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Original Article

Can FDG-PET Assess the Response to Chemotherapy and Predict Tissue Necrosis in Osteosarcoma and Ewing Sarcoma?

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Abstract

Introduction: Osteosarcoma (OS) and Ewing sarcoma (ES) represent the pediatric population's most common malignant bone tumors. 18-Fluorodeoxyglucose positron emission tomography has been shown to be effective in both the diagnostic and staging phases of cancer treatment. In recent years, some studies have also explored the possibility that FDG-PET could have a prognostic role.

Aim: Our research aimed to evaluate if maximum standardized uptake value (SUVmax) variations after chemotherapy could be correlated with tissue necrosis and be linked with patients' survival rates.

Materials and methods: This observational retrospective study included all cases treated for skeletal OS or ES in our institution between 2006 and 2018. We recorded patients' SUVmax values before and after chemotherapy, the necrosis grade (for those who received surgery), and survivorship. Forty-one cases (17 OS and 24 ES) were included. Among the 36 cases that received surgery, 15 were responders, and 20 were non-responders.

Results: Our data suggested a statistically significant correlation between tumor necrosis and differential SUVmax after neoadjuvant treatment (p=0.007). In particular, cases with differential SUVmax higher than 4.7 or a variation higher than 63% had better oncological outcomes.

Conclusion: Our study testifies to the effectiveness of FDG-PET in predicting tissue necrosis on ES and OS, thereby representing a promising prognostic factor.

Keywords

Ewing sarcoma, necrosis, osteosarcoma, PET, prognosis

INTRODUCTION

Osteosarcoma and Ewing sarcoma represent two main challenges in oncologic orthopedics, the two most frequent forms of sarcomas in the pediatric population.[1,2] The survival rate has been significantly improved thanks to a better understanding of the disease within the context of a multidisciplinary approach.

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PENSOFT.

The introduction of adjuvant and neoadjuvant chemotherapy helped raise the survival rate from 15% to 60%.[3] For this reason, being able to evaluate a good response to therapy has been proven to be one of the main prognostic factors.

In modern oncology, fluorine-18-fluorodeoxyglucose positron emission tomography combined with computed tomography (FDG-PET/CT) plays a pivotal role in assessing the diagnosis and staging both Ewing sarcoma and osteosarcoma.[4-9] In recent years, some authors suggested that this exam could also potentially evaluate patients' early response to neoadjuvant chemotherapy, thereby representing a prognostic indicator.[10]

AIM

In this study, we evaluated the evolution of maximum standardized uptake value (SUVmax) values before and after chemotherapy in patients with Ewing sarcoma and osteosarcoma, investigating whether variations of carbohydrate metabolism were associated with the share of tissue necrosis on the surgical specimen.

MATERIALS AND METHODS

This single-center retrospective study was performed following the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Our study consisted of an observational retrospective study of cases treated for skeletal osteosarcoma or Ewing sarcoma in our institution between 2006 and 2018. An inclusion criterion was a multidisciplinary approach, combining neoadjuvant chemotherapy, surgical resection, and adjuvant chemotherapy. Another criterion was the execution of FDG-PET/CT scans at the moment of diagnosis (t0) **(Fig. 1)**, before surgery (t1), and at the end of the therapeutic path (t2).

Time t0 was established as the date of diagnosis before the patient had begun any treatment. T1 represents the end of the neoadjuvant chemotherapy and before the day of surgery. T2 expresses the date on which the last PET-CT scan was performed, approximately one month after the end of the adjuvant chemotherapy. An FDG-PET-TB scanner and a CT system were used in parallel for this study. Before performing the PET-CT, each individual was prepared by monitoring their blood glucose levels. The procedure was carried out exclusively if values were below 150 mg/dL. Image acquisition took place 60 minutes after intravenous administration of the radiopharmaceutical. PET data were obtained in a Whole-Body 3D mode and then corrected for tissue attenuation by low-dose CT acquisition without MDC administration. The uptake of FDG was defined as pathological when it was greater than the adjacent normal bone tissue. Areas with abnormal FDG uptake and their extension were assessed with SUV considering the following parameters: the amount of FDG injected, patient body weight, and regional uptake. The SUVmax of the region of interest was calculated using the following equation: (metabolic activity/volume unit) / (injected dose of radiopharmaceutical / patient body weight).

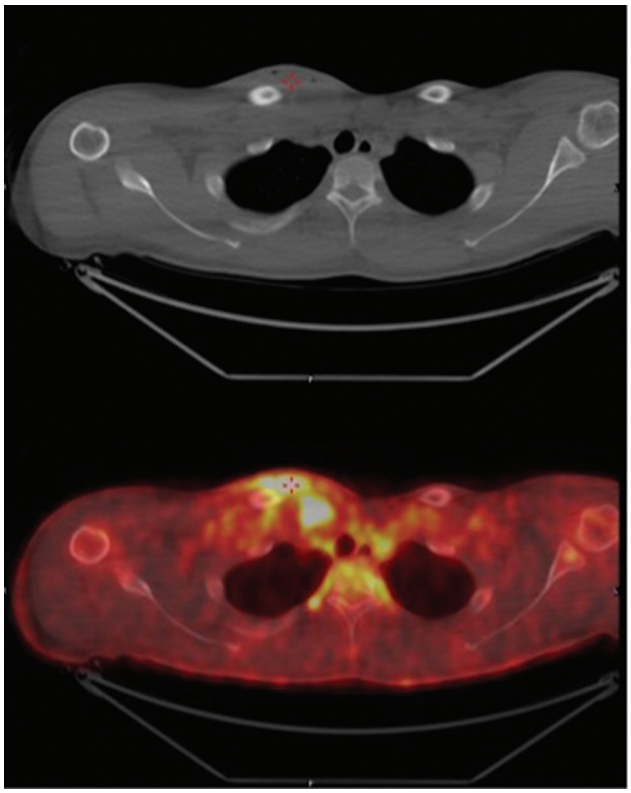

Figure 1. FDG-PET/TC scans of a case with Ewing sarcoma of the left clavicle before chemotherapy (t0).

For each patient, personal data, such as age, sex, and clinical presentation, were collected. The diagnosis was established after a biopsy, according to the findings of our anatomical pathology unit. Cases were divided into subgroups according to their histopathological diagnosis, and we investigated whether the lesion treated was solitary or if the patient already had the disease in other anatomical districts. After surgery, the resected tissue was set to pathological analysis to confirm the previous diagnosis and estimate the necrosis grade, which was classified according to the Huvos or Picci criteria for osteosarcomas and Ewing's sarcomas. Those cases involving 90% or more of the neoplastic volume were considered good responders, whereas those whose necrosis was lower than 90% were considered poor responders. All patients were treated according to the latest ESMO guidelines.[11]

Local SUVMax at t0, t1, and t2 were recorded and compared.

Patients' follow-ups were performed both in oncological and orthopedic units. Survival was noted throughout the whole follow-up period. Local recurrences and metastatic lesions diagnosed during the post-operative intercourse were reported, as well as their subsequent treatment.

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Statistical analysis

Statistical analysis was performed using Stata SE 13 (StataCorp LLC, College Station, TX). Statistical significance was set at 0.05 for all endpoints.

RESULTS

Our review consisted of 41 cases, seven females and 34 males. Their mean age at diagnosis was 21.7 years (range, 3-44 years). Seventeen patients suffered from osteosarcoma: 10 of them were diagnosed with osteoblastic osteosarcoma, 5 had chondroblasts or fibroblastic lesions, whereas a telangiectasic lesion was diagnosed in the remaining 2 cases. Among those 17, eleven had a single localized lesion at the moment of diagnosis, while the other five already had at least one metastasis. Twenty-four patients were diagnosed with Ewing sarcoma. The disease was localized in 13 cases and spread systemically in 11. Femur was the most frequent localization (16 cases, 39.0%), followed by the pelvis (8, 19.5%), humerus (5, 12.2%), and tibia (4, 9.8%).

Among our 41 cases, 36 were able to complete their therapeutic path. The other 6 had a rapid progression of the disease and died before they could undergo surgery. Of those 36 patients, 15 responded to chemotherapy, and 20 were non-responders. The mean necrosis percentage on the surgical specimen was 68.3% (9-100%).

The mean SUVmax was 10.1 at t0, 5.0 at t1 and 3.2 at t2. The mean differential between SUVmax at t0 and t1 was 5.56, and none of our cases increased their SUVmax value between t0 and t1. In particular, responders (tumor necrosis >90%) had a mean SUVmax variation between t0 and t1 of 8.6, whereas the same differential in non-responders was only 3.0. These findings were supported by the Student's *t*-test, which assessed that cases with a good response regarding tumor necrosis had a significantly higher SUVmax variation between t0 and t1 compared to poor responders (p=0.014).

Our data suggested a statistically significant correlation between tumor necrosis and SUVmax variation between t0 and t1 (p=0.007) and between t0 and t2 (p=0.006) according to Pearson correlation tests. This result suggests a strict link between necrosis and FDG-PET results. A linear regression analysis identified a linear correlation between the percentage of tissue necrosis and the reduction of SUVmax values. Inside our population, the mean variation between t0 and t1 could be approximated using the equation ΔSUVmax [t0;t1] = −1.60+(0.10 × necrosis percentage) **(Fig. 2)**, whereas the one for the variation between t0 and t2 would be ΔSUVmax [t0;t1] = −1.05+(0.13 × necrosis percentage).

Conversely, those who had a persistent SUVmax between the three PET evaluations (ΔSUVmax [t0;t1] <1.0 and ΔSUVmax [t0;t1] <2.0) had mean necrosis at the surgery of 55%, whereas those who saw a remarkable reduction in their SUVmax values (ΔSUVmax [t0;t1] >1.0 and ΔSUVmax [t0;t1] >2.0) had mean necrosis of 85%.

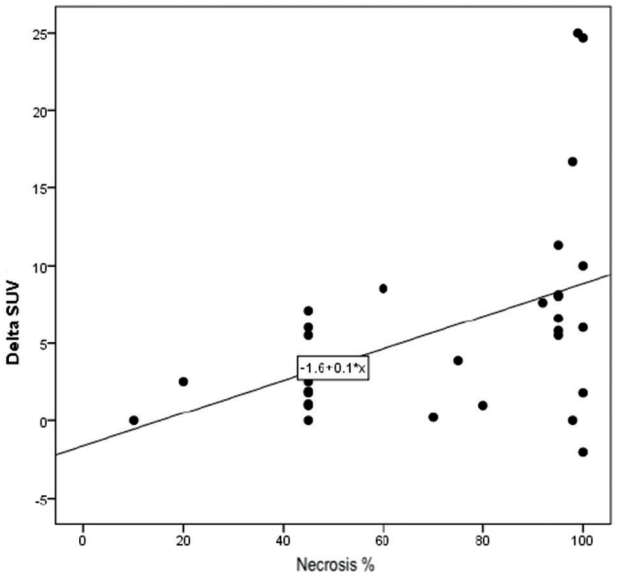

Figure 2. Linear approximation of cases' distribution in terms of differential SUVmax and percentual tissue necrosis.

Evaluating the correlation between SUVmax differentials and surgical necrosis, we searched for a cut-off value that could predict whether the patient would respond to systemic treatment. In our series, establishing the cut-offs for the periods t0-t1 and t0-t2 at 4.7 (or a reduction of 63% of the previous value) and 7.5, respectively, the results were good sensibility (80-78%) and specificity (72-77%) values for assessing patients' response to chemotherapy. In particular, cases with differential SUVmax between t0 and t1 lower than 4.7 or a percentage reduction higher than 63% had a mean event-free survival of 15.6 months and an overall survival of 34.4 months. The remaining patients, instead, had significantly higher values of event-free survival (30.6 months) and overall survival (63.3 months).

Cases with a t1 value equal to or lower than 2.5 had a significantly lower incidence of local recurrence at the patient's latest follow-up (exact Fisher's test: p=0.038).

The Event-Free Survival (EFS) at five years was 73% for the responders and 22% for the non-responders, testifying to the role of tissue necrosis as a statistically significant predictive factor (exact Fisher's test, p=0.009) **(Fig. 3)**.

DISCUSSION

The fluorine-18-fluorodeoxyglucose positron emission tomography combined with computed tomography (FDG-PET/CT) is an imaging tool that measures a tumor's metabolic activity.[12]

Over the last decades, the importance of this exam for diagnosing and staging malignant tumors has been progressively increasing. In fact, since its introduction in clinical practice, the FDG-PET/CT has been appreciated for its capacity to dovetail imaging evidence of the tumoral masses with an assessment of their metabolic activity. It is,

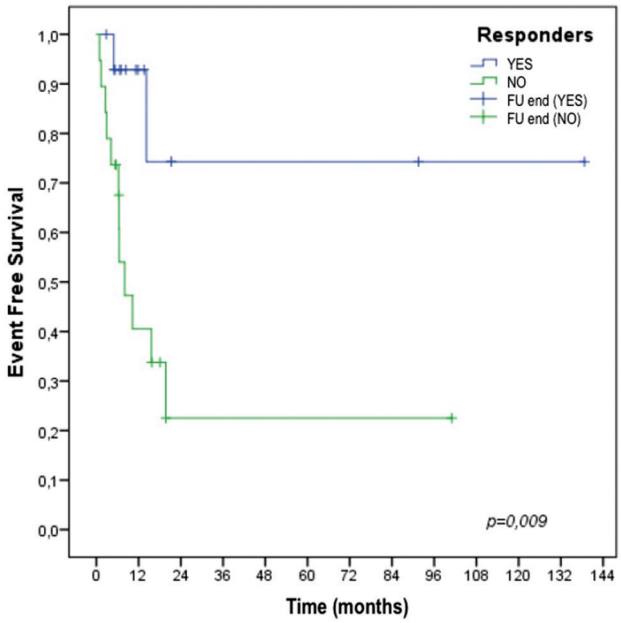

Figure 3. Kaplan Meier curves of patient's Event-Free Survival through their follow-up. The population was divided into responders (blue line) and non-responders (green line).

therefore, a common-use exam for improving the staging accuracy for malignant bone and soft tumors due to its high sensitivity.[13,14]

However, the information provided by the exam is not limited to recognizing areas with increased glucosidic uptake with a reasonable neoplastic nature. It also often allows a more profound and better comprehension of its characteristics. High-grade tumors should have higher standard uptake values (SUV) than low-grade tumors, allowing them to distinguish between different malignancy histologic grades and act as a surrogate marker for tumor grade.[15-20] It has been demonstrated that upregulation of glucose transporter type 1 (GLUT-1) in cancer cells, an increased tendency to cellular glucose intake, and 18F-FDG avidity represent a prognostic factor in various malignancies.[21-23] These findings could explain the relationship between FDG uptake on PET and tumor aggressiveness and suggest PET values as direct prognostic factors in cancer prognosis.[24-26]

FDG-PET/CT has been proven to be a useful tool to evaluate interim response to antibiotic therapy in patients affected by hematogenous spondylodiscitis[27], and others investigated whether it could represent a prognostic factor also in malignant bone or soft tissue sarcomas treatment[26].

In 2017, Bailly et al. analyzed a large cohort of 62 pediatric patients with ES and OS the potential prognostic role of PET/CT parameter, including SUVmax, but they could not find histological response to therapy or overall survival.[28]

In the same year, Palmerini et al. published their experience with a population of 77 cases suffering from Ewing sarcoma or osteosarcoma. In their cases with Ewing sarcoma, the SUVmax recorded at the moment of diagnosis was the only independent pretreatment prognostic factor to retain statistical significance. On the other hand, the same statement was not valid for their cases with osteosarcoma, and neither SUVmax at the end of chemotherapy nor the differential between the two values appeared as statistically significant prognostic factors in their casuistry.[29]

Hawkins et al. had more encouraging results in their population of 36 Ewing sarcomas. Their mean SUVmax value before chemotherapy was 7.9, while the same value decreased to 2.1 at the end of the medical treatment. Patients' SUVmax after chemotherapy was also significantly associated with progression-free survival. The authors proposed a value of 2.5 or lower to represent a positive prognostic factor for disease control and survival.[30] Raciborska et al.[31] obtained comparable results, which found a significant correlation between SUVmax and clinical outcomes after chemotherapy. The median value of those who experienced a disease progression was significantly higher than those who had a better outcome. Furthermore, the study confirmed a positive predictive value of 2.5 or lower for a favorable response to the therapeutic approach as a whole.[31]

Our results corroborate the idea that cases with an SUVmax value below 2.5 after chemotherapy suggest lower risks of local recurrence.

We could also identify a strict link between necrosis and FDG-PET results. Cases with a necrosis percentage above 90% had significantly higher reductions of their SUVmax values after chemotherapy (Student's *t*-test; p=0.014). Furthermore, we detected a statistically significant linear correlation between percentual tumor necrosis on surgical specimens and SUVmax variation (Pearson correlation test; p=0.007). In line with our outcomes, we suggest an overall reduction of 4.7 or a cut of 63% between SUVmax values at the diagnosis and after chemotherapy in order to assess the response to treatment: cases in which chemotherapy induced a SUVmax reduction equal or greater than 4.7 overall or higher than 63% of the first record should theoretically be considered as good responders, whereas lower values should orientate toward a negative response. This cut-off was associated with good sensibility (80%) and specificity (72%) in our population.

Furthermore, the necrotic response was a statistically significant predictive factor for patients' EFS, supporting the idea that SUVmax and overall survival might be indirectly but strictly correlated.

This correlation between necrosis and SUVmax variation could also be helpful for those cases that could not be treated with surgery and whose necrotic percentage is not given. In these patients, the differential SUVmax could even replace necrosis as one of the main prognostic factors after the administration of chemotherapy.

Our study is not free of limitations. One of them is represented by the retrospective nature of our study, which did not allow the complete standardization of the postoperative follow-up procedures for each patient. Another limitation is the wide period covered by our study.

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Between 2006 and 2018, surgical technologies and chemotherapy, radiation therapy, and imaging technologies developed, which have had innovations for more than ten years. These changes inevitably reduced the grade of standardization in our cohort.

Another limitation is represented by the diversity of the patients we analyzed regarding age and histological diagnosis. Due to the relatively limited number of available patients, osteosarcomas and Ewing sarcomas were included despite their differences in histological nature and treatments. These variabilities further reduced the grade of standardization in our cohort. These issues could be overcome in the future by performing similar evaluations, on a prospective basis, on broader populations and performing separate evaluations for Ewing sarcomas and osteosarcomas.

Beyond these limitations, our study provides evidence that the variation of SUVmax values could represent a reliable prognostic factor for patients with osteosarcoma or Ewing sarcoma undergoing multidisciplinary therapeutic approaches.

CONCLUSION

Although further studies with larger cohorts of patients and a prospective nature would still be necessary and should be encouraged, our study testifies to the effectiveness of FDG-PET/CT (in terms of SUVmax variation after chemotherapy) in order to predict tissue necrosis on target Ewing sarcomas and osteosarcomas, thereby representing a promising prognostic factor for patients' outcome. Physicians should pay attention to the SUVmax values' differential since it could represent a pivotal predictive factor, allowing an earlier and more customized cure standard for each case.

Author contributions

All authors contributed equally to the preparation of the study

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Competing Interests

The authors have declared that no competing interests exist.

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Может ли FDG-PET оценить ответ на химиотерапию и предсказать некроз тканей при остеосаркоме и саркоме Юинга?

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Резюме

Введение: Остеосаркома (ОС) и саркома Юинга (СЮ) представляют собой наиболее распространённые злокачественные опухоли костей в педиатрической популяции. Позитронно-эмиссионная томография с 18-фтордезоксиглюкозой (FDG-PET) показала свою эффективность как на диагностическом, так и на стадийном этапе лечения рака. В последние годы в некоторых исследованиях также изучалась возможность того, что FDG-PET может иметь прогностическую роль.

Цель: Наше исследование было направлено на то, чтобы оценить, могут ли изменения максимального стандартизированного значения поглощения (SUVmax) после химиотерапии коррелировать с некрозом тканей и могут ли быть связаны с выживаемостью пациентов.

Материалы и методы: В это обсервационное ретроспективное исследование вошли все случаи, проходившие лечение по поводу скелетной ОС или СЮ в нашем учреждении в период с 2006 по 2018 год. Мы регистрировали значения SUVmax пациентов до и после химиотерапии, степень некроза (для тех, кто перенёс операцию) и выживаемость. Был включен 41 случай (17 OS и 24 СЮ). Среди 36 пациентов, перенёсших операцию, 15 реагировали на лечение, а 20 не реагировали на лечение.

Результаты: Наши данные свидетельствуют о статистически значимой корреляции между некрозом опухоли и дифференциальным SUVmax после неоадъювантного лечения (p=0.007). В частности, случаи с дифференциалом SUVmax выше 4.7 или вариацией выше 63% имели лучшие онкологические исходы.

Заключение: Наше исследование свидетельствует об эффективности FDG-PET в прогнозировании некроза тканей при СЮ и ОС, тем самым представляя собой многообещающий прогностический фактор.

Ключевые слова

Саркома Юинга, некроз, остеосаркома, PET, прогноз