Advanced Non-small Cell Lung Cancer
Effects of Chemotherapy and Impact on Health Related Quality of Life

Nina Helbekkmo

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CONTENTS

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Abbreviations

ASCO	American Society of Clinical Oncology
AUC	Area Under the Curve
BSC	Best Supportive Care
CI	Confidence Interval
EORTC	European Organization for Research and Treatment of Cancer
HR	Hazard Ratio
HRQOL	Health-Related Quality of Life
GC	gemcitabine/carboplatin
NSCLC	Non-small Cell Lung Cancer
PS	Performance Status
QLQ	Quality of Life Questionnaire
QOL	Quality of Life
SAUC	Standardized Area Under the Curve
TTP	Time to Progression
VC	vinorelbine/carboplatin

List of papers

Paper 1

Helbekkmo N, Sundstrom SH, Aasebo U, Brunsvig PF, von Plessen C, Hjelde HH, Garpestad OK, Bailey A, Bremnes RM; for the Norwegian Lung Cancer Study Group: Vinorelbine/carboplatin vs gemcitabine/carboplatin in advanced NSCLC shows similar efficacy, but different impact of toxicity. *British Journal of Cancer* (2007) 97, 283-289.

Paper 2

Helbekkmo N, Aasebø U, Sundstrøm SH, von Plessen C, Brunsvig PF, Bremnes RM; for the Norwegian Lung Cancer Study Group: Treatment outcome in performance status 2 advanced NSCLC patients administered platinum-based combination chemotherapy. *Lung Cancer* (2008) 62, 253-260.

Paper 3

Helbekkmo N, Strøm HH, Sundstrøm SH, Aasebø U, von Plessen C, Bremnes RM: Does chemotherapy improve Quality of Life in NSCLC PS 2? *Acta Oncologica, Accepted.*

1. Introduction

Lung cancer is a severe and aggressive disease affecting many individuals and families in Norway. Globally it is the most frequent cancer, both in number of new cases and in cancer deaths. Life expectancy for patients with advanced lung cancer is short and the prognosis only slightly better today than two decades ago. The fact that most patients already have advanced or metastatic disease at diagnosis, is the main reason for the poor prognosis. Thus, for the majority of lung cancer patients the treatment aim is palliation of troublesome symptoms, better or consolidated health related quality of life (HRQOL) and prolongation of survival rather than cure. Accordingly, knowledge on how the disease and its treatment influence patients' life and HRQOL is of utmost importance.

The VING study was a national multicenter study conducted by the Norwegian Lung Cancer Study Group. It was an open randomized phase III study of two third-generation platinum-based chemotherapy combinations, both employed in the treatment of advanced non-small cell lung cancer (NSCLC), but previously not compared. The study was designed to find out whether one treatment was better than the other regarding survival and patients' HRQOL. Other important tasks were to explore the toxicity profiles and to examine whether consequences from treatment side effects differed between the two treatment options.

From September 2003 to December 2004, 33 hospitals nationwide included 444 patients into the VING study. Of these, 432 were eligible and constitute the study population. The combination of vinorelbine/carboplatin (VC) was compared with gemcitabine/carboplatin (GC). In both treatment arms, the patients received three chemotherapy courses with three weeks intervals. The study patients completed

quality of life questionnaires (QLQ) at study inclusion, before second and third chemotherapy course and then every eight week until nearly one year.

The first paper is the main study report and deals with the comparison of the two treatment arms with respect to survival, HRQOL and toxicity, according to the protocol. Later, the project evolved into new directions. After an inspiring lecture on treatment of lung cancer patients with compromised performance status given by Dr. Sculier at the Nordic Lung Cancer Meeting in Oulu, the idea for the second paper developed. A considerable proportion of lung cancer patients in general, have reduced general condition/performance status (PS) and whether these should receive combination chemotherapy is highly controversial. The second paper therefore compared patients with reduced PS (PS 2) to those with normal to slightly reduced PS (PS 0/1), within the VING-study. Finally, detailed analyses of HRQOL among the PS subgroups of patients are presented in the third paper.

A national phase III study accumulates huge amounts of information, provided by a large number of patients and local investigators. The given information was received, quality controlled and organized. All together, this represents a considerable piece of work reflecting patients' experiences during advanced NSCLC treatment, summarized in this thesis.

2. Background

2.1 Lung Cancer in a global and national perspective.

From being considered a rare disease at the beginning of the 20th century,[1] lung cancer is now the most common cancer globally with estimated 965 446 new cases per year among males and 386 875 per year among women.[2] It is an aggressive disease with poor prognosis which causes nearly 1.2 million deaths per year worldwide. This also makes it the leading cause of cancer related mortality.

In Norway, 1369 men and 953 women were diagnosed with lung cancer in 2006.[3] Among Norwegian men, lung cancer is the second most frequent malignancy, following prostate cancer. The lung cancer incidence among men in Norway doubled during the last 40 years, but has leveled off through the last 10 -15 years. For women, lung cancer is the third most frequent cancer following breast cancer and colorectal cancer. The incidence of lung cancer among women has increased 6-fold since the 1960s and is still rising (Figure 1).

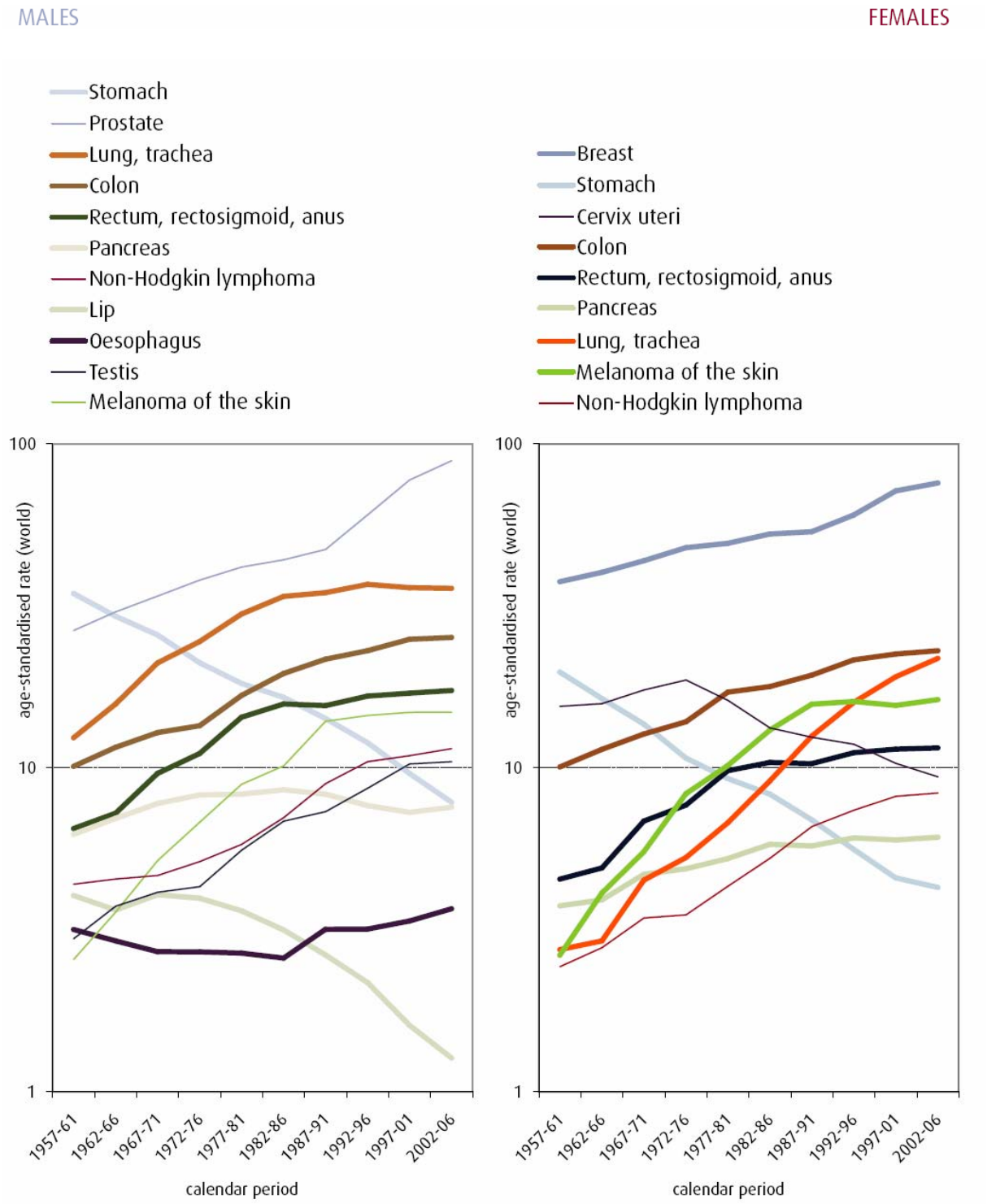

Figure 1. Time trends in age-standardized rates in Norway for selected cancers. From: Cancer Registry of Norway. Cancer in Norway 2006 - Cancer incidence, mortality, survival and prevalence in Norway, Oslo: Cancer Registry of Norway, 2007.

2.2 Etiology

Cigarette smoking is by far the most predominant cause of lung cancer. Tobacco is the single most preventable cause of death in the world today and will kill more than five million people this year, which is more than tuberculosis, HIV/AIDS and malaria combined.[4] Cigarette smoke consists of a complex mix of more than 4000 different chemical compounds of which more than 60 are established carcinogens.[5] Among these, polycyclic aromatic hydrocarbons, N-nitrosamines and aromatic amines are the strongest. Counting for about 90% of all cases, lung cancer would be a rather rare disease in the absence of cigarette smoking.

In 2006, 24% of Norwegian adults were daily smokers.[6] Strategies effectively preventing youths from starting smoking and promoting smoking cessation would thus be the most effective way to combat lung cancer.

In addition, asbestos, radon and industrial/environmental compounds have also been proven causal for the development of lung cancer. Further, cigarette smoking appears to have an enhancing effect on these carcinogens.

2.3 Histopathology

Lung cancers arise from the respiratory epithelium (bronchi, bronchioles, and alveoli). Non-small cell lung cancer (NSCLC) is the most frequent sub-type of lung cancer and accounts for more than 80 % of the cases. According to the new World Health Organization classification of lung tumors, the major histological subtypes are adenocarcinoma, squamous cell- and large cell carcinoma.[7] Adenocarcinoma is the most common subtype in many countries and has increased by 10% in Europe during the last 20 years.[7] Although all histological types of lung cancer have been connected to smoking, lung cancer can also occur in never smokers. The most

common sub-type of NSCLC seen in neversmokers, women, and young patients (<45 years) is adenocarcinoma.[8]

2.4 Investigation, staging and prognosis

Early lung cancers are often clinically silent, so presentation of symptoms often indicates more advanced disease. The most common initial symptom is cough, which is reported by 45-75% of patients.[9] Lung cancer can be detected on chest x-rays based on patients' symptoms or after routine chest investigations for other reasons. A suspicious lesion on chest x-ray normally requires a chest CT. Routine investigations of a chest mass include tissue biopsies to establish the diagnosis. Various techniques are available; bronchoscopy with brush samples or transtracheal needle aspiration with or without endoscopic ultrasound guidance, needle biopsy with or without CT-guidance or surgical techniques like mediastinoscopy, video assisted thoracoscopy or open chest surgery.

After a confirmed diagnosis of NSCLC, staging procedures are necessary to establish the extent of disease and a basis for treatment decisions. A CT scan of the chest should include the upper abdomen to rule out liver metastasis or enlarged adrenal glands. MRI of the brain may be useful when large tumor burden or neurological symptoms are present, as lung cancer often spread to the brain. In case of bone pain or elevated calcium levels in the blood, a bone scan is valuable to rule out metastasis. A PET scan is helpful to rule out mediastinal and distant metastasis and to limit the gross volume target for radiation therapy.[10,11] PET is today considered a routine investigation in most parts of the industrialized world.

NSCLC is staged according to the clinical stage classification from 1997:[12] This classification is under revision and will be replaced by a revised version in 2009.

Table 1. TNM staging of lung cancer

Stage	Tumor	Node	Metastasis	Definition
IA	T1	N0	M0	T1: Tumor ≤3cm, without bronchosopic evidence of invasion proximal to the lobar bronchus.
IB	T2	N0	M0	T2: Tumor > 3 cm, or tumor of any size with one or more of the following characteristics: - infiltration of the visceral pleura - invades the main bronchus but > 2 cm distal to the main carina - atelectasis or obstructive pneumonitis that extends to the hilus but does not involve the entire lung and without pleural effusion.
IIA	T1	N1	M0	N1: Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, including direct invasion
IIB	T2	N1	M0	T3: Tumor of any size with invasion of the chest wall including adjacent rib(s), diaphragm, mediastinal pleura, parietal pericardium, or tumor in the main bronchus < 2 cm distal to the carina; or tumor associated with atelectasis or obstructive pneumonitis of the entire lung.
	T3	N0	M0	
IIIA	T1	N2	M0	N2: Metastasis to ipsilateral mediastinal and/or subcarinal lymph nodes.
	T2	N2	M0	
	T3	N1	M0	
	T3	N2	M0	
IIIB	Any T	N3	M0	N3: Metastasis to contralateral mediastinal, contralateral hilar, or ipsilateral and/or contralateral supraclavicular or scalene lymph nodes.
	T4	Any N	M0	
IV	Any T	Any N	M1	M1: Distant metastasis, including separate tumor nodules in a different lobe.

Adapted from CF Mountain. Revisions in the International System for Staging of Lung Cancer. Chest 111:1710, 1997

The prognosis of lung cancer is generally poor. In Norway, the 5-year survival rates for lung cancers diagnosed between 1997 and 2001 were 10% for males and 13% for females.[3] The 5-year survival from NSCLC according to disease stage is given in Figure 2. The results are presented by an International Staging Committee within the International Association for the Study of Lung Cancer and are based on a material of 17 726 NSCLC patients from different countries, Norway included.[13]

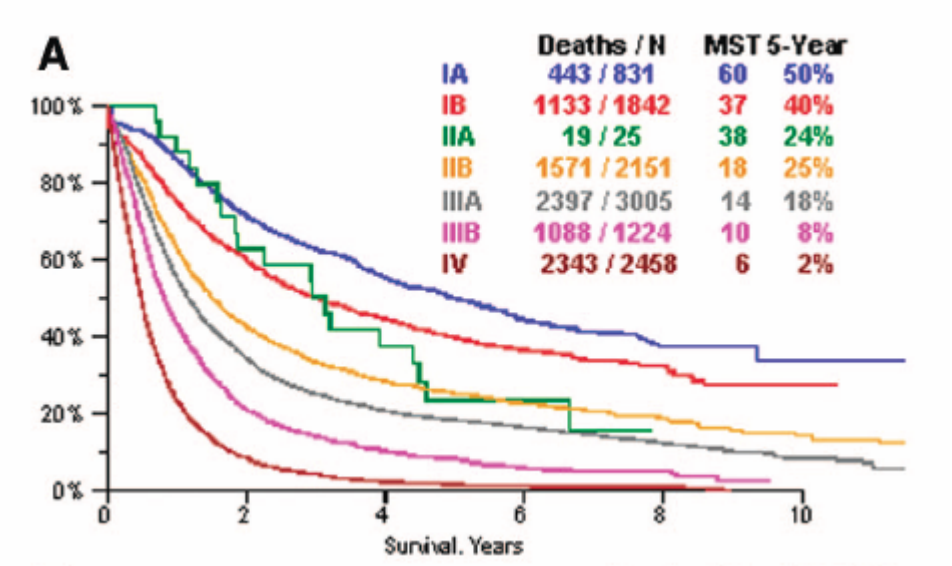

Figure 2. Overall survival, expressed as median survival time and 5-year survival, by clinical stage. As published in J. Thorac. Oncol[13]

In advanced NSCLC, survival is strictly dependent on PS,[14] and PS is the strongest prognostic factor for survival among these patients, followed by tumor size and weight loss.[15] The ECOG PS classification[16] is presented in Table 2. This is a five-point scale worsening from 0 to 5, where PS ≥ 2 is characterized as poor performance. A significant share of the lung cancer patients has compromised performance status at the time of diagnosis. As many as 30 – 40% of advanced NSCLC patients are estimated to have PS 2.[17,18]

Table 2. ECOG performance status*

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

* As published in Am. J. Clin. Oncol.[16]

2.5 Treatment

Less than one third of NSCLC patients have local disease with possibilities of cure. For stages IA, IB, IIA, IIB and some IIIA patients, surgical resection is the treatment of choice followed by adjuvant chemotherapy to stage IIA – IIIA patients in good condition. Postoperative radiation is an option if surgery reveals N2 disease or at non-radical surgical margins. Medically inoperable patients can be treated with localized radiotherapy or combined chemoradiation.[19]

The majority of newly diagnosed NSCLC patients present with locally advanced or metastatic disease.[20] Patients with locally advanced disease should be offered chemoradiation if positive prognostic factors, i.e., tumor size < 7 cm, good performance status and no significant weight loss. For patients with poor prognostic factors or metastatic disease, the aim of the treatment is palliation of symptoms and prolongation of survival.

Advanced NSCLC causes a wide range of distressing symptoms. Locally, the disease gives rise to dyspnea, cough, chest pain and hemoptysis while the systemic component causes fatigue and lack of appetite. Distant metastasis can cause

symptoms and pain from involved areas, and other complications. In addition, anxiety and depression is a considerable burden for these patients. According to Hopwood et al,[21] the advanced NSCLC patient present with 14 symptoms on average. Due to long-term cigarette smoking and a high prevalence of respiratory and cardiovascular diseases, these patients often have massive co-morbidity,[22] which adds to a more complex symptom picture, making treatment more toxic or not feasible at all.

Both chemotherapy and palliative radiotherapy are valuable treatment options for stage IIIB and IV NSCLC. Already in 1948, dr. Karnofsky described favorable symptom relief among lung cancer patients administered nitrogen mustards.[23] Still, the road to acceptance of chemotherapy as a valuable treatment possibility for advanced NSCLC has been long and characterized by nihilism.[24] In 1995, the Non-small Cell Lung Cancer Collaborative Group published "Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials", concluding on a 10% 1-year survival improvement by chemotherapy and best supportive care (BSC) vs. BSC alone.[25] Since then, a large number of clinical studies have been published within this field, establishing the role of chemotherapy in advanced NSCLC. Still, in Norway the treatment of choice during the mid '90s continued to be radiotherapy. This was largely based on a randomized study comparing radiotherapy to chemotherapy in patients with inoperable NSCLC.[26] The study favored radiotherapy regarding response rates, toxicity and QOL.

During the late nineties and the early years of this decade, third generation cytotoxic drugs like vinorelbine, gemcitabine, docetaxel and paclitaxel proved effective in advanced NSCLC both as single drugs and in combinations. Platinum-based doublets including a third generation drug proved to be better than monotherapy, and equal in effect, but less toxic than three drug regimens. In 2004

these doublets were recommended as standard therapy.[27] Which novel non-platinum agent to choose and the optimal treatment duration was debated.[27] In 1997, an expert panel within the American Society of Clinical Oncology recommended a maximum of eight chemotherapy courses in patients with stage IV NSCLC.[28] In the late 1990's, the Norwegian Lung Cancer Study Group wanted to implement chemotherapy to advanced NSCLC patients in Norway. A randomized multicenter trial, the BLANK-study, was conducted in an attempt to establish the optimal duration of chemotherapy to patients with advanced NSCLC.[29] Three vinorelbine/carboplatin (VC) courses were compared to 6 with respect to HRQOL and survival. There were no survival or HRQOL benefits for the longer regimen, consistent with data from two contemporary studies.[30,31] The BLANK-study turned out to be an important contribution to establish shorter treatment regimens for advanced NSCLC. It also confirmed that VC was an appropriate treatment option for these patients at the doses chosen.

Both cisplatin and carboplatin are used in the treatment of advanced NSCLC.[32] Whether carboplatin may substitute cisplatin in 2-drug platinum-based combinations for advanced NSCLC, was investigated in a meta-analysis including abstracted data from 2945 patients.[33] This meta-analysis failed to demonstrate an overall survival advantage for cisplatin-based as compared with carboplatin-based chemotherapy. On the other hand, it demonstrated a survival advantage of 11% in favor of cisplatin in a subset analysis of 2280 patients treated with novel agents in platinum combinations. The CISCA meta-analysis,[34] an individual patient data meta-analysis of 2968 advanced NSCLC patients, found cisplatin-based chemotherapy slightly superior to carboplatin-based chemotherapy with respect to response rate, but not overall survival. The authors conclude that cisplatin should remain the

reference platinum agent for treatment of the least advanced NSCLC patients with good prognosis, indicating that the less toxic and easier administered carboplatin could be preferred for more advanced disease and PS 2 patients.

In the palliative setting, patients' QOL, treatment toxicity and time hospitalized are considered more important issues. Thus, despite the indications that cisplatin gives a slightly better treatment outcome; carboplatin is a valuable alternative with a better toxicity profile, does not require hospitalization in contrast to cisplatin and is the drug of choice in palliative treatment of advanced NSCLC in Norway.

Whether PS 2 patients should receive these new combination regimens is still controversial. Shorter life expectancy and expected enhanced treatment-related toxicity compared to PS 0/1 patients form the basis of this scepticism.[27,35-39] The 2003 ASCO Guidelines concluded that single-agent chemotherapy should be sufficient for NSCLC patients with PS 2.[27] Nevertheless, PS 2 patients appear to have a survival benefit when treated with chemotherapy. Moreover, combination chemotherapy was associated with an improved 1-year survival when compared to single-agent therapy in advanced NSCLC PS 2 patients.[40] Furthermore, in a meta-analysis comparing the newer third generation agents with or without platinum-compounds to best supportive care, individual data from 2714 patients revealed an increased 1-year survival in patients with PS ≥ 2 from 8% to 14%.[41]

In the Norwegian Lung Cancer Study Group, BLANK was followed by the VING-study. Vinorelbine as monotherapy[42,43] and in combination regimens[37,42,44-47] was considered highly promising. Also, the satisfying experience with the VC combination in the BLANK-study made VC the Norwegian standard regimen for advanced NSCLC. Hence, VC was used as the control arm in the VING-study. Meanwhile, gemcitabine had proved promising for advanced NSCLC both as

monotherapy[48] and in platinum-based combinations.[49-52] Gemcitabine/carboplatin (GC) was considered an interesting alternative as first line treatment. Based on the results from the BLANK-study, a randomized comparison between VC and GC would be based on three courses of chemotherapy.

2.5.1 Carboplatin

Carboplatin (cyclobutane-1,1-dicarboxylic acid) is a second generation platinum compound which act against cancer cells by binding to DNA and produce various cross-links which induces apoptosis.[53] It has a different toxicity profile than cisplatin with less nephrotoxicity, ototoxicity and neurotoxicity.[54] The dose limiting toxicity is, somewhat contrasting to cisplatin, bone marrow suppression.[55] Carboplatin does not require hydration, which makes it convenient for outpatient administration. The major route of elimination is renal excretion. Calculation of carboplatin dosage by use of body surface area is considered insufficient.[56] Instead, based on a patient's pre-existing renal function, dosing is calculated according to the estimated area under the concentration versus time curve (AUC in mg/mLmin), either by the Chatelut[57] or the Calvert[58] formula.

Chatelut's formula

Carboplatin dose (mg) = carboplatin clearance / AUC

Carboplatin clearance (mL/min) = 0.134 x weight + [218 x weight x (1 - 0.00457 x age) x (1 – 0.314 x sex) / serum creatinine]

Calvert's formula

Carboplatin dose (mg) = target AUC x (GFR + 25)

GFR (mL/min) = 1.23 x (140 – age) x weight x sex / serum creatinine

2.5.2 Vinorelbine

Vinorelbine, or 3',4'-didehydro-4'-deoxy-C'-norvincaleukoblastine [R-(R*,R*)-2,3-dihydroxybutanedioate], is a semisynthetic vinca alkaloid derived from vinblastine. It inhibits cell growth by binding to the tubulin of the mitotic microtubules and blocks mitosis.[59] Dose limiting toxicity is neutropenia.[55,60]

2.5.3 Gemcitabine

Gemcitabine, or dFdC (2'-deoxy-2',2'-difluorocytidine monohydrochloride), is a novel deoxycytidine analogue originally investigated for its antiviral effects, but since then developed as an anticancer therapy.[61] It is grouped as a pyrimidine antagonist, an anti-metabolite which acts through inhibition of DNA-synthesis and repair in different ways.[53] It is a lipophilic prodrug which in the intracellular environment is phosphorylated to active metabolites that incorporates into DNA and causes damage.[55] Dose limiting toxicity is bone marrow suppression.

Also, gemcitabine is a highly potent radio-sensitizer of human tumor cells.[62] As a consequence, radiotherapy should be postponed until one week after gemcitabine treatment, and if radiotherapy is given, gemcitabine treatment should be awaited for at least two weeks.

2.6 Health Related Quality of Life – HRQOL

Quality of life is a multidimensional term involving physical, psychological and social issues. It is used in many contexts, often without clarification of the exact meaning. The meaning is different for different people, depending on life situation and environment. Intuitively, QOL consists of satisfaction with life and a personal feeling of well-being. Satisfaction can be linked to cognitive aspects of QOL and happiness with emotional. One definition is the subjective experience concerning a persons life.[63] WHO has defined QOL as a state of complete physical, mental and social well-being, and not merely the absence of disease.

QOL is difficult to define precisely and subjective of nature, which makes it difficult to measure. But despite these difficulties, it provides important information. A concern when introducing palliative cytotoxic treatment is whether benefits are overshadowed by toxicity and reduced QOL. Aspects of QOL that may be affected by disease and therapy have thus to be measured to comprehend the implications of offering a specific treatment and be able to compare different treatment alternatives. In this setting, the term health related QOL (HRQOL) is a better approach. HRQOL has been defined as the level of well being and satisfaction associated with an individual's life and how it is affected by disease, accidents and treatment.[64] Measuring HRQOL also facilitates communication with patients regarding problems during different phases of the disease course.

Back in 1948, the importance of HRQOL endpoints in palliative treatment was recognized, as Karnofsky published "The Use of the Nitrogen Mustards in the Palliative Treatment of Carcinoma With Particular Reference to Bronchogenic Carcinoma."[23] Study endpoints were subjective improvement, objective improvement,

changes in PS and duration of improvement. During the last decades, HRQOL has become an increasingly important end-point in clinical studies, particular when the disease is beyond cure. A European experts panel argued in 2004 for HRQOL assessments in evaluating symptom relief and clinical benefit as endpoints in studies of PS 2 NSCLC patients.[65]

Several instruments have been developed to measure HRQOL in diseases in general[66-72] and in subgroups of lung cancer patients.[73-75] Of these, the questionnaires developed by the European Organization for Research and Treatment of Cancer (EORTC) are widely used in malignant disease.

The EORTC quality of life questionnaires (QLQ) are tools for assessing HRQOL of cancer patients participating in international clinical trials. The core questionnaire, the QLQ-C30 (Appendix 1),[69] is a product of more than a decade of collaborative research. It was released in 1993, and has since then been frequently used in clinical cancer trials. It includes five functional scales, three symptom scales, a global health status /QOL scale, and six single items as shown in Table 3. Global QOL, the functioning scales and some symptoms consists of more than one item, and the rest of the symptoms are single items.

The lung cancer module (Appendix 2), LC-13, is constructed for use among a wide range of lung cancer patients.[75] It covers both treatment side-effects like sore mouth, dysphagia, peripheral neuropathy and alopecia and symptoms of the disease like cough, hemoptysis, dyspnea and site specific pain. Dyspnea is assessed by a multi-item scale whereas the others are single items (Table 3). Both the QLQ-C30 and the LC13 are validated and translated to Norwegian.

The patients answer the questionnaire by ticking off the preferred answer in graded boxes. These answers are scored according to the scoring manual from EORTC.[76] The scoring principle is the same in all cases: a raw score (RS) is estimated as the mean of the items contributing to the scale. Then, the RS is linearly transformed into scale scores ranging from 0 to 100:

$$Score_{functional\ scales} = (1 - (RS - 1)/range)100$$

$$Score_{symptom\ scales/\ global\ QOL} = ((RS - 1)/range)100$$

Range is the difference between the maximum possible and the minimum possible value of RS. Most items are scored 1 to 4, giving range = 3, whereas global QOL are 7-point questions with range = 6. A high score represents a higher response level. Then, a high functional score/ global QOL represents high, or good, function/ global QOL whereas a high symptom score represents more severe symptoms.

Missing data in HRQOL trials is a well known and described challenge.[77] Missing data in a series of measures provided by one patient, usually exclude that patient, and thus important information, from the summary analysis. A solution to this problem is to impute the missing data, which can be done in different ways.[78] The advantage is keeping a patient with missing data, and thus the information provided, within the statistical analyses. Including data not given explicit by the patient into the analyses intuitively feels wrong. On the other hand, not imputing missing data is to assume that data from the patients without missing data are representative for the patients whom, for some reason, were missing. Either way, missing data are related to difficulties analyzing and interpreting HRQOL data, and should thus be avoided if possible.

Table 3. Content of the EORTC core questionnaire version 3.0 and the lung cancer module LC-13.

	No. of items	Question no.
QLQ-C30		
Global Health Status/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
QLQ-LC13		
Symptom scales		
Dyspnea	3	3,4,5
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

3. Aims of the thesis

The present thesis aimed to investigate outcome in patients with advanced non-small cell lung cancer receiving two different modern chemotherapy regimens within a national phase III study.

More specified the aims were:

VC vs. GC:

- Examine whether there was any survival difference between patients treated with the two chemotherapy combinations
- Examine whether there was any HRQOL differences during and after chemotherapy between the treatment arms, as measured by the EORTC QLQ-C30 and QLQ-LC13
- Examine possible differences between the treatment arms with respect to hematological toxicity, and needs for interventions due to treatment toxicity

PS 2 vs. PS 0/1:

- Examine the outcome of PS 2 versus PS 0/1 patients with respect to survival, toxicity and HRQOL when treated with modern platinum based chemotherapy
- Evaluate whether PS 2 patients benefit from platinum-based combination chemotherapy?

4. Patients and Methods

4.1 The VING-study - inclusion criteria

- Histologically or cytologically confirmed NSCLC
- Stage IIIB and IV, not eligibly for treatment with curative intention
- WHO PS 0, 1 or 2, which equals ECOG[16] PS
- No upper age limit
- No earlier chemotherapy
- No other active malignancies
- White blood cells > 3.0, platelets > 100
- Serum creatinin < 1.5 x upper reference limit
- Bilirubin, ASAT, ALAT < 2 x upper reference limit
- Fertile female patients could not be pregnant or breast-feeding and had to use contraception
- Ability to understand written and verbal information
- Written informed consent

4.2 Baseline investigation

All patients underwent clinical examination with registration of height and body weight, chest X-ray and CT-scan of chest and upper abdomen. Hemoglobin, leucocytes, platelets, bilirubin, ASAT, ALAT, γGT, LDH, K, Na, creatinine and albumine were measured. The disease was staged according to the clinical stage classification from 1997.[12]

4.3 Randomization

Randomization between VC and GC was done by the Clinical Cancer Research Office at the University Hospital of North Norway, either by phone or by fax. Block randomization was used and patients were stratified for PS (PS 0/1 vs. PS) and clinical stage (III vs. IV).

4.4 Chemotherapy

In both treatment arms, three courses of chemotherapy were given at three week cycles. The chemotherapy was administered as intravenous infusions, mostly on an outpatient basis.

Carboplatin was given as an one hour infusion at day one in each cycle and the dose was calculated by the Chatelut formula[57] using AUC 4. Gemcitabine or vinorelbine was given at days one and eight in each cycle. Gemcitabine at a dose of 1000 mg/m^2 and vinorelbine at a dose of 25 mg/m^2 were used.

For patients aged 75 or older, doses were reduced to 75%. In case of hematological toxicity, doses were reduced as described in Table 4:

Table 4. Chemotherapy dose-reduction guidelines.

White Blood Cells	Platelets	% dose	
		Vinorelbine	Gemcitabine
≥ 3.0	≥ 100	100	100
2.5 – 2.99	75 - 99	75	75
< 2.5	< 75	Therapy postponed one week	

If treatment was associated with febrile leucopenia or leucopenic infections, treatment was delayed until clinical recovery. Later chemotherapy doses were reduced by 25%. Treatment was interrupted in case of disease progression, unacceptable toxicity or on patients' request.

4.5 Patient follow-up

Table 5. Trial plan

	Baseline	Chemotherapy Day 1	Chemotherapy Day 8	Follow-up					
Treatment cycle		1 - 3							
Week	-1 - 0	0 - 6		9	17	25	33	41	49
Informed consent	X								
Medical history	X								
Physical exam		X		X	X	X	X	X	X
Hematology		X	X	X	X	X	X	X	X
Biochemistry	X			X	X	X	X	X	X
CT chest/upper abd	X								
Chest X-ray		X		X	X	X	X	X	X
QLQ	X			X	X	X	X	X	X

At the follow-up visit at week 9, a treatment summary was rendered. Investigators registered the number of chemotherapy courses, and reported the reasons patients did not receive all three courses. These explanations were classified into five subgroups: disease progression, unacceptable toxicity, patients wish, concurrent disease or other.

The lowest values for hemoglobin, white blood cells and platelets during treatment were registered and classified according to the WHO toxicity criteria, which equals the more frequently used Common Toxicity Criteria version 2.0 by the National Cancer Institute[79] (Appendix 3). Also, the number of blood transfusions, platelet transfusions, leucopenic infections, thrombocytopenic bleedings, admissions to hospital due to treatment side-effects and whether the patient received granulocyte colony stimulating factor or erythropoietin, were recorded.

At the follow-up visits every eight weeks from week 17 to 49, performance status and body weight were registered. For evaluation of disease progression, CT scans were done when indicated as a result of the X-ray findings. If the patient's disease had progressed, the date of progression was given.

At the patient's death, or at week 49, further registrations were done: Radiotherapy, surgery or chemotherapy beyond the study medication was registered. Date of progression and localization of the first progression or relapse were recorded. For patients who died, the cause of death and information on whether the patient was examined post-mortem was given.

Site-visits were performed at hospitals which included ≥ 20 patients. Otherwise, missing data were retrieved through phone or mail to the patient's physician.

4.6 Assessment of HRQOL

The baseline questionnaire was handed to the patient and required completed prior to randomization, while the other HRQOL forms were mailed directly to the patients' home address from the randomization office. Questionnaires were completed at weeks 0, 3, 6, 9, 17, 25, 33, 41, and 49. This corresponds to each chemotherapy course, follow up three weeks post chemotherapy and then accordingly to clinical controls every eight weeks until week 49. At lack of response, one reminder was mailed after two weeks

4.7 Study endpoints

The main endpoint was overall survival and secondary endpoints HRQOL and treatment toxicity.

4.8 Statistical considerations

Estimation of study size was based both on survival and HRQOL measures. To detect a difference in survival of 11% or HRQOL of 15% between the groups, provided a power of 80% and a significance level of 0.05 using two-sided tests, 380 patients were required. Based on a 5% drop-out, the required patient-number was 400.

For univariate analysis, survival from time of randomization to the date of death was compared using Kaplan-Meier estimates and statistical differences were estimated by the log-rank test. Multivariate analyses in paper 2 were carried out using the Cox proportional hazards model. Time to progression (TTP) in paper 2 was subjected to uni- and multivariate analyses using the same methods. The administered amount of chemotherapy, differences in hematological toxicity and registered interventions were compared using the chi-square test. The significance level was defined at $p < 0.05$.

HRQOL items were scored for each patient according to the EORTC scoring manual.[76] Mean scores, at baseline, during and after chemotherapy, and changes in scores from baseline, were compared between the groups in all three papers. Mean changes in scores of ≥10 was considered clinically relevant and significant.[80] HRQOL data are complex of nature and since normal distribution can not be assumed, non-parametric statistical testing was performed using The Mann Whitney U-test. This test was used to compare mean score and mean changes between the groups.

The area under the curve (AUC) of HRQOL scores plotted against time is a summary measure of HRQOL, providing each patient's longitudinal HRQOL experience as a single quantity which then can be compared between groups using t-tests or one-way ANOVA.[81] By using this method, the numbers of comparisons are

reduced and the power to detect small but consistent differences that may occur over multiple domains of HRQOL is increased.[82] There were large differences in baseline scores between the PS 2 and the PS 0/1 group. To adjust for these differences, the AUC calculation for each patient was based on changes from baseline. Missing data were imputed in the AUC analyses. If data from one assessment point were missing, the mean value of the two adjacent ones was used. For patients who withdrew or dropped out before week 9, the last value carried forward was used to impute the missing subsequent values. As this may introduce a bias if the main reason for drop-out was deterioration, comparisons were performed with data based on the worse possible score for the missing data. Standardized AUC (SAUC) was estimated as AUC divided by time. SAUC allows for differences in patient survival and corresponds to calculating the average HRQOL.[81] SAUC from baseline to week 9 in paper 3 was compared between PS 0/1 and PS 2 patients using one-way ANOVA.

In paper 3, patients' HRQOL responses were classified as improved, stable or worse for all HRQOL items at week 9 according to the NCIC CTG standard QOL analysis framework.[83] Symptom or function items were considered worse if the change from baseline was ≥ 10 points towards worse without improvement at any time-point. Improvement was defined as ≥ 10 points towards bettering in patients who did not deteriorate. Patients, who had less than 10-point changes from baseline at the HRQOL assessment or failed to meet the criteria for worsening or improvement, were considered stable. Distributions of the categories were tested by χ^2.

Due to multiple comparisons in HRQOL assessments, *p*-values of < 0.01 were considered significant and $p < 0.05$ indicating a tendency.

All analyses were done using the Statistical Package for the Social Sciences, SPSS® for windows, versions 12.0, 13.0, 14.0 and 15.0.

5. Summary of results

5.1 The patient population

From September 2003 through December 2004, 33 hospitals (Appendix 4) nationwide included 444 patients into the VING study. At the time, this was the highest inclusion rate experienced for a Norwegian lung cancer protocol. During the inclusion period, approximately 1570 new cases of NSCLC were diagnosed in Norway (personal communication, The Norwegian Cancer Registry). Of these, 271 had local disease, 521 had regional disease and 643 had distant metastasis. For 132 cases there were no information regarding extent of disease. Assuming that one third of the patients with regional disease and one third of those with unknown extent of disease were candidates for either surgery or radical radiotherapy,1080 patients were candidates for palliative treatment during the period. Hence, approximately 40% of patients eligible during the inclusion period were included in the VING study. This strongly contrasts the US experience where less than 5% of eligible cancer patients are included in treatment trials.[84] Especially elderly patients are underrepresented.[85,86]

The patient flow according to the main randomized study, VC versus GC, is presented in Figure 3. The patient flow according to PS is presented in Figure 4.

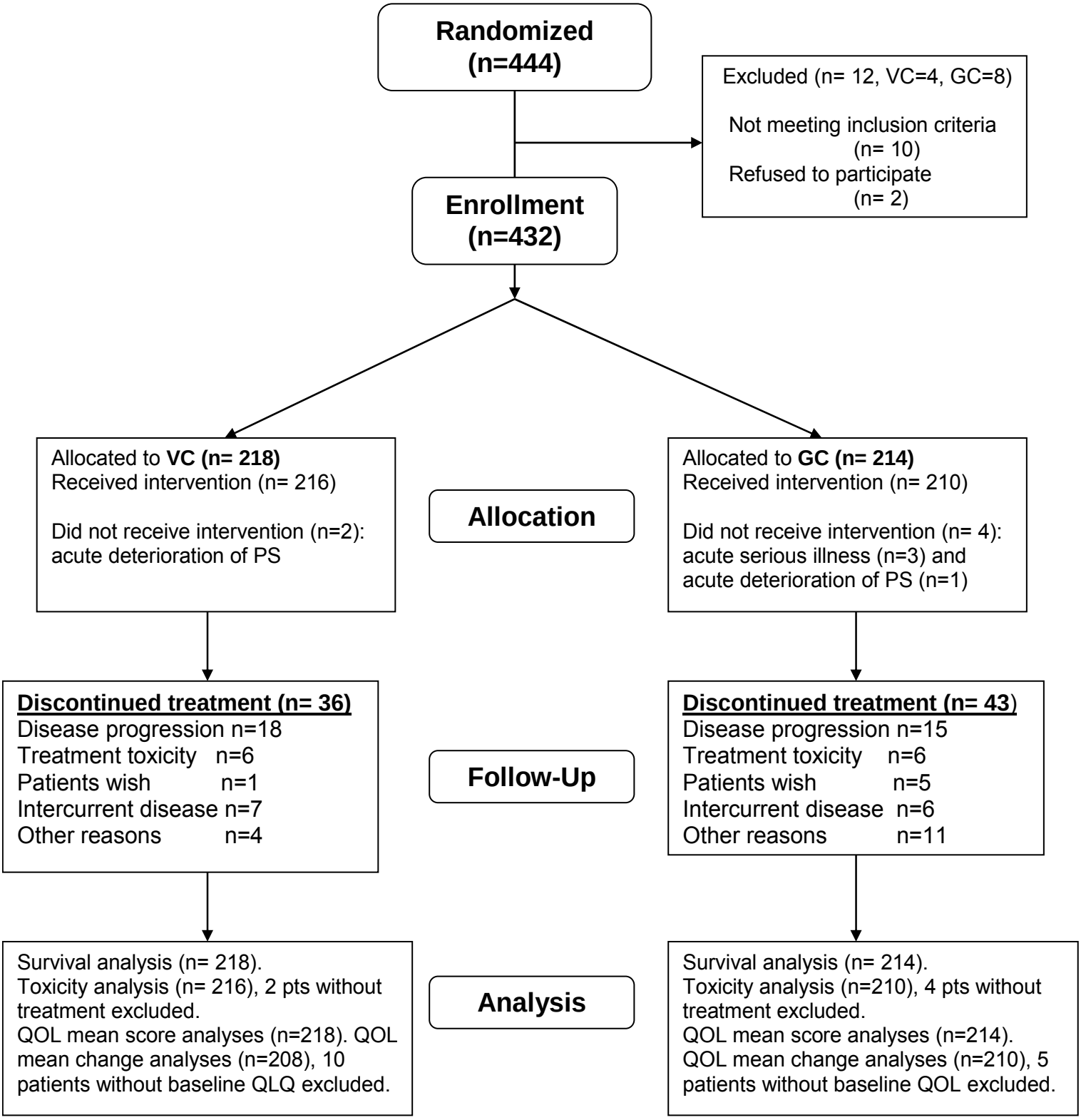

Figure 3. Flow of patients through each stage of the VING study.

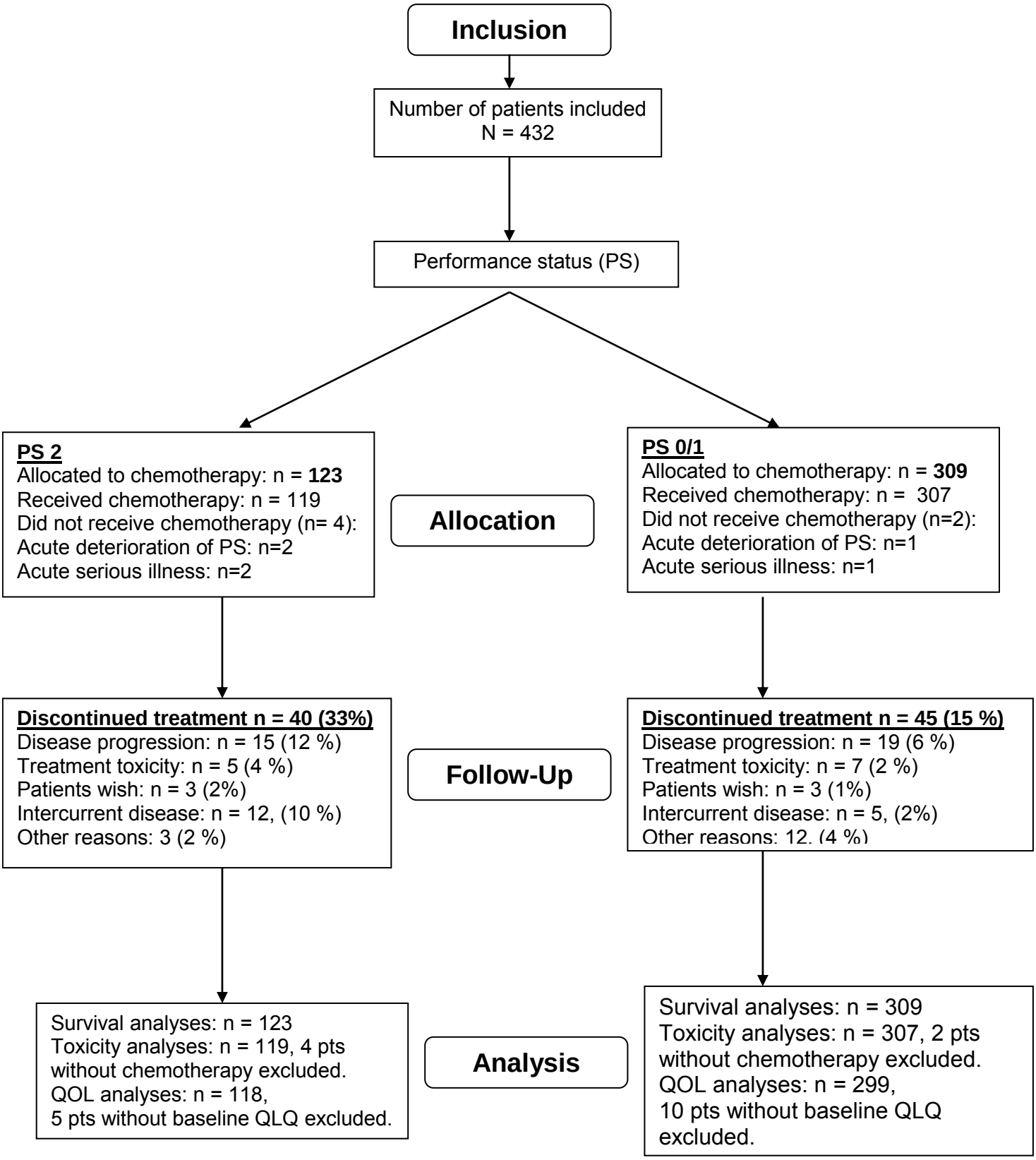

Figure 4. Patient flow according to performance status.

5.2 Paper 1

Vinorelbine/carboplatin vs. gemcitabine/carboplatin in advanced NSCLC shows similar efficacy but different impact of toxicity

This paper presents the first randomized phase III study comparing vinorelbine and gemcitabine in advanced NSCLC. Overall survival, patient assessed HRQOL, toxicity and toxicity-related interventions were compared between the two treatment arms. Global QOL, nausea/vomiting, dyspnea and pain during the first 17 weeks were pre-defined as the primary HRQOL items of interest. In total, 432 patients (VC, n=218; GC, n=214) defined the study population (Figure 3). Median age in the study population was 67 years, 20% were ≥ 75 years old, 61% were male, 71% had stage IV disease, 28% had PS 2 and 48% had adenocarcinoma. The study arms were well balanced with respect to demographic, clinical and histological characteristics.

There were no significant survival differences between the two treatment arms ($p = 0.89$). Median survival was 7.3 months in the VC arm and 6.4 months in the GC arm. The respective 1-year and 2-year survival rates were 28% vs 30% and 7% vs. 7%. The four HRQOL items (global QOL, nausea/vomiting, dyspnea, pain) of major interest showed no significant differences between the treatment arms, neither at baseline nor as change from baseline until week 17. There were more grade 3-4 anemia ($P < 0.01$), thrombocytopenia ($P < 0.01$) and transfusions of blood ($P < 0.01$) or platelets ($P < 0.01$) in the GC-arm. There was more grade 3-4 leucopenia ($P < 0.01$) in the VC-arm, but the rate of neutropenic infections did not differ significantly between the arms ($P = 0.87$).

In conclusion, the VING-study shows no statistical significant survival difference between VC and GC in an unselected patient population mimicking the

everyday clinical setting. HRQOL do not differ significantly between the treatment arms, while grade 3-4 toxicity requiring blood and platelet transfusions are less frequent in the VC arm when compared to GC in advanced NSCLC.

5.3 *Paper 2*

Treatment outcome in performance status 2 advanced NSCLC patients administered platinum-based combination chemotherapy

The basis for this second paper was the lack of consensus regarding platinum-based combination chemotherapy to PS 2 patients with advanced NSCLC. Using data from the VING-study, we evaluated the outcome of PS 2 patients. At inclusion, stratification according to PS 2 vs. PS 0/1 was done. The 123 PS 2 patients in the study were compared to 309 PS 0/1 patients. Survival, TTP, treatment toxicity, required interventions and HRQOL represented by global QOL, nausea/vomiting, dyspnea and pain during the first 17 weeks were compared between the two groups of patients.

The PS groups were well balanced regarding age, gender, disease stage and histology at baseline. Among PS 2 patients, 61 were treated with VC and 62 with GC. Levels of hemoglobin, LD and albumin differed significantly between the two subpopulations ($P < 0.01$). Mean and median hemoglobin levels were 12.1 and 12.0 g/dL in PS 2 patients and 13.0 and 13.1 g/dL in PS 0/1 patients. Mean albumin was 33.3 g/L vs. 37.5 g/L and mean LD 317 U/L vs. 228 U/L in the PS 2 and PS 0/1 subgroups, respectively. PS 2 patients had lower global QOL and more pain, nausea/vomiting and dyspnea at inclusion. They also received less chemotherapy as 68% received all three chemotherapy courses vs. 85% in the PS 0/1 group ($P < 0.01$).

Median and 1-year survivals were lower in the PS 2 group, 4.5 vs. 8.9 months and 10 % vs. 37 %, respectively (P < 0.01). The multivariate analysis indicated PS 2 (P < 0.01, HR 2.09, CI 95% [1.68 – 2.60]) and male gender (P < 0.01, HR 1.30, CI 95% [1.07 – 1.60]) to be independent unfavorable prognostic factors for survival. The causes of death in PS 2 patients did not differ from the PS 0/1 group (P = 0.81). The majority of deaths (87 %) were caused by lung cancer.

Hematological toxicity did not differ significantly between the groups. The frequencies of grade 3 and 4 toxicities as anemia were 16% vs. 12% (p = 0.16), leucopoenia 40% vs. 36% (p = 0.22) and thrombocytopenia 22% vs. 24% (p = 0.49) in the PS 2 and PS 0/1 group respectively. The mean of the lowest recorded individual hemoglobin levels was lower in PS 2 patients (9.3 vs. 9.9 g/100 mL, P < 0.01) and these also had more grade 2 anemia (58% vs. 40%, P < 0.01) when compared to PS 0/1 patients. PS 2 patients needed more blood transfusions (P = 0.03) and were more frequently admitted to hospital (P < 0.01).

Mean HRQOL item changes from baseline to week 3, 6, 9 and 17 revealed clinically meaningful relief of pain and dyspnea in the PS 2 group. There was also a tendency towards improved global QOL at week 6. At week 17, 59% of PS 2 patients and 47% of PS 0/1 patients had improved or stable PS (P = 0.07).

In conclusion, the PS 2 patients have shorter survival than PS 0/1 patients. Noteworthy, they have acceptable toxicity from platinum-based combination chemotherapy and achieve more improvement of HRQOL when compared to PS0/1 patients.

Paper 3

Does chemotherapy improve Quality of Life in NSCLC PS 2?

The background for writing the third paper was the fact that 30 - 40% of patients with advanced NSCLC are in PS 2, and these patients are strongly underrepresented in clinical trials. Data on how the new platinum-based combinations affect their HRQOL are scarce and recommended treatment of this important patient group is controversial. To explore the treatment impact on HRQOL, SAUC for all HRQOL items and HRQOL responses classified as better, stable or worse during the first nine weeks were compared between PS 2 and PS 0/1 patients in the VING-study.

Whereas the demographic data at baseline were well balanced between the groups, HRQOL differed significantly. The PS 2 patients reported lower function for global QOL and all the functional scales ($p < 0.01$). They also had significantly more severe symptoms with more fatigue, pain, dyspnea, swallowing problems, cough, nausea, insomnia, appetite loss and constipation ($p < 0.01$).

The SAUC analyses revealed a tendency towards improved global QOL among PS 2 patients when compared to the PS 0/1 group ($p = 0.049$). For symptoms, PS 2 patients achieved significantly more relief of fatigue, dyspnea, and sleeping problems ($p < 0.01$), and they tended towards less pain and appetite loss ($p < 0.05$). In no items did PS 2 patients experience significant deterioration when compared to PS 0/1 patients.

According to the response analyses, more PS 2 patients achieved improvement in global QOL and cognitive function ($p < 0.01$) and they tended towards more improvement of role function ($p = 0.01$). They also experienced more relief of dyspnea measured by QLQ-C30 ($p < 0.01$), and tended to more

improvement of fatigue, swallowing problems and appetite loss ($p < 0.05$) when compared to PS 0/1 patients.

In conclusion, the PS 2 NSCLC patients had valuable HRQOL benefits from platinum-based combination therapy, with a more profound improvement of global QOL, cognitive function, fatigue, dyspnea, sleeping problems and appetite problems.

6. Discussion

6.1 Paper 1

Platinum in combination with a third-generation drug (gemcitabine, vinorelbine, docetaxel or paclitaxel) has been established as standard first-line treatment of advanced NSCLC. The best combination among these platinum doublets still, however, remains an open question. We showed that the VC regimen already established in Norway at the time, is an adequate treatment alternative and even favorable with respect to hematological toxicity when compared to GC.

A meta-analysis including 4556 patients from 13 randomized trials, found gemcitabine-platinum doublets slightly superior to the non-gemcitabine combinations regarding progression-free survival.[87] When limiting the analyses to the other novel platinum-based doublets, the difference was no longer significant (HR 0.93, CI 0.86–1.01). An expert opinion on GC combination therapy in advanced NSCLC found GC to be among the better tolerated available first-line regimens in this setting, although myelotoxicity can be significant.[88] The opinion was based on an evaluation of pharmacology, preclinical and clinical data, and the aim was to support the use of this regimen. No trials including vinorelbine were referred to.

The median survival in our study was somewhat lower when compared to other phase III trials. This can be explained by the large proportion of PS 2 patients included (28%).

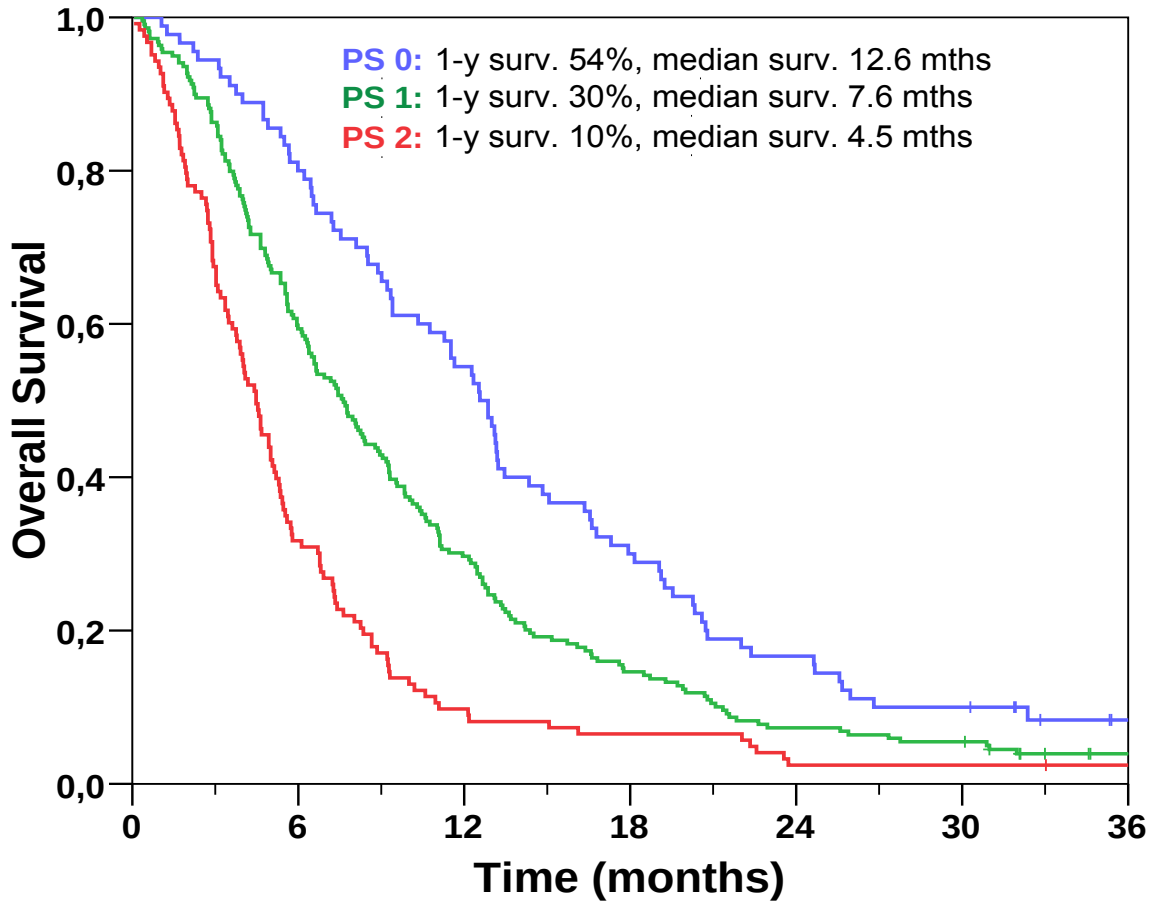

Figure 5. Overall survival according to performance status.

As Figure 5 demonstrates, survival data in advanced NSCLC patients is highly dependent on the patients' PS. In this perspective, thorough analyses of possible reasons for survival differences of a few weeks, is of no interest unless the study populations are similar regarding PS. When PS 2 patients were excluded from our analysis, the median survival increased from 7.3 to 9.0 in the VC and from 6.4 to 8.9 months in the GC arm.

The higher rate of leucopenia experienced in the VC arm (45% vs. 30%) did not result in higher infection rates and was mainly laboratory toxicity without direct impact on patients' lives. On the other hand, the markedly higher incidence of grade 3-4 anemia (19% vs. 6%) and thrombocytopenia (44% vs. 3%) in the GC arm, led to additional symptoms and significantly more frequent transfusions of blood products, requiring hospitalization and further costs. In general, our toxicity data are consistent with previous studies[29,51] and support the chosen chemotherapy doses.

An overall compliance of 88% for completing HRQOL forms during the study period is considered good. The present HRQOL analyses did not reveal any significant differences between the two treatment regimens. The timing of the HRQOL questionnaires was probably not ideal to unmask possible differences in acute chemotherapy-related toxicity between the treatment arms as the patients were asked to complete these forms just prior to chemotherapy. Completing the questionnaires a few days after chemotherapy may have been a better approach.

6.2 Paper 2

This comparison of PS 0/1 and PS 2 patients indicates that despite a modest survival, carboplatin-based combination chemotherapy is tolerated in PS 2 patients and improves these patients' HRQOL.

Combination chemotherapy to advanced NSCLC PS 2 patients is controversial, as accounted for in the background of this thesis. The ASCO Treatment of Unresectable Non-Small-Cell Lung Cancer Guideline: Update 2003[27] stated that single-agent chemotherapy would be sufficient for PS 2 patients. This was based on the fact that non-platinum based doublets were suggested equivalent to platinum doublets in terms of efficacy, but with less nonhematologic toxicity.[89] Still,

non-platinum combinations were described to yield higher toxicity than single-agent chemotherapy and may for that reason not be appropriate for patients with poor performance status. By 2003, no randomized trials comparing combination chemotherapy with single-agent chemotherapy in PS 2 NSCLC patients had been published. On the other hand, subgroup analyses from randomized trials suggested that PS 2 patients had a significantly higher rate of toxicity than PS 0/1 patients. This was based on four randomized trials.[35,37-39] In the ECOG trial 1594,[37] four platinum-based chemotherapy regimens for advanced NSCLC were compared without superiority for any of these. After accrual of 68 PS 2 patients, a high incidence of adverse events including five deaths led to an early terminated inclusion of PS 2 patients. The authors advised against the routine use of platinum-based chemotherapy to patients with a poor performance status. In a subsequent subgroup analysis of the outcome of these 68 PS 2 patients, underlying disease and not the treatment toxicity, was found to be responsible for their poor outcome.[39] Still, the advice against platinum-based combination chemotherapy to NSCLC PS 2 patients was maintained by the authors.

In contrast to this view, Lilenbaum et al[40] compared the efficacy of combination chemotherapy vs. single-agent therapy in advanced NSCLC and observed better survival rates in PS 2 patients treated with combination chemotherapy than those treated with single-agent therapy ($p = 0.02$). Later, a randomized phase II trial, evaluating two dose-attenuated platinum-based doublets in advanced NSCLC PS 2 patients,[90] concluded that the combination chemotherapy was feasible with acceptable toxicity despite inferior survival compared to PS 0/1 patients.

The lack of differences in hematological grade 3 and 4 toxicity between the PS subgroups is in agreement with previous publications [39,40,91,92]. Still, more PS 2

patients received blood transfusions, which probably reflect the lower hemoglobin level already at baseline. More frequent admissions to hospitals among the PS 2 patients might be explained by anemia and symptoms due to more advanced disease.

The present report reveals that despite a shorter survival, PS 2 patients have acceptable toxicity, achieve better improvement of pain and dyspnea and tend towards a better global QOL when compared to PS0/1 patients. Improvements in PS 2 patients' HRQOL is supported by a study published in 2001[35] and in a more recent phase II study.[93] Also, clinical improvement, defined as achieving a good PS during combination chemotherapy, has been reported in advanced NSCLC patients with poor PS.[94]

6.3 Paper 3

In this paper, HRQOL of advanced NSCLC PS 2 patients is explored in detail. To our knowledge, this is the first detailed HRQOL study in advanced NSCLC PS 2 patients administered platinum-based combination chemotherapy. The PS 2 patients had more improvement of global QOL, cognitive function, fatigue, pain, dyspnea, sleeping problems and appetite loss than PS 0/1 patients.

HRQOL data in NSCLC PS 2 patients are highly demanded in the literature. A European experts panel argued for HRQOL assessments in evaluating symptom relief and clinical benefit as endpoints in trials including NSCLC PS 2 patients.[65] An *in press* review on treatment of NSCLC PS 2 patients concludes that chemotherapy appears justified and that the emphasis for these patients' care should be on maintenance and improvement of QOL.[95] Also, the National Institute of

Clinical Excellence[19] describes the need for further research in HRQOL aspects regarding NSCLC PS 2 patients treated with chemotherapy.

HRQOL benefits among NSCLC PS 2 patients have been reported previously. In a subgroup analysis based on two randomized parallel trials of mitomycin, ifosfamide and cisplatin[96], the most significant HRQOL improvements during chemotherapy was observed in the PS 2 rather than the PS 0/1 group.[35] Furthermore, in a recent randomized phase II trial of first line erlotinib monotherapy versus the combination of carboplatin and paclitaxel in advanced NSCLC PS 2 patients,[93] HRQOL tended to improve rather than worsen in both treatment arms. The authors concluded that unselected advanced NSCLC PS 2 patients are best treated with combination chemotherapy in first-line.

In a recently published phase III study, up to six cycles of single-agent paclitaxel poliglumex was compared with single-agent gemcitabine or vinorelbine in chemotherapy-naïve advanced NSCLC PS 2 patients.[97] A total of 477 patients were included between Dec 2002 and June 2004, which according to the authors make this the largest series of NSCLC PS 2 patients in a clinical trial. The primary endpoint was overall survival, followed by efficacy measures and tolerability. The authors concluded that survival rates between the arms were comparable, and patients in the experimental arm (paclitaxel poliglumex) had less toxicity. HRQOL was assessed by the FACT-LCS questionnaire and compared between the arms at baseline and week three without significant differences. Based on information in the article, the HRQOL compliance rate was 70%. In this poor PS patient group, HRQOL results were presented using less than 4 lines, and were not discussed in the article. This paper demonstrates the difficulties in getting through advocating the importance of HRQOL analyses in the palliative treatment of NSCLC.

Analyzing HRQOL data is challenging and so is presentation of such data in a way that make them comprehensible and useful to clinicians without particular training in interpretation of these kinds of results. HRQOL data are complex of nature with several measures at different time points for each patient. Often, the aim is to describe HRQOL over time, which demands summarized measures for each patient and subsequent comparisons between the groups.[81] As emphasized in the paper, analyses of unplanned sub-group comparisons should be interpreted with caution.[98,99] On the other hand, significant findings give rise to new hypotheses and thus initiate important research. The presented subgroup analyses revealed clinically meaningful improvements of symptoms and functions in advanced NSCLC PS 2 patients treated with platinum-based combination chemotherapy.

7. Conclusions and implications for further research

In conclusion, the comparison of VC and GC revealed no significant differences in survival or HRQOL, while clinically relevant toxicity was more frequent in the GC arm. These results supported VC as our standard first line treatment for advanced NSCLC. For subsequent randomized studies initiated by the Norwegian Lung Cancer Study Group, VC has been included as the standard arm. Nevertheless, the GC combination is widely accepted as a valuable treatment option for these patients as well. Future research will probably, to a larger extent, focus on new targeted therapies instead of further exploration of traditional chemotherapy combinations.

Clinical valuable HRQOL benefits from combination chemotherapy were seen among PS 2 patients. This reflects their heavier symptom and disease burden, and the greater potential for treatment effect on symptoms in this group. It will be important to generate more research in this area; hence inclusion of NSCLC PS 2 patients into randomized trials should be encouraged in order to increase our knowledge within this field.

Advanced lung cancer patients in general, and those with PS 2 in particular, suffer from severe symptoms during progression of their disease. There should be a strong focus on these patients' HRQOL and future research on their optimal palliative treatment benefits.

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Erratum

Page 20, ref. 41.

..”individual data from 2666 patients revealed an increased 1-year survival in PS 2 patients from 5% after obsolete chemotherapy to 11% after novel therapy.[41]” should read: …”individual data from 2714 patients revealed an increased 1-year survival in patients with PS ≥ 2 from 8% to 14%.[41]”

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