COVER PAGE

Study Protocol

OFFICIAL TITLE: Comparison of laparoscopic versus open right colectomy for right colon cancer, according to the complete mesocolic excision (CME) principles: a prospective randomized controlled trial

BRIEF TITLE: Laparoscopic versus open right colectomy for right colon cancer

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1. INTRODUCTION

1.1 Literature Review

Colorectal cancer is the third and second most common malignancy in male and female patients, respectively, with up to 1.8 million new cases and 860,000 deaths per year [1].

Anterior resection with total mesorectal excision (TME) was first proposed by Heald in 1982 [2] and is currently the gold standard surgical technique for middle and lower rectal cancer. Heald considered that the metastatic spread of the tumor occurs through micro-implantations in the lymph node network of the mesorectum, and much less through horizontal intramural infiltration, and thus defined rectal resection margins at 5cm or even 2cm for well-differentiated neoplasms. Therefore, he suggested that mesorectum displays a greater risk for micro-metastatic disease and should be removed en-bloc with intact resection margins.

Similarly in 2009, Hohenberger proposed the complete mesocolon excision (CME) concept for the treatment of colon cancer, based on the respective embryological development anatomical planes. After analyzing a large cohort of patients, he concluded that this operation type leads to a significant reduction in the local recurrence and an increase in the overall survival rates [3].

Hohenberger proposed open CME as the optimal surgical technique for colon cancer, under the premise that the following principles are met [3]:

- Dissection of Toldt's fascia and mesocolon preservation
- Central vascular ligation
- Extensive locoregional lymph node dissection

CME technique, as described by Hohenberger in 2008, is an extension of Heald's TME and it is based on the sharp dissection and separation of the visceral fascia that surrounds the colon from the parietal fascia. The aim is to fully mobilize the colon and the corresponding mesocolon, which is surrounded bilaterally by sheets of visceral fascia. This ensures the complete resection of the tumor and the corresponding lymph nodes. At the same time, central vascular ligation allows the dissection of the apical lymph nodes [3].

There are three resection planes: the mesocolic, intramesocolic and muscularis propria plane. The ideal resection plane is the mesocolic, in which the colon is removed, along with the entire mesocolon and all the venous and lymphatic tissue, without violating the visceral fascia [4]. Surgical specimens categorized into either of the other two resection planes are associated with reduced R0 resection rates [6] and with reduced overall survival. Characteristically, the muscularis propria resection plane has been associated with up to 15% reduced survival rate compared to the mesocolic plane [7 , 8].

There are specific morphometric characteristics of surgical specimens that are used to assess their quality. These include tumor and proximal colon high vascular ligation distance, number of lymph nodes, length of resected small bowel and colon, and total area of the mesocolon [7, 8]. These characteristics are directly related to the number of harvested lymph nodes and, therefore, to overall survival [7, 8].

According to initial results, CME specimens were larger in size, contained a longer length of colon, a larger mesenteric surface and a greater number of lymph nodes compared to the standard colectomy specimens [3]. In addition, a greater distance of the tumor from the resection margins was highlighted [3]. Specifically for right colon cancers, recent publications [6–8, 11–14] have shown that CME can achieve better morphometric specimen characteristics and a greater number of lymph nodes. In a recent randomized study, Di Buono et al. [15] compared the completion of CME or not, during laparoscopic right colectomy. A significant difference was found in favor of CME, regarding the specimen length and the lymph node harvest.

Despite these, the literature evidence regarding the morphological and qualitative characteristics of laparoscopic and open CME specimens are still inconclusive. Specifically for right colectomies, in the comparative study by Gouvas et al. [6], it was observed that the percentage of the mesocolic resection level was 100% in open colectomy, in contrast to 85.7% in the laparoscopic approach. However, this difference was not statistically significant. In a retrospective study by Ali Koc et al. [17], no difference was found between open and laparoscopic CME in terms of specimen length, R0 resection rate and number of resected lymph nodes. A recent

publication by Ali Zedan et al. [18], argued that open CME is associated with longer specimens, larger mesenteric area, and increased resection margins. Another interesting finding was that the number of lymph nodes and the distance of the ligation site were greater in the laparoscopic CME group. However, the meta-analysis by Anania et al. [19] failed to validate any difference between the two methods in the total number of lymph nodes. Finally, a comparative analysis of our own series of patients did not show superiority of one technique over the other in terms of resection level, specimen length and number of lymph nodes [20].

Additional qualitative characteristics of a colon cancer operation include operative time, intraoperative blood loss, time of bowel function recovery, length of postoperative hospital stay, postoperative complications, as well as overall survival and local recurrence rate [2, 6, 8–10]. In a recent meta-analysis by Anania et al. [16] applying the principles of CME to right colectomies did not affect the rates of postoperative leaks, bleeding, overall complications, and reoperations. However, CME right colectomy was associated with optimal results in terms of 3-year overall survival and 5-year disease-free survival [16].

Regarding the application of laparoscopy principles to CME colectomies, previous studies [6–8, 11–14] have confirmed that it is a technique with optimal results, such as faster postoperative recovery, shorter hospital stay, and lower morbidity. There is agreement between studies regarding the perioperative benefits of laparoscopic CME right colectomy versus the open method. According to Huang et al. [21], the length of operative time between the two techniques was comparable. Laparoscopic right colectomy was associated with significantly lower intraoperative blood loss and faster initiation of feeding. In addition, these patients were discharged earlier compared to their counterparts in the open colectomy group. Moreover, no differences were observed in complication and local recurrence rates [21]. These findings were also confirmed by the comparative study of Sheng et al. [22], where the application of the minimally invasive technique resulted in lower levels of postoperative pain, and faster recovery. Accordingly, Shin et al. [23], applying propensity score analysis, to remove possible confounding factors, in a sample of 2249 right colectomies and found that the technique is an independent predictor for 5-year disease-

free survival. Pooled data from Anania et al. [19], confirmed the superiority of laparoscopic CME in the rates of postoperative complications, intraoperative bleeding, and length of hospital stay. These are also in accordance with our own experience, where a significant benefit of the laparoscopic approach was shown in the duration of hospitalization and septic complications, at the cost of prolonged surgical time [20].

2. OBJECTIVE

2.1 Description of the proposed project

The purpose of this research protocol is to compare open versus laparoscopic right colectomy (according to the CME technique of complete mesocolic excision) for right colon cancer. This study will be designed as a prospective randomized controlled trial. The comparison of the two techniques will include endpoints regarding the quality characteristics of the specimens and the oncological results. In addition, the effectiveness of the two methods will be evaluated in terms of the early and late postoperative period.

3. MATERIAL AND METHODS

3.1 Population

The sample will consist of males and females aged 18 to 90 years.

3.2 Diseases

The study will include patients with right colon cancer that will be submitted to right colectomy based on the CME principles.

3.3 Inclusion / Exclusion Criteria

Inclusion criteria are the following:

- Histologically confirmed right colon cancer (cecum, ascending colon, hepatic flexure)
- Surgical resection based on the CME principles
- Patient 18 to 90 years old
- ASA score ≤III
- T≤3
- Elective operation
- Signed informed consent of the patient

Exclusion criteria are the following:

- Non elective operation (hemorrhage, perforation, obstruction)
- Locally advanced disease (T4)
- Distant metastases (Stage IV)
- ASA≥IV
- Previous laparotomy
- BMI >35 kg/m2
- Active sepsis or systemic infection
- Untreated physical and mental disability

• Pregnancy or breast-feeding

• Lack of compliance with the protocol process

• Non-granting of signed informed consent

3.4 Study Arms

There will be two study groups in this trial. Patients randomized to the control arm will be submitted to open right colectomy. Accordingly, the experimental study group will undergo laparoscopic right colectomy. Both techniques will adhere to operative principles of complete mesocolic excision (CME).

In the open right colectomy group, the operation will start with a midline incision and dissection based on the lateral to medial approach [6]. The lateral peritoneal fold along Toldt's line will be incised and the ascending colon will be mobilized from the retroperitoneum according to the embryological dissection planes. Dissection will continue until the anterior surface of the superior mesenteric vessels at the third duodenal part. Ileocolic and right colic vessels will be ligated at their origins. For hepatic flexure tumors, the middle colic vessels will be also ligated at their origin [6]. The ileocolic anastomosis will be performed using an automatic stapler. The anastomosis will be completed either with staples or sutures.

In laparoscopic right colectomy subgroup, the patient will be placed in a lithotomy position [21]. Entrance in the peritoneal cavity will be completed via the open Hasson method. With the installation of the pneumoperitoneum (12 mmHg) an exploratory laparoscopy with a 30° optical camera will be performed. Overall, 4 ports will be used: 10mm at the umbilicus for optical entry, 12mm in the left midclavicular line below the umbilicus as the main working port, 5mm at the McBurney point, and 5mm between the umbilicus and the xiphoid process [21]. An incision will be made in the mesenteric peritoneum under the ileocolic vessels [6]. Dissection of the peritoneal fold, under the terminal ileum, will be performed based on the medial to lateral approach. The dissection will continue laterally, below the right paracolic peritoneal fold, and above the pancreas and duodenum, to the conjoined fascias of the lesser epiploic sac. Similar to

the open approach, the ileocolic vessels, as well as the right branches of the middle colic will be ligated at their origin for cecal and proximal ascending tumors. For hepatic flexure cancers, the medial colic vessels will be ligated. Dissection will be completed with the transection of the right gastrocolic ligament, the peritoneum of the right paracolic groove and the peritoneal recess of the terminal ileum. An automatic stapler will be used for the transection of the terminal ileum and the transverse colon. The ileocolic anastomosis will be completed either intracorporeally or extracorporeally, using staples or sutures [6].

3.5 Anesthesia

Patients will receive general anesthesia.

3.7 Primary endpoint

Mesocolic Resection Plane. Occurence of Mesocolic Resection Plane. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. [Time Frame: 1 month postoperatively]

3.8 Secondary endpoints

Secondary endpoints of the present study are:

Open Conversion. Occurrence of Open Conversion. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. [Time Frame: Intraoperative period]

Operative Time. The total operative time will be recorded. Measurement unit: minutes [Time Frame: Intraoperative period]

Type of Anastomosis. Occurrence of Stapled or Handsewn Anastomosis. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO' [Time Frame: Intraoperative period]

Intraoperative Transfusion. Occurrence of Intraoperative Transfusion. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO' [Time Frame: Intraoperative period]

Postoperative Complication. Occurrence of Postoperative Complication. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. [Time Frame: 1 month postoperatively]

Bowel Function Recovery. Postoperative time until the recovery of bowel function is achieved. Measurement unit: days. [Time Frame: 7 days postoperatively]

Length of Hospital Stay. Postoperative time that the patient can be safely discharged. Measurement unit: days. The patient will be discharged when it is ensured that is medically safe to be released. In particular, as the exit time of the patient, will be regarded the time that the patient will fulfil the Clinical Discharge Criteria. [Time Frame: Maximum time frame 39 days postoperatively]]

Negative Resection Margin. Occurrence of Negative Resection Margin. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. [Time Frame: 1 month postoperatively]

Local Recurrence Occurrence of Local Recurrence. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. [Time Frame: 5 years postoperatively]

Disease Free Survival. Occurrence of Disease Free Survival. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. [Time Frame: 5 years postoperatively]

Overall Survival. Occurrence of Overall Survival. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. [Time Frame: 5 years postoperatively]

3.9 Calculation of the sample size

Sample size calculation was based on the primary outcome. According to the literature [6] the percentage of mesocolic plane preservation in open and laparoscopic colectomy is 100% and 85.7%, respectively. Therefore, for a=5%, power=80%, 10% dropout rate, and 1:1 allocation ratio, the calculated sample in each group is 57 patients. Therefore, the total sample of the study is 114 patients.

3.10 Randomization

The randomization of the patients will be performed using a dedicated software with a 1:1 allocation ratio. The allocation group will be concealed with opaque envelopes that will be opened upon entrance of the patient in the operation theatre.

3.11 Blindness

There will be no blindness at the level of the patient, the treating physicians (surgeon, anesthesiologist) and the researcher who will record the data.

3.12 Exit criteria

The patient will be discharged when it is ensured that is medically safe to be released. The exit time will be regarded as the time that the patient will fulfill the Clinical Discharge Criteria. More specifically, the patient should display the following: steady vital signs, fully oriented, without nausea or vomiting, mobilized with a steady gait and without a notable bleeding [22].

3.13 Monitoring

Following hospital discharge, the patient will be called for reassessment one month after the operation to evaluate any postoperative complications. At the same time, the pathology report of the specimen and the adjuvant treatment will be recorded. In addition, at 5 years postoperatively, overall, disease-free survival and recurrence rates will be recorded.

3.14 Medication

Both preoperative and postoperative patient treatment will be standardized. The principles of the ERAS protocols will be applied to patients [23]. More specifically, antimicrobial prophylaxis will include the administration of intravenous antibiotics within 60 minutes prior to the onset of operation. Patients will receive preoperative, mechanical bowel preparation and per-os antimicrobial prophylaxis. Prior to surgery, patients will abstain from solid and liquid foods for 6 and 2 hours, respectively. The nasogastric tube will be removed postoperatively and repositioned only in case of ileus. Postoperative analgesia will include a multidisciplinary approach using analgesics (paracetamol, lornoxicam) in combination with dorsal or epidural analgesia. Opioid administration will be avoided. Postoperative nausea and vomiting prophylaxis will include granisetron 3mg / 3ml IV. Mechanical and pharmaceutical thromboprophylaxis will be used. A zero-balance approach to fluid losses will be applied. Mobilization will be initiated from the first postoperative day. Feeding will be initiated on the basis of the intestinal function recovery.

3.15 Study Group

All participating members have years of experience in their field and have, therefore, completed the learning curve for the required techniques. Data collection and recording will be carried out by an independent, third party, researcher.

3.16 Conducting a Study

The study will be conducted in the Department of Surgery of University Hospital of Larissa. Patient data will be recorded both in the patient charts and in an electronic database. The required laboratory examinations will be defrayed by the patient insurance funds.

4. LITERATURE

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