Complete mesocolic excision for right colon cancer—state of art: a systematic review of the literature

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Abstract: Complete mesocolic excision (CME) is a new concept of right hemicolectomy for colon cancer (CC) set up to improve oncological outcomes and based on three main points: dissection in the embryological plane, central vascular ligation (CVL) and resection of a sufficient length of bowel. During this last decade, many doubts and questions have been arised about safety and efficacy of CME. We conducted a systematic review of the literature to investigate the safety, quality and survival outcomes of this procedure. Literature search resulted in 659 articles found and after the selection process 21 studies properly fulfilling inclusion and exclusion criteria were included. The total number of collected patients was 7,402 (mean age 65.42 years, 51.27% men). The weighted mean number of lymph nodes retrieved was 27.45 and the mean number of metastatic nodes was 1.34. Surgical complication and overall operative mortality rate were 5.5% and 0.5% respectively. Five-year overall survival (OS) and disease-free survival (DFS) rates were 84.3% and 82.8%. Available data from literature have several limitations mostly including non-homogeneous and incomplete reports together with no evidence from randomized control trial (RCT) studies. Therefore, to date, the quality of evidence is low and does not consistently support the superiority of CME over the standard right hemicolectomy, despite a reported trend to improved survival with comparable operative morbidity and mortality. More reliable data from large sample size RCTs are needed before CME can be recommended as the standard of care for right CC.

Keywords: Complete mesocolic excision; right colon cancer (right CC); central vascular ligation (CVL); embryological planes; lymphadenectomy

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Introduction

Colon cancer (CC) is the third most commonly diagnosed cancer across countries but the second in terms of mortality; its incidence is estimated of 1,096,601 number of new cases per year and 881,000 deaths are estimated to occur in 2018 (1). Right-sided cancers (RSCs) are most commonly defined as cancers arising proximal to the splenic flexure while left-sided cancers (LSCs) are located distal to the splenic flexure (2-4). This cut point is often used because most of the transverse colon arises embryologically from the midgut, and only the distal third of it arises from the hindgut. Vascular supply has also been proposed as a defining characteristic of embryologic origin, the superior and inferior mesenteric arteries supplying the midgut and hindgut, respectively. Epidemiological studies have demonstrated gender and age relationship with a higher incidence of RSC in women and elderly people (5,6). There are also differences in pathologic appearance (7-10), and in the molecular biological pattern (11,12). Therefore, it has been suggested to consider colorectal cancer as three distinct tumor entities: RSC, LSC and rectal cancer. There is differential prognosis by stage between patients with right- and left-sided CCs. In literature stage II RSC is reported with a slightly better prognosis as compared to LSC due to a higher prevalence of good-prognosis MSI-high tumors, while stage III RSC has a slightly worse prognosis (3,4,8). Moreover, analyses of prospective clinical trials of patients with stage III colorectal cancer who received adjuvant chemotherapy also demonstrated lower disease-free survival (DFS) in those with right-sided location (HR, 0.70; 95% CI, 0.61–0.81) (13). Patients with metastatic RSC have worse prognosis as compared to those with LSC as well (14).

Before 90's also rectal cancer had a poor prognosis because of high local recurrence rate. In 1988, Heald (15) introduced the concept of total mesorectal excision (TME) for rectal cancer which is based upon sharp dissection following embryological anatomical planes (16,17). TME provides a surgical specimen with an intact coverage, not only of the rectal tumor, but also of the main lymphatic drainage including the majority of regional lymph nodes, lymphatic vessels and surrounding fat tissue lying within mesorectum. Thereafter the development, standardization and widespread adoption of TME, surgery for rectal cancer has been reported with significant reduction of local recurrence rates and improvement of survival (15,18,19).

In 2009, Hohenberger (20) aimed at improving the outcome of patients with RSC by developing the same concept of TME also for RSC.

Therefore Hohenberger introduced the idea of complete mesocolic excision (CME) that is a new conception of right hemicolectomy for RSC based on three main issues: dissection of the embryological plane to remove a complete envelope containing the mesentery together with all the lymph nodes draining the tumor, a central vascular tie to remove the main lymph nodes in the central direction and resection of a sufficient length of bowel to remove the pericolic lymph nodes (20). The objectives of CME were to reduce local recurrence and to improve survival rates. The rationale behind this new concept of surgery for RSC was based on several points: the lymph node metastases of CC follow the supplying arteries; several studies have shown a survival benefit to higher lymph node yields after colonic resection (21); increasing negative lymph node count also correlates with survival in advanced colonic cancer (22,23) and finally, the ratio of lymph node metastases to the total number of harvested lymph nodes, known as the lymph node ratio (LNR), has been reported in several studies to be a better prognostic indicator than the number of involved lymph nodes, or pN status, alone (24).

In this last decade, many doubts and questions have been arised about safety and efficacy of CME together with its worldwide spread. Many authors have questioned whether a survival benefit from a greater lymph node yield truly exists considering that other factors are known to affect lymph node retrieval including patient age, immune status, tumor location, tumor characteristics and institutional factors (25,26).

Several studies have suggested that there isn't any or only a minimal survival benefit in lymph node yield greater than 12 compared to that less than 12, particularly in the presence of good quality surgery and lymph node examination and that it is difficult to define a threshold number for lymph node retrieval (27,28).

Furthermore, several non-CME studies have failed to show a relationship between high vascular tie, and therefore greater lymph node yield and higher number of lymph node metastases, and/or improved survival (29,30). Others argue that metastases in lymph nodes outside conventional ranges of dissection represent distant metastases, and the extended resection will not influence the survival as they are related to a poor oncological outcome (31).

The aim of this systematic review was to investigate the safety, quality and outcomes of CME in patients with RSC.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/ales-20-41).

Material and methods

Literature search and systematic review were done adhering to the Cochrane Collaboration guidance (32) to reduce the risk of bias and error. The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (33). Data collection, randomized controlled trials (RCTs) and non-randomized controlled studies (non-RCSs) concerning CME were searched for this review. No language restrictions were adopted during articles search. This study was registered with PROSPERO (187448).

Search strategy

A systematic search of PubMed, Embase and the Cochrane Library was conducted on 12 December 2019.

The Cochrane database was searched using a combination of the following terms with the Boolean AND/OR operators: "Colonic Neoplasms", "Colectomy", "Colon", "complete-mesocolic-excis", "CME", "central-vascular-ligat", "D3", "lymphadenect", "lymph-nod", "Lymph Node Excision", "right", "ileocol", "ileo-col".

For the PubMed and Embase database searches, these same keywords (and variants) were used as text words and Medical Subject Headings (MeSH terms), and were combined by using Boolean operators as follows: ("Colonic Neoplasms" OR "Colectomy" OR "Colon" OR colon*[tiab] OR colectom*[tiab]) AND (complete-mesocolic-excis*[tiab] OR CME[tiab] OR central-vascular-ligat*[tiab] OR (D3[tiab] AND (lymphadenect*[tiab] OR lymph-nod*[tiab] OR "Lymph Node Excision"))) AND (right*[tiab] OR ileocol*[tiab] OR ileo-col*[tiab]).

Outcomes of interest

- ❖ Safety of CME, including intra-operative and postoperative surgical complications and postoperative mortality;
- ❖ Quality of CME, including total number of lymph nodes retrieved, total number of metastatic lymph nodes; mean ileo-colic and middle colic main trunk vessels lengths; total area and integrity rate (%) of resected mesocolon; details of mesocolic resection;
- ❖ Survival Outcomes, including overall survival (OS) and DFS at 3 and 5 years.

Inclusion and exclusion criteria

Inclusion criteria were as follows

Only English articles were selected at the end. The inclusion criteria were the following:

- ❖ Studies including patients with pathologically verified CC;
- ❖ Studies with satisfactorily definition of CME technique, including a description of dissection in the embryologic mesocolic fascial planes and central vascular ligation (CVL) or D3 lymphadenectomy;
- ❖ Studies including at least one outcome of interest among their results.

Exclusion criteria were as follows

- ❖ Reviews and systematic reviews;
- ❖ Studies with abstract only, videos, oral communications, case reports and letters;
- ❖ Studies with less than 100 patients included;
- ❖ Studies from the same institution or overlapping patients (in these cases, we selected the study that included more patients or that was published later).

Studies selection

Our systematic review was conducted using Mendeley software. Five independent reviewers screened titles and abstracts identified by literature search. A total of 659 potentially suitable articles were initially identified. The first step was to merge the duplicates, resulting in 516 remnant studies. In the second step these studies were checked for the pertinence by reading the titles and analyzing their abstracts. All studies excluded at this second step were documented along with the reasons for exclusion (*Figure 1*). Any discrepancies among reviewers were solved through consensus.

Full papers of selected abstracts were assessed to confirm whether also the full papers totally met inclusion criteria.

Data extraction was performed by five reviewers (FE, GO, LMR, LS, FS) and checked by a sixth reviewer (RR). Selected papers were identified by publication year and by the surname of the first author.

Results

Literature searches and inclusion assessment

Figure 1 summarizes the process of identification and selection of papers for inclusion in this systematic review, following the PRISMA guidelines (33).

Literature searches of electronic databases identified 659 articles. After de-duplication, 516 titles/abstracts were screened by reviewers and 229 articles were excluded as having no pertinence to this systematic review. Titles/abstracts of 287 potentially relevant papers were included for further evaluation. One hundred thirty-two studies have been excluded because they were reviews, abstracts, videos, oral communications, case reports and letters. Finally, 105 papers were excluded because the number of included patients was less than 100. Of these, 29 further papers were left out after examining in detail the full paper; the reasons

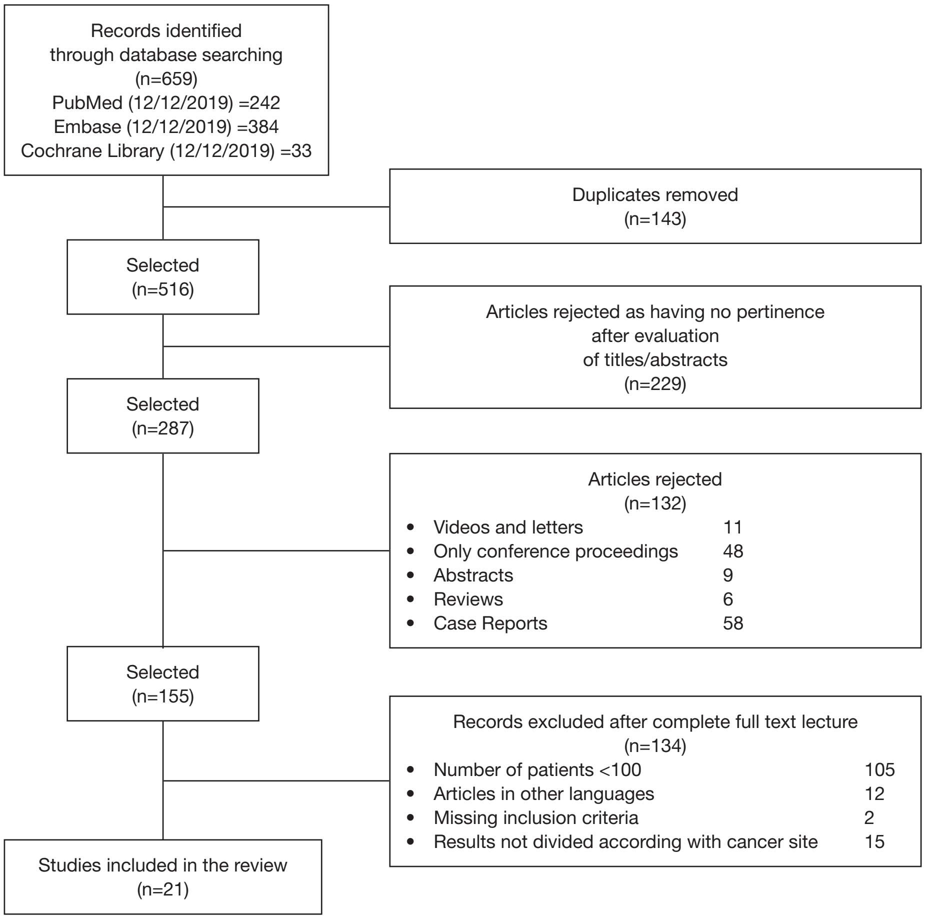

Figure 1 PRISMA flow diagram of the study selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

for rejection are detailed in *Figure 1*.

Overall, we identified 21 studies about CME properly fulfilling inclusion and exclusion criteria (34-53).

Study characteristics

Of the 21 included studies, seven were from Korea, five from Europe, five from China, one was from Japan, one from Taiwan, one from North America and one from India. Most of the included papers were retrospective cohort studies and only two of them were prospective studies. The total number of included patients was 7,402 (*Table 1*).

Baseline patient characteristics

The weighted mean age of included patients was 65.42 (range, 17–94) years; 51.27% (3,670 patients) of them were men (one study did not include patients' gender data) (42). The CME was performed by open technique in 45% of cases and with a minimally invasive approach in the remnant 55% of cases (robotics, laparoscopy and hand-assisted laparoscopy). The weighted mean operative time was 182.74 [35–664] minutes (min). The weighted mean length of stay was 9.86 [1–65] days. These baseline patient characteristics are reported in *Table 1*.

Pathologic outcomes

Pathologic data are summarized in *Table 2*. The weighted mean number of lymph nodes retrieved was 27.45 [1–88] and the mean number of metastatic nodes was 1.34 [0–48]. Only one study didn't report the total number of lymph nodes yielded (50) while the number of metastatic nodes retrieved was detailed in only five articles (40,43,44,49,54).

Table 1 Baseline demographic and operative characteristics of the included studies

Reference, year	Nation	Type of publication	Study period	N	Age (years), [range]	Gender, n male/n female (%)	Type of approach, n (%)	Operative time (min)	LOS (days)
Pramateftakis (50), 2010	Greece	Retrospective	1989–2008	115	65.6 [35–86]	65 (56.52)/ 50 (43.48)	Open 115 (100.00)	NR	NR
Kang (40), 2014	South Korea	Prospective	2009–2012	128	66 [30–86]	63 (49.22)/ 65 (50.78)	LS 128 (100.00)	192 [118–363]	5 [4–37]
Bae (37), 2014	Korea	Prospective	2006–2008	170	64.5 [29–94]	92 (54.12)/ 78 (45.88)	LS 85 (50.00); open 85 (50.00)	186.5 [41–664]	11 [6–65]
Liang (42), 2015	Taiwan	Retrospective	2003–2008	244	64.48 [36–88]	NR	LS 244 (100.00)	224 [168– 280]	11 [8–14]
Cho (54), 2015	Korea	Retrospective	2000–2009	773	61.5 [39–84]	421 (54.46)/ 352 (45.54)	MIS 205 (26.52); open 568 (73.48)	NR	13.51 [2–27]
Subbiah (38), 2016	India	Retrospective	2009–2013	212	61 [34–82]	163 (76.89)/ 49 (23.11)	LS 212 (100.00)	142	5
Huang (39), 2015	China	Retrospective	2006–2013	102	55.52 [39–71]	61 (59.80)/ 41 (40.20)	LS 53 (51.96); open 49 (48.04)	185.83 [75–308]	12.44 [2–26]
Takahashi (36), 2017	Japan	Retrospective	2008–2014	202	57.75 [49–92]	101 (50.00)/ 101 (50.00)	LS 202 (100.00)	160.46 [157– 234]	NR
Siani (51), 2017	Italy	Retrospective	2008–2015	600	72 [57–87]	333 (55.50)/ 267 (44.50)	LS 600 (100.00)	149 [91–207]	2.4 [1–6]
Kim (34), 2016	South Korea	Retrospective	2008–2013	215	67.92 [47–91]	109 (50.70)/ 106 (49.30)	LS 116 (53.95); open 99 (46.05)	175 [35–315]	13.30 [1–40]
Sheng (48), 2017	China	Retrospective	2012–2014	150	61.20 [39–82]	83 (55.33)/ 67 (44.67)	HAL-CME 78 (52.00); open 72 (48.00)	143.52 [100–196]	8,35 [5–13]
Kim (49), 2017	Korea	Retrospective	1995–2010	142	63.5 [41–86]	66 (46.48)/ 76 (53.52)	LS 142 (100.00)	309.0 [160–458]	11.2 [2–20]
Shin (43), 2018	South Korea	Retrospective	2000–2013	2,249	61 median	988 (43.93)/ 1,261 (56.07)	LS 1,010 (44.91); open 1,239 (55.09)	150 median	10.62
Wang (52), 2017	China	Retrospective	2010–2015	172	67 [43–91]	94 (54.75)/ 78 (45.35)	LS 172 (100.00)	113.5 [44.7–182.3]	8.7 [4.5–12.9]
Bertelsen (46), 2019	Denmark	Retrospective	2008–2013	256	73.5 median	116 (45.31)/ 140 (54.69)	LS 107 (41.80); open 149 (58.20)	NR	NR
Li (35), 2018	China	Retrospective	2012–2018	108	67,26 [55–77]	65 (60.18)/ 43(39.81)	LS 108 (100.00)	135.74 [100–210]	11.43 [8–29]
Spinoglio (45), 2019	Italy	Retrospective	2005–2013	202	71.2 [36–95]	104 (51.49)/ 98 (48.51)	Robotic 101 (50.00); LS 101 (50.00)	257.5 [95–540]	7.9 [4–37]

Table 1 (*continued*)

Table 1 (*continued*)

Reference, year	Nation	Type of publication	Study period	N	Age (years), [range]	Gender, n male/n female (%)	Type of approach, n (%)	Operative time (min)	LOS (days)
Pelz (41), 2018	Germany	Retrospective	2009–2016	279	70.6 [17–93]	149 (53.40)/130 (46.59)	LS 24 (8.60); open 255 (91.40)	152 [61–443]	15.5 [2–83]
Lee (47), 2019	Korea	Retrospective	2005–2012	835	63 [56–71]	461 (55.21)/374 (44.79)	NR	207 [171–254]	9 [7–12]
Sammour (44), 2020	Texas, USA	Retrospective	2009–2016	141	64 [38–90]	74 (52.48)/67 (47.52)	LS 122 (86.52); robotic 19 (13.48)	186 median	3 median
Ouyang (53), 2019	China	Retrospective	2011–2013	107	57.6 [39–76]	62 (57.94)/45 (42.06)	LS 107 (100.00)	192.4 [130–255]	7.2 [1–13]
Overall				7402	64.76 [17–94]*	3,670 (51.27)/3,488 (48.73)	Open 2,860 (44.95); LS 3,323 (52.23); HAL-CME 78 (1.23); robot 101 (1.59)	182.74 [35–664]*	9.86 [1–65]*

*, All results are calculated as weighted arithmetic mean, all median values are excluded. LOS, length of stay; MIS, minimally invasive (robotic or laparoscopic); LS, laparoscopic; HAL-CME, hand assisted laparoscopic complete mesocolic excision; NR, not recorded.

Subbiah (38) and Shin (43) were the only authors to report the rate of integrity of the mesocolic plane, which was high in both studies, 94% and 81% respectively. No one referred to Benz's classification (55) to check the quality and completeness of dissection. Only Ouyang's study (53) described the mean ileocolic vessel length, which was 12.6 (range, 10–15) cm. Nobody analyzed the length of middle colic trunk. Most of the analyzed patients (41.6%) had a TNM Stage II disease while 17% of them had a stage I, 39.7% a stage III and only the 1% of patients had a stage IV cancer.

Perioperative morbidity and mortality

Eighteen papers reported perioperative morbidity and mortality details (*Table 3*).

Spinoglio *et al.* (45) described a case of major vessels injury, while no one described intraoperative visceral injuries. Overall surgical complications rate was 5.5% and anastomotic leakage occurred in 1% of patients. The weighted mean operative blood loss was 65.14 [0–371] mL.

Overall operative mortality rate for included studies was 0.5% and no one described intraoperative deaths.

Pelz (41) reported the higher reoperation rate (18.6%) among included studies, compared with a reintervention rate close to 1% of the others.

Survival outcomes

Ten studies detailed the adoption of adjuvant treatment. In total, 65% of patients in these studies underwent postoperative chemotherapy (34,37,44,46-51,54) (*Table 4*).

Five-year local recurrence and distant metastasis rates were 3% and 12.3% respectively.

Most of the included papers reported 5-year DFS and OS survival rates and their weighted means were 82.8% and 84.3% respectively (35,37,43,45,47,49-51,54), whereas only four studies mentioned 3-year OS outcome (weighted mean 89.6%) (34,43,52,53) and only three studies detailed 3-year DFS (weighted mean 82.4%) (34,52,53).

Discussion

Some Authors would like to introduce CME as the standard of care for RSC based on the supposed evidence of its better oncologic outcomes provided with same operative morbidity and mortality as compared to the classic right hemicolectomy (20,24,56,57). CME is claimed as the

Table 2 Pathological and oncological outcomes of the included studies

Reference, year	N of lymph nodes, [range]	N of metastatic nodes, [range]	Ileocolic vessel length (cm), [range]	Middle colic trunk length (cm)	Pathologycal stage pTNM, n [%]	Mesocolic area (cm^2)	Grade of integrity of mesocolic layer, n [%]	Benz score
Pramateftakis (50), 2010	NR	NR	NR	NR	NR	NR	NR	NR
Kang (40), 2014	28 [3–88]	0 [0–48]	NR	NR	NR	NR	NR	NR
Bae (37), 2014	27.5 [8–79]	NR	NR	NR	Stage I 15 [9], stage II 81 [48], stage III 74 [43]	NR	NR	NR
Liang (42), 2015	34.4 [18–51]	NR	NR	NR	Stage I 4 [2], stage II 38 [16], stage III 202 [83]	NR	NR	NR
Cho (54), 2015	33.7 [1–78]	1.57 [0–9]	NR	NR	Stage I 100 [13], stage II 372 [48], stage III 301 [39]	NR	NR	NR
Subbiah (38), 2016	24 median	NR	NR	NR	Stage I 33 [16], stage II 96 [45], \stage III 83 [39]	NR	M plane 199 [94]; I plane 11 [6]; MP 2 [1]	NR
Huang (39), 2015	13.5 [2–26]	NR	NR	NR	Stage I 11 [11], stage II 54 [53], stage III 37 [36]	NR	NR	NR
Takahashi (36), 2017	23.47 [1–55]	NR	NR	NR	p T1 64 [32], pT2 27 [13], pT3 98 [49], pT4 13 [6]; pN0 132 [65], pN1 43 [21], pN2 20 [10], pN3 7 [4]	NR	NR	NR
Siani (51), 2017	27 [21–33]	NR	NR	NR	Stage I 153 [26], stage II 231 [39], stage III 216 [36]	NR	M plane 486 [81]; I plane 96 [16]; MP 18 [3]	NR
Kim (34), 2016	28.84 [5–55]	1.46 [0–10]	NR	NR	Stage I 34 [17], stage II 88 [50], stage III 93 [43]	NR	NR	NR
Sheng (48), 2017	19.54 [14–25]	NR	NR	NR	Stage I 20 [14], stage II 65 [43], stage III 65 [43]	NR	NR	NR
Kim (49), 2017	21.9 [1–48]	NR	NR	NR	Stage I 21 [15], stage II 73 [51], stage III 48 [34]	NR	NR	NR
Shin (43), 2018	27.3 [2–52]	1.32 [0–7]	NR	NR	Stage I 416 [18], stage II 973 [43], stage III 860 [38]	NR	NR	NR
Wang (52), 2017	23.3 [5–42]	NR	NR	NR	Stage I 10 [6], stage II 57 [33], stage III 105 [61]	NR	NR	NR
Bertelsen (46), 2019	38 [28–48]	NR	NR	NR	pT1 11 [4], pT2 27 [11], pT3 166 [65], pT4 52 [20]; pN0 165 [64], pN1 47 [18], pN2 44 [17]	NR	NR	NR
Li (35), 2018	18.45 [12–42]	NR	NR	NR	Stage I 9 [8], stage II 42 [39], stage III 57 [53]	NR	NR	NR
Spinoglio (45), 2019	29.3 [12–74]	NR	NR	NR	Stage I 47 [24], stage II 66 [33], stage III 70 [35], stage IV 17 [9]	NR	NR	NR

Table 2 (*continued*)

Table 2 *(continued)*

Reference, year	N of lymph nodes, [range]	N of metastatic nodes, [range]	Ileocolic vessel length (cm), [range]	Middle colic trunk length (cm)	Pathologycal stage pTNM, n [%]	Mesocolic area (cm^2)	Grade of integrity of mesocolic layer, n [%]	Benz score
Pelz (41), 2018	31.8 [10–73]	NR	NR	NR	Stage 0 44 [16], stage I 47 [17], stage II 77 [28], stage III 70 [25], stage IV 41 [15]	NR	NR	NR
Lee (47), 2019	27 [19–37]	NR	NR	NR	Stage I 174 [21], stage II 365 [44], stage III 295 [35]	NR	NR	NR
Sammour (44), 2020	31 median	NR	NR	NR	Stage I 35 [25], stage II 49 [35], stage III 48 [34], stage IV 9 [6],	NR	NR	NR
Ouyang (53), 2019	23.2 [10–37]	NR	12.6 [10–15]	NR	Stage I 15 [14], stage II 59 [55], stage III 33 [31]	NR	NR	NR
Overall	27.45 [1–88]*	1.34 [0–48]*	12.6 [10–15]*	NR	Stage 0 44 [1] stage I 1,144 [17], stage II 2,786 [42], stage III 2,657 [40], stage IV 67 [1]	NR	M plane 685 [84]; I plane 107 [13]; MP 20 [3]	NR

*, All results are calculated as weighted arithmetic mean, all median values are excluded. M plane, mesocolic plane; I plane, intramesocolic plane; MP, muscolaris propria; NR, not recorded.

adequate treatment for RSC because of the extensive lymph-node dissection which may include remote nodal basins and those along major first-order vessels such as the superior mesenteric artery.

Many studies showed that survival of CC is strictly related to the number of lymph nodes removed, despite the stage of the disease, patient demographics and tumor characteristics (21,58-60). Chen *et al.* reported that removing at least 15 lymph nodes increased median OS by 11 months in patients with stage I, 54 months in stage II and 21 months in stage III cancer. He stated that surgeons must remove at least 15 nodes in every dissection for CCs and concluded "*I would advise surgeons to remember that the number of nodes makes a difference*" (21). Prandi *et al.* showed a direct relationship between the number of lymph node yielded and survival which is even strongly significant in stage B (pN0) patients (58). Swanson *et al.* demonstrated that the prognosis of T3N0 CC is dependent on the number of lymph nodes examined (59). Finally, Le Voyer *et al.* stated that the number of lymph nodes analyzed for staging CCs is, itself, a prognostic variable of outcome, even in lymph node negative disease (60). This significant improvement of survival is related to many reasons; one of these is stage migration, especially in earlier stages (I and II). In the present review the overall weighted-mean number of lymph nodes yielded was high (28,57). This result demonstrates that CME enables surgeons to remove more nodes even than those suggested by Chen (21), providing a better staging and increasing the survival of the disease.

The concept of surgical dissection along embryologic fascial planes allowing the excision of an intact mesocolon containing its regional lymph nodes is another key point of CME. The surgery along embryological fascial planes enables to reduce the hazard of cancer spillage inside the abdominal cavity. West *et al.* (57) showed better survival outcomes in patients with preserved integrity of mesocolic plane of dissection especially for stage III disease. In this review only Subbiah (38) and Shin (43) analyzed the integrity of mesocolic plane in their studies, and no one referred to Benz classification to objectively define the quality of dissection. As one of the main items of CME is the dissection following embryological planes, this lack represents a major limit of the studies included in the present review. Moreover, the absence of an objective procedure to check the quality of surgery makes impossible to assess the real extension of the operations performed in each study and how much the procedures described in the

Table 3 Perioperative morbidity and mortality of included studies

Reference, year	Intraoperative major vascular injuries, n (%)	Intraoperative visceral injuries, n (%)	Anastomotic leak, n (%)	Reoperation, n (%)	Perioperative blood loss volume (mL), [range]	Other surgical complication, n (%)	Nonsurgical complications, n (%)	Intraoperative mortality, n (%)	30-days mortality, n (%)
Pramateftakis (50), 2010	NR	NR	1 (0.9)	NR	NR	Wound dehiscence 8 (6.9); enterocutaneus fistula 1 (0.9); abdominal bleeding 1 (0.9)	mesenteric vein Thrombosis 1 (0.9); deep venous thrombosis 1 (0.9); cerebral vascular accident 1 (0.9); atrial fibrillation 1 (0.9)	0	NR
Kang (40), 2014	NR	NR	NR	NR	NR	Wound infection 1 (0.7)	Ileus 1 (0.7); urinary retention 4 (3.1)	0	NR
Bae (37), 2014	NR	NR	1 (0.58)	NR	41.95 [0–304]	Wound infection 7 (4.1); abdominal bleeding 1 (0.6); abdominal abscess 1 (0.6); chylous leakage 15 (8.8)	Ileus 5 (2.9); pulmonary complication 1 (0.6); urinary tract infection 1 (0.6)	NR	1 (0.58)
Liang (42), 2015	NR	NR	4 (1.6)	NR	104.5 [58–150]	Wound infection 10 (4.0)	Urinary tract infection 8 (3.0); pneumonia 2 (0.8); ileus 4 (1.6); duodenal paralysis 7 (2.9); myocardial infarction 1 (0.4); cerebrovascular accident 1 (0.4); pulmonary embolism 1 (0.4); deep vein thrombosis 1 (0.4)	NR	NR
Cho (54), 2015	NR	NR	5 (0.6)	NR	NR	Wound infection 9 (1.2); abdominal bleeding 1 (0.1); bowel necrosis 1 (0.1)	Pulmonary disease 6 (0.8); ileus 9 (1.2); cerebrovascular infarction 1 (0.1); ARDS 1 (0.1)	0	2 (0.2)
Subbiah (38), 2016	NR	NR	1 (0.5)	NR	NR	Wound infection 4 (2.0); abdominal abscess 1 (0.5)	Ileus 11 (5.0); urinary complication 2 (1.0); respiratory complication 7 (3.0); cardiac complication 1(0.5)	NR	NR
Huang (39), 2015	NR	NR	NR	NR	105.53 [0–350]	Wound infection 4 (4.0); anastomotic bleeding 1 (1.0)	Pneumonia 3 (3.0)	NR	NR
Takahashi (36), 2017	NR	NR	1 (0.5)	NR	43 [20– 100]	Wound infection 10 (5.0); abdominal bleeding 1 (0.5); abdominal abscess 1 (0.5)	Ileus 4 (2.0); Thrombosis 1 (0.5); urinary complication 1 (0.5); cardiovascular complication 1 (0.5); pneumonia 1 (0.5)	NR	0
Siani (51), 2017	NR	NR	15 (2.5)	NR	53 [0–123]	Wound infection 63 (10.6)	Pneumonia 59 (5.8); pleural effusion 38 (4.7); urinary tract infection 36 (6.0); ileus 9 (1.5); deep venous thrombosis 3 (0.5)	NR	NR
Kim (34), 2016	NR	NR	2 (0.9)	NR	75 [0–371]	Wound infection 25 (11.6); abdominal bleeding 3 (1.4); abdominal abscess 4 (1.9); chylous leakage 8 (3.7)	Respiratory complication 11 (5.1); urinary complication 3 (1.4); ileus 13 (6.0)	NR	4 (2)
Sheng (48), 2017	NR	NR	0	NR	0	Wound infection 6 (4.0); chylous leakage 2 (1.3)	Ileus 4 (3.0); respiratory complication 1 (0.6); gastroplegia 3 (2.0)	NR	NR
Kim (49), 2017	NR	NR	NR	NR	NR	NR	NR	NR	NR
Shin (43), 2018	NR	NR	18 (0.8)	NR	NR	Wound infection 61 (3.0)	Ileus 81 (4.0)	NR	1 (0.04)
Wang (52), 2017	0	0	1 (0.6)	2 (1.1)	74.2 [18–130]	Wound infection 3 (1.74); chylous leakage 22 (12.8); anastomotic bleeding 1 (0.58)	Pneumonia 1 (0.6)	0	0
Bertelsen (46), 2019	NR	NR	NR	NR	NR	NR	NR	NR	13 (5)
Li (35), 2018	NR	NR	3 (2.8)	NR	97 [50–300]	Wound infection 3 (2.8); chylous leakage 4 (3.7); abdominal abscess 3 (2.8)	Ileus 1 (0.9); gastroplegia 2 (1.8)	0	0
Spinoglio (45), 2019	1 (0.5)	NR	2 (1.0)	4 (2.0)	NR	Wound infection 15 (7.4); abdominal bleeding 8 (4.0)	Ileus 21 (10.4); pneumonia 4 (2.0); acute respiratory failure 3 (1.5); arrhythmia 3 (1.5); acute myocardial Infarction 1 (0.5); stroke 1 (0.5); urinary complication 4 (2.0)	NR	1 (0.5)
Pelz (41), 2018	NR	NR	NR	52 (18.6)	NR	NR	NR	NR	4 (1.4)
Lee (47), 2019	NR	NR	NR	NR	NR	NR	NR	NR	1 (0.1)
Sammour (44), 2020	0	0	2 (1.4)	1 (0.7)	50 median	NR	NR	0	0
Ouyang (53), 2019	NR	NR	1 (0.9)	1 (0.9)	108.4 [61–156]	Wound infection 3 (2.8); fat liquefaction wound 2 (1.9)	Ileus 5 (4.7); pulmonary infection 1 (0.9); urinary tract infection 1 (0.9)	0	0
Overall	1 (0.2)	0	57 (1.0)	60 (7.0)	65.14 [0–371]*	314 (5.5)	399 (6.9)	0	27 (0.5)

*, All results are calculated as weighted arithmetic mean, all median values are excluded. NR, not recorded.

Table 4 Recurrence, disease-free and OS rates

Reference	Adjuvant therapy, n (%)	5-year local recurrence, n (%)	5-year distant metastasis, n (%)	3-year OS, %	3-year DFS, %	5-year OS, %	5-year DFS, %
Pramateftakis (50), 2010	48 (41.7)	NR	NR	NR	NR	72.4	NR
Kang (40), 2014	NR	NR	7 (5.5)	NR	NR	NR	NR
Bae (37), 2014	133 (78.2)	7 (4.1)	20 (11.8)	NR	NR	84	78
Liang (42), 2015	NR	NR	NR	NR	NR	NR	66.8
Cho (54), 2015	615 (79.6)	34 (4.4)	114 (14.7)	NR	NR	84	82.8
Subbiah (38), 2016	NR	NR	NR	NR	NR	NR	NR
Huang (39), 2015	NR	NR	NR	NR	NR	NR	NR
Takahashi (36), 2017	NR	NR	NR	NR	NR	NR	NR
Siani (51), 2017	425 (70.8)	NR	NR	NR	NR	83.0	78.3
Kim (34), 2016	144 (71.3)	NR	NR	87.4	78.6	NR	NR
Sheng (48), 2017	127 (84.7)	NR	NR	NR	NR	NR	NR
Kim (49), 2017	99 (79.2)	6 (4.2)	NR	NR	NR	82.6	83.5
Shin (43), 2018	NR	47 (2.0)	270 (12.0)	89.7	NR	NR	86
Wang (52), 2017	NR	3 (1.7)	14 (8.1)	89.1	81.7	NR	NR
Bertelsen (46), 2019	78 (30.4)	25 (10.0)	NR	NR	NR	NR	NR
Li (35), 2018	NR	3 (3.0)	16 (14.8)	NR	NR	73.0	57.4
Spinoglio (45), 2019	NR	NR	NR	NR	NR	75.0	84.2
Pelz (41), 2018	NR	NR	NR	NR	NR	NR	NR
Lee (47), 2019	491 (58.8)	NR	NR	NR	NR	91.1	85.6
Sammour (44), 2020	56 (39.7)	0	26 (18.4)	NR	NR	NR	NR
Ouyang (53), 2019	NR	3 (2.8)	6 (5.6)	93.5	91.6	NR	NR
Overall	2,216 (65.0)	128 (3.0)	473 (12.3)	89.6	82.4	84.3	82.8

OS, overall survival; DFS, disease-free survival; NR, not recorded.

different studies are homogeneous.

Recently Perrakis (61), claimed that CME can be implemented in surgical departments after previous adequate teaching without increasing postoperative complications and mortality. Despite a negative report by Pelz *et al.* (41), describing a high reoperation rate (18.6%), the overall postoperative outcomes of the present review showed acceptable findings: reoperation rate was 7%, surgical complications were 5.5%, intraoperative mortality was 0% and 30-day postoperative mortality was 0.5%. These results are consistent with those observed after standard nonCME right hemicolectomy (62,63). Anastomotic leak occurred in 1% of cases; showing the same incidence observed after standard right colectomy (64,65). Nevertheless, this is a really demanding procedure, requiring proved skill in advanced minimally invasive procedures.

Recently, a large retrospective study investigated postoperative and oncological outcomes of 3,518 patients submitted to right colectomy for RSC with different approaches (open, laparoscopic and robotic). The operative times were significantly different among the subgroups: 135.9±89.2 min for open surgery, 142.5±63.3 min for laparoscopy and 187.2±81.4 min for robotic procedures while the length of stay was significantly shorter after minimally-invasive approach (5.2±4.7 and 4.4±2.4 days after laparoscopic and robotic surgery respectively) compared to open surgery (7.9±7.7 days) (62). In the present review the resections were mostly performed with minimally invasive approach (55%); the weighted mean operative time and length of stay (LOS) were 182.74 min and 9.86 days respectively.

In a study of over 83,000 CC survivors based on the Surveillance Epidemiology End Results (SEER) database, the 5-year cause-specific survival was ≥80% for all stages together except from stage IV (48%) (66). In 2018, Qiu (67) detailed cancer-specific survival differences between RSCs and LSCs using SEER database, documenting a 5-year cause-specific survival of 68.1% after standard colectomy for RCS (92,8% in stage I, 85.5% in stage II, 64.9% in stage III and 11.2% in stage IV disease). Narayanan *et al.* recently published a large retrospective study of the National Cancer Database investigating the data from 379785 patients to assess the OS. The Authors found a 3- and 5-year OS of 61% and 51% (68). A recent analysis of 3,622 patients with CC derived from two French digestive cancer registries reported that 1.6% of patients with RSC developed a local recurrence 5 to 10 years after resection (69).

In the present study 3- and 5-year OS was 89.6% and 82.8%; Therefore, it was higher compared with survival results of standard right colectomies reported in recent literature.

This study has several limitations. First, all of the included studies were case series of a prospective or retrospective nature and there was no Level 1 evidence from a RCT. Second, these studies are not homogeneous as concerns the outcomes of interest of this review detailed in materials and methods section; most of them have important missing outcomes; none of them has investigated all of these items and furthermore, the majority of these studies considered only few outcomes of those requested. The last point is that the majority of included patients had early-stage diseases (58.6% stage I–II). This limitation represents a confounding factor for the final analysis of survival outcomes.

In conclusion, despite these limitations, data from extensive literature search document that CME with CVL for RCS is a promising procedure which can provide better oncological and survival outcomes without increasing postoperative morbidity and mortality as compared to standard right colectomy. However, to date, the quality of evidence is limited and does not consistently support the superiority of CME. More reliable data from large sample size RCTs are needed before CME can be recommended as the standard of care for right CC resections.

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Footnote

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