Original Article

Analysis of lymph node metastasis based on consolidation tumor ratio and maximum standardized uptake value in clinical stage IA non-small cell lung cancer

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Background: Sublobar resection has been established as an acceptable treatment for early-stage non-small cell lung cancer (NSCLC). As a result, preoperative prediction of lymph node (LN) metastasis is becoming an important factor in determining surgical strategy. This study aimed to investigate the predictive accuracy of the consolidation tumor ratio (CTR) and the maximum standardized uptake value (maxSUV) of the primary tumor for LN metastasis in patients with clinical stage IA NSCLC.

Methods: We performed a retrospective analysis using data from 1,338 patients with clinical stage IA NSCLC who underwent surgery between 2011 and 2019. Receiver operating characteristic (ROC) curves and the area under the curve (AUC) were used to identify the optimal maxSUV and CTR for predicting LN metastasis. Multivariate logistic regression analysis was performed to identify independent predictors of LN metastasis. Survival analyses were performed using Cox proportional hazards models to identify prognostic factors for death and recurrence.

Results: Among the 896 patients who underwent lobectomy with systematic LN dissection, 9.8% (88 patients) were found to have LN metastasis. The ROC curve for CTR revealed an AUC of 0.689 [95% confidence interval (CI): 0.646–0.732, P<0.001], while the ROC curve for maxSUV yielded an AUC of 0.748 (95% CI: 0.705–0.791, P<0.001) for predicting LN metastasis. In pure solid mass (CTR =1) with maxSUV exceeding 5.0, LN metastasis was observed in 13.8% of tumor 0–2 cm and 25.7% of tumor 2.1–3 cm. Multivariate analysis identified CTR >0.5 (HR =1.741, 95% CI: 1.122–2.701, P=0.01) and maxSUV >5.0 (HR =2.004, 95% CI: 1.421–2.825, P<0.001) as independent prognostic factors for disease-free survival.

Conclusions: In clinical stage IA NSCLC, LN metastasis can be predicted using CTR and maxSUV of the primary mass. It is crucial not to underestimate the rate of LN metastasis when determining the surgical extent.

Keywords: Non-small cell lung cancer (NSCLC); clinical stage IA; lymph node metastasis (LN metastasis); surgery; survival

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Introduction

Treatment of clinical stage IA non-small cell lung cancer (NSCLC) typically centers around surgical interventions (1). The conventional surgical approach for lung cancer, established based on the findings of the Lung Cancer Study Group, considers lobectomy and systematic lymph node (LN) dissection as the standard procedure (2). However, recent studies have compared segmentectomy and lobectomy in patients with early-stage lung cancer, and the results have shown that segmentectomy is non-inferior to lobectomy in terms of long-term survival (3-6). In addition, there is a growing trend in lung cancer screening programs designed to reduce lung cancer related mortality. This trend is expected to increase the rate of early lung cancer diagnosis (7-11). Consequently, it is anticipated that the use of segmentectomy will continue to increase in the future (12).

When comparing segmentectomy with the traditional approach of lobectomy, it is important to ensure sufficient parenchymal resection margin (13-15). Likewise, evaluation for LN metastasis, including those in the mediastinal, hilar, lobar, interlobar, and segmental regions, is equally important (16,17). For this reason, it is recommended to confirm the presence or absence of LN metastasis through a frozen biopsy during segmentectomy (18). In a recent phase III randomized controlled trial comparing segmentectomy and lobectomy, the frequency of LN metastasis was significantly high even in tumor less than 2 cm in size, especially in patients with pure solid mass (3). This increased risk of LN metastasis, especially in the segmentectomy group where segmental LN dissection was less likely to be performed, would be expected to increase the risk of local recurrence. And in this case, patients may require the necessity of repetitive anatomical lung resection. Thus, the preoperative prediction of LN metastasis is important.

The maximum standardized uptake value (maxSUV) obtained from 2-Deoxy-2-[fluorine-18] fluoro-D-glucose (^{18}F-FDG) positron emission tomography-computed tomography (PET-CT) is a well-established predictor of LN metastasis, recurrence, and survival in lung cancer (4,19,20). Its significance lies in its preoperative availability and ability to provide quantifiable and objective measurements. In parallel, the consolidation tumor ratio (CTR) plays a pivotal role in early-stage lung cancer, serving as a crucial indicator related to invasiveness of adenocarcinoma, LN metastasis, and risk of recurrence (21-24). Our objective was to evaluate the predictive accuracy of the CTR and the maxSUV of the primary tumor for LN metastasis in patients with clinical stage IA NSCLC. In addition, we aimed to stratify tumors based on CTR and maxSUV to predict the preoperative risk of LN metastasis and guide appropriate surgical strategies within each risk group. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1780/rc).

Highlight box

Key findings

- In clinical stage IA non-small cell lung cancer (NSCLC), lymph node (LN) metastasis can be predicted using consolidation tumor ratio (CTR) and maximum standardized uptake value (maxSUV) of the primary mass.

What is known and what is new?

- Both CTR and maxSUV were known as prognostic factor for lung cancer. The frequency of LN metastasis tended to increase as CTR and maxSUV values increased.
- In this study, an optimal cutoff value of 5.0 was established for maxSUV, which was found to be associated not only with LN metastasis but also with recurrence, overall survival, and disease-free survival.

What is the implication, and what should change now?

- Establishing an optimal CTR and MaxSUV cutoff values will help identify patients at low risk of LN involvement.
- The results of this study may provide evidence to support the use of preoperative indicators for more personalized surgical treatment strategies in clinical stage IA NSCLC.

Methods

Study design and patient selection

We performed a retrospective observational study at Asan Medical Center to determine the optimal predictive system for LN metastasis in clinical stage IA NSCLC. Our data was collected from a consecutive cohort of patients

diagnosed with clinical stage IA NSCLC who underwent surgical treatment between January 2011 and December 2019. Inclusion criteria were patients aged 18 years or older, with radiologically confirmed clinical stage IA NSCLC according to the American Joint Committee on Cancer (AJCC) 8th Edition Staging Manual, and the availability of complete clinical, radiological, and pathological data. Exclusion criteria included right middle lobe tumor, neoadjuvant therapy, and absence of preoperative PET-CT information. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and ethically approved by Asan Medical Center institutional review board (approval No. 2023-1482, approval date: 18 November, 2023). Informed consent was waived because of the study's retrospective nature.

Preoperative evaluations and PET-CT

Patients included in this study underwent preoperative chest CT and PET-CT for staging work-up. If clinically suspected N2 metastasis was identified on imaging studies, invasive mediastinal LN staging, including mediastinoscopy or endobronchial ultrasound, was performed. PET-CT was performed after fasting for at least 6 hours with a venous blood glucose level of less than 150 mg/dL, using one of the following scanners: Discovery 690, Discovery 690 Elite, or Discovery 710 (General Electric Company, Milwaukee, WI, USA). Image acquisition began approximately 60 minutes after intravenous injection of 5.2 MBq/kg of ^{18}F-FDG. PET-CT images were obtained from the base of the skull to the mid-thigh for 2 minutes per bed position in three-dimensional mode. Data were reconstructed in a 192×192 matrix with a voxel size of 2.6 mm × 2.6 mm × 3.75 mm using the ordered subset expectation maximization algorithm (18 subsets, 4 iteration) and attenuation correction using CT maps.

Treatments

All surgical procedures were performed by thoracic surgeons at Asan Medical Center. During the study period, lobectomy with systematic LN dissection was performed as the standard treatment for lung cancer. Sublobar resection was performed in patients who could not tolerate lobectomy due to poor lung function, comorbidities, performance status, or oncologic considerations. Additionally, sublobar resection was intentionally performed in patients with clinical stage IA peripheral tumors that could secure a resection margin of 2 cm or the size of the tumor. Because of the lack of definitive guidelines, the choice between wedge resection and segmentectomy was determined at the surgeon's discretion. In our institution, systematic mediastinal and hilar LN dissection was preferred even for patients with early-stage lung cancer. However, the extent of LN evaluation was determined at the surgeon's discretion. Frozen-section LN analysis during sublobar resection was not mandatory.

Adjuvant chemotherapy, consisting of a platinum-based regimen, was recommended for patients with pathologic stage II or higher disease. It was initiated within 4 to 6 weeks following surgery and comprised a total of four cycles. Patients with poor performance status or those who declined treatment after consultation with the multidisciplinary team were excluded. For adjuvant radiotherapy, a daily dose of 1.8 Gy was delivered, with a total dose of 50.4 Gy administered to patients with completely resected stage III NSCLC. Patients with positive surgical margins received a total dose of 55 to 60 Gy.

Surveillance protocol

Outpatient follow-up was performed regularly with chest CT scans. For patients with stage I NSCLC, follow-up was performed every 6 months for 5 years. For patients with LN metastasis, follow-up was performed every 3 months during the first two years after surgery and subsequently every 6 months thereafter. If recurrence was suspected, additional imaging tests such as PET-CT and magnetic resonance imaging were performed. The date of recurrence was defined as the date of initial detection on the imaging study. Overall survival (OS) was defined as duration from the date of surgery to the date of death from any cause, or the last follow-up. Disease-free survival (DFS) was defined as duration from the date of surgery to the date of recurrence, death from any cause, or the last follow-up.

Statistical analysis

The primary outcome was the presence of LN metastasis confirmed by histopathological examination of resected LNs after surgery. Demographic and clinical characteristics of patients were summarized using descriptive statistics. The analysis was performed using R, version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria). The performance of each predictive system was assessed using relevant statistical tests, including sensitivity, specificity, positive predictive value (PPV), and negative

predictive value (NPV). Receiver operating characteristic (ROC) curve analysis was employed to calculate the area under the curve (AUC) for each predictive system. If two predictors were selected, DeLong's test was used to compare AUCs. Multivariate logistic regression analysis with stepwise backward elimination was performed to identify independent predictors of LN metastasis, with statistical significance set at a P value <0.05. The Kaplan-Meier method was used to estimate OS and DFS, and the log-rank test was employed to evaluate differences between groups. Cox proportional hazards models with stepwise backward elimination were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for OS and DFS.

Results

Patient demographics

A total of 1,338 patients with clinical stage IA NSCLC were included in this study, with a mean age of 62.3± 9.4 years, and 680 patients (50.8%) were female. Detailed demographic and clinical characteristics of the included patients are summarized in *Table 1*. Adenocarcinoma accounted for the majority (92.6%) of all patients, and all patients had no regional LN involvement (cN0) or distant metastasis (cM0). Among all patients, 896 (67.0%), 264 (19.7%), and 178 (13.3%) patients underwent lobectomy, segmentectomy, and wedge resection, respectively. Tumor with a CTR exceeding 0.5 accounted for a total of 975 cases (72.9%). And there was a significant difference in the lobectomy, segmentectomy, and wedge resection groups, with 704 (78.6%), 158 (59.8%), and 113 (63.5%) cases, respectively. The rate of LN metastasis was 7.9% (106 out of 1,338 patients), with 9.8% (88/896), 3.8% (10/264), and 4.5% (8/178) in the lobectomy, segmentectomy, and wedge resection groups, respectively, showing a significant difference between groups (P=0.001). Among patients with pathologically confirmed LN metastasis, the proportion of those who received adjuvant chemotherapy were 86.4% (76/88) in the lobectomy group, 80.0% (8/10) in the segmentectomy group, and 62.5% (5/8) in the wedge resection group.

Prediction of LN metastasis through logistic regression curve

The relationship between LN metastasis and CTR and maxSUV in patients with clinical stage IA NSCLC with tumor size ≤3 cm who underwent lobectomy is shown in *Figure 1*. As CTR increased from 0 to 0.25, 0.5, 0.75, and 1, there was a corresponding increase in the probability of LN metastasis, which was 0.4%, 1.1%, 2.7%, 6.7%, and

Table 1 Patients' demographics for clinical stage IA non-small cell lung cancer undergoing surgical resection (N=1,338)

Characteristics	Surgical extent			Total (N=1,338)	P
	Lobectomy (N=896)	Segmentectomy (N=264)	Wedge resection (N=178)		
Age (years)	61.4±9.1	62.6±9.7	65.9±9.8	62.3±9.4	<0.001*
Sex					0.72
Female	450 (50.2)	140 (53.0)	90 (50.6)	680 (50.8)	
Male	446 (49.8)	124 (47.0)	88 (49.4)	658 (49.2)	
Smoking					0.33
Current	87 (9.7)	18 (6.8)	21 (11.8)	126 (9.4)	
Ex-smoker	297 (33.1)	82 (31.1)	60 (33.7)	439 (32.8)	
Never	512 (57.1)	164 (62.1)	97 (54.5)	773 (57.8)	
Histology					<0.001*
Adenocarcinoma	801 (89.4)	263 (99.6)	175 (98.3)	1,239 (92.6)	
Squamous cell carcinoma	88 (9.8)	0	3 (1.7)	91 (6.8)	
Others	7 (0.8)	1 (0.4)	0	8 (0.6)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Surgical extent			Total (N=1,338)	P
	Lobectomy (N=896)	Segmentectomy (N=264)	Wedge resection (N=178)		
Tumor location					<0.001*
RUL	310 (34.6)	62 (23.5)	51 (28.7)	423 (31.6)	
RLL	208 (23.2)	58 (22.0)	51 (28.7)	317 (23.7)	
LUL	226 (25.2)	106 (40.2)	48 (27.0)	380 (28.4)	
LLL	152 (17.0)	38 (14.4)	28 (15.7)	218 (16.3)	
Clinical T stage (8th edition)					<0.001*
Tis	49 (5.5)	52 (19.7)	39 (21.9)	140 (10.5)	
T1ami	53 (5.9)	24 (9.1)	16 (9.0)	93 (7.0)	
T1a	133 (14.8)	56 (21.2)	21 (11.8)	210 (15.7)	
T1b	369 (41.2)	87 (33.0)	75 (42.1)	531 (39.7)	
T1c	292 (32.6)	45 (17.0)	27 (15.2)	364 (27.2)	
CTR					<0.001*
0–0.25	90 (10.0)	67 (25.4)	48 (27.0)	205 (15.3)	
0.26–0.50	102 (11.4)	39 (14.8)	17 (9.6)	158 (11.8)	
0.51–0.99	310 (34.6)	46 (17.4)	26 (14.6)	382 (28.6)	
1	394 (44.0)	112 (42.4)	87 (48.9)	593 (44.3)	
Clinical stage (8th edition)					<0.001*
0	49 (5.5)	52 (19.7)	39 (21.9)	140 (10.5)	
IA1	186 (20.8)	80 (30.3)	37 (20.8)	303 (22.6)	
IA2	369 (41.2)	87 (33.0)	75 (42.1)	531 (39.7)	
IA3	292 (32.6)	45 (17.0)	27 (15.2)	364 (27.2)	
FEV1 (%)	91.1±14.5	87.0±14.2	85.4±16.3	89.5±14.9	<0.001*
DLCO (%)	88.7±14.8	85.4±15.0	79.7±15.6	86.9±15.2	<0.001*
Charlson Comorbidity Index					<0.001*
0	343 (38.3)	95 (36.0)	40 (22.5)	478 (35.7)	
1	340 (37.9)	96 (36.4)	70 (39.3)	506 (37.8)	
2	155 (17.3)	50 (18.9)	41 (23.0)	246 (18.4)	
3	50 (5.6)	18 (6.8)	21 (11.8)	89 (6.7)	
4	8 (0.9)	5 (1.9)	6 (3.4)	19 (1.4)	
Invasive mediastinal staging	7 (0.7)	20 (7.6)	17 (9.6)	44 (3.3)	<0.001*
No. of LN removed	26.4±10.2	21.9±9.7	14.6±8.9	24.0±10.7	<0.001*
No. of LN positive	0.3±1.3	0.1±0.9	0.2±1.5	0.2±1.2	0.30

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Surgical extent			Total (N=1,338)	P
	Lobectomy (N=896)	Segmentectomy (N=264)	Wedge resection (N=178)		
Pathologic T status					<0.001*
Tis	1 (0.1)	2 (0.8)	0	3 (0.2)	
T1ami	13 (1.5)	12 (4.5)	9 (5.1)	34 (2.5)	
T1a	19 (2.1)	28 (10.6)	17 (9.6)	64 (4.8)	
T1b	315 (35.2)	139 (52.7)	96 (53.9)	550 (41.1)	
T1c	347 (38.7)	64 (24.2)	34 (19.1)	445 (33.3)	
T2a	201 (22.4)	19 (7.2)	22 (12.4)	242 (18.1)	
Pathologic N status					0.002*
N0	808 (90.2)	254 (96.2)	170 (95.5)	1,232 (92.1)	
N1	45 (5.0)	4 (1.5)	1 (0.6)	50 (3.7)	
N2	43 (4.8)	6 (2.3)	7 (3.9)	56 (4.2)	
N1 LN metastasis	69 (7.7)	9 (3.4)	3 (1.7)	81 (6.1)	0.001*
N2 LN metastasis	44 (4.9)	6 (2.3)	7 (3.9)	57 (4.3)	0.17
Pathologic M status					0.78
M0	895 (99.9)	264 (100.0)	178 (100.0)	1,337 (99.9)	
M1a	1 (0.1)	0	0	1 (0.1)	
Pathologic stage					<0.001*
0	1 (0.1)	2 (0.8)	0	3 (0.2)	
IA1	32 (3.6)	41 (15.5)	25 (14.0)	98 (7.3)	
IA2	298 (33.3)	132 (50.0)	94 (52.8)	524 (39.2)	
IA3	313 (34.9)	61 (23.1)	33 (18.5)	407 (30.4)	
IB	163 (18.2)	18 (6.8)	18 (10.1)	199 (14.9)	
IIB	45 (5.0)	4 (1.5)	1 (0.6)	50 (3.7)	
IIIA	43 (4.8)	6 (2.3)	7 (3.9)	56 (4.2)	
IVA	1 (0.1)	0	0	1 (0.1)	
Adjuvant therapy					0.002*
None	814 (90.8)	256 (97.0)	173 (97.2)	1,243 (92.9)	
Chemoradiation	20 (2.2)	5 (1.9)	3 (1.7)	28 (2.1)	
Chemotherapy	56 (6.3)	3 (1.1)	2 (1.1)	61 (4.6)	
Radiation therapy	6 (0.7)	0	0	6 (0.4)	

Data are presented as mean ± standard deviation or n (%). *, P<0.05. RUL, right upper lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; CTR, consolidation tumor ratio; FEV1, forced expiratory volume in one second; DLCO, diffusion capacity of the lung for carbon monoxide; LN, lymph node; No., number.

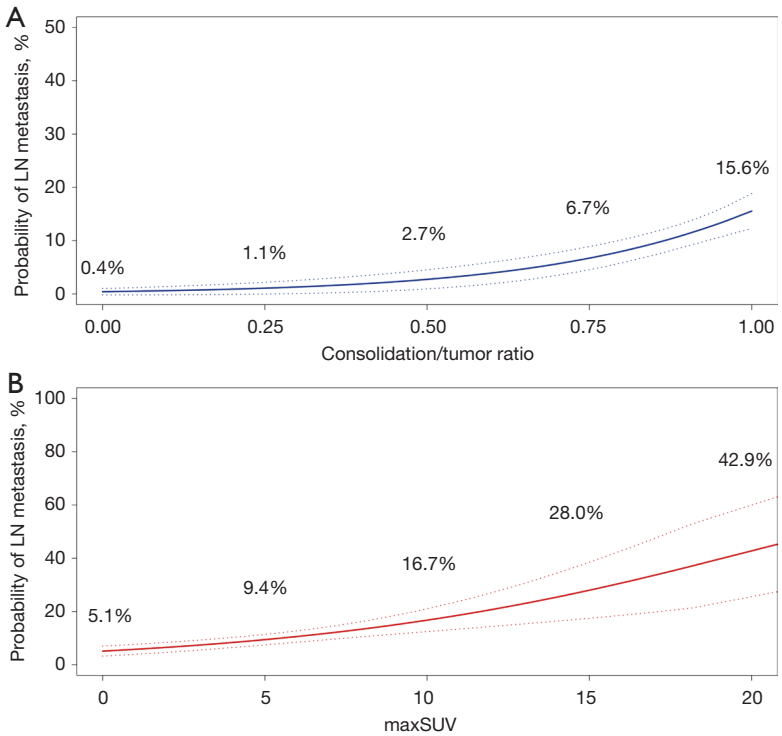

Figure 1 Prediction of lymph node metastasis using logistic regression curves in 896 patients who underwent lobectomy with systematic lymph node dissection for clinical stage IA non-small cell lung cancer. (A) CTR; (B) maxSUV. CTR, consolidation tumor ratio; LN, lymph node; maxSUV, maximum standardized uptake value.

15.6%, respectively. Furthermore, as maxSUV increased from 0 to 5, 10, 15, and 20, the probability of LN metastasis also increased to 5.1%, 9.4%, 16.7%, 28.0%, and 42.9%, respectively (*Figure 1*).

ROC curve analysis

ROC curve analysis was performed to evaluate the predictive performance of CTR and maxSUV in identifying LN metastasis. The ROC curve for CTR showed an AUC of 0.689 (95% CI: 0.646–0.732, P<0.001), while the ROC curve for maxSUV yielded an AUC of 0.748 (95% CI: 0.705–0.791, P<0.001). Both CTR and maxSUV exhibited statistically significant discriminatory ability to predict LN metastasis, with P values <0.05. The sensitivity and specificity of CTR and maxSUV at selected cutoff values to predict LN metastasis are presented in *Figure 2*, demonstrating the superior diagnostic accuracy of maxSUV. The optimal cutoff value for predicting LN metastasis based on maxSUV was found to be 5.0. When 5.0 was applied as the threshold, sensitivity, specificity, PPV, and NPV were 75.0%, 69.7%, 21.2%, and 96.2%, respectively. ROC curves for predicting LN metastasis, recurrence, OS, and DFS are shown in *Figure 2*.

Logistic regression analysis for LN metastasis

Multivariate logistic regression analysis was performed to determine the independent predictive value of CTR and maxSUV for LN metastasis. After adjusting for potential confounders, including age, gender, smoking history, tumor histology, and tumor size, both CTR and maxSUV were identified as independent predictors of LN metastasis (*Table 2*). The odds ratios (ORs) for CTR and maxSUV were 1.690 (95% CI: 1.050–3.110), and 5.050 (95% CI: 3.040–8.660), respectively.

Analysis of LN metastasis in subgroups considering CTR and maxSUV

Additional subgroup analyses were performed to investigate the association between tumor maximum size, CTR, maxSUV, and LN metastasis, and are summarized in

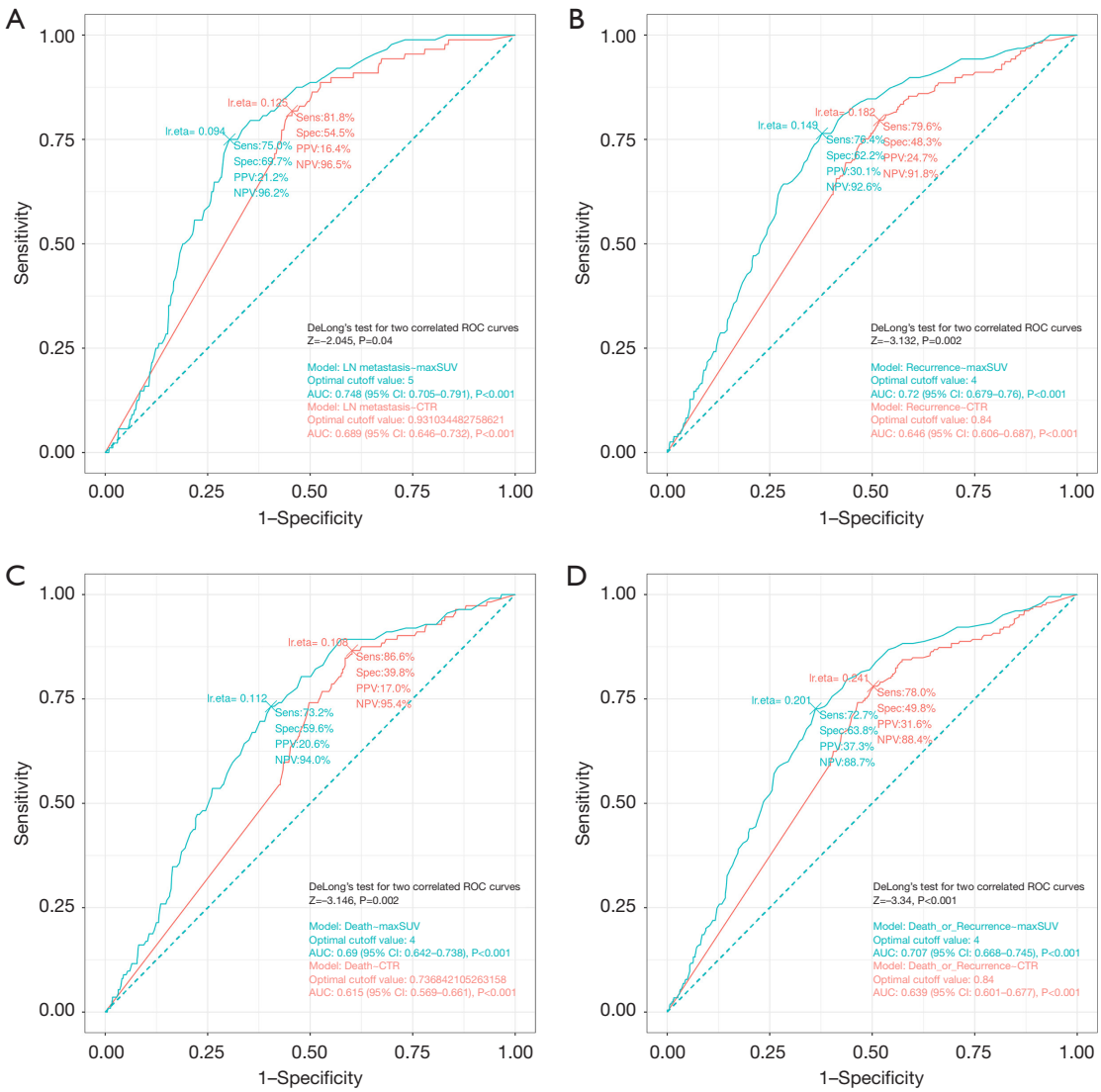

Figure 2 ROC curves for lymph node metastasis (A), recurrence (B), overall survival (C), and disease-free survival (D) in 896 patients who underwent lobectomy with systematic lymph node dissection for clinical stage IA non-small cell lung cancer. The ROC curves in this figure illustrate the predictive performance of two distinct factors: maxSUV, represented by the blue curve, and CTR, depicted by the red curve. Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; lr.eta, optimal cutoff value from logistic regression model; LN, lymph node; ROC, receiver operating characteristic; AUC, area under the curve; CTR, consolidation tumor ratio; maxSUV, maximum standardized uptake value; CI, confidence interval.

Tables 3,4. The frequency of LN metastasis increased with the increase in tumor size, CTR, and maxSUV. Specifically, as CTR increased from 0.25 or less to 0.26–0.50, 0.51–0.99, and 1.0, the rate of LN metastasis also increased to 1.1%, 2.9%, 7.1%, and 15.7%, respectively. In hypermetabolic mass with a maxSUV exceeding 5.0, LN metastasis was observed in 12.7% of tumor sized 0–2 cm and 25.5% of tumor sized 2.1–3 cm (*Tables 3,4*).

Factors influencing recurrence and survival

Multivariate analysis was performed to identify prognostic factors associated with OS and DFS in patients with clinical stage IA NSCLC. Statistically significant prognostic factors related to OS included age, male gender, maxSUV >5, pN status, and the presence of adjuvant therapy. Prognostic factors associated with DFS included CTR >0.5, maxSUV

Table 2 Univariate and multivariate logistic regression analysis for lymph node metastasis in clinical stage IA non-small cell lung cancer 896 patients undergoing lobectomy

Variables	Row name	Univariate analysis			Multivariate analysis		
		OR	95% CI	P value	OR	95% CI	P value
Age	≤61 years	1			–	–	–
	>61 years	1.090	0.700–1.690	0.72	–	–	–
Gender	Female	1			–	–	–
	Male	1.010	0.650–1.570	0.97	–	–	–
Smoking	Never	1			–	–	–
	Ex or current	1.240	0.800–1.930	0.33	–	–	–
Histology	Adenocarcinoma	1			–	–	–
	Non-adenocarcinoma	0.790	0.440–1.300	0.40	–	–	–
Tumor size	0–2.0 cm	1			1		
	2.1–3 cm	2.280	1.420–3.760	<0.001*	1.660	1.010–2.790	0.053
CTR	≤0.5	1			1		
	>0.5	2.520	1.620–4.590	<0.001*	1.690	1.050–3.110	0.049*
maxSUV	≤5	1			1		
	>5	6.650	4.100–11.160	<0.001*	5.050	3.040–8.660	<0.001*

*, P<0.05. OR, odds ratio; CI, confidence interval; CTR, consolidation tumor ratio; maxSUV, maximum standardized uptake value.

Table 3 Investigation of lymph node metastasis frequency based on tumor size and CTR in patients undergoing lobectomy for clinical stage IA (divided into 8 groups based on tumor size and CTR)

Tumor size	CTR				Sum
	0–0.25	0.26–0.50	0.51–0.99	1.00	
0–2.0 cm	0% (0/54)	3.6% (2/56)	4.5% (6/134)	10.3% (17/165)	6.1% (25/409)
2.1–3.0 cm	2.8% (1/36)	2.2% (1/46)	9.1% (16/176)	19.7% (45/229)	12.9% (63/487)
Sum	1.1% (1/90)	2.9% (3/102)	7.1% (22/310)	15.7% (62/394)	9.8% (88/896)

CTR, consolidation tumor ratio.

>5.0, wedge resection, pT status, pN status, and the presence of adjuvant therapy. Notably, maxSUV >5.0 appeared to be an independent prognostic factor for both OS and DFS (*Table 5*).

Considering the high NPV of 96.2% for LN metastasis using a maxSUV cutoff of 5.0, we performed a detailed investigation of DFS in subgroups based on tumor size and CTR, specifically in the maxSUV ≤5.0 group. When CTR was 0.5 or less, no significant difference in DFS was observed with respect to surgical extent, regardless of tumor size (0–2 or 2.1–3 cm). However, for tumor with a CTR exceeding 0.5, a significant difference in DFS was observed when the tumor size was 2.1 to 3 cm. In this subgroup, wedge resection had worse outcomes than lobectomy or segmentectomy (*Figure 3*).

Discussion

The prospective phase III study, Japan Clinical Oncology Group (JCOG) 0802, focused on NSCLC patients with peripheral tumor sized 2 cm or less and CTR greater than 0.5, and included a substantial proportion of patients (50%, 553 patients) with pure solid tumor. This study demonstrated the non-inferiority of segmentectomy

Table 4 Investigation of lymph node metastasis frequency based on CTR and maxSUV in patients undergoing lobectomy for clinical stage IA (divided into 16 groups based on tumor size, CTR, and maxSUV)

Tumor size	CTR				Sum
	0–0.25	0.26–0.50	0.51–0.99	1.00	
0–2.0 cm					
maxSUV ≤5.0	0% (0/52)	1.9% (1/53)	2.9% (3/102)	8.0% (8/100)	3.9% (12/307)
maxSUV >5.0	0% (0/2)	33.3% (1/3)	9.4% (3/32)	13.8% (9/65)	12.7% (13/102)
2.1–3.0 cm					
maxSUV ≤5.0	0% (0/33)	0% (0/43)	2.5% (3/122)	9.4% (8/85)	3.9% (11/283)
maxSUV >5.0	33.3% (1/3)	33.3% (1/3)	24.1% (13/54)	25.7% (37/144)	25.5% (52/204)
Sum	1.1% (1/90)	2.9% (3/102)	7.1% (22/310)	15.7% (62/394)	9.8% (88/896)

CTR, consolidation tumor ratio; maxSUV, maximum standardized uptake value.

Table 5 Multivariate analyses of prognostic factors predicting overall survival and disease-free survival in 1,338 patients undergoing surgery for clinical stage IA non-small cell lung cancer

Variables	Factors	Overall survival			Disease-free survival		
		HR	95% CI	P value	HR	95% CI	P value
Age		1.061	1.034–1.089	<0.001*	1.016	0.998–1.035	0.08
Sex	Female	1			–	–	–
	Male	1.656	1.071–2.562	0.02*	–	–	–
CTR	≤0.5	–	–	–	1		
	>0.5	–	–	–	1.741	1.122–2.701	0.01*
maxSUV	≤5	1			1		
	>5	1.718	1.085–2.719	0.02*	2.004	1.421–2.825	<0.001*
Surgical extent	Lobectomy	–	–	–	1		
	Segmentectomy	–	–	–	0.971	0.588–1.603	0.91
	Wedge resection	–	–	–	2.198	1.424–3.391	<0.001*
pT status	Tis/MIA/T1a	1			1		
	T1b	2.610	0.626–10.883	0.19	2.453	0.886–6.796	0.08
	T1c	3.893	0.933–16.246	0.06	3.455	1.233–9.681	0.02*
pN status	N0	1			1		
	N1	3.762	1.417–9.987	0.008*	7.173	3.488–14.748	<0.001*
	N2	11.953	4.999–28.582	<0.001*	12.636	6.452–24.746	<0.001*
Adjuvant therapy	No	1			1		
	Yes	0.283	0.113–0.717	0.007*	0.237	0.118–0.477	<0.001*

*, P<0.05. HR, hazard ratio; CI, confidence interval; CTR, consolidation tumor ratio; maxSUV, maximum standardized uptake value; p, pathologic.

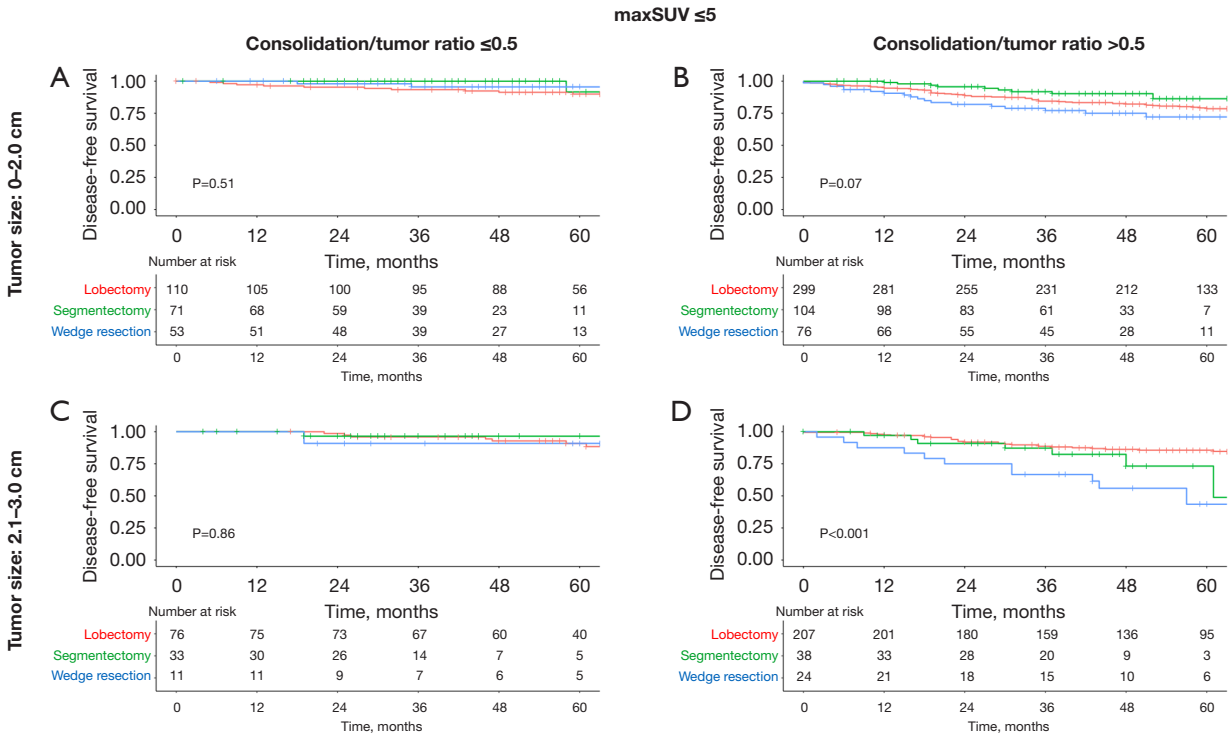

Figure 3 Comparison of disease-free survival based on surgical extent in subgroups stratified by tumor size and consolidation tumor ratio in 1,338 patients who underwent surgery for clinical stage IA non-small cell lung cancer with maxSUV ≤5.0. (A) Disease-free survival for tumors sized 0–2.0 cm with a consolidation/tumor ratio ≤0.5; (B) disease-free survival for tumors sized 0–2.0 cm with a consolidation/tumor ratio >0.5; (C) disease-free survival for tumors sized 2.1–3.0 cm with a consolidation/tumor ratio ≤0.5; (D) disease-free survival for tumors sized 2.1–3.0 cm with a consolidation/tumor ratio >0.5. maxSUV, maximum standardized uptake value.

compared to lobectomy with respect to long-term survival outcomes. However, the frequency of local recurrence was reported to be significantly higher in the segmentectomy group (10.5%) compared to the lobectomy group (5.4%). Notably, within the subset of pure solid tumor, the local recurrence rate was 7.7% (21/274) in the lobectomy group and significantly higher at 16.1% (45/279) in the segmentectomy group (3). This high rate of local recurrence in segmentectomy could be related to the possibility of incomplete LN dissection during segmentectomy, raising concerns about nodal underestimation associated with segmentectomy.

In this context, the aim of this study was to evaluate the frequency of LN metastasis using preoperative indicators. Furthermore, we sought to refine stratification of the frequency of LN metastasis within specific subgroups. These subgroups were initially determined based on tumor size and the CTR from the JCOG study, and with the incorporation of maxSUV. Logistic regression analysis demonstrated that both CTR and maxSUV served as independent predictors for forecasting LN metastasis. In our investigation, we established an optimal cutoff value of 5.0 for maxSUV, which exhibited superior accuracy in predicting LN metastasis compared to CTR, for which the cutoff value was 0.93. This enhanced predictive precision of maxSUV extends not only to LN metastasis but also to recurrence, OS, and DFS.

The optimal cutoff value for maxSUV has been analyzed through various methods in prior studies, with one notable approach involving the ratio of maxSUV in the LN to maxSUV in the primary tumor (19,25,26). While this approach can offer more precise information in comparison to analyzing maxSUV of the primary tumor alone, its applicability may pose challenges in cases akin to the patients in this study who present clinical stage IA and clinical N0. In such cases, LN uptake is not prominently observed, making it difficult to obtain maxSUV data of LN. In addition, in regions with a high prevalence of

conditions like tuberculosis, concerns arise regarding potential inaccurate results due to false positives. Therefore, we investigated the frequency of LN metastasis in each group by incorporating two indicators, including CTR and maxSUV of the primary tumor.

In the lobectomy group, the overall frequency of LN metastasis was 9.8%, and tended to increase as CTR and maxSUV values increased. Because intersegmental or lobar LNs are almost always dissected in the lobectomy group, the result of LN metastasis is thought to be very similar to the actual incidence of LN metastasis. This study included 394 cases of pure solid mass and surprisingly revealed an overall LN involvement rate of 15.7%. Among them, in the subgroup with maxSUV greater than 5.0, the frequency of LN metastasis was 13.8% for tumor measuring 2 cm or less and reached 25.7% for tumor measuring 2.1–3 cm. These findings are closely similar to those reported in JCOG 0802, which indicated that the frequency of LN metastasis in hypermetabolic solid tumor exceeds 20% (3). Furthermore, in this study, 192 patients with a CTR ≤0.5 were included, among whom 4 cases of unexpected nodal upstaging were observed. This is a higher rate compared to JCOG 1211, which aimed to evaluate the efficacy and safety of segmentectomy in patients with ground-glass opacity (GGO)-dominant NSCLC with a total tumor size of 3 cm or less, where unexpected LN metastasis was observed in only 2 out of 395 patients. This discrepancy may be attributed to differences in LN evaluation strategies, as systematic LN dissection was routinely performed at our institution, whereas in JCOG 1211, over 50% of patients underwent hilar-only or intrapulmonary-only dissection. Independent of these differences, our findings highlight the importance of additional stratification using the maxSUV to improve the prediction of LN metastasis. When a maxSUV threshold of 5 was applied, only 1 of 181 patients with maxSUV ≤5.0 exhibited unexpected nodal upstaging, compared to 3 of 11 patients with maxSUV >5.0. This suggests excellent specificity in predicting LN metastasis in clinical practice.

Although we examined the frequency of LN metastasis based on subgroups considering both CTR and maxSUV, it is important to note that the presence of LN metastasis does not necessarily indicate that segmentectomy is inferior to lobectomy. These are separate issues that require further evaluation and consideration. When the maxSUV cutoff value for LN metastasis is 5, the NPV is 96.2%, which is clinically meaningful in that LN metastasis is rarely observed when maxSUV is 5.0 or less. For maxSUV ≤5.0, there was no significant difference in DFS between lobectomy, segmentectomy, and wedge resection groups in the subgroup with CTR ≤0.5, regardless of tumor size. In the subgroup with CTR greater than 0.5, the extent of surgery had no significant effect on DFS for tumor sized 0 to 2 cm. However, for tumor with a CTR >0.5 and a size of 2.1 to 3 cm, the wedge resection group had a worse prognosis compared to the lobectomy or segmentectomy groups. These results suggest that segmentectomy, unlike wedge resection, is not inferior to lobectomy under any circumstances for tumor with a maxSUV of 5.0 or less.

One potential explanation for segmentectomy not being inferior to lobectomy is the likelihood of conducting relatively thorough LN dissection during segmentectomy. In practice, the segmentectomy group had an average total of 21.9 LNs resected. Moreover, since the standard policy involved switching to lobectomy in cases with positive results from intraoperative frozen biopsies, it is reasonable to assume that the segmentectomy group routinely performs more extensive LN dissection. Notably, in this study, for cases where maxSUV was ≤5.0, a total of 30 instances of LN metastasis were found within the lobectomy group, comprising 3.2% (30 out of 934 cases), whereas the segmentectomy group reported no cases with LN metastasis. Another potential reason is that, in the group with LN metastasis, factors related to postoperative adjuvant therapy may have a more significant impact from an oncological perspective than the surgical extent. Several authors have reported that lobectomy offers no survival benefit over segmentectomy in patients with cT1N0M0 NSCLC who exhibit pathologically unexpected LN metastasis after surgery. Furthermore, they have also demonstrated that adjuvant chemotherapy is associated with improved survival in these patients (27,28). Similarly, in our study, when performing multivariate analysis on the 106 patients with LN metastasis, the segmentectomy group did not show statistically significant differences in prognosis compared to the lobectomy group (HR =3.308, 95% CI: 0.715–15.304, P=0.13). However, adjuvant therapy emerged as a significant factor in the analysis (HR =0.188, 95% CI: 0.040–0.811, P=0.03). In summary, the study concludes that segmentectomy can be performed relatively safely when the maxSUV is 5.0 or less.

In this study, 92.6% of patients had adenocarcinoma, and 44.3% were identified as having a clinically pure solid mass, which is known to be more invasive and associated with poorer survival outcomes compared to part-solid tumors. Consistent with these characteristics, our study also

demonstrated a higher likelihood of LN metastasis in pure solid tumors than in part-solid tumors. Regional variations in tumor histology can significantly influence LN metastasis rates and survival outcomes, as evidenced by differences in findings across studies with similar designs, such as JCOG 0802 and CALGB 140503. Therefore, the results of this study should be interpreted cautiously, considering potential regional and study-specific variations.

This study has several limitations. First, it relies on retrospective data accumulated from a single center. Second, the use of maxSUV as a metric in this study may be limited by the potential variability in measurements due to differences in imaging equipment and protocols, which may affect the accuracy and consistency of maxSUV values across different institutions. These variations may affect the generalizability and comparability of study results. Third, although there were several studies comparing the prognosis of different surgical extents with subgrouping based on tumor size and CTR, it is important to note that baseline data between each surgical resection group were not matched. Additionally, there may be treatment allocation bias. Due to the surgical extent was determined at the surgeon's discretion, lobectomy was preferred in patients with clinically suspected poor prognostic factor. As a results, the lobectomy group had a significantly higher number of patients upstaged to pathologic T2a compared to the other groups due to visceral pleura invasion. Despite the limitations mentioned, our results highlight the importance of preoperative indicators as a valuable tool in clinical practice, contributing to more accurate surgical planning and improved patient management.

Conclusions

In conclusion, our study highlights the importance of preoperative parameters, especially CTR, maxSUV, and tumor size, when assessing the frequency of LN metastasis in clinical stage IA NSCLC. In this study, maxSUV was identified as an independent prognostic indicator in NSCLC along with CTR. Establishing an optimal maxSUV cutoff value, as in our study, will help identify patients at low risk of LN involvement. We hope that the results of this study may provide evidence to support the use of preoperative indicators for more personalized surgical treatment strategies in clinical stage IA NSCLC.

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Footnote

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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. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and ethically approved by Asan Medical Center institutional review board (approval No. 2023-1482, approval date: 18 November, 2023). Informed consent was waived because of the study's retrospective nature.

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