ASTR

ORIGINAL ARTICLE

pISSN 2288-6575 • eISSN 2288-6796
https://doi.org/10.4174/astr.2019.96.2.86
Annals of Surgical Treatment and Research

Oncologic evaluation of obesity as a factor in patients with rectal cancer undergoing laparoscopic surgery: a propensity-matched analysis using body mass index

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Purpose: This study evaluated the oncologic impact of obesity, as determined by body mass index (BMI), in patients who underwent laparoscopic surgery for rectal cancer.
Methods: The records of 483 patients with stage I–III rectal cancer who underwent laparoscopic surgery between June 2003 and December 2011 were reviewed. A matching model based on BMI was constructed to balance obese and nonobese patients. Cox hazard regression models for overall survival (OS) and disease-free survival (DFS) were used for multivariate analyses. Additional analysis using visceral fat area (VFA) measurement was performed for matched patients. The threshold for obesity was BMI ≥ 25 kg/m^2 or VFA ≥ 130 cm^2.
Results: The score matching model yielded 119 patients with a BMI ≥ 25 kg/m^2 (the obese group) and 119 patients with a BMI < 25 kg/m^2 (the nonobese group). Surgical outcomes including operation time, estimated blood loss, nil per os periods, and length of hospital stay did not differ between the obese and the nonobese group. The retrieved lymph node numbers and pathologic CRM positive rate were also similar in between the 2 groups. After a median follow-up of 48 months (range, 3–126 months), OS and DFS rates were similar between the 2 groups. A tumor location-adjusted model for overall surgical complications showed that a BMI ≥ 25 kg/m^2 were not risk factors. Multivariable analyses for OS and DFS showed no significant association with a BMI ≥ 25 kg/m^2.
Conclusion: Obesity was not associated with long-term oncologic outcomes in patients undergoing laparoscopic surgery for rectal cancer in the Asian population.
[Ann Surg Treat Res 2019;96(2):86-94]

Key Words: Body mass index, Rectal neoplasms, Laparoscopy

Received July 18, 2018, **Revised** October 5, 2018, **Accepted** October 16, 2018

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•The abstract of this article was presented at the 50th Annual Meeting of the Korean Society of Coloproctology in Seoul, Korea, on April 1–2, 2017.

INTRODUCTION

Obesity is an uncontrollable host factor, and a predictor of surgical outcomes, including technical difficulties, postoperative complications, and anthropometric events in patients undergoing gastrointestinal surgery [1]. Body mass index (BMI) and visceral fat area (VFA) have been widely used to define threshold values for obesity, although these markers do not always reflect the degree of intra-abdominal or intrapelvic fat, which may be associated with technical difficulties during surgical procedures [2]. In colorectal cancer, obesity is not only an etiologic risk factor, but a predictive marker for morbidity and mortality [3]. Moreover, obesity, as evaluated by BMI and VFA, has been reported to affect outcomes in patients with colorectal cancer who underwent open or laparoscopic surgery [4-9].

The impact of obesity in rectal cancer may differ from that in colon cancer because visceral fat and the volume of the pelvis may have greater effects on surgical procedures for rectal cancer. Studies assessing the effects of obesity as determined by BMI on outcomes in rectal surgery patients have yielded conflicting results [10-12]. Previous studies using VFA have also suggested a strong consensus that measures of visceral adiposity are more accurate than BMI, and that these measures of visceral adiposity predict more difficult resections and a higher incidence of postoperative complications, although these studies reached disparate conclusions [9,13].

However, in clinical practice, it may not be feasible for surgeon to take the approach of measurement of VFA for the prediction of surgical outcomes. Furthermore, the long-term oncologic effect of obesity, as determined by BMI in laparoscopic surgery for rectal cancer, remains still unclear. This study therefore evaluated surgical complications and the oncologic impact of obesity, based on BMI, in patients who underwent laparoscopic surgery for rectal cancer, using a matching model that balanced clinicopathologic factors in obese and non-obese patients. Additionally, we investigated distribution of VFA in the matched patients to evaluate a relationship with the BMI.

METHODS

Patients who underwent laparoscopic surgery for stage I–III rectal cancer at the Department of Surgery, Seoul National University Bundang Hospital, between June 2003 and December 2011 were retrospectively analyzed. Rectal cancer was defined as an adenocarcinoma located within 15 cm of the anal verge. Patients with stage IV disease, synchronous colorectal cancer, multiple malignancies or a previous history of abdominal surgery were excluded, as were patients who underwent noncurative resection or trans-anal excision. Patients were divided into 2 groups based on BMI, the BMI cutoff for obesity based on classification by the Asia Cohort Consortium of the World Health Organization (WHO). Patients with a BMI $\geq$ 25 kg/m^2 were defined as obese and those with a BMI $<$ 25 kg/m^2 as nonobese [14].

VFA was preoperatively measured by Fat Scan software, Rapidia version 2.8, on cross-sectional CT scans, obtained at the middle of L4. Adipose tissue was determined by setting the attenuation level within a range of -190 to -30 Hounsfield units [15]. VFA was defined by manual contour tracing and calculated automatically by Fat Scan. The VFA cutoff for obesity was based on the classification in a previous study with VFA $<$ 130 cm^2 defined as nonobese and VFA $\geq$ 130 cm^2 as obese [16].

Differences between nonobese and obese groups, based on BMI and VFA, were investigated. Factors evaluated included baseline characteristics, pathologic parameters (retrieved lymph nodes and circumferential resection margin status), short-term surgical outcomes (conversion, technical difficulty, operation time, estimated blood loss, nil per os [NPO] period, and days hospitalized), postoperative surgical complications, and long-term oncologic outcomes, including recurrence pattern, overall survival (OS) and disease-free survival (DFS). The technical difficulty of surgical procedures was defined as a significant deviation from 3 surgical procedure categories as described; step 1, visualization and localization of the tumor after trocar insertion; step 2, lymphovascular dissection and bowel mobilization; step 3, transection and anastomosis [17]. Preoperative chemoradiotherapy was performed for locally advanced rectal cancer as recommended by the National Comprehensive Cancer Network guideline, which was described in our previous study [18]. Long-course radiotherapy was given over 5.5 weeks at a dose of 50.4 Gy, of which 45 Gy was applied in 25 fractions to the pelvis, and a 5.4 Gy boost was applied in 3 fractions to the primary tumor. The chemotherapeutic regimens consisted of 2 cycles of an intravenous bolus of fluorouracil (400 mg/m^2 per day) and racemic D, L-leucovorin (20 mg/m^2 per day) for 3 days in weeks 1 and 5 of radiotherapy, or continuous oral administration of capecitabine (825 mg/m^2 twice daily) during radiotherapy.

All operations were performed by 2 experienced surgeons, each of whom had performed $>$ 50 laparoscopic rectal operations. Tumor stage was classified using the 7th edition of the American Joint Committee on Cancer staging system. Patterns of recurrence were classified as local (tumor recurrence around the anastomosis or the region of the primary operation), systemic, or combined. In the pathological assessment of the completeness of total mesorectal excision (TME) and the involvement of a pathological circumferential resection margin (pCRM) defined as the shortest distance from a tumor of $\leq$ 1 mm, we examined the quality of the TME specimens from selected patients via a multidisciplinary team approach, using the method of Nagtegaal and Quirke [19]. The quality of the

TME specimens and the pCRM assessment were validated in our previous study [18].

Patients in the obese and nonobese groups, as defined by the BMI cutoff of 25 kg/m^2, were matched 1:1 to adjust for potential biases that may influence surgical and oncologic outcomes as in previous studies [6,7,20]. Covariates for matching included preoperative factors (age, sex, tumor height, American Society of Anesthesiologists (ASA) physical status classification, and preoperative treatment) and postoperative factors (differentiation type, T-stage, N-stage) (Supplementary Fig. 1). All variables including surgical complications, and long-term oncologic outcomes were compared between the obese and nonobese groups. In addition, the radiologic measurement of VFA was performed in only matched patients with the exclusion of 59 patients because the quality of their CT scans was poor. The correlation between BMI and VFA was also assessed by scatter plot analysis.

Categorical variables were analyzed using the chi-square test or Fisher exact test. Continuous variables expressed as means ± standard deviation were compared using Student t-test. OS and DFS were analyzed by the Kaplan-Meier method and compared by the log-rank test. A logistic regression model for overall surgical complications and a Cox proportional hazards regression model for OS and DFS were performed for risk stratification. Risk of overall surgical complications was stratified using tumor location-adjusted multivariate analysis. Multivariable analyses for OS and DFS were performed using the tumor location. Data were analyzed using IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA) and R statistical software (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). Two-tailed statistical significance was set at $P < 0.050$. This study was approved by the Institutional Review Board (IRB) of the Seoul National University Bundang Hospital, Korea (approval number: B-1504-296-109). And the IRB authority did waive the requirement to obtain informed consent because this retrospective study did not include the personal information.

RESULTS

Of the total 982 patients who had undergone surgery for rectal cancer during the study period, 483 patients who underwent laparoscopic surgery for stage I–III rectal cancer were included after 499 patients were excluded (Fig. 1). Based on a BMI cutoff of 25 kg/m^2, there were 119 patient pairs matched by age, sex, tumor height, ASA physical status classification, preoperative radiotherapy, chemotherapy, differentiation type, and T–N stage. Included patients had a mean BMI of 24.61 kg/

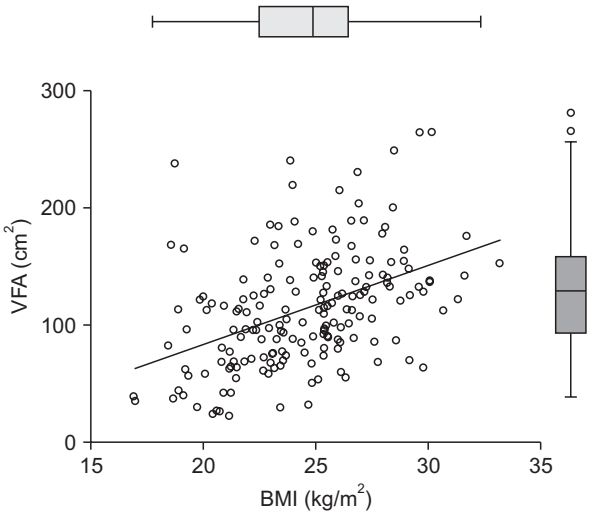


Fig. 2. The relationship of body mass index (BMI) with visceral fat area (VFA). Coefficient of correlation, $R^2 = 0.436$, $P < 0.001$.

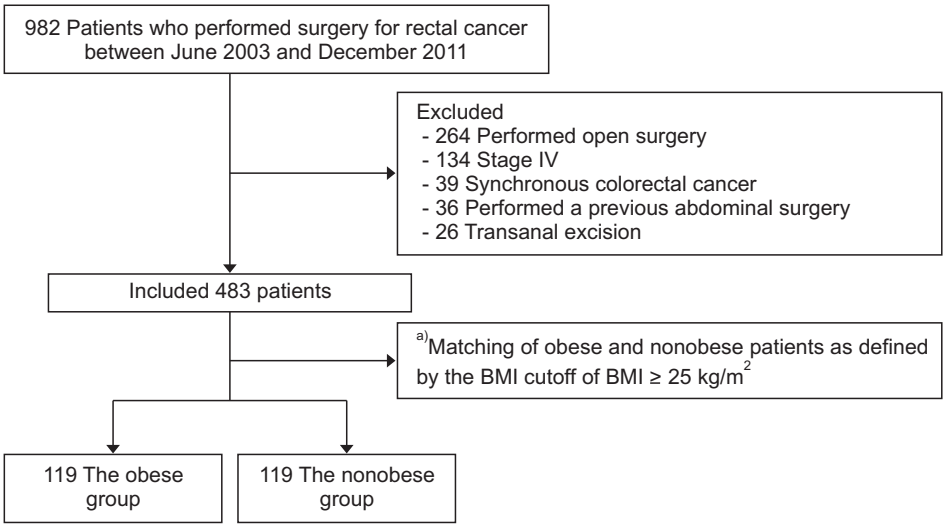


Fig. 1. Flow chart for matching and validation of obese and nonobese patients. a)Matched covariates including age, sex, tumor height, American Society of Anesthesiologists physical status classification, preoperative radiotherapy, chemotherapy, differentiation type and T–N stage. BMI, body mass index.

Table 1. Baseline characteristics and pathologic parameters

Characteristic	BMI < 25 kg/m^2 (n = 119)	BMI ≥ 25 kg/m^2 (n = 119)	P-value
Age at diagnosis (yr)[a]			0.697
< 65	62 (52.1)	66 (55.5)	
≥ 65	57 (47.9)	53 (44.5)	
Sex[a]			0.601
Male	70 (58.8)	65 (54.6)	
Female	49 (41.2)	54 (45.4)	
Tumor height (cm)[a,b]			0.841
≤5	33 (27.7)	30 (25.2)	
>5, ≤10	55 (46.2)	54 (45.4)	
>10	31 (26.1)	35 (29.4)	
ASA PS classification[a]			0.883
I	44 (37.0)	44 (37.0)	
II	68 (57.1)	70 (58.8)	
III	7 (5.9)	5 (4.2)	
Operation type			0.184
Anterior resection	1 (0.8)	3 (2.5)	
Low anterior resection	105 (88.2)	102 (85.7)	
Ultralow anterior resection	8 (6.7)	10 (8.4)	
Abdominoperineal resection	5 (4.2)	3 (2.5)	
Total proctocolectomy	0 (0)	1 (0.8)	
Preoperative radiotherapy[a]			0.819
No	85 (71.4)	83 (69.7)	
Preoperative	27 (22.7)	26 (21.8)	
Postoperative	7 (5.9)	10 (8.4)	
Chemotherapy[a]			0.824
No	57 (47.9)	52 (43.7)	
Preoperative	9 (7.6)	9 (7.6)	
Postoperative	35 (29.4)	42 (35.3)	
Pre- and postoperative	18 (15.1)	16 (13.4)	
Differentiation type[a]			0.851
Well differentiated	20 (16.8)	15 (12.6)	
Moderated differentiated	95 (79.8)	99 (83.2)	
Poorly differentiated	3 (2.5)	4 (3.4)	
Mucinous adenocarcinoma	1 (0.8)	1 (0.8)	
Tumor size (cm)	3.47 ± 0.2	3.51 ± 0.2	0.942
Pathologic T stage[a]			0.470
0	10 (8.4)	10 (8.4)	
1	23 (19.3)	13 (10.9)	
2	34 (28.6)	39 (32.8)	
3	50 (42.0)	56 (47.1)	
4	2 (1.7)	1 (0.8)	
Pathologic N stage[a]			0.430
0	84 (70.6)	79 (66.4)	
1	27 (22.7)	26 (21.8)	
2	8 (6.7)	14 (11.8)	
Lymphatic invasion			0.138
No	85 (71.4)	72 (60.5)	
Yes	26 (21.8)	40 (33.6)	
Not available data	8 (7.8)	8 (6.7)	
Venous invasion			>0.999
No	95 (79.8)	96 (80.7)	
Yes	16 (13.4)	16 (13.4)	
Not available data	8 (6.8)	7 (5.9)	

Table 1. Continued

Characteristic	BMI < 25 kg/m^2 (n = 119)	BMI ≥ 25 kg/m^2 (n = 119)	P-value
Perineural invasion			0.347
No	93 (78.2)	85 (71.4)	
Yes	18 (15.1)	27 (22.7)	
Not available data	8 (6.7)	7 (5.9)	

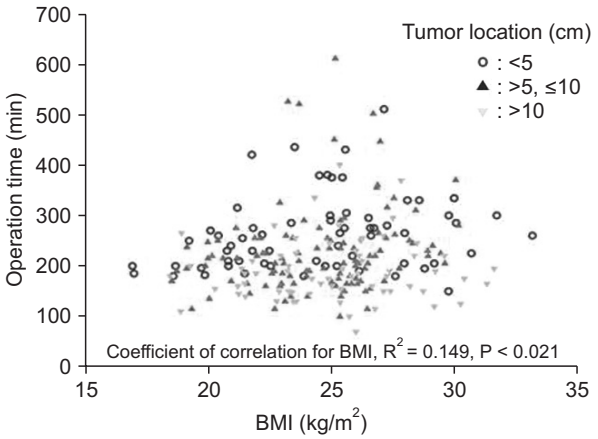
Values are presented as mean ± standard deviation or number (%).
BMI, body mass index; ASA PS, American Society of Anesthesiologists physical status.
[a]Covariates for matching preoperative and postoperative factors in included patients. [b]Tumor height was classified according the distance from anal verge.

Table 2. Surgical outcome including perioperative parameters, short-term complication and, recurrence

Variable	BMI < 25 kg/m^2 (n = 119)	BMI ≥ 25 kg/m^2 (n = 119)	P-value
Conversion			0.281
No	117 (98.3)	113 (95.0)	
Yes	2 (1.7)	6 (5.0)	
Anastomosis method[a]			0.836
Hand-swen	13/116 (11.2)	12/117 (10.3)	
Double stapling	103/116 (88.8)	105/117 (89.7)	
Diverting ileostomy			0.191
No	63 (52.9)	73 (61.3)	
Yes	56 (47.1)	46 (38.7)	
Technical difficulty[b]			0.463
No	112 (94.1)	108 (90.8)	
Yes	7 (5.9)	11 (9.2)	
Sphincter preservation			0.722
No	5 (4.2)	3 (2.5)	
Yes	114 (95.8)	116 (97.5)	
EBL (mL)	197.4 ± 24.6	183.6 ± 15.2	0.631
NPO period (day)	2.0 ± 0.2	2.2 ± 0.1	0.187
Hospital day	9.6 ± 0.4	9.5 ± 0.3	0.892
Retrieved lymph node	28.21 ± 1.4	26.23 ± 1.5	0.197
pCRM			0.622
Negative	118 (99.2)	116 (97.5)	
Positive	1 (0.8)	3 (2.5)	
Surgical complication			
Wound infection	4 (3.4)	3 (2.5)	>0.999
Anastomotic leakage[c]	3 (2.5)	3 (2.6)	>0.999
Respiratory	2 (1.7)	2 (1.7)	>0.999
Urinary tract infection	8 (6.7)	4 (3.4)	0.375
Bowel obstruction	5 (4.2)	9 (7.6)	0.253
Port site herniation	0 (0)	2 (1.7)	0.498
Total	20 (16.8)	19 (16.0)	>0.999
Recurrence patterns			0.214
Local	0 (0)	3 (2.5)	
Distant	1 (0.8)	1 (0.8)	
Combined	6 (5.0)	11 (9.2)	

Values are presented as number (%) or mean ± standard deviation.
BMI, body mass index; EBL, estimated blood loss; NPO, nil per os; pCRM, pathological circumferential resection margin.
[a]Not available data (n = 5). [b]Defined as a significant deviation from the ordinary surgical procedure [25]. [c]Excluded patients who did not perform a sphincter preservation surgery.

A



B

Operation time (min)	BMI < 25 kg/m² (n = 119)	BMI ≥ 25 kg/m² (n = 119)	P-value
Tumor location			
≤5 from AV	249.3 ± 12.0	277.8 ± 14.0	0.137
>5, ≤10 from AV	215.9 ± 10.1	240.1 ± 13.2	0.150
>10 from AV	185.2 ± 9.8	195.7 ± 11.7	0.491
Total	217.4 ± 6.5	236.5 ± 8.2	0.070

Fig. 3. (A) Scatter plots showing the relationships of body mass index with operation time according to tumor location. (B) Operation time was compared between obese and nonobese patients, based on a body mass index (BMI) cutoff of 25 kg/m². AV, anal verge.

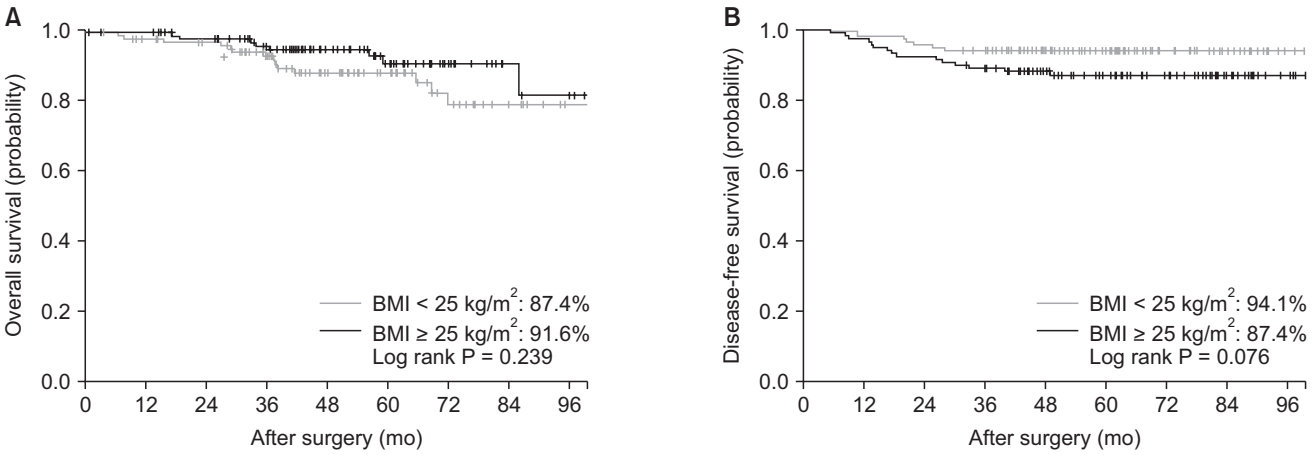


Fig. 4. Kaplan-Meier analyses of overall survival (A) and disease-free survival (B) in the 119 matched pairs of obese and nonobese patients, based on the World Health Organization cutoff of body mass index (BMI) of 25 kg/m². Patients were matched 1:1 based on age, sex, tumor height, American Society of Anesthesiologists physical status classification, preoperative treatment, differentiation type, and T–N stage.

Table 3. The risk stratification for surgical complication and survival according to the body mass index

Variable	Overall surgical complications[a]		Overall survival[b]		Disease-free survival[b]	
	OR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Unadjusted						
BMI < 25 kg/m²	Reference		Reference		Reference	
BMI ≥ 25 kg/m²	0.941 (0.47–1.86)	0.861	0.621 (0.27–1.38)	0.243	2.206 (0.90–5.41)	0.084
Adjusted						
BMI < 25 kg/m²	Reference[c]		Reference[d]		Reference[d]	
BMI ≥ 25 kg/m²	1.018 (0.50–2.05)	0.961	0.649 (0.29–1.45)	0.292	2.366 (0.96–5.81)	0.060

OR, odd ratio; CI, confidence interval; HR, hazard ratio; BMI, body mass index.
[a]Logistic regression model. [b]Cox proportional hazards regression model. [c]Tumor location – adjusted logistic regression analysis. [d]Tumor location – adjusted Cox proportional hazards regression model.

m^2 (range, 16.90–33.15 kg/m^2), and a mean VFA of 114.65 cm^2 (range, 23.14–265.90 cm^2). The median of obesity between the obese and nonobese groups was as follows; BMI, 22.31 *vs.* 26.59 kg/m^2; VFA, 70.75 *vs.* 138.4 cm^2. BMI was significantly associated with VFA (coefficient of correlation, $R^2 = 0.436$, $P < 0.001$) (Fig. 2). Furthermore, the BMI-matched model showed that the characteristics and pathologic parameters of the nonobese and obese patients did not differ significantly (Table 1).

Perioperative parameters, including technical difficulties, conversion rate, anastomosis method and sphincter preservation, did not differ significantly between the nonobese and obese groups (Table 2). Surgical outcomes, including operation time, estimated blood loss, NPO period, and length of hospital stay also did not differ, nor did the number of retrieved lymph nodes and resection margin status. Postoperative surgical complications did not differ in the obese and nonobese groups. Operation time correlated significantly with BMI (coefficient of correlation, $R^2 = 0.149$, $P = 0.021$) (Fig. 3A). Operation time according to tumor location did not differ significantly between the obese and nonobese groups (Fig. 3B).

Kaplan-Meier analysis showed that OS and DFS did not differ significantly in the obese and nonobese groups based on a BMI cutoff of 25 kg/m^2 (Fig. 4A, B). Rates of local (2.5% *vs.* 0%), distant (0.8% *vs.* 0.8%), and combined (9.2% *vs.* 5.0%) recurrence did not differ significantly.

Univariate analyses showed that BMI ≥ 25 kg/m^2 was not associated with overall surgical complications, OS or DFS (Table 3). Multivariate analyses, using a tumor location-adjusted model for overall surgical complications, showed that a BMI ≥ 25 kg/m^2 was a not risk factor for overall surgical complications (odds ratio [OR], 1.018; 95% confidence interval [CI], 0.50–2.05; $P = 0.961$). Multivariable analyses for OS (hazard ratio [HR], 0.649; 95% CI, 0.29–1.45; $P = 0.292$) and DFS (HR, 2.366; 95% CI, 0.96–5.81; $P = 0.060$) showed no significant associations with a BMI ≥ 25 kg/m^2.

DISCUSSION

This study evaluated the oncologic impact of obesity, based on BMI, in patients with rectal cancer who underwent laparoscopic surgery. This study found that obesity did not add to technical challenges or oncologic hazards. These outcomes were further supported by both BMI-matched and VFA-measured models. Similar to our findings, previous studies reported similar oncologic outcomes in obese and nonobese patients, suggesting that obesity did not increase postoperative complications in patients who underwent laparoscopic surgery for colorectal cancer [6,7], although other studies have reported that obesity was useful in predicting surgical complications [5,8,9]. In rectal cancer needing TME procedure related directly to surgical quality and prognosis, visceral adiposity was associated with postoperative, oncologic, and survival outcomes [13].

However, conflicting outcomes were observed in some studies [21] similar to our findings, giving some reasons including a lower rate of positive CRM, the benefit of neoadjuvant therapy, and resections done at a specialty cancer center with dedicated oncologic colorectal surgeons. Even, obesity has been found to have a positive oncologic effect in patients with rectal cancer. Rectal cancer patients with a BMI ≥ 25 kg/m^2 had a higher DFS rate and a lower distant metastasis rate than patients with a BMI < 25 kg/m^2 [12,22]. In this study, only 4 patients had a positive CRM after the completion of TME. Furthermore, we considered that any potential adverse effects of obesity may have been masked in the setting of a high-volume specialized colorectal unit.

Obesity may be oncologically relevant in patients with rectal cancer. Obesity can reveal the underlying nutritional status of patients undergoing major intra-abdominal cancer surgery [23]. Furthermore, cachexia, one of the most life-threatening factors in cancer, can induce alterations in intermediary metabolism through mechanisms that include the release of cytokines, lipid-mobilizing. and proteolysis-inducing factors [24]. During adjuvant treatment, obese patients are less likely to develop chemotherapy-related toxicities than nonobese patients, likely because obesity facilitates the administration of appropriate doses and the continuation of chemotherapy [25].

In this study, the correlation coefficients between BMI and VFA was low but significant, although BMI could not reflect the distribution of intraabdominal adipose tissue in Asian populations having lower BMI but higher proportion of intraabdominal adipose tissue [15,26]. This study also attempted to assess the relationship of obesity with operation time according to tumor location. Determinations of obesity by VFA and BMI may differ in predicting the technical difficulty of laparoscopic rectal cancer surgery. The correlation coefficients between obesity and operation time were very low, showing that BMI was more closely correlated than VFA, in disagreement with previous studies suggesting that VFA could be a better predictor for surgical outcomes than general obesity measured by the BMI [8,9,13]. A possible explanation for these correlations might be that the degree of obesity in our study was not severe without patients excessing BMI > 35 or 40 kg/m^2. Therefore, obesity may seem not to influence rectal cancer surgery in this study. Furthermore, we consider that the VFA measurement may be limited in terms of potential interobserver differences and a difficulty of being generalized due to needing Fat Scan software, compared to BMI simply calculated as weight in kilograms divided by height in meters squared (kg/m^2).

This study had several limitations. First, its retrospective design has resulted in an inherent bias in spite of adoption of propensity score matching to reduce selection bias. Second, our

criterion for obesity, BMI ≥ 25 kg/m^2, differs from that typically used for Western populations (BMI ≥ 30 kg/m^2) [27]. The prevalence of obesity is much lower in Asian than in Western populations, whereas Asians have a higher rate of body fat compared to Caucasians of the same BMI [14]. A prospective cohort study based on a larger population showed that the average BMI of Koreans was 23.2 kg/m^2, with patients having a BMI between 23.0–24.9 kg/m^2 being at lowest risk of death [28]. In this study, only 10 patients, or 2.1%, had a BMI > 30 kg/m^2. Furthermore, because the WHO recommended a lower threshold for obesity in Asian versus Western populations [29], our criteria for obesity may have been reasonable.

In conclusion, the present study showed that obesity was not associated with long-term oncologic outcomes in patients undergoing laparoscopic rectal cancer surgery in Asian populations.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

SUPPLEMENTARY MATERIAL

Supplementary Fig. 1 can be found via https://www.astr.or.kr/src/sm/astr-96-86-s002.pdf.

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Ann Surg Treat Res 2019;96(2):86-94
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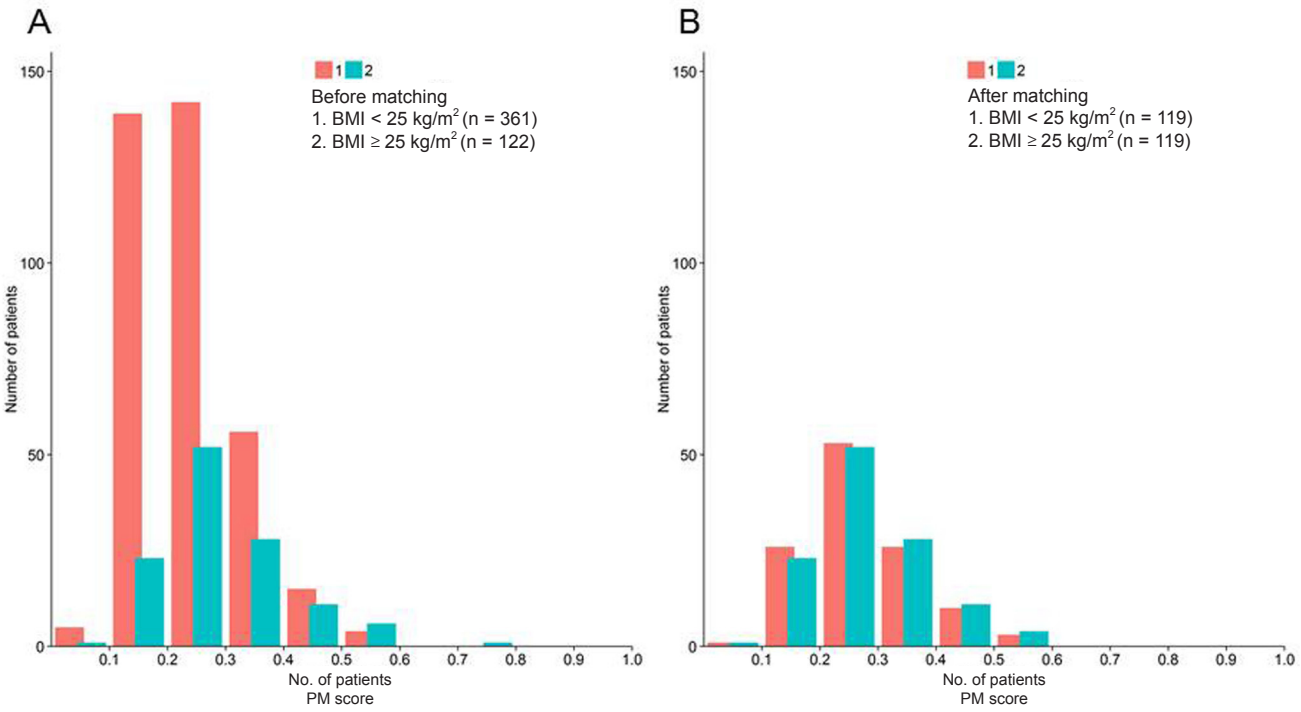

Supplementary Fig. 1. The difference for the matched covariates before and after a propensity score matching. PM scores, propensity matching scores; BMI, body mass index.