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# PET/CT, an important imaging modality in the management of sarcoma patients

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**Abstract**

Sarcomas are a heterogeneous group of malignant tumors of mesenchymal origin. 18 Fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET)/Computed Tomography (CT) is a combined imaging modality that could provide an anatomic and functional assessment of many solid tumors. In this study, the association between primary tumor characteristics (grade, histologic type, stage, localization) and the FDG-PET/ CT data of the primary tumor at the diagnosis were evaluated. The study aimed to determine the diagnostic role of numerical metabolic values determined in PET/CT in predicting grade, prognosis, and other patient characteristics of sarcoma patients. Patients with soft tissue and bone sarcoma who applied to the oncology department of Gazi University Faculty of Medicine between 2000 and 2014 were evaluated retrospectively. All patients underwent PET imaging with FDG before initiation of neoadjuvant chemotherapy or resection. Sarcoma patients (27 soft tissue, 18 bone sarcoma) were evaluated retrospectively in this study. Tumor size was found to correlate with SUVmax. Histologic grade was found to be associated with tumor 18F-FDG, but this was not statistically significant because of the small patient number. The optimal cut-off SUVmax value in showing the difference between low and high grades was 5.5. Overall survival was shown to be shorter in patients with SUVmax ≥5.5. In this study, we aimed to show the relationship between histologic grade and tumor metabolic activity. PET-CT could give an idea about tumor histologic grade and predict survival. It has an important role in diagnosis and also in determining the prognosis.

**Keywords:** Sarcoma, PET-CT, 18F-FDG, neoplasm grading

## Introduction

Sarcomas are rare and heterogeneous malignant tumors that comprise less than 1 percent of all adult malignancies [1]. These tumors originate from mesenchymal tissue; mostly from mesoderm, although a few arise from the neuroectoderm (such as Ewing's sarcoma). Sarcomas have a wide histopathologic spectrum because the embryonic mesenchymal cells from which they originate are capable of maturing into differentiated tissue types.

Histopathologic evaluation is important for the management of sarcoma patients. The histologic type of sarcomas is important both in terms of determining the prognosis and showing the behavioral pattern [2]. Because of its heterogeneous nature, pathological sampling may not always be sufficient in sarcomas. There is a growing interest in imaging techniques that detect heterogeneity in sarcomas. In this way, a biopsy could be taken from the most biologically important localization [3].

18 Fluorodeoxyglucose (FDG)- Positron Emission Tomography (PET)/Computed Tomography (CT) is a combined imaging modality that could supply an anatomic and functional assessment of many solid tumors. FDG-PET/ CT has a promising role in the management of solid tumors [4]. FDG-PET/CT has been shown to be useful for the assessment of local recurrence and metastatic disease and for the evaluation of response to treatment in patients with sarcoma [3]. Some studies have also shown a relationship between tumor grade and FDG-PET/CT in soft tissue sarcoma [5-10].

In this study, the association between primary tumor characteristics (grade, histologic type, stage, localization) and the FDG-PET/ CT data of the primary tumor at the diagnosis were evaluated and analyzed. The study aimed to determine the diagnostic role of numerical metabolic values determined in PET/CT in predicting

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grade, prognosis, and other patient characteristics of sarcoma patients.

## Material and Methods

### Study design and study population

The study was conducted in the Department of Oncology, Gazi University Faculty of Medicine, Türkiye. Patients with soft tissue and bone sarcoma who applied to the oncology department between 2000 and 2014 were evaluated retrospectively. Histopathological, clinical, and imaging data of the patients were recorded. Patients whose pathological assessments and FDG-PET/CT imaging at diagnosis were examined in the Hospital of Gazi University Faculty of Medicine were included in the study. The ethics committee of Gazi University approved the study protocol (reference number:429, date: 09.09.2014). The study was designed in accordance with the Declaration of Helsinki.

### FDG-PET/CT

All patients were evaluated with 18F-FDG PET imaging before the beginning of neoadjuvant chemotherapy or resection. PET/CT imaging was performed according to international recommendations. Patients fasted for at least 6 hours and blood glucose levels were approved to be lower than 180 mg/dl before injection of 0.14 mCi/kg FDG. PET/CT images were obtained on a GE Discovery ST PET/CT camera system (General Electric Medical Systems, Milwaukee, WI) 45–60 min post-injection of FDG. A low dose (120 keV, 10–90 41 mA) CT scan without intravenous contrast was performed. After CT imaging, a whole body PET scan (from skull base to mid-thigh) was performed in 3D mode, with an axial field of view of 15.7 cm and an emission acquisition duration of 3 min per bed position. The spatial resolution of the PET camera system was 5 mm. PET data were confirmed for attenuation by using the CT attenuation maps. Images were processed to produce 3.75 mm thick slices on axial, sagittal, and coronal planes.

All PET/CT images were assessed by one experienced nuclear medicine specialist in the current study. SUVmax values of primary tumors were used for the quantitative evaluation. Calculations were studied on an AW Workstation (AW 4.4- GE Healthcare).

### Statistical analysis

The data were analyzed statistically by using the Statistical Package for the Social Sciences (SPSS) program version 20 software package (released 2011, IBM SPSS Statistics for Windows, Version 20.0., IBM Corp., Armonk, NY, USA). Demographic variables were analyzed using descriptive analyses. Normality of the distribution of continuous variables was checked by using the Kolmogorov-Smirnov test. Categorical variables were analyzed by using the Chi-square test. The data that were not normally distributed were analyzed by using nonparametric tests (Mann- Whitney U test, Spearmen's rank correlation test).

The effect of tumor grade and 18F-FDG uptake on survival was evaluated by Kaplan Meier survival analysis using the Log-Rank test. ROC curve analysis was used to determine the threshold value between tumor grade and SUVmax value, and the sensitivity and specificity of this value. For all statistical analyses, p-value <0.05 was considered to be statistically significant.

## Results

### Patient characteristics

Sarcoma patients, 27 soft tissue sarcoma and 18 bone sarcoma, were evaluated retrospectively in this study. The median age of patients was 46. In the study, 24 patients (53%) were male and 21 patients (47%) were female. Demographic and clinical characteristics were presented in Table 1. Metastasis was seen in 7 (16%) patients at the diagnosis and in 22 (49%) patients on the follow-up. Isolated lung metastasis was seen in 1 patient, 1 patient had lung and cranial metastasis and 3 patients had liver metastases. Tumor excision was made on 33 (73%) patients. Six patients had positive surgical margins. Curative surgery was performed on 17 (40%) patients. SUVmax values of patients ranged from 1.1 to 32.8 and the median value was 6.8.

**Table 1.** Demographic and clinical characteristics of patients

| Variable | |
|---|---|
| **Sex, n (%)** | 45 |
| **Male** | 24 (53%) |
| **Histopathology, n (%)** | |
| **Soft tissue sarcoma** | 27 (60%) |
| **Bone sarcoma** | 18 (40%) |
| **Anatomic distribution, n (%)** | |
| **Upper extremity** | 4 (9%) |
| **Lower extremity** | 11 (24%) |
| **Thorax** | 10 (22%) |
| **Trunk** | 8 (18%) |
| **Head-neck** | 6 (13%) |
| **Pelvis** | 6 (13%) |
| **Tumor size, cm (%)** | |
| **≤5** | 25 (56%) |
| **6-9** | 8 (18%) |
| **≥10** | 12 (27%) |
| **Grade n (%)** | |
| **1** | 9 (4%) |
| **2** | 2 (4%) |
| **3** | 34 (76%) |
| **Surgical margins, n (%)** | |
| **Pozitive** | 6 (13%) |
| **Negative** | 27 (60%) |
| **AJCC stage, n (%)** | |
| **I** | 10 (22%) |
| **II** | 11 (24%) |
| **III** | 11 (24%) |
| **IV** | 13 (29%) |
| **Adjuvant therapy, n (%)** | |
| **Chemotherpy** | 27 (60%) |
| **Radiotherapy** | 13 (29%) |

AJCC: The American Joint Committee on Cancer

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**Relationship between tumor characteristics and PET-CT imaging parameters**

Tumor size was found to be correlated with SUVmax (r: 0.614, p=0.00). There was no statistically significant correlation between tumor localization and 18F- FDG uptake.

Histologic grade was found to be associated with tumor 18F-FDG uptake, but this was not statistically significant because of the small patient number. The patients were classified as low and high grades. Grade 2 patients were included in the high-grade group because the number of grade 2 patients was very small. In the low-grade group, there were 9 patients (8 soft tissue sarcoma, 1 bone sarcoma). SUVmax values ranged from 1.6 to 18.6 and the median SUVmax value was 2.7. In the high-grade group, there were 36 patients (19 soft tissue sarcoma, 17 bone sarcoma). SUVmax values ranged from 1.1 to 32.8 and the median SUVmax value was 7.0. There was no difference in showing histologic grade between SUVmax. There was no statistically significant relationship between high-grade and low-grade sarcoma and SUVmax value.

Higher 18F- FDG uptake was expected in high-grade sarcoma patients. For the SUVmax of the primary tumor, 5.5 was the optimal cut-off SUVmax value to discriminate between low and high grade (sensitivity 61%, specificity 78%; AUC: 0.677).

It was observed that 16 of the patients died on the follow-up. All of these patients were high-grade. The median follow-up time of patients was 18 months (0-130 months). Overall survival was 62±18.786 (25.251–98.785) months in all patients and 46±22.557 (1.788-90.212) months in high grade patients.

The effect of 18F-FDG uptake of the primary tumor on survival was assessed. Patients were classified in terms of SUVmax cut-off value as higher than 5.5 and lower than 5.5. In "SUVmax≥5.5" patients, overall survival was shorter than "SUVmax<5.5" patients (p=0.02) (Figure 1).

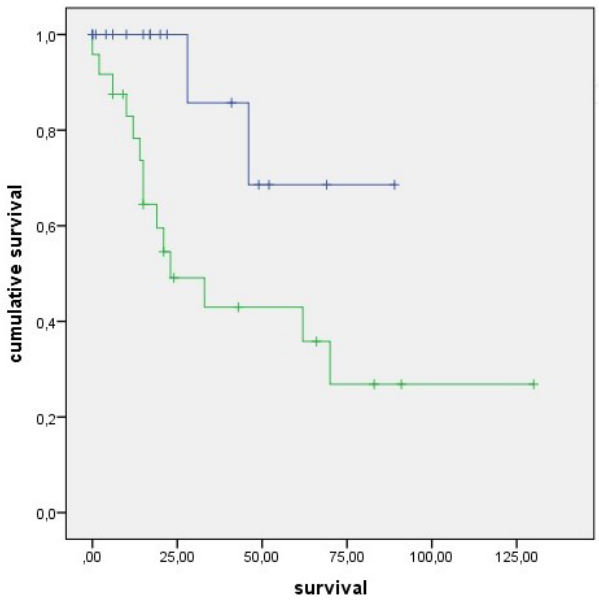


**Figure 1.** Effect of 18F-FDG uptake of primary tumor on survival

There was no statistically significant association between tumor localization and overall survival. When overall survival and 18F-FDG uptake were analyzed together, it was shown that 18F-FDG uptake predicted overall survival. The HR of 18F-FDG uptake for overall survival was 1.1 (95% CI: [1.011-1.146]; p=0.22) (Table 2).

**Table 2.** The relationship between Tumor SUVmax and overall survival

| | p | Hazard ratio | 95.0% CI for Exp (B) | |
|---|---|---|---|---|
| | | | Lower | Upper |
| **Suvmax** | .022 | 1.1 | 1.011 | 1.146 |

CI: confidence interval

## Discussion

Sarcomas are very rare tumors in adults. They are important because they are life-threatening tumors. The stage and grade are important for the management of sarcoma patients, as well as for determining the prognosis. Biopsy cannot indicate all characteristics of the tumor because of the heterogeneity of sarcoma.

There is increasing use of FDG-PET/CT in the management of sarcoma. FDG-PET/CT plays a role in diagnosis, defining the grade and stage of the tumor, detecting recurrence or metastasis, and determining the response to treatment and prognosis [11].

In this study, 18 bone sarcoma and 27 soft tissue sarcoma were evaluated retrospectively. The median age of patients was 47 and this result is younger than the literature. In this case, it was thought that the high number of patients diagnosed with Ewing sarcoma and osteosarcoma was because these sarcomas are generally seen in the younger population [12].

Tumor size was found to be lower than 5 cm in more than half of the patients (56%) and higher than 10 cm in 27% of patients. Tumor size was found to be correlated with 18F-FDG uptake (r: 0.614, p=0.00, r: 0.628 p=0.00) in our study. In the literature, there were conflicting results; a study on mice supported these results; however, in another study that included soft tissue sarcomas, there was no correlation between tumor size and lesion SUVmax value [13,14].

The first study which assessed the role of FDG- PET/CT in sarcoma management included 4 soft tissue and 1 bone sarcoma patient. Kern et al. showed a positive correlation between tumor 18F-FDG uptake and tumor histologic grade in 1988. In the follow-up, the studies continued and the results were found to be different [7]. A retrospective study showed no difference between bone and soft tissue sarcoma in terms of 18F-FDG uptake [15]. A study that included soft tissue sarcoma showed a positive correlation between liposarcoma and 18F-FDG uptake [16]. In our study, there was no statistically significant difference between soft tissue and bone sarcoma in terms of 18F-FDG uptake. The effect of histologic subtypes on tumor 18F-FDG uptake could not be analyzed due to the small patient number.

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It is known that tumor SUVmax value predicts disease prognosis and survival [17,18]. In a retrospective analysis involving 15.382 adult patients with extremity soft tissue sarcoma registered in the SEER database (between 1991 and 2010), it was observed that survival decreased significantly as the grade increased. Overall survival was 62±18.786 ( 25.251–98.785) months in all patients and 46±22.557 (1.788- 90.212) months in high grade patients. In our study, no death occurred in the low-grade patient group.

As with other tumors, there are studies about the relationship between tumor histologic grade and tumor metabolic activity in the literature. In two meta-analyses evaluating the relationship between grade and 18F-FDG uptake in sarcomas, it was shown that 18F-FDG uptake may be useful in distinguishing between low-grade and high-grade tumors [19,20]. However, in a subgroup analysis that only addressed soft tissue sarcomas, no significant difference was found between low-grade and high-grade groups in terms of 18F-FDG uptake [20].

In our study, median SUVmax of high-grade patients was 7.0; the median SUVmax of low-grade patients was 5.0. In high-grade patients, the median SUVmax value was higher than in low-grade patients as expected, but this was not statistically significant because of the small patient number. In a study which included 102 soft tissue sarcoma patients, median SUVmax value was 4.2±1.8 (1.9–8.0) for grade 1, 10.0±7.1 (1.0-29.5) for grade 2, 14.5±10.8 (2.2-52.5) for grade 3 [16]. SUVmax value of the low-grade group was similar to our study, but higher than our high-grade group. Another study showed the difference between benign lesions and moderate-to-high-grade lesions in patients with soft tissue sarcoma. However, this difference could not be shown between benign lesions and low-grade sarcoma [13].

Tumor 18F-FDG uptake could reflect the tumor grade. Studies have shown that there is an increase in tumor 18F-FDG uptake as the grade increases. A threshold SUVmax value could give an idea about histologic grade [19,20]. In soft tissue and bone sarcoma patients, Folpe et al. showed that 93% of the patients whose SUVmax value was higher than 7.5 were high grade [3]. In another study, which included bone and soft tissue sarcoma, threshold SUVmax value was found to be 6.5 for low-high grade sarcoma. In another study, the threshold SUVmax value was found to be 6.6 in soft tissue sarcoma patients (Sensitivity: 71%, specificity: 93%, AUC: 0.83) [11]. The threshold SUVmax value was found to be 5.5 in our study to show discrimination between low and high grades (Sensitivity: 61%, specificity: 78%, AUC: 0.83).

Tumor grade could be associated with disease prognosis. Predicting prognosis is important in the management of tumors. It was shown in the literature that the SUVmax value of the primary tumor could predict survival and a higher SUVmax value could show a poor prognosis [21]. We showed in our study that the survival of patients with SUVmax value ≥5.5 was shorter than patients with SUVmax value <5.5 (p=0.02). In soft tissue sarcoma patients, a higher SUVmax value (>7.2) decreased survival statistically significantly (p<0.001) (24). A study included 28 bone and 40 soft tissue sarcoma patients and assessed the relationship between primary tumor SUVmax value and survival. In this study, the median SUVmax value was found to be 10. Survival was shorter in the patients who had SUVmax higher than 10 [21].

PET-CT is an important imaging method for tumors. It could also show tumor metabolic activity. In sarcomas, PET-CT has an important role in the management of patients. SUVmax value is frequently used in the assessment of PET-CT imaging. However, the SUVmax value could not reflect all metabolic characteristics of the tumor, it showed only the most active part of the lesion. Considering the heterogeneity of sarcomas, this may lead to failure to reflect all characteristics of the tumor. Metabolic tumor volume (MTV), total lesion glycolysis (TLG), and mean SUV value (SUVmean) compensate for this deficiency of SUVmax. Accordingly, investigating the prognostic value of volume-based parameters has inspired different studies [22,23]. At the beginning of this study, we planned to include the SUVmean, SULmax, TLG, and MTV values of the patients in the statistical analysis, but the data could not be analyzed because results were not achieved in a sufficient number of patients.

Our study had some limitations. The first one was the small patient number because sarcomas are rare tumors and the patients whose diagnostic pathologic and imaging tests were not examined in Gazi University Hospital were excluded. Secondly, the study design was retrospective. Therefore, data of some patients could not be reached (MTV, TLG, SULmax, etc.). Further larger and prospective studies are needed.

## Conclusion

In this study, we aimed to show the relationship between histologic grade and tumor metabolic activity. In sarcomas, pathological sampling could be insufficient because of their heterogeneous nature and could not reflect all tumor characteristics. Insufficient biopsy samples or biopsy from the less metabolic active region of the tumor could affect the pathologic evaluation and thus the management of the patient. PET-CT shows the tumor's metabolic activity. PET-CT could give an idea about tumor histologic grade and predict survival. It has an important role in diagnosis and also in determining the prognosis. This idea was supported by the increase in tumor 18F-FDG uptake as histological grade increased and worse survival was associated with higher SUVmax value.

**Conflict of Interests**
*The authors declare that there is no conflict of interest in the study.*

**Financial Disclosure**
*The authors declare that they have received no financial support for the study.*

**Ethical Approval**
*The ethics committee of Gazi University approved the study protocol (reference number:429, date: 09.09.2014).*

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