

Is complete mesocolic excision oncologically superior to conventional surgery for colon cancer? A retrospective comparative study

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Abstract

Background During the last decade, many efforts have been made in order to improve the oncologic outcomes following colonic resection. Complete mesocolic excision (CME) has proved to provide high rates of disease-free and overall survival rates in patients undergoing resection for colonic malignancies. The aim of our study was to further investigate the role of CME in colonic surgery through comparison with a series of conventional resections.

Methods All data regarding resections for colonic cancer since 2006 were obtained prospectively from two surgical departments. Retrieved data from 290 patients were analyzed and compared between those who underwent CME and those who had conventional surgery.

Results The CME group presented a higher rate of postoperative morbidity and readmissions. Histopathological features were in favor of CME surgery compared with the conventional group, in terms of both resected bowel length (33 vs. 20 cm) and lymph node harvest (27 vs. 18). Although CME was associated with better disease-free and overall survival times, only tumor differentiation, adjuvant chemotherapy and age had a statistically significant affect on those outcome values ($P < 0.05$).

Conclusion CME improves histopathologic features, but without presenting oncologic superiority. Larger prospective studies following adequate surgical training are needed to prove the technique's advantages in oncologic outcomes.

Keywords Colon cancer, complete mesocolic excision, oncological outcomes

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Introduction

Total mesorectal excision for rectal cancer has resulted in excellent oncological outcomes, achieving lower rates of local recurrence and higher rates of both disease-free and overall survival rates, because all possible routes of spread are removed in a package, through dissection along well-defined embryological planes [1-3]. Hohenberger *et al* [4] thought that the same principles could be also applied to colon cancer surgery, by introducing the concept of complete mesocolic excision (CME). CME involves sharp dissection of the mesocolon along the embryological planes and high ligation and division of the vessels supplying blood to the colonic segment to be removed. By this technique, the removed colonic specimen should be covered by an intact mesocolic fascia and peritoneum, which, as a package, contains the

tumor-bearing colonic segment and the mesocolon, with draining lymphatics, lymph nodes and possible tumor microdeposits.

Many studies document clearly that CME results in more tissue being obtained in terms of the number of harvested lymph nodes, the distance from high tie to tumor and the surface of removed mesocolon, compared to conventional surgery [4-11]. However, the concept of CME remains controversial, with low uptake worldwide [6,12], mostly because the improved morphological features attributed to CME fail to translate into improved oncological outcomes. Observational studies [4,8,11] show that CME is associated with higher overall survival rate compared to historical series of patients after conventional surgery. More recently, there are comparative, population based studies demonstrating higher overall [12,13] and disease-free [12-14] survival rates after CME compared to conventional surgery, in particular for stage I and II right colon cancers.

The present comparative study aims to add further information based on the aforementioned principles; namely, management of patients under the control of multidisciplinary teams that follow the same guidelines for treatment and macroscopic, microscopic and histopathological assessment of the resected specimen based on the same rules.

Patients and methods

Patients

Adult patients (18 years old or older) from two surgical units were included. All colon cancer patients undergoing surgery were registered in a prospective electronic database. All patients who underwent surgery for colon cancer (lower border of tumor no less than 15 cm from the anal verge as measured by colonoscopy) from October 2006 to December 2011 were included in this study. All patients had histologically-proven adenocarcinoma of the colon and were staged by computed tomography (CT) scans. Exclusion criteria included synchronous metastatic disease and patients undergoing emergency surgery. All CME operations were performed or supervised by one specially trained surgeon (EX) in colorectal surgery. All other surgeons in the two units performed conventional colectomies, but all of them were equally experienced general surgeons with a special interest in colorectal surgery. All operations were performed by the open approach. All patients in the two units were enrolled postoperatively and managed within an enhanced recovery protocol. All CME specimens were freshly photographed and evaluated macroscopically and morphometrically using special software (Adobe Photoshop CS6), using the technique and standard definitions of the pathologists in Leeds, UK [11]. Two specially trained and experienced pathologists (KP, MK) evaluated all specimens from both groups histologically.

Surgical techniques

In left colectomy the procedure commenced by dissecting laterally to medially the embryological plane between the visceral and the parietal layer of Toldt's fascia. The left colon was mobilized in this way from the left paracolic gutter. The inferior mesenteric artery was then ligated and transected approximately 1 cm after its take-off from the aorta, so as to preserve the hypogastric nerve plexus, after which the inferior mesenteric vein was ligated and transected immediately below the inferior border of the pancreas. Dissection extended caudally over the promontory and to the upper "holy plane" and superiorly to the entry of the lesser epiploic sac, after division of the root of the left transverse mesocolon at the lower border of the pancreas. The sigmoid colon was excised in all cases, and a descending colon to mid or upper rectum anastomosis was fashioned using a circular stapler.

In right colectomy, the procedure started with a lateral-to-medial dissection in the plane defined between the two layers of Toldt's fascia to the anterior surface of the superior mesenteric vessels, below the third portion of the duodenum. In cases with a carcinoma located in the cecum or the proximal ascending colon, the ileo-colic vessels were taken from their origin at the superior mesenteric vessels and the right branches of the middle colic vessels at their take-off from the main trunks. When the carcinoma was located in the hepatic flexure or the proximal (15 cm) transverse colon, the middle colic vessels were dissected, ligated and transected at the origin from the superior mesenteric vessels. Then, the mesentery of the colon to be excised was divided, as were the distal ileum and the transverse colon. The anastomosis was fashioned either with sutures or with the use of linear stapling devices. The omentum related to the resected specimen was excised *en bloc*. In addition, for carcinomas of the hepatic flexure and proximal transverse colon, the hypo-pyloric and gastro-epiploic lymph nodes were removed *en bloc* with the specimen.

Non-CME operations also involved the mobilization of the colon by developing the embryological plane between the visceral and the parietal layers of Toldt's fascia. However, the surgeons did not systematically try to preserve the planes intact. Furthermore, the level of the high tie was not standardized according to a fixed anatomical structure, which resulted in leaving behind a considerable amount of lymph tissue along the remaining ligated arterial stump.

Follow up

Chemotherapy was offered to all stage III patients by the Multidisciplinary Team as standard treatment in the form of mFOLFOX6. Stage II patients received adjuvant chemo only if histological and/or clinical adverse features were present, such as invasion of blood vessels or lymphatics, poor differentiation, perineural invasion, number of retrieved lymph nodes below 12, pT4 tumors and tumors causing obstruction. Furthermore, every stage II patient after 2009 without the above adverse pathologic features was tested for microsatellite

instability; if the tumor displayed microsatellite stability the patient was offered adjuvant chemotherapy. All patients were followed according to the international guidelines for patients with colon cancer. The date of last follow up was considered the date of the last chest and abdomen CT scan or the date of any additional test used to identify possible recurrence.

Statistical analysis

Nominal variables are presented using frequencies and percentages, whereas continuous variables are presented as median and interquartile range (normality was tested and did not hold).

The χ^2 test for independence was used to evaluate associations between the procedure group and patients' characteristics. Kaplan-Meier survival analysis was performed in order to evaluate differences in the disease-free survival time and overall survival between the two procedure groups with the use of a log-rank test. Lastly, Cox regression was performed in order to identify factors independently related to the patients' disease-free and overall survival time. The factors entered into the model were those that were statistically significant in the univariate log-rank tests. Results are presented as hazard ratios and 95% confidence intervals (CI).

The criterion of statistical significance was $\alpha=5\%$. All statistical analyses were performed using of Stata SE version 11.1 (StataCorp. 2009, Texas, USA).

Results

Demographics, intraoperative and postoperative outcomes

Two hundred ninety patients were eligible for analysis. Table 1 shows the patients' demographics, preoperative tumor characteristics and types of operation performed. Apart from age, no other statistically significant difference was identified between the two groups.

There were no differences between the two groups as far as intraoperative events are concerned. Overall intraoperative complications ($P=0.652$), and in particular intraoperative bleeding ($P=0.156$) and failure of anastomosis ($P=0.081$), showed no difference between the two groups. Thirty-day mortality rates also did not differ between the groups. The CME group displayed significantly higher rates of postoperative morbidity ($P<0.001$), and when morbidity was further analyzed the CME group had higher rates of chest infection (31 vs. 0 patients, $P<0.001$) and postoperative ileus (31 vs. 7 patients, $P<0.001$). Furthermore, there were significantly more readmissions in the CME group (6 vs. 0 patients, $P=0.013$) whereas reoperation rates, bleeding, leak rates and postoperative ileus cases did not differ between the groups. Although there were more readmissions in the CME group, total hospital stay was significantly shorter when

compared to the non-CME group (6 [4-8] vs. 7 [6-8] days, $P<0.001$). All readmissions ($n=6$) in the CME group were due to prolonged postoperative ileus.

Histopathological and oncological outcomes

Table 2 presents the association between the procedure groups and histopathological and oncological outcomes. The CME group had a significantly lower number of patients who were offered adjuvant chemotherapy ($P=0.012$), possibly because it included a significantly lower number of patients

Table 1 Patients and tumor characteristics in the two groups

Characteristics	n (%)		P-value
	Non-CME n=145	CME n=145	
Age	72 (65-78)*	68 (58-75)*	<0.001
Sex			
Male	79 (54.48%)	88 (60.69%)	0.285
Female	66 (45.52%)	57 (39.31%)	
Tumor location			
Cecum - ascending	55 (39.57%)	42 (29.17%)	0.219
Hepatic flexure - transverse	16 (11.51%)	25 (17.36%)	
Descending - upper sigmoid	17 (12.23%)	22 (15.28%)	
Sigmoid - rectosigmoid	51 (36.69%)	55 (38.19%)	
Localization			
Right	71 (48.97%)	68 (46.90%)	0.724
Left	74 (51.03%)	77 (53.10%)	

*Presented as median (interquartile range)

CME, complete mesocolic excision

Table 2 Histopathological and oncological data

Variable	n (%)		P-value
	Non-CME n=145	CME n=145	
CME grading			-
Mesocolic	-	135 (93.1%)	
Intramesocolic	-	10 (6.9%)	
Muscularis	-	0 (0%)	
Differentiation			
Low	29 (20.00%)	38 (26.210%)	0.210
High	116 (80.00%)	107 (73.79%)	
Adjuvant Chemotherapy			
No	66 (46.48%)	87 (61.27%)	0.012
Yes	76 (53.53%)	55 (38.73%)	

(Contd...)

Table 2 (Continued)

Variable	n (%)		P-value
	Non-CME n=145	CME n=145	
T stage			
T0	0 (0.00%)	1 (0.69%)	<0.001
T1	6 (4.14%)	17 (11.72%)	
T2	11 (7.59%)	37 (25.52%)	
T3	104 (71.72%)	69 (47.59%)	
T4	21 (14.48%)	21 (14.48%)	
Tis	3 (2.07%)	0 (0.00%)	
N stage			
N0	80 (55.17%)	101 (69.66%)	0.021
N1	40 (27.59%)	32 (22.07%)	
N2	25 (17.24%)	11 (7.59%)	
N3	0 (0.00%)	1 (0.69%)	
UICC stage			
Stage I	13 (8.97%)	48 (33.10%)	<0.001
Stage II	67 (46.21%)	51 (35.17%)	
Stage III	65 (44.83%)	46 (31.72%)	
Local recurrence			
No	137 (96.48%)	136 (94.44%)	0.409
Yes	5 (3.52%)	8 (5.56%)	
Metastasis			
No	118 (83.10%)	125 (86.81%)	0.380
Yes	24 (16.90%)	19 (13.19%)	
Death			
No	109 (75.69%)	125 (86.21%)	0.023
Yes	35 (24.31%)	20 (13.79%)	
	Median (IQR)	Median (IQR)	
Lymph nodes retrieved	18 (14-24)	27 (19-37)	<0.001
Bowel length	20 (17-25)	33 (27-42)	<0.001
Ileum length (right only)	5.5 (4-8)	6.5 (4.75-7.25)	0.943
Tumor ligation length	-	14 (12.5-16)	-
Bowel ligation length	-	10 (8.5-12)	-
Mesocolon surface	-	171 (133.5-218)	-

CME, complete mesocolic excision; IQR, interquartile range

with more advanced stages of disease (T, N and UICC stage, $P<0.001$, $P=0.021$ and $P<0.001$, respectively). Patients treated with non-CME had a lower percentage of stage I cancer (8.97%) than patients undergoing CME (33.10%), whereas

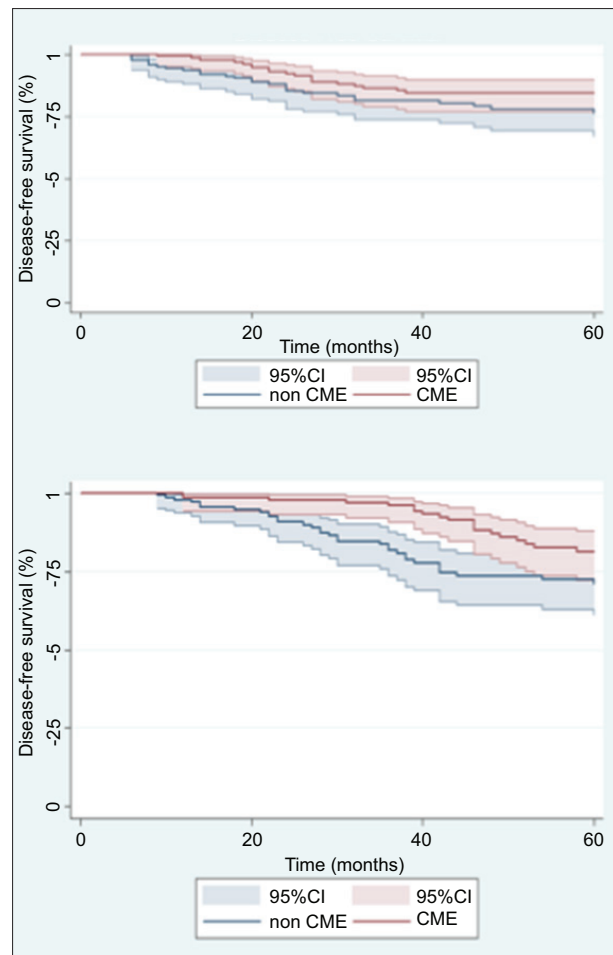


Figure 1 Survival curves by procedure group
CME, complete mesocolic excision; CI, confidence interval

patients who had CME had a longer resected bowel (median 33 vs. 20 cm) and more lymph nodes retrieved (median 27) than patients without CME (median 18).

Survival analysis

Five-year disease-free survival was 84.6% (95%CI 76.9-89.9%) after CME and 76.4% (95%CI 67.1-83.4%) after non-CME (Fig. 1). In general, CME did not statistically significantly improve disease-free survival, but a longer disease-free survival time was observed for patients after CME than after non-CME (mean survival time 54.5 vs. 51.7 months, $P=0.118$). With respect to overall survival, CME procedure improved the survival time significantly ($P=0.014$, Fig. 1). Patients with CME had longer overall survival times than those without CME (mean survival time 56.6 vs. 51.7 months). Five-year overall survival was 81.3% (95%CI 72.1-87.7%) after CME and 70.9% (95%CI 61.2-78.7%) after non-CME.

Stratified survival analysis to explore the association between treatment groups and disease-free survival time in subgroups (Table 3) showed a statistically significant association

Table 3 Stratified associations between treatment group and survival time

Associations	Non-CME	CME	Log-rank
	Mean (95% CI)	Mean (95% CI)	P-value
<i>Disease-free survival</i>			
By stage			
Stage I	60	60	-
Stage II	56.5 (53.6-59.8)	58.2 (55.7-60.6)	0.347
Stage III	45.4 (40-50.7)	44.7 (39.1-50.4)	0.874
By differentiation			
Low	50.1 (42.5-57.8)	48.2 (42.7-53.8)	0.853
High	52.2 (49-55.4)	57.1 (54.9-59.2)	0.013
By localization			
Right	51.1 (46.6-55.5)	54.8 (51.5-58.2)	0.131
Left	52.3 (48.4-56.3)	54.3 (51.2-57.5)	0.553
<i>Overall survival</i>			
By stage			
Stage I	60	60	-
Stage II	53.7 (50.2-57.3)	57.7 (55.3-60.1)	0.157
Stage III	47.9 (43.5-52.4)	51.5 (47.8-55.3)	0.673
By differentiation			
Low	49.9 (43.2-56.5)	53.7 (50.2-57)	0.920
High	52.2 (49.2-55)	57.9 (56.4-59.6)	<0.001
By localization			
Right	51.2 (47.2-55.2)	55.7 (52.8-58.6)	0.108
Left	52.2 (48.6-55.7)	57.4 (55.9-58.9)	0.071

for patients that had high differentiation. Among those who had high differentiation, patients who had undergone a CME procedure had longer disease-free survival time than those undergoing non-CME. Stratification by stage did not show any statistically significant difference between groups (Table 3, Fig. 2). Likewise, there was an interaction between CME and differentiation, as well as adjuvant chemotherapy, for the overall survival time. Among patients who had highly differentiated tumors, it was found that the CME procedure resulted in a longer overall survival time compared to those who had a non-CME procedure (mean 57.9 vs. 52.2 months, $P<0.001$). In terms of survival with reference to death from cancer, interaction was also observed between CME and differentiation ($P=0.005$).

Characteristics that could potentially affect the disease-free survival or the overall survival were tested with the log-rank test. It was observed that disease-free and overall survival were statistically associated with differentiation and stage ($P<0.05$). Patients diagnosed with stage III disease and with low differentiation had shorter overall survival time and disease-free survival time, as expected (Fig. 3, 4). Patients with stage II disease did not have statistically different disease-

free survival time from patients with stage I disease, but overall survival did differ ($P=0.051$ for disease-free and $P=0.003$ for overall survival). Moreover, age was also associated with overall survival ($P=0.001$). No significant difference in disease-free or overall survival was detected for factors such as sex, localization, tumor location, approach, complications, number of lymph nodes retrieved, and hospital stay.

Multivariable Cox regression showed that CME is not an independent predictive factor for higher disease-free survival or overall survival (Table 4), since the hazard ratio was not statistically significant. Differentiation, adjuvant chemotherapy and age were shown to be statistically significant predictive factors for disease-free and overall survival rates ($P<0.05$). Stratified analysis by stage showed that there were no statistically significant factors associated with disease-free and overall survival rates for patients with stage II cancer. In contrast, for patients with stage III cancer, low differentiation was shown to be a statistically significant independent predictive factor for lower disease-free and overall survival rates.

Discussion

The concept of CME with central vascular ligation (CVL) has received very strong criticism. The initial criticism questioned the novelty of the technique. Many maintained that it was a concept already implemented by the majority of colorectal surgeons, in particular for tumors of the left colon [15,16]. In addition, the issue was raised of the reproducibility of the technique, because of the high level of surgical expertise required, along with concerns about higher rates of morbidity and intraoperative life-threatening adverse events. Many experienced and skillful colorectal surgeons claimed that some steps of CME with CVL, as described by Hohenberger *et al* [4], were technically very demanding, some were unnecessary, and because of that the technique was rendered very difficult to teach and to reproduce [13,17-19].

Our study failed to identify CME as an independent predictive factor for better disease-free and overall survival rates when compared with conventional colectomy, even when the disease was stratified by stage. Although survival analysis of the entire groups revealed a statistically significant difference favoring the CME group only as far as overall survival was concerned, when the cohort was stratified by several confounders, such as age, adjuvant chemotherapy, tumor differentiation and CME, the only significant independent predictive factor for both disease-free and overall survival rates, especially for UICC stage III patients, was high differentiation of tumors, which was associated with a significantly better disease-free and overall survival rates in the CME group.

Because there was a significant difference between the percentages of different stages of the disease between the two groups, all analyses were stratified by stage in order to confront this important source of bias. Nevertheless, CME failed to be identified as an independent predictive factor for disease-free and overall survival rates. This finding strongly contradicts many studies in the current literature [4,8,11-14,20]. The most

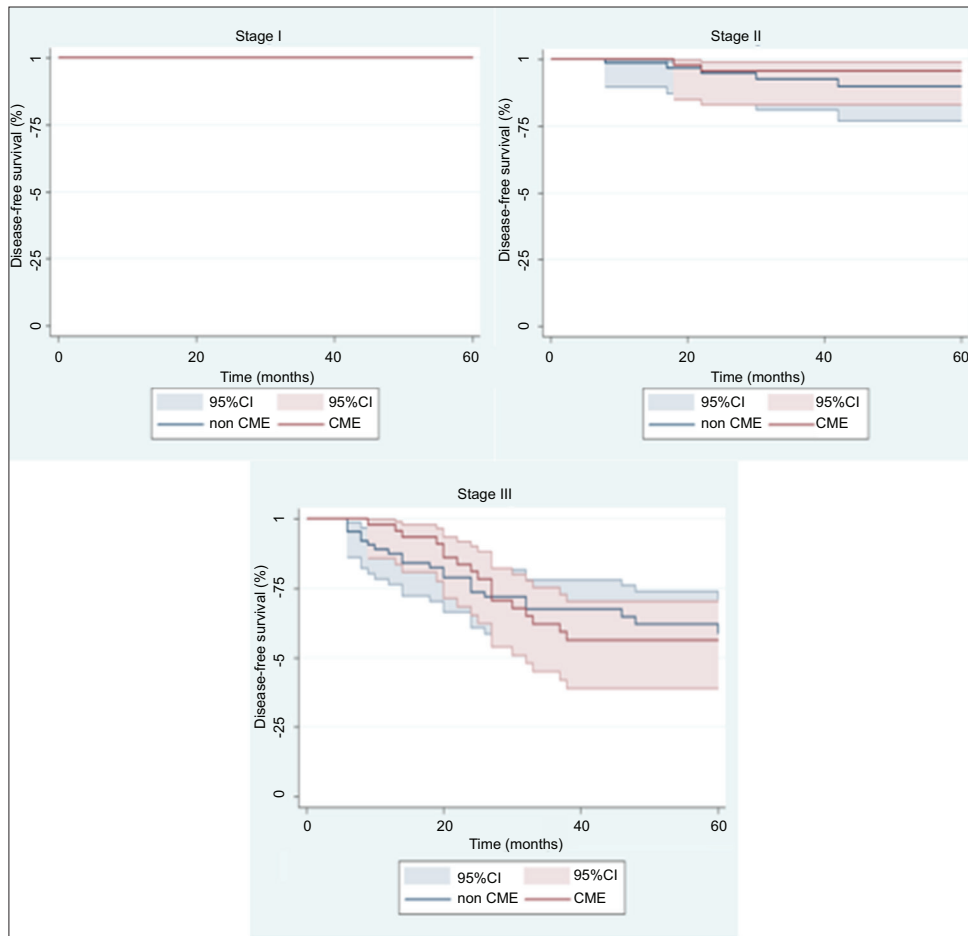


Figure 2 Disease-free survival time between treatment groups, stratified by stage
CME, complete mesocolic excision; CI, confidence interval

recent report, by Merkel *et al*, identified the implementation of CME surgery as one of the most important factors that significantly affected the improvement in disease-free survival and overall survival rates [20]. This could be attributed to several reasons: i) most patients with stage III disease had adjuvant chemotherapy administered, which may affect lymph node metastasis and improve recurrence and survival rates, in this way reducing the absolute effect of CME on the oncological outcome of these patients; ii) as lymph nodes in the CVL region are dissected by CME, but not by conventional colectomy, an upstaging from stage II to stage III is expected to occur in the CME group, whereas in conventional colectomy apical lymph nodes may be missed, leading patients to be classified as stage II if lymph nodes in the vicinity of the tumor are skipped by metastasis; iii) if not meticulous, histopathological examination may miss micro-metastases in apical lymph nodes dissected by CME colectomy. In this case patients are classified as having stage I or II disease. In conventional colectomy such micro-metastases are missed, because apical nodes are not removed, and these patients are also classified as stage I or II disease; and iv) differences in follow-up methods and duration may explain differences in oncological outcomes. In this study

all patients followed a strict follow-up schedule, as described in the methods section.

There have been major concerns about increased intraoperative and immediate postoperative morbidity and even mortality after CME colectomy with CVL. This has been attributed to the extent of mesocolic resection, particularly in colectomies involving the right and transverse colon, where CVL is carried out in the region of the superior mesenteric vessels, increasing the risk of vascular injury and injury of the sympathetic nerve plexus. However, all series of CME with CVL show very low mortality and acceptable morbidity rates, with limited intraoperative blood loss. Furthermore, two comparative studies [13,21] show no significant differences in morbidity, mortality or anastomotic leak rates between CME and conventional colectomy. In accordance with the current literature, in the present cohort of patients, no difference between the CME and the non-CME group could be identified regarding mortality, intraoperative complications or reoperation rates.

Our study is subject to many methodological limitations that are commonly found among all studies available in the literature concerning the same issue. Although CME

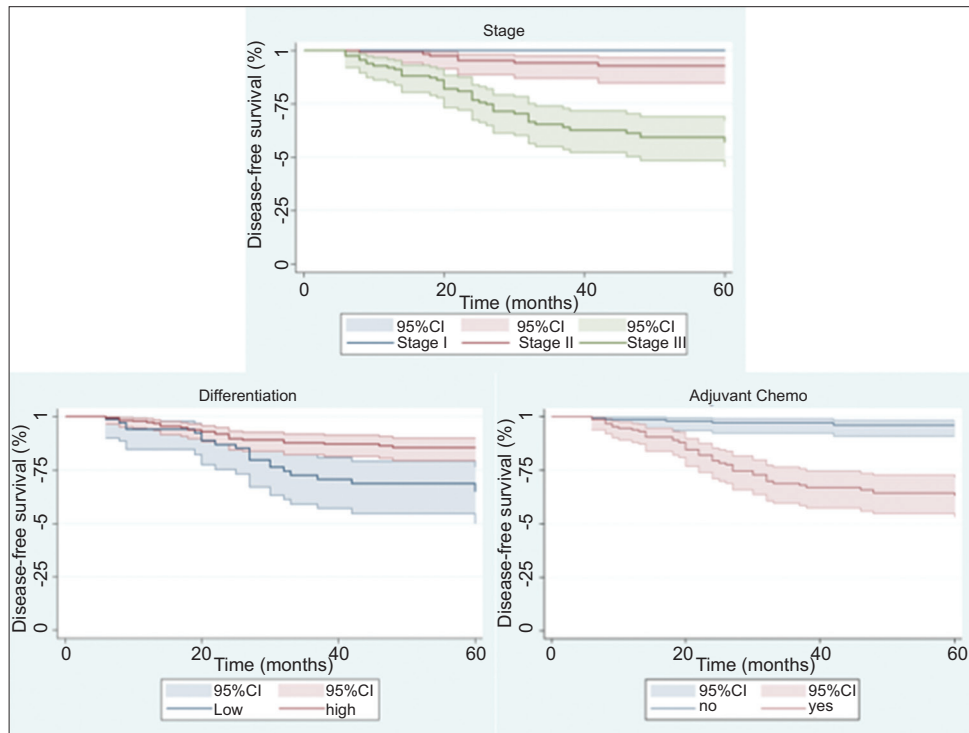


Figure 3 Disease-free survival time by characteristics
CI, confidence interval

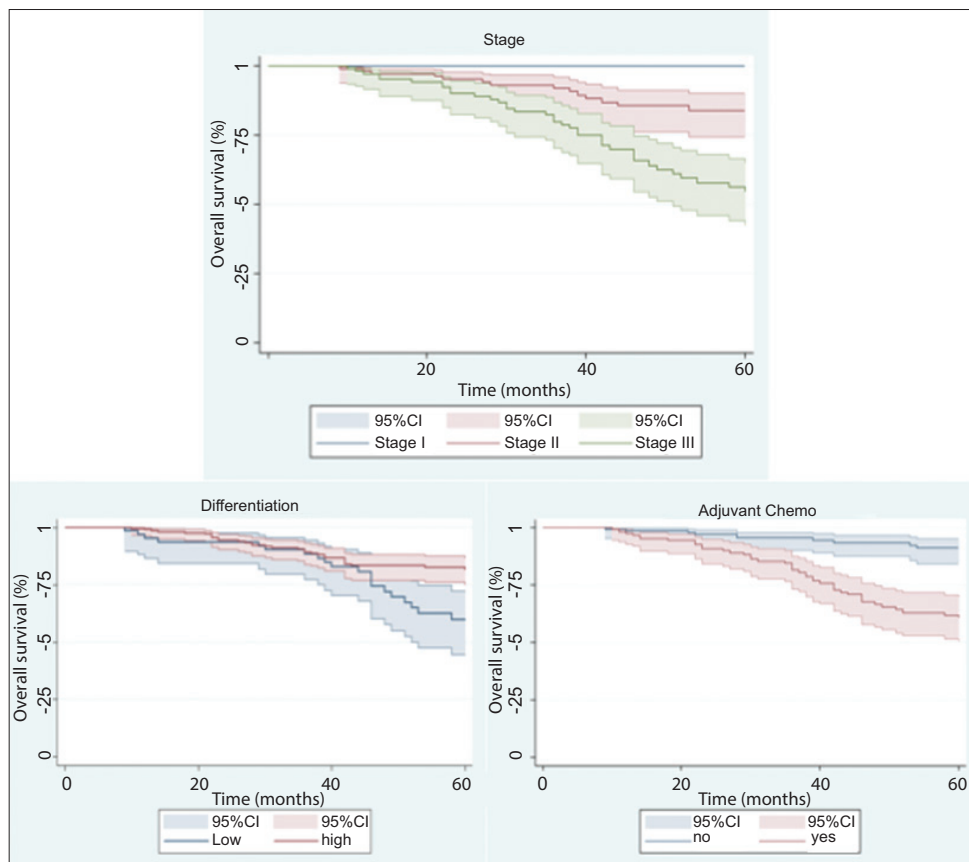


Figure 4 Overall survival time by characteristics
CME, complete mesocolic excision; CI, confidence interval

Table 4 Multivariate Cox regression model to estimate disease-free and overall survival rates

Variable	Disease-free survival		Overall survival	
	HR (95%)	P-value	HR (95%)	P-value
CME	0.868 (0.476-1.584)	0.646	0.764 (0.405-1.442)	0.406
Differentiation (high)	0.476 (0.261-0.866)	0.015	0.441 (0.233-0.833)	0.012
Adjuvant chemotherapy	10.44 (4.084-26.689)	<0.001	14.324 (4.393-46.709)	<0.001
Age	1.036 (1.003-1.070)	0.033	1.041 (1.004-1.078)	0.029
<i>Stratified by stage</i>				
Stage II				
CME	0.532 (0.101-2.798)	0.456	0.576 (0.105-3.169)	0.526
Differentiation (high)	0.396 (0.086-1.817)	0.234	0.706 (0.125-3.984)	0.693
Adjuvant chemotherapy	2.858 (0.632-12.921)	0.173	4.268 (0.773-23.562)	0.096
Age	1.028 (0.952-1.110)	0.483	1.059 (0.965-1.161)	0.227
Stage III				
CME	0.979 (0.510-1.879)	0.950	0.830 (0.145-1.659)	0.598
Differentiation (high)	0.515 (0.216-1.015)	0.050	0.457 (0.222-0.940)	0.033
Adjuvant chemotherapy	3.606 (0.833-15.617)	0.086	4.561 (0.606-34.335)	0.141
Age	1.036 (0.996-1.079)	0.081	1.042 (0.997-1.088)	0.067

HR, hazard ratio; CME, complete mesocolic excision

with CVL is a very well standardized operation for tumors located in the cecum, ascending, descending, sigmoid and rectosigmoid colon, the oncological radicality needed for tumors located along the transverse colon, from the hepatic to the splenic flexure, is still an open matter and remains highly controversial, particularly in terms of the extent of lymphadenectomy. At present, in the literature there are a few studies including series of patients with transverse colon tumors who underwent CME with CVL, by either open or laparoscopic approach, but do not report on transverse colon cancers outcomes separately. In one study [22] there is a considerable incidence of metastases of the extramesocolic lymph node stations, which cannot be underestimated and argues in favor of radical lymph node excision in these regions. Unfortunately, in this study the number of true transverse colon adenocarcinomas is also very limited and the outcomes are not presented separately, but at least the cases are equally distributed between the two groups.

A subgroup analysis on the basis of tumor location is therefore mandatory when reporting outcomes for CME plus CVL. Right-sided and transverse colon cancers constitute a different group of tumors, not only because of different biological behavior but also because colectomy in terms of CME differs hugely from the conventional. In this sense, tumor location along the colon is a significant confounder when all cases are being analyzed together. From this viewpoint, CME with CVL is expected to have a greater oncological impact on right and transverse colon cancers. Furthermore, although conventional colectomy for right-sided colonic tumors is even less standardized, conventional left-sided resections are closer to and sometimes coincide with the concept of CME with CVL, probably because they are less technically demanding,

Summary Box

What is already known:

- Complete mesocolic excision (CME) results in better quality specimens
- CME leads to increased disease-free survival
- CME is well standardized

What the new findings are:

- CME leads to increased lymph node harvesting
- CME improves overall survival in tumors with high differentiation
- CME does not increase postoperative complications

which renders them more feasible. It is easily conceivable that probably one or even two centimeters of difference in the CVL between the groups may be not enough to highlight an anticipated statistical difference.

In conclusion, there is strong evidence from this study that, when CME with CVL is performed, a larger amount of tissue, including a greater number of lymph nodes, is excised compared to conventional colectomy. A statistically significant benefit in overall survival was also observed, an outcome that is subject to several confounders such as age, high differentiation of tumors and adjuvant chemotherapy. CME surgery seems to benefit non-aggressive tumors (high differentiation) as far as both

disease-free and overall survival rates are concerned. However, this study failed to highlight any true oncological superiority of CME compared with conventional colectomy, mostly because of the aforementioned reasons and methodological limitations. On the other hand, this study also demonstrates that CME surgery is a safe, reproducible procedure that is not associated with any increase in severe morbidity and mortality. Large series of patients prospectively undergoing CME with CVL must be accumulated into registries and be compared to conventional surgery cases derived from large archive databases.

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