Modified Complete Mesocolic Excision With Central Vascular Ligation for the Treatment of Right-sided Colon Cancer

Long-term Outcomes and Prognostic Factors

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Objective: To investigate the long-term oncologic outcomes and risk factors for adverse effects in right-sided colon cancer patients who underwent modified complete mesocolic excision (mCME).

Background: Complete mesocolic excision (CME) with central vascular ligation has recently been found to improve oncological outcomes in patients with colon cancer. Our institution has established mCME on the basis of the original concept of CME for the treatment of right-sided colon cancer.

Methods: Between January 2000 and July 2009, 773 patients who underwent mCME for right-sided colon cancer were eligible for this retrospective study. The prognostic factors for survival/recurrence and the risk factors for postoperative complications were investigated.

Results: The mean follow-up period was 61.9 ± 34.7 months. The 5-year overall survival and 5-year disease-free survival rates were 84.0% and 82.8%, respectively. Pathologic stage III disease, postoperative complications, age more than 60 years, and minimally invasive surgery were found to be independent prognostic factors. The 5-year locoregional recurrence (LRR) and 5-year systemic recurrence rates (SRRs) were 4.9% and 13.7%, respectively. The risk of LRR and SRR increased with pathologic stage III disease. An American Society of Anesthesiology score of higher than II was an independent predictive factor of postoperative complications.

Conclusions: We have successfully established the mCME technique, on the basis of the same principle as CME, but with a more tailored approach. The long-term oncologic outcomes and risk of postoperative morbidity were found to be comparable with those seen with the original CME procedure.

Keywords: modified complete mesocolic excision, oncologic outcomes, prognostic factor, right-sided colon cancer

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The introduction of total mesorectal excision (TME) for the surgical treatment of rectal cancer significantly improved oncological outcomes.[1] This technique is based on the principle that dissection in the mesorectal plane produces an intact fascial-lined specimen containing all the blood vessels, lymphatic vessels, and lymph nodes (LNs) through which the tumor may disseminate; TME also reduces the risk of circumferential resection margin involvement.[2,3] With the efforts of leaders in the field and through many nationwide training programs, TME is now a standard surgical procedure for the treatment of rectal cancer. Similar efforts have been made to improve oncologic outcomes following surgical treatment of colon cancer. Recently, complete mesocolic excision (CME) with central vascular ligation (CVL) in colon cancer surgery has been introduced as a concept similar to TME. This surgical technique is based on oncologic resection with careful dissection of the mesocolon along the embryological tissue planes, resulting in a colon and mesocolon specimen lined by intact fascial coverage of the tumor and containing all blood vessels, lymphatic vessels, LNs, and surrounding soft tissue, which may contain disseminated cancer cells.[4] It has been also shown that transecting the supplying vessels at their origin and removing the entire mesocolon lead to crucial surgical planes for curative colonic resection.[1,5,6] Excision of specimens with intact mesocolon has been found to be associated with better survival rates as compared with excision of specimens with defective mesocolon.[5] In practice, applying this technique to resection of right-sided colon cancer seems to be more challenging than its application to resection of left-sided colon cancer. With respect to this surgical concept, several authors have reported successful outcomes after performing CME with CVL in right-sided colon cancer. There have been several previous studies showing good long-term outcomes after CME with CVL for the treatment of right-sided colon cancer; however, only few, if any, have reported long-term adverse effects and factors predictive of adverse effects and prognosis. We have introduced a surgical technique similar to the original CME with CVL for the surgical treatment of right-sided colon cancer. However, some technical points are different from the original CME as described by Hohenberger et al. The aim of this study was to review the long-term outcomes and to investigate risk factors and prognostic factors of the patients who received this modified CME (mCME) with CVL for the treatment of right-sided colon cancer.

PATIENTS AND METHODS

Patients

All consecutive patients with adenocarcinoma arising from the right side of the colon who received mCME with CVL between January 1, 2000, and July 31, 2009, at Yonsei University Health System (Seoul, Korea) were included in this study. Medical records were reviewed retrospectively to analyze long-term outcomes as well as adverse events. The right side of the colon was defined as the colon up to the middle transverse colon. Exclusion criteria included the following: presence of distant metastasis; synchronous or double primary cancer, cancer related to familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer, previous malignancies, or treatment involving palliative resection or an emergency operation. All patients were staged by computed tomographic scans and had endoscopically and a histologically proven malignant tumor of the right side of the colon. To exclude distant metastasis, radiographic imaging studies of the liver and chest were mandatory.

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Surgical Technique

Similar to the original CME procedure, mCME requires the separation of the visceral fascia from the parietal fascia by sharp dissection and transecting the supplying vessels at their origin. However, certain points differed from the original CME procedure. We found that, unlike the original description by Hohenberger et al, complete kocherization was not necessary in most cases unless the tumor invaded the duodenum or perinephric fat tissue. In cases of locally advanced cancer located in the middle ascending colon, our dissection plane went behind Gerota's fascia to include perinephric fat tissues in the specimen. Although we always identified the root of the middle colic artery and skeletonized it, we preserved the root and ligated only the right branch, unless the tumor was located in the transverse colon. The length of the distal ileum was determined by the extent of mesenteric dissection; if the tumor was located in the proximal ascending colon or cecum, we included a few distal ileum branches of the superior mesenteric artery in the specimen, which resulted in a longer distal ileum resection. For open right colectomy, we began the procedure by lateral-to-medial dissection up to the lateral border of the superior mesenteric vessels, exposing the pancreatic head and the third portion of the duodenum. After performing the complete mobilization of the mesocolon with sharp dissection, the supplying vessels were ligated to achieve CVL. If the tumor was located at the cecum or proximal portion of the ascending colon, the ileocolic vessels and the right branch of the middle colic vessels were transected at their origin from the superior mesenteric vessels (Fig. 1A). When the main tumor was located at the hepatic flexure and proximal transverse colon, the middle colic vessels were ligated at their origin from the superior mesenteric vessels (Figs. 1B, C). To achieve maximal LN harvest, we divided the supplying vessels at their origin from the main stalk as previously described. The extent of LN dissection included the paracolic node and mesenteric nodes along the superior mesenteric vessels. For right colectomy performed as minimally invasive surgery (MIS; robot or laparoscopic surgery), the surgical approach was made in either a lateral-to-medial or medial-to-lateral fashion, according to the surgeon's preference. CVL for MIS was performed under the same principle as for open surgery.

Classification of Surgical Complications

Complications were defined as any deviation from the general postoperative course. We used the modified classification system for analyzing surgical complications. This classification consisted of 5 severity grades.[7] Grade I included minor complications not requiring active management with the exception of antipyretics, analgesics, diuretics, antiemetics, and physiotherapy. Wound care, such as wound opening, was also included in this grade. Grade II was defined as potentially life-threatening complications. Supplementary pharmacological treatment other than drugs used for grade I was required for grade II classification. Total parenteral nutrition and blood transfusion were also included in grade II. Grade III was defined as complications causing disability or longer hospital stays. Grade III complications required surgical, endoscopic, or radiological intervention. Grade III was divided into 2 subgroups: grade IIIa, requiring intervention not under general anesthesia, and grade IIIb, requiring intervention under general anesthesia. Grade IV complications were defined as life-threatening complications requiring intensive care unit management. Grade IV also consisted of 2 subgroups: grade IVa, which includes single organ dysfunction, and grade IVb, which includes multiorgan dysfunction. Grade V was defined as patient death.

Recurrence Classification According to Disease Status

Information regarding tumor recurrence was collected by reviewing the medical records of all patients. Recurrence patterns were classified into 2 subgroups. Locoregional recurrence was defined as any clinical or histological evidence of tumor regrowth near the primary site after initial operation and absence of distant metastasis. Systemic recurrence was defined as any distant metastasis with locoregional recurrence confirmed by imaging studies or histological biopsy.

Statistical Analyses

SPSS software version 17.0 (SPSS Corp, Chicago, IL) was used for analyses. The Kaplan-Meier method was used to calculate the 5-year local recurrence rate (LRR) and the 5-year systemic recurrence rate (SRR). Disease-free survival (DFS), disease-specific survival (DSS), and overall survival (OS) after surgery were also assessed by the Kaplan-Meier method. OS was defined as the time from surgery to death from any cause. DSS was defined as the time from surgery to death related to cancer. DFS was defined as the time from surgery to any recurrence. The log-rank test was used to perform univariate comparisons. Multivariate analysis of survival

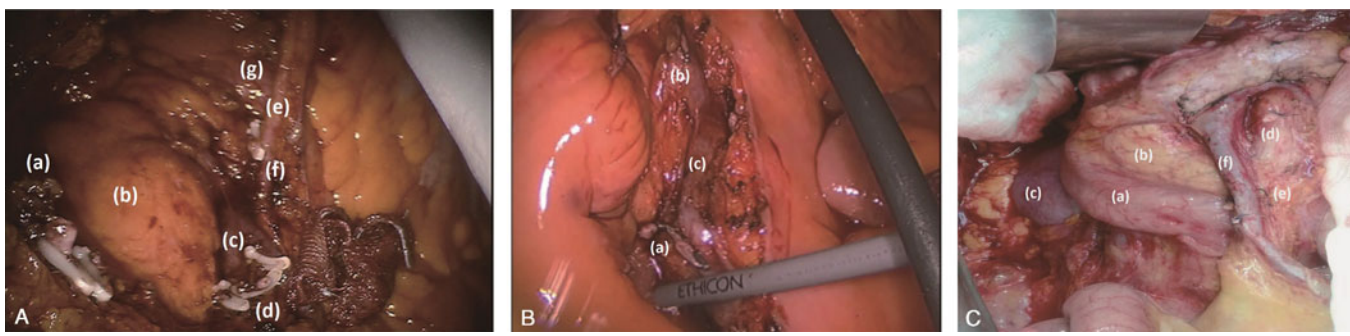

FIGURE 1. Operative fields after modified complete mesocolic excision. A, Operative field after robotic modified complete mesocolic excision following central ligation of supplying vessels: (a) Duodenum, (b) Pancreas, (c) Superior mesenteric vein, (d) Ileocolic vessels were ligated at the root, (e) Middle colic artery, (f) Right branch of the middle colic artery was ligated at the root, and (g) Stomach. B, Operative field after laparoscopic modified complete mesocolic excision following central ligation of supplying vessels: (a) Ileocolic vessels were ligated at the root, (b) The root of the middle colic vein was ligated, and (c) Superior mesenteric vein. C, Operative field after open modified complete mesocolic excision following central ligation of supplying vessels: (a) Duodenum, (b) Pancreas, (c) Perinephric fat tissue in the anterior surface of the kidney was removed, (d) The root of the middle colic artery was ligated, (e) Ileocolic vessels were ligated at the root, and (f) Superior mesenteric vein.

outcomes was performed using Cox regression analysis. Postoperative complications were grouped according to the time of the event; any adverse events occurring within 30 days after the surgery were defined as early postoperative complications whereas those occurring after 30 postoperative days were defined as late events. All the postoperative complications were analyzed using binary logistic regression. All P values were 2-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

A total of 1023 patients underwent mCME with CVL for right-sided colon cancer between January 1, 2000, and July 31, 2009, among which 773 patients were eligible for the final analysis. The mean follow-up period was 61.9 ± 34.7 months (open vs MIS: 70.0 ± 36.3 vs 39.7 ± 14.9 months).

The Analysis of Patient Characteristics

Demographic data is presented in Table 1. In the final study population, 54.5% of patients were men and 45.5% were women, and the mean age was 61.5 ± 11.4 years. Preoperative comorbidities were classified according to the American Society of Anesthesiology (ASA) classification system, and the majority of patients were classified as ASA score I (42.4%) and II (55.8%). The most common location of the main tumor was in the ascending colon [598 patients (77.4%)]. Fifty-six patients (7.2%) had undergone previous abdominal surgery.

The Analysis of Postoperative Pathologic and Perioperative Outcomes

The pathologic data and perioperative outcomes after operation are shown in Table 2. Tumor involvement with surgical margins was not reported. Upon inspection of specimens, the mean length of the bowel was 32.1 ± 14.3 cm. Most patients (87%) showed locally advanced disease designated as stage II or higher. The mean number of resected LNs was 33.7 ± 17.1 in all patients, and 45 patients (5.8%) had fewer than 12 LNs resected. In all patients, the mean number of positive LNs was 1.57 ± 3.6. Combined resection was performed for 57 (7.4%) patients, of whom 20 underwent cholecystectomy because of gallstones, 12 patients underwent oophorectomy because of ovarian cysts, 10 patients required shaving of the liver, and 4 patients required extensive en bloc resections because of invasion into the small bowel wall and right ureter. Others underwent benign mass excisions (n = 2), which included adrenalectomy (n = 2), myomectomy (n = 6), and biopsy of liver nodules (n = 1). In the analysis of adjuvant chemotherapy, 615 (79.6%) patients received adjuvant chemotherapy with 5-fluorouracil and leucovorin with or without oxaliplatin, according to the disease status. All patients with stage III disease received adjuvant chemotherapy. However, adjuvant chemotherapy was also recommended for high-risk patients with stage II disease, according to the National Comprehensive Cancer Network guidelines.

TABLE 1. Characteristics of 773 Modified Complete Mesocolic Excision Cases

	Total Patients (n = 773)
Sex, n (%)	
Male	421 (54.5%)
Female	352 (45.5%)
Age, mean ± SD, yr	61.5 ± 11.4
ASA classification, n (%)	
I	328 (42.4%)
II	431 (55.8%)
III	14 (1.8%)
BMI, mean ± SD, kg/m^2	23.1 ± 3.0
Location of tumor, n (%)	
Ascending colon	592 (76.6%)
Transverse colon	83 (10.7%)
Cecum	89 (11.5%)
Hepatic flexure	9 (1.2%)
Previous abdominal surgery, n (%)	
Yes	56 (7.2%)
No	694 (89.8%)
Missing data	23 (3.0%)
Carcinoembryonic antigen, mean ± SD, ng/mL	
Preoperative	9.59 ± 39.27
Postoperative day 7	2.82 ± 11.04

TABLE 2. Pathologic Characteristics and Perioperative Outcomes After Modified CME

	Total Patients (n = 773)
Tumor size, mean ± SD, cm	5.4 ± 2.7
Resection margin	
Proximal	
Length, mean ± SD, cm	16.4 ± 10.3
Tumor involvement, n (%)	0 (0.0%)
Missing data, n (%)	6 (0.8%)
Distal	
Length, mean ± SD, cm	15.7 ± 9.2
Tumor involvement, n (%)	0 (0.0%)
Missing data, n (%)	11(1.4%)
Total specimen bowel length, mean ± SD, cm	32.1 ± 14.3
TNM stage (AJCC 6th ed)	
I	100 (12.9%)
II	372 (48.1%)
III	301 (38.9%)
Total no. retrieved LNs, mean ± SD	33.7 ± 17.1
No. positive LNs, mean ± SD	1.57 ± 3.6
No. cases with fewer than 12 LNs, n (%)	45 (5.8%)
Histology type, n (%)	
Adenocarcinoma WD	119 (15.4%)
Adenocarcinoma MD	511 (66.1%)
Adenocarcinoma PD	57 (7.4%)
Mucinous adenocarcinoma	80 (10.3%)
Missing data	6 (0.8%)
Combined resection, n (%)	57 (7.4%)
Adjuvant chemotherapy, n (%)	
Yes	615 (79.6%)
No	158 (20.4%)
Chemotherapy regimens, n (%)	
FL	460 (71.3%)
With oxaliplatin	179 (27.7%)
Others	6 (1.0%)

FL indicates fluorouracil and leucovorin; MD, moderate differentiated; PD, poorly differentiated; SD, standard deviation; WD, well differentiated.

The Analysis of Postoperative Morbidities

Early postoperative complications (within 30 days) occurred in 42 (5.3%) patients, and late complications (>30 days) occurred in 27 (3.5%) patients. Twenty (2.6%) patients were found to have grade I complications; these included transient voiding difficulty requiring additional diuretics (n = 5, 0.6%), wound infection (n = 9, 1.2%), and pulmonary disease requiring physiotherapy (n = 6, 0.8%). Thirteen (1.7%) patients had grade II complications; these included postoperative ileus (or intestinal obstruction) requiring total parenteral nutrition (n = 9, 1.2%) and other minor complications (n = 4, 0.5%). Five (0.6%) patients who underwent radiologic intervention for minor anastomotic leakage were included in grade IIIa.

TABLE 3. Univariate and Multivariate Analyses of Factors Affecting Overall Postoperative Complications

	Overall Postoperative Complications		
	Univariate	Multivariate	
Variables	**Value**	**HR (95% CI)**	**Value**
Procedure Open vs MIS	0.944		
Age ≥60 yrs	0.339		
Sex Male vs Female	0.917		
BMI ≥25 kg/m^2	0.307		
ASA ≥II	0.026	1.851 (1.061–3.227)	**0.030**
Preoperative CEA ≥5.0 ng/mL	0.798		
Histology Low vs High risk	0.475		
Tumor size ≥5.0 cm	0.947		
TNM stage III	0.043	1.668 (1.001–2.782)	0.050
Harvested LN ≥12	0.905		
Chemotherapy regimen FL vs With oxaliplatin	0.215		

Statistically significant *P* values are indicated in bold.

FL indicates fluorouracil and leucovorin; High risk, G3 + mucinous adenocarcinoma; Low risk, G1 + G2.

Two (0.2%) patients with postoperative bleeding and bowel necrosis were included in grade IVa. Two (0.2%) patients who died during the immediate postoperative period were included in grade V; one death was attributed to acute cerebrovascular infarction, and the other was caused by acute respiratory distress syndrome. The most common type of late postoperative complication was intestinal obstruction (n = 24, 3.1%), followed by incisional hernia (n = 3, 0.4%). In the multivariate analysis of risk factors for overall postoperative complications, an ASA score greater than or equal to II [$P = 0.030$; hazard ratio (HR) = 1.851; 95% confidence interval (CI): 1.061–3.227) was found to be an independent prognostic factor (Table 3).

The Analysis of Tumor Recurrence Pattern

Overall locoregional and systemic recurrences after primary surgery occurred at a median of 15.5 months (range: 11.0–20.0 months) and 13.4 months (range: 10.7–16.1 months), respectively. Any tumor recurrence, including both locoregional and systemic recurrence, occurred in 148 (19.1%) patients during the study period. Among all of the patients with tumor recurrences, 34 (4.4%) had a locoregional recurrence (with or without systemic recurrence), and 114 (14.7%) had systemic recurrence (with or without locoregional recurrence). The overall 5-year LRR and 5-year SRR were 4.9% and 13.7%, respectively. The most common sites of systemic recurrence were the liver (n = 42, 5.4%) and lung (n = 36, 4.7%), followed by peritoneal seeding (n = 17, 2.2%), ovary (n = 6, 0.8%), para-aortic LN (n = 5, 0.6%), brain (n = 4, 0.5%), and bone (n = 4, 0.5%). Locoregional tumor recurrences were mostly diagnosed in the anastomosis site (n = 8, 1.0%); other sites included the small bowel wall (n = 6, 0.8%), pelvic cavity (n = 6, 0.8%), abdominal wall or trocar site (n = 6, 0.8%), and others (n = 8, 1.0%), including the adrenal gland (n = 2), right paracolic gutter (n = 2), common hepatic artery (n = 1), superior mesenteric vein (n = 1), middle colic vein (n = 1), and duodenal second portion (n = 1). We also analyzed prognostic factors for recurrence (Table 4). In the univariate analysis, a significant association was found between both 5-year LRR and preoperative carcinoembryonic antigen (CEA) levels of 5.0 ng/mL or higher (normal limit: 0–4.99 ng/mL) as well as pathologic stage (greater than III). In the multivariate analysis, the risk of developing locoregional recurrence increased for pathologic stage III disease (HR = 4.286; 95% CI: 2.033–9.035). Preoperative levels of CEA more than 5.0 ng/mL, pathologic stage greater than III, and adjuvant chemotherapy regimen with oxaliplatin were significant prognostic factors in the univariate analysis for 5-year SRR. However, there was no significant association between 5-year SRR and preoperative CEA more than 5.0 ng/mL or adjuvant chemotherapy regimen with oxaliplatin. Only pathologic stage III was found to be an independent prognostic factor for 5-year SRR in the multivariate analysis.

The Analysis of Survival and Multivariate Analysis of Prognostic Factors Affecting 5-Year OS

The 5-year OS rate for all patients was 84.0%. The comparison of 5-year OS between patients with stages I, II, and III disease (Fig. 2A) showed that survival worsened as the stage increased ($P < 0.0001$). The 5-year OS rates were estimated to be 97.3% for stage I, 91.4% for stage II, and 71.0% for stage III disease. The 5-year DFS and 5-year DSS rates for all patients were 82.8% and 85.8%, respectively. When patients were analyzed by disease stage, survival worsened as the stage increased for both 5-year DSS and 5-year DFS ($P < 0.0001$; Figs. 2B, C). The 5-year DSS rates were 97.3% for stage I, 93.6% for stage II, and 73.0% for stage III disease. The 5-year DFS rates were estimated to be 98.4% for stage I, 92.4% for stage II, and 68.5% for stage III disease. The analysis of prognostic factors affecting 5-year OS is shown in Table 4. Open surgery, age 60 years or older, ASA score 2 or higher, preoperative CEA 5.0 ng/mL or more, pathologic stage III, treatment with oxaliplatin, and postoperative complications were all found to be independent prognostic factors for 5-year OS in the univariate analysis. Multivariate analysis revealed that pathologic stage III ($P < 0.001$; HR = 4.483; 95% CI: 2.786–7.215), postoperative complications ($P = 0.001$; HR = 2.946; 95% CI: 1.559–5.565), age 60 years or older ($P = 0.025$; HR = 1.740; 95% CI: 1.072–2.822), and MIS ($P = 0.001$; HR = 3.010; 95% CI: 1.554–5.830) were independent prognostic factors.

The Comparison Between Open Surgery and MIS

The comparison of postoperative outcomes between patients who underwent open surgery and MIS is shown in Table 5. The mean follow-up time was significantly longer in the open surgery group than in the MIS group (70.0 ± 36.3 months vs 39.7 ± 14.9 months; $P < 0.001$). The length of hospital stay was significantly shorter in the MIS group than in the open surgery group (10.2 ± 5.3 days vs 14.7 ± 5.9 days; $P < 0.001$). Four patients initially in the MIS group were required to undergo open surgery because of severe tumor adhesion and intractable major vessel bleeding. No significant differences were noted between the 2 groups in terms of total specimen bowel length, number of positive LNs, numbers of patients with fewer than 12 nodes harvested, postoperative complications, tumor recurrence pattern, and 5-year DFS. The total LN yield was significantly greater in the open surgery group compared with the MIS group ($P < 0.001$). Combined resection was also significantly more frequent in the open surgery group compared with the MIS group ($P < 0.001$). In terms of oncologic outcomes, both 5-year OS (open vs MIS: 82.4% vs 89.8%; $P = 0.023$) and 5-year DSS (open vs MIS: 84.2% vs 90.8%; $P = 0.015$) were significantly better in the MIS group than in the open surgery group.

TABLE 4. Univariate and Multivariate Analyses of Factors Affecting 5-Year Tumor Recurrence and 5-Year OS

	Locoregional Recurrence			Systemic Recurrence			OS		
	Univariate	Multivariate		Univariate	Multivariate		Univariate	Multivariate	
Variables	***P***	**HR**	***P***	***P***	**HR**	***P***	***P***	**HR**	***P***
Procedure	0.808			0.113			**0.023**		**0.001**
Open vs MIS								3.010 (1.554–5.830)	
Age	0.856			0.946			**0.001**		**0.025**
≥60 yrs								1.740 (1.072–2.822)	
Sex	0.109			0.530			0.338		
Male vs Female									
BMI	0.064			0.279			0.234		
≥25 kg/m^2									
ASA	0.081			0.071			**0.001**		NS
≥II								1.305 (0.826–2.060)	
Preoperative CEA	**0.036**		NS	**0.003**		NS	**<0.001**		NS
≥5.0 ng/mL		1.645 (0.818–3.310)			1.203 (0.801–1.807)			1.386 (0.876–2.193)	
Histology	0.134			0.474			0.752		
Low vs High risk									
Tumor size	0.482						0.052		
≥5.0 cm									
TNM stage	**<0.001**		**<0.001**	**<0.001**		**<0.001**	**<0.001**		**<0.001**
III		4.286 (2.033–9.035)			5.017 (3.110–8.092)			4.483 (2.786–7.215)	
Harvested LN	0.498			0.579			0.757		
≥12									
Chemotherapy regimen	0.093			**0.011**			**0.008**		NS
FL vs with oxaliplatin					1.044 (0.686–1.589)	NS		0.932 (0.555–1.568)	
Complications							**<0.001**		**0.001**
Yes								2.946 (1.559–5.565)	

Statistically significant *P* values are indicated in bold.
FL indicates fluorouracil and leucovorin; High risk, G3 + mucinous adenocarcinoma; Low risk, G1 + G2; NS, nonsignificant.

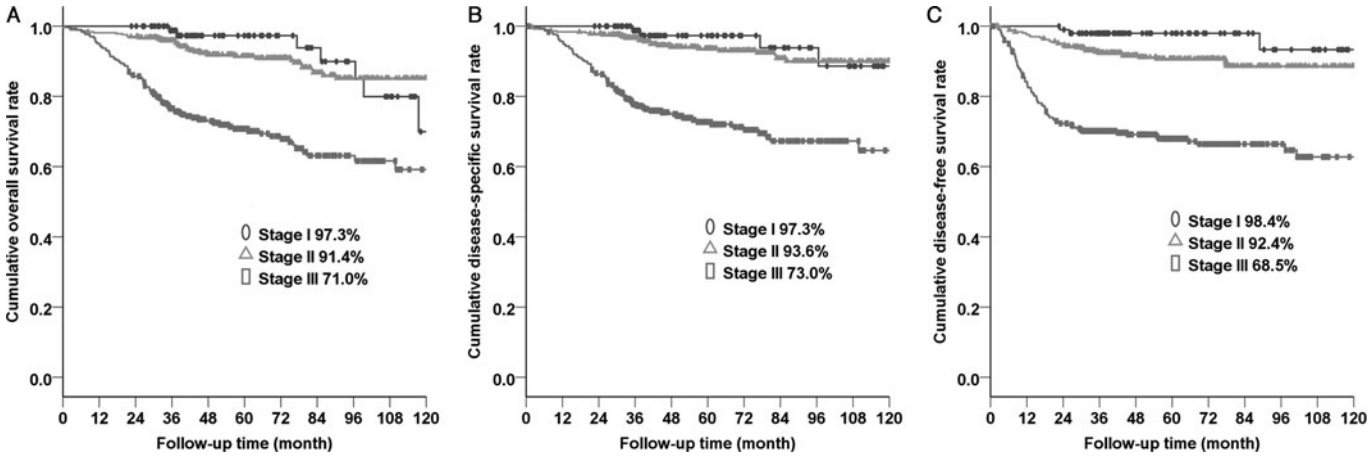

FIGURE 2. Oncologic outcomes according to TNM stage ($P < 0.0001$). A, 5-year OS ($P < 0.0001$); B, 5-year DSS ($P < 0.0001$); and C, 5-year DFS ($P < 0.0001$).

TABLE 5. Comparison of Postoperative Outcomes Between Open Surgery and MIS

	Open (n = 568)	MIS (n = 205)	*P*
Mean F/U period, mo	70.0 ± 36.3	39.7 ± 14.9	**<0.001**
Length of hospital stay, mean ± SD, d	14.7 ± 5.9	10.2 ± 5.3	**<0.001**
Total specimen bowel length, mean ± SD, cm	32.0 ± 14.4	32.2 ± 14.0	NS
TNM staging, n (%)			
I	51 (9.0%)	49 (23.9%)	
II	289 (50.9%)	83 (40.5%)	
III	228 (40.1%)	73 (35.6%)	
Total no. LN retrieved, mean ± SD	35.4 ± 17.6	28.9 ± 14.7	**<0.001**
No. positive LN, mean ± SD	1.7 ± 4.0	1.2 ± 2.5	NS
Fewer than 12 nodes harvested, n (%)	27 (4.8%)	18 (8.7%)	NS
Combined resection, n (%)	54 (9.5%)	3 (1.5%)	**<0.001**
Conversion to open, n (%)		4 (2.0%)	
Complications, n (%)			
Early	29 (5.1%)	11 (5.4%)	NS
Late	21 (3.7%)	6 (2.9%)	NS
Mortality (<30 postoperative days)	2 (0.2%)	0 (0.0%)	
5-yr recurrence, n (%)			NS
Locoregional	26 (4.6%)	8 (3.9%)	
Systemic	93 (16.4%)	21 (10.2%)	
Median time to LRR	12.2 (6.0–18.3)	18.8 (9.6–27.9)	NS
Median time to SR	12.8 (9.6–16.0)	15.3 (9.9–20.6)	NS
5-yr OS	82.4%	89.8%	**0.023**
5-yr DFS	82.0%	82.9%	NS
5-yr DSS	84.2%	90.8%	**0.015**

Statistically significant *P* values are indicated in bold.
F/U indicates follow-up; NS, nonsignificant.

DISCUSSION

CME is a similar procedure to TME, as both involve the complete removal of the tumor-bearing colon together with its enveloping mesocolic fascia and surrounding soft tissue though meticulous dissection into the embryologic fusion plane between the retroperitoneal and visceral plane. Although the term CME with CVL was first used by Hohenberger et al,[5] the concept is not necessarily a new one because similar concepts have already been accepted by many institutions. In particular, many Japanese surgeons would argue that they have been performing a similar procedure known as D3 dissection.[8] Although sharing similar concepts, the technical details may differ between CME with CVL and Japanese D3 dissection, as demonstrated by differences in the length of resected bowels and the area of excised mesocolon, which seem to result from different definitions of sound resection margins.[9] To determine whether these differences result in different oncologic outcomes, further studies are necessary.

At Yonsei University Severance Hospital, we have also been performing surgery for colon cancer using a procedure similar to CME with CVL. This current study of mCME demonstrates comparable long-term results to those originally reported for CME by Hohenberger et al.[5] Although most of the techniques are very similar, mCME differs from what was originally described by Hohenberger et al[5] in 3 major respects. First, although duodenal kocherization is mandatory in the original CME description, we found it was not necessary in most cases. The mesocolic fascial plane is extended in the anterior to the Gerota's fascia, not in the posterior to the duodenum,

pancreas, and superior mesenteric vein. Consequently, this plane is an important landmark for identifying the correct surgical plane and avoiding adverse injuries of the retroperitoneal structures such as the right kidney, adrenal gland, gonadal vessels, and right ureter.[10] However, if the tumor is infiltrating or adhering to adjacent soft tissues, kocherization may be required to clear possible tumor spread in that area. Second, if the tumor is locally advanced and staged as T3 or higher, the entire prerenal soft tissue behind Gerota's fascia may need to be cleared, especially for tumors growing toward the posterior. This surgical concept is similar to that of obtaining a safe circumferential resection margin when performing TME. Scott et al[11] demonstrated that microscopic tumor involvement in the retroperitoneal resection margin of right-sided colon cancer is a marker of advanced tumor stage and is associated with a high incidence of synchronous and metachronous distant metastasis. The third difference of mCME with the originally described CME involves the tailored resection of the mesocolon and ileal mesentery according to tumor location. As mentioned earlier, although we always identified the root of the middle colic artery and skeletonized it, we preserved the root and ligated only the right branch unless the tumor was located in the hepatic flexure or transverse colon. If the tumor was present in these latter sites, we ligated the root of the middle colic artery because LN metastasis could occur along its length. If the tumor was located in the proximal ascending colon or cecum, we included enough distal ileum branches of the superior mesenteric artery in the specimen to obtain a longer distal ileum. This was because LN metastasis occurs predominately along the ileocolic and nearby branches. As a result, the length of the distal ileum was determined by the extent of mesenteric dissection in our technique. In Japanese studies, LN metastasis was seen primarily within 10 cm of the longitudinal spread (oral side or anal side of the tumor), and longitudinal LN spread greater than 10 cm from the tumor was very rare, at 1.0% to 3.9% for right-sided colon cancer.[12,13] Recently, Park et al[14] reported patterns of LN metastasis in patients with right-sided colon cancer on the basis of the tumor location. They demonstrated that patients with cecal and ascending colon cancers most frequently had metastases in the ileocolic LNs. They also found that in patients with hepatic flexure cancer and transverse colon cancer, the middle colic LNs were the most common metastatic LNs.

Do CME or similar procedures have any influence on oncologic outcomes or postoperative morbidity compared with conventional surgery? The currently available data are limited, but encouraging. Some authors have demonstrated superior rates of local recurrence and OS after CME.[5] Others have also demonstrated that the mesocolic plane dissection leads to a 27% 5-year survival benefit compared with impaired surgical plane dissection in patients with stage III disease.[6] In this study, mCME resulted in a high 5-year OS rate of 84.0%, and 5-year DSS rates of 85.8% and 73.0% in all patients and patients with stage III disease, respectively. These results are comparable with survival outcomes reported in the Erlangen group (5-year cancer-related survival 89% for all stages and $\geq$70.0% for stage III disease)[9] and are higher than those of the COST (5-year OS, 76.4%) and CLASSIC trials (3-year OS, 68.4%).[15,16] Several authors have reported that locoregional recurrence of colon cancer leads to severe morbidity and poor survival outcomes.[17] In recent studies, the 5-year LRR has been reported to range from 4.8% to 11.5%.[17–19] We showed a 5-year LRR of 4.9% for all patients. Furthermore, we have shown a relatively low 5-year LRR of 10.9% in patients with stage III disease, similar to the results of the Erlangen group (5-year LRR, 4.9%; 5-year LRR in stage III, 11.1%). We may assume that CME or mCME is an effective locoregional treatment for advanced colon cancer, especially in patients with stage III disease. However, systemic failure is a major problem. In this study, the 5-year SRR for patients with stage III disease was 27.2%. These results indicate that even after radical surgeries such as CME or mCME, systemic adjuvant chemotherapy may still be necessary to prevent systemic failure, especially in advanced colon cancer.

CME in itself is a very aggressive surgical approach; several surgeons may express concerns about an increased risk of postoperative morbidities. In previous studies using standard colonic surgery, postoperative complication rates have been reported to range from 9.0% to 22.5%.[20–23] Several recent studies using CME have shown that postoperative morbidities ranged from 5.7% to 19.7%.[5,24,25] In this study, the rates of early postoperative morbidity and late postoperative morbidity were 5.0% and 8.5%, respectively. Intestinal obstruction is a major complication to consider when performing these surgical procedures. In our study, intestinal obstruction mostly occurred in patients with late complications during the long-term follow-up period. Postoperative morbidity was also found to be an independent factor negatively affecting 5-year OS in the multivariate analysis.

MIS is a rapidly evolving technique, and some authors have recently published results from their own series of MIS-CME. Our institute has established an MIS program for colorectal surgery, which includes laparoscopic and robotic surgery. In this study, we compared the long-term oncologic outcomes between the open group and the MIS group. Interestingly, we found both 5-year OS and 5-year DSS rates were significantly better in the MIS group than in the open surgery group (89.8% vs 82.4%, respectively; $P = 0.023$; 90.8% vs 84.2%, respectively; $P = 0.015$). Further analyses also revealed that there was a selection bias because MIS was performed more frequently in patients with lower ASA scores and early-stage tumors. Another possible statistical confounding factor may be the shorter follow-up period in the MIS group. Possible selection bias may be a major drawback, which is inevitable due to the retrospective nature of the study. Low body mass index (BMI), higher proportion of low grade ASA and low rate of prior operation, which are probably related to ethnic factor, may be an obstacle to apply the findings of the current study universally. Those parameters are related to technical difficulty and thus may have indirect influence upon postoperative outcomes including morbidity, which will be a strong argument as to MIS approach. Despite the limitations inherent to a retrospective study, however, our findings support that concept that mCME could be safely performed through an MIS technique, either laparoscopically or robotically. However, further successive studies are necessary to reveal the true benefit of MIS-CME compared with open surgery.

CONCLUSIONS

We have successfully established the technique of modified CME keeping the same principles as the originally described CME procedure, but with a more tailored approach. The long-term oncologic outcomes were found to be comparable to those resulting from original CME, and the rates of postoperative morbidity were acceptable. However, whether CME or its variants should be a standard treatment for right-sided colon cancer remains controversial and needs to be further investigated. Our results may provide direction for future prospective studies investigating the true benefit of CME for the treatment of right-sided colon cancer.

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