Positron emission tomography for predicting recurrence in stage I lung adenocarcinoma: standardized uptake value corrected by mean liver standardized uptake value

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Abstract

Objective: F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) has become an important staging tool for patients with lung cancer, and determination of the standardized uptake value (SUV) is probably the most widely used method for evaluating patients. Although SUV is recognized as a powerful surrogate marker for lung cancer outcomes, SUV standardization and reproducibility in clinical practice remain major concerns. The aim of this study was to evaluate the corrected SUV as a universal marker for lung cancer recurrence. Methods: We conducted a case–control study in our institute. From May 2004 to February 2010, 141 patients with pathological stage IA and IB adenocarcinomas underwent PET-computed tomography scanning and SUV determination. The corrected SUV was defined as the SUV index, which was calculated as the ratio of tumor SUV_{max} to liver SUV_{mean}. We examined the association between disease-free survival and several clinicopathological factors, including the SUV index. Results: The 3-year overall survival rate after surgery was 94.3% and the 3-year disease-free survival rate was 90.4%. Univariate analysis showed that male gender (p = 0.04), smoking (p = 0.02), and SUV index (p < 0.01) were independent predictive factors for recurrence. Multivariate analysis showed that the SUV index was significantly associated with a high risk for recurrence (p = 0.03). No patient with an SUV index <1.0 experienced a recurrence. Conclusions: The SUV index is a significantly predictive and reproducible factor for recurrence in pathological stage I lung cancers. Patients with an SUV index <1.0 were more likely to have a good prognosis. Additional multi-institutional studies are needed to confirm these study results.

Keywords: Lung cancer; PET-CT; SUV; Stage I

1. Introduction

Current studies support the utility of F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) for determining prognosis [1–8] in lung cancer, even for stage I lung cancer patients [9–14]. Determination of the FDG standardized uptake value (SUV) is probably the most widely used method for evaluating lung cancer patients, and may be a powerful surrogate marker for outcome in non-small-cell lung cancer (NSCLC) patients. We recently demonstrated that patients with high maximum SUVs (SUV_{max}) and lymphovascular invasion were more likely to have recurrence [15]. Although various cutoff values have been reported, high FDG uptake is generally considered to be indicative of more aggressive tumors and a sign of dismal prognosis.

The International Association for the Study of Lung Cancer Staging Committee (IASLC) recently published the seventh edition of the tumor–node–metastasis (TNM) lung cancer staging system [16]. Although the committee recognized the importance of PET [1], no PET results were included in the new staging system. The revised staging manual encourages clinicians to document the use of PET in clinical staging of lung cancer and to record features such as SUV in both primary and any nodal and/or metastatic sites [16]. To apply PET results to TNM staging, multi-institutional patient data are required. However, the absence of standardization of FDG-PET imaging and the poor reproducibility of SUV in recent multi-institutional studies are major concerns that must be addressed [3,17].

The present study was conducted to provide standardization and reproducibility of SUVs in patients staged with IA and IB lung adenocarcinoma according to the seventh edition of the TNM staging system. For this purpose, we reanalyzed a recently reported and updated database [15]. We used the right lobe of the liver as an internal control for tumor SUV_{max}, because the SUVs measured in the normal liver of cancer-free patients have been shown to be constant [18]. Based on the present results, SUV has the potential to be used in multi-institutional studies to determine patient prognosis.

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2. Patients and methods

We updated the patient database that was presented in a recent report [15]. This retrospective study was performed from May 2004 to February 2010. We prospectively collected data at the time of diagnosis regarding age, gender, smoking status, serum carcinoembryonic antigen (CEA) level, timing of surgery, TNM stage (seventh edition) [16], primary tumor SUV$_{\text{max}}$, extent of surgery, pathological findings, time to recurrence, time to last follow-up, time to death, and cause of death. Because the TNM staging system was updated to the seventh edition in 2009, we had to revise the staging data for each case. Inclusion criteria were: (1) complete resection, (2) no induction therapy, (3) preoperative PET-computed tomography (CT), (4) absence of severe diabetes, and (5) adenocarcinoma. Patients with multiple lung tumors were excluded. During the study period, 417 patients underwent lung cancer surgery. After exclusion of cases that did not fulfill the enrolment criteria, 141 patients with pathological stage IA and IB (TNM seventh edition) [16] were evaluated (Fig. 1).

Patients who were planning to undergo surgery were requested to undergo PET-CT. Patients who agreed to undergo PET-CT by providing informed consent were referred to Yamagata Saiseikai Hospital. After the images were independently viewed by two radiologists, they were also viewed by the multidisciplinary team. PET imaging was performed in a routine clinical fashion in accordance with standard protocols. Before scanning, patients fasted for 6 h. A standard dose of 3.75 MBq kg$^{-1}$ FDG was administrated intravenously, and PET and CT images were scanned 60 min later on a Discovery LS instrument (General Electric, Milwaukee, WI, USA). Scanning was performed from the base of the skull to mid-thigh level. After images were obtained, the SUV was calculated and normalized according to the patient’s body weight. We used the tumor SUV$_{\text{max}}$ in this analysis, which was calculated by the region of interest (ROI) placed on the axial PET slice with the highest FDG uptake. ROIs were determined by the radiologists.

Since the main purpose of this study was to identify valid predictive factors, patient PET-CT data were retrospectively investigated. PET-CT data were re-evaluated using the free software, OsiriX v.3.5.1 (http://www.osiriX-viewer.com/).

Because of patient outcome, the mean SUV of the right liver lobe (SUV$_{\text{liver}}$) was examined using OsiriX. ROI shapes were designed to be circular, and right liver lobe ROI diameters were 60 mm (Fig. 2) [19]. This software calculated the liver SUV$_{\text{mean}}$. The corrected SUV was defined as the SUV index, which was calculated as the ratio of tumor SUV$_{\text{max}}$ to liver SUV$_{\text{mean}}$.

Resected specimens were fixed in 10% formalin and cut into 5–10-mm slices. Sections containing tumor tissue were embedded in paraffin, and consecutive 5-μm sections were stained using hematoxylin–eosin or Elastica-Masson reagents [15]. They are antibodies for immunostain. D2-40 and CD34 immunostaining were not performed.

Postoperative follow-up was performed by thoracic surgeons every 3–4 months for 5 years. A routine follow-up consisted of chest X-rays, a physical examination, and blood chemistry tests, including tumor marker analysis. Annual chest and brain CTs were performed. If patients complained of symptoms or when tumor markers were significantly elevated, bone scintigraphy or PET-CT was performed. Recurrence was diagnosed using radiological findings; biopsy was not generally performed to make a diagnosis.

Our institutional ethics committee approved this study and waived the requirement for informed consent from patients as long as patient data remained anonymous. No financial support was received from companies that make PET-CT scanners or from other companies.

3. Statistical analysis

Overall survival, disease-specific survival, and disease-free survival (DFS) were analyzed by the Kaplan–Meier method, and differences in variables were evaluated using the log-rank test. Survival periods were measured beginning with the date of surgery. For disease-specific survival, patients who died without evidence of recurrence were censored. For DFS, patients without recurrence were censored from analysis at the time of last negative follow-up.
To determine the appropriate prognostic SUV index value, we examined SUV index cutoff values using receiver operating characteristic (ROC) curve analysis [20]. The ROC curve and Youden index identified an optimal cutoff value for the SUV index.

Cox proportional hazards regression analysis was used for multivariable analysis. The data were analyzed using version 5.0.1 of the JMP software package (SAS Institute Inc., Cary, NC, USA). A p-value less than 0.05 was considered statistically significant.

4. Results

During the study period, 93 patients with pathological stage IA and 48 patients with stage IB lung cancer were evaluated. Patient characteristics are summarized in Table 1. Tumor SUVmax measurements ranged from 0 to 24.8 (median, 3.4) and liver SUVmean measurements ranged from 1.4 to 3.1 (median, 2.2; mean ± SD, 2.2 ± 0.3).

The median follow-up for surviving patients was 36 months (range, 0–68 months). Nine patients died during the follow-up period; of these, three (2.1%) died from lung cancer. The 3-year overall survival rate, 3-year disease-specific survival rate, and 3-year DFS rate after surgery were 94.3%, 96.9%, and 90.4%, respectively. We recorded one postoperative death (0.7%) due to sepsis. In total, 12 patients (8.5%) experienced recurrence after surgery. Recurrence sites included lung (n = 3), brain (n = 2), pleura (n = 2), mediastinal and hilar lymph nodes (n = 2), adrenal gland (n = 1), bone (n = 1), and liver (n = 1).

Since only three patients (2.1%) died from lung cancer, the associations between predictive factors and DFS were examined. Univariate analysis showed that male gender (p = 0.04), smoking (p = 0.02), and SUV index (p < 0.01) were independent predictive factors for recurrence (Table 2). When all predictive factors were subjected to multivariate analysis, the SUV index was the only significant risk factor for recurrence (p = 0.03).

The ROC curve and Youden index identified an optimal cutoff value of 2.86 for lung cancer recurrence (Fig. 3) [21]. The area under the curve was 0.75. The 3-year DFS rate in patients with an SUV index <2.86 was 93.9%, compared to 79.9% in patients with an SUV index ≥2.86 (p < 0.01) (Fig. 4). To provide a less complex indicator for clinical practice, we analyzed these data using a cutoff value of 1.0. The 3-year DFS rate in patients with an SUV index <1.0 was 100%, compared to 86.6% in patients with an SUV index ≥1.0 (p = 0.002) (Fig. 5).

![Fig. 3. Receiver operating characteristic (ROC) curve of SUVmax for predicting recurrence. The ROC curve identified an optimal SUVmax cut-off value of 2.86 for recurrence (Youden index).](https://academic.oup.com/ejcts/article-abstract/40/5/1165/447374/1167)
5. Discussion

SUV is a semi-quantitative parameter that is calculated from the concentration of radioactivity adjusted by body weight and dose of injected FDG. Meta-analyses have shown that a high SUV is significantly correlated with poor survival after lung cancer surgery [1,2]. However, SUV is affected by many factors, and lacks both reproducibility and standardization. Although some investigators are attempting to develop PET standardization for multicenter trials [22,23], the use of the same SUV cutoff point in multicenter studies requires some deliberation, and determination of the optimal SUV cutoff is a major concern in lung cancer clinical studies. In the present study, we attempted to improve the accuracy of PET by using the liver SUV\textsubscript{mean} as an internal control. The results of this study have demonstrated that the SUV index is a reliable and simple predictive marker of recurrence in patients with early-stage NSCLC.

Using a method described by Kamibayashi et al., this study determined the liver SUV\textsubscript{mean} for each patient and used that value to correct the tumor SUV\textsubscript{max} of the patient [19]. Moreover, the liver SUV is easily used for ROI determination. While the effect of liver disease on liver SUV is not known, the present study did not include patients with severe hepatic disorders. Future studies using liver as a control might have to exclude patients with liver disease.

Ohba et al. reported that FDG uptake measured by the contrast ratio of the SUV to the contralateral lung is superior to other evaluation methods [24]. However, the SUV of the contralateral lung could potentially be affected by various factors, such as lung disease, patient motion, or breathing [17]. Some studies have evaluated lung tumor SUV using the mediastinum as an internal control; however, because the structure of the mediastinum is not clearly seen, compared to the liver, determination of the best ROI position within the mediastinum is more difficult. In addition, the best mediastinal control point has not yet been determined. We therefore believe that liver SUV is much easier to use in a clinical setting.

The present study has some limitations. First, even with SUV correction using an internal control, other factors affecting the SUV [1], such as instrumentation, PET protocols, analytic software, and different radiologists across institutions, cannot be completely excluded. To best optimize image quality and reduce SUV variability, Boellaard reported that patient preparation is important [17], and Paemans et al. noted that the methodology for assessing SUV and the type of FDG—PET instrument are obviously important [2]. In the design of clinical trial protocols using SUV measurements, FDG injection doses and scanning times should also be predetermined.

The second limitation is that this was a single-institution and short follow-up study. However, the advantage of a single-institution study is the assurance that the same PET-CT protocol is followed and that patient follow-up is relatively uniform. Patients were seen every 3–4 months in the outpatient clinic; therefore, clinical changes could be quickly identified. In addition, as this study was a small and single-institution study, patients could be assessed during the study period. Data were obtained after a short follow-up period; thus, a longer follow-up period is required to confirm our results.

The third limitation is that this is a retrospective study. To exclude potential sources of bias, we only used PET data to calculate SUV\textsubscript{mean} values. However, blinding researchers in a retrospective study is impossible, particularly in the present study, in which a previous study with the same primary outcome in the same population has recently been conducted [15].

A final limitation is that lung cancer PET results are known to be correlated with histological cell type [8,11]. In this study, we specifically investigated adenocarcinomas. Among them, pathological examination revealed 25 cases (17.7%) with predominant bronchioloalveolar adenocarcinoma. Among the different types of adenocarcinomas, well-differentiated adenocarcinomas are known to have the lowest SUV\textsubscript{max} [22]. Therefore, PET results might not be useful for predicting prognosis in lung cancer patients with well-differentiated adenocarcinomas. For nonadenocarcinomas, further study is required to demonstrate a relationship between prognosis and the SUV index.

In summary, since SUV is affected by various parameters, the use of SUV as a predictive factor for recurrence is controversial. However, we found that PET-CT results, particularly the SUV index, which is the tumor SUV\textsubscript{max}...
corrected by the liver SUV\textsubscript{mean}, were significantly correlated with recurrence in pathological stage I lung adenocarcinoma. However, as Dooms and Vansteenkiste concluded in an editorial [25], the choice of an optimal ‘prognostic SUV cutoff’ remains uncertain, and standardization and validation of PET results will remain a crucial issue in the near future. The SUV index has the potential to be used in multi-center trials for treatment planning, especially for identifying patients who are good candidates for limited surgery and adjuvant chemotherapy. We are currently planning additional multi-institutional studies to validate the results of the present study.

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References


