Peer Review File

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Reviewer A

Comment 1: I do not believe that a surgical technique influences the prognosis of a disease such as cancer, since even if the approach is different, the procedure must be the same. It would be more interesting to focus on the perioperative problems of the technique, which is what surgeons fear.

Reply 1: We appreciate the reviewer's comments and agree with the sentiment: a change in surgical technique should not compromise an oncologic outcome. However, we do believe that changes in surgical techniques need to be evaluated to ensure that this is the case. At the onset of video-assisted thoracoscopic surgery and robotic-assisted thoracoscopic surgery there was significant concern that these techniques might jeopardize the quality of oncologic thoracic surgery. Likewise, adjunct techniques such as stereotactic body radiotherapy and ablation have been frequently evaluated and compared against preexisting techniques. We believe that any change in technique or technology require both short and long-term assessment.

Change in Text 1: Discussion (page 9 lines 242-246): "It is critical that innovations in surgical technique that improve perioperative outcomes do not compromise oncologic outcomes. We were encouraged that we found no difference in survival in our propensity matched cohorts or when performing subgroup analysis for patients whose indication for resection was a primary lung cancer."

Reviewer B

I have some concerns as followings.

Comment 1. To assess the quality of surgery, the author should also describe the postoperative recurrence rate.
Comment 2. What was the percentage of deaths due to primary lung cancer?
Comment 3. If possible, the author should indicate the surgical margin in anatomical lung resection or wedge resection for tumor.

Response to comments 1-3: Unfortunately, we are limited by our institutional database which is based on the Society of Thoracic Surgery database. This does not include disease free survival, or recurrence rate. It would be extremely difficult to obtain this data for the full cohort of 1,813 patients. We agree that these are major limitations and warrant further discussion. We have modified our discussion to reflect these points.

Change in text 1-3: Discussion (page 12 lines 314-318):
Other limitations include the lack of disease specific survival, recurrence free survival, or distance to margin. These variables were not included in the institutional or STS database and were not available for this study. It is possible that despite similar overall 3-year survival, these variables

differ significantly in patients receiving non-intubated thoracoscopic surgery and that differences in survival would become more apparent at 5 or 10-year follow-up.

Comment 4. Since the operation will be under spontaneous breathing, the workspace is expected to be narrow. Have you used selective bronchial blockers in this study?

Response 4: None of the non-intubated patients had a bronchial blocker placed. An LMA was placed in 9.7 % of the spontaneous breathing patients who underwent non-intubated surgery. For those that were intubated the standard at our institution is a double lumen endotracheal tube. Occasionally a bronchial blocker may be used if the double lumen tube is particularly difficult to place.

Change in Text 4: Methods (Page 5 lines 125-130): Patients in the control arm were intubated with a double lumen endotracheal tube or rarely single lumen endotracheal tube with a bronchial blocker. Non-intubated patients were brought to the operating room and monitored sedation was provided through administration of propofol, midazolam, and fentanyl. Rarely, a laryngeal mask airway (LMA) was placed at the discretion of the attending anesthesiologist. None of the non-intubated patients had a bronchial blocker or similar device inserted in the airway.

Reviewer C

Comment 1: This is an interesting retrospective study, with propensity matched analysis, that compares non intubated and intubated thoracoscopic and minimally invasive thoracic procedures. The manuscript is well written overall. The tables are complementary and so are the supplemental material and the strobe statement.

Although the authors compared malignant cases amongst each other, one of my issues with the paper is that the authors included both malignant and nonmalignant indication in their analysis. These are two completely different patient population. I think what they can conclude is that non intubated thoracoscopic surgery can be performed safely. Comparing long term survival in this setting is a little misleading in my opinion. Even more so that when they matched the cancer operations with the intubated patients, the median number of lymph nodes in the intubated group was only 6; this is rather surprising and I'm not sure it can be justified whether cases are done in a community setting or in a quarternary center. In essence, the authors are proclaiming that the 3 year survival in non-intubated lung cancer surgery cases is as good as in intubated patients who had a median lymph node harvest of six only. I do question the oncological quality of the lung cancer resections in their intubated patients.
It may be best for the authors to focus only on the perioperative morbidity and mortality. I think it is fair to say that they were able to achieve acceptable immediate outcomes, that seem to be comparable to intubated patients…

Response 1: While we agree that comparing and combining long-term survival for oncologic and non-oncologic indications may be problematic, overall experience with, and acceptance of, thoracic operations during spontaneous breathing in North America is limited. For this reason, we report a complete, consecutive clinical cohort. To add a separate focus, we also report a subgroup analysis of

patients with oncologic indications. When we performed this analysis of 3-year survival in unmatched and propensity matched populations, we did not see a differences in overall survival.

Second, the issue of adequate nodal harvest is frequently discussed and reminiscent of similar initial concerns for minimally invasive resection. While during this study the recommended nodal harvest was ≥10 for an anatomic resection, this particular metric was highly criticized, heavily dependent on the practice patterns of pathologists at a given institution, and frequently disregarded. For example, within the STS database among high volume centers only 75% averaged ≥10 (Udelsman et al, 2022). The recent recommendation of sampling 3 mediastinal stations and 1 hilar station remains under investigation and there is a lack of institutional data on this metric. We agree the reviewer's concern deserves further discussion that we have now therefore included in our revised manuscript.

Change in Text 1:
Results:

Page 8 Lines 216-223 Results:
Subgroup Analysis Among Patients with a Primary Lung Cancer:
In a subgroup analysis of primary lung cancer, unadjusted 3-year survival in the intubated was 90% compared to 89% in the non-intubated cohort (p=0.31). Propensity matched overall survival was 92% in the intubated cohort and 89% in the non-intubated cohort (p=0.61) (**Figure 2**). No statistically significant difference was found in clinical or pathologic stage between the propensity matched groups (**Table 4**). The dominant histologic subtype was adenocarcinoma. The average number of harvested nodes and nodal stations did not significantly differ between cohorts.

Page 10 Lines 266-279 Discussion: In subgroup analysis of patients undergoing elective procedures for primary NSCLC, we found no difference between the matched cohorts. A vast majority of lung cancers were early (T1a and T1b) clinical stage I, and pathologic upstaging was rare in both cohorts. The mean of sampled nodal stations and harvested nodes were similar for intubated and non-intubated patients. For part of the study time-period the recommended nodal harvest for anatomic resection was ≥10 nodes (20). In the intubated and non-intubated cohorts, the average nodal harvest was significantly less at 6. However, this may reflect limitations in this quality metric which has since been abandoned. Indeed, within the STS database this metric was frequently missed among participating centers (21). Unfortunately, sampling of three mediastinal stations and one hilar station as recently adopted by the American College of Surgeons Commission on Cancer and National Comprehensive Care Network was not reliable tracked, and rose not to a standard during the majority of the study interval (22,23). While access to mediastinal stations is potentially more difficult in the non-isolated lung (7), tour study did not confirm this assumption, and was therefore consistent with the propensity matched analysis by Liu and coauthors (8).

Comment 2: Another request for the authors is to expand a little more on the other 19 cases of non-intubated patients. Were these empyemas, pleural biopsies, or cyst resection? Did they match for the specific type of benign case in the benign category?

Response 2: We gladly provide additional explanation on non-oncologic outcome and added to our results section as now included in supplementary table 1. In brief, a majority underwent resection of a mediastinal nodule (36.8%). This was followed by decortication for empyema (26.3%) and

pleurodesis (15.8%). Rarely, a pleural biopsy (10.5%) or pericardial window (10.5%) were performed. Our propensity-score matched analysis excluded urgent cases, primarily empyema. We included oncologic indication and type of pulmonary resection (e.g. lobectomy, segmentectomy, wedge) for the procedure in our propensity-score matched analysis but did not differentiate between type of non-oncologic procedure (e.g. mediastinal biopsy vs. pleural biopsy).

Change in text 2:
Page 6 Lines 158-160 Methods: Data elements considered [in the propensity-score matched analysis included] patient sex, age, BMI, comorbidities, type of procedure (lobectomy, segmentectomy, wedge, other), and diagnosis of pulmonary malignancy.

Page 7 Lines 183-185 Results: In patients without primary lung cancer non-pulmonary procedures included mediastinal biopsy (36.8%), decortication for empyema (26.3%), pleurodesis (15.8%), pericardial window (10.2%), and pleural biopsy (10.2%) (**Supplementary Table 1**).

Reviewer D

Thank you for the opportunity of reviewing your interested manuscript.

Comment 1: Please clearly state the novelty that differs from past reports.

Response 1: Recent studies have explored the peri-operative outcomes of standard and uniportal VATS in non-intubated patients Yu et al 2019, Wen et al 2020, Liu et al 2020, Zhao et al 2016. **Unlike these studies we included a 3-year follow up time.** Furthermore, none of these studies were performed on the North American continent. We believe both factors are important and represent significant novelty. First, it is critical that innovations in surgical technique do not compromise perioperative and oncologic outcomes. This study focuses on both. In addition, non-intubated surgery thoracoscopic surgery requires significant buy-in and coordination of care between thoracic surgeons and thoracic anesthesiologists. There are logistic hurdles to overcome in this approach and in North America there has been significant aversion to adoption of non-intubated thoracoscopic surgery. This study is important because it uniquely demonstrates that non-intubated surgery can be performed safely in this setting with maintained oncologic outcomes.

Change in text 1:

Page 9 Lines 240-249 Discussion: More recent studies from Asia and Europe have explored the peri-operative outcomes of standard and uniportal VATS in non-intubated patients (13–16). Unlike these studies we included a 3-year follow up time in a North American center (tertiary and community). It is critical that innovations in surgical technique that improve perioperative outcomes do not compromise oncologic outcomes (17).We were encouraged thatwe found no difference in survival in our propensity-score matched cohorts or when performing subgroup analysis for patients whose indication for resection was a primary lung cancer. We did note a relatively high overall survival in this population with 95% 3 year-survival in the intubated cohort and 89% 3-year survival in the non-intubated cohort. While higher than some previous reports, the patients in this study tended to have early stage disease and the reported survival is similar to that reported in the recent JCOG0802 trial (18).

Comment 2. Please indicate the basis for the number of cases set.

Response 2: The number of non-intubated cases was based on the institutional data set which included cases performed over a 5-year study period. We believe this timeline provided enough perioperative and follow up data to allow for a meaningful comparison with intubated patients. A post-hoc analysis with α of 0.05 we were powered to detect an 5% difference between the two groups.

Change in text 2:

Page 6 Lines 161-164 Methods: The number of non-intubated cases was based on the institutional data set which included cases performed over a 5-year study period. We believe this timeline provided enough perioperative and follow up data to allow for a meaningful comparison with intubated patients. In post-hoc analysis with α of 0.05 we were powered to detect a 5% difference between the two groups.

Comment 3. It is easy to understand that the anesthesia time before and after surgery, such as intubation and extubation, is shorter in the non-intubated group, but why is the pure procedure time shorter? Did you limit to simple or non-risky cases? Didn't you sacrificing the quality of surgery, such as palliative surgery or omitting dissection? You should clearly describe the indication.

Response 3: We suspect that during non-intubated surgery there is more impetus to keep the case moving and reduce any delays. We do not limit to simple cases but do use the criteria included in supplementary material 1 in selecting patients for non-intubated surgery. This includes factors such as lower BMI which was also included in our propensity-score matched analysis). As non-intubated thoracoscopic surgery becomes more widely adopted we may see a paradoxical increase in operative time as the surgical and anesthesiology teams become more comfortable with the procedure. We agree that this surprising result requires further discussion and have included in our revised manuscript excerpted below.

Page 10 Lines 255-263 Change in text 3:
Discussion: More surprisingly the length of procedure time was also reduced in the non-intubated cohort. We suspect that during non-intubated surgery there is more impetus to operate in an expedient manner and reduce any delays. We did not limit to simple cases but did use the criteria included in supplementary material 1 in selecting patients for non-intubated surgery. This includes factors such as lower BMI. While these factors were included in our propensity-score match not all patient and disease factors affecting the operation are accessible to balance, and it is possible there were uncaptured differences. As non-intubated thoracoscopic surgery becomes more widely adopted we may see a paradoxical increase in operative time as the surgical and anesthesiology teams become more comfortable with the procedure.

Comment 4. From the perspective of the surgeon, please describe any disadvantages or stress

during surgery in the non-intubated group.
Comment 5. From the perspective of the anesthesiologist, please write any disadvantages or stress.

Response 4 and 5: As with the adoption of any new technique there was significant apprehension associated with the adoption of non-intubated surgery. However, prior to adoption meetings occurred between surgeons and anesthesiologists. A pre-defined selection criteria (supplementary material 1) was agreed upon which included patients of lower BMI and preference for procedures involving the lower lobes. This helped ameliorate any anxiety associated with adoption. As the number of patients and clinicians involved with non-intubated surgery increased it became more routine and these sources of stress were reduced. By the end of the 5-year study period there was significant accrued experience with 11 anesthesiologists being directly involved in patient care during the procedures.

Change in text 4 and 5:

Page 11 Lines 295-302 Discussion: As with the adoption of any new procedure or technique there was significant initial apprehension associated with non-intubated surgery. However, prior to adoption meetings occurred between surgeons and anesthesiologists. A pre-defined selection criteria (**Supplementary Material 1**) was agreed upon which included patients of lower BMI and preference for procedures involving the lower lobes. This helped ameliorate any anxiety associated with adoption. As the number of patients and clinicians involved with non-intubated surgery increased it became more routine and these sources of stress were reduced. By the end of the 5-year study period there was significant accrued experience with 11 anesthesiologists being directly involved in patient care during the procedures.

Comment 6. For the conversion case to intubation, please describe the reason in a little more detail.

Response 6: We included one case in which a patient was brought to the OR for a planned non-intubated procedure (lobectomy for primary non-small cell lung cancer). This patient experienced a myoclonic event during infusion of propofol. This occurred prior to any surgical incision. The infusion was stopped, the case cancelled, and monitoring/workup was performed in the intensive care unit. The event was believed to be due to a rare reaction to propofol and the case was rescheduled a week later, during which it was performed with a standard double lumen endotracheal tube. While we were prepared for it, no patients required intubation mid-procedure.

Change in text 6:
Page 7 Lines 178-182 Results:
Conversion to intubation occurred in one patient who experienced myoclonus during propofol infusion. The infusion was stopped prior to any surgical incision, and the operation was canceled before any incision. The eventual operation was performed using a standard double lumen endotracheal tube. No patients required intubation mid-procedure.

Reviewer E

General Comment: This article describes perioperative morbidity and 3-year survival in non-

intubated thoracoscopic surgery. The greatest strength of this study is that it shows 3-year survival rates of patients who underwent non-intubated thoracic surgery, however, I believe it is not appropriate to perform the survival analysis, even with propensity matching, because the small number of patients who underwent non-intubated thoracic surgery includes a variety of cases and a variety of procedures.
Therefore, I believe that the authors should add more cases and report again.

Response to General Comment:
We appreciate the reviewer's reading of our work. On the North American continent, where hesitancy persist in adopting non-intubated thoracic operations, only additional clinical reports may lead to greater acceptance. We understand concerns regarding the variety of cases and the relatively low numbers compared to those used in large database analysis. Due to perhaps overly cautious selection, data accrual required 5 years. While this data does represent a variety of indications, we did control for potential differences through both a propensity-score match and subgroup analysis (which included an independent propensity-score match). In addition, we have performed a post-hoc power analysis and using an α of 0.05 we were powered to detect a 5% difference between the cohorts. There are certainly limitations to this work which deserve further expansion (see below). However, we do believe there is merit in sharing this work, to encourage other groups to adopt these techniques.

Changes in text:
Pages 11-12 Lines 306-311 Discussion: The greatest limitation of this work is the inherent selection bias in the patients who undergo non-intubated thoracoscopic surgery. Despite a 5-year accrual period, we were only able to include 72 patients who underwent non-intubated procedure. Moreover, this was a heterogenous study group with oncologic and non-oncologic indications for intervention. We attempted to control for this using propensity-score matching and subgroup analysis of patients with a primary pulmonary malignancy, but it is possible that unaccounted variables effected the results of this study.

Specific Comments the following is a list of points that we believe should be revised.

Specific comment 1 Surgical Anesthetic Methods: Were these procedure done with Uniportal VATS ?
Response to comment 1: All procedures were done with multi-port access as is standard for intubated cases in our center where the surgeon was the teaching assistant in most operations. There were no uniportal VATS procedures.

Changes in text 1:
Page 4 Lines 117-118 Methods: In both the intubated and non-intubated patients, procedures were performed thoracoscopically using a standard multiport approach.

Specific Comment 2 · If the authors want to discuss about 'prognosis' in this study, you should just focus on lung cancer, although the number of cases will be reduced.

Response 2: We understand the difficulty of comparing patients with oncologic and non-oncologic indications. Given this concern we did perform a subgroup analysis in which we only focused on

patients with oncologic indications. We perform this analysis in both unmatched and in a separate propensity-score matched cohort we did not see a difference in overall survival between the two treatment groups.

Change in text 2:
Page 8 Lines 217-224 Results:
Subgroup Analysis Among Patients with a Primary Lung Cancer:
In a subgroup analysis of primary lung cancer, unadjusted 3-year survival in the intubated was 90% compared to 89% in the non-intubated cohort (p=0.31). Propensity-score matched overall survival was 92% in the intubated cohort and 89% in the non-intubated cohort (p=0.61) (**Figure 2**). No statistically significant difference was found in clinical or pathologic stage between the propensity-score matched groups (**Table 4**). The dominant histologic subtype was adenocarcinoma. The average number of harvested nodes and nodal stations did not significantly differ between cohorts.

Specific Comment 3 · Page 7, Line 228; In subgroup analysis, how many patients underwent lobectomy, segmentectomy, and partial resection?

Response to Comment 3: In the subgroup analysis of patients with primary lung cancer 19 patients underwent lobectomy, 9 segmentectomy, and 2 wedge resection. This is now included in the revised manuscript (excerpted below).

Changes in text 3:
Page 8 Lines 218-219 Results: In a subgroup analysis of 30 non-intubated patients with primary lung cancer, 19 (63.3%) underwent lobectomy, 9 (30.0%) underwent segmentectomy, and 2 (6.67%) underwent wedge resection.

Specific Comment 4 · Page 13, Table 1: It's out of alignment.; pFEV1
Response to Comment 4: Thank you for alerting us, the error has been corrected.

Changes in text: Not applicable, see revised table.

Specific Comment 5 · Page 13, Table 1: Procedure; How does the large number of Others in the non-intubated group affect the results? Also what happens after propensity matching?

Response to Comment 5: The majority of non-intubated patients who did not receive a pulmonary resection underwent resection of a mediastinal nodule (36.8%). This was followed by decortication for empyema (26.3%) and pleurodesis (15.8%). Rarely, a pleural biopsy (10.5%) or pericardial window (10.5%) were performed. In our propensity-score matched analysis we excluded urgent cases. This primarily involved the patients with empyema. We did include oncologic indication and type of pulmonary resection (e.g. lobectomy, segmentectomy, wedge) for the procedure in our propensity-score matched analysis but did not differentiate between type of non-oncologic procedure (e.g. mediastinal biopsy vs. pleural biopsy). We have now included this information in the revised manuscript (excerpted below) and in supplementary table 1.

Changes in text 5:

Page 5 Lines 158-159 Methods: Data elements considered [in the propensity-score matched analysis included] patient sex, age, BMI, comorbidities, type of procedure (lobectomy, segmentectomy, wedge, other), and diagnosis of pulmonary malignancy.

Page 7 Lines 184-186 Results: In patients without primary lung cancer non-pulmonary procedures included mediastinal biopsy (36.8%), decortication for empyema (26.3%), pleurodesis (15.8%), pericardial window (10.2%), and pleural biopsy (10.2%) (**Supplementary Table 1**).

Reviewer F

Comment 1: This manuscript describes on perioperative morbidity and long-term survival in non-intubated thoracoscopic surgery: a propensity matched analysis. Lung cancer was indicated for non-intubated thoracoscopic surgery in 30 patients (41.7%), however anatomical lung resection was only 28 (19 lobectomies and 9 segmentectomies) (38.9%). The number of radical operations for lung cancer is too small, and the detailed indication of non-intubated thoracoscopic surgery in this institute was not be described. A 3-year follow-up period cannot be considered long-term survival.

Response 1:

We appreciate the reviewer's comments and hope we can address their concern. We agree that the overall cohort of 72 non-intubated patients including 30 with a primary lung cancer is low compared to large database analysis. However, the control cohort is large, and propensity-score matching and subgroup analysis accounted for potential confounders. Furthermore, in the subgroup analysis of the patients with primary lung cancer the vast majority (93%) underwent an anatomic resection.

In addition, we have performed a post-hoc power analysis. Using an α of 0.05 and $1 - \beta$ of 0.8 we were able to detect a 5% difference between the cohorts. The 3-year outcomes reported in this work may not represent long-term survival but are the longest reported follow-up available for non-intubated patients. We do understand the hesitation with using the word long-term and have removed it from the manuscript (including the title). In short, there are certainly limitations to this work which we have expanded upon in the revised manuscript (see excerpt below). However, we believe there is merit in sharing this work, especially as other groups considering adopting these techniques.

Changes in Text 1:

Pages 11-12 Lines 306-319 Discussion: The greatest limitation of this work is the inherent selection bias in the patients who undergo non-intubated thoracoscopic surgery. Despite a 5-year accrual period, we were only able to include 72 patients who underwent non-intubated procedure. Moreover, this was a heterogenous study group with oncologic and non-oncologic indications for intervention. We attempted to control for this using propensity-score matching and subgroup analysis of patients with a primary pulmonary malignancy, but it is possible that unaccounted variables effected the results of this study. In addition, we were unable to match 5 patients in the non-intubated cohort that underwent nonelective procedures. Missing DLCO and other variables may have influenced treatment decisions. Given the retrospective nature of this work, we did not assess postoperative delirium, of interest because general anesthesia, compared to its avoidance, is associated with increased delirium in older patient populations (28,29). Other limitations include

the lack of disease specific survival, recurrence free survival, or distance to margin. These variables were not included in the institutional or STS database and were not available for this study. It is possible that despite similar overall 3-year survival, these variables differ significantly in patients receiving non-intubated thoracoscopic surgery and that differences in survival would become more apparent at 5 or 10-year follow-up.