Original Article

Repeat FDG-PET for Predicting Pathological Tumor Response and Prognosis after Neoadjuvant Treatment in Nonsmall Cell Lung Cancer: Comparison with Computed Tomography

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Background: The efficacy of fluorodeoxyglucose-positron emission tomography (FDG-PET) for predicting pathological tumor response and prognosis after neoadjuvant chemoradiotherapy followed by surgery in locally advanced nonsmall cell lung cancer (NSCLC) was compared to the predictive value of tumor size as determined by computed tomography (CT).

Methods: Thirty-seven consecutive NSCLC patients who received FDG-PET and CT scans both before and after neoadjuvant chemoradiotherapy were enrolled in this study. The percentage point changes in maximum standard uptake value (SUV) on PET and tumor size on CT after neoadjuvant treatment were defined as the SUV ratio and the size ratio, respectively, and were compared with pathological tumor response and prognosis after surgery. A major pathological response was defined as residual viable tumor cells corresponding to less than one-third the size of the original tumor.

Results: Nineteen and 18 patients showed major and minor pathological responses, respectively, after neoadjuvant treatment. The optimal cutoff values for predicting a major pathological response were 0.6 for the SUV ratio and 0.79 for the size ratio. The SUV ratio predicted the pathological tumor response with higher accuracy than the size ratio did ($P = 0.04$). Neither the SUV ratio nor the size ratio predicted prognosis after surgery.

Conclusion: For predicting the pathological tumor response after neoadjuvant chemoradiotherapy, the SUV ratio on FDG-PET is superior to the size ratio on CT in patients with NSCLC. However, neither the SUV ratio nor the size ratio could predict prognosis. (Ann Thorac Cardiovasc Surg 2010; 16: 394–400)

Key words: positron emission tomography, chemotherapy, radiotherapy, lung cancer

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Introduction

Recently, neoadjuvant treatment followed by surgery has been employed as a multimodal therapy for locally advanced nonsmall cell lung cancer (NSCLC).[1–3] Although several studies have reported that the reduction of fluorodeoxyglucose (FDG)-uptake on positron emission tomography (PET) after neoadjuvant treatment followed by surgery is effective for predicting pathological tumor response[4–6] and prognosis,[7,8] controversies persist.[9–11] The present study compares the usefulness of FDG-PET with that of computed tomography (CT) for predicting pathological tumor response and prognosis after neoadjuvant treatment in 37 consecutive patients with NSCLC who underwent FDG-PET and CT both before and after neoadjuvant treatment.

Methods

Eligibility

The study protocol, performing FDG-PET in patients with lung tumors prior to surgery, was approved by the Ethics Committee of Kumamoto University Hospital. Informed consent was obtained from all patients after the costs and benefits of FDG-PET examinations before and after neoadjuvant treatment had been explained by their surgeons.

Patients

From December 2001 to November 2008, FDG-PET and CT scans were undertaken both before and after neoadjuvant treatment in 37 patients with locally advanced NSCLC (Table 1). Clinical N-staging was conducted by PET and CT without histopathological diagnosis. The pre- and post-FDG-PET and CT scans were conducted within 2 weeks before and again more than 2 weeks after neoadjuvant treatment. Pulmonary resection with systemic lymph node dissection was conducted from 3 to 6 weeks after this treatment. Pathological tumor stages were based on the TNM classification of the International Union Against Cancer.[12] Thirty-two patients received concurrent chemoradiotherapy; four received only chemotherapy; and one received only radiotherapy. The chemotherapy regimens in the patients receiving chemoradiotherapy were a combination of carboplatin and vinorelbine every 3 weeks from 2001 to 2004 and a combination of carboplatin and paclitaxel every week from 2005 to 2008. The four patients given only chemotherapy received a combination of carboplatin and gemcitabine every 3 weeks. The mean number of chemotherapy courses was 2.7 ± 1.2 (range 1–5). The total dose of radiotherapy was 30 Gy from 2001 to 2004 and 40 Gy from 2005 to 2008. Clinical response was evaluated by measuring tumor diameter according to RECIST criteria[13].

Table 1. Patients' characteristics

Mean age		62 years old (range: 36–79)
Sex	Male	30
	Female	7
Histological type		
	Adenocarcinoma	20
	Squamous cell carcinoma	13
	Pleomorphic carcinoma	2
	Adenosquamous carcinoma	1
	Spindle cell carcinoma	1
Clinical stage		
	Ib	2
	IIa	2
	IIb	7
	IIIa	14
	IIIb	12
Pathological stage		
	Complete response	5
	Ia	6
	Ib	4
	IIa	3
	IIb	6
	IIIa	8
	IIIb	5
Clinical tumor response		
	Partial response	12
	Stable disease	25
Pathological tumor response		
	Major response (Ef2 and Ef3)	19
	Minor response (Ef0 and Ef1)	18
Total		37

FDG-PET scanning and data analysis

PET imaging was performed as reported previously.[14,15] FDG uptake was calculated as maximum SUV (SUV max) derived from regions of interest (ROI). The change in FDG uptake in the primary tumor after neoadjuvant treatment was calculated as follows:

SUV ratio = SUV max after treatment/SUV max before treatment.

CT scanning and CT data analysis

The entire thorax was scanned using sections less than 1

cm thick with maximal inspiration. The longest diameter of the tumor was measured before and after neoadjuvant treatment. The change in tumor size on CT after neoadjuvant treatment was calculated with the following formula:

Size ratio = tumor size after treatment/tumor size before treatment.

Pathological response

Pathological response was defined according to the criteria of the Japan Lung Cancer Society,[16] i.e., Ef0 was defined as no therapeutic response. Ef1 as residual viable tumor cells constituting more than one-third of the tumor, Ef2 as residual viable tumor cells constituting less than one-third of the tumor, and Ef3 as no viable tumor cells. Ef0 and Ef1 were defined as a minor pathological response. Ef2 and Ef3 were defined as a major pathological response.

Determining the cutoff values for the size ratio and the SUV ratio

A receiver operating characteristics (ROC) curve was constructed according to the SUV ratio on PET and the size ratio on CT, using SPSS software (SPSS15.0J for Windows, SPSS, Chicago, IL); the cutoff values for predicting major and minor pathological responses were then determined. Tumors with values below the cutoff values of the SUV ratio and size ratio were defined as showing a major response on PET and CT. Tumors with values above those of the SUV ratio and the size ratio were defined as showing a minor response on PET and CT, respectively.

Statistical analysis

Any tumor with a major response on PET or CT showing a major pathological response was defined as a true positive (TP). Any tumor with a minor response on PET or CT showing a minor pathological response was defined as a true negative (TN). Any tumor with a major response on PET or CT showing a minor pathological response was defined as a false positive (FP). Any tumor with a minor response on PET or CT showing a major pathological response was defined as a false negative (FN). Sensitivity was calculated as TP/TP + FN, specificity as TN/TN + FP, accuracy as TP + TN/total, positive predictive value (PPV) as TP/TP + FP, and negative predictive value (NPV) as TN/TN + FN. The differences in sensitivity, specificity, and accuracy between PET and CT were analyzed using the McNemar test. The differences in PPV and NPV between PET and CT were analyzed using the χ^2-test. Postoperative survival estimated by the Kaplan-Meier curve was used to compare major and minor responses on PET and CT by the log-rank test. Statistical analyses were performed using SPSS software. All values in the text and tables are given as means ± standard deviation.

Results

The clinical responses for neoadjuvant treatment determined by CT were a partial response in 12 patients and stable disease in 25 (Table 1). Nineteen of the 37 patients showed a major pathological response, the remaining 18 a minor pathological response.

The mean SUV ratio after neoadjuvant treatment was 0.32 ± 0.16 in the 19 patients with major pathological response, i.e., significantly lower than the 0.80 ± 0.22 in the 18 patients with minor pathological response ($P < 0.001$) (Fig. 1a). The mean size ratio after neoadjuvant treatment was 0.63 ± 0.23 in the 19 patients with major pathological response, i.e., significantly lower than the 0.86 ± 0.19 in the 18 patients with minor pathological response ($P = 0.002$) (Fig. 1b).

The ROC curves for discriminating major from minor pathological responses showed the optimal cutoff value of the SUV ratio on PET to be 0.6 and that of the size ratio on CT to be 0.79 (Fig. 2). With these cutoff values, 19 patients showed a major response by the SUV ratio, 17 a major response by the size ratio (Table 2).

Table 3 shows the correlation between the SUV ratio and the size ratio for sensitivity in predicting a major pathological response. The sensitivity of the SUV ratio was 0.95 (95% confidence interval [CI]: 0.74–1.00), i.e., higher than the 0.68 (95% CI: 0.43–0.87) for CT, but the difference did not reach statistical significance (McNemar test, $P = 0.13$).

Table 4 shows the correlation between the SUV ratio and the size ratio for specificity in predicting a minor pathological response. The specificities of the SUV ratio and the size ratio were 0.94 (95% CI: 0.73–1.00) and 0.78 (95% CI: 0.52–0.94), respectively, i.e., not significantly different (McNemar test, $P = 0.38$).

Table 5 shows the correlation between the SUV ratio and the size ratio for accuracy in discriminating major/minor pathological responses in all 37 patients. The accuracy of the SUV ratio on PET was 0.95 (95% CI: 0.82–0.99), i.e., significantly higher than the 0.73 (95% CI: 0.56–0.86) of the size ratio on CT (McNemar test, $P = 0.04$). The PPV by PET and CT were 0.95 and 0.76, not significantly different ($P = 0.17$). The NPV by PET was 0.94, i.e., higher than the 0.70 by CT, with marginal significance ($P = 0.09$).

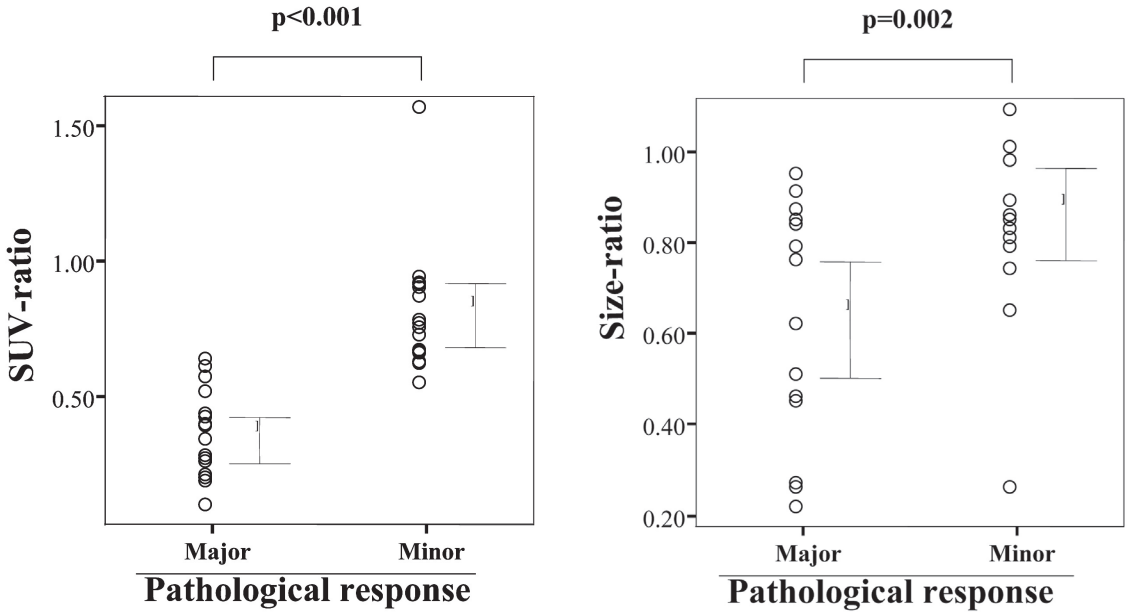

Fig. 1. (**a**) Distributions of the SUV ratios in patients with major and minor pathological responses. (**b**) Distributions of the size ratios in patients with major and minor pathological responses. SUV, standard uptake value.

a | b

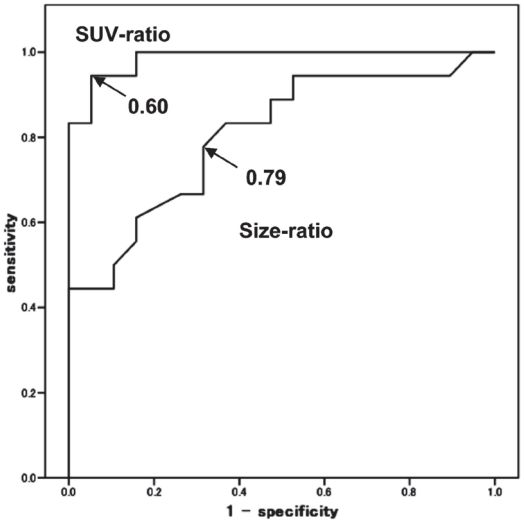

Fig. 2. The receiver operating characteristics curves of sensitivity plotted against 1-specificity for SUV ratios and size ratios for major responders (area under curve = 0.99 for the SUV ratio and 0.81 for the size ratio). SUV, standard uptake value.

Table 2. Relationship between the pathological response and the cutoff values of SUV ratio and size ratio

	Response on SUV ratio		Response on size ratio		
Pathological response	< 0.6	≧ 0.6	< 0.79	≧ 0.79	Total
Major	18	1	13	6	19
Minor	1	17	4	14	18
Total	19	18	17	0	37

SUV, standard uptake value.

Table 3. Correlation between computed tomography and positron emission tomography for predicting major pathological responses

	PET		
CT	True positive	False negative	Total
True positive	12	1	13
False negative	6	0	6
Total	18	1	19

Sensitivity of PET = 0.95 (95% CI: 0.74–1.00)
Sensitivity of CT = 0.68 (95% CI: 0.43–0.87)
McNemar test: $P = 0.13$
PET, positron emission tomography; CT, computed tomography.

Table 4. Correlation between computed tomography and positron emission tomography for predicting minor pathological responses

	PET		
CT	True negative	False positive	Total
True negative	13	1	14
False positive	4	0	4
Total	17	1	18

Specificity of PET = 0.94 (95% CI: 0.73–1.00)
Specificity of CT = 0.78 (95% CI: 0.52–0.94)
McNemar test: $P = 0.38$
PET, positron emission tomography; CT, computed tomography.

Table 5. Correlation between computed tomography and positron emission tomography for predicting pathological responses

	PET		
CT	Correct	Incorrect	Total
Correct	25	2	27
Incorrect	10	0	10
Total	35	2	37

Accuracy of PET = 0.95 (95% CI: 0.82–0.99)
Accuracy of CT = 0.73 (95% CI: 0.56–0.86)
PET, positron emission tomography; CT, computed tomography.

The median follow-up of all patients was 26 months (range: 2–80 months). During this time, 27 patients experienced tumor recurrence. None of the patients died of any complications associated with neoadjuvant treatment or surgery. The estimated 1- and 2-year overall survival rates were 79% (95% confidence interval [CI]: 65–93) and 67% (95% CI: 51–83), respectively. The estimated 1- and 2-year survival rates in the 19 patients with major responses by the SUV ratio were 88% (95% CI: 71–100) and 81% (95% CI: 62–100), respectively, not significantly different from the corresponding 71% (95% CI: 49–92) and 53% (95% CI: 29–77) in the 18 patients with minor responses by the SUV ratio ($P = 0.15$) (Fig. 3a). The estimated 1- and 2-year survival rates in the 17 patients with major responses by size ratio were 87% (95% CI: 69–100) and 73% (95% CI: 51–96), respectively, not significantly different from the corresponding 72% (95% CI: 52–93) and 61% (95% CI: 38–84) in the 20 patients with minor responses by the size ratio ($P = 0.29$) (Fig. 3b).

Discussion

The present study demonstrated two points: (1) The SUV-ratio on FDG-PET had higher accuracy than the size ratio on CT for predicting pathological tumor response after neoadjuvant treatment; (2) Neither the SUV ratio nor the size ratio could predict prognosis after surgery.

The higher accuracy of the SUV ratio as compared to the size ratio was attributable mainly to the NPV difference ($P = 0.09$), suggesting that CT cannot predict minor pathological responses as well as FDG-PET. Because the evaluation of residual tumor by CT scanning is based solely on size, changes in tumor size on CT do not reflect the percent of viable residual cells after neoadjuvant treatment, which probably accounts for the low NPV on CT in the present study.

Several authors have examined the utility of FDG-PET for predicting pathological response after neoadjuvant treatment in patients with NSCLC.[4–6] Ryu et al. and Akhurst et al. demonstrated the usefulness of FDG-PET

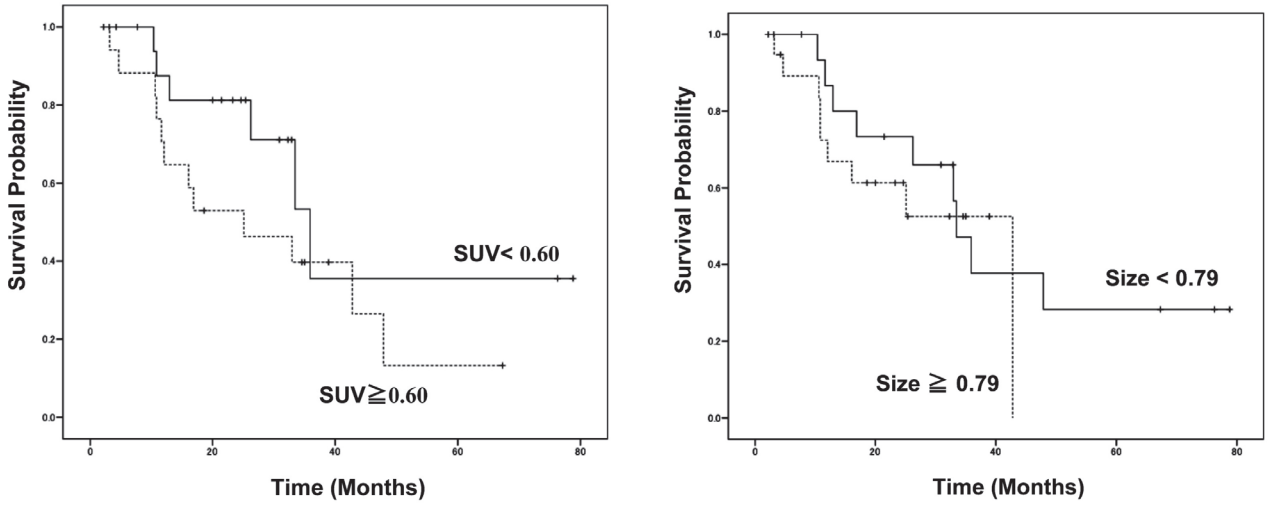

Fig. 3. (**a**) Survival stratified by the SUV ratio on PET (patients with lower vs. higher SUV ratios than the cutoff value). (**b**) Survival stratified by size ratio on CT (patients with lower vs. higher size ratios than the cutoff value). SUV, standard uptake value.

for monitoring the therapeutic effect of neoadjuvant chemotherapy in patients with NSCLC.[4,5] However, these two prior studies examined only the SUV value after neoadjuvant treatment, not the SUV ratio before versus after this treatment. In 2004, Port et al. studied 25 patients undergoing FDG-PET both before and after neoadjuvant chemotherapy and described that a "reduction in the SUV of 50% or more" could not predict the pathological tumor response.[10] On the other hand, Cerfolio et al. in 2004 studied 56 patients undergoing FDG-PET both before and after neoadjuvant chemotherapy or chemoradiotherapy and examined the correlation between the percent of nonviable tumor cells on pathological sections and changes in the SUV on FDG-PET or the size on CT, showing the percent of nonviable tumor cells to correlate significantly with PET, but not with CT results.[6] Their findings are consistent with our present results. Although controversies persist, the results of the present study indicate the pathological tumor response after neoadjuvant treatment to be predicted by the SUV ratio on PET rather than the size ratio on CT and suggest an appropriate cutoff value of the SUV ratio for predicting a major pathological response to be approximately 0.6.

Although several studies have examined the correlation between SUV on FDG-PET and survival after neoadjuvant therapy followed by surgery in patients with locally advanced NSCLC, their results are also controversial.[8,11,17,19] Regarding neoadjuvant treatment using chemotherapy alone, Hoeskstra et al. reported that among 47 patients with stage III NSCLC, those with a reduction of more than 50% in SUV after therapy had significantly longer survival than those with values of less than 50%.[17] In contrast, Tanvetynon et al. studied 89 patients with stages I-III, who showed no significant difference in survival using a cutoff value of 30% reduction in SUV after chemotherapy.[11] Regarding neoadjuvant chemoradiotherapy, Eschmann et al. studied 65 patients with stage III NSCLC and found that those with more than 75% reduction in SUV after chemoradiotherapy had significantly longer survival than those with values below 75%.[8] P-ttgen et al., however, studying 50 patients with stage III, found no significant correlation between SUV reduction after chemoradiotherapy and survival.[18] Although the adjuvant therapy in the present study was either chemotherapy or chemoradiotherapy, neither the SUV ratio nor the size ratio predicted postoperative survival.

We conclude that although the SUV ratio on FDG-PET is superior to the size ratio on CT for predicting pathological responses after neoadjuvant treatment on patients with NSCLC, neither predicts patient survival after neoadjuvant therapy followed by surgery.

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