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The association of nodal upstaging with surgical approach and its impact on long-term survival after resection of non-small-cell lung cancer

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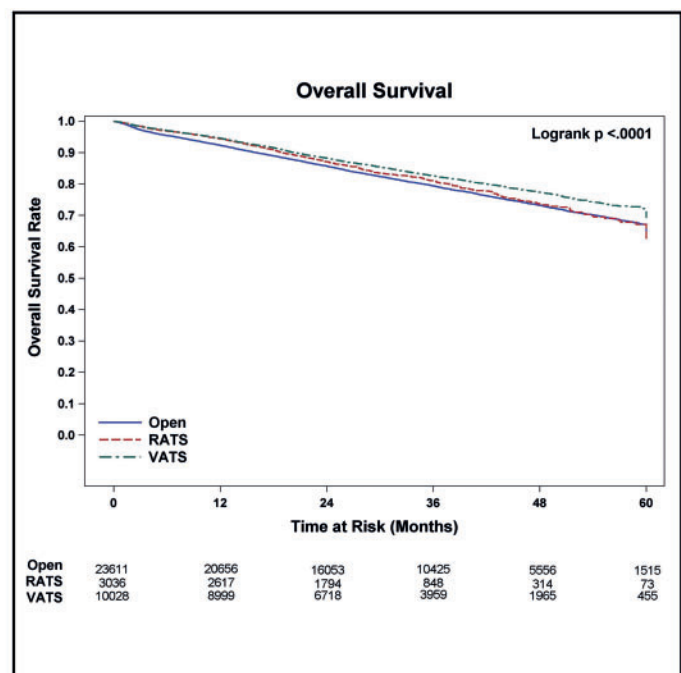
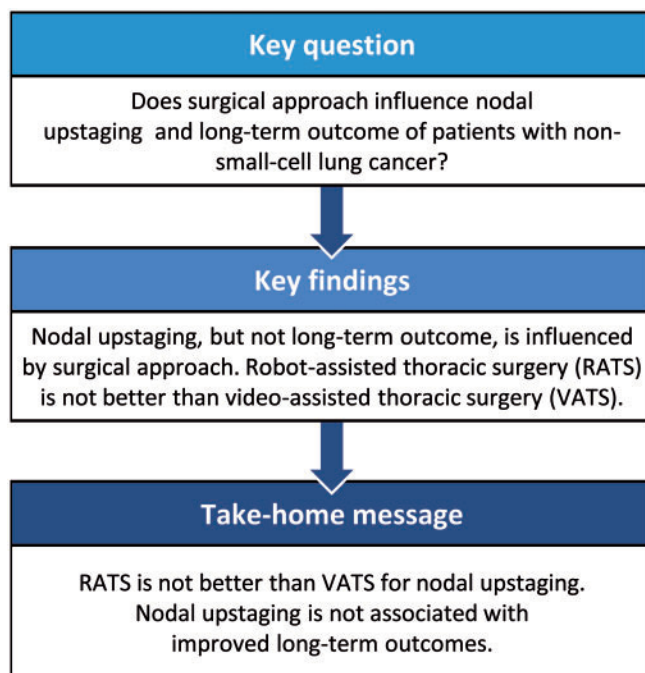
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Abstract

OBJECTIVES: Proponents of open thoracotomy (OPEN) and robot-assisted thoracic surgery (RATS) claim its oncological superiority over video-assisted thoracic surgery (VATS) in terms of the accuracy of lymph node staging.

METHODS: The National Cancer Database was queried for patients with non-small-cell lung cancer (NSCLC) undergoing lobectomy without neoadjuvant therapy from 2010 to 2014. Nodal upstaging rates were compared using a surgical approach. Overall survival adjusted for confounding variables was examined using the Cox proportional hazards model.

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RESULTS: A total of 64 676 patients fulfilled the selection criteria. The number of patients who underwent lobectomy by RATS, VATS and OPEN approaches was 5470 (8.5%), 17 545 (27.1%) and 41 661 (64.4%), respectively. The mean number of lymph nodes examined for each of these approaches was 10.9, 11.3 and 10 ($P < 0.01$) and upstaging rates were 11.2%, 11.7% and 12.6% ($P < 0.01$), respectively. For patients with clinical stage I disease ($N = 46\ 826$; RATS = 4338, VATS = 13 416 and OPEN = 29 072), the mean lymph nodes examined were 10.6, 10.8 and 9.4 ($P < 0.01$), and upstaging rates were 10.8%, 11.1% and 12.1% ($P < 0.01$), respectively. A multivariable analysis suggested an association with improved survival with RATS and VATS compared with OPEN surgery [hazard ratio (HR) = 0.89 and 0.89, respectively; $P < 0.01$] for patients with all stages. In stage I disease, VATS but not RATS was associated with increased overall survival compared with the OPEN approach (HR = 0.81; $P < 0.01$).

CONCLUSIONS: RATS lobectomy is not superior to VATS lobectomy with respect to lymph node yield or upstaging of NSCLC. Increased nodal upstaging by the OPEN approach does not confer a survival advantage in any stage of NSCLC and may be associated with decreased overall survival.

Keywords: Lung cancer • Mediastinal staging • Video-assisted thoracic surgery

ABBREVIATIONS

HR	Hazard ratio
LNE	Lymph nodes examined
NCDB	National Cancer Database
NSCLC	Non-small-cell lung cancer
OPEN	Open thoracotomy
OS	Overall survival
PS	Propensity score
RATS	Robot-assisted thoracic surgery
VATS	Video-assisted thoracic surgery

INTRODUCTION

Accurate assessment of lymph nodes for the presence of the metastatic disease is essential for effective treatment planning and prognostication for patients diagnosed with non-small-cell lung carcinoma (NSCLC). An equally critical component of surgical resection of the primary tumour is an intraoperative evaluation of N1 and N2 lymph nodes, regardless of negative preoperative invasive mediastinal staging results. Debate exists regarding the need for full lymph node dissection versus lymph node sampling, and whether surgical approach affects the results. Retrospective reports have shown improved survival of patients undergoing full lymph node dissection [1–4], yet results from ACOSOG Z0030 demonstrated no survival benefit for patients undergoing mediastinal lymph node dissection compared with those who underwent systematic lymph node sampling [5]. Variation undoubtedly exists in how lymph nodes are removed, assessed and reported. Unfortunately, sometimes lymph node sampling is not performed at all [6].

The impact of the surgical approach on the effectiveness of lymph node assessment is not clear. Since its introduction over 25 years ago, video-assisted thoracic surgery (VATS) lobectomy has become a well-accepted approach for the resection of early-stage NSCLC, and increasingly, more for advanced stages of the disease and complex tumour pathology. Despite evidence suggesting comparable oncologic outcomes for thoracoscopic approaches to lobectomy [6–8], advocates for traditional open approaches, as well as newer minimally invasive approaches using robotic platforms, claim superiority in the accuracy and thoroughness of lymph node assessment. Studies comparing traditional open approaches with VATS approaches have shown

VATS to have a lower number of lymph nodes evaluated [9] and decreased rates of upstaging compared with thoracotomy [9–11].

As VATS lobectomy gained more widespread acceptance, questions regarding oncologic soundness diminished. Reports showed that the number of lymph nodes dissected by VATS approaches equalled that of traditional open approaches [12–14], though rates of nodal upstaging lagged behind in certain cases. As institutional and surgeon experience matured, the effectiveness of lymph node staging was shown to improve [15]. The introduction of robotic platforms into minimally invasive thoracic surgery approaches improved 3-dimensional viewing, and claims of superiority in lymph node sampling for lobectomy. Single institution reports demonstrating superior lymph node sampling compared with VATS approaches began to surface suggesting the need for additional studies with larger cohorts of patients [16].

Herein, we report results using a large multi-institutional database to retrospectively examine the rates of nodal upstaging associated with multiple surgical approaches for lobectomy for NSCLC.

METHODS

Data source/patient selection criteria

The National Cancer Database (NCDB) was used as the data source for this study. This large, nationwide database captures incident cancer cases diagnosed or treated at over 1500 Commission on Cancer-accredited facilities in the USA (ACS). The NCDB captures ~70% of all newly diagnosed cancer cases yearly. The American College of Surgeons and the Commission on Cancer are not responsible for the statistical methodology employed, or the conclusions drawn by investigators analysing the de-identified data received in the form of a Participant User File document.

This research study was deemed exempt by the Roswell Park Institutional Review Board. The selection criteria used to finalize the patient study population are listed in Table 1. Nodal upstaging rates in the whole population and by surgical approach were compared. The approaches examined included open thoracotomy (OPEN), VATS and robot-assisted thoracic surgery (RATS). A subset analysis of patients with stage I disease was performed. Variables included in the NCDB that are able to be analysed include patient age, race, gender, grade, histology, analytic stage, Charlson–Deyo Score, number of lymph nodes examined (LNE), the extent of

Table 1: Criteria for selecting the study population from the NCDB database

Selection criteria	Patient number
All patients with NSCLC from 2010 to 2014	122 950
Patients in whom this cancer was the first	84 832
Patients with lobectomy without neoadjuvant therapy	79 185
Exclude patients with unknown surgical approach	73 470
Exclude stage 0, unknown stage and occult cancer	64 676

NCDB: National Cancer Database; NSCLC: non-small-cell lung cancer.

resection (R0, R1 or R2) and the year of diagnosis. The analytic stage refers to the stage coded using the AJCC Cancer Staging Manual edition in use during the year in which the case was diagnosed. Continuous variables were summarized with means, medians and standard deviations. Frequencies and cumulative frequencies were used to summarize categorical data.

Statistical analyses

Associations between potential covariates and treatment were analysed using the Pearson χ^2 test for categorical variables and Wilcoxon Rank Sum test for continuous variables. The primary endpoints of this study were the lymph node yield and nodal upstaging rate based on the surgical approach. Secondary outcome variables analysed included 30-day and 90-day mortality, as well as overall survival (OS). Univariable and multivariable logistic models were used to assess the effect of surgical approach on 30-day and 90-day mortality. Model results were summarized using estimates and 95% confidence limits for the odds ratio. Univariable and multivariable proportional hazards models were used to assess the effect of surgical approach on OS. The relative prognosis was summarized using estimates and 95% confidence limits for the hazard ratio (HR). Unadjusted differences in overall mortality based on surgical approach are shown using a Kaplan-Meier method. The log-rank test was used for comparison of survival distributions.

Propensity-weighted analyses

For confirmation of the multivariable results, propensity score (PS) methods were used to adjust for baseline covariate imbalances between the surgical approaches. The PS model was specified in advance and included fixed effects for sex (male/female), Charlson-Deyo Score (0/1/2), race (black/white/other), radiation (none/adjunct/unknown), grade (I and II/III and IV/unknown), histology (adeno/squam/others), age at dx (continuous), number of LNE (continuous) and stage (TNM_CLIN_STAGE_GROUP 1, 2, 3, 4).

The PS was estimated with a multivariable logistic regression model for the probability of any surgical approach. Three weighted models were run to test for a difference between all three surgical approaches. For each pairing of surgical approaches, PS adjustment was done with an inverse probability of treatment weight. The whole data set (all stages) was analysed as well as the subset of patients with stage I disease. In total 6 propensity weight analyses were performed. All analyses were conducted using SAS v9.4 (Cary, NC, USA) at a significance level of 0.05.

RESULTS

During this time period, 64 676 patients fulfilled the selection criteria and were included in the study. Patient descriptive characteristics for the entire study population are given in Table 2. The median age of the cohort was 67 years. The number of patients who underwent lobectomy by RATS, VATS and OPEN approaches was 5470 (8.5%), 17 545 (27.1%) and 41 661 (64.4%), respectively. The number of events (deaths) in this cohort during follow-up was 12 205. The mean number of LNE for each of these approaches was 10.9, 11.3 and 10 ($P < 0.01$), and upstaging rates were 11.2%, 11.7% and 12.6% ($P < 0.01$), respectively. For the subset of patients with clinical stage I disease ($N = 46 826$; RATS = 4338, VATS = 13 416 and OPEN = 29 072), mean LNE were 10.6, 10.8 and 9.4 ($P < 0.01$), and upstaging rates were 10.8%, 11.1% and 12.1% ($P < 0.01$), respectively (Table 3). The number of events (deaths) in this cohort during follow-up was 7132. The univariate analysis examining the association between surgical approach and OS in the total population and stage I are shown in Figs. 1 and 2 respectively. Lymph node upstaging rates were higher in academic and integrated network cancer programmes when compared to community cancer programmes (Table 4). Lymph node upstaging was also associated with a greater number of LNE (12.5 vs 10.3; $P < 0.001$). The multivariable analysis suggested an association with improved survival of RATS and VATS when compared to OPEN surgery (HR = 0.89 and 0.89, respectively; $P < 0.01$) for patients with all stages (Table 5). For patients with stage I disease, VATS, but not RATS was associated with the increased OS when compared with OPEN approach (HR = 0.81; $P < 0.01$).

Propensity-weighted analyses

Propensity-weighted analyses for all patients comparing OS based on surgical approach revealed no differences in OS between RATS when compared to VATS (log-rank $P = 0.802$), but statistically improved survival when comparing RATS and VATS to OPEN (log-rank $P = 0.0074$ and < 0.0001). For the subset of patients with stage I disease, the propensity-weighted analysis revealed improved OS only for VATS compared to OPEN (log-rank $P < 0.0001$). No differences were noted when comparing RATS to VATS or RATS to OPEN (log-rank $P = 0.0651$ and $P = 0.3980$).

Additionally, propensity-weighted analyses for 30- and 90-day mortality for all stages revealed statistically improved outcomes for both VATS and RATS compared to OPEN (30-day mortality $P < 0.001$; $P < 0.001$ and 90-day mortality $P < 0.001$; $P < 0.001$). No difference was noted when RATS is compared with VATS ($P = 0.432$ for 30-day mortality and $P = 0.530$ for 90-day mortality). For stage I patients, similar results were noted comparing RATS and VATS to OPEN, and again, no difference when comparing RATS to VATS.

DISCUSSION

Our findings from this analysis utilizing a large, multi-institution database suggest that robotic-assisted (RATS) approaches to lobectomy are not superior to thoracoscopic (VATS) approaches for lymph node evaluation at the time of lobectomy for NSCLC. Consistent with previous reports [9–11], a higher rate of nodal

Table 2: Comparison of patients with all stages undergoing lobectomy by RATS, VATS and OPEN

Variables	Groups	RATS	VATS	OPEN	P-value
Overall count, N (%)		5470 (8.5)	17 545 (27.1)	41 661 (64.4)	
Age (years), mean (SD)		66.8 (9.8)	66.6 (10.2)	66.3 (10.3)	0.001
Gender	Male (%)	2421 (44.3)	7696 (43.9)	19 895 (47.8)	<0.01
Race, N (%)	White	4700 (85.9)	15 235 (86.8)	36 216 (86.9)	<0.01
	Black	532 (9.7)	1446 (8.2)	3833 (9.2)	
	Other	238 (4.4)	864 (4.9)	1612 (3.9)	
Histology, N (%)	Squamous	1214 (22.2)	3877 (22.1)	10 998 (26.4)	<0.01
	Adeno	3880 (70.9)	12 372 (70.5)	27 163 (65.2)	
	Others	376 (6.9)	1296 (7.4)	3500 (8.4)	
Stage, N (%)	I	4389 (80.4)	13 678 (78.2)	29 623 (71.3)	<0.01
	II	730 (13.4)	2599 (14.9)	7998 (19.2)	
	III	267 (4.9)	945 (5.4)	3137 (7.5)	
	IV	70 (1.3)	265 (1.5)	813 (2.0)	
Grade, N (%)	I/II	3443 (62.9)	10 747 (61.3)	24 685 (59.3)	<0.01
	III/IV	1677 (30.7)	5569 (31.7)	14 435 (34.6)	
	Unknown	350 (6.4)	1229 (7.0)	2541 (6.1)	
Conversion, N (%)		515 (9.4)	2878 (16.4)		<0.01
CDS, N (%)	0	2674 (48.9)	9035 (51.5)	21 045 (50.5)	<0.01
	1	2018 (36.9)	6153 (35.1)	14 635 (35.1)	
	2	778 (14.2)	2357 (13.4)	5981 (14.4)	
LNE, mean (SD)		10.9 (7.9)	11.3 (8.9)	10 (7.5)	<0.01
N stage, N (%)	Upstaged	595 (11.2)	1967 (11.7)	4960 (12.6)	<0.01
	Downstaged	156 (2.9)	588 (3.5)	1631 (4.1)	
	Same	4550 (85.8)	14 220 (79.4)	32 869 (83.3)	
30/90-Day mortality (%)		1.8/3.2	1.8/3.1	2.4/4.6	<0.01
LOS, median (days)		4	5	6	<0.01
5-Year survival (HR)		0.65 (0.61–0.68)	0.66 (0.65–0.67)	0.60 (0.60–0.61)	<0.01

CDS: Charlson–Deyo Score; HR: hazard ratio; LNE: lymph nodes examined; LOS: length of stay; OPEN: open thoracotomy; RATS: robot-assisted thoracic surgery; SD: standard deviation; VATS: video-assisted thoracic surgery.

Table 3: Comparison of patients with stage I undergoing lobectomy by RATS, VATS and OPEN

Variables	Groups	RATS	VATS	OPEN	P-value
Overall count, N (%)		4338 (9.3)	13 416 (28.7)	29 072 (62.1)	
Age (years), mean (SD)		66.7 (9.8)	66.6 (10.2)	66.4 (10.3)	0.001
Gender	Male (%)	1864 (43.0)	5597 (41.7)	13 152 (45.2)	<0.01
Race, N (%)	White	3731 (86.0)	11 690 (87.1)	25 378 (87.3)	<0.01
	Black	413 (9.5)	1053 (7.8)	2580 (8.9)	
	Other	194 (4.5)	673 (5.0)	1114 (3.8)	
Histology, N (%)	Squamous	954 (22.0)	2724 (20.3)	6967 (24.0)	<0.01
	Adeno	3108 (71.6)	9822 (73.2)	19 986 (68.7)	
	Others	276 (6.4)	870 (6.5)	2119 (7.3)	
Grade, N (%)	I/II	2843 (65.5)	8704 (64.9)	18 524 (63.7)	<0.01
	III/IV	1222 (28.2)	3771 (28.1)	8760 (30.1)	
	Unknown	273 (6.3)	941 (7.0)	1788 (6.2)	
Conversion, N (%)		389 (9.0)	2030 (15.1)		<0.01
CDS, N (%)	0	2050 (47.3)	6921 (51.6)	14 584 (50.2)	<0.01
	1	1647 (38.0)	4697 (35.0)	10 290 (35.4)	
	2	641 (14.8)	1798 (13.4)	4198 (14.4)	
LNE, mean (SD)		10.6 (7.4)	10.8 (8.4)	9.4 (7.0)	<0.01
N stage, N (%)	Upstaged	460 (10.8)	1451 (11.1)	3380 (12.1)	<0.01
30/90-Day mortality (%)		1.6/2.6	1.4/2.3	2.1/3.8	<0.01
LOS, median (days)		4	5	6	<0.01
5-Year survival (HR)		0.67 (0.63–0.71)	0.72 (0.71–0.74)	0.67 (0.66–0.68)	<0.01

CDS: Charlson–Deyo Score; HR: hazard ratio; LNE: lymph nodes examined, LOS: length of stay, OPEN: open thoracotomy; RATS: robot-assisted thoracic surgery; SD: standard deviation; VATS: video-assisted thoracic surgery.

upstaging was noted with standard OPEN approaches. However, this did not confer a survival advantage as patients in our overall study population who underwent RATS or VATS had improved survival. The increased rate of upstaging was also seen without

an increase in the number of lymph nodes sampled, as the lymph node yield was statistically higher in the VATS group compared to patients treated with RATS or OPEN approaches. These trends were also seen in patients with clinical stage 1 disease.

In direct contrast to results which report significantly higher lymph node yield with lobectomy via thoracotomy than with VATS lobectomy [10], our analysis showed that patients undergoing VATS had significantly more lymph nodes retrieved through dissection than patients in the RATS or OPEN groups. In these previous studies, the difference was largely due to the improved retrieval of N2 nodes with OPEN [9, 17]. Despite the

statistically significant differences noted in this study, the mean number of lymph nodes harvested in each group ranged from 10 to 11.3 lymph nodes, and given the large patient numbers, are likely not clinically significant. Mean lymph node harvest in previous studies included in the meta-analysis by Zhang ranged from 6.1 up to 31. These numbers may suggest a higher proportion of lymph node ‘sampling’ approaches reported in this study as opposed to full mediastinal lymph node dissection, but data pertaining to the specifics of the surgical lymph node evaluation are not included in the NCDB. Though these average numbers meet the recommendation for minimum number of lymph nodes to be harvested during resection of lung cancer (10 nodes) based on American College of Surgeons Commission on Cancer guidelines (<https://www.facs.org/-/media/files/quality-programs/cancer/ncdb/measure-specs-nscl.ashx?la=en>), they fall short of targets for lymph node harvest at the time of lobectomy put forth in previous reports by Wen *et al.* (recommended 12 lymph nodes) and Liang *et al.* who recommend at least 16 lymph nodes be sampled [18, 19]. Figure 3 depicts the distribution of LNE in all stages and stage I NSCLC in this analysis. The distribution of LNE shows that there is significant room for improvement for this metric in the USA.

Other studies examining whether the surgical approach affects lymph node sampling or dissection in terms of the number of lymph nodes retrieved offer mixed results. An analysis of the patients in the ACOSOG Z0030 database showed no significant difference in the number of lymph nodes retrieved based on approach [14]. Additional studies, including an earlier randomized trial by Kirby *et al.*, also found no difference in the number of lymph nodes sampled for biopsy in patients undergoing lobectomy by VATS versus thoracotomy [12, 13]. One recent study comparing RATS to VATS and OPEN found that the number of lymph node stations that were sampled with RATS was significantly higher than with VATS or thoracotomy [20]. However, they did not report on the total number of individual nodes sampled. While the proposed superior visualization and manoeuvrability afforded by robotic-assisted thoracoscopy may allow for more nodal stations to be accessed, our data suggest that the actual lymph node yield is not significantly different than that achieved with open or VATS approaches.

While it is important to consider how many lymph nodes or lymph node stations each surgical approach allows for assessment for occult metastasis, the clinical importance of examining this tissue is to ensure that the disease is staged properly so that the patients receive the appropriate treatment. Nodal upstaging from clinical stage 1 to pathological stage 2 disease has been

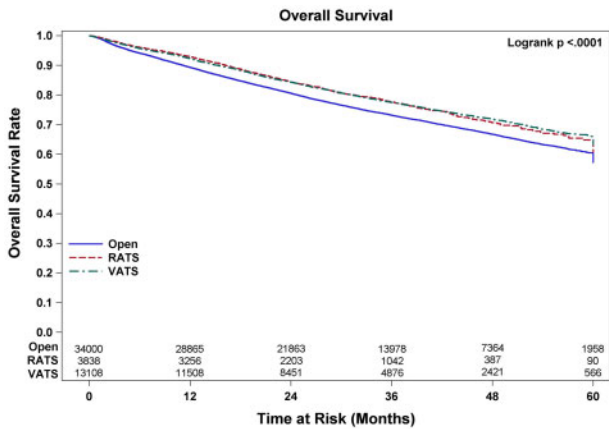


Figure 1: Overall survival of patients undergoing lobectomy for non-small-cell lung cancer. OPEN: open thoracotomy; RATS: robot-assisted thoracic surgery; VATS: video-assisted thoracic surgery.

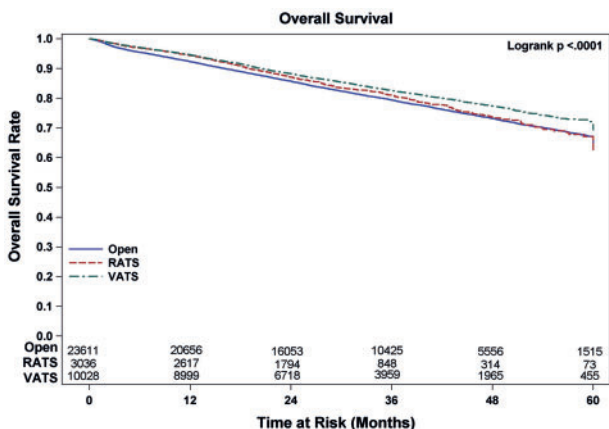


Figure 2: Overall survival of patients undergoing lobectomy for stage I non-small-cell lung cancer. OPEN: open thoracotomy; RATS: robot-assisted thoracic surgery; VATS: video-assisted thoracic surgery.

Table 4: Percentages of nodal upstaging by type of centre

Approach	Community cancer programme	Comprehensive community cancer programme	Academic research programme	Integrated network cancer programme	P-value
All stages					
RATS	10.29	9.67	12.11	12.82	0.03
VATS	9.76	11.27	12.14	12.40	0.12
OPEN	10.93	12.12	13.18	13.93	<0.01
Stage I					
RATS	8.18	9.71	11.31	12.82	0.11
VATS	9.28	10.33	11.81	11.63	0.04
OPEN	10.42	11.54	12.68	13.54	<0.01

All numbers are in percentages.

OPEN: open thoracotomy; RATS: robot-assisted thoracic surgery; VATS: video-assisted thoracic surgery.

Table 5: Univariate and multivariate analyses of variables associated with overall survival

Variables	Reference	Univariate model estimate (95% CI)	Multivariate model estimate (95% CI)
All stages			
N (upstaged)	N (same)	1.92 (1.84–2.01)	Not included in model
N (downstaged)		1.64 (1.52–1.78)	
RATS	Open	0.82 (0.76–0.88)	0.89 (0.83–0.97)
VATS		0.81 (0.77–0.84)	0.89 (0.86–0.93)
Race (black)	Race (white)	0.91 (0.86–0.98)	0.99 (0.93–1.06)
Race (other)		0.72 (0.65–0.80)	0.77 (0.69–0.85)
Grade (III/IV)	Grade (I/II)	1.70 (1.64–1.76)	1.40 (1.34–1.45)
Unknown		0.82 (0.74–0.90)	0.86 (0.78–0.94)
Squamous	Adenocarcinoma	1.61 (1.55–1.68)	1.18 (1.13–1.23)
Histology (others)		1.56 (1.47–1.66)	1.28 (1.20–1.36)
Female	Male	0.60 (0.58–0.63)	0.70 (0.67–0.72)
CDS 1	CDS 0	1.26 (1.21–1.31)	1.18 (1.14–1.23)
CDS 2		1.68 (1.59–1.76)	1.48 (1.41–1.56)
Clinical stage			
II	I	2.01 (1.92–2.09)	1.80 (1.72–1.88)
III		2.61 (2.46–2.76)	2.22 (2.10–2.36)
IV		4.21 (3.83–4.64)	3.92 (3.58–4.30)
LNE		1.00 (1.00–1.01)	1.00 (0.99–1.00)
Age		1.03 (1.03–1.03)	1.03 (1.03–1.04)
Stage I			
N (upstaged)	N (same)	2.16 (2.04–2.29)	Not included in model
RATS	Open	0.93 (0.84–1.02)	0.95 (0.86–1.04)
VATS		0.81 (0.77–0.86)	0.86 (0.82–0.91)
Race (black)	Race (white)	0.90 (0.83–0.99)	1.02 (0.94–1.12)
Race (other)		0.66 (0.57–0.76)	0.74 (0.64–0.85)
Grade (III/IV)	Grade(I/II)	1.69 (1.61–1.77)	1.49 (1.42–1.57)
Unknown		0.70 (0.61–0.79)	0.78 (0.69–0.89)
Squamous	Adenocarcinoma	1.72 (1.64–1.81)	1.24 (1.18–1.31)
Histology (others)		1.49 (1.37–1.62)	1.26 (1.15–1.37)
Female	Male	0.58 (0.55–0.61)	0.66 (0.63–0.69)
CDS 1	CDS 0	1.37 (1.30–1.44)	1.24 (1.18–1.31)
CDS 2		1.91 (1.79–2.03)	1.60 (1.50–1.70)
LNE		1.00 (1.00–1.00)	1.00 (0.99–1.00)
Age		1.04 (1.03–1.04)	1.04 (1.03–1.04)

CDS: Charlson–Deyo Score; CI: confidence interval; LNE: lymph nodes examined; RATS: robot-assisted thoracic surgery; VATS: video-assisted thoracic surgery.

reported to occur in up to 22.6% of NSCLC cases [21] and is an indication for adjuvant chemotherapy [22]. Our study found the OPEN approach to have a higher rate of nodal upstaging even though the number of LNE was less than or equal to the minimally invasive approaches. The reasons for this difference remain unclear, but an explanation may be that more nodal tissue is being removed by traditional OPEN. Unfortunately, the weight or volume of nodal tissue is not a variable that is reported in the NCDB. Another consideration, as has been pointed out previously [10, 11], is that one of the main pitfalls of the majority of studies examining this issue, including the current study, is their retrospective nature and the fact that the reasons behind the surgeons' choices to pursue one surgical approach over the others cannot be ascertained for individual patients. For example, certain characteristics of a tumour beyond its size (central location, airway or vessel involvement) may cause a surgeon to opt for an open approach and pursue a more aggressive lymph node dissection, leading to a higher rate of nodal upstaging. Information reflective of these characteristics is not captured in the data sets used for these studies. The other issue is the perceived importance of lymph node staging. The hypothesis that this impacts the number of LNE is supported by the observation that academic and integrated network programmes show a higher number of LNE irrespective of the surgical approach.

Nonetheless, the increased upstaging we observed with the OPEN approach is in concordance with previous retrospective studies comparing VATS against traditional thoracotomy for patients with stage 1 disease [9–11]. The rates of nodal upstaging in these studies were 10–11.9% for VATS and 14.3–24.6% for thoracotomy, which is similar to our reported rates of 11.1% for VATS and 12.1% for the OPEN approach. Other studies comparing RATS to VATS also found no significant difference in the rates of nodal upstaging between these techniques [16, 23].

When considering surgical options for the treatment of lung cancer, weighing short-term morbidity against the potential for overall long-term survival is critical. While factors such as rates of nodal upstaging certainly affect the long-term survival in patients undergoing resection of NSCLC, there may be other unmeasured factors that can also affect survival. Our results suggest that minimally invasive approaches with VATS or RATS offer survival rates that are comparable to, or at least as safe as the OPEN approach regardless of disease stage. This is in agreement with several previous studies [6–8]. While the overall operative time may be longer than with open approaches, some of the advantages of minimally invasive techniques such as VATS and RATS include comparable intraoperative complication rates, lower postoperative complication rates and hospital length of stay that is about 2 days shorter on average than patients undergoing open resection

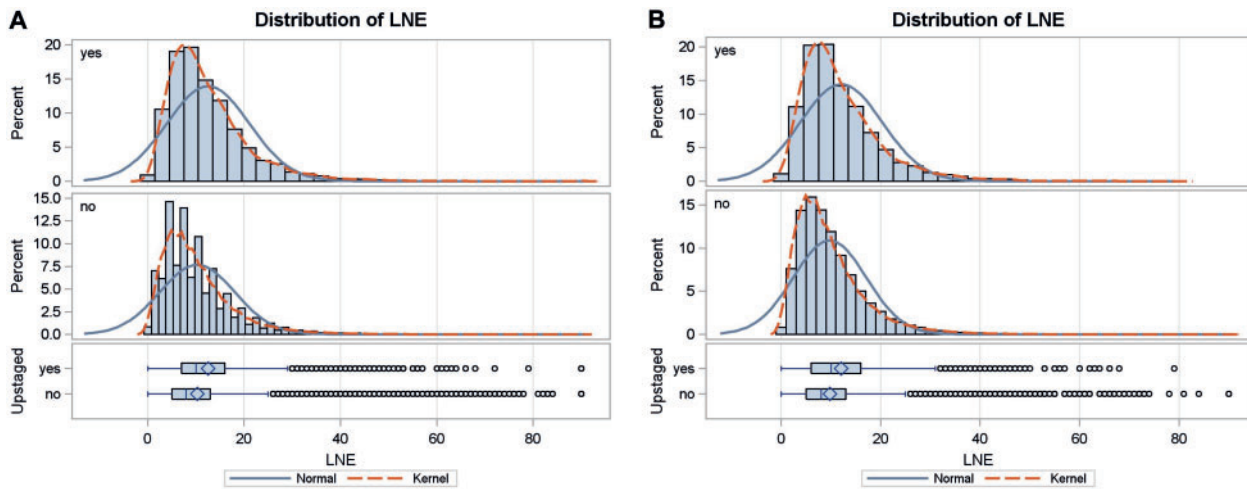


Figure 3: Distribution of LNE in patients with all stages (A) and stage I (B) non-small-cell lung cancer. Both normal distribution and kernel smoothed curves are depicted. LNE: lymph nodes examined.

[12, 14, 24]. Our findings support the assertion that VATS or RATS may be equivalent to, if not superior to, open approaches in the appropriate patient.

Limitations

Limitations of this study include its retrospective nature and the unavailability of important descriptors of lymph node characterization such as volume and mass, which are not reported in the NCDB. Information pertaining to specific lymph node stations assessed is also not available. The overall number of lymph node harvest for each surgical approach reported here is relatively low. Given that the number of lymph nodes resected during lung cancer resection has been shown to impact overall prognosis, the results reported here could be affected by the adequacy of lymph node dissection [18]. There is variation in technique and aggressiveness amongst individual surgeons in performing lymph node dissection or sampling. This is well demonstrated in the meta-analysis by Zhang, which included mostly single-institution studies which had a range of 6.1–31 average lymph nodes harvested. A study in which the mean VATS lymph node harvest was 6.1, compared to the open approach at 7.7, compared to another where VATS harvest was 31 compared to 30 by the open approach, speaks more surgeon variability with the aggressiveness of dissection instead of a surgical approach. Additionally, surgical skill level simply cannot be accounted for in a study of this nature. For example, a highly skilled VATS or robotic surgeon with excellent technique may perform a more thorough lymph node dissection compared to an OPEN done by a surgeon with poor technique. Likewise, the differences in how pathological specimens are processed between individual pathologists and institutions, and how the lymph nodes are reported cannot be accounted for. This variable cannot be controlled and may significantly impact the conclusions of this study. Station identification is likely uniform, but how the number of lymph nodes is arrived at is not. Other factors not controlled for in this analysis include the impact of tumour location, and whether it is central or peripheral, may impact the rate of occult nodal disease and how that may affect these results [25]. While PS matched analyses control for some bias, limitations in the granularity of the data limit the extent to which these biases

can be controlled for. Lastly, given the number of analyses performed on this large data set comparing three different surgical approaches, there is substantial multiplicity that can potentially impact results.

CONCLUSION

The results of our analysis suggest that VATS and RATS approaches are not inferior to OPEN for intraoperative lymph node evaluation, though they may be inferior in the ability to uncover occult lymph node metastases. However, this does not appear to affect long-term survival for patients undergoing minimally invasive approaches. Our results support previous evidence suggesting that minimally invasive approaches such as VATS and RATS are not inferior to OPEN in patients undergoing resection for early-stage NSCLC.

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Author contributions

Mark W. Hennon: Conceptualization; Writing—original draft; Writing—review & editing. **Luke H. DeGraaff:** Methodology; Writing—original draft; Writing—review & editing. **Adrienne Groman:** Formal analysis; Methodology; Writing—review & editing. **Todd L. Demmy:** Conceptualization; Methodology; Writing—review & editing. **Sai Yendamuri:** Conceptualization; Data curation; Formal analysis; Project administration; Supervision; Writing—original draft; Writing—review & editing.

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