From the Department of Molecular Medicine and Surgery
Karolinska Institutet, Stockholm, Sweden

PULMONARY RESECTION FOR MALIGNANT TUMORS

Mamdoh Al-Ameri

Karolinska
Institutet

Stockholm 2018

PULMONARY RESECTION FOR MALIGNANT TUMORS

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Mamdoh Al-Ameri

Principal Supervisor:
Associate professor Ulrik Sartipy
Karolinska Institutet
Department of Molecular Medicine and
Surgery

Co-supervisors:
Professor Anders Franco-Cereceda
Karolinska Institutet
Department of Molecular Medicine and
Surgery

Med Dr Per Bergman
Karolinska Institutet
Department of Molecular Medicine and
Surgery

Opponent:
Professor Henrik Ahn
Linköping University
Department of Medical and Health Sciences

Examination Board:
Associate professor Ylva Trolle Lagerros
Karolinska Institutet
Department of Medicine Solna

Associate professor Per Nilsson
Karolinska Institutet
Department of Molecular Medicine and
Surgery

Associate professor Gunnar Wagenius
Uppsala University
Department of Immunology, Genetics and
Pathology

"Let the beauty of what you love be what you do"
Rumi (1207-1273)

To the soul of my mother

ABSTRACT

Resection of malignant tumors in the lung represents greater than 70% of thoracic surgeries. The continuous evolution of new surgical techniques and management of malignant diseases have improved the clinical outcomes of survival and quality of life. The aim of this thesis is to review important clinical aspects of the surgical resection of malignant tumors in the lung.

Study I A prospective population-based cohort assessment of the relation between preoperative baseline self-reported SF-36 questionnaire data and long-term survival after thoracic procedures. The study included 249 patients planned for thoracic surgery at Karolinska University Hospital, Stockholm, Sweden, between 2006 and 2008. During an 8.0-year (median) follow-up, 48% of patients died. Patients with a physical component summary score less than the reference experienced significantly higher mortality rates compared with those of patients with lower mental component summary scores (hazard ratio [HR], 2.02; 95% confidence interval [CI], 1.34–3.06, p = 0.001) and (HR, 1.32; 95% CI, 0.84–3.06, p = 0.233), respectively.

Study II A population-based cohort study of 184 patients who underwent pulmonary metastasectomy for colorectal cancer at Karolinska University Hospital between January 1, 2004, and December 31, 2015. The median follow-up was 3.2 years, and 36% (66/184) of patients died. Five-year overall survival was 60% (95% CI, 50%–68%), and carcinoembryonic antigen levels were the only statistically significant prognostic factor of mortality (age- and sex-adjusted, [HR, 2.46; 95% CI, 1.15–5.26, p = 0.020]).

Study III A nationwide cohort study to investigate overall survival after surgical resection of pulmonary metastases of colorectal cancer in Sweden and to assess the discriminatory power of a recently suggested risk-prediction model. This study, which used the Swedish national quality register for thoracic surgery (ThoR), included 756 patients who underwent surgery between 2009 and 2015. Five-year overall survival was 56%, and the median follow-up was 2.9 years.

Study IV Evaluation of early and late clinical outcomes after video-assisted thoracic surgery (VATS) and thoracotomy-lobectomy for non-small cell lung cancer of a cohort of patients in Sweden. The study used the ThoR register and included patients (n = 285) who underwent VATS lobectomy at Karolinska University Hospital and patients (n = 1316) who underwent thoracotomy lobectomy at other hospitals in Sweden between 2012 and 2015.

Study V A study of a nationwide cohort conducted in Sweden to determine if the weekday of surgery influenced the long-term survival of patients listed in the ThoR register who underwent surgery for lung cancer between 2009 and 2015.

Conclusions

Study I - Preoperative self-reported physical quality of life lower than the reference value was significantly related to poor long-term survival after thoracic surgery.

Study II - Long-term survival after pulmonary metastasectomy for colorectal cancer (CRC) at Karolinska University Hospital was comparable with the previously reported higher levels, and the number of surgeries increased during the study period. Prethoracotomy carcinoembryonic antigen concentrations ≥4 ng/mL were the only significant prognostic factor for survival.

Study III - In Sweden, long-term survival after pulmonary metastasectomy for CRC was consistent with better survival reported by contemporaneous studies. External validation of a recently proposed risk prediction model achieved good discrimination among Swedish patients.

Study IV - VATS lobectomy achieved better short- and long-term outcomes compared with thoracotomy, indicating the feasibility and safety of the VATS technique for treating patients with early NSCLC.

Study V - There was no significant difference between all-cause mortality and the weekday of surgery of patients with lung cancer in Sweden.

LIST OF SCIENTIFIC PAPERS

I. **Al-Ameri M**, Bergman P, Franco-Cereceda A, Sartipy U.
    Self-reported physical quality of life before thoracic operations is
    associated with long-term survival.
    Ann Thorac Surg 2017;103:484-490

II. **Al-Ameri M**, Persson M, Bergman P, Franco-Cereceda A, Sartipy U.
    Long-term survival after surgery for pulmonary metastases from
    colorectal cancer: an observational cohort study.
    J Thorac Dis 2017;9:4358-4365

III. **Al-Ameri M**, Persson M, Bergman P, Franco-Cereceda A, Sartipy U.
    Surgery for pulmonary metastases from colorectal cancer: survival and
    prognostic factors.
    J Thorac Dis (In Press)

IV. **Al-Ameri M**, Bergman P, Franco-Cereceda A, Sartipy U.
    Video-assisted thoracoscopic versus open thoracotomy lobectomy:
    a Swedish nationwide cohort study.
    J Thorac Dis (In Press)

V. Jackson V, **Al-Ameri M**, Sartipy U.
    Weekday and survival after pulmonary resections for lung cancer:
    a Swedish nationwide cohort study.
    Chest (In Press)

CONTENTS

LIST OF ABBREVIATIONS

GTS	General Thoracic Surgery
VATS	Video-Assisted Thoracic Surgery
NSCLC	Non-Small Cell Lung Cancer
SF-36	Short Form 36
PCS	Physical Component Summary
MCS	Mental Component Summary
HRQOL	Health Related Quality of Life
QOL	Quality of Life
CRC	Colorectal Cancer
DFI	Disease-Free Interval
PET-CT	Positron-Emission Tomography-Computerized Tomography
RMST	Restricted Mean Survival Time
PM-CRC	Pulmonary Metastasectomy for CRC
IPTW	Inverse Probability Treatment Weighting

1 INTRODUCTION

General thoracic surgery (GTS) encompasses a wide range of surgical treatments in the disciplines of oncology, infectious diseases, trauma, and plastic surgery of the chest wall. Surgical resection of malignant tumors in the lung (primary lung cancer and metastases from other cancers) represents approximately 70% of GTS procedures.[1, 2]

The use of GTS for treating cancer has increased during the last three decades. Continuous innovations and advances in the diagnosis and treatment of cancer, together with a dynamic patient population, partially explain this increase.[3, 4]

Pulmonary metastasectomy of metastatic cancers has become an essential part of multimodal treatment of metastatic cancers such as metastatic colorectal cancer (CRC). The continuous improvements in the management of CRC accompanied by the development of minimally invasive GTS provides many patients with the opportunity to undergo surgery, which was previously contraindicated because of a patient's poor general condition or multiple recurrences of the disease.[5] Despite the increasing trend in surgical resection of pulmonary metastases of patients with CRC, we are unaware of strong evidence supporting the conclusion that survival has improved.[4]

Video-assisted thoracic surgery (VATS) lobectomy, introduced during the last three decades, serves as an alternative to conventional thoracotomy in the surgical management of early-stage non-small cell lung cancer (NSCLC). The technique has attracted considerable interest worldwide, with increasing evidence supporting its feasibility and ability to improve clinical short-term outcomes compared with those of thoracotomy.[6] In Sweden, VATS lobectomy was introduced in 2012, and according to the records of the Swedish national quality register for thoracic surgery (ThoR),[7] nearly all procedures performed in the subsequent 4 years were performed at one of eight thoracic centers.

Health-related quality of life (HRQOL) is an important aspect of the health care, particularly for patients with malignant diseases. Recently, the use of self-reported QOL to help make clinical decisions has increased attention on this characteristic to complement other objective health measures.[8-10]

The aim of this thesis was to investigate several important clinical aspects of the surgical resection of malignant tumors in the lung, with emphasis on prognostic factors, surgical outcomes, and surgical techniques.

2 BACKGROUND

2.1 LUNG CANCER

The incidence and death rates of lung cancer worldwide are the highest among cancers. Approximately 1.8 million new cases and 1.6 million deaths were recorded worldwide in 2012, corresponding to 12.9% of new cancers and 19.4% of cancer deaths. Notably, lung cancer accounts for more deaths of men and women than other cancers.[11]

In Sweden, lung cancer is the fifth most common cancer, although it is the leading cancer-related cause of death. The disease has increased among women since the 1980s, while decreasing among men. This may reflect the change in women's smoking habits since the 1960s. In 2011, 3652 new cases of lung cancer were registered, 1869 in men and 1783 in women.[12]

Despite recent developments in cancer treatment, lung cancer survival has only marginally improved in recent decades, and 5-year survival is approximately 16%. Surgery is the best curative treatment for resectable and operable early-stage (I and II) NSCLC, achieving 5-year survival rates of 60%–80% for stage I and 30%–50% for stage II.[13]

2.2 THOR

ThoR includes records for all thoracic procedures except cardiac and great vessel surgery. The registry, which is accessed via the Internet, collects data from the eight thoracic centers in Sweden. Reporting from each center is continuous via a special login to the website. This service gathers relevant information before, during, and after surgery about patients' risk profiles, medical-technical treatments, outcomes, and possible surgical complications. Comparisons can be made among hospitals and regions. Survival data are continuously updated from the Total Population Register (Statistics Sweden).[7]

When ThoR was initiated in 2008, the participation rates were low, subsequently increasing to approximately 50% of centers between 2009 and 2011. Complete coverage of all eight thoracic centers was achieved in 2013 (see table below).

Clinic	2008	2009	2010	2011	2012	2013	2014	2015
Stockholm				386	386	396	452	453
Lund	28	474	498	501	483	466	518	451
Göteborg	231	288	388	349	395	393	352	391
Linköping	205	248	243	297	260	262	313	298
Uppsala	156	132	26	56	43	312	309	305
Umeå	34	10	135	143	155	160	177	225
Örebro	93	81	125	134	131	109	149	150
Karlskrona	9			119	118	102	98	73

Number of operations per clinic year 2008-2015

(Adapted from ThoR Annual Report 2015, available at http://www.ucr.uu.se/thor)

2.3 SHORT FORM 36 (SF-36) HRQOL QUESTIONNAIRE

SF-36 is a validated generic QOL instrument, which is available in various languages and includes reference values from the general population. The instrument evaluates eight dimensions of health as follows: physical function, role limitations caused by physical problems, pain, vitality, perception of general health, social function, role limitations caused by emotional problems, and mental health. Scores for each scale range from 0 to 100. Higher scores indicate better health status. Overall physical and mental HRQOL can be assessed using the scores of the physical component summary (PCS) and mental component summary (MCS).[14]

2.4 ROLE OF HRQOL IN PREDICTING RISK

Whereas objective risk assessment of surgery focuses on mortality, survival, and morbidity, evaluating the HRQOL produces a subjective measure reflecting the impact of disease or its treatment on a patient's physical and mental health. Studies show that objective functional measures and self-reported QOL are two independent measures.[15]

Many instruments are available to measure HRQOL specific to different medical disciplines. In cancer research, most recent studies used well-validated cancer-specific QOL questionnaires. A review of the literature identified 59 different instruments used to measure the QOL of patients with cancer.[16] The European Organization for Research and Treatment of Cancer's Quality of Life Questionnaire-C30 and SF-36 are widely used as a cancer-specific and generic QOL instrument, respectively.[16]

The utility of patient-reported outcome measures for risk prediction has recently garnered increasing interest. For example, HRQOL is associated with survival of patients with cancer after coronary bypass surgery as well as subsequent surgeries for lung cancer.[8-10] Further, Pompili et al. found a significant association between the

preoperative physical components of HRQOL, overall survival, and cancer-specific survival of patients undergoing resection for early-stage NSCLC.[17] This relation requires further investigation and discussion. A possible explanation of the association may be that the HRQOL reflects the unmeasurable effects of lung cancer and its treatment on a patient's physical and emotional status.[17]

Möller and Sartipy used the SF-36 questionnaire to analyze the association between self-reported QOL and outcomes of lung surgery based on data for a population of patients who underwent surgery at Karolinska University Hospital in Sweden between 2006 and 2008.[10, 18] Two studies focused on the relationship between self-reported QOL and survival after lung cancer surgery. In the first study, the investigators found postoperative declines of 10% in the PCS and MCS scores from preoperative baseline scores were associated with 18% and 13% higher risks of death, respectively.[10] The second study assessed the prognostic value of HRQOL for evaluating long-term survival 6 months after lung cancer surgery (median follow-up, 4 years).[18] The results show that the PCS and MCS scores were significantly associated with survival, independent of baseline scores. A compelling finding is that MCS scores less than the mean of the age- and gender-matched normal population were associated with a 3-fold increase in the risk of death.[18]

2.5   LUNG METASTASIS FROM CRC

CRC is the third most commonly diagnosed cancer in males and the second in females, with a worldwide estimate of 1.4 million cases and 693,900 deaths every year.[19] Approximately 25% of patients have metastatic disease at the time of initial diagnosis, and approximately 50% of patients with CRC will have metastasis. The two most common sites of metastatic growth are the liver and lungs, affecting approximately 35% and 5%–15% of patients, respectively.[20] In Sweden, nearly 6000 new cases of CRC are diagnosed each year.[21]

Considerable progress has been made in improving therapy of CRC, including diagnosis and multidisciplinary treatment because of improvements in our understanding of oncogenic signaling pathways, discovery of new tumor-specific markers, and introduction of targeted therapy. These advances have improved the survival of patients with CRC as well as those with liver metastases. For example, patients with metastatic disease had a 5-year survival rate of approximately 25% compared with 50% at the time this review was accepted for publication.[22, 23]

Resection of R0-resectable liver metastases of CRC was adopted in the mid-1990s as a curative treatment, and subsequently this modality has become widely accepted, although the supporting evidence is based entirely on retrospective observational studies. Similarly, pulmonary metastasectomy of CRC (PM-CRC) has become widely accepted in clinical practice to improve long-term survival.[24, 25] Treasure et al. reviewed studies of pulmonary metastasectomy used to treat four common malignant tumors and found that although pulmonary metastasectomy appears beneficial for the management of metastasized germ cell tumors, the evidence is weak regarding

CRC, sarcomas, and melanomas because of an absence of randomized trials, comparative analyses, and selection bias.[4]

Evidence indicating the benefits of PM-CRC is insufficient to generate an unequivocal clinical guideline for surgical indications or to demonstrate an influence on long-term survival. Such evidence comprises mainly retrospective studies and meta-analyses, but not randomized studies.[26]

Evidence demonstrates the prognostic value of the variables as follows: disease-free interval (DFI), number and laterality of metastases, hilar and mediastinal lymph nodes metastasis, previous metastatic disease in the liver, staging of the primary tumor, prethoracotomy carcinoembryonic antigen (CEA) concentrations, *KRAS* status, carbohydrate antigen 19-9 (CA19-9), and location of the primary tumor.[27-30] To our knowledge, few studies propose prognostic models incorporating these variables to improve the selection of patients who will benefit from surgery, although these models are not validated or widely applied.[31]

A survey of current clinical practice among members of the European Society of Thoracic Surgery (ESTS) shows that approximately 40% of pulmonary metastasectomies with curative intent are performed using VATS.[32] This approach is controversial because of the possibility of missing small lesions as well as the restriction of bimanual palpation through the surgical ports. A prospective, sequentially controlled study by Eckardt et al. found that several lesions that were undetected using imaging techniques were discovered via thoracotomy, but not using VATS. A significant proportion of these lesions are not benign (33% metastases and 3% primary lung cancers).[32]

The need for a randomized study on PM-CRC has increased because of variations in surgical practice, continuous pressure to expand the indications of surgical treatment, and absence of strong evidence on its effectiveness. The randomized, controlled Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) trial funded by Cancer Research UK was launched in March 2010, and recruitment continues.[33] The objective of this trial is to study the effectiveness of pulmonary metastasectomy, focusing on clinical outcomes, overall survival, relapse-free survival, lung function, and patient-reported QOL.[33]

2.6 VATS LOBECTOMY

The development of minimally invasive surgery has dramatically changed numerous surgical subspecialties over the past three decades. The driving forces behind these developments are minimal surgical trauma and rapid postoperative recovery.

VATS lobectomy was introduced at the beginning of the 1990s as an alternative to conventional thoracotomy. Since its introduction, the technique has gained worldwide recognition. The continuous endeavor to overcome post-thoracotomy pain, which is one of the most severe types of postoperative pain, was an important incentive responsible for the wide adoption of VATS lobectomy, particularly when

early reports from centers that frequently conduct VATS supported its feasibility and safety for treatment of early NSCLC.[34-36]

The absence of standardization and definition of VATS for lobectomy has generated controversy about its advantages compared with traditional thoracotomy for treating NSCLC. The techniques vary between VATS with simultaneous stapling and hybrid video-assisted minithoracotomy with some rib retraction.[37, 38] Consequently, authentic VATS lobectomy for treating patients with early-stage NSCLC is defined as minithoracotomy (4–8 cm), two 0.5-cm port incisions using a video camera as a guide, and conventional hilar dissection without rib retraction.[6, 39]

Hansen et al. described the Copenhagen experience using a VATS lobectomy protocol that employs a standardized three-port anterior approach.[40] Their study of the outcomes of approximately 1000 patients demonstrates the many advantages of this approach. The figure below demonstrates how the surgeon and assistant stand on the same side of the anterior side of the patient and view the same image, while the scrub nurse stands opposite. A 5-cm utility incision placed over the hilum in the 4th intercostal space anterior to the latissimus dorsi muscle (anterior incision) facilitates the dissection of hilar structures and easy control of major bleeding and rapid conversion if required. The camera-port is positioned lower down in the anterior axillary line at the level of the top of diaphragm, and the last 1.5-cm incision is posteriorly positioned at the same level as the camera-port under the scapula and anterior to the latissimus dorsi muscle. The same approach is suitable for resection of all lobes, and it is recommended to gently push the lung tissue, without grasping forceps, to minimize the risk of lung damage and postoperative air leaks.[40] A review by McElnay et al. found a substantial increase in the number of VATS lobectomies, accompanied by improved safety after adoption of a standardized anterior program.[41]
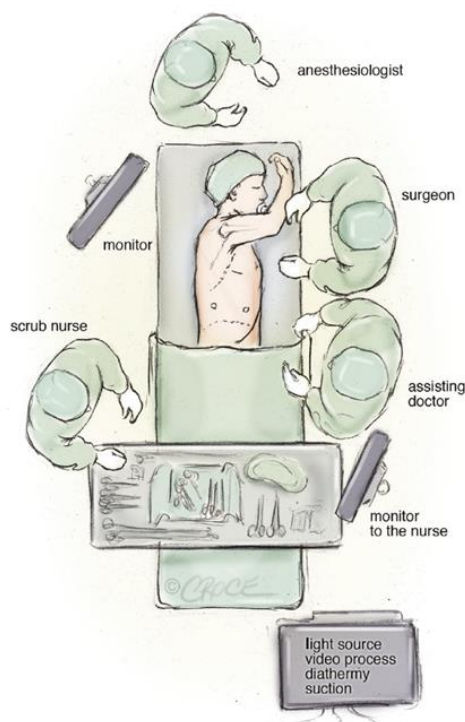
Standard anterior approach

Reprinted with permission from CROCE

The feasibility of VATS lobectomy as a standard approach to treat lung cancer is the subject of investigations of a large series of national databases, large institutional studies, and meta-analyses. Although the evidence is based mainly on comparative nonrandomized studies, certain international guidelines recommend VATS lobectomy as the approach of choice for treating patients with stage I NSCLC.[42] Vannucci and Gonzales in a literature review study found that VATS lobectomy is a safe procedure with lower complications, less post-operative pain and better post-operative quality of life, compared with thoracotomy. VATS has at least equivalent, if not better, post-operative survival, compared with open surgery. While the thoracotomy approach has significantly higher node upstaging than VATS in four articles, the overall survival was not significantly different.[43] In a recent national analysis in USA, Yang et al demonstrated noninferior long-term survival after VATS lobectomy for early stage NSCLC compared with open thoracotomy.[44]

The superiority of VATS lobectomy over thoracotomy associated with short-term clinical outcomes is demonstrated by numerous studies. For example, the benefits include decreased postoperative pain, better QOL, fewer perioperative complications, improved lung function, improved immune responses, better outcomes for high-risk patients with poor lung function, and lower hospitalization costs.[36, 45-50] However, other studies found that postoperative survival, complications, and long-term QOL are comparable with those of thoracotomy.[36]

Technological advances and accumulated experience performing VATS surgery has spawned techniques that allow management of complex cases with results comparable to those of open surgery. Examples include bronchial sleeve, vascular sleeve, and tracheal/cranial resection. Contraindications to VATS lobectomy are relative, depending mainly on the surgeon's experience. Absolute oncological contraindications remain similar for both approaches.[43]

VATS causes less severe trauma, although the oncological principles of surgical resection of NSCLC are the same for thoracotomy and VATS. Consequently, several studies evaluated the efficacy of VATS lobectomy for radical resection of NSCLC and lymph-node upstaging.[43, 44, 51]

In Sweden, the VATS technique has been used for many years to perform simple thoracic procedures such as lung biopsies, wedge resections, and pleurectomies. The VATS lobectomy program started in 2012, and the number of procedures performed annually has increased. However, according to ThoR,[7] almost all patients who underwent the procedure from 2012–2015 were treated at one out of eight thoracic surgical centers.

Uniportal VATS lobectomy, which has undergone development as minimally invasive thoracic surgery during the last 10 years, has generated increasing interest because of growing evidence regarding its feasibility for managing lung cancer and mediastinal tumors, lower postoperative pain, and improved patient satisfaction compared with multiportal VATS.[43]

Subxiphoid uniportal VATS lobectomy, microlobectomy with the VATS technique, and awake-VATS are examples of several ongoing developments in minimally invasive thoracic surgery, although further evidence of efficacy must be provided before they can be widely applied in clinical practice.[52-54]

2.7 WEEKDAY OF SURGERY AND SURVIVAL AFTER PULMONARY RESECTION OF LUNG CANCER

Medical subspecialties expanded extensively during the last decades because of revolutionary developments in medical science. These developments have substantially improved healthcare by achieving better early and late outcomes. However, insufficient continuous availability of highly qualified healthcare providers is generating new challenges and difficulties.[55]

Many studies demonstrate poor clinical outcomes and mortality following admission of patients on the weekend compared with weekdays. There is compelling evidence supporting these results, which is particularly associated with patients with acute conditions.[56] The results of studies conducted during the last decade conflict regarding the "weekday effect" on short- and long-term mortality associated with different surgical disciplines. For example, Aylin et al. conducted a large retrospective study of more than 4 million patients admitted for elective surgery in the United Kingdom and found a higher risk of mortality when the procedures were performed on Friday or during the weekend.[57] Lagergren et al. conducted a study in Sweden that found worse 5-year all-cause and disease-specific mortality when elective surgery for esophageal cancer was performed later in the week.[58] Several other studies conducted in different countries corroborate these results.[59-61] However, a significant effect of surgery performed on weekdays on early- or long-term survival is not demonstrated by other large studies. For example, a study conducted in the Netherlands by Visser et al. failed to detect a significant difference in short- and long-term oncological outcomes associated with performing esophagectomy on weekdays.[62] Similarly, Dalén et al. conducted a large cohort study of patients in Sweden who underwent cardiac surgery, but was unable to uncover evidence of an association of the day of surgery with mortality.[63]

We are unaware of any studies that exclusively investigated the influence of weekday on surgery for lung cancer. In Sweden, thoracic surgeons associated with eight thoracic surgery clinics perform the surgery, which in some clinics, is only performed by dedicated general thoracic surgeons. In general, the surgical resection of lung cancer is an elective procedure that is performed on weekdays.

3 AIMS OF THE THESIS

The general aim of this thesis was to investigate several important clinical aspects of surgical resection of malignant tumors in the lung, which represents >70% of the number of GTS procedures.

Study I

To investigate the association between baseline self-reported HRQOL and long-term survival after thoracic surgery.

Study II

To evaluate long-term survival following PM-CRC at the Karolinska University Hospital and identification of possible prognostic factors to facilitate patient selection.

Study III

To describe overall survival after PM-CRC in Sweden and to validate a recent proposed risk prediction model in the Swedish population.

Study IV

To review the feasibility and safety of VATS lobectomy as an alternative approach to surgical treatment of early NSCLC by conducting a nationwide study in Sweden, comparing VATS with a thoracotomy approach in lobectomy procedures regarding their effects on long-term survival and early postoperative clinical outcomes.

Study V

To conduct a nationwide cohort to investigate the possibility of an association between the weekday of surgery and all-cause mortality following pulmonary resection of lung cancer.

4 PATIENTS AND METHODS

4.1 ETHICAL CONSIDERATIONS

The regional Human Research Ethics Committee in Stockholm, Sweden, approved all studies.

4.2 STUDY DESIGN, POPULATION, AND DATA COLLECTION

4.2.1 Study I

A prospective population-based cohort study including patients scheduled for thoracic surgery at Karolinska University Hospital, Stockholm, Sweden, between 2006 and 2008. Patients completed a preoperative (SF-36) questionnaire. Comorbidities were identified as follows; ischemic heart disease (history of angina pectoris, myocardial infarction, coronary artery bypass surgery or percutaneous coronary intervention), hypertension (high blood pressure requiring treatment), congestive heart disease (history of heart failure or ejection fraction <0.5), diabetes mellitus (diabetes requiring medication), peripheral vascular disease (history of claudication, carotid stenosis, or abdominal aneurysm), and cerebrovascular disease (history of stroke or transient ischemic attack). Smoking status was categorized into 3 groups as follows: current smoker (patient was an active smoker or quit smoking within 1 year of surgical procedure), former smoker (patient stopped smoking more than one year before surgery), and never smoker. The tumor stage was divided into two categories, stage 0 to I and stage II to III. The extent of lung resection was categorized into two groups, sublobar (wedge) resection and lobectomy/pneumonectomy. The patients were categorized with higher or lower QOL compared with that of a reference population. The PCS and MCS scores for each patient were compared with the respective scores of an age- and sex-matched reference population. Patients' data were collected from institutional databases and patients' charts.

4.2.2 Study II

An observational population-based cohort study included all patients with CRC who underwent surgical resection of pulmonary metastases at Karolinska University Hospital, Stockholm, Sweden, between January 1, 2004, and December 31, 2015. Patients' data were collected from institutional databases and patients' charts. Comorbidity was defined as any medical condition with ongoing treatment or one that might affect prognosis, such as hypertension, atrial fibrillation, coronary artery disease, diabetes, or stroke. Smoking status was categorized into the groups as follows: current smoker, patient was an active smoker or quit smoking within 1 month of surgery; former smoker, patient stopped smoking more than 1 month before surgery; never smoker, patient who never smoked; and smoking status unknown. Lung resection was classified as lobectomy vs sublobar resection (wedge resection).

4.2.3 Study III

An observational nationwide population-based cohort study that included all patients registered in ThoR who underwent surgical resection of pulmonary metastases from CRC between January 1, 2009 and December 31, 2015. Comorbidity and smoking status was identified as in Study II. The study created a prognostic index and risk categories, following a recent Japanese study,[31] which employed the preoperative prognostic factors as follows: age ≥70 years, DFI <2 years, extrathoracic lesion, abnormal prethoracotomy CEA level, and ≥3 pulmonary metastases. Patients were assigned to one of three risk categories based on the number of preoperative prognostic factors (0 factor, low risk; 1–2 factors, moderate risk; and ≥3 factors, high risk). In this study, prethoracotomy CEA data were not available, and the calculations of the prognostic index assumed that all patients had normal CEA concentrations.

4.2.4 Study IV

An observational population-based cohort study. The study included all patients registered in ThoR who underwent lobectomy for NSCLC between January 1, 2012, and December 31, 2015. Comorbidity and smoking status was identified as in Study II. All patients who underwent VATS lobectomy at Karolinska University Hospital were included in the VATS group, and patients who underwent thoracotomy at other hospitals were included in the thoracotomy group. The study excluded patients who underwent thoracotomy at the Karolinska Institute during the study period as well as the few patients (n = 14) who underwent VATS lobectomy at other hospitals. Among the 3013 patients who underwent lung resection for NSCLC, 1412 were excluded from the study for the reasons as follows: 1072 no lobectomy, 220 open lobectomy at Karolinska University Hospital, and 120 extended lobectomy procedures (Figure 10).

4.2.5 Study V

A nationwide (Sweden) observational population-based cohort study. The study included all patients registered in ThoR who underwent pulmonary resections for lung cancer between January 1, 2009 and December 31, 2015. Comorbidity was identified as in Study II. Smoking status was defined as follows: 1. Current smoker, if the patient was an active smoker or stopped smoking within 1 month from surgery and 2. Other, the remaining patients. Lung resection was classified as lobectomy or sublobar resection (wedge resection). The very few patients in Sweden who underwent surgery on a weekend or a public holiday were excluded.

4.3 OUTCOME MEASURES

4.3.1 Study I

Association between baseline self-reported HRQOL (PCS and MCS) and long-term survival after thoracic surgery.

4.3.2 Study II

The primary outcome measure was long-term survival after PM-CRC.

4.3.3 Study III

The outcome measure was overall survival after PM-CRC in Sweden.

4.3.4 Study IV

The primary outcome measure was long-term survival after VATS lobectomy compared with open thoracotomy lobectomy in patients with early-stage NSCLC. The secondary outcomes were assessment of early clinical postoperative outcomes and complications associated with these surgeries.

4.3.5 Study V

All-cause mortality after pulmonary resection for lung cancer associated with the weekday of surgery.

4.4 STATISTICAL ANALYSIS

Statistical analyses were performed using Stata version 14.1 in Study I, Stata 14.2 in Study II, and Stata 15.1 in Studies III–V (Stata Corp LP, College Station, TX, United States) and R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) in Study IV.

4.4.1 All studies

Baseline characteristics are described as frequencies and percentages for categorical variables and as the mean and standard deviation (SD) for continuous variables. Person-time in days was counted from the date of surgery until the date of death or the end of follow-up. The Kaplan–Meier method was used to calculate cumulative survival.

4.4.2 Study I

Cox proportional hazards regression was used with and without multivariable adjustment to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) to evaluate the significance of the association between preoperative QOL and long-term survival. Multiple imputation using chained equations was employed to handle missing data. Twenty-five data sets were imputed, and estimates from these data sets were combined.[64]

4.4.3 Study II

Cox proportional hazards regression was used with and without multivariable adjustment to estimate hazard ratios (HR) and 95% CIs of the association between patients' characteristics and all-cause mortality.

4.4.4 Study III

The restricted mean survival time (RMST) was estimated in the three risk categories and was calculated as the difference (95% CI) in survival compared with the low-risk category. Cox proportional hazards regression was used to estimate HRs and 95% CIs of the association between a risk category and all-cause mortality. In this study, DFI data was missing for 188 patients (25%). We handled missing data using multiple imputation by chained equations.[64] Fifty data sets were imputed, and estimates from these data sets were combined.

4.4.5 Study IV

The RMST and the difference in survival between patients who underwent open thoracotomy or VATS lobectomy were calculated. The inverse probability of treatment weighting (IPTW) was used to create a balance in the baseline patients' characteristics between the two groups. The weights were derived from propensity scores estimated using generalized boosted regression modeling. The following variables were used in the estimation of propensity scores: age, sex, body mass index, heart disease, diabetes, stroke, chronic kidney disease, other comorbidities, performance status, preoperative forced expiratory volume per second, prior thoracic surgery, prior sternotomy, smoking status, adjuvant chemo- or radiotherapy, and pathological cancer stage. The balance between treatment groups was assessed through the reporting of standardized mean differences. A standardized difference ≤0.1 was considered ideal, and a standardized difference ≤0.2 was considered acceptable. Cox proportional hazards regression was used to estimate HRs and 95% CIs.

4.4.6 Study V

The patients in the study were categorized into groups according to the weekday of surgery. Crude and multivariable adjusted Cox regression models were fitted to estimate HRs and 95% CIs of the association between weekday of surgery and survival. Patients who underwent surgery on a Monday served as the reference category. Patients' ages were modeled using restricted cubic splines, and other variables were included as categorical terms. The RMST was reported by weekday at 1 and 5 years, and the difference in RMST (95% CI) was determined using Monday as the reference category.

OVERVIEW OF THE STUDY DESIGNS AND METHODS

	Study I	*Study II*	*Study III*	*Study IV*	*Study V*
Design	Observational, population-based (Karolinska)	Observational, nationwide (ThoR)			
Cohort	Adults, GTS	Adults, PM-CRC		Adults, VATS and thoracotomy lobectomy	Adults, surgery for NSCLC
Period	2006–2008	2004–2015	2009–2015	2012–2015	2009–2015
Follow-up	31 Jan 2016	15 Jan 2017	17 Apr 2017		
Outcomes	Overall survival			Overall survival, postoperative outcomes	Overall survival
Statistical methods	Multivariable survival analysis (Cox regression), multiple imputation	Multivariable survival analysis (Cox regression)	Multivariable survival analysis (Cox regression), RMST, multiple imputation	Multivariable analysis (Cox and logistic regression), IPTW	Multivariable survival analysis (Cox regression), RMST

5 RESULTS

5.1 STUDY I

5.1.1 Patients' characteristics and survival

This study included 249 patients (mean age 63.8 years, 48 women). Patients' characteristics are shown in Table 1. Higher and lower summary scores (PCS and MCS) of the patients were compared with those of an age- and sex-matched population.

Among patients with lower scores, 43% (108 of 249) had lower PCS scores and 72% (180 of 249) had lower MCS scores. The median follow-up was 8 years, and 48% (119) of patients died during the study period. Among the patients with lower PCS and MCS scores, 60 % (65 of 108) and 52% (93 of 180) died, respectively. Among the patients with higher PCS and MCS scores, 38% (54 of 141) and 38% (26 of 69) died, respectively. The SF-36 subscale and summary scores for the total population and the age- and sex-matched reference population are shown in Table 2.

PCS scores lower than the reference were significantly associated with higher mortality in the crude (HR, 1.93; 95% CI, 1.35–2.77, $p < 0.001$) and multivariable adjusted analyses (HR, 2.02; 95% CI, 1.34–3.06, p 0.001) (Table 3, Figure 1). However, an MCS score lower than the reference was not significantly associated with mortality according to the crude and multivariate adjusted analyses (HR, 1.52; 95% CI, 0.99–2.36, $p = 0.058$ and HR, 1.32; 95% CI, 0.84–2.08, $p = 0.233$, respectively) (Table 3, Figure 2).

For each 5-point decrease in the baseline PCS score, the risk of long-term all-cause mortality increased by 12% ($p = 0.005$). The sensitivity analyses were repeated with patients categorized according to a 5% difference in the PCS score compared with the reference populations. This adjusted multivariable analysis revealed a significant association of the PCS score, which was 5% lower than the reference, with mortality (adjusted HR, 1.87; 95% CI, 1.2–2.84, $p = 0.003$).

The association between a low PCS score and mortality in selected clinically relevant subgroups was investigated. The data consistently showed that a PCS score lower than reference was significantly associated with increased postoperative long-term mortality (Figure 3).

Patients with low PCS scores were stratified into subgroups of cancer stage as follows: stage 0, stage I, and stages II and III. The analysis was adjusted only for age because of the limited number of patients and mortality in each subgroup. The results are as follows: *stage 0*, 79 patients, 26 deaths, age-adjusted HR, 1.51 (95% CI, 0.70–3.26; $p = 0.294$); *stages II to III*, 45 patients, 31 deaths, age-adjusted HR, 2.08 (95% CI, 1.00–4.34; $p = 0.051$) and *stage I*, 125 patients, 62 deaths, age-adjusted HR, 2.02 (95% CI, 1.22–3.32; $p = 0.006$); and the multivariable-adjusted HR was 2.22 (95% CI, 1.22–4.05; $p = 0.009$).

Table 1. *Baseline Characteristics, Tumor Stages, and Histopathologic Process in 249 Patients Who Underwent Thoracic Operations According to Short Form-36 Physical and Mental Summary Scores*

Characteristic	Total population (n = 249)	Physical Component Summary Higher Than Ref. (n = 141)	Lower Than Ref. (n = 108)	p Value	Mental Component Summary Higher Than Ref. (n = 69)	Lower Than Ref. (n = 180)	p Values
Age, years	63.8 ± 11.7	65.6 ± 9.8	61.4 ± 13.5	0.005	64.4 ± 13.0	63.6 ± 11.2	0.608
Women	119 (48)	74 (52)	45 (42)	0.090	26 (38)	93 (52)	0.048
Men	130 (52)	67 (48)	63 (58)	0.090	43 (62)	87 (48)	0.048
Body mass index, kg/m²	25.2 ± 4.0	25.1 ± 4.0	25.3 ± 4.1	0.730	25.4 ± 3.9	25.1 ± 4.1	0.590
Smoking status				0.049			0.003
Current	37 (16)	26 (20)	11 (11)		15 (24)	22 (13)	...
Former	104 (45)	62 (48)	42 (42)		34 (55)	70 (42)	...
Never	88 (38)	42 (32)	46 (46)		13 (21)	75 (45)	...
FEV₁, L	2.4 ± 0.7	2.4 ± 0.7	2.3 ± 0.7	0.483	2.5 ± 0.7	2.4 ± 0.7	0.366
Ischemic heart disease	20 (8)	8 (6)	12 (11)	0.118	5 (7)	15 (8)	0.778
Congestive heart failure	3 (1)	2 (1)	1 (1)	0.724	1 (1)	2 (1)	0.827
Hypertension	76 (31)	45 (32)	31 (29)	0.586	22 (32)	54 (30)	0.773
Diabetes mellitus	19 (8)	7 (5)	12 (11)	0.070	4 (6)	15 (8)	0.500
Cerebrovascular disease	8 (3)	2 (1)	6 (6)	0.067	0 (0)	8 (4)	0.075
Peripheral vascular disease	11 (4)	8 (6)	3 (3)	0.270	3 (4)	8 (4)	0.974
Hemoglobin, g/L	137 ± 13	138 ± 12	135 ± 15	0.148	138 ± 13	137 ± 14	0.475
Albumin, g/L	37 ± 3.8	37 ± 3.5	37 ± 4.2	0.423	36 ± 3.2	37 ± 4.0	0.151
eGFR, mL/min/1.73 m²	89 ± 29	86 ± 24	92 ± 34	0.144	91 ± 34	88 ± 27	0.420
Operations				0.672			0.907
Sublobar resection	59 (24)	32 (23)	27 (25)	...	16 (23)	43 (24)	...
Pneumonectomy or lobectomy	190 (76)	109 (77)	81 (75)	...	53 (77)	137 (76)	...
Adjuvant therapy	78 (31)	40 (28)	38 (35)	0.250	17 (25)	61 (34)	0.159
Side				0.217			0.932
Right	131 (53)	79 (56)	52 (48)	...	36 (52)	95 (53)	...
Left	118 (47)	62 (44)	56 (52)	...	33 (48)	85 (47)	...
Stage				0.247			0.363
0–I	204 (82)	119 (84)	85 (79)	...	59 (86)	145 (81)	...
II–III	45 (18)	22 (16)	23 (21)	...	10 (14)	35 (19)	...
Histopathologic process				0.253			0.220
Adenocarcinoma	117 (47)	69 (49)	48 (44)	...	27 (39)	90 (50)	...
Squamous cell carcinoma	22 (9)	8 (6)	14 (13)	...	5 (7)	17 (9)	...
Carcinoid	16 (6)	9 (6)	7 (6)	...	7 (10)	9 (5)	...
Other	94 (38)	55 (39)	39 (36)	...	30 (43)	64 (36)	...

Values are mean ± SD or n (%).

eGFR = estimated glomerular filtration rate;   FEV₁ = forced expiratory volume in 1 second;   Ref. = reference population (matched for age and sex).

Table 2. *Short Form-36 Subscale and Summary Scores*

Short Form-36	Total Population (n = 249)	Reference Population	Physical Component Summary Higher Than Ref. (n = 141)	Lower Than Ref. (n = 108)	Mental Component Summary Higher Than Ref. (n = 69)	Lower Than Ref. (n = 180)
Subscale scores						
Physical functioning	72.6 ± 23.9	75.9 ± 10.0	85.8 ± 12.6	55.3 ± 24.2	80.1 ± 23.7	69.7 ± 23.5
Physical role functioning	54.9 ± 43.0	69.1 ± 11.9	81.1 ± 29.5	20.6 ± 32.4	79.7 ± 34.1	45.4 ± 42.3
Bodily pain	75.1 ± 27.2	68.8 ± 4.6	89.8 ± 16.6	55.9 ± 26.3	84.0 ± 21.3	71.7 ± 28.5
General health	60.6 ± 19.8	67.7 ± 5.6	68.6 ± 17.0	50.2 ± 18.3	73.7 ± 17.6	55.6 ± 18.2
Vitality	56.2 ± 25.0	66.6 ± 5.6	67.1 ± 22.2	41.9 ± 21.1	78.1 ± 17.5	47.8 ± 22.3
Social functioning	71.3 ± 26.4	86.3 ± 4.0	78.5 ± 25.3	61.9 ± 24.9	94.7 ± 10.8	62.4 ± 25.1
Emotional role functioning	54.2 ± 43.0	79.0 ± 8.0	64.3 ± 41.0	41.0 ± 42.2	96.1 ± 12.2	38.1 ± 39.6
Mental health	61.4 ± 25.0	80.5 ± 3.5	64.2 ± 26.0	57.8 ± 23.3	88.8 ± 8.7	50.9 ± 20.9
Summary scores						
Physical component	45.6 ± 11.2	44.4 ± 3.9	53.4 ± 5.9	35.4 ± 7.6	46.9 ± 10.2	45.1 ± 11.5
Mental component	39.5 ± 13.7	50.7 ± 1.5	40.6 ± 14.5	38.1 ± 12.5	56.1 ± 3.1	33.1 ± 10.5

Values are mean ± SD.

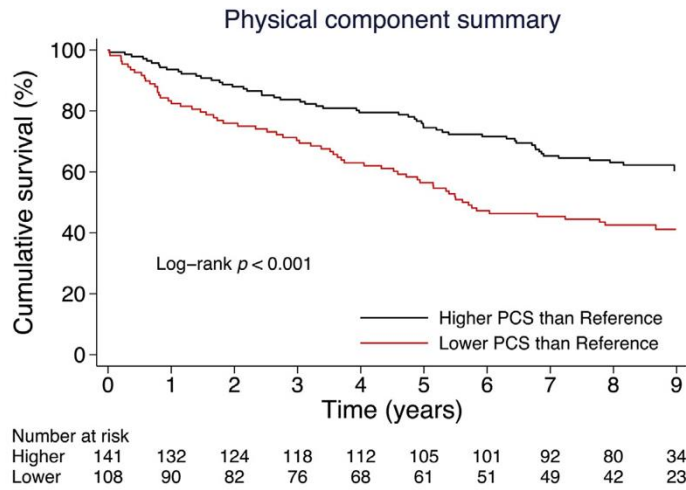Ref. = reference population (matched for age and sex).

Fig 1. Kaplan-Meier estimated survival in 249 patients after thoracic operations according to a preoperative Short Form-36 physical component summary score higher or lower than an age- and sex-matched reference population. Patients who scored lower than an age- and sex-matched reference population for the physical component of quality of life had significantly worse long-term survival. (PCS = physical component summary.)
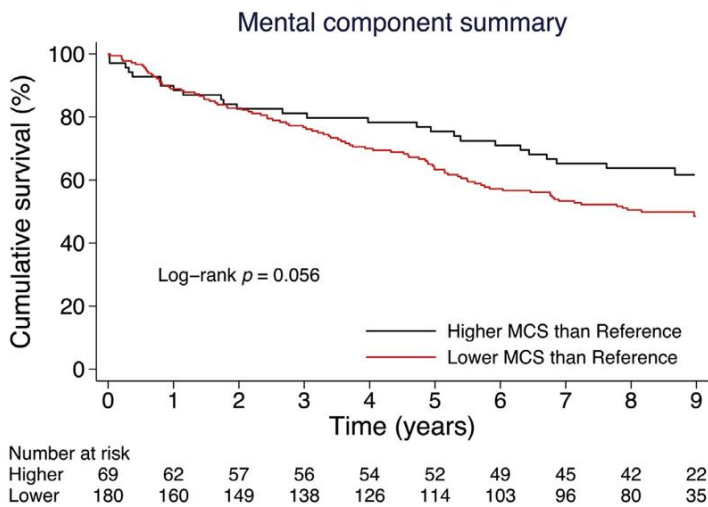
Fig 2. Kaplan-Meier estimated survival in 249 patients after thoracic operations according to a preoperative Short Form-36 mental component summary score higher or lower than an age- and sex-matched reference population. Although the survival curves diverge beyond 2 years, there was no significant difference in long-term survival between patients who scored lower or higher for the mental component of quality of life than an age- and sex-matched reference population. (MCS = mental component summary.)

Table 3. Crude and Adjusted Association Between Short Form-36 Physical and Mental Summary Scores Lower Than Reference and Long-Term Mortality

Association	HR (95% CI)	p Value
Physical component lower than reference		
Crude	1.93 (1.35–2.77)	<0.001
Adjusted for age, sex, and malignancy	2.08 (1.44–3.01)	<0.001
Adjusted for age, sex, and cancer stage	2.25 (1.55–3.25)	<0.001
Multivariable adjustment[a]	2.02 (1.34–3.06)	0.001
Mental component lower than reference		
Crude	1.52 (0.99–2.36)	0.058
Adjusted for age, sex, and malignancy	1.45 (0.93–2.25)	0.102
Adjusted for age, sex, and cancer stage	1.57 (1.01–2.44)	0.044
Multivariable adjustment[a]	1.32 (0.84–2.08)	0.233

[a] Model was adjusted for age, sex, cancer stage, comorbidity, renal function, extent of operations, malignant histopathologic process, adjuvant therapy, hemoglobin, albumin, body mass index, forced expiratory volume in 1 second, and smoking history. In addition, the model for the association between physical quality of life and mortality included the baseline mental component summary score and the model for the association between mental quality of life and mortality included the baseline physical component summary score.
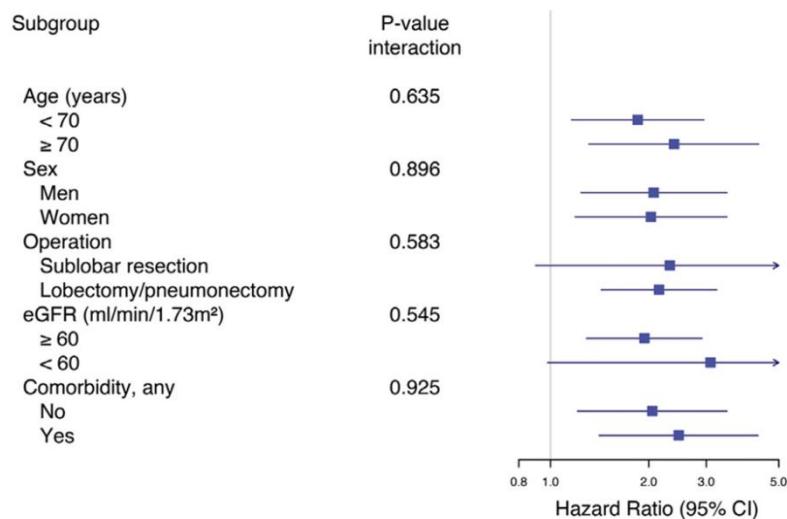
CI = confidence interval;   HR = hazard ratio.

Fig 3. The association between Short Form-36 physical component summary scores lower than reference and long-term mortality in selected subgroups. (CI = confidence interval; eGFR = estimated glomerular filtration rate.)

5.2 STUDY II

This study included 184 patients (mean age 64.8 years, 46% women). Patients' characteristics are shown in Table 4. Pulmonary resection was performed using VATS (46% of patients). Sublobar resection (wedge resection) was the dominant type of resection (78% of patients). Rectal cancer was the primary tumor among 59% of patients followed by colon cancer (20%) and sigmoid cancer (21%). Most patients were classified as performance status 0, and 29% of patients underwent preoperative positron emission tomography–computed tomography (PET-CT). The number of procedures increased during the study period from one in 2004 to 34 in 2015, peaking at 45 in 2014 (Figure 4).

The median follow-up time was 3.2 years, and 36% (66 of 184) of patients died during the study period. The estimated 5-years survival rate was 60% (95% CI, 50%–68%) (Figure 5). Survival within 95% CI of patients who underwent PM-CRC was compared with the expected survival of age- and sex-matched persons from the Swedish population. Figure 6 shows significant divergence of the survival curves after the 1-year follow-up, demonstrating shorter survival of members of the metastasis group.

5.2.1 Prognostic factors of survival

A CEA concentration $>4\,\mu g/L$ was the only significant prognostic factor associated with high mortality in the crude (HR, 2.30; 95% CI, 1.09–4.85; $p = 0.029$) and age- and sex-adjusted (HR, 2.46; 95% CI, 1.15–5.26; $p = 0.020$) analyses. Other relevant characteristics were not significantly associated with mortality (crude or adjusted analysis) (Table 5).
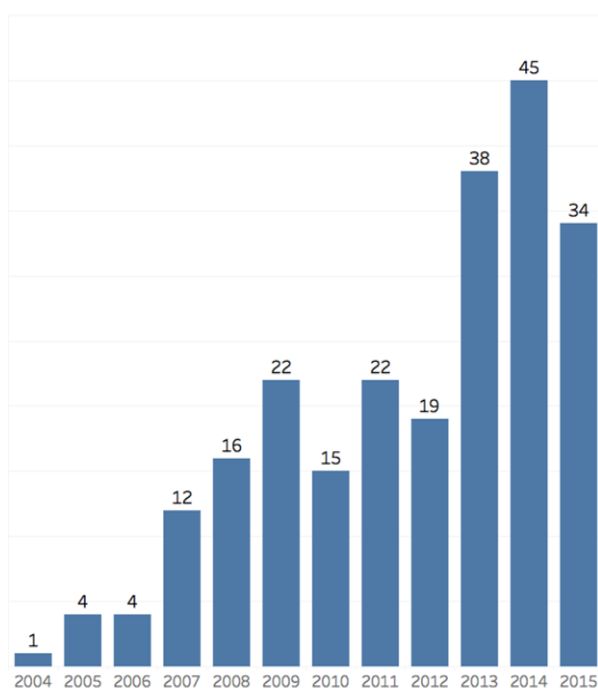
Figure 4
Number of operations (PM-CRC) per year during the study period.

Table 4. Characteristics of patients (n = 184) with colorectal cancer who underwent pulmonary metastasectomy.

| Variable	N (%)
Age, year, mean (SD)	64.8 (10.2)
Sex	
Male	99 (54%)
Female	85 (46%)
Body mass index, kg/m², mean (SD)	26.3 (4.1)
Comorbidity, any	70 (38%)
Performance status (ECOG)	
0 (Asymptomatic)	172 (93%)
1 (Symptoms, but fully active)	12 (7%)
Smoking status	
Never smoker	75 (41%)
Former smoker	15 (8%)
Current smoker	72 (39%)
Unknown	22 (12%)
PET-CT preoperatively	54 (29%)
Location, primary tumor	
Colon	37 (20%)
Sigmoid	39 (21%)
Rectum	108 (59%)
Primary CRC stage	
I	9 (4.9%)
II	46 (25%)
III	86 (47%)
IV	31 (17%)
Unknown	12 (6.5%)
Adjuvant radiotherapy	4 (2%)
Adjuvant chemotherapy	41 (22%)
Other metastases	91 (49%)
Liver	57 (31%)
Lung	30 (16%)
Other	4 (2%)
Disease-free interval	
<24 months	95 (52%)
≥24 months	88 (48%)
Unknown	1 (0.5%)
CEA	
<4 µg/L	94 (51%)
≥4 µg/L	17 (9%)
Unknown	73 (40%)
Extent of resection	
Sublobar resection	144 (78%)
Lobectomy	40 (22%)
VATS	85 (46%)
Number of metastases	
1	141 (77%)
2	29 (16%)
≥3	14 (8%)
Size of pulmonary metastases (largest lesion)	
<20 mm	126 (68%)
≥20 mm	50 (27%)
Unknown	8 (4%)
Hospitalization, days, mean (SD)	5.5 (1.6)

CEA = carcinoembryonic antigen, CRC = colorectal cancer, ECOG = Eastern Cooperative Oncology Group, VATS = Video-assisted thoracoscopic surgery, PET-CT = positron emission tomography–computed tomography

Table 5. Prognostic factors of survival of patients who underwent pulmonary metastasectomy after colorectal cancer.

	Crude HR (95% CI)	p	Age- and sex adjusted HR (95% CI)	p
Age >65 years	1.17 (0.71-1.90)	0.539	1.18 (0.72-1.94)*	0.508
Female	1.07 (0.66-1.73)	0.792	1.08 (0.67-1.76)**	0.745
Any comorbidity	1.58 (0.97-2.60)	0.069	1.56 (0.94-2.59)	0.083
Other metastases (liver or lung)	1.23 (0.76-2.00)	0.407	1.26 (0.77-2.06)	0.361
Liver metastases	1.45 (0.87-2.42)	0.151	1.45 (0.87-2.43)	0.156
More than one pulmonary metastasis	1.39 (0.82-2.35)	0.216	1.42 (0.84-2.41)	0.189
Size of pulmonary metastases ≥20 mm	1.00 (0.59-1.67)	0.990	0.98 (0.58-1.65)	0.945
Disease-free interval <24 months	1.11 (0.68-1.81)	0.668	1.14 (0.70-1.87)	0.595
CEA > 4 µg/L	2.30 (1.09-4.85)	0.029	2.46 (1.15-5.26)	0.020

*Only adjusted for sex **Only adjusted for age
HR = hazard ratio, CI = confidence interval, CEA = carcinoembryonic antigen
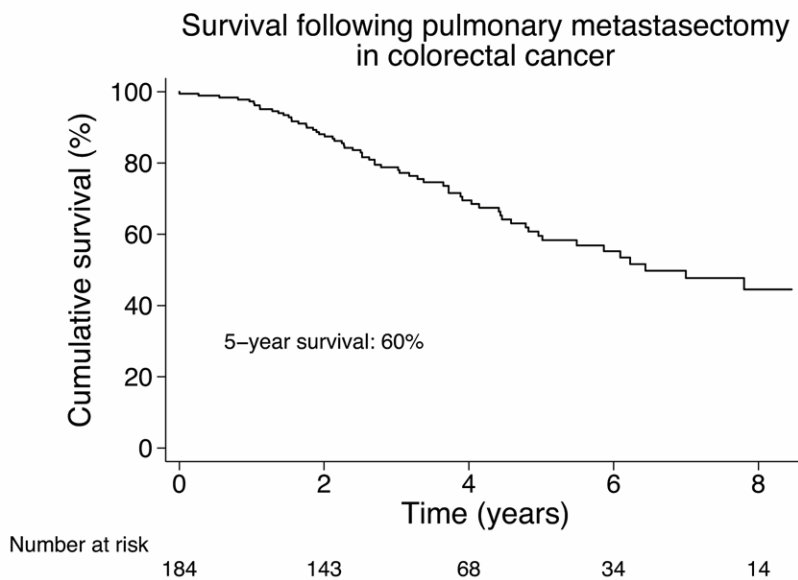
Figure 5. Kaplan–Meier analysis of estimated overall survival of patients with colorectal cancer who underwent pulmonary metastasectomy .
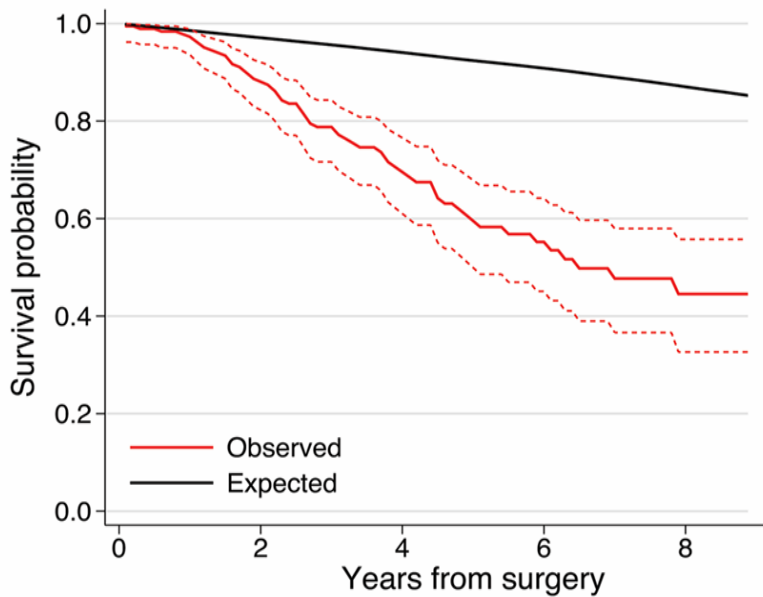
Figure 6. Overall survival (red line) and 95% confidence interval (red dashed lines) of patients who underwent pulmonary metastasectomy for colorectal cancer. Expected survival (black line) of an age- and gender-matched Swedish population.

5.3 STUDY III

5.3.1 Patients' characteristics

This study included 726 patients (mean age 65.8 years, 43% women) who underwent 929 surgical procedures. For patients with multiple entries in the register, only the first record was used. The primary CRC was located in the colon or sigmoid in 59% of patients and in the rectum of 41% of patients. At least three metastases were found in 6% of patients, and 25% of patients had extrathoracic metastases. Sublobar resection and VATS were used to treat 81% and 34% of patients, respectively (Table 6).

5.3.2 Number of surgeries

The number of surgeries increased during the study period. However, the increase in the number of patients operated must be interpreted in light of the fact that ThoR did not include all hospitals in Sweden until 2013.

5.3.3 Risk categories

The patients were classified into the risk categories (described above) as follows: low risk (n = 166), moderate risk (n = 558), and high risk (n = 32). Univariate analysis of preoperative prognostic factors in this model revealed that only the number of metastases (≥3) was significantly associated with all-cause mortality (HR, 2.47; 95% CI, 1.65–3.68, p<0.001). Baseline patients' characteristics according to risk category are shown in Table 7.

5.3.4 Survival outcomes

During the study period, 35% (268 of 756) of patients died, the median follow-up was 2.9 years, and 5-year overall survival was 56% (95% CI, 51%–60%) (Figure 8).

The results of a Cox regression model with risk category as the only independent variable revealed that the HRs of the moderate- and high-risk categories compared with the low-risk category were 1.94 (95% CI, 1.38–2.72, p<0.001) and 4.35 (95% CI, 2.49–7.62, p<0.001), respectively, (C-statistic, 0.58) (Figure 9). The difference in RMST at various follow-up times between the moderate- and high-risk categories and the reference category (low-risk category) is shown in Table 8. At 2 years, the difference in RMST is 1 month in the moderate versus low risk group(p<0.001) and 2 months in the high versus low risk group (p<0.001).This differences increase significantly at 5 years to 6 months and 1.5 between moderate versus low risk group and high versus low risk group, respectively.

Patients who underwent VATS procedures have better survival than patients who underwent thoracotomy procedures in an analysis adjusted for risk category (HR 0.73, 95%CI: 0.55-0.97, p=0.028). Further, no difference in survival between the patients regarding extent of lung resection (lobectomy versus wedge resection) in an analysis adjusted for risk category (HR 1.29, 95% CI: 0.97-1.72, p=0.078).

Table 6. Characteristics of patients (n = 756) with CRC who underwent pulmonary metastasectomy.

Variable	N (%)	% missing
Age, year, mean (SD)	65.8 (10.2)	-
Sex		-
Male	430 (57%)	
Female	326 (43%)	
Body mass index, kg/m^2, mean (SD)	26.5 (4.53)	8.6
Comorbidity, none	407 (54%)	-
Heart disease	67 (9%)	-
Diabetes	57 (8%)	-
History of stroke/TIA	30 (4%)	-
Chronic kidney disease	16 (2%)	-
Other comorbidity	292 (39%)	-
Smoking status		9.3
Never smoker	377 (55%)	
Former smoker	143 (21%)	
Smoker	64 (9%)	
Unknown	102 (15%)	
Performance status (ECOG)		-
0 (Asymptomatic)	662 (88%)	
1 (Symptoms, but fully active)	94 (12%)	
Adjuvant radiotherapy	26 (4%)	4.4
Adjuvant chemotherapy	130 (18%)	4.5
PET-CT preoperative	309 (46%)	10
Extent of resection		-
Sublobar resection	616 (81%)	
Lobectomy	140 (19%)	
VATS	258 (34%)	-
Location, primary tumor		-
Colon/Sigmoid	447 (59%)	
Rectum	309 (41%)	
Disease-free interval		25
<24 months	258 (45%)	
≥24 months	310 (55%)	
≥3 metastases	44 (6%)	-
Synchronous metastases	86 (14%)	21
Other metastases	237 (34%)	9.1
Extra-thoracic metastases	188 (25%)	-

ECOG = Eastern Cooperative Oncology Group, VATS = Video-assisted thoracoscopic surgery, PET-CT = positron emission tomography–computed tomography

Table 7. Risk categories and characteristics of patients (n = 756) with CRC who underwent pulmonary metastasectomy.

Variable	Risk category			
	Low (n = 166)	Moderate (n = 558)	High (n = 32)	p value
Age, year, mean (SD)	60.4 (7.98)	67.1 (10.2)	71.8 (9.69)	<0.001
Sex				0.564
Male	100 (60%)	311 (56%)	19 (59%)	
Female	66 (40%)	247 (44%)	13 (41%)	
Body mass index, kg/m^2, mean (SD)	26.9 (4.68)	26.5 (4.49)	25.3 (4.28)	0.184
Comorbidity, none	95 (57%)	291 (52%)	21 (66%)	0.202
Heart disease	8 (5%)	58 (10%)	1 (3%)	0.043
Diabetes	10 (6%)	46 (8%)	1 (3%)	0.399
History of stroke/TIA	2 (1%)	27 (5%)	1 (3%)	0.106
Chronic kidney disease	2 (1%)	14 (3%)	0 (0%)	0.412
Other comorbidity	62 (37%)	220 (39%)	10 (31%)	0.607
Smoking status				0.008
Never smoker	82 (56%)	280 (55%)	15 (50%)	
Former smoker	22 (15%)	113 (22%)	8 (27%)	
Smoker	24 (16%)	40 (8%)	0 (0%)	
Unknown	18 (12%)	77 (15%)	7 (23%)	
Performance status (ECOG)				0.300
0 (Asymptomatic)	151 (91%)	484 (87%)	27 (84%)	
1 (Symptoms, but fully active)	15 (9%)	74 (13%)	5 (16%)	
Adjuvant radiotherapy	6 (4%)	19 (4%)	1 (3%)	0.988
Adjuvant chemotherapy	27 (17%)	94 (18%)	9 (29%)	0.256
PET-CT preoperatively	70 (49%)	232 (46%)	7 (23%)	0.024
Extent of resection				0.833
Sublobar resection	137 (83%)	454 (81%)	25 (78%)	
Lobectomy	29 (17%)	104 (19%)	7 (22%)	
VATS	55 (33%)	196 (35%)	7 (22%)	0.293
Location, primary tumor				
Colon/Sigmoid	89 (54%)	341 (61%)	17 (53%)	0.176
Rectum	77 (46%)	217 (39%)	15 (47%)	0.176
Disease-free interval*				<0.001
<24 months	0 (0%)	233 (54%)	25 (96%)	
≥24 months	114 (100%)	195 (46%)	1 (4%)	
≥3 metastases	0 (0%)	28 (5%)	16 (50%)	<0.001
Synchronous metastases	8 (6%)	70 (16%)	8 (30%)	0.002
Other metastases	19 (13%)	192 (38%)	26 (84%)	<0.001
Extra-thoracic metastases	0 (0%)	162 (29%)	26 (81%)	<0.001

ECOG = Eastern Cooperative Oncology Group, VATS = Video-assisted thoracoscopic surgery, PET-CT = positron emission tomography-computed tomography
*Only reported for patients without missing information

Table 8. Differences in restricted mean survival time according to risk category.

| | Restricted mean survival difference (95% CI), days | | | | |
| | Risk category | | | | |
Follow-up	Low (*n* = 166)	Moderate (*n* = 558)	p value	High (*n* = 32)	p value
1 year	Reference	-5 (-8 to -2)	0.003	-9 (-25 to 8)	0.306
2 years	Reference	-28 (-42 to -14)	<0.001	-64 (-117 to -10)	0.019
3 years	Reference	-74 (-106 to -42)	<0.001	-199 (-306 to -92)	<0.001
4 years	Reference	-137 (-192 to -82)	<0.001	-382 (-546 to -218)	<0.001
5 years	Reference	-198 (-281 to -115)	<0.001	-537 (-768 to -306)	<0.001

CI = confidence interval
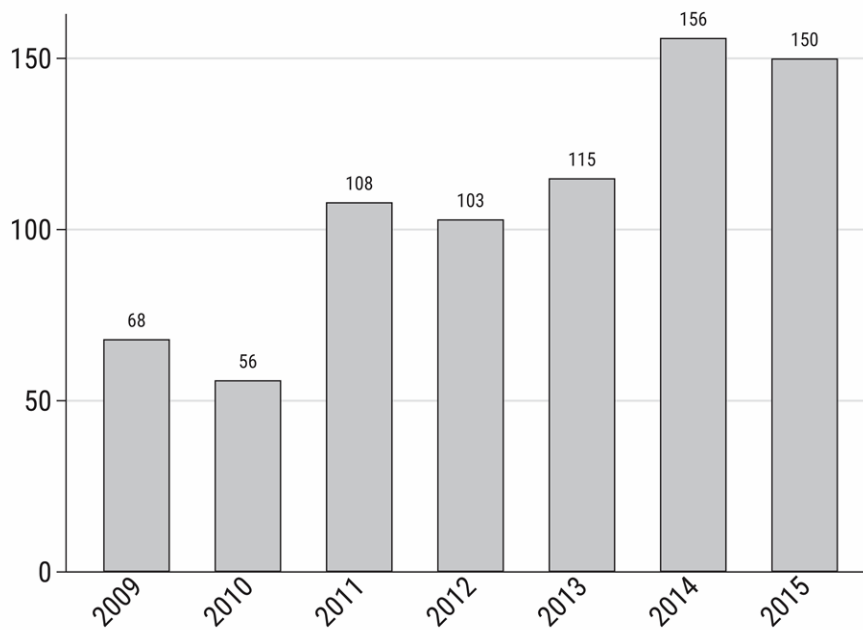
Figure 7. Numbers of annual surgeries.
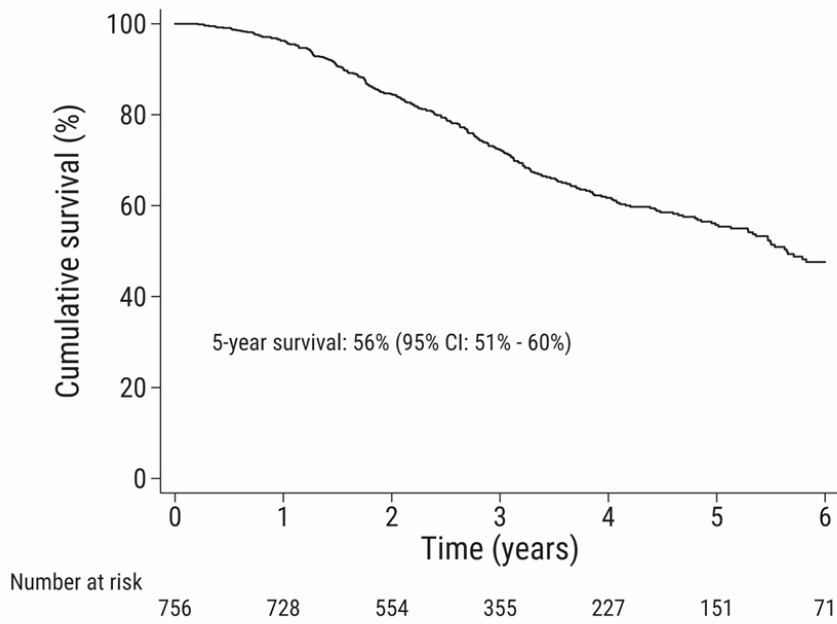
Figure 8. Kaplan–Meier analysis of estimated overall survival of patients with colorectal cancer who underwent pulmonary metastasectomy.
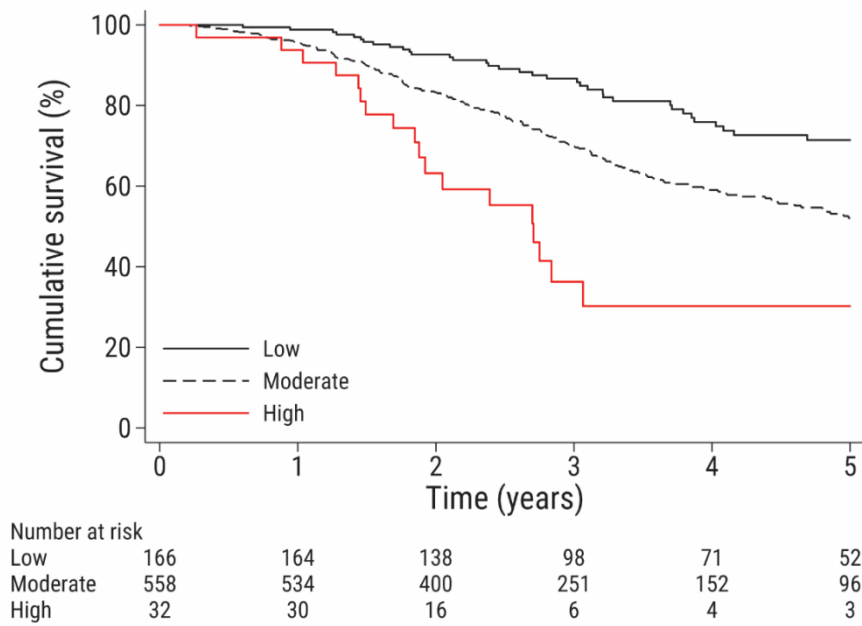
Figure 9. Influence of risk category on the results of Kaplan–Meier analysis of estimated overall survival of patients with colorectal cancer who underwent pulmonary metastasectomy.

5.4 STUDY IV

5.4.1 Patients' characteristics and numbers of surgeries

This study included 1601 patients (mean age 67.7 years) with NSCLC who underwent thoracotomy (n = 1316) or VATS lobectomy (n = 285) (Figure 10). The percentage of women (54%) was higher in the VATS group. There was no difference in the distribution of comorbidities between the two groups, although more advanced-stage patients underwent thoracotomy. The baseline characteristics of the two groups were balanced with the IPTW, and the standardized mean difference among all variables was <0.1 (Table 9).

The number of VATS lobectomies increased during the study period, and in 2015, VATS was the dominant lobectomy procedure at Karolinska University Hospital (123 VATS vs 68 thoracotomies) (Figure 11).

Most patients in the open thoracotomy and VATS groups did not have postoperative complications (83% vs 86%, respectively; p = 0.41. However, significantly shorter drain times, fewer blood transfusions, shorter hospitalizations, fewer reoperations, and fewer cases of postoperative pneumonia were experienced by the VATS group. The 30- and 90-day mortality rates of the open thoracotomy and VATS groups were 0.6% vs 0.7% (p = 0.38) and 1.7% vs 0.3% (p = 0.09), respectively (Table 10). A higher percentage of patients in the VATS group were discharged to rehabilitation compared with the thoracotomy group (63% vs 30%, respectively; p<0.001).

Median follow-up times were 2.6 years and 2.3 years for the open thoracotomy and VATS groups, respectively. The overall 1- and 5-year survival rates were 92% vs 97% and 63% vs 78% in the open thoracotomy and VATS group, respectively (HR [95% CI], 0.47 [0.33–0.68], p<0.001 (Figure 12). These results were confirmed using a standard multivariable-adjusted Cox regression model applied to the unweighted sample and as well as a "doubly robust" covariate-adjusted weighted Cox regression model. Cox regression analysis of a subset of patients restricted to pathological stages I-IIA showed that patients who underwent VATS lobectomy survived significantly longer (HR 0.59, CI 95% [0.39-0.88], p = 0.009).
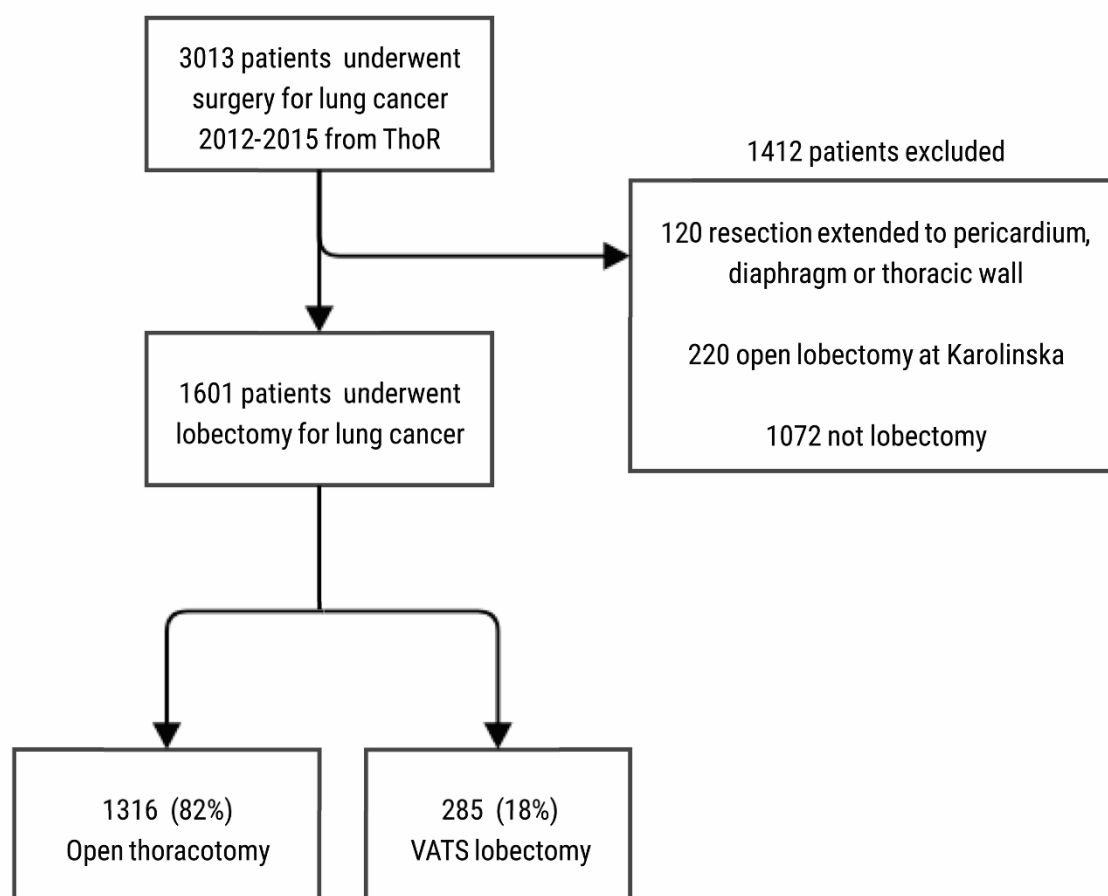
Figure 10. Study inclusion flowchart.

Table 9. Baseline characteristics of patients (n = 1601) who underwent open thoracotomy or minimally invasive VATS lobectomy for lung cancer in Sweden, 2012–2015: inverse probability of treatment weighting.

	Unweighted			IPTW		
	Open	VATS	SMD	Open*	VATS*	SMD
n	1316	285		1571.1	1157.4	
Age, years, mean (SD)	67.7 (8.6)	67.7 (8.3)	0.001	67.7 (8.6)	67.7 (8.0)	0.004
Female	716 (54)	185 (65)	0.215	876.0 (56)	655.5 (57)	0.018
BMI, kg/m^2, mean (SD)	26.4 (4.7)	25.4 (4.4)	0.222	26.2 (4.7)	26.0 (4.3)	0.052
No comorbidity	626 (48)	118 (41)	0.124	734.0 (47)	529.5 (46)	0.019
Heart disease	197 (15)	46 (16)	0.032	233.6 (15)	185.6 (16)	0.032
Diabetes	123 (9.3)	22 (7.7)	0.058	141.9 (9.0)	94.1 (8.1)	0.032
Prior stroke/TIA	69 (5.2)	10 (3.5)	0.085	79.6 (5.1)	51.4 (4.4)	0.029
Chronic Kidney Disease	39 (3.0)	3 (1.1)	0.137	42.6 (2.7)	16.4 (1.4)	0.091
Other comorbidity	526 (40)	141 (50)	0.192	646.9 (41)	505.9 (44)	0.051
Performance status >0	482 (37)	75 (26)	0.223	553.8 (35)	370.6 (32)	0.068
Preoperative FEV1, liter, mean (SD)	2.3 (0.67)	2.2 (0.66)	0.130	2.3 (0.67)	2.3 (0.65)	0.011
Prior thoracic surgery	47 (3.6)	12 (4.2)	0.033	57.8 (3.7)	31.2 (2.7)	0.056
Prior sternotomy	25 (1.9)	11 (3.9)	0.117	32.2 (2.0)	26.4 (2.3)	0.016
Current smoker	367 (28)	98 (34)	0.141	453.1 (29)	362.0 (31)	0.053
Preoperative radiotherapy	34 (2.6)	1 (0.4)	0.186	36.0 (2.3)	13.2 (1.1)	0.089
Preoperative chemotherapy	46 (3.5)	3 (1.1)	0.164	49.8 (3.2)	20.0 (1.7)	0.094
Stage**			0.246			0.066
IA	543 (41)	115 (40)		649.1 (41)	497.8 (43)	
IB	291 (22)	89 (31)		365.7 (23)	285.5 (25)	
IIA	207 (16)	39 (14)		241.8 (15)	161.1 (14)	
IIB	119 (9.0)	15 (5.3)		134.3 (8.5)	91.5 (7.9)	
IIIA-X	156 (12)	27 (9.5)		180.2 (11)	121.5 (11)	

Numbers and percentages are indicated as n (%), unless otherwise noted.
FEV1 = forced expiratory volume in one second, IPTW = inverse probability of treatment weighting, SD = standard deviation, SMD = standardized mean difference, TIA = transient ischemic attack, VATS = video-assisted thoracoscopic surgery,
*The total number of patients in each group is not an integer owing to IPTW.
**Pathological stage

Table 10. Postoperative events and complications after open thoracotomy or minimally invasive VATS lobectomy for lung cancer after IPTW.

|	Total	Open	VATS	Odds Ratio (95% CI)	p value
No complication	84%	83%	86%	1.20 (0.78-1.87)	0.41
Drain removal on day 1	65%	21%	54%	0.23 (0.17-0.31)	<0.001
Reoperation	2.8%	3.8%	1.4%	0.35 (0.14-0.93)	0.03
Transfusion	3.5%	5.0%	1.4%	0.27 (0.10-0.71)	0.008
Pneumothorax and new chest tube	3.4%	2.9%	4.2%	1.48 (0.69-3.18)	0.32
Arrhythmia	4.2%	4.9%	3.3%	0.65 (0.25-1.70)	0.38
Stroke/TIA	0.3%	0.4%	0.2%	0.45 (0.05-3.80)	0.47
Myocardial infarction	0.2%	0.3%	0	-	-
Wound infection	0.4%	0.5%	0.2%	0.43 (0.05-3.52)	0.43
Pneumonia	3.4%	5.5%	0.6%	0.11 (0.03-0.46)	0.002
Empyema	0.3%	0.4%	0.2%	0.53 (0.06-4.58)	0.57
Lymph leak	0.2%	0.3%	0	-	-
Pulmonary embolism	0.1%	0.2%	0	-	-
Reintubation	0.5%	0.7%	0.3%	0.44 (0.06-3.53)	0.44
Recurrence nerve paralysis	0.3%	0.5%	0	-	-
Phrenic nerve paralysis	0	0	0	-	-
Other complication	5.0%	3.6%	6.7%	2.00 (1.04-3.82)	0.04
Death within 30 days	0.6%	0.7%	0.3%	0.39 (0.05-3.10)	0.38
Death within 90 days	1.1%	1.7%	0.3%	0.17 (0.02-1.27)	0.09

VATS = video-assisted thoracoscopic surgery, CI = confidence interval, SD = standard deviation
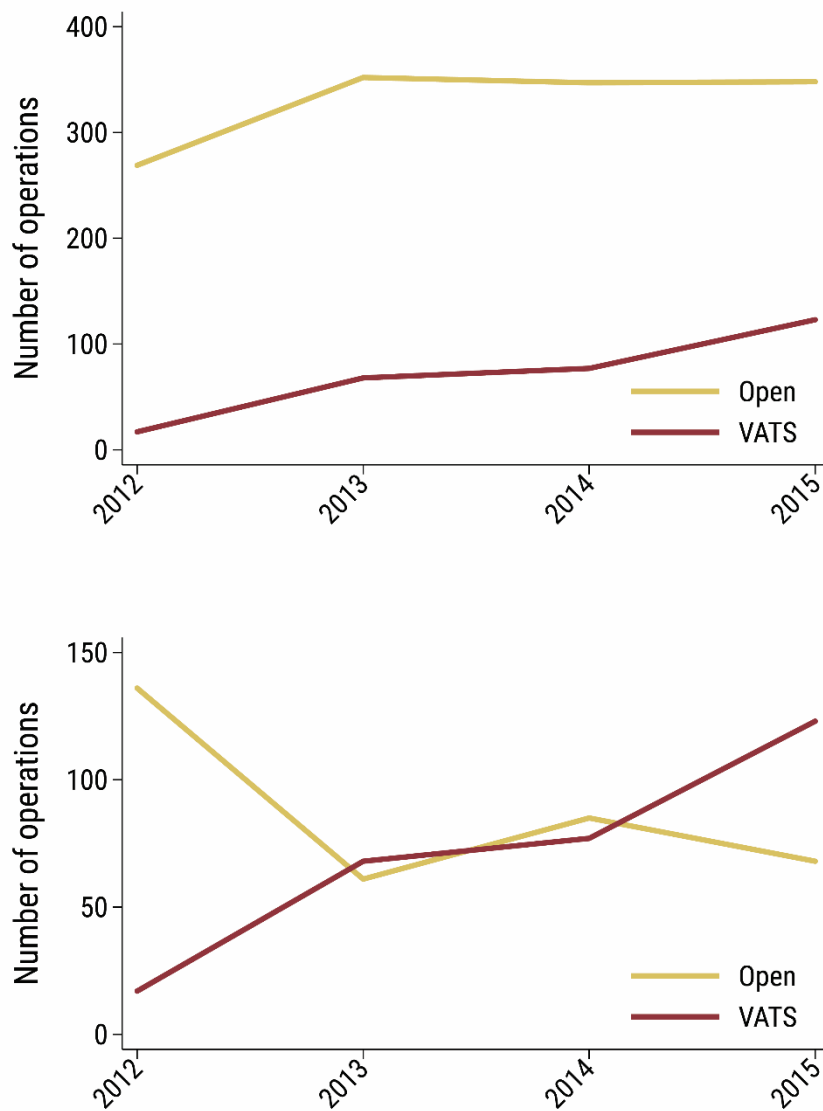
Figure 11. Numbers of annual surgeries.

The upper panel shows the number of surgeries per year. The number of VATS lobectomies increased during the study period, although the number of open thoracotomies was constant. The lower panel shows the numbers of lobectomies performed annually at Karolinska University Hospital and at the end of the study period. VATS lobectomy was performed more frequently than open thoracotomy.
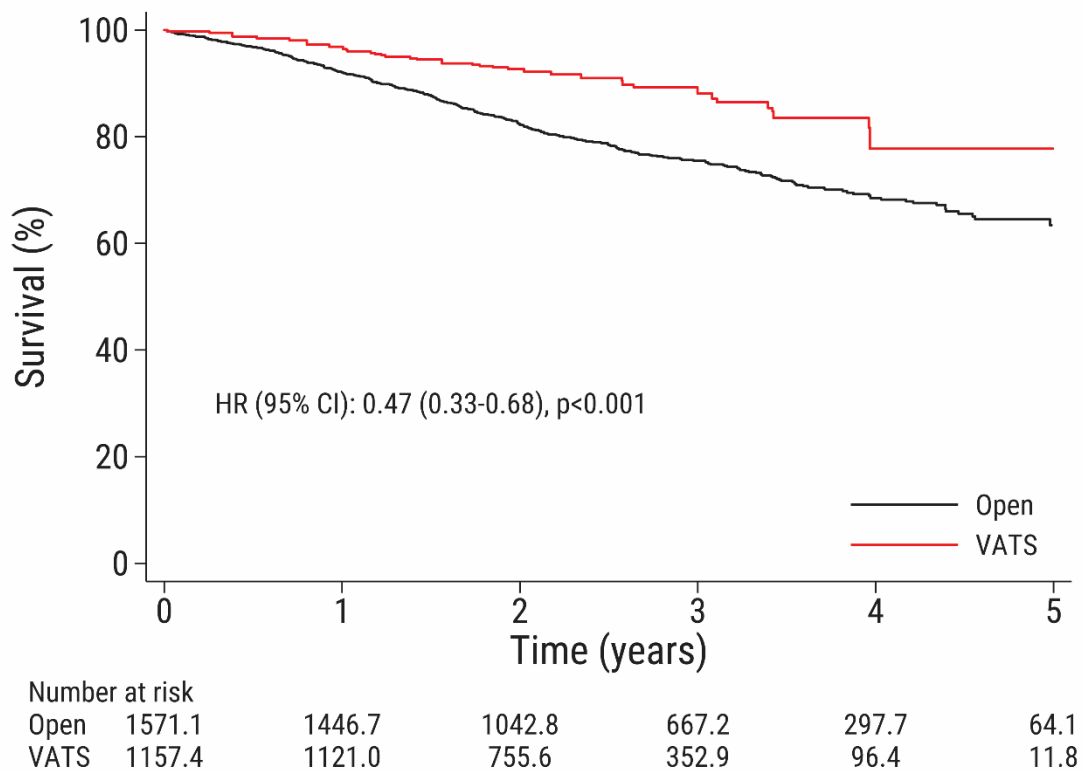
Figure 12. Survival after open thoracotomy or VATS.

The figure shows open thoracotomy (black line) or VATS lobectomy (red line). The group of patients who underwent open thoracotomy lobectomy (black line) served as the reference group. Note that the numbers of patients at risk shown below the graph are not necessarily integers owing to IPTW.

HR = hazard ratio, CI = confidence interval, VATS = video-assisted thoracoscopic surgery

5.5 STUDY V

5.5.1 Patients' characteristics and number of surgeries

This study included 4528 patients who underwent pulmonary resection for lung cancer in Sweden between 2009 and 2015 (mean age, 66.8 years (SD = 9.3); 55%, women; and 1311 (29%) smokers). Age, sex, and smoking status were not significantly different among the groups over the weekdays. Patients who were operated on Wednesday more frequently underwent preoperative radiotherapy. Patients with performance status = 0, compared with 1 or 2, underwent VATS more frequently on Fridays. In general, patients' baseline characteristics (Table 11) were similarly distributed through the week.

The numbers of surgeries performed on Monday, Tuesday, Wednesday, Thursday, and Friday were as follows: 1137 (25%), 1018 (22%), 1001 (22%), 889 (20%), and 483 (11%), respectively.

5.5.2 Survival outcomes

The median follow-up time was 2.9 years (mean, 3.3; SD, 2.0 years). The numbers of deaths per person years for each weekday were 387/3738 on Monday, 355/3452 on Tuesday, 369/3317 on Wednesday, 317/2946 on Thursday, and 170/1513 on Friday. The annual risk of death was 10%–11%, regardless of the weekday of surgery. Compared with Monday, the crude HRs for all-cause mortality (95% CI) were 0.99 (0.86–1.15), 1.08 (0.93–1.24), 1.04 (0.90–1.21), and 1.07 (0.89–1.28) for Tuesday, Wednesday, Thursday, and Friday, respectively. The adjusted HRs for all-cause mortality (95% CI) compared with Monday were 0.98 (0.85–1.13), 1.03 (0.89–1.19), 0.99 (0.85–1.15), and 1.04 (0.87–1.25) for Tuesday, Wednesday, Thursday, and Friday, respectively. There was no significant difference between crude or multivariable adjusted risks for all-cause mortality as a function of weekday, and there was no significant difference in RMST associated with the weekday of surgery at the 1- and 5-year follow-up examinations (Table 13, Figure 11).

Table 11. Patients' baseline characteristics.

	Total population	Mon	Tue	Wed	Thu	Fri	p
N (%)	4528	1137 (25%)	1018 (22%)	1001 (22%)	889 (20%)	483 (11%)	
Age, years, mean (SD)	66.8 (9.3)	67.1 (9.2)	66.5 (9.3)	66.6 (9.8)	66.7 (9.3)	67.1 (8.6)	0.553
Female sex	2499 (55.2)	645 (56.7)	576 (56.6)	554 (55.3)	463 (52.1)	261 (54.0)	0.229
Body mass index, kg/m^2, mean (SD)	26.0 (4.7)	25.8 (4.5)	26.1 (4.6)	26.1 (4.8)	26.2 (4.9)	25.6 (4.7)	0.090
No comorbidity	2083 (46.0)	516 (45.4)	468 (46.0)	466 (46.6)	414 (46.6)	219 (45.3)	0.974
Heart disease	597 (13.2)	163 (14.3)	124 (12.2)	144 (14.4)	103 (11.6)	63 (13.0)	0.243
Diabetes mellitus	414 (9.1)	100 (8.8)	101 (9.9)	92 (9.2)	83 (9.3)	38 (7.9)	0.755
Prior Stroke/TIA	232 (5.1)	48 (4.2)	59 (5.8)	50 (5.0)	45 (5.1)	30 (6.2)	0.397
Chronic kidney disease	83 (1.8)	22 (1.9)	21 (2.1)	17 (1.7)	12 (1.3)	11 (2.3)	0.708
Performance status 1 or 2*	1820 (40.2)	435 (38.3)	427 (41.9)	428 (42.8)	362 (40.7)	168 (34.8)	0.019
Current smoker	1311 (29.0)	325 (28.6)	285 (28.0)	281 (28.1)	274 (30.8)	146 (30.2)	0.593
Preoperative chemotherapy	125 (2.9)	31 (2.8)	30 (3.0)	28 (2.9)	28 (3.2)	8 (1.7)	0.581
Preoperative radiotherapy	195 (4.5)	43 (3.9)	35 (3.6)	55 (5.8)	50 (5.8)	12 (2.5)	0.007
Preoperative PET	3639 (87.3)	910 (87.2)	823 (87.6)	805 (88.7)	714 (86.9)	387 (85.2)	0.485
Lobectomy or more	3467 (76.6)	882 (77.6)	761 (74.8)	779 (77.8)	685 (77.1)	360 (74.5)	0.329
VATS	682 (15.1)	182 (16.0)	145 (14.2)	144 (14.4)	119 (13.4)	92 (19.0)	0.047
Stage IIIA or above**	872 (19.3)	230 (20.2)	193 (19.0)	177 (17.7)	174 (19.6)	98 (20.3)	0.603
Extended surgery	186 (4.1)	36 (3.2)	42 (4.1)	48 (4.8)	46 (5.2)	14 (2.9)	0.087
No microscopic radicality	681 (15.0)	152 (13.4)	173 (17.0)	146 (14.6)	126 (14.2)	84 (17.4)	0.081

Data are represented as n (%) unless otherwise noted. SD = standard deviation. TIA = transient ischemic attack. PET = positron emission tomography. VATS = video-assisted thoracic surgery.
An extended surgery involved any structure other than the lung or lymph nodes that was included in the resection (e.g. thoracic wall, diaphragm, pericardium).
*Compared with performance status 0, there was no patient with performance status 3 or 4.
**Pathological stage

Table 12. Event rates and risks of all-cause mortality.
Event rates and relative risks for all-cause mortality after pulmonary resections for patients with lung cancer in Sweden from 2009 to 2015 associated with the weekday of surgery.

	Number of deaths/Person-Years	Unadjusted mortality rate per 100 Person-Years (95% CI)	Crude HR (95% CI)	Multivariable[*] adjusted HR (95% CI)
Monday	387/3738	10 (9.4-11)	Ref.	Ref.
Tuesday	355/3452	10 (9.3-11)	0.99 (0.86-1.15)	0.98 (0.85-1.13)
Wednesday	369/3317	11 (10-12)	1.08 (0.93-1.24)	1.03 (0.89-1.19)
Thursday	317/2946	11 (9.6-12)	1.04 (0.90-1.21)	0.99 (0.85-1.15)
Friday	170/1513	11 (9.7-13)	1.07 (0.89-1.28)	1.04 (0.87-1.25)

*Model includes all variables reported in Table 1.
Ref. = reference category, HR = hazard ratio, CI = confidence interval.

Table 13. Survival
Kaplan–Meier estimated survival and difference in RMST(days) according to the weekday of surgery 1- and 5-years postoperatively of patients who underwent pulmonary resection for lung cancer (n = 4528).

	K–M estimated survival (95% CI)	Restricted mean survival time, days (95% CI)	Difference in survival time vs Monday, days (95% CI)	p value
1-Year follow-up				
Monday	88% (86-90)	344 (340-348)	-	-
Tuesday	90% (88-92)	349 (345-352)	4.4 (-1.1-9.8)	0.119
Wednesday	89% (87-91)	347 (343-351)	2.5 (-3.1-8.1)	0.381
Thursday	89% (87-91)	346 (342-351)	2.1 (-3.8-7.9)	0.489
Friday	90% (87-92)	346 (340-352)	1.6 (-5.7-8.9)	0.664
5-year follow-up				
Monday	61% (58-64)	1408 (1371-1446)	-	-
Tuesday	60% (56-63)	1414 (1376-1452)	6.0 (-47-59)	0.826
Wednesday	58% (55-62)	1383 (1344-1423)	-15 (-79-29)	0.368
Thursday	60% (56-64)	1391 (1349-1433)	-17 (-73-39)	0.547
Friday	59% (53-64)	1405 (1349-1461)	-3.5 (-71-65)	0.919

CI = confidence interval, K–M = Kaplan–Meier analysis, RMST = restricted mean survival time.
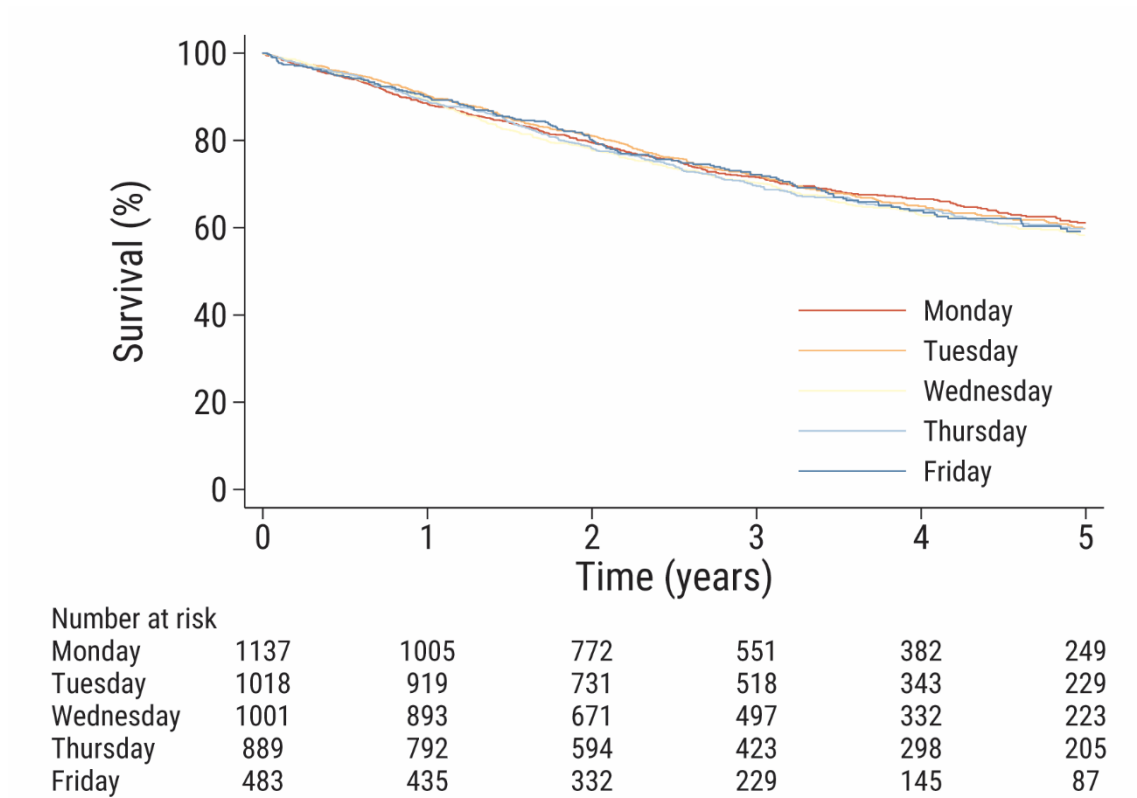
Figure 13. Kaplan–Meier analysis of estimated overall survival of 4528 patients who underwent pulmonary resection for lung cancer in Sweden from 2009 to 2015

6 DISCUSSION

6.1 STUDY I

Study I demonstrates an independent and statistically significant association between preoperative self-reported HRQOL and survival after a median follow-up of 8 years among patients who underwent lung surgery at Karolinska University Hospital. The preoperative physical component of QOL lower than the reference values was associated with poor long-term survival, independent of several patient-related factors, of which the most important were age, histopathological findings, cancer stage, and extent of surgery. Study I used the validated SF-36 questionnaire, taking advantage of its availability in different languages and the opportunity to compare the results with the reference scores of the general population. A recent survey among members of the ESTS shows that approximately 50% of ESTS centers routinely collect HRQOL questionnaires and the widely used SF-36 questionnaire.[65]

In Study I, the association between low PCS scores and subgroups stratified according to tumor stage did not show a statistically significant increase in mortality associated with stage 0 and stages II to III, likely explained by the small number of patients and events (death) in these subgroups. However, the point-estimates suggest a relation between physical QOL and mortality that is similar to our main findings for the total study population.

Möller and Sartipy investigated the association between self-reported HRQOL of thoracic surgery and clinical postoperative outcomes using the SF-36 questionnaire submitted to patients scheduled for thoracic surgery at Karolinska University Hospital between 2006 and 2008.[10, 18] They found that changes in the self-reported QOL, postoperative six months, and a 10% decline in the PCS and MCS scores are associated with 18% and 13% increases in postoperative mortality, respectively.[10] Further, there is an association between HRQOL, sex months after thoracic surgery, and long-term survival, which is independent of preoperative, baseline life quality scores.[10, 18] In Study I, the same population of 249 patients who completed the preoperative questionnaire were included and long-term survival was explored. The median follow-up was 8 years compared with the 4-year median follow-up time of the previous studies.

HRQOL is a subjective measure reflecting the effects of disease or treatment on a patient's physical and mental status. Thus, objective functional measures cannot replace or encompass these aspects of the health assessment. It is reasonable to conclude that HRQOL scores may reflect good general health and its consequences, which may affect health-consciousness, diet, physical activity, and sufficient compliance with medical therapy to improve prognosis.[8]

The association between HRQOL and survival after lung surgery is the subject of several reports. For example, Pompili et al. investigated preoperative predictions of survival based on the physical HRQOL of patients with early-stage lung cancer who

underwent lobectomy.[17] In Study I, the wide inclusion criteria used to select patients and procedures confers the advantage of generalization to clinical practice. Patients with benign and malignant diseases at various stages and different types of lung resections are included in the study.

Study I tested only the SF-36 instrument and speculates that the results from other HRQOL instruments may be similar. However, this hypothesis should be verified by specific studies before firm conclusions can be drawn.

The prediction by Study I of long-term mortality can serve as an important complement to the current risk prediction tool such as the Thoracoscore, which was developed for estimating mortality during hospitalization and subsequently for midterm mortality after thoracic surgery.[66] Accordingly, Study I strongly recommends the inclusion of self-reported HRQOL for the future development of risk-prediction models of long-term survival after thoracic procedures.

6.2 STUDY II

Study II revealed a remarkable increase in the number of pulmonary metastasectomy procedures for treating CRC at Karolinska University Hospital between 2004 and 2015, which achieved 60% 5-year survival. Prethoracotomy CEA concentrations >4 ng/mL was the only significant prognostic factor associated with poor long-term survival.

Recent advances in the management of CRC have significantly improved survival, including patients with metastatic disease.[23] The 5-year survival rate of metastatic CRC increased from 25% to 50%.[67] During the mid-1990s, surgical resection of liver metastases from CRC was adopted and gradually accepted in clinical practice as a component of multidisciplinary management to improve survival, despite the lack of strong evidence to support its influence on improving survival.[24] Similarly, pulmonary metastasectomy of CRC became widely accepted, which depended on growing evidence contributed only by retrospective observational studies.[25] Despite the large number of nonrandomized studies and meta-analyses, the need for a randomized study is increasing to recognize whether the survival benefit conferred upon these patients is attributable to surgical intervention, bias in patient selection, lead-time, or staging migration.[68] The PulMiCC is a randomized controlled trial currently recruiting patients from the United Kingdom and Europe, which is designed to answer clinical questions about the feasibility of pulmonary metastasectomy for CRC to improve survival and to inform and guide clinical practice.[33]

The incidence of CRC in Europe and the United States is decreasing, and the criteria for patient selection for surgery did not change during Study II and therefore cannot explain the continuous increase in the number of procedures.[69] Presumably, recent developments in the diagnosis, surgical techniques, and therapy of CRC contribute to the increased frequency of early discovery of resectable metastases and encourage oncologists and surgeons to employ more aggressive strategies such as surgical resection to manage metastatic CRC.[22, 23]

The long-term survival reported by the present study is comparable with, if not better than overall survival data reported by others. For example, Gonzalez et al. conducted a meta-analysis that revealed that overall 5-year survival rates ranges from 27% to 68%,[27] and another contemporaneous study found that disease-specific 5-year survival is 46.1% (95% CI, 38.5% to 53.7%).[28] These wide differences reflect the differences in the criteria used to select patients for surgery. Moreover, 5-year survival may be higher if patients who are accepted for surgery have a long DFI, solitary metastases, no lymph nodes metastases detected using PET-CT, and low prethoracotomy CEA concentrations. In our institution, all patients are accepted after they are discussed at multidisciplinary team conferences, and we follow the clinical practice guidelines and the team's recommendations.[21, 70] Criteria that justify PM-CRC are as follows: radically treated primary tumor; absence of extrathoracic metastases, or if present, radically treated or amenable to radical treatment; resectable pulmonary metastases; and good general condition consistent with a safe surgical outcome.

Prethoracotomy CEA levels are thoroughly investigated in the literature, and Study II as well as those of others found a consistently significant association between high concentrations of CEA and worse prognosis of survival.[27-29] The cut-off for normal vs elevated CEA concentrations in Study II was 4 ng/mL, and 51% of patients had CEA concentrations <4 ng/mL. In contrast, other studies defined a cut-off level ≤5 ng/mL. Further, Embun et al. conducted a multicenter, prospective cohort study showing that 69% of patients have prethoracotomy CEA concentrations ≤5 ng/mL, and 35% experience DFI >24 months.[28] Similarly, Gonzalez et al. conducted a meta-analysis of 2,925 patients from 25 studies that demonstrated a pooled outcome with a significantly increased risk of mortality associated with high concentrations of prethoracotomy CEA.[27] Similar to Study II, a retrospective study of 94 patients performed by Suzuki et al. found that the prethoracotomy CEA concentration was the only statistically significant prognostic factor of long-term survival, with 5-year survival rates of 57% and 30.9% for patients with normal or high CEA concentrations, respectively (p = 0.038).[29]

As a prognostic factor, prethoracotomy CEA concentrations have conflicting consequences for clinical applications, because high CEA concentrations may lead to further investigations with imaging and early diagnosis of pulmonary metastases suitable for surgical resection.[71] In contrast, high CEA concentrations predict poor survival and may lead physicians not to offer surgery.[71] We believe that prethoracotomy CEA concentrations associated with pulmonary metastasectomy can be used to help detect recurrent disease early during follow-up and consequently may enable rapid intervention.

DFI is considered by many studies as a prognostic factor for survival, although the results conflict and gave conflicting results. For example, Gonzalez et al. and Embun et al. found that short DFI predicts worse survival,[27, 28] although several other studies

do not demonstrate this association.[29, 30, 72] In Study II, 48% of patients with DFI >24 months is not significantly associated with survival.

6.3 STUDY III

Study III, which is a nationwide study conducted in Sweden, found that 5-year survival after PM-CRC is 56%, which is higher compared with the findings of previous report,[27] reflected appropriate selection criteria of patients scheduled for surgery. In Study III, external validation of a recently proposed Japanese prognostic model for survival after PM-CRC, achieved good discrimination among Swedish patients. Thus, low-risk patients achieved statistically significant longer survival compared with the moderate- or high-risk groups, despite the lack of determination of prethoracotomy CEA concentrations. Similar to Study II, the number of surgeries performed between 2009 and 2015 increased, and Figure 7 reveals incomplete reporting to the ThoR register before 2013.

Several prognostic factors were identified in numerous nonrandomized studies that focused on how to facilitate and optimize patient selection for surgery and to predict long-term outcomes after surgery. These prognostic factors include the following: prethoracotomy CEA concentrations,[27-29, 31] DFI,[27, 28, 31] number of pulmonary metastases,[27, 31] and involvement of thoracic lymph nodes.[27, 28, 73] Few of these studies attempted to construct multivariable risk prediction models by combining these and other factors to improve their discriminatory capacity compared with the use of single prognostic factors.[28, 31, 74] However, to the best of our knowledge, none of these models was externally validated or is widely used in clinical applications.

Okumura et al., who recently suggested a practical and well-designed risk prediction model for patients scheduled to undergo PM-CRC, assigned five preoperative risk factors to construct three risk categories depending on the number of risk factors.[31] The study includes data for 785 Japanese patients treated at 46 hospitals in Japan who underwent surgery between 2004 and 2008. The lack of prethoracotomy CEA concentrations in Study III represents a significant limitation to external validation of the proposed prediction model, because some patients were incorrectly classified in the low- and moderate-risk categories instead of moderate- and high-risk groups. Further, external validation of a risk model usually assesses discrimination and calibration. However, in our validation, we were obliged to employ only discrimination because of the lack of prethoracotomy CEA concentrations as well as missing DFI data for 25% of patients. However, the study showed an excellent ability to discriminate among Swedish patients with statistically significant higher mortality of moderate- and high-risk patients compared with low-risk patients. We believe that this promising risk-prediction model can assist patient selection for surgery in a way that will be practical and easy for surgeons and patients.

6.4   STUDY IV

To our knowledge, the first and only report on VATS lobectomy in Sweden, published in 1998, investigated 30 patients who underwent VATS lobectomy with simultaneous stapling technique.[75] The VATS lobectomy program started at Karolinska University Hospital in 2012 as an alternative to thoracotomy for treating lung tumors. After a few years, VATS lobectomy became the standard approach for resection of patients with early-stage NSCLC. The program was conducted by three dedicated surgeons specializing in GTS, following the well-organized Copenhagen model.[40] The same protocol was used for all VATS lobectomy procedures, which includes the standardized three-port anterior approach, the same surgical instruments, and video-thoracoscope. These factors, together with a sufficient number of surgeries per surgeon, are important for maintaining the success and rapid progress of the program. For example, McElnay et al. found a remarkable increase in the rate of VATS lobectomies after the adoption of the Copenhagen program and approach.[41]

Study IV compared patients who underwent VATS lobectomy for early stage NSCLC at Karolinska University Hospital with patients who underwent thoracotomy at other hospitals in Sweden. Study IV excluded patients who underwent thoracotomy–lobectomy at our institution, because they were considered unsuitable for VATS lobectomy at the time of the decision to offer surgery, or some patients were converted from VATS. Further, the few patients (n = 14) who underwent VATS lobectomy at hospitals other than the Karolinska were excluded to facilitate acquiring the data and arriving at conclusions of their significance. The difference in patients' baseline characteristics evaluated using IPTW, which was based on a propensity score, achieved an excellent balance between the groups. Thus, the standardized mean differences among all variables after weighting was <0.1. However, the results of Study IV should be carefully evaluated because of the probability of undetected differences between the groups.

More than 80% of patients in both groups did not experience peri- or postoperative complications; however, the VATS group was associated with fewer blood transfusions, a high proportion of drain removal on the first postoperative day, and less postoperative pneumonia, consistent with the findings of numerous reports.[76-80] We were unable to reach a definitive conclusion about the superiority of the VATS technique vs the thoracotomy approach in Study IV due to the low rate of complications in both groups. These results support our expectations of the feasibility and safety of VATS lobectomy for treating patients with NSCLC.

Although the duration of hospitalization of patients in the VATS group was shorter compared with those of the thoracotomy group, more patients in the VATS group were referred to rehabilitation. This may reflect the differences in practice and policy among institutions in Sweden and not the approach. In a double-blind randomized controlled trail, patients who underwent VATS lobectomy experienced less postoperative pain and better HRQOL compared with patients who underwent anterolateral thoracotomy.[36]

Data acquired by nonrandomized observational studies of long-term survival after VATS lobectomy compared with those for thoracotomy, vary from no differences to better survival achieved by the former approach. For example, a study conducted in the United States by Yang et al. demonstrates shorter hospitalization and noninferior long-term survival after VATS lobectomy compared with thoracotomy.[44] Similarly, Paul et al. showed that VATS lobectomy is associated with equivalent overall survival, cancer-specific and disease-free survival compared with open thoracotomy.[81] The study cited, which employs propensity-score matching of >6000 patients with primary NSCLC, identified 1195 patients in each group after matching.[81] In Study IV, the VATS group experienced longer long-term survival as follows: overall 1- and 5-year survival rates were 92% vs 97% and 63% vs 78% in the open thoracotomy and VATS groups, respectively (HR [95% CI], 0.47 [0.33–0.68], p<0.001). These results are consistent, before and after weighting of the covariates. Moreover, when the analysis of patients restricted to those with cancer stages I and IIA was repeated, we obtained the same statistically significant results (HR [95% CI], 0.59 (0.39–0.88), p = 0.009). Further, a single-center study conducted in Poland by Dziedzic et al. demonstrates better survival after VATS lobectomy compared with thoracotomy.[82] It is important to note the aim of Study IV was to investigate the feasibility and safety of VATS lobectomy for treating patients with early-stage NSCLC, but not to evaluate the direct effects of treatment. Consequently, the results of Study IV, particularly long-term survival, must be interpreted with caution before application to the clinic.

6.5 STUDY V

Study V did not detect a difference in survival outcomes among patients who underwent pulmonary resections for lung cancer on different days of the week. Fewer surgeries were performed on Fridays, and the patients and surgical techniques were comparable among all groups. The HR was not statistically significant for all-cause mortality in crude or adjusted analysis. Using Monday as a reference, we consider the difference in RMST clinically negligible at the 1- and 5-year follow-up examinations (1.6 days to 4.4 days and –17 days to 6 days, respectively). In the Swedish healthcare system, in-theater time is approximately 50% shorter on Fridays, which explains the decreased number of operations compared with other weekdays. The annual risk of death is approximately 10%, independent of the weekday of surgery.

The results of numerous studies on the effects of the weekday of surgery on short- and long-term survival among diverse surgical disciplines are inconsistent. For example, a nationwide cohort study conducted in Sweden of 106 473 patients who underwent cardiac surgery found no evidence of an association of the weekday of surgery on survival, which is consistent with the conclusions of Study V.[63] Another study found that surgery performed later in the week is associated with poor survival of patients with gastrointestinal cancer (e.g. esophagogastric cancer) (HR, 1.57; CI 95%, 1.31–1.88), liver/pancreatic/biliary cancer (HR, 1.49; CI 95%, 1.17–1.88), and CRC, (HR, 1.53; CI 95%, 1.44–1.63), but not for other common cancers such as lung cancer. In patients with lung cancer (n = 2537), the crude and adjusted HRs for

disease-specific mortality for Fridays and Mondays are 0.09 (CI 95%, 0.87_1.37) and 1.04 (CI 95%, 0.82–1.31), respectively.[83] These findings strongly support the results of Study V, because they were published by different investigators who studied cohorts of patients from the same country.

The differences in clinical practice and healthcare systems among clinics and countries makes the comparison between results of studies in this context difficult and complex. For example, a study conducted by Singla et al. found that 7718 patients undergoing surgery on a weekend vs a weekday experienced poor short-term survival. In this cohort, >80% underwent emergency and general surgery that contributed to approximately 40% of early mortality, whereas early mortality after cardiothoracic surgery was 8%. Further, patients who underwent elective cardiothoracic surgery experienced higher early postoperative mortality. These results reflect the inherent high risk of elective cardiothoracic procedures,[59] however, Dalén et al. as well as Study V did not identify a significant association between the weekday of surgery and mortality of patients who underwent cardiothoracic surgery.[63] A retrospective analysis of the national hospital administrative data of English public hospitals evaluated 4 133 346 patients who underwent elective surgery.[57] This study found that 15927 patients who underwent elective lung resections experienced a significant increase in short-term mortality when surgery was conducted on Fridays and weekends compared with Mondays.[57] The results of Study V are inconsistent with these results, but interpretation must take into account the difference in the study populations. Study V only included patients with lung cancer, and the study cited[57] included all patients who underwent lung excision. Moreover, the authors reported significant limitations of their study that included the inability to adjust for inherent selection bias and acknowledged that the adjustment for risk associated with the procedure was not based on clinical severity. In Study V, the ThoR register, with its clinical details and complete reporting since 2013, effectively minimized selection bias.

6.6 LIMITATIONS

6.6.1 Study I

Study I specifically tested the SF-36 tool and its generalizability. Other instruments of HRQOL measures require separate, meticulous studies to test their abilities to predict survival. Data were missing for smoking history (8%) and forced expiratory volume in 1 second (15%). The missing data might have skewed the results; however, the amount of missing data for these variables was not large, and the data were managed using multiple imputation and chained equations.

6.6.2 Study II

The study size (n = 184) was insufficient to recognize small differences between groups; however, the number of patients was acceptable and larger compared with the sizes of numerous other contemporaneous studies on same subject with similar

study designs.[27] Missing prethoracotomy CEA concentrations (40%) represents another limitation, which may confer the probable disadvantage of misrepresenting the results. Nonetheless, the prethoracotomy CEA concentration was the only statistically significant prognostic factor, which is consistent with the results of other reports. Therefore, we believe that complete data for this variable will provide stronger supporting evidence. Other limitations include unknown confounders and bias inherent in all retrospective studies, despite implementation of meticulous statistical measures.

6.6.3 Study III

The lack of prethoracotomy CEA concentrations in Study III was a significant limitation, because this variable is not included in the ThoR register. Consequently, certain patients were incorrectly classified into the low- or moderate-risk categories instead of the moderate- or high-risk categories. Another limitation, caused in part by the lack of CEA concentrations, was the restriction of the external validation of the risk model to only discrimination assessment without calibration. Another limitation was that DFI was missing in some patients.

6.6.4 Study IV

Study IV was limited by its lack of information from the ThoR register on the conversion rate of VATS to thoracotomy, leading to the exclusion of these patients from the study, which exaggerated the expectation of the superiority of VATS compared with thoracotomy. Other limitations were the lack of lymph-node sampling or clearance and the inability to compare tumor upstaging between the two groups as reported in the literature.[84]

6.6.5 Study V

This nationwide study was conducted within the Swedish healthcare system, which limits the generalization of the findings to thoracic centers in other countries.

7 CONCLUSIONS

7.1 STUDY I

Preoperative physical QOL lower than the reference value was significantly associated with worse survival of patients who underwent thoracic surgery. This association was independent of histopathology, cancer stage, extent of surgery, and other patient-related factors. The mental component of the HRQOL was not significantly associated with long-term survival. The study recommends inclusion of physical QOL in future risk models designed to predict long-term survival after thoracic surgery.

7.2 STUDY II

The overall 5-year survival after patients with CRC underwent pulmonary metastasectomy was 60%, which is consistent with the longest overall survival rates previously reported. The number of surgeries increased during the study period. High prethoracotomy CEA level ≥4 ng/mL was the only prognostic factor identified with significant association with poor postoperative long-term survival.

7.3 STUDY III

The overall 5-year survival rate after patients with CRC underwent pulmonary metastasectomy in Sweden (56%) is among the longest compared with the results of contemporaneous reports, suggesting appropriate patient selection criteria. We also showed that a prognostic model, initially developed in Japanese cohort of patients, successfully provided risk stratification in an external validation cohort of Swedish patients.

7.4 STUDY IV

VATS lobectomy of patients with early-stage NSCLC was associated with fewer postoperative complications, improved clinical short-term outcomes, and increased long-term survival compared with thoracotomy. VATS lobectomy was feasible and safe for treating patients with early-stage NSCLC.

7.5 STUDY V

The weekday of surgery was not significantly associated with long-term survival of patients who underwent surgical treatment for lung cancer in Sweden. The results do not support implementing changes in staffing policies or rescheduling of surgery.

8 ACKNOWLEDGEMENTS

9 REFERENCES

1.	Toomes H, Swoboda L. The development of General Thoracic Surgery. *Thorac surg sci*. 2004;1:2-5

2.	Thomas PA. Working the fundamentals. *Eur J Cardiothorac Surg*. 2013;43:455-458

3.	Memtsoudis SG, Besculides MC, Zellos L, Patil N, Rogers SO. Trends in lung surgery: United States 1988 to 2002. *Chest*. 2006;130:1462-1470

4.	Treasure T, Milošević M, Fiorentino F, Macbeth F. Pulmonary metastasectomy: what is the practice and where is the evidence for effectiveness? *Thorax*. 2014:thoraxjnl-2013-204528

5.	Kanzaki R, Inoue M, Kimura T, Kawamura T, Funaki S, Shintani Y, Minami M, Takemasa I, Mizushima T, Mori M. Role of pulmonary metastasectomy in colorectal cancer in the era of modern multidisciplinary therapy. *Surg Today*. 2017;47:1111-1118

6.	Yan TD, Cao C, D'amico TA, Demmy TL, He J, Hansen H, Swanson SJ, Walker WS, Casali G, Dunning J. Video-assisted thoracoscopic surgery lobectomy at 20 years: a consensus statement. *Eur J Cardiothorac Surg*. 2014;45:633-639

7.	http://www.ucr.uu.se/thor/. ThoR. 2018

8.	Gotay CC, Kawamoto CT, Bottomley A, Efficace F. The prognostic significance of patient-reported outcomes in cancer clinical trials. *J Clin Oncol*. 2008;26:1355-1363

9.	Székely A, Nussmeier NA, Miao Y, Huang K, Levin J, Feierfeil H, Mangano DT. A multinational study of the influence of health-related quality of life on in-hospital outcome after coronary artery bypass graft surgery. *Am Heart J*. 2011;161:1179-1185. e1172

10.	Möller A, Sartipy U. Associations between changes in quality of life and survival after lung cancer surgery. *J Thorac Oncol*. 2012;7:183-187

11.	Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66:7-30

12.	Socialstyrelsen. Cancer i siffror 2013. (https://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/19108/2013-6-5.pdf)

13.	Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Treatment of stage I and II non-small cell lung cancer: diagnosis and management of lung cancer: American College of Chest Physicians evidence-based clinical practice guidelines. *CHEST Journal*. 2013;143:e278S-e313S

14.	Ware Jr JE, Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. *Med Care*. 1995:AS264-AS279

15.   Pompili C, Brunelli A. Quality of life after lung resection is not associated with functional objective measures. *Eur Respir J*. 2013;42:283-285

16.   Montazeri A. Quality of life data as prognostic indicators of survival in cancer patients: an overview of the literature from 1982 to 2008. *Health and quality of life outcomes*. 2009;7:102

17.   Pompili C, Salati M, Refai M, Berardi R, Onofri A, Mazzanti P, Brunelli A. Preoperative quality of life predicts survival following pulmonary resection in stage I non-small-cell lung cancer. *Eur J Cardiothorac Surg*. 2013;43:905-910

18.   Möller A, Sartipy U. Quality of life six months after lung cancer surgery is associated with long-term survival. *Acta Oncol*. 2012;51:1029-1035

19.   Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136:E359-E386

20.   Van Cutsem E, Cervantes A, Nordlinger B, Arnold D. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2014:mdu260

21.   http://www.cancercentrum.se. Nationellt vårdprogram 2016. Tjock- och ändtarmscancer (Swedish).

22.   Wang C-C, Li J. An update on chemotherapy of colorectal liver metastases. *World journal of gastroenterology: WJG*. 2012;18:25

23.   Ciombor KK, Wu C, Goldberg RM. Recent therapeutic advances in the treatment of colorectal cancer. *Annu Rev Med*. 2015;66:83-95

24.   Grünhagen D, Jones R, Treasure T, Vasilakis C, Poston G. The history of adoption of hepatic resection for metastatic colorectal cancer: 1984–95. *Crit Rev Oncol Hematol*. 2013;86:222-231

25.   Treasure T, Leonard P. Pulmonary metastasectomy in colorectal cancer. *Br J Surg*. 2013;100:1403-1404

26.   Van Raemdonck D, Friedel G. The European society of thoracic surgeons lung metastasectomy project. *J Thorac Oncol*. 2010;5:S127-S129

27.   Gonzalez M, Poncet A, Combescure C, Robert J, Ris HB, Gervaz P. Risk factors for survival after lung metastasectomy in colorectal cancer patients: a systematic review and meta-analysis. *Ann Surg Oncol*. 2013;20:572-579

28.   Embun R, de Andrés JJR, Call S, de Olaiz Navarro B, Freixinet JL, Bolufer S, Jarabo JR, Pajuelo N, Molins L. Causal Model of Survival After Pulmonary Metastasectomy of Colorectal Cancer: A Nationwide Prospective Registry. *Ann Thorac Surg*. 2016;101:1883-1890

29.   Suzuki H, Kiyoshima M, Kitahara M, Asato Y, Amemiya R. Long-term outcomes after surgical resection of pulmonary metastases from colorectal cancer. *Ann Thorac Surg*. 2015;99:435-440

30. Zampino MG, Maisonneuve P, Ravenda PS, Magni E, Casiraghi M, Solli P, Petrella F, Gasparri R, Galetta D, Borri A. Lung metastases from colorectal cancer: analysis of prognostic factors in a single institution study. *Ann Thorac Surg*. 2014;98:1238-1245

31. Okumura T, Boku N, Hishida T, Ohde Y, Sakao Y, Yoshiya K, Higashiyama M, Hyodo I, Mori K, Kondo H. Surgical outcome and prognostic stratification for pulmonary metastasis from colorectal cancer. *Ann Thorac Surg*. 2017;104:979-987

32. Eckardt J, Licht PB. Thoracoscopic or open surgery for pulmonary metastasectomy: an observer blinded study. *Ann Thorac Surg*. 2014;98:466-470

33. Treasure T, Fallowfield L, Lees B, Farewell V. Pulmonary metastasectomy in colorectal cancer: the PulMiCC trial. *Thorax*. 2011:thoraxjnl-2011-200015

34. McKenna RJ, Wolf RK, Brenner M, Fischel RJ, Wurnig P. Is lobectomy by video-assisted thoracic surgery an adequate cancer operation? *Ann Thorac Surg*. 1998;66:1903-1907

35. Walker WS, Codispoti M, Soon SY, Stamenkovic S, Carnochan F, Pugh G. Long-term outcomes following VATS lobectomy for non-small cell bronchogenic carcinoma. *Eur J Cardiothorac Surg*. 2003;23:397-402

36. Bendixen M, Jørgensen OD, Kronborg C, Andersen C, Licht PB. Postoperative pain and quality of life after lobectomy via video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: a randomised controlled trial. *Lancet Oncol*. 2016;17:836-844

37. Okada M, Sakamoto T, Yuki T, Mimura T, Miyoshi K, Tsubota N. Hybrid surgical approach of video-assisted minithoracotomy for lung cancer: significance of direct visualization on quality of surgery. *Chest*. 2005;128:2696-2701

38. Lewis RJ, Caccavale RJ, Sisler GE, Bocage J-P, Mackenzie JW. One hundred video-assisted thoracic surgical simultaneously stapled lobectomies without rib spreading. *Ann Thorac Surg*. 1997;63:1415-1421

39. Swanson SJ, Herndon JE, D'Amico TA, Demmy TL, McKenna Jr RJ, Green MR, Sugarbaker DJ. Video-assisted thoracic surgery lobectomy: report of CALGB 39802—a prospective, multi-institution feasibility study. *J Clin Oncol*. 2007;25:4993-4997

40. Hansen HJ, Petersen RH. Video-assisted thoracoscopic lobectomy using a standardized three-port anterior approach-The Copenhagen experience. *Annals of cardiothoracic surgery*. 2012;1:70

41. McElnay P, Casali G, Batchelor T, West D. Adopting a standardized anterior approach significantly increases video-assisted thoracoscopic surgery lobectomy rates. *Eur J Cardiothorac Surg*. 2013;46:100-105

42. Postmus P, Kerr K, Oudkerk M, Senan S, Waller D, Vansteenkiste J, Escriu C, Peters S. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28:iv1-iv21

43. Vannucci F, Gonzalez-Rivas D. Is VATS lobectomy standard of care for operable non-small cell lung cancer? *Lung Cancer*. 2016;100:114-119

44. Yang C, Kumar A, Klapper JA, Hartwig MG, Tong BC, Harpole JD, Berry MF, D'Amico TA. A National Analysis of Long-term Survival Following Thoracoscopic Versus Open Lobectomy for Stage I Non-small-cell Lung Cancer. *Ann Surg*. 2017

45. Boffa DJ, Dhamija A, Kosinski AS, Kim AW, Detterbeck FC, Mitchell JD, Onaitis MW, Paul S. Fewer complications result from a video-assisted approach to anatomic resection of clinical stage I lung cancer. *J Thorac Cardiovasc Surg*. 2014;148:637-643

46. Nagahiro I, Andou A, Aoe M, Sano Y, Date H, Shimizu N. Pulmonary function, postoperative pain, and serum cytokine level after lobectomy: a comparison of VATS and conventional procedure. *Ann Thorac Surg*. 2001;72:362-365

47. Decaluwe H, Petersen RH, Hansen H, Piwkowski C, Augustin F, Brunelli A, Schmid T, Papagiannopoulos K, Moons J, Gossot D. Major intraoperative complications during video-assisted thoracoscopic anatomical lung resections: an intention-to-treat analysis. *Eur J Cardiothorac Surg*. 2015;48:588-599

48. Cai Y-x, Fu X-n, Xu Q-z, Sun W, Zhang N. Thoracoscopic lobectomy versus open lobectomy in stage I non-small cell lung cancer: a meta-analysis. *PLoS One*. 2013;8:e82366

49. Swanson SJ, Meyers BF, Gunnarsson CL, Moore M, Howington JA, Maddaus MA, McKenna RJ, Miller DL. Video-assisted thoracoscopic lobectomy is less costly and morbid than open lobectomy: a retrospective multiinstitutional database analysis. *Ann Thorac Surg*. 2012;93:1027-1032

50. Nwogu CE, D'Cunha J, Pang H, Gu L, Wang X, Richards WG, Veit LJ, Demmy TL, Sugarbaker DJ, Kohman LJ. VATS lobectomy has better perioperative outcomes than open lobectomy: CALGB 31001, an ancillary analysis of CALGB 140202 (Alliance). *Ann Thorac Surg*. 2015;99:399-405

51. Petrella F, Spaggiari L. The smaller the better: a new concept in thoracic surgery? *Lancet Oncol*. 2016;17:699-700

52. Dunning J, Elsaegh M, Nardini M, Gillaspie EA, Petersen RH, Hansen HJ, Helsel B, Naase H, Kornaszewska M, Will MB. Microlobectomy: A Novel Form of Endoscopic Lobectomy. *Innovations: Technology and Techniques in Cardiothoracic and Vascular Surgery*. 2017;12:247-253

53. Bertolaccini L, Zaccagna G, Divisi D, Pardolesi A, Solli P, Crisci R. Awake non-intubated thoracic surgery: an attempt of systematic review and meta-analysis. *Video-Assisted Thoracic Surgery*. 2017;2

54. Mineo TC, Ambrogi V. A glance at the history of uniportal video-assisted thoracic surgery. *J Vis Surg*. 2017;3

55. Black N. Higher mortality in weekend admissions to the hospital: true, false, or uncertain? *JAMA*. 2016;316:2593-2594

56. Health Do. Research into the "weekend effect" on patient outcomes and mortality. October 30, 2015

57. Aylin P, Alexandrescu R, Jen M, Mayer E, Bottle A. Day of week of procedure and 30 day mortality for elective surgery: retrospective analysis of hospital episode statistics. *BMJ*. 2013;346:f2424

58. Lagergren J, Mattsson F, Lagergren P. Weekday of esophageal cancer surgery and its relation to prognosis. *Ann Surg*. 2016;263:1133-1137

59. Singla AA, Guy GS, Field JB, Ma N, Babidge WJ, Maddern GJ. No weak days? Impact of day in the week on surgical mortality. *ANZ J Surg*. 2016;86:15-20

60. Zare MM, Itani KM, Schifftner TL, Henderson WG, Khuri SF. Mortality after nonemergent major surgery performed on Friday versus Monday through Wednesday. *Ann Surg*. 2007;246:866-874

61. Njølstad TS, Werner HM, Marcickiewicz J, Tingulstad S, Staff AC, Oddenes K, Bjørge L, Engh ME, Woie K, Tjugum J. Late-week surgical treatment of endometrial cancer is associated with worse long-term outcome: Results from a prospective, multicenter study. *PLoS One*. 2017;12:e0182223

62. Visser E, van Rossum PS, Verhoeven RH, Ruurda JP, van Hillegersberg R. Impact of weekday of esophagectomy on short-term and long-term oncological outcomes: a nationwide population-based cohort study in the Netherlands. *Ann Surg*. 2017;266:76-81

63. Dalén M, Edgren G, Ivert T, Holzmann MJ, Sartipy U. Weekday and Survival After Cardiac Surgery—A Swedish Nationwide Cohort Study in 106 473 Patients. *J Am Heart Assoc*. 2017;6:e005908

64. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30:377-399

65. Pompili C, Novoa N, Balduyck B. ESTS Quality of life and Patient Safety Working Group. Clinical evaluation of quality of life: a survey among members of European Society of Thoracic Surgeons (ESTS). *Interact Cardiovasc Thorac Surg*. 2015;21:415-419

66. Falcoz PE, Conti M, Brouchet L, Chocron S, Puyraveau M, Mercier M, Etievent JP, Dahan M. The Thoracic Surgery Scoring System (Thoracoscore): risk model for in-hospital death in 15,183 patients requiring thoracic surgery. *J Thorac Cardiovasc Surg*. 2007;133:325-332. e321

67. Wang C-C, Li J. An update on chemotherapy of colorectal liver metastases. *World J Gastroenterol*. 2012;18:25-33

68. Åberg T, Treasure T. Analysis of pulmonary metastasis as an indication for operation: an evidence-based approach. *Eur J Cardiothorac Surg*. 2016 Nov;50:792-798

69. Haggar FA, Boushey RP. Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. *Clin Colon Rectal Surg*. 2009;22:191

70. Engstrom PF, Saltz L. Colon cancer. Clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network: JNCCN*. 2003;1:40-53

71. Fiorentino F, Treasure T. Pulmonary metastasectomy for colorectal cancer: making the case for a randomized controlled trial in the zone of uncertainty. *J Thorac Cardiovasc Surg*. 2013;146:748-752

72. Cho JH, Kim S, Namgung M, Choi YS, Kim HK, Zo JI, Shim YM, Kim J. The prognostic importance of the number of metastases in pulmonary metastasectomy of colorectal cancer. *World J Surg Oncol*. 2015;13:222

73. Cho JH, Hamaji M, Allen MS, Cassivi SD, Nichols FC, Wigle DA, Shen KR, Deschamps C. The prognosis of pulmonary metastasectomy depends on the location of the primary colorectal cancer. *Ann Thorac Surg*. 2014;98:1231-1237

74. Salah S, Watanabe K, Welter S, Park J, Park J, Zabaleta J, Ardissone F, Kim J, Riquet M, Nojiri K. Colorectal cancer pulmonary oligometastases: pooled analysis and construction of a clinical lung metastasectomy prognostic model. *Ann Oncol*. 2012;23:2649-2655

75. Hermansson U, Konstantinov IE, Aren C. Video-assisted thoracic surgery (VATS) lobectomy: the initial Swedish experience. *Seminars in thoracic and cardiovascular surgery*. 1998;10:285-290

76. Falcoz P-E, Puyraveau M, Thomas P-A, Decaluwe H, Hürtgen M, Petersen RH, Hansen H, Brunelli A, Van Raemdonck D, Dahan M. Video-assisted thoracoscopic surgery versus open lobectomy for primary non-small-cell lung cancer: a propensity-matched analysis of outcome from the European Society of Thoracic Surgeon database. *Eur J Cardiothorac Surg*. 2016;49:602-609

77. Laursen LO, Petersen RH, Hansen HJ, Jensen TK, Ravn J, Konge L. Video-assisted thoracoscopic surgery lobectomy for lung cancer is associated with a lower 30-day morbidity compared with lobectomy by thoracotomy. *Eur J Cardiothorac Surg*. 2016;49:870-875

78. Yan TD, Black D, Bannon PG, McCaughan BC. Systematic review and meta-analysis of randomized and nonrandomized trials on safety and efficacy of video-assisted thoracic surgery lobectomy for early-stage non–small-cell lung cancer. *J Clin Oncol*. 2009;27:2553-2562

79. Zhang Z, Zhang Y, Feng H, Yao Z, Teng J, Wei D, Liu D. Is video-assisted thoracic surgery lobectomy better than thoracotomy for early-stage non-small-cell lung cancer? A systematic review and meta-analysis. *Eur J Cardiothorac Surg*. 2013;44:407-414

80. Ilonen IK, Räsänen JV, Knuuttila A, Salo JA, Sihvo EI. Anatomic thoracoscopic lung resection for non-small cell lung cancer in stage I is associated with less morbidity and shorter hospitalization than thoracotomy. *Acta Oncol*. 2011;50:1126-1132

81. Paul S, Isaacs AJ, Treasure T, Altorki NK, Sedrakyan A. Long term survival with thoracoscopic versus open lobectomy: propensity matched comparative analysis using SEER-Medicare database. *BMJ*. 2014;349:g5575

82. Dziedzic R, Marjanski T, Binczyk F, Polanska J, Sawicka W, Rzyman W. Favourable outcomes in patients with early-stage non-small-cell lung cancer operated on by video-assisted thoracoscopic surgery: a propensity score-matched analysis. *Eur J Cardiothorac Surg*. 2018

83. Lagergren J, Mattsson F, Lagergren P. Weekday of cancer surgery in relation to prognosis. *BJS*. 2017;104:1735-1743

84. Gonfiotti A, Bertani A, Nosotti M, Viggiano D, Bongiolatti S, Bertolaccini L, Droghetti A, Solli P, Crisci R, Voltolini L. Safety of lymphadenectomy during video-assisted thoracic surgery lobectomy: analysis from a national database. *Eur J Cardiothorac Surg*. 2018