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Kristin Toftaker Killingberg

Twice-daily thoracic radiotherapy in limited stage small-cell lung cancer

Doctoral thesis

NTNU
Norwegian University of Science and Technology
Thesis for the Degree of
Philosophiae Doctor
Faculty of Medicine and Health Sciences
Department of Clinical and Molecular Medicine

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Norwegian University of
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Thesis for the Degree of Philosophiae Doctor

Trondheim, May 2023

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Strålebehandling to ganger daglig for småcellet lungekreft i begrenset stadium

Lungekreft er den kreftformen som tar flest liv, og småcellet lungekreft er den mest aggressive undergruppen. SCLC behandles med en kombinasjon av cellegift og strålebehandling dersom all påvist sykdom kan inkluderes i ett strålefelt (LS SCLC). En tredjedel av pasientene som får denne behandlingen blir i dag friske, men de fleste får tilbakefall og dør av sykdommen innen ett til to år. Noen får tilbakefall i det bestrålte området rundt primærsvulsten. Det er mulig at tilbakefall kan forhindres ved å optimalisere strålebehandlingen. Strålebehandling gitt med 2 daglige mindre doser har vist seg å være den mest effektive behandlingen, men har også gitt alvorlige bivirkninger, spesielt svelgebesvær. I tidligere studier har en ikke funnet bedre overlevelse ved å gi en høyere total stråledose gitt som daglige fraksjoner. Ingen har hittil undersøkt om en høyere total stråledose gitt med to daglige fraksjoner kan bedre overlevelsen.

Norsk lungekreftgruppe har i samarbeid med kolleger i Sverige og Danmark gjennomført en randomisert studie hvor vi sammenlignet strålebehandling gitt med 2 daglige doser i henholdsvis 45 Gy/30 fraksjoner over 3 uker og 60 Gy/40 fraksjoner over 4 uker. Strålebehandling til en totaldose på 60 Gy/40 fraksjoner ga en signifikant og betydelig forbedret 2 års overlevelse og median totaloverlevelse uten at det ga mer bivirkninger.

Helserelatert livskvalitet ble undersøkt før, under og de første to årene etter behandling. De som fikk 60 Gy rapporterte at det tok litt lenger tid før svelgebesværet gikk over, ellers var det ingen forskjell i selvrapportert helserelatert livskvalitet mellom behandlingsgruppene.

Halvparten av pasientene som blir diagnostisert med småcellet lungekreft er 70 år eller eldre. Studier viser at eldre får mindre behandling, sannsynligvis pga. frykt for at gevinsten ikke står i forhold til bivirkningene. Pasienter over 70 år er underrepresentert i kliniske studier, og vi mangler dokumentasjon på hvordan de best mulig skal behandles. Vår studie viser at pasienter som er 70 år eller eldre gjennomførte og tolererte behandlingen i like stor grad som yngre, og oppnådde tilsvarende sykdomskontroll.

Denne doktorgradsavhandlingen understøtter at pasienter med LS SCLC bør tilbys strålebehandling to ganger daglig til en total stråledose på 60 Gy, uavhengig av alder.

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This thesis is found to be worthy of public defense for the degree of
Philosophiae Doctor in medicine
The public defense takes place at auditorium ØHA 11 Øya helsehus
May 16th 2023 at 12.15 pm

Ovennevnte avhandling er funnet verdig til å forsvares offentlig
for graden Philosophiae Doctor i medisin
Disputas finner sted i auditorium ØHA 11 Øya helsehus
16.mai 2023 kl 12.15

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Norsk sammendrag

Lungekreft er den kreftformen som forårsaker flest dødsfall. Lungekreft deles inn i to hovedtyper, ikke-småcellet (NSCLC) og småcellet lungekreft (SCLC). SCLC utgjør 13-15% av tilfellene og kjennestenges av rask vekst og tidlig spredning både til lymfeknuter og andre organ.

Lungekreft har dårlig prognose, men overlevelsen har økt betydelig de siste årene. Bedret overlevelse er forårsaket av nye behandlingsmuligheter for NSCLC, mens for SCLC har behandlingen vært uendret de siste 20 årene og overlevelsen har endret seg lite. En kombinasjon av cellegift (cisplatin og etoposid) utgjør basisbehandlingen. Dersom all sykdom kan inkluderes i ett strålefelt kategoriseres sykdommen som å være i begrenset stadium (Limited stage, LS). Behandlingen av LS SCLC gis med kurativ intensjon i form av en kombinasjon av cellegift og strålebehandling. Med kombinasjonsbehandling kan opptil en tredjedel av pasientene bli friske, men de fleste får tilbakefall og dør av sykdommen og det er stort behov for bedre behandling.

Strålebehandling mot primærsvulsten i lungen to ganger daglig (BID) til en moderat totaldose på 45 Gy har vært anbefalt i retningslinjer. Ettersom mange av tilbakefallene fra LS SCLC kommer i det bestrålt område, har en lenge antatt at en høyere stråledose ville kunne forhindre tilbakefall og dermed bedre overlevelsen. To studier som sammenliknet 45 Gy BID med en høyere total stråledose (66 Gy og 70 Gy) gitt med én daglig fraksjon fant imidlertid ingen forbedring i overlevelse.

Vi har gjennomført en skandinavisk studie der alle pasientene fikk strålebehandling to ganger daglig med 1.5 Gy pr fraksjon. Pasientene ble randomisert 1:1 til en totaldose på 45 Gy i 30 fraksjoner eller 60 Gy i 40 fraksjoner. To år etter behandling var 74% av pasientene som fikk 60 Gy i live, mot 48% i gruppen som fikk 45 Gy. Gruppen som fikk 60 Gy hadde også lenger median overlevelse, med 37.2 måneder mot 22.6 måneder i gruppen som fikk 45 Gy. Det var ingen forskjell i bivirkninger mellom de to behandlingsarmene, og andelen som fikk bivirkninger var sammenlignbare med andre nyere studier.

Vi undersøkte også pasientrapportert livskvalitet før, under og frem til to år etter behandling. Livskvalitetsmålingene underbygger at strålebehandling to ganger daglig er godt tolerert. Pasientene som fikk 60 Gy brukte lenger tid før

svelgevanskene ble borte, men ellers var det ingen forskjell i livskvalitet mellom behandlingsarmene.

Halvparten av pasientene som blir diagnostisert med SCLC er 70 år eller eldre. Eldre pasienter mottar sjeldnere standard behandling på grunn av frykt for bivirkninger og usikkerhet rundt nytten av behandling. Vi fant at eldre pasienter gjennomførte og tolererte behandlingen like godt som yngre pasienter. De eldre pasientene hadde noe redusert totaloverlevelse, mens vi ikke fant noen forskjell mellom aldersgruppene i tid til progresjon eller progresjonsfri overlevelse.

Vår studie understøtter at alle pasienter med LS SCLC bør tilbys strålebehandling to ganger daglig til en total stråledose på 60 Gy. Behandlingen er godt tolerert, og gir en betydelig gevinst i overlevelse.

English summary

Lung cancer is the most common cause of cancer deaths. There are two main categories of lung cancer, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Small cell lung cancer accounts for 13-15% of the cases and is characterized by rapid growth and early spread to lymph nodes and other organs.

Survival for NSCLC has improved significantly in recent years, but there has been almost no improvement for SCLC the last 20 years. The standard treatment for small cell lung cancer is cisplatin and etoposide chemotherapy. Concurrent radiotherapy improves survival when all lesions can be encompassed in a tolerable radiotherapy field (limited stage, LS). One third of patients are cured by chemoradiotherapy, but a majority relapses and dies from the disease and there is a need for better treatment. In many cases, local relapse is the main cause of treatment failure, and it has been hypothesized that a higher radiotherapy dose can improve survival by improving local control. TRT of 45 Gy in 30 fractions given twice daily is the best documented schedule and has been compared with 66-70 Gy given once daily, but the higher doses did not improve survival.

We conducted a randomized Scandinavian trial investigating whether high-dose, twice-daily TRT improves survival. Patients were randomized to receive 45 Gy in 30 fractions or 60 Gy in 40 fractions.

Patients receiving 60 Gy achieved a significantly improved 2-year (74% vs. 48%) and median overall survival (37.2 months vs. 22.6 months) compared with patients receiving 45 Gy. There was no difference in toxicity between treatment arms. The good tolerability was supported by the patient reported HRQoL analyses. Patients in the 60 Gy group reported more dysphagia in the convalescence period, but no other difference in treatment related symptoms.

Half of the patients diagnosed with lung cancer are 70 years or older. There is limited evidence for how to treat these patients because of underrepresentation in clinical trials. Patients 70 years or older had similar toxicity and compliance as younger patients, overall survival was shorter, but there was no difference in progression free survival or time to progression. Thus, we conclude that all LS SCLC patients should be offered TRT of 60 Gy in 40 fractions.

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The presented work has been carried out at the Department of Clinical and Molecular Medicine (IKOM) at the Norwegian University of science and technology (NTNU).

IKOM NTNU has funded the Ph.D. project. The Norwegian Cancer Society, the Liaison Committee for education, research, and innovation in Central Norway, the Nordic Cancer Union, and the NTNU supported the clinical study that this thesis was built upon. The Norwegian Lung Cancer Group (NLCG) conducted the clinical study in collaboration with Swedish and Danish colleges.

First, I want to thank the patients who have participated in the clinical trial which this thesis is built upon; thank you for offering time and effort for the benefit of future patients.

I want to thank Bjørn Henning Grønberg and Tarje Onsøien Halvorsen for inviting me into the lung cancer research group and allowing me to participate in this exciting project. Thank you for sharing your engagement and knowledge about clinical research. Your rapid and constructive feedback has been essential for the process of this work.

Thanks to all co-authors that have contributed to improving the manuscripts. Thanks to doctors and nurses, throughout the twenty-two hospitals which have treated the patients included in the clinical trial.

The scientific work has been combined with clinical work at the Cancer Clinic at St Olavs hospital. Thanks to my colleagues in the clinic, especially Andreas, Heidi, Torgrim, and Øystein on the uro-team, you make me look forward to every day at work.

Finally, thanks to my family Ludvig, Julie, Ludvig jr, Ingebrigt, Rannei, and Hallvard, for encouraging me to take a job at the hospital even if it meant seeing less of you. Thank you for cheering me on, and for enlightening me in other fields of sciences, sports, and arts.

List of papers

Paper I

Bjørn Henning Grønberg, Kristin Killingberg, Øystein Fløtten, Odd Terje Brustugun, Kjersti Hornslien, Tesfaje Madebo, Seppo Wang Langer, Tine Schytte, Jan Nyman, Signe Risum, Georgios Tsakonas, Jens Engleson, Tarje Onsøien Halvorsen. **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.** Lancet Oncol. 2021 Mar;22(3):321-331.

Paper II

Kristin Killingberg, Tarje O Halvorsen, Øystein Fløtten, Odd Terje Brustugun, Kjersti Hornslien, Tesfaje Madebo, Seppo Wang Langer, Tine Schytte, Jan Nyman, Signe Risum, Georgios Tsakonas, Jens Engleson, Bjørn Henning Grønberg. **Patient-reported health-related quality of life from a randomized phase II trial comparing standard-dose with high-dose twice daily thoracic radiotherapy in limited stage small-cell lung cancer.** Lung Cancer. 2022; 166:49-57

Paper III

Kristin Toftaker Killingberg, Bjørn Henning Grønberg, Marit Slaaen, Øyvind Kirkevold, Tarje Onsøien Halvorsen. **Treatment outcomes of older participants in a randomized trial comparing two schedules of twice-daily thoracic radiotherapy in limited stage small-cell lung cancer.** Journal of Thoracic Oncology; published online January 27, 2023

Abbreviations

ADL	Activities of Daily Life
ALP	Alkaline Phosphatase
ASCO	American Society of Clinical Oncology
BED	Biological effective dose
BID	Bis in Die (twice-daily)
BSC	Best Supportive Care
CA ++	Calcium
CALGB	Cancer and Leukemia Group B (USA)
CAV	Cyclophosphamide, Adriamycin, and Vincristine
CCI	Charlson Comorbidity Index
CGA	Comprehensive Geriatric Assessment
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
ES SCLC	Extensive stage small cell Lung
ENI	Elective Nodal Irradiation
EORTC	European Organization for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
G-CSF	Granulocyte Colony Stimulating
GTV	Gross Tumor Volume
G8	Geriatric assessment eight
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
IASLC	International Association for the Study of Lung Cancer
IMRT	Intensity Modulated Radiation Therapy
K+	Potassium
LDH	Lactate Dehydrogenase
LS SCLC	Limited Stage Small Cell Lung Cancer
MRI	Magnetic Resonance Imaging
Na+	Sodium
NCI	National Cancer Institute (USA)
NLCSG	Norwegian Lung Cancer Study Group
NSCLC	Non-Small-Cell Lung Cancer
OD	Once daily
OS	Overall survival
PCI	Prophylactic Cranial Irradiation

PD	Progressive disease
PD-1	Programmed cell Death protein one
PD-L1	Programmed cell Death ligand one
PE	Cisplatin and Etoposide
PET	Positron Emission Tomography
PET-CT	PET and CT combined
PFS	Progression-Free Survival
PR	Partial Response
PS	Performance Status
PTV	Planning Target Volume
QD	Quaque die, once daily
QLQ-C30	Quality of Life Core Questionnaire
QLQ LC13	Quality of Life Questionnaire Lung Cancer module
QUANTEC	Quantitative Analyses of Normal Tissue Effects in the Clinic
RCT	Randomized Controlled Trial
RR	Response Rate
SCLC	Small cell lung cancer
SD	Stable disease
SER	Time from Start of treatment until end of Radiotherapy
TNM	Tumor, Nodes and Metastases
TRT	Thoracic Radiotherapy
VALSG	Veterans Administration Lung Study Group (USA)
VMAT	Volumetric Modulated Arc Therapy
WHO	World Health Organization

1.Introduction

There are two main categories of Lung cancer, non-small cell lung cancer (NSCLC), and small cell lung cancer (SCLC). SCLC is characterized by rapid tumor growth, early metastasis, and a high sensitivity to radio- and chemotherapy. If all lesions can be included in one radiotherapy (RT) field (LS SCLC), standard treatment is concurrent radio- and chemotherapy. Combination chemotherapy consisting of cisplatin and etoposide is preferred. Twice-daily (BID) thoracic radiotherapy (TRT) of 45 Gy in 30 fractions is considered the most effective schedule but have not been widely implemented in clinical practice due to high rates of toxicity and logistical challenges [1-8]. Local recurrence is frequent and associated with shorter survival [9, 10], and it has been proposed that a higher TRT dose might improve disease control and consequently survival.

Maintenance of quality of life is an important outcome for cancer patients [11, 12]. Patient-reported health-related quality of life (HRQoL) adds valuable information, since physicians often overestimate benefits and underestimate treatment related side-effects [13, 14].

Half of the patients with small cell lung cancer are 70 years or older [15]. Population based studies show that few older LS SCLC patients are offered standard chemoradiotherapy, although there is limited evidence for such a policy [4, 16-19].

This PhD-project is based on a randomized trial investigating whether high dose TRT of 60 Gy in 40 fractions improve survival compared with 45 Gy in 30 fractions in LS SCLC. The aims were to:

- Investigate if high-dose twice-daily TRT of 60 Gy results in better survival compared with standard dose (45 Gy) twice-daily TRT
- Investigate the impact of high-dose TRT on patient reported HRQoL before, during and after study treatment
- Investigate whether patients 70 years or older complete, tolerate and benefit from twice-daily TRT as compared with younger patients

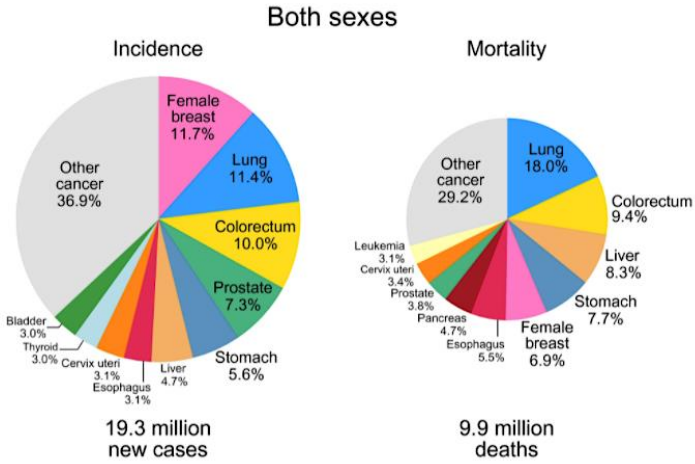
2.Background

2.1 Lung cancer

Lung cancer was first described as a separate entity by Laennec in 1815 [20], and was a very rare disease until the beginning of the 20th century. In autopsies from the University of Dresden in 1878, only 1% of cancers were malign lung tumors [21]. In 1912 Dr. Isak Adler wrote in the world's first monograph on lung cancer that "primary malignant neoplasms of the lung are among the rarest forms of disease" while noting that there seemed to be a "decided increase" in incidence [22].

Lung cancer is now one of the most frequent cancers, accounting for 2.2 million new cases in 2020, and is the leading cause of cancer related mortality, causing 18% of all cancer deaths (1.8 million annually) [23].

Figure 1 Global Lung cancer incidence and mortality 2020, copied from [23].



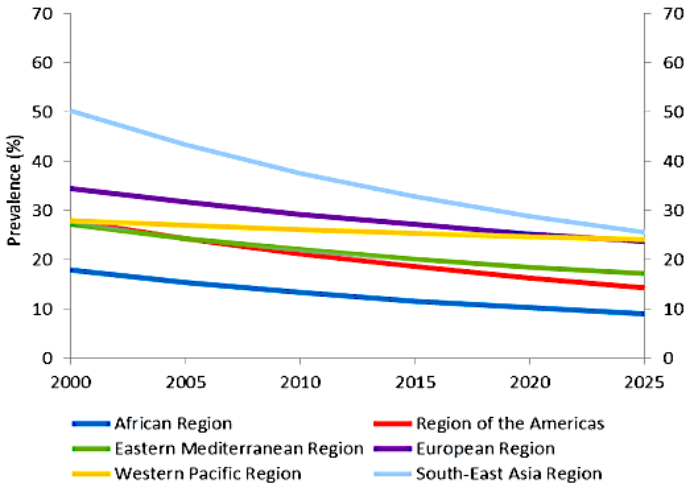
2.1.1 Etiology and epidemiology

As smoking became popular in the first part of the 20th century, an increase in lung cancer followed. The link between lung cancer and cigarette smoke was suspected in the 1930-40s but was not established until the 1950s when Doll and Hill in England and Wynder and Graham in the US published their hallmark case-control studies [24, 25]. Yet it took more than a decade before the association was fully accepted [26, 27].

Tobacco smoking causes 80-90% of lung cancer cases [28, 29]. Compared to nonsmokers, the risk of lung cancer increases >15 times for those who smoke one package of cigarettes per day. For heavy smokers, the lifetime risk of lung cancer is 10% [30]. More than three thousand chemical agents are identified in tobacco smoke including many well-known carcinogens and mutagens [31-33]. Other risk factors for lung cancer includes asbestos, silica, polyaromatic hydrocarbons, air pollution, radon exposure, nutritional factors, and genetic vulnerability [34].

There are still 1.3 billion tobacco smokers in the world [35]. Tobacco control programs have led to a decline in the prevalence of tobacco use in all regions of the world (Figure 2) .Thereby a decline in lung cancer cases is seen in some countries, while the incidence rates are still increasing in others [36, 37].

Figure 2 Trends in current tobacco use among people aged 15 years and older by WHO region copied from [38].



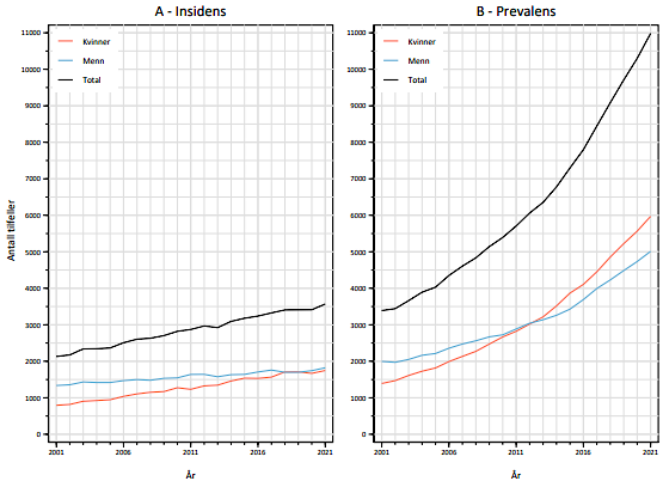
The WHO Framework Convention on Tobacco Control (FCTC) is a supranational agreement that seeks to protect present and future generations from the effects of tobacco [39]. FCTC entered into force in 2005 and have been signed by 168 countries. In Norway, the first tobacco act was implemented in 1975. Today, the age limit for buying tobacco is 18 years, there is a ban on advertising tobacco products and design of tobacco packages are standardized to limit positive associations and advertising of brands. There are health warnings on smoke-packages and tobacco

products are heavily taxed. Smoking is not allowed in bars, restaurants, or workplaces [40].

In Norway, smoking among men increased until the mid-1950s while the increase among women continued until the late 1990s. Since year 2000 the number of smokers has declined, and in 2020, 9% of people aged 16-74 years and only 1% between 16-24 years were daily smokers [40].

There were 3422 new cases of lung cancer in Norway in 2021, 1744 men and 1678 women (Figure 3A) [41]. The numbers are expected to reach 4000 in 2030 due to an increasing number of residents and ageing of our population (Figure 4) before they are expected to decline. The incidence rate has been leveling off for men the past two decades, while the highest rate among women was seen in 2018.

Figure 3 Incidence and prevalence of Lung Cancer in Norway 2001 to 2021 [41].

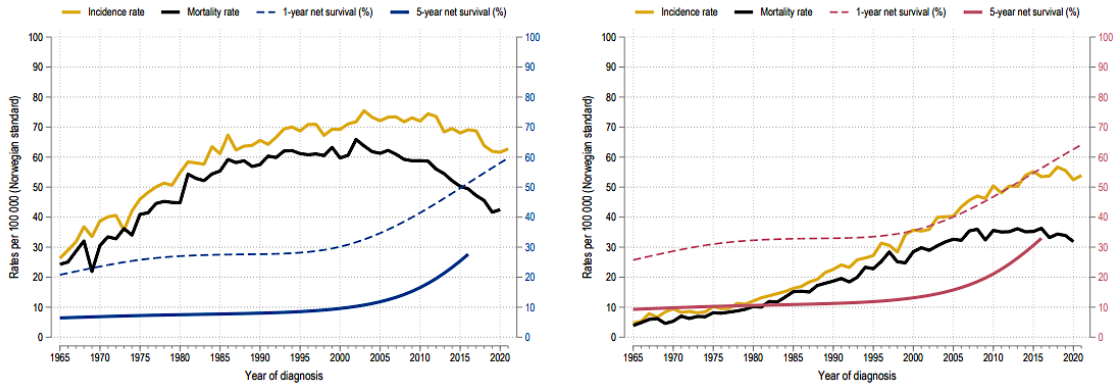


2.1.2 Survival

Overall, the prognosis of lung cancer is poor. Internationally, 5-year survival rate was 10-20% at the beginning of this century [42]. There has been improvement for NSCLC, currently, 5-year survival rate is up to 26%, while it remains low (7%) for SCLC [43, 44].

In Norway, 5-year survival rate of lung cancer has improved from 16% to 30.7% for women and from 9% to 24.6 % for since year 2000 [45], leading to an exponential increase in prevalence (Figure 3B). From 2000 until 2020, the number of lung cancer patients alive more than tripled to 9936 [15].

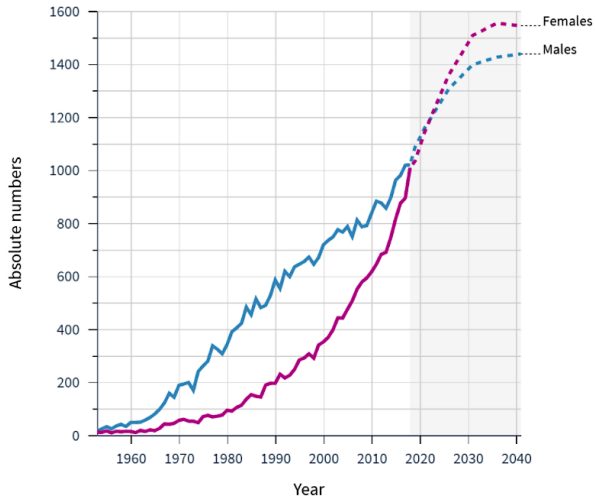
Figure 4 Incidence rate, mortality, 1- and 5-year net survival (%) of lung cancer from 1965 until 2020 in Norway. Copied from [46].



Left male (blue) and right female (red).

The number of inhabitants 80 years or older is expected to double by 2040 [15], and the age group of 70+ years is expected to account for most of the predicted increase in number of lung cancer patients (Figure 5).

Figure 5 Predicted incidence of lung cancer for the age group 70-85+, split for sex. Copied from [47].



2.1.3 Classification

There are two main types of lung cancer: small cell lung cancer (SCLC) accounting for 15% and non-small cell lung cancer (NSCLC) accounting for 85% of the cases. The most important histologic subgroups of NSCLC are adenocarcinomas (50-60%) squamous cell carcinomas (SCC) (25-30%) and large cell carcinomas (5-10%).

Neuroendocrine tumors are categorized as low to intermediate grade, typical carcinoid, atypical carcinoid, and high-grade neuroendocrine carcinoma which includes large cell neuroendocrine carcinoma (LCNEC) and SCLC.

Neuroendocrine lung epithelial cells are believed to be the most common cells of origin, although alveolar type 2 cells (club cells) as well as totipotent epithelial cells are shown to have the ability to form SCLC [48].

SCLC are sub-classified as pure SCLC or combined SCLC with elements of both SCLC and NSCLC, though this has limited clinical implications [49, 50]. It has been proposed to classify SCLC into subtypes based on gene expression profiles, SCLC-A (ASCL1), SCLC-N (neuroD1), SCLC-Y(YAP1), SCLC-P (POU2F3). The last letter refers to the transcription regulator associated with each subtype. However, the clinical relevance of this classification is not established. [51] .

2.2 Small Cell lung cancer

2.2.1 Epidemiology

Small cell lung cancer was first described in 1926 by Barnard in a study aiming to show that “oat-cell sarcomas of the mediastinum” were carcinomas of bronchial origin [52]. In 1959 Azzopardi described cytologic and histochemical features that defined SCLC as a separate entity [53] , and in 1962, Watson and Berg, described the features of SCLC regarding origin, clinical presentation, course of disease, and response to therapy [54].

The proportion of lung cancers that is SCLC have decreased from 25% in 1980 to 13-15% today, probably due to the introduction of low tar cigarettes [55-58]. In Norway 480 new case of SCLC are diagnosed every year [41]. SCLC used to be more common among men, but the incidence is now equal for both genders in Norway [59]. The proportion of patients 70 year or older diagnosed with SCLC have increased from 25% in 1975 to 44% in 2010 [60].

The risk of SCLC increases with the duration and intensity of smoking [61]. SCLC is rare in non-smokers among Caucasians (2%), while proportions of non-smokers up to 23% have been reported in East-Asian studies [56, 62].

2.2.2 Clinical presentation

SCLC arises in a lobar or main bronchus in 90-95% of cases, and usually presents as a centrally located mass, often causing chest pain, cough, dyspnea, hoarseness due to compression of the recurrent laryngeal nerve causing left vocal cord paralysis, hemoptysis, esophageal compression, vena cava superior syndrome (upper body oedema and flushing), pleural- and/or pericardial effusion [63, 64].

Two thirds of patients have extensive stage disease at diagnosis. Predominant metastatic sites are bone, brain, spinal cord, liver, and adrenal glands [65]. Constitutional symptoms include anorexia, weight loss and fatigue [63, 64]. Brain metastases are frequent and can cause headache, nausea, seizures, and cognitive impairment [66, 67].

SCLC is the most common cause of paraneoplastic syndromes which can affect most tissues and organs and might precede other symptoms of lung cancer. Neuroendocrine cells can produce biologically active peptides or hormones causing paraneoplastic neuroendocrine syndromes, most common are syndrome of inappropriate anti-diuretic hormone secretion (SIADH) causing hyponatremia, occurring in 10-15% of SCLC patients, Cushing's syndrome occurring in 5% (secretion of ACTH) and hypercalcemia (secretion of parathyroid related protein).Paraneoplastic neurological syndromes are most often immune-mediated, the most common is Lambert-Eaton myasthenic syndrome occurring in 3-5% of SCLC patients, more rare are -encephalomyelitis, limbic encephalitis, cerebellar degeneration, and sensory- or autonomic neuropathy [68-71].

2.2.3 Diagnostic workup

2.2.3.1 Early detection of SCLC

Screening of patients at high risk of lung cancer with low dose CT reduces mortality in lung cancer [72, 73], but there is no documented benefit of screening for SCLC, probably due to the rapid growth [73-75]. Several protein biomarkers of SCLC and

circulating tumor DNA can be detected in blood but none of these methods are established for screening [76, 77].

2.2.3.2 Imaging

CT of the chest and upper abdomen with intravenous contrast is standard imaging for patients with suspected lung cancer. Candidates for curative treatment then undergo a [18F] 2-fluoro-2-deoxy-D-glucose positron emission tomography CT (FDG-PET-CT). FDG-PET-CT is more sensitive for detection of metastases and enables differentiation between tumors and collapsed lung and adjacent normal tissue [78-81]. SCLC frequently metastasizes to the brain and a brain MRI is recommended [82]. CT is less sensitive than MRI, and PET CT is not useful due to the high FDG uptake in normal brain tissue.

2.2.3.3 Laboratory analyses

To determine fitness for treatment and presence of paraneoplastic syndromes, a blood count, kidney function, liver enzymes, sodium, potassium, glucoses, and lactate dehydrogenase should be measured.

2.2.3.4 Histology

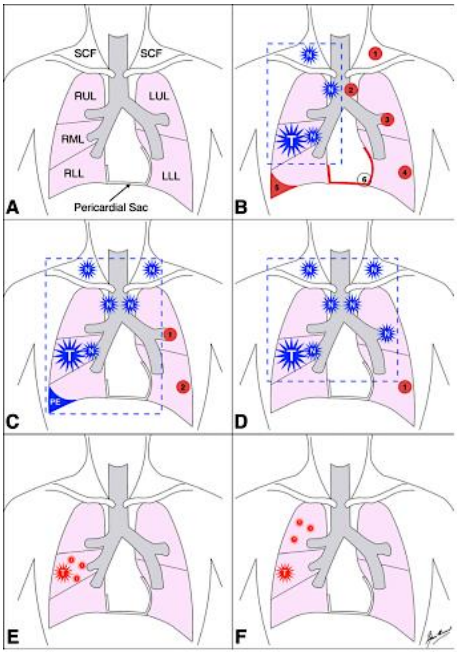
A biopsy (preferred) or cytology is required to confirm the diagnosis. A tissue sample is collected from the primary tumor, lymph nodes or other metastases through ultrasound guided bronchoscopy or CT guided transthoracic biopsy. The tumor sample should preferably be collected from the site confirming the highest disease stage (e.g., suspected lymph node or distant metastasis).

SCLC is usually diagnosed through light microscopy of a hematoxylin and eosin-stained tumor sample showing blue, small, round to fusiform (“oat cell”) shaped cells with scant cytoplasm and hyperchromatic nuclei with fine granular chromatin. Nucleoli are absent or inconspicuous, necrosis frequent and high mitotic activity is typical [83]. Neuroendocrine markers such as synaptophysin, CD56, TTF-1 and chromogranin are often positive on immunohistochemistry [49].

2.2.3.5 Staging

Anatomic extent of disease is the most important prognostic factor. Staging according to the TNM system is encouraged in guidelines, but most only separate between limited stage (LS) and extensive stage (ES) of disease since this is the main variable for selecting treatment.

Figure 6 Illustration of different definitions of LS SCLC. Figure copied from [84].



A) areas of interest B) VALSG definition C) IASLC definition D) TNM classification E) and F) does not classify as LS. The anatomical regions that meet the criteria are shown in blue stars, the radiation port in blue dashed line and the excluded anatomical regions in red circles.

VALSG-definition (figure 6B)

According to the Veterans Administration Lung Study Group (1957), LS is defined as disease confined to ipsilateral hemithorax, hilar, mediastinal, or supraclavicular lymph nodes which can be fitted into a tolerable RT field [85]. Otherwise, or if malignant pleural- or pericardial effusion is present, disease extent is defined as ES.

IASLC definition (figure 6C)

In a consensus report in 1989, the International Association for the Study of Lung Cancer (IASLC) modified the definition of LS SCLC in accordance with the TNM classification system [86] allowing ipsilateral pleura effusion, contralateral mediastinal- and supraclavicular lymph node metastases. Later, a retrospective

review of 109 patients concluded that the IASLC definition was a better prognostic discriminator than the VALSG [87].

TNM (figure 6D)

The TNM classification of malign tumors is the international standard for classification of extent of cancer. The current version for lung cancer classification is version 8 [88, 89]. T describes the extent of the primary tumor, N lymph node involvement, and M metastatic disease. The TNM descriptors are then categorized as an overall disease stage (Table 1). Staging SCLC according to TNM has been recommended by the IASCL and in guidelines since the seventh edition was published in 2007 [90-95]. Survival varies for stages I-V also among patients with LS (Figure 7) [96].

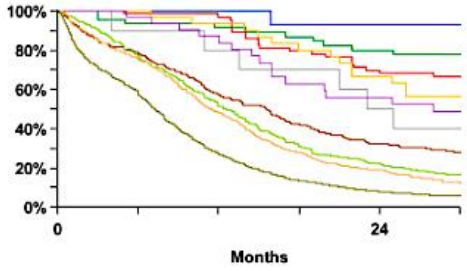
Table 1 TNM staging of lung cancer eight edition, copied from [97].

Table 2. Eighth edition of TNM staging of lung cancer: Stage grouping

Stage group	
Occult carcinoma	(TxN0M0)
Stage 0	(TisN0M0)
Stage IA1	(T1aN0M0) (T1(mi)N0M0)
Stage IA2	(T1bN0M0)
Stage IA3	(T1cN0M0)
Stage IB	(T2aN0M0)
Stage IIA	(T2bN0M0)
Stage IIB	(T (1–2)N1M0) (T3N0M0)
Stage IIIA	(T(1–2)N2M0) (T3N1M0) (T4N(0–1)M0)
Stage IIIB	(T(1–2)N3M0) (T(3–4)N2M0)
Stage IIIC	(T(3–4)N3M0)
Stage IVA	(Any T, Any N, M1a,b)
Stage IVB	(Any T, Any N, M1c)

The recommendation to use TNM in SCLC is based on a prognostic analysis of 8088 patients with SCLC in the IASLC database [96]. In clinically staged patients without distant metastases both T and N categories were discriminatory for overall survival, but there was no significant difference between N0 and N1 disease. The overall stage I-IV was predictive for OS in 4848 SCLC patients from a new database used for developing the proposal for the revision of TNM v. 8 [89, 98].

Figure 7 Survival by stage of SCLC (TNM v.8) copied from [89].



cTNM Proposed	Events / N	MST	12 Month	24 Month
IA1	3 / 14	NR	100%	93%
IA2	27 / 67	NR	97%	68%
IA3	15 / 48	NR	91%	80%
IB	16 / 32	33.0	93%	67%
IIA	6 / 10	24.1	80%	50%
IIB	17 / 38	28.0	87%	56%
IIIA	191 / 254	15.6	58%	32%
IIIB	326 / 402	12.6	52%	22%
IIIC	330 / 400	11.4	48%	19%
IV	2620 / 2926	7.3	27%	8%

2.2.4 Survival

Untreated, survival of SCLC is only a few months [99], but LS SCLC is a potentially curable disease. Median overall survival for LS SCLC in recent RCTs is 22-38 months and 5-year survival rates 25-36% [9, 100-103], while population-based studies report median survival of 18-23 months and 5-years survival of 16.5-31% [1, 4, 104-107].

Although treatment of LS SCLC has been largely unchanged the last two decades, survival has improved slightly, probably due to better staging of disease, implementation of early concurrent and twice-daily TRT, and PCI. In Norway, median overall survival increased from 17.9 months to 25 months from 2000-2004 to 2015-2018 [104] due to implementation of twice-daily and early TRT through our HAST trial.

Median overall survival for ES SCLC is 9-13 months [108-110] with promising 3 years survival rates of up to 18% with the recent addition of immunotherapy to chemotherapy (5-6% among patients who receive chemotherapy alone) [111-113].

2.3 Treatment of LS SCLC

Surgery is offered to the few patients diagnosed with T1-2 tumors without nodal involvement. Chemotherapy is the main treatment of inoperable SCLC. Concurrent thoracic radiotherapy (TRT) improves survival in LS, and consolidation TRT slightly improves survival in ES. Prophylactic cranial irradiation (PCI) improves survival in LS-patients who respond to therapy, while it is unclear whether PCI is better than MRI surveillance in ES. Adding immune check inhibitors (ICI) to chemotherapy improves survival in ES, ongoing studies will clarify the role of ICIs in LS.

Overall, smoking cessation is beneficial for patients with lung cancer including SCLC. It increases the effect of treatment, reduces the risk of secondary tumors, and prolongs survival [114, 115].

2.3.1 Surgery

The first successful treatment of lung cancer was the pneumonectomy performed by Dr Graham in 1933 [116]. Consequently, surgery became the main treatment for lung cancer, including SCLC. When RT was established as cancer therapy, it was offered patients with unresectable disease until the mid-1950s. In the 1960s, it became evident that SCLC in most cases was a more systemic disease than NSCLC, and fewer patients underwent surgery.

Today, only patients with very limited stage (cT1-2N0M0), accounting for less than 5% of patients, are offered surgery [117-120]. Invasive mediastinal staging is recommended prior to surgery, and lobectomy with nodal dissection is the recommended procedure. All patients should be offered adjuvant chemotherapy. In case of R1 (microscopic residual tumor) or R2 (macroscopic residual tumor) resection or pN1-2, concurrent TRT (as for LS SCLC) is recommended [91, 92, 121]. For medically inoperable T1-2N0M0 patients, stereotactic ablative RT is an option [122].

2.3.2 Chemotherapy

The first studies of chemotherapy for cancer started in the late 1940s [123]. SCLC was soon recognized as a chemo-responsive cancer, and cyclophosphamide was the first drug to improve survival compared with best supportive care [124]. Several other agents (adriamycin (doxorubicin), etoposide, ifosfamide, cisplatin, carboplatin,

and vincristine) provided good response rates (up to 62%) in SCLC [125-132], before combinations regimens were established [133, 134]. The combination of vincristine, doxorubicin, and cyclophosphamide (CAV) proved to be more effective than single agents and was the most used regimen until the late 1980s [135-137].

A synergism between cisplatin and etoposide was suggested in animal studies [138]. Cisplatin interferes with DNA repair mechanisms causing DNA damage and induces apoptosis, while etoposide targets topoisomerase II activity inducing DNA breaks [139, 140]. The non-cross resistant combination of cisplatin and etoposide provided high response rates in SCLC [141] and a meta-analysis and a systematic review concluded that cisplatin and etoposide was superior to non-platinum combinations [142, 143]. One reason is that cisplatin is a radiosensitizer, but also better tolerated than anthracycline containing combinations when combined with RT [141, 142, 144, 145]. A Norwegian phase III trial showed that cisplatin and etoposide was superior to CAV in LS and numerically better in ES [109], and since 2000 platinum/etoposide has been the standard regimen [30, 91, 92, 94, 95, 121].

Carboplatin causes less non-hematological side effects (nephropathies, neuropathy, ototoxicity, and nauseas) but more myelosuppression (especially thrombocytopenia). Carboplatin does not require as much hydration as cisplatin and can be delivered IV as a bolus dose over a short period of time [146]. Thus, carboplatin is routinely used in ES, and an alternative in LS when cisplatin is not tolerated or there are concerns about toxicity [91, 92, 95, 121, 147, 148].

A Japanese (and a Norwegian-Swedish) study showed that irinotecan might be superior to etoposide for ES SCLC [149, 150], while these results have not been confirmed in other studies [110, 151, 152] or metanalyses [153-155].

Several studies have investigated dose-intensification by increased doses or adding a third or fourth agent, shorter treatment intervals, use of hematopoietic growth factor and progenitor cell support, resulting in higher response rates, but significantly more toxicity and no survival benefit [156-163].

There are a wide range of side effects from cisplatin, carboplatin, and etoposide. Cisplatin might cause anemia, leukopenia, thrombocytopenia, alopecia, hearing loss, and thromboembolism [164, 165].The dose limiting toxicities are nephrotoxicity and peripheral sensory neuropathy. The dose limiting toxicity from carboplatin is myelosuppression, especially thrombocytopenia [166], while

myelosuppression, predominantly neutropenia, are dose-limiting toxicities from etoposide [167].

For solid tumors the use of G-CSF is recommended in the ESMO and ASCO guidelines as primary prophylaxis in patients when the risk of febrile neutropenia (FN) exceeds 20% (or 10-20% in patients with severe comorbidity or old age) and as secondary prophylaxis for patients who have experienced FN [168, 169]. Using G-CSF reduces the risk of FN, hospitalization and infection [170], while the impact on survival is not well documented [171-173]. ASCO does not, however, recommend G-CSF in patients receiving concomitant radio- chemotherapy involving the mediastinum [169] since a phase III study of LS SCLC showed that patients receiving GM-CSF had more thrombocytopenia, pneumonitis and death from toxicity compared to patients which did not [174]. However, newer studies indicate that there is no negative effect. In the CONVERT trial, the 37% of the patients who received G-CSF did not experience more toxicity or inferior OS or PFS [175]. Phase II and retrospective studies found more thrombocytopenia but similar survival for lung cancer patients receiving G-CSF and CRT [173, 176, 177].

2.3.3 Thoracic radiotherapy for LS SCLC

Studies in the 1960s showed that RT was superior to surgery in LS SCLC [178-180]. Later, it became evident that SCLC often was a systemic disease and combination chemotherapy replaced RT as the main treatment [181].

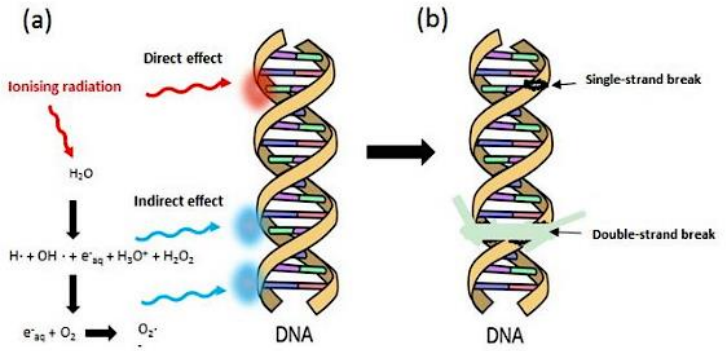
Poor survival and frequent local recurrences led to investigations of combined chemo- and TRT. The first trial combining CAV with TRT and PCI resulted in very good responses but severe and fatal toxicities such as pneumonitis, esophagitis and neutropenic infections were frequent [182]. Anthracyclines are potent radiosensitizer and the combination with TRT causes significant toxicity [183]. More than sixteen trials were conducted during the 1970s and 80s addressing the combination of chemotherapy and TRT with inconsistent results. Several studies showed that the combination increased local control, while not always increasing survival [184-187], possibly because of limited statistical power. It was not until two metanalyses in 1992 concluded that TRT increased 2-year OS with 5.4%, and 3-year survival from 9% to 14% that CRT became standard treatment of LS SCLC [188, 189].

2.3.3.1 Radiobiology

Medical linear accelerators are used to generate external beam radiation. Most commonly they deliver high-energy photons, which interact with the tissue and remove electrons from constituent atoms through ionization [190]. These ejected secondary electrons can interact directly with the DNA, or they can react with water molecules generating free radicals, both causing single or double strand DNA breaks (Figure 8). Irreparable DNA double strand breaks prevents the cancer cells from replicating or induces apoptosis [191]. Most of the DNA damage caused by high energy photons used in RT is indirect effect (70%) [192].

The energy absorbed by the tissue that the ionizing radiation passes through is measured in Gray (Gy). One Gy equals an absorbed dose of 1 joule/kilogram [193].

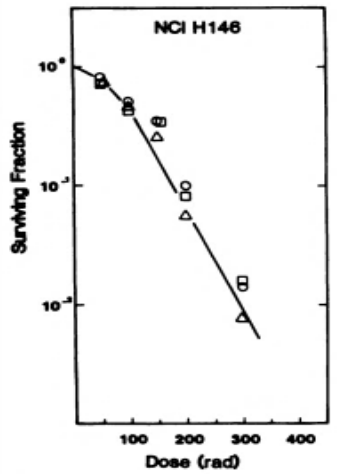
Figure 8 DNA damage from radiotherapy a) through direct or indirect effect, and b) cause single or double strand breaks. Copied from [194].



Cell survival curves are used to describe the relationship between the proportion of surviving cells and dose of radiation. When plotted on a log linear scale with radiation dose on the x-axis and log of cell survival on the y-axis the cell survival curves have a characteristic shape, at low doses the curve is linear, while it becomes increasingly curved with increasing dose of radiation (Figure 9). The region closest to the x-axis is referred to as the shoulder of the survival curve. The width of the shoulder seen at lower doses is reflective of the repair of the sublethal damage. Normal tissue has a broader shoulder, while highly replicating cells have a smaller shoulder.

SCLC is very sensitive to RT and even low single doses results in considerable cell death (Figure 9) [195] . The survival curve for SCLC after a single dose of radiation shows a small to moderate shoulder (Figure 9).

Figure 9 Cell survival curve for SCLC, copied from [196].



Surviving fraction of SCLC cells according to single radiation does (100 rad = 1 Gy).

Several mathematical models have been proposed to capture the relationship between radiation dose and cell survival. The linear quadratic cell survival model (LQ-model) is the most established. The LQ-model assumes that there are two components of cell kill, one that is proportional to the RT dose, and one that is the square of the dose [197].

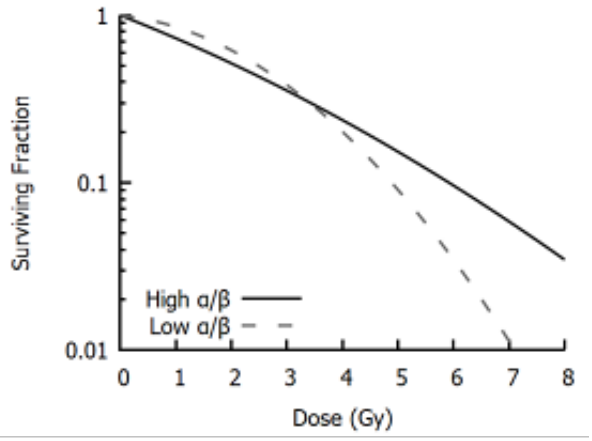
The following equation can be used to estimate the fraction of cells surviving after a single dose of radiation:

$$SF_{(D)} = e^{-\alpha D - \beta D2}$$

$SF_{(D)}$ *is the fraction of survival cells at dose D, e is a constant, α represents the linear component of cell kill (irreversible DNA double strand breaks from a single electron) and ß represents the quadratic component (DNA double strand breaks from two electrons)*.

While the α representing irreversible DNA double strand breaks from a single electron is independent of dose, the ß represents repairable DNA double strand breaks from two electrons and depends on dose of radiation [198]. The shape of the cell survival curve is determined by the α/β ratio. The ratio is determined by finding the dose where the linear and quadratic component cause the same amount of cell killing (Figure 10).

Figure 10 Cell survival curves according to α/β ratio, copied from [199].

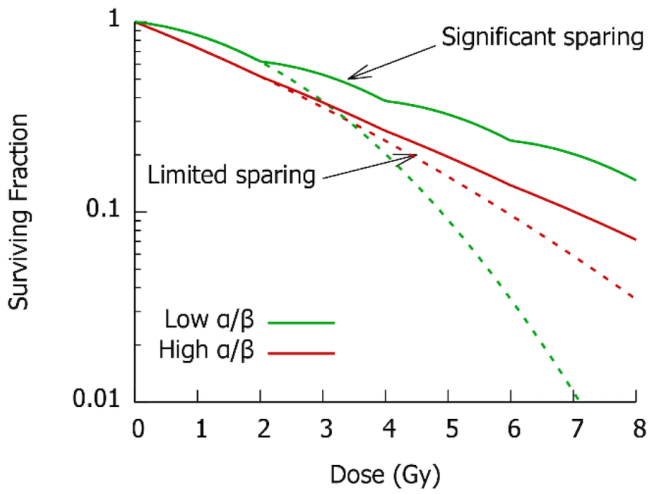


Surviving fraction on the y axis on a log scale, radiation dose in Gy on the x-axis. For tumor cells with a high α/β ratio the survival curve has a linear shape with a constant rate of cell killing with increasing dose (line), while for normal late reacting tissue with a low α/β ratio the survival curve has a more curved shape with a greater killing pr dose at higher doses (dotted line).

Different cell lines, tissue and tumors have different α/β ratios. Most tumors and early reacting normal tissue (e.g., esophageal mucosa) have a high α/β ratio of approximately 10 Gy (range: 5-20 Gy), while the α/β ratio is often estimated to be 3 Gy (range 1.5-5 Gy) for late reacting normal tissue (e.g., lungs, heart) [198, 200, 201].

Fractionated radiotherapy, where the total dose is split into multiple smaller doses, given with a time interval between doses, takes advantage of the differences between normal tissue and tumor. If normal cells are given time to repair between fractions, the shouldered part of the survival curve will, after multiple fractions, reduce the magnitude of the beta component. As illustrated in figure 11, for normal tissue with a low α/β ratio, fractionation will lead to increased cell survival (green line), while for tumor tissue with a high α/β ratio, the sparing is limited (red line) because of a higher α component (which is independent of fraction dose).

Figure 11 The benefits of fractionation. Copied from [199].



Dotted lines represent single dose radiation as compared to fractionated radiotherapy.
In low α/β tissue (lungs, heart) the shoulder part of the initial survival curve will, by delivering smaller fraction of radiotherapy with sufficient time intervals to allow for repair of DNA damage give rise to a significant sparing of cells (green line), while in high α/β tissue (tumor) fewer cells survive (red line).

The mechanism underlying the response of biological tissue to fractionated radiotherapy) can be explained by repair, reassortment, reoxygenation, repopulation, and radiosensitivity known as the five Rs of radiobiology (Figure 12) [202, 203].

Repair refers to tissues' ability to repair DNA double-strand breaks between two fractions of RT. Most tumors and rapidly proliferating normal tissue (e.g., mucus of esophagus) have a low capacity of repair, while other normal tissue (e.g., lungs and heart) has a higher capacity [202].

Cells are most radio-sensitive in the M and G2 phase of the cell cycles, while the late S phase is the most radioresistant phase. Multiple fractions allow for *redistribution (reassortment)* through the cell cycle between fractions which means that cells that were in a radioresistant phase during the first dose of RT might be in a radiosensitive phase when the next radiotherapy dose is delivered.

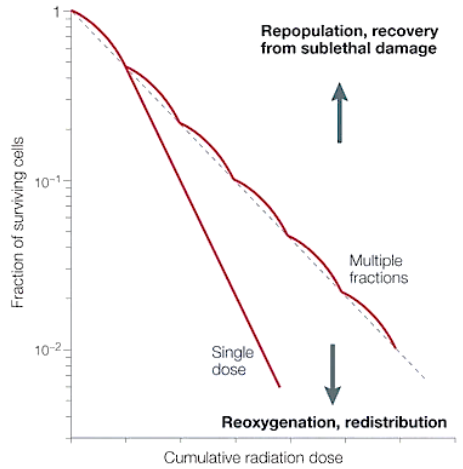
The presence of oxygen is essential for DNA damage by RT to occur. In the absence of oxygen, the radiation dose needed to cause cell death is three times higher than when the irradiated tissue is well oxygenated. In most tumors, there are hypoxic parts due to blockage of blood vessels or limited diffusion, but this can be overcome by *reoxygenation*, e.g., due to death of well oxygenated cells which releases oxygen and reduces oxygen demand in tissues, and distribution and diffusion of oxygen might improve when a tumor shrinks.

Repopulation refers to the increase in the surviving fraction of cancer cells if the interval between RT fractions exceeds the time needed for tumor cells to replicate. Both chemotherapy and radiotherapy can enhance the repopulation by triggering surviving tumor cells to divide more rapidly than normal, a process called accelerated repopulation [204]. Accelerated repopulation starts with varying intervals after initiation of treatment, the time-lag being different for different tumor-types and increases during treatment. Repopulation kinetics have been most studied in poorly differentiated squamous cell carcinoma, where an accelerated re-population is seen after 3 weeks of treatment [205]. For different cell-lines, a dose of 0.5-1.0 Gy per day is required to overcome repopulation. The threshold is estimated to be 0.7 Gy for SCLC [204, 206]. Accelerated fractionation reduces the overall treatment time thereby inhibiting accelerated repopulation.

Radiosensitivity is the primary determinant of response of cells, tissue, or organs to irradiation. The radiosensitivity differ in different tumors and cell types. For

example is SCLC cells more sensitive to radiotherapy than glioblastoma or melanoma cells [207].

Figure 12 Survival curves after a single dose and multiple doses of radiation , copied from [204]



Survival curves after a single and multiple radiation doses. The accumulation of sublethal damages results in an initial shoulder followed by a decrease in survival from increased dose

Conventional fractionation schedule consists of 1.8-2 Gy fractions once daily five days a week. Hypo-fractionated schedules consist of larger doses (>2 Gy), while hyper-fractionated schedules consist of a larger number of smaller fraction doses (<2 Gy). A schedule is accelerated if the total dose is delivered in a shorter time than a conventional schedule of the same dose.

Using the LQ-model, it is possible to compare the effect of different RT schedules on tumor and normal tissue by calculating the biologically effective dose (BED) [197, 200] or biologically equivalent dose in 2 Gy fractions (EQD2) [205, 208]. BED reflects “the total dose required to give the same log cell kill as the schedule being studied at an infinitely low dose rate” taking in to account the recovery capacity of the irradiated tissue, dose per fraction and nominal total dose [200]. Traditionally BED have been the most used term, but EQD2 is becoming more popular as it is more easily understandable in daily clinical work.

For schedules with the same overall treatment time, the following equation can be used to calculate EQD2:

$$EQD2 = D \times ([d + (\alpha/\beta)]/[2 + (\alpha/\beta)] \quad [200].$$

D is the total dose in Gy, d the dose pr fraction and α/β is the alfa beta ratio.

The equation does not, however, account for repopulation, and modified models have been proposed [197]. The accelerated repopulation correction factor (D prolif.) can be used to correct for proliferation during a prolonged total treatment time.

$$\text{Corrected } EQD_2 = EQD_2 - ((T - Tk) * D_{prolif})$$

Tk is the time before the accelerated repopulation starts, and T is the total treatment time, $D_{prolif.}$ is the dose required to overcome accelerated repopulation.

The evidence for the validity of this model is limited, especially when RT is combined with chemotherapy underscoring the need for clinical trials.

2.3.3.2 Fractionation and dose

Initially, conventionally fractionated schedules to moderate total doses of 40-50 Gy were common in LS SCLC, because higher doses caused severe toxicity when combined with chemotherapy [182]. The in vitro observation that SCLC was responsive to even smaller fractions of RT led to the investigation of hyper fractionated schedules such as 1.5 Gy given twice daily. Among others, a study by Brodin et al. of in vitro survival for SCLC cell lines, demonstrated that a great fraction of the cells was killed at lower doses, and there was not difference in in tumor cell survival for 1 ,2 and 5 Gy schedules, indicating that smaller fraction doses over a shorter period might be favorable in SCLC [195]. Smaller fractions allow for better repair of normal tissue between fractions, thereby enhancing the therapeutic ratio. Thus, studies of different radiotherapy schedules were initiated, and small, single arm studies showed promising results from both once and twice-daily TRT combined with cisplatin/etoposide chemotherapy [209-211].

These studies led to the landmark Intergroup 0096 published in 1999 comparing concurrent chemotherapy and TRT of 45 Gy in 30 twice-daily fractions or 1.8 Gy in 25 once daily fractions [10]. Five-year overall survival was significantly improved in the twice-daily arm (23 months vs. 19 months p=0.004). Despite an

improved survival, twice-daily TRT has not been widely implemented since twice-daily TRT cause more esophagitis (33% vs.16%), and logistical challenges. Also, it has been commented that the biological effective dose of the once daily schedule was lower than the twice-daily schedule. Furthermore, a later trial by Schild et al did not find a benefit of twice-daily TRT (50.4 Gy QD vs. 48 Gy BID), probably due to the split course schedule in the twice-daily arm. OS was 20.6 months and 5-year survival 22% in both arms [212].

Hypo-fractionated RT has been frequently used in several countries including Canada and Norway. Hypo-fractionated regimes gives a shorter total treatment time which is favorable for SCLC. To our knowledge, our former study (HAST) is the only to compare hyper-fractionated twice-daily TRT of 45 Gy in 30 fractions with a three-week hypo-fractionated once-daily schedule (42 Gy in 15 fractions). Median overall survival was 6 months longer for patients receiving twice-daily TRT though the difference was not statistically significant. Toxicity did not differ between the RT schedules [213].

Although outcomes in the Intergroup 0096 trial were better in the twice-daily arm, the local recurrence rate was still 36% (52% for the OD arm) [10]. Thus, it has been suggested that higher TRT doses might improve local control and consequently survival.

A phase I study of fifty patients aimed at determining the maximum tolerated dose of twice daily and QD RT. Patients were given cisplatin, cyclophosphamide, and etoposide for three cycles followed by two PE courses, the fourth course starting concurrently with TRT of 40 Gy followed by higher doses to a smaller volume. Maximum tolerated dose (MTD) was defined as the dose which caused ≥ grade 4 esophagitis and/or ≥ grade 3 pulmonary toxicity in >33% of patients. The MTD was estimated to be 45 Gy for the twice-daily schedule and 70 Gy for QD schedule [214]. Interestingly, 6-year survival was 36% among patients who received 70 Gy QD [215]. A phase II study confirmed that 70 Gy QD was tolerable [216], and two phase III studies of high dose once daily TRT were initiated. The CONVERT trial failed to show a survival benefit of 66 Gy once daily compared with 45 Gy twice daily [9]. Toxicity was also similar in both treatment arms (grade 3-4 esophagitis 19% in both arms). The CALGB 30610/RTOG 0538 comparing once daily TRT to a total dose of 70 Gy with the 45 Gy twice-daily schedule also failed to show superiority of the

higher dose (median OS: QD 30.1 months vs. twice-daily 28.5 months p=0.594). Also here, the frequency of grade 3-4 esophagitis was similar in both arms (QD 17.5% vs. BID 16%) [217]. The authors conclude that 45 Gy twice-daily remains the recommended schedule, but 1.8-2.0 Gy once daily to a total dose of 60-70 Gy is an option [37, 91, 92, 94, 95, 218].

2.3.3.3 Timing of thoracic radiotherapy

The timing of TRT and total treatment time have been evaluated in several studies and reviews [219-225]. De Ruysscher and colleagues concluded that early TRT (before chemotherapy-cycle three) and shorter TRT time increased survival [162]. A systematic review by Fried et al indicated an improved 2-year survival of early RT (before cycle three of chemotherapy), and improvement was even greater when twice-daily TRT and platinum combination therapy was used [225].

Both radio- and chemotherapy can trigger accelerated repopulation, and a meta-analysis found that 5-year survival rates improved with shorter time from initialization of chemotherapy to the end of TRT (SER) [226]. However, differences in chemotherapy regimens, compliance and TRT schedules makes it difficult to fully compare results across studies. Thus, the current recommendation is to start TRT as early as possible and preferably along with cycle 1 or 2 [37, 91, 92, 94, 95, 218].

2.3.3.4 Radiation target and treatment volumes

Traditionally, TRT target volumes have included all tumor locations present at diagnosis and regional lymph node stations (elective hilar/mediastinal nodal irradiation, ENI) [10]. The downside with this approach is that target volumes often become large, causing significant toxicity. Studies have demonstrated that target volumes safely can be reduced to post induction chemotherapy volumes without increasing recurrence rates or influencing survival time [227-229].

For staging, it appears that PET or PET-CT provides a more sensitive and accurate assessment of extent of disease than CT alone [78, 230-238]. A systematic review and a meta-analysis from 2020 found that the binary stage of SCLC was changed in 15% of the cases [79]. In another review, staging concordance between PET and CT was 84%. Using PET-CT, 18% were upstaged to ES and 11% down staged to LS, treatment plan was changed for 28% of patients and RT target volumes changed for 68% [239].

It remains, however, unclear whether PET CT staging influences survival. A small single institution study and a registry study indicated that it does [239, 240], while the subgroup analysis of CONVERT participants and a systematic review did not reveal any survival difference between patients staged with PET CT and those only staged with CT [79, 241].

The CONVERT subgroup analyses also showed that patients staged with PET CT had lower radiotherapy doses delivered to normal tissue, and smaller gross tumor volume [241].

Furthermore, it appears safe to omit ENI and limit RT fields to include PET positive lesions. Retrospective studies show that very few patients relapse in PET negative mediastinal lymph nodes that would have been encompassed by ENI [242, 243]. A meta-analysis concludes that ENI was not associated with better survival [244].

Limiting TRT target volumes to post-chemotherapy tumor volume and pre-chemotherapy PET-CT positive lesions is recommended in guidelines even if the approach has not been compared with ENI in prospective randomized trials [91, 92, 95, 121, 218, 245].

2.3.3.5 Radiotherapy techniques

Intensity modulated radiation therapy (IMRT) is an advanced form of conformal RT where the linear accelerator has a computer controlled multi-leaf collimator that shapes the radiation field. The radiation is directed to the tumor from multiple angles and the intensity of the beams can be adjusted. One of the key features of IMRT is inverse planning, i.e. the dose to tumor and organs at risk are prespecified and a computer calculates the optimal intensity and direction of the radiation beams [246]. 4D-motion-CT scans and respiratory gating accounting for tumor motion due to respiration is recommended for IMRT, especially when tumors are located close to the diaphragm.

Volumetric modulated arc therapy (VMAT) is a type of IMRT that uses a single continuously rotating gantry to deliver radiation doses with high precision, limiting radiation to targets as much as possible, resulting in sharper radiation dose gradients between tumor and normal tissue than when using conventional 3D RT [247].

IMRT/VMAT allow for delivering higher RT doses to tumors while sparing normal tissue [248, 249], and for lung cancer patients they seem to lower the risk of pneumonitis and esophagitis [250-252]. A potential downside is that the volume of normal tissue receiving low radiation doses increases. The potential consequences are not yet fully understood, but there has been concerns about increased risk of secondary malignancies [253].

2.3.3.6 Toxicity from thoracic radiotherapy

Side-effects of RT are categorized in acute and late effects. Acute effects are seen 2-3 weeks after the start of RT and is characterized by inflammation and damage to (rapidly) proliferating tissue such as epithelial cells of mucosae. Late effects manifest from 3-6 months after RT and sometimes years later, and is characterized by fibrosis, vascular injury, and damage to slow reacting tissue as the heart, lungs, and cerebrum [254].

RT to a thoracic tumor effect neighboring organs as the esophagus, lungs, heart, and the spinal cord. Esophagitis, pneumonitis, and spinal cord damage are the most important dose limiting toxicities from TRT.

Acute radiation esophagitis is common, occurring in 15-20% of patients receiving CRT for LS SCLC [9, 217]. It is caused by damage of the basal epithelial layer of the esophageal mucosa. Most common symptoms are dysphagia, odynophagia, and substernal pain. Symptoms typically appear 2-3 weeks after the introduction of RT and heal within 3 months. Late effects caused by inflammation and fibrosis of the esophageal musculature causes strictures or altered motility, and in 0.4-1% deaths from perforation or fistulae [255-257].

Radiation pneumonitis occurs 3-12 weeks after exposure and may progress to fibroses in 6 to 12 months. Typical symptoms are non-productive cough, dyspnea, low grade fever and chest pain, and severity ranges from mild to fatal. Risk of radiation induced lung damage is related to dose and volume irradiated [258]. In a systematic review, fraction doses above 2.67 Gy appeared to increase the risk of pneumonitis, while delivering two smaller fractions per day appeared to reduce the risk [259]. Patient-specific risk factors are age, smoking history, comorbidity, gender, and performance status, whereas using IMRT/VMAT appears to reduce the risk [9].

According to a systematic review from 2022, the risk of grade 3-5 pneumonitis ranges from 3.3%- 6.3% and was higher in observational studies than in RCTs [260].

Irradiation of the heart can cause damage to the heart valves, coronary arteries, capillaries, pericardium, myocardium, and the conducting system. Acute toxicity results in pericarditis, while long-term toxicity results in fibrosis of the pericardium, coronary artery disease, cardiomyopathy, valvular disease, and conduction abnormalities [261]

Cardiac morbidity associated with irradiation of the heart are best studied in long term survivors from Hodgkin's lymphoma and breast cancer [262, 263]. Given the poor prognosis, there is limited data on SCLC patients, but in a population-based study of 7060 patients with SCLC, Ferris et al found a 5% increased risk of cardiac event (CE) after RT for all SCLC patients, and a 10% risk for CE for patients with LS SCLC [264]. Other studies have found clinically important cardiac injuries after TRT in NSCLC [265, 266]. Preexisting cardiac disease and concomitant chemotherapy appears to increase the risk.

Radiation injury to the spinal cord causes demyelination and vascular changes [267]. Radiation myelopathy may present with sensory deficits, reduced proprioception and temperature sensation, and paresis which sometimes leads to paralysis and incontinence [268]. There is little data on the risk among LS SCLC patients after CRT, but in general, the risk of myelopathy appears to be 0.2% after receiving a dose of 50 Gy, rising to 6% for doses of 60 Gy and 50% for doses of 69 Gy or higher. The maximum dose to medulla spinalis appears to be the most important risk factor [269, 270].

2.3.4 Prophylactic cranial irradiation (PCI)

Up to 25% of SCLC patients have brain metastases at the time of diagnosis [82], and 50% of LS SCLC patients in complete remission after CRT will develop metastases to the brain [271], probably because the blood-brain barrier limits the chemotherapy effect in the brain.

PCI for SCLC were introduced as early as the 1970s when small trials showed that PCI prevented development of brain metastasis but improved survival [272, 273]. A retrospective review suggested that improved survival was restricted to patients who achieve extracranial disease control from CRT [274]. Thus, RCTs comparing

PCI with no PCI in patients with complete remission was conducted, confirming the decrease in the incidence of brain metastasis, but results regarding a possible survival benefit was inconclusive [271]. Later, two meta-analysis and a retrospective show that PCI reduces the incidence of brain metastases and prolongs survival in LS SCLC patients who achieve extracranial disease control from CRT [275-277].

Two randomized trials failed to demonstrate an advantage of doses above 25 Gy [278, 279] and the recommended dose is 25 Gy in 10 daily fractions [91, 92, 218].

Cranial irradiation might cause both acute and long-term toxicity. The acute side effects of PCI are usually mild. Most common are fatigue (10%), appetite loss, alopecia (80-100%), radiation dermatitis (4%), headache (43%), and nausea (35%) [280, 281].

Long term side effects of PCI are a greater concern, especially among long-term survivors. Cranial irradiation can result in neuro-cognitive and psychological deficits occurring 6-12 months after PCI. More severe side effects are seen when PCI is given concomitant with chemotherapy, in large fractions and high total doses [279, 282]. Older age and primary neurocognitive deficits are associated with worse long term side effects [279, 283, 284]. This is concerning since most LS SCLC patients are of old age and have a history of tobacco smoking, both associated with CNS-comorbidity.

It has been suggested that hippocampus sparing PCI reduces the risk of neurocognitive decline. Two recent phase III trials compared neurocognitive effects of hippocampus sparing PCI with conventional PCI. One study found no benefit, while the other found better cognitive function in the hippocampal avoidance group [285, 286].

PCI is still recommended in guidelines for LS SCLC but has become more controversial following results of a study of PCI in ES SCLC [287]. An European phase III trial showed a reduction in the risk of brain metastases and a survival benefit [280], while a Japanese phase III study showed that although the risk for brain metastases was reduced, there was no survival improvement of PCI compared to MRI surveillance every 12 weeks [287]. Furthermore, a systematic review and a meta-analysis did not find a survival benefit from PCI for resected stage I patients, probably because the risk of brain metastasis was only 12% [288] . Consequently, two large, ongoing phase III studies (the European PRIMA-lung, (NCT04790253) and

the US MAVERICK (NCT04155034)) aim to evaluate whether MRI surveillance is an alternative to PCI followed by MRI surveillance [289].

2.4 Immunotherapy for SCLC

The introduction of immune checkpoint inhibitors (ICI) has revolutionized the treatment of many malignancies and is now the main systemic treatment of NSCLC without driver mutations. Due to the high mutagenicity of SCLC, it has been expected that ICIs also benefit SCLC patients. However, trials of maintenance and relapse ICI therapy are negative [113], and the only setting where ICIs have proven useful so far is when added to primary chemotherapy for ES SCLC [112, 290]. The survival benefit is, however, modest with an increase in median overall survival time of 2-3 months, though there is an encouraging increase in 3-year survival from 5-6% to 15-18% [111, 291].

Several studies investigate the role of ICIs in LS SCLC. So far, only one trial is completed. In the randomized phase II STIMULI trial, there was not survival benefit of nivolumab plus ipilimumab after CRT [292]. Notably, the study treatment was very toxic, median treatment time was only 1.7 months, and results of ongoing trials are awaited. Some studies compare ICI therapy after CRT with observation (NCT03703297), while other deliver ICIs (atezolizumab or pembrolizumab) concurrently with CRT (NCT03811002) (NCT04624204). A randomized phase II trial by our group investigates whether atezolizumab after CRT prolongs survival (NCT03540420).

2.5 Therapy for recurrent SCLC

2.5.1 Chemotherapy

Most patients with SCLC will experience a relapse, which is associated with a poor prognosis. The main relapse treatment is chemotherapy, though palliative RT is an alternative, especially for the few patients with oligometastatic disease.

The effect of second line chemotherapy is strongly associated with response to first line platinum-based chemotherapy [293]. In a pooled analysis of 21 studies on second line treatment of SCLC, response rates for platinum sensitive patients were 27.7% and median OS 7.7 months, compared to 14.8% and 5.4 months in refractory patients [293].

Topotecan it is the only approved drug for second line therapy in Europe and one of two drugs approve in the US based on a trial including patients 141 patients considered unfit for IV chemotherapy which showed a modest survival improvement of 3 months, and a slower decline in HRQoL compared with BSC [294]. However, CAV provides similar response rates and survival as Topotecan, and less hematological toxicity [295]. For platinum sensitive patients, reintroduction of platinum chemotherapy is recommended since it prolongs PFS and causes less toxicity than topotecan [141, 296, 297]. There are also data suggesting that carboplatin/irinotecan, taxanes, temozolomide and vinorelbine have some activity in relapsed SCLC, and might be used for patients with previously good responses to chemotherapy [150, 298-302]. Lurbinectedin showed promising effect in a phase II trial, but the phase III ATLANTIS trial comparing lurbinectedin plus doxorubicin with physicians' choice of chemotherapy did not show a survival benefit [303]. So far, ICIs are not established in this setting, though some activity has been observed in early phase trials [304-309].

2.5.2 Role of molecular targeted agents in SCLC

No targeted agents are yet established in SCLC. There were promising data on rovalpituzumab tesirine, a humanized IgG1 monoclonal antibody-drug conjugate that targets DLL3, but phase III trials failed to confirm a benefit [310, 311].

2.6 Current treatment recommendations for small cell lung cancer

2.6.1. Very limited stage (T1-2N0M0)

Surgery followed by four courses of adjuvant cisplatin and etoposide chemotherapy. PCI should be considered, and TRT is recommended if pathological lymph nodes are detected or there has been insufficient lymph node sampling during surgery.

2.6.2 Limited stage (any T, N0-3M0)

Four (to six cycles) of cisplatin (preferred) or carboplatin etoposide and concurrent TRT starting with the first or second chemotherapy course. Recommended TRT schedules are 45 Gy in 30 fractions (BID) or 2 Gy x (66-) 70 Gy (QD). Norwegian standard is 60 Gy in 40 fractions (BID). Patients who respond to CRT should be offered PCI of 25 Gy/10 fractions [37, 91, 92, 94, 95, 218].

2.6.3. Extensive disease/metastatic disease

Four (to six) courses of carboplatin and etoposide concurrent with either atezolizumab or durvalumab followed by maintenance immunotherapy [30, 91, 92, 94, 95, 121].

Two RCTs have demonstrated that TRT improves local control and prolongs survival in patients who respond to first line chemotherapy [312, 313].

Optimalizations of palliative and supportive care might be important for these patients, and integration of palliative and supportive care in oncology is recommended [314-316].

2.7 Health related Quality of life

2.7.1 Definition of HRQoL

WHO defines quality of life as “an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [317]. Quality of life is a multidimensional and subjective construct thereby the meaning might be different for each person. In medical work and research, we restrict quality of life to the aspects that affect health. Health Related Quality of Life (HRQoL) can be defined as “the extent to which one’s usual or expected physical, emotional, and social wellbeing are affected by a medical condition or its treatment” [318]. HRQoL is subjective and should be assessed by the patients, not by relatives or the doctor.

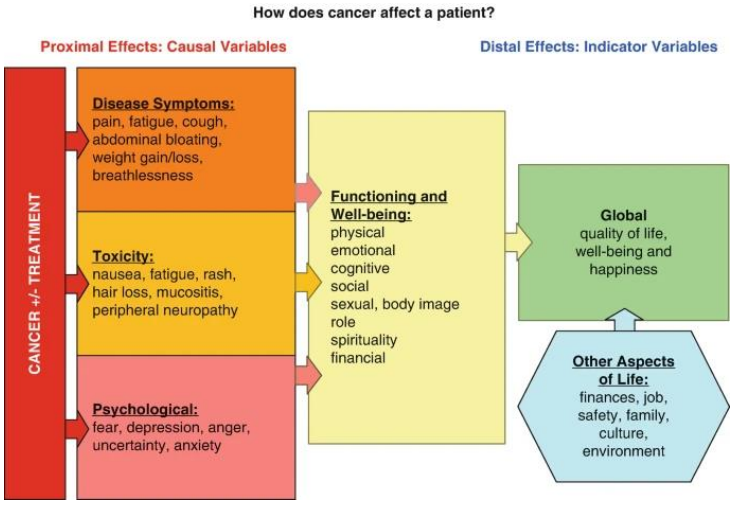
A patient reported outcome (PRO) is a report on any aspect of the patient’s health status that comes directly form the patients. Instruments used to measure PROs are named patients reported outcome measures (PROM) [319]. HRQoL is a specific type of multidimensional PRO.

2.7.2 How cancer affects HRQoL

Cancer causes many symptoms (e.g., pain, cough, fatigue, and involuntary weight loss) which might alter the ability to function and the sense of well-being. This also applies for side-effects of cancer therapy which can have a profound impact on HRQoL (e.g., nausea, esophagitis, neutropenic infections). Both being diagnosed with cancer and its treatment can directly and indirectly affect the patients’

psychological well-being being (Figure 13). When choosing HRQoL endpoints in clinical trials it is important to take into consideration that direct effects are more sensitive to treatment effects that indirect effects [320].

Figure 13 How cancer affects HRQoL. Copied from [320]



2.7.3 Importance of measuring HRQoL in clinical cancer research

HRQoL measurements are considered important in cancer trials for several reasons. HRQoL provide valuable information about the impact of disease and treatment on the patient's daily lives. This information can help researchers and clinicians understand the true benefit of treatment beyond its effect on survival and tumor response. HRQoL is considered a key component by ESMO and ASCO in the evaluation of clinical benefit of anticancer drugs [321, 322]. HRQoL can be used as primary or secondary endpoints in clinical trials and treatment can be effective not only based on its ability to extend survival or shrink tumors but also its ability to improve quality of life. Including HRQoL measurements into clinical trials is encouraged both by the FDA in the US and the European Medicines Agency (EMA) [319, 323].

HRQoL measurements can help identify subgroups of patients who are negatively affected by treatment, e.g., older patients or patients with comorbidities, and used to evaluate benefit vs. risks. Measuring HRQoL is a useful adjunct to physician reported toxicity [324], and can facilitate patient centered care and shared decision making by providing patients with information enabling them to make informed treatment decisions [325].

One might argue that measuring HRQoL is of particular importance in SCLC given the poor prognosis, high symptom burden and frequent treatment toxicity. Although the first lung cancer RCT to include HRQoL measurement was conducted in the 1980s [326, 327], a systematic review of 122 phase III trials of lung cancer show that only two trials of SCLC report HRQoL and both were on ES SCLC [328]. In a systematic review of HRQoL data in SCLC there were no studies on TRT in LS SCLC [329]. Except for the CALGB 30610/ RTOG 0538, our HAST and THORA trials are the only ones to report HRQoL in this setting [330].

In order to optimize the quality of HRQoL data, international guidelines are formed on how to include HRQoL in clinical trials, analyze data, and report data in publications [331-333]. HRQoL should be assessed at baseline, at timepoints relevant for the research question, and continue as long as it is meaningful for the research questions.

2.7.4 HRQoL instruments

A HRQoL instrument is a questionnaire with a relevant set of questions with a standard set of response options, along with algorithms to score patients response into summary scores for analysis and reporting. HRQoL instruments can be generic developed to collect and compare data across different diseases, treatment, healthcare programs, and populations, or disease specific focusing on symptoms and treatment side effects of a specific disease and its treatment.

A HRQoL instrument appropriate for the clinical context, validated and reliable, responsive to changes and easy to interpret should be used [320, 334]. Validity refers to the tools ability to measure what it's supposed to, while reliability refers to its ability to be consistent and reproducible [335]. The ability of the instruments to detect changes and discriminate between various levels of HRQoL is referred to as responsiveness.

More than 50 questionnaires have been developed for measuring HRQoL in lung cancer research [336]. The most commonly used are the Functional Assessment of Cancer Therapy-Lung (FACT-L) and its modification (NCCN-FACT-17), the Lung Cancer Symptom Scale (LCSS), and the EORTC QLQ-C30 and its Lung Cancer module (EORTC-LC13) [337]. QLQ-C30 and LC13 are used in most trials of SCLC and is recommended by The International Consortium for Health Outcomes Measurement (ICHOM) for lung cancer research [338, 339].

The QLQ-C30 consists of 30 questions relevant to patients with cancer and measures QoL on five multi-item functional scales: social, emotional, cognitive, role and physical functioning, three multi-item symptom scales: fatigue, pain, and nausea/vomiting, and six single item symptom scales: insomnia, constipation, diarrhea, loss of appetite, dyspnea and financial impact, and overall global quality of life on a multi-item scale. The QLQ-C30 has been validated and translated into more than 110 languages and used in more than 3000 studies since 1993 [340].

The LC13 questionnaire measures 13 symptoms common in lung cancer [341]. Dyspnea is measured on a multi-item scale, while hair loss, hemoptysis, cough, sore mouth, neuropathy, dysphagia, pain medicine in use, pain in chest, arm, shoulder, or other parts is measured on a single item scale.

On most of the questions for both the QLQ-C30 and the LC13, responses are 1 (not at all), 2 (a little), 3 (quite a bit) or 4 (very much). Exceptions are the questions about pain medicine (yes or no) and the questions about global quality were patients respond on a scale from 1 (very poor) to 7 (excellent).

Raw scores are transformed to a scale from 0 to 100 according to the EORTC scoring manual [342]. A higher score on global QoL and the functional scales reflect a better QoL, while a higher score on the symptom scales means more symptoms and worse QoL. A change in mean score of 5-10 indicates a minor change, 10-20 a moderate change and ≥ 20 a major change [343-345].

2.8 Prognostic and predictive factors in SCLC

TNM stage of disease is the most important prognostic factor in lung cancer, but the separation between LS and ES is still more established in SCLC [97]. PS is the other most important prognostic/predictive factor utilized when making treatment decisions. Studies show important prognostic value of gender [346], and possibly of age and

comorbidity, though there are no consensus on to what extent these factors should be taken into consideration when selecting treatment for individual patients.

2.8.1 Performance status (PS)

A patient's ability to care for themselves and perform activities of daily life is referred to as patients' performance status (PS). Karnofsky performance status (KPS) and the Eastern Cooperative Oncology Group performance status (ECOG PS) are the two most used scales for measuring PS. KPS is measured on a scale from 0-100. A score of 100 reflects normal function, while 0 means a person is dead [347]. The ECOG scale is a simplified, 6-point scale version of the KPS developed in the 1950s and endorsed by the WHO in 1979 [348, 349] (Table 2). A score of 0 reflects normal function, a score of 4 complete disability, and score of 5 death. ECOG PS is a strong independent prognostic factor for survival among cancer patients including SCLC patients [350-352], and most trials only allow PS 0-1 patients.

Table 2 ECOG performance status. Copied and adapted from [349].

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Developed by the Eastern Cooperative Oncology Group

2.8.2 Comorbidity

Comorbidity is a health condition that coexists with the primary disease of interest. Several instruments for measuring comorbidity have been developed. The most used index in cancer research is the Charlson Comorbidity Index (CCI) [353]. The CCI was developed in 1987 by setting scores for nineteen conditions from 1,2,3 or 6 based on one-year mortality risk after hospitalization in an internal medicine department in

Cornell hospital in New York during a one-month period in 1984. The scores take into account the number of conditions, but also partly the severity (e.g., diabetes with or without end organ damage).

Several studies have demonstrated that CCI score is associated with survival among cancer patients including lung cancer patients [354, 355]. For SCLC studies, results are not consistent. Some have found that comorbidity is a negative prognostic factor [356-358], while others have not found such associations [16, 359, 360] .

2.9 Treatment of older patients with cancer

The proportion of older inhabitants is rising worldwide. People live longer and birth rates are declining. According to the UN, one in six people will be 65 years or older by 2050 [361]. More than half of lung cancer patients are already 70 years or older, and this proportion will increase significantly the next two decades [15, 362].

Aging can be defined as accumulation of deleterious changes in cells and tissues causing progressive loss of function [363]. Age dependent changes results in alternation of organ function, reduction of functional and physiological reserves as well as decreased mental capacity [364]. With age, there is a loss of tissue elasticity affecting most organs e.g., the skin, lungs and the cardiovascular system [365]. There is a gradual loss of functional units such as nephrons in kidneys, lung alveoli and cerebral neurons, causing reduced reserves and function [366-368]. A reduction of body water and lean body mass and an increase in adipose tissue causes altered pharmacokinetics and dynamics [369]. Also, there is a loss of bone marrow reserves. Aging is besides biological changes also associated with life transitions as retirement, moving and death of partners and friends which effect psychological and social aspects of life [364].

Age-related changes are multidimensional and there are substantial variations between individuals [370], and life expectancy differ considerably within age-cohort. For example, life expectancy for a 80 year old women varies from 4.6 to 13 years in Norway [371].

The prevalence of multimorbidity and polypharmacy increases with age [372, 373] but there are large inter-induvial differences. Smoking is a common risk factor of lung cancer, cardiovascular disease, and COPD, and consequently many lung

cancer patients have several diseases. Multiple medications increase the risk of adverse drug reactions and interactions [374].

Frailty is reported in up to 50% of older patients [375]. The most common definition of frailty is “an age-associated, biological syndrome characterized by decreased biological reserves, due to dysregulation of several physiological systems, which puts an individual at risk when facing minor stressors and is associated with poor outcomes” [376-378].

Normal age-dependent changes in organ systems, multimorbidity, polypharmacy and frailty influence prognosis and tolerability of cancer treatment. For example, reduced kidney function may alter pharmacokinetics [379], which is important when considering administering nephrotoxic drugs such as cisplatin. Bone marrow suppression following chemotherapy is often more pronounced among older patients. The inflammatory response to illness is less effective at high age [380]. Loss of elastic tissue can cause reduction of respiratory function and cardiac output, especially under stress [381]. The risk of cardiac arrhythmias are increased due to loss of sinus node pacemaker cells [382].

There is, however, little evidence on how older patients should be treated. They are underrepresented in clinical trials, and the few that are included appear to be highly selected and more fit than the average [383]. While treating elderly based up on data from trials of younger patients can lead to overtreatment, withholding standard therapy from older patients is another concern, especially for an aggressive disease as SCLC.

For LS SCLC the evidence on how to treat older patients is sparse. Most population-based studies of LS SCLC report that older patients have worse outcomes than younger patients [19, 384, 385], but older patients are also less likely to receive surgery, RT, and chemotherapy [4, 16, 17, 386]. The impact of age in prospective studies are less consistence. Some studies report similar survival for older and younger patients [387, 388], while others report inferior survival for older patients [385, 389]. Studies indicate that older LS SCLC patients have more hematological toxicity and discontinue chemotherapy due to death or adverse events more often than younger patients, while RT toxicity appears to be more similar across age-groups [385, 387-389].

Preferences of treatment outcome might be different for older compared to younger patients. Studies have demonstrated that preservation of physical and cognitive functions as well as maintenance of quality of life is as important as prolonged survival for older cancer patients [11, 12]. Thus, including HRQoL in studies on older patients is important.

3. Rationale for the project

Approximately one third of LS SCLC patients are cured by CRT, illustrating both that the treatment is potentially curative and that there is a need for better treatment [10, 213]. Since insufficient local control is an important reason for treatment failure, it has been postulated that higher TRT doses might improve local control and survival. A phase II study and a retrospective study show that a higher dose of twice-daily TRT is feasible, tolerable and the phase II study showed a favorable 5-year survival of 30% for the concurrent twice-daily schedule [390, 391].

Using PET CT for staging disease provides a better overview of extend of disease [79, 230, 231, 233]. Omitting ENI by limiting RT fields to PET CT positive lesions and applying modern conformal RT techniques (VMAT/IMRT) reduces normal tissue irradiation and radiotoxicity from TRT, facilitating delivery of higher TRT doses.

Measuring health related quality of life is encouraged by health authorities and adds important perspective on the tolerance of cancer treatment [319, 321-323]. Few have investigated patient reported HRQoL among LS SCLC patients receiving concurrent CRT.

Patients 70 years or older account for 50% of LS SCLC patients [362]. Population based studies show that fewer older than younger patients receive CRT, probably due to concerns of higher toxicity [4, 16, 17, 386]. However, there is limited evidence supporting this practice, and more data on treatment outcomes of older patients is needed.

4.Research questions for the thesis

Paper I:

RQ1 Does twice-daily TRT of 60 Gy in 40 fractions improve survival compared to twice-daily TRT of 45 Gy in 30 fractions?

RQ2 Does twice-daily TRT of 60 Gy result in more toxicity than twice-daily TRT of 45 Gy?

Paper II:

RQ1 Does high-dose TRT of 60 Gy impair patient reported HRQoL more than standard dose TRT of 45 Gy?

RQ2 Are there clinically significant differences in any HRQoL domain from baseline to any timepoint during the first two years of follow-up?

Paper III:

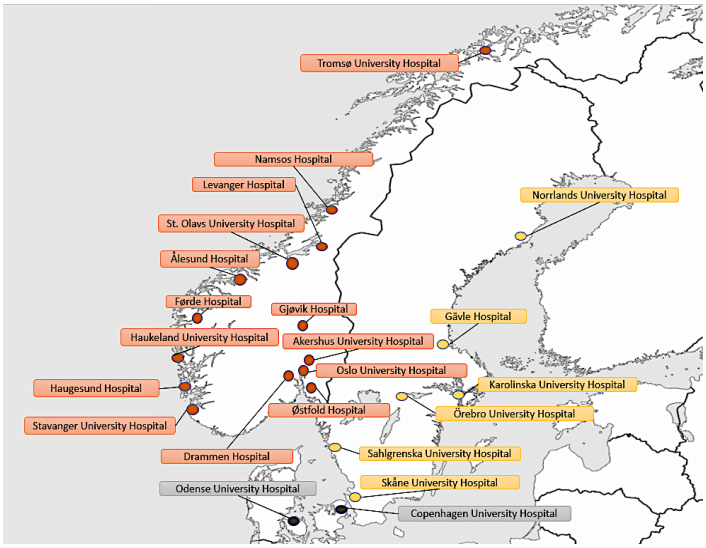
RQ1 Do patients 70 years or older benefit as much as younger patients from CRT?

RQ2 Do patients 70 years or older experience more toxicity or reduction in HRQoL from twice-daily TRT compared to younger patients?

5. Material and methods

This thesis is based on an open label Nordic multicenter phase II randomized controlled trial (RCT) initiated by co-supervisor Bjørn Henning Grønberg on behalf of the Norwegian Lung Cancer Study Group (NLCG) in 2013 [392]. The NLCG is a collaborative group of physicians from all disciplines involved in diagnosis, staging and treatment of lung cancer in Norway. The group develop national guidelines for treatment of lung cancer, as well as conducting basic and clinical research on lung cancer. Patients were recruited from twenty-two hospitals in Norway, Sweden, and Denmark from June 2014 until July 2018.

Figure 14 Hospitals participating in the THORA trial



A PhD project was outlined the last year before enrolment was completed in 2017 and received funding from NTNU.

The PhD candidate has been responsible for collecting, organizing, and analyzing data, and has had a lead role in preparing manuscripts and presenting results.

5.1 Endpoints

The primary endpoint was 2-years survival which is easy to measure, objective, clinically significant and unaffected by interpretation. In Scandinavia we have

extremely low lost to follow up for survival. Migration rates are low, and all three countries have high quality population/death registries.

Paper I

Primary endpoint was 2-year overall survival.

Secondary endpoints were response rates, progression-free survival, overall survival, and toxicity.

Paper II

Primary HRQoL endpoints were dysphagia and dyspnea on the LC13-questionnaire.

All other HRQoL items were defined as secondary endpoints.

Paper III

Primary endpoint overall survival.

Secondary endpoints were toxicity and HRQoL, while exploratory endpoints included response rates, progression free survival and time to progression.

5.2 Inclusion, eligibility criteria and baseline investigations

Patients had treatment naive histologically or cytologically confirmed SCLC and limited stage disease according to the IASLC (disease within one hemithorax, including metastases to ipsi- and contralateral lymph nodes in mediastinum, hili and supraclavicular fossae) ineligible for surgery [86]. Pleural effusion was allowed provided one negative cytology.

All patients gave written informed consent, were ≥18 years, had ECOG performance status 0-2, measurable disease according to RECIST 1.1, adequate biochemistry (leukocytes ≥1,5 x 10^9/l, platelets >100 x 10^9/l, total serum bilirubin <1,5 x ULN, serum alanine transaminase ≤ 3 x ULN, creatinine <100 mol/l and a creatinine clearance >50), no other clinically active malignancy, and no prior RT to the chest. The forced expiratory volume had to be more than 1L or more than 30% of predicted value, and DLCO >30 % of predicted value.

Patients should not have any concomitant disorders that could compromise the ability to complete the study or interfere with the evaluation of efficacy or safety of the study treatment, nor conditions that could prevent adequate information and follow-up.

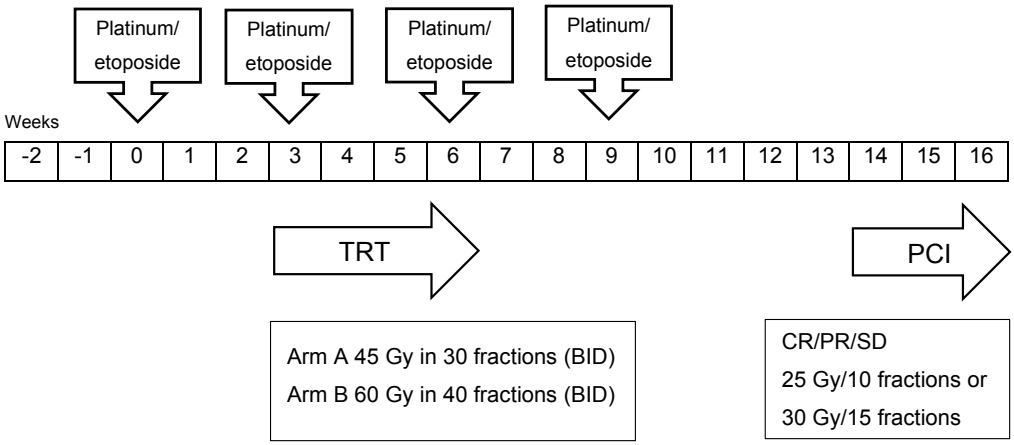
Patients underwent a clinical examination and a blood test for biochemistry, whole body FDG PET CT and an MRI of the brain within 4 weeks prior to the first course of chemotherapy.

5.3 Random assignment

Patients were randomly assigned 1:1 to receive TRT of 60 Gy in 40 fractions or 45 Gy in 30 fractions, in randomly varying block sizes of 4-10, generated by the electronic case report formula (WebCRF v3, Klinforsk NTNU). Randomization was stratified by ECOG performance status (0–1 vs. 2), disease stage (I–II vs. III), and pleural effusion (yes vs. no). Patients and investigators were not masked to treatment allocation.

5.4 Study treatment

Figure 15 Trial design



TRT= thoracic radiotherapy, PCI= prophylactic cranial irradiation

5.4.1 Chemotherapy

Patients were to receive four courses of intravenous chemotherapy: cisplatin 75mg/m2 iv day 1, and etoposide 100mg/m2 iv day 1-3 every 3 weeks. Granulocyte colony stimulating factor or erythropoietin was not permitted.

The dose of chemotherapy was reduced by 20-25% if grade 3-4 neutropenia or thrombocytopenia occurred. Courses were delayed if the absolute neutrophil count

was less than 1.5 × 10^9 cells per L or the platelet count was less than 100 × 10^9 per L. Chemotherapy was discontinued if a course was delayed by more than 3 weeks.

Cisplatin was replaced with carboplatin in case of elevation of creatinine (to > 125 µmol/liter) or in case of severe non-hematological cisplatin-related toxicity (nephropathy, hearing impairment). The dose of carboplatin was recommended to be area under the curve (AUC) 5 or 6 (Calvert's formula) at the investigator's discretion.

5.4.2 Thoracic radiotherapy

A planning CT with intravenous contrast with patients in the treatment position was obtained after the first course of PE. Four-dimensional CT scan for internal target volume definition was preferred but was not mandatory.

TRT started 20-28 days after the first day of the first course of chemotherapy. Patients received two fractions per day, ten fractions a week with minimum 6 hours between fractions. It was recommended to complete RT within 22 days (45 Gy) or 29 days (60 Gy). If timeframes were exceeded a compensation according to local hospitals routine was recommended, preferably by treating patients on weekends, or increasing the fraction dose, but not above 2 Gy. For patients allocated to 60 Gy, lowering the total dose to 54 Gy was allowed to meet normal tissue dose constraints to organs at risk. TRT was to be discontinued in case of severe toxicity.

For RT delivery, Intensity-modulated radiotherapy (IMRT) or volumetric-modulated arc therapy (VMAT) was preferred but was not mandatory.

<u>Target volume definitions</u>

The gross tumor volume (GTV) included the primary lung tumor and PET positive lymph node metastasis. The GTV was delineated according to the planning CT taken after the first course of chemotherapy, including all PET positive lymph nodes prior to chemotherapy. A margin of 0.5 cm for subclinical disease was added to the GTV to form the clinical target volume (CTV).

A four-dimensional CT scan was recommended for defining the internal target volume when available. If unavailable ITV was delineated adding 0.8 cm to CTV in transversal plan, and 1 cm cranial and caudal direction for the primary tumor and adding 0.5 cm in all direction to CTV of the lymph nodes. When using respiratory gating or IGRT, margins were defined according to each departments' routines. A

setup margin was added according to each departments routine for define the planning target volume (PTV).

Organs at risk

Normal tissue constraints were based on a series of reviews (Quantec) of dose/volume tolerance published in 2010 [257, 258, 269, 393-396], and the Norwegian radiation protection authority guidelines for curative radiotherapy for SCLC [397].

Both lungs (minus GTV), the spinal cord (the spinal canal was contoured as planning organ at risk, PRV), the brachial plexus, the heart, and the esophagus from just below the larynx to the gastric-esophageal junction were defined as organs at risk.

Dose-volume constraints for both lungs minus GTV were mean dose not to exceed 20 Gy, volume to receive 20 Gy or more (V20Gy) ≤ 35% and volume to receive 5 Gy or more (V5Gy) ≤ 65%. Dose-volume constraints for the heart were mean dose not to exceed 46 Gy (preferably below 35 Gy), volume to receive 40 Gy or more (V40Gy) ≤ 80%, volume to receive 45 Gy or more (V45Gy) ≤ 60% and volume to receive 60 Gy or more (V60Gy) ≤ 30%. Dose-volume constraints for the esophagus were mean and maximum dose not to exceed 34 Gy and 60 Gy, respectively. Dose to the brachial plexus should not exceed 60 Gy. Dose to the spinal cord was not to exceed a maximum dose of 54 Gy, based on calculations according to the Quantec paper by Kirkpatrick et al [269] with an estimated α/β of 0.87 implicating that the dose pr fraction is considered more important than before.

5.4.3 Prophylactic cranial irradiation (PCI)

Once daily PCI of 25 Gy in 10 fractions or 30 Gy in 15 fractions was offered patients with at least stable disease and was to start within 6 weeks after completing chemo-radiotherapy.

5.4.4 Second-line therapy

Second-line therapy were given according to the treating physicians' recommendation.

5.5 Evaluation and follow-up

The trial plan is presented in figure 15 and table 3. Clinical examination, laboratory tests and assessment of toxicity was performed before the start of each chemotherapy cycle, and at start and end of TRT. Hematology and creatinine were measured on day one and ten of each chemotherapy cycle. Bilirubin, ALAT, LDH, albumin and CRP were measured at inclusion, before the second and after the fourth chemotherapy course.

Overall response to treatment was assessed within three weeks after the fourth chemotherapy course. Patients were evaluated every ten weeks the first year and every third month the second and third year, and every six months thereafter for a total of five years. A CT of thorax and upper abdomen with iv contrast was performed at evaluation week 12, and at every visit thereafter.

Table 3 Trial plan study treatment

Week	**- 4/-2- 0**	**0**	**3**	**6**	**6-8**	**9**	**12**	**15**	**16**
Study treatment	Inclusion/ screen	PE 1	PE 2/ Start of TRT	PE 3	End of TRT	PE 4	Eva- luation	Start PCI	End PCI
Medical history Comorbidity (CCI)	x								
Clinical examination PS, weight	x	x	x	x	x	x	x	x	x
Lab. tests	x		x	x		x	x		
Pulmonary function	x						x		
HRQoL	x				x		x		x
PET CT and MR caput	x								
CT thorax/abdomen	x						x		

PE = cisplatin/etoposide, PCI = prophylactic cranial irradiation CCI= Charlson comorbidity index TRT= thoracic radiotherapy HRQoL=health related quality of life questionnaires PS= performance status

5.6 Assessments

5.6.1 Stage of disease

Stage of disease was assessed according to TNM v 7 [90, 398].

5.6.2 Toxicity

Toxicity was assessed before each chemotherapy cycle, weekly during TRT, at end of TRT, at response evaluation, after PCI, and at each visit and graded according to Common Terminology Criteria for Adverse Events v.4 (CTCAE) [399]. Toxicities for listed conditions are graded from 1 (mild) to 5 (death).

5.6.3 Comorbidity

Comorbidity was scored at inclusion according to the CCI [353]. Patients was divided into three groups according to CCI score, 0 ,1 or ≥ 2 since this categorization is the most used in previous cancer studies.

5.6.4 Patients reported health related quality of life (HRQoL)

Patients reported HRQoL on QLQ-C30 v3 and LC13 [341, 400] (Appendix) at inclusion (week 0), before TRT (week 3-4) at end of TRT (week 6-8), at evaluation (week 12), at the end of PCI (week 16), and at every follow up. Paper II and III include all HRQoL reports from patients with and without progression. Dysphagia and dyspnea were measured on the LC13, while all other HRQoL was measured on both questionnaires.

5.6.5. Response evaluation

Response was evaluated according to RECIST v.1.1 [401]. Target lesions (TL) at baseline was defined as at least one measurable tumor lesion ≥ 10 mm in longest diameter on CT scan (CT slice thickness ≤ 5 mm) and/or pathological lymph nodes of ≥ 15 mm in short axes. A maximum of five TL, no more than two from each organ was identified. Non measurable, or small lesions, were included as non-target lesions.

Level of response was decided by the relative reduction of sum of target lesions diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions (SoD). Non-target lesions were followed as absent or present.

Complete response (CR) was defined as disappearance of all target and non-target lesions, reduction of all lymph nodes to non-pathological size (≤ 10mm in short axis) and a normalization of tumor marker level. Partial response (PR) was defined as at least a 30% decrease in the SoD of target lesions. Progressive disease (PD) was the appearance of one or more new lesions, unequivocal progress of non-target lesions or at least a 20% (minimum of 5 mm) increase in SoD for target lesions. The progression should be clinically significant for the physician to consider changing or stopping therapy.

Stable disease (SD) was defined as a change of SoD between +20% and -30%, and/or the presence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits.

5.7 Statistics

5.7.1 Survival analyses

For survival analyses we used the Kaplan-Meier method [402]. Start was defined as the first day of the first chemotherapy cycle. For overall survival, death of any cause was the event, while for progression free survival the event was progressive disease according to RECIST 1.1 or death of any cause. Time to progression was defined from the first day of the first chemotherapy cycle until progressive disease according to RECIST 1.1 [403]. Individuals still alive, lost to follow up or had no progression were censored in the survival analyses.

In univariable analyses, survival was compared using the Log-rank test. For multivariable analyses, we used the Cox proportional hazards model, adjusting for baseline characteristics [404]. Logistic regression was used for the comparisons of 2-year survival rates.

5.7.2 Comparing toxicity and response

Pearson chi-squared test were used to compare toxicity and overall response rates.

5.7.3 Sample size calculations and statistical significance

In our previous trial of TRT in patients with LS SCLC, 2 years overall survival was 53% in the group receiving 45 Gy twice daily. A relative improvement of 25% was

considered clinically relevant for this trial. As the aim of this phase II trial was to investigate whether the higher dose led to improved survival, sample size calculations were based on a one-sided α for improved power to detect an effect. To show an improvement from 53% to 66% with a one-sided α of 0.1 and β 0.2, 73 eligible patients were required in each group.

However, the level of statistical significance was defined as $p \leq 0.05$ to any side for all analysis to avoid confusion when reporting our results.

5.7.4 HRQoL analyses

There is no standard statistical method to examine health-related quality-of-life assessments. Since HRQoL was a secondary endpoint and the study was powered for the primary endpoint, we limited our analyses to comparisons of mean scores at each timepoint and defined a clinically relevant difference as a difference in mean scores of 10 or more points on a scale from 0 to 100 [343-345]. We did not perform imputation of missing data or missing forms.

5.8 Ethical considerations

Ethical standard for medical research involving humans is stated in the Declaration of Helsinki, which was first approved by the World Medical Association in 1964, and later amended several times. Different aspects of medical research are outlined in 37 points covering central topics as scientific requirements, confidentiality, informed consent, balance of risks and benefits, protection of vulnerable groups and communication of results [405].

Participation in medical research should be voluntary. Potential subjects must be adequately informed of the aim of the research, potential risk, and benefit for the individual patient. Subjects have the right to refuse participation and withdraw consent at any time without specific reason. It is important to ensure that the information is understood. Vulnerable groups should receive extra consideration to avoid incurring additional harm. At the same time excluding vulnerable groups could deprive them the opportunity of medical advancements. All SCLC patients can be considered a vulnerable group as they have a serious disease but are also believed to benefit from improved treatment. Older patients are an additional vulnerable group were its especially important to secure that information is understood and to carefully

follow up the patients during the study to prevent harm. At the same time, it is important to access information on how this group of patients should be treated, and if few are included in clinical trials evidence will be scarce.

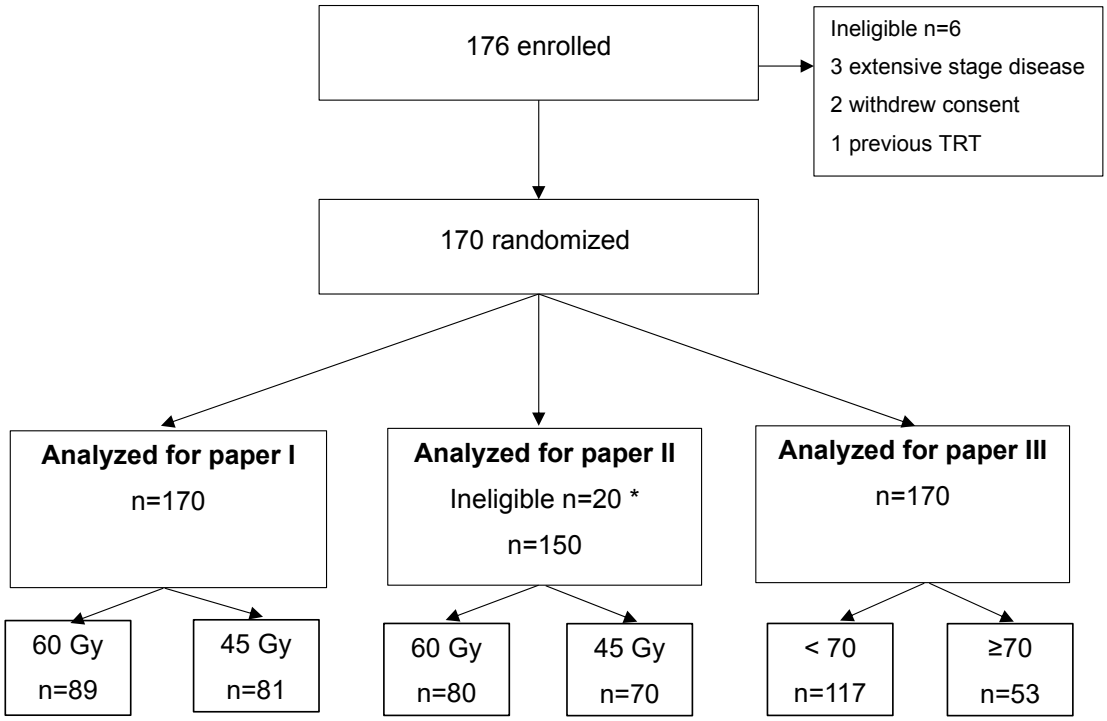
The trial was approved by the Regional Committee for Medical Research Ethics (Central Norway, Norway), the Regional Ethics Board in Gothenburg (Sweden), and the National Committee on Health Research Ethics (Denmark).

5.9 Financial support

The trial was funded by the Norwegian Cancer Society, The Liaison Committee for Education, Research and Innovation in Central Norway, the Nordic Cancer Union and the Norwegian University of Science and Technology. My PhD-position was funded by the NTNU.

6. Summary of papers

Figure 16 Patient selection



** 4 patients did not receive TRT, 16 did not complete the baseline QLQ and 20 did neither.*

6.1 Paper I: High-dose vs. standard-dose twice daily thoracic radiotherapy in LS SCLC

6.1.1 Patients

Between June 2014 and July 2018 176 patients were enrolled at 22 hospitals in Norway, Sweden, and Denmark. Six patients were not randomized due to: prior RT to the chest (n=1), extensive disease (n=3), and withdrawn consent (n=2). Thus, 170 eligible patients were randomized to receive twice-daily radiotherapy of 45 Gy in 30 fractions (n= 81) or 60 Gy in 40 fractions (n= 89) (Figure 16).

Median age was 65 years, 57% were women, 31% were ≥70 years, 98% were current or former smokers, 89% had ECOG status 0-1, and 84% had stage III disease. Baseline characteristics were well balanced between treatment arms (Table 4).

Table 4 Main baseline characteristics

		60 Gy (n=89)		45 Gy (n=81)	
		n	%	n	%
Age	Median (range)	65 (46-81)		65 (36-80)	
	≥ 70 years	25	28%	28	35%
Sex	Female	50	56%	47	58%
	Male	39	44%	34	42%
ECOG PS	0	44	49%	34	42%
	1	37	42%	39	48%
	2	8	9%	8	10%
Stage	IA	-	-	4	5%
	IIA	9	10%	6	7%
	IIB	5	6%	4	5%
	IIIA	38	43%	31	36%
	IIIB	37	41%	36	44%
Pleural fluid	Yes	8	9%	5	6%

6.1.2 Study treatment

Among the 170 patients, 153 (90%) completed all four courses, 124 (73%) had a dose reduction in at least one course, and cisplatin was replaced by carboplatin in one or more course for 75 (44%) patients, with not differences between treatment arms (Table 5).

One hundred and sixty patients (94%) completed TRT as planned and 147 (92%) of these patients completed TRT within the recommended timeframes. One hundred and forty patients (82%) received PCI. There were no statistically significant differences between treatment arms for reception of TRT or PCI.

Eighty patients (47%) received second line treatment; these were evenly distributed across treatment arms. The most common second line regime was platinum-etoposide (63%) and cyclophosphamide, doxorubicin, and vincristine (CAV) (21%) (Table 5).

6.1.3 Response to therapy

One hundred and thirty-one patients (77%) had a complete or partial response (overall response), the proportions did not differ between treatment arms (60 Gy: 77.5%, 45 Gy: 76.5%).

Table 5 Treatment completion and response to therapy.

	60 Gy (n=89)		45 Gy (n=81)	
	n	%	n	%
Number of chemotherapy courses				
1	1	1%	4	5%
2	3	3%	4	5%
3	3	3%	2	3%
4	82	88%	71	88%
Mean	3,87		3,73	
Any dose reduction	58	65%	66	82%
Received carboplatin for one or more courses	31	35%	34	42%
Completed TRT as planned	86	97%	74	91%
Received PCI	72	6%	68	85%
Received second line chemotherapy	41	43%	39	48%
Response to chemotherapy				
Overall response	69	77,5%	62	76,5%
Complete response	16	18%	17	21%
Partial response	53	59,6%	45	55,6%
Stable disease	4	4,5%	6	7,4%
Progressive disease	5	5,6%	5	6,2%
Unknown	11	12,4%	8	9,9%

6.1.4 Survival

Primary survival analyses were performed when all patients were followed for at least two years (July 2020), median follow up was 49 months (IQR 38-56) for OS, 43/89, patients in the 60 Gy group and 26/81 patients in the 45 Gy group were alive.

The overall two-year survival rate was 105/170 (62%) with a statistically significant difference between treatment arms (60Gy 66/89 (74.2%), 45 Gy 39/81

48.1%, OR 3.05 p=0.0005). The difference remained statistically significant in multivariable analysis adjusting for baseline characteristics (OR 4.67, p< 0.0001).

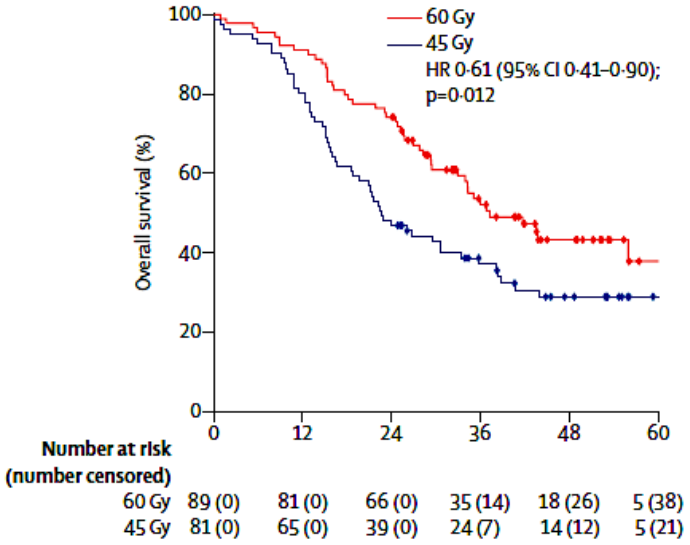
Median overall survival was significantly longer in the 60 Gy group (37.2 months) compared to the 45 Gy group (22.6 months) (HR 0.64, p=0.034), and the difference remained significant in the multivariable analyses (HR 0.54, p=0.0058).

Median progression free survival was 18.6 months in the 60 Gy group and 10.9 months in the 45 Gy group, with no significant difference between treatment groups (HR 0.75, p=0.22).

Of the baseline characteristics only, female sex was associated with improved survival.

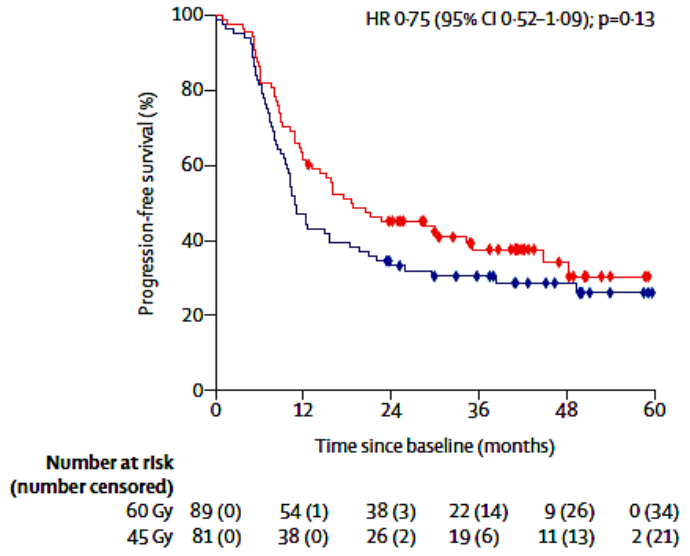
Figure 17 Comparison of twice daily TRT of 60 Gy vs. 45 Gy

A) Overall survival



	Median OS	95% CI
60 Gy	37.2 months	28.1-46.1
45 Gy	22.6 months	17.1-28.1

B) Progression free survival



	Median PFS	95% CI
60 Gy	18.6 months	7.3-30.0
45 Gy	10.9 months	8.7-13.1

6.1.5 Toxicity

The most common grade 3-4 adverse events were neutropenia (60 Gy 81%, 45 Gy 81 % p=0.25, neutropenic infections (60 Gy 27%, 45 Gy 39 % p=0.30), thrombocytopenia (60 Gy 24%, 45 Gy 25% p=0.96), anemia (60 Gy 16%, 45 Gy 20%, p=0.85) and esophagitis (60 Gy 21%, 45 Gy 18%, p=0.85). There were no differences in any toxicity between treatment arms (Table 6).

Overall, there were six treatment related deaths. Among patients randomized to 60 Gy one patients died from neutropenic fever, one from aortic dissection and one from pneumonitis (TRT stopped at 45 Gy), and among patients randomized to 45 Gy one patients died from myocardial infarction, one from cerebral infarction and one from thrombocytopenic bleeding. Two of the 6 patients died before TRT commenced.

Table 6 Toxicity according to the CTCAE v4.0 that occurred in patients who commenced TRT.

	60 Gy group (n=89)				45 Gy group (n=77)				p value
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	
Oesophagitis	33 (37%)	19 (21%)	0	0	34 (44%)	14 (18%)	0	0	0·83
Pneumonitis	8 (9%)	3 (3%)	0	1 (1%)	4 (5%)	0	0	0	0·39
Anaemia	70 (79%)	14 (16%)	0	0	59 (77%)	15 (20%)	0	0	0·85
Thrombocytopenia	47 (54%)	13 (15%)	8 (9%)	0	44 (57%)	10 (13%)	9 (12%)	0	0·96
Neutropenia	13 (15%)	14 (16%)	58 (66%)	0	8 (10%)	17 (22%)	45 (58%)	0	0·25
Neutropenic infection	0	19 (21%)	5 (6%)	1 (1%)	0	24 (31%)	6 (8%)	0	0·30
Thrombocytopenic bleeding	1 (1%)	0	0	0	2 (3%)	0	0	1 (1%)	0·61
Infection	14 (16%)	2 (2%)	0	0	11 (14%)	5 (7%)	0	0	0·14
Kidney failure	10 (11%)	1 (1%)	0	0	10 (13%)	0	1 (1%)	0	0·80
Nausea	15 (17%)	5 (6%)	1 (1%)	0	19 (25%)	3 (4%)	0	0	0·62
Fatigue	11 (12%)	0	0	0	8 (10%)	1 (1%)	0	0	0·83
Erythaema	7 (8%)	0	0	0	6 (8%)	1 (1%)	0	0	0·87
Headache	13 (15%)	1 (1%)	0	0	5 (7%)	1 (1%)	0	0	0·078
Neuropathy	3 (3%)	0	0	0	1 (1%)	1 (1%)	0	0	0·89
Myelopathy	0	1 (1%)	0	0	0	0	0	0	1·0
Myocardial infarction	0	1 (1%)	0	0	0	0	0	0	1·0
Aortic dissection	0	0	0	1 (1%)	0	0	0	0	1·0
Ototoxicity	2 (2%)	1 (1%)	0	0	1 (1%)	0	0	0	1·0
Thromboembolism	0	2 (2%)	0	0	1 (1%)	1 (1%)	0	0	0·79

6.2. Paper II: Patient-reported health-related quality of life from a phase II trial comparing two schedules of twice daily TRT in LS SCLC

6.2.1 Patients

Among all 170 randomized patients, 150 patients commenced TRT and completed at least one HRQoL questionnaire (60 Gy 80, 45 Gy 70).

Median age was 65 years, 28% were ≥70 years, 88% had PS 0-1, and 89% had stage III disease. Baseline characteristics were balanced between treatment arms.

Table 7 Baseline characteristic of 150 patients included in the HRQoL analyses.

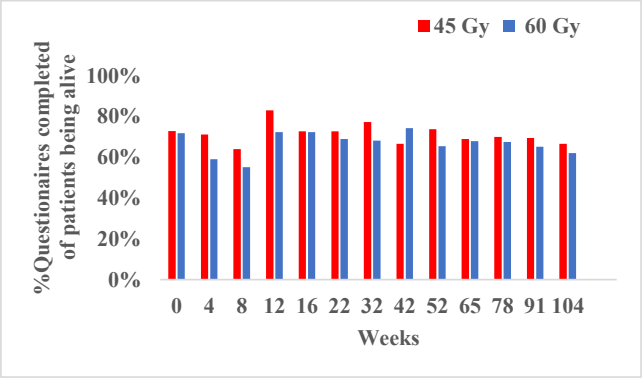
		45 Gy (n=70)		60 Gy (n=80)	
		n	%	n	%
Age	Median (range)	65 (36-80)		65 (46-79)	
	≥70 years	23	32.9%	20	25.0%
Gender	Female	43	61.4%	43	53.8%
Performance status	0	29	41.4%	38	47.5%
	1	33	47.1%	35	43.8%
	2	8	11.5%	7	8.7%
Stage	IA	2	2.9%	-	-
	IIA	5	7.1%	9	10.1%
	IIB	4	5.7%	5	5.6%
	IIIA	24	34.3%	38	42.7%
	IIIB	35	50.0%	37	41.6%
Pleural fluid	Yes	5	7.1%	8	10.0%
Smoking history	Current	53	75.7%	49	61.3%
	Former	15	21.4%	29	36.3%
	Never	2	2.9%	1	1.3%
	Missing	-	-	1	1.1%
Pack years	Median (range)	30 (4-80)		35 (5-114)	
Weight loss last 3 months before inclusion	>5%	16	22.9%	15	18.8%
	Missing	7	10.0%	12	15%

6.2.2 Completion of HRQoL questionnaires

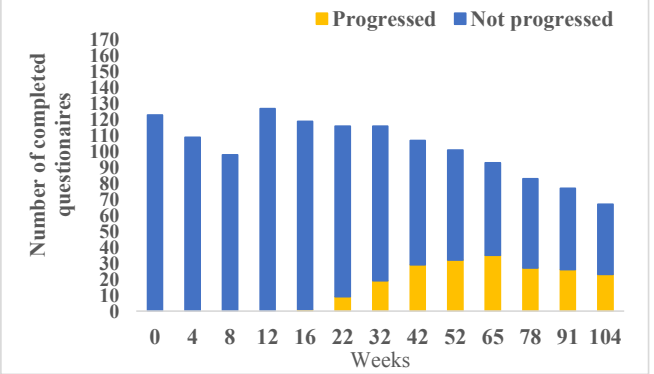
The completion rate for HRQoL questionnaires among all randomized patients still alive was 59-77% at the different timepoints, with no difference between treatment arms. The lowest completion rate was at week 8, the highest at week 12 (Figure 18A). The completion rate was lower year two of follow-up, where 32-38% of the questionnaires were completed by patients with recurrent disease (Figure 18B).

Figure 18 A) Completion rate of HRQoL questionnaires and B) Number of questionnaires completed including disease status.

A)



B)

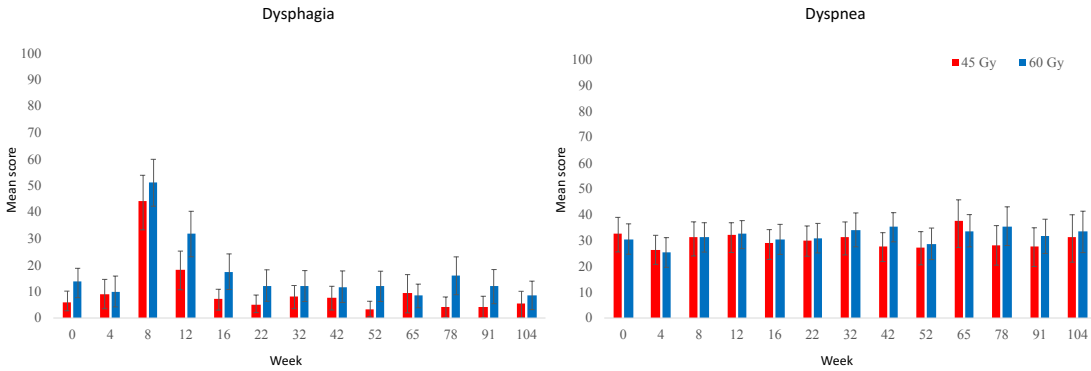


6.2.3. Dysphagia and Dyspnea

Mean HRQoL scores for dysphagia and dyspnea are presented in Figure 19. Overall, baseline mean score of dysphagia was 10, maximum mean score was 47 and reported week 8. Patients in both treatment arms reported a significantly higher mean score of dysphagia week 8 and 12 compared to baseline mean score. Patients in the 60 Gy arm reported significantly more dysphagia week 12 and 16 compared to the 45 Gy arm. At week 16 the differences in mean score from baseline values were less than 10 points in both arms. Mean score of dyspnea did not change significantly

during the study period, and there were no significant differences between treatment arms. Mean score of dyspnea did not change significantly during the study period, and there were no significant differences between treatment arms.

Figure 19 Mean score for dysphagia and dyspnea as reported on the LC13 questionnaires, the error bars show 95% CI for the mean scores.



6.2.4 Remaining HRQoL scales

For all other HRQoL scales there were no differences between treatment arms.
For certain HRQoL scales there was some changes during the study period. At week 8 and 12 corresponding to the end of TRT there was a transient lower score for role and social functioning and a higher score of fatigue. Emotional functioning increased from baseline and remained stable throughout the study period.
There was a modest but clinically significant decline in cognitive function during the two-year study period compared to baseline score. An increase in neuropathy was reported throughout the study period compared to baseline score.

6.3 Paper III: Treatment outcomes of older participants in a RCT comparing two schedules of twice-daily thoracic radiotherapy in LS SCLC.

6.3.1 Patients

Among all 170 randomized patients (69%) were <70 years and 53 (31%) were ≥70 years, 20 (12%) were ≥75 years, and 5 (3%) were ≥80 years. Analysis of toxicity was

performed among the 166 patients who commenced TRT, of these 116 (70%) were <70 years and 50 (30%) were ≥70 years

Baseline characteristics and randomization arms were evenly distributed across age-groups and are described in summer of paper 1 (Table 7).

6.3.2 Comorbidity

Overall, 71 (42%) patients had no comorbidity (CCI 0) (<70 years: 44%, ≥70 years: 36%), 50 (29%) patients had a CCI of 1 (<70 years: 30%, ≥70 years: 28%), and 49 (29%) patients a CCI of ≥2 (<70 years: 26%, ≥70 years: 36%).There were no statistically significant differences in CCI-scores between the two age-groups (p=0.37) (Table 8).

Table 8 Baseline characteristics

		<70 years (n= 117)		70 years (n= 53)		
		n	%	n	%	p
Age	Median (range)	61 (36-69)		74 (70-82)		
Thoracic radiotherapy	45 Gy	53	45%	28	53%	0.36
	60 Gy	64	55%	25	47%	
Gender	Female	67	57%	30	57%	0.94
Performance status	0	57	49%	21	40%	0.38
	1	51	44%	25	47%	
	2	9	8%	7	13%	
Stage	I- II	20	17%	8	15%	0.75
	III	97	83%	45	85%	
Pleura fluid	Yes	9	8%	4	8%	0.97
Smoking history	Never	2	2%	1	2%	0.34
	Former	34	29%	21	40%	
	Current	81	69%	30	56%	
	Unknown			1	2%	
Pack years	Median (range)	35 (10-114)		31 (4-273)		
Charlson Comorbidity Index total score	0	52	44%	19	36%	0.37
	1	35	30%	15	28%	
	2	30	26%	19	36%	

6.3.3 Treatment completion and response rate

Most patients (90%) completed all four courses of chemotherapy. There were no statistically significant differences across age-groups in the proportions who had reductions of chemotherapy-doses or delays of chemotherapy courses, completed TRT as planned, received PCI or second-line therapy. Overall response rates did not differ significantly between the age groups (Table 9).

Table 9 Treatment completion ad response rates

	<70 years (n=117)		≥70 years (n=53)		
	n	%	n	%	p
Completed TRT as planned	111	95%	49	92%	0.37
Completed 4 cycles of chemotherapy	108	92%	45	85%	0.46
No dose-reduction or delay of chemotherapy	18	15%	4	8%	0.19
Carboplatin instead of cisplatin for ≥1 course	41	35%	24	45%	0.23
Prophylactic cranial irradiation	100	85%	40	75%	0.13
Second line therapy	60	51%	20	38%	0.10
Overall response rate	94	80%	37	70%	0.13

6.3.4 Toxicity and fatal events

Overall, grade 3-4 toxicity was reported for 89% of the patients who commenced TRT.

There were no statistically significant differences in the proportions who experienced hematological, non-hematological or any grade 3-4 toxicity between age groups. Specifically, there were no significant differences in the proportions who experienced neutropenic infections, pneumonitis, or esophagitis (Table 10).

There were six fatal events during the study treatment period. Three patients ≥70 died, one from myocardial infarction, one from neutropenic infection, and one from pneumonitis. Three patients <70 years died: one from aortic dissection, one from thrombocytopenic bleeding and one from cerebral infarction. Of these, one patient in each age-group died from a thromboembolic event before TRT

commenced. The proportion of fatal events did not differ significantly between the age groups (p=0.31) (Table 10).

Table 10 CTCAE grade 3-5 toxicity in patients who commenced thoracic radiotherapy

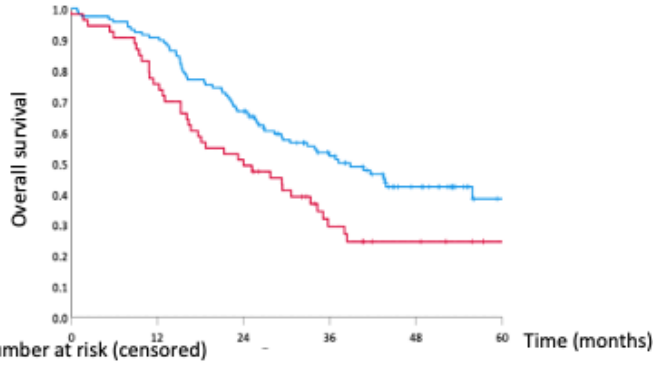
	<70 years (n=116)		≥70 years (n=50)		p
Toxicity	Grade 3-4	Grade 5	Grad 3-4	Grade 5	
Any toxicity	99 (85%)	2 (2%)	46 (92%)	2 (4%)	0.31
Any hematological toxicity	95 (82%)	1 (2%)	46 (92%)	1 (2%)	0.11
Any non-hematological toxicity	60 (52%)	1 (2%)	24 (48%)	1 (2%)	0.74
Esophagitis	24 (21%)		9 (18%)		0.69
Pneumonitis	2 (2%)		1 (2%)	1 (2%)	0.90
Anemia	19 (16%)		10 (20%)		0.57
Thrombocytopenia	25 (22%)		15 (30%)		0.24
Neutropenia	94 (81%)		40 (80%)		0.93
Neutropenic infection	36 (31%)		18 (36%)	1 (2%)	0.53
Thrombocytopeni**c** bleeding		1 (1%)			0.14
Infection	5 (4%)		2 (4%)		0.14

6.3.5 Overall survival, progression free survival and time to progression

Median overall survival was longer among patients <70 years compared to patients ≥70 years or older (<70 years: 37.2 months ≥70 years: 24.0 months, p=0.009) (Figure 20A), while there was no significant difference between the age-groups in PFS or TTP (Figure 20B and 20C).

Figure 20 A) Overall survival, B) progression free survival, and C) time to progression according to age group.

A) Median overall survival

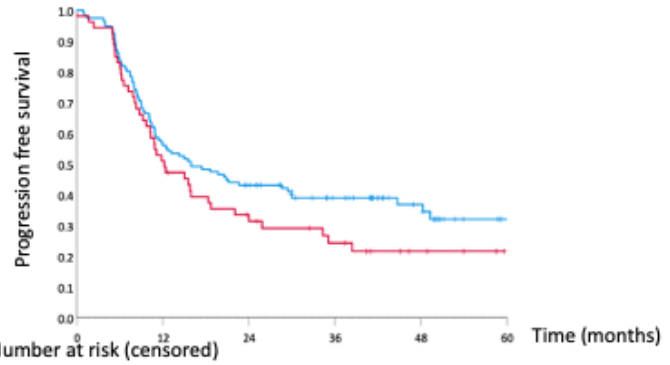


Number at risk (censored)

<70	117(0)	106(0)	78(0)	47(16)	25(30)	7(47)
≥70	53(0)	40(0)	27(0)	12(5)	7(8)	3(12)

	Median OS	95% CI	HR	95% CI	p
< 70 years	37.2	27.6-46.8	1		
≥ 70 years	24.0	12.9-35.2	1.71	1.14-2.56	0.009

B) Progression free survival

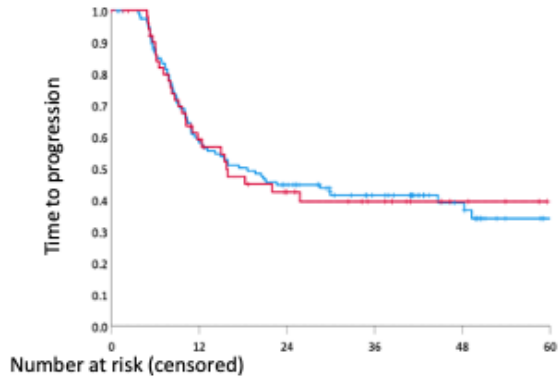


Number at risk (censored)

<70	117(0)	65(1)	48(3)	31(16)	16(30)	2(42)
≥70	53(0)	27(0)	16(2)	10(4)	4(9)	0(13)

	Median PFS	95% CI	HR	95% CI	p
< 70 years	15.9	8.5-23.3	1		
≥ 70 years	12.2	7.5-17.0	1.35	0.92-1.99	0.13

C) Time to progression



Number at risk (censored)						
<70	117(0)	65(5)	48(7)	31(21)	16(35)	2(47)
≥70	53(0)	27(5)	16(9)	10(14)	4(20)	0(24)

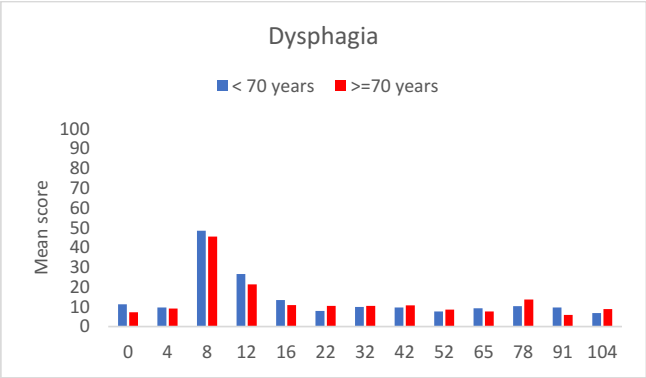
	Median TTP	95% CI	HR	95% CI	p
< 70 years	18.6	10.4-26.8	1		
≥ 70 years	15.8	8.6-29.0	1.0	0.6-1.5	0.96

6.3.6 HRQoL

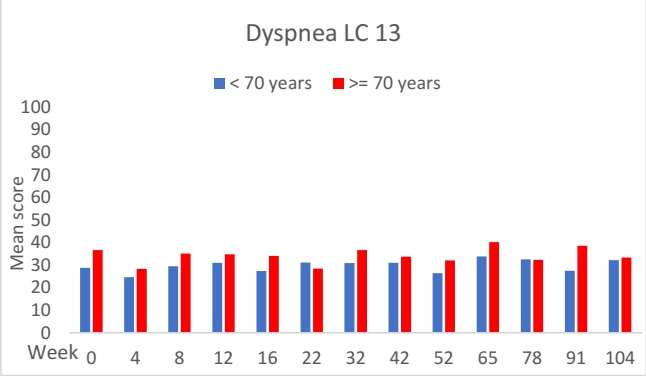
There was no difference in mean scores for any HRQoL scales between age groups the first year after treatment, and there was no difference in mean score for dyspnea and dysphagia at any timepoints (Figure 21). Older patients reported a clinically significant decline in functional scales and more fatigue during the second year.

Figure 21 Mean score of A) dysphagia and B) dyspnea.

A) Dysphagia



B) Dyspnea


Dyspnea LC 13
< 70 years
>= 70 years
Mean score
100
90
80
70
60
50
40
30
20
10
0
Week
0
4
8
12
16
22
32
42
52
65
78
91
104

7. Discussion

7.1 Twice-daily thoracic radiotherapy of 60 Gy

7.1.1. Survival

The THORA trial, which this thesis is based upon, is the first randomized trial to demonstrate a significant survival benefit of an intervention for patients with LS SCLC since the Intergroup 0096 trial was published in 1999.

The 2-year survival in the 60 Gy BID arm is among the highest reported in LS SCLC, including reports from trials delivering higher nominal doses of once daily conventional TRT (Table 11). The only trial reporting similarly high 2-year survival is the Chinese study by Qiu et al. In that trial, patients receiving 65 Gy in 26 daily fractions had a 2-year survival rate of 74%, but notably, this was not much higher than patients on their 45 Gy BID control arm (2-year survival rate of 70%), much higher than in any other trial we are aware of [102]. Final survival data including 5-year survival rates are awaited.

A Japanese trial by Kubota et al comparing platinum/etoposide with platinum/irinotecan is the trial reporting the longest median OS (38 months) and highest 5-year survival rate (36%) [103], but also in this trial, patients receiving platinum/etoposide plus TRT of 45 Gy BID lived longer than in most other studies . Other researchers report median OS within the range of 20.6 to 39.2 months, and 5-year survival rates of 10% to 36% (Table 11). Median survival time for trial participants receiving platinum/etoposide plus BID TRT of 45 Gy ranges from 22.6-38 months (median 28 months), and 2-year survival rates from 47% to 70% (median value 54%) (Table 11). Population based studies report median overall survival times of 21.5-27 months (Table 12), and 2-years survival rates of 35%-54% (reported or estimated from Kaplan-Meier plots) (Table 12).

Table 11 Survival in RCTs using different thoracic radiotherapy schedules [9, 10, 98-101, 107, 183, 192-194, 220]

	Total nominal dose	**Design/ Phase**	**PET staging**	**IMRT or VMAT**	**Median OS**	**2-year OS**	**3-year OS**	**5-year OS**
BID 45 Gy								
Intr.0096 1999	45 Gy	RCT/3	0		23 months	47%		26%
Takada 2002	45 Gy	RCT/3	0		27.2 months	54.4%	29.8%	23.7%
Kubota 2014	45 Gy	RCT/3	0		38 months		53%	36%
Grønberg 2015	45 Gy	RCT/2	0		25 months	53%		23%
Faivre-Finn 2017	45 Gy	RCT/3	57%	16%	30 months	56%		34%
Bogart 2021	45 Gy	RCT /3	NN	60%	28.7 months	58%		29%
Grønberg 2021	45 Gy	RCT /2	100%	31%	22.6 months	48%		
Qiu 2021	45 Gy	RCT/ 2	NN	100%	33.6 months	70%	41.5%	
BID 45 Gy	**Median OS range 22.6-38 months**					**5-y OS range 23-34%**		
BID 54-60 Gy								
Jeremic 1997	54 Gy	RCT/2	0		34 months			30%
Schild 2007	60 Gy	RCT/2	0		22 months			29%
Grønberg 2021	60 Gy	RCT/2	100%	34%	37.2 months	74%		
BID split-course								
Schild 2004	48 Gy	RCT/3	0		20.6 months	44%		22%
QD 45 Gy								
Intr.0096 1999	45 Gy/25 fr				19 months	41%		16%
QD >50-70 Gy								
Schild 2004	50.4 Gy	RCT/3	0		20.6 months	44%		21%
Faivre-Finn 2017	66 Gy	RCT/3	57%	16%	25 months	51%		31%
Bogart 2021	70 Gy	RCT/3	NN	60%	30.5 months	57%		33%
QD 50-70 Gy	**Median OS range 20.6-30.5 months**							
QD hyo-frac.								
Sundstrøm 2002	42 Gy/15 fr	RCT/3	0		15 months	25%		10%
Grønberg 2015	42 Gy/15 fr	RCT/2	0		19 months	42%		25%
Qiu 2021	65 Gy/26 fr	RCT/2	NN	100%	39.2 months	74%		56%

Table 12 Survival from LS SCLC reported in population-based cohort studies [1, 4, 104-107].

	Total dose	n	Median overall survival	2 years OS survival	5 years OS survival
45 Gy BID					
Schreiber 2015	45 Gy	2821	22.1 months	~ 50%	23.9%
Rutter 2015	45 Gy	707	21.5 months	~ 35%	
Damhuis 2018	45 Gy	407	27 months	54%	31%
Yan 2021	45 Gy	110		~ 40%	25.5%
Graabak 2022	45 Gy	313	26.2 months	~ 50%	
Shidal 2022	45 Gy	876	21.6 months	~ 50%	
BID 45 Gy range			**21.5-27 months**		**23.9-31%**
QD 40-45 Gy					
Schreiber 2015	45 Gy/25 fr	996	17.2 months	~ 35%	16.5%
Yan 2021	40 Gy/15 fr	63		~ 40%	29.3%
Graabak 2022	42 Gy/15 fr	792	19.6 months	~ 40%	
QD 45-72 Gy					
Schreiber 2015	60-72 Gy	5017	18.3-19.5 months	~ 38%	17.8-18.1%
Damhuis 2018	45-62.5Gy	414	23 months	52%	28%
Rutter 2015	61.2-70Gy	521	20.2-21.5 months	~ 35%	
Shidal 2022	60-70 Gy	1385	18.9-19.4 months	~ 38%	
QD ≥ 45 range			**18.3-23 months**		**16.5-29.3%**

The 2-year survival of 48.1% and median OS of 22.6 months in the 45 Gy BID group of our study was similar to the Intergroup 0096 trial (2-year survival rate 47%, median OS 23 months) and our previous HAST-study (2-year survival rate 53%, median OS 25 months) [10, 213]. On the other hand, both the CONVERT (2-year survival rate 56%, median OS 30 months) and CALGB 30610/ RTOG 0538 trials (2-year survival rate 56%, median OS 28.7 months) report better outcomes of 45 Gy BID [9, 101]. There are, however, significant differences in patient selection between these trials. CONVERT excluded patients with two or more abnormal laboratory values (low sodium, elevated LDH, elevated ALP), had fewer patients ≥70 years (14% vs. 31%) and included fewer patents with PS 2 (3% vs. 9%). Also, the mean age in the CONVERT trial was 62 years vs 65 years in our trial. The mean age in CALGB 30610/ RTOG 0538 was 64 years, the more conservative VALSG definition of LS was applied, and 5% of patients had PS 2.

There are no obvious reasons for the longer survival in the control arms of the Chinese and Japanese trials [102, 103], but some have suggested that Asian SCLC patients live longer than Caucasian [406, 407]. Participants in the Chinese study were younger than in our trial (58 vs. 65 years) and a higher proportion (15% vs. 1.7%) were never-smokers. Never-smokers might have a favorable prognosis [408]. The Japanese trial excluded patients 70 or older and PS 2 patients, 66% had ECOG 0 compared to 46% in our trial. Stage of disease is not reported and only one patient experienced grade 3-4 dysphagia [103], possibly indicating that target volumes were relatively small.

Extents of disease permitted varies between trials. CONVERT and Qiu et al. used the VALSG definition, CALGB 30610/RTOG 0538 excluded contralateral- hilar and supraclavicular nodes, Kubota et al. excluded contralateral hilar lymph nodes, while we used the IASLC definition which allows metastases to contralateral supraclavicular and mediastinal lymph nodes (Table 13). Whether survival rates are significantly different when applying these different definitions of LS is not known since they all allow N3 disease according to the TNM staging system. In a previous study, we did not find significant differences depending on which N3 stations patients had metastases in but found that involvement of several N3 stations was a negative prognostic factor [409], possibly suggesting that survival is longer when conservative definitions of LS are applied.

There were also differences in RT techniques used. All patients in the study by Qiu et al. were treated with IMRT techniques, while this was the case for 60% in CALGB 30610/RTOG 0538, 16% in CONVERT and 33% of patients in our study. The impact of different radiotherapy techniques on survival is not proven. Modern radiotherapy techniques are applied in clinical practice, but few studies of TRT in lung cancer have compared the outcomes of 3-dimensional conformal radiotherapy (3D-CRT) and IMRT. A retrospective study of 223 LS SCLC patients comparing 3D-CRT and IMRT did not reveal a survival benefit of IMRT [251], whereas two registry-based studies and one retrospective study suggest that IMRT improve survival compared to 3D-CRT in NSCLC [410-412].

Another difference between the studies is the use of PET-CT for staging and radiotherapy target volume definition. PET for staging is used in all patients in our

trial, 57% in the CONVERT trial, and was and option in CALGB 30610/ RTOG 0538 and the Qiu et al studies.

Definition of radiotherapy target volumes also varies in recent LS SCLC trials. In the CONVERT and the CALGB 30610/ RTOG 0538 trial, GTV included all pre-chemotherapy lesions visible on CT/MRI or PET. In the CONVERT trial, a CTV was defined as GTV + 0.5 cm, while the no additional margin to CTV was specified in the CALGB 30610/RTOG 0538 trial other than inclusion of the ipsilateral hilum.

Qiu et al. defined GTV as post-chemotherapy volume for the primary lung tumor (after 2 cycles of chemotherapy for 80% of the patients) and all pre-chemotherapy involved nodal stations, and a 0.5 cm margin to CTV was applied. In our trial GTV was defined as post-chemotherapy (after cycle 1) but included all affected lymph nodes as detected on PET CT before chemotherapy commenced. A 0.5 cm margin to CTV was applied. We are currently analyzing all images and radiotherapy plans, assessing whether TRT was delivered according to the protocol and the location of recurrences, which will provide additional important data on our approach.

Timing of TRT varies across studies. Thoracic radiotherapy started with cycle one in the Intergroup 0096 study, cycle 2 in the CONVERT study, cycle 1-3 (80% cycle 3) in the Qiu study, while CALGB had an option on starting concurrently with cycle 1 or 2 (Table 13). Starting TRT together with the first course of chemotherapy can be logistically challenging and might delay start of therapy. In our country, many patients are diagnosed and commence chemotherapy at hospitals without radiotherapy departments, which is why THORA participants started TRT 21-28 days after the first day of the first chemotherapy course. A potential benefit of this approach is that there is a reduction in tumor sizes after the first chemotherapy course allowing for reducing target volumes, reducing the risk of severe radiotoxicity, and often facilitating delivery of higher TRT-doses [413]. A meta-analysis found that a short time from initialization of chemotherapy to end of TRT was associated with improved survival [226], but the trials included in the analysis had slightly different study treatment plans, and it remains unclear whether delaying TRT to the time of the second instead of the first chemotherapy course impacts survival.

7.1.2 Comparing effectiveness of TRT schedules

The above-mentioned differences in design, methods and definitions may explain the differences in treatment outcomes in the most recent trials of TRT in LS SCLC, especially in the control arms. The question is whether these differences explain the varying outcomes in the experimental arms. Applying the following EQD2 equation:

$$EQD2 = D \times ([d + (\alpha/\beta)]/[2 + (\alpha/\beta)] - ((T - Tk) * D_{prolif})$$

for tumor with a α/β=10 with correction for treatment time, using a D_{prolif} of 0.7 Gy and time being compared to 19 days set as standard (Tk) we calculated the EQD2 doses of the TRT schedules in recent trials (Table 13).

Applying the above equation calculating the biological equivalent doses in 2 Gy fractions, the EQD2 dose of the 45 Gy BID schedule is 43 Gy, and for the experimental arms 48 Gy for CONVERT (median OS 25 months), 50 Gy for the CALGB 30610 trial/ RTOG 0538 (median OS 30.5 months), 53 Gy for THORA (median OS 37.2 months), and 56 Gy for the Chinese trial (median OS 39.2 months). EQD2 for the once-daily schedule in the Intergroup 0096 trial is 34 Gy (median OS 19 months), and 41 Gy for the split course BID schedules used in the trial by Schild et al (median OS 20.6 months).

Interestingly, the experimental arms with the highest calculated EQD2 also have the best survival, supporting results of a systematic review by Zhu et al. concluding that a higher BED was associated with longer survival, and a retrospective Chinese study concluding that survival after TRT with a BED ≥ 57 Gy improved survival compared to BED< 57 Gy, indicating a dose response relationship also at doses higher than delivered in recent LS SCLC trials [414, 415].

Table 13 Design, doses, staging, start of TRT, radiotherapy techniques and ENI for LS SCLC[9, 10, 103, 206, 212, 213, 217, 220, 390]

	Design/ Phase	Total dose nominal	$EQD2_{10}$ *	n	Start of TRT **	Days of TRT ***	PET staging	ENI	IMRT or VMAT	Definition of LS
Jeremic 1997	RCT/2	54 Gy BID	49	103	C1 (vs. C3)	24	0	Yes		anteroposterior-posteroanterior fields to the gross tumor, ipsilateral hilum, entire mediastinum, and involved SCF.
Turrisi 1999 Intergr. 0096	RCT/ 3	45 Gy BID	43	196	C1	19	0	Yes		VALSG Excl. contralat. hilar and contralat. supraclav nodes No pleura fluid Only involved SCF
		45 Gy/25 fr	34	185		33				
Takada 2002	RCT/3	45 Gy BID	43		C1 Vs. afterC4	19	0			No stage I Including contralat.Supraclav. No malign pleural fluid
Schild 2004	RCT/ 3	48 Gy BID split course 4 h apart	48	130	C4 of 6	38	0			VALSG Limited to one hemithorax or ipsilat clavicular.
		50.4 Gy/28 fr	36	131		38	0			No pleural fluid
Schild 2007	RCT/2	60 Gy BID Split course	41	64	C3	42	0			VALSG No pleural fluid
Kubota 2014	RCT/3	45 Gy BID 30 Gy BID + Boost 15 Gy to p.tumor + met.lymph.n	43	129	C1	19	0	30 Gy to ENI , and boost to SNI	0	including ipsilateral hilar, bilateral mediastinal, supraclavicular nodes Non malign pleural fluid < 1cm
Grønberg 2015 HAST	RCT/2	45 Gy BID	43	73	C2	19	0	Yes	0	IASLC,Inkl contralat hilar, mediatinal ,supraclav nodes Cyt neg pleura fluid
		42 Gy/15 fr	45	84						
Faivre-Finn 2017 CONVERT	RCT/3	45 Gy BID	43	274	C2	19	57%	No	16%	VALSG
		66 Gy/33fr	48	273		45			17%	No pleura fl.
Bogart 2023 CALGB 36010	RCT /3	45 Gy BID	43	313	C1(45%)	19	NN	No	60%	Ex.contr lat,Suprac +hilar
		70 Gy OD	50	325	C2(55%)	47				No pleural fluid
Grønberg 2021 THORA	RCT /2	45 Gy BID	43	81	C2	19	100%	No	31%	IASLC
		60 GyBID	53	89		26			34%	Inkl contralat hilar, mediatinal and supraclav nodes Cyt neg pleura fluid
Qiu 2021[102]	RCT/ 2	45 Gy BID	43	94	C3 (80.2%)	19	+/-	No	100%	VALSG
		65 Gy/26 fr	56	88		36	+/-			

** Biologically equivalent dose in 2 Gy fractions with an α/β ratio of 10 [$EQD2_{10}$] for tumor control and acute effects, corrected for time by a D_{prolif} of 0,7 and time being compared to 19 days set as standard. ($EQD_2 = D \times ([d + (\alpha/\beta)]/[2 + (\alpha/\beta)] - (T-t)D_{prolif}$)*

*** c= cycle of chemotherapy*

****Days of TRT approximated including weekends*

7.1.3 Toxicity

The higher TRT dose in our trial did not cause more grade 3-5 esophagitis, and the frequency in both treatment arms (45 Gy:18%, 60 Gy:21%) was lower than in our previous HAST trial (42 Gy QD: 31% and 45 Gy BID: 33%). Patient did, however, report that recovery of dysphagia took a few weeks longer for patients on the 60 Gy arm.

Frequency of grade 3-5 pneumonitis were low both in the THORA (60 Gy: 4.5%, 45 Gy: 0%), and the HAST (42 Gy: 6% vs 45 Gy: 4%) trials. Only one patient in the THORA trial died from pneumonitis (randomized to 60 Gy, but TRT was stopped at 45 Gy due to pneumonitis).

Looking at results from other recent LS SCLC trials, it is evident that TRT now causes much less esophagitis (11-19% grade 3-4 esophagitis) than in the Intergroup 0096 trial (45 Gy QD: 16%, 45 Gy BID: 32%) and the HAST trials [9, 10, 213, 217]. Reasons are probably using PET CT for staging and modern RT planning techniques and limiting target volumes to PET-CT or CT detected lesions. The subgroup analyses of CONVERT showed that patients staged with PET-CT had smaller GTVs, received lower RT dose to normal tissue and had a lower incidence of late esophagitis than those staged with CT alone [241]. A retrospective study from MD Anderson showed that fewer patients treated with IMRT needed a feeding tube than those receiving 3D CT TRT (5% vs. 17%; p=0.005) [251], though the proportions receiving IMRT/VMAT planned TRT varies largely between trials (Table 11).

There is not available data to compare irradiated volumes between trials. Mean PTV (45 Gy: 388 cm^3 vs. 60 Gy 366 cm^3) and laterality of primary tumors or main tumor burden (61% located in the right hemothorax in both arms) were not different between treatment arms in our trial [416]. These data have not been reported in other trials, though median GTVs were 81.6 cm^3 in the BID arm and 85.6 cm^3 in the QD arm of CONVERT [9].

Normal tissue constraints were based on a series of reviews (Quantec) of dose/volume tolerance published in 2010 [257, 258, 269, 393-396], and the Norwegian radiation protection authority guidelines for curative radiotherapy for SCLC [397]. Normal tissue constraints in SCLC have been established based on studies of standard fractionated QD TRT in NSCLC. The good tolerability of 60 Gy indicates that established constraints are applicable also to BID TRT.

Most patients (45 Gy: 97%, 60 Gy: 91%) completed TRT as planned. In the CONVERT and the CALGB 30610/RTOG 0538 more patients on the twice daily arms completed TRT. This might be because the twice daily TRT schedule is shorter, and that the maximum dysphagia often occur when radiotherapy is finished.

Compared with the CONVERT and CALGB 30610/RTOG 0538 studies, more patients in our trial had neutropenia and neutropenic infections, probably because we did not permit the use of G-CSF [9, 100, 217]. In the CONVERT trial, 37% of the patients received G-CSF [175], and in the CALGB 30610/RTOG 0538 G-CSF was allowed for cycle 3 and 4 (after completion of TRT) if patients experienced neutropenia that resulted in delayed chemotherapy for more than a week, and for subsequent chemotherapy cycles. However, the proportion who completed all four chemotherapy courses in our trial (88%) was similar as in the CONVERT trial (81% completed at least 4 cycles), and it is not clearly demonstrated that dose-intensity or neutropenic infections influence treatment outcomes.

There were six treatment related deaths (6 /170,3.5%), 3 in each treatment group in our trial. A similar proportion of grade 5 adverse events was observed in the CALGB 30610/RTOG 0538 study (15/596, 2.5%), and the CONVERT study (12/543, 2.2%).

7.2 HRQoL as an endpoint

We are only aware of two other LS SCLC studies which include patient reported HRQoL [213, 330]. One is our HAST trial which showed that all patients had significantly more dysphagia after TRT, but also that mean scores returned to baseline levels two months after completion of TRT [213]. The other report is an abstract from the CALGB 30610/RTOG 538 trial presented at ASCO 2022 [330]. Of the 638 participants, 417 completed HRQoL questionnaires. Different trajectories were reported, HRQoL was better in the QD arm at week 3, but better for the BID arm at week 12, probably reflecting the differences in treatment time.

All three trials confirm that many patients experience discomfort from CRT, which is well known for physicians who treat SCLC patients, but more importantly, that most patients recover, and one might question whether esophagitis should remain the main dose-limiting toxicity in this setting.

The THORA study was powered for the primary endpoint of 2-year survival, and not for the secondary endpoint of HRQoL. That said, we believe that our sample size is sufficient for descriptive, explorative HRQoL analyses. One might miss a statistical comparison of HRQoL scores, but there is no established approach for such comparisons, and even small differences in mean scores can be statistically significant if the study cohorts are large. In our opinion and experience, and based on previous publications, a difference in mean scores of ≥ 10 reflects a clinically relevant difference [343-345].

Not all patients completed the questionnaires, and the completion rate varies at different timepoints. The lowest completion rate was at the end of TRT. At this timepoint, questionnaires were to be handed to patients by study personnel (questionnaires were mailed to Norwegian patients from the central study office in Trondheim), but some patients received TRT at other hospitals than where they were enrolled and received chemotherapy, and it is likely that the patients never received this questionnaire, since the completion rates at later timepoints were higher. The completion rate of questionnaires and percentage of missing items was within the same range than comparable studies, and similar in both arms [330, 417]. We did not perform imputation of missing scores since it, in our experience such analyses do not change conclusions given the relatively high completion rate.

We limited the HRQoL analyses to include patient reports from the first two years corresponding to the primary endpoint of 2 years overall survival. Quite many patients were dead at this timepoint (38%), and one third of the questionnaires were completed by patients with progressive disease, which makes it complex to understand causality of symptoms and reduced functional status.

Quality of life can mean different things to different persons but can also mean different things to the same person during the course of a disease or during ageing. This process is called response shift and is defined as “changing internal standard, values and conceptualization of quality of life” as an adaption to illness or aging [418]. Response shift can cause biased results in QoL measurements and may result in both over and underestimation of the HRQoL changing. In paper III one cannot rule of that the is an underestimation of HRQoL score due to response shift for older patients.

7.3 Treatment of older patients

The meta-analyses that established concurrent TRT in LS SCLC failed to show a survival benefit for patients 70 years or older [188, 189]. Guidelines are vague and emphasize the need for individual assessment of older patients. Most data come from subgroup analyses of RCTs, a pooled analysis of 11 phase II-III studies [385, 387-389] and population-based studies [17-19, 386]. The number of older patients in RCTs are small (n=50-67) and these patients are probably more fit than the average. Population based studies seldom include data on important characteristics such as PS, comorbidity, and functional status. This limits the evidence base for individualizing treatment for older patients, which probably explains the varying treatment policies observed.

Population-based studies from the US and the Netherland show that 40% of patients ≥70-75 years do not receive chemo- or radiotherapy, though they also show that patient treated with CRT live longer than those treated with chemotherapy alone [4, 17, 386]. A study by our group shows that 45% of all Norwegian LS SCLC patients, regardless of age, do not receive curative TRT [104].

Table 14 Subgroup analyses from RCTS of patients 70 years or older LS SCLC [385, 387-389]

Author	Study	Number ≥ 70 (%)	Overall survival < 70 years vs. ≥ 70 years	Toxicity and fatal events < 70 years vs. ≥ 70 years
Yuen 2000 (Int.gr 0096) Phase III	Concurrent chemotherapy and once or twice daily in LS SCLC	50 (13%)	5 years OS 22% Vs. 16% (p=0.05)	hematologic toxicity (61% vs. 84%; P < 0.01) fatal toxicity (1% vs. 10%; P = 0.01) no differences nonhematologic toxicities
Schild 2005 Phase III	Combined-modality therapy for LS SCLC QDRT or split course BIDRT.	54 (21%)	5 years OS 22% Vs. 17% (p=0.14)	>70 more pneumonitis fatal toxicity 0.5% vs 5.5%
Christodoulou (Convert) 2019 Phase III	Concurrent Once-Daily vs. Twice-Daily Radiotherapy	67 (14%)	OS 29 vs 30 months (p=0.38)	more neutropenia, thrombocytopenia, same sepsis and death
Stinchcombe 2019 Phase III	Individual patient data from 11 phase 2 or 3 trials for LS-SCLC	254 (19%)	Median OS 23.5 months Vs. 17.8 months (p<0.01)	fatal events (3% vs 8%; P < .01) grade 3 + dyspnea (7% vs 11%; P = .03) less grade 3+ esophagitis/dysphagia (19% vs 14%; P = .04)

Age is a continuum and there is no established limit for defining older patients. Many studies use 70 years as the cut-off value, but also 65 years and 75 years have been used. We used 70 years as the limit in study III since this cut-off value has been most used in previous subgroup analyses and population-based studies of LS SCLC [4, 385-389, 419].

In most countries, life expectancy has significantly increased the last century and older people are healthier than before. Thus, a comprehensive assessment of general health and functional status is needed to assess each individual patient's ability to tolerate and benefit from cancer therapy.

Geriatric assessment (GA) is a systematic evaluation of areas were older adults often have difficulties and addresses health status for somatic, functional, psychological, and social domains [420]. Both ASCO and International society of geriatric oncology (SIOG) guidelines include recommendations for assessment of these domains [421, 422]. Performing a comprehensive geriatric assessment in older patients with cancer have been recommended since 2005 but is not widely adopted in routine oncology practice [423], even if performing geriatric assessment often alter the oncological treatment decision, identify undiagnosed impairments and facilitate non-oncological interventions as nutritional support, polypharmacy and comorbidity

optimization, mobility and social interventions. GA lowers complication rates and toxicity, improve physical function and quality of life [424], but does not appear to affect survival time [424].

Comprehensive GA can be time-consuming, which have been a reason for the low implementation rate. Thus, GA tools such as the Geriatric 8 (G8) and the Vulnerable Elders Survey (VES-13) have been developed to screen for older patients who should undergo a more comprehensive assessment. G8 consists of eight questions on appetite, weight-loss, mobility, neuropsychological problems, body mass index, medication, health status compared to others, and age, and is recommended by ASCO and SIOG [422, 425, 426].

Results from study III of my thesis strongly suggest that older patients tolerate CRT as well as younger patients, and that they also achieve clinically relevant disease control. The shorter survival time among older patients is probably due to deaths from other reasons than SCLC since there was no difference in TTP.

However, we did not collect data on patients found ineligible for the trial and considering that median age at diagnosis of lung cancer in the Nordic countries is approximately 70 years and the proportion of patients 70 years or older in our trial was 1/3, it is likely that also in our trial, older patients were more fit than the average. On the other hand, the proportion was larger than in other trials (Table 14).

HRQoL means scores did not differ among older and younger patients the first year after treatment. Year two, older patients had a reduction in mean score of 15-20 points on the functional scales and more fatigue than reported by younger patients. Several factors might have contributed to this observation, such as progressive disease, treatment of progressive disease, late effects of chemotherapy, TRT and PCI, as well as worsening of comorbidities.

Of special interest is the decline in cognitive function, especially for older patients, during the first two years after treatment. Long term side effects of PCI are of great concern if more patients achieve long-term extracranial disease control [279, 283, 427, 428] ,especially among patients of old age and those with primary neurocognitive deficits [279, 283].

7.4 Methodological considerations

7.4.1 Strengths and limitations

Patients recruited to a RCT are often younger and have a better general health than many patients seen in the clinic [429-431]. This is particularly true for older patients, as most studies have inclusion criteria that excludes older patients more than younger [383, 432, 433].Therefore, it is not always straightforward to know how results from trials of selected patients should be implemented in clinical practice.

The inclusion criteria in this RCT were relatively broad and more liberal than other trials of LS SCLC. There was no upper age limit and we allowed PS 2 patients, had few restrictions regarding co-existing diseases and conditions and believe that our study cohort largely reflects LS SCLC patients who receive CRT in routine clinical practice, though we did not register data on non-participating LS SCLC patients diagnosed during the enrolment period. Notably, in our population-based study [104], we found exactly the same benefit of 45 Gy BID as observed in our HAST trial – which more or less employed the same eligibility criteria as THORA [213].

The protocol for delivery of RT was not very detailed, allowing each hospital to adapt their routines to the patients enrolled in the study. We know from experience that there is some variation in how RT is delivered, and a strength of our trial is that it largely reflects clinical practice. For example, the use of IMRT/VMAT or conventional 3D planning technique varied between hospitals and increased during the enrolment period. It is possible that the proportions who experienced radiotoxicity would have been lower if all patients were treated with the most modern RT techniques.

Randomization was performed before a TRT treatment plan was made. It has been commented that a more appropriate approach would be to ensure that all patients could receive 60 Gy before randomizing patients. We do not disagree, but this approach would significantly have complicated conduct of the trial and most likely prolonged enrolment time and possibly reduced external validity.

Another limitation is that we did not perform a central quality assurance of the radiotherapy plans. We acknowledge that more data on radiotherapy plans in this setting is needed and have embarked on a separate PhD-project analyzing all radiotherapy plans which will investigate compliance with the study protocol, assess size and location of target volumes, normal tissue irradiation and toxicity, feasibility with respect to BID 60 Gy and maximum deliverable TRT dose in all patients.

For four patients randomized to receive 60 Gy, investigators decided to deliver only 45 Gy. We will evaluate these plans to assess whether it would have been possible to deliver higher doses using the most modern RT techniques and based on our experience.

There was no central revision of CT scans, which might have influenced assessment of the secondary endpoints response rates and PFS. It is well known from other trials that there often is a difference in local and central assessment of these endpoints. For patients who have received TRT it is even more challenging, since the TRT itself can lead to radiographic changes [434], and we cannot rule out that the higher TRT dose cause more of such changes. On the other hand, PFS was longer in the 60 Gy arm, and there are no reasons to believe that assessment of RR or PFS was performed differently between treatment arms at each site. There was no statistically significant difference in PFS in our primary report, but this was probably due to few events in the high-dose arm and thereby heavy censoring.

ORR was lower than in most trials of CRT in LS SCLC (77% vs. 88%-95%). We cannot rule out that this is due to varying interpretation of CT scans and RECIST criteria since we did not perform a central review, but it can also be due differences in eligibility criteria. Our criteria were more liberal and might have led to inclusion of patients with larger tumor volumes and/or number of metastatic sites, which might have influenced the response rates. On the other hand, the local evaluation of CT scans reflects clinical practice and implementation of trial results.

7.4.2 Sample size

One might ask why we did not do a phase III trial instead of a phase II trial. The reason was mainly concerns about feasibility and toxicity. Based on data from the non-randomized Swedish trial, we did not expect that the higher dose would result in such a large survival improvement as observed. The delta value in our sample size calculation was already quite optimistic.

The expected accrual time was also taken into consideration. Based on our previous trial we expected to enroll 35-40 patients a year and estimated an accrual time of 6 years. This is a major challenge and probably the reason why few LS SCLC trials have been conducted the last decades. For example, the CALGB 30610/ RTOG 0538 trial took 11 years to complete and the CONVERT trial 5.5 years.

This decision to perform a phase II and not a phase III study also limits the validity of the subgroup analysis of older patients. However, since the proportion of older patients was higher than in CONVERT, the absolute number of older patients was within the same range as in that trial and we believe that our data at least provide valuable addition to the existing knowledge base.

8. Summery and conclusion

- Twice-daily (BID) thoracic radiotherapy of 60 Gy in 40 fractions significantly improves 2-year (74% vs. 48%; p=0.0005) and median overall survival (37.2 months vs. 22.6 months; p=0.012) compared with standard BID TRT of 45 Gy in 30 fractions.
- There was no significant difference in toxicity between patients receiving 60 Gy in 40 fractions compared to standard TRT therapy of 45 Gy in 30 fractions.
- TRT of 60 Gy did not cause significantly higher maximum dysphagia, though patients on the 60 Gy arm reported more dysphagia the first 8 weeks of convalescence.
- Dysphagia scores returned to baseline levels at week 16 in both arms.
- Otherwise, twice-daily TRT of 60 Gy did not impair QoL more than twice-daily TRT of 45 Gy.
- Twice-daily TRT was well tolerated and improved disease control also for patients 70 years or older.
- For patients 70 years or older HRQoL, was preserved the first year after treatment, but year two there was a decline in functional scales that was not seen for younger patients.

9. Implications for clinical practice and future research

60 Gy is now standard TRT schedule in Norway and Sweden. The results are already mentioned in review articles and guidelines, and we know from personal communication that it has been implemented in several hospitals internationally.

We performed the primary analyses when all patients had been followed for a minimum 48 months. Final analyses will be performed, presented, and published later this year. It is important to remember that there were not enough events in the experimental arm to accurately assess median OS when we did our primary analyses in June 2020.

For the same reason, we have not yet reported on long term toxicity. Especially long-term dysphagia will be of interest to measure.

Since 60 Gy did not add toxicity and the survival was unexpectedly large, the Nordic group does not find it appropriate to move on to a confirmatory phase III trial. Adding a week of TRT does not add significant costs, and capacity in RT departments is not challenged.

Conducting phase III trials of LS SCLC take time. ICIs are established for ES SCLC, and results from several studies of ICIs in LS SCLC (including our ACHILES trial) are expected soon. It is reasonable to await these results before designing new LS SCLC trials.

After the primary analyses of the THORA trial, we allowed for the 60 Gy schedule in ACHILES. Thus, ACHILES will provide more data on 60 Gy vs. 45 Gy, though patients were not randomized between these schedules. We will repeat our Cancer Registry based study in a few years to assess the impact on a population level.

Enrolment in ACHILES was completed in April 2022. Primary analyses will be performed in Q2 2024.

We believe that the major barrier for improving treatment of SCLC is that we currently are not able to predict or understand the biological rationale for the large variation in disease development or treatment outcomes in SCLC. We have collected comprehensive biological material (tumor, blood, urine and stool samples) in our trials and a regional biobank and have embarked on a larger initiative exploring the prognostic and predictive value of proposed and novel biomarkers. The overall aim is to develop a classification system for individualization of therapy and future research.

10. References

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11. Appendix

EORTC QLQ-C30

EORTC QLQ-LC13

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

Paper I-III

Paper I

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

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

Summary

Background Concurrent chemoradiotherapy is standard treatment for limited stage small-cell lung cancer (SCLC). Twice-daily thoracic radiotherapy of 45 Gy in 30 fractions is considered to be the most effective schedule. The aim of this study was to investigate whether high-dose, twice-daily thoracic radiotherapy of 60 Gy in 40 fractions improves survival.

Methods This open-label, randomised, phase 2 trial was done at 22 public hospitals in Norway, Denmark, and Sweden. Patients aged 18 years and older with treatment-naive confirmed limited stage SCLC, Eastern Cooperative Oncology Group (ECOG) performance status 0–2, and measurable disease according to the Response Evaluation Criteria in Solid Tumors version 1.1 were eligible. All participants received four courses of intravenous cisplatin 75 mg/m² or carboplatin (area under the curve 5–6 mg/mL×min, Calvert's formula) on day 1 and intravenous etoposide 100 mg/m² on days 1–3 every 3 weeks. Participants were randomly assigned (1:1) in permuted blocks (sized between 4 and 10) stratifying for ECOG performance status, disease stage, and presence of pleural effusion to receive thoracic radiotherapy of 45 Gy in 30 fractions or 60 Gy in 40 fractions to the primary lung tumour and PET-CT positive lymph node metastases starting 20–28 days after the first chemotherapy course. Patients in both groups received two fractions per day, ten fractions per week. Responders were offered prophylactic cranial irradiation of 25–30 Gy. The primary endpoint, 2-year overall survival, was assessed after all patients had been followed up for a minimum of 2 years. All randomly assigned patients were included in the efficacy analyses, patients commencing thoracic radiotherapy were included in the safety analyses. Follow-up is ongoing. This trial is registered at ClinicalTrials.gov, NCT02041845.

Findings Between July 8, 2014, and June 6, 2018, 176 patients were enrolled, 170 of whom were randomly assigned to 60 Gy (n=89) or 45 Gy (n=81). Median follow-up for the primary analysis was 49 months (IQR 38–56). At 2 years, 66 (74·2% [95% CI 63·8–82·9]) patients in the 60 Gy group were alive, compared with 39 (48·1% [36·9–59·5]) patients in the 45 Gy group (odds ratio 3·09 [95% CI 1·62–5·89]; p=0·0005). The most common grade 3–4 adverse events were neutropenia (72 [81%] of 89 patients in the 60 Gy group *vs* 62 [81%] of 77 patients in the 45 Gy group), neutropenic infections (24 [27%] *vs* 30 [39%]), thrombocytopenia (21 [24%] *vs* 19 [25%]), anaemia (14 [16%] *vs* 15 [20%]), and oesophagitis (19 [21%] *vs* 14 [18%]). There were 55 serious adverse events in 38 patients in the 60 Gy group and 56 serious adverse events in 44 patients in the 45 Gy group. There were three treatment-related deaths in each group (one neutropenic fever, one aortic dissection, and one pneumonitis in the 60 Gy group; one thrombocytic bleeding, one cerebral infarction, and one myocardial infarction in the 45 Gy group).

Interpretation The higher radiotherapy dose of 60 Gy resulted in a substantial survival improvement compared with 45 Gy, without increased toxicity, suggesting that twice-daily thoracic radiotherapy of 60 Gy is an alternative to existing schedules.

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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.[1,2] Platinum–etoposide chemotherapy is the main treatment for SCLC,[3,4] and concurrent thoracic radiotherapy improves survival for the one-third of patients with limited stage disease.[1,5] Prophylactic cranial irradiation reduces the risk of brain metastases and improves survival among patients who respond to chemoradiotherapy.[6] Only 25–36% of patients with limited stage SCLC are alive after 5 years, and there is a need for better treatment, but there has been no progress in the past 20 years.[2–4,7,8]

Accelerated, hyperfractionated, twice-daily thoracic radiotherapy of 45 Gy in 30 fractions is the best documented, and considered to be the most effective,

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Research in context

Evidence before this study

Between June 15 and July 30, 2020, we searched PubMed, the Cochrane Library, the American Society of Clinical Oncology (ASCO) website, and the European Society for Medical Oncology (ESMO) website for all publications and abstracts in English using combinations of the terms "thoracic radiotherapy", "small-cell lung cancer", "LS SCLC", "LD SCLC", "twice-daily", "high dose", "BID", "hyperfractionated", and "accelerated" with no limitation on the publication date. We also retrieved practice guidelines for small-cell lung cancer (SCLC) from the American College of Clinical Pharmacy, ASCO, ESMO, and the National Comprehensive Cancer Network.

Concurrent platinum–etoposide chemotherapy and thoracic radiotherapy has been standard treatment for limited stage SCLC since the early 1990s. Twice-daily, accelerated thoracic radiotherapy of 45 Gy in 30 fractions is the best documented schedule, but has not been widely implemented due to concerns about toxicity, logistical challenges, and inconvenience for patients. Population based studies show that most patients with limited stage SCLC are treated with once-daily thoracic radiotherapy schedules that have not yet been compared with or proven superior to the twice-daily 45 Gy schedule in randomised trials. Several studies of high-dose thoracic radiotherapy have been done, but most have been single-arm studies. The only completed randomised trial comparing high-dose thoracic radiotherapy with standard-dose thoracic radiotherapy did not show a survival benefit of the higher dose.

Added value of this study

To our knowledge, this is the first randomised trial comparing high-dose, hyperfractionated, accelerated, twice-daily thoracic radiotherapy with the established 45 Gy schedule. Our results show that administering 60 Gy is feasible, does not cause more toxic effects, and suggest that the higher dose provides a large survival benefit. As far as we know, the 2-year and median overall survival are the highest reported in any randomised trial of thoracic radiotherapy in limited stage SCLC. It is also one of few randomised trials limiting radiotherapy fields to ^{18}F-fluorodeoxyglucose PET-CT positive lesions, omitting elective nodal irradiation, and allowing modern radiotherapy techniques.

Implications of all the available evidence

Our study shows that twice-daily thoracic radiotherapy of 60 Gy in 40 fractions is an alternative to established schedules. The toxicity was modest, suggesting that concerns about toxicity from twice-daily thoracic radiotherapy might be unjustified when using modern radiotherapy techniques and limiting radiotherapy fields to PET-CT positive lesions.

radiotherapy schedule for patients with limited stage SCLC. Results from the Intergroup 0096 trial showed that this schedule improved survival compared with once-daily thoracic radiotherapy of 45 Gy in 25 fractions.[3] One possible explanation is that SCLC cells are highly radiosensitive, and even at low fraction doses, tumour cells are killed exponentially while damage to normal tissue is reduced.[9] Furthermore, repopulation of cancer cells accelerates after 3 weeks of radiotherapy,[10] which might explain why shortening the thoracic radiotherapy treatment period improves survival.[11] However, because twice-daily thoracic radiotherapy caused more oesophagitis in the Intergroup 0096 trial than the once-daily schedule, as well as causing logistical challenges, most patients with limited stage SCLC still receive once-daily thoracic radiotherapy.[12,13]

Local relapses are frequent and are associated with death.[3] It has been suggested that higher doses of thoracic radiotherapy might improve local control and consequently survival,[14,15] but this has not been shown in randomised trials.

See Online for appendix

A study from 1998 concluded that 45 Gy was the maximum tolerated dose of twice-daily thoracic radiotherapy in limited stage SCLC.[16] Since then, PET-CT scanning has been shown to be a more accurate method for assessment of disease extent than conventional CT scans, and it has been shown that radiotherapy fields might be limited to PET-CT positive lesions.[17] Additionally, modern techniques enable higher doses of thoracic radiotherapy,[18] and other studies show that a schedule of twice-daily thoracic radiotherapy of more than 45 Gy is feasible and tolerable in some patients.[14,15]

The main aim of this trial was to investigate whether high-dose, twice-daily thoracic radiotherapy of 60 Gy improves survival in patients with limited stage SCLC. Based on data from Sweden[14] and estimates of irradiation of surrounding normal tissue, we deemed 60 Gy to be the maximum dose that could safely be delivered to most patients with limited stage SCLC. To our knowledge, this is the first randomised trial comparing high-dose, twice-daily thoracic radiotherapy with the established schedule of 45 Gy in 30 fractions.

Methods

Study design and participants

This open-label, randomised, phase 2 trial was done in 22 public hospitals in Norway, Denmark, and Sweden (appendix p 4). Eligible patients were aged 18 years or older; were treatment naive; had confirmed SCLC, which was limited stage according to the International Association for the Study of Lung Cancer;[19] had measurable disease according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1); had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; had an alanine aminotransferase concentration of 3 times the upper limit of normal (ULN) or less; had a bilirubin concentration of 1·5 times the ULN or less; had an absolute neutrophil count of $1{\cdot}5\times10^9$ cells per L or

more; had a platelet count of 100×10^9 per L or more; had a creatinine concentration of less than 100 µmol/L; had a creatinine clearance of more than 50 mL/min; and had whole-body ^{18}F-fluorodeoxyglucose PET-CT scans and brain MRI for staging. One negative cytology was required if pleural effusion was present. The forced expiratory volume had to be more than 1 L or more than 30% of predicted value and the diffusing capacity for carbon monoxide had to be more than 30% of predicted value. Patients were excluded if they had serious concomitant disorders that compromised the ability to complete study treatment or procedures. All patients gave written, informed consent. The trial was approved by the Regional Committee for Medical Research Ethics (Central Norway, Norway), the Regional Ethics Board in Gothenburg (Sweden), and the National Committee on Health Research Ethics (Denmark). The protocol is included in the appendix.

Randomisation and masking

Investigators randomly assigned patients (1:1) to receive thoracic radiotherapy of either 60 Gy in 40 fractions or 45 Gy in 30 fractions using a randomisation module in an electronic clinical trial management system. The system used a stratified block randomisation method using a permuted block design with randomly varying block sizes of 4 to 10. Both block sizes and allocation sequences in each block were generated by the system and masked to investigators. Randomisation was stratified by ECOG performance status (0–1 *vs* 2), disease stage (I–II *vs* III), and pleural effusion (yes *vs* no). Patients and investigators were not masked to treatment allocation.

Procedures

Patients received four courses of intravenous cisplatin 75 mg/m² on day 1 plus intravenous etoposide 100 mg/m² on days 1–3 (platinum–etoposide) every 3 weeks. Haematology and creatinine were measured on day 1 and 10 of each chemotherapy course. Concentrations of bilirubin, alanine aminotransferase, lactate dehydrogenase, albumin, and C-reactive protein were measured at inclusion, before the second platinum–etoposide course and after the fourth platinum–etoposide course. Courses were delayed if the absolute neutrophil count was less than $1{\cdot}5\times10^9$ cells per L or the platelet count was less than 100×10^9 per L. Doses of platinum and etoposide were reduced by 20–25% if grade 3–4 neutropenia or thrombocytopenia occurred. Chemotherapy was discontinued if a course was delayed by more than 3 weeks. Replacing cisplatin with carboplatin (area under the curve of 5–6 mg/mL×min, Calvert's formula) was allowed if severe cisplatin toxicity occurred. Granulocyte colony stimulating factor and erythropoietin were not permitted.

Thoracic radiotherapy started 20–28 days after the first day of the first course of platinum–etoposide. Patients in both groups received two fractions per day, ten fractions per week with a minimum of 6 h between fractions. The gross tumour volume included the primary lung tumour and PET-CT positive lymph node metastases. The gross tumour volumes were defined according to the CT planning scan that was done just before the thoracic radiotherapy (after the first course of platinum–etoposide). For each gross tumour volume, a corresponding clinical target volume was defined by adding a 5 mm margin in all directions to each gross tumour volume, although not into bony structures, large vessels, the heart, or beyond the mediastinal parietal pleura, unless there were signs of invasion of these structures.

A four-dimensional CT scan was recommended for defining the internal target volume when available. If unavailable, it was recommended to add an internal margin of 8 mm in the transverse plane and 10 mm in the cranial and caudal directions to the clinical target volume of the primary tumour, and a 5 mm internal margin in all directions to the clinical target volume of the lymph nodes. Finally, a setup margin was added according to each department's routine to define the planning target volume.

Both lungs, the heart, the oesophagus from below the larynx to the gastro-oesophageal junction, and the spinal canal were delineated as organs at risk. The mean lung dose was not to exceed 20 Gy. Less than 35% of the normal lung tissue was to receive 20 Gy or more, and less than 65% of the normal lung tissue was to receive 5 Gy or more. The mean heart dose was preferably not to exceed 35 Gy and was not to exceed 46 Gy. Preferably, less than 80% of the normal heart tissue was to receive 40 Gy or more, less than 60% was to receive 45 Gy or more, and less than 30% was to receive 60 Gy or more. A maximum dose of 60 Gy to the oesophagus was acceptable but was preferably lower. Preferably, the mean oesophageal dose was not to exceed 34 Gy. A maximum dose of 60 Gy to the brachial plexus was acceptable but was preferably lower.

If the doses to organs at risk exceeded recommended levels, a dose reduction to 54 Gy was allowed in the 60 Gy group. If the doses to organs at risk were still too high, the thoracic radiotherapy dose was defined according to local routines.

It was recommended to complete thoracic radiotherapy within 22 days (45 Gy) or 29 days (60 Gy). If timeframes were exceeded, a compensation according to local routines was recommended. Compensation by treating patients on weekends was preferred. Alternatively, the fraction doses were increased, but not above 2 Gy. Thoracic radiotherapy was discontinued if patients had severe toxicity, patients were deemed unfit by investigators to complete treatment, or patient choice.

Patients who responded to chemoradiotherapy were offered prophylactic cranial irradiation of 25 Gy in ten fractions or 30 Gy in 15 fractions, one fraction per day, starting within 6 weeks after the fourth course of platinum–etoposide.

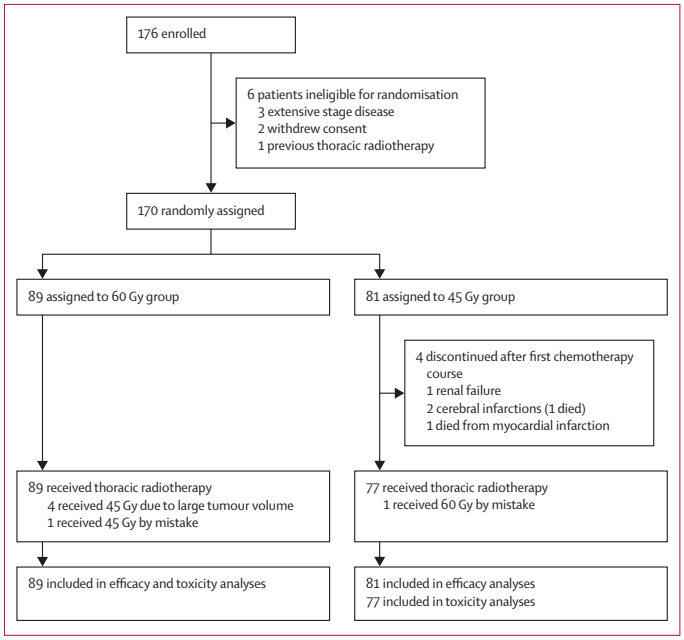

Figure 1: **Trial profile**

A CT scan for response evaluation was done within 3 weeks after the fourth course of platinum–etoposide. A second CT scan for confirmation of response was not required. Patients were then followed up with CT scans every 10 weeks in year 1, every 3 months in years 2–3, and every 6 months in years 4–5. Relapses were treated according to local routines.

Disease stage was assessed according to the TNM Classification of Malignant Tumors version 7,[20] response was assessed by investigators according to RECIST 1.1, and toxicity according to Common Terminology Criteria for Adverse Events version 4.0. Adverse events were assessed before each chemotherapy course, before the start of thoracic radiotherapy, weekly during thoracic radiotherapy, at the end of thoracic radiotherapy, and then at evaluation and follow-up visits.

Outcomes

The primary endpoint was 2-year overall survival (proportion of patients alive 2 years after chemotherapy commenced), because median overall survival was less than 2 years in most studies of limited stage SCLC published when we designed our trial.[3,14,21–23] Secondary endpoints were overall survival, overall response (proportion of patients with a complete or partial response according to RECIST 1.1 at evaluation after chemoradiotherapy), progression-free survival, proportion of patients with local control (no relapse within the radiotherapy fields at evaluation), toxicity, and health-related quality of life (HRQOL). Overall survival was measured from the day chemotherapy commenced until death by any cause; progression-free survival was measured from the day chemotherapy commenced until progression by RECIST 1.1 or death by any cause.

We also report the results of a prespecified exploratory analysis of the associations between baseline characteristics and treatment outcomes. Results of analyses of secondary HRQOL endpoints and exploratory biomarker analyses will be reported elsewhere.

Statistical analysis

In our previous trial of thoracic radiotherapy in patients with limited stage SCLC, 2-year survival was 53% in the group who received 45 Gy in 30 fractions,[21] and we considered a relative improvement of 25% to be clinically relevant. To show an improvement from 53% to 66% with a one-tailed α of 0·1 and β of 0·2, 73 evaluable patients were required in each group. The main efficacy analyses included all randomly assigned patients (intention-to-treat population). In addition, we did progression-free survival and overall survival analyses in patients who commenced thoracic radiotherapy per protocol. All patients who commenced thoracic radiotherapy were included in the toxicity analyses.

Pearson's χ^2 test was used to compare 2-year overall survival when all patients had been followed up for a minimum of 2 years, and for comparisons of toxicity and overall response. Median overall survival and progression-free survival were estimated using the Kaplan-Meier method, and compared using the Cox proportional hazard method after checking that the proportional hazards assumption was met by visual inspection of log minus log plots. Logistic regression was used for the multivariable 2-year survival analysis, and a Cox model was used for the multivariable overall survival and progression-free survival analysis. Both models were adjusted for established prognostic factors (sex, ECOG performance status, disease stage, presence of pleural effusion, and weight loss) and age (as a continuous variable). Preplanned analyses were done of 2-year overall survival data (including odds ratios [ORs]) for subgroups of clinical interest (patients aged <70 *vs* ≥70 years; women *vs* men; ECOG performance status 0 *vs* 1 *vs* 2; disease stage I–II *vs* III; pleural effusion *vs* no pleural effusion; weight loss *vs* no weight loss). We have also included post-hoc comparisons of time from progression until death and the frequency of distant metastases between the treatment groups.

The significance level stated in the statistical analysis plan for the primary endpoint was a one-sided $p<0·10$. Due to the highly significant difference for the primary endpoint, all reported p-values are two-sided and $p<0.05$ has been applied as the significance level. This decision was made by the authors, who include the trial steering committee, and was made after doing the analyses to

avoid confusion about significance levels and p values in the paper. This change was not made to the protocol. Consequently, the significance threshold was lower than planned. The analyses were done using SPSS version 26. No interim analyses were done. This trial is registered at ClinicalTrials.gov, NCT02041845.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between July 8, 2014, and June 6, 2018, 176 patients were enrolled; six were excluded due to extensive disease (n=3), withdrawn consent (n=2), and previous thoracic radiotherapy (n=1), therefore 170 patients were randomly assigned (89 to 60 Gy, 81 to 45 Gy) and included in the efficacy analyses. Four patients in the control group discontinued before thoracic radiotherapy commenced due to renal failure (n=1), cerebral infarction (n=2), and death from myocardial infarction (n=1). One patient in each group received the wrong dose of radiotherapy by mistake. Four patients in the 60 Gy group received 45 Gy because it was not possible to deliver 54–60 Gy due to large tumour volumes. 166 patients were therefore included in the toxicity analyses (89 patients in the 60 Gy group, 77 patients in the 45 Gy group; figure 1).

Baseline characteristics are shown in table 1. Median age was 65 years (IQR 60–71), 53 (31%) of 170 patients were aged 70 years or older, 97 (57%) were women, 166 (98%) were current or former smokers, 152 (89%) had ECOG performance status of 0–1, 142 (84%) had stage III disease, 13 (8%) had pleural effusion, and 34 (20%) a weight loss of more than 5% in the 3 months before enrolment.

	60 Gy group (n=89)	45 Gy group (n=81)
Age, years		
Median	65 (58·0–70·5)	65 (60·0–72·0)
≥70	25 (28%)	28 (35%)
Sex		
Female	50 (56%)	47 (58%)
Male	39 (44%)	34 (42%)
ECOG performance status		
0	44 (51%)	34 (42%)
1	36 (41%)	38 (47%)
2	7 (8%)	8 (10%)
Data missing	2 (2%)	1 (1%)
Disease stage		
IA	0	4 (5%)
IIA	9 (10%)	6 (7%)
IIB	5 (6%)	4 (5%)
IIIA	38 (43%)	31 (36%)
IIIB	37 (42%)	36 (44%)
Pleural fluid present	8 (9%)	5 (6%)
Smoking history		
Current	54 (61%)	57 (70%)
Former	33 (37%)	22 (27%)
Never	1 (1%)	2 (3%)
Data missing	1 (1%)	0
Median pack years for current or former smokers	35 (23·5–50·0)	30 (23·0–40·0)
Weight loss in 3 months before inclusion		
>5%	16 (18%)	18 (22%)
Data missing	17 (19%)	7 (9%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline characteristics**

The mean number of completed chemotherapy courses in each group, the number of patients who received carboplatin instead of cisplatin for at least one course, and the number of patients who had a dose reduction are shown in table 2. In the 60 Gy group, seven (8%) of 89 patients discontinued chemotherapy due to neutropenic infection (n=2), patient's wish (n=2), myocardial infarction (n=1), infection (n=1), and aortic dissection (n=1). In the 45 Gy group, ten (12%) of 81 patients discontinued chemotherapy due to neutropenic infection (n=5), cerebral infarction (n=2), myocardial infarction (n=1), patient's wish (n=1), and unknown reasons (n=1).

The mean time from day 1 of the first course of platinum–etoposide until thoracic radiotherapy started was 24·4 days (SD 10·2) in the 60 Gy group and 23·4 days (6·3) in the 45 Gy group. 86 (97%) of 89 patients in the 60 Gy group and 74 (91%) of 81 patients in the 45 Gy group completed thoracic radiotherapy as planned; 78 (89%) of 88 patients in the 60 Gy group and 69 (95%) of 73 patients in the 45 Gy group completed radiotherapy within the recommended timeframes (data missing for nine patients). Reasons for discontinuation of thoracic radiotherapy in the 60 Gy group were oesophagitis after 46·5 Gy (n=1), death from neutropenic infection after 51 Gy (n=1), and death from aortic dissection after 12 Gy (n=1); reasons for discontinuation in the 45 Gy group were death from thrombocytopenic bleeding after 39 Gy (n=1), oesophagitis after 43·5 Gy (n=1), and withdrawal after 1·5 Gy (n=1). A similar proportion of patients in each group received prophylactic cranial irradiation (72 [85%] in the 60 Gy group *vs* 68 [85%] in the 45 Gy group). Of the four patients who received 45 Gy instead of 60 Gy due to large tumour volumes, one was alive after 49·8 months, one was alive after 68·8 months, one died after 5·4 months (intercurrent disease), and one died after 8·3 months (relapse after 6·1 months). There was no difference between the groups in the proportion of patients receiving second-line chemotherapy (41 [46%] patients in the 60 Gy group; 39 (48%) patients in the 45 Gy group). The most common second-line regimens

	60 Gy group (n=89)	45 Gy group (n=81)
Number of chemotherapy courses		
1	1 (1%)	4 (5%)
2	3 (3%)	4 (5%)
3	3 (3%)	2 (3%)
4	82 (88%)	71 (88%)
Mean	3·87 (0·50)	3·73 (0·78)
Any dose reduction	58 (65%)	66 (82%)
Received carboplatin for one or more courses	31 (35%)	34 (42%)
Completed thoracic radiotherapy as planned	86 (97%)	74 (91%)
Received prophylactic cranial irradiation	72 (85%)	68 (85%)
Received second line chemotherapy	41 (46%)	39 (48%)
Response to chemoradiotherapy		
Overall response	69 (77·5%; 67·4–85·7)	62 (76·5%; 65·8–85·2)
Complete response	16 (18·0%; 10·6–25·5)	17 (21·0%; 12·7–31·5)
Partial response	53 (59·6%; 48·6–69·8)	45 (55·6%; 44·1–66·6)
Stable disease	4 (4·5%; 1·2–11·1)	6 (7·4%; 2·8–15·4)
Progressive disease	5 (5·6%; 1·8–12·6)	5 (6·2%; 2·0–13·8)
Unknown	11 (12·4%; 6·3–21·0)	8 (9·9%; 4·4–18·5)

Data n (%), mean (SD), or n (%; 95% CI).

Table 2: **Treatment completion and response to chemoradiotherapy**

	2-year overall survival		Overall survival	
	Odds ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Treatment group				
45 Gy	1 (ref)	..	1 (ref)	..
60 Gy	4·67 (2·13–10·21)	<0·0001	0·54 (0·34–0·83)	0·0058
Age	1·00 (0·96–1·05)	0·89	1·02 (0·99–1·05)	0·26
Sex				
Male	1 (ref)	..	1 (ref)	..
Female	2·23 (1·05–4·75)	0·038	0·64 (0·42–0·99)	0·043
ECOG performance status				
0	1 (ref)	..	1 (ref)	..
1	0·79 (0·36–1·75)	0·57	1·02 (0·64–1·63)	0·94
2	1·11 (0·26–4·70)	0·88	1·08 (0·47–2·47)	0·86
Disease stage				
I–II	1 (ref)	..	1 (ref)	..
III	0·39 (0·13–1·17)	0·092	1·19 (0·66–2·14)	0·56
Pleural fluid				
No	1 (ref)	..	1 (ref)	..
Yes	0·47 (0·11–1·92)	0·29	1·38 (0·61–3·10)	0·44
Weight loss				
<5%	1 (ref)	..	1 (ref)	..
≥5%	1·35 (0·55–3·31)	0·51	0·94 (0·56–1·59)	0·83

ECOG=Eastern Cooperative Oncology Group.

Table 3: **Multivariable analyses for 2-year overall survival and overall survival**

were platinum–etoposide (50 [63%] of 80) and doxorubicin–cyclophosphamide–vincristine (17 [21%] of 80).

At the time of the analyses for the primary endpoint (July 29, 2020), 46 (52%) of 89 patients in the 60 Gy group and 55 (68%) of 81 patients in the 45 Gy group had died; 56 (63%) patients in the 60 Gy group and 52 (64%) patients in the 45 Gy group had disease progression. Median follow-up was 49 months (IQR 38–56).

At 2 years, 66 (74·2% [95% CI 63·8–82·9]) patients in the 60 Gy group were alive, compared with 39 (48·1% [36·9–59·5]) patients in the 45 Gy group (OR 3·09 [95% CI 1·62–5·89]; p=0·0005). The multivariable analysis also showed a significantly greater overall survival at 2 years in the 60 Gy group compared with the 45 Gy group (table 3). Subgroup analyses of 2-year overall survival are shown in the appendix (p 2). The results were similar for the per-protocol population at 2 years, 63 (75·0% [95% CI 64·4–83·8]) patients in the 60 Gy group were alive compared with 39 (51·3% [39·6–63·0]; OR 2·85 [95% CI 1·46–5·55]; p=0·0022) patients in the 45 Gy group.

Median overall survival was significantly longer in the 60 Gy group than in the 45 Gy group (37·2 months [95% CI 28·4–46·1] *vs* 22·6 months [17·1–28·1]; hazard ratio [HR] 0·61 [95% CI 0·41–0·90]; p=0·012; figure 2), and the difference remained significant in the multivariable analysis (table 3). Of the baseline characteristics, only female sex was associated with improved 2-year overall survival and median overall survival (table 3). All other subgroups assessed in multivariable analyses of 2-year and median overall survival were not significantly associated with outcome (table 3). Median overall survival in the per-protocol population was 37·2 months (95% CI 28·8–45·7) in the 60 Gy group compared with 24·0 months (15·6–32·4; HR 0·64 [95% CI 0·43–0·97]; p=0·034; appendix p 1) in the 45 Gy group.

Median progression-free survival was 18·6 months (95% CI 7·3–30·0) in the 60 Gy group and 10·9 months (8·7–13·1) in the 45 Gy group (HR 0·75 [95% CI 0·52–1·09]; p=0·13; figure 2). There was no difference in progression-free survival between the two dose groups in the multivariable analysis (HR 0·68 [95% CI 0·45–1·03]; p=0·067; appendix p 3). Median progression-free survival in the per-protocol population was 18·7 months (95% CI 7·5–30·0) in the 60 Gy group compared with 11·1 months (6·3–16·0) in the 45 Gy group (HR 0·79 [95% CI 0·54–1·15]; p=0·22; appendix p 1).

A post-hoc analysis showed that the median time from progression until death was longer in the 60 Gy group (14·0 months [95% CI 9·5–18·6]) than in the 45 Gy group (8·2 months [7·3–9·0]; p=0·0009).

69 (77·5% [95% CI 67·4–85·7]) patients in the 65 Gy group had an overall response compared with 62 (76·5% [65·8–85·2]; p=0·88) patients in the 45 Gy group (table 2).

There was no difference in local control between the groups (19 [21%] patients in the 60 Gy group *vs* 28 [35%] patients in the 45 Gy group had relapse within the radiotherapy field; p=0·054), and a post-hoc analysis showed that there was no difference in the frequency of distant metastases (37 [42%] patients in the 60 Gy group *vs* 37 [46%] patients in the 45 Gy group; p=0·59).

Overall, there was no difference in toxic effects between the 60 Gy group and the 45 Gy group. The most common grade 3–4 adverse events were neutropenia (72 [81%] of 89 patients in the 60 Gy group *vs* 62 [81%] of 77 patients in the 45 Gy group; p=0·25), neutropenic infections (24 [27%] *vs* 30 [39%]; p=0·30), thrombocytopenia (21 [24%] *vs* 19 [25%]; p=0·96), anaemia (14 [16%] *vs* 15 [20%]; p=0·85), and oesophagitis (19 [21%] *vs* 14 [18%]; p=0·83; table 4). There were three treatment-related deaths in each group. In addition to the patients who died after thoracic radiotherapy commenced (60 Gy group: one from neutropenic fever, one from aortic dissection; 45 Gy group: one from thrombocytic bleeding), two patients in the 45 Gy group died after the first chemotherapy course (one from cerebral infarction, one from myocardial infarction), and one patient in the 60 Gy group (received 45 Gy by mistake) died from pneumonitis after completing chemoradiotherapy. Overall, there were 55 serious adverse events in 38 patients in the 60 Gy group and 56 serious adverse events in 44 patients in the 45 Gy group. All serious adverse events were considered treatment related except the aortic dissection in the 60 Gy group.

Discussion

To our knowledge, this is the first randomised trial comparing high-dose, accelerated, hyperfractionated thoracic radiotherapy with 45 Gy in 30 fractions in limited stage SCLC. In this trial, we were able to deliver 60 Gy to almost all patients allocated to the high-dose group. Analysis of the primary endpoint, 2-year overall survival, showed a significant survival benefit of the 60 Gy dose: 66 (74·2% [95% CI 63·8–82·9]) of 89 patients in the 60 Gy group were alive at 2 years, compared with 39 (48·1% [36·9–59·5]) of 81 patients in the 45 Gy group. Furthermore, there was a significant improvement in median overall survival in the 60 Gy group compared with the 45 Gy group. To our knowledge, such an improvement in survival has not been observed in previous randomised trials of limited stage SCLC. Of note, our analyses were done when the primary endpoint, 2-year overall survival, was met—ie, 2 years after the last patient commenced treatment—and we did not censor for the primary endpoint. Final 5-year survival data will be available in 2023, and due to the high censoring rate, it is not yet possible to assess whether 60 Gy increases long-term survival. However, the already observed survival benefit is highly relevant for patients, especially because the higher dose did not cause more toxicity, and the frequency of radiotherapy-related toxicities was among the lowest reported in studies of limited stage SCLC.

We are only aware of one other completed randomised trial (CONVERT) comparing high-dose thoracic radiotherapy with the 45 Gy schedule. In CONVERT, patients were randomly assigned to receive 45 Gy in 30 fractions (two fractions per day) or 66 Gy in 33 fractions (one fraction per day).[4] Notably, thoracic radiotherapy in the high-dose group was neither hyperfractionated nor accelerated. The trial was designed to show superiority of the higher dose, but 66 Gy was inferior both in terms of 2-year overall survival (51% *vs* 56%) and median overall survival (25 months *vs* 30 months).[4]

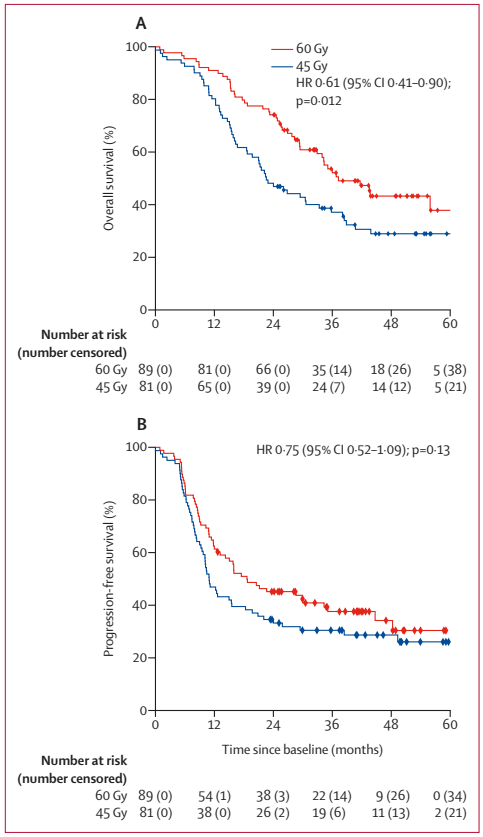

Figure 2: **Univariable analysis of overall survival and progression-free survival in the intention-to-treat population**
(A) Overall survival. (B) Progression-free survival. HR=hazard ratio.

To our knowledge, the 2-year overall survival in our trial is the highest reported in trials in limited stage SCLC, including all trials of high-dose, once-daily thoracic radiotherapy, and adds to the evidence suggesting that accelerated, hyperfractionated thoracic radiotherapy is the most effective approach in this disease. In the Intergroup 0096 trial, the total dose in Gy was the same in both treatment groups,[3] and the 60 Gy in our high-dose group is similar to the 66 Gy in the high-dose group in CONVERT.[4] The important difference between our trial and CONVERT is the shorter treatment time in our high-dose group—4 weeks instead of 6·5 weeks—suggesting that there might be a

	60 Gy group (n=89)				45 Gy group (n=77)				p value
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	
Oesophagitis	33 (37%)	19 (21%)	0	0	34 (44%)	14 (18%)	0	0	0·83
Pneumonitis	8 (9%)	3 (3%)	0	1 (1%)	4 (5%)	0	0	0	0·39
Anaemia	70 (79%)	14 (16%)	0	0	59 (77%)	15 (20%)	0	0	0·85
Thrombocytopenia	47 (54%)	13 (15%)	8 (9%)	0	44 (57%)	10 (13%)	9 (12%)	0	0·96
Neutropenia	13 (15%)	14 (16%)	58 (66%)	0	8 (10%)	17 (22%)	45 (58%)	0	0·25
Neutropenic infection	0	19 (21%)	5 (6%)	1 (1%)	0	24 (31%)	6 (8%)	0	0·30
Thrombocytopenic bleeding	1 (1%)	0	0	0	2 (3%)	0	0	1 (1%)	0·61
Infection	14 (16%)	2 (2%)	0	0	11 (14%)	5 (7%)	0	0	0·14
Kidney failure	10 (11%)	1 (1%)	0	0	10 (13%)	0	1 (1%)	0	0·80
Nausea	15 (17%)	5 (6%)	1 (1%)	0	19 (25%)	3 (4%)	0	0	0·62
Fatigue	11 (12%)	0	0	0	8 (10%)	1 (1%)	0	0	0·83
Erythaema	7 (8%)	0	0	0	6 (8%)	1 (1%)	0	0	0·87
Headache	13 (15%)	1 (1%)	0	0	5 (7%)	1 (1%)	0	0	0·078
Neuropathy	3 (3%)	0	0	0	1 (1%)	1 (1%)	0	0	0·89
Myelopathy	0	1 (1%)	0	0	0	0	0	0	1·0
Myocardial infarction	0	1 (1%)	0	0	0	0	0	0	1·0
Aortic dissection	0	0	0	1 (1%)	0	0	0	0	1·0
Ototoxicity	2 (2%)	1 (1%)	0	0	1 (1%)	0	0	0	1·0
Thromboembolism	0	2 (2%)	0	0	1 (1%)	1 (1%)	0	0	0·79

Table 4: **Toxicity in patients who commenced thoracic radiotherapy**

dose–response relationship at doses greater than 45 Gy when thoracic radiotherapy is accelerated and hyperfractionated.

We are only aware of three studies of accelerated and hyperfractionated thoracic radiotherapy in doses greater than 45 Gy in limited stage SCLC. Jeremic and colleagues observed a median overall survival of 34 months in patients receiving 54 Gy concurrently with the first chemotherapy course,[15] which is similar to what we observed in our high-dose group. However, median overall survival was much shorter (26 months) among those who received thoracic radiotherapy concurrently with the third course in that study[15] and in two other studies.[14,23] In a retrospective, non-randomised, Swedish study, 60 Gy in 40 fractions did not improve survival compared with 45 Gy in 30 fractions, and the median overall survival was 20·8 months.[14] Schild and colleagues observed a median overall survival of 22 months in patients receiving 60 Gy in 40 fractions.[23] However, there are important differences between these studies and ours. Patients in these studies did not have PET-CT scans, and other target volume definitions and radiotherapy techniques were used. Jeremic and colleagues excluded patients aged 70 years and older, and the split course used by Schild and colleagues might allow for repopulation and regrowth, reducing the biologically effective dose.

Survival in the 45 Gy group in our study was as expected, similar to the Intergroup 0096 trial[3] and our previous study of thoracic radiotherapy in limited stage SCLC (which was the basis for our sample size calculation).[21] Only two other trials have reported a longer survival for patients receiving 45 Gy in 30 fractions. In CONVERT, 2-year overall survival was 56%, median overall survival was 30 months, and median progression-free survival was 15·4 months in the 45 Gy group.[4] In a Japanese trial,[7] median progression-free survival was 13 months and median overall survival was 38 months in the group who received platinum–etoposide after radiotherapy. The longer progression-free survival and overall survival in these two trials compared with ours might be explained by differences in patient selection. CONVERT excluded patients with two abnormal laboratory values (low sodium, elevated lactate dehydrogenase, or elevated alkaline phosphatase); used a more conservative definition of limited stage (the Veteran's Administration Lung Study Group's); enrolled fewer patients with ECOG performance status of 2 than in our study (3% *vs* 9%); excluded patients with ECOG performance status of 2 due to comorbidities; enrolled younger patients (median age 62 years *vs* 65 years; 12% *vs* 31% aged ≥70 years); and enrolled fewer women (46% *vs* 57%). Furthermore, only 57% of patients in the CONVERT trial had a PET-CT scan for staging. Patients in the Japanese study were also younger than in our study (median age 61 years *vs* 65 years; patients aged ≥70 years were excluded), there were fewer women (19% *vs* 57%), and there were more patients with ECOG performance status of 0 (60% *vs* 47%). Disease stage was not reported in the Japanese study.

In our trial, the frequency of severe oesophagitis is lower than in the Intergroup 0096 trial[3] and in our previous thoracic radiotherapy trial (27–33%),[21] and is among the lowest reported in studies of limited stage

SCLC.[4,14,22,23] An important reason might be that in this trial, we limited the radiotherapy fields to PET-CT positive lesions, which reduces the target volumes, but might also ensure inclusion of lesions missed when applying elective nodal irradiation.[24] We allowed the use of modern radiotherapy techniques, which reduce the maximum dose to and volume of normal tissue irradiated.[18] These approaches were adopted based on small, non-randomised studies,[17] but were also used in CONVERT without increasing the relapse risk.[25]

Compared with other trials in patients with limited stage SCLC, many patients in our trial had neutropenia or neutropenic infections because we did not allow the use of growth factors. This was because increased toxicity was observed in a trial of sargramostim in limited stage SCLC.[26] Radiotherapy-induced lymphopenia might also have contributed to infections, but our study was not designed to collect lymphopenia data.

In the Intergroup 0096 trial, thoracic radiotherapy started concurrently with the first course of platinum–etoposide,[3] whereas in our trial and the CONVERT trial,[4] radiotherapy started with the second course of platinum–etoposide. Many patients are diagnosed at hospitals without radiotherapy departments, and our design allowed both for early start of chemotherapy and sufficient time to plan thoracic radiotherapy. Furthermore, we have shown in a previous study of thoracic radiotherapy in limited stage SCLC, that the first chemotherapy course significantly reduces tumour volumes, allowing for less irradiation of normal tissue[27] because target volumes can be adjusted to tumour sizes after commencing chemotherapy.[4,14,22,28] Consequently, starting thoracic radiotherapy concurrently with the second course of platinum–etoposide might have contributed to low toxicity in our trial. Overall, we believe that our design complies with current guidelines.[29]

The main limitation of our trial was the sample size. The reason for designing a randomised phase 2 trial instead of a phase 3 trial was concerns about feasibility and toxicity in the high-dose group,[16] and there were no data from randomised trials indicating improved efficacy of 60 Gy when we initiated our trial. The treatment groups were well balanced with respect to TNM stage of disease, but we cannot rule out that there was an imbalance with respect to tumour volumes or volumes of irradiated surrounding normal tissue, and we have not yet assessed whether it would have been possible to deliver 60 Gy to patients in the control group. We plan to publish these data when all radiotherapy plans have been reviewed. There was no central quality assurance of the radiotherapy and the results of this trial reflect clinical practice at participating sites. We do not believe that reporting two-sided p values instead of one-sided p values, as originally planned in the protocol, changes the interpretation of our study because the study was highly positive for the primary endpoint.

The currently immature follow-up for secondary survival endpoints might explain why we found no difference in progression-free survival between the groups. Another reason might be that interpreting images from CT scans after chemoradiotherapy is challenging, which was the reason for not reporting response rates in the CONVERT trial.[4] Similarly, there was no difference in overall response rate between our treatment groups, or in the Intergroup 0096 trial (87% in both groups).[30] The challenge with limited stage SCLC is the high relapse rate, not the lack of response to initial treatment. It is possible that the 60 Gy dose in our study results in different location, timing, and growth speed of metastases, leading to the significant difference in post-progression survival time observed between the two groups. Such post-hoc, exploratory analyses will be done when the 5-year follow-up is completed.

Twice-daily radiotherapy schedules are not widely adopted, probably due to logistical challenges and concerns about toxicity.[12,13] Our study shows that these concerns are no longer justified. None of the patients discontinued due to inconvenience. Because many patients might need to travel long distances and stay away from home during thoracic radiotherapy, completing the treatment in 4 weeks instead of 6–7 weeks could be a benefit to many patients, and the higher dose was well tolerated. Considering the survival benefit, we believe that the 60 Gy schedule is highly attractive for both patients and health-care providers.

Ideally, because this was a randomised phase 2 trial, our results need to be confirmed. However, population-based studies suggest that most patients with limited stage SCLC are already treated with schedules that have not been investigated or proven more effective than twice-daily thoracic radiotherapy of 45 Gy in randomised trials. According to the National Cancer Database in the USA, a majority (85%) of patients receive once-daily thoracic radiotherapy of 46–72 Gy in fractions of 1·8–2·0 Gy.[12] A 2019 European survey suggests that more patients receive twice-daily thoracic radiotherapy after the CONVERT data were published, but 58% of clinicians who responded to the survey still prescribe once-daily dosing.[13] The ongoing, three-armed, CALGB 30610/RTOG 0538 trial comparing 45 Gy in 30 fractions (two fractions per day) with 70 Gy in 35 fractions (one fraction per day) and 61·2 Gy (28·8 Gy in 16 fractions [one fraction per day] followed by 32·4 Gy in 18 fractions [two fractions per day]) will further clarify whether high-dose, once-daily thoracic radiotherapy is a good alternative to twice-daily dosing. Another aspect to consider is that it might take a long time to do a confirmatory trial. The number of randomised trials of limited stage SCLC is low. Studies of immune checkpoint inhibitors in metastatic SCLC have shown a significant, although modest, survival benefit, and there are several ongoing trials of immunotherapy in limited stage SCLC, including one by our collaborative group (NCT03540420),

which will need to be completed before further research is considered. If any of these trials are positive, the complexity of doing confirmatory trials for thoracic radiotherapy will increase. In the meantime, we believe that 60 Gy in 40 fractions is an attractive alternative to current schedules.

In conclusion, hyperfractionated, accelerated, twice-daily thoracic radiotherapy of 60 Gy was feasible in most patients. The higher dose of thoracic radiotherapy resulted in a significant improvement in both 2-year and median overall survival compared with the standard 45 Gy schedule, without adding toxicity.

Contributors

BHG, OTB, JN, and SWL conceived and designed the study. BHG, KTK, JN, TS, and TOH managed the trial. All authors participated in data analyses, interpretation of the data, and manuscript writing. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. KTK, TOH, and BHG accessed and verified the data in the study.

Declaration of interests

BHG has received research funding from Roche and AstraZeneca, and honoraria from Roche, AstraZeneca, Pierre Fabre, Takeda, Eli Lilly, Bristol Myers Squibb, Bayer, and Novartis, all outside the submitted work. OTB has received research funding from AstraZeneca, Pfizer, and Roche, and honoraria from AstraZeneca, Pfizer, Roche, MSD, Boehringer Ingelheim, Bristol Myers Squibb, Novartis, Bayer, Takeda, and Sanofi Aventis in the past 36 months, all outside the submitted work. All other authors declare no competing interests.

Data sharing

The study protocol is available in the appendix. Individual data will not be made publicly available. The study started enrolment in 2014, and we did not plan for data sharing when we designed and initiated the trial.

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Paper II

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Patient-reported health-related quality of life from a randomized phase II trial comparing standard-dose with high-dose twice daily thoracic radiotherapy in limited stage small-cell lung cancer

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ABSTRACT

Objectives: In a randomized phase II trial, twice daily (BID) thoracic radiotherapy (TRT) of 60 Gy/40 fractions improved survival compared with 45 Gy/30 fractions in limited stage small-cell lung cancer (LS SCLC). Notably, the higher dose did not cause more toxicity. Here we present health related quality of life (HRQoL) reported by the trial participants during the first 2 years.

Materials and methods: 170 patients were randomized 1:1 to TRT of 45 Gy or 60 Gy concurrently with cisplatin/etoposide chemotherapy. The 150 patients who commenced TRT and completed a minimum of one HRQoL-questionnaire were included in the present study. Patients reported HRQoL on the European Organization for Research and Treatment of Cancer Core 30 and Lung Cancer 13 Quality of Life Questionnaires. Questionnaires were completed weeks 0, 4 (before TRT), 8 (end of TRT), 12 (response evaluation after chemoradiotherapy) and 16 (end of prophylactic cranial irradiation), then every 10 weeks year one, and every 3 months year two. Primary HRQoL endpoints were dysphagia and dyspnea. A difference in mean score of $\geq$10 was defined as clinically significant.

Results: Maximum dysphagia was reported on week 8, with no significant difference between treatment arms (mean scores 45 Gy: 44.2, 60 Gy: 51.1). The 60 Gy arm had more dysphagia in the convalescence period, but dysphagia scores returned to baseline levels at week 16 in both arms. For dyspnea there were no significant changes, or differences between treatment arms, at any timepoint. There were no significant differences between treatment arms for any other HRQoL-scales.

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Conclusion: TRT of 60 Gy did not cause significantly higher maximum dysphagia, though patients on the 60 Gy arm reported more dysphagia the first 8 weeks of convalescence. The higher dose was well tolerated and is an attractive alternative to current TRT schedules in LS SCLC.
Trial reg Clinicaltrials.gov NCT0204184.

1. Introduction

Small cell lung cancer (SCLC), accounting for 13% of lung cancer cases, is a malignancy with an aggressive clinical course [1]. At the time of diagnosis, approximately one-third of the patients have limited-stage (LS SCLC). Standard treatment for these patients is concurrent chemotherapy and thoracic radiotherapy [2,3]. Up to 36% are alive after 5 years, but since the majority of the patients experience relapse and die from SCLC, there is a need for better treatment [4–6].

Approximately 1/3 of patients experience local failure, and it has been hypothesized that higher doses of thoracic radiotherapy (TRT) might improve local control and, thereby survival [5]. We conducted a phase II trial comparing high-dose, twice-daily (BID) TRT of 60 Gy in 40 fractions with the standard dose of 45 Gy BID in 30 fractions, and our primary analyses show that the high-dose arm achieved a significantly improved 2-year survival (primary endpoint, 74% vs. 48%; p = .0005) and median overall survival (37.2 vs. 22.6 months; p = .012) [7]. This is the first randomized trial of LS SCLC to show a significant survival improvement in more than 20 years. Objectively assessed toxicity did not reveal any significant differences between the treatment arms, and the proportion of patients who experienced severe radiotoxicity was lower than in older trials and similar to other, recent trials of TRT in LS SCLC [5,6,8–10].

Several studies conclude that physicians often underestimate treatment related side-effects, and that patient reported outcomes provide important additional information about the impact of cancer therapies [11,12]. It is well known that a large proportion of LS SCLC patients experience severe treatment toxicity, and radiotherapy induced esophagitis appears to be an important reason for the poor implementation of twice-daily TRT in LS SCLC [5,6,13,14]. However, to our knowledge, a previous study by our group is the only other randomized study of TRT in LS SCLC including patient reported HRQoL [8]. Our trial participants reported health related quality of life (HRQoL) on validated questionnaires. The aim was to assess patient reported HRQoL before, during, and after study treatment and compare HRQoL between patients receiving standard dose (45 Gy) and those receiving the high dose (60 Gy) BID TRT.

2. Methods

2.1. Design and approval

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

2.2. Patients and treatment

Details on the trial design are published earlier [7]. Briefly, patients ≥ 18 years, performance status (PS) 0–2, and confirmed LS SCLC receive 4 courses of platinum/etoposide and were randomized stratifying for PS, stage, and presence of pleural effusion to TRT of in 30 fractions or 60 Gy in 40 fractions. Whole body FDG PET was mandatory for staging and TRT target volumes were limited positive lesions. TRT started 20–28 days after the first day of course of chemotherapy. Responders were offered irradiation of 25–30 Gy in 10–15 fractions. Patients were every 10 weeks year 1, every 3 months years 2–3, and every years 4–5. Relapses were treated according to each hospital's routine. The first publication reported treatment outcomes when the primary endpoint, 2-year survival, was assessed in July 2020, which was also when data collection for the present study was completed. Final survival data will be published when all patients have been followed for five years (June 2023).

2.3. Patient reported outcomes

Patients reported HRQoL on the European organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) version 3 and its lung cancer module, the Quality-of-Life Questionnaire-Lung Cancer 13 (QLQ-LC13). The questionnaires are translated and validated into more than 100 languages, including Norwegian, Danish, and Swedish, and are among the most commonly used for assessing HRQoL in lung cancer research [15–17].

The QLQ-C30 consist of five multiple-items functional scales (social, emotional, cognitive, role, and physical), three multiple-item symptom scales (fatigue, pain, and nausea/vomiting), six single-item symptom scales (insomnia, constipation, diarrhea, loss of appetite, dyspnea, and financial impact), and global quality of life (one multiple-item scale). The HRQoL questionnaire LC-13 measures dyspnea on a multiple-item scale. The single items measure hair loss, hemoptysis, cough, soremouth, neuropathy, dysphagia, pain medicine use, pain in chest, arms, shoulder, or other parts. A higher score on global QoL and functional scales reflects a better HRQoL, a higher score on the symptom scales represents a worse HRQoL.

Patients completed the questionnaires on paper at weeks 0 (inclusion), 4 (before TRT), 8 (end of TRT), 12 (response evaluation), 16 (end of PCI), every 10 weeks year one and every 3 months year two, as well as after progression. Questionnaires were handed to the patients by study personnel at all timepoints in Sweden and Denmark. In Norway, the questionnaires were handed to patients by study personnel at baseline, before and after TRT. At all other timepoints, questionnaires were mailed to the patients from the study office. The patients returned the completed questionnaires in an enclosed, prepaid envelope. A reminder was mailed to patients if completed questionnaires were not received at the study office within two weeks.

2.4. Endpoints

The primary HRQoL-endpoints were defined as dysphagia and dyspnea reported on the LC- 13. All other HRQoL items were defined as secondary endpoints. The period of interest was defined as the time from randomization until the primary endpoint of 2-year survival.

2.5. Analyses

The study was powered for the primary endpoint of 2-year survival [7], and no estimation of power for the HRQoL analyses was performed. Raw scores were transformed to a scale from 0 to 100 according to the EORTC scoring manual [18], and compared between each timepoint and between treatment arms. We did not perform imputations of missing data.

According to Osoba et al and Kings et al, a change in mean score of 5–10 indicate a little change, while a change in mean score of 10–20 indicate a moderate change [19,20]. Based on these studies, a difference in mean score of 10 is commonly defined as the minimum required to detect a clinically significant difference in randomized clinical trials on

HRQoL [21]. Consequently, we defined a difference in mean scores of ≥ 10 as the clinical significance level in the present study. As discussed in the paper by Maringwa et al, in this setting, p-values does not provide information about clinical important differences in mean scores between groups or changes over time [21], and thus, we omitted statistical testing.

Finally, we performed exploratory analyses of the difference in numbers of patients with any (score > 0) or maximal level (score of 100) of dysphagia between treatment arms and change in dysphagia from baseline in individual patients.

3. Results

3.1. Participants

From July 8th 2014 to June 6th 2018, 176 patients were included, of these 170 eligible patients were randomised and included in the efficacy analyses (60 Gy: 89, 45 Gy: 81), 166 received TRT and were included in the safety population (60 Gy: 89, 45 Gy: 77). Of these, 150 patients (60 Gy: 80, 45 Gy: 70) completed at least one HRQoL questionnaire and were included in the present HRQoL-analyses (Fig. 1).

3.2. Baseline characteristics

Median age was 65 years, 43 (28%) were ≥70 years, 86 (57%) women, 146 (97%) current/former smokers, 133 (88%) had PS 0–1, 134 (89%) stage III disease (TNM v.7), 13 (8%) pleural effusion, and 31 (20%) a weight loss of >5% three months before enrolment. Baseline characteristics were well balanced between treatment arms (Table 1).

Table 1
Baseline characteristics.

		45 Gy (n=70)		60 Gy (n=80)	
		n	%	n	%
Age	Median (range)	65 (36-80)		65 (46-79)	
	≥70 years	23	32.9%	20	25.0%
Gender	Female	43	61.4%	43	53.8%
Performance status	0	29	41.4%	38	47.5%
	1	33	47.1%	35	43.8%
	2	8	11.5%	7	8.7%
Stage	IA	2	2.9%	-	-
	IIA	5	7.1%	9	10.1%
	IIB	4	5.7%	5	5.6%
	IIIA	24	34.3%	38	42.7%
	IIIB	35	50.0%	37	41.6%
Pleural fluid	Yes	5	7.1%	8	10.0%
Smoking history	Current	53	75.7%	49	61.3%
	Former	15	21.4%	29	36.3%
	Never	2	2.9%	1	1.3%
	Missing	-	-	1	1.1%
Pack years	Median (range)	30 (4-80)		35 (5-114)	
Weight loss last 3 months before inclusion	>5%	16	22.9%	15	18.8%
	Missing	7	10.0%	12	15%

3.3. Completion of HRQoL questionnaires

The completion rate of the questionnaires were 64–77% of patients in the intention-to-treat population (n = 170) being alive at each timepoint and similar in both arms (Fig. 2). At baseline, 123/170 (72%) patients completed the questionnaires. The lowest completion rate was at end of radiotherapy (week 8: 98/165 alive [59%]), the highest at week 12 (127/164 alive [77%]) and was 64–73% for the remaining study period. Among patients with recurrent disease the completion rate varied between 25 and 71%. During the second year of the study period 32–38% of the questionnaires were completed by patients with recurrent disease (Fig. 2).

3.4. Dysphagia and dyspnea

Overall, the baseline mean score of dysphagia was 10, the maximum mean score was 47 reported at week 8. Compared to baseline mean scores (45 Gy: 5.9, 60 Gy: 13.6), patients in both treatment arms reported a clinically significant higher mean score at week 8 and 12. The maximum mean scores were reported at week 8 (end of TRT) in both arms (45 Gy: 44.2, 60 Gy: 51.1). Patients in the 60 Gy arm reported significantly more dysphagia at week 12 and 16 than patients in the 45 Gy arm, though at week 16, the differences in mean scores from baseline values were less than 10 points in both arms (45 Gy: 7.1, 60 Gy: 17.5) (Fig. 3).

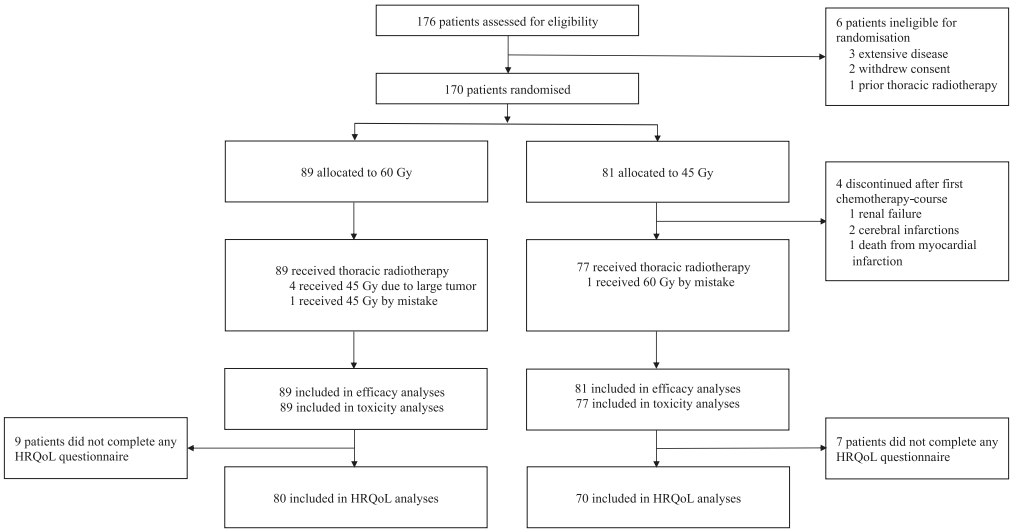

Fig. 1. Consort diagram.

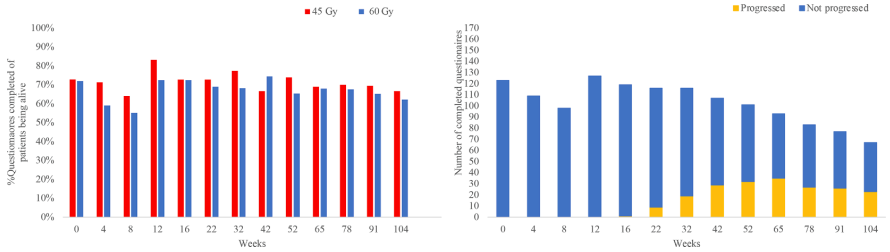

Fig. 2. A) Completion rate of HRQoL questionnaires of patients (intention-to-treat population) being alive at each timepoint split for treatment arm and B) Number of HRQoL questionnaires completed at each timepoint including disease status.

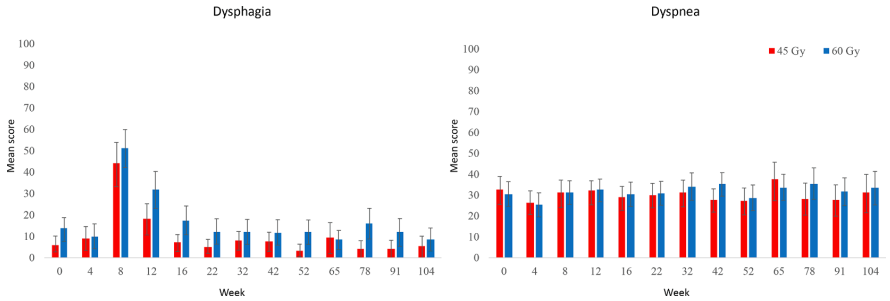

Fig. 3. Mean scores for A) dysphagia and B) dyspnea as reported on the LC-13 questionnaire split for treatment arms. The error bars show the 95% confidence intervals for the mean scores. A higher score represents more symptoms.

The proportions of patients reporting any dysphagia (score > 0) at week 8 or 12 were 44 of 71 (62%) and 52 of 67 (77%) for patients receiving 45 Gy and 60 Gy respectively. The proportions reporting maximum (score of 100) dysphagia week 8 or 12 were 12 of 71 (17%) and 10 of 67 (15%) for patients receiving 45 Gy and 60 Gy, respectively.

Mean score for dyspnea did not change significantly during the study period, and there were no differences between the study arms (Fig. 3).

3.5. Remaining HRQoL scales

For all other HRQoL scales there were no clinically significant differences between treatment arms. There were, however, some clinically significant changes during the study periods for some scales. Patients developed alopecia during the chemotherapy. Overall, there was a decline in cognitive functioning and an increase in neuropathy that exceeded 10 points during the study period. Patients reported more chest-pain at the end of TRT (week 8). After TRT ended (week 8 and 12) there was a transient lower score for role- and social functioning as well as a higher score of fatigue. Emotional functioning increased from baseline and remained stable throughout the study period (Fig. 4).

4. Discussion

In this first trial comparing high-dose with standard-dose twice-daily thoracic radiotherapy in LS SCLC, patients reported an increase in mean scores of dysphagia from 10 points at baseline to 47 points at the end of TRT. Interestingly, there was no significant difference in maximum mean scores between the treatment arms, and no difference in the proportion of patients who reported maximal score of 100 for dysphagia at the end of TRT. Patients receiving the high-dose reported more dysphagia at week 12 and 16 compared to patients receiving the standard-dose, though at week 16, the differences in mean scores from baseline levels were less than 10 points in both treatment arms. There were no significant differences in any of the other HRQoL-scales between the treatment arms.

We are only aware of one other randomized controlled trial of TRT in LS SCLC that included patient reported HRQoL. In this previous randomized phase II trial by our group, we compared hypo-fractionated once-daily TRT of 42 Gy in 15 fractions with 45 Gy twice daily in 30 fractions [8]. The design was similar to the present study, and patients reported HRQoL on the same questionnaires and at similar timepoints. Patients reported significantly higher mean scores for dysphagia after TRT (42 OD: 61, 45 BID: 72) than in the present study (45 Gy: 44.2, 60 Gy: 51.1) [7,8]. In both studies, patients recovered from dysphagia during the 8 weeks after completing TRT. This difference in maximum mean scores for dysphagia between our former and the present trial, corresponds well to the difference in physician reported severe esophagitis, which was observed in 30% of participants in the former trial vs. 20% in the present trial [7,8]. The lower frequency of dysphagia is probably explained by the fact that the former study included elective nodal irradiation, while we limited radiotherapy fields to FDG PET CT positive lesions in the recent trial [6,22–24].

Few studies of LS SCLC have included patient reported HRQoL. In a systematic review of RCT on lung cancer from 2012 to 2018, only 10 out of 122 studies included patients with SCLC [25]. Of these, only two reported HRQoL-data, but the study participants had extensive stage SCLC [26,27]. There were no comparable studies included in a systematic review of HRQoL-data in SCLC [28]. We are aware of three other randomized trials of high-dose TRT in LS SCLC and hitherto, none have reported patient reported outcomes [6,9,10].

The varying completion rate of the questionnaires at different timepoints is a potential limitation of our study. However, the overall completion rate was similar to other studies on HRQoL in lung cancer [29,30]. The lowest completion rate was at the end of TRT at week 8. The most likely explanation is that study personnel forgot to hand out the questionnaire at this timepoint, but we cannot rule out that the lower completion rate was related to treatment toxicity [31]. Furthermore, patients completed HRQoL questionnaires also after progression, and

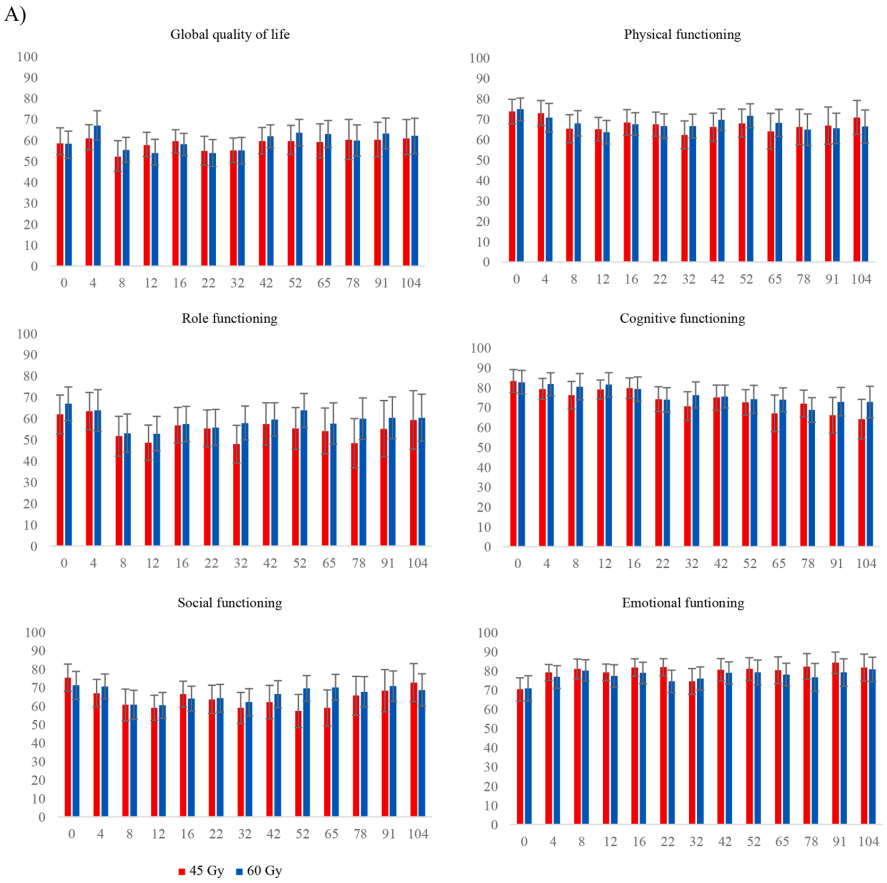

Fig. 4. Mean scores for the remaining scales on the EORTC C30 and LC-13 quality of life questionnaires split for treatment arms. The error bars represent 95% confidence intervals. A) Global quality of life and functional scales on the C30; B) Symptom scales on the C30; C) LC-13 scales. A higher score on the symptom scales reflects more symptoms, while a higher score on the functional scales indicates a better function. The last plot shows proportions of patients using pain medication.

quality of life scores might be influenced by progressive disease and relapse treatment. However, as few patients progressed the first months, results mainly reflects discomfort from chemoradiotherapy.

Differences in radiotherapy technique, anatomical distribution and extent of disease might have influenced our results. However, there was no difference in TNM (version 7) stage between the treatment arms. All radiotherapy plans are currently being reviewed and we will publish comprehensive data on distribution and localization of lesions and normal tissue irradiation separately.

Despite evidence of improved survival, twice daily thoracic radiotherapy has not been widely implemented in clinical practice, mainly due to fear of severe esophagitis [14,32]. Our study shows that there are no longer reasons for such concerns since dysphagia caused by twice daily TRT is transient. This was also observed in our previous study, in which patients reported significantly more esophageal toxicity than in the present study [8]. Thus, the clinical impact of dysphagia is limited, and should not prevent patients from receiving BID TRT.

It has been stated that BID TRT is inconvenient for the patients and that it might impact their quality of life [33]. Our study was not designed to clarify whether twice daily TRT impacts quality of life more than once daily TRT, but the transient and modest change in role- and social functioning and fatigue indicates that the impact on quality of life of twice daily TRT was minimal. The increase in reported chest pain after radiotherapy is most likely due to esophagitis. Alopecia and neuropathy are well known side-effects of platinum/etoposide chemotherapy [34,35]. Emotional functioning improved from baseline, possibly because of the strong association between emotional burden and symptom burden. It is well known that many SCLC patients respond rapidly to chemotherapy and such response might relieve both symptoms and emotional burden [36,37].

There was also a steady, but modest decline in cognitive functioning. There are concerns that PCI cause cognitive deficits [38,39], but on the other hand, it has repeatedly been shown that PCI improves survival [40,41]. It is not possible to accurately assess the causes of the cognitive decline. We did not perform more comprehensive, objective tests of cognitive function, and our study was not designed to thoroughly assess associations between comorbidity, treatment toxicity, disease development, brain metastases and cognitive function. Studies show that chemotherapy might also affect cognitive functioning [42]. Furthermore, most patients have a history of tobacco smoking, and many suffer from cardiovascular comorbid conditions that might negatively affects cognitive functioning [43].

The present study adds further evidence on how BID TRT is perceived by patients. The maximum dysphagia is much lower compared to our

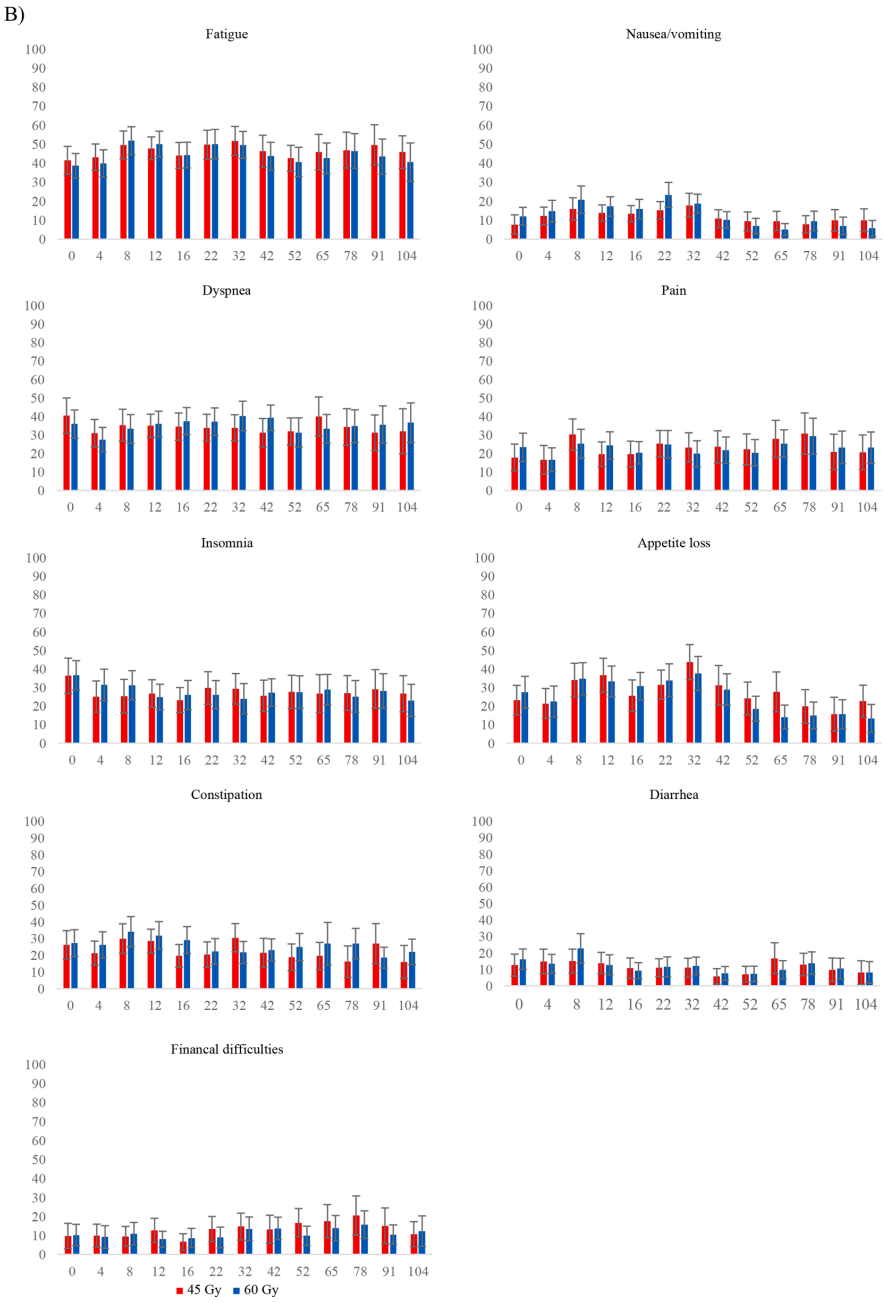

Fig. 4. (*continued*).

previous study, even though half of the patients received a higher TRT dose, since we limited the radiotherapy fields to PET CT positive lesions, while all patients in our former trial received elective nodal irradiation [8]. In our opinion, the transient impact of the higher dose with respect to dysphagia, is acceptable considering the large survival benefit of the higher dose. The normal tissue constraints in our trial were based on accepted norms for conventional, once-daily, TRT schedules [44], and our study results indicate that these constraints are relevant and acceptable also for BID TRT.

5. Conclusion

In conclusion, there was no difference in maximum mean dysphagia between the treatment arms, but patients in the 60 Gy arm reported a

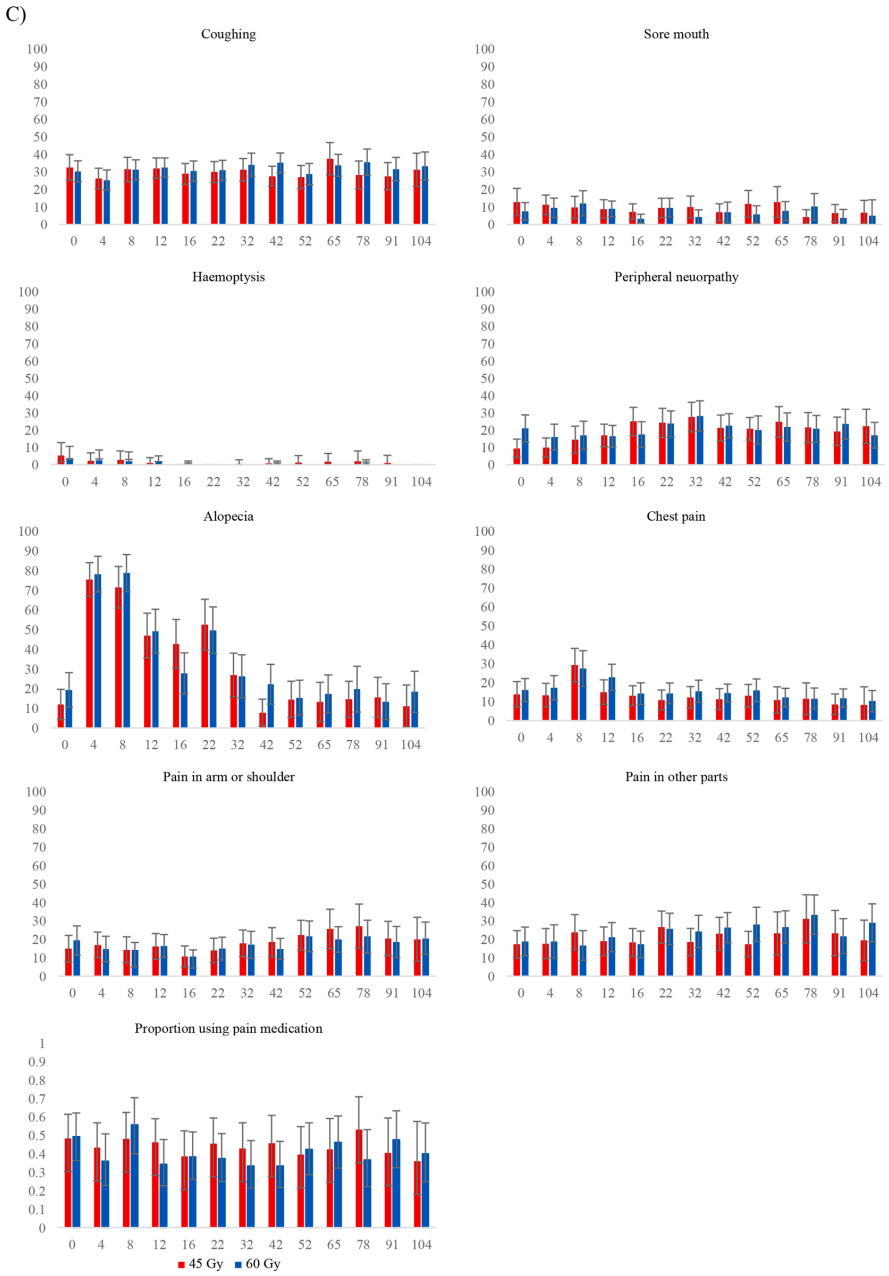

Fig. 4. (*continued*).

higher level of dysphagia compared to patients in the 45 Gy arm during the convalescence period. There were no significant differences between treatment arms in other HRQoL-scales, and overall, patients reported small changes in HRQoL during the first two years. These patient-reported data support the conclusion from our main report, that 60 Gy BID is well tolerated, and given the large survival benefit, an alternative to current TRT schedules in LS SCLC.

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CRediT authorship contribution statement

Kristin Toftaker Killingberg: Project administration, Data curation, Validation, Formal analysis, Writing – original draft, Writing – review & editing. **Tarje Onsøien Halvorsen:** Project administration, Methodology, Formal analysis, Writing – review & editing, Supervision, Validation. **Øystein Fløtten:** Data curation, Writing – review & editing. **Odd Terje Brustugun:** Conceptualization, Data curation, Writing – review & editing. **Seppo W. Langer:** Conceptualization, Data curation, Writing – review & editing. **Jan Nyman:** Conceptualization, Project administration, Data curation, Writing – review & editing. **Kjersti Hornslien:** Data curation, Writing – review & editing. **Tesfaye Madebo:** Data curation, Writing – review & editing. **Tine Schytte:** Project administration, Data curation, Writing – review & editing. **Signe Risum:** Data curation, Writing – review & editing. **Georgios Tsakonas:** Data curation, Writing – review & editing. **Jens Engleson:** Data curation, Writing – review & editing. **Bjørn Henning Grønberg:** Conceptualization, Funding acquisition, Project administration, Methodology, Data curation, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Paper III

ORIGINAL ARTICLE

Treatment Outcomes of Older Participants in a Randomized Trial Comparing Two Schedules of Twice-Daily Thoracic Radiotherapy in Limited-Stage SCLC

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ABSTRACT

Introduction: Half of the patients with limited-stage SCLC (LS SCLC) are above or equal to 70 years old, but they account for less than 20% of participants in most trials. Comorbidities and reduced organ and physical function might lead to more treatment toxicity, and population-based studies indicate that fewer older than younger patients with LS SCLC receive standard chemoradiotherapy, although there is limited evidence for such a policy.

Methods: We compared baseline characteristics, comorbidity, survival, treatment completion, toxicity, health-related quality of life, and treatment outcomes between patients above or equal to 70 years old and those younger than 70 years old in an open-label, randomized phase II trial comparing twice-daily thoracic radiotherapy of 45 Gy in 30 fractions with 60 Gy in 40 fractions in LS SCLC. All patients received concurrent i.v. cisplatin (75mg/m^2) or carboplatin (AUC 5-6 mg/ml x min) day 1 and i.v. etoposide (100 mg/m^2) day 1-3 chemotherapy. This trial is registered at ClinicalTrials.gov (NCT02041845).

Results: A total of 170 patients who were above or equal to 18 years old and had performance status of 0 to 2 were randomized. Of these, 53 patients (60 Gy: 25, 45 Gy: 28) were above or equal to 70 years old and 117 (60 Gy: 64, 45 Gy: 53) were younger. There were no differences in baseline characteristics, treatment completion rates, toxicity, or response rates across the age groups. Health-related quality of life mean scores were similar during year one, but older patients reported more decline on functional scales than younger patients during year two. Overall survival was shorter for older patients, whereas there was no difference in progression-free survival or time to progression.

Conclusions: Patients above or equal to 70 years old tolerated concurrent twice-daily chemoradiotherapy and achieved similar disease control as younger patients, indicating older patients should receive the same treatment as younger patients.

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Introduction

Standard treatment for fit patients with limited-stage SCLC (LS SCLC) is concurrent platinum/etoposide chemotherapy and thoracic radiotherapy (TRT) followed by prophylactic cranial irradiation (PCI) to those who respond to chemoradiotherapy (CRT).[1–6] Five-year survival rates are 25% to 34%.[7–9]

The proportion of patients aged 70 years or older diagnosed with having SCLC increased from 23% in 1975 to 44% in 2010,[10] and as the world's population is aging, the number of older patients with lung cancer is expected to increase exponentially in the next 20 years.[11–13] There is, however, little evidence for how to treat older patients because they are underrepresented in clinical trials.[14,15] The proportion of participants aged above or equal to 70 years varies between 13% and 21% in recent clinical trials of LS SCLC.[16–19] Population-based studies reveal that the proportion of patients receiving standard CRT decreases with age,[20–24] most likely due to concerns about toxicity. A considerable proportion (up to 33%) of participants in trials of CRT in LS SCLC experience severe toxicity.[7,25–27] Comorbidities and reduced organ and physical function make older patients more vulnerable to treatment toxicity, and they might be less able to tolerate side effects when they occur.[28–31]

We conducted a randomized phase II trial comparing twice-daily TRT of 45 Gy in 30 fractions to 60 Gy in 40 fractions. All patients were to receive four courses of i.v. cisplatin (75 mg/m^2) or carboplatin (AUC 5-6 mg/ml x min.) day 1 and i.v. etoposide (100 mg/m^2) day 1-3 chemotherapy, and PCI was offered to the responders. The higher TRT dose resulted in a significantly improved 2-year survival (primary end point) (74% versus 48%; $p < 0.01$) and median overall survival (OS) (37.2 versus 22.6 mo; $p = 0.012$) without adding toxicity.[32] There was no upper age limit in this trial, and 31% of the patients were 70 years old or older.

The aim of the present study was to compare baseline characteristics, treatment completion, toxicity, health-related quality of life (HRQoL), and treatment outcomes between patients below 70 years old and those who were 70 years old or older.

Materials and Methods

Design and Approval

This open-label, randomized phase 2 trial was approved by the Regional Ethics Board in Gothenburg, Sweden, the Regional Committee for Medical Research Ethics, Central Norway, and the National Committee on Health Research Ethics in Denmark.

This subgroup analysis of patients 70 years old or older was preplanned. The primary end point was OS. Secondary end points were toxicity and HRQoL, whereas exploratory end points included response rates, progression-free survival (PFS), and time to progression (TTP).

Patients and Treatment

Details on trial design are published earlier.[32] Between July 2014 and June 2018, 170 patients at 22 Scandinavian hospitals diagnosed with having LS SCLC were included in this randomized, controlled phase 2 study. Median follow-up was 49 months, and all patients were followed up for a minimum of 2 years at the time of the primary analyses. All deaths considered related to the treatment occurring any time during the study period or any death occurring within 4 weeks after completion of the study treatment was reported as a fatal event. Patients aged above or equal to 18 years with performance status (PS) of 0 to 2 received four courses of i.v. cisplatin (75 mg/m^2) or carboplatin (AUC 5-6 mg/ml) day 1 and i.v. etoposide (100 mg/m^2) day 1-3 chemotherapy and were randomized to receive TRT of 45 Gy in 30 fractions or 60 Gy in 40 fractions. Whole-body 18F-fluorodeoxyglucose positron emission tomography computed tomography (FDG PET-CT) was mandatory for staging, and TRT target volumes were limited to FDG PET-CT positive lesions. PCI of 25 to 30 Gy in 10 to 15 fractions was offered to those who responded to CRT. Relapses were treated according to each hospital's routine.

Assessments

Comorbidity was assessed at inclusion using the Charlson Comorbidity Index (CCI),[33] and divided into three groups (CCI 0, 1, $\geq$2), as this categorization is frequently used in studies of patients with cancer.[23,34–36]

Stage of disease was assessed according to TNM version 7,[37] toxicity according to the Common Terminology Criteria for Adverse Events (version 4.0),[38] and treatment response according to the Response Evaluation Criteria in Solid Tumors (version 1.1).[39]

Patients reported HRQoL on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30 (QLQ-C30) version 3 and its lung cancer module, the Quality of Life Questionnaire—Lung Cancer 13 (QLQ-LC13).[40,41] The QLQ-C30 consists of five multiple-item functional scales (social, emotional, cognitive, role, and physical), three multi-item symptom scales (fatigue, pain, and nausea/vomiting), six single-item symptom scales (insomnia, constipation, diarrhea, loss of appetite, dyspnea, and financial impact), and one multi-item scale (global QoL). The QLQ-LC13 measures

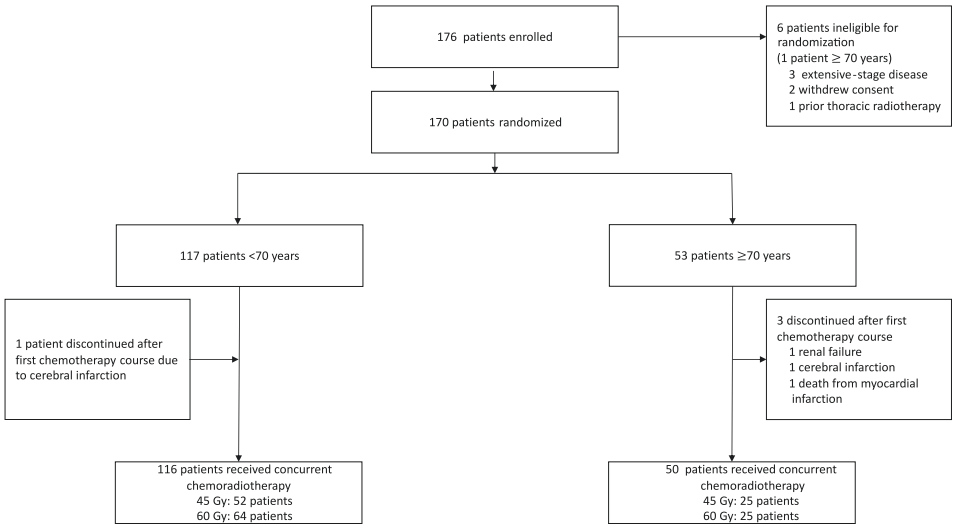


Figure 1. Patient selection.

dyspnea on a multiple-item scale. The single-item scales measure hair loss, hemoptysis, cough, sore mouth, neuropathy, dysphagia, pain (in the chest/arms/shoulder/other parts), and use of pain medication. A higher score on global QoL and functional scales reflects a better HRQoL, and a higher score on the symptom scales represents a worse HRQoL.

Patients completed the questionnaires on paper at week 0 (inclusion), week 4 (before TRT), week 8 (end of TRT), week 12 (response evaluation), week 16 (end of PCI), every 10 weeks on year one, every 3 months on year two, and at progression. Raw scores (the average of the items that contribute to the scale) were transformed to a scale from 0 to 100 according to the European Organisation for Research and Treatment of Cancer scoring manual.[42] Mean scores for each scale or single item were compared between the age groups at each time point. A difference in mean score of 10 or more was considered clinically relevant.[43] Global QoL, physical function, dysphagia, and dyspnea were defined as the primary HRQoL end points. Global QoL and physical function were measured on multi-item scales on the QLQ-C30, whereas the QLQ-LC13 was used to measure dyspnea on a multi-item scale and dysphagia on a single-item scale.

Analyses

OS, PFS, and TTP were estimated using the Kaplan-Meier method. Survival was compared with univariable and multivariable Cox proportional hazards regression models. Logistic regression was used for univariable and multivariable analyses of 2-year survival. Pearson's chi-square test or Fisher's exact test was used to compare baseline characteristics, toxicity, and overall response rates. Multivariable models were adjusted for TRT schedule, sex, age ($<$70 y versus $\geq$70 y), performance status (0 versus 1 versus 2), stage of disease (I–II versus III), presence of pleural fluid (yes versus no), and CCI score (0 versus 1 versus $\geq$2). Reported p values are two sided, and a p less than 0.05 was considered statistically significant. All analyses were performed using SPSS version 27.

Results

Participants

All 170 participants were included in the present efficacy analyses (60 Gy: 89, 45 Gy: 81). Of these, 117 (69%) were below 70 years, 53 (31%) above or equal to 70 years, 20 (12%) above or equal to 75 years, and five (3%) above or equal to 80 years.

Among the 166 patients who commenced TRT and were included in the toxicity analyses, 116 (70%) (60 Gy: 64, 45 Gy: 52) were below 70 years and 50 (30%) (60 Gy: 25, 45 Gy: 25) were above or equal to 70 years (Fig. 1).

Overall, median age was 65 years (36–82 y), 97 (57%) were women, 166 (98%) were current or former smokers, 152 (89%) had Eastern Cooperative Oncology Group performance status of 0 to 1, 142 (84%) had stage III disease, and 13 (8%) had pleural effusion. There were no statistically significant differences in baseline characteristics between younger and older patients (Table 1).

Table 1. Baseline Characteristics

Baseline Characteristics		<70 y (n = 117)		≥70 y (n = 53)		p
		n	%	n	%	
Age	Median (range)	61 (36-69)		74 (70-82)		
Thoracic radiotherapy	45 Gy	53	45	28	53	
	60 Gy	64	55	25	47	0.36
Sex	Female	67	57	30	57	0.94
Performance status	0	57	49	21	40	
	1	51	44	25	47	
	2	9	8	7	13	0.38
Stage	I-II	20	17	8	15	
	III	97	83	45	85	0.75
Pleura fluid	Yes	9	8	4	8	0.97
Smoking history	Never	2	2	1	2	
	Former	34	29	21	40	
	Current	81	69	30	56	0.34
	Unknown			1	2	
Pack years	Median (range)	35 (10-114)		31 (4-273)		
Charlson Comorbidity Index total score	0	52	44%	19	36%	
	1	35	30	15	28	
	≥2	30	26	19	36	0.37

CCI Score

Overall, 71 patients (42%) had no comorbidity (CCI 0) (<70 y: 44%, ≥70 y: 36%), 50 (29%) had a CCI of 1 (<70 y: 30%, ≥70 y: 28%), and 49 (29%) had a CCI of greater than or equal to 2 (<70 y: 26%, ≥70 y: 36%). There were no statistically significant differences in CCI scores between the two age groups ($p = 0.37$) (Table 1).

Treatment Completion

Most of the patients (90%) completed all four courses of chemotherapy (<70 y: 92%, ≥70 y: 85%; $p = 0.46$). There were no statistically significant differences in the proportions who had reductions of chemotherapy doses or delays of chemotherapy courses (<70 y: 85%, ≥70 y: 92%; $p = 0.19$), completed TRT as planned (<70 y: 95% versus ≥70 y: 92%; $p = 0.37$), or received PCI (<70 y: 85% versus ≥70 y: 75%; $p = 0.13$) or second-line therapy (<70 y: 51% versus ≥70 y: 38%; $p = 0.10$) (Table 2).

Grade 3 to 4 Toxicity

Overall, grade 3 to 4 toxicity was reported for 89% of the patients who commenced TRT. There were no statistically significant differences in the proportions who experienced any grade 3 to 4 toxicity (<70 y: 85%, ≥70 y: 92%, $p = 0.31$), grade 3 to 4 hematological toxicity (<70 y: 82%, ≥70 y: 92%; $p = 0.11$), or grade 3 to 4 nonhematological toxicity (<70 y: 52%, ≥70 y: 48%; $p = 0.74$). Furthermore, there were no significant differences in the proportions who experienced neutropenic infections (<70 y: 31%, ≥70 y: 36%; $p = 0.53$) or any of the most important radiotherapy-related toxicities,

Table 2. Treatment Completion and Response Rates

Treatment Completion and Response Rates	<70 y (n = 117)		≥70 y (n = 53)		p
	n	%	n	%	
Completed TRT as planned	111	95	49	92	0.37
Completed 4 cycles of chemotherapy	108	92	45	85	0.46
No dose reduction or delay of chemotherapy	18	15	4	8	0.19
Carboplatin instead of cisplatin for >1 course	41	35	24	45	0.23
Prophylactic cranial irradiation	100	85	40	75	0.13
Second-line therapy	60	51	20	38	0.10
Overall response rate	94	80	37	70	0.13

TRT, thoracic radiotherapy.

Table 3. CTCAE Grade 3 to 5 Toxicity in Patients Who Commenced Thoracic Radiotherapy

Patients Who Commended TRT	<70 y (n = 116)		≥70 y (n = 50)		
Toxicity	Grades 3-4	Grade 5	Grades 3-4	Grade 5	*p*
Any toxicity	99 (85)	2 (2)	46 (92)	2 (4)	0.31
Any hematological toxicity	95 (82)	1 (2)	46 (92)	1 (2)	0.11
Any nonhematological toxicity	60 (52)	1 (2)	24 (48)	1 (2)	0.74
Esophagitis	24 (21)		9 (18)		0.69
Pneumonitis	2 (2)		1 (2)	1 (2)	0.90
Anemia	19 (16)		10 (20)		0.57
Thrombocytopenia	25 (22)		15 (30)		0.24
Neutropenia	94 (81)		40 (80)		0.93
Neutropenic infection	36 (31)		18 (36)	1 (2)	0.53
Thrombocytopenic bleeding	1 (1)				0.14
Infection	5 (4)		2 (4)		0.14
Kidney failure	16 (14)		4 (8)		0.42
Nausea	8 (7)		1 (2)		0.80
Fatigue	1 (1)				0.85
Erythema			1 (2)		0.13
Headache	1 (1)		1 (2)		0.36
Neuropathy	1 (1)				0.43
Myelopathy	1 (1)				0.51
Myocardial infarction	1 (1)				0.51
Aortic dissection	1 (1)				0.51
Ototoxicity	2 (2)		1 (2)		0.31
Thromboembolism	2 (2)		1 (2)		0.80

Note: All values are n (%).
CTCAE, Common Terminology Criteria for Adverse Events; TRT, thoracic radiotherapy.

pneumonitis (<70 y: 2%, ≥70 y: 2%; $p = 0.90$), or esophagitis (<70 y: 21%, ≥70 y: 18%; $p = 0.69$) (Table 3).

Fatal Events

There were six fatal events during the study treatment period. Three patients above or equal to 70 years (one from myocardial infarction, one from neutropenic infection, and one from pneumonitis) and three patients below the age of 70 years (one from aortic dissection, one from thrombocytopenic bleeding, and one from cerebral infarction) died. Of these, one patient in each age group died from a thromboembolic event before TRT was commenced. The proportion of fatal events did not differ significantly between the two age groups (<70 y: 3 of 117 [2.6%], ≥70 y: 3 of 53 [5.7%], $p = 0.31$) (Table 3).

Response to Treatment, PFS, and TTP

The overall response rate was 77% and did not differ between the age groups (>70 y: 80%, ≥70 y: 70%; $p = 0.13$) (Table 2).

Overall, PFS was 15.0 months (95% confidence interval [CI] 10.2–19.9) with no significant difference between the age groups (<70 y: 15.9 mo [95% CI 8.5–23.3], ≥70 y: 12.2 mo [95% CI 7.5–17.0], $p = 0.13$) (Fig. 2*B*).

For the whole cohort, TTP was 16.0 months (95% CI 10.1–21.8). There was no significant difference between the age groups (<70 y: 18.6 mo [95% CI 10.4–26.8], ≥70 y: 15.8 mo [95% CI 8.6–23.0], $p = 0.96$) (Fig. 2*C*).

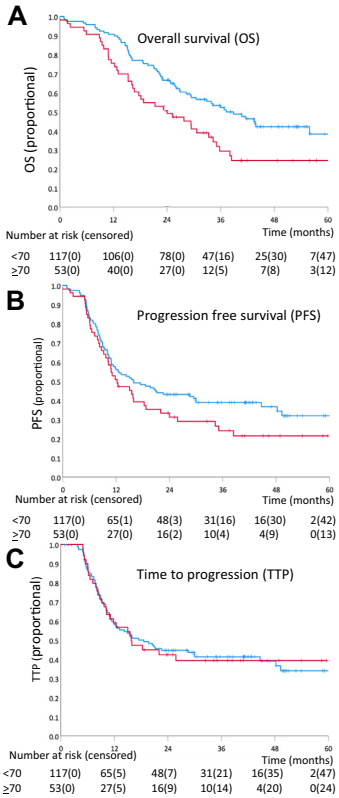
There were no statistically significant differences in PFS or TTP between TRT schedules in either age group (Supplementary Fig. 1).

OS and Two-Year Survival

For the whole cohort, two-year survival rate was 62% and median OS was 33.2 months. There was no statistically significant difference in two-year survival (<70 y: 67% [95% CI 57–75], ≥70 y: 51% [95% CI 37–65]; $p = 0.061$), but median OS was longer among younger patients (<70 y: 37.2 mo [95% CI 27.6–46.8], ≥70 y: 24.0 mo [95% CI 12.9–35.2]; $p = 0.009$) (Fig. 2*A*).

In univariable analysis with age as a continuous variable, there was a trend toward shorter survival with increasing age (hazard ratio 1.03, 95% CI 1.00–1.05; $p = 0.055$).

In multivariable analyses of OS, TRT of 60 Gy ($p = 0.009$), female sex ($p = 0.035$), age below 70 years ($p = 0.046$), and a lower CCI score ($p = 0.002$) were significantly associated with increased survival time. TRT of 60 Gy ($p = <0.001$), stages I to II disease ($p = 0.045$), and a lower CCI score ($p = 0.037$) were associated with improved 2-year survival rate.



	Median OS	95% CI	HR	95% CI	p
< 70 years	37.2	27.6–46.8	1		
≥ 70 years	24.0	12.9–35.2	1.71	1.14–2.56	0.009

	Median PFS	95% CI	HR	95% CI	p
< 70 years	15.9	8.5–23.3	1		
≥ 70 years	12.2	7.5–17.0	1.35	0.92–1.99	0.13

	Median TTP	95% CI	HR	95% CI	p
< 70 years	18.6	10.4–26.8	1		
≥ 70 years	15.8	8.6–29.0	1.0	0.6–1.5	0.96

Figure 2. (*A*) OS, (*B*) PFS, and (*C*) TTP according to age groups. CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

Among younger patients, the higher TRT dose provided a survival benefit (60 Gy: 54 mo, 45 Gy: 44 mo; $p = 0.018$), whereas this was not the case among older patients (60 Gy: 44 mo, 45 Gy: 35 mo; $p = 0.42$) (Supplementary Fig. 1).

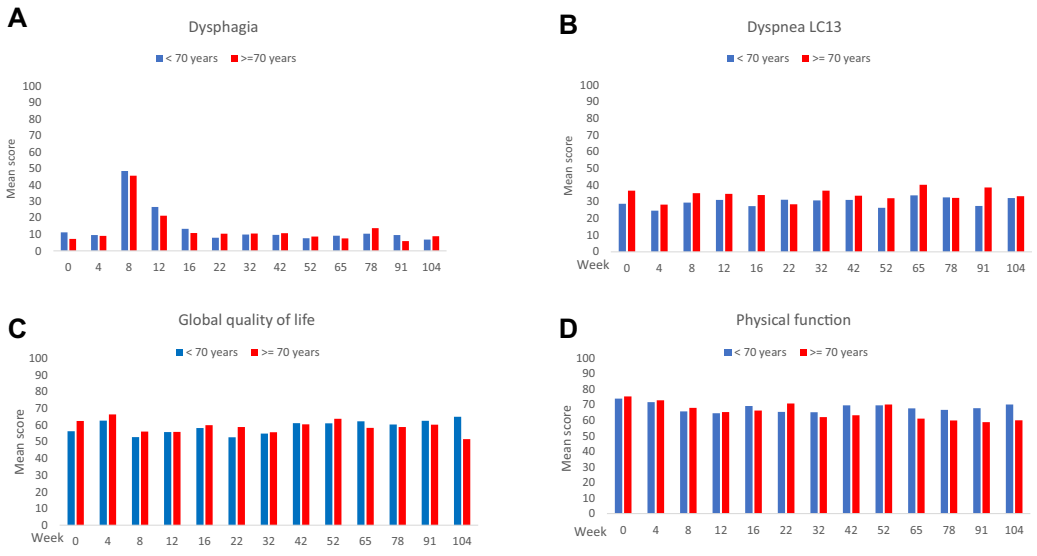
Health-Related Quality of Life

Of the patients commencing TRT, 150 (88%) completed at least one HRQoL questionnaire. The completion rate ranged from 59% to 80% of patients alive at different time points and was comparable for the two age groups (Fig. 3*E*).

There were no clinically relevant differences in mean scores for dyspnea or dysphagia between the age groups at any time point. There were no differences in global QoL or physical functioning between the age groups during the first year. For patients aged 70 years or older, there was a clinically relevant decline in physical functioning during the second year which was not reported by the younger age group (Fig. 3*A*–*D*). The older patients also reported a similar decline in role and social functioning and an increase in fatigue. For cognitive functioning, there was a clinically relevant decline for both age groups, but the reduction was larger among older patients. Emotional functioning remained stable for older patients, whereas younger patients reported marked better emotional functioning on the second year after treatment (Supplementary Fig. 2).

Discussion

In this preplanned subgroup analysis of our trial of high-dose versus standard-dose twice-daily TRT in LS SCLC, we found that older patients completed TRT to the same degree as their younger counterparts, and they did not experience more severe radiotoxicity. There was no difference in completion of chemotherapy, and the frequencies of severe hematological toxicity, neutropenic infections, or fatal events were not different between older and younger patients. These findings were supported by the HRQoL analyses which did not reveal any clinically relevant differences between younger and older patients during the first year of follow-up. Patients



E

Week	0	4	8	12	16	22	32	42	52	65	78	91	104
<70 years	70	65	59	76	69	73	74	72	70	77	72	76	65
≥70 years	77	65	61	80	80	68	73	76	68	63	69	61	59

% completion rate of HRQoL questionnaires

Figure 3. Mean scores for (*A*) dysphagia and (*B*) dyspnea as reported on the QLQ-LC13 questionnaire and (*C*) global quality of life and (*D*) physical function reported on the C30 questionnaire split for age groups. (*E*) % completion rate among patients alive. HRQoL, health-related quality of life; QLQ-LC13, Quality of Life Questionnaire—Lung Cancer 13.

above 70 years old had a shorter OS, but there were no differences in overall response rates, PFS, or TTP.

This is one of few studies of older patients with LS SCLC receiving CRT based on prospectively collected data, the only study in which all patients received twice-daily TRT, the only including high-dose, twice-daily TRT, and to best of our knowledge, the only to include patient-reported outcomes. Eligibility criteria for our trial were liberal with respect to comorbidity, and we allowed patients with performance status of 2.

According to a pooled analyses of 11 randomized controlled trials of CRT of LS SCLC, older patients complete treatment less often than younger patients and discontinue treatment due to death, adverse events, and treatment refusal more often than their younger counterparts.[16] Schild et al.[18] and Christodoulou et al.[19] found that older patients received less chemotherapy, whereas in the CONVERT trial, older patients received less radiotherapy but not less chemotherapy. In our study, fewer older patients completed four cycles of chemotherapy and doses were reduced more often than among younger patients, though the differences were not statistically significant. Nevertheless, compared with other subgroup analyses of older patients with LS SCLC receiving CRT, the completion rates of both chemotherapy (85% versus 64%–78%) and radiotherapy (92% versus 73%) in our trial are among the highest reported.[16–19]

Several studies report the frequency of treatment toxicity split for age groups. Some have found more hematological toxicity among older patients, but similar to what we observed, older patients do not seem to have more radiotoxicity than younger patients,[16,17,19,23] except in one study that found more deaths from pneumonitis among older patients.[18] Nevertheless, studies are not necessarily comparable due to differences in staging procedures, target volume definitions, and radiotherapy planning techniques. In contrast to our findings, most other studies report more fatal events (6%–10% versus 0.5%–3%) among older patients.[16–18] The exception is the CONVERT trial,[19] in which 4% of older patients, similar to what we observed, died during the study treatment period.

Results of studies of the impact of age on survival in LS SCLC are not consistent. In the Intergroup 0096 trial, younger patients had a higher 5-year OS,[17] whereas a pooled analyses of 11 randomized controlled trials of CRT in LS SCLC concluded that older patients had worse

OS and PFS.[16] In contrast, older patients in the CONVERT trial and the trial by Schild et al.[18] and Christodoulou et al.[19] had similar survival as younger patients. Most studies report a median OS of 13.5 to 17.8 months for patients 70 years old or older,[13,16–18,20,24,44] except the CONVERT trial, which reported similar survival as in our study (2-y OS: 53%, median OS: 29 mo).[19] More importantly, population-based studies strongly indicate that older patients who receive CRT live much longer than those who receive chemotherapy alone.[20,44] Notably, the 2-year survival rate of 51% and median OS of 24 months for patients older than 70 years in our study is similar to overall results in many population-based studies and trials of LS SCLC independent of age.[16,24–27,45]

In our study, there was no statistically significant difference in PFS across the age groups and TTP was similar for older and younger patients, possibly indicating the treatment effect on the SCLC was similar for both age groups, that the survival difference might reflect that fewer older patients received relapse therapy, and that some deaths among the older patients were due to other causes than SCLC (competing risk). Considering that most relapses occur within 1 to 2 years and that locoregional tumor control results in less symptoms and better QoL, we believe that these data suggest that older patients benefit from CRT even if survival is shorter than that for younger patients. Furthermore, studies conclude that older patients consider local control and QoL as important as survival.[46,47]

Few studies of LS SCLC have included HRQoL, and we are not aware of other studies of this population which have compared HRQoL across age groups. We did not find any differences in patients reported HRQoL during the first year of follow-up, but older patients reported a larger decrease in functional scales and higher score of fatigue than younger patients during year two. Furthermore, they had a larger decline in cognitive functioning. One possible explanation is that CRT affects older patients more over time than younger patients. There are concerns that PCI causes cognitive deficits, and studies reveal that the impact increases with age.[48–50] Nevertheless, during the second year of the study period, the number of completed questionnaires decreased in both age groups and 32% to 38% of the questionnaires were completed by patients with recurrent disease. Furthermore, a high proportion in the older age group had comorbidities (64%). Thus, it is not possible to assess whether the changes in HRQoL were due to disease progression, long-term side effects of CRT, or deterioration of concurrent diseases or conditions.

The main limitation of our study is the sample size that limits the ability to perform meaningful subgroup analyses. Most importantly, it is difficult to assess whether older patients benefit from the 60 Gy schedule. Among older patients, participants in the high-dose arm had a numerically longer median OS, PFS, and TTP than in the control arm, and considering that older patients did not have more toxicity than younger patients, our study indicates that also older patients should be offered the higher TRT dose. Even though the sample size is limited, more than 31% of the patients in our trial were 70 years old or older, which is a higher proportion than in most studies of CRT in LS SCLC (13%–21%)[16–19] and numerically within the same range as previous studies (n = 50–67 patients).[17–19] Furthermore, the proportion of patients 70 years old or older is similar to a population-based study of patients with LS SCLC receiving CRT from the Netherlands.[24]

Even though the proportion who experienced severe toxicity was not higher among older patients, the study was not designed to assess how long patients had side effects or how much supportive care was needed, and we cannot rule out that the impact on patients' functional level was different between the age groups. This might explain why chemotherapy was more often discontinued and doses were more often reduced among older patients, though the difference was not statistically significant. That being said, severe toxicity is also very common among younger patients with LS SCLC who receive CRT, and it is important to monitor all patients closely and provide timely and sufficient supportive care for patients to be able to complete this potentially curative treatment.

We did, however, not collect data on patients considered ineligible for the trial (screen failures), and most likely, the proportion of elderly patients enrolled was lower than that for younger patients. Thus, it is possible that the older patients in our study were more fit than the average patient with LS SCLC older than 70 years.

In conclusion, we found that patients 70 years old or older were able to complete chemotherapy and twice-daily TRT, overall and in the high-dose arm. They tolerated the therapy well, toxicity was transient, and HRQoL was preserved on the first year after therapy, though older patients reported a larger decline in HRQoL functional scales during year two than younger patients. Survival was shorter for older patients, but considering there were no statistically significant differences in PFS or TTP, our study indicates that older patients with LS SCLC should be offered similar, twice-daily TRT, as younger patients.

CRediT Authorship Contribution Statement

Kristin Toftaker Killingberg: Project administration, Data curation, Validation, Formal analysis, Original draft, Writing—review and editing.

Bjørn Henning Grønberg: Conceptualization, Funding acquisition, Project administration, Methodology, Data curation, Writing—review and editing, Supervision.

Marit Slaaen: Writing—review and editing.

Øyvind Kirkevold: Writing—review and editing.

Tarje Onsøien Halvorsen: Project administration, Methodology, Formal analysis, Writing—review and editing, Supervision, Validation.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2023.01.012.

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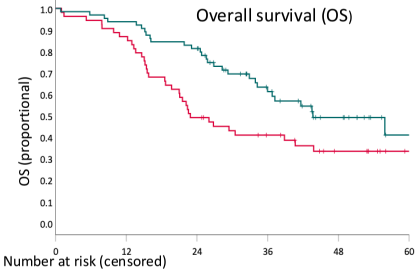
Supplementary Figure 1 A) Overall survival, B) progression free survival and C) time to progression for patients <70 years according to treatment arm. D) Overall survival, E) progression free survival, and F) time to progression for patients ≥70 years according to treatment arm.

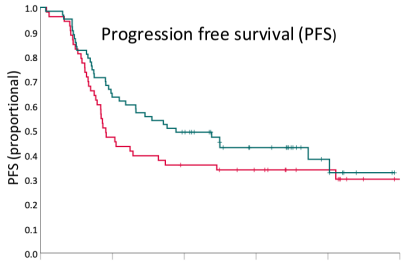
<70 years

A



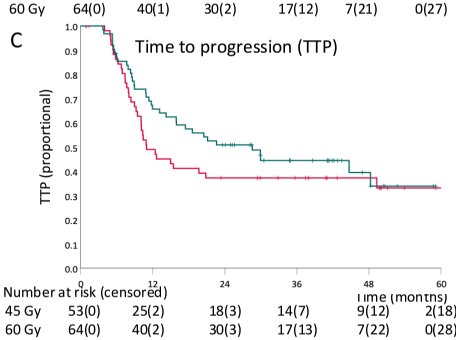
	Median OS	95% CI	p-value
60 Gy	43.7	27.6-46.8	0.018
45 Gy	22.9	16.8-29.0	

B



	Median OS	95% CI	p-value
60 Gy	22.6	10.4-34.9	0.22
45 Gy	10.9	8.3-13.5	

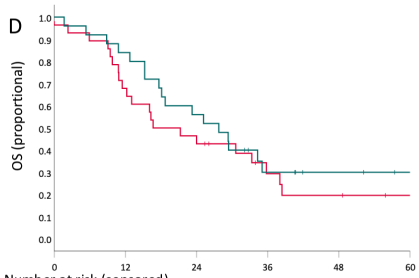
C



	Median OS	95% CI	p-value
60 Gy	28.6	16.0-41.2	0.27
45 Gy	11.0	6.2-15.8	

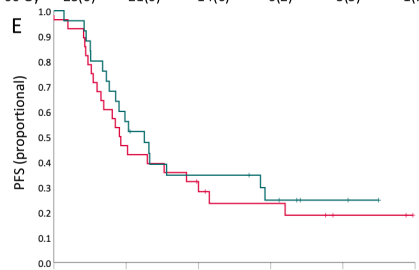
≥70 years

D



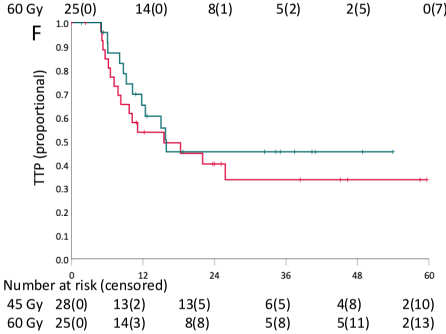
	Median OS	95% CI	p-value
60 Gy	27.8	17.8-37.7	0.42
45 Gy	16.7	6.5-27.0	

E



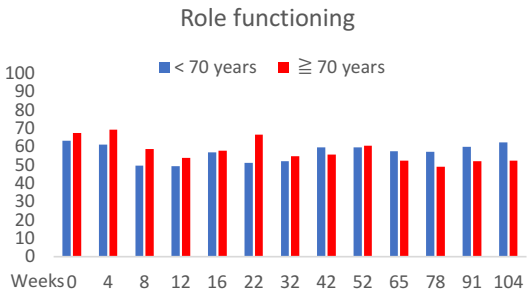
	Median OS	95% CI	p-value
60 Gy	15.0	8.8-21.2	0.52
45 Gy	10.9	7.6-14.2	

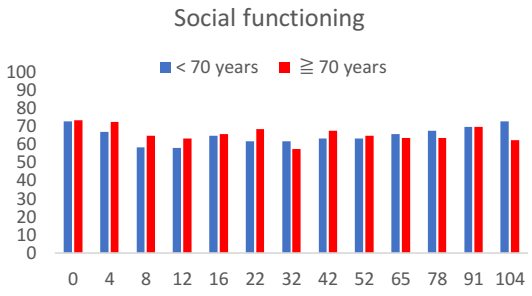
F

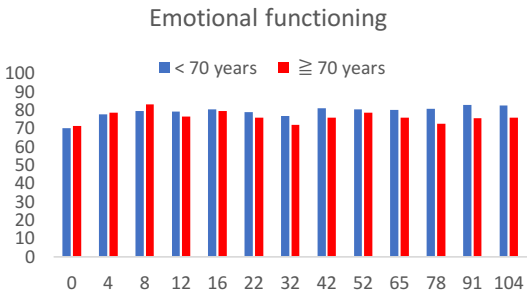


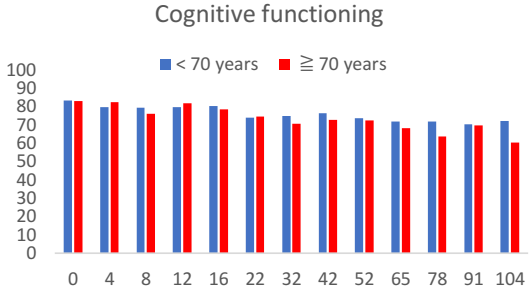
	Median OS	95% CI	p-value
60 Gy	15.5	NA	0.44
45 Gy	15.9	3.4-27.7	

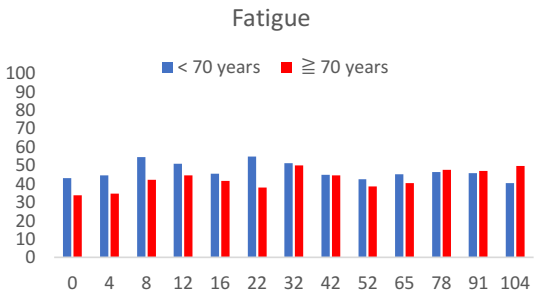
Supplementary Figure 2
Mean scores for functional scales and fatigue reported on the C30 questionnaire split for age groups.











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