

## Can The Advantages Of Video Assisted Thoracoscopic Lobectomy Be Reproduced In A Low Volume Center?

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### Background:

Video assisted thoracoscopic surgery (VATS) has become the recommended approach for treatment of resectable lung cancer. However, no large randomized clinical trial has been conducted formally comparing surgical resections completed by VATS to those done by open thoracotomy (OT) in low volume centers. The current study sought to assess differences in recurrence-free survival (RFS), overall survival (OS), positive margins and postoperative length of stay (LOS) between VATS and OT lobectomies in our center.

### Method:

A single institution retrospective chart review from May 2005 through May 2015 was conducted. All patients diagnosed with stage I through III lung cancer who underwent surgical resection were selected. Patient and tumor characteristics recorded included age at diagnosis, sex, tobacco use, tumor location (side and lobe), stage, size and receipt of chemotherapy or radiotherapy. Chi-square and Wilcoxon-Mann-Whitney tests were used to compare demographics, tumor characteristics and LOS. Multiple logistic and Cox regression analyses were used to compute relative risk (RR) for positive margins and mortality hazard ratios along with 95 percent confidence intervals (95%CI), respectively.

### Results:

Of the 235 patients, 101 subjects had VATS while OT was performed in 134 patients. Age at diagnosis, sex, tobacco use, tumor location, and size were comparable for VATS and OT. No significant difference was observed in the relative risk of positive margins for VATS versus OT, RR = 0.56 (95%CI = 0.26, 1.05). However, VATS had shorter median LOS compared to OT (4 vs. 6 days, respectively), p = 0.002. A comparison of VATS versus OT showed no significant difference in the risk of recurrence, HR = 1.21 (95%CI = 0.74, 2.00), or death, HR = 1.34 (95%CI = 0.88, 2.06), in the intent-to-treat population. Similarly, no significant differences in recurrence or mortality risk were observed between VATS versus OT for analyses conducted separately for each cancer stage group or those limited to patients with negative margins.

**Conclusion:**

Our study indicates that compared to OT, VATS leads to shorter LOS while achieving comparable margins status, recurrence-free and overall survival regardless of tumor stage at diagnosis.

**Key words:** video assisted thoracic surgery, open thoracotomy, recurrence-free survival, overall survival, positive margins, postoperative length of stay.

## INTRODUCTION:

Surgical resection remains the mainstay of treatment in resectable lung cancers. The introduction of video assisted thoracoscopic surgery (VATS) in 1994 [1] sparked interest in minimally invasive tumor resection. VATS has also been shown to have fewer postoperative complications [2] and has been associated with decreased postoperative pain and increased quality of life compared to OT [3]. Several studies have compared these two approaches indirectly, but no randomized controlled trial has investigated the long-term effect on outcomes. We sought to investigate the long-term disease-free survival and overall survival of patients with lung cancer undergoing lung resection by OT or VATS for resectable stage lung cancer.

## PATIENTS AND METHODS:

### *Surgical Methods:*

VATS lung resections were performed via a three-port incision technique including a 4-centimeter anterior axillary working port. The specimens were removed via the working port. Rib spreading was not required. A hilar dissection proceeding from anterior to posterior was performed for lobectomies. For OT resections, a standard posterolateral thoracotomy was used. Generally, bulky tumors, inability to tolerate one lung ventilation, dense adhesions, en bloc chest wall resections, sleeve resections, neoadjuvant radiation therapy, or intraoperative complications were reasons for selecting an OT approach or for requiring a conversion from VATS to OT.

### *Study population:*

Records for patients diagnosed with stage I through III resectable lung cancer treated at Loma Linda University Medical Center from May 2005 through May 2015 were retrieved through a retrospective chart review. Patients were subsequently divided into video assisted thoracoscopic surgery (VATS) and open thoracotomy (OT) groups.

### *Study outcomes:*

Recurrence-free survival was the primary outcome and overall survival was the secondary outcome. Survival was calculated from the date of surgery to the date of recurrence diagnosis/death or end of study follow-up (May 2016).

### *Study covariates:*

Patient and tumor characteristics included age at diagnosis, sex, tobacco use, tumor location (side and lobe), stage, size and type of the treatments including chemotherapy or radiotherapy.

*Statistical analyses:*

Tumor and demographic characteristics were compared using Chi-square and Wilcoxon-Mann-Whitney tests. Purposeful variable selection approach was used to identify covariates that were included in the final models. A covariate-adjusted Cox proportional hazards model was used to compare recurrence-free and overall survival between patients treated with VATS and those treated with OT. Profile likelihood was used to estimate 95 percent confidence intervals. Proportionality was assessed using Schoenfeld residuals correlations and log-log survival plots. All tests were conducted using R software. R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>.

**RESULTS:***Study population description:*

From May 2005 through May 2015, 235 patients were diagnosed with stage I through III lung cancer. Of those, 134 and 101 patients received OT and VATS, respectively (Table 1). Median age at surgery (with interquartile ranges, IQR) was similar for the two groups, OT 69 (IQR = 61, 77) and VATS 70 (IQR = 63,76),  $p = 0.48$ . Similarly, no difference in gender distribution was observed,  $p = 0.92$ . Both VATS and OT had a higher proportion of tumors located in the right lung, 62 (61.39%) and 78 (58.21%) respectively,  $p = 0.31$ . Additionally, more than half of all tumors were located in the upper lobe with a slightly higher proportion seen for OT [78 (57.58%)] than VATS [53 (52.48%)],  $p = 0.02$ . In contrast, a higher proportion of stage I cancers were treated by VATS versus OT,  $p = 0.02$ . There was no significant difference in median tumor size [3 (IQR= 2, 5) vs. 3 (IQR = 2, 4),  $p = 0.41$ ] or percentage of tumors with negative margins [104 (89.66%) vs. 89 (95.70%),  $p = 0.13$ ] between OT and VATS, respectively. Compared to VATS, a higher proportion of OT patients received chemotherapy [38 (28.36%) vs. 13 (12.87%),  $p = 0.02$ ] and radiotherapy [30 (22.39%) vs. 4 (3.96%),  $p <0.001$ ].

*Recurrence-free and overall survival:*

No significant differences in recurrence-free survival (Figure 1,  $p = 0.23$ ) or overall survival (Figure 2,  $p = 0.68$ ) were observed between VATS versus OT in the Kaplan-Meier survival curves. After adjusting for covariates, the Cox regression models (Table 2 and Table 3), show no difference in recurrence-free survival, HR = 1.26 (95%CI = 0.73, 2.19), or overall survival, HR = 1.34 (95%CI = 0.85, 2.10), between VATS and OT.

*Length of stay (LOS):*

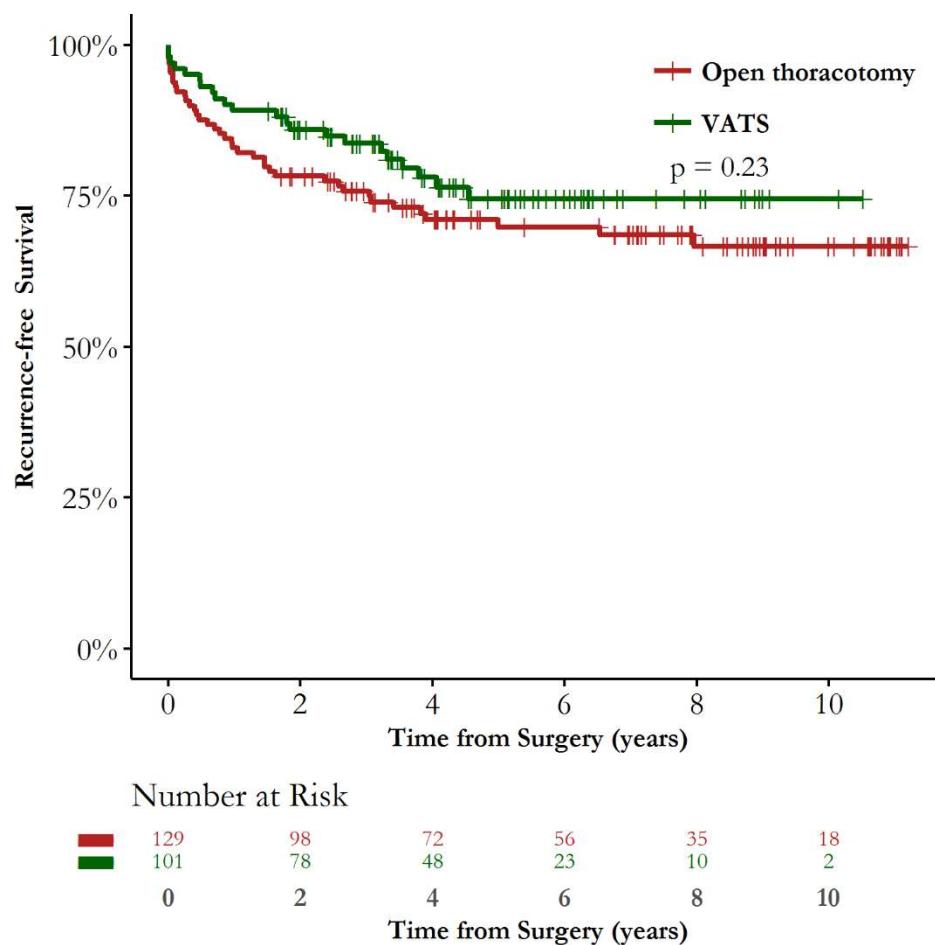
The median LOS was 2 days shorter among patients treated with VATS compared to those treated with OT [4 (3, 6) vs. 6 (4, 7),  $p = 0.002$ ], Figure 3.

Table 1. Patients' characteristics by type of procedure

Patients characteristics	Open thoracotomy (n = 134)	VATS (n = 101)	p-value
Age at diagnosis <sup>†</sup>	69 (61-77)	70 (63-76)	0.48
Sex			0.92
Male	50 (37.31%)	37 (36.63%)	
Female	84 (62.69%)	64 (63.37%)	
Side			0.31
Left	53 (39.55%)	39 (38.61%)	
Right	78 (58.21%)	62 (61.39%)	
Bilateral/unknown	3 (2.24%)		
Lobe			0.02
Lower	33 (25.00%)	40 (39.60%)	
Middle	10 (7.58%)	6 (5.94%)	
Upper	76 (57.58%)	53 (52.48%)	
Bilateral/unknown	13 (9.85%)	2 (1.98%)	
Stage <sup>†</sup>			0.02
1	62 (46.27%)	66 (65.35%)	
2	33 (24.63%)	20 (19.80%)	
3	30 (22.39%)	13 (12.87%)	
Unknown	9 (6.72%)	2 (1.98%)	
Size <sup>‡</sup>	3 (2-5)	3 (2-4)	0.41
Margin status			0.13
Negative	104 (89.66%)	89 (95.70%)	
Positive	12 (10.34%)	4 (4.30%)	
Unknown	18 (13.43%)	8 (7.92%)	
Chemotherapy			0.02
No	85 (63.43%)	80 (79.21%)	
Yes	38 (28.36%)	13 (12.87%)	
Unknown	11 (8.21%)	8 (7.92%)	
Radiotherapy			<0.001
No	99 (73.88%)	97 (96.04%)	
Yes	30 (22.39%)	4 (3.96%)	
Unknown	5 (3.73%)		
Postoperative length of stay	6 (4-7)	4 (3-6)	0.002

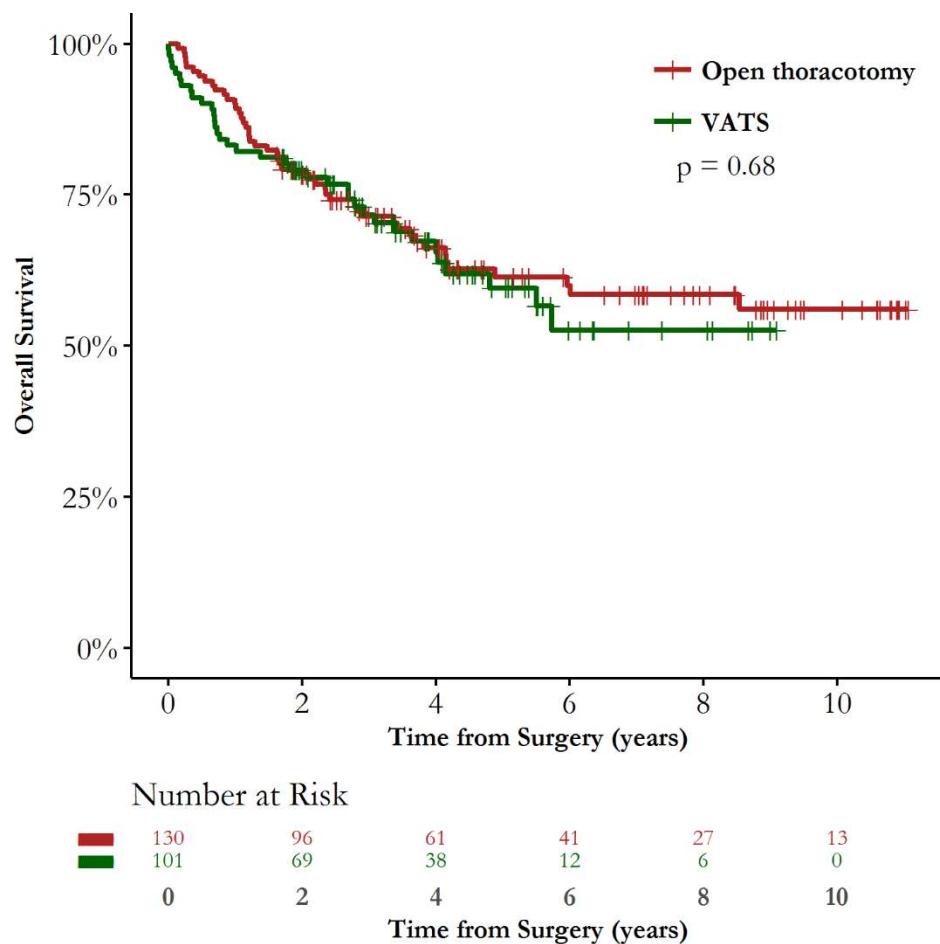
<sup>†</sup>Median with interquartile range (IQR); <sup>‡</sup> Pathological stage; Abbreviations: VATS, video assisted thoracoscopic surgery

Figure 1. Kaplan-Meier survival curves for recurrence-free survival



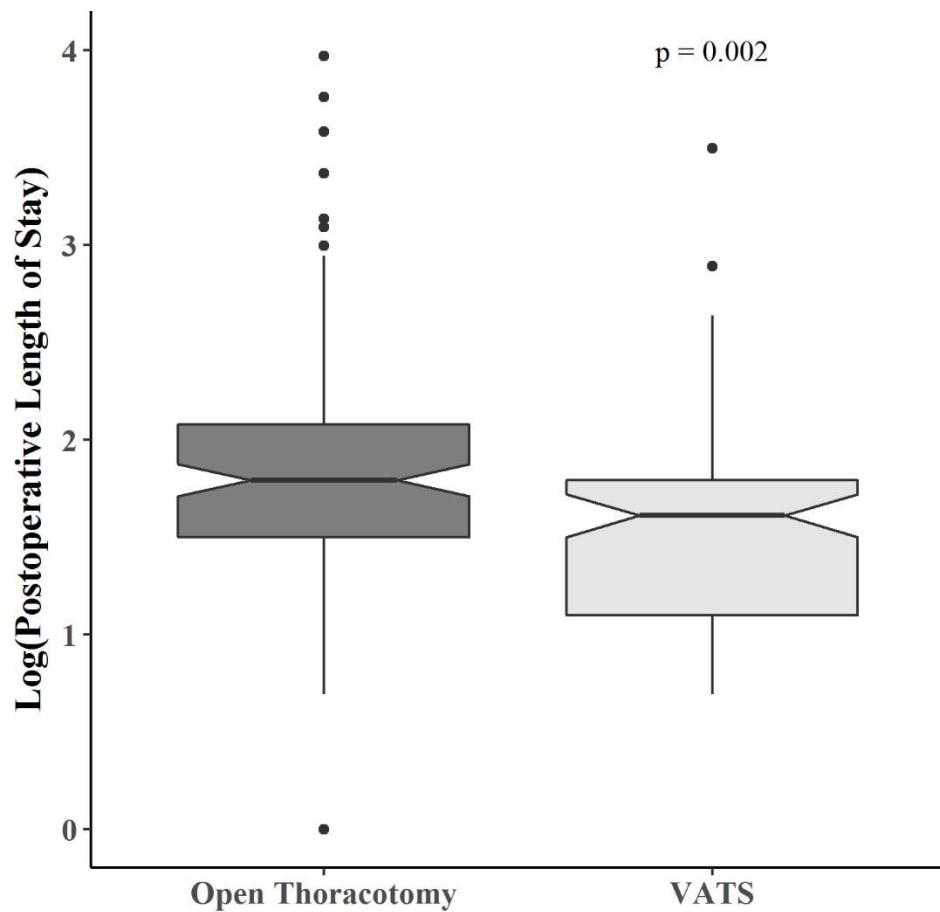
Abbreviations: VATS, video assisted thoracoscopic surgery

Figure 2. Kaplan-Meier survival curves for overall survival



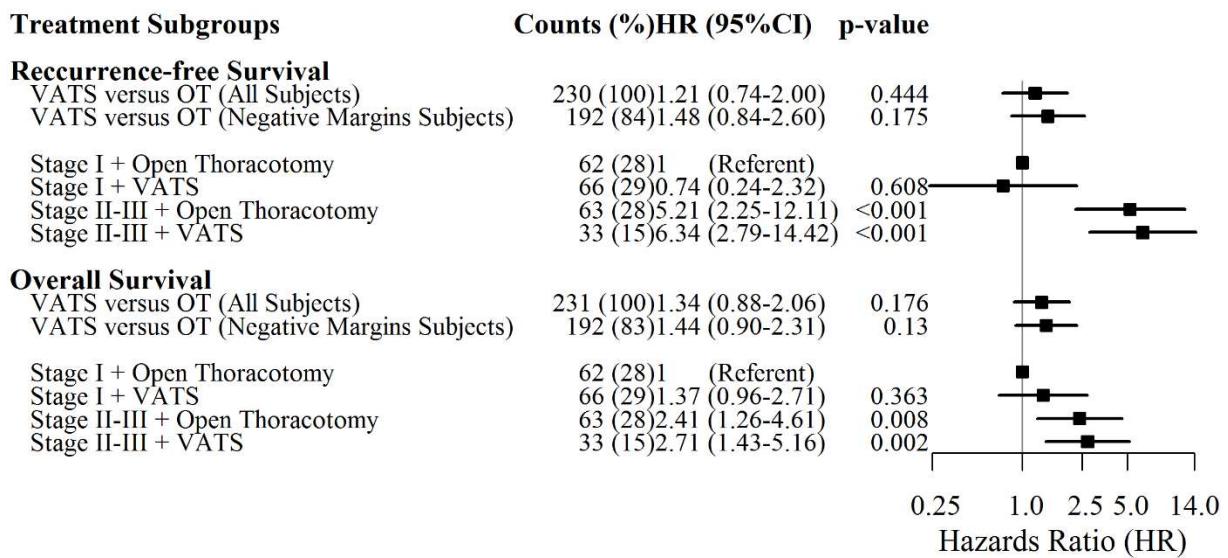
Abbreviations: VATS, video assisted thoracoscopic surgery

Figure 3. Postoperative length of stay by type of procedure.



Abbreviations: VATS, video assisted thoracoscopic surgery

Figure 4. Forest plot for various treatment subgroups.



Abbreviations: VATS, video assisted thoracoscopic surgery; OT, open thoracotomy; HR, hazard ratio; CI, confidence interval

Table 2. Covariate-adjusted Cox regression recurrence hazards ratios with 95 percent confidence interval (95%CI)

Patients characteristics	HR (95%CI)
Procedure	
Open thoracotomy	1
VATS	1.26 (0.73, 2.19)
Age	1.10 (0.90, 1.35)
Stage	
0-1	1
2	5.71 (2.73, 11.93)
3	9.81 (4.87, 19.78)
Unknown	3.18 (0.86, 11.81)
Margin status	
Negative	1
Positive	2.21 (0.92, 5.34)
Unknown	2.21 (1.12, 4.38)

Abbreviations: VATS, video assisted thoracoscopic surgery; HR, hazard ratio; CI, confidence interval

Table 3. Covariate-adjusted Cox regression mortality hazards ratios with 95 percent confidence interval (95%CI)

Patients characteristics	HR (95%CI)
Procedure	
Open	1
thoracotomy	
VATS	1.34 (0.85, 2.10)
Age	1.36 (1.11, 1.68)
Stage	
0-1	1
2	1.82 (1.03, 3.19)
3	3.25 (1.90, 5.55)
Unknown	3.21 (1.30, 7.89)
Margin status	
Negative	1
Positive	2.12 (1.04, 4.32)
Unknown	1.10 (0.54, 2.25)

Abbreviations: VATS, video assisted thoracoscopic surgery; HR, hazard ratio; CI, confidence interval

TABLE 4

Author	N = total pts	Shorter LOS VATS vs. OT	LOS p- value	DFS p-value	OS p-value	DFS / OS years
Higuchi 2015[4]	N = 160  114 VATS  46 OT			No difference  p=0.27	No difference  p=0.55	5
Jung 2015[5]	Propensity score matching 88 per group	VATS  2 days	p<0.05	No difference  p=0.63	No difference  p=0.27	3
Nwogu 2015[6]	Propensity score matching 175 per group	VATS	p<0.05  p=0.35	No difference  p=0.35	No difference  p=0.24	5
Erus 2014[7]	N = 55  25 VATS  30 OT	VATS	p<0.05			
Paul 2014[8]	Propensity score matching 1195 per group			No difference  p=0.46	No difference  p=0.55	3
Kuritzky 2013[9]	80  40 VATS  40 OT			No difference  p=0.44 (IA)  p=0.48 (IB)	No difference  p=0.15 (IA)  p=0.20 (IB)	5
Paul 2013[10]	N = 68350  10554 VATS	VATS	p<0.001			

	57796 OT	2 days				
Papiashvili 2012[11]	N = 389  63 VATS  326 OT	VATS	p<0.001			
Ramos 2012[12]	N = 287  98 VATS  189 OT	VATS	p<0.001			
Park 2011[13]	N = 529  156 VATS  373 OT	VATS  2 days	p<0.05  p=0.43	No difference  p=0.76	No difference	3
Scott 2010[14]	N = 136  74 VATS  62 OT	VATS	p<0.001			
Flores 2009[15]	N = 741  398 VATS  343 OT	VATS  2 days	p<0.001		No difference  p=0.12	5

Abbreviations: LOS, length of stay; VATS, video assisted thoracoscopic surgery; OT, open thoracotomy; DFS, disease-free survival; OS, overall survival

## DISCUSSION:

VATS was performed initially in the 1990's. Since then there have been multiple studies advocating the superiority of VATS over conventional OT in terms of short and long-term side effects as well as hospital length of stay [16-18]. However, some surgeons still prefer OT over VATS. In fact, according the Society of Thoracic Surgeons General Thoracic Surgery Database, the percentage of VATS lobectomies performed in the United States are performed by VATS [19, 20] at high volume centers. One explanation for this may be due to the controversial results between several comparative studies in this field [21] since during the resectable years of its development, there was a lack of a clear definition of VATS between thoracic surgeons [22-24]. The goal of this study was to evaluate the outcomes in a low volume university setting over the last 10-year period, 2005-2015, where VATS was initiated in 2009.

Our study, like other similar articles (Table 4), did not capture any statistically significant findings between VATS and OT groups in terms of recurrence-free survival and overall survival ( $p = 0.23$  and  $p = 0.68$ , respectively). Also similarly, VATS lobectomy was associated with shorter length of stay and non-inferior long-term survival when compared with OT lobectomy. These results support previous findings from smaller single- and multi-institutional studies that suggest that VATS does not compromise oncologic outcomes when used for resectable stage lung cancer [26]. Over the last 15 years, there have been multiple studies (Table 4), which have compared VATS to OT. As noted in the table, these studies consistently showed decreased length of stay and no difference in three to five-year disease free or overall survival. Our data is consistent with other data sets retrospectively comparing VATS and OT for resection of resectable non-small cell lung cancer [8, 26].

VATS lobectomy seems to have similar oncological outcomes as OT lobectomy. In VATS lobectomy the incisions are smaller and rib spreading is not performed. These patients are likely to have an overall faster recovery and may tolerate adjuvant chemotherapy better. They are also likely to have less post-operative complications and hence more likely to start and complete adjuvant chemotherapy in a timely fashion possibly leading to improved long-term outcome [15, 27].

Our study has several limitations. First and most importantly, our study is a single institution retrospective study. Specific information on patient selection criteria as well as differences in surgeons' experience is lacking and may have led to selection bias. VATS, like all newly developed minimally invasive surgical techniques, requires skills and experience in which not all surgeons have been trained.

**Conclusion:**

Our study suggests that patients undergoing VATS lobectomy in a low-medium sized university setting have comparable long-term and short-term outcomes compared to national data in terms of disease-free survival, overall survival, and shorter length of stays. This suggests referrals to high volume centers for lobectomy is not required as even low-medium volume centers with board certified thoracic surgeons trained in VATS can achieve equivalent outcomes.

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