Abstract

Purpose: Change in tumor size as classified by Response Evaluation Criteria in Solid Tumors poorly correlates with histopathologic response to neoadjuvant therapy in patients with soft-tissue sarcomas. The aim of this study was to prospectively evaluate whether positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET) allows for a more accurate evaluation of histopathologic response.

Experimental Design: From January 2005 to January 2007, 42 patients with resectable biopsy-proven high-grade soft-tissue sarcoma underwent a FDG-PET/computed tomography scan before and after neoadjuvant treatment. Relative changes in tumor FDG uptake and size from the baseline to the follow-up scan were calculated, and their accuracy for assessment of histopathologic response was compared by receiver operating characteristic curve analysis. Histopathologic response was defined as ≥95% tumor necrosis.

Results: In histopathologic responders (n = 8; 19%), reduction in tumor FDG uptake was significantly greater than in nonresponders (P < 0.001), whereas no significant differences were found for tumor size (P = 0.24). The area under the receiver operating characteristic curve for metabolic changes was 0.93, but only 0.60 for size changes (P = 0.004). Using a 60% decrease in tumor FDG uptake as a threshold resulted in a sensitivity of 100% and a specificity of 71% for assessment of histopathologic response, whereas Response Evaluation Criteria in Solid Tumors showed a sensitivity of 25% and a specificity of 100%.

Conclusion: Quantitative FDG-PET was significantly more accurate than size-based criteria at assessing histopathologic response to neoadjuvant therapy. FDG-PET should be considered as a modality to monitor treatment response in patients with high-grade soft-tissue sarcoma.

Soft-tissue sarcomas are a rare heterogeneous group of connective tissue malignancies with a disease specific mortality of up to 50% (1–3). Although surgery and radiation therapy have achieved excellent local control, distant metastasis remains a significant problem limiting survival (4–7). In an attempt to improve the outcome of patients with high-risk (large, high grade, recurrent) localized disease and metastatic disease, multimodality treatment regimens have included systemic neoadjuvant and/or adjuvant chemotherapy (8–10). Although it is not clear if neoadjuvant chemotherapy provides a survival or local control advantage over adjuvant therapy, it does provide an early indication of the effectiveness of the treatment as assessed by the percentage of pathologic necrosis in the resected specimen (9). A histopathologic response to treatment had been correlated with a significantly lower rate of local recurrence and improved survival in patient with soft-tissue sarcoma, bone sarcomas, breast cancer, metastatic colon cancer to liver, lung cancer, and a number of other malignancies (9, 11–16). In the setting of unresectable or metastatic disease, it is not possible to assess pathologic response to treatment, and change in size by Response Evaluation Criteria in Solid Tumors (RECIST) is the current standard to assess response to therapy in soft-tissue sarcoma as in other solid tumors. Unfortunately, RECIST has been shown to be unreliable in predicting histopathologic treatment responses (17–20). The importance of determining response to treatment, particularly early in the course of therapy, has prompted investigation into other methods to monitor therapy.

Changes in glucose metabolic activity in response to treatment have been shown to be predictive of patient outcome in many cancers. Studies using positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET) have shown that a decrease in standardized uptake values (SUV) is predictive of...
response to therapy in malignant lymphomas and a variety of solid tumors (21). A recent study showed that FDG-PET may be used to assess response in soft-tissue sarcoma; however, there has not been a direct comparison between metabolic changes assessed by FDG-PET and size changes assessed by computed tomography (CT; RECIST; ref. 22).

The aim of this study was to prospectively evaluate whether a change in tumor FDG uptake and/or a change in size (CT) measured by a combined PET/CT scan could assess histopathologic response to neoadjuvant therapy in patients with high-grade soft-tissue sarcoma.

**Patients and Methods**

**Patients.** Adult patients (≥18 years old) with resectable biopsy-proven high-grade soft-tissue sarcoma who were scheduled to undergo neoadjuvant therapy were prospectively offered enrollment in the UCLA Sarcoma PET/CT Study. The study was approved by the UCLA Institutional Review Board for Human Subjects and written informed consent was obtained. Patients presenting with unresectable disease, with histologic diagnosis of gastrointestinal stromal tumors, and patients receiving targeted therapies such as imatinib were excluded from enrollment.

From January 2005 to January 2007, 46 patients were included in the study. Sarcoma not otherwise specified (n = 12; 26%), liposarcoma (n = 6; 14%) and leiomyosarcoma (n = 6; 14%) were the three most common histologies. The most common site of disease was the extremity (n = 31; 67%), retroperitoneal/abdominal (n = 10; 22%), and chest/trunk (n = 5; 11%). Thirty-four (74%) patients presented with primary disease, 7 (15%) with locally recurrence, and 5 (11%) with metastatic disease.

**Neoadjuvant therapy.** Neoadjuvant therapy consisted of systemic chemotherapy with or without radiation therapy. Standard first-line chemotherapy was ifosfamide-based chemotherapy (n = 34; 81%). Ifosfamide-based chemotherapy consisted of two cycles of high-dose ifosfamide (14 g/m²) followed by doxorubicin (90 mg/m²). Gemcitabine-based chemotherapy consisted of two cycles of gemcitabine (900 mg/m², days 1 and 8) and docetaxel (75-100 mg/m², day 8).

Twenty-four (57%) patients received neoadjuvant external beam radiation therapy. Eighteen (43%) patients were not candidates for neoadjuvant radiation therapy due to either previous radiation therapy or location of disease. The mean length of neoadjuvant treatment was 80 days (median, 74.5; range, 32-176).

**PET-CT imaging.** Patients underwent a whole-body PET/CT before initiating neoadjuvant therapy (Baseline study). The mean interval between the baseline PET/CT and initiation of neoadjuvant therapy was 7 days (mean, 6.5; range, 1-14). After completion of neoadjuvant therapy and before surgery, patients underwent a second whole-body PET/CT (posttreatment study). The mean interval between the end of treatment and the posttreatment PET/CT was 10 days (median, 10; range, 5-15 days). This interval was the same for patients who were treated with (median, 10; range, 5-15 days) and without (median, 10; range, 7-14 days) neoadjuvant external beam radiation therapy. The mean interval between the posttreatment PET/CT and surgery was 8 days (median, 8.5; range, 1-18 days). All PET/CT studies were done on the combined Siemens Biograph duo PET/CT scanner. For PET imaging, patients were injected with 9 to 11 mCi (333–407 MBq) of FDG. Patients were fasted for at least 6 h before FDG injection to standardize blood glucose and insulin levels. Blood glucose levels were measured before injection of FDG. Patients were excluded if their blood glucose levels at any of the scans were >150 mg/dL (23).

The CT acquisition parameters were 130 kVp, 120 mA, 1-s tube rotation, 4-mm slice collimation, and bed speed of 8 mm/s. CT images were acquired after i.v. injection of 110 to 120 mL of Omnipaque 350. Following the whole-body CT scan, PET images were acquired 60 min postinjection and acquisition time per bed position was 1 to 5 min, depending on patient body weight as previously published (24, 25). Emission scans in patients with weights <130 pounds were acquired for 1 min per bed position whereas those in patients with weights >200 pounds were acquired for 5 min. To minimize misregistration, CT and PET were acquired during shallow breathing (26). PET data were corrected for photon attenuation using the CT data.

**Image analysis.** All FDG-PET images were analyzed by one observer (V.E.) who was blinded to the histopathologic response status as well as the size measurements on CT. To quantify tumor FDG uptake, a circular region of interest with a diameter of 1.5 cm was placed at the site of maximum FDG uptake as previously described (27–29). The mean activity concentration within the region of interest was normalized to the injected dose and patient body weight to calculate SUVs (27–29).

Patients were excluded from further analysis if the tumor SUV was <2.5 in the baseline study because in this case relative changes in tumor FDG uptake cannot be reliably quantified by FDG-PET (30).

CT images were read by one radiologist (K.C.) who was blinded to both PET images and the histopathologic response data. Maximum tumor size was measured before and after neoadjuvant therapy and size changes were classified according to RECIST (31).

**Histopathology.** One pathologist (S.N.), who was blinded to PET and CT data, analyzed all specimens in a standard fashion as previously described (9). 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 into 2.0-cm² (average) blocks and processed for histologic examination, along with additional randomly sampled areas. Histopathologic response to therapy was assessed in a manner previously established for soft-tissue sarcoma and quantified as percentage of pathologic necrosis (9). For the purpose of this study, patients with ≥95% pathologic necrosis (<5% viable tumor cells) were classified as histopathologic responders as previously described (9). In addition, tumor grading and margin status were assessed (32).

**Statistical analysis.** The diagnostic accuracy of FDG-PET and CT to assess histopathologic response to neoadjuvant therapy was compared by calculating the area under the receiver operating characteristic (ROC) curves (33). The area under the ROC curve provides a measure for the accuracy of a diagnostic test. It ranges from 0.5 (random guessing) to 1.0 (perfect test).

Quantitative data are reported as the median, range, and mean ± SD. Paired and unpaired comparisons between quantitative parameters were made by the Wilcoxon signed-rank test and the Mann-Whitney test, respectively. All statistical calculations were done by using SPSS 11.5 for Windows (SPSS, Inc.).

**Results**

**FDG-PET/CT.** At the baseline, 42 of the 46 (91%) tumors showed focal FDG uptake with a SUV of >2.5. Four (9%) patients with liposarcomas were excluded after the baseline study because tumor FDG uptake was <2.5. The characteristics of the 42 evaluable patients are summarized in Table 1.

The mean baseline SUV of the 42 tumors was 9.2 ± 4.2 cm (median, 8.5; range, 3.0–20.0 cm). The mean tumor size was unchanged after preoperative therapy (9.2 ± 4.8 cm; median, 8.4; range, 2.5–25.5 cm; P = 0.49 for comparison with baseline; Figs. 1 and 2). Only 2 (5%) tumors showed a decrease of tumor size by >30% (35%) and -31%, respectively) and were classified as responders according to RECIST.

The mean baseline SUV of the 42 tumors was 9.2 ± 6.7 cm (median, 6.7; range, 2.6–31.9), whereas the mean posttreatment SUV was 4.6 ± 3.4 cm (median, 4.2; range, 0.7–16.6; P < 0.001 for comparison with baseline; Fig. 1). The mean relative change in SUV was -42 ± 39% (median, -53%; range,
Changes in tumor size and metabolic activity were not significantly correlated with the chemotherapy regimens (P > 0.13). Reduction of tumor FDG uptake was more pronounced in patients receiving radiotherapy as compared with patients not receiving radiotherapy (-53 ± 27% versus -26 ± 48%; P = 0.049).

**Surgical therapy and histopathologic response.** All 42 patients underwent complete tumor resection. Forty (95%) patients had a negative microscopic margin and 2 (5%) had a positive microscopic margin. The mean percentage necrosis was 55 ± 31% (median, 55%; range, 5-99%). Eight of the 42 (19%) patients had ≥95% pathologic necrosis in the resected tumor and were classified as histopathologic responders. Six of the 34 (18%) ifosfamide-treated patients and 2 of the 8 (25%) gemcitabine-treated patients were classified as histopathologic responders (P = 0.09). The percentage of pathologic necrosis was higher in patients receiving radiotherapy than in patients not receiving radiotherapy (71 ± 24% versus 34 ± 26%; P < 0.001).

**Correlation between histopathologic response and findings on PET or CT.** Changes in tumor size were not significantly correlated with histopathologic response (P = 0.24, Fig. 2). The relative change in tumor size was -8 ± 22% (median, -8%; range, -35-33%) in histopathologic responders and -2 ± 19% (median 0%; range, -21-63%) in histopathologic non-responders. Table 2 shows the correlation between histopathologic response and the individual response categories defined by RECIST. A partial response according to RECIST was insensitive for assessing histopathologic response. Only two of the eight histopathologic responders were also classified as responders according to RECIST (sensitivity for assessment of histopathologic response 25%). On the other hand, a partial response according to RECIST was quite specific for a histopathologic response, as none of the patients without a histopathologic response was classified as a responder according to RECIST (specificity 100%). In an ROC analysis, the area under the ROC curve for assessment of histopathologic response based on size changes was only 0.60 (Fig. 3). Thus, measurement of size changes did not perform significantly better than random guessing of histopathologic response (P = 0.23).

Changes in glucose metabolic activity were significantly more pronounced in histopathologic responders than in non-responders (P < 0.001; Fig. 2). In histopathologic responders, the average change in tumor FDG uptake was -75 ± 9% (median, -78%; range, -60% to -90%), whereas in nonresponders FDG uptake changed only by -34 ± 40% (median, -40%; range, -70-110%). The area under the ROC curve for assessment of histopathologic response by metabolic changes was 0.93, which was significantly higher than the area under the ROC curve for size changes (P = 0.004; Fig. 3). Using a 60% reduction of FDG uptake as threshold value for a metabolic response in PET allowed assessment of histopathologic response with a sensitivity of 100% and a specificity of 71%. Using a stricter definition of metabolic response (70% reduction in FDG uptake) resulted in a specificity of 100% and a sensitivity of 75% (Fig. 3). Figure 4 shows the FDG-PET/CT studies in a histopathologic responder.

**Table 1. Clinical, pathologic, and treatment characteristics (n = 42)**

<table>
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<th>Characteristics</th>
<th>n (%)</th>
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<tbody>
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<tr>
<td>Sex</td>
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<td></td>
<td>Female</td>
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<tr>
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<tr>
<td></td>
<td>Myxofibrosarcoma</td>
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<tr>
<td></td>
<td>Other</td>
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<td>Negative</td>
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<tr>
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<td>IF</td>
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<td></td>
<td>GZ</td>
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<tr>
<td>Response (RECIST)</td>
<td>Complete response</td>
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<tr>
<td></td>
<td>Partial response</td>
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<tr>
<td></td>
<td>Stable disease</td>
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<td></td>
<td>Progressive disease</td>
</tr>
<tr>
<td>Pathologic necrosis</td>
<td>≥95% (responder)</td>
</tr>
<tr>
<td></td>
<td>&lt;95% (nonresponder)</td>
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Abbreviations: Retro, retroperitoneal; NOS, high-grade sarcoma not otherwise specified; MPNST, malignant peripheral nerve sheath tumor; IF, ifosfamide-based chemotherapy; GZ, gemcitabine-based chemotherapy.
Discussion

This prospective study shows that a change in tumor glucose metabolic activity is a significantly more accurate parameter than a change in size at assessing histopathologic response to neoadjuvant therapy in patients with high-grade soft-tissue sarcoma. Using standard size criteria for evaluation of tumor response (RECIST), only 25% of the histopathologically responding tumors were identified in the current study. By comparison, metabolic changes correctly identified all of the histopathologic responders and 71% of the histopathologic nonresponders. These striking differences suggest that in high-grade soft-tissue sarcoma, response assessment according to RECIST is of limited value and should be complemented by imaging of tumor metabolic activity with FDG-PET.

Several previous studies in soft-tissue sarcoma have shown that changes in tumor size are only poorly correlated with histopathologic response and/or patient outcome (34–37). Because of these well-established limitations of size criteria, various functional imaging techniques have been evaluated for monitoring response to therapy in soft-tissue sarcoma. Imaging of tumor glucose metabolism with PET has shown encouraging results in a limited number of previous studies (22, 38, 39). In the largest study reported thus far, Schuetze et al. (22) found that reduction of tumor FDG uptake was significantly correlated with histopathologic response in 46 patients with high-grade localized soft-tissue sarcomas. Furthermore, they found that reduction of tumor FDG uptake was also a strong predictor for progression and overall free survival (22).

Although these studies are encouraging, it is difficult to draw definitive conclusions because response assessment by CT or magnetic resonance imaging was not done in parallel with the FDG-PET studies. To our knowledge, this is the first study to systematically and directly compare response assessment based on size criteria with metabolic changes in soft-tissue sarcoma.

As a parameter for diagnostic accuracy of PET and CT, we used the area under the ROC curve because this parameter does not require an a priori definition of a response in PET or CT. There are no generally accepted criteria for a metabolic response in PET, and RECIST has not been specifically validated to assess histopathologic response in soft-tissue sarcoma. Using predefined criteria for assessing histopathologic response to preoperative therapy by PET or CT could therefore bias the results of the comparison. By using ROC analysis, we could show that irrespective of the threshold value applied, assessment of metabolic changes provided a significantly higher diagnostic accuracy than measuring tumor size (Fig. 3). Importantly, threshold values ranging from 50% to 70% of baseline FDG uptake allowed assessment of histopathologic response with a clinically meaningful accuracy, suggesting that reduction of FDG uptake represents a robust parameter for differentiation of responding and nonresponding tumors and that the exact threshold value defining metabolic response has no major effect on the diagnostic accuracy of PET imaging (Fig. 3).

<table>
<thead>
<tr>
<th>RECIST</th>
<th>Histopathology</th>
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<tbody>
<tr>
<td></td>
<td>Responder (≥95% necrosis)</td>
<td>Nonresponder (&lt;95% necrosis)</td>
<td></td>
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<tr>
<td>Partial response</td>
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<td>0</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>5</td>
<td>29</td>
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</tr>
<tr>
<td>Progressive disease</td>
<td>1</td>
<td>5</td>
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Table 2. Correlation between histopathologic response and tumor response according to RECIST
Compared with the previous study by Schuetze et al. (22), the present study evaluated not only preoperative chemotherapy but also chemoradiotherapy. There have been concerns that radiation-induced inflammation may limit the accuracy of FDG-PET to assess tumor response. Specifically, it has been hypothesized that the extent of tumor necrosis might be underestimated due to high FDG uptake by macrophages and granulation tissue. In the present study, however, we found no evidence supporting this hypothesis. In fact, reduction in tumor FDG uptake was more pronounced in patients receiving radiotherapy than in patients not receiving radiotherapy. This paralleled the significantly higher percentage of necrosis in patients receiving radiotherapy. Thus, for the studied treatment regimen, radiation-induced inflammation does not seem to limit the accuracy of FDG-PET to assess histopathologic response. A similar observation has recently been reported in patients with esophageal cancer treated with preoperative chemoradiotherapy (40).

Whereas all histopathologic responders showed a marked reduction of tumor FDG uptake (≥60%) after neoadjuvant therapy, several tumors showed similar changes in FDG uptake, but <95% of the tumors were found to be necrotic on histopathology. This limited the specificity of FDG-PET for assessment of histopathologic response. Similar observations have been made for other solid tumors treated by neoadjuvant chemotherapy or chemoradiotherapy (28, 40) but the mechanisms for this reduction of FDG uptake in apparently viable tumors and its relationship to treatment outcome are not well understood. Interestingly, the patients with ≥60% reduction in FDG uptake but <95% pathologic necrosis still had evidence of a treatment response with a median pathologic necrosis of 68%. Schuetze et al. (22) found that a metabolic response on FDG-PET may actually be a better predictor of patient survival than histopathologic response. Only long-term follow-up studies will be able to determine the significance of a metabolic response in histopathologically nonresponding tumors.

Apparent limitations of this study are the heterogeneity of the patient population and the fact that neoadjuvant therapy included several treatment regimens. However, the rarity and diversity of soft-tissue sarcoma make it impractical to limit the inclusion criteria of a clinical trial to a specific histologic and anatomic subtype. Because there is currently no established standard for neoadjuvant therapy in soft-tissue sarcoma, regimens were individually selected for each patient considering histologic subtype, tumor location, comorbidities, and previous treatment regimens. For a therapeutic trial, this would represent a very serious limitation because it would be almost impossible to generalize the obtained results. Therefore, it is important to emphasize that the goal of the present study was not the evaluation of a new treatment regimen for soft-tissue sarcoma but to compare the ability of two different diagnostic tests to assess histopathologic response to neoadjuvant therapy. For such a comparison, the inclusion of different treatment regimens is in fact advantageous. A diagnostic test that allows assessment of tumor response for only one particular treatment regimen would be of very limited value for patient management or clinical trials. Therefore, we made no attempts to restrict this study to one specific treatment regimen.

Finally, in 4 of the 46 (9%) patients enrolled in this study, tumor response could not be evaluated by FDG-PET because baseline metabolic activity was too low for quantitative analysis (27). All four of these patients had liposarcomas. Thus, 4 of the 12 (33%) patients with liposarcoma enrolled were not able to be monitored with FDG-PET, potentially limiting its role in this specific soft-tissue sarcoma histology.

In conclusion, FDG-PET was significantly more accurate than size-based criteria (RECIST) at assessing histopathologic response to neoadjuvant therapy in patients with high-grade soft-tissue sarcomas. FDG-PET should be used as a modality to monitor treatment response in patients with high-grade soft-tissue sarcoma.
References


Reduction of Glucose Metabolic Activity Is More Accurate than Change in Size at Predicting Histopathologic Response to Neoadjuvant Therapy in High-Grade Soft-Tissue Sarcomas


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