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Research Article

RESEARCH ARTICLE

Combining quantitative and qualitative magnetic resonance imaging features to differentiate anorectal malignant melanoma from low rectal cancer

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Abstract

Background: Distinguishing anorectal malignant melanoma from low rectal cancer remains challenging because of the overlap of clinical symptoms and imaging findings. We aim to investigate whether combining quantitative and qualitative magnetic resonance imaging (MRI) features could differentiate anorectal malignant melanoma from low rectal cancer.

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Methods: Thirty-seven anorectal malignant melanoma and 98 low rectal cancer patients who underwent pre-operative rectal MRI from three hospitals were retrospectively enrolled. All patients were divided into the primary cohort (N = 84) and validation cohort (N = 51). Quantitative image analysis was performed on T1-weighted (T1WI), T2-weighted (T2WI), and contrast-enhanced T1-weighted imaging (CE-T1WI). The subjective qualitative MRI findings were evaluated by two radiologists in consensus. Multivariable analysis was performed using stepwise logistic regression. The discrimination performance was assessed by the area under the receiver operating characteristic curve (AUC) with a 95% confidence interval (CI).
Results: The skewness derived from T2WI (T2WI-skewness) showed the best discrimination performance among the entire quantitative image features for differentiating anorectal malignant melanoma from low rectal cancer (primary cohort: AUC = 0.852, 95% CI 0.788–0.916; validation cohort: 0.730, 0.645–0.815). Multivariable analysis indicated that T2WI-skewness and the signal intensity of T1WI were independent factors, and incorporating both factors achieved good discrimination performance in two cohorts (primary cohort: AUC = 0.913, 95% CI 0.868–0.958; validation cohort: 0.902, 0.844–0.960).
Conclusions: Incorporating T2WI-skewness and the signal intensity of T1WI achieved good performance for differentiating anorectal malignant melanoma from low rectal cancer. The quantitative image analysis helps improve diagnostic accuracy.

Key words: anorectal malignant melanoma; low rectal cancer; magnetic resonance imaging; quantitative image analysis

Introduction

Anorectal malignant melanoma is a rare and highly aggressive malignancy,[1,2] comprising about 0.1% of all rectal malignancies.[3] It is also the most common mucosal melanoma of the gastrointestinal tract. The prognosis of anorectal malignant melanoma is extremely poor, with a 5-year survival rate of only 10%–17%.[4] Furthermore, increasing incidence of anorectal malignant melanoma has been observed in epidemiological studies.[3,5] However, the occurrence mechanism of anorectal malignant melanoma is still unclear, and there is also a lack of objective and effective diagnostic approaches.[6–8]

Anorectal malignant melanoma shares similar appearance and clinical symptoms with low rectal cancer, presenting as an intraluminal polypoid mass accompanying a series of clinical symptoms, such as rectal bleeding, tenesmus, and a change in bowel habits.[9–11] Currently, endoscopic biopsy is the routine procedure for pre-operative diagnosis of anorectal malignant melanoma. However, previous studies have shown that about 10%–87% of anorectal malignant melanoma are amelanotic,[12,13] and such atypical anorectal malignant melanomas lack the visible surface pigmentation or microscopical melanin and could be easily confounded with poorly differentiated carcinomas. The misdiagnosis rate is as high as 55%,[13] which may lead to delayed diagnosis and ineffective treatment. Up to 67% of patients are at an advanced stage upon initial diagnosis, and most patients die because of distant metastases.[14,15]

In clinical practice, magnetic resonance imaging (MRI) is the most commonly used modality for evaluating and diagnosing anorectal lesions. Previous studies have reported that typical imaging findings of anorectal malignant melanoma were hyperintense on T1-weighted imaging (T1WI) and high or mixed signal intensity on T2-weighted imaging (T2WI), caused by paramagnetic T1-shortening effects with melanin granules.[10,11] However, as mentioned above, melanin granules are absent in about 10%–87% of anorectal malignant melanoma. Additionally, a previous study also indicated that the presence or absence of melanin within anorectal malignant melanoma does not accurately correspond to the typical signal characteristics on MRI.[11] Therefore, the overlap in clinical symptoms and imaging findings make it easy to misdiagnose anorectal malignant melanoma as low rectal cancer, the most common malignancy in the anorectum.

Quantitative medical image analysis plays a vital role in promoting development of precision medicine and shows promising performance for clinical decision support.[16,17] Therefore, combining quantitative image analysis into routine clinical practice might enhance diagnostic accuracy and efficiency. Accordingly, this study aims to investigate whether combining quantitative and qualitative MRI features could differentiate anorectal malignant melanoma from low rectal cancer, with specific emphasis on the valuable indicators that are beneficial for establishing a confident diagnosis.

Methods

Patients

This retrospective study was approved by the institutional review boards of three hospitals with a waiver for informed consent. Patients from three centers were enrolled in this study between January 2010 and September 2020. Anorectal malignant melanoma was pathologically diagnosed without a history of prior melanoma, as well as no evidence of skin or eye involvement on the systemic examination. Low rectal cancer refers to the lower margin of rectal cancer within 5cm from the anal margin. The exclusion criteria were as follows: a) lacking

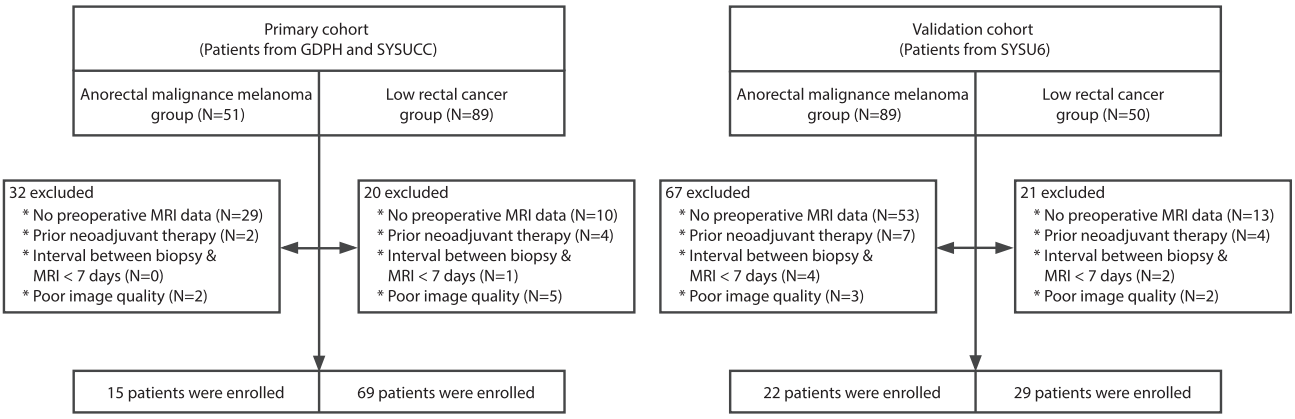

Figure 1. Flow diagram enrollment and exclusion criteria of dataset.

pre-operative MRI imaging; b) any treatment before MRI examination; c) biopsy was performed within seven days prior to MRI examination; and d) poor MRI imaging quality. All anorectal malignant melanoma patients who met the inclusion and exclusion criteria were included in the study. Because of the large number of patients with low rectal cancer, only 98 patients were randomly selected for this study. Finally, 135 patients from three hospitals were finally included in this study (Fig. 1). The primary cohort included 15 anorectal malignant melanoma patients and 69 low rectal cancer patients from Guangdong Provincial People's Hospital (GDPH) and Sun Yat-sen University Cancer Center (SYSUCC) between January 2013 and September 2020. The validation cohort included 22 anorectal malignant melanoma patients and 29 low rectal cancer patients from the Sixth Affiliated Hospital of Sun Yat-sen University (SYSU6) between January 2010 and September 2020. Baseline clinical data, including age, sex, tumor location, with or without melanin granules were also recorded.

Image acquisition

Rectal MRI examination was performed before surgery or more than seven days after the biopsy. T1WI, T2WI, and contrast-enhanced T1WI (CE-T1WI) sequences were acquired in three hospitals. The scanning process was as follows: an initial fat-saturated T1WI pre-contrast scan was acquired, followed by an axial fat-saturated T2WI sequence, and CE-T1WI was then collected after gadolinium-contrast. The detailed parameters of the MRI image acquisition of the three hospitals are listed in the Supplementary data (Supplementary Table S1).

Subjective image evaluation

MRI evaluation was retrospectively performed by two radiologists (L.J.H. and W.T.C., all with eight years of experience in abdominal MRI interpretation) who were blinded to pathological results and worked in consensus. The subjective qualitative MRI findings, including tumor location, tumor thickness, distance from the anal verge, growth pattern, signal intensity on T1WI and T2WI, T1WI-hyperintense and T2WI-hypointense, enhancement pattern, presence of lymphadenopathy, and the diameter of maximal lymph node, were assessed. The imaging evaluation criteria refered to the previous study.[9,11] The location of tumor was defined based on the center of the lesion, including anus, anorectum, and rectum. The maximal thickness of tumor was measured on T2-weighted axial imaging. The growth pattern of tumor was classified into three types, including wall thickening, intraluminal mass, and both of them. The distance from the anal verge to the tumor lower margin was measured on T2-weighted sagittal images. Signal intensity on T1-weighted images was classified as iso- or hypointense, diffuse or patchy hyperintense. Signal intensity on T2-weighted images was classified as homogenous hyperintense, mixed-signal dominated by hyperintense, and mixed-signal dominated by hypointense. T1WI-hyperintense and T2WI-hypointense was defined as the presence of diffuse or patchy hyperintense on T1WI and hypointense on T2WI in the same tumor region. The signal intensity of the mass was compared with the adjacent pelvic floor muscles. Lymphadenopathy was defined as lymph nodes greater than 8 mm in short-axis diameter,[18] and the diameter was recorded. The contrast enhancement of the mass was categorized as hypoenhancement, isoenhancement, and hyperenhancement compared with normal bowel mucosa.

Tumor annotation

For each patient, tumor annotation was performed manually using the ITK-SNAP software (version 4.7.2, https://itk.org/). The volumes of interest (VOIs) of the tumor were delineated blindly in a slide-by-slide way on three sequences (T1WI, T2WI, and CE-T1WI) by two radiologists with five years of MRI experience (M.L.C. and C.L.), and then confirmed by one radiologist with more than eight years of abdominal MRI experience (P.X.L.). Any discrepancy would be resolved in consensus. In this process, the definition of the tumor boundary was based on T2WI and CE-T1WI images. T2WI and CE-T1WI sequences

were taken as references to confirm the tumor boundary on T1WI. The air, mucus, and bowel contents were excluded from the annotation. Additionally, a 20 mm^2 region of piriformis muscle in one slide was also delineated for image normalization.

Feature extraction

To diminish the possible impacts induced by scan machines and parameters, image preprocessing was performed as follows: (1) for each sequence of images (T1WI, T2WI, and CE-T1WI), the mean gray value of the piriformis muscle region was subtracted from each voxel in the tumor VOIs; (2) the tumor VOIs were normalized using the Collewet method; (3) the tumor volume was isotropically resampled at the resolution of 0.5 mm. After image preprocessing, feature extraction was performed with the radiomics toolbox.[19] Fourteen image features were extracted from T1WI, T2WI, and CE-T1WI sequences, respectively. A total of 42 quantitative image features were extracted. Three types of quantitative image features were extracted: (1) shape feature (Volume); (2) histogram features (Mean, Variance, Skewness, Kurtosis); (3) texture features (GLCM_Energy, GLCM_Contrast, GLCM_Entropy, GLCM_Homogeneity, GLCM_Correlation, GLCM_SumAverage, GLCM_Variance, GLCM_Dissimilarity, and GLCM_AutoCorrelation).

Paired feature selection

Feature selection was performed only in the primary cohort. For each image sequence, we used a paired feature selection strategy to minimize the selection bias caused by the unbalanced sample size (15 anorectal malignant melanoma vs 69 low rectal cancer in the primary cohort). The selection process was as follows: first, 10 cases were randomly selected from each group of anorectal malignant melanoma and low rectal cancer. Then, for all 42 features, the AUC was calculated for distinguishing the two tumors. If the AUC value of a feature was greater than 0.70, it was considered to be a potentially significant feature. The above process was repeated 1000 times, and the number of occurrences of significant features with AUC value greater than 0.70 was recorded. Significant features that appeared in more than half of the repetitions (frequency, more than 0.5) were selected for further analysis (Fig. 2).

Statistical analysis

Statistical analysis was performed using the R software (version 4.0.3, https://www.r-project.org/). Thirty cases were randomly selected from the primary cohort for inter-observer agreement calculation for subjective image evaluation and tumor annotation with intraclass correlation coefficient (ICC) and Cohen's kappa. The differences of clinicopathological and image variables between anorectal malignant melanoma and low rectal cancer were evaluated using the Wilcoxon rank-sum test with continuous variables and the chi-squared test with categorical variables. A multivariable logistic regression analysis was performed for those subjective image features with a $P < 0.05$ in the univariate analysis and the selected quantitative features. The discrimination performance was assessed by the area under the receiver operating characteristic curve (AUC) with a 95% confidence interval (CI). To evaluate the classification performance of the selected features, we randomly selected 10 cases from the two tumor groups each time for calculating an AUC value. The above process was repeated 1000 times to calculate the mean value and variance of AUCs. The Student t-test was used to compare two AUC distributions. Bonferroni correction was used to calculate the corrected P value. Two-sided tests were performed in all statistical analysis with a significance of 0.05.

Results

Demographic and clinical characteristics

As shown in Fig. 1, the primary cohort comprised 84 patients and the validation cohort comprised 51 patients. The demographic characteristics of all patients are summarized in Table 1. There was no significant difference found between the two cohorts except tumor site.

In the anorectal malignant melanoma group, 27 patients (73.0%) were female and 10 (27.0%) were male, with a proportion of 2.7:1.0, and the mean age was 58.24 ± 12.02 years. In the low rectal cancer group, 38 patients (38.8%) were female and 60 (61.2%) were male, and the mean age was 55.95 ± 11.19 years. In all patients, a significant difference was detected between the two cancer types in terms of sex ($P < 0.001$), while no significant difference was observed in age ($P = 0.206$). Furthermore, melanin granules were found in 14 (37.8%) patients with anorectal malignant melanoma. There was no significant difference in quantitative and qualitative features between melanotic and amelanotic type of anorectal malignant melanoma ($P > 0.05$) (Supplementary Table S2).

Subjective image evaluation

In all patients, the tumor thickness of anorectal malignant melanoma was larger than low rectal cancer (3.15 ± 1.54 vs 1.76 ± 0.81 cm). Most of the anorectal malignant melanomas were located in the anorectum (N = 25, 67.6%), whereas low rectal cancers were mainly located in the rectum (N = 75, 76.5%). For MRI signal characteristics, the majority of anorectal malignant melanoma (N = 28, 75.7%) patients showed diffuse or patchy hyperintense on T1WI, and more than half of patients (N = 22, 59.5%) showed mixed-signal dominated by hypointense on T2WI. Furthermore, fewer than half of the anorectal malignant melanoma patients (N = 18, 48.6%) presented hyperintense on T1WI and hypointense on T2WI in the same area (T1WI-hyperintense and T2WI-hypointense) (Fig. 3A), whereas the left patients (19,

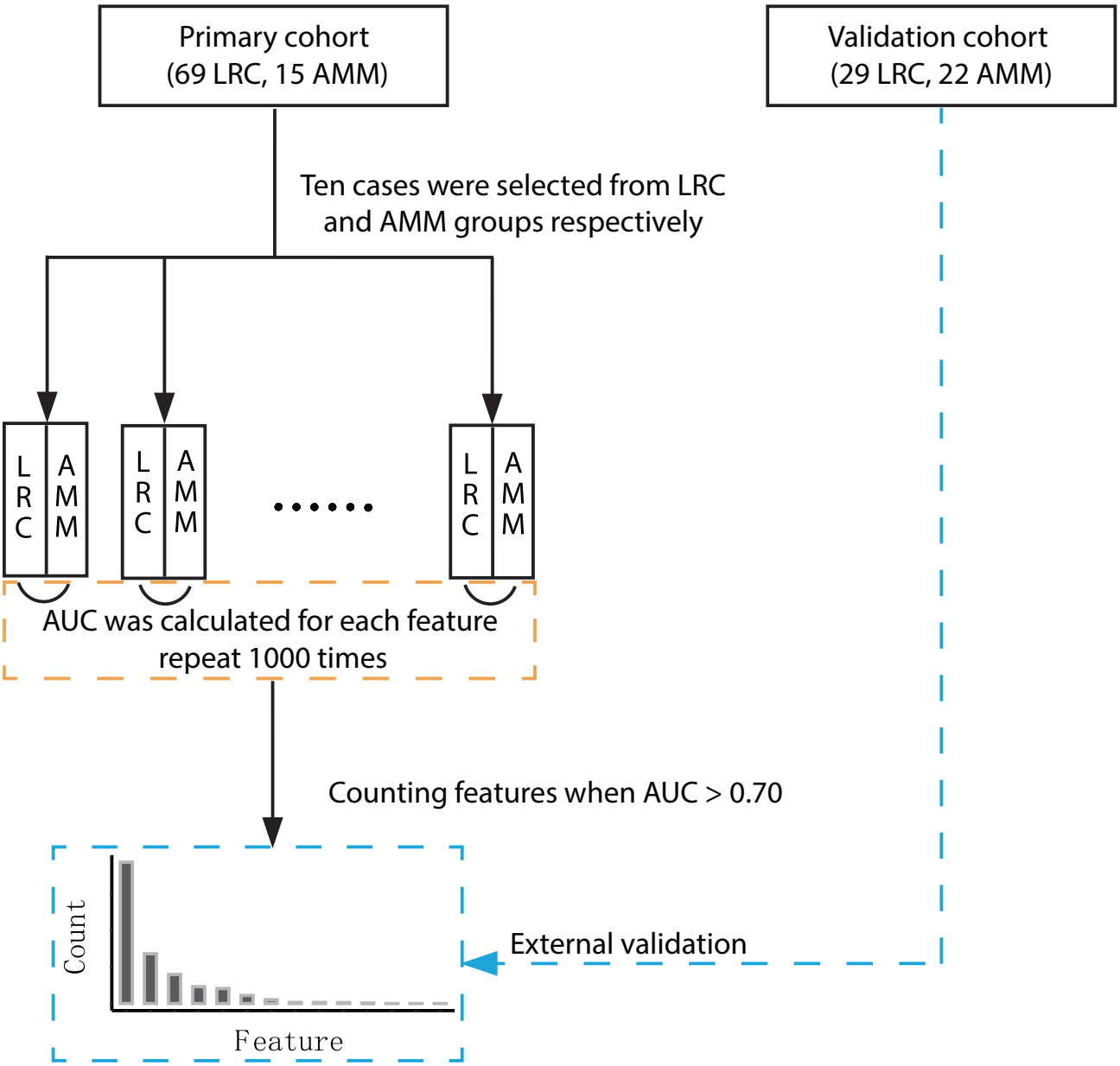

Figure 2. Quantitative image features selection procedure. LRC = low rectal cancer; AMM = anorectal malignant melanoma. AUC = the area under the receiver operating characteristic curve.

Table 1. Demographic data of the two independent cohorts.

Characteristic	Primary cohort	Validation cohort	P
Age (mean ± SD, years)	57.06 ± 10.88	55.78 ± 12.35	0.822
Sex			1.000
Male	44 (52.4%)	26 (51.0%)	
Female	40 (47.6%)	25 (49.0%)	
Tumor location			0.033*
Anus	0 (0%)	1 (1.9%)	
Anorectum	24 (28.6%)	24 (47.1%)	
Rectum	60 (71.4%)	26 (51.0%)	

Data were the number of cases, with percentages in parentheses. The differences were assessed with the Wilcoxon rank-sum test or Chi-squared test. *P < 0.05.

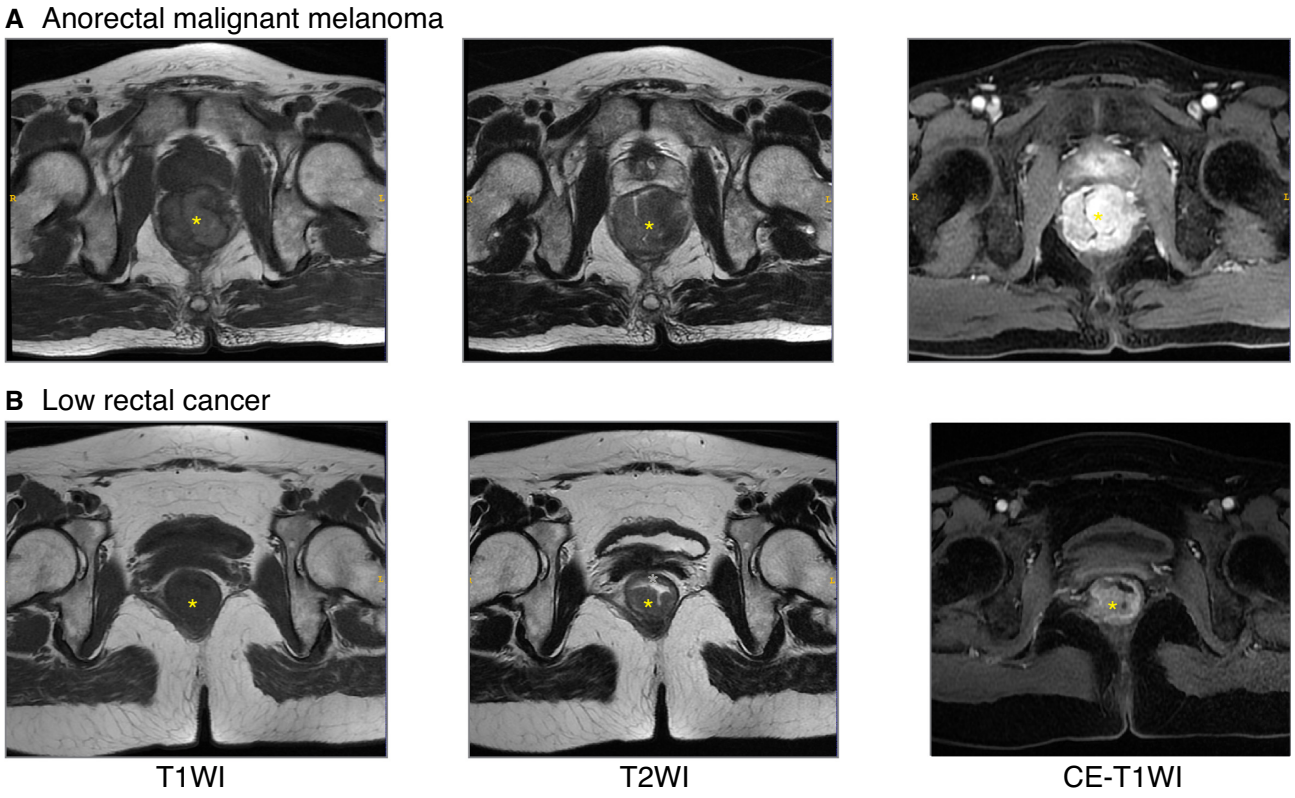

Figure 3. Images from patients with anorectal malignant melanoma and low rectal cancer. (A) MRI characteristics on axial view of anorectal malignant melanoma in a 66-year-old man. A rectal intraluminal mass presented hyperintense dominated signal intensity on TI-weighted imaging (T1WI), hyperintense on T2-weighted imaging (T2WI), and hyperenhancement on contrast-enhanced T1-weighted imaging (CE-T1WI). (B) MRI characteristics on axial view of low rectal cancer in a 49-year-old woman. A rectal intraluminal mass presented isointense on T1WI, mildly hyperintense on T2WI, and isoenhancement or mild enhancement on CE-T1WI.

51.4%) presented atypical imaging findings (Supplementary Figs. S1A and S1B). However, nearly all (N = 95, 96.9%) low rectal cancers showed isointense on T1WI and mixed-signals dominated by hyperintense on T2WI (Fig. 3B). Moreover, the anorectal malignant melanoma was mostly seen as (N = 33, 89.2%) intraluminal mass, while the intraluminal mass (N = 49, 50.0%) and wall thickening (N = 45, 45.9%) were more common in low rectal cancer. Moreover, all of the differences were statistically significant in both primary and validation cohorts ($P < 0.05$). However, the differences in other MRI findings were detected only in the primary or validation cohort, including the distance from the anal verge, the presence of lymphadenopathy, the diameter of maximal lymph node, and enhancement patterns (Table 2). Inter-observer agreement in subjective image evaluation features was moderate to good for all comparisons (the mean ICC for continuous variables was 0.713; the kappa for categorical variables ranged from 0.544 to 1.00).

Quantitative image analysis

The ICCs for tumor annotation were greater than 0.75. Based on the paired feature selection strategy, skewness from the T2WI sequence (T2WI-skewness) was the only one quantitative image feature selected, and neither the T1WI nor CE-T1WI sequence had any feature selected for further analysis (Figs. 4A–4C). Regarding discrimination performance, the mean AUC of T2WI-skewness was 0.852 (95% CI 0.788–0.916) in the primary cohort and 0.730 (95% CI 0.645–0.815) in the validation cohort.

Discrimination performance evaluation

Tumor thickness, location, growth pattern, signal intensity on T1WI, signal intensity on T2WI, T1WI-hyperintense and T2WI-hypointense, and T2WI-skewness were included into the multivariate analysis. The lower T2WI-skewness (odds ratio [OR] 0.104, 95% CI 0.022–0.494, $P = 0.004$) and the hyperintense on T1WI (OR, 0.020, 95% CI 0.003–0.146, $P < 0.001$) were identified as independent indicators for differential diagnosis of anorectal malignant melanoma with multivariable logistic regression analysis (Table 3). The signal intensity of T1WI reached an AUC of 0.844 (95% CI 0.743–0.946) in the primary cohort and 0.864 (95% CI 0.758–0.970) in the validation cohort. The model that incorporated T2WI-skewness and signal intensity of T1WI yielded an excellent discrimination performance with an AUC of 0.913 (95% CI 0.868–0.958) in the primary cohort and 0.902 (95% CI 0.844–0.960) in the validation cohort, with accuracy of 0.952 and 0.824, sensitivity of 0.867 and 0.636,

Table 2. Clinical characteristics and qualitative MRI findings in the primary and validation cohorts.

Characteristic	Primary cohort			Validation cohort		
	Anorectal malignant melanoma	Low rectal cancer	P	Anorectal malignant melanoma	Low rectal cancer	P
Age (mean ± SD, years)	58.27 ± 9.87	56.80 ± 11.14	0.502	58.22 ± 13.53	53.93 ± 11.27	0.212
Sex			0.002*			0.125
Male	2 (13.3%)	42 (60.9%)		8 (36.4%)	18 (62.1%)	
Female	13 (86.7%)	27 (39.1%)		14 (63.6%)	11 (37.9%)	
Tumor thickness (cm)	2.81 ± 1.38	1.72 ± 0.75	<0.001*	3.38 ± 1.63	0.86 ± 0.94	<0.001*
Tumor location			0.001*			0.010*
Anus	0 (0%)	0 (0%)		1 (4.5%)	0 (0%)	
Anorectum	10 (66.7%)	14 (20.3%)		15 (68.2%)	9 (31.0%)	
Rectum	5 (33.3%)	55 (79.7%)		6 (27.3%)	20 (69.0%)	
Distance from anal verge (cm)	2.53 ± 1.19	3.25 ± 1.13	0.048*	2.23 ± 1.10	2.76 ± 1.07	0.088
Growth pattern			0.013*			0.009*
Wall thickening	1 (6.7%)	31 (44.9%)		3 (13.6%)	14 (48.3%)	
Intraluminal mass	14 (93.3%)	36 (52.2%)		19 (86.4%)	13 (44.8%)	
Both	0 (0%)	2 (2.9%)		0 (0%)	2 (6.9%)	
Presence of lymphadenopathy			1.000			0.523
Yes	9 (60.0%)	42 (60.9%)		14 (63.6%)	22 (75.9%)	
No	6 (40.0%)	27 (39.1%)		8 (36.4%)	7 (24.1%)	
Maximum lymph node diameter (cm)	0.96 ± 0.77	0.53 ± 0.38	0.030*	1.15 ± 1.38	0.56 ± 0.37	0.138
Signal intensity on T1WI			<0.001*			<0.001*
Iso- or hypo-intense	4 (26.7%)	66 (95.7%)		6 (27.3%)	29 (100%)	
Diffuse or patchy hyperintense	11 (73.3%)	3 (4.3%)		16 (72.7%)	0 (0%)	
Signal intensity on T2WI			0.005*			0.047*
Homogenous hyperintense	0 (0%)	13 (18.8%)		0 (0%)	4 (13.8%)	
Mixed signal (hyperintense dominated)	8 (53.3%)	47 (68.1%)		7 (31.8%)	14 (48.3%)	
Mixed signal (hypointense dominated)	7 (46.7%)	9 (13.0%)		15 (68.2%)	11 (37.9%)	
T1WI-hyperintense and T2WI-hypointense			<0.001*			<0.001*
Yes	4 (26.7%)	0 (0%)		14 (63.6%)	0 (0%)	
No	11 (73.3%)	69 (100%)		8 (36.4%)	29 (100%)	
Enhancement pattern			0.128			<0.001*
Hypoenhancement	6 (40.0%)	44 (63.8%)		3 (13.6%)	7 (24.1%)	
Isoenhancement	3 (20.0%)	13 (18.8%)		0 (0%)	2 (6.9%)	
Hyperenhancement	6 (40.0%)	12 (17.4%)		19 (86.4%)	20 (69.0%)	

Data were the number of cases, with percentages in parentheses. Continuous variables were reported as means ± standard deviations. The differences were assessed with the Wilcoxon rank-sum test or Chi-squared test. T1WI = T1-weighted imaging; T2WI = T2-weighted imaging. *P < 0.05.

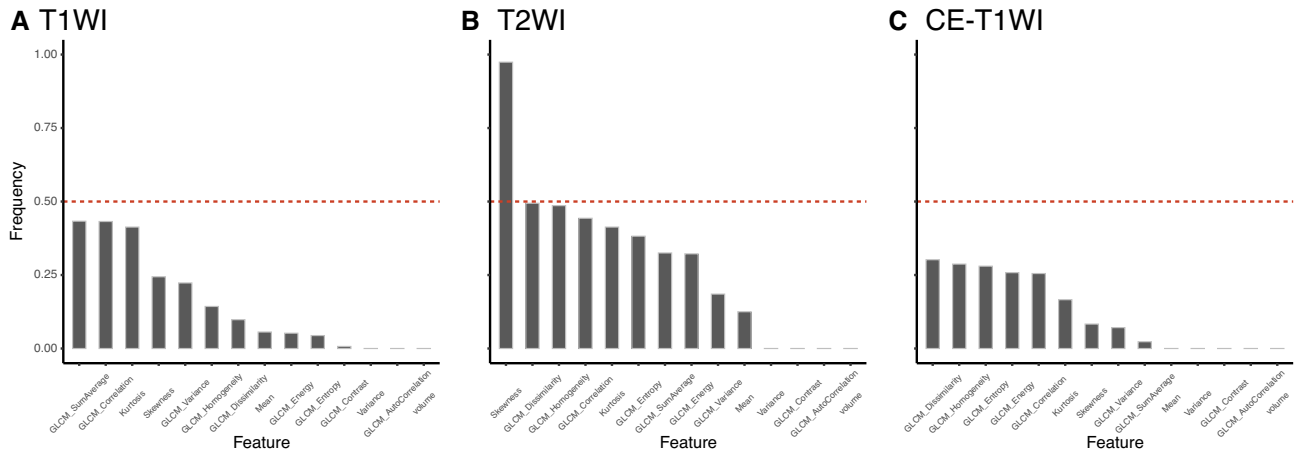

Figure 4. Column graph shows the feature selection results of three sequences. T1WI = T1-weighted imaging, T2WI = T2-weighted imaging, CE-T1WI = contrast-enhanced T1-weighted imaging.

Table 3. Logistic regression model.

	Coefficient	Odds ratio (95% CI)	P
Intercept	0.414		0.620
Signal intensity on T1WI			
Isointense vs. diffuse or patchy hyperintense	− 3.891	0.020 (0.003, 0.146)	<0.001
T2WI-skewness	− 5.421	0.104 (0.022, 0.494)	0.004

T1WI = T1-weighted imaging, T2WI = T2-weighted imaging, CI = confidence interval.

specificity of 0.971 and 0.966, PPV of 0.867 and 0.933, and NPV of 0.971 and 0.778, respectively (Figs. 5A and 5B). Using 1000 times 10-10 paired cases AUC calculation, we found that combining the quantitative image feature (T2WI-skewness) with the subjective qualitative image feature (signal intensity of T1WI) achieved the optimal discrimination performance, better than either alone in both cohorts (all $P < 0.001$, after Bonferroni correction).

Discussion

This study combined quantitative and qualitative analysis based on pre-operative MRI to differentiate anorectal malignant melanoma from low rectal cancer. Our results showed that T2WI-skewness achieved the best discrimination performance among the entire quantitative image features in the differential diagnosis of anorectal malignant melanoma. For objective qualitative MRI findings, the tumor thickness, location, growth pattern, signal intensity on T1WI and T2WI, and T1WI-hyperintense and T2WI-hypointense were significantly different between anorectal malignant melanoma and low rectal cancer in both cohorts. In addition, the multivariable model that combined T2WI-skewness and the signal intensity of T1WI showed good performance for distinguishing the two tumors in the primary and validation cohorts.

As far as we know, there is currently no completely objective and accurate diagnostic method available for anorectal malignant melanoma. It has been reported that anorectal malignant melanomas may originate from melanocytes located in the anal transition zone and usually form a large mass that grows into the intestinal lumen.[20] Kim *et al.*[9] and Park *et al.*[11] reported image findings of 8 and 12 anorectal malignant melanoma cases, respectively, and indicated that anorectal malignant melanoma appears as bulky intraluminal fungating masses with lymphadenopathy in the distal rectum on CT or MRI. The present study is consistent with the reports above, as the anorectal malignant melanomas often present as an intraluminal mass in the anorectum and have a larger tumor thickness compared to low rectal cancer. However, although we observed larger lymph node diameter in anorectal malignant melanoma compared with low rectal cancer, the difference was not statistically significant in the validation cohorts. Furthermore, Park *et al.*[11] also reported the MRI signal intensity of anorectal malignant melanoma, as the lesion showed T1WI hyperintensity, high or mixed-signal T2WI intensity, and hyperenhancement after contrast. Our results are partially in line with this. A previous study indicated that the signal intensity of anorectal malignant melanoma depends on whether it contains melanin particles or not.[10] In our study, only 37.8% (14/37) of patients with anorectal malignant melanoma were melanotic. However, we noted that the MRI signal characteristics of 51.4% (19/37) of cases were not consistent with the melanotic or amelanotic type of melanoma. Although there exist characteristic dark surface and microscopic melanin particles within the tumor, this may not be evident on MRI. This could be because of the low density or content of melanin particles within the tumor. In contrast, amelanotic type melanoma may show patchy hyperintense on T1WI, with or without hypointense on T2WI. It may depend on intratumoral bleeding or necrosis. Of course, sampling error may be one of the reasons; one similar case was also reported by Park *et al.*[11] Therefore, not all anorectal malignant melanoma presents the typical paramagnetic signal performance on MRI, and merely relying on objective qualitative features may not make a confident diagnosis of anorectal malignant melanoma.

Quantitative image features showed promising performance for clinical use. In this study, skewness derived from T2WI achieved the best discrimination performance among the 42 quantitative image features in both cohorts. T2WI represents rich information about the various tissue components of tumors, and the image features derived from T2WI thus have the potential to represent more intrinsic properties of tumors. Yang *et al.*[21] reported that histogram features derived from T2WI might reduce uncertainty when evaluating regional lymph node status in rectal cancer. In addition, we did note that none of the quantitative image features derived from T1WI and CE-T1WI was selected for further analysis based on the paired feature selection strategy. The possible reasons for this difference may be the superior strengths of T2WI and strict feature selection method. Moreover, skewness measures the asymmetric distribution of gray-level pixel values within the VOIs. The greater the skewness, the more asymmetric the distribution. Several studies have demonstrated that skewness might serve as a biomarker for differentiating malignant and benign lesions, as well as predicting prognosis in diverse diseases.[22–24] Yang *et al.*[21] also indicated that the lower T2WI-skewness was associated with regional lymph node metastasis in rectal cancer. Our study found that patients with anorectal malignant

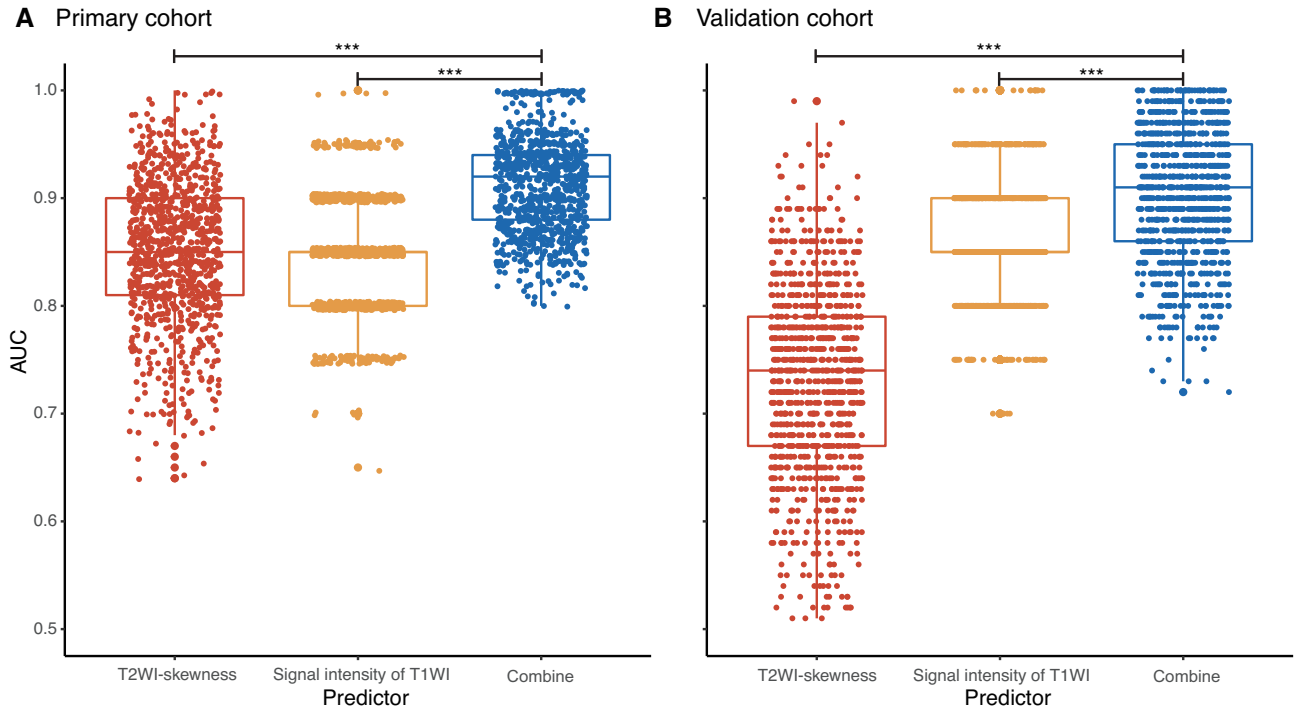

Figure 5. Discrimination performance of predictors in the two cohorts. (A) The primary cohort. (B) The validation cohort. The box extends from lower to upper quartile values, with a line at the median. Whiskers extend from the box to show the range of data. T1WI = T1-weighted imaging, T2WI = T2-weighted imaging, AUC = the area under the receiver operating characteristic curve. ***$P < 0.001$ after Bonferroni correction.

melanoma had significantly lower T2WI-skewness than low rectal cancer. It may be that anorectal malignant melanoma manifested more homogeneous characteristics on T2WI and tended to have a more symmetric distribution.

The multivariate model that combined T2WI-skewness and the signal intensity on T1WI showed outstanding performance with an AUC of 0.913 in the primary cohort and 0.902 in the validation cohort. In addition, the T2WI-skewness significantly improved the discrimination performance of the model in the primary cohort and the validation cohort. The finding indicated that T2WI-skewness might be a useful supplement to establish a confident diagnosis of anorectal malignant melanoma. A previous study has also demonstrated that the quantitative image features obtained from T2WI showed better classification performance than qualitative variables for predicting the treatment response of neoadjuvant therapy in rectal cancer.[25] On the other hand, different from the quantitative imaging analysis results, the signal intensity on T1WI rather than T2WI signals presented the independent discriminative values. It may be that the human eye is more sensitive to the high signal on T1WI, and quantitative imaging methods can be used to effectively analyze the information in T2WI, so as to find more hidden features.

There are limitations to this study. First, our work was based on a relatively small sample size of anorectal malignant melanoma, and larger sample size is needed to verify the results further. Second, DWI and/or ADC images were not included in this study because of lack of complete data. Third, tumor boundaries on T1WI may not be accurately identified when VOIs were drawn, which may affect the results of quantitative image feature extraction. To minimize this effect, we used T2WI and CE-T1WI sequences as references to confirm the boundaries of tumors on T1WI. Fourth, the subjective qualitative MRI findings were evaluated mainly by the less experienced radiologists with consensus. Senior radiologists might be better to perform the subjective MRI evaluation.

In conclusion, our study showed that MRI-based quantitative image analysis provides added value in differentiating anorectal malignant melanoma and low rectal cancer. The model incorporating the T2WI-skewness and the signal intensity on T1WI achieved good discrimination performance, and helped reduce uncertainty in the differential diagnosis of anorectal malignant melanoma. Accurate disease diagnosis is essential for optimizing treatment selection and precision medicine. Our research provides new insights for the accurate diagnosis of anorectal malignant melanoma.

Supplementary data

Supplementary data are available at *PCMEDI* online.

Author contributions

ZYX, KZ, and LJH designed the study. ZYX, KZ, LJH, ZWS, CH, XMH, YQH, and XC wrote and revised the report. ZYL, WCT, and CHL initiated and coordinated the study. MLC,

CL, and PXL annotated images. ZYX, SYL, and YTL collected clinical data and images. KZ and ZYX did the statistical analysis. All authors discussed the early version of the report and provided comments and suggestions for change. All authors have approved the final report for publication

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Conflict of interest

As an Editorial Board Member of *Precision Clinical Medicine*, the corresponding author Zaiyi Liu was blinded from reviewing and making decision on this manuscript.

References

1. Antoniuk PM, Tjandra JJ, Webb BW, *et al*. Anorectal malignant melanoma has a poor prognosis. *Int J Colorectal Dis* 1993;**8**:81–6. doi:10.1007/bf00299333.
2. Weinstock MA. Epidemiology and prognosis of anorectal melanoma. *Gastroenterology* 1993;**104**:174–8. doi:10.1016/0016-5085(93)90849-8.
3. Cagir B, Whiteford MH, Topham A, *et al*. Changing epidemiology of anorectal melanoma. *Dis Colon Rectum* 1999;**42**:1203–8. doi:10.1007/bf02238576.
4. Row D, Weiser MR. Anorectal melanoma. *Clin Colon Rectal Surg* 2009;**22**:120–6. doi:10.1055/s-0029-1223844.
5. Callahan A, Anderson WF, Patel S, *et al*. Epidemiology of anorectal melanoma in the United States: 1992 to 2011. *Dermatol Surg* 2016;**42**:94–9. doi:10.1097/DSS.0000000000000579.
6. Ciarrocchi A, Pietroletti R, Carlei F, *et al*. Extensive surgery and lymphadenectomy do not improve survival in primary melanoma of the anorectum: results from analysis of a large database (SEER). *Colorectal Dis* 2017;**19**:158–64. doi:10.1111/codi.13412.
7. Matsuda A, Miyashita M, Matsumoto S, *et al*. Abdominoperineal resection provides better local control but equivalent overall survival to local excision of anorectal malignant melanoma: a systematic review. *Ann Surg* 2015;**261**:670–7. doi:10.1097/SLA.0000000000000862.
8. Nilsson PJ, Ragnarsson-Olding BK. Importance of clear resection margins in anorectal malignant melanoma. *Br J Surg* 2010;**97**:98–103. doi:10.1002/bjs.6784.
9. Kim KW, Ha HK, Kim AY, *et al*. Primary malignant melanoma of the rectum: CT findings in eight patients. *Radiology* 2004;**232**:181–6. doi:10.1148/radiol.2321030909.
10. Li P, Liu J. Diagnostic value of MRI and computed tomography in anorectal malignant melanoma. *Melanoma Res* 2016;**26**:46–50. doi:10.1097/cmr.0000000000000198.
11. Park HJ, Kim HJ, Park SH, *et al*. Journal Club: primary anorectal melanoma: MRI findings and clinicopathologic correlations. *AJR American Journal of Roentgenology* 2018;**211**:W98–w108. doi:10.2214/ajr.17.18807.
12. Pessaux P, Pocard M, Elias D, *et al*. Surgical management of primary anorectal melanoma. *Br J Surg* 2004;**91**:1183–7. doi:10.1002/bjs.4592.
13. Falch C, Stojadinovic A, Hann-von-Weyhern C, *et al*. Anorectal malignant melanoma: extensive 45-year review and proposal for a novel staging classification. *J Am Coll Surg* 2013;**217**:324–35. doi:10.1016/j.jamcollsurg.2013.02.031.
14. Das G, Gupta S, Shukla PJ, *et al*. Anorectal melanoma: a large clinicopathologic study from India. *Int Surg* 2003;**88**:21–4.
15. Goldman S, Glimelius B, Påhlman L. Anorectal malignant melanoma in Sweden. Report of 49 patients. *Dis Colon Rectum* 1990;**33**:874–7. doi:10.1007/BF02051925.
16. Zheng H, Gasbarrino K, Veinot JP, *et al*. New quantitative digital image analysis method of histological features of carotid atherosclerotic plaques. *Eur J Vasc Endovasc Surg* 2019;**58**:654–63. doi:10.1016/j.ejvs.2019.07.015.
17. Zhou Y, Xu X, Song L, *et al*. The application of artificial intelligence and radiomics in lung cancer. *Precis Clin Med* 2020;**3**:214–27. doi:10.1093/pcmedi/pbaa028.
18. Lucey BC, Stuhlfaut JW, Soto JA. Mesenteric lymph nodes seen at imaging: causes and significance. *Radiographics* 2005;**25**:351–65. doi:10.1148/rg.252045108.
19. Vallires M, Freeman CR, Skamene SR, *et al*. A radiomics model from joint FDG-PET and MRI texture features for the prediction of lung metastases in soft-tissue sarcomas of the extremities. *Phys Med Biol* 2015;**60**:5471–96. doi:10.1088/0031-9155/60/14/5471.
20. Ragnarsson-Olding BK, Nilsson PJ, Olding LB, *et al*. Primary ano-rectal malignant melanomas within a population-based national patient series in Sweden during 40 years. *Acta Oncol* 2009;**48**:125–31. doi:10.1088/0031-9155/60/14/5471.
21. Yang L, Liu D, Fang X, *et al*. Rectal cancer: can T2WI histogram of the primary tumor help predict the existence of lymph node metastasis? *Eur Radiol* 2019;**29**:6469–76. doi:10.1007/s00330-019-06328-z.
22. Jin KP, Rao SX, Sheng RF, *et al*. Skewness of apparent diffusion coefficient (ADC) histogram helps predict the invasive potential of intraductal papillary neoplasms of the bile ducts (IPNBs). *Abdom Radiol (NY)* 2019;**44**:95–103. doi:10.1007/s00261-018-1716-8.
23. Paik W, Kim HS, Choi CG, *et al*. Pre-operative perfusion skewness and kurtosis are potential predictors of progression-free survival after partial resection of newly diagnosed glioblastoma. *Korean J Radiol* 2016;**17**:117–26. doi:10.3348/kjr.2016.17.1.117.
24. Zolal A, Juratli TA, Linn J, *et al*. Enhancing tumor apparent diffusion coefficient histogram skewness stratifies the postoperative survival in recurrent glioblastoma multiforme patients undergoing salvage surgery. *J Neurooncol* 2016;**127**:551–7. doi:10.1007/s11060-016-2063-7.
25. Horvat N, Veeraraghavan H, Khan M, *et al*. MR imaging of rectal cancer: radiomics analysis to assess treatment response after neoadjuvant therapy. *Radiology* 2018;**287**:833–43. doi:10.1148/radiol.2018172300.