University of Alberta

The Relationship between Health Related Quality of Life and Non-Small Cell Lung Cancer Surgery

by

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ABSTRACT

Objectives: To review the studies those have assessed Quality Of Life (QOL) after Video Assisted Thoracoscopic Surgery (VATS) and Thoracotomy for resection of lung cancer, and to determine the impact of post VATS complications on patients' QOL

Methods: For the review, we performed a systematic review, and included studies based on specific inclusion/exclusion criteria according. To determine the impact of surgical complications on patients' QOL, we designed a prospective cohort study.

Results: 5 observational studies were included in this final review; a qualitative as well as a meta-analysis were used to interpret the results. 44 patients were included in the cohort study, there were significant differences based on the complications grade in QOL of patients undergoing VATS lobectomy for lung cancer.

Conclusion: In general patients undergoing VATS resection have a better QOL when compared to thoracotomy up to two years after surgery. Post-operative complications can determine patients' QOL after surgery.

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Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Alberta.

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Chapter One: Introduction

1. LUNG CANCER

1.1 Epidemiology

Lung cancer, both small cell and non-small cell, is the second most common cancer in both men and women, after prostate cancer and breast cancer respectively. It accounts for approximately 15% of all new cancer diagnoses (approximately 222,520 new cases were diagnosed in 2010 in the United States) and 28% of all cancer deaths. [1] Lung cancer primarily occurs in older people, with about two thirds of patients diagnosed with lung cancer being over the age of 65. Fewer than 3% of all cases are found in people younger than the age of 45, and the average age at the time of diagnosis is 71. Overall, the chance that a man will develop lung cancer in his lifetime is 1 in 13, and for a woman, the risk is 1 in 16. These numbers include both smokers and nonsmokers, however the risk is significantly higher in smokers. Despite the poor prognosis of lung cancer, some people can be cured. Lung cancer has been diagnosed in more than 400,000 people currently living in the United States. [1] The 2 main types of lung cancer are small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for approximately 85% of all cases of lung cancer. [2,3]

1.2 Risk Factors

The emergence of the lung cancer epidemic in the 20th century has no doubt been caused by cigarette smoking. The effects of pipe and cigar smoking on the risk of lung cancer are similar to that of light cigarette smoking. [4,5] Because of the slow progress in smoking cessation at present, the decline in lung cancer rates are

forecasted to level off in 20 years. Lung cancer will remain among the top killers for decades unless there are radical reductions in the prevalence of smoking. [6] A causal relationship has been established between passive smoking and lung cancer and is responsible for 1.6% of lung cancer diagnoses. [7] Conversely, the risk of lung cancer declines with smoking cessation. However, even after smoking cessation, the risk never drops to that of never-smokers regardless of their length of abstinence. [8] A meta-analysis and a comprehensive review have shown a relative risk between 1.14 to 5.20 in people who had never smoked but who lived with a smoker. [9,10] Cured meat (sausage, pressed duck, and cured pork), deep-fried cooking, and chili have also been associated with an increased lung cancer risk. [11]

The percentage of lung cancers attributable to urban air pollution in Europe is roughly calculated to be 11%. [7] This effect is likely mediated through oxidative stress, inflammation, and/or induction of a procoagulatory state. [12,13]

1.3 Staging

Staging of cancer is the foundation of the extent of the primary tumor, as well as the extent of spread, if any. Staging guides the treatment of patients, estimates their prognosis, determines the possibility of participation in clinical trials, and also organizes communication between health care providers. The TNM staging is based on the characteristics of the primary tumor, T, the degree of lymph node involvement, N, and the presence or absence of metastases, M. The TNM staging for lung cancer has been recently revised making the 7th edition the most current TNM staging for lung cancer. [14] After determining the T, N, and M stage for the patient, they will be combined to appraise the final stage of the patient with the aim

of grouping people within the same stage with similar prognoses. Finally, TNM staging is divided into clinical and pathological staging, where clinical staging is established by history taking, physical examination and radiologic investigations, while pathological staging is established after tissue assessment of the fully resected tumor.

1.4 Treatment options

Patients with different stages of lung cancer will have different treatment goals and expectations. Patients with early stage lung cancer, defined as stage I and II, (T1 and T2 tumors with or without lymph node involvement and T3 without lymph node involvement) will be considered for curative intent treatment. However, those with more extensive disease will have treatment options that are aimed towards palliation of symptoms and improvement in health related quality of life.

1.4.1 Early Stage Treatment

Surgical resection, in the form of anatomical lung resection, is the cornerstone in the treatment of patients with early stage NSCLC. Over the past decades, surgical resection has evolved with improvements in the surgical techniques, intra- and post-operative patient care, as well as patients' selection for surgery. New approaches, such as Video Assisted Thoracoscopic Surgery (VATS) and robotic surgery are now available and continuously evolving for anatomical lung resections. These procedures offer less invasive alternatives to the traditional thoracotomy approach. If a patient is deemed medically unfit for major pulmonary resection due to insufficient pulmonary reserve or other medical co-morbidities, then options include limited surgical resection and radiotherapy. Limited pulmonary resection, defined as non-

anatomical wedge resection, can be used only for more peripheral T1 or T2 tumors. Randomized trials of lobectomy against limited resection for stage I NSCLC confirmed the increased risk of local recurrence, found a slight trend toward decreased overall survival, and concluded that limited resection, even for small, localized tumors, should not be the only therapy. [15,16] Another option for patients who are deemed to be unfit for surgical resection for their pulmonary tumor, is radiotherapy. With the advancement of current radiotherapy techniques, there is a reduction in local complications, although prognosis is not as good as that seen with surgical resection. Until recently, chemotherapy alone was not found to be of any benefit in the treatment of early stage NSCLC. Although more recent trials using newer chemotherapeutic agents in the form of adjuvant or induction treatment are being conducted, their results are still pending. [17,18]

1.4.2 Advanced local-regional Disease Treatment

Surgery has a restricted role in the treatment of a locally advanced tumor; stage III, except in the form of T4 N0 M0 or T3 N1 M0 where surgical resection can offer a benefit to the prognosis after an induction chemoreadiation therapy. [30] Radiotherapy or combined radiotherapy and chemotherapy are usually the mainstay of treatment for all the other patients with a locally advanced NSCLC.

1.4.3 Distant Metastatic Disease Treatment

Chemotherapy is the mainstay of treatment for patients with stage IV disease. However, at times, patients with single site metastases are encountered, particularly in patients with a solitary brain metastasis. In this highly select group, 5-year survival rates of 10 to 15% can be achieved with surgical excision of the brain metastasis

and the primary tumor, provided it is an early stage primary tumor. [8]

1. Video Assisted Thoracoscopic Surgery (VATS)

2.1 Definition of VATS Lobectomy

Hans Christian Jacobaeus (1879-1937) provided the first description of thoracoscopy in 1910. [19] Trivial progress was then made until the early 1990's when Robert McKenna reported his first series of VATS lobectomy procedures. [20] Since then, the reported rate of VATS anatomical lung resection has been growing. Vaious approaches have been suggested for VATS lobectomy including the use of common open instruments, a posterior approach and a variable camera approach with 2-5 incisions. Currently, the most commonly performed VATS procedure is an anterior approach that involves anatomical hilar dissection with individual ligation of lobar vessels and bronchus as well as hilar lymph node dissection or sampling without rib spreading. [21] Furthermore the procedure is supported by video monitors so the surgeon is not required to look through the 5-cm incision. [21] Using this technique, the surgeon and the assistant are both positioned on the anterior (abdominal) side of the patient, with the surgeon positioned cranially. The scrub nurse is opposite the assistant, following the operation on a separate screen. The patient is placed in the lateral position on the operating table next to the anterior edge leaning slightly posteriorly allowing the lung to retract naturally.. Initially, the chest cavity is accessed via a 2 cm incision that is made in the sixth interspace anteriorly near the costal margin. Following this a 5 mm camera port is positioned in the 8^{th} interspace (in the posterior axillary line) for a 30-degree thoracoscope. The thoracic cavity is evaluated with the camera through this incision in a search for an

unexpected pathology, adhesions, and the level of the diaphragm. Finally, a 4- to 5-cm incision is made in the mid-axillary line (in the auscultatory triangle) without any tissue retractor or rib spreading. During the procedure, this incision (the “utility” incision) is used initially to insert one or several thoracoscopic instruments and then for specimen retraction. On occasion, a final 1.5-cm incision is positioned at the same level but in the paravertebral line which is used for lung retraction and positioning of the stapling devices used during the procedure. This results in a triangle with two nearly 10 cm legs. During the majority of the procedure, the surgeon operates in a bimanual fashion with an instrument in both the utility and anterior incisions. The camera in the inferior aspect of the chest cavity allows a good overview making it unnecessary to change the port during the procedure. [21]

2.2 VATS outcomes

2.2.1 Biological Outcomes

A number of studies have recognized the biological advantage of VATS lobectomy. By examining the acute phase reactants and cellular immune response, these studies have shown that VATS lobectomy leads to a reduced inflammatory response (lower interleukin and C-reactive protein levels), less postoperative decrease in CD4 and natural killer cells, and less impairment of cellular cytotoxicity than open lobectomy. [22]

2.2.2 Oncologic Outcomes

There are few studies that have compared the long-term oncological outcomes of VATS versus traditional thoracotomy lobectomy. A review of the few available studies has recognized that VATS lobectomy results appear to be comparable to the

thoracotomy results. [22]

2.3 VATS Lobectomy Morbidity

Reports from different thoracic surgery centers across North America have shown that the morbidity and mortality rates for VATS lobectomy are comparable to the thoracotomy rates. In fact, the morbidity rates are lower in the VATS group in some reports. [23,24] The largest study to date is from McKenna and colleagues, who followed approximately 1100 patients who underwent VATS lobectomy primarily for lung cancer, presenting a morbidity rate of approximately 15% with an average length of stay about 3 days, blood transfusion rate of 4% and hospital re-admission rate of 1%. No intra-operative deaths were encountered and the post-operative mortality rate was less than 1%. [23] Similar results have been reproduced by other studies from different centers with morbidity rates from 3-15% and mortality rates of 0-2%. [24]

3. Health Related Quality of Life

3.1 What is Health Related Quality of Life?

Health is a term that refers to the general condition of the person. The most widely accepted definition of health is one developed by the World Health Organization (WHO) from 1948 stating that health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity. Different concepts have been used to describe the same domain ranging from health status, physical status, and patient reported outcomes to health related quality of life. There are certain aspects of life that are not classified as part of a person's health although they have a direct or indirect impact on their health status. These aspects include

the individual's environment and financial status. While medical clinicians tend to focus more on the clinical picture of their patients, these aspects of life may mean more to patients, and without improving them one cannot improve their overall perceived level of health.

3.2 Health Related Quality of Life Measures

Policymakers and health care professionals are increasingly recognizing the importance of measuring health related quality of life (HRQOL). Measurement of HRQOL adds a dimension to improving clinical care of patients and to improving health economic and health policy decision-making.

There are different instruments used to determine HRQOL. Some are used to evaluate differences between patients at one point in time within cross sectional studies as a discriminative measure, while other instruments are used to evaluate the difference in HRQOL over a period of time as an evaluative measure. Both self administered or interview based instruments, whether used for discriminative or evaluative purposes need to be 1) valid, measuring what they are intended to measure, 2) reliable, 3) have a high noise to signal ratio, and 4) be responsive or able to detect a fundamental difference, however small.

When the field of HRQOL came into existence, global or generic instruments were used as measurement tools. With its development, more specific measurements have been constructed, evaluated and used. These specific measures could be disease specific, population specific or symptom specific. [28]

3.2.1 Generic Measures

Generic measures for HRQOL assessment are designed for the general population

irrespective of disease status or population age distribution. They are also designed for use in both healthy and diseased patient populations. The benefit of using generic measures are that they enable the comparison of how different disease states impact on quality of life as well as permitting for the comparisons across different diseases or populations. The disadvantage of generic measures is that in certain diseases or conditions, they may not be able to distinguish the differences between different treatments as well as a specific HRQOL measure would. Generic measures can be classified into health profiles and utility measures. Health profiles tend to measure all the essential aspects of HRQOL, including physical, emotional, social and other different daily activities. [28]. On the other hand, utility measures are derived from economic theories and reflect patients' preference for treatment process and outcome. The benefit of utility measures is that health care providers can use them to justify the resources for a treatment.

3.2.2 Specific Measures

The use of specific measures is the other way of assessing HRQOL. As the name implies, these measures focus on certain aspects which could be population specific (children or the elderly), disease specific (asthma or heart failure), or symptom specific (pain or sexual dysfunction). The advantage of this approach is the likelihood of increased responsiveness by including items that are relevant to the disease or the population of interest. It is also more sensitive to small changes resulting from a specific treatment than generic measures. For these reasons clinicians and patients tend to prefer specific measures to generic measures in assessing HRQOL. However, specific measures may be less informative as they

may not detect changes due to co-morbidities and side effects of treatments.

3.3 Interpretation of Health Related Quality of Life Measures

With the increase number of HRQOL instruments, the interpretation of these measures has become a dilemma to both clinicians and psychometricains. Clinicians are used to interpreting the results of physiological tests, as they are familiar with the normal ranges and their units. On the other hand, clinicians may be unable to understand that a change by one point on a quality of life questionnaire makes a statistically significant difference in quality of life.

Interpretation of health related quality of life measures has been an area of intense research over the last decade resulting in two main approaches for interpretation, the first one being distributional based and the second one being anchor based.

3.3.1 Distribution-Based Methods

Also known as norm based methods, these methods compare results of quality of life questionnaires to previously determined population normal distribution in order to detect any difference between the populations undergoing the study to the general population. One of the problems with distribution-based methods is that health status is not always normally distributed.

3.3.2 Anchor-Based Methods

In this method, health status is measured by an instrument and is compared to an external anchor, which should be interpretable and associated with the target instrument. Gold standard test results and global rating by physicians and patients are different approaches of anchor-based methods.

With the intense research in this area, it has become clear that the minimum clinical

important difference (MCID), the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management, is about a half standard deviation of the baseline population distribution or of the normal distribution. [29]

The magnitude of change that is clinically important may depend on different factors like the population's health status at baseline, the size of change, the direction of change, the context as well as the cost and risk of producing the change.

4. Health Related Quality of Life in Lung Cancer

Patients with lung cancer do not experience the same quality of life as their matched peers with other cancers or patients with benign lung diseases. [25] There are few published reports comparing survivors of lung cancer to patients with different cancers (colon, prostate, breast and melanoma) recognizing that patients with lung cancer have the worst acute and long-term quality of life among all the other cancer survivors. [25] Both symptoms and psychological factors have this impact on the poor quality of life affecting lung cancer survivors.

Self reported health related quality of life is a valuable outcome for survivors of lung cancer because clinical and physiological measures, such as pulmonary function tests have failed to capture the overall impact of the disease or the treatment on the patients' overall health, functional and mental status. [26,27]

5.Objectives:

The first objectives of this research is to systematically locate, review, assess and report on the studies that have assessed HRQOL after VATS and Thoracotomy for

resection of non-small cell lung cancer. Secondary objectives include the assessment of HRQOL in the early vs. the late post-operative period between the VATS and the thoracotomy approaches and the assessment of HRQOL based on the post-operative surgical complications. We used three months after surgery as a cutoff for early post-operative period.

The second objective is to assess the effect of post-operative complications on the HRQOL of patient undergoing Video assisted Thoracoscopic (VATS) lobectomy for NSCLC.

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Chapter Two:

A systematic review and meta-analysis to assess Health Related Quality of Life after Video Assisted Thoracoscopic Surgery as compared to Thoracotomy for patients with resectable non-small cell lung cancer.

1. Background:

1.1. Epidemiology:

Lung cancer (both small cell and non-small cell) is the second most common cancer in both men (after prostate cancer) and women (after breast cancer). It accounts for about 15% of all new cancers and for about 28% of all cancer deaths. More than 400,000 people alive today in the United States have been diagnosed with lung cancer at some point. [1] In Canada over 25,000 new patients were diagnosed with lung cancer in 2011. [2] The 2 main types of lung cancer are small cell lung cancer (SCLC) and non-SCLC (NSCLC); NSCLC accounts for approximately 85% of all cases of lung cancer. [3,4]

1.2. Treatment of early stage NSCLC:

According to the National Institute of Health (NIH), surgical removal in the form of anatomical resection depending on the location of the tumor is the mainstay of the treatment for early stage non-small cell lung cancer (defined as stage I and II) based on version 7 of the TNM staging of lung cancer published by the American Joint Committee on Cancer (AJCC). [5,6]

Anatomical resection is defined as segmentectomy, lobectomy, bi-lobectomy and pneumonectomy, while wedge resection is not an anatomical resection.

Over the last decades surgical resection has developed gradually with the improvement in the surgical techniques, intra-operative care of the patients, as well as patients selection for surgery. New approaches, like the Video Assisted Thoracoscopic Surgery “VATS”, are now available and evolving for anatomical lung resections that offer less invasive procedures compared to the classical thoracotomy approach.

1.3. Video Assisted Thoracoscopic Surgery:

The VATS approach involves anatomical hilar dissection with individual ligation of lobar vessels and bronchus as well as hilar lymph node dissection or sampling without ribs spreading and it is monitor based so that the surgeon is not looking through the 5-cm utility incision. [7]

1.4. Health Related Quality Of Life:

Policymakers and health care professionals are increasingly recognizing the importance of measuring health related quality of life “HRQOL” for a variety of reasons, some are clinical and more effective patients care, others are policy decision making and economy related. [8]

Different HRQOL questionnaires are available; some are generic measures, while others are disease or population specific measures.

Over the last few decades, several studies have been conducted to assess the HRQOL of patients with lung cancer after surgery using different measures, comparing different criteria and reaching different conclusions.

No systematic review has been conducted to compare the results of the studies that have assessed HRQOL after lung cancer surgery.

1.5. Reviews comparing VATS to Thoracotomy in Lung Cancer surgery

Whitson et al, conducted a systematic review in 2008 comparing VATS to Thoracotomy for the treatment of early stage lung cancer looking at the following outcomes: chest tube duration, length of hospital stay, 4 years survival and morbidity. The conclusion from this systematic review favored the VATS approach in all the four outcomes. [9]

Rueth et al, conducted another review in 2010 comparing the two approaches for the surgical treatment of lung cancer considering perioperative, biological and oncological outcomes. The results from this review concluded that perioperative morbidity and immunosuppression favor the VATS group and the midterm oncologic outcomes were equivalent. [10]

2. Objectives:

The main objective of this review is to systematically locate, review, assess and report on the studies that have assessed HRQOL after VATS and Thoracotomy for resection of non-small cell lung cancer. Secondary objectives include the assessment of HRQOL in the early vs. the late post-operative period between the VATS and the thoracotomy approaches and the assessment of HRQOL based on the post-operative surgical complications. We used three months after surgery as a cutoff for early post-operative period.

3. Methods:

3.1. Protocol Registration:

A priori protocol developed by the reviewers was registered at PROSPERO database with the following registration number (CRD42012002159).

3.2. Criteria for considering studies:

3.2.1. Inclusion criteria:

- Study designs: Randomized control trials, Quasi experiments, cohort studies, cross sectional studies and prospective case series.
- Participants: Patients with surgical resection for early stage non-small cell lung cancer.
- Intervention: Video Assisted Thoracoscopic Surgery
- Comparison: Thoracotomy anatomical resection
- Outcome: Health Related Quality of Life assessed by valid and reliable HRQOL questionnaires (either generic or specific tools).

3.2.2. Exclusion criteria:

- Study design: Case Control studies, retrospective case series and case reports
- Population: Studies that have included patients with benign diseases, patients with other types of cancers (metastatic disease to the lung or small cell lung cancer
- Intervention/Comparison: Studies that have pooled data for the VATS and thoracotomy together and studies that have compared surgical resection to other modalities of treatment (chemotherapy and radiotherapy)
- Outcome: Studies that have not included HRQOL as an outcome after lung cancer surgery or that have used a custom questionnaire that is not validated.
- Language: Non-English reports are excluded.

3.3. **Search Strategy for identification of studies:**

A research librarian (DS), in collaboration with (SG), developed and implemented a search strategy designed to identify evidence relevant to the question of this review. (SG) worked with the research librarian to improve and test the search strategy parameters, involving a comprehensive set of subject headings and keywords that used in a variety of databases (Appendix A). Using English language and date from inception to 2012 restrictions, we systematically searched the following electronic databases that store resources with this focus: Medline, EMBASE, Scopus, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Google Scholar, Health Technology Assessment Database. Conference proceedings for the last five years for the Society of Thoracic Surgery, the Western Society of Thoracic Surgery and the European Society of Thoracic and cardiovascular surgery were also searched for identification of further abstracts and studies. We also searched the relevant reference lists of included studies and previous reviews in this field. Gray literature search was carried out to identify further studies.

Only full manuscripts were included; abstracts were searched to identify other studies.

3.4. **Screening process:**

Two reviewers (SG and JSP) carried out the first step of the screening process independently which involved reading the titles and the abstracts using broad criteria. Each study was classified as include, exclude or unclear. Articles that

were classified as “include” or “unclear” by either reviewer were included for full text reviewed.

In the second step of the screening process, the same two authors (SG and JSP) again independently assessed each study using a standard form that outlined the predetermined inclusion criteria. A third reviewer (EB) resolved all disagreements.

3.5. Quality assessment:

Assessment of the methodological quality of the included studies was conducted independently by two of the reviewers (SG and JSP) at the study level. A third reviewer (EB) resolved any disagreements.

The Downs and Black assessment tool was used to assess the risk of bias in the included studies. [11]

3.6. Data extraction:

Data extraction was carried out by two reviewers (SG and JSP) and checked by two other reviewers (EB and JK). Disagreements were resolved by discussion among the four reviewers.

All the reviewers used a pilot data extraction form developed specifically to address the research question and collected data were entered into a spreadsheet.

Data that were extracted included: study design, year and country, number of participants, intervention used, surgical procedure performed, outcome(s) and study funding.

3.7. Data analysis and synthesis:

Results of the included studies were grouped based on the different study designs. Then, based on the surgical approach (VATS vs. Thoracotomy) the data were aggregated and analyzed in the different study designs.

The mean difference (MD) was used for continuous data with 95%CI.

Qualitative analysis was carried out to present what have been done in the field and identify the gaps for future research plans.

A Meta-Analysis was conducted for two cross sectional study designs that used the same HRQOL questionnaire with sufficient clinical and statistical heterogeneity assessed by I^2 (for statistical heterogeneity), which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. [12]

In our protocol we planned to conduct two subgroup analyses; the first between early vs. late assessment of HRQOL between the VATS and the Thoracotomy approaches using three months as a cutoff; the second subgroup analysis based on post-operative complications and HRQOL. Since no study had addressed HRQOL based on complications and no data were available to assess early vs. late HRQOL, the subgroup analyses were not performed.

A sensitivity analysis for using six months as a cutoff for early vs. late HRQOL was planned in our protocol but not performed due to the lack of data.

4. Results:

4.1. Study Selection and Flow Diagram:

Our database search yielded 1,336 records; hand search of relevant included

articles and previous systematic reviews added 9 more records.

After removal of duplicates, 619 records were identified for the first step of the screening process.

From reading titles and abstracts by two of the reviewers (SG and JSP), 381 records were excluded. Exclusion criteria at this level were broad and included: study design as being a review or a case report, comments and letters to the editor, Language of abstract is not in English and population did not include patients with lung cancer. We included records that were eligible by either reviewer in the full-text review.

238 articles were included in the full-text review, which was conducted by (SG and JSP). We used our inclusion/exclusion criteria for this review process.

233 articles were excluded at this level for the following reasons:

Language, study design (review articles and editorials), surgical approach and extent of resection, outcome not addressed and population included (Figure 1).

Of the Five articles that met the inclusion criteria, no randomized control trials were identified. One study is a prospective cohort design, two are case series and two are cross sectional. [13-17]

Because we could not extract data from the cohort study (as the groups were divided based on extent of resection, rather than surgical approach) and the two case series included patients with thoracotomy only, the meta-analysis only included the two cross sectional study designs.

The reviewers tried to contact the corresponding author of the cohort study, to get the data required but received no response.

4.2. Risk of Bias Assessment:

The Downs and Black risk of bias assessment tool is a 27 item tool, each question has a score of 1 or 0, except the 5th question which can be scored as 0, 1 or 2 and the last question that have a score of up to 5. The maximum total score of the tool is 31.

The 27 items are summarized into 5 criteria (Reporting, External validity, Bias, Confounding and Power).

Maximum score for each of the criteria is: reporting 10, external validity 3, bias 7, confounding 6 and power 5.

The five included studies in this review scored in total between 15 and 20 (out of 31) on the assessment tool, most of the studies scored high on the power criterion based on the high number of subjects included in these studies which is one of the advantages of conducting an observational study, although large sample size does not decrease the risk of bias by itself.

On reporting and selection bias all the studies scored an average or above average. Most of the studies failed to reach an average score on confounding (except Li et al, which scored 3 out of 6). It was difficult to assess the external validity of the included studies, as most of the studies did not describe well their source population and the centers included in the treatment.

In summary, all the studies are of high risk of bias and results should be interpreted with caution.

(Table 2-1) summarize the results of the risk of bias in the five studies included in this review.

4.3. Summary of the included studies

Balduyck et al, conducted a cohort study in Belgium between 2002 and 2004, included 100 patients in total. This study divided the patients into three groups based on the extent of resection, rather than the approach of surgery (group 1: lobectomy, group 2: pneumonectomy and group 3: wedge resection). The study included patients with VATS and thoracotomy, although one patient only in the lobectomy group had a VATS resection and no patients from the pneumonectomy group had a VATS resection. The study used the European Organization for Research and Treatment of Cancer (EORTC) HROQL questionnaire QLQ30 and QLQ13. The researchers declared no conflict of interest. [13]

One of the reviewers (SG) attempted to contact the authors of this study to get the required data and received no reply.

Baysungur et al, conducted a cross sectional study in Turkey for patients who had surgery between 2007 and 2009. The study assessed HRQOL at 6 months after surgery and had 18 patients in the VATS group and 20 patients in the thoracotomy group. HRQOL was assessed using the EORTC QLQ 30 and QLQ 13 as well as the Health Survey SF-36. The mean age was 63 and 65 years in each group respectively. The researches declared no conflict of interest. [14]

Li et al, conducted a cross sectional study in Hong Kong, China for patients who had surgery between 1994 and 2000. This study looked at HRQOL using the Chinese version of the EORTC QLQ30 and QLQ 13. The median time after surgery when the questionnaire was administrated was 20.8 months for the

VATS group and 37.7 months for the thoracotomy group. This study included 27 patients in the VATS group and 24 patients in the thoracotomy group. The researchers in this study did not report conflict of interest. [17]

Brunelli et al and Ilonen et al, reported on two case series that included only patients with thoracotomy. One hundred and fifty-six and 48 patients were included in each series respectively. We decided to include these two studies in our qualitative analysis to describe the post-operative changes in HRQOL of patients who had thoracotomy for lung resection for NSCLC. Ilonen et al declared no conflict of interest, while Brnuelli et al did not report on conflict of interest. [15,16]

Tables (2-2 and 2-3) summarize the characteristics of the included studies.

4.4. Qualitative results for HRQOL after NSCLC surgery

In the Brunelli et al case series, a comparison of baseline HRQOL to post-operative HRQOL was conducted 1 and 3 months after thoracotomy. The results of this study showed that the Physical Composite Score (PCS) of the SF-36 was lower than baseline at one month after surgery but returned to baseline score at three months after surgery. The PCS is a summary of four domains that include physical functioning, role limitation- physical, bodily pain and general health. The other component of the SF-36 is the Mental Composite Score (MCS) and this did not show any difference at one and three months after surgery when compared to baseline. This study also showed that patients with lung cancer have lower HRQOL measured by the SF-36 at baseline (before surgery) when compared to the general population norms.

In the case series of Ilonen et al, assessment of HRQOL at 3, 12 and 24 months after thoracotomy was compared to baseline HRQOL using the 15D questionnaire. The 15D questionnaire is a generic measure that contains 15 questions regarding different symptoms. The results of this study showed that patients with lung cancer have lower HRQOL scores when compared to the general population at baseline, specifically in the breathing, mental health, discomfort and distress domains. This study also concluded that women report more depression symptoms at three months after surgery than men and that men have lowered sexual function up to 12 months after surgery.

Balduyck et al, concluded that the VATS group have a better HRQOL measured by the EORTC QLQ30 and QLQ13 at three months after surgery mainly in physical functioning and thoracic pain as compared to thoracotomy. Also, the study demonstrated a better HRQOL in terms of bodily pain, global health and physical functioning up to 12 months after surgery.

Baysungur et al used the SF-36 and the EORTC QLQ30 and QLQ13 at six months after surgery. The results showed that the VATS group when compared to the thoracotomy group has better HRQOL mainly in physical functioning and role limitation-emotional measured by the SF-36. The VATS group also did better in the following symptoms: cough, neuropathy, chest pain and shoulder pain, as well as cognitive function measured by the EORTC QLQ 30 and QLQ13.

Li et al, reported on long-term HRQOL after surgery for lung cancer. The median time when the questionnaire was administrated for the VATS group was 20.8 months as compared to 37.7 months for the thoracotomy group. In this study,

patients who had VATS resection tended to have better HRQOL as compared to patients who had undergone thoracotomy, and the most commonly reported symptoms were cough, fatigue, thoracotomy pain and dyspnea.

4.5. Heterogeneity

4.5.1 Methodological:

Although all the included studies in this review were observational, there are some methodological differences between them. Only one study was a cohort study, and the groups in this cohort study were divided based on the surgical resection rather than the surgical approach, as a consequence, we did not include this study in our meta-analysis.

The two case series compared HRQOL before and after surgery for thoracotomy only, so we were unable to include their results in our meta-analysis.

Although the time of assessment of HRQOL after surgery between the two cross sectional studies was different, 6 months for Baysungur et al and 20.8 months for VATS and 37.7 months for thoracotomy in Li et al, we decided to conduct a meta-analysis including both studies.

4.5.2 Clinical:

The patient populations included in all the studies have similar baseline characteristics. It was difficult to assess whether there is any differences between the treating centers or hospitals due to missing information in the reports.

The interventions used in the five studies are similar (including both VATS and thoracotomy).

HRQOL was assessed using different questionnaires; the EORTC QLQ30 and QLQ13 are cancer specific and lung cancer specific questionnaires, respectively. The SF-36 and the 15D are generic health surveys. The cross sectional studies included in our meta-analysis both used the EORTC QLQ30 and QLQ13.

4.5.3 Statistical:

The Cross Sectional studies included in the meta-analysis have an I^2 ranging between 0 and 95% depending on the scale or symptom of HRQOL being assessed.

When assessing scales of global health, role limitation, cognitive scale, physical scale, emotional scale, the I^2 vale was 0% to 40% indicating no to minimal heterogeneity between the studies. On the other hand, symptoms like chest pain, shoulder pain and coughing have an I^2 value of more 90% indicating high heterogeneity between the two studies.

4.6. Meta-Analysis

A meta-analysis was conducted including the two cross sectional studies (Baysungur et al and Li at al). In this meta-analysis we included all the scales of the EORTC and the symptoms that are more relevant to patients with lung cancer after surgical resection in the long term (since the HRQOL in both studies was assessed between 6 months and 37 months after surgery).

Assessing global health, patients undergoing VATS resection had a mean improvement of 8.46 (95%CI, -0.36,17.27) compared to patients who had undergone a thoracotomy resection (Figure 2-2).

In regard to physical scale, patients with VATS resection had a mean difference of 4.45 (95%CI, -3.83,12.73) compared to patients who had undergone thoracotomy (Figure 2-3).

For role limitation scale, patients with VATS resection had a mean improvement of 6.7 (95%CI, -0.88,14.28) as compared to patients who had undergone thoracotomy (Figure 2-4).

Assessing cognitive scale, patients with VATS resection had a mean improvement of 11.47 (95 %CI, 2.62,18.07) as compared to patients undergoing thoracotomy (Figure 2-5).

Comparing the symptoms that are more relevant to patients with pulmonary resections, we included chest pain, shoulder pain and coughing in this meta-analysis. The results of these three analyses showed a high heterogeneity between the two studies but in general favored the VATS group over the thoracotomy group (Figures 2-6,2-7 and 2-8). The high heterogeneity between the two studies was most likely explained by the difference in the time period for which the cross-sectional study was conducted.

4.7. Subgroup analysis and Sensitivity analysis:

As we mentioned in the methods section, the subgroup analysis and sensitivity analysis that we planned to conduct in our protocol were not performed due to the small number of studies available and the lack of data required to perform these analyses.

5. Conclusion and Discussion:

In general patients with NSCLC when compared to the general population have lower HRQOL indices. [15,16] Post-operatively, in patients undergoing thoracotomy there is an initial decline their HRQOL (mainly in the physical component) that returns to baseline around three months after surgery. [15] Women undergoing thoracotomy resection tend to describe more depressive symptoms than male but have better preserved sexual function. [16]

Comparing VATS resection to thoracotomy; the VATS group have a better HRQOL scores that are seen up to 2 years after surgery (mostly related to physical health, rather than mental health). [13,14,17]

Although the meta-analysis supported the qualitative analysis in favoring the VATS group in all the scales and symptoms, it also showed that most of these differences were not statistically significant. This is most likely due to the fact the one of the two studies included examined HRQOL over 2 years post-operatively, where the differences in HRQOL tend to be smaller.

For the same reason, we think that there is a high heterogeneity between the two studies when looking at the forest plots for the symptoms, as symptoms tend to resolve two to three years after surgery.

We encourage the consistent use of a disease specific HRQOL like EORTC QLQ30 and QLQ13 in patients undergoing surgical resection for NSCLC, as this will simplify explaining the results to the patients and help future research.

Future research is required in this area to assess HRQOL between the VATS and thoracotomy approaches mainly in the early post-operative period. A high

quality randomized control trial (RCT) or well-conducted observational studies (if RCTs are not feasible) are encouraged specially in North America, as all of the studies included in this review were from Europe and Asia.

6. Review Limitations:

One of the main limitations of this systematic review is the high risk of bias in the included studies, because there were no RCTs in this area of research. The best evidence that was collected was from observational studies with high risk of bias, so the interpretation of the results should be implemented with caution.

Another limitation is the use of different HRQOL assessment tools, which made the data of each study more difficult and challenging to pool and come up with a strong conclusion.

Publication bias is also a limitation in this review, we did not assess for publication bias in this review due to the small number of studies included, but we suspect that there are studies that have assessed HRQOL and came up with results that did not favor the researches or journals views and were not published. We only included reports in English, which represent another limitation in our review.

There were two studies that have missing data and we attempted to contact the authors to include their results in our review and meta-analysis, but we did not receive a reply from the authors of these studies.

7. Conflict of interest:

Reviewers declare no conflict of interest for this review.

Table 2-1: Results of the risk of bias assessment using the Downs and Black assessment tool

Study ID	Reporting (10)*	External Validity (3)*	Bias (7)*	Confounding (6)*	Power (5)*	Total (31)*
Balduyck et al [13]	5	1	5	2	5	18
Baysungur et al [14]	6	0	5	2	4	17
Brnuelli et al [15]	5	1	5	0	4	15
Ilonen et al [16]	5	1	4	2	4	16
Li et al [17]	8	1	4	3	4	20

* Maximum number can be scored in that criterion.

Table 2-2: Summary of study characteristics

Study ID/ Country	Time	Design	Intervention/ Comparison	HRQOL assessment (Time of assessment in months)
Balduyck et al Belgium [13]	2002-2004	Cohort	VATS/Thoracotomy	QLQ30/13 (1, 3,6,12)
Baysungur et al Turkey [14]	2007-2009	Cross sectional	VATS/Thoracotomy	SF 36 QLQ30/13 (6)
Brnuelli et al Italy [15]	2004-2006	Case Series	Thoracotomy only	SF 36 (1,3)
Ilonen et al Finland [16]	2002-2005	Case Series	Thoracotomy only	15D (3,12,24)
Li et al China [17]	1994-2000	Cross Sectional	VATS/Thoracotomy	QLQ30/13 (20.8:37.7)

Table 2-3: Summary of study characteristics (cont.)

Study ID	Population number (V: T)*	Mean Age (V: T)* in years	Male Sex % (V:T)*	Complications (V: T)*	COI$
Balduyck et al Belgium [13]	100	CED$$	CED$$	NR**	No
Baysungur et al Turkey [14]	(18:20)	(63:58)	(70%: 80%)	(1:1)	No
Brnuelli et al Italy [15]	156	65	79%	NR**	NR**
Ilonen et al Finland [16]	48	63	62%	13	No
Li et al China [17]	(27:24)	(63:66)	(74%: 75%)	NR**	NR**

* V: VATS, T: Thoracotomy, $ COI: Conflict of interest, $$ CED: Could not extract data, ** NR: Not reported

Figure 2-1: Flow chart summarizing the results of the screening process and study selection as per the PRISMA guideline

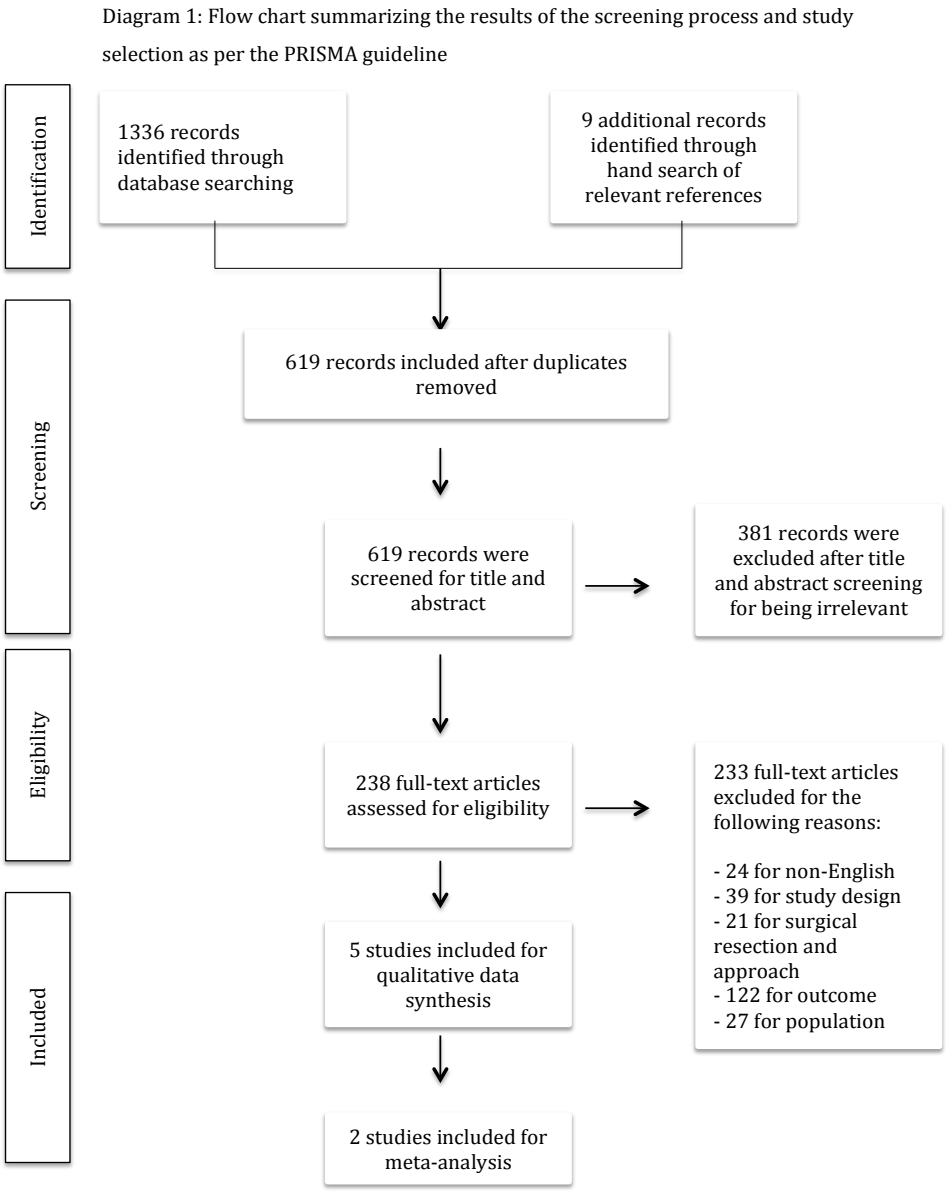


Figure 2-2: Forest plot for Global Health comparing VATS to Thoracotomy

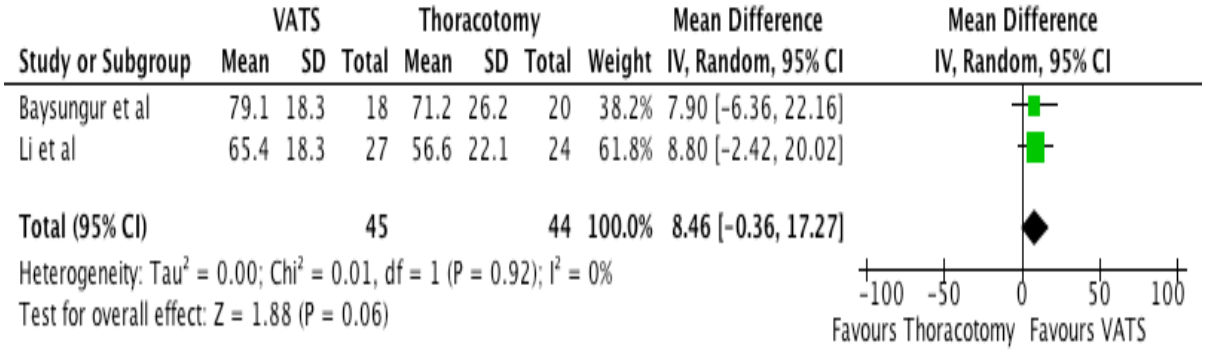


Figure 2-3: Forest plot for Physical scale comparing VATS to Thoracotomy

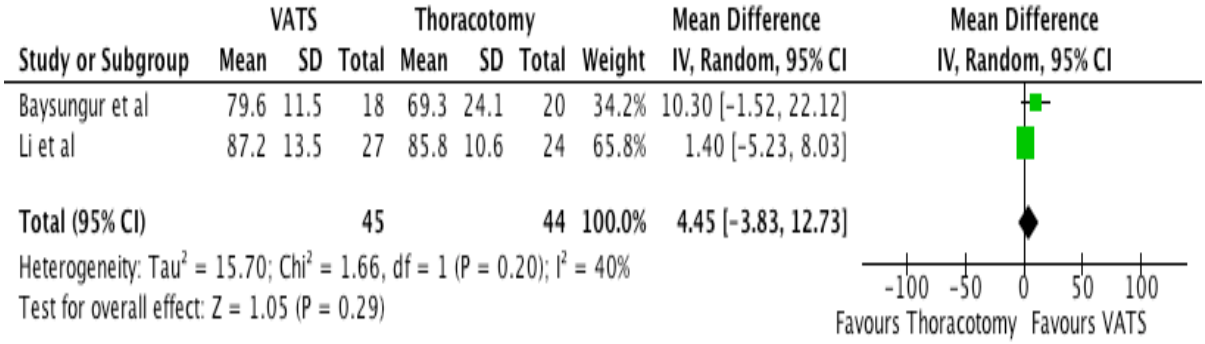


Figure 2-4: Forest plot for role limitation comparing VATS to thoracotomy

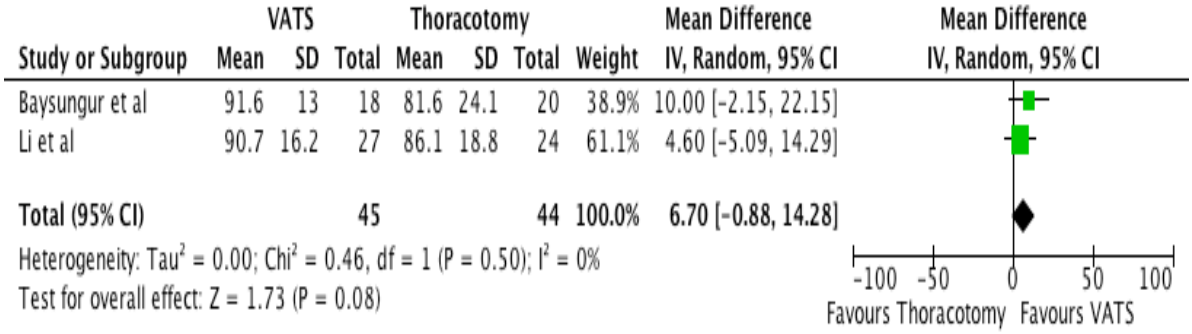


Figure 2-5: Forest plot for cognitive function scale comparing VATS to thoracotomy

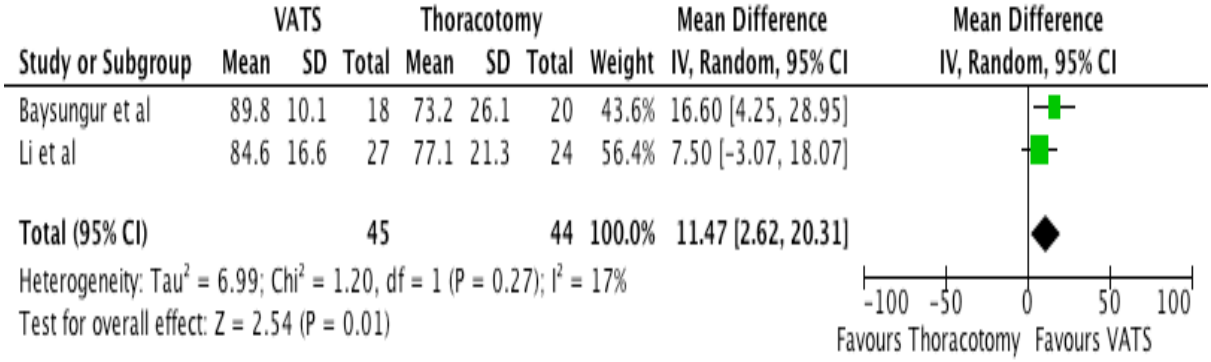


Figure 2-6: Forest plot for coughing comparing VATS to Thoracotomy

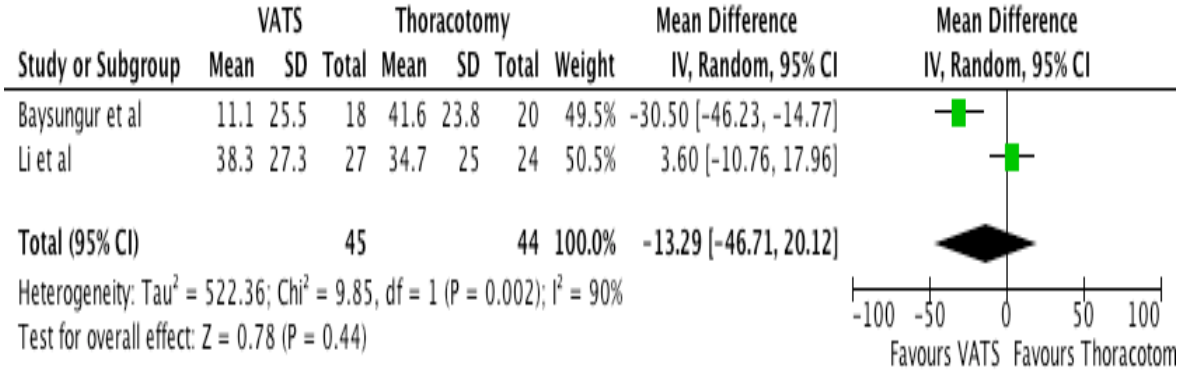


Figure 2-7: Forest plot for chest pain comparing VATS to thoracotomy

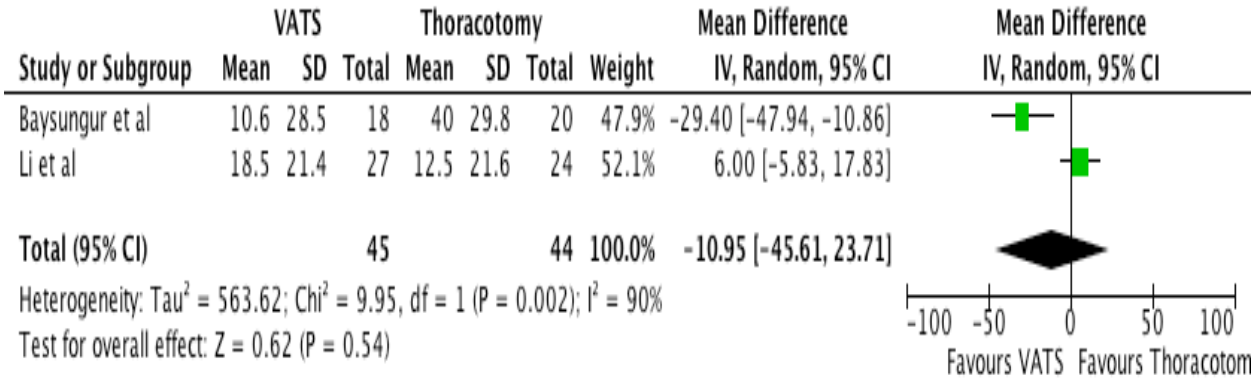
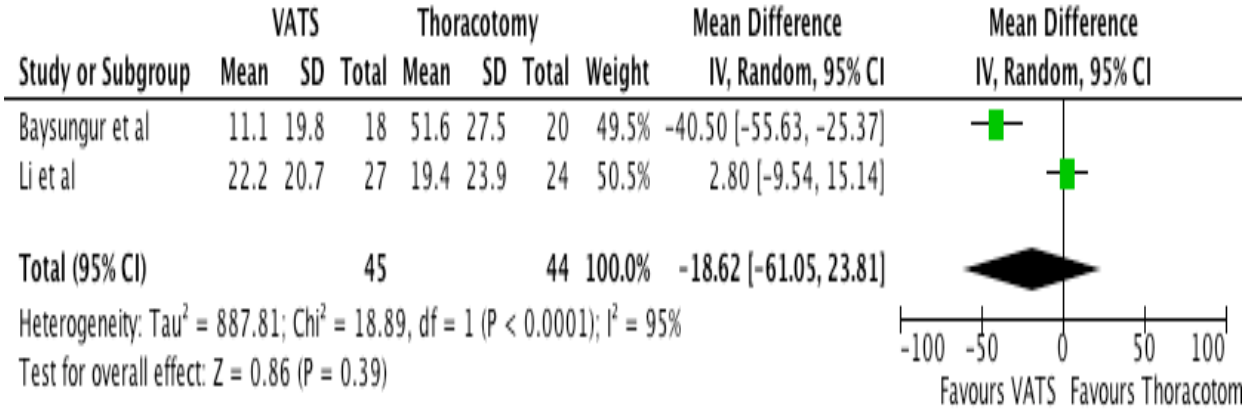


Figure 2-8: Forest plot for shoulder pain comparing VATS to thoracotomy



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9. Appendix:

Appendix A:

Medline search strategy:

1. lung neoplasms/ or bronchial neoplasms/ or carcinoma, bronchogenic/ or carcinoma, non-small-cell lung/
2. (lung adj2 (cancer* or carcinoma* or tumo?r* or malignan*)).mp.
3. 1 or 2
4. thoracoscopy/ or thoracic surgery, video-assisted/
5. (thora* or chest).mp. and (surg*.mp. or su.fs.) and video*.mp.
6. thoracosco*.ti.
7. 4 or 5 or 6
8. 3 and 7
9. exp Questionnaires/ or exp "Quality of Life"/
10. exp Health Status/
11. "Activities of Daily Living"/
12. health surveys/ or exp population surveillance/
13. quality-adjusted life years/
14. treatment outcome/
15. Psychometrics/
16. px.fs.
17. "Outcome Assessment (Health Care)"/
18. (patient reported outcome* or quality of life or quality adjusted life year* or health state or health status or life quality or self report*).ti,ab.
19. (qol or hqol or hrqol or qaly).ti,ab.
20. (short form 12 or short form 36 or euroqol or quality of life questionnaire* or Quality of Wellbeing Index or Medical Outcomes Survey).ti,ab.
21. health utilit* index.ti,ab.
22. Health* year* equivalen*.ti,ab.
23. (endpoint* or end point*).ti,ab.
24. functional outcome*.ti,ab.
25. (health outcome* or outcome measure*).ti,ab.
26. (wellbeing or well being).ti,ab.
27. utilit*.ti.
28. or/9-27
29. 8 and 28

Chapter Three:

The effect of post-operative complications on Health Related Quality of life of patients with Non Small Cell Lung Cancer undergoing VATS lobectomy

1. **Background:**

Patients with lung cancer have lower health-related quality of life (HRQOL) when compared to the general population and to patients with other malignancies (e.g., breast, prostate and colon). [1] Anatomical surgical resection in the form of segmentectomy, lobectomy or pneumonectomy represents the mainstay of treatment for early stage non-small cell lung cancer (NSCLC). [2]. While HRQOL declines following surgical resection of NSCLC, it has been shown to return to baseline function in a period of six to twelve months after surgery, depending on the patient condition at baseline, extent of surgical resection, the presence of severe dyspnea and the need for adjuvant therapy post-operatively. [3,4,5]

Post-operative complications are commonly used for the assessment of quality of care in surgical practice, and may also have an important role in functional recovery and HRQOL for patients undergoing surgical resection for lung cancer. However, to our knowledge, no study has addressed the impact of post-operative complications on patients, in terms of patient reported outcomes. Surgical complication classification system, such as the Clavien system, has been validated in patients undergoing different thoracic surgery procedures. [6]

The objective of this study is to assess the effect of post-operative complications on the HRQOL of patient undergoing Video assisted Thoracoscopic (VATS) lobectomy for NSCLC.

2. Methods:

Approval for this study was obtained from the University of Alberta Human Ethics Board.

The Royal Alexandra Hospital is a tertiary care center for thoracic surgery in Edmonton, Canada. The area served includes Northern Alberta, Eastern British Colombia, Western Saskatchewan, North West Territories and Yukon, for a population of over 2 million. All adult oncologic thoracic procedures are done at this site. The four thoracic surgeons performing Video Assisted Thoracoscopic Surgery for lung cancer participated in the study.

All patients who were referred to the thoracic oncology clinic and assessed by one of the four surgeons were reviewed by one of the study investigators (S.G). Those who were found to have a potentially resectable non-small cell lung carcinoma via the VATS lobectomy approach were considered eligible for the study. Exclusion criteria were: age less than 18 years, inability to speak English, hearing problems, speaking problem, inability to walk, inability to undergo the VATS approach, unresectable tumors, metastatic cancer to the lung and patients who could not tolerate anatomical resection.

Anatomical lung resection is defined as anatomical lobectomy or pneumonectomy depending on the location of the tumor, as it is the mainstay in the treatment of early stage non-small cell lung cancer and locally advanced disease (stage I, II, and IIIa) based on the American Joint Committee on Cancer (AJCC) 7th edition released in 2009.

All eligible subjects were provided with the study information sheet at the time of their final visit to the thoracic surgery clinic before surgery. A research nurse recruited the potential patients during their Pre-Admission Clinic (PAC) visit. Patients who agreed to participate in the study had the baseline HRQOL questionnaires completed at the same day in a face-to-face interview.

The baseline HRQOL questionnaires included are the Medical Outcomes Study Short Form-36 (SF-36) version 2, the EORTC Quality of Life Questionnaire (QLQ) 30, The EORTC QLQ 13 and the utility index EQ-5D.

The post-operative period was categorized as 'early' focusing on the first three months after the anatomical pulmonary resection. We scheduled patient interviews at regular intervals after surgery to capture the changes as well as the time of their occurrence in this time period (Table 3-1). The regular intervals were decided as a priori as the following; the first follow up was at two weeks (+/- 2 days), as a phone interview. The second follow up was at four weeks (+/- 3 days), as a face-to-face interview. The third follow up was at eight weeks (+/- 3 days), as a phone interview. The fourth and final follow up was at three months (+/- 7 days), as a face-to-face interview. The day of surgical resection was considered as time point zero time. To prevent patient fatigue and maximize the retention of patients in the study during the post-operative period, not all the questionnaires were to be completed at each follow up interview (Table 3-1).

Following surgery, all patients were assessed on a daily basis during their hospital stay, by one of the researchers (independent from the clinical treatment team) to identify all the post-operative complications and the treatments implemented for

them. The Clavien classification system, which has been previously validated in patients undergoing thoracic surgery procedures [6], was used to track and classify the post-operative complications. [7] In the Clavien classification post-operative complications are divided into 5 grades based on the treatment needed for any different complication (Table 3-2). Each complication has to meet a priori definition before it become included, the a-priori definition for different complications as applied by Dindo et al. [7].

2.1. Patient population

Fifty consecutive eligible patients consented to participate in the study. Six patients were withdrawn from the study; one patient decided to not have a surgical resection and go for adjuvant therapy only, one patient was excluded at the baseline as he questioned the validity of the HRQOL questionnaires, one patient underwent open thoracotomy, decided on the day of the surgery, instead of the original plan for a VATS approach. Two patients were withdrawn because their final pathology was found to be a metastatic malignancy to the lung rather than a primary NSCLC, and one patient was lost to follow up at 2 weeks. That left us with 44 patients who had completed the follow up.

2.2. Instruments used to measure HRQOL outcomes:

The SF-36 health survey is a generic measure that commonly used in HRQOL assessment both in the general population and the thoracic surgical population, as a valid and reliable measure. [8,9,10] The SF-36 is a brief and simple questionnaire that contains 36 items covering 8 health domains. [Appendix A]

The eight domains assessed by the SF-36 are the following; Physical Functioning, Role Limitation – Physical, Role Limitation – Emotional, Bodily Pain, Vitality, Social Functioning, Mental Health and General Health. Each domain will have a score between 0 and 100, with higher scores indicates better HRQOL. Two norm-based summary scores are also available, the Physical Component Score (PCS) and the Mental Component Score (MCS). [11,12] The RAND scoring system was used to score the SF-36 health survey. The RAND scoring system uses the oblique factor correlation method to construct the physical and mental component scores. This method is based on the assumption that the PCS and MCS are correlated. [13]

The European Organization for Research and Treatment of Cancer (EORTC) has developed and validated the cancer specific questionnaire QLQ 30. The QLQ 30 has thirty questions covering five functional scales and six single items symptoms scales. The five functional scales are; Physical functioning, Emotional Functioning, Role Functioning, Social Functioning and Cognitive Functioning. [13] [Appendix B]

The QLQ 13 is a lung cancer specific module that the EORTC has added to the QLQ 30. It contains 13 questions related to patients undergoing treatment for lung cancer. The thirteen questions of the QLQ 13 will yield one symptom scale (dyspnea scale) and ten single item symptom scales. [14] [Appendix C]

The QLQ 30 and QLQ 13 are both scored the same way, with a final score of 0 to 100, where 100 indicate the best possible health status in the functional scales and 0 represent the best possible health status in the symptom scales. [14]

The QLQ 30 and QLQ 13 scoring was calculated based on the EORTC recommendation. [14]

The EQ-5D is a widely used utility index that measures 5 health dimensions (Mobility, Self Care, Usual Activities, Pain and Anxiety/Depression) and a health state using a visual analogue scale (VAS). Each of the five dimensions has three levels of functioning (no problem, moderate problem and extreme problem) and can therefore yield 243 health states. The EQ-5D uses the time-tradeoff method to calculate the health index. A health utility index score can be produced, based on time-trade off valuations, anchored at 0 and 1, where zero indicates death and one indicate the best health status and individual would have. [15] Based on the scoring system used a score of less than zero can be achieved which indicates a health states of worse than death. [Appendix D] The US (D1) scoring function was used for calculating the index score for the EQ-5D. The D1 scoring function consist of 10 dummies (2 for each dimension), 3 ordinal variables representing the squared numbers of dimensions that are in level 2 or 3, and an ordinal variable called the D1. The D1 term represents the number of dimensions beyond the first that are not in level 1. [16,17]

2.3. Surgical procedure:

All the patients included were candidates for VATS lobectomy. VATS lobectomy was performed using three incisions; one 2 cm incision in the anterior 6th interspace at the level of the costal margin, one 5 mm incision in posterior axillary line of the 8th interspace for a 30-degree 5mm thoracoscope and one 5 cm utility incision located in the fourth intercostal space between the angle of the scapula and the breast anterior to the latissimus dosri muscle. A fourth incision in the paravertebral line of the 8th interspace is used for lung retraction during upper

lobectomies. The procedure is performed without rib spreading and involves individual hilar dissection and ligation of the lobar blood vessels and the bronchus with lymph nodes sampling or dissection at the discretion of the surgeon.

2.4 Statistical analysis:

The sample size estimate was based on the SF-36 domains using a clinically minimal importance difference of 0.5 SD measured from the Canadian norm values. [18] We determined that 38 patients undergoing VATS lobectomy would provide 80% power (2-talied α error probability 5%) to detect the above-mentioned difference.

STATA data analysis and statistical software, version 12, was used for the data analysis. A multiple linear regression with Generalized Estimating Equations (GEE) method (exchangeable correlation) was used to assess the difference over the follow up time in HRQOL measured by each questionnaire compared to HRQOL at baseline between the high complication group and no/low complication group. All regression models were adjusted for age and sex.

3. Results

Forty-four patients were included in the study and completed the follow up. Complications were assessed by the research team independent from the clinical team taking care of the patients during the patients' hospital stay. Thirty-one of the patients had no complications or low-grade complications (grade one and two as defined by the Clavien classification system) and thirteen patients had high-grade complications (grade three, four or discharged home with disability). No deaths

were encountered during the study period. The characteristics of patients involved in the study are shown in Table 3-3.

In the No/Low complication group, twenty patients had no complications and eleven patients had grade I or II complications. The low-grade complications included: atrial fibrillation, pneumonia, electrolyte disturbances, Syndrome of inappropriate ADH secretion, blood transfusion and atelectasis.

Thirteen patients had grade III or IV complications or were discharged home with disabilities and those were the patients in the high-grade complication group.

Figure 1 represents the complications encountered during the hospital stay.

3.1. HRQOL measured by the SF-36

Table 4 lists the mean (SE) of the eight domains of the SF-36 at baseline, 4 weeks and three months, comparing the change over time between the two groups. We found that at the end of three months after VATS lobectomy patients with high-grade complications had lower HRQL measured in all the eight domains of the SF-36, except social functioning which was similar to the low complication group, after adjusting for age and sex. The differences were statistically significant in three domains namely: General Health, Vitality and Mental Health (p value <0.05) (Figures 3-2, 3-3, and 3-4). Although the physical and mental components scores favored the low complications group, the difference was not statistically significant between the two groups.

On the General Health scale, patients in the low complications group scored an average of 6.2 points higher over time than patients in the high complication group after adjusting for age and sex (95% CI 3.2,9.3 and p value <0.001).

Patients in the low complication group had an average 3.5 points higher over time on Vitality when compared to patients in the high complication group, after adjusting for age and sex (95% CI 0.35,5.8 and p value = 0.03).

In mental health, patients in the low compilations group scored an average of 6.1 points higher over time than patients in the high complication group after adjusting for age and sex (95% CI 2.8, 9.5 and P value <0.001).

3.2. HRQOL measured by the EORTC QLQ 30 and QLQ 13

Using the EORTC QLQ 30 and QLQ 13, differences in HRQOL post-operatively were noted until eight weeks after surgery in the high complication group compared to the no and low complications group (Figures 3-5,3-6,3-7,3-8). The differences were statistically significant in the following scales and symptoms; shoulder and chest pain, dyspnea scale, cognitive and emotional functioning, Insomnia and fatigue as well as financial difficulties. (Table 3-5) lists the mean (SE) measured by the QLQ 30 and QLQ 13 questionnaires comparing between the two complications group at baseline, two weeks and eight weeks from surgery.

3.3. HRQOL measured by the EQ-5D

The EQ-5D is a health utility measure that can yield a health index as well as a state of health. Compared to the no/low complications grade, patients with high-grade complications have statistically significant lower HRQOL measured by the EQ-5D VAS but this difference was not consistent over time (Figure 3-9). The health index did not determine any statistically significant difference between the no/low and high complications group at 2, 4 and 8 weeks after surgery (Figure 3-10). (Table 3-6) summarizes the differences between the two groups at baseline

and the different time periods post-operatively. On average, patients in the low complication group had 0.014 points higher over time in the EQ-5d health index when compared to patients in the high complication group, after adjusting for age and sex (p value 0.75); this difference is statistically not significant.

4. Discussion:

Lobectomy is most commonly performed procedure for the treatment of early stage and locally advanced lung cancer. [19,20] The VATS approach for anatomical resection was introduced in the early 1990s and started to gain more popularity over the last few years. [19,21] The early motivation for using the VATS procedure is the widespread assumption by thoracic surgeons that a more minimally invasive approach to lung cancer resection would reduce post-operative complications, hospital length of stay, shorten the recovery time to the preoperative heat state and have equivalent oncologic outcomes (recurrence and mortality) as compared to the traditional thoracotomy.

Few observational studies have reported on the superiority of VATS lobectomy when compared to the thoracotomy approach in terms of post-operative complications, length of stay, blood loss, post-operative pain and inflammatory response. [21,22,23,24]

To our knowledge no studies have assessed HRQOL based on post-operative complications in patients undergoing lobectomy for the treatment of NSCLC. In other indications, HRQOL has been shown to return to baseline function in six to twelve months after lobectomy thoracotomy and less than this time period in patients who underwent the VATS approach. [3,4,25]

In this study we were able to demonstrate that an increasing severity of post-operative complications, as measured by the Clavien classification system, was associated with worsening HRQOL by several objective measures for up to three months following VATS lobectomy.

General Health, Vitality and Mental Health were the main affected domains of the SF-36 generic measure at three months after surgery. Patients with more severe complications had significant decline in HRQOL at two months after surgery as measured by the disease specific measures (QLQ 30 and QLQ 13); these differences were mainly in symptoms like chest pain, shoulder pain, dyspnea, fatigue and insomnia which can lead to considerable decline in productivity and financial difficulties (which was also statistically different between the high and no/low complications group).

The health utility index from the EQ-5D measure did not detect any statistically significant difference between the high and no/low complications group over time after surgery; this could be explained in two ways. The first is because of the small sample size we used which was calculated based on the SF-36 measure, and the second reason is the possibility that the responsiveness of the EQ-5D in this patient population is limited in its ability to determine change over time.

At baseline the EQ-5D health index Standard Deviation (SD) for the total sample was 0.08. By using a 0.5 SD (i.e., 0.04) as the minimal clinically important difference, we will find a clinically significant difference between the two groups at three months after surgery in favor of the No/Low complications groups.

The strengths and limitations of this study are several. One of the main limitations is the observational nature of the study with its associated limitation of confounding and bias. In an attempt to decrease the risk of information bias, the outcome assessors were blinded to the presence and severity of complications that the patients had during their post-operative period (i e: The individuals administrating the HRQOL instruments were not informed of the patients operative and post-operative hospital course a-priori of their administrating the HRQOL instruments).

Since the exposure of interest was post-operative complications and their severity, randomization is impossible, and differences in length of stay and chest tube duration were encountered between the high and no/low complications groups. Other limitations would be the small sample size, the possible confounding effect of other factors (tumor stage and grade, pulmonary function tests, operative time and intra-operative blood loss) and the fact that only one center was included in this study which can limit the external validity of the study.

On the other hand, some of the strength of this study include the low percentage of patients who were lost to follow up (7%) two from the no/low complications group and one from the high complication group. Other strengths include the assessment of post-operative complications and HRQOL by a research team completely independent from the clinical team caring for this patient population, the small group of surgeons experienced with VATS resection for lung cancer, the use of the Clavien system which has been shown to be valid in thoracic surgery,

and the robustness of the GEE analysis that incorporate change over time between and within individuals. [3,4]

5. **Conclusions:**

Surgeons and other physicians caring for patients undergoing VATS lobectomy for lung cancer are often more concerned about post-operative complications, however, patients frequently ask about the changes they can expect post-operatively and the impact of these changes on their life. The severity of post-operative complications can determine the HRQOL in patients undergoing VATS lobectomy up to three months after surgery. This information can be critical in pre-operative patient counseling.

6. **Conflict of interest:** This study was funded by a research grant from Johnson and Johnson pharmaceutical.

Tables and Figures:

Table 3-1: The use of all questionnaires at baseline and all follow up visits

	Baseline	2 weeks	4 weeks	8 weeks	3 months
SF-36	Yes	No	Yes	No	Yes
QLQ 30	Yes	Yes	No	Yes	No
QLQ 13	Yes	Yes	No	Yes	No
EQ-5D	Yes	No	Yes	Yes	Yes

Table 3-2: Clavien grading system of surgical complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention.
III a	Intervention not under general anesthesia.
III b	Intervention under general anesthesia.
Grade IV	Life-threatening complication requiring IC/ICU management.
IV a	Single organ dysfunction.
IV b	Multiorgan dysfunction.
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge, the suffix "d" (for "disability") is added to the respective grade of complication.

Table 3-3: Patients demographics by complications group

	No/Low grade complications	High grade complications	P value
Total number	31	13	
Age (years)	64.8±9.1	66.3±7.3	NS*
Sex M:F	18:13	6:7	NS*
Stage IA	17	7	NS*
Stage IB	8	5	NS*
Stage IIA	2	1	NS*
Stage IIB	3	0	NS*
Stage IIIA	1	0	NS*
Chest tube duration (days)	3.2±2.1	8.4±4.4	P<0.01
Length of stay (days)	4.3±2.4	9.7±6.1	P<0.01

* Not Significant (P > 0.05)

Figure 3-1: High grade complications encountered during hospital stay

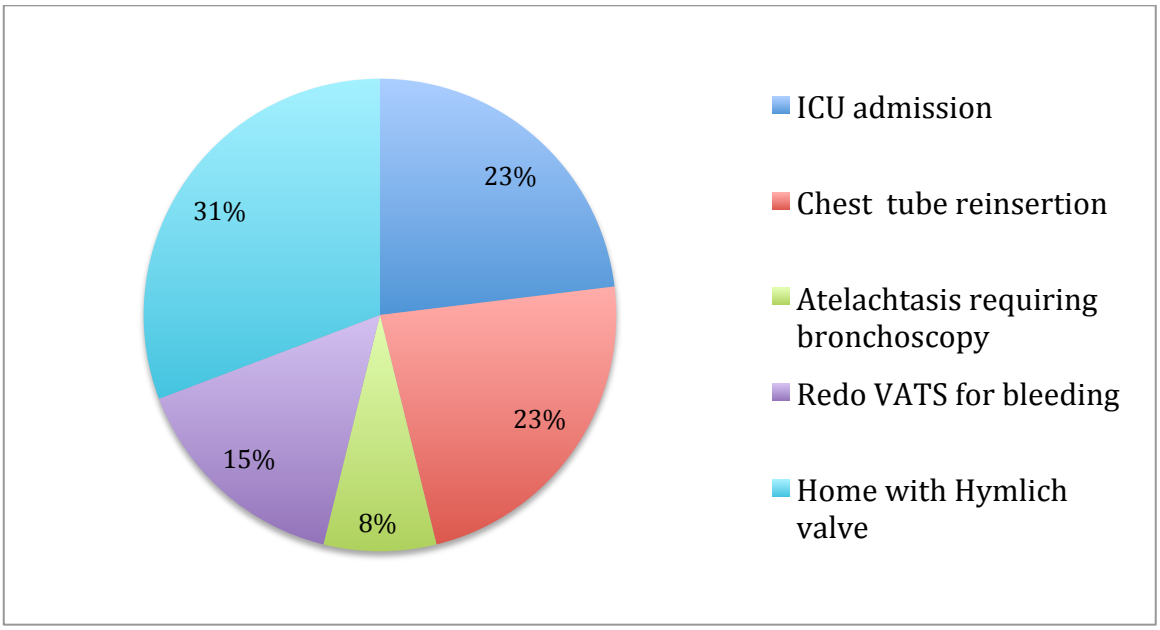


Figure 3-2: SF-36 General Health comparing No/Low to high-grade complications groups

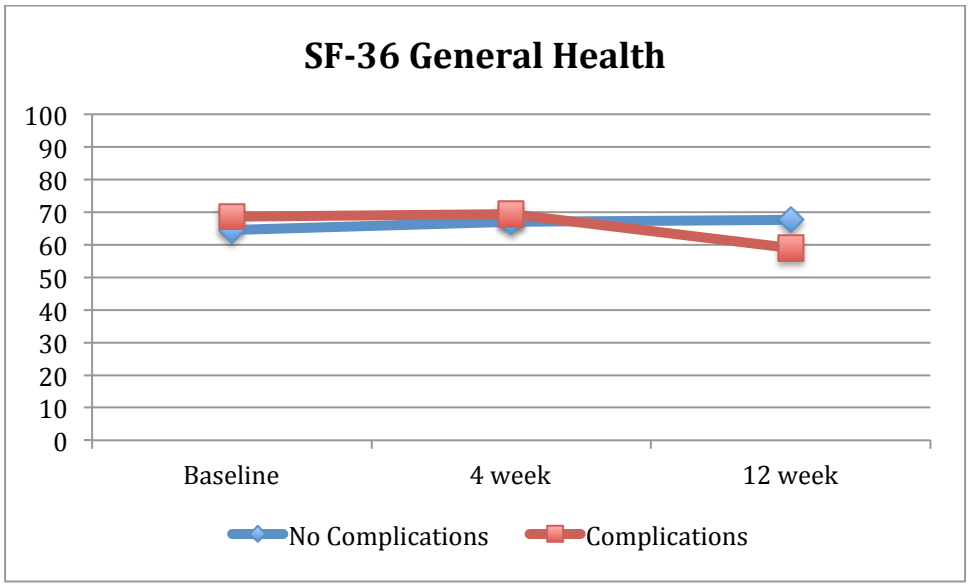


Figure 3-3: SF-36 Vitality comparing No/Low to High complications groups

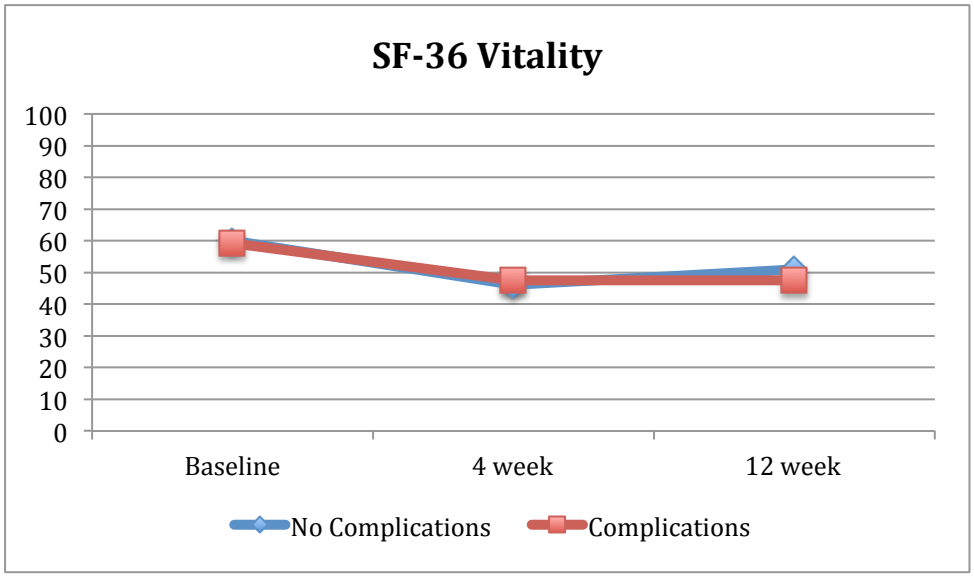


Figure 3-4: SF-36 Mental Health comparing No/Low to High complications groups

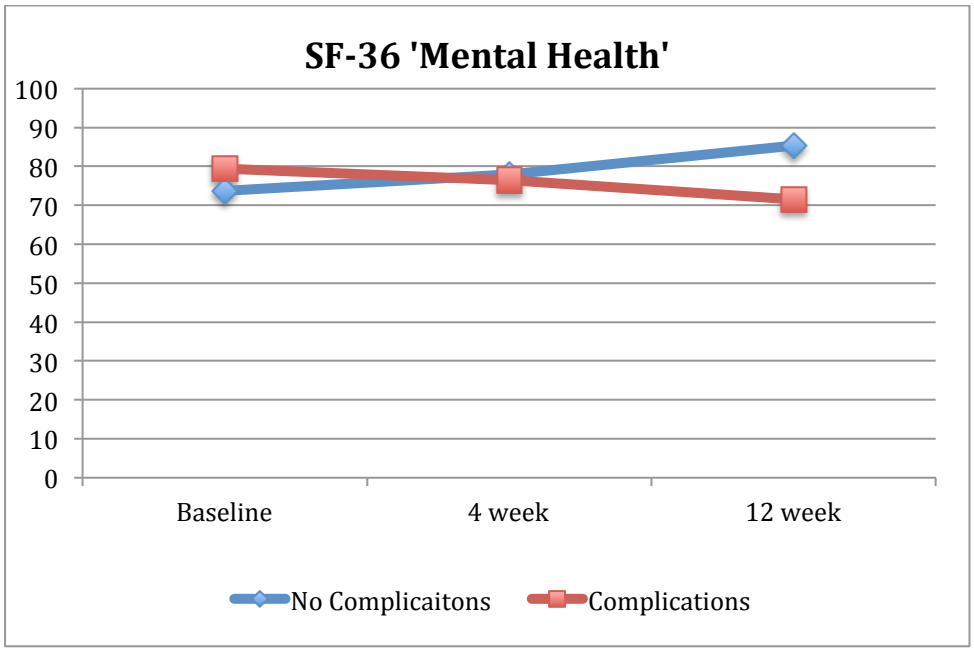


Table 3-4: SF-36 eight domains comparing the two complications group at baseline, 4 weeks and 12 weeks from surgery. Mean (SE)

SF-36 Scale	Complications	Baseline	4 week	12 week	p-value*
Physical Functioning	No/Low	73.2 (4.5)	56.5 (3.8)	71.6 (3.9)	0.06
	Severe	65.0 (6)	50.3 (7.0)	67.0 (6.5)	
Role Physical	No/Low	74.7 (5.9)	30.7 (4.4)	60.2 (6.5)	0.3
	Severe	76.8 (7.6)	28.3 (8.7)	55.2 (8.7)	
Bodily Pain	No/Low	76.3 (4.9)	45.1 (4.2)	71.7 (7.1)	0.1
	Severe	68.6 (4.3)	51.7 (7.4)	67.0 (4.2)	
Vitality	No/Low	60.0 (4.2)	46.1 (3.2)	51.0 (6.6)	0.02
	Severe	59.2 (4.8)	47.6 (8.2)	47.5 (4.8)	
General Health	No/Low	64.5 (3.3)	67.0 (3.8)	67.7 (4.7)	<0.01
	Severe	68.5 (4.4)	69.4 (3.2)	58.9 (4.2)	
Social Functioning	No/Low	79.0 (4.1)	61.1 (5.1)	75.9 (5.5)	0.09
	Severe	83.8 (5.4)	62.5(10.2)	75.0 (7.2)	
Role Emotional	No/Low	83.6 (4.4)	82.0 (4.0)	85.8 (4.1)	0.3
	Severe	86.3 (5.4)	89.0 (4.9)	82.7 (9.0)	
Mental Health	No/Low	73.7 (3.7)	78.1 (2.8)	85.4 (4.1)	<0.01
	Severe	79.4 (4.9)	76.5 (6.2)	71.5 (4.1)	

* p-value from GEE linear regression for differences in change over time between those with and without complications after adjusting for age and sex.

Table 3-5: QLQ 30/13 scales and symptoms at baseline, 2 weeks and 8 weeks after surgery comparing the two complications groups. Mean (SE)

QLQ 30/13	Complications	Baseline	2 week	8 week	p-value*
Chest pain	No/Low	27.4 (6.2)	19.0 (5.8)	20.5 (7.1)	<0.01
	Severe	27.1 (6.2)	31.0 (10.2)	23.5 (5.0)	
Shoulder Pain	No/Low	16.0 (4.2)	31.0 (4.9)	11.5 (2.9)	<0.01
	Severe	10.8 (2.5)	42.3 (7.0)	21.6 (3.5)	
Dyspnea Scale	No/Low	11.5 (2.1)	19.0 (3.2)	14.8 (2.8)	<0.01
	Severe	16.3 (3.6)	30.2 (5.8)	22.2 (1.8)	
Cognitive Functioning	No/Low	86.9 (2.8)	86.3 (3.5)	89.7 (5.5)	0.02
	Severe	95.1 (2.4)	84.5 (5.9)	87.0 (3.8)	
Emotional Functioning	No/Low	79.5 (3.5)	85.4 (3.1)	89.7 (3.5)	0.02
	Severe	87.7 (3.8)	81.5 (7.3)	83.0 (3.5)	
Insomnia	No/Low	27.3 (6.0)	21.4 (8.3)	10.3 (5.8)	<0.01
	Severe	9.80 (4.8)	36.9 (5.8)	27.1 (5.3)	
Fatigue	No/Low	21.4 (3.5)	38.1 (3.9)	26.7 (3.3)	0.03
	Severe	17.0 (3.2)	43.7 (7.9)	30.0 (6.2)	
Financial Difficulties	No/Low	6.00 (3.0)	10.7 (4.6)	11.1 (4.3)	<0.01
	Severe	13.7 (7.0)	26.2 (9.4)	20.5 (8.9)	

p-value from GEE linear regression for differences in change over time between those with and without complications after adjusting for age and sex

Table 3-6: EQ-5D (VAS and Health Index) measured at baseline and 2, 8, and 12 weeks from surgery comparing the two complications groups. Mean (SE)

EQ-5D	Complications	Baseline	4 week	8 week	12 week	P-value*
VAS	No/Low	73.6 (3.7)	64.6 (4.2)	70.4 (5.5)	71.2 (4.4)	0.39
	Severe	76.0 (3.0)	57.6 (3.9)	68.5 (4.0)	68.3 (4.4)	
Index	No/Low	0.84 (0.02)	0.74 (0.03)	0.81 (0.01)	0.80 (0.03)	0.75
	Severe	0.84 (0.02)	0.73 (0.04)	0.82 (0.03)	0.76 (0.04)	

* p-value from GEE linear regression for differences in change over time between those with and without complications after adjusting for age and sex

Figure 3-5: QLQ 13 Chest Pain comparing No/Low to High grade complications groups

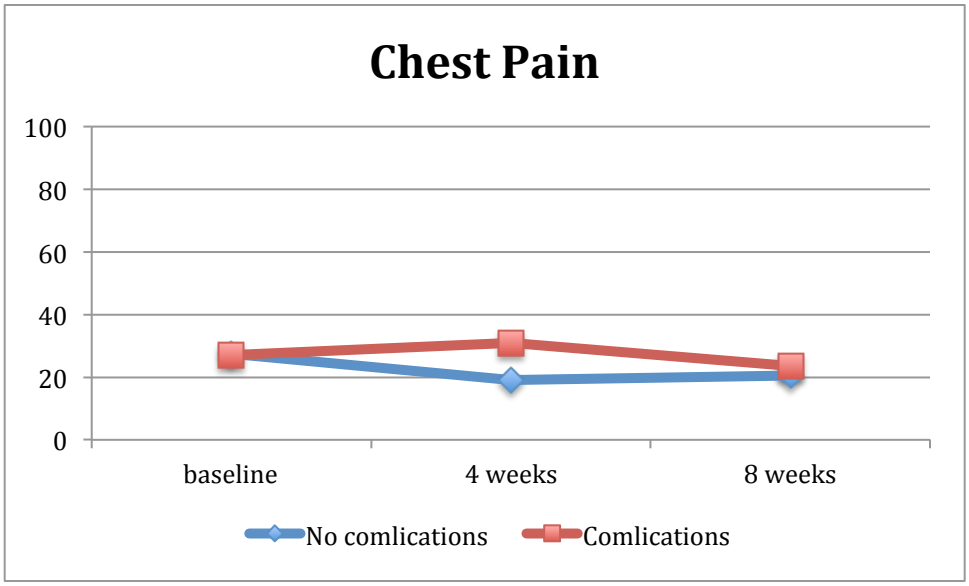


Figure 3-6: QLQ 13 Shoulder Pain comparing No/Low to High grade complications groups

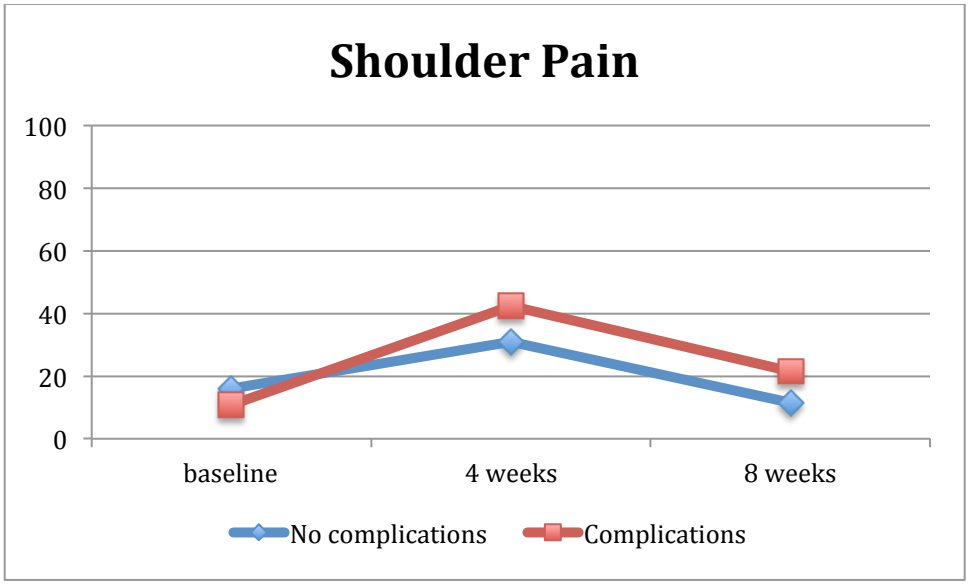


Figure 3-7: QLQ 13 Dyspnea Scale comparing No/Low to High grade complications groups

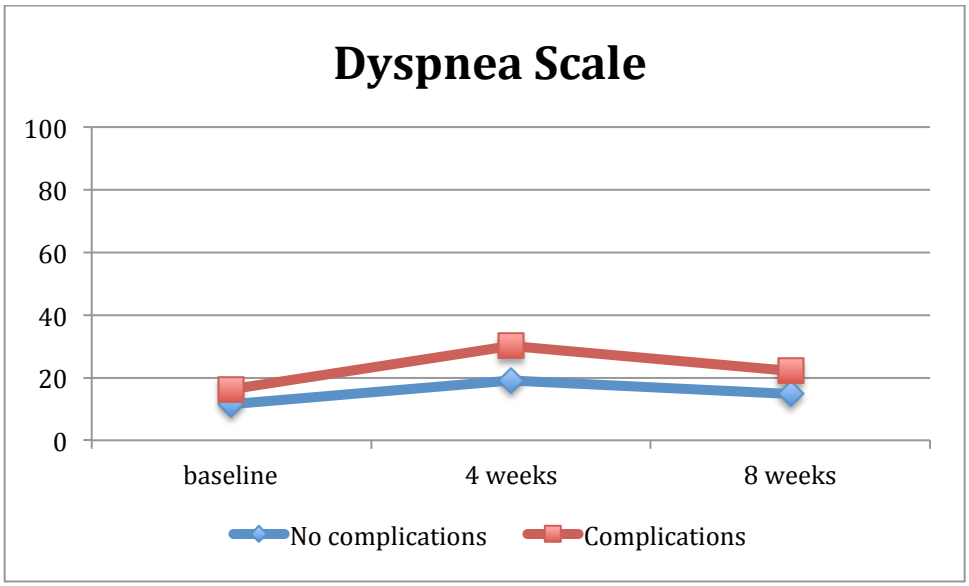


Figure 3-8: QLQ 30 Financial difficulties comparing No/Low to High grade complications groups

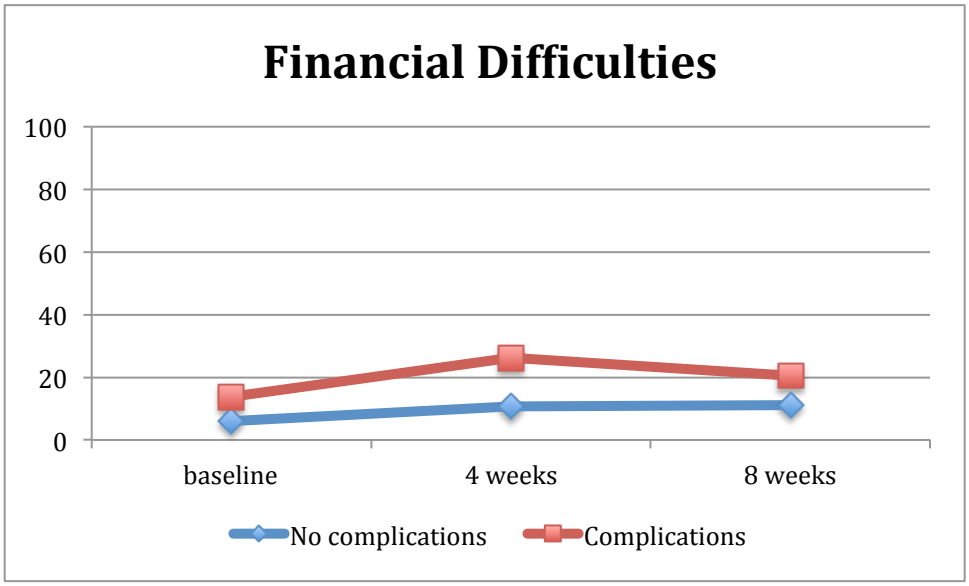


Figure 3-9: EQ 5D VAS score comparing No/Low to High-grade complications groups

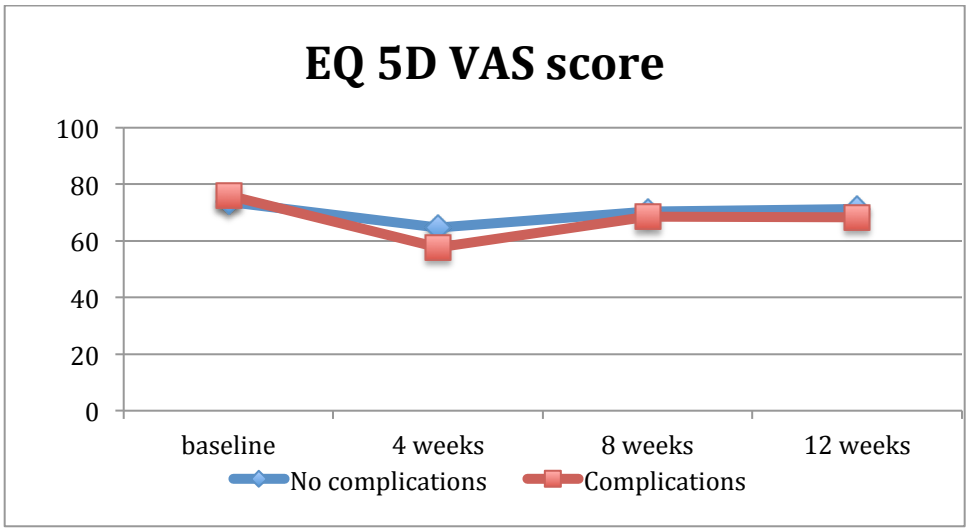
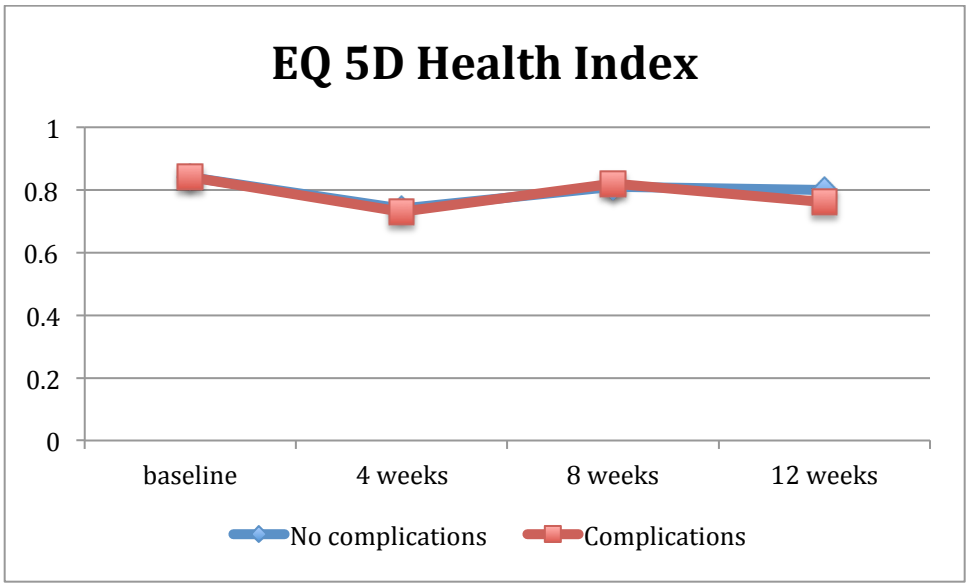


Figure 3-10: EQ 5D Health Index comparing No/Low to High-grade complications groups



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8. Appendices

Appendix A: SF-36 version 2

SF36 Subject #_____ Date_____
Visit: ☐Baseline ☐4 weeks ☐3m

YOUR HEALTH AND WELL-BEING

Thank you for completing this survey. This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

1. **In general, would you say your health is: [Mark an x in a the one box that best describes your answer.]**

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. **Compared to one year ago, how would you rate your health in general now?**

Much Better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐1	☐2	☐3	☐4	☐5

3. **The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? [Mark an x in a box on each line.]**

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	**Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	☐1	☐2	☐3
b	**Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐1	☐2	☐3
c	Lifting or carrying groceries	☐1	☐2	☐3
d	Climbing **several** flights of stairs	☐1	☐2	☐3
e	Climbing **one** flight of stairs	☐1	☐2	☐3
f	Bending, kneeling, or stooping	☐1	☐2	☐3
g	Walking **more than a mile**	☐1	☐2	☐3
h	Walking **several hundred yards**	☐1	☐2	☐3
i	Walking **one hundred yards**	☐1	☐2	☐3
j	Bathing or dressing yourself	☐1	☐2	☐3

4. **During the <u>past 4 weeks</u>, have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?**

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Cut down on the **amount of time** you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b	**Accomplished less** than you would like	☐1	☐2	☐3	☐4	☐5
c	Were limited in the **kind** of work or other activities	☐1	☐2	☐3	☐4	☐5
d	Had **difficulty** performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. **During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?**

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Cut down on the **amount of time** you spent on work or other activities.	☐1	☐2	☐3	☐4	☐5
c	**Accomplished less** than you would like	☐1	☐2	☐3	☐4	☐5
c	Did work or other activities **less carefully than usual**	☐1	☐2	☐3	☐4	☐5

6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
☐1	☐2	☐3	☐4	☐5	☐6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks . . .

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b	Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c	Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d	Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e	Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f	Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g	Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h	Have you been happy?	☐1	☐2	☐3	☐4	☐5
i	Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

11. How TRUE or FALSE is each of the following statements for you?

		Definitely true	Mostly True	Don't know	Mostly false	Definitely false
a	I seem to get sick a little easier than other people	☐1	☐2	☐3	☐4	☐5
b	I am as healthy as anybody I know	☐1	☐2	☐3	☐4	☐5
c	I expect my health to get worse	☐1	☐2	☐3	☐4	☐5
d	My health is excellent	☐1	☐2	☐3	☐4	☐5

Thank you for completing these questions!

ENGLISH

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: _ _ _ _

Your birthdate (Day, Month, Year): _ _ _ _ _ _

Today's date (Day, Month, Year): 31 _ _ _ _ _ _

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

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

Please go on to the next page

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

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ENGLISH

EORTC QLQ - LC13

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

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

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Appendix D: EQ-5D

Health Questionnaire

(Canadian English version)

Subject Number: _____

Visit: _____

Date Completed: ____ / _____ / _____
dd *mmm* *yyyy*

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By placing a check-mark in one box in each group below, please indicate which statements best describe your own state of health today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

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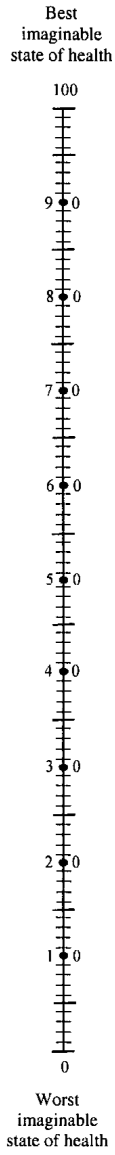
To help people say how good or bad their state of health is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your state of health is today.

Your own state of health today



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Chapter four: General Discussion and Conclusions

1. General Discussion:

Lung Cancer, especially NSCLC, is a commonly encountered medical problem. While limited options can be offered to patients with advanced stage NSCLC, the goal of treatment for the early stage and some cases of locally advanced disease is curative intent and usually includes some form of surgical resection. [1,2]

The HRQOL of patients diagnosed with lung cancer is lower than their matched peers with no cancer or with other forms of cancers. In addition to this, surgery for the treatment of lung cancer adds a significant burden on patients and their quality of life. [3,4]

Since the introduction of VATS for the use in surgical resection for NSCLC about twenty years ago, the procedure has gained more acceptability with published series appearing to demonstrate its' oncological equivalence to outcomes post thoracotomy. As surgeons have gained more experience, the more recent case series from high volume centers have reported even lower complication rates and mortality when compared to thoracotomy. [5]

Often physicians and surgeons appear to be most concerned with post-operative complications and long term-oncologic outcomes. Patients, however, are usually more concerned about their quality of life in general.

The systematic review we carried out, although has some limitation based on the limited number and low quality of studies included in the review, concluded that Post-operatively, in patients undergoing thoracotomy there is an initial decline their HRQOL (mainly in the physical component) that return to baseline around

three months after surgery. [6] No study has assessed the HRQOL for patents undergoing VATS pulmonary resection for NSCLC comparing the post-operative period to baseline HRQOL. At prolonged follow up time, HRQOL measured by disease specific tools favor the VATS pulmonary resections to thoracotomy, mainly in the physical scales and symptoms. [7,8,9] The meta-analysis we performed confirmed the finding from the qualitative review, although the statistical differences were not significant always mainly due to the time of follow up difference between the two studies included in the meta-analysis. We also found that no studies have assessed the effect of post-operative complications on HRQOL of patients undergoing any form of anatomical lung resection. Comparing males to females, there are few differences between the two sexes in HRQOL after pulmonary resection specifically in depressive symptoms that favor males and sexual function that favor females. [10]

There have been studies showing the superiority of the VATS approach to thoracotomy in terms of: post-operative complications, blood loss, pain and inflammatory response. However, no studies have assessed the effect of post-operative complications on HRQOL in patients undergoing pulmonary resections for NSCLC. [11,12,13,14]

Post-operative complications can be used as a quality assurance measure in morbidity and mortality assessment of surgical practice but their direct effect on the patient HRQOL has yet to be determined in thoracic surgery.

In this study we were able to show that up to three months after surgery, the severity of post-operative complications measured by the Clavien classification system can determine the HRQOL of patients undergoing VATS lobectomy. General health, vitality and mental health are the main affected domains measured by the generic measure the SF-36 at three months after surgery.

Patients with more severe complications had significant decline in HRQOL at two months after surgery measured by the disease specific measures (QLQ 30 and QLQ 13), these differences were mainly in symptoms like chest pain, shoulder pain, dyspnea, fatigue and insomnia which can lead to considerable decline in productivity and financial difficulties (which was also statistically different between the high and no/low complications group).

The health index determined by the EQ-5D measure did not detect any difference between the high and no/low complications group at any time after surgery, this could be explained in two ways. The first one is because of the small sample size we used which was calculated based on the SF-36 measure, and the second reason is the possibility that the responsiveness of the EQ-5D in this patient population is low to determine change over time

This study helps to determine the effect of severe post-operative complications of HRQOL, which can be used in the perioperative patients' counseling to address their questions and concerns regarding their post-operative course.

There are few limitations in both the systematic review and the cohort study we performed. In the systematic review, the poor quality and high risk of bias in included studies were high, mainly because of the observational nature of the

studies. Another limitation is the use of different HRQOL tools among different studies, which made pooling the results of some studies impossible. We did not assess for the risk of publications bias due to the small number of studies included in the review but that is another possibility of high risk of bias and limitation in the review.

To assess the impact of complications on post-operative HRQOL, we carried out a cohort study, which represent the highest quality of observational studies, but still can have risk of selection and information bias as well as confounding. To minimize the risk of bias we blinded the outcome assessors to the exposure of interest (severity of post-operative complications).

Other limitations would be the small sample size, the possible confounding effect of other factors (tumor stage and grade, pulmonary function tests, operative time and intra-operative blood loss) and the fact that only one center was included in this study which can limit the external validity of the study.

2. Conclusions:

We recommend higher quality comparative observational studies to be carried out comparing the VATS to the thoracotomy approach for the treatment of early stage lung cancer, if randomized control trials are not an option.

We also recommend the long-term follow up of patients with high-grade complications to identify the impact of such complications on patients undergoing VATS lobectomy. The development of a quality assurance measure that can predict patients with high-grade complications will be ideal, especially if the effect of these complications is of long-term.

The development of a HRQOL measure that is more specific to patients with lung cancer undergoing surgical resection will aid in comparison of results and communications between health care professionals, and address patients concerns to what is related to their diagnosis. While the EORTC QLQ30 and QLQ 13 are measures specific to patients with cancer and lung cancer respectively, they were originally developed for patients undergoing chemotherapy and radiotherapy, rather than surgical resections.

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