Monitoring treatment response in metastatic breast cancer

impact of FDG-PET/CT on survival and costs

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PhD Thesis

Monitoring treatment response in metastatic breast cancer: impact of FDG-PET/CT on survival and costs

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List of original papers

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II. Naghavi-Behzad M, Oltmann HR, Alamdari TA, Bülow JL, Ljungstrøm L, Braad PE, Asmussen JT, Vogsen M, Kodahl AR, Gerke O, Hildebrandt MG. Clinical Impact of FDG-PET/CT Compared with CE-CT in Response Monitoring of Metastatic Breast Cancer. Cancers (Basel). 2021 Aug 13;13(16):4080.

III. Naghavi-Behzad M, Gerke O, Kodahl AR, Vogsen M, Asmussen JT, et al. Cost-effectiveness of FDG-PET/CT vs. CE-CT for response monitoring in patients with metastatic breast cancer: a register-based comparative study. (Under review).

List of supplementary papers

The followings researches conducted during the PhD in field of metastatic breast cancer:

I. **Naghavi-Behzad M**, Petersen CB, Vogsen M, Braad PE, Hildebrandt MG, Gerke O. Prognostic Value of Dual-Time-Point (18)F-Fluorodeoxyglucose PET/CT in Metastatic Breast Cancer: An Exploratory Study of Quantitative Measures. Diagnostics (Basel). 2020;10(6).

II. Hildebrandt MG, **Naghavi-Behzad M**, Vogsen M. A role of FDG-PET/CT for response evaluation in metastatic breast cancer? Semin Nucl Med. 2022;52(5).

III. Hansen JA, **Naghavi-Behzad M**, Gerke O, Baun C, Falch K, Duvnjak S, et al. Diagnosis of bone metastases in breast cancer: Lesion-based sensitivity of dual-time-point FDG-PET/CT compared to low-dose CT and bone scintigraphy. PLoS One. 2021;16(11).

IV. Vogsen M, Bülow JL, Ljungstrøm L, Oltmann HR, Alamdari TA, **Naghavi-Behzad M**, et al. FDG-PET/CT for Response Monitoring in Metastatic Breast Cancer: The Feasibility and Benefits of Applying PERCIST. Diagnostics (Basel). 2021;11(4).

V. Aarstad EM, Nordhaug P, **Naghavi-Behzad M**, Larsen LB, Gerke O, Hildebrandt MG. Prevalence of focal incidental breast uptake on FDG-PET/CT and risk of malignancy: a systematic review and meta-analysis. Eur J Hybrid Imaging. 2019;3(1).

VI. **Naghavi-Behzad M**, Vogsen M, Gerke O, Dahlsgaard-Wallenius SE, Nissen HJ, Jakobsen NM, et al. Comparison of image quality and quantification parameters between Q.Clear and OSEM reconstruction methods on FDG-PET/CT images in patients with metastatic breast cancer. J Imaging. 2023;9;9(3):65.

VII. Vogsen M, **Naghavi-Behzad M**, Harbo FG, Jakobsen NM, Gerke O, Asmussen JT, et al. 2-[^{18}F]FDG-PET/CT is a better predictor of survival than conventional CT: a prospective study of response monitoring in metastatic breast cancer. Sci Rep. 2023;5;13(1):5552.

VIII. Gram-Nielsen R, Vogsen M, Christensen IY, **Naghavi-Behzad M**, Dahlsgaard-Wallenius SE, Jakobsen NM. The Pattern of Metastatic Breast Cancer: a Prospective Head-to-head Comparison of [^{18}F]FDG-PET/CT and CE-CT (Under review).

Abbreviations

MBC	Metastatic breast cancer
FDG	^{18}F-fluorodeoxyglucose
FDG-PET/CT	^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography
CE-CT	Contrast-enhanced computed tomography
MRI	Magnetic resonance imaging
OS	Overall survival
KM	Kaplan-Meier
HR	Hazard ratio
CDK4/6	Cyclin-dependent kinase 4 and 6
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor-2
RECIST	Response Evaluation Criteria in Solid Tumors
PERCIST	Positron Emission Tomography Response Criteria in Solid Tumors
SUV	Standardized uptake values
DRG	Diagnose related groups
QALY	Quality-adjusted life year
ICER	Incremental cost-effectiveness ratio
FAPI	Fibroblast activation protein inhibitor
^{18F}FES-PET/CT	^{18F}Fluorine-oestradiol-Positron Emission Tomography/computed tomography
^{18F}NaF-PET/CT	Sodium ^{18F}Fluoride-Positron Emission Tomography/computed tomography

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English summary

Background: Various diagnostic modalities are being used for staging metastatic disease in breast cancer patients since international guidelines do not yet provide clear recommendations on the modality of choice for this indication. Evidence has confirmed that ^{18}F-fluorodeoxyglucose-positron emission tomography with integrated computed tomography (FDG-PET/CT) has a perfect sensitivity for the diagnosis of distant metastases in this patient group. FDG-PET/CT may therefore also have the potential to improve monitoring of treatment response in patients with metastatic breast cancer, but research in this field has been scarce. We aimed to compare 1) response categories and their clinical impact, 2) survival times, and 3) cost-effectiveness of FDG-PET/CT versus contrast-enhanced computed tomography (CE-CT) for response monitoring in patients with metastatic breast cancer.

Methods: In this observational registry-based study, we included 300 biopsy-verified metastatic breast cancer patients, diagnosed and treated between 2004 and 2018 at the Department of Oncology at Odense University Hospital, Denmark. The response monitoring modalities used in the clinic varied mainly between CE-CT and FDG-PET/CT with the choice of the modality made by the oncologist. The patients were categorized into three groups: a CE-CT group (*n*=144), a FDG-PET/CT group (*n*=83), and a combined group (*n*=73). In the combined group, patients were monitored alternately with CE-CT and FDG-PET/CT, having a minimum of two scans of each modality, while only one of the opposite scan types was accepted in the CE-CT and FDG-PET/CT groups. The clinical and health-related cost information was gathered from patients' medical records, and the patients were followed until August 2019 for survival and cost-efficacy analyses. We analyzed the response categories and their impact on clinical decision making for subgroups of patients in the CE-CT (*n*=34, 286 scans) and the FDG-PET/CT groups (*n*=31, 189 scans). The overall survival time was defined as the time from confirmation of metastasis until death, using the end of the study period as the censoring event. The time to the first progression was defined to be from the baseline scan to the first progression that led to the patient's treatment change in the clinic. The Kaplan-Meier curve was used to estimate the survival function within the study groups. Cox regression model was restricted to the CE-CT group (set as reference) and the FDG-PET/CT group.

Results: The median (range) follow-up time was 33.0 (3.6-130.6) months. The groups were mostly comparable regarding the baseline characteristics, while a few characteristics with significant difference were not in favor of any of the groups. A statistically significant difference (P<0.001) was observed between the groups for the distribution of response categories; FDG-PET/CT reported regressive disease more frequently (46.0% vs. 12.2%), while CE-CT reported stable disease more often (70.6% vs. 31.2%). Median overall survival (month) was lower for the CE-CT group (30.0), compared with the FDG-PET/CT group (44.3) and the combined group (54.0). The hazard ratio was 0.44 (P=0.001) for the FDG-PET/CT group (vs. CE-CT group) after adjusting for baseline characteristics. Five-year survival probabilities were significantly higher for the FDG-PET/CT and the combined groups than for the CE-CT group (advantage of 26.1% and 27.5%, respectively). The first progression, leading to the treatment change, was appearing, on average, 4.7 months earlier in the FDG-PET/CT group than in the CE-CT group (12.9 vs. 17.6 months, P=0.03). The mean (range) total cost per patient was €91,547 (9,585-394,275) for the CE-CT group, €83,965 (17,390-341,934) for the FDG-PET/CT group, and €165,784 (30,269-585,875) for the combined group. Incremental cost-effectiveness ratio (ICER) for FDG-PET/CT (vs. CE-CT) was -527, indicating that response monitoring by FDG-PET/CT resulted in an extra month of survival at a lower cost (€527).

Conclusions: Metastatic breast cancer patients who were response monitored with FDG-PET/CT alone or in combination with CE-CT had an improved overall survival of 14-24 months compared to patients monitored with CE-CT alone. FDG-PET/CT detected changes in response (regression/progression) more frequently than CE-CT, and CE-CT reported stable disease more often. FDG-PET/CT seems to be a more sensitive and cost-effective modality than CE-CT for monitoring treatment response in metastatic breast cancer, while confirmation of these results are warranted in prospective multi-center randomized trials.

Keywords: Metastatic breast cancer; FDG-PET/CT; cost-effectiveness; response monitoring, contrast-enhanced CT; positron emission tomography

Danish summary

Baggrund: Internationale retningslinjer giver ikke klare anbefalinger om valg af billeddiagnostisk modalitet til diagnostik af metastatisk brystkræft, og forskellige modaliteter anvendes derfor og følger ofte lokal praksis. Der foreligger imidlertid evidens om, at ^{18F}Fluordeoxyglucose-positron emissions tomografi /computertomografi (FDG-PET/CT) har høj følsomhed til diagnostik af fjernmetastaser i denne patientgruppe. FDG-PET/CT kan derfor også have potentiale til at forbedre monitoreringen af behandlingsrespons hos patienter med metastatisk brystkræft, men forskning på dette område har været sparsom. Vi havde til formål at sammenligne 1) responskategorier og deres kliniske effekt, 2) overlevelse og 3) omkostningseffektiviteten af FDG-PET/CT versus kontrastforstærket computertomografi (CE-CT) til responsovervågning hos patienter med metastatisk brystkræft.

Metoder: I et observationelt register-baseret studie inkluderede vi 300 patienter med biopsi-verificeret metastatisk brystkræft, diagnosticeret og behandlet mellem 2004 og 2018 på Onkologisk Afdeling, Odense Universitetshospital. Valg af billeddiagnostisk modalitet til responsmonitorering blev foretaget af den behandlende onkolog i klinikken. Valget varierede hovedsageligt mellem CE-CT og FDG-PET/CT. Patienterne blev kategoriseret i tre grupper: en CE-CT-gruppe (n=144), FDG-PET/CT-gruppe (n=83) og en kombineret gruppe (n=73). I den kombinerede gruppe blev patienterne overvåget skiftevis med CE-CT og FDG-PET/CT med minimum to scanninger af hver modalitet. Kun én af de modsatte scanningstyper blev accepteret i CE-CT og FDG- PET/CT-grupper. Kliniske og sundhedsrelaterede omkostningsoplysninger blev indsamlet fra patienternes journaler, og patienterne blev fulgt indtil august 2019, hvor analyser af overlevelse og omkostningseffektivitet blev foretaget. Vi analyserede endvidere responskategorierne og deres indvirkning på klinisk beslutningstagning for undergrupper af patienter i CE-CT (n=34, 286 scanninger) og FDG-PET/CT-grupperne (n=31, 189 scanninger). Den samlede overlevelsestid blev defineret som tid fra bekræftelse af metastase til død, idet slutningen af undersøgelsesperioden blev brugt som censureringshændelse. Tiden til den første progression blev defineret til at være fra baseline-scanningen til den første progression, der førte til behandlingsændring i klinikken. Kaplan-Meier kurver blev brugt til at estimere overlevelsesfunktionen i undersøgelsesgrupperne.

Cox-regressionsmodellen var begrænset til CE-CT-gruppen (sat som reference) og FDG-PET/CT-gruppen.

Resultater: Den mediane (min-max) opfølgningstid var 33,0 (3,6-130,6) måneder. Grupperne var overvejende sammenlignelige med hensyn til baseline-karakteristika. Nogle få karakteristika havde signifikant forskellig fordeling mellem grupperne, men de var ikke var til fordel for nogen af grupperne. For eksempel var det flere patienter i CT-gruppen levermetastaser, mens flere patienter i PET-gruppen var med lungemetastaser. Vi observerede en signifikant forskel (P<0,001) mellem grupperne i fordeling af responskategorier; FDG-PET/CT rapporterede hyppigere sygdomsregression (46,0% vs. 12,2%), mens CE-CT rapporterede stabil sygdom oftere (70,6% vs. 31,2%). Median samlet overlevelse (måned) var lavere for CE-CT-gruppen (30,0) sammenlignet med FDG-PET/CT-gruppen (44,3) og den kombinerede gruppe (54,0). Hazard-ratio var 0,44 (P=0,001) for FDG-PET/CT-gruppen (vs. CE-CT-gruppen) efter justering for baseline-karakteristika. Femårs overlevelsessandsynligheder var signifikant højere for FDG-PET/CT og de kombinerede grupper end for CE-CT gruppen (fordel på henholdsvis 26,1% og 27,5%). Den første progression, der førte til behandlingsændring, forekom i gennemsnit 4,7 måneder tidligere i FDG-PET/CT-gruppen end i CE-CT-gruppen (12,9 vs. 17,6 måneder, P=0,03). Den gennemsnitlige (min-max) samlede pris pr. patient var €91.547 (9.585-394.275) for CE-CT-gruppen, €83.965 (17.390-341.934) for FDG-PET/CT-gruppen og €165.784 (30.287-585) for den kombinerede gruppe. "Incremental cost-effectiveness ratio" (ICER) for FDG-PET/CT (vs. CE-CT) var -527, hvilket betyder, at responsmonitorering med FDG-PET/CT resulterede i en ekstra måneds overlevelse til en lavere pris (€527).

Konklusioner: Patienter i behandling for metastatisk brystkræft, som fik overvåget behandlingseffekten med FDG-PET/CT alene eller i kombination med CE-CT havde en forbedret samlet overlevelse på 14-24 måneder sammenlignet med patienter monitoreret med CE-CT alene. FDG-PET/CT påviste ændringer i respons (regression/progression) hyppigere end CE-CT, der oftere rapporterede stabil sygdom. FDG-PET/CT ser ud at være en mere følsom og omkostningseffektiv modalitet end CE-CT til overvågning af behandlingsrespons hos patienter med metastatisk brystkræft. Disse resultater ønskes imidlertid efterprøvet, helst i et prospektivt multicenter randomiseret forsøg.

Introduction

Breast cancer is one of the leading causes of cancer-related deaths worldwide (1). The therapeutic goal for breast cancer patients with distant metastases is to prolong survival (2). The treatment landscape for metastatic breast cancer (MBC) patients has evolved significantly over the past few decades, whereas the efficacy of treatment options is highly dependent on tumor characteristics (3). Targeted therapies can potentially prolong the survival of MBC patients (4).

Along with effective medical treatment, monitoring of the stage of the disease is recommended to guide treatment decisions over time (5, 6). International guidelines do not provide a clear recommendation on modality of choice for response monitoring of MBC patients (7, 8). Contrast-enhanced computed tomography (CE-CT) is mostly used in clinical practice (8), while results of a meta-analysis have shown a higher sensitivity for ^{18}F-fluorodeoxyglucose-positron emission tomography with integrated computed tomography (FDG-PET/CT) than conventional imaging for diagnosing distant metastases (99% vs. 57%) (9). FDG-PET/CT even showed a similar diagnostic accuracy in predicting progression to Magnetic resonance imaging (MRI) in bone-predominant MBC patients received endocrine therapy (10). A recent prospective study on 87 MBC patients from our institution suggested that FDG-PET/CT could detect the first progression, up to six months, earlier than CE-CT (11). FDG-PET/CT has also been shown to be a superior predictor of progression-free and disease-specific survival than CE-CT in MBC patients, and therefore, response monitoring by FDG-PET/CT may improve the patient management and clinical decision-making (7, 12). However, the cost of using FDG-PET/CT for response monitoring of metastatic disease has been a concern for healthcare providers (3, 13). Yet, no clear economic evaluation comparing the two diagnostic modalities (CE-CT vs. FDG-PET/CT) has been done to determine how efficiently they use healthcare resources to monitor MBC patients (14, 15).

In this retrospective study on 300 biopsy-verified metastatic breast cancer patients, we aimed to provide a comprehensive comparison of using FDG-PET/CT versus CE-CT for monitoring treatment response in metastatic breast cancer patients. The specific objectives were to compare response categories and their impact on clinical decision-making (**Paper I**), survival times (**Paper II**), and cost-effectiveness (**Paper III**) of FDG-PET/CT vs. CE-CT for response monitoring in MBC patients.

Background

Metastatic breast cancer

Breast cancer is the most frequent (11.7%) type of cancer among women, with 2.3 million newly diagnosed cases in 2020 worldwide (16, 17). Despite improvements in primary breast cancer treatment, around 27% of patients experience a distant recurrence (18, 19). The therapeutic goal is to improve the survival, since there is no complete cure for this group of patients (2). Although recent studies confirmed an improvement in survival of metastatic patients over time (20), the 5-year overall survival (OS) is still under 30% in patients with distant metastasis (21). Novel treatments such as CDK4/6 inhibitors have improved life expectancy for MBC patients (22, 23). Estrogen receptor-positive, HER2 negative MBC patients, who received CDK4/6 inhibitors with the addition of endocrine therapy is expected to have OS of up to five years (24). Patients with triple-negative MBC have shorter life expectancy (25), while the patients with bone-only metastases are associated with longer survival times (26, 27). Bone metastases is seen in up to 80% of the MBC patients, and is detected as the first site of metastasis within 25% to 40% of the patients (28). Bone metastases often present as bone pain and is complicated by skeletal-related events, such as pathological fractures, spinal cord compression, and the need for surgery or skeletal radiotherapy (26). Osteoclasts and osteoblasts work in harmony to maintain the integrity of healthy bone through a balance between bone resorption and bone creation. Although osteolytic metastases predominate in breast cancer, mixed osteolytic and osteoblastic lesions are common. Here, a cancer cell-derived protein that is related to parathyroid hormone promotes the development of RANKL, which is linked to enhanced osteoclast maturation and bone resorption, overcoming attempts at osteoblastic bone creation and repair (29, 30). Following therapy, imaging modalities may not be able to distinguish between osteoblastic repair at metastatic sites and initial osteoblastic tumor-induced activity (31). Furthermore, approximately 10% of breast cancer patients present with metastasis initially when diagnosed with primary breast cancer, i.e., de-novo or primary disseminated disease (32, 33). The group of de-novo metastatic patients have relatively longer survival than those with recurrent MBC, while the OS is still poor and reported between 36-38 months (34, 35).

Treatment strategies in in metastatic breast cancer

Treatment options for MBC patients can include systemic therapies, such as chemotherapy (36), hormone therapy (37), and targeted therapy (5), as well as local treatments like surgery and radiation therapy (38). The specific treatment plan for a patient will depend on several factors, including the extent and location of the cancer, as well as the patient's overall health and personal preferences (5). Systemic therapies are typically the mainstay of treatment for MBC and may be given alone or in combination with other treatments (38). Chemotherapy is the traditional treatment option, which may contain different side effects due to toxicity (36). Hormone therapy is used when the cancer is hormone receptor positive, meaning that it needs hormones to grow (37). Targeted therapies are designed to specifically target cancer cells and spare healthy cells, and are often used in combination with chemotherapy or hormone therapy (5). Local treatments like surgery and radiation therapy may also be used to help manage symptoms or control the growth of the cancer in certain areas of the body. For example, surgery may be used to remove a tumor that is causing pain or other problems, while radiation therapy may be used to shrink a tumor that is pressing on a nerve or other vital structure (38).

The landscape of MBC has undergone profound advancements in all MBC-subtypes, and novel treatments such as CDK4/6 inhibitors have improved progression-free and even OS in most of MBC patients (22, 23, 39, 40). However, MBC still represents an incurable condition, meaning that the goal of treatment for metastatic breast cancer is to help patients live as long as possible with the best possible quality of life (5). Treatment decisions should be made in consultation with a multidisciplinary team of healthcare providers, taking into account the patient's individual needs, histopathology profile, and clinical condition (5, 38). The following is an overview of treatment strategies for MBC patients with varying histopathology profiles:

- **ER-positive, HER2-negative metastatic breast cancer**

Estrogen receptor-positive, HER2-negative accounts for approximately two-thirds of all MBC and endocrine-based therapy represents mostly the preferred frontline treatment strategy for advanced disease with the aim of delaying disease progression (5). CDK4/6 treatment was approved in 2016 and very fast became standard treatment, and currently it is the preferred first-line approach for the vast majority

of newly diagnosed HR+/HER2-negative MBC patients (41). In case of disease progression, a different type of endocrine therapy in combination with CDK4/6 inhibitors may be considered as a second-line treatment. If the cancer has become resistant to both endocrine therapy and CDK4/6 inhibitors, chemotherapy may be used as a second-line treatment option. The choice of regimen will depend on factors such as the patient's prior treatment history and individual characteristics (5).

- **HER2-positive metastatic breast cancer**

HER2-positive histopathology profile accounts for 15-20% of MBC patients and represents one of the most aggressive subtypes of breast cancer (42). However, the survival rates have progressively improved by receiving anti-HER2 treatments (5). The current standard of care as first-line treatment is a combination of Pertuzumab, Trastuzumab, and Docetaxel following by (43), following by Trastuzumab Emtansine (T-DM1) as the second established treatment line (44).

- **Triple negative metastatic breast cancer**

Due to high probability of advanced disseminated disease, chemotherapy is still the mainstay of treatment, with taxane and anthracycline-based chemotherapy representing the preferred options in earlier lines, with also a role for platinum salts. If the disease continues to progress or if the patient experiences side effects that make the first-line chemotherapy intolerable, a different type of chemotherapy may be considered as a second-line treatment (45). If the cancer continues to progress after chemotherapy, immunotherapy may be considered as a second-line treatment option.**,** as some MBC patient with triple negative profile have been found to express high levels of a protein called PD-L1, which can make them more susceptible to certain immunotherapy drugs called immune checkpoint inhibitors (46).

- **ER-positive, HER2-psoitive metastatic breast cancer**

A sub-group of HER2-positive MBC patients have the simultaneous expression of HER2 and HR, which accounts for 50% of all HER2-positive MBC patients (47). It has been confirmed that the addition of Pertuzumab or Lapatinib to Trastuzumab plus aromatase inhibitor be more effective and even prolong the survival compared than single anti-Herceptin plus endocrine therapy as the first line treatment (48, 49). Trastuzumab plus chemotherapy suggested as the second treatment line, which may has more effect compared with chemotherapy-free regimens (5).

Response monitoring criteria for metastatic breast cancer

Several imaging techniques and standardized criteria for evaluation of treatment response have been introduced over the years, while most guidelines do not provide a clear recommendation on modality of choice for response monitoring of MBC patients (7, 8). Current recommendations for clinical trials include the CE-CT and the corresponding Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, which is mostly based on anatomical measurements (50). The RECIST 1.1 criteria are widely applied as the endpoints in clinical trials, using objective tumor response with tumor shrinkage over 30% and progression with tumor growth of more than 20% or appearance of new metastatic lesions. The utilization of RECIST criteria in interpreting CE-CT and MRI scans plays a crucial role in evaluating treatment response for MBC patients. By employing RECIST 1.1 criteria, radiologists and clinicians can objectively assess tumor size changes based on anatomical measurements derived from these imaging modalities. The RECIST guidelines have updated the assessment of changes in tumor size over the past years, which provides a standardized and widely accepted method for evaluating treatment efficacy and disease progression, ensuring consistency in response assessment across clinical trials (8, 51, 52). The reliance on anatomical measurements allows for a quantitative assessment of tumor burden and aids in distinguishing between tumor shrinkage, disease stabilization, and disease progression. Moreover, the use of CE-CT and MRI scans in conjunction with RECIST criteria offers additional advantages in assessing the treatment response (8, 53).

The detection of new metastatic lesions by anatomical-based imaging is limited and could be improved by functional imaging such as FDG-PET/CT (8, 54). FDG-PET/CT has been intermittently used for clinical response monitoring in MBC in hospital settings (55), and the corresponding response criteria, PET Response Criteria in Solid Tumors (PERCIST), has recently been suggested as a standardized tool for treatment evaluation in MBC based on more precise prediction of treatment response than conventional imaging (56, 57). Some studies suggested PERCIST as a superior response monitoring method in solid tumors than RECIST 1.1 (58-60). Different approaches in PERCIST have also been discussed, e.g. the one-lesion method defined by the highest standardized uptake values (SUV) normalized by lean body mass (SUL_{peak}) in one lesion, or the method using five target lesions similar to RECIST 1.1 (61).

No significant impact on the prognostic value of response assessment was found between the two approaches in MBC patients (62).

Response monitoring modalities in metastatic breast cancer

Staging and response monitoring in MBC patients have relied on conventional imaging, since anatomic imaging based on change in size of tumor is the current standard for monitoring tumor response and corresponding progression/regression (8, 12). These imaging modalities provide detailed visualization of the tumor and its surrounding tissues, enabling the identification and characterization of specific lesions. Furthermore, the use of contrast agents in CE-CT and MRI scans enhances the detection of vascular changes and tissue perfusion, providing valuable information about tumor biology and vascularity. This comprehensive evaluation allows clinicians to not only assess tumor size changes but also gain insights into the tumor microenvironment and potential treatment resistance mechanisms (8, 53). CE-CT revealed a sensitivity and specificity of 77% and 83%, respectively, for diagnosis of distant recurrence in patients with suspected breast cancer recurrence (63). MRI proved to have a perfect accuracy in detection of bone metastases based on differentiation of healthy from pathological bone marrow, and considered as the gold standard during the past years (64, 65). MRI is also considered a clinically suitable modality to detect liver metastases with a sensitivity of 80% and specificity of 96% (66). Nevertheless, the main advantage of MRI is the higher sensitivity and specificity than CE-CT and FDG-PET/CT for the detection of brain metastases (67, 68). FDG-PET/CT has been introduced increasingly in MBC patients based on excellent sensitivity (over 95%) for diagnosing distant metastases (9). FDG-PET/CT may also have the potential advantage of earlier detection of progression compared with conventional imaging, based on earlier detection of metabolic than morphological tumor changes. Therefore, response evaluation by FDG-PET/CT may improve the clinical management (7, 12). FDG-PET/CT also showed a perfect sensitivity (100%) and specificity (98%) for detection of bone recurrence (63). Comparing this to other modalities, a meta-analysis synthesized results for patient-based sensitivity of FDG-PET/CT, MRI, and CE-CT for detection of bone metastatic disease in MBC patients. They found that FDG-PET/CT and MRI were comparable and both significantly superior to CE-CT with sensitivities of 89.7%, 90.6%, and 72.9%, respectively (69).

Contrast enhanced-Computed tomography (CE-CT)

Computed tomography (CT) is a diagnostic modality that allows cross sectional reconstruction of a patient's body, providing extensive information about the structure and anatomy of the organs as well as, to some extent, their functionality. CT works based on X-ray ionizing to generate images by radiating X-rays from a fan-beam source that rotates around the patient, registering a degree of attenuation (Hounsfield unit) by a ring of x-ray detectors. Through a mathematical technique known as image reconstruction, tomographic images can be formed from X-ray projection data that has been collected from a variety of angles all around the patient. Radiation dose is directly impacted by image reconstruction, which also has a basic impact on image quality. Contrast-enhanced CT (CE-CT) is used to highlight the arteries, soft tissues, and internal organs through blocking X-rays by intravenous injection of contrast agents, which appears white on images. Although CE-CT is most routinely used outpatient procedure, repeated administrations of contrast agents could cause nephrotoxicity in long run (70-73).

Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) provides detailed images by using body's inherent magnetic properties. The magnetic vector works in harmony with the radiofrequency source, resulting in the emission of a signal, and generates the MR images. Various tissues relax at different speeds, following the termination of transmitted radiofrequency pulse, resulting in a distinct emphasis. A series of pulse sequences make up an MR examination. The hydrogen nucleus (a single proton) is used for imaging since it is present in large quantities in both water and fat, which can be distinguished from each other based on different relaxation durations. For instance, by employing a "fat suppression" pulse sequence, the signal from fat will be eliminated, leaving only the signal from any anomalies present inside it. MRI is a sensitive diagnostic modality since most diseases show their symptoms by increasing the amount of water around them. There are no known biological risks associated with MRI since it uses a kind of radiation that is ubiquitous and does not cause any tissue harm as it passes through (74, 75). Therefore, MRI has become a valuable diagnostic modality based on its perfect soft tissue contrast combined with high spatial resolution and the lack of exposure to ionizing radiation (induced by PET/CT) or radiation exposure occurred by CE-CT (76, 77).

FDG-PET/CT

An integrated PET/CT scanner takes the individual pictures from a CT scan and PET-scan and combine them on an integrated platform. 2-deoxy-2-[^{18}F]fluoro-D-glucose is a radiolabeled glucose tracer and the most common radiotracer with PET/CT (FDG-PET/CT). Approximately, 60 minutes after injection of FDG-tracer, the patient is examined on a whole-body PET scanner to detect malignant lesions based on malignant cell's rapid glucose metabolism and subsequent FDG uptake. A low dose CT was usually performed on the same field of view for attenuation correction. FDG uptake is generally described by the maximum and mean standardized uptake values (SUV_{max} and SUV_{mean}, respectively) in the region of interest. These values are known to be associated with the clinical and pathological features (54, 78, 79). However, SUV-based measures may not reflect the total glycolic activity within the entire mass (80, 81). Therefore, volumetric parameters, namely total lesion glycolysis (TLG) and metabolic tumor volume (MTV), were developed as semi-quantitative metrics for FDG accumulation across heterogeneous malignant lesions (81, 82). PET/CT is broadly used in the initial diagnosis, staging, and therapeutic response evaluation of malignant diseases (83). There are continuous technical improvements in PET/CT scanners, leading to improved imaging quality, which is affected by hardware specifications and reconstruction algorithms (84-86).

The Danish healthcare system

Danish healthcare is financed by a national, tax-based insurance system and operates on the principles of free and equal access to healthcare services for all residents. The healthcare system typically offers the highest available quality services regardless of the cost. National Patient Register derives a list of prices of use of inpatient and outpatient hospital care based on Diagnose Related Groups (DRG/DAGS system) from the Danish reimbursement system (87). According to the Danish DRG registration system, an overall DRG rate contains all the costs in case of several services during single visit/admission. The out-of-pocket costs of healthcare services for cancer patients is almost negligible in Denmark as the national healthcare system covers the costs related to treatment and monitoring. All healthcare-related costs are routinely registered and are accessible for research projects according to the principles of the Danish Data Protection Agency (88).

Cost-effectiveness analysis

Cost-effectiveness analysis is an economic evaluation tool, which principally focuses on the efficiency of services provided by healthcare system and analyses health-related outcomes relative to the costs (89). Cost-effectiveness analysis mainly focuses on efficiency (90), while policymakers may consider other principles such as equity (91). Quality-adjusted life years (QALYs) is routinely used to measure the outcomes (89). However, when the more expensive intervention is also the more effective one, the decision-maker must choose whether the gained efficacy is worth to pay the higher cost or not. This could be done through incremental cost-effectiveness ratio (ICER). ICER is the difference in costs divided by the difference in outcomes. The ratio gets more value by considering survival or QALY as the outcome measures, since they can be compared within different types of interventions (92). Policymakers decide about the threshold by considering the healthcare system recourses, as well as the clinical need for a new intervention. **Figure 1** shows an illustration of all possible outcomes for ICER analysis for a new diagnostic modality. An imaging modality with a negative ICER could be cost-effective, in cases where the new modality is less costly and more effective than the gold standard (right lower quadrant), which is the most desirable outcome. A new modality with a positive ICER that is lower than the considered threshold for cost-effectiveness is also counted as a cost-effective strategy, hence the new modality is more effective and more expensive (upper right quadrant) compared to the reference standard (93).

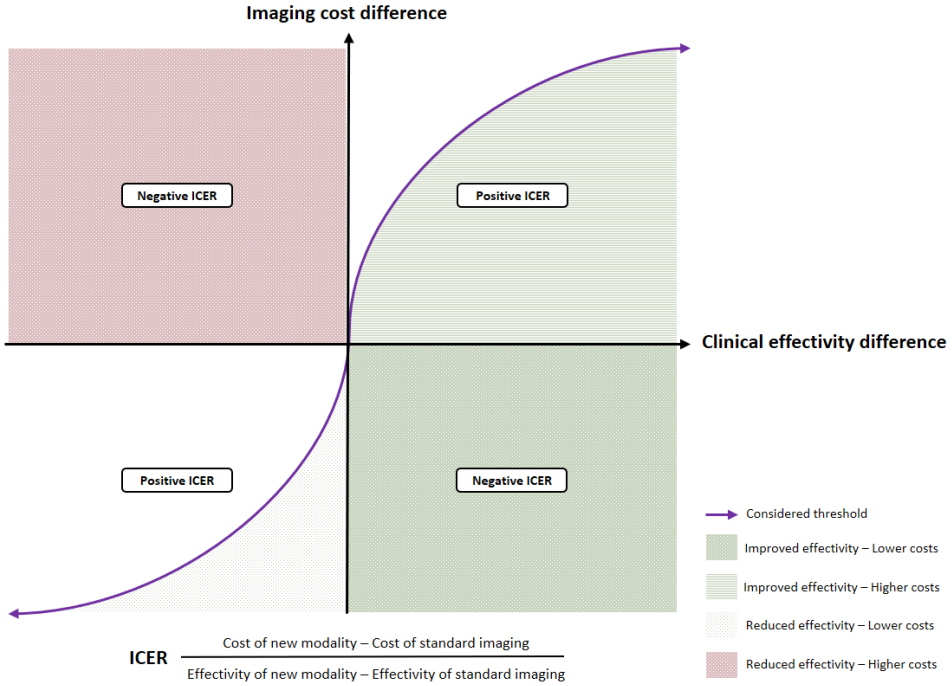


Figure 1. An illustration of all possible outcomes for incremental cost-effectiveness ratio (ICER) analysis for a new diagnostic modality. Clinical effectivity and cost of new diagnostic modality should be compared to the current reference standard.

Rationale and hypothesis

The availability of new effective treatment lines increases the need for accurate methods for assessing treatment response (60, 94). Our hypothesis is that by incorporating FDG-PET/CT as a novel modality for response monitoring, several advantages can be achieved. FDG-PET/CT provides valuable information on tumor metabolism, enabling the early identification of treatment response or resistance (11, 95). This early identification has the potential to facilitate timely treatment adjustments, thereby avoiding the use of costly and ineffective anti-cancer therapies (96). The inclusion of FDG-PET/CT in clinical management therefore provides a rationale for optimizing therapeutic outcomes, minimizing expenses related to ineffective treatments, and improving patient care (97). The impact of this approach on patient survival and cost-effectiveness warrants investigation and may have significant implications for patient management.

Materials & Methods

Study design

This single-centre, observational, register-based study was conducted at the Department of Nuclear Medicine at Odense University Hospital (Denmark) between 2018 (Nov) and 2022 (June). The study protocol, permission to register data from the patients' electronic medical files, and access to information on health-related costs were approved by Danish Patient Safety Authority (Ethics permission code: 3-3013-2448/1) and Ethics Committee of Region of Southern Denmark.

Patient selection

Women diagnosed with metastatic breast cancer in 2004-2018 were eligible for inclusion. They received treatment at the Department of Oncology, and the response monitoring imaging was performed at the Departments of Radiology and/or Nuclear Medicine at Odense University Hospital (Denmark). Inclusion criteria were biopsy-verified distant relapsed MBC or de-novo breast cancer with biopsy verification of the primary breast cancer (plus disseminated disease at baseline scan); baseline and at least one follow-up scan; use of either CE-CT, FDG-PET/CT, or a combination of the two as the main response monitoring modality every 9-12 weeks (98); and clinical follow-up. Exclusion criteria were brain metastasis at baseline scan, other diagnosed disseminated malignancy, acute cardiovascular disease or severe dementia at the time of MBC diagnosis, missing data, lost to follow-up due to emigration, and refusal of treatment.

The responsible oncologist decided the response monitoring modality. There was no internal guideline, and the decision about the choice of response monitoring modality was based on the discretion of the oncologist. Patients were allocated arbitrarily to the treating oncologists, without considering clinical condition. The same oncologist routinely visited the patients during follow-up and he/she made the clinical decisions based on the scan report, performance status, the patient's request, and the potential toxicity of ongoing treatment.

Study groups

Patients were categorized into three groups based on performed modality for response monitoring: CE-CT (n = 144), FDG-PET/CT (n = 83), and the combined group (n = 73). One scan performed on the opposite imaging modality was considered acceptable in the FDG-PET-CT and CE-CT groups, and the patients were assigned to the combined group if they received CE-CT and FDG-PET/CT more than once (**Figure 2**). The scans were performed according to the standard guidelines (8, 99) for performing FDG-PET/CT and CE-CT (Supplementary Material 1, **Paper II**).

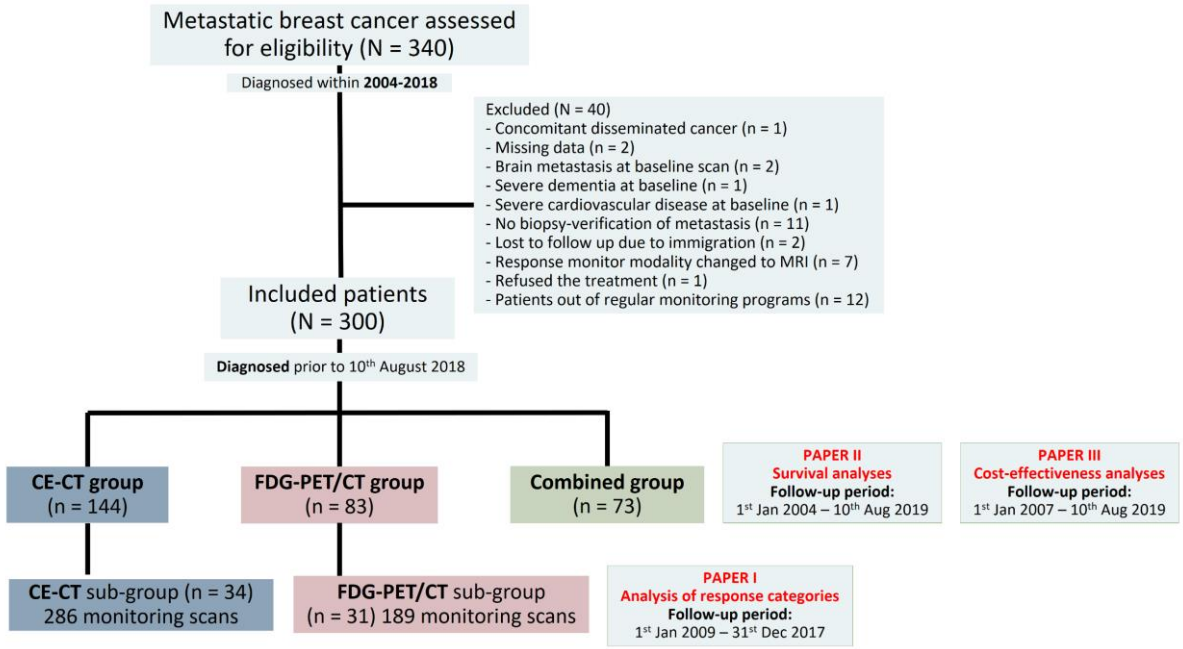


Figure 2. Study flowchart of patient' selection, study groups, and follow-up period for **Papers I-III**

Clinical data collection and variables

Age, performance status on the World Health Organization scale (100), responsible oncologist, clinical and histopathological data, treatments protocols, date and cause of death for non-survivors and of date of last clinical visit for survivors were extracted from patients' medical files.

The overall survival time was defined as the time from the metastasis confirmation until death, with end of study period (10th August 2019) as censoring event. Time to the first treatment change was defined as the time between the baseline scan and first progression leading to treatment change. The patients with detected first progression were followed-up until detection of the subsequent progression, leading to a second treatment change in the clinic.

Report of scans and response categories

We analyzed the response categories and their impact on clinical decision making for sub-groups of patients (treated within Sep-Dec 2017) in the CE-CT (n=34, 286 scans) and the FDG-PET/CT groups (n=31, 189 scans). The visually assessed responses were allocated into categories of complete (metabolic) response, partial (metabolic) response, mixed (metabolic) response, stable (metabolic) disease, progressive (metabolic) disease and equivocal answer. The CE-CT and FDG-PET/CT scans were conducted as part of the routine clinical procedure to monitor patient response. However, not all CE-CT scans were evaluated using RECIST criteria and the FDG-PET/CT scans were only analyzed visually. Follow-up scans were compared with the both baseline and the preceding scans, and the decision of multi-disciplinary radiology conference was considered in cases of uncertainty.

Health-related cost data collection

The perspective of this economic evaluation was on the hospital sector and the study was based on data on the use of hospital resources. All registered use of resources related to the patients' clinical management were registered. The hospital-based resources consisted of 1) admissions, which included short-stay admissions (under 24-hour) and overnight stays; 2) outpatient visits; 3) laboratory tests; 4) imaging modalities; 5) received treatments; 6) surgeries, including minimal biopsies; and 7) palliative care provided by public sector. The patients' use of hospital resources was estimated based on hospital contacts recorded in the National Patient Register (101). Estimates of prices of use of inpatient and outpatient hospital care for each patient were derived from the National Patient Register and based on Diagnose Related Groups (DRG/DAGS system) from the Danish reimbursement system (87). Registered costs were adjusted to the cost levels of 2019. All the rates are valued in Danish krone and reported in Euros (€) at the exchange rate of 7.45 DKK/€. A few examples of routine DRG rates related to the diagnosis, treatment and monitoring of MBC patients are available in Table 1, Paper III.

Outcome measures and statistical analyses

Continuous data were presented using the median (interquartile range) and mean ± standard deviation. Frequencies and respective percentages were given for categorical variables. The significance level was

set at 0.05. All statistical analyses were conducted with STATA/IC (version 16.1, StataCorp, College Station, USA).

A. Response categories (Paper I)

Comparison of the response categories through the FDG-PET/CT and CE-CT scans, and the related impact on clinical decision-making was the primary outcome for this study. A reference standard for true and false progression was assessed using information from subsequent follow-up scans and the decision made in the clinic regarding the treatment change. A chi-squared test was used to test for differences in distributions of response categories between groups.

B. Survival analysis (Paper II)

Comparison of the OS and survival probabilities were the primary endpoints for survival analysis. Median two-year, five-year, and ten-year survival were evaluated for all study groups with 95% confidence intervals (95% CI). Kaplan-Meier survival curves were used for visualization (102). Time to detect first and second progression were compared within study groups. Cox regression model by using a hazard ratio (HR) for quantification of the differences within the study groups was restricted to the two FDG-PET/CT and CE-CT groups. The HR was adjusted for all potential baseline characteristics to take account of any differences between the groups.

C. Cost-efficacy analysis (Paper III)

Comparing the total cost and the mean-based incremental cost-effectiveness ratio (ICER) were the primary outcomes for the cost-efficacy analysis. Graphical displays comprised box plots in which individually indicated data points were either larger than the 3rd quartile plus the interquartile range or smaller than the 1st quartile minus the interquartile range. The ICER was calculated as ratio between the mean cost (€) per patient and gained median survival (month) within the CE-CT vs. FDG-PET/CT by considering death or end of study period as the censoring event for both survival and cost analyses.

Results

Median follow-up time was 33.0 (range: 3.6-130.6) months. The study groups were mostly comparable regarding the baseline characteristics, while a few characteristics with significant difference were not in favour of any of the groups (Table 1 and Table 2 of **Paper II**).

Information on inpatient/outpatient visits, treatment lines, monitoring scans and costs are summarized in **Table 1**. The frequency of outpatient visits and response monitoring scans were comparable within the study groups, while the FDG-PET/CT group had more short-stay admissions (P<0.001), fewer over-night hospital stays (P=0.002), and a lower median number of treatment lines (P=0.005) compared with the CE-CT and combined groups. About the type of received treatments, there were a fewer patients in the FDG-PET/CT group, than CE-CT, who received chemotherapy at least once, and more patients who received CDK4/6 inhibitors as first/second treatment line.

Table 1. Overview of visits, response monitoring scans, treatment lines, and costs during follow-up*

Characteristics	Study Groups		
	CE-CT (n = 144)	**FDG-PET/CT** (n = 83)	**Combined** (n = 73)
Inpatient and outpatient visits, median (range)			
Number of outpatient visit	96.5 (16-346)	96 (19-420)	155 (40-556)
Number of short-stay admission	2 (0-15)	6 (1-25)	3 (0-20)
Hospital overnight stay	12 (0-103)	5 (0-118)	11 (0-167)
Response monitoring scans, median (range)			
Total number of scans	11 (3-36)	11 (3-36)	18 (5-51)
Number of scans per 3 months	1.2 (0.4-3.6)	1.1 (0.3-5.8)	1.2 (0.2-2.7)
Number of treatment lines, median (range)	3 (1-8)	2 (0-8)	3 (1-9)
Treatment strategies of patients*, frequency (%)			
Only endocrine therapy	36 (25.0)	21 (25.3)	14 (19.2)
Only chemotherapy	25 (17.4)	15 (18.1)	9 (12.3)
Endocrine therapy + chemotherapy	51 (35.4)	19 (22.9)	22 (30.1)
Anti-HER2 therapy + chemotherapy	11 (7.6)	5 (6.0)	11 (15.1)
CDK4/6 inhibitors + endocrine therapy	7 (4.9)	13 (15.7)	2 (2.7)
CDK4/6 inhibitors + chemotherapy	12 (8.3)	6 (7.2)	10 (13.7)
CDK4/6 inhibitors as first/second treatment line	6 (4.2)	13 (15.7)	4 (5.5)
Anti-HER2 therapy + endocrine therapy + chemotherapy	2 (1.4)	2 (2.4)	5 (6.9)
Received bone-target therapy (plus main treatment)	105 (72.9)	60 (72.3)	52 (71.2)
Received palliative radiotherapy (plus main treatment)	32 (22.2)	9 (10.9)	12 (16.4)
Cost (€) **during follow-up period**, mean (range)			
Total costs	91,547 (9,585-394,275)	83,965 (17,390-341,934)	165,784 (30,269-585,875)
Hospital-stay costs	19,015 (0-123,600)	15,014 (0-92,778)	25,736 (0-138,807)
Oncology department + imaging costs	75,068 (4,037-388,732)	67,573 (5,810-323,655)	140,403 (18,690-561,358)

CE-CT: Contrast-enhanced computed tomography; FDG-PET/CT: Fluorodeoxyglucose positron emission tomography/Computed tomography
*Two patients in the FDG-PET/CT group had unknown treatment strategy.

Response categories for CE-CT and FDG-PET/CT scans (Paper I)

A total of 286 CE-CT (34 patients) and 189 FDG-PET/CT (31 patients) response monitoring scans were performed. A statistically significant difference was observed in the distribution of the response categories between the groups (P<0.001), which is shown in **Figure 3**. FDG-PET/CT reported regressive disease (green colors) more frequently compared with CE-CT (46.0% vs. 12.2%) did, while stable disease (yellow color) was reported more often in CE-CT (70.6%) than the FDG-PET/CT (31.2%).

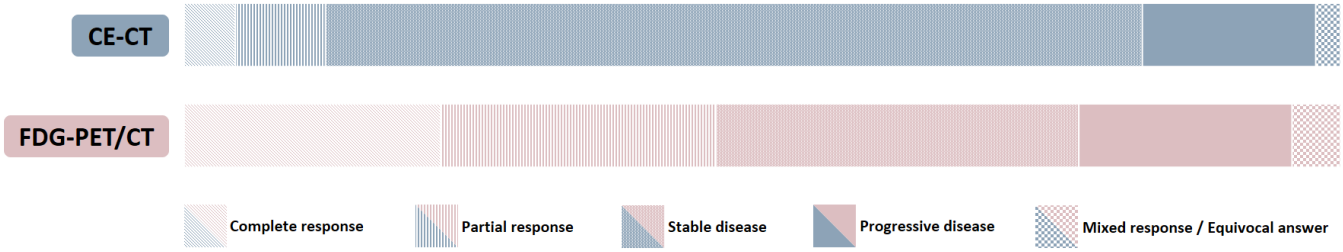


Figure 3. An illustration of response categories' proportion among sub-group of FDG-PET/CT and CE-CT groups.

Time to progression (Paper II)

The first progression, was detected, on average, 4.7 months earlier in the FDG-PET/CT group compared with the CE-CT group (12.9 vs. 17.6 months, *P*=0.03), while the second progression was detected on average 4.0 months later (*P*=0.0001) in the FDG-PET/CT group that the CE-CT group (**Figure 4**).

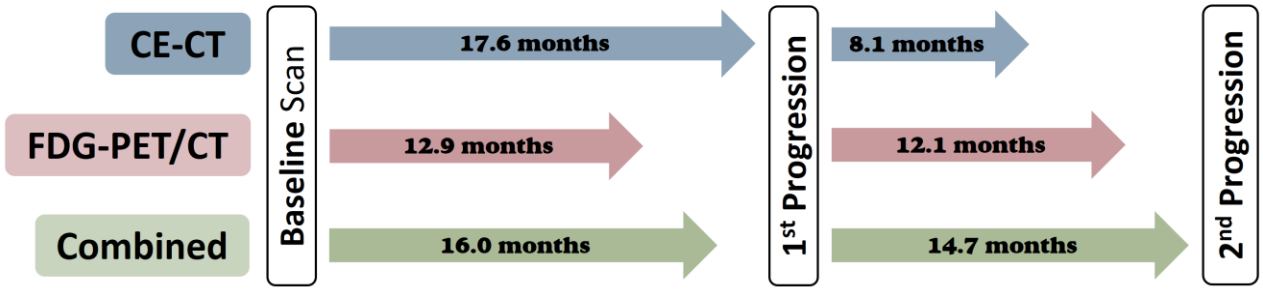
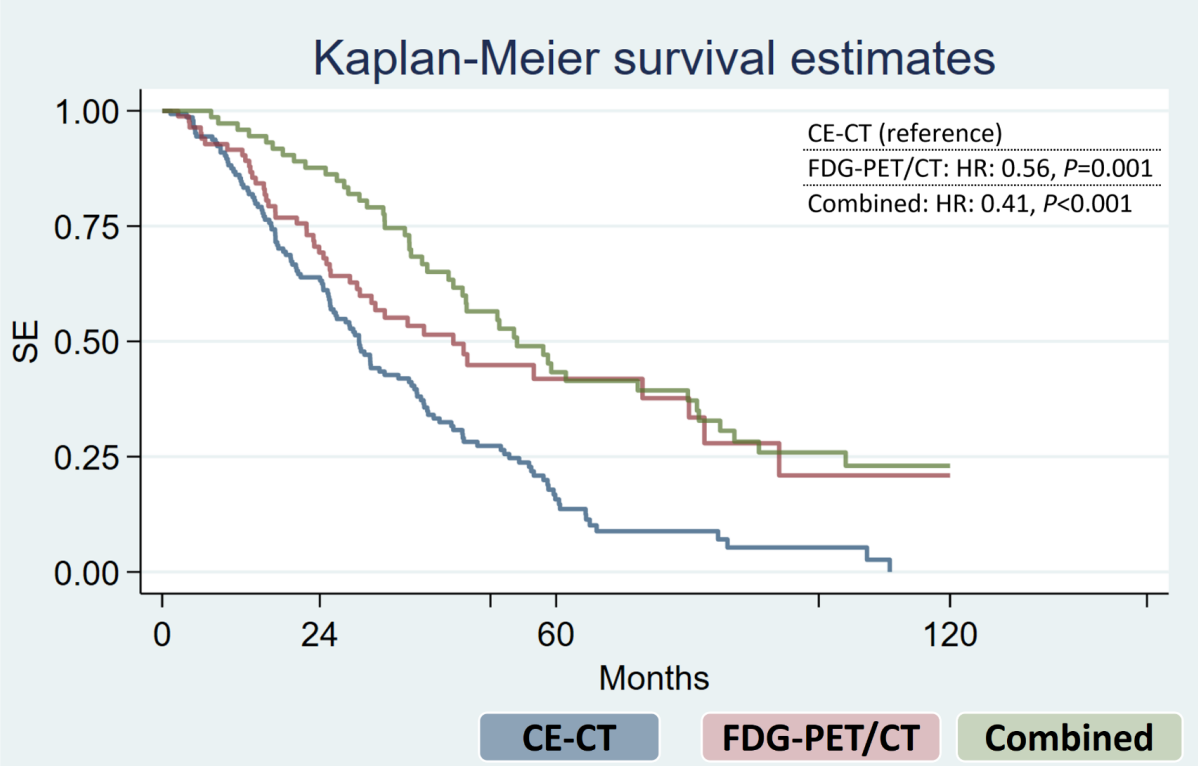


Figure 4. Comparison of mean time to detect first and second progressions, leading to the treatment changes, among the study groups

Survival analyses (Paper II)

Kaplan-Meier survival curves including risk table and survival probabilities are shown in in **Figure 5.** The median OS was longer in the FDG-PET/CT and combined groups compared with the CE-CT group. Five-year OS for the FDG-PET/CT and combined groups were higher than for the CE-CT group.



Median survival time (month)	30.0 (25.4-36.0)	44.3 (29.7-80.2)	54.0 (44.3-80.1)
2-year survival probability (%)	63.9 (55.4-71.1)	69.3 (58.0-78.1)	87.7 (77.6-93.4)
5-year survival probability (%)	15.8 (9.8-23)	41.9 (29.0-54.2)	43.3 (30.6-55.4)
10-year survival probability (%)	-	20.9 (7.4-39.1)	23.0 (12.3-35.7)

Figure 5. Kaplan–Meier plot including risk table showing overall survival of patients according to response monitoring modality

We observed a significant longer survival in the FDG-PET/CT and the combined groups, when considering the CE-CT group as reference in univariate survival analyses **(Figure 5)**. Comparing the FDG-PET/CT group and CE-CT group (reference) and adjusting for baseline characteristics, there was a significant longer survival for the FDG-PET/CT group (HR: 0.44, CI: 0.29-0.68, *P*=0.001).

Cost-effectiveness analyses (Paper III)

Costs were lower in the FDG-PET/CT group than in the CE-CT group with a mean reduction for the FDG-PET/CT group in total and hospital stay costs of €7,581 and €4,001, respectively (**Table 1**). A comparison of the accumulative costs showed that there was no considerable difference during the first two years of follow-up between the CE-CT and the FDG-PET/CT groups, while the FDG-PET/CT group had a considerably lower total cost during the first five years (**Figure 6**). The ICER for the FDG-PET/CT group was €-527/month, meaning that the total cost for FDG-PET/CT group was €527 lower for each month of gained survival rather than CE-CT group.

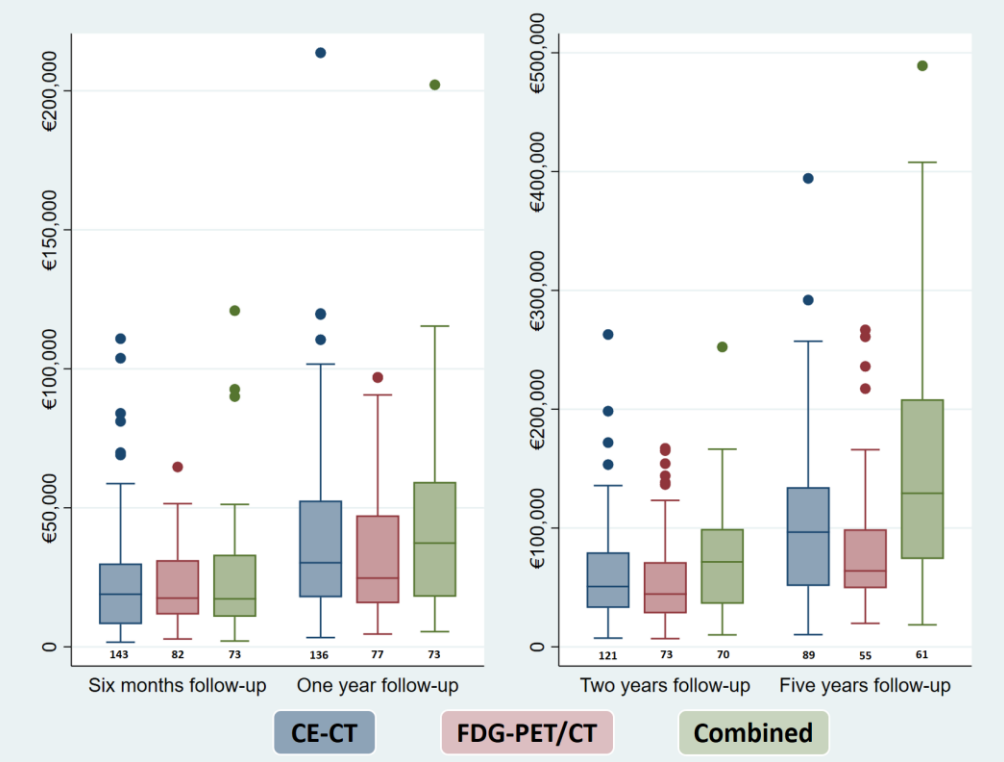


Figure 6. Box plots for comparing the accumulative cost of study groups during different time intervals of follow-up.

Discussion

Principal findings

Our results showed a survival benefit of 14-24 months for patients with metastatic breast cancer who were response-monitored with FDG-PET/CT alone or in combination with CE-CT compared with patients monitored with CE-CT alone. A multivariable Cox-regression analysis confirmed the prolonged survival for the FDG-PET/CT group compared with the CE-CT group (reference standard) after adjusting for baseline characteristics (HR: 0.44, *P*=0.001). The study groups had similar two-year survival rates, while the five-year survival rate was significantly higher in the FDG-PET/CT and the combined groups than in the CE-CT group. The mean total cost per patient in the group of patients monitored with FDG-PET/CT was €7,582 lower than that for patients monitored with CE-CT. Using the CE-CT group as reference, the ICER for the FDG-PET/CT group was €-527/month, indicating that response monitoring by FDG-PET/CT results in gaining an extra month of survival at a lower cost (€527).

FDG-PET/CT detected the first progression leading to the first treatment change five months earlier than CE-CT on average, and we then observed a longer time for patients in the FDG-PET/CT group before they experienced the second progression. Patients in the FDG-PET/CT group experienced fewer overnight admissions than the CE-CT group, which was often due to disease progression or treatment complications (103). This observation could be explained by a more successful treatment planning for patients in the FDG-PET/CT group with patients avoiding toxicity of a non-effective treatment. Another explanation, however, could be the more recent diagnosis of patients in the FDG-PET/CT group than the CE-CT group (2015 vs. 2013), allowing them to receive more advanced treatment protocols and thereby potentially more short-stay admissions and fewer overnight hospital stays. FDG-PET/CT also reported regressive disease more frequently than CE-CT, while we observed more reports of stable disease in the CE-CT scans. This is in line with FDG-PET/CT being a more sensitive modality for confirming treatment effects than the CE-CT, emphasizing the hypothesis that changes in tumor activity happens prior to appearance of morphological changes detectable by conventional imaging (104). Lastly, patients in the FDG-PET/CT group had a lower median number of treatment lines and consequently fewer treatment changes during follow-up compared with the CE-CT group. This may explain

the lower total cost in the FDG-PET/CT group as costs related to the treatment protocols represent the main share of the total cost. Therefore, the slightly increased cost of imaging using FDG-PET/CT could be balanced out over the longer follow-up period, even though FDG-PET/CT itself is a more expensive modality compared with CE-CT.

Limitations

The main limitation of this observational study was its single-center and retrospective design, meaning that patients were not randomly allocated to the study groups. Although a multivariable Cox regression model was applied to adjust for the known potential confounders (e.g. a higher rate of liver/lung metastases at baseline scan in the CT group), we cannot reject the possibility of other confounding parameters. Furthermore, FDG-PET/CT is a newer modality, and more recent diagnosed patients had a higher chance to be monitored by FDG-PET/CT, as the patients in the FDG-PET/CT group were diagnosed two years later than the CE-CT group (2015 vs. 2013). This may provide a higher chance for the patients in the FDG-PET/CT group to receive advanced treatment lines; more patients in the CE-CT group received chemotherapy (69% vs. 54%, P=0.03), while more patients in the FDG-PET/CT group received CDK4/6 inhibitors (23% vs. 13%, P=0.07). Another limitation was the absence of a gold standard for verification of progression (Paper I), as we considered the decision made in the clinic as the reference. Furthermore, the used treatment lines over the long follow-up period (2004-2019) were quite broad and some of them are not currently recommended in clinical guidelines (5). Another limitation of this study was visual evaluation of response monitoring scans without using a standardized set of criteria, as the included patients and related scans were part of daily clinical practice. The RECIST criteria were only applied irregularly for CE-CT, and the PERCIST criteria were not used for the FDG-PET/CT scans analyses, which could affect our results to some degree.

Some limitations are also related to the DRG pricing system, which is the only national pricing system used in Danish healthcare system. The DRG/DAGS rates are based on an average cost of services that includes different patient groups, which is avoiding a precise cost comparison between the study groups. However, the same approach was used for all study groups, minimizing the risk of bias. Further, the Danish DRG system applies a single DRG rate for patients having several services during a single visit

(e.g., if a patient has two outpatient visits in one day, only the most costly visit will have a DRG tariff). Specific cost differences between imaging modalities could not be estimated per patient as these costs are not listed separately during the admissions. We did not include costs related to additional visits in relation to a patient's rehabilitation program, nor costs related to private palliative care centers outside of the hospital organization. Costs related to other resources outside of hospital were not considered in our analyses. Finally, a longer follow-up period could add even better overview of long-term survival analysis, as almost 30% of included patients (mostly from the FDG-PET/CT group) were still alive at the end of the study.

Comparing the results with other studies

Another retrospective study compared the FDG-PET/CT versus CE-CT using the related standardized response evaluation criteria (PERCIST and RECIST, respectively) for response monitoring after the first treatment line in MBC patients. They concluded that PERCIST (FDG-PET/CT) could predict progression-free and disease-specific survival significantly better than RECIST (CE-CT). FDG-PET/CT also reported significantly fewer scans with stable disease compared with CE-CT, which was in line with our results (12). A recent prospective study from our group was conducted on 87 biopsy-verified MBC patients who monitored using combined CE-CT and FDG-PET/CT every 9-12 weeks to evaluate response to first-line treatment. Our results showed that the disease was measurable in approx. 30% more MBC patients with PERCIST than with RECIST, suggesting that FDG PET/CT has the potential for improving standardized response evaluation in the broader group of MBC patients. Furthermore, among the patients who experienced progression during the study period (52/87), progression was seen first on FDG PET/CT in 43/55 (78.2%) of patients. FDG-PET/CT also detected the first progression, on average, six months (95% CI, 4.3-6.4 months), earlier than CE-CT (11). A follow-up prospective study on the same patient population showed that the tumor response on FDG-PET/CT was significantly associated with progression-free survival (HR 3.49, $P<0.001$) and disease-specific survival (HR 2.35, $P=0.008$), while no association was found for tumor response on CE-CT, indicating that FDG-PET/CT acts superior in prediction of response to the treatment rather than CE-CT modality (95). Recently, a

case report published about a 40-year-old woman with HER2-positive breast cancer with liver metastases evaluated by both FDG-PET/CT and CE-CT-based RECIST for evaluation of the treatment response. The results revealed superiority of FDG-PET/CT in monitoring therapeutic response, as the patient, who showed an early response according to FDG-PET/CT, continued to respond to treatment three years after the start of treatment (105).

Due to perfect sensitivity (100%) and specificity (98%) of FDG-PET/CT for detection of bone recurrence (60), it is assumed that FDG-PET/CT could even act specifically better in response monitoring of bone-dominant MBC patients (7). A prospective study evaluating treatment response in hormone receptor-positive bone-dominant MBC patients using FDG-PET/CT demonstrated that 4-week FDG-PET/CT might possess high predictive value for treatment response after 12 weeks, as well as significant prognostic value in terms of progression-free and overall survival. These findings align with our study, suggesting that FDG-PET/CT could serve as a valuable predictor of early treatment response, potentially leading to improved overall survival outcomes (106).A pilot cost-effectiveness study compared the QALY in three countries (US, UK, and Netherlands) among stage II/III breast cancer patients and showed that using FDG-PET/CT as a screening modality to detect distant metastases may result in incremental QALY gains in all countries. They concluded that FDG-PET/CT was a cost-effective modality in the Netherlands and US, but not in the UK due to varying costs of services and different healthcare policies (107). Danish and Dutch healthcare systems may have the highest similarity since cancer-related expenses are mainly covered by the national insurance system in both countries. The “Dutch Council for Public Health and Health Care” and the "England's National Institute for Health and Clinical Excellence" have set informal ceiling ratio of €80,000 and €28,000, respectively, per extra gained QALY for cancer patients (108, 109). These thresholds are far from being reached according to the results of this observational study, revealing a negative ICER for FDG-PET/CT relative to CE-CT when used for response monitoring in MBC patients (3).

CDK4/6 treatments: new preferred first-line approach

CDK4/6 treatments have demonstrated significant survival benefits in the treatment of MBC patients across various subtypes. CDK4/6 inhibitors including Palbociclib, Ribociclib, and Abemaciclib considered as the preferred first and second-line treatments, when used in combination with endocrine therapy (110) . These inhibitors effectively block the activity of cyclin-dependent kinases 4 and 6, key regulators of cell cycle progression and tumor growth. By targeting these crucial pathways, CDK4/6 inhibitors have shown efficacy in extending the time until disease progression and improving overall survival, regardless of the specific subtype of breast cancer (111, 112). In addition to their survival benefits, CDK4/6 inhibitors offer the advantage of reduced need for hospitalization compared to chemotherapy regimens. Unlike chemotherapy, which often requires hospital-based administration and monitoring, CDK4/6 inhibitors can be administered orally in an outpatient setting. This oral administration route not only provides convenience for patients but also reduces the burden on healthcare facilities and resources (113, 114). In the context of monitoring treatment response, FDG-PET/CT has potential advantages over CE-CT when CDK4/6 treatments are employed. FDG-PET/CT utilizes a radioactive glucose analog to visualize metabolic activity within tumors. Since CDK4/6 inhibitors primarily target cell cycle progression and proliferation, FDG-PET/CT can provide valuable information on treatment response by assessing changes in tumor metabolism. This enables the early detection of metabolic changes, allowing for the identification of treatment response or resistance before substantial changes in tumor size become evident. The ability of FDG-PET/CT to detect early metabolic changes makes it a valuable tool in guiding treatment decisions and potentially optimizing therapy for patients receiving CDK4/6 inhibitors (94, 115, 116).

Patients with oligometastatic disease

Patients with oligometastatic disease have been defined as those with fewer than five metastatic lesions in a single organ (117), making metastases-directed therapy attractive (118). Some patients with oligometastatic disease can survive even longer than a decade, following metastases-directed therapy (118), which further emphasizes the importance of offering the most sensitive modality available for diagnosing and monitoring this group of patients (7). MRI already proved promising results for the

diagnosis of oligometastatic disease by improving the lesion detection rate and delineation of lesions from brain, spine, thoraco-abdominal, and pelvis (119). FDG-PET/CT could potentially improve the local treatment control of oligometastatic disease by optimized and individualized treatment strategies. In the case of oligometastatic progression, FDG-PET/CT could also detect the progression at an earlier time point, providing an opportunity for improved treatment planning (120, 121).

Limitation of using FDG-PET/CT in metastatic patients

Firstly, FDG-PET/CT may show less sensitivity in detection of lesions with low or no FDG avidity, specially seen in patients with histopathology of invasive lobular carcinoma (approx. 15%), false positive results in areas of inflammation or infection (122). However, it is important to note that another limitation arises when bisphosphonates are used in conjunction with FDG-PET/CT. Bisphosphonates, commonly prescribed for patients with bone metastases, which may affect the accuracy of FDG-PET/CT imaging, leading to potential limitations in lesion detection and interpretation (123, 124). Secondly, different metabolic activity of metastatic lesions may result in heterogeneous responses of different lesions (125), indicating the importance of using standardized response criteria. In contrast, implementation of PERCIST in clinical routine depends on standardization requirements and could be time-consuming due to scan analyses based on quantitative measurements. Lastly, exclusive expenses of using FDG-PET/CT for monitoring MBC patients has always been an issue (3), while the results of our cost-effectiveness analysis may overcome the concerns to some degree.

Tracers used for response prediction of targeted therapies

A key role in clinical care of MBC patients is to determine the molecular profile of the cancer, since the receptor-positive patient could receive targeted therapies that increases her chances of survival (126). Tumor heterogeneity in lesions from the primary cancer and metastatic lesions are evident and gives rise to therapeutic challenges (127). PET/CT imaging with use of novel radiotracers can provide a better chance for evaluating metastatic lesions, rather than relying only on biopsy from a single metastatic lesion (126, 128). A known radiotracer from this list is ^{89}Zr-pertuzumab that specifically visualizes the HER2-positive cancer lesions. Results of pilot studies suggest that ^{89}Zr-pertuzumab-PET/CT

could be useful to detect biopsy-verified HER2-positive lesions even in MBC patients with HER2-negative histopathology of metastases (126, 128, 129). Another tracer is ^{64}Cu-DOTA-trastuzumab, which can predict the patient benefit from trastuzumab-emtansine treatment (T-DM1). Results of a pilot study suggest that measurement of Trastuzumab uptake via ^{64}Cu-DOTA-trastuzumab-PET/CT may guide clinicians to improved clinical management for MBC patients with HER2-positive profile (130).

^{18F}Fluorine-oestradiol (^{18F}FES) is another radiotracer that has proved to be beneficial for targeting the ER status of metastatic disease (131). Results of meta-analysis comparing the diagnostic accuracy of ^{18F}FES-PET/CT versus FDG-PET/CT in estrogen ER-positive MBC patients revealed that the lesion-based sensitivity for ^{18F}FES-PET/CT was slightly better than FDG-PET/CT (95% vs. 85%, respectively), while patient-based analysis showed almost similar (97% and 94%, respectively) sensitivities (132). These preliminary results indicate the potential of targeted imaging to identify MBC patients for targeted therapies, which may further improve the clinical decision-making (126, 128-130).

Other tracers used with PET/CT

There are a few limitations for clinical indication of FDG-PET/CT due to its relation to glucose metabolism, indicating further need for the continuous development of new PET radiotracers in the field of medical oncology (133, 134). An emerging tracer is the radiolabeled fibroblast activation protein inhibitor (FAPI) that targets the fibroblast activation protein in the cancer microenvironment and consequently marks the cells around the tumor with radioisotopes for PET imaging (135). Preliminary results of FAPI-PET/CT are promising for primary staging of breast cancer and monitoring of metastatic patients (136). FAPI-PET/CT may have an improved diagnostic accuracy compared with FDG-PET/CT, and may be superior for response monitoring of MBC patients based on its theranostic potential (137). FAPI-PET/CT could also detect bone and intrahepatic metastases with low FDG-avidity (138, 139), and even lesions with the lobular histopathology profile (140). Therefore, FAPI-PET/CT may be a game-changer in the field of response monitoring for MBC patients, but it requires testing in future clinical studies (136). Sodium ^{18F}Fluoride (^{18F}NaF) is another positron-emitting radiopharmaceutical used mainly for diagnosis of skeletal metastases, since ^{18F}NaF-PET/CT could act slightly better than FDG-PET/CT in diagnosis of osteoblastic bone metastases. ^{18F}NaF-PET/CT may also be more suitable

modality for detecting low FDG-avid skeletal metastases, while ^{18F}NaF-PET/CT may have challenges for monitoring response of the common osteolytic bone metastases in MBC patients and in extra-osseous metastases (122, 141). A complete overview of all introduced tracers used in response monitoring of MBC patients has been shown in Table 2.

Table 2. Advantages and disadvantages of using FDG-PET/CT compared with other tracers in clinical management of metastatic breast cancer patients

Tracer	Advantage over FDG-PET/CT	Disadvantage over FDG-PET/CT
^{18F}FLT (142)	Potential to measure tumor proliferation more specifically	Limited availability and validation in clinical studies
^{18F}FES (132)	Measures estrogen receptor expression more specifically	Limited availability and validation in clinical studies
^{68}Ga-DOTATOC (143)	Potential to measure somatostatin receptor expression more specifically	Limited availability and validation in clinical studies
^{18F}NaF (141)	Superior sensitivity & specificity for detection of bone metastases	Limited information on metabolic activity and response monitoring of soft tissue metastases
FAPI (137)	Higher tumor-to-background ratio and improved prognostics and diagnostic accuracy	Limited availability and validation in clinical studies
^{89}Zr-pertuzumab (128)	Measures HER2 receptor expression more specifically	Limited availability and validation in clinical studies
^{64}Cu-DOTA-trastuzumab (130)	Measures HER2 receptor expression more specifically	Limited availability and validation in clinical studies

^{18F}FLT: ^{18F}Fluorothymidine, ^{18F}FES: ^{18F}Fluorine-oestradiol, ^{18F}NaF: Sodium ^{18F}Fluoride, FAPI: Fibroblast activation protein inhibitor,

Implications and perspectives

The overall economic burden of MBC is expected to increase due to the rising number of women living with the disease (144, 145). The average lifetime cost of managing patients with advanced breast cancer is estimated to range between €53,000 and €94,000 in European countries (146, 147), which is expected to increase due to treatment landscape improvement and higher cancer-related drug costs (148). A more accurate response monitoring modality could improve clinical management and reduce healthcare costs (149). Our results suggest FDG-PET/CT is a cost-effective modality based on ICER assessments, but other clinical and logistical considerations need to be taken into account (93). The indication of FDG-PET/CT for response monitoring in patients with MBC requires a better understanding of its clinical impact and cost-effectiveness, which could not be granted through this retrospective investigation. Therefore, a prospective randomized trial comparing FDG-PET/CT vs. a gold standard modality (CE-CT) using routine application of PERCIST and RECIST in a clinical, multi-center approach is warranted. A prospective randomized design would ensure the comparability of the groups of patients and could show the clinical impact of using FDG-PET/CT for monitoring up-to-date treatment in patients with metastatic breast cancer.

Conclusions

This single-center, registry-based study indicated that using FDG-PET/CT for response monitoring in patients with metastatic breast cancer could improve clinical decision-making, patients' overall survival and save the healthcare system economic resources. Using FDG-PET/CT for response monitoring, resulted in earlier detection of first progression and led to earlier treatment change. Longer subsequent treatment lines, lower overnight hospital stays, and lower total costs was also consequences of using FDG-PET/CT rather than CE-CT for monitoring MBC patients. Our results showed that FDG-PET/CT was a more cost-effective modality than CE-CT for response monitoring MBC patients with favorable prognostic factors (oligometastatic), while CE-CT was more cost-effective in patients with unfavorable prognostic factors (liver/lung metastases). The advantage of using FDG-PET/CT on patients' survival and costs increased clearly over longer follow-up, which is desirable for a potential future modality of choice. However, these results need to be verified in a prospective randomized trial before recommendations can be considered.

Thank you for reading my thesis!

M. Naghavi Behzad

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