



Complete mesocolic excision for colon cancer: is it worth it?

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Abstract: Total mesorectal excision (TME) has been the miracle surgical technique which has since allowed the outcomes of rectal cancer to surpass that of colon cancer. Complete mesocolic excision (CME) attempts to adopt the same principles as that of TME and apply it to colon cancer surgery. Initial retrospective case series and comparative studies have shown promising oncological outcomes. CME entails the *en bloc* removal of a sufficient length of colonic specimen within an intact peritoneal envelop with extended lymphadenectomy through a high central ligation of vessels. This technique, standardizing the method for resection of right sided colon cancer, has witness promising perioperative and oncological data for both open and laparoscopic methods. However, most data available are mostly retrospective with a glaring lack of level 1 evidence. Despite the technique showing similar outcomes to that of conventional colectomy, parts of the procedure put the patient (and surgeon) at risk of potentially catastrophic complications. As promising as the initial results of CME has been, more well-designed randomized control trials are necessary to justify the increased risks taken and effort to mount the learning curve for CME.

Keywords: Colon cancer; complete mesocolic excision (CME); extended lymphadenectomy; outcomes; morbidity

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Introduction

In the past, rectal cancer patients tended to have a poorer disease-free and overall survival than compared to those with colon cancer (1-5). However, since the advent of total mesorectal excision (TME) by Heald and Ryall, oncological outcomes of rectal cancer surgery remarkably improved (6,7). Disease-free and overall survival were comparable, and in some centres, even surpassing the results of colonic tumours (8,9). With colon cancer being the second most common cancer in women and third most in men, the results of TME has increased the interest in the recently proposed complete mesocolic excision (CME).

First described by Hohenberger in 2009, CME adopts similar principles as TME (10,11). CME, along with central vascular ligation (CVL) radically extends the

lymphadenectomy.

Hohenberger's description of CME involves three key components, namely:

- (I) Sharp dissection in the embryologically plane to remove an intact envelope of mesentery together with the corresponding lymphatic drainage;
- (II) CVL to remove apical lymph nodes and;
- (III) Resection of a sufficient length of bowel.

Hohenberger's description of sharp dissection along embryological planes between the mesocolon and retroperitoneum adheres to Heald's principle of the "Holy Plane". This ensures that the resected specimen remains within an intact "envelope of peritoneum" and with this "package", maximizing the lymph nodes removed. This "intact specimen" also prevents "tumour spillage" and avoid transcoelomic spread of cancer cells during surgery (10,11).

In the west, lymphadenectomy was traditionally performed as an extension of tumour excision. Excising the tumour was regarded as a means of local control while its associated lymphadenectomy was performed more for the purpose of completion of pathological staging and disease-related outcome prognostication (12,13).

A CVL, or “high-tie”, ensures apical lymph nodes are removed. This allows more accurate lymph node staging as we capture all possibility drainage lymphatics within the resected specimen. It is well accepted that colonic lymphatic metastatic spread follows the supplying arteries, however, it does not always obey a stepwise-fashion of spread (14-17). Thus, by including the central or apical lymph nodes within the specimen, afforded by a CVL, there is an increased chance of “stage migration”. This principle is similar to that of an extended lymphadenectomy, or D3 lymphadenectomy, which is practiced in the East, previously for gastric cancer, and increasing recommended for T3 lesions for colon and rectal cancer (12). The difference in lymphatic yield and N-staging may result in whether the patient is offered adjuvant chemotherapy and thus, may improve disease-related or overall outcomes.

In addition, some believes that leaving lymph nodes with disease behind is essentially leaving behind residual disease (14,18,19). This may have implications on local control of disease and may affect the survival. Due to this theory, CVL and extended lymphadenectomy, where apical nodes are removed within the resected specimen, was recommended to minimize the risk of leaving residual disease.

Some recent retrospective studies have demonstrated that increasing the lymph node yield to more than 22 is independently associated with improved 5-year overall survival (14,20-23). Other studies also postulated that the increased ratio of negative to positive lymph nodes is also associated with an improved disease-related survival, especially so in those with stage I-II disease (24-27).

Grading of CME

Grading of TME has been crucial in ensuring quality control (23,28). The importance of quality of resection is highlighted in the corresponding sustained improvement of rectal cancer outcomes over the years.

The accepted grading of the quality of the mesocolic dissection was based on the widely accepted Medical Research Council (MRC) CLASICC trial protocol, which was adopted from the mesorectal grading system used in the MRC CR07 trial (23,28). The colonic grading

system classified surgery based on the plane of dissection, namely the muscularis propria plane (“poor”) if there is little bulk to the mesocolon and there are presence of disruptions extending down to the muscularis propria; the intramesocolic plane (“moderate”) if there is moderate bulk with some disruption to the mesocolic fascia but does not reach the muscularis propria; the mesocolic plane (“good”) if there is an intact mesocolon with smooth peritoneal lining; and the mesocolic plane with a high vascular tie close to the aorta.

Benefits of performing CME

The main benefit of CME lies in the increased number of lymph node yield (23,24,27,29-34). With CVL and resection of even the apical lymph nodes, many studies have showed that lymph nodes attained has consistency be significantly higher than that without CME (29,35,36).

Previously, the number of resected lymph nodes was thought to be of prognostic value, however, more recently, some studies have shown that it may also have an impact on survival (14,20-27). Hohenberger demonstrated that a lymph node yield of ≥ 28 was an independent association with an improved 5-year cancer related survival (96.3% *vs.* 90.7%, $P=0.018$) in node negative patients (11). When compared to non-CME resections, about five different studies, between 2007 to 2013, have also showed that local 5-year recurrence rates have almost halved (10,14,37-39). Han *et al.* reported an improved 5-year overall survival of 70.4% compared to 53.5% for the non-CME patients, these findings were consistently replicated in other studies (38-40). Storli *et al.* and Le Voyer *et al.* have shown an increased disease-free survival from 82% to 89% for stage I-II colon cancers (21,41).

In addition, by performing a CVL and yielding more apical or central nodes, we may also have an increased chance of capturing “skipped lesions” which might affect the eventual N-stage (14,42). There will thus, be a higher chance of stage migration or more accurate staging of the colon cancer which would affect the recommendation for adjuvant therapy and thereby positively affecting the disease-free and overall survival. Another explanation could also be that by removing more lymph nodes, including the apical ones, there is a higher chance of completely resecting all “residual disease”, thereby literally preventing the metastasis process from taking place (14,18,19).

Several studies have shown that increasing negative lymph node count also correlates with survival in more

advanced staged colon cancer (14,20–23). The ratio of lymph node metastases to the total number of harvested lymph nodes, regards as the lymph node ratio (LNR), has been shown to be a better prognostic indicator than the actual N-stage, with the greater the number of negative nodes relative to metastatic nodes, the better than prognosis (24–27).

By performing CME and having an intact mesocolon with its peritoneal lining, West has shown that this also improves overall survival by 15% (24). This finding may not just be related to an increased lymph node yield, it may also be due to the fact that an intact peritoneum reduces the chance of cancer spillage during the time of surgery.

Another proposed advantage of the adoption of CME is that there will now be standardization of colonic surgery (43). Description of surgical techniques as well as the histological grading of completeness CME, similar to that of TME for rectal cancer, can lead to more accurate audits of surgeons performing colonic oncological surgery. Education or Training programmes has been shown to further improve the quality of the specimen (44–47). However, this has yet to translate to improved surgical and oncological outcomes.

Dangers of CME

CME remains a technically more challenging procedure compared to conventional colectomies. With the need for radical dissection obeying embryological planes and with dissection up to the root of the right branch of the middle colic artery and its accompanying vein, critical structures like the superior mesenteric vein (SMV) have a higher tendency to be damaged, leading to catastrophic outcomes (48,49).

Unlike that of the left colon or rectum, there is a greater anatomical variability in the right colon (50). Arterial and venous configurations within the mesentery are more variable, including different lengths of the gastrocolic trunk of Henle, multiple middle colic arteries, varying venous drainage of the middle colic vein. All these lead to an increased possibility of damaging critical structures during dissection (48,49).

The most feared intra-operative complication during CME is damage to the SMV, the main outflow of the small intestines (51,52). One study reported the incidence of intra-operative SMV damage to be 1.6% of all right hemicolectomies (48). Due to its parallel orientation in relation to the middle colic vein, the SMV can potentially be ligated or damaged either because the surgeon mistakes it for the middle colic vein/artery or due to overzealous

traction during the dissection of the middle colic trunk. Excessive retraction of the hepatic flexure medially can also lead to an avulsion of the middle colic vein near its origin along the SMV. A compromised of blood flow through the SMV can lead to congested small bowel, resulting in prolonged ileus, or more disastrous—bowel ischemia.

Other detrimental complications that can occur during CME include genitourinary dysfunction especially for rectosigmoid carcinomas with one study reporting the incidence up to 75.5% with 14.8% having permanent dysfunction (27). Sexual dysfunction is also a commonly reported complication for left sided CME. In addition, due to the more extensive dissection with CVL, there will inevitably be a higher incidence of chyle leak, even though most do not require any intervention and may resolve spontaneously (33,39,53).

Although the duration of hospitalization and healthcare cost can both increase with the occurrence of any morbidities, more worryingly for patients, this also means that time to adjuvant treatment may also be delayed (12). It is already well established that the optimal time for high risk stage II or stage III colon cancer patients to receive adjuvant chemotherapy after surgery is 4–6 weeks. Any morbidity from the surgery may result in the patients requiring a longer time to recuperate and be optimized for chemotherapy. With any delay of adjuvant treatment affecting treatment efficacy, the increased risk of morbidity may also result in an increased risk of worsening disease-related outcomes like survival.

Even with morbidity from the procedure aside, with the procedure being more technically challenging, operation time for CME has been shown to be significantly longer compared with standard colectomy (18,31–34). With a longer operative time, blood and insensible fluid losses would inevitably increase. A challenging procedure would also require a longer learning curve, and with greater usage of laparoscopic surgery for colectomies, this may result in an increased rate of conversion. Many studies on laparoscopic surgery have shown that conversion is an independent risk factor for surgical morbidity. On top of that, with increasing emphasis on healthcare cost, the longer operative time may also affect the efficiency of theatre space usage and impact health economics (12).

Laparoscopic vs. open CME

With CME well acknowledged over the years as a technically challenging procedure, it remains debatable

whether the laparoscopic approach should be performed. While Hohenberger described CME with CVL initially as an open procedure, there has been some studies which has evaluated the efficacy of the laparoscopic technique with that of the open, especially for right sided tumours (27,30,32,34,39,41,46,54-57).

Most of these studies has yielded similar operative times, safety profile and oncological as compared to the open procedure (27,30,32,34,39,41,46,54-57). The studies available have also demonstrated that some benefits of laparoscopic surgery are seen in those with CME, such as an improved length of stay (41,55,56). Mesocolon intactness, distance from high tie and lymph node yield has also been generally similar (39,41,55,57). However, some studies show that oncological outcomes like survival favours laparoscopy, which might suggest some form of selection bias between the two techniques.

The only randomized trial comparing laparoscopic and open CME from Yamamoto *et al.* revealed that the laparoscopic group has a lower complication rate and shorter length of stay which is consistent with that from other retrospective comparative studies (57).

Is it really necessary?

The proponents of CME have displayed anatomical and theoretically logical benefits of CME. The standardization of the technique of colectomies through the principles of CME, as well as the grading of resected specimen would definitely help the quality of surgery performed, which can be extrapolated to an improvement of survival for colon cancer. However, one must question its suitability to be applied to all colectomies.

Distractors of CME would still argue that the role of lymph node yield for colectomies may still be prognostic instead of curative, with the efficacy of chemotherapy and its adjuncts being shown to have improved over the years. There are many authors that question the causal relationship between lymph node yield as well as survival, citing confounding factors like age, tumour characteristics, etc. (12,15,43,58,59). Some studies have also shown that there is minimal survival benefit in patients with more than 12 lymph nodes resected (15).

Radical lymphadenectomy has also been postulated to be much easier in lower BMI, Asian patients, where most D3 lymphadenectomy are performed. Some western surgeons believe that the increased complexity, time and morbidity that CME brings may not be a worthwhile investment for

the more obese western patients (12,15,58,59).

In addition to the above, most studies encouraging the uptake of CME are have been retrospective in nature, with all the disadvantages and biases associated with a retrospective study unavoidable. There has yet to be any well-designed prospective randomized controlled trials comparing CME against conventional colectomies.

Conclusions

Whilst the purported benefits of CME remain enticing, more well-designed randomized control trials are necessary to justify the increased risks taken and effort to mount the learning curve for CME. The authors are in the opinion that CME may still benefit a group of carefully selected patients, however, more evidence is required before they will jump onto this bandwagon.

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Footnote

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