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ORIGINAL ARTICLE

Risk Assessment Based on FDG-PET Imaging in Patients with Synovial Sarcoma

Jennifer W. Lisle MD, Janet F. Eary MD, Janet O'Sullivan MSc, Ernest U. Conrad MD

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Abstract Synovial sarcoma generally is associated with poor prognosis. With recent advances in molecular biology, it has become apparent not all synovial sarcomas share the same tumor biology. ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is useful for risk assessment in several types of sarcomas. We therefore assessed the clinical value of ^{18}F-FDG-PET-derived maximum standard uptake value (SUV_{max}) for predicting survival in patients with synovial sarcoma. ^{18}F-FDG-PET was performed in 44 patients with synovial sarcoma before therapy and resection. SUV_{max} was calculated for each tumor and then evaluated for prognostic usefulness along with metastasis at presentation, tumor grade, histopathologic subtype, age, gender, postsurgical margins, anatomic location, and tumor size for overall survival and progression-free survival. SUV_{max} ranged from 1.2 to 13.0 (median, 4.35). Pretherapy tumor SUV_{max} predicted overall survival and progression-free survival. Patients presenting with a SUV_{max} greater than 4.35 had a decreased disease-free survival and were therefore at high risk for having local recurrences and metastatic disease.
Level of Evidence: Level I, diagnostic study. See the Guidelines for Authors for a complete description of levels of evidence.

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Each author certifies that his or her institution has approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

J. W. Lisle, J. F. Eary, E. U. Conrad
Department of Orthopedics and Sports Medicine, University of Washington, Seattle, WA, USA

J. W. Lisle, J. F. Eary, E. U. Conrad
Department of Orthopedics, Children's Hospital and Regional Medical Center, Seattle, WA, USA

J. W. Lisle (✉)
Department of Orthopedics and Rehabilitation, University of Vermont, Robert T. Stafford Hall Room 426C, 95 Carrigan Avenue, Burlington, VT 05405-0084, USA
e-mail: jennifer.lisle@gmail.com

J. O'Sullivan
Department of Statistics, University College, Cork, Ireland

Introduction

Synovial sarcoma is a rare malignant neoplasm, accounting for only 6% to 10% of all soft tissue sarcomas. There are approximately 800 new cases of synovial sarcoma per year in the United States [26]. Historically, synovial sarcoma has been associated with poor prognosis, with survival at 5 years ranging from 55% to 76% [2, 16, 20, 21, 23, 27]. However, with advances in molecular biology and classification, it has emerged all synovial sarcomas do not share the same tumor biology when it comes to local recurrence, metastasis, and survival [2, 16, 17, 19–23].

Because of the varied biologic aggressiveness of synovial sarcomas, much effort has been placed in identifying prognostic factors with clinical value to better predict survival in individual patients with synovial sarcoma. Primary tumor size [1, 2, 12, 16, 17, 20–23, 27], tumor stage [20, 23], gender [6, 23, 27], age [2, 6, 12, 17, 19, 21, 27], tumor grade [6, 23], histologic subtype [2, 17, 19, 20, 23], tumor necrosis [23], mitotic activity [23], invasion of bone and neurovascular structures [1, 16], and anatomic tumor

location [6, 9, 17, 19, 23] all influence the natural history of primary synovial sarcomas. However, many of these findings have not been consistent so definitive conclusions based on them cannot be made.

During the past decade, FDG-PET has become increasingly available as a clinical tool in the outpatient cancer setting. The SUV_{max} in FDG-PET is a valuable parameter for risk assessment in sarcomas [8, 11]. Specifically, initial pretherapy SUV_{max} has been used for prediction of outcome in Ewing's sarcoma, liposarcoma, and chondrosarcoma [4, 5, 14].

Based on these previous findings, we hypothesized pretherapy FDG-PET SUV_{max} reflects tumor biology and aggressiveness in synovial sarcoma. We therefore (1) prospectively assessed the prognostic value of pretherapy FDG-PET SUV_{max} in survival in patients with synovial sarcoma and (2) determined whether age, gender, histopathologic subtype, grade, margins at the time of resection, tumor size, anatomic location, and metastasis at presentation predicted survival.

Materials and Methods

We prospectively followed all patients presenting with synovial sarcoma using pretherapy FDG-PET SUV_{max} between December 1995 and April 2007. Patients were excluded from the study if they had any type of treatment of their tumor before being enrolled, had a FDG-PET performed and/or read at another institution, or were not candidates for chemotherapy. We enrolled 44 patients with histologically proven synovial sarcoma. We recorded age at presentation, gender, grade, histologic subtype, postsurgical resection margins, size, anatomic site, metastasis at entry, local recurrence, and outcome (survival) for each patient. The age range of the patients at the time of first FDG-PET scan was 8 to 70 years (median, 35 years) (Table 1). The median time from the first FDG-PET scan to last followup or death was 63.4 months (range, 0.1–116 months). Informed consent was obtained by signing Human Subjects and Radiation Safety Committee-approved forms.

Histologic features of the tumor were determined at the time of resection by an experienced sarcoma pathologist (BR, PS) and were graded according to the Fédération Nationale des Centres de Lutte Contre le Cancer system based on differentiation, mitotic index, and necrosis [7, 24]. The histopathologic subtypes of synovial sarcoma were monophasic (29) and biphasic (10). Five tumors received no histopathologic classification. Twenty-eight tumors were designated as intermediate grade, 13 as high grade, and three were not graded (Table 1). Postresection surgical margins were determined grossly by an experienced sarcoma pathologist (BR, PS). Margins were considered negative if no tumor was present at the inked margins. Twenty-four tumors had microscopically positive margins at the time of resection, whereas 20 tumors had margins that were free of tumor (Table 1).

Tumor size was defined as the maximum dimensions on gross pathology. The average size of the tumor was 8.0 cm (range, 2–30 cm) (Table 1). Anatomic site was defined as extremity (any tumor occurring in the limbs), pelvis (any

Table 1. Characteristics of all patients and stratified by FDG-PET SUV_{max}

Variable	All patients	Patients with $SUV_{max} < 4.35$	Patients with $SUV_{max} > 4.35$
Total	44	22	22
Age			
< 18 years	4 (9%)	3 (14%)	1 (5%)
18–29 years	13 (29%)	11 (50%)	2 (9%)
30–50 years	18 (41%)	6 (27%)	12 (55%)
> 50 years	9 (21%)	2 (9%)	7 (32%)
Gender			
Female	28 (64%)	15 (68%)	13 (59%)
Male	16 (36%)	7 (32%)	9 (41%)
Grade			
Intermediate	28 (64%)	18 (82%)	10 (45%)
High	13 (30%)	2 (9%)	11 (50%)
Ungraded	3 (6%)	2 (9%)	1 (5%)
Histologic subtype			
Monophasic	29 (66%)	15 (68%)	14 (64%)
Biphasic	10 (23%)	4 (18%)	6 (27%)
No subtype given	5 (11%)	3 (14%)	2 (9%)
Anatomic site			
Extremity	31 (70%)	16 (73%)	15 (68%)
Trunk	10 (23%)	5 (23%)	5 (23%)
Pelvis	3 (7%)	1 (5%)	2 (9%)
Size			
< 5 cm	13 (30%)	10 (45%)	3 (14%)
5–10 cm	21 (48%)	10 (45%)	11 (50%)
> 10 cm	10 (23%)	2 (9%)	8 (36%)
Margins			
Positive	24 (55%)	12 (55%)	12 (55%)
Negative	20 (45%)	10 (45%)	10 (45%)
Metastasis			
Yes	18 (41%)	2 (9%)	16 (73%)
No	26 (59%)	20 (91%)	6 (27%)
Recurrence			
Yes	7 (16%)	3 (14%)	4 (18%)
No	37 (84%)	19 (86%)	18 (82%)
Died of disease	13 (30%)	1 (5%)	12 (55%)

FDG-PET = ^{18}F-fluorodeoxyglucose positron emission tomography; SUV_{max} = maximum standard uptake value.

tumor in the pelvis or groin), or trunk (any tumors originating in the thorax, retroperitoneum, paraspinal muscles, or axilla). The most common site of disease was the extremity (31), followed by the trunk (10), and pelvis (three).

For primary staging, all patients underwent MRI of the tumor region for local resection planning and CT of the lungs to establish the presence of metastasis. All patients received neoadjuvant chemotherapy. Postsurgical resection chemotherapy was given if the tumor had a good histologic response to neoadjuvant chemotherapy. External beam radiation therapy was given postoperatively if adequate surgical margins were not obtained (margins were not free of tumor). Patients initially were followed for 2 years postoperatively at 3-month intervals. Patients then were followed every 6 months for 3 years. Finally, patients were followed annually for 5 years. Physical examination, MRI of the tumor site, and CT of the lungs were performed at each followup for surveillance for local recurrence and metastasis. Although PET imaging currently is considered an excellent study in detecting tumor recurrence, it was not included for routine surveillance in this study. At the study's inception in 1996 and until recently, PET imaging was not used routinely in imaging for sarcomas and was not routinely covered by insurance. Because only pretherapy PET imaging was funded through the senior author's (JFE) NIH funding, posttherapy PET surveillance was not included in this study.

Detailed methods for PET imaging of patients with sarcoma have been described [10, 13]. PET imaging was performed before surgical resection or neoadjuvant chemotherapy in all patients. All PET scans were performed on one scanner and interpreted by one reviewer (JFE). Imaging studies were performed on an Advance Tomograph (General Electric Medical Systems, Waukesha, WI) operating in a two-dimensional high-sensitivity mode with 35 imaging planes per axial field of view of 15 cm (plane thickness 4.25 mm) and an in-plane resolution of 4 to 5 mm. All patients fasted for at least 12 hours before intravenous injection of 370 MBq ^{18}F-FDG. After the patients were positioned in the tomograph, we acquired a 15-minute attenuation scan over the tumor site followed by an emission scan of the tumor site at 45 minutes after tracer injection. Subsequently, additional adjoining 15-cm fields of view of the greater tumor area were acquired. The FDG-PET scan was performed in limited views of the tumor only to assess the tumor for risk of aggressive biologic behavior. We performed these research studies only to evaluate tumor biology, not to stage the patient for cancer.

Circular or elliptic regions of interest (ROIs) were placed over the tumor site on transaxial images. We performed sagittal and coronal image reconstruction to ensure correct ROI placement. The SUV_{max} for each ROI was calculated automatically by the tomograph software according to the following expression:

$$SUV_{max} 1/4 = A/(ID/m)$$

where A is the maximum tissue activity in the ROI, ID is the injected dose, and m is the patient's body weight. Tumor SUV_{max} ranged from 1.2 to 13.0 with a median of 4.35 (Table 2).

Survival was used as the primary end point in the outcome analysis [15]. All analyses were performed with standard censoring procedures for survival analysis. Cox regression was used to assess the significance of individual variables. The relationship between the time to death and the full set of measured prognostic factors was evaluated using the standard multivariate Cox proportional hazards regression analysis. This analysis permits an examination of the influence of the PET measures and allows control for other variables' impacts. All variables were included in the initial model for multivariate analyses for overall and progression-free survival. Variables then were deleted, individually, based on their contribution (least important variable was deleted) until all remaining variables were noteworthy. Progression-free survival was defined as the time until progression of disease (local recurrence or metastasis). Patients with metastasis at presentation were removed from analysis. For the final multivariate model for progression-free survival, we included only SUV_{max}

Table 2. Data summary for FDG-PET SUV_{max}

Patients	Number	SUV_{max}			
		Median	Standard deviation	Minimum	Maximum
All patients	44	4.35	2.5	1.2	13.0
Patients who died of disease	13	6.6	1.7	4.0	13.0
Patients with metastasis at presentation	5	6.5	1.1	6.0	9.6
Patients who had metastasis develop	13	5.9	1.8	4.0	9.1
Patients with local recurrence	7	6.6	2.4	3.1	7.9

FDG-PET = ^{18}F-fluorodeoxyglucose positron emission tomography; SUV_{max} = maximum standard uptake value.

because no other variables were associated with progression-free survival. To assess the comparability of this data set with historical data, a multivariate analysis for overall survival without FDG-PET SUV_{max} data also was considered. In this analysis, all variables, with the exception of pretherapy FDG-PET SUV_{max}, were included in the initial model and a backward elimination procedure applied.

Results

The median SUV_{max} value of 4.35 was determined as a cutoff to identify patients at high risk for not surviving their disease. Thirteen patients died of their disease. Twelve (92%) of these patients presented with a pretherapy SUV_{max} greater than 4.35 (range, 4.8–13). The remaining patient presented with a SUV_{max} of 4.0 (Table 2). Twenty-two patients presented with a SUV_{max} greater than 4.35. More than ½ (12) of these patients did not survive their disease, six (27%) are currently alive with disease (metastasis and/or local recurrence), and four (18%) are currently without evidence of disease (Table 1). Twenty-two patients presented with a SUV_{max} less than 4.35. Of these patients, one died of disease (pretherapy SUV_{max} = 4.0), three (14%) are alive with disease (metastasis and/or local recurrence), and 18 (82%) are alive without evidence of disease (Table 1). Five patients had American Joint Commission on Cancer [25] Stage IV disease (pulmonary metastasis) and had a median SUV_{max} of 6.5 (range, 6.0–9.6) (Table 2). An additional 13 patients with a median SUV_{max} of 5.9 (range, 4.0–9.1) had pulmonary metastasis develop at a median of 20.4 months (range, 1–56 months) after beginning treatment. Seven patients with a median SUV_{max} of 6.6 (range, 3.1–7.9) had local recurrence of their disease, which occurred at a median of 21.3 months (range, 12–34 months) after diagnosis (Table 2).

Pretherapy SUV_{max}, metastasis at presentation, and gender were associated with overall survival (p = 0.005, 0.0008, and 0.004, respectively) (Table 3; Fig. 1). Age, grade, histology, surgical margins, size, and anatomic site did not predict progression-free survival (Table 4; Fig. 2). When pretherapy FDG-PET SUV_{max} was eliminated from the analysis to compare all other data (age, gender, metastasis at presentation, size, location, histology, grade, and margins) with previously reported risk factors, metastatic status at presentation, gender, and size were associated with decreased overall survival (p = 0.0057, 0.036, and 0.05, respectively), whereas age, location, histology, margins, and grade were not (Table 5).

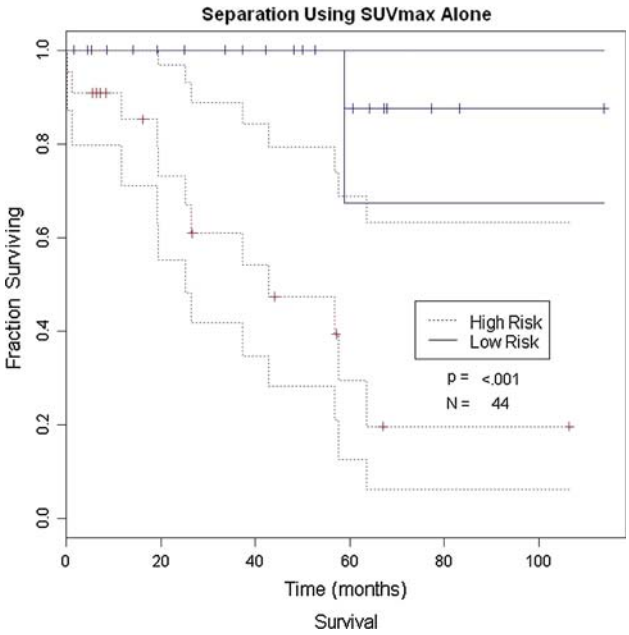

Fig. 1 Overall survival for patients using SUV_{max} alone is shown. High risk is defined as a SUV_{max} greater than 4.35 and low risk is defined as a SUV_{max} less than 4.35.

Table 3. Multivariate analysis for overall survival

Variable	Hazard	p Value
FDG-PET SUV_{max}	6.52	0.005
Metastasis at presentation	18.04	0.0008
Gender	19.42	0.004
Size	1.07	0.16
Age	2.24	0.076
Location	1.76	0.43
Histology	7.95	0.066
Margins	2.09	0.31
Grade	2.07	0.25

FDG-PET = ^{18}F-fluorodeoxyglucose positron emission tomography; SUV_{max} = maximum standard uptake value.

Table 4. Multivariate analysis for progression-free survival

Variable	Hazard	p Value
FDG-PET SUV_{max}	2.54	0.006
Gender	2.53	0.17
Size	1.16	0.08
Age	1.76	0.08
Location	1.65	0.46
Histology	0.71	0.63
Margins	1.03	0.97
Grade	0.864	0.86

FDG-PET = ^{18}F-fluorodeoxyglucose positron emission tomography; SUV_{max} = maximum standard uptake value.

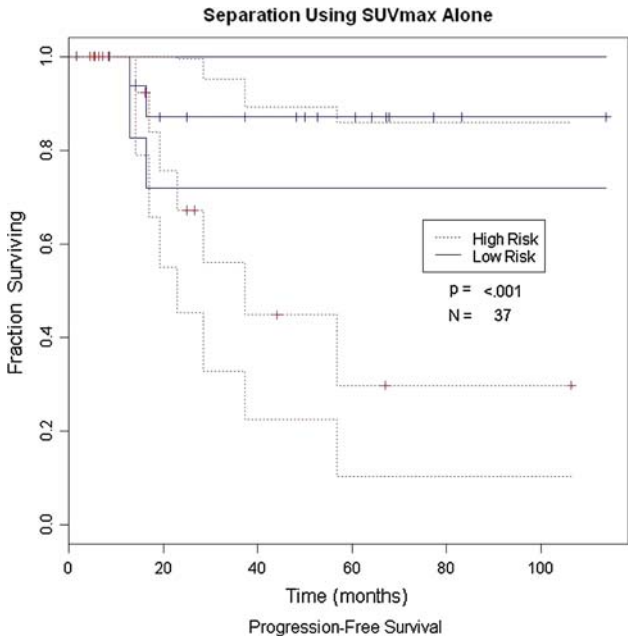

Fig. 2 Progression-free survival for patients using SUV_{max} is shown. High risk is defined as a SUV_{max} greater than 4.35 and low risk is defined as a SUV_{max} less than 4.35.

Table 5. Multivariate analysis for overall survival without FDG-PET SUV_{max} data

Variable	Hazard	p Value
Metastasis at presentation	195.004	0.0057
Gender	38.948	0.036
Size	1.35	0.05
Age	1.059	0.079
Location	3.81	0.24
Histology	3.92	0.22
Margins	0.337	0.33
Grade	1.764	0.7

FDG-PET = ^{18}F-fluorodeoxyglucose positron emission tomography; SUV_{max} = maximum standard uptake value.

Discussion

Pretherapy tumor FDG-PET SUV_{max} predicts survival in patients with several types of sarcoma, including liposarcoma, chondrosarcoma, and Ewing's sarcoma [4, 5, 14]. Synovial sarcoma represents a biologically diverse subtype of soft tissue sarcomas. Currently, there is no reproducible clinical, histologic, or radiographic indictor that has proven useful in assessing patient prognosis. We therefore prospectively assessed the prognostic value of pretherapy FDG-PET SUV_{max} in overall survival of patients with synovial sarcoma and compared these results with age, gender, histopathologic subtype, grade, size, site, and metastasis at presentation.

One of the major limitations of this study is the differences in postresection treatment received by patients. If resection resulted in contaminated surgical margins, patients received adjuvant radiotherapy. If patients had a good histologic response to neoadjuvant chemotherapy, they received adjuvant chemotherapy as well; however, the number of patients in this subgroup was too small to be statistically analyzed. Nonetheless, given that synovial sarcomas are a rare subtype in an already uncommon group of soft tissue sarcomas and that FDG-PET has been clinically available only for the past 10 years, we have one of the largest groups of patients with synovial sarcoma that have undergone pretherapy FDG-PET imaging. Perhaps additional analysis on a larger homogenous data set could take into account the fraction of patients who had additional adjuvant therapy. Another limitation of this analysis may be the inclusion of only patients with tumors we judged at high risk: tumor size greater than 5 cm, tumor palpated deep to the fascia and firmness of the tumor by clinical examination, and MRI findings of tumor greater than 5 cm, deep to the fascia with heterogeneous signal, and peripheral edema. However, the data analysis suggested a substantial survival difference for patients in this high-risk group based on a pretherapy FDG-PET tumor SUV_{max} greater than 4.35. Tumor grade and histologic type (monophasic or biphasic) did not predict survival. As expected, the presence or absence of metastases at presentation was strongly predictive for decreased overall survival.

We found tumor SUV_{max} ranged from 1.2 to 13.0, reflecting the wide range of tumor metabolism in synovial sarcomas. Numerous studies have shown tumor metabolism measured by FDG-PET SUV_{max} reflects biologic aggressiveness [3–5, 10, 11, 13, 14]. Previous data for a group of patients with sarcoma showed this value is correlated with tumor cellularity and mitosis rate [13].

The median pretherapy SUV_{max} of 4.35 in our study predicted overall patient survival. Patients presenting with a pretherapy SUV_{max} greater than 4.35 had an overall decreased ($p = 0.005$) survival when compared with all other variables examined in this study. Conversely, only one patient presenting with a pretherapy SUV_{max} less than 4.35 died of disease. Different sarcoma histologic subtypes exhibit specific FDG-PET SUV_{max} ranges [3–5, 8, 10, 11, 13, 14]. Our group of synovial sarcomas reportedly had a slightly lower median value than other soft tissue tumor types [10]. Our group also showed SUV_{max} varies over a wide range. This finding is exemplified by the subset of synovial sarcomas in this study group with a pretherapy PET SUV_{max} of 2.0 or less (Table 6). These relatively low SUV_{max} values reflect the less aggressive nature of this

Table 6. Characteristics of patients with initial pretherapy FDG-PET SUV_{max} of 2.0 or less

SUV_{max}	Recurrence	Metastasis	Death	Gender	Size (cm)	Location	Grade	Histology	Age (years)
1.2	No	No	No	Female	2.0	Extremity	Intermediate	Monophasic	8
1.9	No	No	No	Female	5.5	Extremity	Intermediate	Monophasic	17
2.0	No	No	No	Male	4.3	Extremity	Intermediate	Monophasic	36
2.0	No	No	No	Male	8.0	Trunk	Intermediate	Monophasic	16
2.0	No	No	No	Male	8.3	Extremity	Intermediate	Biphasic	10

FDG-PET = ^{18}F-fluorodeoxyglucose positron emission tomography; SUV_{max} = maximum standard uptake value.

subtype of synovial sarcoma. Consistent with the findings reported in this study, patients who presented with a lower SUV_{max} of 2.0 or less had no recurrence and no metastasis and are all alive without disease at the time of this study. This highlights the fact that FDG-PET SUV_{max} reflects tumor biology and aggressiveness and may be an underlying reason why the SUV_{max} predicts survival. Although some benign processes, such as fractures, myositis ossificans, and extraabdominal fibromatosis, may show a high FDG-PET SUV_{max}, this reflects only the lesions ability to be locally aggressive and metabolically active. By definition, however, these processes lack the cellular biology to metastasize.

During the last several decades, much effort has been invested in determining prognostic factors affecting overall survival in patients with synovial sarcoma. Histologic subtype, tumor grade, anatomic location, age, gender, tumor size, and surgical margins have been reported to have prognostic implication for a patient's overall survival [1, 2, 6, 9, 12, 16, 17, 19–24]. In our study, histologic subtype, grade, anatomic location, size, age, and surgical margins did not predict overall survival. Furthermore, only pretherapy PET-FDG SUV_{max} predicted progression-free survival.

The use of FDG-PET in cancer risk assessment continues to be explored. Its many advantages for evaluation of patients with sarcomas include ability to provide quantitative, objective tumor metabolic information noninvasively, three-dimensional high-resolution images, and standardization in imaging techniques for tumor restaging and treatment response situations [18]. We used FDG-PET imaging uptake data for synovial sarcomas in a relatively large group. With this experience, we will begin to consider the use of FDG-PET imaging as an important predictor for patient prognosis and treatment planning. The pretherapy tumor SUV_{max} of synovial sarcoma may be useful as a means to identify patients at high risk for poor outcome. In this setting, the tumor SUV_{max} of synovial sarcoma might function as an objective measure of therapy effectiveness for how multimodality treatment affects protocols and surgical approaches.

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