

Research Paper

# $^{18}\text{F}$ -FDG PET/CT as an Indicator of Survival in Ewing Sarcoma of Bone

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## Abstract

**Objective:** The existing literature of  $^{18}\text{F}$ -FDG PET/CT in Ewing sarcoma investigates mixed populations of patients with both soft tissue and bone primary tumors. The aim of our study was to evaluate whether the maximum standardized uptake value (SUV<sub>max</sub>) obtained with  $^{18}\text{F}$ -FDG PET/CT before and after induction chemotherapy can be used as an indicator of survival in patients with Ewing sarcoma originating exclusively in the skeleton.

**Materials and Methods:** A retrospective database search from 2004-2011 identified 28 patients who underwent  $^{18}\text{F}$ -FDG PET/CT before (SUV<sub>1</sub>, n= 28) and after (SUV<sub>2</sub>, n=23) induction chemotherapy. Mean follow up was 3.3 years and median follow up for survivors was 6.3 years (range: 2.6-9.8 years). Multivariate and univariate Cox proportional hazard model was used to assess for correlation of SUV<sub>1</sub>, SUV<sub>2</sub>, and the change in SUV<sub>max</sub> with overall survival (OS) and progression-free survival (PFS).

**Results:** Mean SUV<sub>max</sub> was 10.74 before (SUV<sub>1</sub>) and after 4.11 (SUV<sub>2</sub>) induction chemotherapy. High SUV<sub>1</sub> (HR = 1.05, 95% CI: 1.0-1.1, P = 0.01) and SUV<sub>2</sub> (HR = 1.2, 95% CI: 1.0-1.4, P = 0.01) were associated with worse OS. A cut off point of 11.6 was identified for SUV<sub>1</sub>. SUV<sub>1</sub> higher than 11.6 had significantly worse OS (HR = 5.71, 95% CI: 1.85 – 17.61, P = 0.003) and PFS (HR = 3.16, 95% CI: 1.13 – 8.79, P = 0.03, P < 0.05 is significant).

**Conclusion:**  $^{18}\text{F}$ -FDG PET/CT can be used as a prognostic indicator for survival in primary Ewing sarcoma of bone.

Key words: Ewing sarcoma; FDG PET/CT; SUV; Overall survival; Progression free survival.

## Introduction

Ewing sarcoma (ES) represents 2% of cancers in children and the adolescent population, being the second most common bone malignancy after osteosarcoma [1, 2]. It accounts for 6-8% of all primary malignant bone tumors in the general population [3, 4]. About 225 new cases are reported annually in the United States [5]. Ewing sarcoma has a predilection for males with a male to female ratio of 6:4 [3, 6]. The incidence of Ewing sarcoma shows distinct racial variation affecting Caucasians 9 times more

commonly than African Americans [6, 7]. Several prognostic factors that adversely affect patient survival have been reported such as the presence of metastases at presentation, large size of the primary tumor (volume larger than 100 ml [8], and 150 ml [9]), and poor response to chemotherapy [8-10]. Tumor response to chemotherapy is widely considered an important prognostic factor, which correlates with both local tumor recurrence and patient survival [9-11]. However, chemotherapeutic response cannot

be always easily assessed, especially in tumors arising from bone. A common method used to evaluate the response is the histo-pathological analysis of the degree of tumor necrosis after surgical resection of the primary tumor. However, this cannot be assessed in patients managed without surgery. A way to evaluate response before or in the absence of surgery is by assessing tumor metabolism using 18F-FDG PET/CT (18 F-FDG PET/CT will be referred to as PET/CT) [10]. Although PET/CT has an established role in the staging of malignancies in general and ES in particular [12-17], few reports have investigated for a relationship between FDG uptake and patient survival in ES [18-22]. The majority of prior investigators have studied mixed populations of patients with tumors arising in both soft tissue and bone. The aim of our study was to evaluate whether PET/CT using the maximum standardized uptake value (SUVmax) before (SUV1) and after (SUV2) induction chemotherapy can be used as an indicator of survival in a population of patients with ES originating in bone and not in soft tissue.

## Materials and Methods

### Patient population

After obtaining IRB approval, a retrospective database search was performed from 2004 - 2011 for patients with primary ES of bone. Patients with soft tissue primary tumors were excluded. In addition, we excluded all the patients who did not have histologic confirmation of ES, had PET/CT performed at a different institution, were alive with < 2.5 years of follow-up, or received any treatment before the initial PET/CT scan.

Patient age, gender, the tumor location, and disease stage were recorded. We analyzed the pre- and post-induction chemotherapy PET/CT and measured the SUVmax, and percent change. The measurements were calculated separately by 2

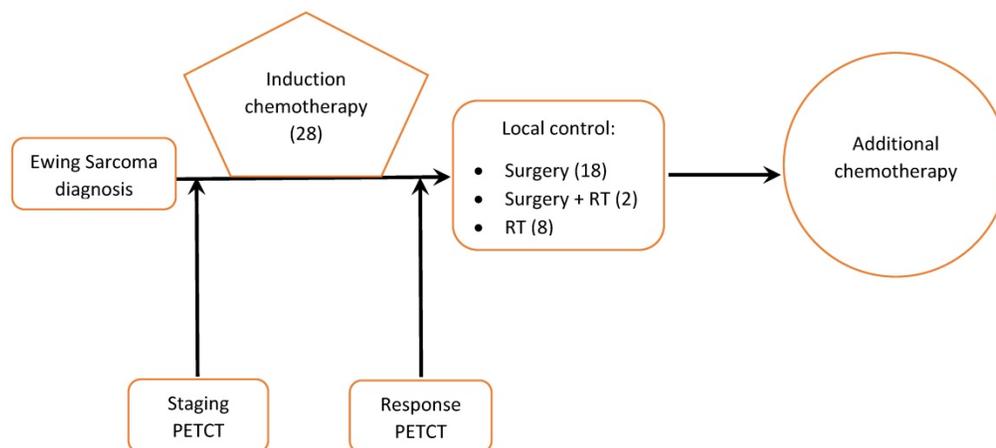
physicians with 6 and 9 years of experience in PET/CT interpretation. No consensus readings were performed. In case of discrepancy between the 2 readers, a musculoskeletal radiologist with 8 years of experience in PET/CT interpretation was used as a tie breaker. Discrepancy was defined by  $\geq 1$  unit difference in SUVmax between reader 1 and 2.

The starting date of induction chemotherapy, the dates of radiation therapy, and the date of surgery (when applicable) were recorded in addition to the date and site of any disease relapse or progression (local or distant disease). The date of the last available follow up for all patients was recorded. If the patient died, we investigated whether it was cancer-related and recorded the date of death. SUV1, SUV2 and percent change were assessed for a relationship with overall survival (OS) and progression free survival (PFS).

Treatment consisted of cycles of multi-agent chemotherapy given prior to local tumor treatment (induction phase) followed by additional cycles of chemotherapy, surgery, radiation, or both for local tumor control (Figure 1).

### PET/CT

The initial PET/CT was performed on chemotherapy-naïve patients prior to the start of therapy. A second PET/CT was performed after the completion of the induction chemotherapy and prior to local tumor control. Integrated PET/CT systems were utilized to acquire imaging data (Discovery ST, STe, or RX, General Electric Medical Systems, Milwaukee, WI). Whole-body examinations were performed from the level of the vertex of the skull or orbits through the upper thighs or lower legs/toes depending on the location of the primary tumor. All patients were fasted for a minimum of 6 hours prior to study, with fasting blood glucose less than 150 mg/dl prior to intravenous administration of FDG. PET scans were obtained in either 2D or 3D mode, with 15



**Figure 1.** Management of Ewing sarcoma patients at our institution (number of patients in brackets)

-20 mCi FDG administered for 2D scans and 7-12 mCi for 3D scans in adults (a dose of 0.1 mCi/kg was used for children up to 100kg), and images were obtained approximately 60 minutes after radiopharmaceutical administration. Unenhanced CT was used for attenuation correction and diagnosis and included 3.75 mm axial slice placement, 140 kV, 120 mA at 13.5 mm table speed.

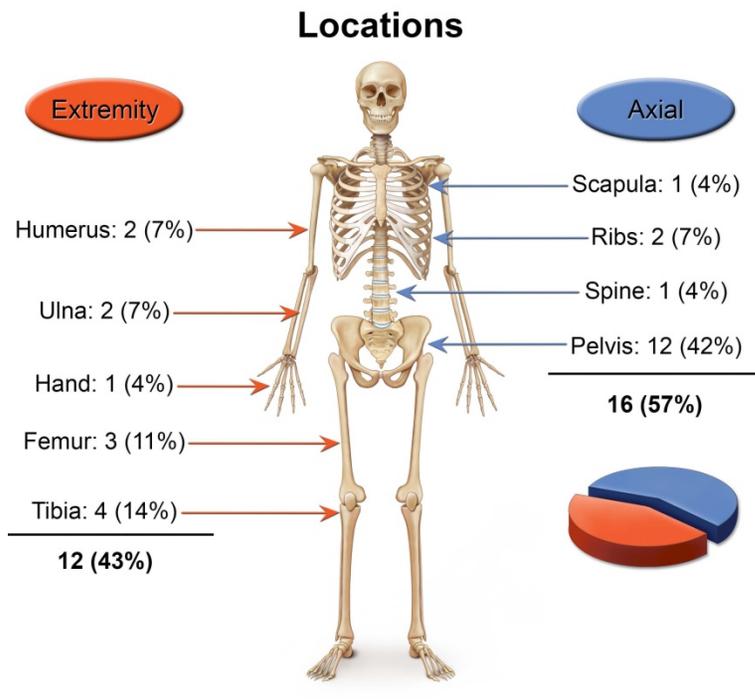
**Statistical analyses**

Univariate Cox proportional hazard model was used to assess effects of SUV1, SUV2, and the change of SUVmax on overall survival (OS) and progression-free survival (PFS). Survival was calculated from the induction chemotherapy start date (for SUV1 analyses) or post-induction chemotherapy PET/CT date (for SUV2 and SUVmax change analyses) to the date of death from any cause or the date of last patient contact for survivors. PFS was defined as the time interval from the induction chemotherapy start date to date of disease relapse/progression or death or to the date of the last patient contact for patients without events. SUVmax were modeled in both continuous and dichotomized form. Recursive partitioning analysis (RPA) was used to identify the optimal cutoff points of SUVs for survival endpoints. Recursive partitioning is used for multivariable analysis where a decision tree classifies members of the population by splitting it into more homogenous sub-populations based on several dichotomous independent variables. Each sub-population may be split an indefinite number of

times (recursive) until the splitting process terminates after a particular stopping criterion is reached [23]. A backwards elimination procedure was used to identify multivariate Cox proportional hazard models for OS and PFS. The ShROUT and Fleiss method was used to calculate intraclass correlation coefficient (ICC) between the two radiologists who independently measured the SUV values of each patient [24, 25]. All tests were two-sided and p-values of 0.05 or less were considered statistically significant. Statistical analysis was carried out using SAS version 9 (SAS Institute, Cary, NC).

**Results**

Twenty-eight patients met our inclusion criteria. Mean follow up was 3.3 years and median follow up for survivors was 6.3 years (range: 2.6-9.8 years). Nine patients had metastatic disease at presentation. Pre-induction chemotherapy PET/CT was available for all patients. Post-induction chemotherapy PET/CT was available for 23 patients. The remaining 5 patients underwent surgery without undergoing post treatment PET/CT. Ten patients received adjuvant radiation to the primary tumor, either at the end of chemotherapy (8 patients) or before surgery (2 patients). No patient received radiation therapy before chemotherapy and all radiation therapy was administered after the second PET/CT scan. Surgical resection of the primary tumor was performed in 20 patients (Figure 1).



**Figure 2.** Locations of the primary tumor

The age of patients at the time of presentation ranged between 4 and 28 years with a mean of 17.4 years and median of 18 years. There were 19 male and 9 female patients. The majority of the tumors originated in the pelvis (Figure 2).

Thirteen of the 28 patients (46%) remained disease-free. The remaining 15 patients had disease relapse or progression (Table 1). Of the 15 patients who had disease relapse or progression, 13 patients died: 12 patients died of disease, and 1 succumbed to treatment-related acute myeloid leukemia.

**Table 1.** Clinical outcome of 28 patients with Ewing sarcoma of bone

Variable	No. of Patients (%)
<b>Disease free</b>	13 (46)
<b>Relapse/Progression</b>	15 (54)
Local	3 (11)
Nodal	1 (4)
Local + bone	1 (4)
Distant	10 (36)
<b>Life status at last follow up</b>	
Alive	15 (54)
Dead	13 (46)
Alive with disease progression	2 (7)
<b>Cause of death</b>	
ES*	12 (92)
Treatment related	1 (8)

\*ES: Ewing sarcoma

We found a significant relationship between the SUVmax and patient survival as a continuous variable (Tables 2 and 3). The higher the SUV1 and SUV2, the worse the prognosis. A high SUV1 was associated with worse OS (1 unit increase HR = 1.05, 95% CI: 1.0-1.1, P = 0.01) and a high SUV2 was associated with worse OS (1 unit increase HR = 1.2, 95% CI: 1.0-1.4, P = 0.01). The change in SUVmax values after receiving induction chemotherapy was not significantly

associated with OS. No correlation to PFS was initially found.

Using recursive partitioning analysis (RPA), we identified an optimal SUV1 cutoff value of 11.6, which correlated with both OS and PFS. Patients with SUV1 higher than 11.6 had significantly worse OS (HR = 5.71, 95% CI: 1.85 - 17.61, P = 0.003) and PFS (HR = 3.16, 95% CI: 1.13 - 8.79, P = 0.03) compared to those with lower SUV1 (Figure 3). No significant SUV2 cutoff value was identified.

No correlation was found between gender, age, tumor location and survival (Table 4). When the same factors were analyzed with SUV1, we found that patients who had SUV1 higher than 11.6 were significantly older than those with lower SUV1 (P = 0.008). Multivariate analysis showed that high SUV1 was significantly associated with worse OS after adjusting for age effect (P=0.02).

**Table 2.** Summary of SUVmax

	N	Mean	Min	Median	Max
SUV1*	28	10.74	2.20	8.95	63.90
SUV2^	23	4.11	1.60	3.20	16.60
SUV Change (%) = 100 x (SUV2 - SUV1) / SUV1	23	-60.33	-80.37	-61.98	-9.09

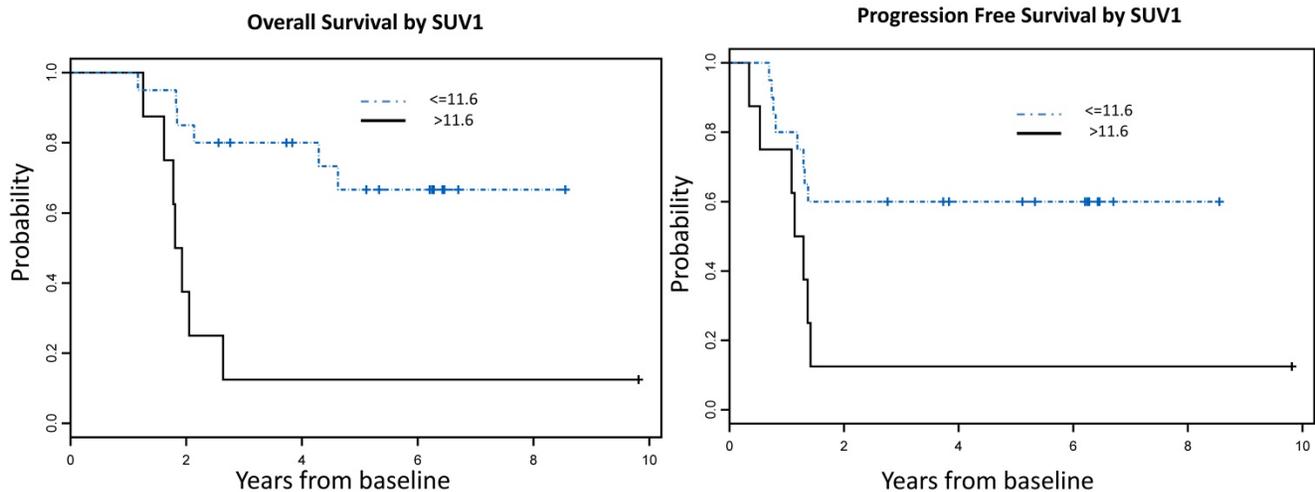
\*SUV1: Standard uptake value before induction chemotherapy; ^SUV2: Standard uptake value after induction chemotherapy

**Table 3.** Summary of univariate Cox proportional hazard model for overall survival (OS)

Variable*	Hazard Ratio^	95% Hazard Ratio Confidence Limits	P-value	Sample Size
SUV1	1.05	1.01 1.09	0.01	28
SUV2	1.21	1.05 1.41	0.01	23
Change in SUVmax	0.98	0.95 1.02	0.43	23

\*SUV values were modeled as continuous variables

^Hazard ratio higher than 1 means worse prognosis



**Figure 3.** SUVmax cutoff values associated with OS and PFS **A:** Overall Survival Probability: Patients with SUVmax >11.6 had significantly worse OS [7 events (deaths) in total number of 8 patients] compared to those with lower SUVmax [6 events (deaths) in total number of 20 patients], (HR = 5.71, 95% CI: 1.85 - 17.61, P = 0.003) **B:** Progression Free Survival Probability: Patients with SUVmax >11.6 had significantly worse PFS [7 events (deaths or progression) in a total number of 8 patients] compared to those with lower SUVmax [8 events (deaths or progression) in a total number of 20 patients], (HR = 3.16, 95% CI: 1.13 - 8.79, P = 0.03)

**Table 4.** Summary of univariate Cox proportional hazard model results by endpoint. Patients with baseline SUVmax higher than 11.55 had significantly worse OS compared to those with lower SUVmax (HR = 5.71, 95% CI: 1.85 – 17.61, P = 0.003). No significant cut-off value was identified for SUV2.

Endpoint	Factor	Comparison	Hazard Ratio	95% LCL	95% UCL	P-value	# Events	# Censored	# Total
OS	Gender	Female vs. Male	0.63	0.17	2.28	0.48	13	15	28
	Mets	No vs. Yes	0.45	0.15	1.35	0.15	13	15	28
	SUV1	>11.55 vs. ≤11.55	5.71	1.85	17.61	0.003	13	15	28
	SUV2	>3.35 vs. ≤3.35	2.90	0.84	9.94	0.09	11	12	23
	SUVmax %change	>-60.45 vs. ≤-60.45	0.49	0.13	1.85	0.29	11	12	23
	Tumor necrosis	>=90% vs. <90%	1.00	0.19	5.21	>0.99	7	13	20
	Age	1 year increase	1.08	0.98	1.19	0.14	13	15	28
	Location	Axial vs Extremity	2.96	0.81	10.77	0.10	13	15	28
	PFS	Gender	Female vs. Male	0.62	0.20	1.96	0.42	15	13
Mets		No vs. Yes	0.71	0.25	2.00	0.51	15	13	28
SUV1		>11.55 vs. ≤11.55	3.16	1.13	8.79	0.03	15	13	28
SUV2		>3.35 vs. ≤3.35	3.06	0.89	10.55	0.08	11	12	23
SUVmax %change		>-60.45 vs. ≤-60.45	0.50	0.13	1.87	0.30	11	12	23
Tumor necrosis		>=90% vs. <90%	1.39	0.15	12.43	0.77	5	12	17
Age		1 year increase	1.04	0.96	1.14	0.34	15	13	28
Location		Axial vs Extremity	2.77	0.76	10.09	0.12	13	15	28

## Discussion

Our results indicate that PET/CT, using the SUVmax value before and after induction chemotherapy, can be used to predict survival in patients with ES of bone. High SUV1 was associated with worse OS (P = 0.01), and high SUV2 was also associated with worse OS (P = 0.01). Using a cut-point of 11.6, a strong correlation was found between SUV1 and OS (P = 0.003). The correlation to PFS was not as strong but was also significant (P = 0.03). No correlation to PFS was initially found, suggesting that PET/CT may be more effective at predicting OS than PFS in ES of bone.

Newly diagnosed patients with ES may undergo PET/CT for initial staging and assessment of tumor burden. After induction chemotherapy, the patient may undergo a subsequent PET/CT to assess for response [26]. PET/CT has been used to evaluate chemotherapeutic response for many tumors such as gastrointestinal stromal tumor (GIST), esophageal cancer, breast cancer and soft tissue sarcomas [15, 27-29]. Studies have also showed its utility for assessing response to radiation therapy in patients with head and neck cancers [30], lung [31] and rectal cancers [32]. Furthermore, it has been used to predict survival, such as in patients with lymphoma and osteosarcoma [33-36].

Few publications address the role of PET/CT to evaluate chemotherapeutic response [16, 17, 37-40] or predict survival in patients with ES [18-22]. This is one of the first and largest studies to evaluate a population of patients with ES originating exclusively in the skeleton. In the literature, most previous investigators have evaluated small heterogeneous cohorts of patients with the “Ewing sarcoma family of tumors” arising in skeletal and extraskeletal sites (Table 5). A prior study of a mixed population of soft tissue and

bone primary ES by Hawkins *et al.* [18], found a significant correlation between SUV2 and outcome, showing improved PFS with SUV2 < 2.5. A more recent mixed population study by Raciborska *et al.* [19], found similar results between SUV2 and improved OS. A study of primary skeletal tumors by Palmerini *et al.* [22], found a significant correlation between SUV1 < 6 and improved PFS in ES, which also supports our results. A summary of the published studies with survival analysis is presented in Table 5. These studies variously demonstrate that PET/CT performed before or after therapy correlates with patient survival.

In our study, we found a significant correlation between SUV1, SUV2 and OS. However, the reduction in SUVmax between the 2 scans was not significantly associated with OS or PFS, which is similar to the results of prior reports [18, 19]. Of the 12 patients who had disease relapse or progression, 8 patients had a marked reduction in SUVmax, ranging from 61% to 80%. In addition, 6 patients had a reduction of SUV2 close to the background muscle activity, ranging from 1.6-3.5, and still had disease relapse/progression.

Our cutoff point for SUV1 was 11.6. We did not find a cutoff point for SUV2 that significantly separated patients with respect to survival, possibly due to the continuum effect of SUV2 on survival. In addition, the lack SUV2 data on 5 patients, who underwent surgery without undergoing post treatment PET/CT, decreased the SUV2 data available for analysis, which may have also contributed to our inability to find a significant correlation between SUV2 and PFS. Our results suggest that the metabolic state of the tumor before treatment may be more indicative of outcome than the post-therapeutic SUV value in patients with primary ES of bone.

**Table 5.** Summary of the published reports investigating PET and/or PETCT in ES and/or ES family if tumors (ESFT) and survival.

Reference	Modality	Tumor site	Single or multi-institution	No. Of patients	Study aim	Results
Hawkins <i>et al.</i> 2005 [18]	PET	Bone and soft tissue	Single	36	Determine the prognostic value of PET response for outcome	1. SUV2** < 2.5 correlated with improved PFS <sup>o</sup> (P=0.01) 2. SUV2:1 was not predictive of PFS <sup>o</sup>
Hyun <i>et al.</i> 2016 [21]	PET	Bone and soft tissue	Multi	115	Determine the prognostic value of PET for monitoring specific therapy (monoclonal antibody to IGF-1R <sup>a</sup> antibody) using SUV corrected for lean body mass (SUL).	1. Progressive metabolic disease on SUV2** correlated with ↑ risk of death. 2. %SULpeak <sup>β</sup> decrease <10.5% (by 9 d after therapy) showed shorter OS <sup>§</sup> (median, 5.5 m; 95% CI <sup>^</sup> , 4.2–6.8 m) than patients with a decrease ≥10.5% (median, 11.7 m; 95% CI, 8.9–18.1 m). P<0.001
Raciborska <i>et al.</i> 2016 [19]	PET/CT	ES (not reported if bone only)	Multi	50	Determine the value of PET/CT to predict response to chemotherapy	1. SUV1 was lower in patients with good histological response (3.8 vs 7.2), P = 0.02 2. SUV2 was higher in patients with disease progression (2.3 vs 1.5), P = 0.04 3. SUV2 ≤ 2.5 was associated with improved OS, P = 0.0004 and PFS P = 0.005 (univariate analysis).
Hwang <i>et al.</i> 2016 [20]	PET/CT	ES <sup>ε</sup> (bone and soft tissue)	Not reported	34	Determine the prognostic value of pre-therapeutic PET/CT.	SUV1* ≤ 5.8 correlated with longer OS <sup>§</sup> , P = 0.002 2. Higher SUV1 (P = 0.003), older age (P = 0.023), and higher stage (P = 0.03) were associated with worse OS <sup>§</sup> .
Palmerini <i>et al.</i> 2016 [22]	PET/CT	ES <sup>ε</sup> and OST <sup>δ</sup> of bone	Single	45 ES <sup>ε</sup> and 32 OST <sup>δ</sup>	Determine the prognostic role of pre-therapeutic PET/CT	1. Tumor necrosis ≥ 90% was 30 % in patients with high (≥ 6) SUV1 and 72 % with low (< 6) SUV1 (p = 0.0004). 2. The 3-year EFS <sup>γ</sup> was 37 % with high SUV1 and 75 % with low SUV1 (P = 0.004).

<sup>o</sup>PFS: Progression free survival; <sup>§</sup>OS: Overall Survival; <sup>a</sup>IGF-1R: Insulin-like growth factor 1 receptor; <sup>β</sup>SUL: Standardized uptake value (SUV) normalized by lean body mass; <sup>\*</sup>SUV1: Standard uptake value before induction chemotherapy; <sup>\*\*</sup>SUV2: Standard uptake value after induction chemotherapy; <sup>^</sup>CI: Confidence interval; <sup>ε</sup>ES: Ewing sarcoma; <sup>δ</sup>OST: Osteosarcoma; <sup>γ</sup>EFS: Event free survival

Our study has several advantages when compared to prior reports. This is one of the first studies of a population of ES arising exclusively in the skeleton to correlate metabolic uptake on PET/CT with survival. We focused only on ES of bone, excluding extra-skeletal Ewing and primitive neuroectodermal tumors. All of our examinations were performed with dual modality PET/CT scanners, not PET only or separate parallel PET and CT scanners. PET/CT has been shown to have significant advantages when compared to PET alone [41]. PET/CT showed better lesion detection and improved tumor localization than PET-only scans, as is reflected in its superior sensitivity, specificity, accuracy, positive predictive value, and negative predictive value in a study of 53 patients with ES [12].

Limitations of our study include small sample size, lack of SUV2 data on 5 patients and a referral bias toward more severe and advanced cases. Furthermore, our study is retrospective and contains a combined population of pediatric and adult patients who received varied therapeutic regimens. Although a known prognostic factor, we did not find a significant correlation between the presence or absence of metastases at presentation and survival. This lack of significance is likely due to our small sample size, and the unequal number of patients presenting with metastases versus without metastases (9 metastatic versus 19 non-metastatic). Our results verify those of other investigators with respect to older patient age and worse outcome [5, 20]. Future work is needed to assess for a difference in the

relationship between FDG uptake and prognosis in pediatric and adult patients with Ewing sarcoma.

## Conclusion

Our study indicates that a high SUVmax on pre-therapeutic and post-therapeutic FDG PET/CT scans correlates with OS, and that a pre-therapeutic SUVmax > 11.6 is associated with worse OS and PFS in patients with ES originating in bone. Future prospective studies including larger numbers of patients are needed to confirm these results.

## Abbreviations

ES: Ewing sarcoma; OS: overall survival; PFS: progression free survival

## Informed consent

IRB Waiver of informed consent

## Competing Interests

Our third co-author is a consultant for Sage Health Management Solutions.

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