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Current utilities of imaging in grading musculoskeletal soft tissue sarcomas

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ABSTRACT

The care of patients with musculoskeletal malignancies has increasingly become a multidisciplinary function. Radiologists play an important role in many areas of these patients' care including initial diagnosis, staging, in many cases guiding therapy, and monitoring treatment response. However, the gold standard for the final diagnosis of these diseases remains the histopathologic proof. Intense efforts have been made to develop non-invasive methods of determining the tumor grade, or a surrogate, in order to predict biologic behavior, aid early treatment decisions, and provide prognostic information. Multiple imaging modalities have been employed in this domain—including computed tomography (CT); anatomic magnetic resonance (MR) imaging techniques; functional MR imaging sequences such as dynamic contrast enhancement (DCE), diffusion weighted imaging (DWI), MR spectroscopy (MRS); and positron emission tomography (PET). This article reviews current available literature in this realm and highlights future directions towards the potential of non-invasive imaging in grading of soft tissue sarcomas.

1. Introduction

Soft tissue sarcomas are a rare, heterogeneous group of over fifty distinct malignancies that represent less than 1% of all malignant tumors with an estimated 11,280 new diagnoses annually in the United States [1,2]. The 5-year mortality for high-grade lesions (grade II or III) has been reported to be 30–60% and 10% for low-grade lesions [3,4]. Histologic grade is widely regarded as the most important independent predictor of metastasis-free and overall survival [5]. The gold standard for the final diagnosis is histopathology, with samples usually acquired by fine needle aspiration (FNA), core biopsy and/or excisional biopsy. A pathologist then determines the apparent cellular origin, an amount of tissue differentiation, as well as degree of necrosis and mitosis. Accurate grading is important for patients with soft tissue sarcoma as those with high-grade tumors may benefit from neoadjuvant chemotherapy and/or radiotherapy, whereas those with lower grade can be spared of potential harmful toxicities related to such treatments.

Two main pathologic grading methods are popular and commonly used in the treatment of sarcomas: the National Cancer Institute (NCI) system for sarcoma grading, (Table 1), and the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) or French Federation of Cancer Centers grading system, (Table 2). Both take into account the cellular differentiation and degree of necrosis, but only the FNCLCC system incorporates the mitotic activity directly. These systems have been shown to be nearly equivalent in predicting metastasis-free and overall survival [6,7]. Other schemes also exist with unique factors for consideration such as the Scandinavian Sarcoma Group prognostic system [8], which incorporates peripheral growth pattern, and the Memorial Sloan Kettering Cancer Center (MSKCC) sarcoma-specific mortality nomogram [4], a tool that incorporates FNCLCC grade with tumor size, depth, site, and patient age to predict a 10-year probability of death from sarcoma. Molecular and genetic approaches to understanding sarcoma tumor biology beyond histologic subtyping and other morphologic features have been developed in the last decade, which take advantage of gene expression profiles[9,10] to differentiate specific tumors as high or low risk, although none have been yet validated in clinical trials.

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Table 1
National Cancer Institute sarcoma grading system.

Grade 1	• Well differentiated liposarcoma • Myxoid liposarcoma • Subcutaneous myxoid MFH • Well differentiated malignant hemangiopericytoma[a] • Well differentiated fibrosarcoma • Well differentiated leiomyosarcoma[b] • Malignant Schwannoma (MPNST)[c] • Myxoid chondrosarcoma[d]
Grade 2	• Other histologic subtypes with <15% necrosis.
Grade 3	• Extraskeletal Ewing's sarcoma • Primitive neuroectodermal tumor (PNET) • Extraskeletal osteosarcoma • Mesenchymal chondrosarcoma • Malignant Triton Tumor • Other histologic types with ≥15% necrosis

[a] With <1 mitotic figure (MF)/high power field (HPF), no necrosis and no hemorrhagic areas.
[b] With orderly fascicular pattern plus no pleomorphism, no necrosis, and <6 MF/10HPF.
[c] If resembles neurofibroma plus mitotic figures with increased cellularity but<6 MF/10HPF.
[d] Uniformly myxoid and hypocellular with no mitotic activity.

Thus, as it stands currently, the differentiation between high-grade and low-grade lesions drives therapeutic decision-making. The question remains what and how much role imagers can take in aiding the clinicians and pathologists towards an accurate, non-invasive evaluation of tumor grade. Multiple imaging modalities have been employed for non-invasive imaging biomarkers and tumor grading—including computed tomography (CT); anatomic magnetic resonance (MR) imaging techniques; functional MR imaging sequences such as dynamic contrast enhancement (DCE), diffusion weighted imaging (DWI), MR spectroscopy (MRS); and positron emission tomography (PET). This article reviews current available literature in this realm and illustrates future directions towards the potential of non-invasive imaging in grading of soft tissue sarcomas.

2. Imaging sarcomas

2.1. General markers of high-grade sarcomas

Most features of sarcomas associated with aggressiveness are histologic and therefore determined by pathology, with the exception of size and depth of invasion. However, many microscopic features have correlative findings on imaging studies and require evaluation. These include extent of necrosis, peripheral growth pattern, neurovascular invasion, cellularity, expression of GLUT-1, cell turnover rates, and neovascularity [5,8,11]. These are discussed in a modality-specific fashion below.

Table 2
FNCLCC grading system.

Tumor Differentiation
Score 1
Sarcomas closely resembling normal adult mesenchymal tissue (eg, well differentiated liposarcoma).
Score 2
Sarcomas for which histological typing is certain (eg, myxoid liposarcoma).
Score 3
Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, osteosarcomas, PNET
Mitotic Count
Score 1
0–9 mitoses per 10HPF[a]
Score 2
10–19 mitoses per 10 HPF
Score 3
>20 mitoses per 10HPF
Tumor Necrosis
Score 0
No necrosis
Score 1
<50% tumor necrosis
Score 2
≥50% tumor necrosis
Histological Grade
Grade 1
Total score of 2–3
Grade 2
Total score of 4–5
Grade 3
Total score of 6–8
Modified from Coindre [60].

[a] HPF measures 0.1734 mm^2.

2.2. Radiography

Radiographs of the involved extremity are crucial for initial screening due to the ability to detect and define cortical bone involvement and abnormal soft tissue calcifications that otherwise could be missed on MRI [12]. Certain findings may help characterize a lesion as non-malignant, such as with mature peripheral calcification and/or heterotopic ossification; fat cleft around a lesion, suggesting slow growth, local steal phenomenon in a slow flow vascular malformation or benign peripheral nerve sheath tumor, ossified lipoma; or phleboliths in a hemangioma. Development of calcifications in certain known tumors, such as neurofibroma, pheochromocytoma, leiomyoma and neuroendocrine tumors may serve as indirect marker of developing or progressing necrosis and malignancy. Certain soft tissue sarcomas have a propensity to calcify more than others—such as synovial sarcoma, leiomyosarcoma and undifferentiated pleomorphic sarcoma. Beyond this, radiographs provide little additional information regarding the tumor grade over cross-sectional modalities. In many cases, patients present with trivial trauma or no trauma history; however, there is a sarcoma mimicking a tender mass. If radiographs are not obtained immediately, biopsy may be performed and the lesion may be over-diagnosed as aggressive (Fig. 1).

2.3. Ultrasonography and computed tomography

The utility of ultrasound (US) is usually limited to differentiating cystic from solid lesions. A subcutaneous echogenic lesion with thin capsule is usually diagnostic of benign lipoma. Other lesions that can be diagnosed as benign using Doppler imaging include hematoma, abscess, glomus tumor and vascular malformations, due to their classic locations, history, clinical findings and appearances [13,14]. Connection to nerves can aid in the diagnosis