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Doctoral Thesis

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Trondheim, March 2010

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PEMETREXED SOM BEHANDLING AV AVANSERT LUNGEKREFT

Lungekreft er den kreftsykdom som tar flest liv. I Norge er det ca. 2500 nye tilfeller, og flere enn 2000 dør årlig av sykdommen.

Ca. 17 % har småcellet lungekreft. De fleste har god effekt av cellegift- og strålebehandling, men de fleste får tilbakefall innen et år.

Majoriteten av pasienter med lungekreft (> 80 %) har ikke-småcellet lungekreft. Godt over halvparten har spredning ved diagnosetidspunktet og tilbys livsforlengende cellegiftbehandling. Ulempen med behandlingen er at den kan gi plagsomme og i noen tilfeller alvorlige bivirkninger. Mange lungekreftpasienter har andre sykdommer - spesielt hjerte-, kar- og lungesykdommer - og det er uvisst om disse pasientene tåler cellegiftbehandling like godt som andre.

Pemetrexed er en relativ ny type cellegift. Bakgrunnen for avhandlingen var studier som antydet at medikamentet er effektivt i behandling av begge typer lungekreft, og at det muligens gir færre bivirkninger enn andre typer cellegift. Målsetningen med avhandlingen var å besvare følgende forskningsspørsmål:

- Er pemetrexed effektivt og godt tolerert som behandling av tilbakefall av småcellet lungekreft?
- Er pemetrexed pluss carboplatin bedre tolerert og like effektivt som et standardregime – gemcitabin pluss carboplatin?
- Har pasienter med alvorlig, annen sykdom, like god effekt og toleranse for cellegiftbehandling som pasienter med bedre generell helse?

34 pasienter med tilbakefall av småcellet lungekreft ble behandlet med pemetrexed. Behandlingen ga lite bivirkninger, men tilbakegang av sykdommen ble kun observert hos en pasient. Dette er klart dårligere enn hva man forventer av behandling med andre typer cellegift.

436 pasienter ble inkludert i en fase III studie hvor man sammenlignet pemetrexed/ carboplatin mot gemcitabin/carboplatin. Det var ingen forskjell i helserelatert livskvalitet eller overlevelse, men pasientene i pemetrexed-armen hadde færre bivirkninger.

Grad av annen sykdom (komorbiditet) ble målt hos 402 av pasientene i fase III studien. Det var ingen signifikante forskjeller i overlevelse eller helserelatert livskvalitet mellom pasienter med og uten alvorlig komorbiditet, men pasientene med alvorlig komorbiditet fikk oftere infeksjoner dersom immunforsvaret ble svekket av cellegiftbehandlingen – og alle som døde av slike infeksjoner tilhørte denne gruppen. Konklusjonen var likevel at pasienter med alvorlig komorbiditet bør tilbys cellegiftbehandling.

Kandidatens navn: ***Bjørn Henning Grønberg***
Institutt: ***Institutt for Kreftforskning og Molekylær medisin***
Veiledere: ***Stein Sundstrøm, Stein Kaasa og Roy M. Bremnes***
Finansieringskilde: ***Samarbeidsorganet Helse Midt-Norge og NTNU***

Ovennevnte avhandling er funnet verdig til å forsvares offentlig
for graden PhD i Klinisk medisin
Disputas finner sted i Auditoriet, Medisinsk Teknisk Forskningssenter
fredag 26. mars 2010 kl. 12.15

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Conducting clinical trials requires efforts and dedication from a lot of people.
First of all I wish to thank all the patients who participated in the studies. Their commitment to the studies has been a great inspiration for me.

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Stein Sundstrøm introduced me to clinical research and has been my supervisor – as well as my mentor in the clinic. He has been a great inspiration by showing that clinical trials from a small country can influence the opinions of the international medical community.

Professor Stein Kaasa has been my other supervisor here in Trondheim. It has been invaluable to have someone with his experience in the office next door whenever I have needed to discuss any aspect of my research – or any other issue. I really look forward to continue our collaboration in my post-doc period.

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Marit Jordhøy came up with the idea of the comorbidity-study and has been the most important collaborator when analyzing and reporting the results. With her

thoroughness and ability to look at things from a different angle, she has taught me more than most other people I know.

Without Marie Botilsrud, we would not have been able to conduct any studies of pemetrexed. After a rather tiresome process, she was able to convince the right people in the company she used to work for to let us conduct the trials.

The most important collaborator on a daily basis has been Karin Tulluan - who works at the Office for Clinical Cancer Research here in Trondheim. With her long experience in clinical research, she has offered invaluable support for a novice.

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

Table of content

List of papers

1 Grønberg BH, Bremnes RM, Aasebø U, Brunsvig P, Fløtten O, Amundsen T, von Plessen C, Wang M, Sundstrøm S; on behalf of the Norwegian Lung Cancer Study Group. A prospective phase II study: High-dose pemetrexed as second-line chemotherapy in small-cell lung cancer. Lung Cancer 63:88-93, 2009

2 Grønberg BH, Bremnes RM, Fløtten Ø, Amundsen T, Brunsvig PF, Hjelde HH, Kaasa S, von Plessen C, Stornes F, Tollåli T, Wammer F, Aasebø U, Sundstrøm S. Phase III study by the Norwegian Lung Cancer Study Group: Pemetrexed plus carboplatin compared with gemcitabine plus carboplatin as firs-line chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 24:3217-24, 2009

3 Grønberg BH, Sundstrøm S, Kaasa S, Bremnes RM, Fløtten Ø, Amundsen T, Hjelde H, von Plessen C, Jordhøy M: Influence of comorbidity on survival, toxicity and health-related quality of life in patients with advanced non-small-cell lung cancer receiving platinum-based chemotherapy. *Submitted*

Abbreviations

BSC	Best supportive care
CCI	The Charlson Comorbidity Index
CIRS-G	Cumulative illness rating scale for geriatrics
CR	Complete response
CT	Computer tomography
CTCAE	Common terminology criteria for adverse events
ED SCLC	Extended disease – small-cell lung cancer
EORTC	European Organization for Research and Treatment of Cancer
EP	Etoposide plus cisplatin
HR	Hazard ratio
HRQoL	Health-related quality of life
LCSS	Lung cancer symptom scale
LD SCLC	Limited disease – small-cell lung cancer
MRI	Magnetic resonance imaging
NLCG	Norwegian Lung Cancer Study Group
NSCLC	Non-small-cell lung cancer
OS	Overall survival
PD	Progressive disease
PET-CT	Positron emission tomography - computer tomography
PR	Partial response
QLQ	Quality of life questionnaire
RR	Response-rates
SCLC	Small-cell lung cancer
SD	Stable disease
TRT	Thoracic radiotherapy
TS	Thymidylate synthase
TTP	Time to progression
ULN	Upper limit normal

Background

Pemetrexed emerged as a new chemotherapeutic agent in the treatment of thoracic malignancies in the late 1990s. It was first registered for the treatment of malignant pleural mesothelioma and showed promising activity in both non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) - with a favorable toxicity-profile. Hence, the Norwegian Lung Cancer Study Group initiated studies to investigate the efficacy of pemetrexed in recurrent SCLC and to compare pemetrexed plus carboplatin with a standard regimen in the first-line treatment of advanced NSCLC.

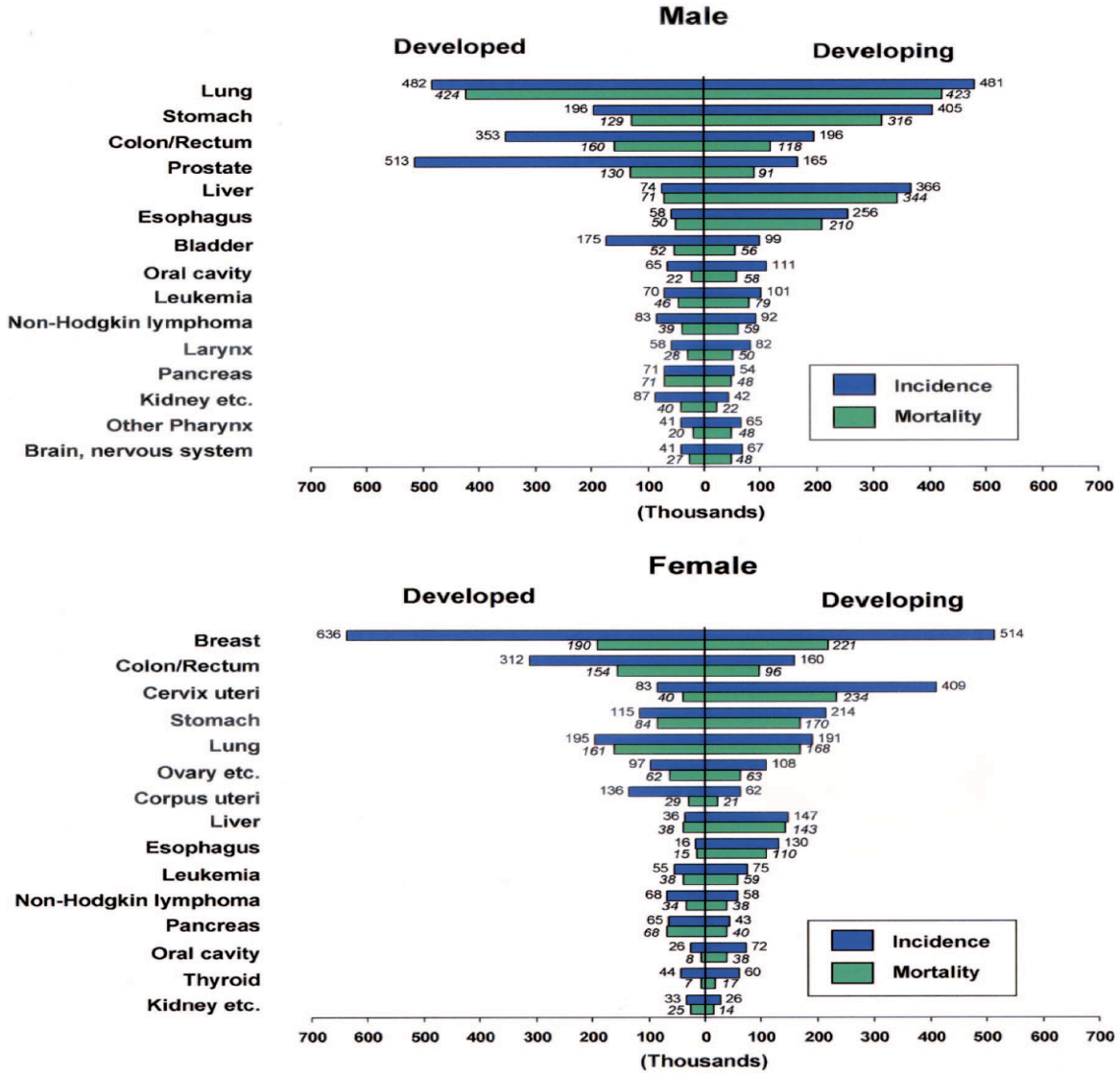
Chemotherapy is the standard palliative therapy for most patients with advanced NSCLC. Many of these patients have co-existing disorders – due to old age or a history of tobacco smoking. Studies have suggested that comorbidity is an independent prognostic factor for survival in NSCLC, but it is unclear whether this is the case for patients with advanced disease receiving platinum-based chemotherapy – and little is known about whether patients with comorbidity have more toxicity or deterioration of health related quality of life (HRQoL) from such therapy. Consequently, the patients in the NSCLC-study were analyzed for the influence of comorbidity on survival, toxicity and HRQoL.

Lung cancer

Epidemiology

Lung cancer is one of the most common malignant diseases and the leading cause of cancer-deaths worldwide. Approximately 1.4 million cases are diagnosed every year, and since the 5-year survival is poor (12-15 %), around 1.2 million die from lung cancer annually (Figure 1).[1]

Figure 1 Estimated numbers of new cases (incidence) and deaths (mortality) of the most common malignant diseases worldwide in 2002.[1] Lung cancer is the most common cancer among men and the fifth most common among women. Among men, it is the leading cause of cancer deaths, while it is number two on the list among women.



In Norway, lung cancer is the third most common cancer (Table 1). In 2007, 2550 new cases were diagnosed – of whom 1076 were women. The year before, 2007 patients – including 794 women - died from lung cancer. This means that more women die from lung cancer than from breast cancer (n=675).

Table 1 The number of new cases of the most common cancers in Norway in 2007 and the number of deaths caused by each type of cancer in 2006.[2]

No.	Site	Incidence 2007	Mortality 2006
1	Prostate	4 391	1 042
2	Breast	2 780	679
3	Lung cancer (all types)	2 550	2 007
4	Colon	2 264	1 160
5	Skin – non-melanoma	1 418	42
6	Bladder, ureter, urethra	1 287	361
7	Melanoma	1 192	249
8	Rectum	1 111	415
9	CNS	994	280
10	Non-hodgkin's lymphoma	797	318
11	Kidney, renal pelvis	697	238
12	Pancreas	678	633
13	Corpus uteri	604	74
14	Stomach	545	349
15	Leukemia	515	323
16	Ovary	449	328
17	Mouth, pharynx	444	137
18	Multiple myeloma	320	260
18	Testis	295	11
20	Cervix uteri	261	79
21	Thyroid	218	44
22	Esophagus	186	177
23	Soft tissue	152	60
24	Liver	145	148
25	Gallbladder, bile ducts	135	62
26	Hodgkin's lymphoma	114	9
27	Mesothelioma	74	60
28	Bone	45	9
	Other	1 282	812
	All sites	25 943	10 366

The incidence of lung cancer is still increasing in Norway, mainly because more and more women are diagnosed with the disease (Figure 2).[3] Women started smoking later than men, and while the proportion of male smokers has declined steadily from the 1960s, the number of daily female smokers peaked in the early 1970s and was stable until 2000 (Figure 3). Today approximately 21 % of the population are daily smokers.[4,5]

Figure 2 The number of new cases of lung cancer per year in Norway from 1953-2007[3]

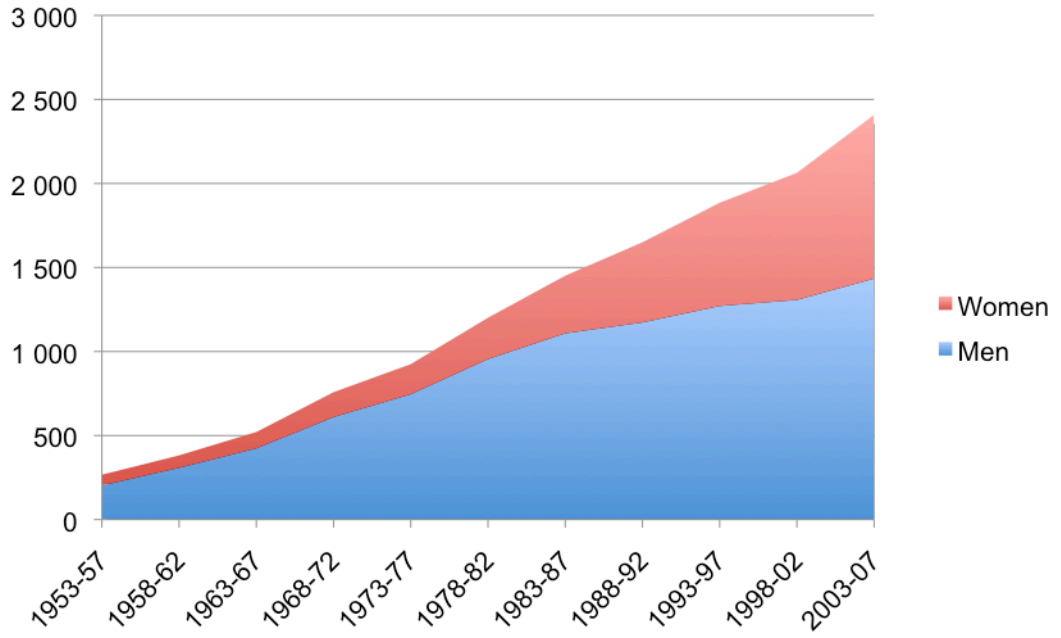
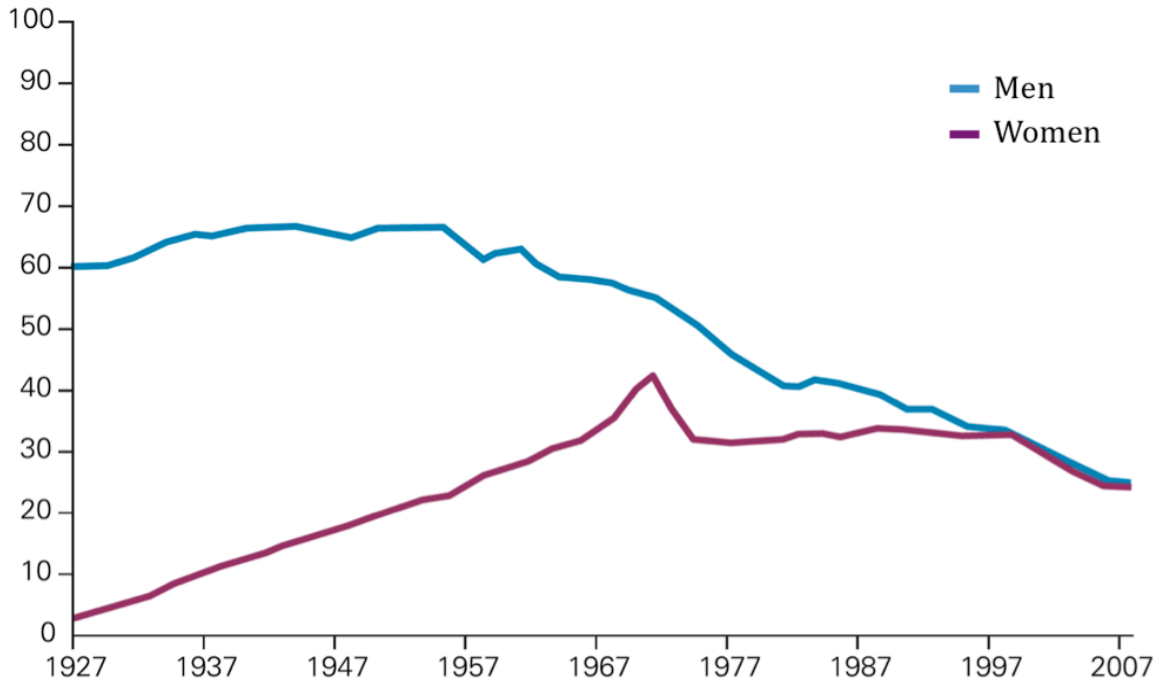


Figure 3 The proportion of daily smokers in Norway from 1927-2007[4]



Etiology

Before tobacco smoking became popular around 1900, lung cancer was a rare disease viewed as "*matters of medical curiosity not known to be in any degree influenced by medicine and too rare to be of much practical importance*".[6] The exception was found in areas where exposure to radon caused lung cancer in 60-80 % of mine workers.[7]

Lung cancer accounted for only 1 % of all cancers seen at autopsy in 1878 in Dresden, Germany. The percentage had risen to 10 % in 1918 and 14 % in 1927.[7] Several etiologic factors were suggested, but already in 1929 the link between tobacco smoking and lung cancer was suspected. Further evidence was provided in the 1940-50s,[8] but it was not generally accepted that tobacco smoking was the main cause of lung cancer (approximately 80-90 % of the cases) until decades later. On July 1, 2004, indoor smoking was banned in all public places in Norway.

Radon, a radioactive gas, is the second major cause of lung cancer (approximately 14 % of the cases). Asbestos is the leading cause of malignant mesothelioma, but can also cause lung cancer. Other carcinogens are arsenic, nickel and chromium.[7] Recent reports suggest that cannabis smoking can cause lung cancer.[9]

Diagnosis and classification

In Norway, most lung cancers are diagnosed from a sample of the primary tumor collected through bronchoscopy. Other methods are CT- or ultrasound-guided per-cutaneous biopsy or fine-needle aspiration - or surgical resection of the primary tumor or a metastasis. The primary analysis is light-microscopy of a tumor sample that has undergone standard staining and/or staining by immunohistochemistry. The techniques to help classifying tumors have improved over the years, and as a result,

the classification system has become more detailed. The current recommendations for the classification of malignant lung tumors were published by the World Health Organization (WHO) in 2004.[10]

The most important distinction is between small-cell (SCLC) and non-small-cell lung cancer (NSCLC), since these subgroups are treated differently. SCLC is sub-classified into small-cell carcinoma (oat cell cancer) and combined small-cell carcinoma, but all patients receive the same therapy. There are more subgroups of NSCLC (Table 2); the most common are adeno-, squamous cell, large cell and adenosquamous carcinomas. Until recently, all patients have received the same therapy, but there are now reports suggesting that some agents are more effective in specific subsets.[11,12]

In some cases, sampling of tissue is not possible or considered to be too risky. The diagnosis is then based on the patient's history of exposure to risk factors, clinical features and radiological examination(s).

Trends in the incidence of subgroups of lung cancer

Adeno-, squamous cell- and small-cell carcinomas account for 80-90 % of all cases of lung cancer, but the incidence of the various subgroups have changed over the last 30 years. In recent years, fewer patients develop squamous cell carcinoma or small-cell carcinoma, whereas adenocarcinoma is now the most frequent subtype.[13] Worldwide, the incidence of SCLC has fallen to approximately 13 %,[13,14] but in Norway the proportion has been stable (around 18 %) as late as in 1997-2004 *(personal communication from the Norwegian Cancer Registry, September 2005).* This means that there are approximately 430 new cases of SCLC annually, which makes it the 18th most common cancer in Norway (Table 1).

The reasons for the changes in the distribution of subgroups of lung cancer are not clear, but the most accepted hypotheses are that this is due to a change in the chemical composition of the tobacco-products[15] and that filtered cigarettes with lower nicotine content lead to deeper inhalation and thereby to exposure of more peripheral parts of the lungs to carcinogens;[16,17] adenocarcinomas are usually more peripherally located than squamous cell and small cell lung cancer.

For some reason, less research focuses on SCLC than NSCLC - even though SCLC causes approximately 4 % of all cancer deaths and is as common as e.g. ovary cancer, myeloma or Hodgkin's lymphoma – all subject to much research activity. Over the last 15 years, the number of publications on NSCLC has increased rapidly while the number of publications on SCLC has been stable (Figure 4).[18]

Figure 4 Numbers of abstracts published for American Society of Clinical Oncology annual meetings between 1980 and 2006 for (1) all lung cancer; (2) non-small-cell lung cancer; (3) small-cell lung cancer.[18]

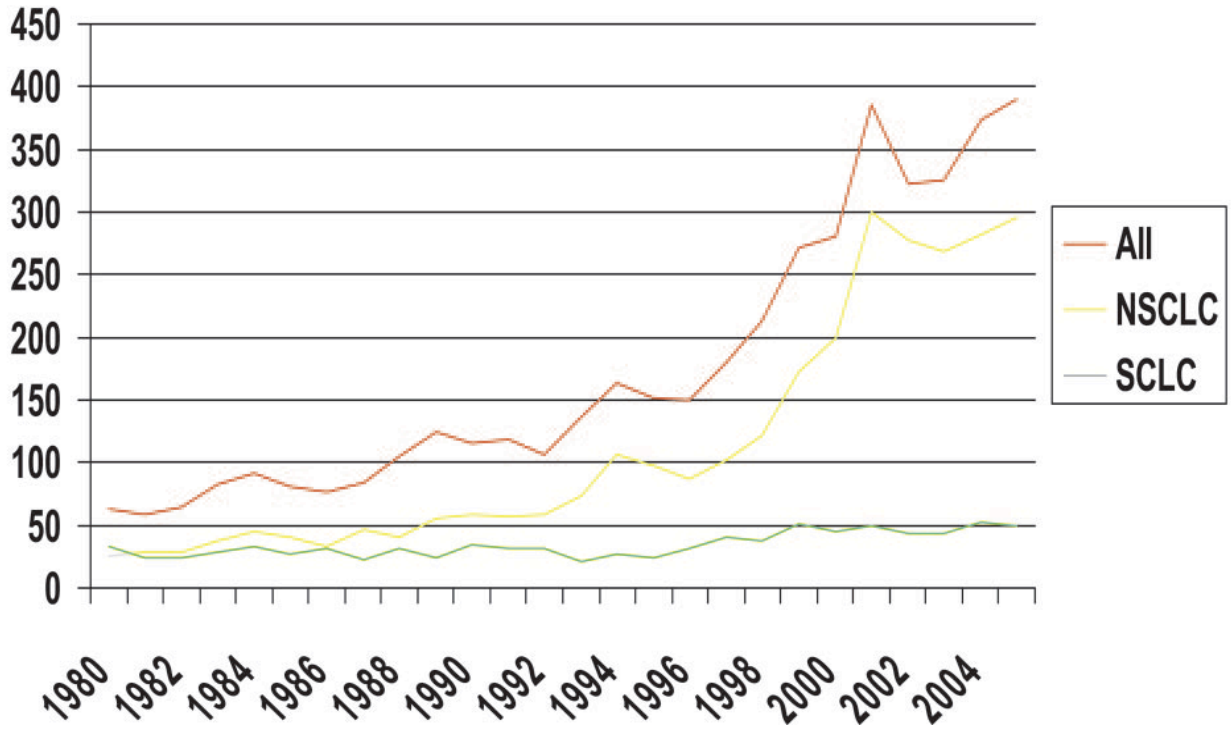


Table 2 The latest classification of lung tumors by the World Health Organization (2004). The distinction between small-cell and non-small-cell lung cancer is the most important since these tumors are treated differently. Adeno-, large cell and squamous cell carcinomas are the most common subgroups of non-small cell lung cancer.[10]

Malignant epithelial tumours
- Squamous cell carcinoma
  - Papillary
  - Clear cell
  - Small cell
  - Basaloid
- Small cell carcinoma
  - Combined small cell carcinoma
- Adenocarcinoma
  - Adenocarcinoma, mixed subtype
  - Acinar adenocarcinoma
  - Papillary adenocarcinoma
  - Bronchioloalveolar carcinoma
    - Nonmucinous
    - Mucinous
    - Mixed nonmucinous and mucinous or indeterminate
  - Solid adenocarcinoma with mucin production
    - Fetal adenocarcinoma
    - Mucinous (“colloid”) carcinoma
    - Mucinous cystadenocarcinoma
    - Signet ring adenocarcinoma
    - Clear cell adenocarcinoma
- Large cell carcinoma
  - Large cell neuroendocrine carcinoma
    - Combined large cell neuroendocrine carcinoma
  - Basaloid carcinoma
  - Lymphoepithelioma-like carcinoma
  - Clear cell carcinoma
  - Large cell carcinoma with rhabdoid phenotype
- Adenosquamous carcinoma
- Sarcomatoid carcinoma
  - Pleomorphic carcinoma
  - Spindle cell carcinoma
  - Giant cell carcinoma
  - Carcinosarcoma
  - Pulmonary blastoma
- Carcinoid tumour
  - Typical carcinoid
  - Atypical carcinoid
- Salivary gland tumours
  - Mucoepidermoid carcinoma
  - Adenoid cystic carcinoma
  - Epithelial-myoepithelial carcinoma
- Preinvasive lesions
  - Squamous carcinoma in situ
  - Atypical adenomatous hyperplasia
  - Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

- Mesenchymal tumours
  - Epithelioid haemangioendothelioma
  - Angiosarcoma
  - Pleuropulmonary blastoma
  - Chondroma
  - Congenial peribronchial myofibroblastic tumour
  - Diffuse pulmonary lymphangiomatosis
  - Inflammatory myofibroblastic tumour
  - Lymphangioleiomyomatosis
  - Synovial sarcoma
    - Monophasic
    - Biphasic
  - Pulmonary artery sarcoma
  - Pulmonary vein sarcoma

Benign epithelial tumours
- Papillomas
  - Squamous cell papilloma
    - Exophytic
    - Inverted
  - Glandular papilloma
  - Mixed squamous cell and glandular papilloma
- Adenomas
  - Alveolar adenoma
  - Papillary adenoma
  - Adenomas of the salivary gland type
    - Mucous gland adenoma
    - Pleomorphic adenoma
    - Others
  - Mucinous cystadenoma

Lymphoproliferative tumours
- Marginal zone B-cell lymphoma of the MALT type
- Diffuse large B-cell lymphoma
- Lymphomatoid granulomatosis
- Langerhans cell histiocytosis

Miscellaneous tumours
- Harmatoma
- Sclerosing hemangioma
- Clear cell tumour
- Germ cell tumours
  - Teratoma, mature
  - Immature
  - Other germ cell tumours
- Intrapulmonary thymoma
- Melanoma

Metastatic tumours

Staging

As for cancer patients in general, the extent of disease is the most significant prognostic factor in lung cancer – and it is also the most important baseline characteristic taken into consideration when recommending therapy (Figure 5).[19]

The TNM Classification of Cancer Stage was developed in the 1940s by Dr. Denoix at the Institut Gustave-Roussy in France and is used to describe the extent of the primary tumor ("T"), lymph node involvement ("N") and whether distant metastases are present ("M") (Table 3). Based on the TNM-status, the stage of disease is then defined (Table 4). The descriptors for T, N and M have changed over the years as they have been based on larger and larger databases. The seventh edition of the TNM classification has been proposed by the International Association for the Study of Lung Cancer (Table 3 & 4)[19] and is due to be released in December 2009 by the UICC – The International Union Against Cancer (www.uicc.org).

For TNM-staging of lung cancer, a CT scan of the thorax and upper abdomen and a clinical investigation including examination of lymph nodes on the neck and in the supraclavicular regions is recommended.[20] An MRI of the brain and a bone scan are routinely conducted when staging SCLC; in NSCLC if metastases to these organs are suspected. A PET-CT scan is recommended for all patients eligible for surgery since it often reveals more extensive disease than a CT scan alone.[21]

SCLC is traditionally divided into limited disease (LD) (approximately 40 % of patients[14]) and extensive disease (ED).[22] In LD, all lesions can be included in a radiotherapy field – this usually means that they are located within one hemi-thorax and the mediastinum. ED-patients have more widespread disease. The rationale for dividing between LD and ED, is that concurrent chemoradiotherapy prolongs survival when compared with chemotherapy alone,[23] but can only be administered to LD-

patients. For research purposes, a TNM-stage should be defined also for SCLC-patients, since the definition of LD vs. ED varies.

Other examinations

Performance status (Table 5) and weight loss are important prognostic factors.[24] Laboratory testing of hematopoietic-, liver- and renal-function gives an impression of overall health status and are necessary for correct dosage of chemotherapy. Heart- and lung function tests are often needed to determine whether patients are eligible for surgery or curative radiotherapy.

Table 3 Descriptors of TNM for lung cancer (seventh edition of the TNM Classification of malignant tumors)[19]

T (Primary tumor)	
Tx	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)[a]
T1a	Tumor ≤ 2 cm in greatest dimension
T1b	Tumor > 2 cm but ≤ 3 cm in greatest dimension
T2	Tumor > 3 cm but ≤ 7 cm or tumor with any of the following features (T2 tumors with these features are classified T2a if ≤ 5 cm): • Involves main bronchus, ≥2 cm distal to the carina • Invades visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor > 3 cm but ≤ 5 cm in greatest dimension
T2b	Tumor > 5 cm but ≤ 7 cm in greatest dimension
T3	Tumor >7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus < 2 cm distal to the carina[a] but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe

N (Regional lymph nodes)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

M (Distant metastasis)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion*b*
M1b	Distant metastasis

[a] The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1.
[b] Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as T1, T2, T3, or T4.

Table 4 Definition of stage of lung cancer based on TNM-status (seventh edition of the TNM Classification of malignant tumors)[19]

T/M descriptor	Proposed T/M	N0	N1	N2	N3
T1 (≤ 2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (> 2-3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (≤ 5 cm)	T2a	IB	IIA	IIIA	IIIB
T2 (> 5-7 cm)	T2b	IIA	IIB	IIIA	IIIB
T2 (> 7)	T3	IIB	IIIA	IIIA	IIIB
T3 invasion		IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)		IIB	IIIA	IIIA	IIIB
T4 (extension)	T4	IIIA	IIIA	IIIB	IIIB
M1 (ipsilateral lung)		IIIA	IIIA	IIIB	IIIB
T4 (pleural effusion)	M1a	IV	IV	IV	IV
M1 (contralateral lung)		IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

Figure 5 Survival by stage of lung cancer (seventh edition of TNM)[19]

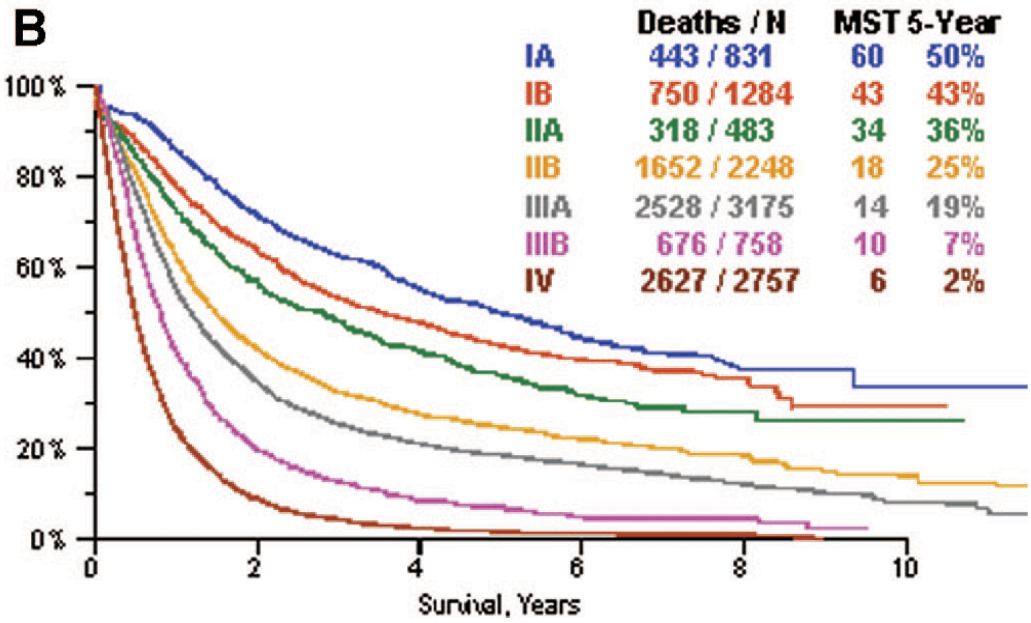


Table 5 WHO performance status[25]

Grade	Definition
0	Asymptomatic (Fully active, able to carry on all predisease activities without restriction)
1	Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)
2	Symptomatic, < 50% in bed during the day (Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours)
3	Symptomatic, > 50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)
4	Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)
5	Dead

The history of the treatment of lung cancer

The first surgical resection for lung cancer was performed in 1821 by Milton Anthony,[26] but it was a successful pneumonectomy by dr. Evarts A. Graham in 1933[6] that first demonstrated that lung carcinoma was a curable disease. Palliative radiotherapy has been used since the 1940s,[27] radical radiotherapy on inoperable patients was first attempted in the 1950s. Chemotherapy was introduced in 1948,[28]

but the role of chemotherapy was not established until a meta-analysis published in 1995 showed that such therapy prolonged survival.[29] Newer, more effective chemotherapeutic agents and conformal radiotherapy were introduced during the 1990s. The benefit of second-line chemotherapy in SCLC was first demonstrated in 1989;[30] in NSCLC in 2000[31]. In the recent years, a new class of drugs – so-called targeted therapy – has been introduced. These compounds are molecules that have been designed to block pathways essential for the proliferation of tumor cells. The first drug entered clinical practice in 2005 when erlotinib demonstrated prolonged survival and improved HRQoL when compared to best supportive care (BSC) alone as second-/third-line therapy in NSCLC.[12]

General recommendations for the treatment of non-small-cell lung cancer

All patients with localized or locally advanced disease (stage I – III) are considered for surgery. Two studies have demonstrated that adjuvant chemotherapy after radical surgical resection improves 5-year survival; from 40.4 % to 44.5 %[32] in one study and from 54 % to 69 % in another.[32,33]

Radical radiotherapy is a treatment option in medically inoperable stage I-II patients[34] and in stage III (locally advanced disease).[35] A Cochrane meta-analysis concludes that concurrent radio-/chemotherapy reduces the risk of death when compared to radiotherapy alone or sequential chemo-radiotherapy.[35]

For patients with more advanced disease, platinum-based two-drug combination chemotherapy is the recommended treatment.[36] This therapy prolongs survival and improves HRQoL.[37] Untreated, the median survival is 4-5 months, while median survival after chemotherapy is 7-12 months.[11,37-40]

There are indications that adding targeted agents to cytotoxic chemotherapy may prolong survival. In one study, the addition of bevacizumab, an anti-angiogenic agent, prolonged survival in patients receiving platinum-chemotherapy from 10.3 to 12.3 months.[40] However, a later study failed to confirm this.[41] In a recent study, patients who received cetuximab in addition to chemotherapy (a monoclonal antibody blocking the EGFR-receptor in tumor cells) had a longer survival than the patients who received chemotherapy alone (11.3 vs. 10.3 months; p=.044).[42]

Second-line chemotherapy and erlotinib are superior to best supportive care alone in recurrent disease.[12,31] Palliative radiotherapy is a treatment option for brain metastases, tumor compression of vital structures, ulcers and painful lesions.

Palliative chemotherapy as first-line treatment of advanced NSCLC

The first report on the use of chemotherapy in inoperable lung cancer was published in 1948 by Karnofsky et al.[28] Of 35 patients, 74 % had symptom improvement and 49 % had objective improvement from one course of methyl-bis (ß-chloroethyl) amine hydrochloride. However, the duration of response was short – from two weeks to two months.

The first randomized trial comparing two chemotherapeutic agents in the treatment of cancer was published in 1960 by Zubrod et al.[43] In this study, 258 patients with breast (n=76) and lung cancer (n=132), malignant melanoma (n=30) and Hodgkin's disease (n=20) were randomized to receive either nitrogen mustard or triethylene thiophosphamide. Among the lung cancer patients, there was a higher objective response-rate, but not significantly longer survival for the nitrogen mustard therapy.

The first evidence of the cytotoxic properties of cisplatin was published in 1969.[44] The first human studies demonstrating activity were conducted in the early 1970s,[45,46] and later studies demonstrated response rates of 20-30 % in NSCLC.[47-49] Several other compounds showed single-agent activity in NSCLC in the same era; cyclophosphamide, etoposide, vinblastine, vindesine, doxorubicin and methotrexate. Soon, studies comparing the efficacy of combination chemotherapy with monotherapy were conducted. Doublets improved response rates, but not survival - and no standard was defined until a meta-analysis was published by the Non-Small-Cell Lung Cancer Collaborative Group in 1995.[29] In this study, which established the use of chemotherapy in NSCLC, cisplatin-containing regimens were found to be superior to no chemotherapy in all patient-categories. In advanced disease, a hazard ratio of .73 in favor of chemotherapy over best supportive care alone was estimated; equivalent to an improvement of 1-year survival of 10 % or an increased median survival of 1.5 months. An updated meta-analysis published in 2008 confirmed the survival benefit of chemotherapy over BSC alone and estimated a prolongation of median OS from 4.5 to 6 months and an improvement in 1-year survival from 20 % to 29 %.[37] Later, meta-analyses have demonstrated that platinum-based combination chemotherapy is superior to single-agent therapy.[50,51]

Several new, “third-generation”, cytotoxic drugs were developed in the 1990s. Most important were vinorelbine, gemcitabine, docetaxel and paclitaxel. Several studies have demonstrated that these agents in combination with cisplatin are more effective than single-agent cisplatin[52,53] and older cisplatin-based combinations,[54-56] but no particular combination has proven to be superior to the others.[57,58] Typically, response rates of 30-40 %, median OS of 7-12 months and a 1-year survival of 30-40

% have been achieved in clinical studies of combinations of third-generation and platinum compounds.

With the introduction of third-generations drugs, there has been some interest in non-platinum doublet chemotherapy. Several combinations have showed similar efficacy and signs of less toxicity compared with platinum-combinations,[59-62] and non-platinum combinations are considered to be an alternative to platinum-doublets.[36] Higher response rates have been observed for three-drug combinations when compared with doublets, but these regimens cause more toxicity and have failed to prolong survival.[51]

Carboplatin

Carboplatin, a platinum-analogue, entered clinical trials in the early 1980s. The compound is easier to administer (since the long pre- and posthydration needed for cisplatin is not required) and causes less neurotoxicity, nephrotoxicity, nausea and vomiting. However, carboplatin induce more myelosupression (especially thrombocytopenia) than cisplatin.[63,64]

There is an ongoing debate whether carboplatin is as effective as cisplatin. No single study has been able to definitely answer this question, but in two meta-analyses, cisplatin was found to give higher response-rates and longer survival when combined with a third-generation drug.[63,64] This difference was not detected in a third meta-analaysis.[65] In palliative therapy, especially in patients with poor performance status, carboplatin is often preferred due to easier administration and less subjective toxicity – though the meta-analyses did not include patient reported outcomes.

In the first clinical trials on carboplatin, the administered dose was around 400 mg/m2. It was soon observed that patients with reduced renal function had more

thrombocytopenia than others.[66,67] Hence, it has become more common to calculate the dose of carboplatin according to the renal clearance of the drug.

Two formulas have been developed to estimate the dose for the individual patient; Calvert's and Chatelut's formula. Calvert's formula was derived from estimating the correlation between the plasma-concentration of carboplatin and glomerular filtration rate (GFR) in patients who received the drug. The formula was then validated in another population and refined to:

Dose (mg) = target area under the free carboplatin plasma concentration versus time curve (AUC) x (GFR + 25).[68]

The best method for estimating GFR is to measure renal clearance of an radioactive isotope such as CrEDTA,[69] but since this method is time-consuming and not available in all hospitals, it is common to estimate GFR by calculating creatinine-clearance using Cockcroft-Gault's formula:[70]

$$\textit{Creatinine-clearance} = \frac{(140 - age[y]) x (bodyweight[kg])}{72 x serum - creatinine[mg/dl]} \textit{ x .85 if a woman}$$

The most common dose in advanced NSCLC is Calvert AUC=6.[71,72]

Chatelut's formula was derived from analyses of 34 patients receiving carboplatin. The formula was then validated in 36 other patients and the following formula was found to best predict carboplatin-clearance (CL):

Dose (mg) = carboplatin-clearance (CL) / AUC[73]

where CL was defined for men as:

$$\textit{CL (mg/dl)} = 0.134 x bodyweight[kg] + 0.686 x \frac{218 x bodyweight[kg] x (1 - 0.00457 x age[y])}{serum - creatinine[mg/dl] x 88.4}$$

and for women as:

$$CL\ (mg/dl) = 0.134 x bodyweight[kg] + \frac{218 x bodyweight[kg] x (1 - 0.00457 x age[y])}{serum - creatinine[mg/dl] x 88.4}$$

A common dose in advanced NSCLC is Chatelut AUC=4.[38,39]

The Calvert's formula is considered the best method for calculating the carboplatin-dose provided the GFR is measured.[68,73] Studies have demonstrated that Calvert's formula substituting the measured GFR with a calculated creatinine-clearance (Cockcroft-Gault's formula) is better for predicting the correct dose of carboplatin than Chatelut's formula,[74,75] and most studies on NSCLC use this method.

Duration of chemotherapy

The optimal duration of therapy has been the subject to several studies.[76] The survival benefit of chemotherapy is limited, and the treatment often causes side-effects that may influence the patient's well-being. Several studies have showed higher response-rates and longer progression-free survival, but not prolonged survival, from more than 3-4 cycles of chemotherapy.[38,77,78]

Worth noticing, however, is that a recent study demonstrated that maintenance pemetrexed therapy prolonged survival when compared to BSC alone in patients who did not progress during four cycles of platinum-based first-line chemotherapy.[79]

Treatment of patients with poor performance status and elderly

Among patients with advanced NSCLC, performance status (PS) (Table 5) is the most important prognostic baseline characteristic.[24,80] There is a general agreement that patients with PS 3 - 4 do not have a survival benefit from chemotherapy and patients with so poor general condition would have a high risk of experiencing severe

toxicity. It is debated what the optimal therapy for PS 2 patients is, while all PS 0-1 patients receive chemotherapy unless there are specific, individual contraindications.

Early it was recognized that PS 2 patients have significantly shorter survival than better functioning patients[24] and subgroup analyses suggest that they experience more toxicity and lower RR.[57,81-83] In a study comparing four of the most commonly used regimens in advanced NSCLC, accrual of PS 2 patients was stopped due to short survival and a high incidence of adverse events including five deaths.[57] On a closer look, however, only two of the deaths were considered related to the study treatment – which was similar to the proportion of treatment related deaths among PS 0-1 patients.[84] On the other hand, in the meta-analysis of chemotherapy compared with BSC alone, the PS 2 had a statistically similar survival benefit as the PS 0-1 patients[29] and a recent publication shows that PS 2-patients had more improvement of HRQoL from chemotherapy than patients with PS 0-1.[85] Unfortunately, PS 2 patients have been excluded from many of the recent large, randomized studies[11,40,79] - due to concerns about tolerability and lack of benefit from the treatment.

Several studies have shown that single-agent therapy with modern agents is superior to BSC alone, and some argue that PS 2 patients should be offered monotherapy since it is less toxic than combination therapy,[86-88] Only one study has compared monotherapy with platinum-doublet chemotherapy in PS 2 patients. Combination therapy led to significantly higher RR (36 % vs 12 %), longer PFS (4 vs. 2.8 months; p=.32) and OS (6.9 vs. 5.2 months; p=.38). Unfortunately, the power of the study was low since accrual was stopped before the target number of patients was reached. Subgroup analyses from larger randomized trials, suggest that doublet chemotherapy increases response rates and prolongs survival when compared to

monotherapy also for PS 2 patients[83,89]. Considering that a large proportion of patients have poor performance status, there is a need to enroll these patients onto clinical studies to gain further knowledge about how they should be treated.

There is also little evidence to define the optimal therapy for elderly. Despite the fact that the median age at diagnosis is approximately 70 years, elderly are consistently under-represented in clinical trials.[90-92] The definition of “elderly” also varies from 65-75 years.

The benefit of chemotherapy among elderly (> 70 years) was demonstrated in a study comparing vinorelbine monotherapy with BSC alone;[86] patients who received chemotherapy had significantly longer survival and reported better HRQoL. In the meta-analysis of chemotherapy compared to BSC alone, the elderly had the same benefit from the therapy as younger patients.[37]

One trial suggested a survival benefit of gemcitabine plus vinorelbine over vinorelbine alone,[93] while others have failed to confirm the superiority of non-platinum doublets over single-agent therapy.[94,95] No studies have compared monotherapy with a platinum-doublet, though subset analyses have indicated that elderly benefit from and tolerate standard chemotherapy as well as younger patients.[96,97] However, looking at the eligibility criteria in these studies, one can question whether the elderly patients analyzed are fully representative for the patients seen in the everyday clinic; patients with performance status 2 or severe comorbidity were excluded.

General recommendations for the treatment of small-cell lung cancer

Untreated, small-cell lung cancer (SCLC) is an aggressive disease with a median survival of 2-4 months.[22] One reason is that SCLC spread rapidly and in most cases

has to be considered a systemic disease even in lower TNM-stages. This is probably the reason why randomized studies have failed to demonstrate a survival benefit of surgery in SCLC.[98,99]

Still, there are data suggesting that surgery may improve survival in very early disease[100,101] and in carefully selected patients;[101,102] possibly due to better methods for staging than when the randomized trials were conducted. Adjuvant chemo- and radiotherapy are often administered after surgery.[101,102] In Norway approximately five patients undergo surgery for SCLC annually.[103]

Chemotherapy is the primary therapy for patients with locoregional or metastatic disease. In 1969, cyclophosphamide was the first drug to demonstrate a survival benefit over best supportive care in SCLC.[22] Later, other agents such as doxorubicin,[104] vincristine,[105] etoposide[106] and cisplatin[107] demonstrated activity in SCLC. Further studies established etoposide plus cisplatin (EP) as the standard combination; a meta-analysis demonstrated that cisplatin-containing regimens were superior to non-platinum combinations[108] and a review concluded that etoposide-containing combinations were superior to other regimens.[109] Later, a phase III confirmed that EP was superior to CAV (cyclophosphamide, adriamycin and vincristine), though the benefit was mainly observed in patients with LD.[110]

In recent years, several studies have investigated the role of irinotecan in SCLC[111-114] after a Japanese study demonstrated that irinotecan plus cisplatin was superior to EP in ED SCLC (9.4 vs. 12.8 months, p=.002).[115] Only one study was able to confirm that irinotecan was superior to etoposide,[114] and cisplatin plus etoposide is still considered the standard regimen; though a review concluded that irinotecan provides a longer overall survival and higher response rates than etoposide.[116]

Since SCLC is very sensitive to chemotherapy, several methods for intensifying chemotherapy have been investigated; three drug combinations with and without granulocyte colony stimulating agents,[117-119] maintenance chemotherapy[120] and high-dose chemotherapy with or without autologous stem-cell transplantation.[121-124] These regimens have resulted in higher response rates, longer progression free survival, but not prolonged overall survival. They are also more toxic.

Carboplatin is more convenient to administer and except for myelosupression, the compound offer less toxicity than cisplatin. For that reason, it may be more suitable to elderly and patients with severe comorbidity. The conclusion of a review was that carboplatin provides the same efficacy as cisplatin in SCLC.[125] However, the studies reviewed had small sample sizes; only one phase III study has compared carboplatin with cisplatin in addition to etoposide in SCLC.[126] In this study, similar efficacy was observed in both arms, but the study only enrolled a total of 143 patients. Thus, cisplatin is considered to be the standard platinum compound – at least in patients with LD SCLC[110,127] and in patients with ED SCLC who have a good performance status.[111,112,128]

The first studies on the combination of chemotherapy and thoracic radiotherapy (TRT) were conducted in the 1970s.[129,130] The role of TRT was controversial until a meta-analysis of 16 trials demonstrated a 14 % reduction in mortality corresponding to an increase in 3-year survival from 8.9 to 14.3 % (p=.001).[131] One reason was that TRT in combination with alkylating agents result in severe toxicity and TRT had to be administered before, in-between or after the chemotherapy. In contrast, TRT can be administered concurrent with EP – which is more effective than sequential therapy; a meta-analysis suggest that minimizing the time from start of chemotherapy until the end of TRT improves survival.[132] The

methods for staging and techniques for radiotherapy at that time may also be reasons for why the survival benefit of combined modality therapy was difficult to detect.

The optimal radiotherapy-schedule remains to be defined. In the first trials, 32-50 Gy were administered in 8-25 fractions, later 45 Gy/25[133] fractions and 40 Gy/15[134] fractions were commonly used schedules. The longest survival has been observed in a trial comparing 1.5 Gy/2 fractions a day in 15 days with 45Gy/25 fractions.[127] The patients who received twice-daily radiotherapy had a significantly longer survival (23 vs. 19 months, p=.04) and a higher proportion survived 2 years (47 % vs. 41 %) and 5 years (26 % vs. 16 %). A question remains, however; if time from start of chemotherapy until end of TRT influences survival, e.g. 40 Gy /15 fractions may provide the same efficacy.

At diagnosis, approximately 10 % of SCLC patients have brain metastases and up to 50 % develop during the course of the disease. Brain metastases often cause severe morbidity and are a common cause of death, especially in patients who have no systemic progression. Since the 1970s, the brain has been considered as a sanctuary where micrometastases survive due to poor penetration of cytotoxic drugs through the blood-brain barrier.[135] Hence, prophylactic cranial irradiation (PCI) was investigated as a method for preventing development of brain metastases. The early studies demonstrated a lower frequency of brain metastases, but not prolonged survival.[136] A possible explanation was that PCI only prolonged survival in patients who had a complete or near complete response to chemotherapy, since patients with systemic progression would die of failure of other organs than the brain.[137] PCI was established after a meta-analysis demonstrated that patients with LD SCLC in complete remission after primary chemotherapy (or chemoradiotherapy) had a 16 %

risk reduction of death corresponding to an improvement in 3-year survival - from 15 % to 21 % - as well as a reduction in the risk for developing brain metastases of 54 %.[138]

A recent study, have demonstrated that also patients with ED SCLC who respond to primary chemotherapy have a lower risk for developing brain metastases (15 % vs. 40 %) and prolonged survival (6.7 vs. 5.4 months) if they receive PCI.[139]

In LD SCLC, approximately 80 % of patients respond to primary therapy and median survival is 15-22 months;[110,127,134] 5-year survival 9-26 %.[110] Patients with ED-SCLC typically respond in 40-50 % of cases and have a median survival of 8-10 months;[110,111] 2-year survival is 4-8 %.[110,111] A large proportion (37 – 60%) of patients are offered second-line[110,111] – and some even third-line[140] – chemotherapy at relapse. Palliative radiotherapy is offered as in NSCLC.

Second-line chemotherapy in recurrent SCLC

Despite high response-rates to primary therapy, few patients with SCLC are cured. In ED SCLC, median progression free survival is 4-6 months,[111,112] in LD SCLC 12-15 months.[134]

At relapse, most patients are considered for second-line therapy. Several regimens have yielded response rates of 10-25 % and a median survival of 25-39 weeks in recurrent disease.[141-144] Response and response-duration after first-line chemotherapy is the strongest predictive factor for response to second-line therapy.[141,145] Patients with a response-duration of > 3 months are therefore defined as “sensitive” and those with shorter response duration as “refractory”.

Few have investigated the absolute benefit of salvage therapy. A study investigating the duration of chemotherapy for SCLC suggested that chemotherapy

at relapse prolonged survival.[30] In this study, patients were first randomized to receive either four or eight cycles of primary chemotherapy (cyclophosphamide, vincristine and etoposide). On disease progression, the patients were then randomized to receive either second-line chemotherapy (up to nine cycles of methotrexate plus doxorubicin) or symptomatic treatment alone. The patients who received four cycles only had an inferior survival (30 weeks) compared with the other groups (38-42 weeks, no significant difference between the groups).

The only randomized study to compare second-line chemotherapy with BSC alone was published as late as in 2006. Onto this trial, 141 patients considered ineligible for intravenous chemotherapy were enrolled. Patients who received oral topotecan had longer survival (26 vs. 14 weeks; p=.01) and slower decline of HRQoL.[146] It is worth noting that the patients enrolled were considered ineligible for intravenous chemotherapy and 53 % were “refractory”. The “sensitive” patients enrolled either refused intravenous chemotherapy due to concerns about toxicity or were found unsuitable for such therapy due to severe comorbidity. One would expect that the survival benefit is even larger for fit, “sensitive” patients, but this has in principle not been thoroughly investigated.

Pemetrexed

Molecular structure, mechanism of action and properties

Pemetrexed, N-[4-[2-(2-amino-3,4-dihydro-4-oxo-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid (LY231514) (Figure 6), is a synthethic antifolate that inhibits enzymes involved in growth and replication of tumor cells; more specifically three enzymes involved in purine and pyrimidine synthesis - thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide

formyltransferase (GARFT) (Figure 7).[147] Purines and pyrimidines are the building blocks of DNA and RNA. The drug is a substrate for the enzyme folylpolyglutamate synthetase (FPGS), which leads to polyglutamation of pemetrexed – converting the drug to a form that is retained intracellularly, producing a prolonged drug effect.[148] The multitargeted inhibition and the prolonged action may explain why pemetrexed shows a broader and more potent antitumor activity than other antifolates such as fluorouracil, methotrexate and raltitrexed.[149,150]

Figure 6 Molecular structure of pemetrexed (LY 231514)

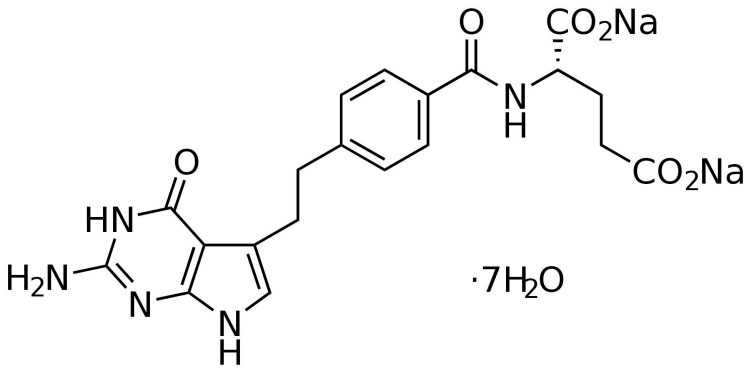
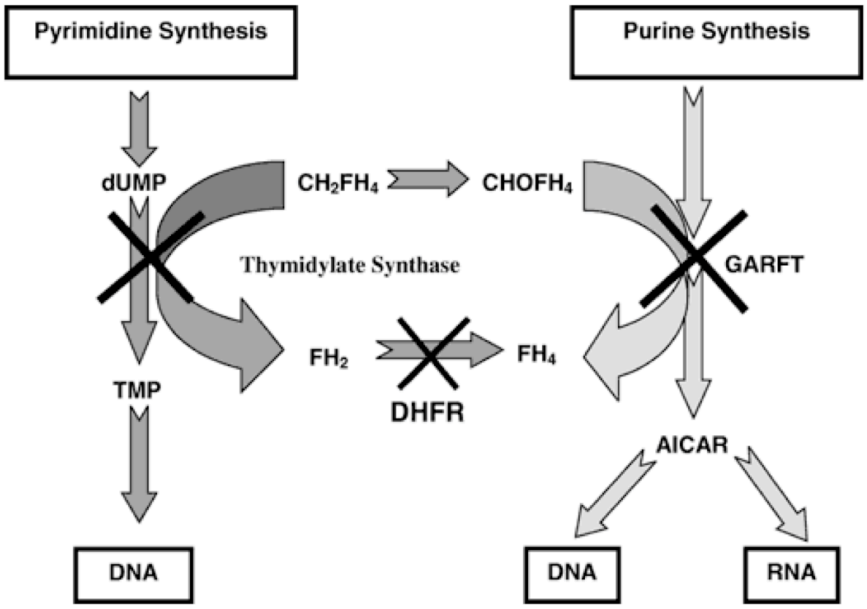


Figure 7 Mechanisms of action of pemetrexed



In preclinical models, pemetrexed has demonstrated activity against several tumor types: Colon, renal and hepatic cancer – as well as NSCLC and SCLC.[147]

Pemetrexed is rapidly eliminated (half-life of 3.5 hours), mainly via the kidneys (70-90 % of the drug is found in the urine within 24 hours).[151] In a phase I trial, increased drug exposure was observed in patients with impaired renal function, and a patient with GFR of 19 ml/min died of drug related toxicity.[152] Hence, it is recommended that patients have a creatinine-clearance of > 45 ml/min and do not use concurrent high-dose acetylic-salisylic acid (ASA) or non-steroidal anti-inflammatory drugs (NSAIDs).

Toxicity profile and the role of supplementation with vitamin B12 and folic acid

After the initial phase I/II trials, a schedule of a 10-minute infusion every 3 weeks of a dose of 500 mg/m^2 was selected for further clinical trials.[153] The dose-limiting toxicity was grade 3-4 neutropenia and thrombocytopenia.[153] Other common toxicities were diarrhea, oral mucositis and rash. Prophylactic use of corticosteroids reduces the frequency of rash.[153]

In the first phase III trial of pemetrexed,[154] onto which patients with malignant mesothelioma were enrolled, there was initially a high incidence of treatment-related deaths. A multivariate analysis in another study showed that elevated levels of homocysteine and methylmalonic acid were associated with febrile neutropenia.[155] Subsequently, all new patients in the mesothelioma-trial were supplemented with folic acid and vitamin B12. This led to a reduction in the frequency and severity of hematologic and non-hematologic toxicities. This again led to longer survival in supplemented patients – probably since they were able to receive more

chemotherapy.[154] The most common side-effects in the supplemented patients were nausea, fatigue, vomiting, diarrhea, dehydration and stomatitis.[154,156]

Later, new phase I trials have demonstrated that a pemetrexed-dose of 1000 mg/m^2 is well tolerated in supplemented patients.[157,158] Consequently, it is recommended that all patients who receive pemetrexed are supplemented with vitamin B12 and folic acid.

Clinical trials

In early clinical trials, single-agent activity was observed in patients with malignant mesothelioma,[71] NSCLC,[159] colorectal,[160] pancreatic, bladder,[161,162] head and neck,[163] cervical,[162] gastric[164] and breast carcinomas.[163]

In the first study to show a significant survival benefit of chemotherapy in malignant pleural mesothelioma, patients who received pemetrexed plus cisplatin had a longer survival than patients receiving cisplatin alone (12.1 vs. 9.3 months, p=.020).[154]

Pemetrexed in lung cancer

Results from several clinical studies of pemetrexed in the treatment of lung cancer were available when our studies were designed.

A phase II study showed promising activity of pemetrexed in combination with carboplatin and cisplatin as first-line therapy of ED SCLC.[165] Response rates, median survival time and 1-year survival was 35 %, 7.6 months, and 33 % for the cisplatin-combination; 40 %, 10.4 months and 39 % for the carboplatin combination. This is similar to what has been observed in studies of EP in ED SCLC.[110,111]

A phase III study of second-line therapy in NSCLC, showed that pemetrexed monotherapy was as effective and less toxic than the standard therapy at that time –

docetaxel monotherapy.[156] Two phase II studies demonstrated single agent activity in chemonaive NSCLC patients.[159,166]

Table 6 Phase II studies of pemetrexed monotherapy as first-line therapy of NSCLC

	Chemotherapy	n	Response rates	Overall survival	1-year survival
Rusthoven[159]	Pemetrexed 5-600 mg/^{2}	33	23 %	9.3 months	25 %
Clarke[166]	Pemetrexed 600 mg/m^2	59	16 %	7.2 months	32 %

Four phase II studies demonstrated that patients receiving pemetrexed-platinum combinations as first-line therapy had similar response rates and overall survival[72,167-169] as observed for standard regimens (Table 7).[57,58] In two of these trials, patients were supplemented with vitamin B12 and folic acid without signs of reduced efficacy.[72,168] The toxicity profile of the pemetrexed combinations appeared to be favorable, especially in patients who were supplemented with vitamin B12 and folic acid (Table 7).

Table 7 Efficacy and hematologic toxicity in phase II studies of pemetrexed-platinum combinations as first-line therapy of NSCLC compared with commonly used regimens at that time. In the studies by Zinner and Scagliotti, the patients were supplemented with vitamin B12 and folic acid.

	Chemotherapy	n	Response rates	Overall survival	1-year survival
Manegold[169]	Pemetrexed 500 mg/^{2} + Cisplatin 75 mg/m^2	36	39 %	10.9 months	50 %
Shepherd[167]	Pemetrexed 500 mg/m^2 + Cisplatin 75 mg/m^2	31	45 %	8.9 months	49 %
Zinner[72]	Pemetrexed 500 mg/m^2 + Carboplatin AUC = 6	50	24 %	13.5 months	56 %
Scagliotti[168]	Pemetrexed 500 mg/m^2 + Carboplatin AUC = 6 *or*	39	32 %	10.5 months	44 %
	Oxaliplatin 120 mg/m^2	41	27 %	10.5 months	50 %
Schiller[57]	Paclitaxel 135 mg/m^2 + Cisplatin 75 mg/m^2	288	21 %	7.8 months	31 %
	Gemcitabine 1000 mg/m^2 + Cisplatin 75 mg/m^2	288	22 %	8.1 months	36 %
	Docetaxel 75 mg/m^2 + Cisplatin 75 mg/m^2	389	17 %	7.4 months	31 %
	Paclitaxel 225 mg/m^2 + Carboplatin AUC=6	290	17 %	8.1 months	34 %

Grade 3-4 toxicity		Anemi	Neutropenia	Thrombocytopenia
Manegold[169]	Pemetrexed 500 mg/^{2} + Cisplatin 75 mg/m^2	14 %	59 %	17 %
Shepherd[167]	Pemetrexed 500 mg/m^2 + Cisplatin 75 mg/m^2	20 %	37 %	3 %
Zinner[72]	Pemetrexed 500 mg/m^2 + Carboplatin AUC = 6	2 %	26 %	2 %
Scagliotti[168]	Pemetrexed 500 mg/m^2 + Carboplatin AUC = 6 *or*	2 %	7 %	2 %
	Oxaliplatin 120 mg/m^2	8 %	26 %	18 %
Schiller[57]	Paclitaxel 135 mg/m^2 + Cisplatin 75 mg/m^2	13 %	75 %	6 %
	Gemcitabine 1000 mg/m^2 + Cisplatin 75 mg/m^2	28 %	63 %	50 %
	Docetaxel 75 mg/m^2 + Cisplatin 75 mg/m^2	15 %	69 %	3 %
	Paclitaxel 225 mg/m^2 + Carboplatin AUC=6	10 %	63 %	10 %

Measuring health related quality of life in lung cancer trials

The definition of health related quality of life

Quality of life (QoL) is a commonly used term, though it is not easily defined. The interpretation of the term varies depending on the context – and it can mean different things to different people. “Quality of life” can be used to describe the level of general health, satisfaction, ability to cope, happiness, being in control and the degree of independence.[170,171]

In medical research, one is usually concerned with evaluating the aspects of quality of life that are related to health - and the term can be linked to the World Health Organization’s definition of health: “A state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity”.[172] To distinguish between QoL in general and the aspects of interest in medical research, the term Health related quality of life (HRQoL) - defined as the dimensions of QoL that are most influenced by health and health-care interventions - has been introduced.[173]

The role of measuring HRQoL

A large proportion of cancer research focuses on improving survival. However, side-effects from therapy are common and the treatment can severely reduce a patient's HRQoL. On the other hand, a new therapy can be beneficial even if it does not improve efficacy (in terms of objectively measurable parameters such as response rates, progression free survival and overall survival) if it provides better HRQoL. Hence, it is of great importance to measure the impact on HRQoL when introducing new therapies – especially when the survival benefit is as limited as in advanced lung cancer. Studies have demonstrated that health care professionals tend to overestimate the benefit and underestimate the side-effects from therapy while the patient's reports may be more valid.[174-176]

Measurement of HRQoL in lung cancer trials

Already in the first trial of palliative chemotherapy in lung cancer, subjective improvement was defined as one of the endpoints.[28] The authors of the meta-analysis of studies comparing chemotherapy in advanced NSCLC with best supportive care alone conclude that chemotherapy most likely improve HRQoL, but the scientific evidence is limited, since so many different methods for assessing HRQoL were used in the studies reviewed.[37] Later studies using more generally accepted instruments for measuring HRQoL confirmed this assumption.[86,177,178] Other studies have demonstrated that second-line chemotherapy[179] and erlotinib[180] improves HRQoL in recurrent NSCLC.

Instruments for measuring HRQoL

There is an international agreement that HRQoL should be measured using a multidimensional, validated instrument. The most commonly used in lung cancer

trials are the Functional Assessment of Cancer Therapy – Lung (FACT-L),[181] the Lung Cancer Symptom Scale (LCSS)[182,183] and the European Organization for Research and Treatment of Cancer Core Questionnaire (EORTC QLQ C30) plus the Lung Cancer supplement (LC 13) (Appendix A).[184,185] There are certain differences in what they measure, but in general none have proven to be superior to the others. The C30 and LC 13 have been validated, have been translated into Norwegian and have been used in several trials in lung cancer - both in first-[38,39,58,86,177] and second-line treatment[179,180] of NSCLC; two of these were conducted by the Norwegian Lung Cancer Study Group.[38,39]

The EORTC QLQ C 30 plus LC 13

The EORTC QLQ C 30 (published in 1993)[184] consists of 30 questions and measures 13 fundamental aspects of HRQoL and symptoms commonly reported by cancer patients (Table 8). Nine of the scales are multi-item scales: Five functional scales (physical, role, emotional, cognitive and social function); three symptom scales (fatigue, pain and nausea/vomiting); and one scale for global health status and quality of life. Six single item scales assess common symptoms (dyspnea, appetite loss, sleep disturbance, constipation and diarrhea) and the perceived financial impact of having a malignant disease.

The Lung Cancer specific module, LC 13, consists of 13 questions and measures symptoms commonly associated with lung cancer and its treatment.[185] Dyspnea is measured with a multi-item scale, the other are single-item scales.

When answering the QLQs, the patients give a score 0-7 for the two questions about global QoL, for the other questions they give a score 0-4. The questionnaires are shown in Appendix A.

Table 8 Content of the EORTC QLQ C30 plus LC13

QLQ	Type of scale	Scale	No. of items	Question no.
C30	**Global Health/QoL**	Global QoL	2	29, 30
	Functional scales	Physical function	5	1-5
		Role function	2	6,7
		Emotional function	4	21-24
		Cognitive function	2	20,25
		Social function	2	26,27
	Symptom scales	Fatigue	3	10,12,18
		Nausea and vomiting	2	14,15
		Pain	2	9,19
		Dyspnea	1	8
		Insomnia	1	11
		Appetite loss	1	13
		Constipation	1	16
		Diarrhea	1	17
		Financial difficulties	1	28
LC13	**Symptom scales**	Dyspnea	3	3-5
		Coughing	1	1
		Hemoptysis	1	2
		Sore mouth	1	6
		Dysphagia	1	7
		Peripheral neuropathy	1	8
		Alopecia	1	9
		Pain in chest	1	10
		Pain in arm or shoulder	1	11
		Pain in other parts	1	12

Analyzing HRQoL reported on the EORTC QLQ C30 and LC 13

Before conducting the analyses, scores for each scale have to be calculated according to the scoring manual developed by the EORTC.[186] In general, the raw scores are transformed linearly to a scale from 0-100 – taking into consideration all items for each scale. A high score on functional scales means a good function/quality of life, while a high score on symptom scales means severe symptoms and hence a poor quality of life. If more than half of the items are not completed, the scale score is defined as missing.

There are several methods for analyzing the HRQoL-scores. The most common analysis is to compare mean scores for each scale at each time-

point.[38,39,86,177] Others have reported the change from baseline scores until defined time-points for re-assessment of HRQoL;[177-179] calculated the area under the curve (AUC) for each scale during the period defined as of interest;[39] compared proportions of patients who had improvement, stable or worse HRQoL during a period;[180] or compared the time to deterioration of HRQoL.[180]

To ensure valid results, one should define which scales that are of primary interest – and what analyses that will be performed. This will limit the risk for finding significant differences by chance. In addition, the period of interest should be defined. In clinical studies of treatment of cancer patients, there may be several factors interfering with HRQoL soon after the study treatment period - such as progressive disease, salvage therapy and other medical symptom relief.

Compliance

A common challenge is to have a high compliance for the quality of life questionnaires (QLQs). In study populations like patients with advanced NSCLC, the participants are old, frail and in many cases, their physical condition deteriorates rapidly.

If data are missing by random, the results are less likely to be biased. In a large, randomized trial this may be the case if compliance is similar within all treatment groups. However, there are data suggesting that the most ill are less likely to complete QLQs as scheduled. Hence, if there is a difference in the efficacy of the different study therapies, this may influence the completion rate in the respective arms.

Missing data may also reduce power of the analyses due to reduced sample size. This can to some extent be overcome by increasing the number of patients on a study, but will not necessarily reduce potential biases.

When it comes to measurement of HRQoL by QLQs, there are two types of missing data – missing QLQs (not handed to the patient, not completed by the patient or lost, completed QLQs) and missing items (partially incompleted QLQs). There are two patterns of missing data – terminal (no further data available) or intermittent (one or more observations missing, but later QLQs completed). Terminal dropout may occur if a patient withdraws from the study, does not want to answer more questionnaires or dies. Intermittent missing forms may be related to intercurrent illness.[187]

There are no established limit for the proportion of responders required for considering the analyses valid, though a compliance of more than 80 % has been suggested as adequate.[188]

In the previous trials by NLCG, the baseline QLQ has been handed to the patient and completed before randomization, and the following QLQs have been mailed directly to the patients from the study office. Compliance has been high (> 80 %), which may be due to the central distribution of the QLQs.[187]

Imputation of missing values

Intuitively, one would believe that only the reported values should be analyzed. This would also be the easiest way of conducting the analyses. However, the sample size would in many cases be significantly reduced since it is very difficult to ensure that all QLQs are completed according to the study plan. In addition, only analyzing reported values may cause a selection bias.

Imputation of missing values is a method for overcoming the problem with incomplete or missing questionnaires; at least when the overall compliance is fairly high and it is reasonable to assume that the data are missing at random. There are several methods for imputation and what method to apply will depend on the

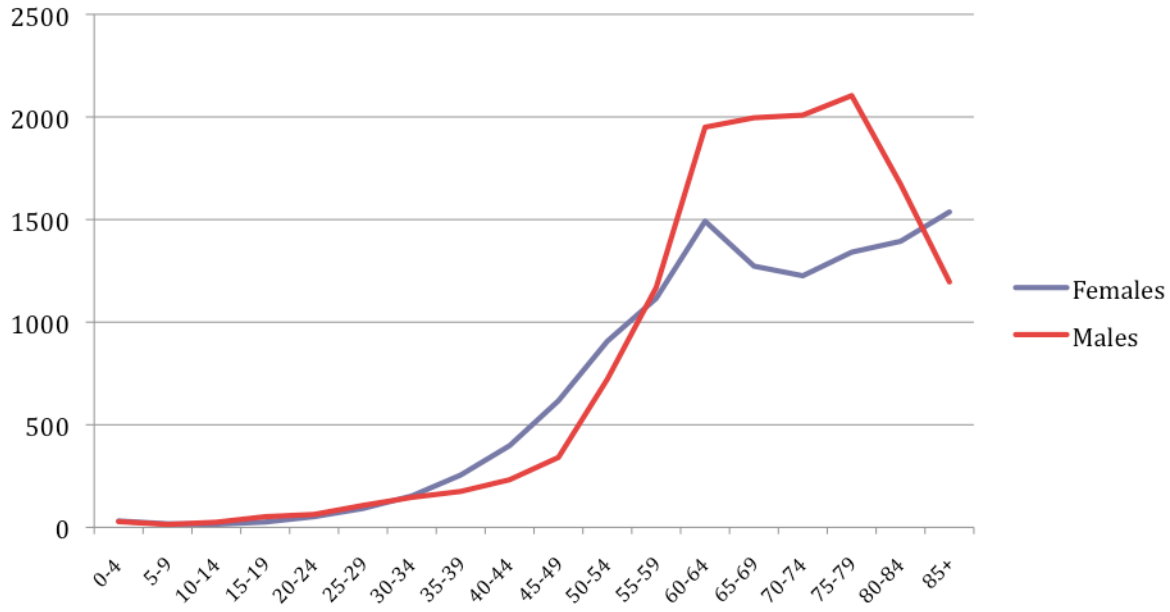
circumstances that have lead to missing data. Most importantly, the methods needs to be predefined and the data should be analyzed using more than one method for imputation (performing a sensitivity test) to test the impact of the model for imputation.[187]

Comorbidity in cancer patients

Comorbidity as a prognostic factor in cancer patients

Cancer is more frequent with increasing age; 74 % of new cases in Norway in 2007 were diagnosed in patients ≥ 60 years, 48 % in patients ≥ 70 years (Figure 8).[2] Due to the general ageing of the population, the number of cancer patients and the proportion of elderly cancer patients are expected to increase in the future.

Figure 8 Age distribution of new cases of cancer in Norway in 2007



Comorbidity - the presence of co-exisiting disorders or diseases – is more frequent in elderly patients,[189,190] and for that reason, knowledge about how physicians are to

treat cancer patients with several or severe disorders is needed. There are reports indicating that these patients do not receive the same therapy as patients with a better general health,[191-193] possibly due to concerns about whether they benefit from or tolerate standard treatment. However, there is little evidence for how patients with several co-existing diseases should be managed. Unfortunately, comorbidity is seldom systematically measured or reported – and elderly and patients with comorbidity are often underrepresented or excluded from clinical trials.[90-92,194] Thus, many of the treatment recommendations are based on studies of patients with other features than a large proportion of the patients seen in the everyday clinic.[194]

Patients need to have a reasonable good general health to tolerate many of the therapies for cancer. Surgery necessitates anesthesia - which can only be given to respiratory and circulatory stable patients. Radiotherapy often leads to impaired function of vital organs, and chemotherapy can only be administered to patients with adequate organ function; particularly hematopoietic, liver and kidney function.

Several studies have shown that patients with severe comorbidity have inferior survival among patients with colon-, breast-, prostate-, lung- and head and neck cancer.[195,196] However, one cannot necessarily apply the results from these trials to cancer patients in general since the methods for assessing comorbidity vary between studies. There may also be different impact of comorbidity on survival depending on what therapy the patients receive - and the prognosis of the underlying cancer. One study has demonstrated that the influence of comorbidity on survival was related to the expected survival time; the longer the patients lived with their cancer, the more likely it was that other disorders deteriorated to such an extent that it influenced the survival time.[196]

Denying elderly or patients with significant comorbidity therapy is hardly an option since these patients are frequent. To better be able to individualize therapy, there is a need for studies of the influence of comorbidity on survival, the efficacy and tolerability of therapy and the impact on HRQoL.

Prognostic and predictive factors in advanced NSCLC

The survival benefit of chemotherapy in advanced NSCLC is limited,[37] the therapy is time consuming and patients frequently experience severe toxicity. Hence, a lot of research has focused on identifying the patients who benefit the most from the therapy – and subgroups that should be offered other treatment or best supportive care alone.

Performance status is the most important prognostic selection factor. PS 3-4 patients are not routinely offered cytotoxic chemotherapy, how to treat PS 2 patients is debated while most PS 0-1 patients receive standard platinum-doublet chemotherapy.

Subgroup analyses have revealed that stage of disease,[11,19] male gender,[11,197,198] a history of smoking,[11,199] poor baseline HRQoL[200-202] and weight-loss[202,203] are significant, negative prognostic factors. However, patients sharing one or more of these characteristics account for a very large proportion of patients and there is not sufficient evidence to deny these patients therapy.

Co-existing disorders in lung cancer patients

Lung cancer patients have a high frequency of co-existing disorders. Comorbidity increases with age, and more than half of the patients are > 70 years at diagnosis. In addition, most have been tobacco-smokers, a well-known cause of a wide range of diseases – especially disorders in the cardiovascular and respiratory systems such

as ischemic heart disease[204,205] and chronic obstructive pulmonary disease (COPD).[206,207]

A large proportion of lung cancer patients are diagnosed with advanced disease - which often causes poor performance status. The treatment is often demanding, and there are concerns about how well patients with severe comorbidity are able to tolerate chemotherapy.[36,84]

Previous research on comorbidity in lung cancer

Several studies have investigated the prognostic value of comorbidity in lung cancer patients. In stage I,[208] stage III[209] and mixed cohorts of lung cancer patients,[196,200,210] comorbidity has been identified as an independent prognostic factor for survival. This has not been observed in the studies that have analyzed patients with advanced disease separately.[196,201,211]

Few studies have looked at the association between comorbidity and tolerability of the therapy and the results are not consistent.[210-212] No studies have investigated the relation to HRQoL in lung cancer patients.

Nevertheless, patients with severe comorbidity are excluded from or underrepresented in clinical trials,[194] and studies have shown that patients with severe comorbidity are less likely to receive standard therapy in the clinic.[191-193]

Measuring comorbidity

Several instruments have been developed for measuring comorbidity. The most commonly used are the Charlson Comorbidity Index (CCI), the Cumulative Illness Rating Scale for Geriatrics (CIRS-G), the Index of Coexisting Diseases (ICED) and the Kaplain-Feinstein index. Recently, the Simplified Comorbidity Score (SCS) was

developed for assessing comorbidity in lung cancer patients (Table 9). All of these indices have been validated, and have been used in studies of cancer patients.

Except for the CIRS-G, the indices rate the presence of a list of conditions that have been identified as significant prognostic factors in different cohorts. In contrast, the CIRS-G rates the presence and severity of *all* disorders on 14 predefined scales/organ systems.

Table 9 Construction of instruments for measuring comorbidity.

Scale	Items and rating	How constructed
The Charlson Comorbidity Index	19 disorders weighted 1 to 6 Total score: 0 – 30	1-year mortality in patients admitted to internal medicine department
The Charlson Comorbidity Index + age	Original Charlson + 1 point added for each decade ≥ 50 years of age Total score: 0 - 35	Same as Carlson + validation study of breast cancer patients with 10 – year mortality as endpoint
The Cumulative Illness Rating Scale (CIRS)	Disorders in 13 organ systems rated 0 – 4 Total score: 0 – 54	Comprehensive listing of diseases weighted by clinician's estimate
The Cumulative Illness Rating Scale for Geriatrics (CIRS-G)	Disorders in 13 organ systems rated 0 – 4 Total score: 0 – 54	Comprehensive listing of diseases weighted by manual – or clinician's estimate if not listed in manual
The Index of Coexisting Disease (ICED)	Disease severity subindex: 14 diseases rated 0 – 4 Functional severity index: 12 conditions rated 0 – 2 Total score. 0 - 3	Anticipated outcome 2 years after hospitalization in breast cancer patients
The Kaplan-Feinstein Index scale	12 conditions (10 diseases plus locomotive function and alcoholism) rated 0 – 3 Total score: 0 - 3	Study of disorders that may influcence survival in diabetics
The Simplified Comorbidity Score (SCS)	7 disorders weighted 1 to 7 Total score: 0 – 20	Retrospective analyses of comorbidities as significant prognostic factors for survival in 735 patients with NSCLC

The Charlson Comorbidity Index (CCI)

By analyzing 559 patients admitted to a hospital department of internal medicine, Charlson and colleagues identified 19 conditions associated with increased mortality within one year.[213] When assessing comorbidity using this instrument, the presence

of these conditions are registered and scored before a final score is calculated. The index was later validated in a cohort of breast cancer patient where it was found to predict mortality over a period of a few weeks to 10 years.[213] In the validation study, adding one point for each decade of age ≥ 50 years was suggested (Table 10).

The CCI is the most commonly used. It is easy to use, and in an adapted version, comorbidity can be scored from databases of diagnose-codes.[214,215] This makes it suitable for large studies and studies involving many sites and investigators.

Table 10 The Charlson index for scoring of comorbidity

Comorbidity	**Present**	**Points**
Myocardial infarct		1
Congestive heart failure		1
Peripheral vascular disease		1
Cerebrovascular disease (except hemiplegia)		1
Dementia		1
Chronic pulmonary disease		1
Connective tissue disease		1
Ulcer disease		1
Mild liver disease		1
Diabetes (without complications)		1
Diabetes with end organ damage		2
Hemiplegia		2
Moderate or severe renal disease		2
2nd solid tumor (non metastatic)		2
Leukemia		2
Lymphoma, multiple myeloma . . .		2
Moderate or severe liver disease		3
2nd metastatic solid tumor		6
AIDS		6
Total points		

Optional extension

Age	**Present**	**Points**
50 – 59		1
60 – 69		2
70 – 79		3
80 – 89		4
90 – 99		5
Total combined score (comorbidity + age)		

The Cumulative Illness Rating Scale for Geriatrics (CIRS-G)

The Cumulative Illness Rating Scale was designed in 1968 as an instrument for comprehensive recording of comorbidity.[216] Later, a manual recommending specific

scores for common conditions among geriatric cancer patients was developed - the Cumulative Illness Rating Scale for Geriatrics.[217] This index scores all conditions on 14 predefined scales/organ systems from 0-4 - similar to toxicity grading using the common terminology criteria for adverse events (CTCAE)[218]. In general, “0” indicates no problem, “1” indicates a current mild problem or a past significant problem, “2” a moderate disability or morbidity that requires “first-line” therapy, “3” a severe/constant significant disability or an "uncontrollable" chronic problem and “4” an extremely severe/immediate treatment required/end organ failure/severe impairment in function. The CIRS-G manual recommends specific scores for common conditions. Total score (= the sum of the score for all scales), the numbers of scores 3 and 4 and severity index (= total scores/number of categories with a score > 0) are then calculated (Table 11).

A major difference from the CCI, is that it includes assessment of non-lethal conditions; some of significance for cancer patients receiving chemotherapy such as hematopoietic, renal and liver dysfunction.

The grading of each condition gives a more detailed picture of the patient’s health than the CCI. The CIRS-G is more sensitive, but the clinical relevance (content validity) of this is unclear – though in two trials on stage I and stage III NSCLC, CIRS-G but not CCI scores were prognostic factors for survival.[208] The drawback is that it requires more training and the scoring takes longer time compared with the less comprehensive indices. Thus, it can only be used in sites that have trained personnel – unless all information about co-existing disorders is sent for a central scoring.

After our study was initiated, an updated version of the CIRS-G has been developed.[219-221]

Table 11 Example of comorbidity assessment in a patient using the CIRS-G

Score	0	1	2	3	4
Heart		X			
Vascular			X		
Hematopoietic	X				
Respiratory				X	
Eyes, ears, nose, throat and larynx	X				
Upper gastrointestinal tract	X				
Lower gastrointestinal tract		X			
Liver	X				
Renal	X				
Genitourinary		X			
Musculoskeletal/integument	X				
Neurological	X				
Endocrine/metabolic and breast	X				
Psychiatric illness	X				

Total number categories endorsed	5
Total score	8
Severity Index (Total score / Total number of categories endorsed)	1.6 (8/5)
Number of categories at level 3	1
Number of categories at level 4	0

RATING STRATEGY
0 - No Problem
1 - Current mild problem or past significant problem
2 - Moderate disability or morbidity/requires "first line" therapy
3 - Severe/constant significant disability/"uncontrollable" chronic problems
4 - Extremely severe/immediate treatment required/end organ failure/severe impairment in function

The Index of Coexistent Diseases (ICED)

The ICED was developed in 1987 as a tool in a study of whether physicians provided less intensive therapy in elderly patients than for younger patients. The purpose was to determine whether the presence of coexisting disorders influenced cancer management. Interestingly, the conclusion was that physicians made treatment decisions based upon age and not presence of comorbidity.[222] The ICED has mostly

been used in studies of the relation between comorbidity and intensity of cancer treatment.[223,224]

The index consists of two subscales; physical and functional. On the physical subscale, conditions are rated 0 to 4 on 14 subscales according to a manual; the functional rates disorders from 0 – 2 on 12 domains. The scores are then transformed into an overall score of 0 – 3.[222]

The Kaplan-Feinstein scale

This index was developed in 1974 and consists of a list of conditions that the authors considered could influence long-term survival in patients with diabetes mellitus. The conditions are grouped into 12 categories and rated 0 – 3 within each group after well defined guidelines. The number and severity of diseases are then transformed into a final score from 0 – 3.[225] The Kaplan-Feinstein index has been used in studies of breast, prostate and head & neck cancer.

The Simplified Comorbidity Score

The SCS was developed by identifying conditions associated with increased risk of death in a population of 735 patients with NSCLC and consists of a list of seven conditions.[226] All conditions give a score according to relative risk of death from 1 to 7 for a total score of 0 – 20. The SCS has been validated in another population of NSCLC patients. In this study, the SCS was found to be more informative than the CCI in predicting outcomes in 301 patients with different stages of NSCLC.[200]

Research questions for the thesis

- Do patients with recurrent small-cell lung cancer respond to and tolerate high-dose pemetrexed monotherapy?

- Does pemetrexed plus carboplatin offer better health-related quality of life with the same efficacy and less toxicity as a standard regimen in first-line treatment of advanced non-small-cell lung cancer?

- Do non-small-cell lung cancer patients with severe comorbidity have a shorter survival, more toxicity or more deterioration of health-related quality of life during first-line chemotherapy than other patients?

Rationale for the studies

Results from preclinical studies[153,227] as well as preliminary results from a phase II study on pemetrexed-platinum combinations as first line therapy in small-cell lung cancer,[165] suggested that SCLC patients respond to pemetrexed therapy. There were also several studies suggesting that pemetrexed may be an effective treatment of NSCLC, and previous studies have demonstrated that agents used in the treatment of NSCLC can be effective in the treatment of recurrent SCLC.[143,144] In addition, pemetrexed appeared to be well tolerated. Second-line therapy is administered to a large proportion of patients with recurrent disease, though there were no standard regimens at that time. Several regimens have demonstrated similar efficacy[141-144] in terms of response rates, time to progression and overall survival. Thus, historical

data were accepted for defining sample size and defining what level of response would warrant further research.

When our study was designed, two other studies administering standard dose of pemetrexed (500 mg/m^2) in recurrent SCLC were already initiated.[228,229] Recent phase I studies suggested that a higher dose was tolerable in patients who were supplemented with vitamin B12 and folic acid.[157,158] In general, it is assumed that a higher dose is more effective than a lower dose when administering chemotherapy. This was the rationale for investigating the efficacy of high-dose pemetrexed monotherapy in recurrent SCLC.

Phase I,[230] II[71,72,159,166,167,169] and III[156] studies had demonstrated activity of pemetrexed (monotherapy or combinations with a platinum-compound) in NSCLC - with a favorable toxicity profile. The survival benefit of chemotherapy in advanced NSCLC is limited, and there are concerns about toxicity for a large proportion of the patients; due to poor performance status, old age and severe comorbidity. If pemetrexed is as effective and less toxic than standard regimens, the drug may provide a better HRQoL. In addition, if more patients were able to tolerate chemotherapy, there may also be a survival benefit. This was the rationale for conducting a phase III study comparing pemetrexed plus carboplatin with a standard regimen, gemcitabine plus carboplatin, as first-line chemotherapy in advanced NSCLC.

Performance status is considered to be the most significant prognostic baseline characteristic. Several studies have demonstrated that the presence of co-existing disorders may be a significant, independent prognostic factor in NSCLC and may predict more toxicity from therapy – which again could influence the HRQoL during therapy. As a result of an ageing population, physicians need to gain

knowledge about how to take comorbidity into consideration when making treatment decisions. Thus, patients who were enrolled onto the study of advanced NSCLC were analyzed for the associations between the presence of comorbidity and outcomes of the chemotherapy.

Patient selection for the thesis

Study populations

Two separate patient populations were investigated (Table 12). The patients were recruited at a majority of hospitals diagnosing and treating lung cancer patients in Norway by investigators that are members of the Norwegian Lung Cancer Study Group.

Table 12 Cohorts investigated.

Paper	Population	Diagnosis	Location	Enrolment period	n
1	1	Recurrent SCLC	Norway	May – October 2005	36
2 & 3	2	Stage IIIB/IV NSCLC	Norway	May 2005 - July 2006	446

Eligibility criteria for all patients

- Signed, written informed consent
- Have the ability to understand oral and written information about potential benefits, side-effects or disadvantages of participating in the trials
- WHO performance status 0-2
- Creatinine clearance > 45 ml/min
- No other clinically active cancer was allowed
- No pregnant or lactating women were allowed
- All fertile patients had to use safe contraception

Rationale for the eligibility criteria

- The concept of voluntary participation is essential for conducting medical research in humans.
- In order to tolerate experimental chemotherapy, a good performance status is needed. Previous studies have demonstrated that patients with advanced lung cancer and performance status 3-4 do not benefit from chemotherapy.
- Pemetrexed is eliminated through the kidneys, and phase I data suggested a higher risk of toxicity in patients with a reduced renal function.[152]
- Other active cancer could possibly influence the analysis and may warrant other, concurrent therapy.
- Cytotoxic compounds may be teratogenic, and would put embryos and breast-fed children at risk.

Study population 1

The patients were enrolled at 16 hospitals in Norway between May and October 2005 onto a phase II study conducted by the Norwegian Lung Cancer Study Group (Fig 9).

Eligibility criteria (in addition to the above mentioned):

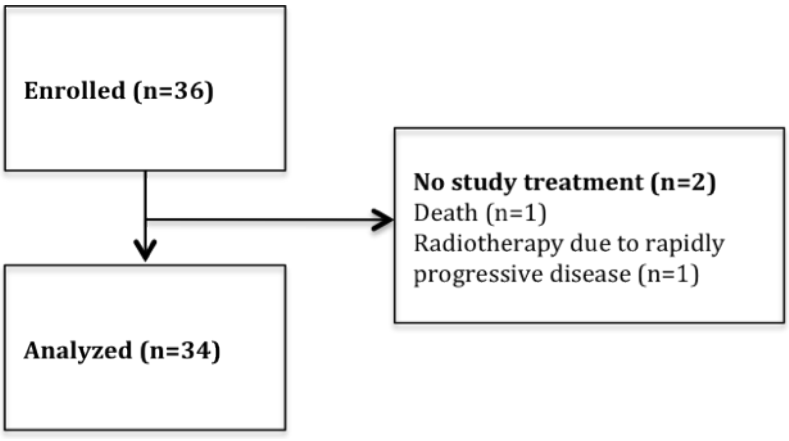
- Histologically or cytologically verified SCLC
- One previous chemotherapy regimen for SCLC (re-induction with same regimen allowed)
- No systemic or experimental cancer-treatment four weeks prior to the first cycle of pemetrexed
- Age 18-75 years
- No symptomatic brain metastases
- ANC > 1.5 x 10^9/L, platelets > 100 x 10^9/L, bilirubin < 1.5 x ULN

- ALT and ALP < 3 x ULN (If liver-metastases were present: < 5 x ULN)
- Measurable disease according to the RECIST-criteria v1.0[231]

Rationale for the eligibility criteria

- To avoid potentially confounding toxicity from other therapy.
- There were no data concerning tolerability of high-dose pemetrexed in elderly patients. In a previous trial investigating second-line therapy of SCLC in Norway,[232] very few patients > 75 years received second-line therapy.
- There was little knowledge about the efficacy of pemetrexed in brain metastases; and there were concerns about whether they would live long enough to be evaluated for the primary endpoint.
- The values of the lab-tests were considered necessary for tolerating pemetrexed therapy.
- Measurable disease was necessary to assess response – the primary endpoint of the study

Figure 9 Patient selection for study 1



Study population 2 & 3

The patients were enrolled at 35 hospitals in Norway from May 2005 - July 2006 onto a phase III study conducted by the Norwegian Lung Cancer Study Group (Fig 10).

Eligibility criteria for the phase III study (Study 2)

- Histologically or cytologically verified NSCLC
- Stage IIIB (not eligible for curative radiotherapy) or stage IV disease
- Age > 18 years
- No previous systemic cancer treatment for NSCLC
- ANC >1.5x10^9/L, platelets >100x10^9/L, bilirubin <1.5xULN, ALT and ALP <3xULN

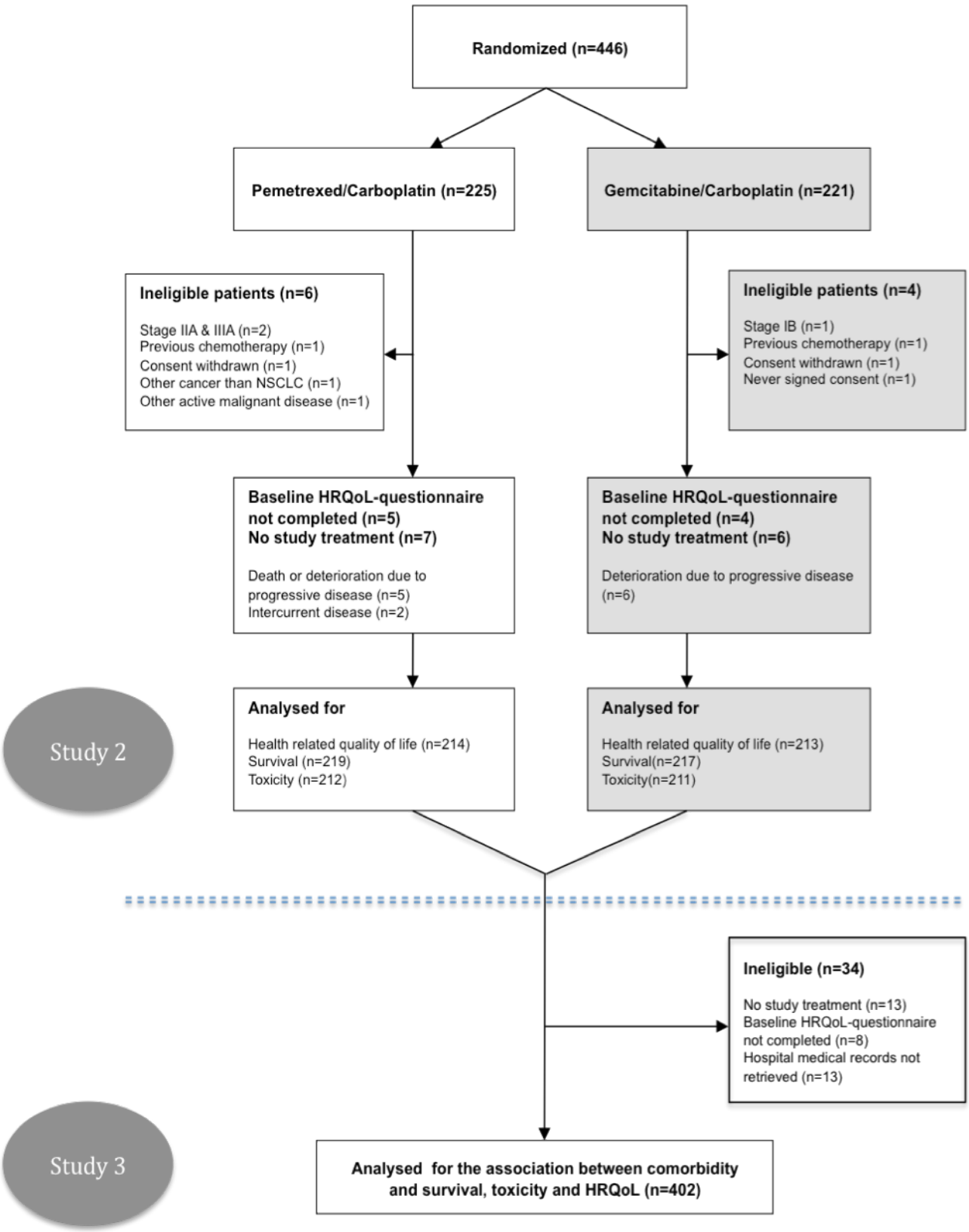
Additional eligibility criteria for the exploratory study of comorbidity (study 3)

- Had received at least one cycle of study treatment
- Had completed the baseline QLQ
- A copy of the patient's hospital medical records for the last 3 months prior to randomization in the phase III study was possible to retrieve

Rationale for the eligibility criteria

- To test the pemetrexed-carboplatin in a population as similar to the patients seen in the everyday clinic, as few limitations for the eligibility as possible were defined.
- To analyze the influence of comorbidity on the outcome of chemotherapy, patients had to have received at least one cycle of study treatment and had to have completed the baseline quality of life questionnaire.
- To ensure consistent comorbidity assessment, a central scoring was preferred. Thus, a copy of hospital medical records had to be available.

Figure 10 Patient selection for study 2 & 3



Study designs

The studies had three different designs:

- An open, prospective, national multicentre phase II study of the efficacy of high-dose pemetrexed monotherapy in recurrent SCLC
- An open, prospective, national, multicentre, randomized phase III study comparing pemetrexed plus carboplatin with gemcitabine plus carboplatin as first-line chemotherapy in advanced NSCLC
- An exploratory analysis of the associations between comorbidity assessed using the CIRS-G and clinical outcomes in patients who received first-line chemotherapy in the phase III study.

Table 13 List of studies

Study	Design	Patient reported	Physician reported	Objectives
1	Prospective phase II	None	Response-rates Toxicity Overall survival	Response rates Overall survival Toxicity Time to progression
2	Prospective phase III	HRQoL on the EORTC QLQ C30/LC13	Toxicity Overall survival	HRQoL (Global QoL, fatigue, nausea/vomiting, dyspnea) Overall survival Toxicity
3	Exploratory analyses	HRQoL on the EORTC QLQ C30/LC13	Comorbidity Toxicity Overall survival	The associations between comorbidity and overall survival, toxicity and HRQoL

Study treatment

Study 1

Up to four cycles of pemetrexed 900 mg/m2 every 3 weeks were administered. The patients were supplemented with folic acid and vitamin B12 from one week before the first and until 3 weeks after the last cycle of study treatment.

Prior to each course, ANC had to be ≥1.5×10^9/L, platelets ≥100×10^9/L,

creatinine-clearance ≥45mL/min and any grade 3–4 non-hematological toxicity had to be resolved. If not, treatment was delayed 1 week. The dose of the following course was reduced by 25% in case of nadir ANC <0.5 $\times 10^9$/L, a neutropenic infection or any grade 3–4 toxicity following the preceding course. A 50% dose reduction was to be performed in case of nadir platelets < 50 $\times 10^9$/L or grade 3–4 mucositis. Any dose reductions were maintained for all subsequent courses. If a patient qualified for a third dose reduction, or had a treatment-related delay of more than 42 days following the preceding course, the study treatment was discontinued.

Study 2 & 3

Patients were randomly assigned to receive pemetrexed 500 mg/m^2 plus carboplatin AUC=5 on day 1 of every cycle - or gemcitabine 1,000 mg/m^2 on days 1 and 8 plus carboplatin AUC=5 on day 1 of every cycle. The carboplatin dose was calculated using Calvert's formula. Patients ≥ 75 years old had a 25% dose reduction. Chemotherapy cycles were repeated every 3 weeks for up to four cycles. All patients were supplemented with folic acid and vitamin B12 from one week before the first and until 3 weeks after the last cycle of study treatment.

The doses of carboplatin and gemcitabine, and the dose-reductions in elderly ≥ 75 years, were recommended due to experiences from a previous trial[39] by the NLCG *(unpublished data)*.

Before the start of each cycle, ANC had to be ≥ 1.0 x 10^9/L, platelets ≥ 75 x 10^9/L, creatinine-clearance ≥ 45 ml/min and grade 3-4 toxicities resolved. Otherwise treatment was delayed by one week. Doses for the following cycle were reduced by 25 % if ANC was 1.0-1.49 x 10^9/L or platelets 75-99 x 10^9/L on day 22 after the preceding cycle, nadir ANC < 0.5 x 10^9/L, or the patient had experienced a grade 3-4

toxicity. Doses were reduced by 50 % in case of nadir platelets < 50 x 10^9/L or grade 3-4 mucositis. Dose-reductions were maintained for subsequent cycles. The study-therapy was discontinued if a patient qualified for a third dose-reduction or a cycle was delayed > 21 days. Omissions or reductions of the gemcitabine-dose on day 8 of a cycle were allowed.

Evaluation and follow-up

Study 1

A baseline CT scan of the thorax and upper abdomen was performed within 1 week prior to the first cycle of chemotherapy. A clinical examination and a CT scan for response-evaluation were performed 3 weeks after the fourth course of chemotherapy and then every 8 weeks until progression (earlier if progression was suspected). Response was assessed according to the RECIST-criteria, but confirmation of response was not mandatory.

All patients were observed for one year or until death. No central review of the CT-scans was performed. Hemoglobin, leukocytes, ANC and platelet count were measured on day 1, 8 and 15 of each treatment cycle. Toxicity was assessed at every visit and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0.[218]

Study 2

A baseline CT scan of the thorax and upper abdomen was performed within 1 week prior to chemotherapy. HRQoL was assessed prior to randomization, before every cycle of chemotherapy, three weeks after the fourth and last cycle of chemotherapy and then every eight weeks until death or one year.

Hemoglobin, leukocytes, ANC and platelet count were measured on day 1, 8

and 15 of each treatment cycle. A clinical examination was performed before every cycle of chemotherapy, three weeks after the last cycle and then every eight weeks until death or one year. Toxicity was assessed at every visit and graded according to the CTCAE v3.0.

Study 3

Hospital medical records for the last three months prior to randomization for patients entered to the phase III study were retrieved. Comorbidity was then assessed from the medical records using the CIRS-G. The associations between comorbidity scores and the outcomes of study 2 were then analyzed.

Methods

Patient reported HRQoL

HRQoL was assessed using the EORTC QLQ C30 plus LC13 (Appendix A). The patients completed the baseline QLQ before random assignment and then before each chemotherapy cycle (weeks 0, 3, 6, and 9) and at follow-up visits (weeks 12, 20, 28, 36, 44, and 52). The baseline QLQ were handed them by an investigator, the following QLQs were sent to the patients from the study office. One reminder was mailed if a questionnaire was not returned within 14 days.

Assessment of response

The response to the study therapy was assessed according to the RECIST-criteria v1.0[231] by comparing the baseline CT-scan with the CT-scan performed three weeks after the fourth cycle of study treatment: Complete disappearance of all lesions was considered to be a complete response (CR), a reduction of the sum or the largest

diameters of all measurable lesions of ≥ 30 % was considered to be a partial response (PR), an increase in the sum of the largest diameters of all measurable lesions of ≥ 20 % was considered to be progressive disease, everything between PR and PD was considered to be stable disease (SD). If response assessment was not done, the patient was considered to be not evaluable (NE). The RECIST-criteria recommends confirmation of response by a repeated CT scan no less than four weeks after the first CT scan suggesting response to therapy, but this was not mandatory in our study.

In case of signs of progressive disease, a CT scan was performed at an earlier time-point and compared with the baseline CT scan.

Assessment and grading of toxicity

Patients underwent laboratory tests before the start of each new cycle of the study treatment and on days 8 and 15 of every cycle. More laboratory tests were taken if indicated. Hemotological and non-hematological toxicities were assessed at each visit and graded using the Common Terminology Criteria of Adverse Events version 3.0.[218]

Definition of time to progression and overall survival

Time to progression was defined as the time from enrolment on the study until progressive disease was proven on CT scans. Survival time was defined as the time from enrolment until the time of death. Time of death was recorded from a national registry of all citizens in Norway. All patients that did not have progressive disease or were alive at one year after the end of enrolment, were censored for the analyses of time to progression and overall survival.

Assessment of comorbidity

Assessing comorbidity using the CIRS-G requires training, and a central, retrospective analysis was preferred in order to ensure uniform scoring, since the CIRS-G has not been in routine use at the participating centres. To ensure reproducibility, comorbidity was assessed from hospital medical records only.

Three physicians, all specialists in oncology, did the scoring (Marit Jordhøy, Stein Sundstrøm and Bjørn H. Grønberg). Before scoring, the three physicians agreed upon how to interpret the scoring manual for common disorders.

Two physicians scored comorbidity independently for each patient from the hospital medical records. In case of different scores, the two physicians agreed on a final score. The most common cause for a different score, was that one of the physicians had overlooked disorders mentioned in the medical records.

Statistical considerations

Sample size estimation for study 1

"Sensitive" and "refractory" patients were analyzed separately. A two-stage Simon design was used to define the sample size in each group. The purpose of this design is to avoid exposing more patients than necessary to an experimental therapy that may be ineffective. A defined number of patients are enrolled in the first stage. If the target number of patients with a response or non-progression is reached, more patients are enrolled onto the study before the final analyses are conducted.[233]

For "sensitive" patients, a rate of non-progressive disease (non-PD) of 40–60% was considered to be of clinical significance. 18 patients were to be enrolled in the initial phase of inclusion. If ≥8 patients showed non-PD (CR + PR + SD), 28 additional patients were to be included in this group. The study treatment would be

considered worth further investigation in this patient population if ≥23 of 46 patients showed non-PD.

For “refractory” patients, a rate of non-progressive disease of 10–25% was considered to be of clinical significance. 21 patients were to be enrolled in the initial phase of inclusion. If ≥3 patients responded to the therapy (CR + PR), 29 additional patients were to be included in this group. The study treatment would be considered worth further investigation in this patient population if ≥8 of 50 patients responded to therapy.

Sample size estimation for study 2

To detect a difference in HRQoL scores of more than 15 (on a scale from 0 to 100) or a difference in 1-year survival rate of more than 11% with an 80% power for a two-sided significance level at 5%, 190 patients on each treatment arm were required. We expected a loss to follow-up of less than 15% and planned to enroll 222 patients per arm.

Definition of the study population for study 3

There were no statistically significant differences in overall survival, HRQoL or grade 3-4 adverse events between the treatment arms in the main study. Hence, all patients were analyzed as one cohort.

HRQoL-analyses

HRQoL scores were calculated according to the EORTC QLQ-C30 scoring manual.[186] The mean scores and AUCs for the first 20 weeks were then compared between the groups of interest. The first 20 weeks included the study treatment period plus the first 11 weeks after completion of chemotherapy, and was considered

to be the most relevant time period; since we expected that the HRQoL of a large proportion of patients would be influenced by progressive disease and/or salvage therapy soon after the study treatment ended.

Mean scores were calculated from the reported values only. Missing data were imputed before calculating AUCs. Missing intermittent scores were replaced by the mean value of the two adjacent scores. Last reported value was carried forward for other missing values unless the patient died. In those cases, the missing values were set to zero from the time of death. A sensitivity test was performed using the same method for imputing missing intermittent values, but with the last value carried forward for the missing values that followed, even after death. The clinically relevant minimum difference in mean HRQoL-scores was defined as 10 points (on a scale from 0-100)[234]. The AUCs for each scale were compared between the groups using linear regression adjusting for the baseline HRQoL-scores.

Categorization of comorbidity scores

A “high severity index” was defined as > 2 and “severe comorbidity” as ≥ one CIRS-G score 3 or 4. Within the group with severe comorbidity, patients with ≥ one CIRS-G score 4 were defined as having an “extremely severe comorbidity”. In two studies of NSCLC, a severity index > 2 and the presence of a CIRS-G score 4 were associated with inferior survival.[208,209] In addition, we defined “severe comorbidity” since it can be difficult to distinguish between a score 3 and a score 4.[235]

Survival and toxicity analyses

Median time to progression and median overall survival were estimated using the Kaplan-Meier method. In the univariate analyses, survival data were compared using

the log-rank test. The Cox proportional hazards method was used to calculate hazard ratios (HR) in the multivariate analyses adjusting for the baseline characteristics found to be significant prognostic factors in the univariate-analyses.

In the comorbidity-study, we investigated the association between survival and well-known prognostic factors: Performance status, stage of disease, gender, smoking history and baseline HRQoL – as well as study treatment and the comorbidity scores.

Several baseline HRQoL-scores have been shown to be prognostic factors. Based on results from two studies, we considered appetite loss and global QoL to be the most important; appetite loss (baseline score > 0) was the most significant prognostic factor in a study of stage III NSCLC,[202] global QoL was another significant prognostic factor in this trial – as well as in a study of chemotherapy in elderly with advanced NSCLC.[201] The cut-off level for global QoL was defined as in these trials (baseline score of 67). Unfortunately, weight loss was only recorded for 215/402 of the patients.

Toxicity-data were compared using Pearson's Chi-Square and Fischer's exact tests.

Significance level

The significance level was defined at $p < .05$ for all analyses.

Results

Study 1

Patients and study treatment

Thirty-six patients were enrolled onto the study, 34 received study treatment (Figure 9). Patients were enrolled until the first 12 “sensitive” patients had been evaluated. Of these, one had stable disease (SD) and 11 had progressive disease (PD). The number of patients with non-PD was inadequate to complete stage two of inclusion of “sensitive” patients. At that time, another study of pemetrexed monotherapy in recurrent SCLC, had stopped inclusion since too few patients responded to treatment.[228] Thus, accrual in our study was stopped even though only nine “refractory” patients had been enrolled.

Median age was 61 (range 43–74), 18 (53 %) were men, 25 had sensitive and 9 refractory disease. Mean number of cycles of pemetrexed was 2.5. One patient (3 %) had a partial response, three (9 %) had stable disease and 29 (85 %) progressed. One patient (3 %) was not evaluable for response or time to progression. Median TTP (n = 33) was 7.7 weeks (“sensitive”: 8.4 weeks, “refractory”: 5.1 weeks). Median OS (n = 34) was 17.6 weeks (“sensitive”: 22.6 weeks, “refractory”: 15.3 weeks).

Toxicity

Of grade 3–4 hematologic toxicity, anemia was observed in 2 (6 %) patients, leukopenia in 6 (18 %), neutropenia in 9 (27 %) and thrombocytopenia in 3 (9 %). Febrile neutropenia occurred in 6 (18%) patients. There were no treatment related deaths.

Study 2

Patients

Four hundred thirty-six eligible patients were enrolled onto the study; 427 were analyzed for HRQoL and 423 for toxicity (Figure 10).

The baseline characteristics were well balanced between the treatment arms. Median age was 65 (range 25-90), 18 % were ≥ 75 years, 58 % men, 88 % had PS 0-1, 28 % stage IIIB, 50 % adenocarcinoma and 8 % had never smoked.

Study treatment

The mean number of courses were 3.3 on the pemetrexed-carboplatin arm (PC), 3.1 on the gemcitabine-carboplatin arm (GC) (p=.037). Significantly more patients in the PC-arm completed four cycles (PC: 72 %, GC: 62 %; p=.03), four cycles without delays (PC: 58 %, GC: 44 %; p=.004) and four cycles without dose-reductions (PC: 50 %, GC: 20 %; p<.001). The study-therapy was discontinued due to toxicity in five percent of the patients (PC: 4 %, GC: 6 %; p=.5). Slightly more elderly were able to complete four cycles without dose-reductions (≥75 years: 38 %, < 75 years: 34 %; p=.49).

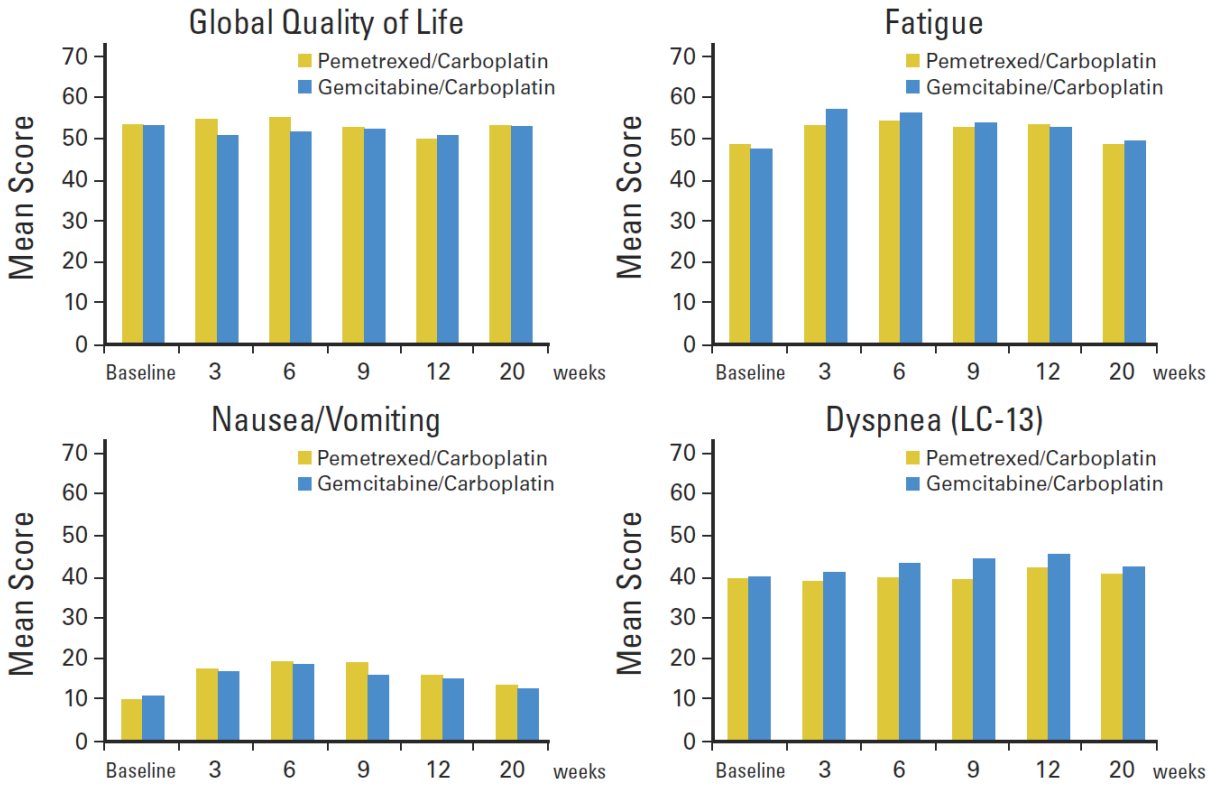
HRQoL

The patients completed 2017/2310 (87 %) of the HRQoL-questionnaires (deceased patients excluded) during the first 20 weeks. Compliance was similar in the two groups (PC: 98 – 80 %, GC: 99 – 78 %).

There were no clinically relevant or statistically significant differences in HRQoL between the treatment arms. The difference in mean score between the groups did not exceed 10 points and there were no differences in AUC: Global quality

of life (p=.72), nausea/vomiting (p=.55), fatigue (p=.55) or dyspnea (p=.48). In addition, the difference in mean scores from baseline through the treatment period did not exceed 10 points for either treatment on these four scales (Figure 11).

Figure 11 Mean scores of global quality of life (QoL), fatigue, nausea/vomiting and dyspnea according to treatment arm. A higher score of global QoL represents a better QoL, whereas a higher symptom score indicates more symptoms. There were no statistically significant differences in mean scores or in areas under the curves (AUC) between the treatment arms.

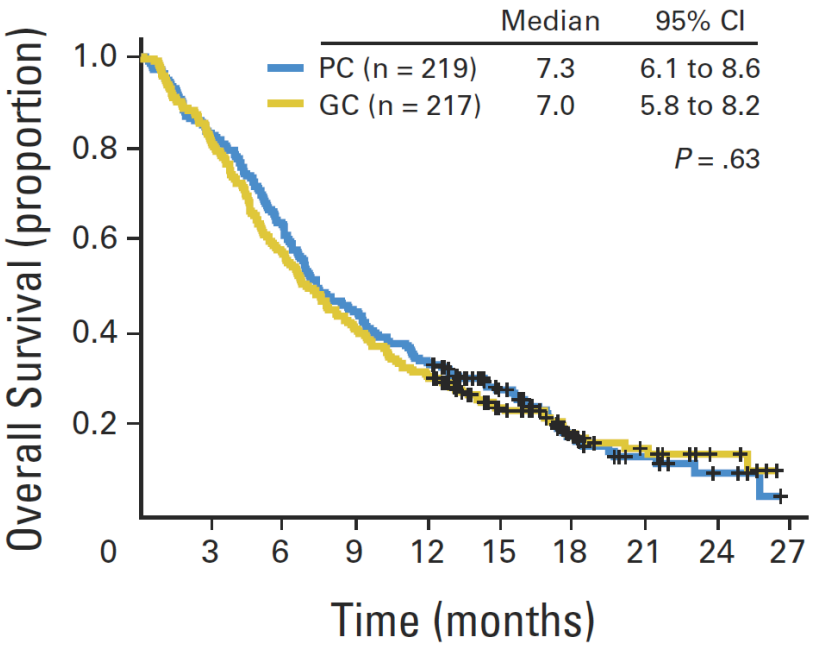


Overall survival

There was no difference in median overall survival (PC: 7.3 months, GC: 7.0 months; p=.63) or one-year survival (PC: 34 %, GC: 31%) between the treatment groups (Figure 12). Neither was there any difference in survival when analyzing patients with adeno- and large cell carcinomas separately (n=248, PC: 7.8 months, GC: 7.5 months; p=.77). Multivariate analyses and interaction tests did not reveal any significant associations between histology and survival.

Among females there was prolonged survival on the PC arm (n=185, PC: 11.0 months, GC: 7.5 months; p=.022). This survival benefit was also statistically significant in a multivariate analysis adjusting for PS and stage of disease (HR 1.43, 95 % CI 1.03 – 1.99).

Figure 12 Kaplan-Meier survival plot for all patients. PC = pemetrexed plus carboplatin, GC = gemcitabine plus carboplatin



There was no significant difference in survival between the two treatment arms among males (n=251, PC: 6.1 months, GC: 6.6 months; p=.16), PS 0-1 patients (n=340, PC: 8.7 months, GC: 7.7 months; p=.51), PS 2-patients (n=96, PC: 4.3 months, GC: 5.1 months; p=.54) or between elderly and younger patients (n=78, ≥ 75 years: 7.1 months, < 75 years: 7.3 months; p=.96).

The multivariate analyses showed that PS (0-1 vs. 2; HR 0.59, 95 % CI 0.46 – 0.75), stage of disease (IIIB vs. IV; HR 0.78, 95 % CI 0.62 – 0.995) and gender (females vs. males; HR 0.77, 95 % CI 0.62 – 0.95) were significant prognostic factors.

Toxicity

The GC-patients had significantly more grade 3-4 leukopenia (46 % vs. 23 %, p<.001), neutropenia (51 % vs. 40 %, p=.024), thrombocytopenia (56 % vs. 24%, p<.001), need for transfusions of red blood cells (43 % vs. 29 %, p=.003) and platelets (9 % vs. 3 %, p=.007) (Table 14). There was no significant difference in the frequency of thrombocytopenic bleedings (PC: 2 %, GC: 4 %; p=.27), neutropenic infections (PC: 8 %, GC 9 %; p=.85) or death from neutropenic infections (PC: 2 %, GC: 1 %; p=.67). There was a trend towards more neutropenic infections among elderly patients (≥ 75 years: 13 %, < 75 years: 7 %; p=.067).

Table 14 Hematologic toxicity, need for transfusions and use of growth factors (EPO = Erythropoietin, GCSF = Granulocyte Colony Stimulating Factor)

	Pemetrexed/ Carboplatin (n=219)		Gemcitabine/ Carboplatin (n=217)		
Toxicity, transfusions and growth factors	No. of patients	%	No. of patients	%	P
Hematologic toxicity					
Anemia					.85
Grade 3	25	12	25	12	
Grade 4	2	1	1	1	
Leukopenia					<.001
Grade 3	37	18	76	36	
Grade 4	10	5	20	10	
Neutropenia					.024
Grade 3	52	25	55	26	
Grade 4	31	15	51	25	
Thrombocytopenia					<.001
Grade 3	28	13	67	32	
Grade 4	24	11	51	24	
Transfusions					
Blood	59	29	88	43	.003
Platelets	6	3	19	9	.007
Use of growth factors					
EPO	3	1	1	1	
GCSF	1	1	0	0	

The most common other grade 3-4 adverse events during the treatment period were infections (9 % in both arms, p=.98) and nausea (GC: 4 %, PC: 3 %, p=.43)

(Table 15). There was no significant difference in the frequency of any single grade 3-4 non-hematological adverse event, but more patients on the GC arm had ≥ 1 grade 3-4 adverse event (28 % vs. 19 %, p=.037).

Table 15 Non-hematologic grade 3 or 4 adverse events during the study treatment period

	Pemetrexed/ Carboplatin (n=219)		Gemcitabine/ Carboplatin (n=217)		
Grade 3 or 4 Adverse events	No. of patients	%	No. of patients	%	P
Neutropenic infection	17	8	18	9	.85
Infections without neutropenia	19	9	19	9	.98
Nausea	6	3	9	4	.43
Thrombocytopenic bleedings	5	2	9	4	.27
Deep venous thrombosis	0	0	3	1	.12
Lung embolism	0	0	4	2	.06
Acute myocardial infarction	1	1	2	1	.62
Mucositis	2	1	0	0	.50
Other	4	2	12	6	.04
Any grade 3 or 4 adverse events	41	19	60	28	.037

Poststudy treatment

Thirty-two percent of the patients received second-line therapy (chemotherapy: 24 %, EGFR-TKIs: 8 %), 7 % received third-line therapy and 41 % had palliative radiotherapy. There was no difference in post-study treatment between the treatment arms. More females than males had second-line therapy (38 % vs. 26 %, p=.004) while there was no difference between the treatment arms among females (PC: 42 %, GC: 35 %; p=.34).

Study 3

Patients

Of the 436 patients analyzed in Study 2, 402 were eligible for Study 3 (Figure 10). Median age of all patients was 65 years, 36 % were ≥ 70 years, 18 % were ≥ 75 years, 58 % men, 79 % had PS 0-1 and 29 % stage IIIB. The baseline characteristics were well balanced between the patients with high and low severity index. There were more elderly, males and stage IIIB among the patients with severe comorbidity than among patients with less comorbidity.

Study treatment

There was no significant difference in the mean number of cycles administered between patients with or without severe comorbidity (3.2 vs. 3.5: p=.05) and the proportions of patients who completed all four cycles were similar (65 % vs. 73 %; p=.08). Fewer of the patients with severe comorbidity received second-line systemic therapy (27 % vs. 26 %; p=.04) and post-study radiotherapy (35 % vs. 48 %; p=.01).

There were no differences in study-treatment or post-study therapy depending on the presence of extremely severe comorbidity or a high severity index.

Comorbidity

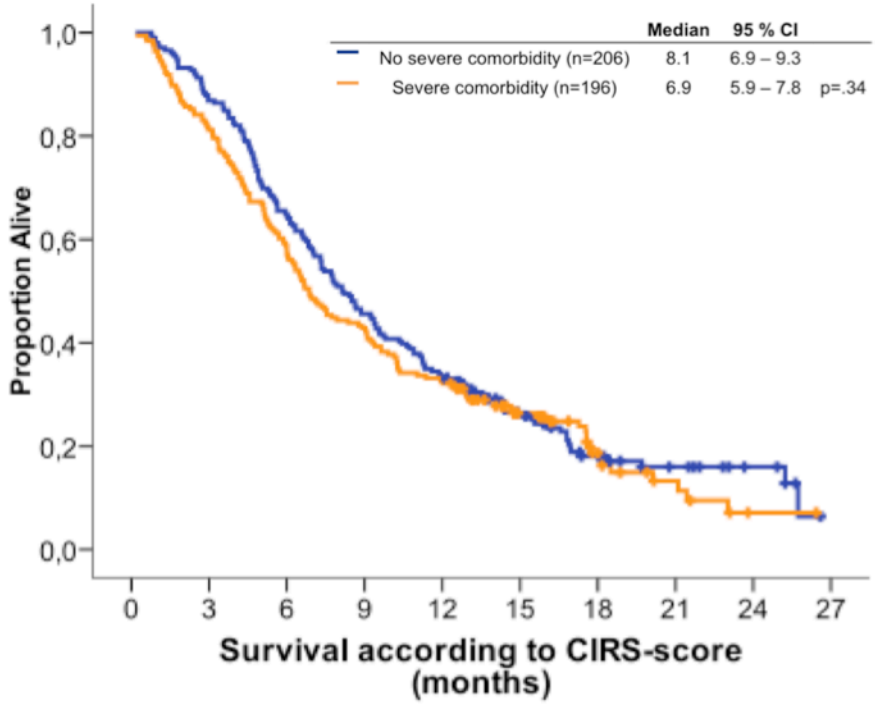
The median total CIRS-G score was 7 (range 0-17). Only three patients had no comorbidity, 8 % had no CIRS-G score > 1, 49 % had severe comorbidity (≥ one CIRS-G score 3-4), 9 % had extremely severe comorbidity (≥ one CIRS-G score 4) and 15 % had a high severity index (> 2). Most CIRS-G scores 3 and 4 were registered on the respiratory (25 %), vascular (10 %) and heart (10 %) scales; 68 % of the patients with severe comorbidity had disorders on these scales only.

Survival

There were no significant differences in survival when comparing patients with and without severe comorbidity (6.9 vs. 8.1 months; p=.34) (Figure 13), with and without extremely severe comorbidity (6.7 vs. 7.7 months; p =.88) and patients with a high severity index with those having a low severity index (8.4 vs. 7.4 months; p=.76). Nor did comorbidity influence survival among the patients with PS 2 or the elderly ≥ 75 years.

PS (p=.001), gender (p=.02), baseline global QoL (p=.004) and appetite loss (p=.006) were significant prognostic factors in the univariate survival analyses. According to the multivariate survival analyses, PS (0-1 vs. 2: HR .74; 95 % CI .56 - .96) and gender (women vs. men: HR .76; 95 % CI .61 - .96) but none of the comorbidity-scores were significant, independent prognostic factors.

Figure 13 Survival according to the presence of severe comorbidity (defined as ≥ one CIRS-G score 3-4)



Toxicity

The patients with severe comorbidity developed significantly more grade 3-4 thrombocytopenia than those with less comorbidity (46 % vs. 36 %; p=.03), but did not experience more thrombocytopenic bleedings (3 % vs. 4 %; p=.65). The frequency of grade 3-4 neutropenia was comparable (48 % vs. 42 %; p=.16) whereas significantly more neutropenic fevers (12 % vs. 5%, p=.01) and all deaths from neutropenic infections (3 % vs. 0 %, p=.03) were observed among the patients with severe comorbidity (Table 16). When looking at the subgroup of patients < 75 years, the same pattern of differences in toxicity depending on the presence of severe comorbidity were observed.

Table 16 Toxicity according to the presence of severe comorbidity (defined as ≥ one CIRS-G score 3-4)

	No severe comorbidity (n=212)		Severe comorbidity (n=198)		
Adverse events	No. of Pts.	%	No. of Pts.	%	p
Grade 3-4 hematologic toxicity					
Anemia	26	13	26	13	.85
Leukopenia	67	33	68	35	.65
Neutropenia	86	42	94	49	.16
Thrombocytopenia	74	36	92	47	.03
Grade 3-4 non-hematologic adverse events					
Infection without neutropenia	14	7	20	10	.22
Neutropenic infection	10	5	23	12	.01
Nausea	10	5	5	3	.22
Thrombocytopenic bleeding	8	4	6	3	.65
Other	12	6	16	8	.36
One or more adverse event	45	22	49	25	.46
Death from adverse events					
Neutropenic infection	0	0	5	3	.03
Infection	4	2	4	2	1.0
Other	1	1	5	3	.11
Total	5	2	14	7	.03

The patients with severe comorbidity who developed neutropenic fevers had disorders on the following CIRS-G scales: Heart (n=8), vascular (n=7), respiratory

(n=11), genitourinary (n=1) and psychiatric (n=1). The patients who died from neutropenic infections had severe comorbidity in the respiratory (n=4) and the vascular system (n=1).

Extremely severe comorbidity or a high severity index did not predict more grade 3-4 adverse events.

Health related quality of life

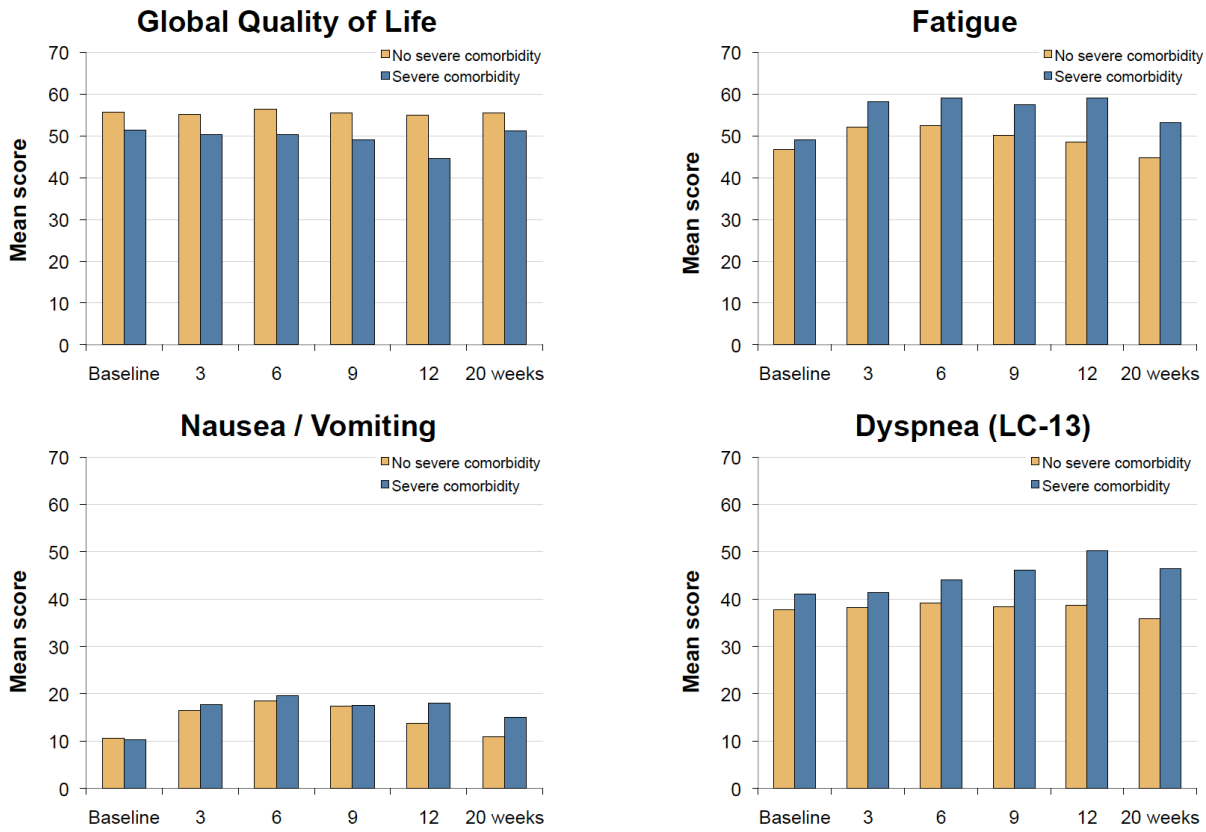
Compliance of the HRQoL-questionnaires during the first 20 weeks was 88 %, and was similar in all subgroups.

The patients with severe comorbidity consistently reported poorer HRQoL on the scales defined as the primary HRQoL-endpoints, and their mean scores deteriorated slightly more than in the patients with less comorbidity (Figure 14). However, the difference in mean score exceeded a clinically significant difference (10 points) only at one time point (week 12) and only on three of four scales (global QoL, fatigue and dyspnea).

When comparing AUCs, the patients with severe comorbidity had significantly worse global QoL (p=.01), more fatigue (p=.001) and dyspnea (p=.01), whereas nausea/vomiting was comparable to what the patients with less comorbidity reported (p=.31). The sensitivity tests confirmed the difference in global QoL (p=.002), but not in fatigue (p=.48), nausea/vomiting (p=.86) or dyspnea (p=.28).

On the other HRQoL-scales, there was a trend towards worse physical and role functioning among the patients with severe comorbidity. Otherwise, no differences were registered. Extremely severe comorbidity or a high severity index did not predict significant differences in HRQoL during study treatment.

Figure 14 Mean scores for the primary HRQoL-endpoints according to the presence of severe comorbidity (defined as ≥ one CIRS-G score 3-4)



Discussion

Tolerability of pemetrexed

The studies demonstrate that pemetrexed is well tolerated by lung cancer patients; both as high-dose monotherapy and at the standard dose in combination with carboplatin. This has also been observed in other studies of similar patient populations.[11,228,229]

High-dose pemetrexed

The number of patients in the phase II study of high-dose pemetrexed monotherapy is limited, but since the frequency of grade 3-4 toxicity was similar in two other studies of pemetrexed monotherapy in recurrent SCLC, it appears that the compound was well tolerated; both in standard- and high-dose. Furthermore, the frequency of hematological toxicity was much lower than in two previous studies of two commonly used regimens for this patient population; topotecan[141,142] and CAV (cyclophosphamide, doxorubicin and vincristine) (Table 14).[142]

Table 14 Hematological toxicity in three studies of pemetrexed in recurrent SCLC and in two studies of other second-line therapy in SCLC

			Grade 3-4 toxicity			
	Regimen	**n**	**Anemia**	**Neutropenia**	**Thrombo-cytopenia**	**Febrile neutropenia**
Ardizzoni[141]	Topotecan 1.5 mg/m^2 IV day 1-5 every 3 weeks	92	12 %	75 %	30 %	6 %
von Pawel[142]	Cyclophosphamide 1000 mg/m^2, Doxorubicin 45 mg/m^2, Vincristine 2 mg IV every 3 weeks	104	19 %	83 %	14 %	26 %
	Topotecan 1.5 mg/m^2 IV day 1-5 every 3 weeks	107	42 %	86 %	56 %	28 %
Jalal[228]	Pemetrexed 500 mg/m^2 IV every 3 weeks	43	9 %	12 %	12 %	10 %
Socinski[229]	Pemetrexed 500 mg/m^2 IV every 3 weeks	56	0 %	16 %	3 %	0
	Pemetrexed 900 mg/m^2 IV every 3 weeks	65	3 %	9 %	5 %	1 %
Grønberg[236]	Pemetrexed 900 mg/m^2 IV every 3 weeks	34	6 %	27 %	9 %	18 %

From the three studies of pemetrexed, it appears that in supplemented patients, there is no significantly increased toxicity from the high dose. This has also been observed in studies comparing standard- and high-dose pemetrexed in recurrent NSCLC[237,238] and as first-line therapy of advanced breast cancer.[239]

Pemetrexed plus carboplatin

The patients who received the pemetrexed-combination were able to receive slightly more cycles of chemotherapy, more of these patients were able to complete all preplanned four cycles and fewer of them had dose-reductions or delays of the chemotherapy than the patients on the gemcitabine-arm. They reported similar HRQoL and since fewer of them had a grade 3-4 hematological toxicity, they needed less transfusion of red blood cells and platelets – and in theory they had a lower risk for complications from the chemotherapy. However, there were no significant differences in the frequency of any single grade 3-4 non-hematological toxicity, though more patients on the gemcitabine-arm had one or more grade 3-4 adverse events during the study treatment period.

Results from the only other phase III study comparing pemetrexed plus a platinum compound with a standard combination in the first-line therapy of advanced NSCLC confirms that pemetrexed is well tolerated in this patient population.[11] In this study, pemetrexed plus cisplatin caused less grade 3-4 hematological toxicity than gemcitabine plus cisplatin. Furthermore, in this study, fewer patients on the pemetrexed-arm developed febrile neutropenia and alopecia; whereas they experienced more nausea.

Efficacy of pemetrexed in lung cancer

The studies suggest that pemetrexed does not have a role in the treatment of SCLC, whereas pemetrexed plus carboplatin may be administered as first-line chemotherapy in advanced NSCLC. Other studies confirm the lack of efficacy of pemtrexed in SCLC, whereas other studies have demonstrated that pemetrexed may be superior to other regimens in the treatment of non-squamous NSCLC.

Small-cell lung cancer

Results from our study suggest that very few patients with recurrent SCLC respond to pemetrexed monotherapy. The number of patients analyzed is limited, but this is due to the fact that enrolment was ended according to predefined stopping rules. However, two other studies of pemetrexed monotherapy confirm the low response rates to pemetrexed in recurrent SCLC..[228,229] Both studies enrolled sensitive and refractory patients. In one study,[228] all patients received standard-dose pemetrexed (500 mg/m2) while in the other study,[229] patients received either standard-dose or high-dose pemetrexed. In total, 159 patients were evaluable for response in these two studies. PR was observed in 3 patients (1.9 %) and SD in 24 patients (15 %). In contrast, response rates of 18-24 % have been observed after second-line therapy with topotecan and CAV (cyclophosphamide, adriamycin and vincristin).[141,142,240]

A phase II trial demonstrated similar efficacy of pemetrexed in combination with carboplatin and cisplatin as previously reported for standard therapy (etoposide plus cisplatin).[165] Response rates were 35-40 % and OS 7.6-10.4 months. The carboplatin combination appeared to be more effective than the cisplatin combination, and a phase III study comparing pemetrexed plus carboplatin with the reference regimen, carboplatin plus etoposide, was conducted.[241] Enrolment on this

study was closed after a preplanned interim-analysis revealed that the pemetrexed combination was significantly inferior to the etoposide-combination with respect to response rates, progression free survival and overall survival.

Based on the results from these trials, the overall conclusion is that pemetrexed does not have a role in the treatment of SCLC.

Table 15 Response rates, time to progression and overall survival for pemetrexed monotherapy compared with results from two other studies of second-line therapy of small-cell lung cancer

	Regimen	Refractory/Sensitive patients	n	RR	TTP	OS
Ardizzoni[141]	Topotecan 1.5 mg/m^2 IV day 1-5 every 3 weeks	Refractory	47	6 %	2.8 m	4.7 m
		Sensitive	45	38 %		6.9 m
von Pawel[142]	Cyclophosphamide 1000 mg/m^2, doxorubicin 45 mg/m^2, vincristine 2 mg IV every 3 weeks	-	104	18 %	2.8 m	5.8 m
	Topotecan 1.5 mg/m^2 IV day 1-5 every 3 weeks	-	107	24 %	3.0 m	5.7 m
Jalal[228]	Pemetrexed 500 mg/m^2 IV every 3 weeks	Refractory	23	4 %	1.2 m	2.7 m
		Sensitive	20	5 %	1.3 m	4.4 m
Socinski[229]	Pemetrexed 500 mg/m^2 IV every 3 weeks	Refractory	25	0 %	1.5 m	3.2 m
		Sensitive	15	0 %	1.3 m	6.1 m
	Pemetrexed 900 mg/m^2 IV every 3 weeks	Refractory	40	0 %	1.2 m	2.5 m
		Sensitive	41	3 %	1.4 m	4.2 m
Grønberg[236]	Pemetrexed 900 mg/m^2 IV every 3 weeks	Refractory	9	11 %	1.2 m	3.5 m
		Sensitive	25	0 %	1.9 m	5.2 m

Dose-level of pemetrexed

The uniform results from all the phase II trials of pemetrexed in recurrent SCLC suggest that the higher dose does not improve efficacy of pemetrexed. This is poorly investigated since almost none of the patients responded to the treatment, but corresponds well with the results from trials in NSCLC and breast cancer, where increasing the pemetrexed dose failed to improve efficacy.[237-239]

Non-small-cell lung cancer

Our study suggests that pemetrexed plus carboplatin provide the same survival benefit as a standard regimen in first-line therapy of advanced NSCLC. In another

study, the overall survival for patients receiving pemetrexed plus cisplatin was similar as for patients receiving gemcitabine plus cisplatin (10.3 vs. 10.3 months; HR .94, 95 % CI .84 - 1.05).[11]

The survival data are similar to what we have observed in previous trials of advanced NSCLC.[38,39] The overall survival is shorter than in other trials of gemcitabine/platinum combinations in advanced NSCLC,[242] whereas the overall survival for patients with a PS of 0 to 1 is comparable to what was observed in these studies. The most likely explanation is the relatively high proportion of patients with PS 2 in our trial (22%); PS 2 is a known negative prognostic factor.[24]

In a phase III study, pemetrexed demonstrated similar efficacy and a more favorable toxicity profile than docetaxel in second-line therapy of NSCLC.[156] A recent study has demonstrated a substantial survival benefit for maintenance pemetrexed therapy over BSC alone in patients who did not progress after four cycles of platinum-doublet chemotherapy.[79] Overall, the patients receiving pemetrexed had a significant survival benefit of 2.8 months (13.4 vs 10.6 months; p=.012), though the benefit was limited to patients with non-squamous histology (15.5 vs. 10.3 months; p=.002). These trials confirm that pemetrexed has a role in the treatment of NSCLC and mainly in patients with non-squamous histology.

Subgroup analyses

In general, there is a great interest in trying to characterize the patients who have the greatest chance for a clinically relevant benefit of chemotherapy; the survival prolongation is limited and side-effects that may provide a poor HRQoL – and in some cases may be life-threatening – are not uncommon.

Conducting subgroup-analyses is controversial. It can provide important additional information and define research questions for further trials – and ethically it

seems optimal to try to answer as many questions as possible once patients have been exposed for experimental therapy. Not to mention that conducting clinical trials take a lot of efforts. On the other hand, the statistical power for such analyses is limited and the risk of finding associations by chance is high. Thus, subgroup analyses should be pre-specified with respect to what analyses to conduct and how to perform them.

When it comes to the main categorization of lung cancer patients, SCLC vs. NSCLC, these subgroups were investigated separately in two defined study populations. The study of the associations between comorbidity and survival, toxicity and HRQoL were predefined, whereas the other subgroup-analyses conducted in study 2 were not. However, they were conducted since there appeared to be an association between histology and efficacy of pemetrexed in other studies.

The association between histology and efficacy of pemetrexed in NSCLC

Subgroup-analyses of several studies of pemetrexed in NSCLC, have revealed that pemetrexed may be more effective in patients with non-squamous tumors and may have inferior efficacy in squamous cell carcinomas when compared with standard regimens; both in first-[11] and second-line therapy[243] and as maintenance therapy in patients who did not progress after four cycles of platinum-doublet first-line therapy (Table 15).[79] Based on these data, pemetrexed is now registered for the use in patients with non-squamous histology only.

In contrast, there were no associations between histology and survival in our study population in univariate, multivariate or interaction tests. There was, however, a significantly longer survival on the pemetrexed-arm among women. At the present time, there are no obvious explanations for these findings. To our knowledge, there

are no other reports of any association between gender and efficacy of any specific cytotoxic therapy, though in the phase III study of pemetrexed plus cisplatin as first-line therapy of NSCLC, there was also a trend towards a survival benefit of pemetrexed among women.[11]

Table 15 Efficacy of pemetrexed according to histology

	Indication	Regimen	Non-squamos histology	p	Squamous cell carcinoma	p
Scagliotti[11]	First-line	Pemetrexed + cisplatin	11.8 mo		9.4	
		Gemcitabine + cisplatin	10.4 mo	.005	10.8	.050
Grønberg[244]	First-line	Pemetrexed + carboplatin	7.8 mo			
		Gemcitabine + carboplatin	7.5 mo	.77		
Ciuleanu[79]	Maintenance	Pemetrexed	15.5 mo		9.9 mo	
		BSC	10.3 mo	.002	10.8 mo	.68
Hanna[156,243]	Second-line	Pemetrexed	9.3 mo		6.2 mo	
		Docetaxel	8.0 mo	.048	7.4 mo	.018

Possible explanations for the varying efficacy of pemetrexed in subgroups of lung cancer patients

The main mechanism of action of pemetrexed is believed to be inhitbion of TS. In case, it seems reasonable that pemetrexed is most effective against tumors with low TS-level. There are indications that tumors with low TS-level have a higher response rate to pemetrexed therapy in breast,[245]colon,[246] and lung cancer.[247] Results from two studies suggest that the TS-level is higher in squamous-cell carcinomas than in adeno- and large cell carcinomas.[248,249] This may explain why pemetrexed is mostly active in non-squamous NSCLC.

Immunohistochemistry analyses of patients enrolled onto the phase III trial of pemetrexed plus carboplatin as first-line therapy of SCLC, revealed that low TS-expression was correlated with OS in the etoposide-arm, but there was no such

association with OS in the pemetrexed-arm.[250] A recent report suggests that the TS-level in SCLC is high[251] and higher than observed in any subgroups of NSCLC.

There are no obvious explanations for why there was no histology-effect or why there was a gender-specific survival benefit for pemetrexed in our trial.

The influence of comorbidity on outcomes in patients with advanced NSCLC

Results from other studies of the influence of comorbidity on survival in advanced NSCLC are not uniform. In one study,[210] comorbidity was associated with inferior survival, but the investigators analyzed a mixed cohort of patients with stage I who had undergone surgical resection and patients with advanced disease that received platinum-based chemotherapy. Unfortunately, the influence of comorbidity for the groups was not reported separately. It is also noteworthy that 69 % of the patients did not have any comorbidity – while in our study, only three patients did not. One reason can be that comorbidity was assessed using the Charlson index - which is less sensitive than the CIRS-G.[235]

In another study, there was no influence of comorbidity on survival in the 1005 patients with advanced lung cancer.[196] Since the analysis was based on a hospital registry, there were no data on what therapy these patients had received. In two small studies, there were no association between comorbidity and overall survival.[201,211]

Two studies have looked at the association between comorbidity and toxicity from therapy. The largest study analysed 1255 patients.[210] However, comorbidity was assessed using the Charlson index and 69 % of patients did not have any comorbidity. Toxicity for patients with advanced disease was not reported separately. The main findings were that patients with comorbidity had more infections, complications in the gastro-intestinal tractus, rash and nausea. In a small trial

(n=46),[211] no association between comorbidity and toxicity from platinum-based therapy was found.

No studies have looked at the association between comorbidity and impact on HRQoL in NSCLC. However, a study of head & neck cancer patients demonstrated that radiotherapy did not have more impact on HRQoL with severe comorbidity than in other patients.[252]

Elderly patients

There is no consensus on the optimal therapy in elderly. Some recommend that elderly should receive the same treatment as younger patients[253] – whereas others suggest that they should receive monotherapy or non-platinum combinations.[36] It is a problem that elderly[90-92] – especially those with comorbidity[194] – are underrepresented or excluded from the clinical trials that treatment recommendations are based upon.

Results from a previous trial, have led the NCLG to recommend a dose-reduction of 25 % to all patients ≥ 75 years.[39] This may seem unnecessary, since the Cockroft-Gault formula takes into consideration age.[70] However, there are a lot of uncertainties regarding calculation of doses of chemotherapy. The Cockroft-Gault's formula is an estimation of renal clearance and Calvert's formula was derived from only 18 patients. Exactly how to calculate the optimal dose in patients with low muscle mass and hence a potentially artificially low serum-creatinine is poorly explored. In addition, pemetrexed and gemcitabine doses are calculated from an estimation of body surface area (BSA). Despite several attempts, no better way of individualizing doses of chemotherapy has entered clinical practice. Recent studies have suggested that adjusting for body composition, particularly the proportion of muscle-mass, may be a method for defining a more optimal dose of

chemotherapy.[254-256] Body composition varies between cancer patients, and it has been demonstrated that elderly in general have lower muscle mass.[257,258]

In our study, the OS for elderly patients was similar as for younger. They had as many dose-reductions as the younger patients and tended to have more neutropenic infections. In general, elderly have more comorbidity and study 3 suggests that the presence of severe comorbidity was associated with a higher risk of acquiring infections when neutropenic. These observations suggest that the elderly patients received an adequate dose of chemotherapy. However, studies comparing monotherapy, non-platinum combinations, standard platinum-combinations and dose-reduced platinum-combinations – and preferably taking into account comorbidity and body composition - in elderly patients with advanced NSCLC are needed to define the optimal therapy for this large group of patients.

Limitations to the studies

Limitations to study 1

A possible limitation to our study is that there was no central review of CT scans for response-evaluation. In addition, the protocol did not warrant confirmation of responses. No central pathology review was conducted; since SCLC and NSCLC have been treated differently for such a long time, we presumed that all pathology departments had good diagnostic procedures to differ between these two entities.

There are no reasons to believe that any of these limitations have influenced the conclusion of our trial, since there was almost no activity of pemetrexed and since our results have been confirmed in two other trials. Furthermore, according to the recently revised guidelines for response evaluation in solid tumors – the RECIST v1.1[259] – confirmation of response is only required for trials with response primary endpoint, but not in randomized studies.

One can question whether it is optimal to conduct a one-armed phase II study as long as there has been a long tradition of administering second-line therapy in SCLC. When there are consistent historical data for comparison from several previous trials available, this may be appropriate. The main reason for conducting a one-armed trial is that it is easier to conduct – especially when the number of patients eligible is limited. However, one should not underestimate the effect of better procedures for diagnosis and staging of cancer, changing methods for assessing efficacy and improved BSC over the years; all of these factors may diminish the value of historical controls. When the efficacy of an experimental drug is as low as in this study, the choice of design probably does not influence the interpretation of the results. But when the efficacy is as promising as in the phase II study of pemetrexed plus carboplatin or cisplatin as first-line therapy of ED SCLC,[165] it is not uncommon to move on to a phase III study – which happened in this case. Hence, many patients received an inferior therapy – which, as the authors comment, may have been avoided if the phase II study had included a randomized comparison with a standard regimen.[241]

Limitations to study 2

There were no significant differences in HRQoL between the treatment arms, although significantly more patients on the gemcitabine-arm experienced one or more grade 3-4 non-hematological toxicity. One interpretation is that the objectively measured toxicity did not reduce the patient's HRQoL. Another explanation may be that it is well recognized among cancer patients that chemotherapy can lead to toxicity, and if the adverse events did not exceed the expectations, they may not automatically lead to a perception of a reduced HRQoL

Another possible explanation is that the timing of the assessment was not optimal to detect a difference in HRQoL due to treatment related toxicity. In our study - as in other, previous trials - HRQoL was assessed immediately before a new cycle of chemotherapy was administered. Previous studies have shown that the level of side-effects due to therapy varies during the cycle, and is most pronounced during the first week after the administration of chemotherapy.[260] Thus, it is possible that most of the adverse events had resolved when the patients answered the QLQs. It is worth noticing that there were more delays of cycles of chemotherapy on the gemcitabine-arm – mostly due to hematological toxicity – and it is possible that these patients then had more time to recover from adverse events than on the pemetrexed arm.

The fact that there were no significant differences in cancer-related symptoms is more easily explained, since the efficacy of the regimens appeared to be similar. For this comparison, the timing of assessment of HRQoL appears to have been optimal, as the QLQs were probably answered during the part of each cycle when the side-effects from the therapy were the least pronounced.

Unfortunately, we did not register the presence of brain metastases and malignant pleural fluid and weight loss over the last months; all significant prognostic baseline characteristics. An imbalance for these factors could potentially influence the survival analyses. At the time of study enrolment, TNM version six was used. In the seventh revision of the TNM, the description of malignant pleural fluid has been changed from T4 to M1 indicating that it is a poorer prognosis than previously believed.[19] In general, the presence of brain metastases is a negative prognostic factor, the median overall survival is approximately 4 months,[261,262] though some subgroup analyses suggest that fit patients with asymptomatic brain metastases who

are found eligible for clinical trials with relatively strict eligibility criteria appear to have the same outcome as other patients.[261,263] In case, the performance status may be of greater importance than the presence of brain metastases, and the two treatment arms in our study were very well balanced for all baseline characteristics registered.

Another limitation is that we did not register RR, TTP or PFS. This is resource demanding, and at the time we started the study, the use of salvage therapy was limited. One can argue that these are surrogate markers for efficacy, and that HRQoL and overall survival are the most important outcomes for each patient. In this trial, more patients received salvage therapy than in previous trials conducted by the NLCG - which may have masked differences in the effect of the first-line therapy. Then again, there were no significant differences in the number of patients who received salvage therapy between the treatment arms or the time to start of second-line therapy (pemetrexed/carboplatin: 4.7 months, gemcitabine/carboplatin 4.6 months; p=.90).

Since the administration schedule and infusion time are different between gemcitabine and pemetrexed, a blind study was not possible to conduct.

Dosage of chemotherapeutic compounds

The gemcitabine-dose of 1000 mg/m^2 on day 1 & 8 of every cycle, was introduced in Norway through a former trial comparing vinorelbine plus carboplatin with gemcitabine plus carboplatin in advanced NSCLC.[39] The dose-level is in the lower range of what is recommended, but there are no established differences in efficacy within the range of 1000-1250 mg/m^2.[242]

In two of the phase II trials investigating the efficacy of pemetrexed plus carboplatin, a carboplatin dose of AUC=6 was administered.[72,264] Based on the

frequency of hematological toxicity in previous studies,[38,39] the NLCG decided to maintain the dose of AUC=5 also for this study. In our study, significantly more hematological toxicity was observed than in the phase II trials, suggesting that the carboplatin-dose was adequate. Most likely, the cause for the difference in hematological toxicity is the wide eligibility criteria in our study.

Since the dosage of chemotherapy was defined to be suitable for a relatively unselected population of patients, one can argue that the dose-levels may be suboptimal for the most fit patients. However, OS for the patients who completed all preplanned four cycles (pemetrexed/carboplatin: 11.0 months, gemcitabine/carboplatin: 10.3 months; p=.93) was similar to what was observed in the overall population in the phase III trial of pemetrexed plus cisplatin (10.3 months).[11] These patients were the ones who were most similar to the patients enrolled onto the latter study.

Limitations to study 3

We did not collect information about the patients diagnosed with advanced NSCLC that were not enrolled onto the trial. Thus, we cannot say whether some patients were excluded from the study due to comorbidity even if they fulfilled the eligibility criteria per se.

There was clearly a variation in how much information about co-existing disorders that was collected in the hospital medical records and there is no way to ensure that all comorbidities have actually been registered. On the other hand, this limitation will apply for most studies of comorbidity and one can argue that our source data are representative for what was considered vital information in the clinic. In addition, the frequency of severe comorbidity was similar to what has been observed

in other studies of comorbidity in NSCLC[190,191,201] and missing information on mild comorbidity would primarily influence the Severity Index – which for this reason may be a less reliable CIRS-G score. To minimize this variation, studies have to be conducted only in sites where specially trained personnel do the assessment of comorbidity.

There was a numerical difference in survival depending on the presence of severe comorbidity and one can argue that the study was underpowered. However, in the studies on lower stage NSCLC that demonstrated a significant prognostic influence of comorbidity on survival, fewer patients were entered.[208,209] In addition, other, well-known, easy-to-assess baseline characteristics were significant prognostic factors also in our study population.

The instrument for measuring comorbidity, the CIRS-G, was developed in 1991.[217] Some of the scores are set depending upon the number of medications for the individual co-existing disorder. It may be that guidelines now recommend the daily use of a higher number of drugs for conditions that are common in lung cancer patients – such as cardiovascular and respiratory disease. In case, a high score may now be set in a higher proportion of patients than earlier. This could result in patients with relatively mild comorbidity being classified as having severe comorbidity. There may also be variation in guidelines for the treatment of co-existing disorders between countries.

A more extensive characterization of the patients may be better for categorizing patients than comorbidity assessment alone.[265,266] However, measuring comorbidity is challenging, and an even more comprehensive, multidimensional geriatric assessment will be difficult to perform in a multicentre trial.

Strengths of the studies

The main strength is that the patients enrolled onto the NSCLC-study are similar to the patients seen in the everyday clinic. During the study enrolment period, 2281 new cases of NSCLC were diagnosed in Norway (all stages of disease). Hence, 20 % of all patients were enrolled onto the study.

Unfortunately, the Norwegian cancer registry does not accurately register the TNM-stage of patients, but it has been estimated that more than 50 % of patients are diagnosed with advanced disease.[37] Some of these patients will be eligible for curative radiotherapy, some will receive palliative radiotherapy – and some will have too poor performance status or organ function to receive platinum-based chemotherapy. If we estimate that 50 % of patients have advanced disease and that 20 % are not candidates for platinum-based chemotherapy, 40-50 % of eligible patients nationwide were enrolled onto our study.

Median age (68 years) is close to the median age at diagnosis in the Norwegian population (approximately 70 years),[2] 22 % had PS 2, 36 % were ≥ 70 years and 18 % ≥ 75 years. In addition, patients with severe comorbidity, brain metastases or malignant pleural fluid were allowed – patients who are often excluded from clinical trials.

Based on general knowledge about immigration in Norway and the names of the patients enrolled onto the study, it is safe to assume that all patients were Caucasians and ethnic Norwegians. This ensures genetic homogeneity; but may also be a limitation to the trial if Norwegians metabolize the investigated cytotoxic compounds differently than other ethnic groups.

Another strength is that comorbidity was assessed from hospital medical records, the most valid source documentation of a patient's health status. This

ensures reproducibility. The assessment of comorbidity was done by trained personnel, and by three physicians only. This ensured good inter- and intra-rater reliability.

Conclusions

- Very few patients with recurrent SCLC respond to high-dose pemetrexed monotherapy, though the therapy appeared to be well tolerated.

- Patients with advanced NSCLC who receive pemetrexed plus carboplatin as first-line chemotherapy, have similar HRQoL and survival, less hematological toxicity and less need for supportive care than patients who receive a standard regimen, gemcitabine plus carboplatin.

- The presence of co-existing disorders does not influence survival in patients with advanced NSCLC receiving chemotherapy. In general, patients with severe comorbidity do not have more toxicity from such therapy, but they appear to have a higher risk of infections when neutropenic. Overall, they also report a poorer HRQoL, but their HRQoL do not deteriorate more than in other patients during chemotherapy.

Implications of the results and topics for future research

The result from ours – and other studies – show that the efficacy of pemetrexed in SCLC-patients is very low and lower than in previous studies of other regimens. Thus, pemetrexed should not be administered to SCLC-patients outside clinical trials. The only rationale for further studies would be that one is able to identify characteristics of patients who have a high chance for responding to the therapy. Preliminary results from a pharmacogenomic study of patients who received pemetrexed plus carboplatin as first-line therapy of ED SCLC, suggest that there

may be genetic markers characterizing the patients who responded to either pemetrexed plus carboplatin or etoposide plus carboplatin.[250] Since so few SCLC-patients respond to pemetrexed, such studies have to be conducted through an international collaboration.

Our study – together with results from another study – demonstrate that pemetrexed plus a platinum compound is an attractive alternative in the first-line treatment of advanced NSCLC. Based on results from other studies, pemetrexed is now approved for the treatment of non-squamous tumors, both as first- and second-line therapy. No association between histology and efficacy was revealed in our study, but there appeared to be a benefit for the pemetrexed combination among women. This finding and the apparent histology effect demonstrated in several other studies, have lead to the initiation of a biomarker study of our patients. All available biopsies have been collected and will be analyzed to see if there are associations between biomarker status and outcomes of the study therapy.

When it comes to clinical trials, the NLCG is currently planning a study that will further explore the efficacy of maintenance pemetrexed after first-line chemotherapy in advanced NSCLC. A main feature of this trial, will be to assess cachexia/sarcopenia as a prognostic factor for survival and a predictive factor for toxicity and deterioration of HRQoL from chemotherapy.

The ability to identify the patients with the highest risk of neutropenic infections would have great clinical implications. The NLCG has performed several studies in advanced NSCLC with more or less similar eligibility criteria. Merging the databases from these studies and then do a case-control study could be a way of gaining further evidence for the apparent association between comorbidity and neutropenic infections. If such studies confirm the results from the present analysis, studies on

prophylactic use of antibiotics and granulocyte colony stimulating factors should be conducted in these patients.

In general, it is not easy to compare results from different studies of comorbidity as a prognostic and predictive factor since the eligibility criteria, study therapy and methods for assessment vary to a great extent. There may be good reasons for varying eligibility criteria (e.g. safety precautions) and study therapies (e.g. introduction of new compounds). However, a standard instrument for the assessment of comorbidity may be necessary to further gain knowledge about how to find the optimal therapy for the large group of patients with co-existing disorders. There appears to be two kinds of instruments for measurement of comorbidity in use today; indices like the Charlson Comorbidity Index that are easy to use – and instruments like the CIRS-G that records and rates all disorders. The main strength of the simple instruments is that they can easily be used in large, multicentre trials and does not require much training. Instruments like the CIRS-G are comprehensive and give a more detailed picture of the patient's health status, but are time and resource demanding.

The optimal assessment of comorbidity will probably have to include a detailed list of all co-existing disorders and diseases, a rating of the disorder using well recognized rating scales and the therapy for each condition. This is the only way to ensure the possibility to compare results over time since the classification and therapy of diseases are not constant. For example, when looking at the rating of cardiovascular disase in the CIRS-G, one can question whether the number of medications today reflects the same degree of illness as when the CIRS-G manual was developed in 1991. E.g. the use of statins was introduced in the mid-1990s and

as a consequence a larger proportion of patients with cardiovascular disease are now treated with at least one more drug than before.

The optimal tool for measuring comorbidity does not exist today. To further develop such an instrument, large databases have to be built through an extensive, international collaboration.

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Appendix A – The EORTC QLQ C30 plus LC 13

PEG-studien **EORTC QLQ-C30** (Versjon 3.0)

QLQnr. 0 1 Pasientnr. ☐☐☐

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

Ditt navns forbokstaver ☐☐☐

Født (dag, måned, år) ☐☐ . ☐☐ . 1 9 ☐☐

Dato for utfylling (dag, måned, år) ☐☐ . ☐☐ . 2 0 ☐☐

	Ikke i det hele tatt	Litt	En del	Svært mye
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?	☐	☐	☐	☐

I løpet av den siste uka:	Ikke i det hele tatt	Litt	En del	Svært mye
6. Har du hatt redusert evne til å arbeide eller utføre andre daglige aktiviteter?	☐	☐	☐	☐
7. Har du hatt redusert evne til å utføre dine hobbyer eller andre fritidsaktiviteter?	☐	☐	☐	☐
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?	☐	☐	☐	☐

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Bla om til neste side

PEG-studien **EORTC QLQ-C30**

QLQnr. 0 1 Pasientnr. ☐☐☐

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 ruten 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**

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Bla om til neste side

PEG-studien **EORTC QLQ-LC13** 0 1 [ ][ ][ ]

QLQnr. 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: ☐

_____

_____

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Appendix B – The RECIST criteria 1.0

Malignant Disease Evaluation

To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. Measurable disease is defined by the presence of at least one measurable lesion.

All measurements should be recorded in metric notation by use of a ruler or calipers. The same method of assessment and the same technique should be used to characterize each identified lesion at baseline and during follow-up. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before being registered for protocol treatment.

The term unevaluable in reference to measurability will not be used because it does not provide additional meaning or accuracy.

At baseline, tumor lesions will be characterized as either measurable or non-measurable.

Measurable Lesions

Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm (2.0 cm) with conventional techniques or as ≥ 10 mm (1.0 cm) with **spiral** CT scan.

If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Non-Measurable Lesions

All other lesions, including small lesions [longest diameter <20 mm (2.0 cm) with conventional techniques or < 10 mm (1.0 cm) with **spiral** CT scan] and truly non-measurable lesions.

Lesions considered to be truly non-measurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

Tumor lesions that are situated in a previously irradiated area are not considered measurable.

Definitions of Response - Target Lesions

Target lesions will be all measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs. Target lesions should be selected on the basis of their size (those with the longest diameters) and their suitability for accurate repeated measurements.

The sum of the longest diameters of all target lesions will be calculated at baseline and reported as the baseline sum longest diameter. This baseline sum longest diameter will be used as the reference by which to characterize the objective tumor response. For lesions measurable in 2 or 3 dimensions, always report the longest diameter at the time of each assessment.

Complete Response (CR)

The disappearance of all target lesions. To be assigned a status of complete response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

Partial Response (PR)

At least a 30% decrease in the sum of the longest diameters of target lesions, taking as reference the baseline sum longest diameter. To be assigned a status of partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

Progressive Disease (PD)

At least a 20% increase in the sum of the longest diameters of target lesions, taking as reference the smallest sum longest diameter recorded since the baseline measurements, or the appearance of one or more new lesion(s).

Stable Disease (SD)

Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. To be assigned a status of stable disease,

measurements must have met the stable disease criteria at least once after study entry at a minimum interval (in general, not less than six to eight weeks).

Definitions of Response – Non-Target Lesions

All other lesions or sites of disease. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Complete Response (CR)

The disappearance of all non-target lesions and normalization of tumor marker levels, if applicable. To be assigned a status of complete response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

Incomplete Response/Stable Disease (SD)

The persistence of one or more non-target lesion(s) and/or the maintenance of tumor marker levels above the normal limits. To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval (in general, not less than six to eight weeks).

Progressive Disease (PD)

The appearance of one or more new lesion(s) and/or unequivocal progression of existing non-target lesions.

Symptomatic Deterioration

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration.

Evaluation of Patient's Best Overall Response

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence, taking as reference for progressive disease the smallest measurements recorded since the treatment began. The table below

provides overall responses for all possible combinations of tumor responses in target and non-target lesions, with or without new lesions.

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval (not less than four weeks).

Overall Response for all Possible Combinations of Tumor Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response / SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = Complete Response; PR = Partial Response; SD = Stable Disease; PD = Progressive Disease

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A prospective phase II study: High-dose pemetrexed as second-line chemotherapy in small-cell lung cancer

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ABSTRACT

Purpose: To investigate the efficacy and tolerability of high-dose pemetrexed as second-line chemotherapy in small cell lung cancer (SCLC).
Patients and methods: Patients with verified SCLC who had received one prior chemotherapy regimen, aged 18–75 years, WHO Performance Status 0–2, no clinical signs of brain metastases and measurable disease were eligible. Patients received pemetrexed 900 mg/m^2 IV every 3 weeks. Four courses were planned for all patients. Patients with relapse later than 3 months since last course of first-line chemotherapy were defined as "sensitive", those with relapse within 3 months as "refractory". Toxicity was graded using the CTCAE v3.0.
Results: 36 patients were accrued, 34 received study treatment. Median age was 61 (range 43–74), 18 (53%) males and 16 (47%) females. Mean number of courses administered was 2.5. One patient (3%) had partial response, three (9%) had stable disease and 29 (85%) progressed. One patient (3%) was not evaluable for response. Median TTP ($n = 33$) was 7.7 weeks ("sensitive": 8.4 weeks, "refractory": 5.1 weeks). Median OS ($n = 34$) was 17.6 weeks ("sensitive": 22.6 weeks, "refractory": 15.3 weeks). Of grade 3–4 haematological toxicity, anemia was observed in 2 (6%) patients, leukopenia in 6 (18%), granulocytopenia in 9 (27%) and thrombocytopenia in 3 (9%). Febrile neutropenia occurred in 6 (18%) patients. There were no treatment related deaths.
Conclusion: High-dose pemetrexed monotherapy to patients with recurrent SCLC yielded moderate toxicity, but limited treatment efficacy.

1. Introduction

A platinum compound in combination with etoposide is widely used as first-line chemotherapy for small-cell lung cancer [1–3]. Patients with limited disease (LD) also benefit from concurrent thoracic radiotherapy [4]. Response rates above 80% have been reported in patients with LD, and 40–50% in extensive disease (ED) [2,3]. The 5-year survival is 10–26% for LD, while few patients with ED survive more than 2 years [1–3].

Despite high response rates to first-line therapy, a majority of patients relapse within 1 year. Palliative radiotherapy is then a treatment option, but most patients have advanced disease and need systemic therapy. Reported response rates to second-line chemotherapy of 12–25% are lower than for first-line therapy [5–10]. However, a survival benefit has been observed after

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second-line treatment [11]. Patients who received oral topotecan had a significantly longer survival than patients who received best supportive care alone.

Important factors predicting efficacy of relapse treatment are response to first-line chemotherapy, time till relapse and WHO Performance Status at relapse [5,12,13]. Patients relapsing later than 3 months after first-line chemotherapy are considered to have "sensitive" disease and have a better prognosis than "refractory" patients who progress within 3 months [5,12].

Patients with recurrent SCLC often have significant comorbidity, poor performance status and poor bone marrow function after first-line chemotherapy. This limits the use of second-line therapy. Consequently, there is a need to explore the efficacy of drugs that might offer less toxicity than the regimens used today.

Pemetrexed is an antifolate registered for the treatment of malignant pleural mesothelioma and second-line treatment of non-small cell lung cancer (NSCLC). The most common side effects are myelosuppression, oral mucositis, diarrhea and skin rash [14]. Prophylactic treatment with corticosteroids reduces the frequency of rash. Since the drug is eliminated through the kidneys, a creatinine-clearance $\geq$40 mL/min is recommended [15]. Based on results from initial phase I/II trials, 500 mg/m^2 was defined as the standard dose [14,16]. Later, it was observed that toxicity was reduced in patients supplemented with vitamin B12 and folic acid [17]. New phase I trials were performed and the recommended dose for patients not heavily pretreated with chemotherapy was defined as 1000–1050 mg/m^2 provided vitamin supplementation [18,19].

Pemetrexed inhibits growth of cell lines from small-cell lung cancer [20]. Several agents effective in the treatment of NSCLC have shown efficacy in recurrent SCLC [8–10]. Pemetrexed has a favorable toxicity profile in second-line treatment of patients with NSCLC [21], a population comparable to patients with recurrent SCLC. In general, it is assumed to be beneficial to administer as high a dose of chemotherapy as possible. A trial investigating the efficacy of pemetrexed 500 mg/m^2 (standard dose) in recurrent SCLC [22] was already initiated when we planned our study. The aim of this study was to investigate the efficacy and tolerability of pemetrexed 900 mg/m^2 (high-dose) in patients with recurrent SCLC.

2. Patients and methods

2.1. Design

The study was designed as an open, multi-center phase II trial and was approved by the Regional Committee for Medical Research Ethics in Central Norway, the Norwegian Medicines Agency, the Norwegian Social Science Data Services and the Norwegian Directorate for Health and Social Affairs.

2.2. Eligibility criteria

Eligible patients had histological or cytological proven SCLC, received one prior chemotherapy regimen (re-induction therapy with the first-line regimen at first relapse was allowed), age 18–75 years, given written informed consent, WHO Performance Status 0–2, no clinical symptoms of brain metastases, platelets $\geq 100 \times 10^9$/L, absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, creatinine-clearance $\geq$45 mL/min (calculated using the Cockroft–Gault formula), bilirubin $<1.5 \times$ ULN, ALT and ALP $<3 \times$ ULN (in case of liver-metastases: $<5 \times$ ULN) and measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST). Pregnant or lactating women or patients with other active malignant disease were not eligible.

2.3. Therapy

All patients were supplemented with folic acid 0.4 mg PO once daily and Vitamin B12 1 mg IM every 9 weeks, starting at least 5 days before the first course of chemotherapy and lasting until 3 weeks after the last course. Dexamethasone 4 mg $\times$ 2 BID (or an equivalent dose of another corticosteroid) was given the day prior to, the treatment day, and the day after every course of study treatment. Pemetrexed 900 mg/m^2 was administered IV over 10 min every 3 weeks. Four courses were planned for all patients.

Prior to each course, ANC had to be $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, creatinine-clearance $\geq$45 mL/min and any grade 3–4 non-hematological toxicity had to be resolved. If not, treatment was delayed 1 week. The dose of the following course was reduced by 25% in case of nadir ANC $<0.5 \times 10^9$/L, a neutropenic infection or any grade 3–4 toxicity following the preceding course. A 50% dose reduction was to be performed in case of nadir platelets $<50 \times 10^9$/L or grade 3–4 mucositis. Any dose reductions were maintained for all subsequent courses. If a patient qualified for a third dose reduction, or had a treatment-related delay of more than 42 days following the preceding course, the study treatment was discontinued.

2.4. Endpoints and evaluation

The primary endpoint was overall response rates (ORR). The secondary endpoints were overall survival (OS), time to progression (TTP) and toxicity.

A baseline CT scan of the thorax and upper abdomen was performed within 1 week prior to chemotherapy. Hemoglobin, leucocytes, ANC and platelet count were assessed on day 8 and 15 of every treatment cycle. All patients were evaluated for response with a CT scan 3 weeks after the fourth course of chemotherapy (earlier if progression was suspected) using the RECIST-criteria. A CT scan was performed every 8 weeks until progression. All patients were observed for one year or until death. No central review of the CT-scans was performed. Toxicity was assessed at every visit and was graded using the CTCAE v3.0. We estimated overall survival and time to progression using the Kaplan–Meier method.

2.5. Statistical considerations

Patients with relapse later than 3 months after the last course of first-line chemotherapy were defined as "sensitive", those with relapse within 3 months as "refractory". A two-stage Simon design was used to define sample size in each group using a one-sided alpha of 10% and a power of 90% [23].

For "sensitive" patients, a rate of non-progressive disease (non-PD) of 40–60% was considered to be of clinical significance. 18 patients were to be enrolled in the initial phase of inclusion. If $\geq$8 patients showed non-PD [complete response (CR) + partial response (PR) + stable disease (SD)] at evaluation 3 weeks after the last course of chemotherapy, 28 additional patients were to be included in this group. However, enrolment was to continue until it was possible to conclude whether the target number of patients with non-PD in the initial phase of enrolment was reached. The study treatment would be considered worth further investigation in this patient population if $\geq$23 of 46 patients showed non-PD.

For "refractory" patients, a rate of non-progressive disease of 10–25% was considered to be of clinical significance. 21 patients were to be enrolled in the initial phase of inclusion. If $\geq$3 patients responded to therapy (CR + PR) at evaluation 3 weeks after last course of chemotherapy, 29 additional patients were to be included in this group. However, enrolment was to continue until it was possible to conclude whether the target number of patients with treatment response in the initial phase of enrolment was reached. The

Table 1
Baseline patient characteristics

	Sensitive patients ($n=25$)		Refractory patients ($n=9$)		All patients ($n=34$)	
Age						
Median (range)	61 (43–74)		65 (58-74)		61 (43–74)	
Gender						
Male	15	60%	3	33%	18	53%
Female	10	40%	6	67%	16	47%
WHO Performance Status						
0	4	16%	1	11%	5	15%
1	14	56%	4	44%	18	53%
2	7	28%	4	44%	11	32%
Stage of disease at diagnosis						
Limited disease	13	52%	1	11%	14	41%
Extended disease	12	48%	8	89%	20	59%
Asymptomatic brain metastases	6	24%	3	33%	9	26%
First-line chemotherapy						
Cisplatin/Etoposide	12	48%	3	33%	15	44%
Carboplatin/Etoposide	9	36%	2	22%	11	32%
Carboplatin/Irinotecan[a]	2	8%	2	22%	4	12%
Cyclophosphamide/Adriamycin/Vincristin[b]	1	4%	2	22%	3	9%
Carboplatin/Vinorelbine[c]	1	4%	0	0%	1	3%

[a] Carboplatin/Irinotecan was offered to patients as part of a clinical trial.
[b] Patients considered unfit for platinum-therapy were offered CAV.
[c] Initially misdiagnosed and treated as non-small cell lung cancer.

study treatment would be considered worth further investigation in this patient population if ≥8 of 50 patients responded to therapy.

3. Results

3.1. Patients

Between May and October 2005, 36 patients were enrolled at 16 hospitals in Norway. Two patients never received any study treatment and have been excluded from the analyses; one died suddenly for an unknown reason while the other received radiotherapy because of rapid progression.

Baseline patient characteristics are shown in Table 1. Median age was 61 years, 23 (68%) patients had WHO Performance Status 0–1, 14 (41%) had limited disease at diagnosis, 25 (74%) had "sensitive" disease and 9 (26%) had asymptomatic brain-metastases, 26 (76%) had received a platinum compound plus etoposide as first-line chemotherapy. Two patients had received re-induction chemotherapy with their first-line regimen at the first relapse. One patient was initially misdiagnosed with non-small cell lung cancer and received carboplatin/vinorelbine as first-line chemotherapy.

3.2. Study treatment

Details are presented in Table 2. The mean number of completed courses was 2.5 ("Sensitive" 2.7; "refractory" 1.9). Dose-reductions were performed in 5/84 (6%) of the courses due to pneumonia before the first course (off-protocol, $n=1$) and hematological toxicity ($n=4$). Four courses were delayed in three patients due to multiple grade 3–4 toxicity ($n=1$), grade 2 pneumonia not considered treatment-related ($n=1$), suspected erysipelas ($n=1$) and patients vacation ($n=1$). Dose-intensity was 97%.

Study-treatment was discontinued in 26 (76%) patients. The reasons were progressive disease ($n=21$), non-hematological toxicity ($n=2$) and a grade 2 pneumonia not considered treatment-related ($n=1$). One patient withdrew because she did not feel the treatment helped ($n=1$). One patient was erroneously considered to have progression after two courses of study treatment and started on third-line chemotherapy.

3.3. Response to treatment

One patient was not evaluable for response. Thus, response and time to progression was assessed in 33 patients. One patient had PR, three had SD and 29 had PD (Table 3).

3.4. Time to progression and survival

Median TTP was 7.7 weeks ("sensitive": 8.4 weeks, "refractory": 5.1 weeks). Median OS was 17.6 weeks ("sensitive": 22.6 weeks, "refractory": 15.3) (Table 3, Figs. 1 and 2).

Table 2
Study treatment administered

	Sensitive patients ($n=25$)		Refractory patients ($n=9$)		All patients ($n=34$)	
No. of courses of pemeterxed						
1	5	20%	3	33%	8	24%
2	6	24%	4	44%	10	29%
3	6	24%	2	22%	8	24%
4	8	32%	0	0%	8	24%
Mean no. of courses		2.7		1.9		2.5
Total no. of courses		67		17		84
No. of courses with dose-reduction	3	4%	2	12%	5	6%
No. of delayed courses	3	4%	1	6%	4	5%
Dose-intensity (planned/administered dose)		98%		96%		97%

Table 3
Response to study treatment, time to progression and overall survival

	Sensitive patients ($n=25$)		Refractory patients ($n=9$)		All patients ($n=34$)	
Best response to treatment						
Complete response	0	0%	0	0%	0	0%
Partial response	0	0%	1	11%	1	3%
Stable disease	3	12%	0	0%	3	9%
Progressive disease	21	84%	8	89%	29	85%
Not evaluable	1	4%	0	0%	1	3%
Median time to progression (weeks) 95% CI		8.4 6.4–10.5		5.1 4.7–5.6		7.7 4.8–10.6
Median overall survival (weeks) 95% CI		22.6 10.7–34.5		15.3 7.8–22.8		17.6 8.4–26.8

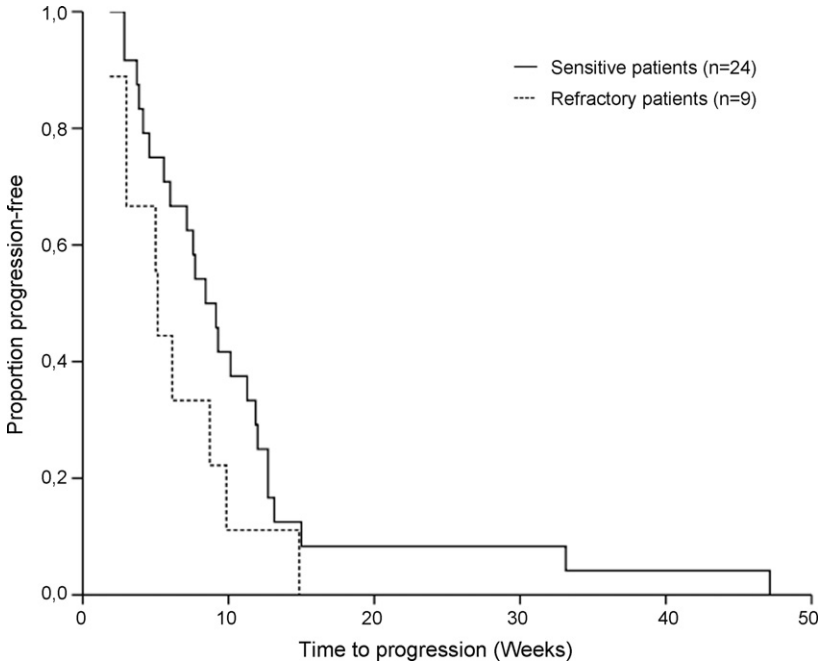

Fig. 1. Time to progression for evaluable patients treated with pemetrexed 900 mg/m^2.

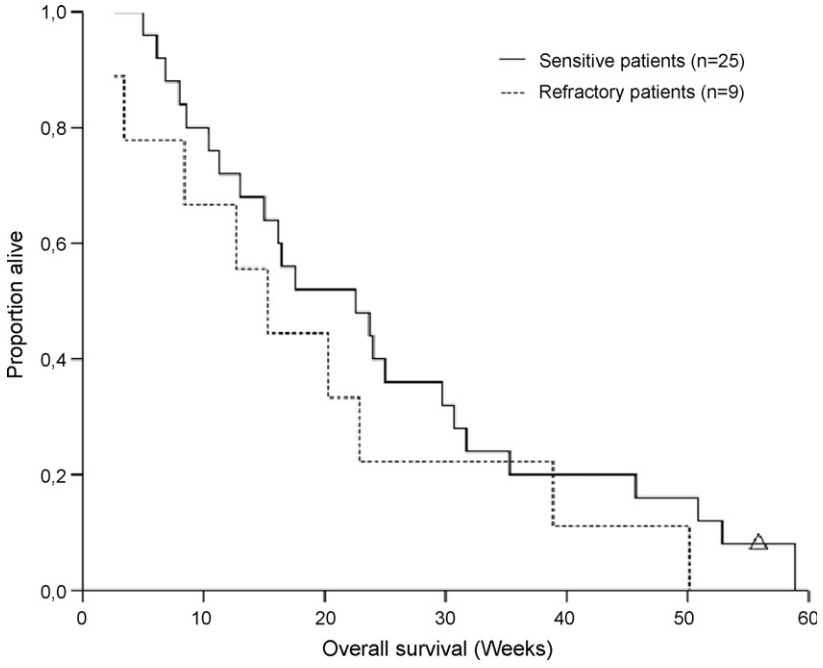

Fig. 2. Overall survival for patients treated with pemetrexed 900 mg/m^2 (Δ = censored).

Table 4
Hematological toxicity

	Sensitive patients ($n=25$)		Refractory patients ($n=9$)		All patients ($n=34$)	
Anemia						
Grade 3	2	8%	0	0%	2	6%
Grade 4	0	0%	0	0%	0	0%
Leucopenia						
Grade 3	3	12%	2	22%	5	15%
Grade 4	0	0%	1	11%	1	3%
Granulocytopenia						
Grade 3	4	16%	0	0%	4	12%
Grade 4	2	8%	3	33%	5	15%
Thrombocytopenia						
Grade 3	1	4%	0	0%	1	3%
Grade 4	1	4%	1	11%	2	6%
No. of patients who received blood transfusion	4	16%	1	11%	5	15%
No. of patients who received platelet transfusion	0	0%	1	11%	1	3%
No. of patients with febrile neutropenia	4	16%	2	22%	6	18%

Primary locations for progression were lung ($n=14$), mediastinal lymph nodes ($n=6$), liver ($n=6$), brain ($n=6$), bone ($n=4$), pleura ($n=2$), neck lymph nodes ($n=1$), skin ($n=1$), kidney ($n=1$), adrenal gland ($n=1$) and spinal medulla ($n=1$). Eleven patients had first progression in multiple locations.

3.5. Toxicity

Grade 3–4 hematological toxicity is presented in Table 4: Anemia was observed in 2 (6%), leucopenia in 6 (18%), neutropenia in 9 (27%) and thrombocytopenia in 3 (9%) patients. Blood or platelet transfusions were administered to 6 (18%) and febrile neutropenia was observed in 6 (18%) patients.

Four patients had grade 3–4 non-hematological toxicity; multiple toxicities (rash, mucositis, neutropenic septicaemia and arthritis urica) ($n=1$), constipation ($n=1$), exacerbation of pityriasis versicolor ($n=1$) and rash ($n=1$). All adverse events resolved. There were no treatment related deaths.

3.6. Poststudy treatment

Fifteen patients received third-line and three received fourth-line chemotherapy. Ten patients received palliative radiotherapy.

4. Discussion

Patients were enrolled until the first 12 "sensitive" patients had been evaluated. Of these, one had SD and 11 PD. The number of patients with non-PD was inadequate to complete stage two of inclusion of "sensitive" patients. At the same time, a study investigating the efficacy of pemetrexed 500 mg/m^2 in a similar patient-population [22] had stopped inclusion since too many patients (both "sensitive" and "refractory") had progressed during study treatment. Based on the results from the study by Hanna et al. [22] and our data, we concluded that pemetrexed monotherapy lack efficacy in recurrent SCLC both at standard and at high dose. Further, we found it unlikely to reach the target number of responses among "refractory" patients in order to complete phase two of the inclusion. Thus, our study group found it unethical to continue inclusion even though only nine "refractory" patients had been enrolled.

Previous studies have shown an ORR between 18–24%, TTP 12–15 weeks and OS 25–39 weeks following second-line treatment of SCLC with topotecan or CAV (cyclophosphamide/doxorubin/vincristin) [5–7]. More hematological toxicity was reported for these regimens when compared with high-dose pemetrexed, but the efficacy of pemetrexed monotherapy appears to be inferior.

Preliminary data from two recent trials support our findings. Hanna et al. conducted a phase II trial in which 43 patients received pemetrexed 500 mg/m^2 every 3 weeks until a maximum of six courses. Only two PR's were observed [22]. Raju et al. have presented results from a phase II trial investigating the efficacy of both pemetrexed 500 and 900 mg/m^2 in recurrent SCLC [24]. The standard dose was administered to 38 and the higher dose to 78 patients. PR was observed in only one patient. Neither efficacy nor toxicity was significantly increased by the higher pemetrexed dose.

Apparently, escalating the dose of pemetrexed does not improve the efficacy in recurrent SCLC. This is consistent with findings in recurrent non-small cell lung cancer and in locally advanced/metastatic breast cancer, where increased pemetrexed doses failed to improve the efficacy [25–27].

In conclusion, high-dose pemetrexed monotherapy to patients with recurrent SCLC yielded moderate toxicity, but limited treatment efficacy.

Conflict of interest

None of the authors have any financial or personal relationships that could influence their work.

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Manuscript for original article

Influence of comorbidity on survival, toxicity and health-related quality of life in patients with advanced non-small-cell lung cancer receiving chemotherapy

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Abstract

Aim of the study: To investigate whether severe comorbidity was an independent significant prognostic factor for survival, predicted more toxicity or worse health related quality of life (HRQoL) in patients enrolled on a phase III trial comparing pemetrexed plus carboplatin with gemcitabine plus carboplatin as first-line chemotherapy of stage IIIB/IV non-small-cell lung cancer.

Patients and methods: Patients were eligible for the phase III trial regardless of comorbidity provided they had performance status 0 - 2 and adequate kidney/liver/bone-marrow function. Comorbidity was assessed from hospital medical records using the Cumulative Illness Rating Scale for Geriatrics, toxicity was graded using the CTCAE v3.0 and the patients reported HRQoL on the EORTC QLQ-C30/LC13.

Results: Data from 402/436 of the patients enrolled on the phase III trial were analyzed in this study (medical records were not retrieveable for 34 patients). No significant associations were found between the presence of comorbidity and overall survival. Patients with severe comorbidity had a similar frequency of neutropenia as other patients (48 % vs. 42 %; p=.16), but experienced more neutropenic fevers (11 % vs. 5%; p=.012) and deaths from neutropenic infections (3 % vs. 0 %; p=.027). Patients with severe comorbidity reported poorer HRQoL, but not significantly more deterioration of HRQoL during the treatment period.

Conclusions: The results from our study suggest that patients with advanced NSCLC who have severe co-existing disorders benefit from and tolerate chemotherapy as well as other patients. However, these patients appear to have a higher risk of acquiring infections when neutropenic.

Introduction

Lung cancer is one of the most common malignant diseases and the leading cause of cancer-deaths worldwide. Non-small-cell lung cancer (NSCLC) accounts for approximately 85 % of the cases and about half of the patients are diagnosed with advanced disease. Platinum-based chemotherapy is the recommended palliative therapy for these patients as it prolongs survival and improves health-related quality of life (HRQoL).[1,2] However, many patients with significant comorbidity, especially elderly, do not receive such treatment.[3] One reason may be concerns about negative side effects in terms of toxicity and deterioration of HRQoL[2,4] – though this is poorly investigated; in clinical trials, comorbidity is seldom systematically assessed and reported, and elderly and patients with significant comorbidity are often underrepresented.[5,6]

Comorbidity increases with age,[7] and due to a growing population of elderly cancer patients, there is a need to define how patients with co-existing disorders should be treated. This is particularly true for lung cancer patients; the median age is approximately 70 years,[8] and as a majority have been tobacco-smokers, a well-known risk factor for a wide range of diseases, the presence of co-existing diseases is frequent.[7,9,10]

Comorbidity has been identified as an independent prognostic factor for survival in several cancers,[11,12] while the results from studies of NSCLC are not consistent. Whereas a negative association between the presence of comorbidity and survival has been demonstrated in studies of stage I[9] and stage III[10] and cohorts of mixed stages,[13,14] this has not been confirmed in advanced disease.[12,15,16] There are indications that NSCLC patients with severe comorbidity experience more

treatment related toxicity than other patients,[13,17] but no studies have investigated the impact on HRQoL during chemotherapy.

The Norwegian Lung Cancer Study Group has conducted a phase III trial comparing pemetrexed/carboplatin with gemcitabine/carboplatin as first-line chemotherapy in advanced NSCLC.[18] In this report, the associations between comorbidity and survival, toxicity and impact on HRQoL during chemotherapy in this study population are presented.

Patients and methods

Approvals

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

Aims

The primary aim was to investigate whether comorbidity was an independent prognostic factor for survival in patients with advanced NSCLC receiving platinum-based chemotherapy. Secondary aims were to investigate whether patients with comorbidity had more toxicity or deterioration of HRQoL during such treatment than other patients.

Patient selection, study treatment, follow up, assessment of HRQoL and main results from the phase III study

Eligible patients had given written informed consent, had stage IIIB (ineligible for curative radiotherapy) or stage IV NSCLC, WHO performance status 0-2, platelets

≥ 100 x 10^9/L, absolute neutrophil count ≥ 1.5 x 10^9/L, creatinine-clearance ≥ 45 ml/min (Cockroft-Gault), bilirubin < 1.5 x ULN, ALT and ALP < 3 x ULN. All other comorbidities were allowed.

Up to four cycles every three weeks of pemetrexed 500 mg/m^2 plus carboplatin AUC=5 (Calvert) on day 1 or gemcitabine 1000 mg/m^2 on day 1 & 8 plus carboplatin AUC=5 on day 1 were administered. Those who were ≥ 75 years had a 25 % dose reduction based on the study-group's experience from a previous trial (unpublished data).

Patients underwent laboratory tests and completed HRQoL-questionnaires before each chemotherapy-cycle (weeks 0, 3, 6 & 9) and at follow-up visits every 8 weeks from week 12-52. Toxicity was graded using the CTCAE v3.0.

HRQoL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30 and the Lung cancer specific module LC13. The QLQ-C30 measures fundamental aspects of HRQoL and symptoms commonly reported by cancer patients in general, the LC13 measures symptoms commonly associated with lung cancer and its treatment.

From May 2005 until July 2006, 436 eligible patients were enrolled at 35 hospitals in Norway. No significant differences in HRQoL or survival were found between the treatment arms.[18] There was more hematologic toxicity on the gemcitabine-arm, but not more of other grade 3-4 adverse events. Thus, for the present study, data from both treatment arms were analyzed jointly.

Assessment of comorbidity

The CIRS-G is an index of fourteen scales/organ systems [19,20]. The severity of disorders on each scale is graded from 0-4. "0" indicates no problem, "1" a current

mild problem or past significant problem, “2” a moderate disability or morbidity requiring “first-line” therapy, “3” a severe/constant significant disability or an "uncontrollable" chronic problem and “4” an extremely severe/immediate treatment required/end organ failure/severe impairment in function. A manual recommends specific scores for common conditions.[20] The total score (= sum of scores on all scales), the numbers of scores 3 and 4, and the severity index (= total score/number of categories with a score > 0) are then calculated (Table 1).

Two physicians independently assessed comorbidity for each patient from hospital-charts for the last three months prior to randomization. Any differences in scores were discussed and the two physicians agreed on a final score. The most common cause of inconsistent scores was that information in the charts had been overlooked. Three of the authors, all physicians and specialists in oncology, did the assessment.

Analyses and statistical considerations

In two studies of NSCLC, patients with a severity index > 2 or a CIRS-G score 4 had inferior survival.[9,10] Thus, we defined “high severity index” as > 2 and “extremely severe comorbidity” as the presence of ≥ 1 CIRS-G score 4. Additionally, we defined “severe comorbidity” as the presence of ≥ 1 CIRS-G score 3 or 4, since it may be difficult to differentiate whether a disorder qualifies for a score 3 or 4.[21]

Survival time was defined as time from randomization until death and was estimated using the Kaplan-Meier method. The log-rank test was used in the univariate survival-analyses to compare survival according to comorbidity-scores and other known prognostic factors in advanced NSCLC; performance-status (PS),[22] stage of disease,[23] gender,[24] smoking-history[25] and baseline HRQoL[14,15,26] – as well

as study treatment. Based on results from previous studies,[15,26] appetite loss (baseline score > 0) and global QoL (cut-off level at 66) were defined as the most important prognostic baseline HRQoL-scores. Cox multivariate-analyses were conducted adjusting for the baseline characteristics identified as significant prognostic factors in the univariate survival-analyses. Toxicity-data were compared using Pearson's Chi-Square and Fischer's exact tests.

Global QoL, fatigue, nausea/vomiting (reported on the C30) and dyspnea (reported on the LC13) were defined as the primary HRQoL-endpoints. Global QoL gives information on overall health. Nausea/vomiting and fatigue are common, important side effects of chemotherapy. Fatigue and dyspnea are key symptoms of lung cancer.

HRQoL scores were calculated according to the EORTC QLQ-C30 scoring manual. The mean scores and areas under the curves (AUC) for the first 20 weeks were then compared. Mean scores were calculated from the reported values only. Missing data were imputed before calculating AUCs. Missing intermittent scores were replaced by the mean value of the two adjacent scores. Last reported value was carried forward for other missing values unless the patient died. In those cases, the missing values were set to zero from the time of death. A sensitivity test was performed using the same method for imputing missing intermittent values, but with the last value carried forward, even after death. The AUCs for each scale were compared using linear regression adjusting for the baseline HRQoL-scores.

The clinically relevant minimum difference in mean HRQoL-scores was defined as 10 points (on a scale from 0-100).[27] Statistical significance level was defined as $p < 0.05$.

Results

Patients

Hospital medical records were not retrievable for 34 patients. Thus, 402 out of the 436 patients enrolled on the phase III trial were analyzed in the present study (Figure 1). Age distribution and the proportion of new cases of NSCLC in Norway accrued in each age group are shown in Figure 2A; 23 % of patients < 70 years and 12 % of patients ≥ 70 years were enrolled (p<.001).

Baseline characteristics for all patients and according to CIRS-G scores are shown in table 2. Median age of all patients was 65 years, 36 % were ≥ 70 years, 18 % were ≥ 75 years, 58 % men, 79 % had PS 0-1 and 29 % stage IIIB. The baseline characteristics were well balanced between the patients with high and low severity index. There were more elderly, males and stage IIIB among the patients with severe comorbidity than among those with less comorbidity.

Study treatment

When comparing patients with and without severe comorbidity, there were no significant differences in the mean number of chemotherapy cycles administered (3.2 vs. 3.5: p=.05) or the proportion who completed all four cycles (65 % vs. 73 %; p=.08). Fewer patients with severe comorbidity completed four cycles without delays (46 % v 59 %; p=.008), but those who completed all cycles did not have more dose reductions (29 % v 35 %; p=.17) (Table 2). Fewer of the patients with severe comorbidity received second-line systemic therapy (27 % v 26 %; p=.04) or post-study radiotherapy (35 % v 48 %; p=.01).

There were no differences in study-treatment or post-study therapy depending on the presence of extremely severe comorbidity or a high severity index.

Comorbidity

The distributions of the total CIRS-score and the severity indices are shown in figure 2B & C. The median total CIRS-G score was 7 (range 0-17). Only three patients had no comorbidity, 8 % had no CIRS-G scores > 1, 49 % had severe comorbidity (≥ one CIRS-G score 3-4), 9 % had extremely severe comorbidity (≥ one CIRS-G score 4) and 15 % had a high severity index (> 2).

Most CIRS-G scores 3 and 4 were registered on the respiratory (25 %), vascular (10 %) and heart (10 %) scales (Figure 2D); 68 % of the patients with severe comorbidity had disorders on these scales only.

Survival

There were no significant differences in survival when comparing patients with and without severe comorbidity (6.9 v 8.1 months; p=.34), with and without extremely severe comorbidity (6.7 v 7.7 months; p =.88) and patients with a high severity index with those having a low (8.4 v 7.4 months; p=.76). Nor did comorbidity influence survival among the patients with PS 2 or age ≥ 75 years.

PS (p=.001), gender (p=.02), baseline global QoL (p=.004) and appetite loss (p=.006) were significant prognostic factors in the univariate survival analyses. According to the multivariate survival analyses, PS (0-1 v 2: HR .74; 95 % CI .56 - .96) and gender (women v men: HR .76; 95 % CI .61 - .96) but none of the comorbidity-scores were significant prognostic factors (Table 3).

Toxicity

The patients with severe comorbidity developed significantly more often grade 3-4 thrombocytopenia than those with less comorbidity (46 % v 36 %; p=.03), but did

not experience more thrombocytopenic bleedings (3 % vs. 4 %; p=.65). The frequency of grade 3-4 neutropenia was comparable (48 % vs. 42 %; p=.16) whereas significantly more neutropenic fevers (12 % vs 5%, p=.01) and all deaths from neutropenic infections (3 % vs 0 %, p=.03) were observed among patients with severe comorbidity (Table 4). When looking at the subgroup of patients < 75 years, the same pattern of differences in toxicity depending on the presence of severe comorbidity were observed.

The patients with severe comorbidity who developed neutropenic fevers had disorders on the following CIRS-G scales: Heart (n=8), vascular (n=7), respiratory (n=11), genitourinary (n=1) and psychiatric (n=1). The patients who died from neutropenic infections had severe comorbidity in the respiratory (n=4) and the vascular system (n=1).

Extremely severe comorbidity or a high severity index did not predict more grade 3-4 adverse events.

Health related quality of life

Compliance of the HRQoL-questionnaires during the first 20 weeks was 88 %, and was similar in all subgroups. At all time points for assessment of HRQoL, the mean scores indicated a poorer HRQoL in patients with severe comorbidity compared to the other patients (Figure 3). However, the difference only exceeded 10 points at one time point (week 12) and only on three of four scales (global QoL, fatigue and dyspnea).

When comparing AUCs, the patients with severe comorbidity had significantly worse global QoL (p=.01), more fatigue (p=.001) and dyspnea (p=.01), whereas nausea/vomiting was comparable to what the patients with less comorbidity reported

(p=.31). The sensitivity tests confirmed the difference for global QoL (p=.002), but not for fatigue (p=.48), nausea/vomiting (p=.86) or dyspnea (p=.28).

On the other HRQoL-scales, there was a trend towards worse physical and role functioning among the patients with severe comorbidity. Extremely severe comorbidity or a high severity index did not predict significant differences in HRQoL during study treatment.

Discussion

None of the comorbidity-scores were significant prognostic factors for survival in our study population. This contrasts the results from previous studies of patients with localized disease and mixed cohorts of NSCLC-patients,[9,10,12-14] but are consistent with studies of patients with metastatic disease[12], elderly (≥ 70 years) receiving non-platinum chemotherapy[15] and elderly (≥ 65 years) receiving platinum-chemotherapy.[16]

A possible explanation why comorbidity does not appear to be a prognostic factor in advanced NSCLC, is given by Read et al.[12] They analyzed patients with breast, colon, lung and prostate cancer and found that the influence of comorbidity on survival is relative to the prognosis of the malignant disease. Whereas comorbidity was a prognostic factor for survival in patients with a long life expectancy, this was not the case in cohorts with a poor prognosis - such as metastastic lung cancer. These patients seem to die from their cancer before other disorders worsen enough to influence survival.

Overall, there was no association between comorbidity and clinically relevant toxicity from the chemotherapy. However, patients with severe comorbidity appeared to acquire more fevers when neutropenic and it is worth noticing that all patients who

died from neutropenic infections in our trial had such disorders – mainly in the cardiovascular and respiratory systems.

The results from other analyses of toxicity in relation to comorbidity are not consistent,[13,16,17] possibly due to small sample sizes and differences in pharmacological profile and intensity of the chemotherapy administered. However, the association between comorbidity and the risk of infection in lung cancer patients has been demonstrated in a previous trial,[13] and studies of patients with several types of cancers have shown that comorbidity increases the risk for complications from neutropenic infections.[28,29] From a clinical point of view it seems reasonable that patients with cardiovascular and respiratory disease may have a higher risk of developing infections when neutropenic. Since 40 % of our study population had such disorders, withholding chemotherapy from these patients does not seem to be an option to avoid neutropenic complications among a few. Prophylactic antibiotics and/or granulocyte colony stimulating factors may, however, be appropriate and beneficial.

The results from the HRQoL-analyses have to be interpreted with caution. When looking at the mean scores, the patients with severe comorbidity reported poorer HRQoL and they had slightly more deterioriation than the patients with less comorbidity. However, the differences in mean scores were only clinically relevant (> 10 points) at one time point (week 12). Statistically, there were significant differences in the primary AUC-analyses for three of the four dimensions defined as the primary HRQoL-endpoints, whereas the sensitivity AUC-analyses confirmed these findings only for one dimension. Overall, we find that the differences in deterioration of HRQoL were not large enough to deny patients with severe comorbidity life-prolonging chemotherapy. There are no entirely relevant reports for comparison, but

in a study of head and neck cancer, patients with severe comorbidity had inferior HRQoL before, but not after radiotherapy.[30]

There are some possible limitations to our study. All comorbidities may not have been recorded in the hospital medical records, and some patients may have been considered ineligible for the study due to significant comorbidity despite broad inclusion criteria. However, the prevalence of severe comorbidity in our population is comparable to what has been registered in other studies of NSCLC-patients.[7,15] The sample size is large, and we find that the study population is quite representative for the patients seen in the everyday clinic; a large proportion had PS 2, and even if elderly are underrepresented also in our trial, more than one third was > 70 years.

The CIRS-G is one of the most commonly used instruments for measuring comorbidity, is comprehensive and has good inter-rater and test-retest reliability[21]. Compared with the Charlson index, the most popular instrument for measuring comorbidity, the CIRS-G is more sensitive since it includes assessment of non-lethal conditions. Some of these may be especially important for cancer patients receiving chemotherapy - such as liver and renal dysfunction. Another reason for using the CIRS-G, was that in two studies of NSCLC, CIRS-G scores but not Charlson scores were significant prognostic factors.[9,10]

In conclusion, comorbidity was not a significant prognostic factor for survival in our study population. In general, the patients with severe comorbidity did not experience more clinically relevant toxicity or more deterioration of HRQoL than other patients, but they may have a higher risk for infections when neutropenic. These findings suggest that patients with advanced NSCLC who have co-existing disorders benefit from and tolerate platinum-based chemotherapy as well as other patients. This is, however, the first study of the influence of comorbidity assessed using the

CIRS-G on a larger scale in patients with advanced NSCLC receiving platinum-based chemotherapy. Thus, the results should be interpreted with caution and need confirmation.

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Conflict of interest statement

None of the authors have any conflicts of interest to disclose.

Writing assistance

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Figure 1 Patient selection

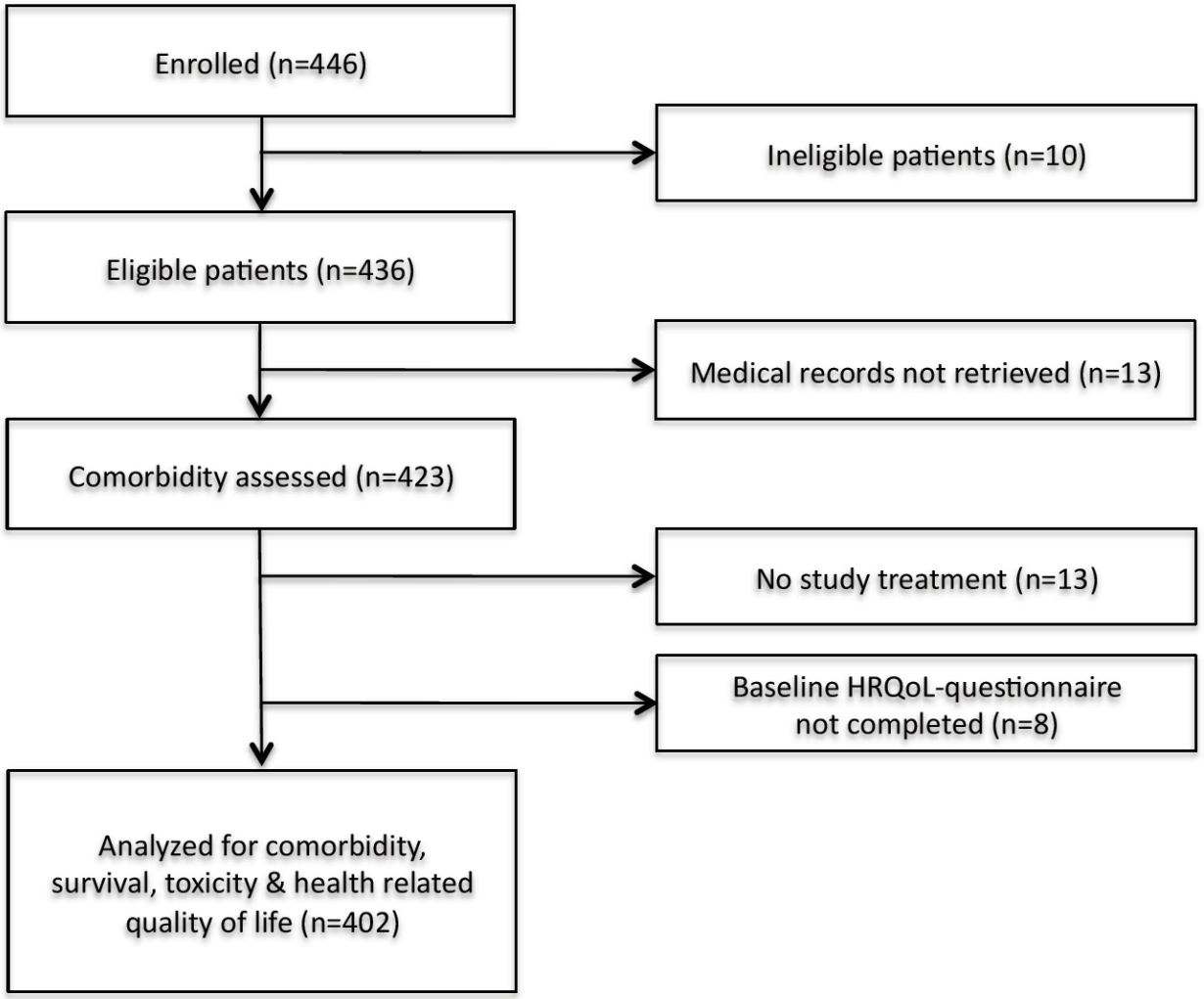
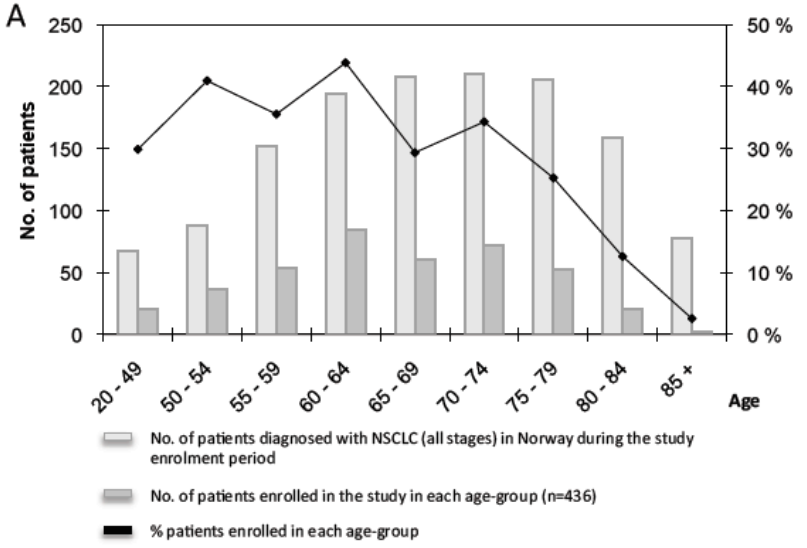
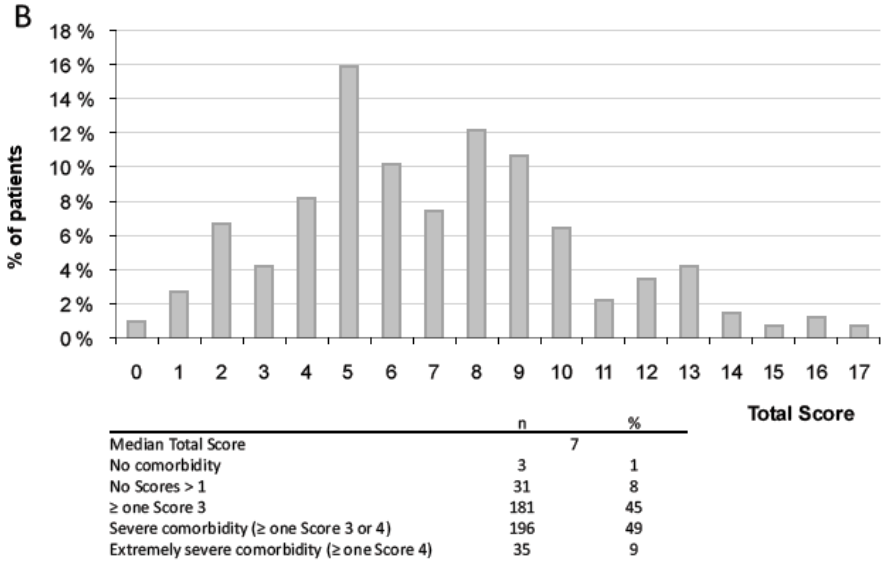
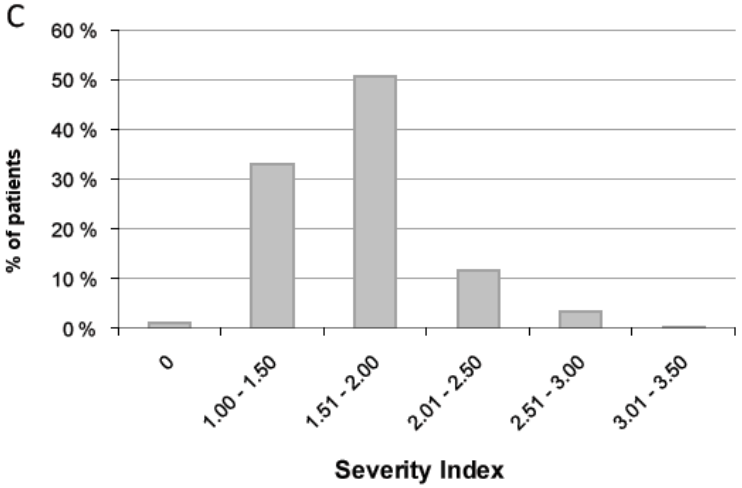


Figure 2 Age distribution of patients and inclusion-rate in each age group (A) distribution of total CIRS-scores and frequency of severe comorbidity (≥ one CIRS-G score 3 or 4) and extremely severe comorbidity (≥ one CIRS-G score 4) (B) the distribution of severity indices (C) and the prevalence of grade 3-4 comorbidity on the different CIRS-G scales (D).





	n	%
Median Total Score	7	
No comorbidity	3	1
No Scores > 1	31	8
≥ one Score 3	181	45
Severe comorbidity (≥ one Score 3 or 4)	196	49
Extremely severe comorbidity (≥ one Score 4)	35	9



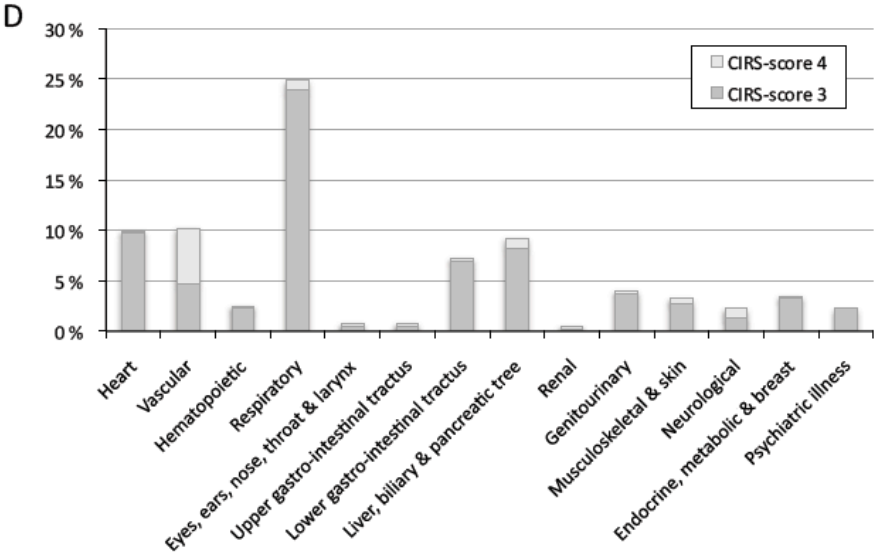


Figure 3 Mean scores for the primary HRQoL-endpoints. A higher score on functional scales (global QoL) represents a better HRQoL, whereas a higher score on the symptom-scales (fatigue, nausea/vomiting and dyspnea) represents more symptoms and poorer HRQoL. The minimum difference to show a clinically relevant difference in HRQoL was defined as 10 points. Severe comorbidity was defined as ≥ one CIRS-G score 3 or 4.

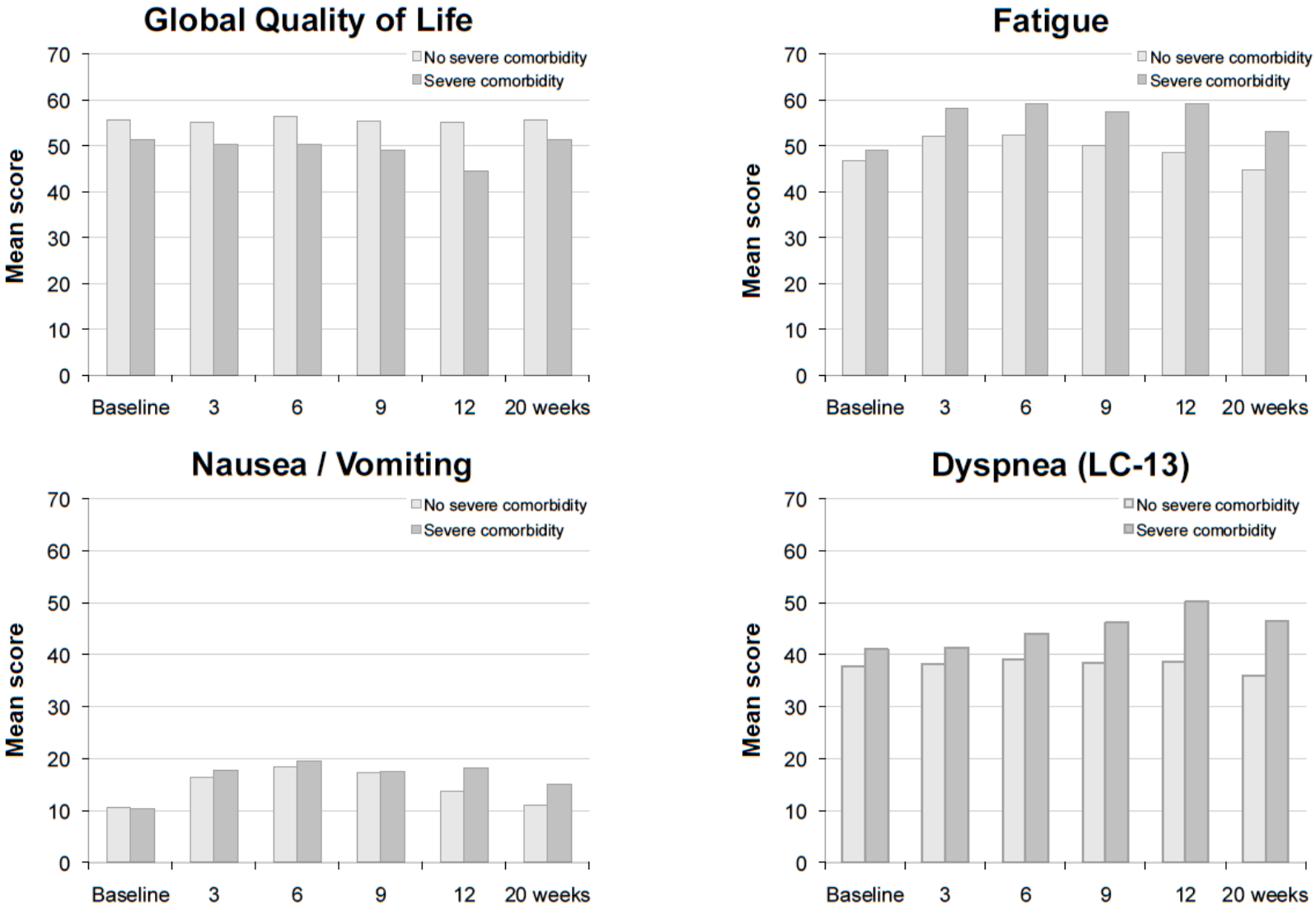


Table 1 Example of comorbidity assessment in a patient using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G)

Score	0	1	2	3	4
Heart		X			
Vascular			X		
Hematopoietic	X				
Respiratory				X	
Eyes, ears, nose, throat and larynx	X				
Upper GI	X				
Lower GI		X			
Liver	X				
Renal	X				
Genitourinary		X			
Musculoskeletal/integument	X				
Neurological	X				
Endocrine/metabolic and breast	X				
Psychiatric illness	X				

Total number categories endorsed	5
Total score	8
Severity Index (Total score / Total number of categories endorsed)	1.6 (8/5)
Number of categories at level 3	1
Number of categories at level 4	0

RATING STRATEGY

0 - No Problem
1 - Current mild problem or past significant problem
2 - Moderate disability or morbidity/requires "first line" therapy
3 - Severe/constant significant disability/"uncontrol1able" chronic problems
4 - Extremely Severe/immediate treatment required/end organ failure/severe impairment in function

Table 2 Baseline patient characteristics, study treatment and post-study therapy for all patients and grouped depending on the presence of severe comorbidity (≥ one CIRS-G score 3-4) or a high severity index (> 2).

	All patients (n=402)		No severe comorbidity (n=206)		Severe comorbidity (n=196)			Low severity index (n=340)		High severity index (n=62)		
Characteristic	No. of Pts.	%	No. of Pts.	%	No. of Pts.	%	P	No. of Pts.	%	No. of Pts.	%	p
Age, years												
Median	65		63		67			65		66		
Range	(25 – 90)		(25 - 90)		(41 – 84)			(25 – 90)		(50 – 84)		
≥ 75 years	74	18	30	15	44	22	.04	62	18	12	19	.83
Gender												
Male	231	57	105	51	126	64		192	56	39	63	
Female	171	43	101	49	70	36	.007	148	44	23	37	.35
Performance status												
0 - 1	318	79	165	80	153	78		270	79	48	77	
2	84	21	41	20	43	22	.62	70	21	14	23	.72
Extent of disease												
Stage IIIB	116	29	48	23	68	35		96	28	20	32	
Stage IV	286	71	158	77	128	65	.01	244	72	42	68	.52
Histology												
Squamous cell carcinoma	99	25	40	19	59	30		80	24	19	31	
Adenocarcinoma	202	50	108	52	94	48		167	49	35	56	
Large cell carcinoma	24	6	11	5	13	7		23	7	1	2	
Other	77	19	47	23	30	15	. 08	70	21	7	11	.16
Smoking history												
Never smoker	29	7	20	10	9	5		26	8	3	5	
Former smoker	210	52	114	55	96	49		178	52	32	52	
Current smoker	159	40	70	34	89	45		133	39	26	42	
Unknown	4	1	2	1	2	1	.05	3	1	1	2	.81
Treatment												
Study treatment												
Pemetrexed/carboplatin	197	49	107	52	90	46		168	49	29	47	
Gemcitabine/carboplatin	205	51	99	48	106	54	.23	172	51	33	53	.70
Completed 4 cycles	279	69	151	73	128	65	.08	239	70	40	65	.36
4 cycles without delay	212	53	122	59	90	46	.008	179	53	33	53	.93
4 cycles without dose reduction	128	32	72	35	56	29	.17	106	31	22	35	.50
Mean no. of cycles	3.3		3.5		3.2		.05	3.4		3.3		.44
Second-line systemic therapy	126	31	74	36	52	27	.04	106	31	20	32	.87
Second-line chemotherapy	94	23	56	27	38	19	.07	79	23	15	24	.87
Seconde-line EGFR-TKI	32	8	18	9	14	7	.56	27	8	5	8	.97
Post-study palliative radiotherapy	167	42	98	48	69	35	.01	147	43	20	32	.11

Table 3 Survival analyses. The multivariate analyses were performed adjusting for all significant prognostic factors in the univariate analyses. A high global QoL was defined as ≥ 66, severe comorbidity as ≥ one CIRS-G score 3 or 4, extremely severe comorbidity as ≥ one CIRS-G score 4 and a high severity index as > 2.

Univariate analyses		**Estimate (months)**	**95 % CI**		**Estimate (months)**	**95 % CI**	**Log-rank p-value**
Performance status	0-1 (n=318)	8.5	7.4 – 9.6	2 (n=84)	5.1	3.8 – 6.5	.001
Stage	IIIB (n=116)	8.8	6.8 – 10.7	IV (n=286)	7.3	6.4 – 8.3	.15
Gender	Women (n=171)	9.1	7.5 – 10.6	Men (n=231)	6.6	5.9 – 7.3	.02
Smoking history	Never-smoker (n=21)	11.9	9.3 – 14.4	Ever-smoker (n=369)	7.3	6.5 – 8.1	.07
Age	< 75 years (n=328)	7.7	6.6 – 8.8	≥ 75 years (n=74)	7.3	4.7-10.0	.89
Study treatment	Pemetrexed/carboplatin (n=197)	7.9	6.5 – 9.4	Gemcitabine/carboplatin (n=205)	7.3	6.1 – 8.5	.46
Baseline HRQoL	High global QoL (n=146)	9.3	7.7 – 10.9	Low global QoL (n=256)	6.7	5.9 – 7.6	.004
	No appetite loss (n=186)	9.3	7.7 – 10.9	Appetite loss (n=216)	6.5	5.7 – 7.4	.006
Comorbidity	No severe comorbidity (n=206)	8.1	6.9 – 9.3	Severe comorbidity (n=196)	6.9	5.9 – 7.8	.34
	No extremely severe comorbidity (n=367)	7.7	6.7 – 8.7	Extremely severe comorbidity (n=35)	6.7	4.0 – 9.4	.88
	Low severity index (n=340)	7.4	6.5 – 8.4	High severity index (n=62)	8.4	5.3 – 11.4	.76

Mutltivariate analyses				**HR**	**95 % CI**	**P-value**
Performance status	0-1 (n=318)	v	2 (n=84)	.74	.56 – .96	.03
Stage	IIIB (n=116)	v	IV (n=286)	.80	.62 – 1.03	.08
Gender	Women (n=171)	v	Men (n=231)	.76	.61 – .96	.02
Smoking history	Never-smokers (n=21)	v	Ever-smokers (n=369)	.66	.42 – 1.024	.06
Age	< 75 years (n=328)	v	≥ 75 years (n=74)	.97	.73 – 1.29	.83
Treatment	Pemetrexed/carboplatin (n=197)	v	Gemcitabine/carboplatin (n=205)	.98	.78 – 1.22	.85
Baseline HRQoL	High global QoL (n=146)	v	Low global QoL (n=256)	.78	.61 – 1.004	.05
	No appetite loss (n=186)	v	Appetite loss (n=216)	.79	.63 – 1.00	.05
Comorbidity	No severe comorbidity (n=206)	v	Severe comorbidity (n=196)	.95	.76 – 1.19	.66
	No extremely severe comorbidity (n=367)	v	Extremely severe comorbidity (n=35)	.98	.66 – 1.44	.90
	Low severity index < 2 (n=340)	v	High severity index (n=62)	1.09	.81 – 1.48	.56

Table 4 Adverse events depending on comorbidity (occuring in more than 1 % of the patients). Severe comorbidity was defined as ≥ one CIRS-G score 4 and a high severity index as > 2.

	No severe comorbidity (n=206)		Severe comorbidity (n=196)			Low severity index (n=340)		High severity index (n=62)		
Adverse events	No. of Pts.	%	No. of Pts.	%	p	No. of Pts.	%	No. of Pts.	%	p
Grade 3-4 hematologic toxicity										
Anemia	26	13	26	13	.85	47	14	5	8	.21
Leucopeni	67	33	68	35	.65	113	33	22	35	.73
Neutropenia	86	42	94	48	.16	150	45	30	48	.57
Thrombocytopenia	74	36	92	46	.03	137	40	29	47	.34
Grade 3-4 non-hematologic adverse events										
Infection without neutropenia	14	7	20	10	.22	28	8	6	10	.71
Neutropenic fever	10	5	23	12	.01	26	8	7	11	.34
Nausea	10	5	5	3	.22	13	4	2	3	1.0
Thrombocytopenic bleeding	8	4	6	3	.65	13	4	1	2	.71
Other	12	6	16	8	.36	25	7	3	5	.60
One or more adverse event	45	22	49	25	.46	81	24	13	21	.63
Death from adverse events										
Neutropenic infection	0	0	5	3	.03	3	1	2	3	.17
Infection	4	2	4	2	1.0	8	2	0	0	.62
Other	1	1	5	3	.11	4	1	2	3	.23
Total	5	2	14	7	.03	15	4	4	6	.51

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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.

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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.

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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.

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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

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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.

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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.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
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

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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
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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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

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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

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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

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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
279. Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS
280. Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
281. Per Olav Vandvik: IRRITABLE BOWEL SYNDROME IN NORWAY, STUDIES OF PREVALENCE, DIAGNOSIS AND CHARACTERISTICS IN GENERAL PRACTICE AND IN THE POPULATION
282. Idar Kirkeby-Garstad: CLINICAL PHYSIOLOGY OF EARLY MOBILIZATION AFTER CARDIAC SURGERY
283. Linn Getz: SUSTAINABLE AND RESPONSIBLE PREVENTIVE MEDICINE. CONCEPTUALISING ETHICAL DILEMMAS ARISING FROM CLINICAL IMPLEMENTATION OF ADVANCING MEDICAL TECHNOLOGY
284. Eva Tegnander: DETECTION OF CONGENITAL HEART DEFECTS IN A NON-SELECTED POPULATION OF 42,381 FETUSES
285. Kristin Gabestad Nørsett: GENE EXPRESSION STUDIES IN GASTROINTESTINAL PATHOPHYSIOLOGY AND NEOPLASIA
286. Per Magnus Haram: GENETIC VS. AQUIRED FITNESS: METABOLIC, VASCULAR AND CARDIOMYOCYTE ADAPTATIONS
287. Agneta Johansson: GENERAL RISK FACTORS FOR GAMBLING PROBLEMS AND THE PREVALENCE OF PATHOLOGICAL GAMBLING IN NORWAY
288. Svein Artur Jensen: THE PREVALENCE OF SYMPTOMATIC ARTERIAL DISEASE OF THE LOWER LIMB
289. Charlotte Björk Ingul: QUANITIFICATION OF REGIONAL MYOCARDIAL FUNCTION BY STRAIN RATE AND STRAIN FOR EVALUATION OF CORONARY ARTERY DISEASE. AUTOMATED VERSUS MANUAL ANALYSIS DURING ACUTE MYOCARDIAL INFARCTION AND DOBUTAMINE STRESS ECHOCARDIOGRAPHY
290. Jakob Nakling: RESULTS AND CONSEQUENCES OF ROUTINE ULTRASOUND SCREENING IN PREGNANCY – A GEOGRAPHIC BASED POPULATION STUDY
291. Anne Engum: DEPRESSION AND ANXIETY – THEIR RELATIONS TO THYROID DYSFUNCTION AND DIABETES IN A LARGE EPIDEMIOLOGICAL STUDY
292. Ottar Bjerkeset: ANXIETY AND DEPRESSION IN THE GENERAL POPULATION: RISK FACTORS, INTERVENTION AND OUTCOME – THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
293. Jon Olav Drogset: RESULTS AFTER SURGICAL TREATMENT OF ANTERIOR CRUCIATE LIGAMENT INJURIES – A CLINICAL STUDY
294. Lars Fosse: MECHANICAL BEHAVIOUR OF COMPACTED MORSELLISED BONE – AN EXPERIMENTAL IN VITRO STUDY
295. Gunilla Klensmeden Fosse: MENTAL HEALTH OF PSYCHIATRIC OUTPATIENTS BULLIED IN CHILDHOOD
296. Paul Jarle Mork: MUSCLE ACTIVITY IN WORK AND LEISURE AND ITS ASSOCIATION TO MUSCULOSKELETAL PAIN
297. Björn Stenström: LESSONS FROM RODENTS: I: MECHANISMS OF OBESITY SURGERY – ROLE OF STOMACH. II: CARCINOGENIC EFFECTS OF *HELICOBACTER PYLORI* AND SNUS IN THE STOMACH

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298. Haakon R. Skogseth: INVASIVE PROPERTIES OF CANCER – A TREATMENT TARGET ? IN VITRO STUDIES IN HUMAN PROSTATE CANCER CELL LINES
299. Janniche Hammer: GLUTAMATE METABOLISM AND CYCLING IN MESIAL TEMPORAL LOBE EPILEPSY
300. May Britt Drugli: YOUNG CHILDREN TREATED BECAUSE OF ODD/CD: CONDUCT PROBLEMS AND SOCIAL COMPETENCIES IN DAY-CARE AND SCHOOL SETTINGS
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