Outcomes following pulmonary resections for lung cancer in Iceland – survival in subgroups of patients

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Thesis for the degree of Philosophiae Doctor

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Árangur skurðaðgerða við lungnakrabbameini á Íslandi - lífshorfur hjá undirhópum sjúklinga

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Ágrip

Lungnakrabbamein er þriðja algengasta krabbameinið á Íslandi og það krabbamein sem leggur flesta Íslendinga af velli. Sjúklingar læknast sjaldnast án skurðaðgerðar og því er markmiðið að beita skurðaðgerð hjá sem flestum sjúklingum þegar ábending er til staðar. Skurðmeðferð kemur hinsvegar eingöngu til greina hjá þeim sjúklingum sem eru með staðbundið lungnakrabbamein og vefjagerðin ekki smáfrumukrabbamein.

Algengasta vefjagerð þeirra sem gangast undir skurðaðgerð er kirtilfrumukrabbamein en flöguþekju- og stórfrumukrabbamein koma þar á eftir. Algengasta skurðaðgerðin er blaðnám en stundum er beitt fleyg- eða geiraskurði ellegar lungnabrottnámi. Skammtíma- og langtímaárangur skurðaðgerða við lungnakrabbameini hefur batnað á síðustu árum og þrátt fyrir að innan við fimmti hver lungnakrabbameinssjúklingur læknist í heildina þá er fimm ára lifun þeirra sjúklinga sem gangast undir skurðaðgerð vegna staðbundins æxlis í lunganu allt að 80%.

Þessi doktorsritgerð tekur til fjögurra vísindagreina (I-IV) þar sem markmiðin voru fjórskipt. Í fyrsta lagi var leitast við að reikna hlutfall sjúklinga með lungnakrabbamein sem gengust undir skurðaðgerð hjá heilli þjóð. Í öðru lagi að meta skammtíma- og langtímaárangur þessara aðgerða með sérstakri áherslu á afdrif sjúklinga sem gengust undir blaðnám, en einnig á afdrif þeirra sem höfðu kirtilfrumukrabbamein eða voru aldraðir (≥75 ára). Í þriðja lagi var markmiðið að meta hvort alþjóðlega flokkun IASLC/ATS/ERS á kirtilfrumukrabbameinum frá árinu 2011 spái fyrir um lifun þessara sjúklinga. Í fjórða lagi að kanna hversu margir sjúklingar eldri en 75 ára gengust undir skurðagerð og af hverju sjúklingar sem taldir voru með skurðtækan sjúkdóm gengust ekki undir aðgerð.

Sjúklingar voru fundnir í þremur aðskildum skráningarkerfum. Sjúklingar sem gengust undir aðgerð voru fundnir í rafrænni aðgerðarskrá Landspítala og gagnagrunni rannsóknastofu Landspítala í meinafræði. Upplýsingar um sjúklinga sem ekki gengust undir skurðaðgerð voru fengnar úr krabbameinsskrá Krabbameinsfélags Íslands. Sjúkraskrár og aðgerðarlýsingar voru skoðaðar og klínískar upplýsingar um sjúklinga skráðar rafrænt. Lifun var metin með aðferð Kaplan-Meier og forspárþættir lifunar metnir með fjölþáttagreiningu Cox. Allar rannsóknirnar fjórar voru afturskyggnar og lýðgrundaðar.

Grein I tók til 397 sjúklinga sem gengust undir 404 skurðaðgerðir við lungnakrabbameini á Íslandi frá árinu 1994 til ársins 2008. Á öllu tímabilinu var hlutfall þeirra sem gengust undir skurðaðgerð 26,4% og 8,7% fengu alvarlega fylgikvilla í kjölfar aðgerðar. Dánartíðni innan 30 daga frá aðgerð var 1% og 5 ára heildarlifun reyndist 40,7%. Sjúklingar sem ekki gengust undir skurðaðgerð höfðu

4,8% fimm ára lifun og fyrir alla lungnakrabbameinssjúklinga í heildina var lifunin 12,4%.

Grein II tók til 489 sjúklinga sem gengust undir blaðnám við lungnakrabbameini á Íslandi á árunum 1991-2014. Dánartíðni innan 30 daga var 0,6% og 4,7% fengu alvarlega fylgikvilla. Heildarlifun fimm árum frá aðgerð var 49,2% og þriggja ára lifun jókst frá 48,3% á árunum 1991-1994 í 72,8% á árunum 2011-2014 (p = 0,0004). Svipuð aukning í lifun sást einnig fimm árum frá aðgerð en skemmri eftirlitstími á síðasta tímabilinu gerir samanburð á þriggja ára lifun áreiðanlegri.

Grein III lýsti árangri aðgerða hjá 285 sjúklingum með kirtilfrumukrabbamein sem gengust undir lungnaskurðaðgerð á árunum 1991-2010 og undirflokkun þeirra samkvæmt IASLC/ATS/ERS flokkuninni frá árinu 2011. Algengasta vefjaundirgerðin reyndist vera þrúgufrumu (acinar) ríkjandi kirtilfrumukrabbamein (46%), þar á eftir þétt (solid) ríkjandi kirtilfrumukrabbamein með slímmyndun (23%) og hreisturlík (lepidic) ríkjandi kirtilfrumukrabbamein (20%). Fimm ára lifun var 45,3%. Ekki sást marktækur munur á lifun eftir undirgerðum kirtilfrumukrabbameins og IASLC/ATS/ERS flokkunin reyndist ekki vera sjálfstæður forspárþáttur lifunar í fjölþáttagreiningu líkt og sumar erlendar rannsóknir hafi sýnt.

Í grein IV var fjallað um aldraða einstaklinga (≥ 75 ára) sem greindust með lungnakrabbamein af ekki smáfrumugerð. Hlutfall þeirra sem gengust undir skurðaðgerð og árangur aðgerða var borinn saman við yngri sjúklinga sem gengust undir skurðaðgerð. Skurðhlutfall hjá öldruðum reyndist 18% borið saman við 32% hjá þeim yngri (p < 0,001). Hvorki reyndist marktækur munur á fylgikvillum né 30 daga dánartíðni milli hópanna. Algengustu ástæður þess að sjúklingar voru ekki teknir í aðgerð þrátt fyrir skurðtækan sjúkdóm reyndust ófullnægjandi lungnastarfsemi (58%), hjartasjúkdómur (17%) og margþætt önnur heilsufarsvandamál (17%). Heildarlifun var betri fyrir yngri hópinn en þann eldri (40% sbr. 44%, p = 0,019) en ekki reyndist munur á krabbameinssértækri lifun (51% sbr. 50%, p = 0,8).

Samantekið þá er hlutfall sjúklinga sem gangast undir skurðaðgerð vegna lungnakrabbameins hátt hér á landi. Skammtímaárangur þessara aðgerða er góður og tíðni alvarlegra fylgikvilla og 30 daga dánartíðni lág. Að frátöldum árangri eftir lungnabrottnám eru langtímalífshorfur sjúklinga svipaðar og í erlendum rannsóknum og lífshorfur fara batnandi.

Lykilorð:

Lungnakrabbamein, skurðhlutfall, kirtilfrumukrabbamein, blaðnám, lífshorfur, aldraðir.

Abstract

Lung cancer is the third most common type of cancer and the prime cause of cancer-related deaths in Iceland. As surgical resection is the only well-defined and well-studied curative treatment, the aim is to offer surgery to as many patients as possible who have resectable disease. However, less than one-quarter of the patients (most often non-small cell lung carcinoma, NSCLC) are diagnosed at the early stages and thus are candidates for surgery.

The most common surgical procedure is lobectomy, but in some cases a sublobar resection (wedge or segment resection) is performed or pneumonectomy is required. The most common histological type of lung cancer is adenocarcinoma (AC), followed by squamous cell carcinoma (SCC) and large cell carcinoma (LCC). The short- and long-term outcomes of pulmonary resections for NSCLC have improved over the past years, and even if the total 5-year survival of lung cancer patients is less than 20%, the survival of patients with resectable localized disease can be up to 80%.

This thesis is based on four peer-reviewed papers (I–IV) and the aim was to investigate four key issues: (1) to investigate the surgical resection rate for lung cancer surgery in a whole nation; (2) to determine short- and long-term outcomes of surgery, with special emphasis on patients who underwent lobectomy, had AC separately, or were elderly (≥ 75 years); (3) to determine whether the international IASLC/ATS/ERS adenocarcinoma classification system from 2011 predicts survival in surgical patients with lung cancer in Iceland; and (4) to determine how many patients aged ≥ 75 years underwent pulmonary resection and to determine the reasons for the operation not being performed in patients with resectable disease.

Three separate registries were used to identify cases. The histology database from the Department of Pathology at Landspitali University Hospital and the diagnosis and operation registry at Landspitali were used to identify patients who underwent surgery for NSCLC, and the Icelandic Cancer Registry was used to find patients who were not operated on. Clinical information was gathered from hospital charts and surgical records, and entered into a data sheet. Survival was analyzed using the Kaplan-Meier method and multivariate Cox analysis was used to evaluate possible independent prognostic factors of survival. All four studies were retrospective, population-based nationwide studies.

In paper I, all 404 cases (397 patients) who underwent pulmonary resection for NSCLC in Iceland during 15 years (1994–2008) were studied. The surgical resection rate was 26.4%, and 8.7% had major postoperative complications. The 30-day mortality rate was 1% and the 5-year overall survival was 40.7%. Patients

who did not undergo surgical resection had a 5-year survival of 4.8%, as compared to 12.4% for all lung cancer patients combined.

Paper II involved 489 consecutive patients who underwent lobectomy for NSCLC in Iceland from 1991 to 2014. The 30-day mortality was 0.6% and 4.7% had a major complication postoperatively. The 5-year overall survival was 49.2% and the 3-year overall survival improved from 48.3% in the period 1991–1994 to 72.8% in 2011–2014 ($p = 0.0004$). Similar improvement was observed in 5-year survival, but 3-year survival was chosen for comparison due to shorter follow-up during the last 4-year period.

Paper III described the outcome of 285 patients with resected primary AC of the lung in Iceland 1991–2010, and their subclassification according to the IASLC/ATS/ERS adenocarcinoma classification from 2011. The most common AC subtype was acinar-predominant (46%), followed by solid-predominant with mucin production (23%) and lepidic-predominant (20%). At 5 years, the overall survival was 45.3% and no difference was found in survival between the histological subtypes. The histological subtype was not found to be an independent predictor of overall survival ($p = 0.7$), in contrast to several studies that have reported more favourable survival for certain subtypes of ACs.

Paper IV was a retrospective study on the surgical resection rate and outcome in elderly patients (≥ 75 years old) who had a pulmonary resection for NSCLC in Iceland between 1991 and 2014. The elderly patients were compared with younger patients (< 75 years), with surgical resection rates being 18% and 32%, respectively ($p < 0.001$). The most frequent reasons for not performing surgery were insufficient pulmonary function (58%), heart disease (17%), and multiple comorbidities (17%). No significant differences in rates of complications or 30-day mortality were observed between the older and the younger groups. Five-year overall survival was significantly different (40% and 44%) in the elderly and younger groups, respectively ($p = 0.019$) but cancer-specific survival was not significantly different (51% vs. 50%; $p = 0.8$).

In summary, the surgical resection rate for non-small cell lung carcinoma and the short-term outcome was good, as reflected in the low rates of postoperative complications and 30-day operative mortality, Furthermore, with the exception of pneumonectomies, the long-term survival after surgical resection was similar to what other studies have shown—and is improving.

Keywords:

Lung cancer surgery, surgical resection rate, adenocarcinoma, lobectomy, survival, elderly.

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Contents

List of abbreviations

AAH - atypical adenomatous hyperplasia

AC – adenocarcinoma

AIS – adenocarcinoma *in situ*

ALK – anaplastic lymphoma kinase

ANOVA – analysis of variance

APA – acinar-predominant adenocarcinoma

ARDS – adult respiratory distress syndrome

ASA – American Society of Anesthesiologists

ATS – American Thoracic Society

BAC – bronchioloalveolar adenocarcinoma

BPF – bronchopleural fistula

BRAF – the gene that codes for the B-Raf protein

CI – confidence interval

CGI – comprehensive geriatric assessment

CHF – congestive heart failure

CIS – carcinoma *in situ*

COPD – chronic obstructive pulmonary disease

CT – computed tomography

cTNM – clinical tumour, node, metastasis

CXR – chest X-ray

DLCO – diffusion capacity of the lung for carbon monoxide

EBUS - endobronchial ultrasound

EGFR – endothelial growth factor receptor

ENB - electromagnetic navigation bronchoscopy

EPA – enteric-predominant adenocarcinoma

ERS – European Respiratory Society

EUS-NA - endoscopic ultrasound-guided needle aspiration

FEV1 – forced expiratory volume in 1 second

FDG – fluorodeoxyglucose

H&E – haematoxylin and eosin

HER2 – human epidermal growth factor receptor 2

HR – hazard ratio

IASLC – International Association for the Study of Lung Cancer

IHD – ischaemic heart disease

IMA - invasive mucinous adenocarcinoma

LC – lung cancer

LCC – large cell carcinoma

LDCT – low-dose computed tomography

LOS – length of hospital stay

LPA – lepidic-predominant adenocarcinoma

MET – proto-oncogene, tyrosine kinase receptor

MIA – minimally invasive adenocarcinoma

MPA – micropapillary-predominant adenocarcinoma

NGS – next-generation sequencing

NSCLC – non-small cell lung cancer

OS – overall survival

PD-L1 – programmed death-ligand 1

PET – positron emission tomography

PO – postoperative

PPA – papillary-predominant adenocarcinoma

pTNM – postoperative tumour, node, metastasis

RET – proto-oncogene, tyrosine kinase receptor

ROS1 – proto-oncogene, tyrosine kinase receptor

SBRT – stereotactic body radiotherapy

SCC – squamous cell carcinoma

SCLC – small cell lung carcinoma

SPA – solid-predominant adenocarcinoma with mucin production

SRR – surgical resection rate

SVC – superior vena cava

TBNA – transbronchial needle aspiration

TKI – tyrosine kinase inhibitor

TNM – tumour, node, metastasis

TTNA - transthoracic needle aspiration

VEGF – vascular endothelial growth factor

List of figures

List of tables

List of original papers

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals:

I. Thorsteinsson H, Alexandersson A, **Oskarsdottir GN**, Skuladottir R, Isaksson HJ, Jonsson S, Gudbjartsson T. Resection Rate and Outcome of Pulmonary Resections for Non-Small-Cell Lung Cancer. A Nationwide Study From Iceland. J Thorac Oncol. 2012; 7: 1164–1169.

II. **Oskarsdottir GN**, Halldorsson H, Sigurdsson MI, Fridriksson BM, Baldvinsson K, Orrason AW, Jonsson S, Planck M, Gudbjartsson T. Lobectomy for non-small cell lung carcinoma: a nationwide study on short and long-term survival. ACTA Oncol. 2017.

III. **Oskarsdottir GN,** Bjornsson J, Jonsson S, Isaksson H, Gudbjartsson T. Primary adenocarcinoma of the lung – histological subtypes and outcome after surgery, using the IASLC/ATS/ERS classification of lung adenocarcinoma. APMIS 2016: 5: 384–392.

IV. Baldvinsson K, **Oskarsdottir GN**, Orrason AW, Halldorsson H, Thorsteinsson H, Sigurdsson MI, Jonsson S, Gudbjartsson T. Resection rate and operability of elderly patients with non-small-cell lung cancer – Nationwide study from 1991–2014. Interact CardioVasc Thorac Surg 2017 1-7.

Declaration of contributions

My contributions to the individual papers were as follows:

I. In 2008, a database on pulmonary resections for non-small cell lung carcinoma was initiated in Iceland. It was designed by Professor Tómas Guðbjartsson, MD, PhD, but Dr Húnbogi Þorsteinsson, MD, Dr Rut Skúladottir, MD, and myself—all medical students at that time— collected most of the data for the first 10-year period, including detailed information data on all lobectomies performed. During the next years, I continued to add clinical and histological information to the database, together with my fellow medical students. One of them, Húnbogi Þorsteinsson, wrote the manuscript and did the statistical analysis under the supervision of Professor Tómas Guðbjartsson. I contributed to the writing of the manuscript and also to the statistical analysis.

II. This study was designed and planned by myself, medical student Hannes Halldórsson, and Professor Tómas Guðbjartsson. I analyzed the data with statistical help from Dr Martin Ingi Sigurðsson, MD, PhD, and Hannes Halldórsson. I wrote the manuscript under the supervision of Professor Tómas Guðbjartsson.

III. This study was designed in collaboration with Professor Tómas Guðbjartsson and Dr Jóhannes Björnsson, MD. I organized the patients' pathological slides and Dr Björnsson reviewed the histology samples. I analyzed all the data, added it to the existing database, and wrote the manuscript under the supervision of Professor Guðbjartsson, with the help of Dr Steinn Jónsson, MD, and Dr Helgi J. Ísaksson, MD.

IV. Dr. Kristján Baldvinsson, MD, designed the study in collaboration with Professor Tómas Guðbjartsson. In addition to the work on the surgical patients in the database, I also participated in collecting data for patients who were not operated on for different reasons. Dr Baldvinsson did most of the statistical analysis, and I participated in interpretation of the data and in writing of the manuscript.

1 Introduction

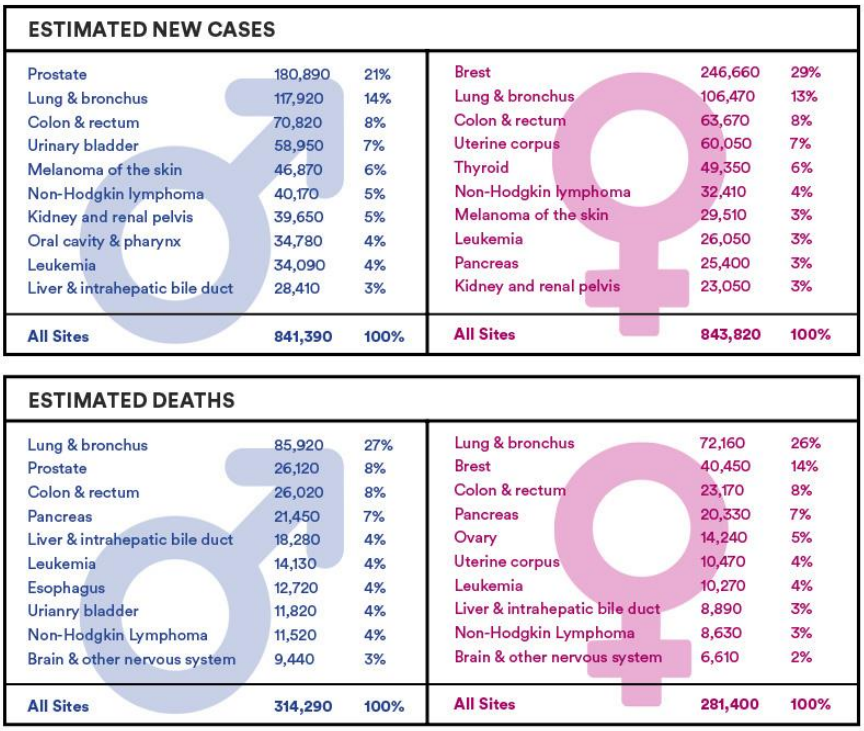
Lung cancer, with its high mortality rate, is a considerable health problem in most parts of the world (Ferlay et al., 2013). As 90% of cases are related to smoking and are therefore preventable (Brawley et al., 2014; CDC, 2016), numerous public health projects are in progress in the western world in order to prevent smoking and lung cancer (Codern-Bove et al., 2014; Coleman et al., 2010; Loke & Mak, 2015). Currently, the only well-defined and thoroughly studied curative treatment for non-small cell lung cancer (NSCLC) is surgical resection, but surgery is only indicated in the early stages of the disease. For more advanced stages, chemo- and/or radiotherapy, immunotherapy or targeted treatment, are the treatments of choice, depending on the patient's disease and condition (Novello et al., 2016). Many factors can be used to predict the prognosis and survival of the patients, but those who undergo surgical resection have a more favourable prognosis than those who are not treated with resection. However, in recent years numerous new treatments for NSCLC have been introduced, and the survival of lung cancer patients as a whole is improving (Goldstraw et al., 2016). Even so, most patients in whom the disease has spread have a dismal prognosis (Siegel et al., 2016).

1.1 Lung cancer

1.1.1 Epidemiology

In Iceland, as in the other Nordic countries and most other parts of the world, lung cancer is the third most common cancer diagnosed, with only breast cancer in women and prostate cancer in men being more common (Engholm et al., 2014; Ferlay et al., 2013; Torre et al., 2015). Lung cancer is, however, the leading cause of cancer-related death, representing 26% of all cancer mortality (Figure 1) (Siegel et al., 2015). In Iceland, lung cancer mortality is higher than that for breast, prostate, and colon cancer combined (Krabbameinsskra, 2016).

In western Europe, the incidence of lung cancer in men is around 42/100,000 inhabitants per year and for women it is 20/100,000 inhabitants (Ferlay et al., 2013). However, since 2011 in Iceland, more women than men have been diagnosed with lung cancer, the incidence being 33.6/100,000 in women and 30.1/100,000 in men. Every year, around 160 individuals are diagnosed with lung cancer in Iceland (Krabbameinsskra, 2016), but with lower smoking rates, a declining age-standardized incidence has been noted—especially in men, as in most developed countries (Engholm et al., 2010; Kohler et al., 2015). In developing countries, however, the incidence of lung cancer is expected to rise due to increased cigarette consumption (Silvestri et al., 2009)



ESTIMATED NEW CASES

Prostate	180,890	21%	Brest	246,660	29%
Lung & bronchus	117,920	14%	Lung & bronchus	106,470	13%
Colon & rectum	70,820	8%	Colon & rectum	63,670	8%
Urinary bladder	58,950	7%	Uterine corpus	60,050	7%
Melanoma of the skin	46,870	6%	Thyroid	49,350	6%
Non-Hodgkin lymphoma	40,170	5%	Non-Hodgkin lymphoma	32,410	4%
Kidney and renal pelvis	39,650	5%	Melanoma of the skin	29,510	3%
Oral cavity & pharynx	34,780	4%	Leukemia	26,050	3%
Leukemia	34,090	4%	Pancreas	25,400	3%
Liver & intrahepatic bile duct	28,410	3%	Kidney and renal pelvis	23,050	3%
All Sites	**841,390**	**100%**	**All Sites**	**843,820**	**100%**

ESTIMATED DEATHS

Lung & bronchus	85,920	27%	Lung & bronchus	72,160	26%
Prostate	26,120	8%	Brest	40,450	14%
Colon & rectum	26,020	8%	Colon & rectum	23,170	8%
Pancreas	21,450	7%	Pancreas	20,330	7%
Liver & intrahepatic bile duct	18,280	4%	Ovary	14,240	5%
Leukemia	14,130	4%	Uterine corpus	10,470	4%
Esophagus	12,720	4%	Leukemia	10,270	4%
Urianry bladder	11,820	4%	Liver & intrahepatic bile duct	8,890	3%
Non-Hodgkin Lymphoma	11,520	4%	Non-Hodgkin Lymphoma	8,630	3%
Brain & other nervous system	9,440	3%	Brain & other nervous system	6,610	2%
All Sites	**314,290**	**100%**	**All Sites**	**281,400**	**100%**

Figure 1: Estimated new cancer cases and estimated cancer deaths in the United States in 2016. Adapted from Siegel et al. (2015).

1.1.2 Smoking and other risk factors

By far the most important and relevant risk factor in the development of lung cancer is cigarette smoking, which is believed to account for around 80–90% of all deaths from lung cancer (CDC, 2016; Siegel et al., 2016). The association between smoking and lung cancer is strongest with small cell lung carcinoma (SCLC) and squamous cell carcinoma (SCC) histology—but somewhat lower for adenocarcinoma (AC), where it is still believed to explain 80–85% of all cases (Miller & Franklin, 1997).

The risk of lung cancer is dose-dependent, with every cigarette smoked having the potential to cause DNA damage (Warren & Cummings, 2013). The exposure to activated carcinogens from tobacco smoke results in the formation of DNA adducts which, if not managed by the cellular repair systems may persist in the cells, thus increasing the likelihood of mutations, leading to the disruption of cell growth, cell proliferation and cell survival (Warren & Cummings, 2013). Indeed, increased mutation frequencies are observed in lung cancers arising in smokers compared to never-smokers (Govindan et al., 2012). Pipe smoking does not seem to be safer than smoking cigarettes (Tverdal & Bjartveit, 2011).

Second-hand smoking has also been shown to be a risk factor for development of lung cancer, although it is not as strong a causative factor as direct smoking (IARC, 2004). Second-hand smoking is thought to affect children and adolescents more than adults, and studies have indicated that around 17% of the lung cancer incidence in individuals who have never smoked is linked to second-hand smoking (Janerich et al., 1990; Thun et al., 2008). Some of the other environmental factors that have been linked to lung cancer are asbestos, arsenic (IARC, 2012b), and radiation (IARC, 2012a).

Many factors other than smoking are involved in the aetiology of lung cancer. The disease is more common in people with chronic obstructive pulmonary disease (COPD) (Skillrud et al., 1986) and in the relatives of lung cancer patients (Etzel et al., 2003). In a study from Iceland, the relative risk of being diagnosed with lung cancer was shown to be double if individuals had a relative with lung cancer, even if the relative was distantly related and the data were corrected for smoking (Jonsson et al., 2004). A meta-analysis published shortly afterwards confirmed these results (Matakidou et al., 2005). Similar reports have been published by other groups, such as the International Lung Cancer Consortium from 2012 (Cote et al.), which reported a 1.5-fold increase in risk due to family history.

Numerous genome-wide association studies have identified common low-penetrance genetic risk alleles that moderate effects on lung cancer risks (Musolf et al., 2017). Among others, regions on chromosomes 15q, 6p, and 5p have been found to be associated with a higher risk of lung cancer (Amos et al., 2008; Hung et al., 2008; Thorgeirsson et al., 2008; Wang et al., 2008). Several other rare genetic variants—such as those located in the EGFR and TP53 genes—have been identified that appear to increase lung cancer risk in a small number of families (Bell et al., 2005; Lou et al., 2016; Zhuang et al., 2016).

1.1.3 Presenting symptoms

Around 90% of all lung cancer patients have symptoms at diagnosis, but 5–10% of cases are detected incidentally (Spiro et al., 2007). However, in patients with resectable disease, the proportion of patients diagnosed incidentally is higher, or around 30% (Raz et al., 2007). The most common symptoms at diagnosis are shown in Table 1.

Cough is the most common symptom, followed by dyspnea, chest pain, and haemoptysis. Chest pain is usually intermittent and ill-defined. Direct pleuritic pain can be caused by invasion of the tumour into the pleura. Haemoptysis is rarely severe or fresh, and usually consists of only blood coloration of the sputum (Spiro et al., 2007).

Table 1: The most common symptoms and signs of lung cancer. Patients can have more than one symptom at the same time. Adapted from Spiro et al. (2007), Pass et al. (2012), and Sandström & Eklund (2015)

Symptoms	Frequency %
Cough	45–75
Weight loss	40–65
Dyspnea	35–60
Pain	20–49
Haemoptysis	15–35
Clubbing	0–20
Fever	0–20
Weakness	0–10
Superior vena cava obstruction	0–4
Dysphagia	0–2
Wheezing and stridor	0–2

Tumour in the upper right lung and bulky metastasis in the right mediastinum can cause obstruction to the superior vena cava, which is called superior vena cava (SVC) syndrome. It can lead to oedema in the head, neck, and arms (Saadeen & Jazieh, 2008). If a tumour invades the stellate ganglion, Horner's syndrome can be seen—which includes ptosis, relative pupillary miosis, and unilateral anhydrosis on the same side as the lung tumour (Martin, 2007). Tumours in the apices of the lungs are called Pancoast tumours, and can invade the brachial plexus and cause neuralgic pain in the patient's arm and shoulder (Detterbeck, 1997) (Figure 2). Wheezing and stridor are usually caused by tumours in the main bronchus or trachea (Spiro et al., 2007). If the tumour involves the recurrens nerve, the patient can present with hoarseness.

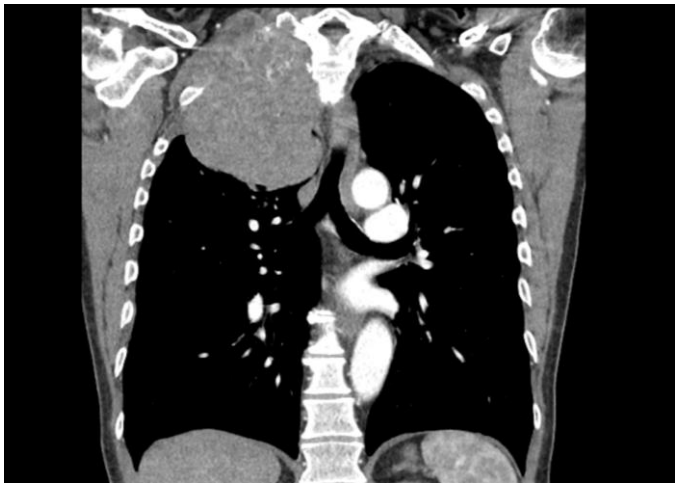


Figure 2: Computed tomography image showing a Pancoast tumour in the superior lobe of the right lung. Image: Stefan Barath, Skånes Universitetssjukhus, Lund.

Around one-third of patients are diagnosed because of symptoms that are caused by metastases, most commonly found in bones, liver, adrenal glands, brain, or spinal cord (Spiro et al., 2007). Pain is a common presenting symptom of lung cancer and often comes from bone metastasis. Around 10% of patients are diagnosed with brain metastases at diagnosis, and can present with symptoms such as headache, seizure, paralysis, and/or personality changes (Spiro et al., 2007).

Paraneoplastic symptoms are well known in lung cancer, occurring in around 10–20% of patients in various forms (Spiro et al., 2007; Sridhar et al., 1998). These are clinical systemic symptoms that are not caused by the growth of the tumour itself or a metastasis. Endocrine disorders are most common, including hypercalcaemia, syndrome of inappropriate antidiuretic hormone production (SIADH), and Cushing syndrome (Spiro et al., 2007). A prospective study on clubbing of fingers showed that it is present in around 30% of patients and is more common in women than in men, and also in patients with NSCLC rather than SCLC (Sridhar et al., 1998). The incidence of hypertrophic pulmonary osteoarthropathy is much lower, however, at around 1% (Ito et al., 2010; Izumi et al., 2010).

1.1.4 Histology

Around 95% of lung cancers fall into four main histological patterns (Figure 3); SCLC, SCC, AC, and large cell carcinoma (LCC). Together, SCC, AC, and LCC are called non-small cell lung carcinoma (NSCLC). In the past decades, an increase in the incidence of ACs has been seen, which is now the most frequent histological type and more often found in females (Dela Cruz et al., 2011). AC is

also the most frequent histological type in patients who are non-smokers (Dela Cruz et al., 2011). The incidence of SCC and SCLC, however, is decreasing. The frequency of smoking is declining, lowering the frequency of SCC and SCLC. Due to the changes in smoking patterns, especially the increased use of filtered cigarettes, there is a decrease of SCC but not AC (Ginsberg, 2005; Stellman et al., 1997).

Each histological type of NSCLC has its own diagnostic criteria. In recent years, molecular markers and immunohistochemistry have been increasingly used in lung cancer diagnosis, and have clinical value regarding the choice of treatment (Travis et al., 2015). Earlier, such as in the 2004 WHO classification of AC, the primary diagnosis was based on H&E examination of the sample. According to the 2004 WHO classifications for lung tumours, to diagnose SCC, keratin must be seen inside or between cells and/or cell-to-cell bridges (Travis et al., 2004). In the 2015 WHO classification (Travis et al.), there have been some changes where immunohistochemistry is used to diagnose SCC and differentiate between keratinizing, non-keratinizing, and basaloid subtypes. According to the 2011 IASLC/ATS/ERS classification, however, the use of immunohistochemical studies, (e.g. p63 staining), histochemical studies (e.g. mucin staining), and molecular studies may be used where and when they are available. Furthermore, in the 2015 WHO classification, LCCs that have pneumocyte marker expression (TTF1 and/or NapsinA) are classified as solid AC—even when mucin is absent. Diagnostic criteria for AC in the 2004 classification are intra-/intercellular mucus and/or gland formation. In 2011, a new classification system for ACs was introduced by the IASLC/ATS/ERS, which is explained further in the following section. In the classification from 2004, LCCs are classified as having big tumour cells without differentiation towards squamous or glandular epithelium (Travis et al., 2004). However, the 2015 classification (Travis et al., 2015) restricts the diagnosis of LCC to resection samples and uses immunohistochemistry to differentiate them regarding which category they belong to. SCLCs account for 13–20% of lung cancers and differ from NSCLCs in numerous ways both clinically, histologically and molecularly. They are of aggressive nature and have usually already metastasized at diagnosis (Simon & Turrisi, 2007). The histology shows that cells in SCLC are twice the size of a lymphocyte and they do not form a distinct pattern. Only a few nucleoli can be seen, and the proliferation rate is high (Simon & Turrisi, 2007).

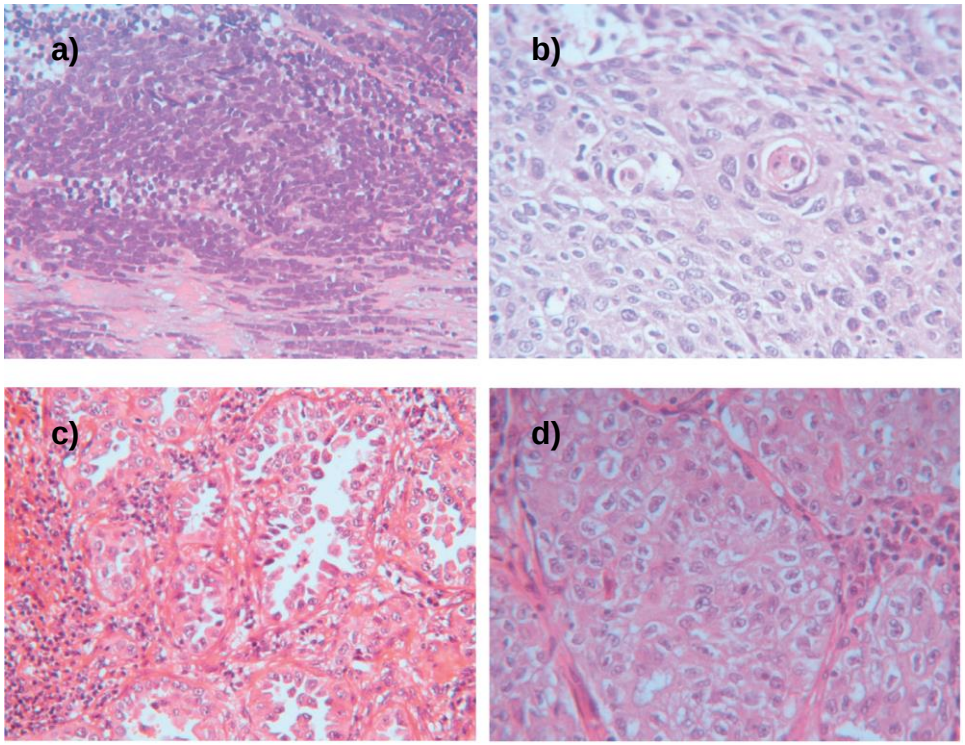


Figure 3: The major histological types of lung cancer: a. Small cell lung carcinoma; b. Squamous cell carcinoma; c. Adenocarcinoma; and d. Large cell carcinoma.

1.1.4.1 Adenocarcinoma subtyping

AC is the most common histological subtype of lung cancer (Devesa et al., 2005; Forman et al., 2013) and has a widely divergent clinical, molecular, pathological, and radiological spectrum. A need for universally accepted criteria for AC subtypes has therefore been needed. In the WHO classification for tumours of the lung from 1999 and 2004, 94% of the ACs were classified in the “mixed subtype” category (Travis et al., 2004). Although histologically correct, this classification had limited clinical relevance and a multidisciplinary approach was needed. In 2011, the International Society for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) launched a new classification system for primary lung ACs (Travis et al., 2013; Travis et al., 2011) with the aim to provide uniform terminology and diagnostic criteria for AC, and at the same time address advances in oncology, surgery, radiology, molecular biology, and pathology that could identify prognostic and predictive factors and therapeutic agents. This system categorizes ACs into four subgroups: pre-invasive, minimally invasive, invasive,

or variants of invasive adenocarcinoma (see Table 2). One of the major changes in the 2011 classification concerns the discontinuation of the term bronchioloalveolar adenocarcinoma (BAC). It was formerly used for a broad spectrum of tumours with similar histology but very different clinical presentation and survival rates. In the most recent classification, it has been categorized into different subtypes, i.e. AC *in situ*, minimally invasive AC, and invasive mucinous AC.

1.1.5 Diagnosis

If a patient presents with symptoms suggestive of lung cancer, chest radiography is often the first imaging method used (MacDonald & Hansell, 2003). On a chest radiograph, the size of the tumour can be evaluated in addition to atelectasis and/or pulmonary effusion (MacDonald & Hansell, 2003). However, invasion of mediastinal structures and lymph nodes is not easily visualized on a plain chest X-ray (MacDonald & Hansell, 2003). Thus, a computed tomography (CT) scan is often indicated (Figure 4), where the size of the tumour can be seen better along with the invasion to surrounding structures. Uncalcified tumours, diameter over 10 mm, irregular edges, and sharp edges are all factors that strongly suggest malignancy (Ginsberg et al., 2007).

Positron emission tomography (PET) scanning is used to better distinguish malignant tumours from benign tumours. The metabolism of cancer cells is higher than that of the surrounding cells, and with higher metabolism there is higher glucose consumption by the cell. Thus, 18F-fluorodeoxyglucose (FDG) can be administered intravenously, followed by a PET-scan to determine the FDG uptake of the tissue. The sensitivity and specificity of PET scanning are 90–100% and 65–95%, respectively (Ginsberg et al., 2007). A PET scanner will be available in Iceland later this year (autumn 2017), but until now patients with NSCLC requiring PET-scan have been sent to Copenhagen for evaluation.

Table 2: The 2011 IASLC/ATS/ERS classification for primary lung adenocarcinoma. Adapted from Travis et al. (2011)

Pre-invasive adenocarcinoma

- Atypical adenomatous hyperplasia
- Adenocarcinoma *in situ*
  o Mucinous
  o Non-mucinous
  o Mixed mucinous and non-mucinous

Minimally invasive adenocarcinoma
- Mucinous - Non-mucinous - Mixed mucinous and non-mucinous
Invasive adenocarcinoma
- Lepidic-predominant adenocarcinoma - Acinar-predominant adenocarcinoma - Papillary-predominant adenocarcinoma - Micropapillary-predominant adenocarcinoma - Solid-predominant adenocarcinoma with mucin production
Variants of invasive adenocarcinoma

- Invasive mucinous adenocarcinoma
- Colloid
- Enteric
- Foetal
  o Low-grade
  o High-grade

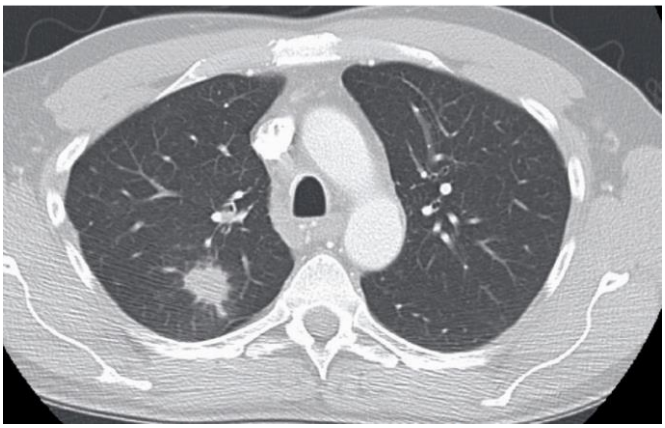


Figure 4: A computed tomography scan demonstrating tumour in the right upper lobe with irregular and sharp edges. Image: Tómas Guðbjartsson, Landspitali University Hospital.

Bronchoscopy is used for both diagnosis and staging of lung cancer. In a bronchoscopy, a sample of the lesion can be taken for histology and/or cells can be taken for cytology with a brush sample or bronchoalveolar lavage. White-light bronchoscopy is the standard method, and has better sensitivity and specificity in large, central lesions (88%) than in small, peripheral ones (33%) (Schreiber & McCrory, 2003). Autofluorescent bronchoscopy in combination with white-light bronchoscopy increases the sensitivity and specificity of finding pre-malignant lesions (Sun et al., 2011).

If the tumour is not reachable with regular bronchoscopy techniques, a CT-navigated percutaneous/transtracheal puncture of the lesion may be necessary for histological confirmation of the disease (Laroche et al., 2000). Although not yet available in Iceland, some centres have started to use electromagnetic navigation bronchoscopy (ENB) to obtain a sample from a peripheral lesion. Single-centre studies have shown the efficacy and safety of the use of ENB (Wang Memoli et al., 2012; Zhang et al., 2015), and a prospective study is in progress (Folch et al., 2016).

Sputum cytology can be used in the diagnosis of lung cancer, but the specificity and sensitivity are not high. They are higher for central lesions than for peripheral ones (Schreiber & McCrory, 2003).

1.1.6 Screening

Lung cancer has many characteristics that suggest that screening for LC may be useful. It is the most lethal cancer for both women and men in the western world, it has a long pre-clinical phase, and there is a cure for the patients who are

diagnosed early (Warner et al., 2010). This is reflected in an overall 5-year survival rate for lung cancer patients in the 10–17% range (Jemal et al., 2010; Siegel et al., 2016; Verdecchia et al., 2007), but the range is 65–83% for patients with localized stage-1 disease (Goldstraw et al., 2016).

Several methods could be used to screen for lung cancer. Chest X-ray (CXR), low-dose CT scanning (LDCT), biomolecular markers in sputum (Carozzi et al., 2010), breath and blood (liquid biopsies) (Esposito et al., 2017; Hofman, 2017; Perez-Callejo et al., 2016; Perez-Ramirez et al., 2016), and fluorescence bronchoscopy (Kennedy et al., 2000) are methods that have been evaluated, with LDCT being the most widely used (Moyer, 2014; Patz et al., 2016).

The first lung cancer screening studies using conventional CXR were done in the 1970s, but the results from the first randomized study on the subject were published in 1986 and suggested that there was no benefit (Fontana et al.).

In 1996, a study was published comparing CXR with LDCT, and LDCT was found to detect more cancers than CXR (Kaneko et al.). None of the studies published to date have shown any difference in overall survival, irrespective of whether they were performed on smokers or the general population (Frost et al., 1984; Marcus et al., 2000; Oken et al., 2011). The first trial to show a difference in mortality in patients was the Lung Cancer Screening Trial (with 53,452 participants) where the relative risk of lung cancer mortality was less, by 20.3% (Aberle et al., 2011). The results of this trial are promising, but more factors must be taken into account. The risks of LDCT scanning are important to consider, such as radiation exposure, increased patient costs, and possible emotional and physical morbidity associated with the follow-up or with overdiagnosis. In 2014, the US Preventive Services Task Force recommended annual screening using LDCT for adult patients aged 55–80 years with a 30 pack-year smoking history, who currently smoke or have stopped in the past 15 years (Moyer, 2014; Patz et al., 2016).

In Europe, many studies on the screening of lung cancer using LDCT are in progress, such as the NELSON lung cancer screening study in Belgium and the Netherlands (Ru Zhao et al., 2011), but also studies in Denmark and Germany (Becker et al., 2012; Pedersen et al., 2009). The Lung Cancer Screening Trial is by far the largest study—and is the only study so far to have shown a survival benefit from screening (Aberle et al., 2011). To validate the survival benefits, the European studies will be pooling their data, to get around 30,000 patients with long-term follow-up (Becker et al., 2012; Pedersen et al., 2009). So far, no screening has been implemented in Iceland, but a protocol for lung cancer screening in the Nordic countries is being developed.

1.1.7 Staging

After the diagnosis of lung cancer, the stage of the disease must be determined, both for deciding the treatment and for prediction of survival.

NSCLC is usually staged using the International Association for the Study of Lung Cancer (IASLC) tumour, node, metastasis (TNM) staging system (see Table 3). The tumour (T) stage is determined by the size, location, and invasion of the tumour. The node (N) stage is determined by the location and number of lymph nodes with tumour invasion. Finally, the metastasis (M) stage is determined by the presence of distant metastasis.

CT scanning is the method of choice for effective evaluation of the T stage in a patient with suspected lung cancer (MacDonald & Hansell, 2003). The specificity and sensitivity for detecting invasive growth in mediastinum are 40–84% and 57–94%, respectively (Munden et al., 2005). The use of whole-body PET is recommended for all patients without confirmed M1 disease. Whole-body PET provides additional evidence that the primary tumour is malignant, and identifies both possible lymph node metastases and distant metastases. The spread to mediastinal lymph nodes is of key importance in staging of NSCLC (Goldstraw et al., 2016). A numbering system has been developed to rank lymph nodes according to their prognostic significance (Figure 5) (Asamura et al., 2015).

Traditionally, lymph nodes under 1 cm in size on a CT-scan have been considered to be benign (De Leyn et al., 2007), but it has been shown that in up to 20% of cases, micro-metastasis is present in lymph nodes smaller than 1 cm. Furthermore, lymph nodes larger than 1 cm may be enlarged without being cancerous, due to nonspecific inflammation (De Leyn et al., 1997). A CT-scan or an MRI can be used to evaluate the size of mediastinal lymph nodes, but the N stage cannot be evaluated with precision. PET scanning adds information on whether the lymph nodes show abnormal metabolic activity. Pet scanning can therefore be used to evaluate both enlarged lymph nodes and smaller mediastinal lymph nodes. PET scanning has greater specificity and sensitivity (89–92% and 70–85%) than CT scanning (82% and 57%) (Toloza, Harpole, & McCrory, 2003). However, invasive methods using endobronchial ultrasound/endoscopic ultrasound (EBUS/EUS) or mediastinoscopy give a more accurate diagnosis of lymph node status and a better indication of whether metastases are present.

Table 3: The 7th edition of the TNM staging of non-small cell lung cancer. Adapted from Edge et al. (2010)

T	**Primary tumour**
T1:	Tumour with the highest diameter, surrounded by lung or visceral pleura, without growth into main bronchus or carina - T1a: ≤ 2 cm - T1b: 2–3 cm
T2:	Tumour 3–7 cm, with one of the following: - T2a: 3–5 cm - T2b: 5–7 cm - Growth into main bronchus at least 2 cm distal to the carina - Growth into visceral pleura - Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T3:	Tumour is - > 7 cm or - Of any size, which directly invades any of the following: parietal pleura, mediastinal pleura, chest wall, diaphragm, phrenic nerve, parietal pericardium, or tumour in the main bronchus less than 2 cm distal to the carina but without involvement of the carina - Associated atelectasis or obstructive pneumonitis of the entire lung or separate tumour nodule(s) in the same lobe
T4:	Tumour of any size, which invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina, or separate tumour nodules in a different ipsilateral lobe
N	**Lymph nodes**
N0:	No regional lymph node metastasis
N1:	Metastasis in ipsilateral peribronchial and/or hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2:	Metastasis in ipsilateral mediastinal and/or sub- or precarinal lymph nodes
N3:	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral, or contralateral scalene, or supraclavicular lymph node(s)
M	**Metastasis**
M0:	No distant metastasis

M1: Distant metastasis

- M1a: separate tumour nodule(s) in a contralateral lobe, tumour with pleural nodules, or malignant pleural (or pericardial) effusion
- M1b: Distant metastasis in extrathoracic organs

Anatomical stage/prognostic groups			
Stage IA	T1a/b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T1a/b, T2a T2b	N1 N0	M0
Stage IIB	T2b T3	N1 N0	M0
Stage IIIA	T1-2 T3 T4	N2 N1-2 N0-1	M0
Stage IIIB	T1-4 T4	N3 N2	M0
Stage IV	T1-4	N0-3	M1

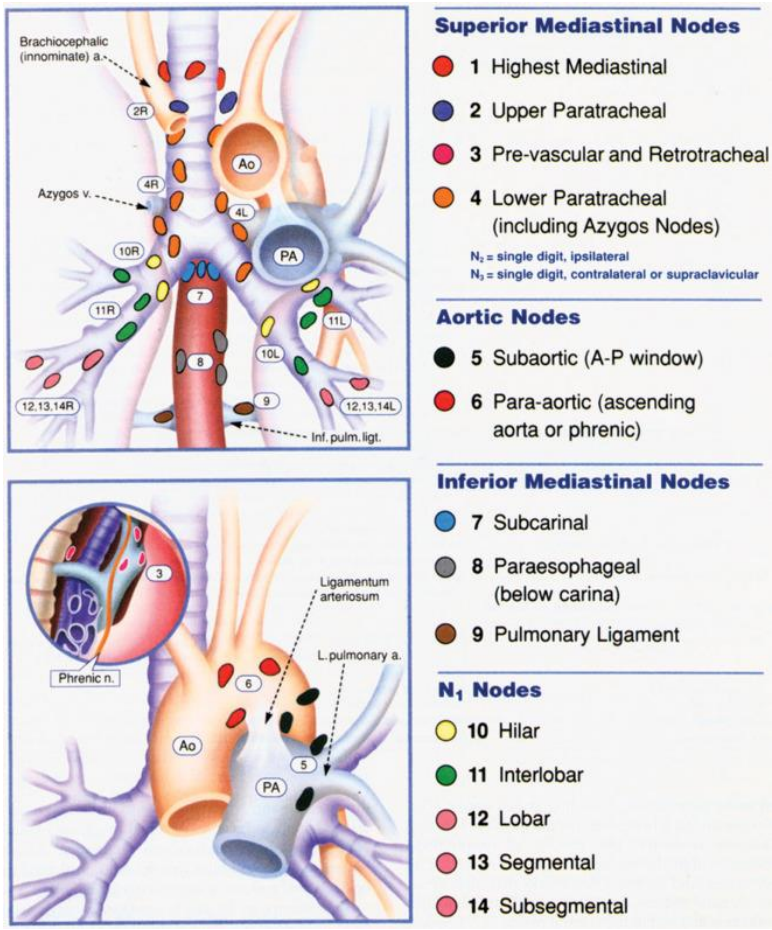


Figure 5: The lymph node zones in the mediastinum (Mountain-Dresler modification) (Rusch et al., 2009). Reused with permission from Elsevier and Copyright Clearance Center.

Until recently, mediastinoscopy was considered to be the most accurate method for staging of mediastinal lymph nodes (Toloza, Harpole, Detterbeck, et al., 2003). Ipsilateral lymph nodes to the tumour (N2) in the upper mediastinum are sampled or resected, together with lymph nodes that drain the lung contralateral to the tumour (N3). Importantly, however, the lower lymph node zones are not accessible with mediastinoscopy—such as lymph nodes in position 9—but positions 4 and 7 still are readily accessible. More recent methods for mediastinal lymph node staging are transbronchial needle aspiration (TBNA) with EBUS, transthoracic needle aspiration (TTNA), and EUS-guided needle aspiration (EUS-NA). Several studies have shown that EBUS-TBNA in expert hands is superior to mediastinoscopy in terms of its diagnostic performance. It is therefore now recommended as the first-line procedure for mediastinal lymph node staging in international guidelines (Slavova-Azmanova et al., 2016; Um et al., 2015; Vansteenkiste et al., 2014).

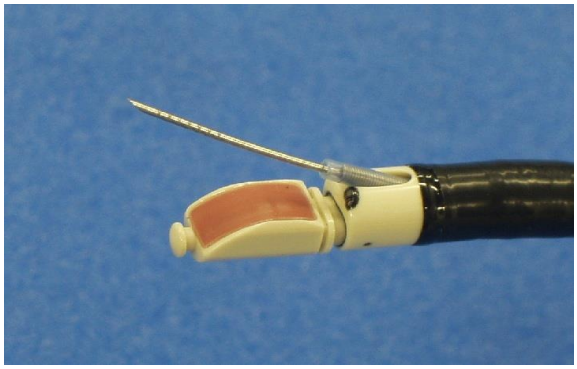


Figure 6: An EBUS bronchoscope, where an ultrasound probe is used along with bronchoscopy to visualize the airway wall and structures around it. Image: Stefan Barath, Skånes Universitetssjukhus, Lund.

As listed here, there are many possible ways to stage the patient, but the selection of the appropriate diagnosis pathway is dependent on the degree of suspicion of metastatic disease, the patient's comorbidities, and the availability and performance characteristics of procedural options (Toloza, Harpole, Detterbeck, et al., 2003).

Last year, the new 8th Edition of the TNM Classification for Lung Cancer was introduced by the IASLC (Goldstraw et al., 2016), and since January 1, 2017, it has become the official staging system for NSCLC. As this system is only being implemented this year, all analysis in this study was done according to the 7th Edition. Changes in the 8th Edition include a further classification of the T factor according to tumour size. There were no changes in the N factor, but the M factor was divided into three categories, with addition of a group for single distant metastasis in one organ (M2b).

1.2 Lung cancer treatment

1.2.1 Surgical treatment

The most effective curative treatment for lung cancer is surgical resection, where the tumour is removed along with the lymph nodes around it. This is an option for NSCLC patients with early-stage disease, and in some cases locally advanced disease, but only occasionally metastatic disease (Novello et al., 2016). SCLC is seldom treated with surgical resection, but rather with chemotherapy and radiotherapy (Novello et al., 2016).

Figure 7: Left panel: pulmonary resection for NSCLC at Landspitali University Hospital. Right panel: an anterolateral thoracotomy. Images: Tómas Guðbjartsson.

1.2.1.1 The history of pulmonary resections for lung cancer

The first reported surgical resection for lung cancer was a lobectomy performed in 1912 by Dr H. Morriston Davies (Davies, 1913). Unfortunately, the patient only survived for a few days. The first successful lobectomy for lung cancer was reported in 1932 by Dr Evarts Graham, who also performed the first pneumonectomy for lung cancer (Horn & Johnson, 2008). At this time, pneumonectomies became the standard surgical treatment for lung cancer. In 1962, lobectomy became the more commonly perfomed procedure, after being shown to be at least as safe as a pneumonectomy. Since then, many studies have shown the benefit of lobectomy over other resections in most patients (Scott et al., 2007).

In the past two decades, new technology has been developed for pulmonary resections, focusing on minimally invasive techniques. Video-assisted thoracoscopic surgery (VATS) (Figure 8) was first applied to lung cancer resections in 1992 (Sihoe & Shing, 2012) and is now used in many centres to perform lobectomies and sublobar resections. Furthermore, robot-assisted thoracic surgery using the da Vinci robot system (Intuitive Surgical, Sunnyvale, CA) is used in some centres in Europe and the United States, but its development is relatively slow due to the high costs and lack of benefit over VATS (B. J. Park et al., 2016; Swanson et al., 2014).

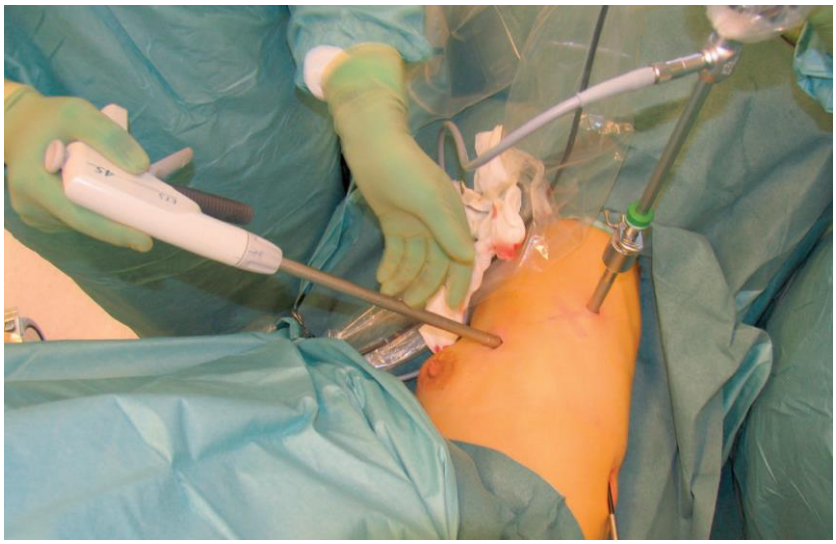


Figure 8: Video-assisted thoracoscopic surgery (VATS) at Landspitali University Hospital. Image: Tómas Guðbjartsson.

1.2.1.2 Preoperative assessment

For a patient to be a candidate for surgery the tumour must be localized in the lung, i.e. it must be at TNM stage I or II. There are exceptions—for example, in some cases with ipsilateral lymph node metastases (stage IIIA), if the tumour grows invasively into some mediastinal organs (T4 disease), or if there is a solitary distant metastasis such as in the brain or adrenal gland in an otherwise healthy patient (Novello et al., 2016). These metastases can be removed in a separate surgery before removal of the primary tumour.

Preoperatively, the patient has to undergo careful clinical evaluation to determine whether surgery is possible. Patients can be excluded from pulmonary resection because of any serious disease where the life expectancy is short, or if there are multiple comorbidities, especially reduced pulmonary function. Age alone should not be a contraindication (Bravo-Iniguez et al., 2014). If it is determined that the patient's medical condition in general is safe for surgery, the pulmonary function tests are evaluated to see whether he/she can afford to lose part of the lung. The main determinants of lung function are FEV1 and DLCO (the diffusion capacity of the lung for carbon monoxide). If either is < 80%, exercise testing or split lung function is recommended (Vansteenkiste et al., 2014) and used in selected cases. This, along with the CT-scan, PET-scan, and histology results, is taken to a multidisciplinary meeting and discussed before deciding on surgery (Novello et al., 2016).

1.2.1.3 The choice of surgical procedure

In patients with early-stage lung cancer who are fit for surgical resection, lobectomy is usually the recommended surgical procedure (Scott et al., 2007; Vansteenkiste et al., 2014). In a lobectomy, one lobe of the lung is removed along with the lymph nodes around it. Sometimes two lobes on the right side have to be removed, which is named bilobectomy. Lobectomy is the preferred method over sublobar resection and pneumonectomy, due to its lower recurrence rate compared to sublobar resection, but also because of its lower mortality and morbidity compared to pneumonectomy (Holmes et al., 1995). In sublobar resections, part of the lobe is removed—either as a wedge or an anatomical segmentectomy. Pneumonectomy—the removal of a whole lung—is a more extensive intervention than lobectomy, with more complications and a higher mortality rate than for either lobectomy or sublobar resection (Suen et al., 1999; Thorsteinsson et al., 2009).

Recently, however, the use of sublobar resection has been recommended for patients with small peripheral stage-I NSCLCs, instead of lobectomy, as comparable outcomes have been reported (Deng et al., 2016; Fiorelli et al., 2016; Yang et al., 2016),

In patients who are believed to tolerate a limited surgical intervention, a sublobar resection is recommended rather than any other intervention—e.g. radiotherapy (Scott et al., 2007; Vansteenkiste et al., 2014). Sublobar resections (wedge resection or segmentectomy) have a higher recurrence rate than lobectomy in general, which is thought to be because of small metastases in intrapulmonary lymph nodes (Holmes et al., 1995). Until proven otherwise, sublobar resection is believed to give better results than radiotherapy alone (Vansteenkiste et al., 2014).

Of all the patients treated surgically, between 10% and 15% need to undergo a pneumonectomy, usually because of a centrally located tumour that involves more than one pulmonary lobe. Pneumonectomy is a considerably more extensive surgical procedure than lobectomy, the complication rate and 30-day mortality being at least twice as high as for lobectomy and sublobar resection (Suen et al., 1999; Thorsteinsson et al., 2009). In selected cases of centrally located upper lobe tumours, a sleeve lobectomy is recommended over pneumonectomy where complete resection can be achieved with either technique (Q. L. Ma et al., 2016).

In selected cases, pulmonary resection can be an option for treatment of patients with locally advanced disease (Eberhardt et al., 2015). If the tumour has grown into the chest wall, diaphragm, or pericardium (stage T4N0-N1 disease), the American College of Chest Physicians (ACCP) recommends evaluation considering surgical treatment (Jett et al., 2007). The relevant organ is then removed along with the lung cancer, and the wound is covered in stretched

polytetrafluoroethylene (Gore-Tex®). Currently, however, surgical resection is usually not recommended where there is N2 involvement (stage IIIA), at least not for bulky metastatic disease (Eberhardt et al., 2015; Jett et al., 2007).

Patients with Pancoast tumours most often receive neoadjuvant chemo- and radiotherapy preoperatively (Eberhardt et al., 2015). The same applies for patients with growth into the mediastinum; in some cases, they can receive neoadjuvant chemo-radiation treatment to shrink the tumour first (Eberhardt et al., 2015).

1.2.1.4 The surgical procedure

The first thoracotomies performed were done under general anaethesia with a posterolateral thoracotomy approach. This method provides good anatomical access for the surgeon to the lung, hilum, mediastinum, trachea, and oesophagus, but requires an incision through the entire latissimus dorsi muscle (Shields et al., 2009). Thus, the use of posterolateral thoracotomy is decreasing in favour of the use of anterolateral muscle-sparing techiques (Nosotti et al., 2010) with minimal rib-spreading. These different thoracotomy approaches result in similar outcomes, but patients have a shorter in-hospital stay and use less pain medication with the muscle-sparing approach (Nosotti et al., 2010). In Iceland, the muscle-sparing approach has been used in the majority of lobectomies in the last 10 years, but before 2005 most operations were performed with a posterolateral approach.

The VATS technique has been used for almost 20 years for all types of surgery for lung cancer, and its use is on the increase. Several non-randomized studies have shown benefits with VATS, such as less scarring and a quicker recovery (Blasberg et al., 2016; Laursen et al., 2016), but superior survival has not been observed depending on the surgical technique used. Open thoracotomy and VATS can therefore both be utilized as appropriate to the expertise of the surgeon (Vansteenkiste et al., 2014). Until now, in Iceland, all lobectomies, pneumonectomies, and most lesser resections have been performed with an open thoracotomy—and VATS has mostly been used for selected lesser resections (Alexandersson et al., 2011).

1.2.2 Radiation therapy

Radiation therapy is extensively used in lung cancer, either with palliative intent for treatment of both regional and distant disease or for selected patients, with curative intent as SBRT for small peripheral tumours or in combination with chemotherapy for locally advanced (stage-III) disease (Nagata et al., 2015). Moreover, radiotherapy is occasionally used in the neoadjuvant (selected stage-III) or adjuvant (not radically resected) setting.

Figure 9: The linear accelerator Þór, used for radiotherapy of cancer patients at Landspitali University Hospital.

For medically inoperable patients where the tumour is small and localized to the lung, stereotactic body radiotherapy (SBRT) is the recommended curative treatment (Vansteenkiste et al., 2014). The radiotherapy beams are then very accurately and precisely aimed at the tumour, with a high dose. The total dose given should be to a biological equivalent of ≥ 100 Gy, prescribed to the encompassing isodose (Vansteenkiste et al., 2014). The treatment is usually well-tolerated, even in old patients (> 80 years) and patients suffering from severe comorbidities (Takeda et al., 2013). There is growing evidence to suggest equivalent outcomes after SBRT and lobectomy (Chang et al., 2015; Nagata et al., 2015). However, to date these studies have often involved only small cohorts of patients with not always completely histologically confirmed cases (Shirvani et al., 2012; Takeda et al., 2013). Thus, larger randomized studies will be needed before SBRT can be used to replace lobectomy as the standard of care for early-stage lung cancer (Vansteenkiste et al., 2014).

Only occasionally, such as in patients with Pancoast tumours or with ipsilateral lymph node metastasis (stage IIIA), radiotherapy is given preoperatively with curative intent (Eberhardt et al., 2015). Otherwise, neoadjuvant radiotherapy has not been shown to increase survival in stage-IIIA or stage-IIIB patients (Sirzen et al., 2003). Its use should therefore be restricted to carefully chosen patients (Eberhardt et al., 2015; Sirzen et al., 2003).

In completely resected early-stage NSCLC, adjuvant radiotherapy is not indicated (Vansteenkiste et al., 2014), as the rate of complications is increased. In contrast, if there is tumour growth in surgical margins, adjuvant radiotherapy should be considered after giving the patient adjuvant chemotherapy (Vansteenkiste et al., 2014).

For patients with NSCLC who are diagnosed at a locally advanced stage, where surgical resection is not indicated (Laroche et al., 1998), concomitant chemotherapy and radiotherapy is the treatment of choice (Peters et al., 2012). The traditional treatment involves 2 Gy once daily, five days a week, up to a total dose of 68–70 Gy. The radiation field should include the tumour itself along with the lymph nodes that are involved (Emami et al., 2003). Radiation pneumonitis and oesophagitis are common early complications after radiotherapy to the lung (Pan et al., 2016; Tang et al., 2016). With concomitant chemo-radiotherapy, the frequency of these complications is higher, so only patients with a good performance status should be offered this treatment regimen (Fruh et al., 2013).

In SCLC, radiation treatment to the area of the tumour is used concomitantly with chemotherapy whenever possible, and in addition, whole-brain radiation is used to prevent brain metastasis (Fruh et al., 2013).

1.2.3 Chemotherapy

Numerous studies have shown that NSCLC patients at stages II–IIIA—and occasionally at stage IB—who undergo surgical resection benefit from receiving adjuvant chemotherapy (Novello et al., 2016). A platinum-based adjuvant chemotherapy with agents such as cisplatin/carboplatin is usually recommended (Burdett et al., 2015; Novello et al., 2016), with the overall survival increasing by 5.4% (Pignon et al., 2008). Patients at stage I, however, do not benefit as much as patients at stages II and IIIA (Scott et al., 2007). Chemotherapy is not without complications, and many patients do experience nausea, stomatitis, malaise and fatigue. Bone marrow suppression, detected as neutropenia, thrombocytopenia and/or anemia, often leads to complications such as infections and bleedings (Burdett et al., 2015). Furthermore, drug-specific side effects may include e.g. nephrotoxicity, cardiotoxicity or ototoxicity from cisplatin and neuropathy or drug administration-induced phlebitis from vinorelbine (Fass-verksamheten, 2016).

Patients with stage-III disease do benefit from concomitant chemo-radiotherapy, as mentioned in the previous section. A platinum-based chemotherapy doublet is then recommended, administered as one cycle before and two cycles during the radiotherapy period. Giving these treatments modalities concomitantly has better anti-tumoural effect as compared to sequential administration, but also entails an increased risk of toxicity (Eberhardt et al., 2015).

Recommended 1st line palliative therapy for advanced NSCLC is a combined therapy of a platinum-based drug such as cisplatin/carboplatin along with a third-generation agent such as pacletaxel, pemetrexed, docetaxel, gemcitabin or vinorelbine. As the purpose is to reduce symptoms and increase the patient's quality of life, many factors have to be considered when choosing which

treatment to give, such as the patient's complaints, symptoms, and performance status (Novello et al., 2016).

Chemotherapy undeniably benefits patients with SCLC. Four cycles of a cisplatin and etoposide, carboplatin and etoposide or anthracycline-based combination should be offered to all patients, even though the disease is rarely curable—unless the patient has mild disease and gets both radiotherapy and chemotherapy (Fruh et al., 2013).

1.2.4 Targeted therapy

For the past two decades, molecular biology has been in focus for the treatment of lung cancer. Since tumorigenic mutations in the *epidermal growth factor receptor* (EGFR) gene were discovered, specific targeted therapies have been intensively studied (Hirsch et al., 2006; Salomon et al., 1995). Targeted therapies are now used routinely as first-line treatments, mostly for patients with two molecular subsets of NSCLC. The best-defined is an activation mutation in the *EGFR* gene that codes for a tyrosine kinase receptor involved in gene transcription, cell proliferation, and cell survival (Salomon et al., 1995). In NSCLC, the EGFR can be deregulated by over-expression, mutations, and gene amplification (Hirsch et al., 2006). Tyrosine kinase inhibitors (TKIs), erlotinib, afatinib, or gefinitib can be used to target *EGFR*-mutated tumours as a first-line treatment, and these patients have a significantly better prognosis than those without any *EGFR* mutation (D'Angelo et al., 2012). Other targetable molecular subsets of lung cancer are those with fusion genes (translocations) involving the anaplastic lymphoma kinase (*ALK*) or *ROS1* genes (Novello et al., 2016), which regulate cell proliferation (Soda et al., 2007). These translocations are present in about 5% of NSCLCs and can lead to uncontrolled proliferation of cancer cells (Morris et al., 1994). Today, tumours with *ALK* or *ROS1* fusions are treated with TKI agents such as crizotinib (Novello et al., 2016), but this drug was first accepted for the treatment of lung cancer in 2011 (Mendez et al., 2011). Other genes involved in lung tumorigenesis such as *MET*, *HER2*, *BRAF*, and *RET*, also have targeted therapy options, although their clinical use is not yet recommended routinely (Novello et al., 2016).

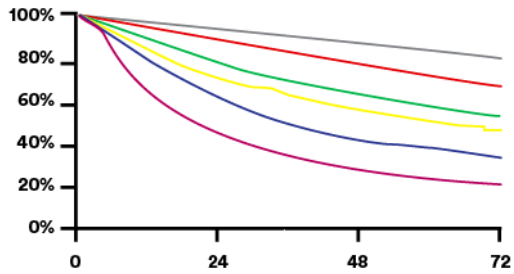
1.2.5 Immune therapy

Patients with NSCLC where *EGFR*, *ALK* or *ROS1* alterations are not present, may benefit from immune therapy (Langer et al., 2016; Novello et al., 2016; Reck et al., 2016). Nivolumab and pembrolizumab have shown overall survival benefits when compared to docetaxel (Novello et al., 2016), the most benefit being seen in those who express programmed death-ligand 1 (PD-L1) (Herbst et al., 2016). PD-1 is a transmembrane protein that has a special role in suppressing the immune system, such as in pregnancy and autoimmune disease (Tripathi & Guleria, 2015). PD-L1 is a ligand for this receptor, and is expressed on

macrophages and dendritic cells (Okazaki & Honjo, 2007; Tripathi & Guleria, 2015). Immune checkpoint inhibitors such as nivolumab and pembrolizumab target this pathway by blocking PD-1, thereby activating the host's own immune system to attack the tumour cells (Novello et al., 2016).

1.3 Survival and prognostic factors

The overall (all-cause) 5-year survival of lung cancer patients is only in the 10–18% range in Iceland, which is similar to the situation in most other western countries (Krabbameinsskra, 2016; Siegel et al., 2015, 2016). The most well-known prognostic factor for survival is the TNM staging (Goldstraw et al., 2016; Spira & Ettinger, 2004) (Figure 10).



7TH ED.	EVENTS/N	MST	24 MONTH	60 MONTH
IA	1837/11423	NR	94%	83%
IB	2168/7711	NR	87%	71%
IIA	1514/3702	NR	77%	57%
IIB	1325/2776	58.9	70%	49%
IIIA	3467/5818	35.0	61%	36%
IIIB	364/506	20.0	45%	23%

Figure 10: Overall survival by pathological stage according to the seventh edition of the TNM staging system by the IASLC Staging and Prognostic Factors Committee. MST, mean survival time (Goldstraw et al., 2016). Reused with permission from Elsevier and Copyright Clearance Center.

Other prognostic factors include histological type (i.e. squamous cell carcinoma vs. adenocarcinoma), age, history of weight loss (Pater & Loeb, 1982; Stanley, 1980), and some gene mutations (i.e. *EGFR, K-ras*, *p53*) (de Melo et al., 2015; Hames et al., 2016; Horio et al., 1993; Kern et al., 1994; Kerr et al., 2014; Slebos et al., 1990).

1.3.1 Survival of patients with adenocarcinoma

The survival of patients with pulmonary AC is better than for other histological types. Despite the recent advances in diagnostic techniques and treatments for primary lung AC, the survival rate is still only in the 30–40% range (Huang et al., 2013; Kauffmann et al., 2013; Q. Ma et al., 2012; Xu et al., 2011). Most studies on the new classification of AC have shown the classification to be an independent prognostic factor for survival (Huang et al., 2013; Russell et al., 2011; Warth et al., 2012). The 5-year disease-free survival for AC *in situ* and minimally invasive AC has been 100% (Behera et al., 2016; Russell et al., 2011; Warth et al., 2012; Yoshizawa et al., 2011). The more benign subtypes of AC are classified as lepidic-predominant (LPA) and acinar-predominant (APA). LPA has an overall 5-year survival of 55.6–100% and that for APA is 43–68% (Mansuet-Lupo et al., 2014; Russell et al., 2011; Warth et al., 2012; Westaway et al., 2013; Yoshizawa et al., 2011). Papillary and solid-predominant subtypes have intermediate outcome, with a 5-year overall survival of between 71% and 74.7% and between 43.3% and 70%, respectively (Gu et al., 2013; Russell et al., 2011; Yoshizawa et al., 2011). Micropapillary and mucinous subtypes of AC are usually categorized as having a poor outcome, with an overall 5-year survival of 0–67% and 51–88% (Gu et al., 2013; Russell et al., 2011; Travis et al., 2015; Yoshizawa et al., 2011).

1.3.2 Survival in the elderly

Numerous studies have suggested that age alone should not be a contraindication for pulmonary resection, with favourable reported short- and long-term survival that is comparable to that in younger patients (Bravo Iniguez et al., 2016; Liu et al., 2013; Rivera, Dahan, et al., 2011; Rivera, Falcoz, et al., 2011). Even so, a careful individual preoperative assessment is needed. Most studies have shown the 30-day mortality rates in the elderly to be higher than in younger patients (Liu et al., 2013; Rivera, Falcoz, et al., 2011), whereas others have shown similar results between age groups (Bravo Iniguez et al., 2016; Fan et al., 2007). Some studies have shown favourable surgical outcome and survival in the elderly (Dillman et al., 2009; Palma et al., 2010), but not all of them (Fan et al., 2007).

The surgical resection rates (SSRs) are lower in the elderly than in younger patients (Bravo Iniguez et al., 2016; Dillman et al., 2009; Palma et al., 2010). Furthermore, it has been suggested that sublobar resection and less invasive surgery are preferable in a selected patient group with early-stage disease (Vansteenkiste et al., 2014), so a new randomized controlled trial is in progress and the results are pending (Yang et al., 2016).

1.3.3 Survival following lobectomy

The overall survival of patients who undergo lobectomy for NSCLC has improved during the past decades, with more recent studies showing a 5-year survival in the 65–82% range (Deng et al., 2016; Nilssen et al., 2016; Paul et al., 2014). The survival of patients with NSCLC is highly dependent on the TNM stage. A recently published meta-analysis of patients with stage-I disease showed a 77% pooled 3-year survival for NSCLC patients undergoing a lobectomy (Deng et al., 2016). In other studies, the 3-year survival has been reported to be 27–51% for stage IIIA (Dickhoff et al., 2016), but up to 96% for stage IA (Okada et al., 2014).

The prognostic factors are the same for lobectomies as for pneumonectomies and sublobar resections; with TNM staging being the most important prognostic factor.

1.4 Lung cancer in the elderly

The probability of being diagnosed with NSCLC increases considerably with age, with half of the patients being diagnosed at more than 70 years of age (Gajra et al., 2016; Siegel et al., 2016). With an ageing population, the number of patients who are diagnosed and treated for NSCLC is expected to increase.

Many older patients with metastatic disease do not receive chemotherapy (Davidoff et al., 2010; Lang et al., 2009), and the surgical resection rate is lower in patients over 70 years of age (Damhuis & Schutte, 1996; van der Drift et al., 2012). The treatment regimen chosen for each patient, regardless of the patient‘s age, must be chosen carefully with an independent assessment of performance status, comorbidities, and other factors (Novello et al., 2016). Comprehensive geriatric assessment (CGA) is a tool based on a multidisciplinary and global approach to elderly patients with cancer and can help to adapt cancer management to the fitness or frailty of each patient (Extermann & Hurria, 2007; Novello et al., 2016).

It is questionable whether palliative chemotherapy prolongs life in the elderly and whether it improves the quality of life. The prospective ELVIS trial (The Elderly Lung Cancer Vinorelbine Italian Study) compared single-agent chemotherapy to best supportive care in elderly patients with metastatic NSCLC. It showed a significant increase in both survival and quality of life, but the recruitment to the study very slowl and had to be terminated early (The Elderly Lung Cancer Vinorelbine Italian Study Group, 1999). In the retrospective analysis by Ansari et al., comparable survival of elderly and younger patients with a good performance status was found, which indicates that chemotherapy also improved survival in elderly patients (Ansari et al., 2011).

Adjuvant chemotherapy has not been studied prospectively in elderly patients (Poudel et al., 2016). A retrospective analysis done on patients in the LACE study (Pignon et al., 2008) did not show any difference in hazard ratio of death and rates of severe toxicity between elderly and younger patients. International guidelines have recommended the use of doublet chemotherapy for those eligible (PS 0–2 and adequate organ function), and the use of carboplatin instead of cisplatin in 70- to 89-year-old patients (Novello et al., 2016). Due to the need for more studies on adjuvant therapy in the elderly, the use of adjuvant therapy in patients over 80 years of age is usually undertaken with extra caution (Gajra et al., 2016).

2 Aims

The general aim of this thesis was to study the outcome and survival in different subgroups of patients who have undergone surgical resections for NSCLC in Iceland.

The specific aims of each paper are listed below:

I. To investigate the surgical resection rate for lung cancer in a whole nation and to determine surgical outcomes in patients who underwent different types of pulmonary resection for NSCLC in Iceland with curative intent.

II. To determine the short- and long-term outcome and survival in patients who underwent a lobectomy for NSCLC in Iceland during the 24-year study period, focusing on 30-day and long-term survival.

III. To determine whether the IASLC/ATS/ERS subclassification of adenocarcinoma, published in 2011, affected survival and to investigate whether the subtypes in Iceland were different to those in other western countries.

IV. To investigate the outcomes of pulmonary resections for NSCLC in elderly patients (≥75 years old), to compare them to those in younger patients, and to assess surgical resection rates, operability, and reasons for excluding elderly from surgery.

3 Materials and methods

All four papers in this thesis were epidemiological cohort studies that focused on pulmonary resections for NSCLC in Iceland. The operations were all performed at Landspitali University Hospital in Reykjavik, which is the only centre in Iceland where cardiothoracic surgery is performed. It serves the whole population of 330,000 individuals (December 2016). For all four of the studies, we used a database at the Department of Cardiothoracic Surgery at Landspitali. This database includes all patients who have been operated for NSCLC in Iceland from January 1, 1991 to the present time, but the four studies included patients operated until December 31, 2014. Cases were also identified and cross-checked using a central, computerized database at the Department of Pathology, Landspitali University Hospital, which has details of all lung histology specimens in Iceland. To further minimize the risk of missing cases, the diagnosis and operation registries at Landspitali University Hospital were checked for patients operated on for lung cancer.

Demographic information and clinical data were collected and registered from hospital charts and surgical reports using a standardized data sheet. Baseline characteristics, age, gender, and comorbidities were registered along with data on presenting symptoms, type of operation, tumour size, stage and histology, complications, and survival (for details, see section 3.2). Patients were staged using the seventh edition of the TNM staging system (Edge et al., 2010) (see section 1.1.7 for more details).

All patients were followed regarding survival using the Icelandic national population registry, Statistics Iceland (www.statice.is). This register has information on the personal identification numbers of all citizens of Iceland. All deaths must be reported to this registry, and causes of deaths are registered in the Icelandic Cause of Death Register.

The Icelandic National Bioethics Committee and the Icelandic Data Protection Authority granted all the approval that was necessary for the studies.

3.1 Study populations

Table 4 gives an overview of the study populations in the four papers. All four studies were nationwide cohort studies, but involved different subgroups of patients who had surgical resection for NSCLC with curative intent in Iceland.

Table 4: Overview of papers I–IV

	Paper I	***Paper II***	***Paper III***	***Paper IV*** ***Elderly/ younger***
Subgroup	All cases	Lobectomies	Adenocarcinoma histology	Age ≥ 75 years
Study period	1994–2008	1991–2014	1991–2010	1991–2014
Number of cases operated on	404	493	285	140/550
Mean age, years (range)	66 (37–89)	67 (35–89)	67 (37–89)	80/65 (75–89/ 35–74)
Proportion of males	52%	46%	43%	59%/45%

3.1.1 Study I

This study included 404 consecutive patients who underwent pulmonary resection at Landspitali for NSCLC between January 1, 1994 and December 31, 2008. All types of resections were included, and the cases were divided and analyzed in three 5-year periods. To calculate the surgical resection rate, information on all histologically confirmed diagnoses of NSCLC (1530 patients) was gathered from the Icelandic Cancer Registry, a registry that covers all cancers diagnosed at all healthcare facilities in Iceland since 1955. Patients who were diagnosed post-mortem were not included in the analysis, and this also applied to patients without a histologically proven diagnosis (n = 133) and patients with small cell carcinoma (n = 306), pulmonary carcinoids, sarcoma, or carcinoma *in situ*. Date of death was registered or the patients were identified as living on July 10, 2010. Mean follow-up time was 49 months (range 0–194).

3.1.2 Study II

From January 1, 1991 until December 31, 2014, 493 lobectomies were performed for NSCLC at Landspitali, corresponding to 75.5% of all curative-intent pulmonary resections for NSCLC during the study period. Eleven patients (11/493, 2.2%) had lobectomy together with a lesser resection performed simultaneously, and four patients (4/493, 0.8%) underwent a bilobectomy. Patients operated with exploration-only thoracotomy, exploratory video-assisted thoracoscopic surgery (VATS), a palliative procedure, or resection for purposes of biopsy only were excluded. Patients were also excluded if pathological

samples showed adenoid cystic carcinoma, mucoepidermoid carcinoma, pulmonary carcinoid, sarcoma, carcinoma *in situ* (CIS) or fibrosis only. Date of death was registered or the patients were identified as living on September 1, 2016. Mean follow-up time was 42 months (range 1–279).

3.1.3 Study III

Study III included all patients who had primary AC of the lung and underwent pulmonary resection with curative intent in Iceland between January 1, 1991 and December 31, 2010. Patients with adenosquamous carcinoma were excluded. Patients who had exploratory, palliative, or lesser resection for biopsy purposes only were excluded. Nine other patients were excluded because of lost histological slides. This left 285 patients for further analysis. Date of death was registered or the patients were identified as living on January 31, 2015. To calculate the five-year survival of the patients according to histological subtypes, only the subtypes containing more than 20 patients were included in the survival analysis. Mean follow-up time was 45 months (range 1–254).

3.1.4 Study IV

Data from the Icelandic Cancer Registry were used to identify 859 elderly patients (≥ 75 years old) who were diagnosed with NSCLC between 1991 and 2014. There were missing data for 77 patients (lost to follow-up, patient charts not found, or diagnosis made post-mortem) and these patients were excluded from further analysis. This left 782 patients for further analysis, 140 of whom underwent pulmonary resection. A flow chart of the study population in study IV is given in Figure 11. The hospital charts of all 782 patients were reviewed and different variables were registered for each patient, as explained in detail in section 3.2. A proportion of these patients had stage-I or -II disease and were not operated on. To investigate why, the reason for exclusion from surgery was also registered.

The 140 elderly patients (≥ 75 years old) with NSCLC who underwent surgical resection were compared to 550 surgical patients younger than 75 years. These patients were all included in the surgical database mentioned in section 3. Date of death was registered or the patients were identified as living on December 31, 2014. Mean follow-up time was 5 years (range 0–23).

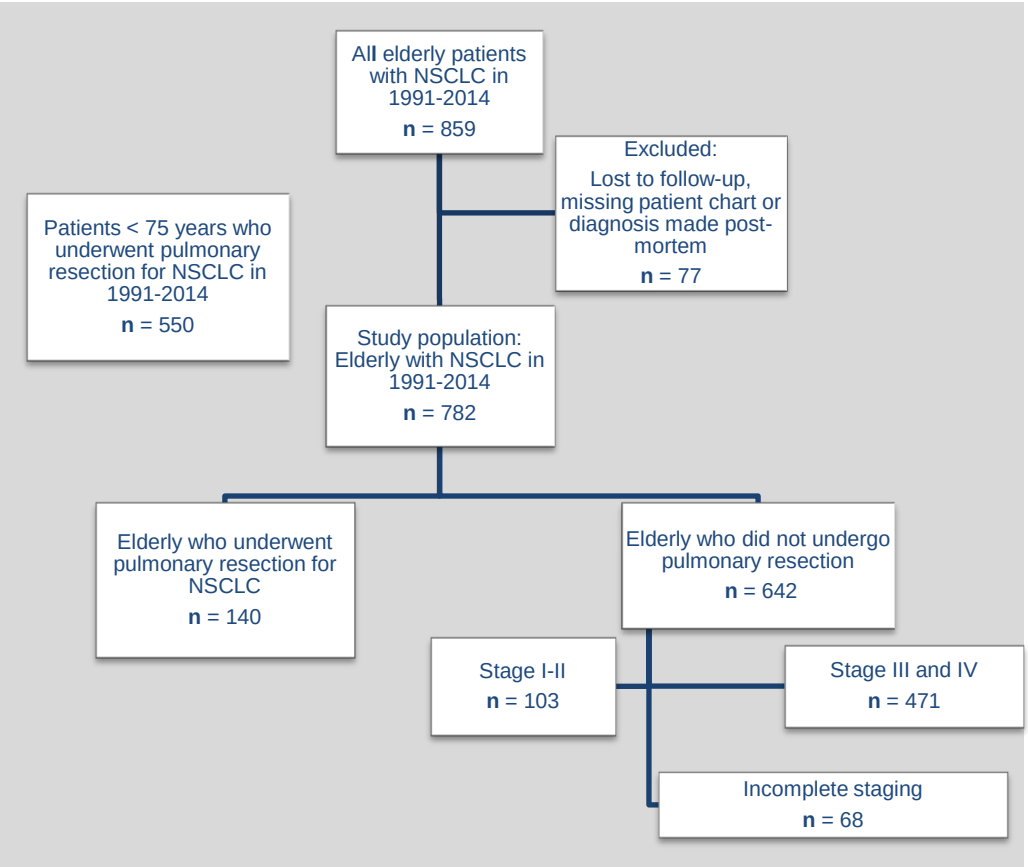


Figure 11: Flow chart of the study population in study IV. Patients were classified as elderly if they were ≥ 75 years of age. NCSLC, non-small cell lung cancer.

3.2 Clinical variables

The following variables, divided into pre-, peri-, and postoperative variables, were registered in the surgical database:

Preoperative: age, gender, indication for surgery, incidental diagnosis, presenting symptoms, history of smoking (current or former), and any comorbidities of significance such as COPD, arrhythmias, or ischaemic heart disease—but also if neoadjuvant chemo- or radiotherapy was administered. Results from preoperative pulmonary function tests, including FEV1 and FVC, were also registered.

Perioperative: operation time (skin to skin), ASA score, whether mediastinoscopy had been performed just before the pulmonary resection (same anaesthesia), and whether major intraoperative bleeding had occurred.

Postoperative: major and minor complications, administration of adjuvant chemo- or radiotherapy, length of hospital stay (LOS), pathology of the tumour (including tumour size, tumour type, and nodal involvement), staging, whether recurrent NSCLC had been diagnosed (long-term), and survival of all the patients—both overall (all-cause) survival and cancer-specific survival.

In study III, a senior pathologist— one of the co-authors (J.B.)—reviewed all the histological slides for patients who had AC histology. The AC subtype was registered according to the 2011 IASLC/ATS/ERS adenocarcinoma classification system (Travis et al., 2011) as described in section 3.3, and the size of the tumour was re-evaluated and registered.

In study IV, for the patients who did not undergo surgery, clinical data were collected from patient records from healthcare centres all over the country, using a standardized data sheet with the following variables: age at diagnosis, gender, date at diagnosis, and date of death. The method used for diagnosis (i.e. clinically/chest X-ray/pathological diagnosis of a metastasis) was registered along with the cTNM stage (clinical tumour, node, metastasis). If the patients had stage-I or -II disease, the reasons for exclusion from surgery were also registered.

3.3 Definitions of variables

Current smokers were defined as patients who had smoked within five years of surgery and never-smokers were defined as patients who had smoked less than 100 cigarettes in their lifetime.

Minor complications were defined as: air leakage for more than 7 days, pneumonia, intraoperative bleeding of more than 1 litre, new-onset atrial fibrillation/flutter, wound infection, and recurrent laryngeal nerve paralysis. Major complications were defined as reoperation for bleeding, postoperative heart failure, acute respiratory distress syndrome (ARDS), myocardial infarction (MI), empyema, stroke, and bronchopleural fistula (BPF). Operative mortality was defined as death occurring within 30 days of surgery.

3.4 Histopathological classification (paper III)

An experienced pathologist and one of the authors (J.B), who was blinded regarding the clinical outcome of the patients, reviewed the slides and subtyped the tumours. The size, tumour count, and subtype were registered.

Haematoxylin- and eosin-stained slides from each case were reviewed and staining for mucin (PAS with and without diastase, alcian blue) was done if indicated. No immunohistological staining was performed for the purposes of this study. The predominant pattern was defined as the morphological pattern occupying the greatest area of tumour.

The primary adenocarcinomas of the lung were divided into four categories using the 2011 IASLC/ATS/ERS classification, as shown in Table 2.

The majority of cases were invasive, a group which is subclassified into five predominant patterns: lepidic-predominant (LPA), acinar-predominant (APA), papillary-predominant (PPA), micropapillary-predominant (MPA), and solid-predominant (SPA) with mucin production. If the tumour was not invasive, it fitted into the other three groups—pre-invasive AC, minimally invasive AC, or variant of invasive AC.

The histology of acinar-predominant AC included round- to oval-shaped glands with a central luminal space surrounded by tumour cells, along with distruction of alveolar architecture or myofibroblastic stroma.

AC *in situ* (AIS), minimally invasive AC (MIA), and LPA all have a lepidic pattern with different amounts of invasion. Lepidic pattern consists of a blend of type-II pneumocytes or Clara cells growing along the surface of alveolar cells. If no invasion was detected in the sample, AIS was diagnosed. If the invasion was less than 5 mm, the sample was categorized as MIA. If the invasion into visceral pleura or lymphovascular space was ≥ 5 mm or there were signs of necrosis, it was diagnosed as LPA.

Papillary pattern (PPA) consists of complex branching papillae with cuboidal to columnar cells growing along a fibrovascular core. The pattern was considered micropapillary (MPA) when the tumour cells grew in papillary tufts without a fibrovascular core, often at the tumour edge.

If there was a sheet of cells without a recognizable pattern that was not compatible with LPA, APA, PPA, or MPA, the diagnosis was solid-predominant AC with mucin production.

Invasive mucinous AC (IMA), formerly mucinous BAC, was diagnosed when the growth was lepidic of columnar or goblet cells with abundant intracellular mucin admixed with other invasive AC pattern.

Colloid AC was diagnosed when there were macroscopically or microscopically visible cystic features. There are abundant pools of extracellular matrix with mucin-secreting tumour cells. The foetal AC subtype has a pattern of glycogen-rich, non-ciliated cells resembling foetal lung tubules.

3.5 The Icelandic healthcare system and the treatment of lung cancer patients

During the study period (1991–2014), the population of Iceland increased from 255,866 to 325,671 (Hagstofa, 2016). Iceland‘s major tertiary care hospital is situated in the capital, Reykjavik, and it is the only hospital in Iceland that performes cardiothoracic surgery. All patients being considered for pulmonary resection for NSCLC are discussed by a multidisciplinary tumour board including thoracic surgeons, pulmonologists, oncologists, radiologists, and pathologists. The preoperative work-up differs between patients, but during the study period it usually included a chest radiograph, a CT-scan of the chest, upper abdomen, and head, bone scintigraphy, and pulmonary function tests. PET-scan was not available in Iceland during the study period. Since 2013, patients who have needed a PET-scan have been sent to Rigshospitalet, Copenhagen, but PET-scan will be available at Landspitali from the autumn of 2017. Tumour samples were obtained through bronchoscopy or transthoracic CT-guided needle biopsy. Mediastinoscopy was perfomed in selected cases, and endobronchial or endoscopic ultrasound (EBUS/EUS) was only used towards the end of the study period.

All patients were discussed at a multidisciplinary meeting after diagnostic work-up. If the patient had early-stage disease and was fit enough for surgery, the surgeon decided whether to perform pneumonectomy, lobectomy, or sublobar resection. All the patients had an epidural placed for postoperative analgesia, and general anaesthesia with double-lumen endotracheal tube for lung isolation. The surgical procedures were performed by nine different surgeons using standardized surgical techniques, and in the last decade, mostly by one of them. During the first half of the study period, posterolateral thoracotomy was the preferred method, but during the last 10-year period, the anterolateral thoracotomy approach was most often used. VATS was only used in selected wedge resections or segmentectomies.

3.6 Follow-up

At Landspitali, the in-hospital stay is usually 5–10 days following pulmonary resection, if the resection has been uneventful and there have been no significant acute complications. One month after discharge, the patient is seen at the outpatient clinic by the surgical team. Further follow-up is in the hands of the referring pulmonologist, who follows the patients every 3–4 months after the surgery for two years, usually with a CXR or CT-scan before the visit. The frequency of check-ups then shifts to every 6 months for the following 3 years. If the cancer recurs, all treatment goes through Landspitali, so there was no loss to follow-up in the patients included in the surgical database.

In study IV, we studied patients who did not have surgical resection, and the loss to follow-up in that study group was 77 out of 859 patients (8.9%). Follow-up time was calculated as the median time for all patients, from surgical resection to either death or censoring.

3.7 Statistical methods

For continuous variables, unless otherwise specified, the mean/median ± the standard deviation is given. Student's t-test was used to compare continuous variables between two groups and ANOVA was used if there were more than two groups. The Kolmogorov-Smirnov test was used to check for the normal distribution of data. For categorical variables, the number of patients along with the percentage of the total patients is given. The Chi-square test was used to compare categorical variables and Fisher's exact test or Chi-square test with Yates' correction was used if expected values were equal to or less than five in studies I and IV, and if equal to or less than 10 in study II. This was necessary because the Chi-square test is not considered suitable for a low number of observations in one sample unless the sample size is large (Daniel & Cross, 2013). In all the statistical analyses, a two-sided *p*-value of < 0.05 was considered significant.

3.7.1 Surgical resection rate

The surgical resection rate was calculated by dividing the number of patients who had pulmonary resection by the total number of patients who had histologically confirmed NSCLC in the same period according to the Icelandic Cancer Registry. The denominator consisted of NSCLC patients where all patients with small cell cancer, carcinoids, carcinoma *in situ*, and sarcomas were excluded. Patients with post-mortem diagnosis were also excluded.

3.7.2 Survival analysis

Survival analysis is a method for comparing the risk of an event (usually death) between groups in a time-dependent manner. All the studies presented in this thesis included survival analysis of a subgroup of lung cancer patients. Overall survival (OS) and cancer-specific survival (CSS) were calculated using the Kaplan-Meier method. The Kaplan-Meier method is the method most commonly used for survival analysis, and has been since it was published in 1958 (Kaplan & Meier, 1958). It is a time-to-event analysis that gives a graphical estimation of survival in one or more groups, in many small intervals. The figure depicts a series of declining or rising horizontal steps representing the events and crosses representing censored events.

The log-rank test—a non-parametric test that evaluates the estimates of the hazard functions of the groups—was used to compare survival. It estimates the difference in survival between groups, but does not permit other variables to be taken into account. In our studies, the Wilcoxon rank-sum test was tried experimentally in study IV, to see whether it would differ from the log-rank test. The Wilcoxon test, a test that emphasizes the first part of the survival curve, is mostly used when censored observations are not present, and it was therefore less relevant than the log-rank test in our studies.

The Cox proportional hazard model was used to evaluate prognostic factors of survival in studies II and III. A univariate analysis was performed on all factors that were thought to be possible prognostic factors of survival. Significant or nearly significant ($p < 0.1$) factors in the univariate analysis and factors thought to contribute to survival were put into the multivariate model. A subset of variables was selected for inclusion in the final model by a stepwise selection procedure using bidirectional elimination—where different variables were fitted in the model by first adding each one at a time and then eliminating them one at a time.

The final multivariate hazard model for overall survival in study II was corrected for age, the time period divided into six four-year periods, stage (TNM), histological type, ischaemic heart disease preoperatively, COPD, postoperative congestive heart failure (CHF), major complication, and free tumour margins. In study III, the final model included gender, age, stage, adenocarcinoma subtype (subgroups with more than 20 patients), size of the tumour, incidental detection, dyspnea, major complication, IHD preoperatively, ARDS as a complication, postoperative pneumonia, and ASA score.

The hazard ratio (HR) is obtained from the Cox proportional hazard model for variables that fulfill the proportional hazard assumption. Global goodness-of-fit test was done to check for assumption of proportionality and for graphic plotting of variables. Stratification was used as required. The results are presented as HR with 95% confidence interval (CI). The HR is considered to be significant when the CI does not include the value 1. A value of < 1 is considered to be protective while a value of > 1 is considered to increase the risk of death. The statistical significance is found by evaluating both the CI and the *p*-value.

3.7.3 Statistical programs

Microsoft Excel (Microsoft Corp. Redmond, WA, USA) was used for discriptive statistics, and we used R version 2.10.1 or 3.1.3 with the help of R studio (Boston, MA, USA) version 0.98.1103 for survival calculations and construction of graphics.

4 Results

4.1 Paper I

Between 1994 and 2008, there were 1,530 histologically confirmed cases of NSCLC in Iceland, of which 404 cases (397 patients) were operated on with curative intent. The surgical resection rate (SRR) for the whole period was therefore 26.4%, and did not significantly change during the study period (Figure 12). The surgical procedures consisted of 73.5% lobectomies (n = 297), 14.9% pneumonectomies (n = 60), and 11.6% sublobar resections (n = 47).

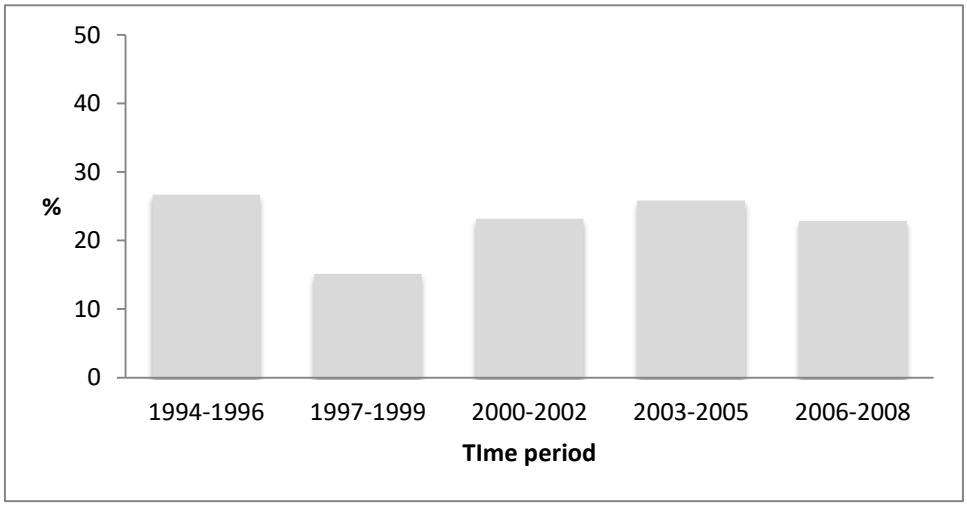


Figure 12: Surgical resection rate (SSR) for NSCLC in Iceland from 1994 to 2008. The difference in SRR between the periods was not statistically significant.

The mean age of the patients was 66 years. Most patients were current or previous smokers (96.5%), and 30.5% of them had an FEV1 less than 75% of the predicted value in preoperative pulmonary function tests. A higher proportion of patients who underwent sublobar resections had COPD or coronary artery disease than patients who underwent lobectomy or pneumonectomy.

The majority of patients (57.4%) had AC histology (Table 5). One-third (31.7%) of the patients had SCC, and the rest had LCC or other NSCLC histological subtypes, including adenosquamous histology. Most patients (87%) were at stages I, II, or IIIA, but 13.9% were at more advanced stages (stages IIIB

or IV) diagnosed perioperatively or postoperatively. The stage distribution did not change significantly between the time periods.

Table 5: The histology, staging, and resection type for the 404 resections performed for NSCLC in Iceland from 1994 to 2008

	n (= 404)	%
Histology		
- Adenocarcinoma	232	57.4
- Squamous cell	128	31.7
- Large cell	23	5.7
- Other	20	5.0
pTNM stage		
- I	224	55.4
- II	94	23.3
- IIIA	30	7.4
- IIIB	35	8.7
- IV	21	5.2
Resection type		
- Lobectomy	297	73.5
- Pneumonectomy	60	14.9
- Sublobar resection	47	11.6

Almost 9% of the patients were diagnosed with at least one major complication, including reoperation for bleeding or empyema. The rate was significantly higher in patients who underwent pneumonectomy (18.3%) than in patients who underwent lobectomy (7.1%) or a sublobar resection (6.4%). The rates of other complications are given in Table 6. Four patients died within 30 days of operation, and the 30-day (operative) mortality was therefore 1.0%.

Total 5-year survival was 40.7% for the whole group and increased from 34.8% in the first period to 43.8% in the last period (log-rank test, $p = 0.039$). Patients who underwent pneumonectomy had a significantly less favourable 5-year survival of 22%, compared to 44.6% for lobectomy and 40.7% for sublobar resection ($p = 0.006$).

Overall 5-year survival in all the patients who were diagnosed with NSCLC in the study period was 12.4%, but it was only 4.8% in the patients who did not undergo surgical resection (n = 1,126).

Table 6: Complications, both major and minor, in patients who underwent pulmonary resection with curative intent for NSCLC in Iceland between 1994 and 2008

	Lobectomy		Pneumonectomy		Lesser resection		All procedures	
	n	%	n	%	n	%	n	%
All major complications	21	7.1	11	18.3	3	6.4	35	8.7
-ARDS	6	2.0	3	5.0	0	0	9	2.2
-Reoperation for bleeding	6	2.0	3	5.0	0	0	9	2.2
-Reoperation for empyema or BPF	3	1.0	4	6.7	0	0	7	1.7
-Heart failure	6	2.0	0	0	1	2.1	7	1.7
-Myocardial infarction	4	1.3	1	1.7	1	2.1	6	1.5
-Empyema	3	1.0	3	5.0	0	0	6	1.5
-Bronchopleural fistula	1	0.3	1	1.7	0	0	2	0.5
-Stroke	0	0	0	0	1	2.1	1	0.2
All minor complications	105	35.4	30	50.0	16	34.0	151	37.4
-Intraoperative bleeding	24	8.1	20	33.3	0	0	44	10.9
-Atrial fibrillation/flutter	18	6.1	15	25.0	1	2.1	34	8.4
-Recurrent laryngeal nerve paralysis	5	1.7	2	3.3	0	0	7	1.7
-Air leakage > 7 days	63	21.2	1	1.7	6	12.8	70	17.3
-Pneumonia	16	5.4	3	5.0	7	14.9	26	6.4
-Wound infection	5	1.7	1	1.7	2	4.3	8	2.0

ARDS, adult respiratory distress syndrome; BPF, bronchopleural fistula.

4.2 Paper II

Between 1991 and 2014, 493 lobectomies (in 489 patients) were performed for NSCLC with curative intent in Iceland and the mean age of the patients was 67 ± 9.5 years (Table 7). A higher proportion of women had smoked within five years of surgery ($p = 0.0007$) and a higher proportion of women had AC histology ($p = 0.0004$). A higher proportion of men had ischaemic heart disease diagnosed before the pulmonary resection ($p < 0.0001$). The mean age of the patients

increased significantly over the time periods, from 63 years in 1991–1994 to 68 years in 2011–2014 (p = 0.009).

Table 7: Demographics of 493 cases operated with lobectomy for NSCLC in Iceland, 1991–2014

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Demographics	n (%)
Descriptive factors	
- Women (ref men)	265 (53.8)
- Age (years)	67 (range: 35–89)
Risk factors, comorbidity	
- Smoking history	468 (94.9)
- Current smoker (within 5 years)	327 (66.3)
- COPD	128 (26.0)
- IHD	121 (24.5)
- Arrhythmias	66 (13.4)
- FEV1 < 75%	138 (28.0)
Period	
- 1991–1994	58 (11.8)
- 1995–1998	59 (12.0)
- 1999–2002	67 (13.6)
- 2003–2006	88 (17.8)
- 2007–2010	94 (19.1)
- 2011–2014	127 (25.8)

COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease; FEV1, forced expiratory volume in 1 second

Table 8 shows the postoperative stage distribution of the 493 cases. Most patients had stage-I disease (55.4%), 30% of whom were at stage IA. Almost one-third of the patients (29.6%) had stage-II disease, and 15% (74 patients) had disease at stage IIIA. Most of the patients with stage-III disease were diagnosed perioperatively or postoperatively. The proportion of patients at stage IA rose from the first period to the last period (25.9% vs. 39.4%; p = 0.03).

The 30-day, hospital, and 90-day mortality was 0.6% (3 patients), 1.2% (6 patients), and 1.4% (7 patients), respectively. The overall 5-year survival in all the patients was 49.2% over the whole 24-year study period. Overall 5-year survival in patients at stage I was 64.2%. Three-year OS increased significantly from the first period (1991–1994) to the last period (2011–2014), from 48.3% to 72.8% (log-rank, p = 0.0004).

Table 8: The postoperative TNM stage distribution of 493 cases that had a lobectomy for NSCLC in Iceland in the 24-year period 1991–2014.

	Stage			
	I	**II**	**IIIA**	**Total**
1991-1994	26 (44.8)	20 (34.4)	12 (20.7)	58 (100)
1995-1998	34 (57.6)	18 (30.5)	7 (11.9)	59 (100)
1999-2002	30 (44.8)	26 (38.8)	11 (16.4)	67 (100)
2003-2006	52 (59.1)	24 (27.2)	12 (13.6)	88 (100)
2007-2010	51 (54.2)	24 (25.6)	19 (20.2)	94 (100)
2011-2014	80 (63.0)	34 (26.8)	13 (10.2)	127 (100)
Total	**273 (55.4)**	**146 (29.6)**	**74 (15.0)**	**493 (100)**

Multivariate analysis on different factors that might predict survival (Figure 13) showed that time period (HR = 0.88, 95% CI 0.82–0.94; p = 0.0003) was a significant prognostic factor for survival, as were free surgical margins (HR = 0.44, 95% CI 0.3–0.65; p < 0.0001). Advanced age (HR = 1.03, 95% CI 1.02–1.04; p < 0.001) and stage (HR = 1.4, 95% CI 1.25–1.46; p < 0.0001) were independent predictors of worse survival.

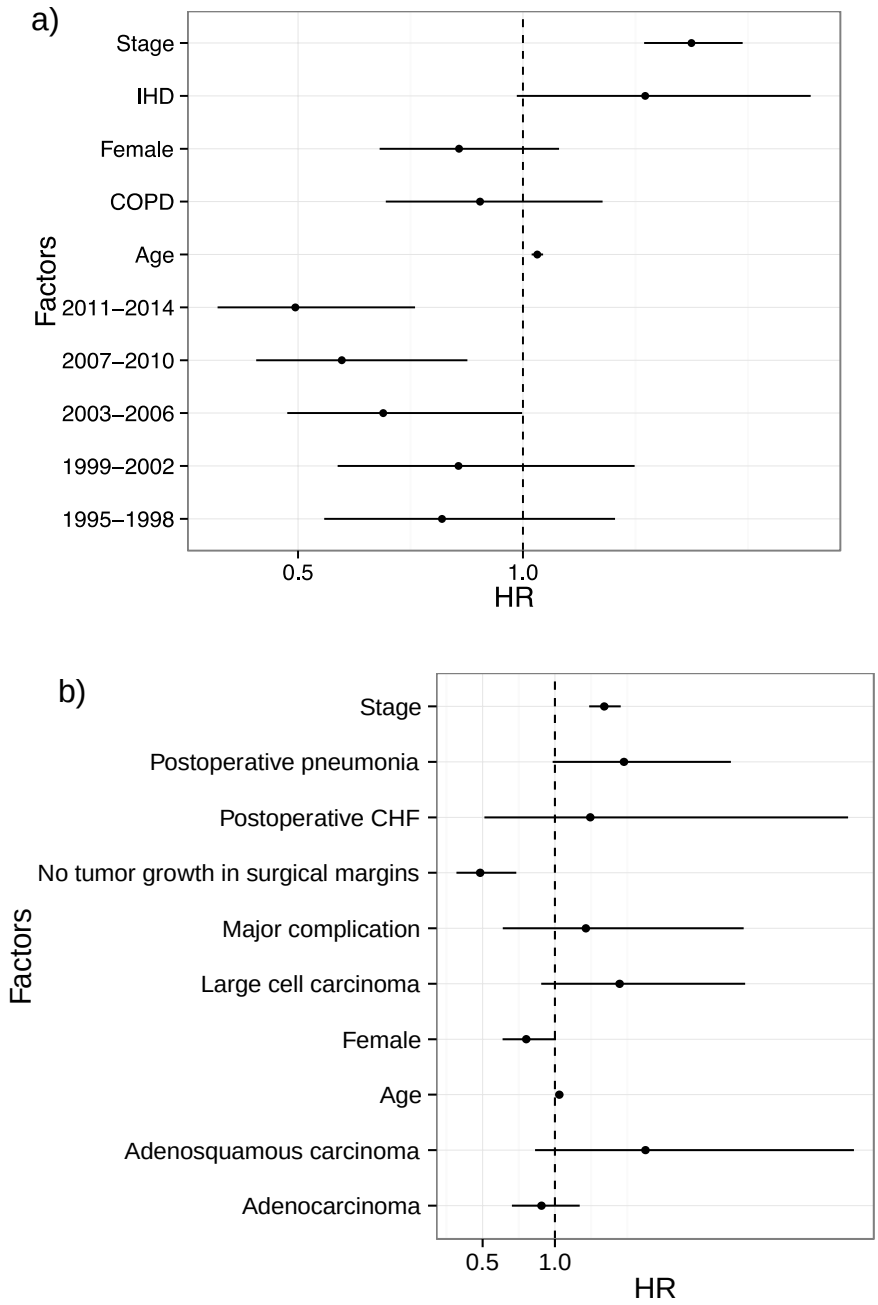

Figure 13: Forest plots showing the results of multivariate analysis of preoperative factors (a) and postoperative factors (b) for 493 patients who underwent lobectomy for NSCLC in Iceland in the period 1991–2014. Lines that cross the dotted line are not significant prognostic factors of overall survival.

4.3 Paper III

During the study period between 1991 and 2010, 285 patients out of 473 patients who underwent surgical resection for NSCLC had AC histology, and 56.8% of them were women. Table 9 shows the patient demographics (with minor corrections made to Table 1 of paper 3). The patients were 67 years old on average and 95.1% were current or previous smokers. Most patients had lobectomy (79%, 224 patients), 12% (37) had a lesser resection, and 24 patients (9%) had a pneumonectomy.

Table 9: Demographics of the 285 patients who had a pulmonary resection with curative intent for primary lung adenocarcinoma in the years 1991–2010. The numbers of patients are given, with percentages in parentheses.

Demographics	**Pneumonectomy n = 24**	**Lobectomy n = 224**	**Lesser resection n = 37**	**Total n = 285**
Age, mean	65	66	68	67
Female	14 (4.9)	129 (45.2)	19 (6.7)	162 (56.8)
Smoking history	22 (7.7)	212 (74.4)	36 (12.6)	271 (95.1)
- Never-smoker	2 (0.7)	11 (3.9)	1 (0.4)	14 (4.9)
- Current smoker	15 (5.2)	153 (53.7)	23 (8.1)	191 (67.0)
Comorbidities				
- COPD	4 (1.4)	57 (20.0)	13 (4.6)	74 (26.0)
- IHD	3 (1.0)	55 (19.2)	17 (6.0)	75 (26.3)
- Arrythmias	1 (0.4)	33 (11.6)	7 (2.5)	41 (14.3)

COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease.

Histological subtyping is shown in Table 10. Almost all—273 (95.8%) of the cases—were invasive ACs, where only nine patients (3.2%) had variants of invasive AC and three patients (1%) had pre-invasive AC. The most common histological subtype was acinar-predominant AC, comprising almost half of the cases (46%). Solid-predominant AC with mucin production was diagnosed in

23% and lepidic-predominant in 20%. No cases of atypical adenomatous hyperplasia (AAH) or enteric-predominant (EPA) AC were identified.

The majority of patients had early-stage disease, with 57.8% being stage-I and 31.5% of those being stage-IA. Two of the patients with pre-invasive AC were at stage IA but the third was at stage IIIA.

Table 10: Adenocarcinoma subtyping according to the pTNM stage of all patients who were diagnosed with adenocarcinoma in Iceland, 1991–2010, and had a surgical resection. The numbers of patients are given, with percentages in parentheses.

Predominant subtype	Stage I	II	IIIA	Total
Pre-invasive	2 (0.7)	0 (0)	1 (0.4)	3 (1.0)
- AIS	1 (0.4)	0 (0)	0 (0)	1 (0.4)
- MIA	1 (0.4)	0 (0)	1 (0.4)	2 (0.7)
Invasive	150 (52.6)	81 (28.4)	42 (14.7)	273 (95.8)
- Lepidic	39 (14.7)	11 (3.9)	5 (1.8)	55 (20.0)
- Acinar	67 (23.5)	38 (13.4)	24 (8.4)	129 (46.0)
- Micropapillary	0 (0)	1 (0.4)	2 (0.7)	3 (1.0)
- Papillary	12 (4.2)	5 (1.8)	4 (1.4)	21 (7.0)
- Solid	32 (11.2)	26 (9.2)	7 (2.5)	65 (23.0)
Variant of invasive	7 (2.5)	1 (0.4)	1(0.4)	9 (3.2)
- Mucinous	5 (1.8)	1 (0.4)	1 (0.4)	7 (2.5)
- Colloid	1 (0.4)	0 (0)	0 (0)	1 (0.4)
- Foetal	1 (0.4)	0 (0)	0 (0)	1 (0.4)
Total	**159 (57.8)**	**82 (28.8)**	**44 (15.4)**	**285 (100)**

AIS, adenocarcinoma *in situ*. MIA, minimally invasive adenocarcinoma. pTNM, postoperative tumour, node, metastasis.

The five-year overall survival for all surgically resected pulmonary ACs during the whole study period was 45.3%. Patients with stage-I disease had a 5-year survival of 61.5%, as compared to 14% for patients with stage-IIIA disease (log-rank test, $p < 0.001$) (Figure 14). The difference in survival between the different subtypes of AC was not statistically significant, as can be seen from Figure 15 (log-rank test, $p = 0.32$). The 5-year survival for LPA was 55%, and it was 38% for APA, 52% for SPA, and 38% for PPA.

The overall survival in patients with SCC ($n = 156$) and LCC ($n = 32$) was 35% and 28%, respectively (log-rank test, $p = 0.02$). When the survival was corrected for stage, the difference in survival was no longer significant ($p = 0.98$).

Univariate analysis showed that gender, advanced TNM stage, increased tumour size, dyspnea at diagnosis, suffering a major postoperative complication, or having ischaemic heart disease was significantly associated with worse OS. In multivariate analysis, only advanced age (HR = 1.03, 95% CI 1.02–1.05; $p < 0.0001$) and TNM stage (stage IIIA: HR = 3.98, 95% CI 2.37–5.98; $p < 0.001$) were independent prognostic factors of OS.

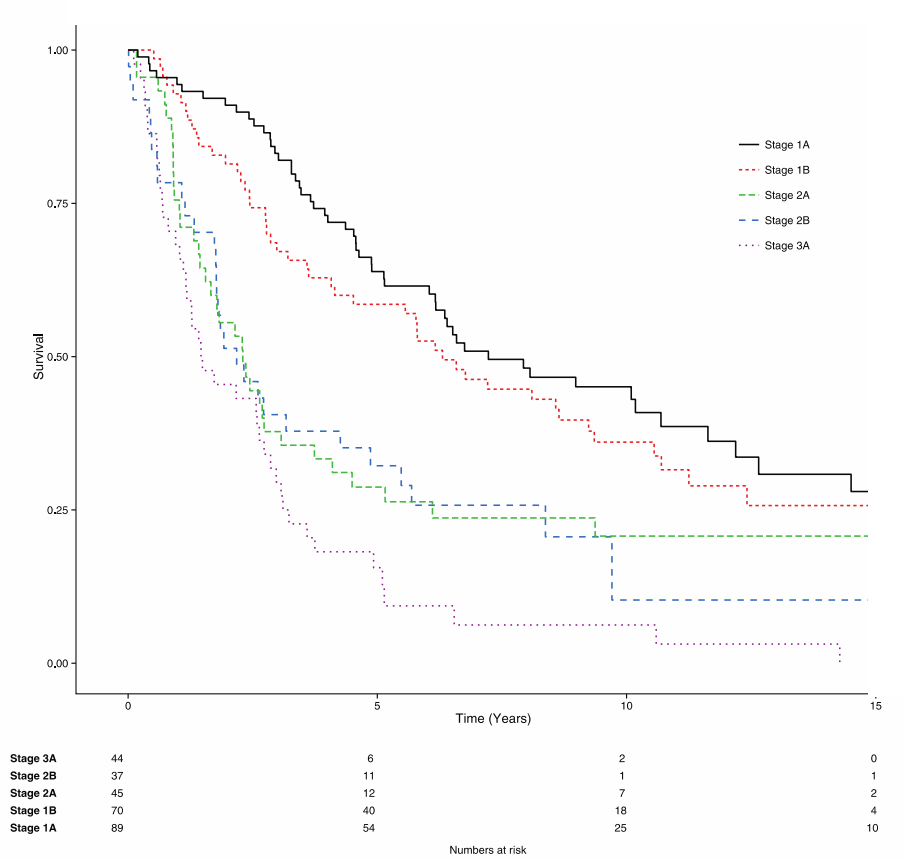

Figure 14: Overall survival in 285 patients with surgically resected adenocarcinoma of the lung in the period 1991–2010, according to stage (log-rank test, $p < 0.001$).

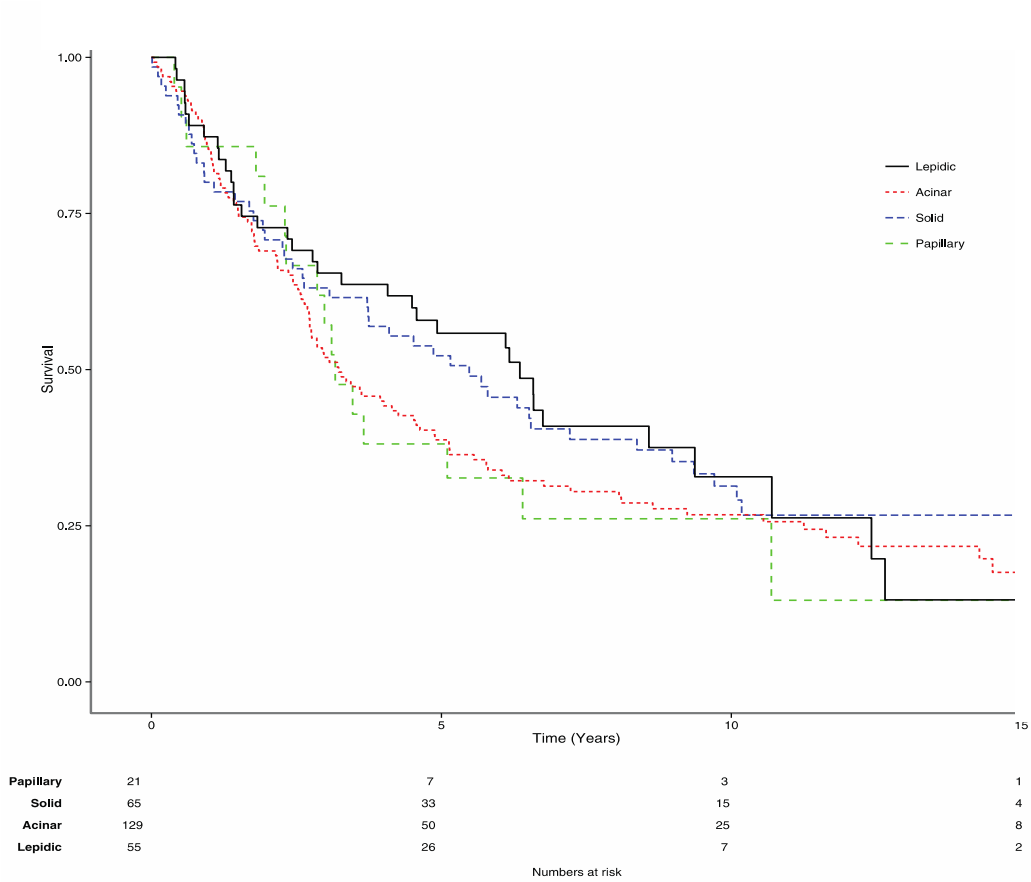

Figure 15: Overall survival of the adenocarcinoma subtypes that had more than 20 patients. The difference was not significant (log-rank, p = 0.32).

4.4 Paper IV

In the years 1991 to 2014, a total of 2,556 patients were diagnosed with lung cancer in Iceland, 859 of whom were elderly (≥ 75 years old). However, 77 of these patients had to be excluded because of missing data, leaving 782 elderly patients (32%, 782/2,479) for further analysis.

AC was the most common histological type (48%) in all the elderly patients, and its proportion rose significantly during the last two 6-year periods. Some 471 patients (62%) were at stage III or IV, 29% were at stage I or II, and the clinical stage could not be determined in 9% (68 patients). The proportion of elderly patients diagnosed with stage-IA disease increased during the last study period ($p < 0.001$), and at the same time the proportion of patients at stage IIB decreased ($p = 0.035$).

Table 11: The stage distribution of all elderly patients (≥ 75 years old) with NSCLC who were diagnosed at early stages (I and II) in Iceland during the period 1991–2014. The numbers of patients are given, with percentages in parentheses.

TNM stage	1991–1996	1997–2002	2003–2008	2009–2014	Total
IA	10 (31)	6 (17)	13 (18)	38 (45)	68 (30)
IB	10 (31)	13 (36)	24 (32)	26 (31)	73 (32)
IIA	8 (22)	8 (22)	17 (22)	12 (14)	44 (19)
IIB	5 (16)	9 (25)	21 (28)	9 (11)	44 (19)

NSCLC, non-small cell lung carcinoma.

The overall surgical resection rate was 18% (140/782) for all the elderly patients, and this did not change significantly during the study period.

The mean age in the elderly group was 80 years, as opposed to 65 years for the younger group. During the study period, the proportion of elderly patients diagnosed with NSCLC increased steadily from 29% in the first study period to 37% in the last ($p = 0.006$).

A total of 103 patients were diagnosed at stage IA, IB, IIA, or IIB, but did not have surgical resection. Another 68 patients did not finish staging work-up. Usually further work-up was not considered necessary in these cases, since it was known beforehand that they would not be offered surgery for various reasons (shown in Table 12). The most common reason for not operating on

elderly patients diagnosed at stages IA to IIIB was insufficient lung function (58%), followed by heart disease (17%), multiple comorbidities (17%), patient refusal of treatment (16%), and poor performance status (13%). There were other, less common reasons as well.

Table 12: The reasons that were given for not performing pulmonary resection on 103 elderly patients with stage-IA to stage-IIB NSCLC in Iceland, 1991–2014.

Reason	**IA–IIB (n = 103) n (%)**	**Incomplete staging (n = 68) n (%)**
Insufficient lung function	60 (58)	32 (47)
Heart disease	17 (17)	11 (16)
Multiple comorbidities	17 (17)	9 (13)
Patient denied operation or further treatment	16 (16)	8 (12)
Frailty and poor performance score	13 (13)	14 (21)
Unresectable tumour location	4 (4)	6 (9)
Patient died of other causes before complete work-up/treatment	4 (4)	2 (3)
Other life-threating or terminal disease	4 (4)	3 (4)
Dementia	3 (3)	6 (9)
Reason for not operating could not be determined	3 (3)	3 (4)

When comparing preoperative patient demographics and risk factors, there were more men in the elderly group ($p = 0.006$), a higher proportion of patients had coronary heart disease ($p < 0.001$), and a higher proportion had a history of arrythmias ($p < 0.001$). The elderly group also had a lower FEV1 ($p < 0.001$), were more likely to have been diagnosed incidentally ($p < 0.001$), and were more

likely to have had a sublobar resection ($p < 0.001$). The younger patients were more likely to have undergone a pneumonectomy ($p < 0.001$) and to have been given adjuvant chemotherapy ($p < 0.001$).

There was no significant difference in 30-day mortality, median length of stay, or rate of postoperative complications between younger patients and elderly patients. There was, however, a significant difference in overall survival (44% vs. 40% at five years; $p = 0.02$) between the groups, but not in cancer-specific survival (50% vs. 51% at five years; $p = 0.8$).

5 Discussion

In this thesis, the epidemiology, diagnosis, treatment, and prognosis of different subgroups of NSCLC patients has been investigated. The patients in all studies represent a whole nation, and the main focus was on short- and long-term outcomes after pulmonary resection in subgroups of patients.

5.1 Long-term overall and cancer-specific survival

The overall 5-year survival for the patients was 40.7% in study I (all types of pulmonary resections), 49.2% in study II (only lobectomies), 45.3% in study III (only AC histology), 40% for elderly patients (all types of resections) in study IV and 44% for younger patients (all types of resection) in study IV. These survival figures only vary with a range of 10% (40–50%), showing the small variation in survival between the different studies and subgroups analyzed. As expected, the most favourable survival was seen in patients who underwent a lobectomy and in patients with AC histology. We analyzed these prognostic factors further by correcting for other factors in the multivariate survival model, such as TNM staging (Goldstraw et al., 2016). Not surprisingly, the TNM staging system was the most significant prognostic factor in all of the studies presented.

Overall survival of NSCLC patients improved with time following pulmonary resection in Iceland. In study I, the 5-year survival rose from 34.8% to 43.8% from the first 5-year period to the last, and in study II the overall 3-year survival for lobectomies increased from 48.3% in 1991–1994 to 72.8% in 2011–2014. The cancer-specific survival also increased during the 24-year study period; underscoring the fact that most NSCLC patients die from their disease and not for other reasons. The reason for the increased survival with time was probably multifactorial. In study I, the stage distribution did not change significantly between periods from 1994 to 2008, but in studies II and IV—which had longer study periods (24 years)—more patients were diagnosed with stage-IA disease in the later time periods, without any change in the ratio of incidentally diagnosed tumours. The increased proportion in stage-IA patients was probably one of the main influential factors in increased survival. Calendar year, however, still remained an independent prognostic factor for survival after correction for stage, age, and other factors in the multivariate analysis (Table 3 of paper II). Thus, the improved survival appears to be influenced by factors other than stage and incidental diagnosis. The rise in the proportion of ACs, as demonstrated in study IV, does not explain this development either, as the time period (calendar year of

diagnosis) also remained a prognostic factor when the histological type was corrected for in the multivariate survival analysis. Improved imaging techniques and improved staging, with increased use of mediastinoscopies and EBUS, have most likely also contributed to the improvement in survival.

As expected, the survival of patients who underwent pneumonectomy was inferior to that for the other types of less extensive operations. The results of study I, however, show that the 5-year survival of patients after pneumonectomy (22%) was disproportionally low in this study compared to other studies, where rates are usually between 27% and 40% (Alexiou et al., 2001; Okada et al., 2000). The reason for this is open to debate, but understaging due to low rates of mediastinoscopies performed during the first half of the study may have played a role. Proper staging is of special importance in patients with tumours that require pneumonectomy, as they are often large and centrally located and have often spread to the lymph node, underscoring the importance of staging work-up.

Importantly, multivariate analysis was performed in studies II and III to assess independent predictive factors of OS. Both studies showed that advanced age and TNM stage were strong independent predictive factors for survival. The histological AC subtype according to the 2011 IASLC/ATS/ERS classification, however, did not turn out to be an independent predictor of OS in study III (multivariate analysis, $p = 0.7$). This was somewhat surprising, as numerous other studies have found the very same classification to predict survival of NSCLC patients (Russell et al., 2011; Warth et al., 2012; Yoshizawa et al., 2013). Still, the study is limited by the fact that it only included 285 patients in the multivariate analysis, which limited the statistical power. In a study by Westaway et al. that included 152 patients, the classification was also shown to have limited prognostic significance in advanced resected pulmonary AC (Westaway et al., 2013), which is similar to our findings (study III). We therefore concluded that more studies might be needed on the possible prognostic relevance of the AC subtype classification.

When comparing different histological types of NSCLC in study III, there was no difference between survival in patients with SCC, AC, or LCC after correction for stage; however, AC was a prognostic factor for survival in univariate analysis. This might suggest that ACs are more often detected at early stages.

A statistically significant difference was observed in OS of the young and elderly patients in study IV (log-rank test, $p = 0.019$), but not in CSS. Interestingly, when the Wilcoxon test was used to compare OS of the groups, no statistically significant difference was observed ($p = 0.109$). Wilcoxon test emphasizes the early events of the survival curve. This may indicate that the OS is initially similar, but due to chronological age and long follow-up time, the

survival curve for the elderly drops after a few years. Other studies have shown similar results (Cerfolio & Bryant, 2006; Fan et al., 2007; Qiang et al., 2015; Schneider et al., 2008). However, study IV was the first study to report these findings for surgically treated NSCLC patients representing a whole nation.

5.2 Complications and 30-day mortality

The rates of major and minor complications following pulmonary resection in studies I, II, and IV are relatively low compared to other reports (Andalib et al., 2013; Irie et al., 2016; Myrdal et al., 2001; Thomas et al., 2014; Yano et al., 1997). Still, however, one must bear in mind that comparison to other studies may be difficult because of the different criteria used.

The major complication rate was 8.7% for all patients who underwent pulmonary resection for NSCLC (paper I). For comparison, Myrdal et al. (2001) reported a rate of 8.8% for surgically treated NSCLC patients in Sweden and the rate was 9.5% in a study by Nathan et al. (2016) performed on patients in the Surveillance, Epidemiology, and End Results (SEER) database. Other studies with wider definitions of major complications have reported rates of 12–36% (Laursen et al., 2016; Maeda et al., 2016; Nojiri et al., 2016; Oor et al., 2016).

Patients who undergo lobectomy usually have fewer complications than patients after pneumonectomy or sublobar resection (Myrdal et al., 2001; Suen et al., 1999; Thorsteinsson et al., 2009). The lobectomy patients (study II) had a major complication rate of 4.7% and a total complication rate of 21.1%. This is lower than reported by Myrdal et al. in Sweden (2001), where it was 5.7% for lobectomies. Other studies have shown *total* operative complication rates in the 9–57% range following lobectomy (Cai et al., 2013; Kent et al., 2014).

The postoperative complications in patients over 75 years old (paper IV) were not significantly different from those in younger patients (major: 11% and 13%, respectively; $p = 0.57$; minor: 36% and 29%, respectively; $p = 0.12$). Actually, heart failure was the only complication that was more common in the elderly (4 vs. 1%; $p = 0.012$). Still, it must be kept in mind that there is a risk for type-II error with such low rates of complications, and relatively small subgroups to compare.

The 30-day operative mortality in studies I (1%), II (0.6%), and IV (> 75 years, 2.0%; < 75 years, 1.0%; $p = 0.387$) was low compared to other studies (Abdelsattar et al., 2016; Bablekos et al., 2016; Irie et al., 2016; Myrdal et al., 2001; Nathan et al., 2016; Pfannschmidt et al., 2007; Schattenberg et al., 2007; Strand et al., 2012). Most studies have had the same definition of operative mortality as we had, and have shown an average operative mortality rate of 1.5–3.8% (Abdelsattar et al., 2016; Bablekos et al., 2016; Irie et al., 2016; Myrdal et al., 2001; Nathan et al., 2016; Pfannschmidt et al., 2007; Schattenberg et al.,

2007; Strand et al., 2012). However rates up to 11% have been reported for pneumonectomy patients operated for stage-III disease (Bablekos et al., 2016; Saha et al., 2014). In the study by Myrdal et al., the 30-day mortality was 0.6% following lobectomy (Myrdal et al., 2001), which is exactly the same rate as reported in study II.

The reasons for the low complication rates and 30-day mortality rates are debatable. The four studies presented here were all nationwide and population-based, and the patients were treated at a single centre. One possible explanation might be regional differences, with good teamwork in the surgical and anaesthesiology teams. Another explanation could be the early use of multidisciplinary discussion of every patient.

5.3 Histology

In all four studies, the histological diagnosis was based on the WHO 2004 or earlier classification of lung tumours (Travis et al., 2004) and the 2011 IASLC/ERS/ATS classification for pulmonary AC (Travis et al., 2011). The most common histological subtype was acinar-predominant AC and, as pointed out earlier (see section 5.1), the new histological subclassification did not turn out to be a prognostic factor for survival of AC patients.

The distribution of histological subtypes of ACs was similar to those in studies from Europe and Australia (Mansuet-Lupo et al., 2014; Russell et al., 2011), with the majority of cases being invasive and around half of them being acinar-predominant AC. Studies on Asian patients, however, usually report more cases of non-invasive AC (Nakagiri et al., 2014; Yanagawa et al., 2014).

There was no significant difference in survival between the histological AC subgroups. However, a trend showing worse survival in the acinar-predominant subgroup was observed (38%), which has also been reported previously in numerous other studies (43–68%) (Russell et al., 2011; Warth et al., 2012; Westaway et al., 2013). Thus, our findings could indicate that the acinar-predominant subgroup should be grouped with poor prognosis subtypes, such as micropapillary-predominant AC. Furthermore, our findings also indicate that this large subgroup, acinar-predominant AC, is a heterogenous group that requires further subclassification based on nuclear features or architecture.

In September 2015, the WHO launched a new classification of lung tumours with significant genetic, clinical, and radiological advances (Travis et al., 2015). The new classification meant substantial differences for lung cancer histology, but not for the 2011 IASLC/ERS/ATS subclassification of lung AC. In the 2015 classification, the term “predominant” is no longer listed in the names for the major AC subtypes, but they should still be classified according to the

predominant subtype. This is of relevance here, especially for study III, where patients with AC according to earlier WHO classifications were included (Travis et al., 2004), as some of the tumours that were defined as LCC in the former classification are now categorized as ACs based on immunohistochemistry. In particular, in the new 2015 classification, tumours that were formerly called LCCs but express TTF1 and/or Napsin A are categorized as solid ACs even if mucin is absent (Travis et al., 2015).

5.4 Surgical resection rate

The surgical resection rate (SRR) in our nationwide, population-based study on all resected lung cancer patients over a 15-year period (paper I) was 26.4% and did not change significantly between the years 1994 and 2008. Furthermore, in study IV, the SRR in elderly patients (≥ 75 years old) was lower than in the younger patients (18% vs. 32%; $p < 0.001$).

Other European studies have shown SRRs to be in the 11–24% range (de Cos et al., 2008; Imperatori et al., 2016; Makitaro et al., 2002; Myrdal et al., 2009; Strand et al., 2012). Our rate of 26.4% therefore appears to be higher than in most other studies. When comparing studies, one must take into account possible differences in the definition of SRR, which are not even always specified in the different studies (Strand, 2012). Some studies have included patients with SCLC; others have included patients with the diagnosis on the death certificate only. The reason for the high SRR in our study is not clear. One explanation may be that there are only a limited number of doctors in Iceland who perform lung cancer surgery, and the operations are all performed at a single institution where all patients diagnosed with NSCLC are discussed at a multidisciplinary meeting and the treatment decided. Another possible explanation might be regional variation, whereby some centres have better outcome than others—as shown in studies from Denmark (Rasmussen, 2016), Spain (de Cos et al., 2008), and Norway (Strand et al., 2012).

The SRR for elderly patients was 18% in paper IV, which is in line with other studies (Mery et al., 2005; Shirvani et al., 2012). A lower proportion of elderly patients underwent pneumonectomy and a higher proportion underwent sublobar resections than younger patients. The elderly patients had favourable surgical outcomes with low rates of major complications, low 30-day mortality, and favourable survival. The only exception was heart failure, which was more common in the elderly group (4% vs. 1%; $p = 0.012$). The low SRR, few pneumonectomies, and a high number of sublobar resections in the elderly might reflect an appropriate selection of patients for surgery. However, it might also suggest that more elderly patients could tolerate surgery—and more often lobectomy than sublobar resection.

Previous studies have shown lower complication rates and mortality with sublobar resections and less invasive surgery (Alexandersson et al., 2011; Dell'Amore et al., 2015; Qiang et al., 2015). A recent randomized controlled trial comparing sublobar resection and lobectomy is ongoing, but the results are not yet published (Yang et al., 2016). It could be argued that SRR in elderly patients could be increased by offering less invasive surgery or sublobar resections, thereby reducing the number of patients who are denied surgery due to insufficient lung function, heart disease, or multiple comorbidities.

6 Conclusions

Lung cancer is the leading cause of cancer-related death in the western world. Despite the great advances in surgical techniques, and also radiation therapy and chemotherapy, the survival in lung cancer is still considered to be poor. In the epidemiological studies presented in this thesis, we have reported short- and long-term outcomes in patients undergoing surgical resection for lung cancer in a nationwide population-based cohort.

The surgical resection rate was high for NSCLC patients in Iceland in the period 1994–2008. Short-term outcome was good, with a low rate of major complications and an operative mortality of only 1%. Furthermore, five-year survival improved significantly over the study period.

The short-term outcome of lobectomy for NSCLC in Iceland in the period 1991–2014 was excellent, as reflected by the low 30-day mortality and low rate of complications. Long-term outcome was acceptable but, importantly, the survival improved significantly over the study period.

The AC subtype according to the 2011 IASLC/ATS/ERS classification was not an independent prognostic factor for survival in our study of 285 patients in the period 1991–2010. Pre-invasive and minimally invasive adenocarcinomas were rare.

Elderly patients with resectable NSCLC were frequently excluded from surgery due to comorbid conditions. They may represent a selected group, but they have a favourable 30-day mortality and favourable long-term survival. This indicates that more patients with NSCLC who are elderly could be operated on.

7 Strengths and limitations

All the data in studies I–IV were based on a nationwide patient cohort with all the patients operated on at a single cardiothoracic centre over a time period of up to 24 years. The patient cohort was well-defined, both clinically and geographically, and a further strength was the fact that all the patients were operated on at a single cardiothoracic centre, reducing the risk of institutional or selection bias. All patients were most likely included, as two registries were double-checked in order to minimize the risk of omitting patients. A further strength was that none of the patients were lost to follow-up in the surgical database, with only very few elderly patents being lost to follow-up in the non-surgical group in study IV. Importantly, the experienced senior pulmonary pathologist who reviewed the histology samples in study III was blinded regarding the clinical outcome of patients, thereby reducing the risk of response bias.

The main limitation of all the four studies included in this thesis was their retrospective design. By recording data retrospectively, factors such as documentation of symptoms and complications are not as reliable as when the studies are prospective. Staging also improved during the study period, with more aggressive and routine use of preoperative mediastinoscopy and other staging methods from 2005 onward. PET-scan has not been available in Iceland, but since 2013 patients have been sent to Copenhagen, Denmark, for staging with PET-scan. Surgical treatment did not change much during the study period that covered 24 years, but in the latter half of the study period adjuvant chemotherapy was offered to most patients at stages II and IIIA. The lack of detailed information on adjuvant therapy in the survival analysis could therefore be considered to be a limitation.

8 Future work

Fortunately, the field of research on lung cancer is expanding rapidly with a vast number of studies being published every year. In this thesis, four studies are presented that have been added to the literature during the past 5 years. This work has led to ideas for many more studies in the field of lung cancer in Iceland.

The role of adjuvant chemotherapy should be looked into further, but many patients with localized disease at surgery later develop recurrent NSCLCs that were in many cases distant metastases. Although adjuvant chemotherapy has been shown to improve survival in stages II and III, its effect has been limited—with only around 5% survival benefit (Novello et al., 2016; Pignon et al., 2008). Future studies should look further into the benefit of this therapy in different subgroups of NSCLC patients, to find out which patients benefit more than others (Burdett et al., 2015; Ganti et al., 2015; T. S. Park et al., 2014). The lung cancer study group in Iceland has already started to collect more detailed information on the adjuvant chemotherapy offered to patients at stages II and III, and has added this information to the surgical database. This has been done in order to determine whether adjuvant therapy has contributed significantly to the observed improvement in survival of NSCLC patients in Iceland (study II) or whether other factors are involved.

Another interesting field for future studies is to take advantage of the almost complete histological samples of the patients in the surgical database. These are kept in a biobank at the Department of Pathology at Landspitali University Hospital and represent all cases of NSCLC diagnosed in a whole and well geographically defined population. Further characterization of these tumours at the DNA and RNA level using rapidly evolving molecular techniques (Lira et al., 2014) could lead to a better understanding of lung cancer subgroups in our material, with future implications for improved diagnostics, refined prognostics, and personalized therapy.

It could also be of interest to construct a prospective database of all lung cancer patients diagnosed in Iceland, to better understand the epidemiology and outcome of different modes of treatment, including pulmonary resections. This cooperation could involve deCODE Genetics, a genetic company located in Reykjavik, which has already contributed with important studies on family history and genetics of Icelandic lung cancer patients. This cooperation would involve extensive collaboration between pulmonologists, oncologists, and thoracic surgeons together with specialists in genetic research, statisticians, and software technicians. Such a registry would be a platform for publication of high-quality studies that not only focus on the short- and long-term outcomes following surgery, but also on the quality of life of the patient.

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Paper I

Resection Rate and Outcome of Pulmonary Resections for Non–Small-Cell Lung Cancer

A Nationwide Study From Iceland

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Background: The proportion of patients with non–small-cell lung cancer (NSCLC) who undergo surgery with curative intent is one measure of effectiveness in treating lung cancer. To the best of our knowledge, surgical resection rate (SRR) for a whole nation has never been reported before. We studied the SRR and surgical outcome of NSCLC patients in Iceland during a recent 15-year period.

Methods: This was a retrospective study of all pulmonary resections performed with curative intent for NSCLC in Iceland from 1994 to 2008. Information was retrieved from medical records and from the Icelandic Cancer Registry. Patient demographics, postoperative tumor, node, metastasis stage, overall survival, and complication rates were compared over three 5-year periods.

Results: Of 1530 confirmed cases of NSCLC, 404 were resected, giving an SRR of 26.4%, which did not change significantly during the study period. Minor and major complication rates were 37.4% and 8.7%, respectively. Operative mortality rates were 0.7% for lobectomy, 3.3% for pneumonectomy, and 0% for lesser resection. Five-year survival after all procedures was 40.7% and improved from the first to the last 5-year period (34.8% versus 43.8%, $p = 0.04$). Five-year survival for stages I and II together was 46.8%, with no significant change in stage distribution between periods. Five-year survival after pneumonectomy was 22.0%, which was significantly lower than for lobectomy (44.6%) and lesser resection (40.7%) ($p < 0.005$). Unoperated patients had a 5-year survival of 4.8%, as compared to 12.4% for all the NSCLC patients together.

Conclusion: Compared with most other published studies, the SRR of NSCLC in Iceland is high. Short-term outcome is good, with a low rate of major complications and an operative mortality of only 1.0%. Five-year survival improved significantly over the study period.

Key Words: NSCLC, Resection rate, Outcome, Complications, Survival.

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Lung cancer is the leading cause of cancer-related deaths in the western world.[1] In Iceland, the mortality from lung cancer is similar to that of breast, prostate, and colon cancer combined, and non–small-cell lung cancer (NSCLC) accounts for about 85% of lung cancer cases.[2] Although surgical resection is still the only well-defined curative treatment for NSCLC, it is only possible for the one third of patients diagnosed with stage I or stage II disease and for selected cases of stage IIIA disease.[3,4,5]

Surgical resection rate (SRR) is one measure of effectiveness in treating NSCLC, for example, in a particular geographic location. SRR has varied considerably, often ranging from 15% to 25% in European studies,[6–9] and it was 29% in a study including more than 700 hospitals in the United States.[5] However, smaller single-institution studies from the United States have found SRRs of up to 37%,[10] and there have been studies from Europe that show SRRs as low as 10%.[6,11–13] None of the previously published studies have found an SRR for a whole nation. The same applies to outcome analysis of surgical treatment of NSCLC. Numerous authors have reported short-term complications and long-term survival for lobectomies, pneumonectomies, and lesser resections separately, with only a few of the studies analyzing all the different procedures together. In these studies, the combined rate of major complications has been around or over 10%,[14–16] and operative mortality has ranged from 1.5% to 7%.[5,8,14,17–19] For pneumonectomies, the figures were often double these values.[14–16]

The aim of this study was to investigate the SRR for the whole nation of Iceland using centralized databases in the country. Another aim was to determine surgical outcomes for the different lung procedures that were performed with curative intent in NSCLC patients in Iceland as a whole.

MATERIALS AND METHODS

This was a retrospective study of all patients in Iceland who underwent pulmonary resection with curative intent for NSCLC from January 1, 1994 to December 31, 2008. Exploratory-only thoracotomies, palliative procedures, and lesser resections for biopsy purposes were excluded.

A central, computerized histology database from the Department of Pathology of Landspitali University Hospital, containing details of all lung histology specimens in Iceland was used to identify cases. To minimize the risk of cases being

missed, we also reviewed the diagnosis and operation registry at Landspitali University Hospital, the only center performing cardiothoracic surgery in Iceland.

We obtained information on all cases with a histologically confirmed diagnosis of primary NSCLC from the Icelandic Cancer Registry.[2] This registry covers all cancer cases diagnosed at hospitals and other healthcare facilities in Iceland since 1955. SRR was calculated by dividing the number of all pulmonary resections with curative intent for NSCLC by the number of all histologically confirmed cases of NSCLC within the same period. One hundred and thirty-three patients (6.6% of all patients with a lung cancer diagnosis) did not have a histologically confirmed diagnosis, and 306 patients had small-cell carcinoma. These two groups were excluded from the NSCLC group that made up the denominator for the calculation of SRR. We also excluded patients with carcinoid tumors ($n = 38$), sarcomas, and carcinoma in situ.

Baseline demographic information and clinical data were collected from hospital charts and surgical reports using a standardized data sheet. Age, comorbidities, and presenting symptoms were collected along with data regarding the type of operation, tumor, postoperative tumor, node, metastasis (TNM) stage, complications, and survival.

Patients being considered for pulmonary resection had been reviewed by a multidisciplinary tumor board including thoracic surgeons, pulmonologists, oncologists, radiologists, and pathologists. The preoperative workup varied between patients, but usually included a chest radiograph, a computed tomography (CT) scan of the chest, upper abdomen and head, and also bone scintigraphy and spirometry. Preoperative biopsies were obtained through bronchoscopy or transthoracic CT-guided needle biopsy. Mediastinoscopy was performed preoperatively in a proportion of the cases, but positron emission tomography (PET) scan has never been available in Iceland.

Patients were staged postoperatively (pathological stage, pTNM) using both the 6th and the 7th edition of the TNM staging system,[20] but data is primarily reported for the 6th version. Preoperative clinical staging (cTNM) was not performed uniformly and is not reported in this study.

All surgical procedures were performed in general anesthesia with double lumen intubation and thoracic epidural anesthesia. The operations were performed by six surgeons using standardized techniques with intraoperative lymphadenectomy of enlarged hilar or ipsilateral mediastinal lymph nodes, but during the last 5-year period these lymph nodes were routinely removed or sampled. A posterolateral thoracotomy was most often performed, but during the last 5-year period an anterolateral approach was used.

Major complications were defined as reoperation for bleeding, heart failure, acute respiratory distress syndrome, myocardial infarction, empyema, stroke, and bronchopleural fistula. Minor complications were defined as air leakage for more than 7 days, pneumonia, intraoperative bleeding of more than 1 liter, atrial fibrillation/flutter, wound infection, and recurrent laryngeal nerve paralysis. Operative mortality was defined as death occurring within 30 days of surgery. To assess trends, the 15-year study period was divided into three 5-year periods.

Statistics

Microsoft Excel was used for descriptive statistics, and R version 2.10.1 for survival calculations. Student's t test, Fisher's exact test, and the χ^2 test were used to compare groups, and differences were considered to be statistically significant when the p value was less than 0.05. Overall survival (OS) was analyzed by the Kaplan-Meier method, and the log-rank test was used to compare survival between groups. All patients were followed up with respect to survival by using data from the Icelandic National Population Registry.[21] In this way, patients could be assigned a date of death or were identified as living on July 10, 2010. Mean follow-up time was 49 months (range, 0–194 months).

The study was approved by the Icelandic National Bioethics Committee and the Data Protection Authority. As individual patients were not identified, individual consent was waived.

RESULTS

There were 1530 histologically confirmed cases of NSCLC during the 15-year period, of which 404 underwent surgery (397 patients). The SRR was 26.4% and did not change significantly between the three 5-year periods (28.2%, 24.3%, and 26.8%, respectively; Table 1). The surgical procedures consisted of 297 lobectomies (73.5%), 60 pneumonectomies (14.9%), and 47 lesser resections (11.6%).

The mean age of patients who underwent surgery was 65.9 years; those in the pneumonectomy group were 6 years younger on average than those in the lesser resection group (Table 2). Over 95% of the patients were current or previous smokers, and many of them had reduced pulmonary function. A history of coronary artery disease and chronic obstructive

TABLE 1. Evaluation of Trends From 1994 to 2008 for Patients in Iceland Who Underwent Surgical Resection With Curative Intent for NSCLC, Divided into Three 5-Year Periods

	1994–1998 ($n = 124$)	1999–2003 ($n = 119$)	2004–2008 ($n = 161$)	All Periods ($n = 404$)
Male sex	66 (53.2)	60 (50.4)	85 (52.8)	211 (52.2)
Mean age	64.4	65.4	67.1	65.8
Age > 69 years	46 (37.1)	48 (40.3)	74 (46.0)	168 (41.6)
Surgical resection rate (SRR), %	28.2	24.3	26.8	26.4
Adenocarcinoma histology	67 (54.0)	64 (53.8)	103 (64.0)	234 (57.4)
Incidental diagnosis	40 (32.8)	38 (31.9)	61 (37.9)	139 (34.6)
Mediastinoscopy performed	11 (8.9)	21 (17.6)	25 (15.5)	57 (14.1)
Stage I or II disease	98 (79.0)	94 (79.0)	126 (7.83)	318 (78.7)
Pneumonectomies	16 (12.9)	18 (15.1)	26 (16.1)	60 (14.9)
5-year survival, %	34.8	40.6	43.8[a]	40.7

The numbers of patients are given with percentages in parentheses, except for age, surgical resection rate, and survival, where mean and percentage are given.

[a]Statistically significant difference between groups ($p < 0.05$).

NSCLC, non–small-cell lung cancer.

TABLE 2. Patient Demographics and Comorbidities in Patients in Iceland, Who Underwent Surgical Resection With Curative Intent for NSCLC, 1994 to 2008

	Lobectomy (n = 297)	Pneumonectomy (n = 60)	Lesser Resections (n = 47)	All Procedures (n = 404)
Male sex	148 (49.9)	42 (70.0)	21 (44.7)	211 (52.2)
Age, years (range)	65.9 (37–89)	62.7 (45–83)	69.1 (43–84)	65.8 (37–89)
History of smoking	285 (96.0)	59 (98.3)	46 (97.9)	390 (96.5)
COPD	73 (24.7)	14 (23.3)	19 (40.4)[a]	106 (26.3)
FEV1 < 75% predicted	83 (27.9)	20 (33.3)	20 (42.6)	123 (30.5)
Coronary artery disease	72 (24.2)	12 (20.0)	26 (55.3)[a]	110 (27.2)
ASA score, mean	2.6	2.6	2.6	2.6

The numbers of patients are given with percentages in parentheses, except for age and ASA score where means are given.
[a] Statistically significant difference between groups ($p < 0.05$).
NSCLC, non–small-cell lung cancer; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; ASA, American Society of Anesthesiologists.

pulmonary disease was significantly more common in patients who underwent lesser resection than in patients who underwent pneumonectomy or lobectomy. A forced expiratory volume of less than 75% of the predicted value in 1 second was also identified in more patients who underwent lesser resection (42.6% versus 28.9% for the other patients, $p = 0.06$; Table 2).

Adenocarcinoma was the most common histological type of lung cancer (57.4%), whereas squamous-cell histology accounted for 31.7% (Table 3). Squamous-cell carcinoma was more frequent in those who underwent pneumonectomy than in the other patients. As shown in Table 3, almost 87% of the patients had stage I, stage II, or stage IIIA disease, but 13.9% had stage IIIB or IV disease in postoperative staging. The proportion of stage I cases was highest in the patients who underwent lesser resection (78.7%). In Table 4 the stage distribution using the 7th edition of the TNM system is also given. The stage distribution did not change significantly between periods (Table 1). A mediastinoscopy was performed preoperatively in 20 of the pneumonectomies (33.3%), in 36 of the lobectomies (12.1%), and in one of the lesser resections (2.1%).

Almost 9% of the patients had major complications, of which reoperation for bleeding (n = 9), reoperation for empyema and/or bronchopleural fistula (n = 7), heart failure (n = 7), and myocardial infarction (n = 6) were the most common (Table 5). The rate of major complications was significantly higher for the patients who underwent pneumonectomy (18.3%) than for those who underwent lobectomy (7.1%) and lesser resection (6.4%) ($p = 0.01$; Table 5).

Two patients died within 30 days of lobectomy and two others died after pneumonectomy, but there was no operative mortality after lesser resection. Operative mortality for the whole group was therefore 1.0%.

Five-year OS for the whole group was 40.7%. It was significantly higher for the last 5-year period than for the first (43.8% versus 34.8%; log-rank test, $p = 0.039$) (Table 1). Figure 1 shows OS for the different procedures. Survival at 5 years was 44.6% after lobectomy, 40.7% after lesser resection,

TABLE 3. Tumor Histology, Disease Stage (pTNM), and Other Pathological Data for Patients in Iceland, Who Underwent Surgical Resections (Lobectomy, Pneumonectomy, and Lesser Resections) with Curative Intent for NSCLC, 1994 to 2008

	Lobectomy (n = 297)	Pneumonectomy (n = 60)	Lesser Resections (n = 47)	All Procedures (n = 404)
Tumor histology				
Adenocarcinoma	179 (60.2)	22 (36.7)[a]	31 (66.0)	138 (57.4)
Squamous-cell	85 (28.6)	32 (53.3)[a]	11 (23.4)	128 (31.7)
Large-cell	19 (6.4)	3 (5.0)	1 (2.1)	23 (5.7)
Other (including adenosquamous)	13 (4.3)	3 (5.0)	4 (8.5)	20 (5.0)
Disease stage (pTNM)				
I	179 (60.2)	8 (13.3)[a]	37 (78.7)	224 (55.4)
II	59 (19.9)	27 (45.0)[a]	8 (17.0)	94 (23.3)
IIIA	19 (6.4)	9 (15)	2 (4.3)	30 (7.4)
IIIB	22 (7.4)	13 (21.7)	0	35 (8.7)
IV	18 (6.1)	3 (5.0)	0	21 (5.2)
Mean size of tumor, mm (range)	39 (4–190)	57 (20–150)	23 (8–50)	40 (4–190)
Positive surgical margins	27 (9.1)	7 (11.7)	9 (18.8)	43 (10.6)

The numbers of patients are given with percentages in parentheses, except for tumor size where means with range are given.
[a] Statistically significant difference between groups ($p < 0.05$).
TNM, tumor, node, metastasis; NSCLC, non–small-cell lung cancer.

TABLE 4. Overall 5-Year Survival According to Both the 6th and 7th Edition of the TNM Staging System for Patients in Iceland With NSCLC Who Underwent Surgical Resection With Curative Intent, 1994 to 2008

TNM Stage	6th Edition (*n*)	Survival at 5 Years (%)	7th Edition (*n*)	Survival at 5 Years (%)
I	224	55.3	194	58.1
II	94	26.6	128	29.4
IIIA	30	19.9	61	22.1
IIIB	35	23.8	3	NA[a]
IV	21	7.1	18	5.4
I + II	318	46.8	322	46.7
III + IV	86	18.4	82	17.8

[a] Only three patients, calculations therefore not available.
NA, not available.

and significantly lower (22.0%) after pneumonectomy (p = 0.006). The NSCLC patients who did not undergo surgery had a much less favorable survival: only 4.8% after 5 years. Survival for all NSCLC patients together was 12.4% at 5 years, but 46.8% for stages I and II together for the operated patients. Survival for the different stages is shown in Table 4 and Figure 2.

DISCUSSION

Our results show that the SRR for NSCLC in Iceland (at 26.4%) is higher than in other European studies, where SRR has usually been reported to be in the 15% to 25% range.[6–9] To the best of our knowledge, this is the first report of SRR for a whole nation. Short-term outcome for all procedures was excellent, with low rates of major complications and an operative mortality of only 1.0%; other studies have found figures between 1.5% and 7%.[5,8,14,17–19]

The rate of major complications was 8.7%, which is low compared to other studies. However, comparisons between studies can be difficult because of the different criteria used. In the study by Myrdal et al.[14] the rate of major complications was 8.8%, and it was 12.4% in the study by Yano et al.[15] In another study, the major complication rate was 13%, but the authors' definition of major complications was wider than that in the present study.[16]

Five-year survival in this study was 40.7% for the whole study period and it improved from 34.8% during the first 5-year period to 43.8% for the last 5-year period (p = 0.04). Survival figures from other studies have ranged from 30% to 60% at 5 years,[10,22–24] and from around 50% to 60% for patients with stage I and II disease, which are somewhat higher than observed for stage I and II patients in our study, or 47%.[20]

Few studies evaluating surgical outcomes of NSCLC have included all three types of operations. In this study, survival after lesser resection was similar to that after lobectomy, even though a higher proportion of patients in the lesser resection group had underlying cardiopulmonary disease. There was, however, a higher proportion of patients with stage I disease in the lesser-resection group. The low complication rate and low mortality rate in the lesser-resection group raises the question of whether some of these patients could have

TABLE 5. Minor and Major Complications in Patients in Iceland Who Underwent Different Lung Operations With Curative Intent for NSCLC, 1994 to 2008

	Lobectomy (*n* = 297)	Pneumonectomy (*n* = 60)	Lesser Resections (*n* = 47)	All Procedures (*n* = 404)
Minor complications	105 (35.4)	30 (50.0)	16 (34.0)	151 (37.4)
Intraoperative bleeding > 1 l	24 (8.1)	20 (33.3)[a]	0 (0)	44 (10.9)
Atrial fibrillation/flutter	18 (6.1)	15 (25.0)[a]	1 (2.1)	34 (8.4)
Recurrent laryngeal nerve paralysis	5 (1.7)	2 (3.3)	0 (0)	7 (1.7)
Air leakage for > 7 days	63 (21.2)	1 (1.7)	6 (12.8)	70 (17.3)
Pneumonia	16 (5.4)	3 (5.0)	7 (14.9)[a]	26 (6.4)
Wound infection	5 (1.7)	1 (1.7)	2 (4.3)	8 (2.0)
Major complications	21 (7.1)	11 (18.3)[a]	3 (6.4)	35 (8.7)
ARDS	6 (2.0)	3 (5.0)	0	9 (2.2)
Reoperation for bleeding	6 (2.0)	3 (5.0)	0	9 (2.2)
Reoperation for empyema and/or BPF	3 (1.0)	4 (6.7)	0	7 (1.7)
Heart failure	6 (2.0)	0	1 (2.1)	7 (1.7)
Myocardial infarction	4 (1.3)	1 (1.7)	1 (2.1)	6 (1.5)
Empyema	3 (1.0)	3 (5.0)	0	6 (1.5)
Bronchopleural fistula	1 (0.3)	1 (1.7)	0	2 (0.5)
Stroke	0	0	1 (2.1)	1 (0.2)

A patient could have more than one complication. The numbers of patients are given with percentages in parentheses.
[a] Statistically significant difference between groups ($p < 0.05$).
NSCLC, non–small-cell lung cancer; ARDS, acute respiratory distress syndrome; BPF, bronchopleural fistula.

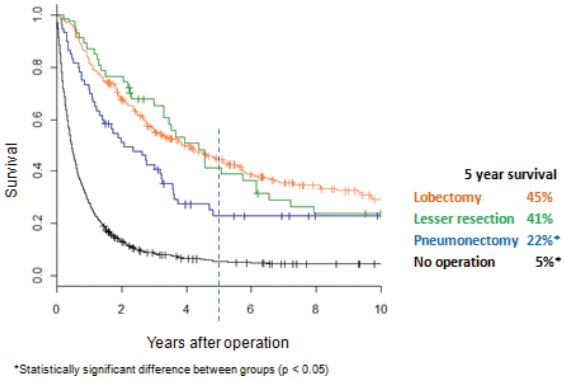

FIGURE. 1. Kaplan-Meier graph showing overall survival of patients with NSCLC who underwent surgical resection (lobectomy, pneumonectomy, or lesser resections) with curative intent in Iceland from 1994 to 2008. Patients who did not undergo surgery are also shown. NSCLC, non–small-cell lung cancer.

tolerated a lobectomy. Alternatively, this could also be an argument for greater use of lesser resections in patients with small tumors. This question is being actively studied, as there is growing evidence that lesser resections are a reasonable approach for small peripheral tumors (of < 2 cm) and also for small ground-glass opacity lesions detected by CT imaging.[25]

As expected, survival after pneumonectomy was significantly lower than after lobectomy and lesser resection. Our result of 22% 5-year survival after pneumonectomy seems disproportionately low when compared to the results of other studies that have shown rates from 27% to 40%.[26–29] The reason for the low survival after pneumonectomy is open to debate, but understaging because of a low rate of mediastinoscopies

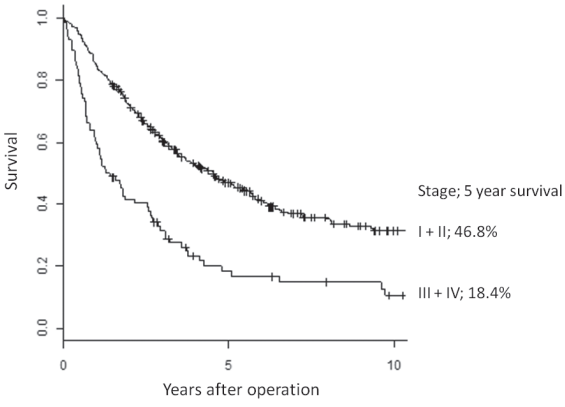

FIGURE. 2. Kaplan-Meier graph showing overall survival of patients with NSCLC, both for stages I and II, and III and IV together, who underwent surgical resection with curative intent in Iceland from 1994 to 2008. NSCLC, non–small-cell lung cancer.

may have had a role. Tumors requiring pneumonectomy are often large and centrally located, and spread more often to the mediastinal lymph nodes, making mediastinoscopy even more important in the workup of these patients.[30] The use of PET scans, which was not available for this patient population, is also known to improve preoperative staging and to prevent unnecessary surgery.

As shown in Table 1, it is unlikely that stage distribution explains improved survival, as it did not change significantly during the study period. A number of advances have been made in the preoperative evaluation and staging of patients with NSCLC in recent years. Improvements in imaging techniques and increased use of mediastinoscopy may have resulted in more patients being excluded from surgical resection because of advanced disease. This could have contributed to the fact that survival improved during the last 5-year period of this study. Improvements in surgical techniques, with increases in the number of cases operated on per surgeon, are also known to play a role.[24] Finally, more frequent use of adjuvant chemotherapy for stage II disease during the last period might also have contributed to improved survival.[31]

This is a retrospective study with the potential bias that it can introduce, problems like lack of a complete preoperative stage and documentation of complications. Furthermore, PET scan was not available in Iceland for staging, and mediastinoscopy was used routinely for mediastinal staging during the last 5 years of the study. The strength of this study is that our cohort consisted of patients from a whole population, all of whom were operated on in a single center. The results were therefore less likely to be affected by tertiary referral.

We have reported resection rate, rates of complications, and survival rates for all patients who underwent surgery with curative intent for NSCLC in the Icelandic population during a 15-year period. In our opinion, these data should be reported together in context to help evaluate the outcome of surgical care for patients with NSCLC. Furthermore, we have reported survival of patients with NSCLC who were not operated on, which is important for comparison.

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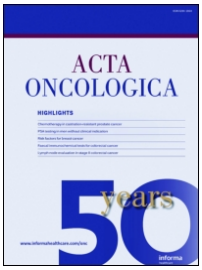
Paper II



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Lobectomy for non-small cell lung carcinoma: a nationwide study of short- and long-term survival

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ORIGINAL ARTICLE

Lobectomy for non-small cell lung carcinoma: a nationwide study of short- and long-term survival

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ABSTRACT

Introduction: Lobectomy is the standard curative treatment for non-small cell carcinoma (NSCLC) of the lung. Most studies on lobectomy have focused on short-term outcome and 30-day mortality. The aim of this study was to determine both short-term and long-term surgical outcome in all patients who underwent lobectomy for NSCLC in Iceland over a 24-year period.

Material and methods: The study involved 489 consecutive patients with NSCLC who underwent lobectomy with curative intent in Iceland, 1991–2014. Patient demographics, pTNM stage, rate of perioperative complications, and 30-day mortality were registered. Overall survival was analyzed with the Kaplan–Meier method. The Cox proportional hazards model was used to evaluate factors that were prognostic of overall mortality. To study trends in survival, the study period was divided into six 4-year periods. The median follow-up time was 42 months and no patients were lost to follow-up.

Results: The average age of the patients was 67 years and 53.8% were female. The pTNM disease stage was IA in 148 patients (30.0%), IB in 125 patients (25.4%), IIA in 96 patients (19.5%), and IIB in 50 patients (10.1%), but 74 (15.0%) were found to be stage IIIA, most often diagnosed perioperatively. The total rate of major complications was 4.7%. Thirty-day mortality was 0.6% (three patients). One- and 5-year overall survival was 85.0% and 49.2%, respectively, with 3-year survival improving from 48.3% to 72.8% between the periods 1991–1994 and 2011–2014 ($p = .0004$). Advanced TNM stage and age were independent negative prognostic factors for all-cause mortality, and later calendar year and free surgical margins were independent predictors of improved survival.

Conclusions: The short-term outcome of lobectomy for NSCLC in this population-based study was excellent, as reflected in the low 30-day mortality and low rate of major complications. The long-term survival was acceptable and the overall 3-year survival had improved significantly during the study period.

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Introduction

Lung cancer (LC) is the leading cause of cancer-related deaths in the western world, including Iceland [1,2], accounting for around 26% of cancer-related deaths globally [1]. In Europe and North America, non-small cell lung carcinoma (NSCLC) accounts for around 80% of LC [3], where surgical resection is the only well-defined and well-studied curative treatment [4]. Pulmonary resection is indicated for patients with localized or regional disease, which currently applies to almost one-third of all patients diagnosed with NSCLC in Iceland [2]. Five-year survival for resected patients is reported to range from 40% to 70%, depending mostly on the TNM stage at diagnosis [5,6], as compared to less than 5% for non-resected patients with metastasized disease [6]. Thus, resection should be offered to all patients where surgery is indicated; that is, for patients at stages I and II [4] and in selected patients who are diagnosed at stage IIIA [7].

Lobectomy is considered the gold standard of treatment for NSCLC [4], as numerous studies have shown that lobectomy has better outcome than sublobar resections with regard to both recurrence of cancer and long-term survival [8,9]. Until recently, segmentectomy and wedge resection have been used when pulmonary function or other comorbidities pose a high operative risk. However, the use of segmentectomy has recently been recommended for small peripheral stage I NSCLCs instead of lobectomy [10,11], as outcomes are comparable to those after lobectomy. On the other hand, pneumonectomy is still reserved for more extensive disease, as the surgical morbidity and mortality are higher than for lobectomy or sublobar resections [7].

Most studies on pulmonary resections for NSCLC – and especially lobectomy – have focused more on short-term outcome than on long-term survival [12,13]. These studies have usually been based on single tertiary-care centers, with the risk of selection bias. With lobectomy being the most common surgical procedure for NSCLC and regarded as the gold standard for curative treatment of NSCLC, this is a subgroup that is important to focus on and report their outcome.

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We performed a whole-nation study in Iceland, taking advantage of centralized population-based registries on the diagnosis and treatment of NSCLC, with complete long-term survival data. The main aim was to investigate both short-term and long-term outcome in NSCLC patients who underwent lobectomy in Iceland over a 24-year period, concentrating especially on 30-day and long-term survival.

Material and methods

This was a retrospective study of all patients who underwent lobectomy for primary NSCLC with curative intent in Iceland from January 1, 1991 until December 31, 2014. We excluded patients who underwent exploratory thoracotomy, exploratory video-assisted thoracoscopic surgery (VATS), pulmonary metastasectomy, palliative procedure, or resection for biopsy only. This also applied to patients with advanced disease who underwent resection without curative intent. Patients were also excluded when the postoperative pathological diagnosis showed only carcinoma *in situ* or one of the following: adenoid cystic carcinoma, mucoepidermoid carcinoma, carcinoid, or sarcoma. Finally, 17 patients who were at stage IV, including those with solitary metastasis to the brain or one adrenal gland at diagnosis, were excluded.

Cases were identified from a centralized database covering all the surgical specimens of LC (in Iceland) at the Department of Pathology, Landspitali University Hospital in Reykjavik. Cases identified were cross-matched with two other independent databases: a diagnosis registry and an operation registry at Landspitali University Hospital. This was done to minimize the risk of missing cases that were operated for NSCLC.

During the study period, 2556 patients were diagnosed with NSCLC in Iceland. Of them, 653 cases were surgical candidates, evaluated to tolerate a pulmonary resection. In 493 cases (75.5%), a lobectomy was performed. This included 11 patients (2.2%) who underwent lobectomy and an ipsilateral sublobar resection during the same operation and four patients (0.8%) who had a bilobectomy. The other surgical resections for NSCLC were 83 sublobar resections (wedge or segment resections; 12.7%) and 77 pneumonectomies (11.8%).

Medical records and surgical reports were reviewed and variables were registered using a standard data sheet. For each patient, over 80 different variables were collected. These included the following: age, gender, smoking habits, comorbidity (e.g., chronic obstructive pulmonary disease (COPD), ischemic heart disease (IHD), and arrhythmias), pulmonary function test results (forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and FEV1/FVC), details of the operation, length of stay in the intensive care unit (ICU), in-hospital stay in days, pTNM stage, postoperative complications, and American Society of Anesthesiology (ASA) score, and also date and cause of death in patients who died during the follow-up period.

Preoperatively, a multidisciplinary tumor board including thoracic surgeons, pulmonologists, oncologists, radiologists, and pathologists reviewed the cases. The preoperative work-up varied between patients but usually included a chest radiograph (CXR) and computed tomography (CT) of the chest, abdomen, and head in addition to bone scintigraphy and pulmonary function tests. Positron emission tomography (PET) scan was not available in Iceland during the study period, but it was done in selected cases at Rigshospitalet, Copenhagen, Denmark. Tumor biopsies were obtained through bronchoscopy or transthoracic CT-guided needle biopsy. Mediastinoscopy was done routinely since 2005 and endoscopic bronchial ultrasound (EBUS) with transbronchial needle aspiration biopsies was performed in a proportion of cases since 2013. The seventh edition of the TNM staging system was used to stage patients postoperatively (pTNM). Detailed clinical TNM (cTNM) staging was not adequately registered for all patients, so only pathological staging (pTNM) is presented in this study.

Landspitali University Hospital is the only hospital in Iceland in which cardiothoracic surgery is performed, and this study was therefore done on a nationwide basis. All the surgical procedures were performed by nine surgeons, one of whom performed the vast majority of them in the last decade. All the patients had epidural placed for postoperative analgesia and general anesthesia with double lumen endotracheal tube for lung isolation. Posterolateral thoracotomy was the method used during more than half of the study period, but during the last 10 years, an anterolateral approach was the preferred method. During the study period, video-assisted thoracoscopic surgery (VATS) was not used for lobectomies but it was used for selected wedge resections and segmentectomies. The lobectomies were standardized with intraoperative lymphadenectomy of enlarged hilar or ipsilateral mediastinal lymph nodes, and from 2005 with routine ipsilateral mediastinal lymphadenectomy according to the ESTS guidelines [14,15].

Ex-smokers were defined as patients who had stopped smoking more than 5 years before surgery, and never-smokers were defined as patients who had smoked less than 100 cigarettes in their lifetime. Surgical complications were divided into major and minor complications. Major complications were defined as: bronchopleural fistula (BPF), myocardial infarction (MI), adult respiratory distress syndrome (ARDS), reoperation for postoperative bleeding, congestive heart failure (CHF), and empyema with or without reoperation. Minor complications were defined as: new-onset atrial fibrillation, postoperative pneumonia, recurrent nerve paralysis, wound infection, air leakage over 7 days, and intraoperative bleeding of >1 L (without reoperation). Operative mortality was defined as death within 30 days of surgery, but hospital mortality and 90-day mortality were also registered. Patients were assigned a date of death or identified as living on September 1, 2016, using data from the Icelandic National Population Registry. Median follow-up time was 42 months (mean 62.6 months, range: 1–279).

To investigate trends in survival, the 24-year study period was divided up into six 4-year periods.

Statistics

Microsoft Excel 2010 was used for descriptive statistics and R version 3.1.3 (Wien, Austria) was used for survival analysis.

Student's *t*-test and ANOVA were used to compare continuous variables between groups of two or more, following use of the Kolmogorov–Smirnov test (KS test) for assessment of normality of the data. Chi-square test was used to compare categorical variables and Fisher's exact test was used if the values had an expected frequency of 10 or less. Differences were considered to be significant when the p value was less than 0.05. The Kaplan–Meier method was used to calculate overall survival (OS) and log-rank test was used to compare survival between groups. In order to identify factors that were prognostic of long-term survival, the Cox proportional-hazards model was used. Factors that had a p value of less than 0.1 in univariate analysis were used in the preliminary model along with factors that have been shown to be significant in other studies. A subset of variables was chosen for inclusion in the final model, using a stepwise selection procedure. To check our assumption of proportionality, a global goodness-of-fit test was done together with graphic plotting of variables.

The study was approved by the Icelandic National Bioethics Committee (reference number: 98-060-CM) and the Data Protection Authority (reference number: 2001011025SJ/eb). As individual patients were not identified, the need for individual consent was waived.

Results

Patient demographics and cardiovascular risk factors are shown in Table 1. Of the 493 lobectomies for NSCLC, 265 (53.8%) were performed on female patients. The mean age was 67 ± 9.5 years, and similar for both genders ($p = .81$). More women had smoked within 5 years of surgery ($p = .0007$), but more men had a history of ischemic heart disease ($p < .0001$). More women had adenocarcinoma histology: 74.3% as compared to 59.6% in men ($p = .0004$). On the other hand, no statistically significant gender differences were found for history of COPD, arrhythmias, preoperative FEV1 < 75%, or ASA score. Altogether, 184 patients (37.3%) were diagnosed incidentally, most often due to diseases or symptoms unrelated to NSCLC that had resulted in a chest X-ray or CT-scan. In the other 309 cases, the patients had symptoms of LC, and cough (36.3%), dyspnea (23.1%), chest pain (17.2%), pneumonia (17.4%), and/or weight loss (15.8%) were the most common symptoms. Other symptoms such as fever (11.4%) and hemoptysis (7.3%) were less common.

The mean operative time was 136 min (range: 30–395 min) and median hospital stay was 9 days (range: 2–144 days). The most common histological types were adenocarcinoma (65.3%) and squamous cell carcinoma (25.8%), but large-cell and adenosquamous carcinomas were less common (5.9% and 3.0%, respectively). In 460 of the cases (93.3%), the patients had cancer-free surgical margins; the remaining 33 patients had microscopic disease at the resection margins (positive margins). The mean size of the tumors was 3.6 ± 2.3 cm, ranging from 0.2 to 19.5 cm.

Postoperative TNM staging is shown in Table 2. More than half of the patients had stage I disease (55.6%), most of them being stage IA (30.0% of the whole study population). Patients at stage II were 29.6%, with 19.5% being at stage IIA and 10.1% at stage IIB. A further 74 patients (15.0%) had surgically resectable locally advanced disease (stage IIIA), most of it being diagnosed perioperatively – with microscopic N2 ipsilateral mediastinal lymph node involvement or T4 tumor with local invasion to the mediastinum. Table 2 shows that the proportion of patients diagnosed at stage IA increased from 25.9% in 1991–1994 to 39.4% in 2011–2014 ($p = .03$). No significant changes between time periods were found for other stages (IB, IIA, IIB, and IIIA). Furthermore, the mean age of patients did increase during the study period, from 63.2 years in 1991–1994 to 67.6 years in 2011–2014 ($p = .009$), and the 30-day mortality did not change significantly between the 4-year time periods ($p = .23$).

Both minor and major complications are listed in Table 1, but some patients had several major and/or minor complications. In 104 cases (21.1%), the patient suffered one or more complications, with 23 patients (4.7%) having at least one major complication and 81 patients (16.4%) having at least one minor complication. The most common complication

Table 1. Patient demographics, risk factors, comorbidities, complications, tumor factors, and staging for 493 cases that underwent a lobectomy for NSCLC in Iceland, 1991–2014. The table also shows univariate association of the patient demographics and comorbidities with long-term survival.

	n (%)	HR	95% CI	*p* value*
Descriptive factors				
Women (ref men)	265 (53.8)	0.72	0.57–0.89	**.003**
Age (years)	67 (range: 35–89)	1.03	1.02–1.05	**<.0001**
Risk factors, comorbidity				
Smoking history	468 (94.9)	1.38	0.77–2.45	.28
Current smoker (within 5 years)	327 (66.3)	1.08	0.85–1.37	.53
COPD	128 (26.0)	0.89	0.69–1.15	.36
IHD	121 (24.5)	1.47	1.15–1.88	**.002**
Arrhythmias	66 (13.4)	1.36	1.0–1.85	**.05**
FEV1 < 75%	138 (28.0)	1.17	0.91–1.48	.22
Period				
1991–1994	58 (11.8)	ref	ref	ref
1995–1998	59 (12.0)	0.74	0.50–1.08	.11
1999–2002	67 (13.6)	0.90	0.62–1.32	.58
2003–2006	88 (17.8)	0.70	0.48–1.00	**.05**
2007–2010	94 (19.1)	0.69	0.47–1.01	**.05**
2011–2014	127 (25.8)	0.45	0.29–0.69	**.0002**
Major complications	23 (4.7)	1.69	1.07–2.66	**.02**
BPF	2 (0.4)	6.75	1.67–27.36	**.01**
MI	4 (0.8)	1.53	0.50–4.94	.43
ARDS	9 (1.8)	1.38	0.68–2.78	.37
CHF	10 (2.0)	2.18	1.16–4.10	**.01**
Empyema	6 (1.2)	2.40	0.99–5.81	**.05**
Reoperation for bleeding	10 (2.0)	1.34	0.66–2.71	.41
Minor complications	81 (16.4)	1.25	0.93–1.67	.14
AF	37 (7.5)	1.26	0.84–1.91	.26
Pneumonia	40 (8.1)	1.58	1.08–2.31	**.02**
RNP	8 (1.6)	1.72	0.85–3.28	.13
Wound infection	7 (1.4)	0.63	0.20–1.95	.42
Air leakage for >7 days	85 (17.2)	1.14	0.86–1.50	.37
Intraoperative bleeding >1 L	35 (7.1)	1.27	0.85–1.90	.24
Tumor factors				
Diameter of tumor (mean, cm)	3.6 (0.2–19.5)	1.12	1.08–1.17	**<.0001**
Squamous cell carcinoma	127 (25.8)	1.28	1.01–1.63	**.04**
Adenocarcinoma	322 (65.3)	0.68	0.54–0.85	**.0006**
Free surgical margins	460 (93.3)	0.33	0.23–0.50	**<.0001**
Stage				
IA	148 (30.0)	ref	ref	ref
IB	125 (25.6)	1.44	1.04–2.00	**.03**
IIA	96 (19.5)	2.64	1.90–3.67	**<0.0001**
IIB	50 (10.1)	2.53	1.70–3.78	**<0.0001**
IIIA	74 (15.0)	3.62	2.56–5.14	<0.0001

COPD: chronic obstructive pulmonary disease; IHD: ischemic heart disease; FEV1: forced expiratory volume in 1 s; BPF: bronchopleural fistula; MI: myocardial infarction; ARDS: adult respiratory distress syndrome; CHF: congestive heart failure; AF: atrial fibrillation; RNP: recurrent nerve paralysis.
*The p values in bold show significance.

Table 2. Stage distribution of 493 cases operated with lobectomy for NSCLC in Iceland over 24 years, divided into 4-year periods, expressed as *n* (% per period).

	Stage					
	IA	IB	IIA	IIB	IIIA	Total
Period						
1991–1994	15 (25.9)	11 (18.9)	17(29.3)	3 (5.2)	12(20.7)	58 (100)
1995–1998	19 (32.2)	15 (25.4)	10 (17.0)	8 (13.6)	7 (11.9)	59 (100)
1999–2002	13 (19.4)	17 (25.4)	15 (22.4)	11 (16.4)	11 (16.4)	67 (100)
2003–2006	19 (21.5)	33 (37.5)	15 (17.0)	9 (10.2)	12 (13.6)	88 (100)
2007–2010	32 (34.0)	19 (20.2)	15 (16.0)	9 (9.6)	19 (20.2)	94 (100)
2011–2014	50 (39.3)	30 (23.6)	24 (18.9)	10 (7.9)	13 (10.2)	127 (100)
Total	148 (30.0)	125 (25.4)	96 (19.5)	50 (10.1)	74 (15.0)	493 (100)

was persistent chest tube air leakage for more than 7 days (17.2%), followed by pneumonia (8.1%) and intraoperative bleeding exceeding 1 L (7.1%).

The 30-day mortality was 0.6% (three patients), hospital mortality was 1.2% (six patients), and 90-day mortality was 1.4% (seven patients). Two of the three patients who did not survive for 30 days died on postoperative day 11 – one from pneumonia, sepsis, and hypotension and the other from cardiogenic shock related to myocardial infarction. The third patient had respiratory failure due to pneumonia that required a tracheostomy and ventilator therapy, but eventually died on postoperative day 23. Patients who died in hospital after postoperative day 30 usually died of respiratory failure, but they all had compromised pulmonary function preoperatively.

OS for all patients is plotted in Figure 1, with the Kaplan–Meier graph showing 85.0%, 60.9%, and 49.2% of the patients being alive at 1, 3, and 5 years postoperatively. Figure 2 shows the OS in different 4-year time periods. CSS is shown in Figure 3 and was estimated to be 85.9%, 63.8%, and 54.6% at 1, 3, and 5 years, respectively. Both OS and CSS improved significantly during the study period, with 3-year OS increasing from 48.3% in 1991–1994 to 72.8% in 2011–2014 (log-rank test, $p = .0004$). The 3-year CSS was 48.3% in 1991–1994 and 76.6% in 2011–2014 (log-rank test, $p < .001$). The 5-year OS was 64.2% for stage I, 35.1% for stage II, and 20.4% for stage IIIA.

Table 1 shows a univariate analysis of the predictors for OS. The predictors of increased mortality were advanced age (HR = 1.03 per year, 95% CI: 1.02–1.05; $p = .001$), ischemic heart disease (HR = 1.47, 95% CI: 1.15–1.88; $p = .002$), any major complications (HR = 1.69, 95% CI: 1.07–2.66; $p = .02$), postoperative congestive heart failure (HR = 2.18, 95% CI: 1.16–4.1; $p = .01$), postoperative pneumonia (HR = 1.58, 95% CI: 1.08–2.31; $p = .02$), squamous cell histology (HR = 1.28, 95% CI: 1.01–1.63; $p = .04$), and advanced stage (HR = 3.62 for stage IIIA compared to stage IA, 95% CI: 2.56–5.14; $p < .0001$), which was by far the strongest prognostic factor. Protective factors regarding mortality were female gender (HR = 0.72, 95% CI: 0.57–0.89; $p = .003$), free surgical margins (HR = 0.33, 95% CI: 0.23–0.5; $p < .0001$), and later calendar year of treatment (HR for the period 2011–2014 was 0.45, 95% CI: 0.49–0.69; $p < .0001$).

Independent negative factors regarding survival were advanced age (HR = 1.03, 95% CI: 1.02–1.04; $p < .0001$) and advanced stage (HR = 1.4, 95% CI: 1.25–1.46; $p < .0001$). After

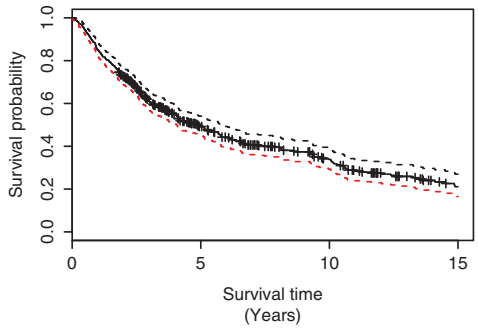
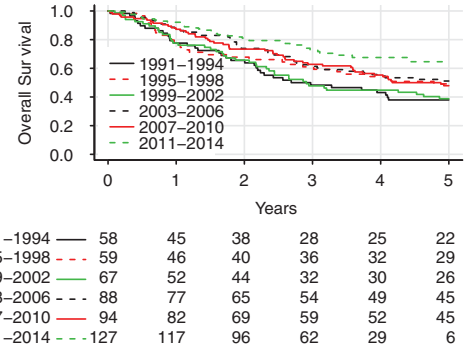
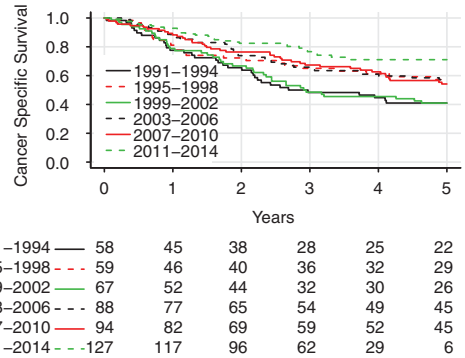


Figure 1. Overall survival of all patients who underwent lobectomy for NSCLC with curative intent in Iceland, 1991–2014. The broken line represents the 95% confidence interval and crosses indicate censored cases.



1991–1994	58	45	38	28	25	22
1995–1998	59	46	40	36	32	29
1999–2002	67	52	44	32	30	26
2003–2006	88	77	65	54	49	45
2007–2010	94	82	69	59	52	45
2011–2014	127	117	96	62	29	6

Figure 2. Overall survival of patients who had a lobectomy with curative intent for NSCLC in Iceland in different 4-year time periods. The difference was significant (log-rank test, $p = .003$).



1991–1994	58	45	38	28	25	22
1995–1998	59	46	40	36	32	29
1999–2002	67	52	44	32	30	26
2003–2006	88	77	65	54	49	45
2007–2010	94	82	69	59	52	45
2011–2014	127	117	96	62	29	6

Figure 3. Comparison of cancer-specific survival in patients operated with lobectomy for NSCLC in Iceland in different 4-year time periods. The difference was significant (log-rank test, $p < .001$).

correction for stage and other significant factors in the multivariate model (see Table 3), later calendar year turned out to be a significant protective factor regarding mortality, with an HR of 0.88 per year (95% CI: 0.82–0.94; $p = .0003$). Furthermore, a cancer-free surgical margin was also found to be an independent factor prognostic of lower mortality

Table 3. Cox multivariate analysis for all patients who underwent lobectomy for NSCLC in Iceland, 1991–2014.

	HR	95% CI	*p* value*
Age	1.03	1.02–1.05	**<.001**
Period (ref: 1991–1994)			
1995–1998	0.86	0.58–1.28	.46
1999–2002	0.90	0.62–1.32	.60
2003–2006	0.71	0.49–1.04	.08
2007–2010	0.60	0.41–0.89	**.01**
2011–2014	0.50	0.33–0.78	**.002**
1991–2014	0.88	0.83–0.94	**<.001**
Stage (ref stage: IA)			
IB	1.30	0.93–1.81	.13
IIA	2.51	1.80–3.51	**<.001**
IIB	2.43	1.62–3.65	**<.001**
IIIA	3.49	2.44–4.99	**<.001**
Histology (ref: Squamous cell carcinoma)			
Adenocarcinoma	0.91	0.70–1.17	.45
Large cell carcinoma	1.45	0.91–2.31	.12
Adenosquamous	1.63	0.86–3.07	.13
IHD	1.28	0.99–1.66	.06
COPD	0.89	0.69–1.17	.41
Postoperative CHF	1.24	0.51–3.02	.63
Major complications	1.21	0.64–2.30	.55
Free tumor margins	0.48	0.32–0.73	<.001

IHD: ischemic heart disease; COPD: chronic obstructive pulmonary disease; CHF: congestive heart failure.
*The *p* values in bold show significance.

(HR = 0.44, 95% CI: 0.30–0.65; $p < .0001$). The patients who did not have free surgical margins usually received adjuvant chemotherapy, and were not reoperated or did not receive adjuvant radiation.

Discussion

In this whole-nation study, we investigated both short-term and long-term outcome after lobectomy for NSCLC over a 24-year period in a well-defined cohort of Icelandic patients. The 30-day mortality was very low – only 0.6% – with almost every second patient (49.2%) surviving for at least 5 years. Furthermore, the 3-year OS improved significantly with time: from 48.3% in 1991–1994 to 72.8% in 2011–2014 ($p = .0004$).

The explanation for the significant increase in OS seen during the last 4-year period is probably multifactorial. However, one of the main influential factors may have been the increased ratio of patients with stage IA disease, which rose from 25.9% to 39.4% between the periods 1991–1994 and 2011–2014 ($p = .03$). The reason for this increase in early-stage NSCLC is unclear, but in Iceland, no screening for lung cancer has been implemented and our analysis did not show that the proportion of tumors that were diagnosed incidentally had increased significantly during the study period ($p = .47$). The increase in early-stage NSCLC is more likely explained by improved imaging techniques and more thorough postoperative follow-up, as well as increased public awareness. When we corrected for stage and higher age in the multivariate analysis, later calendar year was found to be an independent factor of increased survival. The improved outcome therefore appears to be influenced by factors other than stage and incidental diagnosis. Thirty-day mortality, a surrogate marker for surgical technique, perioperative care, and postoperative complications, remained very low during the 24-year study period ($p = .23$) and does not therefore explain improved survival. The minor and major complication rate stayed constant during the study period ($p = .70$ and $p = .46$, respectively). The fact that nine surgeons performed the surgical procedures and one of them performed the vast majority in the last decade could have had an effect on short-term outcomes, such as complications and length of stay. Other possible factors, such as improved diagnostic work-up with increased use of CT scans may have contributed as well as more thorough preoperative staging with mediastinoscopies performed routinely since 2005. This, along with increased use of adjuvant chemotherapy, may also have contributed. Our findings are in line with a recent Norwegian study where similar findings regarding survival to those in the present study were reported for NSCLC patients [16]. Unfortunately, we did not have detailed information on the use of adjuvant chemotherapy in our patients, but it has been offered to most stage II and IIIA patients since 2003. Thus, the direct effect of adjuvant chemotherapy could not be analyzed.

The factors that were prognostic of mortality in the present study were advanced pTNM stage (HR = 3.62 for stage IIIA vs. stage IA, 95% CI: 2.56–5.14; $p < .0001$), positive surgical margins, advanced age, and calendar year of treatment (time period). TNM stage, advanced age, and positive surgical margins have all been reported previously to be negative prognostic factors in other studies [5,6,17]. To our knowledge, however, only very few studies have reported improved survival according to calendar year. The most important is the study by Morgant et al. [18], which found better survival in lobectomy patients from 2005 to 2012 in France, and a Norwegian study by Nilssen et al. [16], which found a gain in 5-year survival from 47% in the period 1997–2003 to 62.6% in 2004–2011, in all resected NSCLC patients. Furthermore, in recent unpublished studies (presented as abstracts) based on the SEER (Surveillance, Epidemiology, and End Results) database, improved survival was reported for patients with stage-II adenocarcinoma and squamous cell carcinoma from 1988 until 2013 [19,20].

Other factors reported to be prognostic of increased mortality in the literature are a history of weight loss and positive tumor markers (i.e., KRAS, EGFR, etc.) [17]. In our retrospective study, weight loss was not a prognostic factor regarding survival and tumor markers were not routinely measured until the later part of the study.

The fact that OS for the whole patient cohort was found to be around 50% at 5 years underscores the fact that many of the patients who undergo lobectomy – even patients with localized stage I disease – later die from spread of NSCLC, a recurrent disease, or other smoking-related diseases such as ischemic heart disease or COPD. In comparable studies, the OS at 5 years usually lies between 40% and 70% [9,21]. The OS found in the present study is therefore in line with other reports. In the study by Morgant et al. [18], which included all pulmonary resections for NSCLC in France operated between 2005 and 2012, the 3-year survival for lobectomy patients was 82%, as compared to 71% in the present study. However, the French study also included non-malignant carcinoid tumors (with typical histology) and other benign tumors in 10% of cases, where the prognosis is very favorable [22] compared to other histological types of NSCLC –

which all the patients in the present study were diagnosed with.

In the present study, 15% of the patients had stage IIIA disease that was usually detected postoperatively after the finding of positive ipsilateral microscopic mediastinal lymph node sampled at surgery, or a T4 tumor that had invaded the mediastinum. In a more recent study – by Dickhoff et al. [13] – the 4-year survival following lobectomy ranged from 27% to 51% in the period 2010–2013. This wide difference in survival was based on different induction therapies, and is in line with our 4-year survival of 27.2% over the whole period, which had improved to 41% in the period 2011–2014. During the last period, adjuvant chemotherapy was offered to all patients at stage IIIA, as recommended by the European Society for Medical Oncology (ESMO) guidelines [7]. The 3-year survival for stages II and IIIA together was 49% in the present study, as compared to 56.6% in a newly published study by Park et al. [23], where all the patients received induction therapy. In our study, very few of the patients had induction therapy.

Compared to other reports, the overall rate of complications was relatively low in the present study (21.1%), with the complications usually being classified as minor (16.4%). Furthermore, the overall rate of major complications was only 4.7%, which also contributed to the very low 30-day mortality (only 0.6%; three patients). For comparison, other studies have reported an overall rate of complications in the 19.1–58.2% range, [24–26] and the 30-day mortality has most often been between 1% and 2.5%. However, 30-day mortality up to 4.1% has also been reported in the literature [24,26,27]. In the study by Irie et al., a lower 30-day mortality than ours was reported (0.5%), and there was an overall complication rate of 19.1% [24]. However, that study only involved 188 patients who were operated at a single center over a 7-year period, with all of them being at cTNM stage I and being operated with VATS technique. The present study, however, covered 24 years with patients at stages I–IIIA, with all of them operated with open thoracotomy.

The most common complication in the present study was prolonged air leakage (17% of cases) – with a range of 9.6–24% in other comparable studies [24,28]. This difference could possibly be explained by different definitions of prolonged air leakage or different management of chest tubes between centers. Other postoperative complications in the present study were also in line with previous reports, such as pneumonia, new-onset atrial fibrillation, and perioperative myocardial infarction [24,29].

The major limitation of our study is its retrospective design, with the drawbacks that this can entail, such as the lack of information on symptoms, the lack of information on clinical staging, and the lack of documentation on complications. During the study period, PET scan was not available in Iceland and mediastinoscopy was only routinely used for staging of mediastinal lymph nodes during the later half of the study period. The main strength of the study, however, is the fact that the patient cohort consisted of patients representing a whole population, with all the patients being operated at a single center, reducing the risk of selection bias and institutional bias. Our single-center nationwide approach therefore eliminated referral bias and made identification of risk profiles more reliable.

Conclusions

According to this population-based study, the short-term outcome of lobectomy for NSCLC is excellent in Iceland, as reflected by a low rate of complications and a 30-day mortality of only 0.6%. Long-term overall survival, with every second patient surviving 5 or more years after surgery, was acceptable and comparable to that in other studies. Importantly, the survival improved over the 24-year study period. The explanation for this gain in survival is not obvious, but it is most likely explained by the combination of improvements in staging, postoperative care, surgical technique, and adjuvant chemotherapy for stage II/IIIA patients.

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Disclosure statement

The authors declare that they have no competing interests.

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Paper III

APMIS ACTA PATHOLOGICA, MICROBIOLOGICA ET IMMUNOLOGICA SCANDINAVICA

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Primary adenocarcinoma of the lung – histological subtypes and outcome after surgery, using the IASLC/ATS/ERS classification of lung adenocarcinoma

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Adenocarcinoma is the most common histological type of lung carcinoma. Recently the histologic classification of adenocarcinomas in the lung was modified to better reflect biologic properties and prognosis. We reviewed the histology of all primary lung adenocarcinomas operated on in Iceland during a 20-year period and assessed the impact of histology on survival. This nationwide study included 285 patients (mean age 67 years, 57% female), who underwent resection in Iceland from 1991 to 2010. Tumors were reclassified according to the current IASLC/ATS/ERS classification system. Overall survival was estimated by the Kaplan–Meier method and Cox regression analysis used to evaluate prognostic factors of overall mortality. Acinar predominant adenocarcinoma was the most common histological subtype (46%) followed by solid-predominant (SPA) with mucin production comprised (23%). Non-invasive carcinomas were rare. A difference in survival between the histological adenocarcinoma subtypes was not seen ($p = 0.32$) and multivariate analysis showed that advanced stage and age predicted worse outcome, but histologic subtyping of adenocarcinoma did not. In this nation-wide study there was not a statistical difference in survival according to adenocarcinoma subtypes and the histological subtype did not predict mortality. Preinvasive and minimally invasive adenocarcinomas were rare.

Key words: Lung adenocarcinoma; histology; classification; adenocarcinoma subtypes.

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Lung cancer is the leading cause of cancer-related deaths in the western world (1). Non-small cell lung carcinoma (NSCLC) accounts for 85% of all lung cancer where adenocarcinoma (AC) is the most common histology (2, 3). The strongest prognostic factors of survival for patients with NSCLC are the TNM stage (4), advanced age, history of weight loss (5), ethnicity (6), and some genetic mutations (i.e., EGFR, K-RAS, p53) (7–10).The three major NSCLC histological types; squamous cell carcinoma (SCC), AC, and large cell carcinoma (LCC) have also been shown to influence survival in some studies (11, 12), but not in all (13, 14). Bronchioloalveolar adenocarcinoma (BAC) that was described as a subtype of AC, has been thought to have a better prognosis than non-BAC adenocarcinomas (15).

A new IASLC/ATS/ERS classification for primary lung adenocarcinoma was published recently (16). The aim was to provide uniform terminology and diagnostic criteria for AC and at the same time address advances in oncology, surgery, radiology, molecular biology, and pathology that could identify prognostic and predictive factors and therapeutic agents. The discontinuation of the term BAC is one of the major changes in the new classification. Previously BAC tumors were regarded as a heterogenous group of tumors with a relatively similar histology; some having favorable survival rates, whereas others had worse outcomes (17). In the

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new classification patients with BAC are divided into four main categories. Three of them were also present in the earlier classification but there are two new subtypes, lepidic and micropapillary.

In this study we have reviewed all cases of AC operated on in Iceland during 20 years using the new AC classification with special focus on the influence of histological subtype on survival. The cohort represents a relatively homogenous and well-defined Northern European population.

MATERIALS AND METHODS

Patient demographics

This nationwide study included all patients who underwent surgical resection with curative intent for primary lung adenocarcinoma in Iceland between January 1, 1991 and December 31, 2010. Patients with adenosquamous carcinoma were excluded and grouped with squamous cell carcinomas. Also excluded were patients who had exploratory, palliative, or lesser resections for biopsy purposes. A total of 294 cases met the criteria, but data were missing in nine cases (lost histological slides) and these cases were therefore excluded.

Cases were identified from a centralized database that contains details of all lung cancer specimens from the Department of Pathology at Landspitali University Hospital in Reykjavik. To minimize the likelihood of missing cases, we also reviewed the diagnosis and operation registry at Landspitali University Hospital, the only center performing cardiothoracic surgery in Iceland.

Baseline demographic information and clinical data were collected from surgical charts and hospital records and entered on a standardized data sheet in Microsoft Excel. In excess of 80 different variables were entered, including age; comorbidities; symptoms at diagnosis; postoperative complications; tumor, node, metastasis (TNM) stage; and survival. Patients were staged postoperatively (pTNM) using the 7th edition of the TNM staging system (18). Information on clinical TNM stage (cTNM) had not been uniformly entered and is therefore not presented in this study.

All patients were followed up with respect to survival by using data from the Icelandic National Population Registry (19). Patients were assigned a date of death or were identified as living on January 31, 2015. Mean follow-up time was 45 months (range: 1–254). Five-year survival was calculated for the subtypes with more than 20 patients, lepidic, acinar, solid with mucin, invasive mucinous, and papillary.

Histology

Original pathology reports were reviewed and the location, size of tumor, and number of tumors recorded. Hematoxylin and eosin stained slides from all cases were reviewed and subtyped by one of the authors (J.B.), who was blinded to the patients' clinical outcome. The 2011 IASLC/ATS/ERS adenocarcinoma classification system (16, 20) was used for subtyping. Stains for mucin (PAS with and without diastase, alcian blue) were obtained if indicated. No immunohistological staining was performed for this study. The predominant pattern was defined as the morphologic pattern occupying the greatest area of tumor.

According to the new classification there are four categories of AC; preinvasive AC, minimally invasive AC, invasive AC, and variants of invasive AC (Fig. 1). The preinvasive category is further subclassified into atypical adenomatous hyperplasia (AAH) or AC *in situ* (AIS). The invasive category has five subclassifications – lepidic-predominant AC (LPA), acinar-predominant AC (APA), papillary-predominant AC (PPA), micropapillary-predominant AC (MPA), and solid-predominant with mucin production (SPA).

The lepidic pattern is included in three subtypes of AC; AIS, MIA, and LPA. This pattern consists of a blend of type II pneumocytes or Clara cells growing along the surface of alveolar walls. If the only histological pattern in the sample was lepidic and no invasion was seen, it was classified as AIS. If there was less than 5 mm of invasion, the sample was classified as minimally invasive AC (MIA). If there were signs of necrosis or $\geq$5 mm of invasion into visceral pleura or lymphovascular space it was defined as LPA.

The acinar-predominant AC (APA) was diagnosed in tumors where there were round- to oval-shaped glands with a central luminal space surrounded by tumor cells. When the alveolar architecture was lost or myofibroblastic stroma was present, it was diagnosed as APA (16).

Papillary-predominant AC (PPA) was diagnosed where there was papillary growth of cuboidal to columnar cells growing along a fibrovascular core. When the tumor cells grew in papillary tufts without fibrovascular cores, we diagnosed micropapillary-predominant AC (MPA) in line with the new classification (16).

Solid-predominant AC with mucin production was diagnosed when the tumor cells grew in a sheet without a recognizable pattern of lepidic, acinar, papillary, or micropapillary AC growth.

The diagnosis of invasive-mucinous AC (IMA) was set if there was lepidic growth of columnar or goblet cells with abundant intracellular mucin admixed with other invasive AC pattern. The amount of the invasion (>5 mm), the size (>3 mm), and the lack of a circumscribed border separated them from AIS or MIA.

Colloid AC was diagnosed when gross cystic features were seen. There was a predominant pattern of abundant pools of extracellular matrix with mucin-secreting tumor cells.

Fetal AC has cells that resemble fetal lung tubules (16). The glandular elements have tubules that are composed of non-ciliated, glycogen-rich cells. These features were used to identify fetal adenocarcinomas in our study.

Statistics

Microsoft Excel was used for descriptive statistics and RStudio, Boston, MA, USA version 0.98.1103 for survival analysis. Chi square test and student's t test were used to compare groups and differences were considered to be significant when the p-value was less than 0.05. Survival was calculated using the Kaplan–Meier method and log-rank test was used to compare survival between groups. Univariate and multivariate analysis were done using Cox regression analysis to assess the histologic subtype as a prognostic factor for survival. The following variables

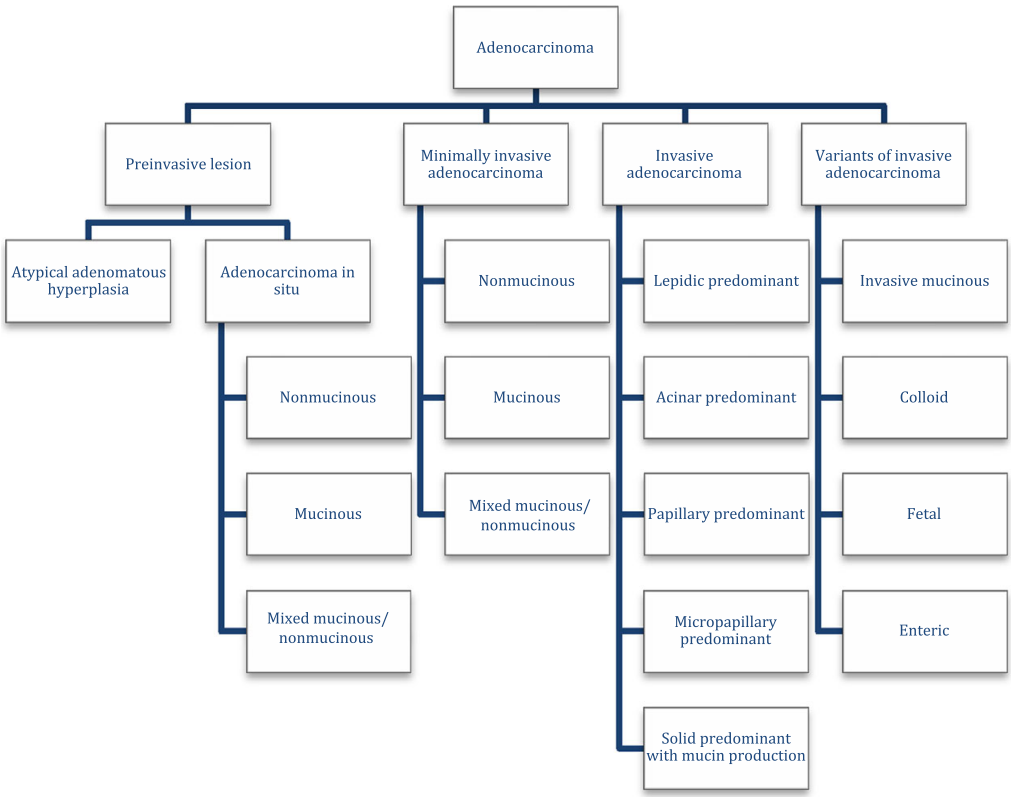

Fig. 1. IASLC/ATS/ERS classification of lung adenocarcinoma in resection specimens.

were used in the univariate analysis: Histological subtype, size, type of surgery, sex, age, incidental finding or not, types of symptoms at diagnosis (cough, productive cough, dyspnea, pneumonia, hemoptysis, chest pain, fever, anorexia), major complication, minor complications, and group TNM stage (I–IV). The variables that were found to be significant or near significant ($p < 0.1$) in the univariate analysis were included in the multivariate analysis to identify prognostic factors of survival. The tumor size and age were included as continuous variables. The hazard ratio of size was interpreted per cm increase and age interpreted per year.

The Icelandic National Scientific Ethics Committee and the Data Protection Authority approved the study. As individuals were not identified, individual consent was waived.

RESULTS

Patient demographics are described in Table 1. Of the 285 patients with adenocarcinoma, 162 (57%) were female and 123 (43%) male. The average age was 67 ± 9 years (range; 37–89). Women were 4 years younger than men at the time of surgery ($p = 0.02$), less often had ischemic heart disease ($p = 0.001$), and more of them still smoked at the time of surgery ($p = 0.006$) (Table 1). Most of the patients were current smokers (67%) and only 5% had never smoked. The mean size of the tumors was 2.8 ± 2.1 cm (range; 0.2–19).

Lobectomy or bilobectomy was performed in 224 patients (79%), 37 (12%) had a wedge resection or segmentectomy, and pneumonectomy was performed in 24 cases (9%) (Table 1).

Histology

Histological subtyping is shown in Table 2, based on thorough review of all the histological slides. Almost half, or 46% of the cases, were acinar-predominant AC (APA), which was the most common subtype. Second came solid-predominant with mucin (SPA) production in 23% of cases, followed

Table 1. Patient demographics on the 285 patients with primary lung adenocarcinoma resected in Iceland 1991–2010. N (%)

Patient demographics	Total	Male (N = 123)	Female (N = 162)
Age (years)			
Range	37–89	42–85	37–89
Mean	67	69	65
Smoking history	271 (95.1)	123 (43.1)	148 (51.9)
Never smoker	14 (4.9)	3 (1.1)	11 (3.9)
Current smoker	191 (67.0)	80 (28.1)	111 (38.9)
Comorbidities			
COPD	74 (26.0)	34 (11.9)	40 (14.0)
IHD	71 (24.9)	43 (15.1)	39 (13.7)
Arrythmias	40 (14.0)	23 (8.1)	17 (6.0)
Type of operation			
Pneumonectomy	24 (8.4)	10 (3.5)	14 (4.9)
Lobectomy/bilobectomy	224 (78.5)	95 (33.3)	129 (45.2)
Wedge/segmentectomy	37 (13.0)	18 (6.3)	19 (6.7)

COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease.

Table 2. Pathologic TNM stage according to the 7th revision of the TNM classification and the histologic subtype/variant for patients with primary lung adenocarcinoma resected in Iceland 1991-2010. N(%)

Predominant Subtype	Stage					Total
	IA	IB	IIA	IIB	IIIA	
AIS	1 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.4)
MIA	1 (0.4)	0 (0)	0 (0)	0 (0)	1 (0.4)	2 (0.7)
Lepidic	23 (8.1)	16 (5.6)	8 (2.8)	3 (1.1)	5 (1.8)	55 (20)
Acinar	39 (13.7)	28 (9.8)	21 (7.4)	17 (6.0)	24 (8.4)	129 (46)
Micropapillary	0 (0)	0 (0)	0 (0)	1 (0.4)	2 (0.7)	3 (1)
Papillary	6 (2.1)	6 (2.1)	2 (0.7)	3 (1.1)	4 (1.4)	21 (7)
Solid	15 (5.2)	17 (6.0)	13 (4.6)	13 (4.6)	7 (2.5)	65 (23)
Mucinous	3 (1.1)	2 (0.7)	1 (0.4)	0 (0)	1 (0.4)	7 (3)
Colloid	1 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.4)
Fetal	0	1	0	0	0	1 (0.4)
Total	90 (31.5)	70 (24.6)	45 (15.8)	37 (13.0)	44 (15.4)	285 (100)

AIS, adenocarcinoma *in situ*; MIA, minimally invasive adenocarcinoma.

by lepidic-predominant (LPA, 20%), and papillary-predominant (PPA) subtypes in 7% of patients.

There were seven (2%) invasive-mucinous ACs (IMA), two (0.7%) micropapillary-predominant ACs (MPA), two (1%) minimally invasive ACs (MIA), and 1 AC *in situ* (AIS). No cases of atypical adenomatous hyperplasia (AAH) or enteric-predominant (EPA) AC were identified.

Staging

The pathological TNM stage is shown in Table 2. The only patient with AIS was diagnosed as stage IA. One patient with MIA was stage IA and the other stage IIIA. LPA, APA, and SPA were most often in early stages, but some patients were in higher stages.

Survival of different adenocarcinoma subtypes

Figure 2 shows overall survival (OS) for all stages and all histological AC subtypes together, being 84.9% at 1 year and 45.3% at 5 years.

Figure 3 shows OS for the different TNM-stages of patients with AC; with 5-year survival in stage IA being 63%; stage IB 58%; stage IIA 26%; stage IIB 29% and IIIA 14% (log-rank test, $p < 0.001$).

Figure 4 shows OS for the different histological AC subtypes, but only subtypes with more than 20 patients are shown. The 5-year survival was 55% for LPA, 38% for APA, 52% for SPA, 38% for PPA. There was no statistical difference in survival between the different subtypes of ACs (Fig. 4, log-rank test $p = 0.32$). If subtypes with similar survival are grouped together (LPA and SPA vs APA and PPA), a trend toward difference in survival was seen between the groups (log-rank test $p = 0.08$).

The one case of AIS was 2.2 cm in maximum diameter. The patient was operated on in 2007 and is currently (November 2015) in good health with no evidence of recurrent disease 8 years later. One patient had non-mucinous MIA. The primary tumor had a 2.1-cm maximum diameter and the patient was disease free for 10 years, when she died from metastatic breast cancer. The other patient

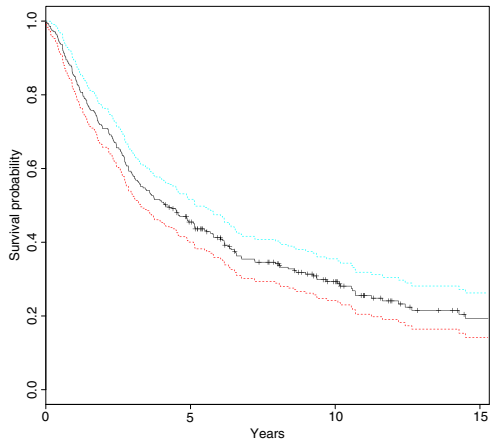

Fig. 2. Overall survival (Kaplan–Meier) of all patients (n = 285) with primary lung adenocarcinoma resected in Iceland in 1991–2010. The 95% confidence interval is shown with broken lines.

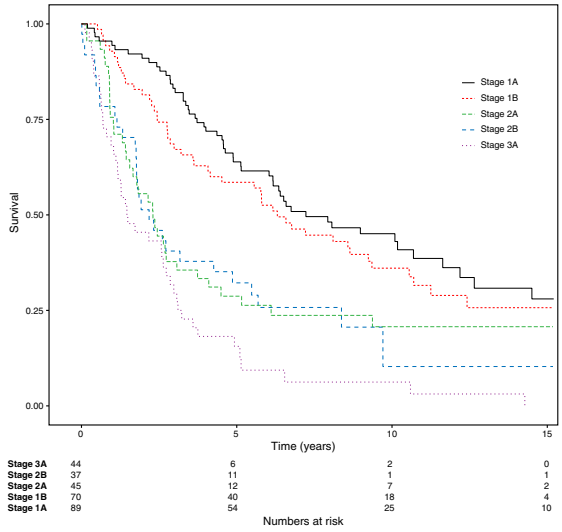

Fig. 3. Overall survival according to stages I–IIIA in 285 patients with primary lung adenocarcinoma resected in Iceland in 1991–2010 (log-rank $p < 0.001$).

with MIA had a mixed-type MIA that was 1.7 cm in maximum diameter. The patient had recurrent disease 2 years later and died from distant metastases 8 years after the operation.

Survival of adenocarcinoma patients compared to other histological subtypes

For comparison with patients with AC the 5-year survival for 156 patients with squamous cell carcinoma and 32 with large-cell carcinoma operated during the same period was 35% and 28%, respectively (log-rank test, $p = 0.02$). When corrected for stage the survival difference was no longer significant ($p = 0.98$).

Predictors of survival

Table 3 depicts the univariate analysis of OS according to the clinico-pathologic parameters. The

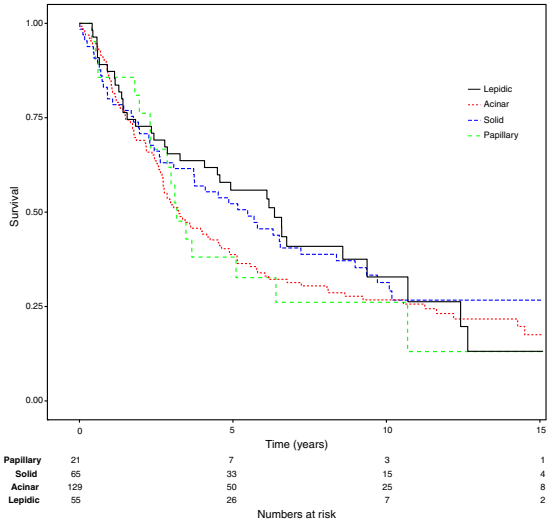

Fig. 4. Overall survival according to the subtypes/variants that had more than 20 patients in patients resected for primary lung adenocarcinoma in Iceland 1991–2010.

following factors were significantly associated with worse OS: Sex, higher TNM staging, increasing size of tumor, dyspnea at diagnosis, suffering a major postoperative complication, or having ischemic heart disease. In multivariate analysis (Table 3) only advanced age (HR 1.03, 95% CI 1.02–1.05, $p < 0.0001$) and TNM staging (stage IIIb HR 3.91, 95% CI 2.37–5.98, $p < 0.001$) turned out to be independent prognostic factors of OS. After correcting for other factors in the model, including age and stage, the different subtypes of AC did not significantly impact survival (HR 0.58–1.32, CI 0.3–5.8, $p = 0.7$), neither in uni- nor multivariate analysis.

DISCUSSION

In this study, we performed histologic subtyping of all lung ACs operated on in Iceland during a 20-year period according to the new 2011 IASLC/ATS/ERS international multidisciplinary lung adenocarcinoma classification and studied its impact on survival. Numerous studies have shown that the new histological classification may be an independent predictor of survival for patients with primary AC of the lung, especially in early stages of the disease (stages I and II) (21). We decided to include patients in all stages of NSCLC disease where surgical resection is an option to represent the whole spectrum of patients operated for NSCLC in a well-defined population.

Table 3. The Uni- and multivariate analysis of survival in patients with resected adenocarcinoma of the lung in 1991–2010. Only the statistically significant ($p < 0.05$) or nearly significant ($p < 0.1$) variables are shown

	HR	p-value
Univariate		
Sex (ref: male)	0.74	0.07
Age	1.02	<0.001
TNM (ref: IA)		
IB	1.35	0.1
IIA	2.19	<0.001
IIB	2.51	<0.001
IIIA	4.21	<0.001
Size	1	<0.001
Incidental detection	0.71	0.06
Dyspnea	1.41	0.02
Major complication	1.7	0.005
IHD	1.35	0.05
ARDS	2.25	0.05
PO pneumonia	1.51	0.07
ASA score	1.22	0.08
Multivariate		
Age	1.03	<0.001
TNM (ref IA)		
IIB	1.15	0.61
IIA	2.09	<0.01
IIB	2.24	0.01
IIIA	3.98	<0.001

TNM, Tumor, Node, Metastasis; IHD, ischemic heart disease; ARDS, acute respiratory distress syndrome; PO, post operative; ASA, American Society of Anesthesia; HR, hazard ratio.

Almost half (46%) of the patients had the acinar-predominant histological subtype, as has been reported in several other studies (21–23). Second

came solid-predominant adenocarcinoma with mucin (SPA) production in 23% of cases, followed by lepidic-predominant (LPA, 20%), and papillary-predominant (PPA) subtypes in 7% of patients. Applying the IASLC/ATS/ERS Classification, only a small proportion of lesions, less than 2% of ACs, belong in the 'early' group. This is in line with other studies from western countries like Australia (21), but a lot lower than in Asian population studies (24, 25).

With respect to overall survival for the different histological AC subtypes, there was not a statistical difference between different subtypes of ACs (log-rank test $p = 0.32$). However, when subtypes with similar survival are grouped together (LPA and SPA vs APA and PPA), a trend toward a difference in survival was seen between the groups (log-rank test $p = 0.08$). These calculations were done for exploratory purposes only and it is unclear whether the results have any clinical relevance. Using a multivariate analysis only advanced age, and the TNM stage turned out to be independent prognostic factors of OS. After correcting for other factors in the model, including age and stage, the different subtypes of AC did not significantly impact survival (HR 0.58–1.32, CI 0.3–5.8, $p = 0.7$).

Recent studies have shown that the prognostic significance of the AC subtype is not always conclusive. In an Australian study that included 210 AC patients that underwent pulmonary resection, the new classification system was shown to be an independent prognostic indicator of survival, even for advanced stage disease (21). Similarly a French study of 407 surgical patients in all stages showed a difference in survival in all stages (26). However, the study by Westaway et al. (22), that included 152 surgical AC patients in stages I–IIIA, the new classification was not shown to be an independent prognostic factor of survival. The new classification system has been studied extensively in early stages (27–30) and the evidence seems to provide sufficient data for prognostic significance. Only a few studies have been published in more advanced stages (21, 22, 26) so more studies might be needed before the new classificaton can replace the older one. In Australia, 28% of the population are immigrants or born outside of the country (31) and in France this number is 19% (32). The Icelandic population is ethnically much more homogenous and consists of 325 000 inhabitants, where only 6% are immigrants or people born outside of the country (33).

The reason for better OS for acinar-predominant AC in some previous studies is not obvious. This subgroup often seems to have an intermediate outcome (23, 27), ranging between 43% and 68% in 5-year survival (21–23, 27), compared to the present study where it was only 38%. Our findings therefore suggest that acinar-predominant ACs should be grouped together with poor prognosis AC subtypes, along with micropapillary and mucinous ACs. Because acinar-predominant histology represents a large proportion of patients with AC, it might also suggest that this is a heterogenous subgroup of AC that needs to be further subclassified according to nuclear features, architecture or proliferative indices, e.g. Ki-67.

There was no difference between survival in the papillary group if we divided the period into four 5-year periods ($p = 0.3$).

No differences in OS were detected between patients with SCL, LCC, and AC in our study after correcting for TNM-stage in the multivariate analysis. The AC subtype had better OS in univariate analysis, however, after correcting for disease stage in multivariate analysis, the difference was not statistically significant. This suggests that ACs are more often diagnosed in early stages.

This is the first study on the impact of subtyping of pulmonary AC to be performed on a nationwide basis. The cohort represents a well-defined population of patients with a relatively homogenous background. Further strengths are that the patients with AC were found using two separate registries and that all of the histological slides were reviewed by a senior pathologist who was blinded to the postoperative clinical outcome. All the patients were operated on and treated at a single center, and they were therefore less likely to be affected by selection bias and none of the patients were lost to follow-up. The weakness of the study was its retrospective design and inadequateness of the statistical power for multivariate analysis with only 285 patients analyzed.

In summary, this study shows that in a population-based homogenous Caucasian cohort there is not a big difference in survival according to different subtypes of AC. Only a minority of the cases was non-invasive. The major histological types of NSCLC also did not show a difference.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

G.N.O., S.J., and T.G. participated in the design of the study and collected the data. G.N.O. and T.G. performed the statistical analyses. J.B.: performed

histological reexamination of all the histological slides. G.N.O. reviewed the literature, drafted the manuscript, and wrote the article. All the authors read and approved the final manuscript.

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Paper IV

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Resection rate and operability of elderly patients with non-small cell lung cancer: Nationwide study from 1991 to 2014

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THORACIC

Abstract

OBJECTIVES: An increasing number of elderly patients are diagnosed with non-small cell lung cancer (NSCLC). We compared the surgical resection rate, operability and survival in this age group (≥75 years) to younger patients using centralized databases in Iceland.

METHODS: The study population comprised all patients diagnosed with NSCLC in Iceland from 1991 to 2014. A total of 140 elderly patients (≥75 years) with NSCLC underwent pulmonary resection and were compared with 550 surgically resected patients less than 75 years, with respect to resection rate, short and long-term survival and complications of surgery. Reasons for exclusion from surgery were registered for elderly surgical candidates (stages IA–IIB).

RESULTS: Surgical resection rate in the elderly group was 18% compared to 32% in the younger age group ($P < 0.001$). The most frequent reasons for not operating on elderly patients in stages IA–IIB were poor pulmonary function (58%), heart disease (17%) or multiple comorbidities (17%). The rate of major complications following surgery was comparable in the elderly versus the younger age group, 13 vs 11%, respectively ($P = 0.578$). The same was true for 30 day mortality (2 vs 1%, $P = 0.397$). Five-year overall survival was 40% vs 44% ($P = 0.019$) and cancer-specific survival 51% vs 50% ($P = 0.802$).

CONCLUSIONS: Elderly patients with resectable NSCLC according to stage are frequently excluded from surgery due to comorbid conditions. Although the operated patients may represent a selected group, their favourable 30-day and long-term survival indicate that more elderly patients with NSCLC could be operated on.

Keywords: Non-small cell lung cancer • Elderly • Resection rate • Operability and survival

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in the Western world [1]. In many European countries, including Iceland, the mortality from lung cancer is similar to that of breast, prostate and colon cancer combined. Surgery is the best curative treatment for non-small cell lung cancer (NSCLC), which accounts for about 85% of all lung cancer cases [2].

With an ageing population the number of elderly patients diagnosed and treated for NSCLC is expected to increase. Until recently the survival benefit of surgical treatment for elderly patients has been unclear. Recent studies have reported acceptable surgical outcomes and favourable long-term survival for elderly patients after pulmonary resections [3–7]. These studies suggest that age alone should not be a contraindication for surgery, although careful individual preoperative assessment is needed. Still, surgical resection rates (SRR) in the elderly population are lower compared to younger patients [8, 9], and elderly patients seem to be more frequently excluded from surgery due to age alone [10].

The aim of this study was to investigate the outcomes of pulmonary resections for NSCLC in the elderly (≥75 years of age) and compare them to younger patients, assess SSRs, operability and reasons for exclusion from surgery, using centralized databases in a well-defined nationwide cohort of patients.

MATERIALS AND METHODS

This was a retrospective whole-population study focused on all elderly patients who underwent pulmonary resection in Iceland with curative intent for NSCLC from January 1, 1991 to December 31, 2014.

At present Iceland has 330,000 inhabitants with an average life expectancy of 81.6 years for males and 84.3 for females. Currently, only 11% of adults smoke but after the second world war the smoking rate was close to 50% [11]. The health care is a single payer system with one major tertiary care hospital where all lung cancer surgery is provided.

The Icelandic Cancer Registry is a centralized database including all cancer cases diagnosed at hospitals and other healthcare facilities in Iceland since 1955. This registry was used to identify all pulmonary tumours diagnosed in Iceland during the study period. Pulmonary tumours that were not NSCLC ($n = 160$) were excluded from the study. Another 77 elderly patients had to be excluded for various reasons, as they were lost to follow-up, their patient charts were not found or diagnosis was made post mortem. To ascertain that no cases were missing, all cases of NSCLC in the Icelandic Cancer Registry were cross-referenced against a central, computerized histology database from the Department of Pathology, Landspitali University Hospital, containing details of all lung histology specimens in Iceland.

SRR was calculated by dividing the number of pulmonary resections performed with curative intent by the number of confirmed cases of NSCLC within the same period. Baseline demographic information and clinical data, for both elderly and younger patients, were collected from hospital records and surgical reports using a standardized data sheet. Comorbidities and presenting symptoms were recorded along with operation type and surgical complications. Tumours were classified according to the 7th edition of the American Joint Committee on Cancer TNM staging system [12]. The patients who had a surgical procedure were staged postoperatively (pTNM-staging). Their clinical (cTNM) staging before surgery, however, was not uniformly recorded and therefore not used for analysis of the surgical patients.

All surgical procedures were performed under general anaesthesia with double lumen intubation and thoracic epidural anaesthesia, most often performed through posterolateral or anterolateral thoracotomy. All cases were performed by 6 surgeons using standardized techniques with intraoperative lymphadenectomy of enlarged hilar or ipsilateral mediastinal lymph nodes, but during the last 10-year period these lymph nodes were routinely removed or sampled.

Major complications were defined as heart failure, adult respiratory distress syndrome, myocardial infarction, empyema, stroke, bronchopleural fistula, pneumonia and major bleeding defined as intraoperative bleeding over 1 litre or reoperation for bleeding. Minor complications were defined as air leakage for more than 7 days, new new-onset of atrial fibrillation/flutter, wound infection, and recurrent laryngeal nerve paralysis. Operative mortality was defined as death within 30 days of surgery. To assess trends, the 24-year study period was divided into four 6-year periods.

For elderly patients who did not undergo surgery, clinical data was collected from patient records from health care centres all over the country using a standardized data sheet. These patients were clinically staged (cTNM) retrospectively and reasons for exclusion from surgery were determined for patients in stages IA–IIB. In some cases more than one reason for exclusion was determined. Stages IA–IIB were chosen since multi-modality treatment is usually recommended for stage IIIA according to the latest international guidelines [13, 14].

Statistics

Microsoft Excel was used for descriptive statistics, and R version 2.10.1 for survival calculations. The Student's *t*-test (*t*) was used to compare continuous variables between the two groups. The Kolmogorov–Smirnov test (KS-test) assess the normal assumption for continuous data. The Chi-square (χ^2) and Fisher exact test (FET) were used to compare categorical variables. The Chi-square with yates correction was used if expected cell frequency was equal to or greater than 5. A *P*-value of less than 0.05 was considered statistically significant. Overall survival (OS) and cancer-specific survival (CSS) was analyzed by the Kaplan–Meier method, and the log-rank test was used to compare survival between groups. Patients could be assigned a date of death or were identified as living on December 31, 2014 using data from the Icelandic National Population Registry. To calculate CSS, the cause of death was determined as either lung cancer or other causes. Mean follow-up time was 5 years (range: 0–23 years).

The study was approved by the Icelandic National Bioethics Committee and the Data Protection Authority. As individual patients were not identified, individual consent was waived.

RESULTS

Demographics of elderly patients diagnosed with NSCLC

A total of 2556 patients were diagnosed with NSCLC in Iceland during the 24-year study-period; 859 (34%) of them were classified as elderly (≥75 years), but 77 of these had to be excluded, most often due to missing long-term data; leaving 782 elderly (32%, 782/2479) for further analysis. Out of these 782 elderly patients, 140 underwent pulmonary resection and they were compared with 550 operated NSCLC patients less than 75 years of age (younger group). The average/median age for all elderly diagnosed with NSCLC was 80/79 respectively compared to 65/63 in the younger group. During the 24-year study the proportion of elderly patients diagnosed with NSCLC increased steadily from 29% ($n = 159$) in the first study period to 37% ($n = 232$) in the last ($P = 0.006$).

Table 1 shows information on tumour histology and clinical staging of all elderly patients with NSCLC stage I and II. Adenocarcinoma (48%) and squamous cell carcinoma (33%) were the most common histological tumour types. The proportion of adenocarcinoma rose significantly during the last two 6-year periods ($P = 0.013$), but the rate of other histological types such as squamous cell, large cell carcinoma and other unspecified NSCLCs remained statistically unchanged. According to clinical staging, 29% of the elderly patients were diagnosed in stage I or II (18% and 11%, respectively). The rate of elderly with stage IA disease rose significantly during the last study period while the rate of stage IIB decreased ($P < 0.001$ and $P = 0.035$, respectively). The number of patients with disease in stage III or IV was 485 (62%) and the number of patients where clinical stage could not be determined retrospectively was 68 (9%).

Surgical resection rate and causes for non-operability

The SRR in the elderly group was 18% ($n = 140$) compared to 32% ($n = 550$) in the younger group ($P < 0.001$). SRR for elderly patients

Table 1: Resection rate, tumour histology and TNM-stage

	1991–1996 (*n* = 32)	1997–2002 (*n* = 36)	2003–2008 (*n* = 76)	2009–2014 (*n* = 85)	Total (*n* = 229)	*P*-value χ^2
Resection rate	17 (53)	17 (47)	41 (54)	51 (60)	126 (55)	0.611
Histology						
Squamous cell	14 (44)	16 (44)	21 (28)	25 (29)	76 (33)	0.153
Adenocarcinoma	10 (31)	12 (33)	38 (50)	50 (59)	110 (48)	**0.013**
Large cell	2 (6)	2 (6)	2 (3)	2 (2)	8 (3)	0.644
Other non-small cell	1 (3)	2 (6)	7 (9)	5 (6)	15 (7)	0.657
Primary tumour of lung without histological verification	5 (16)	4 (11)	8 (11)	3 (4)	20 (9)	0.147
Stage						
IA	10 (31)	6 (17)	14 (18)	38 (45)	68 (30)	**<0.001**
IB	10 (31)	13 (36)	24 (32)	26 (31)	73 (32)	0.946
IIA	7 (22)	8 (22)	17 (22)	12 (14)	44 (19)	0.518
IIB	5 (16)	9 (25)	21 (28)	9 (11)	44 (19)	**0.035**

Resection rate, tumour histology and TNM-stage for all elderly patients diagnosed with stages I and II NSCLC (*n* = 229), during the study period 1991–2014, divided into four 6-year periods. Not included in the table are patients diagnosed with stage III–IV disease (*n* = 465) or when staging was incomplete (*n* = 68). The numbers of patients are given with percentages in parentheses. Statistically significant difference between groups was set at $P < 0.05$.

Table 2: Surgical resection rate (SSR) in elderly patients in different TNM stages

TNM stage	SSR
IA (*n* = 68)	37 (54)
IB (*n* = 73)	46 (63)
IIA (*n* = 44)	24 (55)
IIB (*n* = 44)	19 (43)
IIIA (*n* = 87)	13 (15)
IIIB (*n* = 37)	0 (0)
IV (*n* = 327)	0 (0)

Information regarding staging was unknown for 68 patients and inaccurate for 34 patients regarding stages IIIA–IV and are not shown. The numbers of patients are given with percentages in parentheses.

in different stages is shown in Table 2; it was 54% for stage IA, 63% for stage IB, 55% and 43% for stages IIA and IIB, and 15% for stage IIIA.

Reasons for not operating on elderly patient are shown in Table 3. Insufficient pulmonary function was the most common reason for not operating on elderly patients diagnosed in stages IA–IIB (58%), followed by cardiovascular disease (17%), multiple comorbidities (17%), patient refusal of treatment (16%), frailty or poor performance status (13%).

A total of 68 elderly patients had incomplete staging. Usually further workup was not considered necessary in these cases since it was known beforehand that these patients would not be offered surgery for various reasons listed in Table 3.

Outcome of pulmonary resection in the elderly

Between 1991 and 2014 a total of 690 patients with NSCLC underwent surgery with curative intent. Of these 690 patients, 140 (20%) were defined as elderly (≥75 years of age). When comparing preoperative patient demographics and risk factors, there were more males in the elderly group (59% vs 45%, $P = 0.007$) and a higher proportion of patients had a previous history of coronary heart disease (45% vs 20%, $P < 0.001$) and arrhythmias (23% vs 9%, $P < 0.001$). Elderly patients were also more likely to be diagnosed incidentally (without symptoms of NSCLC), or in 46% vs 30% of cases ($P < 0.001$) (Table 4).

Forced expiratory volume in 1 second (FEV1) in preoperative pulmonary function tests was significantly lower in the elderly compared to the younger patients (mean 2.02 l vs 2.31 l, $P < 0.001$), see Table 4. The results of 62 pulmonary function tests were missing and, therefore, not used in calculations of lung function, 9 of them in elderly patients and 53 in the younger patients.

The most common type of surgery performed was lobectomy for both elderly and younger patients (75% and 70%, $P = 0.284$). However, sublobar resections were more often performed in the elderly (24% vs 3%, $P < 0.001$) and pneumonectomies were less common compared to younger patients (3% vs 15%, $P < 0.001$) (Table 5).

Neoadjuvant chemotherapy was administrated to 16 younger patients (3%) but none of the elderly patients (see Table 4). Furthermore, 7 (5%) elderly patients received adjuvant chemotherapy and 86 (16%) patients in the younger group ($P = 0.002$). No difference was found between adjuvant radiotherapy in older versus younger patients.

Surgical outcome, in terms of 30-day mortality (2% and 1%, $P = 0.397$) and the median length of hospital stay (10 vs 9 days, range: 1–144, $P = 0.22$), was comparable in both age groups (KS-test, $P = 0.08$) (Table 5).

Postoperative complications are shown in Table 5. There was no statistical difference in the rate of major or minor complications between older and younger patients ($P = 0.578$ and $P = 0.135$, respectively). The most common major complication in both groups was profound bleeding, defined as perioperative bleeding exceeding 1 litre and/or reoperation for bleeding. Air leakage extending more than 7 days and new-onset atrial fibrillation were the most common minor complications. Heart failure was the only complication that was significantly more common in the elderly (4 vs 1%, $P = 0.012$).

OS and CSS are shown in Figs 1 and 2. OS for the elderly was 40% at 5 years compared to 44% in the younger group. A

Table 3: Reasons indicated for not operating on elderly patients with NSCLC on cTNM-stages IA–IIB and for not performing a complete staging workup

	IA–IIB ($n = 103$)	Incomplete staging ($n = 68$)	*P*-value
Heart disease	17 (17)	11 (16)	0.888[a]
Insufficient lung function	60 (58)	32 (47)	0.2[a]
Dementia	3 (3)	6 (9)	0.158[b]
Multiple comorbidities	17 (17)	9 (13)	0.718[a]
Frailty or poor performance status	13 (13)	14 (21)	0.237[a]
Unresectable tumour location	4 (4)	6 (9)	0.198[b]
Patients who refused treatment	16 (16)	8 (12)	0.639[a]
Death of other causes before complete workup/treatment	4 (4)	2 (3)	1[b]
Other life threatening or terminal disease	4 (4)	3 (4)	1[b]
Reason for not operating could not be determined	3 (3)	3 (4)	0.683[b]

[a]Chi-square test.
[b]Fischer's exact test.
Note that patients could have multiple indications. The numbers of patients are given with percentages in parentheses. Statistically significant difference between groups was set at $P < 0.05$.

Table 4: Preoperative comparison of demographics and risk factors for elderly and younger patients

	<75 years ($n = 550$)	≥75 years ($n = 140$)	*P*-value
Male sex	250 (45)	82 (59)	**0.007**[a]
History of smoking	526 (96)	131 (94)	0.424[a]
Incidental detection	167 (30)	65 (46)	**<0.001**[a]
Chronic obstructive pulmonary disease	140 (25)	46 (33)	0.1[a]
Coronary heart disease	112 (20)	63 (45)	**<0.001**[a]
Arrhythmia	52 (9)	32 (23)	**<0.001**[a]
pTNM stage			
IA	166 (30)	37 (26)	0.442[a]
IB	103 (19)	46 (33)	**<0.001**[a]
IIA	99 (18)	24 (17)	0.92[a]
IIB	64 (12)	19 (14)	0.632[a]
IIIA	91 (17)	13 (9)	**0.044**[a]
IIIB	4 (1)	0 (0)	0.588[b]
IV	21 (4)	0 (0)	**0.022**[b]
Unclear	2 (1)	0 (0)	1[b]
FEV1 (l)	2.31	2.02	**<0.001**[c]
Neoadjuvant chemotherapy	16 (3)	0 (0)	**0.05**[b]
Neoadjuvant radiotherapy	16 (3)	1 (1)	0.219[b]
Adjuvant chemotherapy	86 (16)	7 (5)	**0.002**[a]
Adjuvant radiotherapy	55 (10)	7 (5)	0.09[a]

[a]Chi-square test.
[b]Fischer's exact test.
[c]Student's *t*-test.
pTNM: postoperative Tumour Node Metastasis; FEV1: forced expiratory volume in 1 second.
The numbers of patients are given with percentages in parentheses. Statistically significant difference between groups was set at $P < 0.05$.

significant statistical difference was found between the groups ($P = 0.019$). However, 5-year CSS for the elderly patients was 51% vs 50% for the younger group ($P = 0.802$) (Fig. 2).

DISCUSSION

This is the first study on the resectability and outcomes of elderly patients with NSCLC performed in a whole population. Our results show that younger and elderly patients who underwent surgery with curative intent for NSCLC had similar short-term outcomes. The low 30-day mortality (2%) observed for elderly patients, compares favourably with the 30-day mortality for younger patients previously reported, however, most studies have shown higher 30-day mortality rates in the elderly [3, 5], whereas others have not shown significant differences [6, 7, 15].

There was no significant difference in rates of minor or major complications between the groups; a finding that is in line with some previously published studies [3, 6, 16]. When comparing the rate of complications and comorbidities between studies it is important to remember that different definitions have been used. Still, most studies have shown a slightly higher rate of

Table 5: Comparison of operation type and surgical outcome for elderly and younger patients who underwent surgery for NSCLC with curative intent

	<75 years (*n* = 550)	≥75 years (*n* = 140)	*P*-value
Operation type			
Pneumonectomy	80 (15)	4 (3)	**<0.001**[a]
Lobectomy	412 (75)	98 (70)	0.284[a]
Sublobar resections	50 (9)	34 (24)	**<0.001**[a]
Major complications			
All major complications	71 (13)	15 (11)	0.578[a]
Bronchopleural fistula	3 (1)	0 (0)	1[b]
Myocardial infarct	3 (1)	3 (2)	0.102[b]
Adult respiratory distress syndrome (ARDS)	10 (2)	3 (2)	1[b]
Major bleeding	55 (10)	8 (6)	0.159[a]
Empyema	9 (2)	1 (1)	0.49[b]
Pneumonia	44 (8)	17 (12)	0.169[a]
Minor complications			
All minor complications	162 (29)	51 (36)	0.135[a]
New-onset atrial fibrillation	41 (7)	18 (13)	0.061[a]
Heart failure	5 (1)	6 (4)	**0.012**[b]
Recurrent laryngeal nerve paralysis	10 (2)	0 (0)	0.135[b]
Wound infection	11 (2)	0 (0)	0.133[b]
Air leakage ≥ 7 days	75 (14)	21 (15)	0.777[a]
Median length of hospital stay	9	10	0.22[c]
30-day mortality	6 (1)	3 (2)	0.397[b]

[a]Chi-square test.
[b]Fischer's exact test.
[c]Student's *t*-test.
The numbers of patients are given with percentages in parentheses. Statistically significant difference between groups was set at $P < 0.05$.

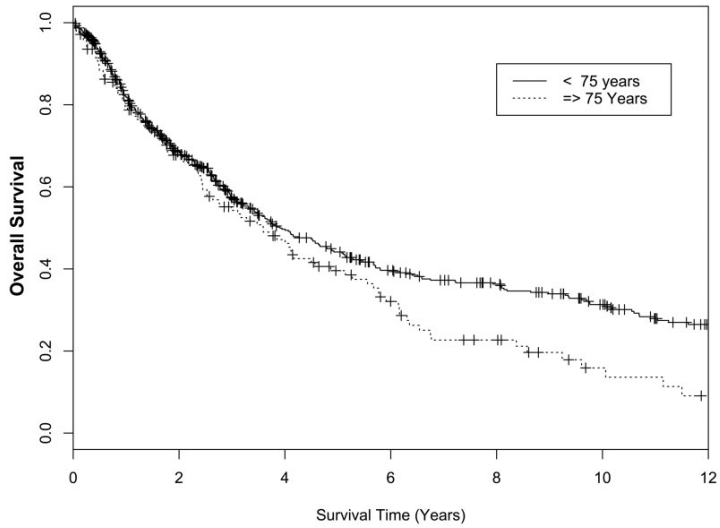

Figure 1: Kaplan–Meier graph showing OS of patients operated for NSCLC from 1991 to 2014. Five-year survival was 40% for elderly patients compared to 44% for younger patients, a significant difference was found between the two groups ($P = 0.019$).

postoperative complications in elderly patients [5, 17]. In the present study, this was only seen for heart failure.

Interestingly the long-term outcome for CSS at 5 years was not significantly different. However, the results for the OS was statistically different. Interestingly, when the Wilcoxon test was used for comparing OS of the groups, a statistical difference was not observed ($P = 0.109$), but this test emphasizes early events of the survival curve. This may indicate that initially the OS in both groups was similar, but due to the higher chronological age and the long follow-up time, the survival curve drops in the elderly group around year six and explains a significant difference in the OS with the log-rank test. Several other studies have

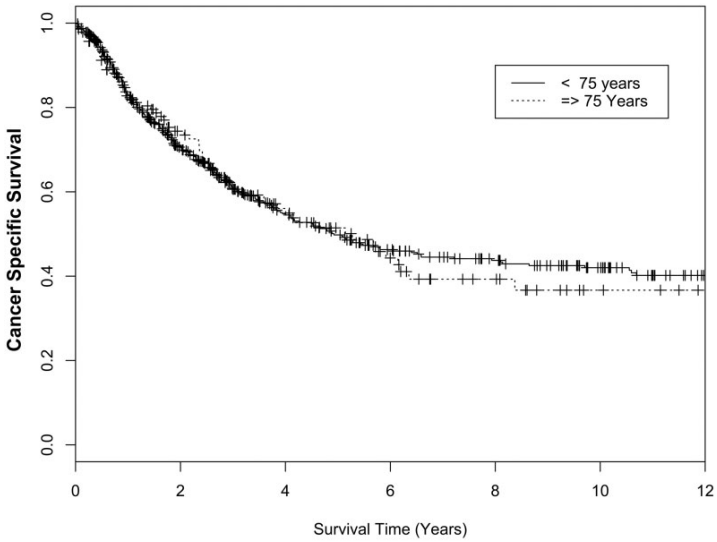

Figure 2: Kaplan–Meier graph showing cancer specific survival of patients operated for NSCLC from 1991 to 2014. Five-year survival was 51% for elderly patients compared to 50% for younger patients ($P = 0.802$).

reported similar findings [15, 16, 18, 19], but these studies often represent material from single institutions as compared with a whole population in the present study.

Our favourable results on surgical outcome and survival may in part be influenced by the fact that resection rate was significantly lower for elderly compared to younger patients. This has also been shown in other studies [19, 20]. These findings might also reflect appropriate selection of elderly patients for surgery, considering the rate of pneumonectomies and sublobar resections in this group of patients. Our results might also suggest that more elderly patients could tolerate surgery, especially limited resections, as a higher complication rate may be accepted in elderly patients [21–23]. Fewer elderly than younger patients had adjuvant chemotherapy (5% vs 15.6%, $P < 0.001$), but adjuvant therapy was not introduced as a routine in Iceland until 2005.

Sublobar resection, as well as less invasive surgery (video-assisted thoracic surgery, VATS), has in previous studies resulted in lower complication rates and mortality [17, 24–29]. An abstract on a new randomized controlled trial on sublobar resection versus lobectomy in the elderly has recently been published [30], so more information about this is pending. Therefore, it could be argued that the SRR in elderly patients with NSCLC could be increased by offering less invasive surgery or limited resections and reduce the number of patients who are denied surgery because of insufficient pulmonary function, heart disease and multiple morbidities, all common reasons for not offering surgery to the elderly NSCLC patients in the present study. We noticed a significant increase in the number of elderly patients with stage IA disease during the last 6-year period, as well as a decrease in stage IIB. The reasons for this increase are unclear, but more frequent use of CT might play a role. PET scans were not available in Iceland until after the study period ended. This may further strengthen the need for less invasive surgery for elderly comorbid patients.

The main strength of this study was that the cohort included all elderly NSCLC patients from a whole country, reducing the risk of selection bias. A further strength was the complete dataset, with patients identified in three separate registries, including the population-based Icelandic Cancer Registry. All patients were operated on and treated in a single centre, decreasing the risk of referral bias. Information on follow-up and survival was relatively complete. One of the main drawbacks, was the study's observational design. Another drawback is the limited power due to the small patient cohort (see above). As the study is retrospective it is susceptible to cases being excluded because of incomplete data and medical record information. Unfortunately DLCO and VO2 max measurements were not performed routinely for all patients and this information was therefore not included.

In conclusion, we have reported resection rate, complications, and survival rates for all elderly patients operated for NSCLC in the Icelandic population during a 24-year period. Our results show that almost every other (45%) elderly patient with potentially resectable NSCLC is excluded from surgery due to co-morbid conditions. The favourable 30-day and long-term survival of the elderly patients observed in this study may likely reflect a careful selection of patients but could also indicate that more elderly patients with NSCLC could be operated on given recent advances in surgical technique and perioperative care.

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