General Thoracic and Cardiovascular Surgery (2019) 67:544–550
https://doi.org/10.1007/s11748-018-01059-2

ORIGINAL ARTICLE

Outcomes and predictive factors for pathological node-positive in radiographically pure-solid, small-sized lung adenocarcinoma

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Received: 27 August 2018 / Accepted: 28 December 2018 / Published online: 9 January 2019

Abstract

Objectives The indication of limited resection for radiographically pure-solid, small-sized lung adenocarcinoma is controversial. This study aimed to reveal the long-term outcome of standard surgical treatment and determine the predictive factors for pathological lymph node metastasis in optimal candidates undergoing limited surgical resection for pure-solid, small-sized lung adenocarcinoma.

Methods The medical records of 107 consecutive patients were retrospectively reviewed at our hospital between December 2002 and December 2013. Inclusion criteria were histopathological diagnosis of lung adenocarcinoma, radiographically pure-solid tumor, ≤ 2 cm tumor size measured using thin-section computed tomography, clinical N0M0, patients who underwent lobectomy with systematic or lobe-specific lymph node dissection, and R0 resection. Overall and disease-free survival curves were calculated using the Kaplan–Meier method. Clinicopathological factors predicting pathological node-positive metastasis were identified by univariate and multivariate analysis.

Results The 5-year overall and disease-free survival rates were 91.4% and 87.3%, respectively. Multivariate analysis demonstrated maximum standardized uptake value > 5 as the independent predictor of pathological node-positive metastasis (odds ratio 3.81; 95% confidence interval 1.25–12.3; $p = 0.02$). In all patients, the pathological node-positive rate was 16.7%; in patients who had a maximum standardized uptake value of ≤ 5, the rate was 7.9%.

Conclusion The long-term outcome of standard surgical treatment was favorable. Maximum standardized uptake value was a significant predictor of pathological node-positive metastasis; however, diagnostic accuracy was not favorable. Therefore, the selection of optimal candidates is difficult, and limited surgical resection may not be applicable in pure-solid, small-sized lung adenocarcinoma.

Keywords Pure-solid tumor, small-sized lung adenocarcinoma · Positron emission tomography · Maximum standardized uptake value · Limited resection

Introduction

The introduction of computed tomography (CT) for lung cancer screening has enabled the detection of small lung nodules and early-stage lung cancer, thereby, improving patient survival [1]. Limited surgical resection for small-sized lung cancer has gradually increased. In Japan, during 2015, limited surgical resection accounted for approximately 24.7% of all primary lung cancer resections, according to a study by The Japanese Association for Thoracic Surgery [2]. In 2017, the eighth edition of the tumor node metastasis (TNM) classification of lung cancer was revised by the International Association for the Study of Lung Cancer (IASLC). According to the eighth edition of the TNM classification, the size of the solid component of the tumor should be used to assign a clinical T category [3]. Radiographically pure ground-glass opacity or part-solid lung cancer is known to have good prognosis and pathological minimal invasiveness [4–6]. Thus, radiographically small-sized pure ground-glass

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11748-018-01059-2) contains supplementary material, which is available to authorized users.

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opacity or part-solid tumors are considered to be good indicators for limited surgical resection; recently, several authors have reported favorable treatment outcomes resection [7–9]. However, radiographically pure-solid lung cancers are considered to be highly malignant in nature, and postoperative nodal involvement is observed in approximately 16–26% of cases even in cases of radiographically small-sized (< 2 cm) lung cancer [10–12]. Therefore, the indications of limited surgical resection for small-sized solid lung cancer remain controversial. Recent studies on segmentectomy for small-sized peripheral lung cancer reported that segmentectomy with lymph node exploration should be considered as an acceptable alternative to surgical treatment; however, patient selection should be strict and intraoperative pathological lymph node examination is needed to confirm pN0 disease [13–15]. Prediction of the pathologic node negative (pN−) status is essential in determining the indication for limited surgical resection.

This study aimed to reveal the long-term outcomes of standard surgical treatment as well as determine the predictive factors for pathological node-positive (pN+) cancers and optimal candidates undergoing limited surgical resection for radiographically pure-solid, small-sized lung adenocarcinoma.

Patients and methods

This study protocol was approved by the local Institutional Review Board and Ethics committee at our hospital. The medical records of 1883 consecutive patients with non-small-cell lung carcinoma (NSCLC) who underwent surgical resection at our hospital between December 2002 and December 2013 were retrospectively reviewed. Inclusion criteria for our study were (1) histopathological diagnosis of lung adenocarcinoma, (2) radiographically pure-solid tumor measuring ≤ 2 cm in size on thin-section CT, (3) cN0M0, (4) patients who underwent lobectomy with systematic or lobe-specific lymph node dissection, and (5) patients who underwent curative R0 resection. Exclusion criteria were synchronous or metachronous multiple lung cancers and patients who underwent any treatment before surgery. We identified 107 patients who met the inclusion and exclusion criteria.

High-resolution, thin-section CT (HRCT) and F-18-fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT together with evaluation of the maximum standardized uptake value (SUV_{max}) were performed for all patients. Clinical lymph node positivity on CT and PET-CT was defined as at least 1 lymph node with a short axis measuring more than 1 cm and/or focally increasing FDG uptake higher than the normal background activity. Radiologists, thoracic surgeons, and respiratory physicians evaluated radiological findings and discussed lymph node positivity. If needed, pathological diagnosis was performed by EBUS-TBNA (Endobronchial ultrasound transbronchial needle aspiration) or mediastinoscopy. The SUV_{max} was calculated for the primary tumor only.

The clinical and pathological stage was determined according to the eighth edition of the TNM classification.

Statistical analysis

The following data were recorded for each patient: age, sex, smoking history (never- or ever-smokers), serum carcinoembryonic antigen (CEA) level (normal, ≤ 5 ng/mL or increased, > 5 ng/mL), solid tumor size (mm), and SUV_{max}.

Overall survival (OS) was defined as the time between surgery and death from any cause or last follow-up. Disease-free survival (DFS) was defined as the time between surgery and relapse or death from any cause or last follow-up. OS and DFS curves were calculated according to the Kaplan–Meier method. To reveal the characteristics of pure-solid, small-sized lung carcinoma, OS and DFS were compared with radiographically part-solid small adenocarcinoma (tumor size was ≤ 2 cm). All patients with radiographically part-solid small adenocarcinoma also underwent lobectomy with systematic or lobe-specific lymph node dissection. The association between variables was analyzed using the χ^2 test and Fisher's exact test for categorical variables and Student's *t* test for continuous categorical variables. Receiver operating characteristic (ROC) curve of SUV_{max} for predicting pathological lymph node metastasis was generated to determine cut-off values that yielded optimal sensitivity and specificity. Multiple logistic regression analyses were performed to determine the independent variables for pathological lymph node metastasis prediction. A p value of < 0.05 was considered statistically significant. All statistical calculations were performed using JMP for Windows (version 9.0; SAS Inc., Cary, NC, USA).

Results

Among 1883 patients with NSCLC who underwent surgical resection at our hospital between December 2002 and December 2013, 107 patients met the inclusion and exclusion criteria.

Median follow-up time was 72 months (range 50–153 months). The 5-year OS was 91.4% in pure-solid tumors and 95.9% in part-solid tumors ($p = 0.26$), and the 5-year DFS was 87.3% in pure-solid tumors and 94.5% in part-solid tumors ($p < 0.01$) (Fig. 1a, b). The clinicopathological characteristics of the patients with pure-solid, small-sized adenocarcinoma and part-solid small-sized adenocarcinoma are summarized in the Supplementary table.

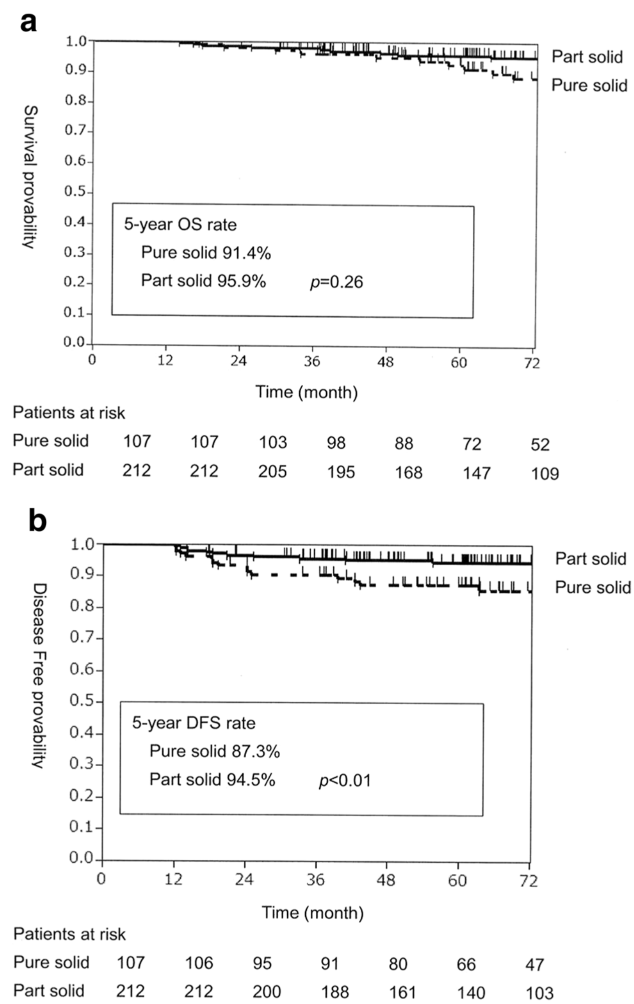

Fig. 1 **a** Kaplan–Meier overall survival (OS) curve of cT1a or T1bN0M0 adenocarcinoma according to the eighth edition of the TNM classification of lung cancer. The 5-year OS rate was 91.4% in pure-solid tumors and 95.9% in part-solid tumors ($p=0.26$). **b** Kaplan–Meier disease-free survival (DFS) curve of cT1a or T1bN0M0 adenocarcinoma according to the eighth edition of the TNM classification of lung cancer. The 5-year DFS rate was 87.3% in pure-solid tumors and 94.5% in part-solid tumors ($p<0.01$)

The overall clinicopathological characteristics of the patients are summarized in Table 1. Among 107 patients, 18 (16%) patients had pathological lymph node metastasis (nine were mediastinal lymph node metastasis, six were hilar lymph node metastasis, five were intrapulmonary lymph node metastasis, overlapping). The median SUV_{max} was 3.9 in pN− patients and 6.1 in pN+ patients. Univariate analysis demonstrated that only SUV_{max} was significantly associated with pN+ ($p=0.01$).

The ROC curve identified the optimal SUV_{max} cut-off value of 5 [area under the curve (AUC), 0.699] for predicting pN+ (Fig. 2). The sensitivity, specificity, and accuracy of SUV_{max} were 72.2, 65.1, and 66.3%, respectively. Multivariate analysis demonstrated that a SUV_{max} value of > 5

Table 1 Comparison of patient characteristics between pathological node-negative and node-positive patients

Variable	PN− ($n=89$)	PN+ ($n=18$)	*P* value
Age	63.6 ± 9.4	60.1 ± 10.6	0.16
Sex			0.13
Male	47 (52.8)	13 (72.2)	
Female	42 (47.2)	5 (27.8)	
Smoking status			0.30
Never-smokers	31 (34.8)	4 (22.2)	
Ever-smokers	58 (65.2)	14 (77.8)	
CEA (ng/mL)			0.17
≤ 5	76 (85.3)	13 (72.2)	
> 5	13 (14.6)	5 (27.7)	
Clinical T status			0.66
T1a (solid tumor size ≤ 1 cm)	3 (3.7)	1 (5.6)	
T1b (solid tumor size 1 <, ≥ 2 cm)	86 (96.3)	17 (94.4)	
SUV_{max}	3.9 ± 3.1	6.1 ± 3.6	0.01
Pathological N status			
N1	–	9 (8)	
N2	–	9 (8)	

Values are mean ± SD or *n* (%)

CEA carcinoembryonic antigen, *pN−* pathological node-negative cancer, *pN+* pathological node-positive cancer, SUV_{max} maximum standardized uptake value

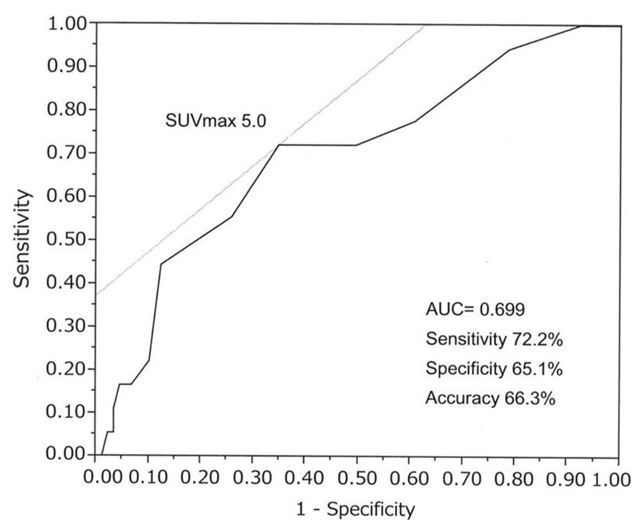

Fig. 2 Receiver operating characteristic (ROC) area under the curve (AUC) for detecting pathological lymph node metastasis for the maximum standardized uptake value (SUV_{max}). The ROC curve identified the optimal SUV_{max} cut-off value of 5 (AUC, 0.699) for predicting pN+ and the sensitivity, specificity, and accuracy of SUV_{max} were 72.2, 65.1, and 66.3%, respectively

Table 2 Univariate and multivariate analysis of the predictive factors for pathological lymph node metastasis

Variable	Univariate OR (95% CI)	*p* value	Multivariate OR (95% CI)	*p* value
Age				
≤ 69 vs > 70	0.65 (0.19–2.17)	0.48	0.49 (0.12–1.64)	0.26
Sex				
Male vs female	0.43 (0.14–1.31)	0.13	0.38 (0.05–1.89)	0.25
Smoking status				
Never-smokers vs Ever-smokers	1.87 (0.56–6.17)	0.30	0.80 (0.11–5.27)	0.81
CEA				
≤ 5 vs > 5	0.44 (0.13–1.45)	0.17	1.44 (0.34–5.54)	0.60
Solid tumor size (mm)	0.98 (0.83–1.16)	0.82	0.97 (0.80–1.18)	0.77
SUV_{max}				
≤ 5 vs > 5	3.58 (1.26–10.18)	0.01	3.81 (1.25–12.3)	0.02

CEA carcinoembryonic antigen, *CI* confidence index, *OR* odds ratio, SUV_{max} maximum standardized uptake value

was the independent predictor of pN+ (odds ratio, 3.81; 95% confidence interval, 1.25–12.3; $p = 0.02$; Table 2). In patients who had SUV_{max} value of > 5, the rate of pN+ was 30.3% (13 patients), while that in those who had SUV_{max} value of ≤ 5 was 7.9% (five patients). The details of patients who had pN+ status are presented in Table 3. Three patients with SUV_{max} value of ≤ 5 had N2 disease.

Discussion

This study investigated the long-term outcomes and predictive factors of pathological lymph node metastasis in pure-solid, small-sized lung adenocarcinoma, in which lobectomy was performed with systematic or lobe-specific lymph node dissection. In this study, the 5-year OS and DFS rates of standard surgical treatment (lobectomy with lymph node dissection) for radiographically pure-solid, small-sized lung adenocarcinoma were 91.4% and 87.3%, respectively. In recent studies on pure-solid NSCLCs measuring ≤ 2 cm in size, the 5-year OS and DFS rates were reportedly 87% and 83% (including limited resection) [10] and 85% and 80% (only lobectomy but including lymphadenectomy extent was sampling only), respectively [16]. The long-term outcome in this study was favorable and satisfactory compared to recent studies. Moreover, in patients at a low risk of surgical complications, pulmonary lobectomy with systematic lymph node dissection can safely be performed, and the 30-day mortality rate is 0.43% in Japan [2].

Many retrospective studies have compared survival after lobectomy versus limited resection (segmentectomy and wedge resection) for NSCLC. Some studies reported that lobectomy confers a significant survival advantage than limited selection [17, 18], while others reported that lobectomy and limited resection may lead to the same survival outcome [19, 20]. In radiographically pure-solid, small-sized NSCLC patients (T1aN0M0 as per the seventh edition of TNM classification), a retrospective propensity score-matched study was performed, which demonstrated a similar oncological outcome after lobectomy and segmentectomy (the 5-year OS and DFS rates were 85% and 80%, respectively, in lobectomy group versus 84% and 77% in segmentectomy group, respectively) [16]. However, in the segmentectomy group, the N1 nodes were intraoperatively assessed, and if positive, the surgical procedure was converted to lobectomy, and these patients were excluded from the study. This method may have caused a selection bias. The final results of the phase III trial conducted by the Japan Clinical Oncology Group (JCOG) 0802 [21] and Cancer and Leukemia Group B (CALGB) 140503 [22] for investigating the efficacy of limited surgical resection for small-sized lung carcinoma will provide a conclusive outcome. However, patients with part-solid and pure-solid lung cancers were included in the JCOG 0802 and CALGB 140503 trials; in our study, pure-solid adenocarcinoma demonstrated a worse 5-year DFS rate than part-solid adenocarcinoma, although the tumor size was ≤ 2 cm. Therefore, patients with part-solid and pure-solid adenocarcinoma should be separately considered.

The prediction of pN− is important in determining the indications for limited surgical resection. A previous study reported that the pathological node-negative criteria in stage IA lung adenocarcinoma (according to the seventh edition of the TNM classification) were a solid tumor size of < 0.8 cm or SUV_{max} of < 1.5 [22]. In this study, the minimum SUV_{max} in patients with pN+ was 1.6; thus, SUV_{max} of < 1.5 may be a meaningful cut-off value. Characteristics of recent retrospective cohort studies on the relationship between SUV_{max} and pN+ are presented in Table 4. In various populations, different SUV_{max} threshold values were reported. Similar to our study, some studies reported that a SUV_{max} value

Table 3 Details of the patients who had pathologic lymph node positive in this study

No	Primary site	Solid tumor size (mm)	SUV_{max}	Station of lymph node
1	Right lower lobe (S10)	15	1.6	#11i
2	Right lower lobe (S9)	15	2.2	#7
3	Right lower lobe (S6)	19	2.2	#7
4	Right lower lobe (S6)	13	2.9	#11 s
5	Left upper lobe (S1 + 2)	14	3.9	#4L
6	Left upper lobe (S3)	18	5.4	#12u, #14
7	Left upper lobe (S3)	16	5.7	#5
8	Right upper lobe (S3)	18	5.8	#4R, #10
9	Right upper lobe (S2)	19	6.0	#13
10	Right upper lobe (S3)	18	6.7	#4R
11	Left lower lobe (S10)	19	7.1	#12 1
12	Right upper lobe (S3)	18	7.4	#4R, #11 s, #12u
13	Left upper lobe (S1 + 2)	12	7.2	#12u
14	Right upper lobe (S3)	14	7.3	#4R
15	Right upper lobe (S1)	18	8.7	#4R
16	Right lower lobe (S10)	13	10.3	#11i
17	Left upper lobe (S4)	19	11.3	#11
18	Left upper lobe (S3)	10	15	#11

SUV_{max} maximum standardized uptake value

of > 5 was a predictive factor of pN+ [11, 23, 24]. However, in those studies, patients with radiographically part-solid nodules who were expected to have a better prognosis than those with pure-solid nodules [23, 24] or patients with only radiographically pure-solid nodule but without adenocarcinoma, squamous cell carcinoma, or other histological-type carcinomas were included [11]. Tumor vascularity and negative glucose metabolism correlated in adenocarcinoma, but not in squamous cell carcinoma, and SUV_{max} of the primary tumor was a prognostic factor for patients with adenocarcinoma, but not with squamous cell carcinoma of the lung [25, 26]. A difference in the histology of the tumor was influenced in SUV_{max}. Therefore, this study may help decide whether or not limited surgical resection should be applied for small-sized but radiographically pure-solid adenocarcinoma, depending on the extent of tumor invasiveness. This study revealed that SUV_{max} value of > 5 was a significant predictor of pN+; however, there were five patients (7.9%) with pN+ who had SUV_{max} values of ≤ 5; in these patients, limited surgical resection may lead to a high locoregional recurrence risk and may lease to worse prognosis. Moreover, some studies were conducted on the analysis of subsegmental and segmental lymph node metastasis and intrapulmonary metastasis in patients who underwent resection for NSCLC. A retrospective analysis involving 124 patients with pN1 NSCLC reported that 57% of pN1 patients had metastasis at lymph node levels 13 and 14, and i n 27% of pN1 patients, lymph node levels 13 and 14 were the only involved stations [27]. Additionally, the rate of non-primary tumor-bearing segmental lymph node metastasis was 3% in patients with adenocarcinoma, in which the tumor size was ≤ 2 cm [28] and 1% in patients with stage IA NSCLC (as per the seventh edition of TNM classification) [29]. For the estimation of segmental and subsegmental lymph node metastasis, intraoperative evaluation of the lobar lymph nodes alone is insufficient.

Table 4 Characteristics of studies on the association between SUV_{max} and pathological lymph node metastasis

Study	Patients	Result (threshold value of SUV_{max})
Hattori et al. [11]	Clinical N0M0, NCSLC Pure-solid, Tumor size ≤ 2 cm *n* = 94	> 5
Ye et al. [23]	Clinical N0M0, Ad Tumor size ≤ 3 cm *n* = 219	> 5
Moon et al. [24]	Clinical N0M0, Ad *n* = 350	> 5
Okada et al. [30]	Clinical N0M0, Ad Tumor size ≤ 3 cm *n* = 502	> 2.5
This study	Clinical N0M0, Ad Pure-solid, Tumor size ≤ 2 cm *n* = 107	> 5

Ad adenocarcinoma, *NSCLC* non-small-cell lung carcinoma, *SUV_{max}* maximum standardized uptake value

Our study has some limitations. First, we used a retrospective study design. Second, we obtained data from a single institution, and the number of cases was small because the inclusion and exclusion criteria were severe to eliminate deviation from baseline characteristics in this study. Third, for selecting optimal patients for segmentectomy with a curative intent, the cut-off value needs to be determined at the point that will completely predict pN−; however, it is difficult to determine the cut-off value for completely predicting pN− based on a SUV_{max} value. Thus, we analyzed the value of SUV_{max} as a predictive factor for pN+.

Conclusion

The long-term outcome of standard surgical treatment was favorable and satisfactory. Radiographically pure-solid adenocarcinoma had high malignant potential, and the rate of pN+ was 16%, although the tumor size was small (≤ 2 cm). Additionally, a SUV_{max} value of > 5 was a significant predictor of pN+; however, the diagnostic accuracy was not satisfactory. Therefore, the selection of ideal candidates is challenging, and limited surgical resection should not be performed for patients with radiographically pure-solid small lung adenocarcinoma.

Compliance with ethical standards

Conflict of interest The authors, Hiroyuki Kayata, Mitsuhiro Isaka, Yukihiro Terada, Kiyomichi Mizuno, Yoshiyuki Yasuura, Hideaki Kojima, Yasuhisa Ohde, have no conflicts of interest to declare.

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