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Prognostic value of preoperative FDG-PET in stage IA lung adenocarcinoma

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ABSTRACT

Background: Maximum standardized uptake value (SUVmax) of 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) has been found to have prognostic value. We previously reported the correlation between SUVmax and pathological invasive area, and determined an SUVmax cut-off value of 2.15 for predicting the recurrence potential of an invasive area of diameter 5 mm. Here, we evaluate the validity of FDG-PET for prediction of recurrence in pathological stage IA lung adenocarcinoma.

Methods: From February 2006 to May 2008, 100 patients with pathological stage IA lung adenocarcinoma underwent complete resection at our hospital. Tumors were classified as air-type or solid-type based on thin-section computed tomography (TS-CT) findings and the influence of TS-CT classification, SUVmax, and clinicopathologic features were evaluated in terms of the incidence of recurrence.

Results: Unlike air-type adenocarcinomas, recurrent disease was detected in 8 of 62 solid-type adenocarcinomas. SUVmax and diameter of invasive area were significantly correlated with recurrence and a shorter time to recurrence. All 8 recurrent cases had pathological invasive area >5 mm. All except one case of recurrence were solid-type adenocarcinomas with SUVmax ≥ 2.15. Three-year disease-free survival rates were 100% in air-type adenocarcinomas, 97.1% in solid-type adenocarcinomas with SUVmax < 2.15, and 74.1% in solid-type adenocarcinoma with SUVmax ≥ 2.15.

Conclusion: Combined evaluation of TS-CT classification and SUVmax had significant value in predicting recurrence in stage IA lung adenocarcinoma, reflecting the aggressiveness of primary lung adenocarcinoma. Prediction of tumor aggressiveness could contribute to decision-making regarding the choice of surgical procedure and treatment after surgery.

1. Introduction

The recent increasing use of thin-section computed tomography scanning (TS-CT) has facilitated the detection of small-sized peripheral lung adenocarcinoma. Surgical resection offers a significant chance of cure for patients with early stage non-small-cell lung cancer (NSCLC); however, even in cases of stage IA adenocarcinoma, some patients experience recurrence within 5 years after surgery.

Many investigators have reported the relationship between TS-CT findings and aggressiveness and survival in patients with lung adenocarcinoma [1]. On TS-CT images, solid areas of a nodule may reflect collapsed alveoli, foci of fibrosis, or tumors with an invasive growth pattern, whereas areas of ground-glass opacity (GGO) represent components of bronchioloalveolar carcinoma (BAC) [1–4]. The authors focused on solid areas seen on TS-CT and reported that small pulmonary adenocarcinomas could be classified according to attenuation on TS-CT images as either 'air-containing-type' (air-type) or 'solid-density-type' (solid-type) [2,4]. No microscopic evidence of metastasis has been revealed in air-type adenocarcinomas, nor any relapses or deaths after resection. In contrast, patients with solid-type adenocarcinomas demonstrated a poor prognosis. Unlike air-type tumors, some solid-type tumors have pathological invasive areas; however, it is difficult to discriminate these areas from the solid component based on the TS-CT findings. The size of the invasive area is related to tumor aggressiveness [1]. Invasive areas of diameter ≤5 mm are reported to have a good prognosis; compared with true BAC type, a small component of invasive tumor does not adversely affect prognosis [1].

Several recent studies have demonstrated the prognostic value of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) for primary lung cancer [5–9]. We previously reported a

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significant correlation between SUVmax (maximum standardized uptake value) and the pathological invasive area of primary lung adenocarcinoma, and determined an SUVmax cut-off value of 2.15 for predicting recurrence potential for an invasive area of diameter 5 mm [10]. Based on this cut-off value, sensitivity was 88.3% and specificity was 84.6% [10]. On the basis of these findings, we evaluated the validity of cut-off SUVmax on FDG-PET to predict recurrence in pathological stage IA lung adenocarcinoma.

2. Materials and methods

2.1. Patients

We retrospectively reviewed the TS-CT and PET reports of 100 patients (39 male, 61 female) who had undergone complete surgical resection of peripheral adenocarcinomas with pathologic T1N0M0 (stage IA) at Kanagawa Cancer Center Hospital, Japan, from March 2006 to May 2008. Of these patients, 40 underwent segmentectomy or wedge resection. Preoperative TS-CT and whole-body FDG-PET were performed on all patients for staging and evaluation of resectability. None of the patients received neo-adjuvant chemotherapy or radiation therapy.

2.2. TS-CT evaluation

All 100 patients underwent TS-CT scanning within 4 weeks prior to surgery. TS-CT images were acquired using an Aquillion CT scanner (Toshiba Medical Systems, Tokyo, Japan). TS-CT images targeted to the tumors were obtained serially at 120 kVp and 200 mAs, with 1–2 mm section thickness, pitch of 1, 1–2 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 lung window settings (level, −600 HU; width, 1600 HU). The TS-CT findings were evaluated and the maximum diameters of the tumor on mediastinal and lung window setting images were measured. The ratio of the maximum diameter of the tumor on mediastinal windows to that on lung windows was calculated. Tumors were defined as air-type for ratio values ≤50% or as solid-type for ratio values > 50%.

2.3. FDG-PET/CT evaluation

All PET/CT studies were performed within 4 week prior to surgery using a lutetium oxyorthosilicate-based whole-body PET/CT scanner (Biograph 16 HI-REZ; Siemens). ^{18}F-FDG (FDG scan Injectable; Nihon Medi-physics Co. Ltd.) was purchased via a delivery system. All patients fasted for at least 6 h before intravenous administration of 130–371 (mean ± SD, 251.4 ± 63.7) MBq ^{18}F-FDG. Prior to tracer administration, the blood sugar level was checked. All 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. Tumors were classified as having a high or low SUVmax using an SUVmax cut-off point of 2.15.

2.4. Pathological evaluation

Hematoxylin and eosin, and elastica van Gieson staining were performed on all sections to evaluate the diameter of invasive area, lymphatic and vascular invasion, and pleural involvement. Immunohistochemical evaluations were performed using the avidin–biotin–peroxidase complex method with 3-μm-thick sections of formalin-fixed, paraffin-embedded specimens. A monoclonal antibody against the Ki-67 antigen (MIB-1; MBL, Nagoya, Japan; 1:100 dilution) was used to assess the proportion of proliferating tumor cells. The Ki-67 labeling index was defined as the ratio of MIB-1-stained tumor cells to all tumor cells counted, multiplied by 100. To evaluate the Ki-67 labeling index, stained tumor cells were counted in at least three high-power fields that showed the highest positivity for each section.

Table 1
Patient and tumor characteristics[a].

CT finding	Air-type (n = 38)	Solid-type (n = 62)	p-Value
Median age (range) (yr)	67(44–77)	68(40–83)	.112
Gender (male/female)	14/24	25/37	.729
SUVmax	0.97 ± 0.95	3.28 ± 3.12	<.001
Low (<2.15)	35 (92.1)	35 (56.5)	<.001
High (≥2.15)	3 (7.9)	27 (43.5)	
Tumor size (mm)	18.6 ± 5.4	20.5 ± 5.7	.602
0–20 mm	25 (65.8)	29 (46.8)	.217
21–30 mm	13 (34.2)	33 (53.2)	
Type of surgical procedure			
Lobectomy	9 (23.7)	51 (82.3)	< .001
Sublobar resection	29 (76.3)	11 (17.7)	
Histology			
BAC	24 (63.2)	13 (21.0)	< .001
Mucinous BAC	0(0)	3 (4.8)	
Non-BAC	14 (36.8)	46 (74.2)	
Lymphatic or vascular invasion			
Negative	38(100)	46 (74.2)	< .001
Positive	0(0)	16 (25.8)	
Invasive area size (mm)			
≤5	–	36 (58.1)	
>5	–	26 (41.9)	
Ki-67 index			
<25	–	50(80.6)	
≥25	–	12 (19.4)	

[a] Data are presented as median (range) or number (%) of patients. SUVmax = maximum standard uptake value; BAC = bronchioloalveolar carcinoma.

2.5. Statistical analysis

Statistical analysis was performed using SPSS software (Dr. SPSS II. for Windows, Tokyo, Japan, released 2001). Disease-free survival was calculated and drawn using the Kaplan–Meier method, and groups were compared using the log-rank statistic. An exact χ^2 test was used to analyze the relationship between risk of recurrence and histopathological findings, SUVmax, tumor size, and type of surgery. Differences were considered statistically significant when $p < 0.05$.

3. Results

3.1. Patient characteristics

The characteristics of patients and tumors are listed in Table 1. Based on the TS-CT findings, there were 38 patients with air-type adenocarcinomas and 62 patients with solid-type adenocarcinomas. The majority of air-type adenocarcinomas (92.1%) showed low SUVmax (<2.15); for solid-type adenocarcinomas, 35 cases (56.5%) showed low SUVmax and the remaining 27 cases (43.5%) showed high SUVmax (≥2.15).

Of the air-type adenocarcinomas, 24 (63.2%) were classified as BAC without stromal destruction and the others were classified as mixed-type adenocarcinoma. In contrast, of the solid-type adeno-