Limited resection for clinical Stage IA non-small-cell lung cancers based on a standardized-uptake value index†

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Abstract

OBJECTIVES: In a previous study, we found that a standardized-uptake value (SUV) index obtained from positron emission tomography (PET)/computed tomography (CT) data was significantly correlated with prognosis in patients with pathological Stage I lung adenocarcinoma. However, this value has not been studied in early stage lung cancer patients undergoing limited resection. In this study, we investigated if an SUV index could be used to identify patients with clinical Stage IA lung cancers that were appropriate for limited resection.

METHODS: This was a retrospective study of prospectively collected data from 183 patients with clinical Stage IA non-small-cell lung cancer undergoing both PET–CT examinations and surgery from May 2004 to December 2010. A corrected SUV was defined as the SUV index, which was calculated from the ratio of the tumour SUVmax to the liver SUVmean. The associations between survival, recurrence and several clinical factors, including the SUV index, were evaluated.

RESULTS: The following pathological stages were identified: Stage IA (n = 133; 72.7%), Stage IB (n = 31; 16.9%), Stage IIA (n = 11; 6.0%), Stage IIB (n = 1; 0.5%) and Stage IIIA (n = 7; 3.8%). There were 50 upstaged cases (27.3%). The 5-year overall survival, 5-year cancer-specific survival and 5-year freedom from recurrence (FFR) rates after surgery were 83.5, 91.6 and 83.1%, respectively. Twenty-six (14.2%) patients developed recurrences. Multivariate analysis showed that an SUV index was a significant predictive factor for recurrence (P < 0.01). The 5-year FFR rates in patients with an SUV indices <1.0 and ≥1.0 were 100 and 77.1%, respectively (P < 0.01). The 5-year cancer-specific survival rates in patients with an SUV indices <1.0 and ≥1.0 were 100 and 88.7%, respectively (P = 0.04).

CONCLUSIONS: In clinical Stage IA lung cancer patients, the SUV index was a significant predictive marker for recurrence. Patients with SUV indices <1.0 were less likely to have a recurrence. Thus, clinical Stage IA patients with SUV indices <1.0 should be candidates for limited resection.

Keywords: Lung cancer • PET–CT • SUV • Stage I

INTRODUCTION

Remarkable progress in the ability of chest computed tomography (CT) to detect small-lung nodules has enabled the identification of patients with lung cancer at a much earlier and curable stage. Bronchioloalveolar carcinoma, in particular, which has been classified by the World Health Organization as a type of adenocarcinoma, has a quite good prognosis and low recurrence rate [1, 2]. With regard to surgical procedures for patients with small-lung cancers, the Lung Cancer Study Group has shown that lobectomy provided superior outcomes compared with sublobar resection [3]. Therefore, lobectomy remains the standard technique for lung cancer, and sublobar, namely limited resection, is optionally indicated for selected patients. Current studies support the utility of thin-section chest CT for determining the prognosis and surgical indications in lung adenocarcinomas with ground-glass opacities (GGOs) or classified as ‘air-containing type’ [4–10]. The use of chest CT findings to determine the type of surgery for patients with small-lung cancers is being studied in ongoing phase III randomized trials in Japan and the USA (Cancer and Leukaemia Group B trial 14053 and Japan Clinical Oncology Group trial 0802/West Japan Oncology Group trial 4607L). However, the surgical indications for lung cancers classified by CT as ‘solid-density types’ are not clear. Positron emission tomography (PET)/CT is widely used for evaluating lung cancer patients, and the PET–CT findings may be very important prognostic factors for patients with non-small-cell lung cancer (NSCLC) [11, 12]. We recently demonstrated that PET–CT results, particularly the SUV index, which we have defined as the tumour SUVmax corrected by the liver SUVmean, were significantly correlated with recurrence in patients with pathological Stage I lung adenocarcinoma [13]. The use of PET data to determine

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surgical indications has not yet been studied. This study was conducted to investigate the use of the SUV index for surgical planning for patients with clinical Stage IA lung cancer.

PATIENTS AND METHODS

Our institution has established a prospective database on patients that was presented in previous reports [13, 14], and updated for this study. This retrospective study was performed from May 2004 to December 2010. At the time of final diagnosis, the following data were prospectively collected: age, gender, smoking status, serum carcinoembryonic antigen (CEA) level, spirometry, camera, date of surgery, TNM stage (TNM Classification of Malignant Tumours, 7th Edition) [15], primary tumour SUV\textsubscript{max}, extent of surgery and pathological findings. We recorded the date of recurrence, date of last follow-up, date of death and cause of death. The patient inclusion criteria were as follows: (i) clinical stage IA, (ii) no induction therapy, (iii) preoperative PET-CT, (iv) absence of severe diabetes, (v) absence of severe liver disease and (vi) no multiple lung cancers. During the study period, 486 patients underwent lung cancer surgery. Since lymphadenectomy was not performed in wedge resection, 27 wedge resection cases were excluded. After exclusion of patients who did not fulfill the enrollment criteria, 183 patients with clinical Stage IA cancer were evaluated. The sizes of the preoperative nodules were measured using chest thin-section CT, and the scans were evaluated by a multidisciplinary team. Hilar and mediastinal lymph nodes were considered to be positive if the short axis of the lymph node was >1 cm.

Chest X-ray, contrast-enhanced CT of the chest and upper abdomen, brain CT, laboratory examination, blood gas analysis and spirometry were performed before surgery. Patients undergoing surgery who agreed to undergo PET-CT by providing informed consent were referred to Yamagata Saiseikai Hospital. Detailed PET-CT procedures have been previously reported [13, 14].

PET imaging was performed in a routine clinical fashion in accordance with standard protocols. Before undergoing scanning, patients fasted for 6 h. A standard dose of 3.75 MBq/kg\(^{18}\)Fluorodeoxyglucose \(\left(18\text{F-FDG}\right)\) was administered intravenously, and PET and CT images were collected 60 min later using a Discovery LS instrument (General Electric, Milwaukee, WI, USA). SUV was normalized according to patients’ body weight.

The corrected SUV was defined as the SUV index, which was calculated from the ratio of tumour SUV\textsubscript{max} to liver SUV\textsubscript{mean} [14]. The free software, Osirix v.3.5.1 (http://www.osirix-viewer.com), was used to evaluate the PET-CT data. The tumour SUV\textsubscript{max} was determined for this analysis from the region of interest (ROI) placed on the axial PET slice with the highest FDG uptake. The tumour SUV\textsubscript{max} was determined using circular ROIs, and ROIs of the right liver had 60-mm diameters (Fig. 1).

Lobectomy was principally indicated for 2.1- to 3-cm lesions, and segmentectomy was indicated for 2-2-cm lesions. In the case of lobectomy, we performed mediastinal lymphadenectomy, and in the case of segmentectomy, we performed hilar lymphadenectomy and lymph node sampling. For poor-risk patients and pure GGO patients, we performed wedge resections. Patients with Stage IB disease were administered uracil-tegafur and those with Stage IIA–IV disease received platinum-based chemotherapy. Postoperative follow-up was performed by thoracic surgeons every 3–4 months for 5 years [13, 14]. The patients were followed for 5 years, and the surviving patients continue to be followed using chest CT.

The diagnosis of recurrence was made by the consensus of a multidisciplinary team. For recurrences found by imaging, the date of recurrence was considered to be the date of imaging. This study was approved by the institutional ethics committee, and the requirement for informed consent from patients was waived as long as patient data remained anonymous. No financial support was received from companies that make PET-CT scanners.

Statistical analysis

A \(\chi^2\) test and logistic regression analysis were used to analyse the stage upgrading and clinical factors. Survival and freedom from recurrence (FFR) were estimated using the Kaplan–Meier method, and differences in variables were evaluated using the log-rank test. The duration of survival and FFR was determined from the date of surgery. Cancer-specific survival was defined as the interval between the date of surgery and the date of death from cancer. FFR was defined as the interval between the date of surgical resection and the date of the first recurrence or the last follow-up.

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

RESULTS

Patient characteristics are summarized in Table 1. The median value for tumour SUV\textsubscript{max} was 3.6. The range of values for liver.
SUV_{mean} was narrow compared with the range for tumour SUV_{max} (Fig. 2). There were 50 upstaged cases (27.3%). By univariate analysis, tumour size >2 cm (P < 0.01) and SUV index ≥1.0 (P < 0.01) were significant factors for stage upgrading. In multivariate analysis, there was no significant independent factor for stage upgrading. The median follow-up time for the surviving patients was 38 months (range 0–90 months). The patient follow-up rate was 99.5%; there was 1 patient who could not be followed. There was one postoperative death (0.5%), which was associated with sepsis. During the study period, 22 (12.0%) patients died during follow-up. Ten (5.5%) patients died of lung cancer; 4 (2.2%) of other malignancies and 8 (4.4%) of causes unrelated to lung cancer. Patients dying of other causes were censored in cancer-specific survival analysis.

Twenty-six (14.2%) patients developed recurrence at the following sites: regional lymph node (n = 8), bone (n = 7), brain (n = 5), lung (n = 5), pleural dissemination (n = 5) and adrenal gland (n = 1). Table 2 summarizes recurrence rates and patient characteristics after surgery for c-Stage IA lung cancer; cases with tumours >2.0 cm were more likely to develop recurrence. In our series, 1 of 32 patients undergoing segmentectomies (3.1%) developed brain metastasis. Because our previous study found that the cut-off value for the SUV index was 1.0 [14], we categorized patients based on an SUV index of 1.0. No patient with an SUV index <1.0 developed a recurrence. The SUV index cut-off value of 1.0 had a sensitivity of 100%, specificity of 33.1%, positive predictive value of 19.8% and negative predictive value of 100% for predicting a recurrence.

The 5-year overall survival rate, 5-year cancer-specific survival rate and 5-year FFR after surgery were 83.5\%, 83.1\% and 83.1\%, respectively. The associations between preoperative clinical factors and recurrence and survival were examined. Regarding FFR (Table 3), SUV index [risk ratio (RR) 1.26, 95\% confidence interval (CI) 1.11–1.40; P < 0.01] was correlated with poor outcome in univariate analysis. By multivariate analysis, gender (RR 0.44, 95\% CI 0.25–0.84; P = 0.02), smoking (RR 0.48, 95\% CI 0.28–0.89; P = 0.02) and the SUV index (RR 1.22, 95\% CI 1.05–1.42; P = 0.01) were significant independent factors for FFR. Regarding cancer-specific survival (Table 4), gender (RR 0.46, 95\% CI 0.18–0.89; P = 0.02), serum CEA level >5 ng/ml (RR 2.38,
95% CI 1.29–4.21; P < 0.01) and SUV index (RR 1.31, 95% CI 1.09–1.52; P < 0.01) were significantly correlated with poor outcome by univariate analysis. By multivariate analysis, there was no significant factor for cancer-specific survival.

The 5-year FFR rates in patients with an SUV indices <1.0 and ≥1.0 were 100 and 77.1%, respectively (P < 0.01; Fig. 3). The 5-year cancer-specific survival rates in patients with an SUV indices <1.0 and ≥1.0 were 100 and 88.7%, respectively (P = 0.04; Fig. 4).

**DISCUSSION**

Because chest CT can easily detect small-lung cancers, performing lobectomy for all patients with Stage IA NSCLC may be controversial. Although the Lung Cancer Study Group found, in a randomized prospective study, that the local recurrence rate of patients undergoing sublobar resection was increased 3-fold over the rate for patients undergoing lobectomy [3], non-randomized studies showed that tumours >2 cm were associated

| Table 3: Univariate and multivariate analyses of freedom from recurrence after surgery |
|---|---|---|
| Variables | Univariate analysis | Multivariate analysis |
| | Risk ratio | 95% CI | P-value | Risk ratio | 95% CI | P-value |
| Gender (female/male) | 0.69 | 0.45–1.04 | 0.08 | 0.44 | 0.25–0.84 | 0.02 |
| Age (≥75/<75) | 1.02 | 0.65–1.78 | 0.92 | 1.08 | 0.66–1.93 | 0.76 |
| Smoking (positive/negative) | 1.06 | 0.72–1.58 | 0.75 | 0.48 | 0.28–0.89 | 0.02 |
| CEA (ng/ml) (>5.0/≤5.0) | 1.53 | 0.93–2.35 | 0.09 | 1.17 | 0.63–1.96 | 0.60 |
| CT (cT1a/1b) | 0.68 | 0.43–1.00 | 0.06 | 0.80 | 0.50–1.23 | 0.31 |
| SUV index | 1.26 | 1.11–1.40 | <0.01 | 1.22 | 1.05–1.42 | 0.01 |
| FEV1% (<70%/≥70%) | 1.15 | 0.75–1.70 | 0.51 | 0.94 | 0.55–1.54 | 0.80 |

CI: confidence interval; CEA: carcinoembryonic antigen; SUV: standardized-uptake value; FEV1: forced expiratory volume in 1 s.

| Table 4: Univariate and multivariate analyses of cancer-specific survival after surgery |
|---|---|---|
| Variables | Univariate analysis | Multivariate analysis |
| | Risk ratio | 95% CI | P-value | Risk ratio | 95% CI | P-value |
| Gender (female/male) | 0.46 | 0.18–0.89 | 0.02 | 0.34 | 0.11–1.00 | 0.05 |
| Age (≥75/<75) | 0.69 | 0.39–1.34 | 0.25 | 0.69 | 0.35–1.48 | 0.32 |
| Smoking (positive/negative) | 1.42 | 0.79–2.74 | 0.24 | 0.61 | 0.28–1.56 | 0.27 |
| CEA (ng/ml) (>5.0/≤5.0) | 2.38 | 1.29–4.21 | <0.01 | 1.84 | 0.85–3.76 | 0.31 |
| CT (cT1a/1b) | 0.58 | 0.28–1.07 | 0.08 | 0.74 | 0.34–1.42 | 0.38 |
| SUV index | 1.31 | 1.09–1.52 | <0.01 | 1.22 | 0.98–1.50 | 0.07 |
| FEV1% (<70%/≥70%) | 1.32 | 0.72–2.35 | 0.35 | 0.65 | 0.27–1.42 | 0.29 |

CI: confidence interval; CEA: carcinoembryonic antigen; SUV: standardized-uptake value; FEV1: forced expiratory volume in 1 s.

![Figure 3: Freedom from recurrence according to the SUV index. SUV: standardized-uptake value.](image1)

![Figure 4: Cancer-specific survival according to the SUV index. SUV: standardized-uptake value.](image2)
with decreased survival by multivariate analysis [16, 17]. Despite tumour heterogeneity, a meta-analysis also demonstrated that limited resection may achieve a better prognosis than lobectomy for patients with early lung cancers [18]. To obtain the best postoperative lung function, sublobar resection may be preferable. Okada et al. [16] revealed that postoperative lung function was significantly better in patients who underwent sublobar resection. Limited resection is considered to have primary therapeutic utility for selected patients with Stage IA NSCLC. This may particularly be the case for tumours in the periphery of the lung or within anatomical segmental boundaries, with no endobronchial component, and that are <2 cm in diameter [19]. However, the surgical indications for limited resection remain controversial, and the biological features of lung cancer cannot be determined by tumour size alone. Three of 13 patients with lung cancers <1 cm were found to have lymphovascular invasion or lymph node metastases [20].

Many reports have indicated that nodules with GGO or classified as ‘air-containing type’ on CT predict good surgical outcomes. The amount of GGO has been significantly correlated with the behavioural nature of the tumour [4–10]. In a multi-institutional prospective study, Suzuki et al. [21] demonstrated that an adenocarcinoma ≤2.0 cm with GGO and with consolidation ≤25% of the maximum tumour diameter was considered to be radiologically early lung cancer.

However, the radiological finding of GGO lesions as an indication for surgery has some limitations. CT cannot provide enough information for lung cancers that do not contain air, i.e. solid-type nodules, before surgery. There are non-invasive cancers that appear solid, such as small squamous cell carcinomas. In addition, if GGO lesions have irregular shapes, their areas are difficult to measure. For these lesions, we speculate that evaluation using PET–CT, and the SUV index in particular, holds promise for identifying invasive lung cancer. If our speculation is correct, the indications for limited resection can be extended, and we may also obtain good surgical outcomes for patients with small solid lung cancers. This study found that 55 of 210 (26.2%) patients were upstaged from clinical Stage IA to pathological Stage IB to IIIA after surgery. Seven of these patients (3%) had a mediastinal lymph node metastasis. However, there were no patients with an SUV index <1.0 upstaged to higher stages. This result suggests that the SUV index is useful for deciding whether to perform a limited resection.

SUV is a semi-quantitative parameter that is calculated from the concentration of radioactivity adjusted by body weight and dose of injected $^{18}$F-FDG. Meta-analyses have shown that a high SUV is significantly correlated with poor survival after lung cancer surgery [11, 12]. Since SUV is affected by various parameters, the use of SUV to predict recurrence and survival is controversial and has limitations. The cut-off value of SUV has been very controversial. To establish a cut-off value, we previously found that the SUV index was significantly correlated with recurrence in pathological Stage I lung adenocarcinoma [14]. The SUV index was originally described by Kamibayashi et al. [22], who determined the liver SUV$_{\text{mean}}$ for each patient and used that value to correct the tumour SUV$_{\text{max}}$ of the patient. Although the SUV index may be affected by liver function, it is a very easy marker to measure for the estimation of patient prognosis after lung cancer surgery. Other investigators have demonstrated the usefulness of PET–CT to evaluate the malignancy grades of lung adenocarcinomas in phantom studies [23–25]. Tsutani et al. showed that solid tumour size and the SUV$_{\text{max}}$ had a greater predictive value for the grade of malignancy and prognosis in patients with clinical Stage IA lung adenocarcinoma than whole tumour size. A phantom study is useful for reducing institutional differences, but the limitations of PET–CT cannot be fully excluded. The SUV index has the same limitations. Even using an internal control for SUV correction, other factors affect the SUV [11], including instrumentation, PET protocols, analytical software and different radiologists, and cannot be completely excluded.

A major limitation of PET–CT is that its resolution is inferior to chest CT. A chest CT is indispensable for the detection of small-lung cancers with GGO that are not detected by PET–CT. However, even with limitations, the SUV index cut-off value of 1.0 is an important and simple tool for estimating the prognosis of patients with small-lung cancers. To determine the indications for limited resection, we believe that PET–CT complements chest CT.

Overall survival, including non-cancer-related death, is usually evaluated in cancer studies. Since the overall survival of patients staged with early lung cancer is improving, larger numbers of patients are needed to detect significant differences among Stage IA subsets. Given the advances in chemotherapy and other supportive treatments, overall survival times may be longer, and FFR is thought to be a realistic end-point for evaluating the surgical procedures. We examined cancer-specific survival and FFR in this study, evaluating the efficacy of the SUV index. FFR depends on the duration of follow-up and on examinations. Although FFR may not be an adequate end-point for clinical studies of cancer, we believe that the FFR was an option for evaluating the efficacy of the SUV index.

We found 36 pathological Stage IB cases. Among these patients, 8 received uracil-tegafur, because in Japan, uracil-tegafur is used for some patients with Stage IB disease. Treatment using uracil-tegafur did not affect recurrence ($P = 0.87$) or survival ($P = 0.57$) rates.

This was a retrospective study of prospectively collected data from an updated database. From 2011, we prospectively investigated the SUV index; however, before 2011, we retrospectively analysed the SUV index, but were blinded to patient outcome. Therefore, this study may be biased. Furthermore, with regard to surgical procedures, we chose sublobar resections for poor-risk patients and pure GGO patients, which introduced selection bias. To increase the robustness of our data, we need to study and evaluate patients who only underwent lobectomy and systematic lymph node dissection.

In summary, we found that the SUV index was a significant predictive marker for recurrence in patients with clinical Stage IA lung cancer. Patients with SUV indices <1.0 were less likely to have a recurrence, which suggests that Stage IA patients with SUV indices <1.0 may be candidates for sublobar resections. Further randomized prospective studies of patients with clinical Stage IA NSCLC are needed to validate and clarify the usefulness of the SUV index.

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