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ORIGINAL ARTICLE

Does the mesorectal fat area impact the histopathology metrics of the specimen in males undergoing TME for distal rectal cancer?

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Abstract

The aim of this study was to evaluate whether the mesorectal fat area (MFA) has an impact on the histopathology metrics of the specimen in male patients undergoing robotic total mesorectal excision (rTME) for cancer in the distal third of the rectum. Prospectively collected data of patients undergoing rTME for resectable rectal cancer by five surgeons during 3 years were extracted from the REgistry of Robotic SURgery for RECTal cancer (RESURRECT). MFA was measured at preoperative MRI. Distal rectal cancer was defined as within 6 cm from the anal verge. Specimen metrics included circumferential resection margin (CRM) measured by pathologists as involved if < 1 mm, distal resection margin (DRM) and TME quality. Of 890 patients who underwent rTME for rectal cancer, a subgroup analysis compared 116/581 (33.4%) with MFA > 20 cm^2 to 231/581 (66.6%) with MFA ≤ 20 cm^2. The mean CRM in patients with MFA > 20 cm^2 was neither statistically nor clinically significantly different from patients with MFA ≤ 20 m^2 (6.8 ± 5.6 mm vs. 6.0 ± 7.5 mm; $p = 0.544$). The quality of TME did not significantly differ: complete TME 84.3% vs. 80.3%; nearly complete TME 12.9% vs. 10.1%; incomplete TME 6.8% vs. 5.6%. The DRM was not significantly different: 1.9 ± 1.9 cm vs. 1.9 ± 2.5 cm; $p = 0.847$. In addition, the intraoperative complication rate was not significantly different: 4.3% ($n = 5$) vs. 2.2% ($n = 5$) ($p = 0.314$). This prospective multicenter study did not find any evidence to support that larger MFA would result in poorer histopathology metrics of the specimen when performing rTME in male patients with distal rectal cancer.

Keywords Total mesorectal excision · Low rectal cancer · Resection margins · Mesorectal fat area · Robotic surgery

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Introduction

Although the mesorectum was first described in 1896, it took almost a century for its clinical significance to become known [1]. Today, one of the main questions regarding total mesorectal excision (TME) is whether a minimally invasive approach is able to keep up with the results achieved with conventional TME. Two randomized controlled trials (RCTs) comparing laparoscopic to open TME for rectal cancer did not meet the criteria for non-inferiority [2, 3]. Of note, the endpoints of the ACOSOG Z6051 and ALaCart trials included specimen histopathology metrics such as circumferential resection margin (CRM), quality of TME and distal resection margin, which directly evaluated the quality of the resection. Conversely, two other RCTs [4, 5] also comparing laparoscopic to open TME for rectal cancer concluded that laparoscopic TME was not inferior. However, the endpoint of the COREAN and COLOR II trials consisted of 3-year survival rates, which is not an outcome measure directly reflecting the quality of surgery. In fact, survival may also be influenced by other factors such as neoadjuvant therapy, tumor biology, and genetic mutations [6].

Even if all four RCTs would have concluded in favor of conventional TME, turning back the clock to go back to open TME would have been unlikely. Furthermore, more and more data have been published suggesting that laparoscopic TME should be abandoned [7]; a fact that in turns refocuses the attention on the role of robotic TME (rTME). Nonetheless, on account of its additional costs, rTME will have to prove its oncological advantages in clinically challenging scenarios. Cancer of the distal third of the rectum (< 6 cm from the anal verge) in a narrow pelvis represents such as scenario particularly when the patient is obese. With regards to the latter point, body mass index (BMI) has been proven unreliable due to significant differences in distribution of body fat [8–10]. In fact, other measurements such as visceral fat area [11], waist circumference [12], and perirenal fat [13] have been studied. In the specific case of the android pelvis, the mesorectal fat area (MFA) [14] makes more sense as it reflects the space relations within the pelvis where the operation takes place. Moreover, a radiological study concluded that visceral fat area correlates extremely well with the MFA in males; this was not the case for BMI [15].

Although MFA has been recently described as an excellent predictor of the "difficulty" in performing TME, such studies [16, 17] failed to report on the histopathology metrics of the specimen. The aim of this study was to evaluate whether MFA has an impact on the such metrics in male patients undergoing robotic surgery for cancer in the distal third of the rectum.

Methods

Patients

In this multicenter study, prospectively collected data on consecutive patients undergoing rTME for resectable rectal cancer over a time period of 3 years were analyzed. Patients operated on by five surgeons were included.

This study is a subgroup analysis of this database focusing on male patients operated for low rectal cancer defined as < 6 cm from anal verge. Within this subgroup, male patients with low rectal cancer and MFA > 20 cm^2 (bulky mesorectum) were compared to male low rectal cancer patients with a MFA ≤ 20 cm^2 (normal mesorectum). The MFA as an indicator for a bulky mesorectum was measured in the preoperative MRI and divided into the two groups.

This study was approved by the Western Institutional Review Board (reference number: 1-1329396-1).

Outcomes

Histopathological outcomes

Histopathological outcomes were provided by the local pathologists of each particular institution the patients were operated at. The current study provides four histopathological outcomes in detail: the CRM in mm, the CRM involvement rate in %, the distal resection margin (DRM) (in cm) and the quality of TME and:

- CRM was measured in mm, describing the lowest measured distance between the resection margin and the tumor in the mesorectum.
- CRM involvement rate: in patients with a CRM of < 1 mm, an involvement of the resection margin was defined and stated in % after pooling all patients.
- DRM was measured in cm, describing the distance between the tumor and the resection margin of the rectum distal the tumor
- The quality of TME was macroscopically classified by one of the following groups by the respective pathologists: complete, nearly complete, or incomplete.

Further histopathological outcomes that were gathered were the number of lymph nodes harvested in the resected specimen, lympho-vascular invasion, perineural invasion, and the length of the specimen extraction site.

Clinical outcomes

Additional clinical outcomes that were surveyed were the operating time, intra- and postoperative complication rate,

length of stay, mortality rate, readmission rate, and reoperation rate.

Statistics

Data were presented in % or mean (average) with standard deviation (SD), where appropriate.

T-student and Chi-squared tests were used to compare continuous and categorical variables, respectively. Multivariate logistic regression with backward elimination was utilized to evaluate for predictors of CRM involvement. Significance was defined as a p value of < 0.05. Statistical calculations were performed using SPSS® version 24 for Windows® (IBM Corporation, Armonk, New York, USA).

Results

A total of 890 patients operated for rectal cancer by five different colorectal surgeons were analyzed for this study. A total of 347 male patients with low rectal cancer (< 6 cm from anal verge) were included in this subgroup analysis. In this study 116 (33.4%) male, lower rectal cancer patients with bulky mesorectum (MFA > 20 cm^2) were compared to 231 (66.6%) male low rectal cancer patients with normal mesorectum (MFA ≤ 20 cm^2).

The mean age was not different in the group with the bulky mesorectum (57.8 years) compared to the an group with the normal mesorectum (59.1 years). The BMI (Body mass index) was significant higher in the group with the MFA > 20 cm^2 compared to the group with the MFA ≤ 20 cm^2 (27.4 vs. 22.7 kg/m^2). In addition, the rate of preoperative chemoradiation (66.4% vs. 48.1%) was significant higher in the group with the bulky mesorectum, compared to the normal mesorectum group. Most patients in both groups were in stage II and III in the AJCC (American Joint Committee on Cancer). Further baseline characteristics as ASA (American Society of Anesthesiologists) classification, comorbidities, previous abdominal surgery CR-POSSUM (Colorectal—Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity) scores, tumor distance from anal verge and the exact numbers of AJCC stage are highlighted in Table 1.

Histopathological outcomes

Circumferential resection margin (CRM)

The mean CRM in mm in male, low rectal cancer patients with MFA > 20 cm^2 were neither statistically nor clinically significantly different from those with MFA ≤ 20 m^2 (6.8 ± 5.6 mm vs. 6.0 ± 7.5 mm; $p = 0.544$) (Fig. 1). In

Table 1 Baseline characteristics in male, low rectal cancer patients comparing a mesorectal fat area > 20 cm^2 to a mesorectal fat area ≤ 20 cm^2

Variables	Mesorectal fat area > 20 cm^2 ($n = 116$)	Mesorectal fat area ≤ 20 cm^2 ($n = 231$)	p value
Age (years)	57.8 ± 11.9	59.1 ± 12.5	0.384
BMI (kg/m^2)	27.4 ± 2.4	22.7 ± 2.2	< 0.001
ASA (n (%))			
I	29 (25.0%)	80 (34.6%)	0.022
II	71 (61.2%)	137 (59.3%)	
III	16 (13.8%)	14 (6.1%)	
Comorbidities (n (%))	61 (52.6%)	114 (49.3%)	0.238
Previous abdominal surgery (n (%))	18 (15.5%)	45 (19.5%)	0.460
CR-POSSUM Physiology Score	4.13 ± 2.9	4.72 ± 3.1	0.147
CR-POSSUM Operative Severity Score	11.9 ± 0.26	11.9 ± 0.39	0.164
CR-POSSUM Mortality Risk (%)	2.8 ± 4.2%	3.4 ± 5.4%	0.357
Tumor distance from AV (cm)	3.8 ± 1.3	3.8 ± 1.3	0.877
AJCC stage (n (%))			
I	10 (8.6%)	22 (9.5%)	0.803
II	45 (38.8%)	96 (41.6%)	
III	43 (37.1%)	85 (36.8%)	
IV	16 (13.8%)	24 (10.4%)	
Unknown	3 (2.6%)	4 (1.7%)	
Neoadjuvant chemoradiation (n (%))	77 (66.4%)	111 (48%)	0.001

The Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity. *AV* anal verge, *AJCC* American Joint Committee on Cancer

BMI body mass index, *ASA* American Society of Anesthesiologists, *CR-POSSUM* ColoRectal

addition, the CRM involvement rates did not differ between both the patient groups (10.3% vs. 10.9%; $p = 0.999$) (Fig. 2).

Distal resection margin (DRM)

The mean DRM in cm in male, low rectal cancer patients with MFA > 20 cm^2 were also neither statistically nor clinically significantly different from those with MFA ≤ 20 m^2 (1.9 ± 1.9 cm vs. 1.9 ± 2.5 cm; $p = 0.847$) (Fig. 3).

Quality of the total mesorectal excision (qTME)

Quality of TME between male, low rectal cancer patients with MFA > 20 cm^2 were also not significantly different from those with MFA ≤ 20 m^2. The rates of complete TME were 84.3% vs. 80.3%; nearly complete TME 12.9% vs. 10.1%; and incomplete TME 6.8% vs. 5.6% (Fig. 4). The p value comparing the rates of incomplete TME rate was 0.741.

Further pathohistological outcomes as the proximal resection margin, the lymph vascular and perineural invasion, the length of the specimen extraction site are listed in Table 2.

Clinical outcomes

The intraoperative complication rate (ureter leaks, bleeding, injuries of other organs, etc.) was not significantly different with 4.3% (n = 5) in the group MFA > 20 cm^2 and 2.2% ($n = 5$) in the group MFA ≤ 20 m^2 ($p = 0.314$). Further clinical outcomes as operation time, postoperative

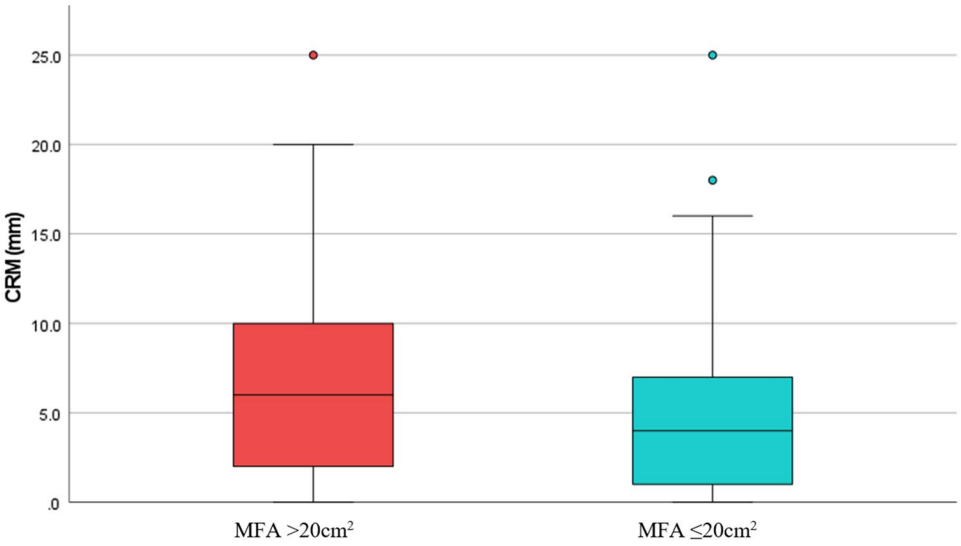

Fig. 1 Mean CRM in mm in **A** male, low rectal cancer patients with bulky mesorectum (MFA > 20 cm^2) **B** male, low rectal cancer patients with normal mesorectum (MFA ≤ 20 cm^2)

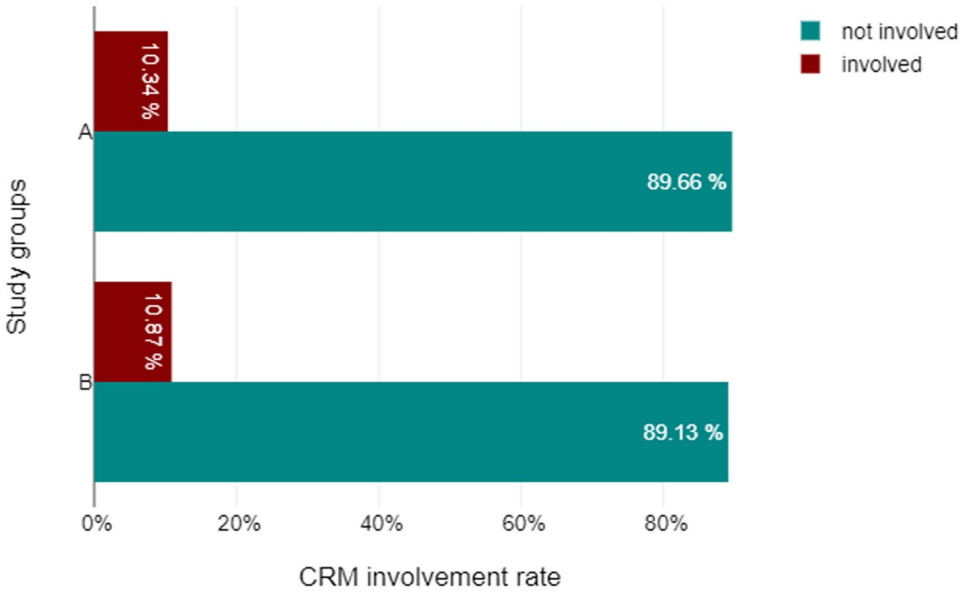

Fig. 2 CRM involvement rate in % in **A** male, low rectal cancer patients with bulky mesorectum (MFA > 20 cm^2); **B** male, low rectal cancer patients with normal mesorectum (MFA ≤ 20 cm^2)

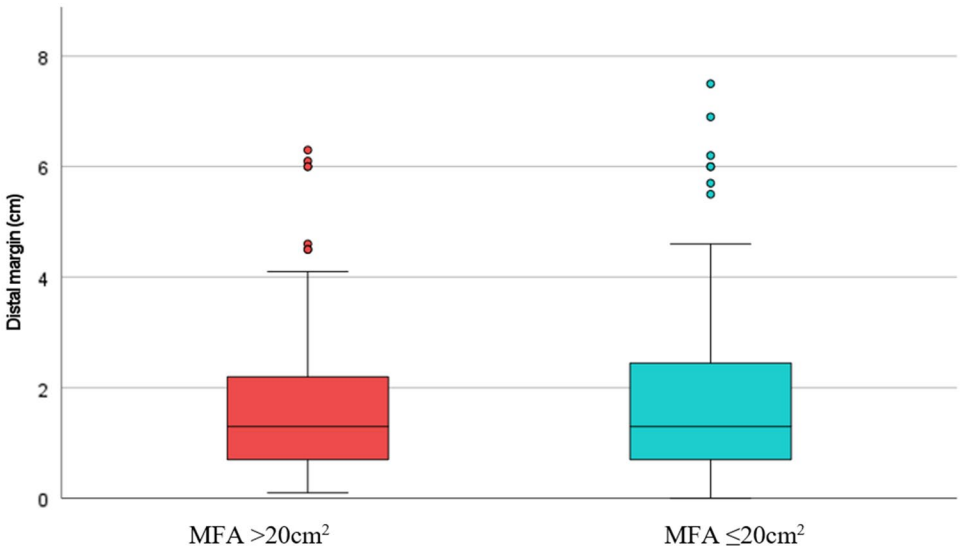

Fig. 3 Distal resection margin in cm in **A** male, low rectal cancer patients with bulky mesorectum (MFA > 20cm^2); **B** male, low rectal cancer patients with normal mesorectum (MFA ≤ 20 cm^2)

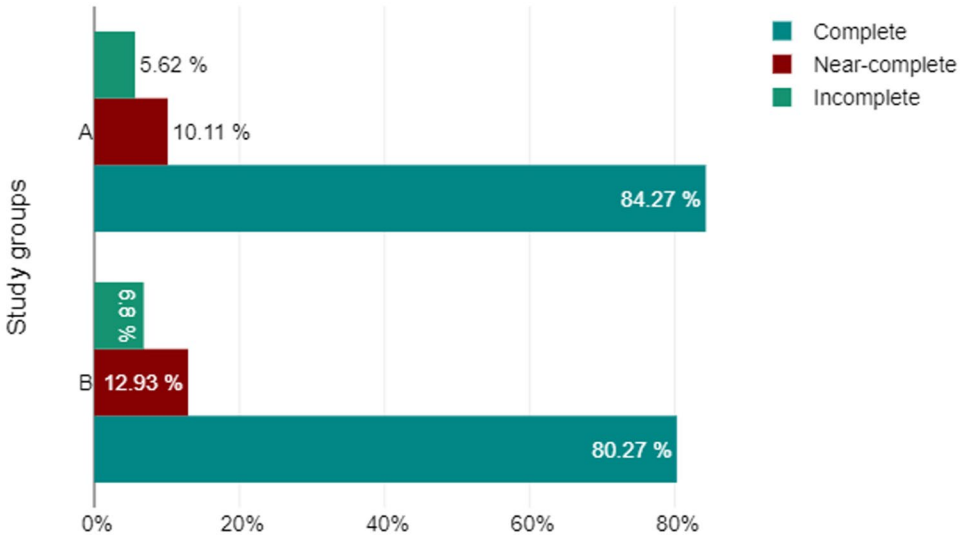

Fig. 4 Quality of the TME quality in **A** male, low rectal cancer patients with bulky mesorectum (MFA > 20 cm^2); **B** male, low rectal cancer patients with normal mesorectum (MFA ≤ 20 cm^2)

complication rate, length of stay, reoperation and readmission rate as well as mortality rate are also listed in Table 2.

Multivariate logistic regression

A multivariable logistic regression model with the independent variable of CRM involvement adjusted for multiple baseline, preoperative, and intraoperative variables was developed. Incomplete TME quality (OR = 23.5; $p = 0.01$) and distance of tumor from the anal verge (OR = 0.28; $p = 0.003$) were the only two significant predictors of CRM involvement. Of note, MFA was neither predictive nor protective for CRM involvement (OR = 0.44; $p = 0.34$).

Discussion

The main finding of this study was that no significant differences (statistical or clinical) were found when comparing the histopathology metrics of the specimens of male patients with statistically different MFA having undergone rTME for cancer located in the distal third of the rectum. This study included data of 5 colorectal surgeons performing 890 operations in 3 years. This is a mean of 59 operations per surgeon each year. It is noteworthy that the surgeons were beyond their personal learning curve. As stated in a recent meta-analysis, a number of 15–29 cases might have an impact on the histopathology metrics of the specimens [18].

Increased BMI has always been seen as a parameter of the difficulty of rectal cancer [8, 9] especially when

Table 2 Perioperative characteristics and outcomes in male, low rectal cancer patients comparing a mesorectal fat area > 20 cm^2 to a mesorectal fat area ≤ 20 cm^2

Variables	Mesorectal fat area > 20 cm^2 ($n = 116$)	Mesorectal fat area ≤ 20 cm^2 ($n = 231$)	p value
Types of surgery performed (n (%))			
LAR	43 (37.1%)	96 (41.6%)	0.072
ISR	68 (58.6%)	109 (47.2%)	
APE	5 (4.3%)	26 (11.2%)	
Operating time (min)	363.6 ± 112.1	340.1 ± 110.7	0.063
Number of lymph nodes harvested (n)	17.4 ± 13.4	18.4 ± 10.9	0.449
Proximal resection margin (cm)	18.9 ± 9.5	19.9 ± 9.0	0.343
Distal resection margin (cm)	1.9 ± 1.9	1.9 ± 2.5	0.847
Circumferential radial margin (mm)	6.8 ± 5.6	6.0 ± 7.5	0.544
CRM involvement rate (n (%))	12 (10.3%)	25 (10.9%)	1.0
Incomplete TME quality rate (n (%))	7 (5.6%)	16 (6.8%)	0.741
Lymphovascular invasion (n (%))	20 (17.2%)	44 (19%)	0.882
Perineural invasion (n (%))	18 (15.5%)	27 (11.7%)	0.304
Length of specimen extraction site (cm)	26.4 ± 5.7	26.1 ± 6.3	0.862
Intraoperative complication rate (n (%))	5 (4.3%)	5 (2.2%)	0.314
Length of stay (days)	13.8 ± 11.4	13.9 ± 14.7	0.939
Postoperative complication rate (n (%))	36 (31%)	64 (27.7%)	0.302
Mortality rate (n (%))	0 (0%)	2 (0.9%)	1.0
Readmission rate (n (%))	34 (29.3%)	57 (24.7%)	0.298
Reoperation rate (n (%))	5 (4.3%)	15 (6.5%)	0.473

CRM circumferential resection margin, *TME* total mesorectal excision, *LAR* low anterior resection, *ISR* inter-sphincteric resection, *APE* abdomino-perineal excision

performed laparoscopically [10]. When operating upon the lower rectum, MFA seems to be a more specific parameter than BMI as the former is an expression of the limited space in the lower pelvis. In 2009, a study of 58 rectal cancer patients by Boyle et al. found a larger MFA at the preoperative MRI of male patients [14]. Moreover, the authors reported that a BMI > 25 kg/m^2 was associated with a greater MFA. Although Boyle et al. did not make any statement on the difficulty of the operations, the authors did examine whether MFA had an impact on one histopathology metric, namely the CRM of the specimens. Boyle et al. concluded that a larger MFA was not associated with increased rates of CRM involvement, which was also the case of our study.

In 2017, Escal et al. screened the data of 164 patients undergoing open, laparoscopic or robotic TME for factors that might have been associated with the difficulty of the operation such as blood loss, conversion to open, resection margins, morbidity and others. The operations identified as difficult were then compared to a number of clinical and radiological parameters. High BMI, large MFA, colorectal vs. coloanal anastomosis, and short intertuberous distance were identified and a four-item score created. When a score of three or more points was reached, the operation was classified as difficult or high risk [17]. In 2019, Yamaoka et al. studied 98 patients with rectal cancer undergoing low anterior resection with TME by one surgeon. Data from MRI pelvimetry as well as clinical data were compared to the operating time of the pelvic phase. The authors concluded that MFA was the only factor to be associated with significantly longer operating time of the pelvis phase in a multiple linear regression analysis [16].

In the study by Boyle et al., the MFA was 21.3 cm^2 in male patients with a BMI < 25 kg/m^2 and 30.0 cm^2 in male patients with a BMI ≥ 25 kg/m^2 [14]. The study by Escal et al. reported that MFA was 19.1 cm^2 in low-risk patients and 22.7 cm^2 in high-risk patients independently of the BMI [17]. Yamaoka et al. concluded that patients with MFA ≥ 26.0 cm^2 were a difficult subgroup of patients to operate on with longer operating time [16].

In the present study, the quality of the surgical procedure was evaluated by the histopathology metrics of the specimens (CRM in mm, CRM involvement rates, distal resection margin in mm, quality of TME), which did not significantly differ when comparing male patients with statistically different MFA. A recent study by Pan et al. [19] claimed that a larger MFA might correlate with early-onset rectal cancer, a fact not supported by the data of the present study. It is noteworthy that the difference in age between the patients in the study by Pan et al. was less than 3 years.

Strengths and limitations

The strength of this study is the relatively high number of male patients presenting with low rectal cancer and bulky mesorectum. The fact that data presented in this study were gathered from different surgeons may also be seen as a strength, as it demonstrates that the results were not depending on one surgeon only. Nevertheless, individual data on the surgeons' subjective impression of the difficulty of the operation were not available.

This study also has a few limitations. The risk of confounding is higher in multicenter studies as compared to single-center studies. This counterbalanced by the advantage of large sample size in the former. One of the limitations of this study was lack of long-term oncologic data, such as overall and cancer-specific survival were not reported. Oncologic outcomes would be skewed substantially in this particular study given the differences in approaches to perioperative chemotherapy and radiation. Another limitation was that the specimens were examined by the local pathologists at the contributing institutions rather than by a centralized pathology.

Conclusion

This multicenter study of prospective collected data did not find any evidence to support the hypothesis that an increased MFA would result in poorer histopathology outcomes when performing rTME in male patients with distal rectal cancer.

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Declarations

Conflict of interest All the authors disclose financial or non-financial interests that are directly or indirectly related to the work submitted for publication.

Research involving human participants and/or animals This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by Western Institutional Review Board (reference number: 1-1329396-1).

Informed consent Informed consent was obtained from all the individual participants included in the study.

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