European Radiology (2019) 29:1240–1247
https://doi.org/10.1007/s00330-018-5723-5

ONCOLOGY

Quantitative assessment of mesorectal fat: new prognostic biomarker in patients with mid-to-lower rectal cancer

Jiyoung Yoon[1] · Yong Eun Chung[1,2] · Joon Seok Lim[1] · Myeong-Jin Kim[1]

Received: 11 July 2018 / Revised: 3 August 2018 / Accepted: 16 August 2018 / Published online: 18 September 2018

Abstract

Objectives To investigate the impact of mesorectal fat area (MFA) on oncologic outcomes in patients with mid-to-lower rectal cancer who received curative-intent surgery.

Methods Patients with mid-to-lower rectal cancer who underwent preoperative abdominopelvic computed tomography (CT) and curative-intent surgery in 2011 were divided into two groups by tumour recurrence (group A) or no recurrence (group B) during a 5-year follow-up. Visceral fat area (VFA) and MFA were measured on preoperative CT and cutoff values were calculated using the Youden index. Univariate and multivariate regression analyses including BMI, VFA, and MFA were performed to investigate meaningful prognostic biomarkers. The Kaplan–Meier method with log-rank testing was used to validate prognostic biomarkers.

Results Group A contained 42 patients and group B had 155 patients. Cutoff values were 25 kg/m^2 for BMI, 130 cm^2 for VFA, and 10 cm^2 for MFA using the Youden index. On multivariate Cox regression analysis, MFA (odds ratio [OR] = 0.426, p = 0.010), TNM stage (p = 0.027), and perioperative complication grade (p = 0.028) were significantly different between groups. BMI and VFA did not show significant differences. By the Kaplan–Meier method with log-rank testing, disease-free survival (DFS) was significantly longer in patients with MFA ≥10 cm^2 compared to patients with MFA <10 cm^2 (p = 0.021), with no significant difference in overall survival (OS).

Conclusions MFA was an independent biomarker for predicting DFS in patients who underwent curative-intent surgery for mid-to-lower rectal cancer.

Key Points

- *Mesorectal fat area is associated with the prognosis of rectal cancer patients.*
- *Mesorectal fat area can be calculated easily in pre-operative CT scan.*
- *Predicting prognosis of the cancer patient before operation is important.*

Keywords Intra-abdominal fat · Body mass index · Colorectal neoplasms · Digestive system surgical procedures

Abbreviations

APR	Abdominoperineal resection
ASA	American Society of Anesthesiologists
BMI	Body mass index
CCRTx	Chemoradiation therapy
CEA	Carcinoembryonic antigen
DFS	Disease free survival
HU	Hounsfield units
ISD	Interspinous distance
LAR	Low anterior resection
LN	Lymph node
MFA	Mesorectal fat area
OS	Overall survival
SD	Standard deviation
TC	True conjugate
TME	Total mesorectal excision
ULAR	Ultralow anterior resection
VFA	Visceral fat area

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00330-018-5723-5) contains supplementary material, which is available to authorized users.

✉ Yong Eun Chung
yelv@yuhs.ac

[1] Department of Radiology, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea

[2] BK21 PLUS Project for Medical Science, Yonsei University College of Medicine, Seoul, Republic of Korea

Introduction

Obesity is an established risk factor for cardiovascular disease and type 2 diabetes, and for many cancers including the oesophagus, stomach, pancreas, gallbladder, liver, colorectum, breast, endometrium, and kidney [1]. For colorectal cancer, obesity is reported to be related to surgical difficulty [2], worse surgical outcomes including postoperative complications and mortality [3, 4], and poorer oncologic outcomes such as disease-free survival (DFS) and overall survival (OS) [5].

Traditionally, body mass index (BMI) is routinely used in obesity-related research because it is easily calculated, with established criteria for overweight and obesity [2, 3, 5–7]. However, BMI cannot differentiate between lean and fat mass. It does not consider possible confounding factors such as age, sex, or ethnicity, and does not reflect body fat distribution. Extra fat accumulation is considered a more meaningful factor than total body fat and visceral fat is thought to be more closely associated with metabolic syndrome and cancer development [8–11]. In line with this paradigm shift, some studies show surgical outcomes after colon cancer surgery to be more highly related to visceral fat area than BMI [4, 12–14]. Furthermore, oncologic outcomes such as DFS and OS seem to be more influenced by visceral obesity than BMI [15, 16].

Since the introduction of total mesorectal excision (TME), local recurrence after rectal cancer surgery has significantly decreased, probably due to more complete excision of microtumours around the rectal cancer [17]. Circumferential resection margin and mesorectal fat are important anatomical landmarks for determining treatment options with TME. However, no studies have explored the clinical importance of the amount of mesorectal fat, which reflects extra fat accumulation around rectal cancers. Hence, the aim of this study was to investigate the impact of mesorectal fat area (MFA) on surgical and oncologic outcomes in patients with mid-to-lower rectal cancer. Furthermore, the relationships between MFA and body fat parameters including BMI and visceral fat area (VFA), and between MFA and pelvimetry were investigated.

Material and methods

The Institutional Review Board of our institution approved this retrospective study and the requirement for informed consent was waived.

Patients

By searching electronic medical records and a radiology reporting system, patients diagnosed with rectal cancer who underwent curative-intent surgery in 2011 were identified. Among them, patients who met the following criteria were excluded: 1) diagnosed with upper rectal cancer, defined as distal margin above the peritoneal reflection; or 2) no preoperative computed tomography (CT; see Fig. 1, which illustrates the patient selection process).

Imaging protocol and assessment

All CT scans were performed with a multidetector CT. Contrast media (Ultravist, Bayer Healthcare LLC) at 2 mL/kg was injected by power injector over 30 s. Using a bolus-tracking technique, hepatic venous phase was obtained 55 s after the Hounsfield units (HU) of the abdominal aorta increased by 100 HU compared with baseline or 30 s after the end of the late arterial phase. CT parameters were: tube voltage, 100–120 kVp; reference mA, 170–240 mA with automated tube current modulation; rotation time, 0.5–0.625 s; and slice thickness, 3–5 mm. Iterative reconstruction was applied for image noise reduction if available in the CT console.

Image analysis used dedicated software (Aquarius Workstation, TeraRecon, Inc.). At the level of umbilicus (for VFA) and ischial spine (for MFA), areas of visceral fat and mesorectal fat [18] were semi-automatically identified for HU values between -190 and -30, followed by manual fine adjustment (Fig. 2a, b). Both VFA and MFA were measured twice to assess intra-observer variability by a reviewer who was unaware of clinical data. Another reviewer measured the VFA and MFA of 50 randomly selected patients to assess inter-observer agreement. Interspinous distance (ISD) was calculated as distance between spinous processes using axial images at the ischial spine level. Length of true conjugate (TC) was calculated as the distance between the uppermost symphysis pubis and sacral promontory using midline sagittal images (Fig. 2b, c)

Clinical assessment

By reviewing electronic medical records, BMI and underlying diseases including hypertension, tuberculosis, diabetes mellitus,

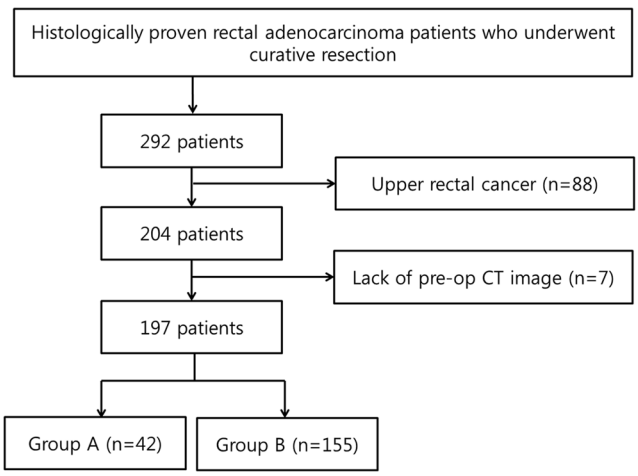

Fig. 1 Patient selection diagram

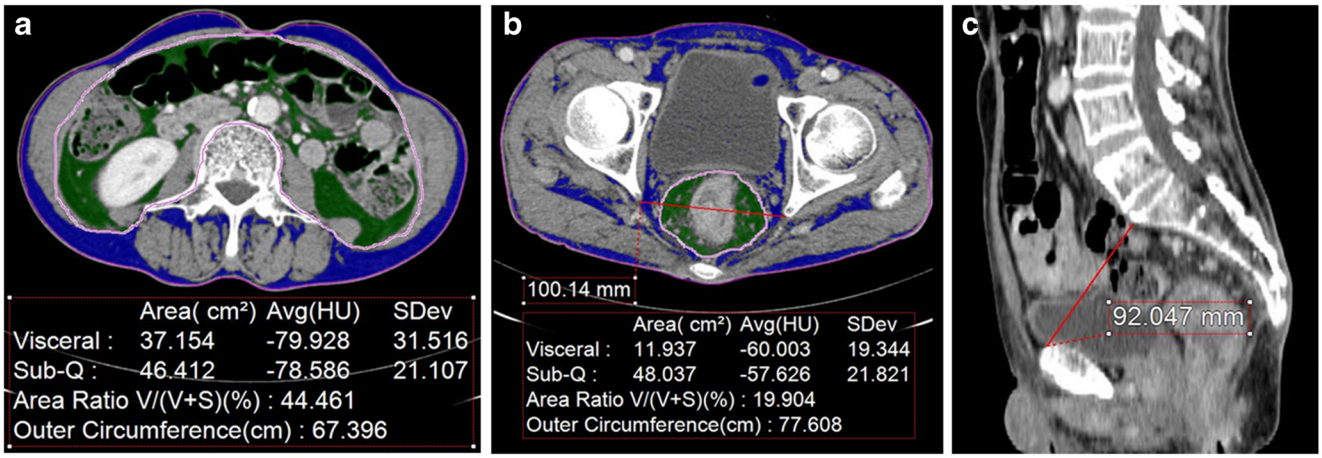

Fig. 2 Quantitative measurement of CT. (**a**) VFA, (**b**) MFA, and ISD were measured using axial CT images at the level of umbilicus (for VFA) and ischial spine (for MFA and ISD). **c** TC was measured using midline sagittal CT images. In this 57-year-old male patient, VFA was 37 cm^2, MFA was 11 cm^2, ISD was 10 cm, and TC was 9 cm

and viral hepatitis were identified, along with smoking and alcohol consumption status and blood carcinoembryonic antigen (CEA). Surgical techniques, American Society of Anesthesiologists (ASA) physical status, total amount of blood lost during surgery, and hospitalisation days were recorded to represent factors of perioperative and postoperative risks. Postoperative complications were graded based on Mazeh et al [19]: minor asymptomatic complications not requiring treatment, complications requiring pharmacological therapy, minor interventions or prolonged hospitalisation, complications requiring nonsurgical intervention, complications requiring surgical intervention or causing permanent loss of organ function, and complications related to death were scored from 1 to 5. Pathology findings including tumour-node-metastasis (TNM) stage based on the seventh edition of the American Joint Committee on Cancer, number of retrieved lymph nodes, and number of metastatic lymph nodes were analysed. In patients who underwent chemoradiation therapy (CCRTx) before surgery, Mandard grade was based on pathology results. DFS, defined as the period between surgery and tumour recurrence, and OS, defined as the period between surgery and death or last follow-up were calculated.

Statistical analysis

Statistical analysis used SPSS software, version 20, MedCalc Statistical Software version 16, and R package version 3.4.3. Patients were divided into two groups by tumour recurrence (group A) or no recurrence (group B) during the 5-year follow-up. Demographics, surgical outcomes, and pathological findings were compared between groups by chi-square test for categorical variables and independent *t* test for continuous variables. Intra- and inter-observer agreements for quantitative evaluation of VFA and MFA were analysed using intraclass correlation coefficients (ICCs). Univariate and multivariate binary logistic regression analyses used factors conventionally known to affect cancer prognosis and BMI, VFA, and MFA to determine factors that affected cancer recurrence. Cutoff values for BMI, VFA, and MFA were determined by Youden index. The Kaplan–Meier method with log-rank testing was used to validate prognostic biomarkers. Internal validation was performed by bootstrapping methods due to the small proportion of patients with local recurrence compared to patients without local recurrence. All p values less than 0.05 were considered statistically significant.

Results

Patient selection and demographics

In 2011, a total of 292 patients were diagnosed with rectal cancer and underwent curative-intent surgery in our institution. Among them, 88 patients with upper rectal cancer and 7 without preoperative CT scans were excluded. We excluded upper rectal cancer from analysis because cancer above the peritoneal reflection is not completely encircled by mesorectal fascia. Data on 197 patients (mean age = 59.38 ± 11.69 years old, male:female = 122:75) were analysed. Among them, 42 patients were classified into group A (59.5 ± 12.4, male:female = 29:13) and 155 into group B (59.4 ± 11.5, male:female = 93:62; Table 1). Average distance between anal verge and lower tumour margin was 7.0 ± 2.2 cm. BMI (p = 0.574) and the ratio between visceral and subcutaneous fat areas showed no significant difference between group A and group B (p = 0.433). In group A, isolated local recurrence developed in 7 patients and distant metastasis in 32 patients during the 5-year follow-up. In three patients, local recurrence and distant metastasis developed synchronously. (For detailed descriptions of recurrence, see Table, Appendix A).

Table 1 Patient Demographics

	Cancer recurrence		
	Yes $N = 42$	No $N = 155$	p value
Age (mean ± SD)	59.5 ± 12.4	59.4 ± 11.5	0.652
Male:female	29:13	93:62	0.284
Past history			
HTN	17 (40.5)	52 (33.5)	0.404
DM	9 (21.4)	19 (12.3)	0.131
Hepatitis	0 (0.0)	7 (4.5)	0.161
Social history			
Smoking	22 (52.4)	68 (43.9)	0.384
Alcohol	26 (61.9)	75 (48.4)	0.120
CEA	18.2 ± 34.0	8.7 ± 29.0	0.012

SD Standard deviation, *HTN* hypertension, *DM* diabetes mellitus, *CEA* carcinoembryonic antigen

Comparison of operation method and perioperative parameters

No significant difference was observed in operation method, technique, ASA grade, amount of blood lost during the surgery, or length of hospital stay between groups. Postoperative complication rates were significantly higher in group A than group B ($p = 0.011$; Table 2).

Comparison of pathological findings

Pathologically confirmed N stage ($p = 0.003$) and M stage ($p = 0.013$) were higher in group A than group B. The number of retrieved metastatic lymph nodes was significantly larger in group A than B (0.5 ± 1.4 vs. 2.2 ± 5.0, $p = 0.000$) Detailed pathological findings are in Table 3.

Table 2 Comparison of operation method and perioperative parameters between groups according to cancer recurrence

	Cancer recurrence		
	Yes N = 42	No N = 155	p value
Operation method			0.300
LAR	36 (85.7)	134 (86.5)	
ULAR	3 (7.2)	10 (6.5)	
APR	3 (7.2)	10 (6.5)	
Total colectomy	0	1 (0.5)	
Operation technique			0.727
Open	6 (14.3)	16 (10.3)	
Laparoscopic	23 (54.8)	93 (60.0)	
Robot-assisted	13 (31.0)	46 (29.7)	
ASA grade			0.117
1	26 (61.9)	86 (55.5)	
2	13 (31.0)	66 (42.6)	
3	3 (7.1)	3 (1.9)	
Blood loss (ml)	264.4 ± 330.7	197.8 ± 264.8	0.111
Length of hospital stay (days)	11.1 ± 5.1	10.3 ± 7.7	0.687
Complications			0.011
Grade 0	17 (40.5)	103 (66.5)	
Grade 1	13 (31.0)	23 (14.8)	
Grade 2	4 (9.5)	12 (7.7)	
Grade 3	3 (7.1)	2 (1.3)	
Grade 4	5 (11.9)	15 (9.7)	

LAR low anterior resection, *ULAR* ultralow anterior resection, *APR* abdominoperineal resection, *ASA* American Society of Anesthesiologists

Table 3 Comparison of pathological findings between groups according to cancer recurrence

	Cancer recurrence		
	Yes N = 42	No N = 155	p value
T stage			0.112
pCR	5 (11.9)	20 (12.9)	
pT1	2 (4.8)	11 (7.1)	
pT2	9 (21.4)	63 (40.6)	
pT3	25 (59.5)	58 (37.4)	
pT4	1 (2.4)	3 (1.9)	
N stage			0.003
pN0	20 (47.6)	114 (73.5)	
pN1	16 (38.1)	34 (21.9)	
pN2	6 (14.3)	7 (4.5)	
Number of metastatic LNs	2.2 ± 5.0	0.5 ± 1.4	0.000
M stage			0.013
pM0	36 (85.7)	150 (96.8)	
pM1	6 (14.3)	5 (3.2)	
Pre-op CCRTx			0.158
(-)	13 (31.0)	68 (43.9)	
(+)	29 (69.0)	87 (56.1)	
Mandard grade			0.475
1	5 (16.7)	16 (18.4)	
2	4 (13.3)	17 (19.5)	
3	15 (50.0)	38 (43.7)	
4	6 (20)	16 (18.4)	

pCR pathologic complete response, *LN* lymph node, *CCRTx* chemoradiation therapy

Table 4 Univariate and multivariate cox regression analysis for groups according to cancer recurrence

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age	1.003	0.997–1.031	0.808			
Hypertension	1.33	0.718–2.464	0.364			
DM	1.908	0.913–3.990	0.086			
Smoking	1.364	0.745–2.500	0.315			
Alcohol	1.676	0.899–3.124	0.104			
TNM stage (ref. = 0)						0.027
1	0.657	0.192–2.244	0.503	0.704	0.204–2.43	0.579
2	1.317	0.406–4.278	0.647	1.297	0.396–4.25	0.667
3	2.453	0.83–7.251	0.105	2.429	0.816–7.236	0.111
4	7.475	1.857–30.095	0.005	4.046	0.875–18.715	0.074
CEA	1.013	1.006–1.020	0.000	1.008	1–1.016	0.058
Complication grade (ref. = 0)						0.028
1	3.047	1.479–6.277	0.003	2.679	1.279–5.61	0.009
2	1.89	0.636–5.618	0.252	1.372	0.453–4.154	0.576
3	7.482	2.183–25.646	0.001	6.452	1.476–28.194	0.013
4	1.886	0.696–5.112	0.212	1.851	0.68–5.035	0.228
Preoperative CCRTx	0.56	0.291–1.078	0.083			
BMI ≥ 25 kg/m^2	1.599	0.831–3.076	0.16			
VFA ≥ 130 cm^2	0.442	0.186–1.049	0.064			
MFA ≥ 10 cm^2	0.526	0.284–0.954	0.041	0.426	0.222–0.817	0.010
Harrell's C-index of the multivariable model: 0.768						
Bootstrap 95% CI: 0.699–0.834						

DM diabetes mellitus, *TNM* tumour-node-metastasis, *ref* reference, *CEA* carcinoembryonic antigen, *BMI* body mass index, *VFA* visceral fat area, *MFA* mesorectal fat area, *CCRTx* chemoradiation therapy

Factors associated with DFS

BMI (26.2 kg/m^2), VFA (129.1 cm^2), and MFA (9.6 cm^2) showed the highest sensitivity and specificity as calculated by the Youden index. Since the computed value was similar to commonly used criteria for obesity by BMI (25 kg/m^2) and VFA (130 cm^2) [12–15, 20], we determined a BMI of 25 kg/m^2 and a VFA of 130 cm^2 as cutoffs for obesity. We set 10 cm^2 as the cutoff for MFA, because no widely applied cutoff exists.

On univariate Cox regression analysis, TNM stage, preoperative serum CEA level, perioperative complication grade, and MFA (odds ratio [OR] = 0.526; 95% confidence interval [CI]:

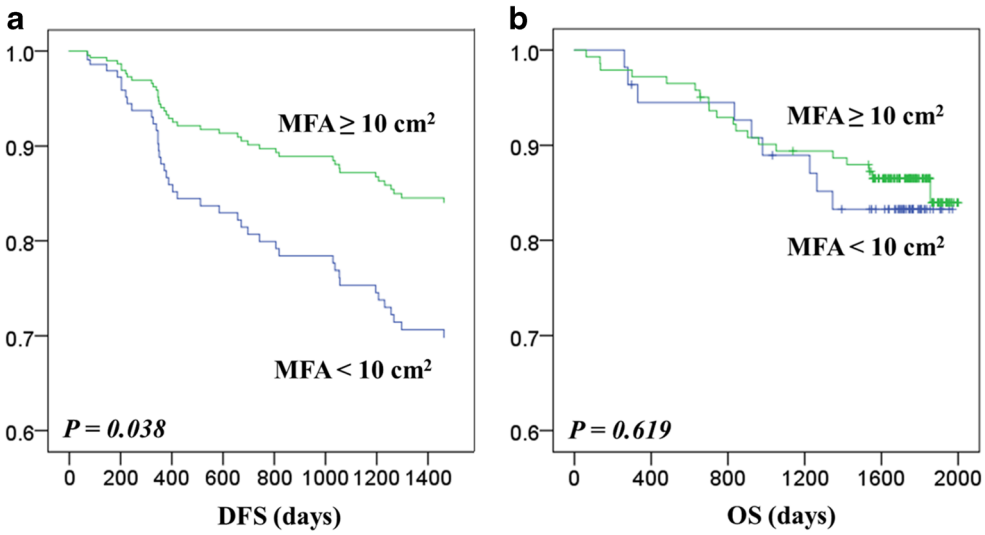

Fig. 3 Disease-free and overall survival according to MFA. **a** By the Kaplan–Meier method with log-rank testing. DFS was significantly longer in patients with MFA ≥10 cm^2 compared to patients with MFA <10 cm^2 (*p* value = 0.038). **b** By the Kaplan–Meier method with log-rank testing, no significant difference in OS was seen between patients with MFA ≥10 cm^2 compared to patients with MFA<10 cm^2 (*p* value = 0.619)

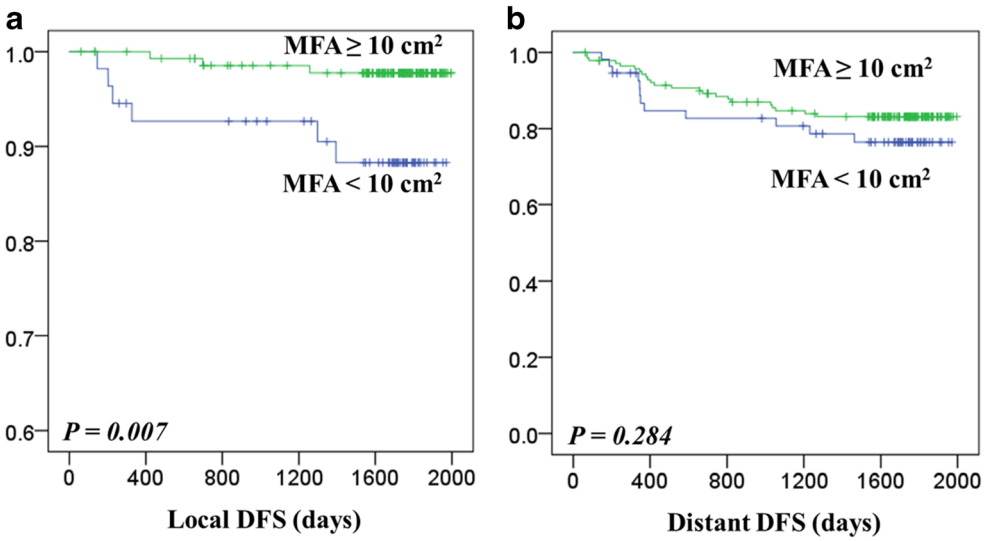

Fig. 4 Local disease-free and distant disease-free survival according to MFA. **a** By the Kaplan–Meier method with log-rank testing, DFS specific for local recurrence was significantly longer in patients with MFA ≥10 cm^2 than patients with MFA <10 cm^2 (p value = 0.007). **b** By the Kaplan–Meier method with log-rank testing, no significant difference in DFS specific for distant metastasis was seen between patients with MFA ≥10 cm^2 compared to patients with MFA<10 cm^2 (p value = 0.284)

0.284–0.954; p = 0.041) showed significant differences between groups (Table 4). On multivariate Cox regression analysis, all factors except serum CEA level were independent predictors of cancer recurrence. These were TNM stage (p = 0.027), perioperative complication grade (p = 0.028), and MFA (OR = 0.426; 95% CI: 0.222–0.817; p = 0.010). Harrell's C-index for multivariable model including TNM stage, perioperative complication grade, and MFA was 0.768 (95% CI using 1000 bootstrap samples: 0.699–0.834; Table 4).

By the Kaplan–Meier method with log-rank testing, DFS was significantly longer in patients with MFA ≥10 cm^2 compared to patients with MFA <10 cm^2, with no significant difference in OS between groups (Fig. 3). In subgroup analysis, DFS specific for local recurrence was significantly different, but DFS specific for distant metastasis was not different between patients with MFA ≥10 cm^2 compared to patients with MFA <10 cm^2 (Fig. 4). Internal validation was done to overcome the small proportion of patients with local recurrence. In 855 bootstrap samples among 1000 samples, DFS specific for local recurrence was significantly longer in patients with MFA ≥10 cm^2 than patients with MFA <10 cm^2. This suggests that our results might be valid despite asymmetry in the number of included patients (Appendix C).

Correlation

MFA showed a significant positive correlation with BMI and VFA. No correlation or weak negative correlation was observed between MFA and ISD and between MFA and TC (Fig. 5, Appendix B).

Intra- and inter-observer agreement

As the ICC was 0.998 (95% CI: 0.997–0.999) for VFA and 0.978 (95% CI: 0.962–0.988) for MFA, intra-observer agreement for measuring VFA and MFA turned out to be excellent. Inter-observer agreement was also excellent both for VFA (ICC = 1.000; 95% CI: 0.999–1.000) and for MFA (ICC = 0.993; 95% CI: 0.988–0.996).

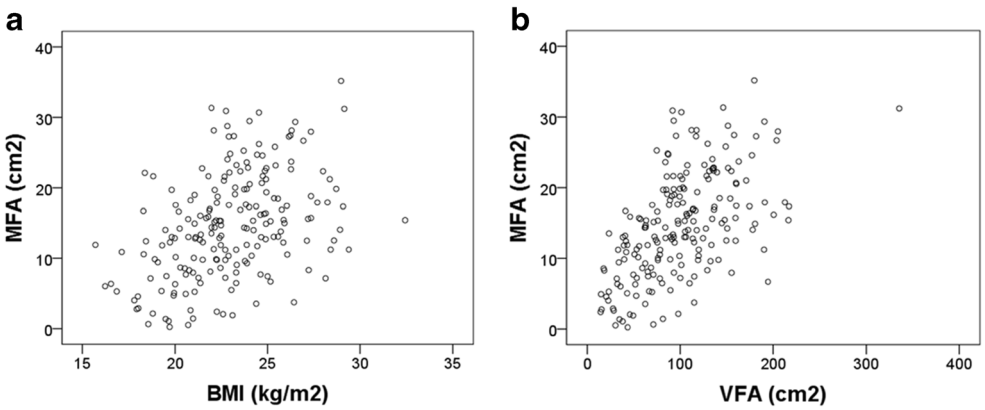

Fig. 5 Correlation between MFA and other parameters. MFA showed significant positive correlation with (**a**) BMI and (**b**) VFA. No significant correlation or weak negative correlation was observed between MFA and ISD or between MFA and TC

Discussion

Our results also suggested that patients with MFA ≥10 cm^2 had significantly longer DFS than patients with MFA <10 cm^2 (OR = 0.477; 95% CI: 0.254–0.894), whereas OS was not different between the two groups. Significant positive correlation was observed between MFA and BMI (0.432, $p < 0.001$) and between MFA and VFA (0.567, $p < 0.001$).

According to a previous study, larger mesorectal volume increases the probability of clear surgical pathologic resection margins after TME [21]. Our study results were in line with a previous study that showed patients with higher MFA (≥10 cm^2) having better 5-year DFS and local recurrence-specific DFS. Greater MFA might lead to a larger capacity for tumour cells within the mesorectal fascia, reduce the chance of CRM invasion by the tumour, and finally result in the absence of residual tumour after TME. Furthermore, mesorectal fat could act as a buffer against local tumour spreading, and protect against intra-mesorectal micro-lymph node metastasis [18, 22, 23]. However, the exact reason for the longer DFS observed in patients with higher MFA should be evaluated in a future study.

According to previous studies, OS is not significantly improved after applying TME or applying both TME and neoadjuvant radiotherapy, although some specific patient groups show a trend of OS improvement [17, 24, 25]. This result might be because both TME and neoadjuvant radiotherapy target local cancer control, although OS is more affected by the presence of distant metastasis [24, 25]. Our results were comparable with these studies: DFS and DFS specific for local recurrence were significantly different according to MFA, whereas OS and DFS specific for distant metastasis were not different between the two groups. OS might predominantly depend on systemic metastasis, which mainly depends on chemotherapy rather than surgical resection [20, 26].

BMI and VFA were considered prognostic factors for patients with colorectal cancer in previous studies. Patients with high BMI or VFA have increased risk of all-cause mortality and cancer-specific mortality, and decreased DFS [5, 15, 16]. In our study, however, no significant difference was seen in BMI or VFA between patients with and without cancer recurrence. This result was probably due to the different study design. Prior studies included limited patient groups such those who received chemotherapy [27] or who were diagnosed with stage II or III cancer [15]. All diagnosed rectal cancer patients regardless of tumour stage or treatment options were analysed in our study. Although patient conditions such as cancer stage or surgical techniques varied, these conditions might be more similar to daily clinical practices. Also, these confounding factors did not show significant differences between the two groups in univariate or multivariate analysis.

Pelvimetry is a factor that mainly affects surgical difficulties or surgical outcomes [2, 28]. In our study, no significant correlation was seen between MFA and ISD and a clinically negligible, weak negative correlation was seen between MFA and TC. This result suggested that MFA was mainly affected by extra fat deposition rather than predetermined pelvic bone size. This hypothesis should be evaluated in a future study.

Intra- and inter-observer agreements for the quantitative evaluation of VFA and MFA were excellent in this study. This might not only be because VFA and MFA were measured semi-automatically, but also because our institution has enough experience in measuring fat as abdominal fat is routinely measured to predict disease risk or for research with the same software being used with the same techniques as this study.

There were several limitations to our study. First is possible selection bias due to the retrospective, single-centre design. However, we included all possible patients who underwent curative-intent surgery at a large-volume centre, so selection bias would be minimised. Second, the analysed patient groups varied in surgical methods and status of CCRTx. However, the effects of important variables were controlled via multivariate analysis. The various medical situations might reflect actual clinical circumstances.

In conclusion, MFA was an independent biomarker for predicting DFS in patients who underwent curative-intent surgery for mid-to-lower rectal cancer.

Funding The authors state that this work has not received any funding.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Dr. Myeong-Jin Kim, Severance Hospital.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry Yunho Rho, Yonsei University, College of Medicine, kindly provided statistical advice for this manuscript.

Informed consent Written informed consent was waived by the institutional review board.

Ethical approval Institutional review board approval was obtained.

Methodology
- retrospective
- diagnostic or prognostic study
- performed at one institution

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