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ORIGINAL ARTICLE

The impact of the mesorectal apparent diffusion coefficient value on surgical difficulty in laparoscopic anterior resection for rectal cancer

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Abstract
Purpose We aimed to clarify the impact of the apparent diffusion coefficient (ADC) value of the mesorectum from preoperative magnetic resonance imaging (MRI) on surgical difficulty in laparoscopic anterior resection (Lap-AR) for rectal cancer.
Methods In total, 67 patients who had undergone curative Lap-AR for rectal cancer in our hospital from January 2008 to March 2015 and had preoperative MRI findings available were included. We randomly calculated the average ADC in three regions of the mesorectum at the level of the upper edge of the superior border of the femur. Univariate and multivariate analyses were performed to evaluate the correlation between the patients' clinicopathological characteristics, including the ADC value and short-term surgical outcomes.
Results The univariate analysis revealed that a lower ADC value was associated with a significantly increased operative blood loss ($p=0.008$) and prolonged operative time ($p<0.001$). The multivariate analysis adjusted for the body mass index, anal verge, tumor location, covering stoma, clinical T factor and conversion revealed that the ADC value was an independent risk factor for a prolonged operative time ($R^2=0.6003$, $p<0.001$). Furthermore, the multivariate analysis adjusted for the body mass index, anal verge, covering stoma, clinical T factor and conversion revealed that the ADC value was an independent risk factor for an increased blood loss ($R^2=0.4345$, $p=0.008$).
Conclusion A lower ADC value of the mesorectum might be a predictor of surgical difficulty in Lap-AR for rectal cancer.

Keywords ADC value · Rectal cancer · Laparoscopic surgery

Introduction

Recently, the use of laparoscopic surgery for rectal cancer has markedly increased since several multicenter, randomized control studies ascertained its feasibility and advantages [1]. However, some cases remain challenging to manage. For example, a narrow pelvis or obesity can interfere with the preservation of the surgical field. In addition, no tactile sensation without the direct use of the surgeon's hand prevents the rapid management of unexpected bleeding, which can result in conversion to open surgery or breaking of the circumferential margin. For these reasons, the Japanese Society for Cancer of the Colon and Rectum Guidelines 2014 for the Treatment of Colorectal Cancer does not recommend laparoscopic surgery as a standard strategy for rectal cancer, instead recommending that a skillful surgeon or well-experienced surgical team consider laparoscopic surgery as an option. Therefore, it is crucial to evaluate the technical difficulty preoperatively, which might be an important indication of laparoscopic surgery [2–5].

Total mesorectal excision (TME) is considered a principle in surgery for rectal cancer. Thus, the magnified view of laparoscopic surgery is useful. However, it might be a drawback in patients with a narrow pelvis or obesity due to the difficulty in preserving the surgical view, as mentioned above. In addition, another issue concerning interference with the surgical plane is the status of the mesorectum due

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to the mesorectal fat condition (MFC), which is influenced by preoperative treatment (i.e., endoscopic resection or neoadjuvant chemoradiation) or inflammation of the fat tissue. Thus, preoperative information about the mesorectum may be a key point reflecting the surgical difficulty of TME.

In rectal cancer, magnetic resonance imaging (MRI) is a very useful tool for determining the depth of tumor invasion into the rectal wall or metastasis of the pelvic or mesenteric lymph nodes [6, 7], and it is routinely performed in all patients with rectal cancer in our institution before their operation. In addition, MRI is excellent for the qualitative evaluation of the soft tissue and is normally used to diagnose solid tumors. Diffusion-weighted MRI (DWI) is a functional imaging technique that analyzes differences in the extracellular movement of water protons to discriminate between tissues of varying cellularity [8]. The apparent diffusion coefficient (ADC) value, which is determined by DWI, shows the relative movement of water molecules in the intercellular space [9]. The value sets the *b* level (strength of the slanted magnetic field) to at least two and is calculated as an absolute value. A decrease in the ADC value means that the water molecules are less free because of a narrower intracellular space [9]. Thus, the ADC value is considered to reflect the congestion of cells in the tissue.

In this study, we attempted to clarify the impact of the ADC value of mesorectal fat obtained via preoperative MRI on the surgical difficulty in laparoscopic anterior resection (Lap-AR) for rectal cancer.

Methods

Patients

We enrolled 67 patients with primary rectal cancer in this retrospective, observational study. All patients had undergone curative Lap-AR for rectal cancer in our hospital from January 2008 to March 2015 and received MRI preoperatively. All surgical procedures were performed or supervised by an experienced colorectal surgeon certified as a qualified surgeon by the endoscopic surgical skill qualification system of the Japanese Society for Endoscopic Surgery.

We collected the patients' clinicopathological characteristics, including their sex, age, body mass index (BMI), distance between the tumor and anal verge (AV), tumor location, tumor size, preoperative T and N categories, vascular invasion, number of harvested lymph nodes, conversion to open surgery and short-term surgical outcomes (i.e., operative time, blood loss, postoperative complications, and hospitalization), from maintained medical records. The description and diagnosis of staging complied with the Japanese classification of colorectal cancer.

Patients who had two cancers or who underwent another operation at the same time were excluded from this study. Patients whose data were missing were also excluded from this study. None of the patients underwent preoperative chemotherapy or radiotherapy.

The ADC evaluation

An ADC map was generated from a preoperative pelvic DWI scan. The ADC map in greyscale was automatically generated by the operating system using a mono-exponential decay model that included all three *b* values. ADC measurement was followed by the previous reports [10, 11]. In brief, practical ADC values at three randomly selected points, which were set at both sides and the lower side of the mesorectum at the level of the upper edge of the superior border of the femur (Fig. 1), were calculated, and their average was considered an individual's ADC value.

Statistical analyses

We statistically analyzed the correlation between the patients' clinicopathological characteristics, including the ADC value, and short-term surgical outcome. Continuous data were analyzed using the linear regression method, and categorical data were analyzed using the logistic regression method. All statistical analyses were performed using the STATA, version 12.0 software program (Stata Corp. LP, College Station, TX, USA). A p value less than 0.05 was considered statistically significant.

Results

Patients' clinicopathological characteristics and short-term surgical outcomes

The characteristics of the patients and tumors are summarized in Table 1. In total, 47 male patients and 20 female patients were included in this study. The median (range) ADC value was 1.380 (0.943–1.733) $\times 10^{-3}$. The patients' median age, BMI, and AV were 64 (37–86) years, 23.0 (15.0–38.4) kg/m^2, and 10.0 (2.0–20.0) cm, respectively. Twenty tumors were located in the rectosigmoid, 27 in the mid-rectum, and 20 in the lower rectum. Regarding the operator, 62 cases (92.5%) were performed by qualified surgeons. Diverting loop ileostomy was performed in 21 patients (31.3%). The perioperative outcomes are shown in Table 2. The operative blood loss and operative time were 10 (5–1155) mL and 305 (178–564) minutes, respectively. The number (range) of dissected lymph nodes was 17 (1–55).

The postoperative complications are shown in Table 2. They included anastomotic leakage, ileus and surgical site

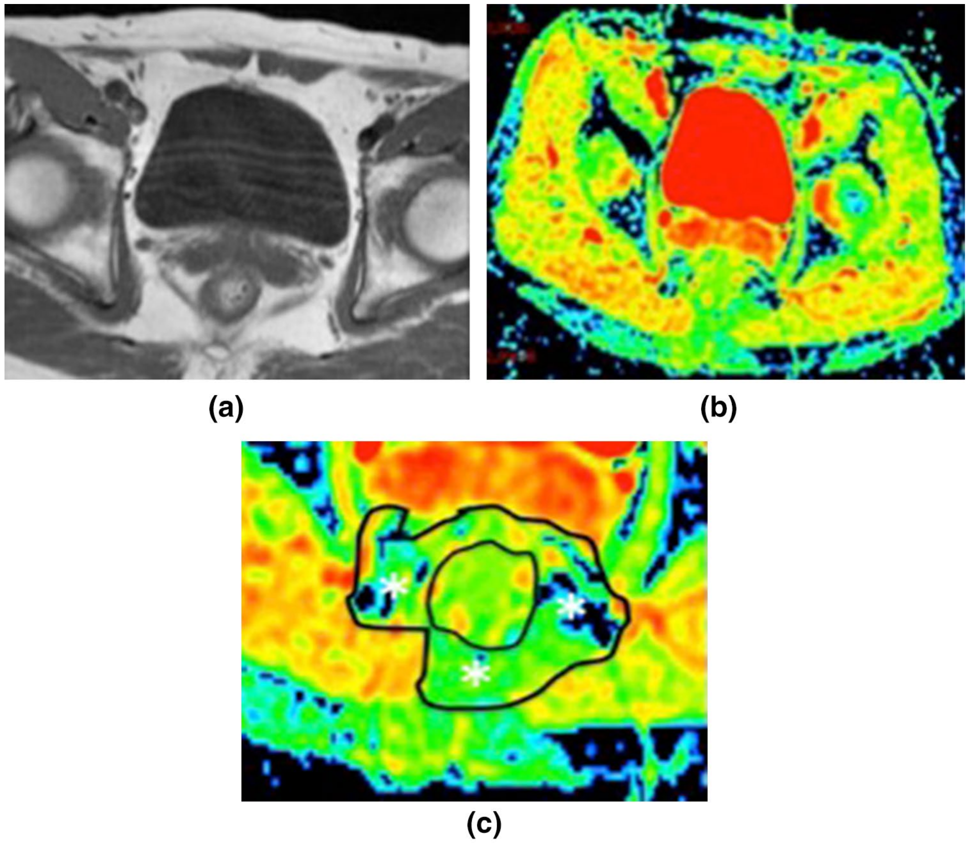

Fig. 1 The measurement of the apparent diffusion coefficient (ADC) value on MRI diffusion-weighted imaging. **a** Diffusion-weighted imaging (DWI) at the level of the upper edge of the femur superior border. **b** An ADC map from signal intensity data obtained on DWI with *b* values of 0 and 1000 s/mm^2. **c** The ADC values at three randomly selected points (on both sides and the lower side of the mesorectum) were calculated, and their average was considered the individual ADC

infection. Eleven patients had anastomotic leakage, and six cases were categorized as more than grade II according to the Clavien–Dindo classification. The mean (range) postoperative hospital stay was 10 (5–50) days.

ADC value and surgical outcomes

The impact of the ADC value on the surgical outcomes in the univariate analyses is shown in Tables 3 and 4. The univariate analysis revealed that a lower ADC value was associated with a significantly increased operative blood loss ($p = 0.008$) and prolonged operative time ($p < 0.001$) (Tables 3, 4). No obvious relationship was observed between the ADC value and postoperative complications or the postoperative hospital stay. The multivariate analysis adjusted for the BMI, anal verge, tumor location, covering stoma, clinical T factor and conversion revealed that the ADC value was an independent risk factor for a prolonged operative time ($R^2 = 0.6003$, $p < 0.001$) (Table 4). Furthermore, a multivariate analysis adjusted for the BMI, anal verge, covering stoma, clinical T factor and conversion revealed that the ADC value was an independent risk factor for an increased blood loss ($R^2 = 0.4345$, $p = 0.008$) (Table 3).

Discussion

We anticipated that the MFC might affect the surgical difficulty in rectal cancer surgery. Consequently, the ADC value was found to be closely linked to the operative time and blood loss, as expected. To our knowledge, this is the first report of such a finding. These results suggest that patients with a lower ADC value of the mesorectum may be at an increased risk of a longer operative time and greater blood loss than those with higher values.

Generally, the ADC value of a tumor has received much attention, and the correlation between the ADC value and pathological findings has been evaluated [11, 12]. A lower ADC value was reported to be linked to higher malignant potential in endometrial cancer, cervical cancer and head and neck cancer. In terms of CRC, Yiqun et al. suggested that the ADC value might be a useful biomarker for assessing the biological features and also to show any possible relationship to the status of identified rectal cancers [13]. Several studies have suggested that the ADC value of tumors can help predict the response to chemoradiation therapy and even the pathologic complete response [14–16], although other papers have disagreed with this suggestion [17–20]. Therefore, the relationship between

Table 1 Patients' characteristics

	Total (n = 67)
Age (years)	64 (37–86)
Sex	
Male	47
Female	20
BMI (kg/m^2)[a]	23.0 (15.0-38.4)
AV (cm)[a]	10 (2–20)
Previous laparotomy	23 (34.3%)
Surgeon	
Qualified surgeon	62
Non-qualified surgeon	5
Tumor size (cm)[a]	3.0 (1.0–8.0)
Tumor location	
RS	20
Ra, Rb	47
Covering stoma	21 (31.3%)
Tumor depth	
cT1	14
cT2/3/4	53
Nodal involvement[b]	
cN0	50
cN1/2/3	17
D3 lymph node dissection	60 (89.6%)
ADC value ($\times 10^{-3}$)	1.380 (0.943–1.733)

AV distance between tumor and anal verge

[a]Median (range)

[b]Preoperative diagnosis by TNM classification

Table 2 The perioperative outcomes and postoperative complications

Operative time (minutes)[a]	305 (178–703)
Blood loss (mL)[a]	10 (5–1155)
Postoperative complication	17 (27.0%)
Anastomotic leakage	11 (17.5%)
Ileus	4 (6.3%)
Surgical site infection	2 (3.1%)
Postoperative hospital stay (days)[a]	10 (5–50)
Dissection of #223 L/N[b]	60

[a]Median (range)

[b]Lymph node

the ADC value and chemoradiation remains controversial. Regardless, no study has reported on the utility of the ADC value of the mesorectum as a biomarker for the surgical quality in rectal cancer. In this study, we focused on the ADC of the mesorectum instead of the tumor and assessed the relationship with an index of surgical difficulty (blood loss or operative time).

We performed this study because we wanted to determine whether or not the ADC value could be applied as a biomarker in clinical practice to predict surgical difficulty. We have clinical experience in that a poor condition of the adipose tissue of the mesorectum, especially that showing inflammation, can lead to misidentification of the layer that must be determined to meet the criteria for TME, thereby leading to increased intraoperative effusion and bleeding.

The relationship between inflammation and the ADC value in the field of inflammatory bowel disease has been reported [21–23]. Schmid-Tannwald et al. reported that the mean ADC value of normal bowel segments was significantly greater than that of inflamed bowel segments, and the mean ADC value of acutely inflamed bowel segments was significantly lower than that of chronically inflamed bowel segments [21]. These findings suggest that a lower ADC value of the mesorectum might reflect potential inflammation, which can cause increased blood loss due to abundant exudate and complicate the determination of the appropriate surgical plane.

Several limitations associated with this study should be mentioned. First, this was a retrospective study; therefore, validation of the findings in other large-scale studies is required. Second, this cohort did not include patients who received preoperative chemoradiotherapy. Thus, the ADC value of the mesorectum should be assessed in such patients. Third, the operative time for the pelvic phase should be used in this study because the ADC of the mesorectum affects only that procedure of TME. Finally, preoperative endoscopic treatment or tumor invasion might affect the mesorectal condition, therefore, a histopathological examination will be required to improve the reliability of our results.

Despite these limitations, this remains the first substantial study to attempt to clarify the impact of the ADC value of the mesorectum on Lap-AR for rectal cancer. Patients with a low ADC value in the mesorectum should be considered difficult cases for Lap-AR, and careful management should be practiced in such cases.

Conclusions

A lower ADC value of the mesorectum might be a predictor of difficulty in Lap-AR for rectal cancer. Further investigations, including a pathological evaluation, may provide more evidence to support this notion.

Table 3 Results of univariate and multivariate analyses assessing the effects of clinicopathological factors on blood loss

	Univariate analysis			Multivariate analysis		
	Coefficient correlation	95% CI	*p* value	Coefficient correlation	95% CI	*p* value
Age	− 1.77	− 6.60 to 3.01	0.461		–	
Sex (male/female)	− 66.0	− 175.2 to 43.1	0.231		–	
BMI (kg/m^2)	17.3	5.08 to 29.6	0.006	14.8	4.09 to 95.5	0.383
Previous laparotomy	− 44.6	− 150.6 to 61.3	0.403		–	
Surgeon qualified/non-qualified	− 66.6	− 277.9 to 144.7	0.531			
AV (cm)	− 13.1	− 25.6 to − 0.60	0.040	− 8.75	− 19.9 to 2.42	0.122
Tumor size (cm)	− 14.0	− 44.5 to 16.5	0.363		–	
Tumor location RS/Ra, Rb	52.6	− 62.5 to 167.8	0.365		–	
Covering stoma	109.4	5.36 to 213.5	0.040	46.2	− 49.0 to 141.4	0.335
cT1 vs. cT2/3/4[a]	− 158.2	− 275.6 to − 40.8	0.009	− 74.5	− 173.2 to 24.3	0.137
cN0 vs. cN1/2/3[a]	− 51.4	− 169.0 to 66.2	0.386		–	
D3 lymph node dissection	− 96.3	− 207.5 to 15.0	0.089		–	
Conversion	620.4	370.0 to 870.7	< 0.001	529.6	304.8 to 754.3	< 0.001
ADC value ($\times 10^{-3}$)	− 3.42E−07	− 5.76E−07 to − 1.07E−07	0.005	− 151,515	− 401,528 to − 98,498	0.008

AV distance between tumor and anal verge

[a]Preoperative diagnosis by TNM classification

Table 4 Results of univariate and multivariate analyses to assess the effects of clinicopathological factors on the operative time

	Univariate analysis			Multivariate analysis		
	Coefficient correlation	95% CI	*p* value	Coefficient correlation	95% CI	*p* value
Age	− 0.93	− 3.21 to 1.35	0.419		–	
Sex (male/female)	− 48.7	− 100 to 2.60	0.062		–	
BMI (kg/m^2)	13.4	8.15 to 18.6	< 0.001	14.1	9.64 to 18.6	< 0.001
Previous laparotomy	− 7.30	− 58.2 to 43.6	0.775		–	
Surgeon qualified/non-qualified	− 10.7	− 112.0 to 90.6	0.833			
AV (cm)	− 10.1	− 15.8 to − 4.51	< 0.001	− 8.07	− 14.9 to − 1.28	0.021
Tumor size (cm)	− 5.79	− 20.4 to 8.83	0.432		–	
Tumor location RS/Ra, Rb	47.2	18.6 to 75.8	0.002	11.9	− 24.1 to 47.8	0.511
Covering stoma	77.2	29.5 to 124.8	0.002	34.9	− 7.95 to 77.9	0.108
cT1 vs. cT2/3/4[a]	− 58.6	− 116.0 to − 1.22	0.045	− 8.96	− 50.6 to 32.7	0.669
cN0 vs. cN1/2/3[a]	7.43	− 49.1 to 63.9	0.794		–	
D3 lymph node dissection	− 30.5	− 84.4 to 23.4	0.262		–	
Conversion	161.3	26.3 to 296.5	0.020	108.4	17.0 to 200.0	0.021
ADC value ($\times 10^{-3}$)	− 199,905	-3.10×10^{-5} to -8.97×10^{-4}	< 0.001	− 60,783	-1.50×10^{-5} to -0.89×10^{-5}	< 0.001

AV distance between tumor and anal verge

[a]Preoperative diagnosis by TNM classification

Author contributions HS and MT contributed equally to all aspects of this study. HS and MT participated in its design and coordination and helped draft the manuscript. KO, TI and YA participated in the design of the study and performed the statistical analysis. SO guided me in the measurement of imaging (i.e., apparent diffusion coefficient). HH and YK conceived of the study, participated in its design and coordination and helped to draft the manuscript.

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Conflict of interest The authors declare that they have no competing interest.

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