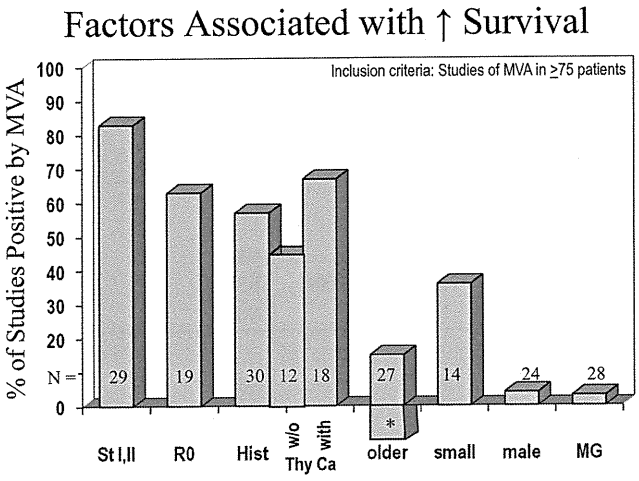

FIGURE 1. Factors associated with increased survival by multivariate analysis. Percentage of studies finding a factor prognostically significant for survival in multivariate analysis in studies of >75 patients from January 1, 1980, to December 31, 2010. *Percentage of patients showing that older patients had worse (not increased) survival. Hist, histologic typing; MG, myasthenia gravis; MVA, multivariate analysis; *N*, number of studies examining this factor; St, stage; Thy Ca, thymic carcinoma; w/o, without.

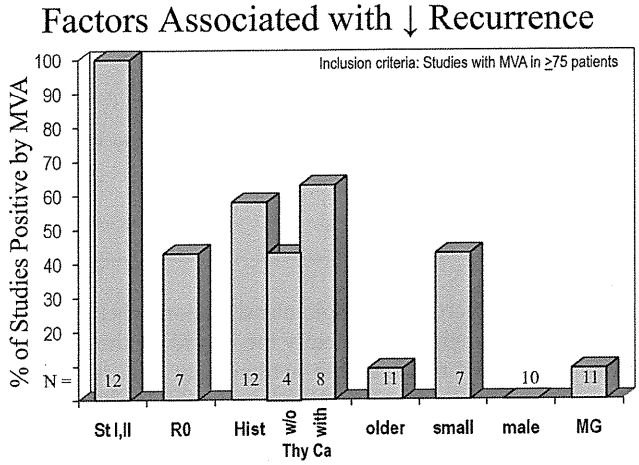

FIGURE 2. Factors associated with decreased recurrence by multivariate analysis. Percentage of studies finding a factor prognostically significant for recurrence or disease-free survival in multivariate analysis in studies of >75 patients from January 1, 1980, to December 31, 2010. Hist, histologic typing; MG, myasthenia gravis; MVA, multivariate analysis; *N*, number of studies examining this factor; St, stage; Thy Ca, thymic carcinoma; w/o, without.

The impact of age seems to be low. Age does not seem to have an impact on recurrence. One might predict that if there is no effect on recurrence, then older age would predict worse survival due to death from other causes. Nevertheless, several studies have found older age to be a good prognostic factor for overall survival, and a similar number found it predicted worse survival. The age threshold has been chosen at various cutpoints. Given the conflicting results, it is probably best to regard this factor as unlikely to be a valid prognostic factor.

A smaller tumor was found to be a good prognostic factor in a minority of studies for both recurrence and survival. Factors that do not seem to have prognostic significance for either survival or recurrence are gender and the presence of MG.

Many additional factors have been investigated sporadically (<5 studies). For overall survival, these include the time period (dichotomized periods),[11,13,15,16] the development of a recurrence,[8,18,24,31] the presence of parathymic syndromes other than MG,[14,16,21,24] symptoms,[16,23] comorbidity,[6,15] lymphoid hyperplasia,[6,28] remission of MG,[8,42] adjuvant RT,[9,42] adjuvant chemotherapy,[22] RT dose,[31] the presence of another nonthymic cancer,[23] great vessel involvement,[17] pleural invasion,[31] development of nodal metastases,[14] distant metastases,[14] Myasthenia Gravis Foundation of America (MGFA) class,[42] performance of a preoperative biopsy,[23] race,[23] cellular atypia or mitotic figures,[16] performance status,[32] and the sequence of multimodality treatment.[31] All these investigated factors were not found to be prognostically significant with the exception of one of four studies examining the time period,[13] one of four studies examining the appearance of a recurrence,[31] one of two studies examining remission of MG,[42] and one of one study examining the presence of great vessel involvement.[17]

Additional prognostic factors that have been investigated relative to recurrence (disease-free survival) in less than three studies include the time period,[15,33] performance of a preoperative therapy,[34] the use of adjuvant chemotherapy,[22] the sequence of multimodality treatment,[31] RT dose,[31] the presence of comorbidity,[6,15] parathymic syndromes other than MG,[21,33] lymphoid hyperplasia,[6,28] invasion of a vessel or structure,[33] pleural invasion,[31] and race.[34] All these factors were negative for prognostic significance except pleural invasion (in a single study).[31]

DISCUSSION

A conceptual framework to classify and integrate prognostic factors into a useful system is currently not available, and the thinking about how to approach this is evolving. The statistical approaches to define valid prognostic factors are much more developed, although not widely appreciated. Because the desire and need to predict outcomes are great, definition of prognostic factors cannot be simply delayed until the appropriate framework has been developed. Nevertheless, we must remember to view the definition of prognostic factors as an evolving process and take what we have at present with a grain of salt.

We attempted to address statistical weaknesses of existing studies to keep the results in proper perspective, but the ability to do this was limited. Overall, the methods used in most of the available studies carry a risk of identifying false-positive prognostic factors, which might not stand up to a more rigorous analysis. A review of the tables, however, suggests similar results in the studies with more versus less robust statistical approaches. Regarding false-negative re-

sults, we did not find that any reported analyses had a very limited power of detection because of trying to evaluate too many factors in a limited data set. Nevertheless, it should be noted that the size of the reported studies allows only detection of prognostic factors with a medium or large effect; the presence of a small effect on prognosis cannot be excluded for any factor.

Many of these studies spanned 20 or more years. Only a few studies analyzed the effect of the time period of treatment as a prognostic factor[11,13,15,16,33]; only one found a statistically significant difference.[13] Nevertheless, the ambiguities introduced by changes in practice over time and by inconsistencies in how various aspects of thymic malignancy have been defined reinforce the need to view this analysis of prognostic factors as preliminary.

The available data suggest that stage and completeness of resection can be viewed as validated prognostic factors. Furthermore, gender and the presence of MG can be accepted as not having prognostic significance. The effect of tumor size warrants further study. There are issues regarding what threshold to use (or series of thresholds?). Furthermore, there are issues of how size should be measured in a tumor that is typically not a round sphere.

The effect of tumor histology also requires further study. Survival curves from individual studies demonstrate quite consistently that thymic carcinoma carries a worse prognosis. Furthermore, this entity has been well recognized in all histologic classification systems. The multivariate studies that have included thymic carcinoma fairly consistently show prognostic value to histologic classification, whereas it is less clearly so when these patients are excluded. A discussion of issues associated with the histologic classification of thymic malignancies is currently ongoing. Therefore, it seems reasonable not to go beyond viewing thymic carcinoma as a validated independent negative prognostic factor and await further investigation before declaring other histologic features to be prognostically significant or not.

Because of the behavior of thymic malignancies, recurrence is a better measure of outcomes than overall survival. In general, the data on prognostic factors for recurrence (Table 2) parallel those for overall survival (Table 1). Nevertheless, the majority of studies have used disease-free survival as an end point, and this may at least partly explain the similar results. It is not wise to count death (from any cause) as the same as the development of a recurrence. Only four studies have focused specifically on recurrence.[22,26,33,34] This is clearly an area that must be addressed by future research on prognostic factors.

CONCLUSION

A review of the available data regarding MVA of prognostic factors in thymic malignancies demonstrates many limitations in our understanding of these. Tumor stage and completeness of resection are important for overall survival, whereas gender and the presence of MG are not. The effect of histologic classification other than identification of thymic carcinoma is unclear, as is the effect of tumor size. Future research on prognostic factors needs to focus on predictors of recurrence. Future research also should investigate novel factors such as biomarkers, as the number of factors that have been examined so far is rather limited. The infrastructure developed by ITMIG should significantly facilitate such investigations.

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Clinical Cancer Research

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Imaging, Diagnosis, Prognosis

Early [^{18}F]Fluorodeoxyglucose Positron Emission Tomography at Two Days of Gefitinib Treatment Predicts Clinical Outcome in Patients with Adenocarcinoma of the Lung

Ryo Takahashi[1], Haruhiko Hirata[1], Isao Tachibana[1], Eku Shimosegawa[2], Atsuo Inoue[2], Izumi Nagatomo[1], Yoshito Takeda[1], Hiroshi Kida[1], Sho Goya[1], Takashi Kijima[1], Mitsuhiro Yoshida[1], Toru Kumagai[1], Atsushi Kumanogoh[1], Meinoshin Okumura[3], Jun Hatazawa[2], and Ichiro Kawase[4]

Abstract

Purpose: Positron emission tomography (PET) with [^{18}F]fluorodeoxyglucose (FDG) is increasingly used in early assessment of tumor response after chemotherapy. We investigated whether a change in [^{18}F]FDG uptake at 2 days of gefitinib treatment predicts outcome in patients with lung adenocarcinoma.

Experimental Design: Twenty patients were enrolled. [^{18}F]FDG-PET/computed tomographic (CT) scan was carried out before and 2 days after gefitinib treatment. Maximum standardized uptake values (SUV) were measured, and post-gefitinib percentage changes in SUV were calculated. Early metabolic response (SUV decline < −25%) was compared with morphologic response evaluated by CT scan and with progression-free survival (PFS).

Results: At 2 days of gefitinib treatment, 10 patients (50%) showed metabolic response, 8 had metabolic stable disease, and 2 had progressive metabolic disease. Percentage changes of SUV at 2 days were correlated with those of tumor size in CT at 1 month ($R^2 = 0.496$; $P = 0.0008$). *EGFR* gene was assessable in 15 patients, and of 12 patients with *EGFR* mutations, 8 showed metabolic response at 2 days and 6 showed morphologic response at 1 month. None of 3 patients with wild-type *EGFR* showed metabolic or morphologic response. Metabolic response at 2 days was not statistically associated with PFS ($P = 0.095$), but when a cutoff value of −20% in SUV decline was used, metabolic responders had longer PFS ($P < 0.0001$).

Conclusion: Early assessment of [^{18}F]FDG tumor uptake with PET at 2 days of gefitinib treatment could be useful to predict clinical outcome earlier than conventional CT evaluation in patients with lung adenocarcinoma. *Clin Cancer Res; 18(1); 220–8. ©2011 AACR.*

Introduction

Treatment of non–small cell lung cancer (NSCLC) has made remarkable progress in the last decade; the epidermal growth factor receptor (EGFR), which is expressed in more than 60% of patients with metastatic NSCLC and correlates with poor prognosis (1), has emerged as an important molecular target for advanced or recurrent NSCLC. Reversible EGFR tyrosine kinase inhibitors (TKI), gefitinib and erlotinib, were found to have antitumor activities in second- or third-line therapy (2–4). Objective responses with these agents were limited to a subpopulation of patients, which included never-smokers, women, East Asians, and patients with adenocarcinoma histology (4, 5). It was later shown that most of these responders harbor specific mutations or increased copy number in the gene encoding EGFR that enhances tyrosine kinase activity (6, 7). Indeed, gefitinib as first-line and single-agent therapy improved progression-free survival (PFS) of patients with NSCLC with the *EGFR* mutations when compared with standard chemotherapy (8–10). Although these genetic markers may be used to predict therapeutic response, they do not guarantee successful treatment as a portion of marker-positive patients did not respond to the EGFR TKIs, whereas a portion of marker-negative patients did respond (11). Moreover, a secondary mutation in the *EGFR* gene or amplification of *c-Met* negates the sensitizing effect, leading to acquired

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Translational Relevance

It remains difficult to accurately predict clinical benefit of gefitinib in patients with non–small cell lung cancer (NSCLC). A recent basic study using a mouse model has shown that gefitinib induces a decrease of fluorodeoxyglucose (FDG) uptake within 48 hours in sensitive NSCLC tumors. We conducted a pilot study to validate the use of early FDG-positron emission tomography (PET) in clinical settings. Assessment of FDG uptake only after 2 days of gefitinib treatment was able to predict tumor response and progression-free survival. This early assessment could help to identify patients who will benefit from gefitinib therapy while allowing for rapid initiation of alternative strategies and minimizing critical adverse effects such as interstitial lung disease when gefitinib is ineffective.

resistance to the EGFR TKIs (12). Thus, it appears difficult to predict clinical benefit accurately only with these genetic biomarkers.

Positron emission tomography (PET) with [^{18}F]fluorodeoxyglucose (FDG) plays a role in the diagnosis and staging of lung cancer. It is based on high glucose metabolism in tumor cells that have an increased level of glucose transport protein expression and hexokinase activity. In addition to diagnosis and staging, [^{18}F]FDG-PET is increasingly used to assess tumor response and to predict outcome. A decrease in FDG uptake in sensitive tumor cells can be detected earlier than structural changes occur (13). This is the case especially in tumors treated with molecularly targeted drugs rather than with cytotoxic agents. In gastrointestinal stromal tumors (GIST), FDG-PET has been shown to be highly sensitive in detecting early response to imatinib mesylate, a small molecule that inhibits c-KIT. Decreases in FDG uptake were observed after 1 week of treatment, whereas volume responses evaluated on computed tomographic (CT) scan were small and developed more slowly (14, 15). In NSCLC, it has remained unknown that how EGFR TKIs downregulate FDG uptake after initiation of treatment in sensitive tumors. Recently, using a mouse xenograft model, Su and colleagues showed rapid decreases of tumor FDG uptake in sensitive xenografts within 48 hours of gefitinib treatment (16). They also found a decline in FDG uptake 24 to 48 hours before inhibition of proliferation and induction of apoptosis in a gefitinib-sensitive NSCLC cell line. A more recent preliminary study, which evaluated [^{18}F]FDG-PET in 5 patients with advanced NSCLC treated with gefitinib, suggested that FDG-PET may be able to predict the response. Patients exhibiting a partial response on CT evaluation already showed a mean of 61% decrease in FDG uptake at 2 days of therapy (17). Thus, further prospective studies are needed to confirm that [^{18}F]FDG-PET provides an early sensitive marker of the effectiveness of gefitinib in patients with NSCLC.

In the present study, we prospectively evaluated FDG-PET only after 2 days of gefitinib treatment in patients with lung adenocarcinoma to predict response and outcome. We used a combined PET/CT scan to provide correct anatomic registration of PET data.

Materials and Methods

Patients

Twenty patients with lung adenocarcinoma who received gefitinib treatment were enrolled from November 2007 to November 2009. Diagnosis was made either histologically or cytologically. Gefitinib at a dose of 250 mg once a day was administered orally 30 minutes after breakfast as the first EGFR tyrosine kinase inhibition therapy, until disease progression, unacceptable toxicity, or patient refusal. Eligibility criteria included an age of 20 years or more, unresectable stage or relapse after surgery, measurable disease, and Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. The study protocol was approved by the Institutional Review Board of Osaka University Hospital, Osaka, Japan, and written informed consent was obtained from all patients.

EGFR mutation analysis

Mutation analysis of *EGFR* in exons 18, 19, 20, and 21 was conducted using biopsy specimens obtained at diagnosis. Genomic DNA was extracted and analyzed by peptide nucleic acid–locked nucleic acid PCR (PNA-LNA PCR) cramp method manufactured in Mitsubishi Chemical Medience Co., as previously described (18).

FDG-PET/CT

[^{18}F]FDG-PET/CT was conducted before (at baseline), 2 days, and 1 month after gefitinib administration using a GEMINI GXL scanner (Philips Medical Systems). Baseline scan was done within 14 days prior to the treatment. All patients were fasted for at least 4 hours before scanning. Their serum glucose levels were less than 150 mg/dL before FDG injection. One hour after the injection of 3.7 MBq/kg [^{18}F]FDG, patients were scanned from the head to the thigh. We calculated accurate [^{18}F]FDG uptake time for each patient and confirmed that there was no significant difference between any metabolic responders and nonresponders. After a 50-mAs low-dose CT scan for attenuation correction, emission scan was obtained in a 3-demensional acquisition mode at 11 to 12 bed positions with 2 min/bed speed. In-plane and axial field of view of the scanner were 576 mm and 180 mm, respectively. In-plane spatial resolution was 6.31 mm full width at half maximum (FWHM) at the center with 144 × 144 pixel size (4 × 4 × 4 mm^3/pixel). Images were reconstructed by line-of-response row-action maximum likelihood algorithm (LOR-RAMLA) method. After acquisition of the PET images, a diagnostic chest CT was conducted by a 16-row multidetector scanner in a helical mode with 120 kV of the tube voltage and 200 mAs of the effective tube current. CT gantry rotation time was 0.5 seconds with an axial field of view of 600 mm,

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producing 5-mm thick slices with a 512 × 512 matrix. Regions of interest were placed over the highest accumulation area, corresponding to tumor sites on the PET images. The maximal standardized uptake value (SUV) was determined as previously described (19).

Response assessment and follow-up

Among measurable lesions according to the Response Evaluation Criteria in Solid Tumors version 1.0 (RECIST 1.0; ref. 20) in fused mode of dual modality PET/CT, up to 5 lesions in order of [^{18}F]FDG uptake level were defined as target lesion on the baseline scan. [^{18}F]FDG uptake was evaluated as the SUV of the target lesions (21). The lowest SUV of target lesions was 1.6, which was still higher than the background (Table 1). On PET/CT at 2 days and 1 month of gefitinib administration, percentage changes in the sum of these SUVs of the target metabolic lesions were determined on the basis of the baseline scan, and time point metabolic response was defined according to the recommendations of the European Organization for Research and Treatment of Cancer (EORTC) PET study group (22). Complete metabolic response (CMR) was achieved when SUVs of all lesions were decreased to uptake equivalent to background. Partial metabolic response (PMR) was defined as percentage change of the sum of SUVs (ΔSUV%) < −25%, stable metabolic disease (SMD) was −25% ≤ ΔSUV% < +25%, and progressive metabolic disease (PMD) was defined as +25% ≤ ΔSUV% or when the extent of [^{18}F]FDG increased greater than 20% in the longest dimension or when new [^{18}F]FDG uptake appeared in metastatic lesions. In analysis of PFS, a cutoff value of −20%, instead of −25%, was also used to separate responders from nonresponders. Changes in tumor size of the same target lesions as [^{18}F]FDG uptake analysis and nontarget lesions were quantified on CT images from PET/CT data at 1 month by 2 of the authors blinded to the PET data, and time point overall response was classified according to RECIST 1.0. Percentage changes in the sum of the longest dimension (ΔCTsize%) of the target lesions were also determined and compared with ΔSUV%. On CT images at 2 days of gefitinib administration, all patients were with stable disease. Chest CT or radiograph was repeated every 4 weeks until disease progression, which was determined by RECIST 1.0. The overall responses classified at 1 month were not confirmed by the repeat assessments in this study.

Statistical analysis

Data were analyzed using JMP statistical discovery software version 8.0.2 (SAS Institute). Correlation between ΔSUV% at 2 days and ΔCTsize% at 1 month was evaluated by Fisher ANOVA. Agreement between the EORTC recommendations–based metabolic response at 2 days and RECIST-based morphologic overall response at 1 month was evaluated using kappa statistic (23). PFS was measured from the first administration of gefitinib to documented progression or death of any cause. Overall survival (OS) was from the first administration of gefitinib to death of any cause. PFS and OS were estimated using the Kaplan–Meier method and compared by the 2-sided log-rank test (24). HRs were calculated using the Cox proportional hazards model. In multivariate Cox model analysis, metabolic response at 2 days and morphologic response at 1 month, significance of which was $P < 0.15$ in univariate analysis, were chosen as variable in addition to smoking history, which was previously shown to be a prognostic factor for patients with gefitinib-treated NSCLC (5). *EGFR* mutation status was not included because it was not determined or tested in 5 patients, and the number of patients with wild-type *EGFR* was only 3.

Table 1. Patient characteristics at baseline

Characteristic	*N*
Total no. of patients	20
Sex	
Male	5
Female	15
Age, y	
Median	69
Range	58–83
ECOG performance status	
0	10
1	10
Smoking history	
Never	15
Ever	5
Clinical stage	
IIIA	2
IIIB	3
IV	15
No. of prior chemotherapy	
0	10
1	6
2	2
3	1
4	1
EGFR mutation status	
Exon 19	6
Exon 21	5
Exon 18	1
Wild-type	3
Not determined	1
Not tested	4
Baseline study	
No. of target lesions	
Median	2.5
Range	1–5
SUV of target lesions	
Median	5.9
Range	1.6–13.0
Size of target lesions, cm	
Median	2.0
Range	1.2–7.7

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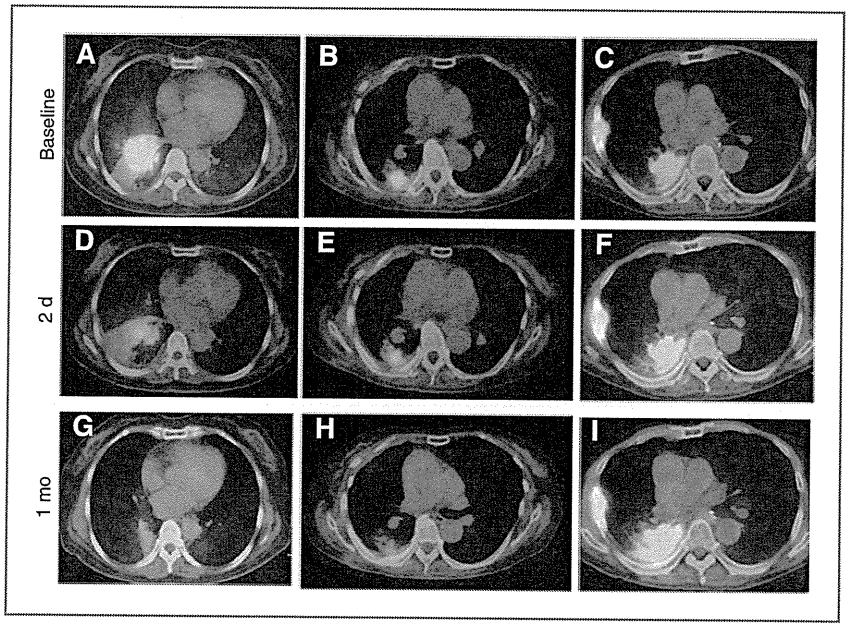

Figure 1. Pre- and posttreatment images of FDG-PET/CT scans of a 67-year-old female (A, D, and G) and a 75-year-old female (B, E, and H), who achieved partial response at 1 month (G and H, respectively), and an 81-year-old male (C, F, and I), who had progressive disease at 1 month (I) as assessed by RECIST 1.0. The first 2 patients already showed partial metabolic response at 2 days (D and E), and the third patient was assessed with progressive metabolic disease at 2 days (F).

Results

Patient characteristics

A total of 20 patients (15 females and 5 males) were enrolled in this study, underwent PET/CT for baseline assessment, and received gefitinib treatment. Nineteen were patients with adenocarcinoma and one with adenosquamous carcinoma. Fifteen patients (75%) had clinical stage IV disease. Five patients at clinical stage III were not treated with surgery or radiation due to the presence of malignant pleural effusion and complicating diseases. Ten were previously untreated and 10 had been treated with 1 to 4 chemotherapy regimens. Detailed patient characteristics are shown in Table 1. Median time between the baseline PET/CT and the start of gefitinib treatment was 4 days (range, 0–13 days), and no chemotherapy was administered during this period. A 77-year-old male patient did not complete PET/CT at 1 month because ground-glass opacity appeared on chest radiograph and gefitinib administration was discontinued at 6 days of treatment; this patient was excluded from later assessment. In all the other patients, gefitinib was continued to documented disease progression, and none of them received additional treatment without documented progression. Overall, early response at 2 days was assessed in 20 patients, and late response assessment at 1 month and PFS analysis were conducted in 19 patients.

Comparative analysis of metabolic and morphologic responses

Metabolic responses could be detected only at 2 days of treatment, when morphologic responses were still unrecognizable. Representative PET/CT images of responders and nonresponders during gefitinib treatment were shown in Fig. 1. Median percentage change of the sum of SUVs (ΔSUV%) of target lesions was −23%. Sixteen patients experienced ΔSUV% reduction ranging from −2% to −52% (Fig. 2A). No patient achieved a complete metabolic response (SUVs of all lesions equivalent to background) and 10 (50%) patients achieved a partial metabolic response (ΔSUV% < −25%). Four patients experienced an increase of ΔSUV% ranging from +6% to +36% and 2 of these were assessed with progressive metabolic disease (+25% ≤ ΔSUV%). These changes of target lesions in SUV at 2 days of treatment were compared with those in tumor size (ΔCTsize%) at 1 month of treatment, which was quantified on CT images, and there was a strong correlation ($R^2 = 0.496$; $P = 0.0008$) as shown in Fig. 2B. There was also a moderate agreement ($\kappa = 0.566$) between metabolic responses at 2 days based on the EORTC recommendations and morphologic overall responses at 1 month according to RECIST 1.0 (Fig. 2C). Of 10 metabolic responders at 2 days, 8 patients were morphologic responders and 2 were with stable disease by RECIST 1.0 at 1 month. Of 7 patients with stable metabolic disease (−25% ≤ ΔSUV% < +25%) at 2 days, 5 patients were assessed with morphologically stable disease and 2 had progressive disease by RECIST 1.0 at 1 month. Median PFS of patients with partial metabolic response, stable metabolic disease, and progressive metabolic disease was 290, 48, and 39 days, respectively. Median PFS of patients with morphologic partial response, stable disease, and progressive disease was 267, 100, and 29 days, respectively.

EGFR mutation

Biopsy samples from 5 patients were not suitable for molecular analysis. Mutation of *EGFR* gene was assessable in 15 patients and 12 were *EGFR* mutation positive:

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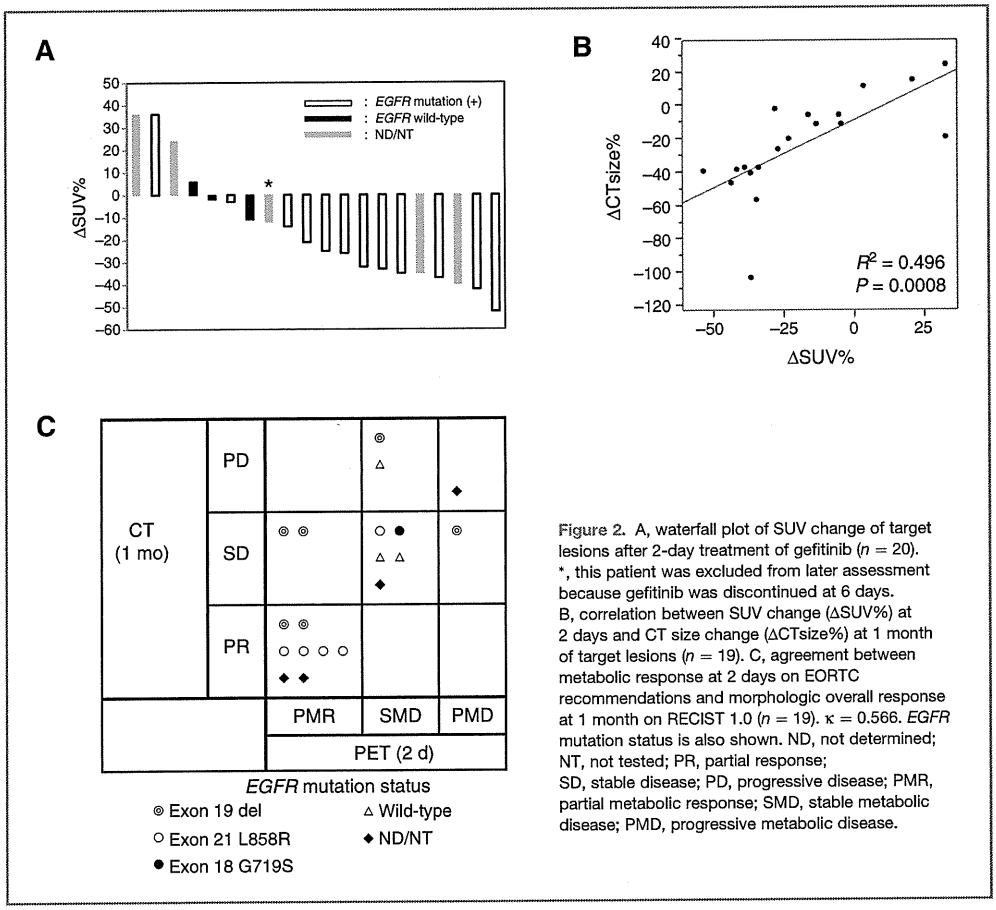

Figure 2. A, waterfall plot of SUV change of target lesions after 2-day treatment of gefitinib ($n = 20$). *, this patient was excluded from later assessment because gefitinib was discontinued at 6 days. B, correlation between SUV change (ΔSUV%) at 2 days and CT size change (ΔCTsize%) at 1 month of target lesions ($n = 19$). C, agreement between metabolic response at 2 days on EORTC recommendations and morphologic overall response at 1 month on RECIST 1.0 ($n = 19$). $\kappa = 0.566$. *EGFR* mutation status is also shown. ND, not determined; NT, not tested; PR, partial response; SD, stable disease; PD, progressive disease; PMR, partial metabolic response; SMD, stable metabolic disease; PMD, progressive metabolic disease.

6 patients had an exon 19 deletion, 5 patients had an exon 21 L858R mutation, and one had an exon 18 G719S mutation. Median ΔSUV% changes of target lesions in patients with mutated *EGFR* and wild-type *EGFR* were −29% and −2%, respectively (Fig. 2A). Of 12 patients with activating *EGFR* mutations, 8 (67%) were metabolic responders and 3 were with stable metabolic disease at 2 days, whereas 6 (50%) were morphologic responders and 5 were morphologically with stable disease at 1 month (Fig. 2C). Conversely, of 8 *EGFR* gene-assessable metabolic responders at 2 days, all had the activating mutations and 6 were assessed as morphologic responders at 1 month. Of 6 *EGFR* gene-assessable morphologic responders at 1 month, all had the mutations and were assessed as metabolic responders at 2 days. An 83-year-old female patient with an exon 19 deletion was assessed as having progressive metabolic disease while being with morphologically stable disease. During follow-up, this patient suffered from a relapse at 48 days. Another 79-year-old female patient with an exon 19 deletion was with stable metabolic disease at 2 days but assessed as having progressive disease because a new lesion appeared on PET/CT images at 1 month. All of 3 patients with wild-type *EGFR* were assessed with metabolically stable disease at 2 days. Two of these were assessed with morphologically stable disease and one had progressive disease at 1 month (Fig. 2C).

PFS according to metabolic and morphologic responses

When a cutoff value of −25% in ΔSUV% was used between metabolic responders and nonresponders, PFS did not significantly correlate with metabolic response at 2 days. Median PFS of the responders and nonresponders was 290 days and 48 days, respectively (log-rank $P = 0.095$; Fig. 3A). This was attributable to a 58-year-old male nonresponder with an L858R mutation who was assessed with 21% decrease of ΔSUV% and experienced the longest PFS of 680 days. When a cutoff value of −20%, which was still within the extent recommended by EORTC (22), was used, this patient was included in responders, and 2-day metabolic responders had significantly prolonged PFS compared with metabolic nonresponders (median, 296 vs. 42 days; $P < 0.0001$; Fig. 3B). When metabolic response was evaluated at 1 month, PFS was also significantly longer in

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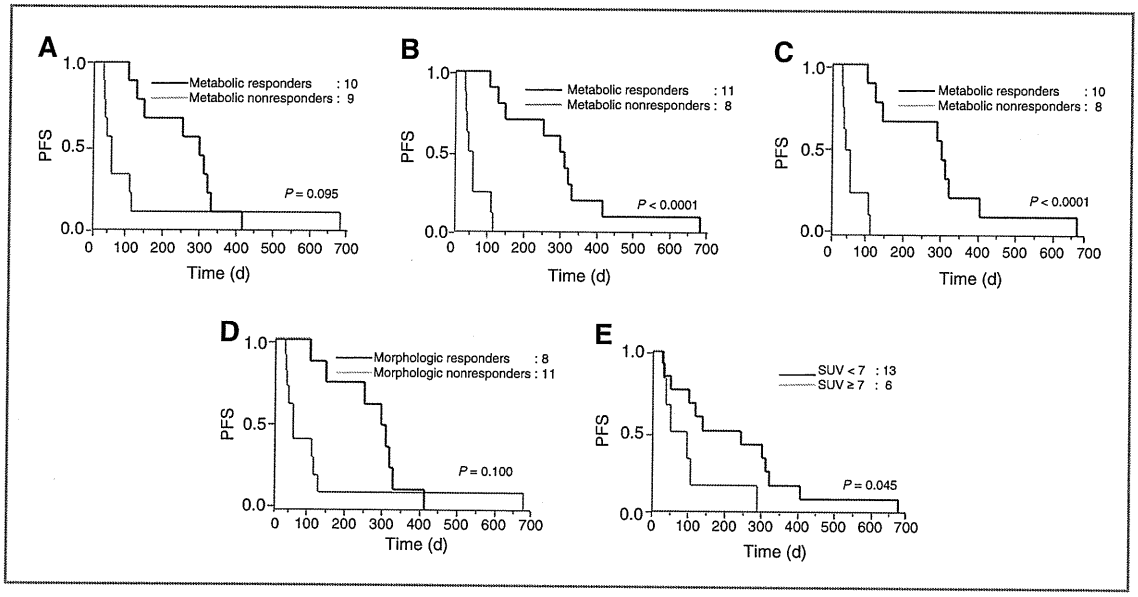

Figure 3. A, PFS of metabolic responders (ΔSUV% < −25%) and nonresponders (ΔSUV% ≥ −25%) at 2 days. B, PFS of metabolic responders (ΔSUV% < −20%) and nonresponders (ΔSUV% ≥ −20%) at 2 days. C, PFS of metabolic responders (ΔSUV% < −25%) and nonresponders (ΔSUV% ≥ −25%) at 1 month. One patient did not have an FDG-PET scan at 1 month, without missing a CT scan. D, PFS of morphologic responders and nonresponders at 1 month. E, PFS according to a single PET activity at 2 days (SUV < 7, black; SUV ≥ 7, gray). *P* values were obtained using the log-rank test.

responders than in nonresponders even with the cutoff value of −25% (median, 302 vs. 42 days; $P < 0.0001$; Fig. 3C). Meanwhile, PFS did not correlate with morphologic response based on RECIST 1.0 even at 1 month of treatment (median, 296 vs. 48 days; $P = 0.100$; Fig. 3D) because the patient with the longest PFS of 680 days was assessed with stable disease. When this patient was excluded, 1-month morphologic response became significantly correlated with PFS ($P = 0.0003$).

In the clinical settings, SUV at baseline PET might be influenced by previous chemotherapy. Therefore, we also investigated whether an early metabolic assessment with a single post-gefitinib PET/CT scan would provide any useful prognostic information. We defined an SUV threshold of 7, which was the nearest integer to the average SUV of the hottest target lesions in PET at 2 days, to separate responders (i.e., SUV < 7) from poor responders (SUV ≥ 7). There was a significant association between post-gefitinib FDG uptake and PFS (median, 244 days with SUV < 7 vs. 71 days with SUV ≥ 7; $P = 0.045$; Fig. 3E). Meanwhile, SUV in baseline PET studies was not predictive of PFS (median, 117 days with SUV < 10 vs. 93 days with SUV ≥ 10; $P = 0.611$).

In univariate analysis using the Cox hazards model, metabolic response using a cutoff value of −20% of ΔSUV% at 2 days was the only predictive factor of PFS (HR = 0.04; $P < 0.0001$), other than *EGFR* mutation status (Table 2).

Table 2. Univariate analysis of predictive factors for PFS

	Analysis		
Predictive factor	***n***	**HR (95% CI)**	***P***
Age (≥70 y)	19	1.69 (0.60–4.58)	0.310
Sex (female)	19	1.19 (0.37–5.29)	0.789
Smoking history (never)	19	1.22 (0.39–5.46)	0.747
Metabolic response at 2 d[a] (yes)	19	0.04 (0.002–0.23)	<0.0001
Morphologic response at 1 mo (yes)	19	0.44 (0.16–1.20)	0.109
EGFR mutation (yes)	15	0.17 (0.03–0.92)	0.041

[a]A cutoff value of −20% in SUV decline was used.

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In multivariate analysis including metabolic response at 2 days, morphologic response at 1 month, and smoking history, metabolic response at 2 days was the only statistically significant factor ($P = 0.0007$).

OS according to metabolic and morphologic responses

OS did not differ significantly between any metabolic responders and nonresponders and between the morphologic responders and nonresponders (Supplementary Fig. S1), although there was a trend for longer survival in metabolic responders who showed post-gefitinib SUV < 7 at 2 days ($P = 0.066$; Supplementary Fig. S1E).

Discussion

It has been evident that EGFR TKIs, gefitinib and erlotinib, induce dramatic responses in a subpopulation of patients with adenocarcinoma. Although the presence of somatic mutations in the *EGFR* gene is considered to be the best predictor of response to these TKIs (9, 10, 25, 26), its efficacy as biomarker is not satisfactory due to technical problems on biopsy, secondary mutation acquiring the resistance to the EGFR TKIs, and recent data showing response of patients with wild-type *EGFR* to erlotinib (27). Thus, an alternative approach optimizing clinical outcome of EGFR TKI therapy is necessary to accurately select patients who will benefit from the therapy and to avoid critical adverse effects such as interstitial lung disease (28).

Early response to therapy assessed by [^{18}F]FDG-PET has been increasingly established as a prognostic biomarker in various malignancies (13). In NSCLC, two studies have just been published to show that early [^{18}F]FDG-PET evaluation can predict PFS and OS in patients treated with erlotinib (29, 30). Another recent study reported that early [^{18}F]FDG-PET predicted histopathologic response in patients with NSCLC treated with erlotinib as neoadjuvant therapy (31). Metabolic tumor responses were assessed 1 to 8 weeks after the start of erlotinib treatment in these studies. Meanwhile, Su and colleagues showed that gefitinib treatment induced rapid decreases of FDG uptake within 48 hours in sensitive tumors using a mouse model, providing a rationale for earlier assessment in clinical settings (16). In these sensitive tumors, glucose transporters rapidly translocated from the plasma membrane to the cytosol, and reduction of hexokinase activity was observed prior to changes in cell-cycle distribution, thymidine uptake, and apoptosis. Such changes were not found in an early decline of FDG uptake in response to conventional cytotoxic chemotherapy (32). A more recent study preliminarily analyzed 5 patients with advanced NSCLC and reported that, only 2 days after initiation of gefitinib therapy, SUV decreased by a mean of 61% in patients who showed partial response by conventional CT evaluation 4 weeks later (17).

Consistent with these studies, SUV decreased by up to a maximum of 52% at 2 days in the present prospective study, and we observed a strong correlation between changes in SUV at 2 days and those in tumor size at 1 month. There was also a moderate agreement between metabolic responses at 2 days based on the EORTC recommendations and morphologic responses at 1 month according to RECIST 1.0. Moreover, metabolic response at 2 days could be a predictor of prolonged PFS when a cutoff value of −20% in SUV decline was used. The cutoff value of −25%, which was used in several other studies (33–35) but did not reach statistical significance in the present study, might be too large for the evaluation only after 2 days and for the sample size as small as 20. A single PET study at 2 days might also provide prognostic information. Patients with favorable response with lower post-gefitinib SUVs (SUV < 7) revealed longer PFS than poorly responding patients with higher SUVs (SUV ≥ 7), although significance was weak. There was a trend for an association between morphologic response at 1 month and improved PFS but it did not reach statistical significance, due to the presence of an *EGFR* mutation-positive patient showing stable disease but with a long PFS. In terms of OS, there was not significant difference, probably due to the small sample size and because OS is influenced by the second-line or later treatment. Together, although our study was a single-centered with a small number of patients, we propose that assessment of FDG uptake at 2 days could be a superior predictor of post-gefitinib outcome to conventional CT evaluation in its accuracy and rapidity.

Of 12 patients with activating *EGFR* mutations, 10 (83%) showed partial response or were with stable disease both in FDG-PET at 2 days and CT evaluation at 1 month. Thus, mutated *EGFR* is a good biomarker for response to gefitinib, as previously reported (6). Exceptionally, an 83-year-old female patient with exon 19 deletion had progressive metabolic disease at 2 days while being with morphologically stable disease at 1 month. She had a PFS of 48 days and this was relatively short for morphologically stable disease, the median PFS of which was 100 days. Another 79-year-old female patient with exon 19 deletion was with stable metabolic disease at 2 days while having morphologically progressive disease at 1 month. Her PFS was 30 days and relatively short for stable metabolic disease, the median PFS of which was 48 days. Thus, there was still inconsistency among *EGFR* mutations, early FDG-PET evaluation, or conventional CT evaluation, and larger prospective studies will be needed to clarify which is the best predictor of survival. Meanwhile, although it appears reasonable that none of 3 patients with wild-type *EGFR* showed metabolic or morphologic response, the number of patients is too small to discuss more about wild-type *EGFR*.

Interstitial lung disease is the most severe adverse effect, which occurs in approximately 1% of EGFR TKI–treated patients worldwide. Onset of symptoms may begin only after 2 days of gefitinib therapy. Median onset was 24 days in Japan and 42 days in United States, and about 1 of 3 of the cases were fatal (28). It has been suggested that [^{18}F]FDG-PET may help to evaluate interstitial lung disease. Positive FDG uptake was observed in 86% of patients with idiopathic pulmonary fibrosis and correlated with disease

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activity (36). In the present study, a 77-year-old male patient showed ground-glass opacity suggestive of interstitial infiltrate on chest radiograph, and gefitinib was discontinued at 6 days of treatment. At 2 days of treatment, his PET images did not show any positive uptake in lung parenchyma, and later on a CT scan, this infiltrate was rather considered a secondary change associated with obstructive bronchus. No other patient presented with interstitial infiltrate on chest radiograph. Thus, we could not determine at the moment whether [^{18}F]FDG-PET can early detect gefitinib-induced lung damage.

In summary, early response assessment by FDG-PET could help to identify patients with lung adenocarcinoma who will benefit from gefitinib treatment. The present study showed promising data suggesting that clinical outcome can be predicted only after 2 days of the treatment. This early assessment may allow for rapid initiation of alternative strategies and minimize critical adverse effects such as interstitial lung disease when gefitinib is ineffective. The main limitation is the small sample size, and validation with prospective studies in a larger patient population is warranted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Prognostic value of preoperative FDG-PET in stage IA lung adenocarcinoma

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ABSTRACT

Background: Maximum standardized uptake value (SUVmax) of 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) has been found to have prognostic value. We previously reported the correlation between SUVmax and pathological invasive area, and determined an SUVmax cut-off value of 2.15 for predicting the recurrence potential of an invasive area of diameter 5 mm. Here, we evaluate the validity of FDG-PET for prediction of recurrence in pathological stage IA lung adenocarcinoma.
Methods: From February 2006 to May 2008, 100 patients with pathological stage IA lung adenocarcinoma underwent complete resection at our hospital. Tumors were classified as air-type or solid-type based on thin-section computed tomography (TS-CT) findings and the influence of TS-CT classification, SUVmax, and clinicopathologic features were evaluated in terms of the incidence of recurrence.
Results: Unlike air-type adenocarcinomas, recurrent disease was detected in 8 of 62 solid-type adenocarcinomas. SUVmax and diameter of invasive area were significantly correlated with recurrence and a shorter time to recurrence. All 8 recurrent cases had pathological invasive area >5 mm. All except one case of recurrence were solid-type adenocarcinomas with SUVmax ≥ 2.15. Three-year disease-free survival rates were 100% in air-type adenocarcinomas, 97.1% in solid-type adenocarcinomas with SUVmax < 2.15, and 74.1% in solid-type adenocarcinoma with SUVmax ≥ 2.15.
Conclusion: Combined evaluation of TS-CT classification and SUVmax had significant value in predicting recurrence in stage IA lung adenocarcinoma, reflecting the aggressiveness of primary lung adenocarcinoma. Prediction of tumor aggressiveness could contribute to decision-making regarding the choice of surgical procedure and treatment after surgery.

1. Introduction

The recent increasing use of thin-section computed tomography scanning (TS-CT) has facilitated the detection of small-sized peripheral lung adenocarcinoma. Surgical resection offers a significant chance of cure for patients with early stage non-small-cell lung cancer (NSCLC); however, even in cases of stage IA adenocarcinoma, some patients experience recurrence within 5 years after surgery.

Many investigators have reported the relationship between TS-CT findings and aggressiveness and survival in patients with lung adenocarcinoma [1]. On TS-CT images, solid areas of a nodule may reflect collapsed alveoli, foci of fibrosis, or tumors with an invasive growth pattern, whereas areas of ground-glass opacity (GGO) represent components of bronchioloalveolar carcinoma (BAC) [1–4]. The authors focused on solid areas seen on TS-CT and reported that small pulmonary adenocarcinomas could be classified according to attenuation on TS-CT images as either 'air-containing-type' (air-type) or 'solid-density-type' (solid-type) [2,4]. No microscopic evidence of metastasis has been revealed in air-type adenocarcinomas, nor any relapses or deaths after resection. In contrast, patients with solid-type adenocarcinomas demonstrated a poor prognosis. Unlike air-type tumors, some solid-type tumors have pathological invasive areas; however, it is difficult to discriminate these areas from the solid component based on the TS-CT findings. The size of the invasive area is related to tumor aggressiveness [1]. Invasive areas of diameter ≤5 mm are reported to have a good prognosis; compared with true BAC type, a small component of invasive tumor does not adversely affect prognosis [1].

Several recent studies have demonstrated the prognostic value of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) for primary lung cancer [5–9]. We previously reported a

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significant correlation between SUVmax (maximum standardized uptake value) and the pathological invasive area of primary lung adenocarcinoma, and determined an SUVmax cut-off value of 2.15 for predicting recurrence potential for an invasive area of diameter 5 mm [10]. Based on this cut-off value, sensitivity was 88.3% and specificity was 84.6% [10]. On the basis of these findings, we evaluated the validity of cut-off SUVmax on FDG-PET to predict recurrence in pathological stage IA lung adenocarcinoma.

2. Materials and methods

2.1. Patients

We retrospectively reviewed the TS-CT and PET reports of 100 patients (39 male, 61 female) who had undergone complete surgical resection of peripheral adenocarcinomas with pathologic T1N0M0 (stage IA) at Kanagawa Cancer Center Hospital, Japan, from March 2006 to May 2008. Of these patients, 40 underwent segmentectomy or wedge resection. Preoperative TS-CT and whole-body FDG-PET were performed on all patients for staging and evaluation of resectability. None of the patients received neo-adjuvant chemotherapy or radiation therapy.

2.2. TS-CT evaluation

All 100 patients underwent TS-CT scanning within 4 weeks prior to surgery. TS-CT images were acquired using an Aquillion CT scanner (Toshiba Medical Systems, Tokyo, Japan). TS-CT images targeted to the tumors were obtained serially at 120 kVp and 200 mAs, with 1–2 mm section thickness, pitch of 1, 1–2 mm section spacing, 512 × 512 pixel resolution, and 1 s scanning time, using a high-spatial-reconstruction algorithm with a 20-cm field of view. All scans were imaged using mediastinal window settings (level, 40 Hounsfield units (HU); width, 400 HU) and lung window settings (level, −600 HU; width, 1600 HU). The TS-CT findings were evaluated and the maximum diameters of the tumor on mediastinal and lung window setting images were measured. The ratio of the maximum diameter of the tumor on mediastinal windows to that on lung windows was calculated. Tumors were defined as air-type for ratio values ≤50% or as solid-type for ratio values > 50%.

2.3. FDG-PET/CT evaluation

All PET/CT studies were performed within 4 week prior to surgery using a lutetium oxyorthosilicate-based whole-body PET/CT scanner (Biograph 16 HI-REZ; Siemens). ^{18}F-FDG (FDG scan Injectable; Nihon Medi-physics Co. Ltd.) was purchased via a delivery system. All patients fasted for at least 6 h before intravenous administration of 130–371 (mean ± SD, 251.4 ± 63.7) MBq ^{18}F-FDG. Prior to tracer administration, the blood sugar level was checked. All measured values were less than 140 mg/dl. Whole-body scanning was performed as an additional scan, from the top of the skull to the middle of the thigh, 60 min after administration of ^{18}F-FDG, with 3 min per bed position. CT images were used for anatomic landmarking. All PET images were reconstructed using iterative algorithms with CT-based attenuation correction. The data were reconstructed with a 128 × 128 matrix and 2-mm slice thickness. SUVmax was evaluated for the maximum value within a region of interest (ROI) drawn around the pulmonary lesion. Tumors were classified as having a high or low SUVmax using an SUVmax cut-off point of 2.15.

2.4. Pathological evaluation

Hematoxylin and eosin, and elastica van Gieson staining were performed on all sections to evaluate the diameter of invasive area, lymphatic and vascular invasion, and pleural involvement. Immunohistochemical evaluations were performed using the avidin–biotin–peroxidase complex method with 3-μm-thick sections of formalin-fixed, paraffin-embedded specimens. A monoclonal antibody against the Ki-67 antigen (MIB-1; MBL, Nagoya, Japan; 1:100 dilution) was used to assess the proportion of proliferating tumor cells. The Ki-67 labeling index was defined as the ratio of MIB-1-stained tumor cells to all tumor cells counted, multiplied by 100. To evaluate the Ki-67 labeling index, stained tumor cells were counted in at least three high-power fields that showed the highest positivity for each section.

Table 1
Patient and tumor characteristics[a].

CT finding	Air-type (n = 38)	Solid-type (n = 62)	p-Value
Median age (range) (yr)	67(44–77)	68(40–83)	.112
Gender (male/female)	14/24	25/37	.729
SUVmax	0.97 ± 0.95	3.28 ± 3.12	<.001
Low (<2.15)	35(92.1)	35(56.5)	<.001
High (≥2.15)	3(7.9)	27(43.5)	
Tumor size (mm)	18.6 ± 5.4	20.5 ± 5.7	.602
0–20 mm	25(65.8)	29(46.8)	.217
21–30 mm	13(34.2)	33(53.2)	
Type of surgical procedure			
Lobectomy	9(23.7)	51(82.3)	< .001
Sublobar resection	29(76.3)	11(17.7)	
Histology			
BAC	24(63.2)	13(21.0)	< .001
Mucinous BAC	0(0)	3(4.8)	
Non-BAC	14(36.8)	46(74.2)	
Lymphatic or vascular invasion			
Negative	38(100)	46(74.2)	< .001
Positive	0(0)	16(25.8)	
Invasive area size (mm)			
≤5	–	36(58.1)	
>5	–	26(41.9)	
Ki-67 index			
<25	–	50(80.6)	
≥25	–	12(19.4)	

[a] Data are presented as median (range) or number (%) of patients. SUVmax = maximum standard uptake value; BAC = bronchioloalveolar carcinoma.

2.5. Statistical analysis

Statistical analysis was performed using SPSS software (Dr. SPSS II. for Windows, Tokyo, Japan, released 2001). Disease-free survival was calculated and drawn using the Kaplan–Meier method, and groups were compared using the log-rank statistic. An exact χ^2 test was used to analyze the relationship between risk of recurrence and histopathological findings, SUVmax, tumor size, and type of surgery. Differences were considered statistically significant when $p < 0.05$.

3. Results

3.1. Patient characteristics

The characteristics of patients and tumors are listed in Table 1. Based on the TS-CT findings, there were 38 patients with air-type adenocarcinomas and 62 patients with solid-type adenocarcinomas. The majority of air-type adenocarcinomas (92.1%) showed low SUVmax (<2.15); for solid-type adenocarcinomas, 35 cases (56.5%) showed low SUVmax and the remaining 27 cases (43.5%) showed high SUVmax (≥2.15).

Of the air-type adenocarcinomas, 24 (63.2%) were classified as BAC without stromal destruction and the others were classified as mixed-type adenocarcinoma. In contrast, of the solid-type adeno-

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Table 2
Correlation of SUVmax and histologic findings in solid-type adenocarcinomas[a].

	Low SUVmax (<2.15) (n=35)	High SUVmax (≥2.15) (n=27)	p-Value
Histology			
BAC	12(34.4)	1(3.7)	
Adenocarcinoma with ≤ 5 mm invasive area	16(45.7)	4(14.8)	
Adenocarcinoma with > 5 mm invasive area	4(11.4)	22(81.5)	
mucinousBAC	3(8.6)	0(0)	
Lymphatic or vascular invasion			
Negative	33(94.3)	13(48.1)	<.001
Positive	2(5.7)	14(51.9)	
Ki-67 index			
<25	34(97.1)	16(59.2)	<.001
≥25	1(2.9)	11(40.8)	

[a] Data are presented as number (%) of patients.

carcinomas, 46 (74.2%) were classified as non-BAC. All 3 cases of mucinous-BAC appeared as solid type on TS-CT. No patient with air-type adenocarcinoma had lymphatic or vascular invasion. Among patients with solid-type adenocarcinoma, 16 (25.8%) had lymphatic and vascular invasion, 26 (41.9%) had invasive area > 5 mm, and 12 (19.4%) had Ki-67 index ≥25%.

3.2. Type of surgical procedure

Of the air-type adenocarcinomas, 9 (23.7%) received lobectomy, while the other 29 underwent sublobar resection (i.e., segmentectomy or wedge resection) because of their small size. Among the solid-type adenocarcinomas, 51 (82.3%) underwent lobectomy, while 11 (17.7%) underwent sublobar resection because of the advanced age or pulmonary hypofunction of the patient.

3.3. Correlation of SUVmax and pathological invasive area in solid-type adenocarcinomas

Table 2 shows the results of further analysis of the relationship in solid-type adenocarcinomas between SUVmax cut-off value of 2.15 and pathological invasive factors, such as the existence of invasive area >5 mm, lymphatic or vascular invasion, and Ki-67 index. Among the 35 solid-type adenocarcinomas with low SUVmax, 12 (34.4%) were diagnosed to be BAC and 16 (45.7%) were adenocarcinomas with invasive area ≤5 mm, while 22 (81.5%) of 27 adenocarcinomas with high SUVmax had an invasive area >5 mm. Lymphatic or vascular invasion was observed in 2 (5.7%) of 35 solid-type adenocarcinomas with low SUVmax, but was observed in 14 (51.9%) of 27 solid-type adenocarcinomas with high SUVmax. Only one adenocarcinoma with low SUVmax had Ki-67 ≥25; there was a lower frequency of high Ki-67 index in adenocarcinomas with low SUVmax compared with those with high SUVmax.

3.4. Disease-free survival data

None of the air-type adenocarcinomas had recurrent disease. In contrast, 8 (12.9%) of the 62 solid-type adenocarcinomas had recurrent disease: 6 had lung metastasis and 2 had bone metastasis. The median follow-up time to recurrence was 14.6 months (range, 9.1–29.4 months).

Table 3 shows the association of recurrence and prognostic significance for each histopathologic factor and molecular marker, in relation to time to recurrence, in solid-type adenocarcinomas. SUVmax, lymphatic and vascular invasion, size of invasive area, and Ki-67 index were significantly correlated with recurrence and a shorter time to recurrence. Among these predictors, SUVmax is the only preoperative factor, with the others being pathological factors. Our examination revealed no significant association between tumor size and recurrence. All cases of recurrence underwent lobectomy. In agreement with the findings of previous reports, no relapse was found in solid-type adenocarcinomas with invasive area ≤5 mm; in contrast, relapse was observed in 8 (30.8%) solid-type adenocarcinomas with invasive area >5 mm. Patients with solid-type adenocarcinomas with invasive area ≤5 mm had a 100% 3-year disease-free survival rate, which was significantly better than that for patients with solid-type adenocarcinomas having invasive area >5 mm ($p = .0003$) (Fig. 1).

Table 3
Risk factors for recurrence and prognostic predictors in stage IA solid-type adenocarcinomas[a].

	Recurrence (no. (%))	χ^2 Test p-value	Log-rank test p-value
Tumor size (mm)			
0–20 mm	5(15.2)	.573	.590
21–30 mm	3(10.3)		
SUVmax			
Low (<2.15)	1(2.9)	.007	.008
High (≥2.15)	7(25.9)		
Type of surgery			
Lobectomy	8(15.7)	.159	.173
Segmentectomy	0(0)		
Histology			
BAC	0(0)	.074	.082
Non-BAC	8(17.4)		
Lymphatic or vascular invasion			
Negative	1(2.1)	<.001	<.001
Positive	7(43.8)		
Invasive are size (mm)			
≤5	0(0)	<.001	<.001
>5	8(30.8)		
Ki-67 index			
<25	3(6.0)	.001	<.001
≥25	5(41.7)		

[a] Data are presented as number (%) of patients.

When solid-type adenocarcinomas were stratified according to SUVmax on preoperative FDG-PET, the disease-free survival in solid-type adenocarcinomas with high SUVmax was significantly lower than that in solid-type adenocarcinomas with low SUVmax ($p = .0077$); however, no significant difference was found in Kaplan–Meier curves between air-type adenocarcinomas and solid-type adenocarcinomas with low SUVmax. Three-year disease-free survival rates were 100% in air-type adenocarcinomas,

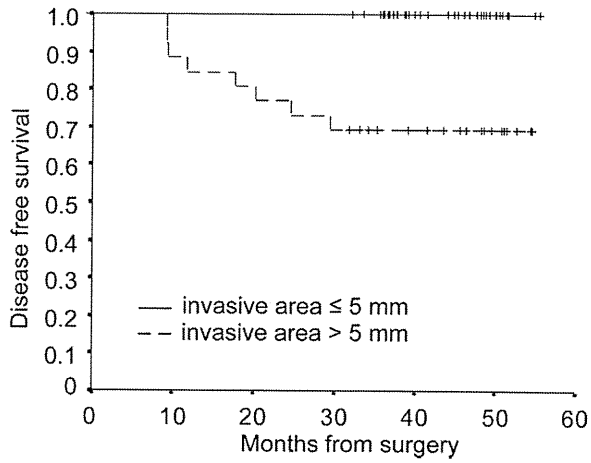

Fig. 1. Disease-free survival for solid-type adenocarcinoma stratified by the presence of pathological invasive area.

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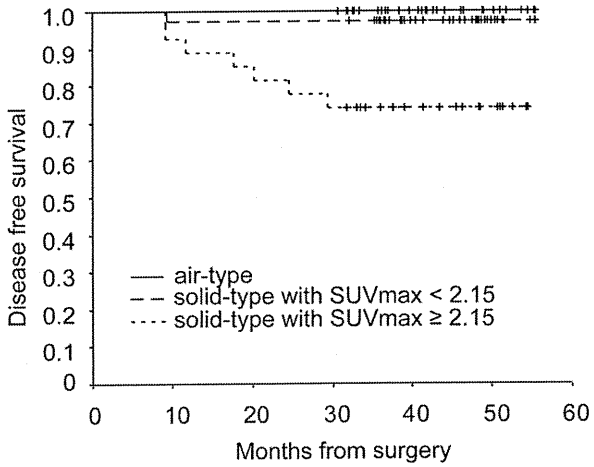

Fig. 2. Disease-free survival for patients with air-type adenocarcinoma or solid-type adenocarcinoma stratified by cut-off value of SUVmax.

97.1% in solid-type adenocarcinomas with low SUVmax, and 74.1% in solid-type adenocarcinomas with high SUVmax (Fig. 2).

4. Discussion

Numerous studies have reported recurrence rates for patients with NSCLC treated by surgical resection with curative intent. In patients with pathological stage I disease, 5-year recurrence rates of 20–39% are reported [11,12], with most recurrences detected within the first 4 years following curative intent surgery [12]. The prediction by preoperative radiological findings of adenocarcinoma with invasive characteristics could play a crucial role in treatment decisions.

In the present study, we reported the preoperative TS-CT and FDG-PET findings to indicate tumor differentiation. A previous study investigated the prognostic value of the ratio of the GGO component in small-sized lung adenocarcinoma of diameter ≤20 mm, reporting a 5-year disease-free survival rate of 100% in patients with air-type tumors on TS-CT who underwent limited resection, but a rate of 60% in patients with solid-type tumors [13]. This classification, based on the ratio of GGO component on TS-CT, could become a useful preoperative indicator when deciding the surgical procedure. Previous studies regarding classification based on the findings of TS-CT are reported for small-sized lung adenocarcinomas of ≤20 mm or less in diameter [2,4,13]. In the present study, we examined peripheral lung adenocarcinomas ≤30 mm in diameter with median follow-up of 42 months. We found no relapse in air-type adenocarcinomas ≤30 mm in diameter, the as same as for adenocarcinomas ≤20 mm in diameter. These results suggest that classification based on the findings of TS-CT could be appropriate for adenocarcinomas ≤30 mm in diameter.

Most of the air-type adenocarcinomas in the present study were BAC. Stromal destruction was revealed in some air-type adenocarcinomas, which are conventionally categorized as having mixed subtypes in the WHO typing, but none showed vascular or lymphatic invasion. In contrast, 74.2% of solid-type adenocarcinomas were non-BAC, 25.8% had vascular or lymphatic invasion, and most had pathological invasive area. Pathological invasive area is known to be associated with prognosis. A diameter of invasive area ≤5 mm is reported to have a good prognosis; a small component of invasive tumor does not adversely affect prognosis, in comparison with the true-BAC type [1]. Of the solid-type adenocarcinomas, 58.1% had invasive area ≤5 mm. Despite the appearances of solid-type adenocarcinomas on TS-CT, no relapses or deaths after resection occurred for invasive area ≤5 mm. This finding indicates that prediction using the diameter of pathological invasive area on solid-type adenocarcinomas could contribute to decisions regarding the choice of surgical procedure and treatment after surgery.

In a previous work, we studied the correlation between SUVmax and pathological invasive area, and reported that an SUVmax cut-off point of 2.15 was the best discriminative value for predicting invasive area >5 mm in solid-type adenocarcinomas ≤30 mm [10]. In the present study, preoperative SUVmax predicted pathological invasive area >5 mm with high accuracy for solid-type lung adenocarcinomas. Of the solid-type adenocarcinomas studied, eight relapsed during the follow-up period of 9.1–29.4 months, and the 3-year disease-free survival was 87%. All eight cases of relapse had invasive area >5 mm. All except one case of relapse were solid-type adenocarcinomas with high SUVmax on preoperative FDG-EPT. Significant difference was found for disease-free survival between solid-type adenocarcinomas with high SUVmax and those with low SUVmax. No statistically significant difference was found regarding disease-free survival between solid-type adenocarcinomas with low SUVmax compared with air-type adenocarcinomas. Therefore, we consider that intentionally limited surgery would be suitable for candidates with solid-type adenocarcinoma with low SUVmax, without lowering the disease-free survival rate. SUVmax on preoperative FDG-PET would be a valuable preoperative indicator for predicting the risk of relapse following curative surgery in stage IA adenocarcinoma.

Because tumor size is known to have prognostic relevance, a new T category was added to the seventh edition of the Tumor, Node, and Metastasis Classification, to include the subclassifications T1a (≤20 mm) and T1b (>20 mm, ≤30 mm). The 5-year postoperative survival rate decreased significantly as tumor size increased [14]. In the present study, no significant difference was found regarding disease-free survival between T1a and T1b adenocarcinomas. Several limitations may have influenced the finding of no significant difference in disease-free survival: (1) the sample size is small; (2) the follow-up period could be insufficient.

The monoclonal antibody Ki-67 detects a nuclear antigen that is present through the cell cycle. Tumor Ki-67 expression is known to be a molecular marker of tumor proliferation, and its overexpression leads to a poorer prognosis in non-small lung cancer [15]. As previously reported, Ki-67 index ≥25% is a prognostic indicator for solid-type adenocarcinomas. In the present study, however, three of the eight cases of relapse had Ki-67 index <25%, which indicates that Ki-67 index does not have a definite prognostic value regarding relapse after resection.

It is important to consider the possibility of false-negative FDG-PET. Despite showing low SUVmax, one patient with solid-type adenocarcinoma had distal relapse to the spine 9.3 months after surgery; the Ki-67 index was 3.8%, which is much lower than the Ki-67 cut-off point of 25%. False-negative PET scan occurs most commonly in small-size tumors because of the partial volume effect [16]. Because SUVmax is affected by Ki-67 expression [17] as well as invasive area, an adenocarcinoma with low Ki-67 index could show low SUVmax, even if the adenocarcinoma had invasive area >5 mm.

The present results suggest that evaluation of SUVmax on FDG-PET in addition to classification by TS-CT findings could predict a poorer prognosis in some patients with solid-type adenocarcinoma. In cases of stage IA lung cancer, the nodule should first be classified as air-type or solid-type according to the TS-CT findings. Solid-type nodules should then be evaluated for tumor aggressiveness by SUVmax on FDG-PET. Patients with IA solid-type adenocarcinomas with high SUVmax would have a high potential for relapse and would therefore benefit from adjuvant therapy. In contrast, limited surgery may be suitable for patients with solid-type adenocarcinoma with low SUVmax. In the present study, however, most of

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the patients with solid-type tumors underwent lobectomy and all of the cases of relapse underwent lobectomy. Therefore, we did not demonstrate the validity of limited surgery for these patients. Further prospective studies are required concerning intentionally limited surgery for patients with small-sized solid-type adenocarcinomas showing low SUVmax.

5. Conclusion

Combined evaluation of the preoperative TS-CT findings and SUVmax on FDG-PET has significant value for predicting recurrence in stage IA lung adenocarcinoma, reflecting the aggressiveness of primary lung adenocarcinoma. Prediction of tumor aggressiveness could contribute to decisions regarding the choice of surgical procedure and post-resection treatment.

Conflict of interest statement

None declared.

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Prognostic Impact of Number of Resected and Involved Lymph Nodes at Complete Resection on Survival in Non-small Cell Lung Cancer

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Background: Lymph node (LN) status is a major determinant of stage and survival in patients with lung cancer. In the 7th edition of the *TNM Classification of Malignant Tumors*, the number of involved LNs is included in the definition of pN factors in breast, stomach, esophageal, and colorectal cancer, and the pN status significantly correlates with prognosis.

Methods: We retrospectively investigated the prognostic impact of the number of resected LNs (RLNs) and involved LNs in the context of other established clinical prognostic factors, in a series of 928 consecutive patients with non-small cell lung cancer (NSCLC) who underwent complete resection at our institution between 2000 and 2007.

Results: The mean number of RLNs was 15. There was a significant difference in the total number of RLNs categorized between less than 10 and ≥10 ($p = 0.0129$). Although the incidence of LN involvement was statistically associated with poor prognosis, the largest statistically significant increase in overall survival was observed between 0 to 3 and ≥4 involved LNs (hazard ratio = 7.680; 95% confidence interval = 5.051–11.655, $p < 0.0001$). On multivariate analysis, we used the ratio between the number of involved LNs and RLNs. The number of RLNs was found to be a strong independent prognostic factor for NSCLC (hazard ratio = 6.803; 95% confidence interval = 4.137–11.186, $p < 0.0001$).

Conclusion: Complete resection including 10 or more LNs influenced survival at complete NSCLC resection. Four involved LNs seemed to be a benchmark for NSCLC prognosis. The number of involved LNs is a strong independent prognostic factor in NSCLC, and the results of this study may provide new information for determining the *N* category in the next tumor, node, metastasis classification.

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Lung cancer has one of the highest worldwide incidence rates and is the leading cause of cancer-related mortality worldwide.[1] In Japan, lung cancer accounts for 60,000 deaths annually, and surgical resections are performed in approximately 27,000 cases, with an overall survival (OS) rate of 60%, according to the annual reports of the Japanese Association for Thoracic Surgery[2] and the Japanese Lung Cancer Registry.[3]

Various pathological and molecular markers have been assessed regarding their status and role in identifying patients at high risk for recurrence. However, the primary tumor, lymph node (LN), and the metastasis (TNM) staging system remain the most important determinant of outcome. Because the prognosis of lung cancer is directly proportional to the presence of LN metastasis, accurate LN assessment is crucial in determining treatment. The role of hilar and mediastinal lymphadenectomy in the staging and treatment of non-small cell lung cancer (NSCLC) remains controversial. Accurate staging of NSCLC requires assessment of the hilar and mediastinal LNs based on pathologic evaluation. In almost all surgical cooperative group trials and clinical settings in Japan, systematic LN dissection in ipsilateral hilar and mediastinal stations is standard. However, there is continual debate regarding the degree to which hilar and mediastinal LNs should be located and removed.

The number of resected LNs (RLNs) has been proven to have prognostic value in colorectal, breast, and bladder cancer.[4–6] Moreover, the number of involved LNs at the time of surgery currently influences staging. However, these items have not yet been incorporated into the latest 7th edition of the TNM classification of lung cancer.[7]

Therefore, we retrospectively investigated the prognostic impact of the number of RLNs and involved LNs in the context of other established clinical prognostic factors, in a series of 928 consecutive patients with NSCLC who underwent complete

resection at Tokyo Medical University. Specifically, we attempted to clarify the number of LNs that should be resected, and the number of involved LNs needed to make an accurate prognosis.

PATIENTS AND METHODS

Patient Selection

From January 2000 to November 2007, a total of 1311 patients underwent resection for primary lung cancer at our institution. Cases of induction therapy, incomplete resection, and limited resection were excluded from this study. Patients whose tumors were classified histologically as small cell lung cancer or low-grade malignant tumors were also excluded. We retrospectively analyzed the remaining 928 consecutive patients with NSCLC who underwent complete resection with curative intent (minimum procedure of lobectomy) with systematic LN dissection of the hilum and mediastinum according to current surgical methods.[8] Patient charts, including pathologic diagnosis and operative reports, were reviewed. Staging was determined according to the international TNM staging system.[9] The histological tumor type was determined according to the World Health Organization classification, 3rd edition. All dissected LNs were examined pathologically and classified according to anatomical location by the numbering system described in the Naruke map.[10] The number of RLNs and involved LNs was confirmed based on the pathological report provided by M.N., J.M., and T.N. These pathologists were blinded to the clinical outcome.

Patient Characteristics

The characteristics of the 928 consecutive patients who underwent surgery for NSCLC were as follows: age, median (range): 65.0 years (22–87 years); sex: 547 (59.0%) men and 381 (41.0%) women; clinical stages: 768 (82.8%) stage I, 84 (9.1%) stage II, and 76 (8.1%) stage III; pathological stage: 677 (72.9%) stage I, 121 (13.0%) stage II, 129 (13.9%) stage III, and 1 (0.2%) stage IV; histopathological diagnosis: 684 (73.7%) adenocarcinomas, 182 (19.6%) squamous cell carcinomas, 52 (5.6%) large cell carcinomas, and 10 (1.1%) others; surgical procedure: 870 (93.8%) lobectomies, 42 (4.5%) bilobectomies, and 16 (1.7) pneumonectomies. The mean number of RLNs was 15 (right side, 15.5; left side, 14.3); the mean number of involved LNs was 4.2 (0–22) (Table 1). The median follow-up time was 3.5 years.

TABLE 1. Patient Characteristics

Variable	Category	*n* (%)
Age (yr)	Mean	65.0
	Range	22–87
Sex	Men	548 (59.0)
	Women	380 (41.0)
Histopathology	Adenocarcinoma	684 (73.7)
	Squamous cell	182 (19.6)
	Large cell	52 (5.6)
	Other	10 (1.1)
Clinical stage	I	768 (82.8)
	II	84 (9.1)
	III	76 (8.1)
Pathological stage	I	677 (72.9)
	II	121 (13.0)
	III	130 (14.1)
Tumor location	Right side	602 (64.9)
	Upper/middle/lower	334/64/204
	Left side	326 (35.1)
	Upper/lower	190/136
Surgical procedure	Lobectomy	870 (93.8)
	Bilobectomy	42 (4.5)
	Pneumonectomy	16 (1.7)
Total number of resected LNs	Mean (range)	15.0 (1–49)
	0–4	59 (6.4)
	5–9	177 (19.1)
	10–14	251 (27.0)
	15–19	201 (21.6)
	≥20	241 (25.9)
Total number of involved LNs in positive cases	Mean (range)	4.2 (1–22)
	0	724 (78.0)
	1–3	122 (13.1)
	≥4	82 (8.9)

LNs, lymph nodes.

Statistical Analysis

We investigated the association between the total number of RLNs or involved LNs and OS. OS was calculated from the date of surgery to the time of death. Observations were censored at final follow-up if the patient was alive. All patients in this series were categorized into four groups according to the number of RLNs less than 5 versus 5 or more, less than 10 versus 10 or more, less than 15 versus 15 or more, and less than 20 versus 20 or more. On analysis of survival differences based on the number of involved LNs, patients were categorized into groups of those with 0 versus 1 or more, less than 3 versus 3 or more, less than 4 versus 4 or more, and less than 5 versus 5 or more of involved LNs. Survival curves were plotted using the Kaplan-Meier method. Differences in survival among the groups were examined using the log-rank test. A two-category comparison was performed using the Pearson χ^2 test and the Student t test for quantitative data. Multivariate analysis was performed using the Cox proportional hazards model to examine any possible association between the ratio of the total number of RLNs and involved LNs and survival, with adjustment for the effects of other potential prognostic factors, including age, sex, histology, tumor factor, and type of surgery performed. All tests were two sided, and p values of less than 0.05 were considered to represent statistically significant differences. StatView version 5.0 software (SAS Institute Inc., Cary, NC) was used for statistical analysis.

Ethical Considerations

The approval of the Institutional Review Board of Tokyo Medical University was obtained, but as this was a retrospective study the need to obtain written informed consent from either the patients or their representatives was waived, in accordance with the AMA Manual of Style (10th edition).