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Therapeutic Response in Musculoskeletal Soft Tissue Sarcomas: Evaluation by Magnetic Resonance Imaging

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Abstract

This paper provides a literature review of the use of magnetic resonance imaging in monitoring the treatment response of soft tissue sarcomas (STS). The basic classification and physiology of the soft tissue tumor is introduced. Then, the major treatment options for STS are summarized with brief coverage of possible responses and grading systems. Four major branches of MR imaging techniques are covered, including conventional T₁- and T₂-weighted imaging, contrast-enhanced MR imaging, MR diffusion and perfusion imaging, and MR spectroscopy, with a focus on the tumor microenvironment. Although this literature survey focuses on recent clinical developments using these MR techniques, research venues in pre-clinical studies, as well as in potential applications other than soft tissue sarcomas, are also included when comparable and/or mutually supporting. Examples from other less-discussed MR imaging modalities are also briefly covered, not only to complement but also to expand the scope and depth of information for various kinds of lesions.

Keywords

musculoskeletal; magnetic resonance imaging (MRI); treatment; soft tissue; tumor; response; sarcoma; therapy

Introduction

Soft tissue sarcomas (STS) are a heterogeneous group of disorders that pose significant diagnostic and therapeutic challenges for clinical care and medical research. The assessment of treatment response in STS following chemotherapy or radiation is one of the most important aspects of patient care, as therapeutic options and the timing of surgery may vary depending on the success of response. As a non-invasive technology with no ionizing radiation, magnetic resonance (MR) imaging offers unique contributions in determining and monitoring therapeutic response in STS. From an anatomic imaging perspective, MR offers higher contrast resolution compared to CT and ultrasound. From the perspective of imaging the tumor microenvironment, MR can provide an assessment of the tumor vasculature, and the potential to provide detailed information about the biochemical environment, tissue composition, and structure. Imaging of STS following therapy must take into account not only post-treatment changes in the tumors themselves, but also any changes in staging and characterization. This review will examine the recent developments in MR imaging, providing an understanding of the imaging techniques as they relate to the complex, evolving biochemical environment that exists during the treatment of STS.

1. Soft tissue tumor classification and physiology

1.1 Classification of soft tissue tumors

Although quite heterogeneous, soft tissue tumors can generally be grouped into nine categories according to their morphological features and cytogenetics, and include benign as well as malignant entities within each category: adipocytic; fibroblastic/myofibroblastic; fibrohistiocytic; smooth muscle; skeletal muscle; pericytic (perivascular); vascular; chondro-osseous; and those of uncertain differentiation [1]. Benign soft tissue tumors may be left untreated or managed with follow-up or surgery, depending on the nature of the lesion and its natural history. For malignant soft tissue tumors (STS), management includes surgery, along with the potential for chemotherapy or radiation, to be administered in the adjuvant or neoadjuvant setting. Central to deciding the optimal treatment in STS is accurate tumor grading. The National Cancer Institute and the French tumor grading system are three-grade systems based on histological type and subtype, tumor necrosis, and mitotic activity [2, 3]. The principle of this system is summarized in Table 1[2]. The classification offered in Table 1 is modified from the work of Guillou et al., after comparing the grading systems of the National Cancer Institute and the French Federation of Cancer Center Sarcoma Group[4]. Generally, the higher the grade of the tumor, the less resemblance it has to normal tissue, with higher mitotic activity and more necrosis. This grading system correlates with prognosis, as it has been reported to be a predictor of local tumor recurrence [5, 6].

The diagnosis of an STS is established with imaging (to characterize extent and enable accurate staging) and percutaneous image-guided biopsy (to establish the histologic type and grade) [7]. Characterizing the grade of an STS is paramount to the treatment plan, as high-grade STS are generally treated with neoadjuvant therapy, and low-grade STS are generally not. While the percutaneous biopsy of an STS is considered the standard of care, an initial work-up with biopsy can occasionally miss the high-grade components of an STS, and only *after* surgery is the true histological grade discovered, creating a missed opportunity for neoadjuvant chemotherapy or radiation[8].

1.2 Physiology of soft tissue sarcomas

While more common in pediatric population, soft tissue sarcomas in adults are rare[9]. The biology of adult and pediatric sarcomas is not identical, as one of the more common sarcoma types in the pediatric population is rhabdomyosarcoma, whereas the most common type of sarcoma in adults is a malignant fibrous histiocytoma/fibrosarcoma. STS, nevertheless, share some common microenvironmental features with benign tumors, growing centrifugally in the soft tissues. Typically, when a benign tumor begins to differentiate from the host, a reactive fibrovascular tissue-limiting capsule forms around it. Aggressive lesions, on the other hand, form tumoral foci (called satellite lesions) inside this reactive pseudocapsule. In fact, these foci can exist at locations far beyond the reactive zone in highly aggressive lesions [10].

During the growth of malignant tumor, certain histological characteristics appear. Aggressive tumor tissue is highly cellular and the intact cell membrane will restrict the diffusion of water molecules, a feature that can be exploited with diffusion-weighted imaging (described below).

Other important features of the microenvironment of STS are the metabolic abnormalities that accompany changes in acidity, oxygen levels, and various metabolites within a tumor. First, an elevation of glycolysis, called the Warburg effect, produces high levels of lactic acid [11, 12]. Studies using ³¹P magnetic resonance spectroscopy (MRS) have revealed a neutral or alkaline tumor intracellular environment where the extracellular space contained an acidic environment relative to normal tissue [13-15]. Combined with tissue water T₂

relaxation, the intracellular pH measured by ^3P MRS was also thought to be predictive of therapeutic response with a 90% sensitivity and an 80% specificity [16].

Second, hypoxia is believed to be the result of poor blood perfusion and its importance is that it makes tumor cells more resistant to radiotherapy. Utilizing preoperative radiation and hyperthermia for high grade STS, earlier studies showed that patients with hypoxic tumors were found to have clearly lower disease-free survival rates than those with well-oxygenated tumor environments [17]. The latter findings echo the notion that hypoxic tumor cells are three to five times more resistant to radiation therapy [18]. Thus, tumor oxygenation is considered a strong prognostic indicator in therapeutic planning. Generally, tumor hypoxia and acidosis are accompanied by poor perfusion and elevated metabolism.

Third, certain metabolites can serve as biomarkers of malignancy in the musculoskeletal system. A well-known biomarker is total choline or tCho. Biologically, choline is involved in cell membrane phospholipid metabolism, including phosphatidylcholine (PtdCho) biosynthesis and oxidation into betaine in the mitochondria. The PtdCho is very important in cell membrane viability and the cell life cycle. Early studies showed that the metabolism of phospholipids is altered with major tumor malignancy growth factors [19, 20]. Total choline is the sum of phosphocholine (PCho), glycerophosphocholine (GPC), and choline (Cho), and can be measured with clinical MR spectroscopy [21-25]. When membrane choline phospholipid metabolism was studied during the transformation from normal to malignant phenotypes, total choline was shown to be a biomarker of malignant disease in the preclinical and clinical studies from other body locations [26-31].

2. Treatment options and imaging needs in STS therapy response

2.1 Summary of STS therapeutic options

The major treatment modalities for STS include surgery, radiation, chemotherapy, and immunotherapy. In general, surgery alone can be used for small, low-grade tumors. For larger tumors, local or global radiotherapy may be used, and may also reduce the incidence of recurrence. Chemotherapy can play a role in diminishing lesion size and preventing post-operative recurrences [9]. The most often used chemotherapy agents are doxorubicin and ifosfamide, with gemcitabine gaining increasing usage [9]. In addition, methotrexate and Cis-diamminedichloroplatinum(II) have been used in some STS, although more commonly in osteosarcomas. Other prominent chemotherapy agents include mitomycin C for hypoxic solid tumors and paclitaxel for angiosarcoma [32]. Thermotherapy is also employed to treat STS. Cryotherapy is an emerging minimal invasive adjunctive therapy in certain cases, as an adjunct to surgical removal [33] and chemotherapy. Cryosurgery technique has evolved from the initial method of pouring of liquid nitrogen onto a tumor bed [34] to the more recent argon-based system. The latter allows controlled formation of an ice-ball surrounding a metallic probe inserted in to the tumor under CT or US guidance. The advantage of using image guidance is to evaluate the formation of the ice ball and the effect of surrounding tissue. On the other hand, heat is used to produce tissue necrosis and/or protein denaturation. Radiofrequency ablation (RFA) induces tissue necrosis in the target area via deployment of the RF probe into the tumor site and using the ionic interaction between the tissue and RF to create heat, which is monitored using CT and/or MR. The desired temperature is from 50-100° C for least 4 to 6 minutes, resulting in tumor destruction. In addition, a newer non-invasive method is being explored for thermotherapy is high intensity focused ultrasound to ablate tumors [35-39].

The primary purpose of imaging subsequent to chemotherapy or radiation in STS is to assess whether an STS has responded to treatment. If so, surgery will continue as planned; if treatment response is inadequate, chemotherapeutic regimens may be changed and this will

affect the timing of surgery. The imaging assessment of an STS following neoadjuvant therapy typically includes macroscopic measurements, such as tumor volumetric information, signal characteristics, the degree of heterogeneity on various MR sequences, the degree of contrast enhancement, and the relationship of the tumor to surrounding vital structures. However, following neoadjuvant therapy prior to surgery, there are three general scenarios that are encountered: 1) due to non-response, the mass may remain stable or enlarge in size; 2) due to treatment-related necrosis, the mass may become smaller or stay the same size; or 3) due to hemorrhage, the mass may enlarge [21]. Hence, many macroscopic features of a tumor after treatment are not reliable predictors of whether neoadjuvant therapy has had an effect on the tumor. Even when macroscopic features abate, microscopic foci of malignancy can persist [40]. Thus, further quantitative metrics, including the assessment of perfusion, water diffusion, and metabolic changes with advanced MR techniques, have been advocated for the assessment of treatment response in a tumor. It is these metrics that may prove most useful in the future for determining treatment response.

2.2 Classification of STS therapy response

Originally, the Salzer-Kuntschik tumor response grading system was used to assess chemotherapy-induced morphological regression [41]. In this system, the chemotherapy response is graded from I (no viable tumor cells remaining) to VI (no effect of treatment identified) [42], utilizing the histological assessment of tumor necrosis. From as early as 2000, Response Evaluation Criteria for Solid Tumors (RECIST) became the most widely used tumor treatment assessment system for soft tissue tumors, and used morphologic size as the major quantitative metric [43, 44]. However, the RECIST criteria, although in common clinical use currently, have been recently challenged [45, 46]. The reason that the RECIST criteria are in question is that they do not incorporate tumor volumetric measurements, changes in density, metabolism, perfusion, or water diffusion, which are available with advanced technologies like PET and MR imaging. One improvement on the RECIST criteria was the Choi criteria which were recently introduced and incorporated density and intensity changes by CT and MR imaging, in addition to changes in size[47].

Finally, to address the inadequacies of the RECIST and Choi criteria, the use of a standardized uptake value (SUV) obtained by PET was incorporated into response criteria to better assess tumor metabolism [48]. Thus, the revised RECIST 1.1 criteria endorsed the functional assessment of tumors following treatment as complementary to anatomic evaluations [49]. Hence, advanced techniques providing functional information, with MR, CT and PET, have emerged for the assessment of treatment response such as PET Response Criteria in Solid Tumors (PERCIST)[50].

3. MR imaging techniques in the assessment of STS

MR imaging is an integral part of the multi-modality approach to the assessment of STS diagnosis and treatment. A comprehensive MR protocol will include a variety of non-contrast sequences (standard T₁- and T₂-weighted sequences, diffusion-weighted imaging, MR spectroscopy) and post-contrast sequences (to assess perfusion and vascular heterogeneity along with delayed enhancement). Using these MR imaging techniques, a morphological assessment of a tumor can be made, as well as an assessment of tissue perfusion, diffusion, and biochemical composition, which will provide information about tumor progression and treatment efficacy. This section will summarize conventional and advanced MR imaging techniques and their applications.

3.1 Conventional T₁- and T₂-weighted imaging

Tumor size and occasionally histologic classification are the most salient pieces of information provided by MR imaging. Compared with healthy muscle, fat, and bone marrow, pathologic tissues have altered T₁ and T₂ relaxation times [51-53]. Thus, a comparison of T₁- and T₂-weighted images (T₁WI and T₂WI) often provides the ability to not only identify the size and borders of the tumor, but also the potential to characterize lesion composition [54].

The most commonly used T₁WI pulse sequences include the spin echo sequence and the gradient echo pulse. T₂WI are generally used with fat suppression to identify fluid in the image, although short tau inversion recovery (STIR) is also used to null the lipid signal (Figure 1.A, 1.B, 1.C). In addition, fast spin echo, turbo spin echo, and rapid acquisition with relaxation enhancement (RARE) are sequences that can achieve a faster scan time.

Both T₁- and T₂-weighted images offer valuable morphological information about tumor treatment effects [38]. As a typical example, decreased T₁ signal intensity and increased T₂ signal were shown to represent marrow edema due to thermal osteonecrosis, which occurred in a tumor following curettage and cryotherapy [55]. In addition to signal intensity changes caused by biological changes, the anatomic size of a mass can be compared to the original pre-treatment scan to detect any increase or decrease lesion region. However, T₁ and T₂ imaging in the post-treatment setting must be interpreted with caution. A mass may change in size, but the degree of necrosis is difficult to determine without the administration of contrast (Figure 1.D, 1.E, 1.F). In addition, signal characteristics may be altered after neoadjuvant therapy, possibly due to necrosis and shrinking of the lesion and associated edema, but the presence of interval hemorrhage may also be responsible for changes in signal intensity. Early degradation into methemoglobin after acute bleeding will show a hyperintense T₁ signal [56], as well as alterations on T₂ and STIR. Vanel et al. concluded that the true value of T₂-weighted images was that the lack of T₂ hyperintensity highly suggested the absence of active tumor in the post-treatment setting [57]. For T₁-weighted imaging, changes in muscle texture patterns were shown to correlate with tumor presence [58], but morphologic changes seen by T₁- and T₂-weighted sequences are otherwise generally of limited use in the assessment of treatment response.

3.2 Contrast-enhanced MR

Contrast agents are one way to improve the specificity of T₁- and T₂-weighted imaging for the assessment of treatment response. Two common contrast agents are paramagnetic complexes and superparamagnetic particles [59]. When injected as contrast agents, paramagnetic agents, such as a gadolinium-based chelate, can reduce the T₁ relaxation time to a much greater degree than the T₂ relaxation time of blood within the tissue vasculature, and thus, are used with T₁-weighted imaging. The superparamagnetic agents generally reduce T₂ time more significantly and are thus best used with T₂-weighted scans. Superparamagnetic iron oxide (SPIO) nanoparticles and Ultra SPIO (USPIO) have been utilized in abdominal and pelvic malignancies, but not in STS, to date [60, 61]. Gadolinium chelates are widely used. Please see Figure 1.F.

Following gadolinium administration, T₁-weighted images may be acquired in a static fashion or as a dynamic study [40, 57, 62]. For the latter examination, T₁-weighted images are quantified to acquire a time intensity curve. The slope and pattern of this curve has been shown to be clearly different between the initial pre-treatment exam and after chemotherapy in patients who demonstrate treatment response [63]. Early and rapid contrast enhancement generally indicates tumor viability, while the lack of early enhancement is believed to reflect necrotic tissue or compromised vascular structure [64-66].

Dynamic contrast-enhanced MR (DCE_MR) can be performed as an MR angiography sequence or a volumetric sequence of slightly higher spatial resolution. First, tumor vascular encasement and invasion can be assessed by DCE_MR [67]. Second, contrast accumulates in areas with high perfusion as well as in disordered and leaky vasculature, as would be expected in tumors. Subtraction of postcontrast from precontrast T₁-weighted images can show the changes in enhancement in a tumor, as well as the vasculature, more conspicuously at the different vascular phases [62]. DCE_MR can also be performed on a whole-body scale, where it has been described for the evaluation of bone marrow focal lesions following chemotherapy and autologous stem cell transplantation (ASCT) in patients with multiple myeloma[68].

The main limitation associated with the use of contrast agents is their lack of sensitivity and target specificity. For example, in order for the currently available gadolinium chelates to effectively enhance imaging contrast, the tissue concentration must be on the order of 10⁻⁷ mol/g [69]. With this concentration, anatomic/morphologic expressions of disease can be identified. However, to visualize molecular components responsible for the evolution of tumor before and after treatment, the targets of imaging are the sparse biomarkers and receptors at a concentration of 10⁻⁹ to 10⁻¹³ mol/g [70]. Recent years have seen various pre-clinical research efforts to address these limitations. For example, cell membrane alpha(nu)beta(3) targeting dramatically increased the uptake of paramagnetic liposomes by multiple rounds of internalization following ligand binding [71]. As another example, strategies to join gadolinium to immunoliposomes are being explored. Encapsulation to the aqueous space, incorporation into the lipid bilayer, and containment on the exterior by polymerizable amphiphilic polymers are some of the methods to load gadolinium to immunoliposomes [59]. Molecular MR imaging is a promising research venue for the assessment of the microenvironment of STS, although it has yet to enter the clinical realm.

3.3 MR diffusion and perfusion imaging

Diffusion weighted imaging (DWI) can provide valuable cellular information about tissue in addition to the conventional T₁- and T₂-weighted imaging [36, 72-81]. DWI provides important information about the movement and functional environment of water in tissue and reflects cellular status of normal and pathological tissue. Furthermore, DWI is sensitive to changes in the micro-diffusion of water within the intra-(ICS) and extracellular spaces (ECS) and cytotoxic edema due to alterations in the dependent sodium-potassium pumps[82-85]. If there are changes in the ICS, ECS or sodium-potassium pumps, the apparent diffusion coefficient (ADC) will reflect these changes and potentially serve as a biomarker of tissue response[73, 79, 86, 87]. For example, after a disruption or restriction of the flow of water within a tissue, cytotoxic edema occurs, such as: changes within the tissue due to growth of tumors[74, 88].; metastatic lesions[77, 89]. or ischemic events (e.g., stroke) [81, 84, 85, 90].

These alterations in different tissue types alter the diffusion of water which results in changes in signal intensity on the DWI (either hyperintensity or hypointensity) generally before they are seen on a T₂-weighted image[81, 90]. The reason for these signal intensity changes on DWI are not exactly known; however, there is evidence that these changes may be attributable to many factors, such as shifts of water from the extracellular space to the intracellular space, increased tortuosity of the diffusion pathways, restriction of the cellular membrane permeability, increased cellular density, and/or disruption of cellular membrane depolarization[80, 82, 85, 90-92]. Moreover, DWI also provides an important quantitative biophysical parameter, called the apparent diffusion coefficient of water (ADC).

The ADC is an indicator of the movement of water within the tissue and provides a measure of the flow and distance a water molecule has moved. The ADC quantifies the combined

effects of both diffusion and capillary perfusion. A “decreased” ADC is interpreted as “reduced” flow of water or diffusion, whereas in tissue with an “increased” ADC there is a less restricted water flow. The ADC has been related to the state of tissue during the growth of tumors or progression of cancer. With proliferating cells, there is an increase in cellular density and a decrease in the relative amount of ICS and ECS available, this leading to a reduction in the ADC [74, 77, 93]. If there is cellular degradation or necrosis, the flow of water is increased with concurrent increases in the ADC. Thus, DWI and ADC have become powerful indicators for characterization of prostate tissue, particularly in differentiating between benign and malignant lesions [36, 73-79].

The application of different diffusion gradient values allows for the creation of trace apparent ADC maps on a pixel-by-pixel basis for quantitative analysis according to the equation.

$$ADC = \sum_{i=1}^n - \frac{\ln(S_i/S_0)}{b_i} \quad (1)$$

where b_i = the diffusion gradient values; $(b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3))$, γ = gyromagnetic ratio, G = gradient strength, δ = diffusion gradient duration, Δ = time between diffusion gradient pulses, S_0 = 1st image ($b=0$), and S_i = i th image.

Diffusion measurement pulse sequences include the Stejskal and Tanner method [94], and the more commonly used single-shot spin-echo echo planar imaging (EPI) method. As well as the above basic pulse sequences, faster pulse sequences, such as multiple RF spin echo-based rapid acquisition with relaxation enhancement (RARE), were designed [95, 96]. Because muscle and fat signals are considerably higher in musculoskeletal soft tissues, newer modified centric-reordered RARE (mRARE) were shown to yield less distortion than those acquired with the single-shot EPI sequence, and provided more anatomic information [97]. K-space projection innovations have also been applied in designing the more recently adapted Periodically Rotated Overlapping Parallel Lines with Enhanced Reconstruction (PROPELLER), primarily applied in the liver and abdomen [98, 99].

In tumors, there is a restriction of Brownian water motion that manifests as a reduced ADC value on diffusion-weighted imaging (Figure 2). During treatment, cellular necrosis is associated with increased cell membrane permeability, thus increasing the ADC values, due to diminished restriction of Brownian motion. Studies have found a clear correlation between changes in tumor volumes and those of apparent diffusion coefficients (ADC) before and after regional or systemic chemotherapy. In one study, ADC values always decreased in association with a tumor volume increase, regardless of the effectiveness of anti-cancer therapy [100]. But, when the degree of tumor necrosis is assessed by the Salzer-Kuntschik histologic classification, necrotic areas within a tumor showed higher ADC values, compared to viable tumor areas following treatment [101]. Active research in the application of DWI to STS in recent years continues to enhance the role of DWI in assessing treatment response [102]. For example, when ADC values were acquired from multiple regions of interests in lesions, minimum ADC values were shown to be more indicative of chemotherapy treatment response in osteosarcoma than were average ADC values [103]. In other organ systems, DWI has also demonstrated much higher specificity and accuracy compared to T_2 -weighted imaging and DCE-MR in assessing the response of muscle-invasive bladder cancer following low-dose chemotherapy [104].

Another application for DWI is in characterizing soft tissue masses to determine malignancy. In one study, ADC values of chronic expanding hematomas (CEHs) were found

to be significantly higher than malignant soft tissue tumors, providing a good discriminating feature between benign and malignant soft tissue tumors [105]. On the molecular imaging level, in a transgenic mouse model (CR2-TAg), DWI was shown to be able to differentiate benign and malignant prostatic tissue at a sub-millimeter scale [106]. Finally, compared to T₁-weighted gadolinium enhanced imaging, DWI performs comparably for the detection of whole body tumors [78, 107]. With its non-dependence on contrast agents, DWI has great potential in the initial and post-treatment assessment of STS.

3.4 MR spectroscopy

In addition to histological composition, morphological features, and perfusion and diffusion properties, the underlying biochemical environment is fundamental to understanding tumor therapy response. MR spectroscopy (MRS) is a means of metabolic –profile with MR that not only can provide useful information about a tumor's characteristics during initial staging [21-25, 108], but can also help in the assessment of treatment-induced biochemical changes during therapy in different tumor types[109].

With ¹H MRS, information about the existence of different hydrogen-containing molecules can be obtained. For MRS acquisition, there are two major single-voxel techniques, a point-resolved spectroscopy sequence (PRESS)[110], and a stimulated echoes acquisition mode (STEAM)[111] pulse sequence. The choice of sequence can influence the spectral quality. In the human brain, PRESS is the choice for a long echo time, as it offers a gain in signal intensity by a factor of two, and is less sensitive to motion and diffusion and not susceptible to multiple quantum effects [112]. STEAM offers an advantage for the observation of metabolites with a short T₂. Another short echo time technique is localization by adiabatic selective refocusing (LASER), which offers a better slice selection without the reduction of signal and less B1 inhomogeneity [113, 114].

Both qualitative measures [21, 22] and relative quantification measures [23, 109, 115] have been described for MRS, while absolute quantitation is gaining momentum for use in clinical applications. As a very common nuclei choice, proton MRS in the musculoskeletal (MSK) system than the much more thoroughly studied central nervous system (CNS) for a variety of reasons. First, because of tissue composition and water content differences between the MSK system and the brain, magnetic homogeneity, susceptibility, diffusion effects, and NMR visibility will be different in musculoskeletal tissues compared to the CNS [116, 117]. Second, the water and lipid compartments in the MSK system are vastly different compared with those found in the CNS. In the CNS, the brain white and grey matter, cerebral spinal fluid (CSF), and NMR-invisible tissues are the major subjects in spectroscopy research[118]. In the MSK system, muscle tissue and intra and extra myocellular spaces are often the major soft tissue compartmentations of spectral analysis [119-121]. Thus, the careful inclusion or suppression of different types of tissue in spectral acquisition is important in the MSK system. Third, the radiofrequency coils in clinical MSK applications differ from those in the CNS system. In MSK spectroscopy, surface receiver coils are used to collect the spectral signal, making the spectral collection strategy and signal processing different from that performed in the CNS. With the use of phased array surface coils, the need to understand and evaluate the common spectroscopy strategies is of great importance. Finally, other considerations in performing clinical MRS include the choice of a single-voxel or a multi-voxel technique. Studies using multi-voxel ¹H MRS have shown greater reliability and improved sensitivity to intramyocellular differences compared to single-voxel MRS [122]. With regard to malignancies, choline metabolism is the focus in multiple types of tumor neoplasia. The rise of phosphocholine and tCho is believed to be characteristic in different types of brain, breast, and prostate tumors in in vivo and in vitro ¹H and ³¹P MR spectroscopy studies [123-126]. For example, an overall increase of tCho (and phosphocholine) is correlated with the progression of human mammary[26] and

prostatic[127] epithelial cells from normal to malignant types. Thus, recently, MRS has gained significant attention in several MSK tumor malignancy studies [21-24]. These studies utilized short and intermediate TE 1H MRS to quantify the tCho concentration for malignant and benign skeletal tumors and found tCho may serve as a marker for malignancy in musculoskeletal tumors. As an example, in figure 3 single voxel MRS data was acquired from a 81 year old woman with pleomorphic rhabdomyosarcoma. Pre-treatment tCho concentration of 2.0 mmol/kg decreased to 1.5 mmol/kg by post-treatment MRS. Histologic analysis revealed 90% treatment-related sclerosis, 5% necrosis and 5% viable tumor.

Treatment response from chemotherapy was also studied by 1H MRS. The tCho concentration, volume ratio, and tCho water ratio were all found to be substantially reduced in partially responsive lymphoma and alveolar sarcoma lesions after chemotherapy[109]. In a preclinical study on mice, vascular-disrupting agent (VDA) ZD6126 was shown to be able to significantly reduce the tCho in the radiation-induced fibrosarcoma 1 (RIF-1)[128]. This result is consistent with the reduction of cell membrane turnover associated with necrosis and cell death following the disruption of the tumor vasculature. In other organ system malignancies such as in breast cancer, patients with a greater reduction in tCho were more likely to achieve pathologically complete response[129]. For glioma patients, the mean tumor tCho/NAA ratio and normalized tCho were also found to be diminished over the course of post-operative radiotherapy [130].

Traditionally, a tCho level change was interpreted to be a result of alterations in cellular proliferation. More recent studies have emphasized the role of several oncogenes and other biomarkers in controlling choline metabolism [131, 132]. For example, Ki-67, P-gp, p53, TLS-CHOP, cyclins, survivin, TERT [133], and activated receptor-associated tyrosine kinase c-kit[134], have been identified in various types of STS. Imaging most of the above biomarkers in the clinical environment is still beyond the capability of MRS, but the development of molecular imaging will definitely provide an opportunity to explore these pathways of Choline metabolism[131].

Although not in common clinical use, 31P MRS has the potential to be utilized in the assessment of treatment response. With 31P MRS, it has been demonstrated that viable tumors characteristically show strong signals of phosphomonoester (PME) (doublets at 6.87 ppm), phosphodiester (PDE) (doublets at 3.20 ppm), and moderately increased signals of Pi and low PCr[135]. Inorganic phosphase is used to measure *in vivo* pH values for human and animal tumors [124, 136, 137]. Figure 4 is an example of elevated ratio of PME/ATP and Pi/ATP and pH values corresponding to the aggressiveness of human leiomyosarcoma[138]. Because the human intracellular volume fraction is generally greater than 50%, the measured pH values are generally considered to be intracellular pH. Thus, this application should be examined carefully because, during pathological states such as necrosis, extracellular Pi can be visible [139, 140]. For tumors in mice, 3-aminopropylphosphate (3-APP) has been used to measure extracellular pH values[137]. Another example is the assessment of isolated limb perfusion (ILP) using 31P MRS by Kettelhack et al. [141]. In this study, the ratio of PME/PCR and PME/ β -ATP was decreased after ILP, with the latter ratio a more promising indicator of therapy response.

Finally, 19F MRS, while not in clinical use, has been used to monitor the pharmacodynamics of surrogate markers in transgenic cancer models [142]. In this study, cytosine deaminase catalyzed conversion of the 5-fluorocytosine prodrug to the chemotherapeutic agent 5-fluorouracil (5-FU) was directly observed by 19F MRS. SR-4554, a fluorinated 2-nitroimidazole noninvasive probe of tumor hypoxia, was also evaluated as a 19F NMR hypoxia reporter agent for NMR spectroscopy [143].

3.5 Other MR imaging modalities

For the imaging of hypoxia, several reporter molecules have been developed, such as pimonidazole, EF5, CCI-103F, Cu-ATSM, and others [144]. When injected intravenously, these molecular agents will reoxidize in the presence of oxygen, and thus, reveal microscopic-scale hypoxia. In addition, blood oxygen level-dependent imaging (BOLD), which is widely used in functional MR in the brain, has been used to study oxyhemoglobin (oxyHb) in breast cancer hypoxia[145] and may one day be applied to the study of sarcomas.

Other means of imaging hypoxia include T_2^* or R_2^* imaging, which can measure the transverse relaxation rate of blood and surrounding tissues. Local magnetic field inhomogeneities, caused by susceptibility differences and hyperintense signal from relatively long T_2^* tissues, are the two major types of T_2^* imaging [146]. For the first type of T_2^* imaging, the deoxyhemoglobin in the red blood cells has a paramagnetic effect, which causes a decrease in the apparent T_2^* through changes in bulk magnetic susceptibility; pulse sequences, such as gradient recall echoes, can generate blood oxygen level-dependent contrast between activated and resting tissues [147]. Because it can demonstrate blood oxygenation-related paramagnetism, for specific types of tumors, this imaging modality can therefore be used to reflect tissue hypoxia [145]. To measure oxygen tension, perfluorooctyl bromide (PFOB) emulsion has been used by ^{19}F MRS [14, 148].

Because angiogenesis is important for tumor growth and metastasis, the *in vivo* detection and quantification of angiogenesis would be of paramount importance to the diagnosis of a tumor and the evaluation of treatment response. To assess post treatment changes in tumor angiogenesis and oxygenation, a technique called Overhauser-enhanced MRI (OMRI) has been devised [149]. With the help of the oxygen-sensitive contrast agent, OX63, OMRI uses hyperpolarized ^1H MRI to study the tissue oxygen level. By acquiring OMRI images at different hyperpolarization levels, local tumor oxygen concentration and microvascular permeability can be simultaneously determined.

Although MRI is the most sensitive noninvasive, nonradioactive method for detection of metastatic disease, it was limited to localized imaging of organs. New paradigms for metastatic lesion detection and monitoring of therapy are emerging, such as the whole-body imaging using MR imaging. Recent developments in the field of MR technology, including gradient systems, RF coils, and “rolling bed” methods allow whole-body coverage. Indeed, conventional and advanced MR imaging sequences can be used such as, inversion recovery T_1 -weighted imaging, T_2 -weighted imaging, and DWI[78, 150-152]. Whole body MR imaging (WB-MR) will enable better spatial resolution and soft tissue delineation for more accurate assessment of STS or other MSK lesions. More importantly, through the use of WB-DWI a better estimation of treatment response in STS may be possible. Indeed, as noted above, DWI and MRS provide functional cellular information that would complement routine anatomical imaging with T_1 - and T_2 -weighted sequences. By capitalizing on these methods in a “whole body imaging setting”, an excellent platform to investigate metastatic disease and to correlate with other biomarkers will be created.

Whole-body acquisition strategies include multiple packages, parallel imaging, and variable flip angles to reduce the specific absorption rate (SAR) and susceptibility-induced difficulties [153-156]. While emerging as a technique for the staging of other malignancies and potentially sarcomas, whole-body MR may become important as a one-stop-shop for the assessment of treatment response in a sarcoma along with re-staging following treatment as shown in figure 5. This study is a representative example of WB-MR and DWI at 3T in a normal female volunteer. Combining the T_2 and DWI information, whole body MR imaging

may prove to play a role in the evaluation of the primary site of disease as well as metastatic foci with subsequent evaluation of these sites for changes following treatment.

4. Conclusions

The role of MR imaging in monitoring the therapeutic response in soft tissue sarcomas continues to evolve. At the present time, MR imaging is part of a more comprehensive process that involves other modalities, such as PET imaging, for the assessment of treatment-related necrosis. Nevertheless, MR imaging has some unique advantages in the study of treatment response. These advantages include the lack of ionizing radiation and its relatively high spatial resolution compared with nuclear medicine studies. Directions for the near future include studies at higher magnetic field strengths with emphasis on diffusion, perfusion and metabolic MR imaging as well as the development of whole-body MR techniques. Although many imaging targets are extensively studied in the laboratory setting, their use in *in vivo* human tissue remains to be realized.

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Figure 1.

A. Pretreatment scan in a 14-year-old girl with Ewing's sarcoma of the left thigh. Axial T1-weighted image (SE, TR/TE 545/11) of the left thigh shows a slightly heterogeneous intramuscular mass of intermediate signal intensity in the medial left thigh. B. Pretreatment scan in a 14-year-old girl with Ewing's sarcoma of the left thigh. Axial fat-suppressed T2-weighted image (FSE, TR/TE 0950/05) of the left thigh shows a slightly heterogeneous intramuscular mass of intermediate to high signal. C. Pretreatment scan in a 14-year-old girl with Ewing's sarcoma of the left thigh. Axial post-contrast fat-suppressed T1-weighted image (VIBE, TR/TE 502/4.92) of the left thigh shows marked solid enhancement of the mass. D. Post-treatment axial T1-weighted image (SE TR/TE 500/14) of the left thigh obtained following chemotherapy shows enlargement of the mass compared with pre-chemotherapy imaging, although size changes are not reliable measures of response. E. Axial fat-suppressed T2-weighted (FSE, TR/TE 3000/47) image of the left thigh obtained following chemotherapy shows enlargement of the mass and slightly heterogeneous increased signal. Signal changes on non-contrast T1- and T2-weighted images are not reliable measures of treatment response. F. Post-treatment, axial post-contrast T1-weighted image of the left thigh following chemotherapy shows persistent contrast enhancement in the mass. Following surgical resection, only 25% necrosis was found histologically, indicating a poor prognosis, and the patient died within two years. In this case, contrast enhancement persistence indicates poor treatment response, although static contrast-enhanced images are not reliable indicators of the degree of necrosis or response.

Figure 2.

A. Pretreatment scan in a 14-year-old girl with a high-grade undifferentiated sarcoma. Coronal STIR (TR/TE 1600/5) shows a large mass in the calf with a slightly heterogeneous increased signal. B. Pretreatment scan in a 14-year-old girl with a high-grade undifferentiated sarcoma. Coronal DWI (b=0) shows a heterogeneous calf mass of increased signal. C. Pretreatment scan in a 14-year-old girl with a high grade undifferentiated sarcoma. Coronal DWI (b=500) shows persistent areas of increased signal, implying the presence of viable tumor. D. Pretreatment scan in a 14-year-old girl with a high-grade undifferentiated sarcoma. Coronal ADC map shows areas of low signal intensity within the mass, indicating the presence of viable malignant tumor cells.

Figure 3.1.

81 year old woman with pleomorphic rhabdomyosarcoma. Pre-chemotherapy (clockwise: A-coronal STIR, B-Axial postcontrast T1, C-MRS) images. Relative to water signal, a clear Cho signal can be seen on the spectrum.

Figure 3.2.

Post- chemotherapy images (clockwise: D-coronal STIR, E-Axial postcontrast T1, F-MRS) show a decrease in size with heterogeneous alterations in signal and contrast enhancement. Relative to water signal, a much reduced Cho can be seen on the spectrum. A slightly different intersection of patient's body is displayed in this figure comparing to figure 3.1 for optimal positioning of voxel.

Figure 4.

In vivo phosphorus MRS before neoadjuvant therapy of a 75 year-old female with a leiomyosarcoma in the gluteal region. The MR data was acquired from a tumor mass with a long diameter of 9-10 cm using a 1.5 Tesla clinical MR scanner (Siemens Helicon, Siemens Medical Corporation, Iselin NJ, USA). The image data and analysis was provided in courtesy of Dr. Fernando Arias-Mendoza of Columbia University, U.S. The grid overlaying the image is the projection of the 3D voxel matrix of the phosphorus data set. Six spectra are shown in green and the three voxels completely inside the tumor were highlighted (yellow boxes) and their spectra (A-C) expanded. Peak assignments: EtnP, phosphoethanolamine; ChoP, phosphocholine; Pi, inorganic phosphate; NTP, the three ^{31}P signals from nucleoside triphosphates (α , β , and γ). Each spectrum shows different spectral qualities, good signals in spectrum A, adequate in B, and minimal in C. The signal quality of spectra A and B correspond to areas with different degree of cellularity, while spectrum C matches with necrosis or large amounts of fibroid/myxoid matrix. The patient's surgical specimen was reported as highly cellular with areas of focal necrosis, matching with the spectral findings. In addition to these, signal quantification in spectra A and B showed important differences. The [EtnP+ChoP]/NTP, Pi/NTP, and pH values in spectrum A were 1.13, 0.42, and 7.07 and in spectrum B 1.46, 0.88, and 7.48, respectively. The higher values of the three parameters of spectrum B are related to a more aggressive sarcoma, in comparison to spectrum A, whose parameters are of a less aggressive form. The more aggressive spectral characteristics of spectrum B are suggestive of a high-grade sarcoma as was the case in this patient.

Figure 5. Representative example of WB-MR and DWI at 3T in a normal female volunteer. A. Whole body coronal T2-weighted images through the center of the body. B. Corresponding ADC maps generated from the DWI images.

Table 1

FNCLCC grading system: definition of parameters

Tumor differentiation	
Score 1	Sarcomas closely resembling normal adult mesenchymal tissue (e.g., well-differentiated liposarcoma)
Score 2	Sarcomas for which histologic typing is certain (e.g., myxoid liposarcoma)
Score 3	Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, osteosarcomas, PNET
Mitotic count	
Score 1:	0-9 mitoses per 10 HPF ⁺
Score 2:	10-19 mitoses per 10 HPF
Score 3:	≥20 mitoses per 10 HPF
Tumor necrosis	
Score 0:	No necrosis
Score 1:	<50% tumor necrosis
Score 2:	≥50% tumor necrosis
Histologic grade	
Grade 1:	Total score 2, 3
Grade 2:	Total score 4, 5
Grade 3:	Total score 6, 7, 8

⁺ A high-power field (HPF) measures 0.1734 mm².