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Concordance of histopathological and radiological grading in soft tissue sarcomas

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ABSTRACT

Aim: The grade of the tumor is essential for planning the treatment strategy in soft-tissue sarcomas (STS). The goal of this study is to determine magnetic resonance imaging features related to histopathological grade and aggressiveness of STS.

Material and Method: This retrospective single-center study involved preoperative contrast-enhanced MRI examinations of 64 patients with STS. MRI findings evaluated were; heterogeneity, necrosis, hemorrhage, and relationship with surrounding tissue in T1-weighted (T1W), T2-weighted (T2W), and T1W post-contrast sequences of the lesion. Histological grade was determined with the Fédération Nationale des Centres de Lutte Contre Le Cancer (FNCLCC) grading system, and the aggressiveness of the lesion was measured with the Ki-67 index.

Results: Sixty-four patients (mean age 45.5±21.6, M/F ratio 34/30) with STS were included. 33 (51.6%) patients graded as FNCLCC grade 3. On MRI examinations, the absence of necrosis was significantly associated with FNCLCC grade 1 and a low Ki-67 index ($p<0.001$). The presence of hemorrhage signal distinguished as a hyperintense signal on T1W, tail sign, and post-contrast peritumoral enhancement was significantly higher in FNCLCC grade 3 soft tissue sarcomas (p:0.008, p:0.001, p:0.004, respectively). The presence of peritumoral edema on T2W imaging in all high-grade patients also showed a strong relationship between these two (p:0.001).

Conclusion: Our study found that the presence of hemorrhage signal, tail sign, peritumoral enhancement, clear borders of 50% and less obtained from conventional MRI features of soft tissue sarcomas are associated with high grade tumors. The absence of necrosis signal, clear borders of 90% and above in MRI were significantly associated with FNCLCC grade 1.

Keywords: Magnetic resonance imaging, FNCLCC grading, soft-tissue sarcoma

INTRODUCTION

Soft tissue sarcomas (STS) are rare malignant tumors that are aggressive, with over 100 different histologic subtypes. They are of mesodermal origin with an incidence of 5/100000 per year. They can arise from any part of the body, but most occur in extremities, and the patients usually present with a painless enlarging mass. The most common ones include liposarcoma, leiomyosarcoma, and undifferentiated pleomorphic sarcoma (1). Tumors are grouped as adipocytic, fibroblastic, skeletal muscle, vascular, smooth muscle, pericyte, and uncertain differentiation category according to the WHO classification of soft tissue tumors (2).

Tumor grade is vital as high-grade tumors may benefit from neoadjuvant chemotherapy and radiotherapy for achieving local control after upcoming resection surgery. The histological grade of the tumor is shown to be strongly linked to the patient's risk of metastasis and overall survival (3-5). Also, proper diagnosis of the grade of the tumor is essential for planning the treatment strategy. A pre-treatment percutaneous needle biopsy is mandatory to diagnose a STS and determine its grade. However, biopsy results may be non-diagnostic as tissue specimens may not represent the whole; this mainly occurs where the tumor contains a mixture of low and high-grade areas (6-8).

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The histological grade of the tumor is determined according to the grading system of Fédération Nationale des Centres de Lutte Contre Le Cancer (FNCLCC), which considers tumor differentiation and mitotic activity and necrosis (9). However, the mitotic count, cell size, and tumor cellularity may be affected by the interval between the surgical resection and fixation of the specimen. The Ki-67 protein, which is encoded by the MKI67 gene, is a cellular marker for proliferation. The high Ki-67 count of STS suggests its high potential for reproducibility and aggressiveness (10,11).

Combining pre-treatment conventional magnetic resonance imaging (MRI) features of the lesion with histopathologic findings is necessary for the decision to repeat the biopsy (12-14). This may be required to find out the correct diagnosis and grade of the tumor, especially in regions where limited resources are available.

Precise determination of the grade of the STS has a critical role in planning an appropriate treatment strategy. MRI is vital for imaging the characteristics and anatomical details of the soft tissue. Although there are some studies in the English-speaking literature, the correlation between MRI features and histopathological findings of STS has still been assessed to a limited degree. This study aimed to determine the MRI features related to the FNCLCC histological degree and Ki-67 grading of STS in a tertiary reference oncology center in a developing country.

MATERIAL AND METHOD

The study was carried out with the permission of Istanbul Medeniyet University Göztepe Prof. Dr. Süleyman Yalçın City Hospital Noninvasive Clinical Researches Ethics Committee (Date: 30.06.2021, Decision No: 2021/0347). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

We retrospectively conducted this single-center study in our clinic. Inclusion criteria were as follows; patients diagnosed with STS between 2016 and 2021 had a baseline intravenous contrast-enhanced MRI study prior to any treatment, histopathologic grade assessment on core needle biopsy before any history of neoadjuvant therapy. Exclusion criteria were patients whose tumor grade was unclear due to insufficient pathological findings and patients without preoperative MRI. Sixty-four patients suited the criteria and baseline characteristics, and histopathological & MRI features were considered (**Figure 1**). Therapeutic and prognostic values have not been in concern of this study.

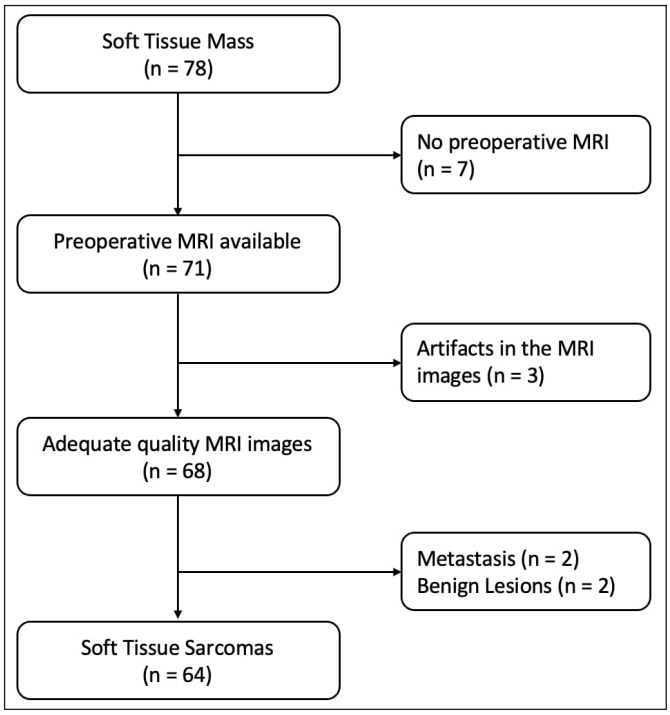

Figure 1. Flowchart of study (n = number of patients).

Baseline characteristics were noted as; age, sex, tumor location (extremity or trunk), and histological type of STS. For histopathological assessment, FNCLCC grade on core needle biopsy, Ki-67 index, necrosis ratio, and mitosis ratio on the specimen. MRI features are as follows; size, depth (deep, superficial, or both), heterogenous signal ratio (homogenous, <%50 or ≥%50 heterogenous), necrosis ratio (none, <%50 or ≥%50), presence of a hemorrhagic signal, border and sharpness (<50%, between 50% and 90%, >%90), tail sign (defined as thickening and enhancement of the aponeurosis with contrast), peritumoral edema, peritumoral enhancement, bone invasion, extension to vessel or nerve on T1, T2, and contrast-enhanced T1W images.

Single senior orthopaedic oncologist routinely performed the core needle biopsies from our institution (K.O., with 16 years of experience in percutaneous biopsy and surgery of STS) with a 14-16 gauge fully automatic core-needle biopsy device (Geotek Maxicore-M® Reusable Biopsy Gun, Ankara, Turkey). The MRI images were analyzed by a senior radiologist (BB, with 20 years of experience in soft-tissue imaging) and a radiology resident (MBD, with 3.5 years of experience in MRI, including 6-months of musculoskeletal rotation). These radiologists first recorded all data blind from the pathology results. The conflicting data was then finalized with a second consensus meeting. Histopathologic evaluation performed by two pathology experts in musculoskeletal oncology (TZ and ANT, over 10 years of experience in pathology).

MRI Protocol

This study was performed with two different MRI devices consisting of 1.5 Tesla GE Optima MR450w and MR360 (General Electric, Chicago, IL, USA). The MR imaging protocol basically consists of T1-weighted (T1W) sequence prior to contrast injection, T2-weighted (T2W) sequence with or without fat-suppression, DWI sequences and T1W sequence after contrast injection. Since the examined tumors were located in different localizations, the parameters were arranged for the relevant area and therefore varied. Repetition time and echo time intervals for T1W imaging were 450-720 ms and 7-12 ms, respectively. For T2W imaging, the same values were 2600-6900 ms and 82-120 ms. Section thicknesses vary between 3mm and 6mm. DWI images were acquired using b values of 0 and 800 s/mm².

Statistical Analysis

Number Cruncher Statistical System (NCSS 2007, Kaysville, Utah, USA) program was used for statistical analysis. While evaluating the study data, besides the descriptive statistical methods (Mean, Standard Deviation, Median, Frequency, Ratio, Minimum, Maximum), the distribution of the data was evaluated with the Shapiro-Wilk Test. Kruskal-Wallis test used in the comparison of quantitative data of three or more groups that do not show normal distribution; Mann-Whitney U Test was used to compare two groups that did not show normal distribution. Chi-square analysis was used to determine the relationship between qualitative data. Significance was evaluated at $p<0.01$ and $p<0.05$ levels.

RESULTS

The mean diameter of STS was measured as 90.1 mm in MRI evaluation. The mean age of sixty-four patients (M/F=34/30) was 45.5 (1.5-85). The majority (59/64) of these tumors were in the extremity. When examined for depth, only three were seen as both deep and superficial, all of which were high-grade tumors. Approximately half of the patients in the study were FNCLCC grade 3. The mean Ki-67 proliferation index value was 32.7 (**Table 1**).

The relationship between MRI findings and histopathological findings was examined in detail and summarized in **Table 2**. The ratio of heterogeneous signal area to tumor volume on T1W or T2W imaging was not associated with the aggressive behavior of the tumor. While the absence of necrosis signal in MRI findings was significantly associated with FNCLCC grade 1 (**Figure 2**) and low Ki-67 index (p:0.001), it was also shown that a ratio of more than 50% necrosis observed in contrast-enhanced T1 and T2W imaging to tumor volume was seen significantly in high-grade sarcomas (p:0.001).

Table 1. Baseline distribution of data of the population study

Characteristic	All Patients (n=64)	FNCLCC grade 1 (n=13)	FNCLCC grade 2 (n=18)	FNCLCC grade 3 (n=33)
Age (y)	45.5 ± 21.6 (1.5–85)			
Sex				
Men	34 (53%)			
Women	30 (47%)			
Size (mm)	90.1 ± 102.1 (10.4-835)	83.2 ± 43.7 (21.8-176.7)	70.1 ± 47.8 (14-196.7)	102.3 ± 135.9 (10.4-835)
Location				
Extremity	59 (92.2%)	11 (18.6%)	18 (30.5%)	30 (50.8%)
Trunk	5 (7.8%)	1 (25%)	0	3 (75%)
Depth				
Superficial	29 (45.3%)	7 (24.1%)	11 (37.9%)	11 (37.9%)
Deep	32 (50%)	6 (18.8%)	7 (21.9%)	19 (59.4%)
Both	3 (4.7%)	0	0	3 (100%)
FNCLCC grade				
Grade 1	13 (20.3%)			
Grade 2	18 (28.1%)			
Grade 3	33 (51.6%)			
Ki-67 index (%)	32.7 ± 27.6 (1-90)			

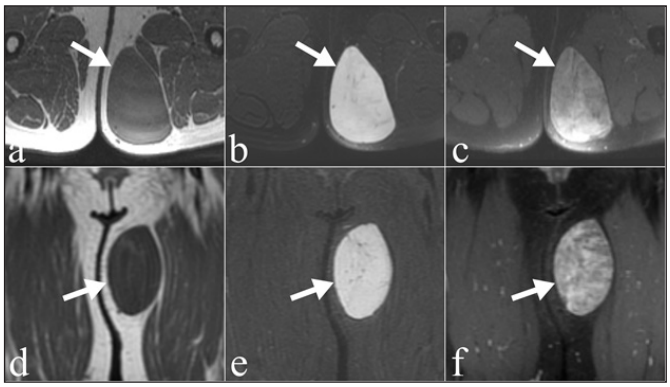

Figure 2. Images show MRI features in a 20-year-old woman with low grade (FNCLCC grade 1) liposarcoma. MRI protocol included, a, axial T1-weighted imaging, b, axial T2-weighted imaging with fat-suppression, c, axial post-contrast T1-weighted imaging, d, e and f, respectively, coronal plans of the same sequences. There is no hemorrhage, peritumoral enhancement, or peritumoral edema in this low-grade tumor.

The presence of hemorrhage signal distinguished as a hyperintense signal on T1W (**Figure 3**), tail sign (**Figure 4**), and post-contrast peritumoral enhancement (**Figure 5**) was significantly higher in FNCLCC grade 3 (**Figure 6** and **7**) STS (p:0.008, p:0.001, p:0.004, respectively). Absence of these features were correlated with low Ki-67 index as well (p:0.015, p:0.006, p:0.010, respectively). The presence of peritumoral edema on T2W imaging in all high-grade patients also showed a strong relationship between these two (p:0.001). Also, according to border and sharpness observed in T2W images in MRI, clear borders of 90% and above were associated with a grade 1 tumor (p:0.009). The presence of bone invasion, vessel, and nerve extension did not significantly correlate with tumor grade or the Ki-67 index.

Table 2. Association of MRI features with Ki-67 proliferation index and FNCLCC grade of specimen

Characteristic	All Patients (n=64)	Ki-67 Index % (mean)	p Value	FNCLCC grade 1	FNCLCC grade 2	FNCLCC grade 3	p Value
Heterogenity (T1W)			0.090				0.563
Homogenous	12 (18.8%)	18.9		4 (33.3%)	4 (33.3%)	4 (33.3%)	
<50%	24 (37.5%)	31.7		5 (20.8%)	7 (29.2%)	12 (50%)	
≥50%	28 (43.7%)	39.5		4 (14.3%)	7 (25%)	17 (60.7%)	
Heterogenity (T2W)			0.156				0.113
Homogenous	2 (3.1%)	25		0	2 (100%)	0	
<50%	28 (43.7%)	25.9		7 (25%)	9 (32.1%)	12 (42.9%)	
≥50%	34 (53.1%)	38.9		6 (17.6%)	7 (20.6%)	21 (61.8%)	
Necrosis			0.001*				0.001*
None	15 (23.4%)	11.07		10 (66.7%)	4 (26.7%)	1 (6.7%)	
<50%	20 (31.3%)	36.4		1 (5%)	6 (30%)	13 (65%)	
≥50%	29 (45.3%)	41.5		2 (6.9%)	8 (27.6%)	19 (65.5%)	
Hemorrhagic signal			0.015*				0.008*
No	26 (40.6%)	24.2		10 (38.5%)	7 (26.9%)	9 (34.6%)	
Yes	38 (59.4%)	38.6		3 (7.9%)	11 (28.9%)	24 (63.2%)	
Border and sharpness			0.402				0.009*
≥90%	17 (26.6%)	27		8 (47.1%)	4 (23.5%)	5 (29.4%)	
Btw 50% -90%	32 (50%)	32.8		3 (9.4%)	12 (37.5%)	17 (53.1%)	
<50%	15 (23.4%)	39.1		2 (13.3%)	2 (13.3%)	11 (73.3%)	
Tail sign			0.006*				0.001*
No	21 (32.8%)	21.4		10 (47.6%)	6 (28.6%)	5 (23.8%)	
Yes	43 (67.2%)	38.3		3 (7%)	12 (27.9%)	28 (65.1%)	
Peritumoral edema			0.001*				0.001*
No	10 (15.6%)	6.5		6 (60%)	4 (40%)	0	
Yes	54 (84.4%)	37.6		7 (13%)	14 (25.9%)	33 (61.1%)	
Peritumoral enhancement			0.010*				0.004*
No	30 (46.8%)	25		10 (33.3%)	11 (36.7%)	9 (30%)	
Yes	34 (53.1%)	39.6		3 (8.8%)	7 (20.6%)	24 (70.6%)	
Bone invasion			0.782				0.360
No	56 (87.5%)	33.1		12 (21.4%)	17 (30.4%)	27 (48.2%)	
Yes	8 (12.5%)	30.7		1 (12.5%)	1 (12.5%)	6 (75%)	
Extension to vessel and nerves			0.224				0.696
No	40 (62.5%)	30.4		9 (22.5%)	12 (30%)	19 (47.5%)	
Yes	24 (37.5%)	36.6		4 (16.7%)	6 (25%)	14 (58.3%)	

DISCUSSION

Histological grading is one of the essential criteria in the treatment planning of STS. Predicting the grade of the tumor from the first diagnosis provides benefits at every step, from the biopsy stage to systemic and local treatments. The heterogeneous internal structure of the tumor may lead to errors in the grading performed by biopsy. Jones C. et al. (15) and several other authors challenged the adequacy of core needle biopsy for determining the treatment (16-18). At this point, MRI stands out because it offers a global examination opportunity before total excision. Zhao et al. (12) previously showed independent MRI feature predictors of high-grade STS. Followed by Crombe A. et al. (13) with supporting imaging features correlating with the grade of the STS. Our study found that the following MRI features were essential predictors for high-grade tumors: Presence of hemorrhage signal distinguished as a hyperintense signal on T1W, tail sign, and post-contrast peritumoral enhancement.

After detecting a soft tissue tumor, MR imaging is performed to distinguish the tumor as benign or malignant and determine its extent and size. Then, if malignancy is suspected, a biopsy is performed for histopathological examination. In addition to the sarcoma diagnosis, the tumor grade is determined by biopsy. It has been reported that the grade of tumor determined by biopsy is lower than the final grade obtained after excision, with a rate of 13.5 to 55% in previous studies (19-21). This shows that biopsy adequacy and repetition should be reviewed in patients whose biopsy results were reported as low grade, while there are MRI findings pointing to a high-grade tumor. In the future projection, it will be aimed to predict tumor grade with MRI, independent of biopsy.

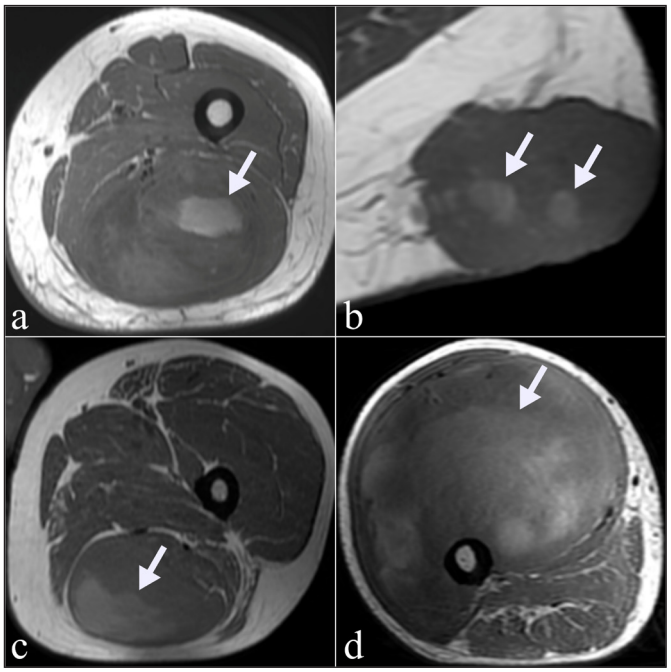

Figure 3. The presence of hemorrhage signal distinguished as a hyperintense signal on T1W is an important indicator for high grade. a. In the thigh MRI of a 41-year-old male patient, pleomorphic sarcoma and the hemorrhage area within the tumor were shown with an arrow. b. In the pelvic MRI of a 28-year-old female patient, angiosarcoma and the hemorrhage area within the tumor were shown with arrows. c. In the thigh MRI of a 40-year-old male patient, undifferentiated pleomorphic sarcoma and the hemorrhage area within the tumor were shown with an arrow. d. Right thigh MRI of a 50-year-old male patient showed myxofibrosarcoma and hemorrhage areas within the tumor with arrows.

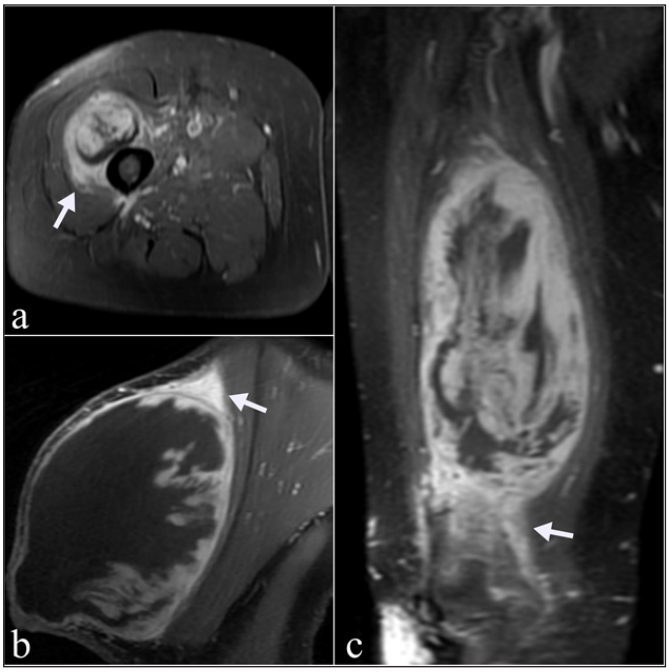

Figure 5. Peritumoral enhancement is more common in high-grade tumors. a. In the thigh MRI of a 62-year-old female patient, pleomorphic sarcoma and peritumoral enhancement were shown with an arrow. b. In the shoulder MRI of a 33-year-old male patient, fibrosarcoma and peritumoral enhancement were shown with an arrow. c. In the thigh MRI of a 67-year-old female patient, undifferentiated pleomorphic sarcoma and peritumoral enhancement were shown with an arrow.

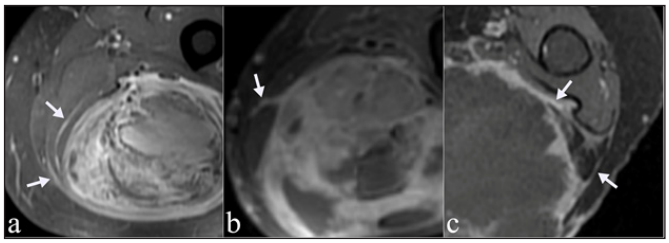

Figure 4. The tail sign is a signal extending curvilinearly along a certain plane with the same enhancement as the main mass in contrast-enhanced series. a. In the thigh MRI of a 41-year-old male patient, pleomorphic sarcoma and tail-sign were shown with an arrow. b. In the thigh MRI of a 62-year-old male patient, myxofibrosarcoma and tail-sign were shown with an arrow. c. Right arm MRI of a 85-year-old female patient, leimyosarcoma and tail-sign were shown with an arrow.

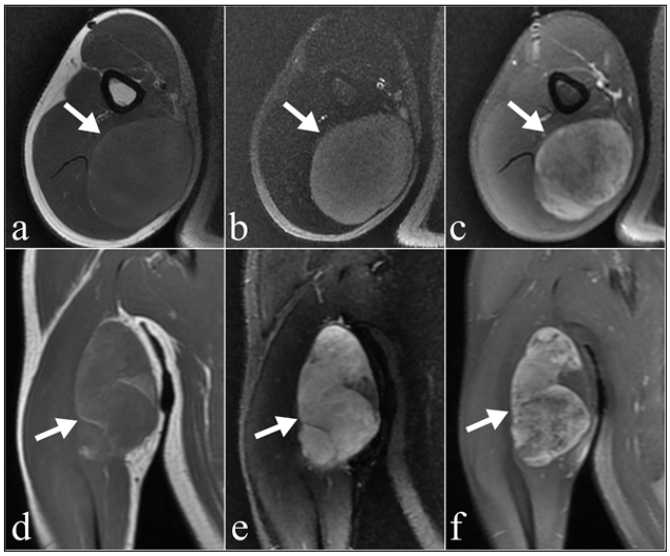

Figure 6. Images show MRI features in a 34-year-old male with FNCLCC grade 2 myxoid liposarcoma. MRI protocol included, a, axial T1-weighted imaging, b, axial T2-weighted imaging with fat-suppression, c, axial post-contrast T1-weighted imaging, d, e and f, coronal plans of the same sequences, respectively. There is a high T1 signal of hemorrhage in the tumor and mild peritumoral edema is present in the inferior.

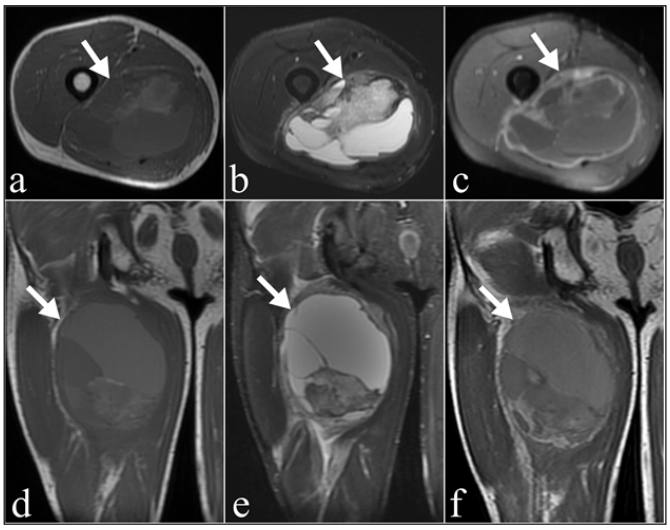

Figure 7. Images show MRI features in a 40-year-old male with FNCLCC grade 3 undifferentiated pleomorphic sarcoma. MRI protocol included, a, axial T1-weighted imaging, b, axial T2-weighted imaging with fat-suppression, c, axial post-contrast T1-weighted imaging, d, e and f, coronal plans of the same sequences, respectively. The tumor is highly heterogeneous in all sequences and has a high T1 signal of hemorrhage. Peritumoral edema and enhancement are present.

In our study, the rate of patients with grade III tumors was 51.6% (12,22,23), similar to the literature (46.1-59.7%). Crombé et al. (13) identified peritumoral enhancement as an independent predictor for high-grade tumors. However, they did not make a recommendation for a hemorrhage signal distinguished as a hyperintense signal on T1W and tail sign. They highlighted the findings of a necrotic component of the tumor, heterogeneous SI greater than or equal to 50% at T2W imaging. The absence of necrosis and a homogeneous signal were also found to be features of low-grade tumors in our study. Combining low-grade tumors into grades 1 and 2 may explain the differing results between studies.

In the analysis by Zhao et al. (12), tumor margin regularity was associated with a high degree of peritumoral edema and contrast enhancement. Our results showed a high degree of correlation between tail sign, peritumoral edema and contrast enhancement, and border irregularity. Presumably, since these indicators suggest invasion into surrounding tissues, it can be expected to be related to the tumor's aggressiveness.

Contrary to previous publications, the association of heterogeneity with high-grade tumors in T1 and T2W imaging showed no significant relevance. Revealing a precise heterogeneity ratio rather than an observation will increase the usability of this feature. Radiomics parameters are gaining in popularity today (24-26). Also, artificial intelligence-assisted pattern-based classification methods show promising results for future use in the quantitative analysis of tumor heterogeneity (27-29).

CONCLUSION

Our study found that the presence of hemorrhage signal, tail sign, peritumoral enhancement, clear borders of 50% and less obtained from conventional MRI features of STS are associated with high-grade tumors. The absence of necrosis signal, clear borders of 90% and above in MRI were significantly associated with FNCLCC grade 1. In case of discordance of these features and the biopsy result, it should be kept in mind that the tumor may be high grade considering that MRI can perform global tumor examination. MRI findings of the tumor will continue to be of increasing importance as a guide in clinical decision-making.

Abbreviations: STS: soft-tissue sarcoma; FNCLCC: Fédération Nationale des Centres de Lutte Contre Le Cancer

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Istanbul Medeniyet University Göztepe Prof. Dr. Süleyman Yalçın City Hospital Noninvasive Clinical Researches Ethics Committee (Date: 30.06.2021, Decision No: 2021/0347).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

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