Survival after surgical resection for non-small cell lung cancer

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2 SUMMARY

Lung cancer is the leading cause of cancer death in men and women worldwide. In Norway during the period 2011 to 2015 and regardless of treatment, the estimated 5-years relative survival for patients with localized disease was 57% for females and 44% for males. Surgical resection is recommended treatment for limited disease of non-small cell lung cancer [NSCLC] in patients fit for surgery. Biological factors such as high age, body mass index [BMI], comorbidities, and histological type of tumor, may influence survival after surgical resection. Although studies of gender related differences in survival after surgery for NSCLC have shown conflicting results, the prevailing opinion is that the prognosis is better for females than for males. In addition, smoking habits and treatment depending factors caused by tumor stage, type of surgical technique and extent of operative resections, may all be factors affecting postoperative outcome. Since patients with lung cancer often carry comorbidities and other risk factors for dismal outcome, it may be suspected that causes other than lung cancer are competing causes of death following surgical resection.

In three published studies, we have analyzed prospectively collected data from our single-centre registry containing relevant clinical, radiological, and pathological data, as well as survival following surgical resection for NSCLC. In the first paper we hypothesized, that chronic obstructive pulmonary disease (COPD) would influence both short- and long-term survival after lung cancer surgery. The second paper postulated females to have improved survival compared to males after surgical treatment. The third study assessed the impact of clinical factors associated with lung cancer mortality and non-lung cancer mortality.

The cohort of the two first studies was included during the period 2003-2013, comprising almost 700 lung cancer patients. In the third study, the timespan was 2007-2016, and 750 NSCLC patients were enrolled. Mortality and survival rates were in all three studies in line with comparable international studies indicating external validity of the results. One year following surgical resection, significantly increased mortality was found in patients with severe COPD compared to those with normal lung function or with mild to moderate COPD. Stratifying the cohort according to female and male gender, there was no significant difference in mortality rate between sexes. Mortality rates were increased in both genders compared to the general population. In a competing risk model, the probabilities of having died from lung cancer or other causes were 36% and 24%, respectively.

The three studies confirmed that patients with early-stage lung cancer and severe COPD had reduced long-term overall survival. Potentially operable patients with mild to moderate COPD should be treated in the same way as patients with normal lung function. The previously recognized gap in survival differences between the genders seems to be diminishing. Lung cancer is the prevailing long-term cause of death also more than 5 years after surgical resection. Surveillance of risk factors associated with increased mortality should be taken into account both in the preoperative selection of patients eligible for surgical resection and in the postoperative follow-up.

3 LIST OF PAPERS

1. Anders Bugge, May Brit Lund, Cathrine Brunborg, Steinar Solberg, Johny Kongerud - Survival after surgery for lung cancer in patients with chronic obstructive pulmonary disease. Ann Thorac Surg. 2016 Jun;**101**(6):2125-31. doi: 10.1016/j.athoracsur.2015.12.057. Epub 2016 Mar 24.

2. Anders Bugge, Johny Kongerud, Cathrine Brunborg, Steinar Solberg, May Brit Lund - Gender-specific survival after surgical resection for early-stage non-small-cell lung cancer. Acta Oncol. 2017 Mar;**56**(3):448-454. doi: 10.1080/0284186X.2016.1253862. Epub 2016 Nov 16.

3. Anders Bugge, May Brit Lund, Morten Valberg, Odd Terje Brustugun, Steinar Solberg, Johny Kongerud - Cause-specific death after surgical resection for early-stage non-small-cell lung cancer. Eur J Cardiothorac Surg. 2017. doi: 10.1093/ejcts/ezx274. Epub 2017 July 25.

4 ABBREVATIONS

ATS = American Thoracic Society

BMI = Body mass index

Carcinoma, NOS = Carcinoma, not otherwise specified

COPD = Chronic Obstructive Pulmonary Disease

CPET = Cardiopulmonal Exercise Test

CRN = Cancer Registry of Norway

CVD = Cardiovascular Disease

DL_{CO} = Diffusing capacity of Lung for carbon monoxide

EBUS-TBNA = Endobronchial ultrasound transbronchial needle aspiration

ECOG PS = Eastern Cooperative Oncology Group Performance Status

ERS = European Respiratory Society

FEV_1 = Forced Expiratory Volume in 1 second

FVC = Forced Vital Capacity

GOLD = Global Initiative for Chronic Obstructive Lung Disease

IASLC = International Association for the Study of Lung Cancer

MDT = Multidisciplinary Team

NCDR = Norwegian Cause of Death Registry

NSCLC = Non-Small Cell Lung Cancer

pTNM = pathological Tumor Nodes Metastasis

SBRT = Stereotactic body radiotherapy

SCLC = Small Cell Lung Cancer

SMR = Standardized Mortality Ratio

TNM = Tumor Nodes Metastasis

WHO = World Health Organization

5 INTRODUCTION

Lung cancer is the leading cause of cancer death worldwide [1]. Biological and clinical factors may influence both incidence and treatment options. Classification of the anatomical extent of the disease (localized, regional, and advanced) aids the choice of treatment modality [2]. While lung cancer incidence is levelling off in males, it is still increasing in females [3]. There are data suggesting that genders differ in terms of onset and symptoms, smoking habits, histology and survival [4].Surgical resection is the recommended treatment for localized lung cancer [5].

The most common environmental risk factor for developing lung cancer is undoubtedly cigarette smoking. In addition, smoking is associated with other diseases such as chronic obstructive airways disease leading to severe lung function impairment and with cardiovascular disease. Reduced lung function and cardiovascular conditions may influence and contribute to increase per- and postoperative risk of mortality.

To avoid futile surgical treatment, selection based on preoperative results from invasive and non-invasive investigations is crucial. Thus, the evaluation of diagnostic methods is important to assess their contribution to postoperative survival.

The goal of early and long-term postoperative follow-up is to identify treatment-associated complications, disease recurrence or development of new primary lung tumors in order to improve overall survival. To our knowledge, little is known concerning preoperative identified risk factors and their association with causes of deaths following surgical resection for lung cancer.

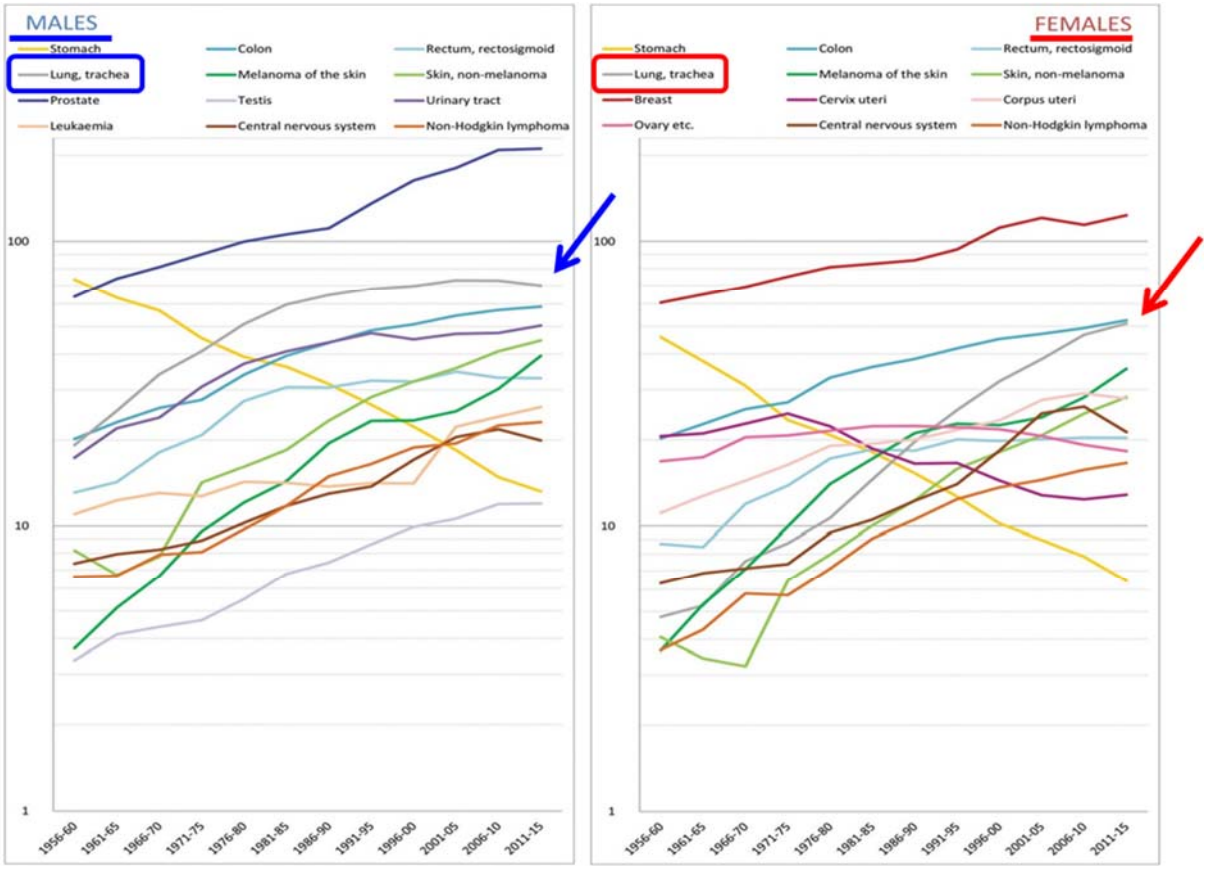
Based on our single-centre data material comprising relevant clinical, radiological and pathological information we set out to examine survival after surgical resection in patients with severely reduced lung function. We wished to identify gender-specific differences in overall survival. We also wanted to assess risk factors contributing to specific causes of death.

5.1 Lung cancer – Incidence and Mortality

During the last decades, the incidence of lung cancer has increased and in 2015 accounting for about 10% of all new cases of cancers in Norway (Figure 1) [3]. This implies that 3035 new cases were diagnosed in 2015, 1564 men and 1471 women. While the incidence of lung cancer seems to be levelling off in men, it is increasing in women [3]. Hence, the gap in incidence between genders seems to narrow. An important shift in incidence was observed in 2015, when for the first time in Norway the incidence of lung cancer was higher among women than men in the age group 50-69 years [6].

Lung cancer is the leading cause of cancer death worldwide, responsible for approximately 1.6 million deaths annually [1]. In Norway 2158 patients died of lung cancer in 2014 [3].

Figure 1* Time trends in age–standardized incidence rates in Norway for selected cancers (semi log-scale), 1956–2015.



***Reproduced from "Cancer in Norway 2015" [3].**

5.2 Etiology of lung cancer

The causes for the incidence changes are not fully understood, but the correlation between lung cancer and various biological, genetic, and environmental factors have been investigated [7]. Globally, tobacco smoking is regarded as the most common risk factor for the development of lung cancer [8]. Even involuntary exposure (secondhand smoke) is associated with increased risk of lung cancer [9]. However, other factors have also been described to increase the risk for lung cancer [10]. Environmental exposures include occupational exposure to asbestos and water-soluble nickel salts [11, 12]. Studies have also shown lung cancer to be associated with exposure to ionizing radiation in areas where environmental exposure to radon is common [13, 14]. Indoor air pollution from burning biomass and fossil fuel for cooking and heating is also a known risk factor of significance, mainly being relevant in developing countries [15]. A relationship has been indicated between ethnicity, socioeconomic status and the incidence and mortality from lung cancer. This was confirmed in a Norwegian study, investigating how type of lung cancer treatment was influenced by income, education and place of residence [16]. In a country with public health service providing universal tax-supported health care, guaranteeing unconstrained access to general practitioners and hospitals, the survival differences may be regarded as unexpected [17].

In addition, certain intrinsic host factors (genetic factors) may affect susceptibility to develop lung cancer. In this respect, a specter of biomarkers of lung cancer are being investigated

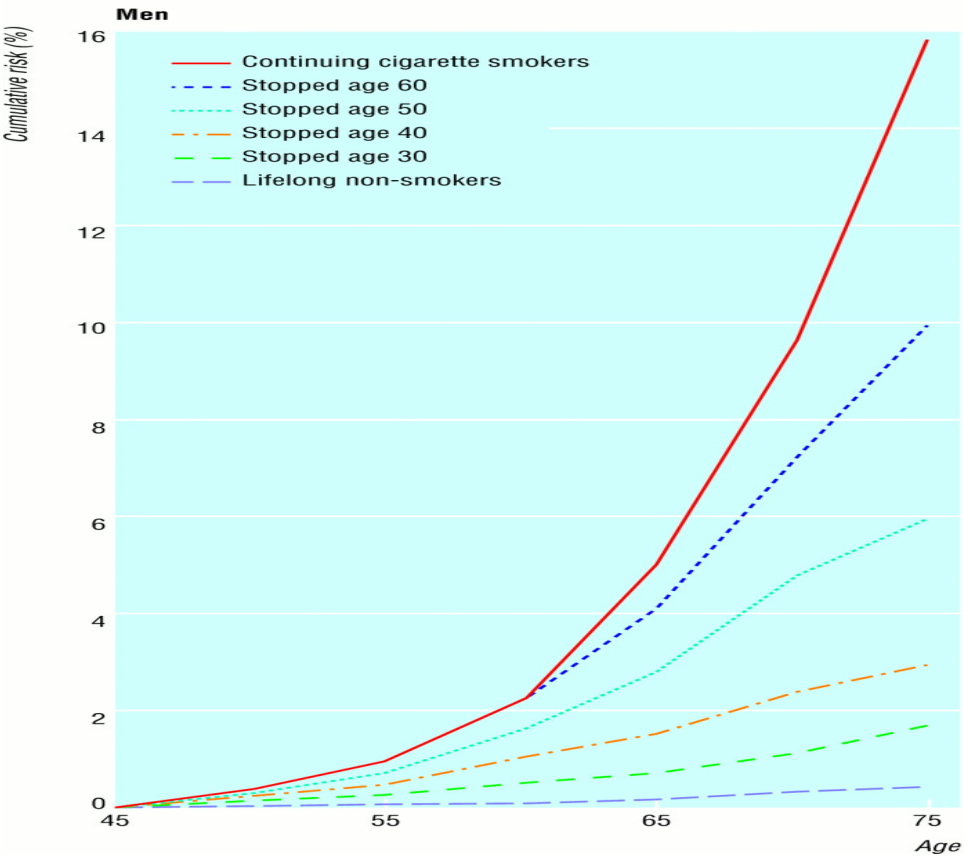
trying to determine genetic characteristics of persons at risk of developing lung cancer [18]. Having a positive family history of lung cancer was associated with increased risk of lung cancer [19]. In addition, acquired lung diseases like obstructive and fibrotic lung diseases (e.g. chronic obstructive pulmonary disease [COPD], idiopathic pulmonary fibrosis and systemic sclerosis) are associated with increased risk of lung cancer [20-22].

5.3 Environmental agents

Tobacco smoking

Beyond doubt, cigarette smoking is the main risk factor for developing lung cancer, accounting for 80 to 90% of all lung cancers in countries where cigarette smoking is common [23]. The percentage of daily smokers in Norway as in other developed countries has steadily decreased since 1990, and in 2015, the age-standardized prevalence of daily smoking was 15% in both men and women [24]. However, the rates of occurrence of lung cancer related to smoking lag behind smoking rates by about 20 years [25]. Hence, the expected decrease in lung cancer incidence due to decreased smoking is now probably seen among men, but not yet in women. Smoking cessation is to be emphasized at all ages. Decrease in cumulative risk of lung cancer after smoking cessation begins after 5 years but never reaches the risk of a non-smoker (Figure 2) [26].

Figure 2* Effects of stopping smoking at various ages on the cumulative risk (%) of death from lung cancer up to age 75, at death rates for men in United Kingdom in 1990. (Non-smoker risks are taken from a US prospective study of mortality [27])

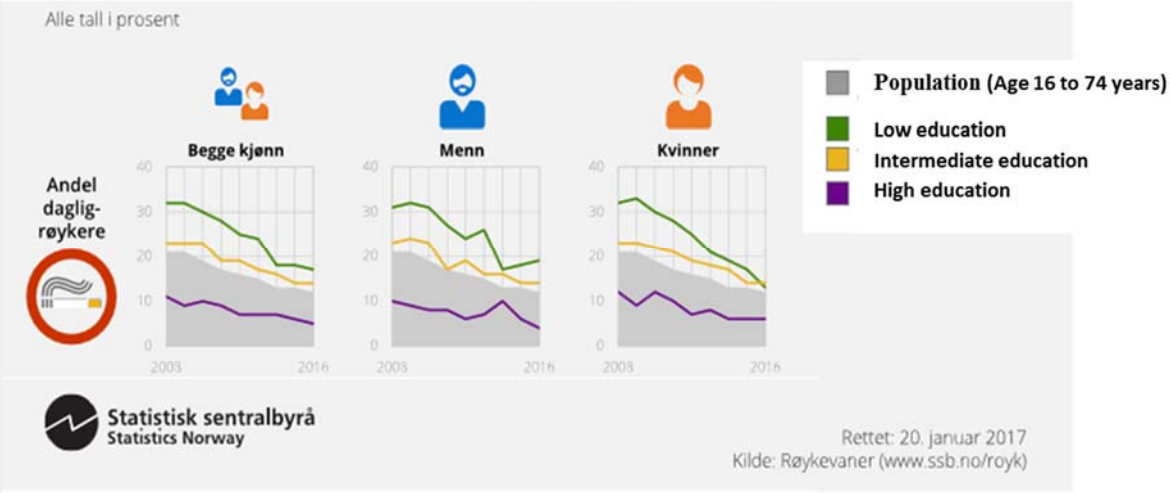


*Reproduced from The BMJ, Peto et al., vol. 321, p 323–9, 2000 © with permission from BMJ Publishing Group Ltd.

Secondhand smoke exposure

There is abundant evidence that nonsmokers who live with a smoker have a 20% to 30% increased risk of developing lung cancer [27]. The indoor air pollution from cigarette smoking was before the ban of indoor smoking substantial in both workplaces and public areas like bars and restaurants. In Norway, indoor smoking was banned in 2004, and since then the percentage of daily smokers has steadily decreased in the total population from 24% in 2006 to 12% in 2016 (Figure 3) [28]. This will have a positive impact on both the individual risk of developing cancer and the cancer risk from second hand exposure.

Figure 3 Daily smokers in Norway, according to gender and level of education 2008-2016.



5.4 Treatment modalities of lung cancer

Lung cancer treatment is based on a number of factors, such as general health, histological differentiation, tumor distribution, and the patient's preferences. Treatment options are surgery, chemotherapy, radiotherapy or targeted drug therapy. In some cases, mainly in patients with advanced disease, the potential benefits of treatment are outweighed by the possible side effects of the treatment, and only palliative care is recommended. The main treatment options for localized (stage I and II) NSCLC is either surgical resection or fractionated conformal stereotactic radiotherapy. For regional and advanced disease (stage III and IV), chemotherapy or radiotherapy alone or in combination is recommended.

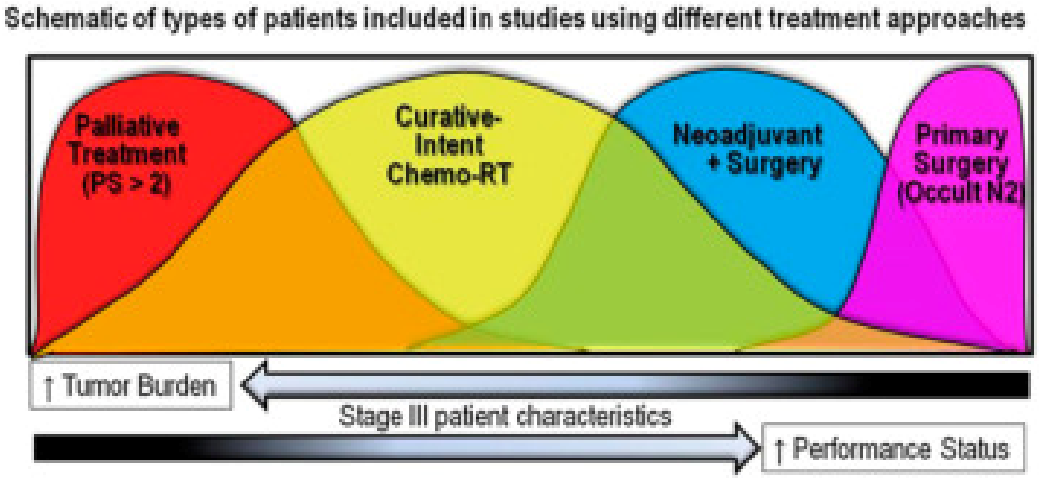
The cornerstone of treatment of early stage NSCLC is surgical resection. In general, for patients with stage I or II NSCLC without medical contraindications to operative intervention, surgical resection is the recommended treatment of choice [5, 29]. The natural history of untreated stage I or II disease consistently shows poor survival (2- and 5-year survival of approximately 20% and 15%, respectively) [30]. On the other hand, according to the International Association for the Study of Lung Cancer (IASLC) the 2- and 5-years survival was 93% and 82%, for stage Ia and 64% and 47%, for stage IIb in patients using all treatment modalities of care.

Patients with stage III NSCLC is a heterogeneous group of different pathological conditions that may be subjects to several treatment modalities, including surgical resection (Figure 4).

Due to the updates in the TNM classifications, patients categorised according to the 6th edition with stage III disease have been moved to stage IV and vice versa in the 7th edition. The poor survival with surgery alone in stage III has led to combination treatment by adding chemo- and/or radiotherapy to the locoregional treatment. However, the inhomogeneous group of patients with stage III NSCLC was not suitable for inclusion in the present thesis.

To increase survival rate in patients with stage II and III NSCLC adjuvant chemotherapy is recommended. Evidence supports use of neoadjuvant platinum-based chemotherapy following complete resection in patients with stage IIIa [31]. During the last 10-15 years the treatment options have been evolving fast and targeted therapies has gradually become important. This treatment work by targeting the killing of cancer cells. Development of histopathological subgroups is based on immunohistochemically and cancer genome (mutational) typing. Personalized or tailored treatment has shown promising results concerning prolonged survival for lung cancer patients. Targeted therapy drugs are often used in combination with chemotherapy drugs.

Figure 4* A depiction of the heterogeneous patient characteristics of stage III lung cancer and the inclusion of various patient subtypes into clinical studies evaluating treatment options for patients with stage III disease. PS = performance status; RT = radiotherapy.



5.5 Patient selection for surgical treatment

A systematic and thorough preoperative workup of all patients is important in order to select patients eligible for surgical treatment. It is of importance to distinguish between the terms "resectable" and "operable", and this distinction is used throughout the thesis. The term "resectable" indicates that the tumor can be completely excised by surgery. "Operable" indicates that the patient has an acceptable, preferably low risk of postoperative death or morbidity.

For patients with NSCLC it is recommended to discuss the preoperative evaluation with a multidisciplinary team [MDT]. Guidelines point out that MDTs have representatives from pulmonary medicine, thoracic surgery, medical oncology, radiation oncology, radiology, and pathology [32].

To consider patients eligible for potential radical treatment, an investigation is required directed towards accurate diagnostic and staging information as possible. In order to select the optimal treatment for all lung cancer patients, national and international guidelines has been developed [10, 29, 33-37]. It is particularly important to perform a thorough preoperative assessment in patients scheduled for surgical or radiological treatment with curative intent.

Diagnosis is based upon various radiological techniques including chest x-ray, multidetector computed tomography (MDCT), [^{18}F] -2-fluoro-deoxy-D-glucose (FDG) positron emission tomography (PET) combined with computed tomography (CT) [FDG-PET/CT]. A variety of invasive techniques in combination with radiological examinations are also being used. These include bronchoscopy, CT-guided transthoracic needle biopsy and fine needle aspiration cytology; Endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) of tumor and mediastinal lymph nodes and more invasive techniques like mediastinoscopy or thoracoscopy. All methods in the purpose of establishing and ensuring a correct histological diagnosis and deciding the extent of the disease. Both EBUS-TBNA and FDG-PET/CT were concurrently introduced during the period 2006 and 2007 in our institution. Hence, we planned to record the results from both examinations in our registry. However, unlike FDG-PET/CT, the work-up with EBUS-TBNA was applied in several of our collaborating hospitals, and an accurate registration of the results from EBUS were unfortunately not possible. Because FDG-PET/CT was performed only in our institution, we had in collaboration with the department of nuclear medicine unrestricted access to the results.

Primarily, preoperative work-up recommends assessment of cardiovascular status and pulmonary function prior to surgical treatment as cardiovascular and pulmonary diseases have been associated with significant perioperative morbidity and mortality due to the risk from smoking to develop lung cancer, chronic pulmonary disease and cardiovascular diseases [CVDs] [35, 38, 39].

When cardiac disease is overt or may be suspected (e.g. personal or family history of cardiac disease, patient >50 years of age), it is recommended to perform a thorough cardiological assessment considering cardiac risk of lung cancer surgery [38].

Preoperative evaluation of lung function is crucial to assess the risk of operative mortality and impact of lung resection on postoperative quality of life. Important predictors of postoperative morbidity and death are the measurements of forced expiratory volume in 1 second (FEV_1) and diffusing capacity of lung for carbon monoxide (DLCO) by performing spirometry and DLCO [35].

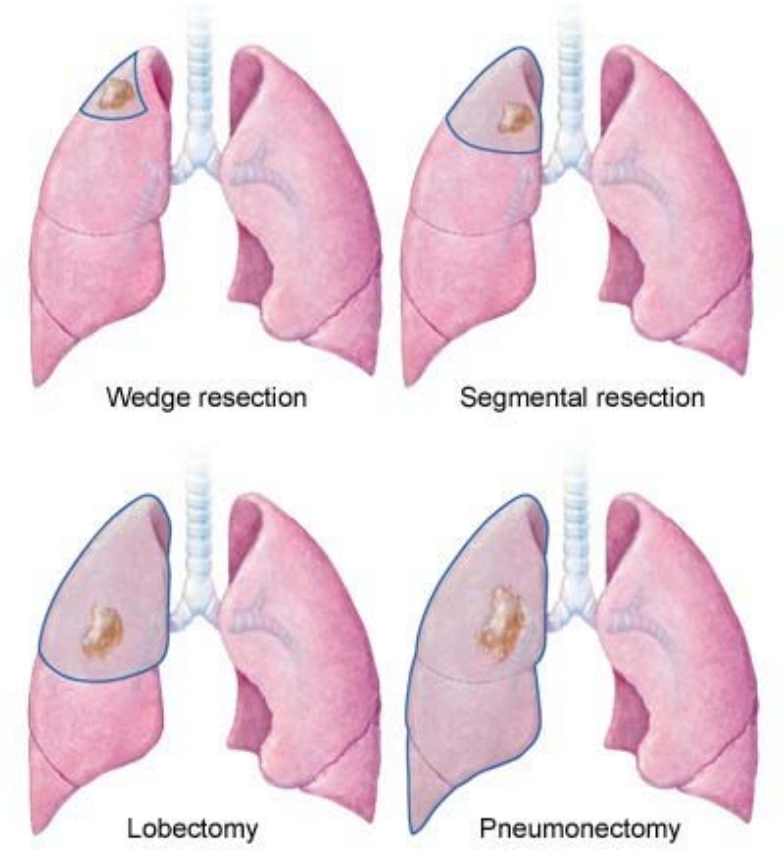
Other important comorbidities including peripheral vascular disease, cerebrovascular disease, diabetes mellitus, renal impairment and hematologic disorders are of importance and may potentiate the risk of postoperative complications, morbidity and mortality. In the present studies the Charlson comorbidity index (CCI) was applied, counting numbers of cardiovascular, endocrine or other present comorbidities at time of surgery.

5.6 Surgical treatment

To gain access to the lung, the surgical approach may be the traditional, open surgical technique or the less invasive video-assisted thoracic surgery [VATS] approach aimed at decreasing morbidity and mortality. In rare cases, it may be feasible to perform a sternotomy or a collar incision. The minimally invasive approach of VATS (thoracoscopy) is now preferred over a thoracotomy for anatomic pulmonary resection [5]. During the period 2007-2015, approximately 20% of all resections of early-stage NSCLC were VATS approaches in our institution.

Standard resections of lung cancer include removal of the affected pulmonary lobe with systematic evaluation of ipsilateral hilar and mediastinal lymph nodes (Figure 5). This is considered standard of care for stage I and II NSCLC. Pneumonectomy is rarely necessary in stage I and II, and bronchoplastic resection is suggested over a pneumonectomy [5]. In our material pneumonectomy was performed in 8-11% of all procedures. Sublobar resections refer to resections that remove less than an entire pulmonary lobe. These can be either anatomical segmentectomies or nonanatomical wedge resections and may be offered as a compromise procedure for patients whose significant limited pulmonary function or other comorbidities make them unsuitable for lobectomy.

Figure 5 Applicable surgical procedures for resecting lung cancer.



Growing evidence emphasizes the importance of educating dedicated lung cancer specialist working in higher volume centers to perform a sufficient number of operations has reduced

per- and postoperative mortality after surgical resection [5]. The recommendations support the treatment of lung cancer being performed by specialists in cancer surgery at higher-volume centers. In Norway, parallel to a centralization of lung cancer treatment, published results confirmed in the period from 1994 to 2007 increasing resection rate and improved one-year survival [40].

6 AIMS

The overall purpose of the present studies was to identify clinical and pathological factors thought to influence postoperative outcome after surgical resection in a cohort of stage I and II non-small cell lung cancer patients.

The following three objectives were:

I. Based upon lung function measurements to investigate the influence of increasing severity of COPD on short and long-term survival after surgical treatment.

II. To assess a possible difference in postoperative outcome between women and men after surgical treatment.

III. In a competing risk model, to examine risk factors associated with lung cancer specific and non-lung cancer specific death after surgical treatment.

7 MATERIAL AND METHODS

7.1 The study population

Since 2003, all patients surgically treated for lung cancer at Oslo University Hospital, Rikshospitalet have been registered in the cancer database of the Department of Respiratory Medicine. This multi-user database (Medinsight) was developed at the Institute for Cancer Genetics and Informatics, Oslo University Hospital [41]. The database provided statutory storage, protection, and backup of all collected data. All variables have been prospectively registered.

The initial data collection was performed by a study nurse, supervised and supported by the responsible pulmonologists. Death date was automatically provided from the National Registry in Norway. Clinical data were collected from the referral letter and from patients' hospital charts. In addition, all patients completed on admittance a self-administered questionnaire (Appendix 1, Figure 13). From this, we extracted data concerning smoking habits, and former diseases. Results from the various tests and examinations during and following hospital stay such as radiology and pathology, were consecutively recorded as they became available.

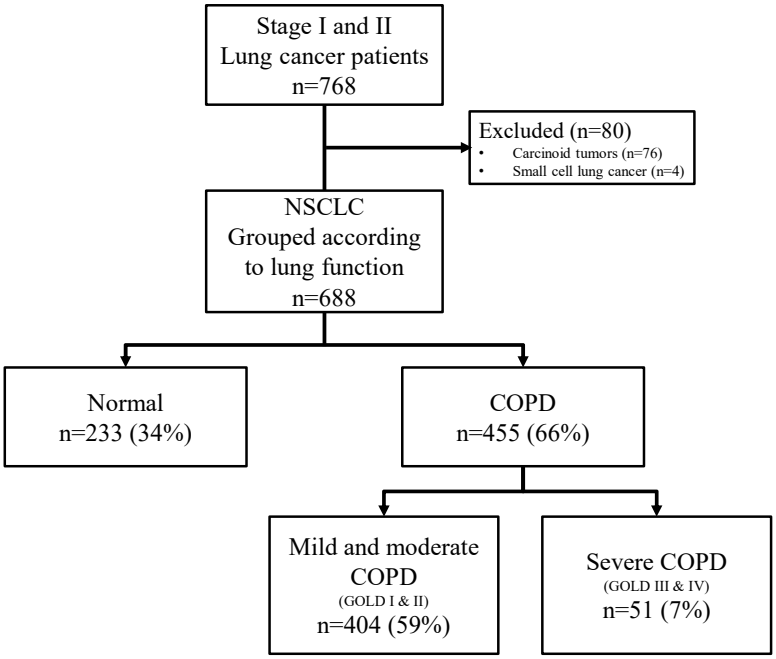
The populations of the three present studies differed slightly. Although most patients represented the same cohort in all three studies, the numbers were diverging. In study number two, there were included four more patients than in study number one. The explanation being a lag in the continuous update of the database. Four patients were not registered when source data extraction to the first study was performed. The period for the third study was changed compared to the two first studies. This alteration was performed due to a reorganization of cardiothoracic surgery with centralization to fewer institutions from 2007. This resulted in an increase in the yearly volume of patients from then on. Also, since 2007 we have registered causes of death for all patients. The cause of death was collected from either patient records, report from the patient's local hospital or from the general practitioner. With regard to cause of death, no patients were lost to follow-up.

All patients considered for surgical resection were referred from hospitals in the South-East of Norway (population approximately 1.2 million) to the weekly MDT meeting conducted as a videoconference at our tertiary University center. This center operates about one-fifth of all lung cancer patients in Norway. Prior to referral, the patients underwent primary assessment in accordance with national guidelines in their local hospitals [34]. There were no records of patients not eligible for surgical resection. All patients were referred back to their respective local hospitals approximately one week postoperatively, after removal of thoracic drainage and obtaining appropriate postoperative control of pain, possible infections or other occurring postoperative events. We do not have records of patients who were found unfit for surgery during primary assessment in their local hospitals.

Study 1

From 2003 to 2013 surgically resected patients with non-small cell lung cancer were included. The final cohort consisted of 688 patients, grouped according to lung function (Figure 6).

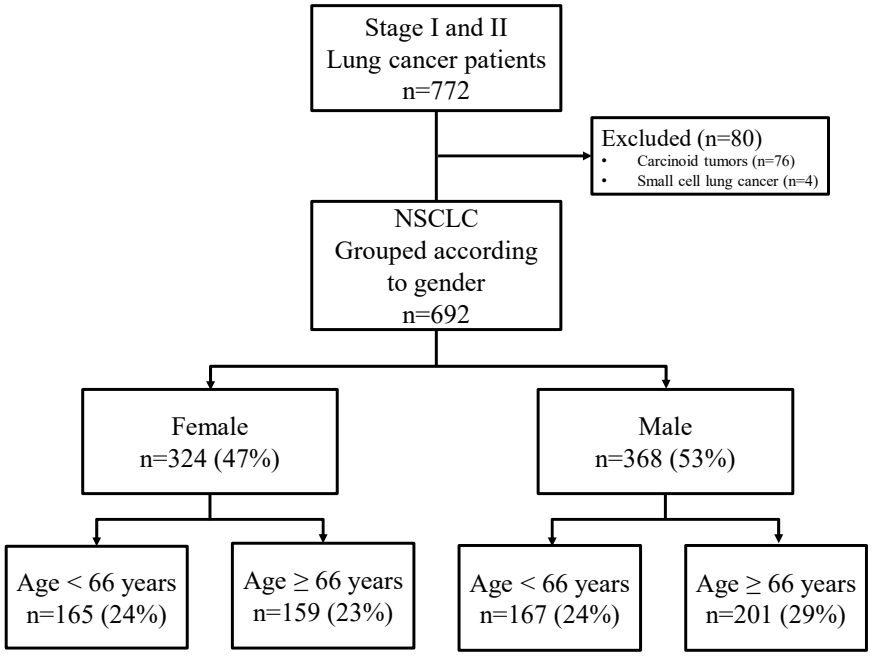
Figure 6 Surgically treated stage I and II lung cancer patients.



Study 2

The cohort comprised 692 patients and were grouped according to gender and age above and below the mean 66 years of age (Figure 7).

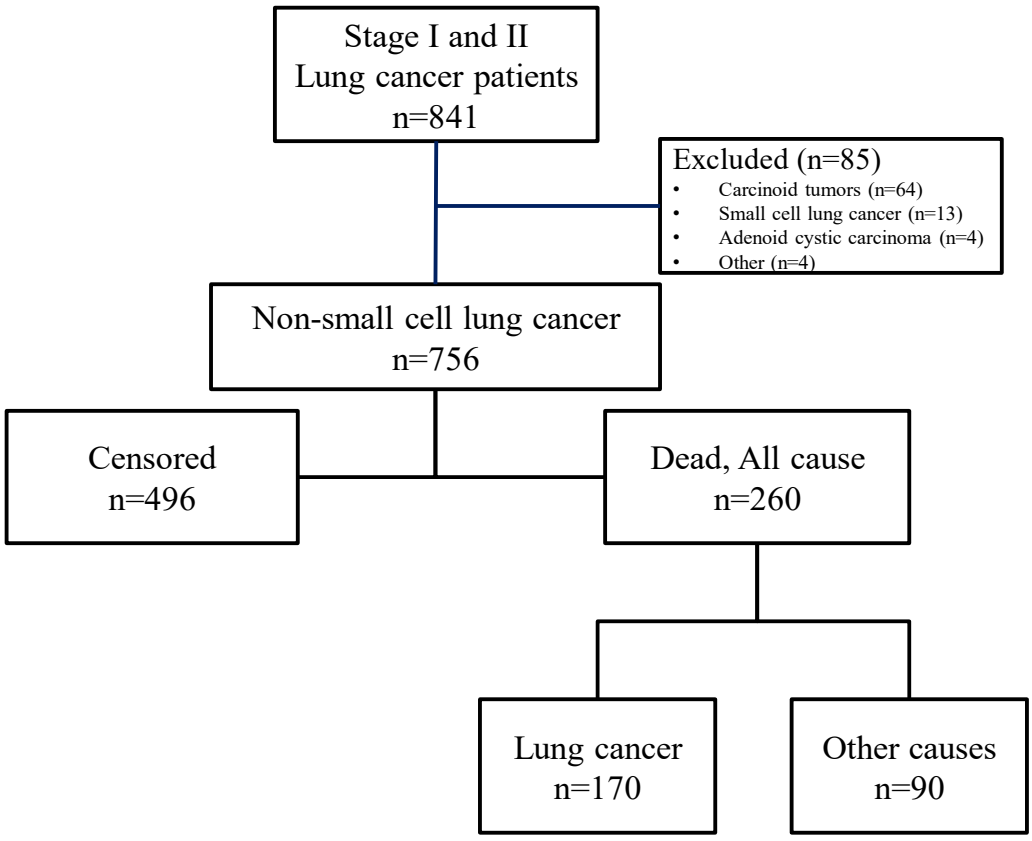
Figure 7 Surgically treated stage I and II lung cancer patients. (NSCLC = non-small cell lung cancer)



Study 3

During the period 2007 to 2015, surgically resected early stage non-small cell lung cancer patients (n=756) were registered (Figure 8).

Figure 8 Surgically treated stage I and II lung cancer patients, 2007-2015.



7.2 Study variables

Demographic characteristics

Variables including gender, age, body mass index [BMI] (Table 1), and the Eastern Cooperative Oncology Group Performance Status [ECOG PS] (Table 2) to assess the preoperative clinical status was registered for all patients [42].

Table 1 Body mass index categorized according to the World Health Organization classification

	BMI kg/m^2
Underweight	< 18.5
Normal	18.5 - 24.9
Overweight	25.0 - 29.9
Obese	≥ 30

BMI is calculated as weight (kg) / height squared (m^2)

Table 2 Eastern Cooperative Oncology Group Performance Status

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

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.

Smoking

Our database contained comprehensive and accurate information concerning consumption of tobacco from the majority of patients. The total numbers of years of smoking as well as the number of pack years were estimated for all former or current tobacco-smoking patients. One pack year equals an annual consumption of 20 cigarettes daily. Unfortunately, we have not collected data concerning smoking or secondhand smoking after surgical treatment.

Lung function

Dynamic lung volumes were measured by spirometry performed according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines, and carried out using the Vmax V6200 automated system (SensorMedics) [43]. The reference values from the European Community for Steel and Coal, recommended by ERS were used [44]. Registered variables were forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and the ratio FEV_1/FVC. FVC and FEV_1 were reported in absoulte values and as percent of predicted. Gas

diffusing variables were the diffusing capacity of lung for carbon monoxide (DLCO) and DLCO divided by alveolar volume.

Measurement of airflow limitation was determined according to The Global Initiative for Chronic Obstructive Lung Disease (GOLD). The GOLD guidelines defines a post-bronchodilator FEV_1/FVC-ratio < 0.7 as a confirmation of persistent airflow limitation [45]. The severity of airflow limitation is classified in four classes, ranging from mild ($FEV_1 \geq 80\%$ predicted) via moderate ($50\ \% \leq FEV_1 < 80\%$ predicted) and severe ($30\% \leq FEV_1 < 50\%$) to very severe ($FEV_1 < 30\%$) airway obstruction. Studies addressing the contribution of lung function to operative mortality risk recommend the estimation of postoperative predicted lung function. Predicted postoperative (PPO) values for FEV1 and D_{LCO} were calculated using the formulae described in the ERS guidelines [35].

Comorbidities

Comorbidities were classified according to the Charlson Comorbidity Index [CCI] being a simple and robust measure for comorbidity [46]. The weighted index takes into account the number and the degree of comorbid disease. It predicts poorer survival by increasing score (Table 3). The scale has been validated in clinical studies with reliable results [47].

Table 3 Charlson comorbidity index

Comorbidity	Weighted score
Myocardial infarction	1
Congestive heart failure	1
Chronic pulmonary disease	1
Peptic ulcer disease	1
Peripheral vascular disease	1
Mild liver disease	1
Cerebrovascular disease	1
Connective tissue disease	1
Diabetes	1
Dementia	1
Hemiplegia	2
Moderate to severe renal disease	2
Diabetes with end organ damage	2
Any prior tumour (within 5 years of diagnosis)[a]	2
Leukemia	2
Lymphoma	2
Moderate to severe liver disease	3
Metastatic solid tumour	6
AIDS (not only HIV positive)	6

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.
a) Except basal cell skin carcinoma.

FDG-PET/CT

FDG-PET/CT was included in the preoperative work-up of lung cancer patients from 2007 in our hospital. In accordance with national and international guidelines, preoperative FDG-PET/CT was intended to be performed in all patients [33, 48]. However, if the capacity was too low so that FDG-PET/CT would postpone surgical treatment, the examination was omitted, primarily in patients with clinical stage IA tumor as the usefulness of FDG-PET-CT is not quite clear in clinical stage IA [33]. Previously published results from the present cohort (n=651) documented usefulness of FDG-PET/CT in 533 patients during the years 2007-2011 [49]. During this period, 512 patients were treated with surgical resection, of which 118 patients did not have FDG-PET/CT examination performed. When applied, FDG-PET/CT was useful in selecting potentially operable lung cancer patients and excluding inoperable patients.

Tumor classification

The International Tumor Nodes Metastasis [TNM] classification system specific for lung cancer was launched in 1973 [2]. The T descriptor defines the size and extent of the primary tumor, the N descriptor defines the extent and location of regional lymph nodes, and the M descriptor defines the extent and localization of distant metastases. The TNM system. The classification system was later revised and refined, and the current 7th edition was published in 2009 and updated in 2011 by the International Association for the Study of Lung Cancer (Table 4) [50].

Table 4 Lung cancer stage groups according to TNM descriptor and subgroups.

T/M	Subgroup	N0	N1	N2	N3
T1	T1a	Ia	IIa	IIIa	IIIb
	T1b	Ia	IIa	IIIa	IIIb
T2	T2a	Ib	IIa	IIIa	IIIb
	T2b	IIa	IIb	IIIa	IIIb
T3	T3 >7cm	IIb	IIIa	IIIa	IIIb
	T3 Inv	IIb	IIIa	IIIa	IIIb
	T3 Satell	IIb	IIIa	IIIa	IIIb
T4	T4 Inv	IIIa	IIIa	IIIb	IIIb
	T4 Ipsi Nod	IIIa	IIIa	IIIb	IIIb
M1	M1a Contra Nod	IV	IV	IV	IV
	M1a Pl Disem	IV	IV	IV	IV
	M1b	IV	IV	IV	IV

Stage Ia
Stage Ib
Stage IIa
Stage IIb
Stage IIIa
Stage IIIb
Stage IV

T3 Inv = Directly invading chest wall, diaphragm, phrenic nerve, mediastinal pleura, or parietal pericardium
T3 Satell = Separate tumor nodules in the same lobe
T4 Inv = Tumor of any size with invasion of heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina
T4 Ipsi Nod = Separate tumor nodules in a different ipsilateral lobe
M1a Contra Nod = Separate tumor nodules in a contralateral lobe
M1a Pl Disem = Tumor with pleural nodules or malignant pleural dissemination

Cases in the database registered before the launch of the 7th edition were manually reclassified to be comparable.

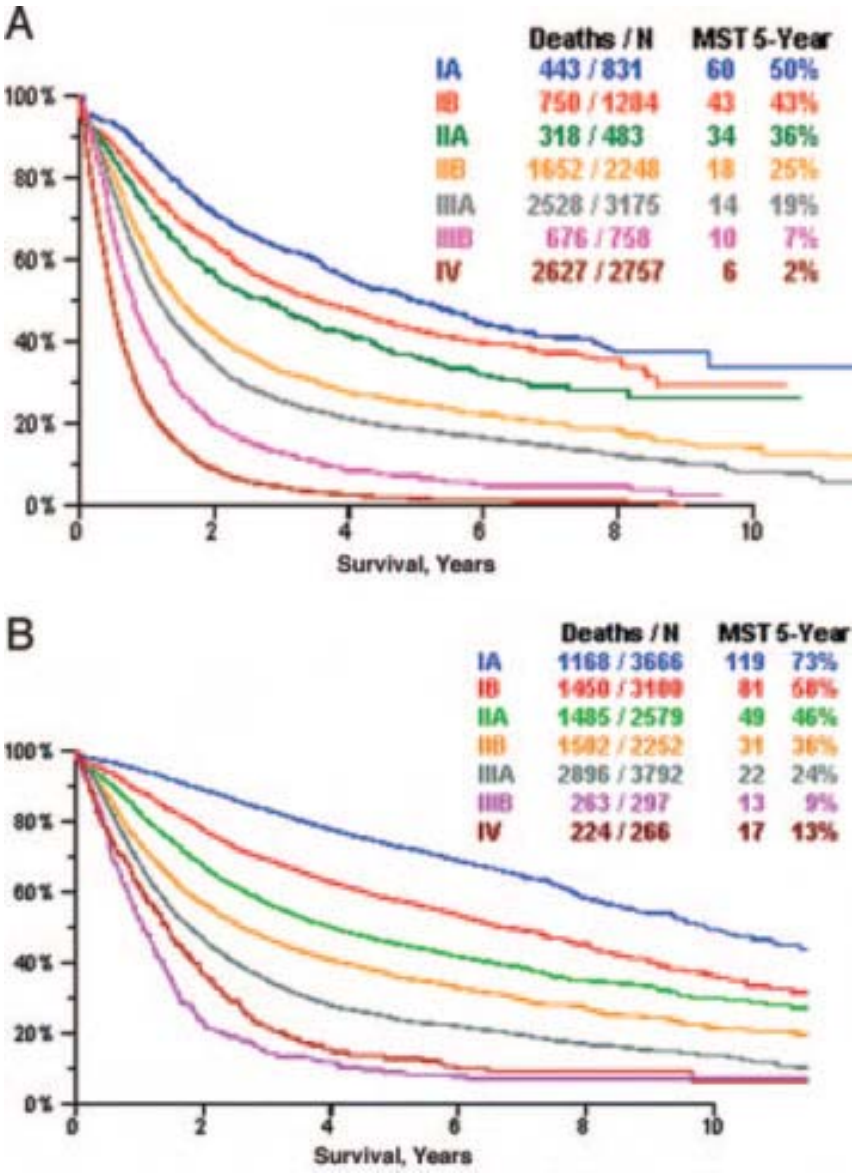
Depending upon which type of assessment being performed, a prefix may be added to the TNM, the most common being clinical - cTNM and pathologic - pTNM (Table 5) [51]. The pathological Tumor Nodes Metastasis classification [pTNM] was used to describe the distribution of the tumor using the surgically obtained tissue specimen at time of surgery.

Table 5 Types of Staging Assessments.

Prefix	Name	Definition
c	Clinical	Prior to initiation of any treatment, using any and all information available (eg, including mediastinoscopy)
p	Pathologic	After resection, based on pathologic assessment
y	Restaging	After part or all of the treatment has been given
r	Recurrence	Stage at time of a recurrence
a	Autopsy	Stage as determined by autopsy

By increasing stage, both short- and long-term survival rate decreases (Figure 9). The stages Ia to IIb are defined as localized disease, accessible for curative intent surgical resection provided no medical contraindications to be present. Stages IIIa and IIIb are defined as locoregional disease and stage IV as advanced disease, primarily available for chemo- and radiotherapy only with palliative intent.

Figure 9 Stage grouping. A: overall survival by clinical stage for the proposed IASLC stage grouping. **B:** overall Survival by pathologic stage for the proposed IASLC stage grouping. Reproduced from Goldstraw et al. [52]



Tumor histology

All patients with confirmed lung cancer were registered in the hospital's lung cancer database. The following NSCLC tumors were included the present studies: Adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and carcinoma, not otherwise specified (carcinoma, NOS). All tumors were classified according to the World Health Organization [WHO] recommendations published in 2004 (Table 6) [53].

Table 6 Malignant Epithelial Lung Tumors [WHO classification 2004]

Squamous cell carcinoma Papillary Clear Cell Small Cell Basaloid
Small cell carcinoma Combined small cell carcinoma
Adenocarcinoma Adenocarcinoma, mixed subtype Acinar adenocarcinoma Papillary adenocarcinoma Bronchioloalveolar carcinoma Nonmucinous Mucinous Mixed nonmucinous and mucinous or indeterminate Solid adenocarcinoma with mucin production Fetal adenocarcinoma Mucinous ("colloid") carcinoma Mucinous cystadenocarcinoma Signet ring adenocarcinoma Clear cell adenocarcinoma
Large cell carcinoma Large cell neuroendocrine carcinoma Combined large cell neuroendocrine carcinoma Basaloid carcinoma Lymphoepithelioma-like carcinoma Clear cell carcinoma Large cell carcinoma with rhabdoid phenotype
Adenosquamous carcinoma
Sarcomatoid carcinoma Pleomorphic carcinoma Spindle cell carcinoma Giant cell carcinoma Carcinosarcoma Pulmonary blastoma
Carcinoid tumour Typical carcinoid Atypical carcinoid
Salivary gland tumours Mucoepidermoid carcinoma Adenoid cystic carcinoma Epithelial-myoepithelial carcinoma
Carcinoma, not otherwise specified

Surgical access

The surgical procedures performed were grouped into open thoracotomy, video-assisted thoracoscopy or other, e.g. median sternotomy. Types of resection were grouped into lobectomy, bilobectomy, sublobar resection, sleeve resection or pneumonectomy. The numbers of days in need of postoperative thoracic drainage were registered for all patients.

7.3 Statistical analysis

We applied the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement guidelines when reporting the three observational studies (16). All *p* values were two-sided, and a *p* value of less than 0.05 was considered statistically significant. Statistical analyses were performed using Stata software (StataCorp LP, College Station, TX), SPSS Statistics software (IBM Corp, Armonk, NY), and R: A language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria) [54]. In addition to standard descriptive statistics, various statistical methods were applied.

Survival analysis

Overall survival was assessed by inspection of the Kaplan-Meier curves, and log-rank test statistics was used to determine differences in survival.

Cox propotional hazard regression

In all three studies, adjustment for possible confounders was carried out using the Cox proportional hazard regression model. To identify risk factors, a stepwise, backwards elimination of insignificant variables was performed. Only significant variables was included in the final models.

Variables

In all studies, potential confounding variables were divided into two or more groups. Continuous variables like number of pack years of smoking, total years of smoking, and days in need of thoracic drainage were dichotomized according to their respective median values. In study III, age was treated as a continuous variable in the analysis, in opposite to the first two studies were age was dichotomized according to the median age in the cohort. The ECOG PS was categorized as ECOG PS ≤1 or ECOG PS >1. Comorbidities were dichotomized as CCI =0 or CCI ≥1. BMI was categorized in four weight groups, underweight, normal weight, overweight, and obese.

Study I - Mantel-Haenzel stratification

In study I, an explanatory strategy was used to investigate the relationship between severe COPD and survival [55]. All other variables were of interest only as possible confounders or effect modifiers of this association. Initially, COPD as an exposure variable was categorized in three groups according to the GOLD-guidelines. Severe COPD (FEV_1 < 50% of predicted), mild to moderate COPD (FEV_1 ≥ 50%), and normal lung function. Due to the similarities in survival rate and non-significant difference in hazard ratios (HR) in patients with mild and moderate COPD and patients with normal lung function, these two groups were merged and compared to the severe COPD group in the final survival analysis.

Incidence rate ratio (IRR) was calculated by the ratio of incidence density of death in severe COPD patients divided by the ratio of incidence density of death in the patients with mild to moderate COPD and normal lung function. A Mantel–Haenzel stratification analysis was performed to quantify confounders and to pinpoint effect-modifiers using the Breslow and Day test of heterogeneity. Quantification of confounding was done by comparing the crude IRR with the adjusted Mantel–Haenzel IRR using the formula $\frac{IRR_{MH}-IRR_{crude}}{IRR_{crude}}$. Tumor stage

as a possible effect modifier and variables with confounding effect > 4% (age, gender, ECOG-status, diagnose, pTNM-stage, surgical approach and type of surgery) were included in the multiple regression model.

Study II – Bivariate analysis

All potentially confounding variables were identified using bivariate analysis and any variable whose univariable test was considered to be a possible confounding factor for the multivariable regression model. The effects were quantified by hazard ratios with its 95% confidence interval (CI). Survival curves were constructed with the Kaplan-Meier method to determine differences between female and male patients, younger and older than mean age. Differences were estimated by the Breslow and log rank test statistics. In continuous variables, differences between the groups were estimated by one-way analysis of variances (ANOVA) or independent sample t-test, as appropriate. The chi-square test for contingency tables with different degrees of freedom was used to detect associations between categorical independent variables.

Study III - Competing risk analysis

Overall survival was first assessed by inspection of the Kaplan-Meier curves. For each risk factor, a univariable survival analysis was performed by using the log-rank test. Any variable whose univariable test had $p < 0.25$ was considered candidate for the multivariable model. Since Kaplan-Meier curves are not valid when studying individual competing causes of death, the empirical cumulative incidence curves were determined for each cause of death using the Nelson–Aalen estimator of the cumulative cause-specific hazards [56]. The influence of each risk factor was assessed in a Cox' proportional hazards model. In the analysis of each competing cause of death, the remaining causes were treated as censored.

7.4 Ethics and approvals

The database was commenced in 2002 and fully operable since 2003. The Hospital's Data Protection Officer for Research approved the registry, Approval no.: 07/9673. The present study was approved by the Regional Committee for medical and health research ethics (REC), project no.: [2.2007.555] (ref 2009/606a), protocol (S-07130a). Written consent for entry in the database was obtained from all registered patients.

8 RESULTS

The results from the present studies confirmed that surgically treated early stage NSCLC patients with severe COPD compared to patients with normal lung function and mild to moderate COPD had decreased survival passing one year after surgical (paper I). Further, there were no differences in overall survival between male and female patients. Compared to population data, standardized mortality ratio was increased in both males and in females (paper II). The cumulative incidence of lung cancer deaths was continuously increasing after surgical resection. The risk of having died from lung cancer surpassed all other causes of death three months after resection. Lung cancer persisted beyond five years after resection to be the most common cause of death throughout the observation period (paper III).

8.1 Survival in patients with severe COPD undergoing surgical resection for non-small cell lung cancer (Paper I)

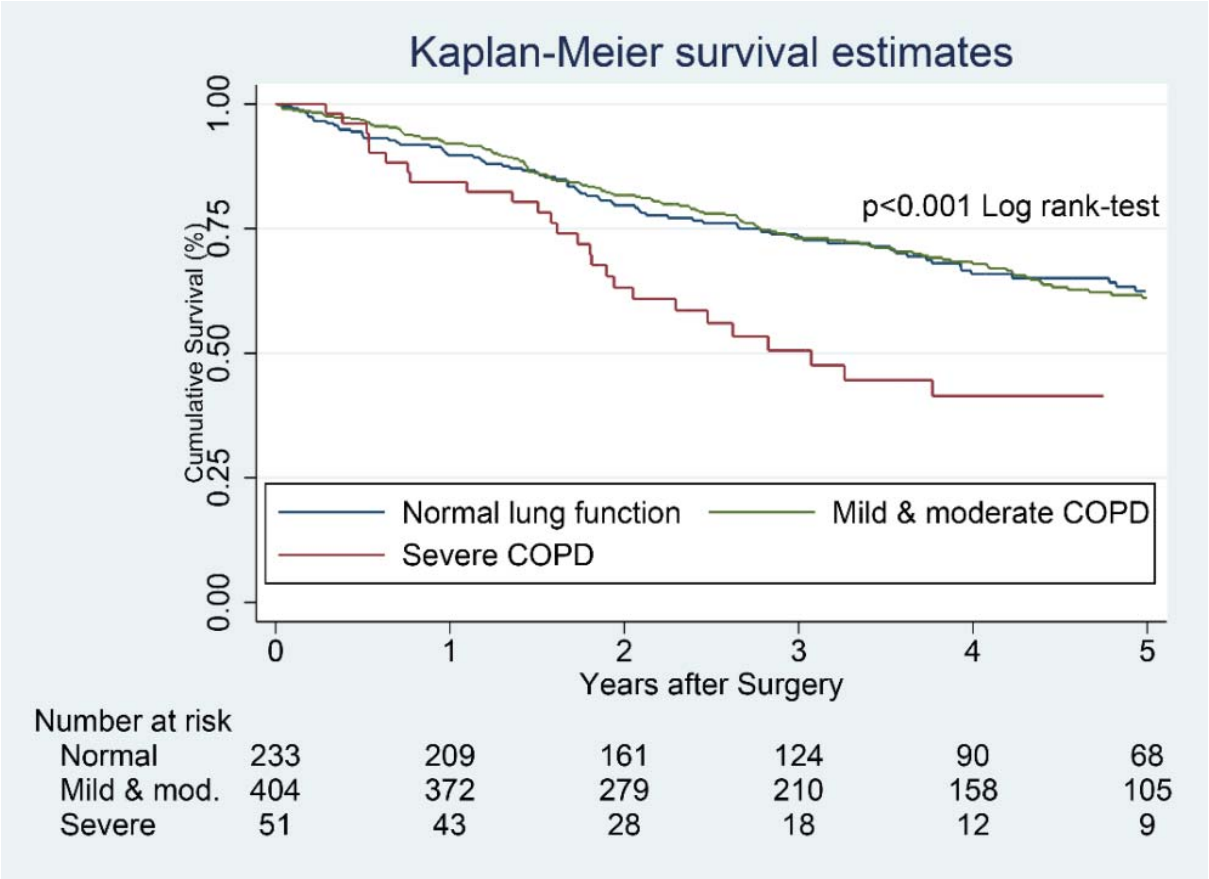
Among the 688 patients 51 (7%) had severe or very severe COPD, GOLD stage III and IV, while 404 (59%) had mild to moderate COPD, GOLD stage I and II. The remaining 233 (34%) patients had normal lung function. The three lung function groups were comparable with respect to age, gender, numbers of comorbidities, and distribution of tumour stage. There were no never-smokers in the severe COPD group. The main surgical procedure was thoracotomy. Video-assisted thoracoscopy and other procedures were more frequently performed in patients with severe COPD compared to the other two groups of patients. Fewer pneumonectomies and more sublobar resections were performed in patients with severe COPD compared to the two other groups.

There were no deaths in the severe COPD group during the first 30 or 90 days of postoperative follow-up. Patients with severe COPD had shorter cumulative survival (median 3 vs. 7 and 8 years respectively, *p-value=0.01*). During the study period, cumulative survival was similar in patients with normal lung function and patients with mild to moderate COPD (Figure 10). In the patients with severe COPD, cumulative survival compared to the other two groups of patients was significantly reduced passing one year after resection.

The crude association between severe COPD and overall survival was IRR =1.73 (95% CI: 1.12– 2.58, *p-value=0.01*), indicating that patients with severe COPD had 73 % higher risk of mortality compared to patients with mild to moderate COPD and normal lung function.

In the multivariable Cox regression analysis, age, stage, ECOG status and pneumonectomy were identified as the strongest confounders. When controlling for multi-confounding, the association between severe COPD and overall survival represented a 69% increased risk ($HR_{adj.}$=1.69, 95% CI: 1.12 – 2.55, *p-value=0.012*) compared to the rest of the patients.

Figure 10 Overall survival after surgery for NSCLC in patients with and without COPD.



8.2 The absence of gender differences in survival among surgically treated patients with NSCLC (Paper II)

The study population (n = 692) comprised 368 (53.2%) males and 324 (46.8%) females. The patterns of smoking were similar in younger males and females. There were more never-smokers among older females (17.0%) than in the other groups. Lobectomy was the most common surgical procedure in older patients (females 80% and males 72%) and pneumonectomy was more frequently performed in younger patients than in the older. Adenocarcinoma was the most frequent histological type in females (64.8%) and there were more squamous cell carcinomas in both younger and older males than in females.

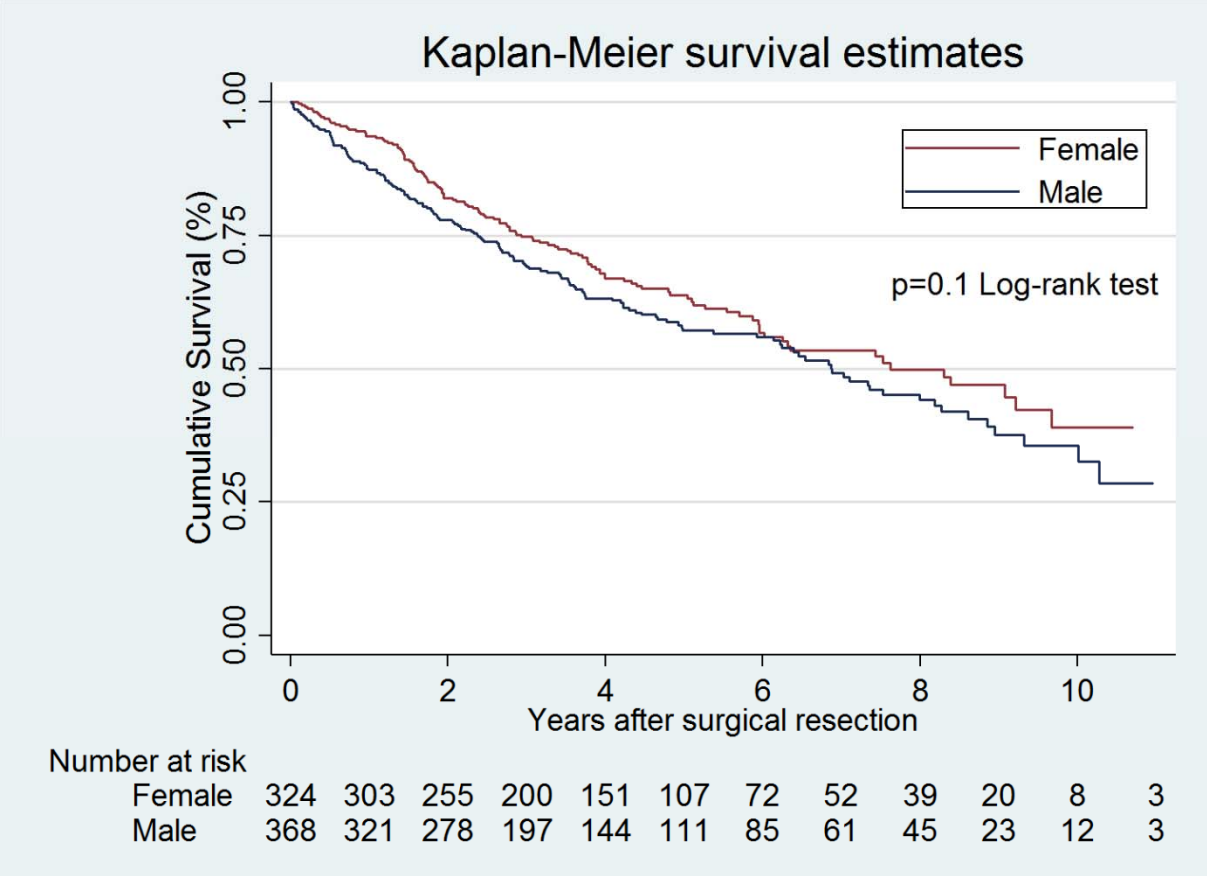
During the median follow-up time of 3.5 years (range 4 days–11.7 years), 288 patients (41.5%) died. Females had nearly 10% increased overall survival compared to males, but the difference did not reach statistical significance. The median cumulative survival of all patients was seven years. During the first five years, cumulative survival did not differ significantly between the four age and gender groups.

Stratifying the cohort according to female and male gender, we found no statistically significant difference in survival (HR 1.21, 95% CI 0.96–1.53, p = .10) (Figure 11). Applying Cox proportional hazard regression model, including tumor stage and lobectomy as covariates (i.e. confounders), no significant gender difference was found.

Tumor stage, lobectomy and large cell carcinoma were identified as confounders when analyzing gender and age groups. Controlling for multi-confounding, there was no difference in overall survival between males and females within the same age groups. Comparing the younger and the older patients adjusted for confounders, the mortality risk was significantly increased in elderly females (HRadj. 1.60, 95% CI 1.12–2.28, p = .01) compared to the younger females.

Based on national data, the SMR in our male patient cohort was 4.1 times higher, compared with the risk of mortality in the comparable male Norwegian population. The SMR in females was 6.5 times the expected mortality risk.

Figure 11 Overall survival after surgical intervention for non-small cell lung cancer according to gender.



8.3 The competing risks of death after surgical resection for NSCLC (Paper III)

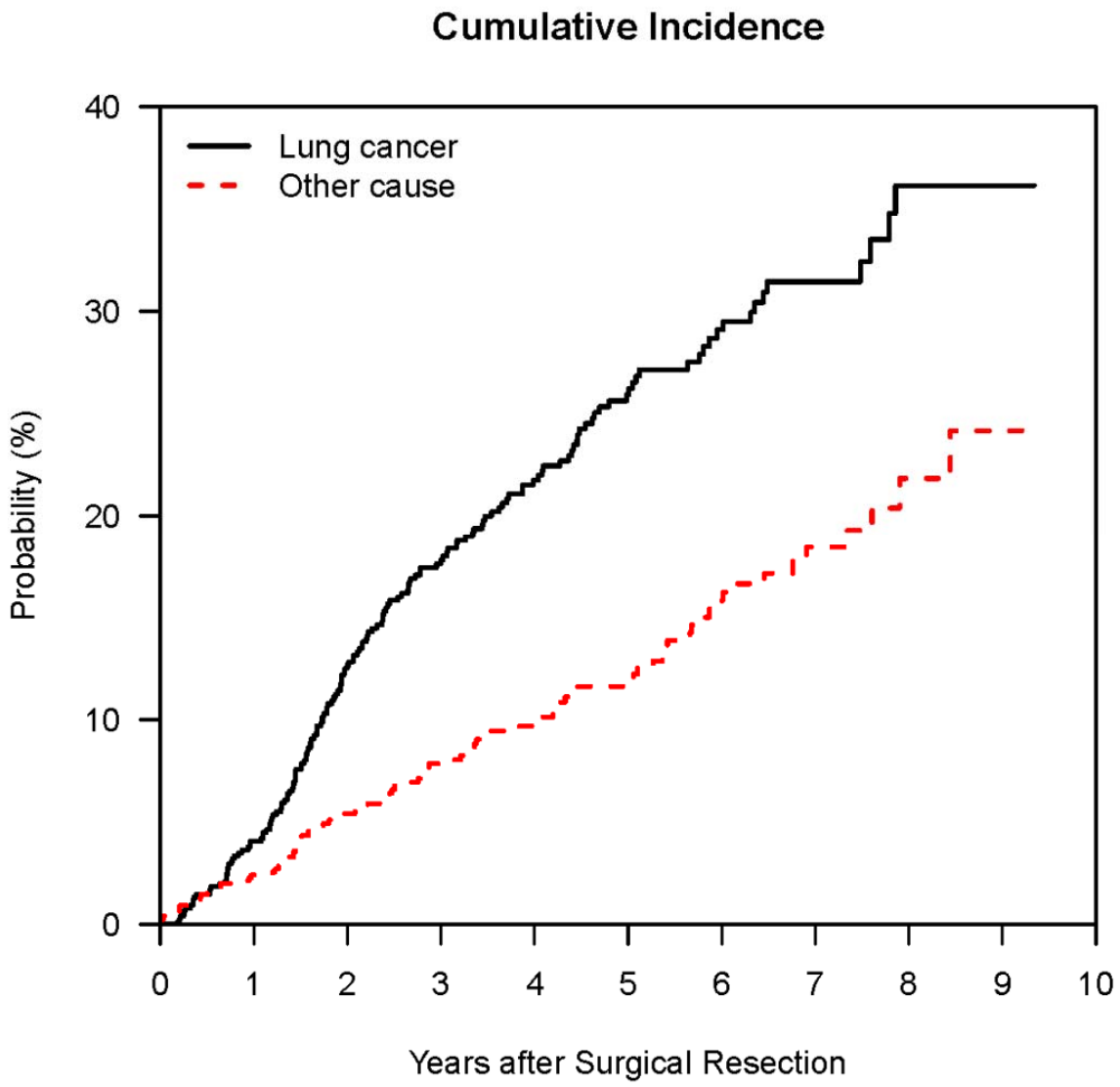
In total, 756 patients surgically treated for early stage NSCLC were included. Follow-up ranged from 3 days to 9.3 years, and median survival time was 7.3 (95% CI 6.0-7.9) years. A total of 260 deaths were observed in the follow-up period, of which 170 were due to lung cancer and 90 to other causes (e.g. CVD, pneumonia, COPD, neurological diseases).

Among all patients, overall 5 years survival was 62%. Three patients (0.4%) died within 30 days after surgical resection. Another seven patients died between day 31 and day 90. Thus, 90 days mortality was 1.3%.

Multivariable analysis showed that increased age, severe COPD, preoperative examination without FDG-PET/CT, ECOG ≥2, tumor histology other than adenocarcinoma and squamous cell carcinoma, and increasing disease stage were associated with increased mortality rate.

Cumulative incidence curves for each cause of death (i.e. the probability of having died due to a specific cause at any given time) were drawn (Figure 12). At day 129 after resection, lung cancer surpassed all other causes of death and remained the most frequent cause of death throughout the study. Risk of death caused by lung cancer persisted beyond five years after surgical resection. At the end of follow-up (9.3 years), the risk of having died from lung cancer or other causes was 36%, and 24%, respectively.

Figure 12 Cumulative incidence of causes of death after surgical resection in a cohort of 756 patients with non-small cell lung cancer.



9 DISCUSSION

9.1 Methodological considerations

Study design and patient selection

The present studies are observational studies with cohort design, comprising patients included at time of lung cancer operation, and followed until death or censoring. Because the surgical treatment was performed with curative intent, all patients were assumed disease free at inclusion.

Cohort studies are important in order to evaluate and potentially reveal differences in outcome between two groups – one that is exposed and the other not exposed. In our case, we studied survival differences between females and males and in patients with and without COPD. The identification of differences in survival may help to change, focus and enhance internal routines of preoperative work-up or treatment of lung cancer patients. We believe the present results to reflect the treatment policy applied on resected lung cancer patients in our institution.

The generalizability of epidemiological studies is dependent on internal and external validity. A study possesses internal validity if it confirms inference between exposure and outcome. In other words, internal validity indicates that there is evidence that the study confirms the postulated hypothesis. Selection bias, information bias and confounding may influence the internal validity. External validity reflects the possibility of generalizing the results of a study to other populations.

Internal validity

Selection bias

The validity of our studies may be compromised by selection bias. According to a national registry maintained by the Norwegian society of cardiothoracic surgery, approximately 22-25% of annual lung cancer operations in Norway were performed in our institution [57]. A paper published in 2012 reported the overall resection rate of patients with NSCLC in Norway to be 22.5% [40]. Our hospital serves approximately 20% of the Norwegian population. Hence, the annual numbers of lung cancer resections was similar to the national average numbers of lung cancer resections. This may support the assumption that the present cohort comprised an average of surgically treated lung cancer patients in Norway. Hence, we may postulate that the selection bias of included patients was low.

The prospective design of the lung cancer registry is of importance in our studies. In retrospective collected databases, the risk of unintentional loss of data registrations due to misclassification is common. The consecutive inclusion of patients was based on multiple patient contacts including the MDT meeting, hospital admittance for surgery and postoperative histology reports. This ensured that very few patients were exempted from inclusion in the registry, and also that the selection bias was low.

Another advantage of the cohort-design is that it enables us to examine the association of outcome and exposure during follow-up. However, we did not perform any postoperative

evaluations of the patients other than notifying survival, deaths and death dates at the time of censoring.

The observation of relatively large numbers of patients (n≈700) undergoing, guideline recommended, preoperative work-up and treatment logarithms for more than ten years, strengthen the quality of the study.

Information bias

A source of bias in cohort studies may be the potential failure to obtain precise and detailed historical and follow-up information. In the present database, data concerning deaths were regularly provided from the National Registry with not more than two weeks delay. This Registry is compulsory for all inhabitants and provides the personal identifier code and, the social security number, - unique for all residents in the country. Hence, follow-up concerning death dates was for practical purposes complete. Extraction of data concerning causes of death from the Norwegian Cause of Death Registry [NCDR] was considered. However, researchers at the NCDR reported in 2015 that the Registry's use of unspecific codes for underlying causes of death remained high, and we therefore chose to use our individually collected data [58]. Most of the data concerning cause of death was reported from the local hospitals or through our own hospital charts concerning additional cancer treatment. In only 4-5% of the cases, we had to contact the patient's local hospital or general practitioner to provide the exact cause of death. To our knowledge, data concerning cause of death was without exceptions complete for all treated patients after 2007.

Confounding

Confounding represents another potential limitation to internal validity and reliability of results in a study. A confounder is a variable correlated to the dependent variable and causally linked to the outcome in the study. In this way, a confounder may have a hidden effect on the outcome of a study. This effect may either falsely create or hide an already existing effect. To handle this unwanted effect, we applied two different statistical methods: a) stratification and b) adjustment in a statistical regression model. In paper I we performed a Mantel–Haenzel stratification analysis to quantify confounders. In paper II and III, all potential confounding variables were identified using bivariate analysis. In all three studies, adjustment for multiple confounders was carried out using the Cox proportional hazard regression model with a manual backward stepwise elimination procedure. This method left only significant variables in the model.

Considering the previously mentioned biases and handling of the confounding factors, by applying appropriate statistical methods, we found the internal validity of the present studies to be of high quality.

External validity

External validity assumes internal validity and expresses the applicability of the results of the studies to be transferable to other populations. In the present studies, the cohort only consisted of patients selected for surgical treatment. Hence, the results may not be transferred to a general population of lung cancer patients. However, supported by the findings in the study by Strand et al., the present cohort comprised an average of the surgically treated Norwegian

lung cancer population as regards age and gender distribution [40]. The 1-year reported survival in the present studies was 90-93% compared to 85% reported by Strand et al. The Strand study included patients with stage III and stage IV disease. In a Danish study published in 2012, the 5-years survival rate for patients with stage I and stage II disease without any comorbidities was 60%, in line with 5-years survival in our patients of 62%. Furthermore, according to the International Association for the Study of Lung Cancer, the overall survival for stage I and stage II NSCLC was 62%.

In our registry, no records were made concerning patients discussed at the MDT meeting who were not found eligible to surgical resection. Unfortunately, this limitation is inherent in registries of our type and may reduce the generalizability of the results. However, detailed clinical information describing the present cohort with regards to risk factors and surgical details may partly compensate this limitation. In this respect, the present studies contained detailed information that strengthened the external validity of the results.

Based on these considerations, and the high internal validity, we believe that the results from our studies are generalizable to a population of surgically resected early-stage NSCLC patients.

9.2 Discussion of main results

The impact of COPD on postoperative mortality (paper I)

In this study described in paper I, the purpose was to explore the impact of COPD on overall survival after surgically treated lung cancer. Severe COPD was not associated with increased 1-year mortality, but after 2 and 5 years, these patients had increased mortality compared to patients with normal lung function and mild to moderate COPD. These results demonstrating the long-term mortality of patients with severe COPD are in accordance with comparable studies [59, 60]. In addition, the coinciding results supports the external validity and generalizability of our study. Further, the thorough information concerning lung function, smoking habits and surgical details strengthens the results additionally. In the present paper, COPD was diagnosed and categorized according to the GOLD guidelines. The lung function measurements were based on accurate, sprometric validation of all patients. Opposed to this, other studies have not had access to detailed data concerning lung function. Thus, COPD was confirmed according to physician-diagnoses rather than spirometic verification. We believe that this level of precision in the present study enhances the reliability of the results.

In contrast to other studies, we did not find any difference in overall survival between patients with normal lung function and patients with mild to moderate COPD. This is contradictory to the findings in a previous paper reporting reduced overall survival in patients with all severities of COPD compared to patients with normal lung function [59]. There are differences between the two studies that may explain the conflicting findings. The two studies differed with respect to gender distribution, degree of COPD, stage distribution and ethnicity, which has been shown to influence survival and therefore make comparisons difficult. Sekine's study included 32% females whereas the proportion of females was 47% in our study. Further, their study contained patients with all tumor stages. Differences in ethnicity

may also be of importance. Sekine's study comprised an Asian population that may not necessarily be comparable to our Caucasian population [61].

Furthermore, in the present study all patients with severe degree of airway obstruction were identified preoperatively. We therefore were able to pay extra attention to this group of patients during their postoperative care. This may at least in part explain why there were no deaths during the first 90 days. Throughout the study period, the number of patients in our tertiary center increased, and the overall early mortality rate of 2.2% is in line with what previously has been reported from "very high volume centers" (def. >190 cases per year) [62]. In addition to the beneficial survival of patients with severe COPD, the findings also suggest that patients with mild to moderate COPD should be offered identical surgical treatment to patients with normal lung function. One limitation of the present study was the lack of registration of results obtained in cardiopulmonal exercise testing [CPET]. Because most patients included in the study were referred from their local hospitals, this investigation was not performed routinely in our institution. Hence, the results of the standardized CPET examination were either not available for registration or a CPET examination was not performed.

Not only COPD was associated with increased mortality after surgical resection of NSCLC. Other comorbidities associated with increased mortality included known cardiovascular and cerebrovascular disease, diabetes type I and II, and osteoporosis [39]. Several of those risk factors were recorded in our database and categorized by the Charlson comorbidity index [CCI]. The CCI was similar across the lung function groups, indicating that severe and non-severe COPD groups were comparable with respect to comorbidity. Additionally, comorbidity was not identified as a confounder in the statistical analysis.

According to a Norwegian study, using the fixed ratio FEV_1/FVC to define airway obstruction in elderly subjects may increase the frequency of diagnosing COPD [63]. Applying this knowledge to our study population may, to some extent explain the similar rates of survival in patients without COPD and patients with mild and moderate COPD. The present cohort comprised patients with median age of 66 years, indicating that a considerable number of elderly patients were in the study. This may have led to over-diagnosis of COPD. However, merging patients with mild and moderate COPD with the patients with normal lung function in the final analysis eliminated the problem of potential misclassification.

COPD is characterized by irreversible airflow obstruction. The condition is also recognized as a systemic inflammatory disorder with numerous pulmonary and extra-pulmonary manifestations [64]. This may indicate that reduced overall survival in COPD patients may be related to systemic effects rather than to low lung function *per se*. Unfortunately we have no available data in the present database to explore this hypothesis further.

The standard extent of resection for lung cancer in our institution has been lobectomy with systematic lymph node dissection. In general, for patients with clinical stage I and II NSCLC, being medically fit for surgical resection a lobectomy rather than sublobar resection is recommended [5]. However, patients with several or severe comorbidities may be more likely

to undergo sublobar resection. In this context, the sublobar resections may represents a possible bias and consequently contribute to a higher recurrence and mortality rate.

The absence of gender difference in postoperative mortality (paper II)

The second paper (paper II) assessed the potential gender differences in mortality after surgical treatment for NSCLC. The prevailing opinion was that female patients had improved prognosis compared to males. To investigate this statement, we tested the hypotheses that female survival was superior to male survival following surgical resection in the present cohort. The analysis did not indicate any significant gender differences, and only displayed a survival difference between patients older and younger than the median age of 66 years. This difference became significant 5 years after surgical resection. The finale analysis was a comparison of the observed to the expected number of deaths in the study population provided the assumption that mortality rate in the study population was the same as in the total male and female Norwegian population [Standardized Mortality Ratio, SMR]. The lung cancer patients in our cohort had an increased mortality rate for males of 4.1 and females of 6.5 times higher than the adjusted mortality rate for age in the normal population.

Several studies have indicated better survival in females with NSCLC than males [4, 65, 66]. Explanations to this difference has been thought to result from diverging clinicophatological characteristics and altered susceptibility to environmental exposures between men and women. In some studies the cohorts in which analysis demonstrated dissimilarities between the genders were small (n=90-200 patients) with low proportion of female patients. Only a small number of studies have been designed to assess gender differences [67-74]. Others were large registry studies without detailed information concerning risk factors such as comorbidities, smoking habits and lung function. In addition, data collection was performed before the turn of the last century, and only data from patients older than 65 years were analyzed [75, 76]. The survival advantage among females was tried to be explained from the spectrum of histological diagnosis with an overweight of adenocarcinomas and large cell carcinomas in females. In our cohort, an even higher proportion of adenocarcinomas was found in female patients, but still we were unable to reveal any survival difference between genders.

The trends in tobacco consumption have changed over the last decades, and this may have influenced prevalence and outcome of NSCLC in males and females. In our cohort, the younger patients (< 66 years of age) had congruent patterns of smoking, with similar proportions of never, current and ex-smokers, 5%, 65%, and 30%, respectively. In elderly patients (> 66 years), the proportion of never smoking females was significantly higher, 17% versus 5% among males. The changing trends in smoking habits, indicates that the male and female proportions of deaths due to smoking induced cancers are converging and may probably cross over in some industrial countries [25]. It has been suggested that females are more susceptible to develop lung cancer from smoking than males. However, in a recent Italian case control study adjusted for confounders including tobacco type and inhalation

depth, the findings did not support a higher female susceptibility to tobacco-related lung cancer [77].

Norwegian studies have suggested females to have better prognosis than males following lung cancer treatment [4, 78]. A retrospective study from Haukeland University Hospital in Bergen (Norway) in which the analysis were based on 351 patients (32% females), relative 5-years survival in patients operated for non-small cell lung cancer was 66.1% for females and 45.7% for males. Female gender was an independent positive prognostic factor related to improved survival. However, they did not adjust for other comorbidities than CVD neither did they include lung function measurements. In addition, the study included patients in stage III, and inclusion of patients started in 1988. These features may have caused less reliable results than findings from our cohort. Another, population-based Norwegian registry study also reported beneficial survival among females [4]. However, the study failed to adjust for comorbidities, smoking and treatment modalities including surgical resection, stereotactic body radiotherapy [SBRT] and chemotherapy. An interesting finding however, was the different rate of increase in overall 5-years cumulative survival between females and males. In the period 1998 to 2002, compared with 2003 to 2007 the overall survival increased from 49.9% to 51.8% in females (only 2%) while the overall survival increased from 31.8% to 40.9% in males (almost 10%).

The life expectancy analysis of SMR in the present study, demonstrated increased mortality rates in both gender compared with population data (6.5 in females and 4.1 in males). The increased mortality rate for both males and females is worrying, but as risk factors for lung cancer coincide with risk factors for many other diseases, the risk profile of these patients may contain more comorbidities, higher levels of smoking, and impaired lung function compared to the general population.

The difference in prognosis seems most closely related to smoking habits among women, since their tobacco consumption reached maximum decades later than in men. Hence, the gender gap in lung cancer mortality is steadily narrowing and is expected to close [10].

The cause specific competing risk of death after surgical resection (paper III)

In the third study (paper III), the time period of data extraction of the cohort was forwarded to the period 2007 to 2015 compared to the two former studies. Hence, we were able to analyze data concerning specific causes of death. The overall survival was 93.5%, 62.3% and 50.3% at 1, 5, and 7 years, respectively. The most common cause of death exceeding 129 days following resection was throughout the study lung cancer. Even after adjusting for confounding risk factors, lung cancer remained to be the main cause of death. We found identical risk factors for overall death and death from lung cancer where increasing age, severely reduced lung function, ECOG ≥2, no preoperative FDG-PET/CT, and increasing tumor stage all contributed significantly. This correlation of risk factors may be explained by lung cancer being the most frequent cause of death. For death due to other causes than lung cancer, increasing age, low BMI, smoking and increased ECOG PS were significantly associated with cause-specific mortality.

The overall survival after surgical resection for NSCLC in the present study was in line with comparable studies. A recent published Danish study with 3150 surgically resected patients

(2005 to 2010), demonstrated that 5-years survival was 69% in patients with disease stage I and no comorbidities [79]. Both the Danish - and the present populations are taken care of by national health services who provide universal, tax-supported health care, guaranteeing unconstrained access to general practitioners and hospitals. Further, the overall survival in our study was in line with estimates from the International Association for the Study of Lung Cancer [80]. These nearly identical findings may to some degree support and confirm the external validity of our results.

A further strength of the present study is that we were able to analyze our data with respect to causes of death. Few studies have had the opportunity to perform analogous analyzes. Hence, our results present new knowledge to this field of lung cancer researcher. The study indicated that the probability of dying from lung cancer was similar in males and females. However, the probability of having died from other causes was lower in females than in males. This may be explained by the higher average life expectancy in women in the general population [81]. Provided eventually cure from lung cancer, it may be assumed that the patients resume normal life expectancy. In the context of study II in which no gender differences regarding survival was identified, the results from the present study further support these findings. It can be imagined that at least in part; the explanation to the claimed gender differences in lung cancer survival is due to female advantage in normal life expectancy. In agreement with our first study, the present study points out severe COPD to be associated with increased mortality risk. This may be due to higher susceptibility to lung cancer in patients with severe COPD.

Another explanation to the increased mortality risk in COPD patients may be a more frequent use of limited resection in patients with severe COPD. Limited resection may increase the risk of relapse and mortality in lung cancer patients [82]. However, when it is the only possible treatment option, limited resection is recommended compared to omit surgery. When collecting data concerning causes of death, we distinguished between death from lung cancer, CVD and other causes, including other types of cancers. Since the numbers of cardiovascular deaths comprised few patients (n=19), we decided to regroup the causes of death into two groups, death from lung cancer and death from non-lung cancer, respectively. The fact that unexpectedly few patients died from CVD may have several explanations. The selection of operable patients eligible for surgical resection may have been too strict with respect to CVD. Further, the number of patients with CVD referred for surgery also depended on assessments and cardiological considerations made by the referring hospitals. However, all referring hospitals - as well as the MDT meeting - followed national and international guidelines when assessing patients for surgical resection [34, 35]. In addition, at the multidisciplinary team meeting we urged the referring physicians to discuss all borderline patients suffering from multiple comorbidities in the meeting, to assess as many patients as possible eligible for surgical treatment. Despite this, we may have had a too timid practice concerning acceptance of patients with CVDs.

Implementing FDG-PET/CT in the preoperative staging of cancer resulted in reduced postoperative mortality in the present study. In general, in Norway it has been a conservative approach to implement FDG-PET/CT in the preoperative evaluation of lung cancer patients. In our opinion, the present results underscored the usefulness of FDG-PET/CT in all lung

cancer patients eligible for surgical resection. This was also supported by the findings in our previous study analyzing data from our database [83]. The study emphasized FDG-PET/CT to aid precise diagnosis of mediastinal lymph nodes in the preoperative staging of lung cancer.

A further bias may be related to the classification of causes of death. Patients dying at home, in nursing homes or in other facilities may not have been correctly classified. When documented that recurrence or metastases and death occurred within a reasonable time span (less than 12 months), the patients were classified as dying of lung cancer, regardless of last known medical condition leading to death. This may have underestimated cardiovascular and other causes of death. An explanation to the relatively high level of early lung cancer deaths may be related to insufficient perioperative lymph node dissection. Despite careful, guideline-recommended dissection of lymph nodes, some patients in our material may have been staged too low [84]. This may have contributed to early tumor relapse. However, at least four out of the five cases of early relapse (within 200 days after resection) were of local, pleural or distant origin and not related to possible retained lymph node stations.

10 CONCLUDING REMARKS & FUTURE PERSPECTIVES

- Patients with early-stage lung cancer and severe COPD have reduced long term overall survival compared to patients with mild to moderate COPD. The survival rates in patients with normal lung function and mild to moderate COPD were similar.

- In a cohort of surgically treated early stage NSCLC patients, no survival difference in male and female patients was found. This is in line with the anticipated diminishing gap in gender differences regarding incidence and outcome of lung cancer. Not unexpectedly, an increase in mortality rate was demonstrated in older patients. The increased SMR in female patients may be associated with lung cancer patients suffering from additional comorbidities and other risk factors for mortality compared to the general population.

- At the end of follow-up, overall mortality was 60% after curative-intent surgical resection for lung cancer. Lung cancer became the prevailing cause of death three months after resection and persisted throughout the study. In a competing risk model, the probability of dying from lung cancer or other causes was 36% and 24%, respectively. For death due to other causes (including cardiovascular disease), age, gender, BMI, smoking and ECOG were significantly associated with cause-specific mortality. The risk factors contributing to death from lung cancer were similar to the risk factors for overall mortality.

- Similar survival rates in patients with normal lung function and mild to moderate COPD suggests that the same indications for lung cancer surgery may be applied. With careful preoperative selection, surgical resection may safely be offered to lung cancer patients with severe COPD with respect to early mortality.

- In spite of increased mortality in elderly patients (>66 years) with NSCLC, a 5-year overall survival of more than 50% may encourage surgical resection also in senior lung cancer patients.

- Surveillance of risk factors associated with increased mortality should be taken into account in the postoperative follow-up after lung cancer resection.

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12 APPENDIX

Figure 13 Self-administered questionnaire.

Oslo universitetssykehus

Oslo universitetssykehus HF
Sentralbord: 02770

LUNGEMEDISINSK JOURNAL – SPØRRESKJEMA
(første gangs innleggelse/poliklinisk undersøkelse)

For å effektivisere undersøkelsen ved Lungeavdelingen, Rikshospitalet, er vi takknemlig om du svarer så godt som mulig på spørsmålene nedenfor, og at du tar med skjemaet når du kommer til oss. På forhånd takk!

Fast lege (utenom sykehus):……..

Hva er dine hovedplager/symptomer nå og hvor lenge har du hatt disse symptomene?

	Symptomer (f.eks. hoste)	**Varighet** (f.eks.4uker)
1.		
2.		
3.		

Navn: ……..
Adr: ……..
Sted ……..
F.nr.: ……

Gift ☐ Ugift ☐ Samboer ☐ Skilt ☐ Enke(mann) ☐ Bor alene: Ja ☐ Nei ☐

Økt forekomst av sykdommer i familien din (barn, søsken, foreldre):
Astma ☐ Emfysem ☐ Hjerte/karsykd. ☐ Andre ☐

Yrke/stilling……

Ev. pensjonert fra (dato):		Ev. sykemeldt fra (dato):		Ev. ufør (dato):	

Har du vært eller er du i arbeidet ditt utsatt for støv, gass eller irriterende damper?: Ja ☐ Nei ☐
I tilfelle ja: Hva slags støv/gass eller damp? Hvor lenge?

1.		
2.		

Tidligere sykehusopphold?

	Tilstand/sykdom (f.eks. lungebetennelse)	**Sykehus** (f.eks. Bærum SH)	**År** (f.eks.1997)	**Behandling/operasjon** (f.eks. antibiotika)
1.				
2.				
3.				

Ev. andre sykdommer/tilstander du har vært behandlet for:

	Sykdom (f.eks. hjertekrampe)	**Behandlet fra** (f.eks. januar 1985)	**Behandlet til** (f.eks. fremdeles under behandling)
1.			
2.			
3.			

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Tuberkulinforhold (finnes blant annet i gamle tuberkulinkort)

Pirquet prøve	Positiv	☐	Negativ	☐	Vet ikke	☐
BCG-vaksinert	Ja	☐	Nei	☐	Vet ikke	☐

Er du allergisk (gjelder også medisiner)? Ja ☐ Nei ☐ Vet ikke ☐

Hvis Ja, for hva: .....

Medikamenter i bruk nå

	Navn (f.eks. Ventoline)	**Styrke** (f.eks. 0,1 mg)	**Dosering** (f.eks. 1 tabl. morgen og kveld)	**Behandlet fra** (f.eks. januar-86)
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				

Bruker du surstoff (oksygen) hjemme?: Ja ☐ Nei ☐ Hvis Ja, hvor mange liter/min:....

Røykevaner

Har du røkt daglig i mer enn 1 år? (Besvares også av tidligere røykere) Ja ☐ Nei ☐

Hvis ja, - hvor mange år har du røkt til sammen? (ca.) _____ år.
- hvor mange sigaretter har du gjennomsnittlig røkt per dag ? _____ sigaretter.
- hvor mange pakker a 50 g har du røkt i pipe per uke? _____ pakker.

(Fabrikkfremstilte og håndrullede 1 pk. (50g) tobakk regnes som 50 sigaretter.)

Sluttet du å røyke for mer enn ½ år siden? Ja☐ Nei ☐

Hvis Ja, for hvor mange år siden? _____ år.

Alkoholforbruk: Daglig☐ Ukentlig ☐ Sjelden ☐ Aldri ☐

Matlyst: God ☐ Dårlig Ev.vektendring siste år Ja☐ Nei☐ _____kg opp/ned

Problemer med vannlating? Ja ☐ Nei☐
Problemer med avføring? Ja ☐ Nei☐

Tidligere røntgenundersøkelser *av lungene:*
Når?_____ Hvor? _____

Hvis du selv oppbevarer disse bildene, vennligst ta dem med ved den avtalte undersøkelsen

Høyde:_____ Vekt:_____