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The Role of Multiparametric Magnetic Resonance Imaging in Post Therapeutic Evaluation of Soft Tissue Sarcomas

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Abstract

Soft-tissue sarcomas (STS) encompass a rare heterogeneous group of mesenchymal tumors, varying in their site of origin, histology, and prognosis. Imaging evaluation of tumor response in STS is challenging, as a mere change in tumoral size may not be adequately representative. Tumoral size changes are often preceded by changes in tumoral functions. To investigate the role of contrast-enhanced magnetic resonance imaging, using both conventional and functional techniques (e.g., DWI and DCE imaging), in the initial evaluation and post-therapeutic response monitoring of pathologically proven soft tissue sarcomas, assessing the added value of these techniques and their advantages over conventional MRI sequences. This was a prospective study performed on fifty-five cases of STS. Conventional, diffusion-weighted imaging and static post contrast MR sequences were obtained for all patients. Dynamic contrast enhanced (DCE) MR sequences were obtained for 10 patients. We recorded the changes in tumors' unidimensional sizes, volumes, ADC_{mean} values and time-intensity curves profiles with treatment. The RECIST 1.1 and the volumetric criteria for the assessment of treatment response showed a significant positive correlation, with some discrepancies in between, suggesting slight superiority of the latter. Lesions categorized as progressive disease (PD) showed corresponding significant reduction in their follow up ADC_{mean} values, while those lesions categorized as non-PD, showed corresponding significant elevation in their ADC_{mean} values. The changes in the ADC_{mean} values were negatively related to the changes in tumors' unidimensional sizes and volumes (all $P < 0.001$). Regarding the DCE-MRI analysis, in the PD group, tumors showed TICs types III, IV and V in the initial and follow up examinations, while in the non-PD group, tumors showed relative reduction in the TICs slopes, presenting with types III, IV and V TICs in the initial examinations and types II, III and V TICs in follow up examinations. However, these TIC changes were statistically insignificant. Multiparametric MRI using anatomical and functional MR techniques, particularly DWIs, can offer a better understanding of the lesions' response to treatment. Semi-quantitative DCE-MRI analysis using TICs did not best represent the lesions' treatment response, requiring further assessment in larger studies.

Keywords: Multiparametric magnetic resonance imaging, Post therapeutic evaluation, soft tissue sarcomas.

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1. Introduction

STS refers to a diverse & uncommon collection of malignancies that arise from mesenchymal tissue, varying in their site of origin, histology, & prognosis. These account for less than one percent of adult-onset and 15% of pediatric-onset malignancies [1]. Magnetic resonance imaging is the modality of choice for the assessment of soft tissue tumors & tumor-like conditions owing to its multi-planar capability, enhanced soft tissue contrast, & absence of radiation exposure. Thus, magnetic resonance imaging is the modality of choice in the assessment of STS, especially with tumors arising from the limbs or along the superficial tissue of the trunk. This is useful for diagnosis, surgical and radiotherapy planning, and post-therapeutic response assessment [2]. Imaging evaluation of tumor response in STS is challenging, as a mere change in tumoral size is not adequately representative. Tumoral size changes are often preceded by changes in tumoral functions, including perfusion, permeability, cellularity, and metabolism [3-4]. The object of this study was to examine the role of contrast-enhanced magnetic resonance imaging, using both conventional and functional techniques (e.g., DWI and DCE imaging), in the initial evaluation and post-therapeutic response monitoring of pathologically proven soft tissue sarcomas, assessing the added value of these techniques and their advantages over conventional MRI sequences.

2. Patients and methods

This was a prospective study carried out at the National Cancer Institute (NCI), Cairo University, after acquiring the Ethical Committee's approval.

2.1. Inclusion criteria

Patients with pathologically proven soft tissue sarcomas, whether diagnosed de-novo or as a post-operative residual or recurrent lesion, who are planned to receive chemotherapy and/or radiotherapy.

2.2. Exclusion criteria

Absence of a confirmed pathological diagnosis of soft tissue sarcoma. Contraindication to MRI, e.g., patients having pacemakers. Contraindications to MRI contrast media administration, e.g., cases with impaired renal functions, unless hemodialysis is scheduled.

2.3. Methods

2.3.1. MRI protocol

Conventional pre-contrast imaging included multiplanar T1-weighted images (T1WIs), T2-weighted images (T2WIs) and short tau inversion recovery (STIR). Diffusion-weighted images (DWIs) were acquired using multiple b values (0, 50, 400 and 800 sec/mm2). ADC maps were generated. Static contrast-enhanced imaging was performed using T1WIs and THRIVE (T1 High Resolution Isotropic Volume Excitation) sequences after bolus injection of 0.1mmol/kg body weight of Gadolinium-DTPA flushed with 20ml of sterile 0.9% saline solution at a rate of 2ml/s using an automatic injector. Dynamic contrast enhanced (DCE) images were done in some of the cases with the generation of the time-intensity curves.

2.3.2. Imaging analysis

2.3.2.1. Conventional MR imaging analysis

Tumor size is measured in cm as the tumor's longest dimension on the post-contrast images. Changes in tumor sizes with treatment were recorded. In compliance with the RECIST 1.1 criteria; patients were divided into: (1) partial response (PR) group with >30% size reduction; (2) stable disease (SD) group with size change between PR and progressive disease (PD) groups; and (3) PD group with >20% increase in lesions' size. Tumor volume, represented in cubic centimeters (cm^3), is assessed using the tumor's longest cross-sectional and craniocaudal dimensions. Patients were divided according to the changes in the lesions' volumes into: (1) PR group with >65% reduction in the tumor volume; (2) SD group with the change in tumor volume lying between PR and PD; and (3) PD group with >44% increase in the tumor volume.

2.3.2.2. Diffusion-weighted imaging analysis

This was done qualitatively and quantitatively. Qualitative analysis was completed by analyzing the signal intensity of all lesions on both the DWIs (at the highest b value) & the ADC map. For quantitative analysis, each tumor was reviewed, and an elliptical region of interest (ROI) was manually placed on the ADC map over the largest area of the tumor having the highest visible signal on the corresponding DWIs to obtain the mean ADC values for each lesion, both in the initial and follow-up examinations.

2.3.2.3. Dynamic contrast enhanced (DCE) MRI analysis

For 10 patients, DCE-MRI was acquired both initially and after therapy. DCE images were analyzed, and ROIs were placed within areas of the tumor showing early arterial enhancement to generate time intensity curves (TIC). These were classified as follows: Type I curve with no enhancement; Type II curve with weak gradual enhancement; Type III curve showing a rapid initial enhancement followed by plateau; Type IV curve showing rapid initial enhancement followed by washout; and Type V curve exhibiting rapid initial enhancement succeeded by progressive late enhancement.

3. Results and discussion

Our study encompassed 55 patients with different histological subtypes of STS (Table 1). We assessed the treatment response using the RECIST 1.1 criteria and the volumetric criteria. There was a statistically significant positive association among the change in the tumors' sizes (longest dimension) and the tumors' volumes. Similar results were also reported by Moustafa et al., (2019) and Saleh et al., (2020) [5-6]. Moreover, there was a significant correlation between both categorization criteria, with 42/55 of our study patients falling under concordant categories using both categorization criteria. However, there were some variations. While RECIST 1.1 classified 28/55 patients as having a SD, these patients showed a wider response spectrum in the volumetric categorization, with 8 of them categorized as having PD (Figure 1) and 2 categorized as having a PR using the volumetric criteria. Meanwhile, 3 patients labeled under the PR group using the RECIST 1.1 criteria showed a SD using the volumetric criteria. Our study also showed a wider variation in tumor volumes compared to unidimensional tumor sizes. The median change in the maximum tumor dimension was 13.95% (ranging from -47.92 to +600%), while a greater median alteration was seen in tumor volume at 57.54% (ranging from -93.88 to +9526.53%). These variations suggest that a unidimensional assessment of treatment response using RECIST 1.1 may not always be sufficient, as tumoral responses are heterogeneous and certainly not unidimensional. Unidimensional measurement may misestimate the entire volume of tumor burden. In 2014, Le Grange et al., (2014) reached similar conclusions. The authors, who studied 55 STS patients receiving pre-operative radiotherapy, reported an association between change in maximum tumor dimension and volume ($p< 0.001$). However, the median change in the maximum tumor dimension was -13.6% (ranging between -40 to +25%), while a greater median alteration of -33% was seen in tumor volume (ranging between -84.7 to +54.9%), suggesting that the maximum tumor diameter may underestimate tumor volume alteration. Moreover, while the RECIST 1.1 criteria demonstrated a SD in 89% of patients, that didn't reflect the volume changes, with 80% of tumors showing volume reduction. Additionally, in some cases, there was a reduction in the maximum tumor dimension but an increase in tumor volume, again suggesting that RECIST 1.1 may not be a consistent surrogate of tumor volume change [7].

We observed the post-therapeutic changes in the ADC_{mean} values. Lesions categorized as showing a PD, in terms of both RECIST 1.1 and volumetric criteria, showed a correspondingly significant reduction in their $ADC2_{mean}$ values compared to the $ADC1_{mean}$ values (all P <0.05). Meanwhile, lesions categorized as showing non-PD disease, in terms of RECIST 1.1 and volumetric criteria, showed correspondingly significant elevations in their ADC_{mean} values all P <0.05 (Figure 2). These results are concordant with the literature stating that post-treatment elevation in the ADC values is consistent with a more favorable response to treatment, as it represents more tumor necrosis leading to greater water-molecule diffusion [8-10]. Our study showed a strong negative association amongst the ΔADC_{mean} & the percentage of change in lesions' unidimensional sizes (Δsize) and volumes (ΔVol), with Pearson correlation coefficients (r) of -0.636 and -0.554 respectively (all p <0.001). In similar studies, ΔADC also showed a negative association with the tumor's unidimensional size and volume variations [5-6]. Another study has shown a negative association between changes in tumor volume and ADC_{mean} values, where a rise in the ADC_{mean} value was always related to a decrease in tumor volume and vice versa [11]. In the literature, reduction in the slope of the TICs is correlated with favorable response to treatment and vice versa [12]. However, analysis of the post therapeutic changes in the TICs' profiles in our study, though informative on a case-by-case basis, were statistically insignificant (Figure 1). Percentage of change in tumor size (Δsize), ranged between -47.92% to 600% with a mean of 43.64% and a median of 13.95%. Percentage of change in tumor volume (ΔVol), ranged between -93.88% to 9526.53% with a mean of 522.21% and a median of 57.54% (Table 2). As per the RECIST 1.1 criteria, patients were classified into PR group (n=7); SD group (n=28) and PD group (n=20). For better assessment of the effect of treatment on tumor progression, we further grouped patients into PD and non-progressive disease (non-PD) groups, with the latter incorporating the SD and PR groups (Table 3). As per the volumetric criteria, patients were classified into PR group (n=6); SD group (n=21) and PD group (n=28). Again, and for better assessment of the effect of treatment on tumor progression, we further grouped patients into PD-Vol and non-PD-Vol groups (Table 4). There were some differences in the response categorization between the RECIST1.1 and volumetric criteria. For 42 patients in our study, both categorization criteria were similar. Ten patients categorized as SD by the RECIST 1.1 criteria were categorized as PD (n = 8) and PR (n = 2) by the volumetric criteria. Meanwhile, three patients in the PR category by RECIST 1.1 showed a SD according to the volumetric criteria. Both categorization criteria showed excellent correlation (P<0.001; Table 5). Table 6 shows that follow-up ADC_{mean} values ($ADC2_{mean}$) were significantly lower than the initial ones ($ADC1_{mean}$) in the PD and PD-Vol groups (P = 0.004 and 0.046 respectively). Additionally, $ADC2_{mean}$ values were significantly higher than $ADC1_{mean}$ values in the non-PD and non-PD-Vol groups (P=0.031 and 0.044 respectively). The percentage of change in the ADC_{mean} values (ΔADC_{mean}) values were negatively related to the Δsize and Δvol (all P <0.00; Table 7). Regarding the patients undergoing DCE-MRI, some showed a PD (n=4) while the others exhibited a non-PD (n=6). In the PD group, tumors showed types III, IV and V TICs in the initial and follow up examinations, with no statistically significant difference between both studies. Meanwhile, in the non-PD group, tumors showed types III, IV and V TICs in the initial examinations and types II, III and V curves in follow up examinations; again, with no statistically significant difference between both studies (Table 8).

Table 1: Histopathological subtypes of STS lesions in our study.

Histopathological subtype	No. of lesions	Percentage
Synovial sarcoma	17	30.91%
Rhabdomyosarcoma	11	20.0%
Ewing sarcoma	6	10.91%
Fibrosarcoma, NOS	5	9.1%
Undifferentiated pleomorphic sarcoma	4	7.3%
Undifferentiated sarcoma	4	7.3%
Solitary fibrous tumor, malignant	2	3.64%
Infantile fibrosarcoma	2	3.64%
Pleomorphic liposarcoma	1	1.8%
Myxoid liposarcoma	1	1.8%
Fibromyxoid sarcoma	1	1.8%
Extra-skeletal osteosarcoma	1	1.8%

Table 2: Percentage of change in tumor sizes and volumes with treatment.

	Mean	Standard Deviation	Median	Minimum	Maximum
ΔSize (%)	43.64	110.84	13.95	-47.92	600.00
ΔVol (%)	522.21	1,607.18	57.54	-93.88	9,526.53

Table 3: Classification of tumor response in concordance with the RECIST 1.1 criteria.

		No. of patients	Total	Percentage	Total
Progressive Disease		20		36.4%	
Non-Progressive Disease	**Stable Disease**	28	35	50.9%	63.6%
	Partial Response	7		12.7%	

Table 4: Classification of tumor response in concordance with the volumetric criteria.

		No. of patients	Total	Percentage	Total
Progressive Disease (Vol)		28		50.9%	
Non-Progressive Disease (Vol)	**Stable Disease**	21	27	38.2%	49.1%
	Partial Response	6		10.9%	

Table 5: Correlation between RECIST 1.1 and volumetric classifications.

		RECIST 1.1 Categorization						P value
		PD		SD		PR		
		Count	%	Count	%	Count	%	
Volume Categorization	**PD**	20	100.0%	8	28.6%	0	0.0%	< 0.001
	SD	0	0.0%	18	64.3%	3	42.9%	
	PR	0	0.0%	2	7.1%	4	57.1%	

Table 6: Variations in ADC_{mean} values with treatment in each of the study groups.

	Progressive Disease (PD)					P value
	Mean	**SD**	**Median**	**Minimum**	**Maximum**	
$ADC1_{mean}$	1.40	0.49	1.30	0.70	2.80	0.004
$ADC2_{mean}$	1.13	0.51	1.00	0.60	2.50	
	Non-Progressive Disease					**P value**
	Mean	**SD**	**Median**	**Minimum**	**Maximum**	
$ADC1_{mean}$	1.25	0.60	1.10	0.20	2.90	0.031
$ADC2_{mean}$	1.55	0.82	1.20	0.40	3.70	
	Progressive Disease-Vol					**P value**
	Mean	**SD**	**Median**	**Minimum**	**Maximum**	
$ADC1_{mean}$	1.39	0.53	1.30	0.70	2.80	0.046
$ADC2_{mean}$	1.24	0.59	1.05	0.50	2.60	
	Non-Progressive Disease-Vol					**P value**
	Mean	**SD**	**Median**	**Minimum**	**Maximum**	
$ADC1_{mean}$	1.23	0.60	1.10	0.20	2.90	0.044
$ADC2_{mean}$	1.56	0.86	1.20	0.40	3.70	

Table 7: Correlation between percentage of change in the ADC_{mean} values and percentage of change in the tumors' sizes and volumes.

		ΔSize	**ΔVol**
ΔADC_{mean}	**Correlation Coefficient**	-0.636-	0.554
	P value	< 0.001	<0.001

Table 8: TIC types in the PD and non-PD groups.

	Progressive Disease				P value	Non-Progressive Disease				P Value
	Initial		Follow up			Initial		Follow up		
TIC type	**Count**	**%**	**Count**	**%**		**Count**	**%**	**Count**	**%**	
II	0	0.0%	0	0.0%	0.564	0	0.0%	2	33.3%	0.129
III	2	50.0%	1	25.0%		1	16.7%	2	33.3%	
IV	1	25.0%	2	50.0%		3	50.0%	0	0.0%	
V	1	25.0%	1	25.0%		2	33.3%	2	33.3%	

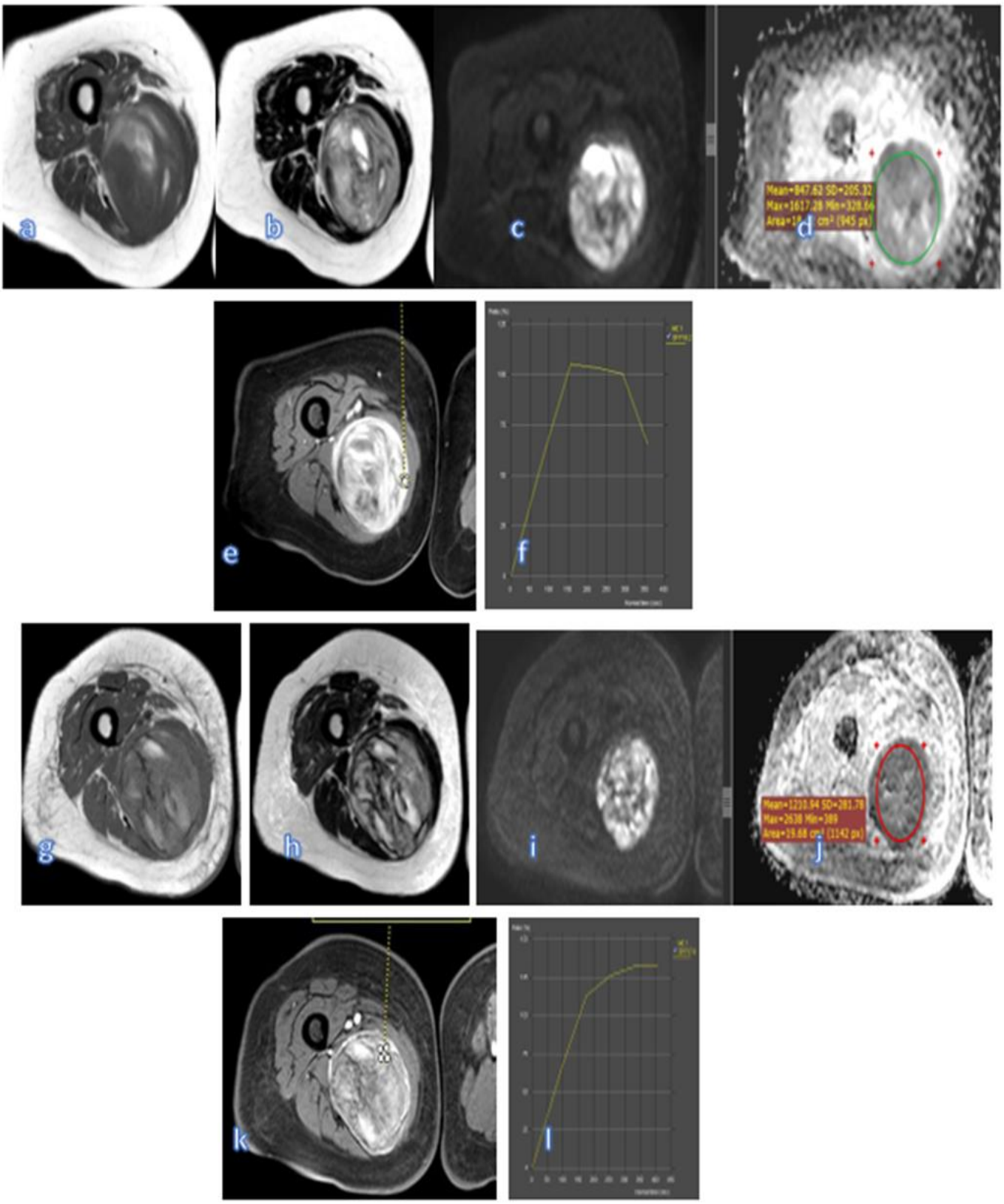

Figure 1: Baseline (a-f) and follow up (g-l) MR images of a 54-year-old female patient, with recurrent thigh undifferentiated sarcoma. The lesion shows size increase, marked as SD by the RECIST 1.1 criteria and PD by the volumetric criteria. Axial T1 and T2 WIs before (a & b) and after (g & h) treatment show more prominent intra-tumoral areas of breaking down/hemorrhage after treatment. Initial and follow up DWIs and the corresponding ADC maps (c, d, I & j) show evidence of diffusion restriction with elevation of the ADC_{mean} value after treatment ($1.2x10^{-3}$ mm^2/s compared to $0.8mm^2/s$ initially). Post contrast axial THRIVE images show mild reduction in the post contrast enhancement of the lesion in the follow up study (k) compared to the initial one (e) with a change of the corresponding TIC profile from a type IV curve initially (f) to a type V curve (l).

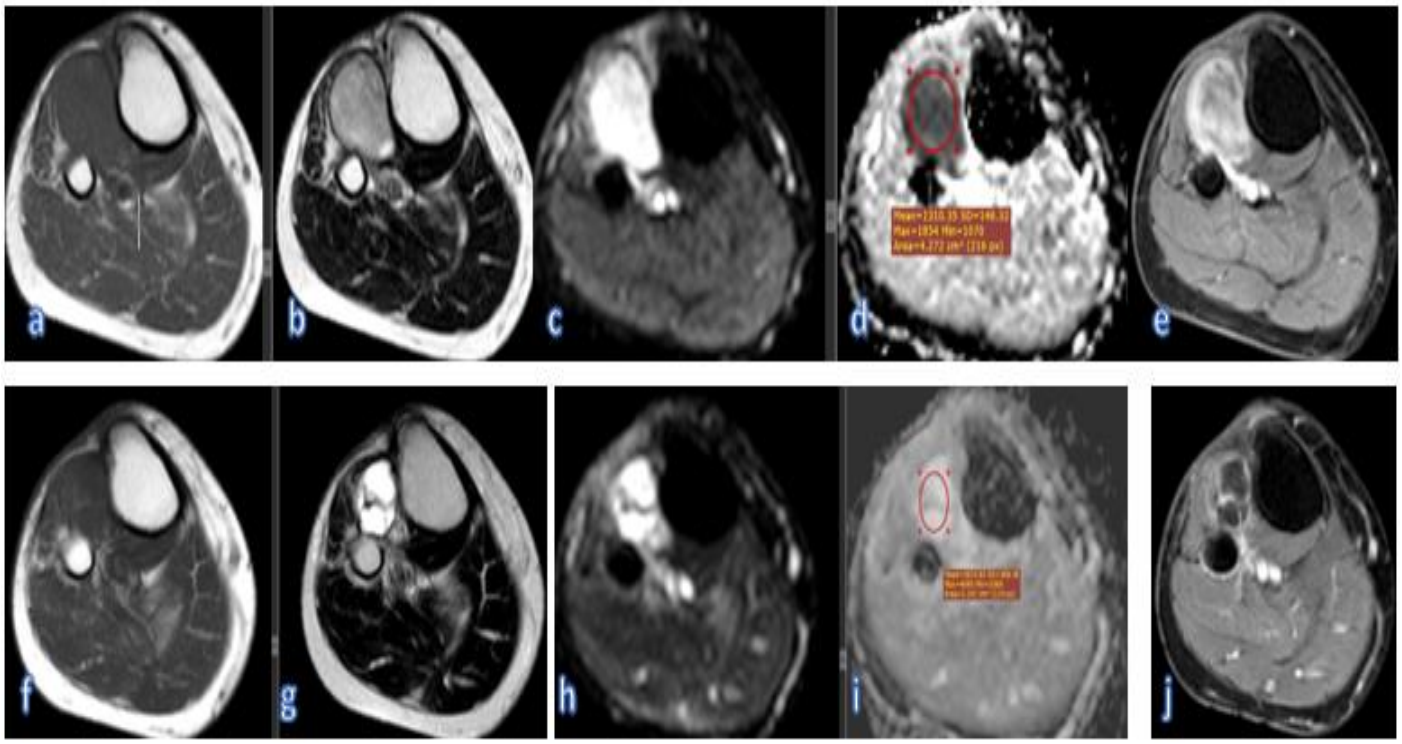

Figure 2: Baseline (a-e) and follow up (f-j) MR images of a 40-year-old male patient with recurrent right leg fibrosarcoma. The lesion shows significant size reduction in the follow up study, marked as PR by both the RECIST 1.1 and the volumetric criteria. Axial T1 and T2 WIs before (a & b) and after (f & g) treatment show more prominent low T1 and high T2 signal of the lesion after treatment with more sizable intrinsic areas of breaking down. Initial DWIs and the corresponding ADC map (c & d) show evidence of diffusion restriction; while the corresponding post therapeutic images (h & i) show evidence of diffusion facilitation with subsequent elevation of the ADC_{mean} value ($3.6x10^{-3}$ mm^2/s compared to 1.3 mm^2/s initially). Reduction of the contrast uptake in the follow up axial THRIVE image (j) compared to the initial study (e) was also noted, with the lesion showing intrinsic breaking down and faint, predominantly peripheral, enhancement.

4. Conclusions

Tumor response assessment of STS is a complex task, that requires the incorporation of the lesions' morphological and functional changes. Multiparametric MRI using anatomical and functional MR techniques, particularly DWIs, can offer a better understanding of the lesions' response to treatment. Semi-quantitative DCE-MRI analysis using TICs may not be the best representative of the lesions' treatment response, requiring further assessment in larger studies.

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