Department of Clinical Medicine

The Conrad Study

A randomised, multicenter phase III trial of combination chemotherapy ±

thoracic radiotherapy in the treatment of patients in poor condition with

stage III non-small cell lung cancer not eligible for radical therapy

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ACKNOWLEDGEMENTS

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ABBREVIATIONS

BSC	Best supportive care
CRT	Combined Chemo- and Radiotherapy = Chemoradiation = Chemoradiotherapy
CT	Computer tomography
CTCAE	Common terminology criteria for adverse events
EGFR	Epidermal Growth Factor Receptor
EML4-ALK	Refers to a mutation on a specific location of the tumor genome
EORTC	European Organization for Research and Treatment of Cancer
EP	Etoposide plus cisplatin
HFX RT	Hyperfractionated Radiotherapy
HR	Hazard ratio
HRQOL	Health-related quality of life
KRAS	Refers to a mutation on a specific location of the tumor genome
LA-NSCLC	Locally advanced non-small cell lung cancer
MRC	Medical Research Council (UK)
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
PS	Performance Status
QLQ	Quality of Life Questionnaire
RCT	Randomised Clinical Trial
RR	Response Rates
SCLC	Small Cell Lung Cancer
SD	Stable Disease
TB	Tuberculosis
TRT	Thoracic Radiotherapy
TTP	Time to Progression
ULN	Upper Limit Normal
WHO	The World Health Organization
QLQ-C30	The EORTC Quality of Life Questionnaire-Core 30

INTRODUCTION

Most lung cancer patients in Norway are diagnosed too late for cure to be an option. The typical patient is about 70 years of age and in poor health. Curative treatment for advanced lung cancer is not possible and aggressive treatment, in a futile situation, is unethical and often shortens and worsens a life already marked by illness.

For many years most clinicians chose to abstain from active treatment when confronted with advanced lung cancer. During the last thirty years, however, new chemotherapeutic drugs have emerged and some of these are found to alleviate symptoms and prolong survival. In this setting, many studies have been conducted to find effective drugs at the right doses in the right combinations, in order to lessen side effects [1]. At present, we are able to prolong survival and improve the quality of life in patients with locally advanced non-small cell lung cancer. Clinical trials indicate that even patients in reduced general condition (PS 2) gain from treatment with chemotherapy [2].

Radiotherapy may be curative, but only when the disease is localized and of small size. A good performance status has been an additional prerequisite. In locally advanced non-small cell lung cancer of poor prognosis, radiation may relieve symptoms, and for this reason palliative radiation has been the treatment of choice[3].

One would expect that the addition of chemotherapy to radiation could be a promising prospect: Palliative doses of radiation may give local symptomatic control and as such alleviate symptoms; The general cytotoxic effect of adjusted doses of chemotherapy may prevent or reduce the tendency to distant metastases, in addition to contribute to local control. Obviously, the side effects would represent a challenge, but by adjusting the therapy to the palliative intent, the treatment should not be too toxic.

This is the idea behind the present study. We have conducted a clinical randomized trial to compare a palliative CRT (chemoradiotherapy) regimen to palliative chemotherapy alone, with respect to survival, health-related quality of life (HRQOL) and toxicity in incurable stage III NSCLC patients with negative prognostic factors.

Derived from the letters of **CON**current **rad**iation the trial has got its name: The CONRAD-study.

The thesis consists primarily of papers written in collaboration with colleagues and have been peer reviewed before publication in international journals. In order to make the rest of the thesis more accessible, I have chosen a language less firm and have elaborated somewhat to explain the historical background on both lung cancer as a disease and the methods used in this work. Still I believe to have adhered to the formal regulations for the degree of PhD at the University of Tromsø [4].

LIST OF PAPERS

1. **Strøm HH, Bremnes RM, Sundstrøm SH, Helbekkmo N, Fløtten Ø and Aasebø U:**
Concurrent palliative chemoradiation leads to survival and quality of life benefits in poor prognosis stage III non-small-cell lung cancer: a randomised trial by the Norwegian Lung Cancer Study Group. British Journal of Cancer, 2013

2. **Strøm HH, Bremnes RM, Sundstrøm SH, Helbekkmo N and Aasebø U***: Poor prognosis patients with inoperable locally advanced NSCLC and large tumors benefit from palliative chemoradiotherapy: A subset analysis from a randomized clinical phase III trial.* Journal of Thoracic Oncology, 2014

3. **Strøm HH, Bremnes RM, Sundstrøm SH, Helbekkmo N and Aasebø U:** *How do elderly poor prognosis patients tolerate palliative concurrent chemoradiotherapy for locally advanced NSCLC stage III? A subset analysis from a clinical phase III trial*

1. BACKGROUND

1.1 Lung Cancer

One hundred years ago most people in Norway died of infectious diseases. TB was the most important and affected primarily children and adolescents. More than 4000 died of the disease every year[5]. In those days few doctors had heard of lung cancer. Even fewer had seen anyone suffering from it.

Today most Norwegians die of chronic diseases related to life style, diseases which mainly affect adults and the elderly. Cancer is one of them. Last year, someone died from lung cancer every fourth hour. As tuberculosis today is virtually non-existent among ethnic Norwegians, we are looking at an epidemiological shift of large proportions.

The decline of tuberculosis cannot be attributed to medical treatment. Most of the decline happened before anti-TB drugs emerged. Preventive measures are the most likely explanation, see figure 1. Lung cancer is also a preventable disease. Still only 16 % of the lung cancer patients survive 5 years.

In the following I will discuss the emergence of lung cancer, it's epidemiology and how this increase in lung cancer incidence came about.

Figure 1. Mortality of Tuberculosis and lung cancer through 100 years – all ages, per 100 000 persons per year, in Norway. (Source: Norwegian Institute of Public Health, Norhealth)
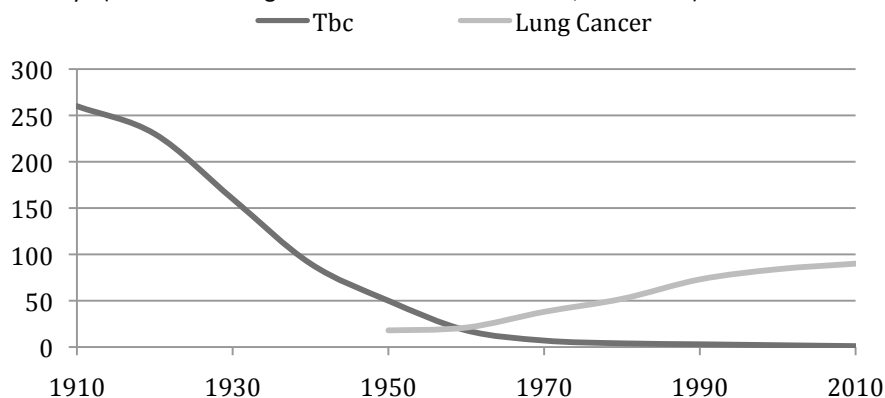
1.2 What is cancer?

The human body consists of living cells. Most of them are self-renewing, i.e. they multiply; they act, they die and are expelled in a strictly organized way. Cell division is essential to life – if we are to grow, to adapt, to heal and thrive. But the mechanism is subject to occasional lapses, mutations, which may result in cells that are altered. It happens inside every one of us, every day, from we are born to the day we die. Most often the mutations are of no importance. And if they are, the immune system eventually destroys the altered cells. However, now and then some escape our disposal service, with consequences that are dramatic and sometimes fatal.

Paradoxically, mutations serve as prerequisites for evolution. Spontaneous mutations sometimes further our ability to live. High altitude populations in the mountains of Tibet and Andes have been subject to a very strong positive natural selection, making them able to sustain life in areas of low oxygen saturation[6]. Over generations they have been genetically adapted to prevent the life-threatening processes, like swelling of the lungs and brain, that low altitude living people often experience when they suddenly find them self at high altitudes. Specific genes, related to physiological features associated with the ability to thrive in higher elevations, have been found[7]. Over time, beneficial mutations have changed their genome and their subsequent phenotype in a beneficial way. In this way, we may consider the phenomenon of mutation as a blessing.

In talking about cancer, we are concerned about the spontaneous mutations that sometime induce changes with fatal consequences. Point mutations are not rare, and by no means synonymous with cancer. As we become older mutations are incorporated in chromosomes of normal cells as well as tumor cells. But in cancer the number and the rate of chromosomal changes is accelerated. Solid tumor cells, as lung cancer, display widespread

changes in chromosome number, as well as deletions, inversions, translocations and other genetic abnormalities[8]. Through a stepwise process of multiple molecular transformations the cells have evolved progressively to a neoplastic state, characterized by an imbalance between tumor suppressor genes and tumor promoting genes. The fine-tuned regulation of cell division is subsequently lost. These new cells resist cell death. They evade growth suppressors and sustain proliferative signaling. They induce angiogenesis and activate invasion and metastasis. They achieve replicative immortality and the result is an uncontrolled growth of a primary tumor[9]. These cells do not respect physiological or anatomical boundaries. They are the cells of a metastatic cancer.

1.3 Molecular aspects of Lung cancer

The most critical event during the neoplastic process is the acquisition of a driver gene, preceded by a driver gene mutation. Directly or indirectly this mutation confers a selective growth advantage to the cell. The driver gene contains driver mutations as well as so-called passenger mutations, and becomes responsible for both the initiation and the maintenance of the cancer. Among the non-small cell lung cancers, the genetic mutation profile will determine what category or to which subtype the tumor belongs. Subsequently the profile will be used for personalized treatment strategies [10].

Traditionally lung cancer has been divided into small cell and non-small cell tumors, and treatment decisions were made on the basis of these two histological types. NSCLC comprised squamous cell carcinoma and adencarcinoma, as well as large cell and carcinomas not otherwise specified. In the last fifteen years a number of oncogenic mutations have been identified and associated therapeutic agents developed. One consequence is that making simple treatment decisions on the basis of histology alone are not possible anymore.

EGFR, EML4–ALK and KRAS gene mutations are typical examples of important driver genes identified and characterized mainly in adenocarcinomas. Usually their presence is mutually exclusive in the same tumor and their prevalence varies in different ethnic populations. Mutations in EGFR are most commonly found in younger, Asian, non-smoking women. In a recent study of a Norwegian cohort of NSCLC patients, EGFR-mutations were found in 11.6%. Among the patients with squamous cell carcinomas, the frequency of EGFR-mutations was 3%[11].

Great expectations were put to the therapeutic effect of different inhibitors, specifically designed to target these oncogenic mutations. Unfortunately, as a consequence of the relentless mutational activity found in solid tumors, the clinical efficacy proved to be temporary. After 9 to 11 months treatment resistance develops and the disease progresses[12]. But advanced NSCLC diagnosed in Norway is now routinely tested for EGFR mutations. In order to prolong survival for patients with non-resectable NSCLC, tyrosin kinase inhibitors are offered as first-line treatment to patients with tumors testing positive for EGFR mutations. In case of no EGFR mutation, EML4-ALK translocation is assessed in young non-smoking NSCLC patients.

A malignant lung tumor may display more than 200 non-synonymous mutations, more than any other type of cancer. Acute myeloid leukemia, by comparison, may display less than ten. For solid tumors, such as lung cancers, the picture is further complicated by a vast genetic heterogeneity. There is heterogeneity among the cells of one tumor; among the different metastatic lesions of the same patient; among the cells of an individual metastasis; as well as among the tumors of different patients. Obviously, this may impact the response to therapeutics and serve to explain the poor treatment results [8].

The number of somatic mutations is also correlated with age. Most often these are passenger mutations, without effect on the neoplastic process. However, in some instances the number reflects the involvement of external potent mutagens in the development of the disease. Lung tumors of smokers are examples of this: They contain ten-fold the number of mutations than the tumors of non-smokers. In the words of Ramaswamy Govindan, an oncologist at Washington University School of Medicine in St Louis: "These genomes are battled scarred by carcinogen exposure"[13,14].

Figure 2. Trends in incidence and mortality rates and 5-year relative survival proportions - Lung and tracheal cancer. (Source: Cancer in Norway 2011)
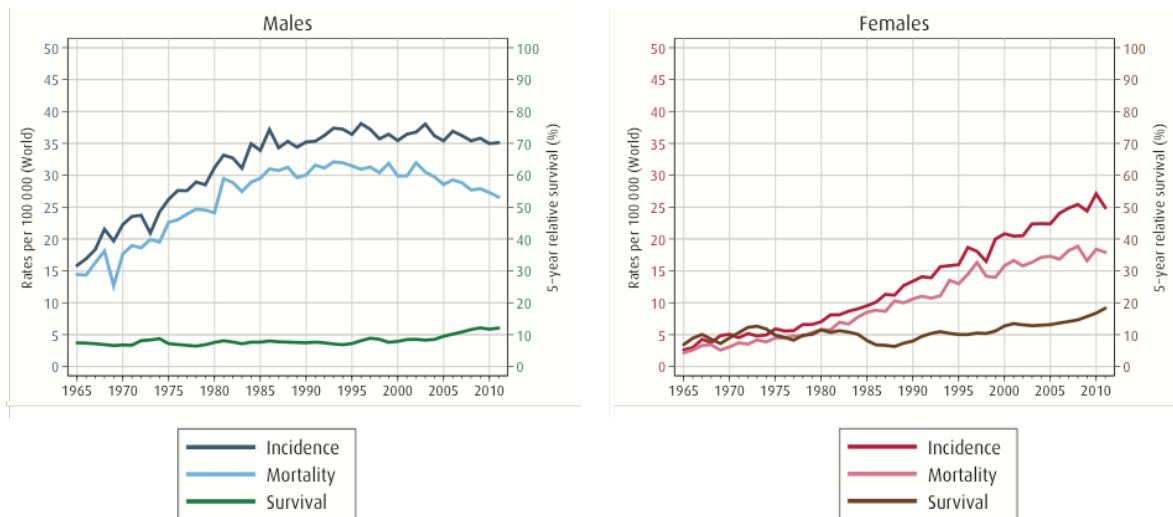
1.4 Histology and epidemiology

Lung cancer accounted for only 10% of the number of new cases of cancer in 2011, but was responsible for 26% of the cancer deaths in men and 20% in women. After a steady increase in both incidence and mortality for men throughout the second half of the twentieth century, a peak was reached around the year 2000. Among women, however, the incidence and the mortality of lung cancer is still increasing (figure 2)[15].

On a population level, the histology changes according to smoking habits, geography, ethnic background and gender [16]. In 1988 less than 30% of the lung cancer patients in Norway were women. The occurrence rates track smoking rates by about 20 – 30 years and changing smoking patterns (see figure 3) is a likely explanation for why women accounted for more than 40% of lung cancer cases in Norway in 2007[17].

Since WHO published a new and nuanced categorization of lung cancer in 2004, small cell lung cancer has been included among the neuroendocrine tumors [18]. In total, these represent approximately 15 % of all lung cancers and except from the carcinoid tumors, they are highly aggressive malignancies, seldom cases for surgical removal. These tumors differ from other types of lung cancer, both in clinical presentation, histology and response to treatment [19].

Historically, adenocarcinomas have dominated among female lung cancer patients world wide, particularly predominant in Asian females (72% in Japan, 65% in Korea), but also in Norway (33% at present)[18]. Before 1999, squamous cell carcinoma dominated among men (33%) in Norway. After 2000, the adenocarcinomas have been the most prevalent, regardless of sex [17]. This shift in incidence is seen all over the world. One reason may be changes in the chemical composition of tobacco-products. Another may be a shift to filter cigarettes with lower nicotine content and subsequent deeper inhalation of smaller particles[20-22]. Adenocarcinomas are even the most commonly found histology among non-smokers with lung cancer[23].

The Conrad trial, however, concerns NSCLC, of which adenocarcinoma and squamous cell carcinoma represents the most dominant histological groups. Together they comprise a majority of all lung cancers in Norway[17].

Figure 3. Percentage daily smokers (per cent) by sex and time, Total 16 – 74 years. (Source: Statistics Norway)
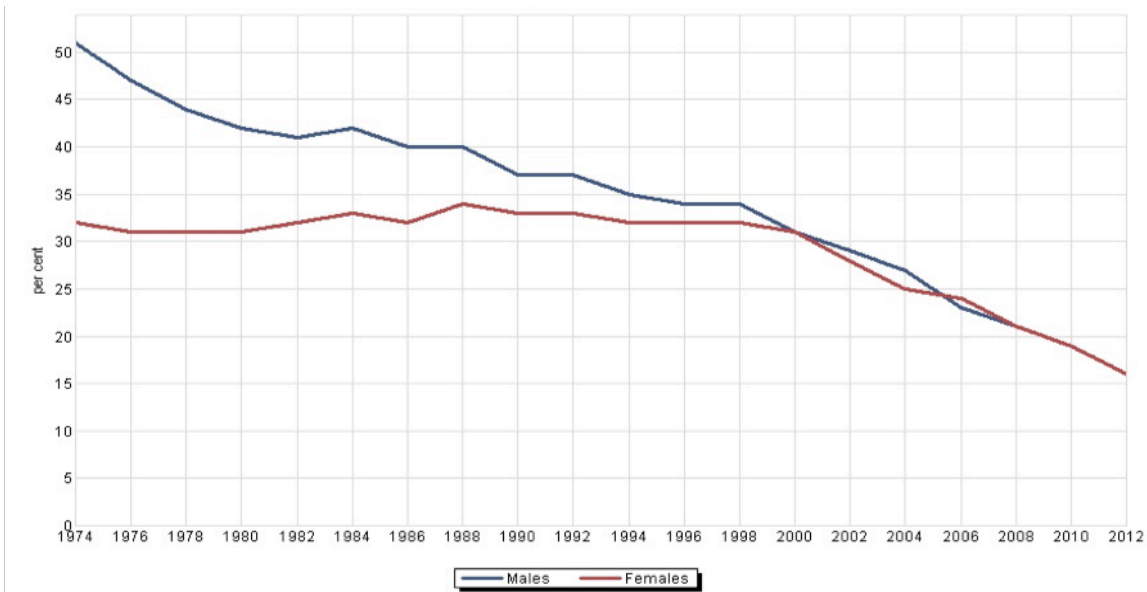
1.5 What can cause lung cancer?

Cancer is primarily considered to be an environmental disease, with only 5 to 10 % of cases attributed to inherited gene defects[24]. The Surgeon General of the U.S. identified smoking as the primary cause of lung cancer 50 years ago [25]. Environmental pollution and radiation are also found to be important factors, as well as occupational exposure for asbestos fibers, crystalline silica, mixtures of polycyclic aromatic hydrocarbons (PAH) and heavy metals [18,24,26].

Smokers have a 20-fold risk of lung cancer compared to never-smokers and no environmental exposure can match such a risk [24].

A framework for understanding how cigarette smoking causes lung cancer is presented in Figure 4. More than 5000 different compounds have been identified in cigarette smoke, of which nicotine is probably the most familiar. Nicotine is an alkaloid and a powerful stimulant drug, highly addictive, and considered the main reason people keep smoking. Nicotine is, however, not carcinogenic. In cigarette smoke 73 other compounds are

found to be carcinogenic, of which more than 20 are lung carcinogens. Among these are polycyclic aromatic hydrocarbons (PAH), volatiles such as 1,3-butadiene and ethylene oxide and metals such as cadmium. Together these cause thousands of mutations in the lungs of smokers, among them in growth-regulatory genes as KRAS and TP53 [27].

Figure 4. An illustration of how cigarette smoking causes lung cancer - a mechanistic framework. All events can occur chronically since a smoker typically uses multiple cigarettes per day for many years. (Source: Hecht SS. Lung carcinogenesis by tobacco smoke. Int J Cancer. 2012 Dec 15;131(12):2724–32.)
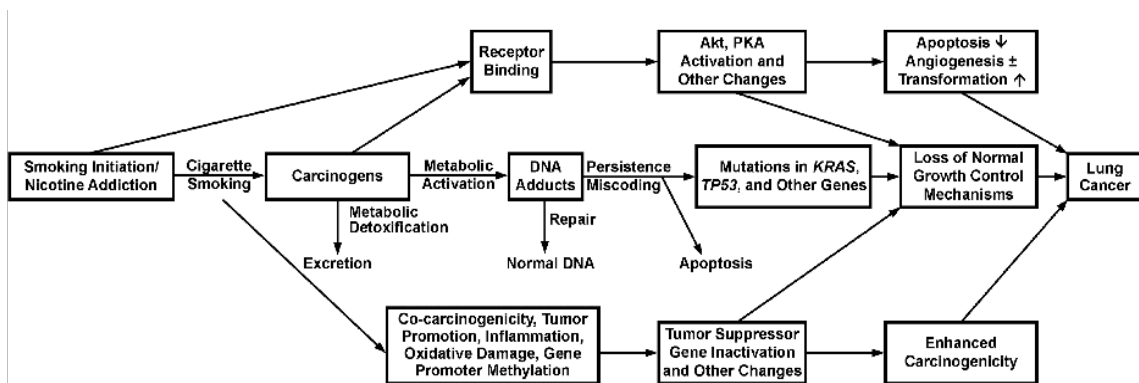
The smoking of tobacco was introduced in Europe by the conquistadors returning from South America in the 15th century. Until the Age of Industrialization, smoking was frequently considered a remedy and reserved men of means and spare time. With the invention of the Bonsack machine in 1883 the industrial production of cigarettes became possible [28].

Smoking of cigarettes became an important part of a new world - The Consumer Society. In past societies the supply and demand were correlated. In the Consumer Society the emerging marketing industry was capable of creating both new needs and desires.

Advertisements appeared in newspapers and on billboards. The manufacturers submitted cigarettes to medical journals as *The Lancet* for approval. Tobacco companies

targeted military personnel and furnished soldiers' rations with cigarettes [29]. During and between the two World Wars the tobacco firms cultivated the activity of cigarette smoking and the consumption of tobacco soared. The annual consumption of tobacco in Great Britain increased to the double in the years from 1922 to 1947. The percentage of smoking in the form of cigarettes increased from 56 to more than 80 percent at the same time. In many ways the marketing of cigarettes became one of the driving forces in the development of a modern advertising industry. They launched a lifestyle – The American way of life – where smoking played an important part, as an activity shared with "The famous and beautiful". Cigarettes could be smoked anywhere and were advertised as torches of economic and sexual equality [30]. During the 1920s and the '30s the boundaries of where and when to smoke expanded into all parts of urban and rural landscapes. Soon it was possible to light up everywhere – in shops, in restaurants, in busses, trains and trams [28].

One hundred years later it took intense campaigning and public imposition to stop smoking in public areas. Even more effort was needed to stop the tobacco industry in their assiduous work to preserve smoking as part of modern culture.

Another important part of the Industrial revolution was the emergence of pollution and toxic compounds linked to the diverse newly developed mechanical processes. Asbestos may serve as an example. In areas where the mineral was naturally occurring, people had been aware of the heat-protecting properties for centuries. But in the age of engines and mass production, asbestos emerged as a versatile material useful in all kinds of new mechanical processes: It combined the ability to isolate against heat, flames and electricity while offering effective protection against acid and intense friction. Just as important were the abilities to form the material according to needs: It could be woven to insulating clothing for humans and electrical cords, sprayed on as fireproof coating, compressed to automobile

brake shoes and formed to strengthen valve casing in steam engines, as well as blended into all kinds of building materials [31].

However, the asbestos generates dust on handling. On inhaling the fine mineral fibers enter the airways and end up in the alveoli. The fibers are rigid, sharp and robust. In the periphery of the lungs they trigger inflammatory processes, mediated by alveolar macrophages and neutrophils. The inflammation promotes oxidative stress, DNA damage and tumor genesis. Tobacco smoking impairs asbestos clearance and contributes to the carcinogenic effect[26].

Asbestos achieved immense popularity, especially triggered by the global boom in construction after World War II. From 1952 to 1956 Kent filter cigarettes were produced with a filter containing crocidolite, the form of asbestos most implicated in causing mesothelioma and lung cancer [32]. In 1955 Doll published a paper on the increased mortality from lung cancer in asbestos workers [33]. Still, the use of asbestos accelerated world wide, reaching an all-time high in 1973 in Great Britain. Today most forms of asbestos are banned in the Western World.

The fraction of lung cancer attributed to work-related causes varies from 5% to 14%, depending on region and gender. In addition to asbestos, silica, diesel fumes and chemicals as cadmium, nickel, chromium and beryllium are the most important carcinogens related to occupational exposure [34].

Finally, residential radon may cause lung cancer, independent of smoking. The magnitude of this effect varies according to geographical location. The significance on the total number of cancer cases is difficult to assess [35]. In the lung tissue, inert radon-gas decay into chemical active compounds. These damage DNA both directly and via the generation of free radicals [36].

But cigarette smoking remains the main cause of lung cancer, responsible for more than 80% of the cases [37]. Retrospectively it is tempting to describe the past century as *The Smoking Century* – a curious incident in the history of man – when tobacco smoking was a strange and dangerous passing fancy in a time of rapid cultural changes.

1.6 Has the incidence of lunge cancer increased?

According to Witschi, few written or visual descriptions of lung cancer are found in art and literature before the 20th Century[38]. At the Institute of Pathology of the University of Dresden, malignant lung tumors accounted for only 1 % of all cancers seen at autopsy in 1878. Forty years later, lung cancer had risen to almost 10% and in the subsequent ten years to more than 14% of the cancers seen at autopsy. Alton Ochsner, a prominent American doctor who eventually founded his own clinic, was surprised to see a case of lung cancer when he became professor of surgery at Tulane University in 1927. It was the second case he had seen in 17 years.

Less than fifteen years later lung cancer had become the second most frequent cause of cancer death in Germany, stomach cancer being number one[38]. In Great Britain, the Health Ministry was alarmed by the unparalleled increase in number of deaths attributed to lung cancer after WWII. The prevalence had increased by 1500 percent between 1922 and 1947. The Ministry found it necessarily to petition the Medical Research Council to find an explanation[39].

However, not everyone agreed upon the rarity of pulmonary cancers before the 20th Century. In his monograph "Primary Malignant Growths of the Lung" from 1912, Isaac Adler considered this an undocumented dogma[40]. He cited the similarity of symptoms to other common diseases and claimed that many patients probably died of cancer, but were left

with a diagnosis of pneumonia or asthma or chronic obstructive pulmonary disease, or –
most probably – tuberculosis. He described the difficulties of diagnosing lung cancer as
"humiliating".

No means of visualizing the disease were available before the introduction of chest x-
ray in the early decades of the twentieth century. From the nineteen fifties and onward, the
availability of bronchoscopes and antibiotics made it possible to distinguish between
pneumonia and cancer. This led to a more accurate diagnosis of fatal respiratory diseases
and the quality of data captured improved. In Norway public registration of cancer diseases
did not become mandatory before 1952[5].

Life expectancy is another confounding factor in the discussion of prevalence of lung
cancer through the ages. Among men in Norway in 1866, the life expectancy in a newborn
child was 47.3 years. In 1900 it was 51.5 years. By 2000, the life expectancy among a
newborn boy had risen to 75.5 years (Statistical yearbook of Norway 2013). In the
preliminary report about smoking and carcinoma of the lung, published by Doll and Hill in
1950, an overwhelming majority of lung cancer patients were older than 50 years of age at
the time of diagnosis. Among the approximately 2800 Norwegians diagnosed with lung
cancer in 2009, the median age at time of diagnose was 70 years, regardless of stage[15,17,41]. In
other words, the generally low life expectancy in 1900 probably prevented many
Norwegians from developing lung cancer.

We may conclude that it is difficult to exactly quantify the increase in incidence of
lung cancer in the past century.

2. REVIEW OF THE TREATMENT OF LUNG CANCER

2.1 Tumor Classification system and Performance Status

In order to create a uniform evaluation of different treatment modalities on different stages of cancer disease, several classification systems have been developed. The TNM system is the most widely adopted, and – after several modifications, the latest the 7th – this system offers a set of specific parameters, by describing the extent of a solid tumor (T), the extent of regional lymph node involvement (N) and the presence or absence of distant metastases (M) [42,43]. See Table 1.

A description based on the TNM system is very accurate and nuanced, but it may complicate the process of comparing one case of NSCLC with another. In order to facilitate the comparison of prognostic factors and the subsequent treatment decisions, cases of NSCLC are thus categorized into four broader categories– stages – based on their TNM description. See Table 2.

As the use of chemotherapy increased, the importance of assessing the general condition of the patient in order to determine appropriate treatment became obvious. At present, the ECOG Performance Status (PS) is the scale most commonly used [44]. See Table 3.

Table 1. TNM Classification, UICC, 7. edition :

TX	Positive cytology only
T1	≤ 3 cm
T1a	≤ 2 cm
T1b	> 2-3 cm
T2	Main bronchus ≥ 2 cm from carina, invades visceral pleura, partial atlectasis
T2a	> 3-5 cm
T2b	> 5 cm – 7 cm,
T3	> 7 cm; chest wall, diaphragm, pericardium, mediastinal pleura, main bronchus ≤ 2 cm from carina, total atlectasis, separate nodule(s) in same lobe
T4	Mediastinum, heart, great vessels, carina, trachea, esophagus, vertebra: separate tumor nodule(s) in a different ipsilateral lobe
N1	Ipsilateral peribroncheal, ipsilateral hilar
N2	Sub carinal, ipsilateral mediastinal
N3	Contra lateral mediastinal or hilar, scalene or supraclavicular
M1	Distant metastasis
M1a	Separate tumor nodule (s) in a contra-lateral lobe; pleural nodules or malignant pleural or pericardial effusion
M1b	Distant metastasis

Table 2. NSCLC Staging, UICC 7. Edition:

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a, b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a, b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a, b, T2a, b	N2	M0
	T3	N1, N2	M0
	T4	N0, N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

Table 3. ECOG Performance Status (PS) *

Grade	ECOG
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 self care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.
5	Dead

*As published I Am.J.Clin.Oncol: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982 and credited to the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

2.2 Surgery

There was no effective treatment of lung cancer in the first half of the 20th century. The American surgeon Evarts Graham performed the first successful pneumonectomy in 1933. The patient, a 48-year-old physician who had undifferentiated squamous cell carcinoma of the left upper lung, recovered completely and went on to practice obstetrics and gynecology for more than twenty years[45].

In all the years since, surgical resection for lung cancer has been the mainstay of curative treatment. However, the typical lack of early symptoms tend to entail that the disease is discovered too late too operate. During the period 1993 - 2002 the resection rate for lunge cancer in Norway was only 16.4 %. Among these the observed survival at 5 years was 40.9% [46].

During the last 15 years, much work has been done to increase the surgical rate and improve the postoperative survival the last fifteen years. In a recent review of the

Norwegian trends of lung cancer surgery, Strand et al found that (excluding those who died within 30 days of the operation) the lung cancer survival was significantly improved from 1993 to 2007[47]. The operations had been centralized from 24 to 13 institutions; the national resection rate increased from 16 to 19%, but with large variations between the counties. The proportion of pneumonectomies was reduced from 27 to 15% and the one-year survival rate increased from 73 to 82%. However, the waiting time from diagnose to surgery had increased from 29 to 40 days.

In the last five years we have seen a stronger awareness around diagnostic workup and staging of lung cancer, and according to the new national guidelines, patients are to get treatment within 20 days of referral to a specialist[48].

2.3 Radiotherapy

The beneficial effect of X-rays on cancer cells has been known for more than hundred years, as have the detrimental effect on healthy tissue. The technical difficulties of balancing the two effects have represented the main obstacle in the development of effective radiotherapy. Planning and monitoring radiotherapy also requires adequate tools for diagnosing and measuring the extent of disease. For many years chest x-ray was the only mean available. As such it was a crude and inadequate instrument for a disease characterized by diverse growth and metastases to organs such as the brain, adrenal glands and the skeleton [49].

The Germans experimented with varying doses of radiotherapy in the years up to 1920. The concept of fractionated protracted radiation was developed in France before the Second World War. In the years during and after the war medical physics was further developed in Great Britain, where radiation oncology became part of the medical

establishment and the need for carefully controlled randomized clinical trials was first

recognized. However, it was not until the 1970s, with the introduction of CT scanning and

the first international guidelines on volume and dosage, that the use of common concepts

and procedures, as well as comparison of results became possible[50,51]. In the latter part of

the last century we have seen the development of radiation oncology as a separate

discipline, with a proliferation of clinical trials and a revolution in medical physics and

computer-controlled technology.

In the last twenty years we have gained more insight into the molecular effects of

ionizing radiation. The effect is primarily thought to be by mediating the programmed cell

death (apoptosis) of tumor clonogens, also known as stem cells. In addition, micro vascular

damage appears to be a key mechanism in tumor response to radiation [52].

Some concepts are relevant for our discussion:

Fractionation gives the strength and the number of single doses radiotherapy

per time unit. Normally one radiation dose per day.

Hyperfractionation is the process of dividing the total radiation dose to

smaller single doses, usually in order to spare normal tissue. Hyperfractionation may allow

an increase in total dose. Normally 2-3 radiation doses per day).

Accelerated fractionation allows the radiation to compensate for

repopulation, i.e. to kill the faster proliferating tumor cells, while normal cells, which

proliferate at a slower rate, will have time to repair before replication.

Chemo radiotherapy (CRT) is the combination of chemotherapy and

radiotherapy, also called chemoradiation. By switching from a **sequential** to a **concurrent**

(simultaneous) delivery, a synergistic effect of chemo- and radio-sensitization of the

cancerous tissue is achieved, mainly through increased inhibition of DNA-repair mechanisms.

2.4 Chemotherapy

The pharmaceutical industry emerged in the late 19th and the beginning of the 20th century. Cancer research accelerated in the years following the Second World War, and many different molecules and chemical compounds were launched and tested as drugs. The initial development of chemotherapy was associated with leukaemia among children: By counting blood cells in the microscope it was possible to measure the therapeutic effect of the different compounds and follow the subsequent course of the disease[53]. No equivalent tool to follow the course of lung cancer existed. Chest x-ray was too crude and inadequate.

Not until late in the nineteen seventies, with the introduction of cisplatin, was chemotherapy adopted as a routine in the treatment of solid tumors. By this time the development of computer tomography (CT) also made it possible to follow the progression of solid tumors, with high-resolution images of the tumor in three dimensions. [50].

2.5 Cisplatin

Barnett Rosenberg was a microbiologist at Michigan State University. His main research interest focused on the behavior of bacteria. One day in 1964 he put a suspension of Eschericha Coli between to platinum electrodes in a strong electrical field. He wanted to see how an electrical field might interfere on the growth process of the bacteria. When he turned on the current something strange happened: Not only was the cell division inhibited, in addition the rod-like bacteria grew into long filaments, up to three hundred times their normal length [54].

Rosenberg knew that E. Coli cells became filamentous under the influence of certain anti cancer drugs. It was not the electrical field itself that produced the changes; he found

the effect required the combination of components in the suspension and the platinum electrodes[55].

Two years later he managed to isolate and identify the active substance. It was cis-dichlorodiammine-platinum, also known as cisplatin: A heavy metal complex first described in the 1800s and known to be poisonous. With the help of other scientists Rosenberg tried cisplatin in a mouse tumor model system and found it completely inhibited the development of solid Sarcoma - 180 tumor[56].

With some problems he managed to find clinicians willing to try cisplatin on humans and the results were encouraging. Soon Lawrence Einhorn and co-workers from Indiana University started studying the effects on testicular cancer. In 1977 the first results were published, demonstrating a change in cure rate for disseminated testicular cancer from 5 to 60% by the use of cisplatin[57,58].

The U.S. Food & Drug Administration approved the drug in 1978 and by the early 1980s cisplatin was introduced in Norway. Now, thirty years later, more than 80% of testicular cancers are cured despite having metastases at the time of diagnosis, thanks to platinum based chemotherapy[59].

Cisplatin produces cross-links between DNA-molecules and prevents DNA strand division and replication of cancer cells. The germinal cells lack several of the enzymes that commonly repair DNA-damage. They are primed for apoptosis. In contrast, the tumor cells in NSCLC are able to repair the detrimental effect of the chemotherapy. This probably explains why the impressing effect on testicular cancers cannot be transferred to other solid tumors[60]. After the initial cisplatin treatment, NSCLC often relapse with drug-resistant disease and few patients survive for more than two years.

2.6 Carboplatin

Prior to modern and more effective treatment of therapy induced emesis in the early 1990s, the side effects of cisplatin were debilitating. Nausea and vomiting came in waves and resulted in weight loss and impaired general condition, often hindering the patient in completing the treatment. In addition, effects such as nerve and kidney damage, as well as hearing loss, occurred. Rosenberg approached various companies and gathered a team to develop drugs with less toxicity. The resulting carboplatin was designed with two bidentate dicarboxylate ligands substituting the two chloride ligands of cisplatinum. The reactivity and the degradation into potentially toxic derivatives were slowed down and the side effects became less prominent[61].

Carboplatin was approved in Europe in 1986. Since then, the two drugs have been compared in many trials. The latest Cochran review compared 10 trials with 5017 patients, where cisplatin and carboplatin were used in combination with a third-generation cytotoxic drug, in the treatment of advanced NSCLC. In conclusion, the two drugs were found equally effective at prolonging survival, but the toxicity profile was different[62].

The nephrotoxic effects of Cisplatin are dose limiting, but hydration with normal saline will effectively decrease the toxicity. In contrast, Carboplatin is excreted unchanged in the kidneys, the clearance approximately 90% after 24 hours. Because the clearance is linearly related to the glomerular filtration rate, renal impairment of any degree will increase the plasma level of carboplatin. This, in turn, may lead to other systemic toxicities[61].

By definition a drug's area under the concentration-time curve (AUC) is the ratio of the amount of the drug that reaches the systemic circulation and the clearance of the drug[63]. Accordingly, the AUC typically correlates with the toxicity and the clinical efficacy of the drug. Calvert et al have derived a formula to calculate the dose of carboplatin necessary to

achieve a particular AUC. This formula has been validated in a prospective study and has been shown to predict AUCs with a margin of error of approximately 15%[64].

The dose-limiting toxicity of carboplatin is myelosuppression, particularly thrombocytopenia and leukopenia. It is cumulative in nature and the degree of myelosuppresion correlates with the clearance in the kidneys. The serious nausea and vomiting, often seen in the use of cisplatin, both immediate and delayed, are negligent in relation to carboplatin. The neurotoxicity and the incidence of neurological side effects among patients receiving carboplatin is reported to be 1-3 %[61].

2.7 Vinorelbine

The instability of the genome is recognized as a key characteristic of malignant tumors. Mutations in so-called driver genes can alter cell behavior and contribute to how cancer as a disease responds to therapy [65]. A logical consequence is that first line chemotherapy should consist of a combination of drugs, in order to prevent or delay the development of resistance to the drugs in use. A prerequisite must be that the drugs act through different molecular mechanisms. The results of several clinical trials support this view [66] [67,68].

In folklore medicine, the Madagascar periwinkle plant has been regarded useful in treatment of diabetes and diabetic ulcers. In the 1960s, while attempting to verify these properties, two alkaloids were isolated and found to have antitumor activity: vinblastine og vincristine[69].

Over time, further so-called vinca alkaloids have been isolated and tested against tumors, among them vinorelbine. All vinca alkaloids act by binding to tubulin and preventing its assembly into microtubules. This ultimately leads to a blockage of mitosis and subsequent apoptosis. Vinorelbine is a semi synthetic drug, which is metabolized in the liver and

excreted in the bile. Only major liver metastasis seems to influence the elimination and

neutropenia is the dose-limiting toxicity [70].

By the time the Conrad study was planned, several studies had demonstrated the

activity of vinorelbine against NSCLC, both as single drug; in combination with cisplatin; and

as part of a combined regimen including radiotherapy [66,71-75]. Two studies had recently

demonstrated an efficacy of oral vinorelbine similar to the intravenously administration of

the drug [72,76]. A fact of importance in the context of our study, as patients with incurable

disease prefer oral administration if possible [77].

In our study vinorelbine was chosen in the combination treatment.

2.8 Targeted Therapies

The first reports on the beneficial effect on NSCLC of so-called "tailored treatment" came in

2004. These were tyrosine kinase inhibitors specially targeting specific mutations in the

tumors[78,79]. Since then several targeted therapies designed to address specific mutations has

emerged. After 2010, patients diagnosed with NSCLC in Norway have been tested for an

increasing number of mutations, among them EGFR, EML4–ALK and KRAS gene mutations[11].

As of now only two tyrosine kinase inhibitors, erlotinib and gefitinib, are recommended as

first-line treatment in Norway, and only to non-resectable NSCLC patients with tumors

positive for EGFR mutation, until progression.

In all probability more new genome-sequencing studies will be published in the near

future, with the aim of matching the patients with therapies that best suit the particular

genetic characteristics of their tumors. Hopefully this way, the personalized treatment of

lung cancers will be increasingly more effective.

As these targeted therapies emerged after 2010, they were not discussed in relation to the treatment choices of the Conrad study.

2.9 Palliation as concept

Despite clear survival benefits, many elderly patients with advanced non-small cell lung cancer have not received chemotherapy [80,81]. On the other hand we have seen a tendency to continue chemotherapy for advanced NSCLC until very near death [82]. These contradictory courses of treatment may have several explanations: Some doctors may be reluctant to offer treatment known to give troublesome side effects, some even harbor the unwarranted assumption that elderly patients do not benefit from therapy [81,83,84]. Patients, on the other hand, may not understand that chemotherapy is unlikely to be curative, and may insist on continuing the treatment, even when chemotherapy is obviously futile [85,86].

Basically, palliative care is defined as end-of-life care. However, the World Health Organization state that palliative care 'is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy' [87].

A recently published study by Temel et al demonstrated that patients receiving early palliative care for NSCLC were in need of less aggressive care at the end of life and had prolonged survival [88].

We wanted to study a population with advanced disease and negative prognostic factors (see page 41). The chances of survival were consequently considered small. Palliation and preserving HRQOL should have the outmost priority – along with survival. The dosages of chemotherapy and radiation had to be adjusted accordingly.

3. THE INTERVENTION

3.1 Choice of Treatment Regimen

Surgery was for many years the only effective treatment of lung cancer. The limitations, however, was obvious: Surgery was not possible in advanced and metastatic disease. Sometimes locally advanced disease rendered a complete resection impossible. Other times the cancer appeared, despite apparently complete surgical resection, as distant metastases in other organs. With simple x-ray as the only mean of imaging, it was impossible to detect the full and complete extent of the disease.

The introduction of computer tomography in the 1970s and early 1980s enhanced imaging of tumors, and made disease staging according to TNM classification much more accurate. Clinical trials in the 1970s established the efficacy of radiation in patients with locally advanced NSCLC (LA-NSCLC). Still, patients experienced a high incidence of local and distant relapse. Despite escalated doses up to 80 Gy the 5-year survival rate never exceeded 10% [89].

In contrast to Small Cell lung Cancer, NSCLC responded disappointingly to early trials of chemotherapy. The response rates were 10-15 % and cytotoxic agents as cyclophosphamide, vinblastine and methotrexate were associated with worse results than best supportive care alone [50,90].

Chemotherapy in NSCLC was not fully established before 1995, when the Non-Small Cell Lung Cancer Collaborative Group published a meta-analysis using data on 9387 patients from 52 randomised clinical trials [91]. In this trial regimens containing cisplatin were significantly superior compared to no chemotherapy in locally advanced disease.

Third generation cytotoxic drugs such as vinorelbine, gemcitabine, docetaxel and paclitaxel emerged during the following two decades. When the Conrad study was planned

several trials had confirmed a modest survival benefit of platinum containing doublets on advanced NSCLC stage III, with median survival up to 7-10 months and one-year survival up to 35-40% [1,92]. Meta-analyses also indicated superior results of the platinum doublets compared to single-agent therapy [66,93]. However, data were limited for elderly and patients in poor general condition [94].

Combining chemotherapy with radiation was seen as a potential future treatment for locally advanced disease, and Table 4 show a series of randomized clinical trials (RCT) that had been published by 2006 and indicated survival benefits [95,96]. A Cochran review published by Rowell and O'Rourke in 2004, stated that the quality of reported trials was on the whole poor [97].

In 2005 Auperin published a metanalysis with a similar conclusion. The available data was insufficient to define the size of the potential treatment benefit and the optimal schedule of chemotherapy [98].

In 2006, NSCLC accounted for 75-80% of all lung cancers in Norway, stage III disease up to 40 % of these [17]. In numbers they amount to a considerable group. However, as CRT with curative intent was physically demanding, a good general condition would be prerequisite. Though most of these patients were elderly and had negative prognostic factors, experience indicated that some would achieve long time remission from more intensified treatment [99].

This was the background as the Conrad study was designed in 2006. In the studies mentioned previously the included patients were almost exclusively of PS 0-1 and quality of life was often not an issue. Considering the demographics, a palliative regimen might be highly relevant for many of these patients. Accordingly we wanted to study how the addition of fractionated palliative radiation to palliative chemotherapy affected overall survival and

Table 4. Studies prior to the Conrad Study, on which the Conrad study are based.

Reference / Design	Number patients	Characteristics	Control Experimental Arm	Treatment Design	Median Survival Months	2 year Survival %	P	HRQOL	Toxicity
Soresi (1988) RCT	95	Unresectable LA-NSCLC stage III	RT (50 Gy) versus RT (50 Gy) + Cisplatin weekly	Concurrent	11 16		NS	No	Mild
Trovo (1992) RCT	173	Unresectable NSCLC stage III	RT (45 Gy/15 versus RT (45 Gy/15 + Cisplatin daily	Concurrent	10.3 9.97		NS	No	Acceptable
Schaake-Koning (1992) RCT	331	Unresectable NSCLC stage I-II-III	RT (55 Gy) versus RT (55 Gy) + Cisplatin weekly versus RT (55 Gy) + Cisplatin daily	30 Gy/10fr/ 3 weeks rest 25 Gy/10fr Concomitant		13 19 26	0.04	No	Acceptable
Jeremic (1995) RCT	169	NSCLC stage III	HFX RT (64.8 Gy) versus HFX RT (64.8 Gy) + Carbo +EP daily versus HFX RT (64.8 Gy) + Carbo+EP daily	Hyperfractionated Concurrent every week Concurrent only 3 cures	8 18 13	25 35 27	0.003 (betw I and II)	No	Acceptable
Blanke (1995) RCT	240	Unresectable LA-NSCLC stage I- II - III	RT (60-65 Gy) versus RT (60-65 Gy) + Cisplatin	Concurrent	46 (weeks) 43 (weeks)	13 18	NS	No	
Dillman (1996) RCT	155	NSCLC stage III	RT (60 Gy) versus RT (60 Gy) & Cisplatin + Vinbl	60 Gy/30 fr Sequential	9.6 13.7	13 26	0.012	No	Moderate
Jeremic (1996) RCT	131	NSCLC stage IIIA and bulky stage IIIB	HFX RT (69.6 Gy) versus HFX RT (69.6 Gy) + Carbo + VP	Concurrent	14 22	26 43	0.021	No	Tolerable
Clamon (1999) RCT	283	Unresectable NSCLC Stage III	Cisp + Vinbl , followed by RT (60 Gy) versus RT (60 Gy)+ Carbo weekly	Induction chemo + Concurrent	13.5 13.4	26 29	NS	No	Acceptable
Ball (1999) RCT	204	Unresectabable NSCLC stage III	RT (60 Gy)/30 fr/6 weeks versus HFX RT (60 Gy)/30 fr/3 weeks versus RT (60 Gy/6 weeks) + Carbo versus HFX RT (60 Gy/3 weeks) + Carbo	Standard RT versus Concurrent RT versus Concurrent HFX RT	13.8 14.4 17.0 15.0	26 28 29 20	NS	No	Acceptable
Furuse (1999) RCT	320	Unresectable NSCLC stage III	Cisplatin+Vindesin+Mitomycin & RT (56 Gy/28 fr) versus Cisplatin+Vindesin+Mitomycin + (RT (28 Gy/14 fr) – rest – RT (28 Gy/14 fr))	Sequential Concurrent	13.3 16.5	27.4 34.6	0.04	No	Higher
Sause (2000) RCT	454	Unresectable NSCLC stage II and III	RT (60 Gy/30 fr) versus 2 mnths Cisplatin + Vinbl and RT (60 Gy) versus HFX RT (69.6 Gy /twice daily)	Sequential Hyperfractionated	11.4 13.2 12	21 32 24	0.04	No	Acceptable
Groen (2004) RCT	160	Unresectable LA-NSCLC	RT (Gy) versus RT (60 Gy) + Carbo	Concurrent	11.7 11.8	20 28	NS	Yes	Mild
Fournel (2005) RCT	205	Unresectable NSCLC stage III	Cisplatin + vinorelb and RT (66 Gy)/33 fr versus RT (66 Gy)/33 fr + concomit Cispl+ EP and 2 consolidating cycles Cisplatin +EP	Sequential Concurrent	14.5 16.3	26.5 39.3	NS	No	Higher
Huber (2006) RCT	303	Inoperable NSCLC stage III	Induction 2 cycles Carbo + Paclitaxel and RT (60 Gy) versus RT (60Gy) / 32 fr + Cisplatin/paclitaxel	After induction Concurrent	14.1 18.7		NS	No	Mild
Gouda (2006) RCT	60	NSCLC stage III	RT (60 Gy) versus RT (60 Gy) + Carbo + Paclitaxel versus Carbo + Paclitaxel + RT (60 Gy) + Ca+ Paclitaxel	Concurrent Induction and Concurrent		40	0.039	No	Tolerable

HRQOL in patients with non-resectable stage III LA-NSCLC with negative prognostic factors.

Based on earlier studies, factors such as tumor size > 8cm, PS 2 and weight loss ≥ 10% last six months before diagnosis were considered negative prognostic factors [100].

3.2 Chemotherapy

In combining chemo- and radiotherapy, several considerations should be taken when selecting the optimal chemotherapeutic agents: The drug(s) should ensure efficacy against NSCLC, as well as having a sensitizing effect of radiation, without inducing too much toxicity.

Non-platinum based chemotherapy was not considered an option. Three randomized studies had been published in the nineties, comparing CRT containing non-platinum based chemotherapy versus radiation alone, without survival advantage [89,101,102].

Our aim was palliation, and in this context carboplatin had major advantages over cisplatin. Not only was Carboplatin less toxic, but it also required less elaborate hydration while retaining acceptable survival benefits [71,103].

In the choice of a chemotherapeutic platinumbased doublet, no particular combination with a third generation cytotoxic drug was found to be superior in relation to survival[74,104]. Consequently, the ability to maintain low toxicity and ease of administration had to be decisive. Many cytotoxic drugs have, in addition to a systemic anticancer effect, also an ability to sensitize or reinforce the effects of radiation. In a curative setting this may be a benefit. In a palliative setting it may be a burden. For example, the considerable radiosensitizing properties of gemzitabine, with subsequent high toxicity, ruled the compound unsuitable for our trial [73,105].

Vinorelbine, however, was available as an oral formulation and two phase II studies had found the oral and the intravenous administrations to be comparable, both in terms of

activity and tolerability [72,76]. In the years up to 2006, the NLCG had conducted two RCTs concerning advanced NSCLC and gained experience with intravenously carboplatin and vinorelbine [1,106]. In addition patients have a preference for oral chemotherapy rather than intravenous [107]. Accordingly we settled for the combination of intravenously carboplatin and oral vinorelbine as platinum doublet in the Conrad study.

3.3 Radiation

Radical Radiation has been established as the treatment of choice for patients with LA-NSCLC with good PS, provided tumors are possible to include in an appropriate radiation field. Throughout the 1990s and later, more fractionated regimens appeared to increase the survival[108]. The publication of the (CALGB) 8433 trial in 1996 established the value of adding induction chemotherapy to radiation [95]. However, the optimal course of treatment, whether the schedule of CRT was to be concurrent or sequential, remained unresolved. In this context **concurrent** was defined as chemotherapy given during radiotherapy and **sequential** as chemotherapy given before or after a course of radiotherapy.

Based on the unsatisfactory studies described in the 2004 Cochran review, Rowell concluded that sequential CRT remained the standard of care in patients with stage III NSCLC [97]. However, during the years preceding the start of Conrad we saw the emergence of several studies documenting a survival benefit of concurrent treatment (See Table 4). Accordingly, we settled for a concurrent model, where the radiotherapy was to start simultaneously or shortly after initiation of the second chemotherapy course.

In order to preserve the practical approach in a palliative setting we wanted a simple radiation regimen. A highly fractionated regimen could be exhausting for the patients and doses around 60 Gy were associated with increased side effects [108].

In 2004 Sundstrøm et al had published, on behalf of NLCG, a study of patients with advanced NSCLC who received radiotherapy as 42 Gy/15 fractions, compared to a more normally fractionated regimen (50 Gy/25 fractions) [109]. The authors found no significant difference in median survival between the regimens. Biologically, 42Gy/15 fractions compares to about 50 Gy in 2 Gy daily fractions. Radiotherapy consisting of 42Gy/15 fractions is considered a slightly hypofractionated radiation regimen, but it has been used safely in Norway since the 1980s[110].

As this regimen was already established, it would allow the treatment planning and dosimetry to be conducted according to the participating institution's standard routines. Accordingly we chose this regimen to be the radiation offered in the experimental arm of the Conrad study.

4. HEALTH RELATED QUALITY OF LIFE

The aim of the treatment in the Conrad study was not cure the cancer, but to extend life without impairing the quality of life. Consequently, assessed quality of life would be a natural endpoint, in addition to survival.

WHO define health as "a state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity". The term *Health Related Quality of Life* (HRQoL) is used to distinguish health related aspects of Quality of Life from those unrelated, for example unemployment and financial difficulties. The European Organization for Research and Treatment of Cancer (EORTC) has worked, since the 1980s, to develop reliable instruments to measure the health related quality of life of cancer patients participating in trials[111]. As health care providers underestimate symptom intensities of cancer patients, the most accurate instruments are questionnaires completed by the patients themselves[112].

The first version of EORTC Quality of Life Questionnaire-Core 30 (QLQ-C30) came in 1987, but the questionnaire has been revised several times and was eventually supplemented with the Lung Cancer module (LC-13). These are now the most frequently employed[113]. In the Conrad study we used Norwegian translations of QLQ-C30 and LC-13, which have been translated, validated and used in several studies conducted by the NLCG [1,106,114].

Combined, the QLQ-C30 and LC-13 consist of 43 questions and measures fundamental aspects relevant to cancer patients (Table 5). Each question is rated on a scale from 1 (Not at all) to 4 (Very much). The two questions concerning global QOL are rated on a scale from 1 (Very poor) to 7 (Excellent)[115].

The questionnaires are found in the Appendix A.

Table 5. Content of the EORTC QLQ C30 plus LC-13

	No. of items	Question no.
QLQ-C30		
Global Health Status/QOL		
Global QOL	2	29, 30
Functional scales		
Physical function	5	1 to 5
Role function	2	6, 7
Emotional function	4	21 to 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

5. AIMS OF THE THESIS

The present thesis aimed to investigate outcome in patients with non-resectable locally advanced non-small cell lung cancer and negative prognostic factors receiving two different palliative treatment regimens within a randomized national phase III study.

More specified the aims were:

- Examine whether there was any difference in overall survival, health related quality of life and toxicity between patients treated with palliative chemotherapy or palliative CRT (article 1).

- Examine how tumor size influenced the treatment outcomes following palliative CRT versus palliative chemotherapy alone (article 2).

- Examine the treatment outcomes of elderly (≥ 70 years) versus younger patients (< 70 years) following palliative CRT versus palliative chemotherapy alone (article 3).

6. METHODS AND MATERIAL

6.1 Study Design

The use of randomization in clinical trials was introduced after the Second World War, in conjunction with testing antibiotics against infections. According to Sir Richard Doll, standard treatments at that time were passed from one textbook to another without ever being adequately evaluated[116].

In a study with random allocation, the differences between treatment groups should behave like the differences between random samples. The observed behavior in the control group will be an expression of the expected. If the treatment has no effect, the observed behavior in the treatment group will be similar to the control group.

In 1946 the British Government bought 50 kg of a new drug called Streptomycin, said to be effective against tuberculosis. The Medical Research Council (MRC) was given the task of conducting a clinical trial to test the drug on humans. Professor Bradford Hill, chief of the Statistical Unit at the Council, decided to use a randomized approach. The resulting trial is later considered to be the first Randomized Controlled Trial[117].

Great care was given to the randomizing process, by reference to a statistical series based on random sampling numbers, prepared by Professor Hill. Otherwise, the statistics of the MRC report, published in 1948, were simple and consisted mostly of calculations as addition and percentages. Only 109 patients were included, but the patients allocated to Streptomycin-treatment had a remarkably greater improvement, and less tendency to relapse and death[118]. The results were taken as proofs of a Streptomycin effect.

In the Conrad study the patients were randomized in a similar way: Respiratory Physicians from hospitals all over Norway reported new patients, eligible for inclusion, to the Clinical Cancer Research Office at the University Hospital of North Norway in Tromsø. A

computer randomized the patients to either chemotherapy alone or to CRT and the result communicated by phone or fax.

The Conrad study was planned during the spring 2006 and approved by the Regional Ethical Committee, the Norwegian Social Data Services, and the Norwegian Medicines Agency and registered in ISRCTN (ISRCTN63778716 – Concomitant chemotherapy for treatment of non-small-cell lung cancer — The Conrad study).

6.2 Patients and Sample Size

The Conrad Study was launched at the annual national gathering of oncology professionals in Norway, Onkologisk Forum, in November 2006. Members of NLCG were encouraged to include patients, according to the following criteria:

- Histologically or cytologically confirmed NSCLC
- Stage IIIA and IIIB, not eligibly for treatment with curative intention
- WHO PS 0, 1 or 2
- 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 < 2 and ALAT < 3 x upper reference limit
- Patients should not be pregnant or breast-feeding and had to use contraception
- Ability to understand written and verbal information
- Written informed consent

The patients were to have one or more of the following negative prognostic factors:

- Tumor size ≥ 8 cm, and/or
- ECOG Performance status 2, and/or
- Weight loss ≥ 10% the last 6 months.

The patients were staged by CT Thorax and upper abdomen only.

Based on the Ving study, we expected a 1-year survival of about 30% (p_s= 0,3) in the chemotherapy arm[106]. In the CRT-arm we expected a 1-year survival of about 45% (p_n=0,45). Provided a significance level of 5% and a statistical power of 80%, the sample size (n= number in each group) is given by the formula[119]:

$$n = \frac{p_n \cdot (1 - p_n) + p_s(1 - p_s)}{(p_n - p_s)^2} \cdot c = \frac{0.45 \cdot 0.55 + 0.3 \cdot 0.7}{(0,15)^2} \cdot 7.9 = 161$$

Where c = 7.9 for a 80% power.

To adjust for expected loss to follow-up, we planned to enroll 175 patients in each arm, a total of 350 patients. Based on our earlier experiences involving monomodality trials we expected to include the planned 350 patients in three years, i.e. 13 patients per month[1,106].

However, the inclusion progressed in a slower rate than expected, and the Regional Ethical Committee accepted an extension of the inclusion period. The protocol was amended accordingly. After five years, in November 2011, the Norwegian Lung Cancer Study Group decided to end patient inclusion due to slow patient accrual. By that time, a total of 191 patients were randomized from 25 hospitals all over the country.

Given the survival differences we found between treatment-arms, presented in Paper 1, calculated power estimates for the included 191 patients are 75% and 97%, respectively for the 1-year and 2-year survival.

Three patients, who in retrospect did not fulfill the inclusion criteria, had to be excluded (Figure 5, Consort diagram[120]). Patients with negative prognostic factors were distributed as in Table 6.

Figure 5: CONSORT Flow diagram for the Conrad Study

Randomised (N=191)

Chemotherapy (N=95)

Chemoradiotherapy (N=96)

Eligible patients (N=94), excluded:
 - stage IV at randomisation

Eligible patients (N=94), excluded:
 - synchronous lung+uterine cancers
 - neuroendocrin tumour

Number Completed Chemotherapy cycles:

0-1	-	4 patients
2-3	-	19 patients
All 4	-	71 patients

Number Completed Chemotherapy cycles:

0 – 1	-	3 patients
2 – 3	-	18 patients
All 4	-	73 patients

Number completed radiotherapy fractions:

0	-	5 patients
6	-	1 patients
10 – 14	-	4 patients
All 15	-	84 patients

Discontinued treatment (N=23)

Disease progression during treatment	14
Treatment toxicity	2
Intercurrent disease	1
Patient wish	2
Other reasons	4
Death from aortic aneurysm	1
Found dead at home	1
Died of pneumonia during treatment	1
Died of COPD exacerbation	1

Discontinued treatment (N=23)

Disease progression during treatment	4
Treatment toxicity	10
Intercurrent disease	2
Patient wish	2
Other reasons	5
Pulmectomy after 2 cures +rad	1
Death related to fract. colli femori	1
Death of Resp. failure after Chemo	1
Death of Myocardial Infarction	1
Sudden death during Radiation	1

Analyzed:

Survival	N=94
Toxicity	see Table 2
Health Related QoL	N=93

Analyzed:

Survival	N=94
Toxicity	see Table 2
Health Related QoL	N=91

Table 6. Distribution of Patients with Negative Prognostic Factors and Randomization

Treatment group	Chemo	CRT	Total
PS 2	19 (20.2)	21 (22.3)	40 (21.3)
Tumor ≥ 8 cm	45 (47.9)	56 (59.6)	101 (53.7)
Weight loss ≥ 10% last 6 months	31 (33.0)	39 (41.5)	70 (37.2)
Total	95	116	

Values are expressed as numbers (% in each group)

6.3 Study Treatment

All participants were to receive four courses of chemotherapy in 3-week intervals: Vinorelbin capsules 60 mg/m2 orally day 1 and day 8 and intravenous carboplatin [area under the curve (AUC)=5 (Calvert's formula)] administered during one hour day 1[64]. Patients > 75 years of age received 75 % of estimated chemotherapy dose. To prevent chemotherapy-induced nausea and vomiting all patients received premedication with intravenous 5-HT3 antagonists and dexamethasone day one and orally the two following days. On day 8 they received oral 5-HT3 antagonists only.

Table 7. Trial Plan

Week	-1-0	0	3	6	9	12	20	28	36	44	52
	Random-izing	1. treatm course	2. treatm course	3. treatm course	4. treatm course	Follow up	Follow up	Follow up	Follow up	Follow up	Follow up
				Radiation							
CRF	1+2	3	4	5+6	7	8+9	10	11	12	13	14
Biochemistry	X		X	X	X	X	X	X	X	X	X
Chest X-ray	X		X	X	X	X	X	X	X	X	X
CT Thorax +up abd	X					X	In field relapse				
Physiical examn	X	X	X	X	X	X	X	X	X	X	X

Before each chemotherapy course, the absolute neutrophil count (ANC) had to be >1.0 x109/L and platelet > 75 x 109/L. The doses were reduced by 25 % if ANC was 1.0-1.49 x 109/L, platelets were 75-99 x 109/L, or preceding nadir ANC <0.5x109/L. Doses were reduced by 50% if the nadir platelet count was <50x109/L, and continued throughout the treatment period. If a treatment course was delayed by more than 21 days, chemotherapy was to be discontinued. If grade 3-4 toxicity or neutropenic infections occurred, chemotherapy was to be postponed until the patients fully recovered, clinically and/or hematological. Subsequent doses were reduced by 25%. Study treatment was discontinued in cases of disease progression, unacceptable toxicity, or at patient request.

In the CRT arm, the radiotherapy was given as 42 Gy/15 fractions. Treatment planning was according to each institution's procedure, but two opposing fields were recommended.

The radiotherapy was to start simultaneously or shortly after initiation of the second chemotherapy course.

In addition, patients received best supportive care according to individual needs. If patients allocated to the chemotherapy alone arm were in need of palliative radiotherapy to the thorax, a hypofractionated regimen of 17 Gy/2 fractions (one week apart) was recommended. If skeletal metastases developed, one 8 Gy/1 fraction was recommended.

After completion of the treatment period, every study site provided a summary of the radiation and the chemotherapy given for each patient, as well as reasons for any discontinuation of the treatment. During follow up visits (weeks 12, 20, 28, 36, 44 and 52) PS and possible progression were registered.

6.4 Health related Quality of Life

The HRQOL questionnaires were distributed to the participants at randomization and at the time of every chemotherapy course, as well as every 8th week after the end of the treatment period, until one year after randomization. Reminders were mailed if questionnaires were not returned within 14 days.

The results of the questionnaires were processed according to the EORTC manual[115]: The raw scores of each item transformed linearly to a scale ranging from 0 to 100. A higher score for symptom domains indicate more pronounced symptoms, whereas higher score for the functional domains indicate better function.

Missing or partially completed forms may represent a problem when working with questionnaires. A limit for proportion of responders required for considering a study valid has not been established. A compliance of more than 80% has been suggested. One established way of compensating for missing forms and missing items is to replace the missing with imputed. We chose to calculate the mean scores from the reported values only.

The HRQOL questionnaires were analyzed according to the EORTC scoring manuals[111,115]. Mean scores were calculated from the reported scores only. The mean changes were calculated by subtracting the baseline score from the score at each designated time point during and after the treatment for each study arm. The scores were compared using ANOVA and the non-parametric Mann–Whitney U-test. A mean change of 10 points was considered clinically relevant and significant[121,122].

6.5 Toxicity

In order to report and record the adverse effects of cancer treatment in a uniform manner, the US National Cancer Institute has produced The Common Terminology Criteria for

Adverse Events. These have been adopted by EORTC and revised several times. Most cancer trials in the western world encode their observations based on this system.

In the Conrad study, blood samples and information about esophagitis were obtained before each chemotherapy course (weeks 0, 3, 6 and 9). Every study site provided a registration of hematological toxicity and esophagitis after completion of the treatment period. More laboratory tests were taken if indicated. Hematological and non-hematological toxicities were then assessed using the Common Terminology Criteria of Adverse Events version 3.0. See Table 8.

Table 8. Excerpts from The Common Terminology Criteria for Adverse Events v 3.0 (NCI. 2006)

Adverse Event	Grade				
	1	2	3	4	5
Hemoglobin	<LLN – 10 g/dL	< 10.0 – 8.0 g/dL	< 8.0 – 6.5 g/dL	< 6.5 g/dL	Death
Neutrophils/ Granulocytes	<LLN – 1.5 x 10^9/L	< 1.5 – 1.0 x 10^9/L	< 1.0 – 0.5 x 10^9/L	< 0.5 x 10^9/L	Death
Platelets	< LLN – 75.0 x 10^9/L	< 75.0 – 50.0 x 10^9/L	< 50.0 – 25.0 x 10^9/L	< 25.0 x 10^9/L	Death
Esophagitis	Asymptomatic pathologic, radiographic, or endoscopic findings only	Symptomatic; altered Eating/swallowing (e.g., Altered dietary habits, Oral supplements); IV Fluids indicated <24 hrs	Symptomatic and Severely altered Eating/swallowing (e.g., Inadequate oral caloric or Fluid intake); IV fluids, Tube feedings, or TPN indicated ≥24 hrs	Life-threatening	Death

6.6 Statistical considerations

Throughout the last century, the development of modern epidemiology was related to the research done on consequences of smoking[123]. The epidemiological methods developed and used in the quest for the causal relationship between smoking and lung cancer has since been considered templates for similar studies up to this day, the Conrad study included[124].

In 1947, the Health Ministry of Great Britain gave MRC the task of finding the explanation for what they considered a lung cancer epidemic. Richard Doll, who was chosen for the job, was a medical doctor, which turned out to be of some importance. In the years after WWII, smoking was deeply entrenched in the British society and statistics were still considered with skepticism among a great part of the medical profession. The results – regardless of what they were – would be more acceptable coming from a medical doctor than from a statistician. If smoking were an issue this would not only have health political implications: The Imperial Tobacco Company alone generated over 14 per cent of the British government's tax revenues at the time[39].

When we investigate possible associations between various factors and the development of a disease we use so-called observational study methods. In the tradition of the day, Doll chose a retrospective case-control investigation.

Three different groups of patients admitted to London hospitals in a certain period were interviewed about their job histories, their environment, lifestyles and their smoking histories. The case group, diagnosed with lung cancer (709 patients), was compared to a control group with cancer in other locations (512 (patients) and a control group with diseases other than cancer (709 patients)[125].

Doll stratified the exposure to find how lung cancer varied according to smoking habits like the number of cigarettes smoked and pipe versus cigarettes. Doll calculated confidence intervals, to define the range that with 95% probability was to contain the true value of the observed factor. Most importantly: Doll and Hill used chi-square test to find out if any of the observed differences between the groups were real or just chance variations.

Even though it is considered essential that an observed association does not indicate a causal relation between variables[126], Doll and Hill were able to conclude that cigarette

smoking was "a factor, and an important factor, in the production of carcinoma of the lung"[125]. Convinced by his own findings, Doll stopped smoking himself.

In the Conrad study we have used similar statistical methods: The patients were stratified by performance status, age and sex. We used chi-square tests, both to ensure that the two treatment arms were similar in characteristics, and to look for significant differences in toxicity depending on the treatment given. Where Doll and Hill used paper, pencil and a slide rule in the analysis and to produce tables; we used a computer and a statistical software package called SPSS.

As expected, Hill and Doll were met by a lot of skepticism and criticism. The most intense from Ronald A. Fisher, an "inveterate pipe smoker" and the worlds leading theoretical statistician at the time[127]. Fisher had been a pioneer in the use of randomization in his agricultural studies, and has given name to Fishers Exact test, which we have used to compare the toxicity-data. He introduced the term "variance" in 1918 and pioneered the development of Analysis of Variance (ANOVA), a set of tests of which we have used one to compare the group means developed from the HRQoL scores[128].

Median time to progression and overall survival were compared using the Kaplan–Meier method and the Log-rank test, based on intention to treat[129]. The date of death was chosen as the date of progression if no other information was available. The Cox proportional hazards method was used to calculate hazard ratios (HR) in the multivariate analyses adjusting for the baseline characteristics.

In order to confront the criticism, Doll and Hill implemented, in the years that followed, a larger prospective cohort study among members of the medical profession in the United Kingdom[130]. This study confirmed the strong association between smoking and lung

cancer, and even suggested an association between smoking and coronary thrombosis. This time the findings convinced even Doll's wife. She finally quit smoking.

Sir Ronald A. Fisher never did.

6.7 Sub group Analyses

The last two studies in this thesis are subgroup analyses of the initial RCT.

Subgroup analyses are associated with problems that needs to be discussed: Trials are seldom powered with subgroup analyses in mind; subgroup analyses are particularly unreliable; they should not be over-interpreted and any apparent lack of effect should be regarded with caution[131].

In a recent review, published in BMJ, Sun et al proposed ten criteria to be used in assessing the credibility of subgroup effects[132]:

Design

- Was the subgroup variable a baseline characteristic?
- Was the subgroup variable a stratification factor at randomization?
- Was the subgroup hypothesis specified a priori?
- Was the subgroup analysis one of a small number of subgroup hypotheses tested (≤5)?

Analysis

- Was the test of interaction significant (interaction P<0.05)?
- Was the significant interaction effect independent, if there were multiple significant interactions?

Context

- Was the direction of subgroup effect correctly pre specified?
- Was the subgroup effect consistent with evidence from previous related studies?
- Was the subgroup effect consistent across related outcomes?
- Were there any indirect evidence to support the apparent subgroup effect—for example, biological rationale, laboratory tests, and animal studies?

In the BMJ editorial accompanying the article by Sun et al, Oxman emphasized the need to consider each subgroup analysis in the context of the original study: *"Are the results of the subgroup analysis and the overall analysis different enough that they would lead to different decisions?"* he asks*. " If the answer is no, the detailed criteria do not need to be applied. "*[133]

In 2005 Peter Rothwell and colleagues wrote a series of articles in Lancet concerning evidence-based practice and the individual. One of the articles was dedicated to subgroup analyses and the application of these[134]. Rothwell discussed the usefulness versus the problems and emphasized the following situations where subgroup analyses should be considered: If there are potentially large differences between groups in the risk of a poor outcome with or without treatment; and if there are doubts about benefit in specific groups, such as elderly people, which are leading to potentially inappropriate under treatment[134].

The two subgroup-analyses presented in this thesis do satisfy most, but not all the criteria set up by Sun et al. However, more importantly, they do satisfy the considerations maintained by Oxman and Rothwell. Accordingly, we consider the findings important and worthy of publication.

7. RESULTS

7.1 Paper 1

This is the main report of the Randomized Clinical Trial.

In the treatment arms, 75.5% (chemotherapy alone) and 77.7% (CRT) completed all four chemotherapy courses. Eighty-nine percent of patients in the CRT arm completed the radiotherapy. The median start times for the second, third, and fourth chemotherapy course were day 22, day 44, and day 68. In the CRT arm, the median radiation start and termination times were day 24 and day 44, respectively.

Reasons for discontinuing therapy differed clearly between the treatment arms. In the chemotherapy-alone arm, 14 of the 23 patients stopped chemotherapy prematurely due to disease progression, whereas in the CRT arm 10 of the 23 stopped treatment because of toxicity.

The median percentages of completed questionnaires the first six months after randomization were 84.0 in the chemotherapy arm and 85.5 in the CRT arm. The percentage of responders declined in the last six months of the observation period (median 67.0% versus 75.0%, respectively).

The median overall survival was significantly longer in the CRT arm than in the chemotherapy-alone arm, with 12.6 and 9.7 months, respectively ($P < 0.001$). One-year survival was 34.0% and 53.2% ($P < 0.01$), and two-year survival 27.7% and 7.4% ($P < 0.01$), respectively. In a multivariate analysis, only PS (except for treatment) were found to have significant impact on survival: HR =1.810 for PS 0-1 versus 2 (CI 1.23 – 2.67, p=0.003).

During the treatment period, the patients in the CRT arm recorded a significant temporary worsening in physical and social functioning, as well as dysphagia. However, post radiotherapy the values returned to a level near baseline. The patients receiving

chemotherapy alone experienced a significant and clinically relevant decline in physical and social function, as well as global HRQOL following the end of the treatment period.

More than 85% of the patients receiving CRT reported various degrees of esophagitis, but none reported grade 4. Neutropenia was somewhat more pronounced (P = 0.258) in the CRT arm and the number of infections related to leukopenia was somewhat higher (P = 0.172). There were also more hospital admissions related to side effects (P < 0.05) reported among the patients receiving CRT.

More patients in the chemotherapy arm received later supplemental radiation than in the CRT arm, 58.0% versus 31.2%, respectively (P < 0.05). Correspondingly, 43.7% in the chemotherapy arm and 24.7% in the CRT arm received supplemental chemotherapy (P < 0.05).

7.2 Paper 2

This subset-study examines how tumor size influenced the treatment outcomes in the Conrad study.

Of the 188 eligible patients in the Conrad study, seventy-six patients had tumors ≤ 7 cm and 108 had tumors > 7 cm. Information about tumor size was missing for 4 patients.

In the group of smaller tumors, all patients randomized to CRT completed radiotherapy. Among patients with tumors > 7 cm randomized to CRT, three did not receive radiotherapy, one due to significantly reduced PS after initial chemotherapy. The mean number of fractions was 13.6 of the planned 15 in this group. There was no significant difference in number of chemotherapy courses between the CRT-groups, regardless of tumor size (mean number = 3.6).

CRT provided significantly better local control when compared to chemotherapy alone in the tumor > 7 cm group, with 41 % initial recurrence in the lungs versus 68 %, respectively (p = 0.01). The need for additional radiotherapy among those treated with chemotherapy alone, was significantly increased in the > 7 cm group.

Among the patients with large tumors, the median survival was 13.4 months in the CRT group versus 9.7 in the chemotherapy group (p=0.001). One year survival in the group with tumors > 7 cm was significantly increased among the patients receiving CRT, compared to the patient receiving chemotherapy alone (55.9% versus 32.7 %, p=0.001, respectively). The 2-year overall survival among patients with tumors > 7 cm increased from 6.1% to 32% (P=0.001) with the addition of concurrent radiotherapy.

In a multivariate analysis, only PS and tumor size were found to have significant impact on survival: HR =1.835 for PS 0-1 versus 2 (CI 1.26 – 2.67, p =0.002) and HR=0.937 (0.881-0.996, p =0.037), respectively. In order not to loose information, tumor size was not dichotomized in this analysis.

The incidence of esophagitis was similar for the two groups receiving CRT, regardless of tumor size.

During the treatment period, patients receiving CRT recorded a temporal worsening in physical and social functioning before returning to baseline levels, regardless of tumor size. All groups experienced a certain decline in physical and social function at the end of the observational period, but the decline was significantly more pronounced among the patients with tumors >7 cm who did not receive CRT.

7.3 Paper 3

In this subset study of the Conrad study, we analyzed the differences in survival and quality of life in patients older and younger than 70 years.

In the Conrad study, 42 % of the patients were ≥ 70 years, while 22 % were ≥ 75 years. We found no significant differences in administered therapy or reasons for discontinuation between the two age groups. There were significantly more men than women among the patients ≥ 70 years receiving CRT.

The one-year survival in the CRT group of patients ≥ 70 years was increased compared to the elderly receiving only chemotherapy, 44% versus 38%. The two-year survival was increased from 7.5% to 23%. Of the CRT treated patients ≥ 70 years, 15% survived 36 months. These differences in survival were not significant. Among patients ≥ 70 years, the median survival was 10.2 months in the CRT group versus 9.1 in the chemotherapy group (p=0.09).

Among the elderly receiving CRT we found significantly less hematological toxicities and less infections related to neutropenia. Esophagitis was less prominent among the elderly, though not significantly so.

Following the treatment period, the patients ≥ 70 years receiving chemotherapy alone, recorded a statistically significant and clinically relevant decline in Global HRQoL, compared to the CRT group. Regardless of age, the patients in the CRT group recorded a temporary clinical relevant worsening in Global HRQoL during the radiation period.

Following the treatment period, the social and physical functions declined among the patients receiving chemotherapy alone. These changes were most pronounced among patients ≥70 years.

Fatigue was reported as the most prominent among symptoms scores, regardless of age and treatment. Patients ≥ 70 years receiving CRT reported increasing fatigue during the treatment period, with some relief later. Those receiving chemotherapy alone reported increasing clinically relevant fatigue in the post treatment course of the disease. Dyspnea gradually increased during the observational period, becoming clinically relevant only among the elderly patients treated with chemotherapy alone. Pain was most pronounced among the younger patients, but was not recorded as clinically relevant at any point during the course of disease for patients ≥ 70 years receiving CRT. In contrast, the elderly receiving chemotherapy alone reported a return of clinically relevant pain after completing the study treatment.

Patients receiving CRT experienced a transient decline in PS immediately following treatment. The PS returned to baseline values later in the observational period. The reported PS scores indicated a continuous declining performance status for patients treated with chemotherapy alone, regardless of age.

8. DISCUSSION

8.1 Sample size & Power

We did not manage to include the planned number of patients, and this is a weakness in our study.

In many ways the conditions are optimal for conducting RCTs in Norway. Health care is publicly funded, the academic environment transparent and the national guidelines for treatment of lung cancer updated and readily available. In the RCTs conducted by NLCG through the last fifteen years, patient accrual has been impressive: Between May 2000 and March 2002 von Plessen et al included 300 patients with NSCLC stage IIIB or IV for a RCT in less than two years[1]. From October 2003 to December 2004 Helbekkmo et al accrued 444 similar patients for another study[106]. Grossly, this accounted for 40% of the appropriate patients diagnosed in Norway in the period. Based on these studies, we expected to include 352 patients with locally advanced NSCLC stage III in three years.

Poor accrual is not an unfamiliar problem. Worldwide less than 5 % of cancer patients are enrolled on clinical trials[135]. Physicians prefer, often in accordance with the patient, the most convenient treatment available. They hesitate to enroll patients with poor PS, and the patients themselves cite geographical barriers among reasons for their nonparticipation, a valid argument in a country as Norway, with a scattered population[136].

Criteria must be met: The patients are to have lung cancer of the right histology and stage; they must consent to participate, have the right performance status, sufficient kidney-functions and hematological values, as well as preserved mental capabilities. The ability to score questionnaires is an additional prerequisite when HRQoL is an endpoint. These requirements represent challenges when the median age at time of diagnose of lung cancer

is 70 years, as is the case in Norway, regardless of stage. In addition, many of the patients

suffer from serious comorbidities.

**Table 9: Patient characteristics stratified by successive 5-year diagnostic periods and sex ***

Stage		1988-1992		1993-1997		1998-2002		2003-2007	
		M	F	M	F	M	F	M	F
Localized disease	(Stage I)	40	37	38	38	29	29	25	27
Regional disease	(Stages II & III)	19	20	22	20	25	23	29	26
Metastatic disease	(Stage IV)	40	42	39	40	46	48	45	46
Unknown		1	1	1	2	1	1	1	1

*(The numbers are percentages - Adapted from Sagerup et al 2011)

In its time, the two cited studies from NLCG offered a convenient treatment regimen

to a large group of patients, consisting of simple chemotherapy combinations. In this period

the proportion of patients with regional and metastatic disease at the time of diagnosis

increased from approximately 60% to approximately 75% (Table 9)[17]. More advanced means

of staging may partly explain this shift. It is difficult to determine whether this contributed to

the disappointing accrual in our study.

In the years following the initiation of the Conrad study, PET-CT was introduced in the

Norway, adding to a more thorough work-up of lung cancer patients and may have reduced

the proportion of localized disease. However, rather than increasing the accrual, this seemed

to reduce the patient inclusion to the Conrad study. The majority of patients was included

from the middle and the northern part of Norway, where access to PET-CT was somewhat

more difficult and accordingly less used during the inclusion period (Figure 6).

Figure 6. Number of patients from each hospital included in the Conrad study
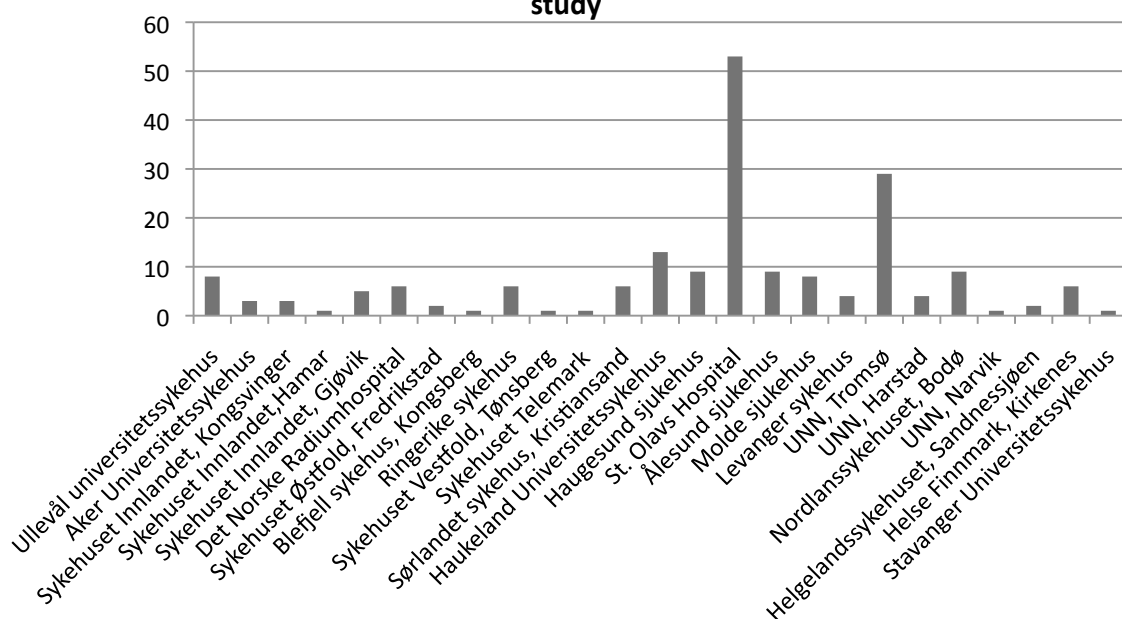
Several authors have tried to explore the obstacles to participation in randomized clinical cancer trials. Grand and O'Brien found these to fall into three main categories – clinician, patient and system[137].

They described clinicians as the gatekeepers of clinical trials, and presented a whole list of factors concerning their ability to get patients to participate in trials. Among the most important were lack of awareness of trial; lack of time; incorrectly considering patients ineligible; age discrimination; and preference for a particular treatment.

The patient perspective has been explored by several authors[136,138]. They are consistent in their identification of factors that have a negative influence on patients' decision to enter RCTs: Lack of sufficient information; lack of conviction that the treatment will serve them; not sufficient trust in their clinician; desire for other treatment; distance from clinic; fear of randomization and fear of toxicity. Older patients did not appear less willing to participate, but the attitude of friends and family, as well involved clinicians, was of major significance[139-141].

Considering the success of the two RCTs conducted by NLCG in the years preceding Conrad, there should be no reason to question the patients' perspective or the ability of the appropriate clinicians to recruit patients to the Conrad trial.

Among the systemic or trial specific factors that are considered of importance is protocol design, such as complex dosing schedule, multimodality, requirement for week-end clinical staff coverage, and multiple departments' involvement; protocol acceptance, such as the importance of scientific question raised and the physicians' agreement on the dosing schedule, and – lastly - competing studies targeting same population of participants.

Obviously, the Conrad study was definitely more complex than some of the previous chemotherapy RCTs conducted by NLCG. Multimodal clinical trials on lung cancer have been particularly difficult to complete[142,143]. This argument becomes even more important if competing trials, targeting the same population of participants, are conducted simultaneously.

Ten months after the start of the Conrad study, the NLCG launched a new RCT, the VG-study, which compared two simple chemotherapy combinations to patients with NSCLC stage IV and IIIB[144]. The rate of accrual in this study may serve as an illustration of how a less complex protocol design is advantageous, compared to a multimodal study. The VG study was launched through the same channels, the patients recruited in the same way, by the same clinicians as the Conrad study. Between September 2007 and April 2009, 444 patients from 35 Norwegian hospitals were randomized[144].

Eligible patients to the VG study were to have NSCLC stage IV or stage IIIB not eligible for curative treatment, and WHO performance status (PS) 0 – 2. Some clinicians will probably perceive this as partly targeting the same population of participants as Conrad. The significance of this relationship, however, is difficult to assess. The main impression is that

the simplicity of the study – whether the study is perceived as laborious or not – is an

essential, if not the most important, factor to sustain an adequate inclusion rate.

Figure 7. Acrual rate the Conrad study - 6 months intervals
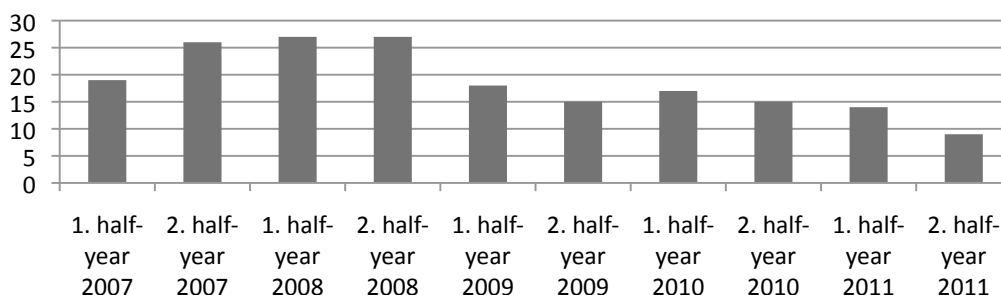
We designed the trial requiring a power of 80%, which is the most commonly used

value for statistical power. There are no formal standards for power, but the basis for

calculating power is the size of the effect we want to measure, i.e. the change in outcome

after the experimental intervention. The main purpose for these calculations is to minimize

the probability of concluding that there is a difference between the groups when no such

disparity exists or – the opposite – finding no difference when there actually is one[145].

Holding other factors unchanged, the effect on survival is harder to detect in smaller

samples. The basis of our calculation was an estimated increase in 1-year survival from 30%

to 45%. Since the increased survival in the experimental arm exceeded the expected, we

achieved a statistical power that should be characterized as satisfactory: Given the survival

differences between the two treatment arms of 94 patients each, the calculated power

estimates for the included patients were 76% and 96%, respectively for the 1- and 2-year

survival.

8.2 Health Related Quality of Life

Traditionally, most authors have been concerned with the changes in quality of life during the treatment period and not during the follow up periods. Several reasons may be found, but one is that the numbers of completed forms decrease during the follow up period. Patients find it difficult to complete the assessment when they become ill with progressive disease. If the proportions of completed questionnaires become too low, the HRQoL assessments will loose their power of expression.

In the Conrad study, the median percentages of completed questionnaires during the first six months after randomization were 84.0 in the chemotherapy arm and 85.5 in the CRT arm, which is well inside the recommended limit. See figures 8 and 9. The percentage of responders declined in the last six months of the observation period to medians 67.0% and 75.0%, respectively, which is slightly outside. However, these are percentages above or similar to other comparable studies[146,147].

Several imputation procedures may be used to compensate for the missing forms, and different arguments may be found for each one. The "last value carried forward"-method is the simplest and least resourceful. The disadvantage of this method is that it assumes the patient's scores remain essentially constant over time, i.e. in the imputed interval. Obviously, in a palliative setting, with a progressive disease, they do not[148].

Fayers and Machin argue that the "hot deck imputation" may be a method better suited, but it is also significantly more demanding. In this method, the QoL scores from another patient in the same population group is selected at random and imputed in place of the missing.

Figure 8. Proportions of HRQoL questionnaires received
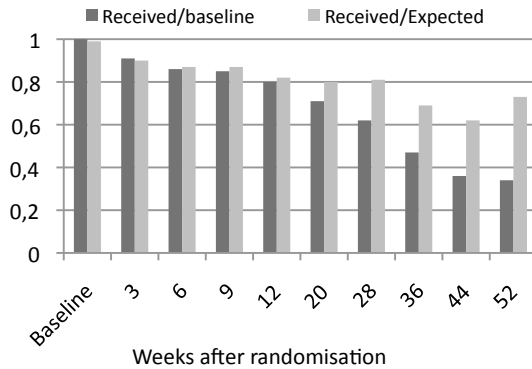
Figure 9. Received of Expected in each group
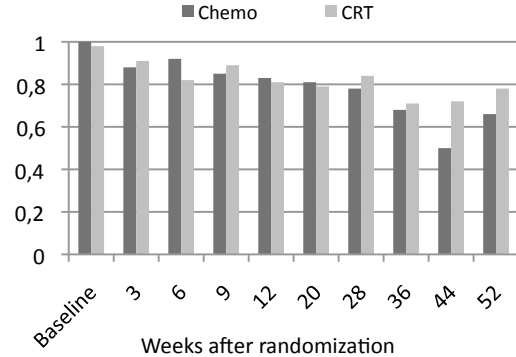
The number of missing forms naturally increases at the end of the observation period (figure 8). This is normally due to a reduced general condition related to progressive disease and accordingly decreased HRQoL[149], i.e. as the mean changes to the worse. Following this argument, we may underestimate the changes to the worse in the chemotherapy group by choosing the "last value carried forward" method, as the largest number of missing forms is found in this group (Figure 9). On the other hand, by choosing the "hot deck imputation", we may overestimate the changes to the worse in the same.

In this situation the benefit of imputation is doubtful, and accordingly we chose to calculate the mean scores from the reported scores only.

A mean change of 10 points is considered clinically relevant and significant [121,122]. We consider the H_0 to be no differences in symptoms or changes between the two groups, regardless of treatment given.

Fortunately, as shown in Figure 10 and 11, we are able to reject the H_0, based on the mean and the mean changes calculated from the reported scores only.

Figure 10. Mean score Fatigue

Figure 11. Mean Changes in Global QOL
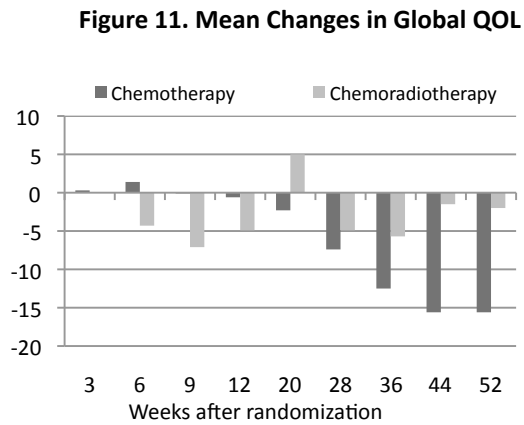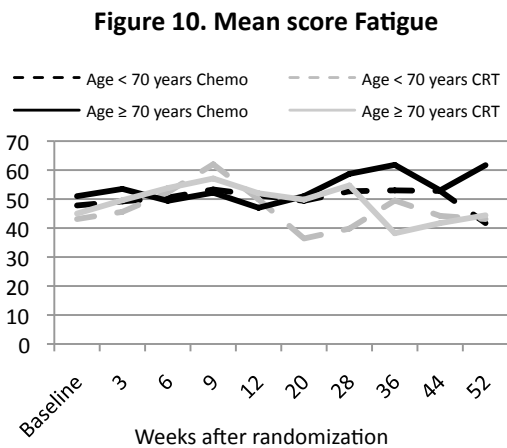
8.3 Paper 1 – Survival, diagnostic workup and planning of radiotherapy.

The lack of available PET-CT scanning in Norway at the time of inclusion may imply that the study group does not reflect the current stage III NSCLC population. By using CT alone one may underestimate nodal involvement and/or overestimate tumor size by unintentionally including atelectasis. PET-CT is also considered more sensitive in detecting distant organ metastases. An inferior investigation may result in patients with more advanced disease being included in the study, i.e. that some of the patients included in Conrad in reality were in stage IV. However, if this is so, this will only strengthen the argument for the beneficial effects of CRT to the subjects in our study.

During the enrollment period, most hospitals in Norway altered their planning routines for palliative radiotherapy from 2D to 3D techniques, although 3D had been in use in curative radiotherapy for a long time. During the study period, an estimated 50 % of the participants in the experimental arm of Conrad were administered 2D-planned radiotherapy, while the rest of the study patients received the radiation 3D-planned.

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In order to make the study as accessible as possible, we had chosen not to give specific instructions on RT techniques or dosimetry in the protocol. Radiotherapy planning was to be according to each institutional procedure and details of planning were not required.

In hindsight, we might speculate how a consistently 3D planned radiation would have influenced the survival effect and or the toxicity of the study. Most probably the toxicity would have been less pronounced in the CRT group.

Today, 2D-planned radiotherapy is considered obsolete, also in Norway.

8.4 Paper 1 – Survival, treatment and Toxicity

The doses of vinorelbine and carboplatin were chosen according to the palliative intent of the study. In both groups around 75 % completed all four courses of chemotherapy and in the experimental arm somewhat more than 10% had to discontinue treatment because of toxicity. Accordingly, increasing the doses of chemotherapy would probably not have provided any additional survival benefit in the CRT group.

Concurrent radiotherapy is now considered to be standard of care for inoperable locally advanced stage III NSCLC patients with good PS and minimal co-morbidities. Definitive-dose thoracic radiotherapy should be no less than the biological equivalent of 60 Gy, in 1.8- to 2.0-Gy fractions to the planning target volume (PTV)[150].

Compared to international literature, the radiation dose in our study – 42 Gy in 2.8 Gy fractions with opposing fields – may be considered low, although it biologically compares with 50 Gy in 2.0 Gy fractions. There are no international publications supporting this fractionation. However, this radiation regimen was chosen with the palliative intent in mind, partly because it has been safely used in Norway since the early 1980s for small cell lung

cancer[110]. In a national randomized fractionation study on advanced NSCLC conducted in the 1990s, the 42 Gy/15 fractions regimen was found to give a slightly better outcome than the normo-fractionated arm (50 Gy/25 fractions)[99].

A high percentage of our poor-risk patient population managed to complete the planned courses of chemotherapy and radiotherapy. But compared to other studies, the proportions of patients in our CRT arm suffering from esophagitis and leucopenia related infections were relatively large[151,152].

At the same time, even though we managed to reduce the risk of local recurrences, the percentages of recurrence and progression in the lungs after CRT (around 40%) were considerably larger than in the limited material of Alexander (11 %)[153]. This may reflect that the radiation dose in our study was too low and not optimally administered.

De Ruysscher et al has pointed to which direction to go in the future in order to maximize the radiation dose without too much side effects[154]. He reported from a study of 2001 stage III NSCLC patients in the Netherlands, diagnosed between 2002 and 2008, among whom 78.2% had N2 and N3 disease. The patients who received traditional sequential chemotherapy and radiotherapy to a dose of 60 Gy in 30 daily fractions had a median and one-year survival of 17.5 months and 63.7%, respectively. Sequential chemotherapy and individualized, isotoxic, accelerated radiotherapy (INDAR) increased the median and one-year survival to 23.6 months and 73.2%, respectively.

There has been a rapid development in Radiotherapy the last fifteen years, driven by technical developments in imaging (CT; MRI and PET-CT), as well as planning techniques (computational algorithms, 3D planning and optimization) and radiological equipment[51]. As until now, most of these techniques have been tried in curative settings only. But they offer

possibilities to reduce the radiological effect on esophagus and bone marrow, and will more likely result in further increase in survival benefits for patients in palliative settings, as well.

Table 10. Cox Regression of Survival – Gender, Age and given Prognostic factors as Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95,0% CI for Exp(B) Lower	Upper
Chemotherapy/CRT	-.600	.164	13.461	1	.000	.549	.398	.756
Gender	.291	.169	2.981	1	.084	1.338	.961	1.861
Performance Status (0-1 versus 2)	.620	.197	9.920	1	.002	1.858	1.264	2.733
10% Weight loss last 6 months	.141	.170	.685	1	.408	1.151	.825	1.606
Tumor diameter	-.042	.031	1.740	1	.187	.959	.902	1.020
Age	-.007	.010	.465	1	.495	.993	.974	1.013

In order not to loose information, age and tumor diameter were not dichotomized in this analysis

8.5 Paper 1 – Survival and Performance Stage

We used the ECOG/WHO-scale (see Table 3) to grade the patients' general well being and activities of daily life. It is estimated that 30 - 40% of the advanced NSCLC patients present with PS 2, depending on whether the patient or the physician do the rating[155]. Historically, these patients have been excluded from clinical trials[156], but Helbekkmo et al have demonstrated that PS 2 patients tolerate carboplatin-based chemotherapy with a modest survival benefit and an improvement in HRQoL[157]. A multivariate analysis of the population in the Conrad study (Table 10), adjusting for the given negative prognostic factors, as well as age and gender, confirms that PS 2 patients do not gain survival benefit from CRT. Neither weight loss the last 6 months before diagnosis, nor tumor size, was found to have a similar negative impact on survival.

Doing a separate multivariate analysis for each of the two treatment arms, confirmed that PS was not a negative predictive factor in the chemotherapy arm (HR 1.68, CI 0.95 -2.95, *p*=0.074). However, in the CRT arm it was highly significant: (HR 2.1, CI 1.2 – 3.5, *p*=0.007).

The distribution of negative prognostic factors is shown in Table 6. Considering the negative impact of PS 2, the Conrad study would not have been as illustrative, had the study population been normally distributed regarding PS 2, i.e. if the PS 2 group had constituted 40% of the whole study population.

8.6 Paper 2 - The Influence of Tumor Size

A tumor diameter of 8 cm or larger was one of the criteria to be included in the trial. Another requirement was the possibility to include the tumor in a pragmatic radiation field. Accordingly, our material consists of selected patients with tumors larger than normal, especially fit for radiation.

We found a significant increased survival in the group of patients with tumors > 7 cm compared to the group with tumors ≤ 7 cm. It is important to state that the Conrad trial was not designed to study this issue. The significant increased survival in the large tumor group compared to the group with smaller tumors is probably a bias caused by the selection of tumors fit for radiation.

Gender and weight loss were not significant predictive factors in our study. However, these are factors known to influence survival[158-163]. In our study, there were a predominance of women in the tumor >7 cm group, but less weight loss, especially for those treated with CRT. This may have contributed to the increased survival in the group of tumors > 7 cm. However, poor performance status (PS 2), which is one of the strongest prognostic factors in NSCLC, was over represented in the tumor >7 cm group and especially for the CRT treated.

Many authors have found the TNM classification system insufficient in predicting the treatment effect on survival in non-operable NSCLC-patients, especially with respect to the impact of tumor size[164-166]. Some have even tried to propose alternative models[167]. The prevailing lack of distinction between predictive and prognostic factors may be one reason[168]. A prognostic factor provides information on the likely outcome of a cancer disease in an untreated individual. A predictive factor provides information about the likely effect of a treatment[169].

Several large studies have recently been published on the prognostic significance of tumor size[170,171]. Morgensztern et al reported from the SEER registry, and identified 12 315 patients with locally advanced stage III NSCLC N2-3 disease strictly on the basis of TNM staging, regardless of the treatment. They found tumor size to be an independent prognostic factor. Ball et al reported on 868 patients of all TNM stages included in The IASLC Staging Project. The tumor diameters were known and the cancers were subjected to radical radiotherapy or combined chemo- and radiotherapy. The authors found that tumor sizes less than 3 cm were associated with a longer survival than larger tumors. The evidence on the prognostic effect for tumors larger than 3 cm was weak. But the basis for the comparison of all these studies has been the treatment effect on smaller tumors. Accordingly, they do not tell us much about how treatment on larger tumors compares to no treatment or best supportive care.

In a small study published in 2008, Werner-Wasik et al found that larger tumor volumes were associated with larger risk of local failure and smaller tumors were associated with improved OS[172]. Their findings were not compared to a control group. Other authors have addressed the prognostic value of tumor size and volume on survival[100,153,166,173]. But these studies have concerned patients who received definitive treatment, and though large

tumors were shown to have varying degrees of negative prognostic impact, the treatment

effect was not specifically addressed in any of the studies. It is important to stress that a

poor prognosis does not preclude an excellent treatment effect. Accordingly, these studies

cannot be used as arguments against treating bulky tumors.

8.7 Paper 3 – The Influence of Age

The Conrad study was not designed to study the issue CRT and age.

However, we find several arguments for conducting a study concerning age and

treatment effect of CRT among patients with negative prognostic factors and non-resected

LA-NSLCL stage III: The percentage of patient ≥ 70 years (42%) was larger than in most

similar trials; the study was stratified with regards to age, and the best treatment approach

for patients of this category has still not been determined.

In several recent trials of elderly patients with non-resected LA-NSLCL stage III

subjected to CRT, the reported overall survival has been considerably longer than in our

study[151,152]. But the patients have been given definite chemoradiation with radiation dose

approximately 60 Gy. Considering that the majority of the elderly patients have

comorbidities, many will have negative prognostic factors and only a minority will endure

such treatment.

We found an increase in overall survival among the CRT patients ≥ 70 years in our

study, but the increase was not significant. However, women with lung cancer are known to

have a better prognosis than males, older women even more than younger[17,174]. In our

material there is a male predominance (77% males in the older versus 55% in the younger

CRT group). This may have influenced the overall survival. In addition, patients > 75 years in

our study were administered 25% reduced chemotherapy doses. Approximately 50% of the

older treatment group (≥ 70 years) was > 75 years old. Though the reduced doses may have corroborated a favorable hematological profile among the elderly, the dose reduction probably influenced the survival rate negatively. Taking all these arguments in to consideration, with a 1- and 2-year survival of 44 and 23 %, respectively, as seen in our study, we have reason to expect survival benefit of CRT treatment to patients ≥ 70 years, even if they have negative prognostic factors and non-resected LA-NSLCL stage III.

Wang et al and Pijls-Johannesma et al have described how most functional scores for HRQoL usually decline over time and symptoms as hemoptysis and pain increase later in the course of the disease[147,175]: Based on HRQoL investigations in two prospective CRT based trials in NSCLC stage III patients, Hallqvist et al reported a gradual worsening of dyspnea and fatigue during the observation period, regardless of age[146].

In our study, the most prominent functional benefit of CRT for the elderly was found in Global HRQO, which remained clinically unchanged throughout the treatment and the observation periods. CRT-related symptoms, such as dysphagia and pain in the treatment period, were found to be transient and less prominent in the group of patients ≥ 70 years. The elderly receiving CRT experienced less dyspnea and fatigue than the elderly non-CRT treated patients.

Our study was only marginally powered to detect the main issue and we cannot expect it to be sufficiently powered to answer others. The non-significant increase in overall survival we found among the patients receiving CRT is probably a type II error. The benefit in HRQoL seemed to be more convincing.

However, if we relate overall survival and HRQoL to age, our conclusion does not differ from those drawn about age and CRT in patients with non-resectable locally advanced

NSCLC stage III by other authors[3,152]. At a time when similar studies regarding patients in the relevant age group are missing, this alone must be considered to be of importance.

9. CONCLUSIONS

In a selected material of poor prognosis patients with locally advanced NSCLC stage III, chemoradiotherapy (CRT) was superior to chemotherapy alone with respect to surival and HRQOL at the expence of more hospital admissions due to toxicity. We did not find any survival benefit of CRT for patients with PS 2. We conclude that tailored CRT may be offered to poor prognosis patients with locally advanced unresectable NSCLC stage III, as long as they do not have performance status 2 or worse.

We explored the effect of tailored CRT in poor risk NSCLC patients with bulky tumor masses. In a selected material of patients with tumors > 7 cm possible to include in an adequate radiation field, we found a significant benefit in both survival and HRQoL, as long as the patients had PS < 2. We conclude that tumor size should be considered a negative prognostic, but not a negative predictive factor, regarding treatment.

We also explored the effect of age ≥ 70 years in the study population. We found Performance Status and HRQoL to be preserved even late in the observation period following tailored CRT. Patients ≥ 70 years also benefited in overall survival, but not significantly. The study was not designed to evaluate the effect of age and several factors may have reduced the treatment effect in the subgroup of elderly in the experimental arm: Patients > 75 years received reduced doses chemotherapy and there was a male predominance in the CRT patients ≥ 70 group. However, this indicates that poor prognosis patients with locally advanced NSCLC stage III and age ≥ 70 years deserve further studies of tailored CRT.

10. FUTURE PERSPECTIVES

Today cancer drug development mostly focuses on therapies that target cancer-proteins, largely identified from translational studies. In the future this will most probably lead to more individualized treatment, where the patient will receive therapy according to the mutation status found in his/her tumor. Most probably this will be a combination of targeted therapeutic agents – in order to overcome the development of resistance[176].

These new therapeutic agents will probably also influence how clinical cancer trials are performed, with focus shifting to smaller trials, in which a greater percentage of patients are expected to benefit from the therapy. Rather than lumping together many patients with diverse mutations, cancer patients will be segregated and treated according to their mutations[14].

The demographic shift caused by an aging population may mean that we will see more cancer patients in poor general condition in the future. If this will be the case, chemoradiotherapy, similar to what we have tried out in Conrad protocol, may be a way to go. But then more modern techniques of radiotherapy should be utilized, and doses of chemotherapy should probably not be reduced in patients > 75 years.

Hopefully, new ways of screening for lung cancer and the public efforts to stop smoking will bring about a reduction in the incidence of this sad disease before that happens.

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