Value of Combined Interpretation of Computed Tomography Response and Positron Emission Tomography Response for Prediction of Prognosis After Neoadjuvant Chemotherapy in Non-small Cell Lung Cancer

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Introduction: The purpose of this study was to assess the value of tumor response evaluation using combined interpretation of [18F] fluorodeoxyglucose positron emission tomography (PET) and computed tomography (CT) for the prediction of clinical outcome and pathologic response in patients with stage III non-small cell lung cancer who underwent neoadjuvant chemotherapy followed by surgery.

Methods: This study was approved by the Institutional Review Board with a waiver of informed consent. Forty-four consecutive patients (M:F = 32:12; mean age, 60.7 years) with locally advanced non-small cell lung cancer received neoadjuvant chemotherapy followed by curative surgery. Time to recurrence (TTR) was stratified by radiologic, metabolic, and radiologic-metabolic response using the Kaplan-Meier method. The accuracy of radiologic, metabolic, and radiologic-metabolic response criteria for the prediction of pathologic response was evaluated.

Results: Radiologic-metabolic responders had a longer TTR than nonresponders (mean TTR, 58.7 months versus 22.3 months, $p = 0.001$ with criteria of ≥30% reduction of size and ≥50% reduction of [maximum standardized uptake value] SUV_{max} and mean TTR, 49.4 months versus 23.5 months, $p = 0.022$ with criteria of ≥30% reduction of size and ≥25% reduction of SUV_{max}, respectively). The TTR of radiologic responders (criteria of ≥30% reduction of size) and metabolic responders (criteria of ≥25% reduction of SUV_{max}) was not different from the TTR of nonresponders ($p > 0.05$). The accuracy for the prediction of pathologic response was 70% in radiologic responders, 52 to 75% in metabolic responders, and 73 to 82% in radiologic-metabolic responders.

Conclusions: Tumor response evaluation using combined interpretation of [18F] fluorodeoxyglucose-PET and CT was more effective than single interpretation of CT response or PET response alone for the prediction of tumor recurrence and pathologic response.

Key Words: Non-small cell lung cancer, FDG-PET, Response Evaluation Criteria in Solid Tumor (RECIST), Response evaluation, prognosis.

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Tumor response after chemotherapy reflects the reduction of tumor burden in a patient and can be used as a predictor of patients' outcome. Change in size according to RECIST using a computed tomography (CT) scan is used as a standard to assess response to therapy, and there have been many attempts to correlate the change in tumor size on CT with the pathologic response or survival of patients with non-small cell lung cancer (NSCLC).[1] Recent data have suggested that tumor response evaluated on [18F] fluorodeoxyglucose (FDG) positron emission tomography (PET) after chemotherapy may have a significant correlation with histopathologic response[2–5] or survival[6–10] in patients with NSCLC.

Although tumor response on both a CT scan and PET scan seems to have prognostic significance among patients with advanced NSCLC, this association has been controversial for patients who have earlier stages of the disease and undergo neoadjuvant chemotherapy. According to a recent article by Tanvetyanon et al.,[11] among patients with resectable NSCLC treated with neoadjuvant chemotherapy, there was no evidence that tumor response on a PET scan after chemotherapy was prognostic of survival, although response on a CT scan was indeed associated with better survival. However, in contrast, many investigators have suggested the value of tumor response evaluation using PET scan with one study reporting that in patients with stage III NSCLC who underwent neoadjuvant chemotherapy followed by surgery, the median overall survival was almost four times longer

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among patients with no residual glucose metabolism detected than those with residual glucose hypermetabolism.[8] Furthermore, in another study, Vansteenkiste et al.[9] showed that a reduction of greater than 50% of the metabolic activity of the tumor on PET scan after induction of chemotherapy was associated with longer survival in patients with stage III NSCLC.

However, to date, the synergistic value of the combined evaluation of PET and CT for evaluation of response has not been evaluated. Therefore, the purpose of this study was to assess the value of tumor response evaluation using combined interpretation of FDG-PET and CT for the prediction of clinical outcome and pathologic response in patients with stage III NSCLC who underwent neoadjuvant chemotherapy followed by surgery.

PATIENTS AND METHODS

Patients

Our Institutional Review Board approved this retrospective study. Written informed consent was obtained for the use of CT and PET studies from all patients.

Among 52 consecutive patients with locally advanced NSCLC who received neoadjuvant chemotherapy between January 2004 and January 2007 followed by curative surgery, six patients showing disease progression after neoadjuvant chemotherapy and two patients lost to follow-up were excluded. Finally, 44 consecutive patients (M:F = 32:12; mean age, 60.7 years) with locally advanced NSCLC (stages IIIA/IIIB) who received neoadjuvant chemotherapy followed by curative surgery were included in this study. All patients underwent integrated PET/CT and contrast-enhanced chest and brain CT before (T0) and after neoadjuvant chemotherapy (T1). Staging procedures included bronchoscopy or mediastinoscopy in all patients. Preoperative chemotherapy consisted of two or three cycles with 175 mg/m^2 of paclitaxel and 60 mg/m^2 of cisplatin.

Imaging and Interpretation

PET and CT scans were first performed less than 2 weeks before neoadjuvant chemotherapy (T0). The second PET and CT scans were performed 4 weeks after final cycle of neoadjuvant chemotherapy (T1).

All chest CTs were performed with Sensation-16 (Siemens Medical Systems, Erlangen, Germany), Lightspeed Ultra (GE Medical Systems, Milwaukee, WI), or Mx8000 (Philips Medical Systems, Best, The Netherlands) with 120 kVp, 150 to 200 mAs, pitch of 0.875 to 1.5, collimation of 1 to 2.5 mm, and reconstruction thickness 5 mm. CT images were acquired after intravenous injection of 100 to 120 ml of Ultravist 370. Two chest radiologists (H.J.L. and H.Y.L. with 10 and 5 years of experience in thoracic CT interpretation, respectively) unaware of the clinical and PET findings and the histologic diagnoses independently assessed the CT scans.

The longest diameters of all target lesions including primary tumor and their percentage change after chemotherapy were measured according to the RECIST.[12] Discrepancies in evaluation among the two readers were resolved by averaging their determined values.

Before intravenous administration of 18F-FDG (5.2 MBq/kg of body weight), patients were instructed to fast for at least 4 hours to ensure a serum glucose level below 140 mg/dl. Whole body PET images were acquired with the conventional three-dimensional protocol of 18F-FDG PET using a Gemini PET/CT camera (Philips Medical Systems, Cleveland, OH) and a two-slice CT scanner. The resulting PET and CT images were coregistered on hardware. Low-dose CT was performed from head to pelvis using a tube voltage of 120 kV, 50 mA, a tube-rotation time of 0.75 seconds per rotation, a pitch of 1.5, and 6.5 mm reconstruction thickness, which matched the PET image section thickness. Low-dose CT was acquired for attenuation correction and anatomic localization without intravenous contrast material, with no breath hold. Immediately after CT, emission PET images were acquired for 2 minutes and 30 seconds per each bed in three-dimensional acquisition mode. Transaxial images from 1 hour acquisition of a patient were analyzed for quantitative analysis. A nuclear medicine physician (K.W.K. with 10 years of experience in PET/CT interpretation) unaware of the clinical and pathologic results evaluated the PET images. For semiquantitative analysis of FDG uptake, a region of interest was placed over the most intense area of FDG accumulation for each patient. FDG uptake within the region of interest was analyzed by the maximum standardized uptake value (SUV_{max}). The maximum SUV was calculated as decay-corrected activity (kBq) per milliliter of tissue volume per injected 18F-FDG activity (kBq) per body mass (g). SUV_{max} measured in the primary tumor on pre- and postchemotherapy PET scans were recorded, and the percent change in the SUV_{max} was calculated.

Response

Radiologic response was determined using RECIST, which considers a 30% or greater reduction in the sum of unidimensional tumor measurements as a response.[12] Metabolic response was determined by semiquantitative analysis. For patients with multiple lesions, the most hypermetabolic lesion was taken as the index lesion. Metabolic response was defined as a 25% or greater reduction in the SUV_{max} as referred from the EORTC PET response criteria.[13] In addition, an analysis based on a 50% or greater reduction in the SUV_{max} was performed.[2,8,9] Radiologic-metabolic responses as a reduction of tumor size of $\geq$30% and a reduction of SUV_{max} of $\geq$25%, $\geq$30%, and $\geq$50% were analyzed.

Pathologic Response

Pathologic response was used as the reference standard of therapeutic response. Resected tissues from primary tumors and mediastinal lymph nodes were formalin fixed and paraffin embedded. An experienced lung pathologist (B.G.J. with 4 years of experience in lung pathology) retrospectively interpreted entire tissue sections sliced at 5- to 10-mm intervals and measured the proportion (%) of viable tumor cells in the primary tumor of the resected surgical specimens. Pathologic response was defined as when viable tumor cells constitute less than 10% of the entire pathologic specimen.[14] The presence of residual viable tumor was evaluated in resected mediastinal lymph nodes.

Postoperative Follow-Up

After the completion of treatment, patients were followed up at 3-month interval with chest CT scans to identify any disease recurrence for 1 year. When there was no evidence of recurrence during first postoperative year, chest CT scans were followed at 6-months interval for second postoperative year. When there was no evidence of recurrence during 2 postoperative years, chest CT scans were followed subsequently at 12-month interval. When there was an evidence of recurrence, additional imaging studies including whole body FDG-PET, brain MRI, and bone scans were performed.

Statistical Analysis

Time to recurrence (TTR) was determined using the Kaplan-Meier method, and TTR curves were stratified by radiologic, metabolic, radiologic-metabolic, and pathologic response criteria. Comparison of the Kaplan-Meier curves was made by the log-rank test. TTR was measured from the date of curative resection to the date of detection of recurrence.

The accuracy of radiologic, metabolic, and radiologic-metabolic criteria for the prediction of a pathologic response was evaluated. The percent change (%) in size on CT and SUV_{max} of the primary tumor were correlated with the proportion (%) of viable tumor cells from pathology using Spearman's correlation analysis. Cox proportional hazards regression analysis was used to assess the prognostic value of response criteria. All analyses were done using SPSS for Windows, version 12.0 (SPSS, Inc., Chicago, IL).

RESULTS

Patient Demographics

Details of the patient characteristics are summarized in Table 1. All 44 patients underwent complete surgical resection and followed by the postoperative follow-up protocol.

TABLE 1. Patient Characteristics ($n = 44$)

Characteristics	Number (%)
Age (y)	
Median (range)	61 (40–74)
Sex	
Male	32 (73)
Female	12 (27)
Histology	
Adenocarcinoma	24 (55)
Squamous cell	17 (39)
Large cell or neuroendocrine	1 (2)
Non-small cell, not specified	2 (4)
Clinical stage	
IIIA	36 (82)
IIIB	8 (18)
Procedure	
Lobectomy	30 (68)
Bilobectomy	5 (11)
Pneumonectomy	9 (21)

The median postoperative follow-up time for all patients was 24.8 months (range, 3.1–66.2 months). By July 2009, 22 patients (50%) developed recurrent disease after surgical resection, and the median TTR was 12 months (range, 4–31 months). Recurrence or metastasis was confirmed by specific organ-dedicated or follow-up imaging studies. The pattern of recurrence was brain metastasis ($n = 8$), lung metastasis ($n = 4$), recurrence at the resection site ($n = 4$), metastasis in mediastinal lymph nodes ($n = 3$), bone metastasis ($n = 2$), and metastasis in extrathoracic lymph nodes ($n = 1$), respectively.

TTR Based on Tumor Response by CT

Kaplan-Meier survival curves stratified by radiologic, metabolic, and radiologic-metabolic response criteria are shown in Figures 1 to 5. The median change in tumor size was a decrease of 35% (ranging from 3 to 65% decrease) before and after neoadjuvant chemotherapy. On the basis of RECIST categories, 23 patients (53%) showed partial response and 21 patients (47%) showed stable disease. Comparing patients with and without radiologic responses, there was no significant difference in the TTR between the two groups (mean TTR, 44.7 months versus 24.5 months and median TTR, not reached versus 16.8 months, respectively; $p = 0.11$; Figure 1).

TTR Based on Tumor Response by PET/CT

The median change in the SUV_{max} before and after neoadjuvant chemotherapy was a decrease of 45% (ranging

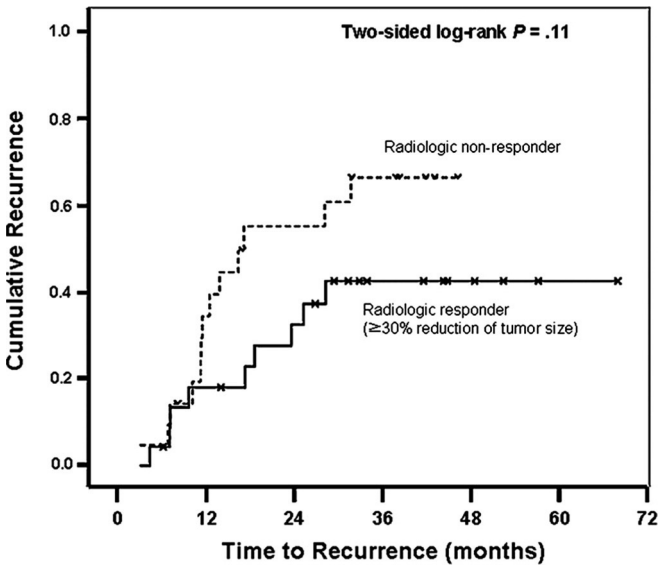

FIGURE 1. Time to recurrence (TTR) based on tumor response on computed tomography (CT). Comparing patients with and without radiologic responses (≥30% reduction of tumor size), there was no significant difference in the TTR between the two groups (mean TTR, 44.7 versus 24.5 months and median TTR, not reached versus 16.8 months, respectively; $p = 0.11$).

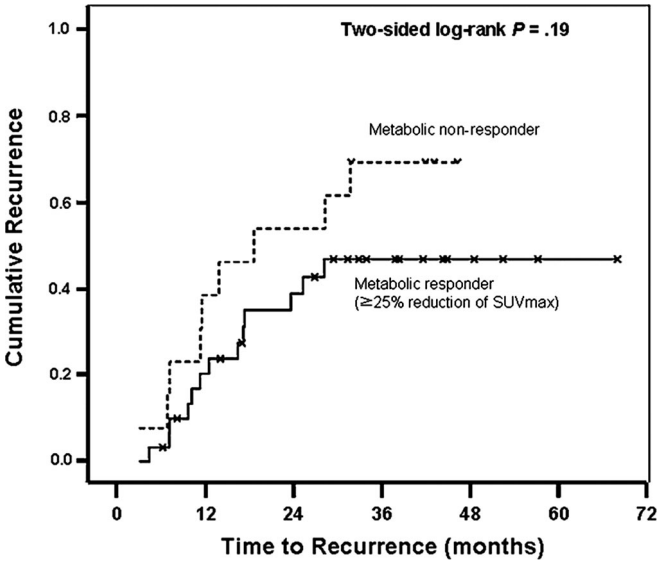

FIGURE 2. Time to recurrence (TTR) based on tumor response by positron emission tomography/computed tomography (PET/CT, ≥25% reduction of SUV_{max}). Comparing patients with and without responses, there was no significant difference in the TTR between the two groups (mean TTR, 42.1 versus 23.9 months and median TTR, not reached versus 18.2 months, respectively; $p = 0.19$). SUV_{max}, maximum standardized uptake value.

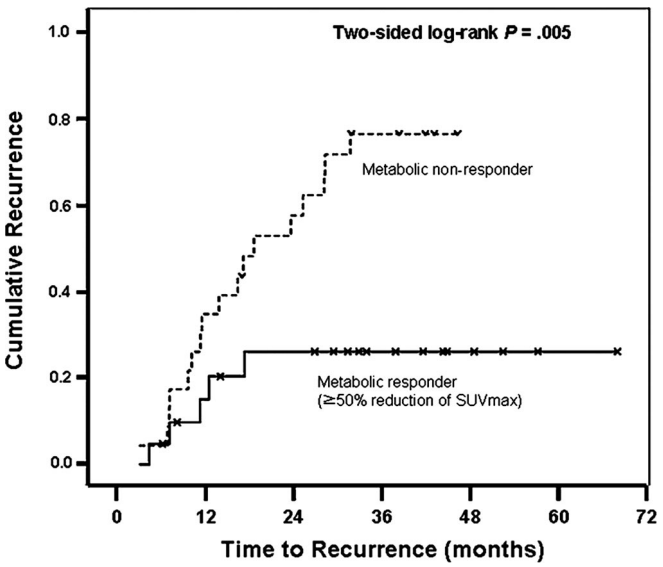

FIGURE 3. Time to recurrence (TTR) based on tumor response by positron emission tomography/computed tomography (PET/CT, ≥50% reduction of SUV_{max}). Patients with a metabolic response of ≥50% reduction of SUV_{max} had a longer TTR than patients without response (mean TTR, 51.7 versus 22.7 months and median TTR, not reached versus 18.2 months, respectively; $p = 0.005$). SUV_{max}, maximum standardized uptake value.

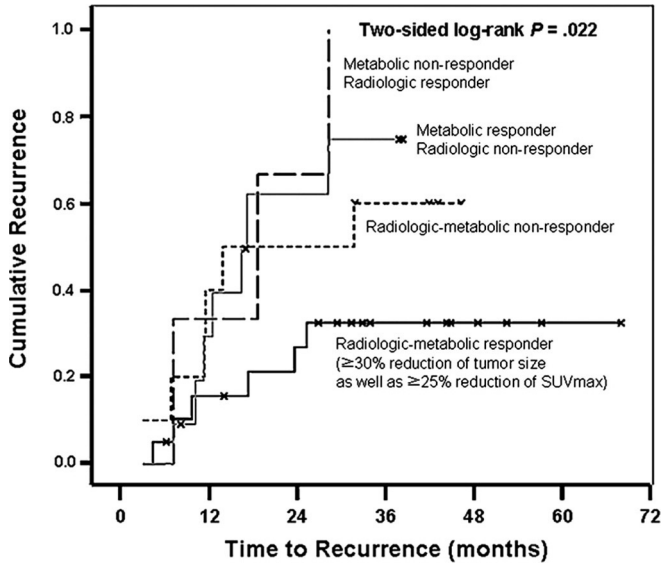

FIGURE 4. Time to recurrence (TTR) based on radiologic-metabolic tumor response (≥30% reduction of tumor size and ≥25% reduction of SUV_{max}). Radiologic-metabolic responders had a longer TTR than patients with radiologic-metabolic nonresponse, radiologic response only, and metabolic response only (mean TTR, 49.4 versus 23.5 months and median TTR not reached versus 16.8 months, respectively; $p = 0.022$). SUV_{max}, maximum standardized uptake value.

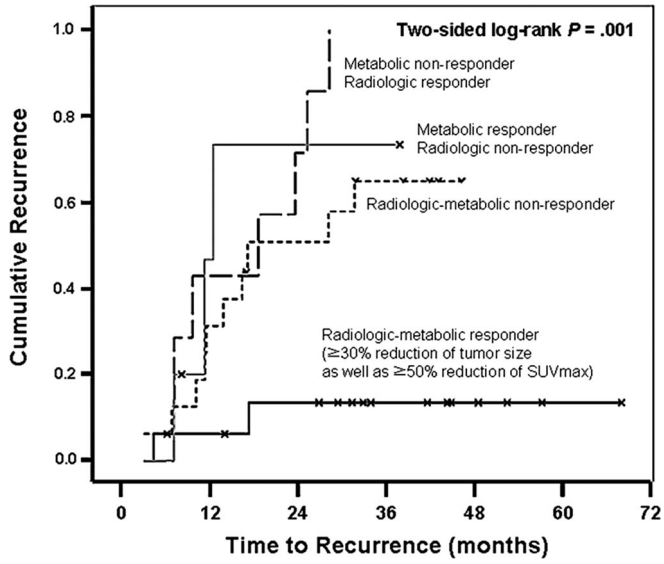

FIGURE 5. Time to recurrence (TTR) based on radiologic-metabolic tumor response (≥30% reduction of tumor size as well as ≥50% reduction of SUV_{max}). Radiologic-metabolic responders had a longer TTR than patients with radiologic-metabolic nonresponse, radiologic response only, and metabolic response only (mean TTR, 58.7 months versus 22.3 months and median TTR, not reached versus 16.8 months, respectively; $p = 0.001$). SUV_{max}, maximum standardized uptake value.

from 100% decrease to 19% increase). By the response criteria of ≥25% reduction of SUV_{max}, metabolic response occurred in 31 patients (70%). Comparing patients with and without responses, there was no significant difference in the TTR between the two groups (mean TTR, 42.1 months versus 23.9 months and median TTR, not reached versus 18.2 months, respectively; $p = 0.19$; Figure 2).

On the other hand, greater degrees of metabolic response seemed to be associated with longer TTR. By the response criteria of ≥50% reduction of SUV_{max}, metabolic response occurred in 21 patients (48%). Patients with a metabolic response of ≥50% reduction of SUV_{max} had a longer TTR than patients without response (mean TTR, 51.7 months versus 22.7 months and median TTR, not reached versus 18.2 months, respectively; $p = 0.005$; Figure 3).

TTR Based on Radiologic-Metabolic Tumor Response

By the response criteria of ≥30% reduction of tumor size and ≥25% reduction of SUV_{max}, radiologic-metabolic response occurred in 20 patients (45%). Radiologic-metabolic nonresponse, radiologic response only, and metabolic response only were found in 10 (23%), three (7%), and 11 patients (25%), respectively. Radiologic-metabolic responders had a longer TTR than patients with radiologic-metabolic nonresponse, radiologic response only, and metabolic response only (mean TTR, 49.4 months versus 23.5 months and median TTR, not reached versus 16.8 months, respectively; $p = 0.022$; Figure 4).

By the response criteria of ≥30% reduction of tumor size and ≥50% reduction of SUV_{max}, radiologic-metabolic response occurred in 16 patients (36%). Radiologic-metabolic nonresponse, radiologic response only, and metabolic response only were found in 16 (36%), seven (16%), and five patients (12%), respectively. Radiologic-metabolic responders had a longer TTR than patients with radiologic-metabolic nonresponse, radiologic response only, and metabolic response only (mean TTR, 58.7 months versus 22.3 months and median TTR, not reached versus 16.8 months, respectively; $p = 0.001$; Figure 5).

Correlation between Pathologic, Radiologic, and Metabolic Response

Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/JTO/A15) shows the correlation between pathologic response and tumor response according to CT and PET. A waterfall plot demonstrating the responses of all 44 patients is shown in Supplemental Figure 1 (see Supplemental Digital Content 2, http://links.lww.com/JTO/A16 for the figure and see Supplemental Digital Content 3, http://links.lww.com/JTO/A17 for the legend). In the 44 resected tumors, 12 resection specimens (27%) were classified as pathologic responders (≤10% of viable tumor cells). Pathologic response showed a strong and significant correlation with change in size on CT ($r = 0.63$, $p < 0.0001$) and showed moderate but significant correlation with change in SUV_{max} ($r = 0.48$, $p = 0.001$).

The accuracy for the prediction of pathologic response in radiologic responders (≥30% reduction of size), metabolic responders (≥25% reduction of SUV_{max}), metabolic responders (≥50% reduction of SUV_{max}), radiologic-metabolic responders (≥30% reduction of tumor size as well as ≥25% reduction of SUV_{max}), and radiologic-metabolic responders (≥30% reduction of tumor size and ≥50% reduction of SUV_{max}) was 70% (31/44), 52% (23/44), 75% (33/44), 73% (32/44), and 82% (36/44), respectively.

Kaplan-Meier survival curves stratified by pathologic response criteria are shown in Figure 6. Patients with a pathologic response of ≤10% of viable tumor cells had a longer TTR than patients without response (mean TTR, 44.2 months versus 31.7 months and median TTR, not reached versus 23.1 months, respectively; $p = 0.015$). Cox proportional hazards regression analysis showed that pathologic, radiologic, and metabolic response after neoadjuvant chemotherapy provided relevant prognostic information, especially that the presence of response was inversely related to recurrence (Table 2).

Impact of Residual Tumor in Mediastinal Lymph Nodes

We found a TTR difference between patients who had no viable tumors and residual viable tumors among mediastinal lymph nodes (mean TTR, 48.2 months versus 21.7 months and median TTR, not reached versus 16.8 months, respectively; $p = 0.019$). Univariate analysis showed that a residual viable tumor in mediastinal lymph nodes was related to recurrence (Table 2).

DISCUSSION

In this study, we found that the TTR of radiologic-metabolic responders was significantly longer than the TTR of radiologic responders only and metabolic responders only. Therefore, combined evaluation of CT response and PET response may be more effective than single interpretation

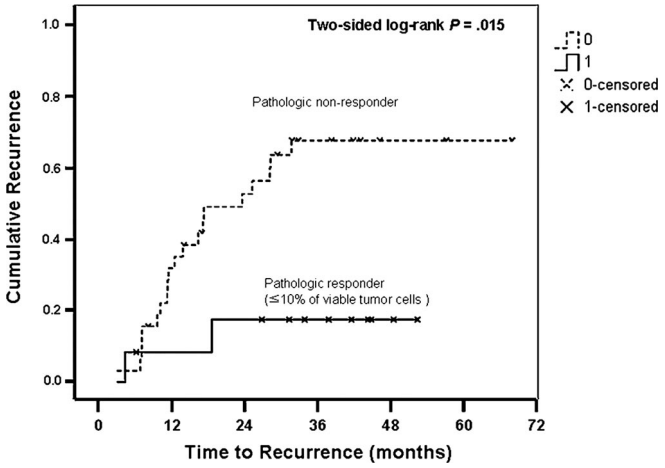

FIGURE 6. Time to recurrence (TTR) based on pathologic response. Patients with a pathologic response of ≤10% of viable tumor cells had a longer TTR than patients without response (mean TTR, 44.2 months versus 31.7 months and median TTR, not reached versus 23.1 months, respectively; $p = 0.015$).

TABLE 2. Prognostic Indicators of Recurrence After Neoadjuvant Chemotherapy Followed by Curative Surgery in Patients with Stage III Non-small Cell Lung Cancer

Indicators	Hazard Ratio	95% CI	*p*
Pathologic response (≤10% of viable tumor cells in tumor)	5.08	1.18–21.83	0.03
Radiographic response (≥30% reduction of tumor size)	1.98	0.84–4.67	0.12
Metabolic response (≥25% reduction of SUV_{max})	1.75	0.75–4.10	0.20
Metabolic response (≥50% reduction of SUV_{max})	3.76	1.38–10.22	0.01
Radiologic-metabolic response (≥30% reduction of tumor size and ≥25% reduction of SUV_{max})	2.86	1.11–7.35	0.03
Radiologic-metabolic response (≥30% reduction of tumor size and ≥50% reduction of SUV_{max})	8.43	1.96–36.27	0.004
Residual tumor in mediastinal lymph nodes	0.35	0.14–0.88	0.03

SUV_{max}, maximum standardized uptake value; CI, confidence interval.

using CT response or PET response alone for the prediction of tumor recurrence in patients with stage III NSCLC who underwent neoadjuvant chemotherapy followed by surgery. Moreover, the accuracy for the prediction of pathologic response was higher when combined evaluation of CT response, and PET response was performed compared with single interpretation of CT response or PET response.

Unfortunately, the value of CT or PET alone as a predictor of patients' outcome remains unclear and controversial. The reason for the controversial results regarding RECIST is that there have been no clear data to support that a change in tumor size on radiologic studies accurately reflects survival. In fact, lung tumors are heterogeneous, and therefore, the host response against therapy is inevitably variable. For instance, chemotherapy, in some instances, may destroy only the susceptible tumor cells, and more virulent resistant tumor cells may continue to proliferate,[15] but in other instances, a robust host inflammatory response to the tumor itself may produce the majority of the radiologic abnormalities.[16–18] Therefore, the concept that tumor cell response equals tumor size response needs to be reconsidered. The controversial results of FDG-PET may be related to the fact that the exact mechanism of FDG uptake and distribution within the various cells in a tumor remains unclear.

However, despite of these limitations of RECIST on CT or PET scan, there is currently no alternative approach to response evaluation, and patients should still be observed with CT or PET scan. From this study, we propose that a combined interpretation of FDG-PET and RECIST provides more reliable information of morphologic and functional changes and would be helpful for stratifying patients with locally advanced NSCLC for therapy and predicting patient outcomes. The value of combining CT response to FDG-PET response was especially more obvious in patients with lower degrees of metabolic response than in patients with higher degrees of metabolic response.

We applied two cutoff values as the standard for metabolic response in our study. According to our study results, metabolic responders of ≥50% reduction of SUV_{max} had a longer TTR than patients of ≥25% reduction of SUV_{max} (mean TTR, 51.7 versus 42.1 months, respectively). Moreover, a significant difference in TTR between metabolic responders and nonresponders was only found by the response criteria of ≥50% reduction of SUV_{max}. These differences were consistently shown in the evaluation of radiologic-metabolic response. In terms of the accuracy for the prediction of pathologic response, greater degrees of metabolic response also seemed to be associated with higher accuracy.

We performed analysis incorporating the status of a residual viable tumor in mediastinal lymph nodes after neoadjuvant chemotherapy, because the nodal down staging of initial N2 or N3 involvement to N0 status in the mediastinum have been shown to be strong predictors of better clinical outcome after neoadjuvant chemotherapy or chemoradiotherapy.[19–26] Our findings are consistent with those reports. TTR was significantly different between patients who had no viable tumors and those with a residual viable tumor in mediastinal lymph nodes, and the presence of a residual viable tumor in mediastinal lymph nodes was a significant prognostic indicator of shorter TTR.

Our study was limited inherently by its retrospective design; however, we dealt with a consecutive data in patients with a homogenous stage III NSCLC in a single tertiary hospital thereby possibly minimizing selection bias. Another limitation is the small number of subjects included in our study. Therefore, the clinical assessment of combined criteria using RECIST and PET for prediction of response to chemotherapy requires further investigation with a prospective design and a larger population.

The proportion of viable tumors in the primary tumor of the surgical resected specimen may not exactly reflect a pathologic response. The predominant cause for the discordance between the response to neoadjuvant therapy and the extent of histomorphologically determined tumor regression is the fact that vital tumor cannot be differentiated from already necrotic tumor tissue or scar formations even in any evaluation method. However, Junker's score that we adopted[14] has been frequently used for the definition of pathologic responder and nonresponder after the neoadjuvant therapy because there has not been better standard reference.

In conclusion, tumor response evaluation using combined interpretation of FDG-PET and CT was more effective than the single interpretation of CT response or PET response alone for the prediction of tumor recurrence and pathologic response in patients with stage III NSCLC who underwent neoadjuvant chemotherapy followed by surgery.

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