FDG-PET/CT Imaging Predicts Histopathologic Treatment Responses after the Initial Cycle of Neoadjuvant Chemotherapy in High-Grade Soft-Tissue Sarcomas

Matthias R. Benz,[1] Johannes Czernin,[1] Martin S. Allen-Auerbach,[1] William D. Tap,[2] Sarah M. Dry,[4] David Elashoff,[5] Kira Chow,[6] Vladimir Evilevitch,[1] Jeff J. Eckardt,[3] Michael E. Phelps,[1] Wolfgang A. Weber,[1,8] and Fritz C. Eilber[1,7]

Abstract

Purpose: In patients with soft-tissue sarcoma (STS), the early assessment of treatment responses is important. Using positron emission tomography/computed tomography (PET/CT) with [^{18}F]fluorodeoxyglucose (FDG), we determined whether changes in tumor FDG uptake predict histopathologic treatment responses in high-grade STS after the initial cycle of neoadjuvant chemotherapy.

Experimental Design: From February 2006 to March 2008, 50 patients with resectable high-grade STS scheduled for neoadjuvant therapy and subsequent tumor resection were enrolled prospectively. FDG-PET/CT before (baseline), after the first cycle (early follow-up), and after completion of neoadjuvant therapy (late follow-up) was done. Tumor FDG uptake and changes were measured by standardized uptake values. Histopathologic examination of the resected specimen provided an assessment of treatment response. Patients with ≥95% pathologic necrosis were classified as treatment responders. FDG-PET/CT results were compared with histopathologic findings.

Results: At early follow-up, FDG uptake decreased significantly more in 8 (16%) responders than in the 42 (84%) nonresponders (-55% versus -23%; $P = 0.002$). All responders and 14 of 42 nonresponders had a ≥35% reduction in standardized uptake value between baseline and early follow-up. Using a ≥35% reduction in FDG uptake as early metabolic response threshold resulted in a sensitivity and specificity of FDG-PET for histopathologic response of 100% and 67%, respectively. Applying a higher threshold at late follow-up improved specificity but not sensitivity. CT had no value at response prediction.

Conclusion: A 35% reduction in tumor FDG uptake at early follow-up is a sensitive predictor of histopathologic tumor response. Early treatment decisions such as discontinuation of chemotherapy in nonresponding patients could be based on FDG-PET criteria.

Optimal clinical evaluation of any cancer therapeutic hinges on our ability to monitor longitudinally treatment effects in patients. [^{18}F]fluorodeoxyglucose (FDG)-positron emission tomography (PET) is an established imaging technique that accurately predicts responses of diverse types of cancer to various treatments (1, 2). Disease-free survival (3), progression-free survival (4), overall survival (5), and degree of histopathologic necrosis in excised tissue (6–8) have been used as reference standards for validating FDG-PET findings and response predictions.

Glucose metabolic imaging has been used successfully in patients with esophageal cancer to determine whether neoadjuvant treatment should be continued or discontinued (9).

We have recently reported in soft-tissue sarcoma (STS) patients that changes in FDG tumor uptake from baseline to end of neoadjuvant treatment but not changes in tumor size by computed tomography (CT) identified accurately histopathologic responders (10).

Because neoadjuvant therapy is highly toxic (11, 12) and frequently ineffective (13), identifying histopathologic responders early during the course of therapy is of great importance. If this could be accomplished with FDG-PET imaging, successful treatments would be continued in responders but discontinued in nonresponding patients. The latter group of patients might then undergo surgery earlier or an alternative neoadjuvant therapy could be initiated.

The aim of the current prospective study was therefore to determine whether FDG-PET/CT after the initial cycle of

Authors' Affiliations: [1]Ahmanson Biological Imaging Division, Department of Molecular and Medical Pharmacology; Divisions of [2]Medical Oncology and [3]Orthopedic Oncology; Departments of [4]Pathology, [5]Biostatistics, and [6]Radiology; and [7]Division of Surgical Oncology, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California and [8]Abteilung Nuklearmedizin, University of Freiburg, Freiburg, Germany

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Requests for reprints: Fritz C. Eilber, Division of Surgical Oncology, David Geffen School of Medicine at the University of California at Los Angeles, 10833 Le Conte Avenue, Room 54-140 CHS, Los Angeles, CA 90095-1782. Phone: 310-825-7086; Fax: 310-825-7575; E-mail: fceilber@mednet.ucla.edu.

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Translational Relevance

In a previous study in *Clinical Cancer Research*, we reported that changes in glucose metabolic activity by [^{18}F]fluorodeoxyglucose (FDG)-positron emission tomography (PET) at the end of neoadjuvant treatment predicted histopathologic tumor responses in soft-tissue sarcomas (STS) with a high accuracy. However, imaging after completion of therapy has limited effect on patient management. Therefore, we investigated in the current study whether FDG-PET imaging after the initial cycle of neoadjuvant chemotherapy also provides accurate response predictions in high-grade STS patients. In this study, all nonresponders were identified by FDG-PET/computed tomography. Moreover, no treatment responders were missed by PET/computed tomography. This observation could now be translated to guiding therapeutic decisions in STS patients. The high negative predictive value of FDG-PET suggests that patients who do not achieve an early metabolic response should be switched to different therapeutic approaches or could be treated surgically earlier, which in turn could reduce toxicity associated with neoadjuvant treatments.

neoadjuvant chemotherapy can identify those sarcoma patients who will be histopathologic responders (≥95% necrosis or fibrosis) following completion of neoadjuvant therapy. Further, we evaluated whether early changes in FDG uptake were as predictive for histopathologic responses as end of treatment FDG-PET evaluations.

Patients and Methods

From February 2006 to March 2008, 56 consecutive patients with high-grade STS were prospectively enrolled in this study. Four patients (2 with liposarcomas and 2 with synovial sarcomas) were excluded because of a standardized uptake value (SUVpeak) at baseline of <2.5. One patient had to be excluded because of technical issues and one patient showed unresectable disease at the time of surgery. Therefore, the study population consisted of 50 patients.

Fifteen (30%) of these patients have been described in a prior publication from our group that reported high accuracy for identifying histopathologic treatment responders when end of treatment reductions in SUVpeak by 60% were used as response criteria (10). Patient characteristics are summarized in Table 1.

There were 24 females and 26 males with a mean age of 51 ± 16 years. Forty-two (84%) patients presented with primary disease, 3 (6%) patients with locally recurrent disease, and 5 (10%) patients with metastatic disease. Of the 5 patients with metastatic disease, 4 (8%) patients had recurrent and 1 (2%) patient had primary disease at the time of the initial diagnosis. All underwent neoadjuvant therapy followed by surgical tumor excision per standard protocols. Histologic diagnosis was obtained in all patients. Exclusion criteria included patient age <18 years, chemotherapy and/or radiotherapy within 6 months of the baseline PET/CT scan, presence of a second malignancy, unresectable disease, and a diagnosis of gastrointestinal stromal tumor. Finally, to avoid data contamination by image noise, patients with a tumor SUVpeak <2.5 were excluded.

A physician explained the details of the study to the research subjects and written informed consent was obtained from all patients. The study was approved by the University of California at Los Angeles Institutional Review Board for Human Subjects.

Neoadjuvant therapy. The neoadjuvant treatments were ifosfamide-based (n = 42; 84%) or gemcitabine-based (n = 8; 16%). Standard first-line ifosfamide-based chemotherapy consisted of two cycles of ifosfamide (14 g/m^2) followed by doxorubicin (60-90 mg/m^2). Standard gemcitabine-based chemotherapy consisted of two cycles of gemcitabine (900 mg/m^2 on days 1 and 8) and docetaxel (75-100 mg/m^2 on day 8; n = 8; 16%). Thirty-four (68%) patients received neoadjuvant external beam radiation between early and late follow-up PET/CT scan. Sixteen (32%) patients were not candidates for neoadjuvant radiation therapy due to location of the tumor (n = 10), prior radiation treatment (n = 3), patient refusal (n = 2), and limb amputation (n = 1).

PET/CT imaging. Patients underwent a baseline scan, a second one after the initial cycle of chemotherapy (early follow-up scan), and a final one after completion of neoadjuvant treatment (late follow-up scan). Two patients had rapid clinical progression after the first cycle of chemotherapy and opted for surgery before undergoing the late follow-up scan.

The time interval between baseline PET/CT and the initiation of chemotherapy was 7.2 ± 5.7 days, whereas the early follow-up study was done 27.3 ± 8.8 days after the baseline PET/CT scan. The late follow-up scan was done 9.4 ± 4.8 days after the end of treatment and 7.4 ± 5.2 days before surgery (Supplement 1).

Table 1. Clinical, pathologic, and treatment characteristics (n = 50)

Characteristics	*n* (%)
Age (y)	
Median (range)	51 (20-80)
Sex	
Male	26 (52)
Female	24 (48)
Site	
Extremity	32 (64)
Retroperitoneal/abdominal	7 (14)
Chest/trunk	11 (22)
Presentation status	
Primary	42 (84)
Recurrent	3 (6)
Metastatic	5 (10)
Tumor size (cm)	
<5	5 (10)
5-10	23 (46)
>10	22 (44)
Histology	
Not other specified	16 (32)
Synovial	7 (14)
Myxofibrosarcoma	7 (14)
Liposarcoma	6 (12)
Leiomyosarcoma	4 (8)
Malignant peripheral nerve sheath tumors	2 (4)
Other	8 (16)
Grade	
High	50 (100)
Chemotherapy	
Ifosfamide-based chemotherapy	42 (84)
Gemcitabine-based chemotherapy	8 (16)
Radiotherapy	
Yes	34 (68)
No	16 (32)
Pathologic necrosis	
≥95% (responder)	8 (16)
<95% (nonresponder)	42 (84)

Table 2. Percent changes in SUVpeak and size

	Responder		Nonresponder	
	Early	Late	Early	Late
ΔSUV (%)	-55 ± 19*	-76 ± 15*	-23 ± 41*	-34 ± 38*
ΔSize (%)	1 ± 22	-14 ± 25	2 ± 10	-2 ± 23

NOTE: Early: PET/CT scan after first cycle of neoadjuvant therapy; Late: PET/CT scan after completion of neoadjuvant therapy.
*P < 0.05 versus baseline SUVpeak.

All PET/CT studies were done using the Siemens Biograph Duo PET/CT scanner. Patients were instructed to fast for at least 6 h before FDG-PET imaging. Serum glucose levels measured before the injection of FDG were <150 mg/dL in all patients (14).

For CT imaging, intravenous contrast (Omnipaque, Novaplus) was administered in all patients at a rate of 2 mL/s 30 to 40 s before imaging commenced. The CT acquisition parameters were 130 kVp, 120 mAs, 1 s tube rotation, 4 mm slice collimation, and bed speed 8 mm/s.

Patients received 0.21 mCi/kg FDG intravenously ~60 min before image acquisition. PET emission scans were acquired for 1 to 5 min/bed position depending on patient's body weight as described previously (15, 16). To minimize misregistration between CT and PET images, patients were instructed to use shallow breathing during the image acquisition (17).

The CT images were reconstructed using filtered back-projection at 3.4 mm axial intervals to match the slice separation of the PET data. PET images were reconstructed using an iterative algorithm (OSEM two iterations, eight subsets). To correct for photon attenuation, a previously published CT-based algorithm was applied (18).

Image analysis. FDG images were analyzed by one observer who was aware of the clinical diagnosis but blinded to histopathologic treatment response and CT size measurements.

All FDG-PET studies were analyzed quantitatively as described previously (19). First, the single maximum pixel value within the slice with the highest radioactivity concentration was detected (SUVmax). Second, a circular region of interest with a diameter of 15 mm was drawn around SUVmax. SUVpeak was defined by the average pixel value within this 15 mm region of interest. This approach was used for baseline and follow-up scans.

SUVs are given as g/mL [SUV = activity concentration in the tumor (Bq/mL) × body weight (g) / injected activity (Bq)].

One radiologist, blinded to PET measurements and histopathologic response data, analyzed all CT images as follows: a soft-tissue CT window was used to display tumor images on CT. Maximum tumor diameter was measured before treatment, after the initial cycle of chemotherapy, and after completion of chemotherapy. Tumor response by CT was determined by using RECIST (20).

Metabolic response. Recent studies in esophageal cancer (7, 9, 21, 22), lung cancer (23), and gastric cancer (24, 25) have shown that a reduction of tumor metabolic activity by >35% early after the start of treatment accurately predicts tumor response and survival. We tested if this threshold of an early metabolic response could also be applied for an accurate early response assessment in STS.

Based on our previous study in sarcomas, we applied a 60% reduction in SUVpeak as the late response criterion (10).

Histopathology. All specimens were analyzed by one pathologist who was blinded to PET and CT data.

Each specimen was bisected along the greatest diameter, and the perimeter of the tumor was defined. The entire cross-sectional area of the bisected tumor was partitioned using a grid of ~2.0 cm^2 blocks and processed for histologic examination along with additional randomly sampled areas. Histopathologic response (% necrosis) was quantified as the fraction of necrotic tissue in the tumor to the nearest 5%. Based on a previous study (13), patients with ≥95% pathologic necrosis (<5% viable tumor cells) were classified as histopathologic responders, because this cutoff value has been significantly correlated with long-term survival (13). In addition, this high cutoff value avoids misinterpretation of any spontaneous necrosis as a histopathologic response.

Statistical analysis. Quantitative data are presented as median, range, and mean ± SD. The Wilcoxon signed rank test and the Mann-Whitney test were used for paired and unpaired comparisons between quantitative parameters. An early metabolic response was defined as a decrease in tumor FDG uptake (SUVpeak) by >35% as described in previous studies (7, 9, 21–25). A late tumor response was defined as decrease in SUVpeak by >60% (10). In addition, we used receiver

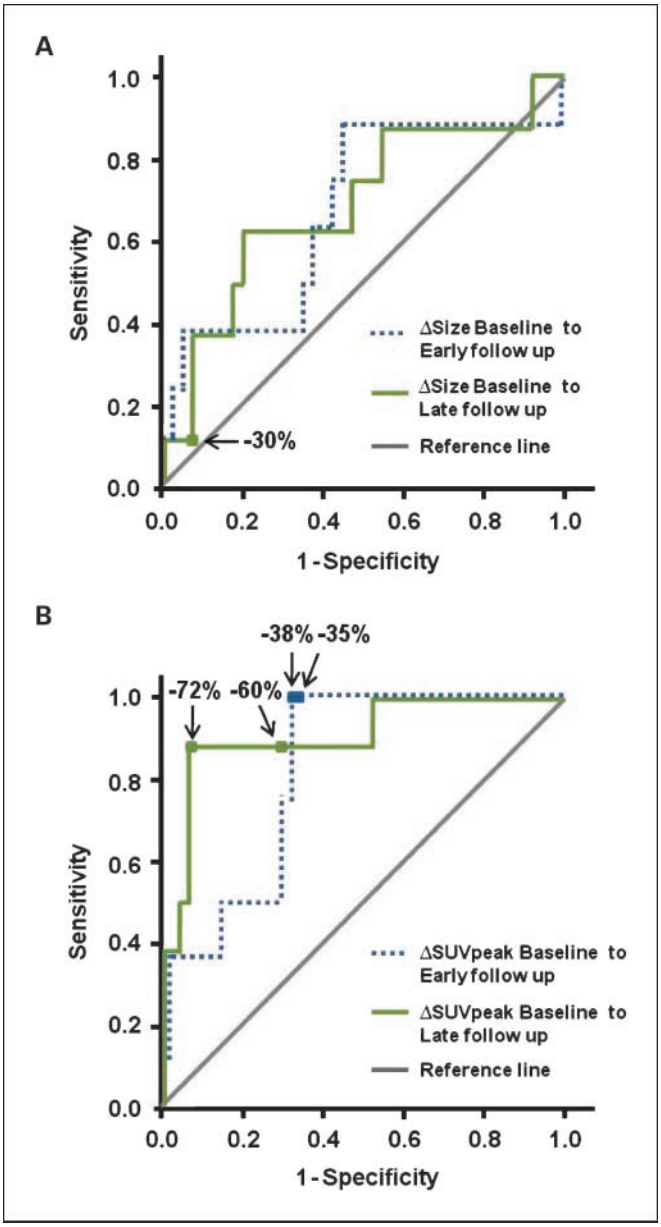

Fig. 1. *A,* ROC curve analysis for predicting histopathologic tumor response by early (*dotted line*, AUR = 0.60) and late (*solid line*, AUR = 0.69) changes in tumor size. *B,* ROC curve analysis for predicting histopathologic tumor response from early (*dotted line*, AUR = 0.83) and late (*solid line*, AUR = 0.90) changes in SUVpeak. A decrease in SUVpeak by 38% was the best early predictor and a decrease by 72% was the best late predictor of histopathologic response. Decreases in SUVpeak by 35% and 60% were the prospectively assigned thresholds.

Table 3. Correlation between histopathologic and early metabolic response

Metabolic response	Histopathology		
	Responder (≥95% necrosis)	Nonresponder (<95% necrosis)	
Responder (≥35% decrease in SUV)	8	14	Positive predictive value 8 of 22 = 36%
Nonresponder (<35% decrease in SUV)	0	28	Negative predictive value 28 of 28 = 100%
	Sensitivity 8 of 8 = 100%	Specificity 28 of 42 = 67%	

operating characteristic (ROC) curves to define optimum cutoff values for metabolic changes for prediction of histopathologic response. The jackknife method (26) was used to examine the variability in the threshold, sensitivity, and specificity in the prediction of histopathologic response using early changes in SUVpeak.

The diagnostic accuracy of early and late metabolic and size changes was also compared by calculating the area under the respective ROC curves. The significance of associations between two categorical variables was examined by using Fisher's exact test. A logistic regression was constructed to test the association of early changes in SUVpeak with histopathologic response (≥95% versus <95% necrosis) controlling for radiotherapy. Statistical analyses were done using SPSS software for Windows (version 14.0; SPSS) and Statistica software for Windows (version V8.0; StatSoft). P values < 0.05 were considered statistically significant.

Results

Changes in tumor diameter. At baseline, mean tumor size averaged 10.2 ± 4.8 cm (median, 9.0 cm; range, 3.5-21.4 cm). It remained essentially unchanged at early and late follow-up (10.4 ± 5.5 versus 9.7 ± 5.3 cm). By RECIST, 47 (94%) patients showed stable disease at early follow-up, whereas 3 (6%) exhibited progressive disease. At late follow-up, 4 (8.3%) of the 48 patients who completed therapy were classified as partial responders, 5 (10.4%) showed progressive disease, and 39 (81.3%) had stable disease.

Changes in tumor FDG uptake. SUVpeak averaged 9.9 ± 6.5 (median, 7.9; range, 2.9-30.7) at baseline and decreased significantly to 6.3 ± 4.6 (median, 4.7; range, 1.8-21.7) at early follow-up ($P < 0.001$) and 5.1 ± 3.5 (median, 4.0; range, 0.7-14.7) at late follow-up ($P < 0.001$). Changes in SUVpeak from early to late follow-up were also significant ($P = 0.01$).

Histopathologic response. The extent of necrosis in excised tumor tissue averaged 55 ± 30% with a median of 50% ranging from 5% to 99%. Eight (16%) patients exhibited ≥95% necrosis in the resected specimen and were therefore classified as histopathologic responders (16% response rate; 5 not otherwise specified, 1 synovial sarcoma, 1 rhabdomyosarcoma, and 1 extraosseous Ewing's sarcoma). Histopathologic response was not significantly correlated with type of chemotherapy ($P = 0.8$).

The extent of tumor necrosis differed among those patients who received chemotherapy combined with radiotherapy (34 of 50 patients; 60.7 ± 26.9%) and those who received chemotherapy only (16 of 50 patients; 42.9 ± 33.5%; $P = 0.05$). However, 5 (15%) of 34 patients who received chemoradiation therapy and 3 (19%) of 16 patients who received chemotherapy alone achieved a histopathologic tumor response of ≥95%. Therefore, the response rates in both groups were almost identical.

Changes in tumor size and histopathologic response. By RECIST, none of the patients had an early treatment response. Histopathologic responders and nonresponders had comparable changes in tumor size from baseline to early (1 ± 22% versus 2 ± 10%; $P = 0.93$) and from baseline to late follow-up (-14 ± 25% versus -2 ± 23%; $P = 0.19$; Table 2). One histopathologic responder and three nonresponders showed decreases in tumor size from the baseline to the post-treatment scan of >30% and were classified as partial responders according to RECIST. The sensitivity and specificity of size changes for assessment of histopathologic response were 13% and 93%, respectively.

ROC curve analysis (Fig. 1A) revealed that measurements of early and late changes of tumor size could not predict histopathologic responses (area under the curve, 0.60 and 0.69, respectively).

Changes in tumor FDG uptake and histopathologic response. SUVpeak at baseline did not differ significantly between histopathologic responders and nonresponders (12.2 ± 5.1 versus 9.4 ± 6.7; $P = 0.26$).

At early follow-up, responders and nonresponders also exhibited comparable SUVpeak (5.7 ± 4.1 versus 6.5 ± 4.8; $P = 0.67$). However, at late follow-up, SUVpeak was significantly lower in responders than nonresponders (2.7 ± 1.4 versus 5.6 ± 3.6; $P = 0.03$).

SUVpeak at baseline, early, and late follow-up failed to predict reliably histopathologic tumor response (areas under the curve, 0.68, 0.56, and 0.74, respectively).

In contrast, changes in SUV provided sensitive response assessments. In histopathologic responders, SUVpeak deceased by 55 ± 19% at early follow-up and by 76 ± 15% at late follow-up ($P < 0.05$ for baseline versus early and baseline versus late follow-up; $P = 0.051$ for early versus late follow-up).

In histopathologic nonresponders, the corresponding decreases in SUVpeak were significant but modest (23 ± 41% and 34 ± 38%; $P < 0.05$ for baseline versus early and baseline versus late follow-up; $P = 0.07$ for early versus late follow-up; Table 2).

By applying the prospective cutoff point of ≥35% reductions in SUVpeak, 22 patients were classified as metabolic responders and 28 patients as nonresponders. Using histopathologic response as reference standard, this threshold resulted in a sensitivity of 100% and a specificity of 67% (Table 3).

Thus, using a cutoff point of 35%, reductions at early follow-up identified all histopathologic responders; however, one third of the histopathologic nonresponders also showed a metabolic response on PET. Accordingly, the negative predictive value of PET for histopathologic response was 100% and the positive predictive value was 36%.

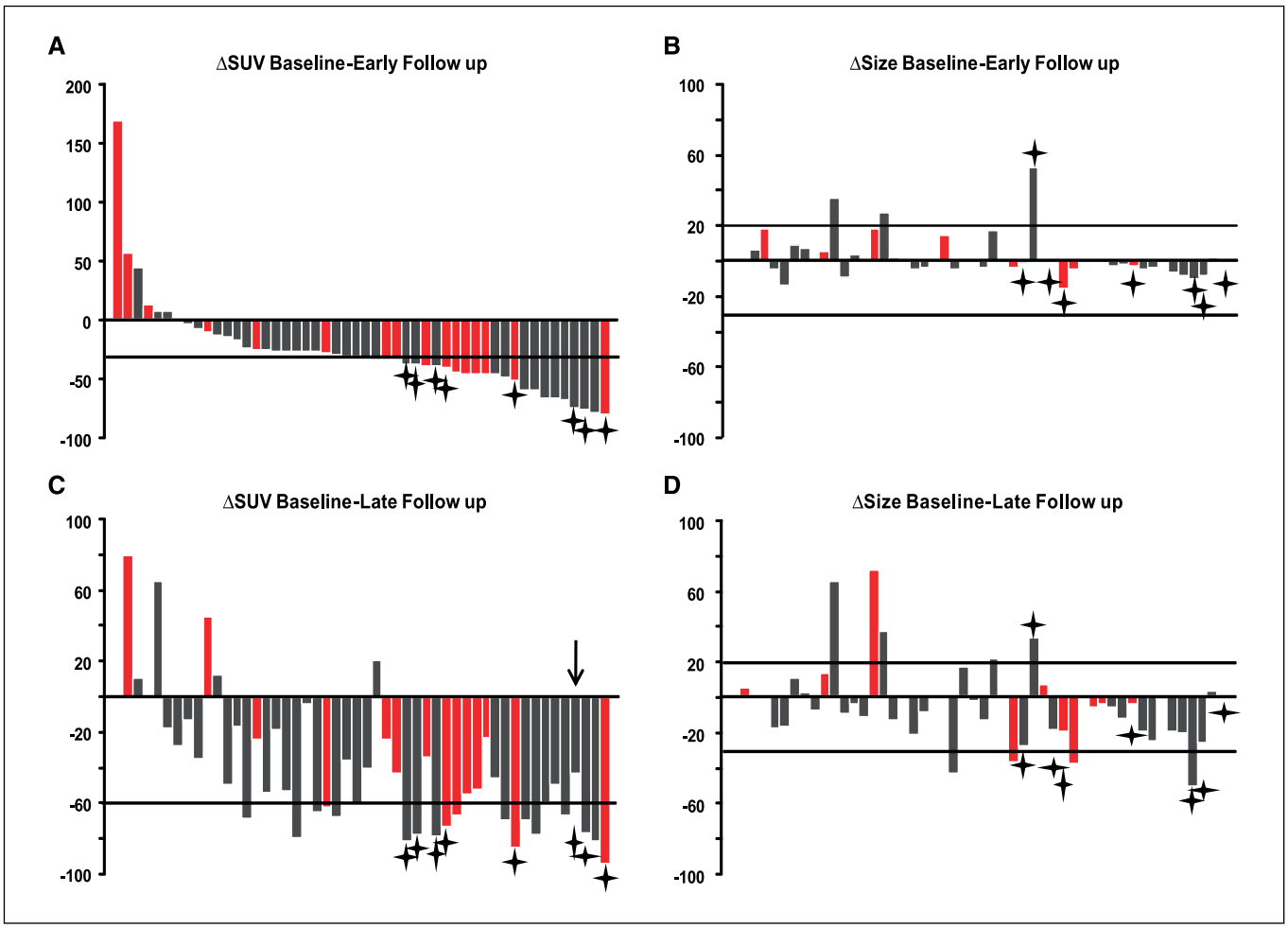

Fig. 2. Changes in SUVpeak after the first cycle (*A*) and after completion of chemotherapy (*C*) and early (*B*) and late (*D*) changes in tumor size. In 8 of 8 histopathologic responders (✦), SUVpeak decreased by ≥35% from baseline to early follow-up scan. All but one histopathologic responder (→) showed a decrease in SUVpeak ≥60% from baseline to late follow-up. Neither early nor late size changes were predictive for histopathologic response (*B* and *D*). *Red,* patients who received chemotherapy alone.

ROC analysis showed that the optimum threshold for separating histopathologic responders from nonresponders at early follow-up was a decrease of baseline SUVpeak by 38% (Fig. 1). The jackknife method was used to validate the threshold, sensitivity, and specificity and we found little variability in these measures across our jackknife subsamples. All subsamples identified a SUV reduction by 38% as the optimal threshold discriminating responders from nonresponders resulting in a sensitivity of 100% and specificities ranging from 68% to 70%.

Separate ROC curve analysis for patients treated with chemotherapy/radiotherapy and patients treated by chemotherapy alone showed that the area under the ROC curve did not differ significantly between these groups (0.82 and 0.90, respectively; $P = 0.59$).

In the logistic regression model, early changes in SUVpeak were a significant predictor of response ($P = 0.014$) even after controlling for radiotherapy. The additional application of radiotherapy was not a significant predictor alone or in combination with early changes in SUVpeak.

At late follow-up, 60% reductions in SUVpeak discriminated between responders and nonresponders with a sensitivity of 88% (7 of 8 responders were indentified) and a specificity of 68%. Using this threshold, the positive predictive value, negative predictive value, and predictive accuracy were 35%, 96%, and 71%, respectively.

By ROC analysis, the best threshold criterion for late metabolic response was a 72% reduction in SUVpeak (Fig. 1). This threshold and the prospectively assigned threshold of 60% resulted in an identical sensitivity (88%), but applying a 72% SUVpeak reduction at late follow-up increased the specificity to 93%, that is, fewer histopathologically nonresponding patients were incorrectly classified as metabolic responders (Fig. 1).

Figure 2 shows waterfall diagrams illustrating the individual metabolic and size changes in histopathologically responding and nonresponding tumors. Figure 3 shows representative patient images.

Discussion

Recently, we showed that changes in tumor FDG uptake from baseline to end of neoadjuvant treatment accurately predicted histopathologic treatment responses in sarcoma patients when reductions in FDG uptake by 60% were used as cutoff point (10). Consistent with other studies (27–30), we also showed

that CT size criteria were poorly correlated with histopathologic response.

The current data suggest that early response assessments with FDG-PET can also identify all treatment responders when a change in SUVpeak by 35% is used as a cutoff point.

Imaging tests for early response assessments need to identify responders with a high sensitivity to avoid denying potentially effective treatments to patients. A high specificity of the test, that is, the number of histopathologic nonresponders that are correctly classified by PET as metabolic nonresponders, is less important. This is because at current practice most sarcoma patients complete neoadjuvant treatment without any early response assessment. If early FDG-PET responses were used to change patient management in the current study, all 8 PET responders who also had a histopathologic response as well as those 14 patients who had a PET response with <95% necrosis

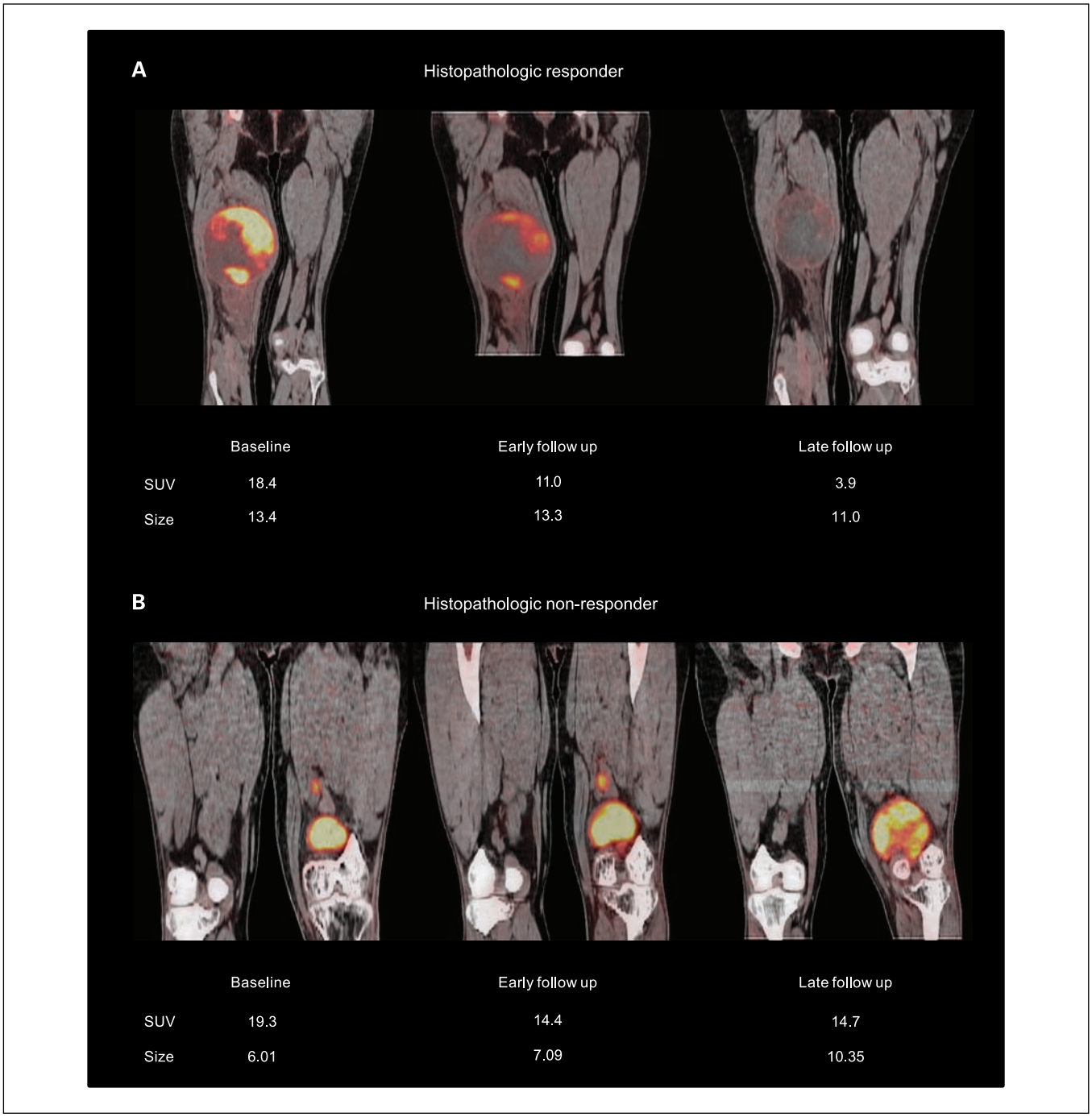

Fig. 3. Baseline, early, and late follow up FDG-PET/CT in a histopathological responder (*A*) and a non-responder (*B*). Changes in tumor SUVpeak and tumor sizes are indicated.

in excised tissue would have continued treatment. However, treatment would have been appropriately discontinued in the majority of patients (the 28 PET nonresponders) based on FDG-PET.

Although neoadjuvant therapy may improve the outcome of patients with STS, particularly in the setting of a pathologic response, the currently available treatments are associated with significant toxicities (11, 12). This toxicity would be minimized if physicians could identify nonresponders and switch them to alternative treatment strategies or earlier surgery. Thus, the central finding of this study, that is, the ability to identify with FDG-PET imaging responders with a high sensitivity and acceptable specificity after the initial cycle of neoadjuvant chemotherapy, has important potential clinical implications.

As shown in this and several previous studies, changes in tumor size cannot predict histopathologic responses and patient outcome early during the course of therapy (31). However, anatomical tumor delineation by CT remains the cornerstone of surgical planning. Therefore, the combination of FDG-PET for response assessments with CT for surgical planning represents a powerful tool in the management of sarcoma patients.

There are no generally accepted criteria for defining early metabolic responses with FDG-PET in STS. However, several studies in other cancers have established that in the neoadjuvant setting an early reduction of SUV by $\geq$30% or $\geq$35% predicts patient outcome with a high accuracy (7, 9, 21–25). ROC curve analysis in the current study revealed a similar threshold that identified all pathologic treatment responders. Thus, future studies might attempt to apply this threshold across a variety of other cancers.

In our previous study (10), a 60% reduction in FDG uptake at the end of therapy was the best late predictor of tumor response in STS. Sensitivity and specificity for identifying histopathologic responders were 100% and 71%, respectively. When prospectively applying this threshold value to the current study, we observed a comparable sensitivity of 88% and a specificity of 68%, thus confirming our previous findings. Again, several studies in other tumor types have also observed a decrease in SUV by >60% in responding tumors (32, 33). Thus, a decrease of tumor SUV of 60% is potentially useful as a criterion for a late metabolic response irrespective of the tumor type and the mode of treatment.

One histopathologic responder with a 76% reduction in SUVpeak at early follow-up exhibited a <60% reduction in SUVpeak (relative to baseline) at late follow-up. The reason for this observation is unknown. However, it might have been due to an inflammatory response to treatment, or the development of resistance to chemotherapy, possibly resulting in increased FDG uptake.

It is unclear why some patients had $\geq$35% reductions in FDG uptake but <95% necrosis in excised tumor tissue. This discrepancy that occurred in 14 of the 50 patients warrants further long-term outcome studies. It is conceivable that reductions in FDG uptake in histopathologic nonresponders could provide additional prognostic information about patient event-free and overall survival.

Alternatively, increases in SUVpeak after one cycle of treatment might reflect progressive disease and might represent a marker of poor outcome.

Ewing's sarcomas (34), rhabdomyosarcomas (35), and synovial sarcomas (36) have been shown to be more chemosensitive than the typical high-grade STS. To avoid any data bias, we conducted a subgroup ROC curve analysis excluding 11 patients with these tumor types. This revealed that the area under the ROC curve was similar for the remaining 39 patients than for the overall study population of 50 patients. Thus, the inclusion of the three more chemosensitive subtypes of sarcoma did not bias the overall results.

After the initial cycle of chemotherapy, 34 patients received combined chemoradiotherapy, whereas 16 patients received chemotherapy only. One could argue that radiotherapy can result in a histopathologic response even if chemotherapy is ineffective. However, in concordance with other studies (23, 37), the current data show that nonresponse to chemotherapy also implies nonresponse to chemoradiotherapy. Using a logistic regression model, we showed that the additional application of radiotherapy was not significantly associated with histopathologic response (P = 0.54).

Potential limitations of the study include the heterogeneity of the patient population that included a variety of different STS subtypes. Moreover, neoadjuvant therapy included several different treatment regimens. However, to limit inclusion criteria to a specific histologic subtype would not be feasible given that sarcomas are rare tumors. Moreover, a clinically useful treatment monitoring tool should be applicable across the various subtypes and therapeutic regimen.

In a previous study, the best cutoff for identifying responders at the end of the study was 60%. A similar but not identical cutoff was found in the current study. Because treatment protocols vary among patients and institutions, the currently reported best cutoff point for reductions in FDG uptake might not be applicable to other patient populations and different treatment protocols.

Although several studies have shown that $\geq$95% necrosis in excised tumor tissue in response to neoadjuvant therapy is associated with better overall survival, it has not been shown that patients with lesser degrees of necrosis did not benefit from chemotherapy compared with a nontreatment group. Therefore, we cannot conclude with certainty that omitting chemotherapy alone or in combination would not adversely affect patient outcome.

Although changes in tumor FDG uptake (3) and histopathologic response (13) were independently correlated with recurrence and survival, clinical follow-up is needed to confirm whether the current results are predictive of patient progression free and overall survival.

In conclusion, treatment monitoring with FDG-PET provides accurate response information after the initial cycle of neoadjuvant chemotherapy in patients with STS. Such information cannot be derived from CT-based serial tumor size measurements. This observation can now be used to prospectively examine whether changes in FDG uptake early after start of treatment can be used to guide therapeutic decisions in sarcoma patients. Such a study could be designed after the MUNICON trial (9) in which glucose metabolic changes by FDG-PET were used to decide whether neoadjuvant treatment in patients with gastroesophageal cancer should be continued or discontinued 2 weeks after start of neoadjuvant therapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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