(F-18) Fluorodeoxyglucose Positron Emission Tomography as a Predictor of Pathologic Grade and Other Prognostic Variables in Bone and Soft Tissue Sarcoma

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ABSTRACT

Positron emission tomography (PET) can be used to measure tumor metabolism in sarcomas by measuring the standard uptake value (SUV) of (F-18) fluorodeoxyglucose (FDG). FDG-PET SUV has been shown to correlate with histological grade. We compared FDG-PET SUV in 89 bone and soft tissue sarcomas with histopathological features, including tumor grade, as well as with markers of cell proliferation and cell cycle regulatory gene expression that may be prognostically or therapeutically important. All patients had undergone PET before biopsy. Features evaluated included grade (National Cancer Institute for soft tissue or Mayo Clinic for bone), cellularity, and the number of mitoses per 10 400× fields. Deparaffinized, formalin-fixed sections were immunostained with antibodies to Ki-67 (MIB-1), p53 (DO7), $p21^{WAF1}$ (EA10), and mdm-2 (1B10). For Ki-67, results were estimated as a percentage of positive cells. For p53 and mdm-2, only cases with >20% positive cells were considered to be overexpressing these proteins. For $p21^{WAF1}$, only cases with <10% positive cells were considered to have lost normal $p21^{WAF1}$ expression. Tumor S-phase percentage and ploidy were determined by flow cytometry. FDG-PET SUV was associated with histopathological grade, cellularity, mitotic activity, MIB labeling index, and p53 overexpression. No association was seen with $p21^{WAF1}$, mdm-2, S-phase fraction, or ploidy. Tumor metabolism data acquired by FDG-PET may help ensure accurate grading and prognostication in sarcoma by guiding biopsy toward the most biologically significant regions of large masses. Further follow-up will be necessary to determine whether FDG-PET provides independent prognostic information.

INTRODUCTION

Histopathological evaluation is the cornerstone on which the rational management of patients with soft tissue and bone neoplasms is based. Increasingly, clinical management, including the institution of neoadjuvant therapy, is being based on the results of small incisional or core biopsies. Sarcomas, however, are notoriously heterogeneous neoplasms, and sampling error is a definite risk with the use of small biopsies. For this reason, there has been increasing interest in imaging techniques that may detect heterogeneity in sarcomas and thus allow direction of biopsy toward the most biologically significant zones.

FDG-PET[2] is increasingly used for the detection and management of soft tissue and bone sarcoma. FDG-PET has been shown to be useful for detection of local recurrence (1) and metastatic disease in patients with sarcoma (2) and has been used to evaluate response to neoadjuvant chemotherapy in sarcoma patients (3, 4). Several small studies have also shown significant differences between tumor FDG-PET values in benign *versus* high-grade malignant soft tissue tumors and between low- and high-grade soft tissue sarcomas (5–9). A similar relationship has not been shown for bone tumors (10). More recently, we have shown in a large heterogeneous series of adult bone and soft tissue tumors that both the MRFDG and the DUR increase with increasing histopathological grade (11).

However, despite the increasing use of FDG-PET in sarcoma management, no study to date has evaluated whether there are pathological features other than tumor grade that are related to an individual patient's tumor FDG-PET scan values. Although traditional histopathological grading remains a cornerstone of sarcoma management (12), some have questioned whether a single grading system is necessarily applicable to all sarcomas (13). For this reason there has been great interest in whether measures of proliferative activity, such as flow cytometrically determined SPF or immunohistochemical detection of Ki-67 protein, and measures of cell cycle control integrity, such as p53, p21, and mdm2 expression, are useful adjuncts for sarcoma prognostication and patient management (14). No study to date has evaluated the relationship between FDG-PET scanning in sarcomas and these proliferative and cell cycle variables.

Because FDG-PET is essentially a measure of metabolic

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[2] The abbreviations used are: FDG-PET, positron emission tomography using radiolabeled FDG; FDG, (F-18) fluorodeoxyglucose; MRFDG, FDG metabolic rate; DUR, dose uptake ratio; SPF, S-phase fraction; SUV, standard uptake value; PET, positron emission tomography; FNCLCC, Federation of Cancer Centers Sarcoma Group; HPF, high-powered field.

activity within a tumor, we hypothesized that factors that might influence FDG-PET values would include not only the tumor grade, but also the level of cellularity, the rate of cell proliferation, and the integrity of the normal mechanisms of cell cycle control. We further hypothesized that if a strong association was present between FDG-PET values and these pathological variables, then PET could serve as a valuable tool in patient management by guiding biopsy to the most biologically relevant areas and possibly by alerting the pathologist and clinician to under- or overgrading of sarcomas. To test this hypothesis, we evaluated 89 adult bone and soft tissue tumors that had undergone FDG-PET, biopsy and/or resection, and complete pathological evaluation at the University of Washington Medical Center. For each tumor, we examined the histological variables of tumor grade and cellularity, cell proliferation as measured by mitotic figure counts, immunohistochemical staining for the Ki-67 proliferative marker, flow cytometry, and cell cycle control integrity, as measured by immunohistochemical staining for p53, mdm2, and $p21^{WAF1}$. For this study, we chose to look at SUV, which was derived directly from summed tomographic images. SUV results are tightly correlated with MRFDG (15).

PATIENTS AND METHODS

Patient Population. The 89 patients in this series ranged from 23–74 years, with a median of 42 years. Subtypes of soft tissue and bone neoplasia included malignant fibrous histiocytoma (16), primitive neuroectodermal tumor/Ewing's sarcoma (17), osteosarcoma (18), fibromatosis (19), liposarcoma (20), giant cell tumor of bone (21), chondrosarcoma (22), fibrosarcoma (23), malignant peripheral nerve sheath tumor (17), synovial sarcoma (23), leiomyosarcoma (20), and other diagnoses (18).

PET Scanning. All patients underwent PET imaging with FDG in the week before initiation of neoadjuvant chemotherapy or resection. Detailed methods for PET imaging of sarcoma patients are published elsewhere (11). Briefly, patients fasted for ≥2 h before the procedure. They then signed informed consent for the procedure and received 7–10 mCi of FDG i.v. over 2 min. After a 45-min equilibration period during which the patient was at rest, attenuation corrected emission images over the tumor were acquired on a General Electric Advance PET scanner. Typically, the tumor extent was captured in two adjoining 15-cm fields of view. Reconstructed attenuation corrected images were viewed in the transaxial, coronal, and sagittal planes. On the transaxial planes, hand drawn regions of interest were placed over the tumor for calculation of the SUV. Regions of interest were drawn to follow the contours of the elevated FDG activity as compared to normal tissue, contralateral to the tumor site. The SUV is generated by the tomograph software as the ratio of activity in the tumor:normal tissue corrected by the amount of radioactivity infused, and the patient weight. The highest SUV for the tumor region, rather than the average SUV, was recorded for analysis in this study. This is both because we expected the most metabolically active regions of the tumor to drive the overall behavior and because the averaging of areas of cystic change and necrosis (areas with very low SUV) would be expected to result in falsely low overall values for the tumor.

Pathological Evaluation. All sarcomas were graded as part of the routine work-up of the biopsies or resection specimens, and the pathologists were unaware of the PET findings. The soft tissue tumors were graded according to the National Cancer Institute grading system (18). In brief, under this system, well-differentiated sclerosing and lipocytic liposarcoma, and myxoid liposarcomas without a "round-cell' component are regarded as grade I tumors. Rare smooth muscle tumors and myxoid fibrosarcomas (myxofibrosarcoma or myxoid malignant fibrous histiocytoma) with only minimal atypism may also be regarded as grade I under this system (24). Almost all other soft tissue sarcomas are regarded as being either grade II (<15% necrotic) or grade III (≥15% necrotic). The National Cancer Institute system does not specifically address Ewing's sarcoma and primitive neuroectodermal tumor; at our institutions, these are regarded as grade III sarcomas. Osteo- and chondrosarcomas were graded in accordance with the grading system of Unni and Dahlin (25), with the modification that grades III and IV were combined into a single grade III.

For sarcomas that received neoadjuvant chemotherapy before definitive resection, tumor grading was based on the initial needle core biopsy examination. All other tumors were graded after evaluation of multiple sections from various regions of the resected specimen, and a single grade was given, reflecting the highest-grade areas. In difficult cases, intradepartmental consultation was used to arrive at a final grade.

Tumor cellularity was estimated as "high", "moderate", or "low" by two observers (A. L. F. and J. T. S.) independently. Discrepancies in this evaluation were resolved by re-evaluation of the case at a dual headed microscope. Mitotic figure counts were performed by the same two observers using the dual headed microscope; twenty 400× microscopic fields were evaluated, with both observers agreeing on all mitotic figures in all fields. These results were expressed as mitotic figures per 10 high-powered fields.

Immunohistochemistry. Immunohistochemical studies for Ki-67 (MIB-1, 1:50; AMAC), p53 (D07, 1:1000; Dako), mdm2 (IF2, 1:100; Calbiochem), and $p21^{WAF1}$ (EA10, 1:200; Calbiochem) were performed using 4–6-μm deparaffinized sections. The sections underwent heat-induced epitope retrieval using a microwave oven for 5 min in a 0.01 M citrate buffer (pH 6). Additional buffer was added as needed. The sections were then microwaved for 3 additional min and allowed to cool for 20 min. Antigens were localized using a standard avidin-biotin or streptavidin-biotin immunoperoxidase technique with nickel chloride enhanced 3,3′-diaminobenzidine as a chromogen. For Ki-67, the estimated percentage of positive nuclei was determined by the two observers and was based on the evaluation of a single representative slide. Cases showing immunohistochemical evidence of P53 and mdm2 overexpression were defined as those that showed ≥20% positive nuclei. Cases with ≥10% positive nuclei were regarded as showing normal p21/waf1 constitutive expression. These cutoffs were similar to those used in previous studies of Ki-67, p53, p21/waf1, and mdm2 expression (14, 24, 26–28), and they were used to allow comparison of data between studies.

Flow Cytometry. Flow cytometry was performed on formalin-fixed, paraffin-embedded tissue. Nuclei were isolated and stained with DAPI, as described previously (29). Histograms

were collected using a Becton Dickinson fluorescence-activated cell-sorting analyzer and analyzed using Multicycle software (Phoenix Flow Systems, San Diego, CA) using corrections for sliced nuclei, debris, and nuclear aggregation.

Statistical Analysis. Univariate descriptive statistics were compiled for all variables, and the Spearman correlation coefficient was used to measure the association between FDG-PET SUV and other nondiscrete prognostic variables. A descriptive summary was made for the distribution of FDG-PET SUV across levels of categorical prognostic measures, and the association between PET SUV and each of these measures was formally assessed using nonparametric tests. Specifically, the Wilcoxon rank sum test was used when the categorical variable of interest had two levels, and its extension, the Kruskal-Wallis test, was used when that variable had three or more levels (20).

In addition to considering the sensitivity of the distribution of FDG-PET SUV to the categories of the discrete prognostic variables, it was also of interest to directly relate FDG-PET SUV values to the category membership for these variables. Logistic regression models were applied for this purpose after first dichotomizing prognostic variables that afforded more than two categories (*i.e.*, tumor grade, cellularity, Ki-67 labeling index, and mitoses per 10 HPF). Specifically, tumor grades of II or III were considered high, and grades of 0 or I were taken as low. Cellularity of "high" was taken as high and cellularity of "low" or "intermediate" as low. For both the Ki-67 labeling index and the mitoses per 10 high powered field, two groups were defined as follows: values above the 75th percentile were considered high and those below that percentile were considered low. In the absence of standard cut points for these variables, these dichotomizations were performed to insure the relative extremity of the "high" groups in each category and to facilitate statistical analysis. To improve the robustness of the models, FDG-PET SUV was treated as a predictor variable after first making a logarithmic transformation. Odds ratios were computed corresponding to a one-logarithm increase in FDG-PET SUV. For all statistical analyses, Ps ≤ 0.05 were considered to be statistically significant.

RESULTS

The distributions of the discrete variables are detailed in Table 1. Table 2 describes the distributions of the variables that were not strictly categorical in nature (*i.e.*, FDG-PET SUV, SPF, S + G_2-M, Ki-67 labeling index, and mitoses per 10 HPF). Table 2 also provides estimates of the correlation between PET SUV and other variables. In Table 3, the distribution of FDG-PET SUV is summarized in terms of the median and interquartile range for each level of the categorical variables. Fig. 1 displays the actual FDG-PET SUV data by histopathological grade. Fig. 2 depicts the scatterplot of the number of mitoses per 10 HPF by FDG-PET SUV, and Fig. 3 depicts the distribution of FDG-PET SUV according to the measure of cellularity. Fig. 4 provides similar plots depicting the association between Ki-67 labeling index and FDG-PET SUV, and Fig. 5 depicts the distribution of FDG-PET SUV by level of p53.

We also evaluated the association between (log transformed) FDG-PET SUV and the odds of group membership corresponding to categorical prognostic variables of interest.

Table 1 Descriptive statistics for discrete variables

Grade (n = 89)	
Benign	15 (16.9%)
I	16 (18%)
II	26 (29.2%)
III	32 (36%)
Cellularity (n = 89)	
Low	16 (18%)
Intermediate	46 (51.7%)
High	27 (30.3%)
p53 (n = 87)	
Normal	48 (55.2%)
Overexpressed	39 (44.8%)
p21 (n = 79)	
Normal	40 (50.6%)
Absent	39 (49.4%)
mdm2 (n = 87)	
Normal	64 (73.6%)
Overexpressed	23 (26.4%)
Ploidy (n = 52)	
Diploid	19 (36.5%)
Aneuploid	33 (63.5%)

Table 4 presents odds ratio estimates for a one-logarithm increase in FDG-PET SUV. For grade, cellularity, Ki-67 labeling index, and mitoses per 10 HPF, these odds ratios refer to the ratio of the odds of being in the high group for two hypothetical individuals, with the first person having a one-logarithmic higher FDG-PET SUV than the second. The high and low groups were defined as discussed in "Patients and Methods." For ploidy, p53, p21, and mdm2, we refer to the ratio of the odds of a tumor having an abnormal result (*e.g.*, overexpression of p53). Table 4 confirms that the likelihood of high pathological grade and high cellularity was very strongly associated with the level of FDG-PET SUV, which is qualitatively consistent with the distribution and results in Table 3 and Figs. 1 and 2. Significant associations with Ki-67 labeling index, mitoses per 10 HPF, and p53 overexpression were also observed.

Values of FDG-PET SUV were highly discrepant among histopathological grades, with increasing SUV seen in tumors of higher grade, as well as in hypercellular tumors ($P < 0.001$ for both). There was little difference in the FDG-PET SUV values of benign and grade I sarcomas, but a marked difference between grade I sarcomas and sarcomas of grades II and III. These findings expand upon our earlier observations and those of others as regards the strong association between tumor SUV and histopathological grade. As shown in Table 3, the median SUV for intermediate- and high-grade sarcomas was 6.05 and 6.85, respectively, as compared with 2.65 for low-grade sarcomas.

As indicated, FDG-PET SUV showed a weak and statistically insignificant positive correlation with SPF and S + G_2-M, but stronger and highly significant positive correlations with Ki-67 labeling index and the number of mitoses per 10 HPF. We hypothesized that elevated SUV values would be seen in highly proliferative sarcomas, and the results of the present study support this. Mitotic activity, *per se*, is not indicative of malignancy in bone and soft tissue tumors, and it is often quite high in reactive or benign processes such as nodular fasciitis and giant cell tumors of bone. However, high-grade sarcomas generally have a higher level of mitotic activity than do tumors of lower grade.

Table 2 Descriptive statistics for nondiscrete variables

Variable	*n*	Minimum	25th percentile	Median	75th percentile	Maximum	Correlation[a] with PET SUV (*P*)
PET SUV	89	0.4	2.8	5.2	8.7	38.7	1
SPF	51	0.2	1.5	4.5	12.3	29.7	0.19 (0.17)
S + G_2-M	48	1.6	3.9	8.9	18.7	36.9	0.25 (0.08)
Ki-67 labeling index	87	3	3	10	25	95	0.35 (<0.001)
Mitotic figures/10 HPF	89	0	0	2	6	50	0.43 (<0.001)

[a] Spearman correlations.

Table 3 Distribution of PET SUV by level of categorical variables

Result	FDG-PET SUV median (interquartile range)	*P*
Grade		<0.001[a]
Benign	3.80 (1.50–6.90)	
I	2.65 (1.55–4.11)	
II	6.05 (3.40–10.25)	
III	6.85 (4.22–19.35)	
Ploidy		0.56[b]
Diploid	4.31 (3.00–11.48)	
Aneuploid	6.00 (3.10–15.30)	
p53		0.029[b]
Normal	3.65 (2.57–7.05)	
Overexpressed	5.70 (3.90–12.30)	
p21		0.52[b]
Normal	5.55 (3.05–10.83)	
Absent	4.12 (2.80–8.70)	
mdm2		0.64[b]
Normal	5.19 (2.80–9.00)	
Overexpressed	4.12 (2.80–8.70)	
Cellularity		<0.001[a]
Low	2.47 (1.38–3.45)	
Moderate	4.55 (3.10–7.10)	
High	8.70 (5.20–19.90)	

[a] Kruskal-Wallis test.
[b] Wilcoxon rank sum test.

Significantly higher values of FDG-PET SUV were seen in sarcomas with overexpression of p53, but not with mdm2 overexpression or loss of normal $p21^{WAF1}$ expression. These findings suggest that some alterations in cell cycle control may contribute to elevated FDG-PET SUV values in sarcomas. p53 overexpression was present in 45% of our cases of soft tissue sarcoma, an incidence slightly higher than that seen in prior studies (14, 16, 30–33). This may be due to our uniform use of heat-induced epitope retrieval for immunohistochemistry (34).

We also noted a significant association between tumor hypercellularity and FDG-PET SUV. This is not surprising because it might be expected that tumors with a greater number of metabolically active cells per unit area would have a higher SUV. Although hypercellularity has not been shown to have independent prognostic value in sarcoma (18, 35), hypercellularity is a common feature of malignant soft tissue and bone tumors.

We further analyzed the relationship of FDG-PET SUV with cellularity, Ki-67 labeling index, and mitotic activity separately for each group of tumors with a certain histopathological grade. For benign tumors and grade I sarcomas ($n = 21$), SUV was significantly higher in tumors with high mitotic figure counts (Spearman's $r = 0.44$; $P = 0.012$) and high cellularity ($P = 0.019$), and there was a trend toward higher SUV values for tumors with high KI-67 labeling indices ($P = 0.11$). For high-grade (grades II and III) sarcomas, there was a trend toward higher SUV values for tumors with high mitotic figure counts (Spearman's $r = 0.22$; $P = 0.10$) and high cellularity ($P = 0.075$), but these did not reach statistical significance. No correlation was seen between SUV values and Ki-67 labeling index in high-grade sarcomas.

Finally, we examined the relationship of a combination of cellularity and Ki-67 labeling index with SUV values. As noted in Table 5, a highly significant ($P = 0.009$) relationship was seen, with the highest PET SUV values in highly cellular and highly proliferative sarcomas and the lowest values in sarcomas with low cellularity and proliferative indices.

DISCUSSION

The earliest report of PET imaging in the evaluation of sarcomas is that of Kern and coworkers (8) who studied five patients with extremity soft tissue (four cases) and bone (one case) tumors and noted a correspondence between FDG uptake rate and tumor grade. Adler and coworkers (6) evaluated five patients with extremity liposarcomas, including three myxoid liposarcomas (grade I) and two pleomorphic liposarcomas (one grade II, one grade III). For the purposes of that study, grade II and III sarcomas were grouped together as "high grade"; a significant difference in the DUR between high- and low-grade liposarcomas was noted. A subsequent study by the same authors evaluated 25 patients with benign (6 cases) and malignant (19 cases) tumors of both bone and soft tissue (5). Interpretation of the results of this study is somewhat hindered by their inclusion of angiosarcomas and osteosarcomas in the grade II group (these tumors are generally regarded as grade III) and by the inclusion of a lymphoma in the grade III tumors (lymphomas are not graded as musculoskeletal tumors). However, significant differences were noted between the DUR of benign masses and high-grade sarcomas (grade II and III; Ref. 5). Griffeth *et al.* (7) noted significant differences between the DUR of 10 benign and 10 malignant soft tissue masses. Nieweg and coworkers (36), in a study of PET in 18 malignant and four benign soft tissue tumors, found a significant association between grade of malignancy and the regional MRFDG, but not between tumor grade and SUV. In contrast, in a study of bone tumors, Kole *et al.* (10) noted no difference in regional MRFDG or SUV when comparing benign and malignant tumors. This may be because certain benign bone tumors, such as giant cell tumors, typically show a very high SUV, which is in the range of high-grade sarcomas. Most recently, in a previous study of 70 soft tissue sarcomas, we

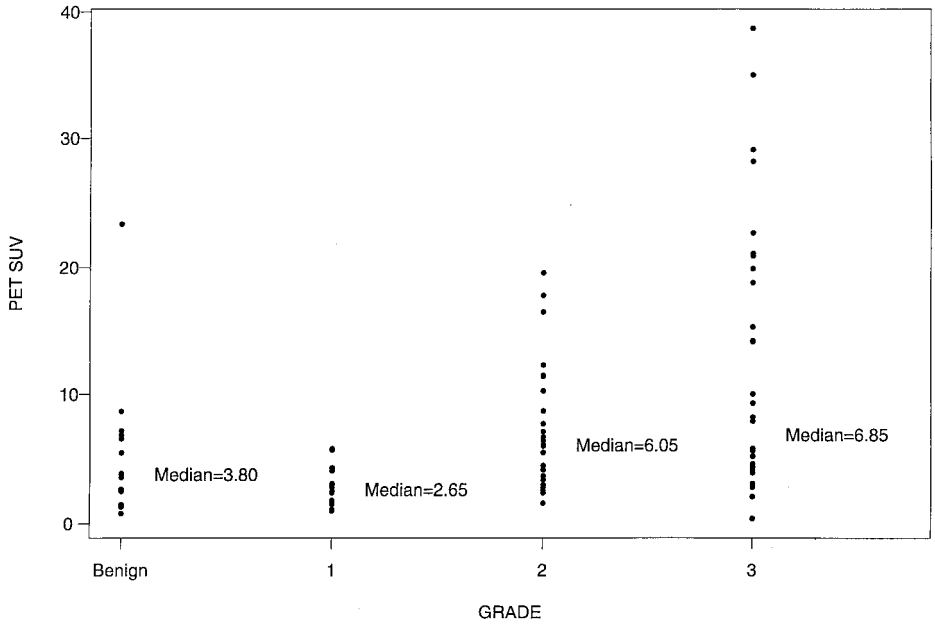

Fig. 1 Plot of PET SUV according to grade.

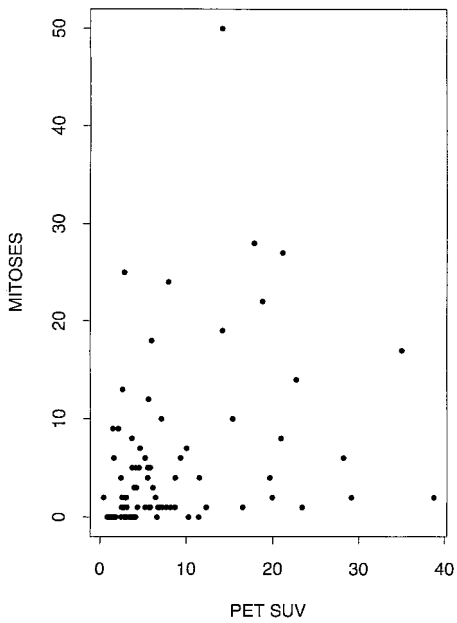

Fig. 2 Scatterplot of mitoses per 10 HPF *versus* PET SUV.

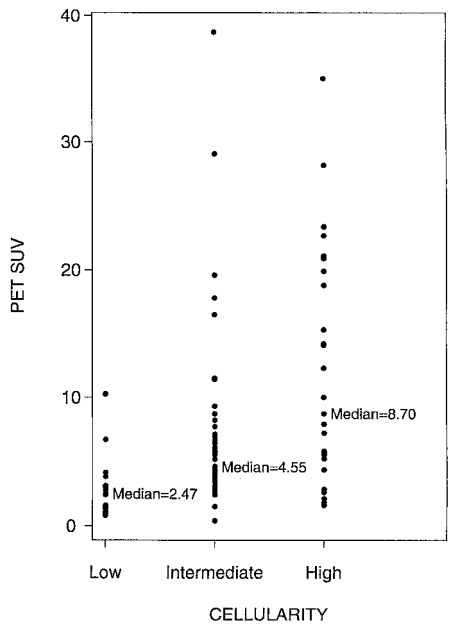

Fig. 3 Plot of PET SUV according to cellularity.

have shown significant differences in the MRFDG and DUR between National Cancer Institute grade I, II, and III tumors (11).

Although these previous studies have shown a relationship between FDG-PET scan values and histopathological sarcoma grade, no study to date has examined why it is that FDG-PET values correlate with grade. Putting it another way, what do FDG-PET values tell us about a sarcoma? Because FDG-PET scans are essentially a measure of tumor metabolism, we hypothesized that pathological features such as proliferative activity, tumor cellularity, and possibly alterations in the normal mechanisms of cell cycle control might be related to PET SUV.

With regards to cell proliferation, we found strong associations between FDG-PET SUV, Ki-67 labeling index, and mitotic figure counts. Ki-67 is a 395-kDa nuclear antigen that is encoded for by a single gene on chromosome 10 and whose expression is confined to late G_1, S, M, and G_2 phases (37). It appears to be localized to the nucleolus and may be a component of nucleolar preribosomes (38). In formalin-fixed tissue, the most widely used antibody against this antigen is MIB-1. Sev-

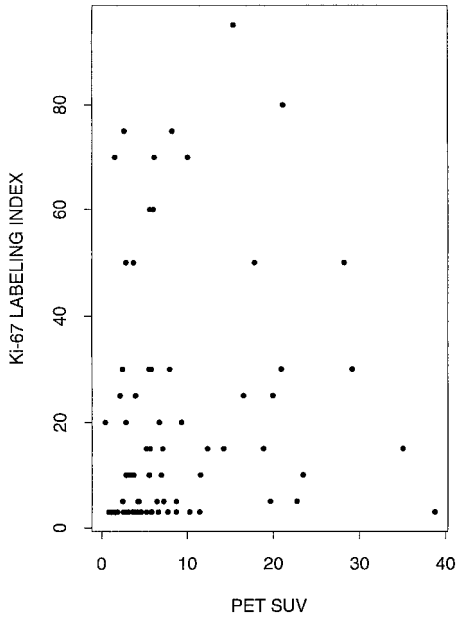

Fig. 4 Scatterplot of Ki-67 labeling index *versus* PET SUV.

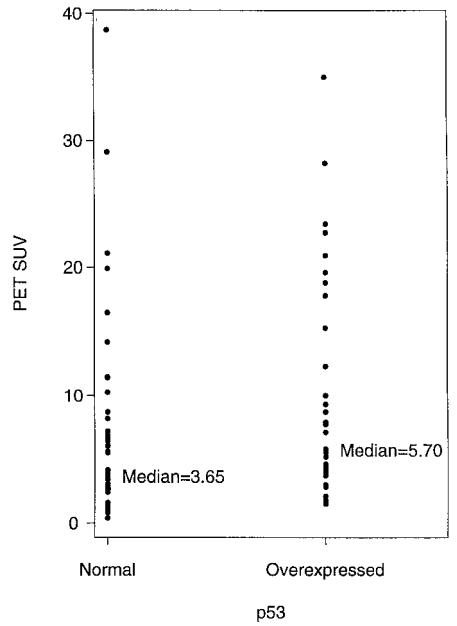

Fig. 5 Plot of PET SUV according to p53.

eral studies have documented a correlation between high Ki-67 labeling index and poor prognostic features in soft tissue sarcoma (22, 16, 39, 40). Most recently, Rudolph and coworkers (28) have shown significant associations between Ki-67 labeling index of >20% and high grade, shortened overall survival, and the development of metastatic disease. In high-grade sarcomas of the extremities, Heslin *et al.* (14) showed a Ki-67 labeling index of >20% to be an independent predictor of distant metastases and tumor mortality.

Table 4 Logistic regression results for associations between PET SUV and dichotomous variables[a]

Variable	Odds ratio for a one-log increase in PET SUV (P)
Grade	3.52 ($P < 0.001$)
Cellularity	2.72 ($P = 0.001$)
Ki-67	1.83 ($P = 0.045$)
Mitoses/10 HPF	2.18 ($P = 0.011$)
p53	1.71 ($P = 0.035$)
p21	0.87 ($P = 0.59$)
mdm2	0.86 ($P = 0.57$)
Ploidy	1.12 ($P = 0.71$)

[a] Dichotomous variables for grade, cellularity, MIB, and mitoses are defined as discussed in the text.

Whereas mitotic activity is not one of the parameters formally evaluated in the National Cancer Institute or Mayo Clinic grading systems (18, 25), it is an important component of the more recently devised FNCLCC grading scheme (35). Recent studies have suggested that the FNCLCC system may more accurately stratify sarcoma patients in terms of metastatic risk and overall outcome (12). Given the correlation we have shown between SUV and mitotic activity, one might hypothesize that an even tighter correlation would be seen between SUV and a grading system that incorporates mitotic activity, such as the FNCLCC system.

We were not able to show any relationship between FDG-PET SUV and flow cytometrically determined SPF or tumor ploidy. This may be because of sampling errors inherent in the use of this technique. Flow cytometry suffers from a number of drawbacks, including destruction of tissue, difficulty in assessing a small subpopulation of cells in a sample, loss of histological architecture, and inability to assign proliferative characteristics to specific cell populations. However, in general, high-grade sarcomas are more likely than low-grade sarcomas to be aneuploid (23, 19, 41, 42) and to have an elevated proliferative rate (17, 41–43). Aneuploid sarcomas have been shown to have a greater risk of subsequent metastasis (21) and a worse clinical outcome (23).

We observed correlations between FDG-PET SUV and p53 overexpression, but not between SUV and $p21^{WAF1}$ or mdm2. The TP53 gene product, p53, is a nuclear phosphoprotein, which appears to regulate transcription by arresting cells with damaged DNA in the G_1 phase (44–47). Mutations of the TP53 gene produce a mutant protein, which loses its tumor suppressing ability and has a longer half-life than wild-type p53 (44); this allows immunohistochemical detection of mutated p53. Overexpression of p53 has been examined in a variety of soft tissue sarcomas, with the incidence ranging from 9 to 41% (14, 26, 30–32, 48, 49). Most studies of p53 expression in sarcomas have shown a correlation between p53 overexpression, higher tumor grade, and worse outcome; however, p53 overexpression has not been shown to have prognostic significance independent of grade (14, 16, 30, 31–33). mdm2, a nuclear phosphoprotein whose transcription is activated by the p53 gene, binds the p53 gene and removes p53's block on the cell cycle at the G_1-S checkpoint (24, 27). mdm2 has also been shown to exert an inhibitory effect through binding of RB protein (50) and a

Table 5 Distribution of PET SUV by combinations of cellularity and KI-67 labeling index[a]

Cellularity	Ki-67 labeling index	N	Mean PET SUV (SD)	Median PET SUV
High	High	10	12.02 (8.87)	8.95
High	Low	16	11.77 (9.72)	7.95
Low	High	9	8.92 (8.94)	6.00
Low	Low	52	5.49 (6.01)	3.85

[a] $P = 0.009$, Kruskal-Wallis test.

stimulatory effect upon the E2F family of transcription factors (51). Although overexpression of mdm2 has been previously documented in between 33 and 37% of sarcomas, it has not yet been shown to be of prognostic significance (26, 52, 53). $p21^{WAF1}$ is a downstream effector of p53 and is an inhibitor of the cyclin/cyclin dependent kinase complexes (54). Loss of normal $p21^{WAF1}$ expression has been documented in a subset of liposarcomas, including dedifferentiated, myxoid, and round cell, but it has not yet been shown to be of prognostic significance (24, 27).

The clinical behavior of a subset of soft tissue tumors, including hemangiopericytoma, solitary fibrous tumor, and gastrointestinal stromal tumor, may be difficult to predict both clinically and pathologically, and these tumors are generally not graded, under either the National Cancer Institute or the more recent French FNCLCC system (18, 35). In these tumors, marked hypercellularity is a feature associated with malignant behavior (55). We observed a strong association between SUV and hypercellularity, suggesting a possible role for FDG-PET in certain scenarios, such as that of an intra-abdominal tumor clinically regarded as likely to be a gastrointestinal stromal tumor, in which the finding of high SUV might argue in favor of neoadjuvant therapy or an extended resection.

In summary, in this study of a large number of well characterized soft tissue and bone tumors, we have shown a significant association between the tumor SUV and several important pathological features, including histopathological grade, tumor cellularity, proliferative activity as measured by mitotic figure counts and by the MIB labeling index, and overexpression of p53. As regards histopathological grade, our findings are in general agreement with the findings of our previous study, although in that study, a larger and significant difference was present between the mean tumor DUR of grade II and III tumors (11). In that previous study, the DUR was derived from dynamic imaging data that was gathered to determine tumor the MRFDG. The tumor SUV data used in this study were similar, but were derived directly from tomograph summed image data, and values were not adjusted for patient serum glucose levels. This is the typical analysis format for a clinical imaging study. This difference in methodology probably accounts for the small difference between our two studies with regards to grade II and III sarcomas.

These findings suggest a valuable role for FDG-PET in the management of sarcomas in terms of identifying low-grade tumors that may safely be approached with conservative surgery and in identifying intermediate- or high-grade sarcomas that may require preoperative adjuvant therapy, depending on size and location. At our institutions, neoadjuvant chemotherapy and radiotherapy are offered to patients with grade III sarcomas and with very large grade II tumors.

However, there are limitations to the use of FDG-PET scanning in the management of patients with soft tissue and bone tumors. Although only grade III sarcomas had SUVs of >20, the very similar medians and the significant overlap of grade II and III sarcomas suggest that PET is not able to distinguish as well between histopathological grades II and III. Additionally, despite a strong association between elevated tumor SUV levels and higher histopathological grade, there remains a significant overlap in SUV scores between low-grade (grade I) and high-grade (grades II and III) sarcomas. Whereas 93% of neoplasms with SUVs >7.5 are high-grade sarcomas, only 42% of high-grade sarcomas have an SUV of this level. Interestingly, in this study, all of the neoplasms with SUVs >7.5 that were not high-grade sarcomas were, in fact, benign (*i.e.*, some benign tumors, but no grade I sarcomas had an SUV >7.5). In particular, the mean SUV for giant cell tumors of bone was 11.2, and moderately elevated SUVs were seen in fibromatoses. This suggests that elevated SUV, indicative of high metabolic rates, may be seen in three subsets of bone and soft tissue tumors: high-grade sarcomas, highly cellular and proliferative tumors (*e.g.*, giant cell tumor of bone), and perhaps in relatively hypocellular and slowly growing tumors with abundant matrix production (*e.g.*, fibromatoses). Obviously, PET scans need to be interpreted in the overall clinical context; whereas the finding of SUVs >7.5 in a large, deeply seated soft tissue mass in an adult is highly suggestive of a high-grade sarcoma, the same is not necessarily true of a smaller, destructive epiphyseal bone tumor. We do not think that PET scans will obviate the need for biopsy and tissue diagnosis in the management of soft tissue and bone masses in the foreseeable future.

One additional area where PET scanning may be valuable is in the recognition of intratumoral heterogeneity (reflected as areas of high and low SUV). Recognition of this heterogeneity and guidance of biopsy to regions that may be of the greatest biological significance (*i.e.*, highest SUV) may allow for more accurate sampling of these often large and heterogeneous masses and more accurate diagnosis, grading, and management of these patients. This might be particularly advantageous in centers that employ neoadjuvant treatment protocols. Our data suggest that biopsy of regions of elevated SUV is most likely to result in identification of the most clinically significant areas in sarcomas. Further clinical follow-up will be necessary to determine whether FDG-PET values have independent prognostic significance in patients with sarcoma.

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(F-18) Fluorodeoxyglucose Positron Emission Tomography as a Predictor of Pathologic Grade and Other Prognostic Variables in Bone and Soft Tissue Sarcoma

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