PET/CT in the diagnosis and prognosis of osteosarcoma

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1. ABSTRACT

Osteosarcoma is an aggressive malignancy that usually occurs in children and young adults, and long-term survival is only about 20% in patients with metastasis or recurrent disease. Traditional non-invasive techniques, such as positron-emission tomography (PET) scanning, magnetic resonance imaging (MRI) or computed tomography (CT) scanning, may not identify single lesions in the early stage or accurately detect small lesions. A novel technique, positron emission tomography/computed tomography (PET/CT), which is widely used in clinical practice, shows more accuracy, sensitivity, and specificity in the diagnosis of osteosarcoma. PET/CT provides information not only for diagnosis of primary lesion and metastases, but also for histological response to neoadjuvant chemotherapy and prognosis. Here, we review the role of PET/CT in the diagnosis and prognosis of osteosarcoma.

2. INTRODUCTION

Osteosarcoma is an aggressive malignancy in a bone with a 5-year survival of 60%-70% after surgery; however, 5-year survival reduces to about 20% in those patients with metastasis or recurrence (1-3). Traditionally, osteosarcoma is non-invasively diagnosed with a combination of positron-emission tomography (PET) scanning, magnetic resonance imaging (MRI) or computed tomography (CT) scanning (4-6). However, those traditional non-invasive techniques in osteosarcoma diagnosis are not able to identify a single lesion in an early stage or accurately detect small lesions. In recent years, a novel technique, positron- emission tomography/computed tomography (PET/CT) using fluorine-18-fluorodeoxyglucose (F-18-FDG) has become widely used in clinical practice.

PET/CT is a nuclear technique combining PET and CT scans to acquire sequential images and provide functional tissue information, which is based on the distribution of glucose metabolism. In the diagnosis of various malignancies, the integration of tissue metabolic activity with anatomical information can improve diagnostic accuracy more that PET or CT alone (7-10). In bone sarcoma, F-18-FDG PET/CT showed a higher sensitivity than F-18-FDG PET in diagnosis, and more accuracy in tumor staging, restaging, and recurrence assessment (11). When compared with MRI, the diagnostic value of PET/CT in osteosarcoma is comparable to the whole-body mode of MRI (12-14). Thus, in this review we will discuss the role of PET/CT in the diagnosis and prognosis of osteosarcoma.

3. PET/CT IN THE DIAGNOSIS OF OSTEOSARCOMA

For the diagnosis of osteosarcoma, PET/CT has showed advantages in the accuracy of diagnosis between benign and malignant lesions. When compared with conventional X-ray, CT, or MRI, F-18-FDG PET/
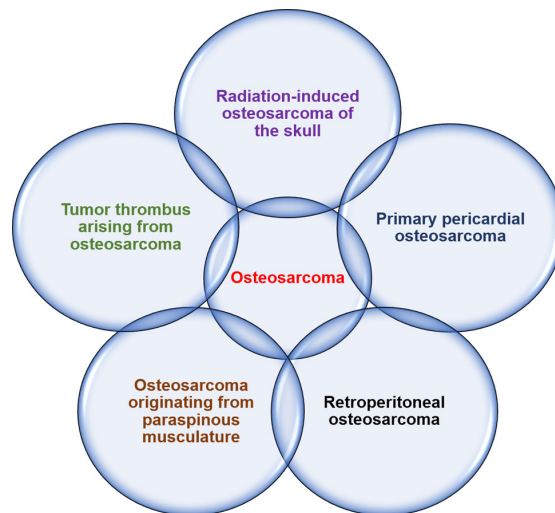
Figure 1. PET/CT in the diagnosis of rare cases. PET/CT could be helpful in the differential diagnosis between osteosarcoma and rare sites, such as radiation-induced osteosarcoma of the skull, tumor thrombus arising from osteosarcoma, primary pericardial osteosarcoma, rare malignant extraskeletal osteosarcoma originating from paraspinous musculature, or retroperitoneal osteosarcoma.

CT could provide whole-body metabolic information, which could be useful in evaluating osteosarcoma, even that secondary to fibrous dysplasia (15). When compared with SPECT, high resolution CT, or ^{99m}Tc-DMSA (V), the technique of F-18-FDG PET/CT could detect subcentimeter lesions even in lung nodules, showing an impressive accuracy in lesion assessment (16). That advantage in accuracy is quite valuable in early diagnosis, considering the poor prognosis of patients with advanced-stage disease (1-3). Moreover, F-18-FDG PET/CT is superior in bone scintigraphy and for detecting bone metastases, providing valuable information in staging and restaging of patients with osteosarcoma and evaluating their overall survival (17). The high sensitivity of F-18-FDG PET/CT in detecting osteosarcoma is due to the relationship between F-18-FDG uptake and cellular proliferation and bone differentiation following MYC inactivation (18).

3.1. PET/CT in the diagnosis of pediatric osteosarcoma

Since osteosarcoma is the most common pediatric malignant bone tumor, the use of PET/CT in pediatric care should be considered (19). In the diagnosis of solid primary tumors in children, F-18-FDG PET/CT is more sensitive than CT in detecting pulmonary metastases with a diameter more than 0.5 cm and lymph node metastases with a diameter of less than 1 cm (20), suggesting the advantage of PET/CT in pediatric tumor diagnosis. There could be a particularly useful role for PET/CT in the diagnosis of childhood osteosarcoma. Walter and colleagues (21) found that F-18-FDG PET/CT had an accuracy of 100% in the diagnosis of pediatric sarcoma, whereas ^{99}Tc-MDP had an accuracy of 82% in a case-based analysis (21). This demonstrated a greater accuracy in the diagnosis of pediatric osteosarcoma by F-18-FDG PET/CT compared

with ^{99}Tc-MDP. Moreover, when compared with CT or MRI, F-18-FDG PET/CT showed similar advantages and excellent performance. The accuracy of F-18-FDG PET/CT in detecting bone lesions is 95%, whereas CT detects 67% of lesions and MRI 86% (22). The accuracy of F-18-FDG PET/CT is related to F-18-FDG uptake by bone. The SUV(max) in bone sarcomas is significantly higher than that in Ewing or soft tissue sarcomas (23). Thus, F-18-FDG PET/CT has advantages in detecting pediatric osteosarcoma, when compared with traditionally non-invasive techniques. It should be widely used for the diagnosis of pediatric patients.

3.2. PET/CT in the differential diagnosis between osteosarcoma and mimic diseases

Examinations using PET/CT have shown its power in the differential diagnosis between osteosarcoma and mimic diseases. Rare benign lesions, such as myositis ossificans circumscripta, reactive periostitis ossificans, and osteopetrosis are reported to be successfully differentiated from osteosarcoma by using F-18-FDG PET/CT (24-26). Even a malignant lesion, a rare osteoblastoma of the mandible, could be differentiated by F-18-FDG PET/CT (27). In addition to F-18-FDG PET/CT, 68Ga-PSMA PET/CT could differentiate fibrous dysplasia and areas of malignant transformation in fibrous dysplasia based on mapping tumor neoangiogenesis in osteosarcoma (28). Precise diagnosis could help the physician offer appropriate treatment to patients.

3.3. PET/CT in the diagnosis of rare cases

Even in the differential diagnosis between osteosarcoma and rare cases, PET/CT shows an advantage in the accuracy of diagnosis. For instance, radiation-induced osteosarcoma of the skull, or tumor

thrombus arising from osteosarcoma could be detected by PET/CT (29,30). Moreover, primary pericardial osteosarcoma, a rare malignant extraskeletal osteosarcoma originating from paraspinous musculature, and retroperitoneal osteosarcoma have also been reported to be detected by PET/CT (31-33) (Figure 1). In these cases, osteosarcoma occurred at rare sites, and this usually leads to a wrong diagnosis or missed diagnosis. The ability of PET/CT to detect these rare cases shows a powerful advantage for accurately and specifically diagnosing osteosarcoma.

However, this technique is less successful in the particular case of a differential diagnosis between osteosarcoma and giant cell tumor, a benign tumor of bone. The maximum standardized uptake value (SUVmax), indicating the glucose taken up in the tissues, is usually higher in malignant tissue than that in a benign tumor. However, the SUVmax of F-18-FDG PET/CT in osteosarcoma is lower than that in giant cell tumor (34), and leads to an inaccuracy in that differential diagnosis. This may be due to the overexpression of hexokinase-2 in giant cell tumor of bone, and high FDG accumulation (34). Thus, cytokines in certain tumor cells that affect FDG uptake may influence the accuracy of F-18-FDG PET/CT in differential diagnosis between osteosarcoma and benign tumors. Until now, only diagnosis of giant cell tumor has been reported to encounter that problem.

4. PET/CT IN THE RELAPSE OF OSTEOSARCOMA

When identifying the local recurrence of bone sarcoma, MRI is usually considered, whereas PET/CT serves as a complementary method. A recent study found that dual-time point F-18-FDG PET/CT has a good performance in assessing local recurrence in high grade osteosarcoma (35). Its sensitivity, specificity, and accuracy in high grade sarcomas at 120 minutes are 100%, 80%, and 89%, but only 50%, 75% and 66% in low grade sarcomas, respectively (35). Furthermore, F-18-FDG PET/CT could detect local recurrence more than 3 years after tumor resection (36). Chang and colleagues (36) followed up 109 patients with osteosarcoma of the extremities. They found that the combination of SUVmax at the time of local recurrence or at the last follow-up with its changes from SUVmax 3 months later was more useful than one measurement alone for the prediction of local recurrence (36).Thus, F-18-FDG PET/CT would be a promising option in detecting local recurrent osteosarcoma of high grade or over a long-term follow-up, and this has been described in a later study (37).

The aforementioned study further found that recurrence in the lung could also be found. The sensitivity, specificity, and accuracy are respectively 80%, 100%, and 92% (37). In addition to a high

incidence of lung tumor relapses, some rare cases of relapse of osteosarcoma could be also sensitively detected by FDG PET/CT. This technique allowed the successful detection of a solitary retroperitoneal metastasis as the initial relapse of osteosarcoma in a 14-year-old boy (38).

## 5. PET/CT IN THE METASTASES OF OSTEOSARCOMA

Because PET/CT can provide whole-body metabolic information, it has advantages in detecting metastases of osteosarcoma. In the detection of bone metastases of 206 osteosarcoma patients, F-18-FDG PET/CT shows that its sensitivity, specificity, and accuracy were respectively 95%, 98%, and 98%, which is more sensitive and accurate than ^{99m}Tc-methylene diphosphonate bone scintigraphy (39); For the latter technique, its sensitivity, specificity, and accuracy were respectively 76%, 97%, and 96% (39).

F-18-FDG PET/CT also has a good performance in the detection of distant metastases of high-grade osteosarcoma. In a study with 89 patients, this technique has a sensitivity and specificity of 95% and 96%, respectively, when detecting distant metastases, and 100% and 90% when detecting lymph node metastases (40). F-18-FDG PET/CT is also accurate for assessing lung nodules in pediatric patients with osteosarcoma; moreover, an SUVmax value larger than 1 is a useful cut-off point to discriminate malignancy from benign lesions (sensitivity and specificity were 90.3% and 90.6%, respectively) (41). As with the lung, the liver is another common site of metastasis. F-18-NaF PET/CT and F-18-FDG PET/CT have been reported to allow accurate detection of hepatic metastases in patients with osteosarcoma (42,43). Recently, a study with dogs explored the use of PET/CT in the identification of gross metastatic lesions that were subsequently treated with stereotactic radiation therapy (44). This study confirms the value of PET/CT for the detection of metastases of osteosarcoma.

In cases witj rare sites of osteosarcoma metastases, PET/CT has been reported to be useful in supporting the diagnosis. Brain, kidney, bone marrow, or even ventricle metastases have been successfully detected by F-18-FDG PET/CT or F-18-NaF PET/CT (45-47). Because of the limitation of sample size, we need further studies using a large sample to confirm the accuracy, sensitivity, and specificity of PET/CT in these rare metastases of osteosarcoma .

6. PET/CT IN THE HISTOLOGICAL RESPONSE TO NEOADJUVANT CHEMOTHERAPY OF OSTEOSARCOMA

The high accuracy, sensitivity, and specificity of PET/CT in detecting osteosarcoma determine its
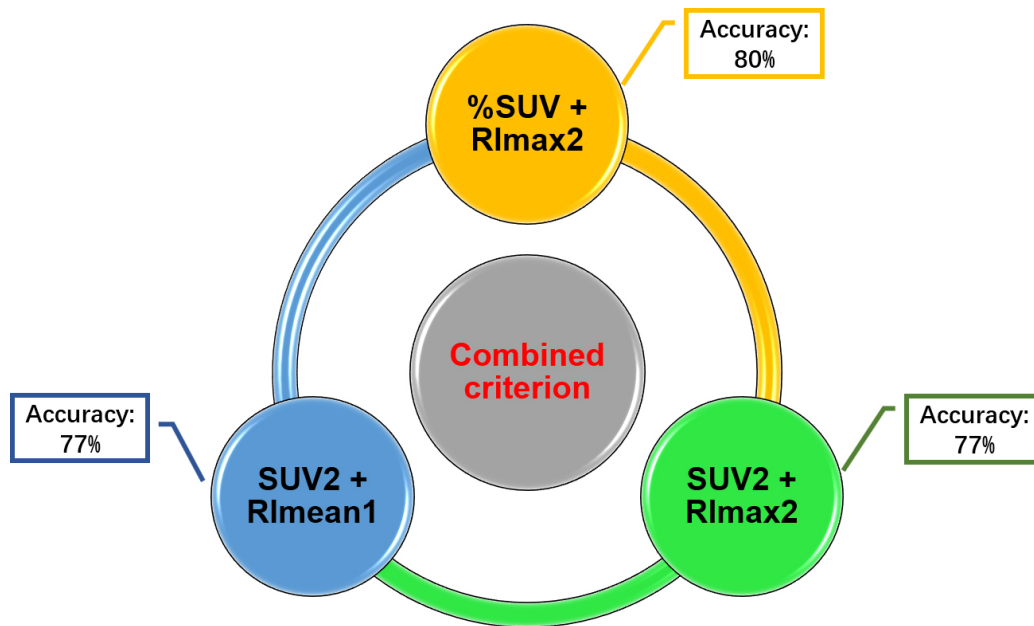
Figure 2. Combined criteria of F-18-FDG PET/CT in the histological response to neoadjuvant chemotherapy of osteosarcoma. In dual-phase F-18-FDG PET/CT, the combination of percentage SUV and RImax2, or SUV2 and RImean1, or SUV2 and RImax2 are also predicative for histological response to neoadjuvant chemotherapy in osteosarcoma. The accuracy is 81%, 77%, and 77%, respectively. SUV: the percentage changes between SUVmax before and after chemotherapy; SUV2: SUV after chemotherapy; RImean1: early/delayed SUVmean change before chemotherapy; RImax2: early/delayed SUVmax change after chemotherapy

usage in assessing treatment response. In patients with resectable, primary high-grade bone sarcomas, the tumor FDG-SUVmax was significantly lower in responders from baseline than in non-responders (48). The 60% decrease in tumor FDG-uptake could be a threshold for metabolic response (48). Even in patients with craniofacial bone sarcomas, F-18-FDG PET/CT has been found more reliable than standard imaging, such as MRI, for evaluating the histological response to neo-adjuvant chemotherapy (49).

For children and young adults with osteosarcoma, the SUVmax at 5 weeks, 10 weeks, and percentage change from baseline at 10 weeks were highly predictive of histological response (50). The SUVmax, SUVmax ratio, and combined metabolic/volumetric index (metabolic tumor volume [MTV] and total lesion glycolysis [TLG]), could predict histological response to neoadjuvant chemotherapy (51). After one cycle of chemotherapy, apart from SUVmax, an MTV more than 47 mL, and TLG more than 190 g were related to a poor histological response. The sensitivity, specificity, and accuracy of these parameters were 71%, 85%, and 77%, respectively, (52). When the MTV at a fixed standardized uptake value threshold of 2.0. is more than 105 ml, histological response to neoadjuvant chemotherapy is likely to be poor (53).

Using dual-phase F-18-FDG PET/CT we found that the following factors were also predictive for histological response to neoadjuvant chemotherapy in osteosarcoma: 1. the combination of the percentage

changes between SUVmax before and after chemotherapy and early/delayed SUVmax change after chemotherapy, 2. SUV after chemotherapy and early/delayed SUVmean change before chemotherapy, or 3. SUV after chemotherapy and early/delayed SUVmax change after chemotherapy (54). The accuracy is 81%, 77%, and 77%, respectively (54). (Figure 2)

When combined with F-18-FDG PET/CT and MRI, the sensitivity, specificity, and accuracy could be 83%, 87%, and 85%, respectively, in predicting histological response after neoadjuvant chemotherapy in osteosarcoma. In comparison, the sensitivity, specificity, and accuracy are 67%, 87% and 78% for ΔSUV, and more than 83%, 73%, and 78% for ΔADC, respectively (55).

Interestingly, in a study with canine osteosarcoma, PET/CT was evaluated to test the dos distribution of [90]Y- hydroxide liquid brachytherapy in the tumor bed and surrounding tissues (56). The significant heterogeneity with multiple hot spots at injection sites shown by PET/CT suggested a potential use in predicting the response to 90Y- hydroxide brachytherapy. Clinical data are needed, and a study on this subject could be investigated in future.

7. PET/CT IN THE PROGNOSIS OF OSTEOSARCOMA

For the prognosis of patients with osteosarcoma, an index of PET/CT could provide

valuable information. Both high SUVmax of F-18-FDG PET/CT before and after chemotherapy were associated with a poor progression-free survival (57,58). The cut-off point of SUVmax may be greater than 15 g/mL before chemotherapy and greater than 5 g/mL after chemotherapy (57). However, there is not sufficient evidence to support the relationship between SUVmax and tumor necrosis (58). For long-term prognosis, examination by F-18-FDG PET/CT showed that patients with SUVmax below 10 may have a high incidence of 5-year survival (40). Notably, the SUVmax of F-18-FDG PET/CT before treatment should be combined with histological grading for prediction of survival in patients with osteosarcoma, and SUVmax alone may be not an independent index in predicting patients' survival (59). Palmerini and colleagues (60) further found that SUVmax before chemotherapy may be the only independent pretreatment prognostic factor, whereas neither SUVmax after chemotherapy or metabolic response was related to 3-year event-free survival. In contrast to SUVmax, the TLG of F-18-FDG PET/CT before treatment may be an independent predictor for survival (61).

8. CONCLUSIONS

The application of PET/CT has the advantage of accuracy, sensitivity, and specificity in the diagnosis of osteosarcoma. It provides information not only for diagnosis of primary lesions and metastases, but also for histological response to neoadjuvant chemotherapy and for prognosis. However, the economic cost of PET/CT in some regions limits its wide use. If the technique of PET/CT is developed and its cost is decreased, PET/CT would bring benefits to more patients in the future.

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Abbreviations: PET, positron-emission tomography; CT, computed tomography; PET/CT, positron emission tomography/computed tomography; MRI, magnetic resonance imaging; F-18-FDG, fluorine-18-fluorodeoxyglucose; SUVmax, maximum standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis

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