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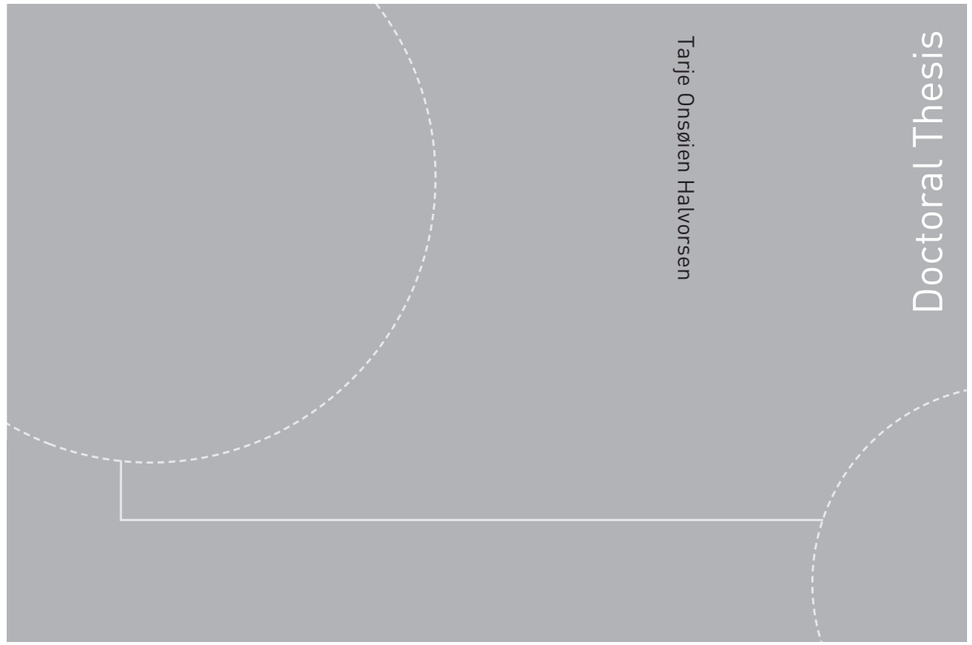

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Tarje Onsøien Halvorsen

Thoracic radiotherapy in limited disease small cell lung cancer

NTNU
Norwegian University of
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Thesis for the degree of Philosophiae Doctor

Trondheim, January 2017

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Thoraksbestråling ved småcellet lungekreft, begrenset sykdom

Lungekreft er den kreftsykdommen som tar flest liv. Småcellet lungekreft (SCLC) er svært aggressiv og utgjør en av syv lungekreft-tilfeller. Mange pasienter med SCLC responderer på behandling, men effekten er kortvarig og de fleste pasientene dør av kreftsykdommen.

Basis i behandlingen er cellegift. En kombinasjon med strålebehandling øker overlevelsen, og gis dersom alle svulster kan inkluderes i et strålefelt (”begrenset sykdom” - LD SCLC). En av fire pasienter kan bli kurert av en slik kombinasjon av cellegift og strålebehandling, men behandlingen er assosiert med alvorlige bivirkninger.

Strålebehandlingen kan gis på flere måter, og det har ikke vært enighet om hva som er best. To små daglige doser strålebehandling gir bedre overlevelse, men også mer bivirkninger. Det har derfor vært vanlig i Norge, og mange andre steder, å gi strålebehandling i form av en litt større daglig dose.

Som de første i verden har Norsk Lunge Cancer Gruppe (NLCG) sammenliknet disse to måtene å gi strålebehandling på. Strålebehandling to ganger daglig ga bedre overlevelse, uten å øke graden av alvorlige bivirkninger. Vår studie understøtter derfor at strålebehandling to ganger daglig skal være standard.

Pasienter med LD SCLC har ofte flere andre alvorlige sykdommer, grunnet høy alder og langvarig tobakksrøyking. Studier viser at slike pasienter ikke tilbys strålebehandling, i frykt for at nytten ikke skal stå i forhold til bivirkningene. Vi fant at pasienter med flere sykdommer ikke hadde mer bivirkninger eller dårligere overlevelse. De bør derfor vurderes for behandling på lik linje med andre pasienter.

Vi identifiserte pasienter med dårlig prognose ved å måle effekt av behandling allerede etter første kur, og videre forskning kan avklare om disse pasientene vil ha bedre nytte av annen behandling.

Name of candidate:	**Tarje Onsøien Halvorsen**
Department:	**Department of Cancer Research and Molecular Medicine**
Main supervisor:	**Bjørn Henning Grønberg**
Co-supervisor:	**Stein Kaasa**
Funding:	**Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU)**

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The public defence takes place at auditorium MTA in Medical Technology Research Centre
Friday 27th January 2017 at 12.15 pm

Norsk sammendrag

Lungekreft er den tredje hyppigste kreftformen, og den ledende årsaken til kreftrelaterte dødsfall. Småcellet lungekreft (SCLC) er den mest aggressive av to hovedtyper lungekreft, og forekommer nesten utelukkende hos røykere. Mange har uhelbredelig sykdom med spredning, "utbredt sykdom" (ED SCLC), på diagnosetidspunktet. Dersom all påvist sykdom kan innbefattes i et tolerabelt strålefelt, er stadiet "begrenset sykdom" (LD SCLC).

En kombinasjon av cellegifter er hovedbehandlingen ved småcellet lungekreft, og fire til seks kurer med cisplatin og etoposid er det anbefalte regimet. Samtidig thorakal strålebehandling øker overlevelsen hos de med LD SCLC, og en av fire kan oppnå langtidsoverlevelse med slik behandling. Thorakal strålebehandling gis på mange måter. Strålebehandling to ganger daglig i tre uker er oftest anbefalt i retningslinjer, basert på en studie som viste at regimet ga lengre overlevelse enn én stråledose daglig i 5 uker. Ulempen var mer bivirkninger fra spiserøret, og regimet har aldri vært sammenliknet med det å gi en større daglig dose i 3 uker, som ofte har vært foretrukket fordi det er mer praktisk.

Mange pasienter med LD SCLC har andre samtidige sykdommer (komorbiditet) grunnet høy alder og langvarig tobakksrøyking. Pasienter med komorbiditet mottar sjeldnere standard behandling pga. frykt for bivirkninger og antatt dårligere utbytte av behandlingen. Imidlertid foreligger det lite kunnskap som understøtter en slik behandlingspolitikk.

De fleste pasientene med LD SCLC (>80%) responderer på behandlingen, men flesteparten får tilbakefall innen 1-2 år og dør av sykdommen. Vi vet lite om hvilke pasienter som har best effekt av behandlingen.

Norsk Lunge Cancer Gruppe (NLCG) har gjennomført en randomisert klinisk studie for å sammenlikne strålebehandling en versus to ganger daglig over 3 uker. Pasienter som fikk to stråledoser daglig oppnådde oftere komplett respons, og hadde en 6 måneder lengre overlevelse, men forskjellen nådde ikke statistisk signifikans. Det var ingen forskjell i bivirkninger mellom de to armene i studien. Pasienter med komorbiditet tolererte behandlingen like godt og hadde sammenliknbar overlevelse med pasienter uten komorbiditet. De fleste pasientene (94%) hadde en reduksjon i tumorstørrelse etter første kur. Det var en positiv sammenheng mellom reduksjon i

tumorstørrelse og utfall av behandling, men selv pasienter uten en reduksjon hadde mye lengre overlevelse enn ved ED SCLC.

Vår studie understøtter at pasienter med LD SCLC bør få to stråledoser daglig, og at pasienter med komorbiditet skal tilbys samme behandling som andre. Respons etter første cellegiftkur er positivt assosiert med utfall av behandling, men kan ikke brukes til å identifisere pasienter som ikke skal ha strålebehandling. Videre studier må gjøres for å avklare hvorvidt respons på første cellegiftkur kan brukes til å individualisere behandlingen for pasienter med LD SCLC.

English summary

Lung cancer is the third most common type of cancer, and the leading cause of cancer related deaths. Small cell lung cancer (SCLC) is the most aggressive of two main types of lung cancer, almost exclusively appearing in smokers. Many patients have incurable disease with widespread metastases, “extensive disease” (ED SCLC), at time of diagnosis. If all proven disease can be encompassed by a tolerable radiotherapy field, the stage is “limited disease” (LD SCLC).

Combination chemotherapy is the main treatment of SCLC, and four to six courses of cisplatin and etoposide is the recommended schedule. The addition of thoracic radiotherapy improves survival in LD SCLC, and one in four can achieve long-term survival with this treatment. Thoracic radiotherapy is delivered in many ways. Twice daily radiotherapy in three weeks is often recommended in guidelines, based on a study that demonstrated improved survival compared to once daily radiotherapy in five weeks. The disadvantage was increased toxicity form the oesophagus and the schedule has never been compared to one larger dose once daily in three weeks, commonly preferred because it is more convenient.

Many patients with LD SCLC have other coexisting conditions (comorbidity) due to high age and a long history of tobacco smoking. Patients with comorbidity are offered standard treatment less often due to concerns of toxicity and expectations of a poorer benefit from treatment. However, there is little evidence supporting such a treatment policy.

Most patients with LD SCLC (>80%) responds to treatment, but most experience a relapse within 1-2 years and eventually die from the disease. There is little knowledge regarding who will benefit most from treatment.

The Norwegian Lung Cancer Group (NLCG) has conducted a national randomised clinical trial to compare once and twice daily radiotherapy in three weeks.

Patients receiving twice daily radiotherapy achieved a complete response more often, and had a six months longer survival, but the difference was not statistically significant. There was no difference in toxicity between treatment arms. Patients with comorbidity had a similar tolerance and survival to patients without comorbidity. Most patients (94%) had a reduction in size of tumours after the first course of chemotherapy. There was a positive association between reduction in size

and outcomes from therapy, but even patients without a reduction had a much longer survival than in ED SCLC.

Our study underpins that patients with LD SCLC should be offered twice daily radiotherapy, and that patients with comorbidity should be offered the same treatment as others. Response after the first course of chemotherapy is positively associated with outcomes from treatment, but cannot be used to identify patients that should not be offered radiotherapy. Further research can decide if response to the first course of chemotherapy can be used to individualise treatment of patients with LD SCLC.

Table of contents

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when I need it the most, and for being patient with me at other times. You will always be most important to me. This is also the time to apologise to my dear friends for the multiple conversations on slightly involuntary topics related to my PhD during these years. I will try to improve. I may not succeed.

This thesis is dedicated to the patients that took part in this research project, some of whom I got to meet. Unneeded to say, this could not have been done without you. Your contribution has been very meaningful to future patients. Thank you!

Trondheim, September 2016
Tarje Onsøien Halvorsen

List of papers

I Gronberg BH, Halvorsen TO, et al. **Randomized phase II trial comparing twice daily hyperfractionated with once daily hypofractionated thoracic radiotherapy in limited disease small cell lung cancer**. Acta Oncologica. 2016 May;55(5):591-7.

II Halvorsen TO, Sundstrøm S, et al. **Comorbidity and outcomes of concurrent chemo- and radiotherapy in limited disease small-cell lung cancer**. Acta Oncologica. 2016 Aug;55(11):1349-1354.

III Halvorsen TO, Herje M, et al. **Tumour size reduction after the first chemotherapy-course and outcomes of chemoradiotherapy in limited disease small-cell lung cancer**. Lung Cancer. 2016 Dec;102:9-14

Abbreviations

ABMT	Autologous Bone Marrow Transplantation
A-CCI	Age-adjusted Charlson Comorbidity Index
ACE-27	Adult Comorbidity Evaluation 27
ACTH	Adrenocorticotropic Hormone
ADH	Antidiuretic Hormone
ADL	Activities of Daily Life
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
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
CCNU	Cyclonexyl-Chloroethyl-Nitrosourea (lomustine)
CGA	Comprehensive Geriatric Assessment
CIRS-G	Cumulative Illness Rating Scale for Geriatrics
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA4	Cytotoxic T-Lymphocyte Associated protein 4
CTV	Clinical Target Volume
DLCO	Diffusing capacity of the Lung for Carbon monoxide
DLL3	Delta (Drosophila)-Like 3 protein
DVH	Dose-Volume Histogram
ED SCLC	Extensive Disease Small Cell Lung Cancer
ENI	Elective Nodal Irradiation
EORTC	European Organization for Research and Treatment of Cancer

ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration (USA)
FEV	Forced Expiratory Volume
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GGT	Gamma-Glutamyl Transferase
GTV	Gross Tumour Volume
G8	Geriatric 8
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
IASLC	International Association for the Study of Lung Cancer
IGRT	Image Guided Radiotherapy
IM	Internal Margin
IMRT	Intensity Modulated Radiation Therapy
IP	Irinotecan and Cisplatin
K+	Potassium
LDH	Lactate Dehydrogenase
LD SCLC	Limited Disease Small Cell Lung Cancer
MRC-BS	Medical Research Council Breathlessness Scale
MRI	Magnetic Resonance Imaging
Na+	Sodium
NCI	National Cancer Institute (USA)
NLCG	Norwegian Lung Cancer Study Group
NRS	Numerical Rating Scale
NSCLC	Non-Small-Cell Lung Cancer
NSE	Neurone Specific Enolase
NT	Neurotoxicity
OD	Once Daily
OS	Overall Survival
PCI	Prophylactic Cranial Irradiation
PD	Progressive Disease
PD-1	Programmed cell Death protein 1
PE	Cisplatin and Etoposide

PET	Positron Emission Tomography
PET-CT	PET and CT combined
PFS	Progression-Free Survival
PG-SGA	Patient-Generated Subjective Global Assessment
POP	Population-based study
PR	Partial Response
PRO	Prospective study
PROM	Patient Reported Outcome Measure
PS	Performance Status
PTD	Primary Tumour Diameter
PTH	Parathyroid hormone
PTV	Planning Target Volume
QALE	Quality-Adjusted Life Expectancy
QoL	Quality of Life
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	Randomised Controlled Trial
RER	Retrospective Review
RR	Response Rate
SCLC	Small Cell Lung Cancer
SCS	Simplified Comorbidity Score
SD	Stable Disease
SER	Time from Start of treatment until End of Radiotherapy
SNI	Selective Nodal Irradiation
SOD	Sum of Diameters
SR	Sedimentation Ratio
TKI	Tyrosine Kinase Inhibitor
TNM	Tumour, Nodes and Metastasis
TRT	Thoracic Radiotherapy
VALG	Veterans Administration Lung Study Group (USA)
VCSS	Vena Cava Superior Syndrome
VMAT	Volumetric Modulated Arc Therapy

WHO	World Health Organization

1. Introduction

Lung cancer is the most common cause of cancer related deaths, causing 1.5 million deaths annually [1]. There are two main types of lung cancer; small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).

SCLC has a high sensitivity to both chemo- and radiotherapy, and combination chemotherapy is the basis treatment. The addition of thoracic radiotherapy (TRT) improves survival if all lesions can be encompassed by a tolerable radiotherapy field, known as limited disease small cell lung cancer (LD SCLC). Approximately 40% of patients with SCLC has LD [2].

Standard chemotherapy is a combination of cisplatin and etoposide. The optimal timing, dose and fractionation schedule of TRT is, however, debated. A 3-week schedule of twice daily (BID) radiotherapy is often recommended in guidelines, but has never been compared to a commonly used 3-week once daily hypofractionated (OD) schedule.

Many patients with LD SCLC suffer from comorbidity. Studies show that these patients often receive less chemoradiotherapy, probably due to concerns about toxicity, although there is little evidence supporting such a practice.

Even though most patients (>80%) will have an objective response, the majority will die from the disease. The addition of TRT to chemotherapy increases toxicity from treatment considerably. Early response to therapy might be associated with progression-free and overall survival, and possibly used to identify patients not benefitting from the addition of TRT.

We analysed patients enrolled in a randomised trial comparing TRT of 45 Gy/30 fractions (twice daily) and 42 Gy/15 fractions (once daily) in LD SCLC. The main aims of this PhD-project were to:

- investigate if hyperfractionated accelerated radiotherapy results in longer survival or more toxicity compared to hypofractionated accelerated radiotherapy.
- investigate if patients with comorbidity have more toxicity or inferior survival from chemoradiotherapy.
- evaluate tumour response from the first course of chemotherapy and its association with survival.

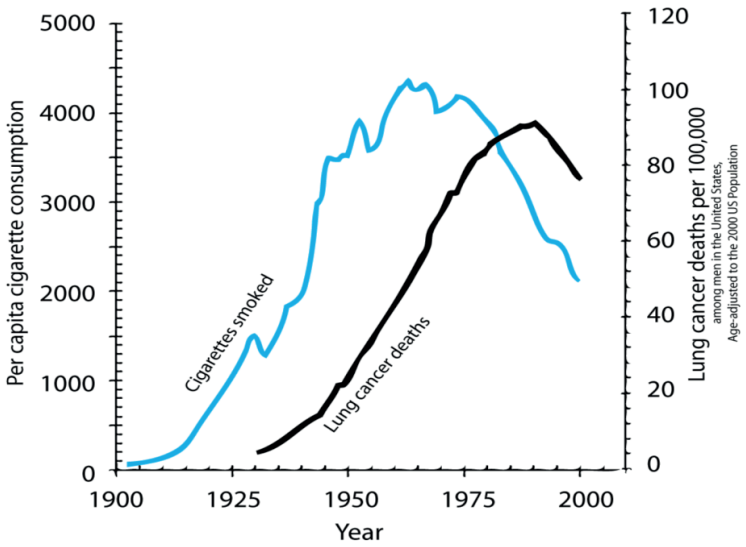
2. Background

2.1 Lung cancer

Lung cancer was first identified as a separate entity in 1815, when Laennec published the work “Encephaloides” [3]. The name was based on the macroscopic resemblance to brain tissue. At that time, lung cancer was a rare disease.

When cigarette smoking became popular during the beginning of the 20th century, lung cancer became increasingly common (Figure 1). Sir Richard Doll and Sir Austin Bradford Hill noted the association between tobacco smoking and incidence of lung cancer in 1950 [4]. Tobacco smoking causes 85-90% of cases [5]. Other risk factors include exposure to second-hand smoke, radon, asbestos, air-pollution and genetic factors.

Figure 1 Tobacco smoking and lung cancer. Figure copied from [6].

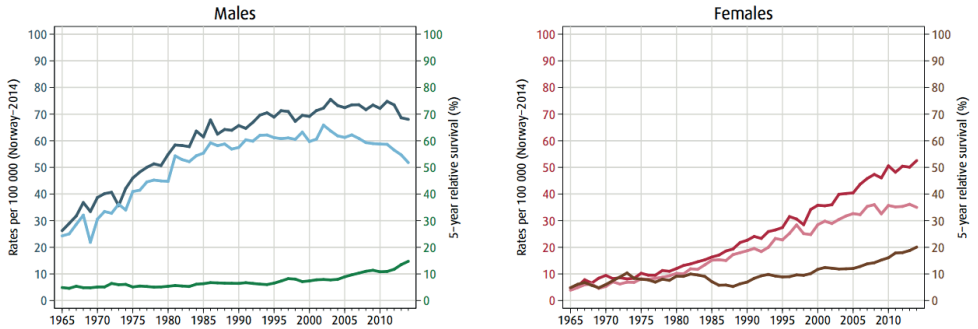


Lung cancer is the most common cause of cancer-related deaths (approximately 20%) and causes >1.5 millions deaths annually world-wide [1, 7, 8]. In 2014, 3019 patients were diagnosed with lung cancer in Norway, and 2158 died from the disease. It is the second most common cancer in men, and the third most common in women [7]. The incidence among men has decreased the last decade, while the incidence is still increasing in women (Figure 2) [7].

The probability of long-term survival decreases with increasing stage of lung cancer. Surgery is the preferred treatment modality in fit patients with localized disease. Inoperable patients may be offered curative intent oncological treatment in forms of radiotherapy, stereotactic radiotherapy or combined chemoradiotherapy. Few patients presenting with metastases can be cured, and have a median survival of approximately 9 months [9].

Due to advances in treatment, survival of lung cancer patients in Norway has improved since the year 2000, but remains low. The 5-year survival was 13% for men and 19% in women for the period between 2009 and 2014 (Figure 2) [7].

Figure 2 Incidence, mortality and 5-year survival from lung cancer in Norway (1965-2014). Figure copied from [7].



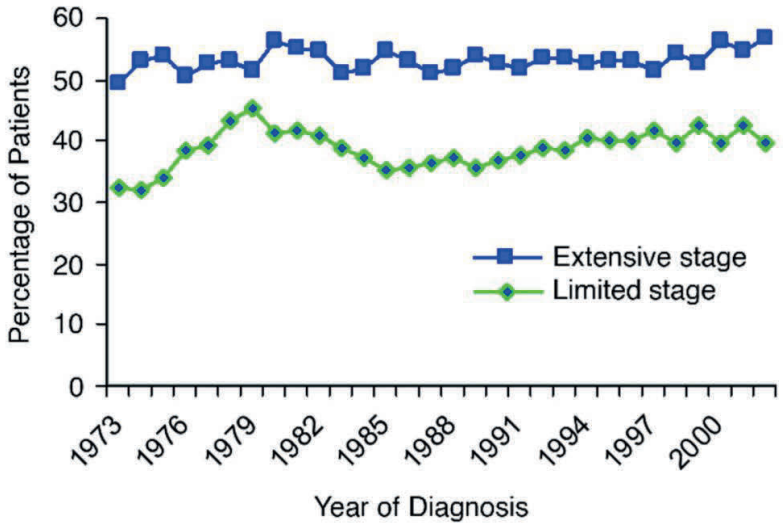
2.2 Small cell lung cancer (SCLC)

Small cell lung cancer was identified and described as a separate entity from non-small cell lung cancer in 1959-62 [10-12], due to a different clinical presentation, with few patients presenting with resectable disease, poor outcomes from surgery, and high response rates from chemotherapy [11, 13]. Compared to NSCLC, the association with tobacco smoking is stronger. While approximately 10-15% of lung cancers occur in non-smokers, SCLC is almost exclusively seen in heavy smokers and very rarely (<5%) in non-smokers [14-16].

2.2.1 Epidemiology

Internationally, there has been a decline in the proportion of lung cancers being SCLC, from 17% in 1986 to 13% in 2002 [2]. Of these, 40% have limited disease (LD SCLC), and this proportion has remained unchanged for decades (Figure 3) [2].

Figure 3 Stage distribution of SCLC over time. Figure copied from [2].



While 70% of cases were male in 1970, the distribution is now equal between genders (Figure 4) [2]. Both the decreasing proportion of SCLC among lung cancers and the increasing proportion of females with SCLC are thought to be related to changes in smoking habits and use of low-tar cigarettes [2, 17].

Most cases of SCLC (>95%) could have been avoided if tobacco-smoking was eliminated [16]. The prevalence of daily smokers in Norway has been halved the last decade, from 25% to 13%, and the prevalence among young male adults has decreased from 50% in 1985 to 21% in 2013 (Figure 5) [18, 19]. A similar trend is observed in other developed countries [20], but the estimated number of smokers is still close to a billion worldwide [21].

Untreated, median survival for SCLC is 2-4 months [22]. With treatment, median survival for LD SCLC is 18-24 months, and the 5-year survival is 20-25%, while for ED SCLC median survival is 9-12 months with less than 10% alive after 2 years [23, 24].

Figure 4 Diagnosis of SCLC by gender. Figure copied from [2].

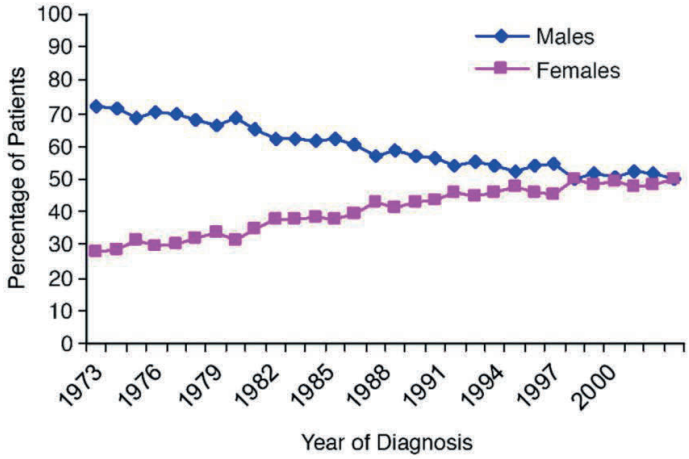
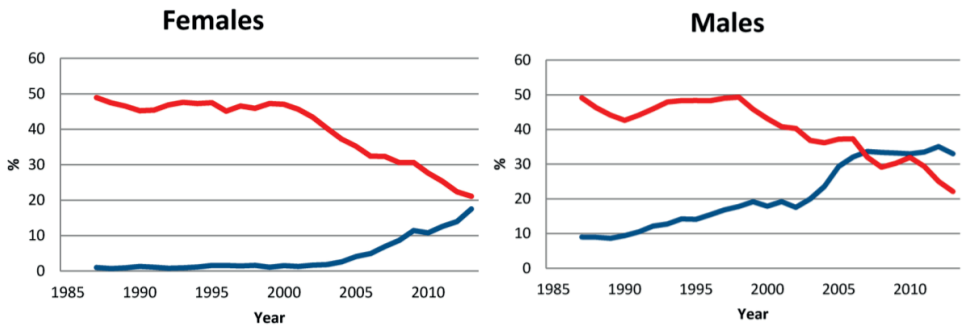


Figure 5 Proportion of daily smokers by gender in Norway.

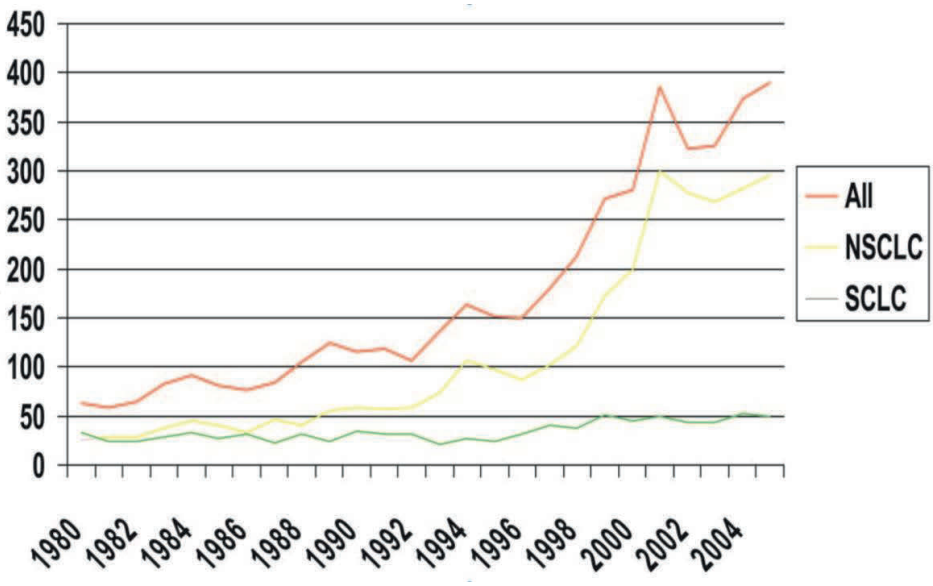


Decreasing proportion of daily smokers (red line) and increasing use of oral tobacco (blue line) in Norway. Figure copied from [19].

Lung tumours can grow substantially before they give symptoms. The majority of patients present with advanced disease without a possibility for cure at time of diagnoses. Although reduced mortality from lung cancer have has observed from screening programs using low-dose CT [25], the overall benefit is debated and screening has not resulted in lower stage at diagnosis or improved survival in SCLC [25-29]. Due to the aggressive growth and potential for early metastases, SCLC is often detected in screening intervals, and at an advanced stage [29].

SCLC has received less scientific attention than NSCLC (Figure 6) [30]. In 2012, only 2% the lung cancer projects run by the National Cancer Institute (NCI) focused on SCLC. A framework to make progress in SCLC has been developed by the International Association for the Study of Lung Cancer (IASLC) and the NCI [31, 32].

Figure 6 Number of abstracts published at the American Society of Clinical Oncology annual meetings between 1980 and 2006. Figure copied from [30].



2.2.2 Clinical presentation of SCLC

Compared to NSCLC, SCLC is characterized by aggressive growth and propensity for early metastases to mediastinal lymph nodes, liver, adrenal glands, bone and brain. SCLC predominantly originates in central airways, commonly presenting as a hilar mass with mediastinal lymphadenopathy. It can sometimes be hard to distinguish lymph nodes from the primary tumour. The tumour masses may compress mediastinal structures and cause vena cava superior syndrome (VCSS), dysphagia (oesophagus), diaphragmatic palsy (phrenic nerve), stridor (central airways) and hoarseness (recurrent laryngeal nerve).

The cells are of neuroendocrine origin and may have ectopic hormone production (e.g. PTH, ADH and ACTH). SCLC is therefore often associated with

paraneoplastic phenomena, e.g. hypercalcemia, syndrome of inappropriate antidiuretic hormone excretion (SIADH) and Cushing´s syndrome [33].

2.2.3 Diagnostic workup in SCLC

The main objectives of the diagnostic workup are to acquire a histological diagnosis, assess stage of disease and the patients' overall health.

A tissue specimen is usually obtained through bronchoscopy or percutaneous, CT guided biopsy. Light microscopy of an eosin and haematoxylin stain is sufficient for the diagnosis, SCLC is characterized by small cells with a round or fusiform shape and little cytoplasm. Because of this appearance, it used to be called oat-cell carcinoma. Currently, neither immunohistochemistry nor mutation-testing has an established role in subclassification of SCLC.

CT of thorax and upper abdomen has been the main method for staging of lung cancer [34]. In SCLC, a MRI of the brain and a bone scan has been recommended to assess sub-clinical metastases. SCLC has a high metabolic activity, and PET-CT has both a superior sensitivity (98-100%) and specificity (92-97%) for pathological lesions (excluding brain) compared to CT and bone scan [35-37]. A cumulative staging concordance between conventional imaging and PET-CT of 84% has been reported, with 18% of patients upstaged to ED SCLC and 11% of patients downstaged to LD SCLC with the use of PET-CT [35].

PET-CT is recommended for patients with LD SCLC eligible for surgery or concurrent chemoradiotherapy, but does not replace MRI for examination of the brain [23, 24, 38-40].

Functional tests including spirometry are performed to assess fitness for treatment. In absence of symptoms or signs of reduced lung capacity, a forced expiratory volume in one second (FEV1) > 2L (or 80% of expected value) in combination with a diffusing capacity of the lung for carbon monoxide (DLCO) above 60% of expected value is sufficient for a pneumonectomy, while a FEV1 > 1.5L / DLCO > 60% is sufficient for lobectomy. Pulmonary physiological testing does not, however, predict risk of toxicity from radiotherapy well. The dose to normal tissue appears to be a more important predictive factor for such toxicity.

2.3 Treatment of limited disease (LD SCLC)

2.3.1 History of thoracic radiotherapy in LD SCLC

2.3.1.1 Chemotherapy versus radiotherapy

In the 1950s, loco-regional lung cancer was primarily treated with surgery, and radiotherapy was reserved for patients with unresectable disease. The Veterans Administration Lung Group (VALG) initiated their first randomised clinical trial in inoperable lung cancer in 1957, and for this purpose they defined limited stage (LD) as disease that could be confined by a tolerable radiotherapy field [41]. Soon after, studies comparing surgery to radiotherapy were initiated, and it became clear that radiotherapy was superior to surgery in the treatment of LD SCLC [42-44].

In the 1960s a high sensitivity to chemotherapy in SCLC was noted. Improved survival was demonstrated from chemotherapy adjuvant to radiotherapy [45, 46]. A multitude of agents have demonstrated effect in SCLC, including nitrogen mustard [47], methotrexate [48], cyclophosphamide [22], ifosfamide [49], adriamycin (doxorubicin) [50], vincristine [51], cisplatin [52], carboplatin [53] and etoposide [54-57].

During the 1970s, improved disease-control was observed from combination chemotherapy [58], and it was evident that combination chemotherapy was superior to single-agent treatment [59, 60], with objective responses in up to 94%, and complete responses in up to 53% [61]. Three- or four-drug combinations based on cyclophosphamide, methotrexate, bleomycin, vincristine or CCNU (lomustine) were commonly used [58, 62], succeeded by the combination of cyclophosphamide, adriamycin and vincristine (CAV). Combination chemotherapy became the main treatment for LD SCLC [59], and attention was directed towards combinations providing higher rates of CR. The addition of radiotherapy to combination chemotherapy was controversial, but radiotherapy had a role as adjuvant or consolidation therapy [13, 63].

The high sensitivity to chemotherapy in SCLC triggered anticipation from more dose-dense schedules of chemotherapy. Several studies investigated the effect of high-dose chemotherapy. One study demonstrated improved 2-year survival in patients that received a higher dose in the first course, indicating an effect from early intensification prior to the development of resistance [64]. Other studies failed to

demonstrate improved survival in patients receiving higher doses of chemotherapy, while toxicity was significantly worse [65-67]. Several studies have investigated increased dose-intensity of chemotherapy. To be able to deliver chemotherapy in a shorter time-period, most of them used granulocyte colony stimulating factors (G-CSF). In some studies the higher dose-intensity was associated with improved survival [68-71], while other studies were not able to demonstrate such a positive effect [72-77].

The first successful bone marrow transplant was performed by Dr Thomas in 1956. Already in the early 1970s, myeloablative treatment with autologous bone marrow transplantation (ABMT) was proposed for the treatment of relapsed or resistant SCLC. The first studies were published in the early 1980s, but results have been disappointing. High rates of complete responses (CR) have been observed, without improvement in survival and at a cost of increased toxicity, including up to 10% procedure-related deaths [78-81].

In conclusion, outcomes of SCLC have not been improved by increasing dose-intensity, peak dose or cumulative dose of chemotherapy, as none of these strategies can overcome the problem of resistance to therapy in SCLC [77]. Furthermore, alternating or sequential chemo-regimens to overcome drug-resistance, by exposing the tumour cells to a multitude of chemotherapeutic agents, have failed to demonstrate a benefit [82-84].

2.3.1.2 Concurrent chemoradiotherapy

After a period where radiotherapy played a smaller role, a high rate of local relapses after chemotherapy motivated the use of radiotherapy. Investigators from the National Cancer Institute (NCI) were the first to research concurrent chemotherapy and radiotherapy in 1976 administering CAV concomitant with prophylactic cranial irradiation (PCI) and thoracic radiotherapy (TRT). The first reports on disease control were promising, with studies reporting 91% CR [85], but the treatment was associated with a high rate of severe pneumonitis and esophagitis complicated by formation of strictures. As many as one in five patients died from treatment-related causes [13, 86, 87].

To reduce toxicity, some investigators gave radiotherapy during a break in chemotherapy, reducing both survival and toxicity [88]. It is now acknowledged that anthracyclines, such as adriamycin, are potent radio-sensitizers, and poorly tolerated

in combination with thoracic radiotherapy.

The demonstration of effect from cisplatin and etoposide (PE) in 1979 [89], was an important step for combined therapy, as it is well tolerated in combination with radiotherapy, without compromising delivery of either. PE is more effective than CAV, though it is also associated with more nausea, vomiting, anaemia and thrombocytopenia [90, 91]. Carboplatin is considered a good alternative if cisplatin is not well tolerated, due to ototoxicity, nephrotoxicity or nausea [92]. Adding a third component to PE, such as ifosfamide or paclitaxel, has not demonstrated a survival advantage, and result in excess toxicity [93, 94].

Many investigators have used 4 courses [95-99], while others use up to 6 [100]. There is a lack of data to determine if this difference in number of courses influences outcomes. In one study of all stages SCLC receiving chemotherapy other than PE, improved survival was observed in patients receiving 8 compared to 4 courses initially, but not in patients offered treatment at relapse, and TRT was not delivered to patients with LD SCLC [101]. Another trial could not demonstrate improved survival in patients receiving six compared to three courses of chemotherapy (non-PE) [102].

Several small studies have investigated chemotherapy beyond 4-6 courses (PE and non-PE), with varying results, but most trials demonstrate no significant survival difference. Although a minor survival benefit was detected in a literature review and a meta-analysis, there is a lack of a properly designed clinical trials, and maintenance chemotherapy increases the risk of severe side-effects [103, 104]. Continuing chemotherapy beyond 4-6 courses increases toxicity and is not recommended in guidelines [23, 24, 38-40].

Several RCTs compared combination chemotherapy with or without radiotherapy, with conflicting results [105-117]. The risk of thoracic failure was reduced from 75-90% to 30-60% by the addition of thoracic radiotherapy [106, 110, 118-120]. However, this did not always translate into a survival benefit [106, 118, 120]. Many of the studies were small with a limited statistical power to detect a positive effect on survival. In some studies, results were negatively influenced by the use of anthracyclines and sequential scheduling of radiotherapy. Based on the available evidence, a consensus meeting in 1988 could not recommend the use of TRT [121]. It was not until the publication of two meta-analyses in 1992, that the role of thoracic radiotherapy in LD SCLC was established. These meta-analyses

demonstrated a 50% reduction in local relapses and a 5% improvement in 2-year survival (from 15% to 20%) and 3-year survival (from 9% to 14%) [122, 123].

2.3.2 Prophylactic cranial irradiation

SCLC has a high potential for metastases to the brain. Depending on the imaging technique, prevalence of brain metastases at time of diagnosis varies between 10% and 24% [124]. MRI has a higher sensitivity for asymptomatic brain metastases than CT. A life-time risk for brain metastases in SCLC of 75% have been reported [125], and more than half of the patients with CR after primary treatment will develop brain metastases [126]. Brain metastases causes shorter survival and distressing symptoms such as headache, nausea, dizziness and cognitive deterioration.

The effect of chemotherapy on brain metastases is limited by the blood-brain barrier. Due to a high rate of brain metastases, the use of prophylactic cranial irradiation (PCI) in SCLC was proposed already in the early 1970s [127]. It is now well documented that PCI reduces the risk of brain metastases and prolongs survival in patients with SCLC and response from treatment [128-130].

It is still unclear whether all patients with LD SCLC benefit from PCI. The meta-analysis that demonstrated a survival-benefit and established PCI in SCLC, only investigated patients with a CR [128]. However, response to primary treatment was assessed on a chest x-ray, and probably included patients with residual disease in the mediastinum and hili. Furthermore, PCI prolongs survival in ED SCLC who respond to primary chemotherapy [130], and there are indications of a survival benefit in patients with LD SCLC achieving at least SD [131]. Thus, it seems reasonable to offer PCI to patients with LD SCLC achieving at least PR [23, 24, 38, 39] or having a “good” response [40].

PCI may result in both acute and long-term toxicity. Acute toxicity most commonly includes alopecia, fatigue, headache and nausea. Some studies indicate both structural and neuropsychological changes from PCI [132-136], while two randomised studies demonstrated no difference in neurological deterioration between patients receiving PCI or not [126, 137]. There is little evidence of a negative impact on quality of life from PCI [136-138].

One study has evaluated benefits and risks of PCI comparing quality-adjusted life expectancy (QALE) in patients receiving PCI or not. As survival in LD SCLC improves, frequency and severity of neurotoxicity (NT) from PCI must be controlled to

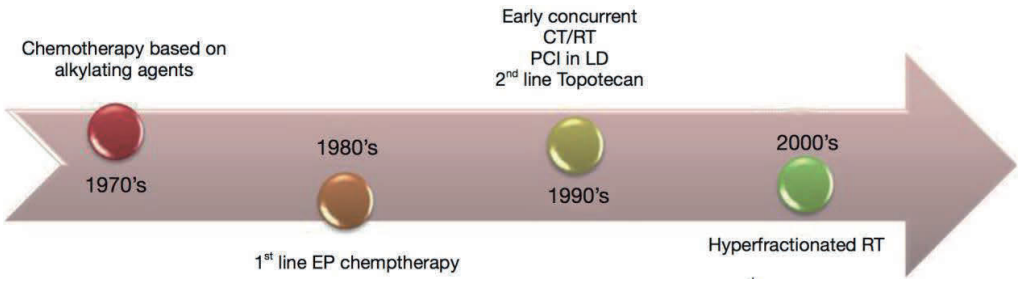
offer a benefit over no PCI. Based on the current 5-year survival (PCI: 26%, no PCI: 22%) and a low rate of neurotoxicity, PCI offered a benefit in QALE over no PCI for both mild and substantial severity of NT [139]. Thus, the negative side-effects are considered acceptable considering the potential devastating consequences of brain metastases.

In our study, we delivered PCI of 30 Gy in 15 fractions, which used to be the standard in Norway. A schedule of 2.5 Gy in 10 fractions (25 Gy) is the current standard, since higher PCI-doses do not improve survival and is more toxic [131, 140].

2.3.3 Advances in primary treatment of limited disease since 1970

Initial therapy of LD SCLC has remained mostly unchanged for decades, with no major advances in treatment for years [141]. The last considerable improvement in systemic treatment came with the introduction of PE more than 35 years ago [89]. Latest improvements have come from radiotherapy in packages of 5% improved 2- or 3-year survival; TRT vs no TRT [122, 123], PCI vs no PCI [128] and early vs late TRT [142] (Figure 7). Collectively, radiotherapy has improved the 5-year survival from <10% from chemotherapy alone, to 20-25% from PE in combination with early TRT and PCI [95, 143].

Figure 7 Time-line of advances in treatment of LD SCLC.



Radiotherapy (RT), prophylactic cranial irradiation (PCI), chemotherapy (CT) and cisplatin and etoposide (EP=PE). Figure adapted from [144].

2.4 Second-line chemotherapy

Second-line treatment improves overall survival and quality of life, compared to best supportive care (BSC) [145], and is recommended in relapsed SCLC [23, 24, 38-40]. Best effect from second-line treatment is achieved in “sensitive relapses” (PFS > 3 months), where 20% objective responses can be expected. “Resistant (refractory) relapses” (PFS ≤ 3 months) are associated with objective responses in approximately 10% of patients. Whether there is a clinical benefit from second-line treatment among patients with the earliest relapses (PFS < 1.5 months) has not been determined.

In sensitive relapses, re-introduction to first-line chemotherapy can result in 50% objective responses (PR + CR) in patients with a long treatment-free interval (> 6 months) [146, 147]. Guidelines recommend re-introduction of first-line treatment in patients with PFS > 3-6 months [23, 24, 38-40].

Topotecan is the only agent with approval by the U.S. Food and Drug Administration (FDA) for relapsed SCLC, and improves median survival from 3.5 to 6.5 months in patients considered unfit for intravenous chemotherapy, compared to best supportive care (BSC) [145]. Less than 10% will have an objective response, and there is no difference in RR, OS or HRQoL between oral and iv topotecan [145, 148]. CAV is a common alternative in the second line setting, and provides similar RR, time to progression and OS as topotecan, although topotecan provides better control of symptoms such as dyspnoea, anorexia, hoarseness and fatigue [149]. CAV is often preferred due to lower price and more convenient administration (1 vs 5 days).

2.5 New agents in SCLC

A Japanese trial demonstrated superior survival when cisplatin was combined with irinotecan (IP) rather than etoposide (PE) in the initial management of LD SCLC [99]. However, the superiority of IP was not confirmed in western populations [150, 151], possibly due to genetic differences.

Amrubicin is a synthetic anthracycline that has demonstrated promising activity, particularly among refractory relapses and in Japanese patients, but has not proven superior to established regimens [152-156]. Other agents that have

demonstrated efficacy in pre-treated SCLC include paclitaxel [157], docetaxel [158], vinorelbine [159], and gemcitabine [160].

In contrast to NSCLC, targeted therapy has not an established role in SCLC yet, but a recent study has demonstrated promising efficacy of rovalpituzumab tesirine, a DLL3 targeted antibody, in relapsed SCLC. Responses was observed in 31% of patients with a high expression of DLL3 (>50%), but the median survival was only 5.8 months [161].

The latest addition to systemic lung cancer therapy is the development of immunotherapy. Two PD-1 check-point inhibitors (nivolumab and pembrolizumab) have received FDA approval for treatment of NSCLC, while the role of immunotherapy is less established in SCLC [162-164]. A combination of nivolumab and ipilimumab (CTLA4 inhibitor) can result in 23% objective response and median survival of 7.7 months in patients with sensitive/refractory relapses at an acceptable level of toxicity. These results are better than expected from chemotherapy, considering more than 50% of patients had received more than two previous lines of treatment [165]. Preclinical data has indicated a synergistic effect from treatment with a CTLA4 inhibitor and chemotherapy, possibly due to an augmented release of tumour antigen from cytotoxic chemotherapy [166]. Results from ongoing clinical trials, including a large phase III study investigating PE + ipilimumab vs PE alone are awaited [167].

2.6 Recommended primary treatment of SCLC

2.6.1 Limited disease (operable T1-2N0M0)

The role of surgery in LD SCLC is debated. Two studies have randomly assigned patients with LD SCLC to surgery. One study compared surgery to radiotherapy, the other radiotherapy with or without surgery. Both studies predated the era of modern staging, and none of the studies demonstrated a benefit from surgery [42, 168]. Five-year survival rates of 30-50% has been reported after surgery in patients with T1-2N0M0 SCLC [169, 170], and surgery is therefore recommended in these patients [23, 24, 38-40]. Patients with T1-2N0M0 tumours constitute less than 5% of patients with LD SCLC, and only about 5 patients undergo surgery for LD SCLC annually in Norway [171]. Postoperative adjuvant platinum-based chemotherapy and

prophylactic cranial irradiation (PCI) is recommended after surgery [23, 24, 38-40]. Postoperative mediastinal radiotherapy concomitant with the adjuvant chemotherapy is recommended if lymph node metastases are detected during surgery, or when systematic sampling is not conducted [38-40].

2.6.2 Limited disease (inoperable T1-2N0M0 and T3-4N1-3M0)

Combination chemotherapy and thoracic radiotherapy is recommended treatment in LD SCLC. Four to six courses of cisplatin and etoposide is given concurrently with thoracic radiotherapy.

The recommended schedule to fit patients is 45 Gy in 30 twice daily fractions over 3 weeks (hyperfractionation) [23, 24, 38-40]. Hypofractionated TRT of 2.67-3.0 Gy once daily to a total of 40-45 Gy is commonly used [143, 172-175], while others administer 2 Gy once daily in 5-7 weeks to a total dose of 50-70 Gy [40, 175].

Early administration of radiotherapy concomitant with the 1. or 2. course of chemotherapy is recommended [23, 24, 38-40]. Patients with response to chemoradiotherapy should be offered PCI of 25 Gy in 10 fractions [23, 24, 38-40].

2.6.3 Extensive disease

Main treatment in ED SCLC is combination chemotherapy. Four to six courses of carboplatin and etoposide is recommended [23, 24, 38-40]. Responders are offered PCI of 25 Gy in 10 fractions. There is evidence that thoracic radiotherapy is tolerated and improves local thoracic control and survival in patients responding to chemotherapy, particularly patients with extra-thoracic CR and residual thoracic disease [176-179]. TRT is suggested, although not clearly recommended, to selected patients with a good response from chemotherapy [23, 24, 38-40].

2.7 Potential for advances in the treatment of LD SCLC

The main challenge in LD SCLC is to convert the high initial sensitivity to chemo- and radiotherapy into long-term survival, with acceptable toxicity from treatment. The biological knowledge on SCLC has increased considerably [180], but there is a need to improve our understanding of the mechanisms behind resistance to therapy.

Regarding treatment of LD SCLC, there are several unresolved issues that have gained attention and been subject to debate, and are believed to be important to overcome in order to improve outcomes.

2.7.1 Thoracic radiotherapy in LD SCLC

The role of thoracic radiotherapy in LD SCLC is well established, although there has been considerable variation in the definition of LD. Further, the optimal targets, volume, timing and fractionation of TRT have been debated. There are concerns about the added toxicity, and need for improved knowledge on how to identify patients that are fit for treatment, and patients possibly in need of alternative treatment.

2.7.1.1 Definition of LD SCLC

According to the VALG definition, LD was disease that could be fitted into a tolerable radiotherapy field, and included disease confined to one hemithorax, although local extensions were allowed. Extrathoracic metastases, except ipsilateral supraclavicular nodes, was not allowed. How to consider patients with contralateral supraclavicular nodes and ipsilateral pleural effusion was neither well defined nor consistently understood. In 1989 the International Association for the Study of Lung Cancer (IASLC) defined LD as disease restricted to one hemi-thorax, allowing ipsilateral malignant pleural effusion and hilar, contralateral mediastinal and contralateral supraclavicular nodes [181]. There is a variation between studies in the diagnostic workup required for staging and how LD is defined. Some investigators have allowed contralateral mediastinal and ipsilateral supraclavicular disease. In the study by Turrisi et al., patients underwent bone marrow aspiration and patients with contralateral hilar or supraclavicular nodes or pleural effusions were excluded [95].

Within the broad definition of LD, the TNM classification is capable of identifying patients with distinct prognosis. The use of TNM classification has been recommended by the IASLC since 2007 [182], and is encouraged in guidelines [23, 24, 38-40].

2.7.1.2 Identification of target lesions

Macroscopic disease, consisting of the primary tumour and pathological lymph nodes, are the main targets for radiotherapy. However, when targeting only

pathological lesions, as defined on CT, the rate of isolated nodal failures is high (11%) [183]. Thus, it has been common to deliver elective nodal irradiation (ENI) to mediastinal lymph nodes to reduce the rate of local failure caused by microscopic dissemination.

Compared to CT, PET-CT has an improved sensitivity and specificity for pathological lesions, and makes it possible to distinguish tumour from atelectasis. Studies that have delivered selective nodal irradiation (SNI) to PET-positive nodes report less than 3% isolated nodal failures [184, 185], suggesting that only PET-positive lesions need to be irradiated. Less normal tissue is unnecessarily irradiated when using SNI.

Results from seven smaller studies (n=211), three prospective [184, 186, 187] and four retrospective [188-191] demonstrated a change in initial management of SCLC in 28% of patients staged with PET-CT. In one third there was a stage shift, and in two thirds the radiotherapy fields were redesigned after PET-CT [24].

2.7.1.3 Volume of target lesion

In most cases patients receive some chemotherapy prior to radiotherapy. Radiotherapy is directed towards all malignant locations on the baseline scan, but delineated according to size on the planning scan. One study has compared margins of different size [192], and two studies have compared radiotherapy to pre- or post-chemotherapy volumes [108, 193], with no difference in outcomes. These are strong indications that it is safe to deliver radiotherapy to a post chemotherapy volume [120].

2.7.1.4 Timing of radiotherapy

In the early days, radiotherapy was usually administered after chemotherapy, due to the high toxicity observed from combining radiotherapy with anthracycline-based chemotherapy. One of the meta-analysis establishing TRT in LD SCLC also addressed the question of timing comparing early versus late, and concurrent versus sequential schedules, but was not able to detect a difference in outcomes [123].
A systematic review and meta-analysis detected a small but significant advantage in survival from early radiotherapy, starting within 9 weeks and before the third course. The effect was largest among patients receiving platinum-based chemotherapy and twice daily radiotherapy [142].

Since the initiation of our study, the question of timing has been addressed in several studies [194-196]. A systematic review and meta-analysis investigated early,

defined as within 30 days, versus late radiotherapy. When a trial using non-platinum therapy was excluded, early therapy was associated with improved survival, and the association was stronger for trials delivering radiotherapy within 30 days [195]. Leading from this, time between initiation of chemotherapy and end of radiotherapy (SER) has been identified as an important prognostic factor, and should be kept as short as possible [197]. Schedules of 45-54 Gy were included in the analyses, and the 5-year survival rate decreased 1.8% for every week of extending the SER beyond the arm with the shortest SER [197]. Thus, early radiotherapy, starting with the first or second course of chemotherapy, is recommended in guidelines [23, 24, 38-40]. Although starting TRT concomitant with the first course results in the lowest SER, TRT is often administered concomitant with the second chemotherapy course due to time-delay in the referral for and planning of TRT [98, 198-200].

2.7.1.5 Fractionation

A standard fractionated schedule of radiotherapy consists of 2 Gray (Gy) once daily 5 days a week, to a total dose of 50-70 Gy. Radiotherapy is accelerated if the total dose is delivered in fewer days, either as larger doses, often > 2.5 Gy, once daily (hypofractionation) or smaller doses than 2 Gy more than once daily (hyperfractionation).

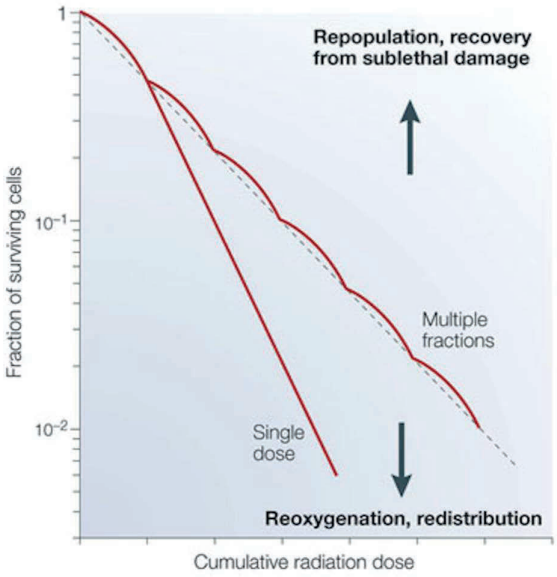
To compare the total dose of different fractionation schedules, the biological effective dose (BED) is calculated, based on dose, number of fractions and the α/β-ratio of the specific tissue (Figure 8). The BED is often reported in 2 Gy equivalents.

SCLC is very sensitive to radiotherapy [201], and sensitivity to radiotherapy is often referred to as the fifth of the four Rs of radiobiology. The four Rs of radiobiology (repair, redistribution, reoxygenation and repopulation) (Figure 8) can be used to describe the improved tolerance and tumour control resulting from fractionation of radiotherapy.

Sub-lethal damage from radiotherapy is more readily repaired between fractions in normal tissue, as repair pathways often are supressed in malignant tissue. The break between fractions allows redistribution of tumour cells in resistant phases of cell division cycle (S) into more sensitive phases (late G2 and M) during later fractions. Furthermore, it allows for reoxygenation of hypoxic parts of the tumour, an important premise for the effect of radiotherapy. Radiotherapy induces repopulation, leading to improved tolerance in normal tissue. The unwanted

accelerated repopulation of tumour cells starting after 4 weeks can be avoided by acceleration of treatment (e.g. 3-week schedules). Hypofractionation is the most common way of accelerating treatment (OD TRT). However, in-vitro cell-survival curves of SCLC lack a “shoulder”, indicating that smaller doses of radiotherapy are sufficient to cause cell kill, while at the same time saving normal tissue [201]. Consequently, hyperfractionated accelerated radiotherapy (BID TRT) may have a role in LD SCLC.

Figure 8 Cell survival curve illustrating the four Rs of fractionated radiotherapy.



Repopulation and repair (recovery from sub lethal damage) improves normal tissue tolerance, while reoxygenation and redistribution improves tumour control. The initial slope of the corresponding survival curve is decided by the linear component α, reflecting the sensitivity to radiotherapy. The quadratic component β represents the repairable portion of the radiation damage and decides the curvature. The α/β-ratio is the dose in Gy where linear cell kill equals quadratic cell kill. At lower doses, linear cell kill will dominate, at higher doses quadratic cell kill will dominate.

Highly proliferative tumours (e.g. SCLC) and early reacting normal tissue (e.g. bone marrow and epithelium of gastrointestinal tract) have high α/β-ratios (e.g. 10 Gy) and are sensitive to standard daily doses (2 Gy) or lower, with a linear relation between total dose and effect (no repeated "shoulder"), meaning the effect from radiotherapy is not reduced by fractionation.

The opposite effect from fractionation is observed in late reacting normal tissue (e.g. CNS, bone, connective tissue and muscle) and tumours with lower α/β-ratios (e.g. 3 Gy) due to a higher repairable portion (β). In such cases damage from standard daily doses are repaired between fractions, leaving a curved relation (repeated "shoulder") between total dose and effect. Accordingly, the effect from radiotherapy is reduced by fractionation. Figure copied from [202].

Turrisi et al. compared radiotherapy of 1.5 Gy twice daily in 3 weeks (hyperfractionated accelerated/BID TRT) to 1.8 Gy once daily in 5 weeks (standard fractionated) in 417 patients with LD SCLC [95]. TRT started with the first of four courses of PE. PCI was administered to patients with CR. BID TRT resulted in an improved median survival (23 months vs. 19 months; p=.04) and 5-year survival (26% vs. 16%). However, twice daily radiotherapy also resulted in significantly more grade 3-4 oesophagitis (BID: 32%, OD: 16%; p<.001). Results from the Turrisi trial have been debated. The control arm was not accelerated and had both an inferior SER (35 days versus 21 days) and BED (39.5 Gy versus 43.9 Gy) [95, 203]. The difference in outcome may be a consequence of these differences.

A shorter treatment time, from accelerated schedules, is associated with improved survival in LD SCLC [195, 197]. A study delivering non-accelerated hyperfractionated radiotherapy with a split-course, failed to demonstrate a benefit from hyperfractionation [204]. A meta-analyses based on these two trials of hyperfractionated radiotherapy in LD SCLC concluded that there was a non-significant trend for improved survival of twice-daily TRT, but with increased oesophageal toxicity [205].

Hypofractionation is the most common way of accelerating radiotherapy, and 40-45 Gy in 15 fractions (OD TRT) is a commonly used schedule in LD SCLC and median survival of 21 months has been achieved – which might not be different from the twice-daily regimen in the Turrisi-study (23 months) [143, 172-175]. A schedule of 42 Gy in 3 weeks has been common in Norway, and provides both an equal SER and a higher BED (45.9 Gy) than the BID schedule [203]. However, hypofractionated accelerated TRT has never been compared to hyperfractionated accelerated radiotherapy in a RCT.

2.7.2 Toxicity and dose of thoracic radiotherapy in LD SCLC

2.7.2.1 Assessment of toxicity

Toxicity from therapy is commonly reported by physicians according to the widely accepted Common Terminology Criteria for Adverse Events (CTCAE) [206-208]. The current version (v4.0) was published in 2009, and the release of an updated v5.0 is planned for September 2016. This system rates adverse events according to specific criteria on a scale from 1-5 (1: mild, 2: moderate, 3: severe, 4: life-threatening or disabling, 5: death). Some adverse events have objective criteria (e.g.

haematological toxicity) while others include level of symptom, interference with activities of daily life (ADL) and intervention needed (e.g. oesophagitis and pneumonitis).

Side-effects from treatment are often under-reported by physicians [209]. It is therefore recommended to include patient reported outcome measures (PROM) such as Health Related Quality of Life (HRQoL). Several instruments exist for this purpose. The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30 (v3.0) and the Lung Cancer specific module LC13 are commonly used in lung cancer research [210, 211]. The QLQ C30 (30 items) consists of 9 multi-item scales (global quality of life scale, 5 functional scales, 3 symptomatic) and 6 symptomatic single-items. The LC13 (13 items) consist of 1 multi item symptomatic scale (dyspnoea) and 9 symptomatic single-items. Functional and symptomatic items are answered on a Likert scale (not at all, a little, quite a bit, very much), while global quality of life is answered on a numerical rating scale (NRS) from 1 (very poor) to 7 (excellent). The QLQ C30 and LC13 are scored according to a scoring manual [212].

2.7.2.2 Main toxicity in LD SCLC

Main toxicity from thoracic radiotherapy comes from the lungs and oesophagus. Grade 3-4 toxicity from the oesophagus, requiring i.v fluids, tube feeding or total parenteral nutrition for more than 24 hours, can be seen in up to every third patient [95-97, 100, 143, 174]. Early intervention with supplements, pain killers and local anaesthetics is important. Although causing severe symptoms, most patients are relieved of symptoms shortly after ending radiotherapy, and late-term complications, as formation of strictures are rarely seen. Radiation pneumonitis is a less frequent, but potentially deadly complication. Grade 3-4 pneumonitis, interfering with ADL and requiring treatment with oxygen, is seen in up to 5% of patients [95-97, 100, 143, 174]. Symptoms may occur from a few weeks to 6 months after radiotherapy. Signs include a dry cough, low-grade fever and shortness of breath. If untreated, it may progress to irreversible pulmonary fibrosis and lead to death. Radiation pneumonitis may be resolved with the use of steroids.

2.7.2.3 Predicting toxicity

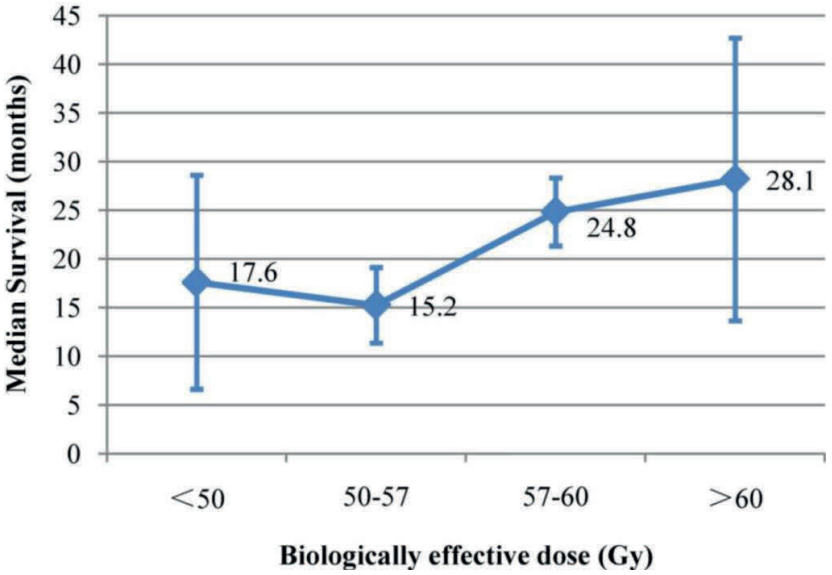
Most important predictors of toxicity from radiotherapy are dose and volume of irradiated normal tissue. Dose-Volume-Histograms (DVH) describe distribution of dose to normal tissue. Threshold doses to normal tissue are used as criteria to control the risk of toxicity. The corresponding probabilities of side-effects are based on previous observations, as published by Emami et al. [213], although these have widely been replaced by the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) papers [214]. Such criteria describe both maximum or mean dose to an organ, as well as proportional volume receiving a particular dose or higher. To keep the risk of symptomatic radiation pneumonitis below 20%, not more than 30-35% of the lung should receive 20 Gy or more ($V_{20} \leq$ 30-35%), with a mean dose ≤ 20-23 Gy [215]. For the oesophagus, a wide range of volumes receiving an above threshold dose (V_{dose}) are predictive of toxicity, but more so for volumes receiving high doses of 40-50 Gy. It is important to avoid hotspots of higher than prescribed doses to even small volumes of the oesophagus. Based on the available data at the time, no specific dose limit could be described in the QUANTEC paper. Doses of 74 Gy to segments of the oesophagus appeared safe even in combination with carboplatin and docetaxel [216]. A mean dose ≤34 Gy is associated with 5-20% risk of grade 3 or more toxicity, while $V_{35} < 50\%$, $V_{50} < 40\%$ and $V_{70} < 20\%$ are all associated with a less than 30% risk of grade 2 toxicity or higher [216].

2.7.2.4 Dose of radiotherapy

Only moderate doses of radiotherapy have been used in LD SCLC [217], due to the high level of toxicity from concurrent chemoradiotherapy. The meta-analyses establishing TRT in LD SCLC were based on studies delivering 40 Gy in 20 fractions [122, 123], and accelerated schedules of not more than 40-45 Gy are still common. In 1998 Choi reported the maximum tolerated dose of radiotherapy to be either 45 Gy as 1.5 Gy twice daily or 70 Gy as 2 Gy once daily in a phase I dose escalation study (n=50) [218]. The use of higher doses within normal tissue constraints is feasible with modern radiotherapy. Intensity-modulated radiation therapy (IMRT), or the more recent volumetric arc therapy (VMAT) allows highly conformal distribution of dose, reducing areas of high doses to normal tissue. Image-guided radiation therapy (IGRT) and 4D CT allows smaller margin for internal motion of targets.

There are indications that higher biological effective doses improve local control, progression-free and overall survival in LD SCLC (Figure 9) [203, 219-222].

Figure 9 Biologically equivalent dose and median survival. Figure copied from [222].



2.7.3 Fitness for concurrent chemoradiotherapy

Population-based studies show that not all patients with LD SCLC receive concurrent chemoradiotherapy, and only 20% receive the recommended twice daily schedule, probably due to concerns of excess toxicity [223-226].

The outcome of a particular disease may depend on a multitude of factors, related to the disease, treatment or the patient (host); e.g. age, performance status and extent of disease. A prognostic factor foresees the effect of disease on outcomes, while a predictive factor foresees the modifying effect from treatment. Factors may be both prognostic and predictive [227-229]. In such cases, the prognostic value is modified by treatment. Variation in treatment and ability to control for other prognostic factors can explain why a factor may be identified as prognostic for survival in some, but not all studies.

Performance status and stage of disease have consistently demonstrated prognostic value in SCLC. Some factors have divergent prognostic value based on stage [230, 231]. In addition to PS and stage, both age, gender, weight loss,

treatment, SER, LDH and NSE amongst others have been reported as prognostic factors in LD SCLC [181, 197, 230-237]. However, only PS and stage are currently used to select treatment to the individual patient.

2.7.3.1 Comorbidity in LD SCLC

Many patients with LD SCLC suffer from coexisting diseases due to old age and heavy tobacco smoking. Comorbidity seem to influence treatment decisions, as population-based studies reveal that patients with comorbidity receive less treatment than others [223-225]. Comorbidity is a prognostic factor in many cancers, including NSCLC [238]. Some studies have identified comorbidity as a negative prognostic factor in SCLC [239-244], while others did not find an influence on survival [223, 224, 245-247].

A recent editorial pointed out the need for stage and treatment specific investigations of comorbidity in lung cancer, as comorbidity may have divergent influence depending on stage and treatment [248].

2.7.3.2 Assessment of comorbidity

While some authors simply report number of coexisting illnesses, or focus on specific conditions, several instruments exist for assessment of comorbidity.

The Charlson Comorbidity Index (CCI) was developed in 559 medical patients in 1987 [249]. Nineteen conditions are given a values of 1,2,3 or 6 based on the relative risk of death contributed by them. Some conditions are represented with different scores based on severity (e.g. diabetes with or without end-organ failure). The total score (CCI-score) is the sum of values for all conditions the patient has, and represents the overall burden of comorbidity. The CCI was validated in a population of breast-cancer patients, and found to predict mortality in a time-frame of weeks to ten years [249]. In the validation-study it was suggested to add one point for each decade of age ≥ 50 in an age-adjusted CCI (A-CCI). Several adaptations to patient-administrative data of the CCI exist, such as the Charlson/Deco, Charlson/Romano and Charlson/D'Hoores [250-252].

The Simplified Comorbidity Score (SCS), also known as Colinet after the first author, was developed in a population of 735 patients with previously untreated NSCLC [253]. Seven conditions associated with increased risk of death were identified in univariate analyses, and given scores according to their hazard ratio in multivariate survival analyses. Unlike the CCI, the SCS also includes tobacco

consumption and alcoholism as comorbidity. The SCS was validated and compared to the CCI in a cohort of 136 patients with NSCLC. The authors concluded that the SCS was better at predicting outcomes, and more convenient as it consists of only 7 items.

The Cumulative Illness Rating Scale in Geriatrics (CIRS-G) is based on the cumulative illness rating scale (CIRS) [254] and was designed for assessing comorbidity in elderly patients [255]. Instead of addressing medical diagnosis, it rates function in different organ systems. Fourteen organ systems are given a value from 0-4, where “0” indicates no problem, “1” indicates a current mild problem or a past significant problem, “2” a moderate disability or morbidity that requires “first-line” therapy, “3” a severe/constant significant disability or an "uncontrollable" chronic problem and “4” an extremely severe/immediate treatment required/end organ failure/severe impairment in function. Specific training is required to use the CIRS-G [256].

Several more instruments exist. There are differences in the definitions of conditions, numbers and characteristics of items included, how detailed information they contain and if prospective registration by trained staff is needed. No standard method for assessing comorbidity in cancer patients has been established. The CCI is commonly preferred because it is easy to use and has a high inter-rater reliability [257, 258]. Furthermore, the CCI can be retrospectively scored based on medical records and registry data, making it attractive for population-based studies.

2.7.4 Individualisation of treatment in LD SCLC

There is a lack of prognostic and predictive factors to define subgroups of LD SCLC that should be treated differently, both at baseline and during treatment. Studies indicate that early response to treatment is associated with outcomes [259-261], and might be a method for identifying patients who do not benefit from TRT, or those who potentially benefit from changes in systemic therapy or TRT.

2.7.4.1 Tumour response assessment

Response from therapy can be measured in different ways, including patient reported outcome measures (PROMS), physical function, biomarkers and the use of imaging techniques. A combination of a biomarker (NSE) and imaging technique (CT) is commonly used to evaluate response from chemoradiotherapy in LD SCLC [262].

There is no established role for PET-CT in routine tumour response assessment [263].

2.7.4.2 Criteria for tumour response on CT

In 1981 the WHO published criteria for evaluating tumour response by use of imaging techniques. A change in sum of bi-dimensional products of lesions relative to baseline was used to assess response [264]. However, there was variation in interpretation of the criteria, and several authors made adaptations to the definition. Because of the resulting confusion in interpreting trial results, an international group was formed in the mid 1990s to standardise and simplify criteria for response.

This initiative led to the commonly used Response Evaluation Criteria In Solid Tumours (RECIST) criteria, first published in 2000 (v1.0) [265], and updated in 2009 (v1.1) [266]. Measurable target lesions chosen and on a baseline CT scan, and their maximal diameter is registered. According to the latest edition (v1.1), the short-axis diameter is used for lymph nodes. The sum of diameters is obtained on baseline and post-therapy scans. The response categories are based on the relative reduction in sum of diameters of measurable lesions. All lesions have to disappear to qualify for a complete response (CR). A non-CR reduction in SOD of ≥ 30% is denoted a partial response (PR), while progressive disease (PD) is any increase in SOD of ≥ 20%. Any change in SOD between +20% and -30% is stable disease (SD). Response categories are also influenced by non-measurable disease or non-target lesions. E.g. a new lesion will qualify for PD independent of development of target lesions.

2.7.5 Implementation of best practice

Patients with LD SCLC should be handled according to the best documented procedures in all aspects of care, including pre-treatment assessment, treatment and follow-up.

Although there has been progress in adherence to quality indicators and standard of care for patients with SCLC over time, there is room for improvement regarding the use of MRI, PET-CT, concurrent chemoradiotherapy and PCI [226, 267, 268].

Hyperfractionated TRT has been recommended in guidelines for many years [23, 24, 38-40], but studies report that still only 1 in 5 patients receive this schedule

(USA and Poland) [226, 268]. Interestingly, 44% of Japanese patients received twice daily radiotherapy, soon after the article demonstrating best survival from this schedule was published in 1999 [267]. In a previous study, we experienced that TRT often was delivered late or not at all [91].

To improve outcomes in LD SCLC, it is important to continue conducting clinical trials. In addition to identifying new and improved treatment, research protocols can be valuable tools for implementing evidence-based practice.

3. Aims for the project

The overall aim of the project was to improve treatment of patients with LD SCLC through a national randomised controlled trial. We evaluated the clinical effects from hypo- and hyperfractionated accelerated radiotherapy in LC SCLC. Furthermore, we investigated the impact of comorbidity on treatment and treatment effects. Finally, we investigated if response from the first course of chemotherapy could identify patients with inferior progression-free or overall survival.

4. Research questions

Paper I

Does twice daily accelerated radiotherapy result in a longer progression-free or overall survival compared to once daily accelerated radiotherapy?

Does twice daily accelerated radiotherapy result in more toxicity than once daily accelerated radiotherapy?

Primary endpoint was 1-year progression-free survival.
Secondary endpoints were response rates, progression-free survival, overall survival, toxicity and health related quality of life.

Paper II

Do patients with severe comorbidity have a shorter progression-free or overall survival compared to others?

Do patients with severe comorbidity experience more toxicity than others?

Primary endpoint was overall survival.
Secondary endpoints were treatment completion and toxicity.

Paper III

How many patients have a reduction in size of tumours after the first course of chemotherapy?

Is there an association between reduction in size of tumours after the first course of chemotherapy and progression-free or overall survival?

Primary endpoint was overall survival.
Secondary endpoints were response rates and progression-free survival.

5. Material and methods

This thesis is based on a national multicentre phase II randomised controlled trial (RCT), initiated by the Norwegian Lung Cancer Study Group (NLCG) in 2005 [269]. The NLCG was established in 1987, and has members from all medical disciplines involved in diagnosis and treatment of lung cancer from all Norwegian health regions. The main activities are clinical research and development of national guidelines for care of patients with thoracic malignancies.

A PhD project was outlined in the last year before enrolment was completed in 2011, and the project received funding from the Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU) in 2013. The PhD candidate has been responsible for collecting, organising, and analysing data for all parts of the thesis, and had a lead role preparing manuscripts and presenting results.

5.1 Inclusion and eligibility criteria

5.1.1 Investigations

Patients had a clinical examination and screening of blood (haemoglobin, leukocytes, platelets, SR, AST, ALT, GGT, ALP, LD, Bilirubin, Albumin, Na+, K+, Ca++, creatinine and NSE).

A CT scan of thorax and upper abdomen, MRI of brain and bone scan were performed within 3 weeks prior to inclusion.

5.1.2 Main eligibility criteria

Eligible patients had limited disease small cell lung cancer (LD SCLC) considered ineligible for surgery. Limited disease was defined as disease within one hemithorax, including metastases to ipsi- and contralateral lymph nodes in mediastinum, hili and supraclavicular fossae. Pleural effusions with at least one negative cytology were allowed. SCLC had to be histologically or cytologically confirmed. All patients gave written informed consent, had age of at least 18 years, performance status WHO 0-2, measurable disease, satisfactory blood tests (leukocytes > 3,0 x 109/l, platelets > 100 x 109/l, total serum bilirubin < 1,5 x upper normal limit, creatinine < 125 mol/l), no other clinically active malignancy, and no prior radiotherapy to the chest. All patients

had to be able to complete quality of life questionnaires. Pregnant or lactating women were not allowed. Fertile patients had to use contraception.

For paper II we analysed patients if medical records 3 months prior to inclusion were available. For paper III we analysed patients that completed TRT and at least two courses of chemotherapy, if a baseline CT scan obtained within 2 months prior and a CT planning scan within 1 month after start of chemotherapy were available.

5.2 Random assignment

Patients were randomised to receive TRT of 42 Gy in 15 fractions (OD) or 45 Gy in 30 fractions (BID). Randomisation was in blocks of eight and stratified for the five Norwegian health care regions.

5.3 Study treatment

5.3.1 Chemotherapy

Chemotherapy consisted of four courses of cisplatin (75 mg/m^2 intravenous day 1) and etoposide (100 mg/m^2 intravenous days 1-3) every 3 weeks (PE). The use of G-CSF was not recommended. A 25% dose-reduction was warranted if leukocytes were 2.5-2.99 x 10^9/l or platelets 75-99 x 10^9/l at the time of the next course. Courses were postponed if values were lower. Dose-reductions were maintained for remaining courses, and chemotherapy was discontinued if a course was delayed more than three weeks or a third dose-reduction was warranted. Carboplatin was allowed if cisplatin was not tolerated.

5.3.2 Thoracic radiotherapy

All patients received 3D conformal radiotherapy. TRT was delivered five days a week and started 3-4 weeks after initiation of the first PE-course. A planning CT scan was performed within one week prior to TRT. Gross tumour volume (GTV) consisted of pathological lesions on baseline scan delineated according to size at planning scan. The clinical target volume (CTV) included GTV with a 1 cm margin in all directions (CTV_{tumor}) plus the central part of the mediastinum comprising lymph node stations 4-7 ($CTV_{mediastinum}$) as an elective nodal volume. An internal margin (IM) of 1.0 cm was

added to the CTV_{tumor} in the transverse plane and 1.0-1.5 cm in the craniocaudal direction. An IM of 0.5 cm was added to the $CTV_{mediastinum}$ in all directions. Finally, a setup margin was added according to each hospitals routine.
Less than 50% of the normal lung tissue should receive more than 20 Gy ($V20_{lung}$ < 50%). Other normal tissue constraints were defined and treatment verification was done according to local routines.

5.3.3 Prophylactic cranial irradiation (PCI)

Prophylactic cranial irradiation (PCI) was offered to patients with a complete or near complete response 3 weeks after completing chemotherapy and thoracic radiotherapy. PCI started within six weeks, and a schedule of 30 Gy in 15 fractions was used.

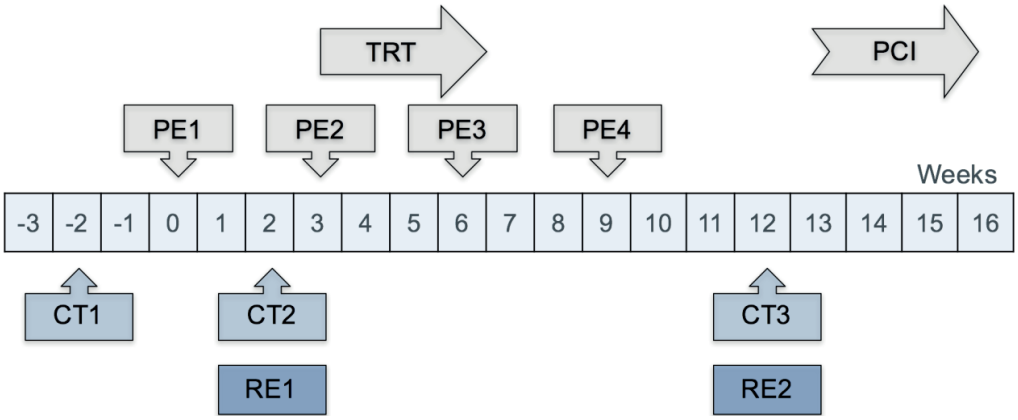
5.3.4 Second-line therapy

There were no restrictions with respect to salvage therapy.

5.4 Evaluation and follow-up

The trial plan is presented in Figure 10 and Table 1. Clinical examination and assessment of toxicity was performed at start of every course of chemotherapy and weekly during radiotherapy. Overall response to treatment was assessed 3 weeks after completion of chemoradiotherapy. Patients were evaluated every eight weeks the first year, every four months the second and third year and every six months thereafter for a total of 5 years. (Table 1). A CT of thorax and upper abdomen was performed at evaluations the first year. Chest x-ray or CT scan (optional), was performed on later evaluations. If progression was suspected on a chest x-ray a CT scan was performed.

Figure 10 Treatment and evaluation schedule.



Patients had a baseline CT scan (CT1) prior to starting chemotherapy consisting cisplatin and etoposide (PE1-4). Early response (RE1) was evaluated on a planning CT scan (CT2) before commencing thoracic radiotherapy (TRT). Response to chemoradiotherapy (RE2) was evaluated on a CT scan (CT3) after completion of therapy. Patients with a CR, or near-CR, at RE2 were offered prophylactic cranial irradiation (PCI).

Table 1 Study procedures.

Trial plan

									Follow up				
Week	**-1 - 0**	**0**	**3-4**	**6**	**6-7**	**9**	**12**	**15-18**	**20**	**28**	**36**	**44**	**52**
	Screen	1. cycle	2. cycle/ start RT	3. cycle	End RT	4. cycle	Evaluation	PCI					
QoL	X		X		X		X		X	X			X
Lab tests	X		X	X		X	X		X	X	X	X	X
Bone scan	X												
MR cerebrum	X												
Chest X-ray	X		X	X		X	X		X	X	X	X	X
CT thorax / u. abdomen	X						X		X	X	X	X	X

5.5 Assessments

Stage of disease was assessed according to TNM v6 [270]. Toxicity was assessed according to CTCAE v3.0 [207]. Patients reported HRQoL on the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30 and the lung cancer specific module LC13 (Appendix A) [210-212]. The questionnaires were completed at inclusion, weeks 3, 6, 12, 20, 28 and 52.

After training, comorbidity was retrospectively assessed by one oncologist (TOH) from medical records (including list of medications) of the 3-months prior to inclusion. Comorbidity was scored according to the Charlson Comorbidity Index (CCI) (Appendix B) [249].

Response was assessed according to RECIST 1.0. Measurable lesions (target lesions) were defined as lesions ≥ 10 mm. Up to 10 target lesions (maximum 5 per organ) were measured. Sum of largest diameter (SOD) of target lesions at CT1 (baseline) was compared with SOD of these lesions at CT2 (planning scan). According to the RECIST criteria, a complete response (CR) is disappearance of all measurable lesions; Partial response (PR) is a non-CR reduction in SOD of ≥ 30%. An increase in SOD of ≥ 20% is progressive disease, while stable disease (SD) is any change in SOD between +20% and -30% [265].

A central review of response after the first course of chemotherapy was conducted by a radiologist (MH) and an oncologist (TOH). Since staging of disease was based on CT alone, using the RECIST 1.0 criteria for response evaluation, we additionally performed all analyses for paper III evaluating only the change in size of the primary tumours. Not all lymph nodes considered pathological according to RECIST 1.0 are defined as pathological according to RECIST 1.1.

5.6 Statistics

Based on results from a previous trial, we expected a 1-year progression-free survival on the control arm of 70%. To detect a 30% improvement from twice-daily TRT (from 70% to 91%) with a two-sided alpha of 0.05 and a beta of 0.20, 75 patients were required on each arm. We expected a loss to follow-up of < 10%, and aimed at enrolling 83 patients in each arm.

HRQoL-scores were calculated using the QLQ-C30 scoring manual [212]. Scores are given on a scale from 0 to 100 for each item. A difference in mean score of at least 10 was considered clinically relevant. We used the Kaplan-Meier method for survival analyses. Progression-free survival (PFS) was defined as time from randomisation until relapse or death. Overall survival (OS) was defined as time form randomisation until death. For comparison of survival we used the log-rank test (univariate) and Cox proportional hazards method (multivariate). Multivariate models were adjusted for study treatment and baseline characteristics. Pearson's Chi-square and Fisher's exact tests were used for group-wise comparisons of categorical data. A $p < 0.05$ was considered statistically significant.

Follow-up for PFS was equal for all studies (July 2013). For paper I, the minimum follow-up for OS was 4 years (April 2015), and for paper II and III minimum 5 years (February 2016).

5.7 Ethics

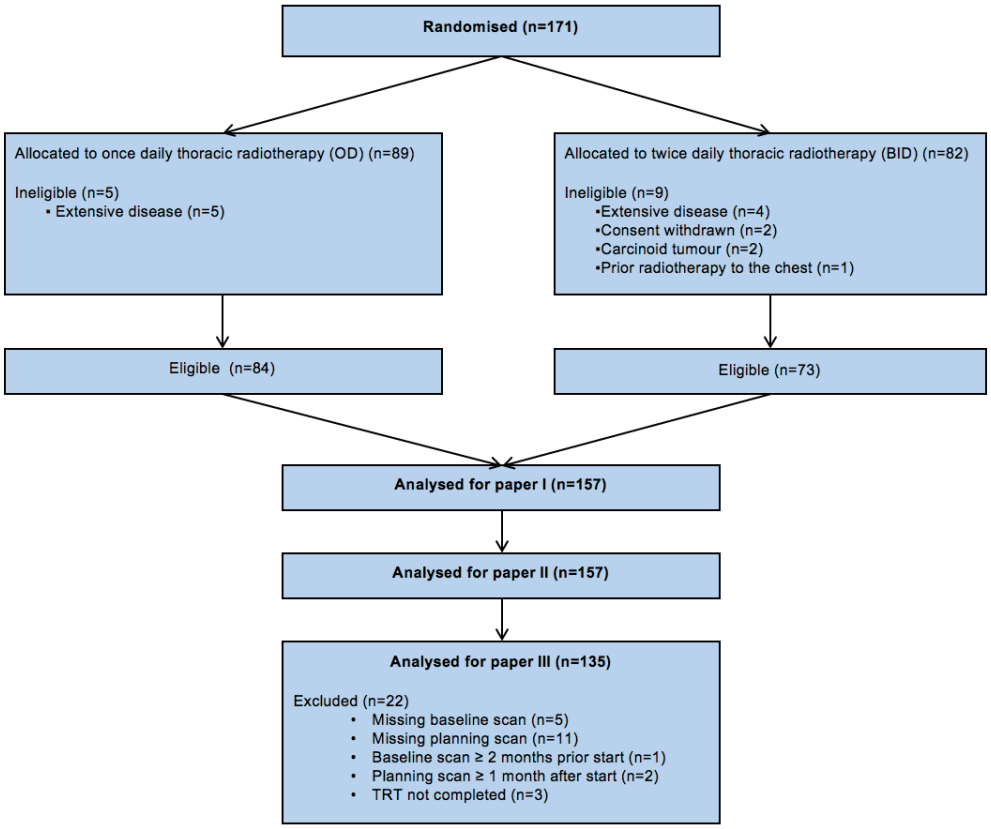
The trial was approved by the Regional Committee for Medical Research Ethics, Central Norway, the Norwegian Social Science Data Services and the Norwegian Directorate for Health and Social Affairs. All patients gave written informed consent. The research was conducted according to the Helsinki declaration and principles of Good Clinical Practice (GCP).

5.8 Financial support

This project was funded by The Norwegian Cancer Society, the Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU).

6. Summary of papers

Figure 11 Patient selection.



6.1 Paper I

6.1.1 Patients

One-hundred-seventy-one patients with LD SCLC were enrolled at 18 Norwegian hospitals between 2005 and 2011. Fourteen patients were ineligible; extensive disease (n=9); withdrawn consent (n=2), carcinoid tumour (n=2) and prior radiotherapy to the chest (n=1). Of the 157 eligible patients 84 were randomised to receive once daily TRT and 73 twice daily TRT (Figure 11).
Median age was 63, 26% were ≥ 70 years, 52% were men, 84% had PS 0-1, 11% cytological negative pleural fluid and 72% stage III disease. Baseline characteristics were balanced for treatment arm (Table 2).

Median follow-up for PFS was 59 months (range: 29-97). Thirty-four were progression-free at time of analyses (July 2013). Median follow-up for OS was 81 months (range: 52-119). Thirty-four were alive at time of analyses (April 15).

Table 2 Baseline characteristics.

		Once daily (OD) (n=84)		Twice daily (BID) (n=73)	
Age	Median (range)	63 (40-85)		63 (44-79)	
	≥ 70 years	26	31 %	15	21 %
Sex	Women	39	46 %	37	51 %
	Men	45	54 %	36	49 %
PS	0	31	37 %	20	27 %
	1	42	50 %	39	53 %
	2	11	13 %	14	19 %
Pleural fluid	Present	11	13 %	7	10 %
Stage	I	7	8 %	6	8 %
	II	7	8 %	9	12 %
	IIIA	34	40 %	21	29 %
	IIIB	30	36 %	28	38 %
	Unknown	6	7 %	9	12 %

6.1.2 Study treatment

6.1.2.1 Chemotherapy

There was no difference in mean number of PE-courses (OD: 3.86, BID: 3.78, p=.33). More patients on the once daily arm completed chemotherapy without delays (OD: 42%, BID: 26%, p=.04). There were no other differences in completion of chemotherapy.

6.1.2.2 Radiotherapy

Completion of TRT was similar in both arms (OD: 96%, BID: 97%, p=1.0). There was no difference in receipt of PCI (OD: 82%, BID: 84%, p=.81).

6.1.3 Second-line treatment

There was no difference in the frequency or choice of second-line therapy between treatment arms (OD: 52%, BID: 44%, p=.36). Re-introduction of PE was most common.

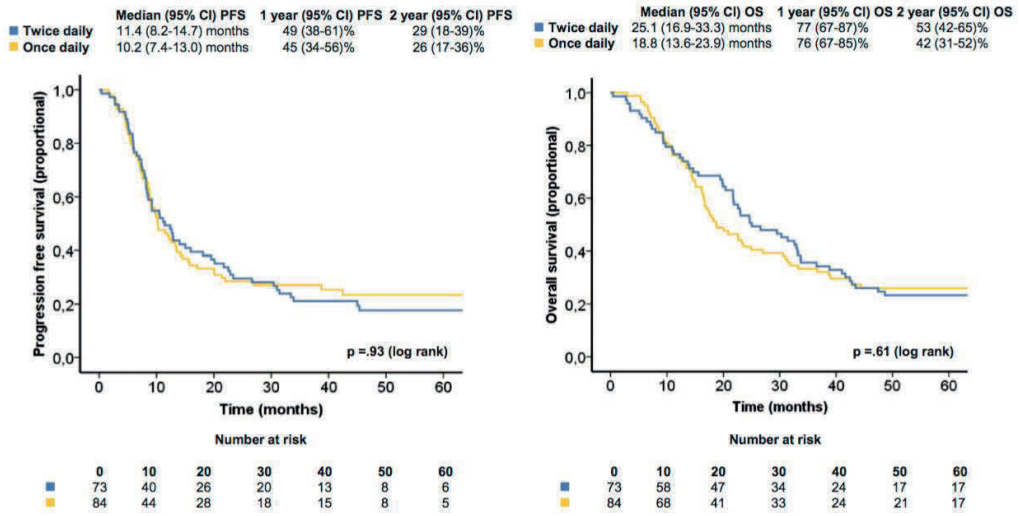
6.1.4 Response to therapy, PFS and OS

There was no significant difference in response rates (OD: 92%, BID: 88%, p=.41), but more patients on the BID arm achieved a complete response (OD: 13%, BID: 33%, p=.003).

There were no statistically significant differences in 1-year PFS (OD: 45%, BID: 49%, p=.61) or median PFS (OD: 10.2 months, BID: 11.4 months, p=.93) (Figure 12).

Patients receiving twice daily radiotherapy had a 6 months longer median survival, but the difference was not statistically significant (OD: 18.8 months, BID: 25.1 months, p=.61). There was no difference in 4-year (OD: 25%, BID: 25%, p=.91) or 5-year OS (OD: 25%, BID: 23%, p=.80) between treatment arms (Figure 12).

Figure 12 Comparison of PFS and OS between OD and BID TRT.



6.1.5 Toxicity

There were no differences in grade 3-4 anaemia (OD: 11%, BID: 22%, p=.06), neutropenia (OD: 86%, BID: 81%, p=.41) or thrombocytopenia (OD: 35%, BID: 38%, p=.62). There were no differences in grade 3-4 neutropenic infections (OD: 44%, BID: 37%, p=.37), non-neutropenic infections (OD: 10%, BID: 10%, p=.99), esophagitis (OD: 31%, BID: 33%, p=.80) or pneumonitis (OD: 2%, BID: 3%, p=1.0) (Table 3). Three patients died within 30 days of chemoradiotherapy (haemoptysis: n=1, coronary disease: n=1 and respiratory failure: n=1). Four patients died from radiation pneumonitis (OD: n=3, BID: n=1). Combined, there was no difference in treatment-related deaths (OD: n=4, BID: n=3; p=1.0).

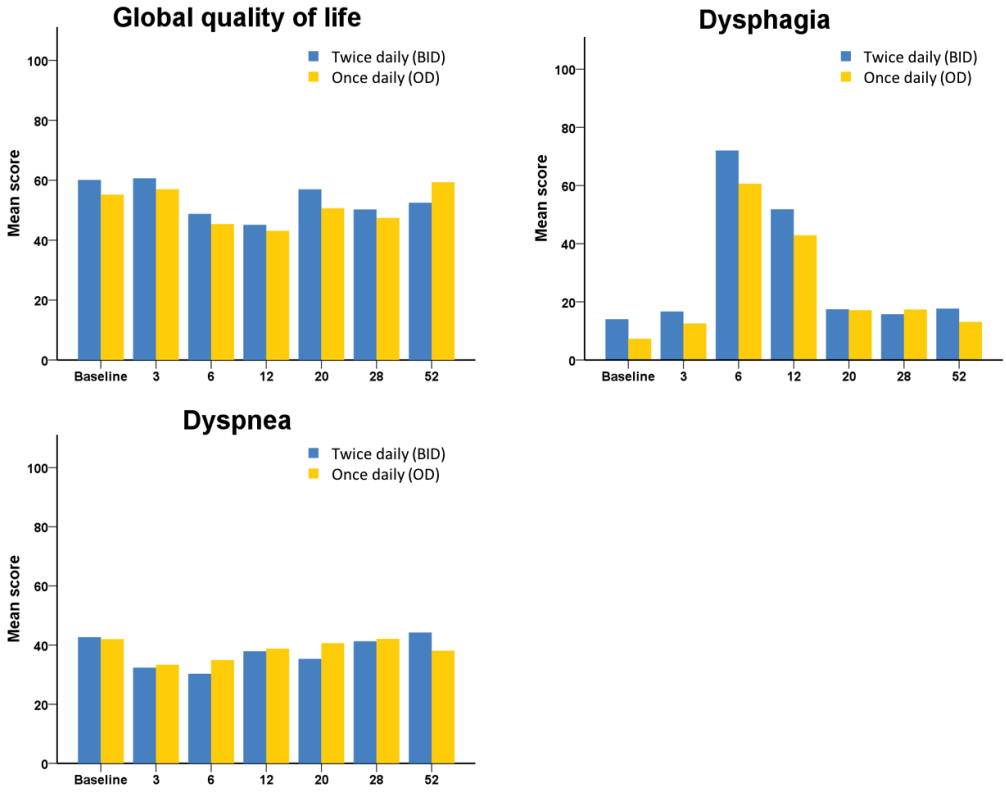
Table 3 Toxicity from once or twice daily radiotherapy.

	CTCAE grade	Once daily (OD) (n=84)		Twice daily (BID) (n=73)		p
Esophagitis	0-2	58	69 %	49	67 %	0.80
	3-4	26	31 %	24	33 %	0.80
	5	-	-	-	-	-
Pneumonitis	0-2	79	94 %	70	96 %	0.73
	3-4	2	2 %	2	3 %	1.0
	5	3	4 %	1	1 %	0.62
Anaemia	3-4	9	11 %	16	22 %	0.06
Leukopenia	3-4	58	69 %	57	68 %	0.20
Thrombocytopenia	3-4	29	35 %	28	38 %	0.62
Neutropenia	3-4	72	86 %	59	81 %	0.41
Neutropenic infections	3-4	37	44 %	27	37 %	0.37
Infection without neutropenia	3-4	8	10 %	7	10 %	.99

6.1.6 HRQoL

Completion of questionnaires was similar in both arms, ranging between 85% and 97% at the different time-points. Patients receiving twice daily radiotherapy reported more dysphagia at baseline, but the difference in mean score was not significant (OD: 7, BID:14). The difference exceeded 10 points during radiotherapy week 6 (OD: 61, BID: 72), but returned to baseline levels after radiotherapy on both treatment arms. There were no other differences in global quality of life (QoL), dysphagia, dyspnoea or in any other HRQoL-domain (Figure 13).

Figure 13 Mean HRQoL scores for patients receiving once or twice daily radiotherapy.



A higher score on the global QoL scale represents a better HRQoL, a higher score on the symptom scales is associated with a worse HRQoL. A difference in mean scores of 10 points was considered clinically relevant.

6.2 Paper II

6.2.1 Patients

All 157 eligible patients from the RCT were included in this study. All patients were analysed as one cohort, as there were no differences in toxicity or survival between treatment arms in paper I. Due to a low number of patients, patients with CCI 3, 4 and 5 were analysed together. Median age was 8-10 years higher, and there were more men, among those with most comorbidity. Otherwise baseline characteristics were balanced between the different CCI-categories (Table 4).

Table 4 Baseline characteristics across CCI -scores.

		Overall (n=157)		CCI 0 (n=63)		CCI 1 (n=54)		CCI 2 (n=23)		CCI 3-5 (n=17)	
		n	%	n	%	n	%	n	%	n	%
Age	Median (range)	63 (40-85)		62 (40-79)		64 (41-79)		64 (51-85)		72 (56-79)	
	<70	116	74%	54	86%	39	72%	17	74%	6	35%
	≥70	41	26%	9	14%	15	28%	6	26%	11	65%
Gender	Women	76	48%	34	54%	28	52%	9	39%	5	29%
	Men	81	52%	29	46%	26	48%	14	61%	12	71%
Performance status	0	51	32%	19	30%	20	37%	9	39%	3	18%
	1	81	52%	35	56%	26	48%	10	44%	10	59%
	2	25	16%	9	14%	8	15%	4	17%	4	24%
Stage	I	13	8%	4	6%	5	9%	2	9%	2	12%
	II	16	10%	9	14%	2	4%	4	17%	1	6%
	III	113	72%	45	71%	45	83%	10	43%	13	76%
	Unknown	15	10%	5	8%	2	4%	7	30%	1	6%
Thoracic radiotherapy	Once daily:	84	54%	29	46%	33	61%	14	61%	8	47%
	Twice daily:	73	46%	34	54%	21	39%	9	39%	9	53%

6.2.2 Comorbidity

Sixty-three patients (40%) had no comorbidity. Mean CCI score was 0.99. Distribution of CCI-scores is listed in Table 5. The proportion with comorbidity was significantly higher among elderly patients (<70 years: 53%, ≥70 years: 78%, p=.006) and they had a significantly higher mean CCI-score (<70 years: 0.78, ≥70 years: 1.59, p<.001) (Table 5).

Table 5 Distribution of comorbidity in overall population and by age.

CCI-score	Overall population		<70 years		≥70 years	
	n	%	n	%	n	%
0	63	40%	54	47%	9	22%
1	54	34%	39	34%	15	37%
2	23	15%	17	15%	6	15%
3	13	8%	6	5%	7	17%
4	3	2%	0	0%	3	7%
5	1	1%	0	0%	1	2%

Most common co-existing conditions were chronic obstructive pulmonary disease (38%), peptic ulcer disease (12%), myocardial infarction (11%), diabetes mellitus (11%), peripheral vascular disease (8%), and cerebrovascular disease (8%).

6.2.3 Treatment completion

There was no significant difference across CCI-scores in the proportion that received four courses of cisplatin and etoposide (p=.09); completed chemotherapy without dose-reductions (p=.07); completed TRT as planned (p=.54); or received PCI (p=.30). The overall dose-intensity of the chemotherapy was 92%, and there were no significant differences across CCI-scores (p=.25). Fewer patients with CCI 3-5 received second-line therapy (p=.010) (Table 6).

Table 6 Treatment completion across CCI-scores.

		Overall population (n=157)	CCI 0 (n=63)	CCI 1 (n=54)	CCI 2 (n=23)	CCI 3-5 (n=17)	p
Chemotherapy	Completed all four courses	86%	94%	82%	83%	77%	.09
	No dose reduction	44%	52%	33%	57%	29%	.07
	Mean dose-intensity	92%	93%	91%	94%	89%	.25
	Received second-line chemotherapy	48%	57%	50%	44%	12%	.010
Radiotherapy	Thoracic radiotherapy completed as planned	97%	98%	94%	96%	100%	.54
	Received prophylactic cranial irradiation	83%	89%	76%	83%	82%	.30

6.2.4 Toxicity

In the overall population, 141 patients (92%) experienced grade 3-5 toxicity. Grade 3-5 haematological toxicity was observed in 89% and grade 3-5 non-haematological toxicity was observed in 69% of patients. The most common non-haematological toxicities included neutropenic infections (41%), radiation esophagitis (32%) and infections without neutropenia (10%). Eight patients (5%) had radiation pneumonitis. Grade 5 toxicity was only observed from radiation pneumonitis (n=4, 3%) (Table 7)

There were no statistical significant differences in the frequency of grade 3-5 toxicity (p=.49), grade 3-5 haematological toxicity (p=.23) or grade 3-5 non-haematological toxicity (p=.98) across CCI-scores. There was no association between CCI-score and grade 3-5 neutropenic infections (p=.86), radiation esophagitis (p=.36) or radiation pneumonitis (p=.76).

Treatment-related deaths were observed in 7 patients (radiation pneumonitis: n=4, coronary disease: n=1, haemoptysis: n=1 and respiratory failure: n=1). There was no significant association between CCI-scores and treatment-related deaths (CCI 0: n=1, CCI 1: n=4, CCI 2: n=1, CCI 3: n=1, p=.36).

Table 7 Treatment toxicity and treatment-related deaths.

Toxicity	Overall population (n=157)	CCI 0 (n=63)	CCI 1 (n=54)	CCI 2 (n=23)	CCI 3-5 (n=17)	p
Any grade 3-5 haematological	89%	87%	88%	100%	82%	.23
Anaemia	18%	19%	17%	22%	12%	.86
Neutropenia	83%	87%	82%	91%	65%	.13
Thrombocytopenia	41%	40%	44%	39%	35%	.94
Any grade 3-5 non-haematological	69%	68%	69%	74%	69%	.98
Neutropenic infections	41%	41%	39%	48%	35%	.86
Radiation esophagitis	32%	38%	28%	35%	18%	.36
Radiation pneumonitis	5%	5%	4%	9%	6%	.76
Any grade 3-5 toxicity*	92%	89%	92%	100%	94%	.49

Treatment related deaths	CCI	Co-existing conditions	Age
Coronary heart disease	3	Myocardial infarction, congestive heart failure and chronic obstructive pulmonary disease (COPD)	62
Radiation pneumonitis	2	Cerebrovascular disease and COPD	75
Haemoptysis	1	COPD	69
Radiation pneumonitis	1	COPD	62
Respiratory failure	1	Peripheral vascular disease	76
Radiation pneumonitis	1	Peripheral vascular disease	73
Radiation pneumonitis	0	-	65

** Grade 5 toxicity was observed in 4 patients with pneumonitis (CCI 0: n=1, CCI 1: n=2, CCI 2: n=1; p=.70).*

6.2.5 Response to therapy, PFS and OS

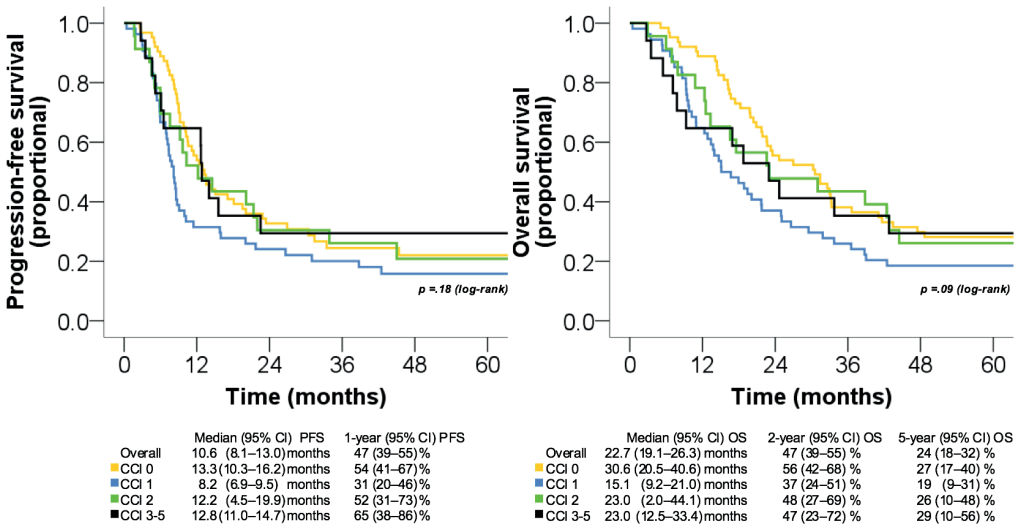
Objective response from chemoradiotherapy was observed in 90% of patients. Rate of response was not significantly associated with CCI-score (CCI 0: 95%, CCI 1: 87%, CCI 2: 87%, CCI 3-5: 82%, p=.20).

Median progression-free survival for the total population was 10.6 months, and the 1-year PFS was 47%. There was no significant difference in PFS across CCI-categories (p=.18), but patients with CCI 1 had a lower 1-year PFS (31%) than others (52-65%) (p=.32) (Figure 14).

For the whole population, median overall survival was 22.7 months, 2-year survival 47% and 5-year survival was 24%. Patients with CCI 1 had the lowest median, 2-year and 5-year survival, but there were no significant differences across CCI-scores (median: p=.09, 2-year: p=.26, 5-year: p=.67) (Figure 14).

Neither CCI-score (p=.23), nor any of the other baseline characteristics were independent prognostic factors in multivariate analyses (Table 8).

Figure 14 Comparison of PFS and OS across CCI-scores.



	Median (95% CI) PFS	1-year (95% CI) PFS
Overall	10.6 (8.1–13.0) months	47 (39–55) %
CCI 0	13.3 (10.3–16.2) months	54 (41–67) %
CCI 1	8.2 (6.9–9.5) months	31 (20–46) %
CCI 2	12.2 (4.5–19.9) months	52 (31–73) %
CCI 3-5	12.8 (11.0–14.7) months	65 (38–86) %

	Median (95% CI) OS	2-year (95% CI) OS	5-year (95% CI) OS
Overall	22.7 (19.1–26.3) months	47 (39–55) %	24 (18–32) %
CCI 0	30.6 (20.5–40.6) months	56 (42–68) %	27 (17–40) %
CCI 1	15.1 (9.2–21.0) months	37 (24–51) %	19 (9–31) %
CCI 2	23.0 (2.0–44.1) months	48 (27–69) %	26 (10–48) %
CCI 3-5	23.0 (12.5–33.4) months	47 (23–72) %	29 (10–56) %

Table 8 Multivariate survival analyses. Age was entered as a continuous variable. Female sex, once daily radiotherapy, stage I, PS 0 and CCI 0 were reference categories for categorical variables. Overall p-value is presented for variables with more than two categories.

Variables*		Hazard ratio	95% CI		p
Age		1.01	0.99	1.04	.27
Gender	Female	1			
	Male	0.96	0.65	1.41	.82
Thoracic radiotherapy	OD	1			
	BID	1.16	0.79	1.71	.45
Stage	I	1			
	II	0.48	0.19	1.22	
	III	1.10	0.58	2.09	.10
PS	0	1			
	1	1.09	0.71	1.66	
	2	1.39	0.79	2.45	.52
CCI	0	1			
	1	1.43	0.93	2.20	
	2	1.04	0.55	1.98	
	3-5	0.77	0.38	1.59	.23

6.3 Paper III

6.3.1 Patients

Since there were no differences in survival or toxicity between patients receiving once or twice daily radiotherapy in paper I, all patients were analysed as one cohort. Twenty-two patients were excluded from analyses due to missing baseline (n=5) or planning (n=11) CT scan; baseline CT scan more than two months prior (n=1) or planning CT scan one month later (n=2) than start of chemotherapy; and TRT not completed (n=3). Thus, 135/157 patients (86%) were eligible for the present study.

Baseline characteristics and completion of treatment is presented in Table 9. Median age was 64 years; 53% were men; 15% had PS 2 and 74% stage III disease.

Mean number of PE-courses was 3.86, 118 patients (87%) completed four courses. Sixty patients (44%) received twice daily radiotherapy. One hundred and

fifteen patients (85%) received PCI, and 64 (47%) received second-line chemotherapy.

Table 9 Baseline characteristics and treatment completion. Cisplatin and Etoposide (PE), Prophylactic cranial irradiation (PCI).

		All patients (n=135)		Partial response after first PE (n=24)		Stable disease after first PE (n=111)	
Age	Median (range)	64 (40-85) years		64 (49-76) years		63 (40-85) years	
	<70	97	72%	17	71%	80	72%
	≥70	38	28%	7	29%	31	28%
Gender	Female	64	47%	11	46%	53	48%
	Male	71	53%	13	54%	58	52%
PS	0:	45	33%	9	38%	36	32%
	1:	70	52%	11	46%	59	53%
	2:	20	15%	4	17%	16	14%
Stage	I:	11	8%	2	8%	9	8%
	II:	12	9%	5	21%	7	6%
	III:	100	74%	16	67%	84	76%
	Unknown:	12	9%	1	4%	11	10%
Thoracic radiotherapy	Once daily:	75	56%	11	46%	64	58%
	Twice daily:	60	44%	13	54%	47	42%
Completed four PE-courses		118	87%	23	96%	95	86%
Completed PCI		115	85%	24	100%	91	82%
Received 2. line chemotherapy		64	47%	12	50%	52	47%

6.3.2 Time between scans

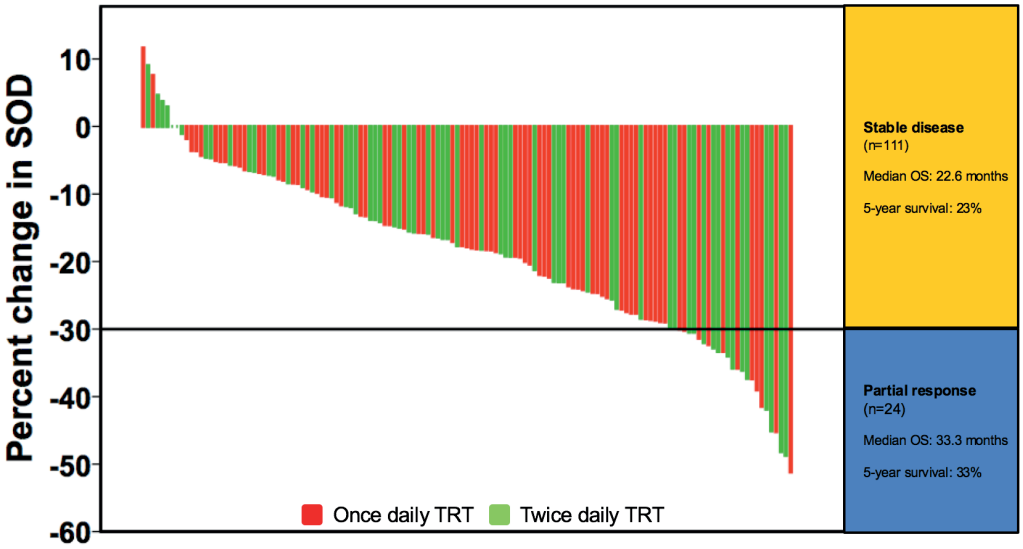
Schedule for treatment and evaluations are presented in Figure 10 and Table 1. Median time from CT1 (baseline) to start of PE1 (first course of chemotherapy) was 17 days (range: 0 - 60). Median time from start of PE1 to CT2 (planning scan) was 18 days (range: 6 - 30). Median time between CT1 and CT2 was 35 days (range: 14 - 85).

6.3.3 Sum of diameters and response to the first course of chemotherapy

On the baseline scan, median sum of diameter (SOD) was 96 mm (range: 14 - 260 mm). On the planning scan median SOD was 76 mm (range: 14 - 196 mm). A reduction in size was observed in 127 patients (94%). Median change in SOD between scans was ÷16 mm (range: ÷84 to +10 mm), corresponding to a median change of ÷18% (range: ÷51 to +12%). According to RECIST, 24 patients (18%) achieved a partial response (PR), and 111 patients (82%) stable disease (SD) after the first course of chemotherapy (PE1) (Figure 15).

There were no significant differences in the proportion completing four PE-courses (p=.31); receiving 45 Gy (p=.29) or second-line chemotherapy (p=.78) between patients with PD or SD at RE1. Patients with a PR were more likely to receive PCI (PR: 100%, SD: 82%; p=.024).

Figure 15 Waterfall plot of percent change in sum of diameters (SOD) of measurable lesions after first course of chemotherapy in all patients (n=135), with corresponding median and 5-year survival for patients with stable disease (SD) or partial response (PR).



6.3.4 Response evaluation at completion of chemoradiotherapy (RE2)

The overall response rate was 90%; 23% achieved CR; 67% PR; 1% SD and 5% PD. Four patients (3%) was not evaluable at RE2.

There was no significant association between increasing SOD reduction and response rates to chemoradiotherapy (p=.15), but there was a significant association with CR (OR: 1.04, 95% CI 1.00-1.07; p=.025).

There was a trend towards more overall responses at RE2 among patients with a PR (100%) compared to SD (88%) at RE1 (p=.08). A CR at RE2 was significantly more common among those with a PR at RE1 (PR: 42%, SD:19%, p=.016) (Table 10).

In multivariate analyses, there was a trend towards increased response rate with increasing SOD reduction (OR: 1.06, 95% CI 0.99-1.12; p=.08), and the association with CR was significant (OR: 1.05, 95% CI 1.01-1.09; p=.013). There was a significant association between PR at RE1 and CR at RE2 (OR: 3.72, 95% CI 1.26-11.02; p=.018).

Table 10 Overall responses, PFS and OS for patients with SD or PR after first course of chemotherapy (RE1).

		All patients (n=135)		Partial response after first course (n=24)		Stable disease after first course (n=111)		p
Response after chemo-	CR	31	23%	10	42%	21	19%	.016
radiotherapy	PR	91	67%	4	56%	77	69%	
	SD	2	1%	-	-	2	2%	
	PD	7	5%	-	-	7	6%	
	NE	4	3%	-	-	4	4%	
Progression-free survival	Median (95% CI) months	11.4 (8.5 – 14.4)		19.5 (6.0 – 33.1)		9.9 (7.6 – 12.3)		.20
	1-year	66	49%	17	71%	49	44%	.018
Overall survival	Median (95% CI) months	23.6 (17.1 – 30.0)		33.3 (21.0 - 45.5)		22.6 (18.5 – 26.7)		.14
	2-year	67	50%	16	67%	51	46%	.07
	5-year	34	25%	8	33%	26	23%	.31

6.3.5 Progression-free survival (PFS)

Median PFS was 11.4 months in the overall population, and improved with increasing reduction in SOD at RE1 (HR: 0.99, p=.043). Patients with a PR at RE1 had a numerically, but not significantly longer median overall PFS (PR: 19.5 months, SD: 9.9 months; p=.20) (Figure 16 and Table 10).

In multivariate analyses, PFS improved significantly with increasing SOD-reduction (HR: 0.97, p=.001), and there was a trend towards improved PFS for those with PR at RE1 (HR: 0.63, p=.10).

6.3.6 Overall survival (OS)

Median overall survival in the whole study cohort was 23.6 months with 25% 5-year survival. There was a trend towards improved overall survival with increasing reduction of SOD at RE1 (HR: 0.99, p=.07); a significantly improved 2-year survival (OR: 1.03, p=.026), but no improvement in 5-year survival (OR: 1.02, p=.19) (Figure 16) (Table 10).

The difference in median overall survival between those with PR and SD at RE1 was not statistically significant (PR: 33.3 months, SD: 22.6 months; p=.14). There was a trend towards improved 2-year survival (PR: 67%, SD: 46%; p=.07), but

not 5-year survival (PR: 33%, SD: 23%; p=.31). Patients without a reduction in tumour size (n=8) had a median overall survival of 19.9 months.

In multivariate analyses increasing SOD reduction resulted in improved overall survival (HR: 0.98, p=.010) (Table 11), 2-year survival (OR: 1.04, p=.011), and there was a trend towards improved 5-year survival (OR: 1.05, 95% CI 1.01-1.09; p=.07). The association was not significant when comparing PR with SD: overall survival (p=.17), 2-year survival (p=.12) or 5-year survival (p=.41).

Figure 16 Comparison of PFS and OS between patients achieving PR or SD after first course of chemotherapy (RE1).

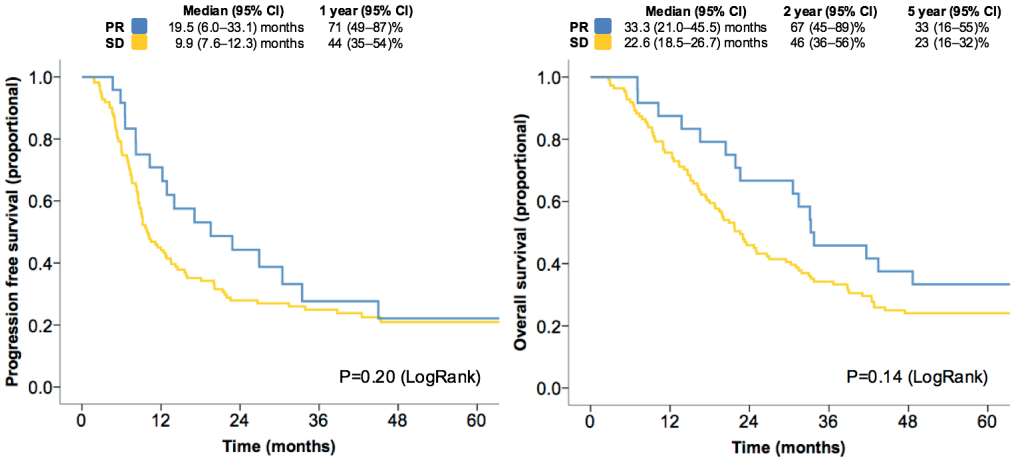


Table 11 Multivariate survival analyses. *Age and percent SOD reduction after first chemotherapy-course was entered as a continuous variable. Female gender, PS 0, stage I and once-daily radiotherapy were defined as reference categories for categorical variables. Overall p-value is presented for variables with more than two categories.

		HR	95 % CI		p
Age*		1.01	.99	1.04	.43
Gender	Female	1			
	Male	.87	.58	1.33	.53
PS	0	1			
	1	1.09	.69	1.73	
	2	1.74	.94	3.21	.18
Stage	I	1			
	II	.43	.14	1.30	
	III	1.31	.65	2.63	.051
Treatment	Once daily	1			
	Twice daily	1.19	.79	1.79	.42
Percent SOD reduction*		.98	.96	1.00	.010

6.3.7 Change in primary tumour size and outcomes of therapy

The median primary tumour diameter (PTD) at CT1 was 62 mm (range: 12 to 137 mm); at CT2 49 mm (range: 10 to 134 mm). Median change in PTD was ÷11 mm (range: ÷44 to +11 mm) corresponding to a median change of ÷18% (range: ÷71 to +24%).

There was no significant association between percentage change in PTD and response rate (p=.26); but there was a significant association with CR (OR: 1.03 p=.029). Percentage change in PTD was significantly associated with improved PFS (HR: 0.98, p=.004); overall survival (HR: 0.98, p=.001), 2-year survival (OR: 1.04, p=.003) and 5-year survival (OR: 1.05, p=.008).

Although there was no significant association between reduction in PTD and response rates in multivariate analyses (p=.13), the association with CR remained significant (OR: 1.05, p=.006). The associations with PFS (HR: 0.97, p<.001), overall survival (HR: 0.98, p=.001), 2-year survival (OR: 1.04, p=.003), and 5-year survival (OR: 1.04, p=.008) all remained significant in multivariate analyses.

7. Discussion

Relative to its contribution in mortality and morbidity, SCLC has received little scientific attention, with little clinical research in LD SCLC, even less in thoracic radiotherapy and "*The obvious necessary trial, a comparison of the twice daily 45 Gy in 3 weeks to a higher dose once daily has been stubbornly rejected in the United States*" (quote Turrisi, 2002) [271].

We have conducted the first trial comparing twice daily TRT of 45 Gy in 3 weeks with a hypofractionated accelerated once-daily schedule. This is also the largest study investigating comorbidity and early response to therapy in LD SCLC-patients receiving concurrent chemoradiotherapy.

The study underpins that twice daily thoracic radiotherapy (BID TRT) should be considered standard in LD SCLC; patients receiving BID TRT had significantly more complete responses, a six months longer median survival, and there were no significant differences in toxicity.

Further, this study indicates that comorbidity alone might not be a reason for withholding concurrent chemo- and radiotherapy; patients with severe comorbidity did not experience more toxicity or inferior survival compared to others.

Finally, this study demonstrates that reduction in tumour size after the first course of chemotherapy is a positive prognostic factor for progression-free and overall survival.

7.1 Twice daily radiotherapy (45 Gy) as the standard in LD SCLC

We concluded that twice daily radiotherapy should remain the standard schedule in LD SCLC. Although a variation of schedules have been used, 45 Gy in 30 twice daily fractions is commonly considered standard in clinical research [96-98, 100], widely recommended in guidelines [23, 24, 38-40] and has demonstrated best results in studies [95, 97].

Results from both our treatment arms were comparable to previous reports (Table 12). We found that patients receiving twice daily radiotherapy had more complete responses and a six months longer median survival. No firm conclusion on efficacy can be drawn from this study alone, there was no difference in our primary endpoint of progression-free survival, and the difference in overall survival was not

statistically significant. Other reports of OD and BID TRT indicate that BID TRT is associated with the best survival; median OS (OD: 14-27 months, BID: 23-38 months) and 5-year OS (OD: 10-25%, BID: 20-36%), and this is further emphasized by this trial (Table 12) [91, 96, 97, 100, 143, 174].

Table 12 Results from BID or OD TRT in randomised clinical trials (RCT) and retrospective reviews (RER).

	Design	RR	Median PFS	2-year PFS	3-year PFS	Median OS	2-year OS	3-year OS	5-year OS
BID									
Turrisi 1999	RCT	87%		29%		23 months	47%		26%
Takada 2002	RCT	97%	~13 months	~30%		27 months		30%	~20%
Bettington 2013	RER		12 months	~18%		26 months			25%
Kubota 2014	RCT	95%	13 months		32%	38 months		53%	36%
Grønberg 2015	RCT	88%	11 months	29%		25 months	53%		23%
Faivre-Finn 2016	RCT					30 months	56%		
OD									
Murray 1993	RCT	85%	15 months		26%	21 months	40%		15%
Sundstrøm 2002	RCT					15 months	25%		10%
Spiro 2006	RCT	81%	11 months	18%	14%	14 months	22%	16%	
Bettington 2013	RER		12 months	~23%		21 months			20%
Socha 2015	RER					27 months		40%	
Grønberg 2015	RCT	92%	10 months	26%		19 months	42%		25%

However, results between studies may not be comparable due to differences in patient selection, staging procedures, chemotherapy, schedules and timing of radiotherapy, response-evaluation and follow-up.

Turrisi et al. reported significantly increased grade 3-5 esophagitis from BID TRT, and the incidence was comparable to patients receiving BID TRT in our trial. Patients on our control arm experienced grade 3-5 esophagitis twice as often as patients on the control arm of Turrisi. This divergence cannot be explained by differences in how radiotherapy was delivered between treatment arms or studies, and is rather a consequence of accelerated treatment to all patients in our study.

The difference in dysphagia at week 6 was small, rested on a baseline imbalance and was only observed at one time-point. There was no difference at later time points (Figure 13), and no difference in severe oesophagitis between treatment

arms. Most patients will experience symptoms of oesophagitis during radiotherapy, but these disappear shortly after and long-term sequela, such as formation of strictures, are rarely seen.

Four percent of patients receiving once-daily radiotherapy died from radiation pneumonitis. This is higher than previous [95, 143] and recent reports [100], but the number of cases was low (n=3).

7.2 Treatment of patients with comorbidity

A high and increasing proportion of patients with LD SCLC suffer from comorbidity [243]. In this study patients with severe comorbidity did not experience more toxicity or have worse survival compared with the other patients. Several other studies report that comorbidity is not a prognostic factor in SCLC [223, 224, 245-247] while some studies indicate that comorbidity is a prognostic factor [239-244]. These studies are not necessarily comparable (Table 13).

Table 13 Studies reporting association between comorbidity and outcomes in SCLC.

	Design	Assessment	Association with survival	Association with treatment
Ludbrook 2003	POP	CCI	No association	Less chemoradiotherapy
Gonlugur 2006	RER	Comorbidity y/n COPD y/n	Negative	
Janssen-Heijnen 2007	POP	Slightly modified CCI Conditions	No association	Less chemoradiotherapy (cardiovascular disease, hypertension, diabetes)
Noguchi 2010	RER	CCI	No association	More dose reductions
Janssen-Heijnen 2011	POP	ACE 27		Less chemoradiotherapy
Kuo 2011	RER	SCS + CCI	Negative (SCS) No association (CCI)	
Rich 2011	POP	CCI	Negative	Less chemotherapy
Caprario 2013	POP	CCI (Devo)	Negative	Less treatment
Janssen-Heijnen 2014	POP	ACE-27	No association	No association
Fiegl 2014	PRO	Conditions	No association	
Aarts 2015	POP	Slightly modified CCI	Negative	
Kaesmann 2016	RER	CCI + A-CCI + MRC-BS + SCS	Negative (CCI + MRC-BS) No Association (A-CCI + SCS)	

Population-based studies (POP), retrospective reviews (RER) and prospective studies (PRO). Charlson Comorbidity Index (CCI), Chronic Obstructive Pulmonary Disease (COPD), age-adjusted CCI (A-CCI), Adult Comorbidity Evaluation 27 (ACE-27), Simplified Comorbidity Score (SCS) and Medical Research Council Breathlessness Scale (MRC-BS).

Three of the studies that reported a negative influence from comorbidity on survival were population-based studies [242-244]. There was variation in age distribution, extent of disease and treatment administered, and data on other important prognostic factors such as performance status were not available in all studies [244]. Furthermore, there is limited information about what treatment patients received in these studies, and only one, small study (n=73) has reported frequency and severity of comorbidity in LD SCLC patients receiving concurrent chemoradiotherapy [240]. Comorbidity was assessed in several different ways, and in two studies the prognostic impact of comorbidity depended on choice of index [240, 241].

Comorbidity may influence survival indirectly by restricting treatment, increasing toxicity-related mortality or modifying the effect from treatment. The direct

influence of comorbidity on prognosis, as a competing cause of death, appears to depend on the overall survival time and is consequently less important in cancers with a short life expectancy such as lung cancer [272]. In such cases, including LD SCLC, patients are more likely to die from their malignancy.

Patients with CCI 1 had poorer survival than both patients with less and more comorbidity. Although patients with CCI 1 had the highest rate of stage III disease, there were no statistically significant differences in baseline characteristics explaining the inferior survival in CCI 1. The relatively poor survival in patients with CCI 1 may be caused by a combined imbalance in baseline negative prognostic factors. The difference in HR became insignificant when we adjusted for baseline characteristics in multivariate analyses.

Interestingly, we did not find any differences in completion of study treatment between those with comorbidity and other patients. In population-based studies, patients with comorbidity received less treatment, but it is not clear whether this was due to more toxicity or concerns about toxicity [223, 224, 242, 244, 273]. In one study, patients ≥ 75 years with comorbidity experienced more toxicity than others, without significant differences in survival [247]. Otherwise there is little evidence indicating that patients with comorbidity have a poorer tolerance to therapy.

Comprehensive geriatric assessment (CGA) is a multidisciplinary process that identifies medical, psychosocial, and functional limitations of elderly [274], and appears to provide more prognostic and predictive information than assessment of comorbidity alone [247, 273, 275].

7.3 Prognostic value of early response to therapy

In this study we found a positive association between early response to therapy and progression-free and overall survival. A few other studies have investigated the association between an early response to therapy and outcomes from chemoradiotherapy in LD SCLC, all demonstrating a positive association. Fuji et al. reviewed patients with objective response from chemoradiotherapy, and found that PFS and OS was significantly longer among patients with objective response already after the first course [259]. Lee et al. found significantly better OS among those with more than 45% reduction in tumour volume after 1-2 courses of chemotherapy and 36 Gy of TRT [260]. van Loon et al. reported significantly longer OS in patients with a

reduction in metabolic volume on PET-CT or tumour volume reduction on CT after the first chemotherapy-course [261].

Due to a delay in the radiotherapy referral and planning process, radiotherapy is commonly started with the second course of chemotherapy [98, 198-200]. We quantified the reduction in size of tumours 3-4 weeks after the first course. This reduction will - in many cases - allow for smaller radiotherapy fields than if TRT starts concurrently with the first course. This will potentially reduce TRT toxicity and may be a requirement for offering TRT to those with widespread thoracic disease at baseline due to normal tissue constraints, and can facilitate dose escalation with acceptable toxicity in other patients.

In this study response from the first course of chemotherapy was positively associated with outcomes, but we did not identify patients that should not receive TRT, even patients without a reduction in tumour size had a median overall survival of 19.9 months - which is much longer than in ED SCLC and what we would expect in LD SCLC from chemotherapy alone [276, 277].

Although initially very sensitive to both chemo- and radiotherapy, SCLC develops resistance to therapy rapidly. One might hypothesise that patients with a poor early response would benefit from a change in therapy based on in vivo sensitivity. Mechanisms for therapy resistance are not fully known, and not necessarily overlapping for chemo- and radiotherapy [180, 201, 278, 279]. Thus, sensitivity to one type of therapy cannot be predicted from sensitivity to another.

While some may take advantage from intensified treatment, futile treatment can be avoided in others. Additional research, using early response to therapy to stratify and randomise patients is needed to answer if such strategies will improve outcomes in LD SCLC.

7.4 Strengths and limitations

7.4.1 Sample-size

Based on observations from a previous Norwegian trial (OD TRT: 14.5 months median and 70% 1-year OS) [91], we expected a 1-year PFS of 70% on the control arm. The RCT was powered to detect a 30% improvement in the primary endpoint (1-year PFS). However, the assumptions were not met. In the present trial, the survival

from OD TRT was longer than estimated (OD TRT: 18.8 months median and 76% 1-year OS), while the 1-year PFS was lower than estimated (45%).

The main reason for conducting a randomised phase II rather than a phase III trial was that we did not want to expose too many patients to a potentially inferior treatment. We also took the expected enrolment time into consideration. The expected accrual period was four years, and it took us nearly six years to enrol the target number of patients. Furthermore, there were concerns about more toxicity from twice-daily TRT since we were not convinced that twice-daily TRT provided a survival-benefit. Thus, we wanted to investigate if there were indications of more toxicity or longer survival from twice daily radiotherapy, and then consider a phase III trial with sample-size based on the estimated difference.

The number of patients exceeded other phase II studies in LD SCLC (n=34-71) [280-283]. We consider this study large enough to guide further research and clinical practice, though the sample size is still a major limitation of the study.

7.4.2 External validity

The external validity, or generalisability, of results is limited to patients with comparable prognostic and predictive factors as those in the study population. Established prognostic and predictive factors are often included as eligibility criteria and sometimes used to stratify patients. This limits potential influence on results from other factors than the intervention. Randomisation equalises factors that cannot be accounted for between treatment groups [284]. To increase the likelihood of positive results, RCTs often exclude patients with negative prognostic and predictive factors. Patients are often younger, with better performance status and limited comorbidity compared to many patients seen in the clinic [285], limiting the external validity. A lower efficacy and more toxicity can be expected in a general population.

In Norway, we have a low rate of migration and loss to follow-up. A national death registry of high quality adds to the validity of survival data. The majority of patients are treated within the public health care system. Based on data from the Norwegian Cancer Registry, an estimated 17% of patients with LD SCLC were enrolled into this trial. The NCI estimates that less than 5% of patients in the USA are recruited into clinical trials [286-290], according to one pattern of care study 3% of lung cancer patients were treated in prospective trials [217].

There may be differences between study cohorts in LD SCLC trials due to the varying definition of LD over time and between studies – especially with respect to pleural fluid, and lymph node involvement. While the VALG definition allowed ipsilateral supraclavicular N3 disease, the IASLC definition allows all N3 lymph node metastases (both contralateral mediastinal, hilar and supraclavicular nodules). Stage according to the TNM system is prognostic in LD SCLC, but the use is limited, and we have little available data on the prognostic value of N3 disease [34]. Further, the TNM staging system cannot describe differences between LD SCLC according to the VALG or IASLC definitions, as it does not provide information about the different locations of N3 disease. In a planned paper, we investigate if there are differences in survival depending on location of N3 disease.

In this trial we used a liberal definition of LD SCLC, allowing all contralateral N3 disease and pleural fluid if it was cytologically negative in one sample, independent of side and amount. We had a high rate of PS ≥ 2 compared to other studies and the protocol had no restrictions on comorbidity (Table 14) [91, 96, 97, 100, 143, 174].

Table 14 Differences between studies in definition of LD SCLC, inclusion of PS ≥ 2 and age ≥ 70 years in randomised clinical trials (RCT) and retrospective reviews (RER).

	Design	LD SCLC	PS ≥2	Age ≥ 70 years
Murray 1993	RCT	-Contralateral nodules not specified -No pleural fluid	11%	Not specified (80 years age limit
Turrisi 1999	RCT	-No contralateral supraclavicular nodes -No contralateral hilar nodes -No pleura effusion	5%	Not specified (17% > 65 years) (no age limit)
Takada 2002	RCT	-No stage I -Including contralateral supraclavicular nodes -No malignant pleural fluid	5%	Not specified (75 years age limit)
Sundstrøm 2002	RCT	-Contralateral nodules or pleural fluid not specified	16%	Not specified (75 years age limit)
Spiro 2006	RCT	-No contralateral hilar or supraclavicular nodes -Pleural fluid not specified	10%	Not specified (75 years age limit)
Bettington 2013	RER	-Not specified	Not specified	Not specified (no age limit)
Kubota 2014	RCT	-Including contralateral mediastinal, and supraclavicular lymph nodes -Including pleural effusion less than 1 cm	0%	None (70 years age limit)
Socha 2015	RER	-Contralateral nodules or pleural fluid not specified	9% Karnofsky 70-80	Not specified (30% ≥ 65 years) (no age limit)
Grønberg 2015	RCT	-Contralateral lymph mediastinal, hilar and supraclavicular nodes. -Cytological negative pleural fluid	16%	26% (no age limit)
Faivre-Finn 2016	RCT	-VALG -Contralateral nodules not specified -No pleural fluid	3%	Not specified (no age limit)

We have no knowledge on patients not included into the trial, and the Norwegian Cancer Registry does not contain sufficient detail for a valid comparison. Therefore, we cannot rule out a selection bias. It is possible that patients with a high level of comorbidity were not offered to participate.

All hospitals treating LD SCLC were invited to participate in the trial, and patients were recruited at 18 Norwegian hospitals over a period of almost 6 years. TRT was delivered at 10 radiotherapy units. Consequently, each study centre had few patients annually. We did not monitor adherence to protocol during the study period, and there may have been differences in handling of patients between centres and over time.

The new Clinical Registry for lung cancer (within the Norwegian Cancer Registry) contains more comprehensive data and will hopefully allow us to at least compare study cohorts with the general population of lung cancer patients [291]. However, compliance for entering data is currently low. In contrast, Sweden has allocated personnel to register data for their clinical registry, and have a live updated registry, where previously entered data are available for health care personnel.

7.4.3 Relevance of endpoints

We chose PFS rather than OS as primary endpoint. Due to the higher frequency of events, this would allow us the opportunity to follow-up with a phase III trial within a reasonable time-frame if indicated. Additionally, PFS is independent of changes in second-line treatment, and less influenced by death from other causes.

However, PFS is a surrogate endpoint with no benefit to patients unless it correlates with improved OS or HRQoL [292]. In LD SCLC, there is evidence of a correlation between PFS and OS [95, 293, 294], and an association between PFS and HRQoL is expected due to severe symptoms from relapses. Such an association between PFS and HRQoL has been demonstrated in patients with NSCLC, supporting that PFS is a relevant endpoint to patients with lung cancer [295].

Nonetheless, PFS may not be the optimal endpoint. It can be difficult to distinguish radiation-fibrosis from relapse on CT scans. Many radiologists were involved, and we had no central review due to a shortage of finances. We do not believe that this has biased our results of PFS considerably; there was no systematic difference between treatment arms, and we report comparable PFS to other studies [95-97]. In LD SCLC, the clinical benefit of detecting an early relapse is uncertain.

Our secondary endpoints of OS, toxicity and HRQoL have a more explicit role in clinical practice. We present mature and robust data on overall survival from a national registry.

7.4.4 Targets for radiotherapy

The use of CT for staging of disease is a limitation. PET-CT was not available in Norway during the study period. Thus, we may have included patients classified as ED SCLC if PET-CT was used. The use of PET-CT is recommended in guidelines and is now standard for staging of SCLC-patients considered for surgery or chemoradiotherapy in Norway [23, 24, 38-40]

With PET-CT, more patients would be expected to be upstaged from LD to ED than the other way around [35]. According to the Will Rogers phenomenon, this will improve survival in both stages of SCLC, as the patients with the poorest prognosis in LD SCLC become the patients with best prognosis in ED SCLC [296].

Selective nodal irradiation (SNI) is an option when patients are staged with PET-CT, since less than 3% experience isolated nodal failures [184, 185]. Thus, compared to PET-based radiotherapy, we may have missed some targets for radiotherapy, as well as including unnecessary large volumes of radiotherapy, resulting in excess toxicity.

There is variation in how elective nodal irradiation (ENI) is delivered. In this study ENI was delivered to bilateral stations 4-7 of the mediastinum, while it was defined as bilateral mediastinum and ipsilateral hilar nodes by others [95-97], and some included un-involved supraclavicular stations [204].

The criteria for evaluation of response have changed, with the introduction of RECIST 1.1, since the initiation of our study [266]. A lymph node now has to be ≥ 15 mm in shortest diameter, as opposed to 10 mm in longest diameter, to be considered enlarged, measurable and as a target lesion for evaluation of response. This changes what is considered pathological lesions, and consequently target volumes for thoracic radiotherapy.

7.4.5 Delivery of radiotherapy

The fact that the protocol only moderately described details on radiotherapy planning and technique is a potential weakness. There were few restrictions on dose to normal structures, and investigators were mostly allowed to follow local procedures. There

may have been some technical development in radiotherapy during the six-year inclusion period.

The annual number of patients per hospital was low, and due to a limitation in resources and technical solutions, we had no central quality assurance of radiotherapy.

Interestingly, we observed a large improvement in median (25.1 vs 14.5 months) and 5-year survival (24 vs 10%) compared to our previous Norwegian study, where TRT was not systematically used [91]. This illustrates the importance of implementing recommended treatment to patients.

Prophylactic cranial irradiation (PCI) was delivered to patients with at least "near" CR at evaluation 12 weeks after completing therapy. There is no uniform understanding of "near" CR, with potential for variation in how this was practiced between centres. In ED SCLC, both patients with PR and CR have a survival advantage from PCI, supporting PCI to all responders of any stage SCLC [130]. Current guidelines recommend PCI to patients with at least PR [23, 24, 38, 39] or having a "good" response [40]. We had a high rate of PCI. All complete responders and 89% of partial responders received PCI, for an overall 91% of responders and 82% off all patients. This is higher than in other studies and a population-based report [91, 97, 100, 172-174, 226]. Rate of PCI is not reported in all clinical trials [95, 96]. PCI consisted 2 Gy in 15 fractions to a total of 30 Gy, and not the current standard of 2.5 Gy in 10 fractions to a total of 25 Gy, which is associated with better survival and less toxicity [131, 140].

7.4.6 Assessment of comorbidity

No standard for assessing comorbidity in LD SCLC exist, and we chose the most widely used CCI [249, 257]. The retrospective assessment of comorbidity from an extract of medical journal, by only one oncologist, may be a potential weakness. However, the CCI considers conditions relevant to mortality and expected to be mentioned in the medical journal, and list of medication was cross-checked for signs of any comorbidity not mentioned. In a previous study, more comorbidity was recorded this way, than what was registered prospectively by investigators [297], possibly because coexisting conditions receive less attention in the presence of an aggressive malignancy such as SCLC. The oncologist scoring comorbidity received

initial training, and any difficulties were discussed with the last author. Furthermore, the CCI has a high inter-rater reliability, which is also our experience [258, 297].

The relative weighting of conditions in the CCI is based on the relative risk of death they contributed in 1987, but severity of conditions is addressed to a limited extent. There have been advances in the treatment of several of the included conditions since then, e.g. chronic obstructive pulmonary disorder (COPD), coronary artery disease and HIV/AIDS. Thus, the weighting may not accurately represent the relative risk of death any more. Further, it may be of particular interest to have detailed knowledge on how to consider highly prevalent conditions such as COPD, with regards to outcomes from radiotherapy and risk of radiation pneumonitis. For this, information on severity of COPD, performance status, pulmonary function tests and DVH is needed.

7.4.7 Assessment of early response to therapy

We assessed early response to therapy on a planning scan after one course of chemotherapy, and we obtained no information on sensitivity to radiotherapy. Monitoring of treatment response at several time points might provide information on sensitivity to both chemo- and radiotherapy, and allow us to track changes during treatment. However, repeated measures of early treatment response was not planned for in the protocol, and evaluation of response to the first course of chemotherapy was convenient due to the available CT scans.

The reduction in SOD might have been underestimated in some instances, as there were variations in time between baseline scans, treatment start and planning scan. Additional growth of tumours is expected in patients with a long time from baseline scan to start of therapy, while the full effect of the first course is not observed in patients where the planning scan was obtained shortly after start of chemotherapy. However, there were no correlation between timing of scans and SOD reduction (data not shown).

Due to the lack of central review of first relapse, we were not able to address the association between early response to therapy and systemic versus in-field failure. Such information would be of use for future studies investigating alternative treatment in patients with poor early response to therapy.

The reduction in tumour size after the first course of chemotherapy may allow smaller radiotherapy fields than if TRT starts concurrently with the first course.

Although it is our impression that many patients had a sufficient reduction in tumour to influence treatment volumes, only a comparison of radiotherapy plans based on both scans can properly answer this. The planning target volume (PTV) depends on both size and anatomical distribution of tumours.

It has been hypothesized that PET-CT, combining functional and anatomical imaging, has an advantage in early response evaluation in SCLC. PET-CT is very sensitive to pathological lesions from SCLC, due to the high metabolic activity. However, there are data suggesting that it poses no benefit to CT in assessment of early response in LD SCLC [261, 298].

8. Summary and conclusion

- There were no statistically significant differences in progression-free or overall survival between patients receiving once or twice daily accelerated radiotherapy, but patients receiving twice daily radiotherapy had a six months longer median overall survival.
- There were no significant differences in toxicity between patients receiving once or twice daily accelerated radiotherapy.
- There was no association between severe comorbidity and progression-free or overall survival.
- Patients with severe comorbidity did not experience more toxicity than others.
- Most (94%) patients had a reduction in tumour size after the first course of chemotherapy.
- Reduction in size of tumours after the first course of chemotherapy was positively associated with progression-free and overall survival.

Conclusion:

- Twice daily accelerated radiotherapy remains the standard TRT-schedule in LD SCLC, and is now recommended in Norway.
- Patients with severe comorbidity should be considered for chemoradiotherapy on the same basis as other patients, provided they have PS ≤ 2 and adequate organ function.
- Reduction in size of tumours after the first course of chemotherapy is a positive prognostic factor for progression-free and overall survival, and might be used for stratification and randomisation in future studies.

9. Implication for clinical practice and future research

This phase II trial was initiated to investigate if there were indications of improved survival or worse toxicity from BID TRT, and decide whether to proceed with a phase III trial. Our conclusion is that 45 Gy/30 twice daily fractions is the preferred schedule, as there were no indications of improved disease control or less toxicity from hypofractionated radiotherapy, although hypofractionation may be more convenient. Due to the lack of clinical equipoise, we have decided not to proceed with a phase III trial, as we believe this will expose many patients to what we now consider an inferior treatment. Rather, we should investigate schedules of potentially higher efficacy or lower toxicity relative to 45 Gy in 30 twice daily fractions.

By using PET-CT for target volume definition and advanced radiotherapy techniques, higher TRT doses can be delivered. Radiotherapy consisting 2 Gy once daily to a total dose of 60-70 Gy in 6-7 weeks is tolerated [218, 299], provide similar outcome to 45 Gy/30 twice daily fractions [300, 301] and has therefore been regarded an alternative to twice daily radiotherapy [40]. Two large randomised studies have compared 70 Gy or 66 Gy once daily to twice daily radiotherapy [98, 302]. Results from the trial using 66 Gy (CONVERT) were recently presented on the American Society of Clinical Oncology (ASCO) annual meeting. A high dose of once daily radiotherapy did not result in improved survival or worse toxicity than 45 Gy/30 fractions twice daily. Interestingly, toxicity from both schedules was lower than expected, possibly due to the use of modern radiotherapy techniques and PET-CT staging [100].

The fact that the CONVERT trial turned out negative, does not necessarily imply that outcomes in LD SCLC cannot be improved by increasing the dose of radiotherapy. It may be that extended treatment time from once daily radiotherapy to 60-70 Gy is disadvantageous. Results from the comparison of 70 Gy to BID TRT are awaited [98].

We believe that hyperfractionation improves efficacy also when delivering higher TRT-doses than 45 Gy, as this acceleration of treatment facilitates a higher BED within a shorter time, and a lower SER, which are all important determinants of survival in LD SCLC. Our study group has therefore decided to initiate a new clinical trial in LD SCLC, comparing BID TRT of 45 and 60 Gy, both delivered as 1.5 Gy twice daily (THORA) [303]. Hospitals in Norway, Sweden and Denmark participate.

In THORA, all patients are staged with PET-CT and we deliver SNI. In addition to the CCI, all patients are evaluated prospectively with a comprehensive geriatric assessment consisting patient reported frailty (G8), nutritional status (PG SGA), timed-up-and-go and 5 meter walk test, patient reported health-related quality of life (EORTC QLQ C30) and assessment of lean body muscle mass. We believe that comprehensive geriatric assessment (CGA) might provide more prognostic and predictive information than comorbidity assessment alone [247, 273, 275].

Although attempts have been made to develop assays to predict sensitivity to both chemo- and radiotherapy in vitro, none of them have reached clinical practice [304, 305]. In the THORA-trial, we collect blood for biomarker analyses at inclusion, start of radiotherapy, at follow-up and at progression. Repeated measures of biomarkers might be used to monitor sensitivity to therapy and provide basis for future studies on individualised therapy.

Despite improvements in radiotherapy-techniques it may not be possible to deliver high doses of TRT at an acceptable level of toxicity to all patients with disseminated intra-thoracic disease, severe comorbidity or poor PS. Thus, some patients might receive TRT doses of 40-45 Gy also in the future. Our study indicates that concerns about toxicity should not be a reason for choosing hypofractionated instead of twice daily TRT.

Several advancements are required to improve the treatment of LD SCLC. This includes better staging of disease, classification of limited disease, identification of prognostic and predictive factors, development of adapted treatment strategies as well as implementation of best documented practice. We need to increase our knowledge on the mechanisms of treatment failure and development of resistance to therapy. Currently, immunotherapy (PD-1 and CTLA4 inhibitors) appears to be a promising new systemic therapy [165], and the first targeted therapy - rovalpituzumab tesirine, a DLL3 targeted antibody - has recently demonstrated efficacy in SCLC [161].

10. References

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11. Appendix A The EORTC QLQ C30 and LC-13

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

12. Appendix B Charlson Comorbidity Index

Charlson Comorbidity Index

ASSIGNED WEIGHTS	CONDITIONS
1	Myocardial infarct
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end organ damage
	Any tumour
	Leukemia
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumour
	AIDS

Paper I

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Paper II

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Paper III

Tumour size reduction after the first chemotherapy-course and outcomes of chemoradiotherapy in limited disease small-cell lung cancer

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Conflicts of interest:

None to declare

Keywords:
Early response, predictive, survival, concurrent, chemotherapy, radiotherapy

Abstract

Objectives

Concurrent chemotherapy and thoracic radiotherapy (TRT) is recommended for limited disease small-cell lung cancer (LD SCLC). TRT should start as early as possible, often meaning with the second course due to patient referral time and the fact that TRT planning takes time. Early assessment of response to the first course of chemotherapy may be a useful way to individualise treatment. The aims of this study were to assess tumour size reduction after the first chemotherapy-course, and whether this reduction was associated with outcomes in LD SCLC.

Material and methods

A randomised trial comparing twice-daily (45Gy/30 fractions) with once-daily (42 Gy/15 fractions) TRT, given concurrently with four courses of cisplatin/etoposide (n=157) was the basis for this study. Tumour size was assessed on CT scans at baseline and planning scans for TRT according to RECIST 1.0.

Results

CT scans were available for 135 patients (86%). Ninety-four percent had a reduction in tumour size after the first chemotherapy-course. The median reduction in sum of diameters (SOD) of measurable lesions was ÷16 mm (÷84 to +10 mm), corresponding to ÷18% (÷51 to +12%). Eighty-two percent had stable disease, 18% partial response. Reduction in SOD was significantly associated with complete response at first follow-up (OR: 1.05, 95% CI 1.01-1.09; p=.013), PFS (HR: 0.97, 95% CI 0.96-0.99; p=.001), and overall survival (HR: 0.98, 95% CI 0.96–1.00; p=.010).

Conclusion

Response from the first course of chemotherapy had a significant positive association with outcomes from chemoradiotherapy, and might be used to stratify and randomise patients in future studies.

1. Introduction

Concurrent chemotherapy and thoracic radiotherapy (TRT) is the recommended treatment for LD SCLC [1-7]. Cisplatin plus etoposide constitutes the standard chemotherapy regimen [2, 8], and should commence as soon as possible due to the potentially rapid progress of SCLC [9]. Guidelines recommend that radiotherapy should be administered along with the first or second course of chemotherapy [1-4], since meta-analyses have shown improved survival when TRT starts within 30 days after start of chemotherapy, and when the time from start of any treatment until the end of radiotherapy (SER) is short [6, 7]. Although starting TRT concomitant with the first course results in the lowest SER, TRT is often administered concomitant with the second chemotherapy course due to time-delay in the referral and TRT planning process [10-13].

There is often a tumour response between the first and second chemotherapy-course, allowing for smaller radiotherapy fields and less toxicity than when TRT starts along with the first course. But little is known about the extent of the response. Most patients (80-90%) with LD SCLC respond to chemoradiotherapy, but the 5-year survival is only 25% [14]. Studies indicate that early response to treatment is associated with better outcomes [15-17], and might be a method for identifying patients who do not benefit from TRT.

We analysed LD SCLC patients enrolled in a randomised trial comparing two three-week schedules of TRT, administered concurrently with cisplatin plus etoposide. The aim was to assess the reduction in tumour size after the first chemotherapy course, and to investigate whether this tumour size reduction was associated with outcomes of therapy.

2. Material and methods

2.1 Design and approvals

The trial was approved by the Regional Committee for Medical Research Ethics in Central Norway, the Norwegian Social Science Data Services and the Norwegian Directorate for Health and Social Affairs.

2.2 Patients

Eligible patients had SCLC confined to one hemithorax, the mediastinum, the contralateral hilus and the supraclavicular regions; WHO performance status (PS) 0-2; and adequate kidney and bone marrow function. Four courses of cisplatin plus etoposide (PE1-4) were planned for all patients, and they were randomly allocated to receive TRT of 45 Gy in 30 fractions (twice daily; BID) or 42 Gy in 15 fractions (once daily; OD). Good responders were offered prophylactic cranial irradiation (PCI) of 30 Gy in 15 fractions.

Patients who completed at least two PE-courses and TRT were eligible for the present study, provided that the baseline CT scan and CT planning scan for TRT were available. Patients with a baseline scan more than two months prior to, or a planning scan more than one month later than start of treatment were excluded. Since there were no significant differences in toxicity, response-rates, progression free survival (PFS), or overall survival (OS) between the treatment arms in the main trial [18], we analysed all patients as one cohort in the present study.

2.3 Response evaluations

Timing of treatment and response evaluation are presented in Figure 1. A baseline CT scan for staging (CT1) was obtained before PE1. Response to the first course (RE1) was assessed by comparing CT1 with the CT planning scan for TRT (CT2) obtained 2-3 weeks after PE1. A CT scan for response evaluation after completion of study treatment (RE2) was conducted 2-3 weeks after PE4 (CT3).

Response to overall therapy (RE2) was evaluated according to the RECIST 1.0 criteria [19]. Measurable lesions were defined as lesions ≥ 10 mm. Up to 10 target lesions (maximum 5 per organ) were measured. Sum of largest diameter (SOD) of target lesions at CT1 was compared with SOD of these lesions at CT2. Complete response (CR): Disappearance of all measurable lesions. Partial response (PR): A reduction in SOD of ≥ 30%. Progressive disease (PD): An increase in SOD of ≥ 20%. Stable disease (SD): A change in SOD between +20% and -30% [19].

A central review of RE1 was conducted by a radiologist (MH) and an oncologist (TH). Since staging of disease was based on CT alone, using the RECIST 1.0 criteria for response evaluation, we additionally performed all analyses evaluating only the change in size of the primary tumours. Not all lymph nodes considered pathological according to RECIST 1.0 are defined as pathological according to RECIST 1.1.

2.4 Other assessments

Stage of disease was assessed according to TNM v6 [20]. PFS was defined as time from randomisation until progression or death; OS as time from randomisation until death of any cause. Median follow-up for PFS was 58 months (range: 30 - 97); 31 patients were progression free when this follow-up ended (July, 2013). Median follow-up time for survival was 89 months (range: 61 - 128); 30 patients were alive when survival follow-up ended (February, 2016).

2.5 Statistical considerations

Survival was estimated using the Kaplan-Meier method and compared using the log-rank test. Pearson's Chi-square and Fisher's exact tests were used for group comparisons. The Cox proportional hazard method was used for multivariate survival analyses, and binomial logistic regression for the other multivariate analyses. Multivariate models were adjusted for baseline characteristics and TRT schedule. Associations between reduction in tumour size and outcomes of therapy were analysed using percent reduction of SOD as a continuous variable and according to RECIST categories. The level of significance was defined as $p<0.05$.

3. Results

3.1 Patients and treatment completion

Complete descriptive and clinical data are presented in Table 1. We enrolled 157 patients at 18 hospitals in Norway between May 2005 and January 2011 [18]. Twenty-two patients were excluded from these analyses due to missing baseline (n=5) or planning (n=11) CT scan; baseline CT scan more than two months prior (n=1) or planning CT scan one month later (n=2) than start of

chemotherapy; and TRT not completed (n=3). Thus, 135/157 patients (86%) were eligible for the present study. Median age was 64 years; 53% were men; 15% had PS 2 and 74% stage III disease. Mean number of PE-courses was 3.86, 118 patients (87%) completed four courses. Sixty patients (44%) received TRT as 45 Gy in 30 fractions. One hundred and fifteen patients (85%) received PCI, and 64 (47%) received second-line chemotherapy.

3.2 Time between CT scans

Median time from CT1 until start of PE1 was 17 days (range: 0-60). Median time from start of PE1 until CT2 was 18 days (range: 6-30). Median time from CT1 until CT2 was 35 days (range: 14-85).

3.3 Tumour size reduction after the first chemotherapy-course

Median SOD on CT1 was 96 mm (range: 14 to 260 mm); on CT2 76 mm (range: 14 to 196 mm). One-hundred and twenty-seven patients (94%) had a reduction in tumour size. Median change in SOD from CT1 until CT2 was ÷16 mm (range: ÷84 to +10 mm), corresponding to a median change of ÷18% (range ÷51 to +12%) in SOD. Besides, 111 patients (82%) had stable disease, and 24 (18%) achieved a partial response (Figure 2).

Regarding the proportion of patients completing four PE-courses (p=.31); receiving 45 Gy (p=.29) or second-line chemotherapy (p=.78), there was no significant difference between patients with partial response and those with stable disease at RE1. Although patients with a PR were more likely to receive PCI (PR: 100%, SD: 82%; p=.024, Table 1).

3.4 Response evaluation at treatment completion (RE2)

The overall response rate was 90%, of which 23% achieved CR, 67% PR, 1% SD and 5% PD. Four patients (3%) were not evaluable at RE2. There was a non-significant association between reduction in SOD and the response rate to chemoradiotherapy (OR: 1.04, 95% CI 0.99-1.09; p=.15), but a significant association with CR (OR: 1.04, 95% CI 1.00-1.07; p=.025).

There was a trend towards higher final response rates at RE2 for those with PR (100%) at RE1 compared with those with SD (88%) (p=.08). Furthermore, patients with a PR at RE1 were more likely to achieve a complete response at RE2 (42% vs. 19%; p=.016) (Table 2). The only other variable significantly associated with response at RE2 was treatment arm: Among those patients receiving twice-daily radiotherapy, more patients had CR at RE2 (BID: 37%, OD: 12%; p=.001).

Multivariate analyses showed a trend towards increased response rate (OR: 1.06, 95% CI 0.99-1.12; p=.08) and significantly more CR (OR: 1.05, 95% CI 1.01-1.09; p=.013) with increasing SOD reduction. There was a significant association between PR at RE1 and CR at RE2 (OR: 3.72, 95% CI 1.26-11.02; p=.018).

3.5 Progression free survival

Median PFS was 11.4 months (95% CI 8.5-14.4 months) in the overall population. PFS improved with increasing reduction in SOD at RE1 (HR: 0.99, 95% CI 0.97-1.00; p=.043). Patients with a PR at RE1

had a numerically, but not significantly, longer median overall PFS (PR: 19.5 months, SD: 9.9 months; p=.20) (Table 2).

Multivariate analyses showed that overall PFS significantly improved with increasing SOD-reduction (HR: 0.97, 95% CI 0.96-0.99; p=.001), and there was a trend towards improved PFS for those with PR compared with those with SD at RE1 (HR: 0.63, 95% CI 0.36-1.10; p=.10).

3.6 Overall survival (OS)

The median overall survival in the whole study cohort was 23.6 months (95% CI: 17.1-30.0 months) with 25% 5-year survival. There was a trend towards improved overall survival with increasing reduction of SOD at RE1 (HR: 0.99, 95% CI 0.97-1.00; p=.07); a significantly improved 2-year survival (OR: 1.03, 95% CI 1.00-1.06; p=.026), but no improvement in 5-year survival (OR: 1.02, 95% CI 0.99-1.05, p=.19).

The difference in median overall survival between those with PR and SD at RE1 was not statistically significant (PR: 33.3 months, SD: 22.6 months; p=.14). There was a trend towards improved 2-year (PR: 67%, SD: 46%; p=.07), but not for 5-year survival (PR: 33%, SD: 23%; p=.31) (Table 2). Patients who did not have a tumour size reduction (n=8) had a median overall survival of 19.9 months.

The multivariate analyses showed significantly improved overall survival (HR: 0.98, 95% CI 0.96–1.00; p=.010), 2-year survival (OR: 1.04, 95% CI 1.01–1.08; p=.011), and a trend towards improved 5-year survival (OR: 1.05, 95% CI 1.01–1.09; p=.07) with increasing percent reduction in SOD (Table 3). The association was not significant when comparing PR with SD: overall survival (HR: 0.68, 95% CI 0.39-1.18; p=.17), 2-year survival (OR: 2.19, 95% CI 0.82–5.82; p=.12) and 5-year survival (OR: 1.58, 95% CI 0.54–4.64, p=.41).

3.7 Change in primary tumour size and outcomes of therapy

The median primary tumour diameter (PTD) at CT1 was 62 mm (range: 12 to 137 mm); the median PTD at CT2 was 49 mm (range: 10 to 134 mm). Median change in PTD was ÷11 mm (range: ÷44 to +11 mm) corresponding to a median change of ÷18% (range: ÷71 to +24%).

There was no significant association between percentage change in PTD and response rate (OR: 1.02, 95% CI 0.98-1.06; p=.26); but the association with CR was significant (OR: 1.03, 95% CI 1.00-1.06; p=.029). Furthermore, there were significant associations with improved PFS (HR: 0.98, 95% CI 0.97-0.99; p=.004); overall survival (HR: 0.98, 95% CI 0.97-0.99; p=.001), 2-year survival (OR: 1.04, 95% CI 1.01–1.07, p=.003) and 5-year survival (OR: 1.05, 95% CI 1.01–1.08, p=.008).

There was no significant association between reduction in PTD and total response rate in multivariate analyses (OR: 1.04, 95% CI 0.99-1.09; p=.13), whereas the association with CR remained significant (OR: 1.05, 95% CI 1.01-1.08; p=.006). The associations also remained significant for PFS (HR: 0.97, 95% CI 0.96-0.99; p<.001), overall survival (HR: 0.98, 95% CI 0.97-0.99; p=.001), 2-year survival (OR: 1.04, 95% CI 1.01-1.07; p=.003), and 5-year survival (OR: 1.04, 95% CI 1.01-1.08; p=.008).

4. Discussion

In this study of patients with LD SCLC receiving concurrent chemoradiotherapy, 94% had a reduction in tumour size after the first course of chemotherapy. The median reduction in SOD of target lesions was ÷18%, and 18% of patients had a partial response according to RECIST 1.0 [19]. Furthermore, there were significant, positive associations between reduction in SOD and complete response after completion of chemoradiotherapy, progression free survival and overall survival.

Three other studies indicate that early treatment-response is associated with better outcomes of chemoradiotherapy in LD SCLC, though there are differences in patient selection, treatment administered, study design, methods for assessment of early response and sample size (n=15-70). Fuji et al. reviewed patients with objective response after chemoradiotherapy, and showed that patients who achieved a PR or CR after the first chemotherapy-course had longer PFS and overall survival than those who responded later [17]. Lee et al. found that those with >45 % tumour volume reduction after 1-2 courses of chemotherapy and 36 Gy of TRT had significantly longer overall survival than other patients [16]. van Loon et al. observed that patients with a reduction in metabolic volume on PET-CT or tumour volume reduction on CT after the first chemotherapy-course had significantly longer overall survival [15].

Though our study is the largest of its kind, the sample size is still a limitation. We did not perform a central review of CT scans obtained for response-evaluation after completion of chemotherapy (RE2), and distinguishing between radiation fibrosis and viable tumour is difficult, which might have influenced the assessment of response rates after completion of chemoradiotherapy and PFS. We present robust survival data collected from a validated national registry.

There was a variation in the time from the baseline CT scan until treatment commenced, and from treatment start until the CT planning scan. Thus, the reduction in SOD might have been underestimated in some cases. Extent of disease in SCLC is assessed more accurately with PET CT than CT alone, but PET CT was not generally available when we conducted the study. Furthermore, we used the RECIST 1.0 criteria for definition of pathological lesions and response evaluation (RECIST 1.1 was published in 2010). The main difference in this setting is that RECIST 1.0 defines lesions with a diameter ≥10 mm as pathological, while the RECIST 1.1 criteria defines lymph nodes as pathological if the short axis diameter is ≥15 mm [21]. Thus, not all lymph nodes considered measurable, pathological lesions in our study were necessarily metastases. However, the results were similar when we ran all the analyses using only the change in diameter of the primary tumours.

In the trial establishing the twice-daily TRT schedule, TRT started concurrently with the first chemotherapy course [14]. However, many start TRT after the second course due to the delay caused by time needed for referral to and planning of TRT. The reduction in tumour size 3-4 weeks after the first course allows - in many cases - for smaller radiotherapy fields than if TRT starts concurrently with the first course. This will potentially reduce TRT toxicity and may be a requirement for offering TRT for those with widespread thoracic disease at baseline due to normal tissue constraints. In others, this reduction can facilitate dose escalation with acceptable toxicity.

Due to the high response rate and chances for cure, most patients with LD SCLC are offered chemoradiotherapy. The 5-year survival of 25% is encouraging, but also demonstrates that better

treatment is needed for the majority. Several new cytotoxic compounds have shown efficacy in LD SCLC, and some studies suggest that higher doses of TRT can improve the outcome [22, 23]. However, no other chemotherapy regimen has shown to be superior to cisplatin/etoposide. Besides, no randomised studies has to date demonstrated improved survival from high-dose versus standard dose TRT [24]. Moreover, there are concerns about more toxicity from higher TRT-doses.

Little is known about how to individualize treatment of LD SCLC. Some prognostic factors have been identified [25, 26], but none are currently used to guide treatment for the individual patient. We did not identify any subgroup with such a poor prognosis that concurrent chemoradiotherapy should not be offered. Even those without tumour size reduction after the first course had a median overall survival of 19.9 months, which is much longer than in extended disease [27, 28]. It is, however, possible that an early response assessment as described herein might be used for randomisation or stratification in future studies. One might, for example, hypothesise that patients with a poor response after the first course would benefit from switching to another chemotherapy-regimen or higher TRT-doses.

5. Conclusion

We found that 94% of patients with LD SCLC had a reduction in tumour size after the first chemotherapy course, and 18% achieved a partial response. Response to the first course of chemotherapy was an independent positive prognostic factor for complete response after chemoradiotherapy, progression free survival and overall survival.

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Table 1 Baseline characteristics and treatment completion

		All patients (n=135)		Partial response after first course (n=24)		Stable disease after first course (n=111)	
Age	Median (range)	64 (40-85) years		64 (49-76) years		63 (40-85) years	
	<70	97	72%	17	71%	80	72%
	≥70	38	28%	7	29%	31	28%
Gender	Female	64	47%	11	46%	53	48%
	Male	71	53%	13	54%	58	52%
PS	0	45	33%	9	38%	36	32%
	1	70	52%	11	46%	59	53%
	2	20	15%	4	17%	16	14%
Stage	I	11	8%	2	8%	9	8%
	II	12	9%	5	21%	7	6%
	III	100	74%	16	67%	84	76%
	Unknown	12	9%	1	4%	11	10%
Thoracic radiotherapy	Once daily	75	56%	11	46%	64	58%
	Twice daily	60	44%	13	54%	47	42%
Four courses cisplatin/etoposide		118	87%	23	96%	95	86%
Prophylactic cranial irradiation		115	85%	24	100%	91	82%
Received 2. line chemotherapy		64	47%	12	50%	52	47%

Table 2 Outcomes of chemo-radiotherapy in patients with SD or PR after the first course of cisplatin/etoposide

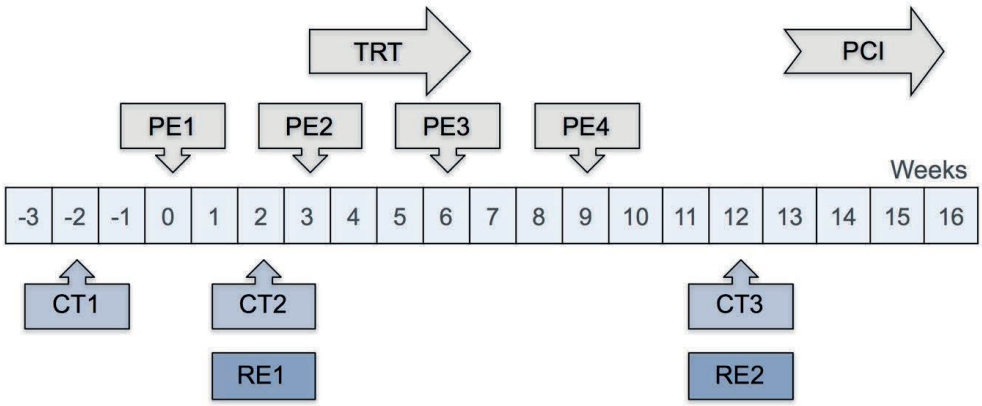
		All patients (n=135)		Partial response after first course (n=24)		Stable disease after first course (n=111)		p
Response after chemo-	CR	31	23%	10	42%	21	19%	.016
radiotherapy	PR	91	67%	4	56%	77	69%	
	SD	2	1%	-	-	2	2%	
	PD	7	5%	-	-	7	6%	
	NE	4	3%	-	-	4	4%	
Progression-free survival	Median (95% CI) months	11.4 (8.5 – 14.4)		19.5 (6.0 – 33.1)		9.9 (7.6 – 12.3)		.20
	1-year	66	49%	17	71%	49	44%	.018
Overall survival	Median (95% CI) months	23.6 (17.1 – 30.0)		33.3 (21.0 - 45.5)		22.6 (18.5 – 26.7)		.14
	2-year	67	50%	16	67%	51	46%	.07
	5-year	34	25%	8	33%	26	23%	.31

Table 3 Multivariate survival analyses. Overall p-value is presented for variables with more than two categories

		HR	95 % CI		p
Age*		1.01	.99	1.04	.43
Gender	Female	1			
	Male	.87	.58	1.33	.53
PS	0	1			
	1	1.09	.69	1.73	
	2	1.74	.94	3.21	.18
Stage	I	1			
	II	.43	.14	1.30	
	III	1.31	.65	2.63	.051
Treatment	Once daily	1			
	Twice daily	1.19	.79	1.79	.42
Percent SOD reduction*		.98	.96	1.00	.010

** Age and percent SOD reduction after first chemotherapy-course was entered as continuous variables. Female gender, PS 0, stage I and once-daily radiotherapy were defined as reference categories for categorical variables.*

Figure 1 Timing of treatment and evaluation of response on CT



Patients had a baseline CT scan (CT1) prior to chemotherapy. PE = cisplatin/etoposide. Early response (RE1) was evaluated on planning CT scans (CT2) before thoracic radiotherapy (TRT). Response to chemo-radiotherapy (RE2) was evaluated on a CT scan (CT3) obtained 2-3 weeks after the last chemotherapy-course. Patients with a good PR or CR at RE2 were offered prophylactic cranial irradiation (PCI).

Figure 2 Percent tumour reduction after the first chemotherapy-course. Median and 5-year survival according to response category

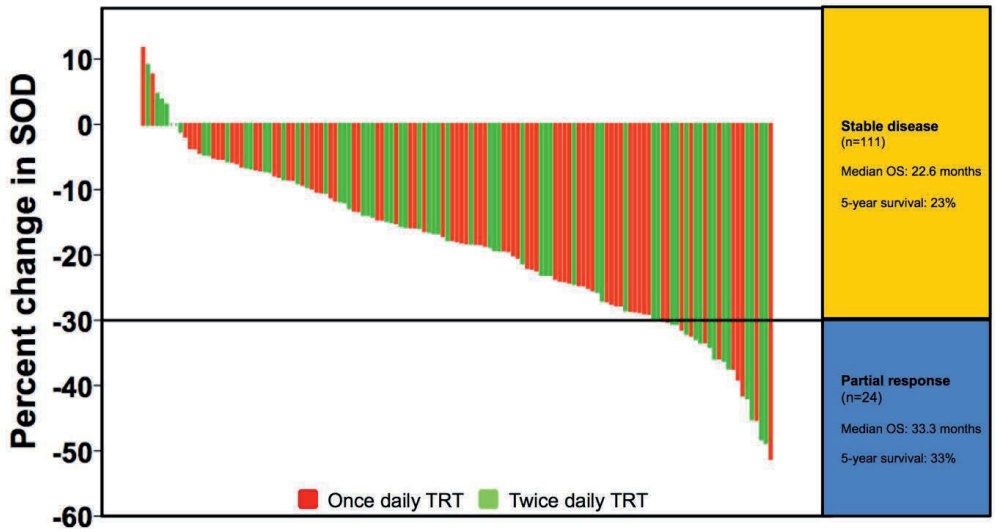


Figure 3 Progression free survival and overall survival