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Complete mesocolic excision and central vascular ligation in colorectal cancer in the era of minimally invasive surgery

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Abstract

Since the 19th century, appropriate lymphadenectomy has been considered a cornerstone of oncologic surgery and one of the most important prognostic factors. This approach can be applied to any surgery for gastrointestinal cancer. During surgery for colon and rectal cancer, an adequate portion of the mesentery is removed together with the segment of bowel affected by the disease. The adequate number of lymph nodes to be removed is standardized and reported by several guidelines. It is mandatory to determine the appropriate extent of lymphadenectomy and to balance its oncological benefits with the increased morbidity associated with its execution in cancer patients. Our review focuses on the concept of "complete mesenteric excision (CME) with central vascular ligation (CVL)," a radical lymphadenectomy for colorectal cancer that has gained increasing interest in recent years. The aim of this study was to evaluate the evolution of this approach over the years, its potential oncologic benefits and potential risks, and the improvements offered by laparoscopic techniques. Theoretical advantages of CME are improved local-relapse rates due to complete removal of the intact mesocolic fascia and improved distance recurrence rates due to ligation of vessels at their origin (CVL) which guarantees removal of a larger number of lymph nodes. The development and worldwide diffusion of laparoscopic techniques minimized postoperative trauma in oncologic surgery, providing the same oncologic results as open surgery. This has been widely applied to colorectal cancer surgery; however, CME entails a technical complexity

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that can limit its wide minimally-invasive application. This review analyzes results of these procedures in terms of oncological 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” relies on the balance between oncologic advantages and increased morbidity. The extent of lymphadenectomy in colorectal cancer surgery is a highly debated issue. The concept of “central vascular ligation” and “complete mesocolic excision” for radical lymphadenectomy in the era of minimally invasive surgery for colorectal cancer have been investigated.

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INTRODUCTION

Cancer represents a social disease related to lifestyle habits, environmental pollution, and aging societies, and its incidence has progressively increased during the last several decades, since 20% of men and 15% of women will be diagnosed with cancer in their lifetime and 12% and 10%, respectively, will die of the disease, namely from metastatic progression[1]. For this reason, preventing metastatic spread is of key importance in cancer treatments. Currently, these treatments are highly integrated, combining neoadjuvant and adjuvant chemotherapy with radiotherapy and early or subsequent surgery in several different settings[2].

The keystone of surgery is removal of an adequate number of lymph nodes that have both staging and prognostic value. Biological bases of lymphatic spread are theorized by the Halsted and Fisher models. The former describes a highly organized and progressive proximal to distal spread of metastases, whereas the latter suggests an early and completely random spread of metastases[2,3]. Regardless, the adequate extent of lymphadenectomy is always advocated in cancer surgery and worldwide consensus guidelines state 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 node removal and improve the radicality of surgery. Complete mesocolic excision (CME) is based on a dissection conducted on the embryological plane separating the right mesocolon and the retroperitoneum and a high tie of ileocolic, right colic, and right branch of the middle colic vessels[4,5]. A key point of the CME technique is the retrieval of an unbreached mesocolon package as the result of 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 feeding vessel just 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 superior mesenteric vein (SMV) and dissection of the lymphoadipose tissue covering the head of the pancreas after section of the superior right colic vein (SRCV) at its confluence in the gastrocolic trunk of Henle (GCTH) if necessary (Figure 1). The latter is a fundamental surgical landmark defined as the venous confluence of the following three veins: right gastroepiploic vein, anterosuperior

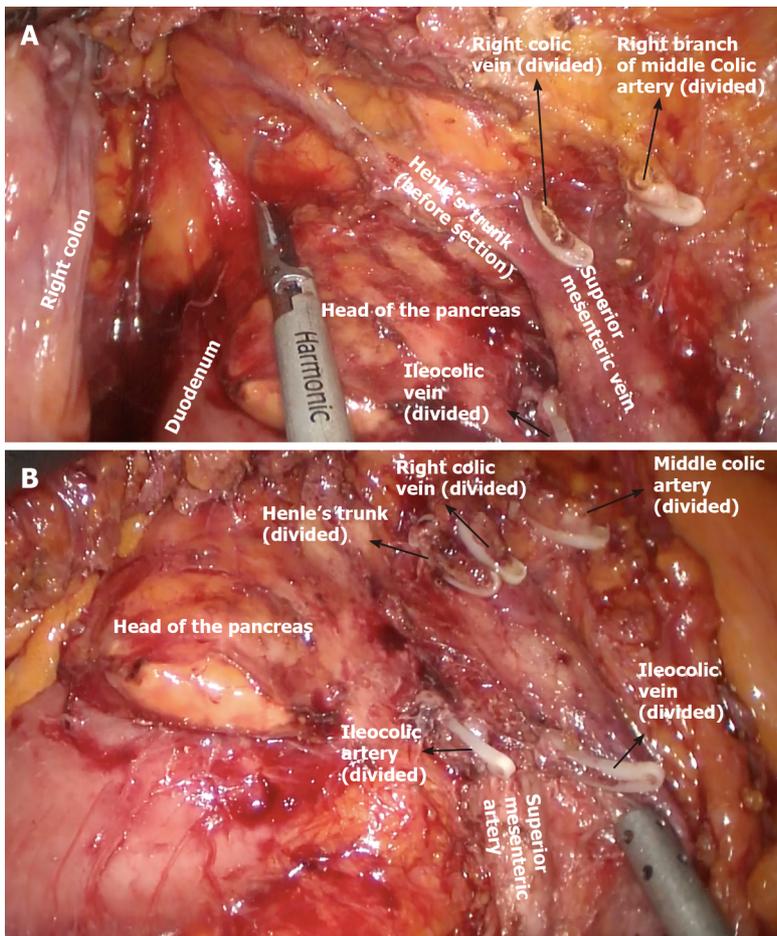


Figure 1 Complete mesocolic excision during right colectomy. A: Lymphoadipose tissue covering the head of the pancreas after sectioning of the superior right colic vein (SRCV) at its confluence in the gastrocolic trunk of Henle (before dissection), and right branch of the middle colic artery; B: Lympho-adipose tissue covering the head of the pancreas after sectioning of the superior right colic vein at its confluence in the gastrocolic trunk of Henle (after dissection), and right branch of the middle colic artery (Courtesy of Prof. Giuseppe Sica, Tor Vergata University of Rome).

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 offer better results if performed together. The authors 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.

COLORECTAL CANCER

Curative treatment of colorectal cancer (CRC) is focused on surgery. The development of cancer is supposed to be a result of interactions among environmental factors, genetic alterations, and immune response that can promote or inhibit tumor cell growth[11-16].

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

Regarding 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 the gold standard for rectal surgery (Figure 2). Again, the underlying concept is that complete removal of lymphatic drainage together with the primary tumor, while preserving the integrity of enveloping fascial layers is able to provide improved local control of disease 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 (odds ratio [OR] = 1.48, 95% confidence interval [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 DFS in right colectomy[24], while little is known about 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 DFS 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. Nagasaki *et al*[27] suggested that lymph nodes are a key element of the tumor-node-metastasis 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. Integrity of the surgical field provided by dissection conducted along the embryological planes is also very important to limit the amount of cancer cells exfoliating from traumatized tissues. In fact, in CRC surgery, intraperitoneal-free cancer cells 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 that disease free survival for patients with pT3 mucinous and signet ring cell tumor is related to emergency presentation and that they have poorest outcomes and survival. Although the debate whether emergency colon surgery is associated with worse 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 allow application of CME and CVL also in these patients, if successfully 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 cell spillage through the en bloc lymph node dissection of the root of the inferior mesenteric artery (IMA); disadvantages include a higher possibility of anastomotic 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 incidence of complications, D3 with LCA preservation was associated with a higher OS[33-37]

Moreover, while Kotake *et al*[38] demonstrated no difference in the OS 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 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 limitations such as outdated staging methods, lack of modern chemotherapy, and no audit of the pathology specimen.

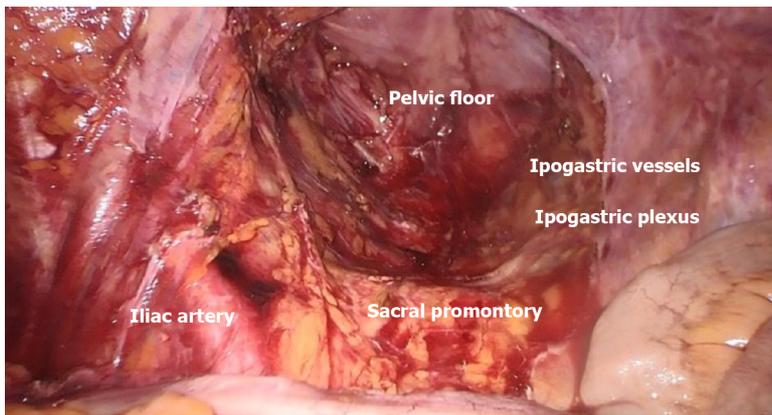


Figure 2 Surgical field after total mesorectal excision dissection in low rectal cancer (Courtesy of Professor Giuseppe Sica, Tor Vergata University of Rome).

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[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 safety of laparoscopy 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 features 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 decreased mortality (2.4% vs 1.0%; $P = 0.048$) and morbidity (35.4% vs 31.8%; $P < 0.001$) in the laparoscopic group.

Regarding the correct performance of CME and CVL, a recent systematic review reported no differences in the local and distant recurrence rate, the 3- and 5-year OS rates and the DFS rates between the laparoscopic and open CME groups[48]. Furthermore, the quality of the surgical specimen from laparoscopic CME/CVL seems to be similar to that obtained with the open technique[50-53]. In one of the few randomized controlled trials, Yamamoto *et al*[54] compared laparoscopic and open D3 colonic resections demonstrating 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. Concerns remain regarding increased rate of postoperative complications[7,24,55]. Different awareness on the benefits and feasibility of these extended dissections is reported for rectal and colonic cancer. Nowadays, TME is considered the gold standard in rectal cancer and it provides an optimal local disease control confining tumor deposits as well as nodal involvement within the mesorectal fascia. 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 integrity of the rectal fascia and mesorectal contents, and sparing the autonomic pelvic nerves and plexuses[5].

In agreement 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 the 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 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 arterial ligation in sigmoid and rectosigmoid colon cancer there is still no 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 surgical approach. Further trials are needed to better investigate the correct role of these techniques in the era of multimodal approach to cancer treatment.

The achievement of reliable of laparoscopic lymphadenectomy in terms of oncological appropriateness has allowed the transfer of the many advantages of minimally-invasiveness to the treatment of gastro-intestinal cancer. Improvement of surgical expertise in minimally-invasive surgery, technical/instrumental innovations and the development of newly designed operative techniques will make it possible to consider laparoscopic CME/CVL as a common surgical technique[9,10].

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