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A systematic review of the literature

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PURPOSE: *Nowadays, there is no standardization in surgical procedures for treatment of colon cancer. Since its introduction, laparoscopic surgery has gained increasing interest in colorectal surgery and it is now performed worldwide for treatment of colon cancer. Following the concept of total mesocolic excision introduced by Heald in 1988 in order to reduce local recurrence* after surgical *treatment of mid/low rectal tumors, the idea of complete removal of the mesocolon mesocolic envelope has been developed also for colon cancer, has evolved longtime and complete mesocolic excision has been recently adopted as the optimal approach for colon cancer. However, complete mesocolic excision, whose purpose is to remove all lymphatics and lymph nodes draining the tumor, is still discussed as far as oncologic results are concerned. Moreover, the role of laparoscopic approach for complete removal of mesocolon has to be defined.*
METHODS: *Selection of studies. A MEDLINE-PubMed database search of the current English Literature was performed using the terms: complete mesocolic excision; high vascular ligation; splenic flexure mobilization.*
Inclusion criteria. The inclusion criteria were report on CME for colonic cancer with high vascular ligation; minimum number of patients included (20 patients). Two independent reviewers (CRS, IE) extracted the data.
RESULTS AND CONCLUSION: *In this article, an update from the Literature on results of complete mesocolic excision was undertaken and data have been discussed. The role of laparoscopic complete mesocolic excision in colon cancer patients has been focused, and it seems to be safe and feasible, it should be standardized and hypothetical oncologic advantages should be expected.*

KEY WORDS: Colorectal-tumor, Complete mesocolic excision, High vascular ligation, Laparoscopic colorectal surgery, Splenic flexure mobilization, Total mesocolic excision

Introduction

Colorectal cancer is one of the most common malignancies in general population and surgery remains the treatment of choice for this disease. Laparoscopic surgery is nowadays performed worldwide for the treatment of colon cancer. The history of colorectal cancer treatment has been characterized by an evolution in term of oncologic concept of radicality.

Following the introduction by Heald in 1982 of the "total mesorectal excision" (TME) [1,2], with having the purpose of reducing significantly the local recurrence of mid/low rectal tumors in a plane-oriented concept, complete mesocolic excision (CME), has been developed by Hohenberger in 2009. Based on embryologic and anatomic evidences, it was initially considered as a vessel-oriented concept, and has been increasingly adopted by many surgeons as the optimal approach for colon cancer [3].
This approach, which can be performed either by open or laparoscopic surgery, responds to the need of large lymphadenectomies as an important step in surgical oncology, in addition to the classical colorectal surgical technique [4].
Even if the available data referring to laparoscopic CME aren't enough to demonstrate better long-term outcomes,

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several retrospective studies seem to point out that CME should be able to remove a higher number of potentially involved lymph nodes and that the laparoscopic approach should be recommended for its better short-term morbidity, length of stay and oncological outcome [5,6].
In this article, we discuss the status of complete mesocolic excision in the laparoscopic surgical treatment of patients operated for colon cancer.

Discussion

Knowledge on embryology and anatomy of the peritoneal layer and of lymphatic drainage are essential to understand the role of mesocolic dissection for the radical treatment of lymphatic spread in colon cancer.
The concept that complete mesocolic excision could be essential for radical treatment of colon cancer, has re-emerged among western surgeons with the adoption of the laparoscopic surgery for colon cancer. Thanks to the magnification of the images and the help of insufflation in the dissection, dissection could be easier to perform and mesocolon complete removal could be accomplished in a more precise fashion.
Lymphatic metastasis in colon cancer have been deeply studied for a long time now. In 1932, Dukes published a staging system for colorectal cancer. He conceived his first classification of this disease, showing that the involvement of the lymph nodes reduces survival. He assigned to lymphatic metastasis a great significance due to the big number of free communications between the lymphatic circulation and the venous system that can lead to the spread of embolic tumor cells in the venous system. These cells, however, seem to be trapped for a variable period inside the lymph nodes, and this can explain the importance of a complete lymph node dissection for curative purposes [7].
The embryologic development can help to understand the anatomy of coelomic mesenteric folds in the adult. As the rotation of the embryologic forerunner of the gastrointestinal tract comes to the end, the initially straight dorsal colon mesentery attaches to the retroperitoneum and medially to the colon sections. Toldt first hypothesized this concept in 1873, who described the interphase between the parietal plane of retroperitoneum and the mesenteric plane. Toldt's fascia is formed by the fusion of the mesocolic visceral peritoneum with the parietal peritoneum of the retroperitoneum. Nevertheless, his description was not accepted at the time, differently from Treves's description, which was universally adopted and reported in surgical textbooks of that time.
Only in the last decades, after the introduction of the laparoscopic technique with its image magnification, Toldt's description of the coelomic planes was revalued and adopted as the anatomical basis of CME. Many studies confirmed that the mesentery is a continuous structure from the duodeno-jejunal flexure to the mesorectum [8,9]. This envelope contains potentially metastatic lymph nodes and by keeping it intact, CME aims to minimize the risk of spillage of cancer cells into the peritoneal cavity [3,10,11,14].
Inside this envelope, the lymphatic vessels run, closely related to the blood vessels, from the colonic walls to the mesentery root to the apical (central or D3) lymph nodes located at the origin of the mesenteric vessels from the abdominal aorta.
A peculiar pattern of lymphatic spread can be observed in case of transverse colon or right colon tumors. In case of hepatic flexure or proximal transverse colon lesions, the presence of connections or aberrant vessels between the colonic flexure, the omentum and the head of pancreas can lead to the invasion of the infrapyloric nodal station in 1.1 – 4%. In that case, a central ligation of the right gastro-epiploic vessels should be accomplished in order to remove the potentially affected gastro-epiploic and infrapyloric nodes. In case of transverse and splenic flexure cancer, metastasis to the gastro-epiploic arcade are reported in 4-5%. In that case, Hohenberger et al. suggest the removal of the infra-pancreatic nodes and of about 10 cm of the gastro-epiploic arcade [12,13,15].
Lymphatic spread can moreover occur in an unpredictable, not stepwise fashion, leading to the formation of skip node metastasis, and this fact remarks the role of CME in both staging and treatment of colorectal cancer.

Left Colon Cancer

The operative principles of CME during the laparoscopic approach are the same as those through the laparotomic approach. The section of the mesenteric vein vessel reveals an avascular plane that makes possible a smooth and fine dissection of the mesocolon from the Toldt's Fascia.
Splenic flexure mobilization is a crucial step for the following laparoscopic procedure when a complete mesocolic excision and a D3 lymphoadenectomy is planned. Mobilizing the splenic flexure, moreover, helps create a tension-free colorectal anastomosis at the end of the whole procedure. During the splenic flexure mobilization, the surgeon should pay particular attention to pancreas, spleen, colic wall, arc of Riolan and to Drummond marginal artery. The role of these vessels is important to maintain a proper blood flow and an accidental injury to these structures would predispose to an increased risk of anastomotic dehiscence.
The identification of the inferior mesenteric artery is then accomplished. It is secured through application of clips or by means of a vascular linear stapler and finally cut at about 1.5-2 cm from its origin. The dissection of the mesocolon and mesosigma continues along the plane of Toldt's fascia until the complete mobilization of the descending colon is done.
After placing the patient in Trendelenburg and putting optics on the trocar placed on right iliac fossa, the dis-

section of the rectosigmoid junction and mesorectum continues as described elsewhere [16,17].

Shortly, mesorectum is dissected using an avascular plane placed behind the presacral fascia leading dissection first on the right side of the rectum, then on the left one. After sectioning lateral rectum ligament, the front side of the rectum is dissected along the cleavage plane located behind Denonvillier's fascia, avoiding injuries to seminal vesicles, prostate, pelvic plexus [16].

Right and Transverse Colon Cancer

Also for the right sided laparoscopic colectomy, we follow the same principles as for laparotomic CME. Mostly a medial to lateral dissection is performed, starting with the dissection of the terminal ileum and the ascending colon on the Toldt's fascia plane, up to the duodenum and to the pancreatic head.

The ileocolic and right colic vessels are progressively identified, ligated and transected at their root on the superior mesenteric vein and superior mesenteric artery. Then the mesocolic excision is performed with dissection of hepatic flexure and the preduodeno-pancreatic fascia and the middle colic vessels are ligated and sectioned. The anterior superior pancreaticoduodenal vein and the right gastroepiploic vein are usually spared, except in case of tumor infiltration.

If the tumor is located at the cecum or at the proximal ascending colon, a right hemicolectomy is performed with ligation of the right branches only of the middle colic vessels. In case of a transverse colon tumor, instead, the middle colic vessels are ligated at the root and an extended right hemicolectomy is performed.

The most commonly used grading system regarding TME and then CME, was developed by the Medical Research Council for the CLASICC trial [17,18].

According to this classification, the extent of mesocolic excision is classified as: grade A ("good" plane of surgery), when there is an intact mesocolon without any serosal defects; grade B ("moderate" plane of surgery) if the layer of dissection breaches in the mesocolon fascia but it does not reach the muscularis propria; grade C ("poor" plane of surgery) if the mesenteric layer of dissection contains disruptions extending down into the muscularis propria.

After its introduction in 1989, laparoscopic surgery has been gaining interest in many surgical centers and it is now performed for several indications in abdominal surgery with, sometimes, better results than traditional surgery [16].

Nowadays it does not seem possible to demonstrate better long-term outcomes for laparoscopic CME, comparing to traditional colon resection, because of the little number of prospective randomized studies available on long-term disease free survival. Several retrospective not randomized studies seem to point out that CME should be able to carry out better oncologic results in terms of potentially involved lymph nodes removal [3,5,17,19,20].

A MEDLINE- PubMed database search of the current English Literature was performed using the terms: complete mesocolic excision; high vascular ligation; splenic flexure mobilization. The inclusion criteria were report on CME for colonic cancer with high vascular ligation; minimum number of patients included (20 patients). Two independent reviewers (EI, RC) extracted the data.

Kontovounisios et all reported in their systematic review 34 articles including 12 retrospective studies, 13 original articles and 9 prospective studies analyzing the median number of examined lymph nodes per patient, postoperative mortality, 5-year rate of loco regional recurrence, the plane of mesocolic resection, postoperative complications and 5-year cancer-related survival, comparing them with the data of traditional surgery. Four of the prospective studies showed survival benefits and a higher number of excised lymph nodes, when in the others a higher specimen quality at the histopathological analysis was shown. Moreover, the study suggests a possible limit of the laparoscopic approach to CME for the transverse colon tumours. The conclusions they reached were that while CME allows a larger removal of lymph nodes without clear evidence of serious adverse events, a real benefit in terms of long-term survival is still to be proved [21].

In 2015 Bertelsen et al. [22], in their population-based study, compared 529 patients who underwent CME surgery with 1710 patients undergoing colon-surgery without CME. In this study, laparoscopy was performed in 48.8% of patients who underwent CME and in 68.9% of control group of patients. This study, even if retrospective is based on a large population and, as it is, offers good possibility to evaluate short-term outcomes after CME, which is statistically comparable to the control group as far as morbidity and mortality are concerned.

No statistically significant increased risk of 30- or 90-day mortality after CME compared with control group was shown according to the comprehensive meta-analysis by Killeen et al. [23], in which no increase in 30-day in-hospital mortality after CME was also found. This could indicate that CME might be performed safely in terms of postoperative mortality but the evidence for short-term outcomes after CME in literature is based mainly on single center, often small, studies. In fact, even if for Killen et al. survival appears improved for CME resections, in their study they strongly highlight the inconsistence of reporting outcomes after they analyzed 21 predominately-retrospective studies involving 5246 patients. For this reason, they have concluded that available data for CME have such limitations that prevent universal adoption.

Bertelsen, on the other hand, underlined the significant, common and nightmare scenario risk for injuries to spleen, SMV (superior mesenteric vein) and non-tumor

segments of the colon during the CME for the higher risk associated with a more central dissection.
A recent study conducted by Kim. et al [24] evaluated the short-term and oncologic outcomes between laparoscopic and open complete mesocolic excision and central ligation. No difference of length of the specimen, ileum, right or left colon was found between the groups and operative time was similar. When comparing overall survival rates between the groups, laparoscopic CME showed better results only when not stratified by TNM stages. On the other hand, the rate of 30-day postoperative complications was higher in the open CME group. According to Kim et al. CME yielded short-term benefits in terms of postoperative complications, ICU care, transfusions, reduced time to soft diet, and length of stay. The author says that the higher postoperative complication rate of the open technique could be attributed to an inclusion of more patients with ASA score of 3 and to the main limits of this study which is a retrospective, small, non-randomized study. They also observed that open CME removed more lymph nodes (27 vs 31) than the laparoscopic procedure, obtaining a similar result observed by Gouvas et al. [25].
Also Bae et al. [26] study about laparoscopic assisted versus open CME for right-sided colon cancer, laparoscopic CME showed best results in terms of postoperative complications: the median time of soft diet, the days of hospitalization and the blood loss were shorter than in open surgery, but the morbidity within 30 days after surgery was comparable between the two groups. The number of harvested lymph nodes, the operation time and the rates of recurrence did not differ significantly, but the 5-year overall survival rates were 77.8% and 90.3% (p = 0.028) in open vs laparoscopic surgery respectively. The disease-free survival rates were 71.8% and 83.3% (p = 0.578) in open vs laparoscopic CME. So this limited retrospective study – applied on the right colon cancer – might show, probably for first, that the laparoscopic CME could be better than the open approach in terms of 5-year overall survival even if the long-term oncological outcomes between the two groups were comparable.
Another Bertelsen's retrospective study [27] aimed to investigate whether implementation of CME improved disease-free survival compared with colon resection without attempting of CME, as it happened in the last decades with implementation of TME for rectal cancer. The study, conducted on a large number of patients (1395) with colon cancer in UICC stage I-III, showed for all patients a 4-year disease-free survival of 85.8% after CME and 75.9% after non-CME surgery, with better results in each stage group. Their conclusion was that implementation of CME surgery might improve outcomes for patients with colon cancer.
A recent study by Storli [5] compares the medium-term and long-term results between laparoscopic and open CME approach.
The study points out a better 4-year time to recurrence (93,9% vs 91,3%) (p=0.71) and 4-year CSS (97% vs 91,3%) (p = 0.42) in laparoscopic patients cancer-specific survival. Anyway, the study has several limitations because it's a prospective single-institution study with a small sample size (56 patients). The results of the study, according to the older studies already mentioned, do not seem to be significant about the medium and long-term outcomes, but suggest that the laparoscopic approach should be preferred for its short-term benefits such as length of stay, lower morbidity, and better oncological outcome.
Lieto et al. reported a comparative study between two different groups of patients submitted respectively to conventional right hemicolectomy and CME. No increase in post-operative complication was recorded in the CME group. Number of harvested nodes was significantly higher in the CME group; thus, the risk of cancer relapse was reduced to as much as one third, and locoregional recurrences were never recorded [28].
Very few Japanese centers reported the benefits of CME [29,30] in term of lower short- and long- term complications, safety of procedure, and better oncologic outcome due to a larger resected mesentery with a higher number of lymph nodes harvested.
Up to now, there is no standardization in surgical procedures for colon cancer. Although CME is a more difficult and challenging procedure than conventional surgery, it seems to be safe and to significantly increase the number of lymph nodes harvested, with a better oncologic outcome. Lower cancer recurrence and higher survival rates recorded after CME, are associated with an intact mesocolon [3,17,18].

Conclusion

In conclusion, so far, no statistical definitive evidence exists in favour of laparoscopic complete mesocolic excision in colon cancer patients. Additional studies are needed to confirm, if any, improvement concerning oncologic outcome and survival after laparoscopic removal of colon cancer with CME. In our opinion, in the meantime, complete mesocolic excision should be recommended, also for staging purposes. Laparoscopic surgery is an adequate approach to accomplish a "good" mesocolic excision, thanks to the magnification of the images and the help of gas dissection with pneumoperitoneum. Besides, its role in teaching this important step of the surgical technique for colon resections is unquestionable.

Riassunto

SCOPO: Al giorno d'oggi, non esiste una standardizzazione nelle procedure chirurgiche per il trattamento del cancro del colon. Fin dalla sua introduzione, la chirurgia laparoscopica ha acquisito un crescente interesse per

la chirurgia del colon-retto ed è ora eseguita in tutto il mondo per il trattamento del cancro del colon. Seguendo il concetto di escissione mesocolica totale introdotta da Heald nel 1988 per ridurre le recidive locali dopo il trattamento chirurgico dei tumori del retto medio-basso, l'escissione mesocolica completa è stata recentemente adottata come approccio ottimale per il trattamento del tumore del colon. Tuttavia, l'escissione mesocolica completa, il cui scopo è quello di rimuovere tutti i linfatici e i linfonodi che drenano il tumore, è ancora discussa per quanto riguarda i risultati oncologici. Inoltre, deve essere definito il ruolo dell'approccio laparoscopico per la completa rimozione del mesocolon.

METODO: Una ricerca della Letteratura inglese corrente nel database MEDLINE-PubMed è stata eseguita utilizzando i termini: completa escissione mesocolica; alta legatura vascolare; mobilizzazione della flessione splenica.

CRITERIO DI INCLUSIONE: I criteri di inclusione considerati sono stati: l'escissione mesocolica completa con legatura vascolare alta, e un numero minimo di pazienti inclusi (20 pazienti). Due revisori indipendenti (EI, RC) hanno estratto i dati.

RISULTATI E CONCLUSIONI: Questo articolo riporta una revisione della Letteratura sui risultati dell'escissione mesocolica completa e ne sono stati discussi i dati. È stato focalizzato il ruolo dell'escissione mesocolica completa laparoscopica nei pazienti con cancro del colon, e sembra essere sicuro e fattibile, dovrebbe essere standardizzato, e ipotetici vantaggi oncologici sembrano possibili.

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