[F-18]-Fluorodeoxy-D-Glucose–Positron Emission Tomography Response Is Associated With Outcome for Extremity Osteosarcoma in Children and Young Adults

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BACKGROUND: Response to neoadjuvant chemotherapy is 1 of the most powerful prognostic factors for extremity osteosarcoma. [F-18]-fluorodeoxy-D-glucose–positron emission tomography (FDG-PET) is a noninvasive imaging modality that is used to predict histopathologic response. To determine the prognostic value of FDG-PET response for progression-free survival (PFS) in osteosarcoma, the authors of this report reviewed the University of Washington Medical Center experience. **METHODS:** Forty patients with extremity osteosarcoma were evaluated by FDG-PET. All patients received neoadjuvant and adjuvant chemotherapy. FDG-PET standard uptake values (SUVs) before neoadjuvant chemotherapy (SUV1) and after neoadjuvant chemotherapy (SUV2) were analyzed and correlated with histopathologic response. **RESULTS:** The median SUV1 was 6.8 (range, 3.0-24.1), the median SUV2 was 2.3 (range, 1.2-12.8), and the median SUV2 to SUV1 ratio (SUV2:1), was 0.36 (range, 0.12-1.10). A good FDG-PET response was defined as anSUV2 $<$2.5 or an SUV2:1 $\leq$0.5. FDG-PET responses according to SUV2 and SUV2:1 were concordant with histologic response in 58% and 68% of patients, respectively. SUV2 was associated with outcome (4-year PFS, 73% for SUV2 $<$2.5 vs 39% for SUV2 $\geq$2.5; $P = .021$). Both the initial disease stage and the histologic response were associated with outcome. **CONCLUSIONS:** FDG-PET imaging of extremity osteosarcoma was correlated only partially with a histologic response to neoadjuvant chemotherapy. An SUV2 $<$2.5 was associated with improved PFS. Future prospective studies are warranted to determine whether FDG-PET imaging may be used as a predictor of outcome independent of initial disease stage. **Cancer 2009;115:3519–25. © 2009 American Cancer Society.**

KEY WORDS: osteosarcoma, fluorodeoxyglucose positron emission tomography, outcome.

Osteosarcoma is the most common malignant bone tumors in children and young adults with an incidence of 600 cases among children, adolescents, and young adults each year in the United States.[1-3] Multiagent chemotherapy and surgery have dramatically improved the prognosis for osteosarcoma,

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resulting in a 60% to 70% progression-free survival (PFS) rate for children with localized disease.[2-7] In addition to facilitating limb-sparing resection, neoadjuvant chemotherapy allows radiographic and histologic assessment of the efficacy of chemotherapy. Histologic response, measured by the percentage of viable tumor cells that remain after neoadjuvant chemotherapy,[8,9] has prognostic value in predicting PFS.[9,10] If a favorable response to therapy is anticipated, then limb-sparing surgical resection may be more feasible.[5,11] However, osteosarcoma usually does not change significantly in size in response to chemotherapy, making computed tomography (CT) scanning or magnetic resonance imaging (MRI) insensitive methods with which to determine chemotherapy responsiveness.[12] Instead, a noninvasive surrogate marker of histologic response would be useful to assess the efficacy of preoperative chemotherapy.

[F-18]-fluorodeoxy-D-glucose (FDG)-positron emission tomography (PET) is a functional imaging method with the potential to assess tumor response to chemotherapy. Malignant cells avidly take up and retain FDG, a glucose analog. We previously reported the correlation between FDG-PET changes and histologic response in patients with pediatric Ewing sarcoma family of tumors (ESFT) and osteosarcoma.[13] We also reported an association between the reduction in the standard uptake value (SUV) and outcome after neoadjuvant doxorubicin-containing chemotherapy in patients with extremity soft tissue sarcomas[14] and ESFT.[15] To determine the value of FDG-PET response for predicting outcome in patients with extremity osteosarcoma, we reviewed the experience at our center with both pediatric patients and young adult patients.

MATERIALS AND METHODS

Patient Population

We analyzed patients who presented to the Seattle Children's Hospital (SCH) or the University of Washington Medical Center (UWMC) with extremity osteosarcoma who were enrolled prospectively in a study of FDG-PET in sarcomas. All patients (or parents for minors) provided written informed consent for participation in the PET study and medical record review, as approved by the UWMC Institutional Review Boards of Human Subjects and Radiation Safety in accordance with institutional and federal guidelines. All eligible patients with extremity osteosarcoma who received treatment at SCH or UWMC between July 1, 1995 and August 1, 2004 underwent evaluation by FDG-PET imaging. This series included 38 patients who received both chemotherapy and surgery at SCH or UWMC and 2 patients who were referred to SCH for surgical resection after neoadjuvant chemotherapy at other institutions. Patients who did not have FDG-PET studies both before and after neoadjuvant chemotherapy were excluded. Patients underwent PET imaging no more than 1 week before the initiation of chemotherapy. All patients received neoadjuvant chemotherapy, including cisplatin and doxorubicin, in most cases with the addition of high-dose methotexate.[4] Other treatment regimens included combined cisplatin, doxorubicin, and ifosfamide[16] and combined cisplatin, doxorubicin, ifosfamide, and high-dose methotrexate.[4] One course of therapy was defined as a treatment cycle of doxorubicin-containing chemotherapy with or without high-dose methotrexate. PET imaging was repeated after the induction course of chemotherapy and before surgical resection. Although the timing of the second FDG-PET study was not standardized, 30 patients (75%) had repeat imaging after 2 courses of chemotherapy. Histologic response to neoadjuvant chemotherapy was evaluated based on the grading system published by Salzer-Kuntschik et al for osteosarcoma.[9] For each patient, the percentage of viable tumor (calculated from multiple samples from the resected bone and surrounding soft tissue specimen) was used to determine the percentage of viable tumor cells using standard histopathologic analysis. A favorable response to chemotherapy was defined as $\leq$10% viable tumor cells, and an unfavorable response to chemotherapy was defined as $>$10% viable tumor cells. All patients (or parents for minors) provided written informed consent.

Positron Emission Tomography Imaging

Detailed methods for PET imaging in patients with sarcoma have been published previously.[17,18] Briefly, patients fasted for at least 2 hours before imaging. Patients received from 7 millicuries (mCi) to 10 mCi of FDG intravenously over 2 minutes. Blood glucose levels were recorded in 30 of 40 patients before the administration of FDG and was $<$120 mg/dL in all patients. Intrapatient

blood glucose levels before injection of FDG varied by <20% in 24 of 30 patients. After a 45-minute equilibration period during which the patient rested, both emission scans and transmission scans were obtained to generate attenuation-corrected images over the known tumor site using a GE Advance Positron Tomograph (General Electric, Waukesha, Wis). Typically, the tumor extent was captured in 2 adjacent 15-cm fields of view. Reconstructed data were rendered into 3-dimensional images using a Hanning filter at a resolution of 4.2 mm. The 3-dimensional image sets were available for review in slice thicknesses from 4.2 mm to 12 mm. Regions of interest for the determination of tumor SUV were then hand drawn around the area of tumor uptake using plain film, MRI, and CT scans as references. The FDG-PET image was inspected visually for heterogeneity in tumor uptake. The tumor SUV was calculated automatically by the tomograph software, and, after careful assessment of the SUV values throughout the tumor, the maximum tumor SUV, rather than the average SUV, was recorded for analysis. SUV1 was defined as the maximal SUV obtained before neoadjuvant chemotherapy, SUV2 was defined as the maximal SUV obtained after neoadjuvant chemotherapy, and SUV2:1 was defined as the ratio of SUV2 to SUV1.

Table 1. Patient Characteristics and Timing of [F-18]-Fluorodeoxy-D-Glucose Positron Emission Tomography and Surgery

Patient Characteristic	Value (Range)
Median age (range), y	15.1 (7.1-31)
Anatomic site, no. of patients	
Femur	20
Tibia	13
Humerus	5
Fibula	2
Metastases at diagnosis, no. of patients	
Present	6
Absent	34
Chemotherapy treatment, no. of patients	
CDM	27
CDI	7
CDMI	5
CDMIE	1
Median time from SUV1 to SUV2 (range), wk	10.3 (6.3-15.7)
Median time from SUV2 to surgery (range), wk	1.1 (0.1-11.3)
Median no. of therapy courses from SUV1 to SUV2 (range)	2 (2-4)
Median no. of therapy courses from SUV2 to surgery (range)	0 (0-2)

C indicates cisplatin; D, doxorubicin; M, methotrexate; I, ifosfamide; E, etoposide; SUV1, maximum standard uptake value before chemotherapy; SUV2, maximum standard uptake value after chemotherapy.

Statistical Analysis

Statistical analysis of PFS was performed using the Kaplan-Meier method for calculating survival curves and 95% confidence intervals (CIs).[19] PFS was defined as the time from initial diagnosis to either disease progression or death from any cause. Patients who had not developed progression or had not died were censored at the date of last contact. Differences in PFS among groups defined by patient or treatment characteristics were analyzed using the log-rank test.[20] PFS data were analyzed as of June 17, 2008 using SPSS for Windows version 13.0 (SPSS Inc, Chicago, Ill).

RESULTS

The clinical characteristics of all 40 patients with osteosarcoma are presented in Table 1. Included in this series were clinical and histologic response data from 8 previously reported patients.[13] All patients underwent surgical resection of their primary tumor. Thirty patients had an SUV2 obtained <2 weeks before surgery. Only 5 patients received additional chemotherapy courses after SUV2 and before surgical resection, in each patient because of problems with surgical scheduling or availability of an appropriate limb-salvage implant. Four patients received 1 course of additional chemotherapy, and 1 patient received 2 courses of additional chemotherapy.

Tables 2 and 3 summarize the FDG-PET imaging and histologic response data. Only 1 patient had an SUV2 that was higher than SUV1. Neoadjuvant chemotherapy resulted in a favorable response to chemotherapy (≤10% viable tumor) in 48% of patients. Favorable FDG-PET responses (SUV2, <2.5; SUV2:1, ≤0.5) were concordant with favorable histologic responses (≤10% viable tumor) in 58% and 68% of patients, respectively.

All patients resumed chemotherapy postoperatively. Four patients received alternative postoperative chemotherapy, including 2 patients who had tumor progression before surgery (both had a confirmed poor histologic response after receiving cisplatin, doxorubicin, methotrexate, and [in 1 patient] ifosfamide preoperatively), 1 patient who received an escalated cumulative dose of doxorubicin (600 mg/m^2)

Table 2. The Maximum Standard Uptake Value Before Chemotherapy (SUV1), the Maximum Standard Uptake Value After Chemotherapy (SUV2), the SUV2:SUV1 Ratio, and the Percentage of Viable Tumor by Tumor Histology

Clinical Feature	Value
Before chemotherapy	
Median SUV1 (range)	6.8 (3-24)
After chemotherapy	
Median SUV2 (range)	2.3 (1.2-12.8)
Reduction in SUV	
Median SUV2:SUV1 ratio (range)	0.36 (0.12-1.10)
Histologic evaluation, no. of patients	
Favorable, ≤10% viable tumor	19
Unfavorable, >10% viable tumor	21

Table 3. Histologic Response Compared With the Maximum Standard Uptake Value After Chemotherapy (SUV2) and the Ratio Between SUV2 and the Maximum Standard Uptake Value Before Chemotherapy

	No. of Patients	
Variable	≤10% Viable Tumor	>10% Viable Tumor
SUV2		
≥2.5	7	11
<2.5	12	10
SUV2:1		
>0.5	2	10
≤0.5	17	11

SUV1 indicates the maximum standard uptake value before chemotherapy; SUV2:1, ratio of SUV2 to SUV1.

Table 4. Univariate Analysis of Progression-free Survival

Variable	No. of Patients	4-Year PFS (95% CI), %	*P*
Overall	40	57 (41-73)	
Initial stage			
Localized	34	67 (51-83)	<.001
Metastatic	6	0 (0-46)	
Histologic response			
≤10% viable tumor	19	74 (54-94)	.061
>10% viable tumor	21	42 (20-62)	
Histologic response, localized only			
≤10% viable tumor	18	78 (58-98)	.18
>10% viable tumor	16	56 (31-81)	
SUV2			
<2.5	22	73 (54-92)	.021
≥2.5	18	39 (16-62)	
SUV2, localized only			
<2.5	22	73 (54-92)	.34
≥2.5	12	58 (30-86)	
SUV2:1			
≤0.5	28	57 (36-78)	.9
>0.5	12	58 (30-86)	
SUV2:1, localized only			
≤0.5	23	69 (49-89)	.62
>0.5	11	64 (35-93)	
SUV1			
≤6	19	63 (41-85)	.41
>6	21	52 (30-74)	
SUV1, localized only			
≤6	19	63 (41-85)	.6
>6	15	73 (40-96)	

PFS indicates progression-free survival; CI, confidence interval; SUV1, maximum standard uptake value before chemotherapy; SUV2, maximum standard uptake value after chemotherapy; SUV2:1, ratio of SUV2 to SUV1.

because of a poor histologic response by protocol design, and 1 patient who received with ifosfamide in place of cisplatin postoperatively because of severe hearing loss and a poor histologic response. None of the other 36 patients had any modification of postoperative chemotherapy because of histologic response.

Seventeen of 40 patients experienced disease recurrence, including 13 at metastatic sites only, 2 at combined metastatic and local sites, and 2 at local sites only. The median SUV2 was 2.1 (range, 1.6-4.4) for patients who had local only recurrences or combined recurrences. One patient died from secondary acute myeloid leukemia without recurrent osteosarcoma; no other patient died before disease recurrence. The median follow-up for patients who survived without progression was 69 months (range, 35-117 months). The 4-year estimated PFS for all patients was 57% (95% CI, 41%-73%) (Table 4). Univariate analysis of potential prognostic factors (Table 4) demonstrated that improved PFS was associated with nonmetastatic disease at initial diagnosis and with an SUV2 <2.5 for all patients (Fig. 1). However, when the patients with metastatic disease were excluded, the difference in PFS according to SUV2 was not statistically significant (Fig. 2). Neither an SUV1 >6 nor an SUV2:1 ≤0.5 was associated with PFS among all patients or among patients with localized disease only (Table 4). A strong trend toward improved PFS was observed with favorable a histologic response (≤10% viable tumor; 4-year PFS rate, 74% vs 42%; $P = .061$). When the patients who had

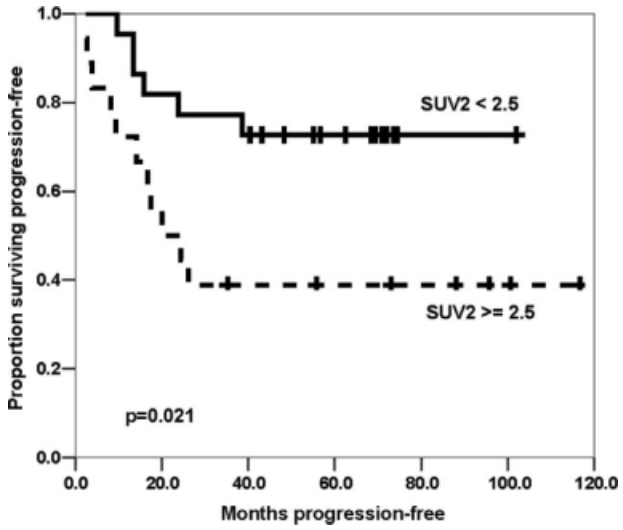

FIGURE 1. This chart illustrates Kaplan-Meier estimates of progression-free survival according to the maximal standard uptake value (SUV) after chemotherapy (SUV2) for all patients.

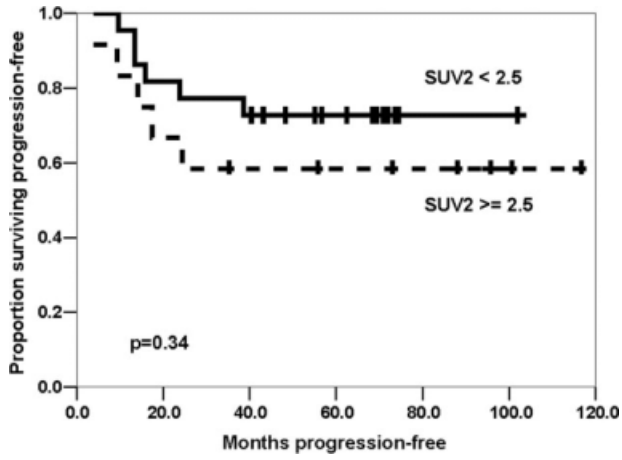

FIGURE 2. This chart illustrates Kaplan-Meier estimates of progression-free survival according to the maximal standard uptake value (SUV) after chemotherapy (SUV2) excluding patients who had metastases at diagnosis.

metastases at diagnosis were excluded, a favorable histologic response had a modest trend toward improved PFS (4-year PFS rate, 78% vs 56%; $P = .18$).

DISCUSSION

Histologic response to neoadjuvant chemotherapy is 1 of the strongest prognostic factors for osteosarcoma.[3-7,10] Histologic response has significant limitations, including the ability to assess only once and only after 10 to 15 weeks of initial chemotherapy. We have reported the utility of FDG-PET imaging as a noninvasive method for assessing the response[13] to neoadjuvant chemotherapy and for predicting the probability of recurrence for soft tissue sarcomas[14,21] and ESFT.[15] The current report expands on our previous series of pediatric bone sarcomas[13] with 32 additional patients, including adults, and reveals an association between SUV2 and PFS for extremity osteosarcoma. In contrast to our observation in ESFT, SUV2 did not maintain prognostic significance when patients with metastatic disease were excluded from the analysis.[15] However, neither categorization of response (histologic or FDG-PET) was completely predictive of patient outcome in our dataset. We previously reported an association between an SUV1 >6[22] and SUV2:1 in soft tissue sarcomas.[14] Neither association was observed in the current cohort of patients with osteosarcoma. We previously observed an increase in SUV2 over SUV1 in 22% of patients with soft tissue sarcoma.[14] In contrast, only 3% of our patients with osteosarcoma experienced an increase in SUV2 over SUV1 after neoadjuvant chemotherapy, illustrating that FDG-PET imaging characteristics may be histology-specific.

To our knowledge, the current report is the first to describe an association between FDG-PET imaging and PFS for extremity osteosarcoma. Our analysis clearly is limited by its relatively small sample size. The association between SUV2 and PFS will need confirmation in a larger, prospective study, particularly to determine whether an SUV2 <2.5 is associated with improved PFS in patients with localized osteosarcoma. The difference in predictive value of SUV2 in patients with localized osteosarcoma versus patients with ESFT[15] suggests that FDG-PET may be less useful in patients with osteosarcoma. Our small study population also prevents a multivariate analysis of other potential prognostic factors, such as tumor site and size.[5] Another limitation of our study is the diversity of treatment characteristics (including neoadjuvant chemotherapy duration) of the study population. Minor differences in chemotherapy regimens or surgery may have influenced patient outcome, confounding the predictive value of FDG-PET.

The concordance between histologic response ($\leq$10% viable tumor) and SUV2 (<2.5) in the current

study was less robust than in our prior combined analysis of pediatric patients with bone sarcoma.[13] We previously speculated[15] on the potential explanations for the discordance between SUV2 and histologic assessments of response, including nonspecific (but bioenergetically intense) inflammatory response and scarring around necrotic tumor. Histologic response is an averaged assessment in a representative plane, in contrast to the 3-dimensional assessment of maximal remaining tumor activity measured by FDG-PET. It is likely that histologic and FDG-PET assessments of response are evaluating a similar biologic process (residual tumor cells after therapy) but with different methodological limitations, generating related but nonconcordant results.

The optimal timing of FDG-PET to determine response remains to be defined. Changes in FDG metabolism can occur within 24 hours after administration of imatinib in gastrointestinal stromal tumors[23] and within 3 to 5 days after administration of AP23573, an inhibitor of the mammalian target of rapamycin, in osteosarcoma and other sarcomas.[24] We previously reported a preliminary analysis of a prospective study of patients with high-grade soft tissue sarcoma by obtaining FDG-PET imaging after 6 weeks (2 courses) of therapy and correlating the results with those obtained immediately before surgery (after 4 courses), suggesting that FDG-PET imaging changes are apparent after only 2 courses and that FDG-PET imaging results after 2 and 4 courses of therapy essentially are concordant.[21] Currently, we are conducting 2 prospective studies with FDG-PET imaging after only 1 course of treatment to explore the rapidity of FDG metabolism change in soft tissue and bone sarcomas. The Children's Oncology Group also is performing a similar study in patients with intermediate-risk rhabdomyosarcoma (ARST0531) to assess FDG-PET response after 3 weeks of chemotherapy.

FDG-PET may have several potential clinical uses. First, orthopedic oncologists may be able to identify patients who are more likely to have a favorable histologic response to neoadjuvant chemotherapy. Such patients would be candidates for less aggressive limb-sparing resections. Patients predicted to have an unfavorable histologic response could be considered for more aggressive local surgery. However, our current data suggest that SUV2 is weakly correlated with histologic response. In contrast, the SUV2:1 was more useful, particularly in identifying patients with poor histologic response. Second, chemotherapy-resistant osteosarcoma may be identified earlier in the neoadjuvant period by an unfavorable FDG-PET response, leading to an alteration in systemic chemotherapy. The success of FDG-PET–guided therapy modification assumes that FDG-PET imaging changes occur early in treatment (as discussed above) and that alteration of systemic chemotherapy will improve the outcome of chemotherapy-resistant osteosarcoma. Nonrandomized clinical trials have suggested that augmentation of chemotherapy in response to a poor histologic response can improve outcome.[7,25] However, others have refuted that observation.[6,26] The current European and American Osteosarcoma Study Group (EURAMOS) trial EURAMOS-1 addresses the benefit of response-adapted therapy with the randomized comparison of continued, standard adjuvant chemotherapy versus standard adjuvant chemotherapy with the addition of ifosfamide and etoposide. It is possible that response-adapted chemotherapy would be more successful if FDG-PET was able to identify chemotherapy-resistant osteosarcoma after only 3 to 5 weeks of neoadjuvant chemotherapy rather than after 10 weeks of neoadjuvant chemotherapy and 4 weeks of adjuvant chemotherapy (which was used in the EURAMOS-1 trial). Finally, FDG-PET may be a surrogate marker of response for patients who have recurrent disease or nonresectable metastases, such as ay distant bone sites. This would be particularly useful in phase 2 studies, in which unidimensional or bidimensional measurements of response may underestimate the activity of a novel chemotherapy agent. The lack of a radiographic response yet the clear clinical benefit associated with FDG metabolic response to imatinib in the treatment of gastrointestinal stromal tumors clearly illustrates the limitations of anatomic imaging to assess response in sarcomas.

In summary, an SUV2 <2.5 after neoadjuvant chemotherapy for osteosarcoma was associated with an improved PFS. The association was less robust than we observed with ESFT and lost statistical significance when patients with metastatic osteosarcoma were excluded. In our small series, neither SUV2 nor histologic response were precisely predictive of PFS. A larger prospective study will be required to determine whether FDG-PET imaging can complement histologic response as a prognostic factor for osteosarcoma and determine whether FDG-PET is a prognostic factor independent of initial

stage. Additional areas of uncertainty include the optimal timing FDG-PET and modification of treatment for patients who are at greater risk for disease recurrence.

Conflict of Interest Disclosures

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