The use of fluorine-18 fluorodesoxyglycose-positron emission tomography for treatment monitoring in patients with soft tissue sarcomas

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Abstract

Positron emission tomography (PET) using 2-deoxy-2-[^{18}F] fluoro-D-glucose (^{18}F-FDG) has been used with increased frequency in the care of patients with soft tissue sarcomas to predict malignant potential of tumours, prognosis of survival and response to chemotherapy. Although there are several other PET tracers, which have found limited use in sarcomas, this review focuses on the use of ^{18}F-FDG, which is the most common used tracer. Recent literature and developments covering major aspects of PET imaging in the management of patients with soft tissue sarcomas will be discussed in this review with focus on treatment monitoring. Positron emission tomography cannot be used instead of histology to diagnose sarcomas, but may aid in biopsy planning. In particular, using the last generation PET/computerized tomography (CT) scanners, it is easily possible to combine morphological information provided by CT and/or magnetic resonance imaging with biological information based on PET. Imaging with PET has been shown to detect accurately primary tumours as well as lymph node and bone metastases in patients with sarcomas. In soft tissue sarcomas, changes in tumour ^{18}F-FDG uptake correlate significantly with histopathological response, risk of tumour recurrence and survival. *In conclusion,* PET is emerging as an important imaging modality in the management of patients with soft tissue sarcomas.

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Introduction

Soft tissue sarcomas are a heterogeneous group of connective tissue malignancies arising from tissue of mesenchymal origin. They constitute less than 1 % of all adult malignancies. The five-year overall survival rate in patients with soft tissue sarcomas of all stages amounts to only 50%-60% [1]. Most patients die of metastatic disease, which becomes evident in 80 % of the cases within two to three years after initial diagnosis [2]. Despite improvements in local tumour control rates, the treatment of patients with high risk soft tissue sarcomas remains challenging. For patients with no evidence of metastatic disease, surgery is the primary treatment of choice. The high rate of distant disease recurrence suggests that undetectable metastatic disease is present in a significant percentage of patients with large, high grade soft tissue sarcomas at the time of surgery. Therefore, an effective systemic treatment with chemotherapy is needed. Doxorubicin and ifosfamide are the most active single-agents in the treatment of soft tissue sarcomas with response rates above 20% [3].

It is important to identify patients who are likely to benefit from chemotherapy early in the course of treatment. Morphologic imaging modalities like computed tomography (CT) and magnetic resonance imaging (MRI) can be used for the assessment of tumour localization, size, and infiltration of the surrounding tissues as well as for the presence of satellite metastases. However, it has not been well established whether or not a significant change in the tumour size after chemotherapy is a meaningful indication for the outcome of patients with soft tissue sarcomas. Standard radiographic response has not correlated consistently with histological response or with disease-free or overall survival [4-6]. Other methods to identify patients with limited, potentially curable disease who are likely to benefit from chemotherapy would be useful. Therefore, 2-deoxy-2-[^{18}F] fluoro-D-glucose (^{18}F-FDG)-PET has found increasing interest and use in the field of oncology, because it allows functional imaging of viable tumour tissue as a nuclear imaging technique providing crude spatial information about metabolic processes rather than only anatomic details [7-8].

In this review, we discuss the role and contribution of PET imaging using ^{18}F-FDG in the assessment of tumour grade, biopsy guidance, surveillance, staging, treatment monitoring,

and outcome, in patients with soft tissue sarcomas, in the context of a rapidly expanding field of molecular imaging.

Positron emission tomography

Positron emission tomography imaging detects the whole-body distribution of positron-emitting radioisotopes that are linked to biologically active molecules. This allows a non-invasive, three-dimensional visualization and quantitative assessment of physiologic and biochemical processes in vivo [9-10]. By far, the most frequently used PET tracer in clinical oncology is ^{18}F-FDG. Most cancers rely on glycolysis rather than oxidative metabolism as their source of adenosine triphosphate even in the presence of oxygen (Warburg effect). The metabolism of glucose, as the predominant substrate for energy production in cancer cells, can be imaged with the glucose analogue ^{18}F-FDG. Furthermore, using the last generation PET/CT scanners, it is easily possible to combine morphological information provided by CT with biological information based on PET.

Assessment of tumour grade using ^{18}F-FDG-PET

It has been proposed in several studies to use ^{18}F-FDG-PET as a "non-invasive biopsy" for determining tumour grade in soft tissue sarcomas [11-14]. It could have been shown that the tumour standardized uptake value (SUV_{max}) differed significantly among the different grading scales, moreover, ^{18}F-FDG uptake correlated significantly with markers of cell proliferation like mitotic activity, Ki-67 and p53 expression. However, there was a considerable overlap of tumour ^{18}F-FDG uptake among different tumour grades especially in the low standardized uptake value (SUV) range. Grade 2 and 3 tumours could not be discriminated reliably. Better results have been reported when using dynamic data acquisition and a two-tissue compartment model for evaluation. Based on six kinetic parameters of the ^{18}F-FDG kinetics, an accuracy of 84% for Grade 3, 37.5% for Grade 2, 80% for Grade 1, and 50% for lipomas was reported [15]. However, it is obvious that ^{18}F-FDG-PET should not be used instead of histopathology to diagnose sarcomas or evaluate histopathological sarcoma grading. Evaluation by pathology remains the gold standard in the diagnosis and grading of soft tissue sarcomas. Nevertheless, ^{18}F-FDG-PET seems to be useful to differentiate high grade sarcomas from low grade sarcomas and benign lesions. Although there is no systematic study, ^{18}F-FDG-PET may help in surgical biopsy planning, because it guides to the region of the most proliferative cells [16].

^{18}FDG-PET for staging of sarcoma patients

A multicenter trial in 46 paediatric sarcoma patients investigated the accuracy of ^{18}F-FDG-PET for initial staging [17]. Fluorine-18 fluorodesoxyglycose-positron emission tomography imaging detected primary tumours, lymph node involvement, and bone manifestations with higher sensitivity than conventional imaging modalities that included ultrasound, computed tomography, magnetic resonance imaging, and bone scintigraphy. Magnetic resonance imaging has been shown to be superior to ^{18}F-FDG-PET in the early detection of spinal metastasis, which could be demonstrated in a retrospective study of 33 patients with myxoid liposarcoma [18]. Taken together, ^{18}F-FDG-PET should not replace computed tomography scans for staging soft tissue sarcomas. However, the use of hybrid PET/CT scanners could overcome the limited ability of ^{18}F-FDG-PET in detecting lung metastases; the hybrid scanner was significantly more accurate than PET alone for staging and follow-up of patients with pulmonary metastases [19].

The value of ^{18}F-FDG-PET for restaging of soft tissue sarcomas was addressed only in small studies [20-21]. For example, FDG-PET correctly identified local disease recurrence in 21 of 24 patients with soft tissue sarcomas and correctly classified 12 of 13 benign lesions as true negative (sensitivity and specificity of 88% and 92%, respectively) [21]. With the advantage of combined PET/CT imaging, soft tissue sarcoma patients can now be staged accurately in a single imaging session [22].

Response assessment to chemotherapy using ^{18}F-FDG-PET

During the last decade, changes in tumour size after chemotherapy treatment have been the only parameter to predict the therapeutic benefit for the patients. However, changes in tumour size in soft tissue sarcomas measured with computed tomography and/or magnetic resonance imaging have not correlated, consistently, with patients' outcomes, and the optimal definitions of response and progression are not known. Therefore, ^{18}F-FDG-PET as an indirect measurement of biologic activity and tumour viability is emerging as the most important imaging modality for monitoring therapeutic effects in cancer patients [8]. Especially for gastrointestinal stromal tumours (GIST), this finding has already been well documented. A study of ^{18}F-FDG-PET in imatinib treated GIST showed that patients with normalization of tumour SUV within the first month of treatment have significantly longer time to disease progression and better overall survival than those patients with increased ^{18}F-FDG accumulation [23]. It appears that ^{18}F-FDG-PET is more useful than conventional imaging in GIST to assess response to treatment. Moreover, there is even doubt if RECIST criteria adequately describe the response status to chemotherapy or to other targeted agents. In a recent issue of the Journal of Nuclear Medicine, a new classification of response criteria, the so called positron emission tomography response criteria in solid tumors (PERCIST) has been introduced, taking into consideration both changes in tumour volume as well as changes in metabolism [24].

Changes in tumour SUVmax to neoadjuvant cytotoxic chemotherapy predicted outcomes in 46 prospectively enrolled patients with localized high grade soft tissue sarcomas in which ^{18}F-FDG-PET was performed at baseline and after

two to four cycles of chemotherapy. Furthermore, metabolic response defined as a 40% or more decrease in SUVmax was associated with improved recurrence-free and overall survival. The multivariate analysis found a correlation between lack of response and increased risk of disease recurrence, metastases and death after appropriate local control of sarcoma [25]. Benz et al. (2008) reported on a study with 20 patients with locally advanced high grade soft tissue sarcomas who have been studied with combined ^{18}F-FDG-PET/CT prior and after the completion of preoperative treatment, which included different chemotherapeutic protocols, while 70% of the patients underwent additional external-beam radiation [26-27]. The authors report on significant differences in SUV changes (mean and maximum) in histopathological responders (70%-78%) as compared to non-responders (27%-40%). Histopathological response was defined as less than 5% viable tumour tissue. In contrast, the changes in tumour volume as measured by computed tomography did not allow prediction of response. Limitations of this study are low number of patients and that only 6 out of 20 patients were responders, which may raise statistical problems regarding the accuracy. Changes in tumour ^{18}F-FDG uptake between baseline and end of neoadjuvant treatment accurately predicted histopathological treatment responses (defined as ≥ 95% pathologic necrosis) in 42 patients with soft tissue sarcomas. In this study, a 60% reduction of SUVpeak in response to treatment was identified as the best discriminator between responders and non-responders (sensitivity and specificity of 100% and 71%, respectively). A direct comparison of changes in ^{18}F-FDG uptake (SUVpeak) and changes in tumour size revealed that RECIST was significantly less accurate than changes in SUV for assessing histopathology response to treatment [28]. RECIST, which defines partial response as a 30% or greater decrease in the sum of the largest diameter of the target lesions, does not optimally assess the response of soft tissue sarcomas to treatment.

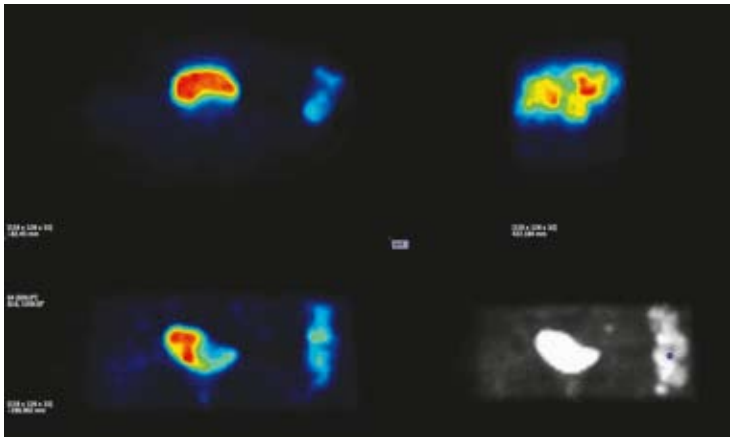

Figure 1. ^{18}F-FDG-PET images, 55-60min post injection prior to chemotherapy, in a patient with a liposarcoma, grade 3, located in the lateral part of the upper left leg. Upper left: transversal image. Upper right: sagittal image. Lower right: coronal image. Lower right: maximum intensity projection image (MIP).

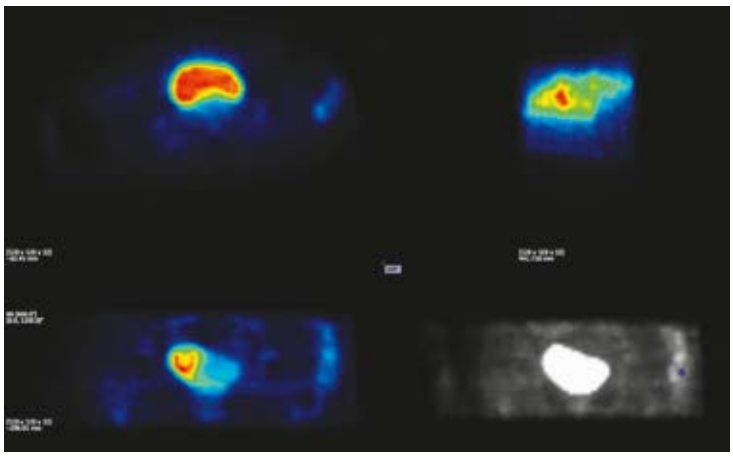

Figure 2. Corresponding ^{18}F-FDG-PET images of the same patient after four cycles of an adriamycin/ifosfamide based chemotherapy. Upper left: transversal image. Upper right: sagittal image. Lower right: coronal image. Lower right: maximum intensity projection image (MIP).

Early metabolic imaging (after the initial cycle of chemotherapy) has recently been shown to predict histopathological responses to treatment with a high accuracy [29-30]. A 35% reduction of SUV_{peak} correctly classified 8 of 8 metabolic responders as histopathologic responders with high sensitivity and 28 of 42 metabolic non-responders as histopathologic non-responders (specificity 67%) [29]. Our own study evaluated 27 patients with high-risk soft tissue sarcomas receiving neoadjuvant chemotherapy consisting of etoposide, ifosfamide and doxorubicin. The main difference between other studies and our data is the early time point chosen for the follow-up in our design (after two cycles of chemotherapy), the consistent scheme for neoadjuvant chemotherapy and the data evaluation. A significant difference regarding progression-free survival for patients with a decrease in SUV (defined as "responders") in comparison to patients with an increase or stable SUV (defined as "non-responders") could be demonstrated (P = 0.0187) [30]. The PET images in Figures 1 and 2 clearly demonstrate response to treatment. An update of our study including 31 patients and evaluating the impact of dynamic ^{18}F-FDG-PET measurements - not only based on quantitative SUV values-including SUV, fractal dimension, a two compartment model with computation of k1, k2, k3, k4, the fractional blood volume, and the influx according to Patlak on the early prediction of treatment outcome, in patients with high risk soft tissue sarcomas following neoadjuvant chemotherapy is being submitted. Taken together, these findings suggest that early treatment monitoring is feasible in patients with soft tissue sarcomas. With the benefit of targeted, predominantly anti-proliferative cancer treatments, the role of ^{18}F-FDG-PET imaging will become even more prominent in

the care of patients with soft tissue sarcomas, as RECIST is unreliable and anatomic treatment responses often occur very late with these agents. Furthermore, our group has recently published a paper on the utility of ^{18}F-FDG-PET in patients with metastatic soft tissue sarcomas undergoing treatment with trabectedin showing SUV stabilization in nearly all monitored patients [31].

Predictive value of pre- and post-treatment ^{18}F-FDG uptake

Eary et al. (2002) retrospectively evaluated the prognostic value of pre-treatment ^{18}F-FDG uptake in 209 sarcoma patients [32]. A baseline SUVmax of less than 6.0 was associated with significantly prolonged disease-free and overall survival. In a subgroup analysis, soft tissue sarcomas with low ^{18}F-FDG uptake appeared to have the best long-term outcome. These findings could be validated by other groups [33-34]. In addition, the degree of pre-treatment tumour heterogeneity as assessed by a new ^{18}F-FDG-PET tumour image heterogeneity analysis method was another prognostic index that significantly predicted long-term survival [35]. Thus, the use of pre- and post-treatment SUV as prognostic markers is evolving and reported threshold values will need to be applied prospectively in larger patient cohorts to verify and validate these initial reports.

With the benefit of targeted, predominantly cytostatic cancer treatments, the role of ^{18}F-FDG-PET imaging will become even more prominent in the care of patients with sarcomas [36-37], as RECIST is unreliable and anatomic treatment responses often occur very late with these agents. Reduction in tumour ^{18}F-FDG uptake in response to treatment has been shown to predict histopathologic response and survival in sarcoma patients. Modification of the existing RECIST classification for solid tumours in general has already been proposed using PERCIST serving as a starting point for the use in clinical trials, particularly assessing the activity of newer cancer treatments that stabilize disease [26]. There is a need for a proper selection of those patients who may benefit from chemotherapeutic or molecular-targeted treatments early in the course of treatment. Imaging with PET may help in response evaluation, therefore implying an influence on therapeutic decisions in the future.

In conclusion, PET imaging is emerging as an important imaging tool in the care of patients with soft tissue sarcomas. Imaging by ^{18}F-FDG-PET and using SUV may complement radiological tomography and histological grading, thus improving the management of patients with soft tissue sarcomas.

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(Brothers Cyril end Methodius were Christian Greek missioners of the 9th century from Thessaloniki, Macedonia, Greece)