Review Article

Complete mesocolic excision for right colon cancer

Serkan Zenger[1], Emre Balik[2], Dursun Bugra[1,2]

[1]Department of General Surgery, VKF American Hospital, Istanbul, Turkey; [2]Department of General Surgery, School of Medicine, Koc University, Istanbul, Turkey

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Correspondence to: Dursun Bugra. Department of General Surgery, VKF American Hospital, Guzelbahce ST, No:20, Tesvikiye, Sisli/Istanbul 34365, Turkey. Email: dursunb@amerikanhastanesi.org.

Abstract: Total mesorectal excision (TME) improves local recurrence rates and so it is accepted as the gold standard surgical method for locally advanced rectal cancer surgery. Based on these experiences, the concept of embryonic plane dissection was translated to surgery of colon cancer as complete mesocolic excision (CME) and central vascular ligation (CVL). CME aims to remove the specimen with an intact peritoneal tissue according to embryonic planes and to ligate the vessels as close as possible to their separation point from the superior mesenteric vessels. With CME technique, more lymph nodes are harvested and better quality specimen is obtained. This procedure is feasible in both open and minimal invasive surgery, however, technical difficulties should not be overlooked. It is very important to learn correctly the anatomy and the embryology of right colon for successful resection. Many studies on this issue have significant limitations, being generally retrospective and non-homogeneous. There is no consensus on the routine implementation of CME due to the lack of prospective randomized controlled trials.

Keywords: Anatomy; complete mesocolic excision (CME); embryology; right colon cancer; surgical technique

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Introduction

Data of the World Health Organization (GLOBOCAN database) showed that colorectal cancers are the second most common cancers in females and the third in males, with 1.8 million new cases and almost 861,000 deaths in 2018 (1). In the United States, annually, approximately 145,600 new cases of large bowel cancer are diagnosed, of which 101,420 are colon (2). In the 1980s, the idea of total mesorectal excision (TME) was presented by Heald *et al.* (3). Basis of TME was the embryological evolution of the rectum, dissection with embryological planes of dorsal mesentery yields a scatheless specimen which includes all vascular and lymphatic pathways and lymph nodes. This dissection provides more chance for clean circumferential margin (4). TME changed the rectal cancer surgery basics and also affected outcomes. Local recurrence rates decreased from 30–40% to 5–15% by TME revolution (5).

Hohenberger *et al.* (6) applied TME philosophy for the surgery of colon cancer. Their study showed that visceral and parietal peritoneum were covered the colon, like a sheath and this was similar with mesorectum anatomy by the way they put forward the idea of complete mesocolic excision (CME). Survival rates increased from 82.1% to 89.1% and local recurrence rates decreased from 6.5% to 3.5%.

With the description of CME, it is stated that more standardized resection can be achieved in colon cancer surgery. CME dissection aims to ligate the vessels at their origin [central vascular ligation (CVL)] and to provide a better pathologic specimen quality which includes all lympho-vascular pathways, and nodal components, with respect to the embryological anatomy (7). CME resection specimen should contain an intact surface with all possible

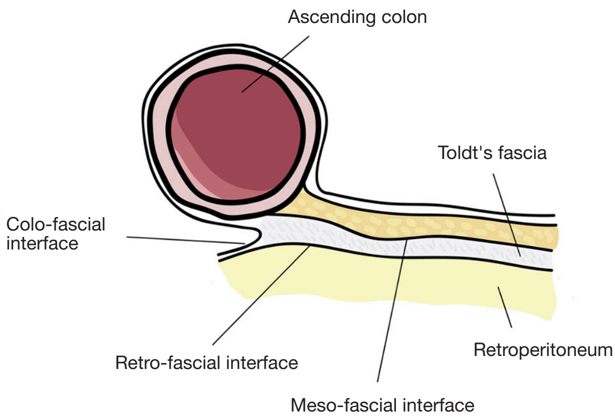

Figure 1 The relationships between the mesocolon, Toldt's fascia and the retroperitoneum [reproduced from the article Siani *et al*. (24)].

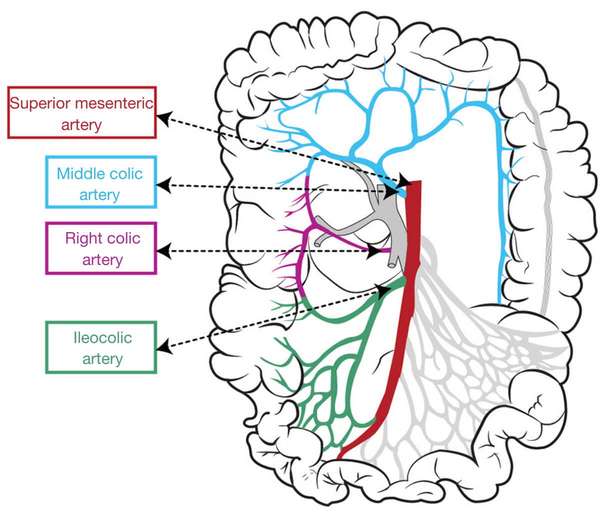

Figure 2 Major colonic arteries of the right-side colon.

tumor spreading routes (8).

Several authors have also reported that survival and local recurrence rates are better with CME (9-13). However, almost all of these studies are retrospective cohort series and many of these have no comparison group (14-17). The most important thing is; any randomized controlled trial for CME has not been published yet.

Embryology and anatomy of the mesocolon

It is necessary to understand the anatomical properties of mesocolon for describing CME. The adult residue of distal mid-gut's and proximal hindgut's primitive dorsal mesenteric tissue generates the mesocolon (18). At the end of the 4^{th} embryologic week, mid-gut's rotation [counterclockwise 270° and along the axis of the superior mesenteric artery (SMA)] determines the dorsal mesentery and the mesocolon (19-21).

Carl Toldt (22) showed that there is an extra fascial plane between the mesocolon and retroperitoneum and called it as "Toldt's Fascia". Culligan *et al.* (23) describe the mesocolic anatomy in detail. They defined three points: (I) Mesocolon starts at ileocecal level and continues up to rectosigmoid level; (II) Mesocolon of the transvers colon and the mobile part of sigmoid mesocolon does not include "Toldt's Fascia". Rest of the mesocolon (ascending, descending, non-mobile part sigmoid colon's) are apposed to the retroperitoneum and "Toldt's Fascia" is defined in these places; (III) confluence of sigmoid mesocolon and mesorectum is the inception of proximal rectum. Three surgical interfaces between two contiguous structures were described by Heald (3): (I) "Colo-fascial interface" (confluence of colonic surface and "Toldt's Fascia"); (II) "Meso-fascial interface" (confluence of mesocolon and "Toldt's Fascia"); (III) "Retro-fascial interface" (confluence of retroperitoneum and "Toldt's Fascia") (24) (*Figure 1*).

Immunohistochemical analysis showed that the lymphatic channels within the mesocolon are densely present in both submesothelial connective tissue and interlobular septations (7,25). In the light of these results, any degradation in the mesocolic surface disrupts lympho-vascular and neuro-perineural networks and may cause tumoral tissue to be spilled into the surgical dissection field (7).

Vascular anatomy of the right colon

Vascular anatomy should previously be learned in details to perform CME for right colon cancers within the proper anatomical planes. SMA has 2 or 3 major branches that provide the arterial blood supply of right colon (*Figure 2*). The most important one of these branches is "ileocolic artery" (ICA). Presence of "right colic artery" (RCA)—which originates from SMA—differs from 0% to 63% at cadaveric reports (26); it can be originated from ICA or "middle colic artery" (MCA) (27). MCA divides into right and left branches but it has many anatomical variations; can be absent (up to 25%), doubled or accessory MCA (28).

Two main arteries—ICA and RCA—are ligated during CME so topography of these two arteries towards SMA should be known. Both these arteries have important

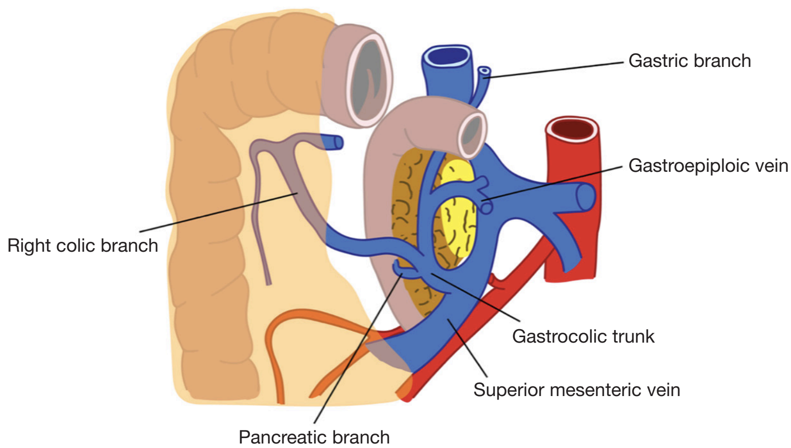

Figure 3 The configuration of gastrocolic trunk of Henle.

neighborliness with "superior mesenteric vein" (SMV). In 63–100% of the cases RCA runs anterior to the SMV, and ICA crosses anteriorly in 17–83% of cases (26,27,29).

Also venous anatomy of the right colon and variations of the venous anatomy should be known to avoid vascular complications during CME. Venous blood flow of cecum, ascending colon, and the right side of transverse colon drain into SMV. Topographical anatomy of right colic vein (RCV), superior RCV, gastrocolic trunk and middle colic vein (MCV) has too many variations (28,29). The confluence of right gastroepiploic vein, superior RCV and anterior superior pancreaticoduodenal vein which is known as "gastrocolic trunk of Henle" present in 46–70% cases (27,30) (*Figure 3*). Study of Yamaguchi *et al.* (31) showed that MCV has two variations. It can join directly with the SMV (in 84.5% of the cases) or with the gastrocolic trunk (in 12.1% of the cases). Also RCV has two variations, it can join directly with the SMV (in 56% of the cases) or with the gastrocolic trunk (in 44% of the cases).

Preoperative preparation and technique of CME

Preoperative preparation

In this part we will describe our daily practice. In our clinic, mechanical bowel preparation and/or oral antibiotics are not being used before right colon surgery. We give a glycerin enema once or twice before surgery. As antibiotic prophylaxis, we prefer one gram of first-generation cephalosporin and 500 mg of metronidazole as single dose half-an-hour before surgery. In case of necessary situations we prolong antibiotic use for 24–48 hours postoperatively. If there is no contraindication, we start low molecular weight heparin the day before surgery for venous thrombosis prophylaxis.

Surgical technique of open CME

A "lateral-to-medial" approach is usually preferred in open CME technique. The dissection starts with the lateral peritoneal fold, and then continues in the mesofascial plane towards medially (27,32). Mesocolon of the right colon is mobilized towards the root of superior mesenteric vessels. Ascending colon, caecum and mesocolon are separated from retroperitoneum with sharp dissection towards the upper border of the duodenum and pancreatic uncinate process (27,33) (*Figure 4*). Duodenal Kocherization in the original description of Hohenberger *et al.* (6) is not routinely performed (33). The autonomic nervous plexus which is situated close to SMA should be preserved during mobilization. When mesocolon and right colon is fully mobilized, vascular ligations begin from ICA. Both structures (ileocolic and right colic vessels) are ligated from their origin at SMA and SMV (*Figure 5*). The dissection is performed through superior mesenteric vessels and all associated fatty tissue and lymph nodes are harvested (33).

MCA's right branch is ligated for cecum and ascendant colon cancers, and transvers colon is prepared for transection at the level of middle colic vessels (6). Also surgical approach is slightly different for hepatic flexure and proximal transverse colon cancers. Primarily right gastroepiploic artery—that runs with a vertical plan to transverse colon—is transected to enter the lesser sac. The

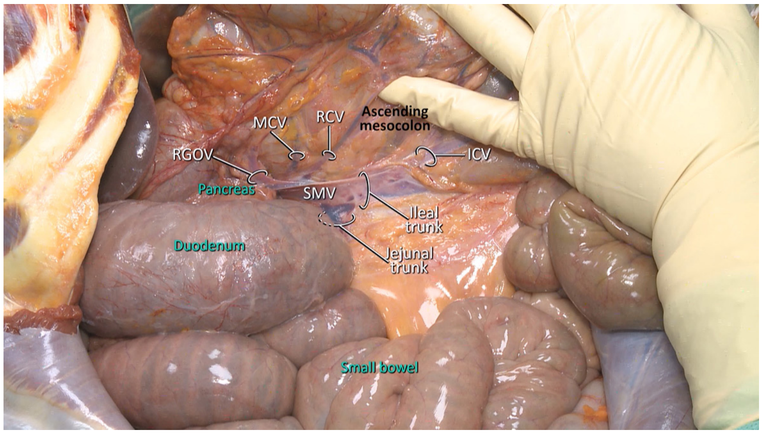

Figure 4 Cecum, ascending colon and mesocolon are separated from the retroperitoneum, and the vessels are revealed after the sharp dissection. ICV, ileocecal vein; SMV, superior mesenteric vein; RGOV, right gastro-omental vein; RCV, right colic vein; MCV, middle colic vein (by courtesy of M. Ayhan Kuzu).

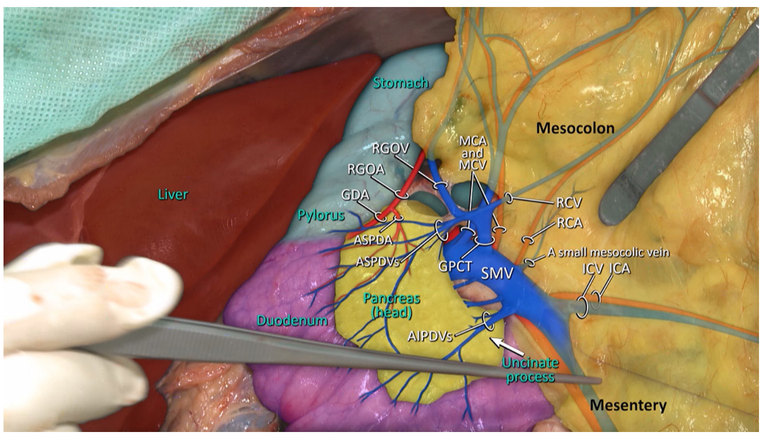

Figure 5 The vessels of the right colon are ligated at their origin from the superior mesenteric vessels. ICV, ileocecal vein; ICA, ileocecal artery; RCV, right colic vein; RCA, right colic artery; SMV, superior mesenteric vein; RGOV, right gastro-omental vein; RGOA, right gastro-omental artery; RCV, right colic vein; MCV, middle colic vein; MCA, middle colic artery; GDA, gastroduodenal artery; ASPDA, anterior superior pancreaticoduodenal artery; ASPDV, anterior superior pancreaticoduodenal vein; AİPDV, anterior inferior pancreaticoduodenal vein (by courtesy of M. Ayhan Kuzu).

MCA and MCV both are ligated at closest point of their origin (SMA and Henle's trunk respectively) (6,33,34). If there are suspected lymph nodes around the head of the pancreas, these lymph nodes are removed by ligating from the root of the right gastroepiploic artery, also—if possible—superior pancreaticoduodenal artery should be preserved during dissection (6,27) (*Figure 6*). After the transection of distal ileum and transvers colon, the resection is completed and the anastomosis is performed by hand-sewn sutures or linear staplers.

Surgical technique of laparoscopic CME

At first, a 10 mm camera port is placed to umbilicus. We start with 5 mm left upper quadrant trocar, we change it to 12 mm if we decide to do intracorporeal anastomosis. 5 mm port is placed to right lower quadrant and another 5 mm port is placed to left lower quadrant (*Figure 7*). Operation is generally done under 20° left tilted slight "Trendelenburg position".

Opposite to open CME, 'medial-to-lateral' approach

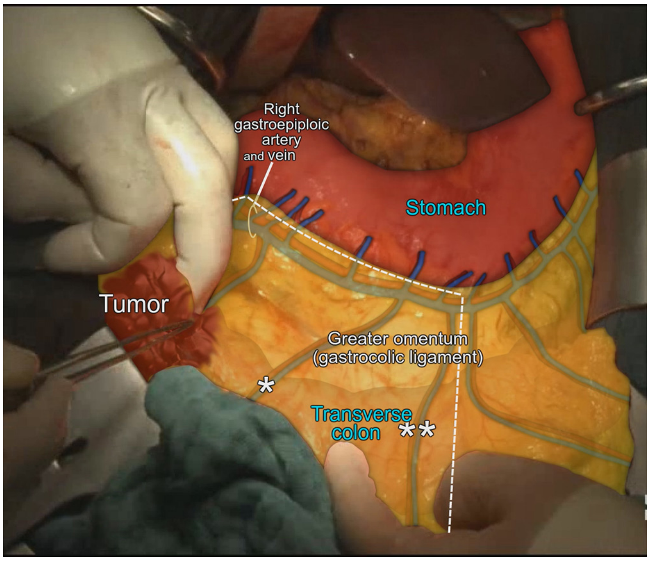

Figure 6 Central ligation of the right gastroepiploic artery (by courtesy of M. Ayhan Kuzu).

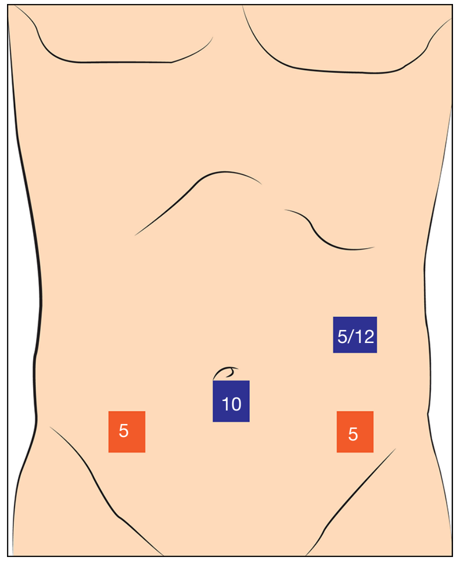

Figure 7 In our daily practice, port placement for laparoscopic CME in right colon cancer. CME, complete mesocolic excision.

is recommended in laparoscopic technique. In very rare special situations, 'lateral-to-medial' approach may also be performed. The dissection begins throughout the superior mesenteric axis close to mesenteric vessels. Right colon vessels (ICA, ICV, RCV and RCA) are ligated at their origin (35). Sharp dissection continues in the fascial plane between the retroperitoneum and mesocolon, to reach the lateral abdominal wall. With the help of this dissection the head of the pancreas is widely separated from transverse colon. For cecum or ascending colon cancers, similar to the open surgery, right branch of middle colic vessels are ligated at their origin and transvers colon is transected at the level of middle colic vessels. For full mobilization of the right colon, hepatic flexure is mobilized, ileocecal peritoneal folds and right lateral peritoneal fold are separated. The ileum is transected at approximately 15–20 cm proximal from the ileocecal valve.

For proximal transverse colon or hepatic flexure cancers, there are some additional manipulations to previous description. The middle colic and right gastroepiploic vessels are ligated at their origin. The variations of venous anatomy should be well known and the dissection should be performed carefully to avoid venous injuries (27,30). Sub-pyloric lymphadenectomy is carried out. The right part of great omentum is resected totally (36). The ileum is transected at approximately 5–10 cm proximal from the ileocecal valve and transverse colon is transected at least 10 cm distal from the tumor.

Anastomotic technique (intracorporeal or extracorporeal) depends on the experience and choice of the surgeon. For intracorporeal anastomosis, a mini-Pfannenstiel incision is generally used for the extraction of the specimen. For extracorporeal anastomosis, a mini vertical incision at the level of the umbilicus is generally used. Several studies showed that 'cranio-caudal' or 'top-to-down' approaches are also appropriate for CME (37-39). Robotic right CME which is another alternative minimally invasive technique, is safe and feasible according to new studies (40-42).

Quality of surgical specimen

The pathological evaluation is well described and standardized (43-45). The specimens were graded as mesocolic, intramesocolic, and muscularis propria plane. Mesocolic plane, defined as "good" plane, has intact mesocolon. Intramesocolic plane, defined as "moderate" plane, has irregular disruption in the mesocolon, but they do not reach down to the muscularis propria. In muscularis propria plane, defined as "poor" plane, the breaches in the mesocolon reaches down to the muscularis propria.

Many studies showed that CME and CVL produces high quality surgical specimens (12,13,35,44). A systematic review revealed that more harvested lymph nodes, larger mesenteric area, and longer distance from the tumor to vascular tie were achieved by CME technique (46).

Nesgaard and colleagues (47) suggested in their postmortem study starting the dissection at the left of the SMA to achieve radical clearance of the lymphovascular bundles. In the same study, the authors defined the quality of the specimen as the weight of the lymphatic dissection rather than the high tie vascular ligation (47).

Oncologic outcomes of CME in the literature

In the meta-analysis encompassing 8,586 patients, comparing CME and non-CME published by Wang *et al*. (46) CME had better 3 and 5 years survival rates even though CME was associated with more complications.

Siani *et al*. (48) reported morbidity rate of 35.5%, mortality rate of 0.5% and average lymph node number of 27±3 in their study of 600 patients. They reported recurrence in 177 (29.5%) patients and overall survival of 83%. In the subgroup analysis overall survival rates were 88.7% in stage 2, 72.4% in stage 3A/B, 71.4% in apical lymph node negative stage 3C and 27.7% in apical lymph node positive stage 3C patients.

Alhassan *et al*. (49) demonstrated that the complications associated with CME were 22.5%. In their systematic review, only Bertelsen *et al*. (50) reported intraoperative outcomes and they indicated that intraoperative organ injuries, especially splenic and superior mesenteric vein injuries, were significantly higher in CME compared with non-CME (CME: 9.1% *vs*. non-CME: 3.6%, P<0.001). But, in the same study the other complications were similar.

Merkel *et al*. (51) analyzed the transformation from non-CME to CME during 1978–2009 in four different stages. They reported an increase in the overall morbidity (rising from 1.8% to 3.7%); however mortality during the hospital stay is not changed. In addition, locoregional recurrence decreased from 6.7% to 2.1% for all stages, and from 14.8% to 4.1% for stage 3 patients (P=0.046). Distant organ metastasis was reported to decrease from 18.9% to 13.3% (P=0.01). Although not statistically significant, 5-year overall survival gradually increased; nonetheless 5-year cancer related survival increased from 61.7% to 80.9% (P=0.01) (51).

In our unpublished study, CME produced similar pathologic outcomes to conventional colectomy except for its association with a higher number of harvested lymph nodes. In CME patients, 3-year overall survival rate was higher with no statistical significance (CME: 94.4% *vs*. non-CME: 86.4%, P=0.13).

Two important studies have been published about survival of CME (9,52). Kontovounisios *et al*. (52) evaluated 5,246 patients in their systematic review, and they indicated the local recurrence rate was 4.5%, and 5-year overall survival was 58.1%. In the other important study showed that disease-free survival rates were higher in the CME group for stage I–III colon cancer (100%, 91.9%, and 73.5%, respectively) (9). Some different studies are summarized in *Table 1* (6,9,10,17,44,51,53-56).

Unfortunately, many studies have significant limitations, being generally retrospective and non-homogeneous, so that at the moment a definitive high level of evidence cannot be drawn and thus no strong grade of recommendation may be assigned (24). The study designs that investigate the CME technique are listed in *Table 2* (9,12,13,35,48,50,51,54,55,57-59).

Prospective randomized trials are needed in large series to allow CME to be considered the gold standard for right colon cancer surgery (24). The results of the prospective randomized ongoing RELARC and COLD studies on CME are eagerly awaited (60,61).

Conclusions

The morbidity of CME is generally higher than the conventional right hemicolectomy. CME needs detailed anatomical knowledge and experience on oncological colon surgery. The CME with CVL offers high quality specimen which possibly reflect good long term oncologic outcomes. Until now, published series on CME are mostly retrospective and non-homogenous. For that reason the interpretation of oncological results should be judged cautiously. The quality of evidence is limited and does not consistently support the superiority of CME.

Table 1 Pathological and oncologic outcome of CME in literature

Reference	Harvested lymph nodes		5-year local recurrence		5-year overall survival		5-year disease free survival	
	Surgical technique	Number	Plane of surgery	Rate (%)	Plane of surgery	Rate (%)	Plane of surgery	Rate (%)
Hohenberger *et al.* (6)	CVL	32	Ms	4.90	Ms	85	Ms	NR
West *et al.* (44)	CVL	30	Ms	4.90	Ms	85	Ms	NR
	Non-CVL	18	Non-Ms	NR	Non-Ms	70	Non-Ms	NR
Siani *et al.* (10)	CVL	30	Ms	NR	Ms	82.6	Ms	73.8
	Non-CVL	18	Non-Ms	NR	Non-Ms	60	Non-Ms	59.7
Kanemitsu *et al.* (17)	CVL	31	Ms	6	Ms	84.5	Ms	91.6
Bertelsen *et al.* (9)	CVL	36	Ms	11.3	Ms	74.9	Ms	85.8
	Non-CVL	20	Non-Ms	16.2	Non-Ms	69.8	Non-Ms	75.9
Bae *et al.* (53)	CVL	28	Ms	NR	Ms	90.3	Ms	83.3
Merkel *et al.* (51)	CVL	32	Ms	4.1	Ms	NR	Ms	80.9
	Non-CVL	18	Non-Ms	14.8	Non-Ms	NR	Non-Ms	61.7
Kotake *et al.* (54)	CVL	18	Ms	NR	Ms	91.9	Ms	NR
	Non-CVL	11	Non-Ms	NR	Non-Ms	90.6	Non-Ms	NR
Agalianos *et al.* (55)	CVL	27	Ms	NR	Ms	81.3	Ms	84.6
	Non-CVL	18	Non-Ms	NR	Non-Ms	70.9	Non-Ms	76.4
Gao *et al.* (56)*	CVL	24	Ms	NR	Ms	97.2	Ms	92.2
	Non-CVL	20	Non-Ms	NR	Non-Ms	98.3	Non-Ms	90
Our unpublished study*,&	CVL	42	Ms	NR	Ms	94.4	Ms	NR
	Non-CVL	34	Non-Ms	NR	Non-Ms	86.4	Non-Ms	NR

All of these series include both right and left colon cancer results. *, 3-year follow-up; &, only right colon cancer. CME, complete mesocolic excision; CVL, central vascular ligation; Ms, mesocolic plane; NR, not reported.

Table 2 Study design of CME in right-sided colon cancer

First author	Year	Country	Design	Journal	Right-sided tumors (CME/total)
West *et al.* (57)	2010	UK	Retrospective	*Dis Colon Rectum*	58/141
Bertelsen *et al.* (35)	2011	Denmark	Retrospective	*Colorectal Dis*	53/118
Galizia *et al.* (13)	2014	Italy	Prospective	*Int J Colorectal Dis*	45/103
Storli *et al.* (12)	2014	Norway	Prospective	*Tech Coloproctol*	45/102
Bernhoff *et al.* (58)	2015	Sweden	Retrospective	*Eur J Surg Oncol*	684/1,309
Bertelsen *et al.* (9)	2015	Denmark	Retrospective	*Lancet Oncol*	189/686
Kotake *et al.* (54)	2015	Japan	Retrospective	*Int J Colorectal Dis*	463/926
Bertelsen *et al.* (50)	2016	Denmark	Retrospective	*Br J Surg*	278/1,168
Merkel *et al.* (51)	2016	Germany	Retrospective	*Br J Surg*	506/859
Siani *et al.* (48)	2017	Italy	Retrospective	*Am J Surg*	486/600
Olofsson *et al.* (59)	2016	Sweden	Retrospective	*Colorectal Dis*	1,694/2,086
Agalianos *et al.* (55)	2017	Greece	Retrospective	*Ann Gastroenterol*	71/139

CME, complete mesocolic excision.

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Footnote

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