Original Article

Preoperative predictors of lymph node metastasis in clinical T1 adenocarcinoma

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Background: The subcategory "solid component of tumor" is a new criterion of tumor categories in the updated eighth edition of the TNM classification. Nevertheless, the predictors of lymph node metastasis among patients with clinical T1 adenocarcinoma, based on the TNM classification 8th edition, remain unclear. This study aimed to identify the preoperative predictors of lymph node metastasis in clinical T1 adenocarcinoma by comparing clinicopathological characteristics between the groups with and without lymph node metastasis.

Methods: We performed a retrospective observational single-center study at the Sendai Kousei Hospital. From January 2012 to September 2019, we included 515 patients who underwent curative lobectomy or segmentectomy and mediastinal lymph node dissection among those with clinical T1 adenocarcinoma according to the UICC-TNM staging 8th edition. They were divided into two groups: those with lymph node metastasis (positive group) and those without (negative group). The clinicopathological factors were retrospectively analyzed and compared between the groups.

Results: In univariate analysis, carcinoembryonic antigen (>5.0 ng/mL) (P=0.0007), maximum standardized uptake (>3.5) (P<0.0001), clinical T factor (T1c) (P<0.0001), and consolidation tumor ratio (>0.85) (P<0.0001) were significant predictors of lymph node metastasis. Multivariate analysis revealed that maximum standardized uptake SUVmax (>3.5) (odds ratio =10.4, P<0.0001) was independently associated with lymph node metastasis. In univariate analysis, carcinoembryonic antigen (>5.0) (P=0.048) was the only predictor of lymph node metastasis among patients of cT1b, while no parameters were identified as significant predictors among patients of cT1c.

Conclusions: SUVmax and CEA are useful preoperative predictors of lymph node metastases in patients with clinical T1 adenocarcinoma, stratified to T1b and T1c, based on the 8th TNM classification.

Keywords: Lymph node metastasis; adenocarcinoma; maximum standardized uptake; fluorodeoxyglucose-positron emission tomography/computed tomography

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Introduction

In recent years, detection of smaller pulmonary nodules, became possible with the development of computed tomography (CT) and the spread of high-resolution (HR) CT as well as low-dose CT examinations.

Some reports have stated that sublobar resection, including segmentectomy or wedge resection, should be performed for small nodules. Clinical studies demonstrated efficacy (1-4). Sublobar resection is more useful, particularly in patients who have many complications, low respiratory function, or advanced aged (5,6). However, higher local recurrence after sublobar resection was observed when a negative surgical margin had been confirmed pathologically (7). The efficacy of sublobar resection has been prospectively evaluated for small nodules (8,9). The appropriate choice is important when considering sublobar resection, based on whether the lymph node is negative for metastasis (10).

Lymph node metastasis can be predicted by CT and ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT); nevertheless, the accuracy is not high. For this reason, many studies have tried to identify predictors for lymph node metastasis.

The proposed predictors of lymph node metastasis have been cancer embryonic antigen (CEA) (11-20), maximum standardized uptake (SUVmax) (19,21-23), the size of tumor (10,11,18,24-26), and solid component of tumor (18,20,22,25,26,33); most of these studies were conducted based on the Tumor Node Metastasis (TNM) classification, 7th edition (27).

The TNM classification was updated to the eighth edition (28) in January 2017, and the new subcategory "the solid component of tumor" was added to the new criteria of the tumor category (T). There remain many unclear features regarding predictors of lymph node metastasis among the patients with T1 adenocarcinoma based on the TNM classification, 8th edition. Therefore, the aim of this study was to identify the preoperative predictors of lymph node metastasis in clinical T1 adenocarcinoma by comparing clinicopathological characteristics between the groups with and without lymph node metastasis.

Methods

Study design, patients, and approval

We performed a retrospective observational single-center study of patients with primary lung adenocarcinoma and conducted at the Sendai Kousei Hospital, Miyagi, Japan. All patients gave written informed consent. From January 2012 to September 2019, we included 515 patients who underwent curative lobectomy or segmentectomy and mediastinal lymph node dissection among clinical T1 adenocarcinoma based on the Union for International Cancer Control (UICC)-TNM staging 8th edition.

The protocols of data collection and analysis were approved by our institutional review board (IRB No. 1-23) at Sendai Kousei Hospital; the requirement for written informed consent was waived because the data were analyzed retrospectively. This article was based on the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement: guidelines for reporting observational studies (29).

The patients were divided into a group with lymph node metastasis (positive group) and a group without lymph node metastasis (negative group). We retrospectively analyzed and compared the following clinicopathological factors between the two groups: tumor markers, maximum standardized uptake value in FDG-PET/CT, and preoperative tumor size.

The exclusion criteria were follows: (I) multiple lesions; (II) induction therapy; (III) preoperative identification of mediastinal lymph node metastases using endobronchial ultrasound-guided transbronchial needLe aspiration (EBUS-TBNA); (IV) mediastinal lymph nodes for which the minor axis was 10 mm or more in size; and (V) pathologically diagnosed lung metastasis from lung cancer (a second primary lung cancer was not excluded).

Radiological measurements and clinical diagnosis

Evaluation of CT findings

All patients underwent preoperative thin-slice contrast-enhanced CT of the 1–2-mm slice 1 month before lobectomy at Sendai Kousei Hospital. We used 320-row-detector (area detector) CT scanners (Aquilion 64, Toshiba Medical Systems, Otawara, Tochigi, Japan) to acquire chest images using the following settings: 1.0-mm section width with 1.0-mm reconstruction interval, volume scan, tube voltage 120 kVp, 100 mA, 512×512-pixel resolution, 0.35-second/lot scanning time, a high-spatial reconstruction algorithm with a 35-cm field of view.

The mediastinal window had a window level 10 Hounsfield units (HU) and window width 300 HU. The lung window had a window level –700 HU and window width –1,500 HU.

The total tumor diameter (TTD) expressed the whole

tumor diameter including the GGN lesion, and the consolidation diameter (CD) was solid component diameter of the tumor. The consolidation tumor ratio (CTR) was defined as the ratio of the CD to TTD.

At least two surgeons evaluated radiation tumor findings using thin section CT and recorded clinical TNM stage according to the 8th edition criteria of the TNM classification. All tumor findings were reevaluated according to the TNM 8th edition following the scoring according to the TNM 7th edition.

Evaluation of ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) findings

The data of FDG-PET/CT were collected in 470 (91.2%) patients, and FDG-PET/CT scanning was performed according to the procedures of our hospital (Sendai Kousei Hospital, Miyagi, Japan). Patients stopped consuming sugar within at least 4 hours before a scan. Blood sugar levels were measured before starting the examination, and the scan was postponed when it was 200 mg/dL or more. First, patients were intravenously administered 5.735 MBq/kg ^{18}F-FDG, and then rested for 90 minutes. We identified the position of the lesion using PET. Using a low-dose of thickness of 3.75 mm from the base of the skull of each patient to the femoral center, the decay correction of the non-revision CT image was subsequently obtained using a standard protocol. These PET scanning/images were acquired at bed positions of 7–9 in a Discovery ST elite PET/CT scanner (GE Medical Systems, Waukesha, WI, USA). The raw PET data were rebuilt using a section image of thickness 3.27 mm to evaluate volume changes in the 3D-ordered subsets expectation maximization (OSEM) algorithm that incorporated CT-based decay correction (2 iteration/28 subsets).

We used a workstation (Advantage Workstation 4.2) for indication and image analysis and calculated SUVmax of the primary tumor. All PET/CT images were interpreted by an experienced nuclear radiation engineer. The definitions of nodal station were based on the International Association of the Study of Lung Cancer (IASLC) lymph node map (30) and pathological diagnoses were based on the 2011 IASLC classification (31).

Preoperative diagnosis

In this study, in most cases, bronchoscopy was performed to confirm a diagnosis preoperatively. When a diagnosis was not confirmed by bronchoscopy, CT-guided needle lung biopsy was performed in several cases.

In cases that did not acquire a diagnosis after these examinations, for example, in particular, a peripheral small nodule, if the patient agreed to undergo lung resection after we provided sufficient explanation for its requirement, lung resection was planned.

Surgical procedures

Surgery was performed under general anesthesia and single-lung ventilation in the lateral position. Thoracotomy was performed by posterolateral incision, and video-assisted thoracic surgery (VATS) was performed using three port incisions. For all patients, segmentectomy or lobectomy was performed. When a diagnosis was not obtained, we confirmed the diagnosis by needle lung (tumor) biopsy or wedge lung (tumor) resection. If it was primary lung cancer, we chose lobectomy. When the invasive diameter of a tumor was 5 mm or less, sublobar resection was performed in patients who could not tolerate lobectomy.

The pulmonary vein, pulmonary artery, bronchus, and lung parenchyma were divided using a stapler (Endo GIATM, Covidien, USA, or ECHELON FLEX TM, ETHICON, USA) or an energy device (HARMONIC TM, ETHICON, US, or THUNDERBEAT TM, OLYMPUS, Japan) or ligated, depending on the situation. Mediastinal lymph node dissection was performed in most patients, but was not performed in patients 80 years or older and in those with severe cardiovascular complications. Lymph node dissection was performed using a protocol modified to the recommendation of European Society of Thoracic Surgeons (ESTS) (32). In our hospital, we perform mediastinal lymph node dissection (ND2a-1). When we perform lung resection for patients suspected having mediastinal lymph node metastasis, we dissect the upper, middle, and lower mediastinal lymph nodes (ND2a-2) (*Table 1*).

Data collection

In our institution, laboratory tests, CT, PET/CT, and magnetic resonance imaging (MRI) are performed preoperatively. The following data were collected: age, gender, Brinkman index, clinical stage, CEA, cytokeratin 19 fragments (CYFRA), TTD, CD, CTR, SUVmax, type of surgical approach, surgical procedure, tumor location, extent of lymph node dissection, histological subtype, and

Table 1 The extent of lymph node dissection in our hospital

Tumor location	ND2a-1	ND2a-2
Right upper lobe	2R, 4R, 10, 11s, 12u, 13, 14	2R, 4R, 7, 10, 11s, 12u, 13, 14
Right middle lobe	2R, 4R, 7, 10, 11s, 11i, 12m, 13, 14	2R, 4R, 7, 10, 11s, 11i, 12m, 13, 14
Right lower lobe	7, 8, 9, 10, 11s, 11i, 12l, 13, 14	2R, 4R, 7, 8, 9, 10, 11s, 11i, 12l, 13, 14
Left upper lobe (upper division)	4L, 5, 6, 10, 11, 12u, 13, 14	4L, 5, 6, 7, 10, 11, 12u, 13, 14
Left upper lobe (lingular division)	4L, 5, 6, 7, 10, 11, 12u, 13, 14	4L, 5, 6, 7, 10, 11, 12u, 13, 14
Left lower lobe	7, 8, 9, 10, 11, 12l, 13, 14	4L, 5, 6, 7, 8, 9, 10, 11, 12l, 13, 14

ND, node dissection.

pathological involvement.

Statistical analysis

The Student's *t*-test, and Mann-Whitney U test were used to compare continuous variables and the Chi-square test was used to compare categorical variables between the groups.

Receiver operating characteristic (ROC) curves to predict lymph node metastasis were used to determine the cutoff value that yielded optimal sensitivity and specificity using the Youden index for each variable.

The method using the Youden index was used to define the maximum potential effective cut-off value in the ROC curve and calculated (sensitivity + specificity − 1; Youden index), and the cut-point that acquired the maximum value was defined as the optimal cut-off value.

Univariate and multivariate analyses were performed to identify the predictors for lymph node involvement using logistic regression. All analyses were performed using JMP® 13 software (SAS Institute Inc., Cary, NC, USA). P values <0.05 were considered statistically significant.

Results

The mean age was 66 years (range, 40–86 years), and the details of all patients are shown in *Table 2*. The median value of CEA and SUVmax was significantly higher in the lymph node metastasis positive group (3.8 and 6.2) than in the negative group (2.3 and 2.1) (P=0.023 and P<0.0001). The clinical T factor showed one patient with Tis, two patients with T1a, 24 patients with T1b, and 34 patients with T1c in the lymph node metastasis positive group. There were 164 patients with Tis, 30 patients with T1mi, 91 patients with T1a, 97 patients with T1b, and 72 patients with T1c in the lymph node metastasis negative group. The median CD and CTR were significantly high in lymph node metastasis positive group compared to the negative group (P<0.0001 and <0.0001, respectively).

Regarding intraoperative characteristics, lobectomy was performed in 508 patients, and segmentectomy in eight patients, while there were 507 cases of VATS and eight cases of open chest surgery. Lymph node metastasis was present in 61 patients, including 26 (43%) with pN1 and 35 (57%) with pN2. The optimal cut-off values of age, Brinkman index, SUVmax, and CTR, defined by the Youden index to predict lymph node metastasis, were 72 [accuracy =0.33; sensitivity =0.89; specificity =0.26; area under the curve (AUC) =0.56; P=0.17], 390 (accuracy =0.58; sensitivity =0.54; specificity =0.59; AUC =0.56; P=0.21), 3.5 (accuracy =0.72; sensitivity =0.88; specificity =0.69; AUC =0.83; P<0.0001), and 0.85 (accuracy =0.58; sensitivity =0.85, specificity =0.54; AUC =0.72; P<0.0001) by the ROC curve.

Univariate and multivariate analyses were performed to identify the predictors of lymph node metastasis between the two groups (*Table 3*). According to univariate analysis, CEA (>5.0 ng/mL) (P=0.0007), SUVmax (>3.5) (P<0.0001), clinical T factor (T1c) (P<0.0001), and CTR (>0.85) (P<0.0001) were significant predictors of lymph node metastasis. Multivariate analysis revealed SUVmax (>3.5) as independently associated with lymph node metastasis [odds ratio (OR) =10.4, P<0.0001].

Subgroup analysis

Among the patients with clinical T1mi, there were no patients with lymph node metastasis. Among the patients with clinical Tis and T1a, there were one and two patients with lymph node metastasis, respectively; however, the data

Table 2 Clinicopathological characteristics of patients with positive and negative for lymph node metastasis

Variables	LN+ (N=61)	LN– (N=454)	P value
Age, mean ± SD (years)	64±8	66±8	0.167[a]
Sex (male/female)	38/23	240/214	0.165[b]
Brinkman index, median (IQR)	450 (0–830)	100 (0–770)	0.205[c]
CEA (ng/mL), median (IQR)	3.8 (1.9–6.1)	2.3 (1.5–3.8)	0.023[c]
CYFRA (ng/mL), median (IQR)	1.8 (1.4–2.4)	1.7 (1.3–2.4)	0.855[c]
SUVmax	6.2 (4.9–8.7)	2.1 (1.2–4.3)	<0.0001[c]
Tumor location			
RU/RM/RL/LU/LL	22/4/10/18/7	164/30/91/97/72	0.621[b]
Clinical T factor			
Tis/T1mi/T1a/T1b /T1c	1/0/2/24/34	34/37/83/182/118	<0.0001[b]
TTD (mm), median (IQR)	22 [19–27]	21 [16–26]	0.139[c]
CD (mm), median (IQR)	21 [17–25]	14 [9–21]	<0.0001[c]
CTR, median (IQR)	1.0 (1.0–1.0)	0.8 (0.4–1.0)	<0.0001[c]
Lob/Seg	61/0	447/7	0.329[b]
VATS/Open	59/2	448/6	0.246[b]
Node dissection			
2a-1/2a-2	59/2	448/6	0.246[b]
N0/1/2	0/26/35	454/0/0	<0.0001[b]

Values are presented as mean ± SD (standard deviation) or median (IQR: interquartile range) or n. [a], compared by the Student *t*-test; [b], compared by the chi-square test; [c], compared by the Mann-Whitney U test. CEA, carcinoembryonic antigen; CYFRA, cytokeratin 19 fragments; SUVmax, maximum standardized uptake value; RU, right upper lobe; RM, right middle lobe; RL, right lower lobe; LU, left upper lobe; LL, left lower lobe; TTD, total tumor diameter; CD, consolidation diameter; CTR, consolidation tumor ratio; Lob, lobectomy; Seg, segmentectomy; VATS, Video-assisted thoracoscopic surgery; N, nodal involvement

could not be analyzed statistically. Among patients of cT1b, according to univariate analysis, CEA (>5.0) (P=0.048) was a significant predictor of lymph node metastasis. Among patients with cT1c, univariate analysis revealed no predictors of lymph node metastasis (*Table 4*).

Discussion

We found that SUVmax of a tumor (>3.5) in FDG-PET/CT predicted lymph node metastasis in clinical T1 lung adenocarcinoma. The value of CEA predicted lymph node metastasis in the subgroup analysis in clinical T1b. This study was a valuable report because there have been few reports regarding the predictors of lymph node metastasis particularly based on the TNM classification 8th edition and there have been few analyses of groups stratified as T1b or T1c.

Uptake of FDG correlated with the proliferative activity of tumor that independently became a prognostic factor for patients with lung cancer (33,34). We believe we can identify lymph node metastasis by CT and PET/CT. However, the sensitivity for node-positivity on CT is 50–80%, and the specificity is 50–90% (35,36). Authors also reported that 10 mm or less in the minor axis of lymph nodes indicated metastasis-positivity on CT. When accumulation of FDG in the lymph nodes was beyond 2.5, lymph node metastases were considered positive; nevertheless, lymph node metastases were often pathologically negative in such cases.

Sensitivity of clinical N using the PET was 60–90%, and the specificity was 70–100% (35,36). In another study, the uptake of FDG was shown to be a potential predictor of nodal metastasis in small primary NSCLC (37). Maeda

Table 3 Univariate and multivariate analyses of predictors after the specification of cutoff values associated with lymph node metastasis in patients with clinical T1 lung adenocarcinoma

Variable	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (<72)	1.96 (0.99–3.89)	0.053	–	–
Sex (male)	1.47 (0.85–2.55)	0.167	–	–
Brinkman index (>390)	1.61 (0.94–2.75)	0.082	–	–
CEA (>5.0 ng/mL)	2.92 (1.57–5.40)	0.0007	1.65 (0.81–3.37)	0.169
SUVmax (>3.5)	15.8 (6.98–35.9)	<0.0001	10.4 (4.30–25.1)	<0.0001
Clinical T factor (T1c)	3.59 (2.07–6.20)	<0.0001	1.61 (0.84–3.11)	0.151
CTR (>0.85)	4.87 (2.52–9.41)	<0.0001	1.63 (0.71–3.75)	0.245

OR, odds ratio; CI, confidence interval; CEA, carcinoembryonic antigen; SUVmax, maximum standardized uptake value; CTR, consolidation tumor ratio.

Table 4 Univariate and multivariate analyses of predictors after the specification of cutoff values associated with lymph node metastasis among clinical T1b and T1c non-small cell lung cancer

Variable	Univariate	
	OR (95% CI)	P value
T1b		
Age (<72)	1.32 (0.47–3.74)	0.598
Sex (male)	1.99 (0.79–5.03)	0.145
Brinkman index (>390)	1.35 (0.58–3.18)	0.489
CEA (>5.0 ng/mL)	2.86 (1.01–8.08)	0.048
SUVmax (>3.5)	1.77 (0.74–4.27)	0.199
CTR (>0.85)	2.18 (0.86–5.50)	0.100
T1c		
Age (<72)	2.39 (0.92–6.25)	0.075
Sex (male)	1.48 (0.68–3.20)	0.322
Brinkman index (>390)	1.01 (0.46–2.21)	0.987
CEA (>5.0 ng/mL)	2.14 (0.93–4.92)	0.075
SUVmax (>3.5)	1.52 (0.64–3.61)	0.340
CTR (>0.85)	2.37 (0.66–8.45)	0.184

OR, odds ratio; CI, confidence interval; CEA, carcinoembryonic antigen; SUVmax, maximum standardized uptake value; CTR, consolidation tumor ratio.

et al. (21) reported that lymph node metastasis was not identified among patients with stage IA NSCLC when the value of SUVmax was 2 or less. In the present study, we also found no patients with lymph node metastasis when the value of SUVmax was 2 or less. Many studies found that high preoperative values of CEA were poor prognostic factors in stage I NSCLC (38).

CEA has been shown to predict lymph node metastasis (11-20). In the present study, among patients with clinical T1b, high CEA levels predicted lymph node metastasis on subgroup analysis. Some studies reported that there was no lymph node metastasis among the patients with GGNs (25,39,40). In fact, in stage IA NSCLC, lymph node metastasis was about 7–26% (19,41). Among the sub-centimeter NSCLC, Casiraghi *et al.* (42) reported no patients with lymph node metastasis, whereas Watanabe *et al.* (43) and Veronesi *et al.* (44) reported patients with lymph node metastasis. In the present study, there were no lymph node metastases in sub-centimeter tumors; however, small tumor size alone cannot be a reason for omitting lymph node dissection.

Incomplete dissection or sampling of lymph nodes could result in local recurrence. Many surgeons advocate for routine systemic nodal dissection so as to secure complete local control of an NSCLC, even if a patient's disease is classified as clinical stage IA; this is because even small NSCLC lesions have considerable potential for lymph node metastasis (1).

Allen *et al.* (45) reported that mediastinal lymph node dissection or sampling causes a high rate of complications (about 38%) and omitting node dissection reduces complications and invasiveness and improves postoperative recovery. Systemic lymph node dissection could be avoided in selected patients if there appears to be no lymph node

metastasis; that is, if we could identify predictors associated with pathological N0. If the minor axis of the mediastinal lymph node is less than 10 mm, it has been suggested that this predicts negative lymph node metastasis. Tsutani *et al.* (22) proposed "N0 criteria" using CT and PET/CT among the stage 1A adenocarcinoma, with a solid component diameter of <0.8 cm or SUVmax of <1.5 for selecting candidates for sublobar resection. Nevertheless, the definitive or universal criteria for prediction of lymph node metastasis have yet not been established.

Many studies have attempted to predict those patients who could avoid systemic lymph node dissection (43,46). We similarly intended to identify predictors of lymph node metastasis. In patients with adenocarcinoma, predictors of lymph node metastasis other than SUVmax in PET/CT were suggested as the following: CEA (12,14,19), solid component (22), GGO status (14,19), histological subtype (19). Our data suggest that in patients in whom accumulation of FDG in lung nodules is high, there are numerous lymph node metastases.

We need to mention some limitations to the present study. First, this was not a randomized controlled study. This study was a retrospective observational study in a single institution; therefore, the evidence level fell moderately. Second, measurements of tumors varied to some extent for each doctor. It appeared to improve when at least two or more doctors perform the measurement. Third, during the early period in this study, there were a few cases in which PET/CT was not performed for small tumors (mainly those <1 cm), which might have affected the results, whereas among patients for whom PET/CT was performed, SUVmax might depend on the modality.

In conclusion, our findings suggest that SUVmax and CEA would be useful as preoperative predictors of lymph node metastasis in patients of clinical T1 adenocarcinoma, with clinical T1b stratified, based on the TNM classification 8th edition. Further accumulation of data is needed to identify the predictors of lymph node metastasis among the patients with clinical T1 adenocarcinoma.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd.2020.03.74). 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. This study was approved by the Institutional Review Board of Sendai Kousei Hospital (IRB No. 1-23).

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