Clinical Guideline

Complete mesocolic excision for colonic cancer: Society for Translational Medicine expert consensus statement

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Abstract: Total mesorectal excision (TME), a revolutionary change and a milestone in the history of surgical treatment for rectal cancer, has been widely recognized as the gold standard and is now a routine procedure. The concept of complete mesocolic excision (CME) was proposed based on the similar philosophy as TME, aimed to achieve better surgical quality and improve the oncological outcomes of colon cancer. In recent years, many surgeons have increasingly adopted the principle and conducted clinical trials to verify the effect of CME; however, whether CME should be used as the standard surgical technique is still controversial. In this article, we reviewed and updated the literature. Experts in this field from nine countries were invited to complete a questionnaire concerning CME, with the aim to illustrate the embryological and anatomical basis and reach a consensus of the current situation and future of CME.

Keywords: Laparoscopy; colonic cancer; complete mesocolic excision (CME); anatomy; embryology; level of evidence, consensus

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Introduction

The concept of total mesorectal excision (TME), proposed by Heald over 20 years ago, marked a revolution in the radical treatment of rectal cancer (1,2). Although essentially based on non-randomized, retrospective or historical comparisons, TME is widely recognized today as the gold standard for radical treatment of middle and low rectal cancer (3). Before this concept was envisioned and popularized, carcinological outcomes for colon cancer resection were long thought to be better than those for rectal cancer (4,5), but with widespread application of TME, the gap between the two narrowed (6), indirectly indicating the TME had a positive effect on outcome. In contrast to rectal cancer, progress in terms of oncological endpoints has been slow and marginal for surgical treatment of colon cancer.

Several authors have underlined the value they gave to radical, complete intra-fascial, excision for gastro-intestinal cancer. As early as 1909, Jamieson and Dobson proposed: "no operation for malignant disease can be considered complete without the removal of lymphatic glands", and further, "The ideal operation consists in removing a considerable length of gut on each side of the growth, the primary glands, together with the vessels running to them from the gut, and the tissues in which these vessels lie—i.e., the so-called "lymphatic area" (7), interpreted as "sufficient excision of the bowels, complete resection of the mesocolon en-bloc, and central ligation of the vessels" (8). In 2003, Bokey *et al.* (9) proposed the term of "'anatomical dissection of the colon" (ADC), for what they and many others believed was already being performed in radical colonic surgery (10,11). In 2009, Hohenberger *et al.* proposed the name of complete mesocolic excision (CME) (12), corresponding to the terminology most widely used today, and that we will maintain in this report. Well beyond a simple disparity in terminology, however, the question of whether CME represents a revolutionary approach for radical surgery and can improve oncologic outcome in colorectal cancer still remains to be answered.

CME has been performed via laparotomy for many years, but morbidity has been reported to be high in non-expert centers (13-15). Minimal access colorectal surgery has matured steadily over the last decades (16): hence the natural spin-off was whether CME can be performed safely and adequately using minimal access techniques.

A previous consensus conference on CME was published in 2014 (17). The authors proposed "there are sound oncological hypotheses for a more radical approach [to colonic cancer] than has been common up to now". As for laparoscopic CME, the consensus was "Laparoscopic resection appears to be equally well suited for resection as open surgery" (17).

In this article we propose to review the embryological and anatomical rational behind CME and update the literature concerning clinical experience [only 5 references (out of 86) in the previously mentioned consensus conference were from 2013 or later] (17), in order to place CME in perspective in 2018.

The questions we intend to address include:

(I) Have the embryonic and anatomic bases of CME been sufficiently delineated?
(II) Has the CME technique been adequately described? (laparotomy, laparoscopy, robotic-assisted surgery)
(III) Is CME feasible and safe (laparotomy, laparoscopy, or robotic-assisted surgery) in all patients and by all?
(IV) What are the specific oncologic outcomes of CME?
(V) How does CME fare compared to D3 resections?
(VI) Are there specific indications for CME? (Should it be performed in all patients, is it necessary for all stages?)
(VII) What are the future perspectives for CME?
(VIII) Can CME be considered the gold standard in 2017?

Several key questions were formulated and submitted to the experts and answers compiled. An extensive literature research was performed (WU and AF). MEDLINE, Embase, PubMed, Cochrane, and Scopus libraries were queried, and all papers analyzing CME or D3 resection of colonic cancer written in English and published from 1980 were considered for inclusion. Related articles found in the reference lists of the studies retrieved for full-text review were used to complete the search.

Several revised versions of the first draft of the manuscript were circulated through electronic mail for critical analysis and modification until obtaining the final version that was approved by all authors in February 2018.

Have the embryonic and anatomic bases of CME been sufficiently delineated?

Consensus

Number of answers =15 (14 yes/1 no)

Literature review

Both the colonic mesentery and the mesorectum are derived from the dorsal mesentery. During intra-uterine growth, this mesentery surrounds the entire future colon and attaches it to the posterior abdominal wall. Treves *et al.* (18) described the dorsal mesentery of the left and right colons as being "fixed" to the retroperitoneal wall and then, by "fusing" with the retroperitoneal membrane, the left and right colonic mesenteries finally "disappeared". Since the transverse colon and the sigmoid mesocolon continue to exist even in adulthood, Treves *et al.* believed that the colonic mesentery was "discontinuous" in adults (18). Thus, in most textbooks on embryology and anatomy, the ascending and descending colons have been and continue to be described as "retroperitoneal" organs whereas the transverse colon and the sigmoid colon are considered "intraperitoneal" organs (19).

However, over the years, it became apparent that there was a natural anatomical plane between colon and retroperitoneum enabling the operator to detach the left or right colon and isolate the entire colonic mesentery, so achieving complete resection of relevant blood and lymphatic vessels, lymph nodes, and adipose tissues. Toldt *et al.* (20) described that the left and right colonic mesenteries persisted through adulthood: these mesenteries separate the retroperitoneal wall via a discrete layer of connective tissue. This proper mesangial layer, the *lamina mesenteria propria* would later be known as the Toldt's fascia (21), confirmed later by others (22,23) who argued, compared with Treves, that this idea was closer to the "real world" findings in surgical operations. In 2014, Culligan *et al.* (24) investigated the colonic mesentery with electron microscopy and confirmed the presence of Toldt's fascia between the mesothelial cell layer of the posterior aspect of the left and right colonic mesenteries and the retroperitoneum.

After extensive anatomic and histological studies, Culligan *et al.* (23,24) stated (I) the mesocolon was continuous from ileocecal to the rectosigmoid; (II) a mesenteric confluence is found at the ileocecal and rectosigmoid junction as well as at the hepatic and splenic flexures; (III) each flexure (and ileocecal junction) is composed of a complex of peritoneal and omental attachments to the colon centered on a mesenteric confluence; (IV) the proximal rectum originates at the confluence of the mesorectum and mesosigmoid and is continuous with the mesorectum; and (V) a plane occupied by Toldt's fascia separates the entire apposed mesocolon from the retroperitoneum. In other terms, the mesocolon and retroperitoneum are separated by two mesothelial layers with a connective tissue layer between them (15), corresponding to the CME plane of dissection (23).

Accordingly, the colonic mesentery described contains the blood and lymphatic vessels and nodes emanating from and going to the corresponding colonic segments (25,26). Thus, combined with more contemporary descriptions (27,28), the embryologic and anatomic bases for clear identification and excision of the entire mesocolon have been laid down.

Recently there has been a move to standardize the terminology, both of the anatomy and of the corresponding colectomies (29-31). For the former, terms such as visceral and parietal fascia, anterior renal fascia, anterior pararenal space, mesocolic plane, intramesocolic plane and muscularis propria plane surgery continue to be used. The anatomic-based nomenclature proposed by Coffey *et al.* (27) includes (I) operation titles used for resectional colonic surgery (i.e., total right mesocolectomy), (II) avoiding disruption of the mesenteric package by dissection in anatomic planes (i.e., colo- and mesofascial planes) and (III) standard dissection technique to ensure complete and intact mesenterectomy (i.e., CME).

Ignjatovic and Bergamaschi have proposed the term of "extended D3 mesenterectomy" to include the dissection of all D3 lymph nodes (31).

The vascular anatomy of the colon also has its importance as many authors have highlighted the extreme variability of arterial and venous colonic vasculature and how these variations may influence the operative tactic, and lymph node yield, particularly in CME or D3 right colectomy (31-34).

Has the CME technique been adequately described?

Consensus

Number of answers =15

- Laparotomy (15 yes)
- Laparoscopy (14 yes/1 no)
- Robotic-assisted surgery (8 yes/7 no)

Number of answers =13

- Single port (4 yes/9 no)

Literature review

CME via laparotomy has been described in detail in Australia (9), Germany (12) and the United States (35). Slight modifications have been made including:

- The timing of duodenal Kocher maneuver (9,36);
- Removal of sub-pyloric and over the pancreatic head lymph nodes (17);
- Removal of lymph nodes along the left gastroepiploic arcade (17,36).

The laparoscopic technique was detailed by several authors (37-43). The technique described by Shin *et al.* (37) is a mix of principles described by Bokey *et al.* (9), Hohenberger *et al.* (12) and the recommendations made by the Japanese guidelines (2,44).

Several authors have highlighted the importance of the starting point and order of dissection. Zhu *et al.* (39) emphasized that three anatomic planes must be found. The first surgical plane is the fascia space between the posterior aspect of the ascending mesocolon and the prerenal fascia, to the right of Toldt's space plane. The second plane separates the posterior ascending mesocolon and the anterior aspect of the pancreatic head and duodenum fascia. The third surgical plane is formed by the posterior aspect of the right-sided transverse mesocolon and the right-sided dorsal mesogastrium fusion fascia.

Likewise, Spasojevic *et al.* (45,46) defined the "D3 area": (I) the cranial border runs 5 mm proximal to the line connecting the origins of the gastrocolic trunk of Henlé (GTH) and the middle colic artery (MCA); (II) the medial border runs along the left-hand side of the superior mesenteric artery (SMA); (III) the caudal border runs 5 mm distal to the line connecting the origin of the ICA and the confluence of ileocolic vein to the SMV; and (IV) the lateral border runs 1 cm parallel to the right-hand side of the SMV.

Most authors perform CME with a lateral to medial approach, Matsuda *et al.* advised a cranial approach for easier access to the middle colic vessels (40). Benz *et al.* proposed to commence central mesentery dissection starts posteriorly at the level of the 4th part of the duodenum (41,42).

Central vascular ligation (CVL) is the cornerstone of radical excision principles (12,28,45-51). The goal of CVL is to remove as much lymph nodes and associated vascular structures in a vertical or ascending direction potentially removing lymph node metastases, as well as vascular and neural invasion of the regional drainage area (12,17).

The robotic technique was described for both right and left colectomy (16,52-55). All of these studies have suggested that robotic CME can potentially facilitate the difficulties encountered in laparoscopic CME and intra-corporeal anastomosis, especially for the novice. In the systematic review by Trastulli *et al.* (55), the authors analyzed 12 studies (total of 4,148 patients) of which 10 indicated their approach to mobilization (mostly medial to lateral), with nearly 50% of intra/extracorporeal and hand-sewn or mechanical anastomoses. They found that robotic surgery was associated with longer operative time and higher costs compared to laparoscopic colectomy, but was feasible. However, as these findings were based on observational studies including operations labeled as "colectomy" and the proportion of CME or D3 colectomies was unknown, it is impossible to extrapolate these conclusions to CME or D3.

Ma *et al.* (56) gave a detailed description of the *single port technique*, compared with their standard 5-port technique.

Is CME feasible and safe (via laparoscopy or other minimal access techniques) in all patients and by all?

Consensus

Number of answers =15

- Feasible via laparotomy (15 yes)
- Feasible via laparoscopy (15 yes)
- Feasible via robotic (13 yes/2 no)
- Feasible via single port (9 yes/5 no/1 no experience)

Number of answers =14

- Safe (acceptable morbidity/mortality) via laparotomy (14 yes)
- Safe (acceptable morbidity/mortality) via laparoscopy (14 yes)
- Safe (acceptable morbidity/mortality) via robotic (10 yes/3 no /1 no experience)
- Safe (acceptable morbidity/mortality) via single port (5 yes/7 no/1 no experience/1 not sure)
- Feasible in the obese? (8 yes/2 no/4 difficult)
- Can be performed by all surgeons? (3 yes/10 no/1 not sure)
- Should be performed by colorectal surgeons only? (7 yes/6 no: 1 not sure)
- Should be performed laparoscopic experts? (12 yes/1 no/7 not sure)

Literature review

Bokey *et al.* (57) reported the outcome of 779 of 905

patients who had a potentially curative resection with the previously described "ADC": overall, the rates of surgical complications were "low" (the exact percentage was not found) and in particular the anastomotic leakage rate was 1.6% (14/864 restorative procedures).

Is CME feasible via laparoscopy?

Continuous progress in technology [application of high-definition (HD) and three-dimensional (3D) and other camera systems, among others] has led to claims of improved precision in lymph node dissection and vascular skeletonization (36,39).

Several single institution non-comparative small studies have reported that laparoscopic CME or D3 resection was feasible and did not compromise patient safety (37,43,44,58-64).

Regarding the comparative studies, Huang *et al.* (65) provided clinical data from 102 patients with right colon cancer who underwent CME (53 by laparoscopy; 49 by open). No conversions were necessary. There was no statistically significant difference found operative time or postoperative complications, but laparoscopic CME was associated with less intraoperative blood loss, shorter duration of hospital stay.

Storli *et al.* (66) comparing the data of 251 patients who had undergone either laparoscopic or open CME, found that incidences of complications were lower in the laparoscopic CME group. West *et al.* (67) compared the specimens obtained via laparoscopic CME or open CME and found that there was no statistically significant difference between the two groups. More recently, Kim *et al.* (68) compared the results between 99 patients who underwent open surgery with 116 patients undergoing laparoscopy and found that there were fewer postoperative complications, reduced time to soft diet, and reduced length of hospital stay with laparoscopic CME.

In the only randomized trial today (69,70), including 1,057 patients, conversion to open surgery was necessary in 29 (5.4%) patients.

Chyle leakage has been cited as a possible complication associated with extensive (CME) dissection compared to the standard approach. Bae *et al.* (71) found that chyle leakage occurred less frequently in the laparoscopic group than in the open group (3.5% *vs.* 14.1%; P=0.015); they attributed this difference to the use of an ultrasound scalpel or vessel-sealing devices for peri-vascular lymph node dissection and a magnified view provided by laparoscopy.

Is CME feasible via single port?

Some studies have suggested that reduced or single port laparoscopic CME was feasible with the potential advantages of reduced postoperative pain and better cosmesis (56,72), but both were non-comparative observational studies.

Is CME safe?

Morbidity and mortality have been summarized in three systematic reviews (28,38,73) with considerable overlap. Killeen *et al.* (38) analyzed 21 non-randomized, mainly retrospective, studies including 5,246 patients: operative mortality rate was 3.2% and cumulative morbidity rate was 21.5%. About one third of the operations (33.5%) were right colectomies, more than half (52.5%) were left colectomies, while the remaining were transverse colectomies (4.9%) or unspecified (9.1%). This review included both comparative and non-comparative studies. Two years later, Athanasiou *et al.* (73) compared the outcomes of eight studies [one randomized trial (69,70) and seven non-randomized trials comparing open *vs.* laparoscopic CME or D3 resections (66,71,74-78)], all published last 10 years. Of note, only one study (76) was included in both reviews. This second review did not find any statistically significant difference in short-term mortality, anastomotic leakage, ileus or deep/surgical site infection/abscess. There was a trend for longer operative time (P=0.05) and shorter duration of hospital stay (P=0.09) with the laparoscopic approach. Laparoscopic right hemicolectomy had a lower surgical site infection rate (P=0.005) compared with open CME. Siani *et al.* (28) reviewed a mix of comparative and non-comparative studies, and finally did not come to any groundbreaking conclusions. All three reviews concluded that, based on the current evidence in 2014 and 2016, the laparoscopic technique appeared to be feasible and at least as safe (morbidity not statistically significantly different) as the open technique whether used to perform D3 lymphadenectomy or CME for colonic cancer. The only randomized trial (69), however, observed that thirty day morbidity was statistically significantly lower in the laparoscopic group [76/533 (14.3%) *vs.* 117/524 (22.3%)] probably explaining why duration of stay was shorter in this group.

One further study (not included in any of the three systematic reviews), a non-randomized study from Korea, Kim *et al.* (68), comparing elective CME either by open surgery (n=99) or laparoscopy (n=116) found that laparoscopic CME conferred short-term benefits in terms

of lower rates of postoperative complications, reduced time to soft diet, and reduced length of hospital stay.

Siani *et al.* recently reported one of the largest series (600 cases) of laparoscopic right colectomy with (79): mortality was 0.5% while morbidity was 35.5%. Readmission and reoperation rates were 5.1% (31 patients; 81% for Dindo-Clavien grade I and II complications) and 2.5% (10 cases for anastomotic leakage and 5 for intestinal obstruction), respectively.

Chyle leakage has been cited as a possible complication associated with extensive (CME) dissection compared to the standard approach. Bae *et al.* (71) found that chyle leakage occurred less frequently in the laparoscopic group than in the open group (3.5% *vs.* 14.1%; P=0.015); they attributed this difference to the use of an ultrasound scalpel or vessel-sealing devices for peri-vascular lymph node dissection and a magnified view provided by laparoscopy.

Is CME safe with robotics?

While laparoscopic colectomy has been compared to robotic colectomy in several studies and summarized in meta-analyses (53,55), there is little if any literature specifically comparing laparoscopic to robotic CME or even D3 colectomy. The reduction of morbidity could not be shown in right colectomy (52); better vision was claimed for left colectomy but there was no real comparison (54). In their systematic review, Trastulli *et al.* (55) found that robotic surgery was associated with less intraoperative blood loss (MD –16.82, P<0.00001) with a lower incidence of overall postoperative complications (OR 0.74, P=0.02) and wound infections (RD –0.02, P=0.03) compared to laparoscopic colectomy. No statistically significant differences were found in the anastomotic leak, or conversion to open surgery rates. However, once again as these findings were based on observational studies only, and the proportion of CME or D3 colectomies was unknown, it is impossible to extrapolate these conclusions to CME or D3.

Is obesity a problem?

One argument often put forward in the discussion why laparoscopic D3 resection (or by extension laparoscopic CME) is performed more often in the East (*vs.* the West) has been the BMI (14). Several papers have looked at the influence of obesity on the outcome of colectomy but few have specifically concerned laparoscopic CME (9,80-86). In a systematic review and meta-analysis of 13 observational studies (again without any specific reference to CME) looking at the influence of obesity (defined as BMI ≥30 kg/m^2 in the Western population, ≥25 kg/m^2 in the Asian population) on laparoscopic colorectal resections (80), the authors concluded that laparoscopic colorectal cancer operations were more technically challenging in the obese as the conversion and postoperative complication rates were higher compared to non-obese patients. Notwithstanding, there were no statistically significant differences found between the two groups as concerned oncologic adequacy.

Of interest, however, when they compared the Asian publications (where the proportion of D3 resections should be high), they also found increased lymph node retrieval in the non-obese compared to the obese. For the authors, this observation may be due to the increased technical difficulty in obese compared to non-obese patients or due to an inherent difference in *in vivo* lymph nodes between these two groups. To date, the association between obesity and adequacy of lymph node retrieval remains unclear (86).

Zou *et al.* (87) recommended the lateral to medial (caudal to cranial) approach in the obese with a thick mesentery, stating that the retroperitoneal approach to the vessels was easier from behind.

Functional outcome

In the prospective multicenter trial ("Safe Radical D3 Right Hemicolectomy for Cancer through Preoperative Biphasic Multi-detector Computed Tomography") in which all soft tissue surrounding the superior mesenteric vessels from the level of the middle colic artery to that of the ileocolic artery was removed, Thorsen *et al.* (88) compared bowel function [Diarrhea Assessment Scale (DAS)] and quality of life (Gastrointestinal Quality of Life Index (GIQLI) in two consecutive cohorts (n=49 in each) undergoing right colectomy, one with and the other without D3 extended mesenterectomy. The authors concluded that small bowel denervation after right colectomy with D3 extended mesenterectomy leads to increased bowel frequency but does not impact gastrointestinal quality of life and as DAS scores bowel frequency scores were lower when jejunal arteries were cranial to the D3 dissection area, individual anatomical variants can affect postoperative bowel function differently despite standardized surgery (88).

It is difficult to state whether CME (or D3) can be performed adequately, safely and via laparoscopy in nonspecialized centers. In Denmark, this was the case for three of the four units specialized in colorectal surgery

and may explain some of the differences observed in outcome (13). Indeed, many surgeons in the Western sphere have been reluctant to apply D3 dissection in the treatment of colorectal cancer considering the surgical difficulty and due to increased postoperative complications (13-15) including more splenic (3.2% *vs.* 1.2%; P=0.004) and superior mesenteric vein (1.7 *vs.* 0.2%; P<0.001) injuries, sepsis with vasopressor requirement (6.6% *vs.* 3.2%; P=0.001) and postoperative respiratory failure (8.1% *vs.* 3.4%; P<0.001) (13).

What are the specific oncologic outcomes of CME?

Consensus

Number of answers =15

- Better lymph node yield (12 yes/1 no/2 not sure)
- Extended length of resection (9 yes/4 no/2 not sure)
- Better staging (11 yes/2 no/2 not sure)
- Lower local recurrence rates (10 yes/3 no/2 not sure)
- Improved survival (10 yes/3 no/2 not sure)

Literature review

Hohenberger *et al.* [1,438 colon cancer patients of which 1,329 were followed for a median of 103 (range, 1–335) months] in their historical comparison, found that 5-year recurrence rate decreased from 6.5% [1978–1984] to 3.6% [1995–2002] and 5-year survival increased from 82.1% [1978–1984] to 89.1% [1995–2002] (12).

However, the duration of the Hohenberger study was 24 years (1978–2002 with the observation period ending in 2006), during which the emergence of neo-adjuvant, adjuvant and targeted therapies, evolving operative and anesthesia techniques, peri-operative care may potentially have impacted the results. Moreover, were excluded from analysis those patients who died, those with unknown tumor status, those with associated inflammatory bowel disease or familial adenomatous polyposis coli, R1 resections, patients with synchronous or previous cancers, patients having undergone neoadjuvant therapy or those where histological data were missing (at least 200 patients).

Olofsson *et al.* (89) identified 2084 patients with right-sided cancer in the Swedish Colorectal and found no statistically significant differences in 3-year overall survival, 3-year disease-free survival and local recurrence rate according to the level of ligation of the ileocolic, middle colic and right colic vessels. Only a limited number of case studies (9,12,79,90) and one comparative study (91) have suggested that CME could significantly lower local recurrence rates and increase survival. Of note, in the retrospective large-scale study in Denmark (91), the 4-year disease-free survival rate (all UICC stages confounded) in the CME group was 85.8% (95% CI: 81.4–90.1), which was significantly longer than that in the conventional resection group (75.9%) (72.2–79.7) (P=0.0010). Multivariate Cox regression analysis indicated that CME was a significant and independent prognostic factor for a higher disease-free survival rate, and this finding also applies to patients with UICC stage II/III colon cancer (91).

In the ADC report by Bokey *et al.* (57) the local recurrence rate was 2.1% (95% CI: 1.3–3.4), the systemic recurrence rate was 10.2% (95% CI: 8.1–12.7), 5-year overall survival was 76.2% (95% CI: 73.0–79.0) and cancer-specific survival rate was 89.8% (95% CI: 87.3–91.9). R0 status was confirmed in 883/905 patients (97.6%; 95% CI: 96.4–98.5). Of note, the width of the confidence intervals in this study was quite narrow, attesting to the robustness of the results, but it remains a single-center (although expert) non-comparative experience.

In another non-randomized historical comparison, Galizia *et al.* compared the outcomes of patients who had undergone CME for right colonic cancer (n=45) to a historical group having undergone conventional right hemicolectomy (n=58) (92). At 4-year follow-up, local recurrence never developed in the CME but in 21% of the historical control group, disease-specific survival improved (93.3% *vs.* 75.9%; P=0.0356), while there was no statistically significant difference found in distant metastasis (13.3% and 13.7%, respectively). There were, however, statistically significantly more early stage cancers in the CME group. Nonetheless, the bias of a historical comparison does not allow any conclusions.

In conclusion, it is not possible today to state with formal evidence that oncological outcomes are better than those for traditional colectomy; more evidence from robust studies is needed to clarify the long-term effectiveness of CME.

Open vs. laparoscopic resections

In the meta-analysis performed by Athanasiou in 2016 (73), no statistically significant difference was found in overall survival, disease-free survival, local recurrence and distant

metastases between the two approaches. However, of note, once again, no distinction was made between the CME and D3 resections that were analyzed together.

The long term results of the only randomized trial comparing laparoscopic and open CME (non-inferiority study) were published just recently (70): the authors were unable to show that overall survival (main endpoint) after laparoscopic D3 was not inferior to open D3 with any statistically significant difference. Because overall survival did not differ statistically significantly between the two groups, and was actually better than expected, the authors concluded that laparoscopic surgery with Japanese D3 dissection appeared to be acceptable as a treatment option for patients with stage II or III colon cancer.

Quality of the specimen

Similar to the grading system of completeness of TME excision (5), Quirke, West and collaborators have developed a grading system based on the grading system used in the MRC CR07 trial for rectal cancer (93):

- Mesocolic plane of resection: "Good" surgery, performed along mesofascial interface; producing intact, inviolate mesocolon with a smooth peritoneal surface;
- Intramesocolic plane of resection: "Moderate" characterized by irregular breaches in the mesocolon, none reaching the muscularis propria of the colon;
- Muscularis Propria plane of resection: "Poor" characterized by disruption of the mesocolon, with breaches the visceral muscularis propria.

West *et al.* (26) assessed 399 specimens obtained from surgeries for colon cancer and found that specimens resulting from dissection along the colonic mesentery plane had a statistically significantly larger area of resected mesentery and distance between the mesenteric margin and proper muscular layer than in the specimens obtained via surgeries that had damaged the colonic mesentery or entered the proper muscular layer (i.e., incomplete colonic mesentery). Based on these findings, West *et al.* elaborated a tissue morphometry procedure (25) in which the distance from the tumor and the closest bowel wall to the high vascular ties, the length of the large and small bowel, and the area of mesentery resected are quantified using the CellD image analyzer (Olympus, Tokyo, Japan) of high-resolution digital color photographs. West *et al.* (67) then compared the quality of specimen from laparoscopic CME to open CME in published series by grading the plane of resection (26) and tissue morphometry (25). They found (I) the quality of the specimen was similar between groups, although the lymph node yield was statistically significantly lower in the laparoscopic group (difficult to explain given the similarities in specimen quality); (II) intact ("good") colonic mesentery or proper muscular layer was statistically significantly associated with longer 5-year survival (67).

However, the relation between the quality of CME and increased survival remains unclear (94).

In addition, quality assessment of the specimen should be unified. The resected colon and mesentery should be measured by an experienced surgeon prior to fixation.

Gouvas *et al.* also compared specimens with morphometric analysis between laparoscopic and open CME (95); specimen quality was not statistically significantly different although there were concerns about the quality of laparoscopic resection for hepatic flexure and transverse colon tumors (shorter length from the tumor to the vascular tie, fewer lymph nodes harvested and a shorter bowel resection).

Lymph node yield

West *et al.* (94) observed that, compared with the conventional operation for colon cancer, CME was associated with more lymph nodes being removed and analyzed.

In the ADC study (57), the median lymph node count was 15 (range, 0–113). R0 status was confirmed in 883/905 patients (97.6%; 95% CI: 96.4–98.5). As noted previously, results can be considered as robust because of the narrow width of the confidence intervals.

Anatomically correct D3 resection according to the "D3 space" (45,46) implies posterior vertical compartment removal, technically more challenging when the ileocolic artery crosses the superior mesenteric vein posteriorly. According to these studies, addition of the lateral vertical compartment lymphadenectomy increases the lymph node yield by 5 to 6 nodes.

In their systematic review, Gouvas *et al.* (96) found that CME produced a longer central pedicle that contained more lymph nodes than conventional surgery for colon cancer, but, as others, concluded that there is limited evidence that CME improves long-term oncological outcomes.

For tumors located in the right colon, the lymph nodes along the ileum, right colon and the root of the middle colon vessels should be completely dissected (97). For

tumors located at the hepatic flexure, the lymph node-positive rate at the head of the pancreas and gastric curvature has been reported to be 5% and 4%, respectively (97). Therefore, extended resection should transect the right gastro-epiploic vein to remove lymph node station 6 and divide and remove the gastroepiploic arteries along the greater curvature of stomach, i.e., 10–15 cm away from the resected tumor along the gastro-epiploic arcade (97).

In their systematic review (98), Bertelsen *et al.* were not able to find any statistically significant relationship between extended lymph node dissection and better oncological outcome.

The non-randomized comparative study by Kim *et al.* (68) found that pathologic (specimen lengths, resection margin distance, number of lymph nodes, and R0 resection) and oncologic outcomes of the laparoscopic CME group were comparable to open CME.

In the recent series of 600 consecutive patients undergoing laparoscopic right colectomy with CME, Siani *et al.* (90) found that survival was poor (27.7%) when the apical nodes were positive.

In summary, CME has been found to be associated with high disease-free survival in patients with stage I–III colon adenocarcinoma in several studies (57,90,91), but causality cannot be inferred as truly unbiased comparisons to "conventional" techniques, taking into account all confounding factors, are lacking. Moreover, no inter-observer or intra-observer validation of outcomes was available.

Notwithstanding several papers describing the lymph node anatomy [most being cadaveric (45,46)], and the feasibility of extended lymph node retrieval via laparoscopy or robotic approaches, further controlled studies are needed to show that the increased lymph node removal in CME leads to improved prognosis, less local recurrence and better overall survival (98) in unbiased high-quality research (96).

How does CME fare compared to D3 resections?

Consensus

Number of answers =14

- Better lymph node yield (4 yes/10 no)
- Extended length of resection (7 yes/7 no)
- Better staging (2 yes/12 no)?
- Lower local recurrence rates (3 yes/11 no)?
- Improved survival (3 yes/11 no)?

Literature review

Japanese surgeons have advocated central node dissection for many years (99). According to the Japanese guidelines, D3 dissection is based on anatomical lymph node dissection at the root of the tumor-feeding artery, and the longitudinal length of large bowel to be resected is determined according to the location of the tumor in relation to the feeding artery (100). CME requires the same high ligation of corresponding vessels and thorough lymph node dissection, as described in D3 resection (14). Moreover, CME puts the emphasis on preservation of anatomic (embryonic) planes with intact mesenteric fascia to which one adds CVL (12). The D3 Japanese guidelines follow the 5–10 cm rule to determine the extent of associated bowel length whereas the length of bowel resected in CME is determined according to the vascular territory (2). While these two techniques differ in their concept, and essentially in the extent of bowel resection, they have the same purpose (67,69,96).

Paquette *et al.* performed a literature search to determine the survival benefit of proximal vascular ligation colon cancer and made pertinent differentiations between the two techniques [Japanese Society of Cancer of the Colon and Rectum recommendations (2) and CME combined with CVL] (101) with regard to the extent of lymph node dissection. The D3 dissection includes the lymph nodes along (D2) as well as those at the junction and along the root vessel. This means that D3 dissection for right-sided tumors includes lymph nodes along the anterior aspect of the SMV and SMA (central lymph nodes) and for left-sided tumors includes lymph nodes around the inferior mesenteric artery (IMA) while CME and CVL implies complete dissection of the lympho-adipose tissue around the SMV and SMA for right sided tumors (after Kocher maneuver and takedown of the mesenteric attachments to the duodenum and uncinate process of the pancreas), removal of the gastro-epiploic lymph nodes for tumors of the hepatic flexure, and central ligation of the middle colic and right gastroepiploic vessels (with preservation of the pancreaticoduodenal artery) for transverse colon tumors (12). The precisions regarding lymph node dissection around and behind the origin of the middle colic and ileocolic vessels proposed by Spasojevic (45,46) remains to be added to these lymph node protocols.

West *et al.* compared the specimens of CME (from Erlangen, Germany) to D3 resections (from Tokyo Medical and Dental University and the Tokyo Metropolitan

Komagome Hospital) (94) and found that, although the mesocolic plane resection rates were high in all series, the Japanese D3 specimens were statistically significantly shorter (162 *vs.* 324 mm, P<0.001), resulting in a statistically significantly smaller amount of mesentery (8.3 *vs.* 18.0 mm^2, P<0.001) and nodal yield (median, 18 *vs.* 32, P<0.001), while the difference in the distance between the high vascular tie and the bowel wall (100 *vs.* 99 mm) was not found to be statistically significant (P=0.605).

In fact, as the definitions of D2, D3 and CME differ somewhat in the literature, it is difficult to understand what the real differences are from the technical viewpoint. Some teams do not make any distinction between the two (14,15,69). Lu *et al.* on the other hand, defined CME as D2 plus removal of the lymphatic and adipose tissue and not only the connective tissues around the SMA but include removal of the whole anterior and posterior aspects of the mesocolon and the lymphoadipose tissues covering the anterior surface of the pancreatic head and neck (102). Again, one of the best definitions of the distinction between the two is provided in the review article by Paquette *et al.* (101).

Are there specific indications for CME?

Consensus

Number of answers =13

- For all locations (10 yes/3 no)
- Right-sided (12 yes/1 no)
- Transverse (including flexures) (12 yes/1 no)
- Left-sided (not sure 13)

Number of answers =9

- For all stages? (4 yes/5 no)
- If no which_____

for metastatic colon cancer, not for early stage, only for clinical stage II & III and IV with curative intent, stage IV should be excluded, only for stage II and III.

Literature review

The 2005 Japanese practice guidelines recommended dissecting Group 3 nodes for cStage II or III colorectal cancer patients (97,99), and since that date, a nation-wide survey of the proportion of patients who underwent D3 LN dissection among Stage II/III patients with CRC found a steady increase in the uptake of the D3 procedure.

In 2012, the Japanese Society for Cancer of the Colon and Rectum (JSCCR) (2) proposed the surgical indications of D3 dissection in its guidelines on the treatment of colorectal cancer as follows (2): D3 lymph node dissection should be performed in patients with lymph node metastasis recognized before or during the surgery or if pre- or intra-operative evaluation indicates that the tumor infiltration has reached the proper muscular layer or deeper.

In 2010, the Chinese Guidelines on the Diagnosis and Treatment of Colorectal Cancer (issued by the Chinese Ministry of Health) (103) also indicated that D3 lymph node dissection should be performed for $T_{2\text{-}4}N_{0\text{-}2}M_0$ colon cancer. In contrast, CME can be proposed for all stages, $T_{1\text{-}4}$, N_x, M_0.

Although it has never been shown formally, some Asian authors claim that D3 colectomy provides better survival in patients with T3 and T4 colonic cancer (104). Whether this can be extended to CME remains to be shown. For Storli *et al.* (105), survival was improved even for node negative disease (TNM stages 1 and 2): 3 year overall survival and disease free survival was statistically superior in patients undergoing CME *vs.* "mid-mesenteric" or D2 colectomy (88.1% *vs.* 79 %, and 82.1% *vs.* 74.3%, respectively). Of note, however, in-hospital postoperative mortality was high (8.6% *vs.* 2.8%) in the D2 colectomy group, perhaps biasing long-term survival, there was an obvious selection bias in patients undergoing CME, the study was retrospective and lymph node retrieval for D2 colectomy may have differed between the two hospitals. Moreover, there were no statistically significant differences in local or overall recurrence between the groups.

According to West *et al.* (25), CME could be expected to be most important and extend long-term survival in patients with positive lymph node findings for stage III colon cancer.

Søndenaa *et al.*, in their 2014 consensus statement (17), proposed that while "there are sound oncological hypotheses for a more radical approach [to colonic cancer] than has been common up to now", "however, this may not necessarily apply in early stages of the tumour stage."

Several authors have found that up to 5–11% of colon cancer patients have central lymph node metastasis, among which 0.8% may be skip metastasis (106,107). In terms of lymph node characteristics, micrometastases (<2 mm) and free clusters (<0.2 mm) of tumor cells can exist within the colonic mesentery lymph nodes (108). Furthermore, 1–5 micrometastases may be found in a single tumor specimen. This may explain why some authors have found increased survival in N0 patients undergoing extended lymph node resection (109,110). In their recent non-

comparative series of 600 consecutive patients, Siani *et al.* (90) found that while overall survival was 83%, survival in stage II, IIIA/B and in stage IIIC with negative apical nodes was 88.7%, 72.4%, and 71.4%, respectively. Conversely, survival was 27.7% in stage IIIC patients when the apical nodes were positive, suggesting once again that CME may not be the entire answer.

What are the future perspectives for CME?

Literature review

In view of the morbidity associated with extended mesenteric resection, and the absence of formal proof of carcinological improvement, further trials are necessary to define if there is a specific population that might best benefit from extended resections.

Several other studies are underway. The objectives of the T-REX study (International Prospective Observational Cohort Study for Optimal Bowel Resection Extent and Central Radicality for colon cancer) (111) are to clarify the actual status of metastatic LN distribution in colon cancer and also provide reliable evidence regarding the optimal length of bowel resection and the extent of central LN dissection (secondary endpoints). Currently underway (1,410 patients recruited up to November 2016) the goal is to include 4,000 patients between May 30, 2013 and Dec 31, 2017. Results are awaited in 2018.

The RELARC randomized trial (102) aims to investigate whether laparoscopic colectomy with extended lymphadenectomy (CME) could improve the oncological outcomes of patients with right-sided colon cancers, compared with D2 lymphadenectomy. This superiority, prospective, multicenter, randomized, two-arm, parallel-group, single-blind clinical trial is expected to last 7 years, including 4 years for recruiting patients and 3 years for follow-up.

Other unanswered questions include: should 3D vascular mapping be mandatory before extended D3 resection (32, 34,112)? The extreme anatomic vascular variability and the danger that can arise when the GCT of Henlé is injured might well justify the precaution (32,46). Additionally, if one admits that one of the key points of CME is to try to eliminate all lymph node deposits, then there may be a role for Indocyanine Green enhanced fluorescence to identify metastatic lymph nodes during operation. Ozben *et al.* (113) and Nishigori *et al.* (114) have described the technique of lymph node dissection under the control of real-time visualization of the lymph nodes and lymphatic circulation to ensure complete metastatic lymph node clearance during CME. This can be performed with the robotic system as well as with conventional laparoscopy. Indocyanine green angiography may have an increasing role in colorectal surgery, not only to map the vascular territories and their distribution but also to ensure the adequate vascularity of the distal, and sometimes also, the proximal segments to be anastomosed (115,116). Johnson *et al.* described their experience in 2016 (117) concluding that fluorescence angiography may provide helpful information when the status of one of the major colonic vessels is unknown or impaired.

Can CME be considered the gold standard in 2017?

Consensus

Number of answers =14 (10 yes/4 no)

Literature review

CME can be performed either via laparotomy, laparoscopically or with single port or robotically-assisted techniques. Technical advances (high-magnification and resolution-based images) have underscored the possibility and the importance of adhering to fundamental surgical planes in order to perform a safe and effective surgery. Surgical specimens can meet the pathological requirements for radical treatment. Although further studies are warranted to identify the potential advantages (e.g., long-term efficacy) of CME for colorectal cancer, it, even as a concept, has the potential to promote the improvement and standardization of surgical techniques (47). As was the case a few decades ago, the concept and the practice of TME was adapted widely without formal proof that it improved cancer outcomes. Even if no one today would challenge the concept, the technique, or the outcomes published, the results observed may not be anything more than a pseudo "Hawthorne" effect (we do things with more application because we have been told that it works). If improved overall survival for CME can be shown across the board, in the same way as happened for TME, it may indeed be the beginning of a new era in the radical treatment of colonic cancer.

In accordance with Willaert and Celen (118) there is no high quality evidence to advocate routine implementation

of CME. The reasons are (I) local recurrence may result from systemic disease, more often than from incompletely removed lymph nodes; (II) there is no proof that higher nodal counts improve outcome; (III) metastasis to locoregional nodes probably occurs early and is stochastic rather than stepwise.

However, in harmony with the tenors of open CME (9,12), and as stated by Kim *et al.* (68), because of fewer postoperative complications, reduced time to soft diet, and reduced length of hospital stay, laparoscopic CME could be considered as a routine elective approach for right-sided colon cancer, if indeed, improved survival and/or less local recurrence can be demonstrated.

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Footnote

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