

# Value of Metabolic Tumor Volume on Repeated $^{18}\text{F}$ -FDG PET/CT for Early Prediction of Survival in Locally Advanced Non-Small Cell Lung Cancer Treated with Concurrent Chemoradiotherapy

Wei Huang<sup>\*1</sup>, Min Fan<sup>\*1</sup>, Bo Liu<sup>2</sup>, Zheng Fu<sup>3</sup>, Tao Zhou<sup>1</sup>, Zicheng Zhang<sup>1</sup>, Heyi Gong<sup>1</sup>, and Baosheng Li<sup>1</sup>

<sup>1</sup>Department of Radiation Oncology (Chest Section), Shandong's Key Laboratory of Radiation Oncology, Shandong Cancer Hospital, Shandong Academy of Medical Sciences, Jinan, China; <sup>2</sup>Department of Medical Oncology, Shandong Cancer Hospital, Shandong Academy of Medical Sciences, Jinan, China; and <sup>3</sup>PET/CT Center, Shandong Cancer Hospital, Shandong Academy of Medical Sciences, Jinan, China

The aim of this study was to investigate the value of standardized uptake values (SUVs) and metabolic tumor volume (MTV) in  $^{18}\text{F}$ -FDG PET/CT to predict the survival of patients with locally advanced non-small cell lung cancer during the early stage of concurrent chemoradiotherapy. **Methods:** A total of 53 patients were included in the prospective study. All patients were evaluated by  $^{18}\text{F}$ -FDG PET before and after 40 Gy of radiotherapy with a concurrent cisplatin-based chemotherapy regimen. Semiquantitative assessment was used to determine the maximum and mean SUVs ( $\text{SUV}_{\text{max}}$  and  $\text{SUV}_{\text{mean}}$ , respectively) and MTV of the primary tumor. The cutoffs for changes in  $\text{SUV}_{\text{max}}$ ,  $\text{SUV}_{\text{mean}}$ , and MTV (37.2%, 41.7%, and 29.7%, respectively) determined in a previous study were used with Kaplan-Meier curves to separate the groups. The prognostic significance of PET/CT parameters and other clinical variables was assessed using Cox regression analysis. **Results:** Overall survival (OS) at 1 and 2 y was 83.0% (46/53) and 52.8% (28/53), respectively. Survival curves for  $\text{SUV}_{\text{mean}}$  and MTV were significantly different using the cutoffs. However, Cox regression analysis showed that the only prognostic factor for OS was a decrease in MTV. **Conclusion:** The use of repeated  $^{18}\text{F}$ -FDG PET to assess survival early during concurrent chemoradiotherapy is possible in patients with locally advanced non-small cell lung cancer. A decrease in MTV according to  $^{18}\text{F}$ -FDG uptake by the primary tumor correlates with higher long-term OS.

**Key Words:** FDG; PET; prognosis; non-small cell lung cancer

**J Nucl Med** 2014; 55:1584–1590

DOI: 10.2967/jnumed.114.142919

**L**ung cancer is the leading cause of cancer death in the world, and 80%–85% of lung cancer cases are classified as non-small cell lung cancer (NSCLC) (1). The combination of platinum-based chemotherapy and radiotherapy is a commonly recommended

standard curative approach in unresectable locally advanced disease (2). A need arises to predict therapy response and survival at an early phase on an individual-patient basis, possibly leading to improved tumor control, a reduction in side effects, and eventually avoidance of the futile costs of ineffective treatment. The TNM staging system is considered the most important tool to estimate prognosis and to date is the most important guide in treatment decisions (3). However, the TNM staging system provides an incomplete biologic profile of NSCLC, does not always provide a satisfactory explanation for differences in recurrence and survival, and is therefore far from perfect as a prognostic indicator (4).

In recent years, PET imaging using the tracer  $^{18}\text{F}$ -FDG has incorporated metabolic tumor function with anatomic localization when integrated with CT imaging. One of the great advantages of  $^{18}\text{F}$ -FDG PET is that it not only can observe but also can quantify  $^{18}\text{F}$ -FDG uptake to distinguish metabolically highly active from less active tumor tissues and therefore offers an opportunity for noninvasive, in vivo tissue characterization. Hence, the number of clinical applications for  $^{18}\text{F}$ -FDG PET/CT in NSCLC continues to increase.  $^{18}\text{F}$ -FDG PET imaging is routinely performed for staging, restaging, treatment planning, and follow-up. Studies have shown that the degree of  $^{18}\text{F}$ -FDG uptake by the tumor, as assessed with maximum standardized uptake value ( $\text{SUV}_{\text{max}}$ ), is a significant prognostic factor in NSCLC (5–8). More recently, metabolic tumor volume (MTV) has been explored as a measure of metabolic tumor burden. MTV indicates the volume of metabolically active tumor, typically assessed with semiautomatic PET analysis software.

Our previous study showed that changes in SUV and MTV between 2 serial  $^{18}\text{F}$ -FDG PET/CT scans, before and after initial concurrent chemoradiotherapy (CCRT), allow prediction of treatment response in locally advanced NSCLC (9). In the present study, long-term follow-up of the previous study investigated the correlation between SUV and MTV changes in the primary tumor on repeated  $^{18}\text{F}$ -FDG PET/CT and overall survival (OS).

## MATERIALS AND METHODS

### Materials

This study included 63 patients with advanced NSCLC diagnosed by histologic or cytologic examination as tumor stage IIIA or IIIB. All patients had a measurable primary tumor according to the Response Evaluation Criteria in Solid Tumors, and all had undergone radiotherapy with concurrent chemotherapy. The patients were selected consecutively

Received May 9, 2014; revision accepted Aug. 4, 2014.

For correspondence or reprints contact: Baosheng Li, 440 Jiyan Rd., Jinan 250117, Shandong Province, China.

E-mail: baoshengli@yahoo.com

\*Contributed equally to this work.

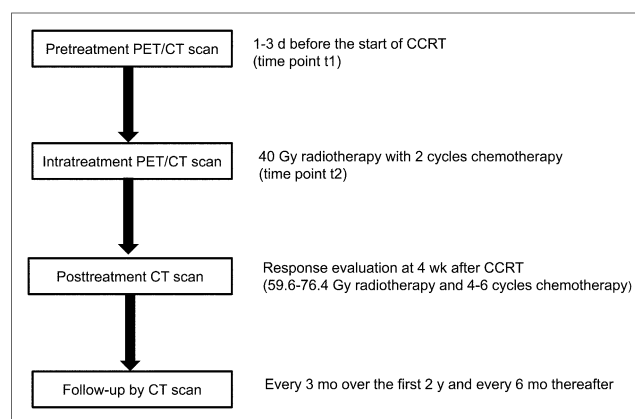
Published online Sep. 11, 2014.

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from those treated at the Department of Radiation Oncology in Shandong Cancer Hospital between September 2008 and June 2011. The study was approved by the institutional review board of Shandong Cancer Hospital, and all subjects signed an informed consent form. Initial routine staging procedures consisted of a clinical examination including lung function tests, bronchoscopy, and mediastinoscopy; contrast-enhanced helical CT of the chest and abdomen; and CT or MR imaging of the brain with and without contrast material. Patients were excluded if they were diabetic or had undergone surgery, previous chemotherapy, or radiotherapy. Two PET/CT scans were included as a component of the initial staging or during the course of therapy. Clinicopathologic data are shown in Table 1.

### CCRT

All patients underwent radiation therapy, which was delivered with megavoltage equipment (6 MV). The delivery technique was intensity-modulated radiation therapy/3-dimensional conformal radiation therapy. Forty grays of irradiation were given conventionally fractionated at five 2-Gy doses per week, and irradiation was accelerated later in the course, with a hyperfractionated 1.4 Gy being given twice daily up to a total dose of 62.4–76.4 Gy. Radiotherapy was based on a planning CT scan. The gross tumor volume included the primary tumor and involved lymph nodes, and the planning target volume included the gross tumor volume with a margin of 1.0–1.5 cm. All patients were treated with 2 cycles of CCRT with a cisplatin-based regimen. The chemotherapy regimens used in this study were cisplatin/gemcitabine,



**FIGURE 1.** Schematic of PET/CT and CT scans.

cisplatin/docetaxel, cisplatin/vinorelbine, and cisplatin/pemetrexed as reported previously (9). These chemotherapy regimens were known to possess similar activity and effectiveness for treatment of NSCLC. After CCRT, patients without tumor progression underwent further chemotherapy with the same regimen, which was administered every 3 wk for a total of 2–4 cycles. Chemotherapy was changed to second-line regimens if progressive disease was present after 2 cycles of CCRT.

### <sup>18</sup>F-FDG PET/CT Imaging

All patients fasted and rested for at least 6 h before undergoing PET/CT (Discovery LS PET/CT system; GE Healthcare). The uptake time was constant for the individual patient. At 45–60 min after intravenous injection of 370 MBq (10 mCi) of <sup>18</sup>F-FDG, PET emission images were acquired from the level of the middle skull to the proximal thigh for 5 min per field of view, each covering 14.5 cm, at an axial sampling thickness of 4.25 mm per slice. CT data were collected in helical acquisition mode. PET images were reconstructed with CT-derived attenuation correction using the ordered-subset expectation maximization algorithm. The attenuation-corrected PET images, CT images, and fused PET/CT images displayed as coronal, sagittal, and transaxial slices were viewed on a Xeleris workstation (GE Healthcare). Pretreatment baseline PET/CT scans, as part of the initial staging, were done about 1–3 d before the start of CCRT (time point 1). The second whole-body PET/CT scan was recorded at the middle of CCRT (40 Gy of radiotherapy with 2 cycles of chemotherapy, time point 2) to exclude tumor progression locally or at distant sites. The mean time ( $\pm$ SD) from points 1 to 2 was  $28 \pm 3$  d (Fig. 1). A commercial radiotherapy pallet was mounted on the PET/CT patient table to facilitate adequate positioning of the patient corresponding to the radiotherapy settings using standard immobilization devices.

### <sup>18</sup>F-FDG PET Image Analysis

The PET/CT images were analyzed by 2 experienced nuclear medicine physicians without knowledge of the patients' history. Initially, <sup>18</sup>F-FDG PET data were transferred into the workstation in DICOM format. Semiquantitative measurements of metabolic uptake in <sup>18</sup>F-FDG-avid tumors after pretreatment and intratreatment scans were compared and evaluated for their potential to predict survival. The calculation methods for  $SUV_{max}$ ,  $SUV_{mean}$ , and MTV were described in detail in our previous study (9). The percentage decrease ( $\Delta$ ) in each of the parameters (P) between baseline (pre) and during treatment (intra) was calculated using the following formula:

$$\Delta P = \{[P_{pre} - P_{intra}] / P_{pre}\} \times 100\%. \quad \text{Eq. 1.}$$

A positive value indicated a reduction in that parameter after therapy, and a negative value indicated an increase. The thresholds for changes

**TABLE 1**

Clinicopathologic Features of 53 Patients with NSCLC

Characteristic	Data
Mean age $\pm$ SD (y)	58.5 $\pm$ 9.5
Sex (n)	
Male	39 (73.6%)
Female	14 (26.4%)
Stage (n)	
IIIA	28 (52.8%)
IIIB	25 (47.2%)
Location (n)	
Right	39 (73.6%)
Left	14 (26.4%)
Pathologic type (n)	
Adenocarcinoma	19 (35.8%)
Squamous cell carcinoma	30 (56.6%)
Other	4 (7.6%)
Chemotherapy (n)	
Cisplatin/gemcitabine	16 (30.2%)
Cisplatin/docetaxel	15 (28.3%)
Cisplatin/vinorelbine	9 (17.0%)
Cisplatin/pemetrexed	13 (24.5%)
RECIST (n)	
Complete response	5 (9.4%)
Partial response	28 (52.8%)
Stable disease	17 (32.1%)
Progressive disease	3 (5.7%)
Mean radiotherapy dose $\pm$ SD (Gy)	67.5 $\pm$ 5.0

RECIST = Response Evaluation Criteria in Solid Tumors.

in  $SUV_{max}$ ,  $SUV_{mean}$ , and MTV defined by ROC curve analysis associated with short-term outcome were 37.2%, 41.7%, and 29.7%, respectively. For consistency with our previous study, these cutoffs were used in the analysis to separate the groups for OS.

### Endpoint and Statistical Analysis

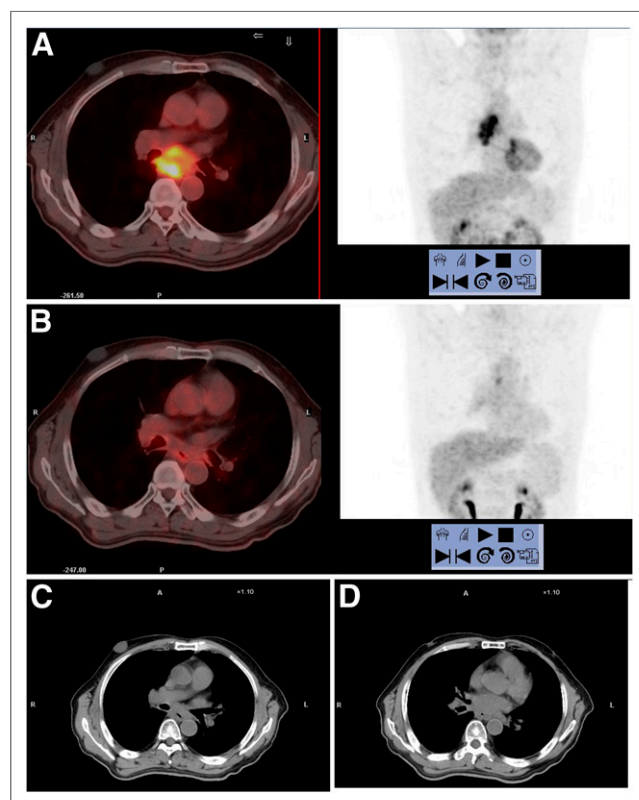
After completion of treatment, all patients were followed up every 3 mo over the first 2 y and every 6 mo thereafter. The endpoint evaluated in this study was 2-y OS. OS was observed from the first day of treatment until death or last follow-up. The data were analyzed by SPSS version 17.0 (SPSS Inc.; IBM Co.). We present data as mean  $\pm$  SD for central tendencies, as median followed by range in parentheses for skewed data, and as frequency and percentage for categorical variables. Cox regression analysis provided a univariate and multivariate analysis of the endpoint with selected prognostic factors including PET/CT parameters and other clinical variables. The level of significance of a series of prognostic factors was estimated using the log-rank test. Survival curves were generated using the Kaplan–Meier method. Differences were assumed to be significant when the *P* value was less than 0.05.

## RESULTS

Figure 2 presents the  $^{18}F$ -FDG PET/CT and CT scans of a typical patient with responding tumor.

### Short-Term Outcome

Short-term outcome was assessed at 4 wk after treatment (62.4–76.4 Gy of radiotherapy and 4–6 cycles of chemotherapy) using the Response Evaluation Criteria in Solid Tumors without knowledge of the results of the PET studies (10). Of the 63 patients, 1 died



**FIGURE 2.**  $^{18}F$ -FDG PET/CT and CT scans in typical patient with responding tumor: pretreatment  $^{18}F$ -FDG PET/CT (3 d before CCRT) (A); intratreatment  $^{18}F$ -FDG PET/CT (at 4 wk) (B); posttreatment CT (at 2 mo) (C); follow-up CT (at 2 y) (D).

**TABLE 2**  
Outcomes of 53 NSCLC Patients

Outcome	Patient number
<b>Alive</b>	
Without known recurrence or distant metastasis	6
With locoregional recurrence only	6
With distant metastasis only	3
With locoregional recurrence and distant metastasis	3
<b>Died</b>	
Of primary relapse	17
Of distant metastasis	11
Of primary relapse and distant metastasis	6
Of complication (radiation pneumonitis)	1

from a heart attack and 1 died from tumor bleeding before response assessment by CT, and 8 patients did not finish the treatment because of economic or personal reasons. As a result, 5 patients with a complete response and 28 with a partial response were assessable for response, and the overall response rate was 62.3%. In contrast, 17 patients achieved stable disease and only 3 patients had progressive disease. Those 3 patients were excluded during the initial CCRT and were changed to second-line chemotherapy.

### Survival Outcome

Minimum follow-up was 2 y. OS at 1 and 2 y was 83.0% (44/53) and 52.8% (28/53), respectively. Median survival was 24.0 mo (range, 9.0–47.0 mo): 26.0 mo (range, 24–47.0 mo) and 19.0 mo (range, 9.0–42 mo) for the surviving and deceased patients, respectively. During follow-up, 6 patients were alive without known recurrent disease or metastasis, and 12 patients had locoregional recurrence or metastasis but were still alive after salvage or palliative treatment. Seventeen of the deceased patients died of tumor recurrence; 11 died of the distant organ metastasis, including brain, liver, and lung; 6 died of both issues; and 1 died of radiation pneumonitis. Table 2 summarizes the outcomes for patients in this study.

### PET Parameters and the Kaplan–Meier Curve

Table 3 shows changes in the parameters for pretreatment and intratreatment  $^{18}F$ -FDG PET/CT scans for all patients. The cutoffs of  $SUV_{max}$ ,  $SUV_{mean}$ , and MTV changes (37.2%, 41.7%, and 29.7%, respectively) determined by the previous study were used in the analysis to separate the groups. The Kaplan–Meier curves for OS at the cutoffs for the decrease in  $SUV_{max}$ ,  $SUV_{mean}$ , and MTV are shown in Figures 3–5. For  $SUV_{max}$ , there was no statistical difference between the 2 groups using this cutoff to separate the 2 groups. However, survival curves for  $SUV_{mean}$  and MTV were significantly different using the cutoffs to divide the dataset into 2 groups (both *P* < 0.001). Median OS was 37.5 mo and 2-y OS survival 75.0% (12/16) in patients with a decrease in  $SUV_{mean}$  of more than 41.7%, compared with a median OS of 19.5 mo and a 2-y OS of 37.8% (14/37) in patients with a decrease in  $SUV_{mean}$  of less than 41.7%.

### Cox Regression and Prognostic Factors

Cox regression analysis for OS was used to analyze the relationships between covariates of interest. The results of univariate analysis are summarized in Table 4. Among the 17 variables of univariate

**TABLE 3**Changes in Parameters of  $^{18}\text{F}$ -FDG PET/CT Scans

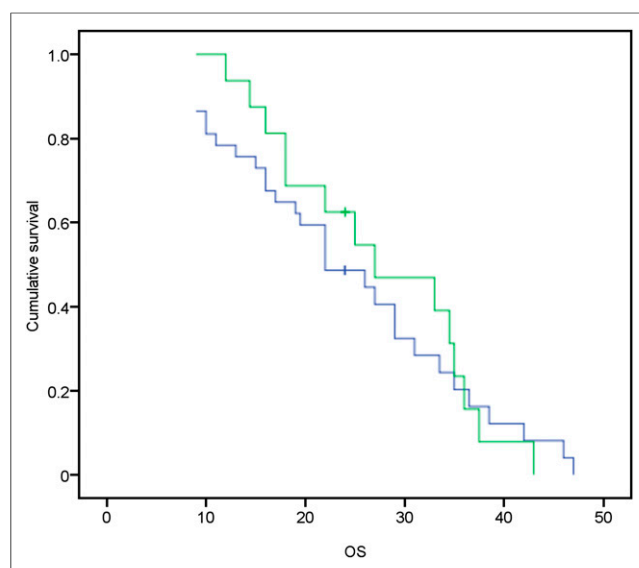
Parameter	Pretreatment	Intratreatment	Decrease (%)
$\text{SUV}_{\text{max}}$	$14.5 \pm 10.0$	$9.4 \pm 6.6$	$31.7 \pm 17.0$
$\text{SUV}_{\text{mean}}$	$6.7 \pm 4.0$	$4.6 \pm 3.1$	$29.8 \pm 17.7$
MTV	$62.3 \pm 6.3$	$46.2 \pm 18.7$	$27.1 \pm 14.6$

Data are mean  $\pm$  SD.

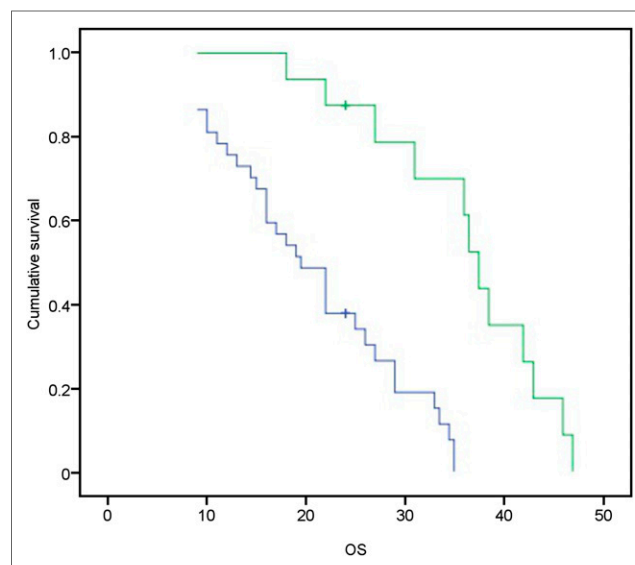
analysis, 6 variables were identified as having prognostic significance: decrease in  $\text{SUV}_{\text{max}}$  ( $P = 0.016$ ), intratreatment  $\text{SUV}_{\text{mean}}$  ( $P = 0.018$ ), decrease in  $\text{SUV}_{\text{mean}}$  ( $P < 0.001$ ), intratreatment MTV ( $P < 0.003$ ), decrease in MTV ( $P < 0.001$ ), and short-term outcome ( $P < 0.001$ ). Multivariate analysis included the 6 prognostic significance factors in univariate analysis. The results of multivariate analysis are shown in Table 5. Multivariate analysis by the Cox proportional hazards model showed that a decrease in MTV was the only independent prognostic factor for survival ( $P < 0.001$ ; 95% confidence interval, 0.000–0.012).

## DISCUSSION

CCRT is a demanding strategy that has a high burden for the patient with NSCLC. Selection of patients up front who will benefit is difficult, and an early assessment of accurate prognosis could allow clinical decision making and treatment selection. PET/CT imaging has become an increasingly important component of staging, tumor localization for radiotherapy treatment planning, and assessment of treatment response in NSCLC (11,12). Our previous study investigated a group of NSCLC patients with repeated imaging after they had received approximately 40 Gy of CCRT, and short-term outcome was evaluated using the Response Evaluation Criteria in Solid Tumors at 4 wk after the end of treatment. Changes in  $\text{SUV}_{\text{max}}$ ,  $\text{SUV}_{\text{mean}}$ , or MTV allowed prediction of the short-term outcome of treatment. However, effect on



**FIGURE 3.** Kaplan–Meier curves showing OS depending on decrease in  $\text{SUV}_{\text{max}}$ . Data are median OS of patients with high ( $>37.2\%$ , green) or low ( $<37.2\%$ , blue)  $\Delta\text{SUV}_{\text{max}}$  (27.0 mo vs. 22.0 mo,  $P = 0.765$ ).



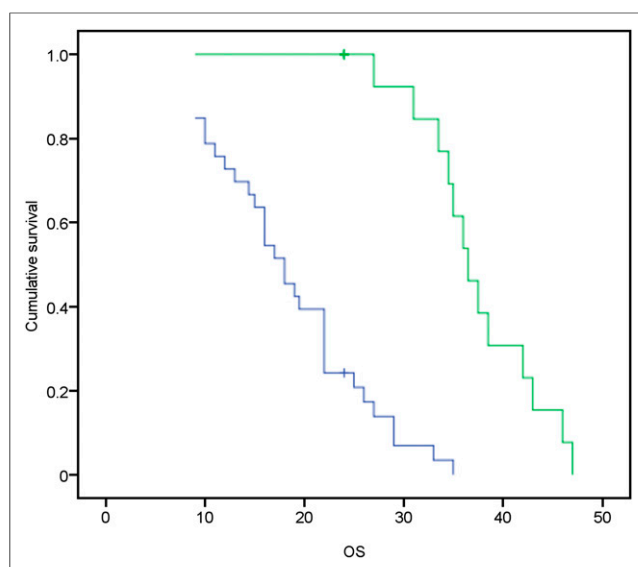
**FIGURE 4.** Kaplan–Meier curves showing OS depending on decrease in  $\text{SUV}_{\text{mean}}$ . Data are median OS of patients with high ( $>41.7\%$ , green) or low ( $<41.7\%$ , blue)  $\Delta\text{SUV}_{\text{mean}}$  (37.5 mo vs. 19.5 mo,  $P < 0.001$ ).

OS was not presented at that time. As is well known, the ultimate objective of treatment is to improve the survival of cancer patients. The ability of  $^{18}\text{F}$ -FDG PET to separate patients with a good prognosis from those with a poor one in the early stage of treatment would be of help in deciding on the most appropriate treatment and particularly in stratifying patients for clinical trials. Therefore, we conducted a follow-up of these patients to determine whether  $^{18}\text{F}$ -FDG PET can also predict survival.

Various parameters are used in measuring changes in tumor glucose metabolic activity with  $^{18}\text{F}$ -FDG PET in response to cancer treatment. However, which of these provides the lowest variability among observers is still controversial. The semiquantitative parameter of  $^{18}\text{F}$ -FDG uptake that is currently most widely used for the assessment of therapeutic response in tumors is  $\text{SUV}_{\text{max}}$  (13,14). The most important concern with  $\text{SUV}_{\text{max}}$  is that a mildly active tumor may have a single hot pixel that may arise from random error rather than actual abnormal uptake in the body. To overcome random variations in  $\text{SUV}_{\text{max}}$ ,  $\text{SUV}_{\text{mean}}$ , which is calculated by averaging the SUVs generated from the entire tumor, can be used (15). More recently, MTV, which indicates the volume of metabolically active tumor, has been explored as a measure of metabolic tumor burden (16,17). For consistency with our previous study, we also used the  $\text{SUV}_{\text{max}}$ ,  $\text{SUV}_{\text{mean}}$ , and MTV of the primary tumor to predict survival in patients with locally advanced NSCLC treated with CCRT.

The prognostic value of  $^{18}\text{F}$ -FDG PET at diagnosis has been evaluated in several studies (18–21). These studies showed that pretreatment  $^{18}\text{F}$ -FDG PET not only improved patient staging but also provided prognostic information. Univariate analyses to determine a cutoff for  $\text{SUV}_{\text{max}}$  in the primary tumor to discriminate between a more or less favorable prognosis have ranged widely from 5 to 20 (4,22,23). Baseline whole-body MTV also has this kind of prognostic ability. Lee et al. performed the first study to show that baseline whole-body MTV measured semiautomatically was a statistically significant prognosticator in 19 patients with lung cancer and was better than  $\text{SUV}_{\text{max}}$  and  $\text{SUV}_{\text{mean}}$  (5). In a larger study by the same author including 328 surgical and





**FIGURE 5.** Kaplan-Meier curves showing OS depending on decrease in MTV. Data are median OS of patients with high (>29.7%, green) or low (<29.7%, blue)  $\Delta$ MTV (36.5 mo vs. 18.0 mo,  $P < 0.001$ ).

nonsurgical patients, baseline whole-body MTV was a prognostic marker independent of stage, treatment intent, patient age, sex, and tumor histology (24). However, baseline  $SUV_{max}$  ( $P = 0.612$ ),  $SUV_{mean}$  ( $P = 0.999$ ), and MTV ( $P = 0.105$ ) had no prognostic value in our population or in other studies (25,26). The cause of

this heterogeneity may be differences in treatment methods, disease stage, enrolled populations, acquisition protocols, or institutional-based technical factors. In contrast, our study had a homogeneous patient cohort in which all patients had the same tumor stage (III) and were treated by the same therapeutic protocol (CCRT) to objectively assess the prognostic value provided by  $^{18}F$ -FDG parameters.

The prognostic value of  $^{18}F$ -FDG PET has not been studied as thoroughly after induction treatment as at diagnosis. There is increasing interest in determining the prognostic value of intratreatment  $^{18}F$ -FDG PET, especially early in the course of first-line therapy. A study investigated the possibility of early response assessment based on  $^{18}F$ -FDG uptake during radiotherapy with respect to OS in patients with NSCLC.  $^{18}F$ -FDG PET was performed before radiotherapy and was repeated in the second week of radiotherapy for 34 consecutive lung cancer patients. The results showed that a decrease in metabolic activity of the primary tumor by as early as the second week of treatment was predictive of survival (25). Our previous study proved that  $^{18}F$ -FDG PET/CT can differentiate responders from nonresponders early in the course of CCRT. The thresholds for changes in  $SUV_{max}$ ,  $SUV_{mean}$ , and MTV determined by ROC curve analysis in the study were 37.2%, 41.7%, and 29.7%, respectively. For consistency with that work, we still use those thresholds as cutoffs to analyze survival in patients with long-term follow-up. When a cutoff of a 37.2% reduction in initial  $^{18}F$ -FDG uptake is applied as a criterion for metabolic response,  $SUV_{max}$  cannot differentiate survival between the 2 groups, but both  $SUV_{mean}$  and MTV can separate the 2 groups successfully. Although a decrease in  $SUV_{mean}$  can separate the 2 groups with the Kaplan-Meier curve, multivariate Cox regression

**TABLE 4**  
Univariate Analysis with Cox Regression

Parameter	B	SE	Wald	df	P	Exp(B)	95.0% CI for Exp(B)
$SUV_{max}$ 1	0.010	0.020	0.257	1	0.612	1.010	0.972–1.050
$SUV_{max}$ 2	0.057	0.030	3.629	1	0.057	1.058	0.998–1.122
$\Delta SUV_{max}$	−3.089	1.277	5.849	1	0.016*	0.046	0.004–0.557
$SUV_{mean}$ 1	0.000	0.050	0.000	1	0.999	1.000	0.907–1.103
$SUV_{mean}$ 2	0.141	0.059	5.640	1	0.018*	1.152	1.025–1.294
$\Delta SUV_{mean}$	−7.693	1.477	27.126	1	<0.001*	0.000	0.000–0.008
MTV 1	0.004	0.003	2.621	1	0.105	1.004	0.999–1.010
MTV 2	0.009	0.003	8.659	1	0.003*	1.009	1.003–1.014
$\Delta$ MTV	−12.153	1.990	37.306	1	<0.001*	0.000	0.000–0.000
Pathology	−0.418	0.285	2.151	1	0.142	0.658	0.377–1.151
Location	0.635	0.450	1.991	1	0.158	1.886	0.781–4.553
Chemotherapy	0.001	0.147	0.000	1	0.994	1.001	0.751–1.335
Stage	−0.468	0.346	1.831	1	0.176	0.626	0.318–1.233
Sex	0.000	0.376	0.000	1	0.999	1.000	0.479–2.091
Age	0.006	0.018	0.095	1	0.758	1.006	0.971–1.042
Radiotherapy dose	0.035	0.037	0.914	1	0.339	1.036	0.964–1.112
RECIST	1.488	0.293	25.871	1	<0.001*	4.430	2.497–7.862

\*Statistically significant.

B = coefficient for constant; Wald = Wald  $\chi^2$ ; Exp(B) = exponentiation of B coefficient; CI = confidence interval;  $SUV_{max}$  1 =  $SUV_{max}$  of pretreatment PET/CT;  $SUV_{max}$  2 =  $SUV_{max}$  of intratreatment PET/CT;  $\Delta SUV_{max}$  = decrease in  $SUV_{max}$ ;  $SUV_{mean}$  1 =  $SUV_{mean}$  of pretreatment PET/CT;  $SUV_{mean}$  2 =  $SUV_{mean}$  of intratreatment PET/CT;  $\Delta SUV_{mean}$  = decrease in  $SUV_{mean}$ ; MTV 1 = MTV of pretreatment PET/CT; MTV 2 = MTV of intratreatment PET/CT;  $\Delta$ MTV = decrease in MTV; RECIST = Response Evaluation Criteria in Solid Tumors.

**TABLE 5**  
Multivariate Analysis with Cox Regression

Parameter	B	SE	Wald	df	P	Exp(B)	95.0% CI for Exp(B)
$\Delta\text{SUV}_{\text{max}}$	2.434	1.897	1.647	1	0.199	11.409	0.277–469.702
$\text{SUV}_{\text{mean } 2}$	−0.007	0.097	0.005	1	0.941	0.993	0.820–1.201
$\Delta\text{SUV}_{\text{mean}}$	−3.885	2.177	3.185	1	0.074	0.021	0.000–1.465
MTV 2	0.004	0.006	0.500	1	0.480	1.004	0.993–1.015
$\Delta\text{MTV}$	−9.660	2.663	13.164	1	<0.001*	0.000	0.000–0.012
RECIST	0.331	0.475	0.486	1	0.486	1.393	0.549–3.534

\*Statistically significant.

B = coefficient for constant; Wald = Wald  $\chi^2$ ; Exp(B) = exponentiation of B coefficient; CI = confidence interval;  $\Delta\text{SUV}_{\text{max}}$  = decrease in  $\text{SUV}_{\text{max}}$ ;  $\text{SUV}_{\text{mean } 2}$  =  $\text{SUV}_{\text{mean}}$  of intratreatment PET/CT;  $\Delta\text{SUV}_{\text{mean}}$  = decrease in  $\text{SUV}_{\text{mean}}$ ; MTV 2 = MTV of intratreatment PET/CT;  $\Delta\text{MTV}$  = decrease in MTV; RECIST = Response Evaluation Criteria in Solid Tumors.

analysis showed that the only significant parameter for OS was a decrease in MTV. Recently, however, Vera et al. reported that the  $\text{SUV}_{\text{max}}$  at PET at the middle of radiotherapy (mean dose, 43 Gy of radiotherapy) was the only variable predictive of death or tumor progression at 1 y in NSCLC patients who underwent radiotherapy with or without concomitant chemotherapy (26). This finding diverges from our conclusion but may have several explanations: first, 77% of the patients in the study of Vera et al. received induction chemotherapy and 27% of those did not receive CCRT, but all our patients underwent CCRT without induction chemotherapy. Second, the stages of their patients varied from IA to IIIB whereas only patients with stage III disease were enrolled in our study.

MTVs generated from the region-growing algorithm are 3-dimensional measures and incorporate both tumor volume and metabolic activity. Therefore, MTV reflects change throughout the entire tumor mass and may be a more sensitive method of detecting change than a single-pixel value. This characteristic may explain why MTV predicted survival more accurately than  $\text{SUV}_{\text{max}}$  and suggests that although the maximally active portion of the tumor may represent the more aggressive part, the maximally active portion has less impact on outcome, possibly because it shows a greater response to treatment. Furthermore, by using MTV as our metric of volumetric tumor burden, we can take advantage of the high signal-to-background ratio of  $^{18}\text{F}$ -FDG PET, making possible rapid semiautomatic computer-based methods that limit interobserver variability. Although the prognostic value of  $\text{SUV}_{\text{max}}$  may be inferior to MTV, we believe that  $\text{SUV}_{\text{max}}$  should still be considered in monitoring disease response. This is one of the first studies showing that repeated  $^{18}\text{F}$ -FDG PET early during CCRT has added value by being a prognostic factor for survival of NSCLC patients (27,28). A decrease in the MTV of the primary tumor correlates with higher long-term OS.

## CONCLUSION

Our data suggest that the MTV of the primary tumor has the potential to become a valuable prognostic biomarker for survival outcome in NSCLC patients. A decrease in MTV according to  $^{18}\text{F}$ -FDG uptake by the primary tumor correlates with higher long-term OS. On the basis of early treatment response assessment using changes in MTV, it might be possible to improve management in NSCLC patients by avoiding ineffective CCRT and to select patients who require more aggressive treatment to improve their outcome.

## DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 USC section 1734. This work was supported by grant BS2013YY057 from the Research Award Fund for Outstanding Young Scientists funded by the Department of Science and Technology of Shandong Province, China. No other potential conflict of interest relevant to this article was reported.

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*J Nucl Med.* 2014;55:1584-1590.

Published online: September 11, 2014.

Doi: 10.2967/jnumed.114.142919

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*The Journal of Nuclear Medicine* is published monthly.  
SNMMI | Society of Nuclear Medicine and Molecular Imaging  
1850 Samuel Morse Drive, Reston, VA 20190.  
(Print ISSN: 0161-5505, Online ISSN: 2159-662X)

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