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Complete mesenteric excision and central vascular ligation in colorectal cancer in the era of minimal invasive surgery

Marzia Franceschilli, Sara Di Carlo, Danilo Vinci, Bruno Sensi, Leandro Siragusa, Vittoria Bellato, Roberto Caronna, Piero Rossi, Giuseppe Cavallaro, Andrea Guida, Simone Sibio

Abstract

Since the nineteenth century, appropriate lymphadenectomy has been considered a cornerstone of oncologic surgery and one of the most important prognostic factors. This idea applies to all gastrointestinal cancer surgery. In colon and rectal cancer surgery, an adequate portion of mesentery is removed together with the bowel segment interested by the disease. The adequate number of lymph nodes to be removed is standardized and reported by several guidelines. To determine the correct extent of lymphadenectomy and to balance it with the increase in morbidity is mandatory in cancer surgery. Our review focused on the concept of “complete mesenteric excision (CME) with central vascular ligation (CVL)” intended as a radical lymphadenectomy in colorectal cancer that gained increasing success in recent years. The aim of the study was to evaluate the evolution of this approach during years, its potential oncologic benefits and morbidity increase as well as the improvements offered by laparoscopic techniques. Theoretical advantages of CME are the better local control due to the complete removal of an intact mesocolic fascia together with the ligations of vessels at their origin (CVL) that should guarantee to remove the highest number of lymph nodes. The development and worldwide diffusion of laparoscopic techniques minimized postoperative trauma in oncologic surgery providing the same oncologic results of open

surgery and this has widely applied to colorectal cancer surgery. However, these procedures account for an increased morbidity and technical complexity that could limit their wide application. This review will analyze results of these procedures in terms of oncologic outcomes, technical feasibility and complexity especially within the context of minimally invasive surgery.

Key Words: Complete mesenteric excision; Central vascular ligation; Colorectal cancer; Lymphadenectomy; Laparoscopy; Minimally invasive surgery

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Core Tip: An optimal lymphadenectomy is the cornerstone of oncologic surgery. The concept of “optimal” or “adequate” lays upon the balance between oncologic advantages and increase in morbidity. Extent of lymphadenectomy in colorectal cancer surgery is yet a highly debated issue. The concept of “central vascular ligation” and “complete mesocolic excision” to provide radical lymphadenectomy in the era of minimal invasive surgery for colorectal cancer has been investigated.

INTRODUCTION

Cancer represents a social disease related to lifestyle habits, environment pollution, ageing societies and its incidence has gone progressively increasing during the last decades, since respectively 20% of men and 15% of women are expected to deal with a cancer diagnosis in their life as well as 12% and 10% of them will die for that and, notably, for metastatic disease^[1]. This is why prevention of metastatic spread is of key importance in cancer treatments that are nowadays highly integrated, combining

neoadjuvant and adjuvant chemotherapy with radiotherapy and early or subsequent surgery in several different settings^[2].

Keystone of surgery is the removal of an adequate number of lymph nodes that reflects both staging and prognostic value. Biological bases of lymphatic spread are well described by the Halsted and Fisher models in which, respectively, an highly organized and progressive proximal to distal spread of metastases and an early completely randomized one are theorized^[2,3]. Regardless to the model applied, an adequate extent of lymphadenectomy is always advocated in cancer surgery and worldwide consensus guidelines state about the minimal number of lymph nodes to be removed for each type of cancer. In this landscape, complete mesocolic excision with central vascular ligation procedures have been developed to optimize lymph nodes removal and to improve radicality of surgery. Complete mesenteric excision (CME) is based on the dissection conducted on the embryological plane separating the right mesocolon and the retroperitoneum and the high tie of ileocolic vessels, right colic vessels and right branch of middle colic vessels^[4]. It doesn't specify if dissection has to be extended at the level of root vessels (superior mesenteric artery and vein) even if proximal ligation is required^[5]. A key-point of CME technique is the retrieval of an unbreached mesocolon package as the result of a careful dissection between mesocolon and retroperitoneum along the Toldt's layer together with central vascular ligation to remove the largest amount of lymph nodes.

To be more specific, D1 Lymph node resection represents transection of the mesenteric vessel at the level proximal to the marginal vessels; D2 resection is a more traditional resection of the main feeding vessels to a given colonic segment and lymphadenectomy that includes the origin of the feeding vessels^[6]; D3 represents an extended lymphadenectomy that includes **dissection of the lymphoadipose tissue covering the medial side of the SMV and dissection of the lymphoadipose tissue covering the head of pancreas after section of the superior right colic vein (SRCV) at its confluence in the gastroduodenal trunk of Henle (GCH) if necessary (Figure 1). The latter is a fundamental surgical landmark defined as the area of the SMV located at the head of**

the pancreas, defined by the venous confluence of the following three veins: right gastroepiploic vein, anterosuperior pancreatic-duodenal vein, and SRCV^[4].

CME and D3 Lymphadenectomy share common oncologic results and, as first described by Hohenberger *et al*^[7], CME and CVL, intended as individual proximal vascular ligation, offer better results if performed together. He proposed a nodal dissection even more extended than the standard D3 proposed by Japanese surgical societies, known as CVL^[7].

Furthermore, in recent years, the wide spread of minimally invasive techniques in colorectal surgery has introduced new issues regarding technical complexity and increased morbidity of these procedures^[8]. Concerns have been raised especially about the proper extent of laparoscopic lymphadenectomy and its feasibility and the use of new devices to perform more comp

COLORECTAL CANCER

Curative treatment of colorectal cancer (CRC) is focused on surgery so far. Development of cancer is supposed to be a result of interactions between environmental factors, genetic alterations and immune response that can promote or inhibit tumor cells growth^[11-16].

Once developed, CRC cells can diffuse away from the primary tumor by mean of the embryological envelope constituted by the primitive dorsal mesenterium, a double layered fibrofatty mesenchymal tissue. The concept of radicality in CRC must include the complete excision of this “meso-structure” which represent the main procedure able to prevent local recurrence. On the other hand, distant metastases spread has to be prevented by mean of an extended local lymph nodes removal. From this point of view, CVL is able to provide an extensive lymph node dissection, limiting regional recurrence and systemic dissemination rates, thus providing improved survival in stage I-III colonic cancers^[17].

As for rectal cancer, the concept of total mesorectal excision (TME) introduced by Heald^[4] demonstrated as a complete excision of mesorectal fascia yields better

outcomes and it has become nowadays the gold standard for rectal surgery (Figure 2). Again, the underlying concept is that complete removal of lymph vascular ways of drainage together with primary tumor preserving the integrity of the layers is able to provide better local control and lower distant diffusion rates^[18]. Definitely, the integrity of the dissection plane described by Heald, remains the principal predictive factor for local recurrence as clearly stated in recent meta-analyses and reviews comparing TME plus lateral lymph node dissection (LLND) *vs* TME alone^[19-22]: to perform LLND doesn't provide significant reduction of recurrence rates or improvement in survival; indeed, LLND is reported to require longer operation time (360 min *vs* 294.7 min, $P = 0.02$) and increased complication rates (OR = 1.48, 95%CI: 1.18-1.87, $P < 0.001$) such as urinary dysfunction^[19].

In recent years, the same concept of extensive dissection adhering to embryological planes (CME) and central vascular ligation (CVL) have also been introduced for colonic resections^[23]. CME is a well standardized procedure providing increased disease-free survival in right colectomy^[24], while little is known about the perioperative morbidity and mortality when it is associated with CVL^[25].

Kanemitsu *et al*^[26] examined 370 consecutive patients who had right colectomy with D3 Lymphadenectomy for right colon cancer; 3% of patients had N3 nodal involvement (patients with T3-T4 tumors) and 13.2% had N2 nodal involvement. The 5-year disease-free survival was 36.4% for the patient with N3 nodal involvement *vs* 83.5% for N2 nodal involvement, suggesting that patients with proximal nodal metastasis exhibit a different tumor biology than patients with more intermediate-level nodal metastasis. In Nagasaki *et al*^[27] lymph nodes are a key element of the TNM staging system and are considered a significant factor for predicting disease-free survival (DFS) and overall survival (OS) in patients with CRC without distant metastasis. The integrity of the surgical field provided by the dissection conducted along the embryological planes is also very important to limit the amount of cancer cells exfoliating from traumatized tissues. Infact, in CRC surgery, intraperitoneal free cancer

cells (IFCC) presence is not routinely investigated but data exist on worse survival for patients who show a positive peritoneal washing^[28-30].

The wide application of CME and CVL techniques seem to be also limited by the large number of CRC patients who present in emergency: a recent study demonstrated as disease free survival for patients with pT3 mucinous and signet ring cell tumor is related to emergency presentation and they have poorest outcomes and survival. Although the debate whether emergency colon surgery is associated with the worst oncological outcome is still ongoing, the finding of a “bridge to surgery” strategy (if possible) might provide better oncologic outcomes in T3 patients^[31] and might to consider CME and CVL to be applied also in these patients when they can be shifted to elective surgery.

However, the correct extent of lymphadenectomy is still debated: 2019 guidelines of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) recommend D3 Lymph node dissection for clinical stage II/III CRC^[32]. However, when performing a left hemicolectomy, it is still unclear whether D3 Lymph node dissection with preservation of the left colic artery (LCA) is different in terms of clinical outcomes, compared to D3 without LCA preservation. The advantages in D3 without LCA preservation have been identified in the prevention of the micrometastatic cells spillage through the en-bloc lymph node dissection of the root of the inferior mesenteric artery (IMA); disadvantages include a higher possibility of leakage and the sacrifice of the autonomic nerves around the IMA; no significant differences in terms of operation time and blood loss have been found. Despite a higher complication incidence, D3 with LCA preservation was associated with a higher Overall Survival (OS)^[33-37]

Moreover, while Kotake *et al*^[38] demonstrated no difference in the overall survival of patients who had T2 colon cancers treated with D2 or D3 resection, Slanetz *et al*^[39] showed that the level of mesenteric resection influenced outcomes only for the patients who had moderate or well-differentiated cancer with intermediate-level nodal involvement. Patients with more than four positive lymph nodes or poorly differentiated tumors had poor survival regardless of the extension of

lymphadenectomy. These studies had limits like outdated staging methods, lack of modern chemotherapy, and no audit of the pathology specimen.

LAPAROSCOPY AND CENTRAL VASCULAR LIGATION: IS IT FEASIBLE?

Minimal invasive surgery, such as robotic and laparoscopic techniques, has revolutionized the approach to gastrointestinal surgery, especially in colorectal surgery, notably lowering surgical and post-operative trauma and shortening post-operative course with improving recovery^[40,41]. The concept of extended lymphadenectomy might appear in contrast with this leading point of view. Technical complexity as well as increased morbidity are important issues to be solved in order to consider these procedures in the scope of minimal invasive surgery. Regarding laparoscopy safety from a general point of view, several trials reported promising results when comparing it to open surgery: the COST trial^[42], COLOR I and II trials^[43;44], CLASICC trial^[45;46] and COREAN^[47] demonstrated non-inferior outcomes to open surgery. A Cochrane Review clearly showed the laparoscopic approach advantages such as decreased blood loss, quicker oral intake, decreased narcotic use, and lower rates of surgical site infections^[48]. Furthermore, Arezzo *et al*^[49] in a meta-analysis including 4539 patients found a mortality reduction (2.4% *vs* 1.0% $P = 0.048$) and decreased morbidity (35.4% *vs* 31.8%, $P < 0.001$) in favor of the laparoscopic group.

As for specific CME and CVL performing, no differences in the local and distant recurrence rate, the three- and five-year overall rates and the disease-free survival rates between the Laparoscopic CME and Open CME groups were found in a recent systematic review^[48]. Even the surgical specimen quality from laparoscopic CME/CVL seems to be similar to that obtained with open technique^[50-53]. In one of the few RCTs, Yamamoto *et al*^[54] compared laparoscopic and open D3 colonic resections which demonstrated lower morbidity rates in the laparoscopic group with the usual benefits of minimally invasive surgery.

CONCLUSION

Central vascular ligation can be considered a widely accepted reality in colorectal surgical oncology with clear benefits in terms of oncologic outcomes as well as main concerns remain regarding the increased rate of postoperative complications^[7,24,55].

Different awareness on the benefits and feasibility of these extended dissections is reported if we talk about rectal or colonic cancer. Nowadays, TME is considered the gold standard in rectal cancer and it provides an optimal disease local control confining tumor deposits as well as nodal involvement within the mesorectal fascia. ⁴ Complete excision of the mesorectum should be performed en bloc with the rectum by dissecting along the rectal fascia in the plane that separates this from the parietal pelvic fascia (the so called “holy plane”), thereby preserving the integrity of the rectal fascia and mesorectal contents, and sparing the autonomic pelvic nerves and plexuses^[5].

³ In agree with this principle, the same concept of preservation of the embryological envelope has been applied to colonic resections^[24]. For what concerns right colectomy, it is author’s opinion that a true CME does not exist without CVL and extended dissection along the vascular plane offered by the anterior surface of the SMV and SMA.

The adherence to the 2019 guidelines of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) for the treatment of CRC recommending D3 Lymph node dissection for clinical stage II/III CRC is suggested and shared by our institution^[34]. For what concerns the arterial ligation in sigmoid and rectosigmoid colon cancer there is still not much consensus, but we agree that LCA preservation should be attempted whenever possible as fewer postoperative complications might contribute to a better prognosis.

The aim of this review is to create an increasing awareness that the idea of an extended lymphadenectomy with CVL must be in the contest of a multimodal approach where neoadjuvant chemotherapy is increasing its role in the treatment of advanced stage cancers, allowing more conservative surgery. This idea appears even more important in a context where minimally invasive techniques and the idea of “less is more” is becoming the standard thought for the surgical approach.

Further trials are needed to better investigate the correct role of these techniques in the era of multimodal approach to cancer treatment.

² The achievement of reliability of laparoscopic lymphadenectomy in terms of oncological appropriateness and the absence of differences as regards the incidence of complications and short-term results between laparoscopic and open approach, has allowed the transfer of the many advantages of mini-invasiveness to the treatment of gastro-intestinal cancer. Surgeons around the world are gaining experience with advanced laparoscopic and robotic skills, new innovations and techniques in minimally invasive colorectal surgery will evolve and ² the development of newly designed operative techniques and the introduction of better technological devices for laparoscopic and robotic surgery^[9,10] together with the undoubted improvement of surgical expertise in minimally invasive surgery will make it possible to consider these procedures as a common surgical technique.

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