Imaging: conventional techniques or PET scanning?

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Introduction

Soft tissue sarcomas (STS) are a heterogeneous group of malignant neoplasms derived from cells of mesenchymal origin and comprise about 1% of all malignant tumours in adults. Although each STS subtype has distinguishing histological characteristics, they also share many clinical and pathological features. STS are characterised by local invasiveness, and the pattern of metastasis is usually haematogenous. Lymph node metastases are uncommon, with the exception of selected cell types (e.g. synovial sarcomas), and are equivalent to any other metastasis with regard to patient outcome. The mainstay of curative treatment is surgical resection. The issues of debate concern how extensive that surgical excision should be and whether it should be preceded or followed by adjuvant therapy.

Important factors for patient outcome are tumour size and depth (determining the ability to perform a complete resection), and histological grade of the tumour (determining the metastatic potential). All these factors are grouped into the current American Joint Committee on Cancer / International Union Against Cancer (AJCC/UICC) staging system of STS [1]. Pathology and imaging modalities are the cornerstone for accurate staging. Imaging involves evaluation of loco-regional extent of the primary lesion and screening the potential sites of metastases. Evaluation of the biological aggressiveness of the tumour is usually evaluated on incisional or core biopsies. Since STS tend be large and heterogeneous, there is a high risk of sampling error with an underestimation of the actual tumour grade. Therefore, there is an increasing interest in using imaging modalities to guide biopsy towards the most biologically active zones.

With its high-contrast tissue resolution and multiplanar imaging capacity, magnetic resonance imaging (MRI) has become the imaging technique of choice for evaluation of the local extent of the primary lesion, whereas computerised tomography (CT) of lungs and liver is the best method for ruling out metastasis. Over the last few years, metabolic imaging with positron emission tomography (PET) seems to be a very promising technique in the management of cancer patients. Since PET relies on the detection of metabolic alterations observed in cancer cells, this examination yields data independently of associated structural characteristics, and therefore allows not only the detection of cancer, but also gives insight into the biological behaviour of the tumour. Furthermore, the ability to perform whole-body imaging within one examination without increasing the radiation burden makes it an ideal technique to "screen" patients for cancer deposits. In this paper, the experience with PET in STS is reviewed and an attempt is made to propose how this new imaging modality could be incorporated into the current imaging strategies.

PET: basic principles and technical aspects

The tracer fluorodeoxyglucose

The most frequently used tracer in PET oncology is fluorodeoxyglucose (FDG). The use of FDG for *in vivo* cancer imaging is based upon the higher rate of glucose metabolism of cancer cells compared with non-malignant tissue. After malignant transformation, cells demonstrate an increased expression of glucose transport proteins and an upregulation of hexokinase activity. FDG, a glucose analogue in which the oxygen molecule in position 2 is replaced by a positron-emitting ^{18}fluorine, undergoes the same uptake as glucose, but its first metabolite, FDG-6-phosphate, cannot be further metabolised in the glycolytic pathways. As most tumours have low phosphatase activity, FDG-6-phosphatase will accumulate intracellularly, resulting in a so-called metabolic trapping. The preferential accumulation of FDG in neoplastic cells permits differentiation between benign and malignant tissue. FDG uptake is, however, not specific for cancer cells and increased FDG up-

take is also observed in neutrophils, eosinophils and macrophages. Therefore, increased FDG uptake can be seen in some inflammatory conditions and is the most common cause of a false positive FDG signal. *In vitro* studies have demonstrated that the amount of FDG uptake in tumour tissue is mainly related to the number of viable cancer cells [2] and their proliferative capacity [3]. Therefore, FDG can be used to evaluated treatment efficacy since tumour cell kill results in a proportional reduction of the FDG signal [4]. Furthermore, the correlation between FDG uptake and the proliferative capacity makes *in vivo* evaluation of tumour aggressiveness possible.

Acquisition protocols and quantification

The biodistribution of positron-emitting tracers can be measured *in vivo* using a PET camera. Positron-emitting isotopes, such as ^{18}F, decay by emission of a positron, the positively charged antiparticle of an electron. After a short distance, this positron will annihilate with an electron resulting in two 511 keV photons, emitted in opposite directions. The detection of numerous of these annihilations by the detector rings of the PET camera generates high resolution three dimensional pictures (resolution 5–10 mm) indicating the sites of tracer accumulation in the body.

The most commonly used imaging protocol in clinical oncology is whole-body imaging with FDG. FDG is injected outside the PET camera. After an uptake period of at least one hour (necessary to obtain a good tumour-to-normal tissue contrast), the patient is positioned into the camera. Since the field of view of the PET camera is limited to 10–15 cm, different bed positions need to be scanned to obtain a whole-body survey. At the end, the data of the different bed positions are reconstructed to a whole-body image by a computer algorithm, taking into account the physical decay of the FDG tracer during the examination. The advantage of this technique is that it allows a fast (usually < 45 minutes) acquisition of information of the total body. The disadvantage is that, since no attenuation correction is performed, this technique only generates images for visual interpretation. Indeed, a considerable number of photons are absorbed into the patient's body. This absorption depends on the position in the body (e.g. superficial lesions are less attenuated than those situated in deep layers of the body) and the type of surrounding tissue (e.g. lung tissue is less attenuating than muscle tissue). Since the intensity of the lesion is position-dependent, the intensity seen on the images does not reflect the actual FDG uptake.

If images are corrected for photon attenuation by a so-called transmission scan, which makes an estimate of the attenuating characteristics of the patient, quantification of the FDG metabolism becomes possible. This transmission scan, which can be performed prior (cold transmission) or after (hot transmission) FDG injection, will, however, prolong the acquisition time substantially. In most clinical studies, FDG uptake is quantified using the Standardised Uptake Value (SUV). The SUV of a lesion is a semi-quantitative index of the glucose utilisation that is obtained by normalising the accumulation of FDG in the tumour to the injected dose and the patient's body weight. Absolute quantification, where the FDG uptake is expressed in mg/g tissue, is also possible using certain kinetic models that describe the behaviour of FDG in a tumour cell. However, this quantification requires a dynamic acquisition over the target lesion from the time of injection until a steady-state situation is reached (usually 1 hour or more) and arterial blood sampling is often necessary to measure the FDG input function. Since this procedure is time consuming, rather invasive and allows imaging in only one camera position (10–15 cm of the patient), its use is limited to more fundamental research studies.

Characterisation and grading of soft tissue masses

Soft tissue masses can be benign or malignant and the ratio of benign to malignant tumours is certainly more than 100 to 1. Accurate differentiation between benign and malignant tumours is essential to define the surgical strategy. Whereas a benign tumour can be resected with a minimal rim of normal tissue, a wider resection is necessary in STS to obtain local control. Once the diagnosis of a sarcoma is made, it is also essential to know the histology and grading of the tumour to define the necessity of (neo)adjuvant treatment in order to try to reduce the distant failure rate in high-grade tumours.

Although MRI with its high contrast resolution is excellent in defining the local extent of the tumour, there is still much controversy regarding its value in differentiating benign from malignant soft tissue masses. Some benign soft-tissue masses (e.g. lipomas, haemangiomas myositis ossificans, etc.) have typical MR appearance and can correctly and confidently be diagnosed as benign [5]. A variety of imaging parameters are associated with malignancy [6,7] such as lesion size >5 cm, high signal intensity on T2-weighted images and inhomogeneity on T1-weighted images, ill-defined margins, peri-tumoral oedema, involvement of adjacent bone, extra-compartmental distribution and encasement of

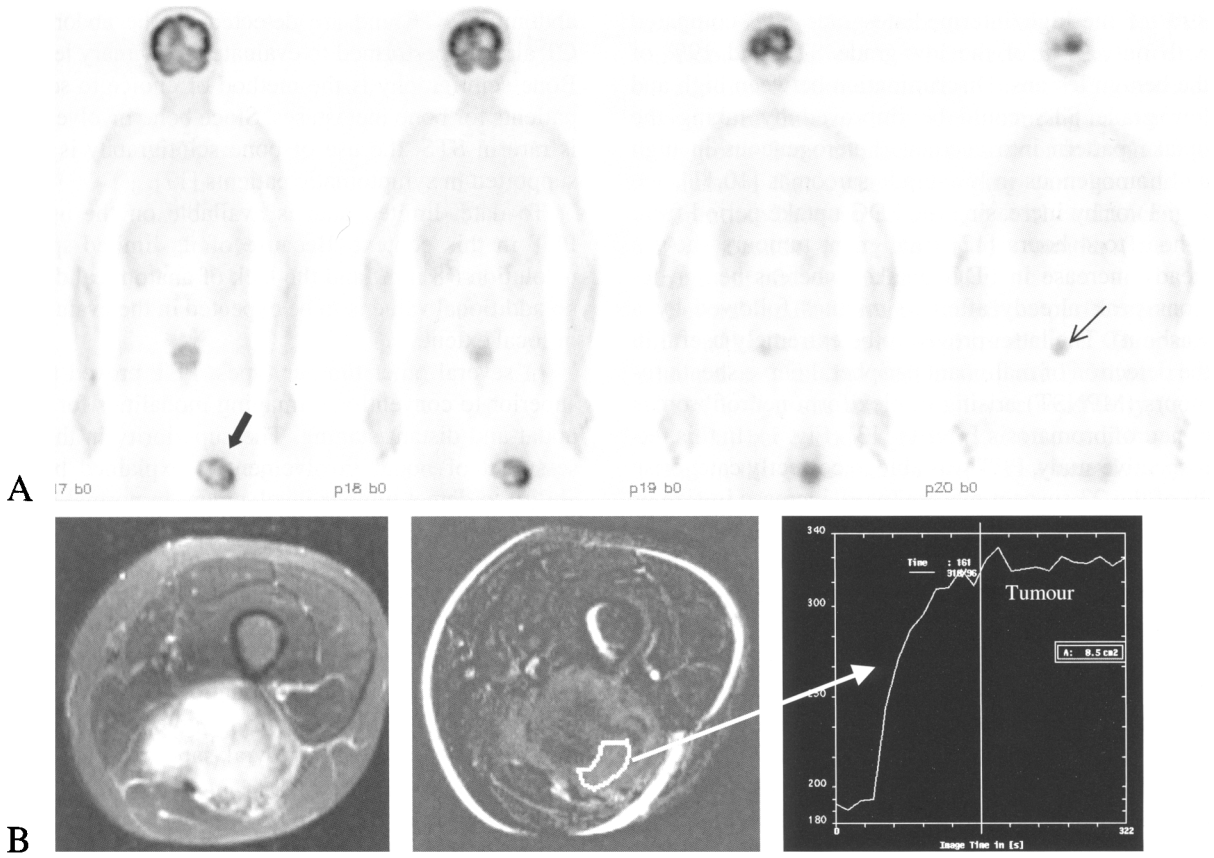

Fig. 1. Patient with neurofibromatosis 1 with a painful swelling of the left thigh. MRI revealed a mass with inhomogenous and fast contrast enhancement on T2-weighted images (B) suggestive for malignancy. PET showed increased and heterogeneous FDG uptake in this painful mass suggestive for malignancy (➨ on (A)) and found an additional lesion with moderate and homogeneous FDG uptake more suggestive for benign disease in the pelvis (→ on (A)). Pathology confirmed the presence of malignancy in the soft tissue mass in the left thigh (MPNST arising within a plexiform neurofibroma) whereas a benign neurofibroma was diagnosed in the pelvis.

the neurovascular bundle. With the introduction of dynamic contrast-enhanced MRI (DCE–MRI), the changes in tissue vascularity and perfusion can also be evaluated. Most malignant STS exhibit an early (within a few seconds) and peripheral enhancement with a steep slope, an early maximum followed by a transition to a stable level or a slight decrease of signal intensity [8] (Fig. 1). But given the substantial overlap between benign and malignant lesions in all of these findings, no single imaging feature or even a combination of features can reliably be used to differentiate benign from malignant lesions. If the typical benign lesions are excluded, sensitivity and specificity is only around 80% [5] and biopsy is still warranted in most cases. The current role of imaging is therefore to recognise patients with benign disease, who can be excluded from further invasive staging, from those with potentially malignant tumours, who should be referred for biopsy. Since STS are often large and heterogeneous, imaging can, however, help to guide the biopsy towards the most aggressive zone.

Several studies have investigated the role of FDG–PET in the characterisation and grading of bone and soft tissue masses. Since most studies focused on the value of PET in addition to conventional imaging, no direct comparison of accuracies between both modalities are available. Recently, a meta-analysis was published, reporting on the results of PET in the characterisation of 441 soft tissue lesions (227 malignant, 214 benign) [9]. For diagnosis of malignancy, sensitivity and specificity were 92% and 73% for visual analysis, 87% and 79% for SUV >2 and 70% and 87% for SUV >3. False negative findings were encountered in low-grade sarcomas, while false positive results were seen in the inflammatory lesions or lesions with high cellularity (e.g. giant cell tumour). FDG uptake correlated with the histological grade of the tumour, with high/intermediate-grade tumours showing significantly higher uptake than low-grade tumours, although there was some overlap. PET was not able to discriminate benign from low-grade tumours. An SUV above 2 was seen in

89% of the high/intermediate-grade STS compared with only 33% of the low-grade STS and 19% of the benign lesions. Discrimination between high and low grade STS could be improved by taking the uptake pattern into account (heterogeneous in high and homogenous in low-grade sarcomas [10,11], see Fig. 1) or by increasing the FDG uptake period from 1 hour to 4 hours [12] (malignant tumours show a steady increase in FDG uptake, whereas benign lesions peak already after 30 minutes followed by a washout). The latter proved to be extremely useful in the detection of malignant peripheral nerve sheath tumours (MPNST) arising in plexiform neurofibromas in neurofibromatosis I (NF1) [13] (Fig. 1). In this retrospective study, PET was able to correctly categorise 20 of the 23 suspect masses (pain, increase in size or neurological deficit) as benign ($n = 13$) or malignant ($n = 7$). PET was false positive in 3 cases, but there were no false negatives. A large multi-centre trial is now ongoing to validate these results in a prospective setting and to evaluate the impact of early detection of malignant degeneration on survival.

The relationship between FDG uptake, pathologic grade and other prognostic factors was further evaluated by Folpe et al. [14]. Besides pathologic grade, they also found a strong correlation between SUV and Ki-67 labelling index, mitotic figure counts and P53 overexpression, criteria all known be prognostically important. The same group also analysed the impact of pretreatment SUV on final outcome [15]. In a retrospective analysis in 209 sarcoma patients (135 STS, 52 bone and 22 cartilage), patients with baseline SUV above 6 had a significant shorter disease-free survival (DFS) ($P < 0.001$) and overall survival (OS) ($P < 0.003$). After adjusting for standard clinical prognostic factors (histology, grade, age, gender), multivariate analysis indicated that SUV was an independent predictor of DFS and OS.

Evaluation of disease extent

The evaluation of local extent is best accomplished with MRI, which can accurately depict the anatomical spaces (compartments) involved by the tumour and its relationship to adjacent bone and neurovascular structures.

The most common site for distant metastases are the lungs. High-resolution CT is the best imaging modality to detect lung metastases. Since the appearance of lung metastases increases with tumour stage, it only proved to be cost-effective in high-grade T2 (>5 cm) lesions [16]. Liver metastases can be encountered as the first distant site in primary intra-abdominal STS and are detected on the abdominal CT already performed to evaluate the primary lesion. Bone scintigraphy is the method of choice to screen patients for bone metastases. Since bone involvement is rare in STS, the use of bone scintigraphy is only supported in symptomatic patients [17].

To date, limited data is available on the use of PET in this context. Because of its limited spatial resolution (8 mm) and the lack of anatomical detail, no additional value is to be expected in the evaluation of local extent.

In several other tumour types, PET proved to be superior to conventional imaging modalities for both nodal and distant staging. The superiority in the assessment of nodal involvement is explained by its ability to detect tumour involvement in normal-sized nodes and to exclude disease in inflammatory enlarged ones. Since nodal metastases are rare in STS, the additional value will be marginal and no data are currently available in the literature. PET can be potentially useful only in selected cases with equivocal lymph nodes on clinical examination and/or conventional imaging or in STS with a higher incidence of lymphatic spread (e.g. synovial sarcoma, clear cell sarcoma).

The possibility to screen the entire patient for tumour deposits without increasing the radiation burden makes PET attractive for distant staging. The additional value is mainly found in the detection of metastases at unexpected sites often outside the "standard field of view" of CT/MRI and by excluding disease in equivocal readings on conventional imaging. Again, data in the literature on the use of PET for distant staging in STS is limited. In only one study, focusing on the characterisation of soft tissue masses, were the results on distant staging at diagnosis also briefly reported [10]. Of the 10 patients with high-grade STS, 3 had distant metastases at presentation. PET was concordant with conventional staging concerning the sites affected (lung and bone), but underestimated the number of lung metastases in 1 patient. The lower sensitivity of PET compared with CT (86% vs. 100%, respectively) is also reported in an other study evaluating PET for detection of disease recurrence [18] and can easily be explained by the fact that a critical mass of metabolically active malignant cells is required for PET diagnosis, by which lesions smaller then 5 mm will rarely be detected. No specific literature is available on the performance of PET for detection of liver metastases in STS. In the study of Delbeke et al. [19] evaluating PET for the detection of liver metastases in a variety of tumours including a few sarcomas, PET had a sensitivity of 100%, but all lesions were larger than 1 cm. However,

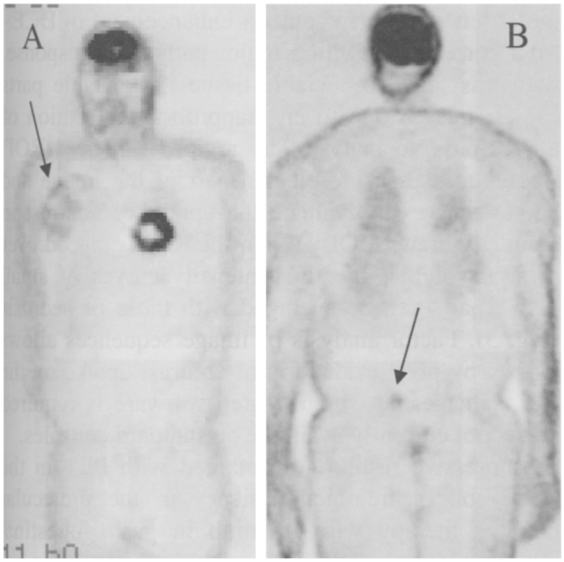

Fig. 2. Patient with a high grade synovial sarcoma of the right axilla (A) with an unsuspected bone metastasis in the right sacro-iliacal joint (B).

most experience in the evaluation of liver metastases has been gained from gastro-intestinal carcinomas. Just as in lung metastases, sensitivity for the detection of liver metastases is also related to tumour size with a sensitivity of 85% for lesions >1 cm compared with only 25% for lesions <1 cm [20]. Because of the ability to perform whole-body imaging, PET can screen the entire body for metastases without increasing the radiation burden. In the study of Lucas et al. [18], unexpected metastases were found in 8/62 patients (Fig. 2). The clinical impact was, however, low, since the majority of the patients also had lung metastases detected on CT.

Detection of recurrence

The majority of recurrences develop within 2 years of resection of the primary tumour. Positive surgical margins are the main predictors for local relapse, whereas grade, size and TNM stage predict the development of distant metastases and overall survival. Early detection and treatment of local recurrence is desirable if surgical control is to be achieved, even if this does not necessary influence the ultimate prognosis of the patient.

MRI is currently the technique of choice for the evaluation of suspected local relapse in the extremities. An easy to follow algorithm has been proposed by Vanel et al. [21] and relies on the mass effect and high water content of tumour with respect to the surrounding soft tissues. The presence of an enhancing mass on T2-weighted images seems to be the best indicator of recurrence. When such a mass is found, the addition of contrast medium to routine sequences allows differentiation of a non-enhancing haematoma or hygroma from enhancing tumour or inflammation. The use of fast dynamic imaging can than further differentiate between recurrence (early enhancement within seconds) and inflammatory tumour (late enhancement after 3–9 minutes).

Several studies have evaluated the performance of PET in the detection of local recurrence. Compared with the results obtained in the initial characterisation of soft tissue masses, a lower sensitivity (81% vs. 95%) but higher specificity (91% vs. 59%) was found in the meta-analysis [9]. False negatives were seen in lesions with minimal tumour load, whereas false positives were related to uptake in inflammatory tissue (e.g. pressure areas with skin breakdown). One study compared the performance of PET and MRI in 60 patients and found both a lower sensitivity (73% vs. 88%) and specificity (94% vs. 96%) for PET [18].

Evaluation of treatment efficacy

Traditionally, the response to cancer treatment in solid tumours is evaluated by subsequent clinical or radiological assessments of target lesions and is defined as a significant decrease in measurable tumour dimensions [22]. There are, however, important limitations to the evaluation of tumour response by volume changes, especially in STS. Accurate measurement of tumour dimensions can be extremely difficult in non-well-defined lesions like bone, bowel or peritoneal metastases. Reduction in viable tumour cell fraction does not always result in volume reduction since tumour tissue can be replaced by necrotic or fibrotic tissue. Volume changes are rather late events. Usually, the first evaluation of objective responses measured by (CT) are performed not earlier than 2–3 months after the start of treatment because earlier changes are seldom significant. Therefore, patients are often unnecessarily exposed to ineffective, toxic or expensive treatments for a prolonged time. In the neo-adjuvant setting, it can even reduce the change of a curative resection by postponing surgery. Finally, the new anti-vascular and cytostatic agents aim at tumour growth stabilisation rather than tumour shrinkage and thus no major volume changes are to be expected. As a result, there is a pressing need to develop additional response parameters to overcome these limitations.

Over the last years, promising results were obtained with PET in the evaluation of treatment effi-

cacy. Because FDG uptake is related to the number of viable cells and necrotic or fibrotic tissue is usually not FDG-avid, accurate differentiation between responders and non-responders seems to be possible early after the start of treatment. Currently, the experience in STS is still limited.

In one study in 20 STS [23], PET was performed before and 2 weeks and 8 weeks after neo-adjuvant hyperthermic isolated limb perfusion (HILP). PET response was correlated with the pathologic response on the resection specimen. Visual analysis after HILP in responding patients showed a rim of increased FDG uptake around a core of absent tracer, which corresponded on pathology to an inflammatory pseudo-capsule (with or without residual tumour tissue) and necrosis, respectively. Patients who achieved a complete pathologic response showed a significantly larger reduction in FDG uptake (mean reduction >80%) compared with those with only partial response (mean reduction <30%, $P < 0.05$) but no accurate discrimination between partial and complete responders in the individual patient was possible. Another study in only 9 patients [24] found similar results in patients treated with HILP, whereas in patients treated with chemotherapy only, the reduction in FDG uptake was more homogeneous throughout the tumour.

More recently, PET response was also correlated with final outcome. In this retrospective study [25], 38 patients with localised, high-grade STS underwent PET imaging before doxorubicin-based chemotherapy and prior to surgery. Seventeen patients remained free of tumour after a median follow-up of 3 years. Patients with a greater than 40% reduction in FDG uptake after chemotherapy had a significantly lower risk of relapse and improved survival. Risk of relapse did not correlate with tumour grade, size or pathologic response to therapy. A possible explanation why pathologic response did not correlate with survival is suggested in a case report coming from the same centre [26]. After neo-adjuvant chemotherapy, no viable tumour was observed in the large residual mass after standard gross pathologic examination. Because PET scan revealed a persistent small focus of intense FDG uptake, the resection specimen was re-analysed and a small area of viable tumour tissue without treatment effects could be identified. The patient developed lung metastases 4 months later. This case report clearly illustrates the heterogeneous response of the tumour to chemotherapy and the importance of evaluating the entire volume. This can be achieved easily with PET imaging, but can be problematic for pathology and even radiology in large residual masses. Indeed, although the absence of early contrast enhancement in DCE–MRI corresponds with a major pathologic response, with less than 10% viable tissue [27], viable parts can be missed due to an inappropriate selection of the region(s) to analyse. This region of interest (ROI) technique uses a preselected part of the image and obtains curves to evaluate the uptake of contrast in manually drawn ROIs. When the ROI is placed over a large volume, the time-intensity curves of small viable parts can be averaged with those of necrosis (Fig. 3). Factor analysis of image sequences allows a pixel-by-pixel evaluation of contrast uptake on the entire image, but sophisticated software is required and is not currently available on standard consoles.

Impressive results are obtained with PET in the evaluation of treatment efficacy to the molecular targeted therapy with imatinib in gastro-intestinal stromal tumours (GIST). A complete metabolic response was achieved within one week after the start of treatment in responding patients and preceded CT response by several weeks to months [28,29]. Furthermore, the effect of imatinib mesylate on the FDG uptake proved to be dose-related (unpublished data, see Fig. 4). Also for the detection of secondary resistance to imatinib mesylate, PET proved to be useful (see Fig. 5). The molecular mechanism responsible for the rapid and dose-dependent decrease in glycolytic activity after imatinib mesylate therapy remains unknown and is in contrast with the more gradual decrease in FDG uptake after effective cytotoxic treatment (reflecting tumour cell kill). One possible explanation could be a direct inhibition of the hexokinase activity by imatinib mesylate as suggested by Boren et al. [30]. In that case, response assessment with FDG–PET is only measuring one of the downstream effects of the blockade of the c-kit receptor rather than being a direct marker of cell viability or proliferation.

Clinical role of PET in STS management

Disease extent

MRI and CT remain the imaging modalities of choice in the initial diagnostic work-up of STS. Because of its limited spatial resolution and lack of anatomical detail, PET is of no use in the evaluation of the local extent of the tumour. Also for the detection of local recurrence, PET has proven to be inferior to (dynamic) MRI.

There are also no data available today supporting the routine use of PET for distant staging in STS. Since PET can miss small metastases in the lungs,

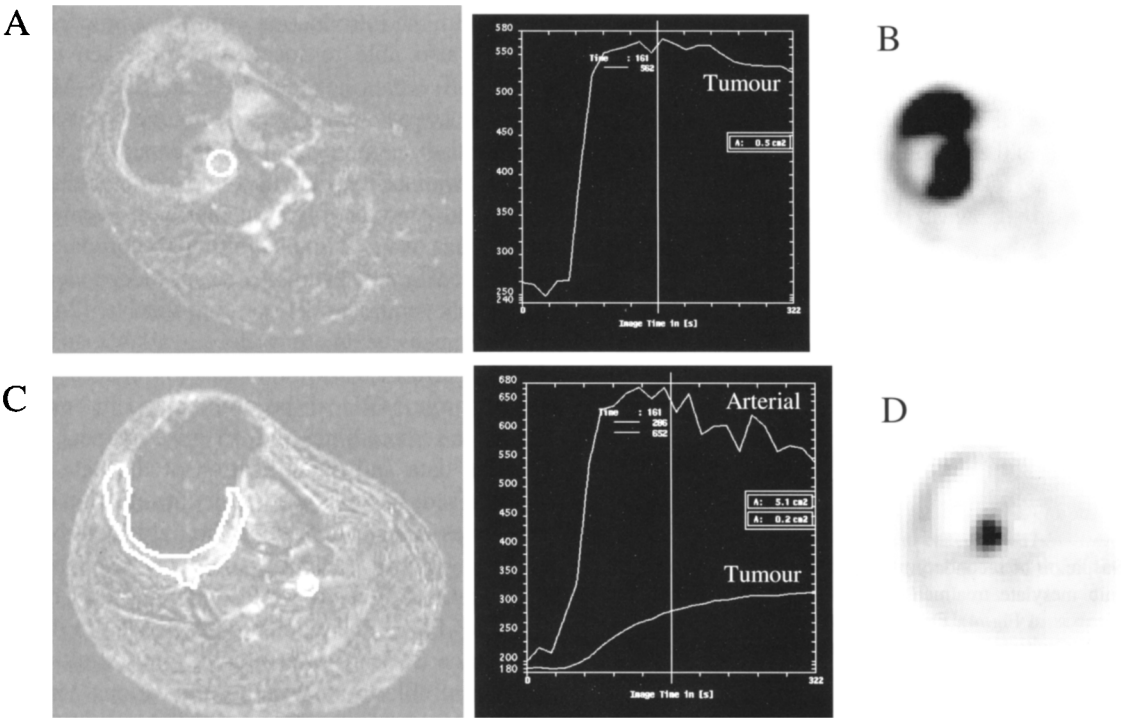

Fig. 3. Axial dynamic T1-weighted MRI images of a patient with a high grade leiomyosarcoma in the left thigh before (A) and 4 weeks after limb perfusion (C) with high dose melphalan and tumour necrosis factor. Before chemotherapy, a fast contrast enhancement suggestive for malignancy is observed (A), while after treatment, a major reduction in both the amplitude and the slope is observed (C), suggesting major tumour response. On PET, high FDG uptake was observed in the periphery of the tumour prior to treatment (B). After treatment, a major reduction in FDG uptake was observed throughout the tumour, except for one small focus, suggesting resistant disease at that place (D). The patient was treated with additional radiotherapy (66 Gy), but progressed locally at this PET resistant 3 months later. The failure of MRI to detect this resistant focus can possibly be explained by the use of a too-large ROI (region of interest) for dynamic analysis.

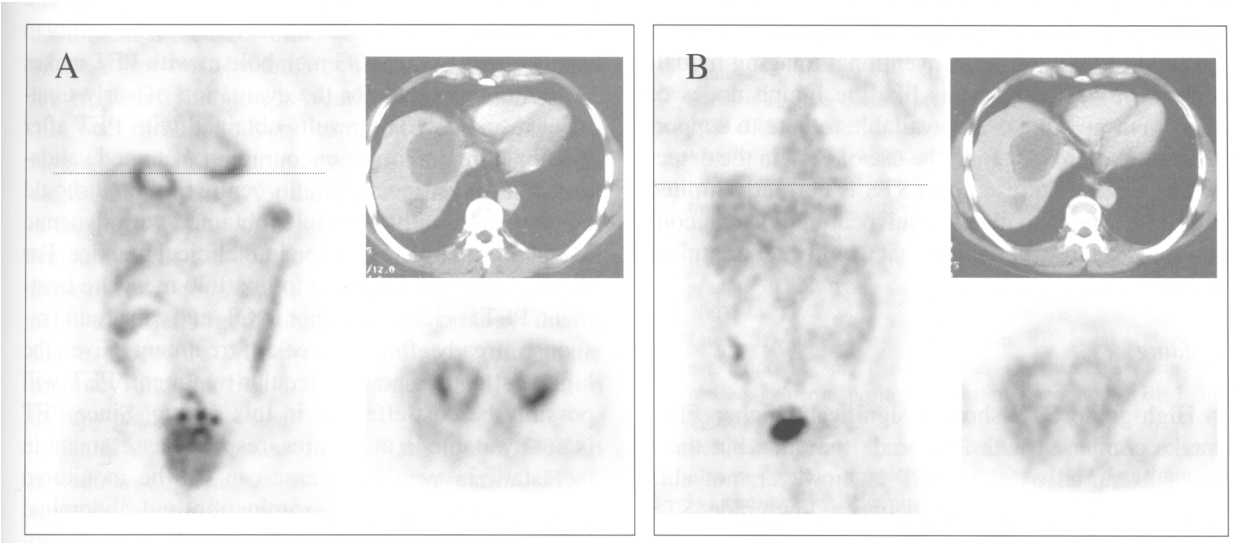

Fig. 4. Patient with an inoperable metastatic GIST with multiple peritoneal and hepatic metastases. No metabolic response was observed on PET and CT after 1 month of imatinib mesylate treatment of 400 mg daily (A). One week after dose escalation to 2×400 mg, a complete metabolic response was observed on PET (B), confirmed after 4 months on CT.

CT of the chest will remain obligatory in high-grade T2 STS. For abdominal STS, the presence or absence of liver metastasis can be assessed on the abdominal CT, already performed to evaluate the primary tumour. Although there are no data available for STS specifically, the experience in other tumour types showed

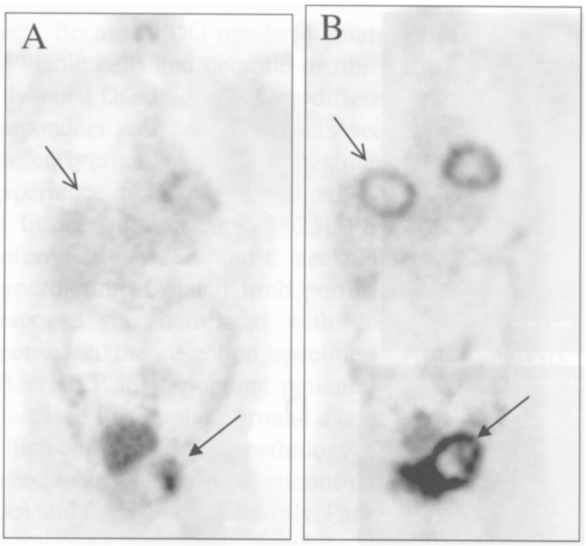

Fig. 5. Suspicion of secondary resistance on CT after 18 months of imatinib mesylate treatment (2 × 400 mg) (data not shown, same patient as in Fig. 4). On PET only the pelvic mass showed increased FDG uptake, suspected for recurrence, while the liver metastasis were still not metabolically active (A). One week after the discontinuation of imatinib mesylate treatment, PET showed a major increase in tumour volume of the pelvic mass and the liver metastasis became metabolically active again (B), suggesting still some residual effect of imatinib mesylate even in apparently resistant disease.

no significant benefit of PET over spiral CT for the detection of liver metastases. Because the entire body is scanned within one image session, a potential role of PET is to detect "unexpected" metastases outside the field of view of the conventional imaging modalities or in "difficult" areas like the lymph nodes or bones, but no studies are available to date to support its routine use. Therefore, the use of PET in the detection of metastatic disease in STS is currently limited to selected cases to clarify equivocal findings on conventional staging modalities that would alter treatment management.

Grading

High-grade STS show a significant higher FDG uptake compared with low-grade tumours, but there is a substantial overlap. PET is, however, not able to discriminate accurately between low-grade STS and benign lesions thus biopsy can not be omitted in suspected soft tissue masses. The potential role of PET is to guide the biopsy towards the most "aggressive" zone since STS often tend to be large and heterogeneous. With the increasing use of adjuvant therapy prior to surgery, any formation that helps the surgeon to take the appropriate tissue sample is important in making optimal treatment decisions. With the introduction of fast dynamic imaging, MRI is also able to locate the most active zone. Comparative data between PET and DCE–MRI are currently not available. Each technique has its advantages and disadvantages. PET is expensive and has limited availability, but the tumour metabolism can easily and reproducibly be quantified. Furthermore, the amount of FDG uptake, although correlated with histological grade, seems to be an independent predictor for overall and disease-free survival [24]. MRI is less expensive, more widely available and often already performed for the evaluation of local extent. But dynamic MRI can be problematic in "moving" organs (e.g. breathing) due to misalignment of the dynamic data and quantification of the data is less standardised. In times where the introduction of new techniques is dependent upon their ability to be cost-effective, future research should try to clarify the incremental diagnostic yield and long-term clinical benefit of FDG–PET compared with MRI in this setting. Since STS are rare tumours, only multi-centre studies are able to answer these questions within an acceptable time-frame. But these trials are difficult to perform given the high cost of a PET and the fact that it is not reimbursed for this indication in most countries.

Evaluation of treatment response

The close relationship between FDG uptake and cell viability or the proliferation rate and the ability to easily quantify the FDG metabolism with PET makes it an attractive tool for the evaluation of early treatment responses. The results obtained with PET after cytotoxic treatment are encouraging, but need validation in large prospective multi-centre trials and should be compared with the results obtained with dynamic MRI before implementation into clinical practice. For the evaluation of response to imatinib mesylate treatment, PET is clearly superior to CT, and can predict response already after one week of treatment. Given the high cost of this new molecular treatment, PET will possibly be cost-effective in this setting. Since PET is not available in all centres, response assessment in metastatic inoperable disease can still be monitored reliably with a clinical examination and abdominal CT, since non-responding patients often show progressive disease within a few weeks after the start of treatment, while the responding ones show early symptom relief if present. The use of PET can than be limited to those with equivocal findings. For the further development of the drug (dosing, combination treatment, neo-adjuvant setting), the use of PET in clinical trials should be encouraged.

Conclusions and future perspectives

Currently, there is no indication for routine use of FDG–PET in the management of patients with soft tissue sarcoma. MRI is the imaging technique of choice to evaluate local extent or recurrent disease, whereas high resolution CT is the best technique to detect pulmonary metastasis. PET can be useful in selected patients in cases of equivocal findings on these conventional examinations. Promising results are obtained with FDG in grading of soft tissue masses and the evaluation of treatment efficacy, but these results need to be confirmed in large multi-centre prospective trials before they can be incorporated into clinical practice.

Routine use of FDG–PET in oncology is still hampered by the high cost and the limited availability of the technique. Further development is expected when commercial isotope distributors will be able to deliver FDG, so that an on-site cyclotron is no longer a prerequisite. FDG has a half-life of 110 minutes, so a practical distribution radius of 200–300 km should be feasible. Moreover, with the introduction of the new generation of PET cameras equipped with LSO (lutetium oxyorthosilicate) or GSO (gadolinium orthosilicate) detectors and with larger field of views (up to 50 cm), the scan time per patient will be substantially reduced (from 45 minutes to 10–15 minutes) resulting in a higher throughput of patients. The use of gamma cameras adapted with a coincidence circuit can increase availability, but the performance of these low-cost systems compared with dedicated full-ring PET scanners is clearly inferior. This means that one should be very careful to extrapolate the results found in literature, coming mostly from dedicated PET systems. Another fascinating development is the introduction of combined PET–CT machines. Not only will the low noise attenuation correction from the CT component speed up the PET component, the merging of anatomy and biology into a single procedure will probably improve diagnostic accuracy and provide better surgery and radiation therapy planning.

Finally, a whole new field of the use of PET in molecular applications is under exploration. FDG, with its possibility to study tumour glucose metabolism, has paved the way for PET in clinical oncology. Several other radiopharmaceuticals can also be used to study processes such as blood flow ($H_2{}^{15}O$), protein metabolism (^{11}C-methionine, ^{11}C-choline) and carbohydrate metabolism (^{11}C-acetate), hypoxia (^{18}F-MISO) and DNA synthesis (^{11}C-thymidine, FLT). Certainly with the development of more biological- or molecular-targeted treatments, assessment of metabolic processes non-invasively becomes increasingly important to assess the efficacy of these drugs. With the introduction of microPET systems, which makes it possible to perform PET studies in small animals like mice and rats, PET can be used to evaluate the kinetics and mechanisms of actions of new drugs in the pre-clinical phase.

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