Response Assessment Using ^{18}F-FDG PET Early in the Course of Radiotherapy Correlates with Survival in Advanced-Stage Non–Small Cell Lung Cancer

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This study investigated the possibility of early response assessment based on ^{18}F-FDG uptake during radiotherapy with respect to overall survival in patients with non–small cell lung cancer. **Methods:** ^{18}F-FDG PET/CT was performed before radiotherapy and was repeated in the second week of radiotherapy for 34 consecutive lung cancer patients. The CT volume and standardized uptake value (SUV) parameters of the primary tumor were quantified at both time points. Changes in volume and SUV parameters correlated with 2-y overall survival. **Results:** The average change in mean SUV in the primary tumor of patients with a 2-y survival was a decrease by 20% ± 21%—significantly different ($P < 0.007$) from nonsurvivors, who had an increase by 2% ± 22%. A sensitivity and specificity of 63% and 93%, respectively, to separate the 2 groups was reached for a decrease in mean SUV of 15%. Survival curves were significantly different using this cutoff ($P = 0.001$). The hazard ratio for a 1% decrease in mean SUV was 1.032 (95% confidence interval, 1.010–1.055). Changes in tumor volume defined on CT did not correlate with overall survival. **Conclusion:** The use of repeated ^{18}F-FDG PET to assess treatment response early during radiotherapy is possible in patients undergoing radiotherapy or sequential or concurrent chemoradiotherapy. A decrease in ^{18}F-FDG uptake by the primary tumor correlates with higher long-term overall survival.

Key Words: PET imaging; response assessment; lung cancer; imaging biomarkers

J Nucl Med 2012; 53:1514–1520
DOI: 10.2967/jnumed.111.102566

Overall survival rates in lung cancer have improved but nevertheless remain low. State-of-the-art treatment of locally advanced-stage non–small cell lung cancer is chemoradiotherapy. Response assessment in the first weeks of radiotherapy would be useful to tailor the optimal treatment strategy for the individual patient. ^{18}F-FDG PET/CT serves as an imaging technique allowing quantification of tumor response to treatment before morphologic changes become visible on standard CT (*1–3*).

Several authors have shown the prognostic value of residual ^{18}F-FDG uptake in the primary tumor after treatment—a finding that indicates poor survival (*4–7*). Early response assessment for chemotherapy has been described by several groups (*1,3,8–10*), but for radiotherapy only a few studies have been performed. For high-dose stereotactic body radiotherapy, elevated levels after treatment do not always indicate residual tumor (*11*). In a smaller study, ^{18}F-FDG PET/CT during treatment could already distinguish metabolic responders from nonresponders based on the maximum standardized uptake value (SUV) (*12*). High ^{18}F-FDG uptake before treatment is known to correlate with poor overall survival (*13,14*); however, the influence of treatment response during chemoradiotherapy is not well described (*4,15–18*).

Assessment of response early during treatment is useful in following patients throughout the course of treatment. Chemoradiotherapy is a demanding strategy that has a high burden for the patient. Selection of patients up front who will benefit is difficult, and an early assessment of treatment response could allow adaptation of the treatment to the individual patient.

In the present study, we hypothesized that early changes in ^{18}F-FDG uptake by the primary tumor are a predictive factor for treatment success. We evaluated all non–small cell lung cancer patients in a fixed period who were treated with curative intent using radiotherapy or sequential or concurrent chemoradiotherapy. We investigated the correlation between metabolic response visualized on repeated ^{18}F-FDG PET/CT in the second week of radiotherapy and overall survival.

MATERIALS AND METHODS

Patient Characteristics and Dose Prescription

For all non–small cell lung cancer patients from July 2008 to December 2008 who were scheduled for radical radiotherapy, we

Received Dec. 29, 2011; revision accepted May 18, 2012.
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Published online Aug. 9, 2012.

performed ^{18}F-FDG PET/CT before therapy and in the second week of radiotherapy. Patients scheduled for stereotactic body radiotherapy were not included in this study. The study was approved by the appropriate Institutional Review Board. Stages II–IV were included in this prospective analysis, and treatment was performed according to the clinical protocol. Treatment consisted of radiotherapy only or sequential or concurrent chemoradiotherapy. The type of chemotherapy for sequential and concurrent chemoradiotherapy was cisplatin–gemcitabine and cisplatin–vinorelbine, respectively. In both cases, a total of 3 cycles of chemotherapy were administered. For concurrent chemoradiotherapy, radiation began at the beginning of the second cycle of chemotherapy. Two cycles of chemotherapy were given during radiotherapy. The treatment consisted of a dose-escalation protocol up to the normal-tissue constraints (*19*). For concurrent chemoradiotherapy, a 45-Gy dose of radiotherapy was given twice daily with fraction sizes of 1.5 Gy for the first 30 fractions. Afterward, the dose was escalated: daily fractions of 2 Gy were given up to the maximum tolerated normal-tissue toxicity or until the maximum prescribed dose of 69 Gy was reached. For the sequential-chemoradiotherapy patients, 3 cycles of chemotherapy were given and then radiotherapy was started. The radiotherapy consisted of 1.8-Gy fractions given twice daily up to the normal-tissue toxicity or a maximum prescribed dose of 79.2 Gy (*19*). This radiotherapy scheme was also used for the radiotherapy-only group.

PET/CT

^{18}F-FDG PET/CT (Biograph 40; Siemens Medical Solutions) was performed after 1 cycle (concurrent chemoradiotherapy) or typically 3 cycles (sequential chemoradiotherapy) of chemotherapy but before radiotherapy. Patients were required to fast for at least 6 h before the acquisition. Blood glucose levels were determined for all patients and were lower than 10 mmol/L, and no correction was applied for the blood glucose level. The scan was obtained in radiotherapy position, and the images were used for accurate tumor delineation and treatment planning. Four-dimensional respiration-correlated CT was acquired to visualize possible tumor movement due to respiration, as is necessary for radiotherapy planning purposes. A separate contrast-enhanced CT scan was also obtained during this imaging session. During the second week of radiotherapy, the imaging session was repeated using the same immobilization devices and setup as the pretreatment ^{18}F-FDG PET/CT procedure. For each patient, the injected amount of ^{18}F-FDG (MBq) was equivalent to 4 × body weight (kg) + 20 (MBq), and the patients needed to rest for 60 min before image acquisition could start. The raw PET data were corrected for scatter and decay, were rebinned, and subsequently were reconstructed using ordered-subset expectation maximization in 2 dimensions with 4 iterations and 8 subsets.

Quantitative Analysis

Quantitative analysis of ^{18}F-FDG uptake was performed using SUV. The maximum SUV and mean SUV inside the primary tumor were calculated, and changes in uptake between time points were analyzed. For mean SUV inside the primary tumor, the volume was defined by voxels having uptake greater than 50% of the maximum SUV inside the primary tumor; we called this volume the PET volume. Survival of the patients was grouped according to the response criteria of the European Organization for Research and Treatment of Cancer (EORTC). A 15% or 25% decrease in ^{18}F-FDG uptake, depending on the number of chemotherapy cycles, is associated with partial metabolic response using the EORTC criteria (*20*), and the PET Response Criteria in Solid Tumors suggest a 30% decrease for response (*21*). These cutoffs were used in the analysis to separate the groups.

Automatic segmentation methods based on the ^{18}F-FDG PET images were used to define tumor volume (*22*). Additionally, we used the gross tumor volume of the primary tumor and the possible involved lymph node volume as delineated on the PET/CT scan by the radiation oncologist. These volumes were subsequently used to design the radiotherapy plan. The gross tumor volume of the primary tumor, as well as the total tumor volume including possible involved lymph nodes, was also investigated for correlation with survival.

Endpoint and Statistical Analysis

The endpoint evaluated in this study was the 2-y overall survival rate. All paired analyses were performed using a Wilcoxon signed rank test, with a P value of less than 0.05 indicating statistical significance. Differences between groups were evaluated using a Mann–Whitney U test. Changes in the SUV parameters of the midtreatment scan were calculated relative to the pretreatment scan. For this threshold, a Cox regression and survival analysis was performed. Survival curves were displayed by Kaplan–Meier curves, and survival between groups was compared by the log-rank test.

RESULTS

For 35 non–small cell lung cancer patients, ^{18}F-FDG PET/CT was performed before radiotherapy and in the second week of radiotherapy. Imaging time points and patient characteristics are summarized in Table 1. Excluded from further analysis was a patient who had a complete response after 3 cycles of chemotherapy before radiotherapy and did not show any tumor mass on the repeated scan. Another patient had 2 primary tumors in the lung; for this patient, the lesion with the largest volume was analyzed. Minimum follow-up was 2 y and 2 mo, with an overall 2-y survival rate of 56% for all patients. Figure 1 shows the survival curves for the different therapy regimens in this study.

The volume of the primary tumor was on average 61.4 ± 56.7 cm^3 and decreased to 56.4 ± 49.2 cm^3 in the second week of treatment, a fractional decrease of 5.8% ± 19.3% in volume. The total tumor volume (primary tumor and nodes) for all patients, including those with nodal involvement (n = 24), was 81.9 ± 63.3 cm^3 and 77.8 ± 59.3 cm^3 for the pretreatment and midtreatment time points, respectively. The average relative decrease in total tumor volume was 4.1% ± 15.3%. The PET volume before treatment was on average 17.5 ± 20.3 cm^3; for the midtreatment time point this volume was 16.5 ± 18.0 cm^3, a fractional change of 7.5% ± 44.2%.

The maximum SUV and mean SUV inside the PET volume for the entire population was 10.0 ± 4.9 and 6.6 ± 3.2, respectively, for the pretreatment scan, compared with 8.8 ± 4.2 and 5.9 ± 2.9, respectively, for the midtreatment scan. Maximum and mean SUV parameters did not reach significance in a Cox regression analysis. The fractional change between time points was −10.8% ± 22.3%

TABLE 1
Patient Characteristics

Characteristic	Value
Sex (*n*)	
Male	24
Female	10
Age (y)	
Mean ± SD	64.2 ± 9.4
Range	45–81
Stage (TNM 6.0)	
IIb	2
IIIa	14
IIIb	16
IV*	2
Timing of chemotherapy	
No chemotherapy	2
Sequential chemoradiotherapy	18
Concurrent chemoradiotherapy	14
Average dose delivered at repeated imaging time point (Gy)	
Mean ± SD	20.7 ± 4.8
Range	12.0–34.2
Average time between start of radiotherapy and imaging time point (d)	
Mean ± SD	8.5 ± 1.9
Range	6–13

*All patients were in stage IV because of tumor in ipsilateral lung but in another lobe.

and −10.4% ± 23.6% for maximum and mean SUV, respectively.

The average change in the CT volume of the primary tumor or the total tumor volume including the involved lymph nodes was not significantly different between patients who survived for 2 y and those who did not (P = 0.215 and P = 0.918, respectively) (Table 2). Also, the change in PET volume was not significant (P = 0.215).

The average change in mean SUV inside the PET volume was −20.2% ± 20.5% for patients who survived for 2 y, compared with +2.1% ± 21.9% for patients who did not (P = 0.007). For maximum SUV inside the gross tumor volume, these numbers were −12.9% ± 23.1% vs. −4.2% ± 18.5% (P = 0.015), respectively. A detailed overview of all parameters is given in Table 2. Figure 2 shows an example of ^{18}F-FDG uptake in the primary tumor before and during treatment for both a metabolic responder and a nonresponder.

The EORTC criterion of 15% for partial metabolic response was used to divide the dataset into 2 groups. For patients with a decrease in SUV of more than 15%, median overall survival was not yet reached and 2-y overall survival was 92%, compared with a median overall survival of 19 mo and a 33% 2-y overall survival, respectively, for the patients with a decrease in mean SUV of less than 15%.

Figure 3 shows the Kaplan–Meier curves for the decrease in mean SUV of the primary tumor. Survival between the 2 groups was statistically different, with a hazard ratio of 1.032 (95% confidence interval, 1.010–1.055) per percentage-point decrease in mean SUV. At cutoffs of 15%, 25%, and 30% decrease, a sensitivity of 63%, 47%, and 42%, respectively, and a specificity of 93%, 93%, and 93%, respectively, were reached.

Figure 4 shows the survival plots for the change in maximum SUV of the primary tumor. The hazard ratio for percentage decrease in SUVmax was 1.027 (95% confidence interval, 1.005–1.049) per percentage-point change in maximum SUV.

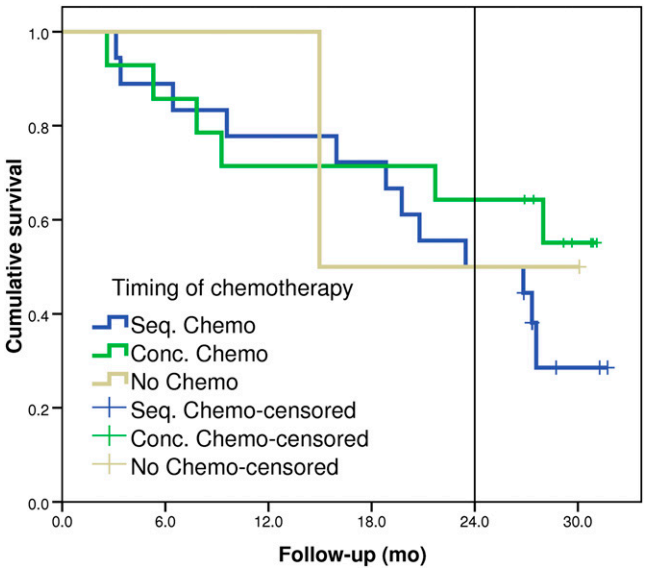

FIGURE 1. Survival curves for different patients grouped according to timing of chemotherapy: either no chemotherapy (n = 2), sequential (Seq.) chemoradiotherapy (n = 18), or concurrent (Conc.) chemoradiotherapy (n = 14).

DISCUSSION

This is one of the first studies showing that repeated ^{18}F-FDG PET early during radiotherapy has added value by being a predictive factor for survival before CT changes become evident (*23,24*). A decrease in metabolic activity of the primary tumor by as early as the second week of treatment was predictive of survival. The simplicity of calculating the average ^{18}F-FDG uptake inside the primary tumor is one of the factors that could be exploited in clinical practice for individualizing treatment.

The EORTC criteria (*20*) indicate a partial metabolic response after 1 cycle of chemotherapy if ^{18}F-FDG uptake decreases by more than 15%. Our study confirmed that this percentage correlates with a more long-term endpoint: the 2-y overall survival. The PET Response Criteria in Solid Tumors (*21*) suggest that a 30% decrease is needed to classify a partial response; however, these criteria are also based on the large variability caused by technical issues, the use of different scanners, and the use of different reconstruction protocols—all decreasing the reproducibility

TABLE 2
Volume and SUV Characteristics for All Patients

Characteristic	Survival > 2 y (n = 19)			Survival < 2 y (n = 15)			P*
	Baseline scan	Repeated scan	Change (%)	Baseline scan	Repeated scan	Change (%)	
Primary-tumor volume (cm^3)							0.215
Mean ± SD	56.1 ± 61.1	51.1 ± 54.2	−10.0 ± 18.7	68.1 ± 51.8	63.1 ± 43.0	−0.5 ± 19.3	
Range	3.1–189	1.3–185.2	−65.9–24.0	1.1–182	1.6–150	−25.8–47.2	
Total tumor volume (cm^3)							0.918
Mean ± SD	71.8 ± 64.3	67.1 ± 55.6	−2.7 ± 12.0	94.6 ± 61.9	91.3 ± 62.9	−2.4 ± 14.0	
Range	19–216	18–185	−23.5–28.3	11–218	11–255	−25.8–31.0	
PET volume (cm^3)							0.215
Mean ± SD	17.9 ± 24.9	15.4 ± 22.2	−4.5 ± 26.0	16.9 ± 13.1	18.0 ± 11.3	22.6 ± 57.5	
Range	2–94	2–95	−44.9–56.6	2–55	3–41	−34.2–153	
Primary-tumor maximum SUV							0.015
Mean ± SD	11.4 ± 5.6	9.2 ± 4.6	−19.3 ± 21.6	8.2 ± 3.2	8.3 ± 3.8	+0.1 ± 18.9	
Range	4.5–26.8	2.1–17.3	−54.2–24.9	2.6–14.1	2.5–15.3	−47.2–26.2	
Mean SUV inside PET volume							0.007
Mean ± SD	7.7 ± 3.7	6.1 ± 3.0	−20.2 ± 20.5	5.4 ± 2.1	5.6 ± 2.7	+2.1 ± 21.9	
Range	3.0–17.3	1.4–11.5	−54.3–14.6	1.6–9.1	1.6–9.8	−51.9–44.2	
SUV peak							0.003
Mean ± SD	9.4 ± 4.7	7.5 ± 3.9	−21.3 ± 18.4	6.8 ± 2.7	7.2 ± 3.7	+5.4 ± 29.3	
Range	3.1–20.7	1.3–14.3	−57.2–6.7	1.9–11.6	2.0–14.2	−49.5–87.3	

*Change between survivors and nonsurvivors.

of the repeated imaging. We have minimized these factors by using the same PET/CT scanner, acquisition protocols, and procedure for both imaging time points. Reproducibility (e.g., test–retest) studies, however, have shown a 10%–15% variability using the same equipment in repeated imaging of the same patient on different days (*21*).

The number of patients (n = 34) in this study was, however, too limited for an in-depth subgroup analysis. A future larger study is necessary that might be able to provide even better prognostic and predictive factors incorporating stage or histologic type.

Van Baardwijk et al. (*12*) showed that nonresponders had an increase in maximum SUV early in treatment. We did not observe this trend in our population. There could be several reasons for this difference. Our imaging time point was in the second week of treatment, whereas the maximum in their publication was found in the first week. Another likely cause is that in our study almost all patients were treated with sequential or concurrent chemotherapy before or during treatment. Chemotherapy is known to suppress the ^{18}F-FDG uptake signal inside tumors (*25,26*). Kong et al. quantified changes in ^{18}F-FDG uptake after a 45-Gy dose of radiotherapy (*18*). They found a correlation between an early metabolic response and a 3- to 4-mo CT-based response, but they did not perform a survival analysis. In addition, Huang et al. recently investigated a group of non–small cell lung cancer patients with repeated imaging after they had received approximately 40 Gy, and short-term outcome was evaluated using the Response Evaluation Criteria in Solid Tumors at 4 wk after the end of treatment (*16*). Changes in maximum or mean SUV allowed prediction of the treatment outcome. However, these studies had imaging time points in the second half of the radiotherapy course, making treatment adaptation less effective because there is not much time left to adapt or improve the treatment. Our study shows that changes in metabolic activity can already be detected in the second week of treatment, when more than half the treatment time is still available for improvement and individualization.

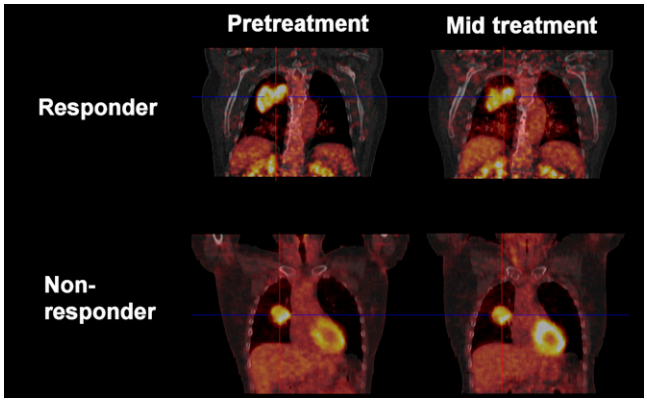

FIGURE 2. Patient example of metabolic responder vs. nonresponder for both pretreatment and mid-treatment ^{18}F-FDG PET/CT. SUV window levels are scaled equally per patient.

To fully characterize the changes in SUV uptake, one needs to look at the individual voxels inside the tumor and assess the response per voxel (*27*). Such an analysis requires a detailed voxel-tracking method, which was outside the scope of this study. Another option for a more

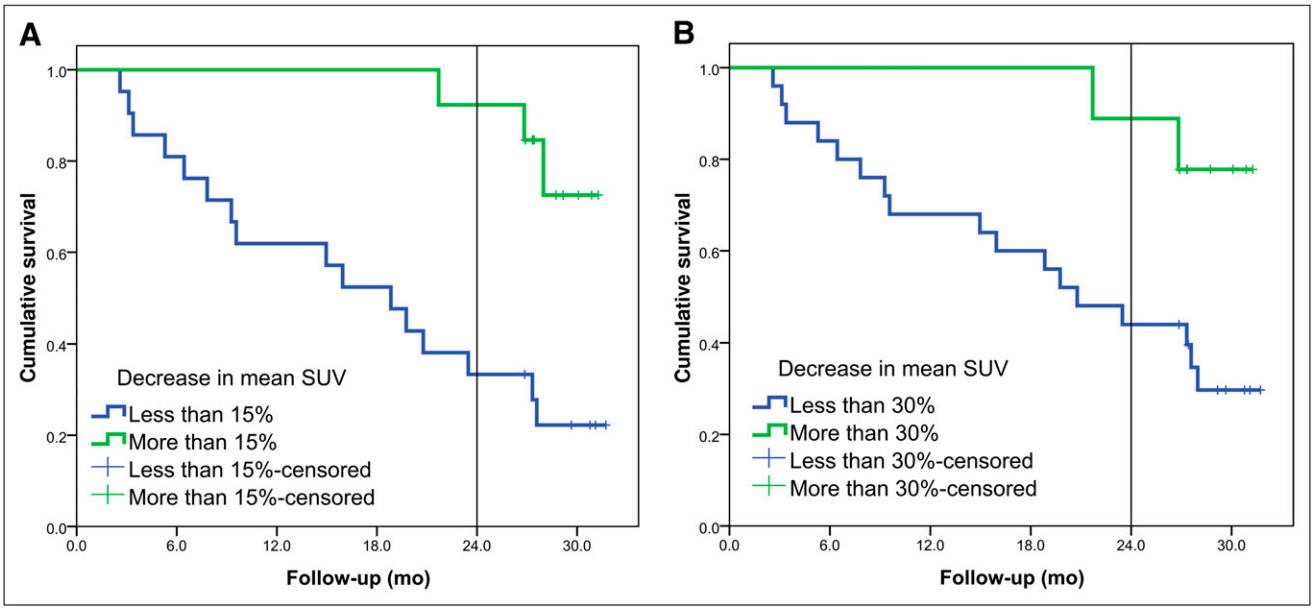

FIGURE 3. (A) Overall survival plots for metabolic responders ($n = 13$) and nonresponders ($n = 21$) defined for decrease of at least 15% in mean SUV of primary tumor ($P = 0.001$). (B) Survival plots if cutoff of 30% decrease in mean SUV is used: 5 metabolic responders vs. 29 nonresponders ($P = 0.026$).

comprehensive tumor quantification is the use of multiple tracers, such as 3′-deoxy-3′-^{18}F-fluorothymidine and ^{18}F-fluoromisonidazole in addition to ^{18}F-FDG, as described by Vera et al. (*28*). Also interesting is an approach described by van Velden et al., who looked at cumulative histograms of SUV distribution and heterogeneity and at the response that might be characterized from these histograms (*29*). This might be an alternative approach to fully voxel-based response analysis. Also, the definition of PET volume using a cutoff of 50% of maximum SUV is highly sensitive to maximum SUV and might also underestimate the true tumor volume. For the repeated PET scan, therapy-induced reduced activity might again enlarge this volume because of reduced maximum uptake. Newly developed methods, for example, gradient-based, might give a more robust volume definition (*30,31*).

To use early information about response in clinical practice, one could investigate the added value of an adaptive protocol based on the results of an ^{18}F-FDG PET scan during treatment. For responders, treatment could be continued as

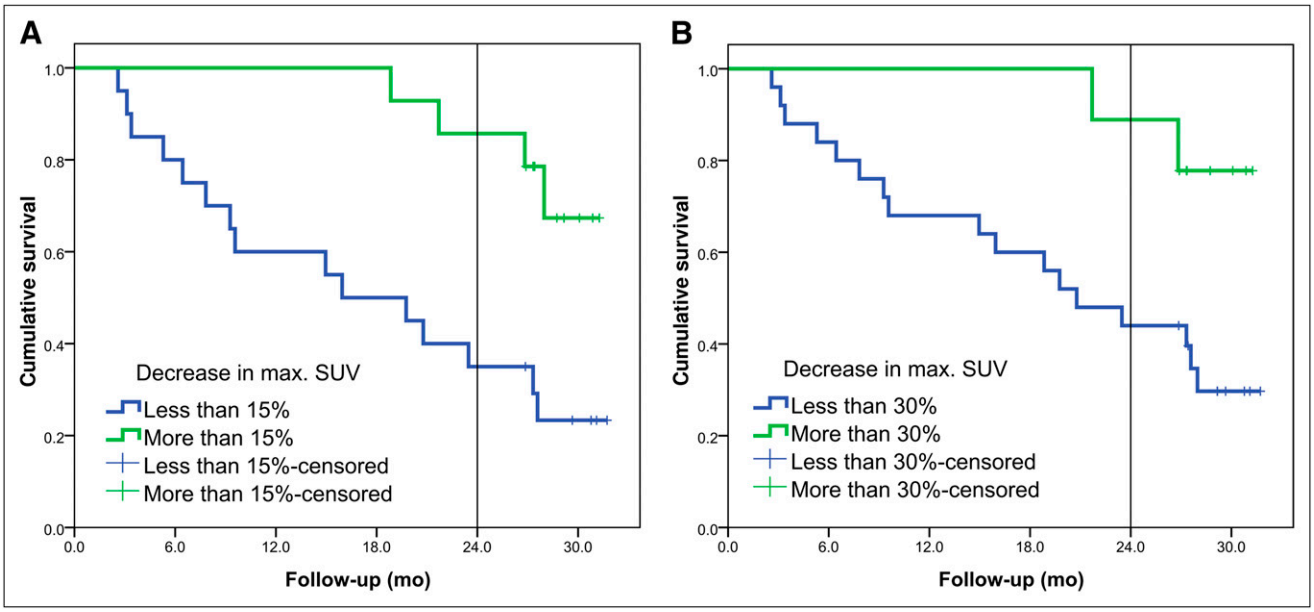

FIGURE 4. (A) Overall survival plots for metabolic responders ($n = 14$) and nonresponders ($n = 20$) defined for decrease of at least 15% in maximum SUV of primary tumor ($P = 0.004$). (B) Survival plots if cutoff of 30% decrease in maximum SUV is used: 9 metabolic responders vs. 25 nonresponders ($P = 0.026$).

planned. In the future, we might envisage designing trials that lower the radiotherapy dose in very favorable responders to decrease toxicity. For nonresponders, treatment could be intensified using a new treatment plan that includes possible volume reductions already observed compared with the planning scan. This change might allow dose escalation of the smaller volume with the same level of normal-lung toxicity. Volume changes in the second week of treatment are, however, small but may trigger additional imaging later during the course of radiotherapy where larger volume changes are reported (*18,32–36*). However, one has to be careful with this type of dose escalation and shrinking-field approach because microscopic disease might not be treated effectively. Therefore, such an approach should be investigated in a clinical trial. The data presented in this study could serve as an estimation of which cutoff for ^{18}F-FDG decrease should be used. The imaging biomarker (e.g., difference in mean SUV of the primary tumor) might then become a predictive marker that could be used in patient-individualized treatment.

CONCLUSION

Early assessment of treatment response is possible by measuring the decrease in average ^{18}F-FDG uptake in the primary tumor on repeated ^{18}F-FDG PET in the second week of radiotherapy. A large decrease in ^{18}F-FDG uptake early during treatment correlates with improved overall survival.

DISCLOSURE STATEMENT

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ACKNOWLEDGMENTS

This study was performed within the framework of CTMM, the Center for Translational Molecular Medicine (www.ctmm.nl), project AIRFORCE number 03O-103. The research was supported by EU FP7 funding (project ARTFORCE) and in part by a KWF fellowship from the Dutch Cancer Society. No other potential conflict of interest relevant to this article was reported.

REFERENCES

1. Hoekstra CJ, Stroobants SG, Smit EF, et al. Prognostic relevance of response evaluation using [^{18}F]-2-fluoro-2-deoxy-D-glucose positron emission tomography in patients with locally advanced non-small-cell lung cancer. *J Clin Oncol.* 2005;23:8362–8370.
2. De Ruysscher D, Kirsch CM. PET scans in radiotherapy planning of lung cancer. *Radiother Oncol.* 2010;96:335–338.
3. Weber WA, Petersen V, Schmidt B, et al. Positron emission tomography in non-small-cell lung cancer: prediction of response to chemotherapy by quantitative assessment of glucose use. *J Clin Oncol.* 2003;21:2651–2657.
4. Aerts HJ, Bosmans G, van Baardwijk AA, et al. Stability of ^{18}F-deoxyglucose uptake locations within tumor during radiotherapy for NSCLC: a prospective study. *Int J Radiat Oncol Biol Phys.* 2008;71:1402–1407.
5. Abramyuk A, Tokalov S, Zophel K, et al. Is pre-therapeutical FDG-PET/CT capable to detect high risk tumor subvolumes responsible for local failure in non-small cell lung cancer? *Radiother Oncol.* 2009;91:399–404.
6. Mac Manus MP, Hicks RJ, Matthews JP, et al. Positron emission tomography is superior to computed tomography scanning for response-assessment after radical radiotherapy or chemoradiotherapy in patients with non-small-cell lung cancer. *J Clin Oncol.* 2003;21:1285–1292.
7. Aerts HJ, van Baardwijk AA, Petit SF, et al. Identification of residual metabolic-active areas within individual NSCLC tumours using a pre-radiotherapy ^{18}Fluorodeoxyglucose-PET-CT scan. *Radiother Oncol.* 2009;91:386–392.
8. de Geus-Oei LF, van der Heijden HF, Visser EP, et al. Chemotherapy response evaluation with ^{18}F-FDG PET in patients with non-small cell lung cancer. *J Nucl Med.* 2007;48:1592–1598.
9. Lee DH, Kim SK, Lee HY, et al. Early prediction of response to first-line therapy using integrated ^{18}F-FDG PET/CT for patients with advanced/metastatic non-small cell lung cancer. *J Thorac Oncol.* 2009;4:816–821.
10. Nahmias C, Hanna WT, Wahl LM, Long MJ, Hubner KF, Townsend DW. Time course of early response to chemotherapy in non-small cell lung cancer patients with ^{18}F-FDG PET/CT. *J Nucl Med.* 2007;48:744–751.
11. Matsuo Y, Nakamoto Y, Nagata Y, et al. Characterization of FDG-PET images after stereotactic body radiation therapy for lung cancer. *Radiother Oncol.* 2010;97:200–204.
12. van Baardwijk A, Bosmans G, Dekker A, et al. Time trends in the maximal uptake of FDG on PET scan during thoracic radiotherapy: a prospective study in locally advanced non-small cell lung cancer (NSCLC) patients. *Radiother Oncol.* 2007;82:145–152.
13. Berghmans T, Dusart M, Paesmans M, et al. Primary tumor standardized uptake value (SUVmax) measured on fluorodeoxyglucose positron emission tomography (FDG-PET) is of prognostic value for survival in non-small cell lung cancer (NSCLC): a systematic review and meta-analysis (MA) by the European Lung Cancer Working Party for the IASLC Lung Cancer Staging Project. *J Thorac Oncol.* 2008;3:6–12.
14. Kim SJ, Kim YK, Kim IJ, Kim YD, Lee MK. Limited prognostic value of dual time point F-18 FDG PET/CT in patients with early stage (stage I & II) non-small cell lung cancer (NSCLC). *Radiother Oncol.* 2011;98:105–108.
15. Zhang HQ, Yu JM, Meng X, Yue JB, Feng R, Ma L. Prognostic value of serial [^{18}F]fluorodeoxyglucose PET-CT uptake in stage III patients with non-small cell lung cancer treated by concurrent chemoradiotherapy. *Eur J Radiol.* 2011;77:92–96.
16. Huang W, Zhou T, Ma L, et al. Standard uptake value and metabolic tumor volume of ^{18}F-FDG PET/CT predict short-term outcome early in the course of chemoradiotherapy in advanced non-small cell lung cancer. *Eur J Nucl Med Mol Imaging.* 2011;38:1628–1635.
17. van Loon J, Offermann C, Ollers M, et al. Early CT and FDG-metabolic tumour volume changes show a significant correlation with survival in stage I-III small cell lung cancer: a hypothesis generating study. *Radiother Oncol.* 2011;99:172–175.
18. Kong FM, Frey KA, Quint LE, et al. A pilot study of [^{18}F]fluorodeoxyglucose positron emission tomography scans during and after radiation-based therapy in patients with non small-cell lung cancer. *J Clin Oncol.* 2007;25:3116–3123.
19. van Baardwijk A, Wanders S, Boersma L, et al. Mature results of an individualized radiation dose prescription study based on normal tissue constraints in stages I to III non-small-cell lung cancer. *J Clin Oncol.* 2010;28:1380–1386.
20. Young H, Baum R, Cremerius U, et al. Measurement of clinical and subclinical tumour response using [^{18}F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. *Eur J Cancer.* 1999;35:1773–1782.
21. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. *J Nucl Med.* 2009;50(suppl 1):122S–150S.
22. Wanet M, Lee JA, Weynand B, et al. Gradient-based delineation of the primary GTV on FDG-PET in non-small cell lung cancer: a comparison with threshold-based approaches, CT and surgical specimens. *Radiother Oncol.* 2011;98:117–125.
23. de Geus-Oei LF, van der Heijden HF, Corstens FH, Oyen WJ. Predictive and prognostic value of FDG-PET in nonsmall-cell lung cancer: a systematic review. *Cancer.* 2007;110:1654–1664.
24. Lin P, Koh ES, Lin M, et al. Diagnostic and staging impact of radiotherapy planning FDG-PET-CT in non-small-cell lung cancer. *Radiother Oncol.* 2011;101:284–290.
25. Yamamoto Y, Nishiyama Y, Monden T, et al. Correlation of FDG-PET findings with histopathology in the assessment of response to induction chemoradiotherapy in non-small cell lung cancer. *Eur J Nucl Med Mol Imaging.* 2006;33:140–147.
26. Eschmann SM, Friedel G, Paulsen F, et al. Repeat ^{18}F-FDG PET for monitoring neoadjuvant chemotherapy in patients with stage III non-small cell lung cancer. *Lung Cancer.* 2007;55:165–171.

27. Lambin P, Petit SF, Aerts HJ, et al. The ESTRO Breur Lecture 2009. From population to voxel-based radiotherapy: exploiting intra-tumour and intra-organ heterogeneity for advanced treatment of non-small cell lung cancer. *Radiother Oncol.* 2010;96:145–152.
28. Vera P, Bohn P, Edet-Sanson A, et al. Simultaneous positron emission tomography (PET) assessment of metabolism with ^{18}F-fluoro-2-deoxy-d-glucose (FDG), proliferation with ^{18}F-fluoro-thymidine (FLT), and hypoxia with ^{18}fluoro-misonidazole (F-miso) before and during radiotherapy in patients with non-small-cell lung cancer (NSCLC): a pilot study. *Radiother Oncol.* 2011;98:109–116.
29. van Velden FH, Cheebsumon P, Yaqub M, et al. Evaluation of a cumulative SUV-volume histogram method for parameterizing heterogeneous intratumoural FDG uptake in non-small cell lung cancer PET studies. *Eur J Nucl Med Mol Imaging.* 2011;38:1636–1647.
30. Lee JA. Segmentation of positron emission tomography images: some recommendations for target delineation in radiation oncology. *Radiother Oncol.* 2010; 96:302–307.
31. Hatt M, Cheze le Rest C, Turzo A, Roux C, Visvikis D. A fuzzy locally adaptive Bayesian segmentation approach for volume determination in PET. *IEEE Trans Med Imaging.* 2009;28:881–893.
32. Feng M, Kong FM, Gross M, Fernando S, Hayman JA, Ten Haken RK. Using fluorodeoxyglucose positron emission tomography to assess tumor volume during radiotherapy for non-small-cell lung cancer and its potential impact on adaptive dose escalation and normal tissue sparing. *Int J Radiat Oncol Biol Phys.* 2009;73:1228–1234.
33. van Elmpt W, Ollers M, van Herwijnen H, et al. Volume or position changes of primary lung tumor during (chemo-)radiotherapy cannot be used as a surrogate for mediastinal lymph node changes: the case for optimal mediastinal lymph node imaging during radiotherapy. *Int J Radiat Oncol Biol Phys.* 2011;79:89–95.
34. Kupelian PA, Ramsey C, Meeks SL, et al. Serial megavoltage CT imaging during external beam radiotherapy for non-small-cell lung cancer: observations on tumor regression during treatment. *Int J Radiat Oncol Biol Phys.* 2005;63: 1024–1028.
35. Spoelstra FO, Pantarotto JR, van Sornsen de Koste JR, Slotman BJ, Senan S. Role of adaptive radiotherapy during concomitant chemoradiotherapy for lung cancer: analysis of data from a prospective clinical trial. *Int J Radiat Oncol Biol Phys.* 2009;75:1092–1097.
36. Fox J, Ford E, Redmond K, Zhou J, Wong J, Song DY. Quantification of tumor volume changes during radiotherapy for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2009;74:341–348.

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J Nucl Med. 2012;53:1514-1520.
Published online: August 9, 2012.
Doi: 10.2967/jnumed.111.102566

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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