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Research article

Distinguishing soft tissue sarcomas of different histologic grades based on quantitative MR assessment of intratumoral heterogeneity

Pei Xiang[a,1], Xiaoling Zhang[a,1], Dawei Liu[b], Chaoyang Wang[a], Lei Ding[a], Fen Wang[b], Zhaohui Zhang[a,*]

[a] Department of Medical Imaging, The First Affiliated Hospital of Sun Yat-sen University, 58 Zhongshan 2nd Road, Guangzhou, Guangdong 510080, PR China
[b] Department of Pathology, The First Affiliated Hospital of Sun Yat-sen University, 58 Zhongshan 2nd Road, Guangzhou, Guangdong 510080, PR China

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ABSTRACT

Purpose: To explore the role of intratumoral heterogeneity on MRI assessed by histogram analysis in differentiating soft-tissue sarcomas (STS) of different grades.

Materials and Methods: Patients with primary STS undergoing MRI prior to iatrogenic procedures were included retrospectively. The histologic grade was assigned according to Federation Nationale des Centres de Lutte Contre le Cancer grading system. T1WI and T2WI were normalized by dividing mean signal intensity (SI) of contralateral/near unaffected muscles. Contrast-enhanced T1WI was normalized by computing enhancement ratio (ER) map as $(SI_{post}\text{-}SI_{pre})/SI_{pre} \times 100$, where SI_{pre} and SI_{post} represent SI of each pixel before and after enhancement. A region of interest (ROI) was manually drawn to include entire tumor area on axial slice with largest tumor diameter. Mean, mode, standard deviation, kurtosis and skewness on ROIs were extracted with ImageJ software. ANOVA/Kruskal-Wallis test was used to determine the significance of differences. ROC curve was applied for statistically significant parameters. P value ≤ 0.05 was considered statistically significant.

Results: Among involved 67 patients, 8 were assigned to grade 1, 38 to grade 2 and 21 to grade 3. Skewness ($P = 0.022$) and kurtosis ($P = 0.035$) on ER maps were significantly different among STS of different grades. The optimal cutoffs of skewness and kurtosis on ER maps were -0.488 (AUC[95% CI] 0.747[0.557–0.937]; sensitivity/specificity, 62.5%/86.4%) and 0.762 (AUC[95% CI] 0.684[0.548–0.821]; sensitivity/specificity, 76.2%/56.5%), respectively.

Conclusion: Intratumoral heterogeneity on MRI quantitatively displayed by histogram parameters can differentiate STS of different grades. Skewness and kurtosis on ER maps show the capacity.

1. Introduction

Soft-tissue sarcomas (STS) include a large group of malignant soft-tissue tumors with various prognoses. Among all the investigated factors, histologic grade is accepted as one of the most important prognostic factors. Grading is mainly applied to predict the probability of distant metastasis and survival [1]. In a large cohort study (n = 1513), it was displayed that patients with grade 3 STS assigned according to the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system (grade 1–3), may benefit from adjuvant chemotherapy, while patients with grade 1 or 2 may not [2]. It prompts that assigning the pre-therapeutic histologic grade accurately is of vital significance for the subsequent treatment plans. However, this intent couldn't be always achieved due to insufficient specimens or sampling errors [3].

To increase the accuracy of grade assessment before therapies, several studies have attempted to use qualitative MR imaging features as assisting information for STS grading. Couples of peritumoral features, including poorly defined margins, peritumoral enhancement, the presence of peritumoral high signal intensity (SI) (or edema-like sign) and the absence of peritumoral low SI (or capsule-like sign) on T2-weighted images, have proved their potential in this respect [4,5]. In comparison, only one intratumoral feature, the visual heterogeneity of SI on T2-weighted images, has stood out [5]. However, it is well known that intratumoral heterogeneity is an intrinsic characteristic of tumors in both genetic and histopathologic levels showing spatial variation in

Abbreviations: STS, soft-tissue sarcomas; ER, enhancement ratio; SI, signal intensity; CI, confidence interval

* Corresponding author.
E-mail address: zzh_zs@qq.com (Z. Zhang).

[1] These authors contribute equally to this work.

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the cellularity, vasculature and stroma. Tumors with high intratumoral heterogeneity tend to have poorer prognoses that may be secondary to aggressive biology or treatment resistance [6].

The concurrent presence of intratumoral necrosis, hemorrhage, myxoid degeneration, calcification and various cells result in the macroscopic intratumoral heterogeneity, which may be visually observed and assessed on routine MR images to some extent. But the intratumoral heterogeneity manifesting in microscopic level, such as cellular morphology, metabolism, angiogenic and proliferative potential, is difficult to be validated and evaluated by visual observation of routine MR images. Histogram analysis of the MR imaging indices allows a deep inspection of their distribution in the scanned areas and can be used to evaluate the intratumoral heterogeneity. It has been successfully applied for the assessment of various neoplasms in various aspects [6,7]. However, the histogram analysis of MR images for STS grading has not yet been reported. Therefore, This study aimed to identify the role of intratumoral heterogeneity on routine MR images reflected by histogram parameters in the aspect of differentiation of STS with different histologic grades.

2. Materials and methods

2.1. Patients

Institutional review board approval was obtained, and informed consent was waived. The inclusion criteria were set as patients with 1) primary STS with or without distant metastasis, and 2) available MRI prior to biopsy, neo-adjuvant therapy, and surgery. The exclusion criteria were as follows: 1) inadequate pathologic findings for the determination of tumor grade, and 2) MR images without quality for histogram analysis. Finally, 67 patients in our medical institution were retrospectively involved from January 2005 to March 2019.

2.2. Histologic analysis

The histologic grades of tumors were determined according to the FNCLCC grading system (grade1–3), where three independent factors including tumor differentiation, mitotic count, and the extent of necrosis are used to define the grade [8]. Two pathologists (4 years and 8 years of experience in soft-tissue tumor pathology) independently reviewed the histologic specimens and a consensus on the final histologic grade of each tumor was achieved in a joint meeting.

2.3. MR imaging protocol

The MR imaging protocols varied because of the different anatomic structures being examined. But every patient's imaging protocol included spin-echo or turbo spin-echo T1-weighted images (repetition time = 400–620 ms, echo time = 10–26 ms), spin-echo or turbo spin-echo T2-weighted images (repetition time = 3000–6340 ms, echo time = 55–120 ms) and contrast-enhanced T1-weighted images (CE T1-weighted images) after intravenous injection of gadopentetatedimeglumine (0.1 mmol/kg of body weight; Beilu, Beijing, China).

2.4. Imaging analysis

Two radiologists (4 years and 20 years of experience in musculoskeletal imaging) without any prior knowledge of final histologic grades independently performed the histogram analysis of MR images using ImageJ software (Version 1.47). The values of histogram parameters were obtained by averaging the two evaluation results.

Considering that radio frequency (RF) coil uniformity, static field inhomogeneity, RF penetration, gradient-driven eddy currents and patient anatomy can result in the variability within and between MR systems [9], MR images were normalized to correct the acquisition-to-acquisition SI variations before histogram analysis. T1- and T2-weighted images were normalized by the process of dividing the mean SI of contralateral or near unaffected muscles. CE T1-weighted images was normalized by computing the enhancement ratio (ER) map on a pixel-by-pixel basis with the following equation: $ER = (SI_{post}\text{-}SI_{pre})/SI_{pre} \times 100$, where SI_{pre} and SI_{post} represent the signal intensity of each pixel obtained before and after contrast enhancement, respectively. Then, a region of interest (ROI) was manually drawn to include the entire tumor area on the axial slice where the tumor showed its largest axial diameter. High SI on T2-weighted images and enhancement on CE T1-weighted images were combined to define the outermost tumor margins [10]. Five widely used histogram parameters including mean, mode, standard deviation (SD), kurtosis and skewness were automatically extracted from the selected ROIs on T1- and T2-weighted images and ER maps. These parameters reflect the grey-level frequency distribution on images and take into account only pixel intensity without consideration of spatial factors. They are considered as members of first-order statistics of statistical-based texture analysis [6,7]. Specifically, mean and SD represent the average and dispersion of the histogram distribution. Mode corresponds to the highest peak in the histogram, which represents the most frequently occurring value. Skewness is a measure of the asymmetry of the distribution. If a histogram has an elongated tail on the left side of the mean, it is negatively skewed. If a histogram has an elongated tail on the right side of the mean, it is positively skewed. Kurtosis is a measure of the peakedness of a distribution. Distributions with positive kurtosis are called leptokurtic distributions, meaning higher peak compared with the normal distribution, and distributions with negative kurtosis are called platykurtic distributions, meaning flatter curve compared with the normal distribution [11,12].

2.5. Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics software (version 21.0 J; SPSS, Chicago, IL). P value $\leq$ 0.050 were considered statistically significant.

Normally distributed data were presented as mean $\pm$ SD, and non-normally distributed data as median (interquartile range). One-way analysis of variance (for normally distributed data) or Kruskal-Wallis test (for non-normally distributed data) was performed to analyze the differences in histogram parameters on MR images among different histologic grade groups. The comparisons between every two groups were also performed. The receiver operating characteristic (ROC) curves were constructed for the statistically significant histogram parameters. The area under the curve (AUC) was calculated and the optimal threshold was determined according to the Youden index. An AUC value < 0.5 indicated poor performance, 0.5–0.7 indicated moderate performance, 0.7–0.8 indicated good performance, and > 0.8 indicated excellent performance. The interobserver agreement between the two pathologists and the two radiologists were evaluated with intraclass correlation coefficient (ICC). It was classified as poor (< 0.40), fair (0.40–0.59), good (0.60– 0.74), or excellent (0.75–1.00).

3. Results

Of the involved 67 patients, there were 36 males and 31 females. The mean age of patients was 45 years with a range of 13–82 years. The histologic subtypes of STS were undifferentiated pleomorphic sarcoma (n = 15), synovial sarcoma (n = 18), malignant peripheral nerve sheath tumor (n = 6), myxoid liposarcoma (n = 2), leiomyosarcoma (n = 3), rhabdomyosarcoma (n = 2), fibrosarcoma (n = 3), dermatofibrosarcoma protuberans (n = 3), malignant solitary fibrous tumor (n = 1), angioleiomyosarcoma (n = 1), epithelioid sarcoma (n = 2), alveolar soft-tissue sarcoma (n = 3), epithelioid hemangioendothelioma (n = 1), low-grade (n = 1) and high-grade (n = 2) myofibroblastic sarcoma, malignant triton tumor (n = 1), and malignant tumor of mesenchymal origin with uncertain differentiation (n = 3).

Table 1
Comparison of Histogram Parameters on MR Images among Soft-tissue Sarcomas of Different Histologic Grades.

	Grade 1 (n = 8)	Grade 2 (n = 38)	Grade 3 (n = 21)	*F* value	*P* value
Mean on T1WI[a]	1.2 ± 0.3	1.1 ± 0.3	1.2 ± 0.3	0.098	0.907
SD on T1WI	0.1(0.2)	0.2(0.1)	0.2(0.2)	NA	0.511
Mode on T1WI[a]	1.2 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	0.569	0.569
Skew on T1WI	0.8(1.6)	0.3(1.1)	0.2(2.4)	NA	0.615
Kurt on T1WI	3.0(10.3)	1.4(3.7)	1.8(4.9)	NA	0.808
Mean on T2WI	4.1(3.2)	3.7(2.3)	3.7(1.8)	NA	0.510
SD on T2WI	1.0(0.6)	1.2(0.8)	1.1(0.9)	NA	0.446
Mode on T2WI	3.8(3.8)	3.9(2.4)	3.4(1.3)	NA	0.504
Skew on T2WI[a]	0.3 ± 0.7	0.2 ± 0.9	0.5 ± 0.8	0.795	0.456
Kurt on T2WI	0.1(4.4)	0.5(2.5)	0.9(1.6)	NA	0.699
Mean on ER map	191.3(59.7)	166.9(77.7)	182.7(67.7)	NA	0.180
SD on ER map[a]	42.2 ± 16.3	48.7 ± 18.7	48.1 ± 16.3	0.452	0.638
Mode on ER map	209.1(105.0)	136.7(98.1)	168.0(117.0)	NA	0.173
Skew on ER map	−0.7(1.5)	0.5(2.1)	0.1(0.7)	NA	0.022
Kurt on ER map	0.9(2.1)	1.5(8.6)	−0.1(2.4)	NA	0.035

Note: T1WI T1-weighted images, T2WI T2-weighted images, SD standard deviation, Skew skewness, Kurt kurtosis, ER enhancement ratio, NA not applicable.

[a] Normally distributed data are analyzed with one-way ANOVA and presented as mean ± SD, while other non-normally distributed data are analyzed with Kruskal-Wallis test and presented as median (interquartile range).

There were 8 patients with grade 1 STS, 38 patients with grade 2 STS, and 21 patients with grade 3 STS. No significant differences among different histologic grade groups were observed for age ($F = 0.288$; $P = 0.750$) and gender ($P = 0.290$).

Skewness ($P = 0.022$) and kurtosis ($P = 0.035$) on ER maps were statistically different among grade 1, grade 2 and grade 3 STS (Table 1 and Fig. 1). For pairwise comparisons, skewness on ER maps differed significantly between grade 1 and 2 groups ($P = 0.030$) and kurtosis on ER maps differed significantly between grade 2 and 3 groups ($P = 0.031$) (Fig. 1). Skewness on ER maps was lower in grade 1 group compared with grade 2 group (-0.7[1.5] vs. 0.5[2.1]), while kurtosis on ER maps was higher in grade 2 STS than that in grade 3 STS (1.5[8.6] vs. -0.1[2.4]) (Table 1 and Fig. 1). The significant differences of these parameters were reflected on the shape difference of histogram graph of ER among STS of different grades, which were shown in Fig. 2 (c-3 and d-3). There seem to be differences of histogram distribution of SI on T1- (Fig. 2 [c-1 and d-1]) and T2-weighted images (Fig. 2 [c-2 and d-2]) among different grade STS, but none of the assessed parameters worked significantly ($P > 0.050$) (Table 1). The ROC curve analysis demonstrated that skewness on ER maps had good accuracy (AUC 0.747; 95% confidence interval [CI], 0.557–0.937; $P = 0.024$) for distinguishing grade 1 STS from grade 2 and 3 STS with a cutoff of -0.488 (sensitivity, 62.5%; specificity, 86.4%) (Fig. 3a). Kurtosis on ER maps showed moderate accuracy (AUC 0.684; 95% CI, 0.548–0.821; $P = 0.016$) for differentiating grade 1 and 2 STS from grade 3 STS with a cutoff of 0.762 (sensitivity, 76.2%; specificity, 56.5%) (Fig. 3b).

Excellent interobserver agreement ($0.75 < ICC \leq 1.00$; $P < 0.001$) was observed in most assessed parameters between the two pathologists and the two radiologists, which were shown in Table 2. The lowest interobserver agreement belonged to kurtosis on T1-weighted images with ICC of 0.518 (95% CI, 0.204-0.708; $P = 0.002$).

4. Discussion

The histologic grade of STS is heavily tied to the patient's risk of metastasis and overall survival, so it's critical for the treatment planning of patients [1,5]. Our study showed that intratumoral heterogeneity on MR images quantitatively assessed by histogram parameters

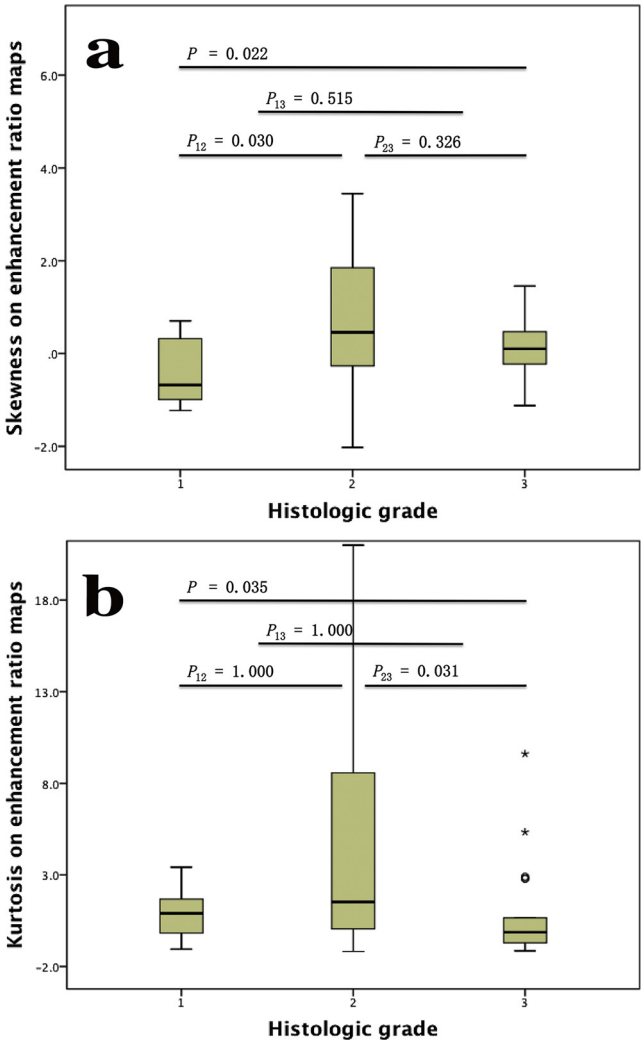

Fig. 1. Box plots show differences in histogram parameters among STS of different histologic grades. The difference in skewness (a) and kurtosis (b) on enhancement ratio maps is significant among grade 1, 2 and 3 STS. For pairwise comparisons, the former parameter is significantly different between grade 1 and 2 groups and the latter differs significantly between grade 2 and 3 groups. (*Note*: STS soft-tissue sarcomas).

was useful in differentiating STS of different histologic grades. Skewness and kurtosis on ER maps were statistically different among grade 1, grade 2 and grade 3 STS. Skewness on ER maps showed the capacity in differentiating grade1 from grade 2 and 3 STS with good accuracy, and kurtosis on ER maps showed the capacity in differentiating grade 1 and 2 from grade 3 STS with moderate accuracy. To our knowledge, no previous study has evaluated the role of histogram analysis of MR imaging indices in STS grading.

There have been studies using histogram analysis of MR imaging indices to evaluate various other neoplasms. For pancreatic neuroendocrine neoplasms (panNENs), skewness on T2-weighted images was significantly higher in the group with higher-grade and vascular involvement than in the group with lower-grade and vascular non-involvement, while skewness, kurtosis on T1-weighted images and kurtosis on T2-weighted images didn't show the significant difference between the two groups [13]. Mean, skewness and kurtosis on T2-weighted images didn't differ significantly between responding and non-responding colorectal liver metastases [14]. Relative low values of SD, skewness and high values of kurtosis on T2-weighted images predicted the high-risk endometrial cancer [15]. However, none of the assessed histogram parameters on T1- or T2-weighted images could

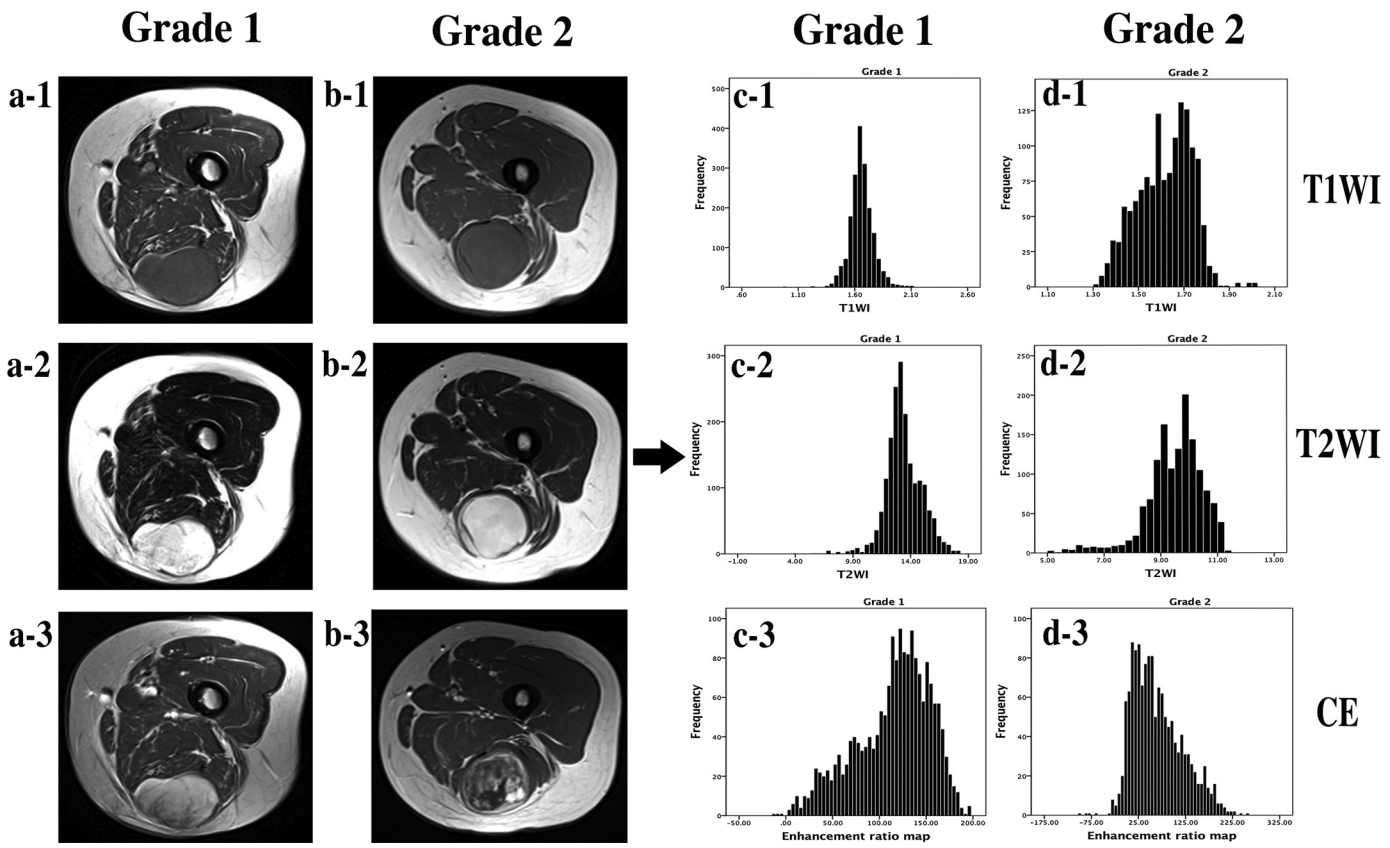

Fig. 2. Comparisons between visual assessment (a and b) and histogram analysis (c and d) of different grade STS on MR images. In almost the same location, a myxoid liposarcoma (grade 1) (a and c) and an undifferentiated pleomorphic sarcoma (grade 2) (b and d) are separately found in a 47 year-old female and a 46 year-old female. It is not able to differentiate them with the visual assessment on T1WI (a-1 and b-1) and T2WI (a-2 and b-2). There seems to be a different distribution of SI on both T1WI (c-1 and d-1) and T2WI (c-2 and d-2) between grade 1 and 2 STS, but neither of them is significantly reflected in the changes of assessed parameters. The grade 2 STS enhances visually more heterogeneous than grade 1 STS (a-3 and b-3). The difference of enhancement between them is also reflected on the histogram distribution of enhancement ratio (c-3 and d-3), which is more left-shifted in grade 2 STS (skewness = 0.657) than grade 1 STS (skewness = -0.615).
(*Note*: T1WI T1-weighted images, T2WI T2-weighted images, CE contrast-enhanced images, STS soft-tissue sarcomas, SI signal intensity).

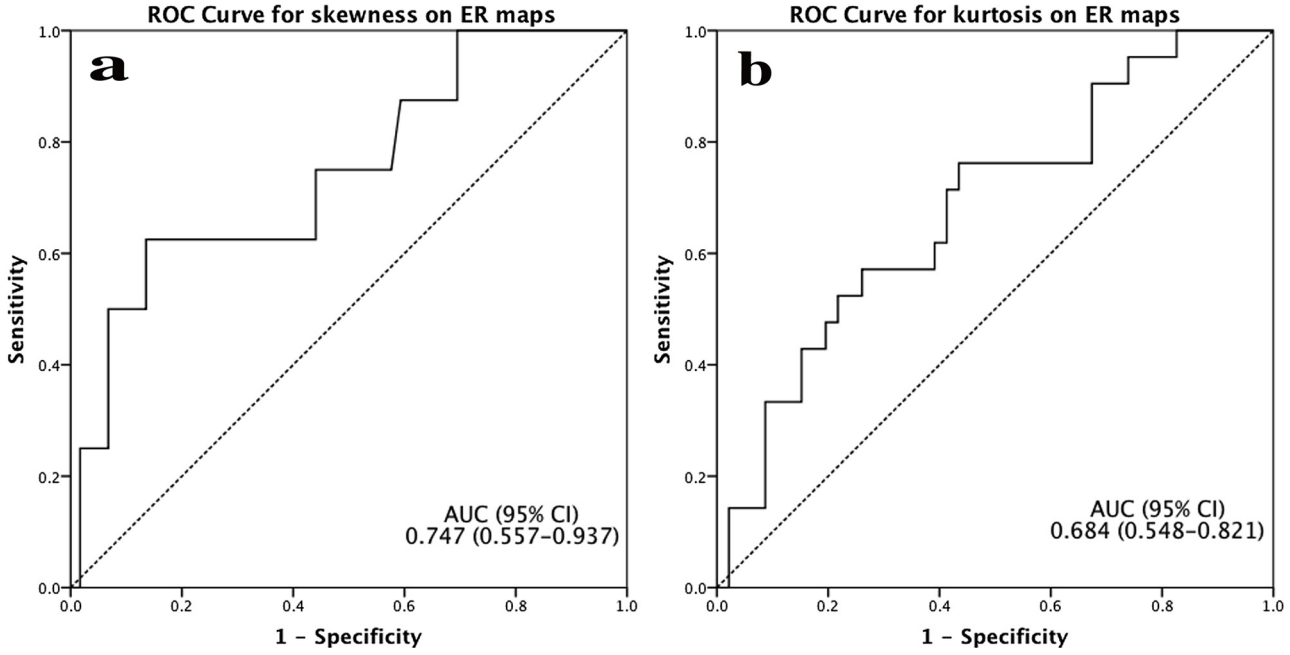

Fig. 3. ROC curves and AUCs for differentiating STS of different histologic grades (dotted line = reference line). (a) Skewness on ER maps has good accuracy for distinguishing grade 1 from grade 2 and 3 STS groups with AUC of 0.747. And (b) kurtosis on ER maps shows moderate accuracy for differentiating grade 1 and 2 STS from grade 3 STS with AUC of 0.684.
(*Note*: ROC receiver operating characteristics, AUC area under the curve, CI confidence interval, ER enhancement ratio, STS soft-tissue sarcomas).

Table 2
Interobserver Agreement in Histologic Grade and Histogram Parameters on MR Images.

	ICC	95% CI	*P* value
Histologic grade	0.914	0.866, 0.945	< 0.001
Mean on T1WI	0.944	0.907, 0.966	< 0.001
SD on T1WI	0.971	0.952, 0.982	< 0.001
Mode on T1WI	0.918	0.864, 0.951	< 0.001
Skew on T1WI	0.830	0.719, 0.897	< 0.001
Kurt on T1WI	0.518	0.204, 0.708	0.002
Mean on T2WI	0.904	0.841, 0.942	< 0.001
SD on T2WI	0.923	0.872, 0.953	< 0.001
Mode on T2WI	0.865	0.777, 0.919	< 0.001
Skew on T2WI	0.915	0.858, 0.949	< 0.001
Kurt on T2WI	0.846	0.744, 0.907	< 0.001
Mean on ER map	0.690	−0.164, 0.888	< 0.001
SD on ER map	0.898	0.823, 0.940	< 0.001
Mode on ER map	0.729	−0.131, 0.905	< 0.001
Skew on ER map	0.769	0.618, 0.861	< 0.001
Kurt on ER map	0.829	0.717, 0.897	< 0.001

Note: ICC interclass correlation coefficient, CI confidence interval, T1WI T1-weighted images, T2WI T2-weighted images, SD standard deviation, Skew skewness, Kurt kurtosis, ER enhancement ratio.

significantly differentiate STS of different histologic grades in our study.

There have been few studies involving histogram analysis of ER map in neoplasm evaluation. Chandarana et al. [16] found that more aggressive clear cell renal cell cancer (ccRCC) presented significantly higher values of mean and lower values of both skewness and kurtosis on ER maps than less aggressive papillary renal cell cancer (pRCC). In the present study, skewness and kurtosis on ER maps were significantly different among STS of different histologic grades. However, for pairwise comparisons, although kurtosis on ER maps was higher in grade 2 STS than that in grade 3 STS, skewness on ER maps tended to be higher in grade 2 group compared with grade 1 group. Mean on ER maps couldn't significantly differentiate STS groups of different histologic grades in our study.

It has been showed that the results of studies using histogram parameters on MR images to assess various neoplasms varied from each other. It may be explained as follows. Different histogram parameters reflect the grey-level frequency distribution in different aspects, as their statistical definitions have indicated [11,12]. However, the alteration of the grey-level frequency distribution in a given situation may not be significant enough in all aspects to cause the significant changes of all histogram parameters. So the significant parameters may be different among similar situations. For example, skewness of the tumor SI on T2-weighted images was significantly higher in panNENs of higher-grade [13]. It may be interpreted that the difference of SI distribution on T2-weighted images between panNENs of different grades was significant enough to cause the discrepancy of their distribution asymmetry. In contrast, there seemed to be a difference of histogram distribution of the tumor SI on T2-weighted images between grade 1 and grade 2 STS groups in our study, as shown in Fig. 2 (c-2 and d-2). But this difference couldn't be significantly reflected in the independent changes of the five assessed histogram parameters. Maybe an unevaluated parameter or a combined model of several parameters could significantly reflect the changes of distribution, which needs further investigations. It reminds us that we shouldn't just bet on the difference of one specific histogram parameter to utterly represent the difference of histogram distribution among compared groups, even though it is a popular parameter like mean because it reflects only one aspect of the distribution of the data being evaluated.

Moreover, SI on MR imaging is usually influenced by multiple physiologic and pathologic factors simultaneously. The change direction of MR imaging index resulting from one factor may be different from the other factor. The final change direction is determined by the factors that play the dominated role. Take enhancement for example, the degree of enhancement results from the joint action of vascularity, capillary permeability, extravascular space volume and so on [17,18]. More aggressive tumors are expected to present with higher degree of enhancement due to the increased vascularity and capillary permeability. However, Huang et al. [19] found that the mean enhancement level in the hepatocellular carcinoma (HCC) patients with microvascular invasion (MVI), which was defined as the presence of tumor emboli in vascular spaces lined by endothelial cells on microscopy and indicative of more aggressiveness, were significantly lower than that in the HCC patients without MVI. It was explained that the presence of MVI would reversely affect the perfusion of a tumor and therefore was inversely associated with enhancement level. In this situation, the presence of MVI in HCC played a more dominated role than vascularity or capillary permeability in the determination of enhancement level. In the study of Chandarana et al. [16], more aggressive clear cell renal cell cancer (ccRCC) showed significant higher values of mean on ER maps than less aggressive papillary renal cell cancer (pRCC), which may result from the dominant role played by the increased vascularity and capillary permeability in ccRCC. However, in our study, all groups of STS included various types of tumors, which may show different degrees of enhancement. Low-grade STS may enhance avidly if, for example, it is highly vascularized. Meanwhile, increased necrosis in higher grade STS is pathologically noted [8], which may reversely affect the overall enhancement seen on images. Therefore, it was not surprised that the mean on ER maps was not significantly different among the STS groups in our study.

Some limitations in the current study should be mentioned. First, only a small number of tumors were studied and the included subtypes may not reflect the true spectrum of STS. Second, as a retrospective study, the MR imaging protocol was inevitably not uniform and may influence the quantitative imaging analysis of intratumoral heterogeneity. Finally, histogram analysis of physiologic imaging indices like cerebral blood volume and apparent diffusion coefficient should be performed for STS in the future.

In conclusion, intratumoral heterogeneity on routine MR images quantitatively reflected by histogram parameters can be used to differentiate STS of different grades. Skewness and kurtosis on ER maps are the useful markers for STS grading.

Declaration of Competing Interest

None.

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