Sarcoma Mid-Therapy [F-18]Fluorodeoxyglucose Positron Emission Tomography (FDG PET) and Patient Outcome

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Background: Our previous research investigated the ability of [F-18]fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging results to predict outcome in patients with sarcoma. Tumor uptake of FDG before and after neoadjuvant chemotherapy was predictive of patient outcome. With this background, a prospective clinical study was designed to assess whether tumor FDG uptake levels in the middle of neoadjuvant chemotherapy added additional prognostic information to pre-therapy imaging data.

Methods: Sixty-five patients with either bone or soft-tissue sarcoma were treated with neoadjuvant-based chemotherapy according to the standard clinical practice for each tumor group. All patients had FDG PET studies before therapy, mid-therapy (after two cycles of chemotherapy), and before resection. Tumor FDG uptake (SUVmax, the maximum standardized uptake value) at each imaging time point, tumor type (bone or soft-tissue sarcoma), tumor size, and histopathologic grade were recorded for each patient. The time from the pre-therapy FDG PET study to events of local tumor recurrence, metastasis, or death were extracted from the clinical records for comparison with the imaging data. Univariate and multivariate analyses of the imaging and clinical data were performed.

Results: Univariate and multivariate data analyses showed that the difference (measured as the percentage reduction) between the pre-therapy and mid-therapy maximum tumor uptake values added prognostic value to patient outcome predictions independently of other patient variables.

Conclusions: The utility of a tumor pre-therapy FDG PET scan as a biomarker for the outcome of patients with sarcoma was strengthened by a mid-therapy scan to evaluate the interim treatment response.

Level of Evidence: Prognostic Level I. See Instructions for Authors for a complete description of levels of evidence.

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[F-18]fluorodeoxyglucose (FDG) positron emission tomography (PET) has made gains in its establishment as a biomarker in cancer imaging[1]. Useful for staging disease and identifying tumor response to therapy in most common cancers, it has become an established part of cancer management. Sarcomas are one of the less frequently occurring malignancies, and many patients with this disease still have poor outcomes despite current therapy. Assessment of tumor response on the basis of criteria involving changes in tumor size is not particularly helpful in these tumors[2]. Our previous research investigated the ability of tumor uptake of FDG, measured with PET, to predict patient outcome[3]. Furthermore, we established that comparison of tumor FDG uptake before and after neoadjuvant therapy was also predictive of patient outcome[4-6].

With this background, a prospective clinical study was designed to assess whether tumor FDG uptake in the middle of

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TABLE I Patient Characteristics

Characteristic	No. of Patients
Age at diagnosis	
Pediatric, 10-20 yr	22
Adult, 21-66 yr	43
Tumor site	
Upper extremity	8
Lower extremity	36
Pelvis	14
Trunk	7
Tumor diagnosis*	
Ewing sarcoma	10
Osteosarcoma	15
Fibrosarcoma	1
Leiomyosarcoma	7
Liposarcoma	6
MPNST	5
Sarcoma NOS	13
Synovial sarcoma	8

*MPNST = malignant peripheral nerve sheath tumor; NOS = not otherwise specified.

neoadjuvant chemotherapy was as predictive of patient outcome as the levels prior to therapy and at the end of neoadjuvant therapy. The goal in this study was to establish the usefulness of the mid-therapy scan as a biomarker of tumor response, enabling an oncology patient care team to use this information to guide treatment decisions and also allowing its use in evaluation of new therapies.

Materials and Methods

Patients

Participating patients were seen in the clinics for either bone or soft-tissue sarcoma and were treated with doxorubicin-based neoadjuvant chemotherapy according to the standard clinical practice for each tumor group. Patients were enrolled in the study from 1995 to 2005 and were selected for inclusion on the basis of their willingness to participate. Inclusion criteria were the presence of untreated primary sarcoma, planned chemotherapy and surgical resection, the ability to provide informed consent, and the ability to lie on the imaging table. All patients provided consent prior to participation in the institution-approved protocol. Postoperative radiation and/or chemotherapy were administered according to the standard clinical practice for each tumor group.

Study Imaging Protocol

All patients had PET studies of FDG uptake before therapy, in the middle of therapy (after two cycles of chemotherapy), and before resection. Tumor uptake (SUVmax, the maximum standardized uptake value) at each imaging time point, tumor type (bone or soft-tissue sarcoma), tumor size, and histopathologic grade were recorded for each patient. Clinical data were also recorded for each patient. For this analysis, the time from the pre-therapy FDG PET study to events of local tumor recurrence, metastasis, or death were extracted from the clinical records.

PET Imaging

Standard FDG PET images were made with use of a PET Advance scanner (GE Healthcare, Waukesha, Wisconsin) according to standard clinical procedures and as described previously[3]. The SUVmax value for the tumor regions of interest in each patient image was determined as described previously[3]. SUVdiff, the percentage change in tumor SUVmax, was calculated as the difference between the square-root-transformed SUVmax values in the pre-therapy and mid-therapy scans divided by the pre-therapy value.

Statistical Analysis

Patient death was considered the primary end point, with secondary end points involving tumor progression (either local recurrence or metastases). Clinical records were used to determine patient disease status. The event-free survival time was defined as the time (in months) from the pre-therapy FDG PET study to local tumor recurrence, metastasis, or death. Patients who were alive and without evidence of disease at the last clinic visit were considered disease-free survivors in the analysis. Patients with metastases at the time of study entry were excluded from the analysis. Initial analysis of tumor SUV and size data showed a skewed distribution; a square-root transformation was applied to those variables to address this issue. Continuous variables were standardized. The reported hazard ratios correspond to a one-standard-deviation change in the covariate. A p value of 0.05 was considered significant.

The question of interest is whether the maximum uptake of FDG by tumors at mid-therapy provides additional prognostic information beyond that provided by the tumor pre-therapy SUV data and other prognostic variables currently used in standard clinical practice[3]. SUVdiff, the percentage change in tumor SUVmax, was calculated as the difference between the SUVmax values in the pre-chemotherapy and mid-chemotherapy scans divided by the pre-chemotherapy value. (As previously noted, SUVmax values were square-root-transformed.) The SUVmax and SUVdiff data from the imaging time points and other prognostic variables were analyzed with use of a Cox regression model to understand the prognostic capability of this additional imaging information[7]. Patient survival, progression-free survival (free of distant and local progression), and local-progression-free survival were studied with use of univariate and multivariate Cox regression models. A set of eight prognostic variables were considered in the analysis; in addition to tumor pre-therapy SUVmax and SUVdiff, these were tumor histopathologic grade, sex, age, tumor size, tumor site, and sarcoma type.

The analyses considered all possible multivariate Cox regression models that contained at least one of the eight prognostic variables (a total of 255 models). A leave-out-one cross-validation procedure was used to assess which of these models provided the most reliable predictive relationship with each type of patient outcome (patient survival, progression-free survival, and local-progression-free survival). Cox model fits were evaluated on the basis of the

TABLE II Univariate Analysis for Patient Survival

Variable	Hazard Ratio*	95% Confidence Interval	P Value
Pre-therapy SUVmax	1.25	0.87 to 1.79	0.23
SUVdiff	0.62	0.4 to 0.97	0.03
Tumor size	1.75	1.1 to 2.8	0.02
Age	1.6	0.9 to 2.84	0.11
Sex	1.11	0.5 to 2.45	0.8
Tumor type (bone vs. soft-tissue sarcoma)	0.32	0.12 to 0.86	0.02
Tumor grade	1.01	0.46 to 2.23	0.98
Tumor site (truncal vs. extremity)	2.63	1.18 to 5.83	0.02

*For a one-standard-deviation change in the covariate.

TABLE III Multivariate Analysis for Patient Survival

Variable	Hazard Ratio*	95% Confidence Interval	P Value
Pre-therapy SUVmax	1.48	1.018 to 2.147	0.04
SUVdiff	0.54	0.328 to 0.872	0.01
Tumor site (truncal vs. extremity)	2.37	1.059 to 5.292	0.04

*For a one-standard-deviation change in the covariate.

likelihood information measure ($-2 \times$ log-likelihood) that has been established as appropriate for Cox regression analysis[7,8]. In addition, models were scored with use of the Akaike Information Criterion measure used with the Cox model, and the Hartell concordance statistic is also reported[9]. Note that model-fit statistics (likelihood or concordance) for the data subset used for validation are expected to be less favorable than those obtained with the full data set. The discrepancy between the two diminishes as the reliability of the model improves and as the sample size increases. Detailed results regarding the model selection are given in the Appendix.

We focused on the model selected by the cross-validation process for the patient survival analysis. The variables selected for this model were then used to define corresponding multivariate Cox models for progression-free survival and local-progression-free survival. We compared the cross-validation error in each of the latter two models with the error in the optimal cross-validated model for the same end point. The results for our final set of models are reported in detail with use of the standard methodology for Cox regression[8]. All continuous variables were scaled so that the hazard ratios presented indicate the hazard associated with a one-standard-deviation increase in the comparison covariate. Progression-free survival and local-progression-free survival were assessed with the same model that was chosen for patient survival; this model was then augmented by each of the remaining covariates and assessed for a further significant increase in prognostic utility. Survival curves are shown to illustrate the differences in predicted risk for death or progression associated with high and low pre-therapy SUVmax values and SUVdiff values in each of the models[8,9].

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Results

Seventy-nine patient imaging studies were available for this analysis. One patient was removed from the analysis because tumor SUVmax data were missing, and thirteen patients were removed because they had metastases at the time of study entry, resulting in a final sample size of sixty-five patients (Table I). Two of the patients who were included in the analysis did not have accurate tumor size information available, and tumor size was estimated from the scans. Figs. 1-A and 1-B show an example of tumor response on PET imaging. The

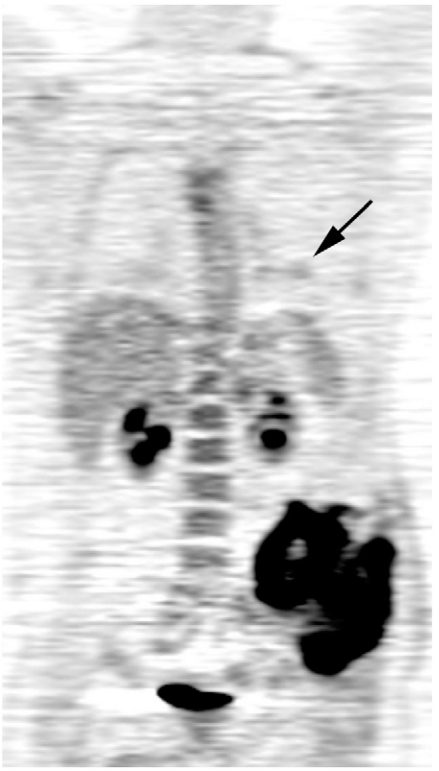

Fig. 1-A

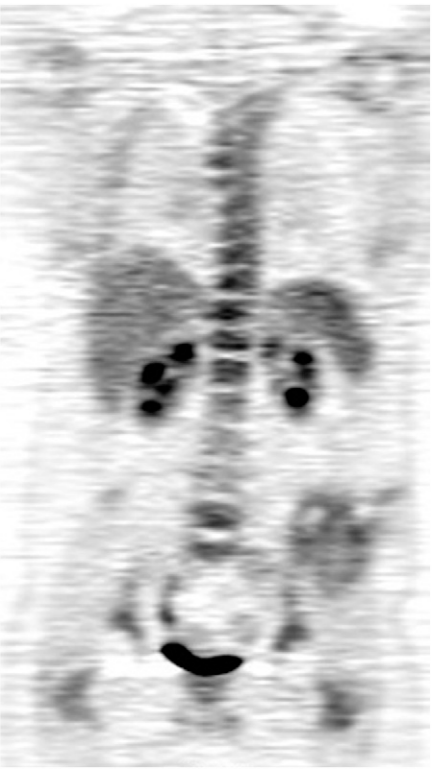

Fig. 1-B

Figs. 1-A and 1-B FDG PET images showing an example of the treatment response in a patient with a large Ewing tumor in the left pelvis. FDG-avid lung metastases are also present (arrow). **Fig. 1-A** FDG SUVmax = 11.5 before treatment. **Fig. 1-B** Tumor uptake of FDG after treatment is much lower; SUVmax = 4.4.

TABLE IV Univariate Analysis for Progression-Free Survival

Variable	Hazard Ratio*	95% Confidence Interval	P Value
Pre-therapy SUVmax	1.09	0.76 to 1.55	0.65
SUVdiff	0.61	0.41 to 0.91	0.01
Tumor size	1.63	1.07 to 2.5	0.02
Age	1.42	0.86 to 2.33	0.17
Sex	1.41	0.68 to 2.9	0.36
Tumor type (bone vs. soft-tissue sarcoma)	0.27	0.11 to 0.65	0.004
Tumor grade	0.78	0.39 to 1.59	0.5
Tumor site (truncal vs. extremity)	3.08	1.51 to 6.29	0.002

*For a one-standard-deviation change in the covariate.

TABLE V Multivariate Analysis for Progression-Free Survival

Variable	Hazard Ratio*	95% Confidence Interval	P Value
Pre-therapy SUVmax	1.35	0.925 to 1.962	0.12
SUVdiff	0.53	0.333 to 0.835	0.006
Tumor site (truncal vs. extremity)	2.93	1.428 to 6.003	0.003

*For a one-standard-deviation change in the covariate.

TABLE VI Univariate Analysis for Local-Progression-Free Survival

Variable	Hazard Ratio*	95% Confidence Interval	P Value
Pre-therapy SUVmax	1.49	1.01 to 2.2	0.04
SUVdiff	0.64	0.39 to 1.06	0.08
Tumor size	2.19	1.3 to 3.66	0.003
Age	1.41	0.77 to 2.61	0.26
Sex	1.05	0.43 to 2.53	0.92
Tumor type (bone vs. soft-tissue sarcoma)	0.40	0.14 to 1.09	0.07
Tumor grade	0.96	0.4 to 2.33	0.94
Tumor site (truncal vs. extremity)	3.51	1.45 to 8.49	0.005

*For a one-standard-deviation change in the covariate.

median duration of patient follow-up was 3.4 years (range, 0.34 to 8.14 years). Disease progression occurred in thirty-one of these patients, there were twenty-five deaths, and twenty patients had local disease recurrence.

In the univariate analyses, tumor size, SUVdiff, tumor site, and tumor type showed significant associations with patient survival (Table II). However, when all covariates were included in the multivariate model, none was significantly associated with patient survival. This was due to high collinearity, which is a common issue in multivariate modeling. However, the model selected by cross-validation revealed that, when the effects of multicollinearity and over-fitting from the five least effective prognostic variables were removed, the associations of pre-therapy SUVmax, SUVdiff, and tumor site with patient survival were significant ($p = 0.04$, $p = 0.01$, and $p = 0.04$, respectively). Tumor type and size, although excellent prognostic variables when used singly, did not add information to the multivariate model, implying overlap between these variables and the variables already present in the model (Table III). Although pre-therapy SUVmax was not a key prognostic factor in the univariate analysis, it became important when included along with SUVdiff and site in the multivariate analysis.

The univariate analysis of progression-free survival (Table IV) revealed a pattern similar to that for patient survival. SUVdiff and tumor size, type, and site were significantly associated with disease progression. When the multivariate analysis model chosen for patient survival was applied to progression-free survival, pre-therapy SUVmax was not a significant predictor, but it was retained as it is integral to the question of interest. The remaining covariates were then added individually and assessed for further prognostic potential. In the multivariate analysis, SUVdiff and tumor site had significant associations with outcome (Table V). No other covariates were found to add any significant prognostic advantage to the original model, although sarcoma type showed a borderline association ($p = 0.06$).

In the univariate analysis of local-progression-free survival, pre-therapy tumor SUVmax, size, and site had significant associations with disease progression (Table VI). The associations for SUVdiff and tumor type were of borderline significance. Applying the multivariate model with pre-therapy SUVmax, SUVdiff, and site, all variables had significant associations with local-progression-free survival (Table VII). No additional variables contributed significantly to the model.

Risks for decreased patient, progression-free, and local-progression-free survival in the multivariate Cox regression analyses derived from the data are shown in Tables III, V, and VII. For all end points, the risk assessment was significantly improved ($p = 0.01$) by including SUVdiff in a multivariate model with pre-therapy SUVmax and tumor site compared with a model with SUVmax and tumor site alone. The results of the analyses point to improvement in the assessment of prognosis provided by the SUVdiff variable. On average, for every 18% (one standard deviation) increase in the SUVdiff variable, there was an associated halving of the risk of death (i.e., the hazard ratio was approximately 0.5). This hazard ratio was quite stable across the patient survival, progression-free survival, and local-progression-free survival end points

TABLE VII Multivariate Analysis for Local-Progression-Free Survival

Variable	Hazard Ratio*	95% Confidence Interval	P Value
Pre-therapy SUVmax	1.82	1.186 to 2.786	0.006
SUVdiff	0.46	0.254 to 0.849	0.013
Tumor site (truncal vs. extremity)	3.24	1.33 to 7.886	0.01

*For a one-standard-deviation change in the covariate.

(0.56, 0.53, and 0.46, respectively). The fit statistics for the optimal models selected by the cross-validation had full-data set data likelihood values of 178.17, 212.27, and 141.29 for the same three end points, respectively; the corresponding cross-validated values were on the order of 1% to 5% higher (180.19, 221.92, and 143.47). Sample concordance statistics for the risk factors in these three Cox models were 0.69, 0.74, and 0.71, and these values decreased to 0.67, 0.71, and 0.70 in the cross-validation analysis, showing the relatively small deviation between the training-sample and cross-validation performance. This is a reflection of the model stability. The optimal cross-validated model for patient survival included three variables: pre-therapy SUVmax, SUVdiff, and tumor site. Although this was not the optimal model for progression-free survival or local-progression-free survival, its cross-validation error was close to that of the optimal model in both cases (see Appendix). For all three outcomes, the variables selected for the optimal cross-validation model include SUVdiff. This highlights the prognostic importance of mid-therapy FDG PET imaging information relative to any other available prognostic variable. Although the analysis used transformed data, the model was tested and yielded similar results for the raw (untransformed) data, indicating robustness of the model and suggesting simple application to the clinical setting. One standard deviation in the percentage reduction from before therapy to mid-therapy in the raw data was approximately 27%, and the median percentage reduction in the raw data was approximately 36%.

The Cox model analysis for patient survival revealed that the total risk for a patient outcome was a weighted sum of the risks estimated on the basis of the PET imaging time points plus an adjustment depending on whether the site of the tumor is extremity or truncal. The coefficients for the model are the natural logs of the hazard ratios; thus, from Table III, the PET-predicted risk for decreased patient survival was quantified as $0.39 \times$ (pre-therapy SUVmax) $- 0.62 \times$ SUVdiff; the site contribution to the overall risk was 0.86 if the tumor was truncal. Within our data, the PET-predicted risk values had a distribution with a mean of 0.56 and a standard deviation of 0.60. This distribution (including the locations of risk values one standard deviation above and below the median) is illustrated in a histogram of PET-predicted risk values in the Appendix.

Our analysis can be used to evaluate survival patterns for different scenarios. Figure 2 shows the estimated patterns (for each end point) for patients with PET-predicted risks above and below the median. The survival curves in the remaining figures in the Appendix were constructed by using a derived estimate for the reference survival curve in the Cox model[8]; they are not standard Kaplan-Meier curves for subgroups of patients. In contrast, the Kaplan-Meier curves for two or four subgroups within a cohort of only sixty-five patients would exhibit much more variability (because those curves do not take into account the Cox model). The curves in the Appendix illustrate the usefulness of the model in understanding projected patient survival. They compare survival for patients for whom the quantified PET-predicted risk might be considered high in value and for those with low risk, demonstrating remarkable differences between the predicted survival experiences of these patients.

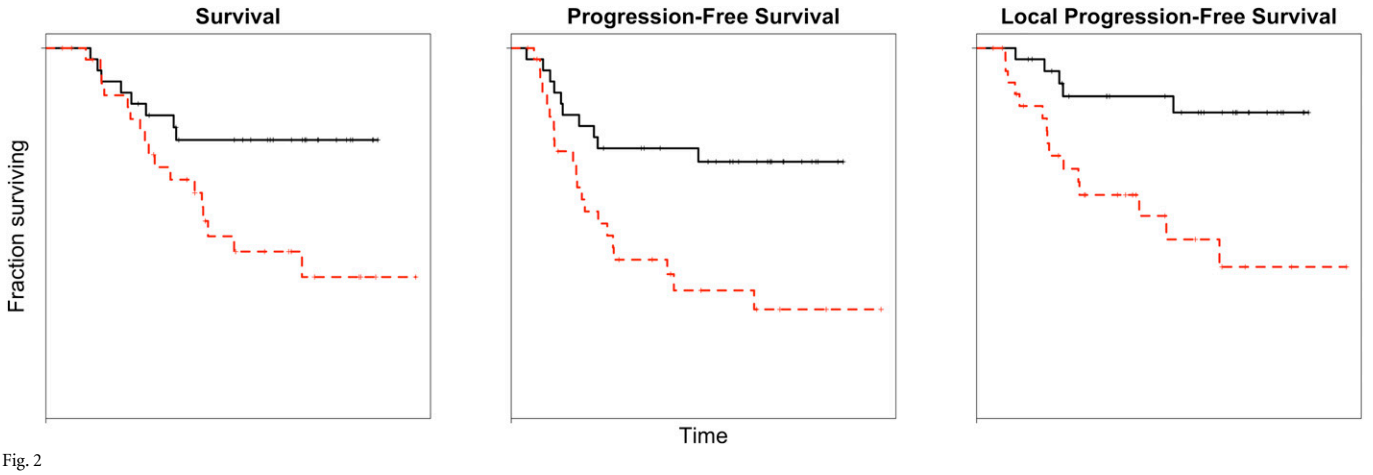

Fig. 2

Kaplan-Meier curves of the patient group for three survival end points. The black (solid) lines represent patients with lower risk (below the median) as defined by the survival models. The red (dashed) lines represent patients with higher risk (above the median).

Discussion

Tumor pre-therapy FDG SUVmax and SUVdiff combined as strong predictors of patient outcome and can be considered in further analyses. The results for the reduced model, in which factors with little influence on the survival estimates were removed from the analysis, showed the effects of SUVdiff to be highly significant across all outcome types. Pre-therapy SUVmax has a significant effect on both patient survival and local-progression-free survival, with a trend toward an effect on progression-free survival. It is encouraging to have such strong results in a relatively small data set, in which nearly one-half of patient outcomes were censored. Tumor type and site were also associated with a risk for poor outcome, consistent with previous reports and clinical experience[10]. Patients with bone sarcoma generally have a better outcome than patients with high-grade soft-tissue sarcoma, and extremity tumors pose less risk for a poor outcome compared with those in truncal sites. Another variable that was significantly associated with survival in the univariate models for all outcomes was tumor size. Tumor size is recognized as a significant prognostic factor in the planning of treatment for soft-tissue sarcoma tumors[10]. Consequently, histologically intermediate-grade soft-tissue sarcomas that are >5 cm in diameter are considered in the same high-risk category for reduced survival as histologically high-grade tumors.

A unique feature of the present study is the addition of a subanalysis of local-progression-free survival. The ability to predict local tumor progression can likely be used clinically to plan whether or not neoadjuvant treatment should include local radiation in addition to combination chemotherapy. Surgical resection options, including limb salvage, can also possibly be considered with more precision on the basis of these results. The high rate of local recurrence in the patient group reflects the distribution of tumor types and sites. The majority of the patients were adults with high-risk soft-tissue sarcomas located in the extremities. The data suggest that patients treated with limb salvage resection following chemotherapy may need additional treatment such as radiation therapy for optimal long-term local control of the tumor bed.

Previously published reports on the ability of FDG PET to quantify therapy response have made important contributions to the use of this imaging modality in the care of patients with sarcoma. These reports have largely, and appropriately, focused on validation of the imaging results through assessment of the association between tumor FDG uptake and the presence or absence of tumor necrosis. The presence of a high level of tumor necrosis in sarcomas is thought to be a strong predictor of long-term treatment response[11-14]. In one study, tumor FDG SUV changes contributed additional information to assessment of the treatment response with magnetic resonance imaging (MRI)[15]. In another study, the SUVdiff value was found to be more accurate for assessing the response than either the presence of substantial tumor necrosis or the RECIST (Response Evaluation Criteria in Solid Tumors) when these were applied to the same group of soft-tissue sarcomas[16]. Benz et al. reported that a reduction in tumor FDG uptake of >35% from the pre-therapy value was predictive of histologically assessed treatment response. These results established specific criteria for post-therapy treatment response assessment in clinical practice[17]. In bone sarcomas, Cheon et al. found that the MR-based volume change, used in combination with pre-therapy and post-therapy tumor FDG SUV data, was associated with the histologic response of the tumor[18]. Cheon et al. demonstrated the contribution that complementary imaging modalities can make to these challenging tumor response assessments. Dimitrakopoulou-Strauss et al. used multiparameter FDG kinetic analysis to demonstrate that the tumor FDG metabolic rate was associated with the histologic response[19].

The present study was designed to examine the ability of mid-therapy PET measurement of FDG uptake by tumors to predict the risk for a poor outcome on the basis of statistical analyses validated by the actual patient outcomes in the study group. This is distinctly different from the goals of the studies cited above, which involved the association of tumor FDG uptake with tumor histologic response as identified in the resected specimen. The significant hazard ratios for the pre-therapy SUVmax value and SUVdiff value obtained in the present study confirmed that these measures have a dose effect on the clinical outcome. The results demonstrated that clinical FDG PET scans made mid-therapy can be used to further stratify patients with sarcoma according to the risk for a poor outcome, with greater certainty compared with pre-therapy observations of tumor metabolic activity alone.

The results remained relevant for the raw (untransformed) data, and the procedure that was used to define the types of clinical outcome in this study can easily be instituted in a clinical setting. The median SUVdiff value for the raw data was 35.7%, and a difference that is smaller implies a higher risk for a poor outcome. The median pre-therapy SUVmax value for the raw data was 7.3. A decision scheme for treatment could be constructed from the data in this study, using the median as a cutoff point between "high" and "low" risk. For example, a patient with a low pre-therapy tumor SUVmax is at low risk for a poor outcome (Fig. 2). A patient who has a high pre-therapy SUVmax and little change in tumor uptake with therapy may consider discontinuing that line of treatment, as the models would predict a high risk for a poor outcome. Conversely, a patient with a high pre-therapy SUVmax but a high SUVdiff could be encouraged to continue treatment, since better survival would be predicted according to the presented models. We suggest using the SUV data as indicators of risk, rather than as cutoff points for decision-making, since the tumor pre-therapy SUVmax values and SUVdiff values are part of a continuum in the biological behavior of the tumor and its response to treatment.

Use of FDG PET data for sarcoma assessment in clinical applications presumes consistent implementation of standard PET procedures. Such consistent implementation has been described previously for the use of FDG PET as a biomarker for treatment response assessment[20]. It also points the way to use of FDG PET as a marker for early response assessment in new

combination therapies or new therapy trials in which changes in tumor uptake predict the clinical outcome. The patient outcomes in the present study validate these results.

Sarcomas are often very large, with heterogeneous metabolism within an individual tumor. As a group, they are histologically and clinically diverse. We hypothesize that responses to neoadjuvant treatment may also vary according to tumor type and size, with some tumors requiring more therapy to achieve a response that is indicative of efficacy and predictive of prolonged survival, and this would be a subject for future studies.

Appendix

eA Figures showing a histogram of risk values in the patient group and predicted survival curves according to SUV values, a table showing the optimal model and chosen model for each survival outcome, and an appendix outlining the derivation of those models are available with the online version of this article as a data supplement at jbjs.org. ■

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