Impact of intratumor heterogeneity on diffusion-weighted MRI as a prognostic indicator in lower rectal cancer

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Research article

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Abstract

Background

Diffusion-weighed MRI (DWI) has the potential to reveal intra-tumor pathological heterogeneity consisting of the stroma. The present study investigated the value of intra-tumor heterogeneity evaluated by DWI for predicting the survival of patients with lower rectal cancer (LRC).

Methods

A total of 172 LRC patients underwent radical surgery between 2009 and 2017. Patients with T1 tumors, distant metastasis, and no pre-operative MRI were excluded. Fifty-eight cases were targeted. Intra-tumor heterogeneity on DWI was quantified by an image analysis (MRI heterogeneous score of DWI: mrHSD). All enrolled cases were divided into two groups (high and low groups) according to median mrHSD.

Results

Median mrHSD was 0.457 (0.170–0.823), with a higher score indicating a more heterogeneous pattern on DWI. The frequency of a clinical diagnosis of lymph node metastasis and extramural vascular invasion was higher in the high group. Three-year overall survival (OS) and relapse-free survival (RFS) rates were significantly higher in the low group than in the high group (OS: 100% vs 84.6%, $p = 0.012$; RFS: 85.9% vs 55.6%, $p = 0.027$). A univariate analysis of RFS showed that the RFS rates of poorly differentiated LRC, a positive circumferential resection margin on MRI, and high mrHSD were worse ($p = 0.097$, 0.086, and 0.049). A multivariate analysis revealed that high mrHSD tended to be an independent factor for predicting post-operative recurrence (HR: 2.836, $p = 0.060$).

Conclusion

The quantitative evaluation of intratumor heterogeneity on DWI has potential as an imaging biomarker for predicting post-operative recurrence.

Background

Over the past few decades, multimodal therapies have been performed for advanced lower rectal cancer (LRC) in order to decrease the rates of post-operative recurrence and a positive circumferential resection margin (CRM) [1, 2]. The indications for these treatments are generally decided by pre-operative TNM staging [3] based on several conventional modalities, such as endoscopy, endoscopic ultrasound (EUS), computed tomography (CT), and magnetic resonance imaging (MRI). However, diagnostic accuracy has not been satisfactory for providing the appropriate treatment for LRC patients [4, 5]. Therefore, the

development of a novel diagnostic method that more accurately predicts treatment outcomes and survival than the TNM system diagnosed by conventional modalities is needed.

In recent years, radiomics has been attracting increasing attention in the development of novel diagnostic biomarkers [6]. This research approach in oncology aims to assess tumor heterogeneity quantitatively through an analysis of medical images using histograms, textures, shapes, and mathematical formulae. The clinical significance of quantitative values calculated by radiomics, such as the prediction of survival, metastasis, treatment outcomes, and postoperative recurrence, was previously confirmed [7, 8]. We also reported that the quantitative value of the intratumor heterogeneity of LRC calculated by an image analysis using a mathematical formula of diffusion images of pre-operative MRI (DWI) was associated with pathological stromal heterogeneity; tumor invasion depth and lymph node metastasis (N(+)) may also be predicted using this value [9]. Radiomics has the potential to predict a number of tumor characteristics based on the tumor structure.

Previous studies identified stromal heterogeneity as a prognostic or therapeutic biomarker, and showed that a heteronomous stromal pattern in pancreatic and breast cancers correlated with a poor outcome [10, 11]. The tumor stroma ratio is used as a prognostic marker in gastric and colon cancers [12, 13]. Therefore, we hypothesized that the quantitative value of intratumor heterogeneity on DWI is also associated with long-term oncological outcomes based on previous studies and our findings. The present study investigated the value of tumor heterogeneity on DWI images for assessing long-term oncological outcomes in patients with LRC.

Methods

Study design and patients

This was a respective study that investigated the clinical value of intra-tumor heterogeneity evaluated by DWI in LRC. The present study included patients with rectal adenocarcinomas that were mainly located under the peritoneal reflection who underwent curative surgery with regional lymph node dissection between April 2009 and March 2017 at the Division of Digestive Surgery of Kyoto Prefectural University of Medicine (KPUM). Exclusion criteria were as follows: (1) patients diagnosed with T1 LRC before treatment initiation; (2) patients diagnosed with distant metastases before treatment initiation; (3) patients who did not undergo MRI with DWI before treatment and surgery. One hundred and forty-six cases fulfilled the inclusion criteria and 114 were subsequently excluded; therefore, data collected from 58 LRC cases were analyzed in the present study (Figure 1).

Surgical procedures

All surgeries were performed or supervised by surgeons with sufficient experience and certificated by The Japan Society of Endoscopic Surgery and The Japanese Society of Gastrointestinal Surgery. The surgical procedure was selected based on the Japanese colorectal cancer guidelines [14]. Lateral lymph node dissection (LLND) was performed for LRC with 5-mm or larger lateral lymph nodes in the short axis

diameter in pre-treatment CT or MRI. Pre-operative CRT was performed for LRC clinically diagnosed as T3 or N(+) in order to secure CRM.

Clinical and pathological diagnoses

Clinical and pathological TNM staging was performed according to the Japanese Classification System [3]. The clinical diagnosis of LRC was based on the findings of the conventional modalities, endoscopy, contrast-enhanced CT, and MRI. The pathological diagnosis was decided by at least two experienced pathologists and evaluated according to the Japanese Classification System. Briefly, lymph nodes in the mesorectum, around the inferior mesenteric artery, and in both lateral areas were defined as the regional lymph nodes of LRC. The tumor differentiation grade was classified according to the differentiated type, which was the main cellular component of tumors.

Pre-operative and pre-treatment MRI

The MRI protocol employed was similar to that in our previous study [9]. Imaging was performed with a 1.5 or 3.0 T pelvic MRI with pelvic phased-array coils at KPUM or related medical centers. T2-weighted axial images with a section thickness of 5–7 mm and sagittal images with fast spin-echo sequences were acquired. An axial diffusion-weighted sequence with background body signal suppression (DWIBS, b-values 800-1000 s/mm^2) was also obtained. Cases without pre-operative CRT underwent MRI for staging within 2 months before surgery, and those with pre-operative CRT underwent MRI for pre-treatment staging and re-staging in order to diagnose therapeutic responses almost 4 to 7 weeks after the completion of CRT. Positive CRM evaluated by MRI (mrCRM) was defined as a tumor, lymph node, extramural vascular invasion (EMVI), or tumor deposit located <1 mm from the mesorectal fascia [15, 16]. EMVI evaluated by MRI (mrEMVI) was diagnosed according to the 5-scale EMVI scoring system suggested by Smith et al. [17], and scores of 3 and 4 were defined as positive mrEMVI. MRI findings were interpreted by a digestive surgeon based on the radiological reports of experienced radiologists.

Quantification of intratumor heterogeneity on DWI images

The intra-tumor heterogeneity of DWI images was quantified as described in our previous study [9]. The heterogeneity was evaluated in only MRI before treatment initiation. Briefly, DWI were evaluated for the maximum cut surface of an axial image of the rectal tumor, which was identified by a T2-weighted axial image (Figure 2A). The distribution of signal intensities in this high-intensity area was evaluated, and the maximum (MAX) and minimum (MIN) values of signal intensities in the tumor were measured (Figure 2B, C). The intra-tumor heterogeneity of the signal intensity on DWI was quantified using the following formula: MRI heterogeneous score of DWI (mrHSD) = [(MAX value of signal intensity) - (MIN value of signal intensity)] / [(MAX value of signal intensity) + (MIN value of signal intensity)].

Statistical Analysis

Comparisons were performed between both groups using the Mann-Whitney U test or Fisher's exact test. P values <0.05 were considered to be significant. Survival curves were constructed using the Kaplan–Meier

method, and differences in survival were examined using the Log-rank test. Uni- and multivariate analyses of the factors influencing survival were performed using Cox's proportional hazard model. Differences were considered to be significant when the relevant p value was <0.1 in Cox's proportional hazard model. These analyses were performed using JMP statistical software (JMP version 10).

Results

Patient characteristics and MRI findings

The clinicopathological characteristics and MRI findings of 58 cases were summarized in Table 1. LRC was clinically diagnosed as T3/T4 in 48 cases and as positive lymph node metastasis (N(+)) in 31. LRC was pathologically diagnosed as T3/T4 in 39 cases, and as N(+) in 31. The histological type of LRC was poorly differentiated adenocarcinoma in 25 cases. Pre-operative CRT was performed for 34 cases. Four cases underwent total peritoneal excision, 18 abdominal perineal resection, 8 intersphincteric resection, and 28 low anterior resection. LLND was performed for 32 cases. In MRI findings before treatment initiation, 16 cases were diagnosed with positive mrCRM and 26 with mrEMVI. Median mrHSD was 0.457 (0.170-0.823), with a higher score indicating a more heterogeneous pattern on DWI. In the enrolled cases, postoperative recurrence occurred in 14 cases. Moreover, 4 cases died from LRC and one from another disease. The median follow-up time was 1117 days (249-3358 days).

Clinical factors related to intratumor heterogeneity on DWI in LRC

All enrolled cases were divided into two groups according to median mrHSD (mrHSD: 0.457): high and low groups. The relationships between mrHSD and clinical factors were statistically analyzed (Table 2). The number of cases diagnosed with regional N(+), lateral N(+), and positive mrEMVI were significantly higher in the high group than in the low group. Furthermore, a higher number of cases in the high group underwent preoperative CRT than in the low group. This result was attributed to the high group containing more clinical N(+) and positive mrEMVI cases.

The value of intratumor heterogeneity on DWI for predicting patient survival

Kaplan–Meier overall survival (OS) and relapse-free survival (RFS) curves were calculated, and the mrHSD status was compared (Figure 3). All LRC cases in the low group survived three years after surgery, and OS rates were significantly higher in the low group than in the high group (3-year OS: 100% vs 84.6%, p=0.012) (Figure 3A). Moreover, RFS rates were significantly higher in the low group than in the high group (3-year RFS: 85.9% vs 55.6%, p=0.027).

We then performed uni- and multivariate analyses of 3-year RFS. The univariate analysis showed that the 3-year RFS rates of cases with non-differentiated LRC, LRC cases diagnosed with positive mrCRM, and the mrHSD high group were worse (p=0.097, 0.086, and 0.049). The multivariate analysis of significant factors (p<0.1) revealed that mrHSD tended to be an independent factor for predicting post-operative recurrence (HR: 2.836, 95%CI: 0.939-10.314, p=0.060).

Discussion

The diversity of stromal distribution in individual cancer tissues was previously demonstrated in the pathological findings of digestive malignant tumors [18, 19]. Highly differentiated cancer cells generally proliferate well, resulting in extensive areas of the tumor being occupied almost exclusively by these cells. In contrast, poorly differentiated cancer cells grow invasively while forming a stromal region around cancer nests. Hence, poorly differentiated tumor tissues mostly contain stromal regions. Furthermore, the mixture of cancer nests with these different histologies has frequently been reported, and the pattern of stromal distribution in histologically mixed tumors is generally heterogeneous. Previous studies reported that the heterogeneity of stromal distribution in pathological findings has potential as a prognostic marker [10, 11], suggesting that the outcomes of patients may be estimated in the pre-operative setting by evaluating the cancer stromal pattern indirectly using imaging modalities.

DWI images of MRI quantitatively reveal the diffusional restriction of water molecules in the stroma of tissues. Previous studies reported that the distribution of stroma in tissue may be predicted using DWI images [20, 21]. In malignant tumors, the stromal region of cancer tissue is generally smaller than that of normal tissue because of the proliferation of cancer cells and their invasion of normal tissue, suggesting that the diffusional movement of water molecules is restricted in cancer tissues. Therefore, solid malignant tumors were observed as a space-occupying region with high intensity in DWI images of MRI. The efficacy of DWI images of MRI for diagnosing primary tumors, lymph node metastasis, and distant metastasis, is similar to that of positron emission tomography-computed tomography (PET-CT) [22].

Due to the superiority of DWI for evaluating the stroma, the complexes and heterogeneities of stromal structures may be predicted using a DWI image analysis. The heterogeneous pattern of stroma in pathological findings was almost consistent with the uniformity of the pathological stromal pattern in our previous study [9]. Based on these findings, we investigated whether the intratumor heterogeneity of DWI was associated with patient survival.

The present results demonstrated that the intratumor heterogeneity of DWI was not associated with tumor histology; however, a correlation with the cN stage and EMVI was observed (Table 2). Although the number of cases that underwent pre-operative CRT was significantly higher among those with highly heterogeneous tumors, the RFS rate of these cases was significantly lower than that of the low heterogeneity group. Furthermore, histology and CRM before treatment initiation were associated with RFS. The multivariate analysis identified tumors with a highly heterogeneous pattern as an independent risk factor for predicting poor RFS. These results suggest that a novel treatment strategy needs to be considered for patients with highly heterogeneous tumors on DWI images, and also that intratumor heterogeneity on DWI may be used as an imaging biomarker for predicting recurrence and planning individual treatment strategies. In the present study, we evaluated intra-tumor heterogeneity after CRT; however, a relationship with clinical factors or patient outcomes was not observed (data not shown). This image analysis has recently been performed in clinical settings using artificial intelligence technology (AI); therefore, the development of detailed evaluations of intratumor heterogeneity by AI is expected in the future [23].

There were some limitations that need to be addressed. The present study was retrospective with a small sample size, which may have limited the statistical power. DWI are often affected by the background on T2-weighted data, which is known as “T2 shine-through” [24]. To avoid this interference, an apparent diffusion coefficient map (ADC) was used. However, ADC data were not obtained because ADC was not routinely made. Inter-observer variability in the interpretation of clinical images also needs to be evaluated; however, the image analysis in the present study was conducted by one clinician. Although the present study had these limitations, the results obtained are of clinical significance.

Conclusions

The quantitative evaluation of intratumor heterogeneity on DWI images has potential as an imaging biomarker for predicting post-operative recurrence. Although the present results need to be validated in studies with large sample sizes, they may contribute to improvements in the pre-operative evaluation of LRC.

Abbreviations

CRM: circumferential resection margin

CT: computed tomography

DWI: diffusion-weighed MRI

EMVI: extramural vascular invasion

EUS: endoscopic ultrasound

KPUM: Kyoto Prefectural University of Medicine

LLND: Lateral lymph node dissection

LRC: lower rectal cancer

MAX: maximum

MIN: minimum

mrHSD: MRI heterogeneous score of DWI

MRI: magnetic resonance imaging

N(+): lymph node metastasis

OS: overall survival

RFS: relapse free survival

Tables

Table 1 Clinicopathological characteristics of patients

Clinicopathological factors		n=58	%
Gender	Male	43	74.1%
	Female	15	25.9%
Age	Mean ± SD	62.8 ± 11.6	
Clinical T stage	T2	10	17.2%
	T3/T4	48	82.8%
Clinical N stage	Positive	31	53.4%
Histology	Differenced type	33	56.9%
	Non-differentiated type	25	43.1%
Pathological T stage	T2	19	32.8%
	T3/T4	39	67.2%
Pathological N stage	Positive	22	37.9%
Treatment			
Pre-operative therapy	CRT	34	58.6%
	None	24	41.4%
Surgical procedure	PE	4	6.9%
	APR	18	31.0%
	ISR	8	13.8%
	LAR	28	48.3%
LLND		32	55.2%
MRI findings			
mrCRM	Positive	16	27.6%
mrEMVI	Positive	26	44.8%
mrHSD	Median	0.457	(0.170-0.823)
Prognosis			
Recurrence		14	24.1%
	Local recurrence	2	3.4%
	Distant metastasis	10	17.2%
	Lymph node metastasis	2	3.4%
Survival	Cancer-related death	4	6.9%

	Death from other diseases	1	1.7%
Follow-up time	median	1117 days	(249-3358)

SD: Standard Deviation, CRT: Chemoradiotherapy, PE: Pelvic Exenteration, APR: Abdominoperineal Resection, ISR: Intersphincteric Resection, LAR: Low Anterior Resection, LLND: Lateral Lymph Node Dissection, MRI: Magnetic Resonance Image, mrCRM: Circumferential Resection Margin in MRI, mrEMVI: Extramural Vascular Invasion in MRI, mrHSD: MRI Heterogeneous Score of Diffusion-weighted mages

Table 2. Relationships between the intratumor heterogeneity of diffusion-weighted images and clinical factors

		mrHSD				
		High (>0.457)		Low (≤0.457)		
		n=29		n=29		*p* value
Histology	Non-differentiated type	12	41.4%	13	44.8%	0.790
	Differentiated type	17	58.6%	16	55.2%	
Clinical T stage	T4	4	13.8%	1	3.4%	0.160
	<T3	25	86.2%	28	96.6%	
Clinical N stage	Positive	20	69.0%	11	37.9%	0.017
	Negative	9	31.0%	18	62.1%	
Clinical LLNM	Positive	12	41.4%	3	10.3%	0.007
	Negative	17	58.6%	26	89.7%	
mrCRM	Positive	8	27.6%	8	27.6%	1.000
	Negative	21	72.4%	21	72.4%	
mrEMVI	Positive	17	58.6%	9	31.0%	0.034
	Negative	12	41.4%	20	69.0%	
Preoperative therapy	None	8	27.6%	16	55.2%	0.032
	CRT	21	72.4%	13	44.8%	

mrHSD: MRI Heterogeneous Score of Diffusion-weighted images, mrCRM: Circumferential Resection Margin in MRI, mrEMVI: Extramural Vascular Invasion in MRI, CRT: Chemoradiotherapy

Table 3 Uni- and multivariate analyses of 3-year relapse-free survival

				Univariate analysis			Multivariate analysis		
Variables		n	3-year RFS	HR	95%CI	*p*	HR	95%CI	*p*
Histology	Non-differentiated	25	58.6%	2.457	0.848-8.001	0.097	2.044	0.673-6.882	0.208
	Differentiated	33	83.7%	Ref			Ref		
Clinical T stage	T4	5	60.0%	1.854	0.286-6.831	0.457			
	<T3	53	73.8%	Ref					
Clinical N stage	Positive	31	77.1%	0.885	0.302-2.585	0.819			
	Negative	27	67.1%	Ref					
CRT	None	24	72.5%	0.741	0.227-2.148	0.587			
	CRT	34	72.4%	Ref					
mrCRM	Positive	16	60.9%	2.701	0.859-8.276	0.086	2.151	0.660-6.852	0.196
	Negative	42	78.1%	Ref			Ref		
mrEMVI	Positive	18	76.5%	0.995	0.273-2.979	0.994			
	Negative	40	70.8%	Ref					
mrHSD	High	29	55.6%	3.014	1.004-11.023	0.049	2.836	0.939-10.314	0.060
	Low	29	85.9%	Ref			Ref		

HR; Hazard Ratio, CI: Confidence Interval, CRT: Chemoradiotherapy, mrCRM: Circumferential Resection Margin in MRI, mrEMVI: Extramural Vascular Invasion in MRI, mrHSD: MRI Heterogeneous Score of Diffusion-weighted images.

Declarations

Ethical approval and consent to participate

The present study was approved by the Research Ethics Committee of the Kyoto Prefectural University of Medicine (No. ERB-C-1187 and ERB-C-1401). Comprehensive informed consent for the use of clinical data and samples was obtained from all eligible patients.

Competing interests

The authors have no conflicts of interest to declare

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Authors' contributions

M.K. and M.N, analyzed and interpreted the patient data, and was a major contributor in writing the manuscript. Y.K., T.A., H.S, J.K., T.K., H.K., A.S., T.K., H.F., and K.O collected the patients' data such as clinicopathological factors and MRI data. M.G. and K.Y. supervised image analysis of MRI data. E.O. supervised all of the present study. All authors read and approved the final manuscript."

References

1. Ryan EJ, O'Sullivan DP, Kelly ME, Syed AZ, Neary PC, O'Connell PR, Kavanagh DO, Winter DC, O'Riordan JM: Meta-analysis of the effect of extending the interval after long-course chemoradiotherapy before surgery in locally advanced rectal cancer. *Br J Surg* 2019, 106(10):1298-1310.
2. van Gijn W, Marijnen CAM, Nagtegaal ID, Kranenbarg EM-K, Putter H, Wiggers T, Rutten HJT, Påhlman L, Glimelius B, van de Velde CJH: Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *The Lancet Oncology* 2011, 12(6):575-582.
3. Japanese Society for Cancer of the C, Rectum: Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma: the 3d English Edition [Secondary Publication]. *J Anus Rectum Colon* 2019, 3(4):175-195.
4. de Jong EA, ten Berge JC, Dwarkasing RS, Rijkers AP, van Eijck CH: The accuracy of MRI, endorectal ultrasonography, and computed tomography in predicting the response of locally advanced rectal cancer after preoperative therapy: A metaanalysis. *Surgery* 2016, 159(3):688-699.
5. Leufkens AM, van den Bosch MA, van Leeuwen MS, Siersema PD: Diagnostic accuracy of computed tomography for colon cancer staging: a systematic review. *Scandinavian journal of gastroenterology* 2011, 46(7-8):887-894.
6. Lambin P, Leijenaar RTH, Deist TM, Peerlings J, de Jong EEC, van Timmeren J, Sanduleanu S, Larue R, Even AJG, Jochems A *et al*: Radiomics: the bridge between medical imaging and personalized medicine. *Nat Rev Clin Oncol* 2017, 14(12):749-762.
7. Jiang Y, Chen C, Xie J, Wang W, Zha X, Lv W, Chen H, Hu Y, Li T, Yu J *et al*: Radiomics signature of computed tomography imaging for prediction of survival and chemotherapeutic benefits in gastric

cancer. *EBioMedicine* 2018, 36:171-182.

8. Li Y, Eresen A, Lu Y, Yang J, Shangguan J, Velichko Y, Yaghmai V, Zhang Z: Radiomics signature for the preoperative assessment of stage in advanced colon cancer. *American journal of cancer research* 2019, 9(7):1429-1438.
9. Kudou M, Nakanishi M, Kuriu Y, Murayama Y, Arita T, Kishimoto M, Konishi E, Goto M, Yamada K, Otsuji E: Value of intra-tumor heterogeneity evaluated by diffusion-weighted MRI for predicting pathological stages and therapeutic responses to chemoradiotherapy in lower rectal cancer. *J Cancer* 2020, 11(1):168-176.
10. Liao JD, Adsay NV, Khannani F, Grignon D, Thakur A, Sarkar FH: Histological complexities of pancreatic lesions from transgenic mouse models are consistent with biological and morphological heterogeneity of human pancreatic cancer. *Histology and histopathology* 2007, 22(6):661-676.
11. Gerashchenko TS, Zavyalova MV, Denisov EV, Krakhmal NV, Pautova DN, Litviakov NV, Vtorushin SV, Cherdyntseva NV, Perelmuter VM: Intratumoral Morphological Heterogeneity of Breast Cancer As an Indicator of the Metastatic Potential and Tumor Chemosensitivity. *Acta naturae* 2017, 9(1):56-67.
12. Zunder SM, van Pelt GW, Gelderblom HJ, Mancao C, Putter H, Tollenaar RA, Mesker WE: Predictive potential of tumour-stroma ratio on benefit from adjuvant bevacizumab in high-risk stage II and stage III colon cancer. *Br J Cancer* 2018, 119(2):164-169.
13. Kemi N, Eskuri M, Herva A, Leppanen J, Huhta H, Helminen O, Saarnio J, Karttunen TJ, Kauppila JH: Tumour-stroma ratio and prognosis in gastric adenocarcinoma. *Br J Cancer* 2018, 119(4):435-439.
14. Hashiguchi Y, Muro K, Saito Y, Ito Y, Ajioka Y, Hamaguchi T, Hasegawa K, Hotta K, Ishida H, Ishiguro M *et al*: Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. *Int J Clin Oncol* 2020, 25(1):1-42.
15. Al-Sukhni E, Milot L, Fruitman M, Beyene J, Victor JC, Schmocker S, Brown G, McLeod R, Kennedy E: Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. *Ann Surg Oncol* 2012, 19(7):2212-2223.
16. Taylor FG, Quirke P, Heald RJ, Moran B, Blomqvist L, Swift I, St Rose S, Sebag-Montefiore DJ, Tekkis P, Brown G *et al*: One millimetre is the safe cut-off for magnetic resonance imaging prediction of surgical margin status in rectal cancer. *Br J Surg* 2011, 98(6):872-879.
17. Smith NJ, Barbachano Y, Norman AR, Swift RI, Abulafi AM, Brown G: Prognostic significance of magnetic resonance imaging-detected extramural vascular invasion in rectal cancer. *Br J Surg* 2008, 95(2):229-236.
18. Li X, Zhao Q, An B, Qi J, Wang W, Zhang D, Li Z, Qin C: Prognostic and predictive value of the macroscopic growth pattern in patients undergoing curative resection of colorectal cancer: a single-institution retrospective cohort study of 4,080 Chinese patients. *Cancer management and research* 2018, 10:1875-1887.
19. Morikawa T, Kuchiba A, Qian ZR, Mino-Kenudson M, Hornick JL, Yamauchi M, Imamura Y, Liao X, Nishihara R, Meyerhardt JA *et al*: Prognostic significance and molecular associations of tumor growth

pattern in colorectal cancer. *Ann Surg Oncol* 2012, 19(6):1944-1953.

20. Hectors SJ, Semaan S, Song C, Lewis S, Haines GK, Tewari A, Rastinehad AR, Taouli B: Advanced Diffusion-weighted Imaging Modeling for Prostate Cancer Characterization: Correlation with Quantitative Histopathologic Tumor Tissue Composition-A Hypothesis-generating Study. *Radiology* 2018, 286(3):918-928.
21. Fan M, He T, Zhang P, Zhang J, Li L: Heterogeneity of Diffusion-Weighted Imaging in Tumours and the Surrounding Stroma for Prediction of Ki-67 Proliferation Status in Breast Cancer. *Sci Rep* 2017, 7(1):2875.
22. Dresen RC, De Vuysere S, De Keyzer F, Van Cutsem E, Prenen H, Vanslembrouck R, De Hertogh G, Wolthuis A, D'Hoore A, Vandecaveye V: Whole-body diffusion-weighted MRI for operability assessment in patients with colorectal cancer and peritoneal metastases. *Cancer Imaging* 2019, 19(1):1.
23. Hosny A, Parmar C, Quackenbush J, Schwartz LH, Aerts H: Artificial intelligence in radiology. *Nat Rev Cancer* 2018, 18(8):500-510.
24. Colagrande S, Belli G, Politi LS, Mannelli L, Pasquinelli F, Villari N: The influence of diffusion- and relaxation-related factors on signal intensity: an introductive guide to magnetic resonance diffusion-weighted imaging studies. *Journal of computer assisted tomography* 2008, 32(3):463-474.

Figures

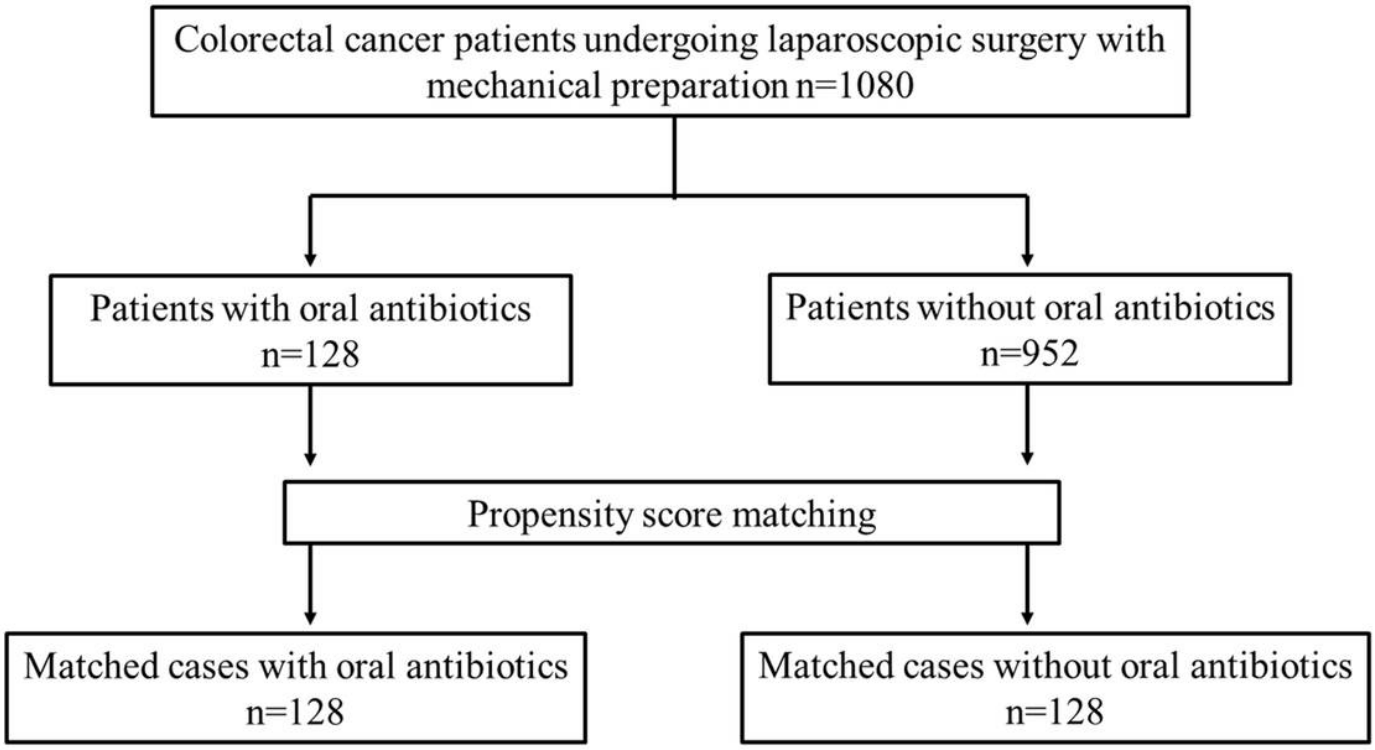

Figure 1

Flow chart showing the selection process for patient inclusion in the present study

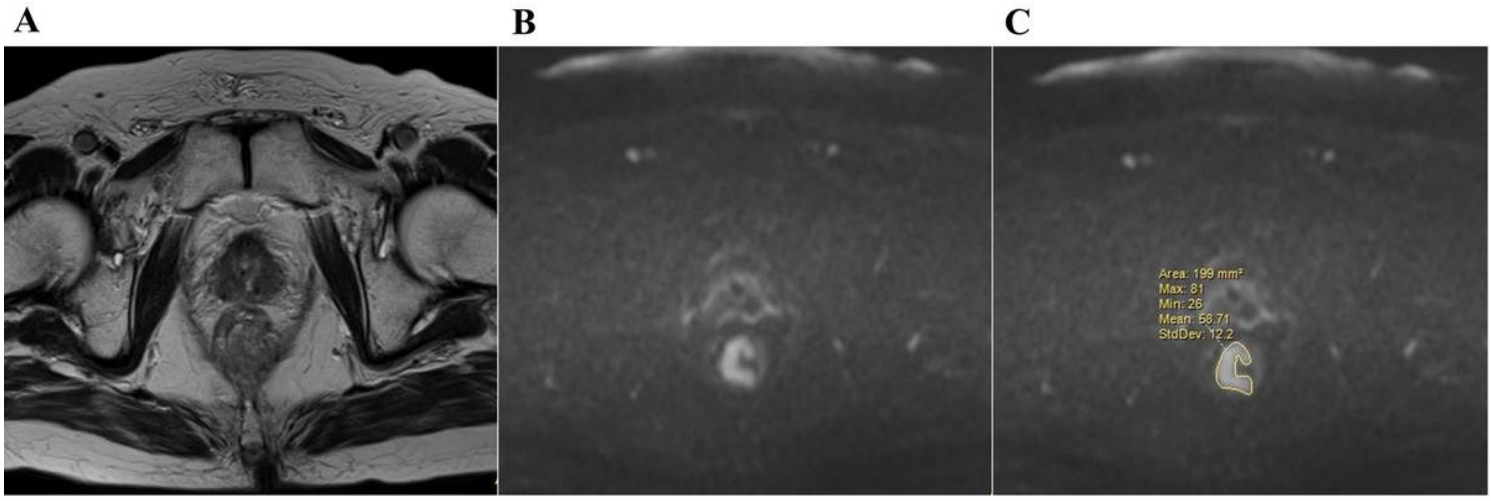

Figure 2

Quantification of intratumor heterogeneity on DWI-image A: T2-weighted axial image of the maximum cut surface of lower rectal carcinoma, B: Diffusion-weighted image of the maximum cut surface of lower rectal carcinoma, C: The distribution of signal intensities on a diffusion-weighted image in the maximum cut surface was assessed.

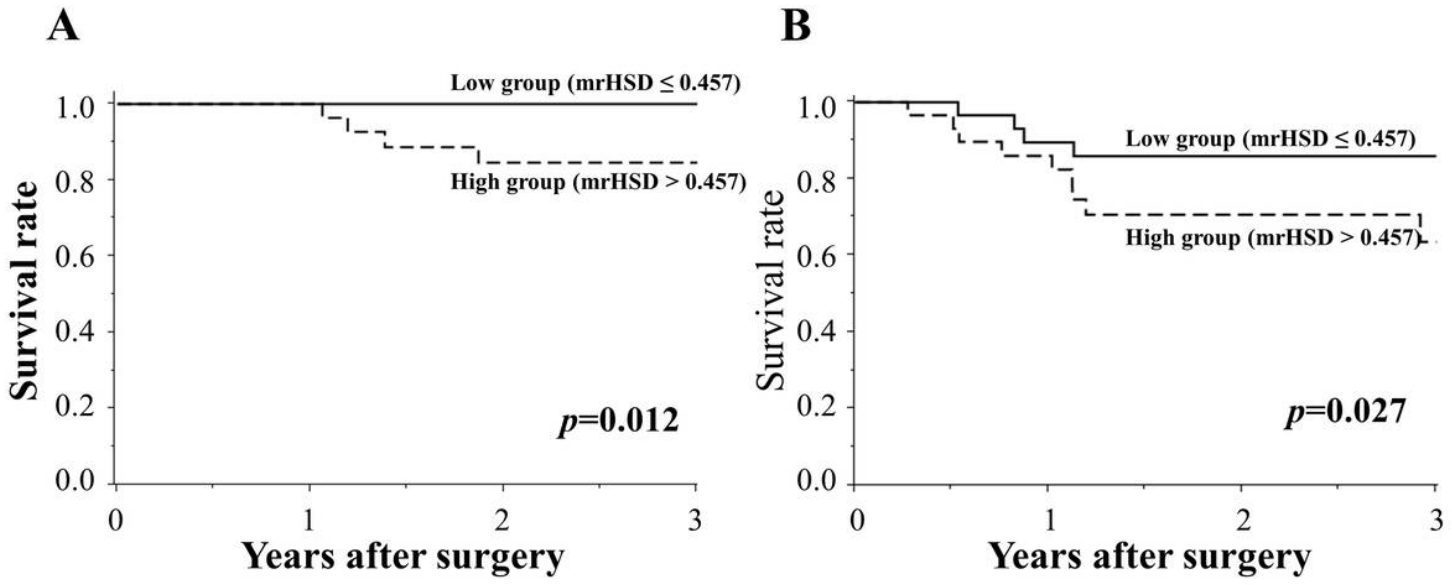

Figure 3

Survival curve of the included patients according to mrHSD A: Overall survival curve of patients after curative resection for LRC according to mrHSD. All patients were classified into two groups according to median mrHSD. B: Relapse-free survival curve of patients after curative resection for LRC according to mrHSD.