Long-term Oncologic Outcomes of Obesity after Laparoscopic Surgery for Colorectal Cancer in Asian Patients

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Purpose: The adverse effects of obesity on short-term surgical outcomes after laparoscopic colorectal surgery have been reported. However, the influence of obesity on long-term oncological outcomes after laparoscopic surgery in Asian patients has not been well understood. The aim of this study was to evaluate the effect of obesity on long-term oncologic outcomes in patients who underwent laparoscopic surgery for colorectal cancer.

Methods: Overall, 424 consecutive patients who underwent laparoscopic resection for colorectal cancer between January 2005 and July 2012 were included in this retrospective study. Patients were classified as non-obese (body mass index [BMI] <25.0 kg/m²) and obese (BMI ≥25.0 kg/m²) according to the categories proposed by the International Obesity Task Force. A survival analysis was performed using clinicopathologic characteristics, including obesity.

Results: Of the 424 patients, 325 (76.7%) were classified as non-obese and 99 (23.3%) as obese. The clinicopathologic characteristics of the obese and non-obese groups were similar, except that there were more underlying comorbidities, a lower frequency of smoking, and fewer tumors in rectum in the obese group. Results of the multivariate analysis showed that older age, elevated serum carcinoembryonic antigen, high-grade histology, advanced tumor stage, and perineural invasion were associated with poorer disease-free survival and overall survival. Obesity was not significantly associated with disease-free survival (hazard ratio [HR], 1.196; 95% confidence interval [CI], 0.686~2.086; *p*=0.528) or overall survival (HR, 1.156; 95% CI, 0.584~2.289; *p*=0.677).

Conclusion: Laparoscopic surgery for colorectal cancer seems to be safe and feasible for obese patients in terms of long-term oncologic outcomes.

Keywords: Obesity, Body mass index, Laparoscopic surgery, Colorectal cancer

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INTRODUCTION

As obesity is a growing public health concern, numerous studies have been conducted to evaluate its effects on surgical outcomes. It has been suggested to be a risk factor that contributes to adverse surgical outcomes, including longer hospital

stays, longer operative times, higher conversion rates, and wound complications.¹⁻³ Furthermore, obesity has been suggested to be a risk factor for wound infections and dehiscence, incisional hernias, stoma complications, obstructions, strictures, and anastomotic leaks.⁴⁻⁶

In Korea, the prevalence of obesity has increased from

26.9% (in 1998) to 32.0% (in 2011), according to the Korea National Health and Nutrition Examination Survey reports.⁷ Considering the increasing population of obese patients, there is a need for an approach that maintains the inherent benefits of minimally invasive surgery while improving outcomes for the obese after colorectal surgery.⁴ Regarding long-term oncologic outcomes, several studies have revealed that the long-term outcomes of laparoscopic surgery for colorectal cancer in obese Western patients were similar to those in non-obese patients.⁶ However, there are differences among ethnic populations in obesity prevalence and body fat distributions. To date, little is known about the long-term outcomes of laparoscopic colorectal surgery with respect to obesity in Asians.

The aim of this study was to compare long-term outcomes between obese and non-obese Asian patients who underwent laparoscopic surgery for colorectal cancer.

MATERIALS AND METHODS

A total of 424 consecutive patients who underwent laparoscopic resection for colorectal cancer between January 2005 and July 2012 at Seoul National University Hospital were included in this study. The medical records of these patients were reviewed retrospectively. The collected data included clinicopathologic variables and surgical outcomes. The clinicopathologic data included age, sex, body mass index (BMI), social history, history of abdominal surgeries, presence of comorbidities, American Society of Anesthesiologists (ASA) score, tumor location, and carcinoembryonic antigen (CEA) level; these were reviewed and compared with pathologic results. Surgical outcomes included conversion rates, intraoperative events, operative time, length of the postoperative hospital stay, recurrence, overall survival, and disease-free survival. This study was approved by the Institutional Review Board of the Seoul National University Hospital. Patients were divided into an obese group and a non-obese group on the basis of their BMI, in accordance with the categories proposed by the World Health Organization's International Obesity Task Force (BMI <25 kg/m², non-obese; BMI ≥25 kg/m², obese).⁷

Laparoscopic colorectal surgery was performed as a standardized procedure. Generally, five trocars were inserted, as follows: one 11-mm, two or three 5-mm, and one or two 12-mm trocars. An 11-mm umbilical trocar was used as the camera port using a 30° angled scope. Ligation of the vessel and mobilization of the colon or rectum was performed laparoscopically. The specimen was extracted through an extended incision of the port in the lower left quadrant, umbilicus, or perineum. In the case of anterior resection or low anterior resection, anastomosis was performed extracorporeally with a circular stapler. In the case of right or left colectomy, anas-

tomosis was performed extracorporeally with two linear staplers.

All patients underwent a postoperative follow-up examination every 3 or 6 months for the first 5 years and every year thereafter that comprised a physical examination, serum CEA measurements, chest radiographs, and abdominal and pelvic computed tomographic scanning. Colonofibrosopic examinations were performed every 1 or 2 years after surgery. Overall survival was defined as the time from surgery to death from any cause. Disease-free survival was defined as the time from surgery to a recurrence or death from any cause.

Data are presented as the number of patients and percentages or as means with standard deviations. Depending on the nature of the data, the chi-squared test, Fisher's exact test, Student's *t*-test, or Mann-Whitney *U*-test was used for comparisons. A survival comparison was performed using the log-rank test of the Kaplan-Meier analysis. A multivariable analysis of survival outcomes was performed with a Cox regression analysis. Statistical analysis was performed using SPSS software, version 19.0 (SPSS, Chicago, IL). A two-tailed *p* value <0.05 was the criterion for statistical significance.

RESULTS

Among the 424 patients, 325 (76.7%) were classified as non-obese and 99 (23.3%) were classified as obese. The clinicopathological characteristics of patients according to their obesity statuses are presented in Table 1. There were no significant differences in clinicopathological characteristics between groups, with the exception of the presence of comorbid diseases, smoking history, and location of the tumor. The obese group had more comorbid diseases, a lower frequency of smoking, and a lower prevalence of colonic tumors than did the non-obese group.

In terms of short-term outcomes, the conversion rates, operative times, transfusion rates, and complication rates were not significantly different between the obese and non-obese groups (Table 2). The length of hospitalization was shorter and the estimated blood loss was greater in the obese group than in the non-obese group.

The mean follow-up duration for patients was 46.3±19.1 (range: 0.6~97.7) months. Table 3 shows the results of the analysis of the risk factors for disease-free survival. In the univariate analysis, older age, elevated serum CEA level, high-grade histology, advanced Tumor-Node-Metastasis (TNM) stage, lymphovascular invasion, venous invasion, and perineural invasion were associated with poor disease-free survival. In the multivariable analysis, age, serum CEA level, histologic grade, TNM stage, and perineural invasion were independent significant risk factors for disease-free survival.

Table 1. Clinicopathological characteristics of patients

Characteristics	Non-obese, no. (%)	Obese, no. (%)	<i>p</i> value
No. of patients	325 (76.7)	99 (23.3)	
Age			0.338
<65 years	177 (54.5)	50 (50.5)	
≥65 years	148 (45.5)	49 (49.5)	
Gender			0.376
Male	200 (61.5)	56 (56.6)	
Female	125 (38.5)	43 (43.4)	
ASA ≥3	11 (3.4)	0 (0.0)	0.075
Presence of comorbid disease	128 (39.4)	56 (56.6)	0.003
Smoking history	45 (13.8)	5 (5.1)	0.018
Alcohol history	84 (25.8)	21 (21.2)	0.350
Location			0.042
Colon	186 (57.2)	68 (68.7)	
Rectum	139 (42.8)	31 (31.3)	
Elevated serum CEA (≥5 ng/ml)	37 (11.5)	11 (11.3)	0.967
Conversion to open	13 (4.0)	1 (1.0)	0.204
Number of tumor ≥2	6 (1.8)	2 (2.0)	0.911
Histologic grade			0.407
Low grade	312 (96.0)	93 (93.9)	
High grade	13 (4.0)	6 (6.1)	
TNM stage			0.346
I	116 (35.7)	26 (26.3)	
II	90 (27.7)	29 (29.3)	
III	109 (33.5)	40 (40.4)	
IV	10 (3.1)	4 (4.0)	
Harvested LN	19.5±9.9	18.9±9.7	0.647
Angiolymphatic invasion	65 (20.0)	24 (24.2)	0.364
Venous invasion	25 (7.7)	5 (5.1)	0.369
Perineural invasion	48 (14.8)	10 (10.1)	0.237
Adjuvant treatment	186 (57.2)	65 (65.7)	0.135
Follow-up duration (month)	45.7±19.5	48.4±17.4	0.205

ASA = American Society of Anesthesiologist; CEA = carcinoembryogenic antigen; LN = lymph node.

In the univariate analysis for overall survival, older age, high ASA score, elevated serum CEA level, high-grade histology, advanced TNM stage, lymphovascular invasion, venous invasion, and perineural invasion were associated with poor over-

Table 2. Short-term outcomes in non-obese and obese groups

Characteristics	Non-obese, no. (%)	Obese, no. (%)	<i>p</i> value
No. of patients	325 (76.7)	99 (23.3)	
Conversion to open	16 (4.9)	2 (2.0)	0.210
Operative time (minutes)	167.9±65.6	175.2±81.2	0.361
Transfusion	12 (3.7)	4 (4.0)	0.874
Hospital stay (days)	9.0±7.9	7.7±2.2	0.007
Complication	86 (26.5)	24 (24.2)	0.659
EBL (ml)	123.2±131.1	158.3±143.1	0.045

EBL = Estimated blood loss.

all survival (Table 4). In the multivariable analysis, age, ASA, serum CEA level, histologic grade, TNM stage, and perineural invasion were independent significant risk factors for overall survival.

Importantly, in the univariate analysis, obesity was not significantly associated with disease-free survival (5-year disease-free survival, 81.1% in the non-obese group versus 82.1% in the obese group; $p=0.694$; Fig. 1) or with overall survival (5-year overall survival, 87.0% in the non-obese group versus 87.3% in the obese group; $p=0.744$; Fig. 2). In the multivariable analysis, obesity was also not a significant risk factor for disease-free survival (hazard ratio, 1.196; 95% confidence interval, 0.686~2.086; $p=0.528$) or overall survival (hazard ratio, 1.156; 95% confidence interval, 0.584~2.289; $P=0.677$).

DISCUSSION

This study showed no significant differences between obese and non-obese patients in long-term survival after laparoscopic colorectal cancer surgery. In terms of short-term outcomes, several studies have shown that obese patients have unfavorable surgical outcomes, such as longer operative times, increased conversion rates, increased postoperative complication rates, and prolonged hospital stays.¹⁻³ These unfavorable short-term outcomes may affect long-term outcomes for obese patients with colorectal cancer. However, some studies in Western patients showed that long-term outcomes for obese patients were not different from those for non-obese patients.^{3,5,6,8} The present study in Asians showed similar results. Thus, considering the results for long-term survival, laparoscopic colorectal surgery appears to be acceptable for obese Asians.

In Asia, lifestyle and dietary changes have resulted in increased rates of obesity, as more Western-style eating habits are now favored.⁷ During the last decade, the overall preva-

Table 3. Univariate and multivariable analysis for disease free survival

Characteristics	Univariate		Multivariable analysis		
	5YR-DFSR (%)	<i>p</i> value	HR	95% CI	<i>p</i> value
Age		0.018			0.047
<65 years	82.2		1		
≥65 years	76.2		1.627	1.006 ~ 2.630	
Gender		0.281			
Male	80.0				
Female	83.5				
ASA		0.112			
1, 2	81.7				
≥3	68.6				
BMI		0.694			0.528
Non-obese	81.1		1		
Obese	82.1		1.196	0.686 ~ 2.086	
Presence of comorbidities		0.205			
No	83.9				
Yes	77.7				
Tumor location		0.196			
Colon	83.2				
Rectum	78.7				
Secum CEA level		0.001			0.005
<5 ng/ml	83.3		1		
≥5 ng/ml	64.7		2.330	1.299 ~ 4.178	
Adjuvant treatment		0.072			
No	87.5				
Yes	77.5				
Number of tumor		0.460			
Single	81.3				
Multiple	80.0				
Histologic grade		<0.001			<0.001
Low grade	83.2		1		
High grade	39.1		3.808	1.802 ~ 8.047	
TNM stage		<0.001			0.027
I	92.6		1		
II	85.6		1.386	0.628 ~ 3.060	
III	72.8		2.067	0.995 ~ 4.290	
IV	28.6		4.243	1.565 ~ 11.506	
Number of Harvested LN		0.639			
<12	80.7				
≥12	81.4				
Lymphovascular invasion		<0.001			0.099
No	86.0		1		
Yes	64.3		1.578	0.918 ~ 2.714	
Venous invasion		0.002			0.877
No	83.1		1		
Yes	59.1		0.943	0.449 ~ 1.981	
Perineural invasion		<0.001			0.006
No	86.0		1		
Yes	53.4		2.236	1.263 ~ 3.958	

Table 4. Univariate and multivariable analysis for overall survival

Characteristics	Univariate		Multivariable analysis		
	5YR-OSR (%)	<i>p</i> value	HR	95% CI	<i>p</i> value
Age		0.002			0.003
<65 years	90.9		1		
≥65 years	82.2		2.536	1.379 ~ 4.662	
Gender		0.352			
Male	86.2				
Female	88.3				
ASA		0.010			0.012
1, 2	87.5		1		
≥3	68.6		5.046	1.426 ~ 17.860	
BMI		0.744			0.677
Non-obese	87.0		1		
Obese	87.3		1.156	0.584 ~ 2.289	
Presence of comorbidities		0.179			
No	89.9				
Yes	82.6				
Tumor location			0.585		
Colon	88.4				
Rectum	84.9				
Secum CEA level		0.003			0.013
<5 ng/ml	88.4		1		
≥5 ng/ml	75.9		2.448	1.208 ~ 4.962	
Adjuvant treatment		0.946			
No	89.2				
Yes	86.2				
Number of tumor		0.143			
Single	87.2				
Multiple	80.0				
Histologic grade		<0.001			<0.001
Low grade	88.8		1		
High grade	42.7		4.957	2.044 ~ 12.018	
TNM stage		<0.001			0.033
I	94.8		1		
II	90.0		0.979	0.372 ~ 2.576	
III	82.3		1.562	0.646 ~ 3.779	
IV	42.9		4.687	1.426 ~ 15.409	
Number of Harvested LN		0.759			
<12	90.3				
≥12	86.0				
Lymphovascular invasion		0.001			0.374
No	90.8		1		
Yes	73.5		1.360	0.691 ~ 2.678	
Venous invasion		0.013			0.868
No	88.1		1		
Yes	73.0		1.080	0.434 ~ 2.685	
Perineural invasion		<0.001			0.019
No	90.1		1		
Yes	68.9		2.429	1.157 ~ 5.102

Fig. 1. Disease-free survival graph according to obesity (p value = 0.694).

Fig. 2. Overall survival graph according to obesity (p value = 0.744).

lence of obesity has also increased in Korea.⁷ With this trend, the penetration rates for laparoscopic resection for colorectal cancer have increased in Korea.⁹ Thus, a greater number of obese patients could undergo laparoscopic surgery for colorectal cancer. The evaluation of outcomes following laparoscopic colorectal cancer surgery in obese patients is therefore urgently required.

A recent systematic review and meta-analysis reported that approximately 20% of all malignancies were associated with obesity.¹⁰ Mortality associated with cancer in obese patients has increased to 24% with the worldwide increased prevalence of obesity over time.¹¹ Published data have shown that obesity and overweight are the cause of about 20% of deaths from cancer in women, while the rate is around 14% in men.¹² The mechanisms underlying the association between obesity and cancer are not fully understood. A high BMI is known to be a risk factor that increases insulin resistance, hyperinsulinemia, and free insulin-like growth factor (IGF)-I.¹³ Chronic hyperinsulinemia is associated with decreased concentrations of IGF-binding protein-1 and -2, which increase free IGF-I with concomitant changes in the cellular environment that favor tumor formation.^{14,15} Likewise, obesity itself may affect outcomes following cancer. In addition, tumor resection can be difficult in obese patients. Obstacles to performing laparoscopic surgery in obese patients include difficulties in obtaining an adequate operative field and difficulties in the intra-abdominal maneuvering of instruments in a restricted working area.^{2,16} These difficulties may also affect oncologic outcomes following colorectal cancer. However, this study showed no adverse effect of obesity on survival following laparoscopic colorectal cancer surgery.

BMI has been broadly used as an index to show a patient's degree of obesity.¹⁷ We used the cut-off value (25 kg/m²) suggested by the International Obesity Task Force.⁷ The cut-

off value in Asian countries is different from that in Western countries (30 kg/m²). This study included only a small number of patients with morbid obesity (30 kg/m²) according to the Asian criteria. The outcomes of morbidly obese patients should be evaluated in a larger multi-center study that includes more morbidly obese patients. Another index for obesity is visceral adiposity. Visceral adiposity is assessed based on the amount of fat evident on abdominal computed tomography or based on waist circumference. Visceral adiposity may more accurately indicate the status of obesity than BMI can. Future studies using visceral obesity are required.

Multiple studies have shown an association between obesity and colorectal cancer. Obesity has been shown to increase the risk of developing colorectal cancer almost 2-fold, with insulin and insulin-like growth factor (IGF) postulated as important mediators in the oncogenic process. However, recent reports suggest that there is insufficient evidence of a strong association between obesity and survival in colorectal cancer.¹⁸⁻²⁰ Therefore, it is unclear whether long-term surgical outcomes are adversely affected by obesity, because there have been many conflicting reports.

Recently, as obesity has become an important issue with respect to outcomes following colorectal cancer surgery, several studies have reported the effects of obesity on surgical outcomes. Obesity has been associated with poor short-term outcomes following laparoscopic colorectal surgery, including longer hospital stays, longer operative times, higher conversion rates, and wound complications. However, obesity was not associated with adverse short-term outcomes in this study, except with respect to estimated blood loss. This discrepancy may be related to differences in the definition of obesity used in the studies.

In a previous study, a greater number of metastatic regional lymph nodes was found in obese patients than in patients

with normal weight. These findings suggest that obesity is an adverse prognostic variable in colorectal cancer surgery.^{19,21} However, several studies have shown that there were no significant differences in survival between obese and non-obese Western patients.^{5,22} To our knowledge, few studies have examined long-term surgical outcomes following laparoscopic colorectal cancer in Asian patients. The results of this study showed no significant differences in disease-free and overall survival between obese and non-obese patients in Asian countries.

In this study, obese patients had more comorbidities than non-obese patients did. This heterogeneity could be a confounder. To evaluate the main effects of obesity on survival, we performed a multivariable analysis that included comorbidities. After adjusting for other significant factors, including comorbidities, obesity was not a significant prognostic factor (disease-free survival: HR, 0.742; 95% CI, 0.422~1.306; $p=0.301$; overall survival: HR, 0.792; 95% CI, 0.398~1.575; $p=0.506$). In the present study, long-term outcomes did not differ between obese and non-obese patients after adjustment for comorbidities. Limitations of the study include its retrospective design and that it included data only from a single institution. Large multicenter studies will provide more definite conclusions. This study may be useful by providing baseline data for further studies.

If information regarding patient obesity is obtained before surgery, it may be useful to develop a strategy to use laparoscopic colorectal cancer surgery. With sufficient experience, laparoscopic colorectal cancer surgery in obese patients may be feasible in terms of long-term survival. Colorectal surgeons should be aware of obesity-related challenges in these patients.

In conclusion, laparoscopic surgery for colorectal cancer in obese Asian patients seems to be safe and feasible based on long-term oncologic outcomes.

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