Original Article

Impact of extended mediastinal lymph node dissection for stage I ground-glass opacity lesions

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Background: Mediastinal lymph node dissection (MLND) is a critical component in lung cancer surgery. With the increasing number of patients with ground-glass opacity (GGO) lesions, the clinical impact of MLND has not been sufficiently assessed, particularly for part-solid lesions. This study aimed to evaluate the impact of extended N2 MLND in patients with GGO lesions with a consolidation tumor ratio (CTR) of 0.3–0.7.

Methods: Among patients diagnosed with stage I adenocarcinoma between 2013 and 2019, we retrospectively reviewed 138 patients with a CTR of 0.3–0.7. They were divided into the following two groups by MLND: limited N2 MLND (<3 N2 stations; n=100) and extended N2 MLND (≥3 N2 stations; n=38). Kaplan-Meier curves were used to compare oncologic outcomes and logistic regression was used to identify the predictive factors for postoperative complications (PoCs). Propensity-score matching regarding tumor characteristics and surgical extent were also performed to compare these two MLND assessments in clinical outcome.

Results: The extended N2 MLND group had larger solid components (9.5 *vs.* 7.0 mm, P=0.002) and more patients underwent lobectomy (P=0.008). Kaplan-Meier survival curves revealed no significant difference in clinical outcomes. After propensity score matching, the difference between two MLND strategies was also non-significant in clinical outcome. However, extended N2 MLND was found to be a significant factor in the development of PoC [odds ratio (OR), 4.57; 95% confidence interval (CI): 1.26–16.6; P=0.021].

Conclusions: For GGO lesions with a CTR of 0.3–0.7, the extended MLND strategy may not be optimal in terms of clinical outcome. It could lead to more frequent early complications with no oncologic benefits. Due to the limited number of cases in this study, further prospective research on MLND for part-solid lesions is required.

Keywords: Mediastinal lymph node dissection (MLND); ground-glass opacity (GGO); part-solid lesion; early lung cancer

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Introduction

The prognosis and management of lung cancer is changing. Outcomes for advanced non-small cell lung cancer (NSCLC) have improved with the development of chemotherapy and immunotherapy (1). Significant advances in lung cancer screening programs (2) and surgery have led to breakthroughs in the outcomes of patients with resectable NSCLC. In terms of parenchymal resection, recent studies from Japan and the United States have suggested a clear evidence suggesting the benefit of sublobar resection for

peripheral lesions of <2 cm (3,4). Now, surgeons need to evaluate another key component of pulmonary resection, mediastinal lymph node dissection (MLND).

Systematic MLND has been considered an optimal strategy for management of resectable NSCLC because it can provide precise staging and identify occult N2 disease. However, it is also associated with high morbidity, such as recurrent laryngeal nerve damage, chylothorax, and postoperative cardiopulmonary complications. Based on the patterns of tumor spread, the need for systematic MLND has been questioned as lobe-specific MLND exhibited similar oncological outcomes in early-stage NSCLC (5,6). However, the criteria for applying each strategy have not been clearly identified. Since the time when original MLND strategy was first developed, the radiological characteristics of NSCLC have changed. The number of pulmonary lesions with ground-glass opacity (GGO) have increased, and more favorable outcomes of them have been described and validated in many studies (7,8).

Determining the appropriate extent of MLND is primary interest to thoracic surgeons. Multiple guidelines on the minimum requirements for adequate MLND have guided thoracic surgeons. The American College of Surgeons Commission on Cancer suggested one hilar and three or more N2 lymph node dissection as a criterion (9). However, the European Society of Thoracic Surgeons (10) and the International Association for the Study of Lung Cancer (IASLC) mentioned specific stations that should be dissected based on the location of primary lesion (11). However, nodal involvement in GGO-dominant lesions is extremely rare (12). Consequently, the application of MLND based on our previous understanding of NSCLC should be reassessed. Previous studies have revealed that it might be an overtreatment to apply MLND for GGO-dominant lesions with a consolidation tumor ratio (CTR) <0.5 (13) but for pulmonary lesions with a CTR of approximately 0.5, there remains uncertainty about the optimal MLND strategy.

In this study, we retrospectively analyzed the oncologic outcomes of pulmonary lesions with a CTR between 0.3 and 0.7, which have significant proportions of two very different radiologic characteristics (GGO and solid). Then, we assessed the clinical impact of MLND according to the number of N2 stations that were resected. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-703/rc).

Highlight box

Key findings

- Extended N2 mediastinal lymph node dissection (MLND) was related to the development of postoperative complication without significant benefit in oncologic outcome.

What is known and what is new?

- Appropriate MLND is related to clinical outcome and the quality of lung cancer surgery. However, the adequacy of previous MLND strategy for part-solid lesions need to be evaluated.

What is the implication, and what should change now?

- This study revealed that the extended N2 MLND could lead poor early surgical outcome without increasing survival benefit. For part-solid lesions, the extent of MLND needs to be reconsidered.

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Gangnam Severance Hospital (No. 3-2023-0169). The requirement for informed consent was waived due to the retrospective design of the study. Electronic medical records of patients who underwent surgery for NSCLC between January 2013 and December 2019 were reviewed. Of the 812 patients, 476 were diagnosed with stage I adenocarcinoma. The exclusion criteria were as follows: adenocarcinoma in situ (AIS), atypical adenomatous hyperplasia, mucinous invasive adenocarcinoma, neoadjuvant treatment, insufficient surgical margins (R1 or R2 resection), and a CTR <0.3 or >0.7. The criteria for CTR were developed to assess pulmonary lesions with comparable GGO and solid proportion. The study included 138 patients with a CTR of 0.3–0.7.

MLND

The preoperative workup consisted of chest computed tomography (CT) with or without contrast enhancement, positron emission tomography (PET)-CT, brain magnetic resonance imaging (MRI), and endobronchial ultrasound (EBUS) for possible N1 or N2 lesions. Patients with negative EBUS results underwent curative resection.

Systematic MLND was not routinely performed in most patients with GGO lesions, in contrast to those with solid lesions. Intraoperatively, a frozen biopsy of the pulmonary lesion was used to guide the extent of mediastinal lymph node assessment because of the favorable clinical course

for minimally invasive adenocarcinoma (MIA). Extensive MLND was avoided for MIA lesions. In cases with enlarged lymph nodes, a frozen biopsy was selectively performed according to the surgeon's discretion. Four surgeons were included in this study, and they made a final decision regarding the stations to be dissected intraoperatively. We classified the patients into two groups based on the pathological reports of lymph node assessment. As many guidelines require three or more N2 MLND as a minimum criterion for the quality of MLND (9-11), we applied it to classify patients. The extended N2 dissection group included patients with three or more N2 stations dissected, and the limited N2 dissection group included patients with fewer than three N2 stations dissected. Here MLND means full dissection of the lymph node stations according to the IASLC node map (14).

Statistical analysis

Continuous variables were compared using the Mann-Whitney *U* test after the normality test, and categorical variables were compared using Fisher's exact test or the chi-square test. Recurrence-free survival (RFS) and overall survival (OS) were estimated using the Kaplan-Meier method and log-rank test. Propensity-score matching was used to adjust confounding variables such as tumor size, activity on PET, and surgical extent; RFS and OS were again compared according to the extent of MLND. Furthermore, logistic regression analysis in the entire cohort was used to identify risk factors related to postoperative complications (PoCs). Factors with a P value <0.10 in univariate analysis were introduced in multivariable analysis, and backward elimination via the P value approach was used to find significant factors.

Statistical analyses were performed using R version 4.0.4 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria). All tests were two-tailed, and variables with a P value <0.05 were regarded as statistically significant.

Results

Perioperative characteristics

The study cohort was predominantly Asian with 60.1% females (83/138) and 76.8% non-smokers (106/138); the median age was 64.0 years. Sublobar resection was performed in 42.0% participants and mean follow-up duration was 51.8 months. *Table 1* describes patients characteristics according to the extent of MLND. Both groups had similar demographic and radiological characteristics, including CTR and radiotracer uptake on PET-CT. The median CTR of both groups was 0.50. However, the extended N2 MLND group had larger median total tumor diameter (20.5 *vs.* 15.0 mm, P=0.005) and solid component diameter (9.5 *vs.* 7.0 mm, P=0.002). Furthermore, the proportion of patients with sublobar resection was significantly lower in the extended N2 MLND group (21.0% *vs.* 50.0%, P=0.008).

Long-term clinical outcome

There was no significant difference in RFS or OS between the two groups (*Figure 1*). The 5-year RFS in the limited and extended N2 MLND group was 93.2% and 89.5%, respectively (P=0.558), while the OS in the same groups was 97.3% and 91.4%, respectively (P=0.401). After propensity-score matching between two MLND strategies (*Table 2*), the difference in clinical outcome was also not significant (*Figure 2*). Cox-proportional hazard regression revealed patients' history of cardiovascular disease as a significant predictor in RFS [hazard ratio (HR), 4.36; 95% confidence interval (CI): 1.10–17.2; P=0.036; *Table 3*]. The extent of MLND was not related to long-term clinical outcomes.

Early postoperative outcome

Although the patients had comparable long-term outcomes, their clinical courses in the early postoperative period differed according to the extent of MLND. Patients who underwent extended N2 MLND had a significantly higher rate of developing PoC of over grade 2 according to the Clavien-Dindo classification (19.4% *vs.* 5.2%, P=0.018; *Table 1*). Specific details of these complication include prolonged air leakage (7/12), pneumonia (1/12), arrhythmia (1/12), chylothorax (1/12), recurrent laryngeal nerve injury (1/12), and others (1/12). Predictive factors for PoC were analyzed using logistic regression. As *Table 4* shows, male sex [odds ratio (OR), 8.90; 95% CI: 1.81–43.7; P=0.007] and extended N2 MLND (OR, 4.57; 95% CI: 1.26–16.6; P=0.021) were significant risk factors for complications. Even after propensity score matching, the incidence of PoC was more observed in the extended N2 MLND (3.2% *vs.* 19.4%, P=0.104; *Table 2*).

Table 1 Patient characteristics according to the extent of MLND

Clinical factors	Limited N2 dissection (<3 N2 stations) (n=100)	Extended N2 dissection (≥3 N2 stations) (n=38)	P value
Sex			0.846
Female	61/100 (61.0)	22/38 (57.9)	
Male	39/100 (39.0)	16/38 (42.1)	
Age (years)	64.0 [53.0, 72.0]	64.0 [60.3, 68.8]	0.699
Ex and current smoker	20/100 (20.0)	12/38 (31.6)	0.177
Hypertension	39/100 (39.0)	12/38 (31.6)	0.554
Diabetes mellitus	15/100 (15.0)	8/38 (21.1)	0.445
Other cardiovascular disease	6/100 (6.0)	3/38 (7.9)	0.706
Laterality of lesions			0.547
Lt	36/100 (36.0)	11/38 (28.9)	
Rt	64/100 (64.0)	27/38 (71.1)	
Radiologic characteristics			
CTR	0.50 [0.39, 0.58]	0.52 [0.44, 0.61]	0.156
Total tumor diameter (mm)	15.0 [10.0, 20.0]	20.5 [13.5, 24.7]	0.005
Solid lesion diameter (mm)	7.0 [5.0, 10.0]	9.5 [7.0, 12.0]	0.002
^{18}F-FDG uptake on PET-CT†			0.157
No uptake	37/80 (46.2)	10/35 (28.6)	
Mild	24/80 (30.0)	16/35 (45.7)	
Hypermetabolic	19/80 (23.8)	9/35 (25.7)	
Operative findings			
Surgical extent			0.008
Wedge resection	31/100 (31.0)	4/38 (10.5)	
Segmentectomy	19/100 (19.0)	4/38 (10.5)	
Lobectomy	50/100 (50.0)	30/38 (78.9)	
Number of N1 stations	1.5 [0.0, 2.0]	2.0 [2.0, 3.0]	0.001
Number of N1 lymph nodes	3.0 [0.0, 6.0]	5.0 [3.0, 9.0]	0.001
Number of N2 stations	1.0 [0.0, 2.0]	3.0 [3.0, 3.0]	<0.001
Number of N2 lymph nodes	1.0 [0.0, 4.0]	7.0 [5.0, 9.0]	<0.001
Number of Total lymph nodes	4.0 [0.0, 9.0]	13.0 [9.0, 17.0]	<0.001
Pathologic findings			
Predominant patterns			0.073
Lepidic	33/100 (33.0)	6/38 (15.8)	
Acinar	61/100 (61.0)	27/38 (71.1)	
Papillary	5/100 (5.0)	5/38 (13.2)	
Solid	1/100 (1.0)	0/38 (0.0)	

Table 1 (*continued*)

Table 1 (*continued*)

Clinical factors	Limited N2 dissection (<3 N2 stations) (n=100)	Extended N2 dissection (≥3 N2 stations) (n=38)	P value
Visceral pleural invasion	2/100 (2.0)	0/38 (0.0)	>0.99
Lymphovascular invasion	4/100 (4.0)	0.38 (0.0)	0.575
STAS	6/100 (6.0)	3/38 (7.9)	0.706
EGFR mutation			0.622
Negative	20/80 (25.0)	6/32 (18.8)	
Positive	60/80 (75.0)	26/32 (81.2)	
TNM staging			0.462
IA	94/100 (94.0)	34/38 (89.5)	
IB	6/100 (6.0)	4/38 (10.5)	
Follow-up duration (months)	45.4 [30.0, 71.0]	49.1 [38.5, 66.4]	0.612
Hospital stay (days)	3.0 [2.0, 4.0]	3.0 [2.0, 6.0]	0.089
PoC	5/97 (5.2)	7/36 (19.4)	0.018
Prolonged air-leakage	3/5	4/7	
Pneumonia	0/5	1/7	
Chylothorax	0/5	1/7	
Arrhythmia	1/5	0/7	
Others‡	1/5	1/7	

Data were presented as n/N (%), median [IQR], or n/N. †, SUVmax was used for classification: mild, 0< SUVmax <2.5; hypermetabolic, SUVmax ≥2.5; ‡, 1 hoarseness due to recurrent laryngeal nerve injury in the extended group and 1 urinary retention in the limited group. MLND, mediastinal lymph node dissection; Lt, left; Rt, right; CTR, consolidation tumor ratio; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; STAS, spread through air space; EGFR, epidermal growth factor receptor; TNM, tumor-node-metastasis; PoC, postoperative complication; IQR, interquartile range; SUVmax, maximum standardized uptake value.

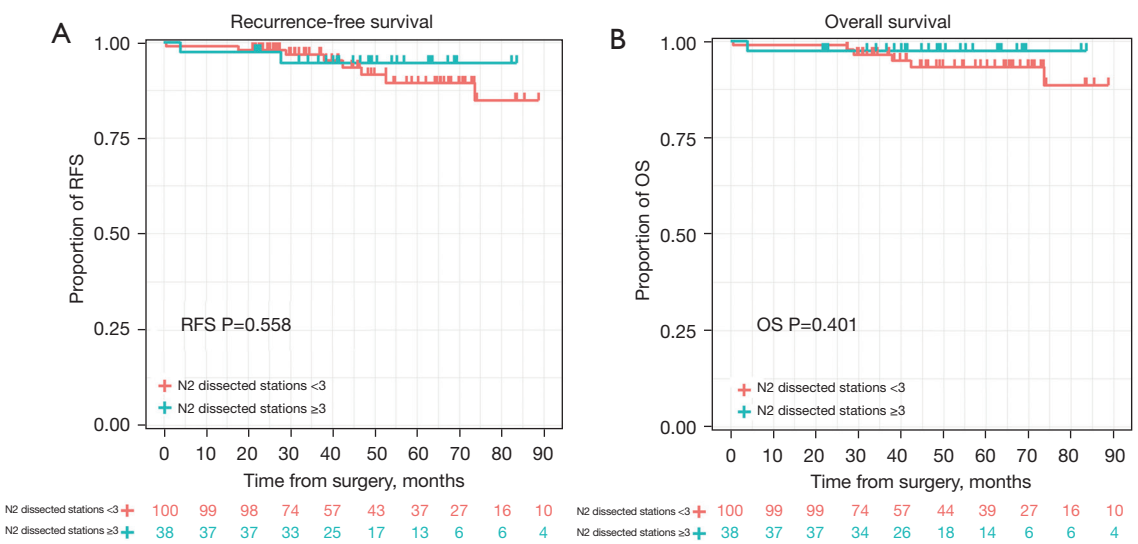

Figure 1 Long-term clinical outcome according to the extent of N2 MLND. RFS, recurrence-free survival; OS, overall survival; MLND, mediastinal lymph node dissection.

Table 2 Patient characteristics according to the extent of MLND after propensity score matching

Clinical factors	Limited N2 dissection (<3 N2 stations) (n=33)	Extended N2 dissection (≥3 N2 stations) (n=33)	P value
Sex			>0.99
Female	20/33 (60.6)	19/33 (57.6)	
Male	13/33 (39.4)	14/33 (42.4)	
Age (years)	66.0 [58.0, 71.0]	64.0 [61.0, 70.0]	0.944
Ex or current smoker	7/33 (21.2)	10/33 (30.3)	0.574
Hypertension	14/33 (42.4)	12/33 (36.4)	0.801
Diabetes mellitus	5/33 (15.2)	8/33 (24.2)	0.537
Other cardiovascular disease	4/33 (12.1)	2/33 (6.1)	0.672
^{18}F-FDG uptake on PET-CT†			>0.99
No uptake	10/30 (30.3)	10/30 (30.3)	
Mild	13/30 (39.4)	13/30 (39.4)	
Hypermetabolic	7/30 (21.2)	7/30 (21.2)	
CTR	0.47 [0.40, 0.57]	0.53 [0.43, 0.61]	0.243
Total tumor diameter (mm)	20.0 [13.0, 25.0]	20.0 [12.0, 24.0]	0.893
Solid lesion diameter (mm)	8.0 [6.0, 12.5]	9.0 [7.0, 12.0]	0.491
Surgical extent			>0.99
Wedge resection	4/33 (12.1)	4/33 (12.1)	
Segmentectomy	4/33 (12.1)	4/33 (12.1)	
Lobectomy	25/33 (75.8)	25/33 (75.8)	
Number of N1 stations	2.0 [1.0, 3.0]	2.0 [2.0, 3.0]	0.141
Number of N1 lymph nodes	4.0 [1.0, 6.0]	5.0 [3.0, 9.0]	0.079
Number of N2 stations	1.0 [0.0, 2.0]	3.0 [3.0, 3.0]	<0.001
Number of N2 lymph nodes	2.0 [0.0, 5.0]	7.0 [4.0, 9.0]	<0.001
Number of Total lymph nodes	8.0 [3.0, 12.0]	13.0 [9.0, 17.0]	<0.001
Pathologic findings			
Predominant patterns			0.492
Lepidic	7/33 (21.2)	6/33 (18.2)	
Acinar	25/33 (75.8)	23/33 (69.7)	
Papillary	1/33 (3.0)	4/33 (12.1)	
Visceral pleural invasion	0/33 (0.0)	0/33 (0.0)	>0.99
Lymphovascular invasion	3/33 (9.1)	0/33 (0.0)	0.238
STAS	4/33 (12.1)	2/33 (6.1)	0.672
TNM staging			>0.99
IA	32/33 (97.0)	31/33 (93.9)	
IB	1/33 (3.0)	2/33 (6.1)	

Table 2 (*continued*)

Table 2 (*continued*)

Clinical factors	Limited N2 dissection (<3 N2 stations) (n=33)	Extended N2 dissection (≥3 N2 stations) (n=33)	P value
Follow-up duration (months)	58.8 [33.2, 73.7]	54.1 [38.6, 68.5]	0.995
Hospital stay (days)	3.0 [3.0, 4.0]	3.0 [2.0, 6.0]	0.384
PoC	1/33 (3.2)	6/33 (19.4)	0.104
Prolonged air-leakage	1/1	3/6	
Pneumonia	0/1	1/6	
Chylothorax	0/1	1/6	
Arrhythmia	0/1	1/6	

Data were presented as n/N (%), median [IQR], or n/N. †, SUVmax was used for classification: mild, 0< SUVmax <2.5; hypermetabolic, SUVmax ≥2.5. MLND, mediastinal lymph node dissection; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; CTR, consolidation tumor ratio; STAS, spread through air space; TNM, tumor-node-metastasis; PoC, postoperative complication; IQR, interquartile range; SUVmax, maximum standardized uptake value.

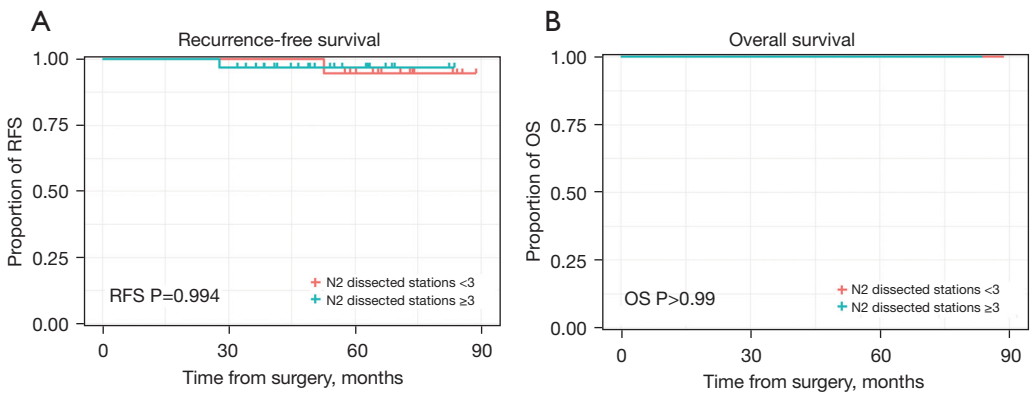

Figure 2 Long-term clinical outcome according to the extent of N2 MLND after propensity score matching. RFS, recurrence-free survival; OS, overall survival; MLND, mediastinal lymph node dissection.

Discussion

With increasing evidence for parenchymal-preserving surgery in lung cancer, progress in MLND has been made recently (8,13,15). This study reported clinical outcomes according to the extent of N2 MLND and questioned its applicability in all patients with early-stage lung cancer.

Because thoracic surgeons encounter many patients with GGO components, the extent of optimal has been debated. Compared to the era when systematic MLND was first introduced, early-stage lung cancer with a smaller size and different radiologic findings have increased (16). As tailored therapy for patients is applied, surgeons may need to decide which mediastinal lymph nodes should be dissected or sampled based on patient characteristics. Accurate staging with meticulous MLND is important. However, if tumor characteristics provide sufficient information regarding less aggressive features and nodal involvements, the universal application of extensive MLND may be detrimental to some patients (6).

A multicenter prospective trial on selective MLND recently revealed several criteria that can be applied depending on the tumor characteristics (13). The authors even did not perform MLND to lesions with a CTR of <0.5 owing to their favorable clinical outcome. Pulmonary lesions with GGO have shown significantly different clinical outcomes from solid lesions. For pure GGO lesions, which are more commonly observed in lung cancer screening programs, the 5- or 10-year recurrence rates seem closer

Table 3 Risk factor analysis for RFS

Clinical factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Cardiovascular disease history	5.81 (1.5–22.54)	0.011	4.36 (1.10–17.2)	0.036
Age over 65 years	4.57 (0.97–21.5)	0.055	3.80 (0.79–18.36)	0.097
Male (ref. female)	1.38 (0.4–4.79)	0.612		
Smoking history (ref. non-smoker)	1.12 (0.29–4.35)	0.872		
Sublobar resection (ref. lobectomy)	2.76 (0.76–10.0)	0.123		
Extended N2 MLND ≥3 stations (ref. limited N2 MLND)	0.63 (0.13–2.98)	0.562		
Tumor diameter	1.06 (0.98–1.14)	0.135		
Stage IB (ref. stage IA)	1.70 (0.21–13.4)	0.62		
^{18}F-FDG uptake on PET-CT (ref. no uptake)				
Mild uptake	1.79 (0.30–10.8)	0.523		
Hypermetabolic	0.79 (0.07–8.84)	0.852		

RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval; ref., reference; MLND, mediastinal lymph node dissection; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

Table 4 Risk factor analysis for the development of PoCs

Clinical factors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Cardiovascular disease history	2.91 (0.87–9.75)	0.084	2.09 (0.51–8.55)	0.303
Age	1.05 (0.99–1.11)	0.104		
Male (ref. female)	8.64 (1.81–41.2)	0.007	8.90 (1.81–43.7)	0.007
Smoking history (ref. non-smoker)	8.43 (2.34–30.4)	0.001	3.00 (0.58–15.5)	0.191
Sublobar resection (ref. lobectomy)	0.26 (0.05–1.25)	0.092	0.38 (0.07–2.12)	0.273
Extended N2 MLND ≥3 stations (ref. limited N2 MLND)	4.39 (1.30–14.9)	0.018	4.57 (1.26–16.6)	0.021
Solid portion diameter over 5 mm	0.61 (0.17–2.17)	0.445		
^{18}F-FDG uptake on PET-CT (ref. no uptake)				
Mild uptake	3.91 (0.74–20.6)	0.108		
Hypermetabolic	1.87 (0.25–14.2)	0.545		

PoC, postoperative complication; OR, odds ratio; CI, confidence interval; ref., reference; MLND, mediastinal lymph node dissection; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

to zero, and some clinicians argue that they should be classified as a different category of NSCLC. Masses with a CTR ≤0.25 were recognized as radiologically non-invasive lesions and their clinical outcomes were reported from the JCOG 0804 trial (17).

Preservation of the normal mediastinal lymph node structure has several clinical benefits. Most N2 nodes are located near important structures, such as the vagus and recurrent laryngeal nerves, bronchial arteries, and other great vessels, and damaging these structures can result

in a poor postoperative course. In our study, specific complications such as arrhythmia, chylothorax, and recurrent laryngeal nerve injury were also related to the damage of these structures. Furthermore, recent studies on immunotherapy in other cancers have demonstrated the benefit of preserving normal lymph node structure. Normal lymph nodes in the tumor-draining area exhibit antitumor activity and suppress tumor growth (18,19); thus, alteration of these structures could result in suppressed immuno-oncologic activity. Although GGO-dominant lesions might not increase the immunologic burden compared with upregulation of immune checkpoints initiated by invasive nodules (20), preservation of lymph node structure may be important in preventing local recurrence or a second primary lung cancer.

Many surgical societies have demanded the standardization of MLND (10,21-23). Recently, following a surgical database study, the concept of uncertain resection R(un) has brought attention to the quality of MLND in lung cancer surgery (21). We agree that reporting on the completeness of lung cancer resection should be prioritized to improve the quality of current procedures. However, if they are applied without considering patient-specific circumstances, surgeons may miss the goal of achieving optimal patient outcomes. Even though extensive resection is not challenging or difficult in terms of surgical technique, it is always important to apply the "do no harm" principle for patients.

This study has several limitations. First, the retrospective design with a limited number of patients could have led to a significant bias in interpreting the data. Second, the criteria for CTR of 0.3–0.7 allowed inclusion of patients with a broad range of tumor characteristics and these should be validated in other clinical settings. Third, the extent of parenchymal resection could bias the clinical outcomes. In the extended N2 MLND group, the proportion of patients who underwent lobectomy was significantly higher than in the limited N2 dissection group. More patients data would be necessary to compare the impacts of sublobar resection or lobectomy. Lastly, intraoperative frozen biopsy results or surgeons' decisions may have led to differences in the surgical extent even though CTR and PET activities were similar between the two groups. These biases should be addressed in future prospective studies.

Conclusions

In conclusion, our study indicates that extended N2 MLND for pulmonary lesions with CTR between 0.3 and 0.7 could have a negative impact on early postoperative outcomes, without significant long-term oncologic benefit. Therefore, the applicability of the general MLND strategy should be reconsidered in patients with GGO-containing lesions. Further prospective studies and thorough discussions among surgical societies are necessary to provide a solid background for applying appropriate MLND approaches according to tumor characteristics.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-703/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-703/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-703/coif). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Gangnam Severance Hospital (No. 3-2023-0169). The requirement for informed consent was waived due to the retrospective design of the study.

References

1. Carbone DP, Gandara DR, Antonia SJ, et al. Non-Small-Cell Lung Cancer: Role of the Immune System and Potential for Immunotherapy. J Thorac Oncol 2015;10:974-84.
2. Scholten ET, de Jong PA, de Hoop B, et al. Towards a close computed tomography monitoring approach for screen detected subsolid pulmonary nodules? Eur Respir J 2015;45:765-73.
3. Saji H, Okada M, Tsuboi M, et al. Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial. Lancet 2022;399:1607-17.
4. Altorki N, Wang X, Kozono D, et al. Lobar or Sublobar Resection for Peripheral Stage IA Non-Small-Cell Lung Cancer. N Engl J Med 2023;388:489-98.
5. Hattori A, Matsunaga T, Takamochi K, et al. Extent of mediastinal nodal dissection in stage I non-small cell lung cancer with a radiological pure-solid appearance. Eur J Surg Oncol 2021;47:1797-804.
6. Woo W, Shin JI, Kipkorir V, et al. Clinical Benefits of Lobe-Specific Lymph Node Dissection in Surgery for NSCLC: A Systematic Review and Meta-Analysis. JTO Clin Res Rep 2023;4:100516.
7. Deng C, Zhang Y, Chen H. Is it really necessary to perform mediastinal lymphadenectomy in surgery for ground glass opacity-featured lung adenocarcinoma? AME Med J 2022;7:24.
8. Hattori A, Matsunaga T, Takamochi K, et al. Significance of Lymphadenectomy in Part-Solid Lung Adenocarcinoma: Propensity Score Matched Analysis. Ann Thorac Surg 2018;106:989-97.
9. American College of Surgeons. National Cancer Database. [Accessed 21st June 2023]. Available online: https://www.facs.org/quality-programs/cancer-programs/national-cancer-database/
10. Lardinois D, De Leyn P, Van Schil P, et al. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. Eur J Cardiothorac Surg 2006;30:787-92.
11. Rami-Porta R, Wittekind C, Goldstraw P, et al. Complete resection in lung cancer surgery: proposed definition. Lung Cancer 2005;49:25-33.
12. Zhang Y, Fu F, Wen Z, et al. Segment Location and Ground Glass Opacity Ratio Reliably Predict Node-Negative Status in Lung Cancer. Ann Thorac Surg 2020;109:1061-8.
13. Zhang Y, Deng C, Zheng Q, et al. Selective Mediastinal Lymph Node Dissection Strategy for Clinical T1N0 Invasive Lung Cancer: A Prospective, Multicenter, Clinical Trial. J Thorac Oncol 2023;18:931-9.
14. Rusch VW, Asamura H, Watanabe H, et al. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. J Thorac Oncol 2009;4:568-77.
15. Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. J Thorac Cardiovasc Surg 2011;141:662-70.
16. Servais EL, Blasberg JD, Brown LM, et al. The Society of Thoracic Surgeons General Thoracic Surgery Database: 2022 Update on Outcomes and Research. Ann Thorac Surg 2023;115:43-9.
17. Suzuki K, Watanabe S, Wakabayashi M, et al. A nonrandomized confirmatory phase III study of sublobar surgical resection for peripheral ground glass opacity dominant lung cancer defined with thoracic thin-section computed tomography (JCOG0804/WJOG4507L). J Clin Oncol 2017;35:8561.
18. Maglioco A, Machuca D, Mundiñano J, et al. Lymphadenectomy exacerbates tumor growth while lymphadenectomy plus the adoptive transfer of autologous cytotoxic cells and low-dose cyclophosphamide induces regression of an established murine fibrosarcoma. Cancer Immunol Immunother 2011;60:389-99.
19. Huang Q, Wu X, Wang Z, et al. The primordial differentiation of tumor-specific memory CD8(+) T cells as bona fide responders to PD-1/PD-L1 blockade in draining lymph nodes. Cell 2022;185:4049-4066.e25.
20. Altorki NK, Borczuk AC, Harrison S, et al. Global evolution of the tumor microenvironment associated with progression from preinvasive invasive to invasive human lung adenocarcinoma. Cell Rep 2022;39:110639.
21. Edwards JG, Chansky K, Van Schil P, et al. The IASLC Lung Cancer Staging Project: Analysis of Resection Margin Status and Proposals for Residual Tumor Descriptors for Non-Small Cell Lung Cancer. J Thorac

Oncol 2020;15:344-59.
22. De Leyn P, Lardinois D, Van Schil P, et al. European trends in preoperative and intraoperative nodal staging: ESTS guidelines. J Thorac Oncol 2007;2:357-61.
23. Verhagen AF, Schoenmakers MC, Barendregt W, et al. Completeness of lung cancer surgery: is mediastinal dissection common practice? Eur J Cardiothorac Surg 2012;41:834-8.

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