



Lymph node dissection in the left upper lobe: clinical outcomes and surgical techniques in Japan

Hiroaki Kuroda¹, Yusuke Sugita¹, Keita Nakanishi¹, Yukinori Sakao^{1,2}

¹Department of Thoracic Surgery, Aichi Cancer Center Hospital, Nagoya, Japan; ²Department of General Thoracic Surgery, Teikyo University School of Medicine, Itabashi, Tokyo, Japan

Correspondence to: Hiroaki Kuroda. Department of Thoracic Surgery, Aichi Cancer Center Hospital, 1-1, Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan. Email: h-kuroda@aichi-cc.jp.

Comment on: Wang YN, Yao S, Wang CL, *et al.* Clinical Significance of 4L Lymph Node Dissection in Left Lung Cancer. *J Clin Oncol* 2018;36:2935-42.

Received: 25 November 2018; Accepted: 15 April 2019; published: 07 May 2019.

doi: 10.21037/med.2019.04.04

View this article at: <http://dx.doi.org/10.21037/med.2019.04.04>

Introduction

Pulmonary resection with mediastinal lymph node dissection (MLND) is a well-known standard treatment for early-stage non-small-cell lung cancer (NSCLC) (1). Promising procedures for early-stage NSCLC, even in segmentectomy with MLND have been reported (2). However, the most significant role of MLND is to help determine precise pathological staging. It has not yet been established whether complete MLND contributes to the improvement of surgical prognosis. However, thoracic surgeons have performed further interventions regardless of this matter completely. Recently, two systemic reviews and meta-analyses concluded that lobe-specific MLND appeared to provide equal survival benefits compared with systemic MLND (3,4). Our team as well as other well-known Japanese authors has shared common perceptions regarding lobe-specific regional lymph node mapping. In this paper, we focus on our recommended lobe-specific regional MLND in left upper lobe (LUL) and surgical techniques particularly on thoracoscopic surgery with reference to recent studies and our experience.

Extra-superior mediastinal lymph nodes (ESMLNs)

In 2006, Sakao *et al.* have reported regarding the spread of metastatic lymph node in pN2 LUL-NSCLCs on median sternotomy and concluded that the most common metastatic stations were the aortic nodes (AN#5+6; subaortic #5 or para-aortic #6) in 71.4% of cases, followed

by the lower paratracheal nodes (LPT#4L) in 42.8%, and the subcarinal nodes (SC#7) in 7.1% (5). This study was limited by its single-center design and small-size analyses (n=14), but a complete analysis of extra-superior MLN (ESMLN) was capable of arousing interests and resulted in detection of 50.0% and 7.1% pN2-NSCLCs of the total and skip metastases, respectively (5). In addition, multivariate analyses found the significance of AN#5+6 metastasis (5). Regarding outcomes of ESMLN metastases, there were no 5-year survivors in seven ESMLN metastases (5). Furthermore, adequate dissection of ESMLN through left-sided thoracotomy or thoracoscopic surgery alone is challenging; therefore, additional right-sided approach is required for accumulation of ESMLN data. Another novel investigation in 2006 by Sakao *et al.* had reported the significance of highest lymph node metastases among ESMLNs (6). The highest ESMLN is located nearest to the venous angle. They have reported that the 3-year overall survival (OS) was 21% in patients with highest ESMLN metastasis and concluded that the prognostic importance of the highest ESMLN metastasis was independent of whether the primary tumor was in the left or right lung on median sternotomy (6). The highest ESMLN metastasis is originally synonymous with “pN3”. Supportive data published in 1995 revealed that most cases (80.0%) with the highest ESMLN resulted in neck lymph node metastases (7). Complete and extent dissection of ESMLN on median sternotomy is the procedure of choice for left-sided NSCLC (8). We considered that the dissection to ESMLNs is clinically unnecessary, but these

articles should be regarded for their valuable findings.

Left upper lobe (LUL)

One large data-based survey of 24,273 stage I NSCLCs has reported the proportions of surgical sites and concluded that the right upper lobe (RUL) was the most common site, which accounts for 35% of cases, followed by the LUL for 27% (9). A recent retrospective study with large sample-size analyses (n=657) regarding the LPT#4L dissection has concluded that the metastasis rate of the LPT#4L was not rare (20.9% of cases) and the #4L dissection appeared to be associated with a more favorable prognosis compared with no LPT#4L dissection in the left-lobe NSCLCs based on propensity-score weighing (10). In our previous study, the metastasis rate of the LPT#4L was 17.7% (74/417) in the LUL-NSCLCs, which was consistent with results of the study by Chi *et al.* (11). Unfortunately, we were unable to compare cases with or without the LPT#4L dissection, where is a decisive difference between our and Chi *et al.*'s data on prognosis. Their report on the LPT#4L is ever unprecedented, and the accumulation of data which paid attention to the prognosis in every station may be essential to determine the range of lobe-specific MLND.

The metastasized pN1 was divided into two groups: the first group implies uninvolved lymph node (pN0) in the inner side of the lobe [peripheral zone (lobar #12 i.e., LOB#12, segmental #13, and subsegmental #14)], and the other group implies behavior similar to that of early-stage pN2 disease [hilar/interlobar zone (stations #10 and #11; HIL#10 and INT#11)] (12). Okada *et al.* have reported equivalent prognoses between hilar N1 disease and N2 single-station disease (13). Several authors have reported that the outcomes were significantly better with pN1 involvement in hilar N1 disease than in N2 single-station disease (12,14). Wang *et al.* have reported that HIL#10 metastasis was significant for the LPT#4L metastasis on multivariate analyses (10). pN1 metastasis has been identified in a combination of subgroups with different prognostic significances in pN1, and the distinct metastasis location of pN1 might be an essential element for pN2 LUL-NSCLC.

Although the existence of skip pN2 metastasis (SN2) is not ignored in the discussion on the spread of metastatic lymph nodes to mediastinum from the LUL, Sakao *et al.* have reported in 2006 that skip EMSD metastasis occurred in 14.3% of cases (5). Previous studies on the mechanisms of SN2 have reported anatomical lymphatic flow, micro-

metastasis, and biological behavior (15). Regardless of the lobe, the incidence of SN2 ranged from 17.2% to 42.3% (15). Shimada *et al.* have reported that the incidence of skip metastasis to the AN#5+6 or LPT#4L was 20% in the left upper division (LUD), but 45% in the left lingular division (LLD) (16). Moreover, our previous retrospective study has reported that skip MLN metastasis was predominantly found in the LUL-NSCLC (8.4%), followed by RUL (4.6%), but the difference was non-significant (P=0.49) (15). MNLD is typically necessary for NSCLCs that can easily cause SN2. Therefore, we considered that it should be necessary to investigate definitive factors in preoperative CT, and concluded that tumor diameter >10 mm on mediastinal setting of CT was associated with a higher incidence of hilar/MLN metastases or SN2 (5,15).

Left upper division (LUD)

Furthermore, certain authors have reviewed that LUD-NSCLCs had a high incidence of regional metastases; therefore, the drainage patterns of the LUD differed from that of the LUL (12,17,18). In LUD-NSCLCs, by scintigraphy analyses, the lymphatic drainage into the contralateral mediastinum was more common from the LLD than from the LUD (19). It is natural to evaluate the lymphatic patterns between the LUD and LLD separately. In our previous study, 154 cases of pN1-2 LUD-NSCLCs metastasized to the LPT#4L, AN#5+6, and SC#7, which accounted for 19.5%, 44.5%, and 3.9%, respectively (11). These results were similar to those of a study by Asamura *et al.*, who have reported that 34 pN2 LUD-NSCLC commonly metastasized to the LPT#4L, AN#5+6, and SC#7, accounting for 32%, 71%, and 12% of cases, respectively (17). A study of Riquet *et al.* on the lymphatic drainage has reported that the AN#5+6 metastasis occurred in 69.8% of cases, followed by the LPT#4L (24.5%) in pN2 single station, and superior mediastinal nodes (SMNs; LPT#4L plus AN#5+6) with or without inferior mediastinal nodes (IMNs) [SC#7 plus lower zones (#8 plus #9)], which accounted for 40.0% and 60.0% of cases with more than one station of lymph node metastasis, respectively (18).

Our previous study has supportively reported that the incidence of SC#7 metastasis was 6.9-fold higher in the LUD than in the LLD and revealed similar patterns of metastatic lymphatic spread between the LUD and LLD; however, metastases to SMNs were not frequent in the LUD than in the LLD (11). A Japanese study has reported that SC#7 metastases from the upper lobe NSCLC were



Figure 1 We present our en bloc left upper mediastinum dissection (#4L to #10) (22).

Available online: <http://www.asvide.com/article/view/31488>

rare and predicted an extremely poor outcome (19). We have previously reported that among pN1–2 LUD-NSCLCs, the 5-year OS was 31.5%, 39.3%, and 50.4% for HIL#10 positive, INT#11 positive, and LOB#12 positive cases, respectively; moreover, either INT#11 or HIL#10 metastases, which had incidence >20%, were independent prognostic factors of pN2 LUL-NSCLCs (11). Additionally, our proposal for LUD-NSCLCs is that it is reasonable to conclude that hilar/interlobar zone has a key role in MLN metastasis, and sufficient MLN including N1 zones should be expected. In addition, SC#7 dissection does not always contribute to the prognosis and its low frequency, and we approve of the suggestions by several authors that dissection of SMNs alone remains indispensable in cases of LUD-NSCLCs.

Left lingular division (LLD)

The discrete data between the LUD and LLD is reasonable from the view of more finely classifying and evaluating anatomical and functional division. However, there are few articles that paid attention to the LLD (20). In our previous study, 69 pN1–2 LLD-NSCLC cases metastasized to #10, #11, and #12u, which accounted for 15.4%, 53.8%, and 42.3% in N1, respectively, and the LPT#4L, AN#5+6, and SC#7, which accounted for 19.5%, 44.5%, and 3.9% in N2, respectively, and our retrospective study has reported that the incidence of subcarinal zone (#7) metastasis was 6.9-fold higher in the LUD than in the LLD (11). In 2005, Shien *et al.* have revealed that the top three metastasis node stations were #12u, #11, and #5 in pN1–2 LLD-NSCLC and were decided as the regional node stations (20). Their

lymphatic behavior is consistent with our results. Another study by Shimada *et al.* have reported that 41 LUD-NSCLC most commonly metastasized to SMNs (100%), whereas 11 LLD-NSCLC most commonly metastasized to SC#7 (27%) (16). Despite the small cohort, Riquet *et al.* have reported that SC#7 metastasis was 100% in 6 (11.1%) pN2 LLD-NSCLC among 54 lobectomies, and the outcomes of lobectomies in the LUL by Riquet reported no significant superiority in the LUD compared with the LLD (18). The 5-year OS was 65.5–72.9% in LLD-NSCLCs (18,21). Although SC#7 metastases from the upper lobe predicted a poorer prognosis, indeed, the necessity for the dissection of SC#7 was advocated as a strategy of MLND in LLD-NSCLC because of the frequency. Additionally, our final proposal is that it is reasonable to conclude that dissection of #11 is as important as that of MDL dissection during both the LUD and LLD segmentectomy and may contribute to accurate pathological staging and treatment.

One concise review from Japan indicated selective MLND in the LUL according to the strategy of selective MLND based on lobe-specific patterns of nodal spread, particularly in cases of early-stage NSCLC (21). The extent of MLND dissection of SMNs is advisable in both LUD- and LLD-NSCLC; that of SC#7 is recommended in LLD-NSCLC; however, it is not always necessary in LUD-NSCLC (21). Given these suggestions, current practicing surgeons should intend to intervene on selective MLND with the preferred choice appropriately.

Surgical techniques and approach (Figure 1)

Finally, we introduce some techniques for the LPT#4L dissection on thoracoscopy (23). Our team's thoracoscopic approach has previously been published. Mun *et al.* have concluded that in surgical technique, the most important issues of performing thoracoscopic surgery lobectomy using systemic MLND for primary NSCLCs are safety and curability with two thoracotomy conversions (2.2%, 2/913) and no 30-day mortality (23). In addition, Nagashima, one of our team members, has demonstrated the aptitude for the LPT#4L dissection (24). Certain authors have indicated that the LPT#4L dissection was more difficult than that for right lung cancer because of anatomic limitations caused by the aortic arch, left recurrent laryngeal nerve (LRLN), and ductus arteriosus (25). Our approach involves the en-bloc dissection of the LPT#4L until the intersection of LRLN and left main bronchus. In cases where in the top

of #4L node is positive, additional dissection is performed to the right paratracheal space in the mediastinal side of LRLN. In our experience, we can avoid paralysis of the recurrent nerve with high probability using this approach and procedural styles. However, a future prospective study is warranted to provide meaningful data on morbidity and prognostic differences of this approach.

In conclusion, although an explicit evidence of contribution to survival benefit, our accumulated data indicated that the enough MLND in LUL was associated with the favorable prognosis while receiving the assistance of several founded inferences.

Acknowledgments

We thank to Dr. Mingyon Mun, Cancer Institute Hospital, Dr. Yosikane Yamauchi and Dr. Takuya Nagashima Kei Suzuki, Teikyo University, and Kanagawa Cancer Center, for providing the surgical data supports as the member of our team.

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by Section Editor Dr. Qin Lin (Department of Thoracic Surgery, Jiangxi People's Hospital, Nanchang, China).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/med.2019.04.04>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

1. Doddoli C, Aragon A, Barlesi F, et al. Does the extent of lymph node dissection influence outcome in patients with stage I non-small cell lung cancer? *Eur J Cardiothorac Surg* 2005;27:680-5.
2. Nomori H, Mori T, Ikeda K, et al. Segmentectomy for selected cT1N0M0 non-small cell lung cancer: a prospective study at a single institute. *J Thorac Cardiovasc Surg* 2012;144:87-93.
3. Deng HY, Qin CL, Li G, et al. Can lobe-specific lymph node dissection be an alternative to systematic lymph node dissection in treating early-stage non-small cell lung cancer: a comprehensive systematic review and meta-analysis? *J Thorac Dis* 2018;10:2857-65.
4. Meng D, Zhou Z, Wang Y, et al. Lymphadenectomy for clinical early-stage non-small-cell lung cancer: a systematic review and meta-analysis. *Eur J Cardiothorac Surg* 2016;50:597-604.
5. Sakao Y, Miyamoto H, Yamazaki A, et al. The spread of metastatic lymph nodes to the mediastinum from left upper lobe cancer: results of superior mediastinal nodal dissection through a median sternotomy. *Eur J Cardiothorac Surg* 2006;30:543-7.
6. Sakao Y, Miyamoto H, Yamazaki A, et al. Prognostic significance of metastasis to the highest mediastinal lymph node in nonsmall cell lung cancer. *Ann Thorac Surg* 2006;81:292-7.
7. Miyamoto H, Hata E, Sakao Y, et al. Evaluation of neck lymph node dissection and extended lymphadenectomy through a collar incision and median sternotomy for lung cancer. *Nihon Kyobu Geka Gakkai Zasshi* 1995;43:1804-9.
8. Watanabe Y, Shimizu J, Oda M, et al. Improved survival in left non-small-cell N2 lung cancer after more extensive operative procedure. *Thorac Cardiovasc Surg* 1991;39:89-94.
9. Varlotto JM, Recht A, Nikolov M, et al. Extent of lymphadenectomy and outcome for patients with stage I non small cell lung cancer. *Cancer* 2009;115:851-8.
10. Wang YN, Yao S, Wang CL, et al. Clinical Significance of 4L Lymph Node Dissection in Left Lung Cancer. *J Clin Oncol* 2018;36:2935-42.
11. Kuroda H, Sakao Y, Mun M, et al. lymph node metastases and prognosis in left upper division non-small cell lung cancers: The impact of interlobar lymph node metastasis. *PLoS One* 2015;10:e0134674.
12. Riquet M, Pricopi C, Mangiameli G, et al. Pathologic N1

- disease in lung cancer: the segmental and subsegmental lymph nodes. *J Thorac Dis* 2017;9:4286-90.
13. Okada M, Sakamoto T, Yuki T, et al. Border between N1 and N2 stations in lung carcinoma: lessons from lymph node metastatic patterns of lower lobe tumors. *J Thorac Cardiovasc Surg* 2005;129:825-30.
 14. Maeshima AM, Tsuta K, Asamura H, et al. Prognostic implication of metastasis limited to segmental (level 13) and/or subsegmental (level 14) lymph nodes in patients with surgically resected nonsmall cell lung carcinoma and pathologic N1 lymph node status. *Cancer* 2012;118:4512-8.
 15. Gorai A, Sakao Y, Kuroda H, et al. The clinicopathological features associated with skip N2 metastases in patients with clinical stage IA non-small-cell lung cancer. *Eur J Cardiothorac Surg* 2015;47:653-8.
 16. Shimada Y, Saji H, Kakahana M, et al. Retrospective analysis of nodal spread patterns according to tumor location in pathological N2 non-small cell lung cancer. *World J Surg* 2012;36:2865-71.
 17. Asamura H, Nakayama H, Kondo H, et al. Lobe-specific extent of systematic lymph node dissection for non-small cell lung carcinomas according to a retrospective study of metastasis and prognosis. *J Thorac Cardiovasc Surg* 1999;117:1102-11.
 18. Riquet M, Rivera C, Pricopi C, et al. Is the lymphatic drainage of lung cancer lobe-specific? A surgical appraisal. *Eur J Cardiothorac Surg* 2015;47:543-9.
 19. Aokage K, Yoshida J, Ishii G, et al. Subcarinal lymph node in upper lobe non-small cell lung cancer patients: Is selective lymph node dissection valid? *Lung Cancer* 2010;70:163-7.
 20. Shien K, Toyooka S, Soh J, et al. Clinicopathological characteristics and lymph node metastasis pathway of non-small-cell lung cancer located in the left lingular division. *Interact Cardiovasc Thorac Surg* 2015;20:791-6.
 21. Watanabe S, Asamura H. Lymph node dissection for lung cancer: significance, strategy, and technique. *J Thorac Oncol* 2009;4:652-7.
 22. Kuroda H, Sugita Y, Nakanishi K, et al. Lymph node dissection in the left upper lobe: clinical outcomes and surgical techniques in Japan. *Asvide* 2019;6:128. Available online: <http://www.asvide.com/article/view/31488>
 23. Mun M, Ichinose J, Matsuura Y, et al. Video-assisted thoracoscopic surgery lobectomy via confronting upside-down monitor setting. *J Vis Surg* 2017;3:129.
 24. Nagashima T. Thoracoscopic left mediastinal lymph node dissection. *Ann Transl Med* 2016;4:10.
 25. Tokar A, Tanju S, Ziyade S, et al. Alternative paratracheal lymph node dissection in left-sided hilar lung cancer patients: comparing the number of lymph nodes dissected to the number of lymph nodes dissected in right-sided mediastinal dissections. *Eur J Cardiothorac Surg* 2011;39:974-80.

doi: 10.21037/med.2019.04.04

Cite this article as: Kuroda H, Sugita Y, Nakanishi K, Sakao Y. Lymph node dissection in the left upper lobe: clinical outcomes and surgical techniques in Japan. *Mediastinum* 2019;3:16.