Role of Positron Emission Tomography/Computed Tomography Findings for Adjuvant Chemotherapy Indications in Stage T1b-2aN0M0 Lung Adenocarcinoma

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Background. **This study aimed to determine the significance of the maximum standardized uptake value (SUV_{max}) on 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) images on postoperative adjuvant chemotherapy for lung adenocarcinoma.**

Methods. **We assessed recurrence-free interval (RFI) and overall survival (OS) based on SUV_{max} values derived from preoperative FDG-PET/CT images in 174 consecutive patients with completely resected pathologic stage T1b-2aN0M0 lung adenocarcinoma.**

Results. **Ninety patients received adjuvant chemotherapy and 84 did not. Adjuvant chemotherapy conferred benefits on RFI and OS when compared with observation ($p = 0.007$ and $p = 0.004$, respectively). Multivariate Cox regression analyses revealed SUV_{max} as an independent prognostic factor for RFI. RFI and OS were significantly longer for patients who received adjuvant chemotherapy compared with those who did not in the group with SUV_{max} greater than or equal to 2.6 ($p < 0.001$ and $p < 0.001$, respectively). However, RFI and OS did not differ significantly between such patients in the group with SUV_{max} less than 2.6 ($p = 0.421$ and $p = 0.452$, respectively).**

Conclusions. **Preoperative SUV_{max} determined from FDG-PET/CT images reflected the effect of adjuvant chemotherapy after complete resection in patients with pathologic stage T1b-2aN0M0 lung adenocarcinoma. Indications for postoperative adjuvant chemotherapy among patients with lung adenocarcinoma might be more precisely determined using SUV_{max} derived from FDG-PET/CT images together with tumor size.**

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Non–small cell lung cancer (NSCLC) is the most common cause of cancer-related deaths worldwide, and adenocarcinoma is the most common subtype, accounting for almost half of all lung cancers [1]. One Japanese study found postsurgical 5-year survival rates of 83.9% and 66.3% for patients with stages IA and IB NSCLC, respectively [2]. Attempts have been made to improve the prognosis using adjuvant chemotherapy, and a pooled analysis of the findings from 5 prospective randomized clinical trials has shown a prognostic advantage of cisplatin-based chemotherapy for patients with stages II and III lung cancer [3]. Tegafur-uracil has been found effective in Japan against stage IA tumors larger than 2 cm and against stage IB lung cancer [4–6].

However, adjuvant chemotherapy for stage I lung cancer improved 5-year survival rates by 3% to 5% [4, 5], and additional predictive factors are required to identify patients who will derive a greater benefit from adjuvant chemotherapy. We previously found that the maximum standardized uptake value (SUV_{max}) on 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) images is an important preoperative factor for predicting grades of pathologic malignancy and prognosis among patients with lung adenocarcinoma [7–11]. Therefore, we investigated whether or not SUV_{max} could predict the effects of postoperative adjuvant chemotherapy in patients with pathologic stage T1b-2aN0M0 lung adenocarcinoma.

Patients and Methods

Between January 2006 and March 2011, we enrolled 174 consecutive patients from Hiroshima University, Hiroshima, Japan, and Hyogo Cancer Center, Hyogo, Japan, who had completely resected lung adenocarcinoma at pathologic stage IA larger than 2 cm in diameter (T1bN0M0) and stage IB (T2aN0M0). These 2 stages are eligible for adjuvant chemotherapy with tegafur-uracil in Japan. Adjuvant chemotherapy was performed at the discretion of the individual physician and according to the patient's wishes. All patients were assessed by FDG-PET/CT before operation and were staged according to the

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Abbreviations and Acronyms

AUC	= area under the curve
CT	= computed tomography
FDG	= 18F-fluorodeoxyglucose
FDG-PET/CT	= 18F-fluorodeoxyglucose positron emission tomography/computed tomography
FOV	= field of view
NSCLC	= non–small cell lung cancer
OS	= overall survival
PET	= positron emission tomography
PET/CT	= positron emission tomography/computed tomography
RFI	= recurrence-free interval
ROC	= receiver operating characteristic
SUV_{max}	= maximum standardized uptake value

TNM Classification of Malignant Tumors, 7th edition [12]. Patients with incompletely resected tumors or multiple tumors or those who had undergone previous lung operations were excluded from the study. Segmentectomy was considered in patients with clinical stage IA tumor that could be removed completely with ample surgical margins. No lymph node metastasis was confirmed intraoperatively using rapid frozen section for enlarged lymph nodes or lymph nodes in the thoracic cavity that were suspected to be diseased. When nodal metastasis was apparent or doubtful, lobectomy was chosen instead. Systematic lymphadenectomy including hilar and mediastinal node dissection can be performed in segmentectomy but not in wedge resection. Wedge resection, therefore, was performed for a tumor that consisted mainly of a ground-glass opacity component on high-resolution CT. This study was approved by our institutional review boards, which waived the requirement for informed consent from individual patients for this retrospective review.

18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography

The patients fasted for at least 4 hours before receiving an intravenous injection of 74 to 370 MBq of FDG. They relaxed for at least 1 hour and then were assessed by FDG-PET/CT. Blood glucose levels of less than 150 mg/dL were confirmed before tracer injection. Patients with blood glucose values greater than or equal to 150 mg/dL were excluded from PET/CT image acquisition. Images were obtained using Discovery ST (GE Healthcare, Little Chalfont, UK) or Biograph Sensation16 (Siemens Healthcare, Erlangen, Germany) integrated PET/CT scanners. Low-dose unenhanced CT images of 2- to 4-mm sections for attenuation correction and localization of lesions identified by PET were obtained from the head to the pelvic floor of each patient using a standard protocol. Immediately after CT, PET covered the identical axial field of view for 2 to 4 minutes per table position depending on the condition of the patient and scanner performance. All PET images with a 50-cm field of view were reconstructed using an iterative algorithm with CT-derived attenuation correction. The SUV_{max} for each patient was established by drawing regions of interest around the primary tumor on attenuation-corrected FDG-PET/CT images and calculated using the integrated software within the PET/CT scanner based on the following formula: SUV_{max} = [*C* (microcurie per milliliter)/*ID* (microcurie)]/*w*, where *C* represents activity at a pixel within the tissue identified by regions of interest and *ID* represents the injected dose per kilogram of body weight (*w*). We used SUV_{max} because measured values are less variable than are those of mean SUV [13].

Follow-Up Evaluation

All patients were followed from the day of the surgical procedure. Postoperative follow-up procedures for the first 2 years comprised physical examinations and chest roentgenograms every 3 months and chest and abdominal CT imaging every 6 months. Thereafter, the patients were followed by physical examinations and chest roentgenograms every 2 months and annual CT assessments.

Statistical Analysis

Summarized data are presented as numbers or means ± standard deviation unless otherwise stated. Frequencies were compared using the χ^2 test for categorical variables, and Fisher's exact test was applied to small samples. Continuous variables were compared using the unpaired *t* test. Receiver operating characteristic (ROC) curves of SUV_{max} and tumor size were analyzed, and recurrence was predicted by comparing the area under the curve (AUC). The patient population was subdivided based on cutoffs for SUV_{max} and tumor size derived from ROC curves. Recurrence-free interval (RFI) was defined as the interval between the surgical procedure and the first event (relapse or death from lung cancer). Survival was analyzed using the Kaplan-Meier method and assessed using the log-rank test. Predictors of recurrence were assessed by univariate logistic regression analysis, and the potential independent effects of SUV_{max} on RFI were assessed by multivariate analyses using the Cox proportional hazards model. A p value less than 0.05 was considered statistically significant. Data were statistically analyzed using EZR (Saitama Medical Centre, Jichi Medical University, Kanda, Japan, 2012), which is a graphic user interface for R, version 2.13.0 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Table 1 shows the clinicopathologic characteristics of the 174 patients evaluated in this study, of whom 90 (51.7%) received an adjuvant chemotherapy regimen composed of oral fluorouracil (n = 76 patients) and platinum-based therapy (n = 14). Patients given adjuvant chemotherapy were younger than patients who were not ($p < 0.001$). Although tumors were significantly larger in the group that received adjuvant chemotherapy compared with the group that did not ($p = 0.003$), SUV_{max} did not differ