High-dose versus standard-dose twice-daily thoracic radiotherapy for patients with limited stage small-cell lung cancer
an open-label, randomised, phase 2 trial

Grønberg, Bjørn Henning; Killingberg, Kristin Toftaker; Fløtten, Øystein; Brustugun, Odd Terje; Hornslien, Kjersti; Madebo, Tesfaye; Langer, Seppo Wang; Schytte, Tine; Nyman, Jan; Risum, Signe; Tsakonas, Georgios; Engleson, Jens; Halvorsen, Tarje Onsøien

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Randomized phase II trial comparing high-dose with standard dose twice-daily thoracic radiotherapy in limited stage small-cell lung cancer

Bjørn Henning Grønberg, M.D.1,2, Kristin T. Killingberg, M.D.1,2, Øystein Fløtten, M.D. 3, Kjersti Hornslien, M.D.4, Tesfaye Mabedo, M.D.5, Seppo W. Langer, M.D.6, Tine Schytte, M.D.7, Odd Terje Brustugun, M.D.8, Jan Nyman, M.D.9,10, Signe Risum, M.D.6, Georgios Tsakonas, M.D.11, Jens Engleson, M.D.12, Tarje O. Halvorsen, M.D.1,2

1Department of Clinical and Molecular Medicine, NTNU, Norwegian University of Science and Technology, Trondheim, Norway
2Department of Oncology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
3Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway
4Department of Oncology, Oslo University Hospital, Oslo, Norway
5Department of Pulmonary Medicine, Stavanger University Hospital, Stavanger, Norway
6Department of Oncology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
7Department of Oncology, Odense University Hospital, Odense, Denmark
8Section of Oncology, Drammen Hospital, Vestre Viken Health Trust, Drammen, Norway
9Department of Oncology, Sahlgrenska University Hospital, Gothenburg, Sweden
10Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
11Department of Oncology, Karolinska University Hospital, Stockholm, Sweden
12Department of Oncology, Skåne University Hospital, Lund, Sweden

Corresponding author:
Bjørn Henning Grønberg,
Department of Cancer Research and Molecular Medicine
NTNU, Norwegian University of Science and Technology
PO Box 8905
7491 Trondheim
Norway

Email: bjorn.h.gronberg@gmail.com
Phone: +47 47297878

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Introduction

Small-cell lung cancer (SCLC) accounts for approximately 13% of lung cancer cases, and has been estimated to cause 4% of cancer deaths.\textsuperscript{1,2} Platinum/etoposide chemotherapy is the main treatment,\textsuperscript{3,4} and concurrent thoracic radiotherapy (TRT) improves survival for those with limited stage (LS).\textsuperscript{5} Prophylactic cranial irradiation (PCI) reduces the risk of brain metastases and prolongs survival among patients who respond to chemoradiotherapy.\textsuperscript{6} Only 25-36% are cured and there is a need for better treatment, but there has been no progress the last 20 years.\textsuperscript{2-4,7,8} Accelerated, hyper-fractionated twice-daily (BID) TRT of 45 Gy/30 fractions has been the best documented schedule after prolonging survival when compared with once-daily TRT of 45 Gy/25 fractions in the Intergroup 0096 trial.\textsuperscript{3} One reason for the benefit of the hyperfractionated schedule is assumed to be that SCLC cells are highly radiosensitive, and even at low fraction doses, tumor cells are killed exponentially while the normal tissue damage is reduced.\textsuperscript{9} Furthermore, repopulation of cancer cells accelerates after three weeks of radiotherapy,\textsuperscript{10} which may explain why shortening the TRT treatment period improves survival.\textsuperscript{11} However, since twice-daily TRT caused more esophagitis in the Intergroup 0096 trial, and is considered inconvenient, it appears that most patients are still offered once-daily TRT.\textsuperscript{12,13} Local relapses are frequent and associated with death.\textsuperscript{3} It has been suggested that higher TRT-doses may improve local control and consequently survival,\textsuperscript{14,15} but hitherto, this has not been proven in any randomized trial. PET-CT provides the most accurate assessment of disease extent, and radiotherapy fields may be limited to PET-positive lesions.\textsuperscript{16} Modern radiotherapy techniques enable higher TRT-doses,\textsuperscript{17} and BID TRT of >45 Gy is tolerable.\textsuperscript{14,15} The main aim of this trial was to investigate whether high-dose BID TRT improves survival in LS SCLC. To our knowledge, this is the first randomized trial comparing high-dose BID TRT with 45 Gy/30 fractions.
Material and methods

Study design

This randomized phase II trial was approved by the Regional Committee for Medical Research Ethics, Central Norway, the Regional Ethics Board in Gothenburg, Sweden, and the National Committee on Health Research Ethics in Denmark.

Participants

Eligible patients gave written informed consent, had confirmed SCLC, limited stage according to the 1989 IASLC definition, measurable disease according to RECIST 1.1, ECOG performance status (PS) 0–2, adequate liver/kidney/bone marrow function, and underwent whole-body FDG PET-CT and brain MRI for staging of disease. One negative cytology was required if pleural effusion was present. The forced expiratory volume had to be >1L or >30% of predicted value and the diffusing capacity for carbon monoxide (DLCO) >30% of predicted value.

Randomisation

Patients were randomized using an electronic CRF in blocks stratifying for PS (0-1 vs. 2), stage (I/II vs. III), and pleural effusion (yes vs. no).

Procedures

Patients were to receive four courses of cisplatin 75 mg/m² iv day 1 and etoposide 100 mg/m² iv days 1–3 (PE) every three weeks. Courses were delayed if absolute neutrophil count was <1.5x10⁹/L or platelets <100x10⁹/L. Doses were reduced by 20-25% if grade 3-4 neutropenia or ne occurred. It was allowed to replace cisplatin with carboplatin (AUC=5-6, Calvert) if severe cisplatin-toxicity occurred. G-CSF and erythropoietin were not permitted. TRT started 20-28 days after the first day of the first PE. All patients received two fractions per day with minimum 6 hours between fractions.
The gross tumor volume (GTV) included the primary lung tumor (GTV\textsubscript{primary tumor}) and all PET-positive lymph node metastases (GTV\textsubscript{lymph nodes}). The size of GTVs were defined according to the CT planning scan performed after the first PE. Corresponding clinical target volumes (CTVs) were defined by adding a margin of 5 mm in all directions to the GTVs, though not into bony structures, large vessels, the heart, or beyond the mediastinal parietal pleura, unless there were signs of invasion of these structures.

A 4D-CT was recommended for defining the internal target volume (ITV). Alternatively, it was recommended to add an internal margin (IM) of 8 mm in the transverse plane and 10 mm in the craniocaudal directions to the CTV\textsubscript{primary tumour}, and an IM of 5 mm in all directions to CTV\textsubscript{lymph nodes}. Finally, a setup margin was added according to each department’s routine to define the PTV.

Both lungs, the heart, the esophagus (from below the larynx to the gastroesophageal junction), and the spinal canal were delineated. The mean lung dose was not to exceed 20 Gy. Less than 35% of the normal lung tissue should receive 20 Gy or more ($V_{20\text{ Gy}}<35\%$), and $V_{5\text{ Gy}}$ should be $<$65%. The mean heart dose should preferably not exceed 35 Gy and was not to exceed 46 Gy. It was recommended to keep $V_{40\text{ Gy}}<$80%, $V_{45\text{ Gy}}<$60% and $V_{60\text{ Gy}}<$30%. A maximum dose of 60 Gy to the esophagus was accepted but should preferably be lower. The mean esophageal dose should not exceed 34 Gy. A maximum dose of 60 Gy to the brachial plexus was accepted.

If the doses to organs at risk (OAR) exceeded the recommended levels, a dose reduction to 54 Gy was allowed in the 60 Gy arm. If the doses to the OAR were still too high, the TRT dose was defined according to local routines.

It was recommended to complete TRT within 22 (45 Gy) or 29 days (60 Gy) including weekends. If these timeframes were exceeded, a compensation according to local routines was recommended. Compensation by treating patients on a weekend-day was preferred. An alternative was to increase the doses of remaining fractions. In case, fraction doses should not exceed 2 Gy.
Responders were offered PCI of 25 Gy/10 fractions or 30 Gy/15 fractions, one fraction per day, starting within 6 weeks after last PE.

A CT scan for response evaluation was performed within three weeks after last PE. Confirmation of response was not required. Patients were then followed with CT scans every ten weeks year 1, every three months year 2-3, and every six months year 4-5. Relapse treatment was administered according to local routines.

Disease-stage was assessed according to TNM v7,19 response according to RECIST 1.1, and toxicity according to CTCAE v4.0. OS was measured from the first day of the first PE until death from any cause, PFS until progression or death from any cause.

Outcomes

The primary endpoint was 2-year survival. Secondary endpoints were overall survival (OS), overall response rates (ORR), progression-free survival (PFS), local control, toxicity and health-related quality of life. The latter will be reported separately.

Statistical considerations

In our previous trial of TRT in LS SCLC, the 2-year survival was 53% for patient who received 45 Gy/30 fractions,20 and we considered an improvement of 25% to be of significant clinical relevance. To show an improvement in 2-year survival from 53% to 66% with a one-tailed $\alpha=0.1$ and $\beta=0.2$, 73 evaluable patients were required in each arm. We expected a drop-out of maximum 5% and aimed at enrolling 154 participants. The main analyses include patients commencing TRT per protocol (Figure 1), the intention-to-treat (ITT) analyses include all randomized patients.

Survival was estimated using the Kaplan-Meier method, and compared using the Cox proportional hazard method. Logistic regression was used for the multivariable analysis for 2-year survival, and a Cox-model for the multivariable overall survival analysis. Both models adjusted for all baseline characteristics. Toxicity was compared using Pearson's Chi-square and Fisher's exact test. By design, the significance level for the primary endpoint is a one-
sided p<0.10, but for convenience, all reported p-values are two-sided and p<0.05 has been applied as the significance level.

The study was registered at clinicaltrials.gov (NCT02041845).

Role of the funding sources

None of the funding bodies had any role in data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From July 8, 2014, to June 6, 2018, 170 eligible patients were enrolled at 22 Scandinavian hospitals. Four patients discontinued before TRT commenced, and two patients received wrong TRT-dose by mistake. We were unable to deliver 60 Gy to four patients in the high-dose arm (all received 45 Gy). Thus, 160 patients are included in the main analyses (45 Gy: 76 patients, 60 Gy: 84 patients) (Figure 1).

Median age was 65 years (range 36-81), 30·0% were ≥70 years, 58·1% women, 98·1% current/former smokers, 88·8% had PS 0-1, 83·1% stage III, 12·5% pleural effusion, 22·8% a weight loss of >5% three months before enrolment. Baseline characteristics were well balanced (Table 1).

At the time of these primary analyses (July 2020), 41·9% of patients were alive with a median follow-up time of 49 months (range 24-72).

There were no differences in mean number of chemotherapy-courses (45 Gy: 3·8, 60 Gy: 3·8; p=0·84), or proportion receiving carboplatin (45 Gy: 42·1%, 60 Gy: 34·5%; p=0·32) (Table 2).

The mean number of days from the first PE until TRT started was similar (45 Gy: 22·9 days, 60 Gy: 24·5 days; p=0·28). There were no differences in TRT-completion (45 Gy: 96·0%, 60 Gy: 96·4% p=0·90), or completion within recommended timeframes (45 Gy: 94·4%, 60 Gy: 94·4%.
89·2%; p=0·24). Reasons for discontinuation are listed in Figure 1. Similar proportions received PCI (45 Gy: 84·2%, 60 Gy: 84·5%; p=0·96).

There was no difference in ORR (45 Gy: 81·6%, 60 Gy: 82·1%; p=0·81) (Table 2). The difference in median PFS was not statistically significant (45 Gy: 11·1 months [95% CI 6·3-16·0], 60 Gy: 18·7 months [95% CI 7·5-30·0]; p=0·22), nor in the multivariable analysis (HR 0·71, 95% CI 0·46-1·10; p=0·12).

Significantly more patients on the high-dose arm were alive after two years (45 Gy: 51·3% [95% CI 39·6-63·1], 60 Gy: 75·0% [95% CI 64·4-83·8]; p=0·002). There was a numerical superiority across all subgroups which was statistically significant in 8/14 subgroups (Figure 2). The multivariable analysis confirmed a substantial benefit in favor of the high-dose arm (OR 4·59, 95% CI 2·02-10·4; p<0·001) (Table 4). The median OS was also significantly longer than in the control arm (45 Gy: 24·0 months [95% CI 15·6-32·4], 60 Gy: 37·2 months [95% CI 28·8-45·7]; p=0·034), and remains statistically significant in the multivariable analysis (HR 0·55, 95% CI 0·35-0·88; p=0·012). No baseline characteristics were significantly associated with 2-year survival or OS (Table 4).

The results were similar for the ITT-population, both for 2-year survival (45 Gy: 48·1% [95% CI 36·9-59·5], 60 Gy: 74·2% [95% CI 63·8-82·9]; p<0·001), median overall survival (45 Gy: 22·6 [95% CI 17·1-28·1], 60 Gy: 37·2 months [95% CI 28·4-46·1]; p=0·012) and median PFS (45 Gy: 10·9 [95% CI 8·7-13·1], 60 Gy: 18·7 months [7·4-30·1]; p=0·130) (Figure 1).

Of the four patients allocated to the high-dose arm who received TRT of 45 Gy, two are alive after 49·8 and 68·8 months, respectively. The other two died after 5·4 months (intercurrent disease), and 8·3 months (due to relapse after 6·1 months).

Overall, there were no significant differences in toxicity, and there were no differences in neither grade 3–4 esophagitis (45 Gy: 18·4%, 60 Gy: 19·0%; p= 0·92), nor grade 3–4 pneumonitis (45 Gy: 0%, 60 Gy: 3·6%; p=0·35) (Table 3). Three deaths occurred during the study treatment period due to aortic dissection (n=1), neutropenic infection (n=1), and thrombocytopenic bleeding (n=1).
There was a trend towards more local failures in the standard arm (45 Gy: 34·2%, 60 Gy: 21·4%; p=0·071), while the frequency of distant metastases was similar (45 Gy: 47·3%, 60 Gy: 42·8%; p=0·47).

There was no difference in proportions receiving second-line chemotherapy (45 Gy: 51·3%, 60 Gy: 46·4%; p=0·54). Most common regimens were platinum/etoposide (61·5%) and adriamycin/cyclophosphamide/vincristine (21.8%). The median time from progression until death was significantly longer in the high-dose arm (45 Gy: 8·3 months, 60 Gy: 13·6 months; p=0·006).

Discussion

In this first randomized trial comparing high-dose accelerated hyper-fractionated TRT with 45 Gy/30 fractions in LS SCLC, we were able to deliver 60 Gy to almost all patients (95·5%) allocated to the high-dose arm. There was a substantial benefit for the primary endpoint, 2-year survival: three out of four patients in the 60 Gy arm were alive at this timepoint, compared with half of the patients in the standard arm (OR 4·59 in the multivariable analysis). Furthermore, there was a significant prolongation in median OS from 24·0 to 37·2 months. To our knowledge, such an improvement in survival has not been observed in any previous randomized trials of LS SCLC. Although survival data are not mature (5-year follow is completed in 2023), we believe that the already observed survival benefit is highly relevant for patients, especially since the higher dose did not cause more radiotoxicity, and the frequency was among the lowest reported in LS SCLC studies.

The only other completed prospective randomized trial comparing high-dose TRT with the 45 Gy schedule is the CONVERT trial, in which patients were randomized to receive 45 Gy/30 fractions (BID) or 66 Gy/33 fractions (one fraction per day). Notably, TRT on the high-dose arm was neither hyper-fractionated nor accelerated. The trial was designed to show superiority of the higher dose, and was negative since 66 Gy was inferior both in terms of 2-year (51% vs. 56 %) and median OS (25 vs. 30 months).4
To our knowledge, the 2-year survival in our trial is the highest reported in any trial of LS SCLC, including all trials of high-dose once-daily TRT, and adds to the evidence suggesting that accelerated, hyper-fractionated TRT really is the most effective approach in LS SCLC. In the Intergroup 0096 trial, the total dose was the same in both arms, and the 60 Gy in our high-dose arm is quite similar to the 66 Gy in the experimental arm in the CONVERT. The important difference between our trial and CONVERT is the significantly shorter treatment time, four weeks instead of six and a half. A possible explanation for the unexpectedly large survival benefit in our trial, is that there is a threshold for killing medium radioresistant tumor cells between 45 and 60 Gy when TRT is accelerated.

We are only aware of three studies of accelerated and hyper-fractionated TRT in doses above 45 Gy in LS SCLC. Jeremic and colleagues observed a median OS of 34 months in patients receiving 54 Gy concurrently with the first chemotherapy-course, which is quite similar to what we observed in our high-dose arm. However, median OS was much shorter (26 months) among those who received TRT concurrently with the third course, and in the other two studies. In a retrospective, non-randomized Swedish study, 60 Gy/40 fractions did not prolong survival compared with 45 Gy/30 fractions, and the median OS was 20·8 months. Schild and colleagues observed a median of 22 months in patients receiving 60 Gy/40 fractions. There are, however, important differences between these studies and ours. Patients did not undergo PET CT, and other target volume definitions and radiotherapy techniques were used. Jeremic and colleagues excluded patients ≥70 years, and the split course employed by Schild and colleagues may allow for repopulation and regrowth, reducing the biologically effective dose.

Survival in our control arm is as expected, similar to the Intergroup 0096 trial and our former study of TRT in LS SCLC (which was the basis for our sample size calculation). Two other trials have reported a longer survival, though: In CONVERT, median OS in the 45 Gy arm was 30 months, and in a Japanese trial, median OS was 38 months in the platinum/etoposide arm. The longer survival may be explained by differences in patient selection. In CONVERT, patients with two abnormal lab values (low serum sodium, elevated
LDH or alkaline phosphatase) were excluded, they had fewer PS 2 patients than in our study (3% vs. 9%), excluded patients with PS 2 due to comorbidities, and patients were younger (median age 62 vs. 65 years, 12% vs. 29% ≥70 years). Patients in the Japanese study were also younger than in our study (median age 61 vs. 65 years, patients ≥70 were excluded), the proportion with PS 0 was higher (60% vs. 46%), and stage was not reported. Interestingly, the frequency of severe radiotoxicity is much lower than in the Intergroup 0096 and our former TRT-trial (27-33%), and among the lowest reported. An important reason may be attributed to the limitation of the radiotherapy fields to PET positive lesions, which reduces the target volumes, but may also ensure inclusion of lesions missed when applying elective nodal irradiation. We allowed modern radiotherapy techniques which reduces the maximum dose to and volume of normal tissue irradiated. These approaches have been adopted based on small, non-randomized studies, but were also used in CONVERT without increasing the relapse risk.

Relatively many patients experienced neutropenia or neutropenic infections since we did not allow growth-factors. The reason was the increased toxicity in a trial of GM-CSF in LS SCLC. In the Intergroup 0096 trial, TRT started concurrently with the first PE, while we, similar to CONVERT, started along with the second. Many patients are diagnosed at hospitals without radiotherapy departments, and our design allows both for early start of chemotherapy and sufficient time to plan TRT. Furthermore, we have shown that the first PE significantly reduces tumor volumes allowing for less normal tissue irradiation, since target volumes may be adjusted to tumor sizes after commencing chemotherapy. This timing may have contributed to the low radiotoxicity. Overall, we believe that our design complies with current guidelines.

The main limitation of our trial is the sample size, which was intentionally limited due to concerns about toxicity in the high-dose arm, and there were no data from randomized trials indicating improved efficacy of the higher dose when we designed our trial. We have not performed a central review of CT scans, but assessing progression in irradiated lung...
tissues is anyway challenging, which may explain why the difference in PFS did not reach statistical significance.

The BID schedule is not widely adopted, probably due to inconvenience and concerns about radiotoxicity. Our study shows that these concerns are no longer justified. None discontinued due to inconvenience. Many patients need to travel far and stay away from home during TRT and finishing in four weeks instead of six to seven is most welcome. The higher dose did not cause more toxicity, and the proportion experiencing severe radiotoxicity was among the lowest reported in LS SCLC. The price of new cancer therapies has become an increasingly important issue in recent years. In comparison, we assume that the costs of an extra week of TRT are easily acceptable. Considering the large survival benefit, we believe that the 60 Gy schedule is highly attractive for both patients and health care providers.

Ideally, since this was a randomized phase II trial, our results need to be confirmed. On the other hand, population-based studies suggest that most LS SCLC patients are already treated with schedules that have not been investigated or proven more effective than BID TRT of 45 Gy in any randomized trial. In a study based on data from the National Cancer Database in the US by Schreiber and colleagues, 85% of patients received once-daily TRT of 46-72 Gy in fractions of 1.8-2 Gy. A more recent European survey suggest that more patients receive BID TRT after the results of the CONVERT trial were published, but still, 58% of respondents prescribe once-daily TRT. The ongoing CALGB 30610/RTOG 0538 trial comparing 45 Gy/30 fractions with 70 Gy/35 fractions (once daily) and 61.2 Gy (concomitant boost) will further clarify whether high-dose once-daily TRT is a good alternative to BID TRT. Another aspect to consider is that it may take a long time to perform a confirmatory trial. The number of randomized trials of LS SCLC is low, and due to positive results of studies of immune checkpoint inhibitors in metastatic SCLC there are several ongoing trials of immunotherapy in LS SCLC, including one by our collaborative group (NCT03540420). If any of these trials are positive, the complexity of performing confirmatory TRT trials increases. In the meantime, we believe that 60 Gy/40 fractions is an attractive
alternative to current schedules. After all, we did not reveal any disadvantages of the higher dose in our trial.

In conclusion, hyper-fractionated, accelerated twice-daily thoracic radiotherapy of 60 Gy was feasible in almost all patients. The higher TRT-dose resulted in a large and significant improvement in both 2-year and median OS when compared with the standard 45 Gy schedule without adding toxicity.

**Contributors**

Conception and design: BHG, OTB, JN, SWL. Trial management: BHG, KTK, JN, TS, TOH

All authors have participated in data analyses, interpretation and manuscript writing. None of the authors have any conflicts of interest to declare.

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