Review Article

A narrative review on lymphadenectomy: from open to minimally invasive surgery

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Objective: One of the most debated topics is minimally invasive lymphadenectomy's safety and quality, in terms of number of lymph-nodes (LNs) dissected, number of mediastinal stations explored and nodal migration rate. With this narrative review, we retraced the history of lymphadenectomy for lung cancer by comparing the main features of open and minimally invasive techniques [video-assisted thoracic surgery (VATS) and robotic surgery].

Background: Lymphadenectomy plays a crucial role during surgical treatment for lung cancer and represents a cornerstone to assess staging and prognosis, since LN involvement is an important factor to define post-operative strategies and to predict oncological outcomes. Nevertheless, unanimous agreement on the extent and the technique of lymphadenectomy is still far from being achieved and even the major societies of Thoracic Surgery and Oncology, proposed different strategies, advice or guidelines on this issue.

Methods: We conducted a PubMed search for relevant literature on lymphadenectomy for non-small cell lung cancer (NSCLC), selecting only those reporting information about feasibility and effectiveness of the various surgical techniques and approaches.

Conclusions: To date, data seem support the value of lymphadenectomy by minimally invasive approaches since outcomes in terms of safety, feasibility, and effectiveness; especially in the treatment of early-stage NSCLC were comparable to those of the open approach. The future discussion about the "perfect lymphadenectomy" will be focused more on other debated arguments that the surgical approach, like the amount of LN material collected (*en bloc* LN or nodal fragments), the most suitable stations to analyse according to the type of intervention or disease's site, and less about comparing the effectiveness of different surgical approaches.

Keywords: Lymphadenectomy; video-assisted thoracic surgery (VATS); robotic-assisted thoracic surgery (RATS); thoracotomy (TX); non-small cell lung cancer (NSCLC)

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Introduction

Lymphadenectomy plays a crucial role during surgical treatment for lung cancer and represents a cornerstone to assess staging and prognosis since lymph-nodes (LN) involvement is an important factor to define post-operative strategies and to predict oncological outcomes [namely overall survival (OS) and disease-free interval] (1,2). According to the 8th TNM edition of non-small cell lung

cancer (NSCLC), in fact, the 5-year survival rates decrease dramatically (independently by the T-factor) from 56% in pathologic (p) N0 to 38% in pN1, 26% in pN2 and 6% in pN3 disease (3).

Nevertheless, unanimous agreement on the extent and the technique of lymphadenectomy is still far from being achieved and even the major societies of Thoracic Surgery and Oncology, proposed different strategies, advice or guidelines on this issue.

In this scenario, one of the most debated topics is minimally invasive lymphadenectomy's safety and quality, in terms of number of LN dissected, number of mediastinal stations explored and nodal migration rate. Since thoracotomy (TX) was progressively superseded by video-assisted thoracic surgery (VATS) or robotic (RATS) approach especially in early-stage cases, the aim of this narrative review is comparing lymphadenectomy features and outcomes between minimally invasive and open surgery.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://vats.amegroups.com/article/view/10.21037/vats-21-33/rc).

Methods

Relevant literature up to January 2020 was searched in PubMed using as keywords: "lymphadenectomy" and "NSCLC" and "thoracotomy OR VATS OR RATS OR video-assisted thoracic surgery OR robotic surgery". The search was limited to English language and relevant studies were identified, screened, and reviewed by all the authors.

We conducted an accurate research focused on the comparison between lymphadenectomy performed by various surgical techniques (VATS, RATS or open TX), and we selected only those with information about number of LNs and nodal stations removed or upstaging rate analysis (*Table 1*). Unpublished material, congress abstracts, and proceedings were not considered.

Lymphadenectomy: the more you search, the more you find

According to Naruke LN map, the European Society of Thoracic Surgery (ESTS) proposed for a radical resection both the dissection and the biopsy of at least stations 4 R/L, 10 R/L, 2 R/L and 7 in all cases of NSCLC patients who underwent surgery, as well as the extension to the stations 5, 6, 8, 9 if clinically involved during the pre-operative evaluation (14).

Similarly, the American College of Surgeons Oncology Group (ACOSOG) guidelines suggested surgical removal of stations 2R, 4R, 7, 8, e 9 for right-side tumors, while 4L, 5, 6, 7, 8 and 9 for the left-side ones (15); while the International Association for the Study of Lung Cancer (IASLC) focused on the hilar dissection by suggesting a proper surgical staging of at least 2R, 4R ,7, 10R e 11R-stations for the right-side NSCLCs and of 5, 6, 7, 10L, 11L stations for those in the left side (16).

More generically, the National Comprehensive Cancer Network (NCCN) invited to investigate at least three mediastinal LN stations to assess an accurate staging (17).

Besides the number of nodal stations to harvest, even the extension of mediastinal lymphadenectomy is still under debate, since it lacks an agreement on the most common techniques proposed between mediastinal LN dissection (MLND) and mediastinal LN sampling (MLNS).

Rami-Porta *et al.* in 2005 proposed a definition of MLNS as removal of one or more nodes suspicious during surgery or by removing LNs closest to the area of resection; while the systematic dissection consists in a complete removal of all mediastinal tissue including, at least, three mediastinal stations, one of which should be the subcarinal station, together with the excision of all hilar and intrapulmonary LNs (18).

In an effort to validate both techniques, in 2011 the American College of Surgeons Oncology Group published results of a randomized controlled trial (ACOSOG Z0300) on the oncological differences between MLND or MLNS in patients with clinical N0 or N1 early-stage NSCLC, reporting no differences between two groups in terms of OS and disease-free interval (19).

On the other hand, in 2012, Cerfolio and colleagues, reported a higher rate of mediastinal upstaging in patients underwent to MLND compared to MLNS during radical surgery for NSCLC (20).

Nevertheless, in 2016 Samayoa *et al*. published an analysis on a large number of patients from the National American Cancer Data Base during a 10-year study period (2004–2014) focused on correlation between the number of LN removed and OS. The study showed an advantage in terms of OS for patients with a higher number of LN removed, with a cut-off of 10 LNs; more in detail, authors observed that the group of patients with a smaller number of LN removed (≤9) was associated with a 12% increased risk of death (HR: 1.12, P<0.001) (21).

Another issue to deal with in the comparative analysis between MLND and MLNS is the peri-operative

Table 1 Comparison of LNs dissection features between different articles

Authors/year	No. of patients	Approach	No. of LN removed	No. of nodal station removed (mean)	Upstaging rate	NCLSC stage	Comments
D'amico 2011 (4)	388	199: VATS, 189: TX	NR	4.80: VATS, 4.40: TX	cN0–cN1, 8.8% VATS, 14.5% TX	83% VATS: I, 31% TX: II–III	Similar number of LN were removed; no significant differences in terms of upstaging
Palade 2013 (5)	66	34: VATS, 32: TX	VATS: 24.00±7.50 for the right side, 25.10±9.30 for the left side; TX: 25.20±7.20 for the right side, 21.10±10.40 for the left side	NR	NR	All patients stage I	No statistically difference both as regard LN dissection and for upstaging rate
Licht 2013 (6)	1,513	717: VATS, 796: TX	NR	4.57: VATS, 4.51: TX	cN0–cN1, 8.1% VATS, 13.1% TX; cN0–cN2, 3.8% VATS, 11.5% TX	All patients stage I	The number of LN stations dissected was not significantly different. The upstaging rate was higher in TX P value <0.001
Zhang 2018 (7)	497	242: VATS, 255: TX	VATS: 16.63, TX: 17.32	4.14: VATS, 3.97: TX	cN0–Pn2, 29% VATS, 25% TX	60% VATS: I, 49% TX: I	MLN dissection under VATS has the similar surgical effectiveness to open procedure. TX has an advantage on dissection MLN in group 71 (P value <0.01)
Toker 2016 (8)	270	68: VATS, 106: RATS, 96: TX	NR	4.60: VATS, 4.90: RATS, 4.6: TX	cN0–cN1, N1: mean 3.8 VATS, N1: mean 6.8: RATS, N1: mean 4.0: TX	53% VATS: I, 60% RATS: I, 25% TX: I	RATS: significantly more N1-level LN could be dissected. P value <0.0001
Bao 2016 (9)	184	113: VATS, 71: RATS	17.40: VATS, 17.90: RATS	NR	cN0–cN1, 15.9%: VATS, 5.8%: RATS	76% VATS: I, 94% RATS: I	The rate of nodal upstaging for VATS resection appears to be superior to robotic resection. P value =0.056; No significant difference was found in numbers of dissected LNs, stations of LNs retrieved
Tang 2020 (10)	57,638	7,452: RATS, 50,186: TX	10.00: RATS, 8.00: TX	NR	cN0–cN1, 11%: RATS, 11.6%: TX	84% RATS: I, 82.9% TX: I	There was no difference in nodal upstaging between patients who underwent open or robotic lobectomy. More LNs were examined in patients who underwent robotic lobectomy. P value <0.001
Kneuertz 2020 (11)	514	118: VATS, 245: RATS, 151: TX	10.80: VATS, 10.30: RATS, 10.00: TX	NR	cN0–cN1, 15% VATS, 38% RATS, 31% TX	90% VATS: I, 85% RATS: I, 82% TX: I	No differences were found in the average total number of LNs resected. No differences statistical significance were found in the role of upstaging

Table 1 (*continued*)

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Authors/year	No. of patients	Approach	No. of LN removed	No. of nodal station removed (mean)	Upstaging rate	NCLSC stage	Comments
Zirafa 2018 (12)	212	106: RATS, 106: TX	14.42: RATS, 14.32: TX	4.95: RATS, 4.22: TX	cN0–cN2, 9.4%: RATS, 2.8%: TX	61 Ia, 37 Ib, 7 IIa, and 1 IIb: RATS; 43 Ia, 39 Ib, 13 IIa, and 11 IIb: TX	A greater rate of upstaged cases in the robotic group, in particular, to the detection of metastatic mediastinal LNs. P value =0.045
Novellis 2021 (13)	169	58: TX, 58: VATS, 53: RATS	VATS *vs.* RATS, 5.00: VATS, 6.00: RATS	RATS *vs.* TX, 5.00: RATS, 4.00: TX, VATS *vs.* RATS, 4.00: VATS, 5.00: RATS	NR	All stage I or II	A significantly higher median number of removed hilar LN and LN stations was observed with RATS compared with VATS; P value =0.001 (station removed); P value =0.01 (medial hilar LN removed)

VATS, video-assisted thoracic surgery; RATS, robot-assisted thoracic surgery; TX, thoracotomy; NR, not reported; LN, lymph-node.

complications rate. According to different authors there was no statistical difference in terms of intra and post-operative complications rate between MLND and MLNS and these results were supported by the findings of the ACOSOG Z0030 trial that reported a complications rate of 37.9% and 38.6% for MLND and MLNS respectively, without significant differences for each specific complication (22-25).

Nevertheless, as reported by Venuta *et al.* in 2017, an agreement on the lymphadenectomy technique is still far from being achieved due to different variables to be considered and evaluated, as the quality of the material removed (i.e., *en bloc* LN dissection), the extent of the parenchymal lung resection, the tumour features and, mostly, the surgical approach (26).

From open to minimally invasive surgery

VATS

The other face of the coin regards the discussion on the value and the effectiveness of lymphadenectomy performed by minimally invasive surgery (*Table 1*).

During the last decades, minimally invasive approaches such as VATS and RATS, gained a wide consensus for the treatment of NSCLC. Recently, VATS lobectomy became the procedure recommended by several thoracic societies to treat operable early NSCLC, since its clinical application spread exponentially worldwide thanks to progressively matured experience and to the encouraging oncological results.

One of the first study on this topic dated 2002 when Sagawa *et al*. wondered how and if a systematic nodal dissection for lung cancer by VATS could be considered safe and equivalent to the open technique. In this prospective study, 35 patients with clinical stage-I NSCLC underwent minimally invasive surgery for lung resection and systematic lymphadenectomy; afterwards, all patients underwent standard TX performed by a second surgeon to eventually complete the nodal dissection. Authors reported a very small number of LN removed during the second time, with an average of 1.2 out of 40.3 nodes in the right side and 1.2 out of 37.1 for the left side, counting for 2.4% and 2.8% of the all the LN dissected, respectively. Moreover, authors described a very low conversion-rate (six cases) during the VATS nodal dissection, caused in most cases by severe adhesion of calcified LNs stuck to the pulmonary vessels, concluding that nodal VATS dissection could be considered as an effective and safe procedure for patients with early-

stage NSCLC (27).

More recently, D'Amico *et al.* in 2011 compared VATS to open surgery to evaluate the efficacy of MLND during lobectomy for lung cancer. This study demonstrated a similar number of LN stations sampled while no significant differences in terms of upstaging or downstaging rate, supporting the oncologic value of thoracoscopic lymphadenectomy, although VATS group had a higher rate of patients (83%) with stage I disease compared with the open group (69%) (4).

Boffa *et al.* in 2012 analysed data from the Society of Thoracic Surgery database on a large number of lobectomies and segmentectomies to evaluate frequency of nodal metastases in clinically node-negative tumors operated by TX and VATS approaches. Authors concluded that mediastinal nodal evaluation by VATS and TX results in equivalent upstaging-rate but, conversely, they found a lower rate of N1 upstaging for the VATS group (28).

Same results were demonstrated by Palade *et al.* in a prospective randomized controlled study on the effectiveness of MLND performed via both VATS and antero-lateral TX for clinical stage I NSCLC. The mean number of the overall removed LNs (intra-parenchymal, hilar, and mediastinal) was comparable between the two groups for both side (P value: 0.98 and 0.32 for the right and left side, respectively) (5).

Similarly, in 2013, a study conducted by Licht and colleagues based on the Danish national registry, focused on the comparison between VATS and TX to assess nodal upstaging, revealed that the number of LN stations dissected was not significantly different between the two techniques.

On the other hand, the nodal upstaging was significantly more frequent during TX, for both clinical N0 and pathological N1; even though this finding has had no impact on the survival as confirmed by the multivariate analysis (6).

Another study that corroborates the effectiveness of VATS lymphadenectomy for NSCLC was published by Zhang *et al.* in 2018. They demonstrated that, compared to TX, patients that underwent lobectomy and MLND via three-port VATS have similar surgical outcomes, except for what concerns dissection of station 7L, which resulted significantly improved in the open surgery group. The authors explained this issue with the peculiar anatomy of this station, due to which the triportal VATS approach is difficult and related to increased risk of bronchial and esophageal injury (7).

Recently, Matsuura *et al.* in 2020 published a retrospective study focused on lymphadenectomy in early-stage lung cancer divided in two groups matched by a propensity score analysis. They reported that surgical approach was not significantly associated with nodal upstaging and, since it was an independent prognostic factor for a worse overall and recurrence-free survival, authors conclude that outcomes between VATS and open were equivalent (29).

RATS

In the era of new technologies and minimally invasive surgery, RATS deserves a special mention. Since 2002, several studies highlighted benefits of robotic technology in the surgical treatment of lung cancer despite its relative limited availability worldwide (30).

In order to analyse the efficacy and differences of lymphadenectomy between techniques, in 2016, Bao *et al.* published a comparison of robotic and video-assisted surgery for lung cancer. They proved that lymphadenectomy was similar in patients operated by the two techniques in terms of both resected number of LNs and LN stations sampled even if nodal upstaging rate in the VATS group was higher than in robotic group (16.0% *vs.* 5.8%) (9).

Alper Toker and colleagues in 2016 demonstrated that RATS allowed a more accurate hilar dissection and a higher number of hilar LN dissected compared to VATS and open procedures. In their discussion, authors speculated that possible explanations may be found in the surgical technique, as the console surgeon should provide to the table assistant a wide and clear area around vessels and bronchi before their closure by dissecting all LNs (8).

Cerfolio *et al.* in 2017, published a multi-institutional retrospective study on data from four different institutions with expertise in robotic thoracic surgery. Herein, authors reported encouraging stage-specific survival of patients with completely resected NSCLC and systematic node dissection (31).

In 2018 Zirafa *et al.* published a study on a large number of patients affected by operable cN0 NSCLC, comparing the upstaging rate in both open and robotic lobectomy. Authors found a comparable number of LN dissected: 14.42 (±6.99) for RATS and 14.32 (±7.34) in open surgery with a favourable difference in terms of mediastinal stations explored by RATS. Moreover, they underlined the effectiveness of robotic surgery on detecting nodal upstaging from cN0 to pN2, with a significant difference when compared to the open approach (9.4% *vs.* 2.8%, P value: 0.045) (12).

In 2020, Tang *et al.* published a study focused on the differences between Robotic lymphadenectomy versus

the open approach by using a National Cancer Database. Authors reported a higher number of LN sampled in the robotic group (10 *vs.* 8, P<0.001) even if there were no differences in terms of nodal upstaging (11.0% with robotic technique *vs.* 11.6% in open cases) (10).

Recently, Novellis and collegues compared the three different surgical approaches for the treatment of early-stage NSCLC in the same institute reporting a significantly higher number of removed hilar LN and of LN stations by robotic approach (P<0.001) (13).

From minimally invasive surgery to open: causes of conversion

In the analysis of lymphadenectomy features in between the three-legged stool of the surgery for NSCLC, should be mentioned the role of conversion-rate from minimally invasive surgery to open technique.

Agzarian and Shargall in a review published in 2017 reported that the most common causes of conversion were the presence of calcified LN close to pulmonary artery branches (32).

Sawada *et al.* in 2009 published a paper focused on the causes of conversion during lung resection for lung cancer by VATS technique reporting that the most frequent reasons for conversion were calcified hilar lymphadenopathy and bleeding, followed by incomplete fissure and lymph-node metastasis (33). In a study of Samson *et al.* published in 2013, authors developed a preoperative computed tomography calcification score based on anatomic location and extent of calcifications in order to evaluate the risk of conversion. Authors collected data on 193 patients who underwent VATS lobectomy, and they performed a comparison between the group who were converted (23%) and the group who did not; patient characteristics were similar between the groups except for the calcification score that was statistically significant higher in the first group (34).

Conclusions

In the comparative analysis of the above-mentioned articles, results seem support minimally invasive approaches since comparable outcomes have been demonstrated in terms of safety, feasibility, and effectiveness of LN dissection; especially for the early-stage NSCLC regardless the extent of the lymphadenectomy.

Unfortunately, an indicator to assess a good lymphadenectomy is not yet widely recognized since different parameters were highlighted by various authors, as the number of LN or nodal stations dissected or the upstaging rate. Hence, a clear comparison among the results described in literature is quite impossible to establish which may be the proper technique and approach.

The goal of oncological surgery is granting the longest survival expectancy possible, and all these techniques have been extensively studied also in terms of long-term oncological outcomes namely OS, disease-free survival, and recurrence-rate.

In 2019 Kneuertz *et al.* performed a retrospective study on 514 patients treated by lobectomy for I-III stage NSCLC of which 254 treated by robotic technique, 118 by VATS and 151 by TX. The rate of complete R0 resection was similar among the three techniques and authors found similar loco-regional recurrence rates, comparable long-term OS and DFS regardless the number of LNs dissected, and the upstaging rate achieved (11).

To date, most studies on the technique used (open or minimally invasive) reported comparable mid and long-time oncological results.

Gossot in an editorial published in 2019 wondered if was still necessary a discussion about the surgical technique to treat early-stage lung cancer. Herein, author reported how all literature comparing surgical approaches has increasingly demonstrated no significant differences for what concerns the oncological outcomes and, the effectiveness of lymphadenectomy, concluding that the only discussion needed should be shifted from a comparison between open and minimally invasive surgery, to a comparison between surgery against non-surgical techniques (35).

The future discussion about the "perfect lymphadenectomy" will be focused more on other debated arguments, like the amount of LN material collected (*en bloc* LN or nodal fragments), the most suitable stations to analyze according to the type of intervention or disease's site, and less about comparing the effectiveness of different surgical approaches.

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Footnote

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