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LONG-TERM QUALITY OF LIFE IN OPERATED NON-SMALL CELL LUNG CANCER PATIENTS

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ABSTRACT

Lung cancer is a nefarious disease causing more deaths than any other cancer worldwide. It is also among the most common cancers in Finland and the leading cause of cancer-related deaths, with 5-year survival rates of only 10-15%. However, more cases are being diagnosed at an earlier, possibly curable stage – radical surgery being the main curative treatment. As more patients survive the disease, long-term results, including quality of life, have attained more weight as treatment outcome measures. Thus, less invasive video-assisted thoracoscopic surgery (VATS) has largely replaced the more invasive thoracotomy as the standard treatment for operable local non-small cell lung cancer (NSCLC) patients.

This study assessed the long-term health-related quality of life (HRQoL) among surgically treated NSCLC survivors, determining possible patient and treatment factors affecting the long-term HRQoL and survival among these patients, and comparing the effects of VATS and thoracotomy on the long-term HRQoL.

For Studies I and II, we gathered patient and operational characteristics on 579 patients operated on for NSCLC in our clinic at Helsinki University Central Hospital between January 2000 and June 2009. The 276 survivors received two HRQoL questionnaires, the generic 15D and the cancer-specific EORTC QLQ-C30, in 2011. The HRQoL of our 230 respondents was compared with that of the age- and gender-standardized general population. Study II utilized the same data to determine factors predicting survival and long-term HRQoL among NSCLC survivors via regression analyses. Study III compared long-term HRQoL between 88 thoracotomy and 92 VATS patients undergoing lobectomy for local NSCLC in our clinic from January 2006 to January 2013. All of the studies were retrospective in nature.

The NSCLC survivors reported significantly lower long-term HRQoL than the general population, with the most severe deterioration observed on the dimensions of mobility and breathing. Long-term survival proved to be moderately predictable by objective patient, disease, and treatment features, such as age, disease stage, and perioperative complications, but the regression models failed to notably predict long-term HRQoL. VATS patients reported significantly lower long-term HRQoL than thoracotomy patients, although the groups had comparable pre- and perioperative characteristics, and particularly no differences favouring the thoracotomy group were observed.

The apparent long-term reduction in HRQoL should be considered in patient counselling, and more resources directed to the pre- and postoperative

rehabilitation of the most severely affected functions. Long-term postoperative HRQoL seems poorly predictable, or at least the commonly measured clinical features fail to have a marked effect on HRQoL.

TIIVISTELMÄ

Keuhkosyöpä aiheuttaa maailmanlaajuisesti eniten syöpäkuolemia ja on myös Suomen yleisimpiä syöpätauteja sekä johtava syöpäkuolemien aiheuttaja viisivuotisennusteen jäädessä 10-15 prosenttiin. Toisaalta yhä useampia tapauksia todetaan aikaisemmassa vaiheessa, jolloin radikaalileikkaus on mahdollinen ja ensisijainen hoitomuoto. Useampien potilaiden selviytyessä myös pitkäaikaiset hoitotulokset, mukaanlukien elämänlaatu, ovat saaneet enemmän painoarvoa. Vähemmän invasiivinen videoavusteinen torakoskooppinen kirurgia (VATS) onkin pitkälti korvannut invasiivisemman torakotomian paikallisen ei-pienisoluisen keuhkosyövän ensisijaisena hoitomuotona leikkauskelpoisilla potilailla.

Tämä tutkimus kartoitti ei-pienisoluisen keuhkosyövän vuoksi leikattujen potilaiden pitkäaikaista terveyteen liittyvää elämänlaatua sekä elämänlaatua ja selviytymistä mahdollisesti ennustavia tekijöitä. Arvioimme myös VATS:n ja torakotomian mahdollisia eroja pitkäaikaisen elämanlaadun kannalta.

Tutkimuksia I ja II varten keräsimme potilas- ja hoitotiedot 579 potilaasta, jotka oli leikattu ei-pienisoluisen keuhkosyövän vuoksi klinikassamme Helsingin yliopistollisessa keskussairaalassa tammikuun 2000 ja kesäkuun 2009 välillä. Vuonna 2011 elossa olleille 276 potilaalle lähetettiin kaksi elämänlaatumittaria, geneerinen 15D ja syöpäspesifinen EORTC QLQ-C30. Ensimmäisessä tutkimuksessa vastanneiden 230 potilaan elämänlaatua verrattiin ikä- ja sukupuolivakioidun verrokkiväestön tuloksiin ja toisessa tutkimuksessa pyrittiin regressioanalyysein selvittämään potilaiden selviytymistä ja pitkäaikaista elämänlaatua määrittäviä tekijöitä. Kolmannessa tutkimuksessa verrattiin tammikuun 2006 ja tammikuun 2013 välillä klinikassamme paikallisen ei-pienisoluisen keuhkosyövän vuoksi lohkonpoistolla hoidettujen 88 torakotomiapotilaan ja 92 VATS-potilaan pitkäaikaista elämänlaatua. Kaikki tutkimukset olivat retrospektiivisiä.

Pitkäaikaisselviytyjien elämänlaatu oli merkittävästi verrokkiväestöä heikompaa ja merkittävimmin se oli alentunut liikuntakyvyn ja hengitystoiminnan osalta. Pitkäaikainen elossaolo oli kohtalaisen hyvin ennustettavissa objektiivisten potilas-, tauti- ja hoitotietojen, kuten iän, taudin asteen sekä hoitokomplikaatioiden, perusteella, mutta regressiomallien selitysaste jäi heikoksi pitkäaikaisen elämänlaadun osalta. VATS-potilaiden elämänlaatu jäi merkittävästi torakotomiapotilaita heikommaksi, vaikka ryhmät olivat pre- ja perioperatiivisilta ominaisuuksiltaan toisiaan vastaavia eikä etenkään torakotomiapotilaita suosivia eroja havaittu.

Ilmeinen pitkäaikainen elämänlaadun alenema tulisi huomioida potilasohjauksessa ja eniten kärsineiden osa-alueiden pre- ja

postoperatiiviseen kuntoutukseen tulisi panostaa enemmän. Pitkäaikainen leikkaushoidon jälkeinen elämänlaatu on heikosti ennustettavissa, ainakaan yleisesti määritettyjen kliinisten tekijöiden pohjalta.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Rauma V, Sintonen H, Räsänen J, Salo JA, Ilonen I. Long-term lung cancer survivors have permanently decreased quality of life after surgery. Clin Lung Cancer. 2015;16:40-45.

II Rauma V, Salo JA, Sintonen H, Räsänen J, Ilonen I. Patient features predicting long-term survival and health-related quality of life after radical surgery for non-small cell lung cancer. Thorac Cancer. 2016;7(3):333-339.

III Rauma V, Andersson S, Robinson EM, Räsänen J, Sintonen H, Salo JA, Ilonen I. Thoracotomy and VATS-surgery in local non-small cell lung cancer: differences in long-term health-related quality of life. Clin Lung Cancer. 2019;20:378-383.

The publications are referred to in the text by their Roman numerals.

Study III has previously been used as part of the thesis by Saana Andersson.

ABBREVIATIONS

ADC	adenocarcinoma
AIS	adenocarcinoma in situ
ASCO	American Society of Clinical Oncology
BAC	bronchioloalveolar carcinoma
CCI	Charlson comorbidity index
ChT	chemotherapy
CI	confidence interval
CNB	core needle biopsy
CT	computed tomography
DLCO	diffusing capacity of the lung for carbon monoxide
DLCO%	DLCO percentage of the predicted value
EBUS-TBNA	endobronchial ultrasound-guided transbronchial needle aspiration
EGP	general population according to the EORTC QLQ-C30 Reference Values manual
EORTC	European Organization for Research and Treatment of Cancer
ESAS	Edmonton Symptom Assessment Scale
ES-NSCLC	early-stage non-small cell lung cancer
ESTS	European Society of Thoracic Surgeons
EUS-FNA	endoscopic oesophageal ultrasound-guided fine-needle aspiration
FDG-PET	2-deoxy-2-(18F)fluoro-D-glucose positron emission tomography
FEV1	forced expiratory volume in one second
FEV1%	FEV1 percentage of the predicted value
FGP	Finnish general population
GGP	German general population
HRQoL	health-related quality of life
ICU	intensive care unit
IHC	immunohistochemical
IQR	interquartile range
LCC	large cell carcinoma
LDCT	low-dose computed tomography
LN	lymph node
MIA	minimally invasive adenocarcinoma
MID	minimal important difference
MRI	magnetic resonance imaging

MSAS	Memorial Symptom Assessment Scale
NRS	numerical rating scale
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
OR	odds ratio
OS	overall survival
PET	Positron emission tomography
PET-CT	Positron emission tomography, computed tomography
PFS	progression-free survival
PFT	pulmonary function test
PN	pneumonectomy
PRO	patient-reported outcome
PROM	patient-reported outcome measure
PTPS	post-thoracotomy pain syndrome
QLI	Ferrans and Powers quality of life index
QLQ-C30	quality of life questionnaire for cancer patients
QLQ-LC13	quality of life questionnaire, lung cancer-specific module
QoL	quality of life
RT	radiotherapy
SABR	stereotactic ablative radiotherapy
SBRT	stereotactic body radiation therapy
SCC	squamous cell carcinoma
SCLC	small cell lung cancer
SD	standard deviation
SF-36	MOS 36-item short-form health survey
SL	sleeve resection
TBNA	transbronchial needle aspiration
TNM	tumour, node, and metastasis
TNM7 and TNM8	seventh and eight versions of the TNM classification
TTFNA	CT-guided transthoracic fine-needle aspiration
VAM	video-assisted mediastinoscopy
VAS	visual analogue scale
VATS	video-assisted thoracoscopic surgery
WHO	World Health Organization
15D	health-related quality of life instrument 15D

1 INTRODUCTION

Lung cancer has two main types, small cell and non-small cell lung cancer (NSCLC), and the latter is further divided into histological subtypes, the most important ones being adenocarcinoma (ADC), squamous cell carcinoma (SCC), and large cell carcinoma (LCC) (Travis et al. 2015). Together they constitute the worldwide leader in both diagnosed cancer cases and cancer-related deaths, with approximately 2.1 million new diagnoses and 1.8 million deaths, ergo 11.6% and 18.4% of all new cases and deaths, respectively, in 2018 (Bray et al. 2018). Lung cancer is mainly diagnosed among the elderly, with the median age at diagnosis being 70 years (Noone et al. 2018). In Finland, the age-standardized incidence has been decreasing (Finnish Cancer Registry).

The absolute main risk factor, accounting for most cases of lung cancer, is tobacco smoking (U.S. Department of Health and Human Services 2004), as long-term smokers have up to a 30-fold risk of lung cancer compared with non-smokers (Mattson et al. 1987). Other significant risk factors comprise radon found in indoor air (Committee on Health Risks of Exposure to Radon (BEIR VI) 1999), exposure to asbestos (Doll 1955, Lee 2001), in-home combustion of solid fuels (Hosgood et al. 2010), and fine particulate air pollution (Pope et al. 2002).

In addition to the relatively high incidence rate, lung cancer has a dismal prognosis, as the 5-year survival rate remains under 20% (Noone et al. 2018). One of the main problems is the late diagnosis; only a quarter of symptomatic patients are diagnosed with local disease (Jett 1993), while 57% of newly diagnosed patients are diagnosed with distant metastases (Noone et al. 2018). The effect of late diagnosis on survival is enormous, with 5-year survival rates of 50% reported for clinical stage I and only 2% for clinical stage IV disease (Goldstraw et al. 2007). Likewise, poor tumour differentiation predicts lower survival (Sun et al. 2006), as do several patient features such as comorbidities and positive smoking history (Woodard et al. 2016).

Although disease stage has a marked impact on survival, screening programmes utilizing chest X-ray are not generally recommended (Postmus et al. 2017) since they have failed to show a survival benefit (Wu and Raz 2016). However, low-dose computed tomography (LDCT) screening has been demonstrated to be effective among high-risk patients (Henschke et al. 2006, National Lung Screening Trial Research Team 2011), and it has been recommended in this context (Postmus et al. 2017). As lung cancer is practically always originally diagnosed through imaging, a computed tomography (CT) scan is typically the method of choice (Lim et al. 2010, Postmus et al. 2017), and it can be combined with positron emission

tomography (PET) to provide more detailed information on the tumour and to reveal possible distant metastases (De Leyn et al. 2007, Stamatis 2015). Magnetic resonance imaging (MRI) may serve to rule out possible brain metastases preoperatively (Vernon et al. 2016, Postmus et al. 2017).

Next, a cytological or histological sample is typically acquired via different biopsy techniques, such as ultrasound- or CT-guided needle biopsies or bronchoscopy (Rivera and Mehta 2007, Rosai 2007, Stamatis 2015, Postmus et al. 2017), and ancillary immunohistochemical, molecular, and genetic analyses may be utilized to enhance the histological diagnosis (Dietel et al. 2016). The tumour is staged according to the tumour, node, and metastasis (TNM) system (Rami-Porta et al. 2017).

Surgery remains the gold standard in curative treatment of local NSCLC and may also be a part of multimodality treatment with locally advanced NSCLC (Lim et al. 2010, Postmus et al. 2017). VATS has largely replaced thoracotomy as the primary surgical approach, thanks to its less invasive nature, favourable short-term outcomes, such as lesser postoperative pain and shorter hospitalization, and at least comparable oncological efficacy (Berry et al. 2014, Nwogu et al. 2015, Vannucci and Gonzalez-Rivas 2016). As with the invasiveness of the surgical technique, the extent of the resection may also affect treatment outcomes, and a transition towards more tissue-sparing resections has been observed (Helminen et al. 2020). Lobectomy is usually preferred in local disease to ensure oncological efficacy (D'Amico 2008), although recent studies have demonstrated comparable treatment outcomes with sublobar resections in select cases (Veluswamy et al. 2015, Koike et al. 2016).

Although recent studies on local NSCLC have suggested novel radiotherapy (RT) techniques to yield treatment results comparable to surgery (Siva and Ball 2016), RT and chemotherapy (ChT) have typically been the treatments of choice to accompany surgery, or on their own with advanced, non-resectable cancer (Postmus et al. 2017). With novel targeted therapies and immunotherapies showing improved treatment outcomes in recent studies, they are also included in modern guidelines (Planchard et al. 2018).

However, as most patients are diagnosed at an advanced stage beyond curable treatment (Jett 1993), and even patients with early-stage disease usually express at least moderate symptom burden (Walling et al. 2015), with fatigue, pain, loss of appetite, coughing, and insomnia being the most common symptoms at the time of diagnosis (Cooley 2000), palliative or supportive care is an essential part of their treatment (Smith et al. 2012, Ferrell et al. 2017). Many guidelines instruct in the assessment and treatment of these symptoms (Kvale et al. 2007), and early activation of palliative care has even yielded a survival benefit among metastatic NSCLC patients (Temel et al. 2010).

Length of hospitalization, complication rate, perioperative mortality, and survival have long served to measure the outcomes of possibly curative

surgical treatment. However, the above-mentioned advancements in both diagnostic and treatment methods have enabled more patients to survive the disease, thus emphasizing the importance of their health-related quality of life (HRQoL). As many symptoms, such as pain and fatigue, have been shown to have a negative impact on HRQoL (Lin et al. 2013), and to last long after curative treatment (Poghosyan et al. 2013), the importance of proper symptom alleviation is emphasized. Patients tend to value HRQoL highly and may even be unwilling to accept significant deterioration in it in exchange for prolonged survival (Rummans et al. 2000, Bridges et al. 2012). Thus, patient-reported outcomes (PROs), such as HRQoL, have attained more weight as indicators of treatment success. While several studies have assessed the postoperative HRQoL among surgically treated NSCLC patients, with somewhat mixed results, and patient, disease, and treatment features possibly affecting the HRQoL (Poghosyan et al. 2013), studies on long-term results beyond two years are scarce (Li et al. 2002, Aoki et al. 2007, Ostroff et al. 2011).

2 REVIEW OF THE LITERATURE

2.1 Epidemiology of lung cancer

Lung cancer is the number one cause of both cancer incidence and mortality worldwide, with over 1.8 million new cases (13% of all cancer cases) and almost 1.6 million cancer-related deaths (19.4% of all cancer-related deaths) in 2012 (Torre et al. 2015). In 2018, the corresponding numbers are estimated at 2.1 million and 1.8 million (Bray et al. 2018). In Finland, lung cancer had the third highest cancer incidence among men and the fourth among women, after exclusion of skin and haematopoietic or lymphoid cancers, in 2017. Nevertheless, it was the leading cause of cancer-related deaths among men and the second leading cause among women, claiming first place in total cancer-related deaths in Finland (Finnish Cancer Registry). Typically, lung cancer is diagnosed in the elderly, with the median age at diagnosis being 70 years in the US, and only 8.6% of cases were diagnosed before the age of 55 years (Noone et al. 2018).

The incidence rate of lung cancer strongly reflects the rate of tobacco consumption in the population during the past decades. Where consumption has been decreasing, as in, for instance, USA, cancer mortality has also decreased since lung cancer is the main cause of tobacco-related cancer mortality (Peto et al. 2015). Figure 1 illustrates the decrease in smoking-related cancer deaths in USA since the 1950s. On the other hand, in developing countries with rising tobacco consumption, the incidence of lung cancer is still on the rise (Brambilla and Travis 2014).

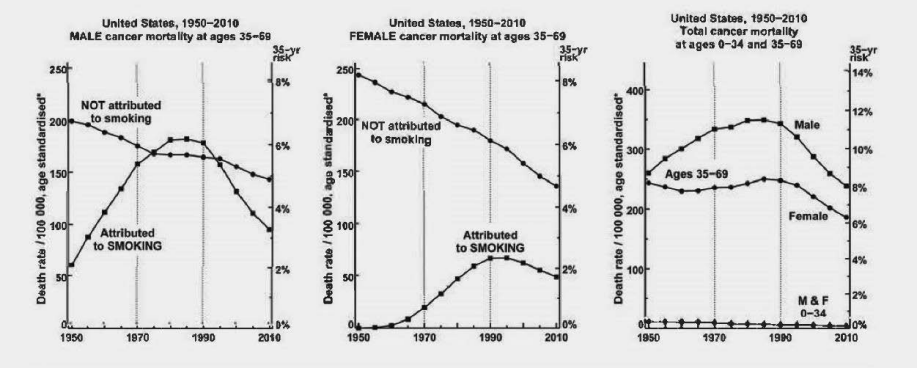

Figure 1 Cancer mortality rates at ages 35-69 years in USA between 1950 and 2010: both attributed and not attributed to smoking. Reprinted with the publisher's permission from Peto R, Lopez AD, Pan H, Thun MJ (2015). The full hazards of smoking and the benefits of stopping: cancer mortality and overall mortality. World Cancer Report 2014: 586-595.

In Finland, the incidence of lung cancer among men is already declining, while due to different trends in tobacco consumption, it is still rising among women, as shown in Figure 2.

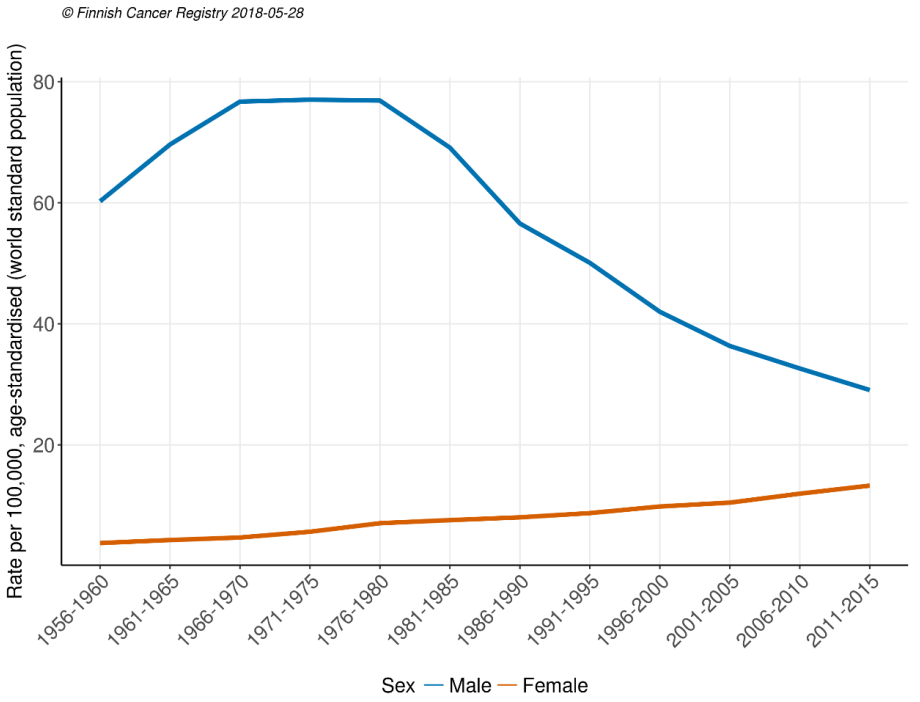

Figure 2 Lung cancer incidence among men and women in Finland in 1956–2015. Reprinted with permission from the Finnish Cancer Registry under the Creative Commons BY 4.0 International license.

Lung cancer has two main subtypes, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), and the latter is further divided into three histological main subtypes: adenocarcinoma (ADC), squamous cell carcinoma (SCC), and large cell carcinoma (LCC) (Travis et al. 2015). Generally, in Western developed countries, ADC is on the rise among both genders, and even SCC and SCLC have been increasing among women (Devesa et al. 2005).

SCLC originates from epithelial cells with neuroendocrine differentiation and constitutes approximately 13-15% of all lung cancer cases. It is the most malignant form of lung neoplasms; mitotic activity is high, early metastasis and paraneoplastic syndromes are common, and the tumour often contains necrosis as an indicator of rapid, uncontrolled growth. SCLC occurs almost exclusively among smokers, and its incidence has been decreasing in industrialized countries over the past decades, likely due to reductions in

tobacco consumption (van Meerbeeck et al. 2011, Bernhardt and Shadia 2016).

ADC constitutes up to 47.9% of new lung cancer cases in USA and has overthrown SCC as the most frequent subtype (Noone et al. 2018), being the typical subtype among women and non-smokers (Devesa et al. 2005, Rivera and Wakelee 2016). It is typically situated in the periphery of the lung (Travis et al. 1995) and has different histological subtypes (Travis et al. 2011) with varying prognosis, lepidic and acinar being more benign than solid, papillary, or micropapillary ADCs (Warth et al. 2012). The correct diagnosis of ADC in situ (AIS), minimally invasive ADC (MIA), and lepidic ADC is important since they seem to lack lymph node (LN) metastases (Yu et al. 2016), which manifests in a 5-year recurrence-free survival rate of 100% for AIS and MIA (Liu et al. 2016). The use of former classifications, including the terms bronchioloalveolar carcinoma (BAC) and mixed subtype adenocarcinoma, was discontinued with the new ADC classification in 2011 (Travis et al. 2013).

SCC is highly associated with tobacco consumption (Khuder 2001), and its incidence is thus rising among women (Devesa et al. 2005). It constitutes 20-30% of all lung cancer cases (Wahbah et al. 2007, Dela Cruz et al. 2011, Noone et al. 2018) and is usually more centrally located than ADC (Travis et al. 1995). Recently, the subtyping was modified to include keratinizing, non-keratinizing, and basaloid SCC, while the use of papillary, clear cell, and small cell subtypes was discontinued (Travis et al. 2015). According to current evidence, the subtypes do not significantly differ in terms of prognosis (Kadota et al. 2014).

LCC constitutes only 1-3% of all lung cancer cases (Dela Cruz et al. 2011, Noone et al. 2018), and its proportion has diminished since the new 2015 World Health Organization (WHO) guidelines have been taken into use for classification of lung tumours (Travis et al. 2015), as some of its former subtypes are now classified under other NSCLC subtypes. LCC can only be diagnosed when the resected tumour cannot be identified as any other subtype through morphological or immunohistochemical (IHC) examinations and should thus not be diagnosed via small biopsy or cytology sample alone (Travis et al. 2015).

There seems to be a separate patient group of never-smokers, who nonetheless develop lung cancer. If regarded as a separate cancer, this group would reach top ten among causes for cancer-related mortality worldwide (Sun et al. 2007). A small minority has even SCLC as the subtype, and they usually present with a positive history of exposure to secondhand smoking and a family history of cancer (Kurahara et al. 2012). Never-smokers with NSCLC usually have ADC as the subtype, and they seem to have a favourable prognosis compared with lung cancer patients with a positive smoking history (Sun et al. 2007, Rivera and Wakelee 2016).

2.2 Aetiology of lung cancer

The incidence of lung cancer increases with age, being proportional to the fourth power of age (Peto 2012), and approximately 70% of cases are diagnosed at the age 65 years or over, with median diagnosis age being 70 years in the US (Noone et al. 2018). Nevertheless, the absolute main risk factor for lung cancer is smoking, as it accounts for approximately 90% of all lung cancer cases (U.S. Department of Health and Human Services 2004), and the relative risk of lung cancer in long-term smokers has been estimated to be as high as 10- to 30-fold that of non-smokers (Mattson et al. 1987). Smoking also causes about 90% of lung cancer deaths in men and almost 80% in women (Thun et al. 1997). The increase in the incidence due to smoking is proportional to the fourth power of smoking duration multiplied by the number of cigarettes smoked daily (Peto 2012).

Besides causing harm to their own health, smokers expose others to tobacco smoke; passive smoking seems to cause an increase of 24% in the risk of lung cancer among non-smokers living with an active smoker (Hackshaw et al. 1997). Quitting smoking is the most efficient way to reduce a smoker's risk of lung cancer. Quitting before the age of 30 years renders only a 3% excess risk compared with never-smokers and quitting before the age of 40 years prevents 90% of the excess risk caused by smoking. Quitting at the age of 60 years still yields on average three extra life years (Peto et al. 2015).

In addition to tobacco smoke, several other exposures increase the risks of lung cancer. The carcinogenic potential of radon, a radioactive chemical element found in indoor air, was originally observed among miners. Since then, multiple studies have focused on estimating its effect on the general population, highlighting its significance as the second leading cause of lung cancer. It causes approximately 10-15% of all lung cancer cases, accounting for cancer incidence especially among non-smokers (Lubin et al. 1995, Committee on Health Risks of Exposure to Radon (BEIR VI) 1999).

Asbestos is another significant occupational risk factor for lung cancer (Doll 1955). Exposure to and inhaling of asbestos have been found to cause an increase in the risk of lung cancer also among non-smokers, yet among smokers the particularly high risk is due to the multiplicative effect of these two factors (Lee 2001). Other environmental risk factors include i.a. the in-home use of solid fuels, e.g. wood or coal, compared with non-solid fuels (Hosgood et al. 2010), and exposure to fine particulate air pollution (Pope et al. 2002).

Female gender seems to predispose to lung cancer with an odds ratio (OR) varying between 1.2 and 1.7 at a certain level of cumulative tobacco smoke exposure, which is considered to result from women being more susceptible to the carcinogens contained in tobacco smoke (Zang and Wynder 1996). However, non-smoking women are also more prone to develop lung cancer than male non-smokers (Wakelee et al. 2007).

Genetic factors may affect one's risk of lung cancer, as can be concluded from the fact that approximately 90% of lung cancer deaths are attributable to smoking (Thun et al. 1997), yet only a minority (10-30%) of smokers die of lung cancer (Peto et al. 2000, Brennan et al. 2006). A large systematic review and meta-analysis established a two-fold increase in the risk of lung cancer among patients, including non-smokers, with a positive family history of lung cancer, especially when disease onset among relatives had occurred at a young age or when there were multiple relatives affected (Matakidou et al. 2005). A large twin study pointed out that although genetic susceptibility plays a role in the risk of lung cancer, the distinct main risk factor is smoking (Hjelmborg et al. 2017).

2.3 Diagnosis and staging of lung cancer

2.3.1 SCREENING

Up to 75% of symptomatic patients diagnosed with lung cancer already have an advanced stage of disease (Jett 1993). In a study by Noone et al. (2018), among all lung cancer patients at the time of diagnosis, the disease stage was localized in 16%, regional in 22%, distant in 57%, and unknown in 5%. Asymptomatic patients seem to have a 5-year survival advantage over symptomatic patients, 66.2% vs. 46.0%, and such a difference was also noted among patients with only stage I disease (Quadrelli et al. 2015). Since disease stage has a strong negative correlation with long-term survival rates (Rami-Porta et al. 2017), early diagnosis at a local stage is crucial for the success of treatment. To answer this need, many screening methods have been tested during the past decades. Early studies concerning screening programmes with chest X-ray with or without sputum cytology failed to improve the survival of patients, and today chest X-ray is not recommended for lung cancer screening (Wu and Raz 2016, Postmus et al. 2017).

Luckily, a recent large study utilizing low-dose computed tomography (LDCT) for annual screening of high-risk patients achieved a significant reduction in lung cancer and overall mortality, compared with annual screening with chest X-ray (National Lung Screening Trial Research Team 2011). In another study, 85% of patients diagnosed with LDCT screening had a local early-stage disease with 10-year survival rates reaching 88% (Henschke et al. 2006). Although the cost-effectiveness of LDCT screening is not yet clearly established (Black et al. 2014), it is already included in some guidelines for high-risk patients with a heavy smoking history (Wu and Raz 2016, Postmus et al. 2017). Besides imaging, other novel techniques for lung cancer

screening, such as the use of a variety of biomarkers from different sources, are being developed (Hasan et al. 2014).

2.3.2 IMAGING

Despite chest X-ray failing to meet the needs of lung cancer screening, it is still usually the first imaging technique utilized in patients expressing lung cancer-associated symptoms (Lim et al. 2010). Since it provides only limited information and has a minimal role in diagnosis and staging of lung cancer, CT is the imaging modality required early in the diagnostic phase. A CT scan from the lower neck to the upper abdomen with intravenous contrast medium is recommended to assess the condition and to determine possible further examinations required (Lim et al. 2010, Stamatis 2015, Postmus et al. 2017). With solitary pulmonary nodules detected either incidentally or by screening, the sensitivity and specificity of a CT scan for identifying a malignant nodule were 98-100% and 54-93%, respectively (Wahidi et al. 2007). However, as the accuracy of a chest CT is not sufficient for mediastinal LN staging, other diagnostic methods are usually required before making treatment decisions, especially prior to operative treatment (De Leyn et al. 2007).

The next step is often 2-deoxy-2-(18F)fluoro-D-glucose positron emission tomography (FDG-PET), which reveals metabolically active lesions, such as distant metastases missed by a CT scan (Weder et al. 1998), thus enhancing the reliability of tumour staging (Stamatis 2015). It is also quite accurate in ruling out mediastinal nodal involvement, as its negative predictive value is comparable to that of medianoscopy, and clinical stage I patients with a reliable negative PET may proceed to curative surgery without invasive nodal exploration. As modern integrated PET-CT scans offer even better diagnostic accuracy, they are recommended over PET whenever available, especially when disease stage enables curative treatment (De Leyn et al. 2007). On the other hand, a recent meta-analysis on LN staging with PET-CT found significant differences, particularly in sensitivity, ranging from 0.13 to 0.98, highlighting the importance of critical assessment of the results (Pak et al. 2015). In Finland, modern guidelines have led to a significant increase in the utilization of PET-CT in preoperative staging (Helminen et al. 2020).

Magnetic resonance imaging (MRI) may be used in the preoperative evaluation of brain metastases among patients suitable for curative treatment; however, its role is controversial (MacDonald and Hansell 2003, Postmus et al. 2017), particularly considering its high price and the low incidence of asymptomatic brain metastases (Vernon et al. 2016). It may also be used to determine the relation of the tumour and mediastinal structures in more detail than with a CT scan (MacDonald and Hansell 2003).

2.3.3 TISSUE SAMPLING

After detecting a potentially malignant lung tumour via the methods described above, the next step is usually obtaining a specimen of the primary tumour, or from a metastasis, for further analysis and pathological confirmation (Postmus et al. 2017). As traditional light microscopy remains the gold standard for lung cancer diagnosis (Rosai 2007), a variety of methods serve for obtaining histological or cytological samples.

Non-invasive sputum sampling may provide a diagnosis in high-risk patients with a central tumour when other diagnostic methods are considered too risky, but a negative finding requires confirmation by other means (Rivera and Mehta 2007). The least invasive methods for obtaining a cytological sample, especially from a central lesion with a visible endobronchial component, include bronchoscopic forceps biopsy, brushing, and bronchoalveolar lavage. Today, these are often combined with transbronchial needle aspiration (TBNA) for higher diagnostic accuracy (Rosai 2007).

Minimally invasive non-surgical methods sample the tumour or LNs via needle biopsies. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and endoscopic oesophageal ultrasound-guided fine-needle aspiration (EUS-FNA) have almost entirely replaced “blind” TBNA with no ancillary imaging (Stamatis 2015). Being minimally invasive, EBUS-TBNA and EUS-FNA are recommended as the next diagnostic and staging procedure after imaging, whenever the tumour or nodal placement allows (Lim et al. 2010, Postmus et al. 2017). EBUS-TBNA performs well in staging mediastinal LNs, with specificity reaching 100% and sensitivity 88-93%, and the complication rate is very low (Gu et al. 2009, Adams et al. 2009). When combined with EUS-FNA, the sensitivity may improve to 96% (Herth et al. 2010), and the combination may outperform PET-CT in mediastinal LN staging (Ohnishi et al. 2011). In a study by Annema et al. (2010), the combination even outperformed the gold standard of mediastinal LN staging, mediastinoscopy, yet the difference was not statistically significant. However, when EBUS-TBNA and EUS-FNA were carried out first, and possible negative findings were verified with mediastinoscopy, the combination yielded significantly higher sensitivity than mediastinoscopy alone, and a significant portion of unnecessary thoracotomies were avoided (Annema et al. 2010). Consequently, needle biopsies are recommended over surgical techniques in mediastinal LN staging (Postmus et al. 2017), and if they fail to provide diagnostic samples or present with a negative nodal status, further testing may be required, depending on the clinical stage and possible treatment options (Rivera and Mehta 2007, Lim et al. 2010, Postmus et al. 2017).

With small or peripheral tumours, a CT-guided transthoracic fine-needle aspiration (TTFNA) may outperform endoscopic techniques in acquiring a sample (Ohno et al. 2003) and is thus recommended whenever necessary for a cytological or histological diagnosis (Rivera and Mehta 2007). TTFNA yields

diagnostic accuracy of up to 94.2% when combined with a core needle biopsy (CNB), and the most frequent complication is pneumothorax, with frequency ranging from 17.9% to as high as 54.3% (Yamagami et al. 2003).

In the case of positive mediastinal LN in CT or PET scan, a negative nodal status in EBUS-TBNA or EUS-FNA is usually verified prior to further treatment decisions through either video-assisted mediastinoscopy (VAM) or video-assisted thoracoscopic surgery (VATS) (Lim et al. 2010, Stamatis 2015, Postmus et al. 2017). VATS, as well as other invasive surgical methods, enables also the acquisition of an intraoperative surgical biopsy for a frozen section analysis, providing high concordance with final pathological diagnosis (Liu et al. 2016, Postmus et al. 2017).

2.3.4 HISTOLOGICAL CLASSIFICATION

The main division of lung cancer into SCLC and NSCLC, and further subtyping of the latter into ADC, SCC, and LCC, is introduced in the epidemiology section and presented briefly in Table 1, although the complete classification of lung cancers also includes many rarer types of lung tumours (Travis et al. 2015).

Table 1 Main histological subtypes of lung cancer.

Histological type	Subtype	Descriptors[1]	Prevalence
Small cell carcinoma			13-15%[2]
Adenocarcinoma			48%[3]
	AIS[A]	○ diameter ≤ 3 cm ○ pure lepidic pattern	
	MIA[B]	○ diameter ≤ 3 cm ○ predominantly lepidic pattern ○ invasion size ≤ 5 mm ○ no lymphatic, vascular, or pleural invasion ○ no tumour necrosis	
	Lepidic predominant		
	Acinar predominant		
	Papillary predominant		
	Micropapillary predominant		
	Solid predominant		
Squamous cell carcinoma			23%[3]
	Keratinizing		
	Non-keratinizing		
	Basaloid		
Large cell carcinoma			1.5%[3]

[A] = adenocarcinoma in situ; [B] = minimally invasive adenocarcinoma

[1] = Travis et al. 2013; [2] = van Meerbeeck et al. 2011; [3] = Noone et al. 2018

2.3.5 HISTOLOGICAL DIFFERENTIATION

Earlier WHO classifications of lung tumours have largely relied on histological and cytological evaluation of haematoxylin-eosin stained tissue samples under the microscope, until the recent incorporation of modern IHC and genetic methods in the classification (Travis et al. 2015). Despite modern and developing diagnostic methods, traditional light microscopy remains an important diagnostic tool and the first step in histological tumour classification thanks to its low cost, availability, and the comprehensive information it yields with a single examination (Rosai 2007).

However, with small biopsies or poorly differentiated morphology, modern ancillary techniques, e.g. molecular markers, IHC, and genetic analyses, may shed more light on the diagnosis, and expert recommendations guide the effective application of these methods (Rekhtman et al. 2011, Travis et al. 2015, Dietel et al. 2016). With emerging personalized therapies targeting the genetic and molecular changes in the tumour cells, the need for individual and detailed disease analyses seems to be on the rise (Maemondo et al. 2010, Rosell et al. 2012, Shaw et al. 2014).

2.3.6 STAGING

The classification of lung cancers according to the anatomical extent of the disease began in the 1950s, but staging according to primary tumour, nodal involvement, and possible metastases began with the first tumour, node, and metastasis (TNM) system in 1966 (Woodard et al. 2016). The seventh version of TNM classification (TNM7) (Mirsadraee et al. 2012), introduced in 2010, was the first one based on large international patient material, validated both internally and externally (Woodard et al. 2016). The disease is further staged according to the TNM classification to group patients with a similar prognosis into the same stage category (Mirsadraee et al. 2012).

As the previous TNM7 was based on patient material collected mainly before the widespread application of PET and other modern diagnostic tools, the need for a new and up-to-date classification was apparent. The eighth and latest version of TNM classification (TNM8) was introduced in 2017, and Table 2 shows the classification in detail. Most changes were made in the tumour component, where i.a. new size groups were created, and ADC received the new subgroups of AIS and MIA. The nodal component remained unchanged, while in the metastasis component, the distant metastasis was further divided into single and multiple extrathoracic metastases (Rami-Porta et al. 2017).

Table 2 Categories, subcategories, and descriptors of TNM8 for lung cancer.

CATEGORY	SUBCATEGORY	DESCRIPTORS
T: Primary tumour		
Tx		Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings, but not visualized by imaging or bronchoscopy
T0		No evidence of primary tumour
Tis		Carcinoma in situ: • Tis (AIS): adenocarcinoma • Tis (SCIS): squamous cell carcinoma
T1		Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in the main bronchus); the uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a
	T1mi	Minimally invasive adenocarcinoma
	T1a	Tumour 1 cm or less in greatest dimension
	T1b	Tumour more than 1 cm, but not more than 2 cm in greatest dimension
	T1c	Tumour more than 2 cm, but not more than 3 cm in greatest dimension
T2		Tumour more than 3 cm, but not more than 5 cm; or tumuor with *any* of the following features (T2 tumours with these features are classified T2a if 4 cm or less or if size cannot be determined and as T2b if greater than 4 cm, but not larger than 5 cm): • Involves main bronchus regardless of distance to the carina, but without involving the carina • Invades visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, either involving part of the lung or the entire lung
	T2a	Tumour more than 3 cm, but not more than 4 cm in greatest dimension
	T2b	Tumour more than 4 cm, but not more than 5 cm in greatest dimension
T3		Tumour more than 5 cm, but not more than 7 cm in greatest dimension or one that directly invades any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumours), phrenic nerve, parietal pericardium; or associated separate tumour nodule(s) in the same lobe as the primary
T4		Tumours more than 7 cm or one that invades any of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral

		body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary
N: Regional lymph nodes		
Nx		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2		Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3		Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral, or contralateral scalene, or supraclavicular lymph node(s)
M: Distant metastasis		
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; most pleural (pericardial) effusions with lung cancer are due to tumour; in a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumour, and the fluid is non-bloody and is not an exudate; where these elements and clinical judgment dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging descriptor
	M1b	Single extrathoracic metastasis in a single organ and involvement of a single distant (non-regional) node
	M1c	Multiple extrathoracic metastases in one or several organs

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The staging system was also updated to correspond to the new TNM classification and to better correlate with the prognosis of each group (Rami-Porta et al. 2017). Table 3 shows the division of tumours into different stages according to the TNM descriptors.

Table 3 TNM8 stage grouping for lung cancer.

STAGE	T	N	M
Occult carcinoma	TX	N0	M0
0	Tis	N0	M0
IA1	T1mi	N0	M0
	T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a,b,c	N1	M0
	T2a,b	N1	M0
	T3	N0	M0
IIIA	T1a,b,c	N2	M0
	T2a, b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
IIIB	T1a,b,c	N3	M0
	T2a,b	N3	M0
	T3	N2	M0
	T4	N2	M0
IIIC	T3	N3	M0
	T4	N3	M0
IVA	Any T	Any N	M1a
	Any T	Any N	M1b
IVB	Any T	Any N	M1c

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2.4 Treatment of non-small cell lung cancer

Among the multiple possible treatment modalities for lung cancer, the gold standard is radical surgery, whenever possible (Lim et al. 2010, Postmus et al. 2017). Other treatment options include radiotherapy (RT), chemotherapy (ChT), targeted therapy, and immunotherapy (Reckamp 2016). They may be applied with curative intent in some cases, but are usually used to accompany surgery or to enhance survival and quality of life (QoL) among incurable patients (Lim et al. 2010, Postmus et al. 2017).

While physicians strive to gain more life years for their lung cancer patients through different treatment modalities, patients tend to value highly the quality of their remaining years (Rummans et al. 2000, Bridges et al. 2012). Differences between factors affecting the treatment decision among patients and physicians have been broadly studied; physicians tend to rely more on traditional objective parameters, such as disease factors, e.g. stage and histology, and patient factors, e.g. age and level of comorbidities, while factors affecting patients' decision-making are harder to interpret, leading to distinct differences between expectations concerning the treatment (Zafar et al. 2009). For instance, physicians often avoid surgical treatment among the elderly, although studies demonstrate that old age does not necessarily mean poor treatment outcome in surgically treated lung cancer patients (Möller and Sartipy 2010), and the same seems to apply to ChT among older patients (Goldberg et al. 2006).

Cykert et al. (2010) found patients' beliefs in the uncertainty of the diagnosis and in surgical treatment to result in lower QoL one year postoperatively. Moreover, among early-stage NSCLC patients experiencing poor communication by medical staff about cancer the probability of undergoing surgical treatment decreased, while 29% of patients declining surgery reported comorbid illness as the reason for doing so (Cykert et al. 2010). Cancer patients' perceptions of the possible trade-off between survival advantage and QoL seem to vary widely and are influenced by the amount and severity of current and expected symptoms (Rummans et al. 2000, Love et al. 2007, Bridges et al. 2012). Perceptions of the patient's spouse and children and whether or not the patient has children living at home seem to affect their decisions (Zafar et al. 2009). Salkeld et al. (2004) found women to be more prone than men to shared decision-making, and younger and treatment-naïve patients to be more willing also to participate in decision-making.

Well-established guidelines determine necessary examinations preceding possible treatment with curative intent (Brunelli et al. 2009, Lim et al. 2010). For example, forced expiratory volume in one second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO) predict postoperative morbidity and mortality (Postmus et al. 2017), and exercise tests may offer

valuable additional information on the operability of moderate-to-high risk patients (Lim et al. 2010). As lung resection usually deteriorates lung function to some extent, predicted postoperative values of more than 40% in both FEV1 and DLCO are usually regarded as acceptable (British Thoracic Society and Society of Cardiothoracic Surgeons of Great Britain and Ireland Working Party 2001, Postmus et al. 2017), even though deterioration in FEV1 seems to predict postoperative function status poorly (Pelletier et al. 1990). Different preoperative scoring systems also help to predict perioperative risk of death or cardiac morbidity (Falcoz et al. 2007, Brunelli et al. 2011).

2.4.1 SURGERY

Although surgery is the gold standard for curative treatment of lung cancer, only approximately a quarter of patients are diagnosed with local and resectable disease since symptoms leading to diagnosis usually develop late in the course of disease (Jett 1993). Furthermore, poor physician-patient communication, together with patient's incorrect perceptions of the certainty of the diagnosis and possible deterioration of QoL due to surgery, may further impair the rate of surgical treatment, as mentioned above (Cykert et al. 2010). In Finland, only 14.4% of all lung cancer patients were operated on between 2010 and 2014 (Gunn et al. 2018), although a recent study found the rate to reach 19.7%, at least in the region covered by the study, largely due to more high-risk patients being surgically treated (Helminen et al. 2020).

Radical surgery with curative intent is recommended for operable patients with local stage I and II disease (Scott et al. 2007, Postmus et al. 2017), and in some cases for locally advanced stage IIIA disease (Robinson et al. 2007, Postmus et al. 2017). In rare cases, surgery may be part of a multimodality treatment for stage IIIB disease (Jett et al. 2007, Postmus et al. 2017). Complete resection should always be the aim, as it yields significantly better prognosis than uncertain resection (Rami-Porta et al. 2005, Gagliasso et al. 2017).

2.4.1.1 Extent of resection

With resectable disease, lobectomy is usually recommended over more limited resections, segmentectomy, and wedge resection, as the latter procedures may yield higher local recurrence rates, thus diminishing the long-term survival rates (Ginsberg and Rubinstein 1995, D'Amico 2008). As the study favouring lobectomy was conducted in 1995, newer studies have suggested some changes to the previous principle; anatomical segmentectomy may suffice in the presence of AIS or MIA (Veluswamy et al. 2015), small radiologically pure solid NSCLC (Landreneau et al. 2014, Koike et al. 2016), a solely ground glass

opacity lesion (Postmus et al. 2017), yet lobectomy is required in the presence of SCC (Veluswamy et al. 2015). Even wedge resection may be plausible for peripheral stage I tumours in frail patients (Onugha and Lee 2016), as it may not expose patients to inferior survival (Nakamura et al. 2005, El-Sherif et al. 2006). The transition toward enabling more limited resections was also evident in a recent study focusing on improvements in treatment due to introduction of modern treatment guidelines (Helminen et al. 2020).

Pneumonectomy is still sometimes indicated (Baumann et al. 2001), although usually regarded as undesirable compared with more tissue-sparing resections due to lower postoperative QoL (Balduyck et al. 2007, Brunelli et al. 2007) and higher operative mortality combined with lower long-term survival (Deslauriers et al. 2004). Whenever possible, bronchial sleeve lobectomy is regarded as favourable in more extensive resections (Terzi et al. 2002, Onugha and Lee 2016).

Sufficient intraoperative mediastinal LN assessment is considered crucial in ensuring complete resection (Gagliasso et al. 2017); however, the primality of mediastinal LN dissection versus mediastinal LN sampling is still controversial, and the latter seems to suffice at least in stage I disease (Huang et al. 2014). The need for and extent of intraoperative LN assessment may also be influenced by the preoperative evaluation of LN status (Postmus et al. 2017).

2.4.1.2 Surgical techniques

Open surgery, i.e. thoracotomy and less often median sternotomy, served long as the technique for lung cancer surgery. Posterolateral, anterior, or axillary thoracotomies with different incisions serve slightly different situations, with each causing considerable tissue damage (Onugha and Lee 2016). A common problem with thoracotomy is the high incidence of postoperative pain due to the size and location of the incision. A study by Bendixen et al. (2016) found 63% of thoracotomy patients reporting clinically relevant pain during the first 24 hours after surgery, while the prevalence of chronic post-thoracotomy pain is decribed to range between 5% and 65% (Macrae 2008). Different types of regional anaesthesia, such as thoracic epidural anaesthesia or intercostal nerve block, may reduce the incidence of post-thoracotomy pain syndrome (PTPS), although a study comparing these methods reported the prevalence to still reach 23-40% at six months postoperatively (Khoronenko et al. 2018).

Since its introduction in the early 1990s, VATS has largely replaced open surgery as the cornerstone of intrathoracic surgery (Vannucci and Gonzalez-Rivas 2016) and is recommended especially for patients with stage I tumours (Postmus et al. 2017). A recent Finnish study found the rate of VATS to reach 81.1% among operated NSCLC patients (Helminen et al. 2020). The three-

port approach (Hansen and Petersen 2012) is commonly utilized, yet even uniportal VATS is possible and has been utilized successfully (Gonzalez-Rivas et al. 2013). Some extensive or technically demanding resections, such as sleeve resections, are sometimes regarded to require thoracotomy (Gonzalez-Rivas et al. 2016). However, with advances in techniques and instruments, even double sleeve lobectomies via VATS have been reported (Gonzalez-Rivas et al. 2014). Normally, both thoracotomy and VATS are regarded as suitable, depending on the expertise of the surgeon (Postmus et al. 2017).

Compared with traditional open thoracotomy, VATS offers several advantages: fewer perioperative complications (Whitson et al. 2008, Nwogu et al. 2015, Falcoz et al. 2016), better perioperative survival (Falcoz et al. 2016), shorter need for chest tube (Demmy and Curtis 1999, Whitson et al. 2008) and hospitalization (Whitson et al. 2008, Nwogu et al. 2015), and less postoperative pain (Bendixen et al. 2016). Chronic pain at six months and within one year postoperatively seems to be less common after VATS than after thoracotomy (Shanthanna et al. 2016, Bendixen et al. 2016). Since VATS is less invasive, preserving lung function better than thoracotomy (Kaseda et al. 2000), it is also regarded as more suitable for patients with preoperatively deteriorated lung function (Ceppa et al. 2012, Oparka et al. 2013) and for patients with comorbitidies (Falcoz et al. 2016). The number of total LNs sampled through VATS is on average smaller than with thoracotomy (Zhang et al. 2016), and nodal upstaging seems to be rarer with VATS (Licht et al. 2013). With at least equal oncological efficacy (Licht et al. 2013, Berry et al. 2014) and long-term disease-free survival (Demmy and Nwogu 2008), and even better prognosis (Kaseda et al. 2000, Whitson et al. 2008, Valo et al. 2020), the comparably lower overall cost (Swanson et al. 2012) of VATS establishes its status as the new gold standard of operative lung cancer treatment (Vannucci and Gonzalez-Rivas 2016). In addition, with evolving techniques, robotic surgery is also becoming more common, and it has already demonstrated good performance and long-term outcomes equalling those of the previous techniques (Park et al. 2012).

2.4.2 RADIOTHERAPY

Today, RT has a potential role in almost every disease stage; it may serve as curative treatment in local disease, as adjuvant therapy before or after surgery for more advanced disease, as part of multimodality treatment together with ChT for advanced disease, or as palliative treatment in advanced disease and with symptoms originating from a local tumour mass (Sampath 2016).

Conventional RT given in multiple fractions over several weeks has failed to yield adequate local control or overall survival (OS) benefit in local or locally advanced NSCLC (Sibley et al. 1998, Rowell and Williams 2001). Fortunately, the introduction of stereotactic ablative radiotherapy (SABR), also known as

stereotactic body radiotherapy (SBRT), has enabled more potent RT treatment, and several advancements in the technique have further improved its results and usability (Sampath 2016).

SABR is currently the recommended non-surgical treatment for local stage I tumours among patients who are inoperable or refusing surgery (Postmus et al. 2017), as even results comparable to surgery have been reported among early-stage NSCLC (ES-NSCLC) patients (Louie et al. 2015, Sampath 2016). SABR seems to perform comparably to surgery among operable patients (Onishi et al. 2011), and evidence supports its role even as an alternative treatment method for surgery in ES-NSCLC (Verstegen et al. 2015, Lindberg et al. 2015, Siva and Ball 2016).

Postoperative RT among totally resected ES-NSCLC patients with N0-1 has been demonstrated to be detrimental, and thus, is not recommended (PORT Meta-analysis Trialists Group 2005, Postmus et al. 2017), although it may be beneficial among totally resected N2 patients (Le Péchoux 2011) and in case of incomplete resection (Postmus et al. 2017).

When the disease is locally advanced and unresectable, RT combined with ChT provides significant OS benefit (Sause et al. 2000, Aupérin et al. 2006). Apart from advanced, unresectable disease, chemoradiotherapy may be utilized as preoperative induction therapy to enable surgical treatment in some cases with a preoperatively diagnosed single station N2 disease (Postmus et al. 2017).

2.4.3 SYSTEMIC THERAPY

Early cytotoxic ChT agents, such as alkylating agents and vinca alkaloids, did not benefit patients significantly, but with the introduction of platinum-based cisplatin, the results improved in terms of both survival and QoL (Marino et al. 1994, Non-small Cell Lung Cancer Collaborative Group 1995).

2.4.3.1 Systemic therapy in multimodality treatment

Today, vast evidence supports the use of ChT, together with surgery, RT, or both, as part of multimodality treatment with curative intent in stage II-III disease with N1-2, and in stage IB with tumour diameter larger than 4 cm, yielding a 5-year survival benefit of approximately 5% (Douillard et al. 2006, Pignon et al. 2008, Cortés et al. 2015), and this is incorporated into modern treatment guidelines (Lim et al. 2010, Postmus et al. 2017). In this setting, ChT is recommended and usually given after surgery as adjuvant therapy, although preoperative neoadjuvant ChT may provide similar results (Gilligan et al. 2007).

The recommended ChT regimen is a two-drug combination with cisplatin as the preferred platinum-based agent, combined with another cytotoxic agent such as vinorelbine (Pignon et al. 2008, Lim et al. 2010, Dietrich and Gerber 2016, Postmus et al. 2017). Novel targeted therapy and immunotherapy agents are not yet recommended outside research settings in guidelines for local or locally advanced NSCLC (Postmus et al. 2017), although with promising results from recent studies, they may replace conventional cytotoxic agents to some extent in upcoming years (Dietrich and Gerber 2016).

2.4.3.2 Systemic therapy in advanced and inoperable disease

With advanced and inoperable NSCLC, the treatment options are ChT, RT, or their combination. The recommended first-line ChT is a cytotoxic doublet regimen including a platinum-based agent (Pignon et al. 2008, Lim et al. 2010, Postmus et al. 2017), typically combined with either docetaxel, paclitaxel, gemcitabine, vinorelbine, or pemetrexed (non-squamous NSCLC) (Dietrich and Gerber 2016). Since cisplatin has usually been associated with higher incidence of adverse effects and increased hospitalization (Santana-Davila et al. 2014), carboplatin may be recommended for advanced disease (Dietrich and Gerber 2016).

As progression is inevitable with advanced NSCLC despite treatment, maintenance therapy options for prolonging the initial treatment response have been studied widely, and continuation with the initial, non-platinum-based agent or with a new non-platinum-based agent is an option in specific cases (Besse et al. 2014, Dietrich and Gerber 2016, Planchard et al. 2018).

After disease progression, second-line ChT may be applied (Dietrich and Gerber 2016), although the OS typically remains low, as demonstrated by the median OS ranging between 34.7 and 37.3 weeks in a meta-analysis (Di Maio et al. 2009), and by docetaxel prolonging median survival from 4.6 to 7.0 months, compared with the best supportive care (Shepherd et al. 2000).

With novel research techniques providing knowledge of molecular changes and driver mutations providing tumour cells with growth and survival advantage and manifesting as tumorigenesis in NSCLC (Vogelstein et al. 2013, Gallant and Lovly 2018), many targeted therapy agents have been developed, and some of them are already standard, and even first-line, treatment in advanced NSCLC (Besse et al. 2014, Stinchcombe 2016, Planchard et al. 2018).

As with targeted therapy, modern research has enabled the development of immunotherapy, which focuses on enhancing the immune response against tumour cells (Castellanos and Horn 2016). It has already been included in modern treatment guidelines under specific disease settings (Planchard et al. 2018), and promising study results demonstrating superiority over

conventional ChT agents seem to be extending these settings (Reck et al. 2016, Socinski et al. 2018, Hellmann et al. 2018, Gandhi et al. 2018, Paz-Ares et al. 2018, Socinski et al. 2018, Planchard et al. 2018, Hellmann et al. 2018). Even anticancer vaccines have been investigated, albeit without great success thus far (Castellanos and Horn 2016).

2.4.4 PALLIATIVE TREATMENT

WHO defines palliative care as "an approach that improves the QoL of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual" (WHO Definition of Palliative Care).

As already mentioned, the vast majority of lung cancers are diagnosed at an advanced stage, thus being incurable (Jett 1993, Noone et al. 2018). The primary tumour, locoregional metastases, distant metastases, and treatment itself may all cause symptoms (Kvale et al. 2007). Compared with other malignancies, patients with lung cancer express typically more symptoms (Degner and Sloan 1995). Among newly diagnosed patients, the most common symptoms include fatigue, pain, loss of appetite, coughing, and insomnia (Cooley 2000).

As most lung cancer patients are symptomatic, with over half experiencing moderate to severe symptoms (Walling et al. 2015), moving palliative care upstream in the treatment schedule has been recommended, as it should be a concurrent part of treatment from the moment of diagnosis (Hennessy et al. 2013, Ferrell et al. 2017). The American Society of Clinical Oncology (ASCO) guidelines highlight the early integration of palliative care into cancer treatment, as this reduces i.a. visits to the emergency department, which commonly occur among lung cancer patients (Barbera et al. 2010, Smith et al. 2012). Evidence also supports this objective, as early palliative care among metastatic NSCLC patients has provided better HRQoL and survival, while reducing burdensome aggressive treatments at the end of life (Temel et al. 2010). Adequate assessment and documentation of symptoms comprise the first step in quality palliative care (Shinde and Dashti 2016).

2.5 Symptoms in lung cancer patients

2.5.1 ASSESSMENT OF SYMPTOMS

Since lung cancer patients typically suffer from multiple symptoms (Degner and Sloan 1995, Cooley 2000), proper symptom assessment is crucial and the initial step in effective treatment planning (Simoff et al. 2013). As health care professionals are prone to underestimating patients' symptom burden, patient-reported measures should guide the treatment (Fallowfield et al. 2001, Laugsand et al. 2010, Simoff et al. 2013), and many guidelines exist in symptom assessment (Naughton and Homsi 2002, Simoff et al. 2013, Shinde and Dashti 2016). In a study by Yount et al. (2014), regular symptom monitoring failed to reduce symptom burden among patients, while Denis et al. (2019) found regular web-based symptom monitoring to enhance survival among patients with stage IIa to IV lung cancer.

Numerous instruments have been developed to assess different symptoms, with most utilizing either visual analogue scales (VAS), numerical rating scales (NRS), or categorical rating scales to measure the symptoms (Chang 2006). Some instruments measure only one symptom, such as the Beck Depression Inventory for depression (Beck et al. 1961), the Baseline Dyspnea Index for dyspnea (Mahler et al. 1984), and the Brief Fatigue Inventory for fatigue (Mendoza et al. 1999), while others, such as the Edmonton Symptom Assessment Scale (ESAS) (Bruera et al. 1991), the Memorial Symptom Assessment Scale (MSAS) (Portenoy et al. 1994), or the Rotterdam Symptom Checklist (de Haes et al. 1990), assess multiple symptoms at the same time. Some HRQoL instruments, such as the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire QLQ-C30 (Aaronson et al. 1993), have also been used to measure symptoms (Laugsand et al. 2010, Simoff et al. 2013), although not originally developed for this purpose.

For example, pain intensity is typically determined and quantified with either a 10-cm-long VAS, an NRS from zero to ten, or a categorical scale, ranging from no pain to the worst possible pain (Chang 2006, Swarm et al. 2019). Simultaneously, proper assessment of pain includes history-taking and a physical examination, supplemented by necessary laboratory and imaging studies (Portenoy 2011, Shinde and Dashti 2016).

2.5.2 PAIN

Between 17% and 20% of lung cancer patients suffer from moderate to severe pain at a given moment, and pain has been reported among almost two-thirds

of even early-stage patients (Kvale et al. 2007, Walling et al. 2015). Huang et al. (2014) reported 25% of NSCLC survivors to suffer from chronic pain at least one year after surgery, while Kenny et al. (2008) noted that one-third of NSCLC survivors without recurrence reported worse or equal pain, compared with the preoperative situation, two years after surgery. As already mentioned earlier, post-thoracotomy pain syndrome (PTPS) is a common complication after lung cancer surgery (Macrae 2008, Khoronenko et al. 2018), although despite its name, Hopkins et al. (2015) found similar incidence of PTPS among lung cancer patients operated on through either thoracotomy or thoracoscopy within one year after treatment. Acute pain within the first days after surgery seems to be a significant predictor of chronic pain (Katz et al. 1996).

Pain may originate from local tissue damage caused by the tumour and associated metastases, but often surgery, ChT, or RT is also accompanied by pain (Kvale et al. 2007). Many guidelines cover cancer pain treatment (Stjernsward 1988, Portenoy 2011) and how to improve it (Gordon et al. 2005). Despite years of research, opioid-based pharmacotherapy remains the standard pain treatment in cancer patients, although the numerous side effects limit its use to only patients with active cancer (Portenoy 2011).

Whenever possible, primary disease-modifying treatment, such as RT in NSCLC, is recommended (Kvale et al. 2007, Portenoy 2011), although additional treatment options are often required. WHO introduced the well-known algorithm for cancer pain medication, the Pain Relief Ladder, in 1986 (WHO's cancer pain ladder for adults). It is a fairly simple model consisting of three steps, as shown in Figure 3.

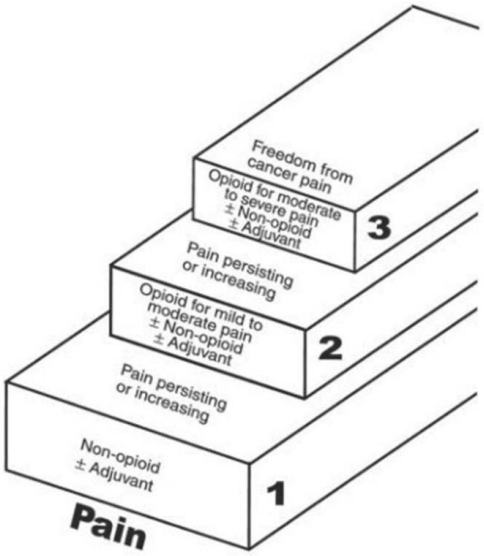

Figure 3 WHO's Pain Relief Ladder. Reprinted from Chest, Volume 132, Issue 3, Supplement. Paul A. Kvale, Paul A. Selecky, Udaya B.S. Prakash. Palliative Care in Lung Cancer: ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition). Pages 368S-403S. Copyright 2007, with permission from Elsevier.

Since the 1980s, many more elaborate recommendations have been published. For mild pain, acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs), possibly with adjuvant analgesics, are recommended, if not contraindicated. As the pain increases, opioids gain more weight in the treatment, and they are regarded as the most important pharmacotherapy in cancer pain. Oral administration is usually recommended due to convenience and cost-effectiveness, and constipation should always be considered as a common adverse effect (Kvale et al. 2007, Portenoy 2011, Swarm et al. 2019).

Although mild opioids are usually recommended initially, modern recommendations offer the possibility to prescribe morphine or oxycodone at low doses already with moderate pain (Portenoy 2011). Even methadone may be used in this setting, as it has some favourable properties and shares the same efficacy as other strong opioids (Bruera, Eduardo et al. 2004, Mercadante et al. 2008, Portenoy 2011). Sufficient long-acting around-the-clock medication is the basis of cancer pain treatment, yet patients often suffer

from transient exacerbations of pain, known as breakthrough pain, which may require acute rescue medication. Usually opioids also serve this purpose, both in oral and in more fast-absorbing forms such as nasal or sublingual fentanyl (Zeppetella 2009).

Besides systemic pharmacotherapy, other means, e.g. nerve blocks and psychological strategies, constitute an essential part of successful pain treatment (Shinde and Dashti 2016).

2.5.3 RESPIRATORY SYMPTOMS

Lung cancer causes typical respiratory symptoms by directly obstructing and damaging airways, by causing atelectasis, pleural effusions, or pneumonia, or by adverse effects of the treatments. Besides disease features, such as stage and location, many patient features, e.g. comorbidities, age, and gender, may predispose to these symptoms (Kvale et al. 2007). Especially with advanced NSCLC, patients describe high incidence of respiratory symptoms; prevalence of shortness of breath, cough, and blood in sputum has been reported to reach values as high as 95%, 93%, and 63%, respectively (Iyer et al. 2014). On the other hand, NSCLC survivors may also suffer from prolonged respiratory symptoms long after surgery (Sarna et al. 2004, Yun et al. 2012), and some studies have found over half of the patients to suffer from increased levels of dyspnoea at least two years after surgery (Kenny et al. 2008, Ostroff et al. 2011). Other studies have associated old age and extensive surgery with worse postoperative dyspnoea among NSCLC survivors (Balduyck et al. 2008, Ferguson et al. 2009).

Dyspnoea, also known as breathlessness, is probably the most disturbing respiratory symptom in lung cancer. Its aetiology has been widely investigated and shown to be multifactorial (Parshall et al. 2012). Severity of dyspnoea is strongly associated with worse QoL (Gupta et al. 2007), and it should be regularly assessed with a standardized scale. After assessment, treatment options must be evaluated. The preferable first step is treating the underlying pathological process such as pleural effusion or local obstruction of an airway. While imaging techniques may be readily available, bronchoscopy typically serves as both the primary diagnostic method and treatment method for airway obstruction caused by intraluminal cancer growth. Bronchoscopic debridement and balloon dilatation enable fast symptom relief and further treatment via other bronchoscopic techniques, including placement of either metallic or silicone stents, laser or photodynamic therapy, electrocautery, cryotherapy, argon plasma coagulation, and brachytherapy, although some of these techniques can also be utilized as the initial treatment (Kvale et al. 2007).

Second, exercising and pulmonary rehabilitation may provide symptom alleviation. Third, pharmacological intervention is usually possible, yet its

universal efficacy remains uncertain. Opioids are considered for persisting dyspnoea without a treatable cause in patients with advanced cancer, although the effect seems to be minor and comes at the cost of such adverse effects as constipation and nausea (Parshall et al. 2012, Barnes et al. 2016). Optimization of inhaled medication, such as bronchodilators, is essential especially among patients with an underlying obstructive airway disease, while oxygen is not generally recommended for patients with dyspnoea without hypoxaemia (Kvale et al. 2007, Parshall et al. 2012).

Cough, both productive and non-productive, is also common among lung cancer patients, as up to 40% of early-stage patients report moderate to severe cough (Walling et al. 2015), and it deteriorates QoL significantly (Iyer et al. 2014, Walling et al. 2015, Shinde and Dashti 2016). Thus, a questionnaire has been developed to assess cough in a standardized and validated manner (Molassiotis et al. 2013). As with dyspnoea, the mechanisms and causes are multifactorial. The treatment instructed in expert guidelines follows the same steps as with dyspnea; primarily treat possible reversible causes, both cancer-specific and comorbidity-related, and then alleviate symptoms with mainly pharmacological treatment such as opioids and antitussives (Molassiotis et al. 2010, Harle et al. 2012).

Haemoptysis causes considerable concern in patients and their families, yet it rarely demands aggressive treatment (Corner et al. 2005, Shinde and Dashti 2016). Minor haemoptysis, the prevalent form, is typically managed with radiotherapy (Reinfuss et al. 2011). Large-volume haemoptysis is defined as an amount greater than 200 ml in 24 hours and often requires intervention. Usually, the first diagnostic and therapeutic step is bronchoscopy, followed by angiography with therapeutic embolization, if necessary. Surgical treatment is generally not an option since patients presenting with major haemoptysis typically have advanced disease and are already deemed unsuitable for surgery (Kvale et al. 2007).

2.5.4 GASTROINTESTINAL SYMPTOMS

Lung cancer patients also suffer from gastrointestinal symptoms, the most typical ones being nausea and vomiting, diarrhoea, and constipation (Rangwala et al. 2012, Shinde and Dashti 2016). Nausea, reported by 32.9-43.1% of patients (Walling et al. 2015), is typically associated with chemotherapy, although the aetiology is usually multifactorial, resulting also from the cancer itself, disease-induced debility, and comorbidities (Glare et al. 2011, Rangwala et al. 2012, Shinde and Dashti 2016). As nausea and vomiting significantly decrease QoL (Bloechl-Daum et al. 2006), many pharmacological interventions, such as metoclopramide, 5-HT3 receptor antagonists, and olanzapine, are used to tackle this problem (Navari et al. 2013, Shinde and Dashti 2016).

Diarrhoea and constipation are two contrary symptoms also often present among lung cancer patients, and guidelines direct the assessment and treatment of these conditions (Fallon and O'Neill 1997, Shinde and Dashti 2016).

2.5.5 FATIGUE

Fatigue is a common symptom among lung cancer patients, as Walling et al. (2015) reported 74.4% of patients with early-stage disease to have fatigue of any severity, while studies on surgically treated NSCLC survivors have found approximately half of the patients to have fatigue, with an underlying pulmonary disease and depressive or anxiety symptoms as predisposing factors (Hung et al. 2011, Huang et al. 2014). Some studies have suggested fatigue to return to preoperative levels soon after surgical treatment (Win et al. 2005a, Brunelli et al. 2007), while others have reported postoperatively increased fatigue persisting up to years after surgery (Kenny et al. 2008). The definition “a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning” (Berger et al. 2015) emphasizes the difficulty of this symptom. Moderate to severe fatigue has been observed in 36.9% of early-stage and in up to 50% of advanced-stage lung cancer patients (Stone et al. 2000, Walling et al. 2015), although it remains largely underreported (Berger et al. 2015). Thus, routine screening and evaluation of fatigue among cancer patients are recommended (Bower et al. 2014, Berger et al. 2015).

Fatigue is typically associated with other disturbing symptoms, such as pain, dyspnoea, depression, distress, and sleep disturbances (Stone et al. 2000, Berger et al. 2015), the efficient treatment of which reduces fatigue (de Raaf et al. 2013). For example, lung cancer patients report high prevalences of sleep disturbances and associated fatigue: insomnia in 36.8%, sleeping more than usual in 34.2%, use of sleeping pills in 40.4%, excessive sleepiness in 39.5%, and overly fatigued in 56.1% of patients (Davidson et al. 2002).

Guidelines include detailed algorithms for the screening, assessment, and treatment of fatigue, aiming to alleviate mild fatigue through education and counselling, while moderate to severe fatigue requires further examination and possible cause-specific treatments. With at least moderate fatigue, the most likely causes, namely pain, distress, sleep disturbances, anaemia, and hypothyroidism, are first evaluated. Second, a more thorough assessment includes comorbidities, medications, and nutritional status. If still no specific cause can be found, non-pharmacologic and pharmacologic interventions to reduce fatigue are recommended. The former include distraction, energy conservation, physical exercise programmes, and physical and psychosocial therapies, while the latter include antidepressants, psychostimulants, and

corticosteroids, especially at the end of life (Mock et al. 2000, Bower et al. 2014, Berger et al. 2015).

2.5.6 DEPRESSION

Depression is a common symptom among lung cancer patients; a study on SCLC and NSCLC patients with inoperable disease reported one-third to have depression, with SCLC patients overrepresented and functional impairment determined as the most important risk factor (Hopwood and Stephens 2000). Another study found self-reported depression in 46.1% of NSCLC patients (Shi et al. 2015), while a third study noted depressive symptoms in 79.5% of early-stage lung cancer patients (Walling et al. 2015). After curative surgery for early-stage NSCLC, depression has been reported in approximately one-tenth of survivors (Hung et al. 2011, Ostroff et al. 2011, Huang et al. 2014). Even though depression is often seen as a consequence of the burdensome disease and other related symptoms, it can also potentiate suffering from these other symptoms (Kroenke et al. 2010). Lung cancer patients have been found to be more prone to suffer from sleep disturbances than patients with other cancers (Davidson et al. 2002).

Against this background, early introduction of concurrent palliative care is meaningful, as it has been shown to significantly reduce depression among patients with advanced lung cancer (Bakitas et al. 2009, Temel et al. 2010, Temel et al. 2017). Both pharmacological and psychosocial interventions appear efficient, with neither showing clear superiority, as is the case also between different antidepressants (Li et al. 2012), although selective serotonin-reuptake inhibitors are often preferred due to their efficacy and low incidence of difficult side effects (Chochinov 2001). In any case, integrated, team-delivered, multimodality treatment has proven effective in alleviating depressive symptoms and enhancing QoL (Walker et al. 2014).

2.6 Prognosis

Lung cancer is diagnosed at a median age of 70 years and lung cancer patients' median age at death is 72 years in the US (Noone et al. 2018). The poor mortality-to-incidence ratio of 0.84 reflects the aggressive nature of this cancer, and it is clearly overrepresented in the worldwide statistics by causing 18.4% of cancer-related deaths, while constituting only 11.6% of new cancer cases (Bray et al. 2018). In the US, the 5-year survival rate reached 18.6%, while in Finland the relative age-standardized 5-year survival rates were 12.2% for men, 18.5% for women, and 14.5% in total (Noone et al. 2018, Finnish Cancer Registry). The 5-year survival rates have slowly increased in the Nordic countries, as shown in Figure 4.

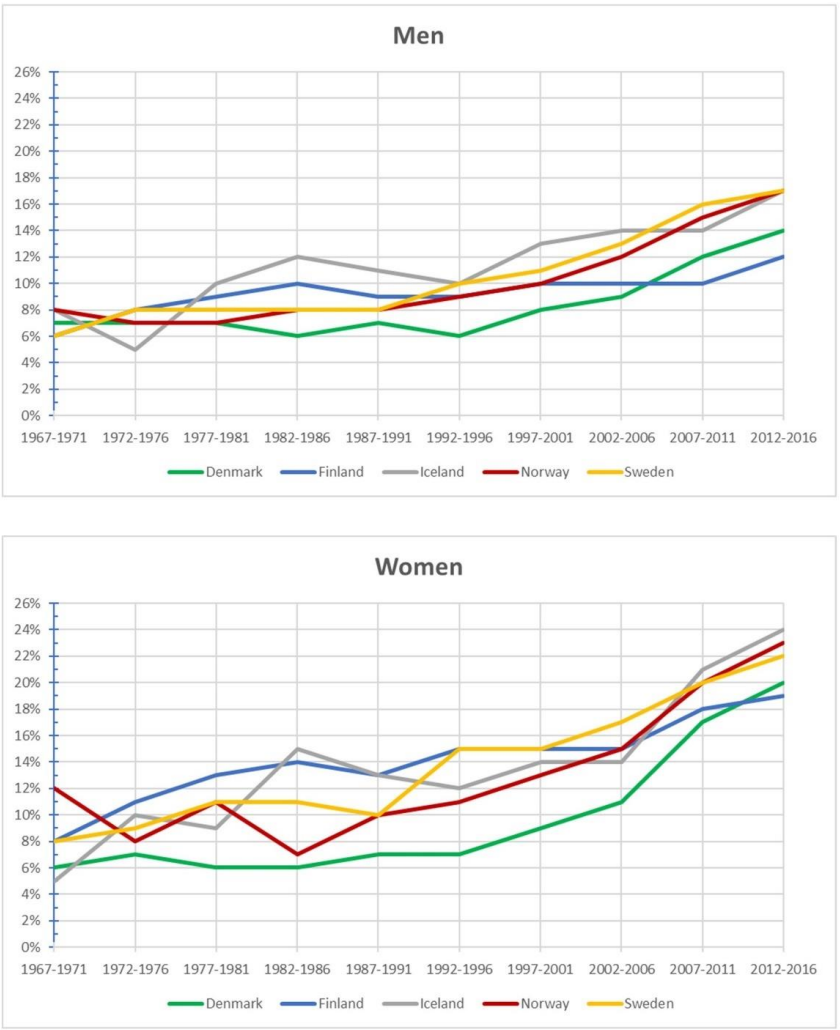

Figure 4 Five-year survival rates for lung cancer patients in the Nordic countries between 1967 and 2016. Reproduced and adapted with the publisher's permission from: Engholm G, Ferlay J, Christensen N, Bray F, Gjerstorff ML, Klint A, Kųtlum JE, Olafsdóttir E, Pukkala E, Storm HH (2010). NORDCAN-a Nordic tool for cancer information, planning, quality control and research. Acta Oncol. 2010 Jun;49(5):725-736.

The stage of the disease has a profound impact on survival, as the 5-year survival rates were 56.3% for local, 29.7% for regional, and only 4.7% for distant disease in recent statistics from the US (Noone et al. 2018), and analogously 50% for clinical stage I and 2% for clinical stage IV disease in a

large international study (Goldstraw et al. 2007). The histological grade, i.e. differentiation, of the cancer is also a strong independent prognostic factor, as patients with undifferentiated, poorly, or moderately differentiated carcinoma faced an 80%, 70%, and 40% elevation of risk of death, respectively (Sun et al. 2006). Patient features associated with a negative effect on the prognosis are higher age, male gender, comorbidities, positive smoking history, and low socioeconomic status (Woodard et al. 2016). The severity of symptoms may also affect survival, as Quadrelli et al. (2015) found asymptomatic patients to have a survival advantage, while depression predicted worse survival in another study (Pirl et al. 2012). Biomarkers for prognosis have also been evaluated, but have to date demonstrated only modest predictive power (Woodard et al. 2016).

Hospital type and case volume typically constitute important prognostic factors, although private clinics with small case volume, with experienced surgeons operating on the patients, may have treatment outcomes comparable to large case volume hospitals (Sioris et al. 2008, Woodard et al. 2016). Operable patients refusing to undergo surgery had median survival time of only 16.6 months and an estimated 5-year survival rate of 10.1% (Rosen et al. 2016), while even the 10-year survival rate may reach 88% among operated stage I patients (Henschke et al. 2006). After surgery, a 5-year recurrence rate of 24% has been observed (Goodgame et al. 2009).

2.7 Health-related quality of life (HRQoL) in lung cancer

2.7.1 DEFINITION AND IMPORTANCE

WHO defines health as “a state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity” (World Health Organization 1995), and QoL as “individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” (WHOQOL Group 1995). With health-related quality of life (HRQoL), the precise definition becomes more difficult. A few different definitions have been presented (Karimi and Brazier 2016) such as “how well a person functions in their life and his or her perceived well-being in physical, mental, and social domains of health” (Hayes and Reeve 2010) and “those aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment” (Ebrahim 1995).

HRQoL is nevertheless a multi-dimensional measure of well-being that combines physical and mental health with other important aspects of life, enabling the comparison of different treatments. This is crucial since objective physiological measurements and even measured exercise capacity often fail

to predict the fluency of daily life (Guyatt et al. 1993). As treating mere objective measurements serves only a limited purpose in health care, and as the HRQoL is valued highly among cancer patients, also with respect to treatments (Rummans et al. 2000, Bridges et al. 2012), HRQoL is a valuable tool in determining the effectiveness of different interventions. Furthermore, preoperative HRQoL is an independent predictor of survival (Ganz et al. 1991, Montazeri et al. 2001, Efficace et al. 2006, Montazeri 2009, Li et al. 2012, Lemonnier et al. 2014).

2.7.2 HRQOL INSTRUMENTS

Many instruments have been developed to measure HRQoL, and as they measure patient-reported outcomes (PROs), they are also known as patient-reported outcome measures (PROMs) (Bouazza et al. 2017). Both generic and disease-specific PROMs exist, and in lung cancer research the latter group can be further divided into cancer or lung cancer-specific measures (Damm et al. 2013, Pompili 2015, Richardson et al. 2016). For example, the MOS 36-item short-form health survey (SF-36) (Ware and Sherbourne 1992), the Ferrans and Powers QoL Index (QLI) (Ferrans and Powers 1985), and the EQ-5D (Brooks 1996) are among the most often used generic HRQoL instruments, while the EORTC QLQ-C30, the FACT-G (Cella et al. 1993), and the Rotterdam Symptom Checklist are among the most often used cancer-specific instruments in lung cancer research (Damm et al. 2013, Poghosyan et al. 2013, Pompili 2015). Lung cancer-specific instruments include the EORTC lung cancer-specific quality of life questionnaire module QLQ-LC13 (Bergman et al. 1994) and the FACT-L (Cella et al. 1995).

Different PROMs have different advantages: generic ones enable comparison to the general population, while cancer-specific ones allow, for example, the identification of typical changes in symptoms and HRQoL due to treatment (Pompili 2015). Although designed for measuring HRQoL, the EORTC QLQ-C30 has also been used to assess symptoms (Simoff et al. 2013) and has been shown to strongly correlate with the multisymptom assessment instrument ESAS (Silvoniemi et al. 2016).

2.7.3 FACTORS PREDICTING AND AFFECTING HRQOL

Numerous studies have evaluated the possible features predicting and affecting HRQoL after lung cancer surgery, which is important, as patients perceive postoperative physical restrictions as very unfavourable and deserve proper information on the subject (Cykert et al. 2000).

Time of assessment, both pre- and postoperatively, and the duration of follow-up affect the results of the HRQoL assessment, while the mode of

administration, via mail, telephone, or in person, seems to influence the results only modestly (Pompili 2015). In addition to these practical factors, multiple patient, disease, and treatment features may affect the HRQoL (Poghosyan et al. 2013, Pompili 2015).

Age seems to affect HRQoL variably; the results are often comparable between young and older patients (Pompili 2015), while some studies have observed a tendency for younger patients to report better physical, but possibly lower mental HRQoL (Poghosyan et al. 2013). Younger patients appear to recover faster and thus achieve, and even exceed, the preoperative HRQoL more often than older patients (Schulte et al. 2010). Gender has mostly been observed to be non-significant regarding HRQoL (Poghosyan et al. 2013). Current smoking at the time of surgery has predicted lower postoperative HRQoL, and this is a possible occasion for intervention (Poghosyan et al. 2013, Pompili 2015). The number of comorbidities has been associated with lower HRQoL (Poghosyan et al. 2013). Although preoperative pulmonary function tests (PFTs) are vital in treatment decision making, they fail to predict postoperative HRQoL (Paull et al. 2006, Brunelli et al. 2007, Ilonen et al. 2010).

Concerning treatment, the extent of resection negatively correlates with HRQoL (Balduyck et al. 2007, Schulte et al. 2009, Möller and Sartipy 2012a), making sleeve lobectomy a favourable alternative to pneumonectomy from this perspective (Balduyck et al. 2008). Between thoracotomy and VATS, multiple studies have demonstrated the beneficial effect of the latter on HRQoL, at least during the first 3-12 months after surgery (Balduyck et al. 2007, Demmy and Nwogu 2008, Handy et al. 2010, Bendixen et al. 2016). VATS patients also have fewer perioperative complications (Nwogu et al. 2015, Falcoz et al. 2016) and less postoperative pain (Bendixen et al. 2016). Accordingly, a recent review regarded VATS as the standard surgical procedure for operable NSCLC, with the precondition of adequate experience and expertise of the surgeon (Vannucci and Gonzalez-Rivas 2016).

Considering RT, modern SABR seems to yield acceptable HRQoL outcomes (Chen et al. 2016). Adjuvant ChT is often associated with deterioration of especially the physical dimension of HRQoL (Paull et al. 2006, Möller and Sartipy 2012a). No significant differences seem to exist in this effect between different conventional cytotoxic ChT regimens, although differences in certain dimensions of HRQoL may be observed (Tanvetyanon et al. 2007). Fortunately, new immunotherapy agents appear superior to cytotoxic ChT agents with respect to HRQoL (Brahmer et al. 2017).

As lung cancer, together with the possible treatments, is a burdensome disease, patients usually present with several symptoms, as described earlier. Pain, fatigue, disturbed sleep, and distress are all common symptoms, which strongly deteriorate HRQoL (Lin et al. 2013), and especially having two or more clinically significant symptoms simultaneously seems particularly

detrimental to HRQoL (Lowery et al. 2014). While Sarna et al. (2004) found that most NSCLC survivors reported at least one significant pulmonary symptom, they also found one-fifth of these patients to spend most of the day in bed due to these symptoms. Among other typical postoperative complications, PTPS has been associated with significantly lower QoL (Hopkins et al. 2015). Different symptoms, such as pain and depression, may even potentiate each other's effect on HRQoL and functionality (Kroenke et al. 2010).

To mitigate the detrimental effect of lung cancer and associated symptoms on HRQoL, a few methods have been investigated. Shared decision-making seems to have a weak, yet significant positive correlation with HRQoL among cancer patients (Kashaf and McGill 2015). Preoperative exercise therapy has a small positive effect on HRQoL (Pouwels et al. 2015), and physical activity has been associated with significantly higher QoL among lung cancer survivors (Solberg Nes et al. 2012). Pulmonary rehabilitation may improve the HRQoL of patients not undergoing surgery (Rivas-Perez and Nana-Sinkam 2015). The integration of early palliative care into standard treatment has proven effective in enhancing HRQoL among non-curable lung cancer patients (Temel et al. 2017).

2.7.4 TIMELY EVOLUTION OF HRQOL WITH RESPECT TO LUNG CANCER TREATMENT

NSCLC patients typically report deteriorated HRQoL preoperatively (Handy et al. 2002, Brunelli et al. 2007), although the opposite findings exist as well (Ilonen et al. 2010). Usually HRQoL deteriorates immediately after surgery, but it may reach preoperative levels already within 3-9 months (Zieren et al. 1996, Win et al. 2005a, Paull et al. 2006). On the other hand, studies have also demonstrated HRQoL impairments lasting much longer after surgery (Kenny et al. 2008, Schulte et al. 2009, Möller and Sartipy 2012b). A study on disease-free lung cancer survivors, with a median of 4.11 years since diagnosis, reported no significant differences in the functioning subscales relative to the age- and gender-matched general population, yet the survivors experienced more dyspnoea, pain, and coughing (Yun et al. 2012). Another study, with a median follow-up time of 3.5 years since surgery, reported impaired physical functioning among lung cancer survivors (Ostroff et al. 2011). However, the long-term HRQoL among operated NSCLC patients and the factors affecting it remain obscure.

3 AIMS OF THE STUDY

The aims of this thesis were as follows:

1. To assess the long-term HRQoL among surgically operated NSCLC survivors using both generic and cancer-specific patient-reported outcome measures (PROMs), and to compare the results with those of the general population.

2. To determine possible patient, disease, and treatment features predicting long-term HRQoL and survival.

3. To compare the long-term HRQoL between VATS and thoracotomy patients undergoing lobectomy for local NSCLC.

4 PATIENTS AND METHODS

4.1 Patients

All patient data, except the HRQoL data, were retrieved from the electronic patient records. The amount of comorbidity was measured with the Charlson comorbidity index (CCI), in which different comorbid conditions have their own weighted scores between one and six, a high score representing a high amount of comorbidity (Charlson et al. 1987). Staging followed the TNM7 classification (Mirsadraee et al. 2012).

4.1.1 STUDIES I AND II

The first two retrospective studies were based on patients who underwent surgical treatment for NSCLC at Helsinki University Central Hospital between January 2001 and June 2009. Of altogether 586 patients, 79 had undergone VATS surgery and 507 had been operated on via thoracotomy. Seven patients were lost to follow-up.

Survival was verified via the Finnish population register (Finnish Population Information System) in June 2011, at which point 301 patients were deceased. Two patients spoke a foreign language not available in the HRQoL PROMs, and thus, did not receive the questionnaries. Altogether 276 patients received the two HRQoL PROMS and were asked to return them completed by mail in June 2011. Non-respondents received a second pair of PROMs after one month, and after two months the non-respondents were contacted by phone and asked to answer the PROMs either on the phone or by mail.

4.1.2 STUDY III

A total of 456 patients underwent lobectomy or sublobar resection for NSCLC at Helsinki University Central Hospital between January 2006 and January 2013: 199 before July 2009, comprising the first cohort, and 257 between July 2009 and January 2013, comprising the second cohort. Survival was verified from the Finnish population register (Finnish Population Information System) and HRQoL sequentially assessed, as described in the above section, in June 2011 for the first, and in May 2016 for the second cohort. Non-respondents in the second cohort were contacted directly by phone after 2 months.

By the time of the HRQoL assessment, 79 patients from the first, and 93 from the second cohort had died. Furthermore, 45 patients were excluded due to too advanced disease (T≥3 or N≥1), 13 patients due to receiving

neoadjuvant therapy, and 27 patients due to a sublobar resection, thus leaving a total of 199 patients in this retrospective study. Of these patients, 73 were from the first, and 126 from the second cohort.

4.2 Methods

4.2.1 SURGICAL TECHNIQUES

The technique chosen depended on many factors, e.g. the surgeon's clinical decision and the designated operating room. Socio-economic selection bias should be minimal due to the universal health care system in Finland, which does not provide financial motives concerning the technique chosen for either the surgeon or the patient. The patients were operated on in sequential order, from a single queue.

Muscle-sparing anterolateral approach (Onugha and Lee 2016) served in thoracotomy, while VATS, introduced in 2006, was performed through the standard three-port approach (Hansen and Petersen 2012). In addition to general anaesthesia, thoracotomy patients received an epidural pain catheter prior to the operation, while for VATS patients ropivacaine was applied as a local anaesthetic for the incisions and for an intercostal nerve block.

4.2.2 HRQOL INSTRUMENTS

Studies I and II utilized two PROMs, a generic one and a disease-specific one, while Study III utilized only the generic one.

15D is a generic, standardized, and self-administered HRQoL PROM. It consists of 15 questions, each representing a dimension of HRQoL on an ordinal scale from 0 to 1, with higher score representing better functionality. The dimensions are mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity. The 15D score, representing the overall HRQoL, is derived from the answers by using population-based utility weights. It also ranges from 0 to 1, 0 equaling death and 1 perfect HRQoL (Sintonen 2001). The minimal important difference (MID) in 15D score is defined as 0.015 (Alanne et al. 2014). A study comparing six general PROMs found evidence supporting more widespread use of 15D, especially among cancer patients (Richardson et al. 2016). The National Health 2000 Health Examination Survey (Aromaa and Koskinen 2004) provided the age- and gender-matched Finnish general population (FGP) data (n = 4191) for Study I.

The EORTC QLQ-C30 is a cancer-specific, standardized, and self-administered HRQoL PROM. It consists of 28 four-point scale questions and two seven-point scale questions. The latter ones constitute a global quality-of-life scale, while the former ones constitute five multi-item functionality scales, three multi-item symptom scales, and six single-item symptom scales (Aaronson et al. 1993).

The QLQ-LC13 is an additional module for assessing specifically lung cancer-related symptoms. It consists of 13 four-point scale questions constituting one multi-item and nine single-item symptom scales (Bergman et al. 1994).

The scales in both the EORTC PROMs are scored from 0 to 100, a higher score representing either better functioning and QoL, or higher level of symptoms (Aaronson et al. 1993). The MIDs in the C30 depend on the scale and whether the status has been improving or deteriorating. For the global quality-of-life scale, the MIDs were 9.4 for improvement and 4.4 for deterioration (Maringwa et al. 2011). As no QLQ-C30 reference values for FGP existed, the EORTC QLQ-C30 Reference Values manual (Scott et al. 2008) provided reference values for the general population (EGP) in order to put our findings into perspective. To further help the interpretation, the age-matched, gender-specific values for a German general population (GGP) (Schwarz and Hinz 2001) were also given.

See Appendices for the HRQoL instruments.

4.2.3 STATISTICAL ANALYSES

The statistical analyses were performed with PASW Statistics for Windows, version 18.0.0 (SPSS Inc., Chicago, IL) in Study I, with SPSS Statistics for Windows, version 21.0.0 (IBM Corp., Armonk, NY) in Study II, and with SPSS Statistics for Windows, version 22.0.0.0 (IBM Corp., Armonk, NY) in Study III.

Results are given as mean and standard deviation (SD), median and range, or median and interquartile range (IQR) for continuous variables, and as n and percentage for categorical variables. In Study I, 95% confidence intervals (CIs) are given for HRQoL differences. A two-tailed $p < 0.05$ was considered statistically significant, unless otherwise specified.

4.2.3.1 Studies I and III

Survival was estimated with the Kaplan-Meier method. Categorical variables were compared using Pearson's Chi-squared test. Continuous variables were compared with independent samples t-test for parametric variables or with

Mann-Whitney U test for non-parametric variables. Linear correlation was measured with the Pearson correlation coefficient.

4.2.3.2 Study II

Possible correlations between independent variables were assessed with Pearson's correlation coefficient to avoid multi-collinearity in the regression analyses. Binary logistic regression served to determine patient, disease, and treatment features significantly predicting the probability of death at a given moment, thus determining the covariates for the predictive models. Model 1 was based on preoperative variables, while model 2 included also perioperative variables. With long-term HRQoL as the dependent variable, multiple linear regression served to determine patient, disease, and treatment features with a significant predictive value. Here again, model 1 included only preoperative variables, while model 2 included also perioperative variables. Multiple linear regression also served to determine variables significantly predicting the two 15D dimensions most severely deteriorated among the study population.

4.3 Ethical considerations

The study protocols were approved by the ethics committee of Helsinki University Central Hospital (reference number 129/13/03/02/2011). Possible participation or opting out did not affect the patient's treatment in any way. The patients returned their signed informed consent with the HRQoL instruments.

5 RESULTS

5.1 Study I

Of the 276 patients receiving the PROMs, 230 (83%) answered, 9 of whom answered only the 15D. Among the non-respondents, 19 declined to answer, 9 were unable to answer, and 18 were not reached by mail or by phone. The mean follow-up for respondents was 5.37 (SD: 2.45) years, and the median follow-up 4.85 (range: 2.01-11.13) years. Survival rates one, two, and five years after surgery were 85.5%, 73.2%, and 51.2%, respectively. Table 4 shows the preoperative statistics of patients divided into respondents and non-respondents. Of the non-respondents, 301 (86.2%) were already deceased by the time of the HRQoL assessment. Table 5 shows the perioperative characteristics of the respondents and the non-respondents. For patients requiring intensive care unit (ICU) treatment after the operation, the median stay in the ICU was 1 (IQR: 1-2) day for respondents and 4 (IQR: 2-10) days for non-respondents. A major complication refers to complications requiring reoperation or being life-threatening.

Figure 5 shows the 15D profiles of the respondents and the age- and gender-matched FGP. Respondents scored 0.831 and FGP 0.859 on the 15D score, the difference of 0.028 (95% CI: 0.012 - 0.043) being both statistically and clinically significant. Compared with the FGP, the respondents reported significantly impaired functioning on the following dimensions, with the absolute difference and the 95% CIs given: mobility 0.089 (95% CI: 0.065 - 0.113), breathing 0.156 (95% CI: 0.126 - 0.186), usual activities 0.068 (95% CI: 0.038 - 0.098), depression 0.044 (95% CI: 0.021 - 0.066), distress 0.035 (95% CI: 0.012 - 0.058), and vitality 0.034 (95% CI: 0.012 - 0.057). Corresponding differences in favour of the respondents were reported on the dimensions of vision 0.019 (95% CI: 0.000 - 0.038), hearing 0.029 (95% CI: 0.011 - 0.047), and mental function 0.043 (95% CI: 0.017 - 0.068).

Table 6 shows the QLQ-C30 results. Also given are the corresponding EGP results and the results for age-matched, gender-specific GGP. Our patients reported inferior physical functioning and more severe dyspnoea compared with these groups.

Significant correlation with a coefficient of 0.70 was observed between the 15D score and the QLQ-C30 Global Health Status score, as well as the following QLQ-C30 functioning scales: physical (0.79), role (0.73), emotional (0.65), cognitive (0.63), and social (0.56). The 15D dimension of breathing was also significantly correlated with the QLQ-C30 (-0.69) and the LC13 (-0.78) dyspnoea scales.

Table 4 Comparison of preoperative characteristics between respondents and non-respondents. Only p-values < 0.05 are given.

Characteristic	Respondents (n = 230) Mean ± SD[H] or n (%)	Non-respondents (n = 349) Mean ± SD[H] or n (%)	*p*
Age	63.0 ± 8.7	66.0 ± 9.3	0.001
Women	108 (47.0)	106 (30.4)	0.001
CCI[A]			
0	136 (59.1)	186 (53.3)	
1	55 (23.9)	87 (24.9)	
2	29 (12.6)	53 (15.2)	
3	9 (3.9)	16 (4.6)	
≥ 4	1 (0.4)	7 (2.0)	
COPD[B]	37 (16.1)	59 (16.9)	
MCC[C]	33 (14.3)	57 (16.3)	
ASVD[D]	9 (3.9)	11 (3.2)	
DM[E]	14 (6.1)	32 (9.2)	
FEV1%[F] (%)	77.7 ± 18.7	75.7 ± 18.5	
Smoking status			
Current smoker	139 (60.4)	214 (61.3)	
Former smoker	60 (26.1)	100 (28.7)	
Never smoker	31 (13.5)	35 (10.0)	
SPY[G]	41.5 ± 19.2	43.4 ± 19.6	
Clinical stage			
IA	91 (39.6)	96 (27.5)	
IB	49 (21.3)	85 (24.4)	
IIA	5 (2.2)	5 (1.4)	
IIB	46 (20.0)	98 (28.1)	
IIIA	20 (8.7)	35 (10.0)	
IIIB	19 (8.3)	26 (7.4)	
IV	0	2 (0.6)	

[A] = Charlson comorbidity index; [B] = chronic obstructive pulmonary disease; [C] = morbus cordis coronarius; [D] = arteriosclerotic vascular disease; [E] = diabetes; [F] = forced expiratory volume in 1 second (FEV1) percentage of the predicted value; [G] = smoking pack years (given for smokers); [H] = standard deviation.

Reprinted and adapted from: Rauma V, Sintonen H, Rasanen JV, Salo JA, Ilonen IK. Long-term lung cancer survivors have permanently decreased quality of life after surgery. Clin Lung Cancer 2015;16:40-5.

Table 5 Comparison of perioperative characteristics between respondents and non-respondents. Only p-values < 0.05 are given.

Characteristic	Respondents (n = 230) Mean ± SD[F] or n (%)	Non-respondents (n = 349) Mean ± SD[F] or n (%)	*p*
Resection			
Pneumonectomy	18 (7.8)	47 (13.5)	
Lobectomy	182 (79.1)	264 (75.6)	
Sleeve	13 (5.7)	21 (6.0)	
Sublobar	17 (7.4)	17 (4.9)	
VATS[A]	42 (18.3)	37 (10.6)	0.009
Side			
Right	142 (61.7)	193 (55.3)	
Left	88 (38.3)	156 (44.7)	
Neoadjuvant therapy[B]	25 (10.9)	41 (11.7)	
Adjuvant therapy[C]	37 (16.1)	58 (16.6)	
Histology			
Adenocarcinoma[D]	124 (53.9)	171 (49.0)	
Squamous cell carcinoma	83 (36.1)	136 (39.0)	
Large cell carcinoma	8 (3.5)	23 (6.6)	
Undifferentiated	15 (6.5)	19 (5.4)	
Pathological stage			0.0001
IA	89 (38.7)	84 (24.1)	
IB	69 (30.0)	99 (28.4)	
IIA	11 (4.8)	9 (2.6)	
IIB	37 (16.1)	65 (18.6)	
IIIA	14 (6.1)	59 (16.9)	
IIIB	9 (3.9)	31 (8.9)	
IV	0	2 (0.6)	
Hospital stay (days)	9.7 ± 15.1	12.4 ± 10.4	0.013
ICU[E]	20 (8.7%)	62 (17.8%)	
Complication	48 (20.9)	139 (39.8)	0.001
Major	18 (7.8)	71 (20.3)	

[A] = Video-assisted thoracoscopic surgery; [B] = Chemo- or radiochemotherapy; [C] = Chemo- or radiotherapy; [D] = Including bronchioloalveolar carcinoma; [E]= Intensive care unit; [F] = Standard deviation.

Reprinted and adapted from: Rauma V, Sintonen H, Rasanen JV, Salo JA, Ilonen IK. Long-term lung cancer survivors have permanently decreased quality of life after surgery. Clin Lung Cancer 2015;16:40-5.

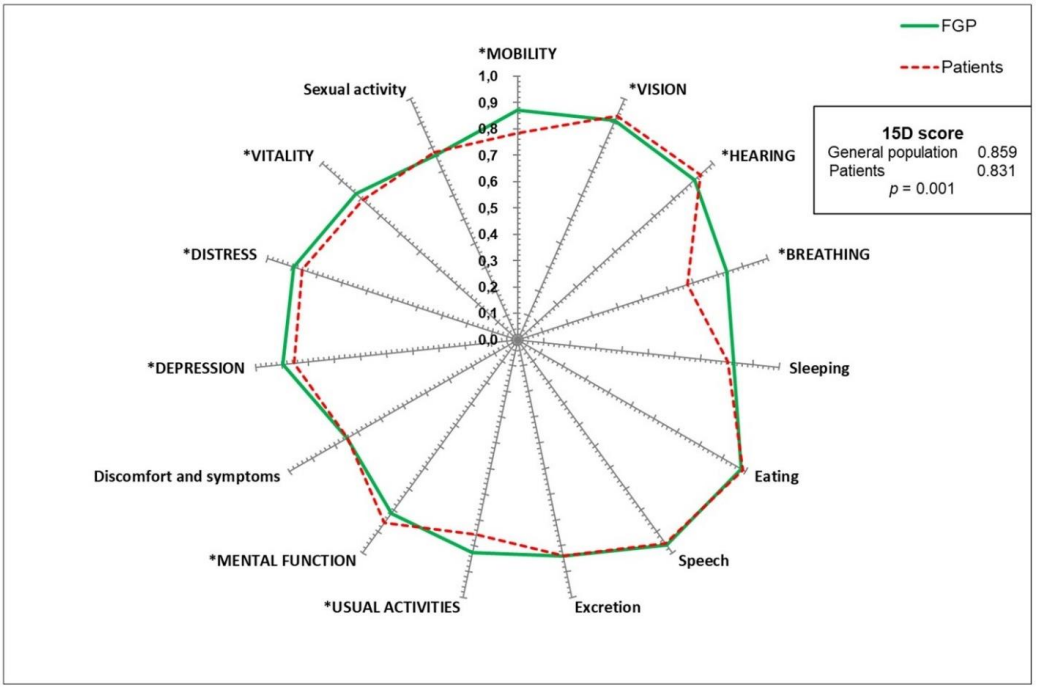

Figure 5 15D profiles of our patients and the age- and gender-matched Finnish general population (FGP). Asterisks and uppercase indicate a statistically significant difference, defined here as $p < 0.03$ (two-tailed). Reprinted and adapted from: Rauma V, Sintonen H, Rasanen JV, Salo JA, Ilonen IK. Long-term lung cancer survivors have permanently decreased quality of life after surgery. Clin Lung Cancer 2015;16:40-5.

Table 6 Mean QLQ-C30 scores for the respondents, the general EORTC QLQ-C30 reference population (EGP), and the age-matched, gender-specific German general population (GGP).

	GHS	PF	CF	RF	EF	SF	FA	PA	NV	DY
Respondents ± SD[A]	66.4 ± 22.8	67.4 ± 22.8	86.2 ± 16.9	75.0 ± 26.2	83.6 ± 19.7	86.2 ± 20.5	28.3 ± 22.0	23.9 ± 25.7	3.5 ± 10.3	33.2 ± 29.8
EGP ± SD[A]	71.2 ± 22.4	89.8 ± 16.2	86.1 ± 20.0	84.7 ± 25.4	76.3 ± 22.8	87.5 ± 22.9	24.1 ± 24.0	20.9 ± 27.6	3.7 ± 11.7	11.8 ± 22.8
GGP										
Men	63.9	83.4	86.9	81.1	79.9	86.5	22.7	22.9	2.9	14.4
Women	60.5	78.6	85.3	77.6	75.2	87.6	28.2	26.6	4.6	16.3

GHS = Global Health Status; PF = Physical Functioning; CF = Cognitive Functioning; RF = Role Functioning; EF = Emotional Functioning; SF = Social Functioning; FA = Fatigue; PA = Pain; NV = Nausea and Vomiting; DY = Dyspnoea. [A] = Standard deviation.

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5.2 Study II

Of the original 579 patients with follow-up data, 55 were further excluded due to insufficient data, leaving 524 patients for the survival analyses. The HRQoL analyses were based on the 230 respondents described previously in Tables 4 and 5. Their mean and median follow-up times are given in the Study I results.

Table 7 shows the characteristics of the patients, with respondents also divided according to the surgical technique used. The thoracotomy and VATS respondents differed significantly on several characteristics: VATS patients were significanlty older ($p = 0.001$), a higher proportion of them were women ($p = 0.032$), they had higher CCI scores ($p = 0.023$), they had had less frequently neoadjuvant ($p = 0.012$) and adjuvant ($p = 0.027$) therapy, they had on average lower disease stage ($p = 0.001$), and underwent a less extensive resection ($p = 0.001$). The use of VATS did not correlate with disease progression or occurrence of complications.

Table 8 shows the patient, disease, and treatment features included as possible covariates in the binary logistic regression analyses for the probability of death, while Table 9 provides the corresponding data on the regression analyses for long-term HRQoL. In both cases, only preoperative features were analysed for model 1, including the surgical technique chosen preoperatively. For model 2, perioperative features were also included in the analysis, pathological stage thus replacing the clinical one. The coefficients, together with their p-values, are given only for the variables included in the final regression models.

In both cases, model 2 was superior in accuracy. The difference was more prominent when predicting HRQoL, and data on perioperative complications seemed to have a substantial impact. The constants for the final models are given, together with the coefficients and their p-values for the features included in the models as covariates. The coefficients state the change in the dependent variable for every one-unit change for continuous covariates, i.e. one year for age, and in comparison with the alternative feature for categorical covariates, i.e. having clinical stage II-IV instead of stage I. In Table 8, a positive coefficient reflects an increase in the probability of death, while in Table 9 a positive coefficient reflects a positive change in the long-term HRQoL.

As the difference in HRQoL between our patients and the age- and gender-matched FGP, reported in Study I, was most prominent on 15D dimensions of mobility and breathing, a regression analysis was utilized to determine possible patient, disease, and treatment features significantly associated with these dimensions. Table 10 introduces these results. As in the case with the overall HRQoL scores in Table 9, the explanatory power of these models remained low.

Table 7 Patient characteristics, with the respondents also categorized according to surgical technique.

Characteristic	All patients (*n* = 524)	Respondents		
		Total (*n* = 230)	Thoracotomy (*n* = 188)	VATS (*n* = 42)
	Mean ± SD[F] or n (%)			
Age	65.1 ± 8.8	63.0 ± 8.7	62.1 ± 8.4	66.9 ± 8.9
Women	201 (37.9)	108 (47.0)	82 (43.6)	26 (61.9)
CCI[A] score				
0	292 (55.0)	136 (59.1)	119 (63.3)	17 (40.5)
1	133 (25.0)	55 (23.9)	43 (22.9)	12 (28.6)
2	76 (14.3)	29 (12.6)	18 (9.6)	11 (26.2)
3	24 (4.5)	9 (3.9)	7 (3.7)	2 (4.8)
≥ 4	6 (1.1)	1 (0.4)	1 (0.5)	0
FEV1%[B]	76.2 ± 18.5	77.0 ± 18.7	77.0 ± 18.4	77.1 ± 20.5
Smokers[C]	468 (89.3)	199 (86.5)	166 (88.3)	33 (78.6)
SPY[D]	42.1 ± 19.2	41.5 ± 19.2	41.5 ± 19.6	41.2 ± 17.5
Clinical stage				
IA	168 (31.6)	92 (40.0)	60 (31.9)	32 (76.2)
IB	119 (22.4)	49 (21.3)	39 (20.7)	10 (23.8)
IIA	10 (1.9)	5 (2.2)	5 (2.7)	0
IIB	138 (26.0)	46 (20.0)	46 (24.5)	0
IIIA	51 (9.6)	20 (8.7)	20 (10.6)	0
IIIB	43 (8.1)	18 (7.8)	18 (9.6)	0
IV	2 (0.4)	0	0	0
Operation				
Pneumonectomy	60 (11.3)	18 (7.8)	18 (9.6)	0
Lobectomy	408 (76.8)	182 (79.1)	147 (78.2)	35 (83.3)
Sleeve	31 (5.8)	13 (5.7)	13 (6.9)	0
Sub-lobar	32 (6.0)	17 (7.4)	10 (5.3)	7 (16.7)
Neoadjuvant therapy	61 (11.5)	25 (10.9)	25 (13.3)	0
Adjuvant therapy	91 (17.1)	37 (16.1)	35 (18.6)	2 (4.8)
Histology				
Adenocarcinoma	273 (51.4)	124 (53.9)	94 (50.0)	30 (71.4)
Squamous cell carcinoma	197 (37.1)	83 (36.1)	72 (38.3)	11 (26.2)
Large cell carcinoma	30 (5.6)	8 (3.5)	7 (3.7)	1 (2.4)
Undifferentiated	31 (5.8)	15 (6.5)	15 (8.0)	0
Pathological stage				
IA	153 (28.8)	89 (38.7)	61 (32.4)	28 (66.7)
IB	150 (28.2)	70 (30.4)	60 (31.9)	10 (23.8)
IIA	20 (3.8)	11 (4.8)	9 (4.8)	2 (4.8)
IIB	99 (18.6)	37 (16.1)	37 (19.7)	0
IIIA	68 (12.8)	14 (6.1)	12 (6.4)	2 (4.8)
IIIB	39 (7.3)	9 (3.9)	9 (4.8)	0
IV	2 (0.4)	0	0	0
Having complications	167 (31.5)	48 (20.9)	43 (22.9)	5 (11.9)
Recurrence	208 (39.2)	25 (10.9)	22 (11.7)	3 (7.1)
RFS[E] (months)		38 ± 24		

[A] = Charlson comorbidity index; [B] = forced expiratory volume in 1 second (FEV1) percentage of the predicted value; [C] = including former smokers; [D] = smoking pack years (given for smokers); [E] = recurrence-free survival;
[F] = standard deviation.

Reprinted and adapted from: Rauma V, Salo J, Sintonen H, Rasanen J, Ilonen I. Patient features predicting long-term survival and health-related quality of life after radical surgery for non-small cell lung cancer. Thorac Cancer 2016;7:333-9. https://onlinelibrary.wiley.com/doi/10.1111/1759-7714.12333

Table 8 Variables included in the binary logistic regression analyses, with coefficients given only for the variables included in the final regression models for the probability of death (n=524).

	Value	Probability of death	
		Model 1	Model 2
Percentage predicted correctly		67.9	69.5
Constant		−5.70	−5.76
	Mean ± SD[F] or n (%)	Coefficient (p-value)	
Preoperative features			
Time since operation (months)	81.2 ± 33.2	0.021 (0.001)	0.021 (0.001)
Age at operation	65.1 ± 8.8	0.056 (0.001)	0.052 (0.001)
Male	330 (62.1)	0.442 (0.027)	0.488 (0.016)
SPY[A]	42.1 ± 19.2		
CCI[B] score	0.72 ± 1.0	0.238 (0.026)	0.242 (0.029)
FEV1%[C]	76.2 ± 18.5		
Clinical stage II-IV[D]	245 (46.1)	0.546 (0.006)	
Neoadjuvant therapy	61 (11.5)		
VATS	68 (12.8)		
Perioperative features			
Lobectomy or segmentectomy	394 (74.2)		
Pathological stage II-IV[D]	228 (42.9)		0.902 (0.001)
Squamous cell carcinoma[E]	197 (37.1)		
Large cell or undifferentiated carcinoma[E]	61 (11.5)		
Adjuvant chemotherapy	77 (14.5)		
Adjuvant radiotherapy	14 (2.6)		
Complications			
Bleeding	15 (2.8)		
Air leak	29 (5.5)		
Infection	59 (11.1)		0.837 (0.013)
Cardiac	16 (3.0)		1.93 (0.070)
Other	48 (9.0)		

[A] = smoking pack years (given for smokers); [B] = Charlson comorbidity index; [C] = forced expiratory volume in 1 second (FEV1) percentage of the predicted value; [D] = compared with stage I; [E] = compared with adenocarcinoma; [F] = standard deviation.

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Table 9 Variables included in the regression analyses, with coefficients given only for the variables included in the final regression models for the long-term HRQoL (n=230).

	Value	15D score		QLQ-C30 Global Health Status	
		Model 1	Model 2	Model 1	Model 2
Adjusted R square		0.060	0.119	0.041	0.088
Constant		0.798	0.854	52.5	54.2
	Mean ± SD[G] or n (%)	Coefficient (p-value)			
Preoperative features					
Time since operation (months)	70.0 ± 29.4		−0.001 (0.041)		
Age at operation	63.0 ± 8.7				
Male	122 (53.0)				
SPY[A]	41.5 ± 19.2				
CCI[B] score	0.63 ± 0.88	−0.028 (0.001)	−0.030 (0.001)	−3.32 (0.067)	−3.23 (0.068)
FEV1%[C]	77.0 ± 18.7	0.001 (0.090)	0.001 (0.087)	0.208 (0.015)	0.179 (0.032)
Neoadjuvant	25 (10.9)				
Clinical stage II-IV[D]	90 (39.1)				
VATS[E]	42 (18.7)		−0.044 (0.031)		
Intraoperative features					
Pathological stage II-IV[D]	71 (30.9)				
Squamous cell carcinoma[F]	83 (36.1)				
Large-cell or undifferentiated carcinoma[F]	23 (10.0)				
Lobar or minor resection	179 (77.8)				
Adjuvant chemotherapy	32 (13.9)				10.9 (0.010)
Adjuvant radiotherapy	5 (2.2)				
Complications					
Bleeding	5 (2.2)		−0.071 (0.140)		−20.6 (0.040)
Air leak	12 (5.2)		0.056 (0.085)		
Infection	17 (7.4)		−0.069 (0.012)		−8.88 (0.111)
Cardiac	1 (0.4)				
Other	13 (5.7)		−0.063 (0.044)		

[A] = smoking pack years (given for smokers); [B] = Charlson comorbidity index; [C] = forced expiratory volume in 1 second (FEV1) percentage of the predicted value; [D] = compared with stage I; [E] = compared with thoracotomy; [F] =compared with adenocarcinoma; [G] = standard deviation

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Table 10 Patient, disease, and treatment features reaching statistical significance in the regression models for 15D dimensions of mobility and breathing.

	Mobility	**Breathing**
Adjusted R square	0.103	0.117
Constant	0.863	0.595
	Coefficient (p-value)	
Time since operation (months)	−0.001 (0.001)	
CCI[A] score	−0.049 (0.001)	
Other complications	−0.099 (0.048)	
FEV1%[B]		0.003 (0.003)
SPY[C]		−0.002 (0.041)

[A] = Charlson comorbidity index; [B] = forced expiratory volume in 1 second (FEV1) percentage of the predicted value; [C] = smoking pack years (given for smokers).

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5.3 Study III

Of the 199 patients included in Study III, 97 (48.7%) were operated on through VATS and 102 (51.3%) through thoracotomy, with the four (4.0%) intraoperative conversions from VATS to thoracotomy included in the thoracotomy group for the analyses. A total of 180 patients (90.5%) responded, 71 (97.3%) in the first, and 109 (86.5%) in the second cohort. Their mean and median ages by the time of surgery were 65.81 (SD: 8.39) and 67 (range: 32-86) years, respectively. VATS was equally utilized in both cohorts, 49.3% vs 48.4%, but the second cohort had a significantly longer mean follow-up time of 55.8 (SD: 12.0) months compared with 42.4 (SD: 10.8) months in the first cohort. As both cohorts reported consistent HRQoL differences between the VATS and thoracotomy patients separately, they were combined for the analyses comparing HRQoL between VATS and thoracotomy patients.

VATS and thoracotomy respondents were comparable in preoperative characteristics, as Table 11 demonstrates. No difference emerged between the groups in terms of comorbidity, even if compared in having none-to-low (CCI 0-1) or a high (CCI ≥ 2) amount of comorbidity. As Table 12 demonstrates, the groups had some differences in perioperative characteristics: ADC was more prevalent in the VATS group, they had fewer nodal stations sampled, and they had on average shorter hospitalization, with median hospital stay being 5 (range: 2-22) days in the VATS group and 7 (range: 3-37) days in the thoracotomy group. The VATS group also had a higher response rate.

Figure 6 compares the 15D profiles of the groups. VATS group scored significantly lower, with the absolute difference given in parentheses, on the dimensions of mental function (0.10), breathing (0.08), usual activities (0.07), vitality (0.06), and speech (0.03).

Table 11 Preoperative characteristics compared between the VATS and thoracotomy groups in Study III. Only p-values < 0.05 are given.

Characteristic	VATS (n=92) Mean (SD[F]) or n (%)	Thoracotomy (n=88) Mean (SD[F]) or n (%)	*p*
Age	66.9 (8.1)	64.7 (8.5)	
Women	42 (45.7%)	51 (58.0%)	
CCI[A]			
0	33 (35.9%)	43 (48.9%)	
1	30 (32.6%)	23 (26.1%)	
2	20 (21.7%)	12 (13.6%)	
3	7 (7.6%)	7 (8.0%)	
4	1 (1.1%)	1 (1.1%)	
≥ 5	1 (1.1%)	2 (2.3%)	
FEV1%[B]	79.0 (19.7)	79.4 (18.2)	
DLCO% [C]	76.4 (17.6)	77.5 (16.8)	
Smoking status			
Former smoker[D]	28 (30.4%)	36 (40.9%)	
Current smoker[D]	45 (48.9%)	37 (42.0%)	
Never smoker	19 (20.7%)	15 (17.0%)	
SPY[E]	40.2 (23.0)	33.9 (21.5)	
Clinical stage			
IA	68 (73.9%)	56 (63.6%)	
IB	18 (19.6%)	23 (26.1%)	
IIA	6 (6.5%)	9 (10.2%)	

[A] = Charlson comorbidity index -score; [B] = patients' FEV1 value compared with the predicted value (%); [C] = patients' DLCO value compared with the predicted value (%); [D] = at the time of the operation; [E] = smoking pack years (given for smokers); [F] = standard deviation.

Reprinted and adapted from: Rauma V, Andersson S, Robinson EM, et al. Thoracotomy and VATS Surgery in Local Non–Small-Cell Lung Cancer: Differences in Long-Term Health-Related Quality of Life. Clinical Lung Cancer 2019;20:378-83.

Table 12 Comparison of the perioperative characteristics between the VATS and thoracotomy groups in Study III. Only p-values < 0.05 are given.

Characteristic	VATS (n=92) Mean (SD[C]) or n (%)	Thoracotomy (n=88) Mean (SD[C]) or n (%)	*p*
Tumour location			
Right superior	40 (43.5%)	22 (25.0%)	
Right inferior	20 (21.7%)	30 (34.1%)	
Right medial	3 (3.3%)	4 (4.5%)	
Left superior	16 (17.4%)	18 (20.5%)	
Left inferior	13 (14.1%)	14 (15.9%)	
Histology			0.006
Adenocarcinoma [A]	75 (81.5%)	52 (59.1%)	
Squamous cell carcinoma	16 (17.4%)	32 (36.4%)	
Large cell carcinoma	1 (1.1%)	1 (1.1%)	
Other	0	3 (3.4%)	
Pathological stage			
IA	60 (65.2%)	53 (60.2%)	
IB	15 (16.3%)	15 (17.0%)	
IIA	11 (12.0%)	13 (14.8%)	
IIB	2 (2.2%)	2 (2.3%)	
IIIA	4 (4.3%)	5 (5.7%)	
No. of nodal stations sampled	3.5 (1.8)	4.5 (1.6)	0.004
Adjuvant therapy [B]	6 (6.5%)	9 (10.2%)	
Hospital stay (days)	6.4 (4.6)	8.7 (5.2)	0.001
Complication	18 (19.6%)	17 (19.3%)	
Progression	8 (8.7%)	8 (9.1%)	
Response rate (%)	94.8	86.3	0.040
Follow-up (months)	50.1 (14.7)	50.7 (11.4)	

[A] = Including bronchioloalveolar carcinomas; [B] = Chemo- or radiotherapy;
[C] = standard deviation.

Reprinted and adapted from: Rauma V, Andersson S, Robinson EM, et al. Thoracotomy and VATS Surgery in Local Non–Small-Cell Lung Cancer: Differences in Long-Term Health-Related Quality of Life. Clinical Lung Cancer 2019;20:378-83.

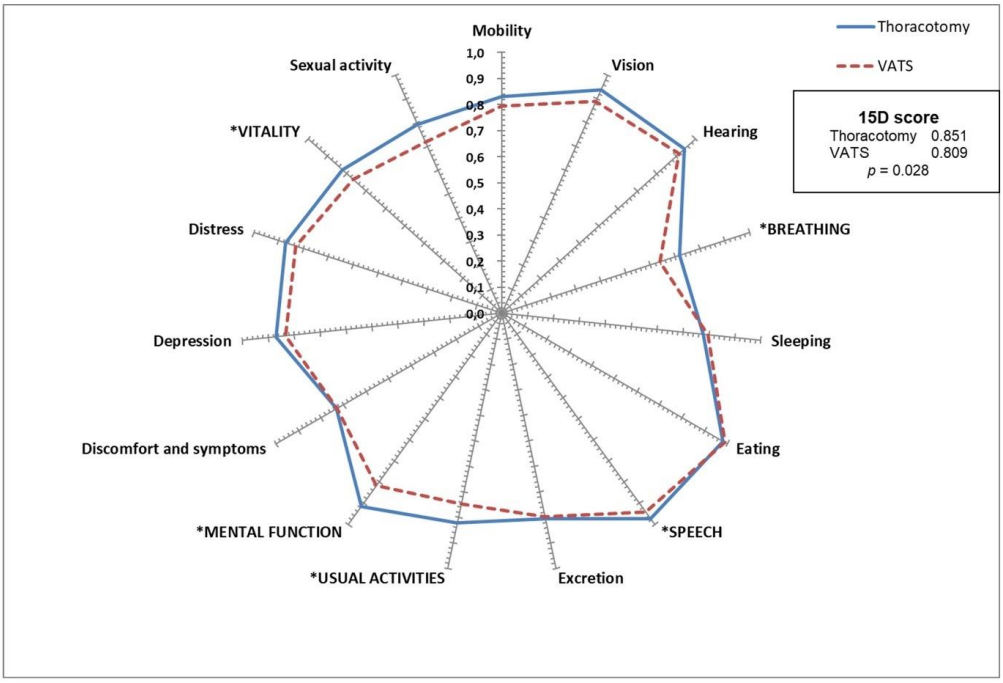

Figure 6 Comparison of the 15D profiles between the VATS and thoracotomy groups in Study III. Asterisks and uppercase indicate dimensions with significant differences. Reprinted and adapted from: Rauma V, Andersson S, Robinson EM, et al. Thoracotomy and VATS Surgery in Local Non–Small-Cell Lung Cancer: Differences in Long-Term Health-Related Quality of Life. Clinical Lung Cancer 2019;20:378-83.

6 DISCUSSION

6.1 Study I

This study demonstrated the significantly lower long-term HRQoL, measured with both a generic and a cancer-specific PROM, among surgically treated NSCLC survivors than among the general population. The patients reported lower overall HRQoL with both PROMs, the generic 15D and the cancer-specific EORTC QLQ-C30, and the most deteriorated individual dimensions in 15D were mobility and breathing, and in QLQ-C30 physical functioning and dyspnoea. The 5-year survival rate of 51.2% was comparable with that observed in other studies (Berry et al. 2014, Noone et al. 2018). With a median follow-up time reaching nearly five years and a response rate of 83% with 230 respondents, the results are robust.

The main limitations of the study were its retrospective nature and the long timespan from 2000 to 2009, during which the patients were operated. As we had no baseline data on the HRQoL, we could only measure the HRQoL differences at a given moment, without being able to specify whether they had already existed preoperatively or were the result of the treatment. Changes in the treatment of NSCLC patients occurred between 2000 and 2009, most notably the introduction of VATS at our clinic in 2006, and these changes may also have biased the results to some degree.

There were also some significant differences between our respondents and the rest of the patients: the respondents were younger, women and VATS were overrepresented, they had on average lower stage and shorter hospitalization, and they encountered fewer perioperative complications. These differences are natural and reasonable, as most of the non-respondents were already deceased by the time of the HRQoL assessment. Although some studies have reported old age predisposing patients to complications (Ferguson et al. 2009) or deterioration of HRQoL (Möller and Sartipy 2012a), it has usually not been observed to predict deterioration in the postoperative HRQoL results (Pompili 2015), and even patients older than 70 years have reported postoperative HRQoL reaching preoperative levels already three months postoperatively (Salati et al. 2009). Likewise, gender seems to play a non-significant role in HRQoL changes after surgery (Poghosyan et al. 2013). VATS has been repeatedly demonstrated to yield better short-term HRQoL results, yet the long-term results remain uncertain (Pompili 2015). The effect of complications on long-term HRQoL has not been extensively investigated, although at least one study found no association between the two (Möller and Sartipy 2012a).

Despite oncologically successful treatment, and the possible recovery of the HRQoL to preoperative levels within a year of surgery (Burfeind et al. 2008), impaired long-term HRQoL has been a common burden in NSCLC survivors. The survivors have reported lower HRQoL one year after surgery than either the general population or patients with other chronic diseases (Welcker et al. 2003), and the HRQoL impairments have been reported to last beyond the two-year follow-up (Möller and Sartipy 2012b). Sarna et al. (2010) found HRQoL among female NSCLC survivors, all operated on through thoracotomy approximately two years previously, to be inferior to that of the general female population, yet similar to that of the general population of the same age. The study found no meaningful change in the HRQoL during the six-month follow-up, suggesting possible stabilization of HRQoL by two years of follow-up (Sarna et al. 2010). A review on HRQoL found patients typically reporting lower mental HRQoL on generic PROMs than the general population, as was the case with our patients. On the other hand, the same review reported good levels of emotional functioning among NSCLC patients, assessed with the cancer-specific QLQ-C30, which was also the case in our study. Regardless, they found general population scoring to overall be higher on both physical and mental HRQoL than the NSCLC survivors (Poghosyan et al. 2013). For comparison, the mean 15D score among our respondents was comparable to the long-term results reported by patients with prosthetization after a major lower limb amputation (Becker et al. 2019).

The observed impairment in subjective respiratory performance is in line with previous studies reporting high rates of respiratory symptoms among NSCLC patients (Muers and Round 1993). As dyspnoea and low subjective respiratory performance have a significant negative effect on HRQoL (Gupta et al. 2007, Grutters et al. 2010, Sarna et al. 2010), the findings are consistent with respect to the overall HRQoL.

Concerning our lack of baseline HRQoL data, results from other studies may provide some insight into the preoperative baseline HRQoL among NSCLC patients, although the findings have been variable. A study on Swedish NSCLC patients found the preoperative physical functioning to be comparable to that of the general population, while the mental functioning was significantly lower among patients (Sartipy 2010). Another study found preoperative HRQoL among Finnish NSCLC patients to be comparable to that of the general population (Ilonen et al. 2010). The fact that our patients reported higher levels of functioning on the 15D dimensions of seeing and hearing, features presumably not affected by the treatment or the disease, might suggest that they were originally in relatively good condition.

Moreover, response shift, a phenomenon possibly predisposing our study to underestimation of the true HRQoL difference between patients and the general population, deserves a few words. After the patient undergoes surgery and time goes by, the internal scale for evaluating symptom severity and

functionality may be re-calibrated, usually towards lower standards, from what it was preoperatively. This may lead to patients reporting higher postoperative HRQoL than they would have rated their current situation according to the preoperative internal scale. Since this re-calibration does not happen, or at least not to the same extent, in the control group not undergoing treatment, this may cause biases in the results (Sprangers et al. 1999). The fact that patients in poor condition, for example, those with disease progression, are less prone to answer PROMs (Fairclough 2010) may further bias the results in favour of the reported HRQoL. Thus, the reported HRQoL among the NSCLC survivors may be overly optimistic.

The QLQ-C30 results for our patients, the EGP, and the GGP, shown in Table 6, are not perfectly comparable with each other. The reported results for EGP have marked variation between countries, and the GGP scored significantly lower on the global health status scale than, for example, the Norwegian general population (Schwarz and Hinz 2001), which might have been a more comparable control group for Finnish patients, had their results been more readily available. The German patients were also interviewed for the GGP reference values, even though the QLQ-C30 was originally designed to be a self-administered instrument (Aaronson et al. 1993). The advantage of the GGP was the possibility to match the groups according to age, even though the results were given separately for men and women. Concerning the EORTC reference data for the general population, the gender distribution with 48% women, was almost identical to ours, yet the patients were significantly younger and again from different countries (Scott et al. 2008).

6.2 Study II

The main finding was the poor predictive power of objective pre- and perioperative patient, disease, and treatment features for the long-term HRQoL among surgically treated NSCLC survivors. However, survival was far more predictable with the same features. The features predicting HRQoL on both PROMs were CCI score, FEV1%, and complications, while smoking pack years and FEV1% predicted respiratory functioning.

The main limitation was the absence of baseline HRQoL data, preventing the determination of possible predictors for changes in HRQoL due to treatment. As preoperative HRQoL has been reported to be the strongest predictor of postoperative HRQoL among surgical patients (Vainiola et al. 2013), its absence probably caused the predictive models in this study to reach only minor explanatory power. Likewise, features possibly correlated with the preoperative HRQoL may have gained too much weight in the analyses as a consequence. The preoperative QoL has also been observed to have a strong predictive value in the overall survival among NSCLC patients (Movsas et al.

2009). As stated earlier with Study I, the long time frame was also a potent source for biases in this study. Additionally, many factors besides the ones included in our analyses and the preoperative HRQoL may affect the long-term HRQoL; e.g. living alone has been observed to have a negative effect on postoperative HRQoL (Barlési et al. 2006).

The only features included in the predictive models for both HRQoL and survival were CCI score and complications, while FEV1% was also included in the models for both HRQoL PROMs. Age correlated significantly with the occurrence of complications, as has been observed in other studies (Ferguson et al. 2009), unlike the CCI score. The negative effect of complications on long-term HRQoL has been noted in some studies; while Handy et al. (2002) reported no correlation, Möller and Sartipy (2012a) found a significant increase in the risk of deterioration in general health and in physical and role functioning scales as a consequence of complications.

Comorbidities, particularly when numerous, seem to decrease HRQoL (Poghosyan et al. 2013). CCI was originally designed to predict operative mortality (Charlson et al. 1987) and it has been validated in NSCLC patients (Birim et al. 2003), although it seems to perform poorly in predicting HRQoL (Fortin et al. 2005). However, Ng et al. (2015) found self-reported CCI to correlate significantly with HRQoL, while CCI derived from medical records failed in this task. Although Sarna et al. (2010) reported comorbidity to affect the long-term HRQoL among female NSCLC survivors, others have not observed this correlation with patient groups consisting of both women and men (Paull et al. 2006, Balduyck et al. 2009). This may be explained by different ways of analysis, as Paull et al. (2006) divided their patients into groups with either a CCI score of zero to two or a CCI score of more than two, while we handled each CCI score as a separate category.

Pulmonary function tests (PFTs) are usually thought to predict postoperative morbidity and mortality (Win et al. 2005b), but not HRQoL (Greillier et al. 2007). According to Pompili et al. (2011), PFTs did not correlate with the QLQ-C30, not even with the dyspnoea symptom scale, or with the SF-36 quality of life questionnaire scores, while another study, although having a small sample size, reported PFTs to correlate with long-term HRQoL five years after surgery (Sterzi et al. 2013). Two studies found poor preoperative DLCO% to predict lower postoperative HRQoL (Handy et al. 2002, Win et al. 2005a), but newer studies have refuted this finding (Paull et al. 2006, Brunelli et al. 2007, Ilonen et al. 2010).

The findings of VATS predicting a lower HRQoL and adjuvant therapy a higher HRQoL were surprising and contradictory to common opinion, largely based on shorter term reports (Pompili 2015, Bendixen et al. 2016). Many previous studies have reported adjuvant therapy as having either a negative or a non-significant effect on HRQoL (Handy et al. 2002, Paull et al. 2006, Sartipy 2009, Grutters et al. 2010). Our finding favouring adjuvant therapy

might be explained by adjuvant therapy being given to patients originally in better shape and with a higher preoperative HRQoL, albeit with a higher disease stage, as the lack of baseline HRQoL data would prevent us from detecting such associations. A prospective study found SF-36 physical composite score and pain to be similar between VATS and thoracotomy patients throughout the one-year follow-up. Interestingly, the mental composite score was constantly lower among VATS patients, reaching statistical significance at four and eight months postoperatively, although not regarded as clinically significant (Rizk et al. 2014). The response rate of 59% at 12 months must also be considered when interpreting the results.

The observed differences between thoracotomy and VATS respondents should not account for the finding of VATS being associated with lower HRQoL, as all of these factors were considered in the regression analyses. As the amount of comorbidity (Poghosyan et al. 2013) and old age (Möller and Sartipy 2012a) may negatively affect HRQoL – although the opposite results have also been reported (Ferguson et al. 2009, Salati et al. 2009) – one could argue that the VATS patients may have been in poorer shape already preoperatively. In this case, the absence of the baseline HRQoL data might have biased the results against VATS.

We found no correlation between the disease stage or extent of resection and the HRQoL. The majority (87%) of our respondents had undergone lobar or sublobar resection, yet only 61% had had stage I disease. The extent of resection has been reported to have a significant impact on the HRQoL, while disease stage has been found to be a non-significant factor in postoperative HRQoL (Sartipy 2009, Möller and Sartipy 2012a).

6.3 Study III

Among the 180 respondents, representing over 90% of the long-term NSCLC survivors included in the study, and with the mean follow-up time exceeding four years, thoracotomy patients reported significantly higher long-term HRQoL results than VATS patients. Besides the overall HRQoL, the difference in favour of the thoracotomy group was both statistically and clinically significant on the dimensions of mental function, breathing, usual activities, vitality, and speech, while no dimension showed differences favouring the VATS group.

The results can justly be criticized. The retrospective nature of the study with no preoperative HRQoL data obviously impairs the reliability of the results. We were only able to reliably determine the HRQoL differences between the patient groups at the chosen time point, but the possible effect of the surgical method on the timely change of the HRQoL within these groups remains unclear. Furthermore, the long time frame of the study, together with

the two-point data collection, may have led to biases. The latter cohort had a longer follow-up time (mean 55.8 vs. 42.4 months, p = 0.001), although both cohorts had similar portions of VATS patients, and their HRQoL results were comparable.

The finding of lower long-term HRQoL among VATS patients conflicts with the few previous long-term studies (Li et al. 2002, Aoki et al. 2007). Li et al. found the long-term HRQoL to be comparable between VATS and thoracotomy groups, with mean follow-up times of 33.5 and 39.4 months, respectively. They assessed HRQoL with the EORTC QLQ-C30, although the study included only 51 patients (Li et al. 2002). Aoki et al. observed higher scores for VATS patients on the dimensions of role-physical and role-emotional in their study comparing HRQoL between VATS and thoracotomy patients three years after surgery with the SF-36 questionnaire. They also reported VATS patients to score lower on the general health scale three and twelve months after surgery, but higher after three years; however, the differences were non-significant. Here again, the study comprised only 33 patients (Aoki et al. 2007). A fairly recent prospective study, with 201 patients included in the final analysis, found less pain and a higher HRQoL in the VATS group one year after lobectomy for stage I NSCLC (Bendixen et al. 2016).

The observed HRQoL differences between our patient groups were most prominent on the dimensions of mental function and breathing. While Rizk et al. (2014) also reported VATS patients to score lower on the SF-36 mental composite score, the difference was regarded as non-significant. VATS patients reporting lower scores on the dimension of breathing seems surprising, as the preoperative PFT results were comparable between the groups, and VATS is usually regarded as yielding objectively better postoperative pulmonary functions (Kaseda et al. 2000).

The only significant differences between the groups in pre- and perioperative characteristics (VATS patients having more often ADC as the histology, fewer nodal stations sampled, and shorter hospitalization) seem unimportant regarding the HRQoL differences. The shorter mean hospitalization among VATS patients has been repeatedly demonstrated (Nwogu et al. 2015, Bendixen et al. 2016), although its significance in HRQoL has not been evaluated to our knowledge. Both our groups had over one day shorter mean hospital stay than the corresponding groups in a recent analysis utilizing the European Society of Thoracic Surgeons (ESTS) database (Falcoz et al. 2016). To our knowledge, no study has associated certain histology with significant differences in HRQoL, as was also the case in Study II, even though ADC is usually situated more peripherally and SCC more centrally (Travis et al. 1995, Brambilla and Travis 2014). As the oncological efficacy was also similar in both groups, the number of nodal stations sampled seems non-significant to HRQoL.

Although in Study II complications were associated with lower HRQoL, no difference in complication rates between the VATS and thoracotomy groups existed. This was also the case in the study carried out by Bendixen et al. (2016), although some studies have reported higher incidence of complications among thoracotomy patients (Whitson et al. 2008, Nwogu et al. 2015).

Even though no significant differences in age, PFTs, CCI score, disease stage, or incidence of complications were observed, our clinical impression was that patients undergoing VATS were on average in poorer condition, i.e. frailer. Frailty is a comprehensive concept of physiological decline associated with ageing, and it has predicted surgical outcomes well (Kim et al. 2014). As the VATS patients scored lower on dimensions of mental function, vitality, and usual activities, and were older with a mean age of 66.9 versus 64.7 years ($p = 0.074$), a more detailed assessment of possible frailty might have demonstrated some underlying differences between the groups. Furthermore, as the response rate among thoracotomy patients was significantly lower, it can be argued that the non-respondents were on average in poorer condition (Fairclough 2010).

Another possible explanation for the observed HRQoL differences might be the different expectations concerning the treatment. As VATS patients may have had slightly different preoperative counselling, possibly highlighting the better short-term HRQoL results observed in previous studies, they might have developed higher or even overly optimistic expectations, predisposing them to disappointments. This phenomenon has been observed with total joint replacement patients, as realistic expectations were more likely to be fulfilled, yielding higher HRQoL gains (Gonzalez Saenz de Tejada et al. 2010), although positive expectations overall were associated with better postoperative HRQoL (Gonzalez Saenz de Tejada et al. 2014).

7 SUMMARY

Lung cancer is among the most common cancers in Finland and worldwide, with non-small cell lung cancer (NSCLC) constituting the majority of cases. Despite its poor prognosis, modern diagnostic and treatment methods enable more patients to survive the disease. This thesis focused on the long-term health-related quality of life (HRQoL) among surgically treated NSCLC survivors operated on at our clinic between January 2000 and January 2013. The HRQoL of patients operated on before July 2009 was assessed with both a generic and a cancer-specific patient-reported outcome measure (PROM) in 2011, while patients operated on after June 2009 answered only the generic PROM in 2016.

Our respondents reported significantly lower HRQoL approximately five years after the treatment than the age- and gender-standardized Finnish general population, with the impairment being most prominent on the dimensions of mobility and breathing. Compared with the reference values of the cancer-specific questionnaire, the respondents scored lower on the scales of physical functioning and dyspnoea.

Although survival was fairly predictable with objective patient, disease, and treatment features, they failed to show a notable effect on the long-term HRQoL. The few factors with any statistically significant association with HRQoL were comorbidities, preoperative FEV1%, use of video-assisted thoracoscopic surgery (VATS), adjuvant chemotherapy (ChT), and perioperative complications. Surprisingly, VATS was associated with lower HRQoL on the generic PROM, as were comorbidities and perioperative complications, while adjuvant ChT and a higher preoperative FEV1% were associated with higher HRQoL on the cancer-specific PROM. On the other hand, disease stage or the extent of resection seemed to have no effect on the long-term HRQoL.

When further comparing the long-term HRQoL in patients treated for local NSCLC through either thoracotomy or VATS, the latter group reported significantly lower scores, although no explanatory differences between the groups were observed. Unfortunately, as we lacked preoperative HRQoL data, the surprising results reliably indicated only HRQoL differences at the time of the assessment, and no definitive conclusions on the timely HRQoL evolution due to the chosen surgical method could be drawn.

8 CONCLUSIONS

1. Long-term NSCLC survivors report deteriorated HRQoL even several years after radical surgery, with physical and respiratory performance most severely impaired, compared with the age- and gender-matched general population. This is relevant considering the preoperative patient information, although the moderate magnitude of the impairment should not discourage possible curable treatment.

2. Objectively measurable clinical features fail to significantly predict long-term HRQoL after surgery, and thus, the assessment of preoperative HRQoL seems essential for both future studies and patient counselling. Long-term survival, however, was more reliably predicted by these features.

3. Contradicting previous studies with shorter follow-up times, VATS was associated with lower long-term HRQoL than thoracotomy, thus questioning the effect of the surgical method on all long-term outcomes. However, especially in younger survivors with a long life expectancy after treatment, speculative differences in long-term HRQoL should not influence the choice of surgical method.

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APPENDICES

Appendix 1. 15D HRQoL instrument

QUALITY OF LIFE QUESTIONNAIRE (15D©)

Please read through all of the alternative responses to each question before placing a cross (x) beside the alternative best describing **your present health status**. Continue through all 15 questions in this manner, giving only **one** answer to each.

QUESTION 1. MOBILITY

1 ( ) I am able to walk normally (without difficulty) indoors, outdoors, and on stairs.
2 ( ) I am able to walk without difficulty indoors, but outdoors and/or on stairs I have slight difficulties.
3 ( ) I am able to walk without help indoors (with or without an appliance), but outdoors and/or on stairs only with considerable difficulty or with help from others.
4 ( ) I am able to walk indoors only with help from others.
5 ( ) I am completely bed-ridden and unable to move about.

QUESTION 2. VISION

1 ( ) I see normally, i.e. I can read newspapers and TV text without difficulty (with or without glasses).
2 ( ) I can read papers and/or TV text with slight difficulty (with or without glasses).
3 ( ) I can read papers and/or TV text with considerable difficulty (with or without glasses).
4 ( ) I cannot read papers or TV text either with glasses or without, but I can see enough to walk about without guidance.
5 ( ) I cannot see enough to walk about without a guide, i.e. I am almost or completely blind.

QUESTION 3. HEARING

1 ( ) I can hear normally, i.e. normal speech (with or without a hearing aid).
2 ( ) I hear normal speech with a little difficulty.
3 ( ) I hear normal speech with considerable difficulty; in conversation I need voices to be louder than normal.
4 ( ) I hear even loud voices poorly; I am almost deaf.
5 ( ) I am completely deaf.

QUESTION 4. BREATHING

1 ( ) I am able to breathe normally, i.e. with no shortness of breath or other breathing difficulty.
2 ( ) I have shortness of breath during heavy work or sports, or when walking briskly on flat ground or slightly uphill.
3 ( ) I have shortness of breath when walking on flat ground at the same speed as others my age.
4 ( ) I get shortness of breath even after light activity, e.g. washing or dressing myself.
5 ( ) I have breathing difficulties almost all the time, even when resting.

QUESTION 5. SLEEPING

1 ( ) I am able to sleep normally, i.e. I have no problems with sleeping.
2 ( ) I have slight problems with sleeping, e.g. difficulty in falling asleep, or sometimes waking at night.
3 ( ) I have moderate problems with sleeping, e.g. disturbed sleep, or feeling that I have not slept enough.
4 ( ) I have great problems with sleeping, e.g. having to use sleeping pills often or routinely, or usually waking at night and/or too early in the morning.
5 ( ) I suffer from severe sleeplessness, e.g. sleep is almost impossible even with use of sleeping pills, or staying awake most of the night.

QUESTION 6. EATING

1 ( ) I am able to eat normally, i.e. with no help from others.
2 ( ) I am able to eat by myself with minor difficulty (e.g. slowly, clumsily, shakily, or with special appliances).
3 ( ) I need some help from another person in eating.
4 ( ) I am unable to eat by myself at all, so I must be fed by another person.
5 ( ) I am unable to eat at all, so I am fed either by tube or intravenously.

QUESTION 7. SPEECH

1 ( ) I am able to speak normally, i.e. clearly, audibly, and fluently.
2 ( ) I have slight speech difficulties, e.g. occasional fumbling for words, mumbling, or changes of pitch.
3 ( ) I can make myself understood, but my speech is e.g. disjointed, faltering, stuttering, or stammering.
4 ( ) Most people have great difficulty understanding my speech.
5 ( ) I can only make myself understood by gestures.

QUESTION 8. EXCRETION

1 ( ) My bladder and bowel work normally and without problems.
2 ( ) I have slight problems with my bladder and/or bowel function, e.g. difficulties with urination, or loose or hard bowels.
3 ( ) I have marked problems with my bladder and/or bowel function, e.g. occasional 'accidents', or severe constipation or diarrhoea.
4 ( ) I have serious problems with my bladder and/or bowel function, e.g. routine 'accidents', or need of catheterization or enemas.
5 ( ) I have no control over my bladder and/or bowel function.

QUESTION 9. USUAL ACTIVITIES

1 ( ) I am able to perform my usual activities (e.g. employment, studying, housework, free-time activities) without difficulty.
2 ( ) I am able to perform my usual activities slightly less effectively or with minor difficulty.
3 ( ) I am able to perform my usual activities much less effectively, with considerable difficulty, or not completely.
4 ( ) I can only manage a small proportion of my previously usual activities.
5 ( ) I am unable to manage any of my previously usual activities.

QUESTION 10. MENTAL FUNCTION

1 ( ) I am able to think clearly and logically, and my memory functions well.
2 ( ) I have slight difficulties in thinking clearly and logically, or my memory sometimes fails me.
3 ( ) I have marked difficulties in thinking clearly and logically, or my memory is somewhat impaired.
4 ( ) I have great difficulties in thinking clearly and logically, or my memory is seriously impaired.
5 ( ) I am permanently confused and disoriented in place and time.

QUESTION 11. DISCOMFORT AND SYMPTOMS

1 ( ) I have no physical discomfort or symptoms, e.g. pain, ache, nausea, itching, etc.
2 ( ) I have mild physical discomfort or symptoms, e.g. pain, ache, nausea, itching, etc.
3 ( ) I have marked physical discomfort or symptoms, e.g. pain, ache, nausea, itching, etc.
4 ( ) I have severe physical discomfort or symptoms, e.g. pain, ache, nausea, itching, etc.
5 ( ) I have unbearable physical discomfort or symptoms, e.g. pain, ache, nausea, itching, etc.

QUESTION 12. DEPRESSION
1 ( ) I do not feel at all sad, melancholic, or depressed.
2 ( ) I feel slightly sad, melancholic, or depressed.
3 ( ) I feel moderately sad, melancholic, or depressed.
4 ( ) I feel very sad, melancholic, or depressed.
5 ( ) I feel extremely sad, melancholic, or depressed.

QUESTION 13. DISTRESS
1 ( ) I do not feel at all anxious, stressed, or nervous.
2 ( ) I feel slightly anxious, stressed, or nervous.
3 ( ) I feel moderately anxious, stressed, or nervous.
4 ( ) I feel very anxious, stressed, or nervous.
5 ( ) I feel extremely anxious, stressed, or nervous.

QUESTION 14. VITALITY
1 ( ) I feel healthy and energetic.
2 ( ) I feel slightly weary, tired, or feeble.
3 ( ) I feel moderately weary, tired, or feeble.
4 ( ) I feel very weary, tired, or feeble, almost exhausted.
5 ( ) I feel extremely weary, tired, or feeble, totally exhausted.

QUESTION 15. SEXUAL ACTIVITY
1 ( ) My state of health has no adverse effect on my sexual activity.
2 ( ) My state of health has a slight effect on my sexual activity.
3 ( ) My state of health has a considerable effect on my sexual activity.
4 ( ) My state of health makes sexual activity almost impossible.
5 ( ) My state of health makes sexual activity impossible.

TERVEYTEEN LIITTYVÄN ELÄMÄNLAADUN KYSELYLOMAKE (15D©)

Ohje: Lukekaa ensin läpi huolellisesti kunkin kysymyksen kaikki vastausvaihtoehdot. Merkitkää sitten rasti (x) sen vaihtoehdon kohdalle, joka **parhaiten kuvaa nykyistä terveydentilaanne**. Menetelkää näin kaikkien kysymysten 1-15 kohdalla. Kustakin kysymyksestä rastitetaan siis yksi vaihtoehto.

KYSYMYS 1. Liikuntakyky

1 ( ) Pystyn kävelemään normaalisti (vaikeuksitta) sisällä, ulkona ja portaissa.
2 ( ) Pystyn kävelemään vaikeuksitta sisällä, mutta ulkona ja/tai portaissa on pieniä vaikeuksia.
3 ( ) Pystyn kävelemään ilman apua sisällä (apuvälinein tai ilman), mutta ulkona ja/tai portaissa melkoisin vaikeuksin tai toisen avustamana.
4 ( ) Pystyn kävelemään sisälläkin vain toisen avustamana.
5 ( ) Olen täysin liikuntakyvytön ja vuoteenoma.

KYSYMYS 2. Näkö

1 ( ) Näen normaalisti eli näen lukea lehteä ja TV:n tekstejä vaikeuksitta (silmälaseilla tai ilman).
2 ( ) Näen lukea lehteä ja/tai TV:n tekstejä pienin vaikeuksin (silmälaseilla tai ilman).
3 ( ) Näen lukea lehteä ja/tai TV:n tekstejä huomattavin vaikeuksin (silmälaseilla tai ilman).
4 ( ) En näe lukea lehteä enkä TV:n tekstejä ilman silmälaseja tai niiden kanssa, mutta näen kulkea ilman opasta.
5 ( ) En näe kulkea oppaatta eli olen lähes tai täysin sokea.

KYSYMYS 3. Kuulo

1 ( ) Kuulen normaalisti eli kuulen hyvin normaalia puheääntä (kuulokojeella tai ilman).
2 ( ) Kuulen normaalia puheääntä pienin vaikeuksin.
3 ( ) Minun on melko vaikea kuulla normaalia puheääntä, keskustelussa on käytettävä normaalia kovempaa puheääntä.
4 ( ) Kuulen kovaakin puheääntä heikosti; olen melkein kuuro.
5 ( ) Olen täysin kuuro.

KYSYMYS 4. Hengitys

1 ( ) Pystyn hengittämään normaalisti eli minulla ei ole hengenahdistusta eikä muita hengitysvaikeuksia.
2 ( ) Minulla on hengenahdistusta raskaassa työssä tai urheillessa, reippaassa kävelyssä tasamaalla tai lievässä ylämäessä.
3 ( ) Minulla on hengenahdistusta, kun kävelen tasamaalla samaa vauhtia kuin muut ikäiseni.
4 ( ) Minulla on hengenahdistusta pienenkin rasituksen jälkeen, esim. peseytyessä tai pukeutuessa.
5 ( ) Minulla on hengenahdistusta lähes koko ajan, myös levossa.

KYSYMYS 5. Nukkuminen

1 ( ) Nukun normaalisti eli minulla ei ole mitään ongelmia unen suhteen.
2 ( ) Minulla on lieviä uniongelmia, esim. nukahtamisvaikeuksia tai satunnaista yöheräilyä.
3 ( ) Minulla on melkoisia uniongelmia, esim. nukun levottomasti tai uni ei tunnu riittävältä.
4 ( ) Minulla on suuria uniongelmia, esim. joudun käyttämään usein tai säännöllisesti unilääkettä, herään säännöllisesti yöllä ja/tai aamuisin liian varhain.
5 ( ) Kärsin vaikeasta unettomuudesta, esim. unilääkkeiden runsaasta käytöstä huolimatta nukkuminen on lähes mahdotonta, valvon suurimman osan yöstä.

KYSYMYS 6. Syöminen

1 ( ) Pystyn syömään normaalisti eli itse ilman mitään vaikeuksia.
2 ( ) Pystyn syömään itse pienin vaikeuksin (esim. hitaasti, kömpelösti, vavisten tai erityisapuneuvoin).
3 ( ) Tarvitsen hieman toisen apua syömisessä.
4 ( ) En pysty syömään itse lainkaan, vaan minua pitää syöttää.
5 ( ) En pysty syömään itse lainkaan, vaan minulle pitää antaa ravintoa letkun avulla tai suonensisäisesti.

KYSYMYS 7. Puhuminen

1 ( ) Pystyn puhumaan normaalisti eli selvästi, kuuluvasti ja sujuvasti.
2 ( ) Puhuminen tuottaa minulle pieniä vaikeuksia, esim. sanoja on etsittävä tai ääni ei ole riittävän
kuuluva tai se vaihtaa korkeutta.
3 ( ) Pystyn puhumaan ymmärrettävästi, mutta katkonaisesti, ääni vavisten, sammaltaen tai änkyttäen.
4 ( ) Muilla on vaikeuksia ymmärtää puhettani.
5 ( ) Pystyn ilmaisemaan itseäni vain elein.

KYSYMYS 8. Eritystoiminta

1 ( ) Virtsarakkoni ja suolistoni toimivat normaalisti ja ongelmitta.
2 ( ) Virtsarakkoni ja/tai suolistoni toiminnassa on lieviä ongelmia, esim. minulla on virtsaamisvaikeuksia tai kova tai löysä vatsa
3 ( ) Virtsarakkoni ja/tai suolistoni toiminnassa on melkoisia ongelmia, esim. minulla on satunnaisia virtsanpidätysvaikeuksia tai vaikea ummetus tai ripuli.
4 ( ) Virtsarakkoni ja/tai suolistoni toiminnassa on suuria ongelmia, esim. minulla on säännöllisesti "vahinkoja" tai peräruiskeiden tai katetroinnin tarvetta.
5 ( ) En hallitse lainkaan virtsaamista ja/tai ulostamista.

KYSYMYS 9. Tavanomaiset toiminnot

1 ( ) Pystyn suoriutumaan normaalisti tavanomaisista toiminnoista (esim. ansiotyö, opiskelu, kotityö, vapaa-ajan toiminnot).
2 ( ) Pystyn suoriutumaan tavanomaisista toiminnoista hieman alentuneella teholla tai pienin vaikeuksin.
3 ( ) Pystyn suoriutumaan tavanomaisista toiminnoista huomattavasti alentuneella teholla tai huomattavin vaikeuksin tai vain osaksi.
4 ( ) Pystyn suoriutumaan tavanomaisista toiminnoista vain pieneltä osin.
5 ( ) En pysty suoriutumaan lainkaan tavanomaisista toiminnoista.

KYSYMYS 10. Henkinen toiminta

1 ( ) Pystyn ajattelemaan selkeästi ja johdonmukaisesti ja muistini toimii täysin moitteettomasti.
2 ( ) Minulla on lieviä vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai muistini ei toimi täysin moitteettomasti
3 ( ) Minulla on melkoisia vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on jonkin verran muistinmenetystä
4 ( ) Minulla on suuria vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on huomattavaa muistinmenetystä
5 ( ) Olen koko ajan sekaisin ja vailla ajan tai paikan tajua

KYSYMYS 11. Vaivat ja oireet

1 ( ) Minulla ei ole mitään vaivoja tai oireita, esim. kipua, särkyä, pahoinvointia, kutinaa jne.
2 ( ) Minulla on lieviä vaivoja tai oireita, esim. lievää kipua, särkyä, pahoinvointia, kutinaa jne.
3 ( ) Minulla on melkoisia vaivoja tai oireita, esim. melkoista kipua, särkyä, pahoinvointia, kutinaa jne.
4 ( ) Minulla on voimakkaita vaivoja tai oireita, esim. voimakasta kipua, särkyä, pahoinvointia, kutinaa jne.
5 ( ) Minulla on sietämättömiä vaivoja ja oireita, esim. sietämätöntä kipua, särkyä, pahoinvointia, kutinaa jne.

KYSYMYS 12. Masentuneisuus

1 ( ) En tunne itseäni lainkaan surulliseksi, alakuloiseksi tai masentuneeksi.
2 ( ) Tunnen itseni hieman surulliseksi, alakuloiseksi tai masentuneeksi.
3 ( ) Tunnen itseni melko surulliseksi, alakuloiseksi tai masentuneeksi.
4 ( ) Tunnen itseni erittäin surulliseksi, alakuloiseksi tai masentuneeksi.
5 ( ) Tunnen itseni äärimmäisen surulliseksi, alakuloiseksi tai masentuneeksi.

KYSYMYS 13. Ahdistuneisuus

1 ( ) En tunne itseäni lainkaan ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
2 ( ) Tunnen itseni hieman ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
3 ( ) Tunnen itseni melko ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
4 ( ) Tunnen itseni erittäin ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
5 ( ) Tunnen itseni äärimmäisen ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

KYSYMYS 14. Energisyys

1 ( ) Tunnen itseni terveeksi ja elinvoimaiseksi.
2 ( ) Tunnen itseni hieman uupuneeksi, väsyneeksi tai voimattomaksi.
3 ( ) Tunnen itseni melko uupuneeksi, väsyneeksi tai voimattomaksi.
4 ( ) Tunnen itseni erittäin uupuneeksi, väsyneeksi tai voimattomaksi, lähes "loppuun palaneeksi".
5 ( ) Tunnen itseni äärimmäisen uupuneeksi, väsyneeksi tai voimattomaksi, täysin "loppuun palaneeksi".

KYSYMYS 15. Sukupuolielämä

1 ( ) Terveydentilani ei vaikeuta mitenkään sukupuolielämääni.
2 ( ) Terveydentilani vaikeuttaa hieman sukupuolielämääni.
3 ( ) Terveydentilani vaikeuttaa huomattavasti sukupuolielämääni.
4 ( ) Terveydentilani tekee sukupuolielämäni lähes mahdottomaksi.
5 ( ) Terveydentilani tekee sukupuolielämäni mahdottomaksi.

Appendix 2. EORTC QLQ-C30 (Aaronson et al. 1993) and QLQ-LC13 (Bergman et al. 1994) HRQoL instruments

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

EORTC QLQ-C30 (version 3.0.)

Selvitämme kyselyssämme joitakin teitä ja terveyttänne koskevia asioita. Pyydämme teitä vastaamaan itse kaikkiin kysymyksiin ympyröimällä parhaiten sopivan numeron. Tässä kyselyssä ei ole "oikeita" eikä "vääriä" vastauksia. Pidämme antamanne tiedot ehdottoman luottamuksellisina.

Täyttäkää tähän nimikirjaimenne: □ □ □ □
Syntymäaika (päivä, kk, vuosi): □ □ □ □ □ □ □ □
Kyselyn täyttöpäivä (päivä, kk, vuosi): □ □ □ □ □ □ □ □

31

	Ei lainkaan	Vähän	Melko paljon	Hyvin paljon
1. Tuntuvatko rasittavat työt kuten painavan ostoskassin tai matkalaukun kantaminen teistä työläältä?	1	2	3	4
2. Tuntuvatko pitkät kävelymatkat työläiltä?	1	2	3	4
3. Tuntuvatko lyhyet kävelymatkat kotinne ulkopuolella työläiltä?	1	2	3	4
4. Pitääkö teidän pysytellä levossa tai istumassa päivän mittaan?	1	2	3	4
5. Tarvitsetteko apua ruokaillessanne, pukeutuessanne, peseytyessänne tai WC:n käytössä?	1	2	3	4

Kuluneella viikolla:

	Ei lainkaan	Vähän	Melko paljon	Hyvin paljon
6. Oliko teillä vaikeuksia suoriutua työstänne tai muista päivittäisistä toimistanne?	1	2	3	4
7. Oliko teillä rajoituksia harrastus- tai muissa vapaa-ajan toiminnoissanne?	1	2	3	4
8. Oliko teillä hengenahdistusta?	1	2	3	4
9. Oliko kipuja?	1	2	3	4
10. Tunsitteko levontarvetta?	1	2	3	4
11. Oliko unettomuutta?	1	2	3	4
12. Tunsitteko heikotusta?	1	2	3	4
13. Oliko ruokahaluttomuutta?	1	2	3	4
14. Oliko pahoinvointia?	1	2	3	4
15. Oksensitteko?	1	2	3	4
16. Oliko ummetusta?	1	2	3	4

Jatkuu seuraavalle sivulle

Kuluneella viikolla:	**Ei lainkaan**	**Vähän**	**Melko paljon**	**Hyvin paljon**
17. Oliko ripulia?	1	2	3	4
18. Olitteko väsynyt?	1	2	3	4
19. Häiritsikö kipu päivittäisiä toimianne?	1	2	3	4
20. Oliko teillä keskittymisvaikeuksia esim. sanomalehteä lukiessanne tai televisiota katsellessanne?	1	2	3	4
21. Olitteko jännittynyt?	1	2	3	4
22. Olitteko huolestunut?	1	2	3	4
23. Olitteko ärtynyt?	1	2	3	4
24. Olitteko masentunut?	1	2	3	4
25. Oliko teidän vaikea muistaa asioita?	1	2	3	4
26. Häiritsikö hoito tai fyysinen kuntonne perhe-elämäänne?	1	2	3	4
27. Häiritsikö hoito tai fyysinen kuntonne sosiaalista kanssakäymistä?	1	2	3	4
28. Aiheuttaako fyysinen kuntonne tai hoito taloudellisia vaikeuksia?	1	2	3	4

Vastatkaa seuraaviin kysymyksiin ympyröimällä numerosarjasta 1-7 teihin parhaiten sopiva vaihtoehto

29. Millainen yleinen terveydentilanne oli kuluneella viikolla?

1	2	3	4	5	6	7
Erittäin huono						Erinomainen

30. Millainen yleinen elämänne laatu oli kuluneella viikolla?

1	2	3	4	5	6	7
Erittäin huono						Erinomainen

FINNISH

EORTC QLQ - LC13

Toisinaan potilaat kertovat, että heillä esiintyy seuraavia oireita. Olkaa hyvä ja merkitkää miten paljon näitä oireita teillä on esiintynyt viime viikon aikana. Rengastakaa numero, joka parhaiten kuvaa oireen laatua.

Kuluneella viikolla:		**Ei/en lainkaan**	**Vähän**	**Melko paljon**	**Hyvin paljon**
31.	Miten paljon yskitte?	1	2	3	4
32.	Yskittekö verta?	1	2	3	4
33.	Olitteko hengästynyt, kun lepäsitte?	1	2	3	4
34.	Olitteko hengästynyt, kun kävelitte?	1	2	3	4
35.	Olitteko hengästynyt, kun nousitte portaita?	1	2	3	4
36.	Onko kielenne tai suunne ollut kipeä?	1	2	3	4
37.	Onko teillä ollut nielemisvaikeuksia?	1	2	3	4
38.	Onko käsiänne tai jalkojanne kihelmöinyt?	1	2	3	4
39.	Onko teiltä lähtenyt hiuksia?	1	2	3	4
40.	Oletteko tuntenut rintakipuja?	1	2	3	4
41.	Oletteko tuntenut kipua käsivarsissanne tai hartioissanne?	1	2	3	4
42.	Onko teillä ollut kipuja muualla vartalossanne?	1	2	3	4
	Jos on, niin missä? _____				
43.	Oletteko ottanut mitään kipulääkettä?				
	1 Ei **2 Kyllä**				
	Jos olette, miten paljon siitä oli apua?	1	2	3	4