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ORIGINAL SCIENTIFIC REPORT

Risk Factors for Occult Lymph Node Metastasis in Peripheral Non-Small Cell Lung Cancer with Invasive Component Size 3 cm or Less

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Abstract

Background In the seventh edition TNM staging system for lung cancer, a high maximum standardized uptake value (SUVmax) on positron emission tomography was regarded as a risk factor for occult lymph node metastasis in clinical T1N0 non-small cell lung cancer (NSCLC). However, in the eighth edition TNM classification, tumors are classified according to the size of the invasive component only, and those with invasive component size ≤3 cm are diagnosed as stage T1. The aim of this study was to reassess the risk factors for occult lymph node metastasis under the eighth edition TNM classification for lung cancer.

Methods From 2010 to 2017, 553 patients with clinical N0 peripheral NSCLC with invasive component size ≤3 cm underwent anatomical lobectomy with systematic lymph node dissection. We analyzed these cases retrospectively to identify risk factors for postoperative nodal upstaging.

Results Among 553 study patients, 54 (9.8%) had nodal upstaging after surgery. In multivariate analysis adopting the eighth edition TNM classification for lung cancer, serum carcinoembryonic antigen (CEA) level (hazard ratio [HR] = 1.113, $p = 0.002$), invasive component size (HR = 2.398, $p = 0.004$), visceral pleural invasion (HR = 2.901, $p = 0.005$), and lymphatic invasion (HR = 9.336, $p < 0.001$) were significant risk factors for nodal upstaging, but SUVmax was not.

Conclusion SUVmax is not a predictor of nodal upstaging in clinical N0 peripheral NSCLC with invasive component size ≤3 cm under the eighth edition TNM classification for lung cancer. Significant risk factors of occult lymph node metastasis are serum CEA level, tumor invasive component size, visceral pleural invasion, and lymphatic invasion.

Introduction

Treatment for lung cancer is mainly determined according to the cancer stage. The standard treatment for stage I lung cancer is anatomical pulmonary resection with lymph node dissection [1], while multimodal treatment is preferred for higher-stage tumors. Therefore, exact determination of cancer stage is very important for successful treatment of lung cancer.

Chest computed tomography (CT) and positron emission tomography (PET)/CT are the main techniques for the clinical staging of lung cancer. Invasive preoperative

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lymph node staging using endobronchial ultrasonography-guided transbronchial needle aspiration might be necessary in selected cases, but it is unreasonable for patients with no sign lymph node metastases at preoperative imaging. According to the guideline of the European Society of Thoracic Surgeons (ESTS), invasive mediastinal lymph node staging can be skipped if there are no suspect lymph nodes on CT or PET/CT, the tumor size on imaging is ≤3 cm, and the tumor is confined to the periphery of the lung [2]. However, even patients who meet the three criteria for clinical N0 (cN0) tumors occasionally have postoperative lymph node upstaging, despite the cN0 diagnosis under the ESTS guideline.

We have reported that the maximum standardized uptake value (SUVmax) of the main tumor on PET/CT scan is a predictor of occult lymph node metastasis in cN0 lung tumors [3], and other studies have confirmed that the tumor SUVmax is a predictor of postoperative nodal upstaging [4–7]. However, lymph node metastasis seldom occurs in lung cancers presenting as ground glass opacity nodules [8, 9], which are characterized by low SUVmax and are well known as less invasive, mainly lepidic adenocarcinomas. Therefore, the effect of SUVmax may not be important when the lepidic component of the tumor is excluded.

Previous studies of nodal upstaging in clinical stage I lung cancer have been based on the seventh edition TNM classification, in which the tumor (T) stage is based on total tumor size, including the lepidic component. In the eighth edition TNM classification, the T stage is determined by the size of the invasive component only, excluding the lepidic component. As a result, we expect that the role of SUVmax as a predictive factor for nodal upstaging may be diminished under the eighth edition TNM staging system.

The purpose of this study was to identify the risk factors for nodal upstaging after surgery in cN0 peripheral non-small cell lung cancer (NSCLC) with invasive component size ≤3 cm, which is classified as clinical stage T1 under the eighth edition TNM classification, and to determine whether SUVmax is a predictor of postoperative nodal upstaging in cN0 lung cancers under the new classification.

Patients and methods

Patients

From January 2010 to December 2017, 1630 consecutive patients were diagnosed with lung cancer and underwent therapeutic surgical resection at a tertiary hospital in Korea. Among these, 553 patients satisfied the following inclusion criteria: (1) anatomical lobectomy with systematic lymph node dissection; (2) tumor stage T1 (invasive component size ≤3 cm) under the eighth edition TNM staging system; (3) cN0; 4) peripheral location; 5) no neoadjuvant treatment.

The patients were classified into two groups according to surgical pathology results: those with cN0 tumors preoperatively and pathologic N0 (pN0) tumors postoperatively (pN0 group) and those with cN0 tumors that were upstaged postoperatively to pN1 or pN2 tumors (nodal upstaging group). Clinicopathological characteristics were compared between the two groups. Operative procedures included lobectomy and bilobectomy, and dissection of more than three mediastinal lymph node stations was performed in every patient by en bloc resection of the lymph nodes and adjacent fat tissues. For patients with right-sided tumors, the paratracheal and subcarinal lymph nodes were routinely dissected and for those with left-sided tumors, para-aortic, subaortic, and subcarinal lymph nodes were routinely dissected. Other visible mediastinal lymph nodes were also resected. N1 lymph nodes, including hilar, interlobar, and lobar nodes, were also routinely dissected. This study was approved by the institutional review board of Seoul St. Mary's Hospital at the Catholic University of Korea.

Preoperative lymph node staging

Preoperative lymph node staging is based on contrast-enhanced chest CT and F-18 fluorodeoxyglucose (FDG)-PET/CT scanning. Lymph nodes with short-axis diameter >10 mm on the CT scan and high SUVmax relative to the surrounding mediastinal structures on PET-CT are considered metastatic. However, lymph nodes with high SUVmax are considered benign if the suspect node contains benign calcifications or if it shows high attenuation with a distinct margin on unenhanced CT [3, 10], and general, symmetric, and equivocal FDG uptake in the mediastinal lymph nodes is interpreted as a reactive change due to inflammation. When tumors are clearly diagnosed as cN0 at preoperative imaging and complete resection appears possible, surgery is performed without invasive preoperative lymph node staging.

Histopathology and re-staging

All surgical specimens were examined by pathologists whose observations were recorded. Each pathology report was reviewed for tumor size, location, lymph node status, pleural invasion, lymphatic invasion, and vascular invasion.

Tumors were restaged according to the eighth edition of TNM classification [11] by measuring the greatest dimension of the invasive component on the pathology specimen [12], and tumors with invasive component size ≤3 cm

were classified as stage T1 in accordance with the eighth edition of the TNM classification. In the case of adenocarcinoma, total tumor size was defined as the greatest dimension of the tumor including lepidic component. On the other hand, invasive component size was defined as greatest dimension of the invasive component excluding lepidic component of the tumor.

Invasion into the visceral pleura was defined as tumor extension beyond the elastic layer of the visceral pleura. Lymphatic invasion was defined as tumor cells observed in the lymphatic lumen. Vascular invasion was defined as tumor cells observed in the vascular lumen. Histologic features, as well as the presence of pleural, lymphatic, and vascular invasion, were determined using hematoxylin–eosin staining. If the findings could not be determined using hematoxylin–eosin staining alone, special staining, such as Verhoeff–Van Gieson elastic stain, was performed as necessary. In particular, Verhoeff–Van Gieson elastic stain was performed for detailed evaluation of visceral pleural invasion where present.

Statistical analysis

Student's *t* test or the Wilcoxon rank-sum test was used for continuous variables, and Chi-squared or Fisher's exact test was used for categorical variables. Univariate and multivariate logistic regression was used to identify predictors of postoperative nodal upstaging. All variables with $p < 0.1$ in the univariate analysis were entered into the multivariate analysis, and $p < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS version 24.0 software (IBM Corp, Armonk, NY).

Results

Comparison of clinicopathological characteristics

Among 553 study patients with peripheral cN0 NSCLC, 54 (9.8%) had postoperative nodal upstaging (26 [48.1%] to pN1, and 28 [51.9%] to pN2: 10 [18.5%] with strictly N1 metastases and 18 [33.3%] with N1 + N2 metastases). A comparison of the clinicopathological characteristics of patients with and without nodal upstaging is presented in Table 1. Patients with upstaged tumors had higher serum carcinoembryonic antigen (CEA) levels (mean 5.1 vs 2.3, $p = 0.004$), tumor SUVmax (6.2 vs 4.1, $p < 0.001$), total tumor size (2.4 cm vs 2.1 cm, $p = 0.003$), and tumor invasive component size (2.1 cm vs 1.4 cm, $p < 0.001$). Patients in the nodal upstaging group also had significantly higher incidence of visceral pleural invasion ($p < 0.001$), lymphatic invasion ($p < 0.001$), and vascular invasion ($p < 0.001$).

Nodal upstaging was more frequent for tumors with higher pathologic T stage (Table 2). There was no nodal upstaging in T1a tumors.

Table 3 shows the incidence and distribution of metastatic mediastinal lymph nodes based on the location of the main tumor. Lymph node metastases from upper lobe tumors were most frequently found in the upper mediastinal lymph nodes (87.5% from right upper lobe tumors and 100% from left upper lobe tumors), while the subcarinal or lower mediastinal nodes were the main sites for metastasis of right lower lobe (70%) and left lower lobe tumors (100%).

Univariate and multivariate analyses for predictors of lymph node upstaging

Table 4 shows the main risk factors for lymph node upstaging according to the logistic regression analyses. In univariate analysis (Table 4A), CEA level, tumor SUVmax, involved lobe, total tumor size, invasive component size, visceral pleural invasion, lymphatic invasion, and vascular invasion had *p* values of <0.1. These variables were entered into the multivariate model, and we conducted two multivariate analyses according to the method of measuring tumor size: multivariate analysis *T*, which adopted total tumor size, including the lepidic component (Table 4B), and multivariate analysis *I*, which adopted invasive component size (Table 4C). In multivariate analysis *T*, serum CEA level, visceral pleural invasion, and lymphatic invasion were significant risk factors for nodal upstaging and SUVmax and total tumor size were not. In the multivariate analysis *I*, serum CEA level (hazard ratio [HR] = 1.113, $p = 0.002$), invasive component size (HR = 2.398, $p = 0.004$), visceral pleural invasion (HR = 2.901, $p = 0.005$), and lymphatic invasion (HR = 9.336, $p < 0.001$) were significant risk factors for nodal upstaging and SUVmax was not. When the postoperative findings of visceral pleural invasion, lymphatic invasion, and vascular invasion were omitted and the multivariate analysis for predictors for nodal upstaging was repeated (Table 5), the serum CEA level (HR = 1.106, $p = 0.001$) and the invasive component size (HR = 3.115, $p < 0.001$) were significant predictors for nodal upstaging, and SUVmax was not.

Distribution of invasive component sizes in non-upstaging and upstaging groups

We created a scatter plot to examine the distribution of invasive component sizes in the two groups (Fig. 1). All tumors in the nodal upstaging group measured at least 1.2 cm. Lymph node metastasis was not detected in cases in which the invasive component size was <1.2 cm, and this result is consistent with the finding that nodal

Table 1 Clinicopathological characteristics in patients with non-upstaged (pN0) and upstaged lymph nodes in peripheral stage I non-small cell lung cancer

Variables	PN0 group (n = 499)	Nodal upstaging group (n = 54)	p value
Age, y (± SD)	63.6 (± 10.0)	63.6 (± 9.0)	0.996
Sex			0.331
Male	206 (41.3%)	26 (48.1%)	
Female	293 (58.7%)	28 (51.9%)	
Current or former smoker	161 (32.3%)	18 (33.3%)	0.873
Pulmonary function			
FEV1 (%)	97.0 (± 15.9)	96.9 (± 16.1)	0.953
DLCO (%)	89.0 (± 17.2)	91.2 (± 20.1)	0.392
Serum CEA level (ng/mL)	2.3 (± 3.0)	5.1 (± 6.6)	0.004
SUVmax (± SD)	4.1 (± 3.7)	6.2 (± 3.2)	<0.001
Lobe			0.222
Right upper	192(38.5%)	12 (22.2%)	
Right middle	48 (9.6%)	6 (11.1%)	
Right lower	100(20.0%)	13 (24.1%)	
Left upper	95 (19.0%)	14 (25.9%)	
Left lower	64 (12.8%)	9 (16.7%)	
Extent of operation			1.000
Lobectomy	495(99.2%)	54 (100%)	
Bilobectomy	4 (0.8%)	0	
VATS	481(96.4%)	52 (96.3%)	1.000
Open thoracotomy	18 (3.6%)	2 (3.7%)	
Histology			0.193
Adenocarcinoma	457(91.6%)	50 (92.6%)	
Squamous cell carcinoma	30 (6.0%)	1 (1.9%)	
Others	12 (2.4%)	3 (5.6%)	
Total tumor size[a] (± SD)	2.1 (± 0.8)	2.4 (± 0.7)	0.003
Invasive component size[b]	1.4 (± 0.8)	2.1 (± 0.5)	<0.001
Number of dissected lymph nodes	14.6 (± 6.6)	15.1 (± 6.9)	0.569
Visceral pleural invasion	91 (18.2%)	28 (51.9%)	<0.001
Lymphatic invasion	158 (31.7%)	47 (87.0%)	<0.001
Vascular invasion	50 (10.0%)	18 (33.3%)	<0.001
Stage			<0.001
Stage 0 (AIS)	4 (0.8%)	0	
Stage IA1 (MIA)	66 (13.2%)	0	
Stage IA1	97 (19.4%)	0	
Stage IA2	164(32.9%)	0	
Stage IA3	77 (15.4%)	0	
Stage IB	91 (18.2%)	0	
Stage IIB	0	26 (48.1%)	
Stage IIIA	0	28 (51.9%)	

pN0 pathologic N0 stage; *SD* standard deviation; *FEV1* forced expiratory volume in 1 s; *DLCO* diffusing capacity for carbon monoxide; *CEA* carcinoembryonic antigen; *SUVmax* maximum standardized uptake value; *VATS* video-assisted thoracoscopic surgery; *AIS* adenocarcinoma in situ; *MIA* minimally invasive adenocarcinoma

[a]Total tumor size = Greatest dimension of the tumor including lepidic component

[b]Invasive component size = Greatest dimension of the invasive component of the tumor

Table 2 Pathologic T and N stages in the nodal upstaging group according to the eighth edition TNM classification

	n = 54
Pathologic T stage	
T1a	0
T1b	12 (22.2%)
T1c	14 (25.9%)
T2a	28 (51.9%)
Pathologic N stage	
N1 disease	26 (48.1%)
N2 disease	28 (51.9%)
N2 only	10 (18.5%)
N1 + N2	18 (33.3%)

upstaging did not occur in patients with stage T1a tumors (Table 2).

Discussion

The accuracy of clinical staging for lung cancer has improved with the evolution of chest CT and PET/CT scanning. However, despite these technical improvements, nodal upstaging is still reported in approximately 10 to 15% of patients with clinical stage I lung cancer [3–5, 13–15]. In this study, nearly 10% of patients (54 of 553, [9.8%]) with peripheral cN0 NSCLC with invasive component ≤3 cm were upstaged to pN1 or N2 disease after anatomic resection.

Accurate prediction of lymph node status before surgery facilities more accurate treatment planning. Patients with N2 disease may have a better prognosis with neoadjuvant chemotherapy, and sublobar resection is not sufficient for clinical N0 tumors with known risk of occult lymph node metastasis. Therefore, the potential for nodal upstaging must be carefully considered in every case.

Under the seventh edition TNM classification, the tumor SUVmax on preoperative PET/CT imaging was a predictor of nodal upstaging [3–7]. In the eighth edition TNM classification, which was published in 2017, the tumor (T) stage is determined by the size of the invasive component only, and the lepidic component is not measured for T staging [12, 16]. Therefore, the importance of SUVmax is relatively reduced because predominantly lepidic tumors, which are usually characterized by a low SUVmax at PET/CT, are re-classified as very small tumors. In this study, we examined risk factors for nodal upstaging under the eighth edition TNM staging system, which classifies tumors with invasive component size ≤3 cm as stage T1 and found that SUVmax is no longer predictive of nodal upstaging in clinical T1N0M0 NSCLC. Instead, the size of the invasive component is a significant risk factor for nodal upstaging. Therefore, we propose that invasive component size can replace SUVmax as a predictor of occult lymph node metastasis. Although the invasive component size is measured definitively only at histology, it can be predicted preoperatively by determining the extent of consolidation in the tumor at CT [16], and this measurement can be used to predict the risk of nodal upstaging. We found that all tumors in the nodal upstaging group were 1.2 cm or larger, while there was no occult lymph node metastasis in tumors smaller than 1.2 cm, which indicates that lymph node metastasis may not be a concern in clinical stage T1aN0M0 lung cancer. This also suggests that extensive lymph node

Table 3 Incidence and distribution of mediastinal lymph node metastasis

	RUL	RML	RLL	LUL	LLL
Number of patients	204	54	113	109	73
Incidence of N2 disease	8 (3.9%)	2 (3.7%)	10 (8.8%)	6 (5.5%)	2 (2.7%)
N2 distribution					
Upper mediastinal lymph nodes	7 (87.5%)	1 (50%)	1 (10%)	6 (100%)	0
Upper mediastinal + subcarinal lymph nodes	0	1 (50%)	2 (20%)	0	0
Subcarinal lymph nodes	1 (12.5%)	0	6 (60%)	0	1 (50%)
Lower mediastinal lymph nodes	0	0	1 (10%)	0	1 (50%)
Lower mediastinal + subcarinal lymph nodes	0	0	0	0	0

RUL right upper lobe; *RML* right middle lobe; *RLL* right lower lobe; *LUL* left upper lobe; *LLL* left lower lobe

Upper mediastinal lymph nodes included lymph node stations 2, 3, 4, 5, and 6

Subcarinal lymph node included lymph node station 7

Lower mediastinal lymph node included lymph node stations 8 and 9

Table 4 Univariate and multivariate analyses for risk factors of nodal upstaging (logistic regression model)

Variable	HR	95% CI	*p* value
(A) Univariate analysis			
Age	1.000	0.972–1.029	0.996
Sex (male)	1.321	0.752–2.319	0.333
Current of former smoker	1.050	0.578–1.905	0.873
FEV1 (%)	0.999	0.982–1.017	0.953
DLCO (%)	1.007	0.991–1.024	0.391
Serum CEA level	1.135	1.067–1.207	<0.001
SUVmax	1.127	1.055–1.204	<0.001
Involved lobe	1	0.714–5.601	0.242
Right upper (reference)	2.000	0.915–4.727	0.187
Right middle	2.080	1.050–5.297	0.080
Right lower	2.358	0.906–5.586	0.038
Left upper	2.250		0.081
Left lower			
VATS	0.973	0.220–4.311	0.971
Histology			0.227
Adenocarcinoma (reference)	1		
Squamous cell carcinoma	0.305		0.247
Others	2.285		0.212
Total tumor size	1.598	1.158–2.205	0.004
Invasive component size	3.377	2.212–5.155	<0.001
Number of dissected lymph nodes	1.012	0.971–1.054	0.568
Visceral pleural invasion	4.828	2.703–8.625	<0.001
Lymphatic invasion	14.491	6.407–32.775	<0.001
Vascular invasion	4.490	2.375–8.488	<0.001
(B) Multivariate analysis *T*			
Serum CEA level	1.111	1.037–1.191	0.003
SUVmax	0.997	0.901–1.103	0.947
Involved lobe			0.256
Right upper (reference)	1		
Right middle	2.760	0.738–10.315	0.131
Right lower	2.592	0.918–7.316	0.072
Left upper	2.675	0.970–7.382	0.057
Left lower	3.208	0.963–10.690	0.058
Total tumor size[a]	1.189	0.750–1.883	0.462
Visceral pleural invasion	3.128	1.508–6.488	0.002
Lymphatic invasion	10.020	3.873–25.925	<0.001
Vascular invasion	1.257	0.550–2.871	0.588
(C) Multivariate analysis *I*			
Serum CEA level	1.113	1.040–1.192	0.002
SUVmax	0.942	0.843–1.052	0.287
Involved lobe			0.278
Right upper (reference)	1		
Right middle	2.861	0.738–11.095	0.129
Right lower	2.502	0.879–7.121	0.086
Left upper	2.719	0.975–7.581	0.056
Left lower	3.074	0.908–10.403	0.071
Invasive component size[b]	2.398	1.321–4.354	0.004

Table 4 continued

Variable	HR	95% CI	*p* value
Visceral pleural invasion	2.901	1.386–6.073	0.005
Lymphatic invasion	9.336	3.567–24.431	<0.001
Vascular invasion	1.117	0.483–2.585	0.796

HR Hazard ratio; *CI* confidence interval; *FEV1* forced expiratory volume in 1 s; *DLCO* diffusing capacity for carbon monoxide; *CEA* carcinoembryonic antigen; *SUVmax* maximum standardized uptake value; *VATS* video-assisted thoracoscopic surgery

[a]Total tumor size = Greatest dimension of the tumor including lepidic component

[b]Invasive component size = Greatest dimension of the invasive component of the tumor

Table 5 Multivariate analysis for predictors of nodal upstaging (logistic regression model)

Variable	HR	95% CI	*p* value
Serum CEA level	1.106	1.041–1.175	0.001
SUVmax	0.998	0.914–1.089	0.955
Involved lobe			0.181
Right upper (reference)	1		
Right middle	2.696	0.776–9.368	0.119
Right lower	2.802	1.042–7.539	0.041
Left upper	3.138	1.179–8.356	0.022
Left lower	2.806	0.909–8.659	0.073
Invasive component size	3.115	1.803–5.381	<0.001

HR hazard ratio; *CEA* carcinoembryonic antigen; *SUVmax* maximum standardized uptake value

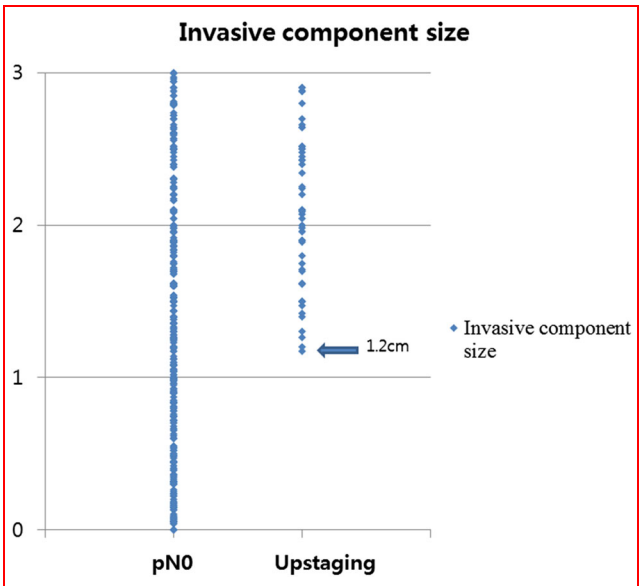

Fig. 1 Lymph node status according to the size of the invasive component. The scatter plot shows that all tumors in the nodal upstaging group (pN1 or pN2) were 1.2 cm or larger

dissection might be safely avoided in tumors with small invasive components.

Our finding that the preoperative serum CEA level was associated with the risk of nodal upstaging was consistent with the results of Yamazaki et al. [17]. This suggests that preoperative serum CEA levels, taken together with the preoperative estimate of the tumor invasive component size, should be useful for noninvasive preoperative assessment of the risk of occult lymph node metastasis in patients with peripherally located cN0 NSCLC of $\leq$3 cm. Visceral pleural and lymphatic invasion were also associated with the risk of nodal upstaging in our patients. When either of these is diagnosed after surgery without adequate lymph node dissection, a treatment plan considering the possibility of occult lymph node metastasis should be established.

Complete resection of lung cancer requires systematic lymph node dissection [18], which is the complete dissection of all mediastinal tissues or dissection of at least three mediastinal lymph node stations, including the subcarinal nodes [18, 19]. Our study population included only patients who underwent lobectomy and systematic lymph node dissection. Therefore, the pathologic lymph node staging is thought to be very accurate. Furthermore, the mean number of dissected lymph nodes was about 15 in this study. Data from the American College of Surgery Oncology Group (ACOSOG) Z0030 trial suggest that resection of 10 nodes might be considered adequate [20], and Dai et al. have reported that lymph node evaluation is important for accurate staging and that removal of 8 to 11 nodes can significantly reduce the risk of undetected nodal positivity [21]. Therefore, we believe that the lymph node evaluation in this study was appropriate in terms of the number of dissected lymph nodes. Systematic lymph node dissection may not be necessary if the possibility of lymph node metastasis is convincingly low. In such cases, local lymph node dissection-like lobe-specific nodal dissection may be appropriate [22, 23]. If the systematic lymph node dissection is omitted, the operation time can be reduced, thereby significantly reducing the general anesthesia time. Our analysis confirmed that upper lobe tumors mainly metastasized to the upper mediastinal lymph nodes and lower lobe tumors metastasized mainly to the subcarinal or lower mediastinal lymph nodes. This could imply that accurate staging and satisfactory outcomes are possible even after local lymph node dissection in patients with a low risk of nodal upstaging. Of course, this must be proven by large-scale studies.

This study had several limitations that should be considered. First, we used a retrospective study design. Second, this study was conducted in patients treated at a single institution. Nonetheless, we were able to collect very detailed clinical information from the electronic medical record, along with data from surgical specimens and pathology reports. In this regard, it was advantageous to have a single institution study. We believe that our data can be used as the basis for future investigations and that our results might be further clarified and refined by future studies with larger patient populations.

In conclusion, under the eighth edition TNM classification, tumor SUVmax is no longer a predictor of nodal upstaging in peripheral cN0 stage I NSCLC, but tumor invasive component size and serum CEA level are. Visceral pleural invasion and lymphatic invasion were also risk factors of nodal upstaging. Future studies that include multi-center data and larger sample sizes are necessary to confirm and supplement these results.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

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