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Propensity score matched comparison of lymph node upstaging in early-stage lung cancer: open versus minimally invasive surgery with standardized lymphadenectomy

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Abstract

Background Lymph node upstaging represents a quality criterion for standardized lymphadenectomy in lung cancer surgery. The aim of the study was to compare whether the quality of standardized lymphadenectomy in lung cancer surgery is comparable in minimally invasive (video-assisted thoracoscopic surgery) and the open approach (thoracotomy). Furthermore, factors associated with lymph node upstaging were assessed, as was its impact on overall survival and progression-free survival.

Methods This retrospective study reviewed data of all patients undergoing lobectomy at the Lung Tumor Center Munich between 2011 and 2020. Inclusion factors were non-small cell lung cancer without nodal involvement (N0) or metastasis (M0) and standardized lymphadenectomy. A propensity score matched analyses was performed. Frequency of categorical outcomes was compared with Chi [2]-test, mean values with t-test. We used logistic and Cox regression models to assess factors associated with upstaging, overall survival and progression-free survival, restrictively.

Results Of 1691 patients undergoing lobectomy, 637 met our inclusion criteria. After propensity score matching 198 patients remained in each group. Univariate analysis showed no significant difference in lymph node upstaging between the two groups ($p=0.12$). Overall affected lymph nodes ($p=0.45$) and overall affected lymph node stations ($p=0.26$) were not significantly different. Multivariate Cox regression analysis showed that overall survival and progression free survival were also independent of the surgical approach. L1 status was the only factor associated with progression-free survival.

Conclusion Minimally invasive approaches achieves comparable lymph node upstaging in patients undergone standardized lymphadenectomy.

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Keywords Non-small cell lung cancer, Lymphadenectomy, Propensity score matching, Tumor staging, Thoracotomy, Video-assisted thoracoscopic surgery, Survival

Introduction

Complete lymphadenectomy remains one of the most important components in curative intent resection of lung cancer. Accurate tumor staging through complete lymphadenectomy is primarily used for further therapy planning and results in potential survival benefit [1, 2].

An important quality criterion of lymphadenectomy is postoperative lymph node (LN) upstaging, which is defined as the unexpected pathological finding of metastasis in hilar (N1) or mediastinal (N2) LNs [3].

The International Association for the Study of Lung Cancer (IASLC) sponsored efforts to standardize lymphadenectomy procedures, resulting in a report on the international workshop on thoracic staging in 1996, which was taken up by the IASLC in 2005 [4, 5]. After 15 years, these standardized procedures were revised by the Commission on Cancer [6]. In the latest edition of the Optimal Resources for Cancer Care (2020 standards), which was first released in February 2023, it is specified that the surgical pathology report associated with any curative intent pulmonary resection for primary lung malignancy must report the oncologic status of LNs for at least one hilar station (pN1) and at least three distinct mediastinal stations (pN2) [6]. A National Cancer Database query and a multi-institutional prospective study showed that adherence to this nodal sampling standards resulted in a significantly better overall survival, improved lymph node yield and stratification of postoperative stage-specific survival curves [7, 8], but adherence to this recommendation is variable.

Unfortunately, in many studies lymphadenectomy has not been performed according to the guidelines. A standardized procedure for lymphadenectomy is the only way to compare minimally invasive surgery (video-assisted thoracoscopic surgery - VATS) and thoracotomy (open surgery) with regard to LN upstaging.

This study aims to compare standardized lymphadenectomy in thoracotomy and VATS to evaluate differences in LN upstaging and survival outcomes.

Methods

Study design, patient cohort and data collection

In this retrospective analysis, we used data of all lung cancer patients with preoperative N0-status undergoing lobectomy through thoracotomy or VATS at the Lung Tumor Center Munich between 2011 and 2020. Only patients with standardized lymphadenectomy were included, as defined by the Commission on Cancer [6].

Preoperatively, all patients were staged according to the current National comprehensive Cancer Network

(NCCN) guidelines and were discussed at the specific tumor board. Patients underwent pre- or intraoperative bronchoscopy, pathological lymph node evaluation and FDG-PET/CT scan. Meanwhile, the method of choice for lymph node evaluation was EBUS-TBNA. In the past, a mediastinoscopy was performed in cases of suspected lymph node involvement. This is still the method of choice for an EBUS-TBNA negative for malignancy in a clinically (FDG-PET/CT and/or CT) positive mediastinum. Patients with clinical stage II and expected N0 status also receive a cranial MRI [9].

Our exclusion criteria were patients with wedge resection, segmentectomy or pneumonectomy, conversion to thoracotomy, patients with preoperative nodal involvement at diagnosis (N1, N2 and N3), patients with distant metastases at diagnosis, and patients with missing pathological N status.

A detailed representation of the inclusion and exclusion criteria of the patient population is shown in Fig. 1.

All information in the dataset was extracted from electronic patient records and archived charts. This data included information about patient characteristics such as age at resection, sex, performance status according to the American Society of Anesthesiologists risk classification (ASA), comorbidities, body mass index (BMI), forced expiratory volume in 1 s (FEV1%), year of lobectomy and smoking status. Tumor characteristics covered clinical and pathological tumor stage, histological type, tumor location, as well as tumor grading, lymphovascular space invasion (L-status) and vascular invasion (V-status). Additionally, we documented the number of assessed and the number of affected LNs for each individual LN station.

Definition of standardized lymphadenectomy and upstaging

Standardized lymphadenectomy was defined as assessing at least one LN station in N1 and assessing at least three LN stations in N2 during surgery, as defined by the Commission on Cancer [6].

As only patients with preoperative N0-status were included, LN upstaging was defined as either having an affected N1- or N2-LN after surgery through lymphadenectomy. We distinguished between upstaging from N0 to N1 and upstaging from N0 to N2.

In addition to LN upstaging we also compared the frequency of assessment of LN stations as well as the number of assessed LNs in each station and overall. We grouped adjacent mediastinal LN stations to paratracheal

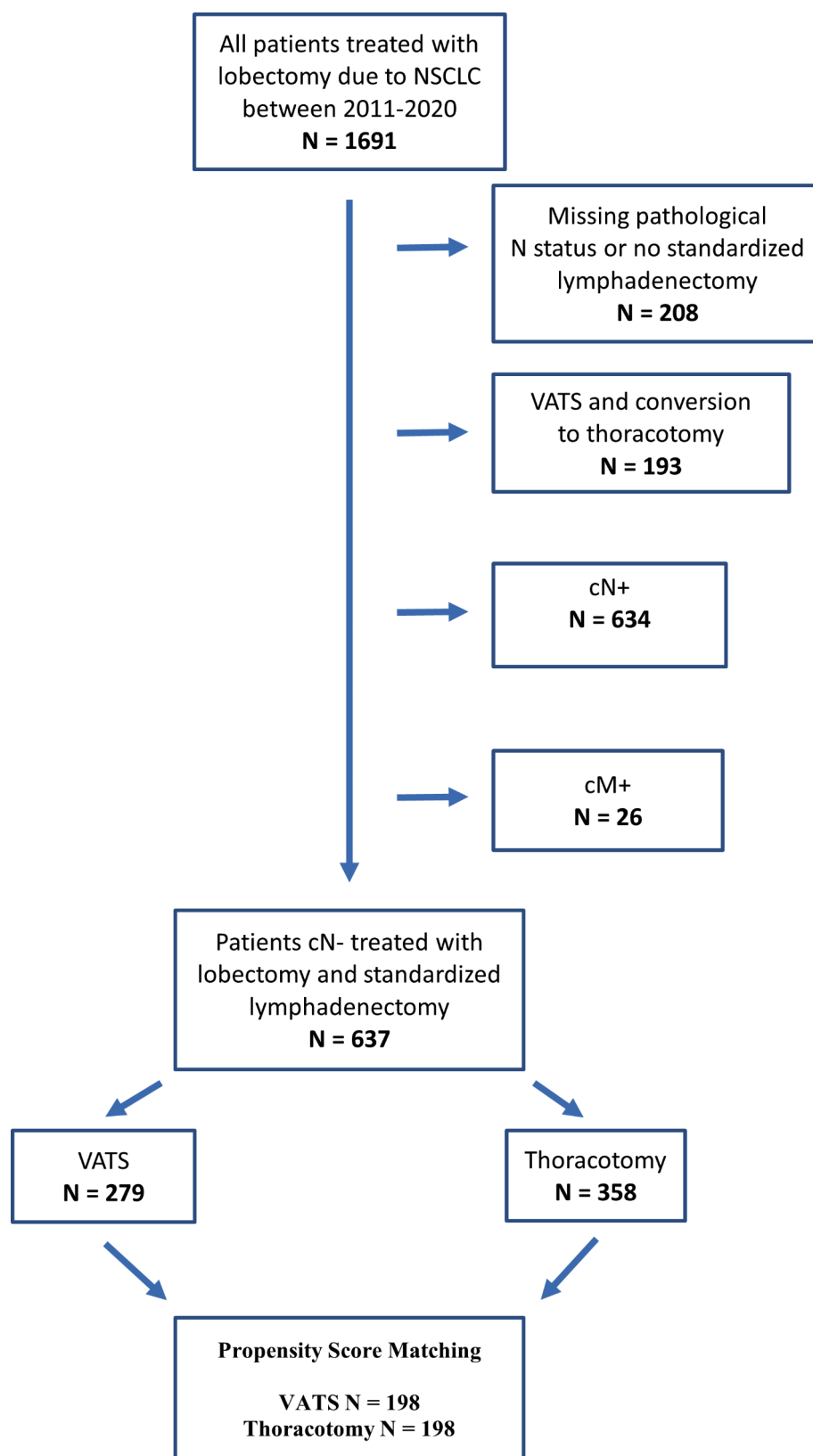


Fig. 1 Patient population. cM += clinical positive distant metastases, cN += clinical positive lymph nodes, N Status = lymph node status, NSCLC = non-small cell lung cancer, VATS = video-assisted thoracic surgery

(#2, #4), and to pulmonary ligament/paraesophageal (#8, #9).

Categorization of variables and handling of missing data

We categorized histological types into adenocarcinoma (ACC), squamous-cell carcinoma (SCC), and neuroendocrine carcinoma (including carcinoids and large-cell neuroendocrine carcinomas) (NEC). All other histological types were summarized under the category “other histology”.

As BMI was missing in 7 patients we used multiple imputation to fill in the missing values, with the methods described in the next paragraph.

Statistical analysis

We applied propensity score matching (PSM) to compare upstaging, overall survival (OS), and progression-free survival (PFS) between patients undergoing VATS and thoracotomy. The primary goal of using PSM was to mitigate potential selection bias by balancing baseline characteristics between the two surgical groups, as patients undergoing VATS may differ systematically from those undergoing thoracotomy in ways that could confound the results. For the propensity score matching, we utilized the nearest neighbor matching method with a caliper of 0.1 to ensure that matched pairs were as similar as possible, minimizing potential biases while retaining a sufficient number of matched patients for analysis. The variables selected for the propensity score model were chosen based on a combination of expert opinion, a comprehensive review of the existing literature, and an assessment of the standardized mean difference (SMD). Expert opinion was sought to identify key clinical factors that could influence the choice of surgical approach and that are likely to impact upstaging, OS, and PFS. A literature review was conducted to further inform this process, ensuring that the selected variables reflected those typically associated with these outcomes in similar patient populations. These factors included age, sex, comorbidities, tumor size, stage of disease, and performance status, among others. To assess the balance between the groups before and after matching, we used the standardized mean difference (SMD), which quantifies the difference in means between the groups, standardized by the pooled standard deviation. An SMD greater than 0.1 indicates a notable imbalance between groups, while an SMD below 0.1 suggests adequate balance. Patient characteristics are presented as mean values with standard deviation (SD) for metric variables and absolute and relative frequencies for categorical variables. They were compared between thoracotomy and VATS patients using Student's *t*-test for metric variables, and Chi [2]-test or Fisher's exact test, when cell numbers were <6, for categorical variables. Statistical significance

for these comparisons was determined using two-sided *p*-values with alpha errors <0.05. Multiple imputation of BMI was performed using the R package “mice,” which applies a conditional multiple imputation method. The variables used in the imputation process—age, sex, BMI, and all assessed comorbidities—were selected because they are known to be closely related to both BMI and the outcomes of interest in this study. Age and sex are fundamental demographic factors that often influence body mass index and can confound relationships between BMI and clinical outcomes. Comorbidities, such as hypertension, diabetes, and cardiovascular disease, are also frequently associated with BMI and can impact both the likelihood of certain surgical approaches and post-operative outcomes. By including these variables in the imputation process, we aimed to improve the accuracy of the imputed BMI values and reduce bias in the analysis, ensuring that missing data did not unduly affect the validity of our results. We used a mixed effects logistic regression model including the match-ID as a random effect to assess the association between upstaging and type of surgery. In this model the number of assessed LNs, tumor grading, L- and V-status were included as possible additional confounding variables not chosen in the PSM. The number of assessed LNs was considered a post-treatment variable, while tumor grading and L- and V-status did not show significant imbalance prior to matching. They were chosen based on their clinical relevance and their potential impact on the likelihood of upstaging. The significance of these variables was assessed using the Wald test. To assess the association of OS, PFS and surgical approach we used Cox regression models including the match-ID as a cluster variable to account for the matched nature of the data. The models were adjusted for additional confounders including CCI score, tumor grading, and L- and V-status as confounders. By adjusting for these additional variables, we aimed to control for potential confounding factors that could bias the relationship between surgical approach and survival outcomes, thereby providing a more accurate estimate of the effect of surgery on OS and PFS.

Data analysis was performed using R Version 4.0.0 and RStudio Version 1.4. Tables and the figure were created in RStudio and Microsoft Excel.

Results

Patient population

In total, 1691 patients underwent lobectomy at our center between 2011 and 2020. After selection according to our inclusion and exclusion criteria, the data of 279 patients with VATS and 358 patients with thoracotomy were analyzed. The following variables were selected to be used in the PSM as they are associated with the relevant outcomes and surgical approach and showed a SMD of

greater than 0.1: age, FEV1% predicted at baseline, BMI, tumor size, sex, ASA, histological type, location of the tumor, diabetes with end-organ-failure, coronary heart disease, and year of resection. PSM resulted in a matched cohort of 198 patients with VATS and 198 patients with thoracotomy. A detailed representation of the composition of the matched patient population is shown in Fig. 1. Characteristics of the final matched study population grouped by VATS and thoracotomy are summarized in Table 1 and shows that the matched sample is well balanced between the two groups.

Upstaging of nodal status after surgical resection

As shown in Fig. 2A, pathological LN upstaging was not significant regarding the surgical approach. We had an overall rate of 12.1% in the VATS group compared to 18.2% in the thoracotomy group ($p=0.12$). This difference in the overall rate of upstaging between VATS and thoracotomy is mainly explained by upstaging from N0 to N1 (7.6% vs. 13.1%). Upstaging from N0 to N2 was similar in both groups (4.5% vs. 5.1%).

Nodal assessment during surgery

The frequency of assessment of the hilar nodal station (#10) was significantly higher in thoracotomy (77.3%) compared to VATS (66.2%) ($p=0.02$). We did not find significant differences in the frequency of nodal assessment regarding all other LN stations. The average overall number of N1 LN assessed was significantly higher in thoracotomy (7.4, $sd=4.6$) compared to VATS (5.8, $sd=4.0$). This was mainly driven by the significant difference in hilar LNs ($p=0.043$). Intrapulmonary LNs were significantly higher in thoracotomy, but cannot be influenced by the surgical approach, because they are located in the lung parenchyma of the lung lobe that is removed. In N2 the average overall number of assessed LNs was significantly higher in thoracotomy (10.2, $sd=7.0$) compared to VATS (8.4, $sd=4.8$) ($p=0.003$). While we found significantly higher numbers of assessed LNs for paratracheal ($p=0.033$) and pulmonary ligaments/paraesophageal stations ($p=0.03$) in thoracotomy than in VATS, no significant difference was shown for the aortopulmonary window ($p=0.47$) and subcarinal ($p=0.15$).

No significant difference was determined for the number of overall, N1 and N2 affected LN stations as well as overall, N1 and N2 affected LNs.

A complete overview on the frequency of assessed stations and the number of assessed LNs stratified by surgical approach can be found in Table 2.

Multivariate regression analysis

In the multivariate logistic regression analysis with regard to upstaging (Table 3) the surgical approach showed no

significant influence ($OR=0.95$, $p=0.38$) as well as all other selected factors.

In the multivariate cox regression analysis with regard to overall survival, no significant factors were identified either. (Table 4)

Regarding PFS (Table 5) only L1 vs. L0 status ($HR=4.24$, $p=0.003$) were associated with a significant detrimental effect on PFS.

Upstaging of nodal status after surgical resection in 2017–2020

We had a switch in frequency of lobectomies by surgical approach in 2017 from mainly open to minimally invasive surgery. From this point on, VATS lobectomy was well established at our center and we can assume a high level of expertise. To minimize possible bias in the overall cohort regarding surgical expertise, we performed a sub-analysis of patients who underwent surgery from 2017 to 2020 (Fig. 2B). Upstaging was found in 16.7% of patients with thoracotomy and 11.1% of VATS patients ($p=0.39$) which was not significant either. Similar to the whole population, upstaging from N0 to N1 was less frequent in VATS compared to thoracotomy, whereas from N0 to N2 it was the same ($p=0.44$).

Discussion

In this study we analyzed the LN upstaging for early stage NSCLC after intraoperative standardized lymphadenectomy in a large cohort. Lymphadenectomy is of great importance in lung surgery. The aim of lymphadenectomy is to remove affected lymph nodes that were not thought to be affected preoperatively. Possible LN involvement changes the initial tumour stage and patients receive adjuvant therapy postoperatively, which also has a positive effect on patient survival. According to the guidelines lymphadenectomy should be done standardized. Unfortunately, an adequate standardized lymphadenectomy is often not performed. Some studies published analysed LN upstaging by comparing the different surgical approaches (VATS vs. thoracotomy), but these either had too few overall LN stations assessed or indicated just the overall numbers of stations assessed and hence lacked information about the individual LN stations [10–14]. This was criticised in some of the comments. The guidelines, first published in 1996, prefer to exceed a minimum of six LNs in three hilar and intrapulmonary (N1) and three mediastinal (N2) stations or in the further course LNs from at least one hilar station (N1) and three mediastinal stations (N2) [4, 6]. The American College of Surgeons Oncology Groups randomized trial Z0030, published in 2011, addressed this question and showed that formal lymph node dissection in patients with early-stage non-small cell lung cancer does not improve survival if the systematic and thorough preliminary examination of

Table 1 Patient and tumor characteristics of study population

	VATS (n = 198)		thoracotomy (n = 198)		p-value	smd
	mean	sd	mean	sd		
age in years	66.8	10.0	67.4	10.4	0.57	0.06
FEV1%	84.6	18.9	84.2	18.6	0.85	0.02
BMI	25.8	4.8	25.6	4.5	0.66	0.04
tumor size in cm	2.8	1.5	2.9	1.9	0.40	0.09
	n	%	n	%	p-value	smd
sex						
male	87	43.9%	89	44.9%	0.9194	0.02
female	111	56.1%	109	55.1%		
current smoker						
yes	55	27.8%	58	29.3%	0.87	0.07
no	141	71.2%	139	70.2%		
unknown	2	1.0%	1	0.5%		
ASA						
1	4	2.0%	4	2.0%	0.990	0.02
2	58	29.3%	56	28.3%		
3	126	63.6%	128	64.6%		
4	3	1.5%	3	1.5%		
unknown	7	3.5%	7	3.5%		
histological type						
adenocarcinoma	128	64.6%	128	64.6%	0.989	0.04
NEC	21	10.6%	21	10.6%		
SCC	45	22.7%	44	22.2%		
other	4	2.0%	5	2.5%		
location						
middle lobe	14	7.1%	17	8.6%	0.84	0.06
upper lobe	116	58.6%	116	58.6%		
lower lobe	68	34.3%	65	32.8%		
Tumor grading						
1	11	5.6%	14	7.1%	0.85	0.08
2	105	53.0%	102	51.5%		
3	70	35.4%	62	31.3%		
4	1	0.5%	1	0.5%		
unknown	11	5.6%	19	9.6%		
Lymphovascular space invasion (L0, L1)						
0	146	73.7%	145	73.2%	0.71	0.05
1	42	21.2%	47	23.7%		
unknown	10	5.1%	6	3.0%		
Vascular invasion (V0, V1)						
0	154	77.8%	158	79.8%	1.00	0.01
1	34	17.2%	34	17.2%		
unknown	10	5.1%	6	3.0%		
Residual tumor classification (R0, R1)						
0	198	100.0%	197	99.5%	1	0.10
1	0	0.0%	1	0.5%		

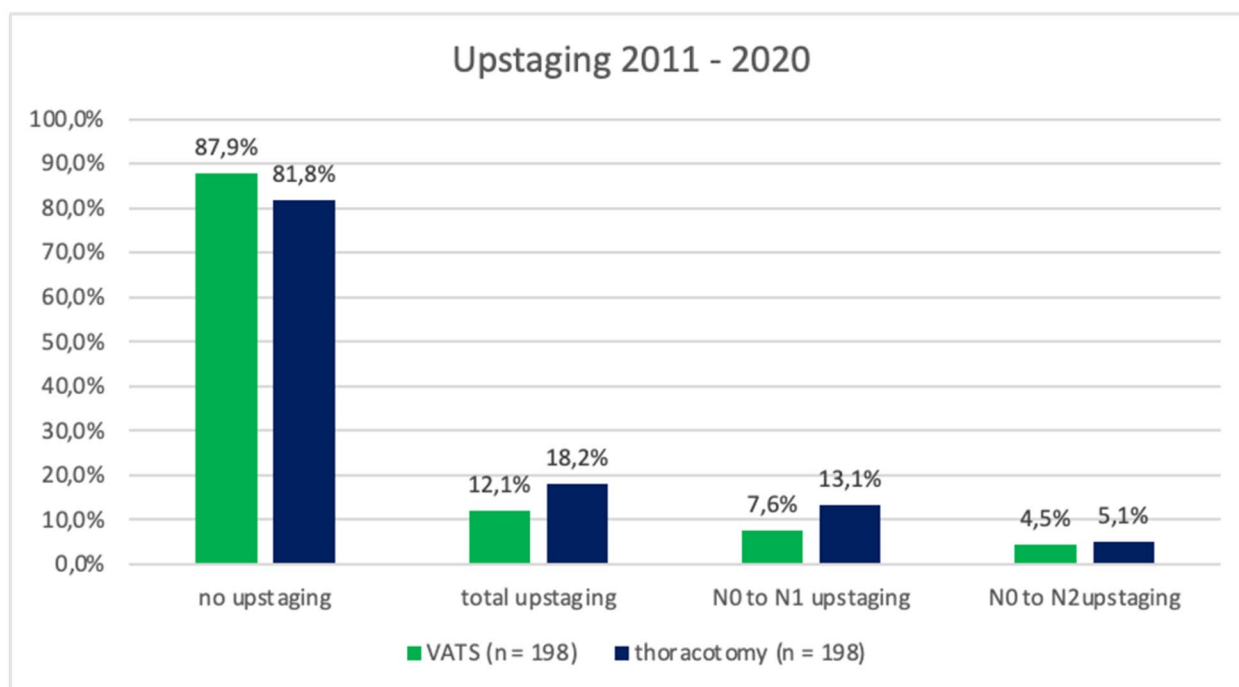
Patient and tumor characteristics of lung cancer patients with lobectomy and standardized lymphadenectomy stratified by surgical approach. Means with standard deviation of numerical variables and absolute and relative frequency of categorical variables

VATS=video-assisted thoracoscopic surgery, sd=standard deviation, FEV1=Forced Expiratory Volume in 1 s, BMI=body mass index, ASA=American Society of Anesthesiologists risk classification, NEC=neuroendocrine carcinoma, SCC=squamous-cell carcinoma

the mediastinal and hilar lymph nodes is negative [15]. Implementation of this approach in the clinical routine was difficult and the 8th edition of the IASLC Lung Cancer Staging Project demonstrated that more than 50% of

resected cases in the staging database were reassigned from R0 to R-undetermined because of incomplete mediastinal lymph node evaluation with significant impact on patient survival [16]. In addition, further analysis of the

A



B

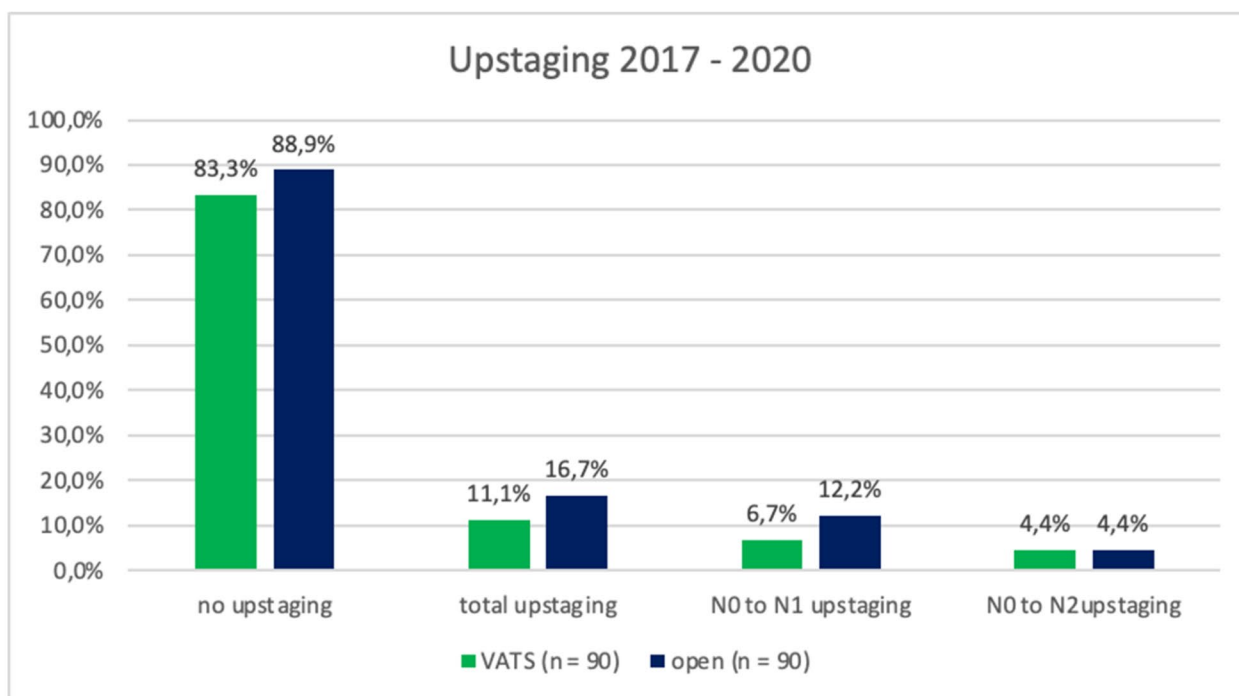


Fig. 2 Upstaging stratified by surgical approach. Upstaging of N stage after lobectomy stratified by type of resection. **A** displays upstaging in all patients (2011 to 2020). **B** shows results in patients with lobectomies between 2017 and 2020. *P*-values from χ^2 -test. VATS=video-assisted thoracoscopic surgery

former Z0030 randomised trial showed that the number of pathological examined lymph nodes was associated with the likelihood of detecting nodal metastasis and survival in the formal lymph node dissection arm [17].

The American College of Surgeons Commission on Cancer addressed this issue in the 2020 standards for the Optimal Resources for Cancer Care. Standard 5.8 states that (1) at the time of lung resection hilar and mediastinal lymph nodes should be thoroughly staged even in

Table 2 Frequency of assessed lymph nodes and number of assessed lymph nodes by stations and surgical approach

	VATS(= 198)		thoracotomy (n= 198)		p-value
	n	%	n	%	
frequency of stations assessed					
N1	472	59.6%	502	63.4%	
hilar (#10)	131	66.2%	153	77.3%	0.02
interlobar (#11)	168	84.8%	167	84.3%	1.00
lobar (#12)	13	6.6%	18	9.1%	0.45
intrapulmonary	160	80.8%	164	82.8%	0.69
N2	554	69.9%	567	71.6%	
paratracheal (#2,#4)	125	63.1%	129	65.2%	0.75
aortopulmonary window (#5,#6)	76	38.4%	76	38.4%	1.00
subcarinal (#7)	182	91.9%	186	93.9%	0.56
pulmonary ligament/paraesophageal (#8,#9)	171	86.4%	176	88.9%	0.54
	mean	sd	mean	sd	p-value
# of LN assessed					
N1	5.8	4.0	7.4	4.6	0.001
hilar (#10)	1.5	1.8	1.9	1.8	0.043
interlobar (#11)	2.2	1.9	2.4	2.1	0.23
lobar (#12)	0.2	0.9	0.2	0.9	0.79
intrapulmonary	2.6	2.3	3.5	3.8	0.007
N2	8.4	4.8	10.2	7.0	0.003
paratracheal (#2,#4)	2.9	3.4	3.8	4.5	0.033
aortopulmonary window (#5,#6)	1.1	1.9	1.2	2.1	0.77
subcarinal (#7)	2.6	2.2	3.0	2.7	0.15
pulmonary ligament/paraesophageal (#8,#9)	2.0	1.7	2.4	2.2	0.03
overall stations assessed	6.1	1.1	6.5	1.2	0.002
overall LN count	15.5	6.8	19.0	9.2	<0.0001
	mean	sd	mean	sd	p-value
# of affected stations					
overall	0.21	0.73	0.30	0.77	0.26
N1 LN	0.14	0.44	0.22	0.55	0.09
N2 LN	0.08	0.40	0.08	0.35	1.00
# of affected LN					
overall	0.38	1.64	0.51	1.66	0.45
N1 LN	0.24	1.00	0.40	1.31	0.16
N2 LN	0.15	0.87	0.11	0.51	0.57

Frequency of lymph nodes stations assessed during surgery, number of assessed lymph nodes, and number of affected lymph nodes and stations by surgical approach. Absolute and relative frequency of stations and mean number of assessed lymph nodes with standard deviation. *P*-values from Chi [2]-test for frequencies and Students t-test for number of lymph nodes and stations

VATS=video-assisted thoracoscopic surgery, sd=standard deviation

Table 3 Results from logistic regression analysis of likelihood of upstaging

	OR	beta	se	z-value	p-value
VATS vs. thoracotomy	0.95	-0.05	0.04	-1.31	0.38
number of assessed lymph nodes	1.04	0.04	0.08	0.50	0.17
grade 2 vs. grade 1	1.01	0.01	0.08	0.16	0.62
grade 3 vs. grade 1	1.01	0.01	0.08	-0.45	0.87
grade unknown vs. grade 1	0.96	-0.05	0.10	1.44	0.65
L1 vs. L0	1.09	0.08	0.06	0.40	0.15
V1 vs. V0	1.03	0.025	0.06	-0.01	0.69

Results from multivariate logistic regression analysis of upstaging and type of surgery, adjusted by number of assessed lymph nodes, tumor grading and L- and V-status

OR=Odds Ratio, VATS=video-assisted thoracic surgery, L=Lymphovascular space invasion, V=Vascular invasion

Table 4 Results from Cox regression analysis of overall survival

	HR	beta	se	z-value	p-value
VATS vs. thoracotomy	0.67	-0.40	0.35	-1.12	0.27
CCI score	1.06	0.06	0.07	0.89	0.38
grade 2 vs. grade 1	3.01	1.10	1.03	1.10	0.27
grade 3 vs. grade 1	2.10	0.74	1.07	0.71	0.48
grade unknown vs. grade 1	1.29	0.25	1.42	0.19	0.85
L1 vs. L0	1.52	0.42	0.62	0.70	0.48
V1 vs. V0	1.37	0.32	0.64	0.51	0.61

Results from multivariate Cox regression analysis of overall survival and type of surgery, adjusted by Charlson comorbidity score (CCI score), tumor grading and L, and V status

HR=Hazard Ratio, VATS=video-assisted thoracic surgery, CCI=Charlson comorbidity index, L=Lymphovascular space invasion, V=Vascular invasion

Table 5 Results from Cox regression analysis of overall progression free survival

	HR	beta	se	z-value	p-value
VATS vs. thoracotomy	1.01	0.01	0.28	0.03	0.98
CCI score	0.97	-0.03	0.07	-0.40	0.69
grade 2 vs. grade 1	2.76	1.02	1.03	0.97	0.33
grade 3 vs. grade 1	4.13	1.42	1.03	1.37	0.17
grade unknown vs. grade 1	2.44	0.89	1.16	0.76	0.45
L1 vs. L0	4.24	1.44	0.41	2.99	0.003
V1 vs. V0	0.62	-0.63	0.45	-1.29	0.20

Results from multivariate Cox regression analysis of overall progression free survival and surgical approach, adjusted by Charlson comorbidity score (CCI score), tumor grading and L, and V status

HR=Hazard Ratio, VATS=video-assisted thoracic surgery, CCI=Charlson comorbidity index, L=Lymphovascular space invasion, V=Vascular invasion

patients undergoing wedge resection, (2) the pathology report must contain lymph nodes from at least one hilar and three mediastinal stations, and (3) the pathologist must specify all nodal stations in a synoptic format [6].

Our study group wanted to carry out an analysis that met the criteria for standardized lymphadenectomy and compare the surgical approaches, VATS and thoracotomy. The study population consisted of patients with assessments in at least one LN station in N1 and at least three LN stations in N2 in the pathological report. On average a total number of 6.1 LN stations were assessed after VATS lobectomy and 6.5 after thoracotomy. The average total LN count was 15.5 in the VATS group and 19.0 in the thoracotomy group. (Table 2) Hence, the definition of standardization is fully met and the average lymph node count in our cohort was comparable to the Z0030 randomized trial from the American College of Surgeons Oncology Group [18]. In this respect, our study differs from others mainly due to an even larger number of removed lymph nodes after standardized lymphadenectomy [19–22].

The univariate analysis showed that LN upstaging in thoracotomy group was not significantly higher compared to the VATS lobectomy (18.2% versus 12.1%; $p=0.12$). (Fig. 2A). The multivariate logistic regression (Table 3) analysis for the likelihood of lymph node upstaging demonstrated no significant parameter either.

We achieved comparable or even higher overall upstaging rates than other published studies [12, 21,

23–25]. However, the difference in upstaging for thoracotomy versus VATS in our analyzes was mainly driven by upstaging from N0 to N1 (13.1 vs. 7.6%), whereas upstaging from N0 to N2 was similar in both groups (5.1% thoracotomy vs. 4.5% VATS). (Fig. 2A).

The fact that the difference in upstaging was mainly driven by upstaging from N0 to N1 has already been described in the literature [12]. Regarding the assessment of LN stations, only the hilar #10 station (Table 2) showed a significantly higher frequency of assessment in thoracotomy. This may also explain that N1 stations, were affected significantly more often in thoracotomy, even if there was no significant difference overall. The thoracic surgeons are sometimes more careful with the minimally invasive approach at the hilus to avoid affections of the phrenic nerve, which could explain the difference.

The multivariate cox regression (Table 4) revealed no significant difference for overall survival ($HR=0.67$, $p=0.27$). In our opinion, this underlines the results of our LN upstaging. We were able to show that VATS does not have significantly lower LN upstaging after standardized lymphadenectomy. It can be assumed that the postoperative tumor stage could be determined equally well in the groups and that this also corresponds to the actual tumor stage. As a result, patients can be treated postoperatively according to their tumor stage and the surgical approach therefore has no influence on survival. This is an extraordinarily good result for VATS in particular.

As a critical aspect, we saw that it is difficult to minimize a possible bias due to surgical expertise in our analysis. In 2011, VATS was not yet established and a new technique for all surgeons to learn. It has already been described in the literature that lymphadenectomy improves with the surgeon's increasing experience and learning curve; more thoracic LN and LN stations are removed [26–28]. This subsequently has an effect on upstaging. We therefore carried out another sub-analysis. From 2017, we performed more VATS lobectomies than thoracotomy lobectomies. It can therefore be assumed that the expertise in VATS lobectomy was improved from this point onwards. The results of the sub-analysis also showed no significant differences with regard to LN upstaging (11.1% VATS and 16.7% thoracotomy; $p = 0.39$).

We have two reasons for this. Firstly, we are of the opinion that, contrary to what is written in the literature, there is no learning curve after performing a standardized lymphadenectomy. We assume that a standardized lymphadenectomy already places high demands on the surgeon and is therefore only performed by experienced surgeons. This also explains the high total number of LN and LN stations represented by our data. As a result, after a standardized lymphadenectomy, the postoperative tumor stage also corresponds to the actual tumor stage. On the other hand, we have a slightly lower upstaging in the sub-analysis than in the overall cohort. This can be explained by the improved preoperative staging that has developed over the years. In the case of large tumors and/or conspicuous LNs, all patients receive a preoperative FDG-PET/CT and an EBUS-TBNA. This has made it possible to detect pre-existing LN involvement in more patients preoperatively. Patients with preoperative positive N-status were not analyzed and thus the rate of upstaging is lower.

In addition to upstaging, we would like to briefly discuss the influence of the lymphovascular space invasion (L1). This was the only factor, which is associated with worse PFS. So far little is known about the significance of the L1 status in early stage NSCLC. It is still under continuous debate. There are only a few studies that have described L1 as a significantly associated factor with early tumor recurrence and independently associated with the presence of regional LN involvement [29, 30]. Our analysis underscores the limited published data and may contribute to the debate on adjuvant treatment after lymphovascular space invasion.

Some limitations of this study have to be considered. First, our study is retrospective. Second, there could be bias by the surgeons. To minimize bias like surgical preferences or the impact of patient's health status and comorbidity we used the following approaches. By only including patients without LN involvement or metastases we excluded patients with a suspected higher tumor stage

and patients with a higher operational risk and a higher likelihood of thoracotomy, which might have affected the outcomes in our study. The primary goal of using PSM was to mitigate potential selection bias by balancing baseline characteristics between the two surgical groups, as patients undergoing VATS may differ systematically from those undergoing thoracotomy in ways that could confound the results. Additionally, we used multivariate regression analyses to adjust for known confounders. Nevertheless, we cannot exclude bias from surgeons deciding that patients with more comorbidities should have thoracotomy in order to achieve e.g. a shorter operating time. This would mean that the thoracotomy group contains sicker patients. Third, other confounding variables that may influence the results are the expertise of the surgeons and the variability of lymphadenectomy techniques. However, to address surgeons' expertise to some extent, we added an analysis for a subgroup of patients with surgery from 2017 onwards. Regarding variability in lymphadenectomy, only patients in whom lymphadenectomy was performed according to the guidelines were included, so the variability is minimized.

Conclusion

We were able to show that after standardized lymph node dissection, lymph node upstaging as a surrogate marker is independent of the surgical approach. If a standardized lymphadenectomy is performed, this results in a large number of removed LN and a representative upstaging. However, this technique requires the necessary expertise.

We were able to achieve LN upstaging of 12–18% in preoperatively expected N0 patients, which has a major impact on further therapy and PFS.

In future research, we recommend validating our results in multicenter randomized controlled trials. It would be important to conduct studies that perform a standardized lymphadenectomy in both cohorts (thoracotomy and VATS) in order to obtain representative results.

Abbreviations

ACC	Adenocarcinoma
ASA	American society of anesthesiologists risk classification
BMI	Body mass index
CCI	Charlson comorbidity index
FEV1	Forced expiratory volume in 1 s
HR	Hazard ratio
IASLC	International association for the study of lung cancer
LN	Lymph node
NEC	Neuroendocrine carcinoma
NSCLC	Non-small cell lung cancer
OS	Overall survival
OR	Odds ratio
PFS	Progression free survival
SCC	Squamous-cell carcinoma
sd	Standard deviation
VATS	Video-assisted thoracoscopic surgery

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Author contributions

JZ: Conceptualization, formal analysis, data curation, investigation, methodology, writing original draft; JW: Conceptualization, formal analysis, methodology, writing original draft; VP: Data curation, review the draft manuscript; JK: Conceptualization, review and editing the draft manuscript; GY: Validation, review and editing the draft manuscript; JS: Data curation, review the draft manuscript; MGS: Review and editing the draft manuscript; CK: Review and editing the draft manuscript; NR: Review and editing the draft manuscript; RAH: Validation, Review and editing the draft manuscript; AT: Conceptualization, Review and editing the draft manuscript; CPS: Conceptualization, formal analysis, data curation, methodology, writing original draft.

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Data availability

Data from 1691 patients were recorded in the database. This data is still being analyzed and further studies are in progress. In order not to jeopardize the data for the new studies, they cannot be disclosed at this time. We ask for your understanding. The data sets and materials of the current study are available on reasonable request from the corresponding author.

Declarations

Ethics approval and consent to participate

Approval for this retrospective, non-interventional study was obtained from the Ethics Committee of the Ludwig-Maximilian's University (reference number 21–0036). This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local ethical and legal requirements. The need for written informed consent was waived by the above-mentioned ethics committee due to retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. D'Amrilli A, Venuta F, Rendina EA. The role of lymphadenectomy in lung cancer surgery. *Thorac Surg Clin May*. 2012;22(2):227–37. <https://doi.org/10.1016/j.thorsurg.2011.12.001>
2. Wright G, Manser RL, Byrnes G, Hart D, Campbell DA. Surgery for non-small cell lung cancer: systematic review and meta-analysis of randomised controlled trials. *Thorax Jul*. 2006;61(7):597–603. <https://doi.org/10.1136/thx.2005.051995>
3. Toker A, Ozyurtkan MO, Kaba E. Nodal upstaging: effects of instrumentation and three-dimensional view in clinical stage I lung cancer. *J Vis Surg*. 2017;3:76. <https://doi.org/10.21037/jovs.2017.04.05>
4. Goldstraw P. October. Report on the international workshop on intrathoracic staging. London, 1996. *Lung Cancer*. 1997;18(1):107–111. [https://doi.org/10.1016/S0169-5002\(97\)00051-2](https://doi.org/10.1016/S0169-5002(97)00051-2)
5. Rami-Porta R, Wittekind C, Goldstraw P. International Association for the study of Lung Cancer staging C. Complete resection in lung cancer surgery: proposed definition. *Lung Cancer Jul*. 2005;49(1):25–33. <https://doi.org/10.1016/j.lungcan.2005.01.001>
6. Cancer Co. Optimal Resources for Cancer Care. https://accreditationdocuments/CoC/Standards/Optimal_Resources_for_Cancer_Care_Feb_2023.pdf
7. Odell DD, Feinglass J, Engelhardt K, et al. Evaluation of adherence to the Commission on Cancer lung cancer quality measures. *J Thorac Cardiovasc Surg Mar*. 2019;157(3):1219–35. <https://doi.org/10.1016/j.jtcvs.2018.09.126>
8. Smeltzer MP, Faris NR, Ray MA, Osarogiagbon RU. Association of Pathologic Nodal staging Quality with Survival among patients with Non-small Cell Lung Cancer after Resection with curative intent. *JAMA Oncol Jan*. 2018;1(1):80–7. <https://doi.org/10.1001/jamaoncol.2017.2993>
9. National Comprehensive Cancer Network NCCN clinical practice guidelines in. oncology (NCCN Guidelines) for non-small cell lung cancer. Version.2.2020. https://www.nccn.org/professionals/physician_gls/PDF/nscl.pdf
10. Kneuert PJ, Cheufou DH, D'Souza DM, et al. Propensity-score adjusted comparison of pathologic nodal upstaging by robotic, video-assisted thoracoscopic, and open lobectomy for non-small cell lung cancer. *J Thorac Cardiovasc Surg Nov*. 2019;158(5):1457–e14662. <https://doi.org/10.1016/j.jtcvs.2019.06.113>
11. Gonzalez-Rivas D, Rami-Porta R, Commentary. Intraoperative lymph node assessment by robotic, video-assisted thoracoscopic surgery, and thoracotomy: none meet the international recommendations. *J Thorac Cardiovasc Surg Nov*. 2019;158(5):1469–70. <https://doi.org/10.1016/j.jtcvs.2019.06.088>
12. Hennon MW, DeGraaff LH, Groman A, Demmy TL, Yendamuri S. The association of nodal upstaging with surgical approach and its impact on long-term survival after resection of non-small-cell lung cancer. *Eur J Cardiothorac Surg May*. 2020;1(5):888–95. <https://doi.org/10.1093/ejcts/ezz320>
13. Sugi K, Kaneda Y, Esato K. Video-assisted thoracoscopic lobectomy achieves a satisfactory long-term prognosis in patients with clinical stage IA lung cancer. *World J Surg Jan*. 2000;24(1):27–30. <https://doi.org/10.1007/s002689910006>. discussion 30–1.
14. Stephens N, Rice D, Correa A, et al. Thoracoscopic lobectomy is associated with improved short-term and equivalent oncological outcomes compared with open lobectomy for clinical stage I non-small-cell lung cancer: a propensity-matched analysis of 963 cases. *Eur J Cardiothorac Surg Oct*. 2014;46(4):607–13. <https://doi.org/10.1093/ejcts/ezu036>
15. Darling GE, Allen MS, Decker PA, et al. Number of lymph nodes harvested from a mediastinal lymphadenectomy: results of the randomized, prospective American College of Surgeons Oncology Group Z0030 trial. *Chest May*. 2011;139(5):1124–9. <https://doi.org/10.1378/chest.10-0859>
16. Edwards JG, Chansky K, Van Schil P, et al. The IASLC Lung Cancer Staging Project: analysis of resection margin status and proposals for residual tumor descriptors for Non-small Cell Lung Cancer. *J Thorac Oncol Mar*. 2020;15(3):344–59. <https://doi.org/10.1016/j.jtho.2019.10.019>
17. Osarogiagbon RU, Decker PA, Ballman K, Wigle D, Allen MS, Darling GE. Survival implications of variation in the thoroughness of Pathologic Lymph Node Examination in American College of Surgeons Oncology Group Z0030 (Alliance). *Ann Thorac Surg Aug*. 2016;102(2):363–9. <https://doi.org/10.1016/j.athoracsur.2016.03.095>
18. Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. *J Thorac Cardiovasc Surg Mar*. 2011;141(3):662–70. <https://doi.org/10.1016/j.jtcvs.2010.11.008>
19. Zhong W, Yang X, Bai J, Yang J, Manegold C, Wu Y. Complete mediastinal lymphadenectomy: the core component of the multidisciplinary therapy in resectable non-small cell lung cancer. *Eur J Cardiothorac Surg Jul*. 2008;34(1):187–95. <https://doi.org/10.1016/j.ejcts.2008.03.060>
20. Krantz SB, Lutfi W, Kuchta K, Wang CH, Kim KW, Howington JA. Improved Lymph Node Staging in Early-Stage Lung Cancer in the National Cancer Database. *Ann Thorac Surg Dec*. 2017;104(6):1805–14. <https://doi.org/10.1016/j.athoracsur.2017.06.066>
21. Zhou H, Tapias LF, Gaissert HA, et al. Lymph Node Assessment and Impact on Survival in Video-assisted thoracoscopic lobectomy or segmentectomy. *Ann*

- Thorac Surg Sep. 2015;100(3):910–6. <https://doi.org/10.1016/j.athoracsur.2015.04.034>
22. Marulli G, Faccioli E, Mammanna M, et al. Predictors of nodal upstaging in patients with cT1–3N0 non-small cell lung cancer (NSCLC): results from the Italian VATS Group Registry. *Surg Today* Jul. 2020;50(7):711–8. <https://doi.org/10.1007/s00595-019-01939-x>
23. Medbery RL, Gillespie TW, Liu Y, et al. Nodal upstaging is more common with thoracotomy than with VATS during Lobectomy for Early-Stage Lung Cancer: an analysis from the National Cancer Data Base. *J Thorac Oncol* Feb. 2016;11(2):222–33. <https://doi.org/10.1016/j.jtho.2015.10.007>
24. Boffa DJ, Kosinski AS, Paul S, Mitchell JD, Onaitis M. Lymph node evaluation by open or video-assisted approaches in 11,500 anatomic lung cancer resections. *Ann Thorac Surg* Aug. 2012;94(2):347–53. <https://doi.org/10.1016/j.athoracsur.2012.04.059>. discussion 353.
25. Reichert M, Steiner D, Kerber S, et al. A standardized technique of systematic mediastinal lymph node dissection by video-assisted thoracoscopic surgery (VATS) leads to a high rate of nodal upstaging in early-stage non-small cell lung cancer. *Surg Endosc* Mar. 2016;30(3):1119–25. <https://doi.org/10.1007/s00464-015-4312-9>
26. Lee PC, Kamel M, Nasar A, et al. Lobectomy for Non-small Cell Lung Cancer by Video-assisted thoracic surgery: effects of cumulative institutional experience on adequacy of Lymphadenectomy. *Ann Thorac Surg* Mar. 2016;101(3):1116–22. <https://doi.org/10.1016/j.athoracsur.2015.09.073>
27. Mao Y, He J, Zhang Z, et al. [Comparison of the lymph node dissection and complications between video-assisted thoracoscopic (VATS) esophagectomy and conventional esophagectomy via right thoracotomy]. *Zhonghua Zhong Liu Za Zhi* Jul. 2015;37(7):530–3.
28. Stamenovic D, Messerschmidt A, Schneider T. Cumulative Sum analysis of the learning curve for Uniportal Video-Assisted thoracoscopic lobectomy and Lymphadenectomy. *J Laparoendosc Adv Surg Tech* Jul. 2019;29(7):914–20. <https://doi.org/10.1089/lap.2018.0802>
29. Al-Alao BS, Gately K, Nicholson S, McGovern E, Young VK, O'Byrne KJ. Prognostic impact of vascular and lymphovascular invasion in early lung cancer. *Asian Cardiovasc Thorac Ann* Jan. 2014;22(1):55–64. <https://doi.org/10.1177/0218492313478431>
30. Higgins KA, Chino JP, Ready N, et al. Lymphovascular invasion in non-small-cell lung cancer: implications for staging and adjuvant therapy. *J Thorac Oncol* Jul. 2012;7(7):1141–7. <https://doi.org/10.1097/JTO.0b013e3182519a42>

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