

Extent of surgery in cancer of the colon: Is more better?

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is rare in CC and usually a manifestation of systemic disease. Secondly, although CME may increase nodal counts and therefore staging accuracy, this is unlikely to affect survival since the observed relationship between nodal counts and outcome in CC is most probably not causal but confounded by a range of clinical variables. Thirdly, several lines of evidence suggest that metastasis to locoregional nodes occurs early and is a stochastic rather than a stepwise phenomenon in CC, in essence reflecting the tumor-host-metastasis relationship. Unsurprisingly, therefore, comparative studies in CC as well as in other digestive cancers have failed to demonstrate any survival benefit associated with extensive, additional or extra-mesenteric lymphadenectomy. Finally, routine implementation of CME may cause patient harm by longer operating times, major vascular damage and autonomic nerve injury. Therefore, data from randomized trials reporting relevant endpoints are required before CME can be recommended as a standard approach in CC surgery.

Key words: Colon; Adenocarcinoma; Surgery; Cancer; Mesocolic excision; Lymph node count

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Abstract

Since the introduction of total mesorectal excision as the standard approach in mid and low rectal cancer, the incidence of local recurrence has sharply declined. Similar attention to surgical technique in colon cancer (CC) has resulted in the concept of complete mesocolic excision (CME), which consists of complete removal of the intact mesentery and high ligation of the vascular supply at its origin. Although renewed attention to meticulous surgical technique certainly has its merits, routine implementation of CME is currently unfounded. Firstly, in contrast to rectal cancer, local recurrence originating from an incompletely removed mesentery

Core tip: The extent of surgery in cancer of the colon is a matter of debate. Proponents of complete mesocolic excision (CME) argue that more extensive en bloc removal of the lymph node harboring mesentery may improve recurrence free survival. Here, we critically review the relevant clinical data and colorectal cancer biology and conclude that at present, routine implementation of a more extensive resection such as CME is unjustified outside the setting of controlled clinical trials.

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INTRODUCTION

Colon cancer (CC) is the third most common cancer in both men and women in the United States^[1]. Surgery is the mainstay of treatment of non-metastatic CC. Since the nineteenth century, little has changed regarding the general surgical approaches used in CC. In contrast, the surgical treatment of rectal cancer has seen considerable changes over the past three decades. Since the general adoption of total mesorectal excision (TME) in mid and low rectal cancer, the formidable problem of locally recurrent disease has been drastically reduced^[2]. In addition, TME entails using embryological planes, which allows avoiding tumor spill, blood loss and autonomic nerve damage.

Recently, the concept of complete excision of the mesenteric envelope was adapted for colon cancer as complete mesocolic excision (CME)^[3,4]. Two principles underlie CME. Firstly, the entire embryological mesocolon is separated from the parietal and retroperitoneal planes and removed in its entirety, avoiding breaching the surface of the mesentery. Secondly, the feeding artery and draining vein(s) are ligated as close as possible to the main vascular trunk. As an example, when performing a right hemicolectomy, the ileocolic vein is ligated flush to the superior mesenteric vein rather than at a conveniently located more proximal location.

Proponents expect that standard adoption of CME will result in a lower local recurrence rate and improved survival in CC^[5,6]. Data from Erlangen suggest that routine application of CME results in an excellent oncological outcome with 5 year cancer specific survival rates of 91.4% in stage II and 70.2% in stage III CC^[3]. However, these benefits remain untested in comparative prospective trials and some have argued that, not unlike TME, CME really is a new nomenclature for a sound surgical approach for CC that many have been implemented for a long time in their practice^[7]. More importantly, in view of recent insights in colorectal cancer biology, the hypothesis that removing more lymph node containing mesentery is causally related to improved survival seems questionable^[8].

Here, we critically review several aspects of colon cancer biology and treatment that impact on the potential of CME as a tool to improve the outcome for colon cancer patients. In essence, CME combines two imperatives: mobilization of the intact mesentery along anatomical/embryological planes and high (proximal) vessel ligation in order to maximize nodal counts. Since most colorectal surgeons will agree that the former aspect constitutes nothing more than “good surgical practice”, we shall focus on the latter.

BIOLOGY OF NODAL SPREAD IN COLON CANCER

Historically, two models have been proposed to explain nodal spread of epithelial cancer. In the first stepwise model championed by Halsted, nodal metastasis temporally

and spatially precedes distant spread and invaded nodes are regarded as temporary “barriers” or “incubators” that eventually will seed cancer cells further down the lymphatic chain and/or into the systemic circulation^[9]. Assuming this scenario is real, efforts at removing a maximal number of (possibly) invaded nodes may prevent further tumor spread and result in a survival benefit. The parallel spread model proposed by Fisher considers distant metastasis to occur very early in the natural history of the disease^[10]. In this model, lymph node metastasis is seen as a marker of the biological behavior and malignant potential of the disease and efforts to remove affected nodes will not impact survival. Several lines of evidence support the concept of parallel progression in CC. Firstly, circulating tumor cells in the peripheral blood of colorectal cancer patients have been found in every stage of the disease, independently of methods and marker(s) used^[11]. In a recent meta-analysis, molecular detection of tumor cells in regional nodes was found to predict disease recurrence and worse survival in node negative colorectal cancer^[12]. Secondly, the estimated growth rates of primary CC and liver metastases are comparable^[13]. Given the average time frame between resection of the primary and the appearance of metastatic disease in CC, the growth rate of metastases would need to be much higher if the linear progression model was correct. Thirdly, genetic analysis at the chromosomal, genomic and DNA level demonstrates a striking disparity between primary CC cells, disseminated tumor cells and cells populating established metastases, suggesting early dissemination of genetically less-advanced clones^[14]. Finally, the linear, stepwise progression model of lymphatic spread is incompatible with the observation that: (1) the number of invaded nodes is of greater prognostic significance than their exact location in the mesentery; and (2) the location of the first draining node when using sentinel mapping techniques is unpredictable and often at a considerable distance from the primary^[15-17]. In addition, several studies have shown that the presence of invaded nodes at the root of the mesentery is associated with a significantly higher risk of systemic spread and surgical removal of these nodes is therefore unlikely to affect the patient's survival^[18].

Taken together, these data suggest that lymphatic spread in CC is a stochastic rather than a stepwise phenomenon and may occur early during tumor progression. Nodal positivity reflects the tumor-host relationship and thus the biological behavior of the disease. Therefore, surgical efforts at maximal nodal clearance are unlikely to affect the risk of systemic spread.

NODAL COUNTS IN THE RESECTED SPECIMEN AND SURVIVAL IN COLON CANCER: CORRELATION VS CAUSALITY

Over the past decade, numerous clinical studies have reported a positive correlation between survival and the

Table 1 Variables confounding the association between nodal count and survival in colorectal cancer

Confounding variables		Effect on LNC
Patient characteristics	↑Age, ↓socioeconomic status, non-Caucasian race	↓
	gender, body mass index	?
Tumor characteristics	↑Tumor diameter, T stage, overall cancer stage, lymphocytic infiltration, MSI-H phenotype	↑
	↑Tumor grade	↓
	Mucinous differentiation, lymphovascular and perineural invasion	?
Surgical factors	Open <i>vs</i> minimally invasive resection	None
	Colorectal <i>vs</i> general surgeons, advanced fellowship training	↑
	Surgeon volume	?
Institutional factors	High-volume centers, teaching hospitals, significant CC surgical practice, academic pathology laboratories	↑
	Preoperative radiochemotherapy for rectal cancer	↓
Factors related to pathology examination	Xylene/alcohol fat clearance, embedding of the entire mesentery <i>vs</i> traditional dissection, <i>ex vivo</i> intra-arterial methylene blue injection, tattooing of neoplasms during colonoscopy, pathologists interested in CRC, use of a standardized protocol to evaluate CC specimens	↑

LNC: Lymph node count; CC: Colon cancer; CRC: Colorectal cancer; MSI: Microsatellite instability.

lymph node count (LNC), *i.e.*, the number of lymph nodes examined by the pathologist^[19-24]. In addition, the lymph node ratio, defined as the ratio of the number of invaded nodes over the number of examined nodes, is increasingly recognized as an independent prognosticator in stage III disease^[25].

It is therefore tempting to imply that a causal relationship exists between the removal of mesenteric nodes and survival. In stage II patients, increased survival may in theory be the result of more extensive removal of lymph nodes harboring isolated tumor cells or micrometastases, which could impact survival by causing either locoregional or systemic recurrence. The presence of metastatic deposits in regional lymph nodes was recently shown to be an adverse prognostic factor in node-negative CRC^[12]. Similarly, in stage III, removal of grossly invaded nodes could prevent either locoregional recurrence or further systemic tumor spread. In reality, however, the relationship between LNC and survival is confounded by a range of clinicopathological variables (Table 1) and a real therapeutic effect of removing mesenteric nodes seems to play a minimal, if any, role^[26]. Several authors have compared limited with extensive surgery for CC (Table 2). In a French multicenter prospective trial, Rouffet *et al*^[27] randomly allocated 260 CC patients to either a left segmental colectomy or a left hemicolectomy. Only the length of tumor-free margins of colon removed was significantly greater after left hemicolectomy. Survival in both groups was, however, similar. In a retrospective single center study, Tagliacozzo *et al*^[28] compared extended mesenteric excision (up to the origin of the mesenteric trunk combined with retropancreatic lymphadenectomy) with standard right hemicolectomy. Although radical resection resulted in a significantly higher LNC, no difference in the number of positive nodes or survival was found. Similarly, a prospective single center trial by Tentes *et al*^[29] compared periaortic lymph node resection for left-sided CC with conventional surgery in 124 patients. Again, despite a significantly higher LNC after radical resection, no significant difference in number of involved nodes or

survival was noted, although improved survival in stage III patients was found after radical resection ($P = 0.04$). A two-center study reported by West *et al*^[30] observed a greater LNC after CME compared to conventional hemicolectomy. This observation was not associated with a difference in the rate of involved nodes. Survival data were not reported in this study. A running prospective, non-randomized, single-center study will assess both procedures in terms of overall survival and disease-free survival (NCT01724775). Hashiguchi *et al*^[31] recently reported retrospective data on 914 T2-T4 CC patients in whom lymph nodes were anatomically mapped and classified as horizontal nodes (epicolic/paracolic nodes), mesocolic nodes and nodes at the origin of the main arterial trunk. They found that resection of main trunk nodes did not improve either staging accuracy or survival compared to resection of pericolic and mesocolic nodes alone. Similarly, Ikeda *et al*^[32] found no difference in survival of separate cohorts of stage II and stage III rectosigmoid cancer, whether or not the main trunk ("apical") nodes were prophylactically resected. In addition, a recent meta-analysis demonstrated that performing a high arterial ligation in CC (which may be assumed to result in removal of apical nodes) does not improve overall survival (OR 0.45-2.22)^[33]. Together, these data fail to demonstrate that extensive surgery or extramesenteric lymphadenectomy improves survival in CC, which argues against a surgical therapeutic effect as an explanation of the observed relationship between LNCs and survival.

LOCAL RECURRENCE IN COLON CANCER

Historically, local recurrence has been a frequent and dreaded manifestation of disease recurrence after rectal cancer surgery. This propensity to recur locally is explained by the anatomical confinement of the (meso)rectum by the bony pelvis, bladder and genital organs and by the fact that the mesorectum may harbor tumor deposits several centimeters distally from the lower margin of the rectal cancer itself^[34]. In colon cancer,

Table 2 Clinical studies comparing limited with extensive surgery for colon cancer

Ref.	Year	Country	Design	Location	Stage	n	Surgical technique	Node count	Node positivity rate	Survival
West <i>et al</i> ^[42]	2012	Japan/Germany	Retrospective multicenter study	Colon	I-IV	254	D3 resection <i>vs</i> CME	More nodes after CMEa	No difference	Not investigated
Hashiguchi <i>et al</i> ^[31]	2011	Japan	Retrospective single center study	Colon	I-IV	914	Left hemicolectomy with variable extent of lymph node dissection	More nodes after vertical dissection	No difference	Shorter if no vertical node dissection. No influence of main node removal or extent of horizontal node dissection
West <i>et al</i> ^[30]	2010	United Kingdom/Germany	Prospective and retrospective multicenter study	Colon	I-IV	89	Hemicolectomy <i>vs</i> CME	More nodes after CMEa	No difference	Not investigated
Tentes <i>et al</i> ^[29]	2007	Greece	Prospective single center study	Left colon	I: 10.5% II: 42.7% III: 40.3% IV: 6.5%	124	Left hemicolectomy <i>vs</i> left hemicolectomy + periaortic lymphadenectomy	More nodes after radical resection	No difference	No difference except longer survival after radical resection for stage III
Tagliacozzo <i>et al</i> ^[28]	1997	Italy	Retrospective single center study	Right Colon	I: 24.3% II: 35.4% III: 40.3%	144	Right hemicolectomy <i>vs</i> right hemicolectomy + retropancreatic lymphadenectomy	More nodes after radical resection	No difference	No difference
Rouffet <i>et al</i> ^[27]	1994	France	Prospective multicenter study	Left colon	I-IV	260	Left segmental colectomy <i>vs</i> left hemicolectomy	Not investigated	Not investigated	No difference

CME: Complete mesocolic excision.

local (anastomotic, nodal or mesenteric) recurrence is far less common. Little is known about the exact incidence of nodal or mesenteric recurrence in CC after resection with curative intent. In a recent population based analysis of 2282 CC patients from the Netherlands, the local recurrence rate was 6.6%^[35]. Locoregional recurrence was defined as tumor regrowth in or near the primary site, irrespective of the presence of distant metastases. In multivariate analysis, advanced T stage (3 or 4), node positive disease, left sided cancer and the absence of adjuvant therapy were independent predictors of locoregional recurrence. Strikingly similar findings were reported by Yun *et al*^[36], who noted a 6.1% local recurrence rate in 994 CC patients who underwent curative resection. The local recurrence was situated at the regional lymph nodes in only approximately 10% of patients. The most powerful predictor of local recurrence was TNM stage pN₂. Although the available data are very limited, locoregional recurrence seems to be a rare event in colon cancer and is usually associated with advanced (T4 or N2) disease^[37]. Taken together, the risk of isolated CC recurrence caused by less than complete removal of the mesentery seems to be very low.

COMPLETE MESOCOLIC EXCISION: CURRENT CLINICAL EVIDENCE

Thus far, the large majority of available studies that evaluated CME are retrospective case series. A small number of studies has compared CME with “standard” colon surgery.

West *et al*^[30] reported that CC resection specimens from Erlangen, Germany, where CME and central venous ligation are routinely performed, are more often in the correct anatomical (mesocolic) plane (92% *vs* 40%, $P < 0.0001$) and have a higher LNC (median 30 *vs* 18, $P < 0.0001$) compared to standard specimens from Leeds, United Kingdom. A similar inter-institutional comparison was performed by the same author between 6 Danish hospitals that performed “traditional” surgery and Hillerød hospital, where surgeons implemented a surgical educational training program in CME^[38]. As expected, the resection specimens from the latter center were characterized by, among others, a larger mesenteric surface (144.6 cm² *vs* 87.1 cm², $P < 0.0001$) and increased LNC (median 28 *vs* 18, $P < 0.0001$). Bertelsen *et al*^[39] recently reported how the introduction of standard CME in their center (since 2008) has affected surgical and pathological outcome. They did not find any changes in the R0 resection rate or the rate of mesocolic

plane resection, while a small (but statistically significant) increase was noted in LNC (from mean 24.5 to 26.2, $P = 0.009$) after the introduction of CME. None of the above studies has reported recurrence or survival data. In a recent retrospective study from Norway, CC survival data were compared between one hospital that used the CME approach and two other centers that used the “standard” approach (termed D2 resection by the authors)^[40]. They observed a better 3 year overall survival (88.1% *vs* 79.0%, $P = 0.003$) and disease-free survival (82.1% *vs* 74.3%, $P = 0.026$) in the CME patient group, while cancer-specific survival was 95.2% in the CME group *vs* 90.5% in the standard group ($P = 0.067$). Age, operative technique and T category were significant in Cox multivariate regression of overall and disease-free survival. Galizia *et al.*^[41] compared CC recurrence and survival data before and after adoption of CME (since 2008) in the same Italian center. Interestingly, local recurrence developed in none of the CME but in 21% of the standard group, while distant metastasis occurred with similar frequency (13.3% and 13.7%, respectively). There were, however, significantly more early stage cancers in the CME group. Although the data from the above two studies are thought provoking, it is clear that any conclusions regarding the survival benefit, if any, from CME should be drawn with caution due to the multiple possible causes of bias.

Although CME seems to be a safe procedure in expert hands, it should be noted that high ligation of vascular trunks may considerably increase the risk of bleeding. Specifically, the technical demands of (laparoscopic) right hemicolectomy, a procedure commonly considered to be of moderate difficulty and often entrusted to surgeons in training, rise sharply with CME and an increased risk of troublesome bleeding caused by damage to the superior mesenteric vein during laparoscopic right hemicolectomy should be anticipated. Similarly, flush ligation of the inferior mesenteric artery when performing a left colon resection may cause severe damage to the sympathetic autonomic nerve supply to the pelvic organs.

CONCLUSION

The introduction of the CME concept certainly has the merit of highlighting the importance of sound judgment and precise technique in the surgical management of colon cancer. However, not unlike the concept of TME in rectal cancer, many will argue that mesocolic resection, preserving the integrity of the mesentery that is mobilized along embryological planes, constitutes nothing more than good surgical practice and has been the standard operative approach of colorectal surgeons. The second tenet of CME, high ligation of the supplying vessels aimed at maximizing nodal clearance and preventing local recurrence, is currently scientifically and ethically unfounded. Although “complete”, “total” and “radical” are cherished epithets in surgical jargon, the reality is that no benefit has been proven in any of the gastrointestinal cancers of extensive surgery

and/or extra-mesenteric lymphadenectomy. As has been apparent since the time of Halsted, the future of surgical oncology lies in more precise, imaging based, less invasive and less morbid surgery, performed as an integral component of a multimodal approach and based on the most recent insights in cancer biology. In colon cancer, several comparative clinical studies have confirmed that “high tie” ligation, extensive *vs* segmental resection, or extensive lymphadenectomy do not improve outcome. Although CME may increase nodal counts and therefore improve staging accuracy, any survival benefit is very unlikely since the relationship that is often observed between nodal counts and survival in CC is almost certainly not causal but confounded by a range of clinical, pathological and provider related factors. Finally, routine implementation of CME carries the risk of patient harm due to longer operating times, vascular damage and autonomous nerve damage. Therefore, in the absence of data from prospective randomized trials with relevant clinical endpoints (*i.e.*, disease free survival rather than nodal counts), CME should be considered investigational. The time is right to organize such a trial as a matter of priority.

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