

2016 Laparoscopic Surgery: Global view

Laparoscopic complete mesocolic excision with central vascular ligation in right colon cancer: A comprehensive review

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Abstract

Aim of the study is to comprehensively review the

latest trends in laparoscopic complete mesocolic excision (CME) with central vascular ligation (CVL) for the multimodal management of right colon cancer. Historical and up-to-date anatomic-embryological concepts are analyzed in detail, focusing on the latest studies of the mesenteric organ, its dissection by mesofascial and retrofascial cleavage planes, and questioning the need for a new terminology in colonic resections. The rationale behind Laparoscopic CME with CVL is thoroughly investigated and explained. Attention is paid to the current surgical techniques and the quality of the surgical specimen, yielded through mesocolic, intramesocolic and muscularis propria plane of surgery. We evaluate the impact on long term oncologic outcome in terms of local recurrence, overall and disease-free survival, according to the plane of resection achieved. Conclusions are drawn on the basis of the available evidence, which suggests a pivotal role of laparoscopic CME with CVL in the multimodal management of right sided colonic cancer: performed in the right mesocolic plane of resection, laparoscopic CME with CVL demonstrates better oncologic results when compared to *standard* non-mesocolic planes of surgery, with all the advantages of laparoscopic techniques, both in faster recovery and better immunological response. The importance of minimally invasive *meso-resectional* surgery is thus stressed and highlighted as the new frontier for a modern laparoscopic total right mesocolectomy.

Key words: Right sided colonic cancer; Complete mesocolic excision; Central vascular ligation; Laparoscopy; Quality of surgical specimen; Oncologic outcome

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Core tip: Laparoscopic complete mesocolic excision

(CME) with central vascular ligation (CVL) is based on resection of the colon within its intact and inviolate mesocolon with high tie ligation, so to improve the quality of the resection specimen produced; up-to-date anatomo-embryological concepts are analyzed in detail, focusing on the latest studies of the mesenteric organ, its dissection by mesofascial and retrofascial cleavage planes, and questioning the need for a new terminology in colonic resections. The rationale behind the CME with CVL is explained and particular attention is paid to the current surgical techniques. The impact on local recurrence, disease-free and overall survival is reviewed. Current literature about laparoscopic CME with CVL demonstrated better quality of the surgical specimen produced and significant survival advantage when compared to standard non-mesocolic resections, stressing the importance of meso-resectional surgery, especially when performed with minimally invasive techniques: higher surgical quality, faster recovery and better immunological response may in fact contribute to better long term oncologic outcome.

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INTRODUCTION

At the end of the 19th century, Emil Theodor Kocher^[1,2], was the first to theorize oncologic resections based on removal of the involved organ along with its lymphatic drainage; this concept was shortly after substantiated by Miles *et al*^[1] and Jemison *et al*^[2] for rectal and colonic cancer respectively. Yet, the real revolution in oncologic surgery was performed seventy years later by Heald *et al*^[3], who introduced the concept of total excision of the mesorectum (TME), the primitive embryological dorsal mesentery of the rectum: Dissection in the mesorectal plane yields an intact fascial-lined specimen containing all the vasculo-lymphatic pathways and lymph nodes, and reduces the risk of an involved circumferential resection margin (CRM)^[3,4]. The embryological right plane of dissection, graded by the pathologist, has been shown to be independently related to the risk of local recurrence, disease free and overall survival^[5,6], so to promptly became the central part of any multimodal treatment of rectal cancer^[7].

In 2009, Hohenberger *et al*^[8] translated the concept of TME to colonic cancer, noting that traditionally more favorable oncologic results of colon neoplasia was eventually overtaken by rectal cancer: Multimodal strategies, not yet applied to colonic tumors, and a more radical surgical approach performed along embryonic planes of development with higher quality

specimens, produce better oncologic outcome; thus, complete mesocolic excision (CME) with central vascular ligation (CVL) was theorized, standardized and eventually validated by several studies^[9,10].

The concept of complete excision of the involved organ along with its primitive mesentery, associated to central ligation of the supplying blood vessels, is progressively gaining acceptance as the next step towards a modern surgical oncology; surgical resection of the primitive embryological mesentery is in fact pivotal for optimal local clearance. The primitive mesentery is the embryological envelope where the neurolymphovascular structures develop within a double-layered mesenchymal fibrofatty tissue and the initial pathway for cancerous diffusion: Its intact, complete excision is thus essential to clear residual disease in the surgical field, with consequent impact on local control.

Furthermore, CVL allows for an extensive lymph node dissection along the feeding vessels, with significant effect on regional recurrence and systemic dissemination, as shown by improved survival in stage I-III colonic cancers treated with enhanced lymph node harvesting^[11,12].

Blending Complete Mesocolic Excision with CVL is thus the logical step in gaining the highest loco-regional control, removing both the intact mesocolon and the apical nodes, with relevant impact on long term outcome. To take advantage of minimally invasive techniques, laparoscopic approach to CME with CVL seems the natural consequence in the evolution of this procedure.

ANATOMO-EMBRYOLOGICAL CONCEPT OF THE MESOCOLON

The mesocolon is the adult remnant of the primitive dorsal mesentery^[13-19]. In the 5 mm embryo (approximately 32 d), the colon develops within a dorsal mesentery for all its length; an approximately 270° counterclockwise rotation of the primitive mid-gut along the axis of the superior mesenteric artery (SMA) causes the folding of the dorsal mesentery, originating the future mesocolon^[13-19].

In 1885, Treves^[20] stated that the right mesocolon fuses with the primitive posterior parietal peritoneum, with the consequent obliteration of the space between these embryonic structures. This view of mesenteric obliteration through a process of fusion was than refuted in the early '900 by the study of Carl Toldt^[21] and Congdon^[22], who affirmed that the mesentery of the colon persists in adulthood not only at the level of the transverse and sigmoid colon, but all along its length, being separated from the posterior parietal peritoneum by a loose areolar connective plane referred to as Toldt's fascia. Later on, Goligher^[23] described the possibility of stripping back the colon and its meso towards the midline, restoring the primitive embryological disposition

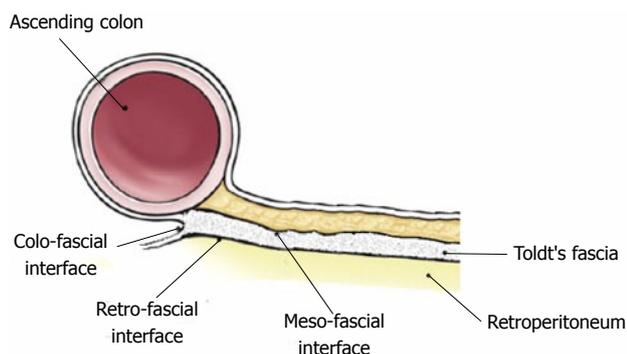


Figure 1 Depiction illustrating the relationships between the mesocolon, Toldt's fascia (schematically exaggerated for descriptive purpose) and the retroperitoneum. Meso-fascial interface is the apposition between the Toldt's fascia and the overlaying mesocolon; Retro-fascial interface is the apposition between the Toldt's fascia and the underlying retroperitoneum.

before its rotation, confirming the Toldt's and Congdon's remarks.

Contemporary view of the mesenteric organ

The increasing focus on the quality of the surgical specimen as an independent variable in the outcome of cancer surgery stresses the need for a more detailed knowledge of the mesocolon anatomy.

Recent papers demonstrated that the mesocolon persists in adulthood as a distinct anatomic structure, continuous from the ileocecal valve to the rectosigmoid junction, with well defined mesocolic, fascial, and retroperitoneal components and related mesofascial (the apposition between the Toldt's fascia and the overlaying mesocolon) and retrofascial (the apposition between the Toldt's fascia and the underlying retroperitoneum) interfaces (Figure 1): These latter are crucial for surgical planes in mesocolic and colonic mobilization^[24,25].

Furthermore, recent studies^[26,27] investigated the mesocolon by light and electron microscopy: Its structure is homogeneous across all locations and is composed of adipocyte lobules separated by thin fibrous septae layered by mesothelium, with lymphatic channels within this lattice; unexpectedly, a further connective, highly cellular submesothelial layer exists between surface mesothelium and the adipocytes.

A detailed appraisal of the lymphatic network within the mesocolon by immunohistochemical analysis^[28], showed that lymphatic vessels occur within both submesothelial connective tissue and interlobular septations, on average every 0.14 mm and within 0.1 mm from the mesocolic surfaces, generating a rich lymphatic network; the authors stressed that breaching the mesocolic surface extensively disrupts this lymphatic network. In the same study, lymphatic vessels were also identified within the Toldt's fascia, with no direct communication with those in the mesocolon, and whose clinical significance (independent or integral part of the mesocolon) should be investigated with further dedicated works: In fact, in mesofascial separation,

mesocolon and fascia are surgically separated with the Toldt's fascia left *in situ* (Figure 2A), whereas in retrofascial separation the mesocolon/fascia complex is separated from the underlying retroperitoneum (Figure 2B); both separations are integral to CME as shown by Hohenberger *et al*^[8], but the exact role of lymphatic channels within the Toldt's fascia could define only retrofascial separation as an oncologically correct plane of resection.

Time for a new terminology?

Some authors^[29-32] advocated the need for a new terminology in describing the mesocolon and its related surgical procedures: Visceral and parietal fascia, pre-renal fascia, parietal plane, somatic fascia may ingenerate confusion and should be standardized in the modern view of the mesenteric organ.

A surgical plane is defined as the interface between two contiguous structures, and in resectional colonic surgery the planes are (1) mesofascial; (2) retrofascial; and (3) colofascial, as shown in Figure 1. In keeping with this, a terminology of total or partial right (left) mesocolectomy has been proposed, being more informative than right (left) hemicolectomy or ileocolic resection because entirely derived for the current anatomical appraisal of the mesenteric organ anatomy.

THE RATIONALE BEHIND

There are three essential components of CME with CVL: (1) development of a mesofascial or retrofascial plane to mobilize an intact and inviolate mesocolon as an intact package; (2) CVL with high tie to maximize the vertical lymph node dissection (central spread); (3) adequate length of bowel to remove pericolic lymphnodes, maximizing the longitudinal lymphnode harvesting (longitudinal spread).

CME allows for removal of the entire envelope of the primitive dorsal mesentery along the anatomic-embryological avascular cleavage planes, and is therefore fundamental for a true radical R0 resection, as the meso contains the whole potential routes of metastatic spread through lympho-vascular, neuroperineural and fibro-fatty tissues^[8-10]. The mesocolon must be excised as an intact, inviolate package as any breach of its surface and underlying structures threatens the radial margin and disrupts the lymphatic network of the meso-structure with consequent *spillage* of neoplastic cells within the surgical field, enhancing the risk of local recurrence. This concept stresses further the need for a correct surgical plane of resection to maximize the local clearance, exactly the same way we conceptually perform TME for rectal cancer: To reduce to reduce the risk of an involved CRM and minimize the risk of local failure^[7].

CVL is essential in obtaining an adequate regional control and impact on survival. The latest 2010 JSCCR guidelines recommends D2 dissection for clinically

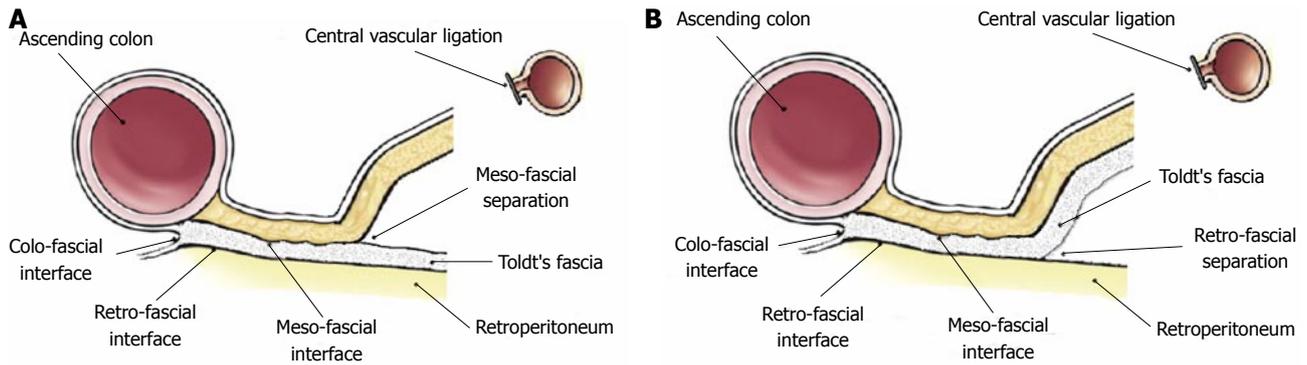


Figure 2 Depiction illustrating the meso-fascial (A) and retro-fascial (B) separation performed in the medial to lateral approach for laparoscopic right meso-colectomy. In Meso-fascial separation (A), the plane of dissection lies between the inferior leaf of the mesocolon and the underlying Toldt's fascia (schematically exaggerated for descriptive purpose), separating both components of the meso-fascial interface. In Retro-fascial separation (B), the plane of dissection lies between the Toldt's fascia and the posterior parietal peritoneum covering the retroperitoneum, separating both components of the retro-fascial interface. Both dissections end with colo-fascial separation.

early stages colorectal cancers and D3 dissection for more advanced disease: Impressive results in terms of local recurrence and patients survival have been reported^[33,34], also by Western authors who claim CME with CVL for right colonic cancer as oncologically effective as D3 right hemi-colectomy performed in Eastern Countries^[8,35,36]. CVL could be crucial in micro-metastatic clearance of central nodes, which are frequently missed by routine histological examination^[37], and thus responsible for loco-regional recurrence and systemic dissemination^[34]. For cancers located in the hepatic flexure and proximal transverse colon, possibly because of an embryological coalescence of mesenteric fascia, metastatic nodes incidence of about 5% for subpyloric station and about 4% for right gastroepiploic arcade has been reported^[38]: Central transection of middle colic vessels, ligation of right gastroepiploic vessels at the origin, 10 to 15 cm of greater omentectomy off the tumor and removal of subpyloric nodes could be beneficial, especially in advanced stages (clinically T3c-d and T4)^[8,39], as shown in Figure 3.

Blending CME with CVL is thus the logical step to ensure the best loco-regional control: CME maximizes the local clearance of the surgical field both increasing the chance for an uninvolved CRM and limiting any neoplastic spillage; CVL enhances regional control, removing apical nodes along the surgical trunk of the superior mesenteric vein (SMV), preventing regional recurrence and systemic dissemination: This is probably plausible for cancer without spread beyond the primitive *meso-structure*, as macroscopic involvement of apical nodes carries a poor outcome, independently from the extension of the surgical resection^[40].

SURGICAL TECHNIQUE OF LAPAROSCOPIC COMPLETE RIGHT MESO-COLECTOMY

Patient is administered general anesthesia and placed in

the supine or lithotomy position; a pneumoperitoneum is maintained at 10-12 mmHg using CO₂. The first step is always a thorough exploration of the abdominal cavity and peritoneal washing for cytology.

Once created the working space, a medial to lateral technique is generally adopted: The ileocolic vessels are stretched so to delineate the Treves arcade, and peritoneal incision is commenced at the base of the created peritoneal fold; dissection of the anterior peritoneal leaf is performed along the left margin of the SMA, with transection of the ileocolic and of the inconstant right colic vessels at their roots. An *en-bloc* lymphadenectomy of the anterior aspect of the SMV from the ileocolic vessels to the gastro-colic trunk of Henle is preformed (D3 lymph node dissection).

The anatomico-embryological plane along the Toldt's fascia is sharply divided from medial to lateral and from bottom to top along the meso-fascial or retro-fascial plane, sometime mobilizing the duodenum, as suggested by Hohenberger *et al*^[8], but usually dissecting along the plane between the intact dorsal mesocolon of the hepatic flexure and the Fredet's pre-duodenopancreatic fascia; the meso-fascial or retro-fascial interface must be carefully identified and components separated without breaching of either, respecting the integrity of the right mesocolon and of the retroperitoneal structures such as right ureter and gonadal vessels. The dissection stops at the lateral aspect of the right colon (right lateral peritoneal fold) exposing the colo-fascial interface, which will be separated later.

In case of caecum or ascending colon cancer, the stretched transverse mesocolon is progressively transected with central ligation of the right branch of the middle colic vessels and the colon is stapled 10 cm off the tumor (Total Right Meso-colectomy; Figure 3, blue lines); for hepatic flexure or proximal colon transversum cancers, middle colic and right gastroepiploic vessels are ligated at their roots, subpyloric lymph nodes are removed, 10 to 15 cm of greater omentum off the tumor is excised and colon stapling is carried out just

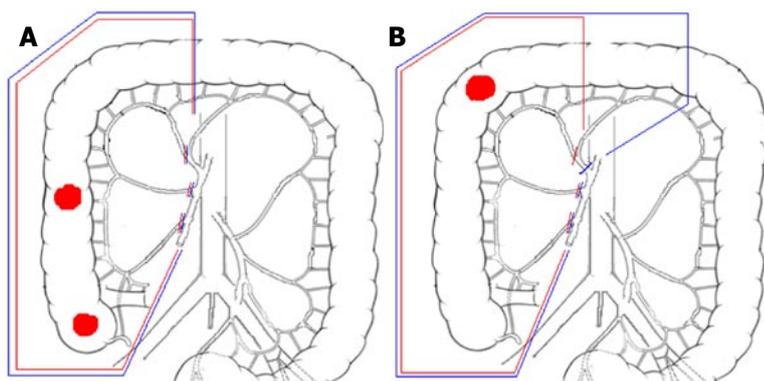


Figure 3 Schematic drawing illustrating the difference between extent of colon resection and lymph node harvesting between D3 right hemicolectomy accordingly to 2010 JSCCR guidelines (red lines) and complete mesocolic excision with central vascular ligation accordingly to Hohenberger's rules (blue lines). A: Cancer located in the caecum or ascending colon; B: Cancer located in the right (hepatic) flexure.

proximal to the splenic flexure (Total Extended Right Meso-colectomy; Figure 3, blue lines).

The hepatic flexure is mobilized by severing the lateral hepatocolic peritoneal fold, with the double components of the superior attachment (right phrenocolic ligament) and the medial attachment (cholecystoduodeno-colic ligament); division of these peritoneal folds demonstrate the colo-fascial interface at this level, which can be easily mobilized.

The right lateral peritoneal fold and the ileocecal peritoneal folds (caecal ligaments) are progressively severed to obtain complete mobilization of the specimen.

The ileum is stapled at 10-15 cm from the ileocaecal valve and the specimen is extracted within a plastic bag through a protected mini-Pfannestiel incision; side-to-side mechanical intracorporeal or extracorporeal anastomosis is fashioned.

Variants to laparoscopic classic CME with CVL

Some authors proposed their experience with modification of the classical approach in CME and CVL: Cho *et al*^[41], adopted a modified CME in respect to 3 major aspects: (1) non performance of Kocherization as described in the original paper of Hohenberger *et al*^[8]; (2) clearance of the pre-renal soft tissue behind Gerota's fascia for T3/4 cancer; and (3) tailored resection of the mesentery and mesocolon according to tumor location.

Feng *et al*^[42] proposed a hybrid medial approach prospectively compared to a completely medial approach: The hybrid approach is based on a first up-to-bottom dissection (section of the gastrocolic ligament and dissection of the middle colic vessels and Henle's trunk) blending with a subsequent classical medial-to lateral bottom-to-top approach; the study demonstrated less time for CVL and fewer vessel-related complications, especially for the pancreatico-duodenal vessels.

Matsuda *et al*^[43] also stressed a cranio-to-caudal approach for total right meso-colectomy, noting that lymph node dissection around the middle colic vessels is technically demanding and potentially exposed to severe intra-operative bleeding: The author suggests a caudal traction of the mesocolon to detect the origin of the middle colic vessels, maneuver suitable for detecting easily various types of middle colic vein

branching and thus reducing the risk of Henle's trunk and/or pancreatico-duodenal vessels injury.

QUALITY OF THE SURGICAL SPECIMEN

Laparoscopic CME with CVL, when performed in the right mesocolic plane, produces high quality surgical specimens. A grading system was developed in the CLASICC trial^[44], with the aim to compare laparoscopically assisted surgery with open resection for colorectal cancer; it was based on translation of the grading system used in the MRC CR07 trial for rectal cancer^[45]: (1) mesocolic plane of resection (“good” plane of surgery; intact, inviolate mesocolon with a smooth peritoneal-lined surface); (2) intramesocolic plane of resection (“moderate” plane of surgery; irregular breaches in the mesocolon, none reaching down to the muscularis propria of the viscus); and (3) Muscularis propria plane (“poor” surgical plane; disruption of the mesocolon down to the muscularis propria).

In the initial study of West *et al*^[46], the *mesocolic plane* translated into a higher quality of the surgical specimen: Wider cross-sectional tissue around the muscularis propria (mean 2181 ± 895 mm² compared to muscularis propria plane with a mean of 1447 ± 913 mm²; *P* = 0.0003), longer distance between the tumor and the mesocolic/retroperitoneal resection margin (44 ± 21 mm vs 21 ± 12 mm for muscularis propria plane, *P* < 0.0001), longer distance between the tumor and the high vascular tie and greater lymph node yield. The same group, in 2010 compared the quality of specimen between the Erlangen and Leeds experience, by precise tissue morphometry and grading of the surgical plane, concluding that CME with CVL routinely performed in Erlangen yields wider mesocolic area (19657 mm² vs 11829 mm²; *P* < 0.0001), longer large bowel (median, 314 mm vs 206 mm; *P* < 0.0001) and ileal (median, 83 mm vs 63 mm; *P* = 0.003) segment, higher distance between the tumor and the high vascular ties (131 mm vs 90 mm; *P* < 0.0001) and more lymph nodes harvested (median, 30 vs 18; *P* < 0.0001), reflecting in higher quality of the surgical specimens and better oncologic outcome^[9]. In 2012, CME with CVL was compared to Japanese D3 resection,

Table 1 Pathological data and oncologic outcome of the principal studies in literature

Ref.	Plane of surgery	High tie	LN harvested	RO	5y LR	5y OS	5y DFS
West <i>et al</i> ^[9]	Ms	90%	CVL 13 cm	CVL 30	Ms 94%	Ms 4.90%	Ms 85%
	NMs	40%	Ctl 9 cm	Ctl 18	NMs 85%	NMs NR	NMs 70%
Hohenberger <i>et al</i> ^[8]	Ms	100%	CVL 13 cm	CVL 32	Ms 97.40%	Ms 4.90%	Ms 85%
	NMs	0%					Ms NR
Siani <i>et al</i> ^[40]	Ms	65%	CVL 13 cm	CVL 30	Ms 97%	Ms NR	Ms 82.60%
	NMs	35%	Ctl 9 cm	Ctl 18	NMs 85%	NMs NR	NMs 60%
Kanemitsu <i>et al</i> ^[34]	Ms	100%	CVL NR	CVL 31	Ms NR	Ms 6%	Ms 84.50%
	NMs	0%					Ms 91.60%
Liang <i>et al</i> ^[48]	Ms	100%	CVL NR	CVL 34 ± 8	Ms NR	Ms 2%	Ms NR
	NMs	0%					Ms NR
Feng <i>et al</i> ^[53]	Ms	94%	CVL NR	CVL 19	Ms NR	Ms NR	Ms NR
	NMs	6%	Ctl NR	Ctl 14	NMs NR	NMs NR	NMs NR
Gouvas <i>et al</i> ^[55]	Ms	68.70%	CVL 8.7 cm	CVL 33	Ms 85.70%	Ms NR	Ms NR
	NMs	31.20%	Ctl NR	Ctl NR	NMs NR	NMs NR	NMs NR
Adamina <i>et al</i> ^[54]	Ms	100%	CVL NR	CVL 22	Ms 100%	Ms NR	Ms NR
	NMs	0%					Ms NR
Bertelsen <i>et al</i> ^[57]	Ms	82%	CVL NR	CVL 36	Ms 97%	Ms 11.30%	Ms 74.90%
	NMs	18%	Ctl NR	Ctl 20	NMs 95%	NMs 16.20%	NMs 69.80%
Shin <i>et al</i> ^[51]	Ms	100%	CVL NR	CVL 27.8 ± 13.6	Ms NR	Ms 3.60%	Ms NR
	NMs	0%					Ms 88%
Bae <i>et al</i> ^[52]	Ms	100%	CVL NR	CVL 28	Ms NR	Ms NR	Ms 90.30%
	NMs	0%					Ms 83.30%

Ms: Mesocolic plane; NMs: Non-mesocolic planes; CVL: Central vascular ligation; Ctl: Control; NR: Not reported.

benchmark for highest survival reported in worldwide literature: Even in this case, CME with CVL showed wider mesocolic area (17957 mm² vs 8309 mm², $P < 0.001$), longer bowel segment (324 mm vs 162 mm, $P < 0.001$) and greater nodal yield (32 vs 18, $P < 0.001$), but equivalent distance between the tumor and the high vascular tie not statistically different (100 mm vs 99 mm; $P = 0.605$), translating in similar impressive long term survival^[10].

RESULTS

The higher quality of surgical specimen translates in better long term oncologic outcome, with significant impact on local recurrence rate, disease free and overall survival: In the pioneering studies of West^[46,9,10], Mesocolic plane of surgery and high tie ligation showed a non-stratified 15% survival advantage at 5 years when compared to *non-mesocolic planes* of resection; interestingly, the survival boost was even more remarkable in the subset analysis for stage III patients, with an increased survival by 27% at 5 years.

These results were confirmed in subsequent studies comparing the different planes of resection, both in open^[8-10,35,36,47] and laparoscopic surgery^[40,48-55], reflecting a significant interest for the brilliant results of CME with CVL. Recently, two important studies further substantiated the effect of the correct plane of resection in colonic cancer: A systematic review on 5246 patients revealed a local recurrence rate, 5 years overall and disease free survival of 4.5%, 58.1% and 77.4% respectively^[56]; and in 2015, a well structured population-based study by the Danish Colorectal Cancer Group^[57] demonstrated a better disease-free survival

for patients with stage I-III colonic cancer, suggesting that both laparoscopic and open CME with CVL may significantly improve outcome.

Unfortunately, these numerous studies (the most relevant reported in Table 1) have significant statistical power limitations, being predominately retrospective and non-homogeneous, so that at the moment a definitive high level of evidence cannot be drawn and thus no strong grade of recommendation may be assigned. This highlights the need for sufficiently powered randomized trials, to definitively address the issue and affirm with conclusive evidence that CME with CVL represents the gold standard in the surgical management of (right) colonic cancer.

CONCLUSION

The current evidence shows the equivalence in terms of tissue morphometry, quality of the surgical specimen and long term oncologic results between laparoscopic and open techniques^[39,43,46,52,55-57], but with laparoscopic approach offering all the advantages of minimally invasive surgery, both in faster recovery and in less immunological stress response which could affect long term outcome^[58-62].

In the multimodal management of right sided colonic cancer, laparoscopic CME with CVL is progressively gaining a pivotal role on the base of high quality surgical specimen, better local recurrence rate, better 5 years overall and disease-free survival when compared to less radical planes of surgery.

Laparoscopic CME with CVL should be regarded as the new frontier of a modern, *meso-resectional* oriented surgery, with all the advantages of minimally

invasive techniques, which allow for faster recovery and better immunological stress response: Higher quality of yielded surgical specimen, less complications when the laparoscopic procedure is *embedded* in an Enhanced Recovery After Surgery program^[63-72] and better immuno-competence due to less surgical stress^[58-62], may thus collectively contribute to better long term oncologic outcome.

Yet, in the absence of high level of evidence which precludes strong grade of recommendation, laparoscopic CME with CVL should be intensely investigated with highly powered, well structured prospective studies, so to define its role in the modern, multimodal management of right colonic cancer.

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