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Christine Damgaard Valan

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Prognostic and predictive factors in limited stage small cell lung cancer

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Trykket av NTNU Grafisk senter

Prognose og risiko for alvorlige bivirkninger ved småcellet lungekreft i begrenset stadium

Lungekreft er den vanligste kreftformen, og den som tar flest liv. I Norge er det ca. 3100 nye tilfeller og flere enn 2000 dør av sykdommen hvert år. Lungekreft deles inn i de to hovedtypene småcellet (15%) og ikke småcellet (85%) lungekreft. Småcellet lungekreft (SCLC) deles inn i «begrenset stadium» og «utbredt stadium» ettersom hvor stor svulsten er og om den har spredning til lymfeknuter eller andre organer.

Basisbehandlingen for SCLC er cellegift. En kombinasjon med strålebehandling øker overlevelsen og gis til pasienter med begrenset stadium. De fleste har god og rask effekt av behandlingen, 25-30% blir kurert, men de fleste får tilbakefall og dør av kreftsykdommen. I tillegg gir behandlingen ofte plagsomme og noen ganger alvorlige bivirkninger.

Generelt er utbredelse av sykdom den viktigste prognostiske faktoren for kreftpasienter. Studier viser at pasienter med liten muskelmasse eller dårlig muskelkvalitet har dårligere overlevelse og flere alvorlige bivirkninger enn andre. Målet med doktorgradsavhandlingen var å undersøke om dette er tilfellet også ved SCLC, siden ingen av delene er godt undersøkt ved denne typen kreft. Slik kunnskap kan brukes til bedre å individualisere behandlingen.

Vi undersøkte pasienter med SCLC i begrenset stadium som var inkludert i en nasjonal studie der vi sammenlignet to typer strålebehandling. Målet var å besvare følgende forskningsspørsmål:

Er det sammenheng mellom hvilke lymfeknuter i brysthulen det er spredning til og overlevelse?
Utbredelse av sykdommen ble vurdert på CT-bilder. Vi fant at de som hadde mest spredning til lymfeknuter hadde en dårligere overlevelse enn andre, men ikke så lav at de ikke bør tilbys standard kombinert cellegift og strålebehandling.

Er det sammenheng mellom mengden skjelettmuskulatur og muskulaturens kvalitet ved diagnosetidspunktet, bivirkninger av behandlingen og overlevelse? Er det sammenheng mellom tap av skjelettmuskulatur og muskelkvalitet i løpet av behandlingsperioden, bivirkninger av behandlingen og overlevelse?
Muskelmasse og muskelkvalitet ble analysert på CT-bilder tatt ved diagnosetidspunktet og etter fullført behandling. Vi fant at de som fikk en høy cellegiftdose per kg muskelmasse opplevde flere alvorlige bivirkninger, men overlevelsen var den samme som for andre. Det var heller ingen entydige sammenhenger mellom endring i muskelmasse eller muskelkvalitet i behandlingsperioden og alvorlige bivirkninger eller overlevelse.

Konklusjon: Alle pasienter med småcellet lungekreft i begrenset stadium bør tilbys standard cellegift og strålebehandling uavhengig av omfanget av lymfeknutespredning, muskelmasse og muskelkvalitet.

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for graden PhD i medisin og helsevitenskap.
Disputas finner sted i seminarrom NSU2 i Nevrosenteret Øst
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English summary

Lung cancer is the most common type of cancer and the leading cause of cancer related deaths. Small cell lung cancer (SCLC) is one of two main types of lung cancer.

Concurrent chemoradiotherapy is recommended for SCLC if all lesions can be included in a radiotherapy field (i.e. limited stage, LS). Patients with more widespread disease are classified as having extensive stage (ES) and receive chemotherapy alone.

There are several definitions of LS, mainly differing in the extent of N3 involvement accepted. The International Association for the Study of Lung Cancer has recommended the use of the tumour, node and metastasis classification system since 2007, but still most studies only distinguish between LS and ES.

Despite high response rates (80-90%), the long-term survival for patients with LS SCLC is only 25-30%. Concurrent chemoradiotherapy for LS SCLC is also associated with considerable toxicity. There is little knowledge regarding who will tolerate and benefit from therapy. Performance status is currently the only used prognostic factor in LS SCLC. Studies suggest that low skeletal muscle index (SMI) and muscle radiodensity (SMD) are associated with inferior survival and severe toxicity in several cancers, including lung cancer. However, in almost all studies of the role of muscle measures in cancer patients, only the baseline muscle measures have been assessed.

The overall aim for the project was to try to identify patients with LS SCLC who do not tolerate or benefit from concurrent chemoradiotherapy. We investigated different N3 involvement, baseline muscle measures and change in muscle measures during chemoradiotherapy.

Our project indicates that all N3 lymph node metastases should be considered LS, with the possible exception of those with involvement of two or more N3 regions. Patients with low baseline SMI and SMD or loss of SMI and SMD during chemoradiotherapy, should be considered for chemoradiotherapy on the same basis as other patients with LS SCLC.

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The work in this thesis has been carried out at the Department of Clinical and Molecular Medicine. The study was supported by the Central Norway Regional Health Authority, the Norwegian University of Science and Technology (NTNU) and the Norwegian Cancer Society. The clinical study was conducted by the Norwegian Lung Cancer Group.

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Finally, I want to thank friends and family for their patience and support.

Trondheim, March 2020

Christine Damgaard Valan

List of papers

1. Valan CD, Slagsvold JE, et al. **Survival in Limited Disease Small Cell Lung Cancer According to N3 lymph Node involvement.** Anticancer Res. 2018;38:871-876.

2. Halvorsen TO, Valan CD, et al. **Associations between low muscle measures, survival and toxicity in patients with limited stage small cell lung cancer.** Submitted, Journal of Cachexia, Sarcopenia and Muscle.

3. Valan CD, Halvorsen TO et al. **Changes in muscle measures during chemoradiotherapy in patients with limited stage small cell lung cancer.** Submitted, Journal of Cachexia, Sarcopenia and Muscle.

Abbreviations

BMI	Body mass index
CAV	Cyclophosphamide, anthracycline (epi- or doxorubicin), and vincristine
CI	Confidence interval
CR	Complete response
CT	Computer tomography
ES	Extensive stage
HR	Hazard ratio
HU	Hounsfield unit
IASLC	International Association for the Study of Lung Cancer
LBM	Lean body mass
LNM	Lymph node metastases
L3	Third lumbar vertebra
LS	Limited stage
MRI	Magnetic resonance imaging
NSCLC	Non-small cell lung cancer
OR	Odds ratio
OS	Overall survival
PCI	Prophylactic cranial irradiation
PD	Progressive disease
PE	Cisplatin and etoposide
PET CT	Positron emission tomography – computer tomography
PR	Partial response
PS	Performance status
SCLC	Small cell lung cancer
SD	Stable disease
SMD	Skeletal muscle radiodensity
SMI	Skeletal muscle index
TNM	Tumour, nodes and metastasis
TRT	Thoracic radiotherapy
VALSG	Veterans Administration Lung Study Group

1 Background

1.1 Lung cancer

1.1.1 Aetiology and epidemiology

Lung cancer used to be a rare disease, but became increasingly common when tobacco smoking became popular during the beginning of the 20th century. Lung cancer is now the most common cancer worldwide, with around 2.1 million new cases annually (11.6% of cases), and the leading cause of cancer related deaths, with 1.76 million deaths (18.4% of cases) annually (Figure 1) (1). It is the most common cancer in men, and the third most common cancer in women after breast cancer and colorectal cancer (1). In 2018, 3135 patients were diagnosed with lung cancer in Norway (2). Of these, 1582 were men and 1553 were women. The median age at diagnosis is 71 years (2).

The incidence of lung cancer has decreased in men the last decade, while it is still increasing in women (Figure 2) (3, 4). The varying trends by sex reflect the different phases of the smoking epidemic in men and women, since tobacco smoking is the main cause in 80-90% of cases (5). Women started smoking later than men and while the proportion of male smokers has declined steadily from the 1960s, the number of daily female smokers peaked in the early 1970s and was stable until 2000 (3, 6). Over the last decade, the prevalence of daily smokers in Norway has been reduced from 21% to 14% (7). A similar trend has been observed in other developing countries, but the estimated number of smokers is still close to a billion worldwide (8).

Other known causes of lung cancer include passive smoking, radon, asbestos, genetic factors and air pollution (9, 10). There are major concerns that the latter will result in a new epidemic of lung cancer in developing countries where air pollution is becoming a major health problem (11).

1.1.2 Survival

Worldwide, the 5-year survival was 17% for men and 24% for women between 2009 and 2015 (4), up from 13% and 18% in previous periods.

The survival improvement has been even larger in Norway. With advances in treatment, the 5-year survival has doubled the last 20 years and was 19% for men and 26% for women for the period between 2014 and 2018 (Figure 2). Consequently, the prevalence of lung cancer patients has increased rapidly, and increased from 3882 in 2005 to 8785 in 2018 (3, 12).

Figure 1. Pie charts presenting the distribution of incidence and mortality for the 10 most common cancers worldwide in 2018. Figure copied from (1). Lung cancer is the most common cancer among men and the third most common among women. Among men, it is the leading cause of cancer deaths, while it is number two on the list among women.

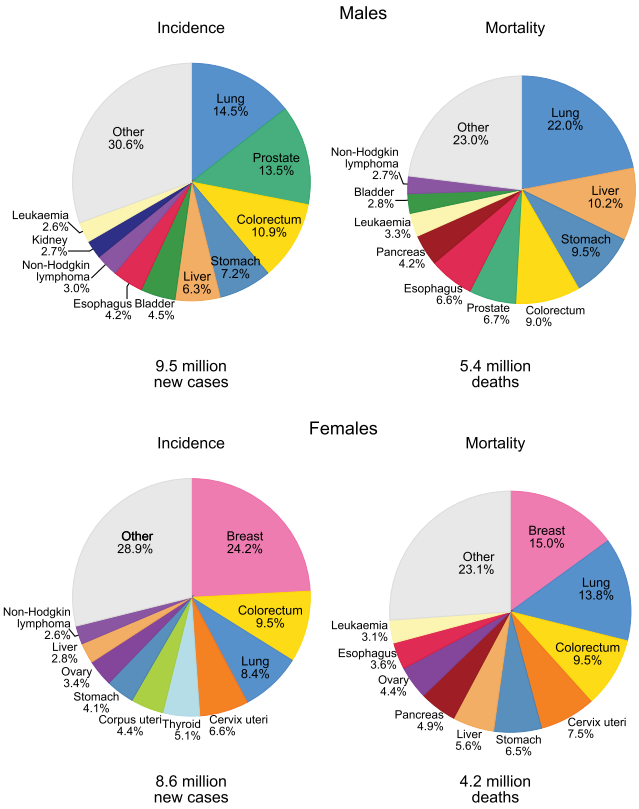
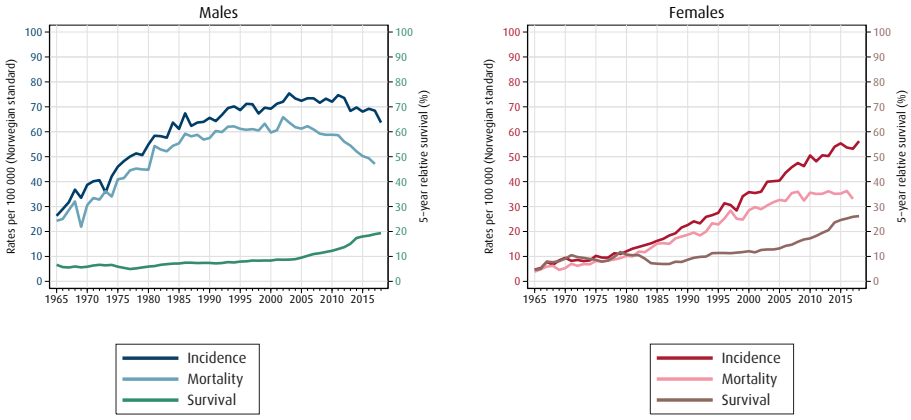


Figure 2. Incidence, mortality and 5-year survival from lung cancer in Norway (1965-2018). Figure copied from (3).



1.1.3 Classification of lung cancer

Traditionally, extent of disease and histologic subtype are the main factors for selecting treatment. Extent of disease is assessed according to the TNM staging system. Histologically, the main distinction has been between small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC is further classified into an increasing number of subtypes. The most important histologic feature is whether a tumour is squamous or non-squamous cell carcinoma. All tumours are tested for PD-L1 expression which is associated with response to immunotherapy, and the presence of mutations/translocations of EGFR, ALK, and ROS1, which predicts response to targeted therapies (13, 14). It is expected that the number of potential targets will increase rapidly in the upcoming years as more molecules targeting driver mutations are developed.

The same development of new therapies has not been seen for SCLC. Chemotherapy and radiotherapy remain the most important treatments, and all SCLC patients receive the same therapies regardless of histologic subtype (14).

1.2. Small cell lung cancer

1.2.1 Aetiology and epidemiology

SCLC is less common than NSCLC. In the United States, SCLC represents around 13% of lung cancers (13), while the proportion was 17% in 1986 (13, 15). In Norway, the proportion of SCLC has decreased from around 17% in 2001 to around 15% in 2018 (2). The proportion of females with SCLC is increasing, and the ratio between genders is now 1:1 (4, 13, 15). Both the decreasing incidence and increasing proportion of females with SCLC are thought to be related to changes in smoking habits and use of filtered cigarettes (15). SCLC is almost exclusively seen in heavy smokers (16-20). The proportion of never smokers with SCLC in Caucasian is lower than in East Asian patients (21). Radon, air pollution and passive smoking have been suggested as possible risk factors in never smokers (22-24).

1.2.2 Symptoms

Lung tumours usually grow substantially before they give symptoms and there are no pathognomonic symptoms. The most common symptoms are hemoptysis persistent coughing, wheezing, dyspnea, frequent or persistent respiratory infections, fatigue and weight loss.

1.2.3 Clinical characteristics

SCLC often originates in central airways and the tumour masses may compress mediastinal structures and cause vena cava superior syndrome, dysphagia, diaphragmatic palsy (phrenic nerve), stridor (central airways) and hoarseness (recurrent laryngeal nerve).

The tumour cells are of neuroendocrine origin and may have ectopic hormone production (e.g. parathyroid hormone, adrenocorticotropic hormone and antidiuretic hormone). SCLC is therefore the type of cancer that is most often associated with paraneoplastic phenomena, e.g. hypercalcemia, Cushing syndrome and syndrome of inappropriate antidiuretic hormone excretion.

SCLC is characterised by a more aggressive growth and rapid development of distant metastases than NSCLC. The most common sites for metastases are mediastinal lymph nodes, liver, adrenal glands, bone and brain.

1.2.4 Diagnosis

Most SCLC are diagnosed from a sample of the primary tumour collected through bronchoscopy or CT guided percutaneous biopsy. The primary analysis is light microscopy. SCLC is characterised by small cells with a round or fusiform shape and little cytoplasm. The immunohistochemistry profile is usually very typical showing positivity for chromogranin, synaptophysin and CD56 (14).

1.2.5 Staging

A CT scan of the thorax and upper abdomen is the main staging procedure for lung cancer. A PET CT scan is now recommended for all patients with LS SCLC who after a CT scan are eligible for surgery or concurrent chemoradiotherapy (25, 26). An MRI of the brain is recommended, since PET CT has an unsatisfactory sensitivity (50%) for subclinical metastases to the brain (27-29).

VALSG staging

SCLC is traditionally divided into limited stage (LS) and extensive stage (ES) (30). This classification was created when the Veterans Administration Lung Study Group (VALSG) initiated their first randomised clinical trial in inoperable lung cancer in 1957. LS was defined as disease that could be included in a tolerable radiotherapy field, including tumours confined to one hemithorax, ipsilateral mediastinal, ipsilateral hilar and ipsilateral supraclavicular lymph node metastases (LNM) (31).

Patients with more widespread disease were classified as having ES (31). Approximately 40% have LS, while 60% have ES at the time of diagnosis (13).

IASLC staging

In 1989 the International Association for the Study of Lung Cancer (IASLC) recommended that also contralateral mediastinal, contralateral hilar and contralateral supraclavicular lymph nodes should be considered LS. However, this recommendation was based on data from lung cancer patients in general and not only SCLC patients (32).

Several trials published since 1989 have used other definitions of LS. One study excluded patients with contralateral hilar LNM (33), others, including the hallmark trial by Turrisi et al., excluded both contralateral hilar and contralateral supraclavicular LNM (34, 35).

This two-stage system has remained the predominant method for staging since the separation between LS and ES and is the main factor taken into consideration when recommending treatment. Patients with LS are offered concurrent chemoradiotherapy, while chemotherapy alone has been the standard treatment for ES (36).

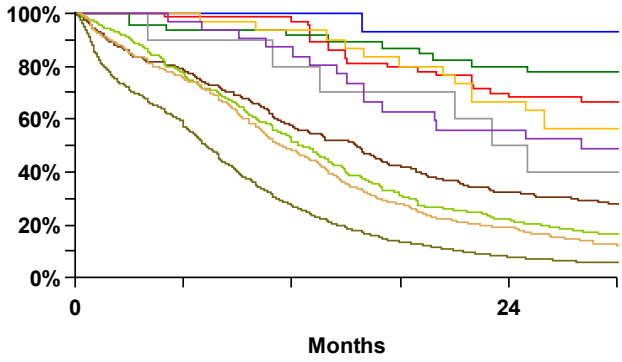
TNM staging

The TNM classification system is the most commonly used system for describing extent of disease in cancer patients. The system classifies extent of the primary tumour ("T"), lymph node involvement ("N") and whether distant metastases are present ("M") (Table 1). Based on the TNM status, the stage of disease is defined (Table 2). Criteria for T, N and M descriptors are adjusted at regular revisions to assure optimal separation in survival according to stage, as this is influenced by advances in diagnostic procedures and treatment policy.

TNM for SCLC has been included in the TNM for lung cancer since the seventh edition that was published in 2007 (37). Through this staging project, led by the IASLC, it became evident that there is significant variability in survival based on TNM stage also among patients with LS (Figure 3) (38). Thus, IASLC has recommended that TNM stage should be reported for SCLC and to stratify by TNM stages I, II, and III when designing clinical trials of early stage disease (37). This has also been encouraged in guidelines (25, 26, 39-41).

The latest edition is the eight edition of the TNM classification. It was written by the IASLC (Table 1) (30) and published in 2016 by the Union for International Cancer Control (www.uicc.org) and the American Joint Committee on Cancer (cancerstaging.org). There are no major differences for staging of SCLC between the 7th and 8th edition, which reflects that still, few assess TNM stage for SCLC patients.

Figure 3. Survival by stage of SCLC (8h edition of TNM). Figure copied from (30).



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

Table 1. Descriptors of TNM for lung cancer (8th edition of the TNM classification of malignant tumours) (42)

T: Primary tumour	
Tx	Primary tumour cannot be assessed or tumour proven by presence of malignant cells in sputum or bronchial washings but not visualised by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1 T1a(mi) T1a T1b T1c	Tumour ≤3 cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)[a] Minimally invasive adenocarcinoma[b] Tumour ≤1 cm in greatest dimension[a] Tumour >1 cm but ≤2 cm in greatest dimension[a] Tumour >2 cm but ≤3 cm in greatest dimension[a]
T2 T2a T2b	Tumour >3 cm but ≤5 cm or tumour with any of the following features[c]: - Involves main bronchus regardless of distance from the carina but without involvement of the carina - Invades visceral pleura - Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung Tumour >3 cm but ≤4 cm in greatest dimension Tumour >4 cm but ≤5 cm in greatest dimension
T3	Tumour >5 cm but ≤7 cm in greatest dimension or associated with separate tumour nodule(s) in the same lobe as the primary tumour or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumours), phrenic nerve, parietal pericardium
T4	Tumour >7 cm in greatest dimension or associated with separate tumour nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina
N: Regional lymph node involvement	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M: Distant metastasis	
M0	No distant metastasis
M1 M1a M1b M1c	Distant metastasis present Separate tumour nodule(s) in a contralateral lobe; tumour with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion[d] Single extrathoracic metastasis[e] Multiple extrathoracic metastases in one or more organs

[a]The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.
[b]Solitary adenocarcinoma, 3 cm with a predominately lepidic pattern and 5 mm invasion in any one focus.
[c]T2 tumours with these features are classified as T2a if 4 cm in greatest dimension or if size cannot be determined, and T2b if >4 cm but 5 cm in greatest dimension.
[d]Most pleural (pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumour and the fluid is nonbloody and not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging descriptor.
[e]This includes involvement of a single distant (nonregional) lymph node.

Table 2. Definition of stage of lung cancer based on TNM status (8th edition of the TNM classification of malignant tumours) (42)

T/M descriptor	Proposed T/M	N0	N1	N2	N3
T1 ≤ 1 cm	T1a	IA1	IIB	IIIA	IIIB
T1 > 1-2 cm	T1b	IA2	IIB	IIIA	IIIB
T1 > 2-3 cm	T1c	IA3	IIB	IIIA	IIIB
T2 > 3-4 cm	T2a	IB	IIB	IIIA	IIIB
T2 > 4-5 cm	T2b	IIA	IIB	IIIA	IIIB
T2 > 5-7 cm	T3	IIB	IIIA	IIIB	IIIC
T3 structures	T3	IIB	IIIA	IIIB	IIIC
T3 > 7 cm	T4	IIIA	IIIA	IIIB	IIIC
T3 diaphragm	T4	IIIA	IIIA	IIIB	IIIC
T3 endobronchial: location/atelectasis 3-4 cm	T2a	IB	IIB	IIIA	IIIB
T3 endobronchial: location/atelectasis 4-5 cm	T2b	IIA	IIB	IIIA	IIIB
T4	T4	IIIA	IIIA	IIIB	IIIC
M1a	M1a	IVA	IVA	IVA	IVA
M1b single lesion	M1b	IVA	IVA	IVA	IVA
M1c multiple lesion	M1c	IVB	IVB	IVB	IVB

1.2.6 Treatment

Surgery

The first surgical resection for lung cancer was performed in 1821 by Milton Anthony (43) and in 1933 Dr. Graham performed the first successful pneumectomy (44). Until the mid 1950s, the primary treatment of lung cancer, including SCLC was surgery, while radiotherapy was reserved for patients with unresectable disease. In 1969, The British Medical Council conducted a randomised trial comparing surgery to radiotherapy for 144 patients with SCLC (45). The median survival was better in the radiotherapy arm than in the surgical arm (43 weeks vs. 28.5 weeks (p=0.04), as was the 5-year survival (4% for radiotherapy vs. 1% for surgery). Hence, the standard treatment for LS SCLC shifted from surgery to radiotherapy. In 1994, a randomised trial failed to demonstrate a survival benefit of surgery in SCLC (46).

In the database for the seventh TNM revision for SCLC (38), 349 of the 8000 cases of SCLC had been surgically resected and pathologically staged. The data revealed a statistically significant survival advantage for stage I and stage II patients when surgically resected; stage IA, 60 months versus 119 months; stage IB, 43 months versus 81 months; stage IIA, 34 months versus 49 months; and stage IIB, 18 months versus 34 months. Five-year survival rates of 30-60% has been reported after surgery in patients with T1-2N0M0 SCLC (47-50), and surgery is therefore recommended in

these patients (25, 26, 39-41). There are, however, few of these patients. Annually, only approximately five patients undergo surgery in Norway (51).

Chemotherapy

Chemotherapy was introduced in the 1940s when Karnofsky et al. described the palliative effects of nitrogen mustard in the treatment of lung cancer patients (52). In 1968, cyclophosphamide was the first drug to demonstrate a survival benefit over best supportive care in SCLC (53). In the 1970s, combination regimens proved to be superior to single agent therapy (54, 55), and until the late 1980s, the cyclophosphamide, anthracycline (epi- or doxorubicin), and vincristine (CAV) was the standard regimen.

First line chemotherapy

A meta-analysis from 2000 demonstrated that cisplatin based chemotherapy was superior to non-platinum combinations (56) and a systematic review the same year concluded that combinations containing etoposide (with or without platinum) were superior to other regimens (57). In 2002, a phase III study by Sundstrøm et al. confirmed that cisplatin in combination with etoposide (PE) was superior to CAV in LS, and equivalent in ES SCLC, establishing PE as standard first line treatment in SCLC (58).

In 2002, a Japanese study demonstrated that irinotecan plus cisplatin was superior to EP in ES SCLC (59). Several studies have therefore investigated the role of irinotecan in SCLC (60-63), but only one study was able to confirm that irinotecan was superior to etoposide (61). Meta-analyses have showed that there might be a survival benefit of irinotecan, but etoposide is still considered the standard, at least in the Western world.

A review concluded that carboplatin provides the same efficacy as cisplatin in SCLC (64). However, the studies reviewed had small sample sizes, and only one phase III study has compared carboplatin with cisplatin in addition to etoposide in SCLC (65). Carboplatin is more convenient to administer and except for myelosuppression, offers less toxicity than cisplatin. Therefore, carboplatin is often offered patients with ES and is often used to replace cisplatin in older patients and LS patients who experience severe toxicity from cisplatin.

Dose intense chemotherapy

Since SCLC is very sensitive to chemotherapy, several methods for intensifying chemotherapy have been investigated; three drug combinations with and without granulocyte colony stimulating agents (66-68), maintenance chemotherapy (69) and high dose chemotherapy with or without autologous stem cell transplantation (70-73). These regimens have resulted in higher response rates, longer progression free survival, but more toxic deaths, and no survival benefit. Thus, it is well accepted that dose intense chemotherapy does not have any role in clinical practice.

Second line chemotherapy

Despite high response rates to primary therapy, few patients with SCLC are cured, at least not among those with ES at diagnosis. There has been a long tradition of offering relapse chemotherapy, and several studies show that up to 25% respond to second line treatment (74-76). However, only one study has compared second line chemotherapy with best supportive care (77). In this trial, patients considered ineligible for intravenous chemotherapy were randomised to receive either topotecan or best supportive care. Patients on the topotecan arm had significantly longer survival (26 weeks vs. 14 weeks, p=0.01) and better symptom control. Since intravenous regimens have shown higher response rates (typically 25%) than topotecan (7%), no similar studies have been performed, and interestingly, topotecan was the only second line therapy approved by the United States Food and Drug Administration for SCLC after progression on platinum-based chemotherapy for 20 years.

Response and response duration after first line chemotherapy is the strongest predictive factor for response to second line therapy (74), and patients with platinum sensitive disease, most commonly defined as progression free survival ≥3 months, are those who benefit the most from relapse treatment – either retreatment with the first line regimen or CAV, which is equally effective and cheaper than topotecan. Several other regimens, including gemcitabine, irinotecan, amrubicin, paclitaxel, vinorelbine, have also shown effect in the second line setting (78-83).

Targeted therapy

No targeted therapy is currently established in SCLC. The most promising drug was the antibody conjugate rovalpituzumab tesirine (50, 51), but larger studies have shown modest anti-tumour activity and relatively high levels of toxicity (84).

Immune therapy

The first line IMpower-133 (atezolizumab) (52) and the Caspian (durvalumab) study (53) demonstrated that adding a PD-L1 inhibitor to EP improved both progression free survival (52) and overall survival (OS) (52, 53) in patients with ES SCLC. Atezolizumab and durvalumab is now approved by the United States Food and Drug Administration for first line treatment of ES SCLC (54). The survival benefit is however modest, follow up is relatively short and it is unclear whether checkpoint inhibitors provide long term survival in SCLC. The role of immunotherapy in LS SCLC is being investigated in ongoing trials.

Thoracic radiotherapy

Due to the lack of new drugs, the most important advances for patients with SCLC have come from radiotherapy the last decade; through optimisation of thoracic radiotherapy (TRT) and introduction of prophylactic cranial irradiation (PCI).

Palliative radiotherapy has been offered lung cancer patients since the 1940s (85), while radical radiotherapy on inoperable patients was first attempted in the 1950s (31). The first studies on the combination of chemotherapy and TRT in LS SCLC were conducted in the 1970s (86, 87). Several randomised controlled studies compared combination chemotherapy with or without radiotherapy, with conflicting results (86, 88-99), and the role of TRT in LS SCLC was controversial. Two meta-analyses published in 1992 showed that adding TRT resulted in an increase in three year survival from 9% to 14% (p=0.001) (36, 100). While TRT was established after these meta-analyses, the timing and schedule of TRT was still debated. A meta-analysis showed that early TRT was better than late, and now that PE has replaced anthracycline-containing regimens, it is accepted that TRT should be administered concurrently with chemotherapy and not sequentially (TRT causes too much toxicity when combined with anthracyclines). Still, several schedules of TRT have been used. One of the most important studies of TRT in LS SCLC compared twice daily TRT of 45 grey (Gy) in 30 fractions with once daily TRT of 45 Gy in 25 fractions, which used to be the recommended schedule in North America. The twice daily schedule showed a significantly longer median OS (23 months vs. 19 months, p=0.04) and 5-year survival (26% vs. 16%), but population-based studies show that not all hospitals have implemented the schedule (101-105). The reasons are probably that the twice daily schedule is inconvenient (patients have to wait >6 hours between fractions), caused more esophagitis,

and that many considered the biological dose in the control arm inferior. This was the background for the randomised trial which the present PhD project is based upon. In this trial, we compared 45 Gy in 30 fractions (twice daily) with the former standard in Norway (and other countries), 42 Gy in 15 fractions, one fraction per day. There were no differences in toxicity, and the median OS on the 45 Gy arm was numerically longer (19 months vs. 25 months), though not statistically significantly different (p=0.61). However, we considered it futile to design a phase III trial aiming at proving that the 42 Gy schedule is inferior and moved on to perform a trial comparing 45 Gy with 60 Gy (twice daily for all patients). Several studies indicated that a higher dose might be more effective, but this has yet not been confirmed in any randomised trial. Hitherto, only one trial comparing 45 Gy in 30 fractions with a higher TRT dose has been published. The CONVERT trial compared twice daily TRT of 45 Gy with once daily 66 Gy. Both the median OS (25 months vs. 30 months) and the 3-year survival (39% vs 43%) was lower on the high dose arm (106). Thus, 45 Gy in 30 fractions remains the most recommended TRT schedule for LS SCLC.

Thoracic radiotherapy in ES SCLC

The role of TRT has also been investigated in ES. In a study by Jeremic et al., responders to primary chemotherapy received another three courses of PE or TRT, and patients receiving TRT had significantly improved survival (107). In a more recent study, Slotman et al. randomised patients with at least partial response after chemotherapy to TRT or observation. The study did not meet the primary endpoint of 1-year survival (TRT: 33%, no TRT: 28%, p=0.066), but there was a small, but statistically significant benefit in 2-year survival (13% vs. 3%, p=0.004) (108). The most recent study, comparing PCI + TRT to PCI alone was closed at a planned interim analysis because the study crossed the futility boundary for OS, and failed to demonstrate a benefit in 1-year survival (TRT: 50.8%, no TRT: 60.1%, p=0.21). However, time to progression favoured the use of TRT (HR 0.53, p=0.01) (109). Thus, TRT remains controversial in ES SCLC.

Prophylactic cranial irradiation

SCLC has a high potential for metastases to the brain. At diagnosis, approximately 10% of patients are diagnosed with brain metastases and up to 50% later develop brain metastases (73). Brain metastases often cause severe morbidity and are a common cause of death.

The effect of chemotherapy on brain metastases is limited by the blood-brain barrier. The use of PCI has been investigated as a method for preventing development of brain metastases since the 1970s. Early studies demonstrated a lower frequency of brain metastases, but not prolonged survival (110). A possible explanation was that PCI only prolonged survival in patients who had a complete or near complete response to chemotherapy, since patients with systemic progression would die of failure of other organs than the brain (111). PCI was established after a meta-analysis showed that LS SCLC patients in complete remission after primary therapy had a 16% risk reduction of death corresponding to an improvement in 3-year survival from 15% to 21% – as well as a reduction in the risk for developing brain metastases of 54% (112).

The benefit of PCI has also been shown in ES SCLC patients who respond to chemotherapy (74) but is controversial after a Japanese trial failed to confirm a survival benefit of PCI (75). Consequently, guidelines recommend surveillance with MRI as an option to PCI in ES SCLC (26, 41).

Current standard treatment for SCLC

Surgery should be considered in patients with T1-2N0M0. All patients should be offered adjuvant chemotherapy with 4 courses of PE. TRT should be offered if metastases are shown in resected lymph nodes or in case of insufficient lymph node sampling. Chemotherapy is the basis treatment for all other SCLC patients, and 4-6 courses of PE is the standard regimen in the Western worlds. Concurrent TRT is offered to patients with LS. TRT should start no later than after the second chemotherapy course. Twice daily radiotherapy of 45 Gy is the most recommended schedule. Selected patients with ES SCLC and response to chemotherapy (residual thoracic disease and low tumour burden) should be considered for sequential TRT. Patients with LS SCLC and response to chemoradiotherapy are offered PCI of 25-30 Gy. Patients with ED SCLC and response to chemotherapy are offered PCI or surveillance with MRI of the brain. Patients with relapse are considered for retreatment with PE if progression free survival is above three months, or second line chemotherapy with CAV or topotecan if PE is poorly tolerated or progression free survival is <3 months (25, 26, 39-41).

1.2.7 Survival for SCLC patients

Untreated, median survival for SCLC is 2-4 months (53). Most patients relapse within 1-2 years and progression free survival and OS remains relatively low. LS has a median survival of 18-30 months and a 5-year survival of 25-34% (106, 113). ES has a median survival of 9-13 months and a 2-year survival of less than 10% (25, 40, 114, 115).

1.2.8 Toxicity from concurrent chemoradiotherapy in LS SCLC

Chemotherapy, TRT and PCI are associated with severe toxicity. Most patients with LS SCLC experience severe side effects from primary treatment and treatment related deaths occur in 2-4% (35, 116) of patients.

The main toxicity from chemotherapy is myelosuppression (anaemia, neutropenia and thrombocytopenia), which may lead to neutropenic infections and thrombocytopenic bleedings. Other common side effects are fatigue and nausea.

The most important TRT toxicities are esophagitis and pneumonitis. Severe radiation esophagitis is observed in 20-30% of patients receiving chemoradiotherapy (106, 116), but most patients are relieved of symptoms within weeks after ending radiotherapy (116). Radiation pneumonitis is a less frequent, but potentially lethal complication that occur in up to 3% of patients (106, 116). These complications are less frequent after TRT for ES SCLC since the administered dose is much lower.

PCI is associated with some acute side effects such as hair loss, fatigue, nausea and loss of appetite, but the most feared side effect is cognitive failure that may occur years after treatment (117, 118).

1.3 Prognostic and predictive factors

The outcome of a particular disease may depend on many factors. A prognostic factor foresees the effect of a disease on outcomes, while a predictive factor foresees the modifying effect from the treatment. Factors may be both prognostic and predictive (119-121). In such cases, the prognostic value is modified by treatment.

Despite relatively uniform guidelines for treatment of SCLC, population-based studies show that there is considerable variation in what treatment is actually administered. There is a substantial

variation in survival both among LS and ES patients, and severe, potentially life-threatening complications are seen both after chemotherapy and radiotherapy. As always in cancer care, most clinical trials exclude a large proportion of patients seen in the clinic – such as elderly and patients with significant comorbidity (122). Thus, there is little evidence for how treatment and treatment intensity should be adapted to the individual patient. Most important for LS SCLC patients, is more knowledge on how to identify patients with the highest risk of severe toxicity from concurrent chemoradiotherapy – and those who have the highest chance of being cured. Such information would enable us to better individualise therapy, but also to provide targeted supportive care before severe complications develop. Furthermore, such knowledge would enable us to identify those who should be offered participation in trials exploring new and promising therapies.

Performance status (PS) and stage are currently the only used factors to select treatment to the individual SCLC patients. Gender, weight loss, treatment, time from start of therapy until end of radiotherapy, lactate dehydrogenase and neuron specific enolase have been identified as prognostic factors in LS SCLC (32, 123-130), but none have consistently demonstrated prognostic value and usefulness for individualising therapy. The most important reasons are that the associations are not considered strong enough for individual treatment selection, and have not been tested in prospective, randomised trials. In general, there are no established cut off values for implementing new selection criteria.

1.3.1 Comorbidity and elderly patients

Many patients with LS SCLC suffer from coexisting diseases due to old age and tobacco smoking. Population-based studies show that elderly patients and those with significant comorbidity often receive less treatment than others, probably due to concerns about toxicity and inferior treatment outcomes (104, 131-133). However, there is little evidence to support such a treatment policy (134). Comorbidity is seldom systematically measured or reported, and elderly patients and patients with comorbidity are underrepresented or excluded from clinical trials (135-138). In a previous study, we did not find any significant associations between comorbidity, survival or toxicity (134). Other studies have identified comorbidity as a negative prognostic factor in SCLC (139-143), while still others did not find an influence on survival (132, 133, 144-146).

1.3.2 Body composition

The human body can be divided in two major compartments; fat mass and fat free mass. Fat free mass is also referred to as lean body mass (LBM). Skeletal muscle constitutes the major part of the LBM.

Patients with the same weight and height may have very different body compositions because of different distributions of fat and fat free mass, and alterations in body composition may occur without a change in weight (147).

Both body size and body composition changes occur normally, is influenced by e.g. diet, physical activity and diseases, and the proportions of the two compartments vary with age and gender. LBM is generally higher in men compared with women (148) and the proportion of LBM usually declines whereas fat mass increase with increasing age (149).

Muscle measures in the elderly

The body composition changes as part of the normal aging process. Usually the amount of muscle mass decreases, and the amount of fat mass increases. The clinical impact of reduced muscle mass was first acknowledged and described within geriatric medicine, and the term *sarcopenia* denoting age related loss of muscle mass was introduced in 1989 by Rosenberg (150). Low muscle mass has been found to be an important feature in elderly causing decreased functional capacity, impairment and decreased survival (151-153).

There is no established definition or diagnostic criteria for sarcopenia (154), but most emphasise a combination of reduced muscle mass and reduced physical functioning. The European Working Group on Sarcopenia in Older People, has defined sarcopenia as “a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death”, with the following diagnostic criteria: 1) low muscle mass (>2 standard deviations below the mean in a young reference population) and either 2) low muscle strength or 3) low physical performance (gait speed of less than 0.8 m/s) (155).

Several studies have shown that loss of muscle mass alone does not fully explain the loss of muscle strength and physical function in older adults. Thus, another muscle measure, referred to as muscle quality or muscle radiodensity, has gained attention (156). Reduced muscle radiodensity

reflects increased lipid content in the tissue (157). Skeletal muscle radiodensity decreases with age, and an association between muscle radiodensity and muscle strength has been shown (158).

Muscle measures in cancer patients

The research activity on the prognostic and predictive value of muscle measures as part of cancer cachexia research has increased rapidly the last years. Involuntary weight loss is considered a hallmark of cancer. The severity varies with the type and extent of the cancer, and is most frequent in pancreatic, gastrointestinal cancers and NSCLC (159). The pathophysiology is poorly understood, and no effective treatment exists. In this setting, the term sarcopenia has mainly been used to describe reduced amounts of muscle mass and has been defined according to cut points related to increased mortality in some of the first study populations. In a consensus statement from 2011 aiming at developing a framework for the definition and classification of cancer cachexia, sarcopenia was incorporated as a measure (160).

One of the first publications about sarcopenia in cancer patients was published by Prado et al. in 2008 (147). In 250 obese (BMI ≥30) patients with solid tumours of the respiratory and gastrointestinal tracts, they found a large variability in body composition. Furthermore, they found that 15% were sarcopenic, and that sarcopenia was associated with worse functional status and was an independent negative prognostic factor for survival. Most interesting was the observation that low muscle mass may occur in people who are not thin or cachectic and has been termed sarcopenic obesity.

Later, several studies have confirmed that sarcopenia is common among cancer patients and has been associated with e.g. more postoperative infections and delayed recovery after surgery for colorectal cancers (161), reduced survival after resection of colorectal liver metastases (162), and increased mortality in breast cancer patients (163). In a study of a mixed population of 1400 patients with lung or gastrointestinal cancer, both weight loss and low muscle radiodensity were negative prognostic factors (163).

Although these reports strongly indicate an association between muscle depletion and negative outcomes, it remains unclear how sarcopenia best should be defined in cancer populations. The cut points used to identify sarcopenia vary between studies and appears to be correlated to the distribution of body mass index in the study cohorts (147, 162, 163). Furthermore, most studies are

baseline studies, and little is known about the muscle status or changes in muscle measures before cancer was diagnosed. Muscle mass and muscle radiodensity in cancer patients may depend on a whole range of factors that may or may not be caused by the underlying malignant disease such as reduced food intake, low physical activity and abnormal metabolism, and the mechanisms on how reduced muscle measurements influence mortality remain uncertain. Finally, almost no studies take into consideration response to cancer therapy, that treatment toxicity may influence muscle measures, or investigate whether muscle measures change in response to these factors.

Assessment of muscle measures

Several methods are available for assessing body composition, among which bioelectric impedance analysis and dual energy x-ray absorptiometry have been most commonly used in clinical practice (164). Recently, image-based body composition analyses have become more common, especially in studies of cancer patients since these patients often undergo imaging for staging and response evaluation. In other populations, their use is limited by costs, availability, and exposure of healthy individuals to ionising radiation. Image based techniques provide accurate measures and are considered the gold standard for body composition analyses (155).

Whole body CT imaging is rarely performed, and a cross sectional image at the level of the third lumbar vertebra (L3) is usually used for body composition analyses. The L3 level is chosen as the optimal standard landmark, as this level is found to correlate strongly to whole body skeletal muscle mass (165). Based on specific attenuation characteristics measured in Hounsfield Units (HU), CT scans enable a precise measure of skeletal muscle. These measures are normalised to individual height and regression equations have been developed to estimate whole body skeletal muscle mass (164). At the same time, the mean attenuation of the muscle area is used to measure muscle radiodensity (166).

2 Rationale for the project

2.1 Disease factors

The evidence for the definition of LS SCLC is poor and there have been varying definitions over time and between studies – mainly differing in the extent of N3 involvement accepted. All accepts ipsilateral hilar, mediastinal and supraclavicular LNM, while not all accepts contralateral mediastinal, hilar, and supraclavicular LNM (33-35). Thus, there may be differences between study cohorts in LS SCLC trials.

Modern staging and radiation techniques have changed what can be defined as a tolerable radiotherapy field. Radiation techniques such as volume modulated arc therapy and intensity modulated radiation therapy reduces the radiation dose to normal tissue. PET CT provides more accurate localisation of tumours and leads to more accurate definitions for target volumes for TRT (167). Higher TRT doses, which may improve disease control, can therefore safely be delivered (168, 169).

Even though the TNM classification is recommended for staging of SCLC, most studies still only distinguish between LS and ES. Accurate TNM classification may enable us to identify patients with distinct prognosis within the broad definition of LS. There is, however, little data available to decide whether all subcategories of N3 disease have the same prognosis.

2.2 Patients factors

Despite high response rates (80-90%) to concurrent chemoradiotherapy, 70-75% of patients with LS SCLC relapse within 1-2 years and eventually dies from the disease (106, 116). Both chemotherapy and TRT are associated with severe toxicity and treatment related deaths occur in 2-4% (106, 116).

Studies suggest that low muscle mass (SMI) and muscle radiodensity (SMD) are associated with inferior survival (170-173) and chemotherapy induced toxicity (147, 163, 174-177) in several cancers, including lung cancer. One study indicate that low muscle mass might be a negative prognostic factor in SCLC (178). Resent research suggest that patients with high drug doses per kilogram (kg) LBM are associated with more toxicity (177, 179, 180). However, little is known about the clinical role of these muscle measures in LS SCLC.

In almost all studies of the role of muscle measures in cancer patients, only the baseline measures have been used for analyses. In a previous study of patients with advanced NSCLC who

received palliative chemotherapy, we demonstrated that SMI may change during the treatment period, that gain in SMI was associated with response to chemotherapy, and that loss of SMI was a stronger negative prognostic factor than the baseline SMI (181). Thus, we hypothesised that the prognostic role of the muscle measures after completion of primary treatment is higher than the baseline measures. Furthermore, side effects of the chemoradiotherapy might cause involuntary weight loss, and consequently loss of muscle mass. Few have investigated the clinical role of SMI or SMD in SCLC, and none have investigated to what extent SMI or SMD changes during chemoradiotherapy.

3 Aims and research questions

The overall aim for the project was to investigate whether an accurate assessment of extent of disease or repeated assessment of muscle mass and radiodensity improve our ability to identify patients with LS SCLC who are at high risk of severe treatment toxicity or those with such a poor prognosis that they probably do not benefit from standard, concurrent chemoradiotherapy.

3.1 Research questions for paper I

- Do patients with N3 disease have inferior survival compared to other patients with LS SCLC?
- Do different subcategories of N3 disease have different prognosis?

3.2 Research questions for paper II

- Do patients who receive high doses of chemotherapy per kg LBM experience more haematological toxicity than other LS SCLC patients?
- Do patients with low SMI or SMD at baseline have inferior survival compared to other patients?

3.3 Research questions for paper III

- Do SMI and SMD change from baseline until end of chemoradiotherapy?
- Do patients who experience severe treatment toxicity have more changes in SMI or SMD than other patients?
- Do patients with loss of SMI or SMD during treatment have inferior survival compared to other patients with LS SCLC?
- Is the prognostic role of SMI or SMD after completion of chemoradiotherapy more important than the baseline measures?

4 Material and methods

This thesis is based on data from a randomised phase II trial comparing two schedules of TRT in LS SCLC (116) performed by the Norwegian Lung Cancer Study Group (182). One hundred fifty-seven patients received four courses of PE and were randomised to TRT of 42 Gy in 15 fractions (once daily) or 45 Gy in 30 fractions (twice daily) between the second and third PE course. Good responders received PCi of 30 Gy in 15 fractions. There was no difference in severe toxicity between the two TRT schedules. The twice daily schedule resulted in significantly more complete responses and a numerically longer median OS, but the difference was not statistically significant.

4.1 Inclusion and eligibility criteria

Patients had LS SCLC ineligible for surgery. LS was defined as disease confined to one hemithorax, including ipsi- and contralateral mediastinal, hilar and supraclavicular LNM. SCLC had to be histologically or cytologically confirmed. One negative cytology was required if pleural effusion was observed. All patients gave written informed consent, were at least 18 years old, had performance status WHO 0-2, measurable disease according to RECIST 1.0 (183), adequate organ function for chemotherapy (leukocytes ≥3.0 × 10^9/L, platelets ≥100 × 10^9/L, bilirubin <1.5 × upper limit normal, and creatinine <125 µmol/L), no other clinically active cancer and no prior radiotherapy to the chest. Pregnant or lactating women were not allowed. Fertile patients had to use contraception.

For the present project, patients were analysed if a staging CT scan (taken within four weeks before start of treatment) was available for analysis and they completed TRT and at least one chemotherapy course. For paper II and III, the staging CT scan had to include the L3 level. For paper III, a CT scan including the L3 level taken within three weeks after the last course of chemotherapy also had to be available for analyses.

4.2 Study treatment

Chemotherapy

All patients were to receive four courses of cisplatin (75 mg/m^2 intravenous day 1) and etoposide (100 mg/m^2 intravenous days 1-3) every three weeks. G-CSF was not allowed. A twenty-five percent dose reduction was warranted if leukocytes were 2.5-2.99 × 10^9/L or platelets 75-99 × 10^9/L at the time of the next course. Courses were postponed if values were lower. The dose reductions were continued

for the remaining courses. Chemotherapy was cancelled if a course was delayed more than three weeks or a third dose reduction was indicated. Carboplatin was allowed if cisplatin was not tolerated.

Thoracic radiotherapy

All patients received 3D conformal radiotherapy. TRT was delivered five days a week. A planning CT scan was performed within one week prior to TRT. The gross tumour volume (GTV) consisted of all pathological lesions on the baseline CT scan, defined according to size at the planning scan. The clinical target volume (CTV) included GTV with a 10 mm margin in all directions (CTV_{tumour}) plus the central part of the mediastinum comprising lymph node stations 4-7 ($CTV_{mediastinum}$) (the elective nodal volume). An internal margin of 10 mm was added to the CTV_{tumour} in the transverse plane and 10-15 mm in the craniocaudal direction. An internal margin of 5 mm was added to the $CTV_{mediastinum}$ in all directions. Finally, a setup margin was added according to each hospital's routine.

Less than 50% of the normal lung tissue was to receive more than 20 Gy. Other normal tissue constraints were defined, and verification of treatment was performed according to local practice.

Prophylactic cranial irradiation

PCI was offered to patients with a complete or near complete response three weeks after completing chemotherapy and TRT. PCI of 30 Gy in 15 fractions was started within six weeks after the last chemotherapy course.

Second line treatment

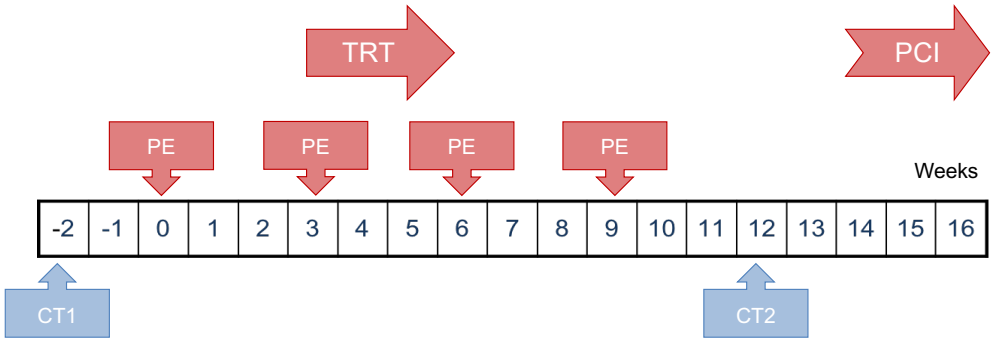
There were no restrictions with respect to second line treatment.

4.3 Evaluation and follow up

The trial plan is presented in Figure 4. Clinical examination and evaluation of toxicity were performed at the beginning of every chemotherapy course and weekly during radiotherapy. Overall response to treatment was assessed three weeks after chemoradiotherapy was completed. Patients were evaluated every eight weeks for the first year, every four months for the second and third year and every six months thereafter for five years. A CT of the thorax and upper abdomen was performed at

evaluations the first year. Chest x-ray or CT scan (optional) was performed on later evaluations. A CT scan was performed if progression was suspected on a chest x-ray.

Figure 4. Treatment and evaluation schedule



Patients had a baseline CT scan prior to starting chemotherapy. Response to chemoradiotherapy was evaluated on a CT scan after completion of therapy according to the RECIST criteria v1.0 (183). Patients with a complete response, or near complete response were offered PCI.

4.4 Assessments

4.4.1 Stage of disease

Extent of disease was assessed according to the TNM v7 (184) from contrast enhanced CT scans obtained before chemotherapy commenced. All CT scans were reviewed by a thoracic radiologist (MH). N3 disease was subcategorised as ipsilateral supraclavicular, contralateral supraclavicular, contralateral hilar and contralateral mediastinal LNM. An oncologist (TOH) and a medical physicist (NL) checked whether all pathological lesions on the CT scans were irradiated.

4.4.2 Response to treatment

The response to study treatment was assessed according to the RECIST criteria v1.0 (183) by comparing the baseline CT scan with the CT scan performed three weeks after completion of chemoradiotherapy. Measurable lesions were defined as lesions ≥10 mm. Complete disappearance of all lesions was considered to be a complete response (CR); a reduction of the sum of the largest diameters of all measurable lesions of ≥30% was considered to be a partial response (PR); an increase in the sum of the largest diameters of all measurable lesions of ≥20% was considered to be a progressive disease (PD); everything between PR and PD was considered to be stable disease (SD).

4.4.3 Toxicity

Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 (185). 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, while others include level of symptom, interference with activity of daily life and intervention needed. Both haematological toxicity after the first chemotherapy course and the overall toxicity during the treatment period was assessed.

4.4.3 Body composition

Body composition was analysed from CT scans using the SliceOMatic software (v.4.3, Tomovision, Montreal, Canada). The total cross-sectional area of skeletal muscle (cm^2) was quantified at the L3 level. One image was selected for each patient. During anatomical land marking, the first image in the caudal direction at L3 with both vertebral transverse processes clearly visible, were used in the analyses. The total cross-sectional skeletal muscle area was divided by height squared (m^2) and expressed as L3 SMI (cm^2/m^2). SMD was measured by use of Hounsfield Units (HU), with well-established thresholds from –29 to +150 (164, 166, 186). LBM was estimated from the equation: Lean tissue (kg) = (0.30 x L3 total cross-sectional area of muscle mass (cm^2)) + 6.06 (164).

Body mass index (BMI) (weight (kg)/height squared (m^2)) was categorised: BMI <20 as underweight, BMI [20,25> as normal weight, BMI [25,30> as overweight and BMI ≥30 as obesity (163). Weight loss, as reported by the patients, was categorised as <5% or ≥5% the last three months prior to diagnosis.

4.5 Survival and statistical considerations

Survival time was defined as time from inclusion in the study until death and was estimated using the Kaplan-Meier method and compared using the log-rank test. The t-test and Pearson's Chi square test were used for group comparisons. In paper I, the Cox proportional hazard method was used to identify prognostic factors for survival, adjusting for baseline characteristics (gender, age, performance status) and TRT schedule. In paper II and paper III, logistic regression and cox regression were used to identify risk factors for toxicity and survival respectively. The multivariable analyses were adjusted for baseline characteristics (gender, age, PS, stage, BMI, weight loss, pleural fluid) and TRT schedule.

SMI and SMD were analysed as continuous variables. In addition, SMI, SMD and cisplatin dose per kg LBM were split into quartiles and change in SMI and SMD were categorised as <5% and ≥5% loss from baseline in the survival analyses. All analyses were two sided, and the significance level was defined as $p<0.05$. SPSS v25 was used for all statistical analyses.

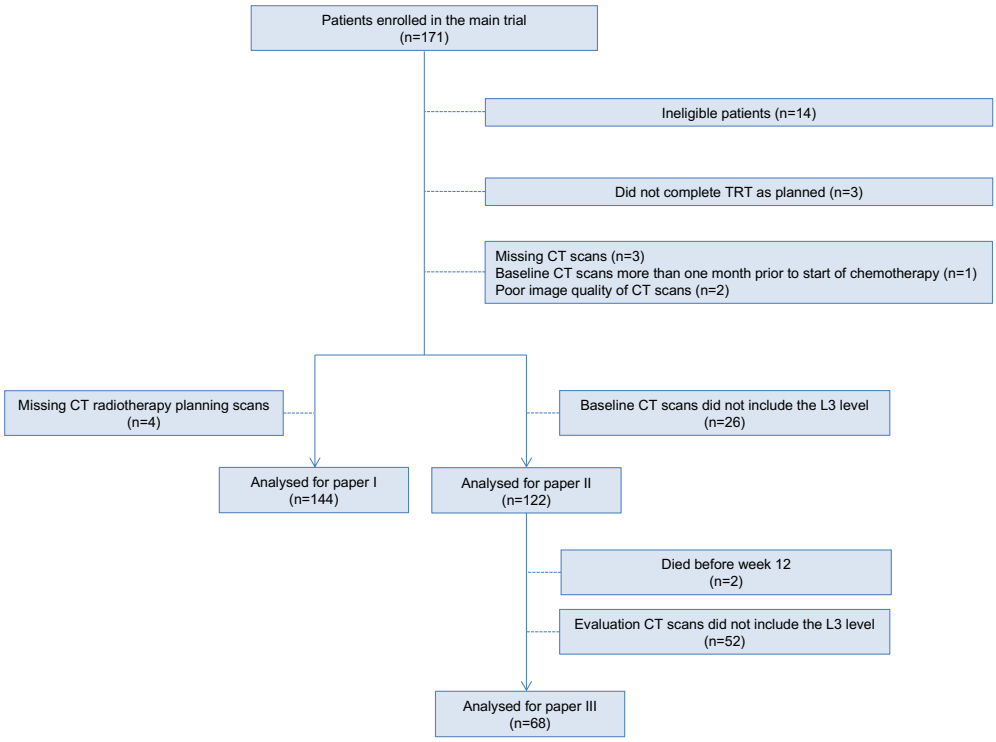
4.6 Ethics

The study 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. The research was conducted according to the Helsinki declaration and principles of Good Clinical Practice.

5 Results

From May 2005 until January 2011, 171 patients were enrolled in the main trial. Of these, 157 were eligible for the analyses (Figure 5). There were no differences in survival or toxicity between patients receiving once or twice daily radiotherapy in the main trial (116). Thus, all patients were analysed as one cohort in all three papers.

Figure 5. Patient selection



5.1 Paper I

5.1.1 Patients

Thirteen patients were excluded from the analyses due to missing CT scans (n=3), missing CT radiotherapy planning scans (n=4), the baseline CT scan was obtained more than one month prior to start of chemotherapy (n=1), poor image quality (n=2) or incomplete TRT (n=3). Thus, 144 patients (91.7%) were eligible for the present study (Figure 5).

Baseline characteristics are presented in Table 3. Median age was 63.4 years (range: 40-85 years), 74 (51.4%) were men, 46 (37.7%) had PS 2, 16 (11.1%) had pleural fluid, 126 (87.5%) completed all four chemotherapy courses and 65 (45.1%) received TRT of 45 Gy.

Median follow up was 89.4 months (range: 61.0-128.8 months) and 32 patients (22.2%) were alive when collection of survival data was completed (February 2016).

Table 3. Baseline characteristics

		Paper 1 (n=144)		Paper 2 (n=122)		Paper 3 (n=68)	
		n	%	n	%	n	%
Age, years	Mean (range)	63.4 (40-85)		63.7 (40-85)		62.9 (44-80)	
Age, ≥75 years		15	10.4	15	12.3	7	10.3
Gender	Male Female	74 70	51.4 48.6	59 63	48.4 51.6	27 41	39.7 60.3
Performance status	0 1 2	47 74 23	32.6 51.4 16.0	38 62 22	31.1 50.8 18.0	19 38 11	27.9 55.9 16.2
Thoracic radiotherapy	42 Gy/15 fractions 45 Gy/30 fractions	79 65	54.9 45.1	63 59	51.6 48.4	29 39	42.6 57.4
Completed 4 courses of chemotherapy	Yes No	126 18	87.5 12.5	107 15	87.7 12.2	61 7	89.7 10.3
PCI	Yes No	122 22	85.7 15.3	102 20	83.6 16.4	59 9	86.8 13.2
Stage	I II III Missing			3 13 103 4	1.6 10.7 84.4 3.3	1 5 62 -	1.5 7.4 91.2 -
Pleural fluid	Yes No	16 128	11.1 88.9	13 109	10.7 89.3	8 60	11.8 88.2
Body mass index	Underweight (< 20.0) Normal weight (20 to 24.9) Overweight (25.0 to 29.9) Obesity (≥ 30)			5 61 35 21	4.1 50.0 28.7 17.2	3 37 19 9	4.4 54.4 27.9 13.2
Weight loss	Yes (≥ 5%) No (< 5%) Missing			36 75 11	29.5 61.5 9.0	26 38 4	38.2 55.4 5.9

5.1.2 Stage of disease

Twenty patients (13.9%) had stage I-II disease, 70 (48.6%) stage IIIA and 54 (37.5%) stage IIIB. Distribution of TNM stage is listed in Table 4. One hundred seven patients (74.3%) had N0-2 disease and 37 (25.7%) had N3 disease. N3 involvement included contralateral mediastinal LNM (n=25, 17.4%), contralateral hilar LNM (n=11, 7.6%) and supraclavicular LNM (n=15, 10.4%). Twenty-five patients had LNM in one N3 region (17.4%), 10 patients in two N3 regions (6.9%), and two patients in three N3 regions (1.3%) (Table 5).

Table 4. TNM stage

		No. of pts. (n=144)	%	Median OS (months)	95% CI	p-value	5-year survival (%)
Stage I-II		20	13.9	33.8	13.6-53.9	0.007	40
Stage I	T1N0	1	0.7				
	T2N0	2	1.4				
Stage II	T1N1	4	2.8				
	T2N1	0	0				
	T3N0	13	9.0				
Stage IIIA		70	48.6	33.0	20.6-45.3		31.4
	T1N2	9	6.3				
	T2N2	12	8.3				
	T3N1	7	4.9				
	T3N2	15	10.4				
	T4N0	25	17.4				
	T4N1	2	1.4				
Stage IIIB		54	37.5	18.8	15.3-22.4		14.8
	T1N3	4	2.8				
	T2N3	4	2.8				
	T3N3	7	4.9				
	T4N2	17	11.8				
	T4N3	22	15.3				

5.1.3 Survival

In the whole cohort, median OS was 23.3 months and the 5-year survival was 26.4%. Patients with stage IIIB had significantly shorter median OS than those with lower disease stage (stage I-II: 33.8 months, IIIA: 33.0 months, IIIB: 18.8 months; p=0.007) (Table 4, Figure 6).

Median OS for the different subcategories of N3 is listed in Table 5. Patients with N3 disease (n=37) had significantly shorter median OS compared with patients with N0-2 disease (16.7 months vs. 33.0 months; p<0.001) (Figure 6). There were no clinically relevant survival differences between the subcategories of N3: contralateral hilar LNM: 15.5 months (95% CI 6.4-24.7), contralateral mediastinal LNM: 16.7 months (95% CI 9.2-24.1) and supraclavicular LNM: 15.1 months (95% CI 12.0-18.2). However, no patients with contralateral hilar LNM were alive after five years, while the corresponding numbers for those with supraclavicular and contralateral mediastinal LNM were 6.7%

and 16.7%. A statistical comparison was not performed since some patients had involvement of more than one N3 region.

There was a trend towards inferior median OS among the patients with involvement of more than one N3 region (one N3 region: 19.9 months, two or three N3 regions: 13.4 months; p=0.052) (Figure 6). Five-year survival for patients with involvement of one N3 region was 20.0% compared with 0.0% for those with involvement of two or three N3 regions (Table 5).

There were no significant survival differences between the T categories (Table 4, Figure 6). Multivariable analyses showed that N3 disease (HR 1.94; 95% CI 1.27-3.0; p=0.002), stage of disease (HR 1.52; 95% CI 1.14-2.04; p=0.048), and involvement of 2-3 N3 regions (HR 3.61; 95% CI 1.91-6.81; p=0.011) remained significant negative prognostic factors. None of the baseline characteristics, T stage, pleural fluid or TRT schedule were independent prognostic factors.

Table 5. Median OS and 5-year survival for N3 LNM

	N	%	Median OS (months)	95% CI	p-value	5-year survival (%)
T1	18	12.5	21.7	14.4-29.0	0.356	27.8
T2	18	12.5	38.8	21.5-56.2		38.9
T3	42	29.2	29.5	18.4-40.6		28.6
T4	66	45.8	21.7	16.2-27.3		21.2
N0-2	107	74.3	33.0	29.7-36.2	0.001*	30.8
N3	37	25.7	16.7	12.2-21.1		13.5
Supraclavicular LNM	15	10.4	15.1	12.0-18.2		6.7
Contralateral mediastinal LNM	25	17.4	16.7	9.2-24.1		16.7
Contralateral hilar LNM	11	7.6	15.5	6.4-24.7		0
One N3-station LNM	25	17.4	19.9	16.4-23.4	0.052	20.0
Two or three N3-station LNM	12	8.3	13.4	6.4-20.4		0
*Significantly different from N3						

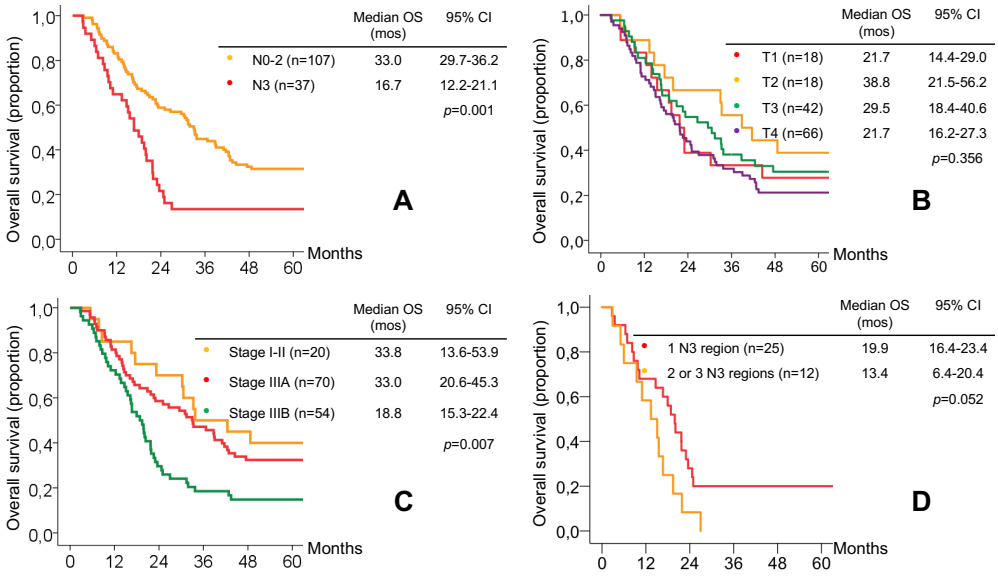


Figure 6. Kaplan-Meier survival plots for (A) N0-2 disease vs. N3 disease, (B) T-stage, (C) stage of disease and (D) involvement of one N3 region vs. two or three N3 regions. P-values were calculated using the log-rank test.

5.2 Paper II

5.2.1 Patients

Thirty-five patients were excluded from the analyses due to missing CT scans (n=3), poor image quality (n=2), the CT scans did not include the L3 level (n=26), the baseline CT scan was obtained more than one month prior to start of chemotherapy (n=1) or incomplete TRT (n=3). Thus, 122 patients (77.7%) were included in the present study (Figure 5).

Baseline characteristics are shown in Table 3. Median age was 63.7 (range: 40-85) years, 59 (48.4%) were men, 103 (84.4%) had stage III disease, 22 (18.0%) had PS 2, 107 (87.7%) completed all four chemotherapy courses, 59 (48.4%) received TRT of 45 Gy and 36 (29.5%) had weight loss ≥5%. Median BMI was 24.6 (range: 15-40); 5 (4.1%) were underweight, 61 (50.0%) had normal weight, 35 (28.7%) were overweight, and 21 (17.2%) were obese.

Median follow up was 88.2 months (range 61-129 months) and 26 patients (21%) were alive when collection of survival data was completed (February 2016).

5.2.2 Muscle mass and muscle radiodensity

Body composition data were normally distributed. Median LBM was 45.2 (range: 16-65) kg. Median SMI was 44.8 (range: 29-77) cm^2/m^2 and the median SMD was 39.3 (range 16-62) HU.

5.2.3 Toxicity

One hundred nine (89.3%) patients experienced grade 3-4 toxicity; 108 (88.5%) developed severe haematological toxicity and 83 (68.0%) severe non-haematological toxicity. Of these, 54 (44.3%) experienced severe neutropenic infections. There were no grade 3-4 thrombocytopenic bleedings. There were 6 (4.9%) treatment related deaths (grade 5 toxicity within 30 days of completion of study treatment); 3 (3.5%) died of pneumonitis, 1 (0.8%) of hemoptysis, 1 (0.8%) of respiratory failure, and 1 (0.8%) of acute coronary disease.

The median dose of cisplatin per kg LBM in the first chemotherapy course was 3.04 mg (range: 2.00-7.00) mg/kg, while the median dose of etoposide per kg LBM was 4.03 mg (range: 2.75-7.67). According to the univariable analyses, both the cisplatin- and etoposide-dose per kg LBM were significantly associated with grade 3-4 haematological toxicity after the first course of chemotherapy (OR 2.98, 95% CI 1.31-6.78; p=0.009 and OR 1.88, 95% CI 1.06-3.34; p=0.031, respectively) (Table 6). The only other factor that significantly predicted toxicity in the univariable analyses was increasing age (OR 1.05, 95% CI 1.01-1.10; p=0.022) (Table 6).

In the multivariable models (Models 1 and 2, Table 6), the significant association between grade 3-4 haematological toxicity and mg cisplatin/kg LBM (OR 7.24, 95% CI 1.57-33.39; p=0.011) remained, and there was a trend towards an association between grade 3-4 haematological toxicity and mg etoposide/kg LBM (OR 2.89, 95% CI 0.99-8.44; p=0.053). Age was no longer significantly associated with haematological toxicity in any of the models. There was, however, a significant association with male gender according to the model including mg cisplatin/kg LBM (Model 1, Table 6), but not according to the model including mg etoposide/kg LBM. No other significant associations were found.

Univariable analyses also showed a significant association between neutropenic infections and the drug-doses per kg LBM (cisplatin: OR 2.73, 95% CI 1.25-5.97; p=0.012, etoposide: OR 1.69, 95% CI 1.00 – 2.85; p=0.049) (Table 7). In the multivariable models, this association remained significant for cisplatin (OR 4.03, 95% CI 1.08-15.10; p=0.038) (Model 3, Table 7), but not for

etoposide (OR 1.62, 95% CI 0.61-4.34; p=0.335) (Model 4, Table 7). None of the other factors included in the models were significantly associated with neutropenic infections.

Table 6. Grade 3-4 haematological toxicity after the first course according to the dose of cisplatin per kg LBM

	Univariable analyses		Multivariable analyses			
			Model 3		Model 4	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
mg cisplatin per kg LBM*	2.98 (1.31-6.78)	0.009	7.24 (1.57-33.39)	0.011	-	-
mg etoposide per kg LBM*	1.88 (1.06-3.34)	0.031	-	-	2.89 (0.99-8.44)	0.053
Age*	1.05 (1.01-1.10)	0.022	1.02 (0.96-1.08)	0.462	1.03 (0.97-1.10)	0.324
Gender Female** Male	 1 1.38 (0.68-2.82)	 0.372	 4.05 (1.14-15.75)	 0.035	 2.87 (0.83-9.90)	 0.096
PS 0-1** 2	 1 1.08 (0.43-2.73)	 0.865	 1.60 (0.50-5.90)	 0.458	 1.53 (0.46-5.12)	 0.494
Disease stage I-II** III	 1 1.42 (0.47-4.26)	 0.537	 2.01 (0.38-2.41)	 0.309	 2.19 (0.59-8.20)	 0.244
Treatment OD TRT** BID TRT	 1 1.06 (0.52-2.16)	 0.866	 1.43 (0.52-3.30)	 0.462	 1.10 (0.45-2.70)	 0.838
BMI Underweight** Normal weight Overweight Obese	 1 1.89 (0.29-12.12) 1.26 (0.19-8.50) 0.75 (0.10-5.58)	 0.335	 2.68 (0.12-59.31) 1.81 (0.77-42.70) 0.58 (0.02-15.14)	 0.150	 3.45 (0.18-65.16) 2.30 (0.11-46.03) 0.68 (0.03-15.23)	 0.097
Weight loss No** Yes	 1 0.59 (0.27-1.32)	 0.201	 0.41 (0.15-1.16)	 0.093	 0.45 (0.17-1.23)	 0.118
Pleural fluid No** Yes	 1 1.28 (0.40-4.05)	 0.676	 1.15 (0.27-4.99)	 0.845	 1.32 (0.33-5.34)	 0.698

*Entered as continous variables
**Reference categories
***Not evaluable due to small number of cases

Table 7. Grade 3-4 neutropenic infections after the first course according to the dose of etoposide per kg LBM

	Univariable analyses		Multivariable analyses			
			Model 3		Model 4	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
mg cisplatin per kg LBM*	2.73 (1.25-5.97)	0.012	4.03 (1.08-15.10)	0.038	-	-
mg etoposide per kg LBM*	1.69 (1.00-2.85)	0.049	-	-	1.62 (0.61-4.34)	0.335
Age*	1.01 (0.97-1.06)	0.510	1.03 (0.97-1.10)	0.309	1.04 (0.98-1.11)	0.200
Gender Female** Male	 1 0.38 (0.18-0.80)	 0.010	 0.67 (0.21-2.11)	 0.488	 0.45 (0.14-1.41)	 0.171
PS 0-1** 2	 1 0.53 (0.20-1.40)	 0.199	 0.41 (0.12-1.42)	 0.159	 0.40 (0.12-1.33)	 0.135
Disease stage I-II** III	 1 1.21 (0.40-3.65)	 0.734	 1.50 (0.36-6.34)	 0.581	 1.52 (0.38-5.41)	 0.559
Treatment OD TRT** BID TRT	 1 0.66 (0.32-1.35)	 0.257	 0.82 (0.32-2.11)	 0.684	 0.63 (0.26-1.57)	 0.325
BMI Underweight** Normal weight Overweight Obese	 1 3.18 (0.34-30.10) 3.78 (0.38-37.28) 3.00 (0.29-31.63)	 0.718	 -*** -*** -***	 0.760	 -*** -*** -***	 0.747
Weight loss No** Yes	 1 0.69 (0.31-1.55)	 0.367	 1.01 (0.36-2.87)	 0.983	 1.10 (0.40-3.01)	 0.849
Pleural fluid No** Yes	 1 1.09 (0.34-3.45)	 0.885	 0.44 (0.10-2.97)	 0.280	 0.52 (0.13-2.11)	 0.360

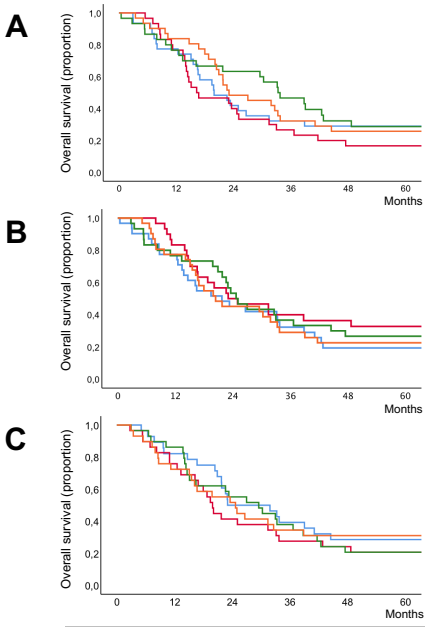
*Entered as continous variables
**Reference categories
***Not evaluable due to small number of cases

5.2.4 Survival

Overall, the median OS was 23 months and the 5-year survival was 25%. In the univariable analyses, no significant associations between survival and any of the muscle measures (SMI: p=0.906, SMD: p=0.829) or the drug doses per kg LBM ((cisplatin: p=0.292, etoposide: p=0.578) were found. Nor were there any significant associations in separate multivariable analyses for each variable (SMI: p=0.836, SMD: p=0.260, cisplatin: p=0.839 and etoposide: 0.198). As an illustration, we have included median OS and survival curves for the quartiles of SMI, SMD and cisplatin dose per kg LBM in Figure 7.

BMI was the only other significant prognostic factor (in the multivariable analysis alone, p=0.018); patients with a normal weight had a lower risk of dying compared to underweight patients (HR 0.20, 95% CI 0.07-0.62).

Figure 7. Kaplan-Meier survival plots according to (A) quartiles of SMI, (B) quartiles of SMD and (C) quartiles of mg cisplatin per kg LBM. P-values were calculated using the log-rank test.



	Median OS (months)	95% CI	
Lower quartile	19.9	12.9 - 26.9	
2nd quartile	16.3	5.0 - 27.5	
3rd quartile	33.3	22.1 - 44.5	
Upper quartile	23.0	12.0 - 34.0	*p=0.703*

	Median OS (months)	95% CI	
Lower quartile	21.7	10.3 - 33.1	
2nd quartile	23.0	10.9 - 35.2	
3rd quartile	24.7	19.3 - 30.1	
Upper quartile	20.4	6.7 - 34.1	*p=0.719*

	Median OS (months)	95% CI	
Lower quartile	23.0	9.2 - 36.8	
2nd quartile	19.9	17.5 - 22.3	
3rd quartile	29.5	17.3 - 41.8	
Upper quartile	24.7	15.6 - 33.8	*p=0.937*

5.3 Paper III

5.3.1 Patients

Eighty-nine patients were excluded from the analyses because the CT scans did not include the L3 level (n=78), due to missing CT scans (n=3), poor image quality (n=2), incomplete TRT (n=3), death during chemoradiotherapy (n=2) or because the baseline CT scan was performed more than one month prior to start of chemotherapy (n=1). Thus, 68 patients (43.3%) were included in the present study (Figure 5).

Baseline characteristics are shown in Table 3. Median age was 62.9 (range: 43.7-79.5) years, 27 (39.7%) were men, 57 (83.8%) had PS 0-1, 26 (38.2%) had stage III disease, 11 (16.2%) had PS 2, 61 (89.7%) completed all four chemotherapy courses and 39 (57.4%) received TRT of 45 Gy. Median BMI was 24.3 (range: 17-37); 3 (4.4%) were underweight, 37 (54.4%) had normal weight, 19 (27.9%) were overweight and 9 (13.2%) were obese.

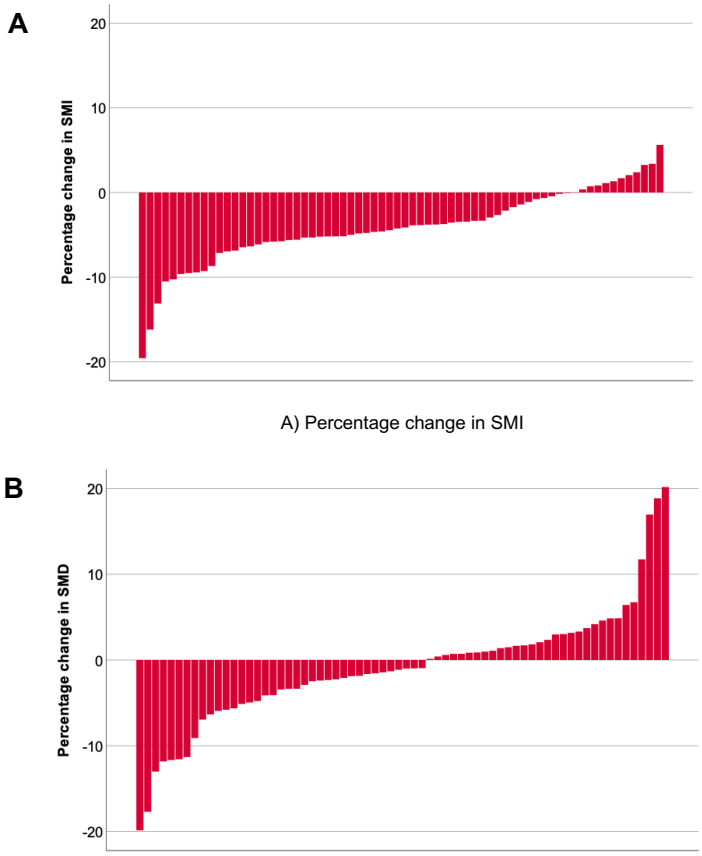
Median follow up was 89.2 months (range: 61-129 months) and 15 patients (22.1%) were alive when collection of survival data was completed (February 2016).

5.3.2 Change in skeletal muscle mass and muscle radiodensity

The percentage change in SMI and SMD from baseline until completion of chemoradiotherapy for all patients is shown in Figure 8. Mean SMI was reduced from 46.25 cm^2/m^2 to 42.13 cm^2/m^2 during the study treatment (mean change: -4.12 cm^2/m^2, 95% CI 3.06-5.19; $p<0.001$). Forty-eight patients (71%) had a reduction of ≥5% with a mean decrease of 6.18 cm^2/m^2. Twenty patients (29%) had a reduction of <5% or increased SMI with a mean increase of 0.82 cm^2/m^2.

Mean SMD was reduced from 38.40 HU to 37.46 HU during the study treatment (mean change: -0.94 HU, 95% CI -0.75-2.63; p=0.272). Twenty-five patients (37%) had a reduction of ≥5% with a mean decrease of 7.17 HU. Forty-three patients (63%) had a reduction of <5% or increased SMD, with a mean increase of 2.68 HU.

Figure 8. Percentage changes in SMI (A) and SMD (B) from baseline until completion of chemoradiotherapy



A) Percentage change in SMI

B) Percentage change in SMD

5.3.3 Toxicity from changes in skeletal muscle mass and muscle radiodensity

Sixty-two patients (91.2%) experienced any grade 3-4 toxicity. Of these, 59 (86.8%) developed grade 3-4 haematological and 48 (70.6%) grade 3-4 non-haematological toxicity. The latter included 30 (44.1%) neutropenic infections, 26 (38.2%) radiation esophagitis and 2 (2.9%) radiation pneumonitis. One patient died within 30 days of completion of study treatment from radiation pneumonitis.

There were no significant association between grade 3-4 toxicity and SMI. In the univariable analyses, loss of SMD was significantly associated with less grade 3-4 toxicity (OR 0.86, 95% CI 0.75-0.98; p=0.027) and less grade 3-4 radiation esophagitis (OR 0.91; 95% CI 0.83-0.99; p=0.029) (Table

8). In the multivariable analyses, only the association between less esophagitis and loss of SMD (OR 0.87; 95% CI 0.78-1.01; p=0.021) remained (Table 8). There were no other significant associations between SMD and severe toxicity.

Pleural fluid was significantly associated with grade 3-4 non-haematological toxicity, both in the univariable analyses (OR 0.20; 95% CI 0.04-0.94; p=0.041) and in the multivariable analyses (OR 0.12; 95% CI 0.02-0.81; p=0.029). None of the other baseline characteristics were significant predictive factors for severe toxicity.

Table 8. Associations between grade 3-4 toxicity and change in muscle measures

	Any grade 3-4 toxicity				Grade 3-4 esophagitis			
	Univariable analyses		Multivariable analyses		Univariable analyses		Multivariable analyses	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Loss of SMI*	0.93 (0.78-1.11)	0.406	1.07 (0.81-1.41)	0.649	1.05 (0.94-1.17)	0.413	1.07 (0.92-1.26)	0.377
Loss of SMD*	0.86 (0.75-0.98)	0.027	0.87 (0.80-1.09)	0.105	0.91 (0.83-0.99)	0.029	0.87 (0.78-1.01)	0.021
Age*	0.96 (0.86-1.07)	0.453	0.96 (0.84-1.10)	0.531	0.95 (0.89-1.01)	0.109	0.95 (0.88-1.02)	0.157
Gender Female** Male	 1 0.59 (0.12-3.39)	 0.592	 1.09 (0.12-9.96)	 0.940	 1 0.71 (0.26-1.94)	 0.500	 0.86 (0.28-2.77)	 0.793
PS 0-1** 2	 1 0.34 (0.05-2.14)	 0.250	 0.41 (0.04-3.97)	 0.443	 1 0.91 (0.24-3.45)	 0.889	 1.06 (0.24-5.05)	 0.940
Disease stage I-II** III	 1 0.00 (0.00- -)	 0.999	 0.00 (0.00- -)	 0.999	 1 3.38 (0.37-30.68)	 0.279	 3.04 (0.29-30.99)	 0.349
Treatment OD TRT** BID TRT	 1 0.24 (0.03-2.20)	 0.208	 0.22 (0.02-2.26)	 0.201	 1 1.02 (0.38-2.75)	 0.964	 1.26 (0.39-3.96)	 0.692
BMI Underweight** Normal weight Overweight Obese	 1 0.00- - (0.00- -) 0.00- - (0.00- -) 0.00- - (0.00- -)	 0.988	 0.00 (0.00- -) 0.00 (0.00- -) 0.00 (0.00- -)	 0.955	 1 0.96 (0.08-11.66) 2.22 (0.17-28.86) 1.00 (0.06-15.99)	 0.571	 0.46 (0.03-7.72) 1.17 (0.8-20.73) 0.48 (0.02-11.98)	 0.496
Weight loss No** Yes	 1 3.79 (0.42-34.509	 0.237	 5.00 (0.39-63.85)	 0.216	 1 0.73 (0.26-2.05)	 0.547	 0.61 (0.02-2.03)	 0.424
Pleural fluid No** Yes	 1 0.63 80.07-6.269	 0.698	 0.62 (0.05-8.46)	 0.718	 1 1.73 (0.39-7.60)	 0.470	 0.65 (0.18-8.76)	 0.556
*Entered as continous variables **Reference categories								

5.3.4 Survival and changes in skeletal muscle mass and muscle radiodensity

Overall, the median OS was 25 months and the 5-year survival was 27%. In the univariable analyses, no significant associations between survival and the muscle measures were found, neither at baseline (SMI: p=0.321, SMD: p=0.289) nor after completion of chemoradiotherapy (SMI: p=0.087, SMD: p=0.479). Nor were there any significant associations in the multivariable analyses (baseline SMI: p=0.670, SMI after chemoradiotherapy: p=0.319; baseline SMD: p=0.695, SMD after chemoradiotherapy: p=0.122).

Uni- and multivariable survival analyses for loss of SMI and SMD are shown in Table 9. Loss of SMI was significantly associated with shorter survival in the multivariable analysis (HR 1.09; 95% CI 1.01-1.19; p=0.037), and there was a trend towards an association in the univariable analysis (HR 1.06; 95% CI 0.99-1.14; p=0.094). Loss of SMD was significantly associated with better survival in both the univariable (HR 0.94; 95% CI 0.90-0.989; p=0.006) and the multivariable analyses (HR 0.94, 95% CI 0.89-0.99; p=0.019). As an illustration, we have included survival curves for patients categorised as having a loss of SMI and SMD of <5% or ≥5% in Figure 9.

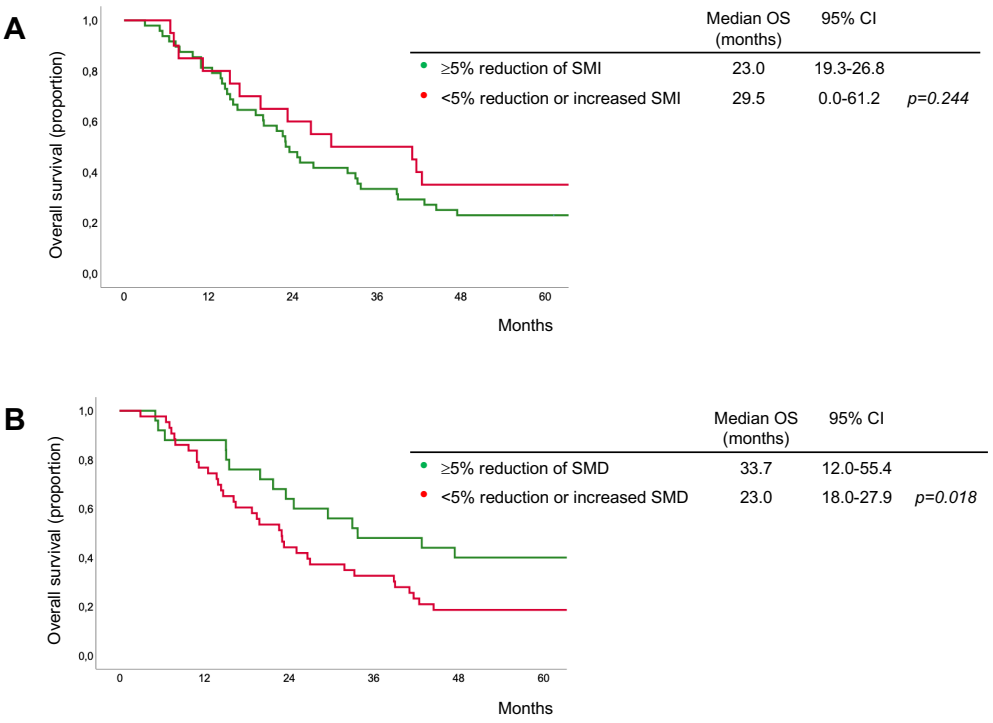
Patients with a normal weight according to BMI had a lower risk of dying compared to underweight patients (HR 0.28, 95% CI 0.08-0.98; p=0.017), but only in the univariable analysis. None of the other baseline characteristics were significant prognostic factors.

Table 9. Associations between baseline characteristics, muscle measures and survival

	Univariable analyses		**Multivariable analyses**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
mg cisplatin per kg LBM*	1.06 (0.99-1.14)	0.094	1.09 (1.01-1.19)	0.037
mg etoposide per kg LBM*	0.94 (0.90-0.98)	0.006	0.94 (0.89-0.99)	0.019
Age*	1.01 (0.98-1.05)	0.478	1.01 (0.97-1.05)	0.645
Gender Female** Male	 1 0.88 (0.51-1.53)	 0.650	 0.81 (0.43-1.53)	 0.515
PS 0-1** 2	 1 1.34 (0.65-2.76)	 0.423	 0.79 (0.35-1.80)	 0.573
Disease stage I-II** III	 1 0.96 (0.38-2.42)	 0.931	 1.20 (0.46-3.13)	 0.717
Treatment OD TRT** BID TRT	 1 1.42 (0.81-2.49)	 0.217	 1.26 (0.69-2.32)	 0.452
BMI Underweight** Normal weight Overweight Obese	 1 0.16 (0.05-0.57) 0.28 (0.08-0.98) 0.15 (0.04-0.63)	 0.017	 0.18 (0.04-0.71) 0.31 (0.07-1.29) 0.16 (0.03-0.81)	 0.044
Weight loss No** Yes	 1 1.06 (0.61-1.85)	 0.845	 0.96 (0.51-1.83)	 0.921
Pleural fluid No** Yes	 1 0.78 (0.33-1.82)	 0.561	 0.81 (0.33-2.01)	 0.648

*Entered as continous variables
**Reference categories

Figure 9. Kaplan-Meier plots for survival according to change in SMI (A) and SMD (B)



6 Discussion

We were not able to identify any subgroups of patients with LS SCLC with such a high risk of severe treatment toxicity and short expected survival that one may question whether they should receive standard chemoradiotherapy.

6.1 Muscle measures and toxicity

We did find that a high dose of chemotherapy per kg LBM increased the risk of haematological toxicity and neutropenic infections. The association was statistically significant for cisplatin, and there was a strong trend towards a similar association for etoposide. Overall, we believe that our results are in line with several publications from multiple cancer types suggesting a relationship between low LBM and increased haematological toxicity. Among those are two Norwegian studies of patients with advanced NSCLC (177, 180), studies of metastatic breast cancer (187), colorectal cancer (179, 188, 189), locally advanced oesophagus and gastric cancers (190) and a mixed sample of advanced cancers (191). None of these studies investigated whether there was an association with neutropenic infections, but it seems reasonable that more haematological toxicity increases the risk of such infections.

Both haematological toxicity and neutropenic infections put patients at risk of serious events that may have a significant impact on quality of life, and that are potentially life threatening. Therefore, one might argue that one should adjust the chemotherapy doses according to kg LBM (179, 187). However, for a new dosing schedule to be acceptable, those who experience severe toxicity needs to be quite precisely identified, and similar efficacy of the cancer therapy needs to be demonstrated for all that receive lower than current standard doses. Thus, prospective randomised trials are required before such a strategy may be introduced in the clinic.

There were no deaths clearly related to the chemotherapy or shorter survival among the patients with the highest drug doses per kg LBM, suggesting that the increased toxicity had no impact on survival. Furthermore, there are indications that patients with LS SCLC who are given a high, standard dose of chemotherapy when treatment commences have a longer survival than those who are offered lower doses (192). Other studies have also shown that lung cancer patients who experience chemotherapy induced haematological toxicity live longer than those who do not (193, 194). Haematological toxicity could therefore be a biological measure of drug activity and might predict

treatment efficacy. Thus, taking LBM into account when calculating chemotherapy doses might reduce the chance of cure for LS SCLC patients. Considering that at least 25% of patients are cured, it is very likely that LS SCLC patients accept more toxicity than those who receive palliative systemic therapy.

Ideally, we should have investigated whether high drug doses per kg LBM predict severe toxicity after the first cycle of chemotherapy for more than haematological toxicity. Unfortunately, the timing of other severe toxicity than haematological toxicity was not accurately registered, only the occurrence of each toxicity during the study treatment period.

An alternative to lowering the chemotherapy doses would be to use growth factors that reduces the risk of neutropenic infections. The role of such supportive care is, however, not established in LS SCLC, since a randomised trial showed that granulocyte colony stimulating factor (G-CSF) increases toxicity from thoracic radiotherapy and causes toxic deaths (195). This should, however, probably be reconsidered since such an association was not present in a recent subgroup analysis of the 40% of patients in the CONVERT trial that received G-CSF (106). Possible explanations are that G-CSF more specifically targets the neutrophil cell line alone, and that modern radiotherapy techniques causes less radiotoxicity (196).

Contrary to what we expected, there were no consistent association between changes in muscle measures and severe toxicity. Surprisingly, we found that patients with decreasing SMD experienced less toxicity, including less esophagitis, and there was no significant association between SMI and severe toxicity. We do not have any good explanations for our observations, especially since no other studies have investigated these associations. The overall impression is that SMD and SMI changes less than expected. In paper III, we only report changes during the study treatment period, but we also analysed CT scans obtained at follow up until one year after study entry. These analyses show that there are small variations in the muscle measures also after chemoradiotherapy. Whether this is due to low impact from the cancer therapy, a good tumour response which counteracts the potentially negative impact from the chemoradiotherapy, or good supportive care is not possible to assess from our dataset. Other knowledge gaps include lack of data on how fast SMD and SMI may change, whether changes in either of the measures occur more rapidly than in the other, or whether either is more susceptible to low nutritional intake or specific cancer therapy. The muscle measures may also only provide parts of the picture, and ideally, we should have had data on physical function,

patient reported outcomes, and nutritional interventions. More data on normal distributions of SMD and SMI in healthy controls with similar age and smoking history would also be most welcome.

6.2 Extent of disease and radiotoxicity

There is most likely a correlation between the volume of irradiated normal tissue and radiotoxicity, and it is natural to assume that patients with more extensive disease have a higher risk of such side effects. Ideally, this should have been investigated in the present cohort, especially since different methods for defining radiotherapy fields and limits for normal tissue irradiation were applied. However, the concept of elective nodal irradiation recommended in the present trial has been replaced by PET CT guided target volume definition. Thus, it is more relevant to explore these association in the subsequent trial (THORA) which we are about to start analysing.

6.3 Muscle measures and survival

Contrary to what we expected, the baseline muscle measures were not prognostic factors for survival in our cohort. There are few other data for comparison, since only two other studies have investigated the prognostic value of baseline muscle measures in SCLC. In the study by Kim et al., 149 patients of both LS and ES SCLC were analysed (178). Baseline SMI was analysed using established cut off values from both the definition of sarcopenia (SMI of <55 cm^2/m^2 for men and <39 cm^2/m^2 for women), and Korean specific cut off values (49 cm^2/m^2 for men and 31 cm^2/m^2 for women). Contrary to our results, SMI was an independent prognostic factor for survival (HR 1.68; 95% CI 1.04–2.72; p=0.034). There was also a numerical difference in OS when applying the Korean cut off values, but the difference was not statistically significant. In general, it is a challenge that there is no consensus regarding cut off values for abnormally low SMI and SMD (166, 176). Dichotomising based on statistical analyses aiming at defining threshold values below which SMI and SMD are associated with poor outcomes is problematic since the cut off values found vary between studies. This probably reflects that the muscle measures are influence by several factors such as type and stage of cancer, age, gender, BMI and ethnicity.

In the study by Bowden et al. from 2019, 194 patients with stage II-IV NSCLC and all stages of SCLC receiving first line chemoradiotherapy were analysed (197). Baseline SMI and SMD were assessed from baseline CT scans at the fourth thoracic vertebral level and analysed using optimal

stratification to determine cut off values for low SMI and SMD. Similar to our study, there was no statistically significant survival difference between patients with low and high SMI, but they did find that low SMD was an independent negative prognostic factor for survival.

These two studies are, however, not necessarily comparable to ours since there are important differences in the study populations; 67.8% of the Korean patients had extensive disease, only 29.5% received chemoradiotherapy, 20.8% only received supportive care and median follow up was only 29.0 months (vs. 88.2 months). In the study by Bowden et al., 58% of the patients had NSCLC, 6% had ES SCLC and median follow up is not stated. Data was retrospectively collected in both studies. Finally, we analysed SMI and SMD as continuous variables, which is recommended for studies on prognostic factors (198).

Low baseline SMI (176, 199) and SMD (170, 171, 174, 200, 201) have been shown to be associated with shorter survival in a wide range of cancers, and the lack of a prognostic role of the baseline muscle measures we observed contrasts a range of studies showing that low SMI (163, 178, 202) and low SMD (163, 197, 203) at baseline are significant negative prognostic factors in lung cancer. A meta-analysis from 2019 analysed 15 studies including a total of 2521 lung cancer patients (202) and found that low baseline SMI is an independent risk factor for death. However, all reports are not consistent, and some studies reveal no association with SMI (197, 203).

A possible explanation may be that LS SCLC patients have less cancer induced muscle depletion, but when comparing the present data with results from one of our previous studies of Norwegian advanced NSCLC patients (203), there were no large differences in SMI (median 43.3 cm^2/m^2 vs. 44.8 cm^2/m^2) or SMD (37.3 HU vs. 39.3 HU). NSCLC and LS SCLC patients are, however, not necessarily comparable. SCLC is considered a more rapidly progressing disease, and the proportion of smokers is higher in SCLC (204, 205).

The most obvious explanation is that the majority of LS SCLC patients respond rapidly and well to both chemo- and radiotherapy. The response rates are much higher than for most other solid tumours, and we have previously shown that most respond well even to the first chemotherapy course (206). Thus, it is possible that changes in muscle measures during treatment are less important for the prognosis of LS SCLC than for other malignant diseases.

In general, less is known about cachexia and weigh loss in SCLC than in NSCLC, though it appears that cachexia is less frequent and pronounced in SCLC (177). This may be due to different

pathophysiology, but possibly also a more rapid progression of SCLC. The exact pathophysiology of cancer cachexia is not completely understood (160). To add to the complexity, many other conditions, such as heart, vascular, lung and muscle diseases and diabetes, are also associated with muscle wasting (207-213). SCLC patients have more comorbidity than most other cancer patients, probably due to older age and since most have a history of heavy tobacco smoking (132, 214, 215). A major weakness of all studies of cancer cachexia and of the clinical role of muscle measures, is the lack of data obtained prior to cancer diagnosis. Consequently, it is not possibly to assess when muscle wasting has occurred, or whether it is due to comorbidities, the cancer disease, or both. Adjusting for comorbidity appears to have limited value (216). It has been suggested that a comprehensive geriatric assessment accounts for a better assessment of cancer patients' general health (145, 217), but our study was not designed to include this.

During chemoradiotherapy, mean SMI decreased from 46.25 cm^2/m^2 to 42.13 cm^2/m^2 and mean SMD from 38.40 HU to 37.46 HU. Loss of SMI during the chemoradiotherapy was significantly associated with shorter survival, while loss of SMD was significantly associated with longer survival.

Our results are supported by studies showing a loss of SMI (181, 218-222) and SMD (218-221) during first line treatment in NSCLC patients. Most studies investigated patients receiving chemotherapy alone, but Kiss et al. studied stage I-III NSCLC patients receiving chemoradiotherapy (220). Similar to our study, there were large variations in changes of muscle measures during the treatment period. Muscle loss was predominant, but Prado et al. found that 55% of the patients had stable or increased SMI (222), Stene et al. found that 46% of the patients had stable or increased SMI (181), and in the study by Cortellini et al., 30% of the patients gained muscle mass (218). None investigated changes in SMD.

Although our observations are in the same range as in other studies reporting change in muscle measures during cancer therapy (181, 219-221), it is unclear whether the change is to be considered large or small. The loss of SMI corresponds to more than 20 years of aging, while the loss of SMD corresponds to five years of aging (223), suggesting that the difference is clinically relevant. However, the variation in muscle measures can be due to differences in CT protocols, as both different slice thickness, tube voltage and use of contrast can result in a variation that exceeds what we observed (224, 225). There is probably little variation due to differences in software or training of staff (226).

This is the first study reporting longitudinal muscle measures in LS SCLC patients who received standard chemoradiotherapy, and only one other study has investigated the prognostic value of change in muscle measures in SCLC. In the study by Nattenmuller et al., 200 patients with all stages of NSCLC and SCLC receiving first line chemotherapy were analysed (221). The changes in SMI (from 45.7 cm^2/m^2 to 44.3 cm^2/m^2) and SMD (from 38.5 HU to 36.4 HU) was within the same range as in our study, but they concluded that both a loss of SMI (HR 1.06; 95% CI 1.03-1.10; p<0.000721) and SMD (HR 1.02; 95% CI 1.01-1.03; p=0.000884) were independent negative prognostic factors. The study is, however, not necessarily comparable with ours, since almost all patients (87.5%) had NSCLC and none received chemoradiotherapy.

A range of studies of several cancer types, including lung cancer, support our findings that loss of SMI (181, 221, 227-230) is significantly associated with shorter survival. It was more surprising that patients experiencing a reduction in SMD had the longest survival. This observation contrasts most studies of changes in SMD (221, 227, 231-233), though some did not find any significant association between change in SMD and survival (218-220, 233, 234). We do not have any evident explanation to offer, but as mentioned before, there is a lot about muscle measures that needs to be better investigated. So far, it seems reasonable to conclude that the prognostic value of baseline muscle measures and changes in muscle measures is very limited in LS SCLC. One reason may be that the potentially negative impact of low muscle mass or poor muscle quality from cancer might be overcome by the good response to treatment.

6.4 Extent of disease and survival

The first study showed that patients with N3 disease had inferior survival compared to patients with N0-2 disease. However, 13.5% of the patients were alive after five years and the median OS was much longer than in recent trials of chemotherapy, chemotherapy plus immunotherapy, and chemotherapy followed by thoracic radiotherapy in ES SCLC (17 months vs. 8-13 months) (108, 114, 115, 235). We did not find a difference in survival between the different subcategories of N3 disease, even though we used the widest definition of LS. This indicate that the expanded definition by the IASLC is as good as the definition by the VALG and that all N3 patients should be treated similarly as other LS SCLC patients. Our sample size was too small to assess whether there were survival differences between important N3 categories such as contralateral (n=2) and ipsilateral

supraclavicular (n=13) LNM. There are no other studies for comparison, but several studies have shown that the number of metastatic N1 and N2 lymph nodes and lymph node stations have an impact on survival in patients with NSCLC who underwent complete resection by lobectomy or pneumonectomy (236-238).

There was a trend towards inferior survival for patients with involvement of two or three N3 regions, though the sample size was small with only 12 patients with multiple N3 lymph node regions. Thus, the associations we detected needs to be confirmed in larger cohorts. However, the databases used for the latest revisions of the TNM system (v7 and 8), which are the two versions that contains a separate recommendation for classification of SCLC, does not contain enough data for confirmation. When the latest revision of the TNM for lung cancer was performed (30), the committee only had complete data on extent of disease and treatment for 103 out of 2931 nonsurgical patients who had received concurrent chemo- and radiotherapy for LS SCLC. The total cohort contained 5002 cases.

What may be considered a tolerable radiotherapy field has changed significantly since the distinction between LS and ES was defined. Using new techniques, the normal tissue irradiation is significantly reduced the last decades. One can speculate that also patients with what has been considered ES, e.g. patients with LNMs on the neck, now may tolerate and benefit from chemoradiotherapy. After all, adding low dose TRT in ES patients have shown a small survival benefit. This can only be explored through an international collaboration based on comprehensive and accurate assessment of extent of disease combined with accurate treatment data, preferably through clinical trials with innovative designs.

PET CT accounts for another major progress in recent decades. PET CT identifies pathological lesions better than CT scans, especially in normal size lymph nodes; provides more accurate staging, and helps distinguishing atelectasis from tumour (167). The scientific evidence mainly arises from small, non-randomised studies, and these studies do not include tissue sampling of all PET positive lesions. Based on these data, most now recommend irradiation of PET positive lesions instead of elective nodal irradiation, since this approach reduces the normal tissue irradiation. There is no clear survival benefit of this approach, but also no data suggesting that omission of elective nodal irradiation has a negative impact on survival (106).

6.5 Limitations and strengths

The main limitation of our studies is the sample size. On the other hand, our trial is one of few prospective randomised studies of LS SCLC the last decades, and the aim was to explore potentially important topics.

Because the study was not designed to investigate muscle measures, we did not have CT scans including the L3 level at all timepoints for all patients. A number of patients were excluded, especially from study II and III, but at least, we consider the exclusion to be random, and not related to specific patient or disease characteristics. In addition, there were not significant differences in baseline characteristics between included and excluded patients.

Overall, patient characteristics, TNM distribution, OS and 5-year survival in our study cohort are similar to other studies of chemoradiotherapy in LS SCLC (33-35, 239). A general limitation of such studies is that most randomised trials exclude patients with negative prognostic and predictive factors in order to increase the likelihood of completing study procedures. As a result, study patients are younger, have better PS and less comorbidity than many patients seen in the clinic (135-138), limiting the external validity.

We used the widest definition of LS (IASLC) (32), had no restrictions regarding comorbidity or age, and a relatively large proportion (16-18%) had PS 2. Based on data from the Norwegian Cancer Registry, an estimated 17% of all patients diagnosed with LS SCLC in Norway during the study enrolment period were included in the trial. This is a relatively high proportion compared with international studies on LS SCLC, but lower than in a previous Norwegian trial of advanced NSCLC, in which the proportion was 40% (240). We know from experience and by looking at the numbers, that some sites enrolled more than 90% of eligible patients, while the ability to recruit patients was lower in other regions of Norway, including the region containing the majority of inhabitants. Still, we consider the study population to be fairly representative for LS SCLC patients, but due to the lack of a comprehensive lung cancer registry, it is not possible to assess to what extent, and there might have been a selection bias towards more fit patients also in our trial.

Since several international population-based studies show that not all LS SCLC patients receive TRT and that few receive twice daily TRT, we are now performing a population-based study of the treatment and survival of all Norwegian LS SCLC patients the last 20 years which to some extent will tell us whether LS SCLC patients in general share features with the HAST population.

6.6 Study procedures

Another major limitation is that PET CT was not part of the diagnostic workup for the patients in our trial, since PET CT for staging of LS SCLC was no available in Norway back then. PET CT is now performed in Norwegian SCLC patients potentially eligible for surgery or chemoradiotherapy (25, 26, 39, 41). It is possible that some patients would have been classified as ES if PET CT had been performed, but these limitations also apply for most other published randomised clinical trials of LS SCLC (33-35, 239). Finally, lymph node mapping for confirmation of suspected LNM was not performed.

As mentioned, the trial this PhD project is based upon was not originally designed to include analyses of CT based body composition. Thus, the collection and analyses of CT scans were done retrospectively. It was a multicentre study involving 18 hospitals and 10 radiotherapy units. The study was designed to evaluate current practice, and due to the lack of consensus and uniform equipment, we did not apply standard protocols for CT scans. This explains the relatively low number of patients eligible for study II and III.

The protocol only included very general guidelines for the radiotherapy planning and technique. There were few restrictions for normal tissue irradiation and adhering to local procedures was encouraged. Most likely, there have been an improvement in radiotherapy during the six-year inclusion period, but we have not evaluated the target volume definition or normal tissue involvement.

7 Conclusion

- Patients with N3 disease had inferior survival compared to those with N0-2 disease
- There were no survival differences between the N3 subcategories with the possible exception of patients with LNM to two or more N3 stations
- Patients who received a high dose of chemotherapy per kg LBM had more haematological toxicity and neutropenic infections than other patients
- None of the baseline muscle measures were independent prognostic factors for survival
- There were large individual variations in changes in muscle measures during chemoradiotherapy, but the majority experienced a loss of both SMI and SMD
- There was no consistent prognostic value of changes in muscle measures and survival or consistent associations with severe treatment toxicity

Thus, our overall conclusion is that LS SCLC patients should receive standard concurrent chemoradiotherapy regardless of N3 disease, SMI or SMD.

8 Future perspectives

Overall, our efforts to develop a better classification of LS SCLC patients with respect to tolerability of established treatment and prognosis failed. On the other hand, this PhD project extends the evidence base for offering all patients standard treatment.

Looking at the rapid and extensive changes in lung cancer treatment in recent years, one might question whether it is realistic to develop better classification systems aiming at individualising therapy based on clinical characteristics. Before an evaluation can be performed, guidelines for standard care have probably changed.

Considering the unmet need for better treatment for SCLC, we believe that developing more effective therapy should be the first priority. We have conducted a trial investigating the benefit of high dose TRT (THORA), and are currently recruiting patients in an international trial investigating the benefit of adding immunotherapy after chemoradiotherapy in LS SCLC (ACHILES).

Since there is always a risk of severe toxicity when exploring new therapies, also these trials do not allow inclusion of patients with a very poor performance status or severe comorbidity. Trials recruiting the latter patients are frequently called for but is probably too challenging in a relatively low frequency cancer type as LS SCLC. With the introduction of modern systemic therapy, the need may also be lower than in the chemotherapy era, since immunotherapy and targeted agents appear to be well tolerated also by elderly and frail patients.

All patients in THORA and ACHILES are staged using PET CT, and there is a great opportunity to investigate whether the results of paper I can be reproduced in a validation cohort which is more accurately staged with respect to extent of disease.

After the initial, quite convincing studies of the predictive and prognostic role of muscle measures, our and others research strongly suggests that there is still a long way to go before these variables may be used in the clinic; and we are not convinced that they will ever be. Thus, instead of focusing on SMI and SMD, we have incorporated other measures that may be used for classification of patients in the THORA trial; physical function tests (five meter walk test and timed up-and-go) and measurement of CRP and albumin, which constitutes the Glasgow Prognostic Score (GPS), one of the most robust prognostic scores in cancer patients, which is easily and objectively measured (241).

Some argue that a more comprehensive assessment, including e.g. patient reported outcomes, a full geriatric assessment, and physical tests should be performed in all cancer patients. A

major weakness is that all scales for such assessments are susceptible for major medical improvements. E.g. there have been dramatic changes in the outcomes of treatment of ischemic heart disease and HIV since the Charlson Comorbidity Index, the most commonly used tool for measuring comorbidity, was developed. Furthermore, comprehensive assessments are not feasible in multicenter trials, and the alternative, analysing cohorts of patients with different types of cancer at a limited number of sites is not optimal due to the large variations in prognosis, response to treatment and toxicity. Comprehensive assessments also generate an amount of data that is impossible to process in a busy clinical practice. It is possible that new approaches such as artificial intelligence may solve this problem, but this will have to be verified in prospective trials.

Another approach may be to offer more targeted and better supportive care to patients during and after primary therapy, and not only during end of life. A commonly cited study showed that early “palliative” care improved outcomes in lung cancer patients when offered concurrently with primary anti-cancer treatment (242). How this should be implemented on a larger scale remains unclear.

It may be better to develop improved molecular classification than processing clinical data – that in nature to a large extent are subjective. Based on tumour and blood samples from the THORA trial, our research group is investigating whether repeated measures of circulating tumour DNA may improve our classification of LS SCLC patients. It is well established that tumour cells shed DNA fragments into the blood stream. These fragments can be isolated and sequenced, and several studies show that there are interesting correlations with e.g. tumour load, response to treatment and early detection of relapse. The main aim of an ongoing project is to identify those who are truly cured after current chemoradiotherapy.

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10 Appendix A Paper I

ANTICANCER RESEARCH *38*: 871-876 (2018)
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Survival in Limited Disease Small Cell Lung Cancer According to N3 Lymph Node Involvement

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Abstract. *Background/Aim: There are several definitions of limited disease (LD) in small cell lung cancer (SCLC), differing with respect to N3 disease accepted. We analyzed patients from a randomized trial comparing two schedules of thoracic radiotherapy (TRT) in LD SCLC to investigate whether there were survival differences between N3 subcategories (n=144). Patients and Methods: Patients with a baseline CT scan available were analysed. Patients received four courses of cisplatin/etoposide and TRT of 45 Gy/30 fractions (twice daily) or 42 Gy/15 fractions (once daily). Results: Median overall survival (OS) was 23.3 months in the whole cohort. N3-patients (n=37) had shorter survival than those with N0-2 (16.7 vs. 33.0 months; p<0.001). There were no significant OS-differences between the N3 subcategories, but patients with metastases to two or more N3 regions had shorter survival than other N3 patients (13.4 vs. 19.9 months; p=0.011). Conclusion: There were no survival differences between the N3 subcategories, suggesting that all N3 disease should be considered as LD.*

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Key Words: SCLC, radiotherapy, TNM, staging, prognostic factor.

Chemotherapy is the basis treatment for small cell lung cancer (SCLC). Concurrent radiotherapy improves survival and is offered if all lesions can be included in a radiotherapy field. *i.e.* limited disease (LD). Patients with more widespread disease are classified as having extended disease (ED) and receive chemotherapy alone (1).

There are, however, several definitions of LD. The first definition was made by the Veterans Administration Lung Study Group (VALSG) in 1957 and defined LD as disease confined to one hemithorax, ipsilateral mediastinal, ipsilateral hilar and ipsilateral supraclavicular lymph node metastases (LNM) (2). The International Association for the Study of Lung Cancer (IASLC) published an article in 1989 recommending that also contralateral mediastinal, contralateral hilar and contralateral supraclavicular lymph nodes should be considered LD, but this recommendation was based on data on lung cancer patients in general and not only SCLC patients (3). Furthermore, several trials published since 1989 have used other definitions of LD. One study excluded patients with contralateral hilar LNM, (4) others excluded both contralateral hilar and contralateral supraclavicular LNM (5, 6).

Internationally, the TNM system is the most widely used classification system for staging of cancer. It is also recommended for staging of SCLC, but still most studies only distinguish between LD and ED. Thus, there is little data available to decide whether all subcategories of N3 disease should be considered as LD; especially with respect to ipsilateral and contralateral supraclavicular LNM. When the latest revision of the TNM for lung cancer was performed, (7) the committee only had complete data on extent of disease and

treatment on 103 nonsurgical patients who had received concurrent chemo- and radiotherapy for LD SCLC. There were no survival differences between N categories among nonsurgical patients and there were insufficient data to investigate whether there were survival differences between the different subcategories of N3 disease. Thus, when both the seventh (2009) and eight edition (2015) of the TNM classification of SCLC were published, it was recommended to report the TNM stage in future studies of SCLC (7, 8).

We analyzed patients enrolled in a randomized phase II trial comparing two schedules of thoracic radiotherapy (TRT) in LD SCLC (9). The aims were to investigate the distribution of TNM stage at baseline, and whether there were survival differences between N categories or the subcategories of N3 disease.

Materials and Methods

Approvals. The study 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.

Patients and treatment. Patients participating in a randomized phase II trial comparing two schedules of TRT in LD SCLC were analysed (9). Eligible patients gave written informed consent; were ≥18 years old; ineligible for surgery; had disease confined to one hemithorax, the mediastinum, contralateral hilar and supraclavicular (both ipsi- and contralateral) lymph nodes; measurable disease according to RECIST 1.0 (10); no other clinically active cancer; no malignant pleural effusion (one negative cytology was required if pleural effusion was observed); no prior radiotherapy to the chest; WHO performance status 0-2; leukocytes ≥3.0×10^9/l; platelets ≥100×10^9/l; bilirubin <1.5× ULN; and creatinine <125 μmol/l.

All patients were to receive four courses of cisplatin plus etoposide and were randomized to receive TRT of either 45 Gy in 30 fractions (twice daily) or 42 Gy in 15 fractions (once daily) starting 3-4 weeks after start of the first chemotherapy course. Good responders were offered prophylactic cranial irradiation of 30 Gy in 15 fractions. There were no significant differences in overall response rates, progression free survival or overall survival (OS) (9). Thus, all patients were analysed as one cohort in the present study.

Patients were eligible for the present study provided the baseline staging CT scan was analysable, all pathological LNM were irradiated they completed TRT and at least one chemotherapy course.

TNM stage. Extent of disease was assessed according to the TNM v7 from contrast enhanced CT scans obtained before chemotherapy commenced. All CT scans were reviewed by a thoracic radiologist (MH). N3 disease was subcategorised as ipsilateral supraclavicular, contralateral supraclavicular, contralateral hilar and contralateral mediastinal LNM. An oncologist (TOH) and a medical physicist (NL) checked whether all pathological lesions on the CT scans were irradiated.

Analyses and statistical considerations. Survival time was defined as time from inclusion in the study until death and was estimated using the Kaplan-Meier method and compared using the log-rank test. Cox multivariate analyses were conducted adjusting for baseline characteristics (gender, age, performance status) (11, 12) and TRT schedule. The significance level was defined as $p<0.05$.

Results

Patients. From May 2005 until January 2011, 157 eligible patients were enrolled in the main trial. Of these, 144 (91.7%) were analyzed in the present study. A total of 13 patients were excluded due to missing CT scans (n=3), missing CT radiotherapy planning scans (n=4), or incomplete TRT (n=6). Patient characteristics are shown in Table I. Mean age was 63.5 years (range=40-85 years), 74 (51.4%) were men, 121 (84.0%) had PS 0-1, 16 (11.1%) had pleural fluid, 126 (87.5%) completed all four chemotherapy courses and 65 (45.1%) received TRT of 45 Gy. Median follow up was 91.1 months (range=61.0-128.8 months) and 32 patients were alive at the time of the survival analyses (February 2016).

Stage of disease. Distribution of TNM stage is listed in Table II. Three patients (2.1%) had stage I disease, 17 (11.8%) stage II, 70 (48.6%) stage IIIA, and 54 (37.5%) stage IIIB. Consequently, stage I and II patients were analysed as one group.

Eighteen patients (12.5%) had T1 tumour, 18 (12.5%) T2, 42 (29.2%) T3 and 66 (45.8%) T4. Forty-one (33.0%) patients had N0 disease, 13 (9.0%) N1, 53 (36.8%) N2 and 37 (25.7%) N3 (Table III). N3 involvement included contralateral mediastinal LNM (n=25, 17.4%), contralateral hilar LNM (n=11, 7.6%) and supraclavicular LNM (n=15, 10.4%). Among the patients with supraclavicular LNM, 13 had ipsilateral while only two had contralateral LNM. Thus, these patients were analysed as one group. Twenty-five patients had LNM in one N3 region (17.4%), 10 patients had in two N3 regions (6.9%), and two had in three N3 regions (1.3%) (Table III).

Survival analyses. In the whole cohort, median OS was 23.3 months and the 5-year survival was 26.4%. There were no significant differences in median OS between men and women (21.8 *vs*. 25.1 months; $p=0.647$), between PS 0-1 and PS 2 patients (23.6 *vs*. 22.6 months; $p=0.365$), or those with pleural fluid *vs*. those without (31.0 *vs*. 22.6 months; $p=0.404$).

Patients with stage IIIB had significantly shorter median OS than those with lower disease stage (stage I-II: 33.8 months, IIIA: 33.0 months, IIIB: 18.8 months; $p=0.007$) (Table II, Figure 1).

Median OS for the different subcategories of N3 is listed in Table III. Patients with N3 disease (n=37) had significantly shorter median OS compared with patients with N0-2 disease (16.7 months *vs*. 33.0 months; $p<0.001$) (Figure 1), but there

Table I. *Patient characteristics*.

	All patients (n=144)		N0-2 (n=107)		N3 (n=37)	
	n	%	n	%	n	%
Age, years						
Mean, (SD), (range)	63.5±8.71, (40-85)		62.8±8.57 (40-79)		65.6±8.9 (44-85)	
Gender						
Male	74	51.4	51	47.7	23	62.2
Female	70	48.6	56	52.3	14	37.8
Performance status						
0	47	32.6	40	37.4	7	18.9
1	74	51.4	53	49.5	21	56.8
2	23	16.0	14	13.1	9	24.3
Pleural fluid						
Yes	16	11.1	12	11.2	4	10.8
No	128	88.9	95	88.2	33	89.2
Thoracic radiotherapy						
42 Gy/15 fractions	79	54.9	60	56.1	19	51.4
45 Gy/30 fractions	65	45.1	47	43.9	18	48.6
Completed 4 courses of chemotherapy						
Yes	126	87.5	95	88.8	31	83.8
No	18	12.5	12	11.2	6	16.2

Table II. *TNM stage*.

	No. of pts. (n=144)	%	Median OS (months)	95%CI	*p*-Value	5-year survival (%)
Stage I-II	20	13.9	33.8	13.6-53.9	0.007	40
Stage I						
T1N0	1	.7				
T2N0	2	1.4				
Stage II						
T1N1	4	2.8				
T2N1	0	0				
T3N0	13	9.0				
Stage IIIA	70	48.6	33.0	20.6-45.3		31.4
T1N2	9	6.3				
T2N2	12	8.3				
T3N1	7	4.9				
T3N2	15	10.4				
T4N0	25	17.4				
T4N1	2	1.4				
Stage IIIB	54	37.5	18.8	15.3-22.4		14.8
T1N3	4	2.8				
T2N3	4	2.8				
T3N3	7	4.9				
T4N2	17	11.8				
T4N3	22	15.3				

were no clinically relevant survival differences between the subcategories of N3: contralateral hilar LNM: 15.5 months (95%CI=6.4-24.7), contralateral mediastinal LNM: 16.7 months (95%CI=9.2-24.1) and supraclavicular LNM: 15.1 months (95%CI=12.0-18.2). However, no patients with contralateral hilar LNM were alive after 5 years, while the corresponding numbers for those with supraclavicular and contralateral mediastinal LNM were 6.7% and 16.7%. A statistical comparison was not performed since some patients had involvement of more than one N3 region.

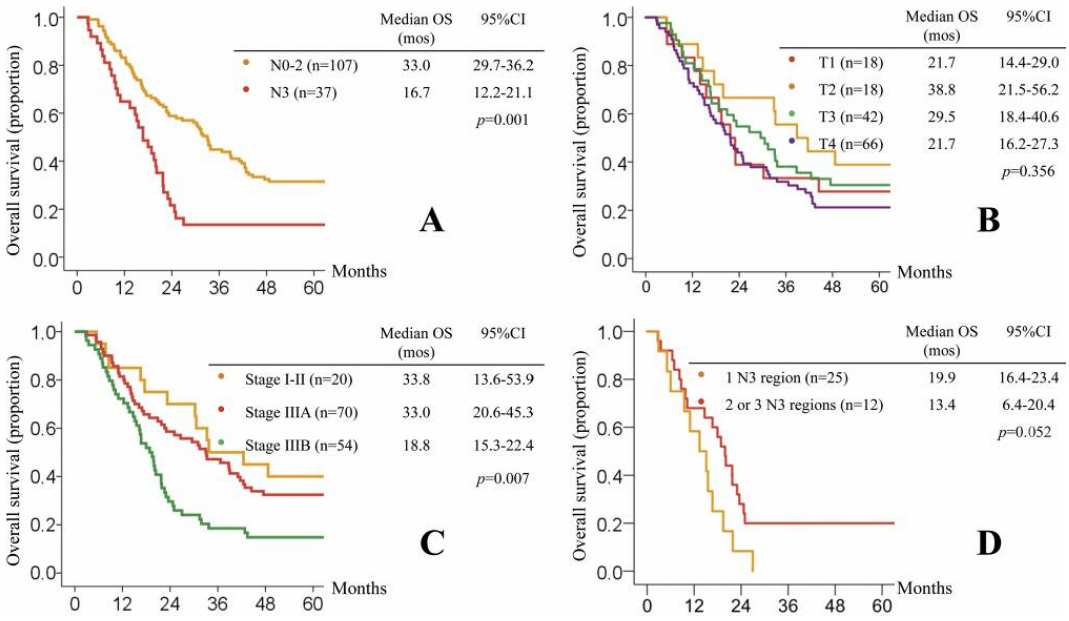

Figure 1. *Kaplan–Meier survival plots for (A) N0-2 disease vs. N3 disease, (B) T stage, (C) stage of disease and (D) involvement of one N3 region vs. two or three N3 regions. p-Values were calculated using the log-rank test.*

Table III. *Median OS and 5-year survival for N3 lymph node metastases.*

	N	%	Median OS (months)	95%CI	*p*-Value	5-year survival (%)
T1	18	12.5	21.7	14.4-29.0	0.356	27.8
T2	18	12.5	38.8	21.5-56.2		38.9
T3	42	29.2	29.5	18.4-40.6		28.6
T4	66	45.8	21.7	16.2-27.3		21.2
N0-2	107	74.3	33.0	29.7-36.2	0.001*	30.8
N3	37	25.7	16.7	12.2-21.1		13.5
Supraclavicular LNM	15	10.4	15.1	12.0-18.2		6.7
Contralateral mediastinal LNM	25	17.4	16.7	9.2-24.1		16.7
Contralateral hilar LNM	11	7.6	15.5	6.4-24.7		0
One N3 station LNM	25	17.4	19.9	16.4-23.4	0.052	20.0
Two or three N3 station LNM	12	8.3	13.4	6.4-20.4		0

*Significantly different from N3.

There was a trend towards inferior median OS among the patients with involvement of more than one N3 region (one N3 region: 19.9 months, two or three N3 regions: 13.4 months; p=0.052) (Figure 1). Five-year survival for patients with involvement of one N3 region was 20.0% compared with 0.0% for those with involvement of two or three N3 regions (Table III).

There were no significant survival differences between the T categories (Table III, Figure 1). Median OS was 21.7 months for T1 tumours, 38.8 months for T2, 29.5 months for T3, and 21.7 months for T4 (p=0.356).

Multivariate analyses showed that N3 disease (HR=1.94; 95%CI=1.27-3.0; p=0.002), stage of disease (HR=1.52; 95%CI=1.14-2.04; p=0.048), and involvement of 2-3 N3

regions (HR=3.61; 95%CI=1.91-6.81; p=0.011) remained significant negative prognostic factors. None of the baseline characteristics, T stage, pleural fluid or TRT schedule were independent prognostic factors.

According to RECIST 1.1, lymph nodes with a short axis diameter of ≥15 mm are considered pathological. There were no significant differences when rerunning the analyses defining ≥15 mm as the criterium for pathological lymph nodes.

Discussion

In this study of patients with LD SCLC receiving concurrent chemo- and radiotherapy, we found that those with N3 disease had a significantly shorter survival than patients with N0-2 disease. There were no survival differences between the subcategories of N3 disease, but those with involvement of two or three N3 regions had significantly worse prognosis. To our knowledge, this is the first study reporting detailed T and N data including subcategories of N3 in a cohort of LD SCLC patients who all received standard chemotherapy and established schedules of concurrent thoracic radiotherapy. According to the authors, there were insufficient data to determine whether there were survival differences between the subcategories of N3 disease in the databases used for the 7th and 8th revision of the TNM for SCLC (7, 8).

Our results may, in some aspects, differ from what was found in the article presenting the 8th revision of the TNM for SCLC (7). In that paper, T stage was a significant prognostic factor among non-surgical patients, while N status was not, and there was no survival difference between stage IIIA and IIIB. The results are, however, not necessarily comparable since a large proportion of the patients in the TNM article had undergone surgery, and details on treatment was not available for all nonsurgical patients. We only analyzed non-surgical patients who received concurrent chemoradiotherapy.

A limitation of the study is the sample size, especially in the N3 subgroups. However, our sample size is still larger than the number of patients who received both chemotherapy and TRT in the database used for the latest TNM revision for SCLC (8th edition) (7). In this database (n=5002) treatment data were available for only 11% of inoperable patients, and among these 2931 nonsurgical patients, it was only confirmed that 103 patients received both chemo- and radiotherapy.

Another limitation is that positron emission tomography (PET CT) was not used for staging of disease in our study. Studies conducted after our trial was initiated have shown that PET CT identifies pathological lesions better than CT scans, providing more accurate staging 13). However, few other published trials of TRT in LD SCLC have yet used PET CT for staging (4, 5, 6, 14).

Patient characteristics, TNM distribution and overall survival in our study cohort are similar to other studies of chemoradiotherapy in LD SCLC, (4,5,6,14) we used the widest definition of LD (IASLC), (3) had no restrictions regarding comorbidity or age, and 16% had PS 2. Thus, we consider the study population representative for LD SCLC patients receiving chemoradiotherapy.

We were not able to detect differences in survival between the subcategories of N3 disease. Thus, until other data emerge, it appears reasonable to consider all N3 disease as LD. The overall survival for all subcategories of N3 disease were longer than in studies of ED SCLC, (15) with the possible exception of patients with LNM to two or more N3 stations. It is also noteworthy that none of the patients with contralateral hilar LNM were alive after 5 years, but the number of patients was small. Our data suggest that incorporating the subcategories and number of involved N3 regions might add to the prognostic value of the TNM staging system, but this needs to be confirmed in larger cohorts. Furthermore, considering the improvement in staging methods with the introduction of PET CT and endobronchial ultrasound guided transbronchial needle aspiration, improved radiotherapy techniques, and the demonstrated benefit of TRT in some ED SCLC patients, the definition of patients who should be offered TRT may be challenged, but requires large databases containing detailed information about disease extent and treatment administered.

In conclusion, patients with N3 disease had inferior survival compared to those with N0-2 disease, but there were no survival differences between the N3 subcategories. Our study indicates that all N3 lymph node metastases should be considered as limited disease, with the possible exception of those with involvement of two or more N3 regions.

Conflicts of Interest

None.

Acknowledgements

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11 Appendix B Paper II

Associations between muscle measures, survival and toxicity in patients with limited stage small cell lung cancer

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Abstract

Background

Standard treatment for patients with limited stage small cell lung cancer (LS SCLC) is concurrent platinum-etoposide chemotherapy and thoracic radiotherapy. Up to 30% of patients are cured, but severe toxicity is common, and we are not able to identify those who are cured or those who experience severe toxicity before chemoradiotherapy commences. Studies of other cancer patients show that low muscle mass and muscle radiodensity are associated with inferior survival and that a high drug dose per kg lean body mass (LBM) is associated with more toxicity, but this has not been investigated in LS SCLC. We analysed patients from a randomised trial comparing two schedules of thoracic radiotherapy (TRT) (n=157) to investigate the prognostic and predictive role of these muscle measures in LS SCLC.

Methods

Patients from a trial comparing once daily hypofractionated with twice daily hyperfractionated TRT were analysed. The skeletal muscle index (SMI), radiodensity (SMD) and LBM were assessed from baseline CT scans at the level of the third lumbar vertebra (L3) using the SliceOMatic software.

Results

Images at the L3 level were available for 122 patients (77.7%). Median age was 64 years, 18% had PS 2 and 84.4% had stage III. Grade 3-4 toxicity was observed in 89%, and 5% died from treatment related side effects. Overall, the median OS was 23 months and the 5-year survival was 25%. Median LBM was 45.2 (range: 16-65) kg, the median SMI 44.8 (range: 29-77) cm^2/m^2 and the median SMD 39.3 (range 16-62) HU. There were no significant associations between survival and any of the muscle measures in the univariable analyses (SMI: p=0.906, SMD: p=0.829) or in multivariable analyses adjusting for baseline characteristics (SMI: p=0.836, SMD: p=0.260). A higher cisplatin dose per kg LBM in the first course significantly increased the risk of grade 3-4 haematological toxicity (p=0.011) and neutropenic infections (p=0.012).

Conclusion

Patients who received a high dose of cisplatin per kg LBM had more haematological toxicity and neutropenic infections than other patients. None of the muscle measures were independent prognostic factors for survival in our cohort of LS SCLC patients who underwent standard chemoradiotherapy.

Keywords: prognostic factor, predictive factor, survival, skeletal muscle index, skeletal muscle radiodensity

Introduction

Concurrent cisplatin and etoposide chemotherapy and thoracic radiotherapy (TRT) is the standard treatment for patients with limited stage (LS) small cell lung cancer (SCLC). Despite high response rates (80-90%), the 5-year survival is 25-30% [1, 2]. Furthermore, the combination of chemotherapy and radiotherapy is associated with severe toxicity and treatment related deaths occur in 2-4% [2, 3]. It is a major challenge that we are not able to accurately identify those who are most likely to be cured or those with the highest risk of severe toxicity. Thus, all patients with a good performance status (PS) are offered standard chemoradiotherapy [2-5].

Loss of skeletal muscle mass and loss of muscle quality in terms of fat deposits, is common among cancer patients. The whole-body skeletal muscle mass is highly correlated with the skeletal muscle index (SMI) measured at the level of the third lumbar vertebra (L3), and the skeletal muscle radiodensity (SMD) reflects the degree of fat deposits. Both measures can be assessed from CT slides using appropriate software (SliceOMatic, Tomovision, Canada) [6-8].

Several studies of cancer patients have shown that both low SMI and SMD are negative prognostic factors [9-12], and that low muscle mass and higher drug doses per kg muscle mass (lean body muscle mass, LBM) are associated with severe toxicity from systemic cancer therapy [13-20]. Whether this applies to SCLC patients has scarcely been investigated. One study indicated that low SMI might be a negative prognostic factor also in SCLC patients, but none have reported whether this is the case for SCLC patients with limited stage [19]. Furthermore, the prognostic role of SMD and the impact of higher drug doses per kg LBM on toxicity in SCLC patients are not known.

We analysed patients enrolled in a randomised phase II trial comparing two schedules of TRT in LS SCLC [21]. The aims were to investigate whether low SMI and SMD are negative prognostic factors for survival and if high drug doses per kilo LBM predict severe toxicity in this cohort.

Materials and methods

Approvals

The study 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.

Patients and treatment

Patients eligible for the phase II trial were ≥18 years old; had stage I-III disease ineligible for surgery; measurable disease according to RECIST 1.0 [22]; no other clinically active cancer; WHO performance status (PS) 0-2; leukocytes ≥3.0 × 10^9/L; platelets ≥100 × 10^9/L; bilirubin <1.5 × upper limit normal; and creatinine <125 μmol/L. All patients provided written informed consent.

All patients were to receive four courses of cisplatin (75 mg/m^2 body surface area (BSA) intravenous day 1) plus etoposide (100 mg/m^2 BSA intravenous day 1-3), though we recommended not to exceed doses of cisplatin 165 mg or etoposide 220 mg corresponding to a BSA of 2.2 m^2. Delays of subsequent courses and dose reductions were recommended if leukocytes were below 2.5 x 10^9/L or platelets were below 75 x 10^9/L on day 22, or if other severe non-haematological toxicity occurred. Patients were randomly assigned to receive TRT of either 45 Gy in 30 fractions (twice daily) or 42 Gy in 15 fractions (once daily), starting 3-4 weeks after start of the first chemotherapy course. Good responders were offered prophylactic cranial irradiation of 30 Gy in 15 fractions. There were no significant differences in overall response rates, progression free survival or overall survival (OS) between the treatment arms [21]. Thus, all patients were analysed as one cohort in the present study.

Patients were eligible for the present study if they completed TRT and at least one chemotherapy course and had a diagnostic CT scan taken within four weeks before start of treatment that included the L3 level.

Assessments

CT scans were analysed using SliceOMatic software, (v.4.3, Tomovision, Montreal, Canada). The total cross sectional area of skeletal muscle (cm^2) was quantified at the L3 level [23]. The total cross sectional skeletal muscle area was identified using well established thresholds from –29 to +150 Hounsfield Units (HU) [6-8], divided by height squared (m^2) and expressed as L3 skeletal muscle index (SMI) (cm^2/m^2). Radiodensity of the skeletal muscle (SMD) was measured in Hounsfield units (HU). Lean body mass (LBM) was estimated from the equation: Lean tissue (kg) = (0.30 x L3 total cross sectional area of muscle mass (cm^2)) + 6.06 [7].

The doses of cisplatin and etoposide in mg per kg LBM administered in the first course were calculated. Based on Body Mass Index (BMI) (weight (kg)/height squared (m^2)), patients were categorised as underweight (BMI <20), normal BMI (20-24.9), overweight BMI (25-29.9), and obese

(BMI ≥30) [16]. Patient reported weight loss the last three months prior to diagnosis was categorised as either <5% or ≥5% of the body weight. Stage of disease was assessed according to the TNM v7 [24] and toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0. The investigators reported haematological toxicity after each chemotherapy course. The minimum follow up of blood counts were measurements of haemoglobin, platelets and leukocytes on day 8, 15 and 22 of each chemotherapy course. Neutropenic infections were defined as any febrile neutropenia or infection while neutropenic during the whole study treatment period.

Statistical considerations

To investigate whether a high drug dose per kg LBM was associated with more toxicity, we used univariable and multivariable logistic regression analyses. Four multivariable models were designed. Model 1 and 2 assessed the relationship between grade 3-4 haematological toxicity and mg/kg LBM of cisplatin and etoposide, respectively. Model 3 and 4 assessed the relationship between occurrence of neutropenic infections during the whole study treatment period and mg/kg LBM of cisplatin and etoposide, respectively. All models were adjusted for baseline characteristics (gender, age, PS, stage, BMI, weight loss, pleural effusion) and TRT schedule. Survival time was defined as time from inclusion until death, was estimated using the Kaplan-Meier method and compared between groups using log-rank tests.

To investigate the prognostic impact of SMI, SMD, mg cisplatin per kg LBM, and mg etoposide per kg LBM, we used univariable and multivariable Cox regression analyses. In the multivariable analyses, we used separate models for each of these measures and adjusted for baseline characteristics and treatment schedule as described above. All analyses were two-sided, and the significance level was defined as $p<0.05$. SPSS v23 were used for all statistical analyses.

Results

Patients

From May 2005 until January 2011, 171 patients were enrolled in the main trial. Of these, 157 were eligible for the analyses. Thirty-five patients were excluded from the present study due to missing CT scans (n=3), poor image quality (n=2), CT scans did not include the L3 level (n=26), baseline CT

scans was obtained more than one month prior to start of chemotherapy (n=1) or patient did not complete TRT (n=3). Thus, 122 patients (77.7%) were analysed in the present study (Figure 1).

Patient characteristics are shown in Table 1. Median age was 63.7 (range: 40-85) years, 59 (48.4%) were men, 103 (84.4%) had stage III disease, 22 (18.0%) had PS 2, 107 (87.7%) completed all four chemotherapy courses, 59 (48.4%) received TRT of 45 Gy and 36 (29.5%) had weight loss of ≥5%. Median BMI was 24.6 (range: 15-40); 5 (4.1%) were underweight, 61 (50.0%) had normal weight, 35 (28.7%) were overweight, and 21 (17.2%) were obese.

Median follow up was 88.2 months (range: 61-129 months) and 26 patients (21%) were alive when collection of survival data was completed (February 2016).

Muscle mass and muscle radiodensity

Body composition data were normally distributed. Median LBM was 45.2 (range: 16-65) kg, the median SMI 44.8 (range: 29-77) cm^2/m^2 and the median SMD 39.3 (range 16-62) HU. Men had a higher SMI than women (median 50.5 cm^2/m^2 vs. 41.8 cm^2/m^2; $p<0.001$), but there were no significant differences between those ≥75 years of age and those <75 (median 45.0 cm^2/m^2 vs. 44.8 cm^2/m^2; $p=0.689$). There was no significant difference in SMD between men and women (median 38.2 HU vs. 37.3 HU; $p=0.592$), but there was a trend towards a difference between patients above 75 years of age and those below (32.4 HU vs. 39.2 HU; $p=0.073$).

Toxicity

One hundred and nine (89.3%) patients experienced grade 3-4 toxicity; 108 (88.5%) developed grade 3-4 haematological toxicity and 83 (68.0%) grade 3-4 non-haematological toxicity. Of these, 54 (44.3%) experienced grade 3-4 neutropenic infections. There were no grade 3-4 thrombocytopenic bleedings.

There were 6 (4.9%) treatment related deaths (death within 30 days of completion of study treatment); 3 (3.5%) died of pneumonitis, 1 (0.8%) of hemoptysis, 1 (0.8%) of respiratory failure, and 1 (0.8%) of acute coronary disease.

Chemotherapy dose per kg LBM and severe toxicity

The median dose of cisplatin per kg LBM in the first chemotherapy course was 3.04 mg (range: 2.00-7.00) mg/kg, while the median dose of etoposide per kg LBM was 4.03 mg (range: 2.75-7.67).

According to the univariable analyses, both the cisplatin- and etoposide-dose per kg LBM were significantly associated with grade 3-4 haematological toxicity after the first course of chemotherapy (OR 2.98, 95% CI 1.31-6.78; p=0.009 and OR 1.88, 95% CI 1.06-3.34; p=0.031, respectively) (Table 2). The only other factor that significantly predicted toxicity in the univariable analyses was increasing age (OR 1.05, 95% CI 1.01-1.10; p=0.022) (Table 2).

In the multivariable models (Models 1 and 2, Table 2), the significant association between grade 3-4 haematological toxicity and mg cisplatin/kg LBM (OR 7.24, 95% CI 1.57-33.39; p=0.011) remained, and there was a trend towards an association between grade 3-4 haematological toxicity and mg etoposide/kg LBM (OR 2.89, 95% CI 0.99-8.44; p=0.053). Age was no longer significantly associated with haematological toxicity in any of the models. There was, however, a significant association with male gender according to the model including mg cisplatin/kg LBM (Model 1, Table 2), but not according to the model including mg etoposide/kg LBM. No other significant associations were found.

Univariable analyses also showed a significant association between neutropenic infections and the drug doses per kg LBM (cisplatin: OR 2.73, 95% CI 1.25-5.97; p=0.012, etoposide: OR 1.69, 95% CI 1.00-2.85; p=0.049) (Table 3). In the multivariable models, this association remained significant for cisplatin (OR 4.03, 95% CI 1.08-15.10; p=0.038) (Model 3, Table 3), but not for etoposide (OR 1.62, 95% CI 0.61-4.34; p=0.335) (Model 4, Table 3). None of the other factors included in the models were significantly associated with neutropenic infections.

Survival

Overall, the median OS was 23 months and the 5-year survival was 25%. In the univariable analyses, no significant associations between survival and any of the muscle measures (SMI: p=0.906, SMD: p=0.829) or the drug doses per kg LBM ((cisplatin: p=0.292, etoposide: p=0.578) were found. Nor were there any significant associations in separate multivariable analyses for each variable (SMI: p=0.836, SMD: p=0.260, cisplatin: p=0.839 and etoposide: 0.198). As an illustration, we have included

median OS and survival curves for the quartiles of SMI, SMD and cisplatin dose per kg LBM in Figure 2.

BMI was the only significant prognostic factor (in the multivariable analysis alone, p=0.018); patients with a normal weight had a lower risk of dying compared to underweight patients (HR 0.20, 95% CI 0.07-0.62). None of the other baseline characteristics were significant prognostic factors *(data not shown)*.

Discussion

In this study of patients with LS SCLC receiving concurrent chemoradiotherapy, there was a significant association between the chemotherapy dose per kg LBM and both haematological toxicity after the first chemotherapy course and neutropenic infections throughout the treatment period. There were no other significant associations between the muscle measures and toxicity or survival.

The observed associations between drug dose per kg LBM and severe toxicity corresponds well with the results of several other studies showing that a high drug dose per kg LBM significantly increases the risk of severe haematological toxicity in cancer patients [18, 20, 25, 26]. None of these studies investigated whether there was an association with neutropenic infections, but it seems reasonable that a higher frequency of haematological toxicity increases the risk of neutropenic infections.

We are aware of only one other study investigating the prognostic value of muscle measures in SCLC [19]. In this Korean study of 149 patients with all stages of SCLC, they defined low SMI using established cut off values from the definition of sarcopenia (SMI of <55 cm^2/m^2 for men and <39 cm^2/m^2 for women) [27], and contrary to our study, they found that low SMI was an independent prognostic factor for survival (HR 1.68; 95% CI 1.04–2.72; p=0.034). When applying Korean cut off values (49 cm^2/m^2 for men and 31 cm^2/m^2 for women) in the same cohort, there was still a numerical difference in overall survival, but the difference was not statistically significant (8.4 months vs. 12.7 months; p=0.144). This study is, however, not necessarily comparable with our study. In the Korean study, 67.8% of the patients had extensive disease, there were more men (85.2% vs. 48.4%), more elderly (67.1% vs. 40.2% above 65 years of age), fewer (29.5% vs. 100%) received chemoradiotherapy, and 20.8% received supportive care only. The median follow up time was shorter than in our study (29.0 months vs. 88.2 months). Furthermore, they did not measure SMD. Several

studies indicate that SMD is a more important prognostic and predictive muscle measure than SMI [12, 16]. Finally, we analysed SMI and SMD as continuous variables, which is recommended for studies on prognostic factors [28] and due to the lack of well-established global cut off values for abnormally low SMI and SMD [6, 15].

Our results contrast a number of studies showing that low SMI and low SMD are significantly negative prognostic factors in patients with a wide range of types of cancer [9-11, 13-16, 19, 29-31]. However, most previous studies have investigated advanced cancer patients receiving palliative treatment. Both the response rate to standard treatment (80-90%) and the 25-30% 5-year survival is much higher for LS SCLC than for most other solid tumours. Thus, the potentially negative impact of low muscle mass or poor muscle quality from cancer might be overcome by the better response to treatment.

Another possible explanation may be that LS SCLC patients have less cancer induced muscle depletion, but when comparing with results from one of our previous studies of Norwegian advanced NSCLC patients [12] with the present data, there were no large differences in SMI (median 43.3 cm^2/m^2 vs. 44.8 cm^2/m^2) or SMD (37.3 HU vs. 39.3 HU), though NSCLC and LS SCLC patients are not necessarily comparable. SCLC is considered a more rapidly progressing disease, and the proportion of smokers is higher in SCLC [32, 33].

The relatively small sample size is the main limitation of our study. It is, however, the first study to prospectively collect data on muscle measures and weight loss in patients with LS SCLC receiving standard chemoradiotherapy. Patient characteristics, TNM distribution, overall survival and 5-year survival are similar to other studies of chemoradiotherapy in LS SCLC [3, 5, 34, 35], we had no restrictions regarding comorbidity or age, and 18.0% had PS 2. Thus, we consider the study population representative for LS SCLC patients receiving chemoradiotherapy.

Our findings support the evidence that a high drug dose per kg LBM increase the risk of haematological toxicity and neutropenic infections. It has been suggested that the dose of cytotoxic chemotherapy should be adjusted according to LBM [26]. However, this may not be appropriate for LS SCLC patients. There were no deaths clearly related to the chemotherapy or shorter survival among the patients with the highest drug dose per kg LBM, suggesting that the increased toxicity had no impact on survival. Furthermore, there are indications that patients who are given a high, standard dose of chemotherapy when treatment commences has a longer survival than those who are offered

lower doses [36], and other studies have shown that lung cancer patients who experience chemotherapy induced haematological toxicity live longer than those who do not [37, 38]. Considering that at least 25% of patients are cured, LS SCLC patients may accept more toxicity than those who receive palliative systemic therapy. An alternative to lowering the chemotherapy doses would be to administer G-CSF which reduces the risk of neutropenic infections. The role of G-CSF is, however, not established in LS SCLC, since a randomised trial showed that G-CSF increases toxicity from thoracic radiotherapy [39], though this was not found in a recent subgroup analysis of a large randomised trial comparing TRT of 45 Gy in 30 fractions and 66 Gy in 33 fractions in LS SCLC [40].

There are no obvious explanations for the weaker association between dose per kg LBM and neutropenic infections for etoposide than cisplatin. However, etoposide more frequently causes neutropenia/neutropenic infection, and may cause neutropenic infection also when the dose per kg LBM is low, possibly weakening the association with neutropenic infections. Another explanation may be differences in pharmacokinetics, but our study was not designed to assess such differences.

In conclusion, patients who received a high chemotherapy dose per kg LBM had more haematological toxicity and neutropenic infection. However, they did not have a shorter overall survival, suggesting that all patients with LS SCLC should receive standard concurrent chemoradiotherapy regardless of their baseline SMI and SMD.

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Conflict of interest

None.

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Table 1. Baseline characteristics

		All patients (n=122)	
		n	**%**
Age, years	Median (range)	63.7 (40-85)	
Age, ≥75 years		15	12.3
Gender	Male	59	48.4
	Female	63	51.6
Performance status (PS)	0	38	31.1
	1	62	50.8
	2	22	18.0
Thoracic radiotherapy	42 Gy/15 fractions (OD)	63	51.6
	45 Gy/30 fractions (BID)	59	48.4
Completed 4 courses of chemotherapy	Yes	107	87.7
	No	15	12.2
PCI	Yes	102	83.6
	No	20	16.4
Stage	I	2	1.6
	II	13	10.7
	III	103	84.4
	Missing	4	3.3
Pleural fluid	Yes	13	10.7
	No	109	89.3
Body mass index	Underweight (<20.0)	5	4.1
	Normal weight (20 to 24.9)	61	50.0
	Overweight (25.0 to 29.9)	35	28.7
	Obesity (≥ 30)	21	17.2
Weight loss	Yes (≥ 5%)	36	29.5
	No (<5%)	75	61.5
	Missing	11	9.0

Table 2. The risk of grade 3-4 haematological toxicity after the first chemotherapy course according to the chemotherapy doses per kg LBM

	Univariable analyses		**Multivariable analyses**			
			Model 1		**Model 2**	
Variables	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
mg cisplatin per kg LBM*	2.98 (1.31 - 6.78)	0.009	7.24 (1.57 - 33.39)	0.011	-	-
mg etoposide per kg LBM*	1.88 (1.06 - 3.34)	0.031	-	-	2.89 (0.99 - 8.44)	0.053
Age*	1.05 (1.01 - 1.10)	0.022	1.02 (0.96 - 1.08)	0.462	1.03 (0.97 - 1.10)	0.324
Gender						
Female**	1					
Male	1.38 (0.68 - 2.82)	0.372	4.05 (1.14 - 15.75)	0.035	2.87 (0.83 - 9.90)	0.096
PS						
0-1**	1					
2	1.08 (0.43 - 2.73)	0.865	1.60 (0.50 - 5.90)	0.458	1.53 (0.46 - 5.12)	0.494
Disease stage						
I-II**	1					
III	1.42 (0.47-4.26)	0.537	2.01 (0.38 - 2.41)	0.309	2.19 (0.59 – 8.20)	0.244
Treatment						
OD TRT**	1					
BID TRT	1.06 (0.52 - 2.16)	0.866	1.43 (0.52 - 3.30)	0.462	1.10 (0.45 - 2.70)	0.838
BMI						
Underweight**	1					
Normal weight	1.89 (0.29 - 12.12)	0.335	2.68 (0.12 – 59.31)	0.150	3.45 (0.18 – 65.16)	0.097
Overweight	1.26 (0.19 - 8.50)		1.81 (0.77 – 42.70)		2.30 (0.11 – 46.03)	
Obese	0.75 (0.10 - 5.58)		0.58 (0.02 – 15.14)		0.68 (0.03 – 15.23)	
Weight loss						
No**	1					
Yes	0.59 (0.27 - 1.32)	0.201	0.41 (0.15 - 1.16)	0.093	0.45 (0.17 - 1.23)	0.118
Pleural fluid						
No**	1					
Yes	1.28 (0.40 - 4.05)	0.676	1.15 (0.27 - 4.99)	0.845	1.32 (0.33 - 5.34)	0.698

**Entered as continous variables*
***Reference categories*

Table 3. The risk of neutropenic infection during the study treatment according to the chemotherapy doses per kg LBM

	Univariable analyses		Multivariable analyses			
			Model 3		Model 4	
Variables	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
mg cisplatin per kg LBM*	2.73 (1.25-5.97)	0.012	4.03 (1.08-15.10)	0.038	-	-
mg etoposide per kg LBM*	1.69 (1.00-2.85)	0.049	-	-	1.62 (0.61-4.34)	0.335
Age*	1.01 (0.97-1.06)	0.510	1.03 (0.97-1.10)	0.309	1.04 (0.98-1.11)	0.200
Gender						
Female**	1					
Male	0.38 (0.18-0.80)	0.010	0.67 (0.21-2.11)	0.488	0.45 (0.14-1.41)	0.171
PS						
0-1**	1					
2	0.53 (0.20-1.40)	0.199	0.41 (0.12-1.42)	0.159	0.40 (0.12-1.33)	0.135
Disease stage						
I-II**	1					
III	1.21 (0.40-3.65)	0.734	1.50 (0.36-6.34)	0.581	1.52 (0.38-5.41)	0.559
Treatment						
OD TRT**	1					
BID TRT	0.66 (0.32-1.35)	0.257	0.82 (0.32-2.11)	0.684	0.63 (0.26-1.57)	0.325
BMI						
Underweight**	1					
Normal weight	3.18 (0.34-30.10)	0.718	-***	0.760	-***	0.747
Overweight	3.78 (0.38-37.28)		-***		-***	
Obese	3.00 (0.29-31.63)		-***		-***	
Weight loss						
No**	1					
Yes	0.69 (0.31-1.55)	0.367	1.01 (0.36-2.87)	0.983	1.10 (0.40-3.01)	0.849
Pleural fluid						
No**	1					
Yes	1.09 (0.34-3.45)	0.885	0.44 (0.10-2.97)	0.280	0.52 (0.13-2.11)	0.360

**Entered as continous variables*
***Reference categories*
****Not evaluable due to small number of cases*

Figure 1. Patient selection

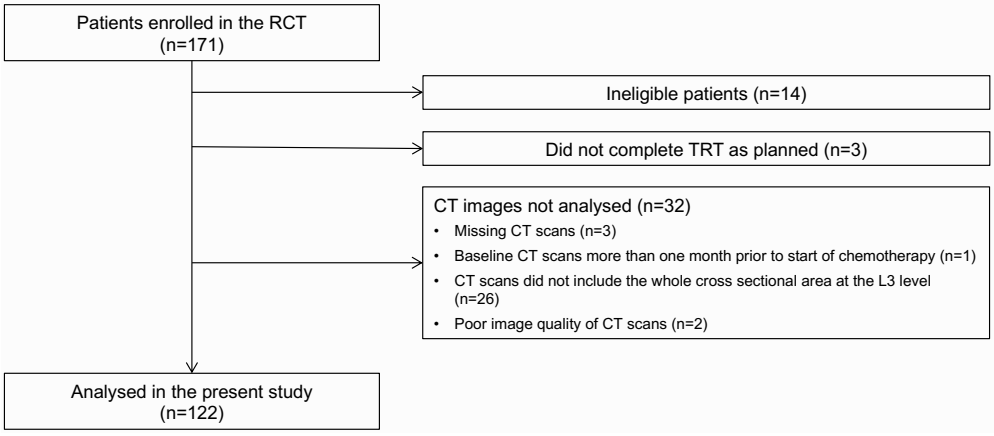
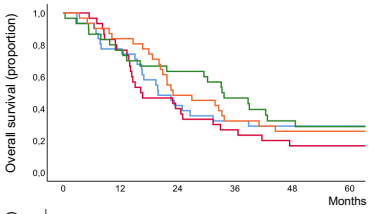


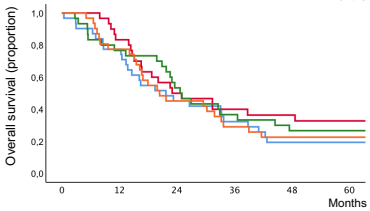
Figure 2. Kaplan-Meier survival plots according to (A) quartiles of SMI, (B) quartiles of SMD and (C) quartiles of mg cisplatin per kg LBM. P-values were calculated using the log-rank test.

A



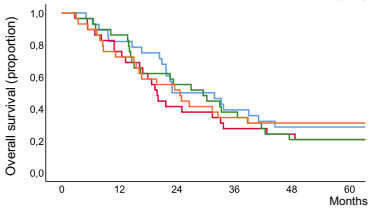
		Median OS (months)	95% CI	
•	Lower quartile	19.9	12.9 - 26.9	
•	2nd quartile	16.3	5.0 - 27.5	
•	3rd quartile	33.3	22.1 - 44.5	
•	Upper quartile	23.0	12.0 - 34.0	*p=0.703*

B



		Median OS (months)	95% CI	
•	Lower quartile	21.7	10.3 - 33.1	
•	2nd quartile	23.0	10.9 - 35.2	
•	3rd quartile	24.7	19.3 - 30.1	
•	Upper quartile	20.4	6.7 - 34.1	*p=0.719*

C



		Median OS (months)	95% CI	
•	Lower quartile	23.0	9.2 - 36.8	
•	2nd quartile	19.9	17.5 - 22.3	
•	3rd quartile	29.5	17.3 - 41.8	
•	Upper quartile	24.7	15.6 - 33.8	*p=0.937*

12 Appendix C Paper III

Changes in muscle measures during chemoradiotherapy in patients with limited stage small cell lung cancer

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