 (95% CI 0.71–1.02) ( P = 0.08 )</td>
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<tr>
<td>Meta-analysis [130]</td>
<td>Cohort 2 Analysed TAM 2–3 years versus TAM 9015</td>
<td>3.9 years</td>
<td>5.0% AI versus 8.1% TAM 3.1% absolute decrease (SE 0.6%) ( P &lt; .00001 )</td>
<td>1.7% AI versus 2.4% TAM 0.7% (SE = 0.3%) absolute decrease ( P = 0.2 )</td>
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<tr>
<td><strong>Extended treatment beyond 5 years</strong></td>
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<tr>
<td>ATLAS [138]</td>
<td>TAM 5 years versus TAM 10 years 3428/3418</td>
<td>NR</td>
<td>RR = 0.90 (95% CI 0.79–1.02) 5–9 years ( RR = 0.75 (95% CI 0.62–0.90) ) later years ( RR: 0.84, 95% CI 0.76–0.94; P = 0.002 ) in ER+</td>
<td>RR = 0.97 (95% CI 0.79–1.18) 5–9 years ( RR = 0.71 (95% CI 0.58–0.88) ) later years ( OS% 7Y = 94% TAM 5 years versus 91% TAM &gt;5 years ( P = 0.07 )</td>
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<tr>
<td>NSABP-B14 [136]</td>
<td>TAM 5 years versus TAM &gt;5 years 579/593</td>
<td>7 years</td>
<td>DFS = 82% TAM 5 years versus 78% TAM &gt;5 years ( P = .03 )</td>
<td>DFS = 82% TAM 5 years versus 78% TAM &gt;5 years ( P = .03 )</td>
</tr>
<tr>
<td>aTTOM [137]</td>
<td>TAM 5 years versus TAM 10 years 6934</td>
<td>4.2 years</td>
<td>415 TAM 5 years versus 442 recurrences TAM 10 years ( RR = 0.94 (95% CI 0.81–1.09) ) ( P = 0.4 )</td>
<td>NA</td>
</tr>
<tr>
<td>MA.17 [143]</td>
<td>TAM 5 years followed LET 5 years versus TAM 5 years 2594/2593</td>
<td>30 months</td>
<td>HR = 0.58 (95% CI 0.45–0.76) ( P &lt; .001 )</td>
<td>HR = 0.82 (95% CI 0.57–1.19) ( P = 0.03 )</td>
</tr>
<tr>
<td>NSABP-B33 [164]</td>
<td>TAM 5 years followed EXE 5 years versus TAM 5 years 779/786</td>
<td>30 months</td>
<td>DFS 4 years 91% versus 89% ( RR = 0.68 (P = 0.07) )</td>
<td>16 deaths versus 13 ( P = 0.1 )</td>
</tr>
<tr>
<td>ABCSG-6a [165]</td>
<td>TAM 5 years followed ANA 3 years versus TAM 5 years 469/387</td>
<td>62 months</td>
<td>HR = 0.62 (95% CI 0.40–0.96) ( P = 0.031 )</td>
<td>HR = 0.89 (95% CI 0.59–1.34) ( P = 0.57 )</td>
</tr>
</tbody>
</table>

AI, aromatase inhibitor; DFS, disease-free survival; ER+, estrogen-receptor-positive patients; HR, hazard ratio; RR, event rate ratio; OS, overall survival; TAM, tamoxifen; LET, letrozole; EXE, exemestane; ANA, anastrozole; LHRH, luteinizing-hormone-releasing agonists; OFS, ovarian function suppression.
Adherence to ET is a concern in patients with EBC as it is believed to impact on the outcome; however, the association between non-adherence and breast cancer mortality is not proven. In ET studies patients are considered to be adherent to treatment if ≥80% of prescribed doses are taken, but the best tool for measurement of adherence is not yet defined, and has varied among studies. It has been reported that adherence to tamoxifen falls to 50% during the course of therapy [144]. Non-adherence to anastrozole has been reported to occur in 1/3 of patients [145]. In a recent population-based study of 8769 patients with BC [146], 32% discontinued treatment with tamoxifen or an AI over the 4.5-year follow-up period, and among those who continued 28% were non-adherent. Younger women were at high risk of non-adherence being 50% more likely to discontinue therapy and 40% more likely to be non-adherent (P < 0.001).

Among patients taking AIs the musculoskeletal toxicities are the main reason for treatment discontinuation/non-adherence [147–149]. Predictive factors of these adverse effects have been studied, but have not been consistent among studies. A retrospective exploratory analysis from the ATAC trial has shown that previous hormone replacement therapy, previous CT and obesity were risk factors for the development of joint symptoms. A recent exploratory analysis from a prospective study, the Exemestane and Letrozole Pharmacogenetics (ELPh) clinical trial [150], found that younger age and prior taxane-based CT were associated with a greater likelihood of treatment discontinuation, but prior tamoxifen therapy, prior hormone replacement therapy and body mass index were not predictors. One third of patients prematurely discontinued adjuvant AI therapy in this study, but it was also seen than more than one third of patients who switched drugs tolerated the second AI, confirming previous results [151].

There is no evidence to demonstrate differences in efficacy and toxicity among AIs. Anastrozole has shown efficacy similar to that of letrozol in the MA.27 trial [152]. The results from the FACE trial comparing two non-steroidal AIs, letrozole and anastrozole, are awaited.

The main predictors of response to hormonal treatment are oestrogen and progesterone receptors [114]. There is no...
evidence to support HER2 status as predictive of different responses to tamoxifen or AIs [129,153]. New genomic tools such as Oncotype DX and PAM50 [30,154] have been predictive of tamoxifen treatment, but their use in clinic has been mainly as a prognostic tool.

Recently an exploratory analysis from the BIG 1-98 trial [155] of 2599 patients treated with tamoxifen monotherapy or letrozole monotherapy, with a 12-year follow-up, showed a significant interaction effect between histology subtype and degree of benefit to letrozole over tamoxifen, with greater benefit being seen with letrozole in women with lobular carcinomas compared with invasive ductal carcinomas. Although these data need further validation, it restores confidence in the use of AI in high-risk lobular tumours.

6. What is the optimal adjuvant anti-HER2 treatment?

For patients with HER2+ early BC the use of trastuzumab and CT is well established and evaluated in six adjuvant trastuzumab randomised clinical trials (Table 5) involving more than 13,000 women: the Herceptin Adjuvant trial (HERA) [156], the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial and the North Central Cancer Treatment Group (NCCTG) N9831 trial [157], the Breast Cancer International Research Group (BCIRG) 006 trial [79], the Finland Herceptin trial (FinHER) [158] and the Protocol Adjuvant dans le Cancer du Sein (PACS-04) trial [159], and in a 2012 meta-analysis [160].

All trials except PACS-04 yielded an improved DFS (HR between 0.6 and 0.77) and OS (HR between 0.55 and 0.77) with the administration of trastuzumab (Table 5).

Cardiac toxicity data from these trials indicate that the rate is higher when anthracyclines are used and with concurrent regimens. Nevertheless, the rates are always low and clinically acceptable.

The 2012 meta-analysis of eight studies, involving 11,991 patients, assessed the benefits of adding trastuzumab to adjuvant CT in patients with HER2+ BC [160]. The inclusion of trastuzumab resulted in an improvement in DFS with an HR = 0.60 (95%CI 0.50–0.71), regardless of trastuzumab treatment duration or administration schedule (i.e. concurrently or sequentially with CT) and an improvement in OS with an HR = 0.66 (95%CI 0.57–0.77).

6.1. Timing of trastuzumab initiation

The decision about whether trastuzumab should be administered concurrently or sequentially after the completion of adjuvant CT as been addressed directly in the N9831 trial. The second planned interim analysis, with a median follow-up of 6 years, indicates that although trastuzumab added sequentially to CT improves DFS, there is a strong trend towards a better outcome with concurrent trastuzumab relative to sequential administration [161].

In the 2012 meta-analysis the benefit in OS was associated with concurrent administration [HR 0.64 (95%CI 0.53–0.76)] but not with sequential treatment of CT followed by single-agent trastuzumab [HR 0.85 (95%CI 0.43–1.67)] [160]. BCIRG-006 also support the use of trastuzumab administered concurrently with CT in the adjuvant setting [79].

6.2. Duration of trastuzumab treatment

One year of trastuzumab is the standard of care in adjuvant therapy. In the HERA trial a comparison between 1 and 2 years of adjuvant trastuzumab after CT concluded that 2 years of treatment was not better than 1 year [162]. The PHARE trial recruited over 3380 HER2+ patients and randomly assigned them to receive either 6 months or 1 year of adjuvant trastuzumab. The trial results were reported as unable to prove the non-inferiority hypothesis of 6 months versus 1 year of adjuvant trastuzumab [163]. In the 2012 meta-analysis trastuzumab administered for 12 months was associated with an improvement in OS [HR 0.67 (95%CI 0.57–0.80)]; although trastuzumab treatment for ≤6 months also showed a trend towards an improvement in OS, it did not reach statistical significance [HR 0.55 (95%CI 0.27–1.11)] [160].

Several trials are still ongoing evaluating the optimal duration and regimen of adjuvant trastuzumab, these might lead to a different conclusion in the future. The relative benefit of 6 months versus 1 year of trastuzumab is being evaluated in the PERSEPHONE trial (which also evaluates sequential versus concurrent trastuzumab) and the HELLENIC trial (using only concurrent therapy). The SHORT-HER and SOLD trials are evaluating 9 weeks versus 12 months of trastuzumab given concomitantly with a taxane, similar to the FinHER trial.

7. Conclusions and future perspectives

(Neo)adjuvant systemic therapy has dramatically changed the natural history of EBC. Together with screening and early detection, it is responsible for the 30% decrease in mortality observed since the 1990s.

The stronger effects are seen with biologically targeted agents such as endocrine and anti-HER2 therapies. Similar advances are still lacking for the heterogeneous groups of triple-negative EBC.

Prognostication has been greatly improved in the last decade, but advances in prediction have been only minimal and remain a research priority.

New technologies and a better knowledge of the biology of the different subtypes of BC, as well as an in-depth understanding of the mechanism of cancer resistance, will hopefully enable us to achieve a true individualised/personalised medicine in the near future.

Conflict of interest statement

The author has a potential conflict of interest with the following companies: Eisai, Roche, GSK, Celgene, AstraZeneca, Novartis, GE Oncology, Merck-Sharp, Merus BV, Genentech and Pfizer.

REFERENCES


20


The role of the pathologist in the decision-making process

Angelo Paolo Dei Tos *

General Hospital of Treviso, Department of Oncology and Pathology, Treviso, Italy

1. Introduction

During the last two decades the pathological classification of breast carcinoma has evolved rapidly. Starting from the pure assessment of conventional morphology, it has gradually been integrated with immunophenotypic evaluation of the hormone receptor, HER2, and Ki67 status. In addition, molecular genetic testing (mostly by fluorescence in situ hybridisation, FISH) for Her2 immunohistochemically ‘equivocal’ cases has become a standard. Pathological evaluation of breast specimens has shifted rapidly from a mere diagnostic process, aimed at establishing the biological potential of a breast ‘lump’, to a far more complex integration of diagnostic, prognostic and predictive parameters. The current landscape has been further complicated by the relatively recent introduction of a ‘molecular’ classification of breast cancer [1]. Since then pathologists and clinicians have struggled in the attempt to translate (or maybe to force) the classic morphological approach into a molecularly based scheme (Table 1).

Whatever the approach, the role played by the pathologist in the clinical decision-making process has never been so central. Establishing the correct diagnosis, as well as accurately evaluating key prognostic/predictive biomarkers, represent the core of the breast cancer pathology report. Even acknowledging the current complexity of personalised treatments, it is broadly accepted that the information mandatory for inclusion in the pathology report represents a milestone for optimal therapeutic planning.

2. Pathological diagnosis

The pathological diagnosis of breast carcinoma still represents the key step. Before considering the complex integration of predictive and prognostic markers, it should not be overlooked that the diagnosis of breast cancer is not always straightforward. The presence, within the breast cancer multidisciplinary team, of a skilled breast pathologist represents a fundamental prerequisite in order to achieve optimal therapeutic planning.

The World Health Organisation (WHO) has recently updated its breast cancer classification, separating invasive breast carcinoma into two broad categories: invasive carcinoma of no special type (formerly known as invasive ductal carcinoma) and special subtypes (Table 2). The recognition of special subtypes is relevant as distinct morphologies often correlate with distinct clinical outcomes [2].

Once the correct diagnosis of invasive carcinoma is made, pathologists are asked to provide a set of morphological parameters representing important clues to prognostic stratifications. These include the size of the lesion, the presence of lymphatic and blood vessel invasion, the status of lymph nodes and the histological grading (Table 3). The currently adopted grading system is that devised by Elston and Ellis, and represents a powerful prognostic tool that represents a key factor in clinical decision-making [3]. The so-called Nottingham system is based on the evaluation of differentiation (as expressed by the amount of tubule formation), nuclear pleomorphism (by comparing neoplastic cell nuclei with adjacent normal breast epithelial cells) and mitotic activity (as expressed by number of mitoses counted per 10 high-power fields). Of course the dimension of a ‘high-power field’ depends on the size of the microscope. The WHO, in its most recent classification, has therefore provided a conversion table aimed at minimising inter-observer variability [2].

As shown, pathological evaluation of haematoxylin-and-eosin-stained slides still represents the cornerstone of breast cancer diagnosis. Even though molecular testing is playing an increasingly key role in several fields of cancer, it is extremely important that morphological expertise is not lost, and that educational efforts are supported in order to maintain diagnostic skills to the highest possible standard.

3. Evaluation of predictive/prognostic markers

The three main biomarkers used in the routine clinical management of invasive breast carcinoma are represented by the oestrogen receptor (ER), progesterone receptor (PR) and HER2. More recently, the evaluation of the Ki67 labelling index has
of expression has been abolished as even 1% of positive cells variably expresses the ER. Any cut-off the help of digital imaging tools. Approximately 80% of inva-
sively) performed on formalin-fixed, paraffin-embedded 
measurement of the ER can be effectively (and relatively inexpen-

ture to hormone therapy. The ER/PR phenotype which predicts unresponsiveness to hormone therapy. The ER/PR cases are associated 
intermediate levels of response, whereas the very existence of true ER/PR cases is still the source of sharp debate.

HER2 (ERBB2) represents a proto-oncogene located on chromosome 17 and is amplified in approximately 15% of breast invasive carcinomas [12]. HER2 amplification strongly correlates with protein over-expression that can therefore be detected immunohistochemically. HER2 represents both a prognostic and a predictive biomarker. HER2 amplification not only correlates with poorer outcome [13] but also predicts response to molecular targeted therapies aimed specifically against HER2 (i.e. trastuzumab and lapatinib) [14,15]. HER2 status is primarily determined immunohistochemically on FFPE tissue and scored according to broadly accepted guidelines [16]. Cases with strong complete membrane staining in more than 30% of neoplastic cells (so-called 3+) are candidates for anti-HER2 therapy. Negative or weakly positive cases (so called 0 and 1+) are generally excluded, whereas cases with continuous but less strong than 3+ membrane staining undergo FISH to assess the presence of HER2 gene amplification that, if present, would also qualify the patients for anti-HER2 targeted therapy. The best response is seen in cases showing strong HER2 over-expression and/or HER2 gene amplification. Lack of accuracy in HER2 testing represents a major obstacle to correct selection of patients and (analogously to ER/PR testing inaccuracy) may impact on clinical outcomes [17].

The PR is also routinely evaluated immunohistochemically [8]. The ER regulates PR expression, and therefore the presence of the latter gives testament to the functional integrity of the ER pathway [9]. Expression of the PR is detected in approximately 60–70% of invasive breast cancers, and as with the ER there is direct correlation between its level of expres-
sion and response to hormonal therapy [8,10].

The best estimation of response to hormone therapy is generated by the combination of both ER and PR expression [11]. The combination ER+/PR− accounts for approximately 70% of invasive breast cancers and correlates with the best anti-oestrogen response (60%). Approximately 25% of patients exhibit an ER-/PR− phenotype which predicts unresponsiveness to hormone therapy. The ER+/PR− cases are associated with intermediate levels of response, whereas the very existence of true ER-/PR− cases is still the source of sharp debate.

HER2 (ERBB2) represents a proto-oncogene located on chromosome 17 and is amplified in approximately 15% of breast invasive carcinomas [12]. HER2 amplification strongly correlates with protein over-expression that can therefore be detected immunohistochemically. HER2 represents both a prognostic and a predictive biomarker. HER2 amplification not only correlates with poorer outcome [13] but also predicts response to molecular targeted therapies aimed specifically against HER2 (i.e. trastuzumab and lapatinib) [14,15]. HER2 status is primarily determined immunohistochemically on FFPE tissue and scored according to broadly accepted guidelines [16]. Cases with strong complete membrane staining in more than 30% of neoplastic cells (so-called 3+) are candidates for anti-HER2 therapy. Negative or weakly positive cases (so called 0 and 1+) are generally excluded, whereas cases with continuous but less strong than 3+ membrane staining undergo FISH to assess the presence of HER2 gene amplification that, if present, would also qualify the patients for anti-HER2 targeted therapy. The best response is seen in cases showing strong HER2 over-expression and/or HER2 gene amplification. Lack of accuracy in HER2 testing represents a major obstacle to correct selection of patients and (analogously to ER/PR testing inaccuracy) may impact on clinical outcomes [17].

4. Towards a molecular classification of breast carcinoma

Molecular analysis of breast carcinoma using a gene expres-
sion array approach has led to the recognition of several genetically distinct forms [1]. Gene expression profile assays measure quantitatively in tumour samples the expression of each gene harboured on the array. These techniques generate great amounts of data that need to be analysed with bioinfor-
matic techniques. Two main approaches are most often used: unsupervised hierarchical cluster analysis and supervised classification. Unsupervised approaches analyse gene expression within a series of tumours without using the clinical and/or pathological information available. Hierarchical clus-
ter analysis then subclassifies tumours into distinct sub-
groups. If the aim of analysis is to identify gene expression patterns predictive of clinical behaviour then a supervised ap-
proach seems to be more appropriate. This technique in fact

<table>
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<th>Table 1 – Molecular classification of breast cancer.</th>
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<td>Subtype</td>
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<td>Luminal A</td>
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<td>Luminal B</td>
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<tr>
<td>HER2-positive (non-luminal)</td>
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<td></td>
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<tr>
<td>Basal-like</td>
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<table>
<thead>
<tr>
<th>Table 2 – WHO classification of breast cancer.</th>
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<td>Invasive carcinoma of no special type</td>
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<td>Special types:</td>
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<tr>
<td>• Invasive lobular carcinoma</td>
</tr>
<tr>
<td>• Tubular carcinoma</td>
</tr>
<tr>
<td>• Cribriform carcinoma</td>
</tr>
<tr>
<td>• Carcinoma with medullary features</td>
</tr>
<tr>
<td>• Metaplastic carcinoma</td>
</tr>
<tr>
<td>• Carcinoma with apocrine differentiation</td>
</tr>
<tr>
<td>• Salivary gland/skin adnexal type tumours</td>
</tr>
<tr>
<td>• Adenoid cystic carcinoma</td>
</tr>
<tr>
<td>• Mucoepidermoid carcinoma</td>
</tr>
<tr>
<td>• Polymorphous carcinoma</td>
</tr>
<tr>
<td>• Mucinous carcinoma (including signet ring variant)</td>
</tr>
<tr>
<td>• Carcinoma with neuroendocrine features</td>
</tr>
<tr>
<td>• Invasive papillary carcinoma</td>
</tr>
<tr>
<td>• Invasive micropapillary carcinoma</td>
</tr>
<tr>
<td>• Inflammatory carcinoma</td>
</tr>
<tr>
<td>• Exceptional rare types and variants</td>
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</table>
specifically correlates gene expression with key clinical parameters such as overall or disease-free survival as well as response to a given therapy.

The unsupervised hierarchical cluster analysis of breast carcinoma has led to a broad division into ER+ and ER– cases [18,19]. If the set of genes expressed by the two categories is examined closely, ER+ cases are linked to breast luminal cells, whereas ER– cases are associated with myoepithelial cells. The next step is the correlation of these subgroups with clinical outcomes. This approach has led to the definition of the entities (intrinsic subtypes) listed in Table 1: namely types luminal A and B, HER2 and basal-like [1,20].

The attempt to correlate gene expression profiles with clinical outcome has generated several gene signatures. The most popular is represented by a 70-gene signature that may determine prognosis in stage-1 or -2 node-negative patients affected by breast carcinomas smaller than 5 cm. The 70-gene signature separates patients into two groups with good and poor prognoses, and appears to work as an independent predictor of metastatic spread [1]. The 70-gene signature has been popularised with the commercial label Mammaprint which has been cleared by the FDA as an in vitro diagnostic multivariate index assay.

An alternative approach is represented by the 21-gene recurrence score [21]. This is a qRT-PCR-based signature commercially named Oncotype DX, that predicts the likelihood of recurrence at 10 years for ER-positive, lymph-node-negative patients. The test provides a continuous recurrence score (RS) and risk category: low (RS < 18), intermediate (RS 18–30) and high (RS > 30). The 21-gene recurrence score apparently may also correlate with benefit from chemotherapy in ER-positive breast cancer patients [21].

The clinical utility of gene expression profiling in breast cancer has generated a lively and still ongoing debate. Even if there is a strong pressure (particularly in the US, United States) towards a broader use of such approaches, their potential benefit seems until now to be restricted to a minority of breast cancer patients. Nonetheless, also in consideration of the rapid evolution (and cost reduction) of molecular genetic techniques, it has to be expected that molecular assays will be implemented increasingly in clinical practice.

5. Conclusions

Pathological evaluation of breast cancer specimens plays a key role in planning the best therapeutic options. In addition to accurate diagnosis of malignancy and cancer subtype, pathologists are central in helping clinicians in the selection of patients for both endocrine therapy as well as for anti-Her2 targeted approaches. Precise evaluation of breast cancer biomarkers still represents a key issue not yet entirely resolved, and it has been shown to impact on clinical decision-making as well as on patient outcome. It is vital that pathology laboratories systematically implement External Quality Control policies aimed at achieving and maintaining the highest diagnostic standard.

The rapid evolution of molecular techniques has in part changed the landscape of breast cancer prognostic biomarkers. The advent of genomic signatures certainly represents a step forward, but their clinical utility is being still debated; complete agreement regarding their clinical as well as their cost-effectiveness is still to be achieved.

Conflict of interest statement

The authors have no conflict of interest relating to this article.

References


Optimal approach in early breast cancer: Radiation therapy

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Radiation therapy significantly reduces by at least 70% the relative risk of local and regional recurrences for breast cancer after surgery. A positive influence on overall survival has been clearly demonstrated, especially for patients with a high absolute risk for locoregional recurrences. However, this is partially counterbalanced by late toxicity (dependent upon the radiation dose) especially to cardiac structures. Apart from this toxicity, a clear influence of radiation-therapy-related factors on functional and cosmetic outcome has also been demonstrated. Over time, technical improvements have led to a marked reduction in dose to the neighbouring organs, with a consequent drop in acute and late toxicity. This has also allowed the introduction of shorter radiation schedules, lowering the burden of treatment to the patient and the hospital. Several tools, techniques and guidelines have been developed to optimise the balance between the desired reduction in recurrence rates and side effects.

The multidisciplinary team should discuss all available treatment options for every individual breast cancer patient. Individualisation of the selection of the optimal combination of treatments, depending on patient and tumour-related factors, is of utmost importance. Apart from direct tumour-related outcomes, cosmesis and potential side effects have to be taken into account. Counselling should include known risk factors for survival and complications, including comorbidity.

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1. Introduction

Radiation therapy (RT) forms an integral component of the management of early-stage breast cancer. Over the years, significant progress – accelerating over time – has resulted from our growing knowledge of the biology and the natural behaviour of breast cancer as well as from technical improvements in RT. While initially research focused on optimising locoregional disease control by combining surgery with RT, the introduction of breast-conserving therapy (BCT) initiated a period of research aimed at lowering the burden of treatment [1,2]. At the same time, adjuvant systemic treatment became widely used, resulting in a reduced risk of metastases and thereby improving overall survival. The interaction between the benefits from both locoregional and systemic treatments opened the way to further improving the clinical outcome for breast cancer patients in terms of survival as well as quality of life.

The 21st century started with a number of developments, including fine-tuning of the indications for RT for each individual target volume (intact breast, post-mastectomy chest wall, axillary, internal mammary and supraclavicular lymph nodes) depending on the clinicopathological features of an individual patient’s disease, as well as hypofractionation and accelerated partial breast irradiation.

2. Prognostic factors influencing locoregional treatment

Several prognostic factors determine the risk of recurrence at local, regional and distant sites. On the basis of this, recom
mendations for both local and systemic treatments for patients with breast cancer are defined.

Factors influencing the risk of recurrence include tumour size, tumour grade, margin status, lymph-node involvement, oestrogen and progesterone receptor status, HER-2/neu status and patient age. Whereas the relative benefit of locoregional and systemic therapy remains largely independent of these factors, they greatly determine the absolute benefit that can be expected. For systemic therapy they also determine the selection of its type (endocrine therapy, chemotherapy, trastuzumab, or a combination of these).

Age may also influence treatment recommendations as it helps to predict the relative risk for death related to cancer compared to death from other causes. In general, treatment tolerability, especially for chemotherapy, tends to decrease with increasing age.

Patients who are BRCA1 or BRCA2 mutation carriers should receive extensive counselling to discuss the possible approaches, including BCT and mastectomy, and even including prophylactic contralateral mastectomy given their increased risk of developing a second primary breast cancer in either breast in the future [3,4].

3. Breast conserving therapy

3.1. Lumpectomy with or without radiation therapy

It is well recognised that up to 80% of patients with invasive breast cancer may benefit from BCT, which offers rates of disease control and survival similar to those of mastectomy. This was confirmed by the meta-analyses of the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) [5]. Candidates for BCT include patients with unicentric disease that can be removed with negative margins and with acceptable cosmetic results.

The size of an invasive breast cancer, in relation to overall breast size, in a patient considering BCT will determine whether neoadjuvant chemotherapy or endocrine therapy is required to reduce the size of the primary tumour prior to definitive surgery. Patients with multicentric tumours and inflammatory breast cancer are not considered candidates for BCT. Patients with multifocal tumours within a single quadrant of the breast – which can be removed in a single segmental resection with clear margins and a cosmetically acceptable result – may be considered candidates for segmental resection followed by whole-breast RT. Oncoplastic surgical techniques that are becoming more widely used clearly extend the range of possibilities for BCT with acceptable cosmetic outcomes in patients that were offered mastectomy in the past.

Excision alone without RT may occasionally be considered for patients at low risk of recurrence. In these cases, it is recommended that the negative margins be wide (≥10 mm). For instance, patients older than 70 years with oestrogen-receptor-positive T1 primary tumours may choose to forgo whole breast RT, if they accept receiving 5 years of endocrine therapy, because of their lower risk of local recurrence in the breast. However, whole breast irradiation in this setting does reduce the risk of local recurrence by at least two thirds [6]. Moreover, adjuvant hormonal treatment – which also carries side effects – can be avoided if RT is given.

3.2. Boost

The purpose of the boost is to deliver additional radiation to the area at the highest risk of harbouring microscopic residual disease: namely, the primary tumour bed and immediately surrounding breast parenchyma. Multiple studies have shown that this area has the highest risk of recurrence in the breast [7,8].

While the EORTC trial 10801 comparing mastectomy and BCT demonstrated equivalent overall survival rates for up to 20 years after treatment, a significant difference in local control was seen between the participating centres, and the high boost dose of 25 Gy that was used resulted in a significant proportion of the patients with severe fibrosis and a poor cosmetic outcome [9]. The next EORTC “boost” trial 22881/10882 paid special attention to quality assurance, fibrosis and cosmetic scoring. The boost dose was lowered from 25 Gy to 16 Gy, which was randomised against no boost at all. This trial and two other prospective randomised trials showed that delivering a boost dose to the tumour bed after whole breast irradiation significantly reduces the local recurrence rate [7,10,11]. Young age appears to be the most significant independent patient factor related to local recurrence. The absolute effect of the boost – reducing the local recurrence rate relatively by 41% overall – was much more marked for younger patients (Fig. 1) [7,12]. The cosmetic results were scored as excellent to good in 86% of patients receiving no boost and in 71% of patients receiving a boost. Apart from the boost dose, other predictors for cosmetic outcome included whole breast dose and megavolt energy, type of boost, energy of electrons, and use of adjuvant chemotherapy or hormonal therapy [13].

An inhomogeneous dose distribution of whole breast RT negatively influenced the risk for developing fibrosis, similar to the findings of Donovan and colleagues [14]. Based on this trial, nomograms have been developed to predict in individual patients the impact of a boost dose of 16 Gy on the rate of ipsilateral breast relapse (http://research.nki.nl/ibr) and fibrosis [13,15].

To evaluate the need for a further increase in the boost dose from 16 Gy to 26 Gy for patients up to 50 years of age, the “Young Boost Trial” (NCT00212121) was run in The Netherlands, Germany and France between 2004 and 2011. Early analysis of the results, without splitting up for the randomisation arm, shows that the estimated local recurrence rate remains far below the results obtained in trials, despite the much younger age in the population investigated.

3.3. Accelerated partial breast irradiation

As previously mentioned, after lumpectomy with surgical axillary staging, the standard of care is whole breast irradiation with or without a boost dose. However, accelerated partial breast irradiation (APBI) is rapidly emerging as a treatment option for early-stage invasive breast cancer in certain clinical scenarios. It may be considered in women who are ≥50 years of age, with tumours that are pathologically ≥3 cm or smaller, and node-negative. Ideally, these patients should be treated in the framework of clinical trials because of the more limited long-term data for APBI compared with those for whole breast...
irradiation [16–18]. It is expected that in the near future, after completion of the prospective randomised clinical trials comparing APBI with standard whole breast irradiation, a precise definition of the place of APBI will become available.

### 3.4. Young patients

It is important to see the clear decrease in local recurrence rates over time in the EORTC 10801, EORTC 22881–10882 and Young Boost trials (Fig. 2) [19]. The explanation of this continuous improvement is multifactorial and includes technical and diagnostic factors and the increasing use of adjuvant systemic treatment. It is well established that chemotherapy and hormonal treatment reduce local recurrence rates by about 35–50%. Indeed, according to the consensus at the time, virtually no patient who participated in the EORTC 10801 trial, and only 31% of the patients participating in the EORTC 22881–10882 trial, received adjuvant systemic treatment, while in the Young Boost trial nearly all patients received systemic treatment, often combined chemotherapy and hormonal treatment [12]. Therefore, results from the past after BCT in young patients should not be considered as a contraindication for offering this treatment today to patients <50 years of age. Some caution might remain for very young patients (<35 years of age) in view of the relative scarcity of data and the possibly different aetiological factors in these patients. Indeed, in two large Dutch population-based cohort studies of young breast cancer patients, conflicting results were found on comparing BCT with mastectomy [20,21].

### 3.5. Ductal carcinoma in situ

For non-invasive disease (ductal carcinoma in situ, DCIS), treatment options depend on the extent of the disease. For mammographically detected unifocal lesions, which can be removed in a single lumpectomy specimen with good cosmetic results, BCT is an excellent option. Clear surgical margins of at least 2 mm are recommended [22]. Postoperative radiation therapy is indicated to eliminate potential residual

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**Fig. 1** – Cumulative incidence of breast cancer recurrence according to age group. Reproduced with permission from [7].

**Fig. 2** – Local breast recurrence rate in three consecutive trials. Reproduced with permission from [19].
microscopic disease. Whole breast irradiation is considered the standard of care after lumpectomy, as it reduces the risk of recurrence in the breast by approximately 50–60% at 10 years of follow-up [23]. Half of the recurrences are invasive cancer and half are DCIS, with a similar risk reduction for both after radiation therapy. A boost dose to the primary tumour bed might further reduce the local recurrence rate [24]. Axillary surgical lymph node evaluation is not required for patients with pure DCIS because it is associated with an extremely low risk of nodal involvement. Sentinel-node biopsy may be considered in the presence of extensive or high-grade DCIS, especially if a mastectomy is performed. For patients with more extensive DCIS, or for those wishing to avoid radiation therapy, total mastectomy with or without breast reconstruction is the preferred option.

4. Mastectomy

4.1. Chest wall irradiation

If mastectomy with surgical axillary staging is selected as the primary surgical treatment option, recommendations for post-mastectomy radiation therapy (PMRT) are based on the risk of locoregional failure in the chest wall or in the undissected regional lymphatics (upper part of the axilla including the infraclavicular region, supraclavicular region, and internal mammary region). Available data are essentially based on comprehensive locoregional treatment, making it currently impossible to define clear recommendations for chest wall irradiation only.

If the primary tumour is <5 cm in diameter and if there is no axillary nodal involvement, the risk of locoregional failure is <10% without PMRT, so RT is not recommended in this clinical scenario [25]. Clinicopathological factors associated with a high risk (≥20%) of locoregional recurrence without PMRT include four or more involved lymph nodes, ≥20% involvement of the number of axillary lymph nodes, T4 tumours, and T3 tumours combined with axillary nodal involvement [25,26]. One to three positive lymph nodes after primary chemotherapy are also associated with a higher risk of locoregional recurrence. Therefore, PMRT is recommended in all these clinical settings [27]. If mastectomy with surgical axillary staging is performed prior to chemotherapy, the current National Cancer Comprehensive Network guidelines strongly suggest that post-chemotherapy radiation be considered to the chest wall and undissected regional lymphatics, also in the setting of one to three positive lymph nodes. Other tumour- and patient-related factors that are associated with a higher risk of locoregional recurrence without PMRT include: T3, tumour size of ≥4 cm with involved lymph nodes, age <40 with involved lymph nodes, grade 3, lobular histology, lymphovascular invasion and involved lymph nodes, largest axillary node ≥2 cm, gross extranodal extension of ≥2 mm, involved lymph nodes with fewer than ten axillary lymph nodes dissected, and premenopausal status with lymphovascular space invasion [28,29]. As the debate on the use of PMRT in intermediate-risk patient groups continues, most guidelines refer to a combination of risk factors [30,31].

Nowadays, most patients presenting with risk factors will receive adjuvant systemic treatment. Especially in locoregionally advanced disease (the typical indication for mastectomy), primary systemic treatment is becoming progressively more popular. In general, the indications for PMRT remain the same, although the pathological stage is not reliably known and the response to systemic treatment might be used for adjusting the recurrence risks. In general, patients presenting with clinical stage III disease (4 or more suspicious or confirmed positive lymph nodes on pretreatment ultrasound, cT3N1 disease, or cT4 disease) prior to chemotherapy should undergo PMRT. Patients presenting with clinical stage IV disease who experience a complete response to systemic therapy or those being treated with curative intent should be considered for PMRT as well. In patients with close or positive margins and clinical T3, N0 disease, PMRT to at least the chest wall should be considered. PMRT should also be considered in patients presenting with T1–2, N1 disease and one or more of the following clinicopathological features: residual tumour size ≥2 cm, residual lymph-node-positive disease after chemotherapy, age <40 years and lymphovascular invasion.

4.2. Radiation therapy and breast reconstruction

The number of women requesting breast reconstruction after mastectomy is increasing. In particular, immediate breast reconstruction (IBR) is becoming more popular for breast cancer patients who are not good candidates for breast-conserving therapy. Uncertainty exists about the preferred type (using implanted material, autologous tissue, or a combination) of IBR in patients requiring PMRT to minimise the complication and reoperation rates and to optimise cosmetic outcome. Other concerns are the safety and efficacy of IBR, the possible risk of a delay in starting adjuvant systemic treatment and the influence on the quality of RT delivery in terms of dose homogeneity and target volume coverage [32,33]. Fewer data exist on PMRT following IBR using autologous tissue, although most authors report that the outcome in terms of complication rates and cosmetic results is better when compared with implant reconstruction only [32,35,36]. Surgical intervention, including free fat grafting, can be used to improve – if needed – long-term results after IBR and PMRT. Most data confirm that IBR is not associated with a significant delay in starting adjuvant therapy. A homogeneous dose of radiation to the chest wall with/without the regional lymph nodes can be delivered with acceptable heart and lung doses if optimised modern RT techniques – including procedures for adjustment of respiratory movement, highly conformal 3D and IMRT – are appropriately used [37,38].

Few data are available on the influence of pre-reconstruction PMRT on tissue expander breast reconstruction. In general, a higher frequency of capsular contracture and a slightly higher reoperation rate for procedures using implants are seen, leading to worse patients’ and surgeons’ subjective evaluations. On the other hand, a history of PMRT alone should not dictate the type of reconstruction [39]. Patients who develop neither severe skin changes nor subcutaneous fibrosis may still be considered for implant-based breast reconstruction.
reconstruction [35,40–42]. Pre-reconstruction RT seems not to influence the overall success rate of reconstruction using autologous tissue, nor to contribute to postoperative complications. However, it increases the rate of vascular complications in free flap breast reconstructions, seen mostly during surgery itself. In general, the cosmetic outcome and satisfaction in women reconstructed with autologous tissue is higher than in those with implant-based reconstruction. The optimal timing for breast reconstruction after PMRT is unclear. Often, an interval of 12 months between PMRT and reconstruction is advised, but some state that breast reconstruction with autologous tissue can potentially be performed earlier [43,44].

5. Regional radiation therapy

The indications for regional RT are independent of the type of surgery to the breast (BCT or mastectomy). Therefore, most of what was stated in the subsection “chest wall irradiation” is also applicable to this chapter.

The EBCTCG overview confirmed that PMRT and RT in the framework of BCT improves specific and overall survival in all breast cancer patient subgroups with involved axillary lymph nodes as well as in node-negative patients treated with BCT [45]. In most older trials, comprehensive locoregional RT was used. Based on this, a division into three risk categories for locoregional relapse is made with a proposal for selecting the target volumes for RT (Tables 1 and 2) [46].

The clinically most relevant drainage of the breast tissue is to the ipsilateral lower axilla. Therefore, staging most often includes at least a sentinel-node biopsy to estimate the degree of axillary lymphatic involvement by the tumour; this provides the most important single prognostic factor for patients with breast carcinoma. In general, nodal involvement occurs in an orderly fashion [47]. The other major route of lymphatic spread is via the ipsilateral internal mammary chain (IMC). They are primarily found in the first three intercostal spaces. Internal mammary chain drainage is correlated with tumour location in the breast [48]. The identification rate for IMC disease with sentinel node procedures depends on the technique of the procedure itself, being high-
est with an intra-tumoural injection of tracer followed by a peri-tumoural injection, and lowest with a subdermal or peri-areolar injection [49].

Supraclavicular nodal involvement generally represents stages of advanced regional disease and carries a poorer prognosis. The major route of cancer spread to the supraclavicular lymph nodes is via the axillary lymph nodes [50].

Since the publication of the ACOSOG Z0011 trial – showing that axillary surgery is probably not required for patients with a positive sentinel-node biopsy and treated with BCT, including tangential field irradiation to the whole breast – uncertainty exists about RT to a positive axilla without further axillary clearance [51]. A proposal based on the combination

### Table 1 – Risk categories for locoregional relapses after mastectomy and axillary clearance. Ax LN +, involved axillary lymph nodes. Reproduced with permission from [47].

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor stage</td>
<td>T1-2</td>
<td>T1-2</td>
<td>T3-4</td>
</tr>
<tr>
<td>Number of Ax LN +</td>
<td>0</td>
<td>1-3</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>Grade</td>
<td>1-2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>ductal</td>
<td>lobular</td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td>&lt; 10%</td>
<td>10-20%</td>
<td>&gt; 20%</td>
</tr>
</tbody>
</table>

### Table 2 – Indication for irradiation of the different target volumes after mastectomy and axillary clearance as well as for regional radiation therapy (RT) in the framework of breast-conserving therapy (BCT). Yes, evidence and generally accepted; Yes?, evidence but not generally accepted; No?, limited evidence, however advocated by some authors; No, no evidence. Reproduced with permission from [47].

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracic wall</td>
<td>No?</td>
<td>Yes?</td>
<td>Yes</td>
</tr>
<tr>
<td>Supraclavicular</td>
<td>No?</td>
<td>Yes?</td>
<td>Yes</td>
</tr>
<tr>
<td>Internal mammary</td>
<td>No</td>
<td>Yes?</td>
<td>Yes?</td>
</tr>
<tr>
<td>Axilla</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
of several treatment- and tumour-related factors is being developed in the Netherlands.

6. Radiation related toxicity

There is ample evidence to suggest that cardiac irradiation is detrimental, although cardiac consequences of RT of the breast have long latencies estimated to become detectable only \( \geq 15 \) years after treatment. The EBCTCG overview of randomised trials demonstrated that the gain in locoregional control was not fully translated into an improvement in overall survival, suggesting that survival benefit with RT becomes at least partially offset by increased cardiovascular deaths [5]. In particular, radiation techniques that have incorporated large volumes of the heart have been shown to negatively impact on overall survival [52].

Therefore, minimising cardiac irradiation is a critical aspect of treatment planning. Depending on the individual case, changing the gantry angle, the collimator angle, or shaping – with small cardiac blocks or MLC leaves – the borders of the medial and/or lateral tangential fields can result in adequate coverage of the primary tumour site and most of the breast while excluding the heart from the high-dose region. These treatment field modifications should be customised to the normal tissue anatomy of the individual patient, the location of the primary tumour bed and the contour of the breast. In addition, in cases where the tumour bed is very close to the heart, treatment at deep inspiration can be advantageous [53–55].

Further research is warranted to understand the dose-response relationship leading to radiation-induced cardiovascular disease. Current research focuses on the one hand on optimising the radiation therapy techniques to limit the exposure of cardiac structures and lung tissue to irradiation, and on the other hand on examining which cardiac substructures are most related to the induction of late toxicity and mortality [52,56–58]. Of importance is also the requirement to conduct proper follow-up, which is indispensable for evaluation of long-term treatment effects after radiation therapy and to advise patients on how to adapt their life style in the case of an elevated risk of cardiovascular toxicity [59].

7. Technical developments

Donovan and colleagues were among the first to confirm on a clinical level the advantages of optimisation of RT dose distribution. In a randomised prospective trial they investigated the influence of dose homogeneity on late adverse effects after BCT to evaluate whether the additional costs in infrastructure and staffing are justified [14]. With forward-planned IMRT, they minimised dose inhomogeneity in the breast significantly. Of great importance is that they were able to associate this with the change in breast appearance during follow-up as scored by photographic as well as by clinical assessment. These results confirm the sensitivity of late normal tissue effects to fraction size [60]. Therefore, 3D dose planning should be routinely implemented, even more with hypofractionated RT schedules.

A broad spectrum of RT techniques are described in the literature, ranging from low complexity (conventional, wedge-based approaches using limited beam angles) to highly modulated, multiple-angle photon techniques [61–63]. As some of the highly complex techniques might lead to a higher dose to the organs at risk (heart, lungs, contralateral breast), their implementation should be carefully considered and coupled with other technological improvements [64].

A rapidly increasing number of RT departments are using hypofractionated RT schedules, especially after the publication of the long-term results of large prospective trials [65–67]. With this, whole breast RT duration can be reduced from the conventional 5 weeks to 3 weeks. Adding to this obvious advantage to the patients, a boost dose for BCT is becoming more selectively applied to only those patients with a high risk of local recurrence, reducing the treatment by 1–1.5 weeks and decreasing the risk of fibrosis.

The use of electrons and brachytherapy as boost modalities is gradually being replaced by 3D-CRT photon beam techniques. Interest in this technique has recently been stimulated with the introduction of the simultaneous integrated boost (SIB) technique, in which the dose to the whole breast is combined with a simultaneous boost to the primary tumour bed [68]. Apart from logistical advantages for the RT department, it significantly reduces the boost field sizes thanks to both improved conformality and electronic equilibrium [69].

Patients with large pendulous breasts may be treated in the prone position to minimise skin folds in the breast, such as the infra-mammary fold. Placing the patient in the prone position also allows the surgical bed to fall farther away from the rib cage, increasing the distance between the cardiac structures and the lumpectomy site.

Breathing-adapted treatment reduces the impact of respiratory motion on the motion of the target volume. Treatment delivery under deep inspiration also increases the distance between the breast and the heart for left-sided breast cancer patients, reducing the RT dose to the heart [53–55,70].

8. Challenges

8.1. Target volume delineation

The primary objective of radiation therapy is to eradicate microscopic residual disease after surgery. The areas at highest risk of recurrence after mastectomy are the chest wall and the undissected lymph-node regions. In the case of BCT, the entire breast can contain residual or potential multicentric disease as well. On the basis of the work by Holland et al., the highest residual tumour cell density is expected to be adjacent to the original tumour site [71]. This explains why at least \( 80\% \) of the early failures after BCT occur in the same quadrant as the original primary tumour.

The regions to be treated constitute the clinical target volumes, to which an additional margin needs to be included to account for internal motion, patient motion, and setup uncertainty, resulting in the planning target volume that will be used for RT planning. The transition from clinically set-up 1D treatments to fully virtually prepared 4D RT plans is highly dependant on proper target volume delineation, which is considered by most radiation oncologists as currently being the weakest link in the quality chain of breast cancer RT, with a
high inter-observer variation [72]. These variations appear to be clinically significant both in terms of dosimetric target coverage as well as exposure of the organs at risk [73]. To improve consistency in target volume delineation, a number of initiatives have been undertaken, after which it has been demonstrated that training as well as the availability of clearly written guidelines decreases inter- and intra-observer variability [72]. ESTRO has given a high priority to increasing its online educational and professional services. Within this resource, a multifunctional platform for volume delineation has been created. This will also be used to facilitate the organisation of teaching courses and the writing of internationally accepted guidelines.

8.2 Individualisation

To properly individualise, we should take into account several factors, including prognosis, risk-to-benefit ratios, patient expectations and specific anatomy. Therefore we should consider every single patient as a unique combination of personal, disease and anatomical factors. Based on this we can discuss proper decision-making in a multidisciplinary setting and with the patient.

As for RT, treatment planning – based on a complete 3D dataset – can now be fully individualised to the patients’ anatomy and the delineated target volumes, taking into account the dose to normal structures. In general, a standard set-up RT technique will fit most patients, and every department should accure experience with a standard approach that best fits their own way of working. However, individualisation of techniques should be done on the basis of the anatomy of each single patient. As an example, the entire chest wall may sometimes be treated with electron-beam fields [57]. With a five-field technique a homogeneous dose to the thoracic wall (and the IMC if indicated) can be delivered with a much lower dose to the underlying lungs and heart compared with tangential photon fields, especially in patients with a markedly curved thoracic wall [74]. Also, a partially wide tangential approach, including the IMC lymph-node region together with the chest wall or breast in a single pair of fields, can be used when a separate IMC field cannot be employed due to the patients’ anatomy.

8. Future perspectives

The future lies in a multidisciplined approach and a coming together of the indications for all types of treatment, including surgery, RT and systemic treatment. At present, few treatments are clinically linked (such as lumpectomy combined with whole breast RT). However, we can no longer neglect the interactions within the therapeutic spectrum. Therefore, we should focus more on treatment packages instead of simply adding one treatment to another.

As an example, the management of the axilla is expected to change markedly in the coming years. Even the standard use of the sentinel node procedure is challenged in some patient categories where the need (or lack of need) for systemic treatment can be estimated on the basis of other prognostic information. Use of axillary clearance as a routine procedure is rapidly decreasing and might even become extinct when results from trials such as the EORTC AMAROS trail become known [75].

Another example is the issue of the patient at very low risk who might be offered years of hormonal treatment or a short course of whole or partial breast RT, with the challenge of demonstrating the added value of combining both approaches together. This fits well into the drive to optimise the cost/benefit ratio of cancer treatment, especially in times of limited financial resources [76].

The response to systemic treatment can be used in high-risk patients as a predictor for improved survival. It is likely that these high-risk patients might benefit most in terms of overall survival from optimal locoregional treatment [77]. Perhaps a proportion of these patients might even be treated without surgery.

Another issue that will only be solved after the presentation of data from recent prospective trials is the selection of the areas to be treated. While irradiation of the IMC lymph-node area is the most strongly debated, an early analysis did not show an increased level of toxicity [78].

New biological targeted agents should be tested in combination with RT. Similar to chemotherapy, several studies testing the prognostic and predictive value of genomic and proteomic tests are being conducted.

The duration of RT for breast cancer has reduced from 6–7 weeks to 3–4 weeks over the last few years. Further reduction to even fewer fractions in a shorter time period is the subject of recent and ongoing trials [79]. This should help to end the discussion about the sequence of RT and systemic treatments by decreasing the possible postponement of the latter with a shorter RT course.

Conflict of interest statement

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REFERENCES


Introduction

Optimal approach for localised rectal cancer

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Rectal cancer remains one of the most challenging tumours in respect of local treatment. The many disciplines involved, the development of new insights and novel treatment strategies, and the close correlation between quality of care and outcome provides a fascinating scenario. In this educational session several of these aspects are discussed, and will be of interest to surgeons, radiotherapists, medical oncologists, radiologists and pathologists.

Conflict of interest statement

The author has no conflicts of interest relating to this article.
Optimal imaging staging of rectal cancer

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1. Clinical significance of imaging

A patient diagnosed with rectal cancer is managed by a multidisciplinary team in which the radiologist nowadays participates as a full sparring partner. His/her imaging findings can influence the treatment decision-making. The local staging work-up consists of endorectal ultrasound and/or magnetic resonance imaging (MRI). The distant staging work-up depends on the local policy but often consists of ultrasound or computed tomography (CT) of the liver and chest X-ray or chest CT. While previously all patients underwent a standardised resection, nowadays there is evidence that imaging can identify the high risk patients with locally advanced rectal cancer whose tumour is threatening or invading the mesorectal fascia and needs preoperative treatment. This article discusses the role of the different imaging modalities for local staging and restaging of rectal cancer and their accuracies for identifying the risk factors for local recurrence and for assessing response to preoperative chemoradiotherapy. The chapter ends with future perspectives in rectal cancer imaging.

2. Staging modalities

2.1. Endorectal ultrasound (EUS)

The main strength of endorectal (or endoluminal) ultrasound (EUS) is its excellent spatial resolution, particularly for tissues that are located near the ultrasound probe. For tissues that are at a greater distance from the probe, the performance of EUS is limited. As a result, EUS is accurate mainly for the assessment of tumour ingrowth in the bowel wall and hence for the discrimination between tumours that are limited to the submucosa (T1) versus tumours showing ingrowth in the muscularis externa (T2). For the evaluation of tumour penetration into the perirectal fat (i.e. T3 tumours), EUS reaches results similar to those of MRI and experiences the same interpretation difficulties; these are related to problems in distinguishing desmoplastic stranding in T2 tumours from tumour stranding in T3 tumours (see section on tumour staging). Because of its limited field of view, EUS is less suitable for the assessment of tumour infiltration into the mesorectal fascia (MRF), tumour extension to the high dorsal pelvic wall and evaluation of lymph nodes – in particular those in the high mesorectum along the superior rectal vessels. Furthermore, it is often difficult to position the ultrasound probe and visualise high and/or stenosing tumours, resulting in inconclusive results in >10% of patients [1]. Another drawback of EUS compared to cross-sectional imaging techniques is that it is highly operator-dependent and requires a learning curve before optimal diagnostic performance can be obtained [2]. A potential benefit of EUS compared to CT and MRI is that it allows for tissue biopsies within one single examination, so that histopathological confirmation can immediately be obtained.

2.2. Computed tomography (CT)

Multislice CT (MSCT) is often considered the modality of first choice for the distant staging of colorectal cancer (e.g. the detection of metastatic spread to the liver and/or lungs). Although it has been proposed by some authors that simultaneous staging of the rectal tumour using CT as a ‘one-stop-shop’ imaging tool may be beneficial, there are several drawbacks to the use of CT for assessing the local tumour status. First of all, the soft tissue contrast of CT is limited, making it more difficult to distinguish between tumours limited to the bowel wall and those which have penetrated the wall. For the assessment of an involved mesorectal fascia, MSCT is reported to have moderate to poor accuracy (54–66%). Interestingly, CT can reach fairly good diagnostic performance for assessing the MRF in tumours that are located in the mid–high rectum with reported positive predictive values (PPVs) and negative predictive values (NPVs) of 86% and 94%, respectively. It is particularly in low rectal tumours where the limited soft tissue contrast of CT hampers a reliable differentiation between the tumour and surrounding structures, resulting in a PPV and NPV of only 53% and 73% in assessing an involved MRF [3]. For the evaluation of lymph nodes, CT experiences the same difficulties as MRI and EUS, which are discussed in detail below.
2.3. Positron emission tomography (PET)

PET allows for the detection of metabolically active tissues (e.g., malignant tumours) using tumour-tracing radiopharmaceuticals, of which in oncology the glucose analogue 18F-fluorodeoxyglucose (18F-FDG) is the most widely adopted. FDG-PET can be performed in combination with computed tomography (CT). This hybrid PET–CT allows for a simultaneous assessment of tumour morphology together with the functional information from PET. The role of PET–CT for the primary staging of colorectal cancer is limited. Because PET is known to miss small metastatic lesions in the liver – due to its limited spatial resolution – it is not recommended as the staging modality of first choice. However, in patients with known liver metastases scheduled for liver surgery, PET–CT is very accurate in excluding the presence of extrahepatic lesions such as lymph-node and bone metastases. In this context, the use of PET can significantly decrease the number of futile laparotomies [4]. A second clinical application of PET–CT is the detection of recurrent tumours in patients with a suspected recurrence after primary surgical treatment for colorectal cancer. In this setting PET has advantages over CT, MRI and EUS in differentiating between recurrent tumour and postoperative scar tissue. Recently there is a growing interest in the use of PET–CT as a tool to predict treatment response in patients with locally advanced rectal cancer treated with chemoradiotherapy. Assessment of the decrease in the standardised uptake value (SUV) during chemoradiation has been reported by several authors to be a strong indicator for therapeutic efficacy [5]. Although at present these findings will not yet impact the treatment plan, in the future early response prediction using functional imaging methods such as PET may be of great clinical value as this may allow for early treatment adaptations to enhance the chance of a good therapeutic response.

2.4. Magnetic resonance imaging (MRI)

MRI using modern phased-array external coils offers the advantages of an excellent soft tissue contrast, high spatial resolution and a large field of view. This makes MRI an invaluable technique for detailed morphological information on both the tumour and its extension into the surrounding mesorectal compartment and neighbouring organs. MRI is the recommended imaging method for staging and restaging of rectal cancer in most European countries. The following sections will elaborate on aspects of MRI relevant for rectal cancer imaging, including the optimal MR protocol.

3. MRI protocol for the staging of rectal cancer

3.1. Patient preparation

MRI using phased array external coils has become the standard technique for state-of-the-art imaging of rectal cancer. MRI using an endorectal coil, although similar in performance to EUS for the assessment of superficial (T1 and T2) tumours, has not gained worldwide acceptance. First, endorectal MRI is more cumbersome in application and less patient-friendly than EUS and does not allow for simultaneous tumour biopsies, which is an added advantage of EUS. Furthermore, coil positioning for endorectal MRI can be very difficult, particularly in high and/or stenosing tumours. For phased array MRI routine use of spasmolytics or bowel preparation is not required. Nevertheless, occasional use of spasmolytics may be helpful when severe bowel movement artefacts are already visible on the (sagittal) planning scan, particularly in patients presenting with tumours situated high in the rectum and thus nearer to adjacent small bowel loops. Use of endorectal contrast or filling (for example using ultrasonography gel) is not recommended as part of standard clinical routine. The main argument for applying endorectal filling is to allow a more confident assessment of the exact tumour location within the lumen, particularly in smaller-sized tumours [6]. However, given the fact that information on the tumour location is given during endoscopy, the use of intraluminal filling does not outweigh its potential disadvantages. Apart from the patient burden, the introduction of endorectal contrast causes stretching of the rectal wall which in turn compresses the mesorectal compartment. Hence, rectal distension may hamper the assessment of lymph nodes in the mesorectal compartment and can also result in overestimation of tumour invasion of the mesorectal fascia [7], which are in fact two of the principal important factors that need to be evaluated with MRI (see also section below on assessing risk factors for local recurrence).

3.2. Imaging sequences

A standard rectal MR protocol should consist of multiplanar T2-weighted Fast Spin Echo (T2W FSE) sequences, since these offer an optimal soft tissue contrast between the tumour, the mesorectal fat and the mesorectal fascia surrounding the mesorectal compartment. The optimal slice thickness of the T2W sequences ranges between 1 and 3 mm and should not exceed 5 mm. A sagittal T2W sequence should be first obtained in order to localise the tumour and allow for proper angulation of the axial and coronal planes. It is of the utmost importance that the axial and coronal planes are angled exactly perpendicular and parallel to the longitudinal tumour axis (as identified on the sagittal scan) so that the relationship of the tumour with the surrounding organs and structures can reliably be assessed. In very low rectal tumours the coronal sequences should be angled parallel to the anal canal to establish the relation of the tumour to the pelvic floor and anal sphincter musculature. There is no solid evidence yet for the routine use of additional sequences other than T2W sequences in three planes. Fat-suppression sequences are not recommended since they do not allow a proper appreciation of the mesorectal fascia. A (non-enhanced) T1-weighted sequence may be useful for the evaluation of coincidental findings in other pelvic organs, but is not required for the staging of rectal cancer. There is no solid indication for the administration of intravenous contrast agents. Gadolinium contrast was shown not to be beneficial for T-stage and CRM evaluation [8]. Although experimental studies have investigated the use of dynamic contrast-enhanced MRI and lymph-node-specific contrasts, at the time of writing these techniques are not yet recommended for daily clinical
Tumour height is an important parameter as low rectal tumours have a higher risk of invasion.

4. Assessing the risk factors for local recurrence using MRI

There are four main risk factors for developing a local recurrence, which are used to determine treatment planning: (1) the tumour height (low, middle or upper third of the rectum), (2) the local extent of the tumour (T-stage), (3) involvement of the mesorectal fascia and (4) nodal involvement (N-stage).

4.1. Tumour height

Tumour height is an important parameter as low rectal tumours (e.g. within the first 5 cm above the anal verge) are known to have a worse prognosis than tumours situated higher in the rectum. As a result of the distal tapering of the mesorectum and consequent decrease of the thickness of the fat plane surrounding the rectum, low tumours have a relatively close relationship with the mesorectal fascia, the pelvic floor muscles and the anterior pelvic organs (prostate/seminal vesicles in men and vagina/uterus in women) and have a higher risk of invasion.

Although the tumour height can be accurately measured on MRI (often using the anorectal junction as a reference point) the surgeon is generally already aware of the tumour location from his endoscopic assessment, so often this is not one of the strong arguments to perform imaging. In the United States, the location of the tumour in relation to the peritoneal reflection is often used as an additional landmark to determine whether a patient requires neoadjuvant treatment (if the tumour is below the peritoneal reflection) or not (if the tumour is above the peritoneal reflection). The level of the tumour in relation to the peritoneal reflection can be accurately assessed using MRI [12].

4.2. Tumour (T-)stage

The overall reported accuracy for T-stage prediction with phased array MRI varies between 67% and 83% [13]. The main strength of MRI is the evaluation of large T3 tumours that penetrate the muscular rectal wall and T4 tumours invading adjacent organs, for which MRI has been reported to achieve sensitivities and specificities of 74% and 76% (in T3 tumours) and 82% and 96% (in T4 tumours), respectively [14]. MRI, however, is known to have difficulties in differentiating between superficial T1 and T2 tumours. As opposed to EUS, with MRI it is not possible to separately appreciate all three layers of the rectal wall. The submucosal layer of the rectal wall is not visualised on phased-array MRI (except when there is oedema). Hence, differentiation between a T1 tumour limited to the submucosa and a T2 tumour penetrating the muscularis propria is not feasible. Consequently, EUS remains the cornerstone technique for the selection of superficial T1 tumours that can be considered for local excision. Another limitation of MRI (as well as EUS) is the differentiation between T2 and borderline T3 tumours. Desmoplastic strands into the mesorectal fat in a T2 tumour without actual tumour infiltration cannot be discriminated from desmoplastic reactions containing tumour nests indicating a T3 tumour. In practice, this results in the over-staging of a considerable number (up to 40%) of T2 tumours because radiologists tend to err ‘on the safe side’ rather than risk under-staging [15,16]. Only when the bowel wall on T2-weighted MR images is visualised as a completely intact hypointense line around the tumour does this indicate an intact muscular bowel layer, which can be used as a reliable predictor for the tumour being limited to the bowel wall (T1–2) with a PPV of 86–91% [17].

4.3. The mesorectal fascia (MRF)

Preoperative knowledge of tumour involvement of the MRF is critical in order to determine whether it will be possible to obtain a complete resection of the tumour. Assessment of the MRF is only relevant in the case of a T3 or T4 tumour. When it is established that the tumour is surrounded by an intact bowel wall (indicating a T1–2 tumour) the MRF will never be involved [13]. In the case of a >T3 tumour, the relation between the tumour and the MRF should be evaluated (i.e. the circumferential resection margin at TME). When the tumour invades the MRF or extends Within a margin of <1 mm, the MRF is involved. It is well known that MRI is very accurate in evaluating tumoural involvement of the MRF. In a large patient cohort the MERCURY study group found an overall accuracy of >90% for MRI in predicting tumour involvement of the MRF [18]. In a meta-analysis of seven individual reports (including the MERCURY cohort) sensitivities and specificities for MRI ranged between 60% and 88% and between 73% and 100% respectively [19].

4.4. Lymph nodes and extramural venous invasion (EMVI)

In addition to MRF involvement, lymph-node status comprises one of the main factors that determine the necessity for the addition of neoadjuvant radiotherapy and/or chemotherapy. Unfortunately, so far MRI, EUS and CT have not proved to be sufficiently accurate to determine the nodal status. The main problem is that imaging relies on nodal size (i.e. short axis diameter) as the main criterion to discriminate between benign and metastatic nodes. In rectal cancer in particular it is known that size is not a reliable predictor because metastases frequently occur in small (<5 mm) nodes [20]. As a result there is no reliable size threshold, and cut-off sizes have been reported ranging from ‘any visible node’ to >1 cm. In practice, the chosen size threshold depends mainly on the desired balance between sensitivity and specificity, more often favouring the former. Two meta-analyses that analysed the pooled data from nodal imaging studies using size criteria on EUS, CT or MRI showed similarly poor sensitivities and specificities in the range of 55–78% [14,19]. Some authors have shown that the use of morphological criteria in addition to size can improve the diagnostic performance of imaging in assessing the lymph nodes with reported sensitivities of 36–85% and specificities of 95–100% [21,22]. Nodes with a sharply delineated border and homogeneous signal
Traditionally, restaging with MRI after neoadjuvant treatment into the final treatment response. A longer interval (i.e. at least 6 weeks) provides better insight and the response evaluation with imaging. It is believed that there is no clear consensus on what should be the time interval between the completion of the neoadjuvant treatment and surgery (a so called ‘wait-and-see policy) in the selected group of very good or complete responding patients have been reported. PPVs, however, are much lower (ranging between 44 and 68%), reflecting the over-staging problems described above[18,28,31]. Park et al. suggested that the evaluation of tumour clearance from the MRF after CRT may be improved by the addition of diffusion-weighted imaging, although these results have not (yet) been confirmed by other studies[32].

5.3. Lymph nodes and EMVI after chemoradiation

As a result of chemoradiation treatment the majority of the lymph nodes will decrease in size or even completely disappear. Hence, the median number and size of lymph nodes after CRT is significantly lower than at primary staging. The main aim of re-evaluating the nodal stage after CRT is to assess tumour clearance from a previously involved MRF. If a fatpad of >2 mm reappears between the tumour and MRF, we can be confident that the MRF will be free of tumour. If there is only some residual (fibrotic) stranding into the MRF, the MRF will also be likely to be free of tumour[31]. NPVs in the range of 91–100% have been reported for reassessment of MRF involvement after CRT indicating that the patients with a free MRF can be reliably selected. PPVs, however, are much lower (ranging between 44 and 68%), reflecting the over-staging problems described above[18,28,31]. Park et al. suggested that the evaluation of tumour clearance from the MRF after CRT may be improved by the addition of diffusion-weighted imaging, although these results have not (yet) been confirmed by other studies[32].
establish whether there are remaining metastatic nodes left inside but also outside the mesorectum, or if all initially suspicious nodes have become sterilised. In the latter case, a patient with a concomitantly good response of his primary tumour may be a candidate for organ-saving treatments (local excision or wait-and-see), yet at the time of writing this is still within the scope of clinical trials and not clinical routine. A careful comparison of nodes before and after chemoradiation is of crucial importance when interpreting nodes on post-CRT MRI. Also, a re-evaluation of any initially suspicious extra-mesorectal nodes should be performed in order to determine whether a lateral lymph-node dissection will be required. The diagnostic performance of post-chemoradiation MRI for restaging of the nodes is reported to be equal or slightly better than with primary staging MRI, with accuracies varying from 64% to 88% [28,33,34]. The criteria used for the restaging of nodes are similar to those used for primary nodal staging (size and, to a lesser extent, the nodal border and signal intensity), but it has been suggested by some authors that size criteria work better in the restaging setting. A possible explanation for this is that many irradiated nodes disappear, and of the remaining small nodes over 80% are sterilised [35]. Hence, nodes that remain large in size after CRT are more likely to be malignant.

There is no evidence (yet) to support the benefit of the re-evaluation of EMVI after CRT. In currently available literature EMVI has been assessed mainly in patients undergoing immediate surgery (without preoperative treatment). In the reports where patients undergoing neoadjuvant treatment were included, no subset analyses were performed to specifically investigate the value of assessing EMVI after preoperative CRT.

6. Future perspectives

The time has passed when imaging was used to only provide information on tumour morphology. Functional imaging techniques give more comprehensive information on tumour morphology and underlying tissue characteristics. Some of these imaging biomarkers have already been implemented into clinical protocols, others are still under investigation. Multiparametric imaging in rectal cancer patients will significantly improve the radiologist's performance, in particular for treatment response evaluation. Apart from that, technical developments in MR scanner hardware allow for innovative moving table techniques which generate whole-body MR images complementary to whole-body PET. The clinical introduction of hybrid PET–MR scanners combining both morphological and functional whole-body imaging within one single examination is the beginning of a new era.

6.1. Diffusion-weighted MRI (DWI)

One of the most promising functional MRI techniques for oncological imaging is diffusion-weighted MRI (DWI). Although originally used for the assessment of brain ischaemia, body applications of DWI are now also increasingly beginning to set the pace. DWI uses differences in the movement (‘diffusion’) of water protons between tissues with different cellular density to differentiate between tumoural and non-tumoural tissues. Moreover, DWI can provide quantifiable data reflecting a tissue’s cellular structure, referred to as the apparent diffusion coefficient (ADC). Both the visual assessment of diffusion images, as well as the quantitative measurement of ADC, have shown great potential for rectal cancer imaging, in particular for the evaluation of the therapeutic response of rectal tumours after chemoradiotherapy. It has been shown by several authors that, compared with standard MRI, DWI offers significantly better diagnostic performance for the selection of patients with a good or complete response of their primary tumour after CRT, with reported AUCs up to 0.88 [30,36,37]. Although at present DWI is being investigated mainly in research settings and its true clinical potential has yet to be proven, DWI sequences are already frequently implemented into clinical protocols.

6.2. Dynamic and lymph node contrast-enhanced MRI

Measurements of tumour microvascular perfusion are known to be valuable for cancer detection and treatment monitoring. Dynamic contrast-enhanced (DCE) or ‘perfusion’ MRI techniques could be a promising adjunct to morphological MRI in early response prediction. A pre-treatment measured $K^{\text{trans}}$ perfusion parameter has been shown in early studies to be valuable in distinguishing between patients with good or poor responses. Another potentially interesting topic in the field of lymph node imaging is the use of ‘lymph-node-specific’ MR contrast agents. Very promising results have been shown for the use of ultrasmall particles of iron oxide (USPIO), but this contrast has so far not been approved by the Food and Drug Administration for clinical use. Other MR contrasts such as gadofosveset-trisodium are currently being investigated. Although initial results seem very encouraging, these will need to be confirmed in large multicentre studies to warrant implementation into clinics.

7. Conclusions and recommendations

Since the treatment for rectal cancer has emerged from a ‘one-size-fits-all’ strategy towards a personalised treatment plan based on a patient’s individual tumour risk profile, the role of the radiologist within the multidisciplinary team has changed. The radiologist now plays a full consulting role, and his imaging findings can influence treatment management. The current role of CTs (and PET–CTs) is mainly for the assessment of distant tumour spread. For local tumour staging MRI and EUS are the main players. EUS remains the best technique for the evaluation of low-risk superficial tumours (T1–2) that may primarily be treated with (local) excision. For the evaluation of larger tumours, in particular for the assessment of large tumours that have a risk for invasion of the mesorectal fascia and neighbouring pelvic organs, MRI is the technique of first choice. Although lymph-node status is an important determinant for treatment, none of the currently available imaging modalities (CT, MRI or EUS) is sufficiently accurate to reliably assess the nodes.

The role of imaging for restaging after neoadjuvant chemoradiotherapy is rapidly advancing. While previously the
surgical treatment plan was established on the basis of the findings of primary staging, this plan may now be altered on the basis of the response of the tumour to CRT and the new findings at restaging imaging. The main difficulty after chemoradiotherapy is the differentiation on imaging between small residual disease and post-radiation fibrosis. Together with the dilemma of accurate nodal staging, these two challenges need to be addressed in the coming years. New hybrid and versatile MRI techniques, however, are on the horizon that may be able to offer a solution.

Conflict of interest statement
None declared.

REFERENCES


Neoadjuvant therapy before surgical treatment

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Neoadjuvant treatment in terms of preoperative radiotherapy reduces local recurrence in rectal cancer, but this improvement has little if any impact on overall survival. Currently performed optimal quality-controlled total mesorectal excision (TME) surgery for patients in the trial setting can be associated with very low local recurrence rates of less than 10% whether the patients receive radiotherapy or not. Hence metastatic disease is now the predominant issue. The concept of neoadjuvant chemotherapy (NACT) is a potentially attractive additional or alternative strategy to radiotherapy to deal with metastases. However, randomised phase III trials, evaluating the addition of oxaliplatin at low doses plus preoperative fluoropyrimidine-based chemoradiotherapy (CRT), have in the main failed to show a significant improvement on early pathological response, with the exception of the German CAO/ARO/AIO-04 study. The integration of biologically targeted agents into preoperative CRT has also not fulfilled expectations. The addition of cetuximab appears to achieve relatively low rates of pathological complete responses, and the addition of bevacizumab has raised concerns for excess surgical morbidity. As an alternative to concurrent chemoradiation (which delivers only 5–6 weeks of chemotherapy), potential options include an induction component of 6–12 weeks of NACT prior to radiotherapy or chemoradiation, or the addition of chemotherapy after short-course preoperative radiotherapy (SCPRT) or chemoradiation (defined as consolidation chemotherapy) which utilises the “dead space” of the interval between the end of chemoradiation and surgery, or delivering chemotherapy alone without any radiotherapy.

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1. Rectal cancer: neoadjuvant therapy before surgical treatment

Rectal cancer is a very heterogeneous disease with different prognostic implications and varying outcomes. Historically, a high local recurrence rate has dominated decision-making. The need for radiation treatment has become deeply ingrained in surgical and radiation oncology culture, prompted by an imperative to avoid local pelvic recurrence at all costs. Local recurrence can be associated with intractable pelvic pain, tenesmus, mucinous discharge and intestinal obstruction, and few patients can be saved [1]. However, recent data suggest that metastases are now the predominant problem [2]. In a pooled analysis of 2795 patients recruited in five European randomised controlled trials, the 5-year distant metastasis rate was 30.8% [3].

Initially, because of the lack of reliable preoperative imaging, attempts to improve outcomes centred on postoperative chemoradiation according to pathological staging. With the emergence of more sophisticated imaging, this strategy has been extrapolated to the neoadjuvant arena, and validated by further phase III trials. Management has therefore moved from a solely surgically treated disease to the current widespread use of neoadjuvant radiation or combined chemotherapy and radiation therapy.

Over the past 3 decades the neoadjuvant management philosophy has also evolved independently in different regions of the world. The individual phase III studies performed
in each country have driven the precise patterns of care. In the United Kingdom refinements in surgical technique – i.e. total mesorectal excision (TME) and extralevator abdomino-perineal excision (ELAPE) [4,5] coupled with improvements in the quality of such surgery [6] – and the use of MRI and universal multidisciplinary team (MDT) discussion, have ensured that isolated local recurrence is now a rare event in 2012, if the surgeon can perform a good quality TME, even without radiotherapy [6]. However, even with expertly performed TME, the rate of distant recurrence has been documented as 18% in stage II patients and 37% in stage III patients in one important retrospective series [7].

Recently there has been enthusiasm for integrating more active systemic chemotherapy to increase down-staging and response and to lessen the risk of metastatic disease. In stage III colon cancer adjuvant chemotherapy based on 5-fluorouracil (5FU) reduced the risk of recurrence and prolonged survival, and hence has been firmly established and recommended as adjuvant treatment in patients following a curative resection [8]. More recent studies have confirmed that the addition of oxaliplatin to 5FU-based chemotherapy improves disease-free survival (DFS) [9,10] and overall survival (OS) [10] in patients with stage III colon cancer (although rectal cancers within 12 cm of the anal verge were excluded from these studies). FOLFOX is now considered an international standard as adjuvant chemotherapy for colon cancer in stage III disease, although there is still controversy regarding its use in high-risk stage II colon cancer. Yet the role of adjuvant chemotherapy in rectal cancer is not as clear-cut as in stage II and stage III colon cancer, and the validity of this standard has been questioned in a recent meta-analysis [11].

In Northern Europe short-course preoperative radiation therapy (SCPRRT) (25 Gy in five fractions) followed by immediate surgery was evaluated as an adjunct to surgery [12,13]. Early trials showed an improvement in survival [12], and there have been subsequent consistent reports of lower local recurrence rates in randomised trials [14,15]. Yet integration into routine practice in other parts of the world has always been slightly tempered by early reports of severe acute and long-term toxicity [12,13,16].

When directly compared with standard chemoradiotherapy (CRT), SCPRRT shows similar efficacy [17,18]. The recent TROG 01.04 trial in clinical stage T3 rectal cancer compared SCPRRT with long-course preoperative CRT [18]. The trial confirmed similar outcomes for SCPRRT and CRT for distant recurrence, overall survival and late effects. After a minimum follow-up period of 3 years cumulative incidences of local recurrence at 5 years were 7.5% for SCPRRT and 5.7% for CRT respectively (P = 0.51). For distal tumours, six of 48 SCPRRT patients and one of 31 CRT patients had a local recurrence (P = 0.21).

In the landmark German CAO/ARO/AIO – 94 Trial [19] a total of 823 patients were randomised between preoperative CRT and postoperative CRT (patients received postoperative adjuvant chemotherapy in both arms of this trial). Acute and late toxicities were significantly reduced with the preoperative approach, although it should be recognised that a higher radiation dose was mandated for the postoperative regimen. Loco-regional failure was only 6% in the preoperative arm versus 13% in the postoperative arm. There was, however, no difference observed in the distant metastases rate, DFS or OS. This advantage is also supported to some extent by the National Surgical Adjuvant Breast and Bowel Project (NSABP R-03) trial results [20] which showed a statistically significant improvement in 5-year DFS (65% versus 53%, P = 0.011) for preoperative therapy (although it included an additional 6 weeks of neoadjuvant chemotherapy). Both trials have therefore served to validate the benefit of neoadjuvant 5FU-based chemoradiotherapy for locally advanced rectal cancer compared with postoperative therapy.

Hence, randomised controlled trials have unequivocally demonstrated that preoperative radiotherapy or chemoradiation [12,13,20–23] is more effective than postoperative chemoradiation therapy in terms of reducing local recurrence, and with less acute and late toxicity than postoperative therapy. Yet the risk of dying from rectal cancer is linked mainly to the development of distant metastases, and to experience a late local recurrence as described by Sauer et al. [23] the patient needs to survive 5 years. As an alternative setting to concurrent chemoradiation (which only delivers 5–6 weeks of chemotherapy), potential options are an induction component of 6–12 weeks of neoadjuvant chemotherapy (NACT) prior to radiotherapy or chemoradiation [20,24–27], adding chemotherapy after SCPRRT or chemoradiation (defined as consolidation chemotherapy) which utilises the “dead space” of the interval between the end of chemoradiation and surgery [28–30], or delivering chemotherapy alone without any radiotherapy [31,32].

In Valentini’s recent pooled analysis of seven chemoradiation trials, the most effective predictive model for developing local recurrence was based on ypT stage, cT stage, age, ypN stage and concomitant delivery of adjuvant chemotherapy. Hence the only preoperative data available were age and cT status. The best model for predicting distant metastases used ypN stage, ypT stage, surgical procedure and delivery of adjuvant chemotherapy (in order of relevance). Hence these nomograms are unhelpful in the preoperative setting [3].

More recently, outcomes have been shown to vary according to predicted (i.e. clinical) T stage of disease (Table 1), and other prognostic factors (mainly extramural vascular invasion and tumour extent in relationship to the circumferential resection margin), which can be determined by preoperative magnetic resonance imaging (MRI). Hence a more individualised approach to treatment selection is now feasible according to the relative risk of local recurrence versus metastatic disease. However, the consistently accurate parallels between clinical imaging and pathological staging obtained in the MERCU5Y study have not been easily reproduced. Both the technical aspects and the immediate demands of the presence of a specialist radiologist for optimal MRI imaging, and the interpretation of the scans, mean there is a significant degree of individual variation between and within centres. All of these factors have contributed to a variable acceptance of the technique worldwide.

In this article for the ESMO educational symposium we discuss the various available options for neoadjuvant therapy, their rationale and the results obtained. We consider the different approaches of long-course CRT and SCPRRT: the intensi-
fication of preoperative radiation and chemoradiation with dose-escalation of external-beam radiotherapy (EBRT), using brachytherapy, intraoperative radiotherapy (IORT), hyperfractionation and various available techniques such as intensity-modulated radiotherapy (IMRT). We make recommendations as to which clinical or imaging features require preoperative CRT or SCPRT to be delivered, and where it could possibly be avoided. The strategies of neoadjuvant, concurrent, consolidation (i.e. immediately following chemoradiation and prior to surgery) chemotherapy with cytotoxic agents are explored. We speculate on the initial attempts to integrate biological agents as future potential strategies of treatment with and separate from radiation.

The current era of precision imaging offers many options for conformal external-beam radiotherapy, such as IMRT, volumetric arc therapy (VMAT), brachytherapy and a plethora of systemically active cytotoxic and biological agents. Practice has also been driven more recently by meticulous refinements in surgical technique, in which all the surrounding mesorectal fat are removed in a neat anatomical package (total mesorectal excision and extralevator abdomino-perineal excision), the availability and quality of preoperative MRI to determine potential risks, an increasing value placed on histopathology and assessments/metrics of the quality of surgery. TME is associated with much lower rates of local recurrence and improved survival [4], but all these advances have contained and driven down the local recurrence rate.

In 2005, investigators from Hong Kong challenged the accepted wisdom and questioned whether low-risk stage II patients benefit from neoadjuvant therapy [33]. With a median follow up of 43 months, they reported a 6% local recurrence rate at 5 years for patients undergoing anterior resection (with a median level of tumour at 8 cm from the anal verge). Recent population-based data [34] and retrospective series exploiting these advances further undermine the approach of a blanket use of radiotherapy when MRI suggests the tumour is easily resectable and the circumferential resection margin (CRM) is not threatened [35–38]. Others have also recently questioned the routine use of chemoradiation for rectal cancer [39,40].

For patients with resectable rectal cancer prior to the current TME era, trials of CRT or SCPRT demonstrate a reduction in loco-regional failure (LRF), but without extending DFS or OS.

More recent randomised trials in locally advanced rectal cancer (LARC) suggest that the high historical local recurrence rate of the 1990s has been reduced to <10% with CRT and/or SCPRT. In the main, local recurrence in rectal cancer has been replaced by an even larger risk of metastatic disease as the current predominant problem. Hence many oncologists have recommended both intensifying chemotherapy in the neoadjuvant setting, and also integrating other cytotoxic drugs, in addition to 5FU, into CRT schedules as the logical next steps to improve outcome in rectal cancer.

In the UK and Northern Europe patients with rectal cancer are selected for preoperative treatment on the basis of clinical staging. Many multidisciplinary teams categorise patients into "the good, the bad and the ugly", which allows the definition of three different clinical settings for rectal cancer [42]. Early cT1/T2 tumours are not usually treated with radiotherapy; more advanced T3 tumours in which the patient is considered at risk of local recurrence [15,43] are advised to receive SCPRT followed by TME; and thirdly patients, with clinically unresectable cancers – where MRI suggests a threatened/breached CRM (10–15% of cases), or the levators are potentially involved, or in cancers which require surgical resection beyond the conventional TME plane – then radiation as a component of CRT is clearly necessary for down-staging.

MRI assessment forms the basis of the recent UK 2011 NICE clinical colorectal guidelines on colorectal cancer (http://guidance.nice.org.uk/CG/Wave16/2) which defines three different risk groups of patients with rectal cancer, according to the risk of local recurrence. MRI is sufficiently sophisticated to allow accurate prediction of mesorectal surgical margin involvement by tumour (within a tolerance of 1 mm) preoperatively, and can also demonstrate macroscopic extramural vascular invasion (EMVI). Both a positive CRM and EMVI carry a high risk of subsequent metastatic disease.

Few patients in any of the randomised phase III studies had standardised staging with MRI. Few had primary rectal cancers staged as T4 or, by MRI criteria, were encroaching on, or extending beyond total mesorectal excision planes, which are considered to require preoperative chemoradiation (and sometimes surgical resection beyond conventional TME planes). Such poor-prognosis patients have an even higher risk of metastatic disease even after successful surgery.

### Table 1 – Japanese-style surgery with laparoscopic pelvic lymph-node dissection (LPLND). Risk of local recurrence and distant metastases. Cut-off for depth of mesorectal involvement ≤ 4 mm.

<table>
<thead>
<tr>
<th></th>
<th>Stage IIA</th>
<th>Stage IIIB</th>
<th>All Stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4 mm Local recurrence</td>
<td>12/295 (4.1%)</td>
<td>14/204 (6.9%)</td>
<td>21/245 (8.6%)</td>
</tr>
<tr>
<td>&gt;4 mm Local recurrence</td>
<td>21/295 (7.1%)</td>
<td>36/204 (17.6%)</td>
<td>47/245 (19.2%)</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>13/295 (7.7%)</td>
<td>23/218 (10.6%)</td>
<td>34/267 (12.7%)</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>28/168 (16.7%)</td>
<td>58/218 (26.6%)</td>
<td>75/267 (28.1%)</td>
</tr>
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</table>
2. Radiotherapy as neoadjuvant treatment

2.1. SCPRT

Several trials with more than 6000 patients support the benefit of SCPRT in reducing local recurrence. The rationale for SCPRT is based on the short overall treatment time (OTT), which allows surgery to take place before the radiation reaction is expressed, but does not allow sufficient time for tumour shrinkage.

The Swedish Rectal Cancer Trial [13] randomly assigned patients with cT1-3 rectal cancer to SCPRT and immediate surgery versus surgery alone (not TME). A significant improvement in both local recurrence and survival was observed in the SCPRT arm. The Dutch group performed the Commissie Klinisch Vergelijkend Onderzoek (CKVO) 95-04 trial, which used the same design but trained and mandated surgeons to perform TME. Both early [43] and more mature long-term reports [44] confirmed a significant improvement in local control with SCPRT, although no difference in overall survival was observed.

The MRC CR07 trial [6,15] randomised 1350 rectal cancer patients to either SCPRT (5 x 5 Gy) followed by immediate surgery or selective postoperative chemoradiation (25 x 1.8 Gy with concurrent 5-fluorouracil) administered only for patients with histologically involved (<1 mm) resection margins. The majority of resections were considered TME, but only 51% were good quality TME in the mesorectal plane [6]. Overall, clinically significant absolute risk reduction in the 3-year local recurrence rate of 6.2% was observed (4.4% for SCPRT versus 10.6% for selective postoperative CRT), corresponding to a relative risk reduction of 61%. At 3 years, disease-free survival was 6% better for SCPRT, but there was no improvement in overall survival. The CR07 trial suggests SCPRT reduces the risk of local recurrence for all tumour locations, all pathological stages, and good, average or poor quality surgery.

SCPRT may also only partially compensate for a positive CRM [45,46] if this threat to the mesorectal fascia (MRF) was not detected on preoperative MRI. This strategy has aims different from those of long-course CRT, where we hope to shrink/down-stage the tumour and facilitate an R0 resection to be performed, or to increase the chances of performing sphincter-sparing surgery.

Other advantages of SCPRT include high compliance, even in the elderly, and low cost. Two large randomised trials have each reported that in resectable cancers, SCPRT and CRT are equivalent in terms of outcomes such as local recurrence, disease-free survival (DFS) overall survival (OS) and toxicity [16,17] (Table 2). In the UK, SCPRT is increasingly being used with an interval to surgery or as a radical treatment ± high dose rate brachytherapy (HDRBT). SCPRT is considered to have the advantage of rapid delivery and high compliance for patients who are frail, elderly and with cardiac and renal co-morbidities which preclude 5FU-based chemotherapy.

However, there is a price to pay. Long-term data from randomised trials of SCPRT versus surgery alone demonstrate almost twice the prevalence of bowel dysfunction after SCPRT [47–50]. The CR07 data suggest that SCPRT caused a significant increase in unintentional release of stools [51]. More recent retrospective analyses suggest that frequency, urgency, evacuatory difficulties and faecal incontinence – i.e. the low anterior resection syndrome (LARS) – are common. Effects on sexual functioning [52] and urinary incontinence [49] have also been documented after SCPRT.

With modern MRI, metabolic imaging with positron emission tomography/computed tomography (PET/CT) and individual biomarkers it should be possible to be more selective for risk of local recurrence. It is therefore difficult to support the current widespread advocacy for routine adjuvant radiotherapy as used in the treatment arms of recent trials. Alternatively for this same reason, efforts have been made to limit the radiation dose to normal rectum.

The histology is only minimally corrupted by the radiotherapy changes, allowing accurate pathological staging in terms of the nodal status, extramural vascular invasion and perineural invasion. Patients treated with SCPRT or HDRBT will undergo surgical resection and receive postoperative adjuvant chemotherapy many weeks earlier than with conventional CRT. Hence selection for and delivery of postoperative adjuvant chemotherapy with systemically active schedules (e.g. FOLFOX) can usually start within 6–10 weeks of diagnosis.

2.2. SCPRT and surgery after an interval

Two retrospective studies [53,54] reported safety and efficacy of SCPRT with an interval of several weeks to allow response. Both reported similar curative resection rates and local control as after preoperative long-course CRT. Although the populations of these studies varied, a pathological complete response (pCR) was observed in 4/37 patients (11%) and 2/24 patients (8%), respectively, who underwent surgery after an interval of a few weeks.

A randomised Polish study of 154 patients with locally advanced rectal cancer who were operated using TME between 1999 and 2006 examined the influence of the time interval between SCPRT and surgery on long-term OS and recurrence rate [55]. Patients were randomised between SCPRT (5 x 5 Gy) followed by surgery either 7–10 days or 4–5 weeks later after completion of RT [55]. With approximately 4 years minimum follow-up, 5-year survival rates were 63% and 73% for immediate and later surgery respectively (P = 0.24). The longer time interval between RT and surgery resulted in a greater down-staging rate (44.2% versus 13%), but did not increase sphincter-saving procedures or curative resections.

A further small randomised trial of 83 patients with resectable (stage II and III) rectal cancer [56] compared the clinical and pathological down-staging from SCPRT and long-course CRT followed by surgery after an interval of 6 weeks in both groups. The preliminary results suggested improved tumour down-sizing from CRT compared to SCPRT. Pathological complete response was observed in one patient (2.7%) in the SCPRT group versus six patients (13.1%) in the CRT group. Postoperative morbidity and R0 resection rates were similar. The ongoing Stockholm III trial – which is randomising between three arms: SCPRT proceeding to immediate surgery within a week, SCPRT and delayed surgery after 4–8 weeks, and 50 Gy in 25 fractions with surgery after a similar interval
The rationale for long-course chemoradiation is to achieve trend to improve overall survival\[59\], relapse-free survival (RFS) and cancer-specific survival with the addition of 5FU to radiation has favourable effects on re- According to the MRI appearances, long-course CRT with the MRF is recognised to have been breached or threatened. The surgeon assesses the tumour as unresectable and/or the CRM/ MRF is not potentially involved, then SCPRT and CRT have been shown to be equivalent in terms of outcomes such as local recurrence, DFS and OS [17,18]. For more advanced cases, where the surgeon assesses the tumour as unresectable and/or the CRM/ MRF is recognised to have been breached or threatened according to the MRI appearances, long-course CRT with the addition of 5FU to radiation has favourable effects on relapse-free survival (RFS) and cancer-specific survival with a trend to improve overall survival [59].

Concerns also remain that the delivery of adjuvant chemotherapy in the postoperative setting has frequently been compromised by delays because of surgical morbidity, slow recovery and healing, poor tolerance, and marked dose reductions, with patient compliance being approximately 50% [19,60,61]. These three studies showed that 20%, 23% and 25%, respectively, failed to start postoperative 5FU-based adjuvant chemotherapy. The observation from Biagi et al. [62] that even a few weeks delay following curative surgery before implementing systemic chemotherapy impacts on survival provides a rationale to administer chemotherapy preoperatively.

Despite the above controversies, consensus guidelines from European groups [63,64], Canada [65] and the United States of America [66] recommend preoperative chemoradiation for the majority of patients with stage II and stage III rectal cancer. This approach has narrowed to the conventional use of 45–50.4 Gy at 1.8 Gy per fraction, irrespective of the stage, site and molecular biology of the cancer [67].

There are also significant long-term late effects, including an increased risk of insufficiency fractures in the pelvis [68,69], and an increased risk of second malignancies from CRT even within 10–12 years. Tubiana [70] warns that large target volumes treated with moderate doses carry a high risk of second malignancy. The incidence of second malignancy has probably been underestimated because, with a median age of 65–70 years, patients in rectal cancer trials had a relatively short life-expectancy after treatment, and follow-up is usually short. With recent gains in survival, longer follow-up, cancer registries and end-result programmes, the cumulative incidence of second malignancies could reach as much as 20% of patients treated by radiotherapy [70].

### 2.3. Chemoradiation

The rationale for long-course chemoradiation is to achieve additive effects from the combination of chemotherapy and radiation, both locally and systemically, with a concurrent fluoropyrimidine, thereby inducing down-staging/downsizing, and in some cases facilitating sphincter-sparing procedures, while at the same time reducing distant metastases and in a small group of patients (approximately 10–15%) achieving tumour sterilisation. The current shortcoming of this approach is that we have only managed to integrate single-agent fluoropyrimidines (intravenous 5FU or capecitabine/UFT) at suboptimal, sub-systemic doses into everyday practice.

In ultrasound-staged resectable cancers (i.e. presumably where the preoperative MRI would now suggest the CRM/ MRF is not potentially involved), where down-staging is not required, then SCPRT and CRT have been shown to be equivalent in terms of outcomes such as local recurrence, DFS and OS [17,18]. For more advanced cases, where the surgeon assesses the tumour as unresectable and/or the CRM/ MRF is recognised to have been breached or threatened according to the MRI appearances, long-course CRT with the addition of 5FU to radiation has favourable effects on relapse-free survival (RFS) and cancer-specific survival with a trend to improve overall survival [59].

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### 2.4. Intensity-modulated radiotherapy (IMRT)

Clinical trials of SCPRT or CRT have almost invariably used three- or four-field techniques. Acute gastrointestinal toxicity is the commonest dose-limiting toxicity in many chemoradiation trials, and provides the main dose-limiting factor for the radiotherapy. In the German CAO/ARO/AIO-94 trial, preoperative chemoradiation led to a 12% rate of G3–4 acute toxicity in terms of diarrhoea, and a 9% rate of gastrointestinal G3–4 late toxicity. Total doses of between 45 and 50 Gy probably lead to a 5% risk of late toxicity for the small bowel at 5 years, and there is a significant association between G3 acute small bowel toxicity and the volume of small bowel irradiated [71–74]. Acute toxicity in trials which have integrated oxaliplatin have even higher rates of G3/G4 diarrhoea at approximately 25%, and might be expected to be associated with a greater risk of late damage to the small bowel. None of the randomised phase III trials to date in rectal cancer have used IMRT.

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**Table 2 – Trials comparing shortcourse preoperative radiotherapy (5X5 Gy) with preoperative chemoradiation.**

<table>
<thead>
<tr>
<th>Trial</th>
<th>No</th>
<th>Stage</th>
<th>chemo</th>
<th>Adjuvant chemotherapy</th>
<th>Local recurrence</th>
<th>RFS/DFS</th>
<th>5 year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polish SCPRT</td>
<td>155</td>
<td>cT3-T4</td>
<td>none</td>
<td>optional</td>
<td>Crude 9%</td>
<td>4 year DFS 58%</td>
<td>4 year OS 67%</td>
</tr>
<tr>
<td>Polish CRT</td>
<td>157</td>
<td>cT3-T4</td>
<td>5FU/FA</td>
<td>optional</td>
<td>Crude 14%</td>
<td>4 year DFS 56%</td>
<td>4 year OS 66%</td>
</tr>
<tr>
<td>TROG SCPRT</td>
<td>163</td>
<td>II-III</td>
<td>none</td>
<td>mandated</td>
<td>3 years 7.5%</td>
<td>5 year RFS 64%</td>
<td>5 year 74%</td>
</tr>
<tr>
<td>TROG CRT</td>
<td>163</td>
<td>II-III</td>
<td>PVI 5FU 225mg/m2</td>
<td>mandated</td>
<td>3 years 4.4%</td>
<td>5 year RFS 61%</td>
<td>5 year 70%</td>
</tr>
<tr>
<td>Latkauskas SCPRT</td>
<td>37</td>
<td>II-III</td>
<td>none</td>
<td>not stated</td>
<td>not stated</td>
<td>not stated</td>
<td>not stated</td>
</tr>
<tr>
<td>Latkauskas CRT</td>
<td>46</td>
<td>II-III</td>
<td>5FU/FA</td>
<td>not stated</td>
<td>not stated</td>
<td>not stated</td>
<td>not stated</td>
</tr>
<tr>
<td>Pach 2012 SCPRT</td>
<td>77</td>
<td>I-III</td>
<td>none</td>
<td>not stated</td>
<td>1.5%</td>
<td>not stated</td>
<td>63%</td>
</tr>
<tr>
<td>Pach 2012 SCPRT</td>
<td>77</td>
<td>I-III</td>
<td>none</td>
<td>not stated</td>
<td>7%</td>
<td>not stated</td>
<td>73%</td>
</tr>
</tbody>
</table>

SCPRT = short course preoperative radiotherapy; CRT = chemoradiation; RFS/DFS relapse free survival/disease free survival; OS = overall survival; FUFA = 5FU and folinic acid.
High-dose-rate intraluminal brachytherapy (HDRBT) is highly conformal; the rapid fall-off in dose allows a high dose of radiation to be delivered at the mucosal surface of the rectum overlying the tumour and reduces doses to surrounding normal structures compared to conventional radiotherapy techniques. Publications are sparse for resectable rectal cancer, and rely mainly on a single institution (McGill University in Montreal) which has reported significant tumour regression in over 300 patients, over 29% of the patients achieving a complete pathological response at surgery [80–82]. Because of the rapid dose fall-off, HDBRT may treat the pelvic lymph nodes less adequately. Preoperative HDRBT (26 Gy over 4 days) followed by surgery after 4–8 weeks compares favourably in terms of complications and outcomes with SCPRT in a recent matched retrospective analysis from Canada and Sweden [83]. Brachytherapy also appears as effective as long-course conventional CRT but may be associated with less severe acute toxicity. However, many radiation oncologists remain uncertain about the late sequelae from use of higher dose rates.

There is a significant dose–response relationship for tumour regression after preoperative CRT [84]. Recent reports describe a 31% pCR and 83% achieving an R0 resection in 34 patients treated with 10 Gy HDRBT boost following downstaging of potentially resectable rectal cancers with long-course chemoradiotherapy [85]. For inoperable tumours, HDBRT has been used to dose-escalate after chemoradiation to achieve a greater tumour response and facilitate a curative resection [86]. A small randomised study (Lyon 96–02) suggests that a higher dose achieves a higher rate of complete clinical response, and hence increases the chance of sphincter preservation from 44% to 76% [87,88].

4. Integration of cytotoxic agents into the neoadjuvant setting

The intentions of integrating oxaliplatin into the multimodality treatment are, first, to assess additional effects from preoperative neoadjuvant using oxaliplatin as a radiosensitiser, to achieve greater tumour response, and to reproduce some of the gains in survival achieved by cisplatin in chemoradiation schedules in cervix cancer/head and neck cancer. Second, the hope is to achieve systemic effects, since in metastatic disease the addition of oxaliplatin to the combination of 5FU and folinic acid (FOLFOX) offers response rates in the range of 50% [89]. Oxaliplatin also has a proven role in the adjuvant setting in CRC.

There are two distinct philosophical approaches for integrating oxaliplatin in rectal cancer. Radiation oncologists aim to integrate oxaliplatin during radiotherapy as a radiosensitiser to increase response (usually at sub-systemic doses for tolerability). In contrast, medical oncologists are designing phase II/randomised phase II trials using systemically active high-dose chemotherapy outside chemoradiation to reduce micrometastases outside the pelvis.

Four randomised phase III studies – Action Clinique Coordonnées en Cancérologie Digestive (ACCORD), STAR-01 and NSABB R04 and CAO/ARO/AIO-04 and PETACC-6 studies – (Table 3) have compared preoperative chemoradiotherapy using a combination of a fluoropyrimidine and oxaliplatin with preoperative chemoradiotherapy using an intravenous or oral fluoropyrimidine alone [91–95]. Early results from these randomised phase III trials have not shown any significant impact on early pathological response with the exception of the German CAO/ARO/AIO-04 study.

The ACCORD trial, which compared capcitabine plus oxaliplatin with capcitabine alone, showed no difference in the pCR rate, which (usually for a phase III) formed the primary end-point (19.2% versus 13.9%, P = 0.09) [92,93]. The STAR-01 trial also showed no difference in the pCR rate (15% versus 16%, P = 0.982). Yet the percentage of patients with pathological M stage was significantly lower in the 5FU-plus-oxaliplatin group (2% versus 11%, P = 0.014), suggesting that addition of oxaliplatin to preoperative CRT might have influenced the development of distant metastases. In contrast, the CAO/ARO/AIO-04 study showed an improved pCR rate in patients receiving oxaliplatin (17% versus 13%, P = 0.038) [96]. In addition, the PETACC-6 trial randomised patients between preoperative RT (50.4 Gray in 25 fractions) with capcitabine alone and the same radiation schedule with capcitabine + oxaliplatin (50 mg/m²). The trial has completed accrual and results are awaited.

4.1. Irinotecan

Several phase II trials have suggested a potential benefit for the addition of irinotecan to preoperative CRT. The random-
ised phase II RTOG-0012 trial showed no benefit [97,98]. The current national trial in the UK (ARISTOTLE) is examining the utility of the incorporation of irinotecan into preoperative CRT in MRI-defined unresectable/borderline resectable rectal cancer (www.controlled-trials.com/ISRCTN09351447).

### 4.2. Integration of biologicals

Standard chemotherapy regimens for CRC have integrated molecularly targeted agents (cetuximab, panitumumab, bev-}

<table>
<thead>
<tr>
<th>outcomes</th>
<th>STAR-01</th>
<th>ACCORD - 0405</th>
<th>CAO/ARO/AIO-04</th>
<th>NSABP R04</th>
<th>PETACC-6 a</th>
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<tbody>
<tr>
<td>G3/G4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diarrhoea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypCR</td>
<td>16%</td>
<td>16%</td>
<td>14%</td>
<td>19%</td>
<td>17%</td>
</tr>
<tr>
<td>Ypn0</td>
<td>74%</td>
<td>71%</td>
<td>70%</td>
<td>72%</td>
<td>72%</td>
</tr>
<tr>
<td>Ypn+</td>
<td>26%</td>
<td>29%</td>
<td>30%</td>
<td>28%</td>
<td>28%</td>
</tr>
<tr>
<td>CRM &lt;1mm</td>
<td>7%</td>
<td>4%</td>
<td>13%</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>R0 resection</td>
<td>94%</td>
<td>97%</td>
<td>Not stated</td>
<td>92%</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

5FU, 5-fluorouracil; CRM, circumferential resection margin.

* Ref. [90]

lower pCR rate of 24% was observed in a phase II study of patients with T3/4N0 or T1-4N1-3 rectal cancer who received induction CT comprising only two cycles of 5FU/LV + oxaliplatin (FOLFOX6) plus bevancizumab, followed by concomitant RT plus FOLFOX and bevacizumab [111]. In this study 9/25 patients (36%) also developed postoperative complications [111].

The more recent AVACROSS study selected 47 patients according to MRI criteria, and used four cycles of induction chemotherapy using capcitabine, oxaliplatin and bev-}
disappointing. A large multinational randomised phase II study EXPERT-C (NCT00383695) has compared neoadjuvant therapy comprising oxaliplatin, capecitabine and chemoradiotherapy with or without cetuximab in 164 patients. Kras status (mutant or wild-type) does not appear to be predictive for pCR in rectal cancer when EGFR inhibitors are integrated into chemoradiation regimens [117,118]. In the more recent Expert C study, in the group of patients with wild-type Kras, who received capcitabine, oxaliplatin and cetuximab, the overall survival at 3 years was 96% [119].

5. Chemotherapy additional to SCPRT or CRT

As an alternative setting to concurrent chemoradiation (which only delivers 5–6 weeks of chemotherapy) potential options are either an induction component of 6–12 weeks of NACT prior to radiotherapy or chemoradiation [24–26], adding chemotherapy after SCPRT or chemoradiation as consolidation, which utilises the “dead space” of the interval between the end of chemoradiation and surgery [28,30], or delivering chemotherapy alone without any radiotherapy [31,32].

5.1. Neoadjuvant/induction chemotherapy prior to chemoradiation

The most popular method of integrating chemotherapy is as induction prior to chemoradiation, which achieves high rates of symptomatic improvement (65%) [120]. Clinical response rates with induction chemotherapy vary between 28% [120], 41% [27] and 59% [119] when cetuximab was added, with no patients observed to have progressive disease.

Phase II randomised studies [25,116,119,121] suggest that neoadjuvant chemotherapy prior to chemoradiation is feasible, and can be delivered with minimal compromise of either the radiation or subsequent surgery. The EXPERT phase II study of 78 patients used a 12-week induction phase of capecitabine and oxaliplatin followed by chemoradiation with capecitabine with chemoradiation (total dose 54 Gy) in locally advanced rectal cancer. The radiological response rate was 81% (two CRs and 50% PRs). The early outcome results of this study appear impressive, but it is not possible to determine the relative contributions of the induction chemotherapy and the concurrent CRT schedule or the high dose of pelvic radiotherapy (54 Gy); however, when compared to the group’s subsequent study, with an identical eligibility and chemotherapy schedule but a lower RT dose (50.4 Gy), the pCR fell from 23% to 14% [119]. Mature results of the EXPERT trial in 105 patients [25] demonstrated a 3-year PFS of 68% and 83% respectively. The 3-year RFS for the 93 patients who had a R0 resection was 74%.

A Spanish study (GCR-3 study) compared a conventional schedule of chemoradiation followed by TME and postoperative adjuvant chemotherapy using capecitabine and oxaliplatin, against induction chemotherapy using capecitabine and oxaliplatin followed by CRT and TME [116]. The pCR rate was similar in both arms, 14% versus 13%, but significantly more patients in the postoperative adjuvant arm had grades 3/4 acute toxicity than in the induction arm (54% versus 19%; $P = 0.0004$, respectively). In the postoperative adjuvant arm, 25% of patients did not begin treatment, and only 51% received all four cycles, whereas 100% of patients in the induction arm began treatment, and 92% received all four (P = 0.001). The relative dose intensity for both capecitabine and oxaliplatin were significantly higher in the induction arm, with no differences in radiotherapy compliance between the two arms (P = 0.001). Despite the high compliance in the induction arm, 3-year DFS was not increased [121].

The NASBP-R-03 (National Surgical Adjuvant Breast and Bowel Project R-03) is the only phase III trial to have integrated neoadjuvant chemotherapy at systemic doses. The trial randomised 267 patients to either preoperative 5FU based CRT (n = 130) or postoperative CRT (n = 137) [20]. In addition, the preoperative arm utilised up-front weekly bolus 5FU/leucovorin (LV) for 6 weeks prior to starting concurrent CRT (5FU/LV for 5 days during the first and fifth weeks of radiation to a total dose of 45 Gy with a 5.4 Gy boost). Thus the trial mandated 3 months of neoadjuvant 5FU/LV in the preoperative arm, followed by postoperative adjuvant weekly 5FU/LV.

The accrual was lower than expected (267 of the planned 900 patients). The preoperative treatment arm failed to demonstrate an improvement in local recurrence. The 5-year cumulative incidence of locoregional recurrence was 10.7% for both treatment arms (HR = 0.86; 95%CI, 0.41–1.81; $P = 0.693$), but had a statistically improved DFS with a hazard ratio of 0.629 ($P = 0.011$) and a trend towards improved overall survival. These findings suggest an effect of the neoadjuvant chemotherapy on systemic disease.

In the CONTRE trial, patients received eight cycles of FOLFOX as NACT followed by CRT and surgery. Preliminary data presented at the Gastrointestinal American Society of Clinical Oncology (GI ASCO) 2013 meeting from the first 32 patients reported a 33% pCR rate and >90% compliance [122].

A recent study with induction FOLFOX and bevacizumab [111] provoked grade 3/4 toxicity during chemoradiation in 19 of 25 patients (76%). In some of these phase II studies the authors do not clearly report the toxicity profiles separately for concomitant chemoradiation and when used as full-dose chemotherapy alone [28]. However, studies of neoadjuvant chemotherapy raise concerns regarding the high rate of toxic deaths. Patients with the more advanced and larger pelvic tumours appear to have a particularly high risk of thromboembolic and cardiac effects [25,123], less so if T4 tumours are excluded [31].

5.2. Consolidation chemotherapy (neoadjuvant chemotherapy following chemoradiation)

Consolidation chemotherapy does not compromise compliance to and delivery of chemoradiation. Retrospective data from the Memorial Sloan Kettering Cancer Center [124] and others [125,126] suggest that increasing the interval between CRT and surgery might enhance the rate of pathological complete responses, although other studies partly contradict this [127,128].

Habr-Gama reported that extending the duration of the chemotherapy post-chemoradiation increased the complete clinical response rate (cCR) of 48%, achieving an overall complete response rate (i.e. including cCR and pCR) of 65% [27]. Recent studies have tested the hypothesis that by delaying...
<table>
<thead>
<tr>
<th>Study</th>
<th>Preoperative treatment</th>
<th>Entry criteria</th>
<th>Status</th>
<th>RT/CRT</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>BACCHUS</td>
<td>FOLFOX + bevacizumab for 5 courses, then final FOLFOX, then surgery versus FOLFOXIRI bevacizumab for 5 courses, then final FOLFOXIRI bevacizumab for 5 courses, then surgery versus FOLFOXIRI then surgery</td>
<td>MRI-defined entry</td>
<td>Yet to open</td>
<td>SCPRT or CRT only for progression/lack of response</td>
<td>Primary endpoint: pCR</td>
</tr>
<tr>
<td>RAPIDO</td>
<td>SCPRT (5 × 5 Gy) followed by Oxaliplatin/capecitabine 6 cycles versus Control capecitabine + CRT</td>
<td>MRI-defined entry</td>
<td>Yet to open</td>
<td>CRT 50.4 Gy/28# with capecitabine</td>
<td>Primary endpoint: 3-year DFS</td>
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<td>COPERNICUS</td>
<td>Panitumumab/FOLFOX for 4 courses for Kras WT then SCPRT FOLFOX for 4 courses for Kras WT then SCPRT</td>
<td>MRI defined entry</td>
<td>Yet to open</td>
<td>SCPRT for all patients</td>
<td>Primary endpoint: proportion of patients who commence neoadjuvant chemotherapy and radiotherapy and then undergo surgical resection</td>
</tr>
<tr>
<td>French phase II</td>
<td>FOLFOX + bevacizumab for 6 courses then CRT(with bevacizumab/5FU) versus CRT alone</td>
<td>No</td>
<td>Ongoing not recruiting</td>
<td>Primary endpoint: pCR</td>
<td></td>
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<tr>
<td>Chinese randomised phase II</td>
<td>FOLFOX (4 cycles) then surgery versus FOLFOX CRT Versus 5FU CRT (control)</td>
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<td>Recruiting</td>
<td>Primary endpoint: 3-year DFS</td>
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<tr>
<td>SWOG study</td>
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<td>T4 rectal cancer</td>
<td>Ongoing not recruiting</td>
<td>Primary endpoint: response</td>
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<td>Polish Study</td>
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<td>Unresectable rectal cancer</td>
<td>Recruiting</td>
<td>SCPRT versus CRT</td>
<td>Primary endpoint: the rate of R0 resection</td>
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<td>Beth Israel Study</td>
<td>Six cycles of modified FOLFOX 6 followed by TME followed by an additional six cycles of FOLFOX 6</td>
<td>MRI T3N0M0 or T1-3N1M0</td>
<td>Recruiting</td>
<td>Primary endpoint: pathological response and complete response</td>
<td></td>
</tr>
</tbody>
</table>

Continued on next page
surgery or increasing the interval between CRT and surgery, and allowing more time for response or even administration of two additional cycles of FOLFOX chemotherapy, it may be feasible to increase down-staging and achieve a higher rate of pCR [29,122].

The ‘Timing of Rectal Cancer Response to Chemoradiation Consortium’ phase II multicentre trial used NACT as consolidation chemotherapy in the interval following CRT prior to surgery, with pCR as the primary endpoint. An initial cohort preserved the standard 6–8 week interval between completion of CRT and surgery, which achieved a pCR of 18%. Sequential cohorts added further cycles of consolidation FOLFOX after CRT prior to surgery, increasing the pCR rates to 25% and 30%, respectively [29]. Postoperative adjuvant FOLFOX chemotherapy was also administered to achieve a total of 6 months of systemic chemotherapy.

The delay in surgery by leaving the primary in situ could potentially increase the chance of metastatic disease. A further question remains as to whether FOLFOX is as effective at preventing metastatic disease if the primary (with presumed stem cells) remains in situ when the chemotherapy is interrupted and attenuated by delivery in a few cycles rather than as a continuous 3–6-month treatment.

5.3. Neoadjuvant chemotherapy without chemoradiation

Neoadjuvant chemotherapy may achieve better access to malignant cells when the tumour has an intact blood supply, and may offer better compliance to treatment [116]. Systemic doses of chemotherapy can be delivered at an early stage of the diagnosis rather than after a delay of up to 18 weeks associated with standard CRT. Two studies from the Memorial Sloan-Kettering Cancer Center support the feasibility of neoadjuvant chemotherapy alone in rectal cancer [31,32]. This feasibility study in patients with clinical stage II–III[31] rectal cancer (but not T4 tumours) used FOLFOX (oxaliplatin and 5-fluorouracil) with bevacizumab [31]. The R0 resection rate was the primary outcome. They reported a pCR in 8/29 patients (27%).

6. Trials in progress (Table 4)

A Polish study (NCT00833131) in unresectable rectal cancer addresses the question of whether SCPRT (25 Gy in 5 fractions) followed by consolidation chemotherapy using FOLFOX4 can increase the rate of R0 resection compared with the standard of conventionally fractionated chemoradiation (50.4 Gy total dose in 28 fractions of 1.8 Gy over 5.5 weeks with FULV or capecitabine).

A similar study (RAPIDO) is a collaboration of Dutch and Swedish study groups and compares chemoradiation followed by delayed surgery and postoperative adjuvant chemotherapy with 5 × 5 Gy SCPRT followed by chemotherapy and then followed by surgery.

The present authors are participating in a randomised phase II neoadjuvant study (BACCHUS (Bevacizumab and Combination Chemotherapy in Rectal Cancer until Surgery)) in resectable rectal cancer where preoperative MRI suggests adverse features such as EMVI, but the CRM is not threatened.

<table>
<thead>
<tr>
<th>Study</th>
<th>Preoperative treatment</th>
<th>Entry criteria</th>
<th>Status</th>
<th>RT/CRT</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memorial Sloan Kettering</td>
<td>Neoadjuvant chemotherapy (FOLFOX and bevacizumab)</td>
<td>No MRI, EBUS only or T1N1, T2N0 or T3N0 by EBUS</td>
<td>Active not recruiting</td>
<td>None</td>
<td>Primary endpoints: DFS, R0 resection rate, pCR, pathological complete response rate.</td>
</tr>
<tr>
<td>NCT0465201</td>
<td>Neoadjuvant chemotherapy (FOLFOX and bevacizumab)</td>
<td>No MRI, EBUS only or T1N1, T2N0 or T3N0 by EBUS</td>
<td>Recruiting</td>
<td>None</td>
<td>Primary endpoints: DFS, R0 resection rate, pCR, pathological complete response rate.</td>
</tr>
<tr>
<td>Japanese study</td>
<td>Neoadjuvant chemotherapy (FOLFOX and bevacizumab)</td>
<td>No MRI, EBUS only or T1N1, T2N0 or T3N0 by EBUS</td>
<td>Recruiting</td>
<td>None</td>
<td>Primary endpoints: DFS, R0 resection rate, pCR, pathological complete response rate.</td>
</tr>
</tbody>
</table>

NCRI, National Cancer Research Institute; RT/CRT, radiotherapy/chemoradiation; MRI, magnetic resonance imaging; SCPRT, short-course preoperative radiotherapy; pCR, pathological complete response; RT, radiation therapy; CRT, chemoradiation; TME, total mesorectal excision; EBUS, endobronchial ultrasound; OS, overall survival; ORR, objective response rate.
The study aims to evaluate the efficacy, toxicity and feasibility of FOLFOX/ bevacizumab versus FOLFOXIRI/ bevacizumab.

7. The future

Many questions regarding the role of neoadjuvant chemotherapy remain. In CRC, as in other malignancies, combination cytotoxic chemotherapy is more effective in improving survival, so is the current standard of SFU or capcitabine the optimal partner to radiotherapy in preoperative CRT? Is the theoretical benefit of additional agents such as oxaliplatin outweighed by the increase in acute toxicity, or disguised/diluted by the short-term duration of weeks rather than months and the failure of current regimens to achieve systematically active doses? Is there a role for altered fractionation in conjunction with concurrent chemotherapy? Should we integrate targeted therapies into CRT or will we find antagonism as with the combination of EGFR and VEGF inhibition and chemotherapy? Can we reduce the acute and late toxicity of CRT with improvements in RT delivery such as IMRT/VMAT?

Finally, is disease stage (i.e. cTN) the best way to select for SCPRT/ CRT treatment? Can we identify patients more or less likely to benefit from preoperative CRT, in terms of defining either patients with a particularly low risk of local recurrence who do not require RT, or patients with a particularly high risk of metastatic disease for whom pelvic RT is probably irrelevant [43].

8. Conclusion

There is strong evidence for the role of radiotherapy in reducing the risk of local recurrence. Radiotherapy remains an important component of the multimodal treatment of rectal cancer, particularly if the CRM is threatened. The two current routinely administered (and evidence-based) different approaches (SCPRT and neoadjuvant CRT) are supported by large randomised phase III trials, and are now endorsed and widely used for resectable rectal cancer (T3–T4 or N+). However, routine use and support for both approaches is not universal. Individual radiation oncologists often favour one or other of these approaches. Arguments usually address the risk of local recurrence, enabling a curative resection and facilitating sphincter-sparing surgery, rather than the integration of systemic chemotherapy and the high risk of metastatic disease. However, CRT has found favour because of the opportunity for response and down-staging and even complete pathological response.

To increase tumour resectability, there is scope for escalating the dose of radiation – particularly to the area where the CRM is threatened on MRI – either with HDRBT or the opportunity for dose-painting with IMRT. For less advanced cases, where the CRM is not threatened, the risk of metastatic disease now predominates over the risk of local recurrence. To reduce metastases, systemically active cytotoxic chemotherapy with or without biological agents is clearly required. Chemotherapy at systemically effective doses is therefore a logical way to improve survival in patients with locally advanced rectal cancer. Concurrent, induction, and consolidation chemotherapy prior to surgery are all potential strategies for improving outcome. Trials are required to assess the role of chemotherapy both with and without radiotherapy.

Increasing surgical precision and a greater recognition of the long-term functional effects of radiotherapy and the risks of second malignancy have reduced local recurrence, and prompted a more selective use of neoadjuvant radiotherapy treatment based on MRI-derived risk. Treatment choices for the individual should now reflect the surgeon’s and multidisciplinary team’s views on a more realistic balance between the relative importance of preventing local recurrence, the adverse impact of radiotherapy on function and quality of life, the avoidance of a permanent stoma and the more predominate risks of metastatic disease.

In the future imaging and biomarkers will increasingly predict the risk of local recurrence, metastatic disease, and those patients more likely to suffer severe late effects from radiotherapy, and thus help to individualise treatment.

Conflict of interest statement

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References


The modern anatomical surgical approach to localised rectal cancer

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1. Introduction

On a worldwide scale, colorectal cancer is one of the leading causes of cancer deaths, affecting millions of people every year. One third of colorectal cancer concerns the rectum. In more than two thirds of the cases rectal cancer is still localised to the pelvis without detectable metastases. In these cases surgical resection is the cornerstone for a curative approach. Since the introduction of the combined abdomino-perineal resection by Miles and Quénu around the beginning of the 20th century [1], rectal cancer became a curable disease. However, for many decades the results of surgery have been disappointing, as it was often spoiled by a local recurrence rate of up to 40% or even higher. Uncontrolled progressive local recurrences, hardly palliated by irradiation or chemotherapy, have brought a miserable death to tens of millions of patients.

This situation lasted till the end of the last century when the anatomical basis of rectal cancer surgery was revived by Heald and Quirke [2,3]. Quirke demonstrated that the radial margin between the tumour border and the surgical resection margin was a strong prognosticator for local recurrence. He pointed out that both tumour progression and surgical quality were important for a safe margin. Poor surgery with incomplete mesorectum or tears into the mesorectal fat or muscular tube of the rectum could reduce this margin and consequently lead to local recurrences. Heald introduced the principle of total mesorectal excision (TME). In doing so he defined the optimal quality of surgery.

Worldwide surgeons have accepted as standard of care that optimally the rectum has to be removed within its enveloping mesorectal fascia. TME emphasises the importance of an anatomical resection in the planes between the mesorectal fascia and the surrounding pelvic fascias. However, the principle of resection of the rectum within its mesorectal fascia seems to fail when analysing low rectal cancer. From the early randomised controlled trials it was learned that patients requiring an abdomino-perineal excision (APE) still had high positive circumferential resection margins [4–7]. The lower rectum and anorectum are not surrounded by a protecting layer of mesorectal fat. Instead, already in an early stage, progressing tumours reach and possibly infiltrate the pelvic floor muscles, which are continuous with the external sphincter more distally. Compared with patients undergoing low anterior resection (LAR) APE patients have tumours located lower and more advanced, therefore new principles of surgery had to be developed [8]. Results of lower rectal cancer surgery improved when the principle of the extra levator approach was introduced [9–12]. This involves removal of the lower rectum during an abdomino-perineal excision en bloc with the external sphincter and levator ani muscles. In the lower rectum the role of complete removal of the mesorectal fascia is replaced by removal of the levator ani muscles. Again, the quality of the surgery can be judged by the completeness of this resection.

Modern rectal cancer surgery can be tailored to the specific topographical relationships of the tumour. In proximal tumours the mesorectal fascia acts as the guiding structure. Transection of the specimen can be performed 4–5 cm distally...
from the lower tumour border or at the pelvic floor when the mesorectum terminates higher. More distal tumours can be removed by either intersphincteric resection – if the tumour is confined within the smooth muscle tube of the muscularis propria, sometimes even allowing for a colo-anal anastomosis – or extralevator resection if the pelvic floor is threatened or already involved by tumour progression. The third option for an abdomino-perineal excision is to take an even wider approach, taking out the ischiorectal fat en bloc with the levator muscles, if the tumour has perforated or fistulated through the pelvic floor muscles into this fatty area. However, this will be the case only in extremely rare circumstances.

Modern rectal cancer surgery is part of a multidisciplinary approach. Preoperative imaging with magnetic resonance imaging (MRI) is able to delineate the tumour very accurately and helps to select those patients requiring downsizing and down-staging, optimising the chances of a good tumour resection [13–15]. The pathologist plays an important role in the feedback to the surgeon, which is necessary to improve surgical outcome [16].

The first step in integration of optimal imaging, treatment modalities and pathology is taken is several countries. The next step will be to optimise treatment for the individual patient, who is interested not only in the oncological outcome but also in functional results and subsequent quality of life. Avoiding and decreasing morbidity, especially in the elderly, will require the development of new innovative strategies.

2. Contribution of pathology to the anatomical approach

It may seem odd to start a discussion on modern surgical approaches to localised rectal cancer with the findings of the pathologist. However, it was a pathologist who demonstrated the importance of the distance of the radial tumour border to the mesorectal fascia, which is called the circumferential resection margin (CRM) in TME surgery [3].

In 2002 Nagtegaal analysed the data of the Dutch TME study, and she confirmed that in 44% of the patients the involved circumferential resection margin was the result of poor-quality surgery. It was also shown that, after incomplete mesorectal excision, the overall recurrence rate was almost doubled, which could be attributed mainly to the excess of local recurrences [16]. Nagtegaal and Quirke performed a meta-analysis on the importance of the CRM in more than 17,500 patients and concluded that CRM involvement predicts not only local recurrence but also distant metastasis and subsequent overall survival. Failure to achieve a negative CRM after neoadjuvant treatment leads to a poorer prognosis compared with no neoadjuvant treatment. Possibly the explanation for this is the selection of patients with tumours more resistant to therapy. This finding could be an argument for restaging after neoadjuvant therapy, and to consider more prolonged neoadjuvant treatment, or to refer to a specialised centre for more extended resection or additional boosting of the area at risk [17].

Thus, the actual feedback of the pathologist to the surgeon should contain information on the CRM and quality of surgery [18]. Another important issue, which will be discussed later in this paper, is the evaluation of the effectiveness of the chosen neoadjuvant treatment. Preferably, macroscopic images of the resected specimens, as well as the microscopic images, should be available for internal audit and continued education and improvement of all member decisions during the multidisciplinary tumour board meetings.

Quirke proposed a 3-point grading system for the evaluation of the macroscopic specimen for both low anterior and abdomino-perineal resections. Good surgery would be qualified by an intact mesorectal fascia with only minor irregularities, or in the case of APE, a specimen with levator ani and external sphincters without any defects deeper than 5 mm and the levator ani attached to the mesorectal fascia [19,20] (see Figs. 1–3).

After moderate-quality surgery the bulk of the mesorectum is removed but shows an irregular surface, however still without exposing the muscularis propria or perforations. In the case of an APE, a specimen which shows waist formation, indicative for a less complete levator ani covering at the anorectal junction, but with intact sphincters, signifies a moderate quality of surgery.

Poor surgery would be characterised by severe irregularities on the surface of the specimen, exposing the muscularis propria or internal sphincter or even showing perforations to the lumen.

Very essential for the grading of the APE specimen is the question of whether the levator ani muscle is still attached to the mesorectum. Thus, waist formation is avoided and the result is a more cylindrical resection. In order to achieve optimal feedback, pathology reports should be standardised, not only regarding the reporting of the TNM status, but also on the quality of surgery [19].

3. The importance of MRI for the surgical treatment of rectal cancer

Magnetic resonance imaging (MRI) is a reliable diagnostic tool for clinical staging of rectal cancer, but other imaging methods for the pelvis are also being used for this purpose. Computed tomography (CT) is able to identify enlarged lymph nodes, although it is not accurate for assessing the morphology of these nodes. Furthermore, the contrast resolution of CT is insufficient to reliably assess involvement of the surgical resection plane in mid and lower rectal cancer. CT, however, is indicated for distant staging of metastatic disease and, if there is no easy access to an MRI, for assessment of resectability of high rectal tumours [21–23]. Endorectal ultrasound (EUS) cannot visualise the mesorectal fascia, but is the modality of choice to differentiate between T1 and T2 lesions for the selection of local therapies. EUS has a high sensitivity to stage depth of submucosal involvement [24]. However, MRI is the king of kings of all imaging modalities in its tissue contrast resolution and provides the necessary detailed anatomical information on pelvic fascias and dissection planes between pelvic soft tissues, which sets the scene for the planning of the resection.

Without the anatomical topographical information of an MRI, the surgeon has to rely on ad hoc decisions when unexpected problems occur during the actual surgical procedure.
and in a worst-case scenario these problems may even go unnoticed, or have become irreversible. With the anatomical information from MRI critical sites of resection can be anticipated and addressed before surgery: i.e. use of neoadjuvant treatment or referral to a centre specialised in extended extra anatomical pelvic resection if TME surgery is not justified.
The Mercury study group reported the reliability of MRI on predicting extramural depth of tumour invasion. Very good correlation of extramural spread on MRI and histopathology was found: the 95% confidence interval being <0.5 mm. The TNM classification lacks specificity in the T3 stage [25]. A T3 tumour with limited extramural spread (outside the muscularis propria) has a different prognosis to a T3 tumour with more extended spread. Merkel et al demonstrated that a cut-off point of 5 mm spread divided patients into groups with good and poor prognoses, provided that a safe CRM was obtained [26]. For the surgeon it is important that patients with limited extramural spread can be treated as T2 patients, and in most cases will not require neoadjuvant treatment with its associated adverse effect on surgical morbidity and functional outcome.

Even more important from the surgical technical point of view is the fact that MRI can reliably anticipate an involved circumferential resection margin. MRI differentiates between high-risk (<1 mm) and low-risk (>1 mm) patients for local recurrence. MR CRM margins >1 mm and <2 mm, >2 and <5 and >5 mm carried a similar risk for local recurrence of around 7%, in contrast to the 20% risk of patients with an anticipated margin of <1 mm [27]. The ability to predict a 1-mm free margin was recently confirmed by a German group [28].

The ability of MRI to discriminate between positive and negative lymph nodes is quite disappointing. Like other imaging modalities, conventional MRI without any MR contrast lacks both sensitivity and specificity to identify or rule out positive nodes, and cannot reliably be used for treatment stratification [29,30]. Size has been an unreliable variable to predict nodal involvement [31,32]. Several contrast agents have been and are under investigation, but at the time of writing results are still inconclusive [33–35]. Diffusion-weighted MRI imaging (DWI) shows a high signal in both benign and malignant nodes and therefore cannot differentiate between the two. A restaging MRI, including DWI, has a high negative predictive value (NPV) for the detection of nodal metastases and can be more reliably used for nodal restaging after neoadjuvant treatment [36]. The most reliable variable seems to be the evaluation of nodal morphology, such as roundness, irregular border or heterogeneous texture. However, this is difficult and subject to large inter-observer variability, especially in nodes <6 mm and in patients with only small nodes of limited value in clinical practices [31,37]. MRI plays an important role in the evaluation of response to neoadjuvant treatment (NT) and the consequences for the final surgical resection. NT is able to downsize the tumour. In particular, large tumours may have been overstaged at the initial MRI.

Sometimes a pushing tumour border seen on primary staging MRI may be mistaken for an infiltrating one. Restaging with MRI after NT may reveal surgical dissection planes which were obscured at the primary staging MRI. As a consequence, surgical planning can be more conservative.

Clinical T and N stage may also alter after NT and allow a change in surgical approach. MRI is furthermore accurately correlated with histopathological down-grading of the tumour. Apart from opening new possibilities for a minimal invasive surgical approach for the very good responders, non-responders can be identified who may require intensification of the treatment plan [38–44].
In order to understand the consequences of NT, it is of crucial importance that radiologists and pathologists participate in the multidisciplinary treatment team.

4. Role of neoadjuvant treatment for the surgeon

The primary objective in rectal cancer surgery is to achieve a free surgical resection margin. The purpose of NT is twofold: first, to sterilise the potential tumour-cell-bearing volume in the pelvis, which is not removed during surgery, more specifically the lateral zones of lymphatic spread; and second, to change the size and stage of the primary rectal cancer in order to facilitate surgical resection and even to allow for more limited surgery. In Japan the lateral lymph nodes are removed as standard procedure during rectal cancer surgery. By doing so, NT can be safely omitted according to the Japanese workers. Comparison between the Japanese results with extended lymphadenectomy and the Dutch TME study (which randomised between TME surgery with and without 5 × 5 Gy preoperative radiotherapy) showed that 5 × 5 with standard TME surgery was as effective as extended lateral lymphadenectomy for the prevention of local recurrences [45].

The Swedish Rectal Cancer Trials, the Dutch TME study and the British CRO7 study have clearly demonstrated that preoperative 5 × 5 Gy followed by immediate surgery (preferably within 1 week) yields excellent oncological results in patients in whom a CRM-negative margin can be achieved [46–49]. A recent update of the third Swedish Rectal Cancer Trial shows that a waiting period after 5 × 5 Gy short-course radiotherapy effectively reduces postoperative morbidity, while also a down-staging effect was noticed [50].

In contrast, advanced tumours, invading the mesorectal fascia or even penetrating into the surrounding pelvic structures, would inevitably lead to positive surgical margins if the surgeon sticks to the principle of dissection along the mesorectal fascia. These patients require a more extended resection, peripheral to the mesorectal fascia. In the pelvis with organs packed tightly together these extended resections often result in loss of autonomic nerves, other pelvic resections frequently result in loss of the autonomic nerves [59].

The anterior mesorectum distally to the peritoneal reflection is thin, but, similarly to the rest of the mesorectum, is also covered with a fascia-like structure (fascia of Denonvilliers), which allows for dissection of the anterior mesorectal fascia from the prostate/vesicles or posterior vaginal wall [60,61]. More distally, this layer ends and is replaced by intertwining bundles of somatic perineal muscles joining with the smooth muscular layer of the muscularis propria of the anorectum. This organisation of muscle fibres anchors the anorectum to the pelvis. More laterally and dorsally at the level of the sphincters, the adherence of the smooth muscles to the surrounding external sphincter muscles is much more loosely organised. The external sphincter may be considered the distal part of the funnel shaped pelvic floor muscles enveloping the smooth-muscular layer of the internal sphincter. As mentioned above, laterally and dorsally the adherence between internal and external sphincters is low and allows for the development of an intersphincteric resection plane. On the anterior side the somatic pelvic floor muscles, which distally join in a tendinous perineal body, are very adherent to the anterior part of the anal rectum. Therefore no such thing as an intersphincteric dissection plane is present on the anterior side of the distal rectum [62]. This is a very important anatomical fact which influences the way low rectal tumours can be dissected. An abdomino-perineal excision (APE) can be performed in three dissection planes: (1) the intersphincteric plane which is close to the internal sphincter and suitable only for tumours which are confined to the muscularis propria of the rectum; (2) the extrarectal plane which
follows the external fascia of the external sphincter continuously along the external fascia of the levator ani muscles and transects these muscles as laterally as possible before entering the abdomen; and (3) the ischiorectal plane which also removes the ischiorectal fat and which follows the external fascia of the pelvis, removing the ischiorectal fat en bloc with the levator ani muscles. Again, the abdomen is entered as laterally as possible at the level of the attachment of the levator ani muscles to the pelvic wall see (Fig. 4).

In most distal rectal carcinomas the extralevator abdomino-perineal excision (ELAPE) is recommended to achieve a complete resection with a negative CRM [63]. Either the patient may be operated in a supine position with the legs in movable stirrups, or the patient may be turned to prone position for the perineal resection [64]. When the operation is performed in the supine position the patient does not need to be turned and the procedure can start with either the perineal phase or the abdominal phase.

In the supine position the dissection starts with an incision around and subsequent closure of the anus [10,19] (Fig. 5). The external perineal fascia which covers the external sphincter can be followed up to the lateral attachment of the levator ani to the pelvic sidewall. At this level the levator ani can be cut, exposing the mesorectum. Dorsally, the anococcygeal ligament has to be transected. Depending on the location of the tumour, the presacral space may be entered ventrally to the coccyx, or in dorsally located tumours, the coccyx may be removed to enter the presacral space. After transection of the levator on both sides, exposing the mesorectum and opening the presacral space exposing the dorsal part of the distal mesorectum, the anterior dissection may commence. The anterior part of the levator ani muscle encloses the internal genital organs and needs to be transected at the level of Denonvilliers’ fascia. After exposing Denonvilliers’ fascia the dissection continues distally; retracting the specimen dorsally helps to identify the somatic perineal muscles, which are closely adherent to the anorectum. The transection takes place in the somatic muscles, avoiding a fausse route into the bowel. If the operation was not started with the abdominal phase, the abdomen is opened now. Dissection is according to TME principles, avoiding nerve damage. As the pelvic floor muscles are already transected, taking out the specimen is a relatively uncomplicated procedure.

If the operation is performed in prone position, the procedure most often starts with the abdominal phase, with the patient lying in supine position [65] (Fig. 6). Again, care must be taken not to push the dissection too deep down because of the risk of coning in, resulting in dissection of the pelvic floor off the mesorectum and subsequent waist formation. However, it is important to develop the presacral space until the os coccygis is exposed. On the lateral side the low hypogastric plexus has to be dissected off the mesorectum and the lateral pillars also have to be transected. Denonvilliers’ fascia has to be exposed before the abdominal phase can be ended and the patient can be turned into prone position for the perineal phase.

In prone position a teardrop like incision is made around the anal skin and extended proximally above the ano-coccygeal joint. After closure of the anus, the deep perineal fascia is followed from the external sphincter to the lateral attachments of the levator ani. After the coccyx has been cut, the already opened presacral space is entered and the lateral
attachments of the levator ani can be cut. After arriving at the level of Denonvilliers’ fascia, the specimen can be everted through the perineal wound and the dissection of the anterior plane of the specimen commences under direct vision. First, the puborectal sling has to be cut, as also the deep perineal muscles which are closely adherent to the anterior part of the anorectum. Again the dissection is carried out proximally to distally. Cutting the perineal body is the last part of the operation before the specimen is taken out. Care must be taken not to damage the urethra and the neural bundles of Walsh, which are very close to this dissection plane.

In both positions a complete extralevator abdomino-perineal excision can be performed. In prone position visibility of the perineal operating field is better at the cost of a wider incision, which requires closure with a (biological) mesh or musculo-cutaneous flap [9]. In the supine position simultaneous access to the tumour from the abdomen and perineum may be an advantage in more advanced tumours. An intersphincteric or ischiorectal approach is more commonly performed in supine position. In both positions, the abdominal phase may also be performed laparoscopically.

6. Future perspectives

6.1. Registry

On a population-based level, outcome of rectal cancer treatment differs not only widely among countries, but also within countries among hospitals and even within hospitals among individual surgeons [18,66–68]. But in the end, the chain of treatments given to an individual patient can be traced back to each individual link of the chain. If the quality of pathology is excellent, it will enable one to unravel the different prognostic variables which apply to an individual patient. Not only can the biology of the tumour be ascertained but also the quality of surgery and the effect of neoadjuvant treatment. Furthermore the anatomical information from the MRI may be linked to the outcome and quality of the surgical procedure.

Registration of these variables will identify the weak links and will allow better quality of the complete chain, improving outcome and reducing the burden of treatment costs for avoidable poor results [69] (Fig. 7).

Fig. 5 – Perineal phases of an extralevator abdomino-perineal excision in supine position. mr, mesorectum; pb, perineal body.
Localised rectal cancer – but also metastasised rectal cancer – must be treated by a multidisciplinary team. In order to achieve the best quality of treatment, the planning of the treatment and the sequence of the different treatment modalities have to be decided upon before any treatment is given. During a multidisciplinary team meeting (MDT), after the results of imaging and histopathological biopsies have become available, the specific problems of a rectal cancer can be identified and the best approach for the individual patient may be selected, depending on the presence/exclusion of metastatic disease, local extent of the tumour and the patient’s condition. It is important for the patient to know who has the role of the director of the treatment. In most cases this responsibility lies with the surgeon, who is responsible not only for the surgery but for all components involved in the treatment planning.

On a local level the use of standard protocols, the registration of the MDT meetings and the registration of the important outcome parameters can help to identify blind spots. These data can constitute the basis for a larger – possibly national – registry [70]. These national registries can be used to compare countries. In Norway, Sweden, Denmark, the UK and the Netherlands mandatory registration has led to almost 100% coverage of the population.

EUROCARE collects colorectal cancer data from all European countries and was able to show large differences in outcome in Europe [66].

A limitation on the overall use of the EUROCARE database is the wide spread in coverage of their populations between the European countries. It is difficult to compare results between countries with coverage of less than 50% and countries with coverage of 100%. Furthermore, the completeness of important clinical data such as stage distribution and cancer subsites varies widely between registries. For example, the United Kingdom had poorer oncological results than France and Germany; however, the UK has coverage of 100% compared with coverage of 18% and 1% respectively for France and Germany. Explaining difference in outcome between countries with different coverage is difficult, particularly when it is unclear whether coverage of less than 50% is representative for the country as a whole.

But then again, there is no need to create a scale of the outcome of different countries. It is more relevant to identify the best practice and to set European guidelines based on the...
best knowledge available [71,72]. The EURECCA colorectal project, which promotes registry based on consensus and subsequent sharing of data, can lead to a better outcome for rectal cancer patients all over the world [66,73–76].

6.2. Centralisation

With the improvement in care during the last decades and the introduction of MDT meetings, the oncological outcome of rectal cancer has greatly improved. Another more recent development and improvement in cancer care is the introduction of centralisation of care for advanced cases and major surgery. In rectal cancer this also plays an important role. In advanced cases the cancer grows through its surrounding fascia into other organs and structures. In those advanced cases, when an exenteration is needed, the resection could consist of an orthopaedic, gynaecological and urological en bloc resection combined with the rectal resection. It is not desirable that such a procedure is performed by multiple surgeons. Therefore the rectal cancer surgeon has to be a complete pelvic surgeon. However, normally these advanced cases have a low incidence in a normal regional hospital. The small numbers increase the risk of performing an irradical resection as the experience with these cases is limited. Centralisation of advanced rectal cancer cases will not only result in less irradical resections but also in better postoperative care. As a hospital treats more advanced cases, all specialties involved in rectal cancer care gain more experience. Furthermore postoperative complications are seen sooner, radiological imaging is interpreted better by the radiologist and pathologists gain more experience with large specimens and the influence of neoadjuvant treatment. All this will result in lower mortality rates and better oncological outcome. Specialisation has led to improved outcome in rectal cancer treatment; how much more this will be true for locally advanced cases requiring more individualised surgery [77–79].

6.3. Patient reported outcome measures

Due to the major improvements in therapy and oncological outcome in the last decades, the influence of treatment on the individual patient has become more and more important. Particularly in the last decade, where outcome of a disease is not the only measurement of adequate treatment, there is an increasing interest in the influence of treatment on patients’ quality of life (QOL). Most of the studies published on quality of life and rectal cancer use generally used questionnaires such as the sf-36, EORTC QLQ-C30 OR EORTC QLQ-C38. These questionnaires are reliable, valid and responsive, but have not been developed to assess treatment on an individual level [80–82].

The modern rectal cancer patient is confronted with a combination of treatments, all of which will to a certain extent influence his way of living. The patient would probably like to be informed about alternatives in their treatment schedule and about the consequences of their choice.

It is important for future research to focus on different and more interesting patient groups, such as frail and elderly patients. In these patients, it is more likely that the assumed benefits of survival give an increase in morbidity and could have an adverse effect on QOL. Future studies on rectal cancer have not only to focus on the effect of additional treatments on survival, but also the influence of the treatment on QOL. If the treatment results in increase in QOL, is the possible
consequent decrease in QOL worthwhile? It is likely that these studies will make the decision process easier for the involved specialties in the treatment of rectal cancer and will result in a more patient-tailored treatment.

7. Conclusion

Surgery is still the cornerstone of rectal cancer treatment for the time being. Therefore, the surgeon should take the role of the director of the treatment plan, and should realise that surgery is an integral part of a comprehensive multidisciplinary approach. The basis for quality assurance is registration. A modern anatomical surgical approach requires also a modern attitude towards quality assurance and an obligation to keep the patient well informed about the choices which have been made and to allow the patient to have his/her own say in the matter.

Conflict of interest statement

None declared.

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Adjuvant chemotherapy

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1. Rectal cancer – less scientific evidence than for colon cancer

In rectal cancer there is much less scientific evidence for clinically relevant gains from postoperative chemotherapy than there is for colon cancer. The large adjuvant trials that revealed the gains in disease-free survival (DFS) and overall survival (OS) included either patients with colon cancer only or a limited number of patients with rectal cancer. In comparison with colon cancer, combination chemotherapy with a fluoropyrimidine and oxaliplatin has not been explored at all in rectal cancer, whereas three large randomised trials in colon cancer all showed improved DFS and possibly OS in patients randomised to combination therapy [1–3].

In colon cancer, the loco-regional therapy has not changed to any major extent during recent decades. This has been the case for rectal cancer, where the quality of surgery has been substantially improved with the introduction of the total mesorectal excision (TME) concept. Furthermore, a great majority of rectal cancer patients now receive preoperative therapy, at least if they belong to the intermediate or locally advanced groups, and postoperative radiotherapy or chemoradiotherapy is seldom given as it often was in recent decades [4–6]. This more complex treatment scenario, and the improvements over time of the loco-regional treatment strategies, have made it difficult to evaluate the effects of adjuvant chemotherapy in rectal cancer.

Two opposing views can be considered when giving recommendations for whether or not to give adjuvant chemotherapy to rectal cancer patients. One is to extrapolate from colon cancer, applying the knowledge achieved from the large trials to rectal cancer under the assumption that they all come from the same organ and all are adenocarcinomas. The other view is to look at the trials in detail, explore what types of loco-regional treatment have been given and then evaluate whether we have randomised evidence for favourable effects in the different clinical situations.

2. Do rectal and colon cancers respond similarly to chemotherapy?

In metastatic disease, the primary location of the colorectal cancer appears to be irrelevant on the basis of numerous studies which have analysed the relevance of the tumour site (colon versus rectum), e.g. Köhne et al [7]. Thus, a possible reason for the apparently greater effect of adjuvant chemotherapy with modulated 5-fluorouracil (5-FU) in colon than in rectum cancer is probably not due to different chemosensitivities. No study has explored the value of capecitabine or a combination regimen with a fluoropyrimidine and oxaliplatin as adjuvant therapy in rectal cancer, whereas these treatments have been extensively used in metastatic disease [8], with no detectable differences according to site.

Detectable metastases do come from tumour cells/cell deposits that once have been subclinical and present at the time of diagnosis. Thus, the lack of difference in the metastatic setting strongly argues against lower chemosensitivity of rectal cancer cells compared with colon cancer cells. However, colon cancer differs in some aspects relevant to tumour biology, and thus potentially chemosensitivity, from rectal cancer [9–11]. The molecular characteristics, however, also differ between parts of both colon and rectum [12]. These differences may not materialise in the metastatic setting, but may be relevant when the disease is only subclinical.

3. Evidence for effects of adjuvant chemotherapy in rectal cancer

A Cochrane report [13], based upon 21 clinical trials including 9221 patients, concluded that significant gains are present in both DFS and OS (Table 1). These patients have been treated over several decades. During this extended time period, both surgery and the use of additional (chemo)radiotherapy have evolved considerably [6]. The hazard ratios (HRs) for gains in
<table>
<thead>
<tr>
<th>Treatment setting</th>
<th>Study/Ref.</th>
<th>No. of pts</th>
<th>Study features</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Cochrane analysis [13]</td>
<td>9221 from 21 trials</td>
<td>All stages, all treatments, all settings</td>
<td>HR for OS 0.88 (0.76–0.91), for DFS 0.75 (0.68–0.83)</td>
<td>Trials running during several decades, great heterogeneity between the trials</td>
</tr>
<tr>
<td>Adjuvant chemotherapy after surgery alone</td>
<td>Sakamoto/Japanese meta-analysis [41]</td>
<td>2310 from three old trials</td>
<td>Stages I–III, 5FU, UFT or carmofur 6 m, mitoC 6 m added in two trials</td>
<td>HR for OS 0.86 (P = 0.049), for DFS 0.77 (P = 0.0003)</td>
<td>No gain in colon cancer (n = 2380)</td>
</tr>
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<td></td>
<td>JSCCR/Japanese meta-analysis [42]</td>
<td>2385 from three trials</td>
<td>Stages I–III, UFT or carmofur 12 m, mitoC 6 m</td>
<td>HR for OS 0.92 (P = 0.04), for DFS 0.83 (NS)</td>
<td>Two trials probably included in the above study</td>
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<tr>
<td></td>
<td>Sakamoto/Japanese meta-analysis [43]</td>
<td>2091 from five trials</td>
<td>Stages I–III, UFT or carmofur12–24 m, mitC 6 m added in three trials</td>
<td>HR for OS 0.82 (P = 0.02), for DFS 0.73 (P &lt; 0.0001) and for LRFS 0.68 (P = 0.003)</td>
<td>Some trials overlapping with the above two meta-analyses</td>
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<td></td>
<td>NSAS-CC [44]</td>
<td>274</td>
<td>Stage III, surgery w/wo UFT 12 m</td>
<td>HR for OS 0.60 (P = 0.034), for DFS 0.66 (P = 0.033)</td>
<td>No gain in colon cancer (n = 334), HR 0.82, P = 0.4. Included in the above meta-analysis, updated results</td>
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<td></td>
<td>Nordic trials [45]</td>
<td>691</td>
<td>Stages II–III, 5FU 4–12 m</td>
<td>OS at 5 y 73% versus 81% for AC in stage II (P = 0.09) and 51% versus 48% for AC in stage III (P = 0.91)</td>
<td>Various 5FU regimens. A numerical gain was seen in colon cancer stage III (n = 708, OS at 5 y 48 versus 55%, P = 0.15), however, dependent upon the time from surgery to start of AC [33]</td>
</tr>
<tr>
<td></td>
<td>NSABP-R01 [46]</td>
<td>371</td>
<td>Stage II–III, SFU, semustine and vincristine</td>
<td>OS and DFS improved (43% versus 53% for AC at 5 y, P = 0.05 and 30% versus 42% for AC, 0.006, respectively)</td>
<td>Postop RT alone had no effect on OS or DFS</td>
</tr>
<tr>
<td></td>
<td>QUASAR uncertain [18]</td>
<td>549</td>
<td>Stage II, III, 5FU 6 m</td>
<td>HR for OS approx 0.85 (NS), for DFS approx 0.75 (NS)</td>
<td>Subgroup analysis from the trial. In all 948 RC patients included, HR for OS was 0.77 (95% CI 0.54–1.00), for DFS 0.68 (0.48–0.96). 86% of all pts included had stage II</td>
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<table>
<thead>
<tr>
<th>Treatment setting</th>
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<th>Results</th>
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<tr>
<td>Adjuvant chemotherapy after postop RT/CRT</td>
<td>Hellenic group [47]</td>
<td>220</td>
<td>Stage II, III, postop CRT alone or with 5FU/FA 4 cycles</td>
<td>AC NS improved DFS at 5 y from 68 to 70% and OS from 73 to 77%</td>
<td>Low compliance with adjuvant chemotherapy, NS improvement in compliant pts</td>
</tr>
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<td></td>
<td>Caiero et al [48]</td>
<td>218</td>
<td>Stage II, III, postop RT w/wo 5FU/Leva 6 m</td>
<td>HR for OS 1.04 (P = 0.9), for DFS 1.12 (P = 0.6)</td>
<td>Approx 75% of pts had at least 6 m treatment. Significant effect seen in colon cancer in the same trial</td>
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<td></td>
<td>Dutch group [49]</td>
<td>299</td>
<td>Stage II, III, postop RT w/wo 5FU/Leva 12 m</td>
<td>HR for OS approx 0.95, for DFS approx 0.90 (NS)</td>
<td>Approx 75% of pts had at least 6 m treatment. Significant effect seen in colon cancer in the same trial</td>
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<td></td>
<td>ECOG Est 4276 [50]</td>
<td>237</td>
<td>Stages II–III, postop RT or CRT</td>
<td>5 yr OS RT 46%, CT 47%, CRT, 50% (NS)</td>
<td>Abstract only</td>
</tr>
<tr>
<td>Adjuvant chemotherapy after preop RT</td>
<td>QUASAR uncertain [18]</td>
<td>201</td>
<td>Stage II, III, postop RT w/wo 5FU 6 m</td>
<td>HR for OS approx 0.80 (NS), for DFS approx 0.65 (NS)</td>
<td>See comment on QUASAR above</td>
</tr>
<tr>
<td></td>
<td>EORTC 22921 [19]</td>
<td>505</td>
<td>cT3, T4, preop RT w/wo 5FU 3 m postop</td>
<td>HR for OS for AC versus no AC 0.85 (0.68–1.04) and for DFS 0.87 (0.72–1.04). LR at 5 y was 17 and 10% in the RT and RT/AC groups, resp</td>
<td>Represents 2 of the 4 arms in this trial. Results not separated for preop RT and CRT (see below) groups. 27% of pts scheduled for AC never started. Difference in LR between preop RT only and the other 3 groups, P = 0.002</td>
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<td></td>
<td>QUASAR uncertain [18]</td>
<td>198</td>
<td>Stage II, III, preop RT w/wo 5FU 6 m</td>
<td>HR for OS and DSF approx 0.55 (NS)</td>
<td>See comment on QUASAR above</td>
</tr>
<tr>
<td></td>
<td>EORTC 22921 [19]</td>
<td>506</td>
<td>cT3, T4, preop CRT w/wo 5FU 3 m postop</td>
<td>See above. LR was 9% and 8% in the CRT and CRT/AC groups, respectively</td>
<td>See above</td>
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<tr>
<td></td>
<td>Italian Group [51]</td>
<td>635</td>
<td>Fixed/tethered RC. Preop CRT w/wo 5FU 4.5 m postop</td>
<td>OS 64% for CRT only and 68% when AC added (NS). No difference in LR</td>
<td>Preliminary data, median follow-up 25 m. Abstract only</td>
</tr>
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<td></td>
<td>Fernandez-Martos et al [52]</td>
<td>108</td>
<td>CRT + surg + AC 4 m XELOX versus 4m XELOX + CRT + surg</td>
<td>No difference</td>
<td>Randomised phase 2, preop CT tolerable</td>
</tr>
<tr>
<td>Adjuvant chemotherapy before and after preop CRT</td>
<td>Expert-C [53]</td>
<td>164</td>
<td>High risk operable RC, neoadjuvant Cape/Oxali 3 m, CRT, postop Cape/Oxali 3 m or same treatment with cetuximab</td>
<td>HR for OS 0.27 (P = 0.035), for DFS 0.81 (P = 0.668)</td>
<td>Results for K-ras wild-type pts only</td>
</tr>
</tbody>
</table>

Preop, preoperative; Postop, postoperative; AC, systemic adjuvant chemotherapy; RT, radiotherapy; CRT, chemoradiotherapy; pts, patients; UFT, uracil-tegafur; carmofur, 1-hexylcarmobyl-5-fluorouracil; m, months; HR, hazard ratio; OS, overall survival; DFS, disease-free survival; LRFS, local relapse-free survival; JSCCR, Japanese Society for Cancer of the Colon and Rectum; HCFU, 1-hexylcarbomoyl-5-fluorouracil; NS, not statistically significant; 5FU, 5-fluorouracil; mitoC, mitomycin C; y, year; w/wo, with or without; Leva, levamisole; approx, approximately; CI, confidence interval; Cape, capcitabine; Oxali, oxaliplatin; resp, respectively.

*5FU was modulated with folinic acid in most trials.
rectal cancer are, according to the Cochrane report, for stages II + III: 0.75 for DFS and 0.89 for OS. No heterogeneity was seen between stages II and III. These HRs appear rather similar to the ones seen in colon cancer stage II but are less than those seen in colon cancer stage III [14–16]. Whether the relative gains differ between colon cancer stages II and III is uncertain, however, since they are to a large extent based upon inter-trial comparisons. The trials predominantly including stage III patients are generally older than those including stage II patients. Furthermore, the estimates for stage II are from a Cochrane report probably including all trials and patients, whereas no such report has been completed for stage III. The large ACCENT (Adjuvant Colon Cancer Endpoints) database gives important information as it includes the majority of the large trials [16] but then also tends to overestimate the gains, since all positive trials were included but not necessarily all negative trials.

It may thus be possible to conclude that adjuvant treatment for rectal cancer should be given as for colon cancer, based upon the Cochrane analyses. Others would argue that the heterogeneity between the trials is so extensive that no firm conclusions can be drawn. An entirely different view was also expressed in a recent systematic review [17] where the different rectal cancer trials were scrutinised according to whether the patients were pretreated, with radiotherapy only or with chemotherapy and radiotherapy, or if they received (chemo)radiotherapy postoperatively. These trials are summarised in Table 1.

4. Discussion of selected individual trials and of an analysis of pooled data

4.1. QUASAR uncertain study

This trial [18] included 984 rectal cancer patients (and 2345 colon cancer patients) in whom the doctors were uncertain about the value of adjuvant chemotherapy. In the group of rectal cancer patients, 5-year OS was increased from 74% in the control group to 78% (HR 0.77, P = 0.05) in the group of patients who were randomised to surgery and adjuvant 5-FU + calcium folinate. This gain was numerically the same in those rectal cancer patients who had surgery alone (n = 549) or preoperative (n = 198) or postoperative (chemo)radiotherapy, albeit not statistically significant. This is probably due to limited patient numbers in the subgroups. This study provides the strongest individual proof that adjuvant chemotherapy has at least some efficacy in rectal cancer.

4.2. EORTC 22921/FFCD9203 (Fédération Francophone de la Cancérologie Digestive)

These two trials [19–21] chiefly tested the value of concomitant chemotherapy and radiotherapy in intermediate rectal cancer, although the European Organisation for Research and Treatment of Cancer (EORTC) trial, having a 2 x 2 design, also explored the value of adjuvant 5-FU/leucovorin. The trials (n = 1011 and 756 patients, respectively) showed that the addition of chemotherapy decreased local recurrence rates (HR 0.54; 0.41–0.78) but not distant progression or OS, even if analysed together to increase power [21]. Although subgroup analyses according to ypT stage indicated that a survival gain was seen in the group of patients whose tumours appeared to respond to the (chemo)radiotherapy [22], the EORTC trial argues against any relevant gain from adjuvant chemotherapy in pretreated rectal cancer patients.

4.3. PROCTOR/SCRIPT/Chronicle (Preoperative Radiotherapy and/or adjuvant Chemotherapy combined with TME-Surgery in Operable Rectal cancer/Simply Capecitabine in Rectal cancer after Irradiation Plus TME)

Due to the scientific lack of firm evidence for benefit from adjuvant chemotherapy in rectal cancer properly operated and pretreated with (chemo)radiotherapy, trials with a surgery-alone group were initiated by researchers in the Netherlands, Sweden and the United Kingdom (UK). These trials have unfortunately been prematurely closed for patient inclusion because of poor accrual. The PROCTOR study included patients who had preoperative 5 x 5 Gy and TME and randomised the patients to surgery alone or 6 months of 5-FU/leucovorin. It was later changed (to SCRIPT) to capecitabine instead of 5-FU/leucovorin. In addition, patients who had received preoperative chemoradiotherapy could be included. In total, over 500 patients were included in these Dutch/Swedish trials until December 31, 2012. The UK Chronicle trial randomised 110 patients who had preoperative chemoradiotherapy to a control group or adjuvant 5-FU/leucovorin and oxaliplatin. There are no mature data from the trials, although an interim report presented at a scientific meeting when 470 patients had been included could not see any gain (van de Velde, personal communication). The trials illustrate the ambitions from scientists to create good scientific evidence and rely on extrapolated data as little as possible [23].

4.4. Other recent trials

In a Finish trial, 278 patients in clinical stage II + III were randomised between TME alone or preoperative 5 x 5 Gy, TME and adjuvant 5-FU/leucovorin [24]. The trial results will again be confounded by radiotherapy, but early and late toxicity of the combined treatment can be properly evaluated against modern surgery alone. No increase in serious surgical complications was seen. Wound infections and perineal wound dehiscence were, as expected, more common after irradiation. If the trial turns out to be negative, it will argue against the value of adjuvant chemotherapy since any survival gains from 5 x 5 Gy with TME is at best limited [6]. The limited number of patients and inclusion also of patients with early stages may prevent firm conclusions.

In two parallel identically designed German trials in colon (n = 855) and rectal (n = 796) cancer, respectively, adjuvant 5-FU/leucovorin was superior to 5-FU alone in colon cancer [67% (95% CI 59–73) versus 54% (95% CI 97–61)] – but not in rectal cancer – [56% (95% CI 99–63) versus 51% (95% CI 43–58)] [25]. The authors speculate that the chemosensitivity of colon and rectal cancer differs.

4.5. Nomogram

Valentini et al. [26] collected information from a total of 2795 patients included in five European clinical trials with the aim
of allowing the selection of patients who might benefit from adjuvant chemotherapy. The trials were heterogeneous in many relevant aspects, and only two of them randomised patients between adjuvant chemotherapy or not [19] (Clonini et al, unpublished). The other three trials either planned to give adjuvant chemotherapy to all patients [20,27] or did not specify this in the protocol [28]. Neither of the two individual trials exploring the value of adjuvant chemotherapy revealed any significant gain in recurrence-free survival, whereas a small gain was seen when all patients were pooled together. Pooling of data from different trials may, however, easily introduce bias. Nomograms were developed for prediction of local recurrence, distant metastases and OS. The pathological stage (ypTN) after preoperative treatment (most patients had chemoradiotherapy to 45–50 Gy) was most important, although the use of adjuvant chemotherapy gave some additional value to the models. This added value was numerically smaller for distant metastases [HR ± 95% CI; 0.90 (0.83–0.97)] than for local recurrence [HR ± 95% CI; 0.81 (0.72–0.92)] and OS [HR ± 95% CI; 0.82 (0.76–0.88)]. The proposed nomogram was considered to have reliable concordance indices (0.73 for distant metastases) and could thus be useful for clinical assistance. The nomogram – which did not account for competing risk of death for recurrence prediction, therefore slightly overestimating the risk – indicated that any gains from adjuvant chemotherapy were minimal (1–2%) for responding patients, whereas the gains were larger for those who did not respond well to the preoperative chemoradiotherapy. The opposite conclusion was reached, as described above, when one of the included trials [19] was analysed retrospectively [22].

5. Recommendations

5.1. High rectal cancers

It is reasonable to conclude that tumours arising in the upper peritonealised third of the rectum should be treated as if arising from the colon. This means that most stage II patients should not have any adjuvant chemotherapy, some high-risk stage II patients should have adjuvant fluoropyrimidine and a few with several or very high-risk features an oxaliplatin combination. Most stage III patients should have an oxaliplatin combination, although some with low-risk features, particularly if they are older than 70 years, should rather be offered a fluoropyrimidine alone. These patients seldom have had preoperative (chemo)radiotherapy, although this may have been used in locally advanced, ugly tumours [6].

5.2. Non-irradiated low and medium-high rectal cancer

Adding 5FU-based adjuvant chemotherapy after surgery alone seems to provide meaningful benefits in terms of OS and DFS and perhaps also local recurrence rates, also in rectal cancers from the lower two-thirds. In practice, this is not often clinically relevant since very few patients with a tumour below about 10 cm from the anal verge with adverse histological features have been treated with surgery alone. Clinical and radiological imaging is not perfect, with a tendency for over-staging being more common than under-staging. What could be discussed in these patients is whether adjuvant chemotherapy then should be given alone or whether they should rather have adjuvant chemotherapy with chemoradiotherapy given either upfront or sometime during the treatment period. There are no data from modern trials to rely upon. If the local recurrence risk is reasonably high, for example if the surgery was non-radical (R1 + R2 or crm+), chemoradiotherapy is probably more relevant than if the risk of local recurrence is limited but the risk of systemic relapse is higher. Extensive lymph-node involvement (N2) and extramural vascular invasion (EMVI+) increase the risk particularly of systemic dissemination but also to some extent of local recurrence. However, it appears as if trial data taken together indicate that adjuvant chemotherapy seems more relevant for most patients than chemoradiotherapy, although this conclusion is controversial due to the lack of good trial data.

6. Timing of chemotherapy

Sensitivity of the subclinical tumour cells potentially present after surgery to the given drug(s) is for obvious reasons crucial for an increase in recurrence-free survival, and hence DFS and OS. However, since the currently available drugs in colo-
rectal cancer have rather limited tumour cell kill effects, the number of tumour cells to be killed is also relevant. The tumour cells have left the primary tumour prior to diagnosis, between the diagnosis and the surgery (or start of a treatment that at least temporarily prevents the tumour cells from being clonogenic) and at the latest during the surgery to remove the primary. The number of cells in the deposits to be killed is also influenced by the delay from surgery to initiation of the adjuvant therapy. The relevance of this delay has been the focus of many retrospective studies and meta-analyses of the studies in colon cancer [31–33]. Most studies have reported poorer survival in groups of individuals who started adjuvant therapy later rather than earlier. The start of treatment is not random (a randomised trial comparing different times is not possible for ethical reasons) but may be caused by many factors that negatively influence particularly survival but also risk of and time to recurrence. The analyses may thus be subject to severe bias. All trials that have shown a benefit from adjuvant therapy in colon cancer had a requirement that it should be initiated within 4–6 weeks. In later trials, the maximum allowed time has been much longer, up to 12–13 weeks, actually diminishing the ability to detect a difference between two treatments. Several national guidelines also permit a delay up to 12 weeks (e.g. [34]). In a survey among 679 out of 1151 patients who received chemotherapy, only 72% met the 12-week benchmark. This proportion was lower in rectal cancer (67%) than in colon cancer (79%).

For many reasons, the time from diagnosis to start of adjuvant therapy is longer in rectal cancer than in colon cancer. The surgery is generally more extensive, with more complications and longer postoperative recovery. The preoperative radiotherapy – which probably efficiently decreases the clonogenic capacity of the tumour cells in the primary, but not in the subclinical distant metastases – is another reason for a longer delay during which tumour cell growth occurs. The chemotherapy given concomitantly with the radiotherapy is not very dose-efficient compared with that when it is used alone, and probably has marginal influence on the risk of distant recurrence. The tendency to prolong the interval between the end of (chemo)radiotherapy and surgery to see more pCRs and down-sizing [35] further prolongs the interval and may cause survival to deteriorate. One apparently positive aspect of likely no benefit for the patients (the treatment has already been given) may be counterbalanced by another aspect. This also relates to the increased use of 5 × 5 Gy with a delay of 6–8 weeks (as explored in the randomised Stockholm II trial [36] outside of trials in intermediate (bad) rectal cancers (designated by most as locally advanced) [6]. The Stockholm III completed patient accrual in January 31, 2013, so survival data will not be available for many years.

7. Conclusions

In many countries the use of adjuvant chemotherapy for rectal cancer is not an issue, meaning that it is recommended and given as for colon cancer. There are no good studies describing how often it is an issue, but several centres in several countries have expressed concerns about the value of adjuvant chemotherapy in rectal cancer [37]. This is not the case for colon cancer, where treatment recommendations are probably very similar to the guidelines presented by the European Society for Medical Oncology (ESMO) [38]. These recommendations are based upon firm evidence when they relate to the entire group of patients with colon cancer, but must be questioned in the different substages. The surgery performed today for colon cancer is of higher quality than it was when the trials were run. Furthermore, and possibly even more relevant, is higher quality of the pathology investigations. This has caused stage migration. The extent of this has not been quantified. However, if we follow the recommendations [38], we treat groups of patients with very low risks of recurrence (even less than 10% with an oxaliplatin combination), gaining very few individuals. When analysed, population data indicate that the use in colon cancer follows the present recommendations (e.g. [39]), whereas greater variability has been reported for rectal cancer (e.g. [40]). The available literature-based documentation from the trials has been briefly summarised here. No one can object to the much less scientific evidence for sufficient gains in rectal cancer compared with colon cancer. However, interpretations differ considerably between different researchers and clinicians, particularly when the surgery has been preceded by (chemo)radiotherapy.

Conflict of interest statement

None declared.

REFERENCES


Introduction

Optimal approach for melanoma

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The incidence of cutaneous melanoma is rising faster than that of any other malignancy, and in some parts of Europe it is now the commonest cancer outside of “the big four” common malignancies: i.e. breast, lung, colorectal and prostate cancers. There is little doubt that the major factors in the development of melanoma are skin type, racial origin and sun exposure. Short sharp bursts of sunlight leading to sunburn are dangerous, especially when they occur in children and adolescents.

Ten percent of melanomas are familial in origin, and as with other cancers, the biology associated with such tumours has helped us to develop an understanding of the molecular genetics of sporadic melanoma. A number of mutations have been described, including those found in CDKN2A, CDK4, RB1, p16ARF, NRAS and particularly BRAF. BRAF mutations are found in approximately 50% of patients with cutaneous melanoma, and the development of targeted agents against mutations in BRAF has been responsible for one of the most dramatic examples of molecular biology in oncology.

Adjuvant therapy for patients at high risk of relapse following treatment for primary melanoma or locoregional disease remains an area of uncertainty. The use of adjuvant interferon, at various doses and schedules, has been the subject of many randomised trials over 25 years. It is of note that some large trial groups such as those in Europe still feel that there is enough uncertainty as to the efficacy of interferon that randomised trials of adjuvant therapy should still be performed with a no-treatment control arm. The one indisputable fact about adjuvant interferon is that it is associated with a relapse-free survival benefit, but some argue that, unlike treatment in the metastatic setting, the purpose of adjuvant therapy is to improve overall survival. A number of meta-analyses of the randomised trials involving interferon have been published, and it appears that the maximum absolute benefit to overall survival is in the order of 2–3% and again, some argue that this is below the threshold of useful clinical utility. Randomised trials of the newer melanoma therapies are now being brought into the adjuvant arena.

Vemurafenib is a BRAF inhibitor, and the results of the first randomised trial of vemurafenib against standard of care – namely, dacarbazine (DTIC) – were dramatic in terms of response rates, progression-free survival and overall survival. The hazard ratio for overall survival at the time of the first analysis was unprecedented in solid tumour oncology. The therapeutic momentum has continued with the development of MEK inhibitors and their combination with BRAF inhibitors. Other targeted therapies are being developed for uveal and acral melanomas, e.g. against c-KIT mutations in the latter.

The most important recent development in immunotherapy has been the targeting of inhibitors of the immune system, e.g. CTLA-4, PD-1 and its ligand PD-L1. Ipilimumab targets CTLA-4 and is the first immunotherapy to have shown an overall survival benefit in melanoma within the context of a randomised trial. The magnitude of benefit can be very great in some patients with prolonged complete remissions; however, it is only a minority of patients that benefit. Early results targeting PD-1 and PD-L1 are particularly exciting because they appear to challenge the dogma that immunotherapy only impacts a minority of patients. Early results suggest that the majority of patients show some benefit without necessarily achieving a complete remission.

The new immunotherapeutic landscape means that our previous view of follow-up needs to change rapidly. We now know that there is an important immunotherapy that is associated with a survival advantage, but that, as with most immunotherapies, it can take some time before the host response becomes effective. This time-frame may be 2–4 months, and therefore it is completely illogical to wait for a patient to become symptomatic from their metastatic disease before investigating and treating them.

Patients must have their metastatic disease diagnosed early, otherwise there is little prospect of a successful outcome to immunotherapy, and therefore patients at high risk of relapse need regular imaging, and treatment should be instituted before high volumes of disease are seen.

Conflict of interest statement

Speaking bureau, Advisory Boards: Pfizer, Roche, Bayer, Novartis, Bristol Myers Squibb, Astellas.
Melanoma epidemiology, biology and prognosis

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1. Introduction

Melanoma is a cancer arising from the malignant transformation of melanocytes. These pigment-producing cells derive embryologically from pluripotent neural crest stem cells. During foetal development they not only predominantly migrate to and differentiate within the epidermis, but also to other extra-cutaneous pigment-containing sites such as the eyes, meninges, oesophagus and mucous membranes. Three subtypes of melanoma can therefore be characterised: cutaneous melanoma (the most common) arising from melanocytes in the epidermis, mucosal melanoma from melanocytes residing in the mucous membranes and uveal melanoma from melanocytes residing in the ocular stroma. In this chapter we will consider each of these melanoma subtypes in turn, highlighting the differences in epidemiology, biology and prognosis between them.

2. Cutaneous melanoma

2.1. Epidemiology

Cutaneous melanoma is by far the most common melanoma subtype, accounting for in excess of 90% of cases of melanoma [1]. Melanoma is reported as the 19th most common cancer worldwide, with estimated age-standardised incidence rates of 2.8–3.1 per 100,000 [2]. There is considerable variation in incidence between countries, with the highest rates reported in Australia (37 per 100,000) and the lowest in South-Central Asia (0.2 per 100,000). This trend is attributed to variations in racial skin phenotype, as well as differences in sun exposure around the world; in the United States (US), for example, 98.2% of cases are reported amongst white-skinned individuals [1].

Europe lags behind Australia and the United States in terms of incidence rates, but the statistics demonstrate that even within Europe incidence rates vary widely [3]; Switzerland has the highest rates (19.2 cases per 100,000) with Greece recording the lowest (2.2 cases per 100,000). There is also evidence of clear North–South and East–West incidence gradients across the continent. The reason for such marked intra-continental variation in incidence is unclear and may well be associated with differences in affluence and consequent recreational sun exposure. However, it is also likely to be (at least in part) related to discrepancies in cancer registration [4] between different countries, in particular in Eastern Europe.

Unfortunately the incidence of cutaneous melanoma around the world has been rising annually [5–7], at a rate faster than that of any other malignancy. This is of particular concern given the unusual age demographics of the disease. Unlike other solid malignancies, where the majority of cases are diagnosed at over the age of 65, melanoma affects a higher proportion of younger patients, with a median age of diagnosis of 57 years. Age-specific incidence rates increase steadily from the third to the ninth decades of life. There is a female preponderance in younger age groups (4:10 in 20–24-year-olds) which changes to a male preponderance (16:10 in >85-year-olds) after a sharp increase in incidence amongst males from the age of 55 onwards [8]. Estimates from the United States [9] quote a lifetime risk of melanoma as 1 in 56 for women and 1 in 37 for men, with UK estimates at 1 in 60 for women and 1 in 61 for men [10], further highlighting global differences. Australia/New Zealand has the highest global melanoma mortality rate (3.5/100,000) followed by North America (1.7/100,000) and then Europe (1.5/100,000) [3]. Overall, mortality rates are higher amongst men than women [11], perhaps because of the later presentation of disease.

Several risk factors thought to be significant in the development of cutaneous melanoma have been identified by epidemiological studies. These can be grouped into environmental factors and genetic factors, but there is clearly interplay between both genetics and the environment to account for such a wide variation in disease demographics.

Pigmentation has an indisputable and significant influence on skin susceptibility to malignant change. The melanocortin 1 receptor (MC1R) is a melanocyte cell-surface receptor that induces pigment production (via the signalling cascade recruitment of MITF) following activation by its ligand, alpha-melanocyte-stimulating hormone (MSH) [12]. There are
many polymorphisms of the MC1R gene, resulting in the numerous skin-colour phenotypes seen in humans; variants such as the red hair, fair-skinned phenotype express low pigmentation, with a consequent increased sensitivity to ultraviolet (UV) light and associated increased melanoma risk [13].

As implied above, the main environmental factor implicated in the development of cutaneous melanoma is UV radiation. The incidence of melanoma is highest in equatorial regions, and decreases with increasing distance from the equator [14,15]. This directly corresponds with UV light exposure, particularly UV-B levels [16–18], and occurs regardless of skin type. Although a direct causal link has not been established, epidemiological studies [17,19] have repeatedly demonstrated an association between the pattern and timing of sun exposure and melanoma. The majority of cutaneous melanomas arise on sporadically (rather than chronically) sun-exposed skin, in sites and individuals more prone to sunburn. The highest rates are seen in individuals with repeated intense sun exposure. This theory is further strengthened by the observation that patients with melanoma who actively reduce their sun exposure after initial diagnosis are consequently at reduced risk of developing a second primary melanoma [20]. On the contrary, individuals with dark skin, or skin that darkens easily in response to sunlight but does not burn, have demonstrably lower rates of melanoma [17]. Patients with xeroderma pigmentosum (XP) commonly develop cutaneous (and conjunctival) melanomas [21]; these individuals have a genetic inability to repair UV-induced DNA damage, providing further support for the significance of UV radiation in melanogenesis.

The age at which sun exposure and/or sunburn occurs also appears to be important. Systematic review [19,22,23] has strongly associated intermittent childhood or adolescent sun exposure with a higher risk of melanoma. In particular, individuals experiencing more than five episodes of severe sunburn had a two-fold increased risk of melanoma [24,25].

Although the melanomagenic effects of UV-B exposure are well evidenced, UV-A exposure is not without risk [26]. Long-term follow-up of psoriasis patients have demonstrated that those receiving UV-A therapy are at increased risk of developing melanoma [27]. Sunbeds emit UV-A radiation; a meta-analysis of studies [28] exploring melanoma incidence following sunbed use reported a 75% increase in risk in individuals under 35 with a history of sunbed use. Further studies support this finding, drawing clear associations between melanoma risk and the amount of sunbed usage, particularly from a young age [29–31]. The association was felt to be sufficiently conclusive for UV light from sunbeds to be formally classified as a human carcinogen [28,32]; unfortunately, despite this evidence and consequent public health warnings, sunbed tanning remains popular.

No other conclusive environmental risk factors – including (unusually) smoking – have been identified. Smoking, a common carcinogen, has not been independently associated with melanoma [33]. Interestingly, however, there is an association between melanoma and comorbidities: for example, individuals who are immunosuppressed (due to organ transplantation) are at demonstrably higher risk of melanoma, including recurrence in individuals with resected primary melanomas prior to transplantation [34,35]. Also, patients who have other skin malignancies (basal- or squamous-cell carcinomas) are at higher risk of melanoma development [36] and subsequent disease-related death [37].

It is also important to consider individual genetics when determining personal risk. Clearly genetic factors such as race and skin phenotype affect risk, as discussed earlier, but it has also been estimated that approximately 10% of melanomas are familial in origin [38]. Some of these occur in specific syndromes – such as familial atypical multiple mole and melanoma syndrome (FAMMM) or dysplastic naevus syndrome (DNS) – wherein individuals have multiple and phenotypically variable moles at high risk of malignant transformation, thereby presenting an almost guaranteed lifetime melanoma risk. Many individuals will not meet the diagnostic criteria for these syndromes but still have numerous naevi, often a reflection of cumulative sun exposure. Observational studies suggest a strong association between high naevus counts and melanoma [39,40]. A personal history of cutaneous melanoma is also a known risk factor for further melanoma primaries [41–43].

2.2. Biology

Aside from these familial syndromes, advances in gene analysis technology have allowed the investigation of less common but high-risk alleles that also appear to contribute to cancer risk in individuals. Linkage studies focused on families with a high incidence of melanomas [44–46] identified a melanoma susceptibility locus on chromosome 9p21, subsequently found to represent the gene locus for CDKN2A [47,48]. This gene locus undergoes complex transcription (from alternate reading frames) and thus encodes two proteins, p16 and p14ARF; the majority of mutations affect the former protein [49,50].

p16 normally interacts with and inhibits cyclin-dependent kinase 4 (CDK4). During the normal cell cycle, CDK4 complexes with cyclin D, resulting in phosphorylation of the retinoblastoma (Rb1) protein, in turn releasing E2F-1 and thus allowing it to induce S-phase gene synthesis; p16 therefore acts as a negative regulator of the cell cycle [47,50]. Mutations affecting this important protein disrupt its inhibitory function, thus deregulating the cell cycle. They are therefore thought to prime melanocytes for malignancy. Evidence [51–53] also exists for a pro-melanomagenic effect of germline mutations affecting CDK4 and Rb1 directly. p14ARF also has an important role in down-regulating p53 activity (through increased activation of MDM2), thus also acting as a tumour suppressor; disruption of this activity through mutations could also be tumourgenic [54].

The actual prevalence of CDKN2A mutations is difficult to quantify. In melanoma family studies estimates have ranged from 20% to 57% [50], but in the general population are thought to be considerably lower, in the region of 1.2–2.9% [55]. Gene penetrance estimates are further complicated by the knowledge that the environmental factors discussed earlier further modulate risk in individuals with CDKN2A. Establishing the relative risk contribution from genes is therefore more challenging. There may also be interaction between genetic mutations to modulate melanoma risk further; for example, some MC1R gene variants can increase the penetrance of CDKN2A mutations, thus increasing risk further.
A link between CDKN2A melanoma and other malignancies (e.g. pancreatic cancer) has also been demonstrated [58–60].

BRCA2 is well associated with increased risk of breast malignancies, but its role in melanoma is not fully established. Given that some studies [61] suggest an increased risk of melanoma in the presence of mutations in this gene, whereas others [62] have been unable to demonstrate this, no sound conclusions can be drawn regarding this gene. Other genes are also being investigated; genome-wide association studies [63–65] have identified several loci that may correlate with increased melanoma risk, but the biological mechanism of many of these has not yet been established.

Genetic mutations affecting protagonists of the mitogen-activated protein kinase (MAPK) pathway have been found in many tumour types. This key cell signalling pathway is activated by ligand binding to a cell-surface receptor tyrosine kinase (RTK), which in turn activates RAS. The RAS family of G proteins consists of three isoforms, the most important of which is NRAS. NRAS activation results in further pathway signal transduction through phosphorylation (and consequent activation) of the RAF proteins BRAF and CRAF [66]. Homo- or hetero-dimer formation of RAF molecules ultimately leads to the activation of extracellular signal-regulated kinase (ERK) which in turn acts on numerous targets to promote cell growth and survival, as well as controlling further MAPK pathway signalling by inducing the expression of negative regulators [67], and directly inhibiting proteins such as CRAF [68].

Mutations affecting this pathway are present in the vast majority of cutaneous melanomas, predominantly affecting the NRAS (approximately 20%) [69] or BRAF (approximately 40–50%) proteins [70]. In the case of BRAF, the vast majority of mutations constitute a single amino acid substitution from valine to glutamic acid at codon 600 (V600E), resulting in a MAPK pathway that is consequently able to signal in a continuous and unopposed fashion down the pathway, facilitating malignant transformation, rather than initiating this. BRAF mutations are more commonly seen in melanomas affecting the PI3 kinase pathway, for example, may also be sufficient to induce melanoma development. Once developed, however, there is clear tumour dependency on persistent activation of the MAPK pathway [72].

2.3 Prognosis

Prognostic factors in cutaneous melanoma have been closely studied; they include histopathological characteristics, patient characteristics, biochemical measures and most recently genetic mutations. Each of these will be considered in turn.

The American Joint Committee on Cancer (AJCC) staging system [74] is globally acknowledged as an invaluable tool in predicting outcomes for patients diagnosed with melanoma. It is based on data derived from analysis of tens of thousands of cutaneous melanoma patients; the current seventh edition was introduced early in 2010 and incorporated new factors not previously used in the estimation of melanoma prognosis.

Histopathological features logically form the main criteria for determining prognosis. Increasing thickness of the cutaneous primary correlates with worsening survival outcomes, dropping from 96% 10-year survival for lesions <1 mm, to 54% for lesions >4 mm; even for lesions <1 mm in thickness, there is further deterioration in outcome between lesions <0.25 mm thickness and those >0.75 mm [75]. Moreover, at each tumour thickness it has been demonstrated that the presence of epithelial ulceration in the primary results in a worse prognosis than if there is no ulceration [76,77]. These two features (tumour thickness and ulceration) are arguably the most powerful independent prognostic factors for cutaneous melanoma [76,78,79]. A third significant pathological feature is the mitotic rate [80,81]; a rate of >20 mitosis/mm² results in a 10-year survival of approximately 48% relative to 93% in those individuals with <1 mitosis/mm². Other features of the primary associated with higher risk of relapse or metastases are high tumour vascularity (i.e. new vessel formation at the base of an invasive melanoma) [82,83] and lymphovascular invasion (tumour invasion of the dermis microvasculature) [84]; the evidence for these factors is not as conclusive as that for those discussed earlier.

The site of the primary also has important prognostic implications; those arising centrally (trunk, head and neck) tend to carry a worse prognosis than those arising on the limbs (lower < upper) [76,85,86]. Additionally, cutaneous melanoma can metastasise to lymph nodes. The presence of lymph-node disease has adverse prognostic implications, with further variation depending on the burden of nodal disease – both in terms of micrometastatic versus macroscopic disease – and the number of lymph nodes involved. The presence of microscopic lymph-node disease results in 10-year survival rates of 63%, but if macroscopic disease is present this drops to 47% [76,87]. Similarly, there is a 10% 5-year survival deterioration with an increase in the number of nodes involved (from 1 to 3) [87]; for those with macroscopic metastases this increased risk is independent of other primary tumour characteristics. Metastases to other sites have adverse prognostic implications. Satellite cutaneous lesions reduce survival by a similar proportion to lymph-node metastases [88], with worsening prognosis with metastases to the lung and further deterioration with any other organ involvement [74,76].

In terms of patient characteristics, it is well established that age is an independent prognostic factor, with worsening outcome associated with increasing age [76,89,90]. Interestingly, for early-stage (I–II) melanoma, female gender also has positive prognostic implications [78,91–93], possibly related to the higher number of thin, non-ulcerated, extremity
lesions diagnosed in women. The histopathological factors previously discussed are more prognostically significant than gender.

With regard to biochemical features, serum lactate dehydrogenase (LDH) is well recognised as an independent prognostic factor in cutaneous melanoma; in multivariate analysis [74,94] a raised LDH level predicts approximately 50% lower survival rates in patients with distant metastases. Other serum prognostic biomarkers have also been studied; the most promising, S100 protein levels, correlate with survival in patients with resected locoregional disease [95,96], with high levels predicting a significantly worse outcome than with normal levels.

The increased use of gene expression profiling is also providing further genetic prognostic clues. The BRAF gene mutation – which as previously described is integral to melanoma pathogenesis – has been investigated as a prognostic marker too. It appears to be linked to known prognostic factors such as age and site of primary, whilst also being unrelated to factors such as site of metastasis and LDH [97]. In advanced disease, meta-analyses have demonstrated that the presence of a BRAF mutation is independently associated with a worse survival outcome [97–99]. The data in this area continue to evolve.

3. Uveal melanoma

Uveal melanoma is the most common primary ophthalmic malignancy in adults and is associated with resistance to available treatments and poor prognosis. The incidence of uveal melanoma in Europe has been estimated as between 2 and 8 per million [100] and the median age at presentation ranges from 55 to 60 years of age [101,102]. Both US [103] and European [100] studies report that the incidence rate has been stable since the 1970s, and disappointingly there has been no improvement in survival over this time period. There is regional variation within Europe with an increase in incidence from South to North, leading to the hypothesis that ocular pigmentation may be protective [100]. Other incidence studies support this hypothesis.

In the USA the majority of cases occur in the white population [103]; there is a low incidence in South African black populations [104] and in Far East Asian populations [105]. Case–control studies provide further supportive evidence that lighter skin [106] and iris [107–109] colours are a risk factor for the development of uveal melanoma. The role of UV-B radiation in the pathogenesis of uveal melanoma is a BRAF mutation is independently associated with a worse survival outcome [97–99]. The data in this area continue to evolve.

3.1. Biology

Disruptions in a number of tumour suppressor genes and/or activation of oncogenes have been implicated in the development of uveal melanoma. Disruption of the activity of the retinoblastoma (Rb) tumour suppressor gene leads to uninhibited progression of melanocytes through the G1–S phase of the cell cycle, resulting in deregulated cell proliferation. Cyclin D4, either by over-expression [113] or lack of inhibition by the tumour suppressor gene INK4a [114], phosphorylates Rb resulting in its inactivation [113]. The p53 tumour suppressor gene is often functionally inhibited by the over-expression of HDM2 resulting in the inhibition of apoptosis [115]. Also PTEN, a negative regulator of the PI3K-AKT pathway, is frequently inactivated or down-regulated in uveal melanoma leading to increased cell proliferation and survival [116].

More recently mutually exclusive mutations in GNAQ and GNA11, genes encoding the alpha subunit of heterotrimeric cell surface G proteins, have been reported. These alpha subunits are involved in mediating signals between G-protein-coupled receptors and downstream effectors such as protein kinases A and C [117]. Mutations in codon 209 of GNAQ and GNA11 have been reported in approximately 46–49% [118,119] and 32% [120] of patients, respectively, and lead to constitutive activation of the G protein alpha subunit and activation of the MAPK signalling pathway (in human melanocyte cell lines), driving cell proliferation [118]. The majority of substitutions at codon 209 of GNAQ and GNA11 involve substitutions of glutamine by leucine or glutamine by proline [118,120]. Mutations at codon 183 of GNAQ and GNA11 also occur, although less frequently, and involve the substitution of cytosine by thymine [118,120] which is characteristic of ultraviolet-radiation-induced mutations [121], thereby supporting the role of UV-B radiation in the pathogenesis of a minority of uveal melanomas. As mutations in GNAQ and GNA11 are common in uveal melanoma, targeting these or downstream effectors such as protein kinase C [122] or members of the MAPK signalling [123] pathway are promising potential therapeutic options. However, the presence of these mutations is not correlated with the development of metastatic disease.

Inactivating somatic mutations of the gene coding for BRCA1-associated protein-1 (BAP1) have been found in up to 85% of metastasising uveal melanomas [124]. BAP1 is a deubiquitinating enzyme (DUB) encoded at the 3p21.1 locus [125]. It regulates cell growth by mediating ubiquitination of the nuclear transcription regulator, host cell factor 1 (HCFC1) [126], and stabilises the BRCA1–BARD1 tumour suppressor complex [127]. Also families with germ-line mutations of BAP1 have been identified with an increased incidence of both uveal and cutaneous melanoma, as well as other malignancies [128–130].

Vascular endothelial growth factors (VEGFs) are a family of five proteins which bind to VEGF receptors (VEGF-Rs) on endothelial cells and promote angiogenesis. Increased VEGF expression is involved in the pathogenesis of a number of solid malignancies. The expression of VEGF is increased in hypoxic environments [131], and raised VEGF-A levels have been found in the aqueous humour of eyes with uveal melanoma [132,133]. Significantly increased levels of VEGF-A have been reported by some groups in patients with metastatic disease [134], although not consistently [135]. The role of VEGF in the pathogenesis of uveal melanoma requires further clarifi-
cation, but trials of anti-angiogenic agents of patients with melanoma, including uveal melanoma, are underway.

3.2. Prognosis

Major aberrations in karyotype are frequently observed in uveal melanoma [136]. Monosomy 3 is the most common and is reported in approximately 50% of cases treated with enucleation [157]. It has been found to correlate with clinical features of poor survival – such as large tumour size, tumours of the ciliary body [138] and epithelioid cytology [139] – and is also closely associated with the development of metastatic disease [140]. Such patients with monosomy 3 uveal melanoma have a poor 5-year survival [141]. This may be due to loss of tumour suppressor genes located on chromosome 3, including BAP-1. It is likely that loss of chromosome 3 is an early event in tumourigenesis, predisposing to other cytogenetic aberrations such as gain of 8q [142]. This is found in around 40% of cases and corresponds to the locus for the MYC proto-oncogene [143]. Together these cytogenetic abnormalities are more common in ciliary body tumours [144] and are associated with the development of metastatic disease [143]. Gain in chromosome 6p is associated with a better prognosis. It has been observed in approximately 25% of tumours and exclusively in tumours without monosomy 3 [143].

More recently gene expression profiling has identified two distinct molecular subtypes (classes 1 and 2) of primary uveal melanoma using a three-gene signature, with significant differences in prognosis [145]. This signature identifies genes which are involved in apoptosis, cell growth and angiogenesis. Class 1 tumours are associated with gain of chromosome 6 and are less likely to metastasise, whereas class 2 tumours are associated with monosomy 3 and demonstrate a propensity to metastasise. Consequently the 92-month survival for class 1 and class 2 subtypes differed significantly at 95% and 31% respectively.

4. Mucosal melanoma

Given that the primary function of melanocytes is pigmentation and protection of the skin and eyes against UV radiation, their presence in unexposed sites such as mucous membranes is not fully understood. There is accumulating evidence that melanocytes function as antigen-presenting cells [146,147], and as mucous membranes form a critical antimicrobial barrier, melanocytes at this site may have a role to play as part of the innate immune system [148]. At leptomingeal sites there is even evidence of a neuroendocrine role [149]. Regardless of their function, mucosal membrane melanocytes are susceptible to malignant transformation in a similar fashion to their cutaneous and uveal counterparts.

4.1. Epidemiology

Mucosal melanoma is the least common of the three melanoma subtypes, accounting for less than 1.5% of all melanomas [1,150]. The incidence rate is similar around the world [151] and estimated at 2.2 [150] and 2.6 [152] cases per million per year in the USA and Europe respectively. Significant regional variation in incidence across Europe has been reported, with the highest rate (2.7 cases per million per year) noted in Northern Europe, and the lowest (0.88 cases per million per year) in Eastern Europe [152], but this may simply reflect differences in classification and reporting of this rare malignancy. Interestingly, unlike cutaneous melanoma (which demonstrates an annual increase in incidence), the annual incidence of mucosal melanoma has remained relatively stable over several decades [1,150,153].

The incidence of mucosal melanoma varies with both gender and age [150]. The median age at diagnosis is 70, with the exception of oral cavity melanomas which tend to occur in younger patients. Incidence increases with age; over 65% of cases are diagnosed in patients over 60. The incidence in women is almost twice as high as in men, possibly because of the higher rates of genital tract melanomas [1,154,155] amongst women. The absolute incidence of mucosal melanoma in white populations is higher (2:1) than in non-whites [1,150,155,156].

Mucosal melanomas arise most often in the head and neck region, female genital tract and anorectal region [150]. No clear risk factors for mucosal melanoma are known. As mucous membranes are not exposed to the sun, UV radiation is not considered an important aetiological factor. The role of viruses – such as human papillomavirus (HPV) or human herpes virus (HHV) implicated in other oral malignancies – has not been substantiated [157–159]; however, a role for the human immunodeficiency virus (HIV) has been postulated [160,161] for anorectal mucosal melanomas. Inhaled chemical irritants such as formaldehyde [162] are also not thought to be significant carcinogens for this malignancy. It has been reported that smoking is associated with a greater prevalence of pigmented oral lesions [163]. Oral mucosal melanoma is thought to be preceded by oral melanosis in one third of cases [157,164,165], but no clear link to smoking has been identified, particularly at other mucosal sites.

4.2. Biology

The advent of next-generation genomic sequencing has enabled detailed investigation of the molecular biology of this rare melanoma subtype, and provided an insight into its pathogenesis. Unlike cutaneous melanoma, V600E BRAF or NRAS mutations are rare in mucosal melanoma [166,167]. Instead a distinct molecular mutation pattern exists, further differentiating mucosal melanomas biologically from their cutaneous and uveal counterparts.

The proto-oncogene, KIT, is a type III transmembrane receptor tyrosine kinase (RTK) that dimerises upon extracellular binding of its ligand stem-cell factor (SCF), activating its intracellular tyrosine kinase domain and thus the receptor. The activated protein, c-KIT, leads to phosphorylation of a downstream intracellular signalling cascade and the activation of MAPK and phosphoinositide 3-kinase (PI3K) pathways crucial for proliferation, migration, differentiation and survival in many cell types, including melanocytes [168,169].

Although the exact mechanism of KIT signalling in melanocytes is not fully understood, studies have demonstrated that inactivating mutations in KIT can lead to amelanotic disorders [170,171] and prevent normal melanocyte development.
Mucosal melanoma has the poorest prognosis of all the melanoma subtypes considered. Five-year survival estimates range from 25% to 40% [1,152]. Interestingly, patients with mucosal melanoma were reported as expressing aberrant c-KIT [181], while others [180] reported their highest rates (35%) amongst genital tract melanomas. It was also noted that mutations of KIT did not occur alongside mutations in NRAS or BRAF [180].

Exon 11 mutations (including point mutations, in-frame deletions and insertions) are the most common KIT mutations; the L576P mutation in particular is found in approximately one third of these melanomas [166,179,180]. This region encodes the juxtamembrane domain of the KIT receptor, which performs an auto-inhibitory role. Mutations in this region lead to constitutive receptor activation and consequent abnormal intracellular growth signals, predominantly via the PI3K pathway [182]. Experimental evidence suggests that such activation alone is insufficient for mucosal melanoma genesis, requiring further triggers within the cellular microenvironment (such as hypoxia) in order to induce malignant transformation [182].

There is clearly still much to learn about the biology of mucosal melanoma, but the knowledge gained thus far about KIT mutations is encouraging further research in this area, focused particularly on exploiting this mutation in the pursuit of effective treatment options for this condition. KIT mutations have been successfully targeted in the treatment of other malignancies such as gastrointestinal stromal tumours (GIST), which also demonstrate an increased prevalence of KIT mutations.

4.3. Prognosis

Mucosal melanoma has the poorest prognosis of all the melanoma subtypes considered. Five-year survival estimates range from 25% to 40% [1,152]. Interestingly, patients with KIT mutations appear to have a poorer prognosis than wild-type patients [183].

The site of these melanomas is often occult; early malignant lesions are usually asymptomatic, and any subsequent symptoms are non-specific, resulting in significant diagnostic delay and enabling the lesion to grow and metastasise. Even supposedly early-stage disease deemed to be fully surgically resectable (and thus curable) often has a poor outcome. This is most likely due to the presence of occult metastatic disease at diagnosis. The lack of knowledge regarding disease risk factors means that, in contrast with cutaneous melanoma, strategies to improve mucosal melanoma outcomes must focus on early detection of the disease rather than avoidance of risk factors and prevention of development.

5. Conclusion

The socio-economic burden of melanoma is disproportionate as its incidence is highest amongst younger, economically active individuals. Both inherited, genetic and lifestyle factors have been shown to affect the malignant transformation of melanocytes. More recently it has become clear that cutaneous, mucosal and uveal melanomas are each distinct disease entities with unique clinical behaviours and characteristic molecular abnormalities. This improved understanding has led to the development of new treatment strategies which have started to improve outcomes. However, there is still a long way to go as melanoma, for now, remains an assortment of diseases with a common poor prognosis – particularly for those with advanced disease.

Conflict of interest statement

Dr. Larkin has received honoraria from Pfizer, Novartis, GSK and BMS for consulting and research funding from Pfizer and Novartis.

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Targeted therapy in melanoma – the role of BRAF, RAS and KIT mutations

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Melanoma today is considered as a spectrum of melanocytic malignancies characterised by clinical and molecular features, including targetable mutations in several kinases such as BRAF or c-KIT. The successful development of therapies targeting these mutations has resulted in new specific treatment options. These include vemurafenib, dabrafenib, trametinib, imatinib and other kinase inhibitors that are selected when the respective mutation is present.

The BRAF inhibitor vemurafenib has resulted in improved survival in patients with BRAF-mutated advanced melanoma. Dabrafenib has shown similar efficacy. The MEK inhibitor trametinib also improved overall survival. In addition, the MEK inhibitor MEK 162 was investigated in a phase II clinical trial and showed promising efficacy in terms of response rate and progression-free survival (PFS) in NRAS-mutated melanomas. After this first success in the treatment of advanced melanoma, there is expectation that combinations of kinase inhibitors will additionally improve overall survival rates and PFS in advanced melanoma.

1. Introduction

Melanoma is the most common lethal cutaneous malignancy. It arises from melanocytes that have their origin in the neural crest. The genetic events and their relationship to the complex interaction with the microenvironment transforming normal melanocytes into melanoma are under intensive investigation.

2. Molecular dissection of melanoma

In the last decade melanoma was dissected into several molecular subgroups on the basis of genomic alterations, including mutations, deletions and amplifications, in addition to clinical features. These subgroups include BRAF, NRAS and KIT mutated melanomas.

First, up to 50% of melanomas derived from the skin without chronic sun damage (intermittently exposed to ultraviolet (UV)) contain mutations in the gene encoding the serine-threonine protein kinase BRAF. BRAF together with ARAF and CRAF activates a second protein known as mitogen-activated protein kinase kinase (MEK), which in turn activates extracellular signal-regulated kinase (ERK).

Second, 20% of melanomas present with RAS mutations. Most of the NRAS mutated melanomas are superficial, spreading melanomas (intermittently exposed to UV). However, NRAS seems also to be involved in melanomas deriving from giant congenital nevi. A recently published model for congenital nevi [1] used a melanoma mouse model over-expressing NRAS under the control of a tyrosinase promoter in combination with loss of INK4a. The phenotype of these mice closely resembles giant congenital nevi. In this model, haplo-insufficiency of the transcription factor SOX10 prevented melanoma formation.

Finally, minor percentages have activating mutations in the KIT gene, most common in mucosal melanomas derived from the genital regions [2,3] or mutations in GNA11 or GNAQ genes in uveal melanomas [4,5]. Some of the targetable mutations in the KIT gene are also found in acral and other mucosal (for example, penile or anal) melanomas but with lower frequency. The KIT receptor protein tyrosine kinase is a transmembrane protein consisting of extracellular and intracellular domains. Most KIT mutations are located in exon 11, which codes for the juxtamembrane domain, and in exon 13, which codes for a kinase domain.

Recently, deep exome sequencing shed further light on the genomic landscape of melanoma [6,7]. Both publications impressively demonstrated that UV light is responsible for most mutations in melanomas derived from UV-exposed skin.

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The best-validated targeted drugs in melanoma are the selective BRAF inhibitors vemurafenib (PLX4032, Zelboraf®) and dabrafenib (GSK2118436, Tafinlar®) as well as the LGX818 (Novartis) compound [9] that appears to have the highest affinity for the catalytic domain of the kinase. All of them are relatively selective for their intended target V600E BRAF, with little cross-reactivity for wild-type BRAF and CRAF [10,11]. A few other kinases are inhibited with 10- to 100-fold of the concentration needed to inhibit V600E BRAF. These molecules selectively inhibit the growth of cells that harbour a V600 mutant BRAF [12]. In phase I clinical trials, where patients were selectively enrolled on the basis of the presence of a tumour harbouring a V600E or V600K mutation, vemurafenib and dabrafenib both demonstrated evidence of tumour regression early in the course of therapy in the majority of patients [11,12,19]. Subsequent phase II and III trials designed to evaluate overall disease control and survival in comparison with standard chemotherapy have documented the durability of response in larger cohorts. In a phase II trial, vemurafenib produced objective responses in 53% of 132 patients with metastatic melanoma harbouring a BRAF V600E or BRAF V600K mutation [14,15]. The median duration of response was 6.7 months. In a phase III trial with single-agent dacarbazine as the control arm, overall survival (OS) was significantly improved amongst 337 patients with BRAF V600E mutant metastatic melanoma receiving vemurafenib compared with 338 patients who received dacarbazine (hazard ratio (HR) of 0.37; 95% confidence interval (CI): 0.26–0.55; P < 0.001) [16]. Progression-free survival (PFS) was also significantly improved (hazard ratio 0.26; 95% CI: 0.20–0.33; P < 0.001) and the response rate was superior in the vemurafenib arm (48% objective response rate versus 5%; P < 0.001). The benefit of vemurafenib was maintained in an updated overall survival (OS) analysis with approximately 10 months median follow-up, as demonstrated by the median OS with vemurafenib of 13.2 months compared with 9.6 months with dacarbazine and a hazard ratio (HR) for death of 0.62 (95% CI 0.49–0.77) in favour of vemurafenib [17]. These data led to approval of vemurafenib in the United States (US), European community and Switzerland. Dabrafenib was compared with dacarbazine (random ratio 3:1) in a phase III trial in patients with previously untreated stage IV or unresectable stage III melanoma harbouring the BRAF V600 mutation. Median PFS was 5.1 months for dabrafenib (187 patients) and 2.7 months for dacarbazine (63 patients), with an HR of 0.30 (95% CI: 0.18–0.51; P < 0.0001) [18]. This drug was recently approved by the Food and Drug Administration (FDA) in the US.

In summary, vemurafenib and dabrafenib have both demonstrated impressive clinical efficacy with response rates in the region of 50% in V600 BRAF mutated advanced melanoma [11,12,19]. Although the response duration is highly variable, as shown by these phase II and phase III trials, these results are a breakthrough in melanoma treatment.

Furthermore, multiple in vitro studies have demonstrated that mutated BRAF signalling is mediated via MEK and ERK [20]. Thus, selective MEK inhibitors have also shown efficacy in patients with BRAF mutant metastatic melanoma. Selumetinib was the first allosteric, selective MEK inhibitor to be evaluated in a phase II clinical trial in patients with metastatic melanoma [21]. This agent produced an objective response rate in patients with BRAF mutant tumours, whereas no response was observed in wild-type tumours, reinforcing the importance of selecting a specific patient population. The addition of selumetinib to dacarbazine has resulted in prolonged PFS in BRAF mutated metastatic melanoma [22] and was the first agent to show clinical activity in uveal melanoma when compared to temozolomide [23]. Trametinib is another, orally available selective inhibitor of MEK1 and MEK2. It demonstrated a reasonable objective response rate and an improved survival compared to chemotherapy in BRAF mutant melanoma. The median PFS was close to 5 months using the MEK inhibitor in comparison to 1.5 months in the chemotherapy group. After 6 months, there was an improvement in the overall survival rate in the trametinib group of 81% (versus 67% in the chemotherapy group). Trametinib (Mekinist®) was recently approved by the FDA for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation.

The combination of these kinase inhibitors clearly shows further encouraging data. The combination treatment with dabrafenib and trametinib was analysed with different dosages in 247 BRAF V600 mutated melanoma patients. Median PFS was significantly improved at 9.4 months for the patients treated with 150 mg dabrafenib twice daily and 2 mg trametinib daily, as compared with 5.8 months for the patients treated with dabrafenib alone (HR for progression or death, 0.39; 95% CI, 0.25–0.62; P < 0.001). The rate of complete or partial response in the combination group was 76% (compared with 54% with monotherapy (P = 0.03) [24]. In other words, the combination of BRAF and MEK inhibitors results in an increased response rate and prolonged PFS [24]. Today, there are several phase III clinical trials that compare the response rates and the PFS in BRAF mutated patients for mono-
therapy with a BRAF inhibitor versus combination of BRAF and MEK inhibitors.

Lito et al. have investigated the ERK-dependent feedback mechanism during BRAF inhibition using a selective inhibitor. They could clearly show that a BRAF inhibitor blocks RAF monomers, resulting in RAF dimer formation. These dimer feedback mechanisms are decreased. The addition of a MEK inhibitor can overcome this problem and enhance the inhibition of the pathway and antitumour efficacy [25].

In vitro investigations using NRAS mutant melanoma cell lines have suggested that MEK inhibitors may be useful in this genetic background. A recent clinical trial using the MEK1/2 inhibitor MEK 162 in a phase II clinical trial has confirmed that advanced NRAS mutant metastatic melanoma can be successfully treated in patients. A response rate of approximately 25% was found, with a PFS similar to that observed using MEK inhibitors in BRAF mutant metastatic disease [26]. Other MEK inhibitors have been investigated in NRAS mutated melanomas with some promising results.

Until recently, most clinical trials investigating immunomodulation, chemotheraphy or targeted therapy have excluded patients with brain metastasis due to concerns about drug penetration through the blood–brain barrier and symptoms such as intracranial bleeding resulting in life-threatening consequences. Lately, the urgent need for medical treatment of this patient population led to a trend change. There are recent data [27] using the anti-CTLA-4 antibody ipilimumab at a dose of 10 mg/kg every 3 weeks for four cycles in melanoma patients with brain metastasis, with a response rate of 16% in asymptomatic and 5% in symptomatic patients. A recently reported trial [13] on dabrafenib in asymptomatic patients with BRAF-mutated melanoma and at least one measurable brain metastasis between 5 mm and 40 mm in diameter has further demonstrated clinical activity. Moreover, in a pilot study [28] of 24 symptomatic, very advanced melanoma patients with brain metastasis and harbouring a BRAF V600 mutation were treated safely and effectively with vemurafenib, improving patients’ performance status and quality of life. Further clinical trials – including combined therapies with other inhibitors, with immunotherapy and with stereotactic radiosurgery – are needed in the near future.

Both BRAF and MEK inhibitors have a very peculiar side-effect profile. As recently reported, BRAF inhibitors are characterised by activating germline mutations of RAS and lead to cutaneous side effects recently defined as RASopathic [29]. They involve both epidermis and adnexa and include inflammatory disorders such as maculopapular exanthema, follicular rash or pruritus, hair and nail changes, as well as keratinocytic proliferations such as keratosis pilaris, palmoplantar hyperkeratosis, acanthopapilloma, keratoacanthoma and squamous-cell carcinoma [30]. Melanocytic disorders and proliferations have also been observed. In particular, vemurafenib causes an important UVA-dependent phototoxicity [31] that needs adequate UV protection. Dabrafenib, on the other hand, does not seem to cause phototoxicity reactions [30]. Its most common adverse events include skin-related toxic effects, fever, fatigue, arthralgia, and headache [18].

MEK inhibitors can cause papulopustular rashes, xerosis cutis (often associated with fissured finger tips), diarrhoea, nausea, vomiting, fatigue and blurred vision [32]. Moreover, self-limiting retinopathy-like dose-dependent retinal disorders with early onset have been described [33]. Only one of the seven described patients was symptomatic. The retinal disorders were transient and resolved even during continuation of MEK therapy. However, a close monitoring of the retina with a specific mark on sub-retinal exudates is highly recommended. The cutaneous side effects during MEK inhibition are similar to those observed with epithelial growth factor receptor (EGFR) inhibitors [34]. Notably, in a recently conducted trial, cutaneous adverse events were observed in over 85% of the patients [35]. This emphasises the importance of regular dermatological follow-up examinations. Thus, regular skin examination and management by experienced dermatologists, as well as continuous prophylactic photo-protection, including a UVA optimised sun screen, are mandatory.

The combination of BRAF and MEK inhibitors interestingly seems to reduce the common cutaneous side effects [24]. The impressive progress observed with the use of kinase inhibitors is unfortunately limited by the development of resistance that is observed after 6 months on average using BRAF inhibitor monotherapy and after 9–10 months using BRAF–MEK inhibitor combination therapy. There is intensive research ongoing to understand the mechanisms behind this clinically very relevant phenomenon. Most investigations have been performed in vitro [36]. It remains unclear which resistance mechanisms are the most frequent in vivo in humans. A recent study using human melanoma xenografts in a nude mouse model has shown that melanoma cells can transcriptionally up-regulate the BRAF molecule in order to compensate the inhibition by vemurafenib. If vemurafenib is removed from the system, there is an over-stimulation of the pathway resulting in decreased proliferation, probably related to oncogene-driven senescence. As a consequence, resistance can be delayed by pulsed therapy with vemurafenib rather than continuous dosing [37]. This observation is interesting and needs to be further investigated in the clinical setting in the near future.

In contrast to BRAF mutated melanoma, the kinase inhibitor imatinib has proven efficacy in patients with advanced melanoma harbouring KIT mutations [38]. KIT mutations are found at low frequencies (<10%) in melanomas arising from mucosal or acral lentiginous surfaces [39]. As the vast majority of patients with metastatic melanoma suffer from primary tumours on glabrous skin (trunk, extremities, and head/neck), the number of patients in the metastatic setting with mutated KIT is small. Durable responses were observed in 16% of a 51-patient cohort with either mutations or amplifications in KIT [40]. In a phase II trial, in which 43 patients with KIT mutations or amplification were enrolled, 23% of patients had objective responses [41]. In both studies, certain mutations in exon 11 and 13 of c-KIT (particularly L576P mutation in exon 11) were associated with the highest response rate. In addition Nilotinib, a tyrosine kinase inhibitor used in imatinib-resistant chronic myelogenous leukaemia (CML), seems another promising agent in the treatment of KIT mutated metastatic melanoma and is currently under clinical investigation. Thus, sensitivity to KIT inhibition exists in metastatic melanoma [21] but it is confined to a subset of this already small subpopulation of patients.
After decades of standstill, progress in understanding the biology of melanomas has resulted in powerful targeted therapies with impact on progression-free and overall survival. Ongoing research is focused on resistance mechanisms and strategies to overcome them [36]. In order to further improve the outcome in this still poor-prognosis population, patients should be encouraged to participate in well-designed clinical trials.

**Conflict of interest statement**

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Immunotherapy of melanoma

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Melanoma is considered one of the immunogenic – if not the most immunogenic – malignancies. This is based on several observations.

1. Spontaneous remissions occur occasionally.
2. In about 5% of melanomas no primary tumour is found. The genetic aberrations of these tumours closely resemble those of cutaneous melanomas, and therefore are suggestive of spontaneous regressions of the primary tumours.
3. Both primary tumours and metastases often have brisk lymphocytic infiltrates, a phenomenon that is correlated with better outcome.
4. Studies of isolates of these tumour-infiltrating T lymphocytes have revealed that a proportion of these cells recognise melanoma antigens.
5. Melanomas respond to immunotherapy.

These observations have led to over 30 years of research on immunotherapy for melanoma; many of these efforts have failed, with only a few exceptions: interleukin-2 (IL-2) and to a lesser degree interferon-a (IFN-α). Recently, new developments in immunotherapy have revolutionised this treatment modality. Anti-CTLA4 has received approval from the Food and Drugs Administration (FDA) and the European Medicines Agency (EMA) for the treatment of stage IV melanomas based on the improvement in overall survival in phase III trials, and more recently blockade of PD1/PDL1 interactions has shown objective clinical responses in a stage IV melanoma in early-phase clinical trials. In addition, several independent single-institution phase I/II trials using adoptive cell therapy have shown a consistently high response rate, including durable complete remissions in a substantial percentage of treated patients.

Now, for the first time, immunotherapy has moved beyond the treatment of melanoma as both CTLA4 and PD1 blockade have been shown to induce objective responses in other tumour types as well.

This chapter will discuss the mechanism of action, clinical efficacy and side effects of IL-2, the novel treatments consisting of the immune checkpoint blockade drugs anti-CTLA4 and anti-PD1 and adoptive cell therapy.

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1. Introduction

Of all treatments for malignancies, immunotherapy has been the most extensively studied in metastatic melanoma. These often experimental, immunotherapeutic interventions can be divided into: (1) biologicals such as cytokines, including interleukin-2 (IL-2), interferons and granulocyte–monocyte colony-stimulating factor (GM-CSF); (2) vaccination strategies such as peptide vaccines, whole-protein vaccines, virus-based vaccines, DNA vaccines and dendritic-cell-based vaccines; (3) adoptive cell therapy with lymphokine-activated killer cells (LAKs), tumour-infiltrating lymphocytes (TILs), peripheral-blood-derived melanoma-specific T cells and gene-modified T-lymphocytes and (4) immune checkpoint inhibitors, including anti-CTLA4, anti-PD1 and anti-PDL1 and immune co-stimulatory molecules, including anti-CD137. These
experiments were initiated because of the observations that not only primary melanomas – especially primary superficial spreading skin melanomas, but also metastatic disease – can spontaneously regress [1]. In addition, about 5% of patients present with melanoma metastases, often lymph-node metastases, and sometimes also visceral metastases, without any sign of primary melanoma on dermatological inspection. Recently, it was shown that the genetic make-up (BRAF and NRAS mutations) of these unknown primary melanomas is very similar to that from non-chronic sun-damaged (non-CSD) skin melanomas, suggesting that the primary melanomas may have spontaneously regressed [2].

Little is known about the exact frequency of spontaneous regressions in melanoma, but it is considered to be low (around 3%), although some reviews have mentioned frequencies above 15%. In a review from 2009, describing 76 cases from 1866 and onwards, the proposed mechanisms for spontaneous regressions are thought to involve immune, endocrine, inflammatory and tumour environmental nutritional factors [3]. Although all of the above are probably involved, the focus of this review is on immune factors.

The role of lymphocytic infiltrates in melanoma was first described by Clemente et al., showing that brisk infiltration by tumour-infiltrating lymphocytes (TILs) into primary melanomas was correlated with better survival [4,5]. Later this was also shown for TILs in metastatic lesions [6], suggesting a causal role for TILs in tumour control. In addition, in the past 20 years many tumour antigens have been discovered that we now know are recognised by TILs. T cells derived from TILs were shown to recognise melanocyte differentiation antigens gp100, tyrosinase and MART-1/Melan-A. Other genes were discovered in the 1990s, such as melanoma-associated genes (MAGE) and NY-eso-1 [7–16]. In contrast to proteins that belong to the melanocyte differentiation antigens, these gene products are derived from aberrantly expressed genes by tumours, which play a physiological role during foetal development, are silenced thereafter, but are still present mainly in the testis. Thus, these genes have been named cancer/testis genes. Very recently, it was demonstrated that TILs can also recognise mutated antigens (van Rooij et al., J Clin Oncol, in press). Melanoma has the highest frequency of mutations of all cancers [17,18]. The vast majority of these mutations carry a typical ultraviolet light signature. Using next-generation DNA sequencing and RNA sequencing of tumours from paired tumour and TIL samples, many mutations that potentially carried a new T-cell epitope were found. Using major histocompatibility complex (MHC) tetramers, TILs from these tumours were screened for the presence of T cells specific for these mutated or neo-antigens. Within four tumour–TIL pairs, four mutated antigen-specific T-cell populations could be detected, some at high frequencies.

On the basis of these studies and clinical responses observed in patients treated with immunotherapy, melanoma can be considered one of the immunogenic types of cancer – perhaps even the most immunogenic cancer.

In the past 30 years many trials focusing on immunotherapy have been performed: in the early days with cytokines, combinations of chemotherapy and cytokines, peptide vaccine trials, other vaccine trials (including DNA vaccines, viral vaccines, whole-protein vaccines, tumour-cell vaccines and dendritic-cell vaccines) and adoptive cell therapy with LAK cells, melanoma-specific T-cell clones or peripheral-blood-derived melanoma-specific T cells. With the exception of high-dose IL-2, many trials failed, including the combination of chemotherapy and cytokines, the LAK cell therapy and many vaccine trials. Others showed responses in a minority of patients, some of which were very durable, but many strategies were not taken to phase III trial level because of lack of activity. In the past decade, immunotherapy has become much more successful, and ipilimumab is the first therapy to show an improvement in overall survival (OS). It is likely that also new developments such as anti-PD1/PDL1 will change the survival of patients. Adoptive cell therapy has become a potent therapy and will hopefully be investigated in randomised controlled trials (RCTs) as well. This review focuses on the therapies that have impacted on the lives of stage IV melanoma patients.

2. Clinical immunotherapy of metastatic melanoma

2.1. Immunotherapy by infusional high-dose IL-2 boluses

High-dose interleukin-2 was tested in murine models of sarcoma and melanoma and shown to lead to regression of established transplantable pulmonary metastases and subcutaneous tumours. The idea was that infusion of high-dose IL-2 led to the activation of lymphocytes, generating lymphokine-activated killer cells in vivo, since infusion of in vitro activated lymphocytes was highly active in murine tumour models. In 1985, based on the observations in mouse models, the first patients with metastatic cancer (mostly melanoma) were treated with purified IL-2, given as bolus infusions intravenously (i.v.) every 8 h. In some patients with melanoma objective partial clinical responses were seen [19]. Toxicity in these patients consisted of fever, chills and gastrointestinal tract symptoms such as nausea and diarrhoea, hypotension, severe weight gain, anaemia, leucocytopenia and thrombocytopenia [20]. In Europe, studies with continuous high-dose IL-2 i.v. infusion led to even more toxicity; many patients required admission to the intensive care unit (ICU) and some patients succumbed to this treatment. In many studies, especially in patients with either metastatic melanoma or metastatic renal cell carcinoma, lower doses of IL-2 have been tested. Although clinical responses were observed in a minority of patients, the durability of these responses has been short. On the basis of consistent achievement of durable complete remissions in 5–10% of patients with high-dose bolus IL-2 infusions in phase II trials, this treatment was Food and Drugs Administration (FDA)-approved for the treatment of metastatic melanoma in 1998, because of an unmet need in this patient population [21]. High-dose IL-2 still is one of the treatment options for stage IV melanoma (and for metastatic renal-cell carcinoma) in the United States (US). In particular, patients with good performance status and M1a or M1b disease may benefit from this treatment. In Europe, high-dose IL-2 for these indications has not been approved and is therefore hardly used.
High-dose bolus IL-2 is given in a dose of 600,000–720,000 IU/kg as an i.v. bolus (15 min infusion), every 8 h for no more than 15 boluses, followed by about 10 days of rest, followed by another 15 infusions. This is considered one course. Patients are followed every 2–4 months for prolonged periods of time.

The exact mechanism of action of high-dose IL-2, despite its presence in the clinic for over 20 years, remains elusive. IL-2, discovered as a T-cell growth factor in 1976 [22], is a 133-amino-acid protein which binds to the IL-2 receptor (IL-2R) present on T cells, B cells and NK cells. The IL-2R can consist of two or three chains, the IL2Rα, IL-2Rβ and IL-2Rγ chains. The IL-2Rα and β chains form the low-affinity IL-2R and all three chains form the high-affinity IL-2R. Both receptors can deliver signals upon binding IL-2. Since the IL-2R is widely expressed on cells from the adaptive immune system, the presence of IL-2R (on subpopulations of cells) is not a predictive biomarker for response to treatment. In fact, so far no biomarker of response has been found for high-dose IL-2 treatment. Recently, in a retrospective study, a non-statistically greater objective response rate was found for patients with melanomas harbouring an NRAS mutation (compared to BRAF mutation or wild-type tumours) [23]. Wang et al. studied the molecular patterns associated with response to treatment and observed that high-dose IL-2 has immense impact on gene profiles of peripheral-blood mononuclear cells (PBMCs), while the molecular changes within the tumours were small and differed between lesions [24]. Analyses of transcriptional profiles pre- and post-treatment with high-dose IL-2 in PBMCs did not reveal a statistically significant signature. Interestingly, within the same tumours analyses on pre- and post-fine-needle aspirates did not show important changes within genetic profiles; however, an immune response signature present pre-treatment was associated with better prognosis: complete remission (CR), partial remission (PR) and stable disease SD versus progressive disease PD. These results suggest that response to immune therapy with IL-2 is predetermined and can be measured by the presence of an immune response genetic signature within the tumour. However, the study was small, and validation in a larger study is warranted before gene profiling can be used to select patients for high-dose IL-2 treatment.

Clinical biomarkers that are associated with response result from pooled retrospective analyses of metastatic melanoma patients treated with high-dose IL-2 in several trials. Durable responses were almost only observed in patients with Eastern Cooperative Oncology Group (ECOG) 0–1 performance status and pulmonary, lymph-node and subcutaneous metastases (M1a and M1b) [25].

Despite the lack of knowledge on the mechanism of action of high-dose IL-2, this treatment remains one of few that gives rise to durable CRs. Probably a large proportion of these CRs are cured from melanoma [26].

In the past years, IL-2 has been combined with other therapies. These combined modalities consisted of IL-2 with or without gp100 peptide vaccination [27], IL-2 combined with stereotactic radiotherapy (RT) [28], IL-2 combined with anti-CTLA4 antibody ipilimumab [29] and IL-2 combined with infusion of ex vivo expanded tumour-infiltrating lymphocytes [30]. The only randomised controlled study was performed by Sch-wartzentruber et al., which illustrated an improved response rate and progression-free survival for the combined modality arm consisting of gp100 peptide vaccine + high-dose IL-2 compared with high-dose IL-2 alone [27]. Combinations of stereotactic RT and IL-2 or ipilimumab and IL-2 were tested in small single-arm phase I/II studies [28,29]. Both combinations showed an unexpectedly high response rate, including complete remissions.

Taken together, high-dose IL-2 has been the oldest approved form of immunotherapy for metastatic melanoma. Despite the development of new immunotherapies, high-dose IL-2 remains a valid treatment option, especially in the US.

### 2.2. Immunotherapy by immune checkpoint blockade

For T-cell activation a dual signalling step is required. The first essential step is binding of the T-cell receptor to its cognate antigen, the major histocompatibility complex (MHC) peptide complex presented by antigen-presenting cells (APCs). The second step is binding of the co-stimulatory molecule CD28 to CD80/CD86 (B7.1/B7.2) on the APC. The combined signalling leads to full T-cell activation, resulting in up-regulation of IL-2 and IL-2R gene expression and cell division. Next to CD28, T cells also express cytotoxic T-lymphocyte antigen-4 (CTLA4), a co-inhibitory molecule, which binds the same ligands as CD28 but with higher affinity [31,32]. Due to differences in both spatial and temporal expression of CD28 and CTLA4, CTLA4 will appear at the cell surface later during the immune response and will then out-compete CD28 signalling [33]. Signalling through CTLA4 will stop IL-2 and IL-2R gene transcription and cell proliferation. Its key role as a regulator of immune responses was well established in CTLA4-deficient mice that, upon exposure to environmental antigens after birth, develop a severe and lethal lymphoproliferative disease due to uncontrolled and persistent T-cell activation, proliferation and infiltration in peripheral tissues [34]. Blockade of CTLA4 signalling by monoclonal antibodies has demonstrated anti-tumour activity in murine models. In the case of immunogenic tumours, single-agent CTLA4 blockade was enough to induce tumour shrinkage, whereas in other models anti-CTLA4 synergised with other treatment modalities to induce efficacious antitumour immune responses (reviewed in [35]). In the B16 melanoma model, the combination of vaccination with irradiated GM-CSF gene transduced tumour cells and CTLA4 blockade was successful in eradicating the tumour [36]. These animals developed autoimmune depigmentation or vitiligo, which was dependent on CD8 T cells, indicating breaking of immune tolerance in these animals. CTLA4 is expressed not only by CD8 T cells, but also by CD4 T cells and even high by CD4 FoxP3 regulatory T cells. Whether anti-CTLA4 works through the blockade of CTLA4 on CD4 and CD8 T cells, or through another mechanism involving regulatory T cells, has still not been revealed [37].

Two fully human monoclonal antibodies were developed for use in humans, ipilimumab (MDX-010) and tremelimumab (CP-675,206). Ipilimumab was the first monoclonal antibody to be tested in patients with metastatic melanoma [38]. In these early studies, which enrolled only a few patients, tumour regressions and autoimmune adverse events were observed.
Ipilimumab was tested in a classical dose-escalating phase I trial [39]. Comparable to ipilimumab, tremelimumab also leads to tumour regression, and also to uncommon toxicities, including dermatitis, colitis, hepatitis and hypophysitis, indicating that immunological tolerance was broken in some patients treated with CTLA4 blockade. Originally, an association between the incidence of immune-related adverse events and clinical response were thought to be present [40]; however, this could not be confirmed in the randomised controlled trials that have been performed with these agents. Ipilimumab was studied in two randomised controlled trials [41,42]. The first trial was a second-line study in stage IV melanoma; 676 HLA-A*0201-positive patients were randomised in a 3:1:1 ratio between the combination of ipilimumab and gp100 vaccine, ipilimumab (+ placebo) and gp100 vaccine (and placebo). In this study ipilimumab was given in a dose of 3 mg/kg every 3 weeks four times. The primary endpoint of the study was overall survival. With a median follow-up of between 17 and 28 months, a statistically significant difference in median survival was observed in both ipilimumab arms (10.0 and 10.1 months) compared to gp100 vaccine alone (6.4 months). The objective response rate for ipilimumab plus vaccine was 5.7% and for ipilimumab alone 10.9% compared with 1.5% for the gp100 vaccine group.

At 3 years, 20.8% of patients in the ipilimumab arm were still alive compared with 12.2% in the DTIC alone arm. In 56.3% of patients grade 3–4 adverse events were observed. Whereas in 11.2 months (compared with 9.1 months). In 56.3% of patients grade 3–4 adverse events were observed, 10–15% of the patients, and seven deaths (1%) were associated with immune-related side effects. Although preclinical data and an early clinical trial suggested synergy between gp100 vaccine and CTLA4 blockade [38], this could not be confirmed in this large RCT. Based on the statistically significant improvement in overall survival, ipilimumab was approved as first- (US) or second-line (European Union (EU)) treatment for patients with stage IV melanoma. In the second phase III trial ipilimumab combined with dacarbazine was compared with dacarbazine alone. Here ipilimumab was given in a dose of 10 mg/kg every 3 weeks four times, followed by maintenance every 3 months.

Comparably to the second-line ipilimumab trial, this trial also found a statistically significant improvement in overall survival in the patients treated with ipilimumab plus DTIC (11.2 months) compared with DTIC plus placebo (9.1 months). At 3 years, 20.8% of patients in the ipilimumab arm were still alive compared with 12.2% in the DTIC alone arm. In 56.3% of patients grade 3–4 adverse events were observed. Whereas in the MDX-010-20 trial gastrointestinal adverse events were most frequent, only 36% of patients received in the second trial all four doses of ipilimumab treatment, mostly because of liver toxicity. This unexpected observation of hepatotoxicity was attributed to the combination of DTIC plus ipilimumab. Hence, the combination of DTIC plus ipilimumab is not recommended.

Tremelimumab was tested in a classical phase I design and the recommended dose for phase II studies was 15 mg/kg every 3 months [43]. Subsequently tremelimumab was studied in a randomised controlled phase III trial in stage IV melanoma patients as first-line therapy compared with dacarbazine [44]. Although a trend towards improved overall survival was seen in this study, this difference was not statistically significant. In part this may have been due to the fact that patients with lactate dehydrogenase levels more than twice the upper limit of normal were excluded from the study, whereas these patients were included in the ipilimumab pivotal trials. Therefore, the survival in the control arm may have been better and the difference in overall survival (OS) between the two arms smaller. In addition, at least 16% of patients in the dacarbazine arm were treated with ipilimumab upon failure, which may also have contributed to a better OS in the control arm. Patients with an objective response to tremelimumab had a considerably longer duration of this response (35.8 months) compared with patients responding to dacarbazine (13.7 months).

Recently, in a series of 752 patients who were treated with ipilimumab for stage IV melanoma, 120 adverse events were described [45]. These adverse events ranged from drug reactions – sometimes severe and accompanied with eosinophilia and systemic symptoms (DRESS syndrome), small bowel perforation, ischaemic gastritis, hepatitis, pancreatitis, nephritis, hypophysitis, aseptic meningitis, alveolitis and even cardiac fibrosis. Others had already described rare conditions such as Guillain–Barré syndrome and sarcoidosis [46,47]. Algorithms have been developed to treat patients that develop adverse events. Most patients will require immediate corticosteroid therapy, and sometimes other immunosuppressive agents such as infliximab in the case of severe colitis that does not respond promptly to high-dose steroid therapy, and mycophenolate mofetil or even anti-thymocyte globulin (ATG) in the case of fulminant hepatitis.

In summary, CTLA4 blockade is an aspecific immunotherapeutic strategy which was the first therapy to show a statistically significant improvement in median overall survival in melanoma in two phase III trials. About 20–25% of patients will experience durable, mostly partial remissions, some even complete remissions. Ipilimumab is the only approved immunotherapeutic drug. Toxicity of ipilimumab occurs in about 50–70% of patients, with 10–20% being serious, mostly immune-related adverse events. Preferably, ipilimumab should be administered to patients by experienced clinicians. Ipilimumab has been approved for first- or second-line therapy in the US and as second-line treatment in Europe. Patients with absolute lymphocyte count >1 x 10^9/L or with an increase in ALC at the second infusion are more likely to benefit [48,49]. However, validated predictive biomarkers are still lacking.

Next to CTLA4, programmed death-1 (PD1) protein is another cell-surface molecule that has inhibitory properties [48,49]. In contrast to CTLA4, PD1 expression is involved in inhibition of T cells in peripheral tissues during inflammation [37,50]. Upon activation, PD1 is expressed on CD4+ and CD8+ T cells and B cells, which results in the inhibition of e.g. T-cell-receptor- (TCR-)mediated signalling, probably through activation of phosphatase SHP2 [51]. The ligands of PD1 are PD-L1 (B7-H1) and PD-L2 (B7-CD) on APCs [52]. However, PD-L1 expression may also be induced on tumour cells [53,54]. Interaction between PD1-positive T cells and PD-L1-expressing tumour cells was therefore suggested to hamper proper T-cell function and appears to be one of the immunosuppressive mechanisms executed by tumours to escape an initially ongoing immune control [54,55]. Similarly to CTLA4 expression on
3. Immunotherapy by adoptive cell therapy

3.1. Tumour-infiltrating lymphocytes (TILs)

In the 1980s, adoptive cell therapy was tested in clinical trials based on the observation in murine models that infusion of in vitro IL-2-activated lymphocytes was highly effective in the eradication of tumours. The infusion of these so-called lymphokine-activated killer (LAK) cells in melanoma patients was compared with high-dose IL-2 alone and was not shown to be statistically significantly superior in response rate, progression-free survival or other outcomes of the trial [59]. It took until early 2000 before the infusion of T cells led to impressive response rates in substantial numbers of patients with metastatic melanoma. Dr. S. Rosenberg and colleagues showed that infusion of in vitro cultured TILs derived from a large melanoma metastasis was able to induce regression of bulky metastatic disease and even complete remissions in some patients [30, 60]. From previous experiments and mouse models, it became apparent that prior depletion of host lymphocytes greatly improved the in vivo survival of the infused TILs, and a short in vitro culture time was important for survival, in vivo expansion and efficacy. Based on these observations, heavily pre-treated metastatic melanoma patients were treated with lympho-depleting chemotherapy, consisting of high-dose cyclophosphamide and fludarabin, followed by infusion of large numbers of TILs (around $1 \times 10^{11}$ cells) followed by bolus infusion of high-dose IL-2 (up to 15 boluses) [30, 60]. This conditioning regimen results in short but deep leukopaenia, including neutropenia and lymphopaenia, but is non-myeloablative and thus does not require peripheral haematopoietic stem cell (HSC) support. Mouse models showed that depletion of the lymphocytic compartment not only results in the creation of physical space for the infused TILs, but also results in much less competition from host lymphocytes for the homeostatic cytokines IL-7 and IL-15, giving a head start to the infused cells [61]. Secondly, lympho-depletion also diminishes the immunosuppressive cell populations, such as regulatory T cells from the circulation. Based on the results from the first trial, in later studies lympho-depleting regimens were intensified to combination of chemotherapy with total body irradiation (TBI) up to 12 Gy [62]. Naturally, this heavy conditioning regimen necessitated bone-marrow rescue by HSC support. In small phase I/II studies each with 25 patients, escalation of TBI combined with cyclophosphamide plus fludarabin resulted in further improvement in response rates to up to 72%, with 10–20% of patients acquiring a durable complete response. Not surprisingly, the treatment was harsher on the patients, resulting in more acute adverse events and prolonged organ dysfunction [62]. In the early studies cultured TILs were selected for reactivity against autologous melanoma cell lines, and if not present HLA-matched allogeneic melanoma cell lines. The
process of selection, however, required extra culture time, since the final dose of infused T cells was around $1 \times 10^{11}$ cells. In subsequent studies, this selection step was deleted from the protocol, which simplified the production process substantially. Importantly, this did not harm the objective response rate, which remained around or above 50%, including the occurrence of complete responses [63]. The simplified protocol of non-selected TILs was subsequently adopted by several laboratories in the US and in Israel [64–66]. By now several studies using this protocol, but without the addition of TBI to the non-myeloablative chemotherapy regimen, have shown a highly consistent objective response rate of 40–50% of treated patients. In order to widely distribute TIL treatment over Europe, a randomised controlled trial is required.

### 3.2. Gene-modified T cells

Because TIL therapy is not always feasible, and because of the complexity of the treatment, alternatives for adoptive cell therapy with TILs have been developed. One of the most promising new strategies is the use of tumour-specific antigen receptors [67]. These tumour-specific receptors can be derived from a tumour-specific T-cell clone with a high-affinity T-cell receptor (TCR) that recognises a human MHC/tumour-derived peptide complex, or from a high-affinity antibody specific for a cell-surface tumour antigen. These antibody-based receptors, called chimeric antigen receptors (CARs), are genetically fused to proteins of the T-cell receptor signalling machinery (CD3ζ, CD28 and others), so that T lymphocytes genetically changed to express these receptors upon antigen binding will be properly activated [68].

For the genetic transfer of TCR or CAR genes to T cells several options exist; however, the most widely used is transfer by retroviral infection. These retroviruses and lentiviruses are genetically modified to contain the genes for a specific CAR/TCR. In addition, these viruses have been crippled to prevent replication. Upon infection of the T lymphocytes these viruses place the genes encoding the CAR/TCR more or less randomly into the host-cell genome. Thus, these receptors can be genetically transferred into peripheral-blood T lymphocytes, thereby creating an army of tumour killer cells.

So far tumour-specific T-cell receptors have been used only for diseases other than melanoma; for example, a high-affinity CD19 binding antibody has been used successfully in B-cell lymphomas/leukaemia [69–71].

For melanoma, patients have been treated with TCR-transduced T cells specific for MART-1, NY-eso-1 and more recently also for MAGE-A3 [72–75]. In all three trials, objective responses have been observed. So far, gene therapy with the NY-eso-1-specific TCR was most effective and safest. In the trials with the MART-1-specific TCR, a substantial portion of patients developed off-target toxicity due to T-cell attack on MART-1-positive cells in the body, leading to severe dermatitis and vitiligo, uveitis and hearing loss (Kogt–Koyanagi–Harada disease). In most instances these side effects were transient and responsive to topical corticosteroids.

Apart from off-target toxicity – which is more likely to occur for TCRs specific for over-expressed gene products or differentiation antigens, as normal tissues often also express these antigens – off-target toxicity is another potential danger of this treatment. The most important reason for this type of toxicity is cross-reactivity of the introduced TCR with an unknown antigen. Since TCRs recognise MHC peptide complexes, and since most individuals have six different MHC class I alleles, the chance of a TCR having affinity for one of these plus an unknown peptide is not just theoretical. Choice of target and knowledge about tissue expression of the antigen for which the TCR is specific is going to be crucial.

Taken together, adoptive cell therapy is still at the level of early clinical trials; however, the efficacy of this treatment is promising, with establishment of durable remissions in some patients. With more centres performing these trials, the experience with this complex therapy is rapidly increasing. Therefore, this treatment should be taken to the next level: randomised controlled trials.

### 4. Conclusion

In conclusion, immune therapy of melanoma is by 2013 an established and expanding strategy that can induce durable responses in advanced-stage melanoma patients, some of whom may be cured for life. Immunotherapy, however, comes with a price. New and unexpected toxicities may develop during the course of the treatment or after cessation of treatment and requires experience in order to properly manage these therapies. In addition, these therapies are costly and sometimes highly complex (TIL and TCR/CAR gene therapy). Therefore research focused on finding biomarkers that predict response to treatment, such as PDL1 tumour expression for response to anti-PD1, will be one of the most important challenges for the coming years.

Apart from immunotherapy as a novel treatment option for patients with stage IV melanoma, targeted therapy has also recently changed the outcome of these patients. Drugs such as vemurafenib, dabrafenib and trametinib have been shown to prolong survival of metastatic melanoma patients harbouring the common BRAF V600 mutation. With all these new therapies now available, studies on selecting the best patient population for each therapy, and on the optimal sequence of treatments, will be key to most effectively prolonging the lives of metastatic melanoma patients, also on the use of these therapies in the most cost-effective manner.

### Conflict of interest statement

None declared.

### REFERENCES


Adjuvant therapy for high-risk melanoma

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Thus far the development of adjuvant therapies in melanoma has suffered greatly from the lack of effective drugs for stage IV melanoma. This has led to adjuvant therapies that are not uniformly used because of rather marginal benefits.

1. Adjuvant therapies other than with interferon

1.1. Early trials with immune stimulants

More than 25 randomised trials have been conducted in stage II/III melanoma with non-specific immune stimulants – such as BCG (bacillus Calmette–Guerin), Corynebacterium parvum, levamisole or combinations of these agents with dacarbazine – without identifying clear benefits [1].

1.2. Adjuvant vaccine trials

Adjuvant vaccine trials in melanoma thus far have failed, results ranging from ineffective (three randomized controlled trial (RCTs) [1]) to harmful (three RCTs [2–4]). Two large trials with Canvaxin ended early because of a detrimental outcome for the vaccine arm. Two large trials with the GMK vaccine (ganglioside GM2/KLH/QS-21) were also stopped early because of inferior outcome in the vaccine arms compared with high-dose interferon (HDI) in the Eastern Cooperative Oncology Group (ECOG) 1694 trial [3] and compared with observation in stage II patients (European Organisation for Research and Treatment of Cancer (EORTC) 18961 trial) [4], evoking fears that prolonged, multiple administrations of vaccines could be harmful [5].

Regarding the adjuvant use of granulocyte-monocyte colony-stimulating factor (GM-CSF), a recent report of the ECOG E4697 trial failed to demonstrate a significant impact on survival [6]. In two randomised trials the GM-CSF-containing arms did worse than the vaccine-alone arms [7,8], again indicating that multiple vaccinations might be harmful.

New vaccine trials are ongoing. The MAGE-A3 protein combined with the immunostimulant AS15 is being evaluated in an RCT in stage III patients after encouraging results were obtained in a randomised phase II EORTC trial [9]. Moreover, a potentially predictive gene profile, characterising mostly immunomodulatory factors, is used to stratify and analyse the results of the RCT [10]. Also a study of an oncolytic herpes simplex virus vector encoding GM-CSF is ongoing in stage III/IV patients after interesting results in phase II patients were obtained [11,12].

1.3. Adjuvant therapy with interferon

Twenty-five years of RCTs in melanoma with interferon-alpha (IFNα) are a testimony that efficacy of adjuvant therapy with IFN is modest at best. Meta-analyses of phase III trials demonstrated that IFN has a consistent effect on relapse-free survival (RFS) but no or only a marginal effect on overall survival (OS) [13–15]. No relationship between dose or duration of treatment and outcome has been demonstrated. These findings suggest that only a minority of patients are sensitive to IFN, and demand that we identify these patients. Based on the EORTC 18991 trial in 1256 patients, the US Food and Drug Administration (FDA) approved pegylated interferon α-2b (PEG-IFN; Sylatron™) in 2011 for stage III melanoma patients [16]. The EORTC 18952 trial in 1388 stage IIB/III melanoma patients compared intermediate doses of interferon α-2b (IFN) with observation [17].

These EORTC RCTs stratified patients by SN-staging (microscopic involvement only: stage III-N1) or gross macroscopic relapse (stage III-N2) as well as by presence or absence of ulceration in the primary tumour. Both stage and ulceration are key prognostic factors [32]. Patients with only micrometastases have a much better prognosis than patients with palpable node metastases [18]. Palpable nodal disease may represent more aggressive disease from the onset or by acquisition of additional mutations over time. Regarding ulceration, for the same Breslow thickness, patients with an ulcerated primary have a 10–25% lower survival probability at 10 years, indicating a distinct biological entity [19]. Also, ulcerated primaries have (a) a distinct gene profile [20]; (b) a severely immunosuppressed status of sentinel nodes [21] and (c) a different stromal response [22].

The meta-analysis of the two largest adjuvant IFN/PEG-IFN RCTs involving 2644 patients demonstrated that both tumour load in the lymph nodes and ulceration of the primary are independent predictive factors for adjuvant IFN therapy [23]. Patients with favourable stage (IIb/III-N1) and/or ulcerated primary tumour benefited significantly from IFN/PEG-IFN treatment (hazard ratios (HRs) 0.56–0.69) with regard to RFS,

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For patients with advanced stage III melanoma, a double-blind RCT comparing adjuvant ipilimumab versus placebo recently collected accrual of 950 patients (EORTC 18071; ClinicalTrials.gov, number NCT00636168) [31]. Preliminary data from another small trial suggest adjuvant ipilimumab activity in advanced resected stage III/IV disease [32]. New adjuvant trials evaluating anti-PD-1 are being prepared.

2.2. BRAF inhibitors and MEK inhibitors

New adjuvant trials in lymph-node-positive melanoma patients have been launched involving BRAF inhibitors either alone or in combination with MEK inhibitors [33,34]. The basis for these trials is their success in stage IV patients. Trials are ongoing, and design and pros and cons will be discussed.

Conflict of interest statement

None declared.

REFERENCES


Introduction

Optimal approach for upfront resectable non-small-cell lung cancer

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Approximately one third of patients with non-small-cell lung cancer (NSCLC) present with resectable disease, defined as clinical stages I and II and some borderline stage III extensions (e.g. T3N0–1). Although radical resection is the cornerstone of treatment in adequately staged patients, its outcome is not always curative, as some patients might be functionally inoperable, refuse surgery, have an unexpected non-radical resection or stage upgrading, or relapse locally or with distant metastases. The following reviews address the current state of the art in the peri- and intra-operative management of patients with resectable NSCLC.

As disease extent is an important predictor of prognosis and determines treatment choices, accurate staging is of prime importance. The 10 modifications and the mediastinal lymph-node map – adopted by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) in their respective seventh revision of the tumour-node-metastasis (TNM) system – are considered a quality indicator for disease extent, initial treatment allocation and the reporting of treatment results. Difficulties arise in accurate prognosis owing to the role of stage migration and the increasing number of biological factors interfering with disease extent. There are many tumour-related pathological factors, but only one is actually routinely used in clinical practice. Most factors probably lack potential clinical usefulness.

Surgical resection remains the standard of care for functionally operable early-stage NSCLC and resectable stage IIIA disease. The role of invasive staging and restaging techniques is currently under debate, but they provide large biopsy specimens which allow for precise mediastinal staging. Different operative procedures are currently available to the thoracic surgeon, and some can be performed by video-assisted thoracic surgery (VATS) with oncological results equal to those of open thoracotomy.

The new multidisciplinary adenocarcinoma classification has profound surgical implications. The role of limited or sublobar resection comprising anatomical segmentectomy and wide wedge resection are considered for early-stage lesions which are more frequently encountered with the recently introduced screening programmes. Large databases are currently collecting many surgical parameters, allowing more precise calculation of mortality and morbidity according to predefined risk factors. Centralisation of care has been shown to improve results. Quality-of-life evaluation is becoming increasingly important and should be considered when deciding on a specific treatment, especially in a multimodality setting.

In the situation of totally resected NSCLC patients, the role of post-operative chemotherapy is now established for stages II and IIIA and remains debatable in stage IB. Various attempts to identify prognostic biomarkers for selecting patients for adjuvant chemotherapy have failed so far. Patient selection for adjuvant therapy should be based upon more discriminatory pathological data than a crude assessment such as stage, but only if supported by evidence. The present recommendations for resected NSCLC from the European Society for Medical Oncology (ESMO) are to deliver a cisplatin-based chemotherapy for stages II and III. The role of post-operative radiation therapy (PORT) in this group of patients remains controversial. In a meta-analysis, the conclusions were that PORT was detrimental to patients with early-stage completely resected NSCLC, but the role of PORT in the treatment of tumours with N2 involvement was unclear, and further research was warranted. Recent retrospective and non-randomised studies – as well as subgroup analyses of randomised trials evaluating adjuvant chemotherapy – provide evidence of possible benefit of PORT in patients with mediastinal nodal involvement.

In summary, these are exciting times for the treatment of early-stage lung cancer as prevalence, classification, staging and treatment have changed, although proof of better outcome has still to be delivered.

Conflict of interest statement

None declared.
Surgical treatment of early-stage non-small-cell lung cancer

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Surgical resection remains the standard of care for functionally operable early-stage non-small-cell lung cancer (NSCLC) and resectable stage IIIA disease. The role of invasive staging and restaging techniques is currently being debated, but they provide the largest biopsy samples which allow for precise mediastinal staging. Different types of operative procedures are currently available to the thoracic surgeon, and some of these interventions can be performed by video-assisted thoracic surgery (VATS) with the same oncological results as those by open thoracotomy. The principal aim of surgical treatment for NSCLC is to obtain a complete resection which has been precisely defined by a working group of the International Association for the Study of Lung Cancer (IASLC). Intraoperative staging of lung cancer is of utmost importance to decide on the extent of resection according to the intraoperative tumour (T) and nodal (N) status. Systematic nodal dissection is generally advocated to evaluate the hilar and mediastinal lymph nodes which are subdivided into seven zones according to the most recent 7th tumour-node-metastasis (TNM) classification. Lymph-node involvement not only determines prognosis but also the administration of adjuvant therapy.

In 2011, a new multidisciplinary adenocarcinoma classification was published introducing the concepts of adenocarcinoma in situ and minimally invasive adenocarcinoma. This classification has profound surgical implications. The role of limited or sublobar resection, comprising anatomical segmentectomy and wide wedge resection, is reconsidered for early-stage lesions which are more frequently encountered with the recently introduced large screening programmes. Numerous retrospective non-randomised studies suggest that sublobar resection may be an acceptable surgical treatment for early lung cancers, also when performed by VATS.

More tailored, personalised therapy has recently been introduced. Quality-of-life parameters and surgical quality indicators become increasingly important to determine the short-term and long-term impact of a surgical procedure. International databases currently collect extensive surgical data, allowing more precise calculation of mortality and morbidity according to predefined risk factors. Centralisation of care has been shown to improve results. Evidence-based guidelines should be further developed to provide optimal staging and therapeutic algorithms.

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1. Introduction

Thoracic surgery remains a major diagnostic and therapeutic modality for patients with non-small-cell lung cancer (NSCLC). However, many controversial issues remain regarding its precise role and application. Invasive staging and restaging procedures are applied more selectively with the introduction of endosonographic techniques. When discussing the different types of operative procedures that are available to the thoracic surgeon, a distinction has to be made between early-stage disease (stages IA/B and IIA/B), locoregionally advanced disease (stages IIIA/B), and metastatic disease (stage IV). Indications for surgical treatment of NSCLC are tailored according to the most recent 7th tumour-node-metastasis (TNM) classification, taking into account that surgery for locoregionally advanced disease remains a highly controversial topic. Intraoperative staging of lung cancer is extremely important to determine the extent of resection according to the intraoperative tumour (T) and nodal (N) status. Systematic nodal dissection is generally advocated to determine the precise nodal involvement. In 2011, a new adenocarcinoma classification was published with adenocarcinoma in situ and minimally invasive adenocarcinoma as new categories. The surgical implications of this relate mainly to the role of limited, sublobar resection. Especially when part of a combined modality regimen, surgical resection has a profound influence on quality of life. Prospective data on short- and long-term effects have recently become available, allowing better counselling of our patients.

In this review invasive mediastinal staging and restaging are discussed, as well as indications for surgical resection, intraoperative staging, the new adenocarcinoma classification and its surgical implications, quality of life after lung resection, and finally surgical quality indicators, including the relationship between volume and outcome.

2. Invasive mediastinal staging and restaging of lung cancer

2.1. Importance of lymph-node staging

In the absence of distant metastases, the prognosis of a patient with lung cancer largely depends on locoregional lymph-node involvement. Pathological staging remains the gold standard in quantifying the extent of locoregional and mediastinal lymph-node involvement. Patients with ipsilateral hilar or intrapulmonary lymph-node metastases (N1) are not precluded from surgery as complete resection provides a good long-term outcome when combined with adjuvant chemotherapy. Patients with ipsilateral mediastinal lymph-node metastases (N2) are currently treated with combined modality therapy, mostly chemoradiation. Only patients with limited N2 disease, in whom down-staging is obtained after induction therapy, may be considered for surgical resection. Patients with contralateral mediastinal or supraclavicular lymph-node involvement (N3) are currently considered unsuitable candidates for surgery due to poor long-term prognosis with multimodality therapy, including surgery.

Currently available invasive staging techniques are summarised in Table 1. Due to refinements in non-invasive and minimally invasive, endosonographic staging techniques, the role of surgical invasive staging and restaging has been redefined.

2.2. Invasive mediastinal staging

Mediastinoscopy was introduced by Carlens in 1959 as a method for inspection and tissue biopsy in the superior mediastinum; it still holds true today [1]. With the routine use of mediastinoscopy, the rate of exploratory thoracotomies could be drastically reduced. Mediastinoscopy is associated with low morbidity (2%) and low mortality (0.08%) but remains an invasive procedure requiring general anaesthesia [2]. With the subsequent advent of new imaging techniques – initially computed tomography (CT), later on positron emission tomography (PET) and integrated PET–CT followed by the minimally invasive endosonographic techniques, endoscopic ultrasound (EUS) and endobronchial ultrasound (EBUS) – the precise role of mediastinoscopy is a matter of constant debate.

The different staging techniques that belong to the surgical armamentarium are listed in Table 1. Comparison of mediastinal lymph-node stations that can be reached by endosonography and invasive surgical staging is given in Table 2. Mediastinoscopy provides a thorough exploration of the superior mediastinum, allowing not only large biopsy samples of the different nodal stations in the superior mediastinum, but also evaluation of possible mediastinal extension of a primary lung cancer. In this way, sufficient tissue becomes available for detailed molecular analysis.

Anterior mediastinoscopy, which is called anterior mediastinotomy when a rib cartilage has to be removed, provides access to the anterior mediastinum and lymph-node stations 5 and 6 on the left side. Some centres have experience with extended mediastinoscopy which is a combination of cervical and anterior mediastinoscopy by the same cervical incision [3]. Also evaluation of the supraclavicular lymph-node station 1 is possible by the latter incision. In many centres anterior mediastinoscopy is now replaced by thoracoscopy or video-assisted thoracic surgery (VATS), allowing a complete exploration of the ipsilateral pleural cavity.

The reported positive predictive value (PPV) and negative predictive value (NPV) of mediastinoscopy for staging of NSCLC are 100% and 96%, respectively [4]. When an extensive lymph-node dissection is performed by video-assisted medi-

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astinal lymphadenectomy (VAMLA) or transcervical extended mediastinal lymphadenectomy (TEMLA) procedures, the rate of false negatives becomes extremely low [5–7].

Combination of EBUS and EUS – so-called ‘medical mediastinoscopy’ – provides access to a larger number of lymph-node stations than classical cervical mediastinoscopy. Both EBUS and EUS can be performed under local anaesthesia, which is a major advantage. Rapid on-site examination (ROSE) by the pathologist definitely increases accuracy. When a positive result is obtained, surgical invasive staging is avoided. For this reason EBUS and EUS are currently the preferred examinations after non-invasive tests, and in experienced hands a high accuracy is reported.

In the randomised Assessment of Surgical Staging versus Endosonographic Ultrasound in Lung Cancer: a Randomized Clinical Trial (ASTER) study, 241 patients with resectable, suspected or proven NSCLC, in whom mediastinal staging was indicated on the basis of CT or PET findings, were enrolled into a randomised controlled multicentre study comparing different strategies for mediastinal lymph-node staging [8]. Nodal metastases were found in 35% by surgical staging alone, 46% by endosonography (EBUS and EUS) and 50% by endosonography followed by surgical staging. NPVs were 86, 85 (P = 0.47) and 93% (P = 0.18), respectively [8].

In a prospective study of 153 patients, Yasufuku and colleagues chose EBUS as the initial investigation for mediastinal lymph-node staging followed by mediastinoscopy [9]. If both were negative, a thoracotomy was performed. Prevalence of N2/N3 disease was 35%. EBUS had an NPV of 91% and mediastinoscopy of 90%, so the conclusion of this study was that EBUS may replace mediastinoscopy. In a recent retrospective study from the same centre, the sensitivities and NPVs of EBUS in evaluating clinical N0 or N1 disease were 76% and 96%, respectively [9]. The role of endobronchial ultrasound-guided transbronchial needle aspiration for differentiating stage I from stage II lung cancer: poster presentation at the 49th Annual Meeting of the Society of Thoracic Surgeons, Los Angeles, California, January 26–30, 2013. However, it should be mentioned that this group comprises thoracic surgeons having a large experience with endosonographic and invasive staging techniques. Can these results from a high-volume dedicated centre be duplicated in everyday practice?

Cerfolio published a retrospective review of 234 patients with NSCLC who were staged by EBUS or EUS for suspected N2 disease on CT or PET–CT [10]. Mediastinoscopy was performed when EBUS/EUS were negative. NPVs for detecting N2 disease by EBUS, EUS and mediastinoscopy were 79%, 80% and 93%, respectively. EBUS was found to be falsely negative in 28%, and EUS in 22% of the cases. In a retrospective study from a single institution by Defranchi, 494 patients, suspected of lung cancer, underwent EBUS [11]. A negative result was followed by mediastinoscopy. Of the patients with suspicious mediastinal lymph nodes, 28% still had N2 disease confirmed by mediastinoscopy despite a negative EBUS. In this way, negative EBUS/EUS results should still be confirmed by mediastinoscopy.

The current indications for surgical mediastinal staging are a matter of judgment and precise knowledge of the various staging modalities and their results. None of the available techniques can be expected to provide perfect results. The main question becomes what false-negative rate one is willing to accept. In patients with suspected mediastinal lymph-node involvement by non-invasive techniques, evaluation by EBUS/EUS followed by mediastinoscopy in cases where no positive lymph nodes are found by endosonographic techniques has produced excellent results, with a reported increase in sensitivity for detection of mediastinal nodal disease of up to 93% [8]. In concordance with the European Society of Thoracic Surgeons (ESTS) guidelines, positive CT, PET or PET–CT findings should be cytologically or pathologically confirmed [12]. EBUS and EUS are complementary to surgical invasive staging techniques with a high specificity but low NPV. Therefore, an invasive surgical technique is still indicated if EBUS/EUS yield a negative result. Fig. 1 provides a flowchart of mediastinal staging of NSCLC that is currently used at the Antwerp University Hospital in Belgium.

### 2.3. Invasive mediastinal restaging

Most patients with pathologically proven N2 disease detected during preoperative work-up will be treated by induction therapy. The mediastinum can be principally restaged by the same techniques as applied in primary staging. At the present time, CT, PET and PET–CT are not accurate enough to make final further therapeutic decisions after induction therapy. The accuracy of CT in restaging after induction therapy is only 58% [13]. PET scanning is more accurate than CT for mediastinal restaging, with a reported PPV to detect persisting nodal disease of 73% [14]. In detecting residual N2 disease, however, PPV was less than 20%. The use of PET–CT fusion images significantly increases the accuracy through better localisation of focal isotope uptake in mediastinal nodes [15]. However, 20% false-negative and 25% false-positive rates have been reported [16]. In cases where there is a suspicion of residual mediastinal disease, invasive biopsies are still required.

Endosonographic techniques are also used for restaging. However, their false-negative rates remain high, ranging between 20% and 30% [17,18]. Therefore, negative findings should still be confirmed by surgical restaging.

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EBUS, endobronchial ultrasound; EUS, oesophageal ultrasound; LN, lymph-node station, L, left; R, right; TEMLA, transcervical extended mediastinal lymphadenectomy; VAMLA, video-assisted mediastinal lymphadenectomy; VATS, video-assisted thoracic surgery.
Results of recent series of repeat mediastinoscopies after induction therapy are summarised in Table 3 [15,19–24]. Remediastinoscopy offers the advantage of providing pathological evidence of response after induction therapy. In this way, it remains a valuable tool to select patients for surgical resection [25]. Survival clearly depends on the findings of remediastinoscopy, patients with a positive repeat mediastinoscopy having a poor prognosis compared to those with a negative remediastinoscopy [21]. In a combined series of 104 patients, nodal status was the only significant factor related to survival in multivariate analysis [22].

An alternative approach consists of the use of minimally invasive, endosonographic procedures to obtain an initial proof of mediastinal nodal involvement. Mediastinoscopy is subsequently performed after induction therapy to evaluate response [26]. In this way, a technically more difficult remediastinoscopy can be avoided.

Only one study has reported the results of VATS for restaging after induction therapy [27]. In this Cancer and Leukemia Group B (CALGB) 39803 trial a negative result of VATS was defined as negative lymph-node biopsies from at least three lymph-node stations, whereas a positive result consisted of a pathological proof of persisting N2 disease in the mediastinum or the demonstration of pleural carcinomatosis. Sensitivity, specificity and NPV of VATS for restaging were 67%, 100% and 73%, respectively.

In the restaging guidelines published by the ESTS an invasive technique providing cytological or histological information is also recommended [12]. Endoscopic or surgical invasive procedures may be utilised, the precise choice depending on the availability of the technique and expertise of the centre [12]. This policy was confirmed in a recent systematic review on restaging after induction therapy for stage IIIA NSCLC [28].

Current restaging algorithms used at the Antwerp University Hospital are depicted in Fig. 2.


3.1. Complete R0 resection

The final aim of surgical treatment for non-small-cell lung cancer (NSCLC) is complete (R0) resection. In this respect, specific criteria have been established by a working group of the International Association for the Study of Lung Cancer (IASLC) [28]. Complete resection is defined as complete removal of the primary tumour with no residual macroscopic or microscopic tumour left behind; moreover, a systematic or lobe-specific nodal dissection must have been performed, and the highest mediastinal lymph node must be negative.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Ref.</th>
<th>n</th>
<th>IT</th>
<th>Morbidity (%)</th>
<th>Mortality (%)</th>
<th>Sensitivity (%)</th>
<th>Negative predictive value (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pitz, 2002</td>
<td>19</td>
<td>15</td>
<td>CT</td>
<td>0</td>
<td>0</td>
<td>50</td>
<td>71</td>
<td>78</td>
</tr>
<tr>
<td>Stamatis, 2005</td>
<td>20</td>
<td>165</td>
<td>CT–RT</td>
<td>2.5</td>
<td>0</td>
<td>74</td>
<td>86</td>
<td>93</td>
</tr>
<tr>
<td>De Waele, 2006</td>
<td>21</td>
<td>32</td>
<td>CT (n = 26)</td>
<td>CT–RT (n = 6)</td>
<td>3.1</td>
<td>0</td>
<td>71</td>
<td>75</td>
</tr>
<tr>
<td>De Leyn, 2006</td>
<td>15</td>
<td>30</td>
<td>CT</td>
<td>0</td>
<td>0</td>
<td>29</td>
<td>52</td>
<td>60</td>
</tr>
<tr>
<td>De Waele, 2008</td>
<td>22</td>
<td>104</td>
<td>CT (n = 79)</td>
<td>CT–RT (n = 25)</td>
<td>3.9</td>
<td>1</td>
<td>70</td>
<td>73</td>
</tr>
<tr>
<td>Marra, 2008</td>
<td>23</td>
<td>104</td>
<td>CT–RT</td>
<td>1.9</td>
<td>0</td>
<td>61</td>
<td>85</td>
<td>88</td>
</tr>
<tr>
<td>Call S, 2011</td>
<td>24</td>
<td>84</td>
<td>CT (n = 49)</td>
<td>CT–RT (n = 35)</td>
<td>4.0</td>
<td>1</td>
<td>74</td>
<td>79</td>
</tr>
</tbody>
</table>

Ref., reference; n, number of patients; IT, induction therapy; CT, chemotherapy; CT–RT, chemoradiotherapy.

* Combined, updated series.

** Subset of patients of Stamatis, 2005 [20].

# Results of restaging after induction therapy.
Although no prospective, randomised trial exists to compare surgery versus radiotherapy in the treatment of early-stage NSCLC, surgical resection has traditionally been considered the treatment of choice. Markedly improved survival rates are reported in surgical series in comparison to patients who did not undergo surgical resection for a variety of reasons [29]. Early-stage disease and T3N1 NSCLC are considered definite indications for surgery.

Resectability and operability of a primary NSCLC depend not only on the clinical and intraoperative staging of the tumour, but also on the functional capacity of the patient. So, detailed cardiopulmonary evaluation to determine the functional status is equally important as this might impact on the extent of resection [30]. After definitive pathological examination, a distinction can be made between R0 resections when there is no residual tumour, R1 with microscopic residual tumour and R2 with macroscopic residual tumour.

3.2. Types of lung cancer resection

Lung cancer resections can be divided into three major groups (Table 4).

Group 1 – standard resections: standard resections include lobectomy (removal of a lobe), bilobectomy (removal of two lobes on the right side) and pneumonectomy (removal of an entire lung). Pneumonectomy was initially considered as the treatment of choice in the years 1940–1950, whilst lobectomy was reserved for patients with diminished pulmonary or cardiac reserve. In later years, lobectomy was found to provide a similar survival rate as pneumonectomy if the lesion could be totally resected by lobectomy.

Group 2 – lung parenchyma saving operations: these operations can be divided into proximal and distal procedures. The proximal interventions comprise all bronchoplastic and tracheoplastastic operations. The most frequently performed bronchoplastic procedure is a sleeve resection of the right upper lobe for a lung cancer invading the upper lobe orifice. The very first sleeve resection was performed in 1947 for a carcinoid tumour in the right upper-lobe orifice in an Air Force cadet to avoid a pneumonectomy which would have precluded his career as a pilot [31]. Distal procedures include segmentectomies and wedge resections.

Regarding the extent of resection, lobectomy is generally considered the procedure of choice in cancers confined to a

<table>
<thead>
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<th>Table 4 – Types of operative procedures</th>
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<tbody>
<tr>
<td><strong>Standard:</strong></td>
</tr>
<tr>
<td>Lobectomy</td>
</tr>
<tr>
<td>Bilobectomy</td>
</tr>
<tr>
<td>Pneumonectomy</td>
</tr>
<tr>
<td><strong>Lung-parenchyma-sparing operations:</strong></td>
</tr>
<tr>
<td>Proximal:</td>
</tr>
<tr>
<td>Bronchotomy</td>
</tr>
<tr>
<td>Rotating bronchoplasty</td>
</tr>
<tr>
<td>Bronchial or tracheal wedge excision</td>
</tr>
<tr>
<td>Bronchial or tracheal sleeve resection</td>
</tr>
<tr>
<td>Distal:</td>
</tr>
<tr>
<td>Anatomical segmentectomy</td>
</tr>
<tr>
<td>(wide) Wedge excision</td>
</tr>
<tr>
<td><strong>Extended procedures (lung + other structure):</strong></td>
</tr>
<tr>
<td>Pericardium (intrapерicardial pneumonectomy)</td>
</tr>
<tr>
<td>Diaphragm</td>
</tr>
<tr>
<td>Chest wall (ribs, vertebrae)</td>
</tr>
<tr>
<td>Superior sulcus (Pancoast tumour)</td>
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</tbody>
</table>
A posterolateral thoracotomy incision is the classical incision for lung cancer resection. This approach is preferred for bilateral procedures, especially bilateral upper-lobe lung cancers. A limited resection was found to have a tripling of local recurrence rate, a 30% increase in overall death rate and a 50% increase in cancer-related death rate in comparison to lobectomy patients. However, these results were only significant at a P-value level of 0.10.

The role of sublobar resection, anatomical segmentectomy or wide-wedge resection is being reconsidered for very early lung cancer following large screening programmes for lung cancer. This is due to the findings of non-solid or part-solid ground glass opacities, so-called GGOs [33]. This will be further discussed with the newly introduced adenocarcinoma classification.

Group 3 – extended operations: extended operations involve resection of lung parenchyma with an adjacent organ or structure invaded by the tumour. Examples include resection of the chest wall, diaphragm, pericardium, left atrium, superior vena cava and apex of the chest in superior sulcus tumours. En bloc resection of the locally involved extrapulmonary structure is advised to avoid tumour spillage and to ensure a complete R0 resection with negative margins.

### 3.3 Different thoracic approaches

A posterolateral thoracotomy incision is the classical incision performed for lung cancer resection. If feasible, a muscle-sparing thoracotomy is preferred to preserve the latissimus dorsi muscle. Sternotomy may be used in patients requiring bilateral procedures, especially bilateral upper-lobe lung cancers. An extended incision such as a hemi-clamshell incision is utilised in selected patients requiring an extended resection. At the present time, VATS is increasingly being used as specific access to the thoracic cavity. In a series of 1100 VATS lobectomies, excellent results were reported, with an operative mortality of 0.8% [34]. Morbidity generally appears to be lower with the VATS approach, although in a nationwide database of 13,619 patients who underwent lobectomy by thoracotomy or VATS, patients who underwent VATS lobectomy were 1.6 times more likely to have intraoperative complications [35]. A recent systematic review and meta-analysis of randomised and non-randomised trials concluded that VATS lobectomy is an appropriate procedure for selected patients with early-stage NSCLC [36]. Currently, VATS has become a standard approach for peripheral wedge resections and lobectomy for stage I tumours. VATS segmentectomy is much less widely performed and its potential benefits and limitations still require further evaluation [37,38]. Although VATS seems to be equal or even beneficial in terms of morbidity, length of stay and survival in comparison to an open approach, further evaluation in large, prospective randomised trials is necessary [39].

### 3.4 Intraoperative staging – systematic nodal dissection

Detailed intraoperative systematic lymph node dissection is important to provide an accurate pathological TNM staging. The different intrathoracic lymph-node stations were originally described by Naruke et al. in 1978 [40] and were recently updated in the 7th TNM classification where the concept of nodal zones was introduced [41]. The nodal zones and stations are listed in Table 5 [41,42].

Thoracotomy provides the final investigation and determination of resectability.

Non-resectable tumours include T4 tumours with invasion into important adjacent structures or tumours with extensive mediastinal metastases. These include involvement of vital mediastinal structures or extracapsular N2 and N3 diseases. For resected N2 disease, invasion of the highest mediastinal lymph node heralds a poor prognosis. Massive involvement of hilar structures is generally a contraindication unless an intrapericardial pneumonectomy can be performed. Pleural metastases are also a contraindication to resection due to a poor long-term survival.

When deciding on the type of operation to be performed, the surgeon should first perform a careful intraoperative exploration, taking into account several strategic points. He/she should determine whether the tumour is peripheral or central, which lymph nodes are involved, and whether or not there is transgression of the fissure. Frozen-section analysis of suspicious lymph nodes or margins can be helpful in determining the extent of resection. Whenever possible, lobectomy remains the procedure of choice. Pneumonectomy is considered ‘a disease in itself’ due to its profound respiratory and haemodynamic implications and associated higher"
complication rates in comparison to lobectomy. Most patients, however, have adapted to living with just one lung [43]. A sleeve lobectomy should be considered as an alternative whenever technically feasible, providing that a complete resection can be obtained [44].

In a large series of 334 patients operated for lung cancer invading the chest wall, 5-year survival rate was 32% in patients who underwent a complete resection, in contrast to only 4% for incomplete resections, and 0% for exploration only [45]. Long-term survival was mainly dependent on nodal involvement and complete resection, and less dependent on the depth of chest wall invasion.

For precise N staging during thoracotomy, a systematic nodal dissection is performed as advocated by Graham et al. [46]. In this technique, dissection of the mediastinal, hilar and lobar lymph nodes proceeds in a systematic fashion. In their classical paper Graham et al. reviewed 240 patients with clinical T1-3 N0-1 NSCLC [46]. Preoperative mediastinoscopy was performed when lymph nodes larger than 1.5 cm were present on chest CT. The rate of exploratory thoracotomy without further resection was only 3%. Following surgical resection pathological N2 disease was found in 20% of patients. There was no subgroup with 0% incidence of N2 involvement and skip metastases were found in 34% of patients with N2 disease. Peripheral tumours less than 2 cm had a 24% incidence of lymph-node metastases. Systematic lymph-node dissection is currently considered the gold standard for the accurate staging of nodal (N) disease and should be routinely performed, also when a minimally invasive approach is chosen.

In a non-randomised study of 373 patients, complete mediastinal lymph-node dissection identified more levels of N2 disease in patients with stages II and IIIA NSCLC, and was associated with improved survival in comparison to systematic nodal sampling but only for right-sided lesions [47]. A survival advantage of complete mediastinal lymph-node dissection has only been demonstrated in one prospective randomised trial [48]. In a recently published multicentre prospective clinical trial, patients with intraoperatively staged T1-2N0-non-hilar N1 NSCLC were randomised to lymph-node sampling versus systematic nodal dissection. The latter identified occult disease in 3.8% of patients but was not associated with a benefit in overall survival [49]. However, all patients in this trial were carefully staged with invasive, pathological analysis of four lymph-node stations. These results should not be generalised to higher-stage tumours.

The technique of systematic lymph-node dissection on the right side includes the dissection of the upper (level 2R) and lower (level 4R) paratracheal nodes, subcarinal (level 7), para-oesophageal (level 8R) and inferior pulmonary ligament (level 9R) lymph-node stations. On the left side, the aortopulmonary, para-aortic and lower paratracheal nodes (levels 5, 6, 4L), and levels 7, 8L and 9L should be resected.

N1 disease also represents a heterogeneous group of diseases. This was demonstrated by Riquet et al., who reported a series of 1174 patients with NSCLC; 22% of the patients had N1 disease, with a 5-year survival of 47.5% [50]. A distinction was made between intralobar N1 (levels 12 and 13) and extralobar hilar N1 (levels 10 and 11) diseases. Five-year survival rate for intralobar N1 was 54% and for hilar N1 39%. This difference was highly significant. The prognosis of intralobar N1 is similar to N0 disease, and extralobar N1 is more closely related to N2 with single-station involvement.

4. Surgical implications of the new adenocarcinoma classification

4.1. New categories

In early 2011, a new adenocarcinoma classification was published by a common working group of the IASLC, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) [51–53]. This classification is listed in Table 6.

Of special interest to thoracic surgeons are the new categories adenocarcinoma in situ (AIS) which represents small (<3 cm) solitary adenocarcinomas consisting purely of lepidic growth without invasion, and minimally invasive adenocarcinoma (MIA) with <0.5 cm invasion. AIS and MIA were introduced because the 5-year disease-free survival approaches 100% if the tumours are completely resected. The term bronchioalveolar carcinoma (BAC) is no longer utilised as it applies to five different categories in the new classification, which gave rise to much confusion [51].

With the advent of helical CT and screening trials in high-risk populations, there is a renewed interest in small nodules, especially those with ground-glass opacity (GGO). Recently, results of the National Lung Screening Trial were published.

<table>
<thead>
<tr>
<th>Table 6 – IASLC/ATS/ERS classification of lung adenocarcinoma in resection specimens [51–53]. Table reproduced with permission from Wolters Kluwer Health.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preinvasive lesions:</td>
</tr>
<tr>
<td>Atypical adenomatous hyperplasia</td>
</tr>
<tr>
<td>Adenocarcinoma in situ (&lt;3 cm, formerly BAC)</td>
</tr>
<tr>
<td>- non-mucinous</td>
</tr>
<tr>
<td>- mucinous</td>
</tr>
<tr>
<td>- mixed mucinous/non-mucinous</td>
</tr>
<tr>
<td>Minimally invasive adenocarcinoma (&lt;3 cm lepidic predominant tumour with ≤5 mm invasion):</td>
</tr>
<tr>
<td>- non-mucinous</td>
</tr>
<tr>
<td>- mucinous</td>
</tr>
<tr>
<td>- mixed mucinous/non-mucinous</td>
</tr>
<tr>
<td>Invasive adenocarcinoma:</td>
</tr>
<tr>
<td>Lepidic predominant (formerly non-mucinous</td>
</tr>
<tr>
<td>BAC pattern, with &gt;5 mm invasion)</td>
</tr>
<tr>
<td>Acinar predominant</td>
</tr>
<tr>
<td>Papillary predominant</td>
</tr>
<tr>
<td>Micropapillary predominant</td>
</tr>
<tr>
<td>Solid predominant with mucin production</td>
</tr>
<tr>
<td>Variants of invasive adenocarcinoma</td>
</tr>
<tr>
<td>Invasive mucinous adenocarcinoma (formerly mucinous BAC)</td>
</tr>
<tr>
<td>Colloid</td>
</tr>
<tr>
<td>Foetal (low and high grade)</td>
</tr>
<tr>
<td>Enteric</td>
</tr>
</tbody>
</table>

BAC, bronchioalveolar carcinoma.
The detection rate of smaller lung cancers in recent times is limited resection of GGO lesions [65]. Responsible delayed cut-end recurrences have been described after 100% survival at 5 years after resection [61–64]. However, positive delayed recurrence after resection concluded that the well-selected use of sublobar resection comprising anatomical segmentectomy or wedge excision – is currently the subject of intensive investigation [53]. For a limited resection to be oncologically valid, a precise pre- and intraoperative diagnosis becomes imperative. In terms of preoperative diagnosis, specific criteria on chest CT as percentage GGO, tumour shadow disappearance rate and histogram analysis have been shown to have a high predictive value [55]. The role of PET and integrated PET-CT scanning and specific tumour markers is currently being evaluated [56].

4.2. Sublobar (limited) resection for lung cancer

The detection rate of smaller lung cancers in recent times is increasing, and therefore the appropriateness of lobectomy for stage I lung cancer, especially those tumours ≤2 cm (clinical T1a disease), is again being questioned [33,57]. Recently, there have been numerous publications suggesting that sublobar resection for early lung cancers may be an adequate surgical treatment. Many of these studies are retrospective and not randomised [58–60]. Most reports showed no difference in survival or in locoregional recurrence between lobectomy and sublobar resection for tumours ≤2 cm in size. Patients with GGO tumours on CT have been reported to have a 100% survival at 5 years after resection [61–64]. However, possible delayed cut-end recurrences have been described after limited resection of GGO lesions [65].

Two recent reviews and one meta-analysis of sublobar resection concluded that the well-selected use of sublobar resection, especially for pure AIS ≤2 cm, yielded survival and recurrence rates comparable to those of lobectomy [66–68]. Thus, sublobar resection is generally considered acceptable for GGO lesions or adenocarcinomas with minimal invasion. Lobectomy is still considered the standard surgical treatment for tumours ≤2 cm in size that have a solid appearance on CT because such tumours are invasive carcinomas. Definite recommendations can only be made when the results of large randomised trials such as Japan Clinical Oncology Group (JCOG) 0802 in Japan, CALGB 140503 in North America and European Institute of Oncology (IEO) S638/311 in Italy become available. These trials randomise patients with tumours ≤2 cm between lobectomy and sublobar resection.

Whether a purely anatomical segmentectomy provides a similar or better result to a wide-wedge resection has not yet been clearly determined. When correlating CT findings of GGO with histopathology, many of these lesions correspond to non-invasive forms of neoplastic growth. [61–64,69,70]. In a recent prospective study from Japan (JCOG 0201), radiological non-invasive peripheral lung adenocarcinoma was defined as an adenocarcinoma ≤2.0 cm with ≤0.25 consolidation [71].

Recent guidelines and a large, randomised screening trial state that small nodules ≤10 mm or ≤500 mm³ that are clearly 100% pure GGO lesions on chest CT, which are suspected to be AIS or MIA, be considered for close follow-up rather than immediate surgical resection [72,73]. Specific CT characteristics to be considered are size, attenuation, shape and growth rate.

4.3. Systematic lymph-node dissection for early-stage adenocarcinoma

In some specific subsets of very early-stage adenocarcinoma, especially pure GGO lesions, systematic lymph-node dissection may not always be required [74]. Recent analysis of the Italian COSMOS screening study showed that systematic nodal dissection can be avoided in the early stage – clinically N0 lung cancer when the maximum standardised uptake value on PET scanning is <2.0 and the pathological node size is ≤10 mm – as the risk of nodal involvement is very low in this subset of patients [75].

In a Japanese prospective study, a specific treatment algorithm has been proposed [76]. Lesions ≤10 mm of any type or pure GGO nodules were initially observed and discussed with each specific patient. When size or density increased, they were subsequently resected. GGO lesions 11–15 mm were treated by segmentectomy and lymph-node sampling. Solid lesions of 11–15 mm and GGO lesions of 16–20 mm were removed by segmentectomy combined with lymph-node dissection. Solid lesions of 16–20 mm were resected by lobectomy with lymph-node dissection. Applying this algorithm, an excellent 5-year disease-free survival rate of 98% was observed for limited resection [76].

5. Quality of life after lung cancer resection

Although mortality and major morbidity rates offer a patient valuable information, these data alone are inadequate in meeting the growing needs for detailed comparison of surgical approaches and rising expectations of patients. Patients may regard immediate postoperative complications as an acceptable risk, but are not prepared to accept significant postoperative quality of life (QoL) impairments [77]. Several publications focus on predictors of QoL after early-stage lung cancer resection. Extent of resection [78–80], surgical approach [81,82], age [83–85] and smoking status [86–88] are considered to be significant.

The extent of resection has a significant influence on the QoL evolution. Several publications evaluated QoL after lobectomy and pneumonectomy [78–80]. Literature data agree that the initial limitations in the physical QoL component observed after both resections are more pronounced after pneumonectomy. Depending on the specific publication, both resections yielded comparable results after 3–6 months. Sublobar resections, indicated in stage IA patients with a tumour located in the periphery of the lung and <2 cm in diameter, are currently often performed. Although these procedures imply a parenchyma-sparing intent, QoL has rarely been reported after sublobar resections. Pompeo et al. evaluated patients with severe emphysema undergoing a sublobar resection for stage I lung cancer [89]. Significant improvements were reported in the domains of the physical QoL com-
ponent, presumably because of a lung volume reduction ef-
fect. Saad prospectively described the evolution in QoL after
different lung resections [90]. A comparable improvement in
the physical QoL was seen after lobectomy as well as after
sublobar resection.

The effect on QoL not only of the muscle-sparing versus
the non-muscle-sparing thoracotomy, but also of minimally
invasive thoracic surgery was recently evaluated. The effect
of the muscle-sparing thoracotomy is mostly seen on the
physical QoL component, with improved shoulder function
and less thoracic pain compared to the non-muscle sparing
thoracotomy [91]. The advantages of VATS over thoracotomy
in terms of QoL are found in the immediate postoperative per-
iod. After postoperative day 4, no significant differences in
QoL are seen [92]. After a VATS procedure Landreneau et al.
found that patients experienced significantly less pain only
on the first 2 days in comparison to a muscle-sparing thorac-
otomy [93].

Conclusions of QoL research in younger patients cannot be
transferred blindly to septuagenarians. Several authors pro-
spectively evaluated QoL after lung-cancer surgery in an el-
derly patient population. In general, age >70 years is an
important risk factor for impairment of the physical QoL com-
ponent, and recovery is not guaranteed until >24 postopera-
tive months [78]. After lobectomy as well as pneumonectomy,
the emotional component returns to baseline the first
3 months after surgery in elderly patients and may reflect a
so-called response shift whereby patients adapt their stan-

dards and perceptions to their expectations and rate their
personal situations better than would otherwise be expected
[94].

Several authors compared QoL between patients aged less
versus more than 70 years. Salati et al. compared QoL after
lobectomy [83]. Preoperatively, elderly patients scored worse
on the physical component of QoL, but scored higher values
on the emotional component. At 3 months after surgery, no
significant differences were seen between the two patient
groups. Burfeind et al. evaluated the effect of lobectomy on
patients who were younger versus older than 70 years [84].
Both groups demonstrated a similar decrement in QoL with
a parallel return to baseline. The one notable exception was
in the physical QoL component, which had returned to base-
line by 6 months in young patients and stayed impaired in pa-
tients >70 years at 6 and 12 months postoperatively.

The effect of smoking habits on postoperative QoL at
6 months was evaluated by Myrdal et al. [87]. Patients who
continued smoking after lung-cancer surgery had signific-
antly lower scores for the emotional QoL component than
former smokers and those who had never smoked. In con-
trast, Sarna et al. could not withhold the smoking status as
predictive for postoperative QoL [88]. In a recent study,
we concluded that smoking cessation is beneficial at any
time point prior to lung-cancer resection [86]. Current smok-
ing at the time of surgery is associated with a longer impair-
ment of QoL functioning as well as symptom scores. Since
smoking status is one of the few prognostic factors in the di-
rect control of the patient, this study offers valuable infor-
mation to promote smoking cessation before lung-cancer
surgery.

There is an ongoing debate on the effect of induction and
adjuvant chemotherapy or radiotherapy on QoL after lung-
cancer surgery [95–97]. Several authors evaluated the effect
of chemotherapy on the QoL of lung-cancer patients, in both
non-surgical and surgical patients. In non-surgical patients,
chemotherapy was associated with worse QoL, unless the pa-
tient responded to treatment [98]. Paull et al. reported that
exposure to postoperative chemotherapy was a risk factor
for poor QoL after surgery for early-stage lung cancer [97].
These results are not consistent with the study of Fiedler
et al. who evaluated QoL after pneumonectomy comprising
early- as well as advanced-stage lung cancer [96]. Adjuvant
chemotherapy had no significant influence on QoL at 6
months.

Although many questions remain concerning QoL evolu-
tion after lung-cancer surgery, QoL data are essential in prop-
er patient counselling and may create realistic postoperative
objectives for patients. The real challenge in the management
of lung-cancer patients consists not only in improving prog-
nosis but also in maintaining or increasing QoL.

6. Surgical quality control

Thoracic surgery comprises a large variety of different pro-
cedures which may prove to be technically challenging, such as
extended resections of the superior sulcus, sleeve resections,
intrapерicardial procedures and extensive operations after
induction therapy. For this reason uniform judgment of surgi-
cal quality is difficult to perform. Overall mortality is only a
crude parameter and risk stratification is necessary. More-
over, dedicated anaesthesiological, intensive-care and nurs-
ing management is required to obtain the best
postoperative results; thus team management will not only
determine the short-term results but also long-term outcome.
This also implies that hospital volume may be a critical
determinant.

Is there a clear relationship between surgeon or hospital
volume and final outcome? In a seminal paper Luft et al. dem-
strated that mortality after open-heart surgery, vascular
surgery and prostatectomy decreases with increasing number
of procedures performed [99]. When analysing data from uni-
versity reports, Hillner et al. showed a relationship between
volume and outcome for complex intra-abdominal and
lung-cancer interventions [100]. When looking at the specific
number of pulmonary resections, mortality was lower in
those centres performing more than 24 interventions on a
yearly basis. Mortality of lobectomy was significantly lower
when performed by a thoracic surgeon compared to a general
surgeon. The latter finding was confirmed in a more recent
study [101]. In another analysis of more than 2000 pulmonary
resections, low-volume centres were compared to high-vol-
ume institutions. Morbidity was lowest and survival highest
in those centres performing more than 67 resections per year
[102]. Also in a Flemish, multicentre, hospital-based lung-cancer
registry, mortality decreased when hospital volume in-
creased [103]. The same holds true for oesophagectomy
[104]. In the latter paper, mortality after lung resection was
not related to technical factors but mainly to severe postoper-
ative complications, underlining the importance of a dedicated multidisciplinary team in taking care of this patient population.

Are results different in teaching hospitals with specific thoracic surgical residents? In a recent analysis of 498,099 lung resections a superior outcome was found in hospitals with a thoracic surgery residency programme [105]. The odds ratio of death in patients undergoing pneumonectomy was reduced by more than 30% compared with hospitals providing training in general surgery.

Although evidence-based minimal volume standards are currently lacking, a recent systematic review and meta-analysis concluded that hospital volume and surgeon specialty are important determinants of outcome in lung-cancer resections [106].

So, centralisation of care seems to be the logical consequence in improving short-term and long-term results. However, most of the presented data come from North America with established training programmes in thoracic and cardiothoracic surgery. What is the current situation in Europe?

In many European countries, general thoracic surgery currently exists as a separate specialty. However, the precise number of centres performing thoracic surgical procedures is unknown and accurate figures on the total number of interventions are not currently available. Certification in thoracic surgery is not uniform throughout Europe. As an example, thoracic surgery is not a specifically defined entity in Belgium, where it falls within the discipline of general surgery together with abdominal, cardiac, vascular, paediatric and trauma surgery.

There is also no uniform European training programme in thoracic or cardiothoracic surgery. To establish a more precise structure of general thoracic surgery a working group has been established by the European Association for Cardio-thoracic Surgery (EACTS) and the ESTS. Recently, the Union Européenne des Médecins Spécialistes (UEMS) has created a specific thoracic surgical division related to the general and cardiothoracic surgical sections. Specific criteria for training and accreditation in thoracic surgery are currently being developed.

To obtain more precise data on the number of general thoracic surgical procedures in Europe, several large databases have been created. The ESTS created a voluntary database for general thoracic surgery. In 2011 a total of 24,574 lung resections were reported, including all diagnoses. Lobectomy represented 57.5% of cases, and pneumonectomy 9.5%. A total of 16,710 cases of primary lung cancer were reported, represented 57.5% of cases, and pneumonectomy 9.5%. A total of 16,710 cases of primary lung cancer were reported, including all diagnoses. Lobectomy and bilobectomy being performed in 76% of cases. This database mortality and morbidity are calculated according to specific risk scores, allowing benchmarking between different units and countries.

To ensure high-quality patient care in thoracic surgery, the EACTS/ESTS working group felt that it should be performed within the logistical and economical framework of specialised units. These units should be designed to allow patient care and treatment according to recommended standards, as well as education of surgical trainees, continuous development and research in thoracic surgery. The working group proposed two types of thoracic surgical centres: highly specialised centres within or associated with a university, performing at least 250 major thoracic procedures per year, and standard units which are free-standing or combined with cardiac, vascular or general surgery. In a standard unit at least 100 major interventions should be performed annually. Lung transplantation and its alternative procedures should be performed only in centres with special interest and with cardiac surgical facilities. According to well-defined criteria in combination with an on-site visit, dedicated thoracic units can obtain an institutional quality certification in general thoracic surgery.

In order to raise the profile of thoracic surgery in Europe, further harmonisation is necessary. Unified databases should become available, detailing not only mortality but also specific outcome measures related to morbidity, survival and quality of life. Postgraduate education remains necessary to ensure a high quality of thoracic surgical interventions as has recently been demonstrated by a study from the Netherlands evaluating completeness of lymph-node dissection in dedicated thoracic surgical centres [107,108].

Thoracic surgeons should be further involved in randomised clinical trials comparing newly introduced treatment modalities – such as stereotactic radiotherapy or radiofrequency ablation – to classical surgical procedures. They should also be prepared to adapt to a new, constantly changing environment. Multidisciplinary collaboration and large-scale prospective studies are necessary to update current diagnostic and therapeutic algorithms ensuring optimal patient care in thoracic surgery [109].

Conflict of interest statement

None declared.

REFERENCES


Role of adjuvant radiotherapy in completely resected non-small-cell lung cancer

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Most long-term survivors of non-small-cell lung cancer (NSCLC) are patients who have had a completely resected tumour. However, this is only achievable in about 30% of the patients. Even in this highly selected group of patients, there is still a high risk of both local and distant failure. Adjuvant treatments such as chemotherapy (CT) and radiotherapy (RT) have therefore been evaluated in order to improve their outcome. In patients with stage II and III, administration of adjuvant platinum-based chemotherapy is now considered the standard of care, based on level 1 evidence. The role of postoperative radiation therapy (PORT) remains controversial. In the PORT meta-analysis published in 1998, the conclusions were that if PORT was detrimental to patients with stage I and II completely resected NSCLC, the role of PORT in the treatment of tumours with N2 involvement was unclear and further research was warranted. Thus at present, after complete resection, adjuvant radiotherapy should not be administered in patients with early lung cancer. Recent retrospective and non-randomised studies, as well as subgroup analyses of recent randomised trials evaluating adjuvant chemotherapy, provide evidence of the possible benefit of PORT in patients with mediastinal nodal involvement. The role of PORT needs to be evaluated also for patients with proven N2 disease who undergo neoadjuvant chemotherapy followed by surgery. The risk of local recurrence for N2 patients varies between 20% and 60%. Based on currently available data, PORT should be discussed for fit patients with completely resected NSCLC with N2 nodal involvement, preferably after completion of adjuvant chemotherapy or after surgery if patients have had preoperative chemotherapy. There is a need for new randomised evidence to reassess PORT using modern three-dimensional conformal radiation technique, with attention to normal organ sparing, particularly lung and heart, to reduce the possible over-added toxicity. Quality assurance of radiotherapy as well as quality of surgery – and most particularly nodal exploration modality – should both be monitored. A new large multi-institutional randomised trial Lung ART evaluating PORT in this patient population is needed and is now under way.

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radiotherapy (RT) have therefore been evaluated in order to improve their outcome. For years, the use of adjuvant CT and/or RT was a controversial issue, as neither seemed to have any impact on survival in individual trials that were often under-powered. However, the meta-analysis including trials comparing surgery alone to surgery + adjuvant CT published in 1995 showed a modest survival benefit of 5% in completely resected patients having received postoperative cisplatin-based adjuvant CT compared with patients without CT [1]. The beneficial effect of adjuvant CT was confirmed in large trials initiated after the meta-analysis. It varies between 4% and 15% at 5 years in favour of surgery plus adjuvant chemotherapy [2–8]. Furthermore, the meta-analysis published in 2010 including 8447 patients with updated data from the old trials, and data from all recent trials show an absolute increase in survival of 4% at 5 years (from 60% to 64%, P < 0.0001) [9]. Thus, most clinicians now consider adjuvant CT as standard treatment in patients with stages II and III completely resected lung cancer. Updated survival analysis of two individual trials has also been published with contrasting results as to the persistent long-term beneficial effect of adjuvant chemotherapy [10,11]. On the other hand, concerning adjuvant RT, an individual data-based meta-analysis evaluating the role of postoperative radiotherapy (PORT) after surgery for NSCLC was also undertaken in the 1990s: it showed that adjuvant RT could be deleterious in patients with early lung cancer (i.e. stages I and II) but that in more advanced lung cancer (i.e. stage IIIA) it should be better explored in new studies, especially in patients with mediastinal involvement [12]. At the current time, adjuvant treatment is focused on chemotherapy and the risk of distant metastases rather than on postoperative radiotherapy which may also have an impact on disease control. It seems, however, that 20–60% of patients may be at risk for loco-regional recurrence. In view of the high proportion of patients still suffering from local failure after a complete resection and adjuvant chemotherapy, a new interest in PORT has been generated, even though PORT remains a controversial issue. We have therefore reviewed the evidence regarding adjuvant radiotherapy in completely resected NSCLC in 2013. Assessing the patterns of failure after surgery and the possible PORT-related toxicity is helpful in evaluating the benefit/risk ratio of postoperative therapy. Even if the risk of local recurrence in early lung cancer is generally considered to be small in comparison with the risk of distant recurrence, the rates of local failure are highly variable in the literature, ranging from 6% to 45% in stage I and from 7% to 55% for stage II disease. There are various reasons for this: problem of definition, and local failures often not reported when they occur at the same time as distant metastases or after distant failure.

An additional difficulty in the decision to administer adjuvant treatment may be the new tumour-node-metastasis (TNM) classification [13,14]. Five-year rates of locoregional recurrence (LRR) for stages IA, IB, IIA, IIB and IIIA disease using TNM-6 were 16%, 26%, 43%, 35% and 40%, respectively. Using TNM-7, corresponding rates were 16%, 23%, 37%, 39% and 30%, respectively, and there about 10–15% ‘stage shifters’ [14,15].

2. Studies evaluating mediastinal postoperative radiotherapy

Several retrospective studies, contemporaneous to the studies included in the meta-analysis, have shown that the risk of local recurrence could be reduced by PORT (25–35%) in historical comparisons [16–22]. However, this finding was not corroborated by most randomised trials.

In this review article, we will focus on randomised trials and on the meta-analyses on PORT [12,23–29]. Several of the trials are old, conducted in the era before computed tomography (CT) scan and positron emission tomography (PET), with patients treated with cobalt 60 (Co60) or even orthovoltage therapy; this resulted in a higher risk of both morbidity and mortality [30,31]. Furthermore, irradiated volumes were often large, fractionations often superior to 2 Gy daily, all these factors contributing to a higher morbidity; other technical factors such as the absence of CT-based planning in most trials or the use of spinal cord blocks which potentially block mediastinal disease may explain several LRRs. As previously stated, the rates of local failures at 5 years vary according to stage, and in several studies patients at low risk for LRR were included, possibly obscuring a radiation-induced benefit in higher-risk patients.

3. Randomised trials of adjuvant radiotherapy in stage I resected NSCLC

Van Houtte et al. [23] conducted a randomised trial in 175 patients who had a complete resection and had no lymph-node involvement. The 5-year survival rate was 24% in the RT arm versus 43% in the control arm. PORT was significantly deleterious, especially after pneumonectomy (16% in the PORT arm versus 43% in the control arm). They concluded that TRT should not be recommended in N0 patients. A more recent Italian randomised trial compared PORT at the dose of 50.4 Gy to no PORT in 104 patients with pathological stage I disease [24]. The patients included in this study benefited from more modern radiotherapy: all patients had a CT-planned treatment, linear accelerators were used and treatment volumes – including the bronchial stump and ipsilateral hilum – were small. Radiotherapy significantly decreased the risk of local recurrence from 23% in the control group to 2.2% in the PORT group (P = 0.002) but there was no significant difference in terms of 5-year overall survival (67% in the PORT group and 58% in the control group). There was no over-added toxicity in the PORT group. However, it may be argued that patients with pathological stage I NSCLC have such a low risk of local recurrence, that routine PORT is generally not recommended except for patients with R1 or R2 resections.

4. Randomised trials of adjuvant radiotherapy in stages II and III resected NSCLC

The Lung Cancer Study Group conducted a randomised study including 230 patients with stage II and III squamous-cell carcinoma to evaluate postoperative PORT at the dose of 50 Gy [25]. PORT significantly decreased the risk of local recurrence:
1% versus 41% in the control arm (P = 0.001). But this effect did not translate into a demonstrable overall survival benefit (5-year survival rate around 40% in both arms), since most recurrences were outside the radiation field or were distant failures. However a subgroup analysis suggested that PORT could prolong disease-free interval in patients with N2 disease. The design of the Medical Research Council study was quite similar but also included patients with adenocarcinoma [26]. Patients with pathologically staged T1–2, N1–2 NSCLC were randomly assigned to receive either surgery alone or surgery and PORT at the dose of 40 Gy in 15 fractions. The results confirmed previous studies: there was no advantage for survival in the PORT group over the control arm, but in the N2 subgroup analysis there was a non-significant trend towards improved survival and local control. Thus, the authors concluded that there was no indication for PORT in N1 disease, but the question remained open for N2 patients. The largest trial evaluating PORT included 728 patients (221 with stage I, 180 with stage II and 327 with stage III disease) [27]. It demonstrated that PORT had a detrimental effect on survival: the 5-year survival rate was 43% for the control group and 30% for the RT group (P = 0.002). In terms of 5-year rate without local recurrence, there was a trend in favour of PORT among N2 patients. The excess mortality rate in the radiotherapy group was due to an increase in intercurrent deaths. A Chinese randomised study of 366 completely resected patients with N1 or N2 nodal disease, PORT significantly reduced the rate of local relapses: the local failure rate was 12.7% versus 33.2% in the control group (P = 0.01), but this had no impact on survival [28].

In conclusion, before the meta-analysis was published, the role of PORT was unclear as the individual trials showed conflicting and inconclusive results. They did not have the statistical power to detect moderate survival differences. Thus the PORT meta-analysis group gathered individual data on 2128 patients from nine randomised trials [12]. Its results indicated that PORT had a significant detrimental effect on survival, with an absolute decrease of 7% at 2 years, reducing the overall survival from 55 to 48% (P = 0.001). Subset analyses suggested that PORT could be deleterious in terms of overall survival, predominantly among patients who had a complete resection and no mediastinal involvement (either pN0 or pN1). However, than authors could observe a 24% relative reduction in local recurrence rate (all stages together), so that the question of PORT in pN2 patients who have a high local recurrence rate remained valid and could warrant further research. This overview was updated in 2005 and included an additional trial by Trodella et al. in the analysis; it still showed PORT to be detrimental, with an 18% relative increase in the risk of death [32]. A very recent letter updating the results of the meta-analysis was published using different statistical methods, confirming that PORT should not be routinely used unless there is supporting evidence from new trials of modern PORT [33]. Unfortunately no phase III trial evaluating more modern PORT versus no PORT has been published since 1998. However, there have been studies on adjuvant chemotherapy as well as chemoradiotherapy. The already mentioned meta-analysis on the role of adjuvant chemotherapy in completely resected patients also comprised a second analysis based on 13 trials and 2660 patients, mostly stage III patients, and compared surgery plus radiotherapy versus surgery plus radiotherapy and chemotherapy [9]. It showed a significant improvement in survival of 4% at 5 years (from 29% to 33%). It should be outlined that a similar 4% absolute benefit was observed in the analysis of trials comparing surgery with surgery and chemotherapy that included mainly patients with stages I and II NSCLC. Thus the effect of chemotheraphy was similar irrespective of which loco-regional treatment was used: surgery alone or surgery plus PORT. The authors concluded that, as this meta-analysis was not designed to study the effect of PORT, randomised trials were needed to assess modern radiotherapy as adjuvant treatment.

5. Studies on adjuvant chemoradiotherapy in stage II and III patients

Until 1998, PORT was considered the standard treatment by many clinicians in stage II and stage III patients; thus the Eastern Cooperative Group (ECOG) completed a prospective trial comparing PORT at the dose of 50.4 Gy in 1.80 Gy fractions with PORT and concomitant chemotherapy combining etoposide and cisplatin [34]. The 3-year survival rate was, respectively, 52% in the PORT arm and 50% in the combined treatment arm (P = 0.56). The loco-regional recurrence rate within the radiotherapy field was about 13% in both arms and was therefore smaller than the rates reported in the literature. A better standardised surgical treatment may explain these results in terms of local control, as well as the use of more modern radiotherapy using CT-scan-based planning. The protocol required a thorough mediastinal lymph-node dissection or sampling according to the American Thoracic Society lymph node definitions [35,36]. There was a significant difference (P < 0.05) between the recurrence rate of patients with mediastinal dissection (50%) and those with mediastinal sampling (60%) [37]. Thus the authors concluded that cisplatin and VP-16 administered concomitantly with PORT did not prolong survival or modify local failures compared to PORT alone. Other phase II trials have evaluated adjuvant concomitant chemoradiation in stage II and IIIA patients [38,39]. In the RTOG 9705 phase II trial, where 86 patients had concurrent paclitaxel/carboplatin and PORT at the dose of 50.4 Gy, the 3-year progression-free and overall survival rate was respectively 50% and 61%, and local failure was a component of first failure in 15% of patients [38]. In another phase II study that included 42 patients (40% of pN1 and 60% of pN2 patients) treated with a similar regimen, the 2- and 5-year Kaplan–Meier estimates of local regional control were 92% and 88%, whereas the 2- and 5-year overall survival rate was 72% and 44%, respectively [39]. Even if these results seemed better that those reported in the Intergroup trial, no randomised trial was undertaken, so that adjuvant concomitant chemoradiation after complete surgery cannot be considered as a standard treatment.

6. Postoperative radiotherapy (PORT): toxicity issues

The excess of toxicity (mostly cardiac and pulmonary) and non-cancer-related deaths observed after PORT in the meta-analysis trials can probably be explained by old radiation 2D techniques, excessive volumes of radiation, too large doses...
and fraction sizes and no CT-scan-based planning. Unfortunately, the authors could not collect data on toxicity or causes of intercurrent deaths in the different studies. Late cardiac complications that are described after mediastinal radiotherapy are linked to the total dose, the fraction size, the irradiated volume, the technique of irradiation, as well as comorbidities (tobacco use, overweight) [40,41]. Pulmonary complications such as pneumonitis and lung fibrosis can also be observed, but they occur earlier; there are strong volume and fractionation effects [42]. In a recent prospective study of 291 patients, cardiopulmonary functions as well as quality of life were evaluated prospectively at baseline and at 2 years among 171 pN2 patients who had PORT and 120 pN1 patients who did not have PORT. The authors found no significant difference in terms of cardiopulmonary morbidity among patients alive at 2 years [43]. The administration of certain radiosensitising drugs such as gemcitabine may increase this risk. In the phase II trial RTOG 9705 evaluating adjuvant concomitant chemo-radiotherapy, a 6% crude incidence of late pulmonary toxicity and similarly a 5% rate of late cardiac toxicity of grade 3 or over were observed [38]. Miles et al. elaborated a mathematical model to describe the tumour stage and field-size-dependent risks/benefits of postoperative radiotherapy and showed that RT-induced mortality was strongly dependent on field size [44]. In the largest published randomised trial, Dautzenberg could determine that the use of fraction sizes >2 Gy resulted in a high risk of late toxicity [27]. The risk of non-cancer-related death was, respectively, 7% in the control group, 16–18% among patients who had daily RT fractions ≤2 Gy and 26% among those who had higher doses per fraction. Several studies reported reduced toxicity and mortality with more modern PORT. A retrospective study focusing on toxicity issues showed that PORT could be administered safely if patients were treated with more modern treatment techniques, more limited volumes of irradiation, daily fraction sizes ≤2 Gy and total doses ≤54 Gy [45]. The 4-year actuarial rate of death from intercurrent disease (DID) for patients treated with PORT within the E3590 trial was 12.9%; not significantly different from the 10.1% expected rate of DID observed in a control population matched for age and gender and corrected for smoking status [46]. A Surveillance, Epidemiology and End Results (SEER) data-based study analysed deaths from heart disease in a group of 6148 pN1 or pN2 patients operated between 1983 and 1993 who were followed up until 2005 [47]. Amongst them, 58% had PORT. PORT delivery was associated with an increase in the hazard for heart disease. However, this increase was only significant in patients treated between 1988 and 1993. For the authors, this could reflect the impact of more modern radiotherapy techniques utilised in the second half of the 1990s on morbidity.

7. Should PORT be considered for patients with mediastinal involvement?

Lally et al. have reported on PORT in a population-based cohort of 7465 patients with stage II and III non-small-cell lung cancer who had surgery [48]. They selected from the SEER database patients treated between 1988 and 2002, out of which 47% received PORT. Patients who had PORT were presumably treated with more modern radiotherapy techniques than patients included in the meta-analysis. The 5-year survival rate was 20% in the no-PORT versus 27% in the PORT group (\(P = 0.0036\)). The authors concluded that PORT offered a significant survival benefit for patients with N2 nodal disease, but that there was a detrimental effect for patients with N0 or N1 nodal disease. However, as with any retrospective study using a large database, one should be cautious with the results. Another recently published trial by Douillard et al. also suggested the possible impact of PORT on survival in patients included in the adjuvant Navelbine International Trialist Association (ANITA) randomised trial [5,49]. In a subgroup analysis according to nodal status, survival was improved in patients with pN2 disease who received PORT, both in the chemotherapy (MS 23.8 versus 47.4 months) and observation arms (median 12.7 versus 22.7 months). The authors concluded that their retrospective evaluation suggested a positive effect of PORT administered after CT in pN2 disease, and that these results supported further evaluation of PORT in prospectively randomised studies. They also could show as in the meta-analysis that PORT seemed to be deleterious in pN1 patients. However, most studies do not specify the exact location of locoregional recurrence. In a large retrospective study of 406 patients with pN2 nodal involvement, the local recurrence rate among the 332 evaluated patients was 39.2% and most of these recurrences occurred in the mediastinum [50]. Some additional interesting issues concerning local control have been outlined by retrospective studies. Kelsey observed that left-sided tumours tended to recur in the contralateral mediastinum more frequently than right-sided tumours, and this could be explained by lymph node exploration techniques as left lymph-node exploration is considered more difficult than right-sided lymph-node exploration [37,51]. Sawyer et al. have tried to divide pN2 patients into three different subgroups according to their respective risk of failure: high-risk (in cases of multiple distant mediastinal nodes involved), intermediate-risk (in cases of involvement of inferior nodes or superior nodes with eventual invasion of hilar nodes), and low-risk (if there is no hilar node involvement) [22]. Several recent monoinstitutional studies have evaluated PORT retrospectively in patients with pN2 nodal involvement and they show positive results not only in terms of local recurrence but also in terms of survival [52–55]. Furthermore, most patients had no adjuvant chemotherapy, no staging according to today’s standards and this delineates the importance of a new randomised study comparing PORT to no PORT in such a frequent cancer as NSCLC.

Another issue is whether patients with proven mediastinal involvement and who have neoadjuvant chemotherapy should have PORT after a complete resection. Many clinicians treat patients with clinical N2 involvement with preoperative chemotherapy. Several studies, as well as a meta-analysis based on literature, have indeed suggested a benefit in terms of survival in favour of preoperative chemotherapy [56–60]. Mediastinal down-staging has been shown to be an important prognostic factor [57,59]. However, the recurrence rate can be quite high as seen in the updated results of a phase II trial of neoadjuvant chemotherapy where at 5-year follow-up, 60% of patients had local relapse [61]. Another recently published
trial also showed a high incidence of local failure in stage IIIA N2 patients down-staged after neoadjuvant chemotherapy. The 5-year local-regional failure (LRF) rate was 31%, and most locoregional recurrences appeared in the mediastinal (92%) and hilar lymph nodes (23.7%), the risk being particularly high in case of N1 disease [62]. In another retrospective study, the 5-year actuarial local control rate was 82% among patients given PORT versus 35% who had no PORT. Thus even if PORT after neoadjuvant chemotherapy followed by surgery may reduce local recurrence as reported in small retrospective studies, this remains to be proven [63,64]. Thereby the question of PORT is also valid among patients who have histologically proven N2 disease before preoperative chemotherapy, whatever their response is: persistent mediastinal involvement or mediastinal down-staging (from N2 histologically proven to pN0 or pN1). No randomised study has been published on this issue.

8. Importance of surgery and preoperative staging in the perspective of modern adjuvant radiotherapy

New data concerning PORT should take into consideration the quality of surgery and the progress made in terms of preoperative staging or re-staging after neoadjuvant chemotherapy. At present, most patients considered for surgery are much better selected on the basis of a PET scan and brain imaging. PET–CT is highly sensitive and specific in detecting mediastinal nodal spread and extracranial metastases [65,66]. After induction chemotherapy for patients with N2 involvement, repeated FDG-PET may select surgical candidates among patients with mediastinal down-staging or persistent minor disease [67].

In the past years there has been an important collaborative effort of thoracic surgeons to define lymph-node exploration and complete resection. The European Society of Thoracic Surgeons (ESTS) has proposed guidelines for appropriate intraoperative and preoperative lymph-node staging [68,69]. The International Association for the Study of Lung Cancer (IASLC) staging committee has proposed a definition of complete resection [70]. All resection margins – including bronchial, venous and arterial stumps and peribronchial soft tissue – should be microscopically free of disease. Systematic nodal examination should comprise at least three intrapulmonary and hilar nodes and at least three nodes from the following mediastinal nodal stations according to the location of the primary tumour. There is no consensus about whether the highest mediastinal node that has been explored and removed should be negative. It is also unclear whether the extent of mediastinal exploration can affect long-term survival. Even if randomised trials have been performed comparing these two mediastinal approaches, there still is a debate between advocates of radical mediastinal node dissection who claim not only a potential prognostic benefit but a better tumour staging and treatment, and opponents of the radical approach because of higher morbidity and mortality and possibly a negative effect on survival because of impaired local immunity [71–73].

Considering resected patients, an exploratory analysis of the IASLC database studied survival after complete resection in relation to the extent of node involvement using the zonal concept [74,14]. Three groups were identified, with significant differences in terms of survival. Group 1 with single-zone N1 disease had a 5-year survival rate of 48%. Group 2 consisting of patients with multizone N1 and single-zone N2 disease had 5-year survival rates around 35%. Group 3 comprised patients with multizone N2 disease, and the 5-year survival rate did not exceed 20%. More recently, two large retrospective studies have tried to question whether the number of lymph nodes involved were of added prognostic significance compared with the pathological nodal stage (pN category) [75,76]. However, among the 2538 pathologically staged N1 and N2 cases in the IASLC database, such results were not observed [77]. The importance of mediastinal node involvement seems therefore the best and most consensual prognostic factor.

9. Implications for a new trial evaluating PORT

At present, based on level 1 evidence, patients who have had a complete resection of the primary tumour with mediastinal lymph-node dissection showing no mediastinal involvement (pN0 and pN1) should not have PORT. The issue of PORT is not as clear among patients with N2 mediastinal involvement. Indication of PORT is currently debated for each individual patient with mediastinal involvement. A new trial is needed addressing PORT in stage IIIA patients. Conformal radiotherapy should be mandatory so as to reduce toxicity and improve outcome [78–80]. The irradiation volume should take into account the data of thoracic CT scan and the eventual PET scan data before surgery, as well as the description of mediastinal exploration and histopathological results. A recent study has shown there are wide variations in target volume definition for PORT [81]. Based on previous studies, it seems reasonable to treat only involved lymph-node stations and uninvolved stations at high risk to better protect surrounding normal structures and consequently minimise treatment-related mortality [82–85]. An atlas of CT-based definition of thoracic lymph-node stations may be helpful [86].

In the ongoing study LungART, the irradiation volume includes the lymph-node stations involved according to the pathological report as well as lymph-node stations considered at high risk of involvement according to tumour location [87].

Among pN2 patients included in the PORT overview, the high rate of distant metastases diluted any real effect of local control on overall outcome. As the standard treatment for patients with mediastinal involvement has changed in the last 10 years from surgery plus adjuvant radiotherapy to surgery plus chemotherapy, and selection of surgical candidates has evolved with PET–CT as well as minimally invasive staging procedures, it is of utmost importance to evaluate whether modern adjuvant radiotherapy can improve survival in patients after complete resection and adjuvant chemotherapy. Lung ART is a randomised trial evaluating modern PORT in patients with mediastinal involvement. Patients may have chemotherapy in the neoadjuvant setting or adjuvant setting. It is an inter-group study involving the Intergroupe Franco-
Conflict of interest statement

The author has no conflict of interest regarding this article but is the coordinator of Lung ART which is a randomised trial evaluating post operative radiotherapy in stage III patients with mediastinal involvement.

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Adjuvant chemotherapy of non-small-cell lung cancer

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1. Introduction

Adjuvant use of chemotherapy has established efficacy in several solid human tumours – breast, colon and lung cancers being among the most frequent. The role of adjuvant treatment – either locoregionally or systemically after local treatment, allowing a complete resection of the primary tumour and locoregional lymph nodes – is to improve cure rates. The goal of adjuvant chemotherapy is to eradicate micrometastases that may already be established but are undetectable as well as to destroy possible circulating tumour cells. The benefit, however, is hypothetical, and patients are generally selected on the basis of the pTNM staging obtained at surgery. One has to keep in mind that most of the patients who will be disease-free at 5 years have already been cured by surgery. The benefit of adjuvant chemotherapy is always limited in terms of magnitude to low percentages, and the risk/benefit ratio for a given patient is low. In addition, adjuvant chemotherapy has its own toxicity that may be acute but also long-lasting even after termination. Taking these considerations into account, the use of chemotherapy and the choice of cytotoxic agents should be based on properly conducted clinical trials, with a well-defined population and a follow-up long enough to assure a real benefit with time. Data from efficacy in metastatic settings should not simply be applied to adjuvant use without results of randomised trials in this situation and a proven level of evidence. Tumour cell biology shows that a given tumour evolves with time, and that metastatic disease is quite a different disease from the adjuvant setting.

The purpose of this Educational Lecture is:

- To review the data on adjuvant chemotherapy for NSCLC.
- To analyse how the concept has evolved with time.
- To present the results of meta-analysis.
- To provide an update on the most recent trials.
- To examine the impact on special populations.
- To look at possible prognostic/predictive biomarkers.
- To provide recommendations for routine practice.

2. The first signal of a possible effect of adjuvant chemotherapy in resected NSCLC

During the last 4 decades of the 20th century, numerous trials of various sample sizes and chemotherapy combinations have been performed in various settings worldwide. Despite an effort to accrue about 10,000 patients in 50 clinical trials, none of them individually has been convincing enough to establish adjuvant chemotherapy as a standard of care. In 1995, the Non-Small Cell Lung Cancer Collaborative Group under the joint auspices of the Medical Research Council (MRC) in the United Kingdom, Institut Gustave Roussy in France and Istituto Mario Negri in Italy published a meta-analysis looking at the impact of adjuvant chemotherapy in resected non-small-cell lung cancer (NSCLC) [1]. They reviewed updated data on individual patients from randomised trials performed between 1965 and 1991. All types of treatment were analysed, including adjuvant chemotherapy, radiotherapy and advanced disease. Among these trials, 14 – including a total of 4357 patients – were performed in the postoperative setting and compared surgery to surgery + chemotherapy. The drugs used were heterogeneous, as were the doses, and overall no benefit on overall survival was shown. The analysis was refined on the basis of the heterogeneity between categories of regimen used, and that was statistically significant. Therefore, chemotherapy regimens were grouped into three categories: (1) long-term alkylating agents, (2) other drugs, and (3) cisplatin-based. No heterogeneity was found within each category, and a separate meta-analysis was performed for each of the three groups. The hazard ratios (HRs) of death showed differences among the groups, already suggesting that the choice of chemotherapy was important: (1) long-term alkylating agents: HR 1.15 (1.04–2.20), P 0.005; (2) other drugs: HR 0.89 (0.72–1.11) P 0.30; and (3) cisplatin-based: HR 0.87 (0.74–1.02) P 0.08. These initial results showed a highly significant detrimental effect of long-term alkylating agents, with a 15% increase in the risk of death from alkylating agents. On the contrary, in the cisplatin-containing regimen group, the benefit, although

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not significant, showed a 13% reduction in the risk of death, translating into an improved 5% survival at 5 years; however, this survival benefit was not significant, and in practice cisplatin-based adjuvant chemotherapy is not a standard of care for resected NSCLC at this time.

Based on the results of the meta-analysis, further randomised trials were performed taking advantage of the “signal” seen earlier with cisplatin-based chemotherapy.

### 3. Evolution of the concept of adjuvant chemotherapy for resected NSCLC

After the initial meta-analysis of adjuvant chemotherapy in resected NSCLC by the Non-Small Cell Lung Cancer Collaborative Group, additional randomised trials were performed and meta-analysed by Hotta and other Japanese investigators [2]. This second meta-analysis included 11 trials with a total of 5716 patients, performed in Japan but also in the rest of the world. Among these randomised trials six had UFT, an oral fluoropyrimidine widely used in Japan, either as a single agent or in combination with cisplatin. The remaining five were more in agreement with what is used in the western world, including etoposide, mitomycin C, vindesine, vinorelbine or vinblastine in combination with cisplatin. Sample sizes were sometime small, trials having 100 patients or fewer. Most of these trials individually showed no significant benefit on the 5-year survival rate, but overall the meta-analysis obtained an HR of 0.87 at a significant $P$ value of 0.001. When only the cisplatin-containing regimens were considered, the HR was 0.89 with a $P$ value of 0.012. In Japanese patients treated in UFT single-agent trials, the risk of death was reduced by 20% (HR 0.799, $P$ value 0.015).

Additional trials based on platinum-containing regimens have also been performed in the western world and will be summarised individually below.

#### 3.1. IALT

The International Adjuvant Lung Cancer Trial (IALT) Collaborative Group [3,4] conducted a pragmatic randomised trial, started in 1995, evaluating the impact of a cisplatin-based chemotherapy in resected NSCLC (stages I–III according to the 1986 AJCC classification). The experimental arm offered three or four cycles of various cisplatin-containing regimens to be compared by observation. Companion drugs associated with cisplatin included one of four drugs (vindesine, vinblastine, vinorelbine or etoposide), the dose of cisplatin was left to the discretion of each centre (ranging from 80 to 120 mg/m²), as was the number of cycles (three or four) or the use of adjuvant radiotherapy. A total of 14 regimens were therefore possible. The trial was planned for 3300 patients, but it discontinued early with 1867 patients because of low accrual due to the emergence and recent results of neoadjuvant chemotherapy. The most frequent chemotherapy regimens used (in 76% of patients) were cisplatin–etoposide and cisplatin–vinorelbine. Additional radiation was delivered in 20–25% of patients. The patient population included 36% stage I (10% IA), 24% stage II and 40% stage III. At the date of publication [3], after a median follow-up of 56 months, a significant overall survival benefit was seen with a 14% reduction in the risk of death and a $P$ value of 0.03, translating into a 4.1% survival benefit at 5 years. No subgroup analysis was reported, but G. Strauss [4] in a separate paper concluded that only stage III patients were benefiting from adjuvant chemotherapy.

The results of IALT were later updated in 2010 [5]. The initial benefit seen with a median follow-up of 56 months was not confirmed when more events were observed after a median of 7.5 years of follow-up. The HR for overall survival moved up from 0.86 to 0.91, with a no-longer-significant $P$ value of 0.10. The analysis of the cause of death showed a slight increase in non-cancer-related death in the chemotherapy arm, possibly reflecting long-term adverse effects of adjuvant chemotherapy (HR 1.36, $P$ value 0.06), the incidence of local recurrences or distant metastases remaining lower in the adjuvant chemotherapy population. This emphasises the need for a sufficiently long follow-up for adjuvant trials.

#### 3.2. Big Lung Trial

The Big Lung Trial [5,6] was a pragmatic, UK-based trial to evaluate the impact of cisplatin-containing chemotherapy in NSCLC in all settings: early, locally advanced and metastatic.

In the adjuvant situation, cisplatin could be combined with several drugs, including mitomycin–ifosfamide (MIC), mitomycin–vinblastine (MVP), vindesine (CV) or vinorelbine (NP). The trial started in 1995 and stopped in 2001. It accrued in the surgical setting only 381 patients out of 1394 planned. It is therefore difficult to draw conclusions from such a small sample size. With a median follow-up of 35 months the HR of 1.02 ($P$ value 0.90) showed no benefit at all.

#### 3.3. ALPI

The Adjuvant Lung Project Italy (ALPI) [6] along with the European Organisation for Research and Treatment of Cancer (EORTC) performed an adjuvant chemotherapy trial in resected stages I, II and III (UICC/ AJCC 1986) NSCLC. Surgery followed by adjuvant chemotherapy with mitomycin, vindesine and cisplatin (MVP) was compared with surgery alone. Three cycles of chemotherapy were planned after randomisation. The study accrued 1209 patients between January 1994 and January 1999. After a median follow-up of 65 months, the overall survival HR was 0.96 ($P$ = 0.589), showing no benefit from adjuvant chemotherapy. This negative trial had several weaknesses: 108 patients from a single centre were excluded from the analysis, only 69% of randomised patients received the three planned cycles of chemotherapy and half of them required dose reduction. The toxicity of MVP was prohibitive with an excess of toxic death during the first year. However, even though the study was negative, the 3.4% overall survival benefit at 5 years was not that different from that of the IALT (4.1%).

#### 3.4. CALGB 9633

In the United States, CALGB 9633 [7,8] evaluated the use of three or four cycles of paclitaxel–carboplatin in the adjuvant setting for resected stage IB only (T2N0 TNM 6 classification). This study planned to accrue 500 patients starting in Septem-
From July 1994 to April 2001, the National Cancer Institute of the need for prolonged follow-up to establish the proof of benefit of adjuvant faded with time and emphasized the importance of time and more events, the overall survival HR went up to low-up did not confirm the initial, preliminary results. With time and more events, the overall survival HR went up to 0.83 (P = 0.12), a 2% improvement on the 5 year-survival rate. Similarly, as seen in the IALT discussed above, in CALGB 9633 the benefit of adjuvant faded with time and emphasised the need for prolonged follow-up to establish the proof of benefit in adjuvant setting.

Interestingly enough, a subgroup exploratory analysis was performed in CALGB 9633 according to tumour size ≥ 4 cm or <4 cm [8]. In the updated analysis with a 74 month follow-up the overall survival in stage IB was not improved in the intent-to-treat population, but an overall survival benefit was seen for patients with a tumour ≥4 cm with an HR of death = 0.69 and a P value = 0.043, a median overall survival of 99 months compared with 77 months in the surgery only arm. On disease-free survival the magnitude of the benefit was similar for tumours ≥4 cm. These data support the adjuvant use of paclitaxel–carboplatin in patients with resected stage pIB ≥ 4 cm NSCLC.

### 3.5. NCIC JBR 10

From July 1994 to April 2001, the National Cancer Institute of the Canada Clinical Trials Group (NCIC-CTG) [9,10] accrued 482 NSCLC patients in the JBR-10 phase III randomised trial of adjuvant cisplatin–vinorelbine versus surgery alone for R0 resected stages pIB (45%) and pII (except T3N0, TNM 6 classification). Patients were randomised to receive four cycles of cisplatin–vinorelbine over 16 weeks in the chemotherapy arm versus observation in the control arm. The results were published after median follow-up of 5.1 years [9] and updated after 9.3 years.

Overall survival was improved after 5 years of follow-up with an HR of death of 0.69, P = 0.009, reflecting a 15% benefit at 5 years (69 versus 54%) and medians of 94 versus 73 months. Similarly, disease-free survival was extended in the chemotherapy group (HR 0.60, P < 0.001). The updated survival data after 9.3 years showed that the benefit was preserved with time with an HR of death = 0.78 (P = 0.04) [10]. Subgroup analysis according to stage IB versus II did not show a statistically significant benefit in stage IB. The benefit was restricted to stage II (HR 0.59, P = 0.004). In the updated analysis with 9.3 years of follow-up, similar findings were reported. Based on the tumour size effect reported in CALGB 9633, this parameter was examined in JBR-10 with a cut-off value of 4 cm in stage IB. Similarly, in JBR-10 a difference was noted, with a potential detrimental effect of adjuvant cisplatin–vinorelbine in stage IB <4 cm (HR 1.73, P = 0.56) and a potential benefit in tumours ≥4 cm (HR 0.66, P = 0.133).

In an attempt to find a predictive biomarker of efficacy, the RAS mutational status (including H, N and KRAS) was evaluated in 451/482 patients. Ras mutational status was not associated with a differential effect of chemotherapy.

Chemotherapy compliance in JBR-10 showed that 45% of patients randomised to cisplatin–vinorelbine received the planned four cycles, 55% three cycles and 64% two cycles. The median number of delivered cycles was three. The most frequent adverse event was neutropenia. Dose of vinorelbine was reduced from 30 to 25 mg/m² weekly after 18 patients were treated initially.

The JBR-10 trial established the benefit of adjuvant cisplatin–vinorelbine (the first third-generation drug combined with cisplatin) in stage II R0 resected NSCLC, and possibly in stage IB ≥ 4 cm.

### 3.6. ANITA 1

ANITA (Adjuvant Navelbine International Trials Association) [11] is an international randomised phase III trial evaluating on overall survival the benefit of 4 cycles of cisplatin–vinorelbine in R0 resected p stages IB (T2N0), II and IIIA NSCLC (TNM 6). From December 1994 to December 2000, a total of 840 patients were accrued, with 407 randomised to chemotherapy. The use of adjuvant radiation therapy – after surgery in the control arm or after chemotherapy in the experimental arm – was allowed, neither randomised nor mandatory but left to the decision of the investigators.

With a median follow-up of 70 months, the primary overall survival end-point was met on the intent-to-treat population (HR of death 0.79, P = 0.013), a benefit of 8.6% at 5 years confirmed at 7 years. Relapse-free survival was also significantly improved (HR of relapse 0.76, P = 0.002). No difference was seen with the surgery alone arm in stage IB (62% versus 64% survival at 5 years). The benefit was actually restricted to stages II and IIIA. In stage II, the 5-year survival rates were 52% versus 39% in the chemotherapy arm versus control arm respectively (HR of death 0.71), in stage IIIA 42% versus 26% (HR of death 0.69). These results do not allow a definitive conclusion, however, since the test of interaction was not significant and no P values were calculated. The impact of the N stage was reported independently of T stage: for pN0 patients median overall survival was 99.6 versus 95.5 months in the control arm and chemotherapy arm respectively. In patients with pN1 disease, median overall survivals were respectively 31.2 versus 65.7 months in favour of adjuvant chemotherapy and 20 versus 32.6 months in patients with pN2 stages. No conclusion can be reached from adjuvant radiation since its use was not randomised, but it showed a potential detrimental effect in pN1 disease after adjuvant chemotherapy and a benefit in pN2 disease [12]. This will have to be confirmed in a clinical trial, presently ongoing, and will be discussed elsewhere.

Chemotherapy compliance, similar to the results of JBR10, showed that 73% of patients received two cycles, 61% three cycles and 50% the planned four cycles, with a relative dose intensity of 59% for vinorelbine and 89% for cisplatin, reflecting the toxicity of the regimen with 85% grade 3–4 neutropenia and 9% febrile neutropenia.

The ANITA trial established the value of adjuvant cisplatin–vinorelbine (the first third-generation drug combined with cisplatin) in stage II and IIIA R0 resected NSCLC.
Within the LACE, a subgroup analysis was performed on patients who received the vinorelbine–cisplatin chemotherapy in the adjuvant setting from JBR 10, ANITA, IALT and BLT, for a total of 1888 patients [13]. Overall, the survival benefit was 8.9% at 5 years (HR of death 0.80, P < 0.001). Stage was a significant predictor of efficacy on 5-year survival: 14.7% in stage III, 11.6% in stage II and only 1.8% in stage I. These results were significantly superior to other cisplatin-based combination chemotherapy regimens used in the LACE meta-analysis (P = 0.04).

4. The impact of adjuvant chemotherapy on special populations

4.1. Adjuvant chemotherapy in elderly patients

The use of adjuvant chemotherapy may be an issue in clinical practice since the life expectancy is increasing and medical progress allows resection in the elderly population, including for NSCLC.

The JBR.10 investigators have reported the results of their trial on elderly patients, with a cut-off age set at ≥65 years, and compared with patients <65 years old [14]. The two groups differed significantly in terms of histology (more adenocarcinoma in the younger group) and performance status (more PS = 0 in the younger group). The benefit of adjuvant cisplatin–vinorelbine on overall survival, reported for the overall population, was also seen in the elderly, >65 years old (HR of death 0.61, P = 0.04). Elderly patients significantly received fewer doses of cisplatin and vinorelbine, and the dose intensity was significantly reduced as well. No differences in toxicity were observed. According to this analysis, adjuvant cisplatin–vinorelbine seems feasible in patients ≥65 years old.

Addressing the same question of the effect of age on cisplatin-based adjuvant chemotherapy, the LACE group compared the overall survival of three groups according to age (<65, 65–69, >70 years old) [15]. The HRs of death were 0.86 for <65-year-olds, 1.01 for the mid category (65–69 years old), and 0.90 in the oldest patients (>70). The test for trend was not significant and the LACE concluded that “chemotherapy should not be withheld from the elderly purely on the basis of age”. Similar to JBR.10, lower doses of cisplatin and fewer cycles were delivered in the elderly. No differences in toxicity were observed.

Based on these two reports, adjuvant cisplatin-based chemotherapy seems feasible in elderly patients and provides a survival benefit with acceptable tolerance.

Age is not the only parameter to consider in practice, however, and patients from clinical trials with strict inclusion criteria are not always reflecting the general practice population. Decisions should also take into account performance status, comorbidities, compliance issues and patient willingness.

4.2. Japanese population

In Japan, as opposed to the Western world or other Asian countries, fluoropyrimidines are widely used to treat NSCLC. UFT, an oral fluoropyrimidine – either as a single agent or in combination with cisplatin – has been evaluated in randomised clinical trials for the adjuvant treatment of resected NSCLC versus surgery alone. Those trials have been meta-analysed. In the meta-analysis by Hamada et al. [16], individual patient data were collected. Among nine trials, six compared surgery versus surgery + UFT; two had a third arm with cisplatin-containing chemotherapy, but the patients for the third arm were not meta-analysed. Most of the patients presented with adenocarcinoma and early stage I disease. They were treated for a period of 1–2 years with oral UFT. In this selected population of 2003 patients, the use of UFT postoperatively showed a significant benefit at 5 and 7 years compared with surgery alone (respectively +4.3% and +7%) with an HR of death of 0.74 (P = 0.001).

Another Japanese meta-analysis – based on published data of adjuvant trials performed worldwide since 1995 – included 11 trials among which six were UFT-based [2]. A separate analysis of the UFT-containing regimen was provided. Most of the trials were not statistically significant due to small sample sizes. The use of UFT as a single agent on 1751 patients showed a significant benefit with an HR of death of 0.799 (P = 0.015). In the UFT-containing regimen trials the use of UFT was prolonged to 1 or 2 years.

The benefit of UFT in adjuvant chemotherapy is so far limited to Japanese patients since the drug is not used for this indication outside Japan.

5. Predictive biomarkers of chemotherapy efficacy in the adjuvant setting

The benefit of adjuvant chemotherapy in NSCLC is still recent. Very few trials have looked at predictive biomarkers that would allow better patient selection. The available data are from retrospective studies with the limitations associated with such an approach.

5.1. ERCC 1

In 2006, the IALT group reported that the level of expression of ERCC 1 (excision repair cross-complementation group 1) by immunohistochemistry was both predictive for the efficacy of cisplatin-based chemotherapy on survival and prognostic [17]. In a subsequent study from the LACE biology, looking at the four protein isoforms of ERCC 1 in the entire population of the LACE group, with additional antibodies mapping ERCC 1, the predictive effect of ERCC 1 was not validated [18]. Based on these results, ERCC 1 cannot be recommended at the present time to select patients for adjuvant cisplatin-containing chemotherapy.

5.2. KRAS

In the JBR10 trial [10], KRAS mutational status was assessed for its potential value as a predictive factor of resistance to chemotherapy. No differential benefit on overall survival was noticed between KRAS wild-type and mutant patients. However, a trend towards a benefit was observed for disease-specific survival (DSS) with adjuvant cisplatin–vinorelbine in the KRAS wild-type patients (HR of DSS 0.72, P = 0.06), with no benefit in mutant patients.
The LACE Bio group retrospectively analysed 1543 patients for their KRAS mutational status on codons 12, 13 and 14 [19]. Overall, KRAS has no prognostic value according to the survival in the surgery-alone arm. There was also no significant difference in overall survival according to the KRAS mutational status between the control arm and the adjuvant chemotherapy arm. Looking more specifically at the mutation type, there is much variability in the effect of adjuvant chemotherapy among the patients harbouring a codon 12 mutation, none of them being significant due to the size of the samples. The codon 13 mutation was associated with a detrimental effect of adjuvant chemotherapy (HR of death 5.78, \( P = 0.002 \)), but this information would require validation from a larger sample.

At the present time, KRAS should not be used for the decision for adjuvant chemotherapy in NSCLC.

5.3. **Other biomarkers**

The LACE Bio group has undertaken an extensive analysis of biomarkers that could potentially act as predictive factors of adjuvant chemotherapy efficacy. In addition to ERCC 1 and KRAS that have been already reported, this search includes beta-tubuline, mucine, P53, P27, P16, cyclin E, Bax, EGFR mutation as well as histology and lymphocytic infiltration.

Another approach undertaken by several groups is to look for a gene signature that would be associated with improved survival and efficacy of chemotherapy. Several sets of genes have been identified in retrospective studies, but none so far has implications in clinical practice.

At the present time, no predictive biomarker has been identified which could be used in clinical practice. Much hope, however, is placed on such tools to better define selected patients who would benefit from adjuvant chemotherapy.

6. **Conclusion**

As in other human solid tumours, adjuvant chemotherapy for resected NSCLC is now part of the standard of care.

It should be offered at all ages in fit patients resected with stage II and III disease. Stage IB might be discussed, mainly with tumours of \( >4 \) cm in diameter.

Adjuvant chemotherapy in Western countries should be cisplatin based. Among the companion drugs to be combined with cisplatin, vinorelbine is the only third-generation drug that has been evaluated and that has demonstrated durable long-term efficacy. All the other drugs tested – including etoposide, vindesine, vinblastine and paclitaxel (combined with carboplatin) – have finally failed to demonstrate a definitive efficacy. The other third-generation drugs docetaxel, gemcitabine and pemetrexed have never been evaluated in proper randomised trials with overall survival as the primary endpoint. Therefore, the only combination to be used in an adjuvant setting for resected NSCLC, on evidence-based medicine, is vinorelbine–cisplatin. Other compounds – including targeted agents – with proven efficacy in metastatic settings have not been evaluated in the adjuvant setting. Anti-EGFR tyrosine kinase inhibitors have failed to demonstrate a benefit in the adjuvant setting of EGFR-mutated NSCLC in the JBR 19 randomised trial. They cannot be recommended for such use.

Metastatic stages and early or locally advanced diseases have different behaviours. It is known that in other tumour types, such as colon cancer, regimens with similar efficacy in stage IV do not translate into similar benefit in earlier stages. Considering the possibility of cure in the majority of patients with surgery alone, and the limited benefit of adjuvant chemotherapy in terms of improved 5-year survival, no added risk should be taken for the patients in a situation where the risk/benefit ratio is rather small.

**Conflict of interest statement**

The author has no conflicts of interest relating to this article.

**References**


1. Introduction

A prognostic factor is one which determines or is related to the natural history of a disease, in the absence of disease-modifying therapy. A literature search provides innumerable studies purporting to describe such factors prognostic for patients with lung cancer. The potential significance of virtually every conceivable histopathological feature and molecular biomarker has been reported in thousands of studies. Yet in clinical practice, the only prognostic features which are regularly used in clinical decision-making are the tumour stage and the patient’s performance status. This paper will address prognostic factors which are features of the tumour, relating to surgically resected lung cancer. It will not discuss those features of the individual patient which have prognostic significance related to the outcome.

The potential value of efficient prognostication in this particular clinical setting is to enable appropriate selection of patients for adjuvant therapy, determining who should benefit from systemic therapy, with that benefit likely to outweigh potential toxicity. To a lesser extent, knowledge of a prognostic factor before surgery may influence the type or extent of surgery which is carried out, but related practice change is still under trial. Adjuvant treatment is aimed at eliminating clinically undetectable micro-metastatic disease which, if present, may be responsible for tumour relapse. Prognostic factors are therefore predictors of a higher or lower probability of disease relapse and indicators of the likelihood that the surgery alone has cured the patient. Adjuvant therapy is therefore speculative.

Currently, adjuvant cytotoxic chemotherapy is offered to patients with pathological Stage II–III non-small-cell lung carcinoma (NSCLC) and reduces the risk of death by approximately 20% [1]. Trials have demonstrated that surgery effectively cures 64% of patients with p-Stage IB disease and 39% and 26% respectively of patients with p-Stage II and III disease. Only an additional 3% of p-Stage IB patients, and 10%/13% respectively of p-Stage II/III patients, will be alive as a result of adjuvant chemotherapy. Adjuvant chemotherapy in p-Stage IB patients cannot be justified by this modest gain in survival [1–3]. Despite adjuvant chemotherapy, 33% of p-Stage IB, 51% of p-Stage II and 61% of p-Stage III patients succumb to recurrent disease.

The implication of these figures is that current decision-making should be improved to optimise whom and how to treat in the adjuvant setting. Prognostic factors that predict more accurately for postoperative disease relapse could improve selection of those patients most likely to benefit from adjuvant chemotherapy and – equally importantly – where it should be avoided. Factors that predict for effectiveness of individual drugs, which are outside the scope of this review, could be used to decide how to select chemotherapy for those who need adjuvant treatment.

1.1. Tumour stage

Tumour stage, a description of the extent of disease, is the only tumour-related prognostic factor regularly used to inform treatment decisions in patients with lung cancer. The latest iteration of the TNM (tumour, nodes and metastasis) system, the 7th edition, is the culmination of over 80 years of historical development and over 10 years of focused project work by the International Association for the Study of Lung Cancer (IASLC) [4]. This work is a ‘tour de force’ that evaluates a large amount of emerging data, changes in imaging, therapeutic approach and tumour biology, and conflicts between the need for retrospective compatibility with earlier systems and the requirement for better separation of prognostically divergent groups. The project involved analysis of more than 80,000 resected lung cancers, over 68,000 of which were NSCLCs. It amalgamated many international databases, but over half of the cases originated from Europe. Rigorous statistical analysis was applied to the database to produce robust data for all lung cancers, including evidence to support use of the TNM staging system in bronchopulmonary carcinoid tumours and small-cell lung cancer [5–12].

In contrast with the TNM 6th edition, the new TNM 7th edition shows better separation of the Kaplan–Meier survival curves for both clinical and pathological staging [8]. The main changes are (a) the introduction of additional cut-offs of
It is clear that pathological assessment of tumour stage in the surgically resected case is at least equally important as is full histological typing of the tumour [12] (see below). In order to facilitate an accurate assessment of a submitted specimen, there is an onus upon the surgeon to communicate all relevant information to the pathologist. Important factors include anatomical labelling of all specimens, especially lymph-node samples; details of surgery performed, especially if non-standard surgery has been performed, to help assist the assessment of margins; and information regarding any neo-adjuvant therapy delivered. There is also a duty for the pathologist to prepare properly the specimens in advance of dissection, examination and block-taking since these latter steps are key to determining adequate histological examination and pathological staging. Inflation fixation of resected lung bearing tumour is, in the authors’ view, a critical step in preparation. Usually this involves per-bronchial instillation of 10% neutral buffered formalin until the lobe or lung is fully inflated with a smooth pleura. Sub-lobar resections may be inflated by injection. Although some pathologists prefer sectioning down the bronchi, especially for central bronchial tumours, parasagittal sectioning (the authors’ preference) or coronal sections give a better view of the parenchyma, and facilitates both examination of peripheral tumours and correlation with radiology.

### 1.2. Pathological assessment of lymph nodes

It is clearly important to assess intrapulmonary, hilar and mediastinal lymph nodes submitted by the surgeon at the time of lung resection for primary carcinoma, since nodal status is a crucial factor in pathological staging. There is, however, debate in the surgical literature regarding how to deal with the mediastinal nodes at thoracotomy, with inspection, node sampling or radical dissection of all tissues at each station location being the three widely different options [13]. Improved staging, better local disease control and improved disease-free survival from more extensive surgery must be set against longer operation times, increased morbidity and no proven overall survival benefit. The concept of sentinel node sampling, a procedure common in the surgical management of other tumour sites, is poorly developed in the lung [14]. The European Society of Thoracic Surgeons guidelines recommend systematic nodal dissection, to include at least three N1 nodes (inter-lobal and hilar) and three nodes from three stations, including the sub-carinal station, in the mediastinum [15]. There is evidence that the number of lymph nodes resected, the number that is positive for tumour and the percentage of resected nodes which are positive have an influence on postoperative outcome [16–18]. Greater clarity is required around these data and the significance of the number of positive lymph node stations, given that true single-station mediastinal lymph-node metastases seem to carry a more favourable prognosis [19,20]. There are practical difficulties relating to assessing lymph node number if nodal fragments rather than whole nodes are delivered to pathology. There is also evidence that inadequate pathological examination may underestimate the degree of nodal involvement [21,22].

Does the degree of nodal involvement matter? Although it is traditionally taught that extracapsular spread of tumour from mediastinal nodes is a poor prognostic factor, some studies have failed to demonstrate a survival disadvantage [23], raising the possibility that this opinion is probably based on assumption rather than on hard data, especially since such spread may render the disease unresectable, rendering information incomplete.

There has been considerably more debate regarding the significance of micrometastatic disease in lymph nodes in patients with surgically resected NSCLC. The fact that a proportion of patients with pStage I (N0) disease relapse and die of tumour recurrence fuels a presumption of undetected micrometastatic disease at the time of surgery. Micrometastatic disease has no clear definition in the context of lung cancer, unlike in some other tumours such as breast cancer where nodal tumour deposits of <2 mm are regarded as micrometastases. Metastatic disease comprising only a few tumour cells may not be apparent on the standard haematoxylin-and-eosin- (H&E-)stained sections but could be detected on immunohistochemistry (IHC) [24]. Various strategies have been employed to detect micrometastases, usually involving immunohistochemistry with or without multiple step-sectioning of lymph nodes [25,26]. Most immunohistochemistry...
has used antibodies to a variety of cytokeratins, but p53 and Ber-EP4 proteins have also been sought [24]. More recently, studies have utilised reverse transcription polymerase chain reactions (RT-PCRs) for a variety of mRNA transcripts of numerous genes, including mucin1, carcinoembryonic antigen (CEA), p53, KRAS, FHIT, CDKN2A, survivin and livin [24,27,28]. These markers are presumed to be sufficiently specific and sensitive to detect metastases of any size.

The outcome of these studies will depend on the adequacy of the ‘standard’ H&E-based initial assessment which determined N0 status. None of the IHC markers used is specific for tumour cells, and benign intra-nodal inclusions present the risk of a false-positive test. The same lack of specificity applies to most (possibly all) of the mRNA-based studies, although more recent work has used markers which are more specific [27]. Other issues with PCR studies include the following:

- The presence of mRNA does not necessarily mean that tumour cells are present, only that macromolecules have been detected.
- Studies have been based upon the homogenisation and mRNA extraction from fresh/frozen lymph nodes; whilst other nodes from the same location have been deemed negative for metastases, it is an open question as to whether those homogenised nodes would have been histologically negative if examined in that way.
- There are practical implications in basing a routine test on fresh, frozen material; however, mRNA from formalin-fixed, paraffin-embedded tissue can be obtained and amplified.

Whatever the pros and cons of the technical approach, it is the outcome that ultimately matters. Can these techniques upstage – in a clinically significant way – patients otherwise regarded as having pN0 disease? Such studies are prone to reporting bias, with several using a range of approaches ‘upstaging’ 20–30% of patients who were considered to be pN0. It has been suggested that upstaging to pN1 may not ‘upstage’ 20–30% of patients who were considered to be pN0. It has been suggested that upstaging to pN1 may not be clinically significant, unlike upstaging to pN2 [25]. A very detailed original study of over 4000 lymph nodes from 266 Stage I resections, plus a meta-analysis of published work up to 2008, demonstrated that identified micrometastatic disease did not significantly decrease postoperative survival [29]. Subsequent publications, however, based upon mRNA PCR, continue to report significantly poorer postoperative survival in patients who are pN0 by histological examination but molecularly N1 or 2 on those nodes examined by PCR [27,28,30]. Notwithstanding the many technical issues around this approach to detect metastatic disease, and the biological significance of the findings, there is still a lack of trial evidence that patients would benefit from adjuvant therapy based upon a molecular upstaging of their tumour.

1.3. Bronchial resection margins

The status of the bronchial resection margin assessed in the resected specimen has been a matter of some controversy, and it is difficult to analyse due to limited and heterogeneous data. The presence of macroscopic disease at the resection margin (R2) is a poor prognostic factor [31]. R1 disease is also a poor prognostic factor although there are variables which need to be considered: the presence of extrachondral disease at the margin, or lymphangitis carcinomatosa, seems to be particularly poor prognostic factors, as both are associated with N2 disease [32–34]. Invasive disease within the mucosa also determines an R1 resection but may indicate a slightly smaller risk of recurrence, especially in the context of Stage I/II disease [32,34]. The significance of carcinoma in situ at the bronchial resection margin is less clear [33,34]. Unless the disease is extensive and involving bronchial glands as well as the mucosal surface [33], there may be insufficient risk of recurrence to warrant any further therapy [32,34].

2. Tumour histology

Although there is an extensive literature on the subject of tumour histology and prognosis, some studies lack statistical power, and it is difficult to determine whether any factor is significant in multivariate analysis, especially in controlling for Stage and rare tumour types. The use of neo-adjuvant or adjuvant therapy may also bias the outcomes of analyses.

2.1. Squamous versus adenocarcinoma

Is there a significant difference in postoperative survival between squamous-cell carcinoma and adenocarcinoma when controlling for Stage? Even this simple question provides issues to debate, but the probable answer is either ‘very little’ or ‘no difference’ (Table 2). A large German series of 2376 cases found squamous-cell carcinoma patients had a better 5-year survival (SYS) than adenocarcinoma: 53.6% compared with 48.2% [35]. A Japanese Lung Cancer Registry study of 13,010 cases found the opposite: SYS for squamous carcinoma was surprisingly similar to that of the German study at 52.5%, but the SYS for all adenocarcinomas was significantly lower at 45.8%.

<table>
<thead>
<tr>
<th>Study</th>
<th>Total cases</th>
<th>5YS (%)</th>
<th>(\text{Adenocarcinoma} \times 100)</th>
<th>(\text{Large-cell carcinoma} \times 100)</th>
<th>(\text{Adenosquamous carcinoma} \times 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfannschmidt et al., 2007 [35]</td>
<td>2376 cases</td>
<td>53.6</td>
<td>48.2</td>
<td>45.8</td>
<td>-</td>
</tr>
<tr>
<td>Asamura et al., 2008 [36]</td>
<td>13,010 cases</td>
<td>52.5</td>
<td>67.3</td>
<td>45.5</td>
<td>42.1</td>
</tr>
<tr>
<td>Chansky et al., 2009 [12]</td>
<td>9137 cases</td>
<td>43</td>
<td>44</td>
<td>41</td>
<td>29</td>
</tr>
</tbody>
</table>

* These cases would include adenocarcinoma in situ (AIS).

b This is the SYS for adenocarcinomas excluding those diagnosed as ‘BAC’ (see text). Given variations in stage distribution and other potential confounding factors, comparison between cell types within studies are probably more meaningful than those between studies.
better at 67.3% [36]. The likely explanation for this difference is the inclusion of significant numbers of cases of adenocarcinoma in situ or minimally invasive adenocarcinoma in this cohort (see Types of adenocarcinoma, below). These lesions are more common in Japanese studies, and until the publication of the new IASLC/ERS/ATS recommendations of adenocarcinoma classification [37] these cases were often classified as well-differentiated adenocarcinoma. It is now known that they pose no metastatic risk and show 100% SYS. In the IASLC staging study cohort of 9137 cases, cases reported as ‘bronchioloalveolar carcinoma’ (BAC) were separated out from other adenocarcinomas and showed a SYS of only 61%. The low figure suggests that this was still a pathologically heterogeneous group, comprising true ‘BAC’ i.e. adenocarcinomas in situ, and other invasive adenocarcinomas incorrectly classified as BAC (see below). The effect of this separation was to leave the non-BAC adenocarcinoma group with a SYS of 44%, not significantly different from the 43% SYS for squamous-cell carcinomas [12].

2.2. Types of squamous-cell carcinoma

The WHO classification of lung tumours [38] describes a papillary variant of squamous-cell carcinoma that generally has a good prognosis, probably because it demonstrates limited invasion and tends to be of low stage. Similarly, so-called ‘creeping’ squamous-cell carcinoma [39], an invasive tumour confined to the mucosa, demonstrates relatively indolent biology and a relatively good prognosis. Peripherally located squamous-cell carcinoma, arising from third-order or greater bronchi, may be increasing in prevalence. The growth pattern of these tumours may be infiltrative and destructive or non-infiltrative with preservation of lung architecture, the so-called alveolar filling growth pattern [40–42]. When this latter pattern is prominent, tumours tend to be of lower stage, show less vascular invasion (see below), and patients survive for longer [40–42]. Despite the relatively poor prognosis demonstrated by basaloïd carcinoma (see Other histological types, below), the basaloïd variant of squamous-cell carcinoma has been shown to be no more aggressive than poorly differentiated squamous-cell carcinoma [43,44].

2.3. Types of adenocarcinoma

The proposed changes in adenocarcinoma reporting and classification for surgically resected cases – authored by a multidisciplinary group of experts representing the IASLC, the European Respiratory Society (ERS) and the American Thoracic Society (ATS) – are largely based upon significant differences in prognosis demonstrated by different histological subtypes of adenocarcinoma [37]. This work acknowledged published descriptions of bronchioloalveolar carcinoma (BAC) and how that diagnosis is often associated with a better postoperative outcome. It also noted that there was enormous variation in type of tumour classified as BAC, in many instances that were clearly not BAC as defined in the 1999 and 2004 WHO classification. This led to the strong recommendation that the use of the term BAC be discontinued; that cases fulfilling criteria for BAC (small, localised lesions lacking invasion and showing only lepidic growth around alveolar walls) be reclassified as adenocarcinoma in situ (AIS), since such lesions pose no metastatic risk and have 100% SYS [45], and that other lesions with evidence of invasion be classified as invasive adenocarcinoma, even if there is widespread lepidic pattern disease.

In resected invasive adenocarcinomas, the degree of invasion in a lesion which is otherwise AIS with a lepidic growth pattern may be very limited in extent. Assuming that some (most?) adenocarcinomas arising in the lung develop in this way, such lesions would be expected. If the focus of invasion in such a lesion is <5 mm in maximum diameter, there is still no metastatic risk and patients have 100% SYS [46,47]. Such lesions are classified as minimally invasive adenocarcinomas (MIAs). If the focus of invasion, characterised by one or more of the other four invasive adenocarcinoma patterns (acinar, papillary, micropapillary, solid with mucus), is >5 mm across, the resected tumour is classified as invasive adenocarcinoma and a qualifier should be added to the classification when the report is issued by the pathologist, indicating which pattern of disease is the predominant one. This is also strongly recommended because of the notable prognostic effect: several studies have shown that resected adenocarcinomas with a predominantly lepidic pattern have a relatively good prognosis, independent of stage. Conversely, cases which are predominantly micropapillary or solid in pattern have a relatively poor prognosis [48–52]. Some studies show poor prognosis for papillary predominant disease [50], whilst others do not [48], possibly due to differences in interpretation of the papillary pattern. Although these patterns can be reliably and consistently identified, some are more difficult than others, notably papillary patterns [53].

2.4. Multiple tumours

The presence of multiple synchronous carcinomas was traditionally considered a poor prognostic factor for both squamous-cell carcinomas and adenocarcinomas [54], presumably reflecting intrapulmonary metastases in many cases. A better understanding of carcinogenesis in these two distinct tumour types, and recognition that multiple synchronous primary tumours – especially adenocarcinoma – are not uncommon, has modified this view. Multifocal disease undoubtedly reflects a biologically heterogeneous group of cases, making generalisations unhelpful. Unusual cases of mucinous or non-mucinous multifocal, predominantly lepidic pattern adenocarcinomas (the mucinous form now referred to as mucinous adenocarcinoma) were formerly considered to be BAC, despite these cases not fulfilling the post-1999 definition. Although demonstrating relatively indolent growth behaviour, these tumours carry a relatively good prognosis, with less propensity to spread widely outside the thorax, although they are invasive and do represent advanced, potentially fatal disease.

2.5. Other histological types

Large-cell carcinomas and sarcomatoid carcinomas appear to be aggressive, often large lesions [38]. Whether the associated poor prognosis is independent of stage is less clear. In the large studies presented in Table 2, large-cell carcinomas...
appear to have a consistently and significantly lower SYS. Sarcomatoid carcinomas are rare lesions which may or may not demonstrate components of differentiated squamous-cell or adenocarcinoma. These tumours are renowned for a poor prognosis and aggressive behaviour, although published series of cases are generally small [55–58]. There are two variants of large-cell carcinoma which are notable for their poor prognosis: basaloid carcinoma and large-cell neuroendocrine carcinoma (LCNEC). Case series of basaloid carcinomas are few, but data suggest an aggressive tumour, often of high stage at presentation, and a propensity for brain metastases [59,60]. LCNEC is a high-grade neuroendocrine carcinoma sharing many epidemiological and genetic features with small-cell carcinoma. This is a highly invasive tumour type prone to widespread metastases [61–63].

2.6. Other histological features

Certain histological features, independent of histological tumour type, have been shown to be independent prognostic factors. Features such as vascular invasion, lymphatic invasion, pleural invasion, tumour necrosis and poor differentiation have been so reported. The first three features are intuitive, and relate to key factors in the TNM system which correlate with poor prognosis. Vascular invasion within the tumour is a feature consistently associated with early relapse featuring distant metastatic disease [64]. Lymphatic invasion is associated with increased risk of lymph-node metastases [65]. The poor prognostic effect of pleural invasion is reflected in this feature, upstaging tumours in the TNM classification [66]. Tumour necrosis is usually associated with larger tumours, more poorly differentiated lesions and greater proliferative activity being indicative of an aggressive phenotype. Poor differentiation has long been associated with aggressive tumour behaviour and most of the other features determining higher tumour stage [38]. Criteria for grading tumours in this way have been poorly described and undoubtedly inconsistently applied by pathologists. However, there is increasing interest in tumour grading as an important factor in lung tumour pathology [67].

Tumour cell proliferation deserves particular consideration. High mitotic activity has long been recognised as an indicator for the presumption of relatively rapid tumour growth, and high mitotic indices are certainly associated with poorly differentiated tumours and tumours which have recognised aggressive biology (small-cell and large-cell neuroendocrine carcinomas). It also is a diagnostic defining feature for carcinoid versus atypical carcinoid tumour, and de facto, of large-cell neuroendocrine carcinoma with most assessments made on resected tumour specimens. This differential diagnosis carries recognised prognostic significance [38].

There are several problems in relying upon mitotic index as an indicator of likely tumour growth rate:

- Mitoses may be difficult to recognise on pathological specimens.
- The mitotic (M) phase of the cell cycle is relatively short so may poorly reflect overall cell cycle activity.
- Actual tumour growth is dependent on the balance between cell production and cell loss, the latter being very difficult to assess in tumours.

Proteins expressed during part or all of the cell cycle have been used as proliferation markers, although strictly speaking they only indicate cell cycle ‘activity’ and do not provide unequivocal evidence of cell division. These markers include proliferating cell nuclear antigen (PCNA), Ki67, a variety of the minichromosome maintenance proteins (MCMs) and histone-H3. MCMs may have an advantage over Ki67 in being evenly expressed throughout all phases of the cell cycle, whereas Ki67 accumulates later in G1, persisting through S, M and G2. PCNA has not shown convincing prognostic significance in NSCLC [68]. By far the greatest literature has been concerned with Ki67 expression in both early, surgically resected and advanced NSCLC, mostly as measured by the MIB1 antibody [68,69]. Two reviews, including publications up until 2006, described 46 reports of Ki67 as a prognostic factor in NSCLC [68,69], of which only 19 (41%) show ‘over-expression’ of Ki67 as a poor prognostic marker. Most found no independent effect on prognosis.

Actual tumour growth rates may be derived from preoperative imaging measurements and expressed as a volume doubling time (vDT) [70,71]. This parameter has been related to postoperative survival, some studies demonstrating an association between short vDT and poorer prognosis, although the relationship is not clear cut [72–74]. vDT is also used as a factor in predicting malignancy during nodule follow-up, often in the context of lung cancer screening [74,75].

3. Tumour molecular pathology

There is probably more literature on the putative prognostic effects of molecular markers in lung cancer than exists for other prognostic features in this disease. This is not surprising since molecular changes are the fundamental factors driving each tumour, making it behave in a unique way. Molecular markers are perceived to be more objective assessments than are some other pathological features. They are also considered to be more easily measured, numerous and to possess ‘scientific’ and ‘topical’ cache.

Studies have ranged from single marker investigations to pan-genomic works using a variety of approaches. Comparing studies of the more commonly investigated biomarkers is hampered by enormous heterogeneity of study design, variation in techniques, case mix and interpretation of data. Contradictory conclusions are frequently drawn, and perhaps because of this – and despite the enormous amount of data available – there is not a single molecular prognostic biomarker in regular clinical use for managing patients with lung cancer. A review of the topic in 1995 identified this issue and proposed trials of biomarkers in selecting patients for adjuvant therapy on the basis of claimed prognostic significance [76]. To date, very little progress has been made. It is only recently that mRNA-based gene signatures have been seriously investigated in this context (see below). Single gene studies have tended to use immunohistochemistry (IHC) to identify the protein product of the gene(s) of interest, although there are many studies looking at gene mutation, fusion or amplification using a variety of techniques. Gene transcription products (mRNA) have also been used, either for specific genes or using a more global approach using array techniques. Global
Following others’ methodology in reviewing the literature [79], in 2006 Zhu and colleagues published an excellent and extensive review of 462 original papers and 12 reviews on immunohistochemical markers of prognosis in NSCLC published between 1987 and 2005 [68]. These studies focused mainly on resected NSCLC. Their data were helpfully grouped according to Hanahan and Weinberg’s original six hallmarks of cancer [80] and accounted for 50 different markers. They identified five markers (EGFR, HER2, Ki67, p53 and bcl2) which had been extensively studied and were the focus of meta-analyses. For Ki67 and p53, higher levels of expression showed a weak but significant poor prognostic effect whilst high bcl2 showed a weak but significant poor prognostic effect. The authors suggested that ‘over-expression’ of cyclinE and VEGF, and p16, p27 and beta-catenin, were ‘promising’ as poor and good prognostic factors respectively. They also highlighted hepatocyte growth factor (HGF) and MET as critical factors to that of Zhu et al. but concentrated on biomarkers around a point elsewhere in the range. It is much better to use a statistical approach to determine the most effective threshold [86]. This is just one of the methodological factors which requires to be standardised if real progress is to be made with tumour biomarker testing and application [68,87].

3.1. Immunohistochemistry

The plethora of literature and inconsistency of data were highlighted in a further review [83] which also suggested that, given the molecular heterogeneity of lung cancer, it was unlikely that a single marker would emerge as universally useful. Essentially this is true, although a decision to treat or not could be based upon a simple binary evaluation of a reliable marker at a certain threshold, including patients with no expression. Such a marker has yet to emerge. Meta-analyses have suggested that TTF1 is a good prognostic factor in resected adenocarcinoma [84], whilst COX2 may be a weak, poor prognostic factor in stage I disease [85].

The determination of the best threshold (cut-off) for a quantifiable biomarker is also frequently unexplained or poorly executed. Simplistic approaches such as present/absent or above/below a median may ignore the biology of the system under study and will fail if the effect sought varies around a point elsewhere in the range. It is much better to use a statistical approach to determine the most effective threshold [86]. This is just one of the methodological factors which requires to be standardised if real progress is to be made with tumour biomarker testing and application [68,87].

3.2. Gene mutation and copy number

Gene mutations potentially have the same pitfalls as single IHC biomarkers, in terms of being ubiquitous and yet adequately discriminating in order to be clinically useful. Unlike with IHC biomarkers, where NSCLC subtype has largely been ignored, mutation studies have demonstrated prognostic effects for some mutations which are mostly found in lung adenocarcinomas.

TP53 mutations are the commonest mutation found in lung cancer and do appear to be associated with poor prognosis, but they are associated with positive smoking status, squamous cell as opposed to adenocarcinoma histology, male gender, poor tumour differentiation and higher stage disease at presentation [88,89]. Analysis of the effect of the mutation, as opposed to other associated factors, is therefore challenging. In multivariate analyses, TP53 mutations have not been reliably independent prognostic factors in two surgical series [88,90], despite being associated with shorter postoperative survival in one of these studies [88].

Mutations in codons 12, 13 and 61 of KRAS are relatively frequent in lung adenocarcinomas, being found in up to 40% of European and North American cases but in around 10% of Japanese cases [88,91,92]. Individual studies and meta-analysis have demonstrated a poor prognostic effect of KRAS mutation [88,90,91,93–95] but some of these associations were rather weak and have not stood up to multivariate analysis [88,90,94,96]. KRAS mutation is associated with positive smoking status, poor tumour differentiation and higher stage, again probably confounding the prognostic effect. The presence of increased gene copy number as well as mutation in KRAS has been associated with poor prognosis [95].

Mutations on the tyrosine kinase domain of EGFR occur in around 50% of adenocarcinomas in East Asian patients and around 15–20% of European/North American patients [92].

Gene mutations potentially have the same pitfalls as single IHC biomarkers, in terms of being ubiquitous and yet adequately discriminating in order to be clinically useful. Unlike with IHC biomarkers, where NSCLC subtype has largely been ignored, mutation studies have demonstrated prognostic effects for some mutations which are mostly found in lung adenocarcinomas.
EGFR mutations, associated with female gender and never smoking, are generally perceived to be a good prognostic factor. Although some studies have shown a good prognostic effect in surgically resected adenocarcinomas, there are many studies in which this effect does not survive multivariate analysis. EGFR mutations are associated with lower stage disease, and tumours with a predominantly lepidic component, all factors known to carry a good prognosis. In adenocarcinomas, high copy number of EGFR was reported as a good prognostic factor in one study, but another found no effect. In studies looking at 'NSCLC', EGFR polymer amplification has been reported as a poor prognostic factor overall, or in squamous-cell carcinoma but not in adenocarcinoma. The overall impression is that whilst EGFR mutations are associated with a better prognosis, this effect is not independent of the other good prognostic factors with which this mutation is associated.

To expand on the statement regarding HGF as a poor prognostic factor, MET is the HGF receptor and increase in MET gene copy number is associated with poorer survival through more aggressive tumour biology, higher tumour stage and histological grade. ALK fusion genes and BRAF mutations are targetable oncogenic drivers in advanced adenocarcinomas. ALK fusion may be a good prognostic factor in surgically resected and advanced-stage adenocarcinomas, even although ALK fusion is associated with solid and cribriform adenocarcinomas with signet ring cells, aggressive histological features, ROS1 and RET fusion both also appear to be good prognostic factors. This may be because tumours bearing these various gene fusions are not associated with tobacco carcinogenesis. BRAF mutations are associated with micropapillary adenocarcinoma histology, a poor prognostic factor.

### 3.3 Pan-genomic studies

Global chromosomal disarray, often reflected in tumour-cell nuclear pleomorphism, has long been associated with aggressive tumour behaviour. More extensive genetic gains and losses shown by comparative genomic hybridisation (CGH) are associated with higher tumour stage, poor differentiation and tumour progression, and early relapse of resected adenocarcinoma.

Oligonucleotide and cDNA expression microarrays can be used to determine the expression of thousands of genes from mRNA extracted from resected tumour samples. This technology has been used extensively to characterise resected lung carcinomas. The clustering of tumours into different groups that share patterns of gene expression has led to subdivisions and molecular classifications of lung adenocarcinomas in particular. These subdivisions have been associated with differential patient survival, but a closer examination of the categories with better or worse prognosis suggests many of these molecular subdivisions are recapitulating histological factors already recognised as prognostic: well and poorly differentiated tumours, or lepidic predominant tumours.

There is also an extensive literature investigating the potential for mRNA-based gene expression profiles to predict overall survival in surgically resected lung cancer, disease recurrence in stage I patients and lymph-node metastatic disease. Panels (signatures) ranging from 2 to 8644 genes were identified for squamous-cell carcinoma, adenocarcinoma or all histological types, but it is striking that there is almost no overlap in the genes identified between studies. Also, depending on the statistical methods applied, it is possible to generate different predictive signatures from the same data set. The extent to which investigators undertook validation of their signature is variable. One large study did attempt multi-institutional validation but essentially failed to produce a robust, consistent signature, although the molecular data did appear to enhance the prognostic value of the clinical data available. One PCR-based study did validate a ten-gene prognostic signature for Stage I adenocarcinoma between a European and a North American centre with 75% accuracy, whilst another validated a 14-gene expression assay in two North American and one Chinese institution, generating three risk groups in resected stage I-III non-squamous carcinomas ranging from 74.1% to 44.6% 5YS. There is no overlap between the 10- and 14-gene sets used by these groups, and neither of these studies included squamous-cell carcinomas.

The appeal of such positive signatures is obvious, but there are many similar and all claim more or less the same prognostic power. None of these has been prospectively tested as a means to select patients for adjuvant therapy, but trials are ongoing and the outcomes are awaited with interest. Whether any of these trials will risk (allow?), in case of adenocarcinomas, any comparison with the prognostic stratification by histology remains to be seen.

Other molecular signatures have been related to prognosis. In studies of squamous-cell carcinoma, a panel of five microRNAs (miRNA) expression has been related to increased mortality risk in squamous-cell carcinomas, whilst miRNA expression was found to be superior to an mRNA signature in predicting overall survival. Lu et al. reported two prognostic miRNA signatures in resected stage I lung cancer, one for all NSCLC types, and a different one for adenocarcinoma only. Promoter methylation of the F16 gene as a mechanism of gene silencing has been suggested as a poor prognostic factor in NSCLC in one meta-analysis. In a case-control study of resected Stage I NSCLC, promoter methylation of P16, CDH13, RASSFIA and APC was associated with early relapse due to tumour recurrence, an effect independent of stage, tumour histology and patient characteristics.

There is no specific conclusion to be reached with regard to resected NSCLC genetics and prognosis. It stands to reason that more aggressive tumour behaviour, with the propensity for postoperative disease relapse, is likely to be driven by genetic changes in tumours. Given the diversity of NSCLC, it seems unlikely that any such ‘genetic signature’ will comprise only one or two altered genes. Combinations of genetic alterations making an individual tumour more aggressive are highly likely to vary from case to case, depending upon histology, aetiology and other factors. It remains to be seen whether clinically useful prognostic genetic signatures can be identified, and what forms of genetic alteration these will be.
4. **Tumour immunology**

The importance of the tumour immune response in tumour progression has been recognised by the inclusion of both tumour-promoting inflammation and mechanisms to avoid immune destruction in the next generation of hallmarks of cancer [146].

Chronic inflammatory cell infiltrates (lymphocytes, plasma cells and macrophages) are common in resected NSCLC but global histological assessment of these infiltrates has failed to show prognostic significance [147]. If, however, the microlocation (stroma versus amongst the tumour cells) and cell content of these infiltrates are taken into account, there is an effect on prognostics in resected NSCLC. Intra-tumoural infiltrates rich in CD4+ lymphocytes and S100+ Langerhans cells are associated with better postoperative survival [148]. Uncommon examples of resected NSCLC showing marked immune cell destruction reminiscent of immunological regression seen in renal and skin cancers have been reported [149]. These cases had a superior postoperative survival, showed evidence of radiological shrinkage prior to resection, and were characterised by infiltrates rich in Langerhans cells, CD4+ and CD57+ lymphocytes and macrophages.

More recent studies have been better able to characterise the nature of intra-tumoural immune-cell infiltrates, and there are several reviews and many reports of tumour-infiltrating lymphocytes (TIL – B cells, CD4+ and CD8+ T cells, natural killer cells), macrophages, plasma cells and others, generally demonstrating that immunological reactions seem to indicate a more favourable prognosis in resected NSCLC [149–152]. There are reports, however, of certain TIL cell types, such as FoxP3+ T cells and macrophages over-expressing IL10 or TREM-1, which seem to be pro-tumourigenic and associated with shorter survival [150]. Prognostic immune gene profiles have also been derived from tumour mRNA extracts [150], supporting the histological data on intra-tumoural immune-cell infiltrates. In an interesting evolution of this argument, mRNA gene signatures derived from circulating blood mononuclear cells have been shown to be prognostic in NSCLC patients [153,154].

5. **Tumour metabolism**

Tumour metabolism, as assessed by 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), has been shown to correlate with tumour stage, lymph-node involvement and postoperative survival [155]. Higher PET positivity (SUV\(_\text{max}\)) indicates higher tumour metabolism and is a poor prognostic factor which also correlates with central tumour location, squamous-cell rather than adenocarcinoma subtype, poor tumour differentiation, larger tumour size, pleural invasion, lymph-node metastases and higher stage. SUV\(_\text{max}\) has been shown to be an independent prognostic variable in resected NSCLC in multivariate analysis [156–158]. In resected stage I adenocarcinomas, patients at high risk of disease recurrence could be identified on the basis of lymphovascular invasion and by SUV\(_\text{max}\) [158]. High SUV\(_\text{max}\) also correlates with high tumour-cell density and high cell cycle activity (Ki67 assay) [157]. In a meta-analysis, 11 out of 13 studies concluded that high SUV\(_\text{max}\) was a poor prognostic factor in resected NSCLC [159]. The threshold SUV\(_\text{max}\) described by various authors separating good from poor prognostic cases is very variable, probably the result of case and histological mix, but also variations in scanners used.

6. **Conclusion**

There is a clinical need for better prognostic markers which more effectively identify patients with resected NSCLC who are at most risk of disease relapse/recurrence, in the hope that more efficient selection will lead to better outcomes from adjuvant therapy. Many studies have identified prognostic factors relating to the tumour type, extent, histopathological features, individual molecular characteristics and more global, multiplex genetic assessments as well as factors related to tumour immune responses and metabolism. Of these, only tumour stage is currently used in clinical decision-making, but the relatively poor survival gains from adjuvant therapy suggest that this approach to patient selection could be improved upon. Given the multiplicity of NSCLC types, frequent intra-tumoural heterogeneity and the biological differences between the two major subtypes of squamous-cell carcinoma and adenocarcinoma, it is unlikely that a single histological feature or molecular change will provide the required finer discrimination. It is also likely that any solution will differ between squamous-cell carcinoma and adenocarcinoma. More complex, multiplex assessments of genetic change may prove more effective, but we should not ignore histopathological classification which, ultimately, is a morphological reflection of the myriad genetic changes present in the lesion. Prospective trials to select adjuvant therapy based upon proven prognostic factors are needed, but these should embrace validated histopathological assessment as well as molecular profiles.

**Conflict of interest statement**

No conflicts of interest declared in relation to this article.

**REFERENCES**


[39] Nagamoto N, Saito Y, Suda H, et al. Relationship between length of longitudinal extension and maximal depth of


Anatomical cancer extent is an important predictor of prognosis and determines treatment choices. In non-small-cell lung cancer (NSCLC) the tumour–node–metastasis (TNM) classification developed by Pierre Denoix replaced in 1968 the Veterans Administration Lung cancer Group (VALG) classification, which was still in use for small-cell lung cancer (SCLC). Clifton Mountain suggested several improvements based on a database of mostly surgically treated United States (US) patients from a limited number of centres. This database was pivotal for a uniform reporting of lung cancer extent by the American Joint Committee of Cancer (AJCC) and the International Union against Cancer (IUCC), but it suffered increasingly from obsolete diagnostic and staging procedures and did not reflect new treatment modalities. Moreover, its findings were not externally validated in large Japanese and European databases, resulting in persisting controversies which could not be solved with the available database. The use of different mediastinal lymph-node maps in Japan, the (US) and Europe facilitated neither the exchange nor the comparison of treatment results.

Peter Goldstraw, a United Kingdom (UK) thoracic surgeon, started the process of updating the sixth version in 1996 and brought it to a good end 10 years later. His goals were to improve the TNM system in lung cancer by addressing the ongoing controversies, to validate the modifications and additional descriptors, to validate the TNM for use in staging SCLC and carcinoid tumours, to propose a new uniform lymph-node map and to investigate the prognostic value of non-anatomical factors. A staging committee was formed within the International Association for the Study of Lung Cancer (IASLC) – which supervised the collection of the retrospective data from >100,000 patients with lung cancer – treated throughout the world between 1990 and 2000, analyse them with the help of solid statistics and validate externally with the Surveillance, Epidemiology and End Results (SEER) database.

The ten modifications and the mediastinal lymph-node map – which were proposed in 2007 and adopted by the AJCC and IUCC in their respective seventh revision of the TNM system – were implemented as of 2010 and were rapidly adopted by the thoracic oncology community and cancer registries. As expected, not all controversies could be fully addressed, and the need for a prospective data set containing more granular information was felt early on. This data set of 25,000 consecutive incident cases will form the base for the eighth revision in 2017 and is currently being collected. Other threats are the role of stage migration and the increasing number of biological factors interfering with disease extent for prognostication. The latter issue will be addressed by the creation of a prognostic index, including several prognostic factors, of which stage will be one. For the time being, the seventh TNM classification is considered the gold standard for the description of disease extent, initial treatment allocation
1. **Introduction**

1.1. **Background**

Prognostication of outcome is of all ages and a distinguishing feature of mankind. Similarly, linking features of a tumour to its natural history has been reported since pharaonic times. Surgical resection often being the only modality available at presentation in those days, anatomical tumour extent was from the early days associated with outcome and became a pivotal driver in treatment allocation and evaluation. It was the seminal work of the French surgeon Pierre Denoix in the 1940s and 1950s that led to the creation of the committee on Clinical Stage Classification and Applied Statistics within the Union for International Cancer Control (UICC), and the development of the tumour–node–metastasis (TNM) classification which is still the current gold standard for the anatomical staging of most solid malignant neoplasms.

In the first edition of the UICC manual, lung cancer was classified with ‘other sites’, although several publications had already addressed the relationship between anatomical extent and outcome [1–4]. The United States (US) surgeon Clifton Mountain progressively introduced new denominators and substages based on the analysis of a mostly surgical database from US institutions [5–10]. Although some of his data were externally validated in other cancer registry series, it became increasingly clear by 1996, when the sixth edition of the lung cancer TNM classification appeared, that a further refinement had become necessary, that the revision procedure had several limitations and that there was a growing need for uniformity in the nomenclature used to describe nodal stations [11–13]. Globally, two nodal maps were in use: the Mountain/Dressler [14] used in North America and parts of Europe, and the Japanese Naruke map [15] used in Asia and other parts of Europe.

The International Association for the Study of Lung Cancer (IASLC) undertook the ambitious International Staging Project in which an international database was assembled, consisting of more than 67,000 cases of lung cancer, treated between 1990 and 2000 by all modalities of care and collected retrospectively from 46 data sources from more than 19 countries around the world [16]. The size of this database allowed validation, both internal and external, of the revisions to descriptors and stages to a degree unprecedented in the history of TNM. The IASLC staging project has delivered a seventh edition of the TNM classification for lung cancer that aligns stage with prognosis more closely than before [17]. It was enacted on January 1, 2010, and all of its proposed revisions were subsequently accepted by the UICC [4] and the American Joint Committee on Cancer (AJCC) [18,19].

1.2. **The seventh edition of the TNM classification of lung cancer**

The major modifications are listed in Table 1 [20,21]. Tumour size has been given added importance [22]. New T size cut-points were originally identified in the node-negative, pathologically staged patients having undergone complete resection, but were also shown to be valid in the clinically staged patient cases: 2 cm separating T1a and T1b, 5 cm dividing T2a from T2b and size >7 cm becoming a T3 descriptor for the first time. If these larger tumours are node-negative, they move to stage IIA if T2b N0 M0 and to stage IIB if T3 N0 M0; previously these were all considered stage I B [23].

When additional tumour nodules are found synchronously with a known lung cancer, the distinction between lung metastases and multiple primary tumours has relied on clinical and morphological criteria [24]. The distinction is easy when tumours are of different cell types, and there is little debate if tumours are of the same cell type but associated with separate areas of carcinoma in situ, although in most cases this is confirmed only after resection. The other criteria are more problematic: the tumours should be distinct and separate, should lie in different segments, lobes or lungs, and should not be associated with any nodal involvement in an area of common lymphatic drainage. Although 20 years later there was a suggestion to modify these criteria by the addition of DNA ploidy [25], the criteria have otherwise remained unchanged despite the enormous advances in imaging, histopathology, immunohistochemistry, mutational analysis and biopsy techniques since that time. In the latest edition, the distinction between synchronous primary tumours of similar histological appearance and metastases has been clarified, and the pathologist has been given a central role in this process, allowing the distinction to be made on biopsy specimens before a decision is taken on the most appropriate treatment. Multiple tumours of similar histological appearance may now be considered to be synchronous primary tumours if in the opinion of the pathologist – on the basis of features such as differences in morphology, immunohistochemistry and/or molecular studies or, in the case of squamous cancers, on the basis of association with carcinoma in situ – they represent different subtypes of the same histopathological cell type. Such cases should also have no evidence of mediastinal nodal metastases or of nodal metastases within a common nodal drainage. Clearly, if the management of any particular patient is dependent on this distinction, the biopsy of more than one lesion may be necessary. In other situations, or where this is considered impractical, one may fall back on a generic principle of giving the patient the benefit of the doubt and assigning the lower T category and/or stage. Multiple synchronous primary tumours should be staged separately. These may be recorded sepa-
rately, or if a single TNM category is required, the highest T category and stage of disease should be assigned and the multiplicity of the lesions categorised as (m), or the number of tumours should be indicated in parentheses, for example: T2(m) or T2(5). If the lesions are concluded to be metastases, then the appropriate T or M category will be dependent on the site of the nodules (Table 2). If in the same lobe as the primary they are now classified as T3 and, when associated with node negativity, are stage IIB. When associated with N1 or N2 disease they are now classified as stage IIIA, not IIIB. Tumours associated with additional nodules in other ipsilateral lobe(s) have been reclassified as T4 rather than M1. When associated with N0 or N1, these patient cases should be designated as stage IIIA, and with N2 or N3 as stage IIIB. Tumours associated with additional nodules in the contralateral lung remain M1 but have been reclassified as M1a.

The T4 descriptor remained unchanged, but when associated with N0 or N1 disease, it was down-staged to stage IIIA, not IIIB. Tumours associated with malignant pleural/pericardial effusion or pleural/pericardial nodules have been reclassified as M1a rather than T4 [26]. These data reflect the algorithm previously developed to treat patients with so-called wet IIIB disease with systemic therapy. Tumours associated with distant metastases have been reclassified as M1b.

Analysis of the IASLC database allowed validation of the existing N categories, which were adopted without change [27]. Both existing lymph-node maps were unified in the IASLC nodal map [28], and the precise anatomical definitions of each nodal station are now recognised by the UICC and AJCC as the recommended means of describing regional lymph-node involvement for lung cancer. An important modification to both previous maps is the observation that the anatomical and oncological midlines in the superior mediastinum no longer coincide. The oncological midline deviates to the left lateral border of the trachea at the thoracic inlet and returns to the midline at the carina. Thus, all nodes in the superior mediastinum that lie anterior to the trachea are grouped with right upper paratracheal station 2 and right lower paratracheal station 4. Involvement of these nodes by a right-sided tumour will now be classified as N2-disease, whereas for a

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**Table 1 – Ten modifications in the tumour–node–metastasis (TNM) of lung cancer in the seventh UICC classification [17–20].**

<table>
<thead>
<tr>
<th>Summary of change</th>
<th>Details of new definition</th>
<th>References</th>
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<tbody>
<tr>
<td>1. Subclassification of T1/2 according to largest tumour diameter</td>
<td>≤ 2 cm: T1a; 2.1–3.0 cm: T1b; 3.1–5.0 cm: T2a; 5.1–7.0 cm: T2b; &gt;7 cm: T3</td>
<td>[22]</td>
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<tr>
<td>2. Reclassification of synchronous additional tumour nodules (ATNs)</td>
<td>See Table 2</td>
<td>[22]</td>
</tr>
<tr>
<td>3. New borders for mediastinal lymph-node stations</td>
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<td>[28]</td>
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<tr>
<td>4. Reclassification of malignant pleural/pericardial effusion</td>
<td>M1a</td>
<td>[26]</td>
</tr>
<tr>
<td>5. Subclassification of M1</td>
<td>Limited to thorax: M1a; extrathoracic spread: M1b</td>
<td>[26]</td>
</tr>
<tr>
<td>6. Use of TNM in SCLC and carcinoid tumours</td>
<td>T2bN0 becomes stage IIA instead of IB; T2aN1 becomes IIA instead of IIB; T4N0/1 becomes IIIA instead of IIIB</td>
<td>[35–37]</td>
</tr>
<tr>
<td>7. Appropriate (sub)stage regrouping (Fig. 1)</td>
<td></td>
<td>[23]</td>
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<tr>
<td>8. Elimination of Mx descriptor</td>
<td></td>
<td>[19]</td>
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<tr>
<td>9. Optional descriptor for pleural (Pl) invasion</td>
<td></td>
<td>[38]</td>
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<tr>
<td>10. Optional descriptor for perineural (Pn) invasion</td>
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<td>[19]</td>
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**Table 2 – The fate over time of multiple synchronous primary tumours.**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Same lobe as primary tumour</td>
<td>Tn +1</td>
<td>T4; at least stage IIIb</td>
</tr>
<tr>
<td>Same lung, other lobe</td>
<td>T4; at least stage IIIb</td>
<td>M1: stage IV</td>
</tr>
<tr>
<td>Other lung</td>
<td>M1: stage IV</td>
<td>M1: stage IV</td>
</tr>
</tbody>
</table>

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left-sided tumour, this will become N3-disease. This is in keeping with the observations of some Japanese colleagues [29]. In addition, the concept of nodal zones has been introduced, amalgamating adjacent nodal stations into larger anatomic units. An exploratory analysis of the IASLC database studied survival after complete resection in relation to the extent of node involvement using the zonal concept. Three groups were identified, with significant differences in survival. Those with single-zone N1 disease had the best survival, at 48% over 5 years. Patients with multizone N2 disease had the worst survival, at 20% over 5 years. The third group, with intermediate survival, consisted of patients with multizone N1 (35% 5-year survival) and those with single-zone N2-disease (34% 5-year survival). This refinement is presently under investigation, in order to make the nodal map of greater use to oncologists and radiologists, who are frequently tasked with classifying more bulky nodal disease that might transgress the boundaries of individual nodal stations.

As many as 40% of the reports on lung cancer resection specimens contain no information on mediastinal node involvement [30]. It is known that the greater the number of lymph nodes removed at thoracotomy, the higher the survival rate [31,32], even if all nodes are shown to be negative, presumably by increasing the certainty of the N0 classification [33]. The development of an internationally agreed nodal classification has allowed the reintroduction of minimum requirements for nodal assessment at surgery and subsequent pathological evaluation. In the latest edition of TNM, there is now an expanded definition of complete resection (R0), which recommends that at least six lymph nodes/nodal stations be removed/sampled and confirmed on histology to be free of disease to confer pN0 status [34]. Three of these nodes/stations should be mediastinal, including the subcarinal nodes (station 7) and three from N1 nodes/stations. It is hoped that the setting of this basic standard will improve nodal assessment and thereby the outcomes of pulmonary resection for lung cancer.

The above mentioned modifications in T and N have led to a migration of cases in between pre-existing (sub)stages (Fig. 1): T2bN0 becomes stage IIA instead of IB; T2a N1 becomes IIA instead of IIB; T4N0/1 becomes IIA instead of IIIB.

Small-cell lung cancer has always been excluded from the TNM classification. However, the seventh edition is the first to show that TNM has greater utility than the limited versus extensive stage split commonly used in clinically staged patients as well as those treated surgically, especially as a stratification factor in clinical trials of earlier-stage disease [35,36]. Although the TNM classification was already used in both the typical and atypical variants of carcinoid tumours, the seventh edition is the first to validate this practice [37].

There has never been an internationally agreed definition of visceral pleural invasion (VPI). This created difficulties for the IASLC staging project when attempting to define the interrelationship between VPI and other prognostic factors such as tumour size. An internationally agreed definition was therefore developed, in which VPI is defined as ‘invasion beyond the elastic layer including invasion to the visceral pleural surface’ [38]. In addition, a comment was added recommending the use of elastic stains when this feature is not clear on routine histology. With these refinements, VPI was carried forward into the seventh edition without change, and the IASLC proposed an optional more detailed classification of pleural invasion, adapting the P category developed by the Japan Lung Cancer Society to create a PL classification [39,40]. The impact of visceral pleural invasion on survival according
to size was reported according to the seventh UICC classification and confirmed its proposed Pl descriptor [41].

Other changes, generic to the seventh edition of UICC, are the elimination of Mx and the introduction of a descriptor of perineural invasion Pn.

1.3. Implications of the 7th edition

Several authors have addressed the magnitude of the impact of the modifications on stage grouping. Van Meerbeeck et al estimated that in the IASLC data set of 15,952 resected patients, the change of p-TNM staging classification from UICC 6 to 7 results in the net migration of 23% of resected cases: stage pIB (-1326), stage pIIA (+2017), stage pIIB (+730), stage pIIIA (+701), stage pIIIB (-745) and stage pIV (+83) (Fig. 2) [42]. The magnitude of up- and down-migration is similar. Substage migration resulted in an increase in 5-year survival of 4% in p-IIB and a decrease of 10% in p-IIIIB. This stage migration should be accounted for when comparing outcome across surgical series using different TNM classifications. In a Norwegian cancer registry series from 2001–2005, the concordance index was 0.68 for both editions, indicating no overall difference in their predictive accuracy [43]. In the seventh edition, 211 (29%) stage IB patients migrated to stage II and 161 (48%) patients migrated from stage IIB to IIA. Stage migrations could change the treatment for up to 326 (17.3%) of the patients in this series [43].

1.4. Strengths

Lung cancer stage definitions have never been subjected to such an intense validation process [44]. Internal validity was addressed by visually assessing the consistency of Kaplan-Meier curves across database types and geographic regions. External validity was addressed by assessing the similarity of curves generated using the population-based Surveillance Epidemiology and End Results (SEER) cancer registry data to those generated using the project database. Cox proportional hazards regression was used to calculate hazard ratios between the proposed stage groupings with adjustment for cell type, sex, age and region. Validation checks were robust, demonstrating that the suggested staging changes were internally and externally stable. Several series coming from cancer registries and surgical series have confirmed some or all of the proposed modifications, adding supplementary external validation to the classification [45,46].

Fig. 2 – (A) Stage migration from sixth to seventh tumour-node-metastasis (TNM) classification in resected cases. (B) Impact of stage migration on overall survival. Reproduced with permission from Van Meerbeeck et al [42].
1.5. Weaknesses

Taken together, the proposed changes are limited in number and most are either intuitive or reflect modifications that were already suggested in the analysis of cancer registries or surgical series. As some of these series were included in the IASLC database, these modifications are self-fulfilling.

With respect to the proposed boundaries for lymph-node stations, they represent a clear improvement for surgeons, but are not unambiguous for radiologists and echo-endoscopists. A recent ultrasonographic lymph-node map based on the anatomical boundaries of the seventh UICC classification might well resolve this issue [47].

The abovementioned reshaping of mediastinal lymph-node borders will result in an increase in so-called ‘minimal N2’, limited to a single station. The magnitude of this phenomenon has not yet been reported. Furthermore, stage IIIA, which used to be heterogeneous in the sixth classification, becomes a cocktail of six different T/N combinations.

Even a database of 67,000+ patients was not able to validate all the descriptors that had accrued within previous editions of TNM. One should remember, however, that many of these data were not originally defined for the purpose of evaluating the staging system, but with some other scientific questions in mind. Their prognostic role was not always confirmed by multivariate analysis. Among the T descriptors that need further study are:

1. The best way to assess tumour size clinically: measuring a single diameter, measuring the greatest diameter or measuring two or three dimensions. Computed tomography (CT) screening has accelerated the development of volumetric software, adding to the debate as to how best to determine tumour size, and whether or not volume is preferable over size [48].

2. The non-size-based descriptors of T2/3 as hilar atelectasis, obstructive pneumonitis and the cytology-negative paraaortic pleural effusion (not considered as a T-modifying condition) [49]. It is hoped that the use of [18]fluorodeoxyglucose–positron emission tomography (FDG-PET) scanning may help unravel the inflammatory and neoplastic elements.

3. The split of which invasion to adjacent structures is assigned to T3 or to T4 could not be answered because there were too few patient cases in which the precise descriptor justifying the T3 or T4 category was recorded, and even fewer in which all of the other descriptors were known to be absent.

4. The extent of dissemination was only partly addressed by the introduction of M1a. The recently increasing interest in the outcome of oligometastatic disease could not be translated into a separate descriptor for this entity.

Other details and areas in which ambiguities and difficulties exist have been reviewed [50].

1.6. Threats

Although the data are definitely more recent than in previous TNM editions, they still are from the past century and do not reflect present-day staging and treatment paradigms, where-in FDG-PET and endoscopic ultrasound are now standard staging techniques for the M and N descriptors. It has been shown in several series that the introduction of both techniques has significantly improved the accuracy of clinical staging and upstaged the stage distribution at diagnosis, hence changing treatment algorithms and improved stage-specific outcomes [51].

This process of improved stage-specific survival has been described previously at the occasion of a previous revision of the lung cancer TNM [52]. This so-called Will Rogers phenomenon has been observed in stage III patients, where the outcome was significantly ‘improved’ by the occurrence of PET staging [53–55].

Whereas pathological staging has a prognostic significance, clinical staging is meant to help the clinician in treatment allocation. The interaction between better staging techniques and improved treatment strategies does not allow the expectation that revisions in staging classification will necessarily translate into a better overall outcome, unless over decades. It is controversial whether treatment should necessarily follow a stage change, as stage should not be considered a ‘cook book’ for treatment allocation. The issue is particularly critical for the ‘down-staged’ additional tumour nodules, single zone N2 and T4N0 cases as described before.

The analysis of the IASLC database was heavily influenced by surgical cases and pathological staging and cannot necessarily be extrapolated to clinical staging, which has been reported to be inaccurate [56]. Besides, individual patients with more advanced stages but an inherent indolent biological behaviour of their tumour have been reported to profit from more ‘aggressive’ surgical or radiotherapeutic approaches, whilst others with more limited stage will be given symptomatic care for reasons such as poor performance or comorbidity. pT2pN0 tumours with a diameter of 5.5 cm were previously considered pIIb and hence not candidates for adjuvant chemotherapy. The same case would now be considered pT2pN0 and staged pIIA and would be offered adjuvant treatment. We should remember that the data supporting adjuvant chemotherapy after complete resection were generated from trials using the sixth edition of the TNM classification, and that offering adjuvant chemotherapy to ‘reclassified’ stage pIIb, pII and pIIIA completely resected cases is therefore not evidence-based [57,58].

A recent pooled analysis of patient cases from two multicentre trials using the size cut-points of the seventh edition of the TNM classification was unable to identify subgroups of patients who did or did not derive significant benefit from adjuvant chemotherapy after complete resection based on tumour size [59].

Prospective data from large adjuvant chemotherapy trials are necessary before clinical guidelines regarding management of surgically resected node-negative non-small-cell lung cancer (NSCLC) can be updated to reflect the changes introduced.

1.7. Opportunities

The aforementioned weaknesses and threats offer some challenging opportunities for further research. All unproven descriptors and hypotheses are carried forward for close evaluation in a 25,000-patient prospective database being collected for the future TNM-revision foreseen for 2016 [60].
The issue of T/pT classification of ground-glass opacities (GGOs) deserves special attention as these are increasingly found at CT-scan screening, with or without a solid component. By histological definition, in-situ adenocarcinoma is defined only for GGOs with a diameter of <3 cm [61]. GGOs are considered non-invasive adenocarcinoma in situ, whilst only the associated solid component is presumed to be invasive. Those ≥3 cm are no longer ‘adenocarcinoma in situ’ and relate to a T2 description. However, their biological behaviour is less aggressive, suggesting that the measurement of the GGO in the evaluation of tumour size be discarded, analogously to the situation in breast cancer, where the tumour is coded for the invasive component only.

The concept that overall burden of lymph nodal disease (nN) might be more important than the anatomical location of the involved nodes comes from similar observations in oesophageal cancer. In a large retrospective series of resected Japanese patients, it was observed that the number of lymph nodes involved was a more precise prognostic determinant than their location and could be considered for the nodal stage classification as is done in other organs [62]. However, it is difficult to assess the exact number of the metastatic lymph nodes pre-operatively, and a uniform definition for pre- and post-operative assessment is preferable to avoid confusion. Besides, fragmentation of lymph nodes produced during the operation might result in an overestimation of the survival risk.

Pleural lavage cytology (PLC) is performed by some surgeons as the initial step after performing thoracotomy. In patients without overt effusion or pleural dissemination, a recent meta-analysis confirmed that PLC shown to be positive for cancer cells has an adverse and independent prognostic impact after complete resection [63]. When PLC is positive, the resection should be classified as R1(cy+). Sophisticated immunohistochemical and genetic techniques permit the detection of very small tumour deposits. A micrometastasis as defined by the UICC and AJCC usually is detected by routine haematoxylin and eosin staining, and typically mitoses and invasion are seen [64]. Such micrometastases in nodes or distant sites are counted as positive and denoted by the symbol (mi): for example, cN1(mi) or pN2(mi). However, the prognostic impact was not evaluated in the IASLC staging analysis. Isolated tumour cells (ITCs) are small clumps of tumour cells typically without mitoses or vascular or lymphatic invasion. ITCs within nodes (or distant sites) are not counted in the stage classification and should be coded as N0 (or M0), regardless of node level harbouring the ITC, for example, pN0(i 1) or pN0(mol 1). The prognostic value of ITCs has been inconsistent. The same applies for circulating tumour cells [65].

A staging classification describes the anatomical extent of a tumour, disregarding its biological behaviour. Stage is hence only one of several prognostic factors to be accounted for in prognostication, together with one or several biological markers which have been repeatedly linked with the outcome regardless of the treatment established [66]. Logistic regression techniques will allow the construction of a composite prognostic index in which different independent predictive factors are weighted and available for use in a nomogram or electronic outcome calculator [67,68].

Quality of health care is of increasing concern and interest. Indicators can help to describe the structural environment, the quality of the staging process and its outcome. The TNM descriptors and denominators lend themselves well as indicators of staging. Examples are the extent of intra-operative lymph-node sampling as an indicator of quality of the resection, clinicopathological correlation of resected tumours as a measure of staging accuracy and outcome according to stage. It is expected that these and others will be increasingly used to peer review medical practice.

2. Conclusion

The publication of the seventh edition of the lung cancer TNM classification has been variously applauded as a ‘seismic shift in staging’ by some or dubbed a laudable effort in ‘lumping, splitting and sorting’ by others [69,70]. It is considered a quantum leap forward in patient care, being based on an unprecedented large international database and involving extensive analysis and validation. Inevitably, the system is also more complex and far from perfect; with more refined data comes greater ability to discern granular details. This necessitates more layers of classification, manifested by additional new descriptors. As with any complex system, rules that seem clear in one context can seem awkward or conflicting in another. Implementation brings ambiguities to light. A clear knowledge of the details and difficulties should help to promote appropriate application and realisation of the full benefits of the new stage classification system.

There is much work to be done to answer these questions before the next revision scheduled for 2016. The IASLC is determined that over future revisions these shortcomings will be addressed as prospective data are accrued. The seventh edition of TNM in its present form remains, however, a surrogate for the anatomical extent of a tumour and a sequel to previous revisions. Unless we succeed in the prequel of building a composite prognostic index, including an increasing number of factors and inclusive biomarkers, ‘we might consider the TNM method for lung cancer staging to be similar to ‘brownstone’ remnants of historical interest and accept biological markers of disease extent and behaviour as the skyscrapers of our future’[71].

Conflict of interest statement

None declared.

References


Introduction

Optimal approach for renal cancer

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In the European Union there are some 84,400 new cases of kidney cancer with 34,700 deaths yearly [1]. With increasing knowledge of the mechanisms that drive renal cancer biology and the development of agents that target angiogenesis, growth and metastases, hope has been given to patients with this disease. Enormous progress has been made in the last few years for patients with advanced and metastatic renal cell cancer (RCC). Since the era of cytokine therapy, overall survival has now doubled, with the approval of many new agents targeting cell signalling pathways.

Six agents which target either the vascular endothelial growth factor (VEGF) pathway or the mammalian target of rapamycin (mTOR) pathway have been developed and approved for use in advanced and metastatic RCC. Increasing knowledge of how to actively manage the side effects of these agents has also greatly added to improving survival. In addition, the realistic hope of novel treatments – such as novel immunotherapy (anti-programmed cell death protein 1 (PD-1), anti-programmed cell death 1 ligand (PD-1L) and inhibition of fibroblast growth factor receptor (FGFR) – may also add to our therapeutic armamentarium.

Improvements in surgical techniques have likewise been important. Notably, cytoreductive nephrectomy remains the standard of care as compared with drug treatment alone, although trials addressing this question are ongoing. Metastasectomy has become common practice, as local therapy of metastases can often be integral to the treatment of metastatic RCC. Surgical resection has traditionally been the preferred approach to metastasectomy, but recent data on stereotactic radiosurgery (SRS) indicate that this treatment modality is a valuable non-invasive alternative. Definite guidelines for surgery of metastatic lesions do not exist, but recommendations can be made. The available evidence for common metastatic sites will be reviewed, including metastasectomy following targeted therapy and non-invasive approaches such as SRS.

This educational section comprises four excellent presentations that review factors which guide treatment selection, the algorithm for advanced RCC from first- to third-line therapies, proper sequencing, novel immunotherapy and details of how therapy may be individualised and surgery integrated in the optimal approach for renal cancer.

Conflict of interest statement

Honoraria from Novartis, GSK, Pfizer.

REFERENCE

Individualising treatment choices in a crowded treatment algorithm

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1. Introduction

Metastatic renal-cell cancer (mRCC) is considered incurable, and systemic therapy is the foundation of patient management. Historically, hormonal therapy was used for palliation of symptoms but had little anti-cancer effect [1]; cytotoxic chemotherapy is beneficial for only a small proportion of patients [2–7]. Immunotherapy, generally interferon-alpha (IFNα), was standard treatment until 2005, when it was replaced by the first inhibitor of the vascular endothelial growth factor receptors (VEGFRs), sunitinib [8]. Since then, another six agents which target either the VEGF or the mammalian target of rapamycin (mTOR) pathways have been developed and approved for use in advanced RCC [9–15]. Notably, cytoreductive nephrectomy was proven in two randomised trials to improve survival in combination with IFN, compared with drug treatment alone [16]. Despite a significant change in the systemic agents utilised in mRCC, this has remained an integral aspect of the treatment approach.

The prognosis for patients with mRCC has improved markedly with the introduction of agents targeting cell signalling pathways [17,18]. The expected survival time for an individual patient can be highly variable, but it is standard practice to categorise patients with mRCC into prognostic groups, originally defined by the Memorial Sloan Kettering Cancer Center (MSKCC) in the immunotherapy era of treatment [19]. This model, which uses clinical and pathological factors to group patients into favourable, intermediate and poor-risk groups, has now been updated and validated in patients treated with VEGFR-tyrosine kinase inhibitors (VEGFR-TKIs) [20] and is an important consideration in the current standards of care.

The treatment algorithm for mRCC in 2013 includes seven targeted agents and cytokine therapy, used in a sequential fashion [21]. This algorithm is becoming increasingly complex as clinical trials attempt to define the optimal treatment regimen to improve progression-free and overall survival and response rates, and to preserve quality of life. Combinations of targeted drug therapy remain experimental; to date, no combination has proved to be superior to monotherapy, and it is frequently poorly tolerated [22]. This educational chapter will summarise the treatment algorithm for advanced RCC and will provide details on how treatments may be individualised within the algorithm. The potential impact of new agents, future trial results and developments in translational research in mRCC will also be discussed.

2. First-line therapies

It has long been recognised that some patients with mRCC have indolent disease biology, and a period of observation is often recommended when metastatic disease is first diagnosed. This approach has clear advantages – it allows assessment of the pace of metastatic disease and can spare patients the chronic toxicities associated with drug therapy, as well as having health economic benefits – but there is only preliminary, retrospective evidence for its safety, and it is not clear for which patients this strategy is most suitable [23]. A deferred drug treatment approach in mRCC is currently being evaluated in a prospective, observational study [24].

Immunotherapy has largely been replaced by targeted therapies, but is considered an acceptable treatment option in patients with low- or intermediate-risk disease; IFN in particular remains a relevant therapy in those countries with restricted or no access to high-cost drugs. A 2005 systematic review of IFN reported modest improvements in disease control rates, 1-year and overall survival compared with non-immunotherapy controls, with approximately 13% of patients achieving a partial or complete response [25]. Notably, high-dose IL-2 (HD IL-2) produces durable response rates in a small proportion of patients with mRCC [26,27]; most recently, the ‘SELECT’ trial of HD IL-2 found an improved response rate (29%) compared with historical results which was attributed to improved patient selection on clinical and pathological
3. Second-line therapies

Accepted second-line treatments for mRCC are the VEGFR–TKIs sorafenib, sunitinib, pazopanib and axitinib, and the oral mTOR inhibitor everolimus. Frequently, the decision is influenced by which first-line treatment the patient has received; for example, there is evidence that sorafenib, sunitinib, pazopanib and axitinib have clinical activity after prior cytokine therapy [10,11,33,39].

The main controversy exists in the decision between everolimus and axitinib, when patients have been previously treated with a VEGFR–TKI. The RECORD-1 study compared everolimus to placebo in previously treated patients [14,40]. This was not strictly a second-line trial only, but patients were stratified by the number of previous VEGFR–TKI treatments; in patients who had received only one prior VEGFR–TKI, the median PFS for everolimus was 5.4 months, and 1.9 months for placebo [41]. Similar results were reported for the analysis of sunitinib- and sorafenib-treated patients. Two further trials, including the large expanded access study of everolimus (REACT), confirmed that everolimus has meaningful clinical activity in anti-VEGF treatment-refractory patients [42,43].

The phase III AXIS study randomised patients who had received prior sunitinib, cytokine, bevacizumab or temsirolimus to second-line treatment with axitinib or sorafenib [11]; approximately two thirds of the 723 patients enrolled had first-line anti-VEGF treatment. Overall, PFS was in favour of axitinib, with a median time of 6.7 months, compared to 4.7 months for sorafenib. This difference was less pronounced, however, in patients who had received prior sunitinib or bevacizumab.

Results of the RECORD-3 study were presented in abstract form in 2013, adding further support to the efficacy of a VEGFR–TKI/mTOR inhibitor algorithm [44]. This phase II trial randomised patients to either first-line everolimus, followed by sunitinib on progressive disease, or sunitinib followed by everolimus. It was designed to prove non-inferiority of PFS with first-line everolimus compared to sunitinib, but did not with its primary end-point (median PFS for everolimus 7.85 months and for sunitinib 10.71 months). Preliminary OS results suggest that the current algorithm of sunitinib in the first line followed by everolimus is superior to the opposite sequence. These results do not resolve the issue of whether a VEGFR–TKI or mTOR inhibitor is superior after failure of first-line anti-VEGF treatment, but add to the evidence base regarding optimal sequencing of systemic agents in mRCC.

With respect to the former question, the efficacy of temsirolimus and sorafenib were compared in patients previously naive patients who met three of six adverse risk features: lactate dehydrogenase (LDH) level of more than 1.5 times the upper limit of normal, haemoglobin level below the lower limit of normal, elevated calcium, time from initial diagnosis of RCC to randomisation of less than 1 year, a Karnofsky performance status of 60 or 70, or metastases in multiple organs [15]. Notably, approximately a third of the patients in this study had not had a nephrectomy. Median PFS in the temsirolimus group was 5.5 months and median OS 10.9 months, and temsirolimus is therefore a standard of care in this group.

The intravenous monoclonal antibody to VEGF, bevacizumab, is an alternative first-line treatment for patients with favourable or intermediate-risk mRCC. Two phase III trials combined bevacizumab with IFN and randomised patients to the combination or to IFN alone [12,13]. Both reported improved response rates (combined analysis 28.4% versus 12.9% [16]) and PFS times (8.5 months versus 5.2 months [12]) and 10.2 months versus 5.4 months [13]) over IFN monotherapy. Overall survival was not significantly improved by bevacizumab in either study, perhaps because of subsequent anti-VEGF systemic treatment in many patients.

Temsirolimus is an inhibitor of the mTOR complex 1 and is the only systemic agent to be studied specifically in a poor-prognosis group of patients with mRCC. A phase III trial of temsirolimus or IFN or the combination enrolled treatment-ground [28]. This remains the only systemic therapy associated with long-term remissions in mRCC, but its potential for severe toxicity and efficacy in a restricted, molecularly undefined subgroup of patients has limited its clinical application.

Sunitinib and sorafenib are kinase inhibitors with multiple targets, including the VEGF-receptors [29–31]. They were the first drugs developed in the VEGFR–TKI class of agents; hence they are associated with extensive clinical experience in mRCC. There is a stronger evidence base for sunitinib as first-line therapy. Sunitinib was compared with IFN in a randomised phase III trial and resulted in a statistically superior response rate (47% versus 12%), and progression-free survival (PFS) time (median 11 months versus 5 months) [8]. The median overall survival time was 26.4 months for sunitinib compared to 21.8 months for IFN-treated patients, which only became significant when those patients who crossed over from IFN to sunitinib were excluded from the analysis [32]. The efficacy of sunitinib was confirmed in a large safety study which enrolled a broader population of patients, including elderly patients, those with poor-risk disease as defined by the MSKCC criteria and those with non-clear-cell RCC [33]. Sorafenib was also compared with IFN treatment in 189 untreated mRCC patients in a randomised phase II trial [34]. Although the median PFS times for sorafenib and IFN were similar (approximately 5.7 months), sorafenib was interpreted as having superior clinical benefit because of improved response rates, tolerability and quality-of-life assessments.

Pazopanib was developed as a multi-targeted kinase inhibitor with improved potency against VEGFR-2, thought to have the most biological relevance of the VEGF receptors in clear-cell RCC [35]. It was registered in the first-line treatment setting on the basis of improved progression-free and overall survival in patients who were either treatment-naïve or who had received prior cytokine therapy, in a placebo-controlled trial [36]. Preliminary results of the COMPARTZ study, comparing sunitinib and pazopanib in first-line treatment for mRCC, were presented in abstract form at the European Society of Medical Oncology (ESMO) meeting in 2012 [37]. The median PFS for pazopanib was 8.4 months and 9.5 months for sunitinib, and interim OS times were 28.4 months and 29.3 months, respectively. This was a non-inferiority study, and although it has been criticised for its design, it would appear to confirm anecdotal experience that the two drugs are equivalent in activity in anti-VEGF treatment-refractory patients [42,43].
treated with sunitinib in the INTORSECT trial, presented at the ESMO meeting in 2012 [45]. Both drugs produced a median PFS of approximately 4 months, but overall survival was significantly better for sorafenib (16.6 months versus 12.4 months for temsirolimus). These results seem to indicate that although VEGF followed by mTOR inhibition is an efficacious strategy, everolimus and temsirolimus are not necessarily interchangeable, perhaps owing to their differing pharmacokinetics [46,47].

4. Factors which guide treatment selection

It is clear that multiple choices now exist for the first- and second-line treatment of patients with mRCC. Currently, the choice of agent is largely determined by the licensed indication for the drug, which in turn depends on the clinical context in which the drug's registration trial took place. However, as the clinical trial portfolio in mRCC has expanded to include more sophisticated trial designs, and eligibility criteria broadened, the decision about optimal treatment has become increasingly complex. To further complicate the issue, there are few direct comparisons between the various agents [11,37,45] and it is therefore difficult to confidently identify a superior drug for a given clinical situation. Nonetheless, there are a number of factors which enable selection of treatment to some degree, and also research initiatives aiming to move the field towards an individualised approach to treatment.

4.1. Disease and patient factors

Clinical risk models such as the MSKCC model provide a formalised assessment of those features which indicate less favourable biology in mRCC [19]. This model, now validated by Heng and colleagues in patients treated with VEGFR–TKIs [20] includes parameters such as haematological, biochemical and performance status to categorise patients into favourable-, intermediate- and poor-risk groups, each with a distinct survival time. However, risk stratification does not predict response to treatment; a nomogram which utilises 11 pre-treatment clinical and pathological variables predicts a 12-month PFS with first-line sunitinib treatment [48]. A more comprehensive model such as this may improve decision-making for individual patients, but it has not been validated. Recently, an analysis of factors influencing survival in sunitinib-treated patients was published, and this confirmed previously published findings but also identified independent predictors of long-term survival, including ethnic origin, bone metastases and adjusted calcium level [49].

Features of the disease are frequently used in clinical practice to guide selection of treatment. The most obvious example is the histological subtype of RCC. Most phase III trials in mRCC enrolled only patients with the clear-cell subtype, but approximately 25% of patients will have non-clear-cell histology, most commonly papillary or chromophobe subtypes. The optimal treatment for these groups has not yet been defined; on balance it appears that the targeted agents currently in use have activity in non-clear-cell RCC, but that the activity may be reduced compared to that in patients with clear-cell mRCC. However, there is evidence from some large therapeutic series that temsirolimus, everolimus and sunitinib have similar efficacy in patients with clear-cell and non-clear-cell disease [33,50,51]. Considering the papillary subtype alone, the reported range of PFS on VEGF-targeted agents varies considerably (1.6–11.9 months) [52–55], but studies have not always analysed type 1 and type 2 papillary patients (in whom there is clearly distinct biology) separately. Response rates in the range of 12–40% and PFS times from 4 to 14 months have been reported for sunitinib, sorafenib, temsirolimus or everolimus in chromophobe mRCC [52,53,55–59], although not always in the first- or second-line setting. The presence of sarcomatoid differentiation, which can occur in any histological subtype, adds a considerable degree of uncertainty as to the best choice of systemic agent (for a comprehensive review, see [60]), because the molecular driver of sarcomatoid change is unknown, the degree to which it is present is highly variable, and there are limited prospective therapeutic studies. Based on available data, the activity of sorafenib and sunitinib seems to be superior to that of cytotoxic chemotherapy, but outcomes are modest at best with these agents [61–64].

The burden and pattern of metastatic disease further influences treatment choice. Patients who are symptomatic from either a high volume of metastatic disease or disease in critical viscera are probably best served by a multi-targeted kinase inhibitor, because these agents are more likely to cause tumour regression than mTOR inhibitors. Response rates to sunitinib and pazopanib as first-line treatment, and axitinib as second-line treatment, can be as high as 40% [8,10,11], whereas reported response rates for temsirolimus and everolimus monotherapy are <10% [14,15]. Decisions about systemic treatment in those with specific metastatic disease sites such as the brain are complex; frequently, integration of local therapies is required, and there are no prospective data on which to base treatment recommendations. In the example of brain metastases, sunitinib has the strongest evidence of clinical activity [65–68].

Patient factors that should be considered when choosing systemic treatment for mRCC include their co-morbidities, age, expectations of and preferences for treatment and social and pragmatic issues such as their ability to attend the hospital. The VEGFR–TKIs have multiple additional targets, and the relative potency of these agents for different targets results in differing side-effect profiles. The toxicities associated with specific agents are described in detail in a separate educational chapter, but these must be balanced against baseline organ dysfunction – including cardiovascular, endocrine, hepato-biliary and haematological problems – when therapy is chosen.

The effect of advanced age on the safety and efficacy of targeted agents is now under careful evaluation, with the recognition that patients treated in drug development trials are not representative of the mRCC population encountered in the clinic. A combined analysis of 4684 patients treated with sorafenib in six clinical trials and two expanded access programmes was recently published [69], including 599 patients aged over 75 years. The authors reported that tolerability of sorafenib monotherapy was similar between the four age groups analysed, but those in the oldest group had a shorter duration of treatment (median 3.1 months) compared to those aged between 55 and 75 (median 4.0–4.2 months). Notably, 17% of patients aged 65–75 and 8% of those over 75 re-
ceived sorafenib treatment for a duration of more than 12 months. Likewise, pooled retrospective data from approximately 1000 patients treated with sunitinib indicate that its efficacy is similar in those under and over the age of 70 [70]. The overall rate of treatment-related adverse events was also comparable between the two age groups, although particular side-effects – such as fatigue, anorexia and weight loss, cough, peripheral oedema and haematological abnormalities – were noted to be higher in the older age group. The sunitinib expanded access study included a significant proportion of patients over the age of 65 (approximately 1/3 of the study population, 1000 patients); the response rate of 17%, median PFS of 11.3 months and median OS of 18.2 months were the same as in the overall study population [33]. Finally, there is evidence that everolimus has a similar efficacy and safety profile in those over 65 years of age, from a retrospective analysis of the RECORD-1 study [71]. In summary, these data suggest that chronological age alone should not be an influential factor in treatment selection, rather that co-morbidities and geriatric syndromes such as polypharmacy may need more careful assessment and weighting in the older patient.

Preservation of quality of life is an important therapeutic goal in mRCC. This can be difficult to achieve, because all targeted agents are associated with at least some degree of toxicity which is chronic. Arguably, patients are best placed to make decisions about treatment based on toxicity and quality of life, but the latter has not been rigorously studied and/or reported in clinical trials. For this reason, the PISCES (patient preference study between first-line pazopanib and sunitinib) trial, presented in abstract form in 2012 [72], has been commended for its novel design. Patients were randomised to receive either drug for 10 weeks, followed by a 2-week washout period before switching to the second drug. A clear patient preference for pazopanib over sunitinib was displayed, although the different drug schedules and timing of quality of life assessments complicate the analysis and in particular may have disadvantaged the evaluation of sunitinib. A similar study design is employed in the TAURUS trial, a phase II trial evaluating patient preference for the potent VEGFR–TKI tivozanib for 12 weeks followed by sunitinib for 12 weeks, or vice versa (NCT01673386). The phase III SWITCH trial will evaluate sunitinib followed by sorafenib and the opposite sequence, but the primary end-point is PFS (NCT00732914). Both of these trials will be conducted in the first-line treatment setting.

4.2 Predictive biomarkers in mRCC

Predicting sensitivity to systemic therapy is the fundamental prerequisite for the delivery of personalised treatment in mRCC. Response to first-line targeted agents appears to be an important indicator of longer-term outcome, with a retrospective analysis demonstrating that PFS below and above an arbitrary threshold of 6 months during first-line treatment was an independent predictor of overall survival (median OS 12.1 months versus 46.8 months, respectively, \( P < 0.0001 \)) [73]. However, when anti-VEGF treatments are used in a first- and second-line sequence, response to the first does not predict response to the second [74,75]; this is somewhat counter-intuitive, but is perhaps further evidence that drug response is probably the result of complex interaction between multiple tumoural, pharmacodynamic and pharmacokinetic factors.

Clinical parameters indicative of response to VEGF-targeted treatments may help to limit patients’ exposure to the drug in the absence of benefit. Drug-induced hypertension is a compelling example of this. A retrospective, pooled analysis of data from four clinical trials of sunitinib treatment in patients with mRCC found that hypertensive patients, defined by systolic blood pressure and diastolic blood pressure to a lesser degree, had improved clinical outcomes [76]. In the AXIS trial, diastolic blood pressure of \( \geq 90 \text{mmHg} \) at 12 weeks was significantly associated with improved overall survival in both the axitinib (20.7 months versus 12.9 months) and sorafenib (20.9 months versus 14.8 months) arms [75], confirming an earlier correlation of axitinib efficacy and diastolic blood pressure in phase II studies [77]. A prospective, randomised assessment of the efficacy of axitinib dose up-titration is currently under way (NCT00835978).

The utility of hypertension in treatment selection for an individual patient is debatable; the identification of a molecular marker that is predictive of response a priori is a key goal of translational research in mRCC. At this time, no such biomarker has been established. In patients treated with anti-VEGF agents, biomarker development efforts based on deficient tumoural von Hippel Lindau (VHL) gene function and resultant angiogenesis, the central abnormalities in clear-cell RCC, have been unsuccessful, perhaps because the pathogenesis involves stromal rather than tumour cells. However, promising discoveries have been made in relation to single-nucleotide polymorphisms (SNPs), inherited variants in DNA sequence, which may influence the biology underlying drug sensitivity. Several retrospective analyses correlated SNPs in VEGF or VEGF-receptors and drug metabolism genes (including CYP3A5, CYP1A1, ABCB1 and 2 and NR113) with sunitinib efficacy or toxicity [78-80]; a fourth study found that an SNP in VEGF was associated with the development of sunitinib-induced hypertension, but no single SNP predicted variation in clinical outcome [81]. A prospective observational study in which all patients received sunitinib demonstrated a significant relationship between polymorphisms in VEGFR3 and CYP3A5*1 with reduced sunitinib response and greater toxicity, respectively [82]. Furthermore, SNPs in angiogenesis or drug exposure genes – including IL-8 and HIF1A – may have predictive value; the IL-8 2767TT and the HIF1A 1790AG variant genotypes were associated with reduced PFS times compared to wild-type genotypes, in patients treated with pazopanib compared to placebo [83]. This finding has biological plausibility in that IL-8 has been identified as a potential mediator of an angiogenic escape and thus resistance to anti-VEGF treatment [84]. High plasma concentration of IL-8 has also been shown to predict for shorter PFS in patients treated with pazopanib in a retrospective analysis of the phase III pazopanib-versus-placebo trial, whereas high concentration of IL-6 predicted PFS benefit from pazopanib [85]. The major issue with the studies relating to SNPs is that they have each evaluated non-overlapping sets of SNPs, and no dominant polymorphism or one common to different anti-VEGF treatments has emerged [86]. Additionally, the frequency of identified SNPs is often low, and the biological processes which underpin the relationship between SNPs and clinical out-
5. Ongoing trials and emerging therapies

The clinical trial portfolio in mRCC continues to expand rapidly, and there are several ongoing trials that may alter the current treatment algorithm. On the other hand, there is debate as to how significantly emerging agents will improve upon current standards. For example, a phase III trial randomising patients to the potent pan-VEGFR inhibitor tivozanib or sorafenib found a PFS benefit in favour of tivozanib (11.9 months versus 9.1 months) but no difference in overall survival between the two drugs [97]. The AGILE study, comparing axitinib and sorafenib in first-line treatment of mRCC, also found improved PFS and response rates for axitinib, but did not meet its statistical primary end-point of PFS [98]. Both of these trials could be criticised for their use of sorafenib as a comparator, and the data are still immature, but in a broader view may suggest that improvements in clinical outcomes with the classes of agents currently available have reached a plateau.

For this reason there is much interest in a new class of systemic agents, the immune checkpoint inhibitors. An immune checkpoint is an inhibitory mechanism whose role is to regulate T-cell response to pathogens and to limit autoimmunity. Tumours can exploit these pathways to evade destruction by the immune system, and two immune checkpoint molecules have therapeutic relevance: the cytotoxic T-lymphocyte antigen 4 (CTLA-4) and the programmed death-1 (PD-1) receptors. Ipilimumab is a monoclonal antibody inhibiting the CTLA-4 receptor that improves survival in metastatic melanoma [99,100]. In RCC, the most highly developed of the checkpoint inhibitors is nivolumab (BMS-936558, MDX-1106), a monoclonal antibody against the PD-1 receptor. PD-1 is an inhibitory co-receptor that is expressed on activated T cells, particularly regulatory T cells, as well as activated B cells and natural killer cells [101]. Its two ligands, PD-L1 and PD-L2, are up-regulated widely in response to inflammation; along with activated B, T, myeloid and dendritic cells, PD-L1 is expressed on a range of endothelial and epithelial cells [102]. As such, the function of the PD-1 pathway appears to be in limiting the activity of T cells in peripheral tissues during an inflammatory response [102]. The rationale for inhibition of this pathway as anti-cancer therapy is strengthened by the observations that the PD-1:PD-L1 pathway is up-regulated abundantly in human cancers, and that PD-1 is expressed on a significant proportion of tumour-infiltrating lymphocytes [103]. Expression of PD-1 in resected RCC appears to have prognostic significance [104].

In 2012, a large phase I trial of nivolumab reported its efficacy and safety results in patients with a range of previously treated, solid tumour types [105]. Among 34 patients with RCC, objective responses occurred in four of 17 patients (24%) treated with a dose of 1 mg/kg and in five of 16 patients (31%) treated with 10 mg/kg. At the time of publication, five of eight evaluable patients had an objective response that lasted 1 year or more, and stable disease lasting at least 24 weeks was observed in an additional nine patients (27%). Common treatment-related adverse effects were fatigue, rash, diarrhoea, pruritis, anorexia and nausea, but these were usually low-grade; however, drug-induced pneumonitis occurred in 3% of patients and was fatal in three patients (1%). Nivolumab is currently being assessed in a phase III trial as second-line treatment against everolimus, in patients with mRCC previously treated with one or two anti-VEGF systemic treatments (NCT01668784), and similar anti-PD-1 antibodies are in development.

These encouraging early results come with the promise of a predictive biomarker. In the phase I study described, PD-L1 tumour expression was assessed by immunohistochemistry on pre-treatment tumour specimens from 42 patients; of 17 patients with PD-L1-negative tumours, none had an objective response, and nine of 25 patients (36%) with PD-L1-positive tumours experienced an objective response (P = 0.006). However, these results require reproduction and validation in other clinical settings. For example, as PD-L1 expression appears to be closely associated with the presence of tumour-infiltrating lymphocytes and secretion of IFN-gamma [106], the effect of multiple prior treatments is uncertain, and the prognostic versus the predictive power of PD-L1 expression must be determined [101].

Anti-PD-L1 agents target the same axis, and there are now two early reports of their efficacy. Theoretically, blockade of

comes, such as increased susceptibility of the tumour or normal tissue to the drug or altered drug metabolism, are not described. However, if validated, germline genetic variants may be very useful in drug selection, and may be particularly relevant to efficacy and safety of drugs between different ethnic groups affected by RCC.

Activation of the mTOR signalling pathway is extensively demonstrated across grades, histological subtypes and tumour sites in RCC, and alteration of some of its components has been shown to confer a worse prognosis [87,88]. Furthermore, there is preliminary evidence that somatic mutations in genes such as mTOR, or the tumour suppressor tuberous sclerosis genes (TSC1 and TSC2) causing gain or loss of function, respectively, are associated with long-term response to mTOR inhibitors [89]. Serum LDH may have a prognostic – and possibly predictive – role in patients treated with temsirolimus or everolimus [40,90,91].

Evidently, the biological relationship between tumour and drug response is multifaceted, and recent work using advanced genomic technology has added further layers of complexity to the picture. Exome sequencing of multiple tumour regions from a small number of patients with advanced clear-cell RCC revealed spatially separated somatic mutations in a large number of low-frequency tumour suppressor genes; the identification of only a small number of genes altered ubiquitously throughout tumour regions, and the clonal hierarchy of the mutations, points to early divergent evolution of these tumours [92]. It is therefore contended that a single biopsy will not represent the mutational range of the entire tumour, and that such intra-tumour heterogeneity will hinder biomarker discovery efforts [93,94]. It is widely recognised that there is a critical need to identify biomarkers predictive of response [17,95], and this is reflected by the now considerable number of biomarker development programmes in RCC (reviewed in [96]). Increasingly, therapeutic clinical trial design includes a tissue collection component to facilitate scientific research.
the PD-1:PD-L1 but not the PD-1:PD-L2 interaction may improve the safety and tolerability profile compared with anti-PD-1 antibodies. In a phase I study, 17 patients with mRCC were treated with the anti-PD-L1 antibody BMS 93-6559 [107]. Two patients (12%) had an objective response, one of which lasted 17 months, and a further seven patients (41%) remained stable for more than 24 weeks. A second phase I trial enrolled a larger cohort of RCC patients and preliminary results were presented at the American Society of Clinical Oncology (ASCO) meeting in 2013 [108]; 53 patients with mRCC, the majority of whom had received previous systemic treatment, received MPDL3280A, an engineered human monoclonal antibody to PD-L1. Notably, both rapid responses and prolonged stability were observed: the response rate was 13%, and 32% of patients achieved stable disease lasting longer than 24 weeks. This treatment was reportedly well tolerated and differed in its side-effect profile from the anti-PD-1 antibodies; in particular, grade 3 or higher pneumonitis did not occur.

6. Conclusions

There are now multiple systemic agents available for use in mRCC, which, particularly when used sequentially, extend the lives of patients and frequently provide effective palliative care. The ever-increasing repertoire of drugs for this condition make decision-making for the individual patient complex. In the absence of a predictive molecular biomarker, treatments are selected using a combination of variables, including the licensed indication of the drug, which in turn can influence funding arrangements, and clinico-pathological factors relating to the patient and the disease biology. The algorithm will be further refined as research into the optimal sequence of treatment, and treatments for smaller patient groups such as those with non-clear-cell mRCC, is further developed. Statistically, the currently available drugs result in clinical benefit for approximately 1 year at best, but clinical experience suggests that the outcome for each patient is highly variable. This emphasises the need for improved understanding of mechanisms of resistance and, furthermore, prediction of drug sensitivity or resistance on an individual level. A large number of biomarker initiatives have received high-level funding, and clinical trial design is adapting to address translational questions. The development of novel agents, such as immunostimulatory antibodies, is a further reason for optimism, with drugs such as anti-PD-1 antibodies offering the possibility of long-term disease control.

7. Conflict of interest statement

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8. Role of the funding source

Nil.

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Abou Youssif T, Fahmy MA, Koumakpayi IH, et al. The mammalian target of rapamycin pathway is widely


Does a reasonable treatment approach beyond second-line exist?

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1. Introduction

In the 1990s, the outlook for a metastatic renal-cell carcinoma (mRCC) patient was particularly bleak, as the disease was resistant to conventional chemotherapy and only small subsets of patients responded to immunotherapy. This outlook improved in 2005 with the introduction of sorafenib, the first targeted therapy; it was followed by the development of other tyrosine kinase inhibitors (TKIs): namely, sunitinib, pazopanib, axitinib, the monoclonal antibody bevacizumab (directed at vascular endothelial growth factor, VEGF) which was used in combination with interferon (IFN) and the inhibitors of the mammalian target of rapamycin (mTORis) everolimus and temsirolimus. Despite the number of available options, sequencing questions remain key, and the choice for first- and second-line treatment is still controversial.

However, there is a consensus that VEGF inhibition is the standard of care for first-line treatment in most cases. The choice of first-line treatment is informed by the results of large randomised clinical trials which have included prognostic models in their design and analysis [1–3]. Recent guidelines have suggested that low- and intermediate-risk patients are candidates for sunitinib, pazopanib or a combination of bevacizumab and interferon, while temsirolimus should be an option for high-risk patients [4].

Second-line therapy for patients with mRCC of the clear-cell type is still an evolving field. All the targeted agents mentioned above have activity in patients previously exposed to cytokine therapy; however, only the orally administered mTOR inhibitor everolimus is approved for patients failing prior treatment with sorafenib and/or sunitinib [5]. Recent data have shown that axitinib, a selective VEGFR TKI, significantly improves progression-free survival (PFS) compared to sorafenib in patients who have previously been treated with sunitinib [6]. Based on these two studies, both agents are currently approved and are used as standard treatment in patients failing a first-line treatment with VEGF inhibitors; they are part of the most recent guidelines [4].

Beyond second-line, there is no consensus and no “officially” approved drug. However, for the first time, the European Society for Medical Oncology (ESMO) guidelines recently opened the gate for third-line options [4]. This chapter is intended to clarify possible options after second-line treatment in mRCC.

Two sequences are currently standard of care, and approved regimen: TKI (or VEGF inhibitor) followed by everolimus, or TKI (or VEGF inhibitor) followed by axitinib. The proposed third-line strategy will depend on this sequence (Table 1).

2. Treatment after TKI (or VEGF inhibitor) followed by everolimus

There is no randomised study demonstrating the activity of any approved agent after this sequence. However, there are some retrospective data suggesting that another TKI can induce clinical benefit in patients still eligible to receive targeted agents [7,8]. In a retrospective database study, third-line sorafenib appeared active and feasible after first-line sunitinib and second-line everolimus or temsirolimus in terms of toxicity profile and median PFS [7]. Recently, 36 patients from French sites who received a TKI after everolimus within the RECORD-1 study have been reported [8]. The received TKI after everolimus was sunitinib in 17 patients, sorafenib in 15 and dovitinib (TKI258) in four. The response rate with TKI re-treatment was 8%, and the disease control rate (response plus stable disease) was 75%. Median PFS with each component of the TKI–everolimus–TKI sequence was 10.7 months (range 1.8–28.5), 8.9 months (range 1.7–34.6) and 8.2 months (95% confidence interval [CI] 5.2–11.9), respectively. Median overall survival from the start of everolimus was 29.1 months (95% CI 21.1 – not reached [NR]), suggesting a benefit in using TKI in this setting.

Another option after the TKI–everolimus sequence is re-challenge with the previous TKI [9]. Re-challenge with the same agent has been examined in those with prior response; for example, in a retrospective study, 23 patients who exhibited long response with sunitinib first-line treatment...
were re-challenged with sunitinib after progression on prior sunitinib were reported. Upon re-challenge, five patients (22%) reached a PR. The median PFS with initial sunitinib was 13.7 months and 7.2 months with re-challenge. Those with >6-month interval between sunitinib treatments had a longer PFS with re-challenge (median PFS, 16.5 versus 6.0 months, \( P = 0.03 \)). Substantial new or increased severity of toxicities was not reported during re-challenge.

Finally, newer TKIs have also demonstrated activity in this setting. In a recent phase II/II clinical trial of dovitinib, an inhibitor of multiple-receptor tyrosine kinases, including fibroblast growth factor receptor (FGFr) and VEGF receptor (VEGFr), in patients with mRCC refractory to standard therapies, 8 of 10 patients previously treated with a TKI–everolimus sequence achieved disease control, with one patient experiencing a partial response [10]. This has been convincing enough to launch a large prospective phase III trial comparing sorafenib and dovitinib in patients who have received one TKI and one mTOR inhibitor (ClinicalTrials.gov identifier: 01223027). This trial, known as the GOLD trial, has completed enrolment and will be reported shortly.

Interestingly, first-line PFS, with 6 months taken as cut-off parameter, appears to be an important prognostic factor for survival and thus for the likelihood of benefit of second- and third-line treatments [11].

### 3. Treatment after TKI (or VEGF inhibitor) followed by axitinib

There is currently no evidence that a third TKI after two TKIs has activity, although axitinib has shown some efficacy after sunitinib and sorafenib, with a response rate of 7% and a PFS of 7.1 months in a small number of patients [12].

By contrast, there is level I evidence that everolimus is active after two TKIs, as recognised in the recent ESMO guidelines [4]. In the aforementioned phase III RECORD-1 trial, everolimus was compared with placebo in patients following sorafenib and/or sunitinib [5]. Among patients who received one previous TKI median PFS was 5.4 months versus 1.9 months (HR, 0.32; \( P < 0.001 \)), and among those who received two previous TKIs median PFS was 4.0 months versus 1.8 months (HR, 0.32; \( P < 0.001 \)) [13]. Although this might suggest that everolimus is more active when given in second-line than in third-line, it more strongly demonstrates that everolimus is still active when given after two TKIs.

### 4. Future of treatment beyond second-line in mRCC

TKIs as well as mTOR inhibitors have been shown to be active in third-line treatment, depending on the previous sequence, as discussed above. In the future, several other options might be available.

Dovitinib, which is currently in phase III, might become a new standard if the ongoing GOLD study turns out to be positive. Interestingly, this study will also demonstrate whether sorafenib is active in a randomised study after the sequence TKI–mTOR.

There is a lot of enthusiasm for targeted immunotherapy, such as anti-PD1 and/or anti-PDL1, in mRCC [14,15]. There is an ongoing phase III evaluating the efficacy of nivolumab (BMS-936558), a T-cell checkpoint (PD-1) inhibitor, after one or two TKIs, in comparison to everolimus (http://clinicaltrials.gov/ct2/show/NCT01668784). Overall survival is the primary endpoint of this study, and this trial will eventually change the standard of care of mRCC treatment if the outcome is positive.

Cabozantinib, a Met and VEGF receptor-2 inhibitor, has shown promising activity in mRCC [16]. The activity of this new TKI will be shortly evaluated in a large phase III trial, in comparison to everolimus, after one or two TKIs. Obviously, this treatment might in the future become a very attractive strategy to overcome resistance.

### 5. Conclusion

There is evidence that treatment beyond the second line is active in mRCC. Depending on the previous sequence used, both mTOR inhibitors have shown efficacy. New strategies are emerging and might change the landscape, dovitinib being the first drug expected to be incorporated in future guidelines.

### Conflict of interest statement

None declared.

### References


Understanding and managing toxicities of vascular endothelial growth factor (VEGF) inhibitors

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1. Introduction

Vascular-endothelial growth-factor (receptor) (VEGF)(R)-inhibiting agents – sunitinib [1–3], sorafenib [4,5], pazopanib [2,6], bevacizumab [7,8], axitinib [5] and tivozanib [9,10] – have changed the therapeutic landscape in metastatic renal-cell carcinoma (mRCC). Five out of six agents have been approved for either first-line (sunitinib, pazopanib and bevacizumab + interferon-alpha) or second-line (sorafenib, axitinib) treatment of metastatic or advanced RCC. With these novel strategies, the median overall survival of patients has increased considerably, often, however, at the expense of chronic side-effects. Common treatment-related side-effects include: (1) general symptoms such as fatigue and asthenia, (2) gastrointestinal symptoms such as diarrhoea and stomatitis, (3) skin toxicities, (4) cardiovascular toxicities and (5) a variety of laboratory abnormalities. Some of these side-effects are clinically highly relevant because they may jeopardise the patient's safety or quality of life, while others may have little clinical relevance. Treating physicians need to be aware of potential side-effects that may occur, how to prevent and/or manage them, and the clinical implications for the ongoing treatment. This is of paramount importance since dose reductions and treatment discontinuations may significantly affect the outcome [11].

2. Incidence of toxicities associated with VEGF inhibitors

Toxicities reported from VEGFR inhibitors in mRCC are outlined in Table 1. Among general symptoms, fatigue (and/or asthenia) has been most commonly reported for sunitinib (up to 63% all grades; grade $\geq 3$: 17%), followed by axitinib (all grades 39%, grade $\geq 3$: 11%) and sorafenib (all grades 37%; grade $\geq 3$: 5%). A high incidence of fatigue has also been reported from the combination of bevacizumab + interferon-alpha (IFNα). However, the incidence of fatigue appears to be low in patients being treated with bevacizumab alone [12,13]; thus, this side-effect may be attributed to IFNα rather than bevacizumab. Interestingly, the newest VEGFR–tyrosine kinase inhibitor (TKI) tivozanib appears to have little effect on fatigue levels (all grades: up to 18%, grade $\geq 3$: 5%).

Gastrointestinal side-effects are extremely common in patients on VEGFR–TKI treatment. In particular, sunitinib and axitinib were shown to cause reduced appetite and/or anorexia in up to 34% of the patients. In the case of sunitinib, this may be caused partly by the high incidence of stomatitis and/or dysgeusia (30% and 46%, respectively). Diarrhoea is another frequent gastrointestinal toxicity: high incidences of all grades of diarrhoea were reported from patients on sunitinib (61%), sorafenib (53%), pazopanib (63%) and axitinib 55%, again with quite a favourable profile for tivozanib (22%).

The most common skin toxicities caused by VEGFR inhibitors are hand–foot syndrome (HFS), skin- and/or hair-depigmentation and rash. The highest incidence of all grades of HFS has been reported from sorafenib (51%) and sunitinib patients (50%), with a higher grade 3 + 4 HFS incidence in sorafenib patients (16%). Similarly, sorafenib was shown to cause rash in up to 32% of patients (all grades). Hair and/or skin depigmentation is commonly observed in patients on pazopanib (up to 38%) and sunitinib (up to 27%).

Among the group of cardiovascular, lung and laryngeal side-effects, hypertension is the most common (up to 46%). Hypertension has been observed with all of these agents and has been considered a fairly reliable biomarker for response, progression-free survival (PFS) and overall survival (OS) [14]. The highest incidence of grades 3 + 4 hypertension has been observed with tivozanib (26%). Cardiac side-effects include congestive heart failure (sunitinib: 13%) and ischaemia or myocardial infarction (sorafenib: 3%; bevacizumab + interferon-alpha 1%). Bleeding events, most commonly epistaxis, have been observed in patients treated with bevacizumab + IFN, sunitinib and sorafenib (33%, 18% and 15%, respectively). While dyspnoea is a common side-effect of mTOR-inhibitors, the incidence is low in patients with VEGFR inhibitors. No direct effect of these agents on lung tissue has been reported so far; thus, the occurrence of dyspnoea might be a secondary event due to lung metastases or...
Table 1 – Toxicities reported from phase III trials (%).

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in sodium, potassium, magnesium and calcium levels in up to 37%, 50%, 31% and 59%, respectively. In addition, pazopanib, sunitinib and tivozanib in particular were shown to cause increased levels of bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in up to 36%, 60% and 61% of the patients, respectively. In the case of tivozanib, international normalised ratio (INR) and partial thromboplastin time (PTT) abnormalities were also reported (82% and 53%, respectively). Sunitinib, sorafenib and tivozanib were shown to increase amylase and lipase levels in approximately 50% of patients. Finally, the induction of hypothyroidism is an observation that may have been underreported in the pivotal trials; in later analyses, up to 36% of patients was shown to develop hypothyroidism.[15]. As with hypertension, the occurrence of hypothyroidism has been linked to a better outcome[15,17].

3. The severity of side-effects and their impact on outcome

The occurrence of grade 3 + 4 toxicities, and to some extent also toxicities of lower grades, may tempt clinicians to reduce the dose, or to interrupt or discontinue treatment. Table 2 outlines the incidence of dose reductions and interruptions, the rate and most common reasons for treatment discontinuations, as well as the most common toxicities that have led to death. Dose reductions occurred in up to 51% of sunitinib patients, 52% of sorafenib patients, 44% of pazopanib patients, 31% of axitinib patients and 14% of tivozanib patients, while no dose reductions of bevacizumab were permitted in the Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial (AVOREN) and CALGB bevacizumab trials. Similarly, dose interruptions and treatment delays were required in 38% of sunitinib patients, 80% sorafenib patients, 62% bevacizumab + IFN patients and 77% of axitinib patients. In contrast, the number of patients with dose interruptions was considerably lower in tivozanib patients (18%). Both dose reductions and treatment interruption may help to prevent or manage treatment-associated side-effects. However, several authors have shown that higher relative dose intensities were associated with better outcome. A pharmacodynamic/pharmacokinetic analysis including six sunitinib trials revealed that response rates, time to progression and overall survival increased with the mean daily exposure to sunitinib[11]. Similarly, intra-patient dose-escalated sorafenib was shown to exert promising antitumour activity and led to a complete/partial response (CR–PR) rate of 48%, with eight out of 44 patients achieving complete remission[18]. Finally, Rini et al. could demonstrate in a randomised phase II study that axitinib dose titration significantly improved overall response rates when compared to placebo in patients eligible

<table>
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<tr>
<td><strong>Leukopenia</strong></td>
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<td><strong>Neutropenia</strong></td>
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<td><strong>Thrombocytopenia</strong></td>
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<td><strong>Lymphopenia</strong></td>
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<td><strong>Metabolic and laboratory abnormalities</strong></td>
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<td><strong>Sildenafil</strong></td>
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<td><strong>ALT</strong></td>
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<td><strong>INR abnormalities</strong></td>
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<td><strong>Increased alkaline phosphatase</strong></td>
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<td><strong>Indurated liver</strong></td>
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<td><strong>Increased uric acid</strong></td>
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<td><strong>Proteinuria</strong></td>
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<td><strong>Bicarbonate abnormalities</strong></td>
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Table 2 – Dose reductions and treatment discontinuation due to adverse events.

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<td><strong>Dose interruptions</strong></td>
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<td></td>
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<td>dermatological</td>
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<td>61.7 [8]</td>
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<td>18 [10]</td>
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<td>events, 80 for</td>
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<td>23 [8]</td>
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<td><strong>Most common</strong></td>
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<td>reason for</td>
<td>Cytopaenia [2]</td>
<td>Constitutional</td>
<td>Liver events</td>
<td>Fatigue, and</td>
<td>nr [9,10]</td>
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<td>discontinuation</td>
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<td>[4], gastrointestinal [4], dermatologic [4], respiratory tract symptoms [4], HFS [5], diarrhoea [5], asthenia [5]</td>
<td>[2]</td>
<td>transient ischaemic attack</td>
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<td>TX-related death or</td>
<td>n = 1</td>
<td>cardiac ischaemia/</td>
<td>ischemic stroke,</td>
<td>events n = 2, GI</td>
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<td>non-PD related</td>
<td>Gastric</td>
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<td>hepatic failure,</td>
<td>perforation n = 1,</td>
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<td>deaths</td>
<td>haemorrhage</td>
<td>2 death [5] from</td>
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<td>n = 1</td>
<td>tumour necrosis</td>
<td>peritonitis and</td>
<td>infarction n = 1,</td>
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<td></td>
<td>Respiratory</td>
<td>causing</td>
<td>bowel perforation</td>
<td>atrial fibrillation</td>
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<td>failure</td>
<td>n = 1</td>
<td>retroperitoneal</td>
<td>bleeding and n = 1</td>
<td>n = 1</td>
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<td>Sudden death</td>
<td>bleeding</td>
<td>GI bleeding</td>
<td>pneumonia n = 1</td>
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<td>n = 1</td>
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<td>n = 3 [8]</td>
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<td>nr, not reported.</td>
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nr, not reported.
for dose titration [19]. The challenge in the management of mRCC patients is to have a balanced approach to maintaining both dose intensity and safety of the patient.

4. Reasons for and incidence of dose adjustments and treatment discontinuation by agent

4.1. Sunitinib

In the final analysis of sunitinib versus IFN-alpha [3], 51% and 19% of sunitinib patients were reported to have required dose reductions or treatment discontinuation, respectively, because of adverse events. Causes of death apart from disease progression included acute renal failure (n = 1), gastric haemorrhage (n = 1), respiratory failure (n = 1) and sudden death (n = 1). In the COMPARZ trial, the most common reason for sunitinib discontinuation was cytopenia (3%).

4.2. Pazopanib

In the pivotal pazopanib trial [6] 33% and 4% of patients experienced grade 3 and 4 toxicities, respectively. The adverse event (AE) profile was similar in treatment-naive and cytokine-pretreated patients, although discontinuation rates because of AEs were higher in the cytokine-pretreated (19%) compared with the treatment-naive patients (12%). Arterial thromboembolic events occurred in 3% of pazopanib patients – myocardial infarction or ischaemia 2%, cerebrovascular accident <1% and transient ischaemic attack (TIA) <1% – compared with none in the placebo arm. The incidence of all-grade haemorrhagic events was 13% in the pazopanib arm versus 5% in the placebo arm. Deaths from adverse events were reported in 4% of pazopanib patients and in 3% in the placebo arm. Four pazopanib patients (1%) had fatal adverse events, including ischaemic stroke, abnormal hepatic function, rectal haemorrhage and peritonitis/bowel perforation. In the COMPARZ trial [2] dose reductions and treatment discontinuations occurred in 44% and 24% of patients, respectively. The most common reasons for pazopanib discontinuation were liver events (6%).

4.3. Sorafenib

In the TARGET trial [4] 10% of sorafenib patients had to discontinue the treatment, mostly because of constitutional, gastrointestinal, dermatological or pulmonary upper respiratory tract symptoms. Dose reductions occurred in 13% of sorafenib patients versus 3% of placebo patients (P < 0.001), and dose interruptions because of adverse events occurred in 21% of sorafenib patients versus 6% of placebo patients (P < 0.001). Dose interruptions were mostly because of HFS, rash or diarrhoea. Cardiac ischaemia occurred in 12 sorafenib patients (3%) and two patients in the placebo groups (<1%), (P = 0.01). Bleeding was more frequent in sorafenib than in placebo patients (15% versus 8%, respectively). In the axitinib phase III trial [5], the most frequent grade 3 and -4 adverse events associated with sorafenib were HFS, hypophosphataemia, lipase elevation and hypertension. Two treatment-related deaths occurred in sorafenib patients and were caused by necrosis with retroperitoneal bleeding and gastrointestinal haemorrhage.

4.4. Bevacizumab + IFN

In the AVOREN trial [7], serious adverse events occurred in 29% of patients who received bevacizumab versus 16% of those who did not. Similarly, AEs requiring treatment discontinuation were more frequent in bevacizumab-treated patients versus placebo patients (28% versus 12%). Grade 3 and 4 AEs in patients who received bevacizumab included four gastrointestinal perforations (1%; grade 4: n = 3) and 10 thromboembolic events (3%; grade 4, n = 4). Moreover, seven (2%) and 5% of bevacizumab patients discontinued treatment because of hypertension and proteinuria, respectively. Deaths due to AEs were reported in 2% of patients who received bevacizumab and 2% who did not. Three deaths (<1%) among the patients who received bevacizumab (n = 2 bleeding events and n = 1 gastrointestinal perforation) were thought to be associated with treatment. The other causes of death of bevacizumab-treated patients included myocardial infarction, atrial fibrillation, pneumonia, hepatic failure (in a patient with a history of hepatitis B) and staphylococcal sepsis.

In the CALGB trial [8] 80% of patients receiving bevacizumab experienced grade ≥3 toxicities compared with 63% IFN patients (P < 0.001). Bevacizumab resulted in significantly more grade ≥3 hypertension (11% versus 0), anorexia (17% versus 8%), fatigue (37% versus 30%) and proteinuria (15% versus <1%). There were four treatment-related deaths in the IFN arm and three in the bevacizumab arm.

4.5. Axitinib

In the axitinib phase III trial [5], the most common AEs of grade ≥3 were hypertension, diarrhoea and fatigue; 32% of axitinib patients had elevations in thyroid-stimulating hormone (TSH) and 27% required initiation or dose adjustments of thyroid hormone replacement. No treatment-related deaths occurred in the axitinib arm.

4.6. Tivozanib

In the phase II randomised discontinuation trial on tivozanib, the most common treatment-related toxicities were hypertension and dysphonia which occurred in 45% and 22% of patients, respectively. Grade 3 and 4 toxicities were rare and included hypertension (grade 3: 11%, grade 4: 1%) and laboratory abnormalities (5%). Dose reductions and interruptions were deemed necessary in 8% and 4% of patients, respectively. Treatment discontinuation because of adverse events occurred in 9% of patients. Causes of death that were not attributed to disease progression included ischaemic stroke (n = 2), coronary syndrome, respiratory failure, cerebral vascular accident, hypotension and embolism (n = 1 each); however, none of these were associated with tivozanib treatment.

Understanding the pathophysiology of individual toxicities, and developing proactive strategies for their prevention and treatment are important aspects of disease management and may avoid dose reductions and treatment discontinuation.
5. Pathophysiology of selected side-effects (involved targets) and management

Targeted agents differ regarding their side-effect profile, and these differences may be attributed to the mode of action; the incidence and severity of side-effects may depend on the number of inhibited targets (single versus multikinase inhibitors), the type of inhibited target (VEGF inhibition versus platelet-derived growth factor, PDGF, inhibition versus Flt-3 inhibition, etc.) and the strength of target inhibition (affinity to the tyrosine kinase, 'on- and off-target' toxicities). While some toxicities have been linked to the inhibition of a specific target, e.g. hypertension and VEGF, the association of other side-effects with a particular target is less clear (e.g. stomatitis, diarrhoea). Moreover, the incidence and severity of side-effects may differ between patient populations depending on single-nucleotide polymorphisms.

5.1. Fatigue, asthenia

5.1.1. Mechanisms
Fatigue and to a slight extent asthenia are frequent symptoms in patients undergoing treatment with VEGF inhibitors. In 1998, Cella and colleagues described fatigue as a 'subjective state of overwhelming and sustained exhaustion and decreased capacity for physical and mental work that is not relieved by rest' [20]. Fatigue induced by VEGF inhibitors may indeed include more symptoms than tiring easily. Patient's description of what their fatigue involves includes a loss of social interest, reduced voluntariness for physical activity, cognitive disorders, reduced appetite and depressive symptoms. Together, these symptoms have been described as sickness behaviour, a common status in patients with acute or chronic diseases [21]. In patients treated with VEGF inhibitors, many factors appear to contribute to fatigue and sickness behaviour. These include several biological processes related to the patient and/or the disease in which inflammation appears to have a major role. Moreover, treatment-related side-effects may contribute to fatigue and asthenia.

The underlying mechanisms appear to involve many aspects: (1) the individual genome of the patient, (2) disease-related factors, either biological or as a result of behavioural and psychological factors that may arise during the disease, (3) cancer treatment itself, which may induce fatigue either on the basis of the specific mode of action or secondarily by leading to side-effects that may be associated with the symptom of fatigue.

Several studies have investigated the relationship between genomic markers and fatigue. An association was found between functional interleukin-6 (IL-6) polymorphism and fatigue in patients and their relatives [22], while Aouizerat and colleagues found evidence for a genetic association between tumour necrosis factor alpha (TNF-a) and the severity of sleep disturbances and morning fatigue [23]. Furthermore, single-nucleotide polymorphisms (SNPs) of several cytokines – including Interleukin-1β, IL-1RN and IL-10 – showed associations with fatigue levels in lung cancer patients [24]. So far, no genomic markers for fatigue have been identified in patients undergoing VEGF inhibitor treatment.

Fatigue has also been strongly correlated with depression in cancer patients [25], and increased stress-induced inflammatory responses were observed in patients with major depression and stress [26]. Moreover, acute psychological stress was shown to influence pro-inflammatory cytokines [27]. Finally, physical inactivity and increased body mass index have been associated with fatigue in patients with breast cancer [28]. Again, no data have been obtained so far with respect to patients treated with VEGF inhibitors.

Many tumour types have been shown to promote progression through inflammatory cells [29]. Chemokines and cytokines were shown to attract immune cells to tumour cells [30], thereby leading to immune-cell dysfunction [31]. Research on neuro-immune signalling has linked pro-inflammatory cytokines with the development of fatigue. For instance, sickness has been shown to be triggered by IL-1α and β, TNFα and IL-6 [32-34]. Although no studies have been undertaken in patients undergoing anti-VEGF-treatment, IL-6 levels have been linked to disease progression in patients with mRCC [25].

Cancer treatment itself is known to induce fatigue. Induction of chronic inflammation has also been recognised as a treatment-related factor that may induce fatigue through pro-inflammatory cytokines produced by monocytes [36]. Wang et al. measured markers of inflammation in patients with gastrointestinal cancers undergoing chemotherapy and their relationship with fatigue. They found that serum concentrations of TNF-R1 were associated with the severity of fatigue [37]. Similar findings have been reported by various other authors with regards to C-reactive protein (CRP) levels, IL-6, etc. It is currently unknown as to whether VEGFR inhibitors can trigger fatigue through inflammation.

Various side-effects associated with VEGF inhibitors may contribute to fatigue and sickness behaviour; persistent fatigue is a common symptom of patients with hypothyroidism [38] and several VEGF inhibitors have been shown to induce hypothyroidism (Table 1). Similarly, hypophosphataemia is frequently observed in patients treated with VEGF inhibitors. Although a low serum phosphate level does not necessarily correlate with clinically relevant total body phosphate depletion, it should be considered that hypophosphataemia may cause muscle weakness [39]. Muscular dysfunction has also been shown to involve the heart [40] by causing myocardial changes and a reversible reduced sensitivity to catecholamines [40]. Muscle weakness may also be explained by an impaired muscle glucose uptake. Muscle activity involves an increased rate of glucose uptake in the contracting muscle. This is enabled by glucose transporter recruitment [41]. Multikinase inhibitors may interfere with signals required for this process, such as protein kinase C, nitric oxide, etc. [42]. Furthermore, TKI-induced hypoglycaemia may also contribute to muscular weakness. Sunitinib, for instance, was shown to decrease blood glucose levels [43]. In a clinical study that sought to distinguish between a central and peripheral cause of fatigue, Yavuszen et al. [44] found that patients with cancer-related fatigue had a greater central fatigue, indicated by shorter endurance time. Central fatigue has been linked to a loss of voluntarily activated muscles because of mechanisms proximal to the neuromuscular junction. On the other hand, muscle fatigue may have a peripheral cause, e.g. due to
metabolic changes within the muscles. Antoun et al. [45] could demonstrate that treatment with sorafenib exacerbates excessive muscle loss and that this loss increased during the course of treatment. A possible explanation for this phenomenon is that VEGF inhibition leads to downstream inhibition of AKT and mTOR, which are of paramount importance for skeletal muscle hypertrophy and muscle protein synthesis [46].

Finally, malnutrition as a result of VEGF-inhibitor-induced anorexia, anaemia and dehydration caused by diarrhoea may account for the high incidence of fatigue, asthenia and sickness behaviour in patients undergoing VEGF inhibitor treatment.

5.1.2. Management
Effective treatment for fatigue includes pharmaceutical and non-pharmaceutical interventions.

5.1.2.1. Non-pharmacological interventions. Patterson and colleagues [47] recently reviewed studies that looked at the impact of eight different types of intervention on fatigue levels. These interventions included (1) psycho-education, (2) cognitive behavioural therapy, (3) exercise combined with education and support, (4) exercise alone, (5) acupressure, (6) energy conservation and activity management, (7) relaxation breathing exercises and (8) distraction. With the exception of cognitive behavioural therapy, all of the above-mentioned non-pharmacological interventions were found to effectively reduce fatigue in patients with various diseases. In particular the impact of exercise has been well studied in patients with cancer-related fatigue. A Cochrane analysis [48] recently revealed that among 56 studies including 4068 participants aerobic exercise significantly reduced fatigue while resistance training and alternative forms of exercise did not. In contrast, Strasser et al. [49] performed a meta-analysis on the impact of resistance training in cancer survivors and found an association between resistance training and positive effects on muscular function and body composition. Finally, a meta-analysis on exercise programmes for cancer patients revealed an impact of these interventions on physical functioning and quality of life [50].

5.1.2.2. Pharmacological interventions. The finding that fatigue is linked to the activation of pro-inflammatory cytokines has led to the hypothesis that agents inhibiting these cytokines may reduce fatigue levels. In a randomised placebo-controlled trial [51] the immunosuppressant etanercept, a recombinant TNFα receptor fusion protein, enabled a significant improvement in fatigue (mean FACIT-F improvement 5.5 versus 1.9; P < 0.0001; 95% CI 1.6–4.5) in patients with psoriasis. Similarly, the monoclonal antibody infliximab was shown to significantly reduce fatigue levels in breast cancer survivors with persistent fatigue [52]. Other pharmacological interventions may include psychostimulants such as methylphenidate [53]. The relationship between inflammation and depression has also generated the hypothesis that the essential amino acid tryptophan might have a role. Tryptophan is a precursor for serotonin, and patients receiving immunotherapy were shown to have a fall in tryptophan plasma levels [54]. Another strategy that might interfere positively with inflammation-induced fatigue is the administration of thyrotropin-releasing hormone (TRH). TRH was shown to be involved in the biological processes of cytokine-induced sickness behaviour [55], and the administration of TRH has been associated with a significant improvement in fatigue levels, sleep disturbances and quality of life. These effects were accompanied by a decrease in CRP levels and an improvement in energy levels [55]. Attempts to interfere with muscle wasting have been made with L-carnitine supplementation, which was shown to have beneficial effects by improving nitrogen balance via increased protein synthesis or reduced protein degradation, inhibition of myonuclear apoptosis and interference with inflammation. Finally, any intervention that reduces the incidence and severity of fatigue-inducing side-effects may secondarily help to reduce fatigue levels: this includes control of anaemia, diarrhoea, hypothyroidism, hypophosphataemia, congestive heart failure and malnutrition.

5.2. Hypertension

5.2.1. Mechanism
Hypertension is a common and dose-dependent side-effect of all VEGF inhibitors. Classical known risk factors for hypertension failed to predict the development of hypertension in patients undergoing anti-VEGF treatment [56]. The development of hypertension in patients undergoing anti-VEGF treatment has mechanistically been linked to the pathophysiology of pre-eclampsia in pregnant women. In both cases, a deficient production of the vasodilator nitric oxide (NO) from endothelial cells and/or decreased NO levels seems to play a central role [57,58]. VEGF activates endothelial NO synthase through AKT [59], and a VEGF antibody has been shown to inhibit this process leading to a decrease in NO levels [58]. Inhibition of NO may cause vasoconstriction and hypertension [56,60]. An additional aspect of impaired NO functioning is related to its role in the control of renal function and salt sensitivity. NO was found to act as a regulator of pressure-natriuresis and plays an important role in the regulation of blood flow to the renal medulla and in the tubular regulation of sodium excretion [56]. It has therefore been concluded that inhibition of NO synthase may result in hypertension through its role in the control of renal water and sodium excretion. Finally, other mechanisms that may contribute to hypertension have been described. High salt intake has been shown to increase lymphatic vessel growth through increased VEGF-C production. Inhibition of VEGF-C by pan-VEGF inhibitors may therefore decrease lymphatic vessel density and increase blood pressure [61]. Apart from the impaired NO production, prostatic drugs may contribute to the development of hypertension under anti-VEGF treatment. VEGF has been shown to activate the production of the vasodilator prostacyclin (PGI2) [62], and reduced levels of PGI2 metabolites were found in patients with pre-eclampsia, suggesting a role for decreased VEGF levels. Another mechanism that appears to trigger hypertension is vascular rarefaction. Inhibition of VEGF signalling was found to cause a loss of endothelial fenestration followed by regression of tumour vessels [63]. Similarly, normal capillaries in healthy tissues were shown to regress after VEGF inhibition [64]. Thus, a reduction in tissue microvessel density may increase blood pressure through an increase in after-load.
involvement of an up-regulated renin–angiotensin–axis resulting from glomerular ischaemia has also been discussed as a potential mechanism for the development of hypertension. However, Kappers and colleagues demonstrated that a sunitinib-induced increase in blood pressure is accompanied by a decrease in renin [65]. The same group also showed that sunitinib was associated with a considerable rise in endothelin-1 levels. In a rat model, pretreatment with atrasentan, an endothelin-A receptor antagonist, completely prevented a TKI-induced rise in blood pressure [66].

5.2.2. Management
Patients undergoing VEGF inhibitor treatment should be checked for existing blood pressure and informed about the importance of monitoring and treating blood pressure. Home monitoring has been recommended as a reasonable method to closely monitor blood pressure. Recommendations regarding the frequency of measurements vary between three times daily [67] to once weekly [68]. Accepted thresholds for initiating antihypertensive treatment are blood pressures of $\geq 140$/90 mmHg and 130/80 in patients with diabetes or chronic renal failure [67,69]. The selection of a specific antihypertensive drug should be based on the general cardiovascular status of the patient, as assessed by electrocardiogram (ECG) and echocardiography before treatment [67]. According to the practice guidelines for the management of arterial hypertension [70], recommendations for optimal treatment may be based on considerations of the underlying pathological mechanisms. As VEGF inhibitors also induce proteinuria, angiotensin-converting enzyme (ACE) inhibitors may be considered appropriate: ACE inhibitors were shown to improve nephrin expression and to improve endothelial function [71]. Angiotensin inhibitors as well as angiotensin-receptor blockers may have an additional advantage since they were shown to exert antitumour activity (also discussed in section on proteinuria). Calcium-channel blockers such as nifedipine may offer the (vascular) advantage of VEGF secretion from coronary smooth muscles cells [72]. In contrast, non-dihydropyridine calcium-channel blockers such as verapamil or diltiazem should be avoided: being Cytochrome P540 3A4 (CYP3A4) inhibitors, they may interfere with the tumour drug metabolism. Finally, it is important to inform the patient to withhold antihypertensive medication in off-treatment periods, where blood pressure mostly normalises.

5.3. Proteinuria

5.3.1. Mechanism
Although proteinuria has been understood as a classical on-target side-effect, such as hypertension, little has been reported from the pivotal RCC studies. This could be due either to the lack of systematic assessment of proteinuria during the trials or to a low incidence, leading to a drop-out from the toxicity tables. No data on proteinuria have been published in the randomised trials of sunitinib, sorafenib, bevacizumab + IFN$\alpha$ and axitinib; in contrast, proteinuria has been noted as a common side-effect in the pazopanib and tivozanib trials trials, with an all-grade incidence up to 71% and a grade 3 + 4 incidence up to 15%. As proteinuria has been linked to VEGF inhibition, it is likely that all of these agents induce proteinuria to a considerable extent. Several mechanisms have been summarised in a comprehensive review on proteinuria induced by VEGF signalling inhibition by Izzedine et al. [73], and include (1) inhibition of VEGF on podocytes which results in loss of endothelial fenestrations in glomerular capillaries, endotheliosis, loss of podocytes and proteinuria [74,75], (2) an anti-VEGF treatment-induced glomerular endothelial cell detachment and hypertrophy [76], (3) a subacute glomerular thrombotic microangiopathy [73] and (4) an adaptive hyperfiltration response to nephrectomy [73].

5.3.2. Management
Any abnormal proteinuria may not only trigger loss of kidney function, it also represents a considerable risk for renal disease and cardiovascular morbidities. In patients with chronic renal disease, structural and functional cardiac changes have been linked to persistent pressure and volume overload [77]. Moreover, strong association between proteinuria and subsequent risk of coronary artery disease have been confirmed in a meta-analysis involving 169,949 patients; in this analysis, the presence of proteinuria was associated with a 50% increased risk for coronary artery events [78]. VEGF inhibitors have enabled many patients to live long enough to experience such additional drug-induced diseases. Thus, both regular monitoring for proteinuria as well as thorough management of proteinuria appears mandatory in patients under chronic VEGF inhibitor treatment. It has been recommended that patients should be assessed for existing kidney disease prior to the start of the treatment [73], and that a dipstick analysis and/or quantitative protein test analysis be performed before each cycle of VEGF inhibitor treatment. In the case of isolated proteinuria of $<1$ g/L, anti-VEGF treatment might be continued along with continued monitoring. In the case of proteinuria $\geq 1$ g/L or proteinuria with microscopic haematuria, a nephrologist should be involved who may decide on whether to perform biopsy. Treatment recommendations include ACE inhibitors or angiotensin-2 receptor antagonists which were both shown to reduce proteinuria [79,80]. Additional measures may include salt restriction and the use of dexamethasone, which may stabilise the podocyte cytoskeleton [81].

5.4. Cardiac toxicities

5.4.1. Mechanism
Cardiac toxicities occurring under VEGFR inhibitors may be the result of both on-target and off-target inhibition. Several kinases inhibited by multikinase inhibitors such as VEGF, Hypoxia-inducible factor (HIF), PDGFR and KIT are physiologically highly relevant for the heart, and the inhibition of these kinases may impair compensatory mechanisms [82–84]. HIF inhibition, for instance, may cause cardiac toxicity since in the cardiovascular system HIF-related gene products are understood as mediators of myocardial response to acute or chronic ischaemia, myocardial remodelling, peri-infarct vascularisation and vascular permeability. Thus, inhibition of these kinases may impair the myocardial response to acute or chronic ischaemia [82–85]. Disruption of PDGF–platelet derived growth factor receptor (PDGFR) signalling may lead to
apoptosis and necrosis of the cardiac myocyte. PDGFR is expressed on cardiac myocytes and endothelial cells. Sunitinib-induced inhibition of S6 kinase may lead to the release of pro-apoptotic factor Apoptosis-regulator (BCL2) antagonist of cell death, BCL2-associated X protein activation and cytochrome C release and activation of the intrinsic apoptotic pathway and cell death [86]. Disruption of KIT signalling may cause cardiac damage by inhibiting repair mechanisms. KIT is expressed on endothelial progenitor cells, and functioning of the KIT receptor might be necessary for the mobilisation of endothelial progenitor cells to sites of injury. Inhibition of KIT was shown to aggravate myocardial remodelling and prevent repair [87–89]. Disruption of VEGF–VEGFR signalling in the heart may induce cardiac dysfunction by preventing compensatory hypertrophy; VEGF is relevant to capillary density in the myocardium and critical for stem-cell differentiation into cardiomyocytes [90,91]. In the murine model, disruption of VEGF–VEGFR signalling during imposition of the pressure load was shown to reduce capillary density, which in turn was associated with contractile dysfunction, fibrosis and heart failure. Thus, inhibition of VEGF–VEGFR signalling in the heart may become relevant to patients with poorly controlled hypertension. Finally, TKI-induced changes to the thyroid function may cause cardiac toxicity. Triiodothyronine has a direct effect on the cardiomyocytes. Any T3 depletion could cause changes at the nuclear level of the myocyte level by influencing T3-regulated transcription of genes that encode Ca\(^{2+}\)-ATPase exchanger, Na\(^+\)/K\(^+\)-ATPase and voltage-gated potassium channels. Moreover, T3 exerts important non-nuclear functions on the myocyte which include ion channels for sodium, potassium and calcium [92]. Finally, low serum T3 levels have been shown to be the single and the most significant predictor of cardiovascular and all-cause mortalities in adults with heart disease [93]. Triiodothyronine also directly affects vascular smooth muscle cells, promoting relaxation [94]. Hypothyroidism was shown to increase vascular resistance [94,95] and to exert endothelial dysfunction due to reduced nitric oxide availability [96,97].

5.4.2. Management
The management of cardiac toxicities may vary among patients and may depend on the drug that has been used, potential existing co-morbidities and concomitant medications that may trigger cardiac events. The clinical presentation may vary as well: a decrease in left ventricular ejection fraction was noticed in 13% of the patients in the sunitinib phase III study [3]. In the target trial on sorafenib versus placebo, 3% of patients experienced cardiac ischaemia or myocardial infarction. Other investigators noticed arrhythmias and conduction disturbances, ST-segment or T-wave changes [84]. Based on the variety of clinical manifestations of cardiac toxicities, no general recommendation can be made. However, this side-effect clearly requires a multidisciplinary approach between oncologist and cardiologist. The risk of developing a cardiac event during TKI treatment should be assessed prior to treatment. On the other hand, patients with existing cardiac co-morbidities should not be deprived of effective cancer treatment. Early management of hypertension and proteinuria appears mandatory to reduce the risk of a cardiac event during TKI treatment. Congestive heart failure that develops under TKI treatment is generally completely reversible but requires treatment interruption and effective management [98]. TKI treatment can usually be resumed after recovery, but should be initiated carefully with close monitoring of the patient. Cardiac ischaemia and myocardial infarction also require treatment interruption and cardiological care. Upon recovery of the patient, the oncologist and cardiologist need to discuss the conditions under which the patient might be able to resume RCC treatment. The concomitant use of aspirin and/or clopidogrel should not necessarily represent a contraindication; however, increased risks for haemorrhage need to be carefully considered. In patients who have experienced either congestive heart failure or myocardial ischaemia or infarction, regular echocardiograms and electrocardiograms should be obtained; the value of cardiac troponin T, Creatine kinase (CK)-MB pro-B-type Natriuretic Peptide (BNP) is questionable. Many patients on TKI smay have increased serum levels of one or all of these markers; however, for various reasons, not all of them are clinically relevant. In asymptomatic patients with increased cTNT, CK-MB and pro-BNP treatment discontinuation should be avoided. Cardiac events under TKI treatment may not require a different approach to that offered to a patient without cancer. The only difference is that: (1) oncological treatment should be temporarily interrupted, and (2) treatment should be resumed upon recovery along with permanent cardiac co-medication and close cardiac monitoring of the patient. In this context, oncologists need to be aware that some agents, particularly anti-arrhythmic agents, may exert additive toxicities: e.g. some patients may receive amiodarone after a cardiac event. Amiodarone and sotalol are agents that prolong QT intervals, thus increasing the risk for torsades de pointes. Sunitinib is also an agent with a possible risk of torsades de pointes. Given together, the risk for torsades might be higher than with each drug alone. Changes in toxicity or activity profile may also result from concomitant cardiac medication. Calcium channel blockers such as diltiazem or verapamil and again amiodarone may be CYP3A4 inhibitors; concomitant use of these agents with sunitinib may require reduction in the dose of sunitinib. In most cases, patients can be effectively treated for both the cardiac event and the oncological condition. It is of paramount importance to inform the cardiologist about the necessity of these agents for the patient and about the change these agents have made to the prognosis of mRCC patients. Discontinuing RCC treatment should be regarded as the worst-case scenario.

5.5. Diarrhoea

5.5.1. Mechanism
In contrast to pure VEGF inhibitors such as bevacizumab, diarrhoea is a frequent side-effect of multikinase inhibitors. The underlying mechanism has not been elucidated so far and may require systematic bowel biopsies and stool analyses from patients treated with VEGF inhibitors. As both highly selective VEGFR-TKIs as well as less selective TKIs were shown to induce diarrhoea; it is also unclear as to whether this toxicity should be attributed to VEGFR inhibition or off-target inhibition (e.g. PDGFR, KIT, etc.). VEGF and VEGF receptors were shown to be highly expressed in adult organs,
including intestines [99]. Thus, VEGF inhibition may indeed induce diarrhoea. This assumption is further supported by data showing that the addition of VEGF(R) inhibitors significantly reduced the capillaries network in pancreatic islets and intestinal villi [100]. All of these findings suggest that VEGF inhibition may impair the function of digestive organs such as intestines and the pancreatic gland. VEGF inhibitors may cause changes in the bowel mucosa, thereby leading to diarrhoea. In the intestinal mucosa, even small perturbations of blood flow can lead to rapid metabolic changes characteristic of ischaemia and hypoxia [101]. Epithelial hypoxia is clinically associated with diarrhoea [102], and changes in the bowel mucosa are consistent with ischaemic colitis [103]. Other possible mechanisms include changes induced by VEGF inhibitors in the exocrine pancreas, where VEGF and VEGFR are highly expressed [99]. Patients with strong VEGFR inhibitor treatment frequently report on fatty stools, and VEGFR inhibitors were shown to decrease the zymogen granules in the pancreas (observed in animals under axitinib [2,104]) and to reduce pancreatic islets capillaries [100]. Targets other than VEGF may be involved as well. For instance, sunitinib is also a c-kit inhibitor, and KIT is expressed by interstitial cells of Cajal, the pacemaker cells of the intestine [105]. Cajal cells are adjacent to the nerve fibres of the myenteric plexus and regulate rhythmic contractions in the muscle layer. KIT inhibition in interstitial cells of the Cajal could be a potential mechanism for diarrhoea induced by KIT inhibitors such as sunitinib and imatinib [106].

5.5.2. Management

The management of TKI-induced diarrhoea includes dietary measures, probiotics and drugs. Among dietary measures is the avoidance of food and drinks that may cause bowel movements, such as raw fruits, lactose-containing foods, spicy foods, foods high in fibre and an increase in bananas, rice, potatoes, etc. [107]. Another dietary measure is the increased consumption of grated oxidised apples. A randomised double-blinded trial conducted in children revealed that the oxidised apples significantly reduced stool frequency in the treatment group compared to the control group [108]. Probiotics have been shown to prevent diarrhoea in inflammatory bowel disease [109]. Preclinical data yielded a similar efficacy in chemotherapy-induced diarrhoea [110,111]. In the clinical setting, Lactobacillus rhamnosus and fibre were shown to significantly reduce the incidence of grade 3/4 diarrhoea (37% versus 22%) in a randomised study in patients with colorectal cancer and chemotherapy [109]. While the use of probiotics has never been investigated in TKI patients, individual patients report considerable benefits.

Although several medical strategies have been established to manage diarrhoea in general, none of these have been investigated with regard to TKI-induced diarrhoea. One of the most commonly used agents is loperamide, which slows transit by decreasing the tone of the longitudinal muscles and increasing the tone of circular smooth muscles of the intestinal wall [112]. This increases the time substances remain in the intestines, allowing for more water to be absorbed. Loperamide also decreases colonic movements and suppresses the gastrocolic reflux. In mRCC treatment, patient’s satisfaction with this therapeutic measure has never been investigated and appears to vary. In clinical practice, some patients report that loperamide successfully controls higher grades of diarrhoea, while others complain that in the case of watery stools a slower transit is perceived as a larger burden than an increased stool frequency. Other medical strategies to manage or prevent diarrhoea include the use of budesonide, a topical corticosteroid which was shown to reduce bowel inflammation in patients with chemotherapy-induced diarrhoea. Budesonide was shown to reduce the grade of diarrhoea in >50% in loperamide-refractory patients treated with chemotherapy [113,114]. There are no data of budesonide in patients on TKI-induced diarrhoea. Another agent with unknown benefit in TKI patients is octreotide, a synthetic somatostatin that is approved for the treatment of diarrhoea related to vasoactive intestinal peptide (VIP)-secreting tumours and symptoms due to carcinoid syndrome. Octreotide was shown to decrease the secretion of VIP to prolong intestinal transit time and to reduce secretion and increase the absorption of fluid and electrolytes [115]. In patients with colorectal cancer receiving 5-Fluorouracil (FU)-based chemoradiation, no difference from placebo was found [116]. Finally, in patients who complain of bowel movements during meals or right after, a pancreatic insufficiency induced by the VEGFR inhibitor might be considered. In this case, treatment with pancreatin might be helpful (5 meals per day, 25,000 U pancreatin with each meal).

5.6. Anorexia

5.6.1. Mechanisms

As with fatigue, anorexia is regarded as a common and multifactorial phenomenon in tumour patients. Anorexia is part of a syndrome often referred to as anorexia–cachexia and involves metabolic and behavioural factors [117]. Anorexia–cachexia has been strongly linked to an interplay between cytokines, tumour products that induce lipolysis and/or protein degradation and neuropeptides [117–119]. TNFα was shown to induce lipid depletion in white adipose tissue [120]. Moreover, TNFα induces IL-6 secretion, which was found to be significantly elevated in patients reporting weight loss [121]. In a murine model, the cytokine IL-1 was shown to induce body weight loss [122]. These cytokines appear to induce anorexia by both their peripheral as well as their central effects [123]. In addition, several neuropeptide dysregulations have been associated with anorexia. Body weight was shown to be regulated by interactions between various orexigenic and anorexigenic central and peripheral neuropeptides [119]. Whether these interactions are influenced by VEGF inhibitors has not yet been elucidated.

5.6.2. Management

Several strategies have been investigated regarding their impact on anorexia–cachexia. These include medroxyprogesterone acetate, eicosapentanoic acid, L-carnitine and thalidomide. A randomised trial that aimed to identify the most effective among these strategies revealed the greatest benefits with a combination of all [124]. Medroxyprogesterone acetate (MPA) for instance was shown to increase body weight and appetite in patients with the cachexia–anorexia syndrome [125]. The underlying mechanism may involve a
down-regulation of high serum levels of IL-6 and TNFα [124]. As MPA has been shown to be increased upon the occurrence of resistance to TKI treatment in mRCC patients [124], the use of this agent may potentially act synergistically with TKIs by preventing or delaying resistance.

5.7. Stomatitis

5.7.1. Mechanisms and presentation

Patients on targeted agents may frequently report changes in the oral mucosa. The symptoms typically differ from chemotherapy-induced stomatitis. It also appears that changes differ between VEGF-TKIs and mTOR inhibitors. In sunitinib patients ulcers, taste alterations and cheilitis have been described [126]. In contrast, oral changes induced by mTOR inhibitors appear differently as superficial ulcers similar to aphthous stomatitis [127].

Dysgeusia or aguesia is quite common in patients undergoing sunitinib treatment. This is a taste disorder where e.g. the taste of meat may be perceived as sweet or a salty taste is not sensed at all. Other VEGFR-TKI patients may complain of oral burning with or without visible signs of inflammation [2,128,129]. Although stomatitis is completely reversible and more or less harmless, it is considered as clinically highly relevant since it often impairs the patient’s quality of life. Moreover, permanent stomatitis or dysgeusia may contribute to chronic refusal of food intake, thereby leading to malnutrition, fatigue and anorexia. As stomatitis resolves rapidly once the drug is withheld or dose-reduced [126], physicians and patients might be tempted to accept treatment delays, dose modifications or even a change of treatment. However, such strategies may affect the outcome. Little is known of the mechanism of stomatitis induced by VEGF inhibitors. Apart from a reduction in the capillary network of the tongue, other mechanisms may contribute to this AE. Interestingly, oral changes – e.g. burning mouth syndrome (BMS) – have also been linked to hypothyroidism [130]. BMS has been characterised by oral burning with or without inflammation, frequently affecting women. In their study, Femiano and colleagues revealed that 85 patients with BMS had thyroid alterations [127]. Thyroid hormones have been shown to influence the maturation and specialisation of the taste buds [132], and it has been speculated that hypothyroidism could therefore lead to a reduction in taste. Other investigators [133] have suggested a dysfunction of the nigrostriatal dopaminergic pathway that may account for the development of BMS. In a study on patients with BMS, Lauria and colleagues [134] detected a lower density of epithelial nerve fibres and axonal degeneration on biopsy of the tongue and suggested that BMS is caused by a trigeminal small-fibre sensory neuropathy. In a randomised placebo-controlled study, the topical administration of clonazepam improved symptoms in two thirds of BMS patients [135]. Finally, based on the assumption that BMS involves a dysfunction of the dopaminergic central nervous system, anti-epileptic drugs have been investigated [136]. López and colleagues reported on a considerable improvement in BMS after treatment with pregabalin. Other mechanisms that have been discussed include shifts in the oral mucosa due to myelosuppression [137], shifts in the ecological balance of oral and gut flora [138], an up-regulation of pro-inflammatory cytokines following cancer treatment [139] followed by NF-κB and cyclooxygenase-2 up-regulation. It remains unclear whether and in which way VEGFR inhibitors are involved in various processes that have been linked to stomatitis.

5.7.2. Management

Recommendations on how to treat or prevent stomatitis most commonly stem from experiences made in patients undergoing chemotherapy. General recommendations include, among others, the avoidance of spicy food, etc., the use of soft toothbrushes and appropriate dental hygiene [140]. No general recommendation exists for the prevention or management of dysgeusia. A review on drug-related taste disturbances in the elderly [141] revealed that zinc replacement might be helpful to enhance taste sensation for sweet, bitter and salty flavours. Patients with dysgeusia may benefit from niacin and vitamin A, and the use of mints, sugarless chewing gums and bicarbonate mouthwashes has been recommended as a palliative measure.

A meta-analysis on prophylactic agents to prevent stomatitis [142] identified 10 interventions that have positive effects on preventing or reducing mucositis. These included amifostine, Chinese herbal mixtures, hydrolytic enzymes such as trypsin, chymotrypsin, wobe-mugo and pepsin. Moreover, a recommendation has been made for ice chips. In patients with haematological malignancies undergoing high-dose chemotherapy, the use of keratinocyte growth factor-1 (palifermin) has been recommended [140], however, no data have been published with regard to VEGF inhibitors. The same expert panel also recommended the use of benzydamine for the prevention of radiation-induced mucositis in patients with head and neck cancer receiving radiotherapy. Stomatitis induced by mTOR inhibitors appears to be different since it involves immune mechanisms. The management might therefore be different, and corticosteroids might be helpful [127].

Treatment of stomatitis may also include mouthwashes with doxycycline and/or sucralfat dissolved in water [143]. Patients who complain of inflammatory lesions may benefit from local trimcinoloneacetonide. As the management of stomatitis can prove challenging, changes in treatment schedules might be considered. Several authors have reported on different modified sunitinib schedules: e.g. from 4 weeks on/2 weeks off to 2 weeks on/1 week off. While such schedules may help to prevent side-effects such as stomatitis, no changes in efficacy were observed [144–146].

5.8. Gastrointestinal perforation

5.8.1. Mechanism and clinical presentation

Gastrointestinal perforations have been rarely reported in patients with renal cell carcinoma [7]. VEGF has been shown to be highly important for the integrity of the intestinal mucosa. Vasoactive agents such as prostaglandins and NO, which are critical for mucosal defence mechanisms, are activated by VEGF [147]. Thus, VEGF has been considered a survival factor.
for endothelial and epithelial cells in the intestines [148]. VEGF inhibition on capillary beds of intestinal villi may directly contribute to perforation by inducing the regression of normal blood vessels [100,149]. The occurrence of gastrointestinal perforations with VEGF inhibitors has been linked to the presence of bowel pathologies [148]. Diffuse abdominal carcinomatosis is associated with a risk of bowel obstruction, increased pressure on weakened bowel areas and microperforations [150]. Other risk factors include ulcer, bowel tumour necrosis, diverticulosis, colitis and prior abdominal or pelvic radiotherapy [151] (Gentech Inc., Avastin prescribing information, June 2006). Finally, a reduction in blood flow to the splanchnic vasculature by thrombosis or vasoconstriction may further increase the risk of bowel infarction and perforation [152]. Presentation of gastrointestinal perforation during VEGF inhibitor treatment varies in type and severity, from free air on the abdominal x-ray which resolves without treatment to colonic perforation with abdominal abscess and fatal outcome.

5.8.2. Management
Patients with risk factors should be carefully monitored for clinical signs of perforation, such as abdominal pain, obstruction, fever, vomiting and leucocytosis [149]. In patients under suspicion of an increased risk of gastrointestinal perforation frequent radiographic evaluations for free peritoneal air, extraluminal contrast and abscess formation may be reasonable [151]. Physicians should also be aware of potential risks associated with co-medications such as non-steroidal anti-inflammatory drugs (NSAIDS). These increase the ratio of endostatin to VEGF and may further contribute to the occurrence of gastrointestinal perforations [153]. In patients who experience gastrointestinal perforation with VEGF inhibitors, treatment discontinuation has mostly been recommended.

5.9. Hypothyroidism

5.9.1. Mechanism
Mechanisms of hypothyroidism induced by VEGFR inhibitors may include both on- and off-target inhibition. VEGFR is
expressed on thyroid cells and endothelial cells of the thyroid gland which are also able to synthesise VEGF [58,154–160]. Thus, VEGF inhibitors may induce capillary regression in the thyroid [64,100], leading to the destruction of normal thyroid cells. In addition, sunitinib was shown to induce hypothyroidism by inhibiting iodine uptake [161] and peroxidase activity [162]. It remains unclear whether off-target(s) inhibition may also contribute to hypothyroidism. Multikinase inhibitors such as sunitinib were shown to strongly inhibit RET/PTC signalling, thus being potentially beneficial in the management of thyroid cancer.

5.9.2. Management
Patients treated with VEGF inhibitors should be monitored for hypothyroidism before and at regular intervals during treatment. Both clinically overt and subclinical hypothyroidism may occur. According to the clinical practice guidelines for hypothyroidism in adults [163], the standard treatment is replacement with L-thyroxine in patients with persistent TSH levels >10 mIU/L. In patients with subclinical hypothyroidism (defined as TSH <10 mIU/L), 92% would be considered for hormone replacement. These guidelines have been established to prevent the long-term damage caused by hypothyroidism in otherwise healthy patients. How relevant are these recommendations in patients with mRCC, and what are the clinical implications for the management of TKI-induced hypothyroidism? This is particularly of interest since several authors have reported on an antitumour effect of hypothyroidism. Hypothyroidism was shown to inhibit tumour cell proliferation in various cancer cells and animal models [164–167]. Moreover, hypothyroidism was shown to inhibit neoangiogenesis and to improve outcome in patients with head and neck cancer [168,169]. Thus, the question arises as to whether we should tolerate TKI-induced hypothyroidism to some extent. Physicians need to be aware that hypothyroidism has considerable effects on cardiac function, including impaired relaxation and ventricular filling, increase in peripheral vascular resistance and increased diastolic blood pressure as well as reduced ejec-
tion at exercise [170]. Therefore, hormone replacement appears to be mandatory in the majority of patients. In this context it is important to note that triiodothyronine (T3) is the relevant hormone for the cardiac myocyte. Interest-
ingly, T3 supplementation was shown to be 50 times less proliferative and less pro-angiogenic than T4, the ‘bad guy’ among thyroid hormones [171]. An advantage of T3 replacement would also be that it reduces T4 levels; however, T3 replacement is difficult in clinical practice due to the short half-life of available formulations. This problem could potentially be solved by the use of a combination of T3 and T4. It has been stated recently that combined T3 and T4 replacement may represent a more personalised approach to treat hypothyroidism [172].

5.10. Hand-foot syndrome

5.10.1. Presentation and mechanism
HFS has been reported to occur between days 14 and 28 of VEGF inhibitor treatment [173]. According to the Common Terminology Criteria for Adverse Events (CTCAE Version 4.0, 2009), patients with grade 1 HFS present with minimal skin changes or dermatitis (erythema, oedema or hyperkeratosis) without pain. In contrast, patients with grade 2 HFS complain of painful skin changes (peeling, blisters, bleeding, oedema and hyperkeratosis) that may limit activities of daily living. Finally, grade 3 HFS has been defined as the presence of severe skin changes associated with severe pain and limited self-care.

Several histopathological changes have been described by Yang and colleagues [174]. The most common include intracytoplasmic eosinophilic bodies reflecting keratinocyte damage, keratinocyte vacuolar degeneration and confluent keratinocyte necrosis associated with intraepidermal cleavage. In addition, an accelerated epidermal cell replication and increased keratinocyte proliferation has been described by the authors. So far, the exact mechanism of HFS with multikinase inhibitors has not been elucidated. The severity of clinical presentation appears to be correlated with drug exposure. Discussed mechanisms include: (1) an increased drug concentration in the capillaries at the papillary dermis, (2) interference by VEGF–PDGFR inhibition associated with pericyte-mediated endothelial survival mechanisms, leading to damage of the capillary endothelium in hands and feet [82], (3) an impaired vascular repair leading to keratinocyte apoptosis and inflammation and (4) a direct effect of the drug in eccrine sweat glands.

5.10.2. Management
The management of HFS in patients treated with VEGF inhibitors has been reviewed by Anderson and colleagues [175]. Prophylactic measures include pedicure before treatment to remove hyperkeratosis, emollients, topical exfoliating products (urea-based and salicylic-acid-based), protection of pressure-sensitive areas (e.g. shoes with soft insoles) and perhaps systemic administration of pyridoxine, glucocorticosteroids and cyclooxgeyase-2 inhibitors. The authors also highlight the importance of frequent and early collaborations between oncologists and dermatologists. Dose reductions and treatment interruptions may be temporarily required. The authors recommend a dose reduction at first occurrence of grade 2 until HFS resolves to grade 0–1 and to increase the dose afterwards; if no improvement to grade 0–1 occurs, treatment interruption for 7 days may be necessary. The dose may then be escalated depending on the HFS grade. In the case of grade 3 HFS, recommendations regarding dosing include the interruption of TKI treatment for 7 days (until toxicity resolves to grade 0–1) and to resume treatment at a reduced dose. If toxicity is maintained at grade 0–1 at reduced dose, dose escalation may be recommended. In the case of recurrent grade 3 HFS, treatment should be resumed at a reduced dose after recovery without further dose escalations. According to the authors, combinations of cortisone creams and topical antibi-
otics might be recommended in cases of severe HFS. These recommendations have been made for patients treated with sorafenib. Although they may also apply to pa-
tients with other VEGFR–TKIs, individual modifications according to the clinical presentation, the type of drug and the drug schedule may be reasonable.
5.11. Myelotoxicity

5.11.1. Mechanisms
Myelotoxicity of tyrosine kinase inhibitors has been linked to their ability to inhibit various targets. (1) They inhibit KIT signalling: KIT receptors are expressed on haematopoietic progenitor cells and are involved in their growth and differentiation. Sunitinib was shown to inhibit phosphorylation of the KIT receptor and cell proliferation [176]. (2) VEGF inhibition may also account for myelotoxicity. Gerber and colleagues [177] described a regulatory loop by which VEGF controls survival of haematopoietic stem cells. Interestingly, ligands selective for VEGF and VEGFR-2 as well as VEGFR-1 agonists were shown to rescue survival of VEGF-deficient haematopoietic stem cells. Moreover, VEGF was shown to be involved in the formation of myeloid and erythroid colonies from progenitor cells [178]. (3) Inhibition of FLT-3 on haematopoietic stem cells and PDGFR signalling has also been linked to myelotoxicity [179,180]. (4) Finally, it has been suggested that thrombocytopenia might be the result of hypertension [181] or may be caused by drug-induced immune thrombocytopenia [182].

5.11.2. Management
In caucasian populations, myelotoxicity is seldom a dose-or treatment-limiting toxicity. In the case of grade 2 neutropenia or thrombocytopenia, dose adjustments are rarely necessary. The occurrence of grade ≥3 myelotoxicity has been reported to occur more frequently in Asian patients [183]. In the case of grade 3 neutropenia or thrombocytopenia temporary treatment interruptions may be required. In the case of sunitinib, dose modifications may depend on the day on which grade 3 myelotoxicity is observed. If observed on day 28 of treatment, prior to the 2-week rest, patients may not necessarily require dose reduction in the next course because neutropenia and thrombocytopenia are usually short-lived and tend to resolve during the 2 weeks off treatment; blood cell counts should be repeated on day 1 of the next course, and if neutrophils and thrombocytes return to normal levels, careful continuation at the same dose level might be possible [107]. Blood cell counts should be obtained every 2 weeks, and in the case of repeated grade 3 myelotoxicity, treatment should be withheld for a few days until toxicity is grade 2 or less. In the case of recurring grade 3 myelotoxicity, dose reduction should be recommended after recovery [184].

6. Toxicities as biomarkers for successful outcome

Several retrospective studies have identified specific side-effects to be strongly associated with outcome. Table 3 summarises these findings. The most common side-effect that has been associated with outcome is hypertension. Additional toxicities that were shown to correlate with the outcome are myelotoxicity [185,186], HFS [186] and fatigue/asthenia [187]. What is the biological basis for this correlation? The toxicity may reflect that (1) the mechanism of action may be appropriate in the individual patient, (2) the chosen drug has a high selectivity and adequate potency to hit the target, (3) the tumour is dependent on the inhibited pathway and (4) the drug exposure is appropriate; this may also be influenced by the presence or absence of specific single-nucleotide polymorphisms that influence pharmacokinetic and pharmacodynamic processes [188,189].

The potential association of toxicities and outcome has several clinical implications and raises three major questions. (1) Should we treat the toxicity, or would this impair the outcome? In this context, correction of hypertension has been well studied. While the occurrence of hypertension appears to be predictive, treating hypertension does not appear to impair the outcome. In a retrospective analysis on hypertension as a predictive factor for outcome with sunitinib treatment, Smitt and colleagues [190] reported that patients who required at least three antihypertensive agents had the longest PFS. Thus, managing hypertension is not only mandatory for the patient’s safety, but it also does not appear to affect the outcome. These findings may, however, vary depending on the toxicity observed. As hypothyroidism was shown to be associated with the inhibition of angiogenesis [168,169] and cell proliferation [164], maintaining a state of (preferably) T4-hypothyroidism may to some extent be beneficial for the outcome. In this context, TSH levels above the upper limit of normal and below the threshold for cardiac impairments (>10 mmol/L) may be acceptable. (2) Should we adjust the dose until toxicity is observed (treating according to toxicity)? In the axitinib dose-titration trial, patients with dose titration and those who did not require dose titration as assessed by the occurrence of hypertension had a better outcome when compared to patients without dose titration [19]. Fig. 1 shows the computed tomography (CT) scans of a female mRCC-patient who did not experience either hypertension (or other dose-limiting toxicities) or remission with axitinib 5 mg bid. Only upon dose adjustment to 7 mg bid did the patient develop hypertension and a reduction in the size of metastasis. These findings suggest that we may consider a potential benefit of the ‘treat to toxicity’ approach. Naturally, such strategies should only be considered in the absence of other dose-limiting toxicities and require careful monitoring. (3) What is the role of agents given to manage the toxicity? Do these agents modify the outcome? We cannot rule out that agents given against the toxicity may have additional benefits against tumour progression. For instance, some antihypertensive agents were shown to exert interesting antitumour properties. Beta-blockers, for example, were shown to induce apoptosis in endothelial cells [191] and have been established as standard of care for infantile haemanangiomass [192]. Moreover, several reports have demonstrated that angiotensin II stimulates growth and migration of cancer cell lines and induces angiogenesis through up-regulation of VEGF; interestingly, this effect can be inhibited by angiotensin-receptor blockers (ARBs) [193]. Losartan, an ARB, was shown to stimulate pro-apoptotic signalling pathways in various tumour types [194,195]. Finally, calcium-channel blockers have been shown to reduce the proliferation and migration of glioma cells [196].
VEGF inhibitors have substantially improved the outcome of patients with metastatic renal-cell carcinoma. Incidence and severity of side-effects may vary between agents and depend on the mode of action of the chosen drug as well as on individual patient-related factors. Physicians need to be aware of both patient- and agent-related risks that may occur during treatment in order to choose the best individual treatment and maintain the patient's safety and quality of life. It should be considered that the majority of side-effects are manageable with proactive supportive measures and close monitoring of the patient. Dose reductions, treatment interruptions and discontinuation should be avoided whenever possible.

Conflict of interest

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Integrating metastasectomy and stereotactic radiosurgery in the treatment of metastatic renal cell carcinoma

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1. Introduction

In the European Union 60,000 patients are diagnosed annually with renal-cell carcinoma (RCC) [1]. Synchronous metastases are present in up to 30% of patients, with multiple sites affected in 95% [2,3]. Since an additional 40% of those undergoing surgery for localised RCC develop metachronous metastasis, approximately 30,000 patients per year are diagnosed with systemic disease, of which an estimated 7000 have non-clear-cell histology.

In a recent population-based analysis, lung metastasis was most frequent at 45.2%, followed by bone at 29.5%, lymph nodes at 21.8% and liver at 20.3% [4]. Adrenal, brain and other locations had a lower frequency. Moreover, it was found that the proportion of patients with multiple metastatic sites was higher in young patients, 16% and 49% of which had brain and bone metastasis, respectively [4].

2. Rationale of metastasectomy

Selecting appropriate treatment modalities for metastatic RCC remains a challenge. Although objective responses following targeted therapy are frequent, complete remissions occur in only 1–3% [5–7]. Moreover, it has become evident that, despite the most effective drugs in first-line treatment, a ceiling is being reached in median overall survival (OS) which ranges between 9 and 40 months, depending on clinical risk scores [8]. Therefore, together with the occasional durable responses achieved with high-dose interleukin-2, removal of all lesions, when technically feasible, provides the only potentially curative treatment. Traditionally, surgical resection has been the preferred approach (metastasectomy), but recent data on stereotactic radiosurgery (SRS) and ablative techniques indicate that other local non-invasive or less-invasive treatment modalities are a valid alternative to surgery. However, only a minority of patients with mRCC are candidates for metastasectomy. No reliable data exist on the proportion of patients with mRCC who will be eligible for this approach. It has been estimated that only 25% of patients with metachronous metastasis are suitable candidates for resection of metastatic disease [9,10]. For patients with synchronous metastasis a recent study addressed this issue. A whole-nation study on prevalence and potential resectability revealed that 154 patients (16.9%) had synchronous lung metastases [11]. However, only 11 with solitary lesions were deemed eligible for surgical resection, and only one underwent metastasectomy. In addition, patient selection for this approach is difficult because of the heterogeneous course of metastatic RCC. Metastasis may present at diagnosis or within a year after nephrectomy with curative intent, whereas in others disease-free intervals of more than 20 years have been observed with a slow growth of lesions. In few cases spontaneous regression of metastases has been documented, leading to the concepts of immune modulation [12,13].

Currently, prognosis and management of mRCC depend on a number of clinical factors such as performance status, the length of the disease-free interval, synchronous or metachronous metastasis, as well as the burden of metastatic disease and the number and location of sites involved [14]. One of the most commonly used prognostic models, the Memorial Sloan Kettering Cancer Center (MSKCC) risk score, uses Karnofsky performance status, time from diagnosis to treatment, and serum haemoglobin, calcium and lactate dehydrogenase to categorise patients as being at favourable, intermediate or poor risk [15]. After the introduction of targeted therapy the MSKCC risk score remains a valid tool together with the validated Database Consortium (DCM) model to assess the prognosis of patients with comparable concordances of 0.66–0.65 [8,16,17]. Metastasectomy is associated with survival and clinical benefit across these various risk groups [10,18].
The bulk of literature on metastasectomy dates back to the abdomen was published. In patients with complete surgical lesions in the lungs, pleura, central nervous system and the first series on metastasectomy in 41 patients with solitary following pulmonary metastasectomy [23]. In 1978, one of absence of effective systemic therapeutic options. In the resectable organ site may have a survival benefit in the resectable metastasis or multiple metastases restricted to one case reports and retrospective series have been published. A case series described three patients after complete resection of liver, lymph node and vertebral metastases following absence of further progression under treatment with sorafenib and sunitinib [19]. Patients remained disease-free after 16, 24 and 29 months.

Targeted therapy has been discontinued after complete resection of metastatic lesions. A series included six patients after complete resection of residual metastases in the lungs, iliac bone, skin and thyroid following treatment with sunitinib. The patients remained off treatment for 5–19 months [20,21]. The largest study included 22 patients receiving metastasectomy following targeted therapy [22]. Metastasectomy was performed in the retroperitoneum, lung, adrenal, bowel, mediastinum, bone and brain. Consolidative metastasectomy proved feasible with acceptable morbidity, although it resulted in a significant time off targeted therapy and long-term disease-free interval. However, it is not known whether this was primarily due to the complete resection of metastatic disease, which has been identified as an independent factor associated with prolonged survival, or the combination of surgery and targeted therapy.

Ultimately, adequate selection for metastasectomy is of critical importance. If applied appropriately, surgical resection alone or in combination with targeted agents may result in outcome that is superior to systemic therapy alone.

### 3. General prognostic factors of metastasectomy

The bulk of literature on metastasectomy dates back to the last century, when it was observed that patients with solitary resectable metastasis or multiple metastases restricted to one resectable organ site may have a survival benefit in the absence of effective systemic therapeutic options. In the 1930s there was a report of a patient who survived 23 years following pulmonary metastasectomy [23]. In 1978, one of the first series on metastasectomy in 41 patients with solitary lesions in the lungs, pleura, central nervous system and abdomen was published. In patients with complete surgical resection, the median disease-specific survival was 27 months, with 59% of the patients alive at 3 years [24]. Several authors concluded similar 3-year and 5-year survival after resection of a solitary lesion [25–27] or observed a significant difference in survival in patients with metachronous and synchronous metastasis [28–30].

In a series involving 179 patients the 5-year survival rate after resection of solitary lesions was 22% for synchronous versus 39% for metachronous metastases [31]. In addition, multiple clinical trials from the cytokine era revealed a strong association of outcome and metastatic sites [32,33]. In a retrospective analysis of 101 patients with resection of a total of 152 metastatic lesions at different organ sites [34], median survival was 28 months for the entire series. Survival was improved after resection of lung metastases when compared to other tumour locations and for patients clinically tumour-free after metastasectomy. Again, the time interval between primary tumour resection and metastasectomy correlated positively with survival.

Others have observed similar differences in 5-year survival rates for solitary metastases (56% for lungs, 28% for skin, 20% visceral organs, 18% peripheral bone, 13% brain and 9% axial bone metastases) [31]. One study evaluated 278 mRCC patients to define selection criteria for patients with solitary metastases [35]. On multivariate analysis, factors associated with a favourable outcome were a solitary site and single metastasis, complete resection of the first metastasis, a long disease-free interval and a metachronous presentation. Since then, multiple retrospective series have been published that support these favourable factors [32,36,37] (Table 1).

In a recent retrospective analysis of 109 patients who underwent primary tumour resection and at least one metastasectomy for mRCC, the following additional factors were associated with OS [38]; primary tumour stage > T3 stage, Fuhrman grade > 3, non-pulmonary metastases, multi-organ metastases and disease-free interval < 12 months were negative pretreatment prognostic factors with an accuracy of 0.87.

As data from Japan suggest, complete metastasectomy is a favourable prognostic factor independent of race or geographical location [39]. No data from prospective randomised trials on metastasectomy for RCC exist, and decision-making relies on retrospective series. It cannot be excluded that the benefit of metastasectomy is due largely to a lead-time bias based on differences in tumour biology. Patients with solitary and oligometastatic disease and a prolonged metachronous interval are more likely to undergo metastasectomy, while those with extensive metastatic burden, rapid progression and reduced performance will probably never be considered for resection. Perhaps not surprisingly, one series found having an aggressive tumour grade to be the only adverse factor for survival [40].

The significance of tumour heterogeneity and aggressiveness should not be underestimated in the interpretation of data which extend the indication for metastasectomy to multiple sites with the aim of achieving complete resection. Complete resection of multiple lesions has been reported as either a resection performed simultaneously at one or more sites or as repeat metastasectomy of asynchronous recurrences after the first resection.
Specifically, asynchronous metastases reflect a more benign course of the disease. In selected cases repeat metastasectomy results in exceptionally long survival lasting more than 10 years [41,42]. In a relatively large study of 141 patients with complete resection of solitary metastases, 5-year survival rates after complete resection of second and third metastases were no different when compared to those of the first metastasectomy (46% and 44%, respectively, versus a 43% 5-year OS rate) [35]. This supports data from an early retrospective study on repeat metastasectomy which led to improved survival compared to non-surgical treatment of recurrence after first metastasectomy [43].

Recently a large study analysed survival of patients after complete metastasectomy for multiple synchronous metastases at one or more sites [9]. Of 887 mRCC patients, 125 were identified who underwent complete surgical resection of multiple metastases (two to three or more metastases); 52% had resection at two or more sites, including lungs, bone, viscera and other locations. Patients with multiple non-lung-only metastases had a 5-year survival rate of 32.5% with complete resection versus 12.4% without. After controlling for performance status and disease burden, an almost threefold increased risk of death remained for patients with incomplete resection. A scoring algorithm from the same institution to predict survival for patients with clear-cell mRCC suggests that complete resection of multiple metastases was associated with a 50% decrease in the risk of death [14]. It cannot be ruled out that multiple metastasectomy benefited those patients who would have had a favourable course of disease regardless of surgical intervention. Collectively, these data underscore that careful selection of patients with multiple RCC metastases should be made according to the general prognostic factors (Table 1).

A prominent feature of RCC is its ability to metastasise to any anatomical location. Generally, there is little information on how to treat rare sites. In these circumstances factors associated with a favourable outcome after metastasectomy at more frequent sites should be considered for treatment selection (Table 1). Individual decisions have to be taken for each case. However, certain metastatic sites are consistent and more frequently observed. This has led to additional information that may guide treatment decisions. Specific management strategies for the most frequent sites will be discussed in detail. In contrast to traditional surgical metastasectomy, stereotactic radiosurgery (SRS) or ablative techniques have been largely applied to certain metastatic sites [44]. Although treatment of RCC metastases with SRS is gaining ground and is likely to be expanded to multiple anatomical regions, most of the experience stems from brain and bone metastasis and will be discussed below. While ablative techniques are minimally invasive and can cause bleeding and thermal damage, cranial and extracranial SRS involves adverse events such as cough, fatigue, skin rash and local pain. Side effects are generally frequent, but mild (grades I–II in 96%) [45].

<table>
<thead>
<tr>
<th>General</th>
<th>Pulmonary metastasis</th>
<th>Skeletal metastasis</th>
<th>Brain metastasis</th>
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<tbody>
<tr>
<td>Solitary or oligometastatic lesions</td>
<td>&lt;7 Metastases</td>
<td>Peripheral location of metastases</td>
<td>RPA class I:</td>
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<td></td>
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<td></td>
<td>1. Karnofsky PS &gt;70%</td>
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<td>2. Age&lt;65 years</td>
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<td>3. Absence of extracranial metastases</td>
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<td>Metachronous metastasis and disease-free interval of &gt;2 years</td>
<td>Absence of mediastinal lymph-node metastases</td>
<td>Wide excision</td>
<td>After SRS: &gt;75% decrease of the lesion</td>
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<tr>
<td>Complete resection</td>
<td>Metastases &lt;4 cm</td>
<td>Clear-cell subtype</td>
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<tr>
<td>Single-organ site</td>
<td>Unilateral lung involvement</td>
<td>Munich I: R0, no risk factor</td>
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<td>Good performance status (Karnofsky, ECOG, WHO)</td>
<td>Munich II: R0, ≥1 factor</td>
<td>Based on Munich Score risk factors:</td>
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<td>MSKCC or DCM good and intermediate risk</td>
<td>Absence of sarcomatoid features</td>
<td>1. Pleural infiltration</td>
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<td>Absence of nodal metastases</td>
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<td>2. Synchronous disease</td>
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<td>3. Retroperitoneal LN</td>
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<td>4. Metastases &gt;3 cm</td>
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<td>5. Mediastinal/hilar LN</td>
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<td>6. Complete resection</td>
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ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organization; MSKCC, Memorial Sloan Kettering Cancer Center; DCM, Database Consortium model; LN, lymph node.

a Recommendations for lymph node, liver, adrenal, pancreatic and thyroid metastasis and other less frequent sites follow the general factors.
Data on nodal metastasectomy are difficult to interpret. They are not regarded as distant metastasis (M) in the tumour-node-metastasis (TNM) classification, and often occur in association with further systemic metastatic sites. As a consequence nodal metastasis can manifest as different disease stages and is generally associated with a poor outcome that resembles that of systemic disease in retrospective series [46]. In few studies are locoregional and distant (mostly mediastinal) lymph-node metastases differentiated. There is evidence that resection of isolated nodes may be beneficial in terms of survival.

In fact, isolated lymph-node metastasis is rare. Between 58% and 95% of patients with lymph-node involvement have associated hematogenous metastases [47,48]. Patients with pathological N0 have a 5-year OS of 75%, versus 20% for patients with lymph-node metastases [46,49]. Despite this, patients with single lymph-node metastases and no metastatic disease can potentially be cured by lymph-node dissection (LND) [49].

Regional lymph-node metastases in RCC range from 13% to over 30%. However, the true incidence of solitary nodal metastasis without further systemic disease is unknown. In nephrectomy and autopsy studies single nodal metastases were observed in smaller tumours in 3–4.5% [46,49,50]. At autopsy, anatomical location of lymph-node metastases was unpredictable [51]. The authors found ipsilateral renal hilar lymph-node metastases in 7%, pulmonary hilar lymph-node metastases in 66.2%, retroperitoneal in 36%, para-aortal in 26.8% and supraclavicular in 20.7% [51]. In addition, single metastases in mediastinal, axillary, supraclavicular and iliac lymph nodes without any further metastasis were described [52,53].

In node-positive cases lymph-node dissection was associated with improved survival and a trend towards an improved response to immunotherapy [49]. Patients with regional nodes and distant metastases had significantly inferior survival to those with either condition alone. However, lymph-node status had less impact on survival than primary tumour stage, grade and performance status. [49]. Current guidelines advise that suspicious lymph nodes either at imaging or on palpation should be removed during nephrectomy because LND for clinically positive lymph nodes is associated with improved survival when performed in carefully selected patients [49].

A recent systemic review of the available literature concluded that data from the majority of retrospective non-randomised studies suggest that a possible benefit in terms of OS exists for patients with node-positive disease [54]. In addition, LND at the time of nephrectomy may avoid symptomatic local recurrences. As most clinically suspicious lymph nodes are removed at the time of nephrectomy, few data exist on the management of metachronous regional lymph-node metastases and are often summarised in series reporting on local recurrences [55], but there is a tendency to choose an investigational approach and pre-treat these lesions prior to surgical removal.

Several cases have been reported with downsizing of nodal metastases following tyrosine kinase inhibitors. Subsequent to sunitinib therapy, complete resection of bulky lymph nodes with encaement of the great vessels not amenable to initial excision was performed in a number of patients with clear-cell histology and no evidence of further lesions [56–59]. Downsizing up to 40% was reported following 5–10 cycles. “Second-look” surgery with complete retroperitoneal LND was feasible in all cases. Despite necrosis, viable clear-cell carcinoma was present in all cases.

4.2. Thoracic metastases

Pulmonary, pleural and mediastinal lymph-node metastases occur frequently in RCC and are found simultaneously in 20–35% of patients [60–62]. Lung lesions are most frequent and have a prevalence rate of 74% in autopsy studies [51]. Metastasis is mostly hematogenous, but direct lymphatic drainage from the kidney into the thoracic duct which subsequently drains into the subclavian vein and pulmonary artery has been proposed [63].

There are many retrospective series on resection of pulmonary metastases, but most of the earlier studies were small [33,35,64–67]. Collectively, recent series with larger patient cohorts observed a 5-year survival rate of 37–54% provided that complete resection of solitary or oligometastatic pulmonary metastases was achieved [9,35,60–62,68–74]. Consistent and robust prognostic factors were identified in multivariate analyses (Table 1). Incomplete resection was associated with a poorer 5-year survival of 0–22% [9,35,60,62,71,74,75], as was the number of pulmonary metastases removed [9,35,62,68,69,75]. Thus, median 5-year survival after complete resection of a solitary lesion was 45.6–49 months versus 19–27 months after complete resection of multiple metastases [68,69,75].

In a large study a significantly longer median 5-year survival was observed for patients with fewer than seven pulmonary metastases versus those with more than seven metastases (46.8% versus 14.5%) [62]. Furthermore, the presence of lymph-node metastasis was associated with shorter survival [60–62,74].

Despite complete pulmonary metastasectomy, mediastinal lymph-node metastases decreased median survival from 102 months to 19 months [60] and the median 5-year survival rate from 42.1% to 24.4% [62]. A short disease-free interval after nephrectomy or the presence of synchronous metastasis had a poor outcome [35,62,69,71,74,75]. Disease-free interval of > or <48 months or 23 months were associated with a median 5-year survival rate of 46% versus 26% [69] and 47% versus 24.7%, respectively [62]. The presence of synchronous pulmonary metastasis had a particularly poor outcome, with a median 5-year survival rate after complete pulmonary metastasectomy of 0% versus 43% for patients with metachronous disease [75].

Size of pulmonary metastasis is an additional factor [61,74,76]. A median 5-year survival rate of 70% versus 35% was observed after complete resection of metastases either < or >0.5 cm [76]. In an attempt to define a prognostic score, 200 consecutive patients with pulmonary metastases were recently evaluated in a single centre [77]. By multivariate anal-
Bone metastases occur in 16–26% of patients with metastatic RCC and are often symptomatic [15]. The prevalence of solitary bone metastasis may be low. In a series of 94 patients with solitary metastasis, single skeletal secondaries were observed in five patients (5.3%) [35]. Another retrospective series reported a rate of 2.5% [25]. Although prolonged disease-free survival has been reported after surgical resection of single and even multiple bone metastases, the most frequent indication for treatment are symptoms such as pain from nerve-root compression and pathological fractures. External-beam radiotherapy may be equally effective, but no randomised data exist specifically for RCC. As for other metastatic sites, outcome after surgical resection of skeletal solitary or oligometastases has only been evaluated retrospectively. Early reports suggested that patients with solitary bone lesions have a better survival after resection [85]. In a small study analysing bone metastasis from RCC in 13 evaluable patients with solitary lesions, a 5-year survival rate of 55% for the entire cohort was achieved [86].

The 5-year OS rate after resection of solitary bone lesions in other series was 40% [35] and 54%, respectively [87], although numbers were very small. Conversely, a series including 25 patients reported a 5-year survival rate of only 13%, despite wide resection of solitary bone metastasis [88]. A recent series evaluated 125 patients after resection of multiple metastases, including 11 with bone as single site (8.8%) and four (3.2%) with bone and lung involved [9]. The majority (75.2%) had more than three metastases removed. For patients with extrapulmonary sites the 5-year OS rate was 32.5% when complete resection was achieved compared with 12.4% among a matched cohort without complete resection.

One of the largest studies on resection of RCC bone metastases included a literature review. Five-year survival rates were 35.8–55%, comparable to OS observed after resection of lung lesions [86]. Patients with peripheral skeletal location of metastases had a 75% 5-year survival rate. Collectively, metachronous disease with a long disease-free interval, peripheral skeletal location with wide excision and solitary metastases were correlated with longer survival [86]. A further prognostic factor is the presence of a clear-cell histological subtype. Interestingly, the additional presence of pulmonary metastases did not predict early death, some patients surviving for years after complete resection of pulmonary and bone disease [9,89].

Similar predictive factors and survival rates were reported in a number of smaller retrospective series [87,88,90,91]. Because of the retrospective data evaluation, the impact on outcome of resection of RCC bone lesions remains controversial. However, surgical resection of bone lesions to effectively palliate pain and symptoms from spinal cord compression is undisputed.

A randomised prospective trial in patients with bone metastasis from various malignancies, including RCC, demonstrated that immediate decompressive surgery and postoperative radiotherapy are superior to treatment with radiotherapy alone for patients with spinal cord compression [92]. In addition, a prospective non-randomised study demonstrated that spinal surgery was effective in improving quality of life in patients with extradural spinal metastases from various cancers by providing better pain control, enabling patients to regain or maintain mobility, and offering improved sphincter control [93]. Surgery resulted in acceptably low mortality and morbidity rates. RCC bone metastases are highly destructive vascularised lesions. The risk of life-threatening haemorrhage poses a serious surgical challenge. The largest retrospective study on surgical approach and outcome included a total of 368 RCC bone metastases to the limbs and pelvis [89]. Surgical procedures involved curettage with cementing and/or internal fixation, en-bloc resection with closed nailing or amputation. The 1-and 5-year OS rates were 47% and 11%, respectively. However, 15 patients (5%) died within 4 weeks after surgery due to acute pulmonary or multi-organ failure.

Regarding palliation, resection of painful RCC bone metastases relieved pain significantly in 91% of patients. A good to excellent functional outcome was achieved in 89%, and 94% with metastatic lesions of the pelvic girdle and lower extrem-
Hepatic metastases are diagnosed in 8–30% of patients with RCC [15]. An autopsy study reported liver metastasis from a variety of cancers where wide excision resulted in improved survival and functional outcome compared to laminectomy alone [93].

Surgery for bone lesions should therefore aim at lasting control at the treated site with a durable fixation or reconstruction to prevent re-intervention. As the only randomised trial performed included radiotherapy in both arms, postoperative radiotherapy is advised [92].

Ablative approaches may be an alternative to surgery in selected cases with bulky bone lesions extending to extraskeletal regions [95,96]. As with other extracranial locations, SRS for spinal metastasis of RCC has been shown to be effective in a series of 48 patients with 55 spinal lesions [97]. The 1-year absence of progression rate in the spine was 82.1%. This early series suggests that SRS to spinal metastases is effective in palliating symptoms. At baseline, 23% of patients were pain-free, and this increased to 44% 1 month and 52% 12 months after SRS. In a retrospective study of 24 painful RCC bone lesions a relationship between dose and stable pain relief was observed in patients treated with a dose of 40 Gy in five fractions [98]. Adverse events were absent except one grade 1 skin toxicity. These data suggest that symptomatic and painful RCC skeletal metastases at various anatomical sites can be effectively controlled and palliated by SRS, and prospective non-randomised trials have been initiated.

5. Intra-abdominal organ metastases

5.1. Liver

Hepatic metastases are diagnosed in 8–30% of patients with RCC [15]. An autopsy study reported liver metastasis from RCC in 41% [51]. Only in 5% were these metastases solitary metachronous lesion [99]. The simultaneous presence of multiple organ sites explains the paucity of reports on liver metastasectomy either by surgery or by ablative techniques [100]. In addition, in contrast to solitary pulmonary metastases, liver metastases are consistently associated with a poor prognosis [31,32,34].

A few retrospective series with 13–68 patients suggest that surgical resection may be beneficial in terms of survival [99,101–104]. Earlier series reported a median survival following resection of solitary liver metastasis of 16–48 months with 5-year survival rates of 8–38.9% [99,101,102,104]. Factors associated with a good prognosis were disease-free interval longer than 6–24 months, performance status and completeness of resection. A large retrospective series analysed the outcome of 88 patients with liver as the only metastatic site [103]. Sixty-eight patients underwent metastasectomy compared to 20 who refused. The median 5-year OS rate after metastasectomy was 62.2% versus 29.3% in the control. In both cohorts 79% received systemic therapy, which suggests that liver metastasectomy may be appropriate for carefully selected patients. Patients with high-grade RCC and synchronous metastases did not benefit from hepatic metastasectomy. Furthermore, metastasectomy is associated with significant morbidity of 20.1% [103]. One series even reported a mortality rate of 31% [99]. In contrast, a contemporary multi-institutional analysis of 43 patients reported a low morbidity and near-zero mortality [105]. Three-year OS was 62.1% with a median recurrence-free survival of 15.5 months. However, recurrence occurs in up to 50% after liver resection [101,105]. Morbidity, mortality and recurrence need to be balanced against a potential benefit when selecting patients. It may be that surgery of small lesions is not superior to the use of ablative techniques in this setting which have been applied effectively [106]. SRS has been applied in a few patients with liver metastasis.

In a Swedish single-centre prospective study including multiple sites three liver lesions were treated successfully [45]. A retrospective analysis of SRS to RCC and melanoma metastases revealed that liver lesions treated with SRS with a SFED of ≥45 Gy had a local control rate at 24 months of 100% [79].

5.2. Adrenal metastases

Adrenal metastasis has been found in 3.1–5.7% in nephrectomy series [107–109]. In up to 23% of adrenal lesions simultaneous metastasis at other sites were present. Adrenal metastasis generally has a poor prognosis despite complete resection of solitary ipsilateral metastases at the time of nephrectomy. It is unknown whether this is directly due to the adrenal involvement or a consequence of an often concomitant advanced locoregional tumour stage. In 347 patients with advanced stage disease (T3-4N0-1M0-1) adrenal metastases occurred in 8.1% [109]. Among 56 patients with adrenal metastases, 82% had pT3 tumours [108]. Presence of distant metastases, vascular invasion within the primary tumour and multifocal growth of renal-cell cancer within the tumour-bearing kidney were identified as independent predictors of adrenal metastases [110].

The majority of radiographically or clinically apparent ipsilateral adrenal metastases are resected at the time of nephrectomy. Isolated, synchronous contralateral and metachronous ipsilateral or contralateral adrenal metastases are rare, and little is known about their management. They are often included in series on the management of local recurrences [55,111,112]. Survival with locally recurrent renal-cell carcinoma is poor, with a 5-year survival rate of 28% [111]. Patients after surgical resection had an improved 5-year survival rate of 51% compared to 18% treated with systemic therapy and 13% with observation alone.

Contralateral adrenal involvement, either synchronous or metachronous, is rare. In one autopsy series of patients after nephrectomy for RCC it was observed in 0.7% [51]. A small series on the outcome of 11 patients after surgery for metastatic RCC in the contralateral adrenal gland reported that synchronous contralateral adrenal metastasis occurred in two patients. The mean (median, range) time to contralateral adrenal metastasis after nephrectomy for nine patients was 5.2 (6.1, 0.8–9.2) years. All patients had adrenalectomy. Despite resection, most patients in this study died from RCC after a median of 3.7 (range 0.2–10) years after adrenalectomy for contralateral adrenal metastasis [113]. Collectively, not more than 60 cases are described in the literature [114–116]. Survival ranges from 8 to
Brain metastasis is observed in 2–17% of patients with RCC, and factors associated with outcome are uncertain. Some observed an association of survival with a metachronous interval of >18 months [115]. In summary, adrenalectomy for isolated metachronous ipsilateral and contralateral adrenal metastasis is recommended because it is associated with long-term survival in individual patients. Ablative percutaneous techniques may be an alternative to open or laparoscopic adrenalectomy [117].

5.3. Pancreatic metastases

Pancreatic metastases of RCC are relatively infrequent but have been described in 411 patients in 170 publications [118]. A systematic literature search reported the clinical outcome of pancreatic RCC metastases [118]. Of the metastases, 321 were treated surgically and 73 non-surgically. In the metastasectomy group 65.3% of the lesions were solitary and symptomatic in 57.4%. Following metastasectomy, 2-year and 5-year disease-free survival was 76% and 57%, respectively. Interestingly, the 2- and 5-year OS rates were 80.6% and 72.6%. Further extrapancreatic disease had no impact on OS in the metastasectomy group. Surprisingly, the time to pancreatic metastasis and the number of pancreatic lesions were not associated with a worse outcome. As expected, patients with unresected pancreatic disease had a significantly shorter 2- and 5-year overall survival rate of 41% and 14%, respectively. These data suggest that metastasectomy may be beneficial in patients in whom the pancreas is the only metastatic site and who are fit enough to undergo pancreatic surgery. In-hospital mortality after pancreatic metastasectomy was 2.8%, and a significant number of patients underwent extensive surgery (pancreatecoduodenectomy in 35.8% and total pancreatectomy in 19.9%). In view of the retrospective quality of the data and the significant surgical morbidity, patients with a short time to pancreatic metastasis following nephrectomy may be best treated with systemic therapy first.

5.4. Brain metastases

Brain metastasis is observed in 2–17% of patients with RCC, and is readily diagnosed by symptoms in more than 80% of cases [119–121]. If left untreated, median survival is poor (3.2 months) [122]. After the introduction of SRT, indications for craniotomy have been largely abandoned except for lesions >2–3 cm, rapid onset of symptoms and in cases of large lesions with midline shift [123–125]. Because of their relative paucity, therapeutic strategies for RCC brain metastases have often been evaluated together with cerebral lesions of various primary tumours. Generally, selection of patients for therapy of brain metastases, regardless of the primary tumour site, involves assessment of performance status, extracranial tumour load and the course of the disease, as summarised in the Radiation Therapy Oncology Group (RTOG) recursive partition analysis (RPA) [126]. Unfortunately, the majority (70–80%) of patients with RCC brain lesions belong to RPA class II – Karnofsky score (KS) >70%, further extracranial metastases – who have a poor median survival of 4.2 months [124,127].

In another study, including 4295 patients, significant prognostic factors for RCC brain metastasis were KS performance status and number of brain metastases [128]. Those with a KS of 90–100% and a single brain metastasis had a median OS of 14.8 months versus 3.3 months for those with a KS <70% and more than three metastases. Others have confirmed these observations [125].

An early retrospective series of whole-brain radiation therapy (WBRT) observed survival of patients with single brain metastases from RCC of 4.4 months only, which suggested that aggressive surgical treatment would be superior [129]. A prospective randomised trial of surgery and WBRT versus WBRT alone was in favour of the combination, although only few of the 63 patients with brain metastases had RCC [130,131].

For patients with extracranial progressive disease WBRT seemed sufficient. In a further study, craniotomy with resection of brain metastases in 50 patients with RCC again proved superior to WBRT, with a median overall survival of 12.6 months [132]. However, the addition of postoperative WBRT did not result in a survival difference. Currently, WBRT is regarded an adequate choice for patients with a poor performance and multiple lesions in whom palliative control of symptoms is the principal aim. In contrast to WBRT, SRS can provide effective local control comparable to surgery, even when multiple lesions and recurrent metastases are present [133].

Experience with SRS in the treatment of brain lesions exceeds that at extracranial sites. This is because SRS has been applied relatively early after its introduction to brain metastases as ‘gamma knife’ or ‘radiosurgery’ with the first series on RCC published in 1998 [134]. In one of the larger series, 85 patients with 376 brain metastases from RCC underwent SRS [124]. The median tumour volume was 1.2 cm (range: 0.1–14.2 cm) although 65% had multiple brain lesions. Median OS was 11.1 months after SRS with a local tumour control rate of 94%. Most patients (78%) died because of systemic progression. RTOG RPA classes I, II and III survived for 24.2 months, 9.2 months and 7.5 months, respectively. Another SRS series of 69 patients observed a median survival of 13 months in patients without and 5 months in those with active extracranial disease [135].

In a recent retrospective analysis 46 patients with 99 brain lesions were treated by SRS [136]. A single brain metastasis was treated in 56.5%. Local tumour control was achieved in 84.7%. Median OS was 10 months, but increased to 18 months for those with a >75% decrease in metastasis volume. It has been argued that survival rates after SRS are inferior to those after craniotomy, but the size of the retrospective series involving patients with RCC brain metastases, and the fact that more patients with a long metachronous interval and fewer brain metastases were candidates for craniotomy [132,137], do not allow a direct comparison.

5.5. Thyroid metastases

The thyroid gland is infrequently involved, and the first cases were reported in the 1940s [138]. The largest retrospective study evaluated 45 resections of solitary thyroid metastases at 15 different centres [139]. The 5-year overall survival rate was 51%. Prognosis was significantly poorer in patients >70 years of age, but no other factors were established. There was a striking coincidence of thyroid and pancreatic metastases (31%).

Another group reported on seven patients with solitary RCC metastases in the thyroid and a median OS after thyroidectomy of 38.1 months [140]. In a clinicopathological study of 36 cases, 64% had documented previous evidence of RCC as
long as 21.8 years before the thyroid lesion developed (mean, 9.4 years). After a mean follow-up of 9.1 years, 36% were alive or had died without evidence of disease [141].

6. Conclusion

Only few and selected patients, especially those with solitary metastases at single-organ sites, may benefit from metastasectomy. Consistently, survival benefit and even cure have been reported after complete surgical resection and SRS (Table 2). However, available data specifically related to RCC are from retrospective non-randomised studies. Therefore it remains unresolved whether the observed survival benefit is a consequence of surgical intervention or a selection of patients with more benign tumour biology who, owing to a mild clinical course, were considered for metastasectomy.

The best outcome has been observed after resection of metachronous solitary or oligometastases in the lung, but similar survival rates were reported for other sites, including liver, pancreas, bone and even multiple sites, provided that complete resection was achieved.

Despite consistent prognostic factors associated with a favourable outcome following metastasectomy, no general therapeutic guideline can be given. Careful patient selection is paramount, and the decision to resect metastases has to be taken for each site and each individual patient. Performance status, risk profiles, patient preference and alternative techniques to achieve local control, such as SRS or ablation, will have to be considered. After the introduction of targeted therapy, more patients with metastatic RCC may become candidates for complete surgical resection; pretreatment and multimodality concepts integrating medical and surgical treatments are being investigated.

7. Conflict of interest statements

A.B. has taken part in advisory boards of Pfizer, Bayer, GSK and Novartis. A.B. is the PI of the EORTC SURTIME trial which is in part supported by an educational grant from Pfizer.

References


Introduction

Mood disorders in cancer patients

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‘If I can’t feel, if I can’t move, if I can’t think, and I can’t care, then what conceivable point is there in living?’

(Kay Redfield Jamison, An Unquiet Mind: A Memoir of Moods and Madness)

Mood is a person’s subjective emotional state. According to the DSM-IV the term mood disorder is used for a group of diagnoses where the primary symptom is a disturbance in mood, or in other words the experience of an inappropriate, exaggerated or limited range of feelings. Mood disorders can mainly be divided into two groups: (1) depressive episode(s) characterised by feelings of sadness, hopelessness, helplessness, guilt, suicidal thoughts, fatigue, appetite changes, concentration problems and troubles engaging in daily living tasks; (2) manic or hypomanic episode(s) characterised by feelings of grandiosity, extreme energy and heightened arousal. Several treatment options are available for mood disorders – e.g. medication, cognitive and/or behavioural therapy – depending on the severity and the evaluation of the health-care provider.

Several studies have shown that mood disorders are common in patients with cancer. In a meta-analysis, the point prevalence of major depression was about 16% and that of anxiety was 10% [1]. The exact causes of mood disorders are largely unknown, but it is hypothesised that an imbalance in neurotransmitters is likely to play a role. The mood disorder can be triggered by the cancer diagnosis on its own, or it can be treatment-induced in cases where the aetiology can be found in the physiological effect of a psychoactive drug or chemical substance.

These articles provide an overview of the most common mood disorders among cancer patients. First, Dr. Dauchy will discuss the prevalence, predictive factors and treatment options of depression, one of the most under-diagnosed and inadequately treated mood disorders among cancer patients. Second, Professor Caraceni will introduce drug-associated delirium, an altered state of consciousness with reduced awareness of self and the environment, which may go hand in hand with the inability to think and talk clearly and rationally, hallucinations, disorientation and cognitive impairment. Third, Dr. Die Trill will discuss anxiety, one of the most frequently reported reactions to a cancer diagnosis, which may persist throughout the cancer continuum. In addition, she will shine her light on sleep disorders, which are frequently associated with psychological disorders. Finally, Dr. Schagen will describe the chemotherapy-related changes in cognitive functioning, which can result in diminished functional independence and can last throughout the survivorship period.

Conflict of interest statement

None declared.

REFERENCE

Depression in cancer patients

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1. Introduction

Depression is frequent in cancerology. Despite its clear impact on patients, it continues to be under-diagnosed and inadequately treated. There are many reasons for this, ranging from the underestimation of depressive symptoms by clinicians, their widespread presence in the context of cancer, the entanglement of depressive symptoms with those associated with the cancer and its treatment, or, indeed, the difficulty of clinicians in exploring emotional symptoms [1,2]. Beyond the fact that depression causes mental suffering that is not taken into consideration, even though it can be extremely intense in nature, this situation has a major impact on both morbidity and mortality through a number of different mechanisms [3,4]:

- Deterioration of quality of life [5].
- Increased sensitivity to pain [6].
- Difficulties observing treatment [7].
- Difficulties communicating with carers, friends and family.
- Significant burden placed on close relatives [8].
- Increased risk of suicide [9].
- Longer periods of hospitalisation [10].
- Reduced expectation of survival [11].

Depression also results in additional medico-economic costs, the extent of which we are only just beginning to understand [12,13].

There is also a risk of over-treatment, with antidepressants being systematically administered for what may only be an intense feeling of sadness, which may nevertheless be appropriate in the context and temporary in duration.

2. What is the prevalence of depression in cancerology?

Although depression is frequently observed in cancerology, the figures reported by the various related studies differ owing to the variability of the clinical forms of depressive disorders – major depressive episode (MDE), dysthymia, adjustment disorders with depressed mood, etc. – and the way in which the diagnosis is performed: clinical interview, questionnaires or self-report questionnaires which may be specific to depression (BDI, CES-D and Zung scale) or more general (HADS, POMS and SCL-90 etc.), variability of the cut-offs, etc. The figures also vary depending on the sample and, in particular, on the patient’s medical status, type of cancer, location, stage, treatment during or after cancer, etc. There may also be a bias associated with the selection of the patients (patients who have agreed to a clinical psychiatric assessment, convenience sample etc.).

On average, studies report a prevalence of MDE of 5–10%, two to three times higher than that in the general population. In a recent meta-analysis of 70 studies (n = 10,071) conducted by Mitchell et al. [14], the prevalence of depressions of all types (ICD, DSM criteria) was 16.3%, with the prevalence of MDE reaching 6%. The corresponding values rose to 24.6–29% and 14.3–16.5% in the analysis of 24 studies (n = 4007) of palliative-phase patients.

The way in which depressive disorders develop during the period of cancer care is still poorly understood because of a lack of longitudinal studies.

A depressive episode may be isolated or may have been preceded by other such episodes. In this latter case, the disorder is a recurrent unipolar depression. The patient’s antecedents may also include one or more phases of hypomanic or manic excitation, or he or she may have presented a hypomanic reaction when under antidepressants. In this case, a bipolar mood disorder is probable. Referral to a psychiatrist will then be necessary for diagnosis and identification of the relevant treatment.

3. What are the predictive factors?

Some of the risk factors for depression are known and must be identified at an early stage [15,16].
Unlike the data obtained in the general population, the role of age (<50 years) remains controversial [14,20].

Recent personal history of negative or stressful life events (bereavement, succession of losses).

Personal psychiatric antecedents (depression, suicide attempt, drug addiction and alcoholism) or familial antecedents (depression, suicide attempt and suicide) [17].

Personality traits – tendency not to express one’s emotions, tendency to consider life events as uncontrollable and inevitable, low self-esteem and poor emotional support and tendency to pessimism [18,19].

Unlike the data obtained in the general population, the most recent meta-analysis conducted by Mitchell et al. [14] suggests that gender is not predictive, possibly owing to the weight of the factors associated with the cancer itself.

The role of age (<50 years) remains controversial [14,20].

Social isolation [21].

Belonging to an ethnic minority [22].

Perceived lack of social support.

Recent personal history of negative or stressful life events (bereavement, succession of losses). The thymic toxicity of certain targeted therapies which cross the hematoencephalic barrier has given rise to a variety of subjective symptoms (at least five, see below) [27], none of which is specific [28]. In most cases, these symptoms are difficult to reveal (for example, social withdrawal that could be explained by cancer treatments), and the most highly visible symptoms (such as tearfulness) are the least specific.

In the case of cancer patients, this complexity is further aggravated by the potentially adapted nature of the depressive emotion in the context of the multiple bereavements that accompany cancer. One important area will therefore be to differentiate between ‘normal’ sadness, on the one hand, and adjustment disorders or depressive episode on the other.

For depression to be diagnosed, it is therefore necessary for at least five symptoms to be present nearly all day for at least 15 consecutive days. In practical terms, the diagnostic approach should consist of the following steps:

Use of two simple questions to attempt to identify one of the major symptoms, namely mental suffering and lack of interest (absence of desire for anything, affective indifference which can lead to social withdrawal and a loss of commitment to contact with friends and family) [29].

If one of these two symptoms is present, identification of the time criterion – almost every day, almost all day, for a minimum of 15 days.

Then attempt to identify associated symptoms (at least three or four from the list below).

Feelings of worthlessness or inappropriate guilt (in particular a painful vision of the past, for example: ‘for my family, I’m now nothing more than a burden’, ‘I’ve been a failure with my children’).

Recurrent thoughts of death or suicide.

Significant weight loss or gain (>5% of body weight), or increase or decrease in appetite.

Insomnia or hypersomnia.

Psychomotor agitation or retardation.

Fatigue or loss of energy.

Diminished concentration or indecisiveness.

A change in character with the appearance of irritability or aggressiveness that is inconsistent with earlier behaviour is also possible.

If five symptoms from the above list, including mental pain and/or absence of pleasure, are present then the patient is very probably depressed, and antidepressant treatment is recommended.

If not, the patient is exhibiting either a temporary depressive reaction (if the criterion of persistence over time is not
met) or an adjustment disorder with depressed mood (if insufficient symptoms are present: for example, sadness on its own without feelings of worthlessness, sleep disorders or anhedonia). Antidepressants are not indicated a priori.

Another difficulty affecting the diagnosis of depression is associated with the distinction between its somatic manifestations (fatigue, anorexia and/or loss of weight, cognitive or sleep disorders, loss of libido) and the physical symptoms associated with the cancerous disease or its treatment [30]. A number of ways of overcoming this difficulty have been described:

- An inclusive approach in which all the symptoms are taken into account, irrespective of whether or not they are attributable to the cancer (which clearly leads to a risk of over-diagnosis).
- An exclusive approach in which the somatic symptoms are systematically excluded from the diagnostic criteria.
- A substitution method in which these very same somatic symptoms are replaced by affective substitute symptoms [31].

When the exclusive and substitution approaches are used, the risk that the diagnosis may be underestimated is high, in particular in the case of patients who conceal or repress their emotions.

In practice, all manifestations that are not clearly linked to another cause (physical or iatrogenic causes) should be considered as contributing to the diagnosis of the depressive syndrome. The chronology of the disorders is particularly useful in this context.

It is therefore necessary to pay special attention to the cognitive and affective symptoms that are not directly linked to the somatic state, together with all their possible nuances:

- Self-devaluation and a painful vision of the past: feelings of uselessness, worthlessness and guilt (invasive, generalised).
- Loss of interest and pleasure: affective anaesthesia, indifference.
- Feeling of worthlessness coupled with feelings of helplessness and hopelessness.
- Desire for death and thoughts of suicide must be systematically explored; far from inducing suicidal behaviour, putting such ideas into words is an opportunity for the patient to become aware of their pathological nature and their link, not to a rational perception of reality, but to his or her own depressive suffering.
- Pathological pessimism.

A final difficulty lies in the fact that patients rarely spontaneously express those depressive symptoms that are primarily purely affective in nature (emotional withdrawal, for example), and that depressive symptoms themselves (psychomotor retardation, social withdrawal and shame) and lack of knowledge or minimisation of depressive symptoms lower this expression. Simple, open questions should therefore be favoured during the interview ("How’s your mood? And everyday life? Are there some good times? etc."). It is important to avoid moralizing phraseology (‘face up to’, ‘keep going’) and closed questions (‘Are you in a good mood? Are you coping?’) which risk blocking the expression of the experienced feelings and increasing the sensation of guilt due the patient’s perception of his or her depressed state. The availability of the carer, whether verbal or non-verbal, is vital for facilitating emotional expression.

The diagnosis must take into account the time of the assessment. The assessment of depressive symptoms is difficult during the days immediately following the announcement of bad news or in the case of an evolutive, uncontrolled somatic symptomatology, in particular if this is associated with the experience of pain. In such cases, the patient should be reassessed at a distance or after the symptoms have been treated.

Finally, the idea of a break with earlier behaviour is also important. The clinician must remain attentive to changes in the patient’s functioning, whether this is revealed by the patient or his or her friends and family. Helping patients become aware of this change may also make it easier for them to grasp the pathological nature of their condition.

5. How to screen for depression in cancerology?

Simple, validated tools can be used, and the aim for screening purposes is to select short tools taking no more than 5 min to complete. A recent review of the various potential tools for the screening of distress undertaken by Mitchell [32,33] identified 35 short tools for the screening of depression, consisting of 1–14 items. Although some of these specifically assess depression and have been validated for use in cancerology, most of them were not specifically designed for administration to patients suffering from a somatic pathology. This fact can be problematic when the deterioration of the patient’s general condition aggravates scores on items that evaluate the respondent’s somatic state; this criticism has been made with regard to the BDI (Beck Depression Inventory), for example [34]. Others, such as HADS (Hospital Anxiety and Depression Scale), assess emotional distress at a more general level but have the advantage of excluding somatic items. The following tools have been validated for use with cancer patients: single verbal item, PHQ1, PHQ2 (and PHQ2 + help question), two verbal items BCFD (Bried Case Find for Depression), Edinburgh Postnatal Depression Scale (EPDS, and Brief EPDS), Hornheide Screening Instrument (and Hornheide Short Form), General Health Questionnaire 9, BDI Short Form, HADS (and HADS depression subscale).

The sensitivity and specificity of the different scales vary as a function of the cut-offs used and of the patient clinical condition. None of the tools used today can be claimed to be irrefutably preferable to any other. It should nevertheless be noted that in most studies the sensitivity and specificity of ultra-short tools (consisting of just one or two questions, ‘low mood’ and ‘loss of interest or pleasure’) have been found to be at least as good as those of longer tools. In the meta-analysis of screening and case-finding tools for depression in cancer conducted by the Depression in Cancer Care consensus group [29], 56 diagnostic validity studies (n = 10,009)
were reviewed. For case-finding, one stem question, two stem questions and the BDI-II all had level 2 evidence. For screening, two stem questions had level 1b evidence. As they are highly acceptable, the stem questions are thus recommended (grade B recommendation). For every 100 people screened, the two questions would accurately detect 18 cases in advanced cancer settings (one missed and seven falsely identified), and 17 in non-palliative settings (two missed, and 11 falsely identified as cases).

By contrast, clinical appraisals that are not guided by at least one or two questions are not recommended, in particular if the clinicians are not trained [35].

In practice, it is important to remember that the diagnosis of depression is too complex for any screening tool, used in isolation, to be able to provide absolute certainty. Nevertheless, their use is recommended and can be incorporated within a more global assessment of the patient’s symptoms (as in the case of the Edmonton Symptom Assessment System, ESAS), supportive care needs or expectations [32]. The main value of these tools – and in particular of those which permit an assessment based on two questions – is that they make it possible to identify with a high degree of certainty those patients who are not depressed, and consequently focus the efforts of the oncologist, carer or psychologist/psychiatrist on obtaining a more in-depth assessment of those individuals who have screened positively.

However, systematic screening for depression has not as yet proved its effectiveness in significantly improving patients’ psychological outcomes [36]. Far from casting doubt on its usefulness, this fact emphasises the vital need to include this type of screening in an overall treatment process that extends through to the proposal and acceptance of appropriate pharmacological and/or psychotherapeutic care.

### 6. Depression and the risk of suicide

Despite the variability that can be found in the literature, owing to problems of both methodology and definition, it is possible to estimate the risk of suicide in the oncological context at 1.95–2.8 times higher than in the general population [9,37]. The wish to die is present in 17% of patients in an advanced phase of cancer.

Certain suicide risk factors are known [20,37]

- Poorly controlled symptoms (pain, fatigue, etc.).
- Masculine gender (relative risk of 1.7 in men and 1.4 in women compared with the general population [38]).
- Disclosure phase (first year following the diagnosis) [37].
- Site of the tumour (head and neck, lung, gastrointestinal, brain tumours [9]).
- Existence of a psychopathological disorder (depression, hopelessness, delirium).
- Familial antecedents of suicide and/or psychiatric illness, previous personal suicide attempts.
- Pathological impulsivity (personality disorder).
- Substance abuse (alcohol etc.).
- Recent loss (bereavement, for example).
- Site of the tumour (head and neck, lung, gastrointestinal, brain tumours [9]).
- Existence of a psychopathological disorder (depression, hopelessness, delirium).
- Familial antecedents of suicide and/or psychiatric illness, previous personal suicide attempts.
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### 7. Treatment plan and overall patient care

The treatment of depression has to start at an early stage [39]. It can take a long time to make patients aware of the psychological nature of their difficulties, encourage them to request a psychological consultation or to accept the prescription of psychotropic or, in particular, antidepressant medications. The more intense the psychological distress the longer this delay may be. It is the systematic attention paid by clinicians to their patients’ psychological distress that permits early diagnoses and the effective elaboration of an appropriate treatment plan.

The treatment of depression must form part of an overall care context. First of all, it is necessary to take account of the patient’s somatic condition, the associated symptoms and any comorbidities that may be present (pain, fatigue and sexual problems). It is not possible, for example, to treat depression in patients with uncontrolled pain [40].

To start from the patients’ expectations – for example, by identifying with them the symptom that causes them the greatest distress, or discussing what they can expect from treatment – may help them to accept depression treatment. Certain patients, for example, who can no longer themselves perceive the loss of the ability to experience pleasure or are unaware of their psychomotor retardation, may primarily complain of sleep-related problems. An initial prescription of drugs that are effective in combating these sleep disorders will encourage subsequent adherence to therapy. The patient’s habitual mode of psychological functioning may also help the clinician guide him or her towards appropriate psychotherapeutic support. It is also necessary to try to identify the representations associated with depression, antidepressant treatments or psychotherapies, together with any possible prior intolerance of antidepres- sive treatment.

Patients must be given information about their socio-professional circumstances and psychosocial resources (family, work and environment). What psychosocial resources can they count on in their family or professional environments? And, conversely, what strains or obligations are imposed on them?

The next step is to check the level of information that patients possess regarding the cancer for which they are being treated, their understanding of the treatment plan and their adherence to it. The quality of the cooperation between the
psychologist or psychiatrist, on the one hand, and the oncologist, on the other, may if necessary make it possible to revisit any information that has been inadequately understood.

Finally, therapeutic care for mental distress, in particular when drug-based treatments are used, must always be initiated by a stage during which the psychological nature of the disorders is explained and clear information about the prescribed psychotropic drug – its purpose and any possible side effects (risk of dependence associated with benzodiazepines or hypnotic substances, for example) – is provided. Nevertheless, given the specific symptoms that characterise depressive states, it can sometimes be difficult to secure the commitment of depressed patients to a course of treatment, in particular when they find it difficult to acknowledge the pathological nature of their condition or when the loss of hope or confidence in the future is significant. Memory and attention disorders may aggravate a patient’s reluctance to agree to psychotropic treatment and impair compliance with it, especially given that the anxiety that is frequently felt at the start of treatment may be associated with an increase in the real or feared side effects.

The discussion of the diagnosis is therefore the first step in the administration of treatment. The information provided to depressed patients enables them to better understand the nature of their distress and retain their independence. The empathy shown by carers in response to their psychological distress also constitutes an initial vital and beneficial experience for depressed patients, who often feel isolated due to the shame and guilt they experience (and withdraw themselves both from their friends and family and from their oncological team) [41].

To treat major depressive episodes it is necessary to prescribe both an antidepressant and, in certain cases, a course of psychotherapeutic care [1,15] or, at the very least, to ensure the availability of psychosocial support to facilitate adherence to treatment [42].

8. When and how to prescribe an antidepressant?

It is appropriate to prescribe an antidepressant for all major depressive episodes. This prescription does not always have to be accompanied by treatment by a psychiatrist except in the case of depression affecting patients with bipolar mood disorders who should be referred to a psychologist for diagnosis and treatment. In a recent Cochrane review [43] it was established that antidepressants outperform placebo level among patients with somatic diseases (OR 2.33, IC 1.8–3, P < 0.00001). This finding redresses a scientific shortcoming in the field of cancerology: in 2008, only 20 studies of the effectiveness of antidepressants had been conducted in this field and none of them had reached a sufficient level of proof [2]. However, we still need to gain a better understanding of the rationale underlying the pathogenesis of depression in the cancer field and, in particular, its links with the immune and inflammatory mechanisms.

| Table 1 – Families of antidepressants. |
| Family                          |
| SNRI : Venlafaxine, minalcipran and duloxetine |
| Nassa : Mianserine and mirtazapine |
| Melatoninergic : Agomelatine |
| Others : Tianeptine |

A preventive treatment is not recommended except in some very specific cases, as in e.g. depression induced by high-dose interferon alpha [44]. Generally speaking, SRIs (serotonin reuptake inhibitors) (Table 1) tend to be the first drugs to be prescribed in the field of cancerology [45]. There is no reason to consider the effectiveness of any antidepressant to be formally superior to that of any other [46–48]. When administered at antidepressant dosage (which is considerably higher than the antalgic dosage), tricyclics (Table 1) are difficult to handle and should be reserved for more complex cases. Escitalopram might be the medicament with the best effectiveness-to-tolerance ratio among patients who have no contraindication for this drug [45]. Furthermore, the choice of an antidepressant is specific to the patient and is determined by individual factors: the side effects of the drug, the patient’s tolerance to it (which includes potential side effects in combination with other drugs being co-administered or that might be used in the future), reactions to earlier treatments, and the patient’s preferences [49]. In particular, it is especially important to make sure that no potential iatrogenics exacerbate the somatic or non-somatic difficulties that are already present (for example, sexual difficulties or asthenia).

In the majority of cases, monotherapy is the rule; to combine two antidepressants is a priori pointless and potentially dangerous. Although exceptions exist, such prescriptions should only be made by specialists. Accompanying prescriptions – for example of anxiolytic or hypnotic drugs – should be restricted. These may be prescribed at the start of treatment but clinicians should attempt to reduce or eliminate them as treatment progresses.

The fact that a period of 2–3 weeks is required before any effect can be observed must be explained to the patient who must also be alerted to the possibility of undesirable side effects. It is important to remain vigilant with regard to the aggravated vulnerability of cancer patients (specific metabolic characteristics, associated treatments) and remain attentive to the identification of secondary effects which sometimes may not be easy to detect in a somatic context. Tolerance to antidepressants varies depending on the drug in question, and tolerance to tricyclic antidepressants is often poor since these drugs frequently produce side effects (orthostatic hypertension, weight gain, sedation, irregular heartbeat, confusion, epilepsy and potentially fatal in the event of an overdose), which is why they are not administered as the first line of treatment. The toxicity of serotonin reuptake inhibitors is less serious and is often restricted to self-limiting disorders (headaches, gastrointestinal disorders). All drugs may also lead to an increase in anxiety. Venlafaxine and duloxetine have also been reported to lead to increased blood
pressure. Mirtazapine and miarserine often lead to weight gain and drowsiness, two effects that can lead to resistance, particularly on the part of female patients at the end of the period of treatment who are already exposed to weight gain owing to other mechanisms.

There are no restrictions relating to prescriptions for patients with suicidal thoughts. According to the review conducted by Möller [50], the risk that such patients will actually take their own lives under the influence of antidepressants appears to be small and decreases from the age of 30 years onwards. If possible, patients who express suicidal thoughts should rapidly be sent for psychological or psychiatric assessment. However, if these thoughts are associated with depression, this referral should not cause any delay to treatment. A drug with only a low stimulant effect (a pure serotoninergic drug such as citalopram or paroxetine, but no noradrenergic products) should be preferred and should only be prescribed for a short initial period (1 week), after which the patient should be reassessed.

If there is a risk of suicide, the introduction of the antidepressant treatment is an emergency, but not such as the organisation of the care that is to be received. While awaiting the results of psychiatric assessment, it is necessary to organise enhanced monitoring of the patient and inform his or her family of the suicidal risk, insofar as professional ethics permit this. Ensuring that the patient is accompanied as much as possible is an important factor in helping to prevent the occurrence of suicide.

In all cases, it may be of value to try to limit the patient's impulsivity by prescribing a sedative and anxiolytic neuroleptic such as cyamemazine (e.g. 25–50 mg/day).

Antidepressants present no carcinogenic risk, at least in the case of SSRIs and tricyclics [51]. Nevertheless, vigilance is recommended in the case of the prolonged administration (more than 10 years) of serotonin-norepinephrine reuptake inhibitors (SNRIs), since for these recent products it has not yet been possible to study the associated long-term risks.

The risk of serotonin syndrome is also frequently cited. This takes the form of excessive serotonergic stimulation which causes motor excitation, hyperreflexia, trembling, myoclonia and dysfunctioning of the autonomous central nervous system and, in extreme cases, epilepsy, comas or death. These effects are not due to any idiosyncratic effect but are caused by the interaction of drugs sharing similar mechanisms or by overdoses [52]. It is extremely difficult to state their frequency since minor forms are probably not recognised and still less often reported [52].

Although a treatment can start to have an effect as of the first few days following prescription, it cannot be viewed as ineffective until 3–4 weeks of administration at an effective dosage level (6 weeks in the case of elderly subjects). The effective dosage can sometimes vary considerably (by a factor of 1–3 or even 1–4), which means that in the case of lack of efficacy it is necessary, providing that the patient tolerates the drug without difficulty, to progressively increase the dosage before moving on to a new drug. If a drug appears to be ineffective, it is also necessary to verify correct adherence (and therefore also tolerance to the correct dosage) on the part of the patient. The minimum period of treatment is 6 months in order to avoid any premature relapse. Treatment must not be interrupted suddenly given the risks associated with withdrawal which, with paroxetine, may appear in less than 48 hours. If oral administration is impossible, it is generally possible to replace the prescribed drug with injectable citalopram, the only SNRI available in this form. If administration has to be performed via a tube, then drugs available in soluble form should be preferred (citalopram, mirtazapine, fluoxetine and paroxetine).

**Table 2** lists the main limitations to prescriptions and contraindications. This should be updated by the clinician in the light of the data available at the time of prescription.

There are also risks of interactions with other drugs or of overdoses. Serotonin reuptake inhibitors are Cyt P450 substrates and may accumulate in individuals with slow metabolism or if Cyt P450 is inhibited. The SNRIs are also Cytp450 inhibitors whose effect varies from drug to drug (in contact with different isoenzymes). There is therefore a risk of interaction. This is due as much to the accumulation of the substrate as to its ineffectiveness when in the form of an inactive prodrug. The important thing is to be aware of the possibility of interactions and to be vigilant [53]. Several internet sites provide regularly updated information that can be consulted if required.

Although the prescription of psychostimulant drugs (primarily methylphenidate or modafinil) may be considered in the case of depressed patients (but in most countries remains outside the scope of marketing authorisation), this should be done only following a specialist assessment; in any case, these products are nowadays subject to an initial psychiatric prescription. Their stimulant effect on vigilance and attention may be of particular value in cases of asthenia associated with the prescription of opiates to overcome pain. In some studies, these drugs have exhibited a rapid antidepressant effect which can be of value, in particular when the end of life is near and the period of action required by antidepressants is therefore unacceptable or in order to obtain an immediate effect during this end-of-life period. However, high-quality studies, in particular involving adequate sample sizes, are still required in this area. Such psychostimulants should be prescribed only to patients for whom the experience of fatigue and the functional constraints that this imposes are perceived as an additional source of stress or an intolerable limitation to their quality of life. Their prescription should never be influenced by a desire for increased performance, in particular when made by friends and family distressed by the patient’s waning enthusiasm and drive and who would be reassured to see him or her recover the roles which he is no longer able to assume.

9. Is it necessary to prescribe a benzodiazepine?

These drugs should not be prescribed systematically. In practical terms, it is justifiable to prescribe a benzodiazepine or anxiolytic:
In the presence of a high level of anxiety, in particular in combination with somatic symptoms which might result in the poor tolerance of antidepressants (attribution to the drug of functional symptoms caused or exacerbated by anxiety).

If the patient is already being treated with a benzodiazepine – this may subsequently be interrupted; however, stopping it straight away may aggravate the clinical picture because of drug withdrawal (which, once again, risks being incorrectly attributed to poor tolerance of the antidepressant).

In depressed, impulsive patients it is often preferable to treat anxiety with low doses of a sedative neuroleptic (e.g. cyamemazine) rather than with a benzodiazepine.

10. What are the roles of the different actors in diagnosing and caring for depression in the field of cancerology?

Various organisational schemas for care administration in response to depressive disorders have been evaluated as a function of the actors responsible for screening, diagnosing or prescribing treatment [54].

It is not essential for the initial prescription to be made by a psychiatrist, in particular given the facts that there are not enough psychiatrists to provide care to all depressed patients, and that some of these patients are reluctant to consult a mental health specialist. Systematic screening followed by the diagnosis and prescription of treatment by the oncological team itself appears to be the most efficient way of providing effective treatment [42] if it includes the arrangement of – at the very least – support services (coordinating nurse, possibly communicating by telephone etc.) or other psychotherapeutic services. A psychiatrist may assist in the task of prescribing in the most complex cases. This approach has been validated in North America and seems to be suitable for use in the European context. It allows issue of an initial prescription without waiting for the psychiatrist, and emphasises the value, in addition to the prescribed antidepressant [1], of providing to the patient individual support by a psychologist or a non-psychologist.

It is advisable to obtain a psychiatric opinion from the outset in the case of patients with schizophrenia, a unipolar or bipolar mood disorder (manic-depressive disorder), a severe personality disorder or suicidal thoughts.

A psychiatric opinion should also be sought as a second line of treatment in the event of resistance to treatment even after an increase in dose, or in the case of any doubt concerning the diagnosis.

Even in the absence of a psychiatric opinion, the question of hospitalising the patient should be discussed if there is a risk of suicide or, in the case of refusal of treatment, agitation, extreme anxiety or delirium. It might also be considered in the case of extremely isolated patients.

All authors have emphasised the value of offering psychological support to patients, either in the form of psychosocial support or in the form of psychotherapy. In major depressive disorders, combining the administration of an antidepressant with the provision of psychotherapeutic care improves the effectiveness of treatment. In a meta-analysis of depression in a non-cancerological environment \(n = 1843\), patients treated with a combination of psychotherapy (of all types) and antidepressants exhibited a considerably higher level of improvement than patients treated with drugs only (OR 1.86, 95%CI 1.38–2.52). Furthermore, the beneficial effect of this combination increased in the case of treatments lasting for 3 months or longer (OR 2.21, 95%CI, 1.22–4.03) [55]. In this context, initial prescription by a psychiatrist would be ideal in order to improve the diagnosis and ensure, from the outset, that the prescription forms part of a coordinated therapeutic approach, possibly accompanied by a psychotherapeutic element [56]. However, this solution is only rarely available.

### Table 2 – Main limitations to antidepressant prescriptions and contraindications.

<table>
<thead>
<tr>
<th>Condition</th>
<th>SSRI, generally not contraindicated; use minimum effective dose and start off with half this dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hepatic insufficiency</td>
<td>Use tianeptine or minalcipran</td>
</tr>
<tr>
<td>Conduction disorders</td>
<td>Avoid tricyclics</td>
</tr>
<tr>
<td>Extension of QT, or co-prescription with drugs associated with this risk</td>
<td>Avoid SNRIs</td>
</tr>
<tr>
<td>Cardiac disorders in general</td>
<td>Prefer mianserine</td>
</tr>
<tr>
<td>Hyponatraemia</td>
<td>Risk of aggravation in response to SNRIs: monitor</td>
</tr>
<tr>
<td>Convulsions or risk of convulsions (cerebral metastases) without anticonvulsive treatment</td>
<td>Only tianeptine does not reduce the threshold of epileptogenesis</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>Avoid venlafaxine</td>
</tr>
<tr>
<td>Prostatic adenoma</td>
<td>Tricyclics are contraindicated. Caution is necessary when minalcipran and mirtazapine, SNRIs authorised but possibility of urination difficulties</td>
</tr>
<tr>
<td>Administration of tamoxifen</td>
<td>Paroxetine and fluoxetine are contraindicated.</td>
</tr>
</tbody>
</table>

SSRI : selective serotonin reuptake inhibitors.
Various types of psychotherapy have been proposed, sometimes in combination:

- Psychoeducation.
- Relaxation training.
- Problem-solving therapies.
- Cognitive behavioural therapies.
- Interpersonal therapies.
- Supportive expressive therapy.

The degree to which these therapies have been validated is sometimes limited and, in both psycho-oncology and psychiatry, the question of the evaluation of psychotherapies and psychosocial interventions continues to be a complex subject. The differing natures of the cancer patients, the approaches and therapeutic goals, the training and experience of the therapists, and the multiplicity of assessment scales, as well as the different periods studied during the health care circuit, all further complicate such analyses and relativise the results [57–59]. In this field, the very idea of randomised trials can be called into question [60] since they do not make it possible to appraise the subtle effects and individual benefits brought about by psychotherapy.

Beyond the above reservations, it is accepted that psychotherapies have a beneficial impact on anxiety, depression, psychological distress and quality of life [61,62]. Although it also seems to be the most depressed patients who gain the greatest benefits [63,64], this is at the same time the population for which the lowest level of evidence is available in the field of cancerology (only three well-conducted studies

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Fig. 1 – Summary of the main stages during diagnosis and the prescription of an antidepressant.
involving CRT and, in the case of metastatic patients, supportive-expressive therapies] [65].

It is important to identify the psychotherapeutic technique that is best suited for each patient as a function of their personality, their expressive capacities, their psychosocial situation, their concern for others and the time at which oncological care is administered. Thus, patients at the start of treatment might more readily accept a cognitive or psychoeducational approach, whereas those suffering from a recurrence of the disease or confronted with a serious development in its course might request a more existential form of psychotherapeutic support. Psychotherapies inspired by psychoanalytical and/or psychocorporal techniques could ideally be offered to all patients who request them provided that their psychotherapists are able, during preliminary interviews, to assess their ability to commit themselves to such activities and benefit from them.

Fig. 1 summarises the main stages during diagnosis and the prescription of an antidepressant.

11. Conclusion

Depression remains highly prevalent in cancer patients, and appears to have a great impact on their quality of life as well as on certain cancer outcomes, even if probably by the means of its impact on compliance, physical activity, social support etc. This broad impact justifies carrying out systematic screening that can be performed by standardised tools but also by one or two simple questions. To be useful, this screening must be followed by an adequate clinical diagnosis that relies on a precise identification of emotional and cognitive symptoms of depression. Considering the prevalence of depressed patients, the oncological teams are expected to do the depression diagnosis and make the first antidepressants prescription by themselves.

To be efficient, depression care must be part of a comprehensive care plan, including treatment of somatic symptoms, and an adequate response to information needs and unmet needs. When possible, and if accepted by the patient, the help of a psychologist is highly appreciated. In all cases, patients should benefit from an accompaniment that can be ensured by a nurse or a social worker.

More research is still needed on factors that may cause varying rates of depression and that predict which patients are mostly at risk. An adequate collaborative care process ranging from depression screening to effective treatment has to be implemented and assessed. Longitudinal studies are still needed to understand the evolution of depressive symptoms. Randomised controlled trials should also help to differentiate between the effectiveness of types of psychosocial interventions. Newer antidepressants and stimulants also should be studied in this population.

**Conflict of interest**

None declared.

**References**


Anxiety and sleep disorders in cancer patients

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1. Introduction

Even though most cancer patients do not meet diagnostic criteria for any specific mental disorder [1], many experience symptoms such as anxiety and sleep disturbances that may interfere with their overall adjustment to their disease. Anxiety is a common reaction to a cancer diagnosis and a normal response to perceived threats like loss of body functions, alterations in appearance, family disruption, death, etc. Anxiety may persist throughout the disease process, affecting the patient’s quality of life significantly, and often coexists with depression in cancer patients. Anxiety tends to appear or worsen at critical points during the course of the illness (diagnosis, beginning and end of treatment, recurrence, survival and terminal stage).

Sleep disorders are frequently associated with the psychological impact of cancer as well as with the physical illness itself, pain, hospitalisation and specific medical treatments. Altered sleep adversely affects emotional wellbeing and daytime performance, and may be an early sign of delirium in the oncology setting. In the general population, persistent insomnia has been associated with a higher risk of developing clinical anxiety or depression [2].

To effectively adjust patient needs to optimal treatment interventions, health-care professionals must be able to distinguish normal adjustment to cancer from altered reactions to the disease. This paper will focus on anxiety and sleep disorders in the oncology setting and will describe their clinical presentation, assessment, aetiology and treatment.

2. Anxiety in the cancer setting

2.1. Description and prevalence

Anxiety is defined as the apprehensive anticipation of future danger or misfortune accompanied by feelings of dysphoria or somatic symptoms of tension [3]. Classification systems used in psychiatry – such as the World Health Organization International Classification of Disorders [4] – require (a) a core of anxiety symptoms such as palpitation or tremor, manifesting the presence of autonomic overactivity, and (b) anxiety to be abnormal, in order to fulfil a diagnosis of anxiety disorder [5].

While anxiety is a normal reaction to threats such as cancer, some patients exhibit overwhelmingly anxious responses that impair their day-to-day functioning. Frequently, anxiety increases as the disease progresses or as treatment becomes more aggressive [6], as well as at transition points that represent threatening events throughout the course of the disease. Patients receiving a cancer diagnosis, learning about a recurrence, or hearing that treatment has been ineffective usually experience initial shock or disbelief followed by emotional turmoil, anxiety and depressive symptoms [7]. Inability to concentrate, diminished sleep, loss of appetite, irritability and intrusive thoughts about the future are also frequent at these times. However, these symptoms tend to decline gradually and resolve within the first 7–10 days after confirmation of cancer diagnosis [8].

Anxiety may affect a person’s behaviour regarding his/her health, contributing to a delay in or neglect of measures that might prevent or treat cancer adequately. Anxiety can lead to an overestimation of negative prognosis. For example, women with high levels of anxiety who learn that they have a genetically higher level of risk of breast cancer than they had previously believed might perform breast self-examinations less frequently [9]. A longitudinal study of women with breast cancer found that anxiety was the factor that was most consistently and strongly associated with an inaccurate perception of and an overestimation of future breast-cancer-related risk [10]. Anxiety may also delay or interfere with the seeking of medical care once symptoms have developed, adversely influencing – in this case – prognosis.

As mentioned already, in most cases the anxious reactions are time-limited and may motivate patients and families to take steps to reduce the reactions, such as seeking medical advice, which may assist in adjusting to the illness. Anxiety may also be part of a normal adaptation to cancer. Normal or successful adjustment is indicated in patients who are able to minimise disruptions to life roles, regulate emotional distress and remain actively involved in aspects of life that con-
Clinical practice shows that anxiety may also decrease as patients accept and come to terms with their medical situation, despite disease progression.

In the United States (US), 1-year prevalence for all anxiety disorders among adults in the general population exceeds 16% [12], and in the United Kingdom (UK) reported prevalence is between 3% and 16% [13]. Anxiety occurs to varying degrees in patients with cancer. Our limited understanding of anxiety in cancer care is illustrated by the wide range of prevalence estimates of abnormal anxiety in cancer patient populations [5]. Estimated current prevalence of anxiety disorders in oncology is within a range 15–28% [14], with variations being due to differences in research methodology. In large studies using standardised psychiatric interviews and applying research diagnostic criteria, estimates of abnormal anxiety in cancer populations ranged from 10% to 30% [4]. Some researchers have found that up to 44% of patients with cancer reported some anxiety, and 23% reported significant levels of anxiety [5,15]. Variation in reported prevalence is due largely to limitations in research methodology: differing study populations (single versus mixed cancer diagnosis, differing tumour sites, early- versus late-stage disease, outpatient versus inpatient; etc.), varying diagnostic criteria and assessment instruments and studies failing to separate anxiety from depression, etc.

Some researchers suggest that anxiety disorders are also prevalent in medically ill patients in general [16]. However, rates of anxiety disorders among primary care outpatients have ranged from 7% to 15% [17], and among general medical inpatients rates of 20% have been reported [18]. In both cases, reported rates seem to be lower than those reported in cancer patients. However, populations studied have varied widely in disease severity and prognosis [16].

In cancer patients symptoms of anxiety often coexist with depression and mixed states, and are perhaps more common than anxiety alone [1,19].

2.2 Clinical presentation and pathological anxiety

In order to understand anxiety we need to differentiate between anxiety as a state and anxiety as a relatively stable personality characteristic or trait (state versus trait anxiety). Patients with high levels of trait anxiety will carry their predisposition throughout the disease course, and thus it is important to identify it in an early phase.

Symptoms are similar in most patients, regardless of whether they represent acute responses to cancer or its treatment, or are part of a pre-existing anxiety disorder, exacerbated by the diagnosis of cancer [16]. Acute anxiety symptoms include:

- uneasiness, unpleasant feeling of arousal, restlessness;
- irritability;
- inability to relax; tendency to startle;
- difficulty falling asleep (leads to fatigue and low tolerance to frustration);
- recurring, intrusive thoughts and images of cancer;
- occasionally, sense of impending doom;
- distractibility;
- helplessness and a sense of loss of control over one’s own feelings;
- symptoms of autonomic arousal: rapid or forceful heartbeat, sweating, unpleasant tightness in stomach, shortness of breath, dizziness;
- vegetative disturbances: loss of appetite, decreased sexual interest;
- parasympathetically-mediated symptoms: abdominal distress, nausea, diarrhoea.

Pathological anxiety can be identified because it tends to be out of proportion to the level of threat; it persists or deteriorates when no intervention is administered, the intensity of symptoms is unacceptable regardless of the intensity of the threat (these include panic attacks, severe physical symptoms, abnormal beliefs such as thoughts of sudden death), and the patients experience a disruption of their usual or desirable functioning [3,4]. However, such criteria are difficult to apply to cancer patients given that cancer is always associated with some form of threat: the threat of loss, death, body functions, roles, body image, etc. In addition, while the duration of symptoms is important in identifying abnormal anxiety, the natural history of anxiety in oncology is uncertain. Disruption of functioning is also common in cancer patients and is frequently associated with anxiety (i.e. intrusive and unpleasant thoughts regarding recurrence, disability or death can disrupt the ability to concentrate, decision-making, sleep patterns, etc.) [4].

Massie and Shakin [20] have categorised anxiety in cancer patients into three groups: reactive anxiety, pre-existing anxiety disorders and anxiety related to medical illness.

Reactive anxiety: Adjustment disorders are emotional reactions to an identifiable stressor, in this case the disease, with a degree of psychopathology that is less severe than diagnosable mental disorders such as generalised anxiety. The patient experiences significant distress that is in excess of what would be expected from exposure to the stressor and a significant impairment in functioning.

CASE: Ms E, a 56-year-old woman recently diagnosed with colon cancer, was referred to the Psycho-Oncology Unit because of increased anxiety that interfered with her ability to decide whether to receive treatment with chemotherapy (CT) or not. Ms E had cared for her mother, who had died of ovarian cancer 2 years earlier after suffering severe treatment toxicity. Psychotherapy focused, among other things, on improving coping skills, deconstructing myths about cancer and its treatment, strengthening supports and introducing the patient to others that had successfully undergone cancer treatment, as well as practicing relaxation techniques in the oncology clinic where treatments were administered. Once her anxiety was significantly reduced, the patient decided to undergo treatment, which ended successfully.
Of hospitalised and ambulatory cancer patients, 32% were found to meet diagnostic criteria for an adjustment disorder [1]. In patients with advanced cancer, prevalence ranges from 14% to 35% [21], and in terminally ill patients rates range from 11% to 16%. Variability in prevalence rates is due to different factors such as differences in stage of disease, type of cancer or diagnostic procedures used for anxiety. The difference between an adjustment disorder and a normal reaction to cancer is based primarily on the duration and intensity of symptoms, as well as on the degree of functional impairment.

Pre-existing anxiety disorders: Panic disorders, phobias, generalised anxiety disorders and post-traumatic stress disorder are distinguished from other anxiety disorders as being long-lasting, often preceding the diagnosis of cancer. They are characterised by the extreme fear of losing control and of being overwhelmed by various circumstances:

Panic attacks are sudden, extreme anxiety reactions accompanied by sympathetic nervous system arousal and an overwhelming urge to escape. Intense anxiety is usually accompanied by severe somatic symptoms such as shortness of breath, dizziness, palpitations, trembling, diaphoresis, nausea, tingling sensations and fears of going crazy or having a heart attack. Panic attacks may be re-experienced when the patient is exposed to medical procedures, treatment toxicity, etc.

 CASE: Ms. A, a 35-year-old woman diagnosed with breast cancer requested psycho-oncological consultation for recurring panic attacks that developed shortly after ending cancer treatment. Ms A described herself as a very controlling, perfectionist, anxious and self-demanding woman for whom the disease was not a logical consequence of her previous behaviour, which had focused on healthy eating habits, reduced alcoholic intake, no smoking and almost daily exercise. She was experiencing between one and three panic attacks per week. Psychotherapy focused on helping the patient regain a sense of control over her life, focusing on the here-and-now while accepting her cancer risk, and developing more efficient ways of handling her anxiety, together with cognitive-behavioural techniques (i.e. training in relaxation, deep breathing techniques, etc.). Pharmacological treatment with benzodiazepines contributed to making the panic attacks disappear.

Phobias are persistent fears, intense anxiety or avoidance of a circumscribed object or situation. Phobias are experienced by cancer patients in a number of ways, the most common of which are fears of witnessing blood or tissue injury (also known as needle phobia) or claustrophobia (fear of closed places). Phobias may interfere with the administration of cancer treatment with patients refusing medical treatment or necessary tests [22], and may lead to anticipatory anxiety [16].

Mr E was a 28-year-old male with testicular cancer who had a needle phobia. Each time the patient had to undergo blood tests or receive IV chemotherapy treatment, his anxiety escalated to the point where, on one occasion, his treatment had to be postponed to the following day. Training in relaxation as well as in deep breathing techniques alternated with techniques to help him regain control over the situation. For example, ‘This is really going to hurt’ was accompanied by ‘Feeling the needle is not going to be very pleasant, but it will help cure my disease’. Mr E was able to undergo treatment with reduced levels of anxiety.

Generalised anxiety disorder is characterised by ongoing, unrealistic and excessive anxiety and worry that the patient finds difficult to control. The worry is pervasive and does not respond to either reassurance or contrary evidence. Symptoms do not have either the sudden onset or intensity of panic attacks and include restlessness, muscle tension, being easily fatigued, irritability, difficulty concentrating and sleep disturbance. Cancer patients with generalised anxiety disorder may, for example, worry or fear that no one will care for them, even though they have adequate social support, or they tend to anticipate medical complications.

Post-traumatic stress disorder (PTSD) develops when a person is exposed to a mentally stressful event that involved actual death or the threat of death, serious injury or a threat to oneself or others, and responds with intense fear, helplessness or anxiety. The person with PTSD re-experiences the traumatic event persistently in the way of recurrent and intrusive distressing images or thoughts, dreams of the event, avoids situations associated with the trauma, and experiences persistent symptoms of increased arousal that were not present prior to the trauma. To be diagnosed with PTSD, these symptoms must last for at least 1 month and cause significant problems in the patient’s personal relationships, employment or other important areas of daily life [3]. For the person who has experienced a diagnosis of cancer, the specific trauma that triggers PTSD is unclear. It may be the actual diagnosis of a life-threatening illness, certain aspects of the treatment process, test results, information given about recurrence or some other aspect of the cancer experience. Because the cancer experience involves so many upsetting events, it is much more difficult to single out one event as a cause of stress than it is for other traumas, such as a natural disaster or rape. PTSD has been studied in long-term non-Hodgkin’s lymphoma survivors who had participated in an earlier survey and were at least 7 years post-diagnosis [23]. Although half of the respondents reported no PTSD symptoms and 12% reported a resolution of symptoms, more than one third (37%) reported persistence or worsening.
of symptoms over 5 years. Those who had a low income, more advanced illness at diagnosis (stage ≥2), aggressive lymphoma, having received chemotherapy and greater impact of cancer at the initial survey had more PTSD symptoms at follow-up. Cancer survivors with PTSD may relive the cancer experience in nightmares or flashbacks and by continuously thinking about it; they may avoid places, events and people associated with the cancer experience, and may tend to be continuously overexcited, fearful, irritable and unable to sleep.

Mr K was a war veteran who underwent a bone marrow transplantation for leukaemia. During hospital isolation, Mr K started re-experiencing the time when he was imprisoned and placed in a cell, isolated for a prolonged period of time, during the war. In the hospital he had recurrent and intrusive images and thoughts about the war episode, frightening dreams of the event, and flashback episodes that gave him a sense of reliving the traumatic event. Other symptoms he exhibited included hypervigilance, insomnia, difficulty concentrating and avoidance of conversations related to the war episode when he was imprisoned. Benzodiazepines were administered. In addition, he was trained in different video games that provided him with cognitive distraction. In the evenings, when other patients were asleep and visitors had left the hospital, Mr K had to be walked in a wheelchair, the appropriate protective measures having been taken, up and down the hallways of the hospital floor to alleviate his sense of being 'locked up'.

Obsessive-compulsive disorder is characterised by: (a) recurrent, persistent thoughts, ideas or images (obsessions) that cause marked anxiety or distress, and are experienced as intrusive and inappropriate, and (b) repetitive, purposeful and intentional behaviours (compulsions) that the patient performs in response to an obsession in an attempt to reduce his/her distress. In order to diagnose an obsessive-compulsive disorder, the obsessions or compulsions should cause marked distress, should be time-consuming (take more than an hour a day) and interfere with the person's normal routine or functioning [3].

Ms T was a 34-year-old woman who had been treated for skin melanoma. Her skin was extremely white and full of freckles all over her face, body and extremities. Ms T was referred to the Psycho-Oncology Unit by her dermatologist, whom she visited frequently and unnecessarily. The patient would spend more than 2 h daily observing her freckles and trying to identify changes in any one of them. She involved her husband in helping her with this task, as she couldn’t view her back. This habit became increasingly incapacitating for the patient, and a source of irritation for her husband. The patient was treated with antidepressant medication and initiated psychotherapy sessions that helped reduce her distress as well as confront her underlying fear of death and other internal conflicts she had.

Anxiety related to medical illness uncontrolled pain, metabolic causes, medication side effects, withdrawal states and hormone-producing tumours may result in increased anxiety levels in the cancer patient. Patients with severe pain are usually anxious, and anxiety in turn can potentiate the pain sensation. Consequently, it is important to treat anxiety in order to adequately manage pain [24]. Anxiety may be the first sign of a change in metabolic state. Sepsis accompanied by chills and fever is often associated with anxiety. Delirium may cause symptoms of anxiety, restlessness and increased agitation. Certain drugs used in cancer, such as corticosteroids, are frequently a cause of anxiety symptoms such as restlessness and agitation. Akathisia is a side effect of several neuroleptic drugs that are frequently used for control of emesis. Withdrawal states from alcohol, narcotic analgesics and sedative hypnotics are often overlooked as causes of anxiety [20]. This is an especially important issue in head and neck cancer patients who often have histories of heavy alcohol and tobacco consumption that place them at increased risk for withdrawal states. Hormone-secreting tumours such as thyroid and parathyroid tumours may be associated with anxiety symptoms.

2.3. Variables associated with anxiety in the cancer setting

Cancer is usually an emotionally stressful event in the lives of patients. In addition to physical discomfort, patients typically face dysfunction, alterations in appearance, changes in family and social roles, disruption of work activities and other complex situations. Various factors have been associated with anxiety in cancer patients. Among them are:

- history of anxiety disorders: premorbid anxious tendencies such as elevated trait anxiety and obsessive personality traits [25,26]; helplessness, fatalism and anxious preoccupation have also been correlated with anxiety in breast cancer patients [27];
- psychological variables such as anxiety at the time of diagnosis [28] and history of trauma [29].

Previously discussed factors have been associated with anxiety in cancer patients and include history of anxiety disorders [25–27] and psychological variables such as anxiety at the time of diagnosis [28] and history of trauma [29]. In addition, medical/physical variables such as functional limitations, pain (described earlier) and advancing disease [6] have been associated with increased levels of anxiety in cancer patients. Cancer treatments, specifically the type of treatment administered and tumour response, have also been associated with elevated anxiety [30]. Anxiety is experienced by patients with anticipatory nausea and vomiting (ANV), a phenomenon that results from a classical conditioning process by which stimuli repeatedly associated with chemotherapy end up producing nausea and emesis prior to treatment administration. Anxious patients seem to develop anticipatory nausea and vomiting more frequently than non-anxious patients [31]. In these cases, patients may feel nauseous or vomit the week/day before treatment, as they approach the clinic, or even just thinking about chemotherapy.
2.4. Screening and assessment

Optimal management of anxiety disorders requires a comprehensive assessment and an accurate diagnosis. The distinction between normal fears and more severe fears that reach criteria for an anxiety disorder is not always clear in the cancer setting. According to Nicholas [32], patients with normal worry compared to those with more serious symptoms of anxiety disorders have only some difficulty concentrating, are able to ‘turn off thoughts’ most of the time, have occasional trouble falling asleep, and crying spells that seem to provide relief, and have few, if any, physical symptoms such as dry mouth, restlessness or racing heart. Worry comes and goes in this group of patients. On the other hand, patients with severe anxiety symptoms are unable to concentrate and to ‘turn off thoughts’ most of the time, have sleep problems most nights as well as crying spells that interfere with daily activities, experience constant worries and have few ways of reducing anxiety. It is important to understand the extent to which anxiety interferes with daily living and quality of life.

Psychometric instruments may be used to complement the clinical interview when assessing anxiety. The scales most frequently used with cancer patients include:

- hospital anxiety and depression scale (HADS) [33], which is a 14-item scale measuring symptoms of clinical depression and anxiety;
- brief symptom inventory (BSI) [34], which is an 18-item scale measuring somatisation, depression, anxiety and general distress;
- profile of mood states (POMS) [35], which is a 65-item scale measuring six mood states: anxiety, fatigue, confusion, depression, anger, vigour;
- state-trait anxiety inventory (STAI) [36], which is a 40-item measure that indicates the intensity of feelings of anxiety; STAI differentiates between state anxiety (a temporary condition experienced in specific situations) and trait anxiety (a general tendency to perceive situations as threatening);
- distress thermometer and problem list, which consists of a 0–10 scale to measure distress that is accompanied by a problem list in which patients are asked to note the nature and source of their distress (physical, social, psychological or spiritual) [37].

Self-report screening instruments must be scored, evaluated and discussed with each patient, and are useful in providing the oncology team with notions of how anxious the patient is.

2.5. Treatment of anxiety disorders

Psychosocial adjustment to cancer is an ongoing process in which the patient tries to manage emotional distress, solve specific cancer-related problems, and gain control over cancer-related events [38]. The purpose of treatment for anxiety in cancer patients is to facilitate successful adjustment to the disease: i.e. to help them minimise disruptions to life roles, regulate emotional distress and remain actively involved in aspects of life that continue to hold meaning and importance to them [11]. The average patient receiving psychosocial intervention for anxiety is less anxious than those not receiving the intervention. The overall positive benefit for psychosocial interventions seems to be greater with those who seem to need it most [39].

Treatment of anxiety should be multimodal, including a combination of pharmacotherapy and different psychotherapeutic interventions. Holland et al. [40], in a randomised study, compared relaxation with alprazolam in the treatment of anxiety and distress in cancer patients. Findings demonstrated both treatments to be equally effective for mild to moderate degrees of anxiety or distress. Alprazolam was more effective for greater levels of anxiety or distress, and had a more rapid onset of the beneficial effect.

Medication is only considered when patients experience severe symptoms, when their anxiety does not respond to psychological intervention and/or when there are no psychosocial services available or the patient refuses to use them. Massie and Shakin [20] describe clear guidelines for the use of pharmacotherapy to treat anxiety in the oncology setting. The choice of benzodiazepine depends on the desired half-life, route of administration available, route of metabolism and the presence or absence of active metabolites. They suggest that drugs with shorter half-lives, multiple routes of administration and no active metabolites are preferable in the medically ill patient, as well as the use of low-dose antipsychotic medications in patients with severe anxiety when treatment with benzodiazepine has not been effective. Benzodiazepines are not indicated in patients with medical conditions such as delirium, because they may exacerbate confusion and disorientation. In any case, use of these agents should be closely monitored and anxiety symptoms re-evaluated, medication being tapered off as symptoms subside [41].

Psychological approaches in the treatment of anxiety include combinations of cognitive behavioural therapy (for example, calming self-talk), insight-oriented and supportive psychotherapy, crisis intervention, support and self-help groups, and relaxation-based interventions such as hypnosis, meditation, progressive relaxation, guided imagery and biofeedback. All have been proven to be effective in reducing anxiety in the cancer patient [42–46].

Different psycho-educational interventions are equally useful. They have aimed at replacing the sense of helplessness with a sense of control, and in the process, reducing psychological distress [16]. For example, a booklet with disease-related information was provided to patients with Hodgkin’s disease, and these patients experienced more reductions in their levels of anxiety than those who did not receive the booklet [47]. Psychoeducational interventions might be provided by the physician and/or nurse, through accurate medical information and support. Anxiety related to medical procedures may be reduced by adequate preparation by a staff member, such that the patient will most likely have more realistic expectations about the procedure.

Regardless of the treatment modality employed to reduce anxiety in the cancer setting, organic causes of symptoms must be discarded prior to initiation of the intervention, and if detected, their correction should be a priority.
2.6. Sleep disorders

Sleep disorders are a common symptom of anxiety, one of the most prominent concerns of cancer patients [48], and one of the main reasons for consultation in oncology [49]. In the general population, people with insomnia report more medical problems than those without insomnia [50]. Altered sleep usually has a profound adverse effect on emotional, cognitive and physical functioning.

Sleep consists of two phases: rapid eye movement (REM) sleep and non-REM (NREM) sleep [51]. REM sleep is the active or paradoxical phase of sleep in which the brain is active. It is also known as dream sleep. NREM sleep is the restful phase of sleep. Both phases alternate in a repeated pattern or cycle of NREM followed by REM, with each cycle lasting approximately 90 min. The sleep–wake cycle is dictated by an inherent biological clock or circadian rhythm. Disruptions in individual sleep patterns can disrupt the circadian rhythm and impair the sleep cycle [52].

2.7. Categories of sleep disorders

The American Academy of Sleep Medicine [53] has defined five categories of sleep disorders:

- disorders of initiating and maintaining sleep: insomnias;
- sleep-related breathing disorders: sleep apnoea;
- disorders of excessive somnolence: hypersomnias;
- disorders of the sleep–wake cycle: circadian rhythm sleep disorders;
- dysfunctions associated with sleep, sleep stages, or partial arousals: parasomnias.

2.8. Sleep disorders in cancer patients

Sleep disturbances occur in about 10–15% of the general population [54] and are often associated with situational stress, disease, ageing and drug treatment [55]. Between one third and one half of cancer patients experience sleep disorders [56]. These are usually associated with pain, hospitalisation, medication, recurring thoughts about the disease and cancer-related fears. Anxiety and depression have been found to be highly correlated with insomnia [56]. Alterations in the sleep–wake cycle can be early signs of delirium.

However, insomnia is often under-recognised and undertreated, partly because it has been seen as a normal and transient reaction to cancer and cancer treatment, and partly because sleep disturbances are under-reported by patients [57]. Patients with cancer report insomnia, poor sleep quality and short sleep duration [58]. Sleep disturbances can persist in time, with a significant number of cancer survivors reporting them as one of the most pervasive problems they face.

Reports over the past 20 years have begun to shed light on the putative relationship between cancer-related sleep disorders and cancer-related fatigue. While most of the studies in this area are correlative in nature, it is generally the case that sleep disturbance is: (a) positively correlated with fatigue, (b) more severe in fatigued than in non-fatigued patients and (c) a significant predictor of fatigue [58–60]. Current understanding of the possible link between cancer-related fatigue and sleep disturbances suggests that interventions targeting sleep disorders and daytime sleepiness could provide promising potential treatments for cancer-related fatigue. Targeted treatment of either symptom may possibly affect the other, given the emerging data suggesting that sleep disturbance is common in patients with cancer and that it may be both a cause and an effect of fatigue [58].

The following risk factors have been described for sleep disorders in cancer patients [61]:

- disease factors, including paraneoplastic syndromes with increased steroid production, and symptoms associated with tumour invasion (i.e. pain, fever, shortness of breath) [62];
- treatment-related factors, including symptoms associated with surgery (i.e. pain, use of opioids and frequent monitoring) [62];
- chemotherapy administration (i.e. exogenous corticosteroids);
- medications such as opioids, sedatives/hypnotics, steroids, some antidepressants and dietary supplements [63];
- environmental factors (i.e. hospital routines and roommates, environmental noise) [64];
- physical and/or psychological stressors [57];
- anxiety and depression [56];
- delirium.

In addition to considering the above risk factors, an adequate assessment of sleep disorders should evaluate the usual patterns of sleep, including usual bedtime, routine before retiring, length of time before onset of sleep and duration of sleep (waking episodes during the night, ability to resume sleep and usual time for awakening). Characteristics of disturbed sleep (changes following diagnosis, treatment and/or hospitalisation), perception of significant others as to quantity and quality of patients’ sleep, and family history of sleep disorders should be taken into account, together with emotional status, exercise and activity levels, diet and care-giver routines [53].

Some studies link sleep with natural killer cell activity [65] and conclude that sound sleep may be important for immune defence against tumour cells [66].

2.9. Treatment of sleep disorders

Multiple psychological interventions – ranging from individual supportive psychotherapy to cognitive behavioural techniques (biofeedback, hypnosis, progressive muscle relaxation) – have proven to be effective in the control of anxiety and sleep disorders [67], and may be combined with pharmacological interventions. Several large randomised trials and meta-analysis have demonstrated the efficacy of cognitive behavioural therapy for insomnia in patients without cancer [68,69] as well as in the cancer population [70–72].

Components of cognitive behavioural therapy (CBT) include:

- cognitive restructuring, such as restructuring negative thoughts, beliefs and attitudes related to sleep, and preventing excessive monitoring or worrying about getting enough sleep [68];
• behavioural strategies including stimulus control and sleep restriction in order to limit the time spent in bed during which the patient does not sleep [68];
• relaxation techniques that can be combined with both cognitive and behavioural interventions are quite useful when accompanied by visual imagery;
• basic sleep hygiene education includes suggesting the following to the patient: sleeping and waking up at regular times, relaxing at least 90 min before going to bed; creating a dark, comfortable sleep environment with a cool temperature, avoiding watching television, using a laptop, or working in bed, getting ample daylight during non-sleep hours, avoiding day naps, avoiding stimulants such as caffeine, nicotine and cigarettes 2–3 h before bedtime, avoiding intake of liquids 2 h prior to sleeping, and getting regular exercise but no closer than 3 h before bedtime.

In one study, 30 cancer patients were assigned to either a three-session relaxation programme or no treatment. Patients receiving relaxation training reported reductions in sleep latency [70]. Espie et al. [72] found CBT to be associated with mean reductions in wakefulness of 55 min per night compared with no change for the care as usual group for persistent insomnia in patients with cancer. Results were sustained 6 months after treatment. Standardised relative effect sizes were large for complaints of difficulty initiating sleep, waking from sleep during the night and for sleep efficiency (percentage of time in bed spent sleeping). CBT was associated with moderate to large effect sizes for five of seven quality-of-life outcomes, including significant reduction in daytime fatigue. No significant interaction was found between any of these outcomes and baseline demographic, clinical or sleep characteristics. Savard et al. [71] studied 57 women with insomnia caused or worsened by breast cancer. Patients in the treatment group participated in CBT group sessions during eight weekly sessions of 90 min duration each, led by a psychologist. Sustained reductions in sleep latency and wakefulness were observed after CBT compared with controls. There was no increase in total sleep, but increases in sleep efficiency (proportion of time in bed spent asleep) averaged 15%.

Long-term pharmacological treatment is not desirable, especially when fatigue is an issue [73,74]. Despite this, 25% of cancer patients have been reported to take sleeping pills [66], and approximately 25–50% of all prescriptions written for patients with cancer are for hypnotics [75]. In cases where CBT is not available, it has not been successful, or when patients have comorbidities contributing to sleep disturbances (i.e. pain, hot flashes, depression, etc.), then pharmacological treatment will be necessary. Several types of medication are used to treat disturbed sleep [61]: non-benzodiazepine benzodiazepine receptor agonist, benzodiazepines, melatonin receptor agonists, antihistamines, antidepressants and antipsychotics that have sedative effects, and melatonin. Most of the approved sleep aids have not been studied in cancer populations; therefore the risk/benefit profiles of these drugs are not delineated in this setting.

3. Conclusion

Patients with cancer report elevated levels of anxiety and sleep disturbances that may intensify throughout the disease course. Symptoms are frequently underestimated, despite the enormous adverse impact they have on patients’ quality of life. Adequate assessment of symptoms is imperative and should identify medical as well as non-medical variables influencing or causing anxiety or sleep disturbance, in order to obtain optimal symptom management. Psychotherapeutic techniques such as CBT have proved to be effective in controlling both anxiety and sleep disturbances. However, the most effective intervention for both anxiety and sleep disorders is that which combines psychotherapeutic techniques with pharmacological treatment, when necessary.

Conflict of interest statement

None declared.

R E F E R E N C E S


Chemotherapy-related changes in cognitive functioning

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1. Introduction

The potentially detrimental effects of cancer and related treatments on cognitive functioning are emerging as a key focus of cancer survivorship research. Many patients with central nervous system (CNS) or non-CNS tumours develop cognitive problems during the course of their disease that can result in diminished functional independence and can continue well into the survivorship period.

In recent years, growing attention is being paid to the potential adverse effects of chemotherapy on brain and cognitive function. This central neurotoxicity may manifest as both acute and delayed complications. Virtually all categories of chemotherapeutic agent have been associated with adverse neurological effects, including both acute and chronic encephalopathy. More subtle cognitive dysfunction has also been demonstrated and frequently manifests as diminished memory, executive function, attention and information processing speed.

In this article on chemotherapy and cognitive functioning we will summarise knowledge on the incidence of cognitive deficits, the neuropsychological pattern and structural brain changes associated with chemotherapy, risk factors identified for developing neurotoxicity and underlying mechanisms as well as current treatment options to prevent or diminish the adverse effects of chemotherapy on cognition.

We will focus on chemotherapy-associated cognitive problems in breast cancer patients, as these symptoms have been particularly well studied in this patient group. In addition, studies on chemotherapy and cognition in adult CNS cancer patients will also be discussed. In this group of patients chemotherapy may be associated with stabilisation or improvement of cognitive function due to better disease control, but may at the same time go hand in hand with CNS toxicity as a consequence of chemotherapy.

2. Neuropsychological studies in breast cancer patients

Over the last 10–15 years, increasing evidence has revealed the occurrence of acute and long-term cognitive problems for a subset of patients following chemotherapy applied in the treatment of non-CNS malignancies. In breast cancer patients alone, over 60 neuropsychological studies have been published that have investigated whether adjuvant chemotherapy is associated with cognitive impairment [1–3]. In the early years most of these studies had a cross-sectional design and provided us with a snapshot of the prevalence of cognitive impairment and the characteristics associated with this impairment at specific moments post-chemotherapy. In recent years, prospective neuropsychological studies on the incidence of cognitive problems arising from pre- to post-chemotherapy supported the previous observed relationship between chemotherapy exposure and cognitive problems by demonstrating cognitive decline post-treatment relative to pre-treatment cognitive performance.

Those prospective studies with a pre-treatment assessment also indicated the importance of a baseline measure, as several studies observed lower than expected cognitive performance in breast cancer patients who are about to undergo chemotherapy in comparison to reference data of non-cancer subjects or cancer patients with lower disease stages who will not need chemotherapy. Up till now, no explanation has been found for these decreased cognitive scores at baseline. Surgery (under general anaesthesia), distress, fatigue or disease-associated immune responses cannot yet clarify this observation.

3. Frequency and pattern of cognitive dysfunction

The vast majority (70%) of the neuropsychological studies demonstrated cognitive impairment and/or cognitive decline...
in breast cancer patients who have been treated with cytotoxic agents compared to breast cancer patients without chemotherapy or compared to non-cancer controls, regardless of the design of the study.

Patients show deficits on a wide range of standardized neuropsychological tests, but core impairments are related to learning new information and accelerated forgetting of information. Impairment in executive functions – such as planning and implementing strategies, flexible shifting and working memory – is also common, as are deficits in psychomotor speed (indicative of a frontal-subcortical profile).

Despite the accumulation of knowledge on the cognitive side-effects of chemotherapy, the actual incidence of this impairment is still a subject of research. Estimates of affected patients vary from 17% to 78% across studies, because of differences between treatment regimens and between individual patients, but also owing to variations in study measures, assessment times and criteria applied to define cognitive impairment and deterioration. When the magnitude of the cognitive deficits as expressed in sizes of effects is studied, a large variation between studies is also observed.

4. Course over time

The literature has shown that cognitive changes can arise during treatment and can persist up to several years after completion of treatment. Studies have largely followed patients up to 1–2 years post-treatment. Only a few studies have investigated the very late (i.e. >5 years post-treatment) effects of chemotherapy, but those that have show long-term cognitive problems in chemotherapy-exposed breast cancer survivors. A recent large study showed that breast cancer survivors who received CMF chemotherapy (cyclophosphamide, methotrexate, 5-fluorouracil) on average 20 years previously were more likely to have lower performance on memory, information processing speed and psychomotor speed compared with women without a history of cancer. The magnitude of the effects was comparable to approximately 6 years of age-related decline in cognitive function [4].

The influence of cancer and cancer treatment on the process of cognitive ageing is a topic that is increasingly receiving attention. There is concern that chemotherapy may induce accelerated ageing and that it can increase an individual’s susceptibility to late-emerging cognitive decline or dementia. The underlying development of cognitive impairment in ageing appears to begin at mid-life. Genetic signatures of brain ageing (i.e. from transcriptional profiling in post-mortem brains) can be identified in subjects as early as their 40s. Substantial evidence demonstrates that a wide variety of variables in early life are determinants of cognition in later life. Furthermore, both lifestyle and health-related risk factors in mid-life are associated with poor cognition decades later. It is plausible that damage to brain health in young to middle-aged women becomes even more clinically evident many years later when the brain is extra vulnerable. Therefore it is essential to investigate how chemotherapy in earlier life may influence cognition in later life.

Different trajectories for chemotherapy-associated cognitive problems have been proposed in the literature. It could be that long-term cognitive problems result from lack of recovery from the acute effects of treatment. It could also be that the initial effect of treatment may produce a cascade of biological events that cause continued cognitive decline with ageing. Alternatively, chemotherapy may not be sufficient to cause enough redundancy loss to immediately affect cognitive function, but may produce a delayed effect as ageing continues, with the slope of change being influenced by a variety of factors [5].

Prospective studies with a very long-term follow-up or studies focusing on older cancer survivors are almost absent. A study on the effects of chemotherapy and cognition in patients >65 years of age showed that these subjects experienced more cognitive decline than unexposed counterparts. Incidence of dementia was not explored in this study, and even though these subjects were of older age, their mean time since treatment was still relatively short [6,7]. A few retrospective studies have been published examining the risk of dementia in breast cancer survivors up to 15 years after completion of cytotoxic treatment; these studies used data from the linked Surveillance, Epidemiology and End Results (SEER)-Medicare database. None of these studies showed any clear evidence for the existence of such a relationship, although several methodological issues limit the validity and interpretation of the studies [8–11].

5. Risk factors

Several factors have been identified that generally increase the risk of developing neurotoxicity associated with chemotherapy. These include: (1) exposure to higher doses due to planned use of high-dose regimens, or to high concentrations of the parent drug and/or its metabolite due to impaired systemic clearance and/or pharmacogenetic modulation of drug pharmacokinetics; (2) additive or synergistic effects of multi-agent chemotherapy; (3) additive or synergistic effect of multimodality therapy that includes administration of chemotherapy either concurrently with or subsequently to cerebral radiation; (4) intra-arterial administration with blood–brain barrier disruption; and (5) intrathecal administration [12–17].

From the literature it is clear that not all patients are affected equally by chemotherapy. The finding that a subgroup of patients experience persistent post-treatment cognitive decline has led to the examination of patient- and disease-related risk factors for cognitive change. Candidate predictors of cognitive dysfunction frequently studied include age, education and pre-morbid IQ; however, no consistent predictors have been identified. Most studies failed to identify a relationship between treatment-related cognitive decline and age, IQ, education, baseline cognitive function and a host of other factors such as depression, anxiety, stress, fatigue, disease stage, haemoglobin levels and treatment-induced menopause. When an association between a sociodemographic or clinical predictor and cognitive dysfunction has been found the relationship is generally weak [3]. However, given the small sample sizes in nearly all studies, exploration of any sociodemographic or clinical predictors is likely to be underpowered. This is also the case for genetic factors (e.g.
vulnerable alleles of genes such as APOE and COMT) that have been examined as potential risk factors for cognitive decline [5].

**Risk factors – endocrine treatment:** a treatment-related risk factor for cognitive decline in breast cancer patients that is of particular clinical relevance is the combined use of endocrine therapy. Breast cancer patients undergoing chemotherapy often receive endocrine therapy as well. These therapies commonly consist of treatment with selective oestrogen receptor modulators (SERMs) such as tamoxifen and/or aromatase inhibitors (AIs) such as exemestane, anastrozole or letrozole. Evidence derived from basic as well as clinical research indicates that estradiol, within a time window of opportunity, can stimulate neuroplasticity in brain areas involved in cognitive behaviour leading to improved performance [18–20]. Since SERMs and AIs also target brain areas involved in the regulation of cognitive behaviour, it is plausible that these substances may contribute to cognitive deterioration in breast cancer patients. Blocking estradiol synthesis with AIs deprives the brain of modulation via estradiol and therefore theoretically results in decreased neuroplasticity and impaired cognitive functioning. However, surprisingly, studies in breast cancer patients seem generally to indicate that AIs less consistently adversely influence cognitive functioning compared with SERMs [21]. Studies specifically addressing the interaction between chemotherapy and endocrine therapy are sparse and the majority of studies have been too small to adequately investigate this interaction. Absence of oestrogen neuroprotective action in the brain – in the natural, surgical or chemotherapy-induced postmenopausal brain – makes the brain possibly extra vulnerable to neural damage by chemotherapy [22].

Particularly in older breast cancer patients, treatment with SERMs seems to have a potentially detrimental effect on cognitive functioning [23]. Basic research is rather conclusive on the neuroprotective properties of SERMs in the absence of circulating estradiol, but the effects of chronic SERM administration on cognitive behaviour are more ambiguous. Clearly more research is needed, particularly on the effects of SERMs on the brain and behaviour in relation to age and the length of deprivation of endogenous estradiol.

**Risk factors – information:** information on chemotherapy-associated cognitive problems is more and more accessible to patients. The reporting of cognitive problems may also be influenced by strictly cognitive mechanisms that are not rooted in psychological distress or negative affect, but simply in the extent to which a patient is informed about the possibility of cognitive problems following chemotherapy. Several studies on cognitive deficits in breast cancer patients showed that mere information about the association between chemotherapy and cognitive problems resulted in lower memory performance and higher complaint reporting [24,25]. These effects occurred independently of negative affect and pre-existing knowledge. The notion that mere information can add to the occurrence and maintenance of cognitive problems is derived from a large body of social psychological research on stereotype threat and priming. Stereotype threat – i.e. fear of confirming a stereotype – has been researched extensively, and evidence shows that activation of a stereotype or schema unconsciously leads to behaviour that is in correspondence with that stereotype [26,27].

Concepts of stereotype threat and priming are important for explaining the effects of treatment-related information on complaint reporting and neuropsychological test scores. Furthermore, it may be that some individuals are particularly vulnerable to these effects. Research shows that stereotype threat effects are stronger among people who are especially cognizant of the particular stigma, and that participants who self-identify more strongly with a stereotyped group show stronger stereotype threat effects on cognitive function [28]. A recent study showed that receipt of stereotypical information about the occurrence of medical problems experienced by cancer patients primed the cognitive accessibility of the cancer patient stereotype and differentially affected women’s cognitive complaints and test scores, depending on their level of consciousness of cancer patient stigma [29].

It is not suggested that these psychological processes should be viewed as alternative explanations for biological influences. Rather, the possibility is raised that, for certain patients, self-regulatory and expectancy processes may also play a role – as a contributing, additive or meditational influence – in cognitive functioning. The next steps for clinical practice include the determination of the severity and duration of priming effects and to further understand the individual variation in these effects. In addition there is a need to explore the possibilities of diminishing or preventing these effects.

### 6. Neuropsychological studies in patients with central nervous system tumours

Evaluating adverse effects of chemotherapy on cognitive function in CNS cancer patients is often challenging because of the variety of other factors that can impact cognition in this population, most notably treatment with radiation and tumour progression. Both radiation and chemotherapy have been reported to share at least one common mechanism for their adverse effect on brain and cognition: disruption of the neural stem and precursor cell function [30]. Only recently clinical practice have incorporated cognitive testing into their study design, providing the opportunity to address these issues in large samples of homogeneously treated patients.

Radiation therapy has been demonstrated to adversely impact brain and cognition through vascular damage and inflammation, and via damage to neuronal progenitor cells affecting hippocampal neurogenesis and oligodendroglial formation [31]. Impairment in processing speed, attention, executive function and memory is commonly seen in brain tumour survivors previously treated with radiation therapy [32]. Several recent retrospective studies have examined the effects of radiation dose on different areas of the brain and cognitive outcomes. These studies provide evidence of a dose–response relationship between radiation to the bilateral hippocampal region and memory function [33], in addition to other brain regions and more heterogeneous cognitive outcomes [34]. Trials are currently under way in many centers to explore the use of technological advances in radiation
delivery to spare normal tissues from radiation exposure, and to explore different forms of radiation such as proton therapy that may similarly achieve reduced-dose exposure to the normal brain and other critical structures.

The standard of care for glioblastoma patients has included concomitant chemoradiation and adjuvant chemotherapy with temozolomide since 2004 [35]. A small single-institution study with standard-dose temozolomide reported cognitive decline in three out of 13 progression-free patients after concurrent chemoradiation and three cycles of adjuvant chemotherapy [36]. Declines were evident in psychomotor speed, attention and executive function, but not in verbal memory or working memory span. The results of a larger multi-institutional cooperative group trial comparing adjuvant standard-dose temozolomide and dose-dense temozolomide have also been reported [37]. In patients that were clinically and radiographically progression-free after concurrent chemoradiation and three cycles of adjuvant chemotherapy, 30% demonstrated cognitive decline, with no differences between arms. Cognitive decline was evident in all domains assessed – including verbal learning and memory, executive function and processing speed – and was prognostic of progression-free and overall survival. A recent study using temozolomide-administered rodents has demonstrated reduced hippocampal neurogenesis, decreased theta activity as measured by electromyography during an eye blink conditioning task and disrupted learning [38].

Due to the importance of angiogenesis in the growth and spread of cancer, there has been a great interest in inhibitors of vascular endothelial growth factor (VEGF), such as bevacizumab. Anti-VEGF agents have been demonstrated to produce rapid radiological improvement, ostensibly due to their ability to reduce tumour and blood-brain barrier permeability associated with leaky blood vessels. There is concern that this represents a ‘pseudoresponse’ which complicates the interpretation of traditional imaging end-points [39]. A phase II non-comparative study of bevacizumab in a recurrent glioblastoma multiforme (GBM) population included tests of cognition to characterise changes in brain function associated with bevacizumab therapy. In patients who achieved an objective radiographic response or who were clinically and radiographically progression-free at 24 weeks, the majority (75% and 70%, respectively) demonstrated stable or improved hippocampal neurogenesis, decreased theta activity as measured by electromyography during an eye blink conditioning task and disrupted learning [38].

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The long-term outcomes and associated reanalysis from the RTOG 9402 trial recently reported [41] a doubling of overall survival rates in pure or mixed anaplastic oligodendroglioma patients with 1p/19q co-deletion who received procarbazine, CCNU and vincristine (PCV) chemotherapy. This trial did not assess patient-oriented outcomes such as cognitive function to help determine the net clinical benefit of this survival advantage. However, two single-institution studies assessed cognition in anaplastic glioma [42] and GBM [43] patients treated with regimens that included PCV. Of patients with anaplastic glioma, 35% who were re-evaluated at a median of 8 months after initiation of treatment demonstrated cognitive decline. In GBM patients retested at a mean of approximately 8 months after initiating treatment, decreased cognitive function (in 44–52% of patients) was most commonly observed in the domains of psychomotor speed, executive function and memory. Unfortunately, these studies were not designed to distinguish the effects of chemoradiation from adjuvant chemotherapy and did not control for tumour progression, complicating the interpretation of these results as evidence of chemotherapy-related neurotoxicities.

Cognitive dysfunction is a frequent presenting/occurring sign in patients with primary CNS lymphoma (PCNSL). However, unlike patients with primary brain tumours, many PCNSL patients who receive chemotherapy with or without radiation therapy show evidence of improvement in cognitive function [44]. For example, Correa et al [45] reported improvements in executive function and verbal memory up to 2 years after treatment in newly diagnosed PCNSL patients who were treated with induction rituximab, methotrexate, procarbazine and vincristine followed by reduced-dose whole-brain radiation and consolidation high-dose cytarabine.

7. Neural substrate and underlying mechanisms

Despite evidence of cognitive changes associated with chemotherapy in cancer patients, the pathophysiology of these changes needs further elucidation.

Neuroimaging studies in breast cancer patients indicate structural changes in the brain associated with certain chemotherapeutic agents, and have started to shed light on the brain alterations that may be part of the mechanisms underlying the observed cognitive dysfunction in patients following administration of chemotherapeutic compounds without targeted CNS delivery.

8. Imaging studies

Several structural imaging studies have been conducted among breast cancer patients treated with adjuvant regimens, with assessments generally occurring from months to 3 years after completion of treatment [46–50], although two studies examined patients 10 and 20 years after completion of treatment [51,52]. Nearly all of these studies are indicative of structural brain differences between patients that received chemotherapy and either healthy controls or breast cancer controls that did not receive chemotherapy. White-matter pathology has been observed within months up to 10 years post-treatment, after both high-dose and standard-dose regimens. Studies using voxel-based morphometry have reported volume reductions in white and grey matter 1 year to 20 years after completion of chemotherapy. A prospective study observed focal grey matter volume decrease 1 month after the cessation of chemotherapy, which recovered in some but not all regions at 1 year post-treatment.

The cerebral white matter seems particularly vulnerable to the effects of chemotherapy. Studies investigating cerebral white matter integrity using diffusion tensor imaging (DTI) reported lower fractional anisotropy (FA) in the genu of the corpus callosum, lower FA in frontal and temporal white matter
and higher mean diffusivity in frontal white matter of breast cancer patients who received standard-dose anthracycline-based regimens compared with breast cancer controls and healthy controls. In a study conducted 10 years after completion of high-dose chemotherapy, DTI also showed lower FA in several white-matter tracts compared with breast cancer patients who never received chemotherapy [53]. In a large study conducted on average 20 years after completion of treatment, it was shown that in the absence of significant group differences in white matter integrity, time since treatment was inversely associated with lower global and focal white matter integrity within the breast cancer group [54]. This cross-sectional indication of affected white matter integrity was supported by a prospective study showing that breast cancer patients who received chemotherapy displayed significant decreases in FA in frontal, parietal and occipital white-matter tracts from pre- to post-chemotherapy, whereas for both a healthy control and a breast cancer control group, FA values were the same between baseline and follow-up [55].

Moreover there seems to be a link between the abnormal microstructural properties in white-matter regions and the cognitive impairments seen in breast cancer patients treated with chemotherapeutic agents; several studies observed correlations between abnormal diffusion properties and cognitive problems on neuropsychological testing [53].

The observed changes in DTI parameters may be related to demyelination of white matter axons or axonal injury after chemotherapy. Although caution is warranted in directly translating changes on structural imaging measures into biological changes, a rapidly increasing number of preclinical animal studies are helping define potential mechanisms underlying chemotherapy-induced cognitive dysfunction, and their results relate to a significant extent to the observations in human studies.

9. Animal studies

Valuable insights have come from preclinical studies on the potential pathogenic mechanisms involved in cognitive impairment related to systemic administration of chemotherapeutic compounds without targeted CNS delivery, although the precise mechanisms remain insufficiently understood. Many factors have been proposed to play a role in chemotherapy-induced neurotoxicity, including the directly toxic effects of chemotherapeutic agents on various brain cells, vascular injury and the indirect immune-mediated inflammatory processes. It is unlikely that a single mechanism can explain much of the major cognitive problems observed in cancer patients following chemotherapy.

Experimental studies have shown that many chemotherapeutic agents, when administered peripherally and in clinically relevant dosages, are associated with adverse effects on neurobiology and cognition (including 5-fluorouracil, methotrexate, doxorubicin, paclitaxel, cisplatin, BCNU and cyclophosphamide). In behavioural studies in animals, chemotherapy-related deficits have been observed in rodents on tasks that require involvement of the hippocampus and frontal systems. Toxicity is observed in multiple CNS cell types and multiple CNS regions [56]. Specifically, chemother-

apy-induced damage of mature post-mitotic oligodendrocytes and immature progenitor cell populations required for ongoing neurogenesis, gliogenesis and maintenance of white matter integrity seems to be an important aetiologic factor in the development of neurotoxicity [57].

Research focusing on the development of strategies to inhibit specific transporters to enable drugs to cross the blood–brain barrier (BBB) in sufficient amounts is also relevant for understanding the mechanisms by which chemotherapeutic agents not targeted to reach the CNS cause cognitive and brain changes. Gong et al. [58] propose in their stem-cell hypothesis that differential sensitivities of glioma stem cells and neural stem cells to alkyating agents, temozolomide, cisplatin and targeted agents such as erlotinib and bortezomib hold the key to the resistance of primary brain tumours and the occurrence of chemotherapy-associated neurotoxicity in non-CNS disease.

The development of modalities that enhance delivery of drugs to brain tumours will also increase the drug exposure of the normal brain tissue, and may place patients at risk for treatment-induced cognitive decline. Until now, several preclinical studies have investigated pharmacological prevention strategies that further underscore the relevance of several hypothesised mechanistic pathways underlying the effects of chemotherapeutic agents on the brain and behaviour. Konat et al. [59] showed that N-acetyl cysteine, an antioxidant, ameliorated cognitive impairment in Wistar rats after combined administration of cyclophosphamide and doxorubicin. Two recent studies further explored potential candidates for interventions. A study by Lyons et al. [60] demonstrates that fluoxetine, when administered before and during treatment with 5-FU in rats, may prevent cognitive impairment and the loss of normal cell proliferation in the hippocampus observed after administration of 5-FU. Vijaynathan et al. [61] demonstrated that treatment with a glutamate receptor antagonist improved cognition after intrathecal administration of methotrexate in rats.

10. Interventions

Cognitive dysfunction is a common consequence for many cancer patients, and it does not always fade away. As indicated, pharmacological interventions to prevent or intervene against cognitive symptoms are in an early stage of development. Agents that have been examined or that are currently under investigation in patients include erythropoietin, methylphenidate, modafinil, donepezil and melatonin [62,63]. Some of these agents are promising, but the need for their rigorous testing with appropriate study designs and sufficient sample sizes precludes translation and implementation in daily practice.

Within the area of neuropsychological rehabilitation roughly two models can be distinguished: the restoration model and the compensation model [64]. The restoration model is directed at restoring damaged cognitive functions through function training, often using a so-called repeated practice approach, based on the assumption that specific stimulation induces plasticity. But evidence is still lacking that the benefits of training on specific tasks will transfer to
other untrained tasks or lead to any general improvement in the level of cognitive functioning. Compensation techniques, on the contrary, are proven to be successful. Improvement in daily life functioning can be achieved using intact cognitive abilities and strategies. Neuropsychological rehabilitation based on the compensation model together with psycho-education and coping strategies can be offered to cancer patients confronted with cognitive problems to maximise their ability to function [65].

11. Conclusion

Evidently, people with a history of cancer constitute an increasing group in our community. From this viewpoint, we have an obligation to obtain information on the cognitive effects of chemotherapy from a descriptive and preventive standpoint, and from an individual as well as a societal perspective. Chemotherapy is a necessary component in the management of many types of cancer, and the choices between different regimens in terms of adequate cancer control and minimal side-effects are restricted. Many cancer patients are returning to employment or other activities that may be affected by cognitive functioning. It is critical to identify cognitive effects of cancer treatment, to explore the mechanisms underlying these cognitive effects and to explore possible interventions that follow from these mechanisms and that may minimise cognitive side-effects and their severity and impact.

Conflict of interest statement

None declared.

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Drug-associated delirium in cancer patients

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1. Delirium definition and clinical characteristics

Delirium is a disorder of consciousness and attention; it is one of the most common neurological complications seen in general in the medically ill hospitalised patient, and is also common in the medical oncology ward [1,2]. Delirium seen in different settings contributes to defining the diagnoses of diverse specificities: postoperative delirium, delirium in the ICU, withdrawal delirium or delirium tremens, terminal restlessness and others.

Before considering specific clinical contexts or diagnoses it is necessary to recognise the general characteristics of delirium as a syndrome and its clinical implications. There is now almost universal agreement on the definition of delirium, or acute confusional state, according to the DSM. However, acute confusional state is a synonym of delirium and is still a useful clinical definition, particularly in non-English-speaking countries. Delirium is a syndrome and not a disease, and its pathophysiology has not been fully elucidated. Different theories have favoured alternatively the failure of a common final pathway – mainly regulating the cholinergic projection to the cerebral cortex – or a more diffused or multifocal impairment of different areas in the CNS which contribute to maintaining the normal level of vigilance and attention.

Clinically, delirium is an altered state of consciousness with reduced awareness of self and of the environment, which may present with inability to think and talk clearly and rationally; at times there are hallucinations, delusions, disorientation with respect to time and space, altered sleep–wakefulness cycle and cognitive impairment. Psychomotor agitation can be present in the hyperactive deliria, but hypoactive deliria will show psychomotor retardation and somnolence. One extremely important clinical aspect of delirium is fluctuation of the clinical presentation; symptoms can change suddenly, often under repetitive conditions (such as in the classic nocturnal worsening often described in the elderly with cognitive impairment and called in the past 'sundowning'). These sudden changes from a near-to-normal mental state to frank delirium often surprise nursing and medical staff and find them unprepared in front of the patient and a distressed family.

The clinical presentation of delirium varies, and no defined association of symptoms and signs can be considered specific [3]. For the purposes of diagnosis and clinical evaluation it is easier to use the DSM criteria as they give a systematic approach to the core clinical elements [4]. All four of the following criteria have to be fulfilled to make a diagnosis.

Disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain and shift attention; to fulfil this criterion the levels of both consciousness and attention need to be affected.

Change in cognition (such as memory deficit, disorientation and language disturbances) or perception disturbances that are not better explained by a pre-existing established or evolving dementia. Testing cognitive function with simple bedside examinations such as the Minimental test is often enough to describe disorientation with respect to time and space, difficulties in performing calculations and in writing and simple memory tests. In the elderly with previous cognitive failure or being already demented it may be difficult to distinguish a failure in cognition as part of a chronic condition from a newly developing delirium (Table 1). Perceptual disturbances are illusions and hallucinations. Most often hallucinations are visual, but they are present only in a percentage of delirious patients and their absence is not a determinant for the diagnosis [3].

The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day. This criterion specifically aims to distinguish delirium from chronic conditions, particularly from dementia (Table 2), but in elderly patients with longstanding medical complications it may be difficult to differentiate the contribution of pre-existing neurological factors and incident acute factors. This distinction may be academic in
many cases but it is relevant, as described below, to explain many complex cases. Also in the case of advanced cancer patients, with multiple clinical problems and polypharmacy, delirium can be a long-lasting complication either characterising the final phase of the disease or being a reversible condition [5].

There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition. This last criterion conceptually distinguishes delirium from primary psychiatric disease (mainly acute psychosis) (Table 1). In the old taxonomy this criterion was included in the construct of organic brain disorder or of recognising an organic cause of psychiatric symptoms. This terminology is no longer accepted by the latest DSM versions, but it can be used to clarify the scope of criterion 4.

Based on the clinical presentation, delirium is distinguished into hypoactive, hyperactive and mixed types. The hyperactive deliria are usually associated with delusions and hallucination, disruptive or agitation behaviour and often worsening of symptoms during the night. Hypoactive deliria, in contrast, show a somnolent detached state of consciousness and may be missed or mistaken for depression if the patient is not assessed more carefully with formal mental task testing. Mixed hyper- and hypoactive presentations are most frequent and the transition from hyperactive to hypoactive delirium, stupor and coma can be seen as one of the ways of dying.

2. Frequency and assessment

The frequency of delirium is high in the acutely hospitalised patient population, with a prevalence which may be around 10% in the medical ward (excluding the cases of postoperative delirium). The most relevant patient populations seen by oncologists are summarised in Table 2, which shows that the frequency of this complication can not only increase in more advanced disease, but also that it is common in the elderly and as well as in the general oncology ward [6,7].

Table 1 – Main differential diagnoses of delirium.

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Delirium</th>
<th>Dementia</th>
<th>Acute psychosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Slow</td>
<td>Acute</td>
</tr>
<tr>
<td>Circadian course</td>
<td>Fluctuating</td>
<td>Stable</td>
<td>Stable</td>
</tr>
<tr>
<td>Level of consciousness</td>
<td>Affected</td>
<td>Spared unless in severe cases</td>
<td>Spared</td>
</tr>
<tr>
<td>Attention</td>
<td>Impaired</td>
<td>Initially spared</td>
<td>Can be impaired</td>
</tr>
<tr>
<td>Cognition</td>
<td>Impaired</td>
<td>Impaired</td>
<td>Can be impaired</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Poorly visual</td>
<td>Often absent</td>
<td>Often auditory</td>
</tr>
<tr>
<td>Delusions</td>
<td>Poorly systematised and fleeting</td>
<td>Often absent</td>
<td>Sustained and systematised</td>
</tr>
<tr>
<td>Psychomotor activity</td>
<td>Increased, reduced mixed with alternating course</td>
<td>Often normal</td>
<td>Can vary, with bizarre behaviour depending on the psychosis</td>
</tr>
<tr>
<td>Involuntary movements</td>
<td>Asterixis, myoclonus or tremor can be present in some subtypes</td>
<td>Absent in most forms</td>
<td>Absent</td>
</tr>
<tr>
<td>EEG</td>
<td>Abnormal&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Abnormal&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Normal</td>
</tr>
</tbody>
</table>

EEG, electroencephalogram.
*See text for more details.

Table 2 – Frequency of delirium in different patient populations admitted to hospital, hospice or home palliative care programme.

<table>
<thead>
<tr>
<th>Population</th>
<th>Prevalence (%) at admission</th>
<th>Incidence (%) during admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly ≥65 admitted to acute hospital unit</td>
<td>10.5</td>
<td>31.3</td>
</tr>
<tr>
<td>Elderly ≥70 admitted to acute hospital unit</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td>Elderly ≥70 admitted to acute hospital unit</td>
<td>18.0</td>
<td></td>
</tr>
<tr>
<td>Medical oncology unit</td>
<td>18.0</td>
<td></td>
</tr>
<tr>
<td>Medical oncology unit</td>
<td>16.5</td>
<td></td>
</tr>
<tr>
<td>Hospice</td>
<td>28.0</td>
<td></td>
</tr>
<tr>
<td>Hospital palliative care unit</td>
<td>42.0</td>
<td>45.0</td>
</tr>
<tr>
<td>Palliative care programme including home care</td>
<td>28.0</td>
<td>–</td>
</tr>
<tr>
<td>Dying cancer patients in specialised palliative care unit</td>
<td>80</td>
<td></td>
</tr>
</tbody>
</table>

Modified from Caraceni and Grassi [2].
As with any new neurological sign or symptom, in a patient demonstrated in 15% of patients in one case series [11]. If cancer, even without focal neurological signs, to be an initial lesion, imaging should be performed. In a patient with cancer, the case of neurological findings suggesting a structural brain examination and, if available, neurological consultation. In patients with cancer a change in mental status requires a neurological association with immunosuppressive therapies (cyclosporine, tacrolimus), as a complication of transplant, high-dose multi-drug chemotherapy (cytarabine, cisplatin, gemcitabine, vincristine, FOLFOX regimen and methotrexate) and of the new drug chemotherapy (cytarabine, cisplatin, gemcitabine, vinorelbine, catatonia). Still, a more careful and systematic approach [10] adopted by the nursing staff is a reasonable strategy and is to be recommended in oncology and particularly in palliative care settings such as a hospice. The diagnosis finally relies on the DSM criteria and requires specific expertise. The main differential diagnoses and their characteristics are listed in Table 1.

### 3. Diagnostic procedures

As with any new neurological sign or symptom, in a patient with cancer a change in mental status requires a neurological examination and, if available, neurological consultation. In the case of neurological findings suggesting a structural brain lesion, imaging should be performed. In a patient with cancer, depending on the stage of the disease, it is not rare for delirium, even without focal neurological signs, to be an initial presentation of brain or meningeal metastases, as demonstrated in 15% of patients in one case series [11].

Encephalitis of infectious origin can occur particularly in immunocompromised patients and occurs not infrequently after bone-marrow transplantation conditioning chemotherapy.

Cancer patients are at increased risk of posterior reversible encephalopathy syndrome (also known as posterior reversible leuкоencephalopathy), a syndrome that is probably caused by damage to the brain vasculature and is found in association with immunosuppressive therapies (cyclosporine, tacrolimus), as a complication of transplant, high-dose multi-drug chemotherapy (cytarabine, cisplatin, gemcitabine, vincristine, FOLFOX regimen and methotrexate) and of the new biological therapies such as anti-angiogenetic antibodies and others (bevacizumab, rituximab, bortezomib and motesalib) [12]. The syndrome usually includes seizures, cortical visual deficit and headache, but at presentation changes in mental status, or delirium, can dominate the clinical picture.

When seizures are not associated with obvious generalised or focal convulsions, the differential diagnosis of delirium can be difficult. In fosfamide encephalopathy, obtundation of consciousness and myoclonus reflect a continuous seizure-like activity in the electroencephalogram (EEG).

Patients with a history of psychiatric disorders can develop acute psychotic reactions, especially when confronted with serious medical illness such as cancer, with clinical presentations such as unresponsiveness and catatonia that can be confused with delirium. These patients are usually young, and the clinical context helps to exclude the most common causes or risk factors of delirium.

True paraneoplastic neurological syndromes presenting with altered mental state (limbic encephalitis) are indeed very rare; specific expertise is required for their diagnosis and they are usually found in association with initial cancer with the onset of the neurological syndrome preceding the diagnosis of cancer [13].

Table 3 summarises the elements which can guide clinical reasoning and a diagnostic strategy when faced with a cancer patient with delirium that is not occurring after surgery and general anaesthesia. The clinical context, risk factors, prognosis, associated symptoms and goals of care will influence the diagnostic path and completeness or futility of any interventions eventually required.

### 4. Pathophysiology, risk factors and aetiology

The complex pathophysiology of delirium is beyond the scope of this chapter [14], but it is important to remember that the brainstem, thalamic and hypothalamic projections into the cortex are implicated in the regulation of normal vigilance and in modulating the level of consciousness between the physiological states of wakefulness and sleep. This system has a neurotransmitter organisation, including acetylcholine, dopamine, serotonin, histamine and γ-aminobutyric acid.
Drug toxicity, in the setting of medical therapy or abuse, is an extremely frequent cause of delirium (Table 5). The ability to identify one drug as a cause for delirium depends on anecdotal clinical observation, pharmacological knowledge and clinical studies. One recent systematic review of the literature supports the association of psychoactive medications, considered together, and use of opioids, which have an independent increased risk of developing delirium in cancer patients [18]. Another review focusing on patients at risk of developing delirium (elderly patients admitted to hospital for medical reasons or in the postoperative period) suggests avoiding the use of benzodiazepines in this population [19].

Experimental human studies demonstrated that anticholinergic drugs such as scopolamine, ditran and atropine can cause delirium depending on dosage [20]. Lower doses usually produce somnolence (scopolamine 0.3–0.8 mg), higher doses (atropine ≥ 5 mg, scopolamine = 1 mg) agitated florid delirium; paradoxical effects of low doses have also been demonstrated.

In fact the list of drugs with anticholinergic activity is very long (Table 6), and such drugs should be used with caution, especially in the elderly with poor general conditions, multiple medical problems and polypharmacy. Unfortunately all these conditions are commonly found in cancer patients of advanced age, with progressive disease and who need appropriate palliative therapy for symptom control. Appropriate selection of drugs with simplified metabolic pathways and lack of interference would reduce the risk of adverse reactions.

<table>
<thead>
<tr>
<th>Table 4 – Factors associated with the risk of developing delirium resulting from multivariate analysis in cancer. Modified from Caraceni and Simonetti [17].</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potentially specific predisposing factors: Advanced age</td>
</tr>
<tr>
<td>Previously impaired cognition</td>
</tr>
<tr>
<td>History of delirium</td>
</tr>
<tr>
<td>Metastatic CNS lesion</td>
</tr>
<tr>
<td>Non-specific factors associated with disease progression/</td>
</tr>
<tr>
<td>deterioration of general function:</td>
</tr>
<tr>
<td>Functional impairment</td>
</tr>
<tr>
<td>Severity of illness</td>
</tr>
<tr>
<td>Low albumin</td>
</tr>
<tr>
<td>Bone metastases</td>
</tr>
<tr>
<td>Liver metastases</td>
</tr>
<tr>
<td>Haematological malignancies</td>
</tr>
<tr>
<td>Potentially specific incident factors:</td>
</tr>
<tr>
<td>Metabolic abnormalities</td>
</tr>
<tr>
<td>Metastases to brain or meninges</td>
</tr>
<tr>
<td>Opioids (dose-related)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Corticosteroids (dose-related)</td>
</tr>
</tbody>
</table>

(GABA). An imbalance in some of these neurotransmitters is thought to have a primary role in delirium pathophysiology. An impaired cholinergic transmission from the brainstem and enhanced dopaminergic tone are also thought to play a causal role in delirium [14]. All drugs with anticholinergic activity are sedating and can cause delirium. The cholinergic hypothesis can also explain the increased susceptibility to delirium of the elderly and of patients with cognitive impairment or dementia, considering that all these situations are characterised by a reduced function of the cholinergic central activating system.

Delirium may have many causes, but in most cases a multifactor model can best explain its pathophysiology, with the combination of some predisposing conditions and incident noxious factors. This model was suggested by clinical observation in early studies on the syndrome [15] and has been confirmed by well-conducted cohort studies demonstrating that the combination of specific baseline conditions – such as advanced age, cognitive impairment, dementia and severity of illness – was associated with an increased incidence of delirium when combined with new factors, occurring during the hospital stay, in elderly patients [16]. Among incident factors, infections and medications were noted. The results, summarised in Table 4 [17], can be interpreted by classifying the associated factors such as structural lesion or functional abnormalities potentially impairing specific CNS functions (brain metastases, previous cognitive failure), being direct or indirect indicators of progression of the disease (metastases), or of poor general condition and toxic factors (benzodiazepines, opioids and steroids).

### 4.1. The role of drug toxicity

Drug toxicity, in the setting of medical therapy or abuse, is an extremely frequent cause of delirium (Table 5). The ability to identify one drug as a cause for delirium depends on anecdotal clinical observation, pharmacological knowledge and
4.3. Steroids

The use of steroids is very common in cancer patients. High doses and prolonged administration can induce delirium, also called in the past steroid psychosis [27]. Also sudden discontinuation of steroids can cause hypocortisol syndrome and delirium. It is very important that steroids are given for a limited amount of time and tapered slowly when no longer necessary. Usually at least a week or two of therapy is needed to develop psychiatric complications [28]. The symptoms can range from depression to mania and psychosis. The true incidence of mental changes related to steroid administration in palliative care is unknown. High doses are often reported to cause euphoria.

<table>
<thead>
<tr>
<th>Table 5 – Case reports of delirium associated with drug toxicity. Modified from Caraceni and Grassi [2].</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotropics:</td>
</tr>
<tr>
<td>Clozapine</td>
</tr>
<tr>
<td>Diphenhydramine</td>
</tr>
<tr>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Mianserin</td>
</tr>
<tr>
<td>Promethazine</td>
</tr>
<tr>
<td>Lithium</td>
</tr>
<tr>
<td>Risperidone</td>
</tr>
<tr>
<td>Antibiotics, antimalarials and antivirals:</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Clarithromycin</td>
</tr>
<tr>
<td>Mefloquine</td>
</tr>
<tr>
<td>Ofloxacin</td>
</tr>
<tr>
<td>Acyclovir</td>
</tr>
<tr>
<td>Gancyclovir</td>
</tr>
<tr>
<td>Drug combinations:</td>
</tr>
<tr>
<td>Benzodiazepine/clozapine combination</td>
</tr>
<tr>
<td>Diphenhydramine/paroxetine combination</td>
</tr>
<tr>
<td>Paroxetine/benzotraine combination</td>
</tr>
<tr>
<td>Lithium/neuroleptic combination</td>
</tr>
<tr>
<td>Tacrine/ibuprofen interaction</td>
</tr>
<tr>
<td>Ethanol/niacin coingestion</td>
</tr>
<tr>
<td>Sertraline/haloperidol/benzotraine combination</td>
</tr>
<tr>
<td>H-2 receptor blockers:</td>
</tr>
<tr>
<td>Famotidine (six cases)</td>
</tr>
<tr>
<td>Ranitidine</td>
</tr>
<tr>
<td>Ranitidine and cimetidine</td>
</tr>
<tr>
<td>Opioids:</td>
</tr>
<tr>
<td>Fentanyl</td>
</tr>
<tr>
<td>Oxycodone</td>
</tr>
<tr>
<td>Morphine</td>
</tr>
<tr>
<td>Hydromorphone</td>
</tr>
<tr>
<td>Antiblastic:</td>
</tr>
<tr>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Vincristine</td>
</tr>
<tr>
<td>Ifosfamide</td>
</tr>
<tr>
<td>Cytosine arabinoside</td>
</tr>
<tr>
<td>Cisplatin</td>
</tr>
<tr>
<td>Methotrexate</td>
</tr>
<tr>
<td>Thiotaopma</td>
</tr>
<tr>
<td>Etoposide</td>
</tr>
<tr>
<td>Nitrosurea</td>
</tr>
<tr>
<td>Biological drugs used in cancer:</td>
</tr>
<tr>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Rituximab</td>
</tr>
<tr>
<td>Other:</td>
</tr>
<tr>
<td>Diet pills (phentermine)</td>
</tr>
<tr>
<td>Amiodarone</td>
</tr>
<tr>
<td>Cyclosporin</td>
</tr>
<tr>
<td>Donepezil</td>
</tr>
<tr>
<td>Herbal medicine loperamide, theales and valerian</td>
</tr>
<tr>
<td>Levodopa</td>
</tr>
<tr>
<td>Nizatidine</td>
</tr>
<tr>
<td>Omeprazole</td>
</tr>
<tr>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Steroids</td>
</tr>
<tr>
<td>Tacrine</td>
</tr>
<tr>
<td>Ziconotide</td>
</tr>
<tr>
<td>Zolpidem</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 6 – Drugs with anticholinergic activity in each category. The agents are listed from the more pronounced to less pronounced anticholinergic potency.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prototypical anticholinergics:</td>
</tr>
<tr>
<td>Belladonna alkaloids</td>
</tr>
<tr>
<td>Atropine</td>
</tr>
<tr>
<td>Scopolamine</td>
</tr>
<tr>
<td>Hyoscine butylbromide</td>
</tr>
<tr>
<td>Robinul</td>
</tr>
<tr>
<td>Antidepressants:</td>
</tr>
<tr>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Imipramine</td>
</tr>
<tr>
<td>Desipramine</td>
</tr>
<tr>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Paroxetine</td>
</tr>
<tr>
<td>Trazodone</td>
</tr>
<tr>
<td>Mirtazapine</td>
</tr>
<tr>
<td>Antihistamines:</td>
</tr>
<tr>
<td>Marzine</td>
</tr>
<tr>
<td>Diphenhydramine</td>
</tr>
<tr>
<td>Promethazine</td>
</tr>
<tr>
<td>Biperidine</td>
</tr>
<tr>
<td>Trihexyphenidyl</td>
</tr>
<tr>
<td>Cimetidine</td>
</tr>
<tr>
<td>Ranitidine</td>
</tr>
<tr>
<td>Neuroleptics:</td>
</tr>
<tr>
<td>Chlorpromazine</td>
</tr>
<tr>
<td>Flufenazine</td>
</tr>
<tr>
<td>Clozapine</td>
</tr>
<tr>
<td>Prochlorperazine</td>
</tr>
<tr>
<td>Trifluorperazine</td>
</tr>
<tr>
<td>Olanzapine</td>
</tr>
<tr>
<td>Thioridazine</td>
</tr>
<tr>
<td>Haloperidol</td>
</tr>
<tr>
<td>Quetiapine</td>
</tr>
<tr>
<td>Risperidone</td>
</tr>
<tr>
<td>Ziprasidone</td>
</tr>
<tr>
<td>Anti-Parkinsonian:</td>
</tr>
<tr>
<td>Amantadine, Levodopa</td>
</tr>
<tr>
<td>Other:</td>
</tr>
<tr>
<td>Metoclopramide</td>
</tr>
<tr>
<td>Baclofen</td>
</tr>
<tr>
<td>Entacapone</td>
</tr>
</tbody>
</table>
4.4. Serotonin syndrome

This significant toxic reaction became more frequent with the spread in the use of serotonin selective inhibitors (SSRIs, e.g. paroxetine) such as antidepressants. It is usually seen after the addition of a serotonergic drug to a drug regimen already containing serotonin-enhancing drugs, and it combines signs of encephalopathy (confusion, restlessness, myoclonus, hyper-reflexia, rigidity and coma) and of autonomic instability (fever, diaphoresis, diarrhoea, flushing, tachycardia, tachypnea, blood-pressure changes, midriasis, shivering and tremor). It may be fatal or may have a more benign course. Interactions of different drugs, often used in cancer patients, should be monitored (SRRI with tramadol, ketobemidone and venlafaxine). Table 7 lists a number of cases reported in the literature of drug combinations leading to serotonin syndrome. Caution should therefore be exercised not only in the use of the drugs reported but with all agents with serotonergic action, such as duloxetine and tapentadol, in particular when considering their use in combination with other serotonergic agents.

4.5. Drug pharmacological interactions

The role of metabolic interactions as a cause of toxicity is more and more likely as the number of drugs increase and the general patient condition deteriorates. The induction or inhibition of hepatic enzyme metabolism is an important source of variability in drug effects and can lead to unexpected toxic reactions. The P450 system comprises a family of more than 20 isoenzymes, among which the CYP 2D6 and the CYP 3A4 metabolise 80% of known drugs. A relatively recent review [29] reports on a number of examples of drugs commonly used in oncology and palliative care that have high or moderate probability of interacting with the same metabolic pathways and of leading to unexpectedly high or low levels of a drug, with the consequence of under- or over-dosing; examples of such drugs include methadone, codeine, oxycodone, haloperidol, tricyclic antidepressants (TCAs), SSRIs, monoamine oxidase (MAO) inhibitors, benzodiazepines, macrolides, azoles, rifampin and antifungals. Table 8 shows a list of interactions that can be particularly relevant in the management of symptoms in cancer patients.

However, the clinical role of drug interaction in producing specific effects may be very difficult to ascertain; laboratory in vitro data may not be applicable to the clinical situation, while in vivo other circumstances may be operating to change the effect that was expected on the basis of laboratory data. For instance, in dogs the co-administration of ketoconazole and midazolam resulted as expected in a reduced elimination of midazolam but did not affect the elimination of fentanyl [30]. Case reports suggest that these interactions are indeed at times important [31,32].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>Carbamazepine, Prazosine, MAOIs, Moclobemide, Nefazodone, Tramadol, Mirtazapine</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Alone, Nefazodone, Moclobemide</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Risperidone, Moclobemide</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Isocarboxazide, Nortriptyline, Tranilcypropromine, Erythromycin, Buspirone, Loxapine</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>Fluoxetine, Non-selective MAOIs, Clomipramine</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Alone</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Buspirone, Nefazodone</td>
</tr>
<tr>
<td>Moclobemide</td>
<td>Citalopram, Imipramine</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Iproniazid, MAOIs, Moclobemide</td>
</tr>
<tr>
<td>Phencelzine</td>
<td>3,4-Methylenedioxy-methamphetamine</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>Non-selective MAOIs</td>
</tr>
<tr>
<td>Dothiepine</td>
<td>Alone</td>
</tr>
</tbody>
</table>

Table 8 – Potential drug interactions with potential elevation of blood plasma levels of central nervous system active agents.

<table>
<thead>
<tr>
<th>CYP2D6 inhibitors</th>
<th>Drugs metabolised by CYP2D6 whose plasma levels can increase when combined with inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>Oxycodone</td>
</tr>
<tr>
<td>Desimipramine</td>
<td>Tramadol</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Risperidone</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Paroxetine</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Desipramine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CYP3A4 Inhibitors</th>
<th>Drugs metabolised by CYP3A4 whose plasma levels can increase when combined with inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>All imidazole antifungals</td>
<td>Fentanyl</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Alfentanil</td>
</tr>
<tr>
<td>Norflaxacine</td>
<td>Methadone</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>Midazolam</td>
</tr>
</tbody>
</table>
The number of potential pharmacological interactions is extremely large and variable according to clinical conditions and antineoplastic, supportive and combined therapies. Dexamethasone, anticonvulsants and cisplatin or asparaginase have specific interactions, to give only one example. In cases of delirium, a specific review of drugs and their metabolism is mandatory. Conversely the choice of drugs with the least metabolic interference potential is to be recommended. Guidelines to treat pain and depression, for instance, should recommend as first choice morphine, mirtazapine or citalopram, while TCAs should not be used as first choice in combination with morphine because of their strong anticholinergic effects and also because they increase morphine bioavailability [33]. However, oral gabapentin has been shown to increase oral morphine bioavailability [34], but the clinical impact of this observation has never been clarified.

4.6. Alcohol and drug withdrawal

Patients with known alcohol and or drug abuse, in particular chronic use of benzodiazepines, should be considered at risk of withdrawal in the case of reduced or suspended intake of alcohol when admitted to the hospital or hospice. Alcohol withdrawal delirium should be treated with benzodiazepines; in severe cases (delirium tremens) this can be life-threatening and requires specialist advice or intensive care. More subtle cases can result from the sudden discontinuation of the chronic use of benzodiazepines in patients with reduced ability to swallow when admitted to a care facility, which may go unnoticed without a very careful assessment of the patient history.

4.7. Delirium as a complication of the terminal phase of advanced cancer

In patients with advanced cancer undergoing palliative care and admitted to a hospice, delirium episodes are particularly frequent; this can be expected from the progressive accumulation of the risk factors described, and indeed the prevalence of delirium tends to increase as the terminal phase of illness approaches, reaching 80% in the last days of life, and it is per se a prognostic factor of shortening life expectancy [7,35]. On the other hand, in palliative care units and in hospices delirium episodes can be reversible – owing to modifiable etiologies, such as drugs and infections – in as many as 50% of the cases [5,36]. It is therefore of extreme importance to assess delirium reversibility in advanced disease, to direct treatment goals and family counselling. When a single drug toxicity can be identified the probability of reversing toxicity is also high [36], but on the other hand when the clinical situation is complex – due to multiple concurrent factors, organ failure and in an advanced phase of the disease – reversibility is less likely and delirium can be viewed as one aspect of the terminal phase of the illness. In this last case, not only can it be impossible to modify the eventual contribution of drugs to the delirious state, it could also be futile or even inappropriate if comfort and quality of dying is the goal of care. Interventions directed at dealing with and managing the impact of delirium on family distress and anxiety are particularly appropriate at this time [37].

5. Delirium management

Screening of potential etiologies, starting with an accurate medication list, is the first step in delirium management; consequently a first recommendation is to withdraw all medications that are not absolutely necessary. Very often finding the aetiology is delayed, and the time to recovery after modifying etiological factors can be significant. In a number of cases, as already discussed above, the multifactor pathophysiology can be part of a complex clinical picture which does not allow for recovery or is even part of the dying process. All of these conditions require symptomatic management – in particular to control hallucinations, delusions and psychomotor agitation – be it temporary until recovery or continuously until death. The first-line pharmacological intervention for delirium is neuroleptics, and haloperidol is the first-choice drug according to all clinical guidelines [38–41]. In patients with mild to moderate delirium, oral medication may be indicated, but more difficult cases will require parenteral administration. Haloperidol initial dose can vary from 0.5 to 1 mg, orally or parenterally b.i.d., according to patient age, and should be titrated in the following hours depending on the severity of delirium symptoms. Titration of the dose is a fundamental step before a real lack of clinical response can be documented, as many treatment failures are failing this recommendation. Parenteral haloperidol can be used via intramuscular administration. This can be necessary in patients without an IV line and with very disruptive behaviour, otherwise an IV infusion can also be adopted. The use of haloperidol should be preceded by cardiac monitoring with electrocardiography (ECG), according to some national regulations, while its intravenous infusion is not officially approved, although commonly used in different settings of care. Prolongation of the Q–T interval on the ECG may contraindicate the use of haloperidol. This caveat is based on reports of cases of fatal cardiac arrhythmia following haloperidol administration.

Pharmacological treatment of delirium aims at patient tranquilisation, abolishing hallucinations and delusions, reducing psychomotor agitation, and improving night-time sleep. Haloperidol, risperidone or olanzapine, while sharing a strong tranquilising action, are not primarily sedating drugs and haloperidol has the least sedating properties among all the neuroleptics. If required, more sedating neuroleptics can be used: for example quetiapine (25–50 mg b.i.d.), eventually giving a higher dose at bed-time. If this approach fails, more specific drugs can be added to control symptoms by keeping the patient sedated, including antihistamines, benzodiazepines and eventually alfa-2 agonists (clonidine, dexmedetomidine). All these regimens require specialist advice, be it from the neurologist, psychiatrist or palliative medicine consultant, depending on the clinical conditions and setting [17].

6. Conflict of Interest

The author has no conflict of interest relating to this article.
REFERENCES


Introduction

Lung cancer in non-smokers

Rolf A. Stahel

Klinik für Onkologie, Universitätsspital, Zürich, Switzerland

The decrease in lung cancer mortality in many Western societies is being attributed to a large extent to smoking prevention measures. However, lung cancer also occurs in non-smokers, with an estimated frequency of 10–25%. The identification of oncogenic driver alterations which are successfully targetable, being more prevalent in lung cancer in non-smokers, has encouraged interest in these tumors. The current knowledge on the molecular alterations in lung tumors of patients who have never smoked is summarised in the article of Drs. Subramanian and Govindan. Smoking prevention is of particular importance for pregnant women. The effect of intrauterine exposure to tobacco smoke is a growing area of research in the field of passive smoking. Current knowledge on its potential health consequences is summarised by Dr. Nawroth and colleagues.

Conflict of interest statement

None declared.
Prevention – Passive smoking and pregnancy

Tim S. Nawrot *, Bianca Cox, Bram G. Janssen, Michelle Plusquin

Centre for Environmental Sciences, Hasselt University, Belgium
Leuven University, Department of Public Health & Primary Care, Belgium

1. Introduction

Epidemiological studies have demonstrated that tobacco smoke is a major cause of both cancer and vascular diseases. More than 3800 chemicals are present in tobacco smoke, which may cause oxidative stress via biotransformation or by macrophage activation. In 1954, Richard Doll and Bradford Hill published the first prospective evidence on cigarette smoking and lung cancer [1,2]. In 1962, Framingham investigators published data showing that smoking increased the risk of heart disease [3]. Nevertheless, despite the strong evidence, uncertainty was manufactured and enlarged. This strategy is a common practice to reduce the public health implications from epidemiological findings and was used not only by tobacco companies but also by other industrial arms, including asbestos and lead factories [4]. For almost half a century, the tobacco companies hired scientists to dispute first that smokers were at greater risk of dying of lung cancer; second, the role of tobacco use in heart disease; and finally, the evidence that environmental tobacco smoke increased disease risk in non-smokers [5,6].

The effect of in-utero exposures on health in childhood and later in life is a growing area of research interest, with major public health implications. Children are vulnerable to the adverse effects of environmental tobacco smoke as their lungs and immune system are undergoing further development. The first publications of detrimental health effects of parental smoking on children’s respiratory health were published in the early 1970s [7]. Exposure to environmental tobacco smoke in the first 2 years of life has been estimated in some European countries by Pattenden et al. [8] and ranged from 19% in Germany to 70% in Bulgaria.

2. Meta-analytical evidence of early-life effects

There is pooled evidence that constituents of cigarette smoke cross the placenta, induce pregnancy complications, reduce intrauterine foetal growth and increase the risk of preterm delivery (Table 1) [9,10]. Meta-analytical evidence has also shown increased risk of respiratory and ear infections [11–13], overweight [14] and an increase in blood pressure [15] in early life and/or childhood, suggesting that maternal smoking in pregnancy influences the foetal development of different organ systems. Indeed, low birth weight and pre-term delivery are also determinants of health risks later in life, including childhood asthma [16,17]. A cross-sectional study of 11,500 participants of 8–11-year-old children showed that prenatal exposure to cigarette smoke has a stronger effect on childhood asthma compared with postnatal smoke [18]. Prenatal exposure to maternal smoking without subsequent postnatal exposure to environmental tobacco smoke was related to the presence of asthma at school age with an odds ratio (OR) of 1.8 (95%CI: 1.1–2.9) [18].

Parental smoking increases the risk of acute lower respiratory tract diseases in children [12,13]. The pooled estimates showed a higher risk in association with smoking by the mother (OR: 1.56, 95%CI: 1.51–1.62) than with smoking by the father (OR: 1.31, 95%CI: 1.20–1.42) [12]. The higher risk related to the mother’s smoking could be explained by the fact that young children usually spend more time with their mother or by the interplay with maternal smoking during pregnancy. In addition to lower respiratory tract infections (OR: 1.51 95%CI: 1.44–1.52), exposure to environmental tobacco smoke has been associated with an increased risk of otitis media (OR: 1.32, 95%CI: 1.14–1.52) [12].

Exposure to prenatal tobacco increases the level of genetic damage in newborns and children. A meta-analysis performed in children exposed to environmental tobacco smoke showed that children and newborns had, respectively, 1.3 and 6.7 times higher levels of haemoglobin adducts compared with non-exposed newborns [19]. Available meta-analytical evidence of an association between in-utero exposure to tobacco smoke from the parents and childhood cancer seems weak. Maternal smoking was estimated as an increased risk...
<table>
<thead>
<tr>
<th>Disease</th>
<th>Author/Year (population)</th>
<th>Design</th>
<th>N articles</th>
<th>N</th>
<th>Pooled Estimate</th>
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<td>Placenta previa</td>
<td>Castles et al. [9] (North America, Western Europe)</td>
<td>Case–control</td>
<td>6</td>
<td>50.695 Patients</td>
<td>1.58 (1.04–2.12)^a</td>
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<td>Abruptio placenta</td>
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<td>Cohort</td>
<td>8</td>
<td>57.302</td>
<td>1.62 (1.46–1.77)^b</td>
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<td>Ectopic pregnancy</td>
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<td></td>
<td>9</td>
<td>10.632</td>
<td>1.77 (1.31–2.22)^b</td>
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<td>Preterm PROM</td>
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<td>6</td>
<td>34.668</td>
<td>1.7 (1.18–2.25)^b</td>
</tr>
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<td>Preterm delivery (&gt;32 weeks but &lt;37 weeks of gestation)</td>
<td>Shah et al. [10] (Europe, North America)</td>
<td>Case–control</td>
<td>20</td>
<td>Cases: &gt;100.000</td>
<td>1.27 (1.21–1.33)^b</td>
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<td>Pre-eclampsia</td>
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<td>6</td>
<td>4.451</td>
<td>1.27 (1.21–1.33)^b</td>
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<td>Acute lymphoblastic Leukaemia (Childhood)</td>
<td>Boffeta et al. [20] (Europe, North America)</td>
<td>Case–control</td>
<td>4</td>
<td>Primary Not Given</td>
<td>Paternal smoking during pregnancy1.17 (0.96–1.42)^b</td>
</tr>
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<td>Acute otitis media</td>
<td>Milne et al. [23] (Europe, North America, Australia)</td>
<td>Case–control</td>
<td>11</td>
<td>Cases: 1994</td>
<td>Paternal smoking around the time of conception1.15 (1.06–1.24)^b</td>
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<tr>
<td>Asthma</td>
<td>Moritsugu et al. [12] (Europe, North America, Australia, Asia, Africa)</td>
<td>Case–control</td>
<td>3</td>
<td>Primary Not Given</td>
<td>Smoking by Either Parent0.99 (0.70–1.40)^a</td>
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<td>Bladder cancer</td>
<td>Van Hemelrijck et al. [51] (Asia, Europe, North America)</td>
<td>Case–controlCohort</td>
<td>8</td>
<td>~223.000 Participants</td>
<td>Childhood Exposure1.19 (0.88–1.62)^b</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Brion et al. [15] (Primary not given)</td>
<td>Cohort</td>
<td>9</td>
<td>16.690 Participants</td>
<td>Maternal Smoking During Pregnancy Systolic Blood Pressure0.67 mmHg (0.31 to 1.04)</td>
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<td>Breast cancer</td>
<td>Pirie et al. [52] (Asia, Europe, North America)</td>
<td>Case–controlCohort</td>
<td>25</td>
<td>~220.000 Participants</td>
<td>Childhood Exposure: 0.98 (0.88–1.08)^b</td>
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<td>Childhood cancer (overall)</td>
<td>Boffeta et al. [20] (Europe, North America)</td>
<td>Case–control</td>
<td>12</td>
<td>900 participants 6351 cases 6253 controls</td>
<td>Maternal smoking during pregnancy1.10 (1.03–1.19)^b</td>
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<td>Cough</td>
<td>Moritsugu et al. [12] (Europe, North America, Australia, Asia, Africa)</td>
<td>Case–control</td>
<td>39</td>
<td>Primary not given</td>
<td>Cough Smoking by either parent: 1.35 (1.27–1.43)^b</td>
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<td>Cancer of the nervous system (childhood)</td>
<td>Boffeta et al. [20] (Europe, North America)</td>
<td>Case–control</td>
<td>12</td>
<td>Primary not given</td>
<td>Maternal smoking during the pregnancy 1.04 (0.92–1.18)^b</td>
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<td>Genetic damage in children</td>
<td>Neri et al. [19] (Australia, Europe, USA, South America)</td>
<td>Case–control</td>
<td>6</td>
<td>Primary not given</td>
<td>Children exposed to environmental tobacco smoke: 1.38 (0.98–1.96)</td>
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<td></td>
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<td>Cohort</td>
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<td>5</td>
<td>Prenatal Exposure: 6.67 (2.56–17.24)</td>
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</table>

SCE: Prenatal exposure: 1.02 (0.94–1.10)^d
<table>
<thead>
<tr>
<th>Condition</th>
<th>Study Details</th>
<th>Study Design</th>
<th>Study Size</th>
<th>Primary Information</th>
<th>Lower respiratory illnesses</th>
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<td>Moritsugu et al. [12] (Europe, North America, Australia, Asia, Africa)</td>
<td>Case-control</td>
<td>38</td>
<td>Primary not given</td>
<td>Smoking by either parent: 1.51 (1.44–1.59)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cohort</td>
<td></td>
<td></td>
<td>Maternal smoking: 1.56 (1.51–1.62)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
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<td></td>
<td>Paternal smoking: 1.31 (1.20–1.42)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td>Hospitalisation for respiratory illness 1.93 (1.66–2.25)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td>Serious infections0–2 years: 1.71 (1.33–2.20)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>3–6 years: 1.25 (0.88–1.78)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Maternal smoking during pregnancy 1.03 (0.90–1.17)</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>Li et al. [11] (Asia, Europe, North America)</td>
<td>Case-control</td>
<td>13</td>
<td>32,945 cases</td>
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<td></td>
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<td>Cohort</td>
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<td>Maternal smoking during pregnancy 1.03 (0.90–1.17)</td>
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<td>Paternal smoking 1.31 (1.20–1.42)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Lymphatic and haematopoietic Neoplasm (childhood)</td>
<td>Boffeta et al. [20] (Europe, North America)</td>
<td>Case-control</td>
<td>9</td>
<td>Cases: 3610</td>
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<td>Boffeta et al. [20] (Europe, North America)</td>
<td>Case-control</td>
<td>5</td>
<td>Cases: 442</td>
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<td></td>
<td>Moritsugu et al. [12] (Europe, North America, Australia, Asia, Africa)</td>
<td>Case-control</td>
<td>6</td>
<td>Cases: 2536</td>
<td>Paternal smoking 1.31 (1.20–1.42)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Middle ear effusion</td>
<td>Boffeta et al. [20] (Europe, North America)</td>
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<td>Smoking by either parent: 1.51 (1.44–1.59)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Moritsugu et al. [12] (Europe, North America, Australia, Asia, Africa)</td>
<td>Case-control</td>
<td>6</td>
<td>Primary not given</td>
<td>Maternal smoking: 1.56 (1.51–1.62)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Paternal smoking: 1.31 (1.20–1.42)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Hospitalisation for respiratory illness 1.93 (1.66–2.25)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>3–6 years: 1.25 (0.88–1.78)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Maternal smoking during pregnancy 1.03 (0.90–1.17)</td>
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<td>Non-Hodgkin lymphoma (childhood)</td>
<td>Boffeta et al. [20] (Europe, North America)</td>
<td>Case-control</td>
<td>4</td>
<td>Primary not given</td>
<td>Maternal smoking during pregnancy 0.95 (0.76–1.19)</td>
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<td>Overweight&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Oken et al. [32] (Australia, Europe, North America)</td>
<td>Cohort</td>
<td>14</td>
<td>84,563 Participants</td>
<td>Maternal smoking during pregnancy 0.95 (0.76–1.19)</td>
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<tr>
<td></td>
<td>Moritsugu et al. [12] (Europe, North America, Australia, Asia, Africa)</td>
<td>Case-control</td>
<td>9</td>
<td>Primary not given</td>
<td>Paternal smoking 1.31 (1.20–1.42)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Recurrent otitis media</td>
<td>Boffeta et al. [20] (Europe, North America)</td>
<td>Case-control</td>
<td>4</td>
<td>Primary not given</td>
<td>Smoking by either parent: 1.32 (1.14–1.52)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Moritsugu et al. [12] (Europe, North America, Australia, Asia, Africa)</td>
<td>Case-control</td>
<td>4</td>
<td>Primary not given</td>
<td>Maternal smoking: 1.37 (1.19–1.59)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td>Paternal smoking: 0.90 (0.70–1.15)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Paternal smoking during the pregnancy 2.08 (1.08–3.98)&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
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<td>Recurrent otitis media 1.50 (1.36–1.65)&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Respiratory tract infections</td>
<td>Peat et al. [13] (Asia, Australia, Chili, Europe, New Zealand, USA)</td>
<td>Case-control</td>
<td>14</td>
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<td>Paternal smoking 1.31 (1.20–1.42)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
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<td>Hospitalisation for respiratory illness: 2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
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<td>Lower respiratory tract infection: 1.7&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Early respiratory illness: 1.6&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Maternal smoking during pregnancy 3.93 (3.78–4.08)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Paternal smoking, mother does not smoke 1.49 (1.25–1.77)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sudden infant death syndrome (after prone-sleep-position intervention programs)</td>
<td>Mitchell et al. [24] (Europe, New Zealand, US)</td>
<td>Case-control</td>
<td>24</td>
<td>Cases: 15,694</td>
<td>Smoking by either parent: 1.26 (1.20–1.33)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Wheeze</td>
<td>Moritsugu et al. [12] (Europe, North America, Australia, Asia, Africa)</td>
<td>Case-control</td>
<td>45</td>
<td>Cases: 3,592,021</td>
<td>Smoking by both parents: 1.41 (1.23–1.63)&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
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<td>Controls: 719</td>
<td>Maternal smoking: 1.28 (1.21–1.35)&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Controls: 4885</td>
<td>Paternal smoking: 1.22 (1.12–1.32)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Odds ratio.

<sup>b</sup> Relative risk.

<sup>c</sup> PROM, premature rupture of membranes is a rupture (breaking open) of the membranes (amniotic sac) before labour begins. If PROM occurs before 37 weeks of pregnancy, it is called preterm premature rupture of membranes (PPROM).

<sup>d</sup> MR is a point estimate of the relative effect of the exposure on biomarker level detected in each study taking the value 1 when there is no effect, values >1 when exposure is associated with a decreased level of the investigated biomarker.

<sup>e</sup> SCE: sister chromatid exchange is the exchange of genetic material between two identical sister chromatids. The reason for the SCE is not known but it is required and used for mutagenic testing of many products. Four to five sister chromatid exchanges are in the normal distribution, 14–100 exchanges are not normal and present a danger to the organism.

<sup>f</sup> Primary analysis of overweight has been chosen, defined as BMI \( > 85\)th percentile or \( > 90\)th percentile for age and sex.
of 10% (95% CI: 1.03–1.19) for childhood cancer, yet no significant elevated risk was found for lymphomatic and haematopoetic neoplasm, or for cancer of the central nervous system or kidney cancer (Table 1) [20]. When considering maternal and paternal in-utero exposure to genotoxic compounds, a difference in the mode of action is implied in the direct transplacental effects versus the preconception alterations. Carcinogens in tobacco can induce DNA damage in sperm: male smokers have higher levels of 8-oxo-2-deoxoguanosine in their semen than non-smokers, which may result in oxidative damage to sperm DNA [21,22]. Paternal smoking during conception and acute lymphoblastic leukaemia are related with a pooled odds of 1.15 (CI: 1.06–1.24), paternal exposure during pregnancy is not [20,23]. Furthermore, meta-analytical work suggests an increased risk after paternal exposure to tobacco smoke with childhood non-Hodgkin lymphoma and tumors in the central nervous system [20].

Based on pooled evidence of 25 studies [24], maternal smoking was associated with almost a 4-fold time increase in risk of sudden infant death syndrome. The corresponding risk of paternal smoking with absence of maternal smoking was 1.49 (Table 1). While the effect of smoke exposure in utero seems to be stronger, postnatal environmental tobacco smoke has been found to increase the risk of sudden infant death syndrome even after controlling for prenatal exposure. However, in most cases this is difficult to distinguish as most children that have been exposed in utero are also exposed during their first months of life.

3. Smoking ban and health gains

The positive effect of smoking cessation suggests a causal association between active smoking and cardiovascular disease [25]. Evidence from observational studies shows a decrease in cardiovascular events in progression of atherosclerosis in those who quit smoking compared with those continuing to smoke cigarettes. Along with this, evidence from cohort studies and ecological evidence on recent smoking bans (introduced by law) consistently shows a rapid decrease in hospitalisation for myocardial infarction (MI). The pooled aggregated data showed that the rate of acute MI hospitalisation in countries that implemented a smoking ban law, decreased 12 months after its implementation, on average by 17% (95% CI: 20–13%) [26]. The rapid decrease in MI after introduction of bans suggests an interplay between chronic and acute processes, including triggers. A trigger can be defined as an external stimulus that produces acute physiological or pathophysiological changes. The idea of the pathophysiological relevance of triggers leading to the onset of acute myocardial infarction (MI) has been proposed [27]. In general, ageing leads to functional and structural abnormalities of the arterial wall, which are amplified by hypertension and atherosclerosis [28]. A vulnerable atherosclerotic plaque might lead to an occlusive thrombus which is more likely to be formed if other factors come into play to narrow homeostasis and increase vasoconstriction. The role of triggers such as alcohol [29], anger [30,31], physical exertion [31,32] and use of marijuana [33] in the onset of MI is recognised [34].

Recently gained evidence supports the notion that premature birth is also a syndrome which might have trigger components, including ambient temperature and smoking [35,36]. Recent Scottish [36] and Belgian [35] data support reductions in the rate of preterm births after the implementation of smoking bans, whereas no such decrease was evident in the years or months before these bans.

In Belgium, smoke-free legislation was implemented in different phases (in public workplaces and most workplaces in January 2006, in restaurants January 2007, and in bars during food January 2010). We were able to demonstrate a consistent pattern of changes in preterm delivery with stepwise reductions over the different enactments. In an analysis using a birth register comprising 606,877 live-births, we observed an immediate change in the risk of spontaneous preterm delivery of –3.13% (95% CI: –4.37% to –1.87%; P < 0.01) on 1st January 2007 (ban on smoking in restaurants), and an annual slope change of –2.65% (–5.11% to –0.13%; P = 0.04) after 1st January 2010 (ban on smoking in bars serving food). In 716,941 Scottish newborns, the risk was decreased by 11.72% (95% CI: –15.87 to –7.35) 3 months prior to the introduction of the comprehensive smoking ban in 2006. Similarly to Belgian findings, a study on the impact of the Irish workplace smoking ban on birth weight and preterm birth found a protective effect only on the latter outcome [37]. Although their analysis was limited to a comparison of rates 1 year before and after the ban, they even found an increase in the risk of low birth weight.

The smoking ban studies must be viewed as an investigation of the possible impact of a ‘population intervention’ rather than an investigation of changes in individual behaviour. It is possible that unmeasured confounders were responsible for the observed changes. Nevertheless, it is hard to conceive of a factor that could change the population risk of preterm births after the introduction of the different successive smoking bans. It is unlikely that our observations could be explained by abrupt changes in therapeutic strategies coinciding with the smoking bans. Nevertheless, the Belgian study collected data on the prescription of atosiban and on cervical cerclage treatment from a social security organisation covering 42% of the population. Atosiban is an inhibitor of oxytocin and was approved and is specifically used to halt premature labour. Cervical cerclage is used for the treatment of cervical incompetence, a condition where the cervix has opened slightly and there is a risk of miscarriage.

Given that even a mild reduction in gestational age has been linked to adverse health outcomes in early and later life, these population interventions have important public health implications. Indeed, a Swedish study found that, even among those born late preterm (34–36 weeks), preterm birth was associated with a 31% (13–50%) increase in mortality in young adulthood [38].

4. Molecular epidemiological aspects

The human placenta forms the interface between foetal and maternal circulation, and by controlling nutrient supply plays a critical role in the regulation of foetal growth and development. Maternal smoking causes perturbations in this uteroplacental exchange as it increases the risk of low birth weight [39,40] and preterm delivery [35,41]. The mechanisms underlying these observed effects remain unclear, but emerging data suggest that biochemical, genetic and epigenetic activi-
ties respond to and are modified by in-utero tobacco exposure. Nutrients and potential pollutants are metabolised, making the placenta a molecular ‘footprint’ to which the foetus has been exposed in utero.

Mitochondria are abundant in placental cells, they provide energy for the functioning of this metabolically active organ. Each cell contains approximately 200–2000 mitochondria, carrying between two and ten copies of mitochondrial DNA (mtDNA). Recently, by assessing the relative mtDNA content (a marker of mitochondrial damage and dysfunction), its functioning has been linked to various disease mechanisms [42,43]. The placental mtDNA content has been shown to be very adaptive to environmental insults, including maternal smoking [44] and air pollution [45]. The relative mtDNA content is decreased by 37% (P < 0.02) in placentas of mothers who smoke [44] compared with a decrease of 17.4% (P = 0.05) for each 10-μg/m3 increase in PM10 exposure during the third trimester of pregnancy [45].

Important questions remain concerning how mitochondrial biogenesis and maintenance are regulated as a response to tobacco exposures, and how these relate to placental functioning. An attractive link between adverse insults and altered foetal development is gene regulation. Maternal smoking during pregnancy can lead to changed placental gene expression levels, which is epigenetically regulated by DNA methylation, histone modifications or non-coding RNAs. Epigenetic changes can occur throughout the course of life as a result of environmental conditions. Much of the epigenome is already established in germ cells and embryos as it appears to be particularly important for the regulation of embryonic growth and placental development [46]. Recently, studies investigating cord blood and placental tissue showed that the epigenetic system is sensitive to tobacco exposure in utero. Global DNA methylation levels in cord blood is lower among newborns with smoking mothers (mean = 15.04%; 95% CI: 8.4–21.7) compared with second-hand smokers (21.1%; 95% CI: 16.6–25.5) and their non-smoking counterparts (mean = 29.2%; 95% CI: 20.1–38.1) [47]. An epigenome-wide methylation study in cord blood of newborns exposed to tobacco smoke during pregnancy showed that genes that play an important role in detoxifying components of tobacco smoke (AHR and CYP1A1) are differentially methylated [48]. Accordingly, Suter and colleagues reported site-specific changes in DNA methylation of the CYP1A1 promoter, and this hypomethylation correlated with an increase in CYP1A1 gene expression in the placenta [49]. They showed in an epigenome-wide methylation study on placental tissue that methylation levels of 623 genes are deregulated in a CpG site-specific manner [50].

Despite a limited number of (epi)genomic studies in cord blood and placental tissue, we are getting a better picture of how maternal tobacco smoke can alter placental functioning and contribute to adverse pregnancy outcomes. Therefore the potential health consequences of changes in mitochondrial functioning, gene expression and epigenetics in early life should be further elucidated.

Conflict of interest statement

None declared.

REFERENCES


Molecular profile of lung cancer in never smokers

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c Alvin J. Siteman Cancer Center at Washington University School of Medicine, St. Louis, USA

Tobacco smoking is the most common cause of lung cancer, but approximately 10–25% of patients with lung cancer are life-long never smokers. The cause of lung cancer in never smokers is unknown, although tobacco-smoke exposure may play a role in some of these patients. Lung cancer that develops in the absence of significant tobacco-smoke exposure appears to be a unique disease entity with novel genomic and epigenomic alterations and activation of molecular pathways that are not generally seen in tobacco-smoke-induced lung cancer. These molecular alterations are very likely responsible for the unique clinico-pathological features of lung cancer in never smokers (LCINS), and some of these molecular alterations – such as the activating EGFR TK mutations and EML4–ALK fusion – significantly influence therapeutic choices and treatment outcomes. In the last few years there has been a number of studies exploring the molecular characteristics of LCINS, and some of them have reported new and significant findings. Here we review the key findings from these studies and discuss their potential therapeutic implications.

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1. Introduction

Globally, over a million patients are diagnosed with lung cancer each year, making it the most common type of cancer in the world [1]. Even though tobacco smoking is considered to be the most common cause of lung cancer, it is estimated that 10–25% of all patients diagnosed with lung cancer are never smokers [2]. Never smokers with lung cancer are more likely to be women, have adenocarcinoma histology and are of East Asian ethnicity when compared to tobacco smokers with lung cancer [3–5]. Apart from these now well-established epidemiological differences, recent research has uncovered several key molecular alterations that are more frequently detected in never smokers with lung cancer. Some of these molecular alterations – such as activating mutations in the tyrosine kinase (TK) domain of the epidermal growth factor receptor (EGFR) gene and the EML4–ALK fusion – have therapeutic relevance in the treatment of patients with advanced-stage lung cancer [6–10]. Comprehensive genomic analysis by whole genome sequencing has also identified significant differences between the tumour genome of lung cancer in never smokers (LCINS) and tobacco smokers with lung cancer [11] (Table 1). In this review we will discuss the genomic and epigenomic findings that characterise LCINS.

2. Inherited susceptibility to LCINS

Despite the fact that tobacco smoking is the primary cause of lung cancer, identification of familial clustering of patients with lung cancer is suggestive of an inherited risk factor. Several studies have reported that patients with LCINS are more likely to have a family member diagnosed with lung cancer than a tobacco smoker with the same disease [12–15]. A systematic review of 11 studies identified that a positive family history of lung cancer increases the risk of developing lung cancer by 1.5-fold in never smokers [16]. A linkage study of 52 families with two or more members diagnosed with lung cancer identified the 6q23–25 region to be a major
Significant differences have been reported in the frequency of genes (have shown specific polymorphisms involving DNA repair limited number of molecular alterations. Individual studies LCINS in each individual study, and they were focused on a findings are limited by the small sample size of patients with only in Caucasians, not in Asians [22]. However, these find-

genes involved in carcinogen metabolism, DNA repair and inflammation are associated with increased risk for develop-
ing LCINS. Pooled analysis of studies evaluating CYP1A1 and GSTM1 polymorphisms identified that CYP1A1-I462V poly-
morphism was associated with two- to three-fold increased risk for developing LCINS. Interestingly, the CYP1A1-I462V polymorphism was associated with increased risk for LCINS only in Caucasians, not in Asians [22]. However, these find-
ings are limited by the small sample size of patients with LCINS in each individual study, and they were focused on a limited number of molecular alterations. Individual studies have shown specific polymorphisms involving DNA repair genes (XRCC1 and ERCC2) and genes involved in interleukin production (IL1, IL6 and IL10) to be associated with increased risk for LCINS [23–25]. These studies are limited by their relatively small sample size and require independent validation to ascertain that these polymorphisms are associated with increased risk for LCINS.

3. Markers of tobacco exposure

Significant differences have been reported in the frequency and patterns of gene mutations between LCINS and lung cancer in tobacco smokers (reviewed in [26]). Some of the earliest studies identified that mutations in the tumour suppressor gene TP53 were less frequent in LCINS (8–47%) when compared with tobacco smokers with lung cancer (26–71%) [27–29]. Also a significant dose-response relationship between tobacco smoke and TP53 mutations has been reported in patients with non-small-cell lung cancer (NSCLC) [27]. In a sample of 30 resected NSCLC tumor samples the odds of having TP53 mutations in a patient smoking 20 cigarettes per day for 30 years were 5.3 when compared with a patient with LCINS. Tobacco-smoke exposure was also associated with a distinct mutational spectrum in the TP53 gene, with increased frequency of G → T transversion mutations when compared to LCINS [30,31].

Mutations involving the KRAS oncogene are rare in patients with LCINS and are more frequently reported in tobacco smokers with lung cancer [32–36]. In a sample of 106 patients with adenocarcinoma, the incidence of KRAS mutations was significantly higher in the smokers cohort versus the never smokers (43% versus 0%, P = 0.001) [35]. Similarly KRAS mutations are more frequently identified in tobacco smokers and are predominantly G → T transversion mutations [31].

4. Fusions and mutations involving kinase genes

Analyses of tumor samples from patients with excellent response to treatment with EGFR TK inhibitors led to the discovery of activating mutations involving the EGFR TK gene [6,7]. At around the same time it was also discovered that patients with LCINS had a better response to EGFR TK inhibitors such as gefitinib [37]. Several retrospective studies subse-

Table 1 – Characteristic molecular variations in lung cancer in never smokers (LCINS).

<table>
<thead>
<tr>
<th>Markers</th>
<th>Lung cancer in tobacco smokers</th>
<th>LCINS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genomic changes</td>
<td>Point mutations in protein coding regions</td>
<td>Primarily G → T transversions</td>
</tr>
<tr>
<td>KRAS mutation</td>
<td>Common, 30–43%</td>
<td>Rare, 0–7%</td>
</tr>
<tr>
<td>EGFR mutation</td>
<td>Rare, 0–7%</td>
<td>Common, 45%</td>
</tr>
<tr>
<td>TPS3 mutation; G → T to G → A ratio</td>
<td>14%</td>
<td>3%</td>
</tr>
<tr>
<td>STK11 mutations</td>
<td>2–3%</td>
<td>5–15%</td>
</tr>
<tr>
<td>EML4-ALK fusion</td>
<td>&lt;1%</td>
<td>1.5–6%</td>
</tr>
<tr>
<td>RET fusion</td>
<td>&lt;1%</td>
<td>2%</td>
</tr>
<tr>
<td>Epigenomic changes</td>
<td>Methylation index (MI)</td>
<td>High MI</td>
</tr>
<tr>
<td>p16 and APC methylation</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Loss of protein expression in hMSH2</td>
<td>Less common, 10%</td>
<td>More common, 40%</td>
</tr>
</tbody>
</table>

susceptibility locus for lung cancer [17]. In addition, three large genome-wide association studies (GWASs) identified the 15q24–25.1 locus as the site harbouring genetic polymorphisms associated with lung cancer risk [18–20]. However, a pooled analysis of data from all three studies did not find the 15q24–25.1 locus to be associated with increased risk for LCINS [21].

Studies have also examined whether polymorphisms of genes involved in carcinogen metabolism, DNA repair and inflammation are associated with increased risk for developing LCINS.Fooled analysis of studies evaluating CYP1A1 and GSTM1 polymorphisms identified that CYP1A1-I462V polymorphism was associated with two- to three-fold increased risk for developing LCINS. Interestingly, the CYP1A1-I462V polymorphism was associated with increased risk for LCINS only in Caucasians, not in Asians [22]. However, these findings are limited by the small sample size of patients with LCINS in each individual study, and they were focused on a limited number of molecular alterations. Individual studies have shown specific polymorphisms involving DNA repair genes (XRCC1 and ERCC2) and genes involved in interleukin production (IL1, IL6 and IL10) to be associated with increased risk for LCINS [23–25]. These studies are limited by their relatively small sample size and require independent validation to ascertain that these polymorphisms are associated with increased risk for LCINS.
setting in patients with EGFR TK mutations [41–43]. Results from these trials have now established EGFR TK inhibitors as the standard front-line treatment for patients with advanced-stage NSCLC that is positive for EGFR TK mutation.

Mutations involving the HER2 gene have been shown to be more frequent in never smokers with adenocarcinoma [9]. In a sample of 671 NSCLC tumours, the overall frequency of HER2 mutations was low at 1.6% (11/671), but they were more frequently identified in never or light smokers (8 of 248, 3.2%; P = 0.02). The HER2 mutations were not detected in tumours harbouring either the activating EGFR-TK or KRAS mutations.

The STK11 gene encodes a serine–threonine kinase and plays an important role in cell proliferation and survival. Mutations involving the STK11 gene have been reported in 8% of all patients with lung cancer. In addition, they are more frequently present in tobacco smokers with lung cancer than in patients with LCINS (14% versus 3%; P = 0.007) [44].

EML4–ALK is a novel fusion gene present in approximately 5% of patients with NSCLC and is associated with an excellent therapeutic response to treatment with an Alk kinase inhibitor [10,45,46]. The fusion gene was more frequently identified in never smokers and younger patients with lung cancer. In addition, it appears to be mutually exclusive to EGFR TK and KRAS mutations.

Two new transforming fusions involving the RET and ROS1 kinase genes at the 3’ end have been identified in patients with lung cancer [47]. In one study, tumour samples from 936 patients with surgically resected NSCLC were tested for RET fusion genes by the reverse transcriptase polymerase chain reaction (PCR). The RET fusion was detected in 13 patients (1.4%), and these patients predominantly had adenocarcinoma histology (84.6%), were never smokers (82%) and many of them were younger: age < 60 years at the time of diagnosis (73%) [48]. RET fusions have been shown to promote cell proliferation, and treatment with vandetanib, a multi kinase inhibitor with activity against RET kinase, was able to inhibit RET-induced cell proliferation [47]. Fusions involving the ROS1 gene in lung cancer were first reported in 2007 [49] and in a subsequent study, a fluorescent in situ hybridisation (FISH) based assay of 1000 NSCLC tumour samples identified ROS1 fusions in 18 (1.7%) samples [50]. Similar to patients with ALK or RET fusions, ROS fusions were found primarily in younger patients who were never smokers and had adenocarcinoma histology. Cell lines expressing ROS fusion were sensitive to treatment with the ALK inhibitor crizotinib. Overall, fusion genes involving the ALK, RET and ROS kinases are relatively rare molecular events in patients with NSCLC. These patients have similar clinicopathological features, including that of being a never smoker. In addition, these fusions appear to be mutually exclusive to each other and to other known driver mutations in lung cancer, such as EGFR TK and KRAS mutations.

5. Epigenetic alterations

Methylation of tumour suppressor genes – including p16\textsuperscript{INK4a}, DAPK, RASSF1A, RAR\textsubscript{b}, APC, CDH13, MGMT, hMLH1, hMSH2 and GSTP1 – leading to epigenetic silencing has been reported in lung cancer (reviewed in [51,52]). Studies have reported that methylation of the tumour suppressor gene p16 is less frequent in LCINS compared to lung cancer in tobacco smokers [53–57]. In a sample of 514 NSCLC tumours, which included 112 never smokers with adenocarcinoma, p16 (P = 0.007) and APC (P = 0.0007) methylation rates were significantly lower in never smokers than tobacco smokers with adenocarcinoma [54]. There was no significant difference in the methylation rate of the other tumour suppressor genes RASSF1A, RAR\textsubscript{b}, CDH13, MGMT and GSTP1 between the two groups. The methylation index (total number of genes methylated/total number of genes examined) was significantly higher in tobacco smokers with lung cancer when compared to LCINS. In a follow-up study of 383 NSCLC tumours, the authors confirmed that the p16 methylation rate and the methylation index were significantly lower in LCINS (P < 0.0001) [55]. The methylation rate for APC was significantly lower (P < 0.0001) in never smokers when the analysis was restricted to adenocarcinoma. Subsequent studies have also reported a low p16 methylation rate in never smokers with adenocarcinoma [56,58]. There was no significant difference in the methylation rates of RASSF1A and DAPK between tobacco smokers with lung cancer and LCINS [56].

The loss of protein expression in protein mismatch repair genes hMLH1 and hMSH2 was reported to be more frequent in LCINS than in lung cancer in tobacco smokers [59]. In a sample of 77 resected NSCLC tumours, the loss of protein expression for hMLH1 (70% versus 46%) and hMSH2 (40% versus 10%) was more frequent in LCINS. The authors also reported that promoter methylation was the predominant mechanism for the loss of protein expression in both genes.

6. Next-generation sequencing in LCINS

The advent of next-generation sequencing technologies now allows us unprecedented access to the tumour genome. Recently, next-generation sequencing of several tumour–normal pairs from patients with NSCLC was reported, and some of these patients were never smokers. Whole genome and transcriptome sequencing was performed in 17 patients with NSCLC, including five never smokers and 12 tobacco smokers [11]. The total number of mutations involving genes in protein coding regions was significantly higher in smokers than in never smokers; median 209 versus 18. In addition, the mutations in tobacco smokers were primarily G → T transversions, whereas in LCINS they were G → A transitions. For the first time this study identified that the G → A transition point mutations in never smokers is a genome-wide phenomenon and is not restricted to KRAS and TP53 genes.

Genomic and epigenomic profiling of tumour–normal pairs from six Korean patients with LCINS with exome seq, RNA seq, micro RNA seq and methylated DNA immunoprecipitation-sequencing (MeDIP-seq) confirmed the low mutation rate in LCINS [60]. They reported a total of 47 somatic mutations from the six LCINS tumour samples. In addition, they identified several novel fusion genes, including CCDC6–RET fusion which has been previously reported and could be a potential therapeutic target. Pathway analysis identified that genes involved in cell cycle regulation – particularly in
7. Conclusion

Cancer is a disease that is characterised by genomic and epigenomic alterations that result in malignant transformation of normal tissue. Such transforming genomic and epigenomic alterations are considered the drivers of the malignant disease and determine the clinical behaviour of the disease. In the case of lung cancer, tobacco-smoke exposure appears to be an important factor in determining the type of oncogenic drivers associated with the disease. This is well exemplified by findings from several studies showing that mutations involving TP53 and KRAS genes are more frequent in tobacco smokers with lung cancer, whereas LCINS is characterised by EGFR TK mutations, ALK, RET and ROS fusions. The differences between LCINS and lung cancer in tobacco smokers are not restricted to a few genes. Recent next-generation sequencing studies have found that the genome of LCINS is significantly different from the tumour genome of a tobacco smoker with lung cancer (Fig. 1). Overall, the number of mutations is significantly lower in LCINS, and the point mutations are primarily G → A transitions.

The higher number of genomic alterations seen in smokers with lung cancer is very likely due to the mutagenic field effect of tobacco-smoke exposure. The vast majority of these genomic alterations in tobacco smokers with lung cancer are believed to be passengers that do not have any role in the malignant transformation or progression. In contrast, in LCINS the absence of tobacco-smoke exposure and the relatively smaller number of identified genomic alterations suggest that most if not all of them play a role in its malignant transformation. Hence the LCINS genome may provide us with a relatively enriched and easily identifiable set of oncogenic drivers for lung cancer. In addition, the relatively small number of genomic alterations in LCINS also presents better opportunities for the development of targeted therapies against LCINS. With the advances in sequencing technology and decreasing costs it is possible that, in the near future, advanced-stage LCINS may be primarily treated with molecularly targeted therapy, and it would be possible to achieve prolonged periods of disease control similar to the treatment of chronic myeloid leukaemia (CML) and gastrointestinal stromal tumour (GIST).

Conflict of interest statement

The author is not a government employee. For the last 2 years, he has been a consultant for Pfizer, Roche Genentech, Bristol-Myers Squibb, Merck, Boehringer-Ingelheim, Abbott Oncology and Covidien.

REFERENCES


Bone metastases: Causes, consequences and therapeutic opportunities

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1. Introduction

Although the skeleton is a common site of metastasis for many solid tumours, metastatic bone disease is particularly relevant in prostate and breast cancers. Thus, bone is the most frequent – and often the only – location of metastasis in patients with advanced prostate cancer. Moreover, up to 70% of patients with metastatic breast cancer develop bone metastases over the course of their disease.

Metastatic bone involvement usually results in multiple skeletal complications leading to a significant deterioration in the quality of life for cancer patients. Pain, hypercalcemia and skeletal-related events (SREs) – such as the use of radiotherapy or surgery of bone, pathological fractures and spinal cord compression – are problems typically derived from bone metastases [1].

The pathogenesis of bone metastases is a complex process involving many interactions between tumour cells and osteoclasts and osteoblasts. Receptor activator of nuclear factor-κB (RANK) ligand (RANKL), which is expressed by osteoblasts and marrow stromal cells, is a potent inducer of osteoclast formation. In bone metastases, cytokines and growth factors secreted by tumour cells (interleukins 1 and 6, parathyroid-hormone-related peptide, tumour necrosis factor, prostaglandin E2, and macrophage-colony-stimulating factor, amongst others) increase the expression of RANKL on marrow stromal cells and osteoblasts [2]. Following this, RANKL binds to its receptor, RANK, on the surface of osteoclast precursors and stimulates the differentiation of these cells to mature osteoclasts. This excessive RANKL-induced osteoclast activity results in increased bone resorption and local bone destruction, leading to the release of growth factors from the bone matrix that subsequently promotes tumour progression. This relationship between tumour and bone cells constitutes the vicious cycle of bone metastases.

For all these reasons, patients with metastatic bone involvement who show higher levels of bone turnover markers have a particularly high risk for SREs in addition to worse clinical outcomes [3].

Treatment of bone metastases requires a broad strategy with different therapeutic options, including both local and systemic therapies. External-beam radiotherapy remains the mainstay of treatment for symptomatic bone metastases. However, considering that osteoclast-mediated bone resorption plays a critical role in the development of metastatic bone disease, its inhibition represents an attractive target for treating bone metastases. Below, some of the major management approaches are very briefly summarised.

2. Bisphosphonates

Bisphosphonates are chemically stable derivatives of inorganic pyrophosphate. These compounds are potent inhibitors of osteoclast-mediated bone resorption through two well-recognised mechanisms of action. On the one hand, first-generation non-nitrogen-containing bisphosphonates (i.e. clodronate) are metabolised by osteoclasts to cytotoxic ATP analogues; on the other hand, second- and third-generation nitrogen-containing bisphosphonates, such as zoledronic acid and pamidronate, act by inhibiting farnesyl diphosphate synthase, a key enzyme of the mevalonate pathway.

Over the last two decades these agents – in particular zoledronic acid and pamidronate – have been the most effective treatments in delaying or preventing SREs in patients with bone metastases from solid tumours, as well as in patients with multiple myeloma [4].

3. Denosumab

Denosumab is a fully human monoclonal antibody that binds to RANKL in order to inhibit osteoclast activity. Denosumab has been evaluated in three identically designed, randomised, double-blind, phase III clinical trials [5–7]. Patients were
Other bone-targeting agents are currently under investigation, although the clinical development of SRC- and C-MET inhibitors is further along. Both have shown important bone-specific activity in patients with breast or prostate cancer, as well as in preclinical models [11,12].

### Table 1 – Phase III studies with denosumab in patients with bone metastases or myeloma multiple.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Type of tumour</th>
<th>Time to first on-study SRE</th>
<th>Overall survival</th>
<th>Time to disease progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1904</td>
<td>Prostate cancer</td>
<td>HR = 0.82 (P = 0.0002 for non-inferiority analysis; P = 0.008 for superiority analysis)</td>
<td>HR = 1.03</td>
<td>HR = 1.06 (P = 0.3)</td>
</tr>
<tr>
<td>1776</td>
<td>Myeloma multiple; solid tumours (except breast and prostate)</td>
<td>HR = 0.94 (P = 0.0007 for non-inferiority analysis)</td>
<td>HR = 0.95</td>
<td>HR = 1 (P = 1)</td>
</tr>
<tr>
<td>2046</td>
<td>Breast cancer</td>
<td>HR = 0.82 (P &lt; 0.001 for non-inferiority analysis; P = 0.01 for superiority analysis)</td>
<td>HR = 0.95</td>
<td>HR = 1 (P = 0.93)</td>
</tr>
</tbody>
</table>

SRE, skeletal-related event; HR, hazard ratio.

randomly assigned to receive either subcutaneous denosumab 120 mg and intravenous placebo or intravenous zoledronic acid 4 mg and subcutaneous placebo every 4 weeks. The primary endpoint was time to first on-study SRE (defined as pathological fractures, the use of radiotherapy or surgery of bone, or spinal cord compression). These studies are summarised in Table 1.

Overall, adverse events and serious adverse events were similar with both treatments, although more acute-phase reactions and renal adverse events occurred in the zoledronic acid group, whereas hypocalcemia was more frequent with denosumab. Additionally, the rate of osteonecrosis of the jaw was low in both arms (~2%).

### 4. Other agents

#### 4.1. Mammalian target of rapamycin (mTOR) inhibitors

mTOR inhibition decreases osteoclast maturation and increases osteoclast apoptosis, resulting in reduced bone resorption in animal models [8].

In the randomised phase III trial with everolimus in metastatic breast cancer (BOLERO-2), a total of 724 postmenopausal women with oestrogen-receptor-positive breast cancer refractory to non-steroidal aromatase inhibitor therapy were treated with exemestane and randomised (2:1) to everolimus or placebo. The addition of everolimus significantly improved median progression-free survival, the primary endpoint of this study (6.9 months versus 2.8 months; HR = 0.43; P < 0.001) [9]. An exploratory endpoint also included the evaluation of changes in bone turnover marker levels and the rate of progressive disease in bone, defined as unequivocal progression of a pre-existing bone lesion or the appearance of a new bone lesion [10]. Everolimus added to exemestane significantly decreased bone turnover marker levels at 6 and 12 weeks. Moreover, the cumulative incidence rate of progressive disease in bone was lower in the combination arm.

### 5. Novel compounds

Other bone-targeting agents are currently under investigation, although the clinical development of SRC- and C-MET inhibitors is further along. Both have shown important bone-specific activity in patients with breast or prostate cancer, as well as in preclinical models [11,12].

### 6. Conclusions

A better understanding of the biology of bone metastases is establishing an exciting scenario in the treatment of this disease. This explosion of data has led to a large increase in knowledge and the subsequent introduction of new bone-targeted therapies in daily practice.

### Conflict of interest statement

Jose Perez-Garcia and Eva Muñoz-Couselo have no conflict of interest to declare. Javier Cortés is a consultant for Novartis, Roche, Celgene and declares honoraria (speech) from Novartis, Roche, Celgene, Eisai.

### References


Bone-targeted therapy in prostate cancer

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1. Introduction

Androgen deprivation therapy (ADT) is standard for advanced prostate cancer and is now increasingly used as adjunct therapy in high-risk or locally advanced disease and for the treatment of recurring disease based on rising prostate-specific antigen levels. Testosterone stimulates bone formation directly by stimulating the osteoblast proliferation, inhibiting the apoptosis of both osteoblasts and osteoclasts, and indirectly by being a precursor of oestrogen which is also involved in inhibiting osteoclastic function (bone resorption). The effects of testosterone on preserving bone health are lost in the hypogonadal state induced by ADT[1]. The impact of ADT on bone loss and osteoporosis is well established through multiple studies. In one of these studies, non-metastatic prostate cancer cases were followed for 10 years; none of the patients on ADT had normal bone mass density (BMD) at the end of the study, and the prevalence of osteoporosis (T score < –2.5) was approximately 50% by 4 years and 80% by 10 years in men on ADT[2].

Bone metastases will occur in over 90% of men with lethal castration-resistant prostate cancer (CRPC). Due to the combined effect of bone fragility due to ADT and the presence of bone metastases, almost all patients will experience some form of morbidity related to bone metastases prior to succumbing from the disease. Complications go beyond pain and include pathological fracture, the need for palliative radiation or surgery, and spinal cord compression. These events impair quality of life and place a significant burden on health-care resources.

2. Management options

2.1. Life style modification and supplementation

Regular exercise, smoking cessation, lowering alcohol and caffeine intake, as well as oral vitamin D (800 IU daily) and calcium (500–1500 mg daily) supplementation are helpful in attenuating ADT-related bone loss, but they are insufficient to prevent or treat ADT-induced bone loss[3].

2.2. Bone targeted therapy (anti-resorptive agents)

Bisphosphonates are the first and most widely used of the anti-resorptive agents. Due to their structural similarity to pyrophosphate, a normal component of bone matrix, they are integrated in the bone matrix by binding to hydroxyapatite crystals, resulting in inhibition of osteoclast-mediated bone resorption. Non-nitrogen-containing bisphosphonates are metabolized by osteoclasts to cytotoxic compounds, while nitrogen-containing bisphosphonates exert their effects on osteoclasts and tumour cells by inhibiting a key enzyme in the mevalonate pathway and by inducing osteoclast apoptosis. Nitrogen-containing bisphosphonates (e.g., pamidronate, zoledronic acid) are more potent than non-nitrogen-containing bisphosphonates (e.g., clodronate). Zoledronic acid is unique in that it contains two nitrogen groups, and it has been shown to be 40–850-fold more potent than other bisphosphonates [4].

In the setting of non-metastatic prostate cancer, bisphosphonates have consistently been found to reduce BMD loss associated with ADT in multiple randomized controlled trials, but none have had sufficient power or duration to demonstrate a reduction in fractures[5].

Zoledronic acid is the only bisphosphonate and the first osteoclast-targeted agent that has shown a protective effect against skeletal-related events (SRE) in patients with metastatic castration-resistant prostate cancer. The phase 3 study showed a 48% reduction in the mean annual incidence of SRE (P = 0.005), 5 months prolongation in the median time to first SRE (P = 0.009) and 36% reduction in the ongoing risk of SREs at 24 months [6,7].

Bisphosphonate-induced nephrotoxicity is a major concern, especially with intravenous bisphosphonates. Renal function monitoring and dose adjustment according to creatinine clearance are crucial to prevent significant deterioration in renal function. Other side effects include self-limiting flu-like symptoms occurring with the first infusions, hypocalcaemia and osteonecrosis of the jaw (ONJ) [8].

The zoledronic acid bone metastases prevention study recently reported their results. The Zometa European Study [ZEUS] reported that there was no difference in the
metastases rate after 4 years in high-risk non-metastatic prostate cancer. Of note, the incidence of new metastases was very low at approximately 13% [9].

Denosumab is a receptor activator of nuclear factor kappa B (RANK), a member of the tumour necrosis factor (TNF) receptor superfamily expressed by osteoclast precursors, and its ligand (RANKL) plays an essential role in regulating the osteoclast life cycle at different levels. Binding of the RANKL, secreted by osteoblasts and bone-marrow stromal cells, to its receptor RANK leads to differentiation, activation, and survival of osteoclasts which induce bone resorption [10].

Denosumab is a fully human monoclonal antibody that specifically targets RANKL, thus effectively inhibiting osteoclastic function and bone resorption. In a randomised placebo-controlled study in patients with non-metastatic prostate cancer receiving ADT, denosumab (60 mg subcutaneously every 6 months) was associated with significant improvements in BMD at the lumbar spine (6.7%), the total hip (4.8%) and distal one third of the radius (5.5%). Denosumab was also the first agent to show a reduction in the incidence of new vertebral fractures (1.5% versus 3.9%; \( P = 0.006 \)) in patients on ADT [11].

In the setting of metastatic CRPC, denosumab (120 mg subcutaneously every 4 weeks) compared to zoledronic acid (4 mg intravenously every 4 weeks) significantly improved the time to first SRE (20.7 versus 17.1 months; \( P = 0.001 \) for non-inferiority; \( P = 0.008 \) for superiority). Overall survival and progression-free survival were similar for both drugs. Hypocalcaemia was more common with denosumab (13%) than with zoledronic acid (6%) (\( P < 0.0001 \)) and a non-significant trend towards higher osteonecrosis of the jaw was seen with denosumab (2.3% versus 1.3%; \( P = 0.09 \)) [12]. Calcium and vitamin D supplementation and monitoring of calcium levels while on therapy are essential to reduce the risk of hypocalcaemia.

In another placebo-controlled trial in non-metastatic CRPC, denosumab (120 mg monthly) significantly increased the bone-metastasis-free survival in patients with non-metastatic CRPC by a median of 4.2 months (29.5 versus 25.2 months; HR, 0.85; 95% CI, 0.73–0.98; \( P = 0.028 \)) [17]. Although hypocalcaemia was much lower in the setting of non-metastatic CRPC, the risk of ONJ was higher given the longer exposure time to denosumab [13].

### 2.3. Osteonecrosis of the jaw (ONJ)

Osteonecrosis of the jaw is defined as exposed necrotic bone in the maxillofacial region that persists for more than 8 weeks. The incidence of ONJ in patients with CRPC receiving denosumab was similar to that in patients receiving zoledronic acid [12]. Although the aetiology is unclear, duration of therapy, poor dental hygiene, invasive dental surgery or ill-fitting dentures, concomitant corticosteroid use, radiotherapy and chemotherapy are identified risk factors. A conservative approach to the management of ONJ is recommended and includes oral rinses, antibiotics, pain control and minimal surface bony debridement to reduce sharp or rough bone surfaces. Biopsies are not recommended unless metastasis to the jaw is suspected. Good oral hygiene, baseline dental evaluation for high-risk individuals and avoidance of invasive dental surgery during therapy reduce the risk of ONJ [14–16]. Most of the cases that were reported had had a tooth extraction or some other form of trauma that may have contributed to the development of ONJ. Most cases were treated conservatively, and less than 10% required bone resection. It is estimated that the risk is approximately 1–2% per year of exposure to bone-targeted therapies such as zoledronic acid and denosumab. Although bone-targeted therapy is beneficial, one must consider the risk of ONJ after 2 years of therapy when deciding whether to continue therapy.

### 2.4. Radiopharmaceuticals – (radium-223)

In a recently completed phase III study of patients with metastatic CRPC, patients were randomized on a 2:1 basis to either radium-223 (an alpha-emitting bone seeker) or placebo. To be eligible for the study patients had to have bone metastases and to have progressed after chemotherapy or were not eligible to receive chemotherapy. Patients received either radium-223 or placebo every 4 weeks intravenously. Overall survival (OS) was the primary endpoint. Median survival was 14 months for the treated patients as opposed to 11.2 months for those who received a placebo, conferring approximately a 30% improvement in OS (HR = 0.699, \( P = 0.0022 \)). The updated analysis involving 921 patients confirmed the radium-223 survival benefit (median, 14.9 months vs. 11.3 months; hazard ratio, 0.70; 95% CI, 0.58 to 0.83; \( P < 0.001 \)). The study also showed a 5-month delay in time to skeletal-related events. This agent has recently been approved by the FDA and is the first bone-targeted agent to demonstrate a survival advantage.

### 3. Conclusion

Patients with metastatic prostate cancer are at high risk for skeletal complications, including debilitating bone pain often requiring palliative radiation therapy, pathological fractures, and spinal cord compression. These complications impair quality of life and place a significant burden on health-care resources. They are due to the combined effects of bone metastases and ADT-related bone loss. The use of bone-targeted therapy (denosumab and zoledronic acid) has been shown to significantly delay and reduce the risk of these skeletal complications. Studies have also suggested that introduction of these therapies prior to PAIN or SREs may further improve efficacy. Denosumab (60 mg every 6 months) has recently been approved for prevention of bone loss related to ADT. Most recently the radiopharmaceutical, radium-223, was shown to delay skeletal complications and also to improve overall survival in patients ineligible for or having failed chemotherapy. The combination of early bone-targeted therapy followed by radium-223 later in the disease continuum appears to lead to further improvements in the management of bone metastases in CRPC.

Conflict of interest statement

Consultant and research conducted with Amgen, Bayer, Novartis.
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Current role of human papillomavirus in head and neck oncology

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Tobacco and alcohol were, until recently, considered to be the major risk factors in carcinogenesis of head and neck cancer (HNSCC). However, during the past decade a causal association between infection with human papillomavirus (HPV) and HNSCC has been established [1], and this ‘new’ aetiological factor has changed the conventional understanding of HNSCC because of the extensive influence of the virus on the epidemiology, clinical presentation and treatment outcome for patients with HNSCC.

Association with HPV is predominantly a matter of concern in tumours of the oropharynx, especially in tonsillar cancer [2,3], and a dramatic increase in the incidence of oropharyngeal cancer (OPC) has been reported in several Western countries over the past 30 years [4-8]. Based on the observations that, simultaneously, there has been an increase in the frequency of HPV-positivity among OPCs [4,9], infection with HPV seems to be the dominant cause of this development. Moreover, in the same time period a decrease in tobacco-smoking seems to be responsible for a reduction in the incidence of HNSCC outside the oropharynx [6], at least in Western countries. The natural history of oral HPV infection remains to be fully elucidated, and although the exact mechanism is not known, oral-genital contact is assumed to be the primary mode by which HPV is transmitted to the oral mucosa, and several case-control studies have shown an association between HPV-related HNSCC and sexual behaviour (reviewed by Gillison et al. [3]). The optimal method for detecting HPV in tumours is controversial, and both in-situ hybridisation and the polymerase chain reaction (PCR) are commonly used; p16-immunohistochemistry has gained broad acceptance as a surrogate marker and is also widely used in the clinical setting [10,11].

HPV-related HNSCC constitutes a clinically distinct subgroup of cancers in terms of molecular biology, patient characteristics and sensitivity to treatment, and this on the whole differentiates it markedly from HPV-negative tumours. The molecular profile of HPV-related HNSCC is distinct, with P53 degradation, retinoblastoma RB pathway inactivation and p16 up-regulation. By contrast, HPV-negative tumours are characterised by TP53 mutation and down-regulation of p16 [12,13]. Patients with HPV-related HNSCC tend to be younger, have less comorbidity and a better performance status [14-16], and are less declined to be abusers of tobacco and alcohol [6,15] compared with HPV-negative patients.

Tumour HPV status has a major impact on outcome for patients with HNSCC, and compared with HPV-negative patients, tumour-control and survival are highly significantly better for patients with HPV-positive tumours. This has been shown repeatedly in several clinical trials and with the use of a variety of different treatment schedules [17-22] and is believed to be caused in part by a higher sensitivity to radiotherapy of HPV-positive tumours, presumably because of the distinct molecular profile [23], combined with a better general health status in this group of patients. Smoking negatively affects survival in HNSCC, and the accumulated lifetime number of pack years independently impacts prognosis for both HPV-positive and -negative tumours [21,24]; implementation of smoking history in the risk stratification of HNSCC is under consideration.

As a consequence of this profound impact of HPV in HNSCC, this ‘new’ type of cancer has attracted a lot of attention, and separate therapeutic treatment strategies based on tumour HPV status are in the pipeline. In light of the enhanced sensitivity to treatment of HPV-related HNSCC, de-intensification of present treatment strategies in order to avoid excessive toxicity has been proposed for selected patients with minimal risk of distant metastasis [25]. On the other hand, patients with HPV-negative tumours have a very poor prognosis, and efforts should be made to improve treatment efficacy and compliance in this group of patients.

Conflict of interest statement

None declared.
REFERENCES


Novel therapeutic targets in diffuse large B-cell lymphoma

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Diffuse large B-cell lymphoma (DLBCL) represents the most frequent lymphoma subtype and is considered a heterogeneous diagnostic category [1]. Using gene expression profiling, two major molecular subtypes termed germinal centre B-cell-like (GCB) DLBCL and activated B-cell-like (ABC) DLBCL can be distinguished [2]. Their gene expression profiles suggest that they arise from B-cells at different stages of differentiation. The GCB DLBCLs appear to originate from germinal centre B-cells, whereas the ABC DLBCLs may arise from post-germinal-centre B-cells that are in transition to being differentiated into plasma cells. Intriguingly, these two subtypes differ not only with respect to the expression of thousands of genes, but also utilise different oncogenic pathways and have significantly different survival rates following therapy [3,4]. ABC DLBCLs are characterised by inferior survival compared with GCB DLBCL patients when treated with a combined approach of the anti-CD20 antibody rituximab and CHOP chemotherapy [5].

Recent advances in the understanding of the biology of these entities lead to the identification of a variety of potentially novel therapeutic targets for the treatment of affected patients. ABC DLBCLs are characterised by constitutive activation of the oncogenic nuclear factor-κB (NF-κB) pathway, which promotes cell proliferation and differentiation and suppresses apoptosis [6]. NF-κB signaling is mediated by a family of transcription factors that are normally kept inactive in the cytoplasm by binding to inhibitory IκB proteins. The constitutive activation of NF-κB in ABC DLBCL is caused in the vast majority of cases by somatically acquired mutations that affect positive (CARD11, CD79B and MYD88) and negative (TNFAIP3) NF-κB regulators [7–10]. Inhibition of NF-κB was toxic to preclinical models of ABC DLBCL [6]. Therefore, targeting the NF-κB pathway seems to be an attractive therapeutic approach. Such a strategy was taken by Dunleavy and colleagues in a recent phase II study in which the efficacy of bortezomib was investigated in DLBCL [11]. Preclinical data suggest that bortezomib inhibits NF-κB by blocking IκB degradation. The efficacy of bortezomib in combination with chemotherapy was evaluated in relapsed/refractory ABC and GCB DLBCL patients [11]. Interestingly, the response rates were significantly higher in ABC compared with GCB DLBCL, and even more importantly, patients with ABC DLBCL had a significantly superior overall survival. These results potentially suggest that inhibition of NF-κB might be a promising approach in ABC DLBCL. This hypothesis was further supported by recently presented data on the efficacy of the Bruton agammaglobulinemia tyrosine kinase (BTK) inhibitor ibrutinib [12]. BTK plays an important role in activating NF-κB following B-cell receptor stimulation. Using this inhibitor, impressive response rates in relapsed and refractory ABC DLBCL could be achieved. Collectively, these data indicate that inhibition of the oncogenic NF-κB pathway might be a future option to overcome the adverse prognosis of patients affected by ABC DLBCL.

While patients with GCB DLBCL are characterised by superior prognosis compared with ABC DLBCL [5], a substantial proportion of GCB DLBCL patients are not cured by standard treatment. GCB DLBCLs frequently express the transcriptional repressor BCL-6 that plays an important role in the germinal centre reaction. BCL-6 therefore might represent a novel target for GCB DLBCLs. In preclinical models, specific BCL-6 inhibitors showed impressive efficacy [13,14]. GCB DLBCLs are furthermore frequently characterised by deregulation of the phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway [4]. The PI3K signaling cascade is initiated with the phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3), resulting in cellular processes such as proliferation, cell survival and cell

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Various PI3K inhibitors are currently being evaluated in different cancer types and might represent a promising therapeutic approach in GCB DLBCL.

In summary, ABC and GCB DLBCL represent molecular subtypes that are dependent on different oncogenic signaling pathways. In clinical reality this biological diversity is still insufficiently taken into account. Efforts to distinguish these entities using gene expression profiling or next-generation sequencing will pave the way to more specific and less toxic treatment strategies.

Conflict of interest statement

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Novel treatment options in early-stage non-small-cell lung cancer

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1. Introduction

Early-stage lung cancer refers to patients presenting with clinical stages I and II non-small-cell lung cancer (NSCLC) according to the TNM classification. They represent approximately 20–25% of incident cancer cases in most population-based cancer registries, and radical surgical resection is considered the treatment of choice in operable and fit patients [1]. Although no prospective, randomised trial exists to compare surgery versus radiotherapy in the treatment of early-stage NSCLC, surgical resection has traditionally been considered the treatment of choice. Markedly improved survival rates are reported in surgical series in comparison to patients who did not undergo surgical resection for a variety of reasons [2]. This abstract will address some of the challenges of novel treatment options in these patients.

With low-dose computed tomography (CT) scan screening becoming the new standard of early detection of lung cancer, physicians and surgeons will be confronted with an increase in T1a lung cancer, disguised as non-calcified nodules. Although it is tempting to proceed to a parenchyma-sparing resection for issues of functional operability, the risk of local recurrence and inadequate intraoperative lymph-node staging should not be neglected. Whether some of these lesions can be treated by so-called sublobar resection – consisting of either anatomical segmentectomy or wedge excision – is currently the subject of intensive investigation by appropriate randomised trials. For a limited resection to be oncologically valid, a precise pre- and intraoperative diagnosis is imperative. In terms of preoperative diagnosis, specific criteria on chest CT as percentage ground-glass opacity (GGO), tumour shadow disappearance rate and histogram analysis have been shown to have a high predictive value [3]. Three similar trials – JCOG 0802 in Japan, CALGB 140503 in North America and IEO S638/311 in Italy – are currently enrolling patients, and collaboration is highly regarded [4,5].

More tailored, personalised surgical therapy has recently been introduced. Quality-of-life parameters and surgical quality indicators become increasingly important to determine the short-term and long-term impact of a surgical procedure. International databases currently collect extensive surgical data, allowing more precise calculation of mortality and morbidity according to predefined risk factors. Centralisation of care has been shown to improve results [6].

Functionally inoperable patients are nowadays proposed stereotactic ablative body radiotherapy (SABR), in which hypofractionated doses are administered over a short period of time [7,8]. Although lung-cancer-specific time-to-event outcome data seem very promising, unusual late toxicity is increasingly being reported, and there is concern regarding the inclusion of variable fractions of non-pathologically proven non-calcified nodules [9]. Clearly, before extrapolating these results to functionally operable patients, large randomised trials with an unequivocal non-inferiority design should be carried out [10]. Other radiotherapeutic techniques in development to improve local control with minimal pulmonary toxicity are the application of different breath control devices and the introduction of hadron/proton therapy.

Radiofrequency ablation is another way of tackling pulmonary masses and nodules whereby a transthoracic radirobe is inserted under CT guidance, allowing for a subsequent ‘cooking’ with electromagnetic energy. The technique is well known in the treatment of primary liver cancer and metastases, and several uncontrolled series have been reported in a mixed series of patients with primary lung cancer and lung metastases [11]. However, the technique lacks standardisation and long-term results, but is promising for centres which cannot afford SABR. There are currently no ongoing randomised trials [12]. An endobronchial application is certainly promising.

Adjuvant chemotherapy is the present standard of care in completely resected stages pII and III NSCLC, albeit toxicity is considerable and the observed improvement in outcome modest. Patient selection using molecular and biological biomarkers and signatures is likely to increase the fraction of patients benefiting from it. The large BIO-IALT study has described a number of prognostic and predictive factors, although recent reports challenge the accuracy of the
techniques used [13,14]. One of the most critical issues regarding tumour biomarkers concerns methodology. Techniques for carrying out the test, the reagents used, methods used to score/quantify the results, the analysis and interpretation of the results are all critical yet prone to variability and error. Some are more subjective than others; many are simple and readily available, others are complex, expensive and less accessible. Complexity does not guarantee accuracy, greater reliability or relevance. In terms of biomarker testing of tumour samples, the handling and processing of the tissues prior to testing is of critical importance yet difficult to standardise, but these factors are often ignored or overlooked [15].

Biomarkers might be selected for patients preferably treated with agents targeted at hallmark pathways of oncogenesis: e.g. sustained proliferation, angiogenesis and avoiding immune destruction. Trials investigating the efficacy of adjuvant epithelial growth factor receptor (EGFR) tyrosine kinase inhibitors, vascular endothelial growth factor (VEGF) inhibitors or vaccines against melanoma antigen (MAGE) are currently ongoing, and their results are expected to alter clinical practice [16,17].

Although neoadjuvant chemotherapy is better tolerated and its added value to outcome is similar to that of adjuvant, its widespread use suffers from a low rate of pathological remission, which is a precondition for a lesser resection to be carried out. Window-of-opportunity trials with neoadjuvant targeted agents and biological imaging are promising [18]. They have so far not been conducted in a biomarker-selected population.

The role of postoperative radiotherapy is currently limited to non-radically resected cases, although there are uncontrolled observations of its efficacy in subgroups of completely resected patients. In the ongoing randomised LUNGART trial, its role is explored in patients with clinical or pathological N2 disease [19].

An important handicap in present-day patient selection is the inaccuracy of clinical staging. Half or more of clinically staged patients are up- or down-staged at surgery [20]. Positron emission tomography–CT (PET–CT) scan and minimally invasive mediastinal ultrasound techniques are expected to improve on this figure and result in a stage shift.

Conflict of interest statement

None declared.

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Oncoplastic surgery – Standard of care

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1. Introduction

Over the last decade the whole approach to breast cancer surgery has changed radically from its ‘general surgery’ roots. There are few surgical specialties that have changed so much. The initial phase was the attention to wide local excision surgery, employing a more sensitive take on breast conservation, with scar placement and parenchymal reshaping. Then the concept of avoiding mastectomy by means of more extensive wide tumour excision together with partial breast reconstruction led to a flurry of innovations involving volume replacement and displacement techniques [1]. Oncoplastic breast surgery as a specialty now encompasses all elements of breast cancer surgery: appropriate cancer resection, skin-sparing mastectomy and immediate breast reconstruction, the full elements of total and partial breast reconstruction and adjustment for breast asymmetry by augmentation, reduction mammoplasty or mastopexy for the contralateral unaffected breast [2].

The legacy of historical surgical training has meant that until recently few surgeons have been equipped to offer this cancer surgery/cosmetic/reconstructive breast surgery hybrid approach. This is changing with training initiatives. Over the last decade approximately 90 surgeons in the United Kingdom have undergone 1-year-long senior fellowships in oncoplastic breast surgery in nine tertiary centres, trained by both breast and plastic surgeons seamlessly. This approach is changing the quality of surgical care for the benefit of women. It has also led to a rejuvenation of breast surgery away from purely resection-based operations that had remained unchanged for many decades, to an innovative specialty with creative concepts and aesthetic detail. In turn, the result in the UK has been marked interest amongst trainee surgeons to enter breast surgery as a career, and applications for the national fellowships are highly competitive.

Nevertheless much breast cancer surgery is still delivered by general surgeons, so care for individual women may involve surgeons from general as well as plastic/reconstructive surgery backgrounds now working together in an ‘oncoplastic multidisciplinary team’.

In 2007 extensive guidelines were developed in the UK to address inequalities in surgical provision. Oncoplastic Breast Surgery – a guide to good practice was a joint venture between the Association of Breast Surgery at BASO, the British Association of Plastic, Reconstructive and Aesthetic Surgery (BAPRAS), and the Breast Surgery Interface Training Committee at The Royal College of Surgeons of England [3]. This was intended to be for women with breast cancer, and all those involved in their care, to ensure the highest standards in setting up and delivering an oncoplastic breast service.

In 2012 the guidelines were revised and newly published, and constitute a fully comprehensive document describing high standards of care for all aspects of oncoplastic and reconstructive breast surgery. They also cover aspects of the processes, the patient’s journey and arrangements for both equipment needs and team participants. The advantage of the revision is that the 5 years’ experience in developing models of care has been incorporated by the multispecialty team of writers into the 2012 document. The UK document is unique in its ambition to raise surgical quality nationally, to ensure that patients are aware of what is available, and to inform surgeons, allied professionals and hospital administrators about what is required to provide a modern high-quality standard of care for women with breast cancer. These guidelines can be accessed online through either the Association of Breast Surgery or BAPRAS websites: ‘Oncoplastic breast reconstruction – Guidelines for Best Practice, 2012, Eds Dick Rainsbury and Alexis Willet’ [http://www.associationofbreastsgurgery.org.uk/media/23851/final_oncoplastic_guidelines_for_use.pdf].

The role of surgery in the management of women with breast cancer remains all important and fundamental. Its role in the prevention of breast cancer for women at high risk by virtue of family history or gene mutation is increasing.

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Conflict of interest statement

None declared.

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Role of aggressive surgery for peritoneal metastases

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1. Peritoneal cavity: a particular site of metastasis

The spatial conformation and the poor prognosis of peritoneal metastases (PM) make it an original entity. Once contaminated by tumour cells, disease spread is rapid and multidirectional over a surface that is equal to the body surface area in m². The prognosis of PM is poorer than that of metastatic spread elsewhere; patients with colorectal metastases treated with chemotherapy and targeted therapies have a median survival of 15 months with PM versus 21 months without PM (P < 0.001) [1]. The presence of PM is thus traditionally deemed a fatal event.

Complete cytoreductive surgery (CCRS) resects all visible peritoneal deposits, and the remaining invisible disease is subsequently treated with a high local concentration of chemotherapy potentiated by hyperthermia (HIPEC) in one session. This aggressive surgery can therefore be proposed only for disease confined to the peritoneum. According to the origin of the disease, such treatment is administered in two out of three colorectal carcinomas, one out of three gastric carcinomas, seven out of ten ovarian carcinomas, nine out of ten pseudomyxomas and eight out of ten mesotheliomas.

2. Aggressive surgery as a state of the art: pseudomyxoma and mesothelioma

CCRS + HIPEC is considered the gold standard treatment for these two peritoneal malignancies. In a retrospective multicentric registry, including 2298 patients with pseudomyxoma from 16 specialised units using this combined approach [2], median survival was 16.3 years and 10-year survival was 63%. Mortality was 2%, and major complications occurred in 24%. The main prognostic factors in the multivariate analysis were the histological subtype, a high extent score and no HIPEC. CCRS achieved the best outcome. Similar conclusions were drawn for malignant mesothelioma in a multi-institutional registry including 405 patients [3] in which only 46% underwent CCRS. Median survival was 53 months and 5-year survival was 47%.

3. Aggressive surgery as a new therapeutic approach: colorectal carcinoma

3.1. Long-term results after CCRS plus HIPEC

Ten years ago the results of a randomised study [4] – which included 105 patients treated for colorectal PM (systemic chemotherapy versus surgery plus HIPEC) – demonstrated significantly prolonged survival in patients treated with surgery plus HIPEC, with a median survival twofold higher (P = 0.03), although CCRS was achieved in only 38% of cases. This was confirmed in another study [5] comparing two similar groups in terms of the main patient characteristics. All patients underwent a laparotomy and had resectable PM; 48 patients were treated with CCRS + HIPEC in one centre, and 48 were treated in five other centres without HIPEC. After a minimal follow-up of 63 months, 5-year overall survival was 51% in the CCRS + HIPEC group and 13% for patients in the no-HIPEC group (P < 0.05).

Long-term results of primary CCRS + HIPEC demonstrated that definitive cure of PM was possible in 16% of the 93 patients treated between 1995 and 2004 [6], a rate which is close to that obtained with a similar long follow-up after hepatectomy for liver metastases (LM). Median survival was 36 months at that time, but attained 48 months in 2011 [7], emphasising a learning-curve effect and better patient selection.

CCRS + HIPEC is wrongly reputed to cause excessive morbidity, but in specialised centres and in selected patients mortality is lower than 5% and grade 3–4 morbidity is lower than 30%.

Aggressive surgery plus HIPEC is also considered costly, but its clear superiority over the usual palliative therapies in terms of QALY (cost-efficacy) has been demonstrated.

Regarding prognostic factors, the results of the French Registry – which analysed 523 patients treated with CCRS + HIPEC – showed that the extent of PM (scored with the peritoneal cancer index, PCI) is the main prognostic factor [8]. There were no survivors when the PCI exceeded 20, and we now consider a PCI above 20 to be a contraindication.
3.2. Role of complete cytoreductive surgery alone

No randomised study has compared CCRS to systemic chemotherapy. The results of four retrospective series provide some elements of response: median survival was 28 months, with 5-year survival at 24%, showing clear but limited superiority over systemic chemotherapy alone. In contrast, an incomplete resection (R2) afforded no advantage, with survival rates similar to those reported with chemotherapy alone [8]. In conclusion, CCRS benefits patients with limited PM and a good general status.

3.3. Role of hyperthermic intraperitoneal chemotherapy

No randomised study has been published to date. We are awaiting the results of Prodige 7, the French randomised trial comparing the survival of patients treated with CCRS + HIPEC to that of patients treated with CCRS alone, whose accrual was recently completed (n = 260). This study will define the real impact of HIPEC.

3.4. Future

As this aggressive surgery gives far better results for limited PM, it should be used mainly to treat patients at a very early stage, but early diagnosis of PM cannot be done by clinical or imaging examinations. Only systematic second-look surgery (SLS) can detect PM early, but this aggressive approach should be proposed exclusively in patients at high risk of PM. In such patients (limited PM resected with the primary, a history of ovarian metastases and a perforated primary tumour) with no preoperative evidence of PM, SLS has allowed us to find macroscopic PM in 55% of cases [9], and to treat PM earlier with CCRS + HIPEC. A randomised multicentric trial (Prophylochip) comparing the standard treatment (follow-up) in these high-risk patients to the new one (second-look + HIPEC) is ongoing.

4. CCRS + HIPEC to treat PM of other origins

Indications are in progress for ovarian-, gastric-, NET- and rare disease-derived PM. The initial results of CCRS + HIPEC were disappointing, but progress in techniques and in indications in ongoing prospective trials is giving promising results.

5. Conclusion

CCRS + HIPEC yields long-term survival in patients with PM. No clear and widely accepted definition of resectable PM exists. However, we postulate that when the patient has a good general status and when the extent of PM is limited, without extraperitoneal disease, this approach is beneficial.

Conflict of interest statement

None declared.

References

Successful clinical translation of preclinical combinations of radiation and immunotherapy

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1. Introduction

Ionising radiation (IR) can induce immunogenic cell death in tumours, an effect likely to contribute to the success associated with radiotherapy (RT) for cancer. Recent studies suggest that radiotherapy can be applied as a powerful adjuvant to immunotherapy, and can even contribute to converting the irradiated tumour into an in situ vaccine, resulting in specific immunity against metastases [1].

Importantly, preclinical models of syngeneic tumours have reliably predicted clinical success in several distinct tumour settings and with several different immunotherapy/radiation combinations. As a proof-of-principle trial, we have translated the preclinical evidence of a successful combination with Flt3 ligand and RT to a protocol of granulocyte–monocyte colony-stimulating factor (GM-CSF) and IR, and demonstrated out-of-field objective responses in 27% of patients with multiple metastases of solid tumours, defined as an abscopal effect [2].

In parallel, mechanistic studies in the laboratory were conducted in the syngeneic mouse models of metastatic breast cancer. Results showed that radiation was synergistic with anti-CTLA-4 treatment, a strategy to break immune tolerance to the tumour. Multiple mechanisms contributed to this synergy, including the RT-induced upregulation of a chemokine that promoted homing of effector T cells to the tumor. Intravital microscopy demonstrated that while both IR and CTLA-4 blockade given as monotherapy enhanced the motility of activated CD8 T cells infiltrating 4T1 tumours, IR with anti-CTLA-4 increased the arrest of T cells in contact with tumour cells, promoting the formation of an immune synapse between cytotoxic T cells and their targets. The latter required interaction between NKG2D on CD8+ T cells and its ligand, retinoic acid early inducible-1 (Rae-1), on the tumour cells, which was up-regulated by IR. Blocking NKG2D–Rae-1 interactions markedly increased the motility of anti-CTLA-4 treated T cells within irradiated tumours, inhibiting their contact with tumour cells and also abrogated immune-mediated tumour rejection [4].

The preclinical success of the combination of anti-CTLA-4 antibody and IR was mirrored by abscopal responses seen in metastatic melanoma and non-small-cell lung cancer (NSCLC) patients irradiated in one lesion during ipilimumab therapy. These clinical observations strongly suggest that the effects of IR identified in experimental models are relevant to patients. IR can stimulate the anti-tumor immune response, increasing the proportion of patients who respond to checkpoint blockade treatment, an hypothesis currently being tested in clinical trials. The same pattern of abscopal responses has been observed in preclinical models was also demonstrated in clinical cases of lymphomas and breast cancers treated by combinations of RT and toll-like receptor agonists. Finally, blocking tumour growth factor beta (TGF-beta) during RT preclinically has demonstrated abscopal effects that have been confirmed in one patient accrued to a trial of anti-human TGFβ antibody fresolimumab and RT. While promising, this evidence remains preliminary and warrants more research to define the optimal combinations of immunotherapy and RT, to best exploit this novel role of ionising radiation [3].

Conflict of interest statement

The content to be presented at 17th ECCO – 38th ESMO – 32nd ESTRO European Cancer Congress does not pose any conflict of interest.

REFERENCES

At what price do we treat patients with testicular cancer?

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In 2013 testicular cancer (TC) represents the most curable solid tumour. The high cure rate is associated with a significant long-term morbidity. Long-term effects after TC treatment can be divided into life-threatening (e.g. secondary tumours and cardiovascular disease) or effects on single organs (e.g. nephro-, neuro- and pulmonary toxicity, hypogonadism or decreased fertility). Psychosocial effects are also a major issue, with fatigue, influence on sexuality, work, cognitive function, quality of life, lifestyle factors, etc. Some of these side effects are discussed below, with a focus on future studies. Testicular cancer survivors are at significantly increased risk of solid tumours for at least 35 years after treatment, with a higher incidence in patients who have had a seminoma compared to non-seminoma [1,2]. However, published studies lack detailed information concerning treatment or refer to formerly used treatments.

Several studies have demonstrated increased risk of cardiovascular disease [3–7]. A Norwegian study found a 5.7-fold higher risk for coronary artery disease after bleomycin, etoposide and cisplatin (BEP) treatment, with a median observation time of 19 years [3]. Hypogonadism, hyperlipidaemia [4] and metabolic syndrome [4,7] have been mentioned as risk factors. Metabolic syndrome in particular could be linked to subclinical testosterone deficiency.

It is necessary to increase our knowledge concerning the impact of cisplatin-based chemotherapy, lifestyle factors (diet, tobacco, physical activity), hypogonadism, family history concerning cardiovascular disease (CVD), alcohol, abnormal blood samples and gene changes on the development of cardiovascular disease in TC patients. Given the increased incidence of CVD in TC patients it would be relevant to look at genetic markers which in the general population have been found to predispose to these diseases. To develop risk models that include the above-mentioned factors, international cooperation is needed. This could make it possible to stratify TC patients into risk groups and develop evidence-based intervention according to the risk factors.

Testicular cancer patients should be tested for subclinical hypogonadism. We know that after treatment, the serum testosterone concentration is in the lower part of the normal range [8] and that 12–16% of long-term survivors have developed hypogonadism. Most younger TC patients exhibit some dysfunction of the Leydig cells, which is compensated by an increase in luteinising hormone (LH) levels. Whether this compensation is adequate in elderly TC patients is not known. The clinical significance of low testosterone levels is under discussion, but most people believe that a sustained reduction in testosterone is a contributing factor in the development of metabolic syndrome, type-2 diabetes, osteoporosis, decreased quality of life and premature ageing [9]. Hypogonadism could be a significant and independent predictor for the development of CVD, and if this is the case, testosterone replacement should be examined.

All TC patients treated with cisplatin will experience a decline in glomerular filtration rate (GFR). This reduction will in some patients be reversible, whereas in others GFR shows a permanent decrease of up to 30% or more [10,11]. There is no long-term monitoring of renal function in TC patients treated with cisplatin. Experimental and clinical data suggest that hypomagnesaemia is important for the development of nephrotoxicity [12]. There are several unanswered questions related to nephrotoxicity in this group of patients. It is unknown whether the natural age loss in GFR is accelerated in TC patients treated with platinum or whether the nephrotoxicity is exacerbated in older platinum-treated TC patients. Another important issue to clarify is the influence of a decline in GFR on the development of cardiovascular disease and death from all causes.

The high survival rate and young age of patients with TC entails that the treatment effect on reproductive function, fertility and offspring health is a very significant factor. Affected Sertoli-cell function and impaired Leydig-cell function in a subset of TC patients result from testicular dysgenesis syndrome [13] which may explain the increased incidence of oligo-and azospermia in TC patients both before and after orchiectomy, but before further treatment.

Most long-term survivors after treatment for TC can become biological fathers without medical assistance [14].
the 10-year paternity rate is reduced by 30% compared with the normal population. All studies concerning gonadal function in TC patients is based on data from a single department, with a limited number of patients and few details about the treatment.

With the development of modern assisting reproductive techniques, even men with significant gonadal dysfunction will be able to have children. Cryopreservation of semen, optimally performed before orchiectomy, is offered in most places in order to increase the likelihood of subsequent fatherhood. In view of the increased opportunity and use of frozen semen for later artificial insemination, it is important to clarify whether pregnancies obtained with frozen semen of low quality are subject to more abortions, stillbirths or deformed children. These data will be essential in order to advise the TC patients. Larger-scale data concerning fertility in patients with TC treated with either surveillance or chemotherapy (three or four cycles of BEP) are needed.

Data regarding the factors leading to long-term side effects of treatment remain scarce. Molecular testing methods might help in identifying patients at high risk for therapy-related complications and guide risk-adapted screening and intervention strategies. In recent years, screening for variations in polymorphisms has proved to be a valuable tool to investigate the genetic predisposition for late effects. There is a relatively high incidence of single-nucleotide polymorphisms (SNPs) in genes which affect the cellular response in relation to the cytotoxic treatment for TC [15].

In order to gain further knowledge on the development of late effects in TC patients we need to have detailed information about treatment, to include genetic research methods, and to study side effects over time. The hope is that increased knowledge can lead to interventional studies with reduction or prevention of late effects.

REFERENCES

Collaborative international oncology nursing research is improving but still has a long way to go! Experiences, possibilities and challenges

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In this interactive teaching lecture I will draw on my experiences from a variety of successful and less successful international research projects, with roles as researcher, collaborator and advisor. Topics that will be addressed include the process from vision to collaboration, benefits of collaboration, the need for and qualities of leadership in driving such projects, key components of collaborative endeavours and challenges faced in forming and carrying out research collaborations. Discussion of these topics will be based on ongoing and completed collaborative projects. Reflections from the participants are welcome throughout the session.

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Epidermal growth factor receptor targeting and its role for individualisation in radiation oncology

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Because of its over-expression in many human tumours and its association with a poor prognosis, the epidermal growth factor receptor (EGFR) is used as a therapeutic target in clinical routine and in clinical trials. Two major classes of inhibitors are used: anti-EGFR antibodies and EGFR tyrosine kinase inhibitors (TKIs). On simultaneous application of the anti-EGFR antibody cetuximab with radiotherapy in head and neck squamous-cell carcinoma (HNSCC) patients, an improvement in locoregional tumour control and survival has been shown as compared with radiotherapy alone, leading to the approval of this drug as the first molecular targeted agent in a curative radio-oncological setting. However, so far there is no hint of a superiority of this combination over simultaneous cisplatin-based radiochemotherapy; thus, both treatments are used today as alternative schedules.

While it is evident from preclinical as well as from clinical data that a major heterogeneity exists among the responses of individual patients to the combined treatment, apart from skin reactions under cetuximab treatment, there is so far no validated biomarker predicting response to cetuximab-based combined treatment, nor to cisplatin-based radiochemotherapy. Establishing predictive biomarkers would highly increase efficacy of the treatment due to the positive selection of patients. Some conclusions can currently be drawn from translationally oriented studies: at least for HNSCCs (others have not been well investigated), cetuximab application during radiotherapy improves locoregional tumour control in many but not all individual tumours, with individually impressive responses. For EGFR–TKI all local tumour control studies have been negative so far, whereas palliative effects have been shown in most HNSCCs. A promising candidate biomarker for the effect of combined radiotherapy and cetuximab in HNSCC is genetic EGFR over-expression measured by the fluorescence in situ hybridization (FISH) test. This marker has to be further validated in clinical settings, as well as for other tumour entities or combination schedules. Because of interactions between the treatment modalities, such biomarkers can be different between single-modality and combined-modality treatments.

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FURTHER READING


Squamous-cell carcinoma of the head and neck is the fifth commonest neoplasm worldwide. Over 50% of patients present with stage III/IV disease: so-called locally advanced head and neck cancer (LAHNC). For LAHNC, the treatment paradigm has shifted from mutilating, ablative surgery towards organ-preserving concomitant cisplatin-based chemoradiotherapy [1]. Compared with surgery, chemoradiotherapy delivers equivalent or better locoregional control and disease-free survival with significantly better functional outcomes [1]. Nonetheless, 5-year disease-free and overall survival (30–40%) rates are suboptimal [2]. Strategies to improve outcomes by escalating conventionally delivered radiotherapy and/or cytotoxic chemotherapy are appealing, but they pose unacceptable risks of severe acute and late normal tissue damage and threaten chronic structural, cosmetic and functional deficits that negatively impact quality of life [3].

Recent technical developments in physical targeting of radiation delivery, including intensity-modulated and image-guided therapy, offer a way of safely escalating tumour dose without exceeding normal tissue tolerances. Also, a clearer understanding of the radiation-induced DNA damage response (RIDDR) opens up the possibility of developing tumour-selective biological response modifiers to enhance the effect of radiotherapy/chemoradiotherapy. The potential value of such therapies has been proven by the translation of therapy targeted to the epidermal growth factor receptor (EGFR), cetuximab, from preclinical studies to a positive phase III trial in combination with radiation [4]. In addition, small-molecule tyrosine kinase inhibitors have been tested [5,6].

Recently, biological studies have characterised LAHNC as a disease spectrum, divisible into different prognostic groups on the basis of demographic (tobacco exposure), clinical/radiological (T and N stage) and molecular pathological (human papillomavirus (HPV) status) variables [7]. In addition, we are beginning to understand the molecular landscape of LAHNC more clearly [8]. As a result, we can escape the standard model whereby all patients receive treatment according to a ‘one size suits all’ philosophy. Instead, we are moving towards treatment individualisation according to prognostic risk group.

Until recently, it was accepted that the standard of care for patients with LAHNC was concomitant cisplatin-based chemoradiotherapy. However, recent data on prognostic subgroups suggest that this is a significant oversimplification: patients with poor prognosis disease may receive suboptimal treatment, while those with good prognosis disease may be over-treated with unnecessary risks of toxicity. Therefore, there has been a realignment towards developing effective, molecularly targeted strategies that offer personalised treatment to individual patients based on prognostic factors. The clearest view of prognosis comes from post hoc analysis of patients with oropharyngeal cancers treated in the RTOG-0129 phase III trial [7]. This study defined prognostic groups using specific demographic, clinical/radiological and molecular pathological characteristics: (1) poor-risk disease affected 27% of patients with heavy tobacco use, T4 tumours and HPV/p16\(^{INK4a}\)-negative status; (2) low-risk disease occurred in 43% with HPV-positive status and little prior tobacco exposure (or, if >10 pack-year smoking history, by N0–N2a nodal status) and (3) intermediate-risk disease was represented by the 30% with either HPV-positive tumours and >10 pack-year tobacco exposure and N2b/N3 neck disease or HPV-negative tumours and <10 pack-year tobacco exposure and T2/T3 tumours.

A particularly attractive approach to targeted therapy focuses on developing combinations of radiotherapy or chemoradiotherapy with targeted agents that modulate RIDDR to exploit differences between malignant and normal tissues. Mutations in p53 have been reported in many LAHNC and correlate with exposure to tobacco/alcohol. p53-mutant LAHNC show relative resistance to radiation, as evidenced by increased locoregional recurrence rates after radical or adjuvant irradiation [9], and reactivation of p53 has been shown to increase responses to radiation/chemoradiation. In addition, abnormalities in DNA repair signalling involving ataxia-telangiectasia mutated (ATM) and meiotic recombination 11 (MRE11) upstream of p53 are associated with radioresistance.
In contrast, HPV-positive LAHNC does not harbour disruptive p53 mutations but, rather, p53 is inactivated by HPV-E6 [10]. In both situations, functional loss of the p53 pathway renders tumour cells reliant on effective G2/M cell cycle checkpoint control (Fig. 1). Also, the importance of repair of single-strand DNA breaks, especially in the context of deficiencies in homologous recombination, is well recognised, and targeting this pathway has been shown to increase the response of head and neck cancer cells to radiation in vitro and in vivo [11].

There is now significant experience in translational pre-clinical/clinical studies of small molecules and biological agents in LAHNC. In newly-diagnosed LAHNC, agents that target cell cycle checkpoint kinase 1 (Chk1) and heat shock protein-90 (HSP90) have provided proof-of-principle for the potential radiosensitising effects of modulating DNA damage responses at the G2/M checkpoint. Chk1 is key in cellular responses to DNA damage and replication stress. It is phosphorylated in an ataxia telangiectasia-mutated- and Rad3-related-(ATR-)dependent manner that is required to trigger the G2/M checkpoint. Chk1 inhibition, either by relatively specific Chk1 inhibitors or multi-targeted agents (heat shock protein (HSP90) inhibitors), is likely to exert potent radiosensitisation in both prognostic subgroups.

![Fig. 1 – Mechanistic basis for targeting S and G2/M checkpoint control in locally advanced head and neck cancer (LAHNC). In human papillomavirus (HPV)-negative, intermediate-/poor-risk disease, p53 mutations render tumour cells reliant on S and G2/M checkpoints to repair radiation-induced DNA damage. HPV-positive, low-risk disease will also rely on this checkpoint (due to viral E6-mediated degradation of p53). Chk1 inhibition, either by relatively specific Chk1 inhibitors or multi-targeted agents (heat shock protein (HSP90) inhibitors), is likely to exert potent radiosensitisation in both prognostic subgroups.](image)

In summary, our improved knowledge of the molecular biology of LAHNC has revealed that specific disease subtypes may be amenable to personalised treatment approaches. The challenge for the next decade is to optimise these treatments to improve antitumour effects and to minimise toxic effects in normal tissues.

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REFERENCES


Metastatic melanoma: New paradigms of treatment and new toxicities

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1. Introduction

Metastatic melanoma was historically designated the “drug killer cancer” because for decades no drug had demonstrated any benefit in terms of overall survival (OS) for patients with metastatic melanoma. This situation has radically changed over the last 2 years. Melanoma appears today as a “pilot” disease for which the most innovative therapeutic strategies have demonstrated significant efficacy. The two strategies are immunotherapy on the one hand and targeted therapy on the other. These two significant breakthroughs led to the authorisation in the United States (US) and in Europe of two drugs: the anti-BRAF agent vemurafenib and the anti-CTLA-4 monoclonal antibody ipilimumab. More recently, two additional targeted agents, dabrafenib and trametinib, were authorised in the US. Moreover, the field continues to improve with the exciting development of new drugs following these two new approaches.

2. Immunotherapy: anti-CTLA-4 and anti-PD-1

The anti-CTLA-4 monoclonal antibody ipilimumab was the first drug ever to demonstrate a significant OS benefit in the context of a randomised phase III trial [1]. This pivotal trial showed that ipilimumab at the dose of 3 mg/kg, alone or in combination with a peptidic vaccine and compared with vaccination alone, prolonged the survival of patients with pretreated metastatic melanoma. Median OS of patients was around 10 months with ipilimumab versus 6.4 months with the vaccination. A second pivotal trial evaluated ipilimumab at 10 mg/kg, combined with the standard chemotherapy dacarbazine (DTIC), compared with dacarbazine alone in first-line treatment. The ipilimumab-containing arm demonstrated a significant survival benefit compared with dacarbazine alone (HR = 0.72; \( P < 0.001 \)) with a median OS of 11.2 months versus 9.1 [2]. This trial did not suggest that the combination of DTIC with ipilimumab added any benefit, but rather added toxicity, especially in terms of hepatotoxicity.

Clinical results with ipilimumab are characterised by low objective response rates, usually below 20%, but frequent long-term responses. Responses are often delayed, being observed after at least 4 months following initiation of therapy, and can even occur after an initial tumour progression or the appearance of new lesions.

As expected for a new mechanism of action, blocking CTLA-4 is associated with a new spectrum of adverse events. These are frequent, occurring in 40% of the patients and are mostly immune-related, as expected for an immunostimulatory agent. The most frequent side effects are skin rashes, diarrhoea and colitis resembling Crohn’s disease, hypophysitis and hepatitis. Adverse effects usually resolve spontaneously or after steroid therapy. High-dose steroids have to be prescribed in cases of severe immune-related adverse events; rarely, stronger immunosuppressive agents, such as anti-TNF-alpha (infliximab), can be needed.

Challenging questions remain to be answered to optimise the efficacy of this new treatment. Indeed, the survival benefit concerns few patients, and we currently lack predictive clinical or biological markers of response. Furthermore, the two pivotal trials have explored two different doses, 3 or 10 mg/kg, and two schedules of follow-up treatment designs. Thus, the optimal administration schedule is still unknown.

Programmed death-1 receptor (PD1) and its ligand (PD-L1) are new, highly promising targets in immunotherapy. PD1 protein is another immune checkpoint expressed on many T cells in response to inflammation. The engagement of PD1 on the lymphocyte surface by one of its ligands, PD-L1, that can be expressed on melanoma cells, delivers inhibitory signals resulting in T-cell function down-regulation [3].

In contrast to CTLA-4/CD28 interaction that down-regulates T-cell activation in lymphoid organs during naïve T-cell
BRAF and MEK are protein kinases involved in the MAP-kinase pathway that is activated in the vast majority of melanomas due to BRAF, NRAS, MEK and KIT mutations in (respectively) about 50%, 15%, 8% and 3% of the cases [7].

Very compelling results of phase I trials evaluating two anti-PD1 antibodies nivolumab and lambrolizumab were recently published [4,5]. Various dose and schedule regimens were evaluated in phase I trials. Response rates were around 30–40% for both antibodies, with the vast majority of responding patients still in response after median follow-up durations of more than 1 year. The safety profiles of these new anti-PD-1 agents seem tolerable, with 10–12% of grade 3 or 4 adverse events, usually manageable except in rare cases of severe pneumonitis.

Combined blockade of PD-1 and CTLA-4 has also been explored in a phase I trial in 86 patients, and also gave extremely promising clinical results with tolerable adverse events [6].

Combination of nivolumab and ipilimumab was associated with a 53% rate of treatment-related adverse effects that most frequently corresponded to changes in biological parameters (lipase, transaminase elevation) with no clinical manifestation.

3. The second strategy relies on the use of targeted drugs: anti-BRAF and anti-MEK agents

BRAF and MEK are protein kinases involved in the MAP-kinase pathway that is activated in the vast majority of melanomas due to BRAF, NRAS, MEK and KIT mutations in (respectively) about 50%, 15%, 8% and 3% of the cases [7].

Among BRAF mutations, the most frequent one – accounting for more than 90% of the somatic mutations of this oncogene – results in the V600E amino acid replacement. Small kinase inhibitors directly targeting the mutated BRAF protein have been developed. The first one, vemurafenib, was recently approved as a first-line treatment for patients with unresectable or metastatic melanoma harbouring the V600E BRAF mutation, based on the results of a randomised phase III trial showing a significant improvement in overall survival with vemurafenib (HR: 0.37, P < 0.001) and a median progression-free survival (PFS) of 5.3 months versus 1.6 months (HR: 0.26, P < 0.001) with dacarbazine and a high response rate around 50% [8]. Dabrafenib, another BRAF inhibitor, showed similar results in terms of PFS and objective response rate (ORR), but could not demonstrate OS benefit because the design of the phase III trial included a cross-over [9].

BRAF inhibitors are usually well tolerated, the most common adverse events being arthralgia (56% of the patients), fatigue (46%) and cutaneous manifestations such as rash (41%), photosensitivity (41% for vemurafenib only) and squamous-cell carcinoma of the keratoacanthoma-type (10–25% of the patients depending on the type of BRAF inhibitor used).

However, two major concerns are associated with all specific BRAF inhibitors evaluated so far. The most challenging is the short median duration of the clinical responses, with most of the patients relapsing in the 4–12 months after initiation of therapy. Numerous distinct resistance mechanisms have been identified that can reactivate the MAPK pathway (ERK-dependent) or use additional proliferation pathways [10].

The second issue when using these agents is that they paradoxically activate the MAPK pathway in cells devoid of BRAF mutation, especially in the presence of an additional somatic event occurring in this pathway, such as a RAS mutation. This explains the appearance of squamous-cell neoplasia (keratoacanthomas and squamous-cell carcinomas) as well as new melanomas in a subpopulation of patients [11].

One strategy to decrease secondary resistance as well as neo-tumourigenesis associated with anti-BRAF monotherapy is to combine it with an inhibitor of MEK1 and MEK2 downstream from BRAF. Indeed, several MEK blockers are in development, and one of them, trametinib, has shown a significantly increased PFS in patients with V600E metastatic melanoma in a phase III randomised trial, and was recently approved by the FDA [12]. Another MEK Inhibitor, selumetinib, also demonstrated an improvement in PFS when combined with dacarbazine compared with dacarbazine plus placebo in a randomised phase III trial [13]. Anti-MEK drugs are associated with numerous skin side effects, as are most anticancer targeted agents, but potentially serious adverse events involving the retina and myocardia are rare and mostly reversible.

The most promising approach at present is the combination of BRAF and MEK inhibitors. Indeed, this approach not only seems to give higher response rates and longer PFS but is also associated with a significantly decreased incidence of neo-skin-derived proliferation [14].

4. Conclusion

A revolution in the metastatic melanoma treatment paradigm is going on. We now have several effective weapons via both the immunotherapy and the direct targeted therapy approaches. Our challenges are to optimise the design of treatments in terms of combination and/or sequences and to optimise safety regarding the new adverse events that are occurring.

Conflict of interest statement

Caroline Robert is a consultant for Roche, BMS, Merck, Novartis and GSK.

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Pharmacogenetics in the clinic

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Pharmacogenetics is one of the first clinical applications of the postgenomic era; it studies the role of heritability of drug responses. It promises personalised medicine rather than the established 'one size fits all' approach to drugs and dosages. This should ultimately lead to more efficient and safer drug therapy. In recent years, pharmacogenetic information has been included in drug labels (especially for oncology drugs), and commercially available pharmacogenetic tests have been approved by the Food and Drug Administration (FDA), but their application in routine patient care remains limited. Indeed, the implementation of pharmacogenetics in routine clinical practice presents significant challenges. The clinical value and the interpretation of pharmacogenetic tests are found difficult. Now, pharmacogenetics-based therapeutic (dose) recommendations, based upon the systematic review of the literature, are available for 53 drugs associated with genes coding for CYP2D6, CYP2C19, CYP2C9, thiopurine-S-methyltransferase (TPMT), dihydropyrimidine dehydrogenase (DPD), vitamin K epoxide reductase (VKORC1), uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), HLA-B*44, HLA-B*5701, CYP3A5 and factor V Leiden (FVL). These two large initiatives are made available through the pharmacogenomics knowledge base and may help clinicians to make use of current pharmacogenetic knowledge. In the teaching lecture specific clinical examples of challenges for implementation of pharmacogenetics are discussed, and best practices for implementation will be presented.

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None declared.

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Radiotherapy for rectal cancer: Short course versus long course – When and how

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Prior to the introduction of improved surgical techniques such as total mesorectal excision, local recurrence rates after resection were unacceptably high with surgery alone. Phase III trials were designed to determine the benefit of the addition of radiotherapy to radical surgery, and these have reported significant reductions in local recurrence.

Two different strategies were evaluated in the preoperative setting. Initially in Scandinavia the approach of a hypo-fractionated 1-week course of radiotherapy performed prior to radical surgery was evaluated in a series of phase III trials. In contrast, the strategy of integrating fluoropyrimidine chemotherapy with long-course fractionated radiotherapy in the postoperative setting was then evaluated preoperatively. Two key trials determined that the addition of fluoropyrimidine to neoadjuvant radiotherapy compared with radiotherapy alone significantly reduced the risk of local recurrence.

Following the increasing use of total mesorectal excision and the associated lower rates of local recurrence, in the Netherlands and in the United Kingdom (UK) two phase III trials were conducted. The Dutch TME and MRC CR07 trials showed a reduction in local recurrence from the addition of short-course preoperative radiotherapy but without any impact on overall survival.

The two strategies (short-course and long-course treatment) have developed in parallel. This leads to a number of questions:

- When preoperative radiotherapy is combined with radical surgery to reduce the risk of local recurrence, is there any difference in the efficacy of the two approaches?
- Is there any difference in the acute toxicity of the two approaches?
- Is there any difference in the late toxicity between the two approaches?

Two phase III trials have directly compared short-course preoperative radiotherapy followed by immediate surgery versus long-course concurrent chemoradiotherapy followed by a delay in surgery. The Polish trial was designed to determine whether long-course chemoradiotherapy would increase the chance of sphincter preservation, whereas the TROG trial was designed to compare local recurrence rates between the two approaches.

Given the relatively low rates of local recurrence seen in routine clinical practice and within the trials, both studies are underpowered for a formal comparison of efficacy. However, neither trial has reported a significant difference in local recurrence between the two approaches.

With respect to acute toxicity, long-course chemoradiotherapy is associated with the concomitant administration of fluoropyrimidine chemotherapy. The acute toxicity is higher with this approach compared with short-course hypo-fractionated radiotherapy. In terms of long-term toxicity, neither the Polish nor the TROG trials have reported any evidence of any significant difference in late toxicity between the two approaches.

The trials that have compared these two approaches have focused on the neoadjuvant use of radiotherapy combined with radical surgery. The current evidence does not suggest any major differences in efficacy and long-term outcome in patients with resectable disease. However, where the margin of excision is threatened or involved, current consensus is that long-course chemoradiotherapy is the preferred approach. There are limited non-randomised studies that have reported the use of short-course preoperative radiotherapy followed by an elective delay to surgery from both Sweden and Leeds. There are also comparative interim data from the Stockholm III trial. Short-course preoperative radiotherapy followed by an elective delay to surgery is a treatment option that could be considered in patients who are considered unsuitable for concurrent chemoradiotherapy.

The use of these two radiotherapy strategies needs to be considered within the changing landscape of rectal cancer management. There is increasing interest in organ-preserving approaches where surgery is deferred or avoided. In this context dose escalation of the radiation dose is likely to increase the complete response rates. This approach is more easily and safely obtained by dose-escalating long-course 1359-6349/$ - see front matter Copyright © 2013 ECCO - the European CanCer Organisation. All rights reserved. http://dx.doi.org/10.1016/j.ejcsup.2013.07.044
concurrent chemoradiotherapy. Dose escalation of short-course radiotherapy should be approached with caution and within the context of a clinical trial. The efficacy of short-course radiotherapy and delay in early rectal cancer is the subject of an ongoing study within the UK (TREC). The Dutch CARTS study has evaluated chemoradiotherapy followed by local excision.

A further area of interest is the use of neoadjuvant chemotherapy that is integrated closely with neoadjuvant radiotherapy. In this context the use of short-course radiotherapy may have some advantages and needs to be tested in clinical trials. This will be illustrated by discussion of both the European RAPIDO and the North American PROSPECT trials.

Conflict of interest statement

The author is the Chief Investigator of the MRC CR07 trial.

FURTHER READING


State of the art in neoadjuvant therapy of breast cancer

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1. Introduction

Neoadjuvant therapy is no longer an option just for locally advanced operable cancers in order to facilitate breast-conserving surgery, but also for all early breast cancers when an indication for chemotherapy is given [1]. Pathological complete response (pCR) – defined as the absence of residual invasive or sometimes even in-situ cancer on breast and lymph nodes after preoperative therapy – has been shown to predict long-term outcome in patient-based analyses of several randomised clinical trials [2–4]. Achieving pCR is important mainly for those patients with an unfavourable initial prognosis, such as HER2-positive/hormone-receptor- (HR-)negative, triple-negative breast cancer (TNBC) and some luminal-B-like tumours. In contrast, the survival benefit of patients with pCR was less pronounced in luminal-A-like tumours (HR-positive, HER2-negative, grade 1–2) [2,4].

Because of the different behaviours of breast cancer subtypes, a neoadjuvant strategy tailored on clinicopathological criteria should be considered the optimal option (Table 1).

2. HR-positive disease

The GeparTrio trial [5] investigated a response-guided approach based on early response assessment; the treatment was either intensified with two additional cycles in the case of an early response, or changed to a different chemotherapy in the case of no response. Response-guided strategy led to a higher pCR rate in patients with HR-positive tumours, without a significant improvement in disease-free survival. These discordant results might be explained by the established weak prognostic impact of pCR in HR-positive disease [2,4].

3. HER2-positive disease

In studies adding trastuzumab to neoadjuvant chemotherapy, patients with HER2-positive/HR-negative tumours achieved the highest pCR rate across subtypes [3]. Otherwise, in the German neoadjuvant trial experience, an increasing number of chemotherapy cycles might be related to a higher pCR rate in patient with HER2-positive/HR-positive disease [4]. Moreover, results from the Tryphaena study showed that six to eight cycles of a taxane-based chemotherapy, including either an anthracycline or carboplatin, plus trastuzumab and pertuzumab lead to an increased pCR rate of >60% [6].

Currently, a sequential chemotherapy approach containing anthracycline–cyclophosphamide and a taxane plus trastuzumab is the better choice for patients with HER2-positive disease. The addition of pertuzumab to this sequence, or to a taxane–carboplatin combination, could be a future option when it becomes available.

4. TNBC

The simultaneous application of docetaxel, doxorubicin and cyclophosphamide (TAG) for six cycles accounts for the highest pCR rates in TNBC patients in the German neoadjuvant studies, particularly for patients with an early response after only two cycles [7].

As shown in the GeparQuinto study, the treatment effect might be further improved by adding bevacizumab to neoadjuvant chemotherapy [8]. However, even considering the non-confirmatory results of the NSABP B40 trial [9], the use of this anti-angiogenic drug in the neoadjuvant setting should be further investigated.

In the near future the role of bevacizumab and carboplatin will be better defined by the GeparSixto study [10] which is investigating bevacizumab given simultaneously to weekly carboplatin, paclitaxel, and pegylated doxorubicin in TNBC and HER2-positive patients; and by the CALGB 40603 study [11] which is evaluating three weekly carboplatin and bevacizumab in a 2 by 2 factorial design in patients treated with weekly paclitaxel followed by dose-dense doxorubicin/cyclophosphamide.

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5. Conclusion

In conclusion, considering that HER2-positive/HR-negative and TNBC patients who achieve pCR showed a prognosis comparable to that of patients with luminal-A-like tumours [2], a neoadjuvant strategy tailored to different breast cancer subtypes can completely change the natural history of some cancers.

Conflict of interest statement

Dr. von Minckwitz has received consultancy, speakers’ hono-
raria, and research funding from Roche and Sanofi-Aventis. Dr. Fontanella has no conflict of interest to disclose.

REFERENCES


Table 1 – Different neoadjuvant approaches according to breast cancer subtypes.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Neoadjuvant treatment</th>
<th>Reference</th>
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<tbody>
<tr>
<td>HR-positive</td>
<td>EC–Pw</td>
<td>Meta-analyses of several neoadjuvant studies [2–4]</td>
</tr>
<tr>
<td></td>
<td>TAC × 2 — response-guided chemotherapy</td>
<td>GeparTrio [5]</td>
</tr>
<tr>
<td>HER2-positive</td>
<td>EC(H)–TH</td>
<td>Meta-analyses of several neoadjuvant studies [2–4]</td>
</tr>
<tr>
<td></td>
<td>FECHP–TH or TCH (plus P if available)</td>
<td>Tryphaena [6]</td>
</tr>
<tr>
<td>TNBC</td>
<td>TAC</td>
<td>Meta-analysis of seven German neoadjuvant studies [7]</td>
</tr>
<tr>
<td></td>
<td>EC–Pw</td>
<td>Meta-analyses of several neoadjuvant studies [2–4]</td>
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<td>Role of bevacizumab is uncertain</td>
<td>GeparQuinto [8] and NSABP 40 Waiting for GeparSixto [10]</td>
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<td></td>
<td>Role of carboplatin is uncertain</td>
<td>Waiting for GeparSixto [10] and CALGB 40603 [11]</td>
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</table>

E, epirubicin; C, cyclophosphamide; Pw, paclitaxel weekly; T, docetaxel; A, doxorubicin; F, 5-fluorouracil; H, trastuzumab; P, pertuzumab; TNBC, triple-negative breast cancer.

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Neuroendocrine tumours (NETs) usually have an indolent course, developing slowly over many years, and when there is a lack of overt hormonal symptoms they may have been present for a considerable period of time before diagnosis. Therefore, NETs are commonly found with metastatic disease at diagnosis, especially in the most common variant small-intestinal NETs (SI-NETs). Surgical treatment of NETs varies somewhat according to site of origin and extent of disease. Surgical treatment of liver metastases is generally indicated if there are less than about five tumours, if they are confined to one lobe or in the case of large tumours as a debulking operation to reduce hormonal release.

However, there are several alternative options. First of all, stabilisation of disease is important, usually achieved by offering biotherapy (SI-NETs) or chemotherapy (pancreatic or pulmonary NETs). In addition, treatment with $^{177}$Lu-lutetium-labelled somatostatin analogues in tumours expressing somatostatin receptors has emerged as a possible option for initial treatment. After stabilisation of the disease, or even reduction of the tumour burden, often achieved by these treatments, surgery may become an option. A likewise targeted metastasis-directed therapy is ablation by radiofrequency (RFA), microwave (MW) or recently also irreversible electroporation (IRE). Another available option is hepatic artery embolisation.

Therefore, surgical management of liver metastases may be offered at different stages of the disease. In some cases the goal is total eradication of metastases from the liver, in other cases as another method to keep the disease ‘under control’ or as a debulking procedure to reduce hormonal levels. RFA or MW for SI-NETs has been evaluated and found to be safe, to reduce hormonal levels, and to reduce symptoms such as diarrhoea and abdominal pain. However, there seems to be no improvement on survival, although no randomised trial to test this has yet been conducted.

Surgery has classically involved standard resections such as segmentectomies or hemihepatectomy, but recently a more local approach has been utilised as an alternative to the likewise local RFA or MW. No studies have compared liver surgery for NETs with the alternatives, but studies have demonstrated the safety of – and clear benefit as a result of – surgery as a debulking procedure.

Studies in SI-NET have shown that the recurrence rate of liver metastases is very high. In careful microscopic evaluations of resected liver specimens it is clear that there are almost always several previously unrecongnised metastases present, perhaps indicating the impossible goal of reaching microscopic R0.

In pancreatic NETs the situation may be different. Unless diffusely spread, R0 may be achieved in the liver, and if combined with proper chemotherapy an impressively stable disease may be achieved compared with previously.

Liver transplantation has been advocated in patients with pancreatic NETs, Ki67 < 10% and lack of extrahepatic disease. In practice, however, this situation is rather rare, since lymph-node and skeletal metastases are often present, nowadays visualised with the more sensitive tools of today (Ga-DOTATOC/TATE PET). For SI-NET, liver transplant would be theoretically preferable considering the high rate of unknown liver metastases, but the survival for such patients has a median of >20 years, raising doubts about whether liver transplant is an option. Indeed, the metastases in SI-NETs commonly also occur at other sites than in the liver – but may still be controlled with the appropriate biotherapy treatment, as well as with $^{177}$Lu in certain cases. Indeed, there are reports of very successful liver transplant case series, but also cases with recurrence of disease in the new liver associated with short survival.

Overall, no comparative or randomised studies are available to support any evidence-based recommendations. There are several patient case series describing long survival and improvement of symptoms after liver surgery, but these are of small value because of lack of comparisons. On the other hand, liver surgery or ablative procedures may still be chosen by the individual patient when offered, as a variant of personalised medical care.

Conflict of interest statement

None declared.
Application of sentinel nodes in gynaecological cancer therapy

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The sentinel-node procedure was introduced in cancer therapy in order to reduce the morbidity that is associated with full lymphadenectomy without compromising survival rates. In gynaecological cancer the application of the sentinel-node procedure has been investigated in vulvar, cervical, and endometrial cancer.

In vulvar cancer, the Groningen International Study on Sentinel nodes in Vulvar cancer (GROINSS-V) showed that it was safe to omit inguinofemoral lymphadenectomy in patients with a negative sentinel node. Eligible patients who underwent the procedure had unifocal squamous-cell cancer of the vulva, with a maximum diameter of 4 cm and no suspicious groin nodes at palpation. In the case of a negative sentinel node, no inguinofemoral lymphadenectomy was performed, and patients were followed up regularly. Both short-term and long-term treatment-related morbidities were significantly lower when only the sentinel node was removed. Groin recurrences were observed in 2.3% of the patients with a negative sentinel node [1]. An analysis of the patients with a positive sentinel node showed an increasing risk for involvement of non-sentinel nodes with increasing size of the metastasis in the sentinel node. Furthermore, the prognosis was significantly worse for patients with sentinel-node metastases >2 mm [2]. More recently Levenback and colleagues published the results of the Gynaecologic Oncology Group study on the sentinel node procedure in vulvar cancer (GOG-173). They included 452 patients; all patients underwent inguinofemoral lymphadenectomy after sentinel-node detection. They found a false-negative predictive value of 3.7%. In women with a tumour <4 cm, the false-negative predictive value was 2.0%, a result resembling that of GROINSS-V [3]. Pitfalls of the sentinel-node procedure are gross nodal involvement that may obstruct lymph flow and thereby cause bypassing of the sentinel node and confusion about the number of sentinel nodes [4]. Preoperative groin imaging with computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound (US) is mandatory to exclude gross nodal involvement, while preoperative lymphoscintigraphy gives adequate information on the number of sentinel nodes per groin and presence of unilateral or bilateral sentinel nodes. Controversies remain regarding the method of preoperative imaging, the therapeutic benefit of inguinofemoral lymphadenectomy in case of micrometastases in the sentinel node, and alternative treatment options in patients with a positive sentinel node. An ongoing second observational study, GROINSS-V-II, is investigating the safety of radiotherapy instead of inguinofemoral lymphadenectomy in patients with a positive sentinel node. Preoperative imaging is mandatory in this study to exclude gross nodal involvement. The GOG has joined GROINSS-V-II; this international collaboration will help shorten the duration of studies in rare malignancies like vulvar cancer.

In cervical cancer single-institution case series had already demonstrated the feasibility of the sentinel-node concept, when Altgassen and colleagues in 2008 published the results of their multicentre study on the detection rate and diagnostic accuracy. The detection rate of pelvic sentinel nodes was 88.6% in 590 patients. They also showed a significantly higher detection rate when blue dye and a radioactive tracer were combined. The sensitivity was 77.4% overall, but 90.9% in women with tumours ≤2 cm. They concluded that the sensitivity of the sentinel-node concept was low, but that patients with tumours ≤2 cm might profit from this concept [5]. The results of the SENTI-COL study, by Lécuru and colleagues, showed that in 139 stage IA1 with LVSI-IB1 cervical cancer patients the sentinel-node procedure yielded a sensitivity of 92.0% and a negative predictive value (NPV) of 98.2% for detection of nodal metastasis. No false-negative results were observed in those patients in whom the sentinel node was identified bilaterally. They concluded that the sensitivity of the sentinel-node concept was low, but that patients with tumours ≤2 cm might benefit from this concept [6]. These results were confirmed in a recent study by Cibula and colleagues in their study in 645 patients [7]. The same authors showed that the presence of micrometastases in
the sentinel node was associated with a significant reduction in overall survival, which was equivalent to that in patients with macrometastasis. No prognostic significance was found for isolated tumour cells [8]. Recently a single-institution study showed that when comparing a prospectively collected patient cohort (in whom a pelvic lymphadenectomy was omitted in the case of a negative sentinel node) with historic controls in whom a full lymphadenectomy was performed, the sentinel-node technique yielded a higher proportion of patients with lymph-node metastases, indicating a higher sensitivity of the sentinel-node technique [9]. However, the clinical impact of sentinel-node biopsy in cervical cancer needs to be further evaluated in observational or preferably randomised studies comparing sentinel-node biopsy with sentinel-node biopsy plus lymphadenectomy (NCT01157962).

Finally, in endometrial cancer the sentinel-node procedure is still in a preliminary stage of evaluation. Different techniques of tracer injection have been proposed; however, there is no consensus about the most accurate method for identifying the sentinel node. Cervical and intramyometrial subserosal injections are safe and simple, but probably do not reflect the expected endometrial cancer lymphatic drainage. Also the detection rate is low. Hysteroscopical injection might better reproduce the drainage of the tumour; however, this is complex, costly, and also shows a high variability in detection rate. Different studies showed identification rates varying from 45% to 100% [10]. Recently transvaginal ultrasound-guided myometrial injection of the radioactive tracer was suggested as a safe, feasible method for sentinel-node detection [11].

In conclusion, GROINSS-V and GOG173 have provided adequate evidence for the safety of sentinel-node detection in selected early-stage vulvar cancer patients. The sentinel-node procedure is now part of standard therapy in vulvar cancer patients with a unifocal tumour <4 cm with no palpable lymph nodes. Only in the hands of an experienced multidisciplinary team should the procedure be considered safe. In cervical cancer, the sentinel-node procedure seems a promising tool, especially in patients with tumours ≤2 cm and when bilateral drainage is found. The results of a large randomised trial comparing sentinel-node biopsy to sentinel-node biopsy plus lymphadenectomy are expected in a few years. In endometrial cancer, studies are still evaluating the best diagnostic method.

Conflict of interest statement
None declared.

REFERENCES

Best management of locally advanced inoperable breast cancer

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Locally advanced breast cancer (LABC) is a heterogeneous disease; it includes disease which is either extensive within the breast and/or in ipsilateral nodal areas. These cancers vary widely in biological characteristics and clinical behavior, ranging from locally aggressive but systemically "indolent", to de novo generalised disease. LABC includes: (1) large breast tumours (>5 cm in diameter); (2) cancers that involve the skin of the breast or the underlying muscles of the chest; (3) cancers that involve multiple local lymph nodes (those located in the arm pit or the soft tissues above and below the collar bone) and (4) inflammatory breast cancer (IBC). The clinical management of LABC is complex and should be tailored to the individual patient, according to the biological features of the disease. A multidisciplinary approach is recommended combining systemic therapy (chemotherapy and/or hormone therapy and biological agents) and in some cases radiotherapy. LABC is reported to occur in 10–15% of all new primary breast cancer diagnoses [1]. At least 20–30% of women with breast cancer wait more than 8 weeks from the initial symptom(s) until they seek clinical assessment [2,3]. Richards et al reported a 12–19% decrease in 5-year survival in those women with delays of 3 months or more versus those with a shorter time to diagnosis [4]. The following factors have been cited as causes of patient delay: poor access to health care, lack of preventive health-care habits, increasing age, having child-care/elder care obligations, notion that the symptoms are benign, poor education, misperception of risk, embarrassment, fear of chemotherapy and breast loss and concern about being a hypochondriac and pessimist about survival [3–5,6].

IBC is an aggressive disease that progresses rapidly and carries a very grim prognosis. It is characterised by erythema, rapid enlargement of the breast, skin ridging and a characteristic “peau d’orange” appearance of the skin secondary to dermal lymphatic tumour involvement. Although a palpable tumour may not be present, about 55–85% of patients will present with metastases to the axillary or supraclavicular lymph nodes. Accurate diagnosis is critically important, as multimodal therapy can significantly improve outcomes if instituted early enough. The treatment of LABC is complex, and to complicate matters further, when it appears as a recurrent disease it can be considered as a “moving target” since previous treatment delivered in the adjuvant setting may affect treatment choice at recurrence.

Patients with stage IIIA or IIIB disease – including those with IBC and those with isolated ipsilateral internal mammary or supraclavicular lymph-node involvement – are often inoperable. Patients with stage IIIB or IIIC disease who respond to primary chemotherapy should be treated until the response plateaus or to a maximum of six cycles (minimum four cycles), after which several case series have demonstrated that locoregional control is improved [7–12]. The loco-regional management of patients with stage IIIC disease who respond to chemotherapy is unclear and should be individualised. In the absence of evidence on this subgroup of patients, it is reasonable that they receive locoregional radiotherapy (including nodal irradiation). The role of completion mastectomy should be individualised and based on technical and disease factors. Following the completion of chemotherapy, pre- or postmenopausal patients with locally advanced (operative and inoperable) hormone-responsive tumours should receive endocrine therapy according to their menopausal status. Patients with HER2-positive breast cancer who received chemotherapy in combination with trastuzumab should receive trastuzumab maintenance therapy.

In the case of inflammatory breast cancer the role of anti-angiogenic agents has been explored in either HER2-positive or -negative disease. Inflammatory breast cancer is characterised pathologically by high vascularity and increased micro-vessel density because of the high expression of angiogenic factors such as vascular endothelial growth factor (VEGF). Use of bevacizumab, a VEGF-targeting monoclonal antibody, resulted in substantially improved progression-free survival and response in patients with advanced breast cancer and showed neoadjuvant activity in patients with previously un-

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treated locally advanced breast cancer or IBC. In a recent study, neoadjuvant treatment with bevacizumab, trastuzumab and chemotherapy was efficacious and well tolerated in patients with previously untreated primary IBC [13–15]. Treatment of LABC and IBC requires a coordinated multidisciplinary approach that should be individualised depending on tumour characteristics and response to treatment. The treatment may include a combination of chemotherapy, endocrine therapy, biological therapy and radiotherapy. While the prognosis in these cases is poor compared with that for other presentations of breast cancer, a reasonable survival and quality of life can be obtained with a team approach to treatment. All patients with LABC and IBC should be considered candidates for clinical trials to evaluate the most appropriate fashion in which to administer the various components of multimodality regimens.

Conflict of interest statement

No conflict of interest to declare.

REFERENCES

Preclinical microscopy has greatly enhanced our mechanistic understanding of cancer invasion and metastasis, the contribution of the tumour microenvironment to metastatic progression, and how invasion and the microenvironment jointly support cancer cell survival and resistance. Using organotypic models in vitro, live-cell imaging in three-dimensional (3D) tissue culture has identified how cytoskeletal, adhesion and protease systems drive invasion and metastasis [1]. When altered at the molecular level, these pathways underlie the unexpected diversity of the invasive process [2]. The recent use of intravital microscopy has further suggested that cancer invasion into interstitial stroma in vivo: (1) occurs mostly as collective invasion in which cells remain coupled to neighbouring cancer cells, (2) is guided by and responsive to signals delivered by connective tissue structures and (3) that invasion pathways cross-talk with pathways of cancer cell survival and resistance to anticancer therapy [3].

1. Principles of collective cell invasion

Collective cell migration is defined as the movement of multiple cells that retain cell–cell contacts, coordinate their actin dynamics and intracellular signaling, and thereby form a structural and functional unit for joint translocation [1,4]. In contrast to single-cell migration, moving cell masses remain mechanically coupled by cell–cell adhesion receptors, most notably of the cadherin and integrin families, and form a coordinated cortical structure of the actin cytoskeleton, occasionally referred to as a ‘super-cell’ [4]. Besides cancer invasion and metastasis, collective cell movement contributes to cell migration in morphogenesis and tissue repair [5], suggesting homologous underlying mechanisms.

As in all known types of actomyosin-based cell migration, collective migration is plastic, i.e. it undergoes modification with altered intracellular signaling or an altered environment [2]. Interference with molecules that maintain or regulate collective cell behaviour can lead to single-cell detachment. Depending on the type of single-cell migration obtained after dissociation, two types of conversion are currently known: the epithelial–mesenchymal transition (EMT) and the collective–amoeboid transition (CAT). EMT is a well established molecular process that leads to the down modulation of cell–cell adhesion, whereby the migration machinery remains intact, which induces cell detachment and scattering from multicellular groups [1] (and references therein). Mechanisms that enable single-cell detachment include reduced cadherin expression, loss-of-function mutations in cadherin and catenin [mit Leerzeichen ersetzen] signaling pathways, and deregulated function of proteases degrading cadherins and other cell–cell adhesion molecules [4]. In vivo, EMT corresponds to the loss of differentiated epithelial morphology in usually small regions towards a sarcomatous, stromal and, hence, invasive and likely metastatic phenotype. CAT is the transition from collective invasion to amoeboid single-cell crawling after simultaneous weakening of cell–cell and cell–ECM interactions, such as after EMT-independent down-regulation of cadherins (data not shown) or inhibition of β1 integrins in collectively invading melanoma explants [5] and in tumour xenografts in vivo (data not shown). Detached cells then survive, continue to move via amoeboid shape change (similarly to interstitial migration of amoeboid leukocytes [6]), and eventually cause distant metastasis (S. Alexander, MD Anderson Cancer Center). These findings suggest that collective migration represents an invasion mode of high cellular and molecular order that, after loss of function of particular adhesion pathways, interconverts to single-cell dissemination and metastasis. The understanding of the signals maintained by simultaneous cell–cell and cell–matrix communication during collective invasion and secondary plasticity will be important in defining the cross-talk between strategies of invasion and resistance signaling [3].
2. Intravital multiphoton microscopy of collective cancer invasion in vivo

Multiphoton microscopy (MPM) has become the method of choice for investigating cell structure and function in tissues and organs, including the invasion and progression of cancer lesions [7]. Particularly suited for cancer research is infrared multiphoton microscopy, which enables deep tissue penetration and detects multicellular, collective invasion of melanoma and soft-tissue sarcoma lesions in vivo [8]. Recent evidence from intravital microscopy further suggests that collective invasion is strongly associated with resistance to radiation therapy and chemotherapy.

3. Joint mechanisms of cancer invasion and resistance

Based on the multiple inputs from the tumour microenvironment and their overlapping signaling pathways, invasive tumour-cell migration and resistance are now considered as interconnected cell functions. To gain deeper insight into the steps and niches of concurrent resistance and dissemination, preclinical animal models followed by time- and space-resolved molecular imaging are necessary to detect tumour responses to therapy at a cellular level. The signals required for both single-cell and collective cancer invasion include the activation of integrins, cadherins, small GTPases Rac...
and Rho, as well as Ras pathways, and the engagement of intracellular signaling networks that include PI3K, mTOR, Src and Map kinases (Fig. 1). Consequently, druggable signaling hubs that may serve to target both tumour invasion and resistance include growth factor and chemokine signaling, integrin engagement, as well as downstream Ras/MAFks, PI3K and mTOR signaling. Thereby, the residual niches that withstand targeting of conventional therapy can consist of a limited number of cells which, after surviving cycles of therapies, regrow, initiate migration and thereby re-establish an invasive tumour.

4. Outlook

Collective invasion types contribute and provide particular challenges to the progression and therapy of cancer disease. The cell mass likely produces high autocrine concentrations of promigratory factors and matrix proteases. Because many cells move as one functional unit, cells of different clonal origin or different biological abilities may be linked and invade together (‘mixed clone’ behaviour). Furthermore, it can protect inner cells from immunological assault through cytotoxic lymphocytes. As a particular challenge, the joint signaling from tissue structures and cell–cell junctions may activate survival pathways not engaged in quiescent, non-invading tumour regions. Thus, preclinical in vivo microscopy will enable both fascinating insight into the basic mechanisms of cancer biology as well as advance preclinical validation of drugs and the identification of resistance mechanisms.

Conflict of interest statement

None declared.

REFERENCES

Nurse navigation is helpful for cancer patients, but with some restrictions

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1. Background

Much development in nursing care is not based on research but is created from the ideas of health-care professionals, for instance, about benefit for patients. One example is case management (CM), where newer models focus on transitions in the health-care system and have a holistic and empowering approach to information, coordination and other kinds of support needed by the patients [1]. Within CM, nurse navigation (NN) is an innovation in which availability also characterises the model [2,3].

2. Aims

We were keen to investigate who could benefit from the help on offer and what significance female cancer patients attach to NN.

3. Methods

A longitudinal phenomenological–hermeneutical study was carried out among 21 consecutively included women. They were referred on suspicion of gynaecological cancer and were followed by first author form the referral had reached a university hospital in Denmark and 3 months ahead. The women were offered help from one of two female NNs from a surgical department, from the time of referral and until they were referred further or hospitalised for cancer surgery. The method has been thoroughly described elsewhere [4–6] and includes patient diaries, observational studies and semi-structured interviews, where women made graphical representations of their emotions over time as visual aid to their memory [6]. From verbatim transcriptions, an open-minded analysis on three analytical levels, inspired by Riceour [7], leads to a comprehensive understanding.

4. Findings

An overlap was found between women's experiences of their relationship with the health-care professionals before communicating with the NN, and the subsequent significance an NN had for the women. Important themes were trust and guarded trust [4]. Moreover, although the women said that they were anxious, and to various degrees felt ignorant and feared death, an NN could have or not have a special meaning, and this meaning could be either positive or negative [5] (Table 1).

5. Comprehensive understanding and discussion

Each woman had benefit of having a specific health-care professional, whom she trusted could and would help her through the course of her cancer. If the woman did not have such a relationship with a health-care professional at the time of referral, the woman could use the trusting relationship the NN offered. Trust, guarded trust or distrust towards another is created primarily from our interpretations of the other's non-verbal signals, where we judge whether the corresponding person behaves as expected [8]. A health-care professional's efforts to maintain or gain patient's trust therefore requires a kind of cultural sensitivity, which is tested every day and the test is not always passed, if trusting patients are the goal. On the one hand, offering an NN in cancer care can therefore be seen as a patch on a system which is not functioning optimally, but on the other hand we can ask whether optimising

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communication by health-care professionals can remove all the patient's needs for extra help from an NN. When help from the NN became useful for the women, the women's descriptions were similar to those of close providers (see Table 1). The women were aware of the period of availability of the NN, but nonetheless they still expected her attention. When this was in vain, the patients became disappointed and felt rejected and let down. This cannot be explained solely by patients' wishes for continuity in care. Bowlby's attachment theory [9] explains that in a period where death was felt as a possible close event, the NN offered herself as a special caring figure – an attachment figure – with high levels of availability, knowledge and help. The referred woman without a health-care professional attachment figure started making emotional bonds with the NN. Therefore, a further referral, for instance, which changed the NN's mode of action, would feel very harsh, although the woman rationally knew that the NN was no longer available. Cancer patients have various degrees of critical periods in the course of their cancer [10], and should emotional bonds to an NN have to be terminated, we recommend that health-care professionals consider both the timing and ways to do this. Our results cannot be generalised but are rather transferred to similar places.

6. Conclusion

Women's trust and guarded trust in health-care professionals are key points in relation to the use of an NN, but we do not know how to find those who need the extra effort. Moreover, the NN might become an attachment figure for the individual woman, and sustain special importance. Therefore, it must be considered whether health-care professionals in general should increase their focus on communication, in combination with offering an NN for a longer duration, if possible in a never-ending attachment.

### Conflict of interest statement

None declared.

### Table 1 – Significance of women who choose or do not choose help from a nurse navigator (NN), and the significance they attach to the NN.

<table>
<thead>
<tr>
<th>A woman's experience of the relationship with the health-care professionals before communication with an NN*</th>
<th>The significance female cancer patients attached to an NN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trusting that a health-care professional among the close relatives can and will help</td>
<td>No special meaning. The NN was a nurse in the crowd of nurses and her help was not useful outside the outpatient setting</td>
</tr>
<tr>
<td>Trusting that a known physician can and will help</td>
<td>A special person providing useful help, also after the initial outpatient setting [5]</td>
</tr>
<tr>
<td>Not fully trusting that a known health-care professional can and will help. The women felt guarded trust in one or more health-care professionals of special importance</td>
<td>In the period with an available NN the women felt a special affinity with the NN and the women felt that the NN was:</td>
</tr>
<tr>
<td>Guarded trust followed the women's interpretation of non-verbal signals from a physician they counted on in relation to their own health. Such interpretations were always told as the women's latest experiences with an important physician before the contact to the NN</td>
<td>– Trustworthy, knowledgeable and someone special, who as an easily accessible health-care professional was nice and helpful to act immediately, inform, support, reassure and provide an overview and empowerment in the period after an available NN the women felt the NN was</td>
</tr>
<tr>
<td>– Disappointing, failing and repelling</td>
<td></td>
</tr>
</tbody>
</table>

### Acknowledgements

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### References


Nutritional status in relation to treatment modalities

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1. Influence of nutritional status on chemotherapy and radiotherapy

The prevalence of disease-related malnutrition in patients with cancer ranges from 40% to 80%, which is the highest of all hospital groups. This variation in prevalence is the result of the different definitions of malnutrition used, and it also depends on tumour type, stage and anticancer treatment. Malnutrition is associated with negative outcome, including increased morbidity, poor prognoses and tolerance to treatment, decreased quality of life and increased health-care costs [1]. Head and neck cancer patients who experience a weight loss >20% of their total body weight during or following radiotherapy are at an increased risk of toxicity and mortality. Stage 3 or 4 disease and smoking more than 20 cigarettes a day should be reason enough for early enteral feeding. A prophylactic percutaneously placed endoscopic gastrostomy (PEG) feeding tube is also beneficial when there is pretreatment weight loss [2].

Nutrition screening is the process of identifying patients with characteristics commonly associated with nutritional problems that may require full nutritional assessment. Screening can be applied to all patients. The malnutrition screening tool (MST) is a validated, quick and simple nutrition screening tool. The patient-generated subjective global assessment (PG-SGA) can be applied for a full nutritional assessment [1].

The identification of baseline risk factors to assess a patient’s fragility or ability to tolerate treatment is desirable to predict outcome of chemotherapy toxicity, not only for medically unfit patients but also amongst patients with an apparently good medical condition, since the high inter-individual variability in drug exposure remains an unresolved issue. Chemotherapy-induced DNA damage might become more cytotoxic to normal tissue in the presence of perturbations of the cellular immune response because of high protein catabolism and stimulation of acute-phase protein responses (APPRs). The nutritional and inflammatory status (NIS) appears to correlate with increased risk of severe haematological toxicity following anticancer chemotherapy. This status takes into account (1) C-reactive protein, (2) alpha-1-acid glycoprotein, (3) albumin and (4) prealbumin: NIS = (1 + 2)/ (3 + 4) [3].

Malnutrition has been associated with changes in drug disposition, including changes in absorption, protein binding, hepatic metabolism and renal elimination. In malnourished patients reduced concentrations of plasma proteins may significantly increase the likelihood of toxicity from the administrations of agents that are highly protein-bound, such as prednisolone, etoposide, teniposide, cisplatin, paclitaxel and SN-38 [4].

Anticancer treatment can induce a poor nutritional status by inducing nausea, vomiting and anorexia and gastrointestinal disorders as mucositis and diarrhoea [4]. Reversible lactose intolerance – associated with diarrhoea, flatulence and poor nutritional status – is not infrequent in patients treated with chemotherapy based on 5-fluorouracil (5-FU). Hypolactasia can easily be diagnosed with a lactose tolerance test. Dietary lactose restriction might improve tolerability of treatment [5]. Malabsorption may be caused not only by fluorouracil but also by other drugs affecting cell proliferation such as thioguanine, methotrexate, vinca’s alkaloid, actinomycin D, hydroxyurea and daunomycin [6].

2. Influence of nutritional deficiencies on chemotherapy and vice versa

Trace elements consist mostly of metal ions which act mainly as basic components of essential enzymatic systems or proteins that play major roles in the physiology of the gastrointestinal tract (Jackson, 1989). Studies suggest that trace elements serve as cofactors in several metabolic pathways, and a decrease in their concentration may facilitate the malnutrition process that takes place in cancer patients. Negative acute-phase reactants such as selenium and zinc are decreased in cancer patients, whereas serum levels of copper are increased. Selenium deficiency may interfere with...
More than 80% of the patients with cancer surveyed in 2000 in the United States reported using complementary and alternative medicine (CAM) [11]. While the body of literature related to the use of CAM is growing, the extrapolation and applications with procoagulant properties should be avoided with the use of cisplatin. Cachectic patients with decreased dietary carnitine uptake may develop carnitine deficiency when treated repeatedly with chemotherapies that include cisplatin. They have a tenfold increase in renal carnitine excretion [9].

Pemetrexed, a multitargeted antifolate, is associated with life-threatening toxicity, especially myelosuppression, if not administrated after supplementation with folic acid and vitamin B12. One week prior to commencing pemetrexed, folic acid (0.5 mg by mouth each day) and vitamin B12 (1 mg by intramuscular injection every 9 weeks) should be given [10].

Antioxidants represent one of the largest categories of dietary supplements. Reactive oxygen species (ROSs) are a natural consequence of living in an aerobic environment. Oxidative stress occurs when natural defence systems are inadequate to combat the production of ROSs. Antioxidants could be protective against the adverse effects of chemotherapy, but some of these agents rely for their antineoplastic activity on the production or interaction with ROSs. Agents with a high reliance on ROSs for their antineoplastic activity are alkylating agents and mitomycin C. Mitoxanthrone is less likely to be dependent on ROSs.

The use of dietary supplements with anticoagulant properties, alone or concomitantly with conventional anticoagulants or antiplatelet medication, may pose a risk for bleeding due to additive or synergistic effects on the coagulation pathway. Agents with coumarin constituents – such as angelica root, agents that inhibit platelets such as panax ginseng, agents with salicylate constituents such as black cohosh, garlic, ginkgo, saw palmetto – may increase the risk of bleeding. Supplements with procoagulant properties should be avoided with hormonal treatments such as tamoxifen, and with erythropoietic growth factors, estramustine or thalidomide.

4. Conclusion

Nutrition and nutritional status are influenced by the presence of cancer but also have an important influence on antitumor treatment and treatment outcome. It is important that the oncologist has an insight into the possible interactions and complications that nutritional agents may have with chemotherapeutic agents.

The ability to identify and locate reliable information regarding dietary supplements is vital. The use of more than one reference is necessary to complete the analysis of dietary supplements for a patient. Counselling patients with cancer about dietary supplements requires a systematic thought process that considers the available theories and data, as well as the patient’s views about these agents [13]. More attention should be paid to patient nutritional status, and cooperation with a dietician is essential in the care of the cancer patient.

Conflict of interest statement

None declared.

3. Influence of nutritional supplements on chemotherapy

More than 80% of the patients with cancer surveyed in 2000 in the United States reported using complementary and alternative medicine (CAM) [11]. While the body of literature related to the use of CAM is growing, the extrapolation and applications with procoagulant properties should be avoided with the use of cisplatin. Cachectic patients with decreased dietary carnitine uptake may develop carnitine deficiency when treated repeatedly with chemotherapies that include cisplatin. They have a tenfold increase in renal carnitine excretion [9].

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R E F E R E N C E S

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The best treatment for older patients with breast cancer

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1. Introduction

One of the biggest risk factors for the development of breast cancer is age, and over 40% of all breast cancers diagnosed are in women aged 65 years or older [1]. Despite this, there are few standardised guidelines for the management of older breast-cancer patients, primarily due to the lack of level-I evidence and the lack of representation of older women in adjuvant therapy trials. Thus clinicians are often required to make treatment decisions for elderly patients in the face of uncertainty. This often leads to undertreatment, or less frequently, overtreatment of elderly patients, with resultant poorer outcomes.

In order to address this issue, a task force created by the International Society of Geriatric Oncology (SIOG) and the European Society of Breast Cancer Specialists (EUSOMA) has developed a set of evidence-based guidelines for the management of breast cancer in elderly individuals [2]. It is important to note that these guidelines are predominantly applicable only to elderly patients who are fit, rather than those who are less fit or frail, due to the scarcity of data relating to treatment of this latter group. Key recommendations are summarised as follows.

- For an older individual with breast cancer it is critical that all management decisions take into account physiological age, life expectancy, potential risks versus absolute benefits, treatment tolerance, patient preference and potential barriers to treatment.
- Elderly breast-cancer patient management should involve collaboration between geriatricians and oncologists. Elderly patients are at higher risk for competing comorbidities, which may not be evident on oncological assessment. Comprehensive evaluation of functional status with a multidomain geriatric assessment (CGA) is ideal, although this may not be possible in all patients. Alternatively, it is reasonable to perform a functional screening assessment to identify which patients are at increased risk for functional deficits on the extended CGA. In patients in whom reversible functional deficits are detected, proactive management of these can improve quality of life and survival. Similarly, identification of interval decrease in functional status through the use of repeated geriatric assessments allows appropriate intervention and potentially improved outcomes.

2. Early breast cancer

- Surgical options for patients 70 years or older should be equivalent to those of younger patients, with age itself not an indication for less-than-standard surgical management. In some older patients it might be reasonable to omit either sentinel lymph-node biopsy or completion axillary lymph-node dissection, though this is an area of ongoing debate.
- All elderly patients undergoing breast-conserving surgery should be offered whole breast irradiation as a means to significantly reduce local relapse rates. Elderly patients with high-risk tumour (T3–4 or at least four lymph nodes involved) should be considered for post-mastectomy radiotherapy.
- Treatment of estrogen-receptor (ER) positive breast cancer with endocrine therapy alone is a suitable treatment strategy only in an elderly individual who has a limited life expectancy (less than 3 years), who is considered unfit for surgery after optimisation of medical conditions, or who refuses surgery. Geriatrician input to guide the management of comorbidities and to accurately assess life expectancy is strongly recommended.
• Tamoxifen and aromatase inhibitors have similar efficacy in older as in younger patients and are recommended as initial adjuvant hormone therapies. The choice between tamoxifen or aromatase inhibitors should be made by balancing the slightly higher efficacy of aromatase inhibitors with the increased vulnerability of elderly patient to their toxicities. For patients who commence on tamoxifen, a switch from tamoxifen to aromatase inhibitor after 2–3 years should be considered on the basis of treatment tolerability. Similarly, for healthy elderly patients, extended endocrine therapy with an aromatase inhibitor after 5 years of tamoxifen is reasonable. In elderly patients with very low-risk tumours (pT1aN0) or severe comorbidities, the risks and toxicities of endocrine therapy may outweigh the benefits; in these circumstances it may be reasonable to omit adjuvant endocrine therapy.

• Fit elderly patients gain as much benefit as younger patients from adjuvant chemotherapy. Chemotherapy decisions should be made based on potential benefits, which are highest in node-positive, hormone-negative disease, compared with risks and toxicities. Four cycles of an anthracycline-containing regimen are usually preferred over cyclophosphamide methotrexate 5-fluorouracil (CMF). Substitution of anthracycline with taxane is also a reasonable option to reduce the risk of cardiac toxicity.

• Adjuvant trastuzumab in combination with chemotherapy should be offered to all elderly patients with HER2-positive breast cancer, without cardiac disease, and who are suitable for chemotherapy treatment. Use of single-agent trastuzumab in patients not suitable for chemotherapy might be an option, although limited outcome data are available in support of this approach.

3. Metastatic breast cancer

• Chemotherapy is indicated for ER-negative, hormone-refractory, or rapidly progressing disease.

• Single-agent chemotherapy is generally preferred, although oral combination chemotherapy is also a reasonable option in elderly patients. There is no good evidence in support of routine dose or schedule modifications in elderly patients. However, this may be appropriate in certain circumstances, based on the known toxicities and pharmacology of the chemotherapy agents coupled with comorbidities in the patient.

• All patients with human epidermal growth factor receptor 2 (HER2) positive disease should be offered HER2-targeted therapy. In fit elderly patients, anti-HER2 therapy should be given in combination with chemotherapy. Anti-HER2 therapy plus endocrine therapy is a reasonable treatment option in patients with HER2-positive ER-positive disease in whom chemotherapy is contraindicated. Similarly patients with HER2-positive ER-negative disease who are not suitable for chemotherapy may be candidates for trastuzumab monotherapy.

• While bevacizumab has demonstrated benefit in terms of improved progression-free survival in both elderly and younger patients alike, concerns regarding both toxicities and cost efficacy make its place in elderly breast cancer management uncertain.

Increased comorbidities and polypharmacy are both more common in elderly patients. Additionally, physiological ageing can be associated with altered pharmacokinetics (drug absorption, distribution, metabolism and excretion). Each of these factors can affect the efficacy and toxicity of anti-cancer agents, making it critical that drug prescription in elderly patients be done with care. Eliminating or reducing the risk of drug interactions is best achieved with a thorough medication review before making any treatment decisions.

Poor compliance or non-compliance with oral anti-cancer medications is not uncommon in older breast-cancer patients [3–5] and can lead to reduced efficacy of therapy. It is important to consider causes of non-compliance, which may often include poor tolerability of treatment. Thus, close adverse-event monitoring and addressing specific toxicity concerns and side-effects are crucial to improve compliance, treatment tolerability and efficacy.

Older breast-cancer patients often rely more strongly on the recommendation of the cancer specialist regarding breast cancer management decisions; however, it is important to recognise that some older patients may wish to take a more active role in decision-making. While older patients are as likely to accept therapy as younger patients, they may be less willing to risk deterioration in quality of life for a potential improvement in survival [6]. For this reason, careful and clear discussions regarding diagnosis, prognosis and treatment options, as well as expectations of treatment and potential toxicities, are essential.

Conflict of interest statement

None declared

REFERENCES


Mechanisms of treatment-related symptoms in cancer patients

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Despite significant gains in our understanding of cancer biology, this progress has not matched what we know about the biology underlying the symptoms and toxic effects that therapies produce. These adverse symptoms can cause substantial discomfort, functional loss and distress to patients; they limit treatment tolerability, and can persist indefinitely in post-treatment survivorship [1]. Effective control of treatment-related symptoms could enhance therapeutic outcomes by improving patient health status, minimising toxicities that impair function, increasing adherence to curative treatments, maintaining health-related quality of life and potentially increasing survival. A mechanistic understanding of treatment-related symptoms would be of benefit in drug development, drug evaluation and early integration of appropriate supportive care in treatment planning. This presentation will present steps in a translational pathway for understanding and controlling treatment-related symptoms.

Cytotoxic therapies (chemotherapy, radiation) are expected to produce symptoms, because normal tissue and function are disrupted as cancer cells are killed. Targeted anticancer therapies were expected to destroy cancer cells specifically and therefore to cause less general toxicity, yet different and often severe toxicities have emerged, with each novel agent having its own unique toxicity profile. A translational pathway for symptom research is presented in Fig.1, using fatigue as an example [3].

Early components of the pathway include discovery research steps and decision points based on longitudinal observational studies of patients, including patient interviews and determination of specific symptoms associated with disease, stage or treatment. Correlational studies showing the co-variation of biomarkers (such as inflammation) and symptom expression, although an important step, do not provide sufficient information on the mechanistic basis of symptom production for the development of potential agents targeted at symptom control. Instead, hypotheses about mechanisms underlying symptom expression are developed through examination of longitudinal symptom data, clinical correlates, biomarkers (genes, proteins) and brain imaging data obtained from patients. These hypothesised mechanisms are then tested in animal models. Candidate agents that may affect these mechanisms are developed in the laboratory, then applied in animal models of the specific disease. Agents that give some signal of effectiveness in preventing or reducing the specific cancer without excessive toxicity then move forward into patient research.

For some symptoms, such as bone-related pain, sufficient progress has been made in animal models to provide a basic understanding of the mechanisms involved and to test agents that might have a clinical benefit. In contrast, much less is known about the development of animal models of such symptoms as treatment-related cognitive impairment, fatigue and treatment-related distress. Animal models of cognitive impairment and reduced motivation are available, but the effects on these models of having cancer and being treated for cancer have not been assessed.

Biomedical research is largely dependent on having animal models of the targets of interest. The same applies to symptom science, where exploratory and confirmatory studies in humans can be conducted in parallel in animal models of symptom translational research in a bedside-to-bench and bench-to-bedside collaboration. Fatigue research is an excel-

1. A translational pathway for treatment-related symptoms

The difficulties inherent in translating laboratory findings into patient benefit are widely recognised in every disease area. In 2005, the National Cancer Institute created a Translational Research Working Group to speed the application of the findings of molecular oncology to patient care [2]. In response, the working group developed a model for a translational research pathway. Although the model was developed for new curative therapy, a similar model might be used to conceptualise how to move the collective basic and clinical symptom research into the clinic. A schematic illustrating such a translational pathway for symptom research is presented in Fig.1, using fatigue as an example [3].

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that modulate disease and those that modulate symptoms, to ensure that symptom control does not compromise curative benefit.

Cancer-related symptoms are affected not only by treatment but also by individual host characteristics. There is substantial variation in the degree to which symptoms will impair patients, much like there is variance in the ability of a given drug to control cancer. Being able to predict this risk would benefit personalised cancer care. Potential predictors of high behavioural toxicity can be studied using advanced molecular genetic technologies. Analysis of genetic predictors for symptom occurrence and severity during treatment will help us to understand the biological basis of symptoms, identify susceptible individuals, develop tests with prognostic power, design novel drug targets and predict therapeutic outcomes.

Finally, methods to reduce treatment-related symptoms will require early clinical investigation. Too many large-scale phase III symptom-focused clinical trials have been performed with negative results. Potential reasons for this include (a) lack of knowledge of the potential mechanisms producing the symptoms, (b) inadequate preclinical testing and (c) small early trials in patients to detect a signal. Just as with curative therapies, early use of adaptive clinical trial design could be employed to sort among agents that show promise for mitigating symptoms and to quickly cull those that do not [5].

Conflict of Interest statement

None declared.

REFERENCES

Modern management of penile cancer

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1. Introduction

Multidisciplinary management is the standard of care for common cancer subtypes, and it is particularly important for rare cancers such as penile cancer. Often clinical expertise may have to be concentrated into defined regional or supra-regional cancer centres; thus patients may have to be treated at centres distant from their home town. For comprehensive management of the needs of penile patients, close communication is needed between the specialist cancer teams and local medical services, including community support services, particularly in the aftercare of surgery, for follow-up and in the palliative management of end-stage disease.

2. Background (epidemiology, incidence, path and biology)

Penile cancer is relatively rare, representing about 0.5% of male cancers. It has an incidence in Western societies estimated at 1:100,000 [1]; a higher incidence is reported in non-Western societies such as South America, Africa (particularly Uganda) and Asia. Whilst it is more prevalent in older men, about 25% of cases are found in men younger than 40 years of age and about 10% in men under 30 years of age [2].

Predisposing factors include both cultural and religious practices as well as social and hygienic habits [3]. Of these, circumcision in newborns and before puberty, together with good hygiene, is associated with a reduced risk (by 3–4-fold) of penile cancer. Other risk factors include smoking [4], phimosis, inflammatory conditions such as lichen sclerosus or balanoposthitis, ultraviolet radiation [5] and the presence of human papilloma virus (HPV) that is related to sexual promiscuity. However, there is no clear evidence yet that the presence of HPV in penile cancer confers a worse prognosis [6], but rather that it may predict a favourable outcome [7].

The major histopathological subtype is squamous-cell carcinoma (SCC), and this entity represents 95% of penile cancers. Other subtypes include melanoma and basal-cell carcinoma. Herein we will concentrate on malignant SCC of the penis. It has been reported that penile SCC may demonstrate four different patterns of growth [8] differing in natural history and prognosis [9]: superficial spreading, vertical growth, verrucous growth and multicentric growth. This will be relevant to surgical management to ensure that any surgical resection adequately encompasses the potential patterns of spread.

3. TNM (primary tumour, regional nodes and metastasis) classification

The 2009 TNM classification listed in Table 1 has provided an update for the T1 category but still suffers from limitations in the T2 category, where corpus spongiosum involvement has been reported to be associated with a better prognosis than corpora cavernosa involvement [10]. Another limitation of the current TNM system is the lack of differentiation between T2 and T3 disease. One improvement is that the identification of retroperitoneal nodal disease is now accurately regarded as extra-regional disease or distant metastasis (M1).

4. Prognostic factors

Early diagnosis and adequate staging is crucial to ensure that management is organised appropriately. Full examination of the penis and particularly of the surrounding nodal drainage regions is needed, as the primary drainage of the penis is into the inguinal nodes. In the clinically negative inguinal the use of ultrasonic sound may identify suspicious nodes suitable for fine-needle aspiration (FNA). Recent advances and improved techniques...
for sentinel-node biopsy have provided better identification of the relevant inguinal node(s) and have permitted extraction of the node for full histological evaluation compared with the limitations of using FNA.

5. Clinical presentation and diagnosis

It is important to make a detailed examination of the penis with attention to the dimensions and location of the lesion and its relationship to the musculature of the penis. A deep biopsy is needed in equivocal cases, with dorsal slitting if there is a tight phimosis. Full assessment of the regional drainage regions, i.e., inguinal, is mandatory. If there are palpable nodes, then an FNA with or without ultrasound guidance should be undertaken. Further staging of the pelvis and abdomen will be needed using a computed tomography (CT) scan of the thorax, abdomen and pelvis. The role of magnetic resonance imaging (MRI) and positron emission tomography (PET) staging has not been fully established and remains under investigation. In clinical cases of negative inguinal nodes, where there is moderate to high risk of nodal involvement (>T1 G2), then dynamic sentinel node examination should be undertaken. The management schema described herein provides the policy guidelines followed within our supra-regional centre, one of the largest services within the United Kingdom.

6. Management of primary disease

Ta lesions are treated conservatively, usually with circumcision for lesions located over the prepuce, whilst lesions on the glans can be treated using a wide local excision for smaller lesions, or for larger lesions a total glans resurfacing or glansectomy. T1 lesions of the prepuce are treated with circumcision, while lesions on the glans can be managed by either penis-preserving surgery or radiotherapy. Penis-preserving surgery may utilise a wide local excision that may include skin grafting or glansectomy and skin grafting. Radiotherapy may be delivered using external-beam irradiation or brachytherapy which is the implantation of radioactive wires within the vicinity of the extent of the lesion.

T2/T3 lesions of the penis can also be treated conservatively with surgery if there is only distal involvement of the glans and/or corporal heads, but frozen sections of the resection margins are needed to ensure adequacy of surgical clearance. The penis-preserving surgical methods include glansectomy and skin-graft reconstruction, or glansectomy and distal corporectomy and reconstruction. If clinically appropriate, penis preservation may also be considered for proximal lesions. In these cases, delayed reconstruction with a penile lengthening procedure may be considered. If penis preservation surgery is not possible, then another alternative
is to use radiotherapy as described above, or radical penectomy with perineal urestomy.

T4 lesions of the penis often require multimodal therapy for adequate local control. Down-staging with neo-adjuvant chemotherapy should be considered. The standard chemotherapy is usually a platinum-based regimen, often in combination 5-fluoro-uracil (5-FU) or capecitabine. The surgery is a penectomy with perineal urestomy. Alternatively, radiotherapy can be considered for local control in selected cases.

7. Management of the regional nodes

7.1. Clinically node negative at presentation

G1 Ta to T1 disease: in these cases, those patients with a negative ultrasound and FNA are at very low risk of nodal disease and they can safely be observed.

G2 T1 lesions and above or T2 lesions G1-3: those patients with both a negative ultrasound FNA and dynamic sentinel node study are managed with surveillance. The surveillance programme involves clinical 2-monthly follow-up for the first year, 3-monthly follow-up for the second year and 4-monthly follow-up for the third year. During each follow-up visit, a full physical examination of the region is conducted, with ultrasound examination of the inguinal regions. A CT scan is undertaken only where there are specific clinical indications. For patients in whom the ultrasound FNA or dynamic sentinel node study is possible, then a modified radical inguinal node dissection will be performed on the ipsilateral side, with observation of the contralateral inguinal region. In these cases, all patients should have a staging CT scan of the thorax, abdomen and pelvis as a baseline, and this should be repeated every 6 months for 3 years.

7.2. Clinically node positive at presentation

Those patients with clinically positive nodal disease should receive a modified radical inguinal-node dissection on the ipsilateral side and a dynamic sentinel-node study on the contralateral side. Baseline CT staging is also needed, with any other imaging based on clinical indications.

Those patients who have been found to have extracapsular disease involvement should be offered postoperative radiotherapy to the ipsilateral region. For patients with multiple or bilateral superficial nodes, then bilateral inguinal-node dissection should be performed with consideration of pelvic nodal dissection. Postoperative radiotherapy should be offered in the presence of extracapsular disease involvement of the inguinal or pelvic nodal regions. Alternatively, if pelvic-node dissection cannot be undertaken, then external-beam radiotherapy can be used to cover the regions of risk together with the inguinal regions of extracapsular disease involvement. If there is large-volume pelvic disease then consideration should be directed towards combination therapy using chemotherapy to the pelvis followed by consolidation chemotherapy or initial chemotherapy followed by chemotherapy to the pelvis. There are currently no evidence-based data on the most suitable management course or sequence of therapies in these cases.

Chemotherapy for node-positive or high-risk disease is not given routinely. Where possible, recruitment into clinical trials of adjuvant therapy is strongly encouraged.

7.3. Fixed or fungating inguinal nodes

In this situation, palliative inguinal-node dissection with appropriate covering flaps undertaken by a supporting plastic surgery team should be considered. External-beam radiotherapy may also be used postoperatively if there is extensive residual disease or as monotherapy for symptomatic palliative intent.

7.4. Metastatic disease

The common sites of metastatic penile cancer disease are in the lungs, liver or nodal regions outside of the pelvis. The aim of palliative chemotherapy is to limit disease progression and to improve symptoms with the aim of maintaining a good quality of life for a good duration. Chemotherapy regimens are usually platinum-based (cisplatin or carboplatin, depending on renal clearance) in combination with either capecitabine or 5-fluorouracil. Other regimens include the combinations of carboplatin, methotrexate and bleomycin if fluoropyrimidines are contraindicated for cardiovascular disease. Alternatively taxane-containing regimens have been used. For localised metastatic lesions, palliative radiotherapy is effective in reducing painful symptoms.

8. Palliative care

Palliative care is an important aspect of management that requires multidisciplinary input as outlined in the introduction. Integrated coordination between cancer teams and local support teams is vital and should be initiated early in the course of management.

9. Conflict of interest statement

The author has disclosed no conflict of interest for this body of work.

For further reading, please see references [11–19].

REFERENCES


Practical tips and tricks with recently approved molecular targeted agents in non-small-cell lung cancer

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The detection of driver mutations in the epidermal growth factor receptor (EGFR), the rearrangement of anaplastic lymphoma kinase (ALK) genes and the subsequent development of targeted therapy have transformed the treatment of lung cancer. In a Caucasian population, as illustrated by the Biomarker France database, these alterations represent 9.4% and 4.0%, respectively, in 10,000 samples of non-small-cell lung cancer (NSCLC) [1]. Of these patients, 56.9% received treatment according to their molecular profile, either with labelled drugs or in a bio-guided trial. Similarly, the Lung Cancer Mutation Consortium, after testing more than 1000 patients with lung adenocarcinoma, found 15% to harbour an EGFR mutation and 8% an ALK rearrangement [2]. An actionable driver alteration was detected in 62% of these tumours. The use of targeted therapies has raised practical questions related to therapy sequences and durations, the role of chemotherapy, the role of combination with chemotherapy, the validity of Response Evaluation Criteria in Solid Tumours (RECIST) criteria, utility of therapeutic rechallenge with the same drugs and several additional issues that arise in the wake of all significant medical progress. This article will address some of these questions and highlight some areas of controversy.

2. Whom and when to test?

The College of American Pathologists recommends testing for EGFR mutations and ALK rearrangements in all patients with lung adenocarcinoma, irrespective of clinical characteristics. In the setting of lung cancer resection specimen availability, EGFR and ALK testing is recommended for adenocarcinomas and mixed lung cancers with an adenocarcinoma component, but is not recommended in lung cancer that lacks any adenocarcinoma component. In the setting of more limited lung cancer specimens (biopsy, cytology) where an adenocarcinoma component cannot be excluded, EGFR and ALK testing may be performed in cases showing squamous- or small-cell histology, with clinical criteria such as young age and lack of smoking history being useful in selecting the subset for testing. Primary tumours or metastatic lesions are considered equally suitable for testing, and testing of many different areas within a single tumour is not necessary. For patients with multiple, apparently separate, primary lung adenocarcinomas, each tumour should be evaluated. Testing should be ordered at the time of initial diagnosis of advanced-stage disease (stage IV according to the tumour-node-metastasis (TNM) staging system 7th edition) or at the time of recurrence or progression in patients who originally presented with lower-stage disease. Testing for EGFR should be prioritised over other molecular markers, followed by ALK, and only later other molecular markers in lung adenocarcinoma, for which published evidence is insufficient to support the development of testing guidelines at the present time [3].

3. When to start treatment?

First-line EGFR tyrosine kinase (TKI) therapy in patients whose tumour harbours an activating mutation of the EGFR gene has not translated into prolonged overall survival in four randomised trials with mature overall survival (OS) data [4–7], owing to the fact that the vast majority of patients receiving chemotherapy as first-line treatment received EGFR TKI as salvage therapy upon disease progression [4–9].

Why do guidelines advocate use of first-line over chemotherapy [10]? To start with, EGFR mutational status may be altered under first-line chemotherapy, and selection of patients for targeted therapy on the basis of molecular testing on the initial biopsy may be inadequate [11]. Furthermore, in the randomised trials, up to 41% of patients treated with initial chemotherapy did not receive second-line EGFR TKI, mostly because of rapid tumour progression leading to death or reduced performance status, thus excluding these patients from the opportunity to receive the most efficient treatment [5–7]. Quality-of-life data also favour use of EGFR TKI over...
chemotherapy in first-line treatment. Finally, the high intracranial response rate of EGFR TKIs may defer use of cerebral radiotherapy in patients with central nervous system metastatic disease.

ALK TKIs such as crizotinib are being studied for first-line treatment. Their use is restricted to second and further lines at the present time. OS has not been reported, and is unlikely to be improved as the study design allowed for cross-over to crizotinib in the control arms upon disease progression.

4. Which TKI to choose?

Gefitinib, erlotinib and afatinib have shown significant prolongation of progression-free survival (PFS) in the first-line setting as compared with a platinum doublet. No adequately powered trial has compared these TKIs. Gefitinib and erlotinib are both appropriate as first-line treatment, afatinib being commercially unavailable at the present time with a possible slightly higher gastrointestinal toxicity.

5. When to stop treatment?

All patients on EGFR TKI ultimately develop acquired resistance, which translates into progressive disease as per RECIST criteria. However, only a fraction of tumour clones might carry a resistance mechanism, and interruption of TKI therapy may result in tumour flares. The ASPIRATION trial (NCT01310036) currently compares PFS evaluated by RECIST criteria with PFS until ‘progressive disease according to the investigator’, defined as symptomatic progression, multiple progression or threat to a major organ. A randomised phase II trial compared chemotherapy plus erlotinib with chemotherapy alone in EGFR TKI-responsive NSCLC that subsequently progresses [12]. No improvement in PFS or OS could be detected, although the number of enrolled patients was low and the trial terminated early. Improvement in RR but not in PFS or OS could be shown in a recent retrospective trial [13]. However, the controversy about continuing EGFR TKI beyond progression is ongoing, with promising retrospective results reported against the switch to chemotherapy [14,15] or by adding local treatment to TKI [16], or combining TKI with chemotherapy [17]. The IMPRESS trial is an ongoing phase III trial expected to clarify the role of TKIs beyond progression. For progression limited to the brain, local therapy to the area of progression may lead to prolonged disease control.

6. What to do upon disease progression?

Despite initial activity of EGFR TKIs, all patients eventually develop acquired resistance. The most common mechanism of resistance is the EGFR T790M secondary mutation, which accounts for 50–60% of cases, and results in increased kinase affinity for adenosine triphosphate [18]. Second-generation EGFR TKIs – such as neratinib, afatinib and dacomitinib – are effective in preclinical gefitinib- and erlotinib-resistant EGFR T790M models, but to date their delivery in EGFR TKI-resistant patients have shown disappointing results in the clinic. Combination of afatinib with cetuximab in EGFR TKI-resistant patients resulted in a 30% response rate and 75% disease control rate, with significant gastrointestinal toxicity [19]. Other mechanisms of resistance include MET amplification, with no commercially available inhibitor, HER2 amplification potentially amenable to treatment with anti-HER2 monoclonal antibodies or histological transformation to small-cell lung cancer, which requires cytotoxic chemotherapy. Additional potential mechanisms of acquired resistance to EGFR TKIs may develop, including altered EGFR trafficking, amplification or activation of downstream or overlapping pathways and expression of drug-efflux transporters. Standard treatment upon progression on EGFR TKI remains cytotoxic chemotherapy. Later rechallenge with EGFR TKI may result in some modest degree of response (range 4–24%) and a significant disease control rate (range 45–67%) [20–22]. Resistance mechanisms to crizotinib are multiple, and include ALK-dominant mechanisms such as resistance mutations and copy number gain, and ALK non-dominant mechanisms through the outgrowth of clones containing a separate activated oncogene. In contrast to the EGFR setting, where the T790M mutation predominates, the spectrum of ALK resistance mutations is broad. Several distinct second-generation ALK inhibitors which are potentially efficient in preventing/overcoming TKI resistance are under development. A response rate of 80% has been observed during treatment with LDK378 in patients who had experienced disease progression after crizotinib treatment [23]. Similarly to EGFR TKIs, successful later rechallenge with ALK inhibitors has been reported in case reports [24].

7. What toxicity to expect?

Grade 3 or 4 toxicities occur infrequently with EGFR TKIs, with the exception of skin rash, fatigue and diarrhoea (13%, 6% and 5%, respectively in the Caucasian European Randomised Trial of Tarceva versus Chemotherapy (EURTAC) cohort). Grade 1 or 2 toxicities, however, occur in most patients, with rash, fatigue and diarrhoea bothering the majority of patients (67%, 51% and 52%, respectively), and with appetite loss, alopecia, anaemia and arthralgia occurring in a minority of patients (31%, 14%, 11% and 10%, respectively). Rare but potentially fatal interstitial pneumonitis occurs in 1% of patients. Overall, one third of patients require dose reduction or treatment discontinuation because of adverse effects [9]. Topical skin care is mandatory. Systemic antibiotics and anti-diarrhoeal drugs may be necessary to manage higher-grade toxicity.

Frequent toxicities of the ALK inhibitor crizotinib include vision disorders (62%), nausea (53%) and diarrhoea (43%). Patients are less frequently affected by oedema (28%), constipation (27%), fatigue (20%) decreased appetite (19%), dizziness (16%) and dysgeusia (12%). Potentially dose-limiting, increased alanine aminotransferase levels occur in 13% of patients, with less than 5% being of grade 3 or 4. Rapid-onset low testosterone is common in male patients. Renal cysts and pneumonitis have been described, but their frequency is unknown [25,26].

Conflict of interest statement

None declared.
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Role of expert centres in the management of sarcomas

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1. Introduction

Sarcomas are rare tumours of the connective tissue which may resemble a variety of tissues – such as muscle, nerve and bone – although many sarcomas have no normal tissue counterpart. The annual incidence of soft-tissue sarcomas (STSs) in England and Wales between 1990 and 2007 was 2300, which equates to about 40 per million per annum. Bone sarcomas are significantly less common, representing only 0.2% of all malignancies. Treatment within specialised multidisciplinary teams (MDTs) is crucial since a body of expertise in all areas of diagnosis and treatment is required to manage them appropriately. Studies have shown that conformity to approved treatment guidelines is improved when patients are treated by an MDT in a reference centre [1].

2. Diagnosis – histopathology, radiology

The risk of a tumour being metastatic at diagnosis, and of subsequent death, is directly related to tumour size [2]. Earlier diagnosis could have a huge impact, and guidelines are now in place in the UK to encourage early referral of suspicious lumps (or X-rays in the case of bone tumours).

Once a tumour is suspected, the two key diagnostic tools are radiology and histopathology. The initial assessment of suspicious lumps will be by physical examination and probably ultrasound, followed by core needle biopsy. Core needle biopsy has an accuracy of >90% as well as the ability to distinguish high-grade from low-grade lesions and in most cases the specific sarcoma subtype [3].

Cross-sectional imaging is required prior to surgery, in order to plan treatment and for staging. This is usually in the form of magnetic resonance imaging (MRI) for the primary disease site and computed tomography (CT) for staging purposes. It is common for the diagnosis of patients referred with a diagnosis of sarcoma to be revised to another subtype, another disease, or even a benign condition [4]. Reported discrepancy rates between referring and expert pathologists are generally in the order of 25%, with a benign to malignant discrepancy of 5%.

3. Sarcoma surgery

The primary management of most sarcomas is surgical excision. Unplanned operations, performed on the assumption that the “lump” is benign, can make the eradication of disease much more difficult. A study demonstrated that patients who had unplanned surgery had a much higher local recurrence rate and poorer long-term disease control, in spite of definitive surgery and radiotherapy [5]. All sarcoma operations should be performed in specialised centres in order to ensure optimum outcomes. For retroperitoneal surgery, where multivisceral resections are common, guidance is available [6]. The NICE (National Institute for Health and Care Excellence) Improving Outcomes Guidance (IOG) for people with sarcoma recommended that specialised centres should treat a minimum of 100 STS a year and 50 in the case of bone sarcomas. The IOG, which also addresses wider issues concerning the sarcoma MDT, can be obtained using the following URL: http://guidance.nice.org.uk/CSG

4. Radiation oncology

Adjuvant radiotherapy improves the local control of high-grade extremity soft tissue sarcomas [7]. Research continues into the appropriate timing, dose and field size of adjuvant irradiation. The complexity of pre- and post-operative radiotherapy for sarcomas is such that specialised centres are best placed to offer the appropriate expertise, in the context of the MDT.
5. Medical oncology

Chemotherapy for most sarcomas is palliative, but nevertheless valuable. Recent years have seen a significant increase in treatment options and tailoring of treatment to the individual disease subtype. The standard agents, doxorubicin and ifosfamide, remain useful, but other drugs are now in routine use, including gemcitabine plus docetaxel for leiomyosarcoma and pleomorphic sarcoma [8,9], trabectedin for leiomyosarcoma and liposarcoma [10] and paclitaxel for angiosarcoma [11]. The management of gastrointestinal stromal tumour (GIST) was transformed by the introduction of imatinib [12,13], and subsequently sunitinib [14]. More recently another tyrosine kinase inhibitor, pazopanib, has been licensed for treatment of STS [15]. Certain rarer diseases require special approaches: e.g. the use of rapamycin analogues for PEComa, imatinib for chordoma, tamoxifen for fibromatosis and aromatase inhibitors for endometrial stromal sarcoma.

6. Clinical trials and data collection

Clearly, for such a rare group of diseases it is essential that care be concentrated in specialised centres which can treat patients in appropriate clinical trials. These will not be available in smaller centres, putting patients at a disadvantage. The cumulative experience of the MDT together with the amalgamation of clinical and laboratory data also represent a major resource for research and the opportunity to use these data directly for the benefit of patients.

7. The wider multidisciplinary team

In addition to surgeons, radiation and medical oncologists, radiologists and histopathologists, the MDT will have clinical nurse specialists, physiotherapists, dieticians, palliative care physicians and site-specific specialists. As described, the management of sarcomas is truly multidisciplinary, increasingly complex and, as more molecular targets are identified, more likely to be treated with highly specific targeted therapy. The need for specialised centres has been recognised in the UK, and a process, informed by the NICE IOG, is leading to the concentration of care in a limited number of centres. We hope that earlier diagnosis, fewer unplanned operations and better integrated care will lead to a significant improvement in outcomes, which have not changed over the last 20 years (http://www.ncin.org.uk/publications/data_briefings/soft_tissue_sarcoma). We can only hope to do better.

Conflict of interest statement

None declared.

References

Therapeutic procedures in liver metastases: Conventional and future measures

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1. Background

Resection of liver metastases from colorectal carcinoma (CRC) is associated with 5-year survival rates of 30–40%, with the possibility of cure, even in the absence of systemic therapy. This demonstration of a local therapy improving outcomes for ‘oligo-metastatic’ CRC is well accepted. Long-term survivors have also been reported following resection of liver metastases from sarcoma, renal-cell carcinoma, breast cancer and melanoma, with 5-year survival rates of 23–36% in a series of non-CRC liver metastases. Resection of neuroendocrine liver metastases has also been associated with favourable survival.

Stereotactic body radiation therapy (SBRT) is an attractive option for patients with liver metastases. Liver SBRT requires a planning computed tomography (CT) simulation scan with intravenous (IV) contrast for target definition. Multimodal imaging with contrast-enhanced magnetic resonance imaging (MRI) or positron emission tomography (PET) may improve target delineation. Breathing-related liver motion should be assessed by respiratory-correlated (or 4D) CT, cine-MRI or 2D kV fluoroscopy to determine appropriate planning target volume (PTV) margins. Highly conformal dose distributions are desirable using multiple beams or arcs in coplanar or non-coplanar geometries. The nominal prescribed dose should reflect the isodose that encompasses the PTV (or 95% of the PTV) with hotspots within the PTV. Immobilization of the liver using controlled breath holds, shallow breathing, abdominal compression and gating of the RT (radiation therapy) beam during specified phases of the respiratory cycle, medications and tumour tracking of implanted fiducial markers may help reduce the adverse effects of breathing motion. Image-guided RT (IGRT) based on orthogonal imaging, ultrasound or volumetric imaging such as MV or kV cone beam CT, is required at every fraction in order to reduce PTV margins for setup uncertainty. MR IGRT is an area of active research that may benefit patients requiring liver SBRT.

Advantages of SBRT include increased convenience for patients. Furthermore, there are preclinical data demonstrating dose-per-fraction effects (e.g. endothelial and immune effects), with a threshold of approximately 8 Gray (Gy). Clinical experience in SBRT for liver metastases is rapidly increasing.

2. Methods

Updated results from Princess Margaret Cancer Centre phase I/II studies of SBRT for liver metastases are presented, as well as a review of previously published SBRT studies and consensus statements of radiation therapy for liver metastases.

3. Results

In our centre in Toronto, a phase I/II study of individualised IGRT-guided SBRT was conducted in 107 patients with 172 unresectable or medically inoperable liver metastases from CRC, breast cancer or other primary sites [1]. The median tumour volume was 75 ml. Extrahepatic disease was present in 40 patients (43%), and 75% had received prior systemic therapy. Patients were treated with six-fraction SBRT (median dose 42 Gy, range 24–48 Gy). No radiation-induced liver toxicity was observed. Median survival was 18.1 months. The presence of extrahepatic disease was associated with worse survival. Prognostic factors for improved local control included breast primary site, dose and tumour volume. Some patients with CRC or breast cancer liver metastases are alive with no progressive disease more than 5 years post-SBRT.

In a subset of patients from the Toronto cohort with unresectable liver metastases who had kV cone-beam CT scans at each fraction, the cone-beam CTs were used in combination with deformable image registration to deter-
mine the accumulated delivered dose (versus the prescribed dose). Accumulated minimum doses to the GTV (gross tumour volume) of <35 Gy, 35–45 Gy and >45 Gy, in six fractions were associated with 18-month local control of 33%, 55% and 83%, respectively. The dose–response relationship was steeper for accumulated dose compared with prescribed dose.

Most published SBRT studies have prescribed doses in the range 30–60 Gy in 1–6 fractions, for ≤5 metastases, with maximal tumour sizes ≤6 cm. CRC liver metastases are the most frequent tumour type. However, an increasing number of patients with liver metastases from breast and lung cancer are being included in recent SBRT series. In the published series, survival rates have been better than those expected following systemic therapy alone. Toxicity is uncommon as long as enough uninvolved liver can be spared from radiation therapy (e.g. >700 ml receiving 15 Gy in three fractions or mean liver dose <18 Gy in six fractions). Local control of the irradiated liver metastases at 1 year ranges from 67% to 100%. The median survival of patients treated with SBRT ranges from 18 to 37 months, with the best outcomes seen in a more recent series.

A dose response has been observed in most series, with an increased chance of sustained local control (80–90% at 2 years) when doses >42 Gy in three fractions are used. Local control is also improved in patients with metastases <3 cm in maximal size and in breast cancer metastases compared to colorectal cancer metastases.

In a pooled analysis of SBRT for CRC metastases [2], dose was the only significant prognostic factor for local control and extra-hepatic disease and local recurrence were associated with impaired survival. A dose of 48–51 Gy in three fractions was estimated to be associated with a 1-year local control rate of 90%.

An international subcommittee – with members from the American Society for Radiation Oncology (ASTRO), the European Society for Therapeutic Radiology and Oncology (ESTRO), the Canadian Association of Radiation Oncology (CARO) and the Trans-Tasman Radiation Oncology Group (TROG) – led by Hoyer et al [3] developed a consensus statement of liver metastases radiation therapy. Ideal candidates for SBRT were described as patients with good performance status (ECOG 0–1), possessing adequate hepatic function, with no extrahepatic disease, having ideally ≤5 liver metastases and an uninvolved liver volume >700 ml. As outcomes are best following higher-dose SBRT, most suitable patients include those with a focal distribution of metastases, at least 1 cm from luminal gastrointestinal organs. Breast cancer metastases appear more sensitive than CRC metastases. The consensus statement described uncommon toxicity in the liver, with increased risk in patients re-irradiated and/or with prior liver disease. Luminal gastrointestinal toxicity and chest wall and rib fractures have also occasionally been seen. Of note, the consensus statement briefly reviewed non-SBRT methods of delivering high-dose radiation therapy to liver metastases, including conformal radiation therapy, selective internal radiation therapy (e.g. hepatic arterial delivery of yttrium) and interstitial or intraluminal brachytherapy.

In addition, patients with diffuse symptomatic liver metastases were highlighted as a population largely understudied, in whom low-dose palliative whole-liver radiation therapy may be of benefit. In a pilot study of 20 patients with symptoms from diffuse liver metastases at the Princess Margaret Cancer Centre, approximately 50% of the patients had a patient-reported benefit in pain or discomfort at 1 month following 8 Gy in one fraction. Based on this, a phase III study of simple palliative radiation therapy compared to best supportive care is planned (HE.1, through the National Cancer Institute of Canada Clinical Trials Group).

### 4. Conclusions

SBRT is a promising treatment for patients with focal ‘oligo’ liver metastases. The most suitable patients with liver metastases are those with three or fewer metastatic tumours, each <6 cm, with no extrahepatic disease and with metastases at least 2 cm from the luminal gastrointestinal tissues. More research is required regarding optimal dose-per-fraction and mechanisms, as well as the most appropriate patient selection.

### Conflict of interest statement

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### References

Together we are better: Establishing a community oncology nursing programme to improve cancer care through shared working

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1. Background and introduction

One in three people in Ireland will develop cancer during their lifetime, and over 29,000 new cases of cancer are diagnosed each year [1]. Due to an aging population and improved screening/detection of cancer, the incidence is expected to rise exponentially to over 40,000 per year by 2020 [1] with an estimated 100% increase in cancer incidence over the next 20 years [2].

Many, if not all, of these people will require nursing care during their cancer experience. Currently, 42% of the men and 50% of the women diagnosed with cancer survive for 5 years and longer [1,2] and require ongoing follow-up, support and/or treatment(s). The increasing number of individuals with cancer receiving potentially life-threatening treatments which have significant side-effects causes a considerable challenge for acute hospital services.

2. Community care

Most individuals receiving treatment for cancer attend a treating cancer unit for therapies and are then discharged home; thus most side-effects are experienced within the community setting. This model of cancer care has the aim of retaining the patient in their own environment, yet oncology health professionals are cognisant of the requirement to provide continuous, safe and efficient cancer care.

3. Development of a training programme

The National Cancer Strategy (2006) for Ireland recognised the need for improved integration between specialist and primary health-care services. Since 2007, specialist oncology personnel in a district general hospital in a rural county in Ireland (County Donegal) have collaborated with community nursing colleagues to provide specific procedures in the community to patients undergoing systemic therapy.

Following discussions between the national department for cancer care in Ireland (National Cancer Control Programme), the local oncology hospital and community nursing staff, it was agreed that this initiative could be formalised and developed to provide a more holistic shared care approach. This programme could then be accredited by educational authorities to make it available nationally.

4. Delivery of the community training programme

In 2010, the National Cancer Control Programme developed the Community Oncology Nursing Programme. Its aim was to build capacity, confidence and competence in community professionals to provide integrated seamless care throughout the patient journey. The course was delivered over a 6-month period and involved local staff delivering appropriate education on cancer care relevant to community nurses. The training was theoretical and skill-based and was approved by the Irish Nursing Board (An Bord Altranais).

National and local governance structures and processes were established through a local implementation group. Ethical approval was sought and obtained through the local hospital ethics committee. Project design, implementation, data collection, analysis and evaluation involved collaboration with relevant nursing, medical and management representatives from community, hospital and nurse education.

A key safety feature built into the programme included assessment of community nurses’ knowledge, skills and competence upon completion of training. A designated referral
form and a Community Oncology Nursing Resource Book [3] were developed to support the Community nurses’ extended roles.

A full evaluation of this educational initiative was performed by the National Cancer Control Programme and is currently in press [4]. The evaluation involved patient interviews, focus groups with community and hospital staff and analysis of longitudinal data obtained from patient interventions in both hospital and community.

5. Evaluation of patient outcomes

This programme reduced the patient’s burden of travel and the additional pressures on their family of having to make repeated journeys to the hospital. For the majority of patients in the study, the return hospital trip was 1½–2 h. Patients appreciated not having to travel for all of their care, particularly at times when they were weak and unwell. Patients valued having aspects of their care delivered at home, and they reported that it improved their quality of life. Most importantly the patients expressed confidence in the community nursing service and no adverse patient events occurred throughout the evaluation period.

6. Evaluation of nursing outcomes

A benefit for nursing included an increased scope of practice for the community nurses involved, but the additional workload, particularly within an already stretched service, was identified as a challenge. By its nature, the timelines and immediacy of some cancer interventions resulted in rescheduling of other non-cancer patient visits and clinics. There was a dramatic decrease in hospital attendances for defined clinical procedures that were then performed in the community. Consequently hospital capacity was improved and no adverse patient events occurred.

7. Future plans

The collaborative approach offered by local hospital oncology specialists, community nurses and educational leaders helped to develop the required skills and attitudes to provide innovative and safe patient care. University accreditation is currently being sought for this educational programme, and once this is obtained it will then be expanded nationally. In addition, the service is a good example of patient-centred integrated care and could be further developed as a model for other chronic diseases.

To ensure continued safety, auditable systems and formalised policies/standard operational procedures are vital for shared care between the hospital and the community. It is hoped that these will be developed in the future.

The evaluation highlighted that for community nurses there is great variability in the interventions performed since they have been trained. Consequently ongoing training continues to be made available locally (up to four times a year) in a theoretical and skills-based workshop format to ensure maintenance of competence.

8. Conclusion

This programme has been successful in terms of quality of life for patients. By taking an integrated approach to patient care and delivering appropriate care in the community, the potential exists to meet the growing demands of oncology care. The community nursing service has adapted and expanded to embrace this new initiative, has increased its scope of practice and has increased its partnership with hospital staff in the care of individuals with a cancer diagnosis.

This programme demonstrates that safe, seamless and efficient nursing care can be delivered so long as there is prior and extensive planning, detailed collaboration and efficient leadership. Shifting oncology care to the community can have a positive impact on the patient’s quality of life and can improve hospital capacity through shared working.

In line with the national cancer nursing strategy [5], this programme will be offered again and extended nationally once third-level educational accreditation is obtained. It will require ongoing evaluation and local planning and development with clinical leaders who are cognisant of appropriate utilisation of resources. The potential for improvement for cancer care in Ireland through shared working between hospital and community staff will continue to be promoted and maximised in the future.

9. Conflict of interest statement

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