INTRACORPOREAL VS. EXTRACORPOREAL ANASTOMOSIS IN PATIENTS UNDERGOING LAPAROSCOPIC RIGHT HEMICOLECTOMY: A MULTICENTER RANDOMIZED CLINICAL TRIAL (THE IVEA-STUDY)

INTRODUCTION AND JUSTIFICATION OF THE WORK:

BACKGROUND AND CURRENT STATUS OF THE SUBJECT

Colon cancer is the third most frequent malignant tumor currently constituting a major health problem in Western countries. In Spain, it represents approximately 15% of the incidence of all tumors, registering more than 25,000 new cases per year, and is the second cause of cancer death (more than 13,000 deaths / year).
The average survival in our country is 48% at 5 years after the diagnosis of colon cancer[1], possibly because it is performed late in most cases and because of the little introduction of screening programs for this neoplasm.
The objective of the surgical treatment of colon cancer is the block resection of the tumor with correct margins of safety, as well as the exeresis of all the corresponding lymph node territory with the ligation of the vessels at their origin. Usually, a proximal and distal margin of at least 5 cm is considered correct, although this is further determined by the vascularization of the colonic segment. When the colon has invaded the surrounding structures locally, a block resection should be scheduled[2,3.]
Tumors located in the cecum or ascending colon require 5-10 cm of terminal ileum with ligation of the ileocolic pedicle and right branch of the middle colic vessels, with resection at the level of the middle transverse colon (right hemicolectomy). A tumor located at the hepatic angle or in the proximal transverse colon requires an enlarged right hemicolectomy, with ligature of the ileocolic artery, right colic and middle colic, and resection of the distal transverse or descending colon[2].
Intestinal reconstruction is performed by a manual or mechanical ileocolic anastomosis. For years, multiple investigations have been realized to determine the best technique for ileocolic anastomosis (suture in one or two planes, simple or continuous suture, resorbable or non-absorbable material, mechanical sutures, etc.), but until now there have been no differences regarding the rate of suture dehiscence.
Lymphadenectomy has different objectives: staging the tumor in the surgical act and trying to perform a complete resection to improve oncological results, this way evaluating the quality of the surgical procedure. There is a direct correlation between the number of lymph nodes excised, and therefore evaluated, with survival. For a long time is known that the existence of ganglia in the surgical piece depends on the surgical technique and the methodology used. The Clinical Guidelines recommend a minimum of 12 lymph nodes studied for a correct tumor stage[3-4].
For years, minimally invasive surgery is performed in a large number of interventions in a safe way. Jacobs et al[5] described the first laparoscopic resection in sigma cancer in 1991. Since then the experience has grown rapidly, and different clinical trials[6,7,8] showed improvements in the postoperative period of the patient without oncological differences. Only the Lacy study showed greater lymph node excision with the laparoscopic technique[9.]
At present laparoscopic surgery has show to be a safe technique, which a better recovery of the patient (decreasing postoperative ileus, early oral diet, more controlled pain, fewer days of hospital stay ...) and also reduces the rates of complications if performed by experienced surgical teams[10]. The most recent randomized studies have shown no oncological differences with respect to open surgery. The percentage of conversion in the literature varies from 2 to 46% depending mainly on the experience of the team.
Among surgical techniques by means of minimally invasive surgery, right colectomy can be considered a particular case in which the technical difficulty added by the frequent anatomical variations, especially vascular ones, have meant a more gradual acceptance of the laparoscopic approach[11]. Unlike the technique used in rectal-sigmoid neoplasms, ileocolic anastomoses after right hemicolectomy can be performed in two ways: extracorporeal or intracorporeal.

The extracorporeal anastomosis is performed by externalizing the ileum and colon through the incision through which the surgical specimen is extracted. The intracorporeal anastomosis is performed completely laparoscopically, and the incision made is only to remove the surgical specimen.

JUSTIFICATION:

Right hemicolectomy using a minimally invasive technique allows for an earlier recovery, with less postoperative pain and less hospital stay. After right hemicolectomy, the ileocolic anastomosis is not performed "naturally" as is habitually done in low anterior resections or sigmoidectomies. There is, therefore, no standardization in the reconstruction technique, with two possibilities: intracorporeal and extracorporeal anastomosis[14].
The intracorporeal anastomosis allows proper visualization of it, ensuring adequate conformation (absence of rotation or traction), in addition allowing the closure of the mesos and avoiding the possible appearance of internal hernia, also allowing to choose the location and length of the incision necessary for the extraction of the piece. On the other hand, it is a difficult technique that requires high training in advanced laparoscopy.
The extracorporeal anastomosis is performed by extracting both ends (terminal ileum and transverse colon) through the incision through which the piece is obtained, and the anastomosis is performed. It does not require, therefore, an important training in intracorporeal sutures. On the contrary, it forces to make the abdominal incision in the area that allows the extraction of said ends. In obese patients it can be difficult since the mesos are short and do not allow their extraction easilywith ,so sometimes, it forces excessive traction. In addition, intestinal rotations during the anastomosis may go unnoticed.
Although there are currently defenders of both techniques, the extracorporeal anastomosis is currently the most performed in our environment and will be used as a reference treatment in the present study.
Numerous studies have been published comparing both techniques[11-20]. A very recent meta-analysis[21], including 12 non-randomized comparative studies with 1492 patients, concluded that intracorporeal anastomosis is associated with less morbidity and a reduction in hospital stay, suggesting a faster recovery. To date, no well-designed, prospective, randomized and randomized study exists in the literature. We believe it is necessary, therefore, to carry out a project that compares both surgical techniques in the treatment of right colon cancer and assess which is associated with a lower postoperative morbidity.

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OBJECTIVES:

The objectives of our study are:

GENERAL:

- To compare perioperative morbidity between laparoscopic right hemicolectomy with intracorporeal anastomosis versus extracorporeal anastomosis within 30 days after surgery.

SPECIFIC:

- Quantify, by means of the Visual-Analogue Scale (VAS), postoperative pain 24 hours after surgery and the day of hospital discharge, and determine which of the two laparoscopic right hemicolectomy techniques produces less pain.
- To evaluate and compare the rate of anastomotic dehiscence in both groups of anastomoses up to 30 days after surgery.
- To evaluate the difference in surgical time between right hemicolectomy with intracorporeal versus extracorporeal anastomosis.
- To evaluate the infection rate of the surgical site in both groups up to 30 days after surgery.
- To compare the difference of days of hospital stay in both groups of anastomoses.

WORK HYPOTHESIS:

In patients with right colon cancer, laparoscopic right hemicolectomy with intracorporeal anastomosis presents less perioperative morbidity than extracorporeal anastomosis.

MATERIALS AND METHODS:

Patients treated in 4 Spanish South-east hospitals with preoperative diagnosis of right colon neoplasm were included. All participating hospitals have vast experience in minimally invasive approach.

Study Design
The IVEA-study is a prospective multicenter randomized trial with two parallel groups being done IA or EA in laparoscopic right hemicolectomy for right colon neoplasia. The patients were randomized using http://www.randomization.com.

Inclusion and Exclusion Criteria
- Inclusion criteria. All patients had to be 18 years of age or over, to be programmed for laparoscopic surgery for right colon neoplasm and provide a signed written consent form.
- Exclusion criteria. All patients who do not meet all the inclusion criteria were excluded. The other exclusion criteria included the need for emergency surgery, renal failure defined by haemodialysis, Crohn's disease, ulcerative colitis, T4 tumor invading adjacent organs, synchronous colorectal neoplasm, metastasis or carcinomatosis at diagnosis, bowel obstruction, psychiatric disorders or contraindication for laparoscopic approach.

Outcome Measures
Patient baseline characteristics at the time of surgery; age, gender, ASA score, major comorbidities and operative variables were obtained from each patient. The 30-day postoperative complications were recorded. Complications were defined as any deviation from the normal postoperative course and graded using Clavien-Dindo classification. The term anastomotic leakage (AL) defines all conditions with clinical or radiologic anastomotic dehiscence, with or without the need of surgical revision. Wound infection was defined as spontaneous drainage of purulent material from the wound or from the surgeon´s deliberate revision and a positive culture of drained serous fluid. The length of hospital stay (LOS), reinterventions, postoperative pain according to the visual analogical scale were also documented. For the subsequent analysis of the patient, the conversion to an extracorporeal anastomosis among the totally laparoscopic procedures or conversion to open surgery has not been included.

Surgical technique
Perioperative care was identical for both groups. Bowel preparation was not used, and intravenous antibiotics were administered preoperatively. Under general anesthesia, the patients were placed supine on the operating table, with open legs. Urinary catheter was inserted. Pneumoperitoneum was induced using carbon dioxide insufflated to an average pressure of 12 mmHg by placement of a infraumbilical trocar. Three additional ports were inserted: 12 mm in the left lower quadrant and two 5-mm trocars in the right lower quadrant and upper left quadrant. Laparoscopic right colectomy was performed with a medial-to-lateral approach, starting with ligation of the blood vessels at their origin followed by mobilization of the bowel and lateral

dissection of the terminal ileum and colon attachments. The colon and ileum were transected with a 60-mm laparoscopic stapler in that order, followed by an ileo-transverse anastomosis.

- **Intracorporeal anastomosis:**

The specimen was preferentially extracted via a small Pfannenstiel-type incision with the protection of an Alexis Wound Protector (Applied Medical, Rancho Santa Margarita, California, USA). The incision for the extraction of the right colon is sutured in two layers by absorbable suture. The ileum was held by the assistant to prevent rotation of its mesentery. A stay suture was applied 10 cm proximal and distal to the stapled ends of the terminal ileum and colon, respectively, and then held by the assistant. An enterotomy and colotomy were made sharply at the antimesenteric corner of the staple lines. An isoperistaltic side-to-side anastomosis was fashioned with a 60-mm laparoscopic stapler. A 2-0 double-barbed suture was used to close the enterocolotomy, in two planes (the first submucosal, and the second sero-serous). The mesenteric defect and the mesocolon after the construction of either type of anastomosis were not closed. Drains were not used routinely.

- **Extracorporeal anastomosis**

The mobilized colon was externalized preferentially via a transverse or midline incisión with the protection of an Alexis Wound Protector (Applied Medical, Rancho Santa Margarita, California, USA). A stay suture was applied 10 cm proximal and distal to the stapled ends of the terminal ileum and colon. An enterotomy and colotomy were made sharply at the antimesenteric corner of the staple lines. An isoperistaltic side-to-side anastomosis was fashioned with a 60-mm laparoscopic stapler. A 2-0 double-barbed suture was used to close the enterocolotomy, in two planes (the first submucosal, and the second sero-serous). The mesenteric defect and the mesocolon after the construction of either type of anastomosis were not closed. The incision for the extraction of the right colon and the realization of the anastomosis is sutured in two layers by absorbable suture. Drains were not used routinely.

Postoperative Management

After surgery, nasogastric tubes were not used, the urinary catheters were removed on postoperative day 1. Early mobilisation was practised and oral fluids administered early, switched to a diet after first passage of flatus. and endovenous hydrations were suspended. Criteria for discharge included pain control, absence of nausea and tolerance of a soft diet without restrictions and passage of gas and stool. All patients were followed-up for at 30 days.

Ethics

The study was presented to the Hospital Ethical Board and accepted as a multicenter randomized trail. The research was conducted conformed to the Helsinki Declaration and to local legislation. Patients gave informed consent to participate in the study. This study has been registered in XXXXX register with the number XXXXX.

Sample Size Calculation

The hypothesis of this trial is that IRA will reduce overall postoperative 30-day morbidity rate. The sample size calculation is based on the detection of significant difference in the primary endpoint parameter of the trial. We assumed a postoperative complication rate of 30% in ERA according with several complication rates after colorectal surgery. With an expected complication rate of 11% in IRA, the sample size necessary for the trial with a power of 80% and one-sided significance level of 0.05 was calculated to be 75 patients per group. An assumed 10% drop-out rate in this trial will raise the sample size to 84 patients per group. Therefore, at least a total of 168 patients have to be included to the trial.

Statistical Analyses

Statistical analyses of any differences between the 2 groups were performed using SPSS version 22 (SPSS Inc. Chicago, IL). Data were presented as means ± standard deviations or as medians and interquartile ranges where appropriate. For dichotomous outcomes, treatment groups were compared by means of the $\chi 2$ test. The Mann–Whitney U test and Kruskal–Wallis tests were used for continuous, not normally distributed outcomes. For continuous normally distributed data, the ANOVA test was used.

Insurance policy
An insurance policy will not be subscribed given that it is not a clinical trial with medications, and that the following conditions are met:
1. The surgical treatments that are applied in the trial are authorized in Spain and their use is adjusted to the conditions authorized and of usual practice. 2. The interventions to which the subjects will be submitted for their participation in the trial suppose a risk equivalent or inferior to the one that would correspond to their attention in the usual clinical practice; complying with the criteria of clinical trial of low level of intervention as specified by Royal Decree 1090/2015, of December 4 that regulates clinical trials with drugs, the Research Ethics Committees with medicines and the Spanish Registry of Clinical Studies.

CHRONOGRAM-PHASES OF WORK:

- SURGICAL INTERVENTION: We will perform surgical interventions throughout the first 18 months of the study. Patients will be randomized and, depending on the group, the technique will be performed by intra-or extracorporeal anastomosis. During the first eighteen months.

- FOLLOW UP: Patients will be assessed daily during their hospital stay, and subsequently in consultation according to the protocol that is attached in methodology.

- DATA COLLECTION: All data will be included in the data collection notebook, and will be added in a Microsoft Access XP database, throughout the entire study.

- STATISTICAL STUDY: Once all the data have been collected, a statistical study will be carried out using the SPSS program as described in the data analysis (methodology). One month

- REDACTION OF RESULTS. The results will be written when the definitive statistical study is carried out according to: introduction, objectives, hypothesis, patients and methods, results, discussion, conclusions and bibliography. Five months.

AVAILABLE MEDIA: MATERIAL (PROVIDED BY THE OWN CENTER):

There is adequate surgical space with all the necessary material for the realization of both interventions: Operating room; two laparoscopic towers (camera source, light source, CO2 insufflator, monitors), laparoscopic optics of 0º and 30º; optics and last generation laparoscopy tower; laparoscopy box for colorectal surgery (complete equipment of laparoscopic instruments); hemostasis and cutting device (Ligasure®, Ultracision®) ...
In addition, a computer system is available in an intrahospital network so that the database of the coloproctology unit can be consulted from different teams.

AVAILABLE MEDIA: RESEARCH TEAM:

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