Stein Sundstrøm

Improving treatment in patients with lung cancer.

Results from two multicentre randomised studies.

Doctoral thesis
for the degree of doctor medicinae

Trondheim, March 2006

Norwegian University of
Science and Technology
Det medisinske fakultet
Institutt for krefforskning og molekylær medisin (IKM)

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ISBN xxxxxxxx (printed ver.)
ISBN xxxxxxx (electronic ver.)
ISSN 1503-8181

Doctoral Theses at NTNU, 277

Printed by Tapir Uttrykk

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Cancer Society

Table of content

Acknowledgement

A lot of friends and colleagues have contributed in the process up to this thesis. Since I started working at St. Olavs Hospital and was delegated the responsibility for lung cancer patients, I have collaborated closely with the Norwegian Lung Cancer Study Group. This group was founded by Erik Thorud in the late 80s. During these years, the group has initiated several clinical trials, from which two of these are the basis for this thesis. The collaborative work in the group is appreciated. My gratitude goes especially to Ulf Aasebø, Paal Brunsvig and Roy Bremnes, who all are central in the running and management of the group. The annual financial assistance to the group from the Norwegian Cancer Society is also appreciated.

My colleague and friend Roy Bremnes has acted as a co-supervisor. He has the quality of always giving precise, fast and to the point feedback. During the course of interpretation, writing and finishing the articles and the thesis, he has been indispensable and I am grateful for his support in this process.

Stein Kaasa has acted as my principal supervisor in all these years. Since we first discussed the design and initiation of the palliative radiotherapy study, the years have gone, and he shall have credit for not loosing enthusiasm, belief and never ending support for finishing this work. Stein's pioneering work with quality of life aspects in lung cancer, my own delegated responsibility for lung cancer patients, and at that time the frustrating lack of radiotherapy resources, was the main reason for the upcoming of the TRT study. Both randomised trials are designed in close collaboration with Stein, and the quality-of-life part of the studies relies directly upon his previous work and collaboration with EORTC. The small cell lung cancer study was initiated at The Norwegian Radium Hospital by Erik Thorud, Stein Kaasa and Steinar Aamdal, and I am grateful for getting the opportunity to complete the data collection and initiate the writing process.

The running of these studies has been managed together with daily clinic, which not had been possible without support from good colleagues. In that respect, I am especially thankful to Ragnar Telhaug, Ragnhild Klepp and Olbjørn Klepp. Olbjørn, as head of Department of Oncology when the studies were running, has been an important source of inspiration in all these years. Bjørn Henning Grønberg, co-responsible for much of my tasks in the clinic during the recent years, has relieved me for much work giving me the opportunity to finish this thesis, which I very much appreciate. Karin Tulluan, giving secretarial assistance at the Clinical Research Office at St. Olavs Hospital, is also greatly appreciated.

I also want to thank my brother Bror and my good friends Klaus and Tom for our wonderful trip to Canada in 2002, with exciting wild life experiences and memories, giving me the ultimate inspiration for ending this work.

And finally, last, but not at least, during all these years a family has taken the load with a husband and father working too much, too often in too many years. I am very grateful to my wife Berit and to Marie, Kristine and Magnus for tolerating all this work.

List of papers

I Sundstrøm S, Bremnes RM, Kaasa S, Aasebø U, Hatlevoll R, Dahle R, Boye N, Wang M, Vigander T, Vilsvik J, Skovlund E, Hannisdal E, and Aamdal S for the Norwegian Lung Cancer Study Group. Cisplatin and Etoposide Regimen Is Superior to Cyclophosphamide, Epirubicin, and Vincristin Regimen in Small-Cell Lung Cancer: Results From a Randomized Phase III Trial With 5 Years' Follow-Up. J Clin Oncol 20: 4665-4672, 2002

II Sundstrøm S, Bremnes RM, Kaasa S, Aasebø U, and Aamdal S for the Norwegian Lung Cancer Study Group. Second-line chemotherapy in recurrent small cell lung cancer. Results from a crossover schedule after primary treatment with cisplatin and etoposide (EP-regimen) or cyclophosphamide, epirubicin, and vincristin (CEV-regimen). Lung Cancer 48: 251-261, 2005

III Sundstrøm S, Bremnes RM, Aasebø U, Aamdal S, Hatlevoll R, Brunsvig P, Johannessen DC, Klepp O, Fayers PM, and Kaasa S. Hypofractionated Palliative Radiotherapy (17 Gy per two fractions) in Advanced Non-Small-Cell Lung Carcinoma Is Comparable to Standard Fractionation for Symptom Control and Survival: A National Phase III Trial. J Clin Oncol 22: 801-810, 2004

IV Sundstrøm S, Bremnes RM, Brunsvig P, Aasebø U, Klepp O, Fayers PM, Kaasa S for the Norwegian Lung Cancer Study Group. Immediate or delayed radiotherapy in advanced non-small cell lung cancer (NSCLC)? Data from a prospective randomised study. Radiother Oncol 75: 141-148, 2005.

List of abbreviations

WHO	World Health Organisation
SCLC	Small-cell lung cancer
NSCLC	Non-small cell lung cancer
LD-SCLC	Limited disease SCLC
ED-SCLC	Extensive disease SCLC
HRQOL	Health related quality-of-life
RT	Radiotherapy
3D-CRT	3-dimensional conformal radiotherapy
NLCG	Norwegian Lung Cancer Study Group
TRT	Thoracic radiotherapy
PCI	Prophylactic cranial irradiation
PS	Performance status
BSC	Best supportive care
MRC	Medical Research Council
RCT	Randomised controlled trial
EORTC	European Organisation for Research and Treatment of Cancer

Background

General

Although lung cancer is the fourth most common cancer, it is the leading cause of cancer related deaths in Norway [1], as well as throughout the western world [2]. In Norway, the annual incidence of lung cancer was 2250 in 2003, of which 1387 were males and 863 females [1]. A 60% incidence increase is registered in females during the last decade, while it is stable in males. The long-term survival is low with only 10% surviving 5 years following diagnosis. According to the National Cancer Registry [1], there has been only incremental increase in long-term survival during the last decades, which is in accordance with international reports [3].

Cigarette smoking is by far the most important etiologic factor for lung cancer, responsible for about 90% of the cases [4]. In 2002, the fraction of daily smokers among Norwegian adults fell below 30% [5]. However, the percentage of female smokers in Norway is still among the highest in Europe [5].

In order to improve survival, symptom palliation, as well as overall quality-of-life, high-quality randomised constructed trials are necessary to perform, evaluate the treatment, and hopefully implement beneficial results into daily clinical practice.

Histopatohology

The World Health Organisation (WHO) classification on histological typing of lung tumours was first published in 1967, with a revised edition in 1981. Since then a considerably progress has been made in the understanding of the biology of lung cancer, and the concept of neuroendocrine lung carcinoma has been accepted. Table 1 lists the different types of primary malignant epithelial lung tumours [6].

These carcinomas arise from the bronchial epithelium or bronchioalveolar surface epithelium and constitute up to 95% of all malignant lung tumours. The major histological types are squamous cell carcinoma, small cell lung carcinoma (SCLC), adenocarcinoma and large cell lung carcinoma. The three subtypes apart from SCLC are grouped as non-small cell lung cancer (NSCLC), since the biology and the natural course of the disease is different from SCLC. Most often the histopathologic image is typical with a distinct classification in these four subtypes. Some tumours represent

Table 1. WHO Histological classification of lung tumours

Tumour type		Frequency
I.	Squamous cell carcinoma (epidermoid carcinoma)	30-50%
II.	Small cell carcinoma Variants: • Combined small cell carcinoma	17-20%
III	Adenocarcinoma Variants: • Acinar • Papillary • Bronchioalveolar • Solid adenocarcinoma with mucin	25-50%
IV	Large cell carcinoma Variants: • Large cell neuroendocrine carcinoma (LCNEC) • Large cell basaloide carcinoma • Large cell clear cell carcinoma	5-15%
V	Adenosquamous carcinoma	1-2%
VI	Carcinoid tumours Variants: • Typical carcinoid • Atypical carcinoid	0.5%
VII	Others	0.2-0.5%

variants with heterogenic differentiation into several directions. The determined histologic subclassification done by the pathologist should be compatible with the tumour's dominant microscopic image. The heterogeneity is often prominent in tumours with both SCLC and NSCLC features. The variant combined small cell carcinoma is typical where at least 10% of the tumour consists of NSCLC components, but appears otherwise as a pure SCLC. However, the major clinical question to be answered is whether a lung tumour is a SCLC or a NSCLC, since this will have fundamental implications for choice of therapy.

Pulmonary neuroendocrine tumours are a subgroup of lung neoplasms with microscopic and biologic neuroendocrine differentiation. These tumours are separated into low-grade tumours (indolent typical carcinoid), medium-grade tumours (atypical carcinoid), and high-grade tumours [large-cell neuroendocrine carcinoma (LCNEC) and SCLC]. LCNEC tumours were recognised as a separate entity in the late 1980s and show an increasing incidence [7]. With more widespread use of immunohistochemistry, NSCLC tumours are more frequently identified with neuroendocrine differentiation. Carcinoid tumours have a much better prognosis than high-grade neuroendocrine lung tumours. However, LCNEC and NSCLC with some neuroendocrine features have not been found to have specific clinical characteristics

requiring a different treatment strategy. Thus, these tumours are treated as ordinary NSCLC tumours [8].

Diagnosis, staging and prognosis

At the suspicion of a malignant lung tumour, the diagnostic procedure should end up in a conclusive histology and clinical disease stage of each patient. A chest X-ray followed by thoracic CT and bronchoscopy is mandatory. Otherwise, a minimum of diagnostic procedures should be performed routinely providing a precise TNM classification for NSCLC and a distinction between limited and extensive disease in cases of SCLC [9]. If metastatic disease is apparent at presentation, investigation should be minimised to define the histology and to verify advanced metastatic disease.

Patients with NSCLC and localised disease are candidates for surgery [10]. A mediastinoscopi should be carried out if the CT examination reveals enlarged mediastinal nodules (> 1 cm) [11]. If the tumour is found to be technically operable, a precise examination of the cardiovascular and lung function should be performed [12].

Patients with SCLC histology should primarily be categorised as with limited (LD-SCLC) or extensive disease (ED-SCLC) [13]. Cases where tumour and local spread can be included within a single radiation port, i.e. tumour within the ipsilateral hemithorax, should be grouped as LD-SCLC. All others, included pleural fluid with positive cytology and/or verified metastatic disease, is defined as ED-SCLC.

Due to a relatively poor correlation between clinically detected (CT) enlarged lymph nodes and verified pathological lymph nodes in the resected specimen, there is a significant difference between the clinical (cTNM) and the pathological TNM (pTNM) status regarding the prognosis. Table 2 shows the 1- and 5-year survival rates based on cTNM status [14]. Survival based on pTNM is better for each TNM stage [15]. For instance, the 5-year survival increases from 61% to 67% and from 34 to 55% between cTNM and pTNM for stage IA and stage IIA, respectively [15].

Table 2. Clinical Staging of Lung Cancer and survival (adapted from Mountain CF) [14]

Stage	Tumour	Node	Metastasis	General Description	Survival Rate (%) 1 Yr	5 Yr
Non-small-cell lung cancer						
Local						
cIA	T1	N0	M0	T1 tumour: ≤ 3cm, surrounded by lung or visceral pleura	91	61
cIB	T2	N0	M0	T2 tumour: > 3 cm, involving main bronchus ≥ 2 cm distal to carina; invading pleura; atelectasis or pneumopathy of less than the entire lung	72	38
cIIA	T1	N1	M0	N1: involvement of ipsilateral peribronchial or hilar nodes and intrapulmonary nodes by direct extension	79	34
	T2	N1	M0		61	24
cIIB	T3	N0	M0	T3 tumour: invasion of chest wall, diaphragm, mediastinal pleura, pericardium; main bronchus < 2cm distal to carina; atelectasis or pneumonitis of entire lung	55	22
Locally advanced						
cIIIA	T3	N1	M0		56	9
	T1,T2,T3	N2	M0	N2: involvement of ipsilateral mediastinal or subcarinal nodes	50	13
cIIIB	T4	N0, N1, N2	M0	T4 tumour: invasion of mediastinum, heart, great vessels, trachea, oesophagus, vertebral body, carina; separate tumour mass in the same lobe; malignant pleural effusion	37	7
	Any T	N3	M0	N3. Involvement of contralateral (lung) nodes or any supracalvicular node	32	3
Advanced metastatic						
cIV	Any T	Any N	M1	Distant metastasis	20	1
Small-cell lung cancer						
Limited disease				Evidence of tumour confined to ipsilateral hemithorax; can be encompassed by a single radiation port	65	15
Extensive disease				All other disease, including metastatic disease	20	1

Non-small cell lung cancer (NSCLC)

Non-small cell lung cancer constitutes about 80% of lung cancer cases and is divided in three major subgroups (Table 1). Squamous cell carcinoma in Norway accounts for 30-50% of NSCLC with a declining incidence, and adenocarcinoma represents 25-50% with a correspondingly increasing incidence. The same shift in histologic types is recognised in the rest of Europe and North America [16]. The most likely explanation for this is the introduction of low-tar filter cigarettes causing deeper inhalation bringing the carcinogens more distant in the lungs and leaving the bronchioalveolar epithelium more exposed. Large cell carcinoma constitutes 5-15% of the cases.

At diagnosis, about 20% of the patients have localised disease (stage I and II), 40% are in locally advanced stage (stage IIIA and IIIB), and 40% have metastatic disease (stage IV).

Surgery

All patients considered technically and medically operable (stage I and II) should be offered surgery. The prognosis is fairly good in early disease. However, only about 60% of patients with clinically detected small tumours without lymphatic spread (cIA) will survive for 5 years. The explanation to this is the early metastatic course of NSCLC and the underdiagnosis of lymphatic spread. On the other hand, the early metastasis justifies the use of adjuvant chemotherapy in early stage disease.

Surgery in stage IIIA is more complex and controversial. Stage T3N1 is considered technical operable by most surgeons. However, surgery in N2 disease remains unclear, which indicate that patients should be treated within the context of randomised clinical trials. Preoperative chemotherapy seems promising, but warrants conclusive evidence in larger phase III trials [17,18]. Patients not candidates for surgery should receive radical curative RT alone or with concomitant chemotherapy. The benefit of surgery after neoadjuvant chemotherapy (downstaging) in N2-disease versus neoadjuvant chemotherapy followed by radical RT is the main research issue in a large ongoing Nordic trial [19].

Stage IIIB is considered inoperable, both technically and biologically.

Chemotherapy

The most active cytostatic drugs in NSCLC are those of the platinum family: cisplatin, an alkylating drug which cross-links DNA, and carboplatin which is a less toxic cisplatin analogue. In combination with other drugs most studies suggest that carboplatin is as effictive as cisplatin. While etoposide and mitomycin C were most used in the 80s [20], today several "new drugs" like the taxans (docetaxel, paclitaxel), gemcitabine and vinorelbine are most often combined with cis- or carboplatin (Table 3). The preferred combination is mainly based on the administration feasibility, toxicity, and cost-benefit evaluation. None of the new drug combinations have shown superiority compared to the other [21]. The combination of carboplatin with vinorelbine or gemcitabine is most often used in Norway due to moderate costs and the feasibility of an outpatient administration.

Table 3 Chemotherapy for NSCLC

Drug	Type of agent	Major adverse effects	Comments
Platinum agents			
Cisplatin (Platinol)	Atypical alkylator	Nausea and vomiting, nephrotoxicity, ototoxicity, neuropathy, myelosuppression, electrolyte disorders	Hydration required before and after administration
Carboplatin (Paraplatin)	Atypical alkylator	Myelosuppression (trombocytopenia), nausea and vomiting (mild), neurotoxicity (rare), nephrotoxicity (rare)	Dosage using AUC, less hydration
Non-platinum agents			
Etoposide (Vepeside)	Topoisomerase II inhibitor	Myelosuppression, nausea and vomiting, stomatitis, diarrhea	Stomatitis and diarrhea rare with normal dose
Gemcitabine (Gemzar)	Antimetabolite	Myelosuppression, nausea and vomiting, diarrhea, edema, influenza-like syndrome, skin reaction	Increased monitory of liver function necessary
Pacliatxel (Taxol)	Microtubuli inhibitor	Myelosuppression, mucositis, peripheral neuropathy, hypersensitivity reaction, nausea and vomiting	Requires pretreatment with dexamethasone, H2-inhibitor and antihistamine
Docetaxel (Taxotere)	Microtubuli inhibitor	Myelosuppression, edema and fluid retention, mucositis, diarrhea, hypersensitivity reaction, nausea and vomiting	Requires treatment with dexamethasone before during and after infusion
Vinorelbine (Navelbine)	Microtubuli inhibitor	Myelosuppression, nausea and vomiting, phlebitis	Mild vesicant

Two-drug regimens with cis-/carboplatin as basis are superior to single-drug and not inferior to three-drug regimens [22,23]. However, in a recent meta-analysis of phase III trials comparing cisplatin- and carboplatin-based combinations in advanced NSCLC,

a possible benefit in favour of a cisplatin combination was found, especially when cisplatin was combined with a novel agent [24].

Compared to SCLC, NSCLC is less sensitive to chemotherapy. Nevertheless, there is considerably evidence that treatment with chemotherapy in advanced NSCLC patients with a reasonable good performance status (PS 0-1(2)), increases survival, improves health related quality-of-life (HRQOL) and reduces disease related symptoms [25].

Although early phase III trials with adjuvant chemotherapy after completely resected non-small tumours failed to show effect [26,27], subsequent larger trials have shown evidence of benefit from adjuvant chemotherapy [28-32]. There is now consensus that radically operated patients should be offered adjuvant chemotherapy if considered physically fit [33,34].

Whether chemotherapy has a role in the neoadjuvant setting before surgery remains to be determined. This treatment principle has shown to benefit in localised stage IB and stage II disease [35], as well as in cN2 disease (stage IIIA) [17,18,36,37]. Subsequent studies have, however, not been able to reproduce these results [35,38].

Table 4 gives an overview of chemotherapy effect in NSCLC.

Table 4. Effect of Chemotherapy in Non-Small Cell Lung Cancer

Stage	Treatment intention	No of courses	Main effect
cIB-IIIA - adjuvant	curative	3-4	4-8 % improved 5-year survival
cIB-IIIA - neoadjuvant	curative	2-3	Downstaging with improved rate of surgery Survival benefit still questionable
cIII & cIV	palliative	3-4	Improved 1- and 2-year survival Improved HRQOL Improved symptom control

Radiotherapy

Radiotherapy (RT) is widely used in the treatment of NSCLC. A curative result with RT is feasible in stage I and II disease not candidates for surgery, and in localised stage III disease. The RT is given by use of a three-dimensional conformal radiotherapy (3D-CRT) planning system to secure a homogenous dose to the tumour area and sparing of normal lung tissue. In localised stage I and II disease, a 5-year survival of about 20-30% is achievable by RT only [39,40]. The treatment is most often

given with a conventional fractionation schedule, but the same 5-year survival in early disease has also been attained with a hypofractionated technique [41]. Stereotactic RT using a body frame and high dose external RT in few fractions yields a high degree of local control and a fairly good one-year survival. Long-term survival with this technique is still not reported [42]. The possibility of eradicating a tumour with RT is clearly correlated to the tumour volume [43].

Locally advanced inoperable disease (stage III) is a more heterogeneous group. Radical RT can be offered to patients with favourable prognostic factors, while patients with poor prognostic factors should be treated with a palliative intent. Conventional radiotherapy given with a curative intent can produce long-term survival with a 5-year survival rate of 5% [44,45]. With the introduction of 3D-CRT in the 80s it was possible to treat the tumours with higher dose while reducing the side effects, especially related to the total lung volume and spinal irradiation. However, an increased long-term survival has not ben proven [46].

Of patients failing treatment with a curative intent, about one third will relapse locally, one third will develop distant metastasis, and one third will develop both. Since lack of local control, explained by rapidly proliferating clonogenic cells, is a major problem, accelerated radiotherapy has been tested. Accelerated treatment gave a longer 2- and 3-year survival, but the 5-year survival rate was not increased [47,48].

Enhancement of the radiotherapeutic effect can be achieved by use of concomitant chemotherapy radiosensitizing the tumour [49,50]. Cisplatin is most used, but other drugs are also candidates [51]. An ongoing randomised trial from the Norwegian Lung Cancer Study Group (NLCG) [52] is testing docetaxel 20 mg/m^2 once weekly with 60 Gy 3D-CRT compared to 60 Gy 3D-CRT alone. Since distant metastasis is a major problem, the logic approach to localised inoperable stage III disease would be to add systemic chemotherapy to treat subclinical micrometastasis either up front or after completed radiotherapy. This approach has been tested with two to three induction chemotherapy courses before radiotherapy. No gain in long-term survival has so far been documented [53,54]. The treatment is feasible, but yields increased toxicity [55,56].

When the treatment intention is palliative, either in stage III disease with negative prognostic factors or stage IV disease, the treatment can be simplified with the use of a short course or hypofrationated radiotherapy [57,58]. However, in stage III patients with good performance status (PS 0-1), a protracted higher dose palliative

radiotherapy schedule yields more long-time survivors than hypofractionated schedules [59-61].

The effect of RT in NSCLC in different stages is summarised in Table 5.

Table 5. Treatment Effect of RT in Non-Small Cell Lung Cancer

Stage	Treatment intention	Technique	Dose (Gy)	1 year (%)	5 year (%)
cI	curative	3D-CRT	55-70	75	20-30
		Stereotactic	10-15 Gy x 3	52	not reported
cII	curative	3D-CRT	55-70	70	20
cIII (positive prognostic factors)	curative	conventional	≥ 60	40-50	5
		3D-CRT	≥60	50-60	5
		CHART/accelerated	54-70	55	5
		3D-CRT + concurrent	≥60	55-70	5-8
		Neoadj + 3D-CRT + concurrent	≥60	60-70	5-8
cIII (negative prognostic factors)	palliative	Simple A-P	39-50	25	3-4
		Simple A-P	10-17	25	0
cIV	palliative	Simple A-P	10-17	25	0

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Small cell lung cancer (SCLC)

Small cell lung cancer constitutes 20% of all lung cancer cases (Table 1). Forty per cent of the patients are diagnosed with LD-SCLC, while 60% present with ED-SCLC.

Surgery

Due to an aggressive tumour growth, nearly all these cancers have spread either to regionally lymph nodes in the mediastinum (N2/N3) or distant metastasis to other organs at time of diagnosis. Very few SCLC tumours are diagnosed at an early enough stage where surgery may be possible (< 5%). However, if such a situation occur (peripheral T1N0 or T2N0 tumours), radical surgery should be performed [62,63], followed by adjuvant chemotherapy [64].

Chemotherapy

SCLC is highly sensitive to chemotherapy [65]. The majority will initially achieve a complete or good partial response on combination chemotherapy, but most tumours will relapse and the patients will succumb from chemotherapy-resistant disease. Long-term survival is achievable in LD-SCLC with 15% 5-year survival, whereas long-term survival is uncommon in ED-SCLC patients [66].

During the 70s, combination chemotherapy with the CAV regimen (cyclophosphamide, adriamycin, vincristine) became standard treatment in SCLC [67]. During the following decade, combination of cisplatin and etoposide (EP-regimen) revealed favourable efficacy, although randomised phase III studies failed to prove a definitive survival benefit when compared to CAV [68,69]. Nevertheless, the EP-regimen became the most used chemotherapy regimen for SCLC, mostly due to better feasibility with concurrent chest irradiation [70]. The superiority of the EP-regimen is subsequently shown in two meta-analysis [71,72]. However, the efficacy in ED-SCLC is more limited leaving anthracyclin-containing regimens still an option in this group.

Since SCLC is highly sensitive to cytostatic drugs, intensified chemotherapy would be a logic approach. This can be done in different ways; 1) higher dose with use of granulocyte colony-stimulation factor (G-CSF); 2) adding more drugs (three- or four-drug combinations); 3) alternating regimens; or 4) high dose with bone

marrow rescue. However, such treatment options induce higher response rates, but no improvement of survival [73,74]. In a study performed by NLCG, adding paclitaxel to cisplatin and etoposide in LD-SCLC, survival was not improved [74].

New drugs have been tested in SCLC, but none has been found clearly superior to older drugs or drug combinations [75]. One phase III trial, strictly looking at ED disease comparing cisplatin and etoposide to cisplatin and irinotecan has shown significant superiority in favour of the irinotecan arm [76]. A phase III trial from NLCG comparing carboplatin/etoposide versus carboplatin/irinotecan in the same patient group is recently completed, waiting for the results [77]. A recent publication, however, does not support the superiority of cisplatin-irinotecan combination in ED-SCLC [78].

Radiotherapy

When the tumour and adjacent enlarged lymph nodes can be included in a single radiation port, the disease is defined as LD-SCLC, in contrast to ED-SCLC. This is a pragmatic differentiation in order to select treatment combined with or without RT. During the late 80s, the addition of thoracic radiotherapy (TRT) [79] and prophylactic cranial irradiation (PCI) [80,81] in LD-SCLC patients resulted in a significant survival benefit and have become part of routine treatment. In contrast, TRT and PCI do not increase survival in ED-SCLC patients.

TRT should be delivered concurrently with chemotherapy and early administration is better than delayed [82,83]. There is also evidence for better results with accelerated (twice daily) compared to once daily TRT. The best results reported are achieved with accelerated TRT given concurrently with the first cycle of chemotherapy [84] achieving a 26% 5-year survival in the accelerated arm. However, these results have not been reproduced by others. A new study from NLCG initiated in 2005, will compare accelerated TRT (1.5 Gy/twice daily/30 fractions) to the Norwegian hypofractionated standard (2.8 Gy/15 fractions) in LD-SCLC. TRT are to be started early after the second chemotherapy course (week 4) using a 3D-CRT technique [85].

An overview of the treatment principles in SCLC is outlined in Table 6.

Table 6. Treatment Principles in Small Cell Lung Cancer

Stage	Surgery	Chemotherapy	Radiotherapy	Survival (%) 1-year	5-year
T1/T2N0	Yes	Adjuvant	No	70	40-50
LD-disease	No	EP-regimen	TRT 40-50 Gy concurrent with chemotherapy - early start of TRT - accelerated TRT (?) - PCI in complete or good partial responders	65	15
ED-disease	No	EP-regimen CAV/CEV-regimen	Not routinely	15	1-2

Prognostic factors and the clinical decision making process

At diagnosis, most lung cancer patients have advanced disease and are beyond the possibility of cure. Even though the treatment intention for these patients is palliative, the beneficial effect of cytotoxic drugs and/or radiotherapy is well documented. The benefit on survival seems to be closely related to individual patient characteristics, often classified as prognostic factors for survival. Some common prognostic factors for survival are universal for lung cancer and should be used routinely in the clinical decision-making process.

The most important prognostic factors are stage of the disease, performance status (PS), (WHO-scale, Karnofsky scale), and weight loss.

Table 7. Performance status (PS)

Description Karnofsky Scale	KPS score	WHO score	Description WHO Scale
Normal, no complaints, no evidence of disease	100	0	Able to carry out all normal activity without restriction
Able to carry on normal activity, minor signs or symptoms of disease.	90	1	Restricted in physically strenuous activity, but ambulatory and able to carry out light work
Normal activity with effeort, some signs and symptoms of disease.	80		
Cares for self, unable to carry on normal activity or do active work.	70	2	Ambulatory and capable of all self-care, but unable to carry out any work up and about more than 50% of waking hours
Requires occasional assistance, but is able to care for most personal needs.	60		
Requires considerable assistance and frequent medical care.	50	3	Capable of only limited self-care; confined to bed or chair more than 50 % of waking hours
Disabled, requires special care and assistance.	40		
Severly disabled, hospitalisation indicated; death not imminent.	30	4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair
Very sick, hospitalisation indicated; death not imminent.	20		
Moribund, fatal process progressing rapidly.	10		

Prognostic factors in NSCLC

Disease stage is the dominant prognostic factor, since there is no available curative treatment if the tumour has spread outside the chest. Within each stage there is a correlation between tumour size, N-status and prognosis (Table 2). Also within each classified T-stage the tumour size correlates with the prognosis. The possibility of

eradicating the tumour, either with TRT alone or with TRT combined with chemotherapy, seems to be at a maximum tumour diameter of 6-8 cm [43, 86].

PS is the second most important prognostic factor and should be evaluated prior to treatment decision. NSCLC patients with PS 3-4 should not routinely receive tumour specific treatment, but be assigned to best supportive care (BSC) [25,87,88]. Chemotherapy for these patients may give more toxicity than clinical meaningful benefit. PS 2 patients experience increased toxicity and have shorter survival than PS 0-1 patients, indicating that these patients should possibily be chemotherapy treated only within clinical controlled trials [25].

Weight loss is common and is most often categorised according to the normal body weight before diagnosis and to the time interval over which the weight loss have developed (none versus < 5-10 % versus ≥ 10 % of normal body weight) over the last 3-6 months. Weight loss is a consistent and strong prognosticator [25,87,88]. A weight loss ≥ 10 % over the last 3 months is a very strong negative prognostic factor, and most patients should probably be treated with a palliative intent regardless of other prognostic factors.

Prognostic factors in SCLC

Since SCLC is highly sensitive to chemotherapy, a clinical meaningful benefit from chemotherapy may be achieveable also in PS 3-4 patients. All patients with a diagnosis of SCLC should therefore be considered for tumour specific treatment.

Otherwise, disease stage (LD versus ED) is the strongest prognosticator [89,90]. In a large study from NLCG, extent of disease and PS were revealed as the most powerful prognosticators [91]. LD-SCLC patients with favourable prognostic factors should be treated with a curative intent. Although some long-term survivors with ED-SCLC appear, the treatment intention in these patients is primarily palliative.

Table 8. Prognostic Factors and Treatment Principles in Lung Cancer

		Curative intent (Surg, CT, 3D-CRT)			**Palliative intent (CT, RT)**			**Best supportive care**		
	stage	PS	Weight loss	Tumour size	PS	Weight loss	Tumour size	PS	Weight loss	Tumour size
NSCLC	I	0-1	< 5%	any	2	5-10%	any	3-4	any	any
	II	0-1	< 5%	any	2	5-10%	any	3-4	any	any
	III	0-1	< 5%	< 8-9 cm	0-2	any	>10 cm	3-4	any	any
	IV				0-2	any	any	3-4	any	any
SCLC	LD	0-2	< 5-10%	any	3-4	any	any			
	ED				0-4	any	any			

Surg = surgery, CT = chemotherapy

Assessment of palliative treatment

Success in cancer treatment has traditionally been measured in terms of cure rate, increased survival and tumour response. However, when the treatment intention is to palliate, the improvement of symptoms and quality-of-life should be the main goals [92,93]. Oncologic palliation is defined as treatment with surgery, radiotherapy, hormone therapy, chemotherapy or other tumour modulating treatment given as a single modality or combined in patients who cannot be cured. These treatments relieve symptoms by reducing tumour burden and may sometimes prolong life. In addition symptomatic treatment for pain with opiods, 5HT-3 antagonists for emesis, and megesterolacetate for weight loss is essential for lung cancer patients. For all palliative treatments, the benefits must outweigh their risks and burdens [94]. Treatment-related side effects should always be detected and registered systematically. Criteria for classifying side effects are defined and implemented in most clinical trials (WHO Toxicity Criteria, NCI Common Toxicity Criteria) and reported as important end points. In contrast, the concept of quality-of-life is complex and represents more than toxicity and side effects. Quality-of-life is perceived as a multidimensional phenomenon and is defined in different ways, most often by a psychosociological definition, or in a medical/health-related definition (HRQOL). When assessing HRQOL, the use of patient self-assessment questionnaires is advocated [93,95].

Questionnaires

Several questionnaires for use in cancer patients have been developed and introduced in cancer research over the last two decades. These include the Functional Living Index Cancer (FLIC) [96], the Toronto Scale [97], the Rotterdam Symptom Checklist (RSCL) [98], the Cancer Rehabilitation Evaluation System (CARES) [99], the Functional Assessment of Cancer Therapy Scale (FACT) [100] and the EORTC Core Quality of Life Questionnaire (EORTC QLQ C-30) [101]. These instruments have been validated and found suitable in large-scale clinical trials.

The EORTC QLQ C-30 questionnaire is a brief core questionnaire designed for use in the general cancer patient in order to detect common symptoms and problems. Moreover, additional diagnosis-specific modules have been developed in

order to intercept symptoms related to a specific tumour type [102]. One of these is the lung cancer module, QLQ LC-13 [103]. This module together with the core questionnaire has been validated in clinical trials in both NSCLC and SCLC. This instrument is widely used in the Nordic countries. All randomised lung cancer trials performed by NLCG during recent years, have used these questionnaires as the main method for assessing HRQOL.

Physician-performed assessment of palliative benefit

In general, physicians and other caregivers have a tendency to overestimate the benefit of a treatment and to underestimate the side effects of a given treatment [104-106]. Since HRQOL is a multidimensional subjective phenomenon, comparison between patient- and physician-rated estimation of HRQOL are frequently restricted to compare more categorical variables like PS, pain and other disease-specific symptoms. The level of agreement between patients and their observers is investigated both at the group level and at the individual patient level. At the group level there is often a reasonably good patient-observer agreement [107,108], while this is not the case at the individual patient level [109,110].

Specific disease related symptoms can be assessed by clinicians if these symptoms are well defined in advance and scored according to a categorised scale. The studies from the Medical Research Council (MRC) in the United Kingdom pioneered the use of a systematic clinician-assessed evaluation of symptoms together with patient-rated self-assessment of symptoms and HRQOL [57,58]. These studies used a 4-point rating scale (none, mild, moderate, severe) for different disease-specific symptoms. Provided a systematic completion of symptom scales by the clinicians during the follow-up period, valuable information about the palliation of symptoms is achievable. However, the gold standard should nevertheless be patient-reported information, while observer assessments will be complementary and can be used for conformation [111].

Clinical trials

Why do clinical trials?

Progress in the treatment of patients is based on observation of effects and side effects following a specific intervention. A planned intervention in patients with well-defined baseline characteristics and with systematic collection of outcome data, is defined as a clinical trial. A clinical trial is a prospectively performed investigation, and properly conducted trials provide the only reliable scientific basis for evaluating new treatment strategies [112].

There are several good reasons for treating cancer patients within clinical trials. Patients in trials will be offered high quality treatment and high quality follow-up. It is suggested that physicians who participate in clinical trials take better care of their patients [113]. It is unclear if this is because participation in protocols is a form of continuing medical education, or if better clinicians are drawn to clinical trials participation.

According to the criteria's from the Catalan Agency for Health Technology Assessment, a system for categorisation of scientific evidence in medicine is proposed. This system is approved in Norway through the National Cancer Plan (NOU 1997) [114]. Meta-analysis of randomised trials using analysis of individual patient data is considered the ultimate level of evidence, level I. Level II is defined as large sample randomised controlled trials, whereas small sample randomised trials are categorised as level III. Non-randomised comparative studies are rated level IV evidence. According to the NOU criteria, two large phase III trials are required before a treatment change in cancer patients is recommended, whereas in small groups where a limited number of patients may prevent phase III studies, five non-randomised comparative studies with equivalent results are accepted as evidence [114].

Randomised clinical trials

The gold standard in clinical research is the randomised controlled trial (RCT) [112]. RCTs are the most rigorous way of determining whether a cause-effect relation exists between treatment and outcome, and for assessing the effectiveness of a treatment [115]. This technique provides a random allocation to the intervention groups, thereby

avoiding selection bias regarding treatment arms. The randomisation procedure secures that the intervention groups will be similar with respect to baseline prognostic factors, provided large enough patient groups. Ideally, all patients included in a phase III controlled clinical trial should be analysed, even though the planned treatment was not completed or started (intention-to-treat analysis). The size of a phase III study should be based on an estimation of difference in predefined outcome parameters between the intervention groups.

Comparative clinical trials

The selection bias problem in a study population is avoided by a randomisation procedure. This is not the case for a non-randomised comparative study, thus the findings should therefore be interpreted with caution. However, a non-randomised trial is nevertheless valuable in clinical research provided a rigorous registration of outcome effects and events, especially if the study population is large [116].

Well-designed RCTs have strict inclusion criteria in order to achieve appropriate and comparable intervention groups. The inclusion criteria will, however, often expel a large part of the relevant patient population, leaving a limited part which fulfils the inclusion criteria to be randomised [117,118]. Even though, results from large and well-designed RCTs will often be extrapolated to be normative for the entire population of interest. On the other hand, advocates for non-randomised clinical trials, claim that the accrual selection is lower and the study may more accurately reflect the population of interest [119].

Aims and objectives

The purpose of the present thesis is to improve the treatment for patients with advanced lung cancer by performing multicentre randomised clinical trials.

Small cell lung cancer - chemotherapy trial

1. *Background:* Combination chemotherapy is the primary treatment modality in SCLC patients. When the given study was planned, some evidence existed that cisplatin-containing chemotherapy is perhaps more effective than anthracyclin-containing chemotherapy in prolonging survival, while the latter was considered the treatment of choice at that time.
   Research question: Is cisplatin-based chemotherapy (EP-regimen; etoposide, cisplatin) superior to anthracyclin-based chemotherapy (CEV-regimen; cyclophosphamide, epirubicin, vincristin) as first-line treatment?
2. *Background:* CEV- and EP-chemotherapy are considered non-cross resistant in SCLC. Some studies indicate that EP-chemotherapy in previously CAV treated patients is more effective regarding survival than the reverse sequence. A crossover study of the randomised study population (1) at relapse was performed.
   Research question: Is EP-chemotherapy superior in CEV-treated patients, compared to the reverse sequence, as second-line treatment?

Non-small cell lung cancer - palliative TRT-trial

1. *Background:* Palliative thoracic radiotherapy (TRT) is considered to be beneficial in patients with advanced NSCLC. No consensus regarding total dose and fractionation exists.
   Research question: Is hypofractionated TRT (8.5 Gy x 2) comparable with high dose fractionated (2.8 Gy x 15; 2.0 Gy x 25) palliative TRT concerning effect on symptoms, HRQOL and survival?
2. *Background:* Patients with advanced NSCLC with none or minimal symptoms (NS) will often be treated with palliative TRT up front before symptoms develop.
   Research question: Will NS patients given immediate TRT achieve maintained HRQOL and prevention of tumour-related thoracic symptom development?

Material and methods

Setting

This thesis is based on two large study populations, the first one in SCLC patients (paper I and paper II) and the second one in advanced NSCLC patients (paper III and paper IV). The studies were performed as national multicentre trials with patients included from all health regions in Norway.

Both studies were performed within the context of the Norwegian Lung Cancer Study Group. This group was established by Erik Thorud in the 80s with the aim of improving the treatment and care of lung cancer patients and to undertake clinical research. The group is multidisciplinary with physicians from different specialities (oncology, pulmonology, surgery, epidemiology, pathology, radiology). One major task for this group is to initiate, administer and publish national lung cancer trials.

Study population and design, paper I

Patients with SCLC were the target population for this study. Both LD-SCLC and ED-SCLC patients were included. Verified histology and PS 0-2 were the main inclusion criteria. 440 patients were included in the period from January 1989 to August 1994 from 25 hospitals. Four patients were ineligible due to incorrect diagnosis (NSCLC) leaving 436 patients in the study. 214 patients were classified with LD-SCLC and 222 patients with ED-SCLC. All patients were treated with five chemotherapy courses. LD-SCLC patients received additional TRT between course three and four. Patients with LD-SCLC disease obtaining complete remission after induction chemotherapy were recommended PCI. From November 1989 to December 1993 the patients were invited to participate in a HRQOL part of the study. The inclusion criteria are described in paper I.

The patients were randomised to two different chemotherapy regimens consisting of: A) etoposide 100 mg/m^2 followed by cisplatin 75 mg/m^2, both intravenously (IV) on day one, with oral etoposide 200 mg/m^2 on days 2-4 (EP-regimen), and B) epirubicin 50 mg/m^2, cyclophosphamide 1000 mg/m^2, and vincristine 2 mg, all IV on day one (CEV-regimen). The EP-regimen was considered

the experimental treatment arm. 218 patients were allocated to the EP-regimen and 218 patients to the CEV-regimen. The primary end-point was survival. Provided no difference in survival, toxicity and HRQOL should be decisive for treatment recommendations. These were therefore considered as secondary end-points.

Study population and design, paper II

At the time when the SCLC study was planned, CAV- and EP-regimen were acknowledged as non-cross resistant regimens. Some evidence existed that EP chemotherapy in previous CAV-treated patients could be more effective than the reverse sequence. According to the protocol, the patients were recommended the other regimen at relapse if they were considered for second-line chemotherapy. Among patients with quality assured follow-up information regarding recurrence and retreatment, 286 patients were diagnosed with relapse. Of these, 120 patients were retreated with chemotherapy, 52 with crossover CEV chemotherapy, 56 with crossover EP-regimen, and 12 with the previous induction regimen. A comparison between the two crossover regimens was performed. In addition, the data gave the opportunity to compare the effect of actively chemotherapy-retreated patients (N=120) with those who were not (N=166).

Study population and design, paper III

Patients with advanced stage III or stage IV NSCLC disease, not considered for curative treatment, were included in this study. The patients should have disease related airway symptoms or with centrally located tumours threatening the central airways. The patients should be able to understand and fill out HRQOL questionnaires. All established radiotherapy centres in Norway participated in the study accruing patients from December 1993 through September 1998. One centre alone (The University Hospital in Trondheim, Department of Oncology) contributed with 52% of the patients. In total, 421 patients were included in the trial. The inclusion criteria are described in paper III.

The study was a RCT of three different TRT strategies evaluating the palliative effect on tumour-related symptoms from central airways. The objectives were to address whether a hypofractionated schedule (17 Gy/2 fractions, Arm A)

(N=143) was comparable to the standard fractionation in Norway (42 Gy/15 fractions, Arm B) (N=140). Moreover, our standard regimen had for several years been disputed as an inferior regimen. Therefore, a third arm (50 Gy/25 fractions, Arm C) (N=124) was incorporated in the study. The primary end-points were patient-assessed and clinician-assessed symptom relief of dyspnoea, cough and hemoptysis, while survival and the other domains in the HRQOL questionnaire were secondary end-points. Due to an anticipated limited survival of the majority of the patients, the period up to week 22 from study entry was defined as the period of primary interest.

Study population and design, paper IV

At study entry, the patients included in the palliative TRT study were stratified according to symptoms present (S-patients) or with none or minimal symptoms (NS-patients). This stratification was based on the clinical examination by the responsible physician on site prior to randomisation. 407 patients were eligible for the study, 107 categorised as NS-patients and 300 as S-patients. Nearly all eligible patients (N=395; 97%) accepted to participate in the HRQOL part of the study. Since the compliance of the questionnaires was very high, the HRQOL data could be explored longitudinally to assess the effect of immediate palliative TRT in NS- versus S-patients in a non-randomised comparative fashion.

The EORTC QLQ-C30 and LC-13 questionnaire

This questionnaire is developed by the European Organisation for Research and Treatment of Cancer [101,103]. The questionnaire incorporates five functional scales (physical, role, emotional, cognitive, social), three symptom scales (fatigue, nausea/vomiting, pain), a global health and overall quality-of-life scale, and five single items; dyspnoea, appetite loss, sleep disturbance, constipation and diarrhea, and financial impact of disease and treatment (see appendix for the entire questionnaire). The QLQ-LC13 module contains disease specific items for measuring dyspnoe, cough, hemoptysis, mucositis, dysphagia, peripheral neuropathy, alopecia, pain, and analgesic consumption/effect (see appendix). All scales and single-item were linearly transformed to a scale from 0 to 100. The scoring procedure followed the EORTC QLQ C-30 Scoring Manual [120]. A high score for the functional scales and the global

health scale represents a high/healthy level of functioning, whereas a high score for the symptom scales represents a high level of symptomatology/problems.

In both RCTs the first questionnaire was delivered to the patient from the responsible physician at the time of receiving informed consent. Later questionnaires were mailed from the data center to the patients at 2, 6, 14, 22, 30, 38, 46, and 54 weeks from the start of treatment. A reminder was sent to patients not returning the questionnaire within 2 weeks. Patients still non-compliant after one reminder received no further questionnaires.

Outcome assessments

Prospective assessments of HRQOL and symptoms are central in paper I, paper III, and paper IV in this thesis.

Longitudinally HRQOL data will often be presented graphically and can be visualised in several ways: 1) reporting the proportion of patients exceeding a certain level (cut point; categorical scale), 2) mean or median scores of all scales and all items, and 3) individual data points [121]. Assessing patients exceeding a specific value or level will reduce the study population and can therefore attribute to a selection bias. Using mean or median scores secures studying all patients, but a concealing effect of the inter-individual variability will occur. Individually data plots may be confusing and difficult to interpret. According to common recommendations, the method of presenting mean scores was chosen in this thesis due to a straightforward interpretation if the patient number between the intervention groups is balanced and fair-sized.

In paper III the HRQOL data were also explored using the method of patients exceeding score ≥ 2 (mild) at baseline and the percentage of these patients achieving an improvement, defined as at least one step change in the better direction on the 4-point rating scale, following treatment. This was performed for the primary end-points cough, dyspnoea and hemoptysis.

A method of presenting change in mean scores from baseline to different assessment times is easy to understand and interpret [122]. This technique was explored in the palliative TRT study (paper III), but gave essentially the same results as using mean scores and was consequently not presented in the publication.

A fundamental problem concerning the interpretation of longitudinal HRQOL data is the patient compliance and the patient attrition [123,124]. Patient non-compliance will generate missing questionnaires and incomplete data. This occurs more frequently in palliative clinical trials than in curative treatment trials. Patients with progressive disease and severe disease-related symptoms have a tendency of not fulfilling the questionnaires, generating questionnaire completion from the healthiest patient population. This may introduce a selection bias and render HRQOL scores too "good", and not representative for the patient population. Techniques for handling missing data have been implemented and advocated, but there is no widely accepted consensus [125]. The best way to overcome this problem is to achieve a substantially high compliance rate in the study population. Patients' compliance of questionnaires should therefore always be reported when patient self-assessment methods are used.

The evaluation of HRQOL in this thesis was explored at group level and based on mean scores at each assessment time calculated in all patients with completed questionnaires. A difference in HRQOL of five to 10 points has been considered as minor changes and of uncertain clinical relevance, while a change of 10 to 20 points represents a moderate to major change [126,127]. Thus a difference of 10 points or more has been regarded as clinically significant at group levels.

Clinician assessment of symptoms was central in the TRT study (paper III). This was performed for the primary end-points cough, dyspnoea and hemoptysis and used as a confirmatory method. Moreover, clinician-assessment of predefined categorised symptom development over time was essential also in paper IV. In both papers the system from the Medical Research Council was adopted [57,58] using a 4-point rating scale (none, mild, moderate, severe) addressing cough, hemoptysis and other disease-related symptoms, and a 6-point scale addressing dyspnoea. In paper IV the patients were evaluated at different follow-up times (week 2, 6, and 14) after completed TRT and the data were compared to baseline values.

Survival was defined as the primary end-point in paper I and II, and as a secondary end-point in paper III. In paper II survival was the only end-point in a non-randomised comparison between two crossover treatment groups. Paper IV compared HRQOL between two different stratified groups without survival as an end-point

since the original exploration revealed no difference in survival according to the randomly assigned treatment arms (paper III).

A summary of end-points and assessment methods according to study is shown in Table 9.

Table 9. End-points and assessment methods

	Primary end-points	Secondary end-points	Primary assessment methods	Secondary assessment methods
Paper I	Survival	HRQOL	Survival using the method of Kaplan-Meyer	EORTC C-30 + LC-13 questionnaires
Paper II	Survival		Survival using the method of Kaplan-Meyer	
Paper III	Symptom relief of dyspnoea, cough, hemoptysis	1)HRQOL 2) Predefined categorised symptoms 3) Survival	EORTC C-30 + LC-13 questionnaires evaluating the primary symptoms	1) EORTC C-30 + LC-13 questionnaires evaluating the other domains 2) Clinician assessed effect on primary symptoms 3) Survival using the method of Kaplan-Meyer
Paper IV	HRQOL	Predefined categorised symptoms	EORTC C-30 + LC-13 questionnaires	Clinician assessed effect on predefined symptoms

Randomisation centres and data quality

The Cancer Research Trial Office at the Norwegian Radium Hospital served as the randomisation centre and data management office for the SCLC study (paper I and paper II), while The Cancer Research Trial Office at the University Hospital in Trondheim handled the TRT study (paper III and paper IV). In both studies the HRQOL questionnaires were mailed from the data centre to the patients on identical time schedules (week 2, 6, 14, 22, 30, 38, 46, and 54). The baseline questionnaires were delivered to the patients by the physician's during the process of receiving informed consent and thereafter sent to the trial office.

Baseline clinical data and clinical information after fixed follow-up times were collected prospectively from the physicians. Reminders were sent to responsible clinicians in cases where forms were missing.

Attempting to increase the data quality, a retrospective review of the medical records was performed in the SCLC study in patients recruited from major centres (Central Hospital in Østfold-Fredrikstad, Ullevål University Hospital, University Hospital in Bergen-Haukeland, Norwegian Radium Hospital, University Hospital in Trondheim, and University Hospital in Tromsø). These centres were responsible for 348 of 436 eligible patients (80%).

In the TRT study, a retrospective review of the medical records was carried out in all patients.

Statistics

Survival was calculated from randomisation date using the Kaplan-Meyer product-limit method with the log-rank test applied for comparison of survival [128,129]. All survival analyses were calculated using the intention-to-treat principle. A complete follow-up of survival status was secured in all patients via the national death registery. Survival status was projected to 5-year and 3-year in the SCLC and TRT study, respectively.

Due to large sample sizes and a randomised design, a normal distribution of baseline demographic and clinical patient characteristics was anticipated. Comparison between categorical baseline and treatment variables were analysed using parametric tests like Pearson's chi-square tests or Fischer's exact test. A level of $P<0.05$ was considered statistical significant.

In contrast, the multiplicity and complexity of HRQOL data do not ensure normative distribution. A non-normative distribution will most often be the case, especially in longitudinal studies due to attrition and missing data. Non-parametric tests are therefore recommended. HRQOL measurements between the treatment groups were analysed either with the Mann-Whitney U test for two independent samples (paper I and paper IV) or the Kruskal-Wallis test for several independent samples (paper III). In general, analysis of HRQOL data entails a large number of comparisons and repeated testing. Hence, the conventional criterion of statistical significance is not advisable. Therefore a P-value of <0.01 was considered necessary for statistical significance. However, the magnitude of observed differences must also be considered before interpretation. A consistency between several domains at different assessment times should also be exposed before clinical significance can be drawn [123].

In one paper (paper II) exploration of possible prognosticators for survival was performed. Possible prognostic indicators were first tested for significance in univariate analyses using the method of Kaplan-Meier. Variables reaching statistical significance (<0.05) in the univariate analysis were tested in the multivariate analysis

using the proportional hazards model of Cox [130]. Probability for forward stepwise entry and removal was set at 0.05 and 0.10, respectively.

All analyses were done by SPSS for Windows.

Results and summary of papers

Paper I

Cisplatin and Etoposide Regimen Is Superior to Cyclophosphamide, Epirubicin, and Vincristin Regimen in Small-Cell Lung Cancer: Results From a Randomized Phase III Trial With 5 Years' Follow-Up.

This paper describes the hitherto largest performed RCT comparing an anthracyclin containing regimen (CEV-regimen) (cyclophosphamide (C), epirubicin (E), vincristin (V)) versus etoposide (E) and cisplatin (P) (EP-regimen) in SCLC. In total, 436 patients were studied. Stratification was performed for extent of disease. 214 patients had LD-SCLC and 222 patients ED-SCLC. Survival analysis revealed a significant benefit in favour of EP chemotherapy with median survival of 10.2 versus 7.8 months in the EP and CEV arm, respectively (P=0.0004). However, this benefit in survival was restricted to the LD-SCLC patients with median survival of 14.5 versus 9.7 months in the EP and CEV arm, respectively (P=0.001). In ED patients, a trend in favour of EP-chemotherapy with median survival of 8.4 versus 6.5 months in the EP and CEV arm, respectively, although without statistical significance (P=0.21). Overall 5-year survival was 3.5% in all patients, with 6% in LD-SCLC and 1% in ED-SCLC. During follow-up, several long-term survivors died of other causes than SCLC, giving a 5-year disease-specific survival of 8.5% in the LD-SCLC group; 13% in EP-treated and 4% in CEV-treated patients.

HRQOL analysis did not show any consistent difference between the two randomly assigned treatment groups, except for more nausea and vomiting in the EP-chemotherapy group during the induction treatment period. Due to inferior compliance in completing questionnaires at baseline (66%), resulting in a low number of patients in the LD and ED groups, the HRQOL analyses were presented in the entire group only.

The results from this trial scientifically established cisplatin and etoposide as the routine primary chemotherapy regimen in LD-SCLC patients. In ED-patients, the survival data were equivalent in both treatment arms with no consistent differences in

HRQOL scales. Thus, anthracyclin-based chemotherapy is still, in addition to EP, an alternative in ED-SCLC disease.

Paper II

Second-line chemotherapy in recurrent small cell lung cancer. Results from a crossover schedule after primary treatment with cisplatin and etoposide (EP-regimen) or cyclophosphamide, epirubicin, and vincristin (CEV-regimen).

This paper describes, in a non-randomised design, the follow-up of patients from the SCLC study with respect to recurrence and relapse-treatment. Detailed follow-up information were available in 382 (88%) of 436 patients. Of these, 286 patients (75%) developed relapse. Second-line chemotherapy was administered to 120 patients (42%) while the rest were treated with BSC without the use of chemotherapy. Among patients retreated with chemotherapy, 108 were treated with the opposite crossover regimen (52 with crossover CEV; 56 with crossover EP) and 12 retreated with the same induction regimen as they received in the primary situation. No survival difference was found between the two crossover groups with a median survival of 3.9 and 4.5 months in the EP- and CEV-group, respectively (P=0.71). Due to quality assured follow-up data, a comparison between retreated patients versus patients receiving BSC was possible. This comparison showed a highly significant difference in favour of second-line chemotherapy with a median survival of 5.3 and 2.2 months in the retreated and the BSC group, respectively (P<0.0001). However, exploration of prognostic factors at baseline showed that the BSC group in general had a significantly worse prognosis when compared to the others. In patients administered crossover chemotherapy, possible prognostic factors for survival were investigated in univariate and multivariate models, revealing PS at relapse as the only independent prognostic factor of significance (P<0.001).

To summarise, no differences between CEV- and EP-chemotherapy at relapse were seen, leaving both regimens optional for second-line chemotherapy. However, due to the non-randomised fashion of this comparative study, conclusions have to be interpreted with caution. Moreover, PS should be established in all relapsed SCLC patients, and used in the treatment decision-making process to evaluate the potential for meaningful treatment benefit.

Paper III

Hypofractionated Palliative Radiotherapy (17 Gy per two fractions) in Advanced Non-Small-Cell Lung Carcinoma Is Comparable to Standard Fractionation for Symptom Control and Survival: A National Phase III Trial.

This RCT compared different palliative radiotherapy schedules in locally advanced or metastatic NSCLC. Comparing one hypofractionated TRT schedule (17 Gy/2 fractions, Arm A) versus two higher dose fractionated TRT schedules (42 Gy/15 fractions, Arm B; 50 Gy/25 fractions, Arm C). 421 patients were included, of which 395 participated in the HRQOL part of the study. The compliance rate of HRQOL questionnaires at baseline and throughout the follow-up time was very good (baseline 97%, minimum 76%). No differences in palliative effect between the various TRT schedules were revaled, measured by patient completed questionnaires or by clinicians' assessment. The beneficial effect on dyspnoea, cough and hemoptysis was equivalent across the treatment arms throughout the period of primary interest (up to week 22). Furthermore, no consistent differences in HRQOL outcomes until one year follow-up were seen. Finally, local symptomatic control within the radiotherapy fields was equal between the treatment arms, with about 40% being without significant tumour-related chest symptoms at the latest assessment time (P=0.64).

Moreover, no difference in survival was observed with a median survival of 8.2, 7.0, and 6.8 months in arm A, B, and C, respectively (P=0.83). Subgroup analysis in locally advanced disease (stage III) did not show any statistical significant difference in median survival (arm A, 9.2 months; arm B, 8.1 months; arm C, 7.5 months) (P=0.47). However, a trend to more long-time survivors in the higher dose fractionated arms was found when good PS patients (Karnofsky score ≥ 80) were analysed, with a 3-year survival of 1%, 9%, and 6% in arm A, B, and C, respectively (P=0.06).

Toxicity evaluated by the HRQOL questionnaires and clinicians' assessment did not reveal any differences in side effects. Radiotherapy-induced oesophagitis appeared earlier in the short-course TRT-arm (Arm A) compared to the higher dose schedules (Arm B and C), but this was temporary and manageable.

The patients included in this trial were highly homogenous related to other treatment interventions, as only six and seven patients received chemotherapy either

before or after TRT, respectively. This fact makes the HRQOL results interpretable according to the assigned treatment and follow-up period.

The overall interpretation of this trial is that short-course palliative TRT with 17 Gy in two fractions is safe to administrate and comparable with more protracted higher dose palliative TRT considering symptomatic effect, HRQOL and survival.

Paper IV

Immediate or delayed radiotherapy in advanced non-small cell lung cancer (NSCLC)? Data from a prospective randomised study.

This paper is studying the same cohort of patients as in paper III. At baseline, the patients were stratified according to symptoms present (S-patients) or with none or minimal symptoms present (NS-patients). This separation gave the opportunity to explore the symptom development and HRQOL in two patient cohorts, differing with respect to disease-related symptoms, administered immediate TRT. 107 patients were categorised as NS-patients and 300 as S-patients. In general, NS patients had significantly better baseline characteristics concerning Karnofsky PS, weight loss, and stage distribution. These factors are all well known as significant prognosticators for survival in NSCLC and do explain the observed survival difference with median survival of 11.8 and 6.0 months in the NS- and S-group, respectively ($P<0.0001$). However, within each of the two stratified groups there were no differences in survival regarding the various TRT schedules.

According to better baseline characteristics in NS-patients, the HRQOL baseline data were significantly better in most scales compared to S-patients. Whereas the HRQOL results were improved or stable in S-patients in the period of primary interest (up to week 22), there were a consistent deterioration and worsening in NS-patients in the same period. From week 14, the HRQOL mean scores were overlapping (95% CI). Both groups developed a significant radiotherapy induced oesophagitis in the first weeks.

Clinicians' symptom assessments were consistent with the patient reported HRQOL data. As for HRQOL, S-patients had significantly more disease-related symptoms at baseline in all sacles except for emotional function, congnitive function and diarrhea, when compared to NS-patients. At follow-up, 14 weeks after completed

TRT, symptoms were equal in the two groups with exception of fatigue. At this point fatigue was still more frequent in the S-patient population.

Since this study is a non-randomised comparison, the results should be interpreted with caution. However, longer term prevention of disease related symptoms and maintaining a reasonably good HRQOL in NS-patients given immediate TRT do not seem to occur. Furthermore, dysphagia and radiotherapy oesophagits were unnecessary induced in these otherwise symptom-free patients. Our data may indicate that patients with minimal or no tumour related chest symptoms do not benefit from immediate palliative TRT.

Discussion

The basis for this thesis is two randomised national multicentre studies performed through NLCG. The Norwegian health care system provides an equal treatment policy independent of adress, social status and financial income. Furthermore, the quality assurance of cause of death is reliable through the national death registry. Since the community of lung cancer treating physicians in Norway is rather transparent, the loyalty to treatment guidelines and protocols is favourable. Thus, the percentage of potential patients enrolled in protocols is high, yielding a low selection bias. This renders high quality trial data, representative in the everyday clinic.

HRQOL assessments made by patients were one of the main goals in these studies. The SCLC study was initiated in the late 80s and the TRT study in 1993. The recognition of the importance of HRQOL assessments in palliative clinical trials has evolved during the 90s. The early studies by Kaasa et al. [131,132] during the mid 80s, pioneered evaluating quality-of-life aspects in lung cancer patients within clinical trials. These papers describe a self-developed questionnaire containing items on different disease- and treatment-related symptoms. The experience from this research was put into collaboration with the European Organisation for Research and Treatment of Cancer (EORTC). About 1990, the EORTC developed a core questionnaire for use in cancer patients (EORTC QLQ C-30) [101]. Later, a lung cancer specific module to be used together with the core questionnaire was developed (QLQ LC-13) [103]. The questionnaires were validated through international field studies and were found reliable and valid in lung cancer patients [133]. These questionnaires (version 1) were therefore chosen as the main method for evaluating HRQOL in the studies described herein.

SCLC, chemotherapy study

The SCLC study represents the first large-scale oncology trial in Norway using HRQOL as one of the major end-points.

The median survival difference of 7.8 to 10.2 months in favour of the EP-regimen is highly statistically significant (P=0.0004). Important to notice is that the survival difference is not only a gain in median survival. The survival benefit is maintained throughout 5-years of follow-up.

This SCLC trial is the only published randomised trial strictly comparing EP- and CEV/CAV-chemotherapy. Two previous 3-armed RCTs have been performed, both with the third arm consisting of an alternating CAV/EP-regimen. The trial from Roth and colleagues [68] studying 437 ED-SCLC patients with CAV, EP, or alternating CAV/EP, did not find any survival difference across the arms, which is in accordance with the findings in our study. The study from the Japanese Group [69], including both LD- (N=146) and ED-patients (N=142), compared CAV (N=97), EP (N=97), and alternating CAV/EP (N=94). The investigators reported a significantly higher overall survival for LD patients receiving the alternating CAV/EP therapy (2-year survival of 30%) when compared with CAV (15%) or EP (21%). However, no difference was observed between the EP- and the CAV-treatment group. In ED-patients, no difference between the treatment arms was seen. Our study is hitherto the largest study in LD-patients. The demonstrated survival benefit establishes the EP-regimen as the superior chemotherapy regimen and should be used routinely in LD-SCLC patients [134,135].

In our trial the thoracic radiotherapy was administered to LD-patients between course three and four to a total dose of 42 Gy in 15 fractions over three weeks. When this study was initiated, 42 Gy was considered an internationally acceptable fractionating scheme [136]. Subsequent investigations have revealed that concomitant radiotherapy is more beneficial than sequential [83,137]. Furthermore, accelerated radiotherapy may be even more effective if rapid clonogenic cells exist. The study by Turissi and co-workers [84] giving radiotherapy concurrent with EP-chemotherapy from day one, either normofractionated (1.8 Gy/25 fractions) or accelerated twice daily (1.5 Gy twice daily/30 fractions), reported impressive 2- and 5-year survival rates. Median survival was 19 versus 23 months for those receiving once-daily therapy and twice-daily therapy, respectively (P=0.04), with the corresponding 5-year survival rates of 16% versus 26%. Our results are inferior compared to the Turissi study [84], but their promising results have not been been reproduced by others. Compared to other reports, however, our results in LD-disease are acceptable [135], but somewhat lower survival when compared with phase II and phase III reports from North America [138]. The difference in outcome in LD-SCLC patients might be explained by less selection bias in our study compared to the US studies. Given the national SCLC incidence rates in Norway during the study period, close to 40% of all potential patients were actually included in this trial. In contrast, the Turissi study [84] was more selective

regarding the study population with patients primarily in PS 0-1, less weight loss and lower median age, when compared with our study population. Moreover, data from the US indicate that less than five percent of eligible patients in general are included in trials [139].

Since there was no difference betwen the treatment arms with respect to ED-patients in our study, an anthracyclin-based regimen seems an acceptable alternative to EP. However, two meta-analyses considering the role of cisplatin in SCLC found a significant survival improvement following cisplatin-based chemotherapy [71,72]. Moreover, Chute et al. [140] reviewed 21 published phase III trials in North America with a total of 5746 ED-SCLC patients treated between 1972 and 1993. Trials from 1972 through 1981 were mainly anthracyclin-based, while trials in the period 1982 to 1990 were cisplatin-based. From the first to the second period, the authors found an increased survival from 7.0 to 8.9 months (P=0.001). These results are comparable with the findings in ED-patients in our trial where a survival of 6.5 and 8.4 months (P=0.21) in the CEV- and EP-arm were found, respectively. Keeping in mind the results of the meta-analysis, the superiority of EP chemotherapy in ED-SCLC is therefore likely to exist, but difficult to show in single trials with inadequate power.

HRQOL assessment, defined as a secondary end-point, was considered essential in this trial, especially if the primary treatment outcomes turned out equal in the two treatment arms. Interpretation of HRQOL scores was, however, difficult due to a low baseline compliance (66%). Thereafter, the compliance rate was above 70% until week 38, but dropped to 62% at week 54. Due to logistic circumstances, HRQOL participation was restricted to 4 years of a total of 5.6 years accrual time. As a consequence, 72% of the patients were enrolled in this part of the study. Because of the low baseline compliance, the possibility of interpreting HRQOL data in subgroups became limited. Hence, HRQOL data are only presented in the entire group and not in the LD- and ED-subgroups.

No substantial HRQOL differences between the two treatment groups were found, except for more emesis until week 14 in the EP group. Modern antiemitics with 5HT-3 antagonists were introduced in Norway around 1991, during this trial period. Exploration of HRQOL before or after this period revealed the same result with more emesis in the EP-arm. As the survival is equivalent in the ED-group, the chemotherapy regimen in ED-patients should be a matter of choice. However, based on the results of the meta-analysis [71,72] and the possibility of replacing cisplatin by

carboplatin, many clinicians today will choose carboplatin and etoposide as first choice in ED disease.

Whereas 316 patients accepted to participate in the HRQOL evaluation, the compliance at baseline was 66% (N=209), while it was 89% (N=281) at week two. The reason for this low baseline compliance is obviously related to the physicians who either were not delivering or collecting the questionnaires at study entry. At the time when this study was running, research nurses or research assistants were not common in Norway. The high compliance from the mailed questionnaires, however, shows that most patients are positive to HRQOL-questionnaires. Studies with allocated research assistants and inclusion criteria requesting completed baseline HRQOL questionnaires prior to randomisation, is therefore recommended in order to improve HRQOL assessment in future studies [141].

The crossover study (paper II) tested the alternative regimen at relapse. Former studies had shown that treatment with EP in previously anthracyclin-treated (CAV-regimen) patients [142] was perhaps more effective than the reverse sequence [143]. When the present study was designed (paper I), these two regimens were considered to be non-cross resistant [144,145]. Thus, the alternative regimen was recommended at relapse. However, exploration of survival as the principal outcome did not reveal any difference between the crossover groups. No difference in survival in previously CEV treated patients retreated with EP, compared to the reverse setting, was exposed. There are many possible explanations for this lack of difference. Even though the baseline characteristics are similar in both groups, the two groups might be different biologically at the time of relapse. A significant difference in survival after first-line induction chemotherapy indicates that EP chemotherapy is more effective in SCLC. This disparity can lead to a non-reliable distinction in resistant and sensitive disease at relapse. Secondly, one could argue that the CEV- and EP-regimens are not equipotent. Finally, the sample size of the study population may be too small to detect any possibly existing difference. Therefore, having these considerations in mind, the interpretation of this study should be with caution. A more precise interpretation may be to regard the two crossover groups as two separate phase II studies with limited importance when compared to each other.

Nevertheless, our results with a median survival of 5.3 months and a 1-year survival of 12 to 14% are comparable with findings from other second-line studies

using novel cytotoxic agents. No substantial increase in either median or 1-year survival is achieved when testing paclitaxel [146], gemcitabine [147], or topoisomerase I inhibitors like irinotecan [148] and topotecan [149]. These phase II studies achieved a median survival of 5.0 to 7.1 months, and a limited 1-year survival of 10 to 20% with no long-time survivors. One phase III trial, comparing single drug topotecan versus the CAV-regimen, achieved survival rates comparable with our study [150]. Thus, hitherto, no single standard salvage regimen has been recommended in the second-line setting.

Since valid follow-up data were accessible in most patients in the first-line protocol, we were able to compare patients receiving second-line treatment with those receiving BSC. Baseline characteristics of these two cohorts of patients revealed that patients selected to be retreated had significantly more favourable prognostic factors than the others. Therefore, the large difference in median survival between retreated patients and the BSC group may primarily reflect the prognostic features of the accrued patients and not the efficacy of the retreatment.

Recently, a phase III trial comparing oral topotecan versus BSC in patients with recurrent SCLC, ineligible for further intravenously chemotherapy, has been published [151]. Even though the study population was limited (N=141), a significantly improved median survival from 14 to 26 weeks (P=0.01) was achieved with less deterioration of HRQOL in favour of the topotecan treated patients. Although the evidence for benefit of second-line chemotherapy in recurrent SCLC is sparse, most clinicians will advocate chemotherapy if the patient's PS is good. In our study, a prognostic factor analysis among the retreated patients revealed PS as a highly significant prognosticator for survival. Furthermore, the BSC patients had significantly worse PS at relapse compared to the actively treated patients. This emphasises the importance of PS as the main selection criteria for choosing which patients should receive second-line chemotherapy. Thus, if second-line treatment is considered, this should probably be restricted to PS 0-1 patients only. Consequently, estimating PS is mandatory and should be used actively in the clinical decision-making process before giving second-line chemotherapy in relapsed SCLC patients.

NSCLC, palliative radiotherapy study

The TRT study was initiated in 1993 with the principal aim to evaluate HRQOL and the treatment effect on symptoms in radiotherapy treated advanced NSCLC patients. Participation in the HRQOL part in this study was optional, however, 97% (395/407) of eligible patients volunteered to participate. Only ten baseline questionnaires were missing, giving an initial compliance of 97%. The compliance throughout the planned follow-up time was minimum 76% at week 38 and 81% at the latest assessment time at week 54. This high compliance rate makes the interpretations of the HRQOL data from this study highly valid and representative.

All together, there were no differences in outcome of primary symptoms or HRQOL across the treatment arms, either in the period of primary interest or until week 54. Subgroup analyses according to NS- and S-patients were also performed, but still no differences were seen between the assigned treatment arms. The HRQOL results were supported by the clinicians' assessment of the primary symptoms. With the equal survival in mind, these results support hypofractionated TRT with 17 Gy in two fractions in these patients.

A Cochrane Collaboration review on palliative RT in advanced NSCLC [61] has evaluated ten RCTs (2001). Our study (unpublished summarised data) was one of these trials. Trials comparing RT with chemotherapy alone or in combination with RT were not included. After completion of this review, three other phase III trials have been published [152-154]. These trials, addressing the question about fractionation, have used a large variety of schedules, ranging from 10 Gy in one fraction to 60 Gy in 30 fractions. Table 10 gives an overview of these trials.

The trials from the MRC in UK pioneered patient self-assessment as a major method for evaluating the effect on disease-related symptoms, in addition to clinicians' assessment of primary symptoms. The first study (MRC I) [57] tested patients with a reasonably good PS by comparing hypofractionated or short-course TRT (8.5 Gy x 2) versus a traditional TRT fractionation schedule (3 Gy x 10). The second study (MRC II) [58] included patients with poor PS (PS 2-4) comparing a single fraction TRT (10 Gy x 1) versus the experimental arm in the MRC I study (8.5 Gy x 2). Both studies used a diary card system, restricted to 6 months. There were no differences in palliation or survival across the arms. The inferior survival in MRC II compared to MRC I is explained by worse PS in the MRC II study. However, a

subgroup analysis of patients with stage III disease in the MRC I study, suggested that survival might be improved by protracted fractionation.

Table 10. Different RCTs considering palliative TRT in advanced NSCLC

				Symptom assessment			Median S	
	N	**Randomisation**	**PS-status**	Patient	Physician	Outcome	(months)	**Long-term S**
Simpson (1984)	316	4.0 Gy x 10 (split 2 wk) 3.0 Gy x 10 2.0 Gy x 20	0-2 (3)	no	yes	equal	6.2 6.4 6.9	 3-year not reported no difference
Teo (1987)	291	2.5 Gy x 18 (45 Gy) 7.8 Gy x 4 (31.2 Gy)	0-2 (3)	no	yes	better palliation in arm 45 Gy	5.0 5.0	2-year 5% no difference
MRC I (1991)	369	8.5 Gy x2 (17 Gy) 3 Gy x 10	0-2 (3)	diary cards	yes	equal	5.9 5.9	2-year 5% no difference
MRC II (1992)	235	8.5 Gy x 2 (17 Gy) 10 Gy x 1	2-4	diary cards	yes	equal	3.3 4.0	2-year 2-3% no difference
Abratt (1995)	84	3.5 Gy x 10 (35 Gy) 3.0 Gy x 15 (45 Gy)	0-2	no	yes	equal	8.5 8.5	 not reported
MRC III (1996) Macbeth	509	3.0 Gy 13 (39 Gy) 8.5 Gy x 2 (17 Gy)	0-2	questionnaires diary cards	yes	equal	8.9 7.1	2-year 12% * 2-year 9%
Rees (1997)	216	8.5 Gy x 2 (17 Gy) 4.5 Gy x 5 (22.5 Gy)	0-3	questionnaires	no	equal	6.0 6.0	2-year not reported no difference
Reinfuss (1999)	240	4.0 Gy x 10 (split 4 wk) 2.0 Gy x 25 observation (wait and see)	1-3	no	no	not reported	9.0 12.0 6.0	2-year 6% * 2-year 18% * 2-year 0%
Nestle (2000)	152	2.0 Gy x 30 2.0 Gy/twice/day x 8 (32 Gy)	0-3	diary cards	yes	equal	8.3 8.4	2-year 9% no difference
Bezjak (2002)	230	4.0 Gy x 5 (20 Gy) 10 Gy x 1	0-3	questionnaires diary cards	no	better palliation in arm 20 Gy	6.0 * 4.2	not reported
Sundstrøm (2004)	407	8.5 Gy x 2 (17 Gy) 2.8 Gy x 15 (42 Gy) 2.0 Gy x 25 (50 Gy)	0-3	questionnaires	yes	equal	8.2 7.0 6.8	3-year 1% 3-year 6% 3-year 6%
Kramer (2005)	297	8.0 Gy x 2 (16 Gy) 3.0 Gy x 10	0-3(4)	questionnaires	no	longer palliation in arm 30 Gy	not reported	3-year 2% 3-year 6% *
Senkus-Konefka (2005)	100	8.0 Gy x 2 (16 Gy) 4.0 Gy x 5	1-3(4)	questionnaires	yes	equal	8.0 * 5.3	no difference

S = survival

* = p< 0.05

Therefore, a third study (MRC III) [59] was implemented comparing higher dose (3 Gy x 13) versus short-course (8.5 Gy x 2) TRT in good PS patients with stage III tumours. The main end-point for this study was long-term survival. The trial was therefore extended to be the hitherto largest performed trial. To assess palliative benefit, questionnaires (Rotterdam Symptom Checklist [98]) together with diary cards were used. The results showed that the palliative effect occurred more rapidly in the short-course arm, but the magnitude of palliation was equal. A small, but significant survival benefit was revealed in the higher dose TRT schedule, 2-year survival of 12 versus 9% (P=0.03), respectively.

Five other trials (Simpson [155], Abratt [156], Rees [157], Nestle [158], and Senkus-Konefka [154]), using various dose schedules, have not shown any difference in symptom palliation or long-term survival in favour of higher doses. However, three

trials have reported a difference in palliation [152,153,159], in which two also revealed a difference in median survival [152,153], in favour of higher dose schedules. The Canadian trial [152] compared a single fraction of 10 Gy versus 20 Gy in five fractions. A diary card method and questionnaires were used, but limited up to one month. Assessment of symptoms showed a greater improvement in several scales in favour of fractionated therapy. A significant difference in median survival with two months extended survival compared to the single fraction arm was exposed; however, this difference was restricted to good PS patients with stage III disease only. The recently published Dutch trial [153], comparing 8 Gy x 2 versus 30 Gy/10 fractions primarily in stage IV or poor PS stage III patients, revealed a better survival and longer duration of palliative response in the high dose arm. The older trial from Teo and colleagues [159] investigated a higher dose normofractionated schedule (2.5 Gy x 18) versus a higher dose hypofractionated schedule (7.8 Gy x 4). The palliative effect, assessed by clinicians exclusively, was significantly better in the 45 Gy arm. No survival difference was exposed.

The Canadian study [152] did show an inferior survival in good PS stage III patients given single fraction TRT. This was not shown in the MRC II [58] study, confined to low PS patients only. No other trials using a single fraction in one arm are published. A hypothesis of an existing dose-response relation between single fraction (10 Gy) versus 17 Gy/2 fractions or higher doses, can, however, explain the conflicting results from the Canadian trial [152].

The results from the Dutch trial [153], mostly stage IV disease, showed improved survival in the high dose arm. These results are in contrast to all other trials including stage IV disease. However, the benefit was restricted to good PS patients. The Polish study [154], using the same hypofractionated schedule (8 Gy x 2), did, however, show a better median survival in the 16 Gy/2 fraction arm, which is in contrast to the Dutch results.

Compared to the trials using diary cards and/or questionnaires for evaluating the palliative effect, our trial has the strength of high compliance rate and more extended evaluation (week 54). In our trial, no consistent long-term differences in HRQOL were seen beyond 6 months. Overall, there is no convincing evidence that higher dose TRT gives better palliation in the short- or the long-term perspective, and recommending a hypofractionated low dose schedule should be safe, at least in poor PS patients (PS ≥ 2).

However, some concern remains about TRT fractionation and long-term survival in localised stage III disease. There is a trend that some patients are long-term survivors and might be cured with protracted higher dose TRT, even when the aim of the treatment is palliation. The MRC III [59] trial is the only trial performed with a sufficient power to detect a difference in long-term survival. The 3-arm trial in localised stage III disease from Reinfuss et al.[160], comparing a split-course technique (4 Gy x 5 - split 4 weeks - 4 Gy x 5) versus a conventional fractionation schedule (2 Gy x 25) versus wait and see (TRT when symptoms), supports this trend. No patients in the wait and see arm survived 2-years, compared to 18% and 6% in the fractionated and split-course schedule, respectively. While the statistical significant difference at 2-years is based on a comparison between the two TRT arms combined versus wait and see, a survival comparison between the two TRT arms was not reported. The long-term survival data from our study show a trend (P=0.06) towards better survival in stage III good PS patients given the higher dose TRT (42 Gy/15 fractions, 50Gy/25 fractions). Updated survival data reveal that the difference is maintained up to 5-years. At this time, 5% is still alive in the protracted fractionated arms in contrast to none in the hypofractionated arm [161].

Due to the large heterogeneity among these trials, the Cochrane Collaboration did not attempt performing any meta-analysis [61]. The review concludes that the majority of patients should be treated with short-course radiotherapy since there is no strong evidence of greater palliation with more protracted TRT regimens. Moreover, there is evidence for a modest increase in survival in stage III patients with better PS given higher dose TRT. The use of higher dose palliative regimens should therefore be considered for selected patients with locally advanced disease and good PS.

In paper IV, the HRQOL development in TRT treated patients without (NS-patients) versus those with symptoms (S-patients) at base-line is explored. This paper describes, in a non-randomised comparison, that the HRQOL is stable or improved in S-patients during the first 14 weeks in contrast to a negative development in NS-patients. After week 14, there are no significant differences between the two groups based on mean scores with 95% CI. These findings suggest that administering TRT up front in patients without symptoms, yields no long-term benefits, but radiotherapy-induced side-effects such as oesophagitis.

For many years, there has been a controversy about the effect of immediate palliative TRT in asymptomatic stage III NSCLC patients [162-167]. Studies addressing this topic are presented in Table 11. The study from Durrant and colleagues [162] reported early in the 70s different treatment policies in locally advanced disease where a wait and see policy was one option. The radiotherapy given was 40 Gy in 13-14 fractions compared to chemotherapy alone or TRT and chemotherapy combined. No differences were found regarding survival or in relation to a simplified HRQOL evaluation. The strength of this study is that it was a randomised trial. However, the TRT was given with cobalt-60 or orthovoltage therapy and may therefore be considered as suboptimal related to modern megavoltage radiotherapy.

Table 11 Different trials evaluating benefit of immediate TRT in localised asymptomatic NSCLC

	N	Treatment	N treatment arms	Design	Palliative outcome	Median S (months)
Durrant (1971)	249	Wait and see	63	randomised	equal	8.4
		Immediate TRT	62			8.3
		Chemotherapy	63			8.7
		Combined	61			8.8
Carroll (1986)	134	Wait and see	48	non-randomised	not assessed	not reported
		Immediate TRT	86			
Falk (2002) MRC	230	Wait and see	115	randomised	equal	7.9
		Immediate TRT	115			8.3
Sundstrøm (2005)	407	Immediate TRT non-symptomatic	107	non-randomised	inferior	11.8
		Immediate TRT symptomatic	300		stable/improved	6.0

S= survival

Carroll and co-workers [167] published a comparison between immediate TRT or watchful waiting until treatment was required due to symptoms. In each case, thorough information about the different treatment strategies was presented to the patients at diagnosis. A watch policy was chosen in patients accepting a wait and see strategy. Of these, 46% were estimated not to require any TRT in the follow-up period. However, neither HRQOL nor survival data were presented.

In 2002, Falk and colleagues [168] published a randomised trial of immediate or delayed TRT in patients judged with minimal or no tumour related chest symptoms at diagnosis. This MRC trial [168] performed a thorough evaluation of HRQOL and symptoms using the same methods as in previous MRC trials [57-59]. The majority of patients were treated with either 17 Gy in two fractions or a single fraction (10 Gy). No significant differences were found in survival, or in activity level, anxiety, depression, and psychological distress as recorded by the patients. In the delayed group, 42% received TRT during follow-up. Only two patients were treated with

chemotherapy. It was concluded that immediate TRT, when compared to TRT delayed until symptoms, yielded no improvement of symptom control, HRQOL, or survival.

The patients accrued in this MRC trial [168] as well as the NS patients in our present trial, were categorised with minimal or none disease-related chest symptoms at diagnosis. However, baseline characteristics were different as our NS-patients had more favourable PS and less chest symptoms when compared to the MRC patients. In fact, a large proportion of the patients in the MRC study did have some symptoms at baseline, and may not be comparable with our NS-patients. The observed difference in median survival (NS patients 11.8 months, MRC immediate 8.3 months, MRC delayed 7.9 months) may be explained by this discrepancy.

Since the late 90s, palliative chemotherapy has been considered standard treatment in advanced NSCLC [25]. Thus, a repeated confirmatory TRT trial in this setting is therefore not ethically or possible to perform. Anyway, since our patients were treated with TRT only, our trial is comparable with the Falk study [168]. No other confounding treatment modalities were used. The decreasing HRQOL observed in our NS patients after the TRT administration, strongly supports the conclusion from the MRC trial. Thus, a wait-and-see policy, i.e. delaying palliative TRT in advanced NSCLC patients until symptomatically needed, appears to be safe and acceptable.

Conclusions and clinical significance of the studies

The results from this thesis can be summarised as follows:

- Chemotherapy with the EP-regimen is superior to CEV in small cell lung cancer. A highly significant difference in LD-SCLC shows that EP should be standard regimen in this subgroup of patients. The lack of survival difference between the treatment arms in ED-SCLC leaves anthracyclin-based chemotherapy (CEV/CAV-regimen) an alternative to EP in this patient subgroup.

- Second-line chemotherapy in recurrent SCLC disease is associated with poor prognosis. No difference in treatment effect in either crossover treatment (EP versus CEV) was found, making the choice optional for which second-line regimen to be used. PS is an independent prognostic factor in recurrent SCLC and should be used as the principal selection marker in the treatment decision for or against second-line chemotherapy.

- Hypofractionated palliative TRT (17 Gy in two fractions) in advanced NSCLC is comparable with more protracted higher dose TRT with respect to HRQOL, disease related symptom relief and survival. In most NSCLC patients where palliative TRT are needed, this fractionation schedule should be used. Selected stage III patients with favourable PS should be treated with a protracted fractionated higher dose TRT schedule.

- Advanced NSCLC patients with disease-related chest symptoms at diagnosis will benefit from palliative TRT. Patients without or with minimal symptoms do not benefit from immediate TRT. On the contrary, they experience a reduced HRQOL due to therapy-induced side effects. A wait and see policy considering palliative TRT is recommended until the patient develops symptoms.

Strategy for further clinical research - within the context of the Norwegian Lung Cancer Study Group

This thesis is based on multicentre studies from the collaborative work by the Norwegian Lung Cancer Study Group. The collaboration is focused around clinical research in lung cancer patients. The strength of the group is the multiprofessionality of clinicians participating, a common agreement on protocols and issues to be investigated, a high loyalty and compliance into protocols, and an organisation with alternating sites to be responsible for research protocols. This makes it possible to carry out national trials ensuring low selection bias in the study populations.

Most of our trials focus HRQOL evaluation as a central end-point. One main lesson from the trials addressed in this thesis is that compliance of baseline questionnaires is critical. After the first study presented herein, completed baseline HRQOL questionnaires became a crucial inclusion criterion.

The collaborative work of the group has expanded through the 90s and in the middle of this decade with several trials completed, ongoing or forthcoming. The group will continue its main focus on clinical trials (phase II and phase III), increase the quality of lung cancer detection, staging, treatment, and follow-up through published “National Guidelines”. Further, our collaborative group will also act as a national reference group for advice on treatment recommendations.

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Paper I

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Paper II

Lung Cancer (2005) 48, 251–261

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Second-line chemotherapy in recurrent small cell lung cancer
Results from a crossover schedule after primary treatment with cisplatin and etoposide (EP-regimen) or cyclophosphamide, epirubicin, and vincristin (CEV-regimen)

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Received 18 March 2004; received in revised form 20 October 2004; accepted 25 October 2004

KEYWORDS
Small-cell lung cancer;
Relapse;
Best supportive care;
Crossover chemotherapy

Summary

Purpose: To evaluate the benefit of crossover chemotherapy with etoposide and cisplatin (EP) versus cyclophosphamide, epirubicin, vincristine (CEV) at relapse after primary treatment with the opposite regimen in patients with small cell lung cancer (SCLC). Further, to compare the crossover group with patients not receiving chemotherapy.

Patients and methods: Among 286 patients diagnosed with relapse after first-line chemotherapy, 120 patients received second-line chemotherapy and 166 patients received best supportive care. Fifty-six patients received EP after previous treatment with CEV, 52 received CEV after EP, and 12 patients were re-treated with the same regimen. Possible prognostic factors in the crossover group were identified at time for first-line chemotherapy and at relapse. The EP therapy comprised five courses of

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0169-5002/$ – see front matter
doi:10.1016/j.lungcan.2004.10.016

etoposide 100 mg/m^2 IV and cisplatin 75 mg/m^2 IV on day 1, followed by oral etoposide 200 mg/m^2 daily on day 2–4. The CEV-regimen was five courses of epirubicin 50 mg/m^2, cyclophosphamide 1000 mg/m^2, and vincristine 2 mg, all IV on day 1.
Results: Patients administered second-line chemotherapy lived significantly longer with median survival 5.3 months compared to 2.2 months in patients with best supportive care only ($P < 0.001$). The best supportive care patients had significantly worse PS status and more resistant disease. The crossover treatment group was well balanced regarding possible prognostic factors prior to initial treatment and at recurrence. No difference in survival was found ($P = 0.71$). Univariate analysis revealed PS at recurrence, objective tumour response from initial chemotherapy, disease stage at first-line, LDH-, NSE-, and ALP at first-line to be significant prognostic factors for survival in the second-line setting. In a multivariate analysis, only PS at time of recurrence remained an independent prognostic factor ($P < 0.0001$). **Conclusion:** Patients administered second-line chemotherapy had significantly longer survival than patients administered best supportive care. However, this difference can be explained by more negative prognostic factors in the best supportive care group. No survival difference between EP and CEV crossover chemotherapy was found. Multivariate analysis revealed PS at time of relapse as the only independent predictor of survival in the crossover recurrent SCLC group.

1. Introduction

Combination chemotherapy as first-line treatment in small cell lung cancer (SCLC) is associated with high objective response rates and prolonged survival [1]. Long-term survival is however, achieved only in a minority of patients. This is most often seen in limited-stage disease (LD), whereas long-term survival is uncommon in extensive-stage disease (ED) [2,3]. The majority of these patients will relapse, usually within the first year after diagnosis. The clinical benefit of chemotherapy in the relapse situation is significantly less when compared to response and survival rates from first-line chemotherapy. There is presumably some benefit from re-treatment, however, no randomised trial have ever been performed with active second-line chemotherapy versus best supportive care. The magnitude of clinical benefit has been suggested to correlate with type of first-line chemotherapy, treatment-free period, the extent of disease at relapse, and performance status (PS) [4,5].

Combination chemotherapy with cisplatin and etoposide (EP-regimen) is accepted as the standard regimen in SCLC, regardless of disease stage [6–8]. However, anthracyclin-based regimens with cyclophosphamide, doxorubicin, and vincristin (CAV-regimen) have been widely used due to treatment tradition and more convenient administration. The EP and the CAV regimens have been acknowledged as non-cross resistant regimens [9,10]. Based upon the Goldie–Coldman model, alternating non-cross resistant chemotherapy is expected to enhance treatment efficacy and overall survival [11]. The alternating approach using these two regimens has been explored in several trials, but without documenting any clinical benefit [12–14]. In the second-line setting, EP chemotherapy has been reported to give better response rates in patients primarily treated with CAV regimens, when compared to the reverse sequence [10,15]. Patients relapsing shortly after completed induction therapy have less chance of tumour response compared to patients relapsing after longer intervals. Furthermore, reduced PS, and weight loss at relapse are associated with inferior survival [4,5].

The original study was initiated with the main objective to evaluate, in a randomised fashion, whether EP was superior to the three-drug combination of CEV (cyclophosphamide, epirubicin and vincristin) [6]. The protocol recommended crossover-therapy with the alternative regimen at relapse. The aim of this crossover part of the study was to assess any survival benefit of the EP-regimen, in comparison to the CEV crossover regimen. The effect of second-line chemotherapy could also, in a non-randomised fashion, be compared with best supportive care.

2. Patients and methods

2.1. Patients, eligibility and staging

Among 436 patients previously treated with EP or CEV in a randomised fashion [6], detailed follow-up information regarding recurrence and re-treatment

were available in 382 patients (88%). Of these, 286 patients (75%) were diagnosed with relapse of which 120 received further chemotherapy. A total of 108 patients (38%) were administered crossover therapy with the other cytostatic combination at time of relapse, while twelve patients (4%) were re-treated with the induction regimen. The other 166 patients were not treated with cytotoxic agents, but received best supportive care inclusive palliative radiotherapy when needed. At recurrence, the date of relapse and PS was registered in all patients. The choice of whether to administer second-line chemotherapy or not was based on judgements by the individual physician to what extent more chemotherapy might benefit the patient.

Patients included in the relapse crossover protocol should fulfil the following eligibility criterias: completed induction chemotherapy either with the EP or CEV-regimen; clinical and radiological recurrent disease; fit to tolerate second-line chemotherapy; WHO PS ≤ 3; upper age 75 years; and adequate bone marrow and renal function (white blood cell count $\geq 3000\,\mu l^{-1}$, platelet count $\geq 125{,}000\,\mu l^{-1}$, serum creatinine < 125 μmol/l). Patients considered to benefit for second-line chemotherapy were re-staged according to localised disease in the chest only (LD) or distant disease (ED) based on a simplified investigation with physical examination, chest X-ray and followed by subsequent exploration with ultrasound, bone scan and/or CT scanning. The classification as LD or ED was in accordance to accepted guidelines.

2.2. Therapy, evaluation and follow-up

At relapse, eligible patients received the crossover first-line regimen. The EP-regimen consisted of etoposide 100 mg/m^2 followed by cisplatin 75 mg/m^2, both intravenously (IV) on day 1. In addition, daily oral etoposide 200 mg/m^2 were administered on days 2–4. Standard pre- and posthydration procedures were followed in conjunction with cisplatin administration. The CEV-regimen consisted of epirubicin 50 mg/m^2, cyclophosphamide 1000 mg/m^2, and vincristine 2 mg, all IV on day 1. Dose-reductions were performed according to standard recommendations. For both chemotherapy regimens, the treatment was given up to five courses every 3 weeks unless intolerable toxicity, progressive disease, or patient refusal. Clinical and radiological evaluation was performed prior to the third course. For patients with progressive disease, the chemotherapy was terminated, while patients with stable disease or objective response received further courses. All patients were followed until death. Palliative radiotherapy was administered whenever needed based on individual patient symptoms.

2.3. Prognostic factors

Possible prognostic factors (demographic, clinical, laboratory) were registered prior to second-line chemotherapy. Factors of prognostic significance in the first-line setting [16] were also assessed for their predictive prognostic value following second line chemotherapy. Laboratory values were dichotomised according to normal or elevated values. PS assessed prior to first-line induction chemotherapy and at time of relapse was categorised as PS 0–1 versus ≥ 2. Response to induction chemotherapy was categorised as CR/PR and SD/PD, and age as ≤ 65 versus >65 years. The time to relapse period was dichotomised in ≤ 3 months versus >3 months. Based on the effect from the first-line therapy and time to relapse, the patients were grouped as sensitive or refractory relapse according to the following definitions: resistant grade 1, completed or not completed first-line chemotherapy due to NC or PD and relapse ≤ 3 months; resistant grade 2, first-line chemotherapy completed with CR/PR and relapse ≤ 3 months; sensitive grade 1, relapse >6 months; sensitive grade 2, relapse >3 to ≤ 6 months [17].

2.4. Statistical methods

Categorical variables were analysed using Pearson Chi-Square Test or Fisher's Exact Test. Continuous variables were analysed using the Wilcoxon rank-sum and the Kruskal–Wallis test. In the cohort of patients receiving crossover therapy, survival was calculated from initiation of second-line chemotherapy. The treatment-free period was in all patients calculated from the date of the last induction course till relapse was diagnosed by clinical and radiological investigation. When comparison between active treatment or not, survival was calculated from date of relapse. All survival analysis was calculated using the Kaplan–Meier product-limit method [18] with the log-rank test applied for comparison of survival. Univariate analyses related to survival estimates were performed on possible prognostic factors at start of initial chemotherapy and prior to the second-line chemotherapy, using the method of Kaplan–Meier. All variables reaching statistical significance (<0.05) in the univariate analysis were tested in the multivariate analysis using the proportional hazards model of Cox

[19]. This analysis was performed to assess the independent impact on survival of each pre-treatment variable in the presence of other variables. Probability for forward stepwise entry and removal was set at 0.05 and 0.10, respectively. The significance level was in all tests set at 0.05 using two-sided test.

3. Results

3.1. Patients

Among 286 patients diagnosed with relapse, 120 patients (42%) were administered second-line chemotherapy while the remaining 166 patients (58%) received best supportive care (Table 1). There was no difference between the groups with regard to gender, age at relapse, number of administrated induction courses, initial staging and initial PS status. At relapse, patients receiving best supportive care had significantly lower PS status ($P = 0.04$), shorter treatment-free period with a higher proportion of patients with treatment-free period $\leq$3 months ($P = 0.001$), and more resistant disease ($P < 0.001$).

Among patients treated with second-line chemotherapy, 108 patients received the crossover regimen and 12 patients were retreated with the induction regimen. Fifty-two patients with previous EP chemotherapy were administered CEV, while 56 with previous CEV received EP. Patient characteristics for the crossover group are presented in Table 2. The treatment groups were well balanced at start of crossover therapy. Median age was 63 years and 39% were female. The large proportion of WHO PS 0–1 patients at first-line treatment (74%) had declined to 52% at the time for second-line therapy. Still, one third had limited disease (LD) at time of relapse. The treatment-free period was similar in the two groups with median 4.0 and 3.9 months in the CEV group and EP group, respectively. The distribution between sensitive and resistant disease was equal in the two crossover groups. About one-third was

Table 1 Characteristics of all patients at relapse

Characteristics		Best supportive care ($N = 166$)	Second-line chemotherapy ($N = 120$)	P-value
Gender (%)	Male	63	63	0.99
	Female	37	37	
Age at relapse (years)	Median	64	63.5	0.61
	Range	40–76	40–75	
No. of induction courses at first-line	Median	5.0	5.0	0.06
	Mean	4.6	4.9	
Initial staging (%)	LD	51	47	0.45
	ED	49	53	
Initial PS (WHO)[a] at first-line (%)	0–1	73	75	0.69
	$\geq$2	27	25	
PS (WHO)[a] at recurrence (%)	0–1	38	50	0.04
	$\geq$2	62	50	
Treatment-free period (months)	Median	2.6	3.9	0.19
	Range	0.2–29.1	0.3–53.0	
Treatment-free period (%)	$\leq$3 (months)	57	37	0.001
	>3 (months)	43	62	
Sensitivity/resistance to treatment (%)[b]	Resistant grade 1	21	4	
	Resistant grade 2	36	36	< 0.001
	Sensitive grade 2	23	28	
	Sensitive grade 1	20	32	

Comparing between patients administered second-line chemotherapy and those receiving best supportive care.

[a] Performance status according to the World Health Organization.

[b] Resistant grade 1, completed or not completed first-line chemotherapy due to NC or PD and relapse $\leq$3 months; resistant grade 2, first-line chemotherapy completed with CR/PR and relapse $\leq$3 months; sensitive grade 1, relapse >6 months; sensitive grade 2, relapse >3 months to $\leq$6 months.

Table 2 Characteristics of all eligible patients receiving crossover second-line treatment

Characteristics		Crossover CEV ($N=52$)	Crossover EP ($N=56$)	P-value
Gender (%)	Male	63	59	0.63
	Female	37	41	
Age at relapse (years)	Median	64	62.5	0.85
	Range	42–75	40–75	
PS (WHO)[a] at recurrence (%)	0–1	54	50	0.69
	2–3	46	50	
Relapse status (%)	LD	33	32	0.95
	ED	67	68	
Treatment-free period (months)	Median	4.0	3.9	0.51
	Range	0.7–53.0	0.3–30.0	
No. of induction courses at first-line	Median	5.0	5.0	0.17
	Mean	4.7	4.9	
Initial staging (%)	LD	40	50	0.32
	ED	60	50	
Initial PS (WHO)[a] at first-line (%)	0–1	73	75	0.82
	2	27	25	
Initial response rate (RR) at first-line (%)	CR/PR	78	79	0.93
	SD/PD	22	21	
Sensitivity/resistance to treatment (%)[b]	Resistant grade 1	6	2	0.65
	Resistant grade 2	37	39	
	Sensitive grade 2	25	30	
	Sensitive grade 1	33	29	

[a] Performance status according to the World Health Organization.
[b] Resistant grade 1, completed or not completed first-line chemotherapy due to NC or PD and relapse ≤3 months; resistant grade 2, first-line chemotherapy completed with CR/PR and relapse ≤3 months; sensitive grade 1, relapse >6 months; sensitive grade 2, relapse >3 months to ≤6 months.

categorised as with sensitive grade 1 disease, one-third with sensitive grade 2, and one-third with resistant grade 2. Few patients had resistant grade 1 disease.

3.2. Relapse treatment and follow-up

During the relapse therapy, the recommended five chemotherapy courses were completed in only 29% of patients treated with crossover EP and in 33% of those with crossover CEV ($P=0.32$). The median number of administered courses at relapse was three in both groups, with mean 3.4 and 3.2 courses in the crossover CEV and EP arm, respectively. Due to disease progression or unacceptable toxicity, large proportions of the patients in both groups, 26 (46%) with EP and 17 (33%) with CEV, received only one or two courses. Palliative radiotherapy was administered to 36% of the second-line treatment group, while this was the case in 50% ($P=0.017$) of the best supportive care group.

3.3. Survival

There was no survival difference between the two crossover treatment groups. The median survival was 3.9 and 4.5 months in the crossover EP and CEV group, respectively (Fig. 1, $P=0.71$). The 1- and 2-year overall survival in the crossover EP arm was 16% and 0% compared to 12% and 2% in the crossover CEV arm. No patients were alive at 3 years. In the LD subgroup, the median survival was 6.4 and 5.4 months in the crossover EP ($N=17$) and CEV ($N=17$) arm ($P=0.25$), respectively, whereas the corresponding result in the ED subgroup was 3.9 and 4.4 months (EP, $N=39$; CEV, $N=35$) ($P=0.29$). Patients with resistant disease at relapse ($N=45$) had a median survival of 3.9 and 3.7 months ($P=0.18$), compared to median survival 4.7 and 5.6 months in sensitive patients ($N=63$) ($P=0.20$) in the crossover EP and CEV group, respectively (plots not shown).

Comparison between the second-line chemotherapy and the best supportive care group reveals a significant better survival in favour

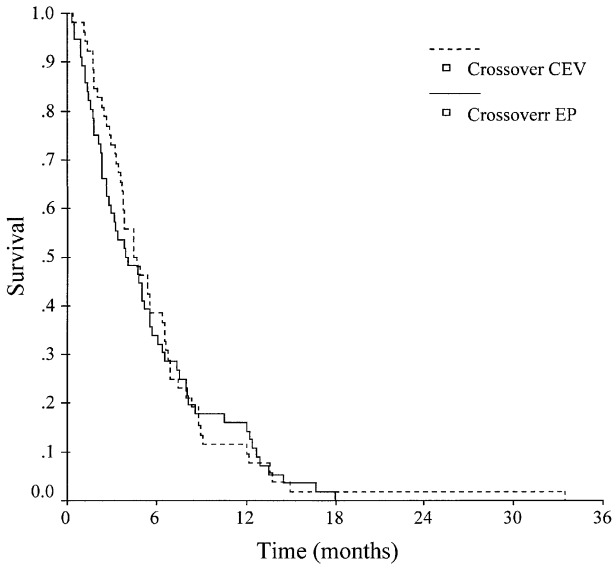

Fig. 1 Overall survival of all SCLC patients ($N=108$) according to treatment arm ($P=0.86$). Crossover CEV (dotted line), $N=52$; crossover EP (solid line), $N=56$.

of the chemotherapy group, with a median survival of 5.3 and 2.2 months, respectively (Fig. 2, $P<0.0001$).

3.4. Prognostic factor analysis in the crossover population

In total, 19 different demographic, clinical, and laboratory variables in the actively treated group were tested for prognostic significance in univariate analyses (Tables 3 and 4). Seven variables were found to be possible prognostic indicators for survival in recurrent disease. The most prominent factors were PS status at time of relapse ($P<0.0001$, Fig. 3) and clinical response of initial induction chemotherapy ($P=0.0002$), whereas PS assessed prior to the first-line chemotherapy did not associate significantly with survival following relapse. Among baseline laboratory determinants at first-line chemotherapy protocol, LDH ($P=0.002$), NSE ($P=0.002$), and ALP ($P=0.04$) were found to have prognostic significance in the relapse situation, while γGT, haemoglobin, WBC, platelet count and ESR were without prognostic relevance. Stage distribution (LD versus ED) assessed prior to first-line therapy was significantly associated with prognosis following relapse ($P=0.01$). Stage distribution assessed at time for relapse tended in the same direction ($P=0.06$). Length of the treatment-free period differentiation between therapy-sensitive and -resistant patients did not show any prognostic relevance in the crossover group. Age, gender, and initial weight loss had no influence on survival.

Since different prognostic factors may covariate, all statistically significant variables from the univariate analyses were included in Cox multivariate regression analyses to identify possible independent prognostic factors. Due to missing data, these calculations were performed on data from 88 patients. PS at relapse emerged as the only, however, a highly significant independent prognostic indicator ($P<0.001$, Table 5).

4. Discussion

Recurrent SCLC is inevitably fatal and treatment is palliative with short survival expectations. A large proportion of the patients have chemotherapy resistant disease at relapse, either related to intrinsic or acquired drug resistance. According to the Goldie–Coldman model, alternating non-cross resistant schedules would theoretically enhance the probability of treatment response [11]. Randomised phase III trials have, however, failed to prove this approach beneficial in chemotherapy naïve SCLC [12–14]. Based upon the same theoretical considerations and problems with acquired drug resistance, re-treatment with a non-cross resistant regimen is considered the most optimal approach in relaps-

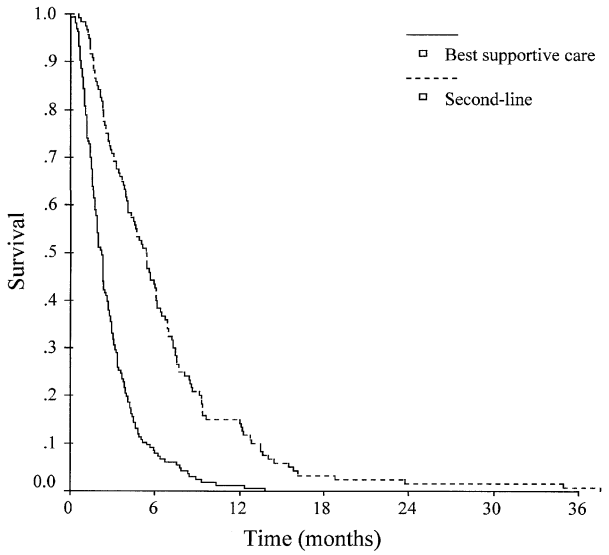

Fig. 2 Overall survival of all SCLC patients with detailed follow-up, according to actively treatment with second-line chemotherapy or not ($P < 0.0001$). Second-line (dotted line), $N = 120$; best supportive care (solid line), $N = 166$.

ing patients. However, the theoretical model is only partly applicable in SCLC, as crossover therapy appears beneficial for rapid relapses with short (≤3 months) treatment-free intervals [4,5] whereas re-induction of the previous regimen appears equally effective after long (>6 months) treatment-free periods [20,21].

Since the chemotherapy combinations EP and CEV in the prestudy period was considered non-cross resistant [9,10], our treatment recommen-

Table 3 Prognostic parameters at time of recurrence as predictors for disease-specific survival following crossover treatment

Characteristics		No. of patients	Median survival (months)	*P*-value (Log-rank test)
Gender	Male	66	3.8	0.18
	Female	42	5.0	
Age at recurrence (years)	≤65	69	4.7	0.87
	>65	39	4.4	
Type of crossover therapy	CEV	52	4.5	0.71
	EP	56	3.9	
PS (WHO)[a]	0–1	56	6.6	< 0.0001
	2–3	52	2.4	
Extent of disease at relapse	LD	34	5.4	0.06
	ED	71	3.9	
Treatment-free period (months)	≤3	42	3.8	0.35
	>3	66	4.9	
Sensitivity/resistance to treatment (%)[b]	Resistant grade 1–2	45	3.8	0.27
	Sensitive grade 1–2	63	5.0	

[a] Performance status according to the World Health Organization.
[b] Resistant grade 1, completed or not completed first-line chemotherapy due to NC or PD and relapse ≤3 months; resistant grade 2, first-line chemotherapy completed with CR/PR and relapse ≤3 months; sensitive grade 1, relapse >6 months; sensitive grade 2, relapse >3 months to ≤6 months.

Table 4 Prognostic parameters at time of first-line chemotherapy as predictors for disease-specific survival following crossover treatment

Characteristics		No. of patients	Median survival (months)	*P*-value (Log-rank test)
PS (WHO)[a]	0–1	80	4.9	0.15
	2	28	3.3	
Extent of disease	LD	49	5.6	0.01
	ED	59	3.7	
Response rate (RR)	CR/PR	84	5.0	0.0002
	SD/PD	23	2.9	
Weight loss (%)	No	51	5.0	0.80
	≤10	38	3.6	
	>10	18	4.4	
ESR (mm/h)	≤30	44	5.0	0.27
	>30	61	4.1	
Hemoglobin (g/dl)	Normal	70	4.8	0.42
	Anaemia	38	3.3	
WBC count (10^9/l)	≤10	82	3.9	0.21
	>10	26	4.9	
Platelet count (10^{12}/l)	≤400	73	4.4	0.80
	>400	35	4.5	
LDH (U/l)	≤450	56	5.7	0.002
	>450	50	3.8	
Alkaline phosphatase (U/l)	≤270	82	4.7	0.04
	>270	23	3.3	
γ-Glutamyl transferase (U/l)	Normal	77	4.5	0.38
	Elevated	29	4.4	
NSE (μg/l)	≤13	26	7.5	0.002
	>13	66	3.8	

[a] Performance status according to the World Health Organization.

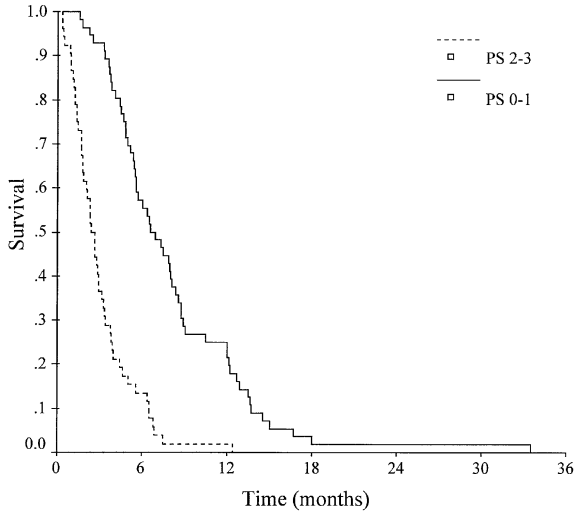

Fig. 3 Overall survival of all SCLC patients according to recurrent PS status ($P < 0.0001$). PS 2–3 (dotted line), $N = 52$; PS 0–1 (solid line), $N = 56$.

Table 5 Results of Cox regression analysis ($N=88$)

Covariate		Relative risk	95% CI		*P*-value
			Lower	Upper	
PS (WHO)[a] at recurrence	0–1 vs. 2–3	4.2	2.5	7.3	<0.001
NSE at first-line (μg/l)	≤13 vs. >13	1.5	0.8	2.6	0.20
LDH at first-line (U/l)	≤450 vs. >450	1.4	0.8	2.2	0.21
ALP at first-line (U/l)	≤270 vs. >270	1.4	0.8	2.6	0.23
Extent of disease at relapse	LD vs. ED	1.3	0.8	2.0	0.33
Extent of disease at first-line	LD vs. ED	1.2	0.7	2.0	0.40
Initial response rate (RR) at first-line	CR/PR vs. SD/PD	0.7	0.4	1.5	0.45

[a] Performance status according to the World Health Organization.

dation at relapse was the other alternative regimen. The second-line crossover treatment was non-randomised and thus subjected to the risk of selection bias. Moreover the relapse study population may be considered a selected subgroup since only a limited part (42%) of the initially treated patient population were considered to be suitable for second-line chemotherapy at the time of disease progression [6]. When compared to the best supportive care group, the second-line chemotherapy group survived significantly longer. This can be explained by the better PS status, one of the most important prognostic indicators for survival in SCLC. The two crossover chemotherapy groups were comparable with respect to demographic, clinical, and treatment characteristics at time for relapse. There was no difference in survival between the crossover regimens, with an observed median survival of 4.4 months, and no patients survived 3 years or more. Based on this crossover study, the data lend no support for favouring one of these regimens over the other in the relapse situation.

Only two studies have strictly compared EP chemotherapy in previously anthracyclin (CAV) based first-line chemotherapy and vice versa in SCLC patients [10,15]. In the study by Evans et al. [10] of 78 patients previously treated with the CAV regimen, 43 patients (55%) achieved objective response (CR/PR) from re-treatment with the EP-regimen. Twenty-four patients had LD-SCLC whereas 54 had ED-SCLC. The median survival for LD and ED patients responding to the second-line chemotherapy were 10.5 and 6.5 months, while patients with stable or progressive disease had shorter median survival time, 4.5 and 3.7 months, respectively. In contrast, Shepherd et al. [15] reported that re-treatment with the CAV regimen in 29 patients previously treated with EP revealed an objective response in eight patients (28%), with 3.7 months overall median survival, 8.5 and 2.3 months in CR/PR and SD/PD patients respectively. The results from the study by Shepherd and co-workers are comparable with the results in our crossover CEV arm, but survival in our crossover EP arm is, however, somewhat lower.

Several prognostic indicators for survival have been identified in first-line and second-line chemotherapy studies of SCLC. Extent of disease (LD versus ED), performance status, weight loss, and LDH have been proposed the strongest prognosticators in first-line treatment [3,22,23], whereas initial treatment response and length of therapy-free interval have been the most important prognostic factors for survival in the relapse setting [4,5]. In the initial randomised phase III study, multivariate analyses performed prior to first-line therapy demonstrated that extent of disease, PS, weight loss, LDH, gender, platelet count, and NSE were of independent prognostic value[16]. In the relapse setting, we detected, by univariate analyses, five demographic and clinical variables at time for first-line therapy and two variables at time for second-line therapy to be possible significant predictors of survival in the crossover population. Of these, only PS assessed at relapse appeared to have an independent prognostic impact. None of the other variables were found to have independent prognostic impact at relapse.

The large difference in survival between the actively treated second-line therapy patients versus best supportive care was not surprising. The selection for second-line therapy was pragmatic, based on the individual examination and judgement from the responsible physician whether further chemotherapy would benefit the patient or not. The highly significant impact of PS status on expected survival supports our selection.

EP chemotherapy is considered the standard first-line regimen in SCLC [6–8], while there still is no consensus on second-line therapy. Though no randomised phase III trial hitherto has compared chemotherapy or best supportive care in recurrent SCLC, there is consensus that these patients, if considered fit, should be offered second-

line chemotherapy. Since the prognosis for relapsing SCLC patients is miserable, novel cytostatic drugs are explored in this setting [24,25]. Such new drugs as the topoisomerase I inhibitors, show high activity, but with no substantial increase in long-term (1 year) survival [26–29]. One large phase III study in recurrent SCLC (211 patients), comparing topotecan monotherapy versus the three-drug combination of CAV, did not show any difference in survival. Median survival was 6.3 and 6.2 months respectively, and 1 year survival was 14% [30]. Though the topotecan arm showed a better symptom improvement profile ($P < 0.05$) in four of eight categories. Two other studies, using paclitaxel in chemotherapy-resistant patients (therapy-free interval ≤ 3 months), demonstrated promising response rates, but moderate survival [31,32]. The 1 year survival in these studies were 9 and 12%.

In conclusion, our study showed no difference in survival between the crossover chemotherapy regimens EP and CEV in relapsed SCLC. Moreover, no differences were observed in neither resistant nor sensitive patients. Our findings of equal benefit from these two crossover regimens, and survival data similar to more novel regimens, either combination regimen can be used in the second-line setting. PS is the most important independent prognostic indicator at relapse, and should be used in the treatment decision-making process by assessing the potential for treatment benefit.

Acknowledgements

This study was initiated and performed by the Norwegian Lung Cancer Study Group. The financial support from the Norwegian Cancer Society is acknowledged.

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Paper III

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Paper IV

Radiotherapy and Oncology 75 (2005) 141-148
www.elsevier.com/locate/radonline

Phase III randomised trial

Immediate or delayed radiotherapy in advanced non-small cell lung cancer (NSCLC)? Data from a prospective randomised study

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Abstract

***Background and purpose*: To compare the course of symptoms and health-related quality-of-life (HRQOL) after immediate thoracic radiotherapy (TRT) between symptomatic (S) and non-symptomatic (NS) patients with advanced NSCLC.**

***Patients and methods*: 407 stage III/IV patients were initially treated with immediate TRT within a randomised phase III trial comparing different fractionation schedules. At inclusion, patients were prospectively stratified according to presence (S) or absence (NS) of tumour-related chest/airway symptoms to facilitate comparison between these groups. The EORTC QLQ-C30 and LC-13 were used for symptom and HRQOL assessments at baseline and at regular intervals up to 1 year ($N=395$).**

***Results*: NS patients had significantly more favourable baseline characteristics when compared to S patients with a median survival of 11.8 versus 6.0 months ($P<0.0001$), respectively. At baseline, S patients demonstrated HRQOL scores inferior to those of NS patients ($P<0.01$) for most scales. Until week 14, NS patients developed more symptoms while S patients experienced symptom relief in most scales. After week 14, no significant differences could be observed between the groups.**

***Conclusion*: This study indicates that immediate TRT, given to patients with minimal/none chest symptoms, does not prevent development of disease-related symptoms and diminished HRQOL. A wait-and-see policy appears to be acceptable.**

Keywords: Palliative radiotherapy; Lung cancer; NSCLC; Immediate treatment; Quality-of-life

Most patients diagnosed with locally advanced or metastatic non-small cell lung carcinoma (NSCLC) will present with or develop symptoms caused by intrathoracic malignancy. The most frequent symptoms are shortness of breath (dyspnoea), cough and haemoptysis, while chest pain, fatigue, and reduced performance status (PS) are common accompanying symptoms [8,16]. The psychological burden of being diagnosed with advanced lung cancer is threatening for patients and their families, due to poor prognosis and fear of severe symptoms [1,4,15].

Radiotherapy (RT) yields effective relief of symptoms caused by intrathoracic tumours inducing central airway obstruction [8,16,22]. Different RT fractionation schedules have been employed in palliative thoracic radiotherapy (TRT), but no schedule has proven superior with respect to symptom palliation [18,24]. For patients with no or only minimal thoracic symptoms, it is still questioned when the appropriate time is to start TRT [5-7,9,11,21]. A hypothesis for administrating immediate treatment also to NS patients has been based on the assumption that early treatment will yield long-term symptom control and maintain HRQOL.

In a recent randomised study from the Medical Research Council (MRC) [12] comparing immediate palliative TRT with TRT delayed until symptoms developed, there were no differences with respect to survival, health-related quality-of-life (HRQOL) or adverse events.

In our previously published phase III fractionation study (17 Gy/2 fractions versus 42 Gy/15 fractions versus 50 Gy/25 fractions), patient-reported HRQOL and clinician-assessed symptom relief of dyspnoea, cough and haemoptysis were

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primary end-points [23]. Since patients were prospectively stratified according to clinician-assessed presence (S patients) or absence (NS patients) of categorised chest/airway symptoms at study entry, the trial data could also be used to assess the symptomatic efficacy of immediate palliative TRT in NS versus S patients. The research questions were as follows: will immediate TRT prevent development of tumour related central airway symptoms, and what are the side effects of immediate TRT in otherwise non-symptomatic NSCLC patients.

Patients and methods

Patients

This study on the symptomatic efficacy of palliative immediate TRT in NS versus S patients is based on 407 patients included in a TRT fractionation trial between December 1993 and September 1998. The eligibility criteria were: histologically/cytologically confirmed NSCLC, stage III or IV disease, age $\geq$18, Karnofsky performance status (PS) $\geq$40%, expected survival $\geq$2 months, centrally located tumour with airway symptoms present or threatening central airway obstruction, no previous TRT, and no previous malignant disease. Among patients with stage IIIA disease, only those with poor prognostic factors like tumour diameter ($>$7 cm, Karnofsky PS $\leq$70% or weight loss $\geq$10% the last 6 months were eligible. Previous chemotherapy was permitted.

The distinction between presence and absence of chest/airway symptoms was based on the clinical examination prior to randomisation, and the patients were stratified accordingly in the database. The examining physician categorised symptoms such as cough, haemoptysis, pain, nausea and vomiting, hoarseness, fatigue, appetite loss and dysphagia according to the following 4-point rating scale: none (score 1), mild (score 2), moderate (score 3), and severe (score 4). Dyspnoea was categorised in a 6-point scale: able to climb hills or stairs without dyspnoea (score 1), walk any distance on flat ground without dyspnoea (score 2), walk more than 100 m without dyspnoea (score 3), dyspnoea from walking 100 m or less (score 4), dyspnoea from mild exertion (e.g. undressing) (score 5), and dyspnoea at rest (score 6). Patients categorised with none or minimal thoracic symptoms should have scores $\leq$2 and $\leq$3 related to the symptom scales and dyspnoea scale, respectively. Patients with higher scores were categorised as symptomatic.

The local pathologist established the histopathological diagnosis according to the WHO classification [25]. The Regional Ethics Committee approved the study. Before randomisation, informed written consent was obtained from all patients.

Clinical examination and staging

At study entry physical examination, radiological investigations (chest X-ray and/or CT scan of chest including liver and adrenal glands), and chemistry profile [cell counts, erythrocyte sedimentation rate (ESR), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma glutamyl transpeptidase (γGT), and neuron specific enolase (NSE)] were performed in all patients. Karnofsky PS and weight loss during the last 6 months were registered. Cerebral CT/MRI examinations or bone scans were carried out when indicated due to symptoms. The clinical stage classification from 1986 was used [19].

Thoracic radiotherapy (TRT)

TRT was given as two opposing anterior-posterior fields with a 1.5-2-cm margin, encompassing the primary tumour and the regional mediastinal lymph nodes. The portals should not exceed an area of 200 cm^2, and the supraclavicular region was not routinely treated unless palpable nodes or primary tumour were located in the apical region of the lung. Megavoltage RT with 6 or 15 MV photon beam was given with the following fractionation schedules: 17 Gy/2 fractions (1 week); 42 Gy/15 fractions (3 weeks); 50 Gy/25 fractions (5 weeks). For the 42 Gy/15 fractions scheme, a shield was inserted in the posterior field to reduce the spinal cord exposure to 2.6 Gy per fraction, and thereby, not exceeding an ED-value of 1180 ret. The maximal length of spine irradiation was set to 12 cm. Lengths above 12 cm were not allowed unless a lead block was inserted. To prevent possible side effects from the largest fractions (8.5 Gy$\times$2), these patients were prophylactically administered prednisolone 50 mg bid days -1, 0, and $+1$. TRT start was within 1 week from randomisation.

Health-related quality-of-life (HRQOL)

For quality-of-life assessments, the EORTC QLQ-C30 and the lung cancer specific module QLQ-LC13 were used [2,3]. HRQOL improvements are indicated by increased scores of functional scales and reduced scores of symptom scales [13]. The patients filled out the first questionnaire prior to TRT start. Later questionnaires were mailed to the patients at 2, 6, 14, 22, 30, 38, 46 and 54 weeks from treatment start. Those who were non-compliant after one reminder received no further questionnaires.

Follow up

Planned follow-up with clinical examination, rating of the clinician assessed symptom scales and chest X-ray, was performed at 2, 6 and 14 weeks after TRT. Improvement was defined as subsequent rating of at least one better score in the less symptomatic direction of the rating scales. Follow-up beyond week 14 was optional according to the individual patient's need and follow-up policy at the respective institutions. All patients were followed until death or for a minimum of 3 years.

Statistical methods

The Cancer Research Trial Office at the University Hospital in Trondheim performed the randomisation based on a block-randomisation method for each radiotherapy centre. At inclusion, stratification between S patients and NS patients was performed. Categorical variables were analysed using the Pearson χ^2-test. Survival was calculated from randomisation date using the Kaplan-Meier product-limit method with the log-rank test applied for comparison of survival. The treatment effect at each assessment time performed by the doctors was evaluated by using

the Pearson χ^2-test. The significance level was set at .05, using a two-sided test.

Differences in HRQOL were calculated using group scores for the mean value of each variable [13], and differences were tested using the Mann-Whitney rank sum test. A difference in mean scores ≥ 10 points was considered clinically significant, while a difference <10 points was considered as a moderate change and of uncertain clinical relevance [14,20].

Results

Patient population

Three hundred patients were categorised as having moderate to severe symptoms (S), while 107 had none or minimal symptoms (NS). Patient characteristics are given in Table 1. When compared to the NS group, S patients had significantly more advanced stage, lower Karnofsky PS, more weight loss, and higher γGT, ALP, and ESR. The different fractionation schedules were well balanced between NS and S groups. Regarding two patients in the NS group with Karnofsky PS ≤ 60, one had lower limbs paresis, and the other a longstanding serious chronic obstructive lung disease where the lung tumour was found accidentally. Both were categorised without chest symptoms from tumour.

Treatment

All, but six patients were chemonaive at inclusion, four in the NS group and two in the S group. Every patient in the NS group completed the planned RT. Among S patients, three did not start TRT and 26 terminated the TRT prematurely due to disease progression. Only two of these 29 patients were treated in the hypofractionated schedule. Twenty-seven percent ($n=29$) and 21% ($n=64$) of the NS and S patients, respectively, were reirradiated to metastatic sites outside the chest ($P=0.73$), most often with 8-10 Gy in one fraction or 20 Gy per five fractions. After completion of TRT, a small minority of patients received palliative chemotherapy at progression, four patients in the S group and three patients in the NS group.

Survival

Overall survival according to stratification is shown in Fig. 1. There is a significant survival difference in favour of the NS group with a median survival of 11.8 versus to 6.0 months ($P<0.0001$). 1-, 2- and 3-year survival were 48, 17, and 8% in NS patients and 23, 8, and 3% in S patients,

Table 1
Characteristics of all eligible patients according to assigned stratification

Characteristics		Non-symptomatic, *N* (%)	Symptomatic, *N* (%)	*P*-value
Gender	Male	83 (78)	222 (74)	0.46
	Female	24 (22)	78 (26)	
Age (years)	Median	68	69	0.96
	Range	44-86	41-88	
Histology	Squamous cell carcinoma	51 (48)	141 (47)	
	Adenocarcinoma	28 (26)	87 (29)	0.25
	Large cell carcinoma	5 (5)	27 (9)	
	Undifferentiated carcinoma	23 (21)	45 (15)	
Radiotherapy schedule	17 Gy/2 fractions	34 (32)	109 (36)	
	42 Gy/15 fractions	38 (36)	102 (34)	0.68
	50 Gy/25 fractions	35 (33)	89 (30)	
Karnofsky scale	90-100	68 (64)	69 (23)	
	70-80	37 (35)	196 (65)	<0.0001
	≤60	2 (2)	35 (12)	
Weight loss	None	61 (59)	88 (30)	
	<10%	26 (25)	93 (31)	<0.0001
	≥10%	16 (16)	114 (39)	
Stage	St III A	22 (21)	32 (11)	
	St III B	68 (64)	190 (63)	0.01
	St IV	17 (16)	78 (26)	
LDH (U/l)	Normal	70 (68)	194 (66)	0.66
	Elevated (>450)	33 (32)	102 (34)	
ALP (U/l)	Normal	87 (84)	213 (72)	0.02
	Elevated (>270)	17 (16)	82 (28)	
NSE (μg/l)	Normal	65 (76)	188 (78)	0.77
	Elevated (≥13)	20 (24)	53 (22)	
ESR (mm/h)	≤50	57 (56)	123 (44)	0.04
	50	45 (44)	157 (56)	
γGT (U/l)	Normal	89 (86)	211 (72)	0.003
	Elevated (f≥50, m≥80)	14 (14)	84 (28)	
Hgb (g/dl)	Normal	59 (55)	144 (48)	0.22
	Anemia (f<11.5, m<13.5)	48 (45)	155 (52)	

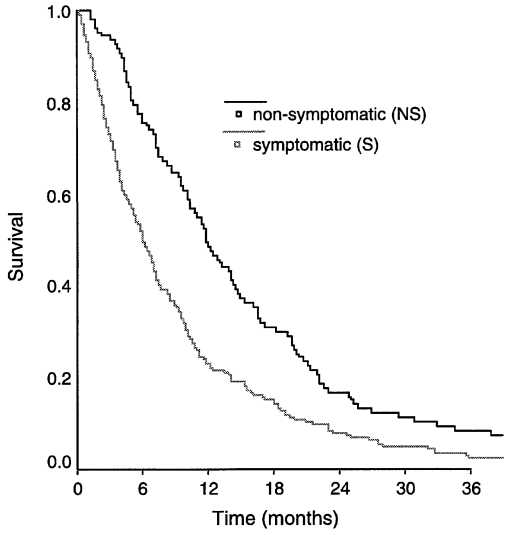

Fig. 1. Overall survival of all patients ($n=407$) with respect to the presence (grey line, $N=300$) or absence of chest/airway symptoms (black line, $N=107$) at baseline ($P<0.0001$).

respectively. There were no survival differences within the NS or S group with regard to the various TRT fractionation regimens. The median survivals were 11.5, 11.8, and 13.1 months in the NS group ($P=0.51$) and 6.6, 5.4, and 5.4 months in the S group ($P=0.68$), for 17 Gy/2 fractions, 42 Gy/15 fractions, and 50 Gy/25 fractions, respectively.

HRQOL analysis

Ninety-seven percent ($n=395$) of the eligible patients volunteered for the HRQOL part of the study. Of these, 97% ($n=385$) completed the baseline questionnaire before treatment. Subsequently, compliance declined over time, but was minimum 72 and 81% at week 54 (Table 2). A compliance difference between the groups was observed at weeks 2 and 14 in favour of the NS group.

In Table 3, the mean scores for all scales of the EORTC QLQ-C30 questionnaire and the single items cough, haemoptysis and dysphagia from the LC-13 module are presented for baseline and for eight different assessment times (2, 6, 14, 22, 30, 38, 46 and 54 weeks). Some of the most central HRQOL scales are graphically visualised in Fig. 2 with the corresponding 95% confidence intervals (CI). At baseline, all symptom scales and most physical scales and single items were significantly better in the NS group, when compared to the S group. Over time, there was a decline in mean scores for most functional scales and an increase in mean scores for symptom scales indicating a reduced HRQOL. From baseline till week 14, the NS group experienced increased symptoms, reduced function or steady state, whereas the S group experienced steady state or improvement. Thus, the total symptom burden in the two groups converged. A similar pattern was seen for dyspnoea and cough. Haemoptysis was stabilising in the NS group compared to improvement in the S group. In both groups there was a TRT-related increase in dysphagia during the first two weeks. Beyond week 14 and later in the follow-up period, deterioration in symptoms and functions developed in both groups with no consistent statistical significant differences. Moreover, exploration of the HRQOL data within the S and the NS group across the TRT schedules did not show any differences related to the TRT strategy (data not shown).

Table 2
Patient compliance (%) of HRQOL questionnaires for all patients assigned to stratification

Time of assessment	All patients, $N=395$	Non-symptomatic, $N=107$	Symptomatic, $N=288$	P-value
Week 0	97	96	98	0.35
Week 2	93	98	90	0.01
Week 6	87	92	85	0.06
Week 14	83	90	80	0.03
Week 22	80	86	77	0.09
Week 30	80	85	77	0.18
Week 38	76	81	72	0.19
Week 46	77	84	72	0.11
Week 54	81	82	80	0.76

Clinicians' symptom assessments

The clinician-assessed symptoms, displayed in Table 4, showed a similar pattern as the patients reported symptoms. At baseline, significant differences in symptoms were observed in favour of the NS group for all assessment scales except nausea, vomiting and dysphagia. Throughout the assessment period differences between the groups diminished. From week 14, there were no significant differences between the groups with respect to chest symptoms such as cough, haemoptysis, and chest pain or general symptoms like nausea, vomiting, and appetite loss. Dyspnoea, fatigue and hoarseness were, however, still less in the NS group (<0.05). Data for in-field malignancy or tumour-related symptoms from the radiotherapy field at time of death or 3-year follow-up, were recorded by a retrospective review of the patient records and radiological information. At time of death or 3-year follow-up, 62% of the S group still had symptoms from a chest tumour, while 50% of the NS group had developed local tumour-related symptoms ($P=0.12$).

Discussion

Patients with advanced NSCLC have a poor prognosis and the therapeutic options in order to improve survival are limited. Whereas TRT was the treatment of choice a decade ago, there is today evidence to use platinum-based chemotherapy in advanced NSCLC [10]. Still, TRT is an effective treatment modality: (1) in relieving intrathoracic symptoms in patients' not found to be candidates for palliative chemotherapy [24], (2) at local tumour progression after chemotherapy, or (3) as a general modality for symptomatic treatment with or without chemotherapy.

The treatment intention for these patients is palliative, either to prevent or to relieve symptoms. Thus, the principal

Table 3
Mean scores for EORTC QLQ-C30 and the single items cough, haemoptysis and dysphagia from the LC-13 module

	Baseline		Week 2		Week 6		Week 14		Week 22		Week 30		Week 38		Week 46		Week 54	
	S, $n=282$	NS, $n=103$	S, $n=256$	NS, $n=105$	S, $n=220$	NS, $n=97$	S, $n=165$	NS, $n=90$	S, $n=128$	NS, $n=74$	S, $n=100$	NS, $n=66$	S, $n=79$	NS, $n=56$	S, $n=57$	NS, $n=51$	S, $n=51$	NS, $n=41$
Functional scales[a]																		
Physical	60	77**	55	71**	56	70***	59	65	56	66	56	61	54	63	51	51	49	60
Role	56	71*	45	65**	51	68*	52	65*	54	65	54	59	54	61	48	51	48	66
Emotional	70	81	72	85*	75	83	76	82	74	82	75	80	74	81	76	75	77	79
Cognitive	81	86	78	88	81	86	81	83	80	83	82	82	80	78	78	70	82	79
Social	66	79*	63	76*	66	73	65	70	65	77	62	68	63	68	61	61	64	68
Global QOL	50	68**	50	60	51	59	51	56	50	58	48	54	46	56	41	48	45	54
Symptom scales[b]																		
Fatigue	50	33**	55	42*	52	44	49	42	50	42	50	43	49	42	53	53	54	44
Emesis	10	3***	15	7***	13	6	11	5	11	8	11	9	10	8	12	11	9	8
Pain	31	18*	32	23*	32	22*	34	26	35	27	38	34	37	28	34	35	39	30
Single items[b]																		
Appetite loss	37	13**	45	27**	39	23**	35	21*	37	23*	34	27	36	24	34	33	25	23
Dyspnoea	54	37**	53	38**	49	38*	50	45	57	47	58	52	60	51	57	57	60	50
Sleep disturbance	36	18**	33	18**	29	17*	27	20***	27	21	26	23	26	19	27	22	23	22
Constipation	29	16*	32	22***	30	21	27	23	30	25	30	22	28	23	28	37	16	30
Diarrhea	9	7	9	7	8	3	8	7	9	6	5	6	5	6	9	8	8	11
Cough	43	29**	43	34*	39	34	42	35	44	41	44	37	44	38	43	36	38	38
Haemoptysis	14	4**	10	6	6	2*	4	2	6	3	7	4	8	3	7	11	7	8
Dysphagia	8	2*	33	32	25	17	10	7	12	9	14	9	15	9	13	9	10	8

*$P \leq 0.01$, **$P \leq 0.001$, ***$P \leq 0.05$.
[a] Higher score indicates better function.
[b] Higher score indicates more symptoms.

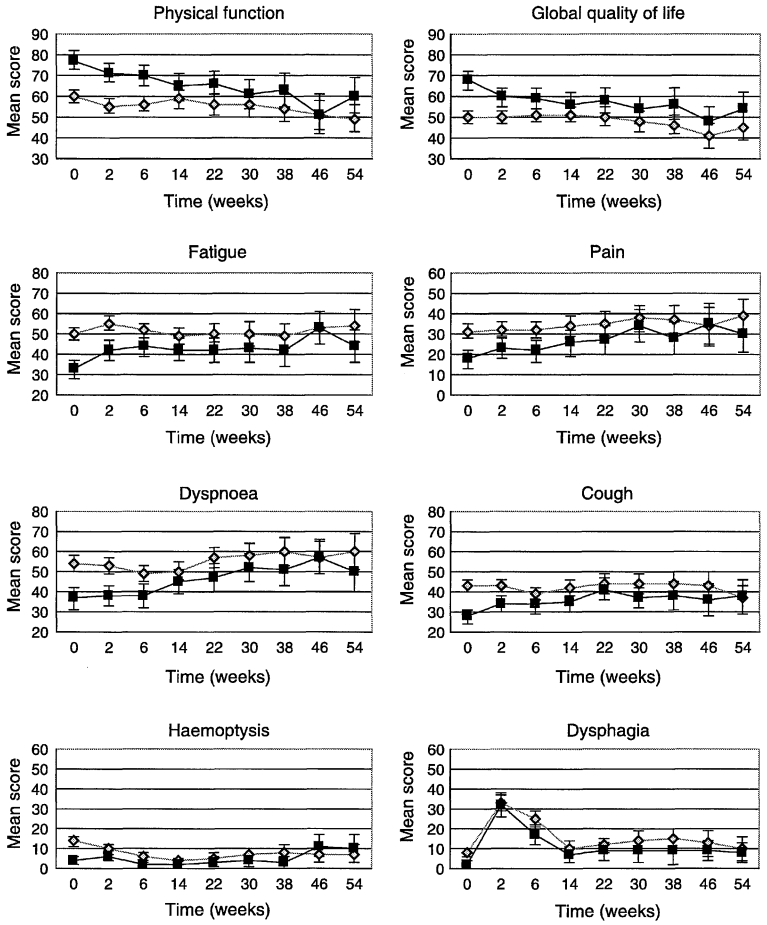

Fig. 2. Line plots representing mean values with 95% CI error bars for central HRQOL items. Grey lines represent symptomatic patients; black lines represent non-symptomatic patients.

aim should be the best possible symptom control with the least toxicity for the patient, the minimum of time confined to the treating clinic, and maintaining the most favourable HRQOL over time. In patients with tumour-related intrathoracic symptoms, the treatment rationale can be achieved with hypofractionationed TRT, yielding good palliation throughout most of the patient's lifetime. If TRT is given to patients without or with only minimal chest symptoms, the treatment goal should be symptom prevention with maintained HRQOL for a significant period of time. The challenge is to achieve this treatment goal without inflicting distressing side effects and reduced HRQOL in otherwise non-symptomatic patients.

As all patients in our previously published fractionation study [23] received immediate TRT, the possibility to assess whether or not NS patients achieved long-term absence from thoracic symptoms with maintained HRQOL when compared to S patients, existed.

The inferior survival in the group of symptomatic patients was consistent with less favourable baseline characteristics. It also corroborated the less favourable baseline HRQOL scores for most items. Over time, there was a deterioration of HRQOL scores for several scales, most evident in the non-symptomatic patients. While symptomatic patients showed a small and temporary trend toward improvement for emotional function, sleep disturbance, haemoptysis, and dyspnoea, there was a stabilisation or slow deterioration in the non-symptomatic group. For several scales the mean scores converged reflecting no clinically relevant differences between the groups (<10 points difference) after week 14.

Changes in patient-reported HRQOL data were consistent with the clinician-assessed data on intrathoracic symptoms. Moreover, when clinicians assessed tumour-related intrathoracic symptoms immediately before death or at 3 years follow-up, there was no statistically

Table 4
Clinician's assessments of symptoms at baseline, at week 2, 6 and 14 after completion of radiotherapy (symptoms present defined as score ≥ 2 in all symptom scales, and ≥ 3 in the dyspnoea scale)

	Baseline			2 weeks after completion of radiotherapy			6 weeks after completion of radiotherapy			14 weeks after completion of radiotherapy		
	Symptoms present/patients at risk (%)			Symptoms present/patients at risk (%)			Symptoms present/patients at risk (%)			Symptoms present/patients at risk (%)		
	S	NS	*P*-value	S	NS	*P*-value	S	NS	*P*-value	S	NS	*P*-value
Cough	249/297 (85)	62/106 (58)	<0.001	171/233 (73)	65/92 (71)	0.48	139/213 (65)	64/94 (68)	0.70	120/163 (74)	52/85 (61)	0.18
Haemoptysis	108/297 (36)	16/107 (15)	<0.001	35/233 (15)	7/92 (8)	0.16	14/214 (7)	6/94 (6)	0.81	13/163 (8)	7/85 (8)	0.38
Chest pain	148/298 (50)	30/107 (28)	<0.001	90/234 (38)	27/92 (29)	0.26	90/213 (42)	29/94 (31)	0.19	79/164 (48)	30/86 (35)	0.11
Nausea	31/298 (10)	5/107 (5)	0.29	50/234 (21)	9/92 (10)	0.07	36/213 (17)	6/94 (6)	0.07	21/164 (13)	8/85 (9)	0.42
Vomiting	22/297 (7)	3/107 (3)	0.36	27/234 (12)	2/92 (2)	0.06	21/213 (10)	4/94 (4)	0.25	11/164 (7)	3/85 (4)	0.56
Hoarseness	91/297 (31)	14/107 (13)	0.003	64/234 (27)	9/92 (10)	0.003	60/213 (28)	9/94 (10)	0.002	47/164 (29)	12/85 (14)	0.02
Fatigue	232/297 (78)	46/107 (43)	<0.001	179/230 (78)	59/92 (64)	0.01	157/212 (74)	55/94 (59)	0.008	111/164 (68)	45/86 (52)	0.002
Appetite loss	163/297 (55)	20/107 (19)	<0.001	117/229 (51)	30/92 (33)	0.01	94/213 (47)	26/94 (28)	0.02	72/164 (44)	26/85 (31)	0.17
Dyspnea	168/296 (57)	18/107 (17)	<0.001	120/234 (51)	30/92 (33)	<0.001	104/214 (49)	33/93 (35)	0.02	85/165 (52)	39/85 (46)	0.03
Dysphagia	26/297 (9)	2/107 (2)	0.11	100/232 (43)	26/92 (28)	0.08	38/212 (18)	12/94 (13)	0.48	15/165 (9)	4/84 (5)	0.36

S, symptomatic patients; NS, non-symptomatic patients.

significant difference between the groups as 62% of the symptomatic group still had symptoms, while 50% of the non-symptomatic group had developed symptoms. This suggests that prophylactic TRT does not provide long-term prevention of symptom development from intrathoracic tumours.

This problem has also been addressed by MRC in a recent report [12]. NSCLC patients with locally advanced disease, unsuitable for surgery or radical TRT and with none or minimal intrathoracic symptoms, were randomised to TRT immediately or delayed until needed for symptom treatment. Palliative TRT was most often given as 17 Gy per two fractions or 10 Gy in one fraction. Main outcome measures were: alive without symptoms at 6 months, HRQOL, side effects, and overall survival. The authors concluded that in minimally symptomatic patients, no persuasive evidence was found indicating that immediate palliative TRT improves symptom control, HRQOL, or survival, when compared to delaying TRT until treatment requiring symptoms.

The median survival in our patients with none or mild thoracic symptoms (11.8 months) was longer than that reported by Falk and co-workers (7.9 and 8.3 months) [12]. This may be explained by better prognostic factors among our patients rather than the immediate TRT. When compared to Falk et al. [12], our patients with none or mild thoracic symptoms had more favourable PS (WHO 2-3, 8 versus 32%), less cough (58 versus 78%), and less dyspnoea (17 versus 79%). However, age and the prevalence of stage IV disease, haemoptysis, and chest pain were similar in both studies.

The study by Macbeth et al. [17], comparing 17 Gy/2 fractions versus 39 Gy/13 fractions, have shown a small, but clinically relevant survival benefit from higher dose TRT. In our subpopulation of locally advanced disease (stage III) and good PS patients (Karnofsky PS ≥ 80%) only ($N=211$), no survival differences were found across the various fractionation groups [23]. At 3 years, however, a trend ($P=0.06$) toward a survival difference in favour of the normofractionated arms was found. In patients with none or only minimal symptoms at baseline, no differences were detected across the TRT schedules, but this may be explained by the low total patient number ($N=107$).

The MRC study is the only study comparing immediate versus delayed TRT in advanced NSCLC with none or minimal symptoms at diagnosis in a randomised fashion [12]. The study was a multicentre study in UK, Ireland and South Africa, originally planned to include 300 patients with 150 in each arm. After nearly 7 years accrual, originally projected for 2 years, the study was stopped after an interim analysis of 230 patients. However, since completion of this study, chemotherapy has been shown to prolong survival and improve disease-related symptoms in patients with advanced NSCLC [10]. Thus, the currently preferred primary treatment in advanced NSCLC patients is chemotherapy, making a new confirmatory randomised study in this setting impossible.

As this study is a non-randomised comparison between the symptom development in NS and S patients, the results should be interpreted cautiously. However, our data may indicate that patients with minimal or no tumour-related thoracic symptoms do not benefit from immediate palliative

TRT with regard to improved long-term symptom control and HRQOL based on either patients' or clinicians' assessments of chest/airway symptoms. Meanwhile, TRT may induce significant dysphagia in otherwise symptom-free patients. A wait-and-see policy, i.e. delaying TRT until symptomatically needed, appears to be safe and acceptable.

Acknowledgements

This study was initiated and performed by The Norwegian Lung Cancer Study Group. The secretarial assistance at the Clinical Research Office, The University Hospital of Trondheim is greatly appreciated.

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Received 16 June 2004; received in revised form 8 February 2005; accepted 8 March 2005; available online 11 May 2005

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Appendices

Appendices

- Editorial paper I:
  - Johnson DH. “The Guard Dies, It Does Not Surrender!” Progress in the Management of Small-Cell Lung Cancer? J Clin Oncol 20: 4618-4620, 2002

- Editorial paper II:
  - Postmus PE. Second-line for small cell lung cancer: how-to-do-it? Lung Cancer 48: 263-265, 2005

- Editorial paper III:
  - Bogart JA. Hypofractionated Radiotherapy for Advanced Non-Small-Cell Lung Cancer: Is the LINAC Half Full? J Clin Oncol 22 765-768

- EORTC core quality of life questionnaire, EORTC QLQ-C30 (version 1)

- Lung cancer module QLQ-LC13 (version 1)

EDITORIAL

"The Guard Dies, It Does Not Surrender!" Progress in the Management of Small-Cell Lung Cancer?

FOR SEVERAL DECADES now, small-cell lung cancer (SCLC) has been characterized as a "chemosensitive" and potentially "curable" neoplasm.[1,2] Indeed, there are a number of chemotherapy agents capable of effecting high objective response rates in this disease. Among the many available drug combinations used to treat SCLC, cisplatin and etoposide (PE) combination tends to be the preferred regimen in North America and Japan, whereas anthracycline-based regimens tend to predominate in Europe.[3] Both types of regimens are active against SCLC and both are conveniently administered in the outpatient setting. However, given the extant differences in national health care financing and practice patterns around the globe, it is not surprising that neither regimen has emerged as the international consensus best treatment for SCLC.

In this issue of the *Journal of Clinical Oncology*, Sundstrøm et al[4] present the results of a randomized trial in which they prospectively compared the activity of cyclophosphamide, epirubicin, and vincristine (CEV) with that of PE in patients with SCLC. Epirubicin is the preferred anthracycline in Europe due in part to its decreased cardiac toxicity relative to doxorubicin.[5] Thus, CEV can be viewed as a European version of cyclophosphamide, doxorubicin, and vincristine (CAV), an anthracycline-based drug combination commonly used in North America throughout the 1970s and 1980s.[2,6] Although the comparability of the single-agent activities of epirubicin and doxorubicin has not been fully established in SCLC, it is reasonable to believe that these anthracyclines possess essentially identical efficacy.

The trial conducted by Sundstrøm et al[4] enrolled 440 SCLC patients with both limited-stage (LS) and extensive-stage (ES) disease. LS patients also received thoracic radiotherapy (TRT) between the third and fourth cycles of chemotherapy. Overall survival was significantly better among the group randomized to PE compared with CEV (10.2 months *v* 7.8 months; $P = .0004$). There were no meaningful differences noted in the quality of life between the two arms. The authors, therefore, concluded that PE is superior to CEV in the treatment of SCLC. In a subset analysis, the superiority of the PE regimen seemed to be restricted to patients with LS disease (14.5 *v* 9.7 months), with no survival improvement noted in patients with ES disease (8.4 *v* 6.5 months).

Do these data now firmly establish PE as a regimen superior to anthracycline-based therapy for SCLC? The results of the Sundstrøm et al trial will come as no great surprise to most lung cancer experts. Over the past two decades, several groups have prospectively compared anthracycline-based chemotherapy regimens to PE.[7-10] Most of these trials failed to demonstrate a survival advantage for PE, possibly because many of the trials were conducted exclusively in ES SCLC patients.[8-11] However, in a recent overview of United States (U.S.) National Cancer Institute–sponsored ES SCLC trials conducted between 1972 and 1990, Chute et al[11] demonstrated that platinum-containing chemotherapy does impart a relatively modest median survival benefit of approximately 2 months compared with nonplatinum regimens. Perhaps more importantly (at least to patients), the platinum-based regimens are generally better tolerated than the anthracycline-containing regimens.[9,10] This is particularly true if one substitutes carboplatin for cisplatin.[12] In fact, on the basis of these clinical observations, oncologists in North America have long accepted that platinum-based therapy is at least as good as anthracycline-based regimens for the treatment of ES SCLC and probably better. However, the real "advantage" for platinum-based therapy comes from the ease with which these regimens can be delivered concomitantly with TRT, an absolute necessity if one is to achieve maximum survival outcome in LS patients with good performance.[13] Efforts to combine anthracycline-based regimens concurrently with TRT have proved difficult and, in some cases, even life-threatening.[14,15] Thus, when PE is included in the induction regimen of LS SCLC treatment programs, one frequently observes a modest survival benefit (albeit not always a statistically significant improvement).[9,16,17] Like previous investigators, Sundstrøm et al[4] also noted a survival benefit in LS SCLC with the use of PE.

There are several interesting aspects to the Sundstrøm trial. First, the median survival times of the ES SCLC patients (CEV, 6.5 months *v* 8.4 months) nearly perfectly mirror those reported by Chute et al[11] in their review of the 1972 to 1990 U.S. cooperative group ES SCLC experience. For example, the median of the median survival times of the patients treated in the U.S. between 1972 and 1981 on the control arms was 7.0 months. These patients were treated primarily with cyclophosphamide- or anthracycline-based chemotherapy regimens. By contrast, patients treated in the U.S. between 1982 and 1990 enjoyed a median survival time of 8.9 months ($P = .001$) and these patients were treated using platinum-based regimens. Although it may be tempting to invoke the specter of "stage shifting" to account for this improvement in survival,[18] an analysis of the Surveillance, Epidemiology, and End-Results database over the same time period shows a similar 2-month prolongation in median survival time of ES SCLC patients.[11] This suggests that stage shifting alone is *not* the explanation for the improved survival observed in U.S. cooperative group studies. Second, the median survival times of the LS SCLC patients enrolled onto the Norwegian study were rather poor (PE, 14.5 months; CEV, 9.7 months). By comparison, in North American cooperative group trials median survival typically exceeds 17 to 18 months and was more than 20 months in the most recent intergroup LS SCLC study.[19,20] In fact, similar good results were being reported over a decade ago, around the time cisplatin was first introduced into the indication regimens of LS SCLC.[21] Because the characteristics of the patients enrolled onto the Sundstrøm trial more or less mirror those recorded for participants in recent U.S. cooperative group studies, one has to wonder what additional factors played a role in the relatively poor outcome observed in the Norwegian study.

One possible explanation for the disappointing results observed in LS SCLC in the Sundstrøm trial relates to the TRT dose and schedule used (42 Gy in 15 2.8-Gy fractions). Although medical oncologists might be loath to admit it, refinements in radiation therapy delivery and technique have made a greater contribution to survival prolongation of LS SCLC in recent years than have improvements in chemotherapy. This was borne out in a recent review conducted by Janne et al.[19] Among LS SCLC patients treated within the context of U.S. cooperative group trials, some modification in radiotherapy accounted for the improved survival noted in all of the positive trials. In other words, in none of the National Cancer Institute–sponsored randomized trials carried out between 1972 and 1992 did a change in chemotherapy alone account for an obvious survival improvement. In the Sundstrøm trial, the TRT dose and fractionation differed from those commonly used in North American trials. Was the dose and fractionation schedule optimal radiotherapy circa 1990? Possibly. Was the TRT adequate to maximize local tumor control? Doubtful. This is a critical issue since we know that improved local control is a prerequisite for improved survival.[20] How to achieve improved local control is the subject of ongoing investigations, but some possible options include increasing the total dose of radiotherapy or changing fractionation.[22]

Although one could debate some of the particulars of the Sundstrøm trial design, in general, it was a well-designed randomized study seeking to address a straightforward question. This was not simply a Sisyphean exercise, and the results should alter practice patterns, at least in countries where anthracycline-based therapy still predominates. These findings are particularly relevant to the treatment of LS SCLC where maintaining maximum dose-intensity of both radiotherapy and chemotherapy is critical. Indeed, one should also avoid ad hoc changes in established and well-tested treatments plans. The consequences of such changes are unknown and could prove disastrous. Finally, in most cancers, the best outcome is usually obtained when a team of highly experienced experts cares for the patient. This means that SCLC patients, and especially those with LS disease, should be treated by highly qualified medical and radiation oncologists using an integrated, multidisciplinary approach with appropriate chemotherapy regimens. Patient volume and overall physician experience do matter.[23] When approached in this manner, optimal outcome will be realized in the highest possible number of cancer cases.[24] The results of this trial may be viewed as further validation of practice patterns in North America and Japan. By contrast, physicians unalterably opposed to the use of platinum-based therapy in SCLC may attempt to find fatal flaws in the Sundstrøm trial design to justify their refusal to include cisplatin in their treatment programs. Perhaps General Count Etienne Cambronne said it best at the Battle of Waterloo: "La Garde meurt, elle ne se rend pas!" "The Guard dies, it does not surrender!"

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Lung Cancer (2005) 48, 263–265

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EDITORIAL

Second-line for small cell lung cancer: how-to-do-it?

Many trials have addressed the question what is the best treatment of small cell lung cancer at diagnosis. Currently worldwide, the combination of cisplatin-etoposide is accepted as the standard for limited and extensive disease patients. In striking contrast with this abundance of trials, is the lack of research to come to evidence-based second-line treatment. In fact, there are no randomized comparisons of active cytotoxic therapy versus best supportive care in the relapse setting published. The single study to provide evidence that second-line treatment does result in prolongation of survival was published in the late 1980s [1]. Symptom improvement has formally been assessed in two randomized studies evaluating the role of topotecan in relapsed SCLC [2,3]. In both studies, unvalidated symptom scores based on the Lung Cancer Symptom Scale were used. Improvement in the eight domains studied (chest pain, shortness of breath, cough, haemoptysis, anorexia, insomnia, hoarseness, and fatigue) as well as interference with daily activity was observed in 25–35% of patients. With caution, one may conclude that in general second-line chemotherapy for relapsed SCLC results in modest prolongation of overall survival and symptom improvement in approximately one-third of patients.

Pretreatment variables predictive for response to second-line treatment are less well defined than for first-line treatment. Good performance status, female sex, and type of response to first-line treatment were found as favorable factors, while presence of liver metastases and previous radiotherapy may be negative. Retrospective studies found a significantly higher probability of response for those patients who had a treatment-free interval of more than 2.6 months at least [4–7]. The importance of treatment-free interval was further emphasized by studies investigating the value of reinduction chemotherapy at relapse [8–10]. Patients who had a treatment-free interval of more than 4.5 months had a higher probability of achieving a second response to the same chemotherapy as used in first-line as compared to those patients who relapsed within 4.5 months. Without further prospective testing, a distinction has been made and accepted between so called sensitive patients at relapse, i.e. those with a response to first-line therapy and a treatment-free interval of at least 90 days and resistant patients, i.e. no response to first-line treatment and relapse within 90 days. Little is known of the influence of the composition of first-line treatment on the probability of response to second-line treatment. Whether patients treated with first-line platinum containing regimens have a less probability of response as compared to those treated with non-platinum containing regimens is not known. Some older studies have suggested that patients treated with cisplatin-etoposide treated with cyclophosphamide, doxorubicin, and vincristine in second-line have lower survival times as vice versa [11–15].

Also the study by Sundstrøm et al. [16] fails to prove that treatment at relapse is better than best supportive care. In this study, the authors demonstrate that patients recurring or progressing after two different first-line regimens have a comparable outcome if, at relapse, these patients were treated in a crossover design with the other,

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doi:10.1016/j.lungcan.2004.12.009

so-called non-cross resistant regimen. In both groups, the result was for the treated patients better than for the non-treated patients. A "no treatment decision" was based on clinically relevant prognostic factors as decided by the responsible physician. In general worse performance status, shorter time to recurrence, and more assumed resistance were the main differences between treated and not treated groups. Regarding the design of the study this is not the way to test a concept of second-line or non-cross resistance. In fact, the authors describe two poorly designed phase II studies with two regimens that were not equipotent as demonstrated in a previous report [17]. They confirm that in these two groups the performance status is the most important prognostic factor although the selection of the patients was, among other factors, based on performance status.

The assumption of the authors that for second-line treatment a non-cross resistant combination might be of value is based on theoretical considerations without any clinical proof. Demonstrating clinically relevant non-cross resistance is difficult, if at all possible [18], and even then this may not have any clinical impact [19].

At this stage, there is no best salvage regimen or drug. For the daily practice, the most important factors for decision-making remain, besides performance status, the sensitivity to the first-line treatment in combination with a progression free period of more than 3 months. For these patients, retreatment with the induction regimen is appropriate, for all others, it is 'trial and error' of single agents or combinations. Among these the paclitaxel containing regimens have response rates that warrant application in patients without response or a very short treatment-free interval after first-line treatment [20,21]. An effective treatment for palliation of specific symptoms and isolated intrathoracic relapses might be radiotherapy.

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7 December 2004

VOLUME 22 · NUMBER 5 · MARCH 1 2004

JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Hypofractionated Radiotherapy for Advanced Non–Small-Cell Lung Cancer: Is the LINAC Half Full?

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The origin of fractionated radiotherapy dates back to observations by French investigators Regaud and Coutard, among others, during the 1920s and 1930s [1]. Before this time, there was considerable controversy regarding appropriate radiotherapy delivery, and treatment was generally administered in a single dose or in a few large fractions. Regaud documented improved tumor control of uterine carcinoma when the time of application of radium was extended to 1 week, and Coutard subsequently demonstrated that external beam therapy applied in a similar manner could cure head and neck cancer without the severe sequelae associated with single large doses [2,3]. Consequently, fractionated treatment was widely adopted throughout Europe and North America. During the intervening years, varied regional standard treatment schemes have evolved, often guided by empiric observations and practical constraints rather than objective data. It should, therefore, not be surprising that there is little consensus regarding appropriate radiation regimens for all situations.

Although the presumption of a dose-response relationship is a core tenet driving the clinical practice of radiation oncology, few studies have established that higher doses of conventionally fractionated radiotherapy result in improved outcomes. Whether the substitution of fewer radiotherapy fractions, or hypofractionation, can lead to equivalent or improved results has been investigated in the definitive and palliative setting. For example, the potential role of hypofractionation for lung cancer was the subject of a recent review [4]. The practical benefits of limiting the number of sessions in the palliative setting are self-evident. On the other hand, common concerns regarding the delivery of large radiation fractions include the potential for reduced biologic efficacy and the observation that late toxic effects of therapy are enhanced as the dose per fraction delivered to normal tissues increases, particularly when large volumes of normal tissue are irradiated [5,6].

Sundstrøm et al [7], from The Norwegian Lung Cancer Study Group, are to be commended for successfully completing a large, well-designed trial of hypofractionated therapy for lung cancer palliation. Appropriately, the designated primary end-points were palliative, including symptom relief from dyspnea, cough, and hemoptysis, as reported by patients and physicians. Detailed quality of life data were also obtained. In the end, all treatment regimens produced similar palliation and health-related quality of life, while differences in the toxic effects of therapy were minimal, although dysphagia appeared significantly earlier with short-course therapy. Local symptom control was achieved in 40% of patients, confirming the palliative efficacy of radiotherapy, and the concordance in the reporting of symptom relief (with the exception of cough) between patients and physicians is reassuring. The present study expands the number of randomized phase III trials examining palliative radiotherapy, as recently summarized in a Cochrane analysis [8]. A dozen trials are now included, and most support the notion that hypofractionated therapy is safe and effective in the palliative setting (Table 1) [7-19]. Recent evidence suggests, however, that perhaps one dose is not enough. A study conducted by the National Cancer Institute of Canada assigned patients to receive either a single fraction of 10 Gy or 20 Gy in five fractions [9]. While there was no difference in symptom control as judged by patient-completed daily diary cards, changes in scores on the Lung Cancer Symptom Scale indicated patients treated with fractionated radiotherapy had greater improvement in symptoms related to lung cancer, ability to carry out normal activities, and better global quality of life. Similarly, Gaze et al [10] recently reported that fractionated radiotherapy, 30

Table 1. Randomized Trials of Palliative Radiotherapy for Advanced Lung Cancer

Trial	No. of Patients	Regimens Compared	Results
Abratt [17]	84	35 Gy/10 F *v* 45 Gy/15 F	Trend to increased esophagitis with higher dose
Gaze [10]	148	10 Gy *v* 30 Gy/10 F	Better symptom relief and reduced anxiety with 30 Gy
MRC [13]	369	30 Gy/10 F or 27 Gy/6 F *v* 17 Gy/2 F	No significant differences in outcome
MRC [13]	235	17 Gy/2 F *v* 10 Gy/1 F	Increased esophagitis in 17 Gy arm
Macbeth [15]	509	36 or 39 Gy/12 or 13 F *v* 17 Gy/2 F	More rapid palliation with 17 Gy/2 F. Improved survival with 39 Gy/13 F
Nestle [19]	152	32 Gy/16 F *v* 60 Gy/30 F	No significant differences in outcome
Rees [16]	216	17 Gy/2 F *v* 22.5 Gy/5 F	Trend to increased esophagitis and better palliation with 17 Gy
Reinfuss [12]	240	50 Gy/25 F *v* 40 Gy/10 F *v* delayed therapy	Improved survival with 50 Gy
Simpson [11]	316	40 Gy/20 F *v* 30 Gy/10 F *v* 40 Gy/10 F	Trend to increased toxicity and reduced palliation with 40 Gy/10
Teo [18]	273	45 Gy/18 F *v* 31.2 Gy/4 F	Symptomatic response better with 45 Gy
Bezjak [9]	230	20 Gy/5 F *v* 10 Gy/1 F	Improved survival with protracted therapy
Sundstrøm [7]	407	Current trial	

NOTE. Table adapted from reference [8] with permission.
Abbreviations: F, fractions; MRC, Medical Research Council.

Gy in 10 fractions, resulted in better symptom relief than a single dose of 10 Gy.

Are the results of the current study likely to impact clinical practice? In the United States, the answer may be a very guarded "perhaps." Woven into the fiber of most radiation oncologists trained in the United States is the belief that prolonging the course of therapy will provide more durable tumor control and symptom relief. While American radiation oncologists may be comfortable with regimens of 30 Gy in 10 fractions or even 20 Gy in five fractions, the pen starts to quiver when writing a prescription for extreme hypofractionation (eg, one or two fractions). In the arena of distant metastatic disease, this attitude may begin to shift given the results of the recent Radiation Therapy Oncology Group (RTOG) trial confirming that a single fraction of 8 Gy provides equivalent palliation to 30 Gy in ten fractions in patients with painful bone metastases from breast or prostate carcinoma [20]. However, palliative thoracic radiotherapy has been studied less frequently in recent times. The last US cooperative group trial to address this issue was initiated in 1973 by the RTOG, when 30 Gy continuous course therapy was compared to 40 Gy given in either split course or continuous fashion [11]. Similar palliative effects were observed in all arms, while slightly higher toxicity was seen with split-course therapy. Given the lack of benefit from the higher dose, 30 Gy in 10 fractions became the standard of care. Interestingly, the trial from The Norwegian Lung Cancer Study Group employed two regimens that are more protracted and resource-consuming than the standard US regimen.

One issue not addressed by this study is the role of palliative radiotherapy in the era of systemic therapy. In contrast to current clinical practice, surprisingly few patients received chemotherapy. Randomized trials during the past two decades have demonstrated a small, but statistically significant, survival benefit for patients receiving cisplatin-based chemotherapy compared with best supportive care [21,22]. Recent data suggests this benefit extends to elderly patients as well as patients with borderline baseline performance status [23,24]. Even before the development of effective chemotherapy regimens, the role of immediate radiotherapy was questioned, and a recent Medical Research Council trial—which did not permit chemotherapy—demonstrated no benefit for immediate radiotherapy compared to delayed palliative radiotherapy in patients with minimal symptoms [25]. Moreover, the majority of patients in the delayed arm never received radiotherapy. Detailed information regarding the palliative effects of chemotherapy is also available, including a randomized trial comparing gemcitabine to best supportive care using quality of life as the primary outcome [26]. Patients receiving chemotherapy reported improved quality of life and symptom relief, and at the 2-month assessment, 9% of patients assigned to receive gemcitabine required palliative radiotherapy compared with 58% of patients receiving best supportive care. Overall, however, 49% of patients on the gemcitabine arm eventually received radiotherapy, indicating that defining an appropriate palliative radiotherapy regimen remains clinically relevant. Whether combining radiotherapy with systemic chemotherapy improves symptom relief or quality of life for selected patients with advanced non–small-cell lung cancer (NSCLC) has not been extensively explored, and may be reasonable ground for future investigation.

Perhaps the most important lesson from trials of palliative radiotherapy is that extended survival is possible. Patient selection is critical, and despite the unfathomably slow progress in the treatment of lung cancer, a nihilistic

approach is not warranted. In fact, the authors' conclusion that protracted radiotherapy "renders no improvement in ... survival" is potentially misleading. Three-year survival was 6% in each of the protracted arms, yet only 1% in the hypofractionated arm. Moreover, when the survival analysis was limited to patients with good performance status with stage III disease (roughly half of all eligible patients), 3-year survival was 9% and 6% in the two high-dose arms, compared with 1% in the 17 Gy arm ($P = .06$). Similar findings were recently reported from the National Cancer Institute of Canada trial comparing protracted therapy (20 Gy in five fractions) with a single fraction of 10 Gy. Again, the survival benefit appeared limited to patients with good performance status and localized disease [9]. Other earlier trials, which limited enrollment to patients with good performance status, also demonstrated the potential for prolonged survival with protracted regimens [12,15]. Given the emergence of effective strategies for favorable-risk stage III NSCLC, with an expectation of long-term survival in as many as one fifth of patients treated with simultaneous radiation and chemotherapy, patients with localized disease must be carefully screened before being relegated to receive palliative therapy [27].

While there is now an abundance of randomized trials to guide decision making for lung cancer palliation, strikingly few modern phase III studies have been designed to elicit an optimal curative radiotherapy regimen. The widely accepted standard regimen, 60 Gy in 2 Gy daily fractions, defined by an RTOG trial conducted in the 1970s, was selected based on short-term (and nonstatistically significant) differences in outcome [28]. However, no alternative radiotherapy regimen has proved superior in a North American Cooperative Group trial [29]. Although a large-scale United Kingdom trial documented improved long-term survival for patients treated with continuous hyperfractionated accelerated radiotherapy, high-dose accelerated radiotherapy is difficult to administer simultaneously with chemotherapy [30]. Moreover, treatment regimens employing multiple daily fractions have not been widely embraced, as witnessed by the inability of the recently reported Eastern Cooperative Oncology Group trial of thrice daily radiotherapy to complete patient accrual [31]. While the boundless enthusiasm for studying novel systemic agents and molecular targeted therapies is well founded, defining the appropriate radiotherapy regimen to serve as the backbone for future investigation should also be considered a research priority.

In summary, evidence from the current trial confirms that short course radiotherapy is a safe and effective tool for palliating lung cancer symptoms and is appropriate for select poor-prognosis patients. Importantly, the suggestion of improved long-term survival for favorable-risk patients treated with higher radiation doses illustrates the critical need to appropriately triage patients with locally advanced NSCLC. The challenge for the next decade will be to shift this fervor toward defining an optimal radiation schedule in the curative setting.

Author's Disclosures of Potential Conflicts of Interest

The author indicated no potential conflicts of interest.

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EORTC QLQ-C30

(Version 1.0)

Pasientnummer: ☐☐☐

Pasientens initialer: ☐☐☐

Vi er interessert i forhold vedrørende deg og din helse. Vær så vennlig å besvare hvert spørsmål ved å sette et kryss x i den boksen som best beskriver din tilstand. Det er ingen «riktige» eller «gale» svar. Alle opplysningene vil bli behandlet konfidensielt.

	Ja	Nei
1. Har du vanskeligheter med å utføre anstrengende aktiviteter, slik som å bære en tung handlekurv eller en koffert?	☐	☐
2. Har du vanskeligheter med å gå en lang tur?	☐	☐
3. Har du vanskeligheter med å gå en kort tur utendørs?	☐	☐
4. Er du nødt til å ligge til sengs eller sitte i en stol i løpet av dagen?	☐	☐
5. Trenger du hjelp til å spise, kle på deg, vaske deg eller gå på toalettet?	☐	☐
6. Er du redusert på noen måte slik at du ikke kan arbeide eller gjøre husarbeid?	☐	☐
7. Er du helt ute av stand til å arbeide eller gjøre husarbeid?	☐	☐

I løpet av den siste uka:	**Ikke i det hele tatt**	**Litt**	**En del**	**Svært mye**
8. Har du vært tung i pusten?	☐	☐	☐	☐
9. Har du hatt smerter?	☐	☐	☐	☐
10. Har du hatt behov for å hvile?	☐	☐	☐	☐
11. Har du hatt søvnproblemer?	☐	☐	☐	☐
12. Har du følt deg slapp?	☐	☐	☐	☐
13. Har du hatt dårlig matlyst?	☐	☐	☐	☐
14. Har du vært kvalm?	☐	☐	☐	☐

Bla om til neste side

Pasientnummer: ☐☐☐

I løpet av den siste uka:	**Ikke i det hele tatt**	**Litt**	**En del**	**Svært mye**
15. Har du kastet opp?	☐	☐	☐	☐
16. Har du hatt treg mage?	☐	☐	☐	☐
17. Har du hatt løs mage?	☐	☐	☐	☐
18. Har du følt deg trett?	☐	☐	☐	☐
19. Har smerter påvirket dine daglige aktiviteter?	☐	☐	☐	☐
20. Har du hatt problemer med å konsentrere deg, f.eks. med å lese en avis eller se på TV?	☐	☐	☐	☐
21. Har du følt deg anspent?	☐	☐	☐	☐
22. Har du vært engstelig?	☐	☐	☐	☐
23. Har du følt deg irritabel?	☐	☐	☐	☐
24. Har du følt deg deprimert?	☐	☐	☐	☐
25. Har du hatt problemer med å huske ting?	☐	☐	☐	☐
26. Har din fysiske tilstand eller medisinske behandling påvirket ditt familieliv?	☐	☐	☐	☐
27. Har din fysiske tilstand eller medisinske behandling påvirket dine sosiale aktiviteter?	☐	☐	☐	☐
28. Har din fysiske tilstand eller medisinske behandling gitt deg økonomiske problemer?	☐	☐	☐	☐

Som svar på de neste spørsmålene, sett et kryss i den boksen fra 1 til 7 som best beskriver din tilstand.

29. Hvordan har din helse vært i løpet av den siste uka?

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

Svært dårlig Helt utmerket

30. Hvordan har livskvaliteten din vært i løpet av den siste uka?

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

Svært dårlig Helt utmerket

EORTC QLQ-LC13

Pasientnr.

En del pasienter opplever av og til at de har hatt noen av følgende symptomer. Vær vennlig å angi i hvilken grad du har hatt disse symptomene i løpet av den siste uka.

I løpet av den siste uka:	Ikke i det hele tatt	Litt	En del	Svært mye
31. Hvor mye har du hostet?	☐	☐	☐	☐
32. Har du hostet blod?	☐	☐	☐	☐
33. Har du vært tung i pusten i hvile?	☐	☐	☐	☐
34. Har du vært tung i pusten når du har gått?	☐	☐	☐	☐
35. Har du vært tung i pusten når du har gått i trapper?	☐	☐	☐	☐
36. Har du vært sår i munnen eller på tungen?	☐	☐	☐	☐
37. Har du hatt svelgproblemer?	☐	☐	☐	☐
38. Har du hatt prikninger (stikninger) i hendene eller i bena?	☐	☐	☐	☐
39. Har du hatt håravfall?	☐	☐	☐	☐
40. Har du hatt smerter i brystet?	☐	☐	☐	☐
41. Har du hatt smerter i arm eller skulder?	☐	☐	☐	☐
42. Har du hatt smerter i andre deler av kroppen?	☐	☐	☐	☐

Hvis ja, hvor har du hatt vondt? _____

43. Har du brukt smertestillende medisiner?

☐ Nei ☐ Ja

Hvis ja, hvor mye har det hjulpet?	☐	☐	☐	☐

Vennligst kontroller at alle spørsmålene er besvart !

Hvis du har ytterligere kommentarer, vennligst spesifiser nedenfor: ☐

_____

_____

_____

3477

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40. Kjell-Arne Rein: THE EFFECT OF EXTRACORPOREAL CIRCULATION ON SUBCUTANEOUS TRANSCAPILLARY FLUID BALANCE.
41. Arne Kristian Sandvik: RAT GASTRIC HISTAMINE.
42. Carl Bredo Dahl: ANIMAL MODELS IN PSYCHIATRY.

1989

43. Torbjørn A. Fredriksen: CERVICOGENIC HEADACHE.
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46. Nils Petter Jørgensen: DRUG EXPOSURE IN EARLY PREGNANCY.
47. Johan C. Ræder: PREMEDICATION AND GENERAL ANAESTHESIA IN OUTPATIENT GYNECOLOGICAL SURGERY.
48. M. R. Shalaby: IMMUNOREGULATORY PROPERTIES OF TNF-α AND THE RELATED CYTOKINES.
49. Anders Waage: THE COMPLEX PATTERN OF CYTOKINES IN SEPTIC SHOCK.
50. Bjarne Christian Eriksen: ELECTROSTIMULATION OF THE PELVIC FLOOR IN FEMALE URINARY INCONTINENCE.
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1990

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55. Eva Hofsli: TUMOR NECROSIS FACTOR AND MULTIDRUG RESISTANCE.
56. Helge S. Haarstad: TROPHIC EFFECTS OF CHOLECYSTOKININ AND SECRETIN ON THE RAT PANCREAS.
57. Lars Engebretsen: TREATMENT OF ACUTE ANTERIOR CRUCIATE LIGAMENT INJURIES.
58. Tarjei Rygnestad: DELIBERATE SELF-POISONING IN TRONDHEIM.
59. Arne Z. Henriksen: STUDIES ON CONSERVED ANTIGENIC DOMAINS ON MAJOR OUTER MEMBRANE PROTEINS FROM ENTEROBACTERIA.
60. Steinar Westin: UNEMPLOYMENT AND HEALTH: Medical and social consequences of a factory closure in a ten-year controlled follow-up study.
61. Ylva Sahlin: INJURY REGISTRATION, a tool for accident preventive work.
62. Helge Bjørnstad Pettersen: BIOSYNTHESIS OF COMPLEMENT BY HUMAN ALVEOLAR MACROPHAGES WITH SPECIAL REFERENCE TO SARCOIDOSIS.
63. Berit Schei: TRAPPED IN PAINFUL LOVE.
64. Lars J. Vatten: PROSPECTIVE STUDIES OF THE RISK OF BREAST CANCER IN A COHORT OF NORWEGIAN WOMAN.

1991

65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.
66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.

68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

1992

74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

1993

82. Gunnar Bovim: CERVICOGENIC HEADACHE.
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85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
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91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

1994

92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
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103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

1995

104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.

109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

1996

110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANSER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

1997

124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

1998

132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.

139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

1999

141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

2000

158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.

168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

2001

178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
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195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM

198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

2002

201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
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2003

216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL

224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

2004

235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

2005

248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS

251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS
260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
263. Eszter Vanky: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN PREGNANCY
264. Hild Fjærtoft: EXTENDED STROKE UNIT SERVICE AND EARLY SUPPORTED DISCHARGE. SHORT AND LONG-TERM EFFECTS
265. Grete Dyb: POSTTRAUMATIC STRESS REACTIONS IN CHILDREN AND ADOLESCENTS
266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

2006

269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE
271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT
272. Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT
273. Ingvild Saltvedt: TREATMENT OF ACUTELY SICK, FRAIL ELDERLY PATIENTS IN A GERIATRIC EVALUATION AND MANAGEMENT UNIT – RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
274. Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS
275. Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276. Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES
278. Hilde Pleym: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION