Review Article

Lymph node dissection during sublobar resection: why, when and how?

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Abstract: Appropriate lymph node (LN) assessment is a hallmark of surgical quality of curative intent operations for non-small cell lung cancer (NSCLC). Even in the era of extensive pre-treatment work-up including routine PET-scanning and brain imaging, and selective invasive LN evaluation, unexpected LN metastases are found at surgery in more than 10% of patients with a cT1aN0 tumor. Systematic lymphadenectomy minimizes the risk of leaving tumor-LN behind and thus the risk of an incomplete resection, and provides the most truthful pTNM, which is decisive in directing adjuvant chemotherapy. Removal of interlobar, hilar, and mediastinal LNs is necessary during sublobar resection, as it is during lobectomy. In addition, segmental LNs should be dissected at both the resected and nonresected lobar segments, because the lymphatic flow from the resected segment can go directly to the neighboring segmental LNs to join the lymphatic network at the roots of the lobar bronchi, especially for tumors in anteriorly located segments. Finally, several anatomical studies described direct lymphatic vessels from the lower lobes into the upper lobar bronchi LN rendering also advisable clearance of the upper lobar LN in case of lower lobe NSCLC. Given that intralobar LN dissection is impossible within the remaining lobe after wedge resection, omission of segmental and intralobar LN retrieval may also explain the high incidence of loco-regional recurrence observed after wedge resection. Thus, segmentectomy should be preferred to wedge resection as the recommended type of sublobar resection.

Keywords: Segmentectomy; sublobar resection; lymphadenectomy; non-small cell lung cancer surgery (NSCLC surgery)

Submitted Dec 17, 2017. Accepted for publication Jan 03, 2018.
doi: 10.21037/jtd.2018.01.30
View this article at: http://dx.doi.org/10.21037/jtd.2018.01.30

Since more than 20 years, lobectomy combined with systematic lymph node (LN) dissection, so-called radical lobectomy, has been standardized as the surgical treatment for localized non-small cell lung cancer (NSCLC) (1). Nowadays, the early-stage lung cancer population is delineated on the basis of 18FDG positron-emission tomography, routine brain imaging, and high-resolution CT scan findings, which result in more reliable staging of the disease. Furthermore, launching of low-dose helical CT scan screening programs leads to the diagnosis of lung cancer at a smaller tumor size and at an earlier stage (2). Changes in the epidemiology of the disease, as well as precise identification of minor changes in the density within ground-glass nodules combined with a better understanding of histological tumor biology introduced subgroups with indolent behavior, low propensity to spread to LNs, and finally more favorable outcomes (3). This context renewed the interest with intentional segmentectomy as an alternative to lobectomy for clinical stage I NSCLC from the viewpoints of nodal assessment and surgical margins.

Several retrospective case series and database analyses

have been published comparing lobar and sublobar resections with some contradictory results, especially in regards to tumors smaller than 2 cm (4-13). The ongoing multicenter phase III clinical trials of the value of radical segmentectomy in the United States (CALGB-140503) (14) and Japan (JCOG0802/WJOG4607L) (15) are thus keenly awaited, and will be carefully watched. Incorrect outcomes in these clinical trials induced by procedural errors not only in terms of insufficient resection margins but also inadequate LN evaluation would be a major concern. Indeed, appropriate LN assessment is a hallmark of surgical quality of curative intent operations for NSCLC, even if what constitutes adequate lymphadenectomy varies considerably among international guidelines (16-18). One should also point out that adherence to these guidelines is rather poor in "real life" clinical practice (19). The latter may be explained by at least two common beliefs and one shared acknowledgment: (I) the incidence of LN metastases is very low in clinical stage I patients when screened with modern investigations, i.e., routine 18FDG positron-emission tomography and selective invasive LN evaluation; (II) the removal of invaded LN in that context does not carry any relevant survival benefit and is thus superfluous; and (III) complete lymphadenectomy is technically demanding, especially when using a minimally invasive approach.

Is any kind of intraoperative LN evaluation still necessary in clinical stage I disease?

Contemporary analyses of large nation-based databases show a 15–20% incidence of nodal upstaging in patients with clinical stage I NSCLC and treated by lobectomy, even in the FDG-PET/CT era (20-22). Overall, the greater the number of LNs assessed, the higher the likelihood of a patient being upstaged: cN0/pN1 upstaging is found in the range of 3% to 13%, while cN0/pN2 upstaging varies from 1% to 8%, depending on the number of LNs harvested and examined (21). Focusing on cT1a tumors that represent the target of sublobar resections, the recent surgical literature shows unexpected LN metastases in more than 10% of the cases. In a retrospective series of 498 cT1aN0 NSCLC patients who underwent a lobectomy or segmentectomy with systematic nodal resection between 2008 and 2013, Xiong *et al.* found 34 patients (6.8%) with pN1, and 64 patients (12.9%) with pN2 disease, leading to an overall 19.7% LN upstaging rate (23). According to prospective data derived from the Dutch Lung Surgery Audit in 2013 and 2014, 6.2% of patients presenting with a cT1aN0 tumor had a pN1 disease, and 4.6% a pN2 disease, leading to an overall 10.8% LN upstaging rate (22). The performance of routine endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for systematic nodal staging of lung cancer patients with a N0 disease by CT and integrated PET-CT has received little attention, and is totally unknown in the specific setting of cT1aN0 tumors. The available experience with bigger tumors does not suggest that preoperative EBUS-TBNA could replace intraoperative LN assessment (24,25).

Is systematic lymphadenectomy beneficial in clinical N0 disease?

The lastly published meta-analysis of randomized trials comparing systematic lymphadenectomy with sampling disclosed a hazard ratio of 0.78 (95% CI, 0.69–0.89) favoring systematic lymphadenectomy and this equated with an absolute reduction in risk of death at 5 years of 7.6% (26), which is higher than what is provided by adjuvant chemotherapy: 4% (95% CI, 3–6) at five years (27). However, the high risk of bias in the 5 trials included in this meta-analysis made the overall conclusion insecure. The hypothetic rationale of the potential survival benefit of removing cN0 LN relies to the stage migration phenomenon related to more accurate staging through the resection of unexpected pN1N2 LN. Indeed, systematic lymphadenectomy minimizes the risk of leaving tumor-LN behind and thus the risk of an incomplete resection, which is a robust surrogate for survival (28). Moreover, it provides the most truthful pTNM, which is decisive in directing adjuvant chemotherapy and affording additional chances for cure at five years (27). Some data would argue against this hypothesis like the absence of negative impact on long-term survival of the use of a minimally invasive approach for performing lobectomy despite the fact that this technique has been reported to carry a higher risk of overlooking LN involvement when compared to thoracotomy (20,29). An alternative provocative hypothesis is that the potential benefit may also come from the removal of pN0 LN. Several large cohort studies have shown that increased LN retrieval was associated with improved overall and cancer specific survival (21,30-34), but with no consensual threshold value. In the most recent analysis of the National Cancer Database and more than 51,000 patients, patients with more than 14 nodes assessed demonstrated improved survival in both upstaged and non-upstaged cohorts (21).

Several analyses of huge nation-based databases in the US showed that patients who had undergone a sublobar resection had consistently fewer nodes removed than patients having had bigger lung resections. A tremendously high proportion of patients, 40% to 70%, have not even

one single LN removed or examined (35-37), and this proportion is worse following wedge resection when compared to segmentectomy (36). Even in the frame of the randomized ACOSOG Z4032 trial designed to specifically evaluate surgical outcomes, and comparing sublobar resection alone with sublobar resection with brachytherapy in patients with clinical stage I non-small lung cancer, more than one third of the patients did not receive any kind of LN evaluation (38). With this background, the incidence of regional recurrence after stereotactic body radiation therapy (SBRT) or surgery is intuitively expected to be comparable, as shown by the available evidence (39).

Yet, patients with pNX resections have been shown to have survival corresponding to pN1, not to pN0, demonstrating the importance of LN retrieval for adequate staging and treatment (40). A retrospective single institution series disclosed that NSCLC patients undergoing wedge resection with LN removal appear to have better survival and less local and regional disease recurrence than patients without LN sampling (41). Another retrospective study suggests that segmentectomy may play a role in local control in patients with cT1 N0 M0/pN1-2 NSCLC if combined with systematic LN dissection and sufficient surgical margin (42).

The added value of lymphadenectomy in patients receiving segmentectomy for an early stage NSCLC has been scarcely studied prospectively. Cheng *et al.* (43) provided the sole comparative analysis of long-term outcomes and local regional recurrence in elderly (≥70 years) clinical stage I-A NSCLC patients undergoing lobectomy or segmentectomy combined with 2 types of LN dissection: so-called "regional LN dissection", which consisted of a lobe-specific lymphadenectomy, versus "selected LN dissection", which consisted of the selective removal of those LN suspected to be metastatic at surgical exploration. Patients were not randomized but allocated into different subgroups according to their order of admission to the hospital. Among the patients who underwent segmentectomy, those who had regional LN dissection showed a similar 5-year survival to that of patients treated with lobectomy, and a significantly higher 5-year survival rate than those having undergone segmentectomy with selected LN resection (55.6% *vs.* 27.6%, P=0.034).

Lymphadenectomy associated with sublobar resection: how should it be done?

As clinical staging of NSCLC is more precise, and the risk of overlooking LN involvement becoming consistently smaller, there is a concurrent trend to promote with sublobar resection some minimal LN dissection, such as lobe-specific LN dissection. This trend is even more sensitive since the advent of video-assisted thoracoscopic approaches because of additional technical difficulties related to LN clearance (44). Several anatomical and clinical studies have shown that lobe-specific lymphatic drainage was preponderant but not exclusive (45-48). In a huge multi institutional series of more than 5,000 patients, Ishida *et al.* reported that systematic mediastinal LN dissection permitted to disclose a significantly bigger pN2 population than lobe specific LN dissection (49). In addition, the frequency of skip mediastinal LN metastases, up to 20–40% of patients (47), does not allow the surgeon to omit mediastinal LN dissection even when hilar or interlobar nodes have been proved to be negative with frozen sections, as emphasized again by the results of the ACOSOG Z030 trial (50). Therefore, systematic interlobar, hilar, and mediastinal LN dissection is necessary during segmentectomy even in patients with cT1 N0 M0 NSCLC, as it is during lobectomy.

On the basis of their experience on intraoperative sentinel nodes identification, Nomori *et al.* (51) showed that the lymphatic flow from the anteriorly located segment could frequently (29% of their cases) go directly to the segmental LNs of the posteriorly located segment to join the lymphatic network at the roots of the lobar bronchi. Therefore, for staging purpose, they concluded that segmental LNs should be dissected at both the resected and nonresected segments during segmentectomy, especially for tumors in anteriorly located segments. Consistently, Yamanaka *et al.* who examined the distribution of metastases at station 13 in patients with small peripheral NSCLC, found LN metastases only at the tumor-bearing segments in 60% of the cases, at the non-tumor-bearing segments in 10%, and at both in 30% (52). Subsequently, Nomori *et al.* examined the role of segmentectomy with such extended lymphadenectomy as a local control in patients with cT1 N0 M0 NSCLC. In patients in whom pN1 or N2 disease was diagnosed, and a completion lobectomy was performed, they did not find any single patient with residual LN metastases within the specimen. Moreover, in those high-risk patients who did not receive completion lobectomy despite the identification of a pN1 or N2 disease at surgery, the overall prognosis was not negatively affected (42).

The anatomical studies performed by Riquet (45,46) warned early on the frequent existence of direct lymphatic vessels from lung lobes to the mediastinum, explaining the N2 skip metastasis phenomenon. They also disclosed a high

frequency of the lymphatic drainage from one lobe towards non-"lobe-specific" LN-stations in the mediastinum. The comparison made between anatomy and oncology lymph mode of spread showed that both were parallel in nature (46), thus supporting the recommendation of complete mediastinal LN dissection at surgery for NSCLC. These studies finally described direct lymphatic vessels into the upper lobar bronchi LN, six times from the right lower lobes and 13 times from the left lower lobes in 260 cases, rendering also advisable clearance of the upper lobar LN in case of lower lobe NSCLC (45).

LN-dissection completeness is expected to be particularly demanding to achieve during sublobar resections. Intralobar LN dissection (stations 12–14) is tough and time-consuming when dissecting along the bronchi after segmentectomy, while it is impossible within the remaining lobe after wedge resection. Omission of segmental and intralobar LN retrieval, by the surgeon or the pathologist, might explain the high incidence of loco-regional recurrence observed after wedge resection (41) or segmentectomy (53). Any kind of surgery without thoughtful LN evaluation strangely resembles to what occurs to patients receiving SBRT for stage I NSCLC. Indeed, as they are typically staged clinically with PET/CT, up to 7.6% of them may be found to have occult N1 metastasis on pathologic review (54).

Conclusions

Systematic LN dissection is required while performing intentional curative sublobar resection. All accessible interlobar, hilar and mediastinal LN should be removed as it is recommended with lobectomy. In addition, segmental peribronchial LN, as well as all those accessible and located at the origin of neighboring segments and lobes, should be removed. Wedge resection does not allow such accurate LN evaluation. In contrast, "radical segmentectomy" should be defined on the basis of the extent of LN dissection. It seems quite similar to the "radical lobectomy" proposed by Cahan (55) in 1960, as a curative alternative to pneumonectomy, and which still is the standard procedure for NSCLC to date, even for N1 or N2 disease.

From an ethical insight, available evidence suggests that those surgeons who do not embrace these statements should offer SBRT in priority to their patients presenting with a peripheral cT1aN0 tumor and are otherwise potential candidates to a sublobar resection as it is the less invasive and really ambulatory curative alternative option to non-radical surgery.

Acknowledgements

None.

Footnote

Conflicts of Interest: Honorarium from Ethicon Endosurgery & Medtronic for educational "Hands on" sessions.

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Cite this article as: Thomas PA. Lymph node dissection during sublobar resection: why, when and how? J Thorac Dis 2018;10(Suppl 10):S1145-S1150. doi: 10.21037/jtd.2018.01.30

