



Prognostic significance of maximum standardized uptake value on ¹⁸F-fluoro-2-deoxyglucose positron emission tomography/computed tomography in bone sarcomas

Kemik sarkomalarında maksimum standart alım değerinin ¹⁸F-floro-deoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografi üzerindeki prognostik anlamı

Cüneyt Tamam, MD¹, Müge Tamam, MD²

¹Department of Orthopedics and Traumatology, Specialist Private Practice, İstanbul, Turkey

²Department of Nuclear Medicine, University of Health Science, Okmeydanı Training and Research Hospital, İstanbul, Turkey

ABSTRACT

Objectives: This study aims to evaluate the prognostic significance of maximum standardized uptake value (SUV_{max}) on ¹⁸F-fluoro-2-deoxyglucose positron emission tomography/computed tomography (¹⁸FDG-PET/CT) for bone sarcoma.

Patients and methods: We retrospectively evaluated 34 patients (24 males, 10 females; mean age 36.6±24.2 years; range, 5 to 77 years) with pathologically proven bone sarcoma who underwent ¹⁸FDG-PET/CT for initial staging between September 2013 and September 2017. SUV_{max} of primary lesions were measured. Cumulative survival rate was calculated to evaluate the prognostic value of ¹⁸FDG-PET/CT findings. Survival duration was defined as the elapsed duration from the date of pre-treatment ¹⁸FDG-PET/CT scanning until the date of the final examination before the date of death.

Results: The cut-off value for SUV_{max} in the definition of progression was 8. Mean SUV_{max} of the progressive group was statistically significantly higher than the non-progressive group. Distant metastases were present in 14 (41.1%) cases. Mortality and cumulative survival rates were 14.7% and 79.1±0.08%, respectively.

Conclusion: Semiquantitative estimation of primary tumor metabolic activity in terms of baseline SUV_{max} using ¹⁸FDG-PET/CT can predict the overall survival of patients with bone sarcoma.

Keywords: Bone sarcoma; ¹⁸F-fluoro-2-deoxyglucose positron emission tomography/computed tomography; maximum standardized uptake value; survival.

ÖZ

Amaç: Bu çalışma kemik sarkomu için maksimum standart alım değerinin (SUV_{max}) ¹⁸F-floro-deoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografi (¹⁸FDG-PET/CT) üzerindeki prognostik anlamı değerlendirildi.

Hastalar ve yöntemler: Eylül 2013 - Eylül 2017 tarihleri arasında ilk evreleme için ¹⁸FDG-PET/CT uygulanan, patolojik olarak kanıtlanmış kemik sarkomu olan 34 hasta (24 erkek, 10 kadın; ort. yaş 36.6±24.2 yıl; dağılım, 5-77 yıl) geriye dönük olarak değerlendirildi. Primer lezyonların SUV_{max}'i ölçüldü. ¹⁸FDG-PET/CT bulgularının prognostik değerini değerlendirmek için kümülatif sağkalım oranı hesaplandı. Sağkalım süresi, tedavi öncesi ¹⁸FDG-PET/CT taraması tarihinden ölüm tarihinden önceki son muayene tarihine kadar geçen süre olarak tanımlandı.

Bulgular: Progresyon tanımındaki SUV_{max} için cut-off değeri 8 idi. Progresif grubun ortalama SUV_{max}'i progresif olmayan gruptan istatistiksel olarak anlamlı şekilde yüksek idi. On dört olguda (%41.1) uzak metastaz vardı. Mortalite ve kümülatif sağkalım oranları sırasıyla %14.7 ve %79.1±0.08 idi.

Sonuç: ¹⁸F-floro-deoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografi kullanılarak bazal SUV_{max} açısından primer tümör metabolik aktivitesinin yarı-kantitatif tahmini, kemik sarkomu olan hastaların genel sağkalımını öngörebilir.

Anahtar sözcükler: Kemik sarkomu; ¹⁸F-floro-deoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografi; maksimum standart alım değeri; sağkalım.

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Correspondence: Müge Tamam, MD. Okmeydanı Eğitim ve Araştırma Hastanesi Nükleer Tıp Kliniği, 34400 Şişli, Okmeydanı, İstanbul, Turkey.
Tel: +90 212 - 221 77 77 e-mail: mugeonertamam@gmail.com

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Bone sarcomas are rare malignant mesenchymal derived bone tumors, which may or may not produce osteoid. Despite their rarity, primary malignant bone tumors comprise approximately 5% of all childhood and approximately 1% of all adult cancers in European countries.^[1,2] Primary malignant bone tumors include two major sarcomas of children and young adults: osteosarcoma and Ewing sarcoma.^[3-5]

The diagnostic work-up of bone sarcoma includes conventional imaging modalities that mainly provide morphologic information on the primary tumor and potential metastases. Functional imaging offers functional data on tumor metabolism.^[6]

¹⁸F-fluoro-2-deoxyglucose positron emission tomography/computed tomography (¹⁸FDG-PET/CT) is a dual-modality imaging technique that combines metabolic (PET) and anatomic (CT) evaluation of the malignancy. FDG accumulation is thought to be indicative of the metabolic activity of a targeted lesion, increased in proportion to their higher proliferative index, undifferentiating grade and metastatic spread.^[7]

Standardized uptake value (SUV), a commonly used semi-quantitative measure of FDG uptake, represents the point of greatest metabolic activity in the tumor, and its physical location can be ascertained with standard imaging software. High metabolic activity on FDG-PET has been shown to correlate with overall survival and thus provide additional information that may guide management. Therefore, in this study, we aimed to evaluate the prognostic significance of maximum SUV (SUV_{max}) on ¹⁸FDG-PET/CT for bone sarcoma.^[8]

PATIENTS AND METHODS

We retrospectively evaluated 34 patients (24 males, 10 females; mean age 36.6±24.2 years; range, 5 to 77 years) with pathologically proven bone sarcoma who underwent ¹⁸FDG-PET/CT for initial staging or assessment for recurrence of disease at Okmeydanı Training and Research Hospital between September 2013 and September 2017. ¹⁸FDG-PET/CT of one patient was obtained at another imaging center and the entire images were evaluated. The clinical and pathological records of each patient were reviewed, and the following information was gathered: age, gender, initial location, tumor diameter and SUV_{max}. The study protocol was approved by the Okmeydanı Training and Research Hospital Ethics Committee. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients were included if they had histopathologically proven bone sarcoma, undergone ¹⁸FDG-PET/CT for suspected recurrence (clinical/imaging) or for routine follow-up, and had a minimum of six months of clinical/imaging follow-up after ¹⁸FDG-PET/CT.

Patients were excluded if they had extraskeletal sarcoma, undergone previous treatment, and/or had not undergone ¹⁸FDG-PET/CT before treatment, and if they had insufficient clinical data with no histopathology of the primary tumor or clinical and/or radiologic follow-up of a minimum of six months.

Whole body PET/CT imaging was performed on a biograph (Siemens Biograph 6, Chicago, IL, USA) using a full-ring HI-REZ LSO PET and a six-slice CT scanner. The ¹⁸FDG-PET/CT scans were acquired after patients had fasted for at least six hours and had blood glucose levels lower than 200 mg/dL. The low-dose CT image acquisition was performed with oral contrast material, followed by PET image acquisition.

¹⁸F-fluoro-2-deoxyglucose PET/CT images were analyzed in at least three planes transaxial, coronal and sagittal in the gray scale color table for PET. In patients with metallic implants or prosthesis in situ, images without attenuation correction were also evaluated to rule out overcorrection artifacts. To perform a quantitative analysis, the SUV was calculated using the following equation: decay-corrected activity [MBq]/mL of tissue volume/injected F-18 FDG activity [MBq]/g of body weight.^[8] The SUV_{max} of each primary and/or most intense metastatic lesion was measured. Cumulative survival rate was calculated to evaluate the prognostic value of the ¹⁸FDG-PET/CT findings. Survival time was defined as the time from pre-treatment ¹⁸FDG-PET/CT scan to the date of the detection of death or to the date of the last patient file at our hospital.

Statistical analysis

Statistical analyses were performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). The normal distribution of parameters was evaluated by the Shapiro-Wilk test. Student t-test was used to compare descriptive statistical methods (mean, standard deviation, frequency) as well as the two-group comparison of parameters with normal distribution in the comparison of the quantitative data. Chi-square test, Fisher-Freeman-Halton test, Fisher's exact test and continuity (Yates) correction were used for comparison of qualitative data. Pearson's correlation analysis was used when the relationships between the parameters with normal distribution suitability were examined.

Receiver operating characteristic (ROC) analysis was used for cut-off point detection. Overall cumulative survival was analyzed by the Kaplan-Meier method and differences in survival between subgroups were compared using a log-rank test. Significance was assessed at $p < 0.05$ level.

RESULTS

Patients' characteristics are listed in Table I. Thirty two percent of the patients were 19 years of age or under, while 68% were over 19 years. Tumor diameter values ranged from 3 to 18 cm with a mean of 6.97 ± 5.1 . SUV_{max} ranged from 3 to 45 with a mean of 12.46 ± 8.12 .

Of the patients, 61.8% had pathological type of osteosarcoma, 32.4% had Ewing sarcoma, and 5.8% had chondrosarcoma. Tumor sites were located in the lower extremity in 24 patients (72.9%), in the upper extremity in five patients (14.5%), in the vertebrae in three patients (8.8%), in the trunk in one patient (3%) and in the cranium in one patient (3%). Of the 34 patients, 41.1% were progressive, 32.4% were in remission, 8.8% were in partial regression, 14.7% were local recurrence and 3% were stable.

Follow-up times ranged from 6 to 73 months with a mean of 33 ± 21 .

Distant metastases were present in 14 cases (41.1%), lungs being the most common (Figure 1). Mean tumor diameter of the progressive group was statistically significantly higher than the non-progressive group ($p < 0.05$). The mean SUV_{max} of the progressive group was statistically significantly higher than the non-progressive group ($p < 0.05$). There was no statistically significant relationship between progression and age and gender ($p > 0.05$).

In progressive patients, the rate of tumor placement at lower extremity (70.7%) was statistically significantly higher than the non-progressive group ($p < 0.05$). The rate of distant metastases (82.1%) in the progressive group was statistically significantly higher than the non-progressive group ($p < 0.05$).

In cases with bone sarcoma, ROC curve was drawn for SUV_{max} in case of progression (Figure 2). The area under the curve was 0.782 and the standard error was 0.09. The area under the ROC curve was significantly higher than 0.5 ($p < 0.05$). The cut-off point for SUV_{max} in the definition of progression was 8. Sensitivity of

TABLE I

Patients characteristics

	Progression (+)				Progression (-)				p
	n	%	Mean±SD	Median	n	%	Mean±SD	Median	
Tumor diameter (cm)			7.79±4.81				5.0±4.3		0.030*†
SUV_{max}			13.9±9.5	11.5			9.7±6.6	7	0.020*‡
Age (year)									0.332§
≤19	7	17.9			6	30			
>19	32	82.1			14	70			
Gender									1.000¶
Male	15	71.4			9	69			
Female	6	28.6			4	31			
Tumor location									
Lower extremity	18	85.7			6	46.3			0.021*
Upper extremity	2	9.5			3	23			
Cranium	0	0			0	0			
Rib	1	4.8			1	7.7			
Vertebrae	0	0			3	23			
Distant metastases									0.000*¶
Positive	32	82.1			0	0			
Negative	7	17.9			20	100			
Local recurrence									
Positive	5	12.8			0	0			0.156§
Negative	34	87.2			20	100			

SD: Standard deviation; SUV_{max} : Maximum standardized uptake value† Student t test; ‡ Mann-Whitney U test; § Fisher's exact test; ¶ Continuity (Yates) correction; || Fisher-Freeman Halton test; * $p < 0.05$.

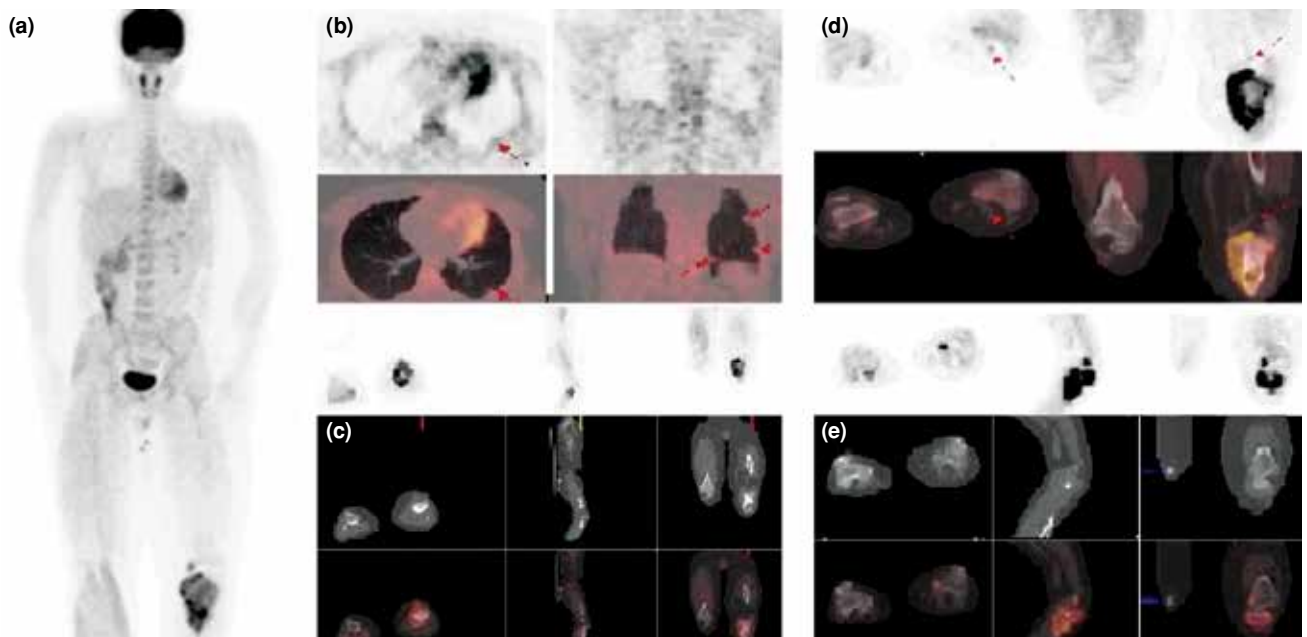


Figure 1. ¹⁸F-fluoro-2-deoxyglucose positron emission tomography/computed tomography was applied to a 17-year-old male patient with conventional type osteosarcoma of left tibia diagnosed by incisional biopsy. **(a)** Maximum intensity projection images showed increased fluoro-2-deoxyglucose uptake in proximal left tibia and distal medial femur. **(b)** ¹⁸F-fluoro-2-deoxyglucose positron emission tomography/computed tomography images showed multiple metastatic nodular lesions with minimal ¹⁸fluoro-2-deoxyglucose uptake in both lung parenchymas (maximum standardized uptake value: 3.7). **(c)** An irregular bordered mass lesion with a soft tissue component of 100×83 mm in size with intense increased activity (maximum standardized uptake value: 12.3) is seen in left tibial proximal diaphyseal and metaphyseal area. **(d)** A nodular lesion showing focal increased ¹⁸fluoro-2-deoxyglucose involvement was observed in left popliteal fossa resembling a lymph node. **(e)** Focal increased ¹⁸fluoro-2-deoxyglucose uptake was also observed in medial condyle of left femur (maximum standardized uptake value: 8.8).

this value was 90%, specificity was 71.4%, positive predictive value was 81.8% and negative predictive value was 82.4%.

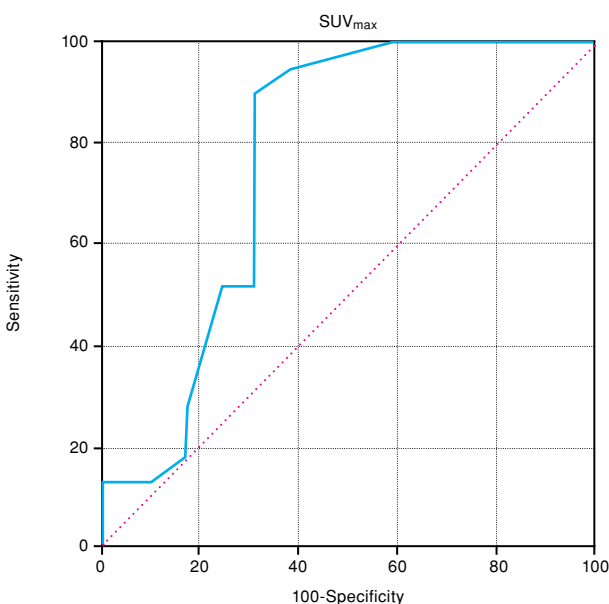


Figure 2. Receiver operating characteristic curve was drawn for maximum standardized uptake value in case of progression. SUV_{max}: Maximum standardized uptake value.

Of the 34 patients included in the survival analysis, mortality rate was 14.7% (n=5). Mean survival time was 62.1±4.4 months and median duration was 72 months (Figure 3). The cumulative survival rates of one year, three years, and five years were 87±0.05%, 74±0.08%, and 67±0.09%, respectively. The cumulative survival rate was 79.1±0.08%.

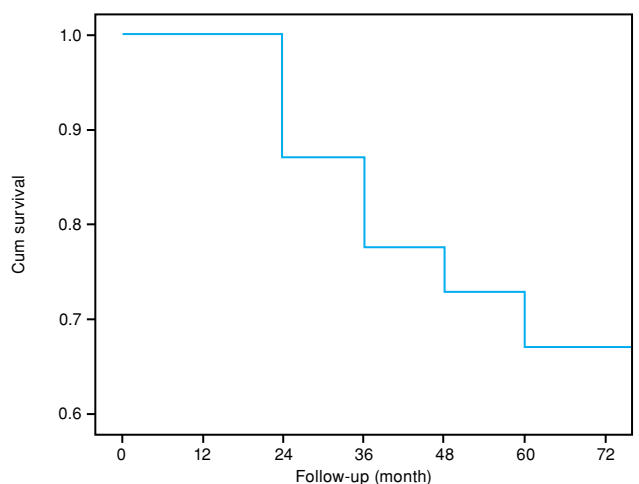


Figure 3. Survival analysis for all patients.

DISCUSSION

The importance of ^{18}F FDG-PET/CT in cancer management has been established due to its great value in detection, tumor staging and grading, local or distant recurrence detection and follow-up management.^[9] The easily-readable SUV_{max} , which reflects the highest metabolic activity, is currently the most applied parameter in clinical practice. Eary et al.^[10] were the first to suggest that SUV_{max} is a statistically significant independent predictor of sarcoma patient survival and tumors with higher SUV_{max} had significantly poorer prognosis.

Recent studies supported that baseline SUV_{max} using ^{18}F FDG-PET/CT demonstrates independent properties beyond histologic grading for prediction of survival. Andersen et al.^[11] reported a cut-off point of 9, whereas Hwang et al.^[7] and Skamene et al.^[12] revealed cut-off points of 5.8 and 10.3, respectively. In our study, findings were consistent with the literature stating that higher SUV_{max} has significantly poor survival outcomes in sarcoma patients. High SUV_{max} was associated with worse bone sarcoma, using a cut off-point of 8, a strong correlation was found between SUV and bone sarcoma.

In the literature, the five-year overall survival rate for bone sarcoma is 63.6%.^[13] In our study, we concluded that five-year survival rate for bone sarcoma is $79 \pm 0.08\%$.

This retrospective study has several limitations that warrant consideration.^[8] A major limitation was the relatively small number of patients included. Secondly, the patient group was heterogeneous, containing both adult and pediatric patients. Thirdly, the study was inherently limited by its retrospective design. And finally, we only analyzed patients in a single institution.

In conclusion, semi-quantitative estimation of primary tumor metabolic activity in terms of baseline SUV_{max} using ^{18}F FDG-PET/CT can predict the overall survival of patients with bone sarcoma. The predictive efficacy of SUV_{max} in diverse clinical settings should be validated in future studies.

Declaration of conflicting interests

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