

Review Article

PET/CT in Ewing Family Tumors.

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INTRODUCTION:

Ewing Sarcoma (ES) was described by James Ewing in 1921 as an undifferentiated tumor involving the diaphysis of long bones; less commonly, it arises in soft tissue. It became evident that these entities are actually part of a spectrum of neoplastic diseases known as the Ewing sarcoma family of tumors (EFT), which also includes PNET, malignant small-cell tumor of the thoraco-pulmonary region and atypical ES ⁽¹⁾.

The EFT is common in the pelvis and axial skeleton. Their peak incidence are between the age of 10 and they have a tendency towards rapid spread to lungs, bone, and bone marrow and also respond to the same treatments that include chemotherapy and radiotherapy.

A favorable response to chemotherapy also allows orthopedic oncologists to be more aggressive in pursuing limb-sparing surgery. An accurate and non-invasive preoperative marker of response would be ideal for planning surgical margins and as a prognostic tool ⁽²⁾.

PET/CT is a functional imaging modality that has been shown to correlate with histologic assessment of response to chemotherapy in ES with concordance rates for SUV max with histologic response range from 58 to 100%. PET/CT is gaining a more important role in the post-chemotherapy preoperative staging. It is important to clarify if PET is a suitable modality for predicting outcome of Neoadjuvant chemotherapy ^(3,4).

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Diagnosis of EFTs

Approximately 80 % of patients present with clinically localized disease, although subclinical metastatic disease is presumed to be present in nearly all. Overt metastases may become evident within weeks to months in the absence of effective therapy. The significance of this lies in the frequent delay between the onset of symptoms and diagnosis, which in one report averaged over nine months ⁽⁵⁾.

The presence of fever, an interval between onset of symptoms and diagnosis less than three months, and age older than 12 years. The rate of metastatic disease at presentation in the subset of patients with none of these risk factors was only 4 % with two factors it was 23 %, while it was almost double 44 % if three or four factors were present ⁽⁶⁾.

Sites of metastatic disease at diagnosis are similar to those seen with recurrent disease; lung and bone/bone marrow metastases predominate, in roughly equal proportions. The spine is the most frequently involved bone. Lung metastases represent the first site of distant spread in 70 to 80 % of cases, and are the leading cause of death for patients with EFT.

Lymph node, liver, and brain involvement are distinctly uncommon ⁽⁷⁾.

CT shows similar radiological findings to plain radiographs but better delineates the extent of cortical destruction and soft tissue disease. Its contrast resolution permits visualization of the extra-osseous soft tissue mass and involved bone marrow. However, in chemo-responsive tumors, CT changes in the affected bone marrow do not differentiate active tumor from intra-medullary necrosis ⁽⁸⁾.

The metastatic work-up should include a CT scan of the chest to evaluate the thorax for metastatic disease. Criteria to guide the evaluation of suspected pulmonary metastases are available from the Children's Oncology Group that was adopted from the European Ewing Tumor Working Group Initiative of National Groups Ewing Tumor Studies ⁽⁹⁾.

MRI is preferred in most cases because of its superior definition of tumor size, local intra-osseous and extra-osseous extent, and the relationship of the tumor to fascial planes, vessels, nerves, and organs. Imaging of the entire involved bone is necessary to exclude the presence of skip lesions.

Follow-up MRI showed a response to therapy with a reduction of tumor size. However, there is contrast-enhancement of the larger lesions, which is suspicious for residual viable tumor tissue; however it cannot be reliably differentiated from granulation tissue, reactive hyperemia and capillary sprouting in necrotic areas ⁽⁸⁾.

Dynamic MR Studies have been used to improve MR images for assessing response to chemotherapy. Combined with histo-pathologic assessment, dynamic imaging parameters are recommended for evaluating the effect of Neoadjuvant chemotherapy in patients with Ewing's sarcoma. Dynamic MRI does have some limitations, as it has been observed to yield some false-positive results. The large pathologic vessels in a zone of active subperiosteal new bone formation, and the physeal vessels in young patients, occasionally lead to overestimation of tumor extent, especially towards the growth plate ⁽⁸⁾.

Skeletal Scanning with ^{99m}(MDP) is not useful for evaluating primary tumors because they often exaggerate the extent of the tumor. However, serial scans have been used to measure activity in the tumor, which is compared with activity in normal contra-lateral bone.

These dynamic studies of ^{99m}Tc-MDP have been utilized to distinguish between good responses and poor responses to chemotherapy ⁽¹⁰⁾.

Radionuclide bone scan is recommended to evaluate the entire skeleton for the presence of bone metastases.

Several studies have assessed the **quantitative changes in MIBI** uptake before and after chemotherapy and associated with the pathological evaluation of the degree of tumor necrosis. Also evaluate the diagnostic efficacy of (^{99m}) Tc-MIBI scintigraphy versus computed tomography (CT) and/or magnetic resonance imaging (MRI) in detecting the status of the disease and its recurrences.

The lesion/normal (L/N) uptake ratio was calculated in both early and delayed images and the washout rate (WR %) of (^{99m}) Tc-MIBI was obtained. Following 3-4 courses of chemotherapy, bone tumors were assessed by comparing the uptake ratio in the viable tumors with the amount of necrotic processes described in the surgically removed specimens. It was concluded that Tc^{99m} MIBI scan is a valuable diagnostic tool in assessment of response to chemotherapy in patients with bone sarcomas; its results are comparable to histopathological data ⁽¹¹⁾.

The utility of integrated PET/CT for initial staging is unclear. At least three series reported better sensitivity for PET over bone scan or other conventional imaging modalities for detection of bone metastases (9, 12).

PET/CT may have greater utility for monitoring the response of Neoadjuvant chemotherapy and in the postoperative evaluation for possible recurrence (13). Nevertheless, PET/CT is increasingly used for the initial staging of patients with Ewing sarcoma. Consensus-based guidelines from the National Comprehensive Cancer Network recommend a PET/CT scan and/or bone scan for initial workup, and a baseline PET is recommended at presentation by the Children's Oncology Group, if the primary bone tumor is negative on bone scintigraphy (14, 15).

Role of FDG PET/CT in Ewing Family of tumors (EFTs)

I- Initial Staging:

An effective evaluation for treatment of patients with Ewing's tumor depends upon an accurate assessment of the primary tumor extent and of the presence of metastatic disease. Currently, there is not a universally accepted staging system for the evaluation of the Ewing's tumors.

It has been demonstrated that the PET/CT helps in determining the presence and extent of sarcomas and may allow for the estimation of the histological stage of such tumors.

The measured standard uptake value (SUV) of a sarcoma has been utilized to predict the therapeutic response both before and after Neoadjuvant therapy, and such SUV is an independent and significant predictor of survival of patients in general; additionally, it allows for the identification of the areas with greater biological productivity within the lesion, guiding biopsies, thus reducing the probability of tumor grade underestimation and consequential adoption of inappropriate approach (16).

PET/CT and other conventional imaging methods can detect practically 100% of the primary tumors. However, a study has demonstrated that PET/CT was superior in the detection of lymph node metastases (sensitivity of 90% versus 25% respectively) and bone metastases (sensitivity of 90% versus 57%). In cases of Ewing's sarcoma, the superiority of PET/CT over bone scintigraphy in the detection of bone metastases was significant (sensitivity of 88% versus 37%, respectively) (17).

The higher sensitivity of PET/CT, as compared with bone scintigraphy in the detection of bone metastases is presumably due to the direct capability of PET/CT to identify lesions on the basis of the increased metabolic activity neoplastic cells.

On the other hand, bone scintigraphy identifies the lesions indirectly based on bone remodeling and repair (osteoblastic activity). That is particularly important in Ewing's sarcoma metastasis, which is typically mediated by the osteoclasts with bone destruction ⁽¹⁷⁾.

II- Assessment of chemotherapy response:

CT and MRI have been utilized to evaluate the therapeutic response of Ewing's tumors. However, such methods are limited, as minute structural and morphological alterations may be observed even in tumors whose viability is significantly reduced after treatment. Based on the intensity of FDG uptake by the lesions, PET/CT allows for the detection of tumor regression and progression even before the identification of morphological alterations by anatomical imaging methods such as CT and MRI. It is important to remind that the metabolic response precedes the volumetric decrease of the tumors ⁽¹⁸⁾.

The PET/CT findings either during or after the treatment can aid in important decision making about maintaining or modifying therapy, besides providing prognostic data ^(19,20).

The method relies on the quantitative analysis of SUV as well as on visual qualitative analysis to evaluate the degree of FDG uptake by the lesion. Neoplastic tissues with 30% decrease in SUV (quantitative analysis) as compared with the baseline, i.e. pre-chemotherapy study, are classified as good responders to the instituted treatment ⁽²⁰⁾. On the other hand; a 30% increase of SUV characterizes disease progression. Some authors also advocate that a SUV reduction to less than 2.5 after chemotherapy is associated with an increase in disease-free survival, with 79% positive predictive value for favorable response (less than 10% of viable neoplastic tissue in the lesion). According to the above-mentioned data, PET/CT can be an excellent tool for the evaluation of therapeutic response of tumors of the Ewing's sarcoma family. However, studies with larger populations are still necessary to determine which imaging method is best, either anatomical methods such as CT and MRI or physiological methods such as PET/CT, by means of glucose metabolism ⁽²⁰⁾.

Clinical utility of other volume-based F-18 FDG PET imaging markers in assessment of therapy response:

Many studies investigating the metabolic parameters of FDG PET/CT have focused on SUV max and have indicated that SUV max is correlated with histo-pathological grade and clinical outcomes in sarcoma patients ^(21, 22 and 23).

Also SUV max has been suggested being a significant prognostic factor for overall and progression- free survival ^(24, 25).

Volume-based F-18 FDG PET imaging markers in terms of metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been introduced to overcome the obvious limitations of SUV max, by including several important prognostic tumor characteristics, such as heterogeneity, size, and burden; that is, an inclusion of the total volume and total activity of metabolically active tumor cells.

This theoretical advantage has been verified by several studies reporting

significant prognostic properties in terms of prediction of treatment response and survival in a diversity of solid tumors ^(26, 27).

Metabolic tumor volume (MTV) is defined as the volume of the tumor demonstrating FDG uptake. It represents a volumetric and metabolic biomarker, and estimates tumor volume based on the distribution of metabolic activity. Therefore, unlike SUV max, which is a single-pixel representation of the maximum FDG uptake by the tumor, MTV quantifies the overall tumor burden ^(28, 29).

TLG is defined as the tumor volume multiplied by SUV mean of included voxels. Because this parameter incorporates both the MT and SUV, it represents both the degree of FDG uptake and the size of the tumor. Like MTV, TLG theoretically represents the total activity of the metabolically active cancer cells ⁽³⁰⁾.

Figure 1 showed good response to chemotherapy using TLG with histological prove as compared to SUV max.

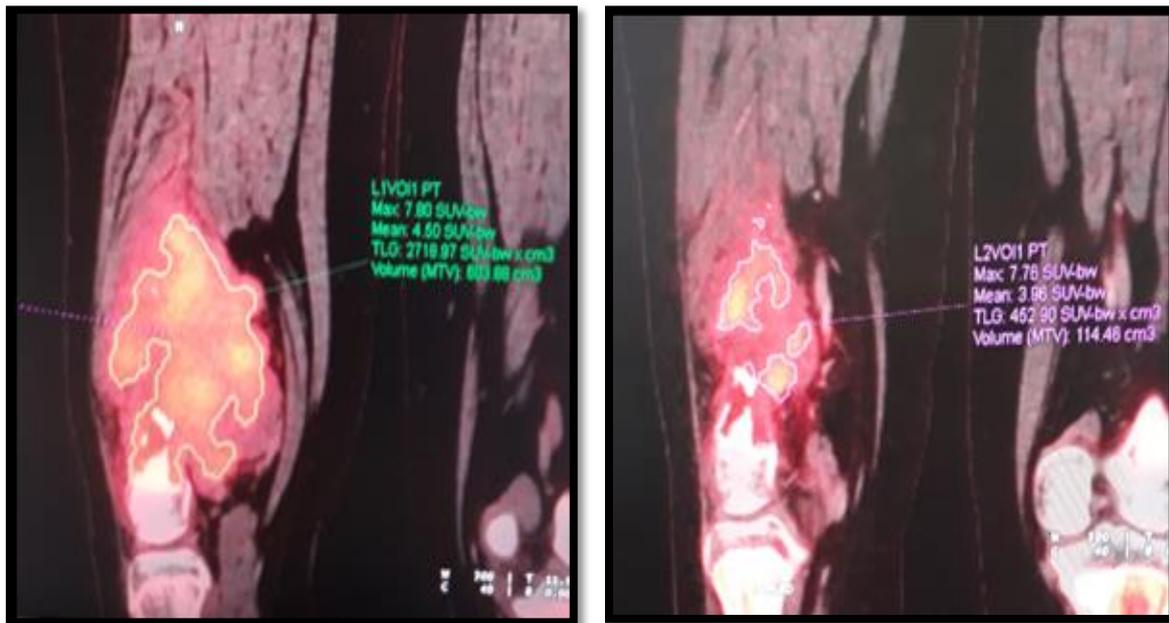


Fig (1): 12 yrs male with Ewing Sarcoma. (A) Initial PET/CT and after 2 cycles of chemotherapy with histological response post-resection 98%. SUV max was the same pre and post-chemotherapy = 7.8, while TLG significantly decrease (TLG pre-chemotherapy = 2718 and Post-chemotherapy = 452).

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