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REVIEW ARTICLE

Comparison between conventional colectomy and complete mesocolic excision for colon cancer: a systematic review and pooled analysis

A review of CME versus conventional colectomies

Noura Alhassan[1,2,3] · Mei Yang[1] · Nathalie Wong-Chong[1] · A. Sender Liberman[1,2] · Patrick Charlebois[1,2] · Barry Stein[1,2] · Gerald M. Fried[2] · Lawrence Lee[1,2]

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Abstract

Background Complete mesocolic excision (CME) is advocated based on oncologic superiority, but not commonly performed in North America. Many data are case series with few comparative studies. Our aim was to perform a systematic review comparing outcomes between CME and non-CME colectomy.

Methods A systematic review was performed according to PRISMA guidelines of MEDLINE, EMBASE, HealthStar, Web of Science, and Cochrane Library. Studies were included if they compared conventional resection (non-CME) to CME for colon cancer. Quality was assessed using methodological index for non-randomized studies (MINORS). The main outcome measures were short-term morbidity and oncologic outcomes. Weighted pooled means and proportions with 95% CI were calculated using a random-effects model when appropriate.

Results Out of 825 unique citations, 23 studies underwent full-text reviews and 14 met inclusion criteria. Mean MINORS score was 13.3 (range 11–15). The mean sample size in CME group was 1166 (range 45–3756) and 945 (range 40–3425) in non-CME. Four papers reported plane of dissection, with CME plane achieved in 85.8% (95% CI 79.8–91.7). Mean OR time in CME group was 167 min (163–171) and 138 min (135–142) in conventional group. Perioperative morbidity was reported in six studies, with pooled overall complications of 22.5% (95% CI 18.4–26.6) for CME and 19.6 (95% CI 13.6–25.5) for non-CME. Anastomotic leak occurred in 6.0% (95% CI 2.2–9.7) of CME resections versus 6.0% (95% CI 4.1–7.9) in non-CME. CME had more lymph nodes, longer distance to high tie, and specimen length in all studies. Nine studies compared long-term oncologic outcomes and only three reported statistically significant higher disease-free or overall survival in favor of CME. Local recurrence was lower after CME in two of four studies.

Conclusions The quality of evidence is limited and does not consistently support the superiority of CME. Better data are needed before CME can be recommended as the standard of care for colon cancer resections.

Keywords Colon cancer · Complete mesocolic excision · Central vascular ligation · Lymph node dissection · Systematic review · Oncologic outcomes

The association between the quality of surgical resection and oncologic outcomes has been well established for patients with rectal adenocarcinoma. The adoption of total mesorectal excision [1], that is, dissection in the avascular mesorectal fascial planes to provide an intact mesorectum, resulted in a significant decrease in local recurrence rates by 50% [2–4] However, these enveloping fascial planes are not limited to the rectum, but rather extend along the entire mesocolon all the way to the root of the mesentery. Therefore, the complete mesocolic excision (CME) technique applies the same principles of rectal cancer surgery to colon cancer, that is, sharp dissection along these embryologic fascial planes enveloping the colonic mesentery. This allows for

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Noura Alhassan
noura.alhassan@mail.mcgill.ca

Extended author information available on the last page of the article

intact removal of the mesocolon and its encompassing lymph nodes and decreases the risk of tumor spillage into the peritoneal cavity. Pathologic assessment of the resected colonic specimen demonstrated that patients with specimens in the mesocolic plane of dissection may have superior oncologic outcomes compared to those with the muscularis propria plane, especially for stage III disease [5]. CME can also maximize lymph node harvest by central vascular ligation (CVL) of the main feeding vessel(s) at their origin, which has also been associated with improved survival [6]. In the seminal paper by Hohenberger et al., local recurrence was reduced from 6.5 to 3.6% and cancer-related 5-year survival increased from 82.1 to 89.1% in patients that underwent CME compared to patients who received a conventional resection [7].

Despite these theoretical advantages and promising early data, CME has not been widely adopted, especially in North America [8]. CME is technically demanding and has been associated with more intraoperative organ injuries and severe non-surgical complications compared to conventional colectomy [9]. The seminal papers by Hohenberger et al. and West et al. that provided much of the initial evidence base in support of CME have important methodologic flaws [10]. Most of the CME literature is limited to case series with few comparative studies between CME and conventional colectomy and with little survival data [11]. Therefore, the objective of this study is to perform a systematic review of the short- and long-term outcomes between CME and conventional colectomy in patients with colon cancer.

Materials and methods

Search strategy

A systematic literature search of all English- and French-language full-text articles published up to August 2017 was performed. No lower date limit was applied. The Medline, Embase, HealthStar, PubMed, Web of Science, Scopus, Cochrane Library, CINAHL, and the Database of Abstracts of Reviews of Effects (DARE) databases were searched. Electronic search terms used in the systematic search are shown in Table 1. In addition, the reference lists of key records were examined for additional relevant studies. Recognized experts in the field were also contacted to identify additional studies. Records were first screened for relevance based on their title and abstract, and full-text articles were retained if they met the following criteria: if they were comparative studies reporting perioperative or oncologic outcomes of CME versus conventional colectomy for colon cancer (i.e., no case series). Studies were only included if the CME technique was satisfactorily defined, including a description of dissection in the embryologic mesocolic fascial planes and CVL or D3 lymphadenectomy [12]. For studies using the Japanese D1-3 nomenclature, D3 dissection was considered as CME, and D2 and D1 dissection to be conventional colectomy [12, 13]. Studies were excluded if the surgical technique was missing, or if they represented overlapping data from the same institution. However, overlapping studies were included if additional outcomes were reported. Two authors (N.A. and M.Y.) independently assessed each record for eligibility and extracted the data, including quality assessment, from full-text articles that met the inclusion criteria. Disagreements were resolved by consensus, and if no agreement could be made, a third author (L.L.) was consulted.

Data extraction and synthesis

Study design and population characteristics (including age, gender, disease stage, tumor location, included procedures, and surgical approach) were recorded. Perioperative outcomes were defined as safety (operation duration, blood loss, intraoperative complications, postoperative morbidity and mortality, with specific attention to anastomotic leakage) and quality (length of resected bowel, distance to high tie, area of resected mesentery, plane of surgery, and lymph node harvest) variables. Oncologic outcomes included duration of follow-up, overall or disease-free/specific survival, and local and distant recurrence.

Quality was assessed using the methodological index for non-randomized studies (MINORS) [14]. This is a validated

Table 1 Detailed search strategy using a combination of medical subject headings (MESH) terms and keywords, divided into broad search categories

Complete mesocolic excision
Complete mesocolic excision.m_titl OR complete mesocolic excision.mp OR mesocolic$.tw
Central vascular ligation
Central vascular ligation.mp OR central vascular ligation.m_titl OR ligation$.tw OR high ligation$.tw
Extended/D3 lymphadenectomy
D3 lymphadenect$.tw OR extended lymphadenect$ OR d3$.tw OR lymphadenect$.tw OR lymph node dissection.tw OR Lymph Node Excision/
Surgery for colon cancer
Colorectal surgery/OR colectomy/OR colonic neoplasms/[su] OR mesocolon/[su]

Terms that end with "/" represent MESH terms tool for the methodological assessment of non-randomized surgical studies whether comparative or non-comparative. For comparative studies, 12 criteria are used and items are scored from 0 to 2: 0 (not reported), 1 (reported but inadequate), 2 (reported and adequate). The global ideal score for comparative studies is 24.

Data were reported as n (%), mean (SD), or median [IQR]. Weighted pooled means and proportions with 95% CI were calculated using a random-effects model when appropriate. It was decided a priori to use a random-effects model to calculate pooled effect estimates as it was anticipated that the studies included for meta-analysis would include heterogeneous patient populations and surgical procedures. Subgroup analyses were performed between studies that reported CME sample size $<$ or $\geq$100 cases to account for the possible effect of experience and volume–outcome relationship. All statistical analyses were performed using STATA 15.1 (StataCorp, College Station, TX).

Results

Out of a total of 825 unique citations, 23 studies underwent full-text reviews and 14 studies met inclusion criteria (Fig. 1) of which three were overlapping studies [15–17] and 11 were unique series [9, 18–27]. Study design and characteristics are reported in Table 2. Of the 14 included studies, 3 originated from Japan [20, 21, 23], and the remainder were European [9, 15–19, 22, 24–27]. There were no North American studies. All studies were retrospective. Four studies used historical controls [17, 22, 24, 27]. The mean sample size in the CME group was 1166 (range 45–3756) and 945 (range 40–3425) in the non-CME group. Four studies only included right-sided resections [19, 22, 25, 27]. Only five studies reported surgical approach [9, 15, 16, 21, 26], with 52.2% (95% CI 31.0–73.3, $I^2 = 98.9\%$) pooled proportion of laparoscopic CME.

Mean MINORS score 13.3 (range 11–15). The MINORS score was similar between the Japanese papers with a mean score 13 (range 12–14) and the Western papers with a mean score 13.4 (range 11–15). Only three studies used matching methods to reduce bias (Table 2) [16, 20, 21].

Perioperative outcomes

There were three studies that reported operative duration [19, 22, 25], of which two reported longer procedure times for CME [19, 22]. Perioperative morbidity was reported in six studies [9, 15, 19, 22, 24, 25] with pooled overall complications of 22.5% (95% CI 18.4–26.6, $I^2 = 83.4\%$) for

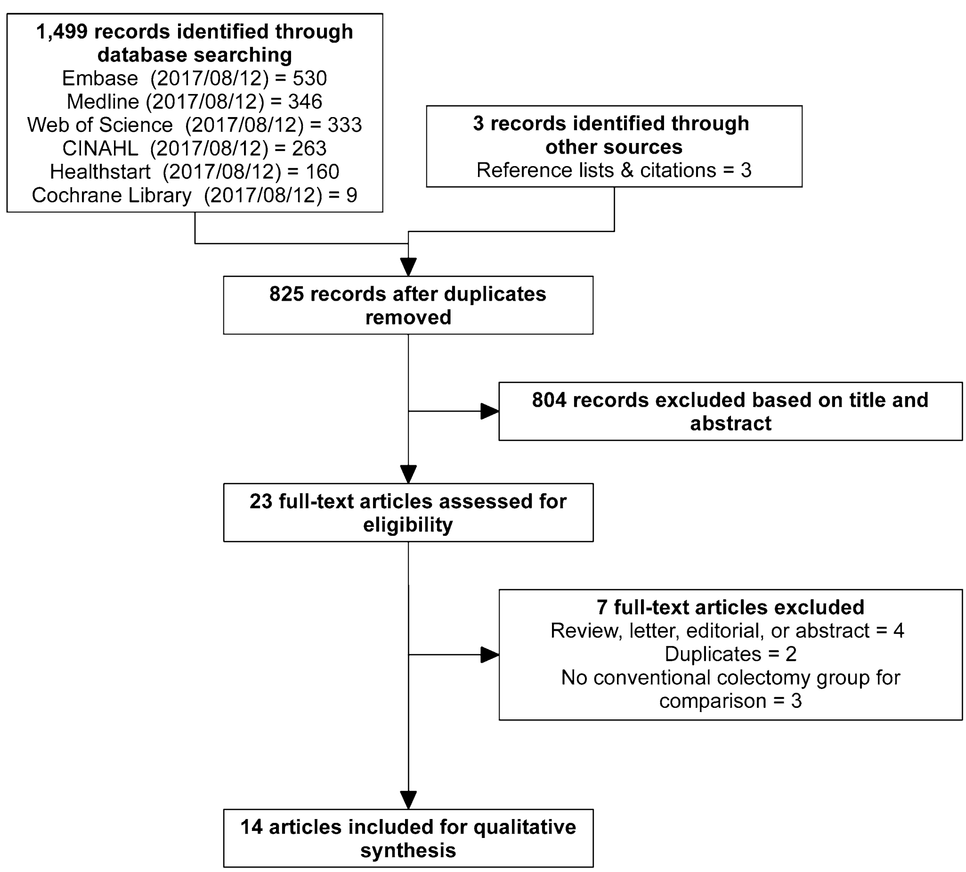

Fig. 1 Study identification and selection flowchart

Table 2 Characteristics of included studies

Study ID	Study period	Control group	Country of origin	Stage	MINORS score (/24)	Mesocolic excision	N	Age, years	Male (%)	Tumor location (right/left/transverse) (%)	Laparoscopy (%)	OR time (min), mean (SD)	Blood loss (ml)	Anastomotic leak (%)	Overall complications (%)	Mortality (%)
Tagliacozzo and Tocchi [19], Int J Colorectal Dis, 1997	1979–1989	Contemporary	Italy	Dukes A, B, C	14	CME	60	63 (6.5)[a]	56.7	100/–/–	–	156 (24)***	–	–	11.6	6.6
						Non-CME	84	61 (7.0)[a]	53.6	100/–/–	–	145 (20)	–	–	10.4	4.7
West et al. [17], J Clin Oncol, 2010	1999–2008	Contemporary + historical	Germany, UK	I–IV	11	CME	49	–	49.0	61.2/38.8/0***	–	–	–	–	–	–
						Non-CME	40	–	47.5	40/52.5/7.5	–	–	–	–	–	–
West et al. [18], Dis Colon Rectum, 2010	2008–2009	Contemporary	Denmark	I–IV	13	CME	93	70 [60.5–78.0][b]	60.2***	44.1/37.6/18.3***	–	–	–	–	–	–
						Non-CME	170	72 [62.8–78.0][b]	44.1	33.5/50.6/14.7	–	–	–	–	–	–
Bertelsen et al. [15], Colorectal Dis, 2011	2007–2009	Contemporary	Denmark	I–IV	13	CME	93	70 (38–92)[b]	55.9	49.5/41.9/2.2	46.2	–	250 (0–6000)[b]	8.6	22.6	6.5 (30-days)
						Non-CME	105	73 (42–89)[b]	49.5	57.1/37.1/1	41.9	–	270 (0–5500)[b]	7.6	20.0	7.6 (30-days)
Galizia et al. [22], Int J Colorectal Dis, 2014	2004–2012	Historical	Italy	Dukes A–D	14	CME	45	67 (13)[a]	48.9	100/–/–	–	178 (21)***	280 ± 40[a]***	4.4	13.3	–
						Non-CME	58	68 (11)[a]	56.9	100/–/–	–	130 (20)	200 ± 30[a]	5.2	12.1	–
Kotake et al. [20], Int J Colorectal Dis, 2014*	1985–1994	Contemporary	Japan	II, III	12	CME	3425	64.6 (10.5)[a]	55.2	53.9/46.1/–	–	–	–	–	–	–
					13*	Non-CME	3425	64.6 (11.5)[a]	54.4	53.8/46.2/–	–	–	–	–	–	–
Storli et al. [26], Tech Coloproct, 2014	2007–2008	Contemporary	Norway	I–III	15	CME	84	72.5 (11.3)[a]	52.4	45.2/45.2/2.4	29.8	–	–	–	–	2.8 (30-days)
						Non-CME	105	72.6 (12.6)[a]	51.4	43.8/47.6/1.0	20.0	–	–	–	–	8.8 (30-days)
Bertelsen et al. [16], Lancet Oncol, 2015	2008–2011	Contemporary	Denmark	I–III	12	CME	364	71.5 [64.3–77.8][b]	51.6	46.4/45.9/0***	49.0***	–	–	–	–	5 (30-days)
						Non-CME	1031	73.0 [66.0–79.9][b]	45.8	43.6/49.8/1.6	65.0	–	–	–	–	4 (30-days)
Kotake et al. [21], Int J Colorectal Dis, 2015*	1995–2004	Contemporary	Japan	–	13	CME	463	–	60.3	45.6/54.4/–	11.9	–	–	–	–	–
					14*	Non-CME	463	–	54.9	44.5/55.5/–	14.3	–	–	–	–	–
Bertelsen et al. [9], Br J Surg, 2016	2008–2013	Contemporary	Denmark	I–III	13	CME	529	71.7 [76.0–78.3][b]	51.0	46.7/45.9/–	48.8***	–	–	8.5	30.6	6.2 (90-days)
						Non-CME	1701	72.9 [66.0–80.1][b]	47.4	46.1/48.1/–	68.9	–	–	7.1	28.5	4.9 (90-days)

Table 2 (continued)

Study ID	Study period	Control group	Country of origin	Stage	MINORS score (/24)	Mesocolic excision	N	Age, years	Male (%)	Tumor location (right/left/transverse) (%)	Laparoscopy (%)	OR time (min), mean (SD)	Blood loss (ml)	Anastomotic leak (%)	Overall complications (%)	Mortality (%)
Ishihara et al. [23], Int J Colorectal Dis, 2016	1997–2007	Contemporary	Japan	I–III	12	CME	3756	D3–64[b,***]	D3–52***	36/53/11***	–	–	–	–	–	–
						Non-CME	2185	D1–68[b] D2–67[b]	D1–60 D2–57	D1–27/46/26 D2–15/55/20	–	–	–	–	–	–
Merkel et al. [24], Br J Surg, 2016	1978–2014	Historical	Germany	I–III	14	CME	1099	66 (28–90)[b,c] 67 (17–93)[b,d] 67 (23–91)[b,e]	58.9	30.5/51.2/18.3***	–	–	–	3.0***	21.3***	2.7
						Non-CME	429	65 (27–89)[b,***]	51.5	17.0/64.1/18.9	–	–	–	4.3	17.2	3.7
Olofsson et al. [25], Colorectal Dis, 2016	2007–2009	Contemporary	Sweden	I–IV	14	CME-RMC	1360	73.6[a]	43.0	100/–/–	–	151	215	–	22.1	2.0
						CME-MC	334	71.6	46.0	100/–/–		158	250		23.4	3.6 (30-days)***
						Non-CME	390	74.2[a]	41.0	100/–/–	–	148	204	–	20.8	0.8 (30-days)
Thorsen et al. [27], Tech Coloproct, 2016^	2007–2014	Contemporary + historical	Norway	–	14	CME	49	67 (27–75)[b]	38.8	100/–/–	–	–	–	–	–	–
						Non-CME	49	65 (28–75)[b]	40.8	100/–/–	–	–	–	–	–	–

CME-RMC CVL with ligation of right branch of middle colic artery, *CME-MC* CVL with ligation of middle colic artery

*Propensity score matching

^Matched for age and sex

***p Value < 0.05

[a]Mean (SD)

[b]Median (range)

[c]1995–2002

[d]2003–2009

[e]2010–2014

CME and 19.6 (95% CI 13.6–25.5, $I^2 = 90.0\%$) for non-CME surgery. In the higher volume studies, the pooled overall incidence of complications was 24.4% (95% CI 20.0–28.9, $I^2 = 88.1\%$) and 15.9% (95% CI 9.0–22.8, $I^2 = 45.6\%$) in lower volume studies. Only one study demonstrated higher incidence of complications after CME [24], as the remaining did not show a difference between the two groups. Furthermore, only one study reported intraoperative outcomes [9]. In this study, CME was associated with significantly higher intraoperative organ injuries (CME 9.1% vs. 3.6% non-CME, $p < 0.001$), in particular splenic and superior mesenteric vein injuries. However, overall postoperative and surgical complications were similar in that study. The pooled proportion of four studies reporting anastomotic leak was 6.0% (95% CI 2.2–9.7, $I^2 = 84.4\%$) after CME resections versus 6.0% (95% CI 4.1–7.9, $I^2 = 50.1\%$) after non-CME colectomy [9, 15, 22, 24]. In the higher volume studies, the pooled leak rate was 5.6% (95% CI 0.2–11.0, $I^2 = 93.9\%$) and 6.6% (95% CI 2.5–10.8, $I^2 = 48.4\%$) in lower volume studies. Only one study reported a statistically significant difference in anastomotic leak rate [24], although it was lower in the CME group. Operative blood loss between the groups was similar in the three studies that reported this outcome [15, 22, 25], but one study noted that the CME group had a significantly higher rate of excessive bleeding (> 350 ml) [25].

Histological outcomes

There were four papers reporting plane of dissection [15–17, 22], with the pooled proportion of CME plane of dissection being 85.8% (95% CI 79.8–91.7, $I^2 = 67.4\%$). In the single high-volume study, 81.3% (95% CI 76.9–85.2) of specimens were graded in the mesocolic plane. In low-volume studies, the pooled proportion of specimens in the mesocolic plane of dissection was 87.9% (95% CI 80.8–95.0, $I^2 = 57.6\%$). The distance to high tie, area of resected mesentery, and specimen length were poorly described (Table 3) and were mostly in favor of CME when reported. Using the CME criteria defined by Sondenaa et al. [12], only one study [17] included all of the relevant outcomes of bowel length, distance to high tie, and plane of dissection. Lymph node harvest was reported in all studies except two [9, 15, 17–22, 24–27]. Nodal yield was higher in the CME group in all studies except for two [26, 27]. However, one of the studies demonstrating a difference had a mean lymph node yield less than 12 in the non-CME group [21].

Oncological outcomes

There were nine studies that compared long-term oncologic outcomes between CME and non-CME resections (Table 3) [16, 19–26]. Overall survival was higher for the CME group at years in stages I–III in one study [26] and for stage III only in the other [24]. The five other studies reporting 3- or 5-year overall survival did not demonstrate a difference between CME and non-CME resections. Disease-free or disease-specific survival was higher for the CME group in three of the six studies [16, 24, 26] .One study reported significantly lower 5-year disease-specific survival for D3 resections compared to D1/D2, although the difference was small (D3 91% vs. 92% for D1 and 95% for D2) [23]. Local and distant recurrence was included in four studies [22, 24–26], with two studies reporting lower recurrence in favor of CME [22, 24]. The local recurrence rates in the non-CME group for these two studies were 20.6% (Dukes A–D) [22] and 14.8% (stage III only) [24].

Discussion

CME applies many of the same principles of the total mesorectal excision concept for rectal cancer to colon cancer surgery. Dissection along the 'holy plane' at the mesorectal fascia has shown to minimize CRM involvement and is associated with improved outcomes in rectal cancer. Similarly, CME involves a meticulous dissection along the embryological planes surrounding the colon and its mesentery, resulting in an intact mesocolic envelope. CME also includes a division of the supplying vessels at their origin (CVL) to improve lymph node harvest. Early data suggested improved oncologic outcomes with the CME technique, but data are sparse. Past systematic reviews have not included much of the newer data and have also included case series without a comparison group [11, 28, 29]. We performed a systematic review on the perioperative and long-term outcomes of CME, but only included comparative studies. In the present study, the available evidence does not consistently demonstrate the superiority of CME over conventional colectomy.

There are several elements that are essential in CME surgery [12]. First, the dissection is performed in the embryologic plane between the colonic mesentery and the parietal fascia of retroperitoneum. This allows for the removal of vascular, lymphatic, and perineural tissues as a complete undisturbed package en bloc with the colon. Second is CVL, where all the regional lymph nodes, including the apical or D3-level nodes, are removed with high ligation of the vascular pedicle. The third element is adequate bowel length of the resected specimen and the removal of the pericolic lymph nodes in the longitudinal direction. There were few studies that reported these important elements of CME, with only one study reporting all three. While the relationship between these histopathologic variables and oncologic outcomes is unclear, these variables are important in determining the quality of the CME in comparison to what is considered 'conventional' colectomy. The one variable that

Table 3 Summary of pathologic and oncologic outcomes

Author, journal, year	Mesocolic excision		Pathologic outcomes					Oncologic outcomes					
			Bowel length (cm)	Distance to high tie (cm)	Mesentery area (cm^2)	Lymph node harvest	Complete plane of dissection (%)	Overall survival (%)	Disease-free survival (%)	Disease-specific survival (%)	Local recurrence (%)	Distant recurrence (%)	Follow-up, median (range)
Tagliacozzo and Tocchi [19], Int J Colorectal Dis, 1997	CME	Mean (SD)	–	–	–	22 (2.4)***	–	64.3 (5 years)	–	–	–	–	96 (60–120) months
	Non-CME	Mean (SD)	–	–	–	14 (2)	–	62.8 (5 years)	–	–	–	–	
West et al. [17], J Clin Oncol, 2010	CME	Median [IQR]	32.0***	13.0***	200.0	30 [23–39]***	Overall—90 Right—88 Left—100	–	–	–	–	–	–
	Non-CME	Median [IQR]	22.0	9.0	125.0	18 [12–24]	–	–	–	–	–	–	–
West et al. [18], Dis Colon Rectum, 2010	CME	Median [IQR]	31.5 [25.9–44.1]***	10.5 [8.4–12.9]***	145 [98–217]***	28 [24–37]***	–	–	–	–	–	–	–
	Non-CME	Median [IQR]	24.7 [20.4–28.3]	8.4 [6.7–10.1]	87 [66–114]	18 [14–23]	–	–	–	–	–	–	–
Bertelsen et al. [15], Colorectal Dis, 2011	CME	Mean (95% CI)	–	9.6 (8.9–10.3)***	–	26.7 (24.6–28.8)***	81.5	–	–	–	–	–	–
	Non-CME	Mean (95% CI)	–	7.1 (6.5–7.6)	–	24.5 (22.8–26.2)	–	–	–	–	–	–	–
Galizia et al. [22], Int J Colorectal Dis, 2014	CME	Mean (SD)	28.8 (2.7)	10.6 (1.3)***	–	20 (9)***	91	–	–	95 (3 years)	0.0***	13.0***	–
	Non-CME	Mean (SD)	27.4 (4.1)	8.7 (1.7)	–	15 (6)	–	–	–	87 (3 years)	20.6	13.8	–
Kotake et al. [20], Int J Colorectal Dis, 2014*	CME	Mean (SD)	–	–	–	21.8 (14.3)***	–	No difference at 5 years	–	–	–	–	–
	Non-CME	Mean (SD)	–	–	–	14.9 (0.2)	–		–	–	–	–	–
Storli et al. [26], Tech Coloproct, 2014	CME	Mean (SD)	26.2 (14.5)	–	–	16.1 (9.7)	–	88.1 (3 years)***	82.1 (3 years)***	95.2 (3 years)	1.2	2.4	50.2 (0–62) months
	Non-CME	Mean (SD)	27.4 (19.2)	–	–	14.8 (6.8)	–	79.0 (3 years)	74.3 (3 years)	90.5 (3 years)	2.9	8.6	
Bertelsen et al. [16], Lancet Oncol, 2015	CME	–	–	–	–	–	82	74.9 (5 years)	85.8 (4 years)*** Stage I 100*** Stage II 91.9*** Stage III 73.5***	–	–	–	2.98 (1.99–2.93) years[f]
	Non-CME	–	–	–	–	–	–	69.8 (5 years)	73.4 (4 years) Stage I 89.9 Stage II 77.9 Stage III 67.5	–	–	–	2.14 (1.02–3.11) years
Kotake et al. [21], Int J Colorectal Dis, 2015*	CME	Mean (SD)	–	–	–	18.1 (12.0)***	–	91.9 (5 years)	–	–	–	–	–
	Non-CME	Mean (SD)	–	–	–	11.6 (11.2)	–	90.6 (5 years)	–	–	–	–	–

Table 3 (continued)

Author, journal, year	Mesocolic excision		Pathologic outcomes: Bowel length (cm)	Distance to high tie (cm)	Mesentery area (cm^2)	Lymph node harvest	Complete plane of dissection (%)	Oncologic outcomes: Overall survival (%)	Disease-free survival (%)	Disease-specific survival (%)	Local recurrence (%)	Distant recurrence (%)	Follow-up, median (range)
Bertelsen et al. [9], Br J Surg, 2016	CME	Mean (SD)	–	–	–	36 (26–47)***	–	–	–	–	–	–	–
	Non-CME	Mean (SD)	–	–	–	20 (15–28)	–	–	–	–	–	–	–
Ishihara et al. [23], Int J Colorectal Dis, 2016	CME	–	–	–	–	–	–	–	–	D3–91.0 (5 years)***	–	–	81.7 months
	Non-CME	–	–	–	–	–	–	–	–	D1–92 D2–95	–	–	
Merkel et al. [24], Br J Surg, 2016	CME	Median (range)	–	–	–	27 (3–86)[c] 28 (1–92)[d] 25 (12–61)[e]	–	Stage I–II 83.9[c]/83.0[d] Stage III 69.7[c]/68.6[d,]*** (5 years)	–	Stage I–II 91.7[c]/95.2[d] Stage III 75.4[c]/80.9[d,]*** (5 years)	Stage I–II 0.9[c]/1.1[d] Stage III 7.1[c]/4.1[d,]***	Stage I–II 6.5[c]/7.8[d] Stage III 32.3[c]/25.4[d]	10 (0–36) years
	Non-CME	Median (range)	–	–	–	25 (4–100)***	–	Stage I–II 86.2 Stage III 53.1 (5 years)	–	Stage I–II 89.9 Stage III 61.7	Stage I–II 1.8 Stage III 14.8	Stage I–II 8.1 Stage III 35.5	
Olofsson et al. [25], Colorectal Dis, 2016	CME-RMC	Mean	–	–	–	19.2***	–	79.4	73.8	–	4.0	13.1	–
	CME-MC					19.2		76.9 (3 years)	71.8 (3 years)		2.7	15.0	
	Non-CME	Mean	–	–	–	17.5	–	78.5 (3 years)	69.4 (3 years)	–	2.3	16.4	–
Thorsen et al. [27], Tech Coloproct, 2016^	CME	Mean (SD)	24.2 (7.2)	–	–	38 (22–75)[b]	–	–	–	–	–	–	31 (6–74) months
	Non-CME	Mean (SD)	23.2 (7.3)	–	–	21 (10–46)[b]	–	–	–	–	–	–	14 (6–30) months

CME-RMC CVL with ligation of right branch of middle colic artery, *CME-MC* CVL with ligation of middle colic artery

*Propensity score matching

^Matched for age and sex

***p Value < 0.05

[a]Mean (SD)

[b]Median (range)

[c]1995–2002

[d]2003–2009

[e]2010–2014

[f]With supplementary data from DCCG database

was consistently reported was lymph node yield, which was higher in all studies except for two (Table 3) [26].

In this review, CME and D3 dissection were considered in the same manner; however, there are several differences between the two techniques. The amount of bowel resected is based on tumor location in the CME techniques, whereas the bowel transection margins are generally limited to 10 cm from the tumor and 5 cm from the feeding vessels in D3 dissection [12, 20, 21]. Consequently, bowel length and area of resected mesentery is higher in CME compared to D3 dissection, although nodal harvest is similar [13, 30]. The planes of dissection between the two techniques are identical. Some of these differences may be explained by the level of expertise, as D3 dissection is considered standard of care for stage II and III colon cancer according to Japanese practice guidelines published in 2005, and over 75% of colectomies are performed by the D3 technique [31].

There was variability in the description of the CME technique amongst the included studies. The Japanese studies tended to only describe the extent of the lymphadenectomy, detailing their surgical approach to D1, D2, and D3 [20, 23]. Japanese D3 dissection is generally considered similar to CME as described above, except for the length of bowel that is resected, which is lower in the D3 technique. For the Western studies, the surgical technique was clearly described in most. Only one study had a vague description of CME, but did mention the extent of lymphadenectomy in each group as well as performing CVL in the study group [19]. Another study focused on the extent of vascular ligation to delineate the differences in the study groups, where we considered CVL to be the study arm and the remaining groups as standard technique.

Survival data were also equivocal. There were nine studies that reported long-term oncologic outcomes, of which only four reported improved overall or disease-free survival [16, 24, 26], or decreased local or distant recurrence in favor of CME [22, 24]. One study reported lower disease-specific survival for D3 dissection compared to D2 and D1, although this difference was no longer significant on multiple regression analysis [23]. There were important methodologic limitations in the four studies demonstrating favorable results. Two of the studies compared outcomes from one hospital performing CME to other hospitals performing conventional colectomy [16, 26]. There may have been other important differences in the referral status, hospital and surgeon volume, and treatment characteristics between the hospitals that may have further biased the results. The other two studies compared patients undergoing CME with historical controls [22, 24]. There have been important advances in the treatment of colorectal cancer over time that may also explain the improvements in outcomes beyond CME, especially for the study by Merkel et al. [24] which compared CME outcomes from 1995 to 2002, 2003–2009, and 'pre-CME' era of 1978–1984. Clearly, perioperative morbidity and mortality, as well as chemotherapy regimens, have significantly changed over these time periods [10]. Similarly, the seminal study by Hohenberger et al. [7], which was not included in this systematic review as it did not adequately describe the patient and surgical characteristics of the non-CME group, demonstrated favorable outcomes for CME, but compared to historical controls over an extended time period that also included significant advances in the treatment of colorectal cancer. The two studies reporting lower local recurrences in favor of CME had exceedingly high local recurrence rates in the non-CME group (20.6% [22] and 14.8% [24]), which calls into question the adequacy of the resection in these patients. Locoregional recurrence in the randomized trials comparing laparoscopic and open 'conventional' colectomy for colon cancer [32–35] have all reported lower rates with longer follow-up (highest rate was 10.6% after 10-year follow-up of the Lacy et al. trial [35]) than the two studies in this review. Only one of these studies also included overall survival data, which was in favor of CME [24]. It is unclear whether this was a result of the high incidence of local recurrences.

CME is generally thought to be more technically difficult compared to 'conventional' colectomy due to the central vascular dissection, especially in patients with significant visceral obesity. Perioperative outcomes such as overall morbidity, anastomotic leak, and mortality were inconsistently reported, and generally do not demonstrate a difference between CME and conventional colectomy. However, only one study reported intraoperative complications [9], which demonstrated a significantly higher incidence of injuries to the superior mesenteric vein and spleen, although overall morbidity was similar. The lack of reporting of intraoperative complications was a significant gap in the available literature, especially as many surgeons that have not adopted the CME technique are especially wary of the potential significant intraoperative complications that may occur with the central dissection during CME. It is unclear if the purported survival benefits are offset by these complications [36]. Other data have shown an important association between perioperative morbidity and decreased long-term survival after colon cancer surgery [37].

The results of this systematic review should be interpreted in view of several other limitations. Most importantly, there is a lack of high-quality data. There were no randomized trials, and all of the remaining observational studies were retrospective in nature. There was significant heterogeneity in study design amongst the included studies, with little standardization of the CME technique [36]. We attempted to account for possible learning curve and volume–outcome effect by performing subgroup analysis based on sample size (<100 vs. ≥ 100 cases), but the requisite volume is not yet known. There was significant heterogeneity in the reported outcomes which limited our ability to perform a pooled analysis for many of the variables. This is especially important as many of the studies had small sample sizes and therefore are subject to potential type II error. Quality assessment was also difficult, as there is no consensus on the best instrument to evaluate non-randomized studies, as well as the multiple study designs of the articles included in this systematic review. We used the MINORS instrument, which was been specifically designed and validated for surgical studies, but many other instruments exist.

In light of the available literature, more comparative research is needed before CME can be widely recommended and implemented. The first requirement of future studies should be a standardized definition of CME and its outcomes. This systematic review demonstrated that the important 'quality of surgery' outcomes specific to CME are poorly described in the literature, in particular plane of surgery. Without these important data, the true effect of CME may never be clearly elucidated. Consensus guidelines exist which provide recommendations on the extent of bowel resection and vascular ligation [12]. There also needs to be more data on the incidence of CME-related intraoperative injuries and perioperative morbidity, in particular amongst those who are starting to implement this technique. Finally, comparisons of long-term oncologic outcomes should be performed with contemporary controls to avoid biases due to changes in management over time.

In summary, the quality of the current evidence is limited and does not consistently support the superiority of CME. Better data are needed before CME can be recommended as the standard of care for colon cancer resections.

Compliance with ethical standards

Disclosures Dr. A. Sender Liberman is on the medical advisory committee on ERAS for Merck, and on the advisory committee meeting for Novadaq. Drs. Noura Alhassan, Mei Yang, Nathalie Wong-Chong, Patrick Charlebois, Barry Stein, Gerald M. Fried, and Lawrence Lee have no conflicts of interest or financial ties to disclose.

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Affiliations

Noura Alhassan[1,2,3] · Mei Yang[1] · Nathalie Wong-Chong[1] · A. Sender Liberman[1,2] · Patrick Charlebois[1,2] · Barry Stein[1,2] · Gerald M. Fried[2] · Lawrence Lee[1,2]

[1] Centre for Colon and Rectal Surgery, McGill University Health Centre, Montreal, QC, Canada

[2] Steinberg-Bernstein Centre for Minimally Invasive Surgery and Innovation, McGill University Health Centre, 1650 Cedar Ave, E19-125, Montreal, QC H3G 1A4, Canada

[3] Department of Surgery, College of Medicine, King Saud University, Riyadh, Saudi Arabia