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FDG-PET in lung cancer

The maximum standardized uptake value (SUVmax) on FDG-PET is a strong predictor of local recurrence for localized non-small-cell lung cancer after stereotactic body radiotherapy (SBRT)

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ABSTRACT

Background: The maximum standardized uptake value (SUVmax) of FDG-PET may predict local recurrence for localized non-small-cell lung cancer (NSCLC) after stereotactic body radiotherapy (SBRT).
Methods: Among 195 localized NSCLCs that were treated with total doses of either 40 Gy or 50 Gy in 5 SBRT fractions, we reviewed those patients who underwent pre-treatment FDG-PET using a single scanner for staging. Local control rates (LCRs) were obtained by the Kaplan–Meier method and a log-rank test. Prognostic significance was assessed by univariate and multivariate analyses.
Results: A total of 95 patients with 97 lesions were eligible. Median follow-up was 16.0 months (range: 6.0–46.3 months). Local recurrences occurred in 9 lesions. By multivariate analysis, only the SUVmax of a primary tumor was a significant predictor ($p = 0.002$). Two years LCRs for lower SUVmax (<6.0; $n = 78$) and higher SUVmax ($\geqslant 6$; $n = 19$) were 93% and 42%, respectively. In subgroups with T1b and T2, LCRs were significantly better for lower SUVmax than for higher SUVmax ($p < 0.0005$ and $p < 0.01$). In both subgroups that received 40 Gy and 50 Gy, LCRs were also significantly better for lower SUVmax than for higher SUVmax ($p < 0.001$ and $p < 0.01$).
Conclusions: SUVmax was the strongest predictor for local recurrence. A high SUVmax may be considered for dose escalation to improve local control. Additional follow-up is needed to determine if SUVmax is correlated with regional recurrence, distant metastasis, and survival.
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Although surgical resection is the standard of care for operable stage I non-small-cell lung cancer (NSCLC), some patients are inoperable because of co-morbidities, such as chronic obstructive pulmonary disease, cardiac disease, and/or old age. In addition, some patients refuse surgery. For these patients, stereotactic body radiotherapy (SBRT) is a promising new technology that provides accurate delivery of a high dose of radiation to a target lesion with a short treatment period. This radiotherapeutic dose concentration results in increased biologic effects to a target region compared with conventional fractionated radiotherapy, and also minimizes toxicity to the surrounding normal tissues. Although SBRT has a rather short history in the treatment of lung cancers, its outcomes have been reported to be equivalent to surgical outcomes [1–4] and prospective studies are currently underway [5,6].

[^{18}F] Fluorodeoxyglucose positron emission tomography (FDG-PET) has been recognized as an important tool for the initial staging of NSCLC [7,8]. In addition, the maximum standardized uptake value (SUVmax) of FDG in a primary tumor was shown to be an independent prognostic factor for survival for patients with surgically resected NSCLC [9–11].

In this study, we retrospectively investigated whether or not pre-treatment FDG-PET could predict local control (LC) in patients with localized NSCLC treated with SBRT.

Patients and methods

Patients

From November 2006 through July 2010, 186 patients with 195 localized NSCLCs (T1a-4N0M0) were treated with total doses of either 40 Gy or 50 Gy in 5 SBRT fractions with radical intent in the Ofuna Chuo Hospital. In addition to pathologically proven NSCLC cases, these patients included those with clinically diagnosed NSCLC with subsequent tumor growth on CT scans, increases of tumor markers, and/or elevated SUVmax on FDG-PET. The reasons for unproven histology were negative pathological studies,

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patients' refusals, or technical difficulties when attempting biopsies. Among all the patients, a total of 157 (80.5%) underwent ^{18}F-FDG PET scans for staging before treatment. For this study, we selected eligible patients who were followed for more than 6 months after their treatments and who underwent ^{18}F-FDG PET scans before the treatment by a single scanner at Yuai Clinic, in order to avoid errors arising from different scanners and the measurement methods.

Patient characteristics recorded at baseline included age, sex, operability, tumor cell type, location (central [6] or peripheral), tumor maximum diameter, and clinical stage (according to the TNM 7th edition staging system). This retrospective study was approved by the ethics committee of Ofuna Chuo Hospital (No. 2010-005). Informed consent was obtained from patients for the staging tests, treatments, and follow-up studies.

FDG-PET and data analysis

Each patient received an FDG-PET test before SBRT. After fasting for 6 h, 3.5 MBq/kg body weight of FDG was intravenously injected if the patient's blood sugar level was lower than 200 mg/dl. Image acquisition was started 60 min after the injection using a single PET/CT combined scanner (Eminence-SOPHIA, Shimadzu, Kyoto, Japan). Image emission data from the eyes to the mid-thigh area were acquired over a period of approximately 20 min. After attenuation corrections were made for the obtained image data, they were reconstructed using a dynamic row-action expectation maximization algorithm [9]. Then, the reconstructed sectional images were evaluated visually and quantitatively using the SUVmax inside a volume of interest (VOI) placed on the lesions. SUVmax was calculated by: [(maximum activity in VOI)/(volume of VOI)]/[(injected FDG dose)/(patient weight)].

SBRT

We have previously reported the details for our SBRT technique [10,11]. In general, we treated peripheral NSCLC with a total dose of 50 Gy in 5 fractions. The prescribed dose was defined as 80% of the maximum dose in the planning target volume (PTV). The dose covering 95% of the PTV (D95) was consistent with the prescribed dose [10,11]. For cases where the target lesions were located adjacent to a critical organ, such as a main bronchus, pulmonary artery, esophagus, or heart, we treated patients with a decreased total dose of 40 Gy in 5 fractions. In our definition of treatment dose, the biologically effective doses assuming α/β ratios of 10 Gy (BED10) for the prescribed doses of 40 Gy and 50 Gy in 5 fractions at the periphery of the PTV were 72 Gy and 100 Gy, respectively, and those at the isocenter were 100 Gy and 141 Gy, respectively.

Follow-up

Our follow-up procedures were previously described in detail [12]. In brief, all patients were followed-up monthly during the first 6 months. CT scans were performed at 1 and 3 months after SBRT and at 3-month intervals during the first 2 years thereafter. Subsequently, follow-up interviews and CT scans were obtained at 4–6-month intervals. In addition, FDG-PET and brain MRI were performed at 1 year after SBRT.

Statistical analysis

Differences in local controls were compared using Kaplan–Meier curves and log-rank tests. Univariate and multivariate Cox regression analyses were used to determine if any of the clinical or treatment-related variables were predictors of local control. For all tests, a p-value < 0.05 was considered significant. Statistical analyses used SPSS, Version 17.0 software (SPSS, Inc., Chicago, IL).

Results

From a total of 157 NSCLC patients with staging PET and SBRT, 95 patients with 97 lesions were eligible for this study. They included a total of 60 patients with pathologically proven NSCLC and 37 patients with clinically diagnosed NSCLC; that is, not pathologically proven. These patients' characteristics are shown in Table 1. The median follow-up period was 16.0 months (range: 6.0–46.3 months). Their median age was 77 years (range: 60–89 years). A total of 77 tumors were treated with 50 Gy in 5 fractions, and 20 tumors were treated with 40 Gy in 5 fractions in order to reduce treatment-related risks.

On FDG-PET studies, the median SUVmax in pathologically proven and unproven primary tumors were 3.6 (range: 0.7–13.3) and 3.4 (range: 0.7–12.2), respectively; these were not significantly different ($p = 0.97$). One-year and 2-year local control rates for primary tumors with malignant pathologies were 93% and 83%, respectively, and for those that were unproven, these rates were 100% and 78%, respectively; these rates from pathologically proven and unproven tumors were not significantly different ($p = 0.74$) (Fig. 1). Therefore, we consolidated the data for pathologically proven and unproven cases and analyzed these together.

Local, regional, and distant recurrences occurred in 9, 7, and 15 patients, respectively. There were 14 cause-specific deaths and 12 deaths due to other reasons. Local recurrences occurred in 6/9 (67%) cases within 16 months and in 9/9 (100%) cases within 24 months.

The results of univariate and multivariate analyses for local control are shown in Table 2. From the univariate analyses, T stage ($p = 0.003$), tumor diameter ($p < 0.001$), the total dose ($p = 0.035$),

Table 1
Patients and tumor characteristics.

	Pathologically Dx NSCLC	Clinically Dx NSCLC
Total	60	37
Median age	77(61–89)	77(60–89)
Gender		
Male	49	25
Female	11	12
Operability		
Operable	19	4
Inoperable	41	33
Median maximum diameter	2.8(1.0–6.2)	2.4(1.0–4.7)
T classification		
T1a	18	19
T1b	18	9
T2a	19	9
T2b	2	0
T3	0	0
T4	3	0
Histology		
Adenocarcinoma	29	0
Squamous cell ca.	19	0
Unclassified NSCLC	12	0
Histologically unproved	0	37
Location		
Central	17	12
Peripheral	43	25
Total dose		
50 Gy/5 fr	49	28
40 Gy/5 fr	11	9

A total of 97 patients were treated; 93 patients treated once and 2 patients treated twice.
Abbreviations: Dx, diagnosed; NSCLC, non-small-cell lung cancer.