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Value of 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) in assessment of response to preoperative chemotherapy in pediatric sarcoma

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Abstract

Background: The aim of this retrospective study was to highlight the role of FDG PET/CT in the assessment of tumor response to preoperative chemotherapy in pediatric sarcoma. Eighteen patients were included in our study: 13 patients were males and 5 were females ranging between 1 and 18 years with a mean age of 13.3 years. The patients had pathologically proven osseous or soft tissue sarcoma. All patients underwent sequential 18F-FDG PET/CT before (PET-CT1) and after (PET-CT2) neoadjuvant chemotherapy. Maximum standardized uptake value (SUVmax) was measured in the primary lesion on PET/CT1 (SUV1) and PET/CT2 (SUV2). After surgery, the effects of neoadjuvant chemotherapy were evaluated histopathologically: $\geq 90\%$ necrosis indicated was considered a good response and $< 90\%$ necrosis was considered a poor response. The correlation between SUV2 and the histologic response was assessed.

Results: The sensitivity, specificity, positive predictive value, and negative predictive value of SUV2 for assessment of treatment response were 100%, 91.67%, 85.71%, and 100%, respectively. The overall accuracy was found to be 98.3%.

Conclusions: 18F-FDG PET/CT provides a reliable non-invasive diagnostic tool in assessment of response to preoperative chemotherapy in pediatric sarcoma.

Keywords: PET/CT, Sarcoma, Chemotherapy

Background

Pediatric sarcomas differ according to histologic subtype, but as a whole, represent about 13% of all pediatric malignancies [1].

The most common are soft tissue sarcomas. Soft tissue sarcomas have wide range according to genetic makeup, have more than 50 histologic subtypes, and are often associated with differing clinical and prognostic features [2]. These tumors, which arise in the soft tissues namely muscle, fat, blood vessels, nerves, tendons, or synovium,

include embryonal rhabdomyosarcoma in children, synovial sarcoma in young adults, and high-grade pleomorphic sarcoma, liposarcoma, and leiomyosarcoma in adults. The extremities (most common in the thigh) are the most common location. Few otherwise can occur in the chest wall and retroperitoneum [1].

On the other hand, the most common primary malignant bone tumors in pediatric age are osteosarcoma and Ewing sarcoma [3]. Osteosarcoma originates from primitive bone-forming mesenchymal stem cells and mainly occurs in the metaphyseal portion of the long bones [4]. Ewing sarcoma equally originates from the axial and the appendicular skeleton [5].

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Standard preoperative treatment of bone sarcomas and some subtypes or stages of soft tissue sarcoma includes chemotherapy. A timely noninvasive evaluation of response to chemotherapy is recommended to improve patient management and to avoid unnecessary toxicity and costs. Sarcomas can also be adequately controlled with surgical excision and adjuvant radiotherapy [6].

Anatomic imaging alone is not accurate enough for evaluation of bone and soft tissue tumors after the end of treatment, the sequel to posttreatment changes, including dysmorphic normal anatomy, disruption of normal tissue planes, and metal artifacts [7].

Evaluation of response by size-based criteria as defined in the response evaluation criteria in solid tumors (RECIST) criteria has its limitations and is of questionable value in the response evaluation of sarcomas [8].

Sarcomas are histologically heterogeneous tumors that vary in growth rate and contain a large volume of non-malignant cells or extracellular material. For example, in slowly growing sarcomas, a slow progression during chemotherapy may be misinterpreted as a stable disease and thus a response to chemotherapy by CT, as the tumor volume has hardly changed in the interval between two studies. The volumes of nonmalignant material in the tumor, or the replacement of malignant parts by fibrous material, can form the rest mass after chemotherapy. Therefore, the response to chemotherapy does not necessarily include a reduction of the size of the tumor [9, 10].

Percentage necrosis is prognostic in bone sarcomas, in Ewing sarcoma, 5-year disease-free survival (DFS) was 95% in good responders whereas 34% in poor responders [11]. After neoadjuvant chemotherapy for osteosarcoma, patients with < 10% viable tumor or $\geq 90\%$ tumor necrosis at the time of surgical excision are classified as “good responders” [12].

Furthermore, a high SUVmax following neoadjuvant chemotherapy commonly associated with a worse prognosis [13], whereas low SUVmax after neoadjuvant chemotherapy was shown to correlate with an improved progression-free survival (PFS) [14].

It was also suggested that complete metabolic response (CMR) in patients with rhabdomyosarcoma following neoadjuvant chemotherapy and radiation therapy is associated with an improved local relapse-free survival [15].

The histologic response following neoadjuvant chemotherapy was used by several investigators to guide the selection of alternative postoperative chemotherapy in an attempt to improve event-free survival (EFS) [16].

Fluorodeoxyglucose (FDG)-PET/computed tomography (CT) is an imaging modality, which includes both anatomic localization by CT and functional characterization using PET imaging and which has an emerging role in the assessment of sarcomas [17].

And so, FDG-PET/CT imaging is a noninvasive modality for restaging and assessment of treatment response of patients after sarcoma treatment and has been found to have a profound effect on overall prognosis [18].

The aim of this retrospective study was to highlight the role of FDG PET/CT in the assessment of therapy response in pediatric sarcoma.

Material and methods

Eighteen patients in the pediatric age group were included in this retrospective study. The patients had pathologically proven osseous or soft tissue sarcoma, who were evaluated for degree of response to chemotherapy in the immediate preoperative period. None of our cases underwent surgery before completion of therapy. All the patients were subjected to thorough history taking, clinical examination, and F18-FDG PET/CT.

F18-FDG PET/CT study was done twice, one before administration of chemotherapy (SUV1) and one after finishing chemotherapy just before surgery (SUV2) using a dedicated PET/CT scanner (Biograph, True-Point; Siemens). The study was done about 4–6 weeks after the last cycle of chemotherapy. Fortunately, all the examined cases were nondiabetics, so there was no need for specific radiotracer dose adjustment.

This machine integrated a PET scanner with a dual-section helical CT scanner (40 slice Emotion; Siemens), and this allows the acquisition of co-registered CT and PET images in one session.

The CT protocol included the acquisition of a low-dose CT scan (26 mAs, 120 kV, 0.5 s per rotation, 5-mm slice thickness) from the skull base to the mid-thigh or to the toes, depending on the location of the sarcoma. CT data were used for attenuation correction, characterization, and adequate anatomic localization of PET lesions. The PET scan was performed directly after CT data acquisition.

All patients fasted for at least 4 h before the injection of 0.22 mCi/kg body weight of FDG. Blood glucose levels did not exceed 150 mg/dL. Scanning started 60–90 min after the injection of the tracer. Patients sat quietly in a dimly lit room during the uptake phase. Patients were asked to void just prior to image acquisition. The CT and PET scans were obtained with the patient in a quiet respiration. Patients were allowed to drink water during the uptake period. They were instructed to avoid any kind of strenuous activity 24 h prior to the examination to avoid physiologic muscle FDG uptake. Intravenous contrast agent was administered in some patients.

Patients were examined in the supine position with an elevation of arms. CT scanning was started. The CT study took about 60–70 s. PET scans over the same

Table 1 Distribution of the studied cases according to different parameters ($n = 18$)

	No. (%)
Sex	
Male	13 (72.2%)
Female	5 (27.8%)
Age (years)	
< 15	9 (50.0%)
≥ 15	9 (50.0%)
Median (Min.–Max.)	15.0 (1.0–18.0)
Mean ± SD	13.33 ± 5.10
1ry site	
Femur	3 (16.7%)
Head and neck	3 (16.7%)
Humerus	2 (11.1%)
Fibula	2 (11.1%)
Urinary bladder	2 (11.1%)
Iliac bone	2 (11.1%)
Tibia	2 (11.1%)
Scapula	1 (5.6%)
Abdominal wall	1 (5.6%)
Histopathology	
Osteosarcoma	7 (38.9%)
Ewing sarcoma	5 (27.8%)
Rhabdomyosarcoma	4 (22.2%)
Myeloid sarcoma	1 (5.6%)
Synovial sarcoma	1 (5.6%)
SUV1	
Median (Min.–Max.)	6.0 (2.80–13.0)
Mean ± SD	6.71 ± 3.22
SUV2	
Median (Min.–Max.)	2.30 (1.20–20.0)
Mean ± SD	4.86 ± 5.80
Histologic response	
Good responder	12 (66.7%)
Poor responder	6 (33.3%)

region were performed immediately after acquisition of the CT images (2–3 min/bed position).

The CT data were used for the attenuation correction of the PET emission data. PET/CT, PET, and CT images were displayed and reconstructed in the axial, sagittal, and coronal planes.

Side-by-side image interpretation was done by two experienced nuclear medicine physician and radiology physician.

Standard uptake values before (SUV1) and after (SUV2) chemotherapy were analyzed. SUV2 values were correlated with chemotherapeutic response assessed by histopathology which was performed to all patients following surgical excision of the tumors.

Statistical analysis of the data was fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov-Smirnov test was used to verify the normality of the distribution of variables. Mann-Whitney test was used to compare between two groups for not normally distributed quantitative variables. Agreement between markers was done using sensitivity, specificity, PPV, and NPV. Significance of the obtained results was judged at the 5% level.

Results

A total of 36 PET/CT studies were performed in 18 patients of our study: 13 patients were males (72.2%) and 5 patients were females (27.8%). Their ages ranged between 1 and 18 years with a mean age of 13.33 years (Table 1).

The most common primary tumor site was the femur, 3 cases (16.7%). The most common histopathological diagnosis was osteosarcoma in 7 cases (38.9%). These results were illustrated in (Table 1).

All patients underwent sequential 18F-FDG PET/CT before (PET/CT1) and after (PET/CT2) neoadjuvant chemotherapy. Maximum standardized uptake value (SUVmax) was measured in the primary lesion on PET/CT1 (SUV1) and PET/CT2 (SUV2). SUV1 calculation of the 1ry tumor site ranged from 2.80–13.0 with a mean

Table 2 Relation between histologic response according to SUV

	Histologic response		<i>P</i>
	Poor responder ($n = 6$)	Good responder ($n = 12$)	
SUV1			
Median (Min.–Max.)	8.5 (3.5–13.0)	5.5 (2.8–12.4)	0.151
Mean ± SD	8.5 ± 3.7	5.8 ± 2.7	
SUV2			
Median (Min.–Max.)	8.1 (3.6–20.0)	1.8 (1.2–3.2)	< 0.001
Mean ± SD	10.7 ± 7.2	1.9 ± 0.6	

Table 3 Agreement (sensitivity, specificity) for SUV2

		Good responder(n = 12)	Poor responder (n = 6)	Sensitivity	Specificity	PPV	NPV	Accuracy
SUV2	< 2.5	11	0	100.0	91.67	85.71	100.0	94.44
	≥ 2.5	1	6					

value of 6.71 ± 3.22 . SUV2 calculation of the 1ry tumor site ranged from 1.20–20.0 with a mean value of 4.86 ± 5.80 (Table 1).

After the histopathological assessment, 12 patients (66.7%) were good responders and 6 patients (33.3%) were poor responders. SUV2 in good responders ranged from 1.2–3.2 with a mean value of 1.9 ± 0.6 . Three patients in our study showed postchemotherapy increased SUV, all of which were poor responders. SUV2 in poor responders ranged from 3.6–20.0 with a mean value of 10.7 ± 7.2 (Table 2). SUV2 significantly correlated with the histologic response ($P < 0.001$), and the calculated sensitivity, specificity, PPV, NVP, and accuracy were 100.0, 91.67, 85.71, 100.0, and 94.44, respectively (Table 3).

Among the responders, 11 cases (91.6%) showed no postchemotherapeutic morphological changes and only 1 case (8.33%) showed postchemotherapeutic morphological

changes in the form of moderate size reduction. Whereas among the nonresponders, 4 cases (66.6%) showed size progression and 2 cases (33.3%) showed no postchemotherapeutic morphologic changes (Figs. 1, 2, 3, 4, 5, 6 and 7).

Discussion

It was established that neoadjuvant and adjuvant chemotherapy increased survival rates in sarcoma patients [19]. Many trials were done to predict response to neoadjuvant therapy by diagnostic imaging to gain prognostic information or even to direct preoperative or operative therapy [20]. Therapy response in clinical practice is commonly assessed on the basis of change in the longest tumor diameter for soft-tissue sarcomas (response evaluation criteria in solid tumors); however, a reduction in the soft-tissue component of bone sarcomas in response

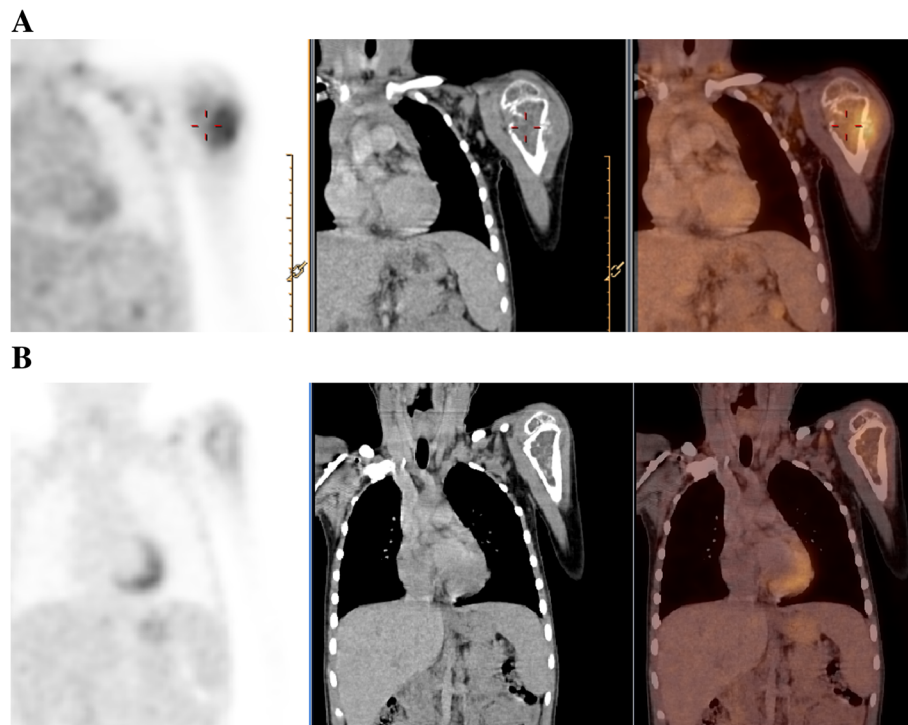


Fig. 1 A 17-year-old male patient with left humeral Ewing sarcoma. **a** Coronal PET (left), coronal CT (middle) and coronal fused PET/CT PET (right) images for staging revealed pathological uptake (SUV = 3.9) at the primary tumor site matching with pathological results. **b** Follow-up scans after chemotherapy revealed regression in SUV uptake (2.3). This patient underwent limb salvage surgery and pathological assessment revealed 95% tumor necrosis (good responder)

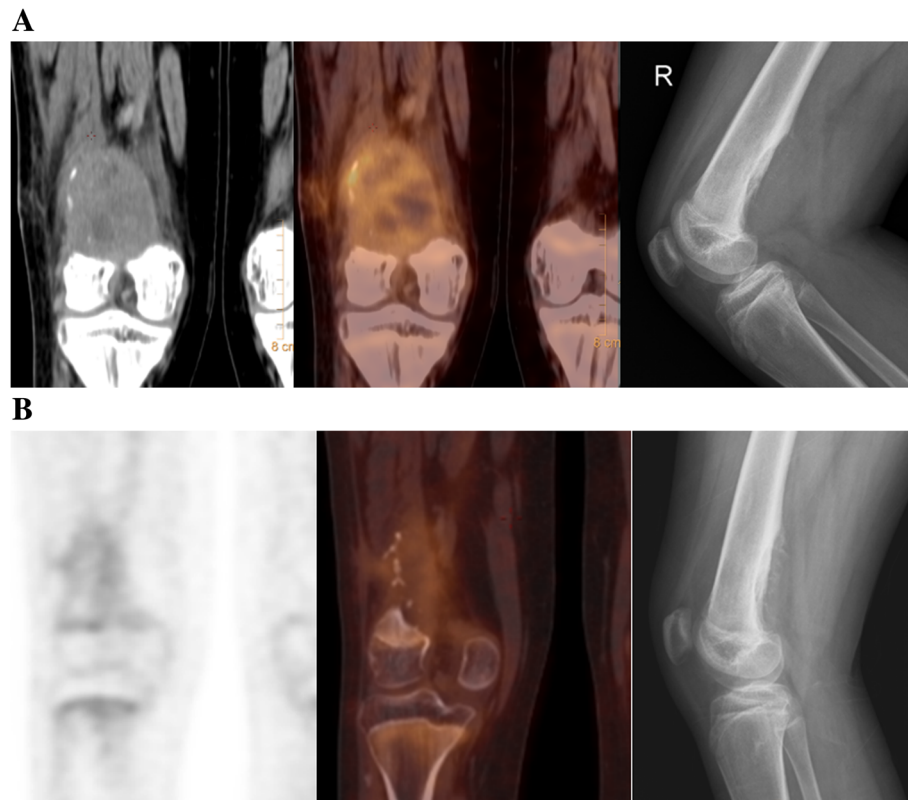


Fig. 2 A 17-year-old male with right femoral Ewing sarcoma. **a** Prechemotherapy coronal CT (left), PET/CT (middle) showed right femoral metabolically active FDG avid lesion with SUV about 4.7. X-ray (right) revealed posterior distal femoral lesion with a wide zone of transition and aggressive periosteal reaction. **b** Postchemotherapy coronal PET (left), PET/CT (middle) revealed metabolic regression regarding the distal femoral mass lesion (SUV 2.3). The patient underwent limb salvage surgery and pathological assessment revealed 95% tissue necrosis (good responder). No morphologic changes regarding conventional imaging features (right)

to chemotherapy does not necessarily correlate with favorable response [21].

The standard therapy for sarcoma is a combination of surgery and chemotherapy [22]. F-18 FDG PET examinations before and after neoadjuvant chemotherapy are commonly used now to monitor treatment response and to help time surgical treatment [23]. In addition, surgeons might decide on the type of operation depending on responsiveness to chemotherapy, as limb salvage cannot be recommended to patients in whom wide margins cannot be safely achieved [23]. Chemotherapy-induced necrosis is the most important prognostic factor in surgically managed patients [24].

18FFDG-PET/CT has a rising role to provide complementary information in sarcoma diagnosis and treatment planning and has been established as a diagnosing imaging tool in the staging, restaging, and assessment of the therapeutic response of soft-tissue as well as bone sarcomas [25].

It was difficult to collect extensive PET/CT data of pediatric malignancies owing to the relatively low incidence and wide range of pediatric malignancies as

well as the relatively conservative application of PET/CT in pediatric age. Thus, most of the previously published studies have focused on childhood lymphomas [26].

The main limitation in this study was the relatively small sample size of the patients and the heterogeneity of the sample as regards the histological diagnosis of different soft tissue and osseous sarcomas; however, the presence of sufficient radiological and pathological data for all the patients allowed adequate statistical analysis and interpretation of the results. The current study is one of the first to investigate the accuracy and added the diagnostic value of integrated 18F-FDG PET/CT in the assessment of treatment response in pediatric sarcomas. Previous studies mainly assessed the performance of molecular imaging for initial tumor staging, and they did not focus on cancer subtypes like Ewing sarcoma [27]. The results in the current study indicated that integrated 18F-FDG PET/CT is an effective noninvasive diagnostic tool for assessment of therapy response in pediatric patients who have a history of bone or soft tissue sarcoma.

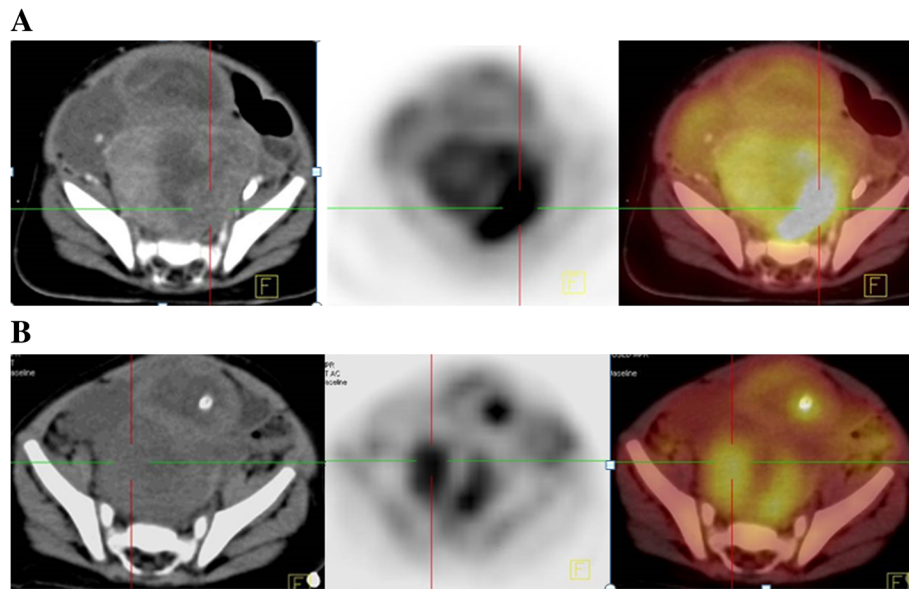


Fig. 3 A 1-year-old boy presented with bladder mass which proved to be embryonal rhabdomyosarcoma came for assessment of treatment response. **a** Prechemotherapy axial CT (left), axial PET (middle), and axial fused PET/CT (right) revealed metabolically active FDG avid primary mass (with SUV = 5.4). **b** Postchemotherapy axial CT (left), axial PET (middle), and axial fused PET/CT (right) revealed regression of the FDG uptake (SUV = 3.6). Radical cystectomy was done and the pathology showed that there was 85% viable tumor (poor responder)

Good responders to chemotherapy considered to have 90% or greater necrosis and poor responders who had less than 90% necrosis. This is in concordance with what Hawkins et al. mentioned [28].

SUV2 of 2.5 is considered a cutoff value between pathological and nonpathological uptake; this is also in agreement with Andrei Iagaru et al. [23].

Hawkins et al. [28] stated that using a cutoff SUVmax of less than 2.8, 18F-FDG PET/CT differentiated responders

from nonresponders with up to 100% accuracy after completion of neoadjuvant therapy.

Kumar et al. [29] also considered SUV2 as an accurate noninvasive prognostic indicator; they found that disease progression-free survival (PFS) is 72% for SUV2 less than 2.5 versus 27% for SUV2 more than or equal to 2.5.

Rosen et al. [30], Picci et al. [31], and Asha Kandathil et al. [1] concluded that histologic response, measured

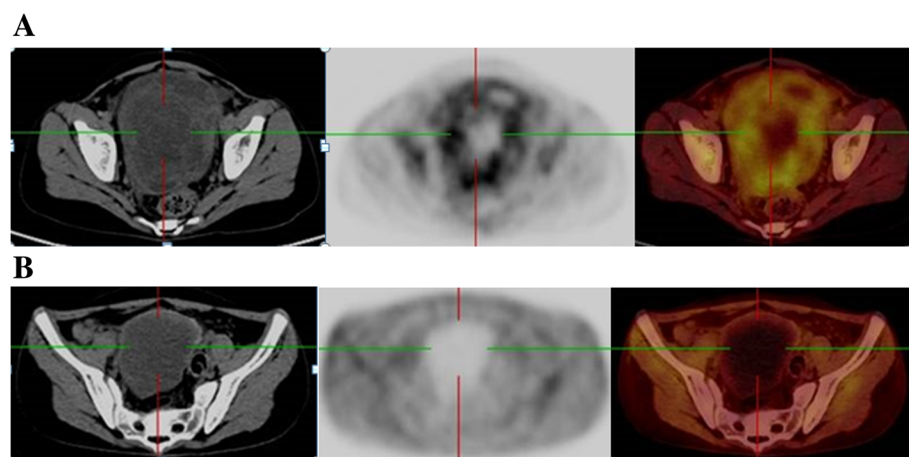


Fig. 4 A 13-year-old boy presented with urinary bladder mass; the mass was proven by a biopsy to be embryonal rhabdomyosarcoma. **a** Prechemotherapy axial CT (left), axial PET (middle), and axial fused PET/CT (right) revealed metabolically active FDG avid 1yr tumor lesion (SUV = 2.9). **b** Postchemotherapy axial CT (left), axial PET (middle), and axial fused PET/CT (right) revealed marked regression of the FDG uptake (SUV = 1.5) as well as moderate size regression. The mass was excised without tumor viability detected on histopathology

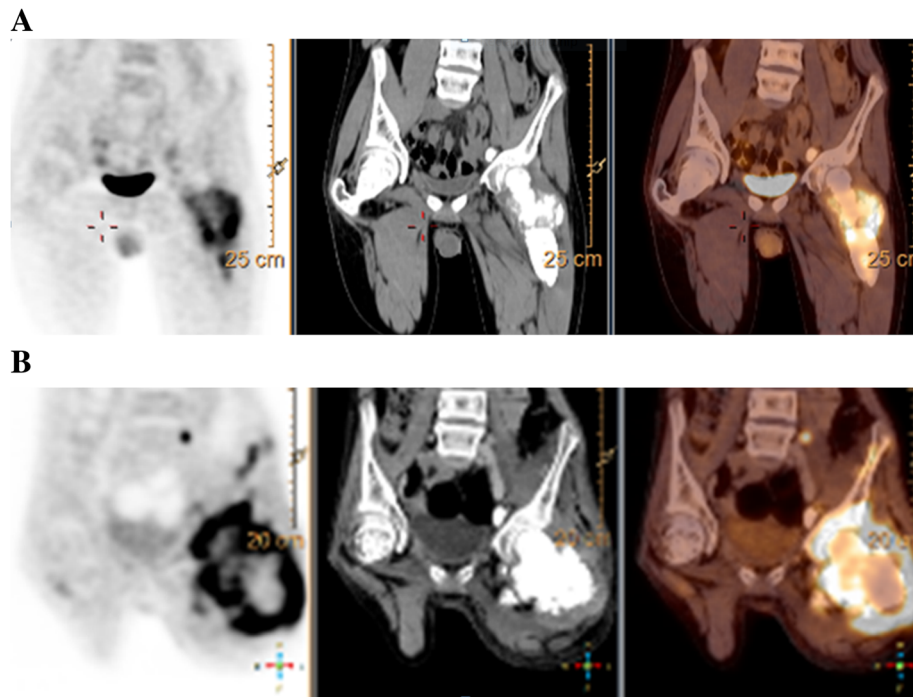


Fig. 5 A 18-year-old male with left femoral osteosarcoma. **a** Prechemotherapy coronal PET (left), coronal CT (middle), and coronal fused PET/CT (right) images revealed metabolically active FDG avid 1st tumor (SUV 9). **b** Prechemotherapy coronal PET (left), coronal CT (middle), and coronal fused PET/CT (right) images revealed progression regarding size and FDG avidity (SUV = 19). Amputation was done and histopathology showed that there was 90% viable tumor (poor responder)

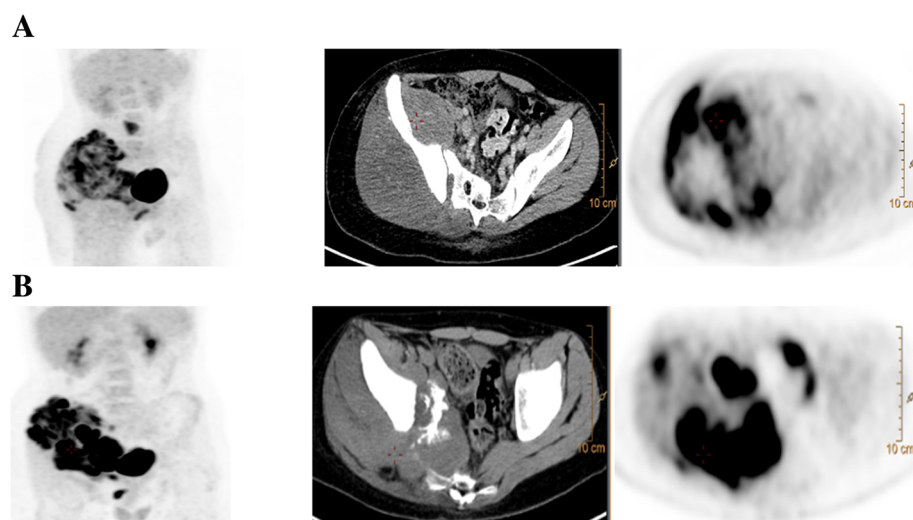


Fig. 6 A 16-year-old male with right iliac bone osteosarcoma. **a** Prechemotherapy coronal PET, axial CT, and axial PET revealed high pathological FDG uptake (SUV = 12) at the primary tumor site. Postchemotherapy coronal PET, axial CT, and axial PET revealed disease progression regarding size and FDG avidity (20 in the study). Amputation was done and histopathology showed that there was 90% viable tumor (poor responder)

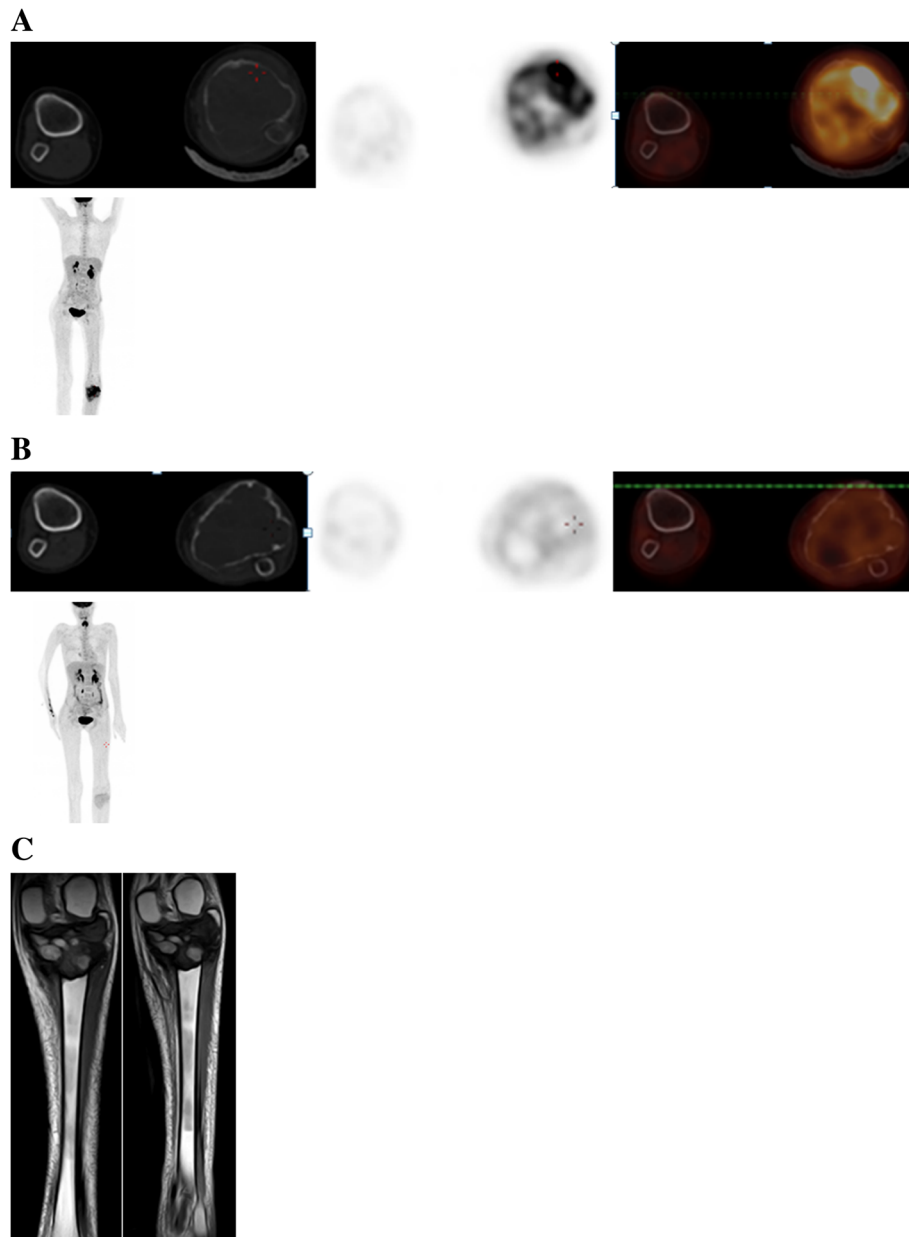


Fig. 7 A 14-year-old female patient suffered from left proximal tibia telangiectatic osteosarcoma. **a** Prechemotherapy PET/CT revealed metabolically active FDG left proximal tibial mass lesion (SUV = 12.4). **b** After the end of treatment, PET/CT revealed no pathological uptake (SUV = 1.8). The patient underwent limb salvage surgery and surgical pathology revealed good histological response (100% tissue necrosis). **c** No corresponding morphologic improvement was seen between the premanagement MRI (left) and postmanagement one (right)

by the percentage of necrotic tumor cells remaining after neoadjuvant chemotherapy, has prognostic value in predicting event-free survival (EFS) in children with osteosarcoma (OS) and Ewing sarcoma.

SUV2 was found to significantly correlated with the histologic response ($P < 0.001$); the calculated sensitivity, specificity, PPV, NVP, and accuracy were 100.0, 91.67, 85.71, 100.0, and 94.44, respectively. This is in concordance with Douglas et al. [28] who proved that SUV2

was correlated with a histologic response in pediatric bone sarcomas.

The change in SUV after chemotherapy was found not matching with morphological changes detected on CT images. Among the responders, only 1 case (8.33%) showed postchemotherapy morphologic changes in the form of moderate size reduction (Fig. 4), and the other 11 cases (91.6%) showed no postchemotherapy morphologic changes.

Murphy et al. [32] and McCarville et al. [33] stated that sarcomas, frequently do not change in size in response to chemotherapy, radiographic evaluation of response by computed tomography (CT), or magnetic resonance imaging (MRI), do not distinguish between responders and nonresponders and that only minimal morphologic change may be detected at conventional imaging in spite of a significant reduction in tumor viability after therapy.

Denecke et al. [21] and Bredella et al. [34] reported that an overall tumor SUV and SUVmax on posttreatment 18F-FDG PET/CT scans were more accurate for the assessment of treatment response than changes in tumor size.

Conclusions

18F-FDG PET/CT provides a reliable noninvasive diagnostic tool in the assessment of response to preoperative chemotherapy in pediatric sarcoma which is valuable in the decision of the type of surgery specially in cases with limb involvement whether considering limb salvage technique or amputation and also of benefit in assessment of prognosis of the patients following treatment.

Abbreviations

CMR: Complete metabolic response; CT: Computed tomography; DFS: Disease-free survival; EFS: Event-free survival; FDG PET/CT: 18F-fluorodeoxyglucose positron emission tomography/computed tomography; PFS: Progression-free survival; STS: Soft-tissue sarcoma; SUVmax: Maximum standardized uptake value

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Authors' contributions

AR shared in obtaining the radiological data in this study, shared in the interpretation of results of the study, shared in the design and coordination of the study, and helped in drafting the manuscript. AA shared in the interpretation of the results of this study, performed the statistical analysis, shared in the design and coordination of the study, and helped in drafting the manuscript. SF shared in obtaining the clinical data included in this study. WO shared in obtaining the radiological data in this study and shared in the interpretation of the results of the study. KM shared in the final revision of the manuscript of this study and revised the obtained results and data. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Approval for this study was obtained from the Research Ethics Committee of Alexandria Faculty of Medicine. All study procedures were carried out in accordance with the Declaration of Helsinki regarding research involving human subjects.

Consent for publication

All patients included in this research gave written informed consent to publish the data contained within this study. If the patient was less than 16 years old, deceased, or unconscious when consent for publication was

requested, written informed consent for the publication of this data was given by their parent or legal guardian.

Competing interests

The authors declare that they have no competing interests.

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