Evidence-Based PET for Cutaneous, Musculoskeletal and Unknown Primary Tumours

8

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8.1 Introduction

PET/CT is extremely useful method in cutaneous and musculoskeletal tumours. In this chapter, the evidence from the literature concerning PET or PET/CT in melanoma, sarcomas, bone metastases, cancer of unknown primary (CUP) and paraneoplastic syndromes were analysed.

8.2 PET in Malignant Melanoma

8.2.1 Introduction

Melanoma is a highly malignant tumour having its origin in melanocytes from the epidermal skin layer. As prognosis is highly dependent on lymph node involvement and presence of distant metastases at the time of diagnosis, a precise staging is important for determining prognosis and choosing the fittest therapy for the patient [1–4].

8.2.2 Staging

^{18}F -FDG PET/CT in staging melanoma has to be performed as a whole body protocol from head to toe to visualize the whole skin. Nonetheless, the usefulness of ^{18}F -FDG PET/CT is limited in staging of tumour expansion and detection of satellite metastases. For the recognition of lymph nodal metastases, ultrasound and histological examination of the sentinel lymph node have a higher sensitivity and specificity than ^{18}F -FDG PET/CT [5, 6]. Vural Topuz et al. showed that ^{18}F -FDG PET/CT is probably negative in the first year post-surgery if the sentinel lymph node biopsy was negative. Hence, performance of ^{18}F -FDG PET/CT is not recommended in early stage melanoma for not providing any significant clinical contribution [7].

In contrast, ^{18}F -FDG PET/CT is well established for imaging of distant metastases. In a meta-analysis of nine studies, Rodriguez Rivera et al. found out usefulness of ^{18}F -FDG PET/CT in staging of stage III melanoma having a high sensitivity (89.4%) and specificity (88.8%) [8]. Also Xing et al. valued ^{18}F -FDG PET/CT as the most sensitive and specific method for detecting distant metastases [6]. ^{18}F -FDG PET/CT is even superior to morphologic imaging and has replaced CT and magnetic resonance imaging (MRI) almost completely [1].

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8.2.3 Restaging and Treatment Monitoring

The early detection of disease progression or recurrence has a huge impact on prognosis of melanoma. The usefulness of ^{18}F -FDG PET/CT has been proven not only for the staging of advanced melanoma but also for the detection of recurrences showing a sensitivity of 96% and a specificity of 92% [7]. Accordingly, ^{18}F -FDG PET/CT frequently leads to a change of treatment plan [6]. Due to a scarce number of prospective studies regarding use of ^{18}F -FDG PET/CT in melanoma, more studies are needed to find the most effective and cost-effective intervals in follow-up.

8.3 PET in Sarcomas

8.3.1 Introduction

Sarcomas are malignant tumours originating from mesenchymal cells. They are a relatively rare cancer and represent only 1% of all malignant tumours but extremely frequent in children. They can be divided in soft tissue, osseous and chondral sarcomas. Soft tissue sarcomas are a group of heterogeneous tumours as rhabdomyosarcoma, leiomyosarcoma, fibrosarcoma, liposarcoma, angiosarcoma, etc. and they are the fourth most common solid tumours in children. The bone sarcomas are the osteosarcoma and the Ewing sarcoma. Classical imaging methods for sarcomas are X-ray, CT for control of stability and MRI for the illustration of the expansion in soft tissues. Biopsy and histopathological examination ensure diagnosis [9, 10].

8.3.2 Staging

PET/CT offers the possibility of simultaneous acquisition of bone lesions and their expansion in soft tissue and is very useful for the staging of sarcomas due to its high sensitivity, specificity and accuracy. The performance of ^{18}F -FDG PET/CT in the initial staging provides information of

the initial metabolism activity of the tumour. This is important for the follow-up and the evaluation of the therapy response [11]. About ^{18}F -FDG PET/CT in sarcomas, according to evidence-based data, the values vary between 86 and 96% for sensitivity and from 80 to 96% for specificity [12–15]. In particular, this hybrid imaging method is very useful for detecting distant metastases, as osseous and lung metastases [12, 15]. Furthermore, ^{18}F -FDG PET/CT might have a relevant impact on the development of treatment strategy plan [15]. Additional to the high diagnostic quality, ^{18}F -FDG PET/CT has also a prognostic value in sarcomas. Chen et al. found out that semi-quantitative PET parameters showed a significant prognostic value for overall survival and thus are useful tools in identifying high-risk patients [16]. These findings were confirmed by other authors reporting that a high maximum standardized uptake value (SUVmax) may predict a significantly shorter overall survival period [17].

8.3.3 Restaging and Treatment Monitoring

^{18}F -FDG PET/CT is a valuable method for detecting post-surgery recurrence in patients with sarcomas [12]. Liu et al. found a sensitivity of 92% and a specificity of 93% for the detection of recurrence in sarcoma [14]. Hongtao et al. reported that ^{18}F -FDG PET/CT is valuable for predicting the histological response to chemotherapy as they found a response to neoadjuvant chemotherapy in osteosarcomas with a sensitivity of 73% and a specificity of 86% [18]. Muheremu et al. showed that ^{18}F -FDG PET/CT assesses the efficacy of neoadjuvant therapy with a sensitivity and specificity of 79% and thus is a reliable imaging method not only in diagnosis but also in treatment control of osseous and soft tissue tumours [13]. Also Chen et al. valued post-treatment SUVmax as useful in monitoring therapy response [16]. Li et al. had similar results confirming that SUVmax before and after chemotherapy has effective prognostic significance for survival outcomes [19].

8.4 PET for Bone Metastases

8.4.1 Introduction

Bone metastases originate most frequently from breast cancer in women and from prostate carcinoma in men (each 60%) followed by lung carcinoma (25%), renal cell and thyroid carcinoma. Bone metastases can be differentiated in osteoblastic metastases which are typical for the prostate carcinoma, osteolytic metastases which occur in renal cell, thyroid or colon carcinomas and mixed osteoblastic and osteolytic metastases for example from breast or lung cancer. They are localized often in the spine (60%) but also in the pelvis, proximal femur and skull, rarely in distal bones. Symptoms are mainly pain, radicular symptoms if a spine metastasis causes nerve root compression and functional impairment. Furthermore, metastases can cause instability of the bone with the consequent risk of fracture [20].

8.4.2 Detection of Bone Metastases

The probably most frequently performed imaging method for osseous staging is the bone scintigraphy (BS). In the actual development, this method is being replaced by PET/CT with different tracers as ^{18}F -FDG (which has the advantage to represent nearly all body districts) and ^{18}F -Fluoride which is more osseous specific. In a meta-analysis, Liu et al. found a sensitivity of 93% and a specificity of 95% for ^{18}F -fluoride PET/CT in the detection of bone metastases. This method showed significantly higher sensitivity and specificity compared to BS and thus a superior diagnostic performance in bone metastases detection and higher accuracy [21]. Shen et al. achieved similar results showing a sensitivity of 92% and a specificity of 93% for ^{18}F -fluoride PET/CT. Compared with BS, it showed both higher sensitivity and specificity, whereas compared with ^{18}F -FDG PET/CT it showed only a higher sensitivity but no significant difference in specificity. Consequently, the authors describe an excellent diagnostic capacity for the detection of

bone metastases and advantages compared with BS and ^{18}F -FDG PET/CT [22].

Duo et al. analysed the performance of PET/CT with different tracers in comparison with gadolinium-enhanced MRI for detecting bone metastases: similar sensitivity and specificity values for each method were found and consequently an excellent diagnostic performance for the detection of bone metastases for both methods [23]. On the contrary, regarding only vertebral metastases, MRI showed a better performance than PET/CT both in sensitivity and specificity. This procedure outranged also all other imaging methods as CT or BS with tomographic acquisition (SPECT) [24].

Concerning the prognostic value of ^{18}F -FDG PET/CT, Jeong et al. showed that patients with solid tumours and a lower level of ^{18}F -FDG uptake in the bone marrow have a better event free and overall survival than patients with higher bone marrow ^{18}F -FDG uptake and therefore propose to use the ^{18}F -FDG uptake in the bone marrow for risk stratification of tumour progression [25].

8.5 PET for Cancer of Unknown Primary (CUP) and Paraneoplastic Syndromes

8.5.1 Introduction

Cancer of unknown primary (CUP) is a syndrome defined by the presence of a metastatic disease without identified primary tumour. In 2–5% of all malignant tumours, the localization of the primary tumour is unknown. CUP occurs in a heterogeneous group of cancers most frequently in malignant melanoma, neuroendocrine tumours, carcinoids, small cell lung carcinoma and head and neck cancer. Despite of modern imaging methods, CUP remains a challenge in clinical routine. As prognosis is rather poor, the identification of the primary tumour can be important to adjust therapy and improve survival [26].

Paraneoplastic syndromes arise from tumour secretion of hormones, peptides or cytokines or

from immune cross-reactivity between malignant and normal tissues. Paraneoplastic syndromes may affect diverse organ systems, most notably the endocrine, neurologic, dermatologic, rheumatologic and hematologic systems. The most commonly associated malignancies include small cell lung cancer, breast cancer, gynaecologic tumours and hematologic malignancies. In some instances, the timely diagnosis of these conditions may lead to detection of an otherwise clinically occult tumour at an early and highly treatable stage [27].

8.5.2 Impact of PET in Patients with CUP

Since patients with CUP syndrome usually underwent a vast diagnostic procedure with negative results, the patients setting in which ^{18}F -FDG PET/CT is performed with this question is highly selected. Consequently, the search for a primary tumour in CUP syndrome is more difficult than in other diseases. Nevertheless, Burglin et al. found a detection rate of unknown primary tumours in 41% of cases by using ^{18}F -FDG PET/CT and they recommended an early use of ^{18}F -FDG PET/CT to obviate too much useless diagnostic procedures [28].

8.5.3 Impact of PET in Patients with Paraneoplastic Syndromes

In patients with suspected paraneoplastic syndrome, ^{18}F -FDG PET/CT showed a high accuracy for the detection of underlying malignancies with a sensitivity of 81% and a specificity of 88% [29]. Also in patients with paraneoplastic neurological syndrome, ^{18}F -FDG PET/CT showed a high diagnostic performance with a detection rate of 15%, a sensitivity of 87% and specificity of 86% [30]. Generally, a heterogeneity in study design and diagnostic workup and the small number of patients in the available studies reduce interpretability of the data [29, 30].

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