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Imaging response evaluation after neoadjuvant treatment in soft tissue sarcomas: Where do we stand?

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ABSTRACT

Soft tissue sarcomas (STS) represent a broad family of rare tumours for which surgery with radiotherapy represents first-line treatment. Recently, neoadjuvant chemo-radiotherapy has been increasingly used in high-risk patients in an effort to reduce surgical morbidity and improve clinical outcomes. An adequate understanding of the efficacy of neoadjuvant therapies would optimise patient care, allowing a tailored approach. Although response evaluation criteria in solid tumours (RECIST) is the most common imaging method to assess tumour response, Choi criteria and functional and molecular imaging (DWI, DCE-MRI and ^{18}F-FDG-PET) seem to outperform it in the discrimination between responders and non-responders. Moreover, the radiologic-pathology correlation of treatment-related changes remains poorly understood. In this review, we provide an overview of the imaging assessment of tumour response in STS undergoing neoadjuvant treatment, including conventional imaging (CT, MRI, PET) and advanced imaging analysis. Future directions will be presented to shed light on potential advances in pre-surgical imaging assessments that have clinical implications for sarcoma patients.

1. Introduction

Soft tissue sarcomas (STS) are a heterogeneous group of rare neoplastic diseases accounting for more than 70 different histologies (WHO, 2021). Locally-advanced sarcoma may benefit from neoadjuvant radiotherapy/chemotherapy to reduce surgical morbidity and improve clinical outcomes. Predicting the efficacy of neoadjuvant treatments is challenging; however, early identification of non-responders offers the potential to prevent unnecessary, potentially toxic treatment and select patients who truly benefit from neoadjuvant therapy. Therefore, exploring robust methodologies to assess the predictive value of imaging for tumour response to neoadjuvant therapies is relevant and timely (Subbiah et al., 2017).

Although serial biopsies may, in theory, monitor the tumour response, they are invasive and prone to sampling errors which are significant in heterogeneous tumours. Moreover, a proper understanding of the correlation between imaging and chemotherapy- and/or radiation-induced changes in histology is crucial for the development of reliable imaging biomarkers (Schillaci et al., 2019; Hartman et al., 2016). Unfortunately, insights into changes at tissue level after systemic

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or local therapy remain limited. Thus, considerable interest has recently risen in radiology-pathology correlation in STS before and after neoadjuvant therapies to identify predictive factors able to influence patient management.

This review gives an overview of the evidence for imaging of the STS in the neoadjuvant setting, identifying strengths and weaknesses and providing directions for future research.

2. Neoadjuvant treatment for soft tissue sarcomas

Neoadjuvant treatment is increasingly used in patients with STS. Specific nomograms can be used to better stratify patients and support clinical decisions (Callegaro et al., 2016; Donahue et al., 2010; Callegaro et al., 2017). Neoadjuvant radiotherapy is predominantly employed to reduce post-surgical local recurrence rates. In particular, radiation therapy may represent the only strategy for local control when surgery is declined, too morbid or not possible (Larrier et al., 2016). Preoperative radiotherapy is usually preferred because late morbidity (e.g. fibrosis, arthrosis, oedema and bone fractures) tends to be lower than in the adjuvant setting, resulting in improved long-term functional outcome and quality of life (Haas, 2018).

Moreover, high-risk STS may be treated upfront with systemic therapy to treat potential micro-metastases and thus prevent metastatic spread. For specific histotypes with locally advanced diseases (e.g. myxoid liposarcomas), chemo/radiotherapy can also be administered as an induction therapy to shrink the tumour volume and enable organ sparing resection (Pasquali and Gronchi, 2017; Salduz et al., 2017). Recently, the European Organization for Research and Treatment of Cancer (EORTC) and Soft Tissue and Bone Sarcoma Group (STBSG) underwent a survey among their members that confirmed a substantial heterogeneity of treatment strategies and agents used both for pre- and postoperative chemo/radiotherapy in STS (Rothermundt et al., 2018). Multi-agent chemotherapy, like anthracycline plus ifosfamide, is the most common and accepted strategy, whereas doxorubicin and dacarbazine may be used for leiomyosarcoma (D'Ambrosio et al., 2020; Judson et al., 2014).

Some chemotherapy agents, like bevacizumab, sorafenib, sunitinib, pazopanib, and trabectedin, can also act as sensitizers prior to radiotherapy (Yoon et al., 2011; Gronchi et al., 2019; Jakob et al., 2016; Canter et al., 2014). Preoperative conventionally-fractionated RT is usually preferred, but hypo- and hyperfractionated schemes have also been proposed (Koseła-Paterczyk et al., 2014). Neoadjuvant chemo-radiation is a combined strategy for poorly resectable tumours with synergic effects and the potential to lower required RT doses (Look Hong et al., 2013; Spałek et al., 2020; Lehane et al., 2016). Hyperthermic isolated limb perfusion is a further neoadjuvant approach, and can be considered an alternative to amputation in specific circumstances (Song et al., 2019).

3. Response criteria for neoadjuvant treatments

Imaging assessment pursues different aims depending on which kind of therapy is delivered. After local therapy, radiology should investigate the persistence of viable tumour and possibly provide prognostic information about local recurrence. Conversely, imaging assessment after systemic therapy provides insights on histological response and envisages the possibility to provide prognostic information, similarly to what have been demonstrated in osteosarcoma and Ewing's sarcoma (Bielack et al., 2002; Picci et al., 1997). Traditionally, tumour response has been evaluated using RECIST 1.1 criteria, which uses unidimensional measurements (Eisenhauer et al., 2009). Apart from some reports on the effect of radiotherapy on tumor shrinkage in different histotypes, there is no information on a clear association between prognosis, the amount of tumour shrinkage or true histological response in STS treated by chemo/radiotherapy (Roberge et al., 2010; Tanaka et al., 2018; Canter et al., 2010; le Grange et al., 2014; Gui et al., 2019; Miki et al., 2010; Betgen et al., 2013). The lack of relationship between percentage tumour shrinkage and survival was shown by Grünwald et al. in an EORTC analysis, suggesting that absence of progression rather than extent of tumour shrinkage defines prognosis in advanced STS patients treated with palliative chemotherapy (Grünwald et al., 2016). There is no evidence that the RECIST criterion of 30 %-unidimensional shrinkage of the target lesion always truly reflects a superior anticancer effect. The RECIST 30 %-cut-off is entirely arbitrary and dates back to the time when tumours were measured by physical examination. The main goal of RECIST was to standardise and harmonise endpoints of clinical trials in solid tumours. Furthermore, RECIST does not consider tumour changes like cystic transformation or haemorrhage, which can result in an increase in size even in case of a true histological response (Roberge et al., 2010; Tanaka et al., 2018; Canter et al., 2010; le Grange et al., 2014; Gui et al., 2019). To overcome this important limitation, Stacchiotti et al. demonstrated in 2009 how MR-based Choi criteria, which incorporate both signal intensity and size (Choi et al., 2007), were more accurate in predicting patient outcomes than RECIST (Stacchiotti et al., 2009). Further publications have confirmed such observations (Betgen et al., 2013; Marrari et al., 2020; Esser et al., 2018), and highlighted that RECIST responses are scarce and restricted to a few sarcoma types after neoadjuvant treatment (e.g. myxoid liposarcoma after radiation treatment) (Betgen et al., 2013; Chung et al., 2009; Lansu et al., 2020; Taieb et al., 2015; Stacchiotti et al., 2012). Nevertheless, in the absence of a validated alternative, most clinical sarcoma trials continue to use RECIST 1.1 as a response evaluation system (Schuetze et al., 2008). An alternative and standardised approach for imaging evaluation is needed to incorporate noninvasive imaging information into the decision-making algorithms of multidisciplinary sarcoma teams. This includes the definition of optimal acquisition and timing protocol along with a structured and objective image interpretation method. Timing of imaging assessment differs between radiation therapy and chemotherapy, as surgery is performed immediately following chemotherapy, whereas the interval between the end of radiation and surgery is usually 6–8 weeks (Subbiah et al., 2017).

Regarding the imaging evaluation of tumour response, there is no consensus on the choice of imaging modality. In 2016, a standardised approach for MR longitudinal evaluation of STS following preoperative radiotherapy (RT) was proposed by a task force endorsed by the EORTC-STBSG and Image Groups (Messiou et al., 2016). The paper advocated a standard MRI protocol to be performed at 4–6 weeks following neoadjuvant radiotherapy as close to the surgical date as possible to minimise the potential for pseudo-progression due to the acute effects of radiotherapy including vascular disruption, possibly causing an increase in size and enhancement. To ensure consistency in longitudinal evaluations, the same or comparable MRI equipment should be used. Furthermore, technical refinements regarding contrast medium administration have been recently proposed, highlighting how a 60s-acquisition delay optimises the response evaluation when adopting Choi criteria (Crombé et al., 2019a). Morphological pre- and post-contrast-enhanced sequences should be supplemented by diffusion-weighted MRI to explore changes in tissue cellularity (DWI) (Messiou et al., 2016; Costa et al., 2018). DWI is gaining interest as a widely available and quick quantitative MRI technique for oncology imaging. Predictive and prognostic data in STS are limited, but ongoing studies are shedding light on the role of multi-parametric MRI (which include contrast-enhanced imaging and DWI, but can also be complemented with additional DWI for estimation of intra-voxel incoherent motion (IVIM) and with multiple gradient-echo imaging, among others) for response assessment after neoadjuvant therapy (Costa et al., 2018; Dudeck et al., 2008; Winfield et al., 2019). Dynamic contrast-enhanced (DCE)-MRI has been investigated and shows some promise, but their widespread adoption in clinical practice is limited due to more extensive post-processing requirements and variability in acquisition (Crombé et al., 2019a; Soldatos et al., 2016). Despite a few preliminary reports, MRI-spectroscopy is not yet considered a feasible and reliable tool for

the response assessment of neoadjuvant treatment, since it is not available in most centres and the current evidence is debatable (Zhang et al., 2016).

Finally, ^{18}F-FDG-PET imaging is a well-established technique for assessing metabolic activity (Gennaro et al., 2020), and has been shown to be helpful in the early identification of chemotherapy responders (Grueneisen et al., 2019; Lim et al., 2019). Alongside the EORTC-STBSG paper on imaging response evaluation guidelines (Messiou et al., 2016), the same group published in 2016 a standardised approach for pathology evaluation after neoadjuvant therapy, highlighting the importance of radiology-pathology correlation (Wardelmann et al., 2016). The proposed protocol provides specific instructions on the handling and photography of surgical specimens to enable correlation with radiologic findings. Moreover, such correlation may serve as a useful guide for pathologists to select the most representative pathology samples. The two publications were proposed as frameworks to build new evidence. Unfortunately, the first study to assess the prognostic value of the EORTC-STBSG response score failed to correlate the amount of viable tumour cells with the clinical outcome (Schaefer et al., 2017).

4. Radiology-pathology correlation in soft tissue sarcoma

Pathology is considered the gold standard for the definition of tumour changes after therapy. The most important factors for predicting tumour response and survival after chemo-radiotherapy are pre-treatment grading and histological subgroup. High-grade tumours and undifferentiated pleomorphic sarcomas (UPS) have been associated with improved response rates to the combination of doxorubicin and ifosfamide in the metastatic setting as compared to single agent doxorubicin (Young et al., 2017). Imaging findings have recently been shown to be complementary to tissue findings for the assessment of tumour grade (Fisher et al., 2016). A grade difference between biopsy and excision specimens of leiomyosarcomas was found in 68 % of cases, with all these cases showing an increase in grade from biopsy to excision specimen (Schneider et al., 2017). CT and MRI imaging features (e.g. necrotic areas) have been proposed to be complementary to improve the accuracy of histopathological grading (Mcaddy et al., 2020; Crombé et al., 2019b; Zhao et al., 2014). CT and MRI texture analysis is an advanced image analysis referring to characterisation of regions in MR images, including DCE-MRI and DWI sequences, by their texture content. Both CT- and MRI-based texture analysis may also play a relevant role in this regard (Peeken et al., 2019; Hong et al., 2020; Zhang and Ren, 2020).

Dependent on histology and treatment, several changes in the specimen can be recognised after therapy, including the presence of ghost cells (necrotic cells with loss of nuclear and cytoplasmic detail), reduced cellularity (intended as reduction of stainable cells), granulation tissue (observed as foamy macrophages and lymphocytes), fibrosis, adipose tissue, hemosiderin deposition, changes in vessel micro density, development of calcifications, atrophic or regenerating non-neoplastic skeletal muscle (Lucas et al., 2008). A further complicating factor is the well-known substantial discordance in the evaluation of histological subtype, tumour grade and definitions of post-treatment changes existing between pathologists working at reference institutions and those who are not (up to 40 % of cases) (Young et al., 2017). To date, there is no agreement on measuring the effects of neoadjuvant chemotherapy/radiation therapy on STS. Expert pathologists recommend describing the morphological changes throughout the tumour (represented as a percentage), including the percentage of viable tumour, necrosis, haemorrhage, sclero-hyalinosis, reparative fibrosis, fibro-histiocytic reaction with deposits of hemosiderin, myxoid and cystic changes. In this setting, adequate sampling is of paramount importance (almost 1 sample per cm), including necrotic areas. The gross appearance of the tumour can be misleading, as areas that appear necrotic may represent myxoid or oedematous tissues (Shah et al., 2016; Rubin et al., 2010). A standardised system proposed in 2016 by the aforementioned EORTC-STBSG task force is summarised in Table 1 (Wardelmann et al., 2016).

Table 1
Assessment of tumour response proposed by EORTC-STBSG in 2016 (Wardelmann et al., 2016).

Histological findings	Response grade
No stainable vital tumor cells	A
Single stainable tumor cells or small cluster (overall < 1%)	B
≥1% <10 % stainable vital tumour cells	C
10 % <50 % stainable vital tumour cells	D
≥50 % stainable vital tumour cells	E

Different imaging modalities like MRI, CT and ^{18}F-FDG PET aim to macroscopically depict those changes, with a particular interest in detecting necrosis, as 95 % necrosis after neoadjuvant therapy was initially correlated to a halved risk of local recurrence and metastatic spread and pathology-related deaths at 5 and 10 years (Cousin et al., 2017; Eilber et al., 2001). These results are still controversial and advocate for larger studies to confirm that the extent of histopathological necrosis after neoadjuvant treatment may influence patient management, as several papers were unable to correlate extended tissue necrosis with improved survival (Canter et al., 2010; Vaynrub et al., 2015; Mullen et al., 2014; Menendez et al., 2007). This could be because necrosis does not reflect the biological behaviour of the tumour and its metastatic potential, including circulating tumour cells. Recently, the extent of hyalinization/fibrosis has also been suggested as a better predictor for recurrence-free survival and overall survival, supporting the hypothesis that histologic appearance can predict tumour biology and represent a future endpoint for neoadjuvant trials (Schaefer et al., 2017). Reliable imaging biomarkers would allow radiologists to complement pathology assessment and provide non-invasive, predictive and prognostic information (Chen et al., 2013).

Integration of multi-modality imaging with clinical data may support experienced radiologists to better interpret imaging changes in patients treated with neoadjuvant therapy. Beneath, we present the latest evidence for each imaging modality that has allowed a better understanding of radiologic-pathology correlation after neoadjuvant treatments in STS.

4.1. Magnetic resonance imaging (MRI)

MRI is the preferred imaging modality for STS, particularly for extremity STS. Its predominant role is to define the local extent of disease and to accurately depict anatomy (Raghavan, 2017). MRI imaging features include morphology, signal intensity on different sequences and enhancement after contrast medium. Features including peritumoral contrast enhancement and oedema, heterogeneous T2 signal intensity and necrotic areas have been associated with high histological grade and poorer outcomes (Crombé et al., 2019b; Zhao et al., 2014). Despite a preliminary study describing T1W hyper-intensity correlation with improved survival, relapse, and time to relapse (Sala et al., 2010), conventional morphologic MRI characteristics are subjective and generally inadequate in discriminating between patients with positive or negative clinical response (Favinger et al., 2018). Moreover, necrosis on imaging lacks an agreed/validated definition and is mostly defined as areas of low tumour perfusion, T2W hyper-intensity and high apparent diffusion coefficient (ADC) values at DWI (Soldatos et al., 2016; Crombé et al., 2019b; MacVicar et al., 1992) (Fig. 1). However, such correlations are not always straightforward, as pathological entities may show high ADC values (myxoid liposarcoma), as well as certain types of necrosis may manifest can also manifest with low ADC values (e.g. coagulative necrosis) (Figs. 2 and 3). Semi-automated volumetric segmentation techniques provide more objective measurements and have been shown to identify necrosis on MRI with similar accuracy compared to histopathology (Monsky et al., 2012). A study of multi-parametric MRI, entailing DCE and DWI MRI for assessing response to radiotherapy, has

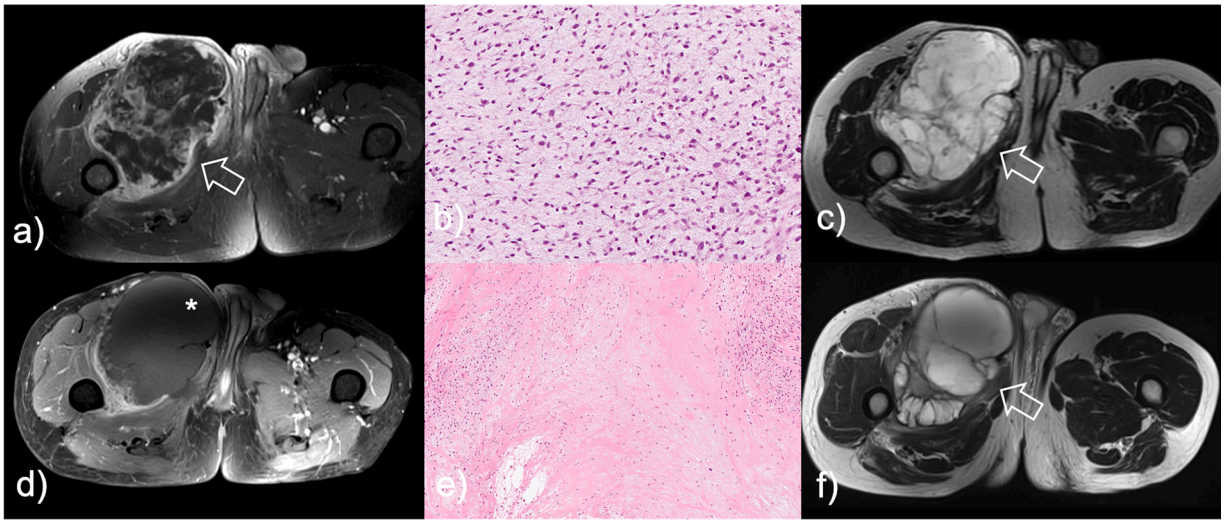

Fig. 1. a) Large lesion in the right thigh of a 52-year old man with heterogeneous contrast-enhancement on T1-weighted MRI due to internal areas of necrosis. b) Pre-treatment core needle biopsy shows high-grade spindle cell sarcoma with myogenic differentiation (Ki67 80 %). c) Liquid/myxoid content is shown on T2-weighted images and d) Contrast-enhanced T1-weighted MRI after chemoradiotherapy (3 cycles of adriamycin-dacarbazine and 50 Gy/25 fractions) shows no intralesional contrast-enhancement in keeping with response to therapy although the mass is stable by RECIST 1.1. e) Post-surgical pathology shows large areas of necrosis and reduction in neoplastic cellularity, partly visible on the top-right and accounting for 70 % of the whole specimen. f) Fibrohistiocytic changes and sclerosis are also present and are represented by hypointense septa on T2-weighted images.

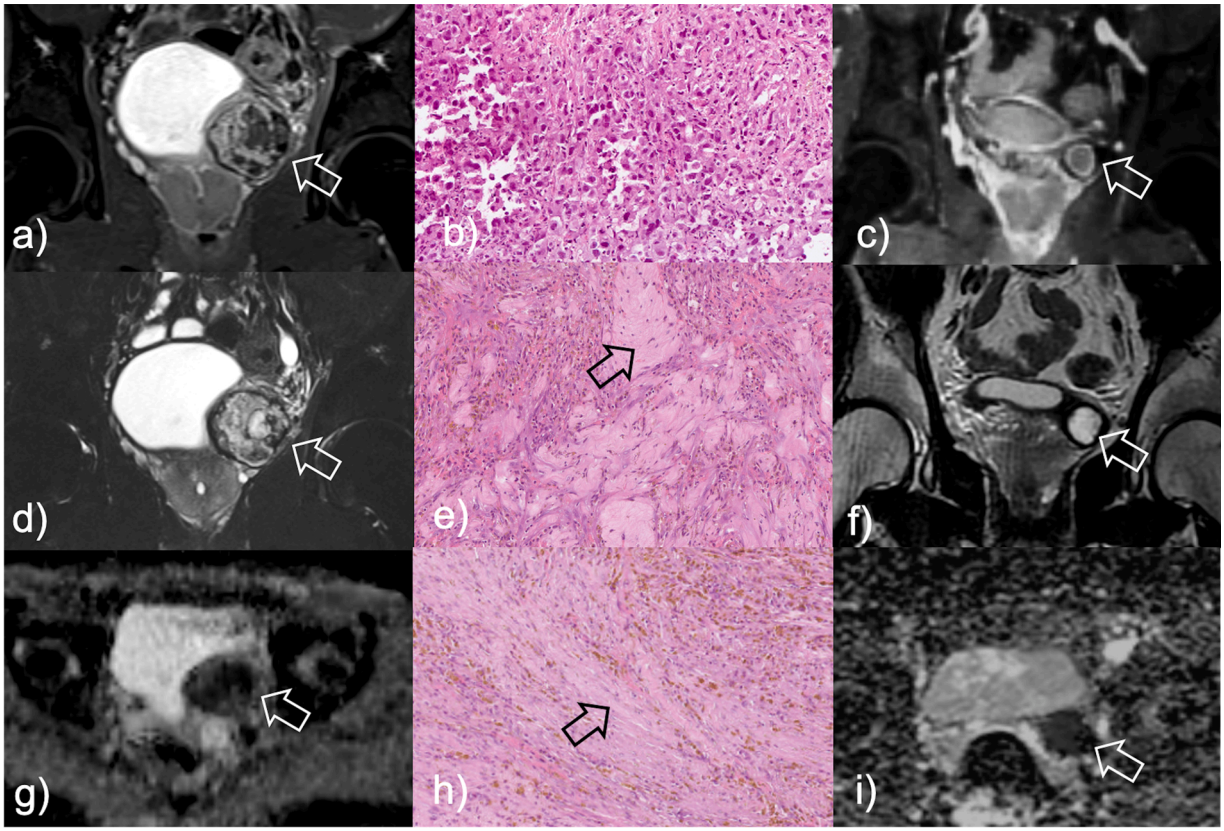

Fig. 2. a) Soft tissue mass arising from the left wall of the bladder of a 30-year old patient. a) Contrast enhanced T1-weighted MRI showing areas of non-enhancing internal necrosis (arrow). b) Pre-treatment core needle biopsy shows high grade mesenchymal neoplasm characterized by atypical vascular structures consistent with epithelioid angiosarcoma (Ki-67 80 %). c) Post-chemotherapy (3 cycles of adriamycin-ifosfamide) contrast-enhanced T1-weighted MRI shows reduction in tumor size and diminished contrast-enhancement (arrow) d) Pretreatment T2-weighted images showing heterogeneous signal with liquid/myxoid areas (arrow). e) Post-surgical specimen shows florid reparative fibrosis (arrow) and fibrohistiocytic reaction with hemosiderin deposition. f) There is a homogenous bright signal on post-treatment T2-weighted images (arrow) g) Pre-treatment ADC map showing low signal corresponding to high tumor cellularity, h) Higher magnification demonstrates foci of sclero jalinosis (arrow) and deposition of hemosiderin and foamy histiocytes. i) The post-treatment ADC map demonstrates low signal/ restricted diffusion possibly corresponding to coagulative necrosis and haemosiderin.

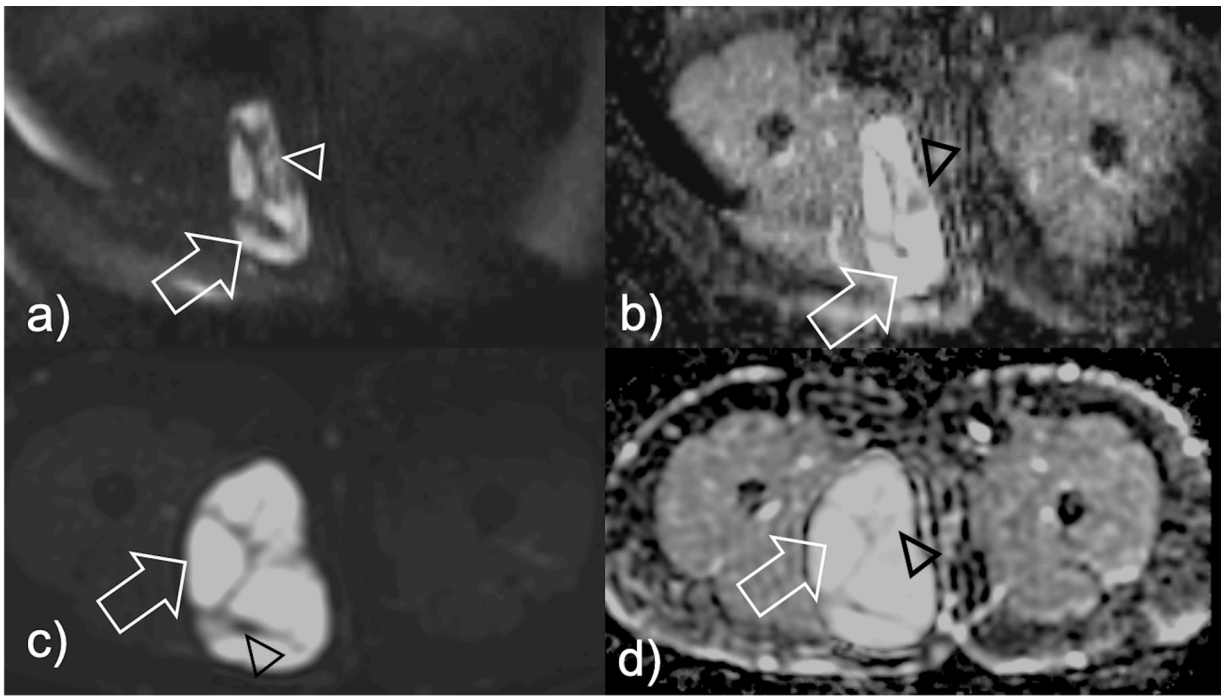

Fig. 3. a) Axial DWI scan shows a myxoid liposarcoma (<1/10 HPF) in the right thigh, composed of myxoid/cystic areas (arrow) and nodular septa (arrowhead); b) Despite the malignant nature, the mass is hyperintese at ADC map due to the high content in myxoid matrix c) After chemo-radiation, axial DWI and d) ADC map scans show a considerable increase in dimensions, especially of the myxoid areas. However, pathology described only 5% of viable cells (5/10 HPF) with 50 % fibrosis.

confirmed that ADC is not only a highly reproducible parameter but showed significant increase (suggesting response) post radiotherapy despite size stability. Furthermore, histopathological correlations confirmed correspondence between restriction and degree of cellularity (Winfield et al., 2019). More recently, attention has shifted from the core of the tumour, where necrosis is easily found after neoadjuvant therapy, to the tumour periphery, where viable cells may persist (Baur et al., 2003). An infiltrative margin on post-contrast images has been

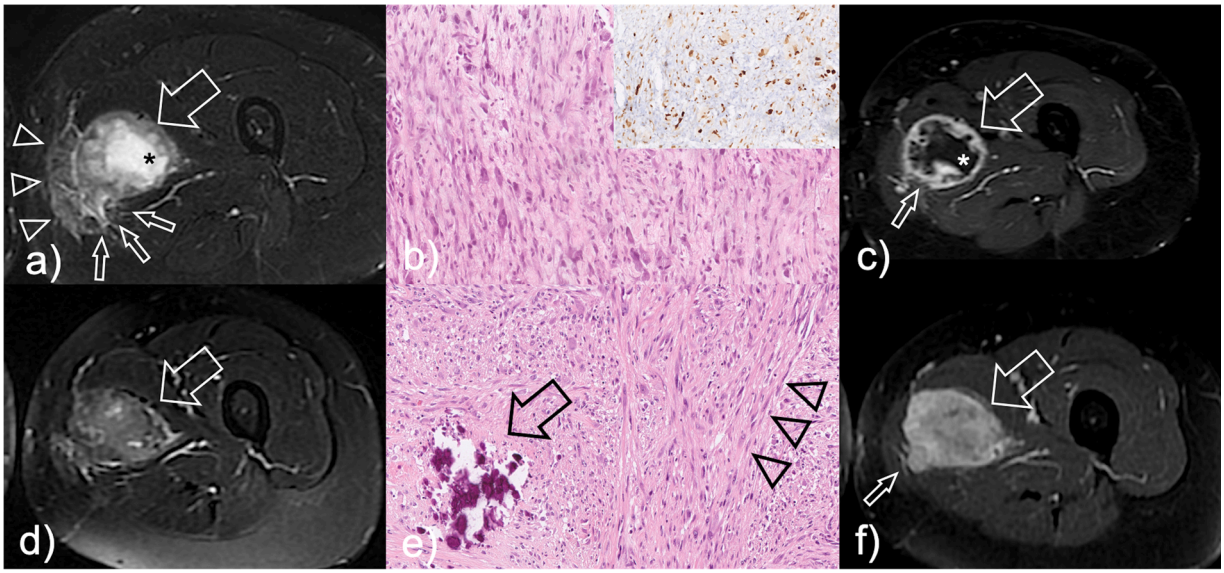

Fig. 4. a) Baseline axial fat-suppressed T2W showing a deep-seated mass in the right thigh (arrow) with perilesional oedema (arrowheads), internal cystic/myxoid areas (asterisk), with ill-defined margins in its posterior lateral surface (small arrows); b) Baseline core tissue biopsy reveals pleomorphic and spindle cells coherent with myxoid liposarcoma, grade III (7/10 HPF, Ki67(MIB1)60 %) with MDM2 amplification (right upper box); c) Baseline axial fat-suppressed contrast-enhanced T1W shows peripheral enhancement (arrow), internal necrotic areas (asterisks) and ill-defined margins (small arrow); d) After chemo-radiotherapy (doxorubicin, adriamicine 3 cycles and 50 Gy) axial fat-suppressed T2W shows no significant changes in tumour size (arrow), but cystic/myxoid areas are not assessable anymore (arrow); e) core tissue biopsy shows >95 % vital cells represented by dedifferentiated spindle cell (arrowheads) and pleomorphic liposarcoma cells (2/10 HPF) with small areas of low-grade, well-differentiated liposarcoma cells. Post-radiotherapy changes are clearly visible in the right lower corner (calcification, arrow); f) Axial fat-suppressed contrast-enhanced T1W shows homogeneous enhancement with no internal necrotic areas (arrow) and further invasion of nearby structures (small arrow), coherent with poor response to chemo-radiotherapy.

associated with a lower disease-specific and metastasis-free survival (MFS), highlighting the importance of peripheral growth pattern on MRI and histology (Fig. 4) (Nakamura et al., 2017; Liu et al., 2008).

Changes in peri-tumoral regions also appear to play a role in the assessment of response. In fact, the presence of satellite tumorous cells on surgical specimens is predictive of lower survival and disease-free survival (Kandel et al., 2013). Peritumoral oedema has been hypothesised to be proportional to peritumoral tumour satellites (Hanna et al., 1991; Beltran et al., 1987). Conventional MRI sequences accurately identify peritumoral oedema through fluid sensitive images, including T2W, T2W-FS or T2W-STIR. Stability or increase of peritumoral oedema has been recently associated with a poor histological response (>10 % viable cells), as well as stability or increase of pre-existing contrast-enhanced peritumoral areas (Crombé et al., 2018), but the clinical significance of peritumoral oedema is still controversial (White et al., 2005). Functional quantitative imaging refers to a collection of imaging parameters that aim to depict biological information and are showing encouraging results compared to morphological imaging in the definition of tumour response. Changes in DCE-MRI parameters evaluated after the second cycle of neoadjuvant chemotherapy have been shown to be highly predictive of histological response, whereas RECIST 1.1 was not (Cousin et al., 2017). A recent publication showed poor predictive value of conventional MRI (T1W, T2W, T2W with fat suppression images and T1W after contrast administration) for response when neoadjuvant therapies induce fibrosis and/or granulation tissue instead of necrosis (Soldatos et al., 2016). However, over 5% of early tumour enhancements and an average ADC value $>$ 2.2 X10 $^{-3}$ mm^2/sec are considered markers of positive response, both reaching 100 % sensitivity in determining nonviable tumour areas (Soldatos et al., 2016). Further, studies confirmed the emerging role of quantitative DCE-MRI in early prediction using absolute parameters like K_{trans}, k_{ep}, AUC60 or time-to-peak (Huang et al., 2016; Meyer et al., 2013; O'Connor et al., 2011). DCE-MRI was validated in vivo models for the very early assessment (24 h) after isolated limb perfusion, once again with promising results (Alic et al., 2013; Preda et al., 2004).

Frontline research in MRI evaluation of tumour response includes the innovative concept of "imaging habitats" (Napel et al., 2018). This mapping technique consists of a systematic approach of (1) intratumour segmentation into sub-regions based on pixel intensity (2) qualitative or quantitative analysis within each distinctive habitat to explore heterogeneity (3) estimation of percentage of necrosis (Sala et al., 2017). Pilot studies have already shown that necrosis can be identified with a 76 % accuracy through the analysis of radiologically-defined habitats on T2W and contrast-enhanced T1W images, possibly predicting the treatment outcome as well as the development of distant metastasis (Farhidzadeh et al., 2015a, b). A recently published method consists of plotting the voxel-based signal intensity distribution by histogram for analysis of the relative signal intensity compared to tumour volume. This approach allowed discrimination between viable (enhancing) tumour and necrosis (non-enhancing component) using a cut-off signal intensity threshold (Fields et al., 2020). Unsupervised clustering of such habitats can discriminate between responders and non-responders by analysing changes in k_{ep}, k_{trans}, and percent volume when DCE-MRI information is available (Yu-Cherng et al., 2019; Y-CC et al., 2017; Diwanji et al., 2019). Habitat imaging approaches are now also supported by machine learning (Blackledge et al., 2019). MRI texture analysis has already been shown to distinguish low from high-grade soft tissue sarcoma, and could be further explored in the assessment of tumour response (Corino et al., 2018). Recently, a T2-based Δ-radiomics approach has identified three features (Δ_Histogram_Entropy, Δ_Elongation, Δ_Surrounding_Edema) associated with good tumour response, defined as <10 % viable cell at pathology (Crombé et al., 2019c).

4.2. Computed tomography (CT)

CT is not frequently used for local staging due to poorer contrast resolution compared to MRI. In general, areas that cease to enhance after treatment are considered necrotic and contribute to the definition of Choi criteria through the measurement of Hounsfield Units (Fig. 5). Unfortunately, contrast-enhanced CT cannot differentiate between hypo-densities caused by necrosis and or subacute-to-late haemorrhage or cystic components. Differentiating tumour enhancement from granulation or fibrosis is also very challenging with CT (Crombé et al., 2019b). Evaluation of neoadjuvant therapy using RECIST with MRI or CT has been used to predict radical resection and survival. Unfortunately, they did not correlate to other clinical or pathology treatment characteristics (Chen et al., 2013).

Recently, CT texture analysis has also been performed alongside with the evaluation of descriptive semantic tumour features, which include shape, size, location and attenuation (Esser et al., 2018; Tian et al., 2015). Fine to coarse texture parameters (e.g. entropy, mean value of positive pixels, skewness and kurtosis) were extracted from non-enhanced CT and compared with biologic markers of angiogenesis, showing that the mean value of positive pixels (defined as the average brightness of positive values of the image) showed a better clinical outcome and a definite correlation with micro-vessel density on immunohistochemistry. Interestingly, the entropy parameter also showed positive correlations with plasma VEGF and SVEGFR-1, which likely represent biomarkers for antiangiogenic therapy (Hayano et al., 2015). When analysing contrast-enhanced CT, mean perfusion peak (MPP) parameter correlated with necrosis on histology and allowed for differentiating (with 85 % sensitivity and 71 % specificity) responders from non-responders. Therefore, the authors suggested that MPP might be chosen as the best predictor for treatment response of STS, as shown in other non-sarcoma histologies (Goh et al., 2011; Ravanelli et al., 2013).

4.3. ^{18}F-FDG positron emission tomography (^{18}F-FDG-PET)

Recent research has shown that changes in standardised uptake value (SUV) are more accurate than changes in tumour size or density (measured on contrast-enhanced CT) to predict pathological response to neoadjuvant chemotherapy. Conversely, evidence pertaining to radiation therapy or chemo-radiotherapy is still limited (Favinger et al., 2018; Evilevitch et al., 2008; Tateishi et al., 2011; Benz et al., 2008, 2009). Both early and late metabolic response measured by means of changes in SUV peaks were the only two predictors of survival in a prospective study on 78 patients (Herrmann et al., 2012). Similarly, the metabolic response on ^{18}F-FDG PET using PET Response Criteria in Solid Tumors (PERCIST) predicted PFS and time to local and distant progression after 2–4 cycles of neoadjuvant chemotherapy with regional hyperthermia in sarcoma patients. When the predictive performance of PERCIST was compared with RECIST 1.1 and Choi, PERCIST was superior in identifying responders (Fendler et al., 2015).

A recent meta-analysis showed that a ≥60 % decrease in FDG-uptake resulted in a sensitivity and specificity of 100 % and 71 % respectively for assessment of histopathologic response (Lim et al., 2019). Despite the promising results, PET cannot replace MRI for surgical planning as surgeons require highly accurate anatomic visualisation for procedural planning. PET and MRI thus have a synergistic value in such assessment, and either the diffusion of hybrid PET/MRI equipment as well as post-processing software for fusion imaging might ease its application (Gennaro et al., 2020; Cassarino et al., 2020). It is partly with this ambition that efforts are being made in implementing PET and MRI standardised protocols across multi-vendor platforms to ensure reliable quantification of imaging biomarkers in multicentre trials (deSouza et al., 2018; Boellaard et al., 2015; Winfield et al., 2016).

5. Future research

Unlike bone sarcoma, where the prognostic value of tumour necrosis induced by neoadjuvant chemotherapy has been extensively validated

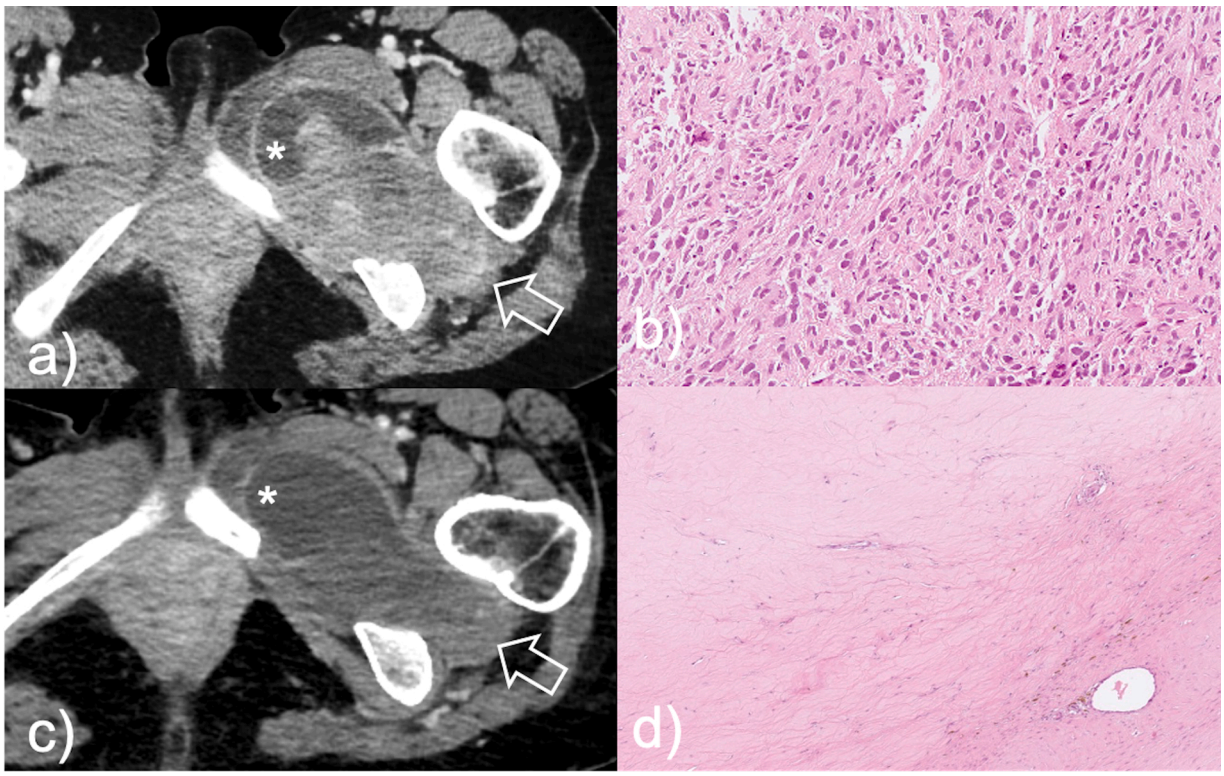

Fig. 5. a) Contrast-enhanced CT demonstrates a soft tissue mass occupying the left adductor compartment in a 37-year old female. The lesion is predominantly solid with some low density (arrow), likely representing cystic changes or necrosis (asterisk) b) Pre-treatment core-needle biopsy shows spindle and pleomorphic cells with 80 % Ki67 representing high-grade undifferentiated pleomorphic sarcoma c) Contrast enhanced CT post-chemo/radiotherapy (3 cycles of adriamycin-ifosfamide and 50 Gy/25 fractions with VMAT) shows no significant reduction in size and but there is a marked reduction in enhancement (arrow) and in the extent of the necrotic areas (asterisk); d) The surgical specimen reveals <1% viable tumor cells, isolated spindle and pleomorphic cells in a vast sclerotic stroma (<99 %); haemosiderin deposits are also present.

(Bielack et al., 2002; Picci et al., 1997), STS still lacks radiological and histological markers of tumour response and patient survival. In order to deliver personalised treatment strategies, clinicians demand from imaging a reproducible, objective assessment of the efficacy of local and systemic therapies, and they advocate imaging and histologic features capable of predicting the clinical behaviour of STS. Without a robust understanding of radiology- pathology correlations, developing solid imaging biomarkers is challenging. For this purpose, innovative techniques such as radiomics and radiogenomics complementing conventional imaging have arisen, where quantitative radiomic features derived from routine images are linked to tumour biology (Bodalal et al., 2019; Crombé et al., 2020). While still in its infancy, radiogenomics promises to address many of the pitfalls of current biological profiling by analysing the full tumour burden of a patient (to account for intratumoural and intertumoural heterogeneity). Additionally, once radiogenomic models are better fine-tuned, longitudinal imaging will be the new frontier of AI imaging research. Both diagnostic disciplines, pathology and radiology, are likely to play complementary roles (Jha and Topol, 2016). In theory, the complementary data from these two diagnostic modalities can be integrated into a single AI algorithm with the potential for higher predictive performance (Bodalal et al., 2018; Chibon et al., 2019).

The recent introduction of the concept of "imaging habitats" to improve radiological mapping of different microenvironments has brought radiologists and pathologists closer in the characterisation of tumour heterogeneity (Blackledge et al., 2019; Gatenby et al., 2013). In-vivo models can also aid in the comprehension of radiologic-pathology treatment-related tissue changes, especially in the case of innovative imaging modalities (Shapiro et al., 2018; Sigal and Sebro, 2018). The huge potential of artificial intelligence models seems promising in identifying features hidden in radiological images, possibly predicting or complementing histological and molecular information or even outcomes. Along with tissue and imaging biomarkers, correlations with serum/molecular biomarkers and circulating tumour cells/DNA might also be further explored (Aggerholm-Pedersen et al., 2019; Wang et al., 2019; Kambadakone et al., 2015).

6. Conclusion

Imaging can depict various changes induced by neoadjuvant therapies in the treatment of STS, but these changes are poorly correlated with histology and clinical outcomes. Evidence so far shows that Choi criteria, along with functional and molecular imaging information (DWI, DCE-MRI and ^{18}F-FDG-PET), outperform commonly used response criteria like RECIST 1.1 in identifying good responders based on necrosis and viability of tumour cells after treatment. The introduction of advanced quantitative image analysis such as unsupervised clustering, texture analysis and dynamic post-contrast imaging appears promising in improving non-invasive evaluation of treatment response in soft tissue sarcoma, therefore complementing histological information. Histological and radiological response criteria advocated by the EORTC-STBSG and EORTC Imaging Group should shed light on the biological efficacy of neoadjuvant therapies through future studies. Such studies would not only help radiologists identify prognostic and early response predictive imaging biomarkers, but also help us understand how far imaging can interrogate cancer biology in the description of tumour response. This will allow for improved personalised treatment within the heterogeneous group of STS patients.

Declaration of Competing Interest

The authors report no declarations of interest

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