



What Should Thoracic Surgeons Consider during Surgery for Ground-Glass Nodules?: Lymph Node Dissection

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Thoracic surgeons need to be aware of several important points regarding intraoperative lymph node dissection during surgery for non-small cell lung cancer with ground-glass opacities. The first point relates to the need for lymph node dissection during sublobar resection. Since even patients undergoing sublobar resection may benefit from lymph node dissection, it should be selectively performed according to adequate indications, which require further study. Second, there seems to be no difference in postoperative morbidity between systematic sampling and systematic dissection, but the survival benefit from systematic dissection remains unclear. The results of randomized controlled trials on this topic are conflicting, and their evidence is jeopardized by a high risk of bias in terms of the study design. Therefore, further randomized controlled trials with a sound design should investigate this issue. Third, more favorable survival outcomes tend to be positively associated with the number of examined lymph nodes. Minimum requirements for the number of examined lymph nodes in non-small cell lung cancer should be defined in the future. Finally, lobe-specific lymph node dissection does not have a negative prognostic impact. It should not be routinely performed, but it can be recommended in selected patients with smaller, less invasive tumors. Results from an ongoing randomized controlled trial on this topic should be awaited.

Keywords: Lung neoplasms, Ground-glass nodule, Lymph node excision, Surgery, N stage

Introduction

Approximately 20% of patients with non-small cell lung cancer (NSCLC) are diagnosed after the cancer has spread to the ipsilateral mediastinal lymph nodes (LNs; N2 metastasis), and due to the risk of occult microscopic systemic metastasis and resultant distant recurrence, their prognosis after surgery alone is poor [1]. Despite a thorough mediastinal staging workup to identify the presence of nodal involvement, the incidence of unforeseen N2 disease during surgery is reported to range from 4% to 18% [2-13]. Therefore, it is of considerable importance to predict N2 metastasis given its prognostic implications before deciding on a therapeutic strategy. Numerous researchers have investigated the predictors of occult N2 metastasis, including histologic type, tumor location, tumor size, size of consolidations or ground-glass opacities, and fluorodeoxyglucose uptake on positron emission tomography (Table 1) [2-15].

For instance, patients with features such as invasive adenocarcinoma, a centrally located tumor, tumor size greater than 2 cm, a higher consolidation/tumor ratio (≥ 0.5), or higher maximum standardized uptake values on positron emission tomography are more likely to have occult N2 metastasis. Therefore, performing a thorough staging workup for patients with these features is important. Conversely, patients who do not present with these features are typically candidates for sublobar resection. However, there is no consensus regarding the type of LN assessment that is appropriate in these patients undergoing sublobar resection. In other words, the question arises: is it truly necessary to perform complete LN dissection in patients who are less likely to have occult N2 disease?

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Table 1. Predictors of occult nodal metastasis

Study	Year	No. of patients	Histologic type	Stage	Predictors of occult nodal metastasis
Kanzaki et al. [6]	2011	224	NSCLC	cN0–1	Adenocarcinoma, upper/middle lobe, size (3 cm), SUVmax (4)
Gomez-Caro et al. [4]	2012	153	NSCLC	cT1–2N0	Size (5 cm), pN1, adenocarcinoma, female
Koike et al. [14] (2012)	2012	894	NSCLC	cStage IA	Age (≤ 67 yr), size (2 cm), CEA (3.5 ng/mL), C/T ratio (0.89)
Li et al. [7]	2013	189	NSCLC	cT1–2N0	Size (3 cm), SUVmax (4.3)
Miyasaka et al. [9]	2013	265	NSCLC	cN0	C/T ratio (0.5), SUVmax (10)
Cho et al. [3]	2013	770	NSCLC	cStage I	Solid nodule, clinical T stage, CEA, GGO
Ye et al. [12]	2014	651	Adenocarcinoma	cStage IA	Part-solid nodule, CEA (5 ng/mL), SUVmax (5), histologic subtype
Wang et al. [11]	2015	292	NSCLC	cStage IA	Size (2 cm), C/T ratio (0.5), micropapillary pattern
Haruki et al. [15] (2015)	2015	876	NSCLC	cStage I	C/T ratio (0.5), CEA (5 ng/mL)
Lin et al. [8]	2016	284	NSCLC	cN0	SUVmax (2.6)
Moon et al. [10]	2016	350	Adenocarcinoma	cN0	SUVmax (5), lymphovascular invasion, micropapillary pattern
Hung et al. [5]	2016	471	Adenocarcinoma	cN0 (<3 cm)	Size, micropapillary/solid pattern
Yeh et al. [13]	2016	297	Adenocarcinoma	cN0–1	Micropapillary pattern
Bille et al. [2]	2017	1,667	NSCLC	cStage I	Adenocarcinoma, vascular invasion

NSCLC, non-small cell lung cancer; SUVmax, maximum standardized uptake value; CEA, carcinoembryonic antigen; C/T ratio, consolidation/tumor ratio; GGO, ground-glass opacity.

Intraoperative nodal assessment during sublobar resection

For non-invasive or minimally invasive lung tumors such as adenocarcinoma *in situ* or minimally invasive adenocarcinoma, it is reasonable to perform sublobar resection while omitting LN dissection. Likewise, for invasive adenocarcinomas larger than 2 cm, lobectomy and complete LN dissection should be conducted. However, for tumors with borderline features, the optimal extent of pulmonary resection and whether to perform complete nodal dissection remain a topic of debate. Cao et al. [16] investigated the prognostic impact of lymphadenectomy in patients undergoing sublobar resection for stage IA NSCLC tumors smaller than 2 cm using data from the Surveillance, Epidemiology, and End Results (SEER) database. They demonstrated that more extensive regional LN dissection (≥ 4 regional LNs) was associated with better lung cancer-specific survival rates than less extensive regional LN dissection (1–3 regional LNs). Their findings suggest that adequate LN assessment is required even in patients undergoing sublobar resection for stage IA NSCLC. Similarly, Stiles et al. [17] compared the oncologic effectiveness between lobectomy and sublobar resection according to the extent of LN dissection in patients with stage I NSCLC smaller than 2 cm from the SEER database. When propensity-matched cohorts of patients with at least 1 LN removed were examined, the survival rate of sublobar resection was worse than that of lobectomy. However, when cohorts were propensity-matched for having had ≥ 9 LNs examined, the

difference in overall survival or cancer-specific survival disappeared. These findings imply that the oncological outcomes of sublobar resection can be equivalent to those of lobectomy as long as an adequate LN assessment is performed.

Adequate extent of nodal assessment: sampling versus dissection

Regarding the adequate extent of LN assessment, whether systematic LN sampling is sufficient or the lymphatic tissue and surrounding fatty tissue within the LN station should be completely removed along its anatomical boundaries is also a matter of debate. Compared with systematic sampling, the accuracy of staging can be enhanced after complete lymphadenectomy, resulting in increased detection of occult N2 disease. However, complete lymphadenectomy could lead to increased postoperative morbidity such as chylothorax or recurrent laryngeal nerve injury. Nevertheless, whether complete lymphadenectomy can translate into therapeutic effectiveness and a resulting survival benefit remains unclear. Five randomized controlled trials (RCTs) have been published on this topic (Table 2) [18–22]. Except for an American multi-institutional trial [18], all the studies were single-institutional trials. While patients with stage III disease were included in a German trial [19] and Chinese trials [21,22], the Japanese and American trials [18,20] only enrolled patients with stage I or II disease. Except for the American trial, which enrolled about 1,100 patients, most studies were limited to a small

Table 2. Summary of randomized controlled trials on the extent of optimal nodal assessment

Study	Year	Country	No. of participating centers	Stage	No. of patients	Morbidity	Staging accuracy	Survival outcomes	Critical points
Izbicki et al. [19]	1994	Germany	Single	I-III A	Dissection (n=76) Sampling (n=93)	D ≈ S	D > S	D ≈ S	- Small sample size - More SqCC in the dissection group
Sugi et al. [20]	1998	Japan	Single	Peripheral <2 cm	Dissection (n=59) Sampling (n=56)	D > S	D ≈ S	D ≈ S	- Small sample size - Short follow-up duration
Wu et al. [21]	2002	China	Single	I-III A	Dissection (n=240) Sampling (n=231)	D ≈ S	NR	D > S	- Small sample size - More stage III A in the dissection group
Darling et al. [18]	2011	USA	Multiple (ACOSOG)	N0-N1	Dissection (n=525) Sampling (n=498)	D ≈ S	D > S	D ≈ S	- Rigorous sampling before randomization
Zhang et al. [22]	2013	China	Single	I-III A	Minimal LND (n=107) Complete LND (n=95)	D ≈ S	D ≈ S	D > S	- Small sample size

D, dissection; S, sampling; ≈, 2 groups are similar; SqCC, squamous cell carcinoma; ACOSOG, the American College of Surgeons Oncology Group Z0030 trial; NR, not reported; LND, lymph node dissection.

sample. There were no significant differences in the incidence of postoperative morbidities between sampling and dissection. The German and American trials reported that dissection was better than sampling in terms of detection of occult N2 disease [18,19], whereas the remaining trials found no difference between groups. Importantly, while 2 Chinese trials observed better survival after dissection than after sampling [21,22], the other trials reported no difference in survival outcomes between groups.

Despite the clinical implications of these trials, many critical limitations are still present. In the trial by Wu et al. [21], more patients with stage IIIA disease were included in the dissection group than in the sampling group. The American trial was criticized for its study design, in which the difference between groups was intrinsically impossible to detect since all the patients had already undergone extensive sampling before randomization [18]. Moreover, there were serious uncertainties and risks of bias in the methods of all the studies, including the lack of an intention-to-treat analysis (5 trials) [18-22], unclear random sequence generation (4 trials) [18,20-22] or allocation concealment (5 trials) [18-22], and impossible blinding (5 trials) [18-22]. To overcome the limitations of each trial, some researchers have conducted meta-analyses (Table 3) [23-25]. So far, 3 meta-analyses have been published. Among them, the first study by Wright et al. [25] analyzed 3 RCTs, showing that dissection was associated with better survival than sampling. As the American trial that did not

find a difference in survival between groups was included in the second meta-analysis by Huang et al. [23], the difference in survival outcomes subsequently disappeared. In contrast, the third meta-analysis by Mokhles et al. [24] demonstrated a survival difference between groups again because it included the Chinese RCT by Zhang et al. [22] that showed a difference in survival outcomes. Mokhles et al. [24] indicated that the claimed survival benefit from mediastinal LN dissection is not supported by reliable evidence, and they emphasized that the overall value of LN dissection should ideally be tested in a large pragmatic RCT involving contemporary diagnostic, surgical, and oncological practice.

Issues regarding the prognostic implications of the number of examined lymph nodes

The absolute number of LNs removed is a surrogate marker of the quality and extent of LN assessment. However, there is no strict guideline on the number of harvested LNs in lung cancer treatment, whereas the minimum requirements for the number of LNs to assess have already been published for various kinds of solid malignancies other than lung cancer. Some investigators have recently attempted to determine the minimal threshold for the examined LN count by correlating the number of examined LNs with long-term survival in NSCLC [26-30]. Of note,

Table 3. Summary of meta-analyses of RCTs on the extent of optimal nodal assessment

Study	RCTs	Morbidity	Survival	Local recurrence	Distant metastasis
Wright et al. [25]	Izbicki et al. [19] (1994) Sugi et al. [20] (1998) Wu et al. [21] (2002)	D ≈ S	D > S	NR	NR
Huang et al. [23]	Izbicki et al. [19] (1994) Sugi et al. [20] (1998) Wu et al. [21] (2002) Darling et al. [18] (2011)	D ≈ S	D ≈ S	D ≈ S	D ≈ S
Mokhles et al. [24]	Izbicki et al. [19] (1994) Sugi et al. [20] (1998) Wu et al. [21] (2002) Darling et al. [18] (2011) Zhang et al. [22] (2013)	D ≈ S	D > S	D ≈ S	D ≈ S

RCT, randomized controlled trial; D, dissection; S, sampling; ≈, 2 groups are similar; NR, not reported.

Liang et al. [27] found that a greater number of examined LNs was associated with more accurate nodal staging and better long-term survival of resected NSCLC. Therefore, they recommended 16 examined LNs as the cut-off for evaluating the quality of LN examinations. Some researchers have argued that the ratio of metastatic LNs to total examined LNs is a better predictor of survival after surgery for NSCLC [26,28–30]. Nwogu et al. [28] explored the prognostic implication of the LN ratio by stratifying the percentage of positive LNs into 3 groups (1%–24% versus 25%–49% versus 50%–100%) in NSCLC patients who underwent curative resection and had at least 1 LN examined from the SEER database. They found that more LNs resected and lower ratios of positive LNs to total examined LNs were associated with better survival. However, we should be cautious in interpreting the results of the numerous reports that showed the prognostic value of LN number or LN ratio. First, the number of examined LNs can be overestimated since grasping LNs with more force and traction during surgery could result in fragmentation of LNs due to accidental cutting and crushing. Second, there are no standardized criteria for LN counting during the pathological examination. Third, the cut-off points of the adequate LN number or ratio are too arbitrary.

Lobe-specific lymph node dissection

It is well known that the lymphatic drainage pattern differs among the lobes of the lung. Tumors in the upper lobe are more likely to metastasize to the upper mediastinal LNs, whereas tumors in the lower lobe are more likely to metastasize to the lower mediastinal LNs [31]. If the primary tumor is located in the upper lobe, only the LNs in the upper mediastinum are removed, and the lower mediasti-

nal LNs are left undissected and vice versa. This could result in adequate LN assessment without unnecessary dissection of the LNs where tumors are unlikely to metastasize. Okada et al. [31] emphasized that lower mediastinal LN dissection is not needed if the hilar and upper mediastinal LNs are found to be free and vice versa based on the lobe-specific lymphatic drainage pattern. Recently, Adachi et al. [32] compared the oncological efficacy between lobe-specific LN dissection (LS-LND) and systematic LN dissection (S-LND) in a multi-institutional database of surgery for NSCLC using a propensity score-matching method. They demonstrated that the survival rates and pathologic N2 detection rates of LS-LND were not inferior to those of S-LND. Similarly, Hishida et al. [33] assessed the surgical outcomes of 5,392 patients with clinical stage I or II NSCLC according to the extent of mediastinal LN dissection using a nationwide registry database. Although there was no significant difference in the incidence of postoperative complications between LS-LND and S-LND, the survival outcomes of the former were better than that of the latter. This might be due to the fact that the LS-LND group had smaller tumors at an earlier stage than the S-LND group.

Despite the promising results of LS-LND, the data must be interpreted carefully. First, higher mediastinal LN recurrence has been reported after LS-LND in some studies. Second, most studies showed that LS-LND did not substantially decrease postoperative morbidities despite the compromise in LN assessment. Third, the favorable outcomes of LS-LND might be due to selection bias, given that LS-LND is more likely to be conducted for pathologically less invasive tumors. In some studies, LS-LND was converted to S-LND during surgery upon suspicion of LN metastasis. More importantly, there have been no RCTs on

this topic. Above all, the opponents of LS-LND insist that not all tumors follow lobe-specific lymphatic drainage patterns. For example, Chinese researchers reported that different primary tumor locations had different propensities to be sites of mediastinal LN metastases [34]. However, once mediastinal LN metastasis occurs, each zone has the potential to be involved and should not be neglected based on the lobe-specific lymphatic drainage pattern. Therefore, we need to specify the indication of LS-LND based on further studies and select LS-LND in the borderline zone between patients who do not need LN dissection and those who must receive complete LN dissection. A randomized phase 3 trial of lobe-specific versus systematic LN dissection for clinical stage I or II NSCLC (Japan Clinical Oncology Group [JCOG] 1413) is currently underway [35], and we need to await the results of this trial before reaching a conclusion on this topic.

Conclusion

In summary, thoracic surgeons need to be aware of several important points about intraoperative LN dissection during surgery for NSCLC with ground-glass opacities. The first point relates to the need for LN dissection during sublobar resection. Since even patients undergoing sublobar resection may benefit from LN dissection, it should be selectively performed according to adequate indications, which require further study. Second, there seems to be no difference in postoperative morbidity between systematic sampling and systematic dissection, but the survival benefit from systematic dissection remains unclear. The results of RCTs on this topic are conflicting, and their evidence is jeopardized by a high risk of bias in terms of the study design. Therefore, further well-designed RCTs must be done to clarify this point. Third, there is a tendency for more favorable survival as more LNs are examined. Minimum requirements for the number of examined LNs in NSCLC should be defined in the future. Finally, LS-LND does not have a negative prognostic impact. LS-LND should not be routinely performed, but it can be recommended in selected patients with small, less invasive tumors. Results from the ongoing RCT on this topic should be awaited.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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