Clinical Significance of Positron Emission Tomography in Subcentimeter Non-Small Cell Lung Cancer

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Background. This study evaluated the clinical significance of maximum standardized uptake value (SUVmax) on positron emission tomography (PET) in patients with subcentimeter non-small cell lung cancer (NSCLC).

Methods. Between 2008 and 2014, 189 patients were investigated preoperatively by PET for c-N0 subcentimeter NSCLC, and SUVmax was reviewed. Pathologic invasiveness (PI) was defined as having at least one of the following factors: lymphatic invasion, vascular invasion, pleural invasion, or nodal metastasis. Survival rates were calculated by Kaplan-Meier estimation methods using the log-rank test.

Results. Mean SUVmax was 1.7 ± 1.8 (range, 0.6 to 13.0), and the median was 1.0. PI was found in 28 (15%) patients with subcentimeter NSCLC. Multivariate analysis revealed that SUVmax was an independent significant clinical predictor of PI ($p = 0.0251$) and a prognostic factor of overall survival (OS) ($p = 0.0485$). A receiver operating characteristics curve elucidated the predictive cutoff value of PI as SUVmax = 2.0. The high-SUVmax group (SUVmax >2.0; n = 42) had significantly more radiologically pure-solid lesions (91% vs 14%; $p < 0.0001$) and postoperative nodal involvement (12% vs 0%; $p < 0.0001$) than the low-SUVmax group (SUVmax ≤2.0; n = 147). The 5-year lung cancer–specific OS (LCS-OS) elucidated significant difference between the high-SUVmax and low-SUVmax arms of the study (LCS-OS: 92.3% vs 96.9%, respectively; $p = 0.0054$), and cancer recurrence was found exclusively in pure-solid subcentimeter NSCLC on thin-section computed tomography. In the high-SUVmax arm of the study, lobectomy was associated with better 3-year recurrence-free survival compared with sublobar resection despite the subcentimeter disease (88.3% vs 50.0%; $p = 0.0453$).

Conclusions. SUVmax on PET reflected tumor invasiveness and had a great impact on the prognosis of subcentimeter NSCLC, especially when a tumor showed a pure-solid appearance on a thin-section computed tomography scan.

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Because of the rapid advances of radiologic modalities including thin-section computed tomography (CT), small and early-stage lung cancers have been detected in daily practice [1]. Moreover, the opportunity to detect subcentimeter non-small cell lung cancer (NSCLC) is gradually increasing [2–6]. Tumor size is one of the most evident prognostic factors in a clinical T descriptor [7]. The eighth edition of the tumor, node, and metastasis (TNM) classification of lung cancer suggests that the prognoses of small NSCLCs are evidently different based on tumor size, and these experts recommend further changes to subclassify T1 into T1a (≤1 cm), T1b (>1 to ≤2 cm), and T1c (>2 to ≤3cm) [8, 9]. However, even c-N0 subcentimeter NSCLCs are not always in the early stage, and these tumors sometimes have nodal metastases and potential spread to locoregional or distant lesions after surgical resection [3, 5]. This finding indicates that "tumor size less than 1 cm" does not always indicate early-stage disease or absence of tumor spread. Additionally, the malignant behavior of these tumors is considered to be fully related to consolidation status on thin-section CT scans even for subcentimeter NSCLCs [3, 5].

Fluorine 18 (^{18}F)–fluorodeoxyglucose PET (FDG-PET) is widely used as an accurate noninvasive imaging test for identifying pulmonary malignant lesions. In general, the appropriate roles of FDG-PET in the evaluation of subcentimeter NCSLC remain unclear, mainly because of the high frequency of false-negative results caused by limitations in the resolution of the PET scanner, especially for small adenocarcinomas with a predominant lepidic component [10–12]. Conversely, we previously reported that FDG-PET was potentially effective to predict nodal involvement of subcentimeter NSCLC, which was strongly correlated with the consolidation status based on the findings of thin-section CT. Hence, FDG-PET could be a promising method as a quantitative assessment to predict the potential for malignancy even for subcentimeter lesions [3].

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Nonetheless, there are few data on the clinical and prognostic significance of FDG-PET for nodules that are 1 cm or less in diameter. For further evaluation of malignant potentials and to predict oncologic outcomes in patients with subcentimeter NSCLC, it is necessary to elucidate the clinicopathologic features, prognosis, and appropriate operative strategies. Therefore, in the current study, we retrospectively reviewed surgically resected c-N0 subcentimeter NSCLCs with a preoperative FDG-PET evaluation in our institution to explore the clinicopathologic significance of FDG-PET in this cohort.

Material and Methods

Study Population

Between 2008 and 2014, we retrospectively evaluated 189 patients with a preoperative FDG-PET evaluation for surgically resected c-N0 subcentimeter NSCLC (ie, 1 cm or less in size). This retrospective study was performed under a waiver of authorization approved by the Institutional Review Board of Juntendo University School of Medicine, Tokyo, Japan.

Fluorodeoxyglucose–Positron Emission Tomography/Computed Tomography

PET was performed, and the maximum standardized uptake value (SUVmax) was recorded for all patients. In all cases, a PET/CT scan was performed at the Yotsuya Medical Cube (Tokyo, Japan). The technique used for the FDG-PET/CT scanning was as follows: All patients were asked to fast for at least 6 hours before FDG injection to minimize their blood insulin level and normal tissue glucose uptake. They were then injected intravenously with 3.5 MBq/kg of ^{18}F-FDG, and static emission images were obtained 60 minutes after the injection. Image acquisition was performed using a Discovery ST PET/CT scanner (GE Medical Systems, Waukesha, WI). After CT image acquisition, emission scanning was performed from the head to the midthigh in six bed positions. The acquired PET/CT data were reconstructed to volumetric images with a two-dimensional-OSEM (ordered-subsets expectation-maximization) algorithm (2 iterations/15 subsets) incorporating CT-based attenuation correction. All PET/CT images were interpreted by one or two experienced nuclear medicine radiologists. A workstation (Xeleris; Elegems, Haifa, Israel) was used for image display and analysis, and SUVmax of the primary tumor was obtained.

Radiologic Evaluations on Thin-Section Computed Tomography

Our group reviewed the findings of the preoperative thin-section CT scans in detail for all patients. Tumor size was determined preoperatively based on the thin-section CT scan findings. In addition, all tumors were subsequently evaluated to estimate the extent of ground-glass opacity (GGO) by thin-section CT scan with 2-mm collimation. The consolidation tumor ratio (CTR) was defined as the ratio of the maximum size of consolidation to the maximum tumor size on thin-section CT scan [13]. Pure-GGO tumor was defined as a lung tumor without a solid component (ie, CTR = 0); part-solid tumor was defined as a lung tumor with both a GGO and a solid component (ie, 0 < CTR < 1.0); whereas pure-solid tumor was defined as a tumor showing only consolidation without GGO on thin-section CT (ie, CTR = 1.0) [14, 15]. With regard to clinical nodal assessment, clinical-N0 meant nonenlarged lymph nodes on thin-section CT or negative uptake on PET/CT. Invasive modalities for mediastinal lymph node staging, including mediastinoscopy or endobronchial ultrasound-guided transbronchial needle aspiration, were used preoperatively when nodal involvement was suspected based on radiologic findings.

Histologic and Pathologic Evaluations

All patients in the present study were reclassified according to the TNM classification of malignant tumors, 7th edition [7]. Among the cases of subcentimeter NSCLCs, lung adenocarcinoma was classified according

Table 1. Clinicopathologic Characteristics

Factors	No. (%), Mean ± SD (range)
Sex (male/female)	76 (40)/113 (60)
Age (years)	64.0 ± 10.2 (27–88)
Pack-year smoking	17.8 ± 28.2 (0–175)
CEA (ng/mL)	3.0 ± 4.8 (0.2–45.6)
SUVmax	1.7 ± 1.8 (0.6–13.0)
Maximum tumor dimension (mm)	8.6 ± 1.9 (2–10)
Consolidation status	
Pure-GGO/part-solid/pure-solid	49 (26)/81 (43)/59 (31)
Operative procedure	
Lobectomy/segmentectomy/wedge	84 (44)/60 (32)/45 (24)
Histologic classification	
AAH/AIS/MIA/LPA	6 (3)/42 (22)/36 (19)/31 (16)
Other invasive adenocarcinoma	60 (32)
Squamous cell carcinoma	9 (5)
Other NSCLC	5 (3)
Pathologic nodal involvement (present)	5 (3)
Lymphatic invasion (present)	15 (8)
Vascular invasion (present)	15 (8)
Pleural invasion (present)	13 (7)
Pathologic invasiveness[a] (present)	28 (15)
Pathologic stage	
IA/IB/IIA/IIB/IIIA/IIIB	173 (92)/11 (6)/3 (1)/0 (0)/3 (1)/0 (0)

[a] Pathologic invasiveness is defined as having at least one of the following factors: lymphatic, vascular, and pleural invasion.

Categorical data are shown as numbers (%) and continuous data as mean ± SD (range).

AAH = atypical adenomatous hyperplasia; AIS = adenocarcinoma in situ; CEA = carcinoembryonic antigen; GGO = ground-glass opacity; LPA = lepidic-predominant invasive adenocarcinoma; MIA = minimally invasive adenocarcinoma; NSCLC = non-small cell lung cancer; SUVmax = maximum standardized uptake value.