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Review

Personalising sarcoma care using quantitative multimodality imaging for response assessment

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Over the last decades, technological developments in the field of radiology have resulted in a widespread use of imaging for personalising medicine in oncology, including patients with a sarcoma. New scanner hardware, imaging protocols, image reconstruction algorithms, radiotracers, and contrast media, enabled the assessment of the physical and biological properties of tumours associated with response to treatment. In this context, medical imaging has the potential to select sarcoma patients who do not benefit from (neo-)adjuvant treatment and facilitate treatment adaptation. Due to the biological heterogeneity in sarcomas, the challenge at hand is to acquire a practicable set of imaging features for specific sarcoma subtypes, allowing response assessment. This review provides a comprehensive overview of available clinical data on imaging-based response monitoring in sarcoma patients and future research directions. Eventually, it is expected that imaging-based response monitoring will help to achieve successful modification of (neo)adjuvant treatments and improve clinical care for these patients.

Introduction

Sarcomas form a group of rare and biologically diverse malignancies, arising in connective tissue (muscle, fat, blood vessels, nerves, tendons, and the lining of joints) and bone. Over 70 histological subtypes of sarcoma exist, all showing a distinct clinical presentation, course of progression, and response to treatment.[1] In general, these tumours are categorised as bone or soft-tissue sarcomas. The estimated yearly incidence of patients with bone and soft-

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tissue sarcomas in Europe is 4,000 and 23,500, respectively, and 3,600 and 13,130 in the United States.[2,3] The biological diversity and low incidence of these tumours often cause delay in diagnosis, while timely and adequate treatment is specifically essential in these frequently young patients. Furthermore, a subset of these tumours has a high metastatic potential. Around 45–60% and 32–42% of patients with a high-grade bone and soft-tissue sarcoma, already have metastatic disease at first presentation, contributing to a poor prognosis.[4]

For patients without metastases, surgical resection of the primary tumour is the treatment of choice. Depending on the subtype of sarcoma, surgical resection can be preceded by neoadjuvant and/or followed by adjuvant treatment. Despite the introduction of new, increasingly intense treatment strategies, approximately 40% of patients will have either local recurrence or distant metastases within a period of 2 years after resection.[5] In these patients, the prognosis is significantly impaired, with a 5-year survival rate of approximately 19%.[6] Treatment personalisation has the potential to select optimised, tailored treatment strategies, increasing the effectiveness of treatment while decreasing side effects and costs. Consequently, an increasing demand exists for accurate tools to predict and monitor response to therapy and ultimately select patients who will benefit from certain interventions.

Medical imaging already has an important role in personalising clinical management of oncological patients.[7] It provides a means to non-invasively detect, quantify and monitor a myriad of different biological parameters, referred to as imaging biomarkers. Development of new imaging methods, tracers, contrast media, and protocols in magnetic resonance imaging (MRI), X-ray computed tomography (CT) and positron-emission tomography (PET), continue to provide new ways of characterising the tumour biology underlying therapy response with great precision and accuracy. These developments have resulted in the integration of various medical imaging techniques in standard clinical care for sarcoma patients. In this review, we discuss the current and future role of state-of-the-art medical imaging concepts in response-based clinical management of patients suffering from sarcoma.

Search strategy and selection criteria

References for this review were identified through searches of PubMed with the search terms “sarcoma,” “response,” “imaging, magnetic resonance,” “tomography, X-ray computed,” “fMRI”, “MR spectroscopy,” “PET-CT” and “molecular imaging,” “^{68}Ga-FAPI,” “^{18}F-FLT,” “^{18}F-FAZA,” “^{18}F-FMISO” from 2000 until April 2020. Articles were also identified through searches of the authors’ own files. Only papers published in English were reviewed. The final reference list was generated based on originality and relevance to the broad scope of this review.

Current practice

(Neo)Adjuvant treatment in non-metastatic disease

Depending on the sarcoma type, surgical resection can be preceded and/or followed by (neo)adjuvant radiotherapy, systemic chemotherapy, and/or isolated limb perfusion. For the purpose of response monitoring, MRI and PET are the most frequently used imaging methods, although there is no broad consensus on the specific timing or type of imaging that should be used. The European Society for Medical Oncology (ESMO) guidelines report that dynamic MRI gives information on response to chemotherapy in osteosarcoma and that integrated 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG)-PET/CT might be advantageous in high-grade craniofacial osteosarcoma.[8] Comparable recommendations for soft-tissue sarcomas are lacking.[9] The limited standardisation of current clinical practice emphasises the importance of optimisation of imaging protocols and development of specific recommendations for the purpose of response monitoring.

In high-grade osteo-, Ewing, and selected high-grade soft-tissue sarcomas neoadjuvant chemotherapy is standard of care. Chemotherapy in high-grade osteosarcomas normally consists of a combination of doxorubicin, cisplatin, and high-dose methotrexate. In Ewing sarcoma, a combination of vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide is typically used. In other bone sarcomas, such as conventional chondrosarcomas and parosteal (low grade) and periosteal (intermediate grade) osteosarcomas, chemotherapy usually plays no role in the treatment.[8,9] The sensitivity for chemotherapy in soft-tissue sarcomas is variable among the subtypes. At present, except for paediatric rhabdomyosarcomas and selected high-risk soft-tissue sarcomas, no histotypes-guided chemotherapy regimens are used in soft-tissue sarcoma. In paediatric rhabdomyosarcomas, combinations of vincristine, dactinomycin, and cyclophosphamide are typically used.[10]

Apart from paediatric rhabdomyosarcoma, the decision to administer (neo)adjuvant radiotherapy in patients with a soft-tissue sarcoma is based on the grade of the tumour, as determined by the FNCLCC grading system.[11] Current guidelines state that intermediate- and high-grade (grade 2/3) soft-tissue sarcomas can be treated with neoadjuvant or adjuvant radiotherapy, whereas there is no indication for low-grade (grade 1) soft-tissue sarcomas, unless resection margins are positive or intra-operative spill occurred during resection.

In general, combinations of above-mentioned cytotoxic and cytostatic systemic and radiotherapeutic treatments are expected to alter biological tumour characteristics, such as proliferation and metabolism, to a varying extent. Visualisation of these tumour characteristics and changes in characteristics via imaging provide tools to monitor response to treatments.

Histopathological response assessment

In current clinical practice, tumour response is determined on histopathology after resection. A common way of assessing the effectiveness of therapy is the pathological analysis of the percentage of viable tumour cells after resection of the tumour.[12] For this assessment, it is recommended to embed a whole slab including the largest tumour dimension.

In osteosarcomas and Ewing sarcomas, the percentage of viable tumour cells has been linked to the effectiveness of neoadjuvant treatment. In osteosarcomas, a cut-off is often set at <10% viable tumour for good responders.[13] For Ewing sarcoma, assessment of histopathological response is more challenging as there is often a volume effect that is not accounted for during histological analysis. Moreover, while previously a cut-off of 10% viable tumour cells was proposed, recent studies suggested that only 0% viable tumour cells is correlated to a better outcome.[14,15] In soft-tissue sarcoma, studies and results are more heterogeneous and, thus, difficult to interpret. Studies report a varying median between 30–80% necrosis, and consensus regarding the cut-off defining good responders is lacking. This is partly explained by the number of changes that can be observed in responsive tumours, such as the formation of fibrosis, granulation tissue, hyalinisation, and inflammation. Therefore, the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) recently proposed a standardised work-up and response score amongst soft-tissue sarcoma based on the percentage of "stainable" (viable) cells.[16] Some studies, however, show no predictive value of this response score. One of these studies did show correlation between hyalinisation/fibrosis and recurrence-free survival and overall survival instead.[17]

Determination of response to neoadjuvant treatment after resection does not render the possibility to perform early treatment adaptation in non-responsive tumours. Therefore, current research is directed to using medical imaging to non-invasively characterise the response to treatment at an early stage during (neo)adjuvant treatment.

Imaging based early response monitoring

The goal of medical imaging in determining treatment response is to enable image-guided treatment adaptations. In current clinical practice, this might lead to an advanced resection in progressive disease. In this regard, earlier adequate assessment of response potentially allows variability of image-guided treatment adaptions, including adjustment and personalisation of radiotherapy plans and chemotherapy schemes. Currently, adjustments in systemic treatment in GIST patients, based on response assessment with PET imaging, are already performed in routine clinical practice.[18] Furthermore, in retrospective studies, personalised radiotherapy plans in sarcomas were linked to improved target coverage, local control rates, and reduced toxicity to normal tissues, suggesting personalisation of neoadjuvant treatment could improve outcomes.[19]

Response assessment in oncology is usually performed using unidimensional or bidimensional measurements of target lesions on CT or MRI, according to the response evaluation criteria in solid tumours (RECIST) or World Health Organization (WHO) criteria[20,21]; however, the ability to perform early response monitoring using such criteria is limited, given that changes in morphology occur relatively late after treatment initiation. Moreover, soft-tissue sarcomas can have the counterintuitive tendency to not change, or even increase in size while they have a substantial response to treatment (pseudo-progression).[22] This can be explained by the occurrence of treatment-induced necrosis, haemorrhage, fibrosis, hyalinisation, and cystic changes in the tumour.[23] This is emphasised in a study, showing that soft-tissue sarcomas with increasing size during radiotherapy, as determined by RECIST 1.1, do not show less pathological response or worse prognosis[24]; however, in 70% of myxoid liposarcomas, a reduction in tumour size is observed after radiotherapy, which is correlated with histopathological response.[25] Furthermore, in contrast to most soft-tissue sarcoma subtypes, there is evidence that in osteosarcoma reduction in radiological tumour volume is linked to a good pathological response with a sensitivity of 80.2% and a specificity of 68.6%.[26] Differences in changes in tumour size following neoadjuvant treatment might be caused by both the kind of treatment given and tumour biology. The insufficiencies in current response assessment render the need to acquire more extensive insight into the correlations of biological behaviour, response, and imaging biomarkers.

Imaging biomarkers and response to treatment

Image quantification (radiomics)

Imaging features can be categorised into semantic and agnostic features. Semantic features are traditionally used by radiologists and describe the tumour globally, including size, volume, and uptake or enhancement. In addition to visual assessment, using quantification of different physical and physiological properties of medical imaging provides important information on tumour biology, including tumour aggressiveness and treatment resistance. Developments in imaging protocols and mathematical methods aim to quantify several important hallmarks of tumour biology, as described by Hanahan and Weinberg.[27] In this regard, there is a continuous effort to extract quantitative image descriptors describing characteristics covering vascularity, glucose metabolism, hypoxia, cell proliferation, and metabolite concentrations amongst others.[28]

Agnostic features quantify the shape and texture of a tumour expressed in a distribution of voxel values individually (first-order), between voxels (second-order) or of patterns (higher-order). There are several studies showing the correlation between agnostic features and characteristics of sarcomas. In CT, MRI and PET-CT features,

quantification of tumour texture, correlates significantly with pathological and clinical outcomes. Therefore, these studies highlight the high potential of agnostic features for improving insight in multiple biological characteristics correlated with pathophysiology and treatment response.[29–31] The conversion of images to these high-dimensional, semantic and agnostic data is called radiomics. The rationale for extracting radiomics features is that these provide more precise and standardised information on relevant tumour characteristics than solely visual assessment.[32,33]

Vascularity

Several studies investigated the possibility to assess response to neoadjuvant treatment in sarcoma patients through characterisation of tissue perfusion and vessel permeability. In Doppler ultrasound imaging, a decrease of flow velocity in a tumour-feeding artery, calculated as the resistive index, compared to the contralateral artery after neoadjuvant therapy, correlates with good pathological response in bone sarcoma. Furthermore, a reduction of intratumoural velocities, suggesting a reduction in arteriovenous shunting, indicates a good response to therapy.[34]

The use of contrast agents allows assessment of perfusion and permeability in other techniques. The rationale of such measurements is that extravasation of a contrast agent in the intercellular space reflects perfusion and vessel permeability. Therefore, rapid enhancement can discriminate viable tumour from slower enhancing normal and non-enhancing necrotic tissues.[35,36]

Dynamic contrast-enhanced (DCE) MRI with gadolinium (Gd) chelates as a contrast agent is the most extensively studied technique regarding vascularity. Time–intensity based parameters, such as wash-in rate and area under the curve for a specific range of interest, are frequently used (Fig 1). These parameters are rendered to be semi-quantitative, as they are dependent on factors that are near estimates, such as the speed of contrast medium injection. Nevertheless, Amit *et al.* observed that a 60% reduction in contrast medium wash-in rate in tumour tissue is correlated to response on chemotherapy in 14 bone sarcomas[37]; however, tissue granulation demonstrates similar contrast enhancement as viable tumour tissue, complicating the discrimination between viable tumour tissue and granulation.[38]

In addition to time–intensity based semi-quantitative parameters, quantification of perfusion, vessel permeability, and fluid volume fractions can be performed through the Tofts two-compartment model, based on fluid distribution over intravascular and extracellular space.[39] In this model, parameters can be derived from the shape of the wash-in and wash-out phases of the signal intensity–time curves. The transfer constant, Ktrans, is the most used parameter and describes the leakage of contrast medium in extracellular space (Fig 1). In a study by Guo *et al.*, vessel permeability was significantly decreased in a population of 71 patients with osteosarcoma treated with neoadjuvant therapy. Moreover, vessel permeability differed significantly for pathological responders and non-responders. This implies that quantifying perfusion characteristics has the potential to determine therapy response in these patients.[40] Additionally, a study by Alec *et al.*, analysed parametric maps of Ktrans in 21 patients with irresectable soft-tissue sarcoma before and after neoadjuvant treatment, concluding intratumoural biological heterogeneity can be used to determine therapy response.[41]

Cellularity

In addition to perfusion, diffusion-weighted MRI (DWI) has been used to characterise the diffusion of water molecules in tumours. The diffusion of water is inversely correlated with cellular density in tissues, where a high cellular density restricts movement of water molecules in the interstitial space. Considering high cellularity is correlated to viable tumour, DWI is useful in sarcoma to detect viable tumour tissue (Fig 2).[42,43] A commonly used measurement is the apparent diffusion coefficient (ADC). The ADC reflects the magnitude of diffusion of water molecules, mainly in the interstitial space and to a lesser extent in the intracellular space. Therefore, tissues with low ADC are considered to be tissues with high cellularity. In highly mucinous tumours, however, the usefulness of ADC is limited due to the biological composition with relatively low cellularity.[44]

As apoptosis after therapy happens before the alteration of tumour size, ADC has the potential for fast assessment of response. Where optimal timing in other imaging methods remains unclear, a rise in the ADC within 3–11 days after therapy was found to render the response to therapy in non-sarcoma tumour types.[45] In osteosarcoma, high whole-tumour ADC values were correlated with poor tumour response after four rounds of chemotherapy in two studies including 22 and 35 patients.[46,47] Furthermore, Soldatos *et al.* found a slight, but not specific improvement of sensitivity for prediction of therapy response by adding ADC evaluation to conventional MRI evaluation by radiologists in high-grade soft-tissue sarcoma after neoadjuvant therapy.[36]

Calculation of ADC is based on the presumption that water molecules follow an isotropic diffusion pattern, assuming a Gaussian distribution, which might not apply to biological tissues with structures such as cell membranes. In diffusion kurtosis imaging (DKI), a kurtosis coefficient describes the deviation of the distribution of water molecules to a Gaussian model, thus the tissue cellularity accounted for the spatial limitation of diffusion of a water molecule. Mean kurtosis showed high sensitivity and specificity of 96.3% and 93.8%, respectively, for differentiation between benign and malignant musculoskeletal tumours.[48] Although not yet used for determining therapy response in sarcoma, these results suggest a potential value.

Glucose metabolism

PET imaging with the radioactively labelled glucose analogue FDG allows quantification of glucose metabolism

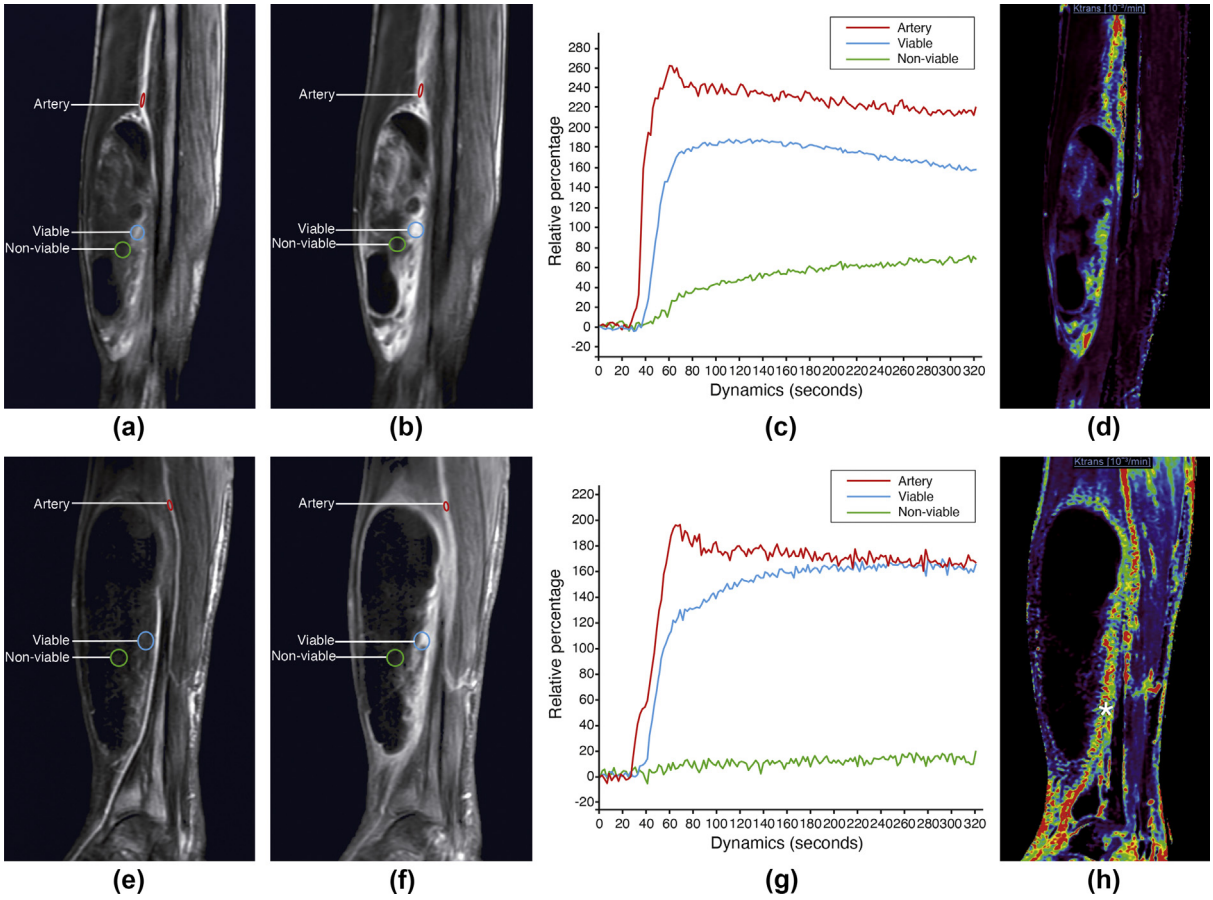

Figure 1 Undifferentiated pleiomorphic sarcoma in the right lower leg before (upper row) and after (lower row) radiotherapy. After resection an EORTC-STBSG response score C (1–10% viable) was found. (a) Sagittal DCE image 10 seconds after the arrival of contrast medium in the feeding artery showing early enhancement in many areas of the tumour. (b) Sagittal DCE image 5 minutes after the arrival of contrast medium in the feeding artery showing heterogeneous sustained enhancement in some tumour areas. (c) Graph showing enhancement patterns of the artery, a fast enhancing viable tumour component and a less viable tumour component. (d) Ktrans map, quantifying leakage of contrast medium in the extracellular space. (e) Post-radiotherapy sagittal DCE image 10 seconds after the arrival of contrast medium in the feeding artery showing reduced overall early enhancement. (f) Sagittal DCE image 5 minutes after the arrival of contrast medium in the feeding artery showing remaining sustained enhancement in dorsal tumour areas. (g) Graph showing reduced enhancement patterns of the less viable tumour components and remaining enhancement in dorsal tumour components, indicating partial response. (h) Ktrans map showing remaining leakage of contrast medium in the extracellular space in the dorsal parts of the tumour.

and has been proposed for early response assessment in sarcoma patients (Fig 3). In patients with gastrointestinal stromal tumours (GISTs), with a non-KIT exon 11 mutation specifically, FDG-PET is the established technique for early response assessment in patients treated with imatinib in a neoadjuvant setting, leading to changes in management in 27% of patients.[18] Furthermore, in osteosarcoma and Ewing sarcoma, early changes in FDG-uptake, as reflected by quantification of maximum standardised uptake value (SUVmax), even after one cycle of chemotherapy, were predictive for treatment response in two studies.[49,50] Similarly, early changes in SUVmax during neoadjuvant treatment provide accurate response assessment in soft-tissue sarcomas. After the first cycle of ifosfamide or gemcitabine-based chemotherapy in 50 high-grade sarcomas, a significant difference in SUVmax decrease of 55% in histopathological responders versus a decrease of 23% in non-responders was observed. Applying a cut-off value of 35% decrease in SUV after the first cycle of chemotherapy, resulted in a sensitivity of 100% and specificity of 67% to predict histopathological response.[22] In late response assessment (i.e., after completion of neoadjuvant therapy), a cut-off value of 60% decrease in SUV is commonly used, showing a sensitivity of 100% and specificity of 71% to predict histopathological response.[51] Overall, this makes PET a promising technique for quantitative assessment of tumour response.[52] Nevertheless, variable results have been obtained with regard to predicting histological tumour response in different sarcoma subtypes.[22,49] These results endorse the need for personalisation of treatment for different sarcoma subtypes.

Agnostic parameters in response assessment

As discussed, agnostic parameters have been studied extensively in the field of oncology; however, most of these

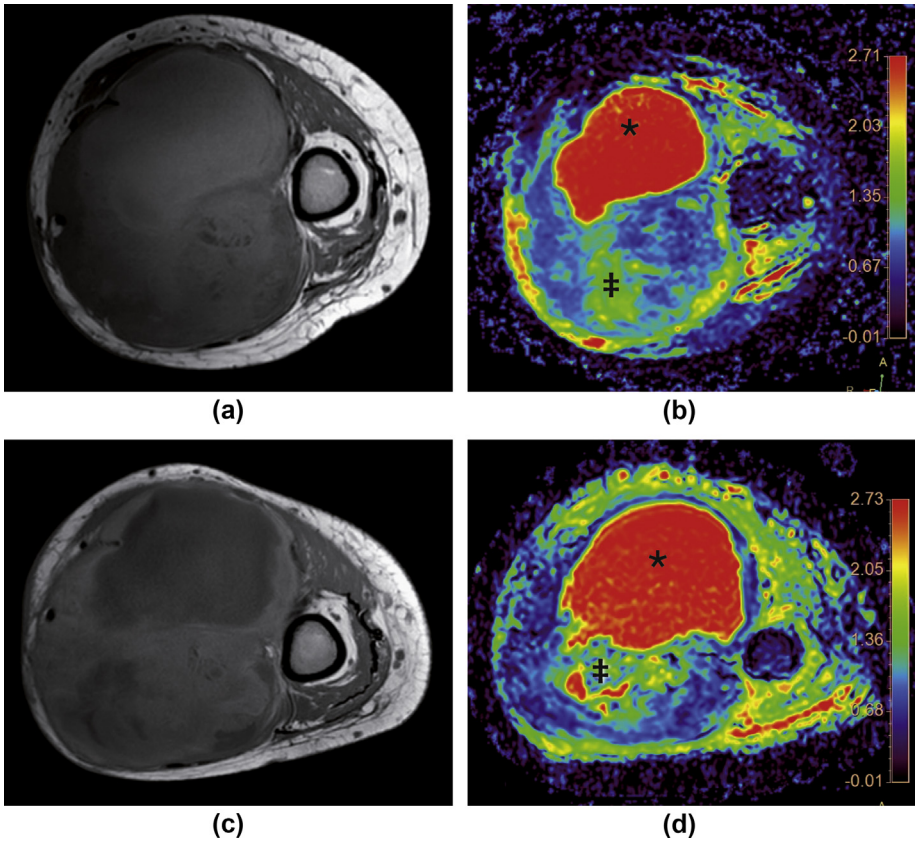

Figure 2 Malignant peripheral nerve sheath tumour of the left thigh before (upper row) and after (lower row) radiotherapy. After resection an EORTC-STBSG response score C (1–10% viable) was found. (a) Transversal T1W MRI image showing a multilobulate tumour. (b) ADC map showing a liquefied component (*) with high ADC and heterogeneity in cellularity of solid tumour components (†). (c) Transversal T1W MRI image post-radiotherapy showing increase in tumour size compared to previous imaging. (d) ADC map showing increase in size of the liquified component (*) with high ADC and development of new liquified components (†) in the heterogenic solid tissue on previous imaging.

studies have aimed for improvement in diagnosis, grading, and staging. Only few data are available on the use of agnostic features for assessment of response in sarcomas. Mean positive pixels (MPP) and entropy (NGLDM) in CT are texture parameters described as predictive for therapy response in sarcomas.[53,54] Furthermore, Lin *et al.* included differences between eight CT radiomics features before and after chemotherapy, in combination with the development of lung metastases during neoadjuvant therapy in a model to predict a pathological necrosis fraction of ≥90% in osteosarcoma. This model achieved an area under the receiver operating characteristic curve (AUC) of 0.87 and 0.80 in the training cohort (n=137) and validation cohort (n=54), respectively.[55]

Comparable results are found on MRI as Crombé *et al.* build a classification model based on three radiomic features in MRI for therapy response in soft-tissue sarcoma. It showed an AUC of 0.86 in the training cohort (n=50) and 0.63 in the test cohort (n=15). Moreover, the prognostic value of this model was higher than that of semantic evaluation.[56] Further studies correlating agnostic parameters to pathological response are necessary to optimise imaging-based response assessment.

Treatment response in metastatic disease

For patients with metastatic disease, prescribed treatment is dependent on the disease extent. In the case of solitary or oligo-metastatic lesions, resection, radiotherapy, radiofrequency ablation, or microwave ablation of metastatic lesions can be performed. Patients with multiple unresectable metastases are eligible for systemic treatment and/or radiotherapy.[8,9] The major aim of treatment in a metastatic disease setting is disease control (regression/stabilisation), in combination with the preservation of quality of life. In this regard, imaging can be used to assess prognosis and treatment effectiveness. As in local disease, currently unidimensional and bidimensional measurements of target lesions according to RECIST and WHO are used for this purpose. Response evaluated through these criteria correlates to improved survival[57]; however, in metastatic lesions specifically, assessing volume might be of more value as the goal of treatment is reduction of pressure on surrounding critical structures.

Nevertheless, as studied in localised sarcoma, assessments of response with size measurements have limitations due to heterogeneous biological response to treatment. In

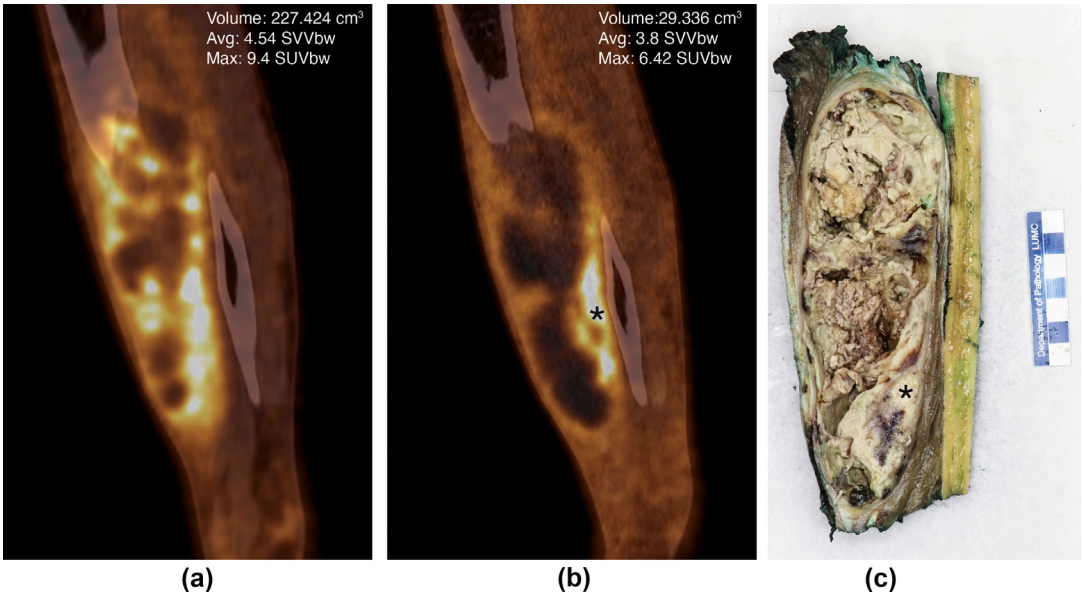

Figure 3 Undifferentiated pleiomorphic sarcoma in the right lower leg. This is the same tumour as depicted in Fig 1. (a) Sagittal FDG-PET/CT image showing heterogeneity in glucose metabolism before neoadjuvant radiotherapy. (b) Sagittal FDG-PET/CT image after neoadjuvant radiotherapy showing overall reduction in glucose metabolism and metabolic tumour volume, indicating partial response. Elevated metabolism diffusely remains, mainly in the dorsal tumour compartment (*). (c) Macroscopic photo in the sagittal plane of the surgical specimen. The pathological evaluation found 2% viable tumour cells (EORTC response score C), 10–20% hyalinisation and 80–90% necrosis. Dorsally, viable tumour was found (*), corresponding with DCE-MRI and FDG-PET findings.

metastatic disease, this concerns heterogeneity within one tumour as well as intertumoural heterogeneity. Although dependent on sarcoma subtype, small studies have already shown use of functional parameters for response monitoring in metastatic sarcoma to some extent.[58] In other malignancies, such as lung and breast cancer, quantification of whole-body metabolic tumour burden using PET has been shown to be highly indicative for monitoring treatment effectiveness.[59] Therefore, studies investigating the added value of FDG-PET-CT or functional MRI in response assessment and treatment adaptation in metastasised sarcoma patients should be pursued.

Challenges in quantitative response assessment

Image harmonisation

An important issue pertinent to using image biomarkers for characterising tumours and measuring treatment response is the quantitative accuracy. With a multitude of imaging protocols, hardware manufacturers, and software developments, data acquired from different institutions are typically not directly comparable.[60] This is particularly important in light of the low incidence and biological diversity of sarcomas, as pooling of data is necessary to improve the statistical power of different studies. Therefore, synchronisation of imaging protocols, a concept known as image harmonisation, is receiving more attention. Image harmonisation has already been performed in PET imaging. The European Association of Nuclear Medicine (EANM), published guidelines aiming to standardise FDG-PET/CT imaging to make multi-institutional comparisons possible.[61] Currently, such guidelines are not available for CT and MRI, making absolute quantification of different biological properties more challenging. Alternative strategies focused on harmonising data from heterogeneous sources are also increasingly being investigated. These methods involve mathematically transforming data from different scanners and protocols, making image features derived from these images more comparable. One of such methods is the combatting batch effect (ComBat) method, originating from the field of genomics. The ComBat method has been successfully applied to PET and MRI images.[62] Moreover, it has shown to improve prognostic value in prediction models in other types of tumours.[31] The use of such methods could contribute to finding robust imaging features related to tumour biology and treatment effectiveness in sarcoma.

Multiparametric imaging

Although quantification of different physical and physiological properties reflecting local tumour biology has proven to be useful to assess treatment response, different images are normally analysed separately in clinical routine. There seems to be the additional value in combining the information from different images, also known as multiparametric imaging, for tumour evaluation (Figs 4 and 5).[63] There are only limited data available on multiparametric imaging in response monitoring in sarcoma. Nevertheless, in high-grade soft-tissue sarcoma the added value of a multiparametric model is shown in the increase of specificity by adding ADC-

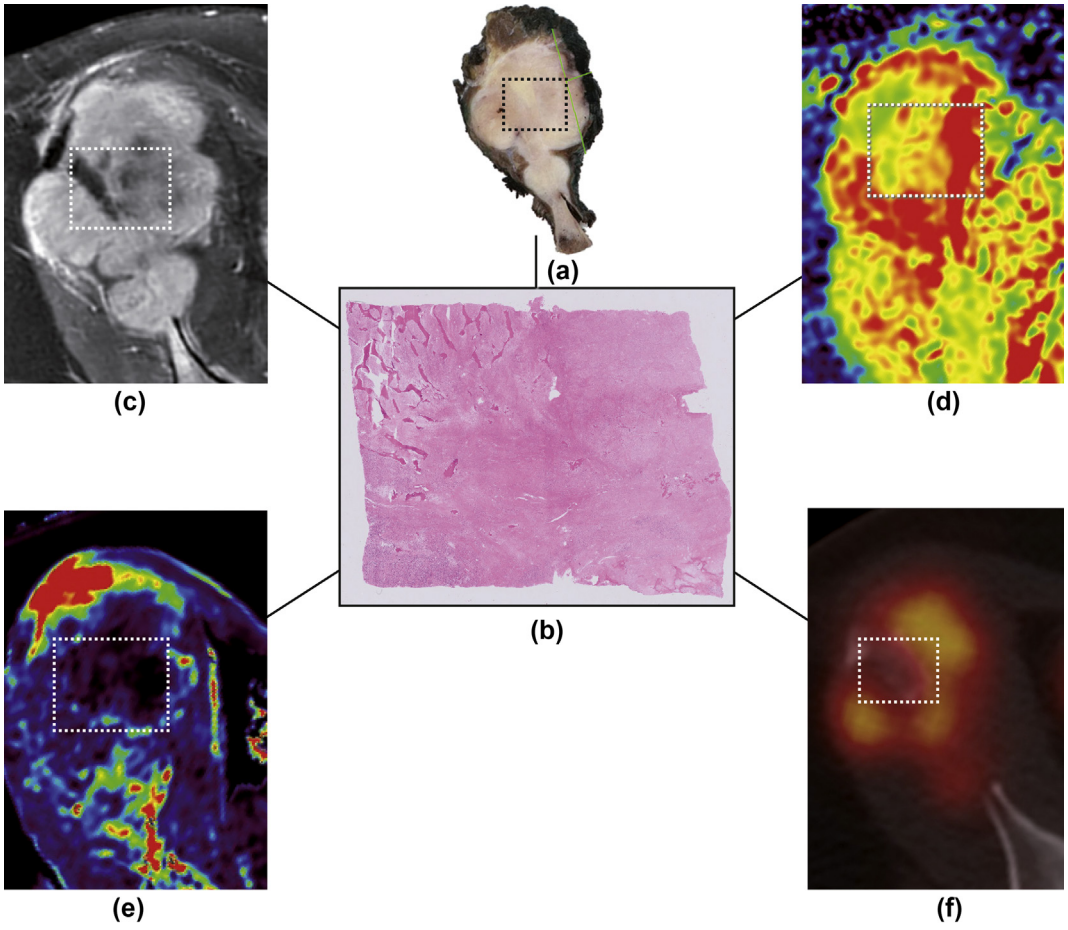

Figure 4 Rhabdomyosarcoma of the right iliac crest after chemotherapy and radiotherapy. (a) Macroscopic photo in the transversal plane of the surgical specimen. The pathological evaluation found an EORTC-STBSG response score E (>50% viable tumour, 10–20% fibrosis, 10% necrosis). (b) Digitalised image of the embedded central part of the tumour showing >50% viable tumour. (c) Transversal T1 fat suppressed post-Gd chelates. (d) Ktrans map suggesting low perfusion and low permeability in the corresponding tumour compartment. (e) ADC map suggesting high cellularity in the corresponding tumour compartment. (f) Fused FDG-PET-CT image shows high and heterogeneous glucose metabolism in the periphery and relatively low uptake in the central part of the tumour. The combination of characteristics on multimodality imaging theoretically indicate aggressive tumour cells, namely viable tumour cells that proliferate fast despite a limited supply of nutrition.

mapping to a model to predict tumour response based on static anatomical MRI. In particular, the ADC-mapping improved detection of tumour fibrosis, while the use of solely T1-weighted, fluid-sensitive and static contrast-enhanced MRI had a lower sensitivity for detecting tumour fibrosis.[36] In another study, the combined use of DWI and FDG-PET, specifically the change in ADC and SUV, before and after neoadjuvant treatment, for prediction of histological response was evaluated. Accuracy was 78% for both parameters separately but increased to 85% when combined.[64] Furthermore, such multiparametric imaging approaches have been used to improve the accuracy in tumour characterisation using radiomic models.[63] In a study by Vallières *et al.*, the use of higher-order radiomics features derived from both PET and MRI improved the prediction of development of lung metastases in high-grade soft-tissue sarcoma, suggesting possible use in response assessment. Currently, the added value of PET/MRI in assessing response to neoadjuvant radiation therapy in high-grade soft-tissue sarcomas has been assessed in several clinical trials. In a clinical trial (NCT03076333), the pathological response to treatment is correlated with changes in PET and MRI parameters. Such prospective multimodality imaging trials have great potential in developing accurate response metrics based on multiparametric imaging.

The link between imaging and biology is essential to further develop new imaging features that accurately reflect tumour characteristics (Fig 4). In other types of cancer, studies are investigating these biological links by registration of histopathology and imaging to correlate imaging features spatially with underlying tumour biology.[65] In response assessment, where imaging-based differentiation between histopathological entities, such as necrosis, fibrosis, hyalinisation, granulation, and viable tumour cells, is a complicating factor, this link will be of major importance.

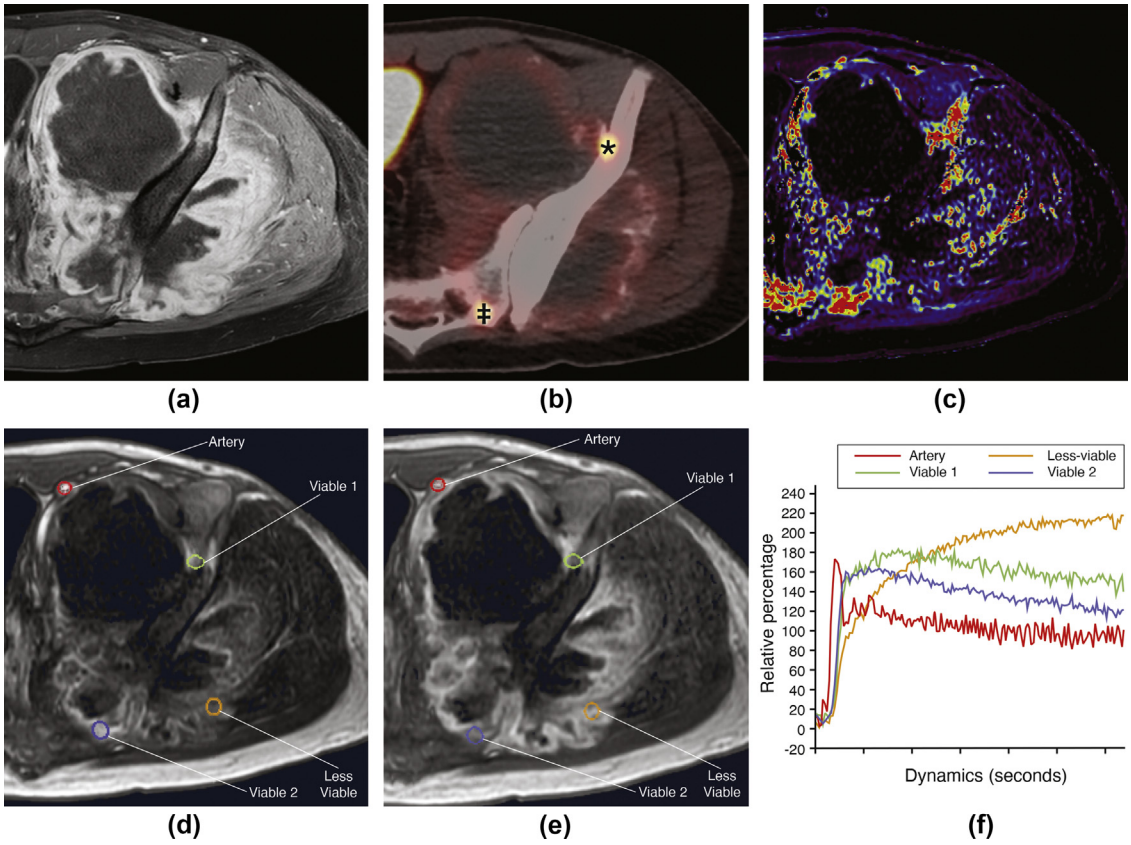

Figure 5 Osteosarcoma of the left iliac crest after chemotherapy. Approximately 80% viable tumour tissue and 20% necrosis was found during pathological evaluation. (a) Transversal T1 SPIR post-Gd chelates. (b) Fused FDG-PET/CT showing diffuse uptake with reduced central uptake suggesting central necrosis and two metabolically active foci (*,†). (c) Ktrans map suggesting low perfusion or low endothelial permeability in the central tumour compartment and diffuse perfusion and permeability in the tumour periphery. (d) DCE image 10 seconds after the arrival of contrast medium in the feeding artery showing overall early enhancement in the tumour periphery. (e) DCE-MRI 5 minutes after the arrival of contrast medium in the feeding artery showing homogeneous sustained enhancement in the tumour periphery and little enhancement in the central tumour compartment, suggesting low perfusion or high interstitial pressure. (f) Graph showing fast enhancement reaching a plateau value suggesting viable malignant cells in the ranges of interest 'Viable 1' and 'Viable 2' and relatively slow and sustained enhancement in another range of interest 'Less-viable' suggesting less viable cells. The ranges of interest 'Viable 1'and 'Viable 2' correspond with * and † in (b). The combination of characteristics on multimodality imaging indicates diffuse viable tumour cells in the periphery of the tumour and two specifically viable and aggressive foci.

Prospects of imaging in response assessment

Cellular proliferation

Multiple imaging techniques have not been studied in the light of response assessment in sarcoma, but have theoretical use in quantifying biological mechanisms correlated to the therapy response. Increased cell proliferation is one of the hallmarks of cancer and different imaging methods have been developed to quantify cellular proliferation. Certain MRI protocols can characterise the biochemical composition of tissues. In this regard, MR proton spectroscopy (MRS) is used to determine concentrations of metabolites in tumours. Choline is a quantifiable metabolite and is involved in the synthesis of cell membranes. Given the elevated proliferative activity of tumour cells, the concentration of choline is often increased in malignancies. Subhawong *et al.* detected choline in a poorly responsive osteosarcoma while there was a lack of detectable choline levels in two chemotherapy-responsive Ewing sarcomas and one undifferentiated pleiomorphic sarcoma, each with 100% histological necrosis.[66] In this study, no direct comparison with baseline imaging was performed, making it difficult to estimate the change in choline concentration during neoadjuvant treatment.

Although quantifying cellular proliferation in PET imaging has not been extensively studied in the context of response monitoring in sarcoma, it has been used in grading and staging, using multiple tracers. ^{11}C-choline was used as a radiotracer visualising choline as a precursor for the synthesis of phospholipids, which is used to build new cell membranes. Highly proliferative tumours, therefore, show more choline uptake than the surrounding healthy tissue. A study showed improved staging of nodal metastases with ^{11}C-choline-PET versus conventional imaging methods.[67] Correct N-staging was achieved in all of 16 patients using ^{11}C-choline-PET, while accuracy was only 63% with conventional imaging ($p<0.05$).

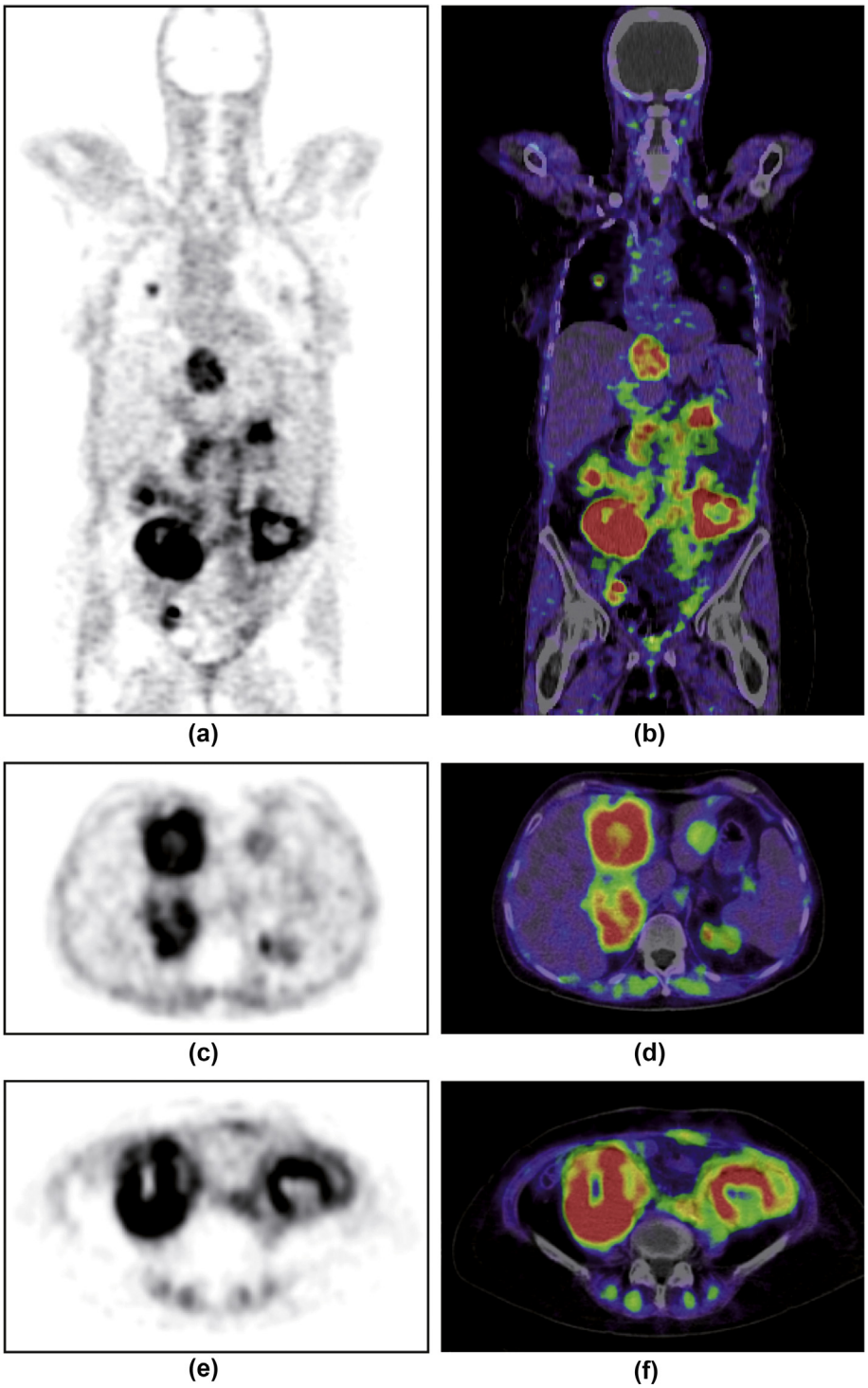

Figure 6 FAPI-PET and FAPI-PET-CT images of a woman with metastasised leiomyosarcoma of the uterus after hysterectomy, abdominal and retroperitoneal metastasectomies, radiotherapy, and systemic treatment. (a,b) Coronal plane showing high uptake of FAPI in peritoneal/retroperitoneal, liver and lung lesions. (c,d) Transversal plane showing multiple liver lesions with heterogenic uptake. (e,f) Transversal plane showing multiple peritoneal lesions with heterogenic uptake. Image courtesy of C. Kratochwil, Department of Nuclear Medicine, University Hospital Heidelberg.

The tracer ^{18}F-fluoro-3′-deoxy-L-thymidine (FLT) reflects the activity of thymidine kinase, which is an indirect proxy for cellular proliferation. One study found correlation between FLT-uptake and histological grade. Uptake in six grade 1 sarcomas was significantly lower than uptake in 14 grade 2 or 3 sarcomas.[68] Furthermore, all pulmonary metastases in all patients were detected. These results in grading and staging warrant further

validation of ^{11}C-choline and ^{18}F-FLT for early response monitoring.

DNA replication is a hallmark of proliferation and is reflected by quantification of protein metabolism. ^{11}C-methionine (MET) is the most widely used radiotracer for visualisation of amino-acid transport. A study comparing MET- with FDG-PET before and after chemoradiotherapy for prediction of pathological tumour response in nine patients with soft-tissue sarcoma scheduled for resection, showed a higher predictive value for FDG-PET.[69] Yet, possible use for differentiating between inflammation and tumour tissue requires further exploration of the utility of MET compared with other tracers.

Hypoxia

Radiotherapy resistance and increased aggressiveness of tumour cells is known to be correlated to hypoxia.[70,71] Thus, accurately quantifying hypoxia might assist in personalising radiotherapy plans by performing dose escalation to radioresistant tumour volumes. Blood-oxygen-level dependent (BOLD) MRI is a technique quantifying hypoxia. Deoxyhaemoglobin increases the MRI transverse relaxation rate (R_2*) of water. R_2* is therefore dependent on perfusion, oxygenation, and static tissue characteristics.[72] BOLD has not been extensively studied in sarcomas but might be a useful method to analyse the ability of sarcoma cells to resist apoptosis in a hypoxic environment. Currently, a trial (NCT03054792) investigating the use of BOLD MRI in rhabdomyosarcoma is being undertaken.

PET is more extensively used to investigate hypoxia in sarcoma. Small patient studies have not yet revealed a correlation between hypoxia and the level of accumulation of hypoxia tracers such as ^{18}F-fluoromisonidazole (FMISO) and ^{18}F-1-(5-fluoro-5-deoxy-α-D-arabinofuranosyl)-2-nitroimidazole (FAZA).[73,74] Therefore, the use of hypoxia tracers in soft-tissue sarcoma is currently addressed in several clinical trials. NCT03730077 is a registered trial in which both FDG and FMISO-PET are performed in 30 patients. This trial aims to evaluate the clinical value of FMISO to determine hypoxia in vivo. Another trial, NCT03418818, aims to measure the hypoxic volume in 14 sarcomas using FAZA-PET/MRI, before and after neoadjuvant treatment.

Fibroblast activation

Recent studies with ^{68}Ga-labelled fibroblast activation protein inhibitors (FAPI) tracers show promising results for visualising many different cancer types by specifically targeting cancer-associated fibroblasts. In eight sarcoma lesions, FAPI-PET showed high uptake of this tracer with an average SUVmax around 17 (Fig 6).[75] Next to sarcoma, other tumour entities showed a remarkable high and specific avidity in tumour tissue. A tumour-specific high uptake compared to other tracers makes a tracer more potent for early response monitoring and assessment of total tumour burden. Therefore, although the use of FAPI is not yet investigated in regard of response monitoring in sarcoma patient, the results of this study and theoretical considerations are promising.

Conclusion

Personalising treatment in patients with a sarcoma remains challenging due to the biologically diverse nature of these tumours. With an ever-increasing number of possible treatment options, clinicians have difficulty optimising treatment for individual patients. This review describes the established and potential role of imaging for personalising treatment for sarcoma patients through response assessment. With developments in new tracers, imaging protocols, and analytical methods, the challenge is to acquire a practicable set of imaging features for specific sarcoma subtypes. Eventually, it is expected that imaging-based response monitoring will help to achieve successful modification of (neo)adjuvant treatments and improve clinical care for these patients.

Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: G.M. Kalisvaart is the recipient of an educational grant from Philips Electronics Nederland B.V, Eindhoven, The Netherlands, during writing of this manuscript.

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