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# SURGICAL INNOVATION IN COLON CANCER: STUDY OF ROLE OF LAPAROSCOPY IN COMPLETE MESOCOLIC EXCISION (CME) FOR RIGHT-SIDED COLON CANCER. FEASIBILITY, SAFETY AND SURGICAL OUTCOME.

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# 1. Abstract

The aim of this project is to evaluate the role of technological innovation in patients with colon cancer undergoing laparoscopic right hemicolectomy. Taking the correct diagnostic and therapeutic management of these patients as a starting point, we performed a thorough preoperative radiological assessment using 3D CT angiography to identify any anatomical abnormalities that could guide the surgical procedure. Instead, to evaluate the efficacy of the surgical procedure, we performed a randomized clinical trial selecting as primary endpoint the perioperative outcomes of patients undergoing laparoscopic right hemicolectomy with conventional or CME technique (Tab. 1)

# 2. Summary

**Background:** Colon cancer represents a major malignancy in industrialized countries. In recent years, numerous advances have been made in the surgical management of these patients. In particular, in 2009 Hohenberg et coll. described the principles of Complete Mesocolic Excision (CME) according to which it is possible to identify embryological planes of surgical dissection of right colon tumors that must be kept intact and removed in toto in order to obtain the best oncological result. Thus, the principle is similar to what Heald demonstrated in 1982 with TME in rectal cancer, which dramatically reduced local disease recurrence. The possibility of correclyt performing CME, which always and necessarily involves Central Vessel Ligation (CVL), however, poses many practical problems related respectively to the increasing diffusion of laparoscopic techniques that make the procedure more complex, to the need to perform a fine dissection in the proximity of major vascular structures (superior mesenteric vessels) and visceral structures (duodenal-pancreatic block) and to the higher rate of anatomical variability of the vascular structures responsible for arterial supply and venous drainage of the right colon. In addition to these purely surgical issues, there are a series of variables related to the patient, cancer pathology and the anatomopathological evaluation.

**Methods:** In an initial phase, our aim was therefore to preoperatively identify by 3D CT angiography any features (vascular anatomical variants, lymph node status along the mesenteric axis) responsible for greater difficulty in surgical dissection and consequently potentially cause intraoperative complications. Subsequently, by conducting a randomized clinical trial, we evaluated differences in short-term outcomes in patients with colon cancer undergoing conventional laparoscopic right hemicolectomy or CME.

**Results:** Preoperative CT scan identified fusion fascia of Fredet in 56 patients (48.3%) and only in 7 cases (12.5%) we recognized its entire course. In contrast, the correct surgical dissection plane between the fascia of Fredet and Toldt's fascia was identified in all patients undergoing successful laparoscopic CME. The ileocolic artery was identified both radiologically and surgically in all patients and, as per surgical technique.In contrast, higher variability was observed for the right colic artery,

right branch of the middle colic an gastrocolic trunk of Henle. The CT scan also allowed measurements on the distance between the root of the different vessels in order to direct the subsequent laparoscopic dissection. Analysis of results demonstrated that there is no precise correspondence between radiological staging and histopathological evaluation in terms of neoplastic lymph nodes because of the simple size criterion adopted to identify any pathological lymph nodes. The results of the randomized clinical trial showed that in the face of a longer average operative time in patients undergoing CME, a better-quality specimen was observed in terms of number of lymph nodes removed and length of the resected colon without a significant increase in intra- and peri-operative complications compared to the group undergoing conventional right hemicolectomy.

**Conclusion:** The preoperative CT scan assessment of the patient has proven its real potential to anatomically evaluate the characteristics of these patients and has indirectly contributed to implement clinical collaboration between the radiologist and surgeon. We found that in experienced hands laparoscopic CME and CVL is a safe and feasible technique, associated with greater nodal harvest without a significant increase in perioperative complications. On the basis of these short term data it is unknown whether there is oncologic benefit associated with the technique, and there is greater expense (due to increased operative time), thus it would seem appropriate to recommend the procedure for selected patients.

# 3. Background

The oncological principles governing the surgical treatment of colon cancer are based on the work of Moynihan, Miles, and Jamieson, which now dates back more than a century ago. En bloc resection of the neoplasm with unscathed margins, no-touch technique, central vascular ligation, and lymphadenectomy are now universally accepted and practiced. The surgical gesture is dictated by knowledge of the anatomy of the colon vessels and the biology of the tumor with development of metastases by lymphatic route. Already in 1909 Jamieson wrote: "*no operation for malignant disease can be considered complete without the removal of lymphatic glands"*. His proposal to distinguish lymph nodes into epicolic, paracolic, intermediate, and main (located at the root of the vessels) groups is still valid up to this very day [1]. Lymphadenectomy should include both longitudinal and proximal spreading stations, located at progressively growing distances of the neoplasm from the root of the vessels [2]. In 1982 Heald et al [3], taking up the concept of longitudinal spreading of lymph node metastases within the mesorectal fascia space, proposed Total Mesorectal Excision (TME) as the standard in the treatment of colon cancer [4]. Preservation of the mesorectal fascia in rectal resection reduces the rate of local recurrence [5, 6]. This has been associated with a constant improvement in the oncological outcome [7]. As determined for mesorectal dissection, assuming that the spread of cancer cells also occurs for the colon within an embryologically defined space, in 2009 Hohenberger et al [8] proposed the concept of Complete Mesocolic Excision (CME) and Central Vascular Ligation (CVL) for right-sided colon cancer.According to principles of TME for rectal cancer. The original study reported a significant decrease in local recurrence, from 6.5% to 3.6%, and improvements in the cancer-related 5-year survival. Nevertheless, this technique seems to expose patients to a higher risk of surgical complications, and several reports have shown that patient outcomes remain controversial. Toldt's mesolic embryological fascia envelops the mesocolon. The potential space between the mesocolic plane and the parietal plane of Gerota's fascia is also called Toldt's space. Dissection along this space with ligation of the vessels at their origin, the principle behind CME, ensures complete removal of the central adipose and lymphatic tissue, preventing incomplete or damaged dissection of the mesocolon. Surgical interruption of this plane carries the risk of cancer cell spillage into the peritoneal cavity, particularly in patients with advanced disease. To safely achieve these goals, the

traditional surgical approach and the extent of dissection have been modified so that complete mobilization involves not only the colon and its mesocolon, but also the entire mesenteric root and duodenum with the pancreatic head in order to allow safe access to the vascular root [9, 10]. Complete Mesocolic Excision (CME) and Central Vascular Ligation (CVL) has the dual goal of performing vascular ligation at the origin and respecting embryological planes in order to obtain a surgical resection with intact mesocolic fascia and lymphatic elements that may contain occult metastases [11, 12]. Standard right hemicolectomy involves a D2 lymphadenectomy, defined as the removal of D1 (epicolic, paracolic) and D2 (intermediate) lymph nodes, whereas the CME and CVL concept also involves performing a D3 lymphadenectomy with removal of the major lymph nodes at the root of the vascular axes en bloc with the affected mesentery [13, 14]. Although the CME concept is now well defined and several papers have been written on the subject, there are still unresolved problems with regard to validation of the quality of the surgery performed. Numerous parameters have been proposed and are mainly based on the observation of specimens by the pathologist with assessment of mesocolic resection plane integrity, morphometric characteristics in terms of number of excised lymph nodes, distance of the tumor from resection margins, length of vascular pedicles, length of the bowel, and area of the resected mesocolon [15, 16]. Other studies have been conducted to evaluate the surgical and oncologic outcomes of patients undergoing right hemicolectomy with CME [17 - 19]. In 2017, Wang C et al [20] conducted an important meta-analysis in which they selected 12 studies with a total of 8576 patients, of whom 3610 were treated with CME. It showed that CME was an effective technique to improve the quality of life and survival of the patients. However, it involved a higher rate of complications and in particular a higher incidence of intraoperative bleeding and postoperative complications. Bertelsen CA et al [21] set out to investigate whether CME in patients undergoing right hemicolectomy might be associated with an increased risk of long-term bowel dysfunction and reduced quality of life compared with conventional colon cancer resections. A questionnaire was administered to 762 patients. Primary outcomes measured were: risk of diarrhea (Bristol stool scale score of 6-7), 4 or more bowel movements per day and impact of bowel function on quality of life. Secondary outcomes referred to other bowel symptoms, chronic pain, and quality of life as measured by the European Organisation for Research and Treatment of Cancer QLQ-C30. At the end of this study, it was concluded that CME in subjects undergoing right hemicolectomy did not appear to be

associated with either bowel dysfunction or impaired quality of life compared with conventional surgery. A recent systematic review by Alhassan N et al. [22] on a total of 14 selected studies confirmed some results already obtained (longer operative time, higher incidence of intraoperative bleeding, higher number of removed lymph nodes) without, however, reaching definitive results in terms of oncological outcome. Indeed, descriptions of the specific results obtained by performing CME are lacking in the literature. Without this important data, the actual oncological effect of CME cannot be clearly assessed. Further data is also needed on the incidence of CME-related intraoperative complications and perioperative morbidity, particularly among those who use this technique regularly. Finally, comparisons of mid- and long-term oncological outcomes should be carried out on patient cohorts with concurrent controls to avoid outcome bias related to different oncological management. Many of the studies conducted in the past and those by Hohenberg aimed at demonstrating the oncological superiority of CME, in fact, took into consideration a control group consisting of a historical cohort of patients who had undergone conventional right hemicolectomy several years earlier and therefore with significant differences due to the chemotherapy treatment received [8]. Therefore, all authors concluded that the quality of the evidence was limited and did not support with certainty the superiority of CME in terms of oncological outcome, which, however, was assumed in light of the higher number of lymph nodes removed and a better quality of the surgical resection. More recently in 2019, Bertelsen CA et al [23] published the results of a prospective, multicenter, nonrandomized clinical trial which evaluated the outcomes in terms of incidence of cancer recurrence in 256 patients undergoing right hemicolectomy with CME compared with 813 patients undergoing conventional right hemicolectomy during the same time period. At the 5-year follow-up, the recurrence rate was 9.7% in the CME group versus 17.9% in the conventional group. Therefore, the authors concluded that CME actually reduces the risk of recurrence in patients with right-sided colon cancer. These results have enlivened the scientific debate and warranted several ongoing randomized clinical trials whose primary endpoint is the oncological outcome of patients with right-sided colon cancer undergoing CME [24].

The most important prognostic factor in colon cancer is the assessment of lymph node status at the time of surgery. The survival rate of patients with lymph node metastases decreases significantly compared with those without lymph node metastases. The number of lymph nodes examined in the

case of colon resection for invasive carcinoma not only provides information for correct staging of patients for possible adjuvant therapy, but is also associated with overall survival. It was seen that the number of lymph nodes collected and examined depends on a combination of several factors, both surgical and pathological, related to the patient, surgeon, and anatomic pathologist. The literature indicates that the number of lymph nodes removed may be related to the site and extent of the tumor, the age and BMI of the patient, the accuracy of the surgical procedure as well as the degree of expertise of the anatomic pathologist in conducting the analysis of the lymph nodes [25].

The guidelines of the National Comprehensive Cancer Network (NCCN) state that proper lymphadenectomy in colon cancer should include:

- ✓ the removal of lymph nodes up to the origin of the supplying blood vessels is done for these to be submitted to pathological examination;
- ✓ clinically positive lymph nodes not included in the resection should be considered suspicious and should be biopsied and removed if possible;
- ✓ positive lymph nodes left in place indicate incomplete resection (R2);
- ✓ no fewer than 12 lymph nodes should be examined to determine proper N staging [26].

Therefore, adequate lymphadenectomy and subsequent evaluation of lymph nodes from the excised specimen are crucial to ensure accuracy in staging and avoid understaging of the tumor. In addition, it has been shown that a higher number of sampled lymph nodes is an independent prognostic factor for improved survival in colon cancer although there are currently conflicting findings on this. Thus, there is an ongoing debate about how many lymph nodes need to be removed for optimal staging. Some studies have shown that the collecting more than 12 lymph nodes is a significant prognostic factor in locally advanced carcinoma (T3/T4) although the number of lymph nodes removed still depends on the factors described above. Another essential prerequisite of CME and CVL is therefore the performance of D3 lymphadenectomy. To achieve this, as described above, it is necessary to isolate the surface of the superior mesenteric vein, perform a ligation at the root of the vessels, and remove all adipose and lymphatic tissue present at this site. However, identifying the superior mesenteric vessels and removing their central lymph increase the potential risks of intraoperative bleeding. Precisely for the purpose of estimating the risk of bleeding complications, numerous radiological and cadaver

studies have been conducted to assess the vascular anatomy of patients undergoing CME and to identify preoperatively any anatomic variables, frequent on the right, that are potentially responsible for intraoperative bleeding complications [27, 28]. Some authors have even made a 3D-printed cast of the vascular anatomy of the right colon to assess the distances and morphology of the different vascular structures and compare the results with measurements obtained intraoperatively in order to facilitate surgical resection [29]. The CME can be performed by either traditional open or laparoscopic technique [30, 31]. The latter certainly offers the most interesting results in terms of functional outcome for the patient, but in fact it is much more complex from a technical point of view and therefore can be performed by experienced surgeons in high volume centers. The results of CME and CVL are still under discussion and the subject of ongoing randomized clinical trials. Among these, for instance, is RELARC [24, 32]. This is a multicenter, prospective, randomized, controlled trial that compared CME with standard D2 lymph node dissection in laparoscopic right hemicolectomy. The D2 procedure involves removal of mesocolon and lymph node and adipose tissues covering the anterior portion of the head and neck of the pancreas (mesenteric roots of the ascending and transverse colon). This procedure is followed by vessel ligation. The CME procedure involves, in addition to what is evaluated in the D2 dissection, the removal of lymph node and adipose tissue on the surface of the mesenteric vessels (superior mesenteric artery and vein). The primary endpoint of this study is 3-year disease-free survival. Secondary endpoints, whose results were recently published, evaluate rates of postoperative complications, postoperative mortality, and percentage of positive lymph nodes. The trial is currently nearing completion and has already provided short-term results demonstrating significant differences between the two techniques only with regard to the risk of intraoperative bleeding (greater in the CME group), but without statistically significant differences in other perioperative complications. We are also confident that completion of the study will also provide meaningful results on the actual oncological benefit of performing CME. While clinical trials similar to what has been described on oncological outcomes are underway, the preliminary results already obtained do not allow settling many controversies concerning the perioperative outcomes in terms of intraoperative complications (intraoperative bleeding, anastomotic leak and postoperative complications according to Clavien-Dindo classification). In fact, most of the previously published studies report an increase in complications in patients undergoing right

hemicolectomy and CME. Several studies have evaluated incidence of anastomotic leak, intra- and peri-operative bleeding rates, gastric emptying time, onset of respiratory failure, mortality, and length of hospital stay. The results show that right hemicolectomy with CME and CVL is associated with increased intra- and postoperative complications. Based on these assumptions and considering that the diffusion of the technique should hopefully include a progressive improvement of perioperative outcomes that are the result of the gradual optimization of the surgical procedure, we have conducted two prospective studies. The first of these aims to perform a radiological assessment to preoperatively evaluate factors indicative of any anatomical and vascular alterations/variables. In the second study, instead, the primary endpoint was the perioperative outcomes of patients undergoing laparoscopic right hemicolectomy with CME compared with a group of patients undergoing conventional laparoscopic right hemicolectomy.

# 4. Complete Mesocolic Excision (CME) and Central Vascular Ligation (CVL) in right-sided colon cancer: surgical and radiological assessment. A prospective observational study.

### 4.1 Introduction

Colorectal surgery has made progressive advances in recent years related on one hand to the implementation of diagnostic methods that allow an early diagnosis of tumors and on the other hand to the development of therapeutic options based on laparoscopic surgery [33, 34]. The concept of Complete Mesocolic Excision (CME) and central vascular ligation (CVL) in right colonic resections appears to improve the oncological outcomes of these patients at the cost of an increased rate of complications. The highest rate of complications in patients undergoing CME was related to intraoperative bleeding due to the central vascular dissection that is performed. Anatomical knowledge of the fusion fascia of Fredet and the vascular anatomy of the superior mesenteric vessels and their branches (right colic artery., right branch of the middle colic artery, Henle's trunk) is a fundamental prerequisite for this type of surgery and in itself increases the technical challenge [36]. At the same time, the need for laparoscopy further increases the degree of difficulty because of the limited operative field and/or its rather arduous exposure and the greater complexity of surgical maneuvers [37, 38]. Recently, technological advances in radiological diagnostics and the use of special software have made it possible to perform CT angiography with multiplanar and three-dimensional reconstructions with the possibility of obtaining a detailed preoperative map of the vascular and lymphatic anatomy of these subjects [39]. This radiological technique has two undoubted advantages: it is less invasive than traditional angiography, which today can no longer be used exclusively for diagnostic purposes; through three-dimensional reconstructions, it makes anatomy more easily accessible to surgeons and therefore allows preparing a precise strategy for the procedure.

**4.2 Methods**

We prospectively enrolled 116 patients with diagnosis of right-sided colon cancer and undergoing laparoscopic right hemicolectomy with CME and CVL between January 2013 and December 2020 at the Policlinico University Hospital of Palermo. We excluded 9 patients with metastatic disease or receiving palliative treatment, 7 cases in which CT angiography could not be performed. At the beginning of our experience, 5 patients were excluded because we preferred to perform a traditional colonic resection with D2 lymphadenectomy due to intraoperative difficulties. All patients had provided written informed consent to the procedure and a positive opinion was obtained from the ethics committee.

*Radiological protocol and image analysis*

CT was performed using a 128-slice scanner (SomatomSensation, Siemens Healthcare). Patients were scanned craniocaudally in the supine position. The scanning ranged from the dome of the liver to the level of the perineum. The following parameters were used: tube voltage 120 kV, tube current mAs 200-650 adjusted according to patient size; section thickness, 0.625 mm. All images were reconstructed with a section thickness of 2.5 mm with the same increment. Patients received a bolus of 80-100 mL of nonionic contrast material containing a high concentration of iodine (iomeprol 400 mg I/kg [Iomeron 400, Bracco Imaging, Milan, Italy]) at a flow rate of 3-4 mL/sec, followed by 30 ml of saline chaser at the same injection rate, through an 18-gauge IV catheter inserted into an arm vein. Contrast material was administered using a mechanical power injector (Invision CT, Medrad). CT scan was acquired immediately before contrast material injection and during arterial and venous phase. Arterial phase was obtained using the bolus tracking technique with an automated scan-triggering software (CARE Bolus CT, Siemens Medical Systems). The acquisition was started immediately after the contrast in the abdominal aorta, above the origin of the renal arteries. reached 150 Hounsfield units. Venous phase was acquired 70 seconds after the start of the contrast injection. CT images were reviewed by an abdominal radiologist with more than 10 years of experience on a Picture Archiving and Communication System (PACS) monitor (AGFA IMPAX 6.4, Agfa Gevaert, Belgium). Reader was aware of the purpose of the study, but was blidend to surgical charts. Image analysis was performed using multiplanar reformations (MPR), maximum intensity projection (MIP)

and 3D volume rendering (VR) technique.

*Identification of vascular and anatomical structures*

The purpose of the radiological study was to identify three different parameters necessary for proper performance of CME and CVL and to compare preoperative observations with intraoperative evidence. All surgeries were performed by teams experienced in laparoscopic colorectal surgery. We evaluated:

- Fascia of Fredet: located between Toldt's fascia involving the ascending colon and the peritoneum of the pre-duodenopancreatic region; it is fundamental for the dissection necessary for the subsequent CME and to avoid a possible tumor spillage in the most advanced cases [40].
- vascular structures: the ileocolic, right colic and middle colic arteries are identified as branches starting from the superior mesenteric artery in the section between the cecum and the middle third of the transverse colon. The gastrocolic trunk of Henle, on the other hand, is at the upper duodenal bend/head of the pancreas.
- lymph nodes: a fundamental prerequisite of CME is the D3 dissection of lymph nodes located along the superior mesenteric axis [41]

**4.3 Results**

*Identification of the fascia of Fredet*

At preoperative CT scan, this fascia was identified in 56 patients (48.3%) and only in 7 cases (12.5%) we recognized its entire course (Fig. 1 – 2). The association with sex and BMI was also evaluated to highlight a possible role of visceral fat in facilitating or not facilitating the radiological assessment of these patients, but no statistically significant differences were found. In contrast, the correct surgical dissection plane between the fascia of Fredet and Toldt's fascia was identified in all patients undergoing successful laparoscopic CME. We also evaluated whether failure to identify the fascia of Fredet radiologically was associated with greater difficulty during surgical dissection assessed in terms of mean operative time related to this step. Operative times were recorded live during surgery and confirmed later by video recording made in all patients. The results obtained showed no statistically significant differences between the two groups of patients (Table 2).

*Vascular structures*

The ileocolic artery was identified both radiologically (Fig. 3) and surgically in all patients and, as per surgical technique, it was clipped at its origin after identifying and isolating the surface of the superior mesenteric vein from its fat (a fundamental prerequisite for the subsequent execution of D3 lymphadenectomy). The right colic artery was radiologically identified in 97 patients (83.6%), whereas in the remaining cases it was not highlighted. Intraoperatively, it was identified in 103 cases (88.7%). In contrast, the greatest variability was observed for the right branch of the middle colic artery, which was present at radiographic imaging in 84 cases (72.4%) and isolated surgically in 98 patients (84.5%). Only in 2 cases (1.7%) both the right colic artery and the right branch of the middle colic artery were absent at radiologic examination. In both of these patients intraoperatively, the right colic artery was identified. Henle's trunk was identified radiologically in 111 patients (95.7%) and in 83 cases (74.7%) consisted of 2 vessels while in 28 cases (25.2%) it consisted of 3 vessels. Intraoperatively, Henle's trunk was detected in 114 patients. In three cases, difficulty in dissection maneuvers resulted in bleeding, which in two cases was controlled laparoscopically using clips and hemostats matrix. In one case conversion to laparotomy was required. The radiographic study also allowed measurements on the distance between the root of the different vessels in order to direct the subsequent laparoscopic dissection (Table 3).

*Lymph nodes dissection*

Lymph node dissection along the superior mesenteric vein (D3 lymphadenectomy) is closely linked to the performance of CME and is reasonably correlated with a better oncological outcome in these patients [42]. Preoperative radiological evaluation of central lymph nodes also could facilitate laparoscopic dissection maneuvers. In this study, we identified central lymph nodes increased in volume (diameter > 10 mm; range 11 - 23 mm) in 38 patients (32.7%). On the other hand, histopathological evaluation showed that 61 patients (52.6%) had lymph nodes with cancer cell spillage.

**4.4 Discussion**

In several articles in the literature, laparoscopic right hemicolectomy with CME and CVL is associated with a larger area of resected mesentery and a significant number of lymph nodes removed at the cost of an increased complication rate [43]. The potential increased risk of complications of this surgical technique is related, on the one hand, to the dissection maneuvers along the vascular axis of the superior mesenteric vessels and in the duodeno-pancreatic area and, on the other hand, to the considerable variability of arterial and venous vessels that feed the right colon [44, 45]. Precisely for the purpose of reducing difficulties during surgical dissection, several studies have been conducted on the role of 3D CT angiography in patients with right-sided colon cancer. In particular, Mari FS et al [39] demonstrated that an adequate preoperative study reduces operative time and the incidence of complications related to incorrect identification of the superior mesenteric vessels. In this study, we considered patients undergoing right hemicolectomy and CME with the aim of knowing preoperatively the presence or absence of the right colic artery, right branch of the middle colic artery and features of Henle's trunk. In cases where the right colic artery is absent, it is possible to misundertand the right branch of the middle colic artery as well as to measure preoperatively the distance between the root of the various vessels can facilitate lymph node dissection and prevent major bleeding. Right colic artery was identified in 83.6% of patients, but the greatest variability was observed for the right branch of the middle colic artery identified radiologically in only 72.4%. Numerous studies in the literature carried out both with cadaveric dissection and with targeted preoperative radiological evaluation have identified an extreme variability both in the presence and at the root of these vessels and therefore the results are to be considered inconsistent in absolute terms [46-49]. At the same time, such variability further justifies the value of adequate preoperative radiological evaluation on a case-by-case basis in order to reduce the risk of complications. Murono K et al. [28] also evaluated the course, ventral or dorsal, of the right colic artery with respect to the superior mesenteric vein, demonstrating that while the ileocolic vessels run ventral to the superior mesenteric vein in only 50.6% of cases, the right colic artery runs anterior in the majority of cases (89.4%). Another key landmark during the performance of laparoscopic right hemicolectomy with CME is Henle’s trunk. This venous trunk has undergone several descriptions, differing to varying degrees from what was originally described by Henle [50] in 1868 based on cadaver studies and on

the type and number of tributary vessels. Recently, He Z. et al [51] performed a multicenter observational study about the features of Henle's trunk during right hemicolectomy. The authors used a classification into 4 different types based on the number of tributary colic veins [52] observing that in most cases (68.4% in total) the venous trunk presents the classic conformation with 2 tributary veins (right gastroepipolic and anterior superior pancreaticoduodenal) or with 3 tributary branches (in addition to the previous right colic vein or right branch of the middle colic artery). This study also showed that a type II venous trunk with two colic tributary branches (right colic vein and middle colic vein) was observed in 24.8% of cases. The gastrocolic trunk of Henle therefore represents a complex vascular structure both for its position in close contact with the duodenal-pancreatic block and because of its extremely variable conformation. In this study, we evaluated preoperatively by 3D-CT angiography the characteristics of this structure with an incidence of bleeding of 2.63% (3 patients out of a total of 114 in whom it was identified intraoperatively) and with need for conversion in one case only. Performing a proper CME involves dissection between the ascending colon and the retroperitoneum while maintaining the integrity of Toldt's fascia, which is a landmark well known to colorectal surgeons. Less well known, however, is the fascia of Fredet, a plane of embryologic adhesion that develops between the ascending mesocolon and the peritoneum of the duodeno-pancreatic region. In the last years, Garcia-Granero A et al. [27, 37, 53] have conducted several studies with extensive description of both Toldt's fascia and the fascia of Fredet. According to these authors, it has always been possible to perform dissection along these embryologic planes without the need to dissect vascular structures or manipulate the duodenum. Despite this evidence, to our knowledge, there are no studies to date in the literature evaluating the fascia of Fredet with preoperative CT. For this reason, we hypothesized the possibility of preoperatively identifying such surgical dissection planes in order to clarify whether different radiological imaging was associated with intraoperative dissection difficulty as assessed by mean operating time and/or complication. Our results showed no statistically significant differences between the two groups. This result could be explained by the real difficulty of preoperative CT scan to identify these anatomical structures, which are very thin in size and affected by many variables including the quality of acquisition of the examination. According to the results obtained, the radiological study does not seem to influence the surgical dissection in these patients. On the other hand, the results obtained by comparing the radiological evaluation of the

central lymph nodes with histopathological examination are interesting. In fact, only in 32.7% of cases are lymph nodes with increased volume along the mesenteric vessels (diameter > 10 mm) assessed, while at the following histological examination 52.6% of patients were found to have neoplastic localizations in this site. This observation actually increases the importance of CME and D3 lymphadenectomy in patients with right-sided colon cancers by reducing the number of understaged patients. It is possible to make a clinical consideration according to which the simple dimensional parameter obtained by CT scan does not allow a correct evaluation of these patients who must therefore undergo optimal surgical treatment and a rigorous oncological follow-up in order to identify early the presence of any residual minimal disease.

**4.5 Conclusion**

The preoperative radiological study in patients with right-sided colon cancer is essential not only to assess the presence of any distant metastases, but also to clarify particular aspects of the subsequent surgical treatment. The possibility of identifying the characteristics and course of the vascular structures along the axis of the superior mesenteric vessels certainly takes on the most important role because of the possible complications, even serious, that may occur during surgical dissection. Images should be evaluated by experienced radiologists and carefully discussed with the surgical team with particular reference to the right colic artery, middle colic artery, and Henle's trunk as these are the structures that tend to show most anatomic variability. The radiological study of the fascia of Fredet is difficult to perform and not always possible, contrary to what occurs in surgical dissection in which the identification of this structure represents a fundamental landmark in all patients for the execution of a correct CME. It is desirable that radiologists are also more familiar with Toldt's fascia and the fascia of Fredet in order to identify those cases in which dissection could potentially be more difficult especially if performed by less experienced surgeons. Moreover, the results obtained in this study showed that there is no precise correspondence between radiological staging and histopathological evaluation in terms of neoplastic lymph nodes because of the simple size criterion adopted to identify any pathological lymph nodes. In the light of all these considerations, further studies on a larger number of patients are needed to validate the results and to investigate other possible factors responsible for potential complications in patients undergoing laparoscopic right hemicolectomy with

CME and CVL.

# 5. Feasibility and safety of laparoscopic Complete Mesocolic Excision (CME) for right-sided colon cancer: short-term outcomes. A randomized clinical study [35].

### 5.1 Introduction

Tthe aim of this study was to evaluate the feasibility and safety of laparoscopic CME for right-sided colon cancer in a referral surgical department for colorectal surgery. To the best of our knowledge, there are no published randomized clinical trials comparing laparoscopic CME and standard laparoscopic right hemicolectomy.

### 5.2 Methods

Between January 2015 and December 2019, 134 patients who underwent to laparoscopic right colonic resection were enrolled in this study and randomly allocated to receive conventional right-sided colonic resection or CME. Between January 2015 and December 2019, 134 patients who underwent laparoscopic right colonic resection were enrolled in this prospective study and were randomly allocated to receive either conventional right-sided colonic resection or CME. We performed an analysis of preoperative data, intraoperative procedures, and postoperative results (Table 4). We compared the short-term outcomes in patients who underwent laparoscopic right hemicolectomy using the CME and CVL technique (CME group) to those in patients who underwent conventional right-sided colonic resection (not CME, NCME group). Computerized randomization was performed by our department, and the information regarding planned procedures was sent to the surgical team on the morning of the surgery. The allocated procedure was not concealed to the investigators or patients (Fig. 4). This clinical study is referred to as the LaCoMEStaR (Laparoscopic Complete Mesocolic Excision versus Standard Right hemicolectomy) study, which was publicly registered (number ISRCTN71842827). The randomization was successfully performed because all surgical procedures

were performed in a high-volume center by two surgeons experienced in colorectal resections and laparoscopic CME (more than 35 procedures) before the beginning of the study in order to obtain proficiency in the standard technique. Only in two cases was there was a technical crossover between the two groups. In particular, in two patients allocated to undergo CME, complete exposure of the superior mesenteric vessels did not occur despite subsequent dissection involving the Fredet fascia. These patients were thus excluded from the final analysis.

*Preoperative data*

We collected preoperative data; all patients eligible for inclusion underwent a complete clinical study [56] in order to evaluate their performance status and American Society of Anesthesiology (ASA) score. In all cases, we performed a colonoscopy for the diagnosis and a computed tomography contrast-enhanced abdominal scan for tumoral staging [57, 58]. Inclusion criteria were age ≥18 years, right-sided colon cancer, no distant metastasis, and written informed consent. Exclusion criteria were open surgery, right colonic resections for inflammatory bowel disease (IBD), and associated major surgical procedures. We excluded five patients with IBD, two patients with synchronous right-sided rectal cancer managed with a combined procedure and transanal extraction of the specimen, and two patients who underwent laparoscopic treatment for colonic neoplasm and liver metastasis in the same surgical step.

*Surgical procedure*

The patient was placed on the operating table in the light Trendelenburg position with the legs apart. No patients underwent bowel preparation before the surgical procedure. Instead, we administered preoperative oral antibiotics. To induce pneumoperitoneum, we used both the trans-umbilical open technique and a Veress needle in the left subcostal region with an optical 10-mm trocar in the left peri-umbilical region [59, 60]. We positioned the other three trocars in the left hypochondrium (5 mm), left flank (12 mm), and suprapubic region (12 mm). We chose to position two 12-mm trocars to create the possibility of using the laparoscopic endostapler alternately from the left side and from the suprapubic trocar, respectively, for the section of the terminal ileum and the transverse colon.

Here, we describe the surgical details of CME. The procedure started with traction of the caecum and

the terminal ileum to detect the ileum-colic vessels (Fig. 5). This was the first fundamental step in performing CVL and, subsequently, CME, because in this phase we identified the ileocolic vessels with ligation at the origin from the superior mesenteric vessels (Fig. 6). We continued with the dissection of the Toldt's fascia between the visceral peritoneum of the ascending colon and the Gerota fascia (Fig. 7). After a medial-to-lateral and bottom-up dissection, and preparation of the last ileal loop, we removed the lymph nodes and adipose tissue covering the duodenum and the head of the pancreas, with the identification of the fusion fascia of Fredet [27], complete detachment of the mesocolon, and ligation at the origin of the right colic vessels, gastrocolic trunk of Henle, and right branch of the middle colic vessels. We used a 45-mm endostapler (Echelon Flex® Endopath stapler, Ethicon or EndoGIA®; Medtronic Inc., Minneapolis, MN, USA) to section the terminal ileum and transverse colon. We performed an extracorporeal anastomosis or a side-to-side intracorporeal anastomosis with endo-stapler and a double-line continuous resorbable barbed suture and intra-corporeal knotting (Fig. 8). In these last patients, at the end of the procedure, surgical specimens were removed through a mini-laparotomy on a suprapubic 12-mm trocar.

In the NCME group, after traction of the caecum and terminal ileum, we identified and ligated the ileum-colic vessels, with no exposure of the superior mesenteric vessels and with no dissection of the pre-duodeno-pancreatic tissue. Often, in these cases, it was not necessary to ligate at the origin of the right colic vessels or gastrocolic trunk because of the surgical dissection in the context of the mesentery (Fig. 9).

*Evaluation of surgical outcomes*

We evaluated the feasibility and safety of laparoscopic CME within a follow-up period of 30-days (short-term outcome). Several primary endpoints were evaluated (operative time, intraoperative blood loss, other complications, conversion rate, and anastomotic leak) and secondary endpoints (overall postoperative complications by the Clavien-Dindo classification, with particular attention to the reoperation rate [Grade IIIb] and admission to the intensive care unit [ICU] [Grade IV]) [61]. In addition, we evaluated histopathologic data, including specimen length and lymph nodes harvested, as objective signs of the quality of CME, related to oncological outcomes. The number of reported lymph glands was contingent upon both the technical prowess of the surgeon and the diligence and

techniques of the pathologist. Therefore, we involved a team of three pathologists experienced in colorectal cancer (more than 250 colorectal cancer examinations with lymph-node detection) who were blinded to the method of surgery (CME or NCME). The pathologists used a standardized report for the pathological analysis, detailing the length of the specimen, size, and location of cancer, the margin from the tumor, the number and involvement of lymph nodes, grading of the neoplasm, and the pathological staging of the disease. The surgical specimen was fixed in 10% formalin solution and then processed routinely for paraffin embedding. Conventional methods of visual inspection and palpation were used to identify the nodes. There were no differences amongst the pathologists in terms of the number of nodes identified. We did not use a specific technique for a special fat clearance in the lymph-node detection. Tumor tissue genotyping was used instead as the routine approach in the oncological management of these patients because of its ability to guide first-line chemotherapy most effectively (e.g. identification of KRAS and/or BRAF) and identify recurrences (e.g. circulating tumor DNA). Statistical analysis was performed with SPSS 25.0 (SPSS Inc., Chicago, IL, USA) in a blinded manner, reviewed by an external statistician. Quantitative variables were expressed as mean (range) and categorical variables as count (percentage). Continuous data were analyzed with the Student's t-test and categorical variables were compared with the Chi-squared test. A p-value $<0.05$ was considered statistically significant. A power analysis determined that 59 patients would be required to demonstrate a clinically acceptable 30-minute difference in operative time between the CME and NCME groups at a significance level of 5% and power of 80%. Furthermore, 44 patients would be required in each group to demonstrate a clinically acceptable difference (5) in the number of lymph nodes between the CME and NCME groups at a significance level of 5% and power of 80%.

**5.3 Results**

Between January 2015 and December 2019, we collected data from 132 patients (70 male and 62 female) who underwent laparoscopic right colonic resection and were eligible for this study. The main demographic characteristics of the included patients are reported in Table 5. The mean age was 67.8 years (range 26–88), with a significant difference between the CME and NCME groups (70.2 years versus 65.3 years, $p<0.05$). For other variables such as sex, BMI, ASA classification, and anastomosis technique, no statistically significant differences between the groups were seen. Table 6 lists the

operative outcomes of all patients. The CME group had a significantly longer mean operative time than that in the NCME group (216.3 min versus 191.5 min, p=0.005). However, the CME group had a higher number of lymph nodes (23.8 versus 16.6, p<0.001) and larger surgical specimens (34.3 cm versus 29.3 cm, p=0.002). No differences were reported with respect to intraoperative blood loss, conversion rate, leakage, or other postoperative complications. In terms of intraoperative blood loss, no patient in either group underwent intraoperative blood transfusion. In the postoperative period, five patients in the CME group and four patients in the NCME group required blood transfusions. In the CME group, we observed two conversions to open surgery (3%) because of voluminous cancer with infiltration of the parietal peritoneum. In the NCME group, three conversions were due to visceral adhesions (n=2) or lesion in the colonic flexure (n=1). No conversion was linked to difficult mesocolic dissection or vascular injuries. We also registered two cases of intraoperative complications in the CME group: one case of jejunal perforation repaired with laparoscopic sutures, and one colonic perforation during dissection with no cancer dissemination. In the NCME group, there was one case of colonic perforation of the hepatic flexure with conversion to open surgery.

**5.4 Discussion**

In the present randomized clinical trial, there were no significant differences in terms of bleeding and blood transfusion between the two groups. In the CME group, we observed a significantly longer mean operative time, a higher number of lymph nodes, and larger surgical specimens. In the pathological examination, we considered the length of the surgical specimen and the distance of the tumor from the margin, which was greater than 5 cm in all cases. We only reported the total length of the specimen because with CVL, this implied a greater mesocolic resected area, though this is not a certainty because it could be argued that the two variables (length of the specimen and mesocolic resected area) are not necessarily co-linear. In the CME group, 25.2% of patients had positive lymph nodes (pT1 and pT2), while in the NCME group, only 17.8% of patients had positive lymph nodes. Therefore, the difference in positive lymph nodes between the two groups (CME and NCME) was statistically significant, and CME probably reduced the understaging of right-sided colon cancer. To prove with certainty that the CME reduced the understaging of right-sided colon cancer we seemingly should perform NCME resection, followed immediately by resection of additional mesentery by CME

technique or detailed anatomic analysis of the resected mesentery demonstrating that some patients had positive nodes only in areas that would be considered part of the CME resection, but not the NCME resection. Both these condition were not admissed in the clinical practice. However, the explanation of our positive results could be related to the careful research of embryological landmarks such as the fascia of Toldt and the fusion fascia of Fredet. In the CME group, we prospectively described the dissection along the pancreatic-duodenal block, with complete detachment of the mesocolon and CVL, and these data were retrospectively confirmed by a thorough review of the surgical video in order to obtain a rigorous group classification. In the 67 patients in the CME group, we did not observe significant intraoperative bleeding. In laparoscopic right hemicolectomy, correct embryological sharp dissection with preservation of the visceral fascia and complete removal of the regional lymph nodes could be supported by the use of advanced energy devices and accurate vision systems, such as 3D or 4K [38, 62]. In the CME group, we observed two visceral intraoperative complications: a jejunal perforation and a colon perforation. These are uncommon complications, and both were observed in patients with history of previous surgery. The jejunal perforation occurred in a patient with cancer of the ascending colon and a previous median laparotomy for open splenectomy, performed in a trauma emergency. In this case, we found severe adhesion syndrome in the left abdominal quadrants, with difficult trocar placement. During this maneuver, we observed a millimetric jejunal perforation, which was repaired with intracorporeal sutures. A colon perforation occurred in a patient with cancer localized in the caecum and a history of laparotomic cholecystectomy (20 years prior), with severe adhesions between the colonic flexure and hepatic margin. These rare complications were due to adhesion syndrome, and had no relationship with the execution of CME. Our primary endpoint is rightly represented by the perioperative outcomes which are notoriously influenced by many parameters. Precisely for this reason to evaluate feasibility and safety of laparoscopic CME we identified several endpoints like operative time, intraoperative blood loss, other intraoperative complications, conversion rate and anastomotic leak, that all together were the perioperative overall outcomes. When we designed this study we thought that simply expression "overall perioperative outcomes" could imply a limitation or a confounding factor because this outcome is influenced by many surgical and non-surgical conditions. In literature the same operative time is associated with increased rate of complications and in our study CME group had significant

longer operative time than NCME group, but no higher rate of complications. In the patients of the two groups (CME and NCME), in addition to the total operative time, we also registered the duration of the different surgical maneuvers to expose any differences related to the surgical technique that were not attributable to the execution of CME. In particular, we measured the following surgical phases: induction of pneumoperitoneum and positioning of the trocars, dissection of the Toldt's fascia and the Gerota fascia, central vascular ligation and identification of the fusion fascia of Fredet with complete detachment of the mesocolon (CVL and CME), anastomosis (intracoporeal or extracorporeal). The only statistically significant difference was in the central vascular dissection and thus in fact in the execution of the CME. Although previous studies in literature reported a longer operative time when an intracoporeal anastomosis was performed, in our study there were no significant differences in other surgical maneuvers (except for central vascular dissection) and in the time of anastomosis (mean time for intracorporeal anastomosis: 14 min and 50 sec, range 9 - 24 min; mean time for extracorporeal anastomosis: 13 min and 35 sec, range 7 - 19 min; p-value > 0.05). In the present study, we also considered secondary endpoints, such as postoperative complications, and found no differences between the two groups. Among the major complications, we reported two cases of reoperation (Grade IIIb sec. by the Clavien-Dindo classification) in the CME group due to postoperative acute alithiasic cholecystitis and one anastomotic leakage approached by laparoscopy [63]. In the NCME group, we observed two cases of anastomotic leakage and a patient who developed intraabdominal collection. In contrast, many other authors have found that CME was associated with more postoperative surgical complications than NCME, probably caused by extensive dissection and visceral lesions. On this basis, Strey et al. [64] attempted to describe a standardized surgical procedure, with identification of the "critical views", in order to improve the quality of CME and reduce the surgical complication rate. In the present prospective study, we also collected histological data, such as the specimen length and the number of harvesting lymph nodes, which are objective signs of quality of CME and are directly related to oncological outcomes [65 - 67]. Many authors assigned intraoperative bleeding to vascular injuries during the central dissection of the superior mesenteric vessels and/or gastrocolic trunk [68, 69]. Hohenberger et al. [8] described a significant increase in cancer-related survival (82.1% to 89.1%) with the use of CME. Several studies that reported better results for CME in terms of large bowel length, area of mesentery, and total lymph

nodes presented with an internal selection bias due to the inclusion of both open and laparoscopic CME [70, 71]. A recent review by Alhassan et al. [22] stressed the differences between CME and D3-lymphadenectomy because both techniques ensured similar lymph nodes harvesting, but CME was superior in terms of bowel length and area of resected mesentery. This could influence oncological outcomes. Other studies compared the oncological results of CME with an historical control group that had an internal bias related to the patient selection and progressive improvement of chemotherapy [72, 73]. A recent single-center study by An et al. [74] showed no differences between CME and NCME in the 5-year disease-free survival rate, but the overall survival was better in the CME group. We can infer from this that a greater mesentery area and lymph node field results in improved survival rates, but better data are needed to finally validate these results [75]. To the best of our knowledge, this is the first randomized clinical trial on the use of CME in laparoscopic right colonic resection. Correct randomization is crucial for an accurate result analysis. In this single-center study, we involved a surgical team that was experienced in laparoscopic colorectal surgery, with standardization of the technique and a low possibility of crossover between the two arms. In the description of the surgical procedures, the only differences concerned the induction of the pneumoperitoneum and the type of anastomosis. The dissection was performed precisely as described in the methods session, and was subsequently confirmed through a careful viewing of the videos. At the same time, our study had several limitations. First, it was a single-center study and the limited number of Italian patients could represent a potentially bias in terms of preoperative characteristics (BMI distribution, comorbidity, ASA score, and previous surgery) and postoperative results. In the present study, the mean BMI was 25.5 kg/m², and although the mean BMI did not differ between the CME and NCME groups, the range of BMI did differ. A high BMI can increase the difficulty of laparoscopic surgery and/or the rate of conversion to open surgery and complications, but in the present study, BMI did not influence the feasibility and safety of laparoscopic CME. Second, we only recorded the surgical and postoperative outcomes over a short-term period in the assessment of the feasibility and safety of the CME technique, and there was a lack of oncological outcomes over a long-term follow up. Furthermore, we measured the specimen length and number of lymph nodes, but we did not report the length of the vascular pedicle and the area of the resected mesentery.

### 5.5 Conclusion

This prospective study considered patients who underwent laparoscopic right colectomy in a single high-volume university hospital from January 2015 to December 2019, and all procedures were performed by an experienced colorectal and laparoscopic surgical team in order to achieve a standardized technique. Moreover, data from both the CME and NCME groups were collected during the same period, with no bias linked to significant surgical and technological improvements. In this single-center randomized clinical trial, we found that in experienced hands laparoscopic CME and CVL is a safe and feasible technique, associated with greater nodal harvest without a significant increase in perioperative complications. On the basis of these short term data it is unknown whether there is oncologic benefit associated with the technique, and there is greater expense (due to increased operative time), thus it would seem appropriate to recommend the procedure for selected patients. Multi-center randomized controlled trials with larger numbers of patients and long-term follow up are needed to validate the surgical and oncological results of laparoscopic CME for right-sided colon cancer.

# 6. Conclusion

The results obtained from these studies are interesting because they allow an optimization of the peri- and intraoperative management of patients with right-sided colon cancer in order to obtain a progressive improvement of the surgical outcome. The preoperative radiological assessment of the patient through a widely used method, such as CT scan, which is easy to perform and necessary for the correct staging in all patients with colon cancer requiring surgery has proven its real potential to anatomically evaluate the characteristics of these patients and has indirectly contributed to implement clinical collaboration between the radiologist and surgeon. This is always desirable in order to achieve the best management of the individual clinical case. On the other hand, the randomized clinical trial comparing CME with conventional right colonic resection for the first time demonstrated that when performed by surgical teams experienced in advanced laparoscopy and at high volume centers, right hemicolectomy with CME and CVL is a safe and feasible technique, not burdened by a significant increase in intraoperative and short-term complications compared to conventional surgery. In light of these considerations it is possible to state that preoperative 3D-CT angiography, when not contraindicated (renal diseases, hypersensitivity to contrast material administration), should be performed on all patients with right-sided colon cancer in order to identify any characteristics (vascular anomalies and/or size of central nodes) that can modify the coefficient of technical difficulty and consequently the surgical approach. The execution of CME and CVL, although from our results is not per se responsible for a significant increase in intra and perioperative complications, is associated with a longer operative time and is however associated with a potential risk of complications. For these reasons it should be reasonably performed in selected patients with better performance status, able to tolerate any adjuvant chemotherapy and ultimately with a longer life expectancy. Further studies, on a larger number of patients and possibly extended to more centers, are still needed to confirm these results and possibly identify which patients may actually gain the most clinical advantages

# 7. Table and figures

| | |
|---|---|
| **Preoperative radiological assessment of CME** | ✓ To identify preoperative features that can modify the technical difficulty of surgical procedure<br><br>✓ Prospective observational study about the use of preoperative 3D-CT angiography in patients with right-sided colon cancer<br><br>✓ Evaluation of characteristics of<br>- fusion fascia of Fredet<br>- vascular structures and anomalies<br>- central lymph nodes |
| **Feasibility and safety of CME** | ✓ To show differences among two surgical technique<br><br>✓ Randomized clinical trial about the use of laparoscopic CME versus conventional right colonic resection<br><br>✓ Evaluation of short-term outcomes:<br>- intraoperative complications<br>- operative time<br>- postoperative complications<br>- number of resected lymph nodes |

**Table 1.** Highlights of the two clinical studies of this PhD thesis.

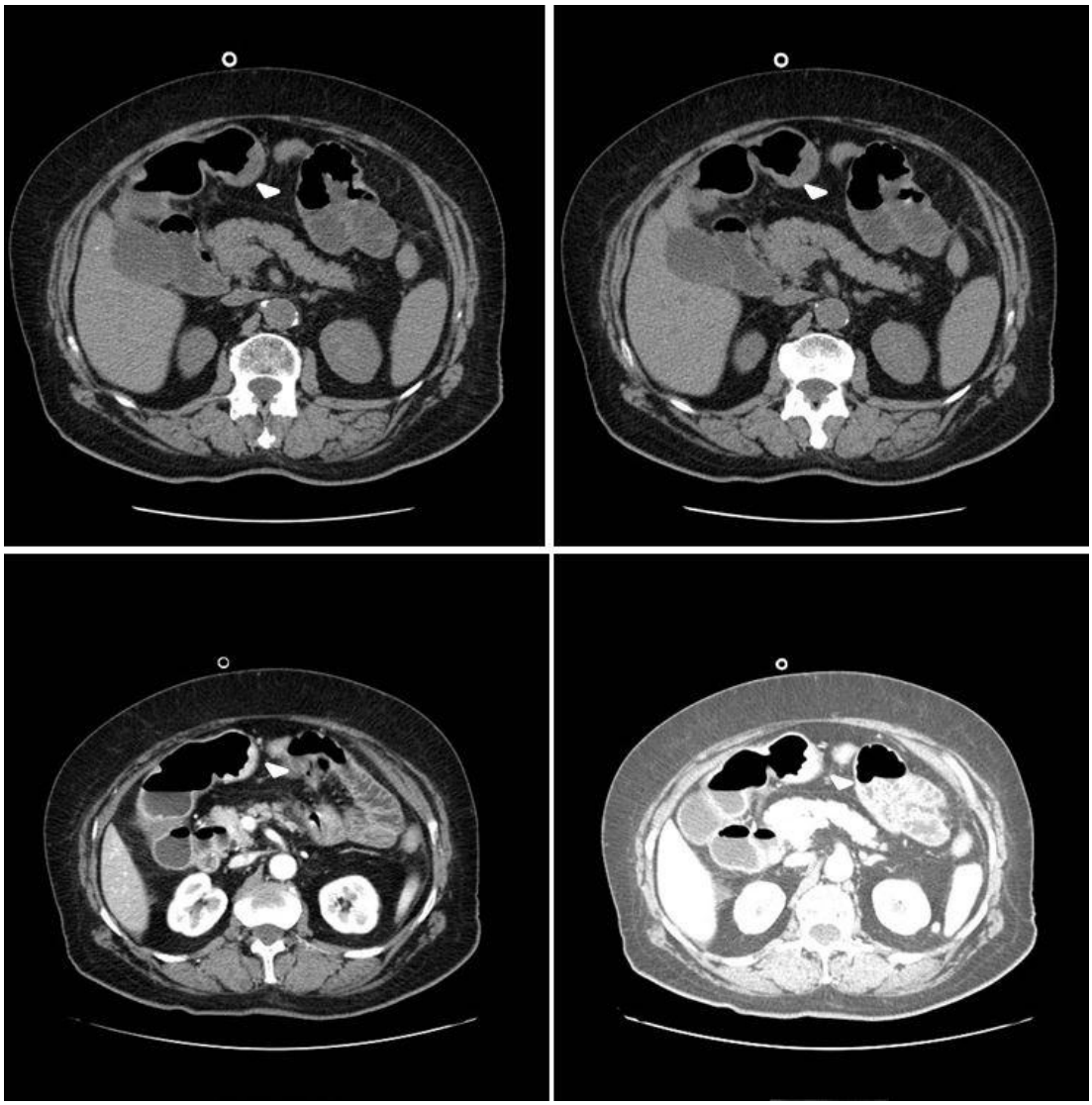

**Fig. 1.** Preoperative CT scan with identification of fusion fascia of Fredet (arrows) in correspondence of the duodenum-pancreatic area.

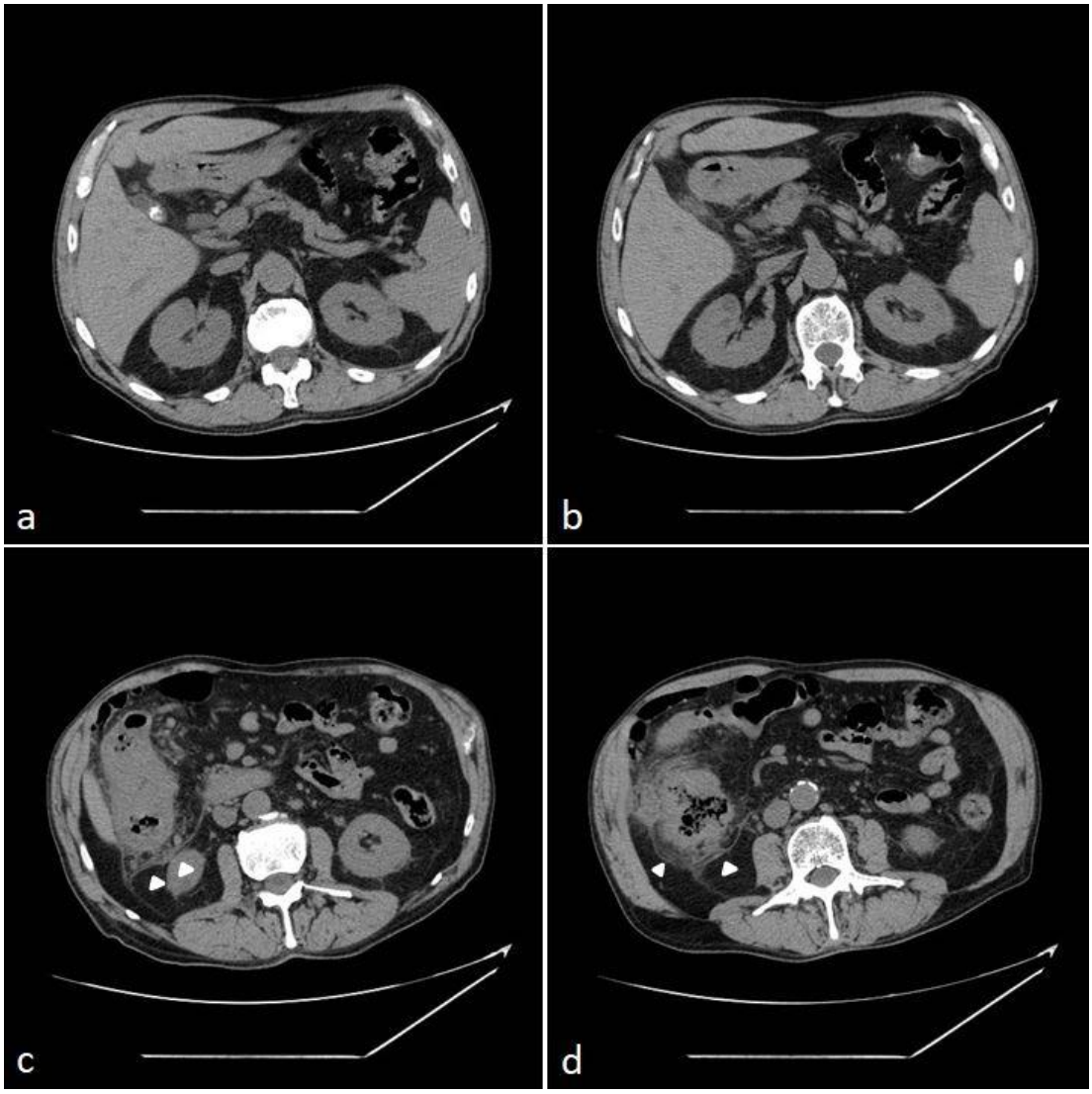


**Fig. 2.** Preoperative CT scan. a-b) in this clinical case is not possible radiological identification of fascia of fredet. c-d) the same patient with clear detecting of Toldt's fascia and Gerota's fascia.

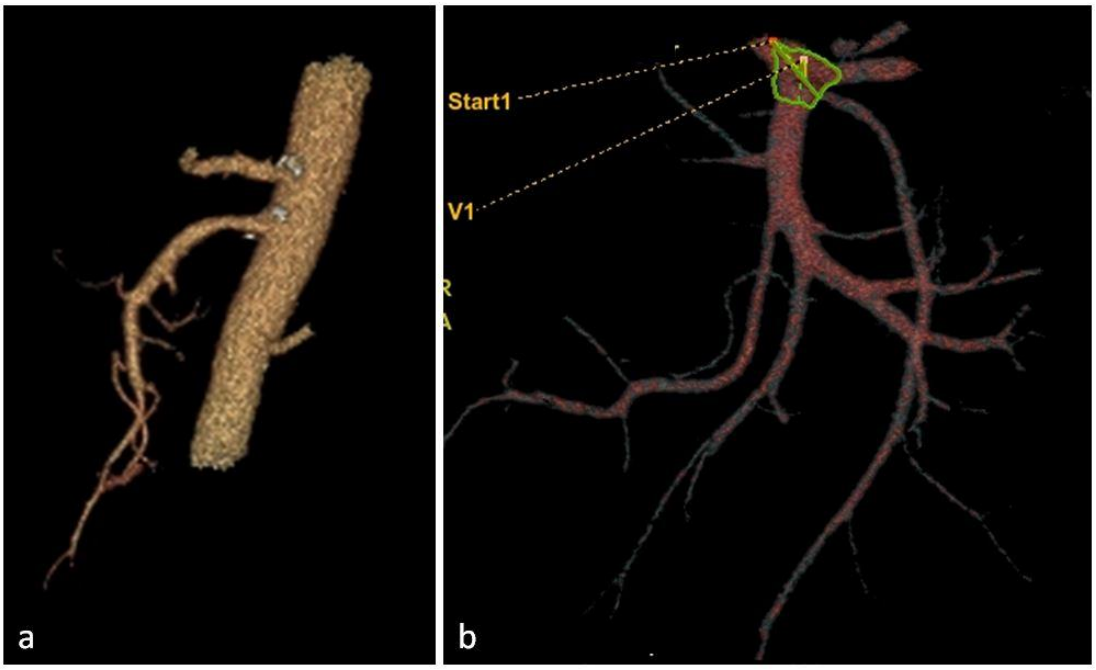


**Fig. 3:** a) Three-dimensional volume-rendered CT angiogram shows the superior mesenteric artery and its branches; b) Three-dimensional volume-rendered CT angiogram shows the superior mesenteric vein and its branches.

| | ***Fredet (n. 56)*** <br> ***Median (range) or %*** | ***No Fredet (n. 60)*** <br> ***Median (range) or %*** | ***Total (n. 116)*** <br> ***Median (range) or %*** | ***P*** <br> ***value*** |
|---|---|---|---|---|
| ***Gender*** <br> *M* <br> *F* | <br> 32 (57.1%) <br> 24 (42.8%) | <br> 36 (60%) <br> 24 (40%) | <br> 68 (58.6%) <br> 48 (41.4%) | <br> NS |
| ***BMI*** | 26.3 (18 – 31.2) | 27.5 (19.2 – 31.6) | 26.9 (18 – 31.6) | NS |
| ***Operative time*** | 16.5 min (13 – 22) | 18.7 (15 – 21) | 17.6 min (13 – 22) | NS |

**Table 2.** On the basis of preoperative CT scan detection of fascia of Fredet we divided the patients in two groups (Fredet and no Fredet). Sex, BMI and operative times of surgical dissection of Fredet's fascia was registered in order to identify any differences influencing radiological features among the two groups of patients. The results obtained showed no statistically significant differences between the two groups.

| **Vascular structures** | **Mean distance (mm)** | **Range (mm)** |
|---|---|---|
| Ileocolic vein – Henle's trunk | 36.07 | 16.5 - 75 |
| Ileocolic vein – middle colic vein | 34.6 | 13 - 58 |
| Henle's trunk – middle colic vein | 9.03 | 2 - 13 |
| Ileocolic artery – right colic artery | 27.8 | 10 - 47 |
| Ileocolic artery – middle colic artery | 28.4 | 12 - 48 |

**Table 3.** CT scan measurements on the distance between the root of the different vessels in order to direct the subsequent laparoscopic dissection.

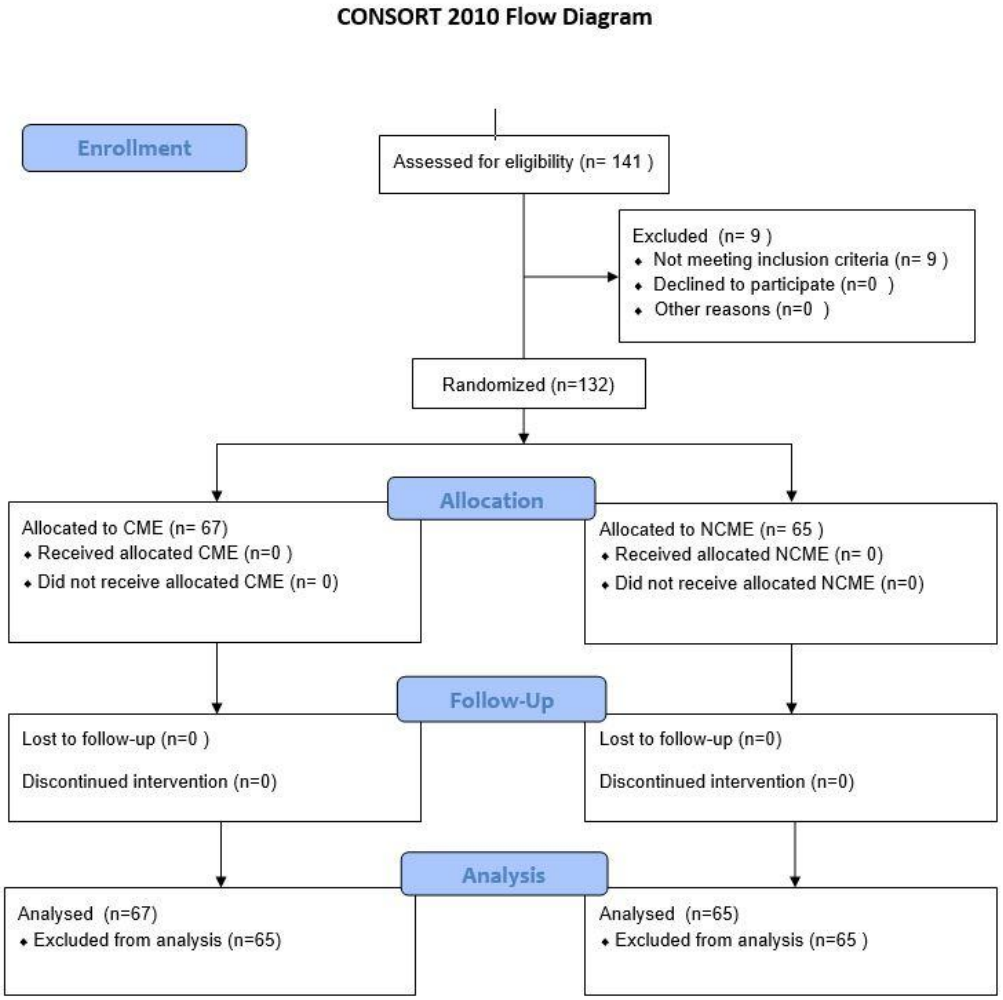


**Fig. 4:** Trial schema

| **Preoperative data** | **Intraoperative procedures** | **Postoperative results** |
|---|---|---|
| Demographic data | Operative time | Overall complications rate |
| Previous abdominal surgery | Intraoperative blood loss | Reoperation rate |
| ASA score | Other complications | Specimen length |
| Tumor location | Conversion rate | pTNM |

**Table 4.** Database with analysis of patients preoperative data, intraoperative procedures and postoperative results

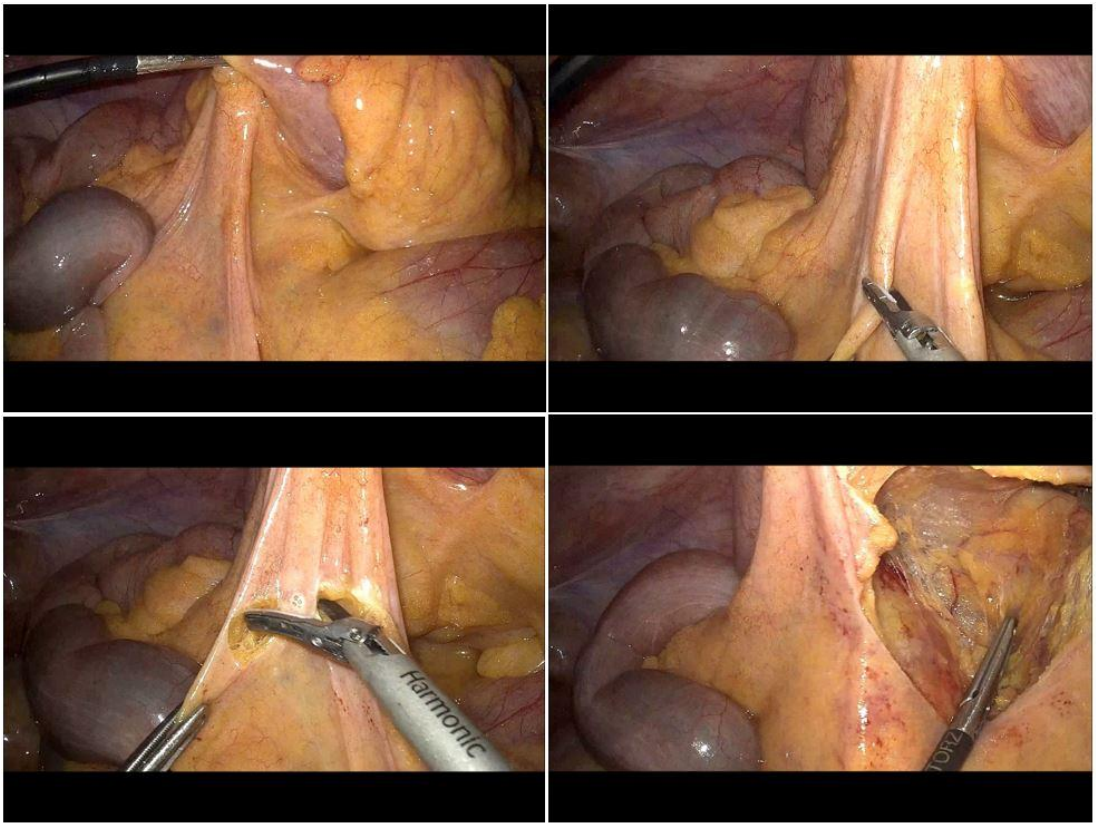


**Fig. 5:** The procedure started with traction of the caecum and the terminal ileum to detect the ileum-colic vessels

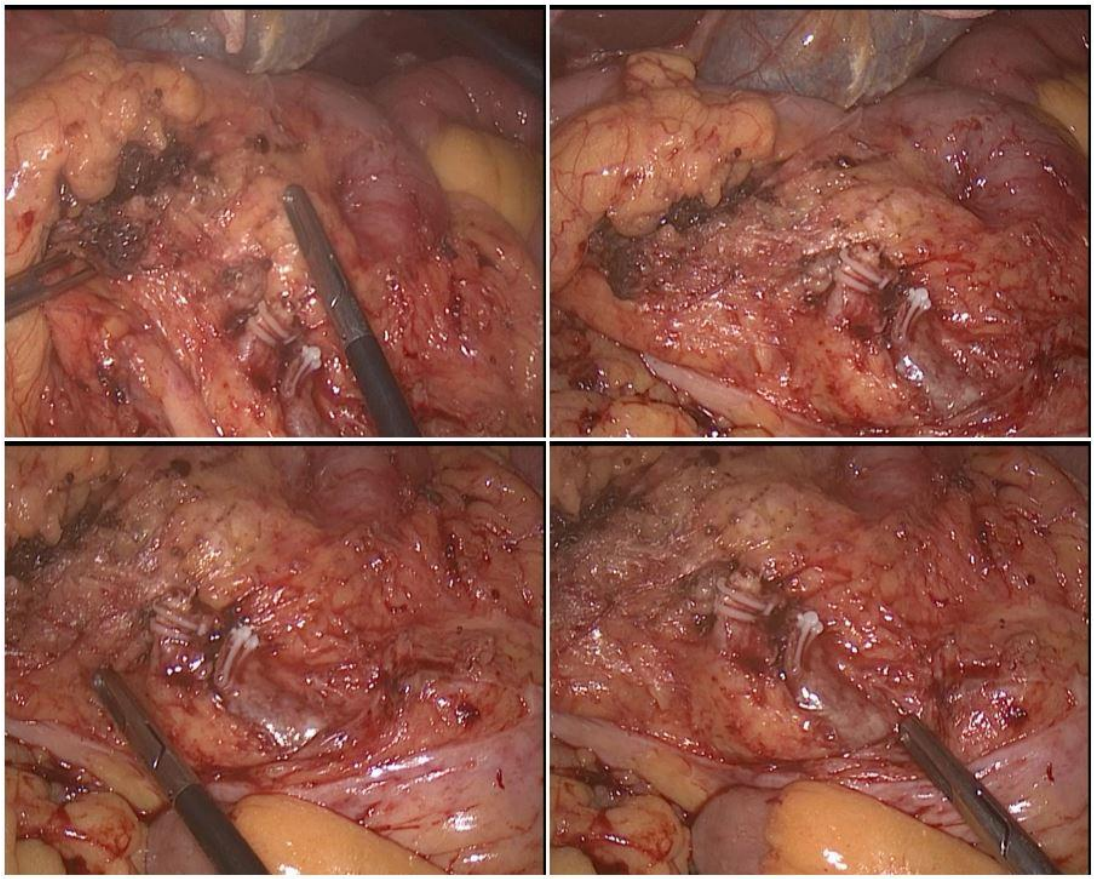

**Fig. 6:** the final results of dissection in CME group with CVL and exposure of mesenteric vessel and duodenum-pancreatic block previous detachment at the origin of fusion fascia of Fredet. These manuevers are fundamental to perform CME and D3 lymphadenectomy.

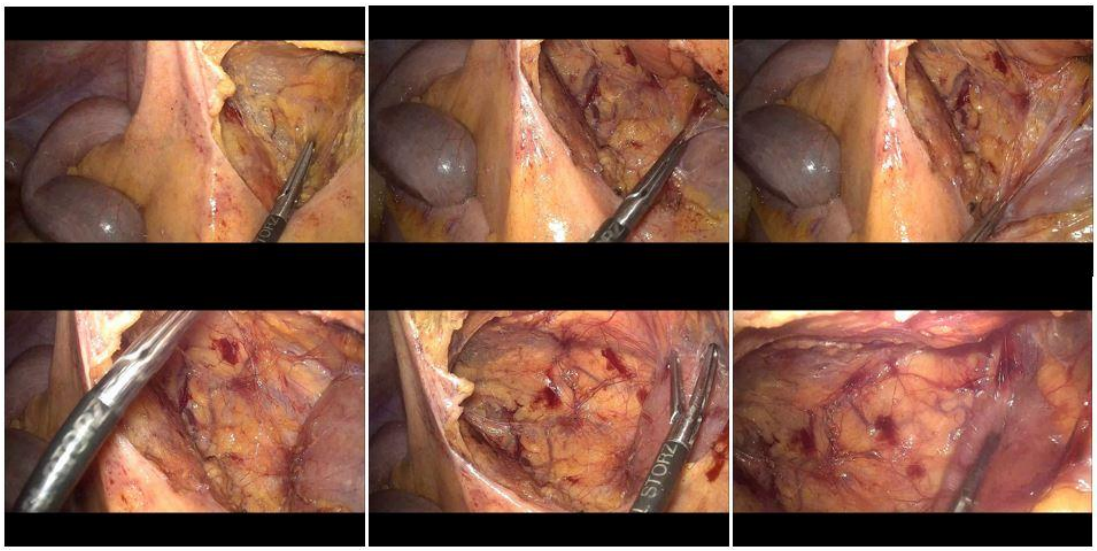

**Fig. 7**: dissection of avascular plane between Toldt's fascia and Gerota.

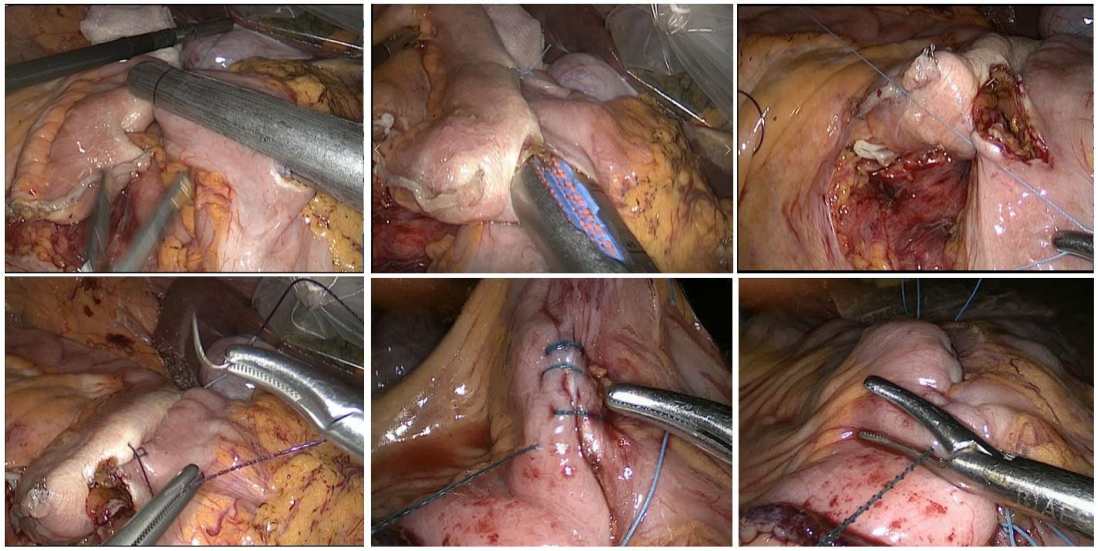

**Fig. 8**: side-to-side intracorporeal anastomosis with endo-stapler and a double-line continuous resorbable barbed suture and intra-corporeal knotting

**Fig. 9**: as described in the NCME group, vascular dissection was carried out after ligation at the origin of the ileocolic vessels without exposure of the superior mesenteric vessels. Often, in these cases, it was not necessary to interrupt at the origin of the right colic vessels and of the right branch of the middle colic vessels. However, this dissection allowed us to obtain an adequate D2 lymphadenectomy as demonstrated by the average number of 16.6 lymph nodes removed in the NCME group.

| | ***CME (n. 67)*** | ***NCME (n. 65)*** | ***Total (n. 132)*** | ***P value*** |
|---|---|---|---|---|
| | ***Median (range) or %*** | ***Median (range) or %*** | ***Median (range) or %*** | |
| ***Age (years)*** | 70.2 (44 - 85) | 65.3 (26 - 88) | 67.8 (26 - 88) | *0.023* |
| ***Gender*** | | | | |
| *M* | 38 (56.7%) | 34 (52.3%) | 72 (54.5%) | |
| *F* | 29 (43.3%) | 31 (47.7%) | 60 (45.5%) | |
| ***Body Mass Index*** | 24.9 (20.2 - 30.5) | 26.2 (19.0 - 34.7) | 25.5 (19.0 - 34.7) | *0.285* |
| ***BMI distribution***<br>*n. of patients (%)* | | | | |
| *< 25* | 33 (49,5%) | 28 (43,1%) | 61 (46.2%) | |
| *25 - 30* | 31 (46.3%) | 33 (50.7%) | 64 (48.5%) | |
| *> 30* | 3 (4.5%) | 4 (6.1%) | 7 (5.3%) | |
| ***Comorbidity*** | 67 (100%) | 64 (99.9%) | 131 (99%) | *1.000* |
| *Cardiovascular diseases* | 51 (75%) | 46 (71.4%) | 97 (73.5%) | *0.98* |
| *Lung diseases* | 17 (25%) | 12 (19%) | 29 (22%) | *0.719* |
| *Renal* | 3 (5%) | 6 (9.5%) | 9 (6.8%) | *0.98* |
| *Diabetes* | 13 (20%) | 18 (28.6%) | 31 (23.5%) | *0.719* |
| *Others* | 7 (10%) | 24 (37%) | 31 (23.5%) | *0.067* |
| ***Previous surgery*** | 11 (16.4%) | 13 (20%) | 24 (18.2) | *0.98* |
| ***ASA score*** | | | | *0.684* |
| *ASA 2* | 5 (7.5%) | 6 (9.2%) | 11 (8.3%) | |
| *ASA 3* | 57 (85.1%) | 54 (83.1%) | 111 (84.1%) | |
| *ASA 4* | 5 (7.5%) | 5 (7.7%) | 10 (7.6%) | |
| ***Tumor location*** | | | | *0.495* |
| *Cecum* | 18 (26.9%) | 29 (44.6%) | 47 (35.6%) | |
| *Ascending* | 33 (49.2%) | 26 (40%) | 59 (44.7%) | |
| *Hepatic flexure* | 12 (18%) | 7 (10.8%) | 19 (14.4%) | |
| *Proximal transverse* | 4 (5.9%) | 3 (4.6%) | 7 (5.3%) | |

**Table 5**. Details of patients preoperative characteristics.

| | ***CME (n. 67)*** | ***NCME (n. 65)*** | ***Total (n. 132)*** | ***P value*** |
|---|---|---|---|---|
| | ***Median (range) or %*** | ***Median (range) or %*** | ***Median (range) or %*** | |
| ***Operative time (min)*** | 216.3 (130 – 300) | 191.5 (120 – 310) | 204 (120 – 310) | 0.005 |
| ***Blood loss (ml)*** | 185 (50 – 350) | 200 (50 – 300) | 190 (50 – 350) | *0.98* |
| ***Conversion*** | 2 (3%) | 3 (4.6%) | 5 (2.3%) | *0.98* |
| ***Anastomotic leak*** | 1 (1.5%) | 2 (3%) | 3 (3.8%) | *0.77* |
| ***Specimen length (cm)*** | 34.3 (21.5 – 67) | 29.3 (17.5 – 68) | 31.8 (17.5 – 68) | *0.002* |
| ***Lymph nodes (n)*** | 23.8 (12 – 38) | 16.6 (5 – 37) | 20.3 (5 – 38) | *0.001* |
| ***T stage*** | | | | *0.712* |
| *T1* | 26 (38.8%) | 31 (47.7%) | 57 (43.2%) | |
| *T2* | 8 (12%) | 9 (13.8%) | 17 (12.9%) | |
| *T3* | 29 (43.3%) | 21 (32.3%) | 50 (37.9%) | |
| *T4* | 4 (5.9%) | 4 (6.1%) | 8 (6%) | |
| ***N stage*** | | | | *0.001* |
| *N0* | 33 (49.2%) | 41 (63.1%) | 74 (56.1%) | |
| *N1* | 24 (35.8%) | 19 (29.2%) | 43 (32.6%) | |
| *N2* | *10 (14.9%)* | *5 (7.7%)* | *15 (11.4%)* | |
| ***M stage*** | | | | *0.98* |
| *M0* | 64 (95.5%) | 63 (97%) | 127 (96.2%) | |
| *M1* | 3 (4.5%) | 2 (3.1%) | 5 (3.8%) | |
| ***Intraoperative complications*** | 2 (3%) | 1 (1,5%) | 3 (2.3%) | *0.886* |
| ***Postoperative complications sec. Clavien-Dindo*** | | | | |
| Grade I - II | 13 (19.4%) | 11 (17%) | 24 (18.2%) | *0.675* |
| Grade IIIa | 2 (3%) | 1 (1,5%) | 3 (2.3%) | *0.886* |
| Grade IIIb | 2 (3%)[1] | 3 (4.6%)[2] | 5 (3.8%) | *0.98* |
| Grade IV[3] | 6 (8.9%) | 7 (10.7%) | 13 (9.8%) | *0.98* |
| Grade V | 2 (2.9%) | 1 (1.5%) | 3 (2.3%) | *0.98* |

[1]two cases of anastomotic leak; [2]two cases of anastomotic leak and one patient with intra-abdominal collection.
[3]In Grade IV complications sec. Clavien-Dindo classification we included all patients that required ICU management in postoperative period.

**Table 6**. Operative outcomes and short-term complications rate

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