Review Article



# A narrative review: complete mesocolic excision in right-sided colonic cancer resections—present paradigm and future directions

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**Background and Objective:** Complete mesocolic excision (CME) is thought to achieve better oncological outcomes in colon cancer surgery, but adoption in right-sided colon resections has not been as complete as total mesorectal excision (TME) in rectal cancers, and the technique is not as standardized. In addition, higher rates of intra-operative complications in early studies have limited its wide-scale adoption in routine surgical practice. We aim to determine if the literature supports a universal or selective application of CME in right-sided colonic cancer resections.

**Methods:** We conducted a data search in PubMed using a comprehensive set of MeSH and text word search terms, between 1st January 2008 to 28th December 2022 without any language limitations. Additional relevant papers identified through the authors' collaborative networks were also included.

**Key Content and Findings:** There is variability in the literature regarding what constitutes CME, and it is difficult to separate the impact of D3 lymphadenectomy and central vascular ligation (CVL) from that of CME itself. In addition, the quality of the evidence base for CME is generally poor. Nevertheless, there is some oncologic advantage to CME in terms of better specimen quality, but this does not always translate into better disease-free survival (DFS) or overall survival (OS) rates. Earlier studies noted longer operative times, higher complication rates, and longer hospital stays in the CME arm, mitigating any longer-term advantages. The use of a tool such as the Kanemitsu nomogram or pre- and intra-operative advanced imaging may allow selection of patients most likely to benefit while sparing others the risks.

**Conclusions:** A selective approach to CME, balancing survival benefit and quality of life (QoL) against operative risks, is recommended.

**Keywords:** Central vascular ligation (CVL); colon malignancy; operation; patient outcomes; radical (D3) lymphadenectomy

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## Introduction

### Background

Complete mesocolic excision (CME) is a surgical technique which was developed to improve patient outcomes from colon cancer through standardization of surgical technique, similar to that of rectal cancer surgery following the widespread adoption of total mesorectal excision (TME). Hohenberger's (1) seminal paper has been widely accepted as the first historical description of the concept of CME, albeit the principal of radical lymphadenectomy (D3) has been a longstanding common practice amongst Japanese surgeons (2). In a comparative case series of CME *vs.* non-CME, CME specimens were shown to result in almost doubling of both the number of lymph nodes (LNs) retrieved and the completeness of the mesentery resected (3,4).

### Rationale and knowledge gap

Despite reduction in local recurrence and improved survival rates with CME (5), higher rates of intra-operative complications such as haemorrhage, organ injuries, severe post-operative complications and mortality rates of more than 6% in other reported case series (6-8) have limited its wide-scale adoption in routine surgical practice. The procedure poses significant technical challenges as it requires dissection of vessels at the origin of the superior mesenteric vein (SMV) and superior mesenteric artery (SMA), and furthermore, familiarity is required with the inconsistent vascular supply and venous drainage of the intestinal midgut, particularly of the gastrocolic trunk of Henle (GCTH) (9). Complications arising from this area, particularly haemorrhage, can be difficult to control and are potentially life-threatening.

### Objective

CME is thought to achieve better oncological outcomes in colorectal cancer surgery, but adoption in right-sided colon resections has not been as complete as TME in rectal cancers, perhaps due to higher rates of intra-operative complications in early studies. Hence we wanted to determine if the literature supports a universal or selective application of CME in right-sided colonic cancer resections. Given the uncertainty of the long-term benefit from CME in the era of newer targeted oncological therapies and better understanding of cancer biology, we aim, in this review, to determine if the literature supports a universal or selective application of CME in right-sided colonic cancer resections. We present this article in accordance with the Narrative Review reporting checklist (available at https://ales.amegroups.com/article/view/10.21037/ales-23-4/rc).

## Methods

### Data search strategy

The PubMed database was searched for relevant studies from the 1st January 2008 to 28th December 2022. A comprehensive set of MeSH and text word search terms was developed using the following combination of keywords: 'complete mesocolic excision' OR 'vascular ligation' OR 'D3' OR 'survival' OR 'laparoscopic' OR 'robotic' OR 'open' OR 'surgery' OR 'operation' AND 'cancer' OR 'malignancies' OR 'neoplasm'. Additional papers identified through authors' research networks were also included (*Table 1*).

### Data selection strategy

Three authors (Khong TL, Aziz MRA, Aziz NA) independently screened the retrieved studies based on the titles, abstracts and contents for inclusion into this review. Studies that were included in the analysis met the following criteria: (I) focused on colorectal cancer; (II) surgeries were right-sided resections; (III) full text articles were available. Exclusion criteria included: (I) case reports or small case series; (II) left-sided resections. Studies that were shortlisted by all three authors were studies selected by at least one author were discussed with two other authors (Roslani AC and Rajandram R) before a final decision was made regarding inclusion (*Table 1*).

All relevant data was independently extracted by the authors and tabulated in an Excel spreadsheet format. The main data extracted from these articles included: (I) definition of CME; (II) study design and duration; (III) operative approach and dissection technique; (IV) short- and long-term outcomes; (V) key findings. Where studies reported a mix of both right and left sided resections the data pertaining to right sided resection was still included. The final inclusion of articles was a consensus decision of all authors, taking into consideration the importance of each finding and possible implications (*Table 1*).

## Definitions of CME

While CME, central vascular ligation (CVL) and D3 have

**Table 1** The search strategy summary

| Items | Specification |
|---|---|
| Date of search | 28th December 2022 |
| Databases and other sources searched | PubMed |
| Search terms used | 'complete mesocolic excision' OR 'vascular ligation' OR 'D3' OR 'survival' OR 'laparoscopic' OR 'robotic' OR 'open' OR 'surgery' OR 'operation' AND 'cancer' OR 'malignancies' OR 'neoplasm' |
| Timeframe | 1st January 2008 to 28th December 2022 |
| Inclusion criteria | (I) Original articles; (II) systematic reviews and meta-analysis; (III) review articles; (IV) colorectal cancer; (V) right-sided resections; (VI) full text articles were available; (VII) all languages |
| Exclusion criteria | (I) Case reports or small case series; (II) left-sided resections only |
| Selection process | Participating authors identified relevant articles based on content, clinical relevance and date of publication |
| | The final inclusion of articles was a consensus decision of all authors, taking into consideration the importance of each finding and possible implications |
| Any additional considerations | Three authors independently screened the retrieved studies based on the titles, abstracts and contents following the inclusion and exclusion criteria |

been defined, the terms are sometimes used interchangeably even though they refer to different aspects. At its most basic level, CME is sharp dissection of embryonic planes with avoidance of mesenteric tears because it removes hidden tumor deposits and avoids interruption of lymphatic and vascular drainage that may cause peritoneal cancer cell spillage (10). Hohenberger described it as a resection of the tumour together with an intact mesocolon, but he also included radical (D3) lymphadenectomy and proximal ligation of the vascular pedicles at their origins (CVL). The length of bowel resected was determined by the optimal LN harvest along the longitudinal axis from the primary tumour site. Nevertheless, not all surgeons routinely perform D3 lymphadenectomy in CME resection due to a higher rate of complications (11).

Sammour *et al.* reported that CVL (D3) was determined by the primary surgeon based on a balance between patient factors such as body mass index (BMI), previous abdominal surgery, baseline comorbidity and pre-operative staging (presence of nodal disease on preoperative imaging). In this study, D3 lymphadenectomy was done by trained colorectal surgeons or surgical oncologists (11) and the procedures were performed either laparoscopically or robotically. In Japan, CME with D3 lymphadenectomy is commonly performed for patients with T3 and T4 colonic cancer. The surgical technique of D3 LN dissection is similar to that described by Hohenberger, but the resected colon is shorter in the Japanese D3 procedure (2).

Comparison of study outcomes is difficult due to variability in CME definitions. Furthermore, independent histological confirmation of the extent and completeness of resection is inconsistently reported and may impact the reported outcomes in comparative studies (12).

## Anatomy

In order to achieve the ideal oncologic specimen, sharp dissection is required to separate the embryonic fusion fascia of the mesocolic visceral plane from the retroperitoneal parietal fascia. Dissection along natural embryonic planes, paralleling that of TME for rectal cancer surgery, ensures an intact mesocolon is preserved, thus reducing exfoliation of tumor cells into the peritoneal cavity. Awareness of the anatomical fascial planes assists surgeons in performing the technique more safely, minimizing intraoperative risks and shortening the learning curve (13).

Several fascial planes have been described for optimal CME. However, there is lack of standardization in anatomical terminology used to describe these surgical planes. Zhu *et al.* (13) described three fascial or surgical planes and proposed a stepwise surgical approach centred upon these embryological fascial planes.

The first surgical plane (FSP) includes the fascial space between the posterior surface of the ascending mesocolon and the prerenal fascia. The boundaries are: caudally, the lower edge of the ileocolic vessels (ICVs); medially, the second part of the duodenum; cranially, the hepatocolic ligament; and laterally, the right paracolic sulcus (RPCS) or white line of Toldt (13).

The second surgical plane (SSP) includes the fascial plane between the posterior surface of the ascending mesocolon and the anterior surface of the pancreatic head and duodenal fascia. The caudal, cranial, medial and lateral boundaries of the SSP are formed by the third part of the duodenum, the transverse mesocolon root, right edge of the SMV and the lateral boundary of the second part of the duodenum respectively (13).

The third surgical plane (TSP) is formed by the posterior part of the right-sided transverse mesocolon and the dorsal mesogastrium fusion fascia. The caudal and lateral TSP boundaries include the cranial boundary of the SSP, with the medial and cranial boundaries formed by the middle colon vessels and the gastrocolic ligaments respectively. These planes were demonstrable on CT imaging and correlated well with intraoperative findings especially where there was evidence of fascial invasion on pre-operative CT imaging (13).

Garcia-Granero *et al.* (14) highlighted the importance of the fascial plane between the visceral peritoneum of the ascending mesocolon and the visceral duodenal-pancreatic peritoneum known as the fusion fascia of Fredet (3,6,15). The fascia of Fredet bears similarities to Zhu's SSP (13), as dissection along this plane would mobilise the mesocolon off the anterior surface of the duodenum and pancreas, exposing the SMV and the GCT. Awareness of how to enter and develop this plane can be useful for D3 lymphadenectomy, particularly in reducing the risk of intraoperative bleeding from the SMV (14).

Between the ascending mesocolon and the pre-renal fascia (PRF) lies a fascial plane which comprises mainly of loose areolar tissue known as Toldt's fascia (16). This anatomical plane has significant overlap with Zhu's FSP (13), and bears close resemblance to the retrocolic space (RCS) described by other authors (17,18).

The boundaries of the right retrocolic space (RRCS) are formed anteriorly by the ascending mesocolon, posteriorly by the prerenal fascia, medially by the SMV, and laterally by the peritoneal reflection along the RPCS, also known as the white line of Toldt. Cranially the RRCS is bound by the inferior margin of the transverse (third) part of the duodenum, beyond which lies the transverse retrocolic space (TRCS), and caudally by the inferior margin of the mesenteric root (18).

The TRCS refers to the avascular space between the transverse mesocolon and the pancreas and duodenum which is bordered cranially by the root of the transverse mesocolon and caudally by the inferior margin of the transverse (third) part of the duodenum (18). The TRCS bears gross resemblance to the SSP and TSP as described by Zhu *et al.* (13).

## Surgical strategy

Several surgical strategies for CME have been described, namely the lateral to medial, medial to lateral, caudal to cranial or cranial to caudal approaches. Furthermore, such approaches can be performed through open, laparoscopic (single/multiport/hand-assisted) and robotic surgery. Irrespective of the type of approach or modality, the safe surgical technique for CME respects the 'holy' embryological plane of the colon and mesocolon, an extension of the concept commonly employed for rectal cancer surgery.

## Surgical approach

The open technique conventionally utilises a lateral to medial approach, where the lateral paracolic peritoneal fold is initially released, facilitating the dissection of the colon and mesocolon off the retroperitoneal parietal fascia. Hohenberger described a more radical procedure, where the duodenum together with the pancreatic head were mobilised in a Kocher's maneuver, and the mesenteric root was mobilized up to the origin of the superior mesenteric artery for optimal exposure of the supplying vessels (1). Furthermore, the authors advocated radical clearance of peri-pancreatic, gastro-epiploic, subpyloric LNs particularly in hepatic flexure and transverse colon cancer (19). The emphasis on mesentery-oriented surgery together with ligation of the vessels at the origin was associated with significantly higher LN harvest.

The widespread adoption of minimally invasive surgery (MIS) has made it a standard modality for performing most routine bowel resections, and has led to the development of several surgical techniques which exploit native embryological surgical planes as the surgical dissection path for performing right hemicolectomy.

In the caudal-medial to superior-lateral or 'vessel-first' approach (13,18) the initial dissection of the SMV is performed to reveal the root of the ICV. Continued lateral dissection along ICV would permit entry into the FSP or RRCS along Toldt's fascia. Upon revealing the root of the ICV and the SMV, dissection along the inner edge of the ascending mesocolon on the SMV surface and the anterior surface of the pancreas along the pancreatic-duodenal fascia permits entry into the SSP. This maneuver bears similarities to surgical techniques reported by others where the fascia of Fredet is dissected to expose the anterior surface of the pancreas and duodenum (14) thus allowing entry into the TRCS in a bottom-to-top fashion (18,20).

Further dissection along the SMV would reveal the right colic vein (RCV), the root of the middle colic artery (MCA) together with its branches, and the GCT and its branches. The RCV is ligated and divided, and the right gastroepiploic vein (RGEV) is used as the posterior boundary to expose the TSP or TRCS further. Following ligation of the right branch of MCA at its origin, the TSP can be exposed further by dissection in the cephalad direction. Division of the gastrocolic ligament allows entry into the omental bursa which facilitates takedown of the hepatic flexure by dividing the hepatocolic ligament. Detaching the peritoneal fold at the RPCS or white line of Toldt completes the CME procedure.

In a cranial to caudal (top-down) approach (also described as the hybrid medial approach) (20) the gastrocolic ligament is incised to allow initial entry into the inter-mesenteric space or omental bursa. Using the RGEV as a landmark, dissection is continued caudally to expose the GCT (21). Further dissection of the middle colic vessels and the GCT within the TRCS allows mobilisation of the transverse mesocolon by dissection up to the inferior edge of the pancreas. The procedure would typically be completed with a medial approach for complete mobilisation of the right colon and mesocolon.

Both caudal-medial and cranial to caudal approaches have been compared in a prospective randomized trial and the caudal-medial approach was associated with a shorter operative time with no difference in LN yields (20).

In the caudal to cranial (down-to-up) approach, the right colon and mesocolon are initially dissected off the prerenal fascia to reveal the duodenum and head of pancreas (22). The procedure begins by incising the peritoneum at the retrocaecal recess located at the caudal aspect of the mesenteric root. Sharp dissection is continued in the cephalad direction with entry into Toldt's fascia, posterior to the jejunoileal mesentery to allow separation of the colon and mesocolon away from the parietal fascia. Following exposure of the pancreatic head and the duodenum, dissection continues to reveal the root of the ICVs, right colic vessels, middle colic vessels and the GCT.

As the colon and mesocolon are mobilised off the retroperitoneum before isolation of the vessels of interest, this step may potentially reduce risk of injuries to retroperitoneal structures such as ureter and gonadal vessels. Furthermore, the process of identification and isolation of the vascular pedicles at their origin during SMV dissection could be performed more safely and easily with the dorsal aspect of the vessels exposed following the caudal to cranial dissection.

Several novel techniques have been developed to overcome the steep learning curve of laparoscopic CME. A hand-assisted technique, which is currently under evaluation in a randomised controlled trial, employs the use of a hand access device inserted through an umbilical incision (23). The purported advantage of hand-assist surgery is that it can overcome technical challenges of standard laparoscopy by returning tactile sensation to the operating surgeon whilst conferring the benefits of MIS. Furthermore, use of the hand access device permits parts of a complex procedure to be carried out extracorporeally thus enabling easier identification of key anatomical landmarks for safe dissection and reduction in operative time.

In addition, the classic straight-fixed laparoscopic instruments are thought to contribute to the challenges in performing laparoscopic CME with D3 lymphadenectomy. Articulating laparoscopic instruments, such as the ArtiSential®, were developed to improve ergonomics, providing a wider range of movement and synchronization with the surgeon's hand movements (24). The articulation offered by ArtiSential® could prevent internal collisions between laparoscopic instruments and could be manipulated to provide the optimal image for the operating surgeon by avoiding occlusion of the laparoscopic camera view.

Most current literature on MIS for CME and D3 lymphadenectomy have utilised the laparoscopic technique, but of late, the robotic technique has been increasingly reported. The technical advantages of robotic systems over laparoscopy are purported to overcome the complexity of CME in MIS by conferring better visualization and depth perception through enhanced 3-dimensional visualization, stable tissue retraction with articulated instruments of greater degrees of motion and instrument stabilization, precise dissection and improved ergonomics (21).

The intra-operative near-infrared (NIR) fluorescence imaging system incorporated into the robotic system could also assist with LN dissection by visualization along the colic branches of the superior mesenteric vessels near the central vascular trunk. In addition, NIR imaging permits tissue perfusion assessment and can assist with identification of the transition point between perfused and ischaemic parts of the transverse colon and distal ileum for intracorporeal anastomosis (25).

## Outcomes

### *Short-term outcomes*

#### Safety

Early retrospective studies on right CME describe safe techniques and identify pitfalls that subsequent authors tried to address (15).

#### Intraoperative complications

Most authors noted no reported differences in overall intraoperative complications between CME *vs.* conventional surgery for colon cancer [relative risk (RR) 1.06, 95% CI: 0.97–1.14, P=0.189] (26). However, some authors found increased intra-operative organ injuries (9.1% *vs.* 3.6%, P<0.001) and more severe non-surgical complications, that led to associated operative mortality rate of more than 6% in some series (11).

***Bleeding***

The main intra-operative pitfall of CME is bleeding, especially during vascular dissection where a single error may lead to potentially life-threatening haemorrhage (15,25). Bleeding has led to increased rates of injury to surrounding tissues (24). Increased conversion rates have been described in laparoscopic CME, whereby an 8.3% rate of conversion is due to uncontrolled bleeding (27). One study (n=995) singled out bleeding as a statistically significant complication in CME *vs.* non-CME (8). Nevertheless, given the large amount of data and considerable variations in technical expertise, individual retrospective studies may not accurately reflect the true risks of CME.

However, in a separate study examining blood loss, there was no difference between CME *vs.* conventional surgery for colon cancer [weight mean difference (WMD) 3.50 mL, 95% CI: −29.13 to 36.12, P=0.0834] (26). An early meta-analysis of 12 studies showed increased intraoperative blood loss with CME (28). However, of 9 more recent meta-analyses, none showed increased bleeding with CME, and 2 conversely showed reduced operative blood loss with CME *vs.* non-CME (29). Also, 6 out of these 9 reviews also demonstrated similar length of hospital stay for CME *vs.* non-CME (29).

These differences may be explained by the variability in technical standardization in each study. Emphasis on safe entry into, and dissection of fascial planes allows better exposure and marked reduction of the risk of vascular injuries and bleeding from the SMV (14). Re-training surgeons in cadaveric workshops to improve recognition of anatomical variants has also been shown to reduce intra-operative bleeding in laparoscopic CME (14).

***Vasculature mapping with perioperative imaging***

Pre-operative CT imaging has been shown to improve identification of the fascial space of the posterior surface of the mesocolon. This allows more complete dissection to separate the visceral fascia and the parietal fascia as required in CME (13,14,30).

Additional preoperative imaging, such as CTA in combination with CT Colonoscopy increases prediction rates of Henle trunk tributaries compared with CTA alone. This preoperative 3D mapping of colon in relation to its vasculature improved OT time by shortening operative time related to obtaining control of bleeding (31).

***Anastomotic leak***

An early retrospective descriptive study reported only one anastomotic leak (<1%) (15). However, studies with long term follow up suggested leak rates of up to 5.6% (7) with associated mortality (27).

Results from comparative studies are mixed. Higher anastomotic leak rates have been reported in CME (3.4%) compared with non-CME (1.8%) (12), but others show no statistically significant difference (1–2%) (6). Interestingly a systematic review subsequent to the period of our literature search had lower leak rates (32).

Nevertheless, based on a systematic review and meta-analysis between CME *vs.* conventional surgery for colon cancer, there were no differences in anastomotic leakage (RR 1.02, 95% CI: 0.81–1.29, P=0.849) (26).

***Operative time***

In general, the studies show that CME/D3 surgery is associated with a longer operative duration. The weighted mean difference in operative time for CME/D3 *vs.* conventional is 27.7 min (95% CI: 1.11–54.3, P=0.041) (26). Where CME was performed by laparoscopic technique (30), and subsequently robotic (32), the operating time was also much longer compared to open CME surgery (27).

#### 30-day mortality

Early studies on the outcomes of CME reported no immediate post-operative mortality, which suggested its safety (14). In fact, higher CME completeness was associated with decreased postoperative mortality in a Swedish population study (33). Furthermore, no difference in early mortality was reported in open *vs.* laparoscopic *vs.* robotic right CME (27,30,32).

More recently, a systematic review and meta-analysis revealed no difference in 30-day post-op mortality between colonic CME and non-CME surgery (RR 0.96, 95% CI: 0.38–2.38, P=0.925) (26). This is also true in right CME (8,33,34).

### *Long-term outcome*

#### Oncologic outcomes

##### *5-year survival*

Earlier studies reported modest long-term outcomes for CME with 5-year survival rates at 72.4% (15). Subsequent systematic reviews demonstrated better 5-year survival rates ranging between 82.1% and 89.1% (n=273) (35), with an increase in 5-year cancer-related survival rate by 7% (from 82.1% to 89.1%) following implementation of CME.

Improved survival is more clearly seen with longer follow up. A large (n=26,640) recent study showed that although there were no differences in overall survival (OS) between the CME/D3 and conventional cohorts at 1 year (RR 0.85, 95% CI: 0.67–1.09, P=0.201), 3- and 5-year OS favoured the CME/D3 group [RR 0.69 (95% CI: 0.51–0.93, P=0.016) and RR 0.78 (95% CI: 0.64–0.95, P=0.011) respectively] (26). They concluded that OS favoured D3/CME (26) over non-CME.

##### *Cancer mortality*

Risk of cancer-related death has been shown to be reduced by over 50% in CME patients (10), and a few recent studies demonstrated that none of the patients who underwent CME had died within a 3-year follow-up period (8) and 5-year follow up period (26).

##### *Locoregional recurrence*

At 3-year follow up, local and locoregional recurrence rates have been reported to be lower amongst patients who had CME *vs.* non-CME surgery (36), particularly in node-positive patients (10). The cumulative incidence of local recurrence was almost halved with CME *vs.* control (3.7% *vs.* 7% respectively) at 5-year follow-up (37). Similarly, Shin *et al.* reported locoregional recurrence rates to be decreased by 2.9% (from 6.5% to 3.6%) at 56 months follow-up (7). Improvements are clearly seen in the 3-year local recurrence-free survival (LRFS) rate in stage II and stage III (36).

##### *Disease-free survival (DFS)*

DFS has been shown to be better in CME/D3 compared to conventional cohorts at 1, 3 and 5 years [RR 0.60 (95% CI: 0.45–0.81, P<0.001); RR 0.72 (95% CI: 0.62–0.83, P=0.001); RR 0.67 (95% CI: 0.52–0.86, P<0.001) respectively] (26). Long-term, stage II and III patients were more likely to benefit from CME resections (5-year DFS stage II: 95.2%, stage III: 80.9%) (7).

CME has been shown to achieve an absolute risk reduction over 5 years of 3.1% for distant recurrence alone and 3.4% for local and distant recurrences (37). However, this benefit is not uniformly seen. Gao *et al.* could not show any significant difference in the 3-year OS, DFS, and MFS rates between CME and non-CME groups. Subgroup analysis however showed that improvements are clearly seen in the 3-year LRFS rate in stage II and stage III. Hence, CME may be more suited for patients with stage III disease, and high-risk stage II (36).

Others have also reported reduced recurrences and improved survival in node-positive patients, perhaps through reduced tumour spillage (10). Lymphovascular infiltration (LVI), a component predictor of survival, is better preserved in CME dissections (36), and this may be another mechanism by which CME improves survival.

Similarly, a systematic review reported no significant benefit of CME as locoregional recurrence and distal metastatic rates, 5-year OS and DFS were not statistically different compared to standard surgery (32). However, there were survival benefits for patients diagnosed with stage II and III cancers, particularly in patients where larger number of LNs were harvested during surgery.

#### Quality of life (QoL) measures

To date there have been no studies examining the QoL of patients using patient reported outcome measures post CME surgery. An ongoing multicentre RCT conducted in Italy will be determining the QoL using various instruments such as the EORTC QLQ-CR29/QLQ-CR30 and SF36 questionnaires, and this study is expected to complete in 2027 (38).

#### Quality of resection

##### *Histopathological criteria*

As defined by Hohenberger (1), CME involves preservation of mesenteric fascia, central node removal (D3) and CVL. In an early study of open conventional *vs.* CME right hemicolectomy (n=103, conventional n=58, CME n=45), the number of harvested nodes and length of vascular ligation were shown to be significantly better in the CME group.

Colon cancers resected with an intact mesocolon achieve 5-year OS 15% better than those with mesocolic defects on the specimens (14). This may be because better preservation of planes allows the clear demonstration of LVI status, which predicts locoregional recurrence and survival (8,36). In addition, better harvest of LNs allows for improved nodal staging, another predictor of survival. Interestingly, CME quality is significantly better in D3 *vs.* D2 resections (34).

All in all, comparison of histopathological quality and oncologic outcomes imply that the benefit from CME is predominantly from the central lymphadenectomy, rather than differences in longitudinal margins or plane of dissection (26). However, given that there is no convincing evidence that CME is less traumatic and morbid, universal application cannot be recommended (35).

***LN yield***

Care should be applied in interpreting the CME studies, as some have included left-sided resections. A more focused examination of LN yields from right sided resections is needed (39).

Higher LN yield is found to be the common feature of CME (12,26). Although earlier colonic (right and left) CME studies did not show any increases in the total number of positive LNs compared with non-CME, the incidence of apical LN metastasis in the CME group was noted to be high. This is considered pivotal as apical LN positivity directly affects the stage and survival of cancers (7,36,39). Apical LN metastasis was associated with LVI (OR: 5.109, P=0.038) and the number of positive LNs (OR: 1.476, P<0.001). This suggested that CME is particularly necessary for patients with stage III disease and cases with LVI (7,36).

Similarly, an ongoing study of only right sided resections by Benz noted higher LN yield in CME (12). Higher apical node yield, with metastases in the central LNs were also detected in the CME group (8). Another study by Yang, found that together with an increase in LN yield in right CME (mean total LN 26.8±1.9 *vs.* 23.2±3.4) there was also an increase LN positivity rate (40).

Higher LN yields are also obtained when the operation is done laparoscopically compared with open (27). A head-to-head comparison of laparoscopic classic *vs.* laparoscopic CME also showed increased LN yield in the laparoscopic CME arm, confirming that increased yield is due to CME rather than surgical modality (30). Utilization of articulating wristed instruments and robots also showed increased LN yield (24,32).

Interestingly, early results from the COLD study, which compared D2 and D3 resections in a CME approach, found that although there was no difference in LN yield, N-positive status was more common in the D3 group (34), further supporting increased node positivity detection rates. Morbidity rates trended slightly higher in the D2 arm, (47% in D2 *vs.* 48% in D3) but this was not statistically significant. Like most right CME studies, it has not yet reported survival benefit of increased LN positive rate detection.

Therefore, while right-sided CME mimics the overall colonic CME total LN yield and boosted apical LN harvest, the impact of increased LN positivity in right CME on long-term patient outcomes is less clear.

**Impact of surgical approach**

***Laparoscopic vs. open resections***

Prevost *et al.* compared complication rates of laparoscopic CME (retrospective cohort) against open non-CME (historical cohort) resections, showing no difference in anastomotic Fleak rates. However, there was an increased risk of aspiration and death in the CME arm (6). Despite the inherent biases due to technical and temporal differences in the arms, this suggests early on that the central nature of dissection in CME affects return of gut function. Furthermore, caution should be exercised when contemplating a laparoscopic approach to more technically complex resections.

Nevertheless, the laparoscopic approach has potential benefits. In a prospective randomized trial-laparoscopic CME was associated with a shorter length of hospital stay (9.13 *vs.* 13.04 days P<0.001), similar to other lap colonic resections, as compared with open CME. However, as a trade-off, there was a significant increase in time of operation (201 *vs.* 152 minutes, P<0.01). The study found that lap technique yielded higher LN and longer mesenteric length to high tie as compared to open. At a mean follow up of 3 years, however, these pathological features translated to having no significant difference on recurrence and distant metastases OS: 3-year OS in the laparoscopic CME *vs.* open CME (78.2% *vs.* 63.2%, P=0.423). DFS at 3-year laparoscopic CME was higher (74.5% *vs.* 60.0%, P=0.266) than the open group but did not reach statistical significance (27).

***Laparoscopic CME***

When compared against laparoscopic non-CME *vs.* laparoscopic CME has higher LN yield {CME *vs.* non-CME 23.8 [12–38] *vs.* 16.6 [5–37], P<0.001} but again, at a cost of increased operative time (216.3 *vs.* 191.5 minutes, P<0.005) (30). This group reports similar complication rates and notes that laparoscopic CME is safe and feasible comparatively to laparoscopic non-CME.

Two other recent laparoscopic studies have found similar short-term outcomes regardless of the operative method of dissection (20) or number of ports used (41). Laparoscopic CME has been shown to be safe in elderly patients (aged >70 years old) with comparable insignificant complication rates and improved oncological outcomes post CME (n=207). The improved survival benefit is still true despite high refusal rates for chemotherapy (42).

One of the technical challenges in performing laparoscopic CME is that conventional straight instruments do not provide true wristed freedom of movement. Novel wristed instruments, such as the ArtiSential®, may overcome this. In a study comparing laparoscopic CME with and without ArtiSential® (ArtiSential®: n=33, Conventional: n=43), there were no significant differences in operation time, mean estimated blood loss and intra-operative and post-operative complications. However, the number of harvested LNs was higher and the length of hospital stay was shorter in the ArtiSential® arm (24). It remains to be seen if this will translate into longer term benefits.

***Robotic CME***

The number of operations necessary to complete the learning curve for robotic colorectal surgery is reported to be between 15 and 35 cases in general series. A retrospective analysis on robotic right sided CME with intracorporeal anastomosis reported that it is also a feasible technique with acceptable short-term outcomes. With a mean follow-up, 14.8±9.2 months, there were no recurrence or disease-related mortalities (21).

Ozben *et al.* reported mean numbers of harvested LNs (41.8) in robotic CME that were higher than the majority other studies (21). It is known that the robot affords tremor-free articulated movement, high degree of freedom of the monopolar scissor and steady traction by another robotic grasper. Together with intra-operative NIR fluorescence imaging system, which allows detection of vessels and demarcation zones during anastomosis, in experienced hands, robotic CME appears to provide superior histological specimens.

Short-term outcomes are mixed. In a direct prospective systematic review and meta-analysis investigation comparison robotic CME (n=740) *vs.* laparoscopic CME (n=4,617), conversion to open rates and R0 histology were similar between both approaches. However, postoperative morbidity morbidity [17% (95% CI: 14–20%) *vs.* 13% (95% CI: 12–13%); $I^2$=90.7%] and anastomotic leak rates [2% (95% CI: 0–3%) *vs.* 1% (95% CI: 1–2%); $I^2$=0%] were higher in the robotic group compared to the laparoscopic group. The robotic group, however, had a shorter hospital stay [6.3 days (95% CI: 4.7–8.0) *vs.* 8.0 days (95% CI: 7.4–8.6); $I^2$=100%] reduced intraoperative blood loss [23.9 mL (95% CI: 23.6–24.2) *vs.* 69.1 mL (95% CI: 59.9–60.3); $I^2$=100%] and a higher amount of harvested LNs [robotic CME (RC) =35.7 (95% CI: 32.8–38.6) *vs.* 26.3 (95% CI: 24.7–27.8)] than the laparoscopic group (32).

Pooled 5-year OS and DFS in the robotic CME *vs.* laparoscopic CME group was 84% (95% CI: 80–87%, $I^2$=93%) and 73% (95% CI: 70–77%, $I^2$=98%), respectively, citing improved dexterity and decreased inflammatory response of the RC technique as purported explanation for improved outcome (32).

Nevertheless, despite its advantages, the downsides of the robotic technique are the limited availability of advanced energy instruments (25), increased mean operative times compared with open or laparoscopic CME procedures, and increased direct costs (21). While the robot provides the wrist articulation and dexterity which is crucial in CME, the availability of wristed instruments for laparoscopic procedures, such as the ArtiSential®, may reduce that advantage.

## Discussion

Despite advancements in multimodality therapy, surgery remains the mainstay of treatment for most stages of colorectal cancer. While adjuvant therapies have reduced the radicality of resections in some other cancers, meticulous dissection, adequate margins and LN harvest continue to be deemed important for long term oncologic outcomes in rectal cancer.

The evidence for this with regards to CME for colon cancer is less clear. In part, this is due to the variable definitions in the literature of what constitutes CME. Furthermore, it is difficult to separate the impact of CME from that of D3 or CVL, as data on the latter two are not always reported in CME literature and are possibly conflated with CME. In addition, the quality of the evidence base for CME is generally poor, with most papers limited to case series or technical papers with short-term follow-up (26).

Nevertheless, some themes have emerged. While early retrospective literature on open CME (37) suggested it was a better oncologic resection and offered a survival advantage, more recent randomized controlled trials have shown that while specimen quality is better with CME, with higher LN positivity in D3 resections, and that specimen quality can be maintained with the laparoscopic approach (27), this does not translate into better DFS or OS rates (8,34,43). Earlier studies also noted longer operative times, higher complication rates, and longer hospital stays in the CME arm, mitigating any longer-term advantages. Additionally, there is a lack of data on readmission rates. A more recent meta-analysis that included higher quality studies, confirmed a longer operative time of about 20 minutes when CME, CVL and D3 were used in combination, but unlike the earlier studies, complications, hospital stay, function and mortality did not differ significantly (29).

However, more recently, even in the hands of expert surgeons, longer operative times with a higher risk of vascular injury have been noted in the CME arm of randomized controlled trials (8,34), although overall complications are noted to be similar. This was true even using the laparoscopic approach (30). Although some of these operative outcomes could be attributed to a learning curve, it does beg the question of the generalizability of CME to different levels of surgical expertise, and appropriateness for universal application, especially given the marginal oncologic benefit. The CoME trial, due to complete in 2027, may be able to shed further light on these outcomes (38).

In addition, there are some distinct differences in the surgical approaches in the East and West. East Asian countries, such as Japan and China, have defined CME anatomy into several planes, and map the GCTH using fusion of multimodal imaging to minimize the intraoperative complications related to D3 LN dissection (31). Nevertheless, OS, DFS and recurrence rates are not superior to conventional CME with D2 LN dissection.

On the other hand, in the West, the adaptation of the Hohenberger technique without D3 lymphadenectomy has been popularized. Since the morbidity rate between the Eastern and Western approaches is similar, it remains unclear whether extended lymphadenectomy provides oncological advantages in colorectal cancer.

Perhaps a more suitable approach would be to select patients most likely to benefit from CME for the procedure. For instance, a selective approach for D3 in CME, using pre- and post-operative nodal imaging, has been shown to yield comparable oncologic clearance without increasing adverse operative outcomes (11). More importantly, emphasis should be placed on patient-centred outcomes—survival and QoL. Combining the use of a tool such as the Kanemitsu nomogram, which predicts survival and recurrence based on criteria which include pathologic analysis, with pre- and intra-operative advanced imaging, together with patient-reported goals of therapy and cost-effectiveness, may allow surgeons to more objectively weigh up the survival benefit against the risks of longer surgery for individual patients, while preserving QoL. Hence, studies which evaluate the use of the nomogram in CME should be recommended to better refine patient selection.

The variability in study designs limit direct comparisons between the studies in our narrative review, however the strengths are the inclusive data search and selection strategy allow nuanced discussion of the topic, not limited to findings of meta-analyses only.

## Conclusions

A selective approach to CME, balancing survival benefits and QoL against operative risks, is recommended.

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