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 (SUVmax) 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 SUVmax.

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 SUVmax: group 1: solid tumor size ≤2 cm, SUVmax ≤1.8; group 2: solid tumor size ≤2 cm, SUVmax >1.8; group 3: solid tumor size 2–3 cm, SUVmax ≤3.6; and group 4: solid tumor size 2–3 cm, SUVmax >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 SUVmax 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
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 (SUVmax) on 18F-fluorodeoxyglucose (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 SUVmax 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 SUVmax on PET/CT [11]. Here, we attempted to employ promising factors such as solid tumor size on HRCT and SUVmax 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 SUVmax of >1.5 in these lymph nodes.

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.

FDG-PET/CT

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 χ² 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 SUVmax 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 \( \leq 2.0 \) 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 \( \leq 2.0 \) 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\(_{\text{max}}\) for predicting pathologic tumor invasiveness (lymphatic, vascular, or pleural invasion) in each solid tumor size group (solid tumor size of \( \leq 2.0 \) cm or 2–3 cm). These ROC curves identified optimal SUV\(_{\text{max}}\) cutoff values of 1.8 [area under the curve (AUC) = 0.85; sensitivity = 77.3%; specificity = 79.3%] for a solid tumor size \( \leq 2.0 \) 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\(_{\text{max}}\) cutoff values: group 1: solid tumor size \( \leq 2.0 \) cm and SUV\(_{\text{max}}\) \( \leq 1.8 \); group 2: solid tumor size \( \leq 2.0 \) cm and SUV\(_{\text{max}}\) \( > 1.8 \); group 3: solid tumor size 2–3 cm and SUV\(_{\text{max}}\) \( \leq 3.6 \); and group 4: solid tumor size 2–3 cm and SUV\(_{\text{max}}\) \( > 3.6 \).

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 \( \leq 2.0 \) cm and SUV\(_{\text{max}}\) \( \leq 1.8 \); proposed c-T1b (groups 2 + 3): solid tumor size \( \leq 2.0 \) cm and SUV\(_{\text{max}}\) \( > 1.8 \), solid tumor size 2–3 cm and SUV\(_{\text{max}}\) \( \leq 3.6 \); proposed c-T1c (group 4), solid tumor size 2–3 cm and SUV\(_{\text{max}}\) \( > 3.6 \).

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

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

SUV\(_{\text{max}}\): maximum standardized uptake value.
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 SUVmax 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 versus proposed c-T1b, \( P < 0.0001 \); proposed c-T1b versus proposed c-T1c, \( P = 0.015 \) (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 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].

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.
references