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INVITED COMMENTARY

Uehara and colleagues [1] provide insight into the parallel between computed tomography (CT) morphology and positron emission tomography (PET) maximum standardized uptake value (maxSUV), suggesting increased virulence in small lung adenocarcinomas, usually associated with excellent prognosis. This prognostic association of lower ground glass opacity (GGO) ratio and increased maxSUV has not been clearly appreciated in the literature. We salute the researchers' efforts in bringing this point forward in a convincing way. We are, however, concerned with the "patient data set" and the investigational methodology of this work. We are also perplexed by the treatment recommendations of these small, modestly PET positive lesions.

Patient data set concerns relate to the absence of a true patient "denominator" in this multiinstitutional experiuence with high-resolution CT and PET imaging. What of similar pulmonary lesions that were followed rather than operated upon? What is the prognosis for patients either observed or operated on at a later date, once tumor growth was appreciated? How many of these presumed "high risk" pulmonary lesions were actually found to be benign, false positive resections. Finally, it appears that both stage 1A and stage 1B patients were grouped into this analysis.

Methodology concerns relate to the relatively low maxSUV values presumed to be indicative of aggressiveness, and the means of standardizing maxSUV between different institutions is suspect to us. The subjective estimate of GGO ratio gives no description of standardization by computer programming or central interpretation. Also, how was the intermediate risk "group 2" established and validated?

How do we use this information? Can we observe low risk nodules primarily until change is noted, and recommend early resection for high risk nodules? Vital information regarding the lesion "denominators," including benign and malignant lesions, is missing in this analysis. The survival difference between cautious "watching and waiting" and immediate resection of these lesions is not known.

Small adenocarcinomas with low GGO ratios and modestly high PET maxSUV may be more aggressive; however, we cannot accept the investigators' "leap of faith" that more aggressive pulmonary resection will improve survival. Their suggestion that lobectomy is a preferred treatment option for these small adenocarcinomas is contrary to their earlier work and ours demonstrating equivalent survival with anatomic segmentectomy or lobectomy for stage 1A lung cancer [2, 3]. Adjuvant chemotherapy for such stage 1 patients is unsubstantiated; however, we support further investigation. So what now?

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Solid tumor size on high-resolution computed tomography and maximum standardized uptake on positron emission tomography for new clinical T descriptors with T1 lung adenocarcinoma

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Background: To better describe clinical T descriptors using solid tumor size (the maximum dimension of the solid component of the tumor) on high-resolution computed tomography (HRCT) and maximum standardized uptake value (SUV_{max}) on F-18-fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT).

Patients and methods: We examined 610 consecutive patients with clinical stage IA lung adenocarcinoma who underwent complete resection. Recurrence-free survival (RFS) was assessed on the basis of whole tumor size (maximum dimension of the tumor), solid tumor size, or a combination of solid tumor size and SUV_{max}.

Results: RFS based on whole tumor size was not significantly different between patients with tumors measuring ≤2 cm and 2–3 cm ($P = 0.089$), whereas RFS based on solid tumor size was significantly different ($P < 0.0001$). We divided patients into four groups on the basis of solid tumor size and SUV_{max}: group 1: solid tumor size ≤2 cm, SUV_{max} ≤1.8; group 2: solid tumor size ≤2 cm, SUV_{max} >1.8; group 3: solid tumor size 2–3 cm, SUV_{max} ≤3.6; and group 4: solid tumor size 2–3 cm, SUV_{max} >3.6. Groups 2 and 3 were combined because they showed similar RFS each other. RFS was significantly different among these groups: group 1 versus groups 2 + 3, $P < 0.0001$; groups 2 + 3 versus group 4, $P = 0.019$.

Conclusions: Both solid tumor size on HRCT and SUV_{max} on FDG-PET/CT reflect prognosis well in patients with clinical stage IA lung adenocarcinoma and may support new clinical T descriptors.

Key words: lung adenocarcinoma, positron emission tomography, T descriptor, TNM classification

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introduction

Adenocarcinoma is the most common histologic subtype of lung cancer in most countries, accounting for ~50% of all lung cancers [1]. The widespread use of low-dose helical computed tomography (CT) for screening tumors has increased the early detection rate for smaller non-small-cell lung cancer (NSCLC), particularly adenocarcinoma [2]. These tumors often comprise a nonsolid component presenting as ground-glass opacity (GGO) on high-resolution CT (HRCT) [3].

A GGO component is closely associated with a pathologic lepidic growth component [4]. Because lepidic growth components are considered to have little effect on patient survival [5], GGO components may also have little effect on patient survival. We previously demonstrated that solid tumor size excluding GGO component on HRCT had a greater predictive value for pathologic tumor invasiveness and prognosis compared with whole tumor size for clinical stage IA lung adenocarcinoma [3]. We have also observed that the maximum standardized uptake value (SUV_{max}) on 18F-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET)/CT was an important preoperative factor for predicting the pathologic malignant grade and prognosis in lung adenocarcinoma [3, 6–9]. Both solid tumor size on HRCT and SUV_{max} on FDG-PET/CT were independent predictive factors for pathologic tumor invasiveness and prognosis [3, 9].

The tumor–node–metastasis (TNM) staging system for NSCLC is internationally accepted and used to determine the disease stage, which in turn guides disease management and determines prognosis [10]. Regarding clinical T descriptors, tumor size is usually measured as whole tumor size including solid and GGO components, without considering qualitative parameters such as SUV_{max} on PET/CT [11]. Here, we attempted to employ promising factors such as solid tumor size on HRCT and SUV_{max} on FDG-PET/CT as better clinical T descriptors of pathologic tumor invasiveness and prognosis compared with the present T descriptors based on whole tumor size.

patients and methods

patients

We enrolled 610 patients with clinical T1 N0 M0 stage IA lung adenocarcinoma from four institutions (Hiroshima University, Kanagawa Cancer Center, Cancer Institute Hospital, and Hyogo Cancer Center, Japan) between 1 August 2005 and 30 June 2010 to evaluate the significance of FDG-PET/CT. Patients with incompletely resected tumors (R1 or R2) and those with multiple tumors or previous lung surgeries were not included. This multicenter patient database was maintained prospectively and was retrospectively analyzed for this study.

HRCT and FDG-PET/CT followed by curative R0 resection were carried out for all patients staged according to the TNM Classification of Malignant Tumours, 7th Edition [10]. Mediastinoscopy and endobronchial ultrasonography were not routinely carried out, because all patients had undergone preoperative HRCT and FDG-PET/CT. HRCT revealed no enlargement of mediastinal or hilar lymph nodes measuring >1 cm; FDG-PET/CT showed no accumulation of an SUV_{max} of >1.5 in these lymph nodes.

Segmentectomy was considered for patients with clinical stage IA tumors that could be completely resected with ample surgical margins. No lymph node metastasis was intraoperatively confirmed using rapid frozen sections for enlarged lymph nodes or lymph nodes that were suspected with disease in the thoracic cavity. In cases of apparent or suspected nodal metastasis, lobectomy was chosen. Systematic lymphadenectomy including hilar and mediastinal node dissection can be carried out during segmentectomy but not during wedge resection. Therefore, wedge resection was carried out for tumors mainly exhibiting a GGO component on HRCT. Patients who had pathologically confirmed lymph node metastasis (N1 or N2) underwent platinum-based chemotherapy after surgery.

Surgically resected tumors were fixed with 10% formalin and embedded in paraffin. Consecutive 4-μm sections had been cut and evaluated histopathologically using hematoxylin and eosin and elastic van Gieson staining. Pathologic findings were evaluated by independent pathologists from each institution.

The inclusion criteria were preoperative staging determined by HRCT and FDG-PET/CT, curative surgery without neoadjuvant chemotherapy or radiotherapy, and a definitive histopathologic diagnosis of lung adenocarcinoma. This study was approved by the institutional review boards of the participating institutions. The requirement for informed consent from individual patients was waived, because this study was a retrospective review of a patient database.

HRCT

See supplementary File, available at *Annals of Oncology* online.

FDG-PET/CT

See supplementary File, available at *Annals of Oncology* online.

follow-up evaluations

All patients who underwent lung resection were followed up from the day of surgery. Patients underwent postoperative follow-up procedures, including physical examinations and chest roentgenography every 3 months and chest and abdominal CT every 6 months, for the first 2 years. Subsequently, they underwent physical examinations and chest roentgenography every 6 months and chest CT every year.

statistical analysis

Results were presented as numbers (%) or median values unless otherwise stated. The χ^2 test for categorical variables was used to compare frequencies and the Fisher's exact test was used for small samples. Receiver operating characteristic (ROC) curves of SUV_{max} for predicting pathologic tumor invasiveness were generated to determine the cutoff value yielding optimal sensitivity and specificity. Recurrence-free survival (RFS) was defined as the time from the day of surgery until the first adverse event (relapse or death from any cause) or until the last follow-up. Kaplan–Meier curves were used to assess RFS duration, and a log-rank test was used to assess differences in RFS. Statistical Package for the Social Sciences (SPSS) software (version 10.5; SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. The level of statistical significance was set at $P < 0.05$.

results

Table 1 summarizes the characteristics of the 610 patients evaluated in this study. Of these, 376, 97, and 137 underwent lobectomy, segmentectomy, and wedge resection, respectively. No 30-day postoperative mortality was observed in this

population. The median follow-up period following surgery was 41.5 (1.5–75.7) months, during which tumors recurred in 58 patients. There were 22 local-only recurrences, including mediastinal lymph node metastasis, and 36 distant ± local recurrences. There was no difference in the incidences of local-only recurrences between patients who underwent lobectomy and those who underwent sublobar resection [16 of 376 (4.3%) and 6 of 234 (2.6%), respectively, $P = 0.37$].

The median whole tumor and solid tumor sizes on HRCT were 2.0 and 1.2 cm, respectively. Lymphatic, vascular, and pleural invasions were detected in 89 (14.6%), 104 (17.0%), and 66 (10.8%) patients, respectively, and lymph nodes were involved in 41 (6.7%) patients. Three were intrapulmonary, 17 were hilar, and 21 were mediastinal lymph node metastases.

No significant difference in RFS was observed between patients with a whole tumor size of ≤2.0 cm (3-year RFS rate: 91.0%) and those with a whole tumor size of 2–3 cm (3-year RFS rate: 86.3%; $P = 0.089$; Figure 1A). In contrast, a significant difference in RFS was observed between patients with a solid tumor size ≤2.0 cm (3-year RFS rate: 91.7%) and those with a solid tumor size of 2–3 cm (3-year RFS rate: 77.6%, $P < 0.0001$; Figure 1B).

We generated ROC curves to decide the optimal cutoff values of SUV_{max} for predicting pathologic tumor invasiveness (lymphatic, vascular, or pleural invasion) in each solid tumor size group (solid tumor size of ≤2.0 cm or 2–3 cm). These ROC curves identified optimal SUV_{max} cutoff values of 1.8 [area under the curve (AUC) = 0.85; sensitivity = 77.3%; specificity = 79.3%] for a solid tumor size ≤2.0 cm and 3.6 (AUC = 0.79; sensitivity = 73.8%; specificity = 77.6%) for a solid tumor size of 2–3 cm (supplementary Figure S1A and B, available at *Annals of Oncology* online). Therefore, the patient population was subdivided into four groups on the basis of solid tumor size and optimal SUV_{max} cutoff values: group 1: solid tumor size ≤2.0 cm and SUV_{max} ≤1.8; group 2: solid tumor size ≤2.0 cm and SUV_{max} >1.8; group 3: solid tumor size 2–3 cm and SUV_{max} ≤3.6; and group 4: solid tumor size 2–3 cm and SUV_{max} >3.6.

The 3-year RFSs for groups 1, 2, 3, and 4 were 95.6%, 83.3%, 85.0%, and 70.8%, respectively (group 1 versus 2, $P < 0.0001$; group 2 versus 3, $P = 0.87$; group 2 versus 4, $P = 0.030$; Figure 2A). Because groups 2 and 3 had similar survival rates, we proposed the new clinical T descriptors as follows: proposed c-T1a (group 1): solid tumor size ≤2.0 cm and SUV_{max} ≤1.8; proposed c-T1b (groups 2 + 3): solid tumor size ≤2.0 cm and SUV_{max} >1.8, solid tumor size 2–3 cm and SUV_{max} ≤3.6; proposed c-T1c (group 4), solid tumor size 2–3 cm and SUV_{max} >3.6.

Table 1. Patient characteristics ($N = 610$)

Age (year)	66 (31–89)
Gender	
Male	268 (43.9%)
Whole tumor size (cm)	2.0 (0.6–3.0)
Solid tumor size (cm)	1.2 (0–3.0)
SUV_{max}	1.6 (0–17)
Clinical T descriptor	
T1a	354 (58.0%)
T1b	256 (42.0%)
Procedures	
Lobectomy	376 (61.6%)
Segmentectomy	97 (15.9%)
Wedge resection	137 (22.5%)
Lymphatic invasion	
Positive	89 (14.6%)
Vascular invasion	
Positive	104 (17.0%)
Pleural invasion	
Positive	66 (10.8%)
Lymph node metastasis	
Positive	41 (6.7%)

SUV_{max}: maximum standardized uptake value.

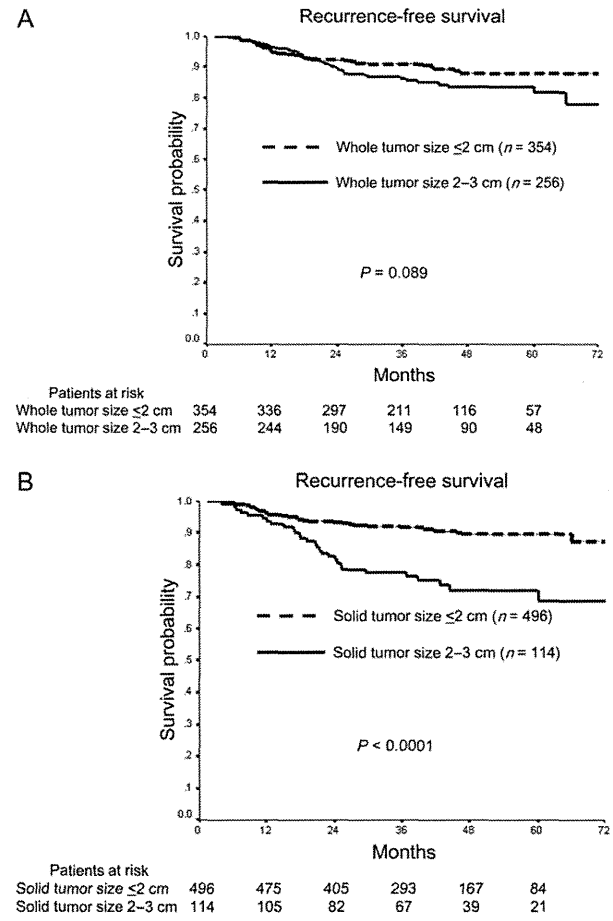

Figure 1. Recurrence-free survival (RFS) curves for patients with clinical stage IA lung adenocarcinoma based on whole tumor size (A) and solid tumor size (B). (A) Three-year RFS rates of 91.0% (mean RFS, 69.2 months; 95% confidence interval [CI]: 67.1–71.2 months) and 86.3% (mean RFS, 65.4 months; 95% CI: 62.7–68.1 months) were identified for patients with whole tumor size of ≤2 cm and those with whole tumor sizes of 2–3 cm, respectively ($P = 0.089$). (B) Three-year RFS rates of 91.7% (mean RFS, 69.8 months; 95% CI: 68.2–71.5 months) and 77.6% (mean RFS, 59.4 months; 95% CI: 54.6–64.2 months) were found for patients with solid tumor size of ≤2 cm and those with solid tumor size of 2–3 cm, respectively ($P < 0.0001$).

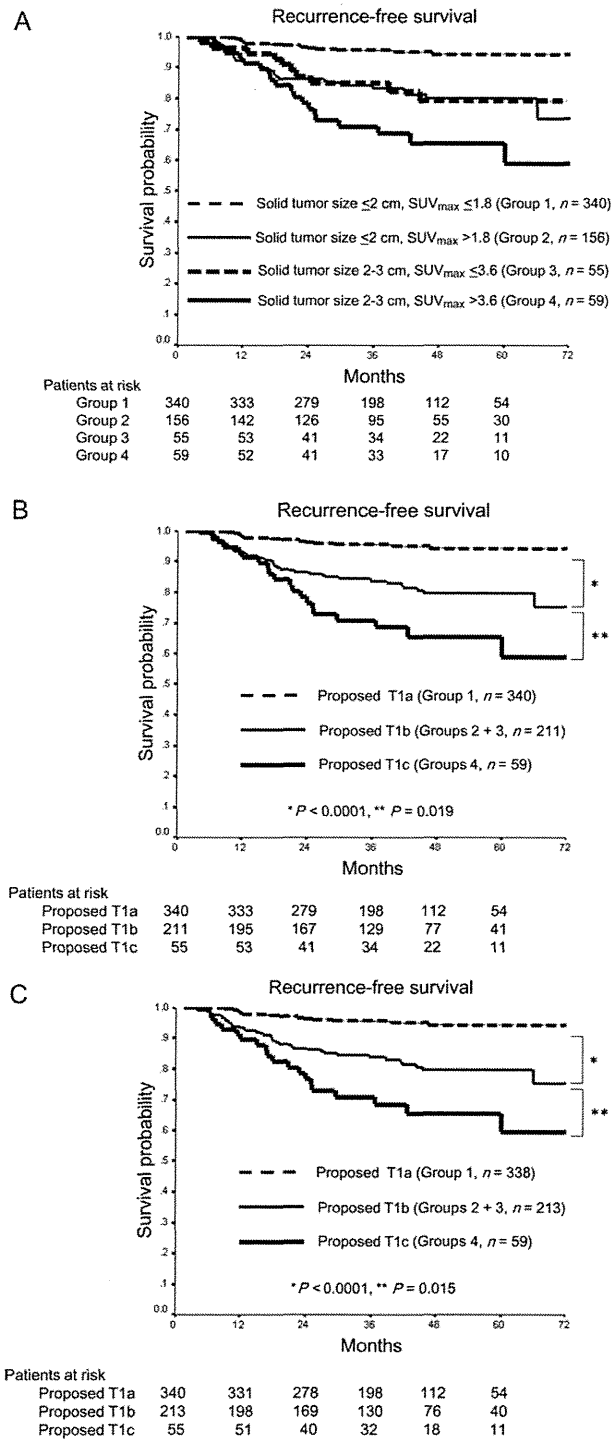

Figure 2. Recurrence-free survival (RFS) curves for patients with clinical stage IA lung adenocarcinoma based on solid tumor size and maximum standardized uptake value (SUV_{max}). (A) Group 1: solid tumor size ≤2 cm, SUV_{max} ≤1.8; group 2: solid tumor size ≤2 cm, SUV_{max} >1.8; group 3, solid tumor size 2–3 cm, SUV_{max} ≤3.6; group 4, solid tumor size 2–3 cm, SUV_{max} >3.6. Three-year RFSs for groups 1, 2, 3, and 4 were, respectively, 95.6% (mean RFS, 72.7 months; 95% confidence interval [CI], 71.2–74.1 months), 83.3% (mean RFS, 62.4 months; 95% CI: 58.7–66.2 months), 85.0% (mean RFS, 61.4 months; 95% CI: 55.7–67.0 months), and 70.8% (mean RFS, 55.2 months; 95% CI: 48.1–62.3 months). Group 1 versus 2, $P < 0.0001$; group 2 versus 3, $P = 0.87$; group 2 versus 4, $P = 0.030$. (B) Proposed c-T1a = group 1 in (A); proposed c-T1b = groups 2 + 3 in (A); proposed c-T1c = group 4 in (A); SUV_{max} was based on revised values. Three-year RFSs for proposed c-T1a, c-T1b, and c-T1c were 95.6% (mean RFS, 72.7 months; 95% CI: 71.2–74.1 months), 83.7% (mean RFS, 62.7 months; 95% CI: 59.5–65.8 months), and 70.8% (mean RFS, 55.2 months; 95% CI: 48.1–62.3 months), respectively. There were significant differences in RFS between proposed clinical T descriptors: proposed c-T1a versus proposed c-T1b, $P < 0.0001$; proposed c-T1b versus proposed c-T1c, $P = 0.019$. (C) Groups were the same as in (B), except SUV_{max} was based on original values. Three-year RFS results for proposed c-T1a, c-T1b, and c-T1c were, respectively, 95.6% (mean = 72.7 months; 95% CI: 71.2–74.1 months), 83.9% (mean = 62.8 months; 95% CI: 59.7–65.9 months), and 70.7% (mean = 55.0 months; 95% CI; 47.9–62.2 months). There were significant differences in RFS between proposed clinical T descriptors: proposed c-T1a versus proposed c-T1b, $P < 0.0001$; proposed c-T1b versus proposed c-T1c, $P = 0.015$.

The 3-year RFSs for proposed c-T1a (group 1), c-T1b (groups 2 + 3), and c-T1c (group 4) were 95.6%, 83.7%, and 70.8%, respectively. There were significant differences in RFS between the proposed clinical T descriptors: proposed c-T1a (group 1) versus proposed c-T1b (groups 2 + 3), $P < 0.0001$; proposed c-T1b (groups 2 + 3) versus proposed c-T1c (group 4), $P = 0.019$ (Figure 2B). The incidences of local-only recurrences were significantly different among the proposed T descriptors [2 of 340 (0.6%) in proposed T1a (group 1), 13 of 211 (6.2%) in proposed T1b (groups 2 + 3), and 7 of 59 (11.9%) in proposed T1c (group 4), respectively, $P < 0.001$].

There were also significant differences in pathologic findings (lymphatic, vascular, and pleural invasion, and also lymph node metastasis) among the proposed clinical T descriptors (all $P < 0.001$; Table 2).

Table 3 summarizes the differences in the distributions between the present T descriptors and our proposed descriptors. Among those with presently defined T1a tumors, 123 of 354 (34.7%) were upgraded to proposed T1b (groups 2 + 3). Among those with presently defined T1b tumors, 59 of 256 (23.0%) were upgraded to proposed T1c (group 4), while 109 of 256 (42.6%) with presently defined T1b tumors were downgraded to proposed T1a (group 1).

When we used the original SUV_{max} values before revision, the 3-year RFSs for proposed c-T1a (group 1), c-T1b (groups 2 + 3), and c-T1c (group 4) were 95.6%, 83.9%, and 70.7%, respectively. Significant differences in RFS remained between the proposed clinical T descriptors: proposed c-T1a (group 1) versus proposed c-T1b (groups 2 + 3), $P < 0.0001$; proposed c-T1b (groups 2 + 3) versus proposed c-T1c (group 4), $P = 0.015$ (Figure 2C).

discussion

In this study, the comparison between the present clinical T descriptors based on whole tumor size and solid tumor size on HRCT showed that the latter could be successfully used to subdivide the patients into different prognosis groups, indicating that GGO components had little effect on patient survival. We previously reported that solid tumor size on HRCT predicted pathologic tumor invasiveness better than whole tumor size for clinical stage IA lung adenocarcinoma [3].

Recently, another report also showed that excluding a GGO component resulted in improved prognostic performance for recurrence and pathologic vessel invasion in T1–2 N0 M0 lung adenocarcinoma [12]. Our results were consistent with those of previous reports, and the importance of solid tumor size when excluding a GGO component for predicting survival was confirmed. Solid tumor size excluding a GGO component should be used instead of whole tumor size to determine T descriptors in lung adenocarcinoma.

SUV_{max} on FDG-PET/CT was indicated as a prognostic factor for NSCLC [13], particularly for lung adenocarcinoma [3, 6–9]. SUV_{max} also has the potential to be a T descriptor as a quantitative factor for predicting pathologic tumor invasiveness and prognosis. One limitation of applying SUV_{max} to T descriptor is the cutoff value. In a multicenter study, variations in SUV quantitation resulting from differences in the quality of PET/CT scanners are disadvantages [14]. To adjust for these variations, we used an anthropomorphic body phantom that conformed to the National Electrical Manufacturers Association standards [15]. To determine the optimal cutoff values, we used ROC curves for SUV_{max} to predict pathologic tumor invasiveness (lymphatic, vascular, or pleural invasion). We determined cutoff values of 1.8 and 3.6 for the solid tumor size of ≤2 and 2–3 cm, respectively. Interestingly, the predictive capabilities of pathologic tumor invasiveness based on these cutoff values were quite similar in each group based on solid tumor size (sensitivity = 73.8%–77.3%; specificity = 77.6%–79.7%). This suggested that these cutoff values were reasonable.

Regarding prognosis, patients with the solid tumor size of ≤2 cm and SUV_{max} of >1.8 had similar RFS results, compared with those with the solid tumor size of >2 cm and SUV_{max} of ≤3.6. This was also an interesting finding. Based on this, we proposed the following new T descriptors: proposed T1a: solid tumor size ≤2 cm and SUV_{max} ≤1.8; proposed T1b: solid tumor size ≤2 cm and SUV_{max} >1.8 or solid tumor size 2–3 cm and SUV_{max} ≤3.6; and proposed T1c: solid tumor size 2–3 cm and SUV_{max} >3.6. This indicated that high SUV_{max} tumors could be upgraded. Based on our proposed T descriptors, RFSs and pathologic tumor malignancies were significantly different among these groups.

Comparing our proposed T descriptors with present descriptors, 34.7% present T1a tumors were upgraded to proposed T1b, 23.0% present T1b tumors were upgraded to proposed T1c, and 42.6% present T1b tumors were downgraded to proposed T1a. This indicated that the present T descriptors did not successfully represent tumor malignancies and prognosis, which may be due to the heterogeneities of lung adenocarcinomas. Solid tumor size on HRCT and SUV_{max} on FDG-PET/CT could explain these heterogeneities of lung adenocarcinomas as preoperative radiologic findings.

For clinical practice, it was important that using the original SUV_{max} retained the prognostic differences among the groups based on our proposed new T descriptors. When the original SUV_{max} was used, our proposed T descriptors could successfully subdivide our patients into different prognostic groups. To confirm our proposed T descriptors, a validation study with another cohort and international standardization protocols of FDG-PET/CT are needed. These were limitations of our study. Another limitation was that our database did not include tumors with a whole tumor size of >3 cm. Therefore, whether our proposed clinical T1c can be regarded as T2a is unknown. Further studies including large tumors are warranted. We used two-dimensional measurements of tumor sizes for this study. Three-dimensional measurements such as metabolic tumor volume using HRCT and FDG-PET/CT may also have a potential to be considered as new T descriptors [16].

Table 2. Pathologic findings based on our newly proposed clinical T descriptors

	Proposed T1a (N = 340)	Proposed T1b (N = 211)	Proposed T1c (N = 59)	P-value
Lymphatic invasion	12 (3.5%)	52 (24.6%)	25 (43.4%)	<0.001
Vascular invasion	8 (2.4%)	59 (28.0%)	37 (62.7%)	<0.001
Pleural invasion	6 (1.8%)	36 (17.1%)	24 (40.7%)	<0.001
Lymph node metastasis	4 (1.2%)	27 (12.8%)	10 (16.9%)	<0.001

Table 3. Differences in distributions between the present T descriptors and our proposed clinical T descriptors

	Present T1a (N = 354)	Present T1b (N = 256)
Proposed T1a (N = 340)	231	109
Proposed T1b (N = 211)	123	88
Proposed T1c (N = 59)	0	59

Sublobar resection for treating small lung cancer has under debate for a long time [8, 17–20]. Selecting optimal candidates for sublobar resection is important. Our proposed new T descriptors may contribute to selecting patients for sublobar resection. Patients with our newly proposed T1a tumors may be good candidates for sublobar resection, because they have less pathologic invasiveness such as lymphatic, vascular, or pleural invasion, and lymph node metastases.

In conclusion, T descriptors should be based on solid tumor size on HRCT, which is more useful for predicting pathologic tumor invasiveness and prognosis than whole tumor size. Furthermore, SUV_{max} on FDG-PET/CT, which also successfully predicts tumor invasiveness and prognosis of early lung adenocarcinoma, has adequate potential to be a new T descriptor. The combination of solid tumor size and SUV_{max} predicts the survival better than solid tumor size alone and may contribute to decision-making for sublobar resection in patients with clinical stage IA lung adenocarcinoma. We hope that solid tumor size on HRCT and SUV_{max} on FDG-PET/CT will be taken into account in the next revisions for T descriptors.

disclosure

The authors have declared no conflicts of interest.

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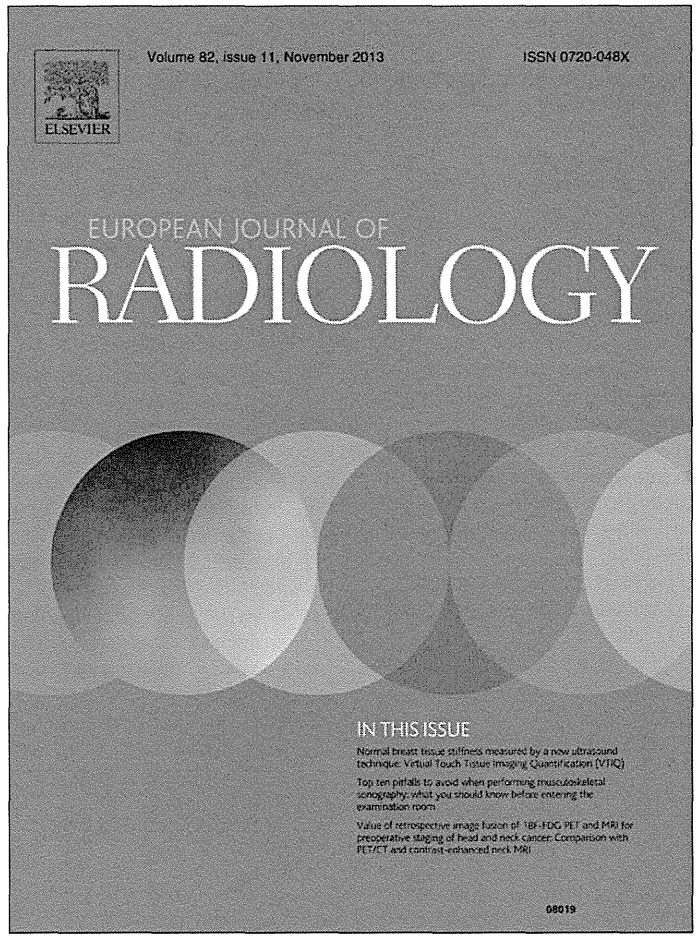

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^{18}F-fluorodeoxyglucose uptake on positron emission tomography in mucinous adenocarcinoma

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ABSTRACT

Background: The prognostic value of maximum standardized uptake value (maxSUV) on ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is known for localized pulmonary adenocarcinoma, which is most commonly non-mucinous adenocarcinoma. We examined the validity of thin-section computed tomography (TS-CT) and FDG-PET findings in mucinous adenocarcinoma.
Materials and Methods: TS-CT and FDG-PET were performed on 25 patients with mucinous lung adenocarcinoma that was subsequently resected between January 2009 and March 2013. Based on the percentage reduction of maximum tumor diameter on the mediastinal window image compared with the diameter on the lung window image on TS-CT, tumors were classified as air-type (≥50%) or solid-type (<50%). All resected specimens were pathologically diagnosed according to the International Association for the Study of Lung Cancer (IASLC) classification, and the diameter of the pathological invasive area was assessed.
Results: Most mucinous adenocarcinomas were located in the lower lobe. All except two were classified as solid-type tumor on TS-CT. Multiple regression analysis revealed the correlation of maxSUV with pathological tumor size and diameter of pathological invasive area; these two parameters showed no significant correlation with each other ($r = 0.354$, $p = 0.083$). maxSUV was significantly lower for tumors with invasive area ≤5 mm than for tumors with invasive area >5 mm (1.62 vs. 3.77, $p = 0.01$), but no statistically significant difference was found in terms of other pathological invasive findings such as the presence of lymphatic or vascular invasion, pleural involvement, or predominant histological subtype.
Conclusions: Most mucinous adenocarcinomas had appearances of solid-type tumor on TS-CT. maxSUV on FDG-PET indicates the pathological invasive area in mucinous adenocarcinoma as well as non-mucinous adenocarcinoma.

1. Introduction

According to the latest World Health Organization classification, lung adenocarcinoma is categorized on the basis of mucin production: as non-mucinous, mucinous, or mixed mucinous/non-mucinous and intermediate cell type [1]. There are numerous radiological analyses regarding non-mucinous adenocarcinoma; however, few investigations have studied mucinous lung adenocarcinoma because this type occurs so infrequently.

On thin-section CT (TS-CT) images of non-mucinous adenocarcinoma, solid nodular areas indicate collapsed alveoli, foci of fibrosis, or tumors with an invasive growth pattern, whereas areas of ground-glass opacity (GGO) represent components of lepidic growth pattern [2–4]. Based on these imaging appearances, several studies showed that for peripheral small adenocarcinomas, tumor shadow disappearance rate (TDR) on TS-CT is useful for predicting patient prognosis [5–7]. In these reports, tumors were classified as air-type or solid-type according to the TDR, defined as the ratio of the maximum tumor diameter on mediastinal window settings to that on lung window settings.

However, mucinous adenocarcinomas have abundant mucin within the alveolar lumina. Therefore, TS-CT images of mucinous adenocarcinoma may show mucin-filled alveoli as solid areas, even in the absence of an invasive area. It is uncertain whether TDR can be applied to mucinous adenocarcinoma.

^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is generally accepted as having a high accuracy in distinguishing benign from malignant lesions when the nodule is

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solid in attenuation and greater than 10 mm in diameter [8]. We previously reported a strong correlation of maxSUV with the diameter of the pathological invasive area, and that maxSUV could be a preoperative predictor of progression [9,10]. However, the correlation between maxSUV on FDG-PET and the clinicopathological characteristics of mucinous adenocarcinoma has not been fully investigated.

The purpose of the present study was to investigate the validity of TDR on TS-CT and that of maxSUV on FDG-PET in mucinous adenocarcinomas, and to evaluate whether pathological aggressiveness can be predicted based on the FDG-PET findings.

2. Materials and methods

2.1. Patients

Between January 2009 and March 2013, 31 patients who had undergone curative surgical resection were diagnosed with pulmonary mucinous adenocarcinoma at Kanagawa Cancer Center Hospital, Japan. We retrospectively reviewed the TS-CT and FDG-PET reports of 25 patients (11 male, 14 female) who had undergone preoperative TS-CT and FDG-PET studies at our institution for the purpose of staging and evaluation of resectability.

2.2. TS-CT evaluation

All 25 patients had undergone TS-CT scans within 1 month prior to surgery. TS-CT images were acquired using an Aquilion CT scanner (Toshiba Medical Systems, Tokyo, Japan). TS-CT images targeted to the tumors were obtained serially at 120 kVp and 200 mAs, with 1 mm section thicknesses, pitch of 1, 1 mm section spacing, 512 × 512 pixel resolution, and 1 s scanning time, using a high-spatial-reconstruction algorithm with a 20-cm field of view. All scans were imaged using mediastinal window settings (level, 40 Hounsfield units (HU); width, 400 HU) and pulmonary window settings (level, −600 HU; width, 1600 HU). Maximum tumor diameter was measured on both lung and mediastinal window settings. The percentage reduction of the maximum dimension between the mediastinal and lung windows was calculated. Tumors were defined as air-type for ratios ≥50% or as solid-type for ratios <50%.

2.3. FDG-PET/CT evaluation

All PET/CT studies were performed using a lutetium oxyorthosilicate-based whole-body PET/CT scanner (Biograph 16 HI-REZ; Siemens). ^{18}F-FDG (FDG scan Injectable; Nihon Mediphysics Co. Ltd.) was purchased via a delivery system. The ^{18}F-FDG dose per body weight cannot be determined under this delivery system because the delivery of ^{18}F-FDG occurs at three set times per day. All patients fasted for at least 6 h before intravenous administration of ^{18}F-FDG, and blood sugar levels were checked prior to tracer administration. In all patients except two, measured values were less than 140 mg/dl. Whole-body scanning was performed as an additional scan, from the top of the skull to the middle of the thigh, 60 min after administration of ^{18}F-FDG, with 3 min per bed position. CT images were used for anatomic landmarking. All PET images were reconstructed using iterative algorithms with CT-based attenuation correction. The data were reconstructed with a 128 × 128 matrix and 2-mm slice thickness. SUVmax was evaluated for the maximum value within a region of interest (ROI) drawn around the pulmonary lesion.

2.4. Pathological evaluation

Hematoxylin–eosin and periodic acid-Schiff reagent, and elastic van Gieson (EVG) staining were performed on all sections to investigate tumor size along the long axis, the diameter of invasive area, lymphatic and vascular invasion, and pleural involvement. The microscopic hallmark of mucinous adenocarcinoma is tumor cells, which mainly comprise goblet or columnar cells. Neoplasms formerly termed as bronchioloalveolar adenocarcinoma are now recognized to have invasive components in the majority of cases. In the present study, we classified mucinous adenocarcinoma as adenocarcinoma in situ (AIS; a small (≤30 mm) adenocarcinoma with lepidic growth, lacking stromal, vascular, and pleural invasion), as minimally invasive adenocarcinoma (MIA; a small lepidic growth predominant adenocarcinoma with ≤5 mm invasion), or as invasive adenocarcinoma (IA; including lepidic predominance with >5 mm invasion, acinar, papillary, micropapillary, or solid predominance), according to the new classification of lung adenocarcinoma by the International Association for the Study of Lung Cancer (IASLC) [1]. Stages were determined according to the 2010 TNM classification.

Table 1
Patient characteristics[a].

Characteristic	(n = 25)	p-Value
Age, years (median)	40–83 (69)	
Gender		
Male	11 (44%)	
Female	14 (56%)	
Smoking history		
Non-smoker (male/female)	13 (1/12)	0.0002
Smoker (male/female)	12 (10/2)	
Brinkman index	789 ± 315	
Post-operative stage		
IA	9 (36%)	
IB	9 (36%)	
IIA	1 (9%)	
IIB	0 (0%)	
IIIA	1 (9%)	

[a] Values are given as the range (median) or number of patients (%).

2.5. Statistical analysis

Statistical analysis was performed using SPSS software (Dr. SPSS II for Windows, Tokyo, Japan, released 2001). Pearson's correlation analysis was used to analyze correlations of maximum diameter on the mediastinal-window CT images with the pathological invasive area (SUVmax) on PET; Student's t-test and Fisher's exact test were used to analyze differences between unrelated groups. Differences were considered statistically significant when $p < 0.05$.

3. Results

3.1. Patient characteristics

The characteristics of the 25 patients are summarized in Table 1. The median age was 69 years (range, 40–83 years) and 12 patients were smokers, with a mean Brinkman index of 379.1 ± 455.8 (range, 0–1260). Ten of the 11 (91%) male patients were smokers, while only 2 of the 14 (14.3%) female patients were smokers. The distribution of surgical stages was follows: stage IA (pT1aN0M0, pT1bN0M0), n = 9; stage IB (pT2aN0M0), n = 9; stage IIA (pT2bN0M0), n = 1; stage IIB (pT3N0M0), n = 5; stage IIIA (pT2bN2M0), n = 1. Lymph node metastasis was found in only one patient.

3.2. TS-CT findings

The tumors were most commonly located in the lower lobe: right lower lobe, n = 9 (36%); left lower lobe, n = 11 (44%). Maximum tumor diameter on lung-window images was

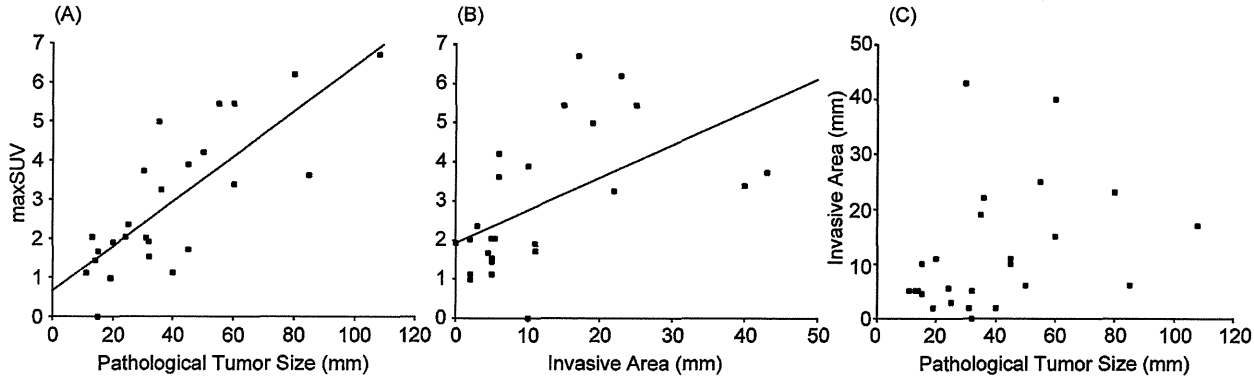

Fig. 1. Linear regression analysis of maximum standardized uptake value (maxSUV) (A), maximum pathological diameter (B), and maximal diameter of pathological invasive area (C).

37.4 ± 21.4 mm (range 11–110 mm), while maximum tumor diameter on mediastinal-window images was 30.0 ± 21.8 mm (range 8–106 mm). All except two tumors were classified as solid-type tumor on the basis of the TS-CT findings (Table 2).

3.3. TS-CT findings and FDG-PET

maxSUV correlated positively with maximum diameter on the lung-window CT images ($r = 0.626$, $p = 0.001$), maximum diameter on the mediastinal-window CT images ($r = 0.662$, $p < 0.001$), pathological tumor size ($r = 0.793$, $p < 0.001$; Fig. 1A), and diameter of the pathological invasive area ($r = 0.536$, $p < 0.001$; Fig. 1B). As expected, pathological tumor size correlated significantly with maximum diameter on the lung-window CT images and on the mediastinal-window CT images; however, pathological tumor size showed no significant correlation with diameter of the pathological invasive area ($r = 0.354$, $p = 0.083$; Fig. 1C). Multiple regression analysis revealed that diameter of the pathological invasive area and pathological tumor size are the only independent factors for maxSUV (Table 3). The maximum tumor diameter on lung window image and mediastinal window image did not affect maxSUV significantly.

3.4. Pathological invasive area and FDG-PET

In agreement with the results of previous report [9], a significant relationship between maxSUV and diameter of the pathological invasive area was found in mucinous adenocarcinoma. Moreover, the correlation was stronger for diameter of pathological invasive area ≤30 mm ($r = 0.729$, $p < 0.001$). The mean maxSUV in 10 adenocarcinomas with invasive area ≤5 mm was 1.62 ± 0.46, which is significantly lower than that in the 15 adenocarcinomas with invasive area >5 mm (3.77 ± 1.84, $p = 0.01$) (Fig. 2). Six tumors were diagnosed pathologically as AIS or MIA, and 19 tumors were diagnosed as IA. Of these 19 IAs, 9 were lepidic predominant and the other 10 were as follows: acinar predominant, $n = 3$; papillary predominant, $n = 6$; and micropapillary predominant, $n = 1$. Mean maxSUV in lepidic-predominant invasive adenocarcinoma was 3.26 ± 1.74 and that in other types was 3.38 ± 2.04; there was no significant difference between these two groups ($p = 0.602$). Lymphatic or vascular invasion, or pleural involvement was found in 7 tumors, and 18 tumors had no findings of pathological invasion. Mean maxSUV of the 7 tumors with invasive findings was 3.10 ± 1.99 and that of the 18 tumors without these findings was 2.84 ± 1.76; there was no significant difference between the two groups ($p = 0.816$).

Table 2
Pre-operative CT findings.

Finding	($n = 25$)
Tumor location	
Right upper/middle/lower lobe	1/1/9
Left upper/lower lobe	3/11
Tumor diameter on lung-window images (mm)	37.4 ± 21.4
Tumor diameter on mediastinal-window images (mm)	30.0 ± 21.8
TDR classification	
Air type	2 (8%)
Solid type	23 (92%)

TDR: tumor disappearance rate.

4. Discussion

Previous studies have investigated the radiological and pathological characteristics of mucinous lung adenocarcinoma [11,12], although most of these studies considered a small number of patients. It can be difficult to diagnose mucinous adenocarcinoma as malignant tumor radiologically because the radiological findings are different from those of non-mucinous adenocarcinoma [13,14].

Lung cancer is reported to occur predominantly in the upper lobe of the lung, whereas in the present study, 80% of mucinous adenocarcinomas were found in the lower lobe. Even though the present sample size is small, it could be a characteristic of mucinous adenocarcinoma that this tumor is located predominantly in the lower lobe, which is consistent with the findings of previous reports [15,16]. Non-mucinous lepidic-growth adenocarcinoma is reported

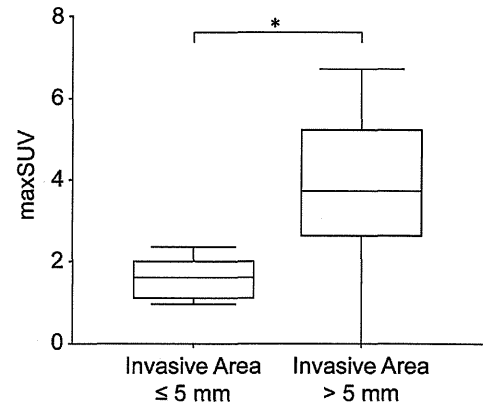

Fig. 2. Comparison of maximum standardized uptake value (maxSUV) between tumors with invasive area ≤5 mm and >5 mm.
*$p = 0.01$, as determined by Student's t-test. Horizontal bar, median value; columns, interquartile range; vertical bar, smallest and largest data points within 1.5 interquartile ranges from the median value.

Table 3
Multiple regression analysis of the relationship of maxSUV to each of invasive area, pathological tumor size, tumor size on lung-window image, and tumor size on mediastinal window-image.

	Regression coefficient	SE	*p*-Value	95% CI
Invasive area	0.052	0.020	0.018	0.010–0.093
Pathological tumor size	0.068	0.017	0.001	0.032–0.104
Tumor diameter on lung-window image	−0.030	0.032	0.357	−0.098 to 0.037
Tumor diameter on mediastinal-window image	0.047	0.033	0.889	−0.065 to 0.074

SE: standard error; CI: confidence interval.

to be less dependent on tobacco exposure, and disproportionately affects women [17]. Unlike non-mucinous lepidic-predominant adenocarcinoma, mucinous adenocarcinoma is known to be significantly associated with a history of smoking [18]. Interestingly, in the present study, 91% of males had a history of smoking, compared with only 14.3% of females. Although the pathogenesis of mucinous adenocarcinoma is unclear, the different distribution of predominant location and smoking status would suggest a difference in pathogenesis between mucinous and non-mucinous adenocarcinoma.

On TS-CT images of non-mucinous adenocarcinoma, GGO indicates the components of lepidic growth pattern. However, mucinous adenocarcinoma has abundant mucin within the alveolar lumina. Therefore, CT attenuation values are significantly higher for mucinous lepidic-predominant adenocarcinoma than for non-mucinous lepidic-predominant adenocarcinoma, and mucinous adenocarcinoma can have the appearance of a solid or part-solid tumor [14]. We have previously reported the correlation between CT findings (evaluated by TDR) and pathological subtype of adenocarcinoma in non-mucinous adenocarcinoma, and between CT findings and prognosis [7]. In small-sized tumors, AIS and MIA were air-type tumors, and all invasive adenocarcinomas appeared as solid-type tumors. Based on these findings, measurement of TDR is valid for predicting the pathological subtype of adenocarcinoma and the postoperative prognosis. Indeed, several studies have reported a good prognosis for air-type tumors. However, 92% of mucinous adenocarcinomas appeared as a solid-type tumor because of mucin filling the alveoli. Therefore, measurement of TDR is not useful for predicting the pathological subtype of mucinous adenocarcinoma.

FDG-PET has been shown to be of great value not only in detection, staging, and monitoring of response to treatment, but also in evaluation of the malignant potential of a tumor [19,20]. FDG-uptake is correlated with the number of viable tumor cells as well as histological characteristics such as tumor grade and differentiation. Bronchioloalveolar cell carcinoma is known to exhibit significantly lower maxSUV compared with invasive adenocarcinoma and commonly shows negative FDG-PET [21,22]. We have previously reported a similar result of a strong correlation of maxSUV with the diameter of pathological invasive area in the majority of non-mucinous adenocarcinomas, and the finding of a significantly lower maxSUV in AIS and MIA than in IA [9].

Shim et al. and Sawada et al. reported that among mucinous adenocarcinomas, maxSUV was lowest for mucinous bronchioloalveolar carcinoma, which had the highest value of 2.6 [12,15]. Moreover, Shim et al. reported a high percentage (82%) of false-negative maxSUV for mucin-producing lung adenocarcinomas, and found no significant association between tumor size and maxSUV [12]. In the present study, maxSUV was correlated with the diameter of the pathological invasive area, which would reflect the aggressiveness of the tumor. Mean maxSUV was significantly higher in adenocarcinomas with invasive area >5 mm than in those with invasive area ≤5 mm (consistent with non-mucinous adenocarcinoma). In contrast, the predominant subtype of invasive adenocarcinoma and findings consistent with pathological invasion, such as vascular and lymphatic invasion or pleural involvement, did not affect the maxSUV of tumors. These features are different from those of non-mucinous adenocarcinoma, which may be due to the low frequency (28%) of pathological invasive findings and the small number of patients; nevertheless, this result is similar to that reported previously by Shim et al. [12].

The present study has a number of limitations. First, because we excluded patients who underwent preoperative examinations at other institutions, our results may not be generalizable to patients treated at other institutions, particularly with regard to maxSUV values. Second, the patients in the present study were operable, and therefore the frequency of lymph node metastasis and other pathologically invasive findings may have been underestimated. Third, the number of patients was small. Fourth, the correlation regarding maxSUV and postoperative recurrence has not been sufficiently evaluated because of the short follow-up period following surgery.

Despite these limitations, the finding that maxSUV reflects the pathological invasive area of tumor in mucinous adenocarcinoma as well as non-mucinous adenocarcinoma, and that maxSUV was lower in mucinous adenocarcinoma with invasive area ≤5 mm despite its appearance as a solid-type tumor may be beneficial in radiological interpretation of solid-type tumors that are encountered in the clinical setting. However, compared with non-mucinous adenocarcinoma, mucinous adenocarcinoma is associated less frequently with lymph node metastasis, and more frequently with intrapulmonary metastasis [23–25]. From the fact that pulmonary metastasis is the most common form of postoperative recurrence in mucinous adenocarcinoma, prediction of invasive area by FDG-PET could not affect the clinical outcome of patients. On the other hand, as most mucinous adenocarcinomas are classified as solid-type adenocarcinoma on TS-CT, classification based on TDR on TS-CT would be useful in the case of mucinous adenocarcinoma from the point of view of predicting prognosis.

In conclusion, most mucinous adenocarcinomas appeared as solid-type on CT because of abundant mucin within the alveolar lumina, even in the case of lepidic-predominant adenocarcinoma. Accordingly, it is difficult to predict the histological sub-type and presence of invasive areas of lung cancer from the CT findings. However, maxSUV on FDG-PET does reflect invasiveness in lung adenocarcinoma. Further studies are required to evaluate the validity of preoperative maxSUV in predicting the clinical outcome of patients with mucinous adenocarcinoma.

Conflict of interest statement

None declared.

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Oncologic outcomes of segmentectomy compared with lobectomy for clinical stage IA lung adenocarcinoma: Propensity score–matched analysis in a multicenter study

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Objective: Our objective was to compare the oncologic outcomes of lobectomy and segmentectomy for clinical stage IA lung adenocarcinoma.

Methods: We examined 481 of 618 consecutive patients with clinical stage IA lung adenocarcinoma who underwent lobectomy or segmentectomy after preoperative high-resolution computed tomography and F-18-fluorodeoxyglucose positron emission tomography/computed tomography. Patients (n = 137) who underwent wedge resection were excluded. Lobectomy (n = 383) and segmentectomy (n = 98) as well as surgical results were analyzed for all patients and their propensity score–matched pairs.

Results: Recurrence-free survival (RFS) and overall survival (OS) were not significantly different between patients undergoing lobectomy (3-year RFS, 87.3%; 3-year OS, 94.1%) and segmentectomy (3-year RFS, 91.4%; hazard ratio [HR], 0.57; 95% confidence interval [CI], 0.27-1.20; $P = .14$; 3-year OS, 96.9%; HR, 0.49; 95% CI, 0.17-1.38; $P = .18$). Significant differences in clinical factors such as solid tumor size ($P < .001$), maximum standardized uptake value (SUVmax) ($P < .001$), and tumor location (side, $P = .005$; lobe, $P = .001$) were observed between both treatment groups. In 81 propensity score–matched pairs including variables such as age, gender, solid tumor size, SUVmax, side, and lobe, RFS and OS were similar between patients undergoing lobectomy (3-year RFS, 92.9%, 3-year OS, 93.2%) and segmentectomy (3-year RFS, 90.9%; 3-year OS, 95.7%).

Conclusions: Segmentectomy is suitable for clinical stage IA lung adenocarcinoma, with survivals equivalent to those of standard lobectomy. (J Thorac Cardiovasc Surg 2013;146:358-64)

GTS

Segmentectomy for treating small lung cancer has been a topic of debate for a long time. In 1995, the Lung Cancer Study Group conducted a prospective randomized controlled trial comparing limited resection (including segmentectomy and wedge resection) with lobectomy for clinical T1 N0 M0 non–small cell lung cancer (NSCLC). The study concluded that limited resection resulted in higher local recurrence and lower survival.[1] A recent study from the Surveillance Epidemiology and End Results database showed that lobectomy conferred a significant advantage compared with segmentectomy in stage I NSCLC.[2] In contrast, several studies reported that the survivals after segmentectomy and those after lobectomy were similar.[3-7] However, few reports compare between segmentectomy and lobectomy with matched patient variables affecting survival.

Recently, we[8,9] reported that solid tumor size, defined as the maximum dimension of the solid component excluding the ground-glass opacity (GGO) component on high-resolution computed tomography (HRCT), and maximum standardized uptake value (SUVmax) on [18F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT), are useful for predicting the pathologic invasiveness or prognosis in clinical stage IA lung adenocarcinoma. These preoperative radiologic findings are important when choosing treatment strategies for NSCLC, particularly for lung adenocarcinoma.[8,9]

The purpose of this retrospective study was to compare the oncologic outcomes between lobectomy and segmentectomy in patients with clinical stage IA lung adenocarcinoma, adjusted for preoperative factors including HRCT and FDG-PET/CT findings, to minimize the effect of patient selection bias. Segmentectomy and wedge resection are considerably different procedures for lung cancer; the former can be used to approach hilar lymph nodes and to get sufficient margin, whereas the latter cannot. Therefore, we excluded wedge resection from this study.

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Abbreviations and Acronyms

CI = confidence interval
FDG-PET/CT = [18F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography
GGO = ground-glass opacity
HRCT = high-resolution computed tomography
NSCLC = non–small cell lung cancer
OS = overall survival
RFS = recurrence-free survival
SUVmax = maximum standardized uptake value

PATIENTS AND METHODS

Patients

We enrolled 618 patients with clinical T1 N0 M0 stage IA lung adenocarcinoma from 4 institutions (Hiroshima University, Kanagawa Cancer Center, Cancer Institute Hospital, and Hyogo Cancer Center, Japan) between August 1, 2005 and June 30, 2010, to evaluate the significance of FDG-PET/CT. Patients with incompletely resected tumors (R1 or R2) and those with multiple tumors or previous lung operations were not included in the database. The database has been maintained prospectively. The patient data obtained from this multicenter database were retrospectively analyzed in the present study. HRCT and FDG-PET/CT followed by curative R0 resection were performed for all patients staged according to the TNM Classification of Malignant Tumors, seventh edition.[10] Mediastinoscopy or endobronchial ultrasonography was not routinely performed because all patients received preoperative HRCT and FDG-PET/CT; HRCT revealed no swelling of mediastinal or hilar lymph nodes and FDG-PET showed no accumulation in these lymph nodes. Sublobar resection was allowed in cases of complete removal of the disease, using the optional procedure instead of lobectomy for a peripheral T1 N0 M0 tumor. The other patients underwent standard lobectomy. All patients who underwent segmentectomy were suitable for lobectomy and all patients who underwent lobectomy were technically suitable for segmentectomy. Patients who had lymph node metastasis pathologically received platinum-based chemotherapy after operation.

The inclusion criteria were preoperative staging determined by HRCT and FDG-PET/CT, curative surgery without neoadjuvant chemotherapy or radiotherapy, and a definitive histopathologic diagnosis of lung adenocarcinoma. The study was approved by the institutional review boards of the participating institutions; the requirement for informed consent from individual patients was waived because the study was a retrospective review of the patient database. Of the 618 patients, 137 who underwent wedge resection were excluded; the remaining 481 were included in this analysis.

HRCT

Sixteen-row multidetector CT was used to obtain chest images independent of subsequent FDG-PET/CT examinations. For high-resolution images of the tumors, the following parameters were used: 120 kVp, 200 mA, 1- to 2-mm section thickness, 512 × 512-pixel resolution, 0.5- to 1.0-second scanning time, a high-spatial reconstruction algorithm with a 20-cm field of view, and mediastinal (level, 40 HU; width, 400 HU) and lung (level, −600 HU; width, 1600 HU) window settings. GGO was defined as a misty increase in lung attenuation without obscuring the underlying vascular markings. We defined solid tumor size as the maximum dimension of the solid component measured on lung window settings, excluding GGO.[8] CT scans were reviewed and tumor sizes were determined by radiologists from each institution.

FDG-PET/CT

Patients were instructed to fast for at least 4 hours before intravenous injection of 74 to 370 MBq FDG and were then advised to rest for at least 1 hour before FDG-PET/CT scanning. Blood glucose levels were calculated before the tracer injection to confirm a level of more than 150 mg/dL.[11] Patients with blood glucose levels of 150 mg/dL or more were excluded from the PET/CT imaging. For imaging, Discovery ST (GE Healthcare, Little Chalfont, United Kingdom), Aquiduo (Toshiba Medical Systems Corporation, Tochigi, Japan), or Biograph Sensation 16 (Siemens Healthcare, Erlangen, Germany) integrated 3-dimensional PET/CT scanner was used. Low-dose nonenhanced CT images of 2- to 4-mm section thickness for attenuation correction and localization of lesions identified by PET were obtained from the head to the pelvic floor of each patient according to a standard protocol.

Immediately after CT, PET was performed with the identical axial field of view for 2- to 4-min/table position, depending on the condition of the patient and the scanner performance. An iterative algorithm with CT-derived attenuation correction was used to reconstruct all PET images with a 50-cm field of view. An anthropomorphic body phantom (NEMA NU2-2001, Data Spectrum Corp, Hillsborough, NC) was used to minimize the variations in SUVs among the institutions.[12] A calibration factor was analyzed by dividing the actual SUV by the gauged mean SUV in the phantom background to decrease interinstitutional SUV inconsistencies; the final SUV used in this study is referred to as the revised SUVmax.[13,14] When the SUVmax ratio was expressed as the SUVmax of each institute relative to the SUVmax of the control institute, the adjustment of interinstitutional variations in SUV narrowed the range from 0.89-1.24 to 0.97-1.18. The original SUVmax values were determined by radiologists from each institution.

Follow-up Evaluation

All patients who underwent lung resection were followed up from the day of surgery. Postoperative follow-up procedures, including a physical examination and chest radiograph every 3 months and chest and abdominal CT examinations every 6 months, were performed for the first 2 years. Subsequently, a physical examination and chest radiograph were performed every 6 months, and a chest CT examination was performed every year.

Statistical Analysis

Data are presented as numbers (percent) or the median unless otherwise stated. The χ^2 test for categorical variables was used to compare frequencies, and Fisher's exact test was applied to small samples in all cohorts. McNemar tests were used to analyze the propensity-matched pair patients. Both *t* tests and Mann-Whitney *U* tests were used to compare continuous variables in all cohorts. Wilcoxon tests were used to analyze propensity-matched pair patients. Recurrence-free survival (RFS) was defined as the time from the day of surgery until the first event (relapse or death from any cause) or last follow-up. Overall survival (OS) was defined as the time from the day of surgery until death from any cause or the last follow-up. The Kaplan-Meier method was used to analyze the duration of RFS and OS; the Cox proportional hazard model was used to assess differences in RFS and OS. We applied propensity score matching to balance the assignment of the included patients and to correct for the operative procedure (lobectomy or segmentectomy), which confounded survival calculations. The variables were age, gender, solid tumor size, SUVmax, side, and lobe. Because no segmentectomy was performed for a tumor located at a middle lobe, we excluded patients who underwent middle lobectomy from the scoring for a fair comparison. Each variable was multiplied by

TABLE 1. Patient characteristics

	Lobectomy (n = 383)	Segmentectomy (n = 98)	*P* value
Age	66 (33-84)	67 (34-89)	.08
Gender			.75
Male	169 (44.1%)	45 (45.9%)	
Whole tumor size (cm)	2.2 (0.8-3.0)	1.7 (0.6-3.0)	<.001
Solid tumor size (cm)	1.5 (0-3.0)	0.5 (0-3.0)	<.001
SUVmax	2.1 (0-17)	1.2 (0-10)	<.001
Side			.005
Right	261 (68.4%)	52 (53.1%)	
Lobe			.001
Upper	200 (52.2%)	50 (51.0%)	
Middle	45 (11.7%)	0 (0%)	
Lower	138 (36.0%)	48 (49.0%)	
Lymphatic invasion	77 (20.1%)	6 (6.1%)	.001
Vascular invasion	89 (23.2%)	6 (6.1%)	<.001
Pleural invasion	51 (13.3%)	4 (4.1%)	.008
Lymph node metastasis	44 (11.5%)	1 (1.0%)	<.001

SUVmax, Maximum standardized uptake value.

a coefficient that was calculated using logistic regression analysis, and the sum of these values was taken as the propensity score for individual patients. C statistic of variables was 0.819 (95% confidence interval [CI], 0.776-0.863; $P < .0001$). After the calculation of their propensity scores, the subjects were divided into 3 groups according to tertile to compare characteristics between lobectomy and segmentectomy in each tertile. For matching, lobectomy and segmentectomy pairs with an equivalent propensity score were selected by a 1-to-1 match. Statistical Package for the Social Sciences (SPSS) software (version 10.5; SPSS Inc, Chicago, Ill) was used to statistically analyze the data.

RESULTS

Table 1 summarizes the characteristics of the 481 patients analyzed in this study. Of these, 383 patients underwent lobectomy and 98 patients underwent segmentectomy. There was no 30-day postoperative mortality in this population. The median follow-up period after surgery was 43.2 months, during which the tumor recurred in 50 patients. There were 20 local-only recurrences, including mediastinal lymph node metastasis, and 30 distant ± local recurrences. Age and gender were not significantly different between patients who underwent lobectomy and those who underwent segmentectomy. Lobectomy was performed significantly more often for patients with large whole and solid tumor size, high SUVmax, pathologically invasive tumors (presence of lymphatic, vascular, or pleural invasion), and lymph node involvement. Tumor location was significantly different between patients who underwent lobectomy and those who underwent segmentectomy. Detailed procedures in segmentectomy were shown in Table 2.

Local recurrence occurred in 17 patients who underwent lobectomy (2 involving the bronchial stump, 1 involving the hilar lymph nodes, 11 involving the mediastinal lymph nodes, and 3 involving the pleura) and 3 patients who underwent segmentectomy (1 involving the residual lobe, 1 involving the surgical stump, and 1 involving the pleura).

TABLE 2. Details of segmentectomy (n = 98)

Site	No.	Site	No.
Right		Left	
S1	4	S1 + 2	7
S2	12	S3	3
S3	3	S1 + 2 + 3	10
S6	23	S1 + 2 + 3c	1
S8	5	S4	2
S7 + 8	1	S5	1
S8 + 9	3	S4 + 5	7
S7 + 8 + 9 + 10	1	S6	10
		S8	1
		S9	3
		S6 + 8 + 9 + 10	1

Table 3 shows the multivariate analyses of distant and local RFS. Gender, solid tumor size, and SUVmax were significant independent prognostic factor for distant RFS, whereas whole tumor size was not. Regarding local RFS, solid tumor size and SUVmax were independent prognostic factors, but whole tumor size was not. RFS was not significantly different between patients who underwent lobectomy (3-year RFS, 87.3%) compared with segmentectomy (3-year RFS, 91.4%; hazard ratio [HR], 0.57; 95% CI, 0.27-1.20; $P = .14$, Figure 1, *A*). OS was not significantly different between patients who underwent lobectomy (3-year OS, 94.1%) compared with segmentectomy (3-year OS, 96.9%; HR, 0.49; 95% CI, 0.17-1.38; $P = .18$; Figure 1, *B*).

After the calculation of the propensity score, the subjects were divided into 3 groups according to tertile (Table 4). The numbers of patients in tertiles 1, 2, and 3 according to the operative procedures (lobectomy; segmentectomy) were 79 and 66, 118 and 27, and 141 and 5, respectively. Solid tumor size was smaller and SUVmax was lower in the lowest tertile group, indicating that segmentectomy trended to be performed in patients with a tumor of smaller solid tumor size and lower SUVmax. There were some differences in background characteristics, especially in the lowest tertile group. Therefore, we performed propensity score matching to compare the survival between lobectomy and segmentectomy groups.

When propensity score matching was used and variables such as age, gender, solid tumor size, SUVmax, side, and lobe were included, lobectomy and segmentectomy pairs were well matched (81 patients each) without significant differences in clinical and pathologic factors (Table 5).

Among propensity score–matched patients, no difference in RFS was identified between patients who underwent lobectomy (3-year RFS, 92.9%) compared with segmentectomy (3-year RFS, 90.9%; Figure 1, *C*). In addition, similar OSs were observed between patients who underwent

TABLE 3. Multivariate analyses for distant or local RFS

Variables	HR (95% CI)	*P* value
Multivariate analysis for distant RFS		
Model 1		
Age	1.00 (0.96-1.04)	.86
Gender		
Male vs female	2.62 (1.15-5.95)	.022
Whole tumor size (cm)	1.17 (0.60-2.27)	.65
SUVmax	1.26 (1.14-1.39)	<.001
Procedure		
Lobectomy vs segmentectomy	1.44 (0.41-5.00)	.57
Model 2		
Age	1.00 (0.96-1.03)	.80
Gender		
Male vs female	2.57 (1.14-5.78)	.023
Solid tumor size (cm)	1.86 (1.09-3.16)	.023
SUVmax	1.19 (1.06-1.34)	.003
Procedure		
Lobectomy vs segmentectomy	0.90 (0.24-3.36)	.88
Multivariate analysis for local RFS		
Model 1		
Age	1.04 (0.99-1.10)	.15
Gender		
Male vs female	0.59 (0.24-1.46)	.26
Whole tumor size (cm)	1.44 (0.66-3.12)	.94
SUVmax	1.17 (1.03-1.33)	.015
Procedure		
Lobectomy vs segmentectomy	1.06 (0.29-3.86)	.36
Model 2		
Age	1.04 (0.98-1.09)	.19
Gender		
Male vs female	0.58 (0.24-1.43)	.24
Solid tumor size (cm)	2.89 (1.52-5.50)	.001
SUVmax	1.09 (0.94-1.27)	.26
Procedure		
Lobectomy vs segmentectomy	0.54 (0.14-2.13)	.38

RFS, Recurrence-free survival; *HR,* hazard ratio; *CI,* confidence interval; *SUVmax,* maximum standardized uptake value.

lobectomy (3-year OS, 93.2%) compared with segmentectomy (3-year OS, 95.7%; Figure 1, *D*).

DISCUSSION

The current study compared oncologic outcomes between patients who underwent lobectomy and segmentectomy for clinical stage IA lung adenocarcinoma. In all cohorts, when preoperative clinical factors were not adjusted, RFS and OS of the segmentectomy group were not significantly different from those of the lobectomy group. The survival curves of the segmentectomy group appeared to be better than those of the lobectomy group. However, each patient group was different in terms of solid tumor size and SUVmax, which could affect the patient's survival.[8,9,13-16] In addition, the number of patients who had lymph node metastasis was inevitably larger in the lobectomy group than in the segmentectomy group, which also could affect the survival. To minimize patient selection bias, we used propensity score matching analyses. In the model that matched for potentially confounding variables such as age, gender, solid tumor size, SUVmax, tumor location, in lobectomy and segmentectomy pairs, there were no significant differences in clinical features or pathologic factors such as lymphatic, vascular, pleural invasion, or lymph node metastasis. Even in our matched model, RFS and OS in the segmentectomy group was similar to the lobectomy group, indicating that segmentectomy could be an optimal surgical procedure for clinical stage IA lung adenocarcinoma selected on the basis of HRCT and FDG-PET/CT.

The strength of this study was that variables such as findings from HRCT (solid tumor size) and FDG-PET (SUVmax) were included in the propensity score–matched analysis. We reported that solid tumor size on HRCT and SUVmax on FDG-PET/CT had higher predictive values with respect to pathologic invasiveness such as lymphatic, vascular, pleural invasion, and prognosis compared with whole tumor size.[8,9] In addition, once matching for solid tumor size and SUVmax, pure solid tumor and solid tumor with GGO showed equivalent survivals.[17] Indeed, whole tumor size was not an independent factor for distant or local RFS in this study, whereas solid tumor size and SUVmax were. Solid tumor size does represent tumor malignancy compared with whole tumor size. Therefore, we did not include whole tumor size in matching variables. Inasmuch as SUVmax on FDG-PET/CT was a prognostic indicator for lung adenocarcinoma, not for squamous cell carcinoma in our previous study,[16] the database included only adenocarcinoma, which is a major histologic type for NSCLC. Although several studies have indicated equivalent survivals for segmentectomy and lobectomy in patients with clinical stage IA lung cancer, to our knowledge, this is the first study adjusting for preoperative HRCT and FDG-PET/CT findings, both of which should be considered when selecting patients for limited resections such as segmentectomy. Furthermore, we used an anthropomorphic body phantom to minimize the interinstitutional variability in SUV, which may be influenced by factors such as preparation procedures, scan acquisition, image reconstruction, and data analysis.

Most previous studies that showed favorable outcomes with segmentectomy indicated this procedure for T1 N0 M0 NSCLC of 2 cm or less.[4-6] We included patients with a whole tumor size of 2 to 3 cm (ie, clinical T1b tumor) in this study. We[9] have reported that patients with T1b lung adenocarcinomas selected on the basis of HRCT and FDG-PET/CT findings could be candidates for sublobar resection with a sufficient surgical margin. Inasmuch as clinical T1b N0 M0 lung adenocarcinomas occasionally show large GGO components and/or low SUVmax (signs of

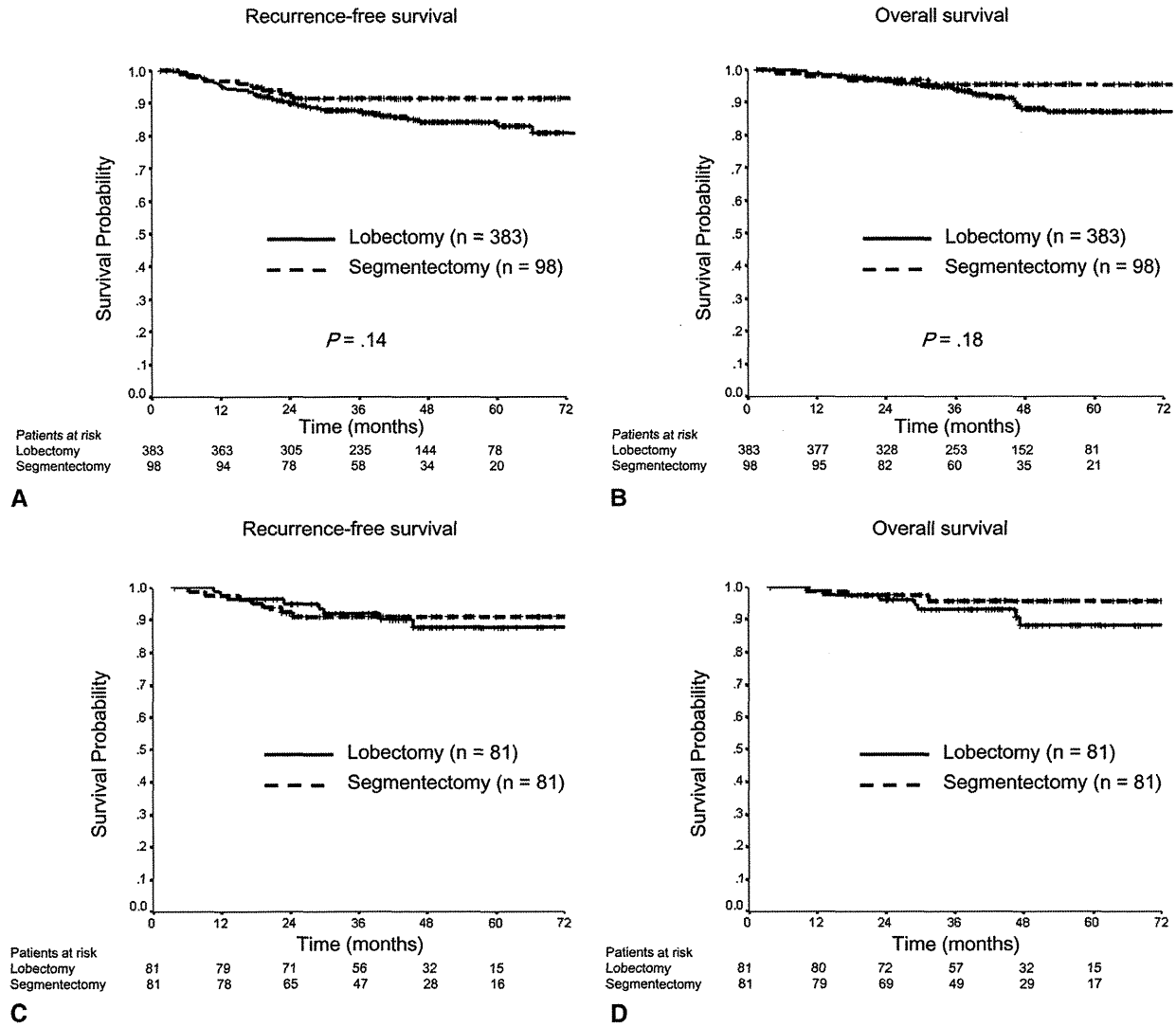

FIGURE 1. Recurrence-free survival (RFS) curves and overall survival (OS) curves for patients who underwent lobectomy and segmentectomy. A, In all cohorts, 3-year RFSs of 87.3% (mean RFS, 66.8 months; 95% confidence interval [CI], 64.6-69.4 months) and 91.4% (mean RFS, 70.3 months; 95% CI, 66.9-73.8 months) were identified for patients who underwent lobectomy and segmentectomy, respectively (hazard ratio [HR], 0.57; 95% CI, 0.27-1.20; $P = .14$). B, In all cohorts, 3-year OSs of 94.1% (mean OS, 70.4 months; 95% CI, 68.7-72.1 months) and 96.9% (mean OS, 72.9 months; 95% CI, 70.3-75.4 months) were identified for patients who underwent lobectomy and segmentectomy, respectively (HR, 0.49; 95% CI, 0.17-1.38; $P = .18$). C, In propensity score–matched patients, 3-year RFSs of 92.9% (mean RFS, 68.6 months; 95% CI, 64.9-72.2 months) and 90.9% (mean RFS, 70.2 months; 95% CI, 66.4-73.9 months) were identified for patients who underwent lobectomy and segmentectomy, respectively. D, In propensity score–matched patients, 3-year OSs of 93.2% (mean OS, 69.3 months; 95% CI, 65.8-72.7 months) and 95.7% (mean OS, 73.2 months; 95% CI, 70.6-75.8 months) were identified for patients who underwent lobectomy and segmentectomy, respectively.

low malignant behavior), such tumors could be treated with lesser resection.[9]

This study has several limitations. Because this study was retrospective, patients who underwent segmentectomy were possibly highly selective. In addition, we could not match intended procedures in the study because the database included only performed surgical procedures, not intended procedures, and patients with R1 or R2 resection were never included in the database. Most patients who underwent segmentectomy in this study tended to have relatively low-malignancy tumors, with small solid tumor size and/or low SUVmax, and thus low pathologic invasiveness. The present study revealed that large solid tumor size on HRCT and high SUVmax on FDG-PET/CT were significantly associated with both local and distant recurrences. The outcome of segmentectomy for relatively high-malignancy clinical stage IA lung adenocarcinomas with large solid tumor size and high SUVmax is unclear.

TABLE 4. Patient characteristics divided into 3 groups according to tertile based on the propensity score

	Tertile 1			Tertile 2			Tertile 3		
	L (n = 79)	S (n = 66)	*P* value	L (n = 118)	S (n = 27)	*P* value	L (n = 141)	S (n = 5)	*P* value
Age	68 (48-82)	68.5 (42-89)	.53	65 (40-83)	65 (34-86)	.92	65 (33-84)	64 (53-83)	.5
Gender			.87			.28			1.0
Male	36 (45.6%)	29 (43.9%)		46 (39.0%)	14 (51.9%)		65 (46.1%)	2 (40.0%)	
Whole tumor size (cm)	2.0 (0.8-3.0)	1.7 (0.9-3.0)	.01	1.8 (1.0-3.0)	1.6 (0.6-2.9)	.048	2.5 (1.2-3.0)	2.4 (1.5-3.0)	.51
Solid tumor size (cm)	0.5 (0-2.0)	0.3 (0-1.0)	.056	1.4 (0-2.0)	1.2 (0-2.0)	.03	2.3 (1.0-3.0)	2.2 (1.0-3.0)	.71
SUVmax	1.2 (0-4.9)	1.0 (0-4.1)	.002	1.9 (0.6-8.3)	1.9 (0.4-9.8)	.77	3.9 (0.7-16.9)	2.1 (1.5-4.3)	.13
Side			.41			1.0			1.0
Right	44 (55.7%)	32 (48.5%)		69 (58.5%)	16 (59.3%)		103 (73.0%)	4 (80.0%)	
Lobe			.51			.53			1.0
Upper	41 (51.9%)	30 (45.5%)		66 (55.9%)	17 (63.0%)		93 (66.0%)	3 (60.0%)	
Lower	38 (48.1%)	36 (54.5%)		52 (44.1%)	10 (37.0%)		48 (34.0%)	2 (40.0%)	

L, Lobectomy; *S*, segmentectomy; *SUVmax*, maximum standardized uptake value.

Although surgical procedure did not correlate with local or distant recurrence in this study, segmentectomy for such tumors (ie, with large solid tumor size or high SUVmax) should be carefully considered. A clinical trial is being conducted by the Japanese Clinical Oncology Group/West Japan Oncology Group (JCOG0802/WJOG4607L), which aims to compare the surgical results between lobectomy and segmentectomy for T1 N0 M0 NSCLC measuring 2 cm or less.[18] This prospective study includes patients with radiologically invasive tumors, such as solid dominant tumors, that have large solid tumor size on HRCT. The results of this trial may provide an important insight into this issue.

Segmentectomy is beneficial because it preserves lung function. Although the database used in this study did not incorporate lung function data, several reports have demonstrated that segmentectomy has functional advantages over lobectomy.[5,19,20] If similar oncologic outcomes are expected, segmentectomy should be considered for patients with clinical stage IA lung adenocarcinoma.

In conclusion, the oncologic outcomes of segmentectomy are similar to those of standard lobectomy for patients with clinical stage IA lung adecnocarcinoma, as determined by the matched model adjusting for preoperative clinical factors such as HRCT and FDG-PET/CT findings. Segmentectomy could be favorable for selective patients with stage IA lung adenocarcinoma.

TABLE 5. Propensity score–matched comparison of clinical and pathologic factors between patients who underwent lobectomy and segmentectomy

	Lobectomy (n = 81)	Segmentectomy (n = 81)	*P* value
Clinical factors			
Age	66 (48-82)	65 (34-86)	.68
Gender			.74
Male	37 (45.6%)	34 (42.0%)	
Whole tumor size (cm)	2.0 (1.0-3.0)	1.7 (0.6-3.0)	.11
Solid tumor size (cm)	0.7 (0-2.0)	0.8 (0-3.0)	.17
SUVmax	1.4 (0-7.0)	1.2 (0-9.8)	.23
Side			.63
Right	33 (40.7%)	37 (45.6%)	
Lobe			.23
Upper	51 (63.0%)	43 (53.1%)	
Lower	30 (37.0%)	38 (46.9%)	
Pathologic factors			
Lymphatic invasion	10 (12.3%)	6 (7.4%)	.42
Vascular invasion	6 (7.4%)	6 (7.4%)	1.0
Pleural invasion	7 (8.6%)	4 (4.9%)	.45
Lymph node metastasis	3 (3.7%)	1 (1.2%)	.63

SUVmax, Maximum standardized uptake value.

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