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ORIGINAL ARTICLE

Predictors of pathological non-invasive lung cancer with pure-solid appearance on computed tomography to identify possible candidates for sublobar resection

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Abstract

Purpose This study aimed to establish favorable predictors for patients with clinical stage IA radiological pure-solid lung cancer to identify possible candidates for sublobar resection.

Methods We examined 275 patients with surgically resected clinical stage IA radiological pure-solid lung cancer. Pathological grade PL0, Ly0, V0, or N0 disease was defined as non-invasive pure-solid lung cancer (NIPS).

Results Nodal involvement was observed in 63 (23 %) patients with clinical stage IA pure-solid lung cancer, while NIPS was identified in 77 (28 %). Multivariate analysis revealed that air bronchogram ($p = 0.0328$), clinical T1a ($p = 0.0041$), and SUV_{max} ($p = 0.0002$) were significant clinical predictors of NIPS. When these clinical predictors were combined and the relevant patients' disease was classified as favorable, the frequency of nodal involvement was only 4 %. Furthermore, the 3-year overall survival (OS) of the patients with "favorable" clinical stage IA pure-solid lung cancer was 100 % despite their operative modes. In contrast, the 3-year OS even for patients with clinical stage IA disease, if they had neither of these clinical predictors, was 74.1 %.

Conclusions Tumor size, the presence of air bronchogram, and the SUV_{max} level were significant favorable predictors of pathological non-invasive status, and patients with these clinical predictors could be candidates for sublobar resection for clinical stage IA pure-solid lung cancers.

Keywords Lung cancer · Sublobar resection · Pure-solid nodule · Survival

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Introduction

The feasibility of sublobar resection for small-sized lung cancers has been the subject of debate for decades [1]. The only randomized prospective trial comparing lobectomy with sublobar resections was conducted by a Lung Cancer Study Group (LCSG) in 1995. As this found a significantly higher recurrence rate for sublobar resections, lobectomy is generally favored for resection of clinical stage IA non-small cell lung cancer (NSCLC) [2]. However, the recent use of computed tomography (CT) for the screening of lung cancer and advances in thin-section CT scans has made it possible to detect smaller and fainter lung nodules [3, 4]. Moreover, several authors have suggested that lung adenocarcinomas seen as a wide area of ground-glass opacity (GGO) on CT scans are likely to be associated with a good prognosis and in most cases their pathologic features are minimally invasive [5–9]. Thus, patients with these tumors are considered as candidates for limited surgical resection, as confirmed by the prospective JCOG 0201 study in Japan [10]. In fact, this cohort has an excellent prognosis with recent 5-year survival rates of more than 90 % [11].

Despite these considerations, controversy still surrounds limited surgery for lung cancer with a solid appearance on thin-section CT scans; namely, invasive lung cancer [4, 12]. The efficacy of sublobar resection has been prospectively evaluated for radiologically part-solid or pure-solid lung cancers 2 cm or less in size, in both Japan [13] and USA [14]. Postoperative nodal involvement is found in approximately 15–20 % of patients, even those with clinical stage IA disease [15], and postoperative nodal involvement is frequently found in patients with radiologically pure-solid lung cancer on thin-section CT scan [4, 12]. Thus, radiologically pure-solid lung cancer is considered to be highly invasive and in a different category of lung cancers with a solid appearance on thin-section CT scans. Several institutional retrospective studies have suggested that survival and recurrence may be identical after lobectomy and sublobar resection [16–19]; however, the efficacy of sublobar resection for pure-solid lung cancers has never been discussed.

We conducted the current retrospective study to establish the favorable predictors of radiologically pure-solid lung cancers and identify possible candidates for limited surgical resection of clinical stage IA pure-solid lung cancers, based on the results of pathological nodal involvement and prognosis.

Materials and methods

Radiological evaluations on thin-section CT scan

Between January 2008 and December 2013, 958 patients underwent pulmonary resection for clinical stage IA lung cancer at our institute. We reviewed the preoperative CT findings of all patients. A thin-section CT scan was performed to evaluate the main tumor for preoperative staging and measure the tumors preoperatively. All tumors were subsequently evaluated with thin-section CT scans using 2 mm collimation to estimate the extent of GGO. The lung was photographed as a "lung window" with a level of −500 to −700 H and a depth of 1000–2000 H. A solid component was defined as an area of increased opacification that completely obscured the underlying vascular markings. GGO was defined as an area of slight, homogeneous increase in density that did not obscure the underlying vascular markings. In the current study, a radiological "pure-solid" tumor was defined as a lung tumor showing only consolidation without GGO on thin-section CT. In other words, the ratio of the maximum diameter of consolidation to the maximum tumor diameter (consolidation/tumor ratio, C/T ratio) was equal to 1.0. Any clinical stage IA lung cancer with a GGO component was excluded from this study. Furthermore, air bronchogram was a radiological finding on thin-section CT scan, which was defined as an air-filled bronchus surrounded by fluid-filled airspaces in the primary tumor. Typical images of pure-solid lung cancers and those with air bronchogram are shown in Fig. 1a, b. Among 958 clinical stage IA lung cancer patients, 275 (28.7 %) with clinical stage IA lung cancer had a "pure-solid" appearance on thin-section CT.

Positron emission tomography (PET)

PET was performed and the maximum standardized uptake value (SUVmax) was recorded for all patients in this study. PET/CT scan was performed at the Yotsuya Medical Cube (Tokyo, Japan) for all patients. The technique used for ^{18}F-FDG PET/CT scanning at the Yotsuya Medical Cube

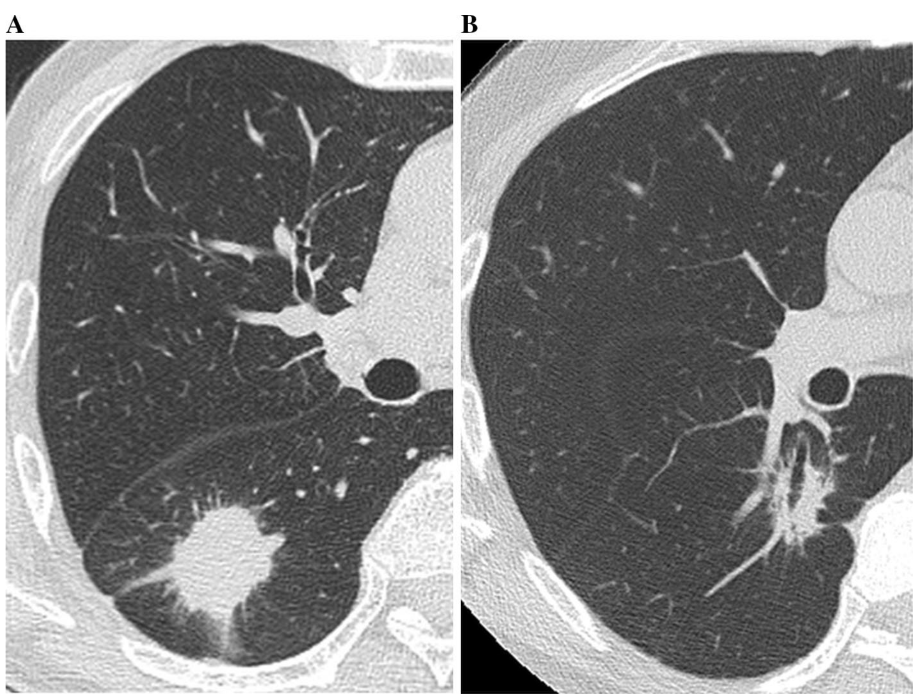


Fig. 1 Typical images of pure-solid lung cancer (**a**) and pure-solid lung cancer with air bronchogram (**b**). An air-filled bronchus was surrounded by a lung tumor showing consolidation without ground-glass opacity on thin-section CT scan

was as follows: patients were asked to fast for at least 6 h before FDG injection to minimize their blood insulin level and normal tissue glucose uptake. The subjects were given an intravenous injection of 18F-fluorodeoxyglucose (^{18}F-FDG), 3.5 MBq/kg, and static emission images were obtained 60 min afterward. Image acquisition was performed using a Discovery ST PET/CT scanner (GE Medical Systems, Waukesha, WI). After CT image acquisition, emission scanning was performed from head to mid-thigh in six bed positions. The acquired PET data were reconstructed to volumetric images with a 2D-OSEM algorithm (2 iterations/15 subsets) incorporating a CT-based attenuation correction. All PET/CT images were interpreted by one or two experienced nuclear medicine radiologists. A workstation (Xeleris; Elegems, Haifa, Israel) was used for image display and analysis, and the SUV_{max} of the primary tumor was obtained.

Operation policy

Until recently, major lung dissection with systemic lymph node dissection was indicated for a pure-solid tumor in our institute, whereas now, intentional segmentectomy is indicated for part-solid or pure-solid lung cancers 2 cm or smaller according to the Japan Clinical Oncology Group (JCOG 0802 [13]). Non-anatomic wedge resection was performed for a few elderly patients or for patients with high cardio-pulmonary risk.

Pathological evaluations

To evaluate pathological pleural invasion (PL), all sections were stained in our institute by the elastic van Gieson method to assess the presence or absence of preservation of the preexisting elastic layer of the visceral pleura. PL was classified according to the UICC TNM [20] criteria. In this study, pathological PL0 status was defined as PL(−), whereas pathological PL1 and PL2 were defined as PL(+). Moreover, pathological lymphatic invasion (Ly) and vessel invasion (V) was evaluated by identifying tumor cells in the lymphatic lumen or vein vessel lumen. To assess Ly and V, all sections were stained by D2-40 to assess the presence or absence of preservation of lymphatic or vessel invasion. The presence of Ly or V was defined as Ly(+) or V(+), whereas their absence was defined as Ly(−) and V(−), respectively.

Statistical analysis

Under a waiver of authorization approved by the institutional review board of Juntendo University School of Medicine, we reviewed the medical records of each patient. Even in patients with clinical stage IA pure-solid lung cancer, which is considered to be highly invasive, lesions without any factors of PL, Ly, V and N may be optimal candidates for sublobar resection. Therefore, to identify candidates for sublobar resection among patients with clinical stage IA pure-solid lung cancer, the patients were classified into two groups; namely, those with non-invasive pure-solid lung cancer (NIPS) and those with invasive pure-solid lung cancer (IPS). The patients in the NIPS group had pathological PL(−), Ly(−), V(−), and N0 disease, whereas those in the IPS group showed positivity for at least one of them.

We investigated the relationships between these two groups and several clinical factors to identify significant predictors of suitability for sublobar resections for clinical stage IA pure-solid lung cancer. An unpaired *t* test or Chi-square test was used to compare two factors. Multivariate analysis was performed to identify the favorable clinical factors for predicting NIPS in clinical stage IA pure-solid lung cancer by logistic regression analysis using SPSS Statistics 21 (SPSS Inc.). To identify the significant clinical factors for predicting prognosis, the Cox proportional hazard model was used. Forward and backward stepwise procedures were used to determine the combination of factors that were essential for predicting the prognosis. Overall survival rates were calculated by the Kaplan–Meier estimation method using log-rank test. The date of surgical resection was selected as the starting point and the date of death of all causes or last follow-up date as the end point. Reported continuous data are shown as means with standard deviation (SD) for normality. Statistical analysis was considered significant when the probability value was less than 0.05.

Results

The subjects of this study were 275 eligible patients with clinical stage IA pure-solid lung cancers (181 men and 94 women; age range, 35–89 years; average age, 68.0 ± 9.6 years). Table 1 summarizes the clinical characteristics of the patients. Pathological nodal metastasis was found in 63 (22.9 %) patients, and PL(+), Ly(+), and V(+) were found in 100 (36.4 %), 63 (22.9 %), and 139 (50.5 %) patients with clinical stage IA pure-solid lung cancer, respectively. Standard lobectomy was performed in 222 (80.7 %) patients, with nodal metastases found in the N1 station in 26, and in the N2 station in 34; segmentectomy was performed in 31 (11.3 %) patients, with nodal metastases found in the N1 station in 1, and in the N2 station in 2; and wedge resection was performed in 22 (8.0 %) patients, with no nodal metastasis found. The 5-year overall survival (OS) and recurrence-free survival (RFS) of the 275 patients with clinical stage IA pure-solid lung cancer was 75.9 %

Table 1 Clinicopathological characteristics of the patients with clinical stage IA pure-solid lung cancer

Factors	Number of patients ($N = 275$), mean ± SD (range)
Gender	
Male/female	181/94
Age (years)	68.0 ± 9.6 (35–89)
Pack-years of smoking	35.1 ± 36.7
CEA (ng/ml)	6.8 ± 10.7 (0.5–82.7)
SUV_{max}	6.4 ± 4.2 (0.7–23.4)
Maximum tumor dimension (mm)	19.8 ± 6.1 (5–30)
Clinical T status	
Clinical T1a/clinical T1b	155/120
Radiological pleural tail	
Absent/present	147/128
Air bronchogram	
Absent/present	176/99
Operative procedure	
Lobectomy/segmentectomy/wedge resection	222/31/22
Histology	
Adenocarcinoma/squamous cell carcinoma/others	202/60/13
Lymphatic invasion	
Absent/present	212/63
Vascular invasion	
Absent/present	136/139
Visceral pleural invasion	
Absent/present	175/100
Pathological nodal involvement	
N0/N1–2	212/63

CEA carcinoembryonic antigen, *SUV* standardized uptake value, *SD* standard deviation

and 68.4 %, respectively, with 31.2 months of median follow-up time (MFT; Fig. 2).

The patients with clinical stage IA pure-solid lung cancer were divided into two groups to identify the feasible candidates for sublobar resection. Overall, NIPS was observed in 77 (28 %) patients and IPS was observed in 198 (72 %) patients. The OS and RFS were significantly different in patients with NIPS vs. those with IPS (3-year OS; 95.3 % vs. 75.2 %, $p = 0.0264$, 3-year RFS; 87.9 % vs. 62.4 %, $p = 0.0004$; Fig. 3a, b).

Table 2 shows the results of a univariate analysis for predicting the pathological non-invasive status of patients with clinical stage IA pure-solid lung cancer. A lower CEA level, lower SUV_{max} level, clinical T1a, and radiological presence of air bronchogram were more significantly related to NIPS compared with IPS ($p = 0.0281$, <0.0001, 0.0008, 0.0040, respectively). Sublobar resection was performed significantly more frequently in the NIPS group ($p = 0.0148$). Multivariate analysis revealed that the following clinical factors were significantly predictive of NIPS: the presence of air bronchogram ($p = 0.0328$), maximum tumor dimension (mm) ($p = 0.0040$), and SUV_{max} level ($p = 0.0002$; Table 3).

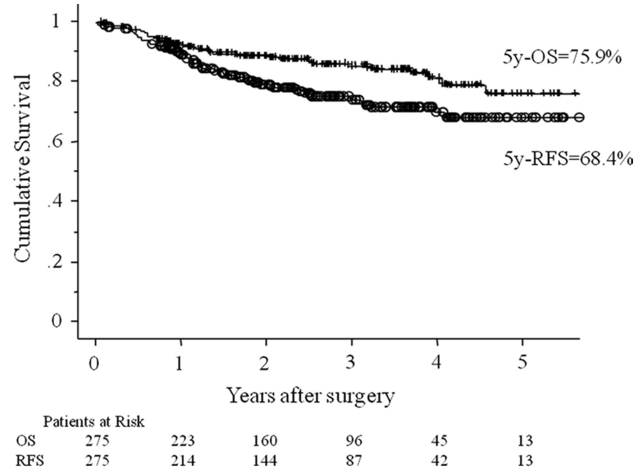


Fig. 2 The 5-year overall survival rate (OSR) and relapse-free survival (RFS) rate of patients with clinical stage IA pure-solid lung cancer were 75.9 and 68.4 %, respectively

Regarding SUV_{max} on PET, the receiver operating characteristic (ROC) curve revealed that the optimal cutoff value for predicting pathological non-invasive status in patients with clinical stage IA pure-solid lung cancer was an SUVmax of 3.2 (area under the curve; 0.773, standard error; 0.034) (Fig. 4). This cutoff value yielded a sensitivity of 0.890 and a specificity of 0.610 for SUV_{max}.

Based on the results of a multivariate analysis and the ROC curve, we divided the patients into two categories to identify the optimal candidates for sublobar resection; namely, a "favorable" group of patients ($n = 25$; 9.1 %) with the three prognostic factors of clinical T1a, presence of air bronchogram, and SUV_{max} <3.2, and an "unfavorable" group of patients ($n = 250$; 90.9 %), who did not meet these criteria.

Table 4 shows the probability of pathological nodal involvement in patients with clinical stage IA pure-solid lung cancer. While the frequency of nodal involvement was 4 % in the "favorable" group, 35.8 % had nodal metastases in the absence of these predictors ($p = 0.0027$). The 3-year OS and RFS of the "favorable" group patients were both 100 %, even for clinical stage IA pure-solid lung cancer, despite their operative modes. In contrast, the 3-year OS and RFS of the "unfavorable" group patients were 74.1 and 63.0 %, respectively (Fig. 5a, b). Locoregional or distant metastases were found in 45 (18.0 %) patients from the "unfavorable" group of patients with clinical stage IA

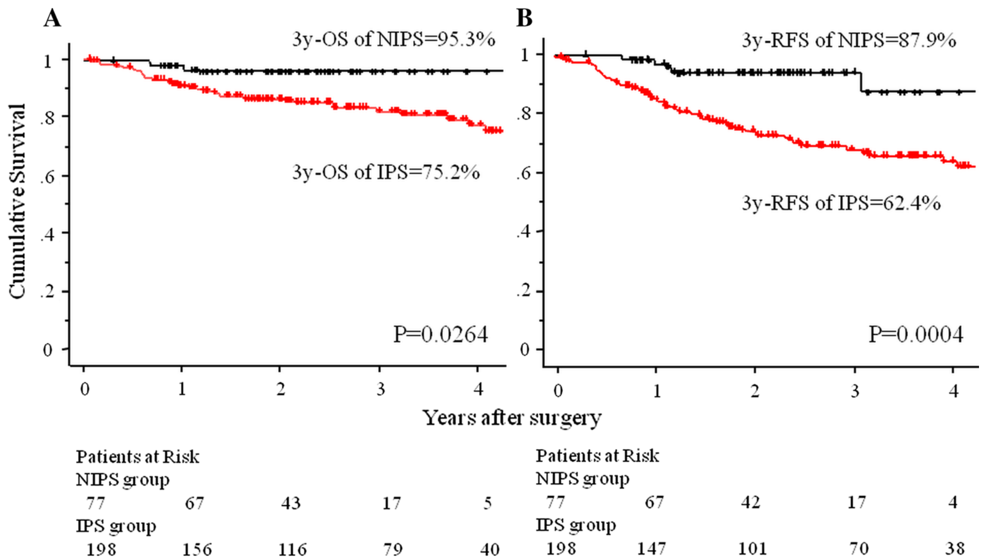


Fig. 3 The 3-year overall survival rate and relapse-free survival rate differed significantly between the NIPS group and the IPS group among patients with clinical stage IA pure-solid lung cancer (**a** $p = 0.0264$, **b** $p = 0.0004$)

Table 2 Results of a univariate analysis of the predictors of pathological non-invasive status in patients with clinical stage IA pure-solid lung cancer

Clinical factors	Clinical stage IA pure-solid lung cancer		
	NIPS group	IPS group	*p* value*
Total number of patients	77	198	
Age	68.2 ± 9.53	67.9 ± 9.68	0.8004
Gender			
Male/female	44/33	137/61	0.0586
Pack-years of smoking	30.9 ± 32.7	36.7 ± 38.1	0.2352
CEA (ng/ml)	4.52 ± 5.82	7.68 ± 12.01	0.0281
SUVmax	3.91 ± 3.20	7.33 ± 4.13	<0.0001
Clinical T status			
Clinical T1a/clinical T1b	56/21	100/98	0.0008
Radiological pleural tail			
Absent/present	40/37	107/91	0.7548
Air bronchogram			
Absent/present	39/38	137/61	0.0040
Operative procedure			
Lobectomy/sublobar resections	55/22	167/31	0.0148

The NIPS group indicated clinical stage IA pure-solid lung cancer with pathologically PL0, Ly0, V0 and N0 status, whereas the IPS group showed positive status for at least one item

CEA carcinoembryonic antigen, *SUV* standardized uptake value, *PL* pleural invasion, *Ly* lymphatic invasion, *V* vessel invasion

* *p* value in Chi-square test or unpaired *t* test

Table 3 Results of multivariate analysis for predictors of pathological non-invasive status in patients with clinical stage IA pure-solid lung cancer

Variable	Hazard ratio	95 % confidence interval	*p* value*
Air bronchogram (presence)	0.495	0.260–0.544	0.0328
Maximum tumor dimension (mm)	1.087	1.027–1.150	0.0041
SUV_{max}	1.245	1.109–1.298	0.0002

SUV standardized uptake value

* *p* value in logistic regression analysis

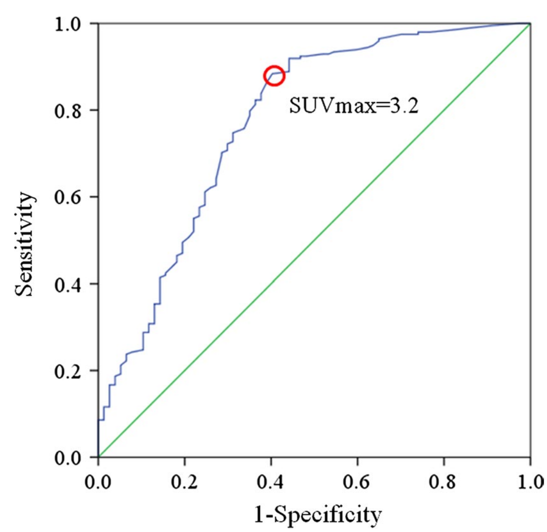


Fig. 4 The ROC curve of SUVmax on PET for the prediction of non-invasive pure-solid lung cancer (NIPS) in clinical stage IA diseases, with a cutoff value of 3.2

radiological pure-solid lung cancer. Locoregional recurrence was found in 26 (10.4 %) of these patients, distant recurrence was found in 19 (7.6 %), and both locoregional and distant metastases were found in 10 (4.0 %).

Discussion

The greatest concern surrounding the indications for limited surgery for patients with "solid" lung cancer is the potential risk of pathological nodal metastasis, despite the small size of the tumor [4, 12]. Radiologically pure-solid lung cancers exhibit more malignant behavior and are associated with a poorer prognosis than part-solid lung cancers, even when the solid component size is the same in both tumor types [5, 21]. These cohorts have a dismal prognosis with pathological nodal involvement in approximately 20 % of cases and even in clinical stage IA diseases [4, 12]. Furthermore, invasive lung cancer can be associated with occult lymph node metastasis, which would result in incomplete resection following limited surgical resection [22]. Therefore, any decision on limited surgical resection should be made cautiously for pure-solid lung cancers.

Because of the possible highly invasive nature of radiologically pure-solid lung cancer, even in clinical stage IA disease, in this study, we defined tumors with pathologically PL0, Ly0, V0, and N0 status as a non-invasive clinical stage IA pure-solid lung cancer (NIPS). These patients were considered optimal candidates for sublobar resection. According to multivariate analysis, the presence of air bronchogram in the tumor, maximum tumor dimension, and SUVmax level were the significant clinical factors predictive of NIPS. When we combined these radiological findings and the SUV_{max} level, nodal metastasis was found postoperatively in one (4 %) patient with clinical stage IA pure-solid lung cancer, who had all these favorable predictors. On the other hand, 35.8 % of patients with none of these predictors had pathological nodal involvement. Furthermore, the 3-year OS and RFS of the patients with the favorable predictors were both 100 %, despite their operative modes, whereas they were 74.1 and 63.0 % for the patients even with c-stage IA disease, who had none of these clinical predictors. According to these results, the combination of tumor size, the presence of air bronchogram, and a low SUV_{max} level may be alternative radiological findings associated with a good prognosis for clinical stage IA pure-solid lung cancer.

We reported previously that the prognostic significance of air bronchogram in radiologically pure-solid lung cancer was identified as a useful predictor of negative lymph nodes in our institute [23]. An intratumoral air bronchogram is mainly identified in areas with a slight, homogeneous increase in density on thin-section CT scan, such as a GGO lesion. This indicates that the main tumor structure is preserved by the alveolar and bronchiole space, which is a radiological feature of minimally invasive lung cancer. The existence of air bronchogram in pure-solid lung cancer combined with the SUV_{max} level of the main tumor may help to identify patients who are candidates for limited surgical resection [23].

In this series, sublobar resection was frequently performed for pure-solid lung cancer in patients with NIPS (29 %) compared with those of IPS (16 %), based on the preoperative patient selection (Table 2; $p = 0.0148$). With regard to the oncological efficacy of sublobar resection for clinical T1a NSCLC with a radiologically "part-solid or pure-solid" appearance, the final results of the JCOG [13] and CALGB [14] trials should help thoracic surgeons decide whether limited surgery is suitable for patients who are at low risk. We suggest that major lung resection with systematic mediastinal lymph node dissection should be the standard treatment for tumors that show a pure-solid appearance on thin-section CT scan. Based on the findings of this study, we should consider a pure-solid lung cancer as an invasive tumor, even in clinical stage IA status. Approximately 23 % of such patients in this series had pathological nodal involvement and were possible candidates for adjuvant chemotherapy. To perform accurate nodal staging and administer appropriate adjuvant therapy to these patients, thorough lymph node dissection is mandatory. Sublobar resection should be avoided for these tumors if the patients are at low risk and can tolerate lobectomy [1].

Considering the benefit of sublobar resection for clinical stage IA radiologically pure-solid lung cancer, further classification of small-sized lung cancers with a pure-solid appearance is warranted, to establish the optimal indications for limited surgical resection. In this context, the combination of tumor size, presence of air bronchogram, and low SUV_{max}

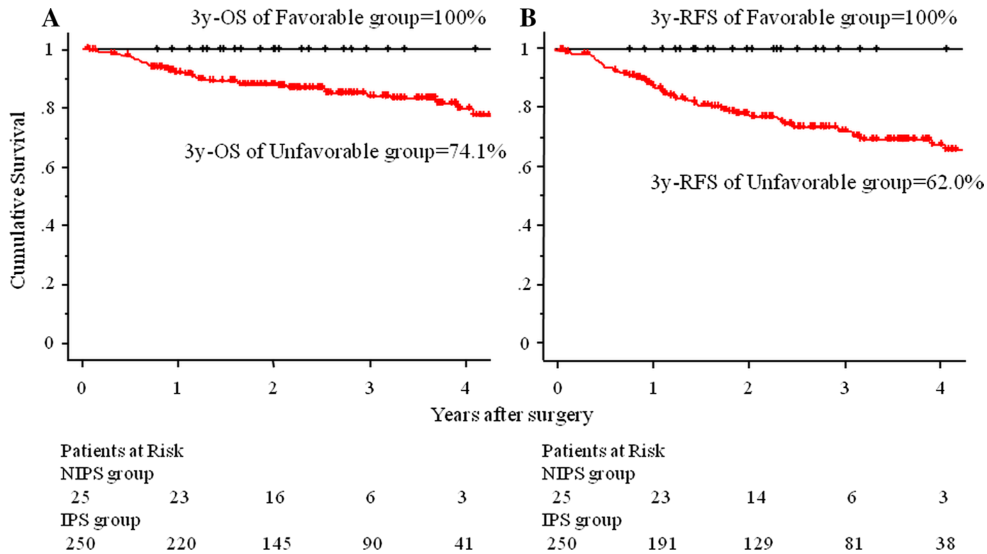
Table 4 Probability of the presence of nodal involvement in patients with clinical stage IA pure-solid lung cancer

Subgroups	Number of patients	Number of patients with nodal involvement (%)	p Value*
Total clinical stage IA disease	275	63 (22.9)	
Clinical T1a, presence of air bronchogram and SUV_{max} ≤3.2			
With all of these factors	25	1 (4.0)	0.0027
With one or two of these factors	183	38 (20.8)	
With none of these factors	67	24 (35.8)	

SUV standardized uptake value

* *p* value in Chi-square test

Fig. 5 The 3-year overall survival rate (OSR: a) and relapse-free survival rate (RFS: Fig. 5b) of the "favorable" group of patients with clinical stage IA pure-solid lung cancer were both 100 %, whereas those of the "unfavorable" group were 74.1 and 62.0 %, respectively



level was shown to be significantly effective for predicting a non-invasive nature in clinical stage IA radiologically pure-solid lung cancers. For these patients, segmentectomy with thorough lymph node dissection may be a feasible option, even for those with tumors having a pure-solid appearance. However, attention needs to be paid to the relatively low frequencies of these favorable cohorts (9 %) among clinical stage IA pure-solid lung cancers. Thus, the indications for sublobar resection for pure-solid lung cancers should be considered carefully, if the patient can tolerate lobectomy with adequate pulmonary and cardiac function.

This study was limited by a short median follow-up period and the small number of patients who underwent sublobar resection for radiological pure-solid lung cancers. However, because of the highly invasive nature of radiological pure-solid lung cancer, our findings could assist in determining the validity of limited resection for radiological pure-solid lung cancer in a relatively short follow-up period. Despite these limitations, we could identify the predictors of pathological non-invasive lung cancer with a radiologically solid appearance on thin-section CT scan. These patients could be candidates for sublobar resection for radiological invasive lung cancer in the future and further investigations are warranted.

In conclusion, although lobectomy with lymph node dissection is the standard surgical treatment for clinical stage IA lung cancer with a radiologically pure-solid appearance, tumor size, the presence of air bronchogram, and SUV_{max} level were significantly favorable predictors of a pathological non-invasive status. These clinical predictors could yield a beneficial clue for adopting sublobar resection even for patients with pure-solid lung cancer. In contrast, the indications for sublobar resection for pure-solid lesions without any favorable factors should be considered carefully because of the high potential for recurrence.

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Conflict of interest Aritoshi Hattori and his co-authors have no conflicts of interest.

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