European Journal of Cardio-Thoracic Surgery 54 (2018) 664–670
doi:10.1093/ejcts/ezy098 Advance Access publication 20 March 2018

ORIGINAL ARTICLE

Cite this article as: Gonfiotti A, Bertani A, Nosotti M, Viggiano D, Bongiolatti S, Bertolaccini L *et al*. Safety of lymphadenectomy during video-assisted thoracic surgery lobectomy: analysis from a national database. Eur J Cardiothorac Surg 2018;54:664–70.

Safety of lymphadenectomy during video-assisted thoracic surgery lobectomy: analysis from a national database†

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Received 25 September 2017; received in revised form 5 February 2018; accepted 11 February 2018

Abstract

OBJECTIVES: The Italian VATS Group database was accessed to evaluate whether preoperative and intraoperative factors may affect the safety of lymphadenectomy (LA) during video-assisted thoracic surgery lobectomy.

METHODS: All video-assisted thoracic surgery lobectomy procedures performed between 1 January 2014 and 30 March 2017 for non-small-cell lung cancer with cN0 or cN1 disease were identified in the database. LA safety was evaluated based on intraoperative (operative time, bleeding and conversion rate) and postoperative (30-day morbidity and mortality, chest drain duration and length of stay) outcomes and was correlated with the number of resected lymph nodes and the rates of nodal upstaging. Continuous variables were presented as mean ± standard deviation and compared using the unpaired *t*-test; the χ^2 test was used for categorical variables. Univariable analysis was performed on selected variables. Significant variables ($P < 0.30$) were entered into a Cox multivariable logistic regression model, using the overall and specific occurrence of complications as dependent variables. The Spearman's rank correlation coefficient was applied as needed.

RESULTS: A total of 3181 cases (2077 men, 65.3%; mean age of 69 years) met the enrolment criteria. Final pathology was consistent with adenocarcinoma ($n = 2262$, 67.5%), squamous cell ($n = 520$, 15.5%), typical ($n = 184$, 5.5%) and atypical carcinoid ($n = 48$, 1.4%) and other ($n = 335$, 10%). The mean number of resected lymph nodes was 13.42 ± 8.24; nodal upstaging occurred in 308 of 3181 (9.68%) cases. Six hundred and fifty-five complications were recorded in 404 (12.7%) patients; in this series, no mortality was observed. Univariable and multivariable analyses did not show any association between the extension of LA and intraoperative or postoperative outcomes. The number of resected lymph nodes and nodal upstagings showed a minimal correlation with intraoperative outcomes and a moderate correlation with postoperative air leak ($\rho = 0.35$ and $\rho = 0.48$, respectively), arrhythmia ($\rho = 0.29$ and $\rho = 0.35$, respectively), chest drain duration ($\rho = 0.35$ and $\rho = 0.51$, respectively) and length of stay ($\rho = 0.35$).

CONCLUSIONS: Based on the VATS Group data, video-assisted thoracic surgery LA proved to be safe and displayed good outcomes even when performed with an extended approach.

Keywords: Video-assisted thoracic surgery • Lobectomy • Lung cancer

INTRODUCTION

Video-assisted thoracic surgery lobectomy (VATS-L), compared to lobectomy by thoracotomy, is associated with superior postoperative outcomes and fewer postoperative complications [1, 2]. However, the safety of VATS lymphadenectomy (LA) performed in limited-volume centres or during the learning curve (LC) phase is still debated [3]. This aim of this study was to analyse the Italian VATS-L database (www.vatsgroup.org) to evaluate which factors may influence the safety of LA performed during VATS-L for clinical N0 and N1 non-small-cell lung cancer (NSCLC). An analysis from a large sample size and national database may allow a more comprehensive understanding of VATS LA.

†Presented at the 31st Annual Meeting of the European Association for Cardio-Thoracic Surgery, Vienna, Austria, 7–11 October 2017.

MATERIALS AND METHODS

Data source

The Italian VATS Group database (www.vatsgroup.org) is a multi-centre, web-based database, including clinical data, outcomes and patterns of care of patients treated with a VATS-L. The Italian VATS Group has maintained this prospective database since January 2014 [4]. At the time of the latest report, the database included 55 affiliated centres (general thoracic surgery units or services) and 5053 collected cases. Data may be inserted in the database using a standardized form that includes information about patient demographics, medical history, surgical procedures, cancer staging and outcomes. Follow-up are requested at 30 days, every 6 months for the first 2 years and yearly thereafter. Data are handled by the VATS Group Scientific Advisory Board. The database implements rigorous quality assurance and safety procedures to maintain a high level of accuracy and security of data such as real-time web-based input checks, quality assurance reports provided by data managers and on-site audits by a Quality Committee. Security features include firewall security, web password-protected access and data encryption over the Internet. To be included in the database, patients must meet the criteria of a VATS-L as defined by the VATS Group policy: surgery performed exclusively by monitor vision, access incision <6 cm without rib spreading, 1–3 additional 1-cm ports, individual dissection of hilar structures with associated LA and use of an endobag for specimen extraction. The extent of LA is defined following the European Society of Thoracic Surgeons (ESTS) guidelines for intraoperative lymph node (LN) staging in NSCLC [5].

Patient population

The study population included patients undergoing VATS-L as a primary procedure for NSCLC within accredited VATS Group centres and enrolled in the VATS Group Database between 1 January 2014 and 30 March 2017. The other inclusion criteria were at least 30 days of complete follow-up, >75 VATS-L case-centre experience, a final diagnosis consistent with at least one of the American Joint Committee on Cancer-defined NSCLC subtypes [6], no previous radiotherapy or surgery on the same side, cN0 or cN1 disease and at least 1 dissected LN. Patient records in the VATS registry included age, gender, Charlson and Eastern Cooperative Oncology Group (ECOG) comorbidity score [7, 8] and the technique of VATS lobectomy. The preoperative clinical stage was determined based on the results of preoperative computed tomography scan, positron emission tomography scan, mediastinoscopy and endoscopic bronchial or oesophagal ultrasound. The lower limit of 75 cases was used in the analysis to include only data from high-volume experienced centres and excluding, on the contrary, centres in the initial phase of the LC. The final postoperative pathology report was available for all patients. Specific data on intraoperative LN management were also recorded following the European Society of Thoracic Surgeons (ESTS) guidelines on intraoperative staging [5] and including the number of resected LNs (overall count N1 + N2; N1 nodes and N2 nodes counted separately). Complications were defined as any deviation from the standard postoperative course [9] and recorded according to the Clavien–Dindo classification [10], including pulmonary, pleural, cardiac, renal, gastrointestinal, neurological, wound and other complications. Given the relatively short follow-up time, long-term overall and disease-free survival data were not yet available for this population. The end-point of the study was to analyse the safety of LA performed during VATS-L. To accomplish this task, intraoperative (operative time and conversion rate) and postoperative (30-day morbidity and mortality, chest drain duration and length of stay) outcomes were analysed and correlated with the extension of VATS LA. The extension of LA was evaluated based on the number of dissected LNs (total number, N1 nodes and N2 nodes) and on the rate of overall nodal upstaging (NU); N0-to-N1, N0-to-N2 and N1-to-N2 upstaging were also separately evaluated. Data were pooled from the registry using a dedicated query on 14 January 2017. The study was peer reviewed and approved by the Italian VATS Group scientific advisory board and by the Institutional Research Reviewer Board (IRRB) for data collection, transmission, storage and analysis (81/2014/O/Oss). All the patients included in the Italian VATS group prospective database study signed a dedicated informed consent, and each participating centre obtained their own IRRB approval. The informed consent contained detailed information on the use of all collected data for scientific purposes.

Statistical analysis

Continuous variables were reported as the mean ± standard deviation, whereas categorical variables were given as percentages. Unpaired Student's *t*-test was used to compare continuous data, and Pearson's χ^2 and Fisher's exact test were used for categorical variables. Univariable analysis was performed on selected variables. The variables resulting significant at the 0.30 level were entered in a Cox multivariable logistic regression model using the occurrence of overall and specific complications as dependent variables. The significance was set at the 0.05 level. The Spearman's rank correlation coefficient was applied when needed; associations were defined as minimal (coefficients between 0.10 and 0.29), moderate (coefficients between 0.30 and 0.49) or strong (coefficients ≥0.50) [11]. Statistical analysis was performed using SPSS 24.0 (SPSS Inc., Chicago, IL, USA) and R 3.3.1 (R Core Team, 2016).

RESULTS

In the selected time frame, 4542 cases of VATS-L were enrolled in the database. Of these, 318 patients were excluded for the following reasons: benign disease (n = 73), malignancy other than NSCLC (n = 156), previous thoracic surgery (n = 58), clinical N2 disease (n = 19) and preoperative radiotherapy (n = 12). Data from the 23 centres who referred >75 cases and passing the data quality check, according to the ESTS [12], eventually generated a data set of 3181 VATS-L (men: 2077, 65.3%; mean age 69 years) eligible for analysis. Demographics and tumour characteristics are presented in Table 1. The majority of the patients (2922, 91.9%) presented in clinical N0 stage, while 259 (8%) patients in N1 stage. LA was defined as systematic lymph node dissection (LND) in 2439 (76.7%) and as LN sampling in 742 (23.3%) patients [5].

The total (N1 + N2), N1 and N2 mean number of resected LNs was 13.42 ± 8.24, 6.32 ± 4.56 and 7.10 ± 5.63, respectively. The distribution of the number of resected LNs per centre was homogeneous, as shown in Fig. 1. NU occurred in 308 (9.68%) patients: N0-to-N1 NU [153 (4.81%)], N0-to-N2 [139 (4.37%)] and N1-to-

Table 1: Demographics and tumour characteristics

Characteristics	n (%)
Male	2077 (65.3)
Female	1104 (34.7)
Median age (range)	69 (34–89)
cTNM stage	
IA	2383 (79.4)
IB	535 (16.8)
IIA	177 (5.6)
IIB	72 (2.3)
IIIA	14 (0.4)
Lobectomy	
LUL	867 (27.2)
RUL	1118 (35.6)
ML	229 (7.2)
LLL	561 (17.6)
RLL	585 (18.4)
Histology	
Adenocarcinoma	2262 (67.5)
Squamous	520 (15.5)
Typical carcinoid	184 (5.5)
Atypical carcinoid	48 (1.4)
Other	167 (10.1)
pTNM stage	
IA	1683 (52.9)
IB	723 (22.7)
IIA	292 (9.2)
IIB	366 (11.5)
IIIA	117 (3.7)

cTNM: clinical tumour, node and metastasis; LLL: left lower lobe; LUL: left upper lobe; ML: middle lobe; pTNM: pathologic tumour, node and metastasis; RLL: right lower lobe; RUL: right upper lobe.

N2 [16 (0.50%)]. Overall NU was significantly associated with the total number (N1 + N2) of resected LNs ($P < 0.001$), with the number of resected N1 nodes ($P < 0.001$) and with the number of resected N2 nodes ($P = 0.012$).

The mean operative time was 187.4 ± 69.9 min; conversion occurred in 297 (9.3%) cases, of which 92 (2.9%) for major bleeding, 80 (2.5%) for calcified pulmonary artery nodes, 71 (2.2%) for a tumour crossing fissures and/or in an advanced stage and 54 (%1.7) for other reasons. The mean chest drain duration was 4.64 ± 3.36 days; hospitalization lasted on average 6.43 ± 5.54 days. No 30-day mortality was recorded in this population (compared with an overall database 30-day mortality of 9 of 4542, 0.20%). We recorded 655 complications (20.6%) in 404 of 3181 (12.7%) patients. The distribution of postoperative complications is presented in Table 2.

After univariable analysis, no significant association was found between the number of resected LNs and intraoperative and postoperative outcomes; multivariable analysis showed a growing risk of prolonged air leak with the number of resected LNs (Table 3).

The association between NU and intraoperative and postoperative outcomes is presented in Table 4. While on univariable analysis there is a significant association with conversion rate, multivariable analysis failed to confirm this finding.

Spearman's rank correlations between the operative outcomes and the extension of LA are presented in Table 3 (number of resected LNs) and Table 4 (NU). We found a minimal association with operative time, major intraoperative complications (such as major bleeding for vessel damages) and conversions. A minimal association was also found with the type of performed LA (LND, $\rho = 0.21$; LN sampling, $\rho = 0.20$). The other specific outcome measures were as follows: (i) a postoperative arrhythmia showed

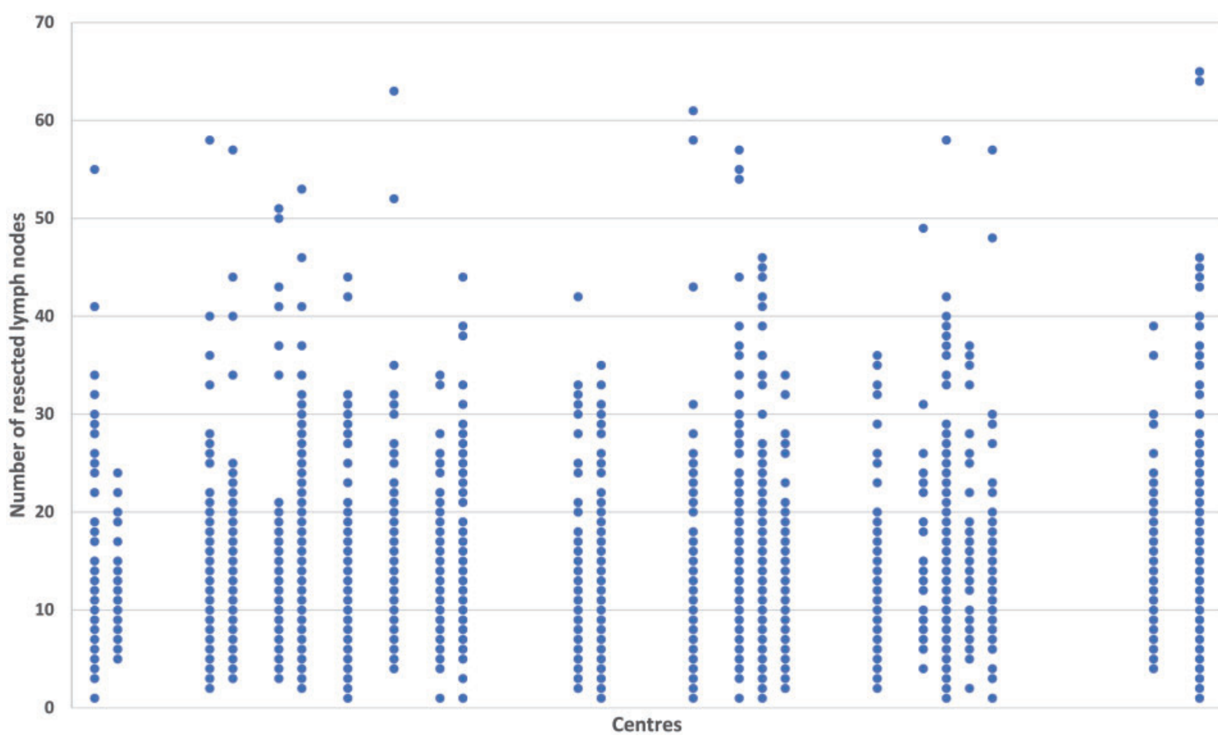

Figure 1: Distribution of the number of resected lymph nodes among the 23 participating centres.

Table 2: Thirty-day postoperative complications

30-Day postoperative complications	*n* (%)
Arrhythmia	193 (29.5)
Prolonged air leak	190 (29.0)
Pneumonia	84 (12.8)
Atelectasis	58 (8.8)
Sputum retention	63 (9.6)
Haemothorax	29 (4.4)
Chylothorax	7 (1.0)
Recurrent laryngeal nerve injury	10 (1.5)
Respiratory failure	11 (1.7)
Acute respiratory distress syndrome	6 (0.9)
Bronchial fistula	5 (0.7)
Overall complications	655 (100)

a minimal association, with the number of resected LNs ($\rho = 0.29$) and a moderate association with N0-to-N1 NU ($\rho = 0.35$); (ii) a prolonged air leak showed a moderate association with the total number of resected LNs ($\rho = 0.35$), with the number of resected N1 LNs ($\rho = 0.35$) and with N0-to-N1 NU ($\rho = 0.48$); (iii) chest drain duration had a moderate association with the total number of resected LNs ($\rho = 0.35$) and a strong association with the number of resected N1 LNs ($\rho = 0.50$) and with N0-to-N1 NU ($\rho = 0.51$) and (iv) the length of hospitalization was only correlated with the number of resected LNs (moderate association: $\rho = 0.35$). A minimal association (close to 0) was found with the following postoperative complications: pneumonia, atelectasis, sputum retention, haemothorax, chylothorax, recurrent laryngeal nerve injury, respiratory failure, acute respiratory distress syndrome and bronchial fistula.

DISCUSSION

VATS-L has recently gained increased popularity, compared with lobectomy by thoracotomy, because of its association with improved postoperative outcomes and less postoperative complications [1, 2]. Although several authors have demonstrated the efficacy of VATS-L, the issue is still debated [13, 14]. Notably, the effectiveness and safety of VATS LA outside speciality centres or during the LC is considered a critical point [2]. Several authors compared LA during VATS and open surgery and found similar results in terms of number of resected LNs, number of sampled or dissected stations and overall survival. D'Amico *et al.* [15] analysed the National Comprehensive Cancer Network NSCLC database to compare the efficacy of mediastinal LND during VATS-L (199 patients) and thoracotomy (189 patients) and found no significant difference in the effectiveness of LA between the 2 approaches. Watanabe *et al.* [16] evaluated the effectiveness of VATS LA based on the number of dissected LNs per station, comparing VATS-L (221 patients) with thoracotomy (190 patients) and observed no differences. Several other studies focus on comparing VATS versus open thoracotomy LA, while just a few papers evaluate whether the extension of VATS LA may affect intraoperative or postoperative complications or, in other words, the safety of VATS-L. Our study is based on a large, well-audited database and focuses on the safety of LA performed during VATS-L; using this data set, we searched for correlations between the extension of LA performed by VATS and the intraoperative and postoperative outcomes.

Extension of LA has been evaluated based on the number of resected LNs and on the rate of NU, as a predictor of the efficacy of intraoperative LN management. These parameters have been consistently shown to be effective measures of the quality of VATS LA [16–18].

Data from the VATS Group institutions have been considered only if complying with the cut-off of 75 cases. Unfortunately, the database does not include information about the LC of the participating centres.

By setting the limit of 75 cases, higher than the 50 cases threshold that is usually set as a LC period [1, 19], we aimed at (i) selecting high-volume centres that definitely completed their LC (at least in the period covered by the study) and excluding low-volume centres or early VATS adopters. However, we cannot completely exclude that cases belonging to the LC have been included in the study.

In our series, an overall mean number of 13.42 nodes was harvested from N1 + N2 stations, while a mean number of 6.32 and 7.10 nodes were retrieved from N1 and N2 stations, respectively; these data matched those of other sizeable VATS-L series in the literature [20]. Unfortunately, the Italian VATS Group database does not contain data about the number and location of the specific N2 and/or N1 LN stations resected. Similarly, the NU rate of 9.68% compares well with the rates reported from other large multicentre databases such as the National Cancer Database (12.8% for open lobectomies vs 10.3% for VATS) [21]. Furthermore, as expected, the number of resected LNs is significantly associated with the rate of NU, confirming that the more the nodes are resected, the higher is the accuracy of nodal staging.

Based on these results, we considered VATS LA within the Italian VATS community as an efficient and oncologically correct procedure in line with other large series.

The extension of VATS LA did not influence operative time (mean time: 187.4 ± 69.9 min) and showed no correlation with the number of resected LNs and NU rates. Decaluwe *et al.* [22] reported a conversion rate of 5.5% in a large multicentre series (*n* = 3076 VATS lobectomies). Our conversion rate is higher (9.3%) but shows no correlation with the extension of LA. Notably, the same series reported vascular damage as a cause of conversion in 2.9% of the cases; we recorded the same incidence of intraoperative vascular injury but, again, no correlation was found with the number of resected LNs and NU. Advocates of an extended LA argue that radical resection of mediastinal LNs not only represents an accurate staging technique but is also associated with improved survival [18, 19, 23]. Nevertheless, a VATS extended LA is more frequently technically demanding, and several postoperative complications can be related to an aggressive mediastinal dissection (phrenic and recurrent laryngeal nerve injury, chylothorax, bleeding, bronchial fistula, etc.). A limited mediastinal dissection (such as sampling) could provide better outcomes, a shorter chest drain duration and hospital stay that are frequent features of VATS-L series. Mokhles *et al.* [24], in a review comparing the results of systematic mediastinal LA versus mediastinal sampling (a total of 1980 patients during the period 1989–2007), found higher (but not statistically significant) rates of perioperative complications (including bleeding, chylothorax and recurrent nerve palsy) with systematic LA. In our series, the extension of VATS LA did not affect postoperative mortality (absent in this population) and morbidity (accounting for 12, 7%); on both multivariable analysis and Spearman's rank correlation, the incidence

Table 3: Association between the total number (N1 + N2) of resected lymph nodes and outcomes: univariable and Cox multivariable logistic regression analyses and Spearman's rank correlation (relationship with the separate count of N1 or N2 resected nodes is presented in case of moderate or high correlation)

Variables	Univariable	Multivariable			Spearman coefficient (N1 + N2)
	P-value	HR	95% CI	*P*-value	
Operative time	0.59				0.20
Intraoperative bleeding	0.16	0.95	0.93–1.12	0.57	0.12
Conversion rate	0.11	1.25	1.01–2.96	0.06	0.29
Overall complications	0.95				0.27
Arrhythmia	0.24	1.02	0.78–1.45	0.78	0.29
Prolonged air leak	0.28	1.41	1.01–1.64	0.03	0.35 N1 = 0.35
Pneumonia	0.99				0.03
Atelectasis	0.61				0.04
Sputum retention	0.60				0.05
Haemothorax	0.86				0.12
Chylothorax	0.78				0.14
Recurrent laryngeal nerve injury	0.75				0.18
Respiratory failure	0.65				0.06
Acute respiratory distress syndrome	0.94				0.05
Bronchial fistula	0.99				0.03
Chest drainage duration	0.62				0.35 N1 = 0.50
Hospital length of stay	0.30	0.89	0.83–1.11	0.81	0.35

CI: confidence interval; HR: hazard ratio; SD: standard deviation.

Table 4: Association between overall nodal upstaging rates and outcomes: univariable and Cox multivariable logistic regression analyses and Spearman's rank correlation (relationship with specific N0-to-N1, N0-to-N2, N1-to-N2 upstaging is presented in case of a moderate or high value coefficient)

Variables	Univariable	Multivariable			Spearman coefficient (overall NU)
	P-value	HR	95% CI	*P*-value	
Operative time	0.43				0.02
Intraoperative bleeding	0.17	1.00	0.99–1.00	0.10	0.12
Conversion rate	0.01	1.33	1.09–2.01	0.17	0.01
Overall complications	0.17	1.63	0.60–4.42	0.33	0.13
Arrhythmia	0.22	1.78	0.82–1.96	0.06	0.29 N0-to-N1 = 0.35
Prolonged air leak	0.20	1.76	0.85–2.32	0.08	0.33 N0-to-N1 = 0.48
Pneumonia	0.82				0.03
Atelectasis	0.56				0.04
Sputum retention	0.66				0.05
Haemothorax	0.78				0.12
Chylothorax	0.84				0.14
Recurrent laryngeal nerve injury	0.82				0.18
Respiratory failure	0.63				0.06
Acute respiratory distress syndrome	0.92				0.05
Bronchial fistula	0.98				0.03
Chest drainage duration	0.30	1.03	0.96–1.10	0.35	0.21 N0-to-N1 = 0.51
Hospital length of stay	0.68				0.11

CI: confidence interval; HR: Hazard ratio; NU: nodal upstaging; SD: standard deviation.

of postoperative complications was not affected by the number of resected LNs and by NU. Notably, the rate of N0-to-N2 and N1-to-N2 upstaging did not affect any intraoperative or postoperative outcome measure; based on these results, we could speculate that LA of N2 stations by VATS is safe and does not influence the intraoperative and postoperative course. On the other side, prolonged air leak, arrhythmia, chest drain duration and hospital length of stay are moderately influenced by the number of resected N1 nodes and by N0-to-N1 NU; this result could suggest that an aggressive hilar (station 10), interlobar (station 11) and lobar (station 12, same or different lobe) LA could have a negative influence on the postoperative course compared to LA of N2 stations. No correlation at all was found between the extension of VATS LA and the incidence of postoperative chylothorax, bleeding, nerve injuries, bronchial fistula and other parenchymal complications (acute respiratory distress syndrome, pneumonia and atelectasis).

Taken as a whole, our data show that VATS LA among the Italian VATS community resulted in postoperative mortality and morbidity rates in line with other large series [1, 2, 13]. Unfortunately, at the present time, we do not have enough data to evaluate the influence of VATS LA on survival.

The current study captures the practice patterns of general thoracic surgeons at 23 Italian institutions and includes every patient eligible for analysis during the time frame of the survey. Although this is a retrospective analysis and does not have the consistency of a prospective study, the database reflects the practice of surgeons outside the potential bias of a trial specifically focused on LN assessment. The database provides the advantages of a large sample size, the comprehensiveness of the data elements included, the inclusion of multiple institutions and rigorous quality control.

Limitations

This study has several limitations. The database is large and multi-institutional but is limited to Italy, and the practice patterns may not be representative of other centres outside Italy. This analysis is subject to selection bias in the choice of procedure, considering the higher percentage of patients with clinical stage I disease. Moreover, this report does not include disease-free or overall survival, which hopefully will be available for later studies. Finally, this database includes the number of LN resected and NU rather than the number of LN stations, which is another important parameter in evaluating the quality and extension of LA; therefore, station-specific complications (e.g. left recurrent laryngeal nerve injury for station 5) could not be assessed.

CONCLUSION

In conclusion, based on the Italian VATS Group database, performing an extended LND during VATS-L in experienced centres did not increase the risk of intraoperative and postoperative complications.

ACKNOWLEDGEMENTS

List of collaborators of the Italian VATS Group: Carlo Curcio (Monaldi Hospital, Napoli); Dario Amore (Monaldi Hospital, Napoli); Giuseppe Marulli (University of Padova); Samuele Nicotra (University of Padova); Andrea De Negri (San Martino Hospital, Genova); Paola Maineri (San Martino Hospital, Genova); Gaetano di Rienzo (Vito Fazzi Hospital, Lecce); Camillo Lopez (Vito Fazzi Hospital, Lecce); Duilio Divisi (University Hospital L'Aquila-Teramo); Angelo Morelli (S. Maria delle Misericordia Hospital, Udine); Emanuele Russo (IRCCS ISMETT-UPMC, Palermo); Francesco Londero (S. Maria delle Misericordia Hospital, Udine); Lorenzo Rosso (General Hospital, University of Milan, Milano); Lorenzo Spaggiari (IEO Hospital, Milano); Roberto Gasparri (IEO Hospital, Milano); Guido Baietto (Maggiore della Carità Hospital, Novara); Caterina Casadio (Maggiore della Carità Hospital, Novara); Maurizio Infante (Borgo Trento Hospital, Verona); Cristiano Benato (Borgo Trento Hospital, Verona); Marco Alloisio (IRCCS Humanitas, Milano); Edoardo Bottoni (IRCCS Humanitas, Milano); Andrea Giovanardi (Carlo Poma Hospital, Mantova); Giuseppe Cardillo (Forlanini Hospital, Roma); Francesco Carleo (Forlanini Hospital, Roma); Franco Stella (S. Orsola Hospital, Bologna); Giampiero Dolci (S. Orsola Hospital, Bologna); Francesco Puma (University of Perugia); Damiano Vinci (University of Perugia); Giorgio Cavallesco (University of Ferrara); Pio Maniscalco (University of Ferrara); Desideria Argnani (AUSL Romagna Hospital Forli); Luca Ampollini (University of Parma); Paolo Carbognani (University of Parma); Alberto Terzi (Negrar Hospital, Verona); Andrea Viti (Negrar Hospital, Verona); Giampiero Negri (S. Raffaele Hospital, Milano); Alessandro Bandiera (S. Raffaele Hospital, Milano); Reinhold Perkmann (Bolzano Hospital, Bolzano); Francesco Zaraca (Bolzano Hospital, Bolzano); Mohsen Ibrahim (S. Andrea Hospital, Roma); Camilla Poggi (S. Andrea Hospital, Roma); Felice Mucilli (S. Maria Annunziata Hospital, Chieti); Pierpaolo Camplese (S. Maria Annunziata Hospital, Chieti); Luca Luzzi (University of Siena); Marco Ghisalberti (University of Siena); Andrea Imperatori (University of Varese); Nicola Rotolo (University of Varese); Luigi Bortolotti (Humanitas Gavazzeni Hospital, Bergamo); Giovanna Rizzardi (Humanitas Gavazzeni Hospital, Bergamo); Massimo Torre (Niguarda Hospital, Milano); Alessandro Rinaldo (Niguarda Hospital, Milano); Armando Sabbatini (Ospedali Riuniti, Ancona); Majed Refai (Ospedali Riuniti, Ancona); Mauro Roberto Benvenuti (Spedali Civili, Brescia); Diego Benetti (Spedali Civili, Brescia); Alessandro Stefani (Ospedale Policlinico, Modena); Pamela Natali (Ospedale Policlinico, Modena); Paolo Lausi (Ospedale Molinette, Torino); Francesco Guerrera (Ospedale Molinette, Torino).

Conflict of interest: none declared.

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