Lung cancer is the leading cause of cancer-related death in both men and women in many countries, including Japan. In spite of major advances in cancer treatment, its prognosis has not improved significantly over the past two decades. Approximately 20%–40% of patients with surgically resected stage I non-small cell lung cancer (NSCLC) develop recurrent disease. The proportion of cases of lung cancer that are diagnosed at an early stage is increasing because of advances in diagnostic imaging.

Positron emission tomography (PET) with the glucose analogue 18F-fluorodeoxyglucose (FDG) has an established role in the treatment of lung cancer. A recent systematic review and meta-analysis performed by the European Lung Cancer Working Party for the International Association for the Study of Lung Cancer (IASLC) Lung Cancer Staging Project concluded that the maximum standardized uptake value (SUVmax) on FDG-PET is a prognostic factor for recurrence.
a prognostic factor in patients with NSCLC. Several studies have addressed the relationship between tumor SUVmax and outcome in NSCLC. However, NSCLC is a heterogeneous disease because it includes several histological subtypes that have different biological behaviors. The purpose of this study was to confirm the predictive value of SUVmax on FDG-PET in patients with stage I lung adenocarcinoma treated with surgery, with respect to cancer recurrence.

Patients and Methods

Patient characteristics
This retrospective study included 138 consecutive, eligible patients treated at the Division of Chest Surgery of Fukushima Medical University from January 2005 to October 2010. The inclusion criteria were: FDG-PET examination during preoperative staging, surgical treatment with curative intent and without preoperative induction chemotherapy or radiotherapy, and a definitive postoperative diagnosis of stage I adenocarcinoma according to the latest revision of the international system for staging lung cancer. There were 78 females and 60 males in the study. Patient clinicopathological data are summarized in Table 1.

FDG-PET examination
All patients underwent diagnostic or staging FDG-PET prior to surgical resection. The images were obtained using Discovery Light Speed (LS) PET scanner (GE Medical Systems, Milwaukee, Wisconsin, USA). After at least 6 hours of fasting, patients received an intravenous injection of 3.7 MBq/kg FDG. About 60 min later, whole-body emission PET was performed. A region of interest was drawn over the primary tumor, guided by computed tomography (CT) images. SUVmax was calculated for each tumor.

Histopathological examination
Tumors were evaluated by an experienced pathologist, according to the 2004 World Health Organization classification for NSCLC. All specimens were formalin-fixed, paraffin-embedded, and stained with hematoxylin and eosin. Pleural (pl) invasion, lymphovascular (ly) involvement, and vascular (v) involvement were determined with Elastica Masson staining, as well as hematoxylin-eosin staining.

Treatment and follow-up
Outpatient follow-up was performed by thoracic surgeons every 2–3 months until 12 months, then every 6 months until 60 months, and then yearly. Standard follow-up consisted of chest X-ray, laboratory testing including measurement of tumor markers, and clinical examination. Chest CT was performed every 6 months until 2 years, and then yearly. Further CT scans were only performed if there were suspicious radiological, serological,
or clinical findings. Adjuvant chemotherapy was administered if the tumor measured >2.0 cm in diameter, using oral tegafur/uracil (UFT™, Taiho Pharmaceuticals, Tokyo Japan) for 2 years according to the Japanese standard adjuvant chemotherapy regimen.3)

**Statistical analysis**

Correlations between preoperative SUVmax and clinicopathological factors were analyzed using the two-tailed Pearson’s chi-square test. Differences in SUVmax between groups were tested using the Mann-Whitney test. Survival probabilities were estimated using the Kaplan–Meier method. The significance of differences in disease-free survival (DFS) between groups was tested using the log-rank test. The univariate Cox proportional hazards model was used to quantify the risk of recurrence as a function of sex, age, histology, tumor size, and dichotomized SUVmax. The multivariate Cox proportional hazards model was used to identify potential independent effects of SUVmax after adjustment for the effects of other significant variables.

**Results**

We identified 138 consecutive patients who were diagnosed with pathological stage I adenocarcinoma from January 2005 to October 2010, and who met our inclusion criteria. Patient characteristics are shown in Table 1. Of 138 patients, 68 had T1a tumors; 30, T1b; and 40, T2a. Histological types included papillary (67 patients), acinar (11 patients), BAC with other components (46 patients), and others (14 patients). The median follow-up time was 46.1 months. Twenty two patients (15.9%) developed recurrence after surgery. The recurrent sites were as follows; other pulmonary lobes (12 patients), mediastinal lymph nodes (4 patients), pleural dissemination (3 patients), brain (2 patients), and bone (1 patient). There were no local recurrences at the surgical margin or ipsilateral lymph node recurrences.

Receiver operating characteristic (ROC) curve of SUVmax was significantly correlated to recurrent disease (p <0.0001). The calculated SUVmax cut-off value was 2.5, with 95.7% sensitivity and 45.2% specificity. ROC curve: receiver operating characteristic curve; SUVmax: maximum standardized uptake value.

The 5-year DFS and overall survival rates were 77.7% and 91.4%, respectively. We divided the patients into groups according to cutoff values for SUVmax of 2.5, ly involvement and tumor diameter of 2.0 cm. The 5-year DFS of patients in these groups is shown in Fig. 2. The 5-year DFS was significantly better in the group with SUVmax ≤2.5 than the group with SUVmax >2.5 (97.1% versus 66.0%; p = 0.0003) (Fig. 2A), and the 5-year DFS in the group without ly involvement was also better than that with ly involvement (82.1% versus 58.1%; p = 0.0018) (Fig. 2B), while there was no significant difference in the 5-year DFS rates between the groups with tumor diameter ≤2.0 cm and >2.0 cm (78.8% versus 77.4%; p = 0.4040) (Fig. 2C), and with tumor diameter ≤3.0 cm and >3.0 cm (80.7% versus 73.1%; p = 0.0508) (Fig. 2D). The 5-year DFS curves of all four groups according to both SUVmax and ly involvement are shown in Fig. 2. The 5-year DFS rate was 97.0% in patients with SUVmax ≤2.5 and without ly involvement, 100% with both SUVmax ≤2.5 and ly involvement, 70.2% with SUVmax >2.5 and without ly involvement,
and 53.1% with both SUVmax >2.5 and ly involvement (Fig. 3).

**Discussion**

Treatment of lung cancer by surgery sometimes leads to disappointing results. The 5-year recurrence rate in patients with pathological stage I NSCLC is reported to be 20%–39%.4,5) Current research is, therefore, directed towards developing combined-modality therapy, even for stage I NSCLC. Currently, tumor size is the only factor used to decide whether a patient with pathological stage I adenocarcinoma should receive adjuvant chemotherapy.3) However, tumor size may not always give a satisfactory indication of prognosis. New risk stratification markers and models are urgently needed to determine which patients with resected stage I lung adenocarcinoma are at highest risk of relapse and would, therefore, need adjuvant chemotherapy.

Meta-analysis results have demonstrated that patients who have tumors with higher metabolic activity, as measured by SUVmax, have shorter survival times than patients with tumors with lower metabolic activity.6) Our results show that FDG uptake measured by SUVmax is a prognostic factor in stage I lung adenocarcinoma treated with surgery, which is consistent with the results of previous studies. However, the definitions and implications of high- and low-risk PET findings have yet to be determined. Goodgame, et al.7) suggested that SUVmax >5.5 best defines a high-risk population, whereas our
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Fig. 2  (A) The 5-year DFS rate was significantly better in the group with SUVmax \( \leq 2.5 \) than in the group with SUVmax >2.5 (97.1% versus 66.0%; \( p = 0.0003 \)). (B) The 5-year DFS in the group without ly involvement was also better than that with ly involvement (82.1% versus 58.1%; \( p = 0.0018 \)). (C) There was no significant difference in 5-year DFS rates between the groups with tumor diameter \( \leq 2.0 \) cm and >2.0 cm (78.8% versus 77.4%; \( p = 0.4040 \)). (D) There was also no significant difference in 5-year DFS rates between the group with tumor diameter \( \leq 3.0 \) cm and >3.0 cm (80.7% versus 73.1%; \( p = 0.0508 \)). DFS: disease-free survival; SUVmax: maximum standardized uptake value; ly: lymphovascular

Fig. 3 The 5-year DFS rate was 97.0% in patients with SUVmax \( \leq 2.5 \) and without ly involvement, 100% with both SUVmax \( \leq 2.5 \) and ly involvement, 70.2% with SUVmax >2.5 and without ly involvement, and 53.1% with both SUVmax >2.5 and ly involvement. DFS: disease-free survival; SUVmax: maximum standardized uptake value; ly: lymphovascular

data suggest that SUVmax >2.5 is more appropriate for defining a high-risk population. Their study population was histologically heterogeneous, including patients with NSCLC other than adenocarcinoma. In general, SUVmax tends to be higher in squamous cell carcinoma than adenocarcinoma because of the difference in cell density. Our data are, therefore, more useful because of the relatively homogeneous histology and staging in our study population. Murakami, et al.\(^8\) also evaluated the usefulness of FDG-PET for predicting recurrence in patients with stage IA adenocarcinoma, and suggested an SUVmax cutoff value of 2.15. Ohtsuka, et al.\(^9\) suggested a cutoff value of 3.3. We speculate that differences in cutoff values of SUVmax will occur even in homogeneous populations because of differences in scanning devices and methods among institutions. Shiono, et al.\(^10\) used a corrected SUV, which they termed the SUV index, and calculated this as the ratio of tumor SUV (max) to liver SUV (mean). They found that the SUV index was reproducible and was a significant predictor of recurrence.
of pathological stage I NSCLC. Even pathological stage I lung adenocarcinoma is a biologically heterogeneous disease, depending on histological classification. In this study, we classified the population according to histological subtype, depending on the ratio of BAC components. Pure BAC tumors clearly have a better prognosis according to previous reports.1–14) The prognosis of mixed type tumors, with both BAC and solid components, is worse than that of pure BAC type tumors and is associated with SUVmax. This indicates that, in small adenocarcinomas, which include BAC components, the prognosis might depend on the histological subtype. This concept is supported by the results of the study by Kadota, et al.,15) which showed that SUVmax on FDG-PET correlated with the IASLC/American Thoracic Society/European Respiratory Society classification and could be used to stratify patients into prognostic subsets.

We think that Japanese patients with pathological stage I adenocarcinoma who have tumors measuring >2.0 cm in diameter are good candidates for adjuvant chemotherapy using oral tegafur/uracil. In this study, tumor size did not predict prognosis. This survival similarity may be attributable to adjuvant chemotherapy administered to the >2.0 cm group or the >3.0 cm group using oral anti-cancer agent for 2 years. That is, the prognostic predictivity of tumor size may have been hidden by the adjuvant chemotherapy. Multivariate analysis identified SUVmax and ly involvement as predictors of recurrence after surgery. In particular, patients with both SUVmax >2.5 and ly positive would be a high risk group of any recurrence, and the group with SUVmax >2.5 and ly negative would be relatively high risk, therefore, they might consider a multidisciplinary approach to therapy. We hope that such combinations will be further evaluated in prospective clinical trials to better stratify lung cancer patients.

Conclusions

The results of this study suggest that SUVmax and ly involvement could be used to predict the prognosis of patients with pathological stage I adenocarcinoma. The combination of these prognostic factors could also identify the high risk group of recurrence.

Disclosure Statement

All authors declare that they have no financial or personal relationships with people or organizations that could inappropriately influence this report.

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