Universitat de Girona
Facultat de Medicina

Intracorporeal vs. Extracorporeal Anastomosis in Laparoscopic Right Hemicolectomy for cancer

FINAL DEGREE PROJECT

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1. ABBREVIATIONS

AAS: acetylsalicylic acid.

ASR: age-standardised rate.

ASA: American Society of Anaesthesiology.

BMI: body mass index.

CCE: colon capsule endoscopy.

COX-2: cyclooxygenase 2 inhibitors.

CRC: colorectal cancer.

CT: computed tomography.

EA: extracorporeal anastomosis.

EUS: endorectal ultrasound.

HDI: human development index.

IA: intracorporeal anastomosis.

IBD: inflammatory bowel disease.

IV: intravenous.

MDCT: multidetector computed tomography.

MRI: magnetic resonance imaging.

NHS: National Health System.

NSAID: non-steroidal anti-inflammatory drugs.

SBO: small bowel obstruction.

SSI: surgical site infection.

PET-CT: positron emission tomography- computed tomography.

TNM: tumour, node and metastasis.

2. ABSTRACT

Background: Surgery remains the most definitive treatment for colon cancer. Laparoscopic procedure has been developed as a better alternative to the open technique. After the bowel resection, its reconstruction can be performed in an intracorporeal or an extracorporeal way. The majority of right laparoscopic colectomies continue to be performed with an extracorporeal anastomosis due to inherent technical difficulties in acquiring advanced laparoscopic suturing skills. Few studies have been carried out comparing the differences between the two techniques, and their results described better outcomes in favour of the intracorporeal way, with a reduction of short-term morbidity and a decrease of the length of stay, suggesting faster recovery. However, all of them were retrospective and controversies are still unsolved.

Objective: The aim of this study is to evaluate the recovery of the bowel function after two different techniques of anastomosis in the treatment of right colon cancer. We will also evaluate the early complications after surgery and the time of hospitalization.

Design: A randomized, single-blinded, controlled clinical trial which will be carried out in Hospital Universitari Josep Trueta within the General Surgery Service from April 2017 until 2021.

Method: 158 patients with right colon cancer will be recruited with a non-probabilistic, consecutive method. They will be randomly assigned to one of the treatment groups, either extracorporeal anastomotic technique or intracorporeal anastomotic one. Non parametric U-Mann Whitney test or Student-T test will be used for the statistical analysis of the primary and one of the secondary endpoints, depending if they are or they are not normally distributed. The last endpoint will be analysed with a chi-square test, and a confidence interval of 95% will be assumed.

Key words: Intracorporeal anastomosis, extracorporeal anastomosis, complications, morbidity.

3. INTRODUCTION

3.1. ANATOMY SUMMARY

The colon is variable in length, with an average of approximately 150 cm, which corresponds to a quarter of the length of the small intestine. The anatomical differences between the small and the large bowel include the position, calibre and degree of fixation and, in the colon, the presence of three distinct characteristics: taeniae coli, haustral sacculations and epiploic appendages.

We can divide the colon into three different portions. The first portion is usually located in the right iliac fossa and is called the ceccum. It is almost entirely or at least in its lower half, invested with the peritoneum. Is the sacculated segment of the large bowel that protrudes downward into a blind bag 6 to 8 cm below the ileum entrance. From the level of the ileocecal junction to the hepatic flexure, lateral to the psoas muscle and anterior to the iliacus, the quadratus lumborum and the inferior pole of the right kidney, ascends the ascending colon, also covered by peritoneum anteriorly and on both sides. Its posterior surface is replaced by Toldt's fascia. The second portion is the transverse colon and it is the longest segment of the large bowel. It crosses the abdomen to the splenic flexure and it is completely covered by the peritoneum. The descending colon is the third segment, and it descends from the splenic flexion to the edge of the true pelvis. Similarly to the ascending colon, the descending colon is covered by peritoneum only on its anterior and lateral aspects. Posteriorly, it rests directly against the left kidney and the quadratus lumborum and transversus abdominis muscles (1)(Fig. 1).

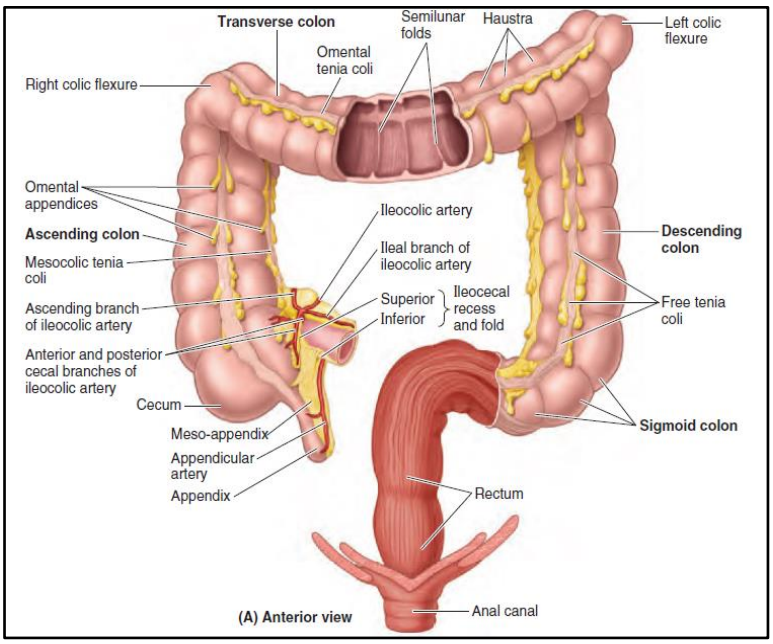

Figure 1. Anatomy of the colon (59).

3.2. EPIDEMIOLOGY

Colorectal cancer is a global health problem. It represents almost the 10% of the world's cancer incidence in both sexes, with an estimated mortality of 8.5%. The recently available data of 2012 placed it in the world's third most incident cancer, after breast, prostate and lung cancer, with a total of 1.360.500 new cases. Among these, 746.296 cases were diagnosed in men and 614.204 in women, the third and second most frequent respectively.

Almost 55% of the cases occur in more developed regions according with the data reported by GLOBOCAN. There is wide geographical variation in incidence across the world and the geographical patterns are very similar in men and women: incidence rates vary ten-fold in both sexes worldwide, the highest estimated rates being in Australia/New Zealand (ASR 44.8 and 32.2 per 100,000 in men and women respectively), and the lowest in Western Africa (4.5 and 3.8 per 100,000).
Mortality is higher (52%) in the less developed regions of the world despite of the lower incidence, reflecting a poorer survival. There is less variability in mortality rates worldwide (six-fold in men, four-fold in women), with the highest estimated mortality rates in both sexes in Central and Eastern Europe (20.3 per 100,000 for men, 11.7 per 100,000 for women), and the lowest in Western Africa (3.5 and 3.0, respectively). The sex ratio thus increases with the level of development, with low HDI countries exhibiting 5-year male:female prevalence ratios of around 0.6 compared to estimates of about 1.1 in very high HDI areas (2,3).

There were just over 3.4 million new cases of cancer (excluding non-melanoma skin cancers) in Europe in 2012, 53% (1.8 million) occurring in men and 47% (1.6 million) in women. Taking both genders into account, colorectal cancer occupied the second position (447,000, 13.0%), following breast cancer (464,000 cases, 13.5% of all cancer cases) who was the most common site of cancer (4). But, according with the data from REDECAN, in Spain colorectal cancer was the most common neoplasm, followed by prostate, lung and breast cancer, where 41.441 new cases were diagnosed in 2015, 24.764 in men and 16.677 in women, and the age-standardized incidence rate to Europe was of 77.8 in men and 42.0 in women. Therefore, colorectal cancer was more frequent in men both worldwide and specifically in Europe and Spain. Moreover, in Spain, the evolution of this cancer has been in constant increase, mostly among men and more intense until 90's, which became slightly attenuated in both sexes, with an increase of 35% in men and 11% in women. But this increase can't be because of the systematic screening which was

implemented at 2000 in Catalonia and in 2006 in Comunitat Valenciana and Murcia. Therefore, the increase of the incidence should respond to the influence of different risk factors such as changes in dietary habits, including a higher consumption of sugar and red and processed meat, lower consumption of fibre, fruits and vegetables, and less physical activity (5–7).

Finally, according to the data from the Tarragona Cancer Registry, the colorectal cancer is the second most frequent malignant tumour diagnosed in Catalonia, and also the second cause of death from malignant neoplasm(8). Otherwise, according to the data from The Girona Cancer Registry and taking both sexes into account, the colorectal cancer is the most frequent malignant tumour diagnosed at the province of Girona (Fig. 2), being the second cause of death from cancer. However, if we take gender separately, colorectal cancer is the second most frequent malignant tumour diagnosed in both sexes (9).

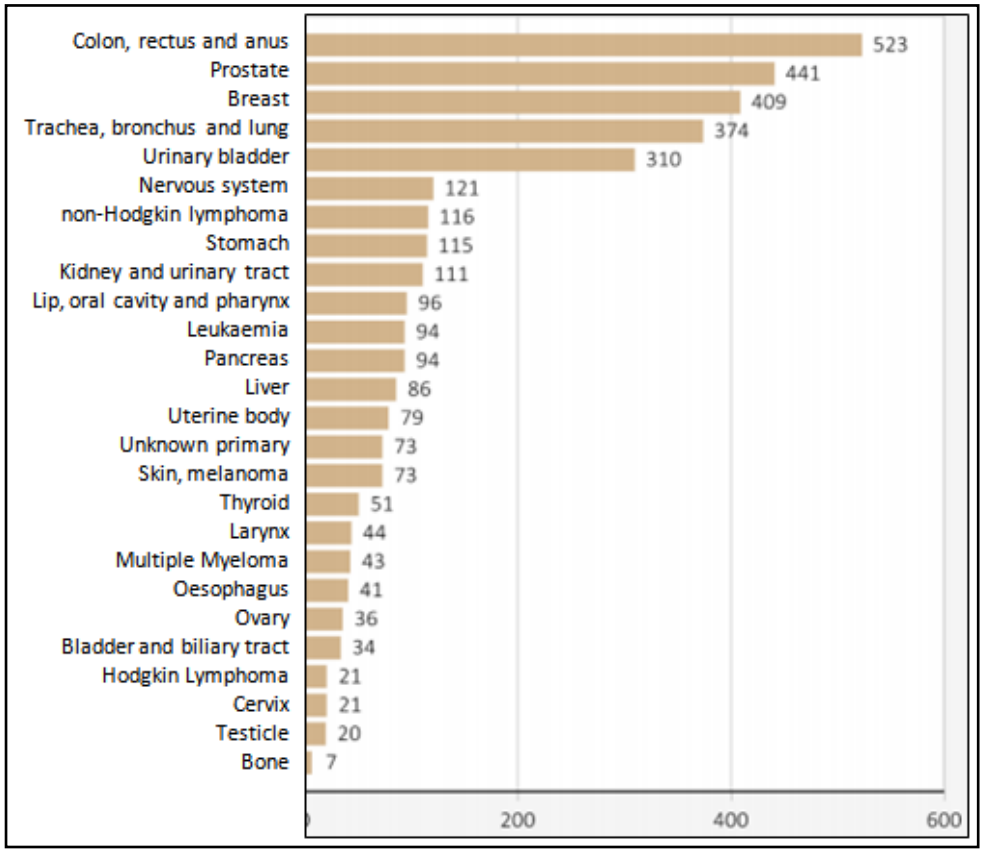

Figure 2. Incidental cases on principal tumour localizations at the province of Girona. Adaptation from text (9).

3.3. AETIOLOGY

The specific cause of colorectal cancer is not known. However, a number of genetic and environmental factors have been associated with the disease. We can divide them on protective and risk factors (10):

-Protective factors:

- Dietary fibre and vegetables

  The relationship between diet and CRC risk is at best unclear. There has been much interest over the years in the possible protective effect of vegetables, fruit, and grains against colorectal cancer. In some studies, a weak inverse association of fruit and vegetable consumption was observed with colon but it could be modified by other factors like smoking and alcohol intake. At last, the findings from epidemiologic cohort studies have produced inconsistent results (11–13).

- AAS and COX-2

  Regular use of aspirin seems to be effective in the primary prevention of colorectal cancer(14). Many pharmacological agents have been studied as chemoprevention agents for colorectal cancer in individuals with previous colorectal neoplasia. According to the findings, non-aspirin NSAIDs and aspirin are effective for the prevention of advanced metachronous neoplasia (15).

- Physical Exercise

  Higher levels of physical exercise are associated with modest reductions in risk of colon cancer in men and women (16).

-Risk factors:

- Meat and fat

  Several biological mechanisms have been suggested to explain the association of red and processed meats with colorectal cancer. These include the potential mutagenic effect of heterocyclic amines contained in meat cooked at high temperature and the endogenous formation in the gastrointestinal tract of N-nitroso compounds.

  Some studies and meta-analysis have found a low association between red meat intake and an increased risk of colon cancer (but not for rectal cancer) but is difficult to rule out the possibility that the apparent effect of red meat on the

development of CRC may be confounded or modified by other dietary or lifestyle factors (17–19).

- Smoking and alcohol

  A meta-analysis of 106 observational studies had found statistically significant dose relationship with an increasing number of pack-years and cigarettes per day. However, the association was statistically significant only after 30 years of smoking and it was stronger for cancer of the rectum than of the colon (20).

  Evidence have been found an association between the risk of CRC and higher lifetime and baseline alcohol consumption levels, with more apparent risk increases for alcohol intakes greater than 30 g/day (21,22).

- Obesity

  An association between obesity and risk of colorectal cancer varies by sex and cancer site. Obesity appears to increase the risk of colon cancer in both men and women, but the association seems to be stronger in men and premenopausal women.

  Epidemiologic evidence suggests that abdominal obesity may be more predictive of colon cancer risk than overall obesity (high BMI) (23,24).

- Personal and Familiar history

  In a meta-analysis of 59 studies, the relative risk of developing colorectal cancer with one first degree relative affected was 2.24 (95% CI 2.06 to 2.43). This meta-analysis also showed a relative risk of 3.97 (95% CI 2.60 to 6.06) having at least two affected first-degree relatives with CRC (25).

  Some of the increased risk attributed to family history may be a result of hereditary factors, such as mutations in the APC gene (Familial adenomatous polyposis) or DNA mismatch-repair (MMR) genes (Turcot syndrome) , MSH2, MLH1, MSH6, or PMS2 (Lynch syndrome). MLH1 and MSH2 account for almost 90% of all identified mutations and MSH6 accounts for almost 10% (26).

- Inflammatory Bowel Disease

  Inflammatory bowel disease (IBD) is a strong risk factor for colorectal cancer. The risk correlates with the age of onset and extent and duration of active disease (10).

  In a meta-analysis of 116 studies of patients with ulcerative colitis, the overall prevalence of CRC was estimated to be 3.7% (95% CI 3.2–4.2%). They found an

accumulative probability of CRC of 2% after 10 years of disease, 8% after 20 years, and 18% after 30 years (27).

In patients with Crohn's disease with colonic involvement, the development of CRC has been less consistently demonstrated (1).

3.4. CLINICAL PRESENTATION

Colorectal cancer screening in the asymptomatic patient based on age, and also any other associated risk factors that would increase the risk and require earlier screening is really important because is beneficial that colon cancers are diagnosed when patients are asymptomatic.

The clinical presentation of a patient with colon cancer will depend on the size of the tumour. Is because of that than colon cancer does not have any early signs, and symptoms are often absent until a tumour has grown to significant size.

The apparition and the kind of symptoms are also influenced by the localization of the tumour and they are more frequently associated with a more advanced stage.

Right colon tumours often cause occult bleeding. As the stool there is still liquid or at most semisolid, proximal colon tumours may grow to relatively large size before they can cause an obstruction. Left colon tumours produce changes in bowel habits (constipation or false diarrhea).

When the patient has symptoms, he usually complains about unexplained weight loss, anaemia and weakness from chronic blood loss, flatulence, or episodes of colicky abdominal pain, unless he presents with a tumour complication (eg, bowel obstruction, bleeding, perforation, or fistula formation).

In addition to the local symptoms, we can find symptoms due to distant metastasis, such as neurological disorder, bone pain, dyspnoea because of pulmonary dissemination, etc. Ascites is frequent if there is peritoneal carcinomatosis.

A good medical history and physical exploration should be developed to determinate the patients' nutritional state and to identify other medical conditions such as cardiopulmonary and renal state. Preoperative tests are aimed at providing evidence for pathophysiologic effects of the tumour and ruling out general health problems that could have an effect on the patient's general operability (10,28).

3.5. DIAGNOSIS AND PREOPARATIVE STAGING

When patients' symptoms are suggestive of colon cancer, a complete evaluation should have been carry out to determinate the treatment we are going to perform, since it may be influenced by the localization of the tumour and the presence of synchronous tumours, by the locoregional extension of the disease, by the presence of distant metastasis, and by the patients' operability (overall condition and comorbidities).

To localize the tumour, the *colonoscopy* is the gold standard. It provides accurate information about the entire colonic mucosa and it may be used to determinate the circumferential and longitudinal extent of the colonic lesion and to remove synchronous neoplastic polyps. In addition, biopsy samples can be taken during the colonoscopy to make a histological diagnosis.
Radiographic contrast enemas alternatively can be used for a colonic evaluation. A barium-air double contrast can be used. However, if there are any contraindications, a water-soluble contrast material such as Gastrografin should be used. Nowadays, this technique is rarely performed due to the implementation of better procedures.
Sometimes, the colonoscopy can be unsuccessful because of the growth of the tumour, which can cause an obstruction. In that case, a *CT colonography* (virtual colonoscopy) or a *CCE* (colon capsule endoscopy) are a high-tech alternative (10).

Correct staging is imperative for CRC, both for prognosis and therapeutic guidance. Overall survival is strictly correlated with stage at presentation: the 5-year survival rate drops dramatically from stage I (93%) to stage IV (8%).

Locoregional staging (T and N stage) with imaging is not well supported in the literature. Most studies show that imaging is best utilized to identify advanced T stage and distant metastases, with locoregional nodal staging being relatively less accurate and of marginal clinical utility.
Additionally, the role of preoperative imaging to predict T-stage and N-stage is of questionable value, given that neoadjuvant therapy has not been shown to significantly improve survival over surgery alone, and the standard surgical approach is radical resection. Preoperative imaging of colon cancer appears to be of most benefit in identifying distant metastases, regardless of its ability to predict T-stage and N-stage. However, preoperative cross-sectional imaging (CT, MDCT or MRI) has become the standard of care:

- Computed tomography (CT) has the potential to visualize local tumour characteristics in addition to its role in detecting any distant metastatic disease.
- MDCT (multidetector CT) has resulted in improvement in staging colon cancers with encouraging results for detecting local tumour invasion as well as lymph nodes.
- Although MRI and endorectal ultrasound (EUS) have been valuable for staging rectal cancers, they are currently not routinely used for staging colonic tumours.

As we have seen before, an important role of imaging in staging patients with colorectal cancer is the detection of distant metastases, which can be accomplished with CT, positron emission tomography (PET)/CT, and MRI. All 3 of these modalities benefit from the use of intravenous (IV) contrast, with new MRI contrast agents allowing hepatobiliary phase imaging to improve accuracy.

The most common sites of metastatic involvement in colorectal cancer are the liver and lungs. MRI is more accurate than CT in detecting liver metastases but because of limited sensitivity of MRI for lung nodules, a chest CT with or without contrast can be performed in addition to MRI for complete staging. PET/CT may help to exclude other sites of disease (29,30).

3.5.1. TNM staging

The extent of a cancer at time of diagnosis is a key factor used to define treatment and to assess the chance of successful treatment outcome. Codify the extent of a cancer by staging systems provide to clinicians and patients the means to quantify prognosis for individual patients, to compare groups of patients in clinical trials and who receive standard care around the world, and to compare the results of various treatment regimens.

Currently, the most widely used staging system among clinicians for colon cancer in the United States and Europe is the 7th edition of the TNM system maintained by the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC) (31) (Annex 1).

3.6. TREATMENT (32–34)

3.6.1 Surgical Treatment

Surgery remains the most definitive treatment for colon cancer. Colectomy for cancer follows four oncologic principles:

- Adequate lymphadenectomy of greater than 12 lymph nodes.

- A minimum 5cm proximal and distal margins resection.
- High ligation of the primary feeding vessel.
- Complete mesocolic excision (CME), which involves the sharp dissection of the visceral fascia from the parietal fascia of the retroperitoneum and central ligation of the primary vasculature.

The length of bowel and mesentery resected is dictated by tumour location and distribution of the primary artery (Annex 2). Tumours located in "border zones" should be resected with both neighboring lymphatics to encompass possible bidirectional spread. If a tumour is adherent to or invading an adjacent organ such as the kidney or small bowel, an en bloc resection should be performed where technically feasible (35,36).

There are two techniques to perform a right hemicolectomy in the treatment of right colon cancer; the resection can be performed safely and effectively via either an open (laparotomy) or minimally invasive (laparoscopy) approach.

The open right hemicolectomy may be performed through transverse/oblique incision or midline incision (Fig. 3). According to the data, the transverse laparotomy offers some advantages compared to the midline laparotomy, such as a less postoperative pain, pulmonary morbidity, and better aesthetic results. Furthermore, a lower incidence of incisional hernia has been observed after the transverse incision than after the midline one (37).

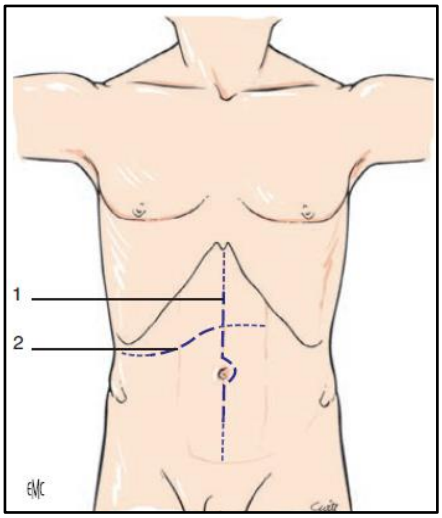

Figure 3. 1- Midline incision; 2- Transverse/ oblique incision (32).

In the laparoscopic approach, the patient is placed supine on the operating table, with a left inclination and some anti-Trendelenburg, to facilitate the exposition of the abdominal content and the displacement of the small bowel to the left side of the peritoneum. Surgeons can adopt two positions and the placement of the trocars will be influenced by surgeons' choice (Fig. 4).

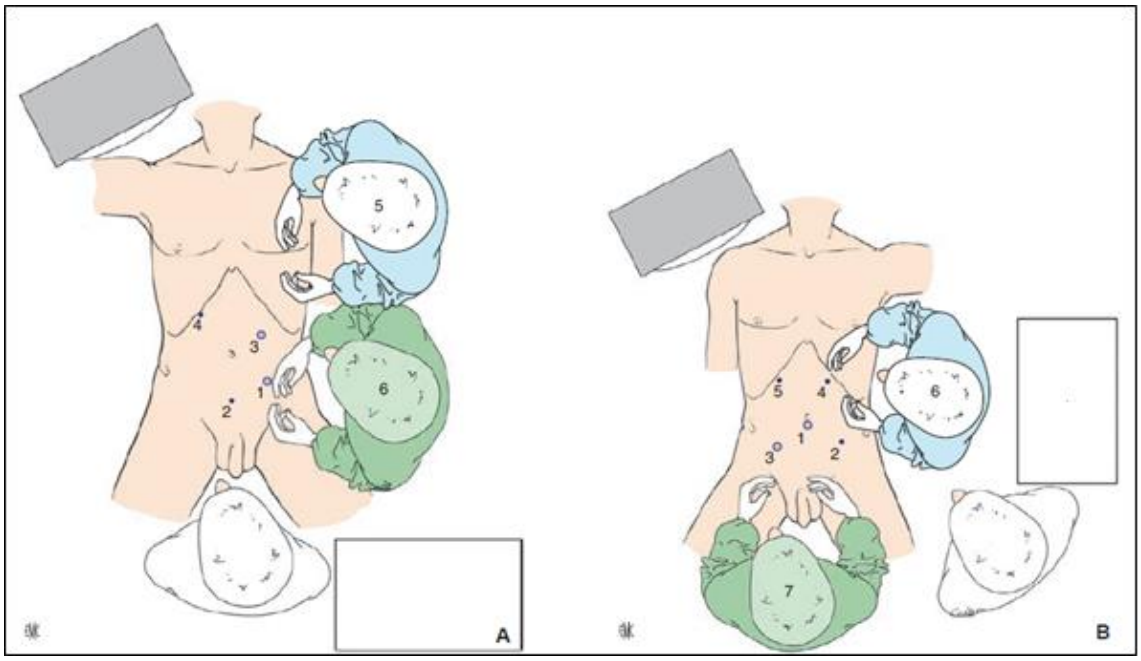

Figure 4. Surgeon position and trocars' location (32).

- **A.** Surgeon (6) at left hip level (right hand/trocar 1; left hand/trocar 2), assistant (5) at left shoulder level (right hand/trocar 4, left hand/trocar 3 (optic)).
- **B.** Surgeon (7) between the legs (right hand/trocar 2, left hand/trocar 3), assistant (6) at left flank (left hand for the optic, trocar 1, right hand/trocar 4 or 5). This position allows surgeons not cross their hands.

Usually, the first port is positioned umbilically (Hasson's trocar) via cut-down procedure, allowing a rapid establishment of pneumoperitoneum and then with the optic surgeons make an initial exploration to ensure no prohibitive adhesions. Then, second port is placed 2 cm medial to the left anterior superior iliac spine, third port is placed 2 cm medial to the right anterior superior iliac spine, and the last one port is placed laterally, on the left side just rostral to the umbilicus.

When surgeons are inside of the abdominal cavity, there are two approaches that can be performed in both techniques (laparotomy and laparoscopy) to resect the right colon; one begins laterally by mobilizing the colon and progresses medially, while the other begins medially by identifying the lymphovascular bundle and progresses laterally. The approach is at the discretion of the surgeon.

Usually, when the surgery is undergoing with a laparoscopy procedure, surgeons use a medial to lateral mobilization because with this technique the first objective is the vascular ligation before the mobilization in order to maintain necessary traction and exposure of the mesenteric structures; however, this approach is also easily applied in the open setting by surgeon preference.

- **Lateral to medial approach:** begins by retracting the colon medially and dividing the lateral peritoneal attachments of the cecum and ascending colon along the white line of Toldt. After that, the peritoneum and the colon are separated from the loose areolar tissue by dissection (Fig. 5). At the retroperitoneum plane, is important to avoid injury to the duodenum, right ureter and gonadal vessels during the dissection and the hepatic flexure mobilization. The renocolic ligament has to be divided using electrocautery. Then, the dissection will go distally along the colon until the gastrocolic ligament (a portion of the greater omentum) is encountered. When the lesser sac is opened, the gastrocolic ligament is divided from left to right, completing mobilization of the hepatic flexure. Once the mobilization has been completed around the hepatic flexure, the right colon is attached only to its vascular supply and is ready for resection. For that, surgeons have to identify the lymphovascular pedicles by retracting the small bowel to the left side of the abdominal cavity and elevating the right colon to expose the root of the mesentery, and then they have to ligate the right colic vessels (Fig. 6).

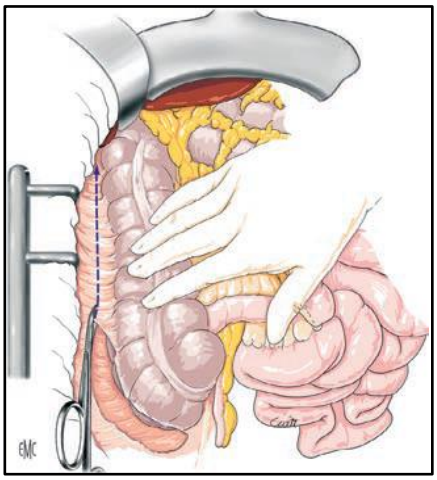

Figure 5. Toldt's fascia dissection (32).

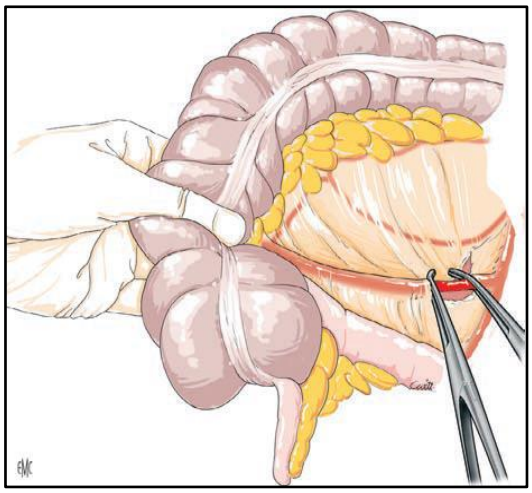

Figure 6. Vessel ligation (32).

- **Medial to lateral approach** (Fig. 7)**:** begins with the ligation of the mesenteric lymphovascular pedicle. To do that, surgeons have to retract the small bowel to the left side of the abdominal cavity and they have to elevate the right colon to expose the root of the mesentery. Because there is variable anatomy of the right colon blood supply, it is essential that the origins of the ileocolic, right colic, and right branch of the middle colic vessels relative to the superior mesenteric artery are clearly delineated before ligation is attempted. The superior mesenteric artery has to be identified to prevent injury or inadvertent ligation. After de identification of the correct vessels, surgeons have to clamp them in close proximity to their origins (Fig. 8). After the ligation, surgeons start the dissection of the retroperitoneal medial structures to the lateral ones, following the superior mesenteric axis until the external insertions of the hepatic angle. Here, the dissection changes its direction and goes down across Toldt's fascia. The dissection should not stop at the cecum, but must extend over the root of the mesentery. This stage of the intervention is continued until complete mobility of the last Ileal loop. Finally, with a bipolar coagulation, the last 15 cm before the ileus valve's mesentery have to be sectioned.

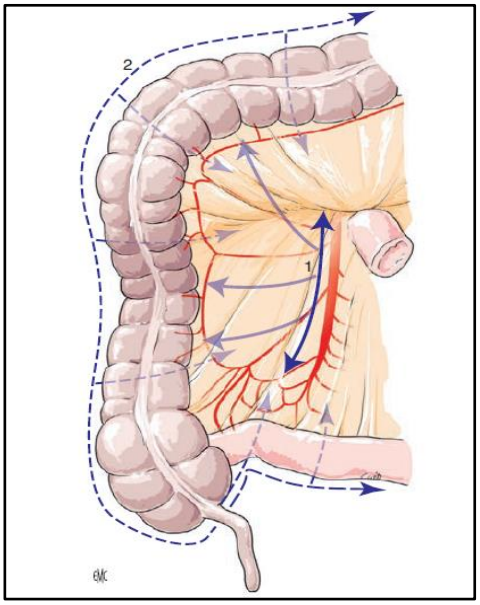

Figure 7. Medial to lateral strategy. External ligations are dissected ultimately (32).

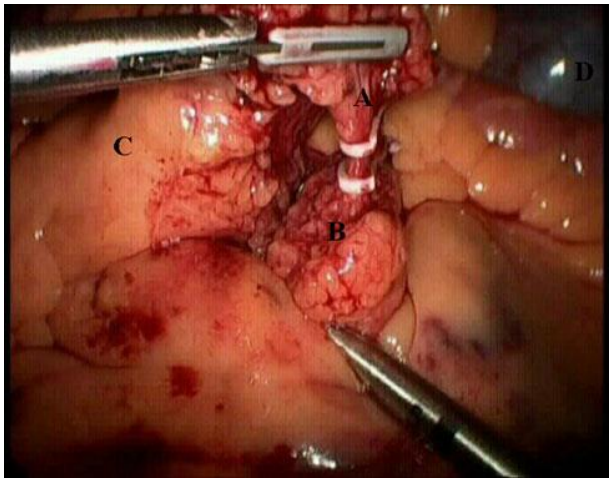

Figure 8. Ligation of ileocolic vessels. A. Ileocolic vessels secured between clips, B. Distal continuation of superior mesenteric vessels, C. Mesentery of ascending colon (60).

After the dissection, the bowels have to be resected and then, its ends can be reanastomosed. In the laparoscopic approach, the anastomosis can be extracorporeal or intracorporeal. The extracorporeal anastomotic technique is similar to that performed during open surgery. It requires greater mobilization and exteriorization of the bowel

through the abdominal incision, extending the supraumbilical port-site incision around the right side of the umbilicus to 4 to 6 cm in length (Fig. 9) or making a new subcostal incision. Intracorporeal anastomosis allows completion of the anastomosis without any externalization of the bowel.

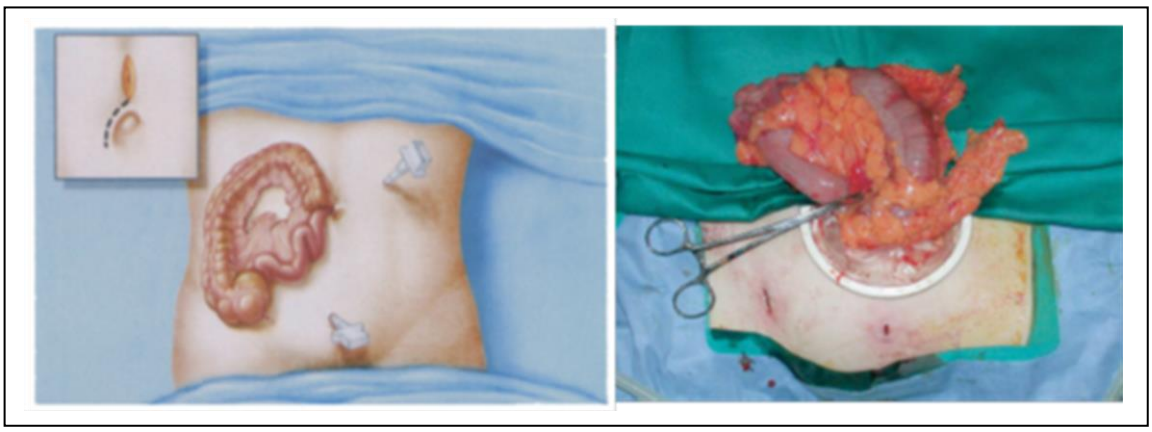

Figure 9. Extension of the supraumbilical port site incision around the umbilicus and exteriorization of the terminal ileum, right colon, and proximal transverse colon (Left (34), Right (61)).

Prerequisites for a successful anastomosis are meticulous technique, well-vascularized and healthy appearing tissues, apposition of bowel ends without any tension, and good nutrition status of the patient whit an albumin level greater than 3.0mg/dL. If not, the risk of an anastomotic leak increases and may cause infection and sepsis. Options for restoring bowel continuity include a side-to-side or an end-to-side ileocolic anastomosis, which is performed with a stapling device or hand-sewn. A systematic review of The Cochrane Library had provided evidence that the stapling technique has the advantage of a lower anastomotic leak rate than handsewn anastomosis (38). Therefore, in this paper we are going to talk about the stapling technique.

In the **extracorporeal anastomosis**, sufficient bowel and mesentery must be exteriorized though the subcostal incision or the extension of the supraumbilical port-site incision after the vessel ligation. The next step is the bowel resection. This step must be done taking into account bowels' vascularization, so surgeons will cut out since the last 5 cm of the ileum to a proximal portion of the transverse bowel, according with the previous vascular ligation. When the terminal ileum and the right hemicolon are resected, a stapled anastomosis is performed. This anastomosis can be a stapled side-to-side functional end-to-end anastomosis or a stapled end-to-end anastomosis. Experience, surgeon's preference, and availability of equipment dictate the type of anastomosis a surgeon performs in a given situation.

In patients undergoing **an antiperistalic stapled intracorporeal anastomosis,** mesentery, right colon and terminal ileum are liberated via medial-to-lateral retroperitoneal dissection. After that, ileum and colon are transected with a stapled (Endo-GIA) taking also into account the previous vascular ligation, and then the anastomosis is fashioned. A side-to-side antiperistalsis is created with a 45mm endostapler, and the enterotomy is closed with continuous suture.

- **Stapled side-to-side functional end-to-end anastomosis** (39)**:**

The proximal ileal and the distal colonic transection points are defined and freed up from fatty attachments. The mesentery is divided about 2 cm towards the remaining bowel ends to prepare for transverse stapling (Fig. 10b). The anastomosis is a side-to-side antiperistaltic anastomosis, which is by use of a long linear cutting stapler (75–100 mm) creating a functional end-to-end connection.

1. Small transverse incisions of 5 mm are made on the tenia and the anti-mesenteric ileal border of the specimen sides and dilated. Babcock clamps are placed in order to allow for easy insertion of the linear cutting stapler (Fig. 10a); the small side of the device is inserted into the small bowel, and the large one enters the large bowel. The stapler is closed, and interposition of the mesentery is ruled out (Fig. 10b). The staple device should ideally stay in place for about 15" to allow for tissue compression before cutting.
2. The unified enterotomy site is transversally joined using the Babcock clamps. The linear cutting device is placed in transverse fashion across the ileocolic anastomosis. The joined enterotomy site is held under traction by the Babcock clamps, and the enterotomy site and specimen are removed by firing the linear cutting stapler.
3. The staple lines are reinforced by four sutures placed at the three notorious weak spots: (a) the root point of the horizontal staple line, (b) inversion of the two "dog ears" on both ends of the transverse staple line, and (c) U-stitch to secure the "angle of sorrow" at the crossing of transverse and horizontal staple line (Fig. 10d).

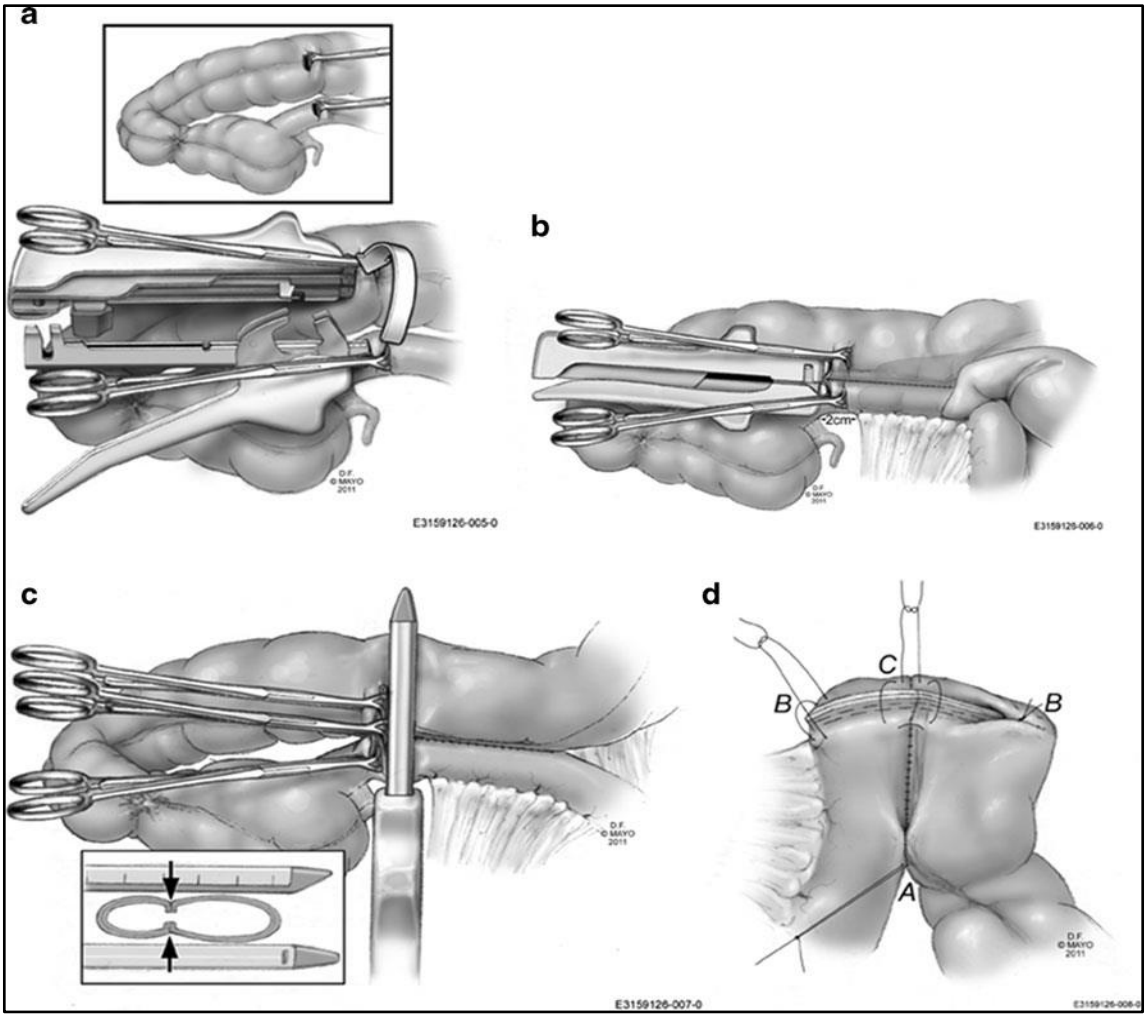

Figure 10.Three steps of side-to-side stapled ileocolic anastomosis. (1)The branches of a long linear cutting stapler are inserted via at the terminal ileum and the transverse colon. The stapler is closed (a). Before the stapler is fired, we test its position to avoid injury to or interposition of the mesentery into the staple (b). (2) Three to five Babcock clamps are used to close the enterotomy site and to align the anterior and posterior aspect of the horizontal staple line. The defect is closed by a second transverse firing of the linear cutting stapler, and the specimen can be removed (c). (3) The crossing of the staple lines (A) and the extremities of the transverse (B) and horizontal (C) staple lines are reinforced by four interrupted sutures using a slowly resorbable monofilament suture material (39).

- **Stapled end-to-side anastomosis** (33)**:**

1. The distal ileum is prepared for the anastomosis by clearing the mesentery and sharply dividing the bowel against a distal clamp. Electrocautery can also be used to divide the bowel (Fig. 11). The anvil of a circular stapler is placed into the bowel lumen and secured with a manually- or stapler-placed purse-string suture (Fig. 12).
2. A longitudinal colostomy is made on the specimen side of the colon at least 10cm proximal to the site chosen for transection, the circular stapler is inserted, and the spike of the stapler is brought though the antimesenteric side of the colon 1cm to the distal to the transection site (Fig. 13).

3. The anvil and spike are connected and the circular stapler closed and fired, creating an anastomosis between the end of the ileum and the side of colon (Fig. 14, 15). A linear stapler is used to transect the colon from the specimen. Any bleeding points can be oversewn with a silk suture (Fig. 16).

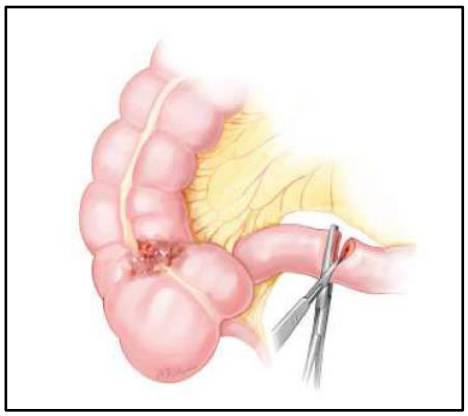

Figure 11. Transecting the ileum and colon (33).

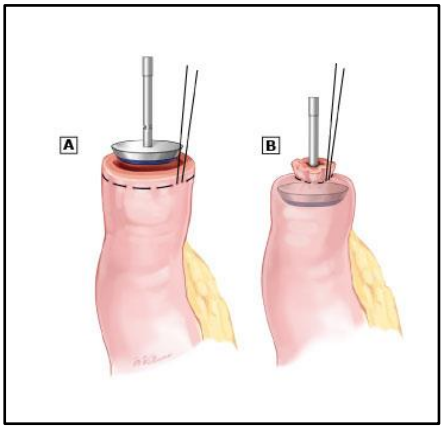

Figure 12. Insertion of circular stapler into ileum (33).

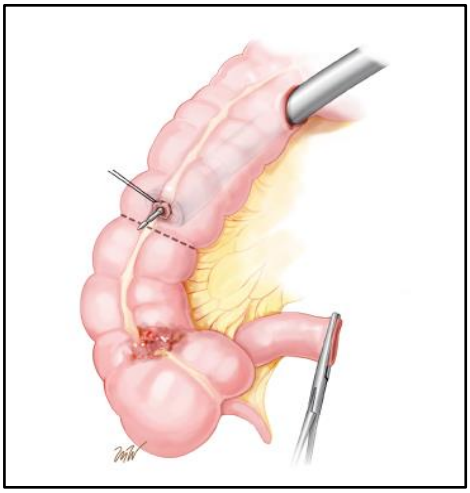

Figure 13 . Insertion of circular stapler into colon (33).

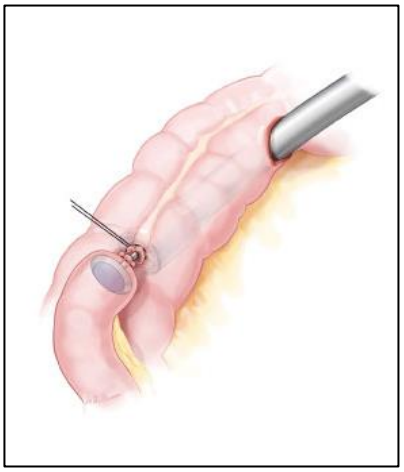

Figure 14 . Creation of the anastomosis (33).

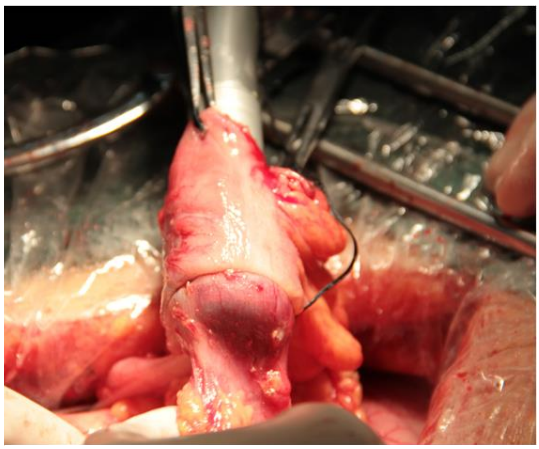

Figure 15. Withdrawal of circular stapler (62) .

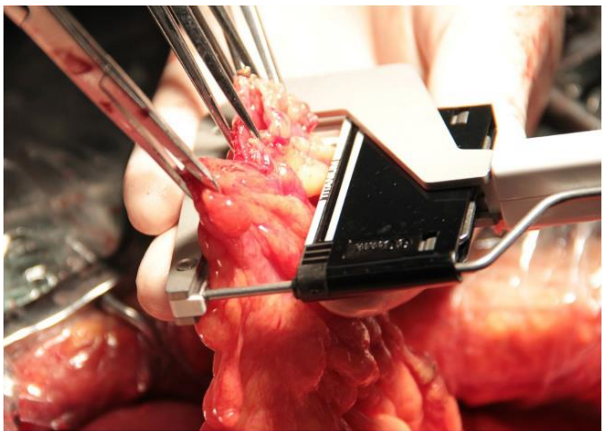

Figure 16. End-to-side anastomosis: closure of colon by linear stapler (62).

After the extracorporeal procedure, the completed anastomosis is returned to the abdominal cavity. A retractor is introduced through the periumbilical incision as ports are removed allowing visualization of trocar sites to observe for port-site bleeding and is often more expeditious than reestablishing the pneumoperitoneum. If there is abdominal bleeding, it is often better to close the small midline incision, reinstitute the pneumoperitoneum and find and cauterize the source of bleeding, which is often in the hepatic flexure. The collections should be aspirated, always checking the pouch of Douglas, where most spills are accumulated during the operation. The extended supraumbilical incision and the trocar sites are closed at the fascia level to prevent hernias (34).

After the intracorporeal procedure, when the anastomosis is performed, the specimen is extracted through a Pfannenstiel incision. The incision for specimen extraction is protected in all cases with an isolation device. The trocar sites are closed at the fascia level to prevent hernias (40).

3.6.2. Adjuvant treatment

Depending on the stage of the disease at the presentation, surgical treatment will be enough or it will be accompanied by adjuvant treatment (41).

- **Stage I** (T1-2N0M0) disease carries an excellent prognosis of up to 95% 5-year survival rate after resection, and surgical treatment alone is considered sufficient; adjuvant treatment is not indicated.
- **Stage II** (T3-4N0M0) disease also has excellent 5-year survival, averaging 70–80%, but a subset of high-risk patients have poorer prognosis and they will have recurrence and ultimately die from their disease. However, according with meta-analyses of CCOPGI (Cancer Care Ontario Practice Guideline Initiative), there is no evidence to routinely treat stage II colon cancer patients with adjuvant chemotherapy. Although, the QUASAR (Quick and Simple And Reliable) trial found a borderline improvement in survival with chemotherapy with 5-FU and folinic acid. Is because of that than there is a controversy in the utilization of adjuvant treatment in these patients (42,43).
- **Stage III** (TanyN1-2M0) disease has an overall 5-year survival after curative surgery from approximately 40–60%. Recurrences are often systemic, hence the need for adjuvant treatment such as FOLFOX (leucovorin /5-fluorouracil/oxaliplatin) in these high-risk patients.
- **Stage IV** (Metastatic): in this case, treatment approaches must be individualized based on the extent and resectability of local and distant disease, the presence or absence of bowel obstruction, performance status, and co-morbidities. Sometimes, surgical

resection of the primary tumour and if indicated, of the metastatic lesions can be the first step of the treatment, followed by adjuvant chemotherapy such as FOLFOX or FOLFIRI (leucovorin/ 5- fluorouracil/irinotecan).

3.7. COMPLICATIONS

The overall perioperative mortality within 30 days of the resection is between 3.5 and 6% after an elective surgery. Complications can be classified based on the time of their occurrence (10,44):

- **Intraoperative complications:** they include injury to adjacent organs, bleeding, and infection:

1. Small bowel and duodenal injury, with a risk less than 1-3%, also because of the colon mobilization. The management includes a primary operative repair.

2. Pancreatic and gastric injury, with a risk less than 1-3%, and usually during the mobilization of the left colon or while repairing a splenic injury.

3. Pelvic and genitourinary structures (blood vessels, ureters, bladder), can be injured during colorectal surgery. Rates are also low (less than 1-8%), and the management use to be a primary surgical repair.

4. There is an inherent risk of gross contamination of the peritoneal cavity with a colorectal operation, because they are clean-contaminated procedures, and the incision can result with a surgical site infection (SSI). SSI are classified as incisional or intraabdominal (table 2). The rate of SSIs following colorectal surgery varies in different reports from less than 1 to 30%. However, superficial SSI may be less common in right colectomies compared with the left ones. (5.9 vs. 8.2%).

- **Early surgery complications (first 30 days):**

1. Vascular complications can be presented such as Anastomotic bleeding. It can be a minor bleeding, when it does not require blood transfusion and/or intervention and cesses within 24h, or a major bleeding, when it is defined as hemodynamic instability, needing of blood transfusion or an emergency procedure is warranted (eg, endoscopic, angiographic, surgical). The report rate in most studies is from 0,5 to 4,2% (45). It seems to be more common after a stapled anastomosis, especially with a long side-to-side anastomosis and

in colonic and ileal pouches. Finally, it can be presented such as pelvic bleeding, because of the lesion of any abdominal structures.

2. Infectious complications usually occur after the third postoperative day and may be located intra-abdominally and in the wound. As we have seen before, colorectal operations have a risk of developing a SSI. It has been seen that some actions before and during surgery have reduced the rate of SSI. The preventive SSI actuations consists on measures such as mechanical bowel preparation with specific diet to "clean" the bowel tract, preparation of the surgical field with chlorhexidine, maintenance of euglycemia and normothermia during the perioperative period, and glove change before fascial closure.

3. Abdominal complications (46): postoperative paralytic ileus can be one of them and it refers to constipating and intolerance of oral intake due to nonmechanical factors that disrupt the normal function of the gastrointestinal tract after surgery, and the symptoms persist for more than three to five days. There is not a specific therapy, other than supportive care, to resolve it. An early postoperative small bowel obstruction (SBO) can be another complication. It is the most frequent complication in the early postoperative period after colorectal surgery with an incidence of 1.2-8.1%. However, not all patients with an early postoperative SBO require an operative intervention, and sometimes it is resolved spontaneously or with conservative management.

4. An anastomotic leak (47) has an incidence of 2-7%, with the lowest leaks in ileocolic anastomosis (1-3%) and the highest with coloanal anastomosis (10-20%). Most anastomotic leaks usually become apparent between 5 and 7 days postoperatively. Therefore, sometimes it occurs when the patient has been discharged. It may present with insidious symptoms such as fever, tachycardia, abdominal distension, ileus, or peritonitis. Occasionally, a leak may present with sudden general deterioration, with a generalized peritonitis and septic shock as the result of a significant and rapid contamination of the peritoneal cavity. Therefore, leak should be suspected in any patient who is not progressing to the expected degree. Imaging studies to define the presence of an anastomotic leak include a water-soluble contrast enema to visualize extravasation of the contrast material and/or a CT scan with contrast material. Treatment will depends on the clinical presentation and the presumed extension of the abdominal affectation. Sometimes, a resection and a formation of a new anastomosis is enough but this is not always successful and a second failure can happen. It that cases, the anastomosis should be taken down and the ends should be exteriorized in an ostomy.

4. JUSTIFICATION

Open surgery used to be the only option available in the treatment of colon cancer. However, laparoscopic resection has been developed as an alternative. Several studies such as COLOR trial and UK MRC CLASSIC trial have shown that laparoscopic resection of colorectal cancer is as effective as open surgery in short and long-term results, it is associated with a reduced number of patients requiring blood transfusions, faster return of bowel function, and a shorter duration of hospital stay, and it does not compromise the long-term oncological results. For that tan reason, in 2006, the National Institute for Health and Clinical Excellence of the UK modified its initial guidance and stated "laparoscopic resection is recommended as an alternative to open resection in individuals with colorectal cancer in whom both laparoscopic and open surgery are considered suitable"(48–50).

In the laparoscopic procedure, both in left and right hemicolectomy, the anastomosis can be performed in an intracorporeal or an extracorporeal way. A mail-in survey by Jamali et al revealed that laparoscopic right colectomy with extracorporeal anastomosis is considered technically more difficult than sigmoidectomy, and that difficulty significantly increases when anastomosis is performed intracorporeal (51). Therefore, while laparoscopic sigmoidectomy with intracorporeal anastomosis is widely used, laparoscopic right colectomy with intracorporeal anastomosis is still rarely performed, due to the technical difficulties in using mechanical linear staplers together with the need for having to perform laparoscopic manual sutures. These reasons perhaps explain why most surgeons today do not perform this procedure with an intracorporeal anastomosis.

Few studies have been carried out comparing the differences between the extracorporeal and the intracorporeal anastomotic procedures in the right hemicolectomy, most of them are very recent, and almost all of them had been retrospective chart reviews (52–55) or systematic reviews (56,57) of PubMed, Embase, Cochrane Central Register of Controlled Trials, CINAHL, BioMed Central, and Science Citation Index databases. These systematic reviews are also about retrospective observational case-control studies with only one prospective study (58).

The retrospective studies were about short- and/or long-term results comparing both techniques and they had found (but not always) statistically significant differences in post-operative outcomes such as better bowel recovery and lower rate of postoperative

complications like surgical site infection. Meta-analysis of non-randomized, comparative studies had also shown that intracorporeal anastomosis in laparoscopic right hemicolectomy was associated with reduced short-term morbidity and decreased length of stay, suggesting faster recovery. These results can be related with a potentially more precise visceral alignment and mesenteric defect suture, possible resulting in a lower risk of anastomotic twisting or internal hernias, and a global reduction in visceral pulling and manipulation, possibly resulting in a faster postoperative recovery. In addition, a cosmetic benefit can be also found, because a shorter laparotomy in a more "aesthetic" site is required. That is to say, these entire findings point to the same: a randomized controlled trial is warranted to confirm these findings.

The aim of this study is to analyse the recovery of the bowel function in the intracorporeal anastomotic procedure compared to the extracorporeal anastomotic one. Early post-operative complications and length of hospital stay also are going to be analysed and compared between the two groups. There are still no solid conclusions about if the intracorporeal approach is the better way to fashion the anastomosis after laparoscopic right colectomy, and the results of the different studies provides the rationale for a randomized clinical trial, which would be useful to give definitive conclusions.

5. HYPOTHESIS

Patients who undergo intracorporeal anastomosis (IA) in right hemicolectomy have better recovery of the normal bowel function compared to those who undergo extracorporeal anastomosis (EA).

6. OBJECTIVES

6.1 Primary objective

The primary aim of the study is to compare the return to a normal bowel function of the experimental (IA) group and the control (EA) group after the hemicolectomy.

6.2. Secondary objectives

1. To analyse post-operatory complications, understanding that with the apparition of anastomotic leakage, paralytic ileus and wound infection defined as a superficial incisional infection that occurred and compare the results in the two groups.
2. To analyse the length of hospital stay after the surgery in both groups and compare the results.

7. MATERIAL AND METHODS

7.1. STUDY DESIGN

In order to be able to confirm or refuse our hypothesis with the level of evidence expected, we propose a non-placebo controlled, opened, prospective randomized controlled clinical trial with the aim to compare the patient recovery after right hemicolectomy.
Patients will be randomly divided with a 1:1 ratio in two groups. The intervention group will be included in the intracorporeal anastomosis surgery group, and the control group of patients will form part of the extracorporeal anastomosis surgery group.
They will be followed up from the right hemicolectomy with the anastomosis until 30 days after the surgery.

7.2. SETTING AND POPULATION OF STUDY

The study will take place in Hospital Universitari Josep Trueta, where the patients will be selected, operated and followed.
The study population is based in adult patients (+18) who undergo an elective surgical treatment for right colon cancer with a laparoscopic procedure of a right hemicolectomy with a side-to-side anastomosis. Patients will be placed in either of both groups randomly in a 1:1 ratio.

7.2.1. Patient inclusion criteria

- Patients over 18 years old.
- Surgical procedure with curative purpose.
- Elective laparoscopic surgery.
- American Society of Anaesthesiologists Physical Status (ASA) I, II, III and IV.
- Patients who have read the Information sheet for participants and have signed the Informed consent form.

7.2.2. Patient exclusion criteria.

- Patients under 18 years old.
- Patients with an advanced disease (Stage IV).
- Urgent surgery.
- Open or converted operations.
- Patients who refuse to sign the informed consent.

7.2.3. Participant withdrawal or termination

An intention-to-treat analysis will be used in this study; therefore, if a patient leaves or dies during it or the follow up is lost, data will not be excluded from the final analysis.

Subjects withdrawn from the trial will not be replaced.

7.3. SAMPLE

7.3.1. Sample selection

To conduct our study, a non-probabilistic consecutive sampling will be performed.
Patients with right colonic neoplasm who undergo a laparoscopic right hemicolectomy with a stapled side-to-side anastomosis will be potential candidates for our study. If the patients meet all the inclusion criteria, they will receive an information sheet which describes the study. If the patient accepts to participate in our study, we will proceed to give the informed consent form (Annex 4).

7.3.2. Sample size

The sample size estimation is based on the literature review. All information we have about the recovery of the normal bowel function is from retrospective studies and they showed a medium time of 3.8 days with a standard deviation (SD) of 1.1 on the apparition of the first dejection and a medium time of 2.4 days with a SD of 0.9 on the apparition of the first flatus. So, we use the program GRANMO to calculate the necessary sample.
Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral contrast, we need a total sample of 158 patients, 79 for each group, to detect an equal or superior difference of 0.5, assuming a SD of 1.1 and an anticipation of a 3% drop-out rate.

7.3.3. Estimated time of recruitment and enrolment

It has been estimated that 158 patients are needed for this study. According to the data accessed by the researchers of this protocol, the number of patients who were treated of right colon cancer the last years and meet our inclusion criteria at Hospital Universitari Josep Trueta was about 40-45. Therefore, we will need four years to recruit the whole sample. Candidates will be informed (Annex 4) and invited to participate voluntarily, having to sign the informed consent of the study (Annex 5) and of the surgery (Annex 6).

7.3.4. Randomization methods and masking techniques

We will randomize the patients of our study in order to avoid the selection bias. Therefore, each patient admitted in the study will be assigned in a group randomly.

At the beginning of the study, main investigators will decide which intervention, IA or EA, will correspond to each group of the study (group 1 and group 2). Statistician expert will create a database containing the participants and they will be assigned to a code. Then, with a simple 1:1 randomization, patients will be assigned in either to the group 1 or group 2, without knowing the technique of each group. Therefore, the statistician expert and the patients will be blinded. The tool he will use for the randomization will be the SPSS software.

In studies that apply surgical techniques, is not possible to blind the surgeon because he will know the procedure he is going to carry out. So, they have a detection bias, making impossible to do a double-blinded study. Usually, the patients cannot also be blinded because when they firm the consent informed form, they are informed about the procedure.

In this case, although the surgeon will know the procedure in every case, when patients will firm the consent form, they will agree not to know with which of the both techniques (IA and EA) they are going to be treated. Therefore, this study will be simple-blinded.

7.4. VARIABLES

7.4.1. Independent variables

Independent variables **represented by the two compared approaches**. Independent variable in our study is to be allocated in the Intracorporeal anastomosis group or in the Extracorporeal anastomosis group in the right hemicolectomy for the treatment of right colon cancer.

This is a qualitative nominal variable and therefore it will be expressed in proportions or percentages.

7.4.2. Main dependent variables

The main dependent variable in our study will be the **time to return to a normal bowel function**. At the post operatory, the surgical team will register on each patient the time of the first flatus and the first dejection after the surgery. It will be defined as a quantitative continuous variable.

7.4.3. Secondary dependent variables

- **Surgical morbidity,** defined as early complications within 30 days after surgery. We are going to taking into account anastomotic leakage, ileus and wound infection.

  The first one will be all conditions with clinical or radiologic anastomotic dehiscence. Thus, only leaks that required an intervention (either percutaneously or operatively) will be counted as an anastomotic leak in both groups.

  The second one will be considerate only when the skin or subcutaneous tissue of the incision is involved and having at least one of the following: (1) purulent drainage, with or without laboratory confirmation, from the superficial incision, (2) organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision or (3) at least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness or heat.

  The last one will be defined as delayed flatus and oral feeding beyond 5 days or reinsertion of a nasogastric tube for longer than 1 day.

  They are a dichotomous qualitative variable and we will record it in the case report form and express it with percentages
- **Length of hospital stay**, defined as the total number of days spent in the hospital after the surgery. Is a quantitative continuous variable.

7.4.4. Covariates

The covariate variables are other factors that can influence our result as they are related with our independent and dependent variables. We will include them in the multivariate analysis in order to assess its impact in the future results.

- Gender (male or female): dichotomous variable.
- Age (measured in years): continuous variable.
- American Society of Anesthesiologists risk class (ASA) score (measured in grades): discrete variable.
- Body mass index (ratio): continuous variable.

7.5. DATA COLLECTION

For the process of data collection, it is vital that the general surgery department of the hospital is aware that this study is being carried out. All the personal will have to work together for data collection, so the surgeon in charge have to inform the rest of the members of the unit (surgeons and nurses) about this study. Also the patients will play an important role in our study because we will need them to help us complete the case report form with the apparition of the signs of the bowel function restoration.
For gathering the information concerned with our study, we will proceed following a specific circuit of the study, explained below. Also a flowchart was created (Fig. 19):

- **Trial entry: 1st visit**

  Patients who have been diagnosed a right colonic tumour and who meet the inclusion criteria will be asked if they want to participate in the trial. The first step required for data collection will be the acquisition of the informed consent signed (Annex 5 and 6) when they agree to participate. Before that, the patient has read the informative sheet (Annex 4).

  In our trial, patients won't know with which of the two surgical techniques they will be treated. If the patient has signed the informed consent, he or she will be randomly placed in one of the two surgical procedures.

- **Anaesthesiology visit**

  In this visit, the anaesthesiologist will classified the patient into the different stages of ASA (American Society of Anaesthesiology) classification according with their operatory risk. They will also have to sign the anaesthesiologist informed consent for the intervention.

- **2nd visi**

  After the anaesthesiology visit, patients will be visited again in external consults to give them the indications for their preparation the days before and the same day of the surgery (Annex 7).

- **Surgery**

  Patients will be operated according to the hospital waiting list with a laparoscopic right hemicolectomy and the anastomotic technique will be the one that has randomly played.

- **Hospitalization**

  Patients will be checked during the early postoperative period to control the recovery of the bowel function. Patients will be checked every 8 hours for one surgeon of the team and will be controlled for the nurses of the section.

  Signs and symptoms of early postoperative complications will also be daily evaluated. As these we will consider anastomotic dehiscence, paralytic ileus and wound infection. It will be assessed by the surgeon with anamnesis and physical examination. In case of anastomotic dehiscence is suspected, a radiological procedures will be considered to the final diagnosis. The information will be collected in the Participant Data Sheet (Annex 8).

  After recovery of the normal bowel function, the ambulation, and the oral feeding is tolerated, patients will be discharged.

- **Ambulatory follow up (1 month after surgery)**

  After the discharge, patients will be followed up at external consults of the hospital to control they recovery, the total wound cicatrisation and the correct evolution of the bowel anastomosis. They will be visited two times, at 7th and 30th days. All adverse events that occurred within this period of 30 days after surgery will be considered early complications. However, patients will be able to make any appointments if they consider it necessary because of the deterioration of their clinical status. The information will be collected again in the Participant Data Sheet (Annex 8).

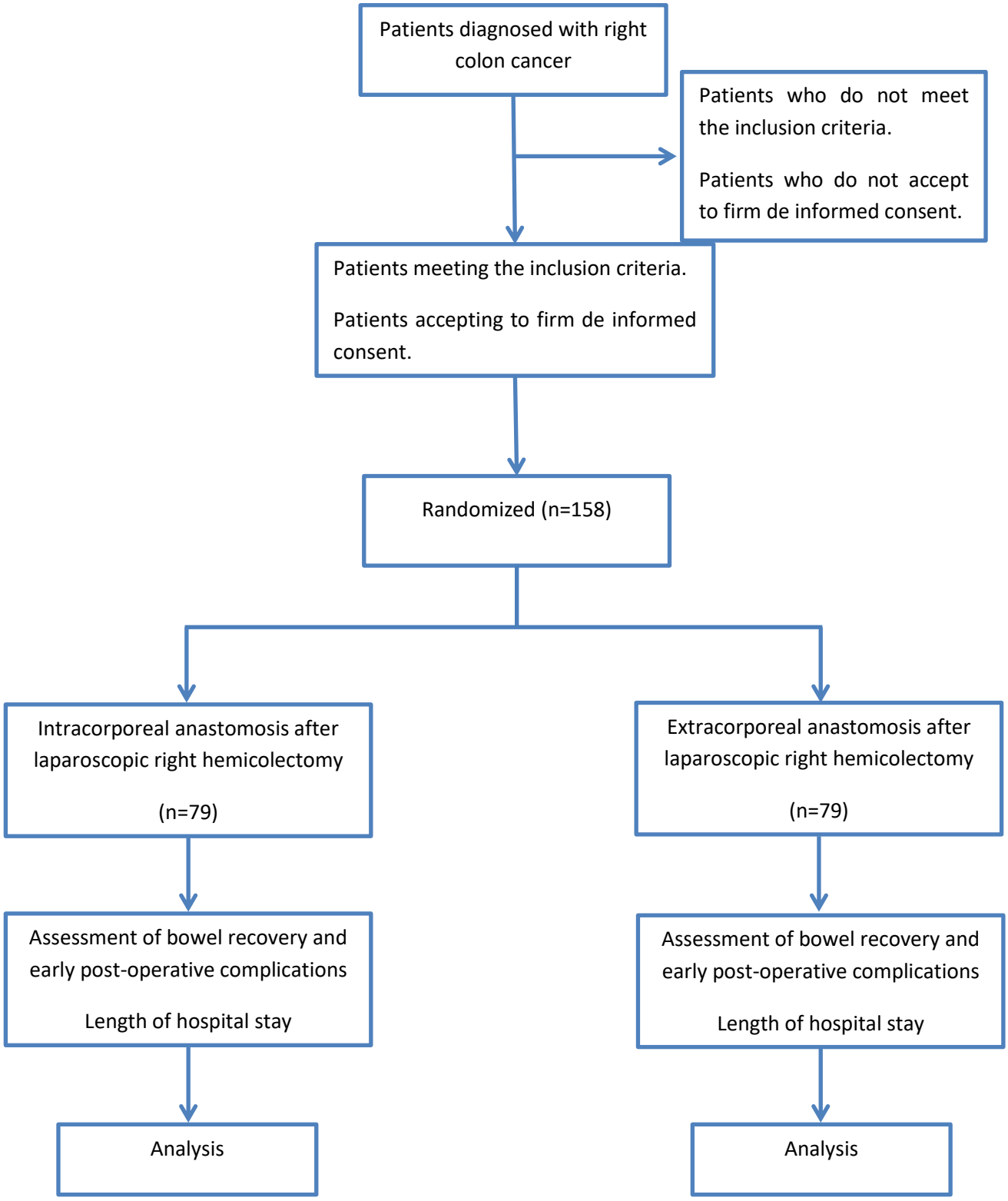

Figure 17. Flowchart of the data collection.

7.5.1. Interventions

As we have expounded above, the patients participating in our study will be divided in two groups depending on the applied technique.

One group will be treated with an intracorporeal anastomosis while the other group will be treated with an extracorporeal anastomosis after the hemicolectomy.

The initial steps of both procedures are similar. Pneumoperitoneum will be established through a 10-mm subumbilical port. The other three ports will be fitted in the left hypochondrium and two iliac fossae to act as working ports. Right colon resection will be carried out through a medial to lateral approach starting with ligation of the blood vessels at their origin followed by mobilization of the bowel via medial-to lateral and dissection of the terminal ileum and colon attachments.

- ***Intervention A: Intracorporeal anastomosis***

After the colon is mobilised systematically via medial-to-lateral retroperitoneal dissection, final ileum will be located and both will be transected with a reticulating laparoscopic linear stapler. Then, the specimen will be moved to the pelvis or left abdomen. When the orientation of the terminal ileal and transverse colon stumps will be confirmed, an enterotomy will be made in each limb, and the limbs will be anastomosed in side-to-side isoperistaltic anastomosis with a 60-mm endostapler, and the enterotomy will be closed with continuous suture (3-0 Vicryl).

The mesenteric defect will be left open. The specimen will be extracted through a Pfannenstiel incision after a wound protector is placed. Finally, the abdominal wound will be closed, the peritoneal cavity will be reinsufflated, and all trocars will be removed under direct visualization.

- ***Intervention B: Extracorporeal anastomosis***

After all the mobilization, a small subcostal incision will be made, a wound protector will be inserted and the mobilized right colon will be exteriorized. The colon and ileum will be transected with an 80-mm linear 3.5-mm stapler and the specimen will be removed. Finally, the two limbs will be anastomosed in a side-to-side anastomosis using the 80-mm linear 3.5-mm stapler along their antimesenteric surfaces, taking care to maintain the proper orientation of the ileal and the colonic limbs to prevent a twisted anastomosis. The remaining enterotomy will be closed with a non-cutting TA-60 3.5mm stapler. Finally, the completed anastomosis will be returned to the abdominal cavity and the subcostal incision and the trocar sites will be closed at the fascia level to prevent hernias.

7.6. STATISTICAL ANALYSIS

All statistical analysis will be performed with Statistical Package for the Social Sciences (SPSS) for Windows®.

Univariate analysis

In the univariate analysis, the variables will be defined as categorical nominal, quantitative continuous or quantitative discrete.

The results will be expressed as percentages for categorical variables, and as mean +/- standard deviation (SD) or median for quantitative variables depending on whether or not they are normally distributed.

Bivariate analysis

In the bivariate analysis, for primary objective, the independent variable was defined as a nominal categorical variable and the dependent variable as a quantitative continuous variable. Before the comparison of these variables, the dependent one has to be evaluated to look if it is normally distributed. The Kolmogorov-Smirnov test will show us that. If it is normally distributed, T-Student test will be used. If is not normally distributed, Mann-Whitney U test will be used.

For the first of the two secondary objectives, the dependent variable was defined as nominal categorical one (like the independent variable). Therefore, the Chi-squared test will be used.

Finally, for analysing the last dependent variable, which was also defined as quantitative continuous, we will use again the Kolmogorov-Smirnov test to see if it is or is not normally distributed, and depending on the results, the T-Student test or the non-parametric U-Mann-Whitney test will be used.

A confidence interval of 95% will be assumed and $p<0.05$ will be considered statistically significant.

Multivariate analysis

A multivariate analysis will be accomplished to adjust our variables for co-variables, thus we will try to avoid potential confounders that could modify the results. It will be done using a logistic regression model.

In order to include the amount of days in hospital also in the multivariate analysis, as it's a quantitative continuous variable, a generalized lineal model will be used.

7.7. WORK PLAN AND CHRONOGRAM

This study is expected to last 5 years plus 4 months for protocol elaboration and coordination. The activities carried out during this time by the researcher team will be organized in 5 phases which are detailed below (Annex 8):

1. **Preparation and coordination phase (4 months)**

In this first phase, from November 2016 to February 2017, the study will be elaborated. It will be done with the collaboration of investigators, surgeons, nurses and the statistician involved in the trial. The hypothesis, objectives, variables and methods will be discussed. The chronogram will also be arranged at this point and the methods for data collection will be discussed and set up.

Once the protocol is ready, it will be presented to the Ethical Committee for its evaluation and approval.

As the study is longitudinal and it will last about 6 years, the researchers decide to organize meetings every three months in order to control the data collection and to assess the progression of the study. The aim of this is to identify deficiencies of the study design and correct the methodological flaws.

2. **Field work**

- Sample recruitment (4 years): patients who undergo a right hemicolectomy of a right colonic tumour, and who meet the inclusion criteria for the study will be collected and distributed randomly into two different groups (intracorporeal anastomosis and extracorporeal anastomosis after the laparoscopic right hemicolectomy). Since there are around 40 cases like this per year at the Hospital Universitari Josep Trueta it will take four years to recruit all the needed patients.
  It is important to remember that the informed consent must be signed by the patient.

- Intervention (4 years): each patient incorporated in the study will go through his assigned treatment.
- Follow up (30 days): every patient will be followed during 30 days after the surgery. First days of follow up will be at hospital until the discharge, and then at external consults of the hospital to control the correct evolution of the patient.

Our patients are affected for colon cancer and the normal follow up for these patients is five years. Therefore, after the 30 days of our study when no more collection of data will be necessary for us, follow-up will be continued with the mandatory visits for the disease.

3. Data collection (4 years and 6 months)

While the trial is taking place, the data collected from each patient will be registered in our database.
This collected data will be periodically evaluated and analysed by our statistician to control if the protocol is being followed.

4. Data analysis and interpretation (6 months)

After processing the database, all data will be analysed using the appropriate statistical tests set in the protocol for each objective. This will be performed by a blinded statistician.

After the interpretation of the results is done, the corresponding article will be written.

5. Publication (6 months)

The researchers will write and edit a scientific paper to publish.

8. ETHICAL AND LEGAL ASPECTS

As regulated by the law 14/2007 of the 3rd of July about Biomedical Investigation, this study protocol will be evaluated by the Clinical Research Ethics Committee of the Hospital Universitari Josep Trueta, and it will not be applied unless it has its approval. This committee shall ensure that the study respects the ethical principles for medical research involving human subjects established by Helsinki's Declaration, and that the privacy of all the participants is protected and confidential as well as their personal information. Any further recommendation from the Committee will be taken into account in order to improve the procedure.

This trial is designed in accordance with the medical ethics requirements defined on the World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects (last revised in October 2013), which also rules the principles of human experimentation, and the committee will also ensure that the study respects all these ethical principles.

As it is now recommended, the trial will also been registered with an International Standard Randomised Controlled Trial Number (http://www.controlled-trials.com) and will been submitted to ClinicalTrials.gov (http://clinicaltrials.gov).

Previous to the inclusion, the interventions and the clinical trial will be presented to the candidates and an information sheet will be provided to them by presenting the risks, the benefits and the alternatives of the different interventions using the best update data available at that point. They will participate voluntarily. Therefore, they must understand and sign the informed consent if they want to entry the study. Thus the principle of autonomy will be respected.

Since this study includes an invasive procedure performed on the participants of both groups, the Spanish law 14/2007 of the 3rd December about Biomedical Investigation will be respected.

Patients' data will be handled respecting Spanish organic law 15/1999 of the 13th of December about data protection, confidentiality and protection of personal data, and RD 1720/2007 of the 21st of December on personal data protection. Furthermore, to maintain confidentially of personal data, an identification number will be used instead of the

patient's name. This way again, the principle of autonomy will be respected. The Spanish Constitution of 1978, in the article 43, talks about the right of Health protection, and this is undoubtedly preserved on this trial.

Finally, exclusion criteria have been set respecting the principles of justice and beneficence, since most of the patients have the opportunity to be part of the study, and doctors and other medical workers who take part in it are accredited and well prepared for their assigned tasks, so the principle of non-maleficence will be respected.

9. STRENGTHS AND LIMITATIONS

Several limitations to this study need to be accepted.
First of all, the main limitation of this clinical trial is that its design is a simple blinded one, since the surgeon cannot be blinded. That means the doctors and the research team will know in which approach is the patient included, which can cause a detection bias. With the intention to overcome this limitation, the statistician will be blind when analysing the obtained data. This way the bias can be reduced.

The second limitation is related to the method of the study. The consecutive recruitment is non-probabilistic and may not obtain the best representative population, so a selection bias may have been done. Nevertheless, to minimize this bias, very few exclusion criteria have been set, and we can conclude that the reference population to whom the protocol results are directed is very similar to the components of our sample.
Moreover, these exclusion criteria have been set to diminish the possible confusing factors without excluding the main study population, such as the conversion to an open surgery after the initiation with a laparoscopic procedure or an emergent surgery because of a tumour complication.

Loses and withdrawals during the surgery and the follow up are another limitation that we need to keep in mind, and can also cause a selection bias. In order to reduce it, we will calculate the sample size with expectations of future loses (3% in this case). Intention-to-treat analysis will be used for missing data and withdrawals will be registered in the study and described in the results. However, a short follow-up and the importance of the disease can be a strong point, leading to fewer withdrawals and loses.

The fourth limitation is related to the recruitment time and the development of the study. We are aware that during these years, new studies of the same subject can be carried out and published with important results or a better treatment can be described making our study less justified.

We will perform a unicentric study. Therefore, this will cause an increased time of patient enrolment. A multicentric study with a shorter time of recruitment and a bigger sample size would be interesting for increasing statistical power, not only for our objectives, but also for other ones such as less common complications.

One of the strengths is that randomization will help to distribute symmetrically the participants on both groups and we will be able to compare the results between them. Apart from that, it will allow us to extrapolate the future results on general population reducing the selection bias.

Sample size and methods are designed to study the primary objective; therefore, the secondary objectives may not have a significant result. However, we estimate that only anastomotic leakage may not achieve significant clinical values.

10. FEASIBILITY

The study proposed will take place exclusively in Hospital Universitari Doctor Josep Trueta de Girona, where all the means necessaries for its development will be available and provided. It has a 24h working digestive and general surgery department with specialized surgeons in colorectal surgery, and it also has a radiology department where the needed radiological procedures can be performed.

The personnel who are going to be part of this study (main surgeon, other colorectal surgeons, nurses, and statistician) are well trained and have experience on this field.

To carry out the study, the hospital will provide all the necessary means such as personnel salaries, surgeries, cures and radiological procedures. The informatics equipment needed for processing the database for the study development and statistical analysis will be also dispensed by the hospital.

We estimated that in the Hospital Universitari Doctor Josep Trueta de Girona around 40 patients undergo a laparoscopic right hemicolectomy for right colon cancer per year. To find the main hypotheses relevant, we explained before that the sample size should be 79 patients per group. Therefore, we expect that in 5 and a half years (starting May 2017) of patient recruitment, follow up and data collection, we will have the final results of the study.

11. BUDGET

The realization of this study does not include an increase of the costs of the surgical intervention, an increase in the number of the personnel or additional training process and formation, because it is the procedure used in the clinical practice nowadays and both techniques are currently performed in the Hospital Universitari Dr. Josep Trueta for the treatment of colorectal cancer. Therefore, no additional cost for medical staff will be included. Necessary material for the surgery will not be included in the budget due to it is currently in the stock of the department.

After the surgical procedure, patients will be hospitalized during few days. Our hospital includes hospitalization in his postoperative plan, so we will not take in account this cost. Currently, the hospitalization period is in charge of the National Health System. Ambulatory appointments will also be in charge of the National Health System.

It is necessary to hire a statistical expert for the randomization and codification of the patients, the development of the database and the realization of the statistical analysis. It is estimated that we will need 200 hours of his or her services, with a salary of 25€/h, which means an estimated cost of 5000€.

Also, a skilled staff to carry out the data monitoring, quality control data and regular submission to the Spanish Medicine Agency is required. 1h of work per week is needed, achieving a total of 216h (4h x 54 months) of work with the cost of 25€/h. budget is estimated to be 5,400€. We will also hire a statistical consultancy firm through the Institut d'Investigació Biomédica de Girona (IDIBGI) with the cost of 300€.

The cost of printing and material needed (for information sheets, information consent sheets and participant data sheet) will be of 50€. Pens, paper, staplers and other office materials will be included in "Office Supplies", with the estimated cost of 50€.

Once the study is finished, all data collected will be reflected on a scientific paper to be published and disseminated to the scientific community with the following costs:

- Translation services: 200€.
- Publication expenses in international scientific journals: 1000€.
- Attendance of National and International Congresses for the broadcasting of the results: to the National Congress of Coloproctology and the European Congress of

Coloproctology, with a cost of 450€ and 1000€ respectively. The costs of the trips are still unknown due to the localization of the congresses are not established yet. However, we can do an approximation of the costs in 400€ per person for the national congress and 600€ per person for the international one, and two people will attend to these congress, in total of 1000€ per person.

	Price	Quantity	Total cost
STAFF AND SERVICES			
Medical staff	Provided by the National Health System (NHS)		
Statistical expert for data analysis	25€/h	200h	5.000€
Clinical Research Associate	25€/h	216h	5.400€
Statistical consultancy firm	300€	1	300€
Translation services	200€	1	200€
MATERIAL			
Surgical Material	Provided by the NHS		
Hospitalization	Provided by the NHS		
Ambulatory appointments	Provided by the NHS		
Printing and other materials	50€	1	50€
Office Supplies	50€	1	50€
IMB SPSS Statistics license	300€/year	1	300€
Box of 200 envelopes	20€/unit	1	20€
Data storage (pen-drives, hard-drives)	10€/unit	5	50€
PUBLICATION AND DISSEMINATION			
Publication expenses	1000€	1	1000€
Inscription to national congress	450€	2	900€
Inscription to international congress	1.000€	2	2.000€
Travel, accommodation and food	1000€	2	2.000€
TOTAL		**17.270€**	

12. IMPACT

The main aim of this project is to achieve more information about the indication, safety and benefits of the utilization of an intracorporeal anastomotic approach in a laparoscopic right hemicolectomy.

Due to the high frequency of the diagnosis of right colonic cancer, the treatment use to be by surgery, and the intracorporeal anastomosis seems to be a better approach according to the observational studies have been carried during the past years, we consider that the necessity of assess this treatment is needed in order to make reliable recommendations, and that is the reason why we decided to propound this protocol.

If the results obtained are relevant enough and our hypothesis is validated, at least, for our population of study, we will be confident to implement this technique for the benefit of our patients. Firstly, because the rates of recovery will be better, secondly because the rates of complications will be lower and finally because the length of hospital stay will be reduced in benefit of our patients and of the hospital administration.

As a whole, as far as we could confirm that the use of an intracorporeal anastomotic approach during the surgical treatment of a right colonic cancer is a better approach, we will be offering our patients a general improvement in the management of their disease, that is to say, we will be presenting them a series of benefits in comparison with the extracorporeal procedure.

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14. ANNEXES

ANNEX 1

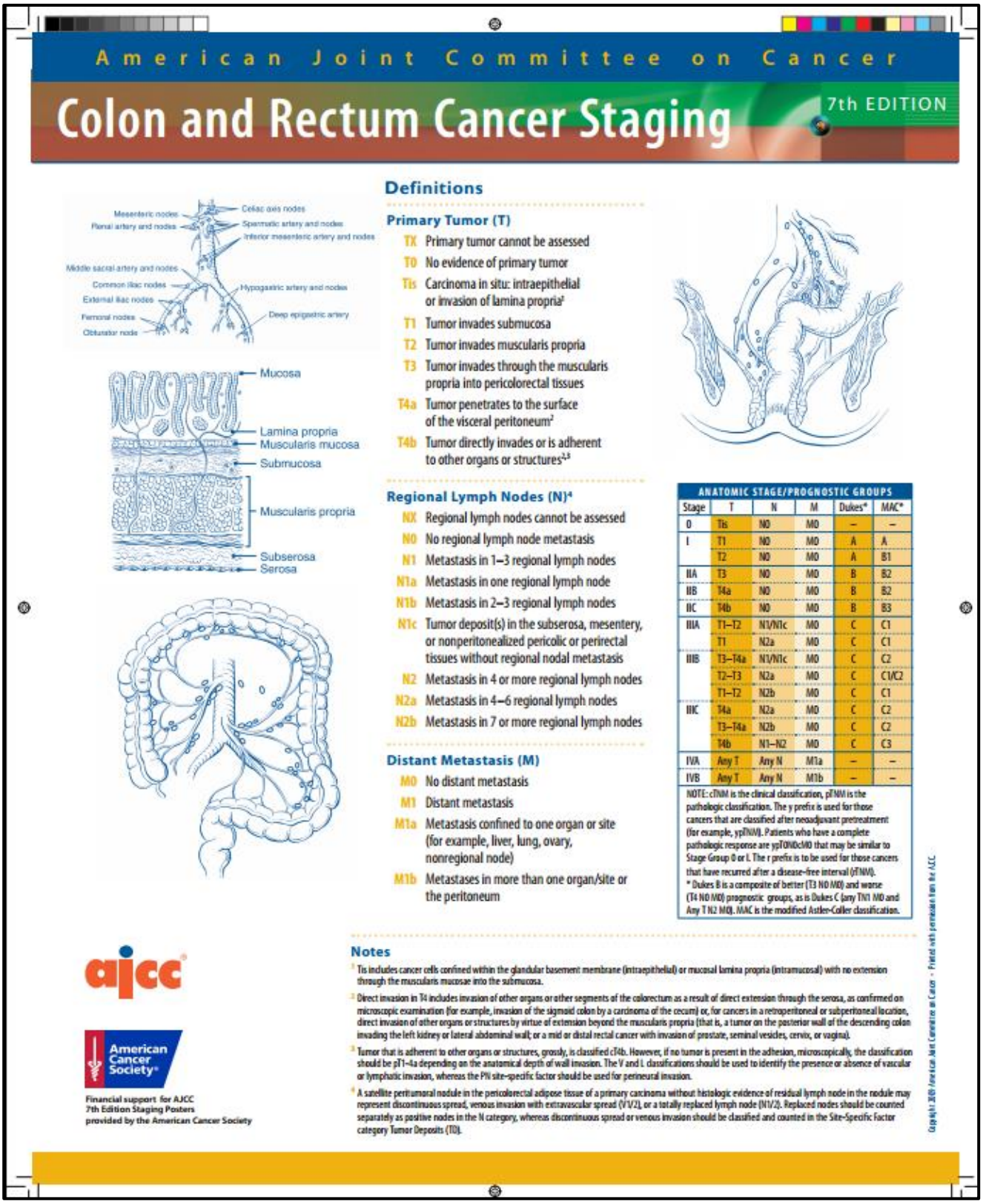

Figure 18. Colon and rectum cancer staging (63).

ANNEX 2

Table 1. Standard resections of the colon (10).

Tumor Location	Resection	Description of Extent	Major Blood Vessel	Safety Margin (cm)
Cecum	Right hemicolectomy	Terminal ileum to midtransverse colon, right flexure included	Ileocolic artery, right colic artery, right branch of mid colic artery	5
Ascending colon	Right hemicolectomy	Terminal ileum to midtransverse colon, right flexure included	Ileocolic artery, right colic artery, right branch of midcolic artery	5
Hepatic flexure	Extended right hemicolectomy	Terminal ileum to descending colon (distal to left flexure)	Ileocolic artery, right colic artery, midcolic artery	5
Transverse colon	Extended right hemicolectomy (Transverse colon resection)	Terminal ileum to descending colon (distal to left flexure) Transverse colon (including both flexures)	Ileocolic artery, right colic artery, midcolic artery Midcolic artery	5
Splenic flexure	Extended left hemicolectomy	Right flexure to rectosigmoid colon (sigmoid, beginning of rectum)	Midcolic artery, left colic artery, inferior mesenteric artery	5
Descending colon	Left hemicolectomy	Left flexure to sigmoid colon (beginning of rectum)	Inferior mesenteric artery, left branch of midcolic artery	5
Sigmoid colon	Rectosigmoid resection	Descending colon to rectum	Superior hemorrhoidal artery, inferior mesenteric artery	5

ANNEX 3

Table 2. Criteria for defining surgical site infection (SSI) (44)

Superficial incisional SSI
Infection occurs within 30 days after the operation
AND
Infection involves only skin or subcutaneous tissue of the incision
AND at least **ONE** of the following:
1. Purulent drainage, with or without laboratory confirmation, from the superficial incision.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat **AND** superficial incision is deliberately opened by surgeon, **UNLESS** incision is culture-negative.
4. Diagnosis of superficial incisional SSI by the surgeon or attending physician.
Do **NOT** report the following conditions as SSI:
1. Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration).
2. Infection of an episiotomy or newborn circumcision site.
3. Infected burn wound.
4. Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI).
NOTE: Specific criteria are used for identifying infected episiotomy and circumcision sites and burn wounds.
Deep incisional SSI
Infection occurs within 30 days after the operation if no implant* is left in place or within 1 year if implant is in place and the infection appears to be related to the operation
AND
Infection involves deep soft tissues (eg, fascial and muscle layers) of the incision
AND at least **ONE** of the following:
1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site.
2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain, or tenderness, unless site is culture-negative.
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.
NOTES:
1. Report infection that involves both superficial and deep incision sites as deep incisional SSI.
2. Report an organ/space SSI that drains through the incision as a deep incisional SSI.
Organ/space SSI
Infection occurs within 30 days after the operation if no implant* is left in place or within 1 year if implant is in place and the infection appears to be related to the operation
AND
Infection involves any part of the anatomy (eg, organs or spaces), other than the incision, which was opened or manipulated during an operation and at least one of the following:
1. Purulent drainage from a drain that is placed through a stab wound¶. If the area around a stab wound becomes infected, it is not an SSI. It is considered a skin or soft tissue infection, depending on its depth into the organ/space.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of an organ/space SSI by a surgeon or attending physician.

* National Nosocomial Infection Surveillance definition: a nonhuman-derived implantable foreign body (eg, prosthetic heart valve, nonhuman vascular graft, mechanical heart, or hip prosthesis) that is permanently placed in a patient during surgery.
¶ If the area around a stab wound becomes infected, it is not an SSI. It is considered a skin or soft tissue infection, depending on its depth.

Data from: Mangram AJ, Horan TC, Pearson ML, et al. Guideline for prevention of surgical site infection. In: Infection Control and Hospital Epidemiology, CDC 1999; 20:247.

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ANNEX 4

HOJA DE INFORMACIÓN AL PACIENTE

ANASTOMOSIS INTRACORPÓREA vs. ANASTOMOSIS EXTRACORPÓREA EN LA HEMICOLECTOMIA DERECHA LAPAROSCÓPICA PARA CÁNCER.

INTRODUCCIÓN.

Nos dirigimos a usted para informarle sobre un estudio al que se le invita a participar. El estudio ha sido aprobado por el comité ético de investigación clínica del Hospital Universitario de Girona Dr. Josep Trueta.

Nuestra intención es que usted reciba la información correcta i suficiente para que pueda evaluar i juzgar si quiere o no participar en este estudio. Para esto lea esta hoja informativa con atención i nosotros le aclararemos las dudas que le puedan surgir después de la explicación. Además, puede consultar con las personas que usted crea convenientes.
Nos gustaría proveerle con esta hoja de información en relación a un Proyecto de investigación que se está llevando a cabo en nuestro centro, en el cual está invitado a participar. Nos gustaría que considerase este Proyecto y decidir si le gustaría participar en él. Por favor, lea con detenimiento la siguiente información antes de tomar una decisión.

PARTICIPACIÓN VOLUNTARIA
Debe saber que su participación en este estudio es voluntaria y que puede decidir no participar y retirar su consentimiento en cualquier momento, sin que esto le suponga una alteración de la relación médico-paciente ni se produzca perjuicio alguno en su tratamiento. Si decide participar en el estudio tendrá que firmar el consentimiento informado después de leer esta hoja de información.

DESCRIPCIÓN DEL ESTUDIO
Cuando un paciente tiene el intestino afectado con un tumor, el tratamiento que se suele llevar a cabo es una cirugía, en la cual se extirpa el trozo de intestino que está afectado. Después de la extirpación, es necesaria su reconstrucción, por lo que hay que juntar y suturar los dos extremos intestinales. Esta sutura se puede llevar a cabo dentro o fuera del cuerpo. En nuestro estudio queremos comparar y ver si una de las reconstrucciones es superior a la otra. Para poderlo hacer, a cada paciente que participe en nuestro estudio se le tendrá que asignar un procedimiento o el otro de manera aleatoria y posteriormente, el cirujano llevará a cabo un seguimiento de su recuperación, tanto funcional como para controlar la posible aparición de las complicaciones que puedan surgir después de la cirugía.
Este estudio se lleva a cabo en el Hospital Universitario Dr. Josep Trueta y recogeremos datos de aproximadamente 158 pacientes. A partir de esta información recopilada, se hará un análisis estadístico para poder observar si una técnica es superior a la otra. Con esto queremos mejorar la información que tenemos acerca de la técnica para poderla implementar como técnica de rutina.

Por lo tanto, usted será operado con una técnica quirúrgica validada y elegida de manera aleatoria y, posteriormente, seguido durante un periodo de 30 días. Acabado el

seguimiento relacionado con el estudio, se le llevará a cabo el seguimiento establecido en la práctica clínica habitual.

Si necesitase otra visita durante este proceso debido a cualquier complicación extra se puede pedir una cita en cualquier momento.

¿POR QUÉ HA SIDO INVITADO A PARTICIPAR?
Usted se va a someter a un procedimiento quirúrgico para tratar un tumor de colon derecho y, por lo tanto, se va a someter a uno de los procedimientos quirúrgicos que queremos estudiar. Además, cumple los criterios de inclusión de este ensayo clínico.

BENEFICIOS Y RIESGOS EN LA PARTICIPACIÓN DEL ESTUDIO
Es posible que los resultados obtenidos en esta investigación tengan poco valor predictivo para usted, pero podrá ayudar a conocer mejor el tratamiento y pronóstico de su enfermedad en los futuros pacientes.

No se prevé ningún riesgo adicional para usted ya que utilizaremos para el estudio las dos técnicas que habitualmente se pueden realizar.

Los resultados del estudio podrían ayudar a futuras personas, sometidas a extirpación de intestino y su reconstrucción posterior y conseguir así, mayores tasas de éxito en su tratamiento y menor morbi-mortalidad asociada.

Puede negarse a realizar el estudio y puede revocar su consentimiento en cualquier momento, sin tener que dar explicaciones y sin ninguna repercusión en la atención médica que reciba.

TRATAMIENTOS ALTERNATIVOS
La inclusión en este estudio no cambiará la normal estrategia diagnostica-terapéutica para el tratamiento de su enfermedad. El médico del estudio le dará más información si la quisiese.

RESPONSABILIDAD Y SEGURO
Usted estará asegurado ante cualquier daño que pueda sufrir como resultado de su participación en este estudio, de acuerdo con la ley vigente.

CONFIDENCIALIDAD
El tratamiento, la comunicación y la cesión de los datos de carácter personal de todos los sujetos participantes se ajustarán por lo dispuesto en la Ley Orgánica 15/1993, del 13 de diciembre de protección de datos de carácter personal. De acuerdo con lo que se establece en la legislación mencionada, usted puede ejercer los derechos de acceso, modificación, oposición y cancelación de datos, para lo cual se tendrá que dirigir a su médico del estudio. Los datos recogidos para el estudio estarán identificados mediante un código y sólo su médico del estudio o colaboradores podrán relacionar estos datos con usted o con su historia clínica. Por tanto, su identidad no será reveada a ninguna persona exceptuando excepciones, en caso de urgencia médica o requerimiento legal.

Sólo se tramitarán a terceros y a otros países los datos recogidos en el estudio, que en ningún caso contendrán información que lo pueda identificar directamente, como el nombre y apellidos, iniciales dirección, número de la Seguridad Social, etcétera. En caso de que se produzca esta cesión será para la misma finalidad del estudio descrito y garantizando la confidencialidad como mínimo a nivel de protección de la legislación vigente en nuestro país.

El acceso a su información personal quedará restringido al médico del estudio, colaboradores, autoridades sanitarias (Agencia Española del Medicamento y Productos Sanitarios), al Comité Ético de Investigación Clínica y personal autorizado por el promotor, cuando lo precisen para comprobar los datos y procedimientos del estudio, manteniendo la confidencialidad de los mismos de acuerdo con la legislación vigente. El acceso a su historia clínica será solo por lo que hace al estudio clínico.

COMPENSACIÓN ECONÓMICA

El promotor del estudio es el responsable de gestionar la financiación del mismo, por lo que su participación en este no le supondrá ningún gasto.

OTRA INFORMACIÓN RELEVANTE

Si usted decide retirar su consentimiento para participar en el estudio, no se incluirá ningún dato nuevo a la base de datos.

También ha de saber que puede ser excluido del estudio si el promotor o los investigadores del mismo lo consideran oportuno, ya sea por motivos de seguridad, o por cualquier evento adverso. En cualquier caso, usted recibirá una explicación adecuada del motivo por el cual se ha decidido la retirada del estudio.

El promotor podrá suspender el estudio siempre que sea por alguno de los supuestos de la legislación vigente.

Al firmar la hoja de consentimiento adjunta, se compromete a cumplir con los procedimientos del estudio que se le han expuesto.

CONTACTO:

Si tiene alguna duda durante el estudio por favor contacte con los investigadores: Dr. Antonio Codina Cazador y Alba Aramburu Munoa.
Hospital Universitari Dr. Josep Trueta
Av/ de França, s/n. 17007 – Girona

Gracias por leer esta información. Procure guardar esta hoja hasta que su participación en el estudio haya concluido. Para cualquier duda, por favor no dude en contactarnos.

Si acepta participar en el estudio, por favor firme el consentimiento informado.

PATIENT INFORMATION SHEET

INTRACORPOREAL vs. EXTRACORPOREAL ANASTOMOSIS IN LAPAROSCOPIC RIGHT HEMICOLECTOMY FOR CANCER.

INTRODUCTION.

We are writing to inform you about a study you are invited to attend. The study was approved by the ethical committee of clinical research of the University Hospital of Girona Dr. Josep Trueta.

Our intention is that you receive the correct and sufficient information to enable you to evaluate and judge whether or not you want to participate in this study. Therefore, read this fact sheet carefully and we will clarify the doubts that may arise after the explanation. In addition, you can consult with people you think are convenient.
We would like to provide you with this information sheet in relation to a research project that is being carried out in our centre, in which you are invited to participate. We would like you to consider this Project and decide if you would like to participate in it. Please, read the following information carefully before making a decision.

VOLUNTEER PARTICIPATION.

You should know that your participation in this study is voluntary and that you may decide not to participate and withdraw your consent at any time, without this implying an alteration of the doctor-patient relationship or any harm to your treatment. If you decide to participate in the study you will need to sign informed consent after reading this fact sheet.

STUDY DESCRIPTION.

When a patient has the intestine affected with a tumour, the treatment that is usually carried out is a surgery, in which the piece of intestine that is affected is removed. After the removal, it is necessary a reconstruction, so the two intestinal ends have to be joined and sutured. This suture can be performed inside or outside the body. In our study we want to compare and see if one of the reconstructions is superior to the other. In order to do this, each patient participating in our study will be assigned in one procedure or the other in a randomly and after the procedure, the surgeon will monitor their recovery, both functional and to control the possible complications that may arise after surgery.

This study is carried out at the University Hospital Dr. Josep Trueta and we will collect data from approximately 158 patients. From this information collected, a statistical analysis will be done to be able to observe if one technique is superior to the other. With this we want to improve the information we have about the technique to be able to implement it as a routine one.

Therefore, you will be operated with a validated and randomly selected surgical technique and then followed for a period of 30 days. Finishing the follow-up related to the study, you will be followed with the usual clinical practice.

If you need another visit during this process due to any extra complication, you can request an appointment at any time.

WHY HAVE YOU BEEN INVITED TO PARTICIPATE?
You are going to undergo a surgical procedure to treat a right colon tumour and, therefore, you are going to undergo one of the surgical procedures that we want to study. In addition, you meet the inclusion criteria of this clinical trial.

BENEFITS AND RISKS OF PARTICIPATION ON THE STUDY.
It is possible that the results obtained in this research have little predictive value for you, but may help to a better understand of the treatment and prognosis of your disease in future patients.

No additional risk is anticipated for you since we will use for the study the two techniques that usually can be realized.

The results of the study could help future people who undergo intestinal excision and subsequent reconstruction to achieve higher success rates in treatment and lower associated morbidity and mortality.

You can refuse to do the study and can revoke your consent at any time, without having to give explanations and without any impact on the medical care you receive.

ALTERNATIVE TREATMENTS.
Inclusion in this study will no change the normal diagnostic-therapeutic strategy for the treatment of your disease. The study doctor will give you more information if you want.

RESPONSABILITY AND INSURANCE.
You will be insured against any damages you may suffer as a result of your participation in this study, in accordance with applicable law.

CONFIDENTIALITY.
The treatment, communication and transfer of personal data of all the participating subjects will be adjusted by the provisions of Organic Law 15/1993, of December 13, on the protection of personal data. In accordance with what is established in the aforementioned legislation, you can exercise the rights of access, modification, opposition and cancellation of data, for which you will have to contact your study doctor. The data collected for the study will be identified by a code and only your study doctor or collaborators will be able to relate this data to you or your medical history. Therefore, your identity will not be disclosed to any person excepting exceptions, in case of medical urgency or legal requirement.

Data collected in the study will be only processed to third parties and other countries, which in no case will contain information that can directly identify with you, such as name, address, Social Security number, etc. In the event that this cession occurs, it will be for the same purpose of the study described and guaranteeing the confidentiality at least with the level of protection of the legislation in force in our country.

Access to your personal information will be restricted to the study doctor, collaborators, health authorities (Spanish Agency for Medication and Health Products), the Ethical Committee for Clinical Research and personnel authorized by the promoter, when it will be necessary to verify the data and procedures of the study, keeping the confidentiality of the same in accordance with current legislation. Access to your medical history will be only for the clinical study.

ECONOMIC COMPENSATION.
The promoter of the study is responsible for managing the financing of the same, so your participation in this will not involve any expense.

OTHER RELEVANT INFORMATION.
If you decide to withdraw your consent to participate in the study, no new data will be included in the database.

You should also be aware that you may be excluded from the study if the sponsor or investigators consider it appropriate, either for safety reasons, or for any adverse event. In any case, you will receive an adequate explanation of why you were withdrawn.

The promoter may suspend the study whenever it is for any of the assumptions of the current legislation.

By signing the attached consent sheet, you agree to comply with the study procedures that have been set forth.

CONTACT:
If you have any doubts during the study, please contact with the investigators: Dr. Antonio Codina Cazador y Alba Aramburu Munoa.
Hospital Universitari Dr. Josep Trueta
Av/ de França, s/n. 17007 – Girona

Thank you for reading this information. Try to save this sheet until your participation in the study has been completed.

If you agree to participate in the study, please sign the informed consent.

ANNEX 5

Hospital Universitari de Girona Doctor Josep Trueta

Institut Català de la Salut

CONSENTIMIENTO INFORMADO.

TITULO DEL ESTUDIO: "INTRACORPOREAL vs. EXTRACORPOREAL ANASTOMOSIS IN LAPAROSCOPIC RIGHT HEMICOLECTOMY FOR CANCER."

Yo.....

Confirmo que:

- He leído la hoja de información que se me ha entregado.
- He podido hacer preguntas sobre el estudio.
- Han respondido mis preguntas de manera satisfactoria.
- He recibido suficiente información sobre el estudio.

He hablado con (nombre del investigador / cirujano general y digestivo / enfermero):
.....

Comprendo que la participación es voluntaria.
Comprendo que puedo retirarme del estudio:
1.- Cuando quiera.
2.- Sin necesidad de dar explicaciones.
3.- Sin que ello repercuta en los cuidados médicos.

En consecuencia, doy mi conformidad para entrar en este estudio.

Sí No

Permito al personal del estudio que consulte la mi historia clínica con la finalidad de verificación delos datos.

Sí No

Permito que todos los datos sobre el procedimiento y la demás información recopilada durante el estudio realizado sean utilizados en investigaciones futuras en el ámbito de Cirugía General y Digestiva.

Sí No

Firma del participante: Firma del investigador:

Nombre: Nombre:

Fecha: _ _ / _ _ / _ _ Fecha: _ _ / _ _ / _ _

Hospital Universitari de Girona Doctor Josep Trueta

Institut Català de la Salut

INFORMED CONSENT.

TITLE OF THE STUDY: "INTRACORPOREAL vs. EXTRACORPOREAL ANASTOMOSIS IN LAPAROSCOPIC RIGHT HEMICOLECTOMY FOR CANCER."

I……

Confirm that:

- I have read and understood the information sheet
- I have had time to think and consider this information
- I have had the opportunity to ask any questions and be answered
- I have received sufficient information about the study.

I have spoken with (name of the investigator / general and digestive surgeon /nurse):
……

I understand that my participation is entirely voluntary.
I understand that I can withdraw this study:
1. - whenever I want.
2. - Without the necessity of give any explanations.
3. - Without any consequences for the healthcare I receive.

In consequence, I give my conformity to enter this study.

Yes No

I allow the personnel of this study to consult my clinical history with the aim of verification of the data.

Yes No

I allow the use of the gathered data for further investigation in the General and Digestive surgery department.

Yes No

Signature of the participant: Signature of the investigator:

Name: Name:

Date: __ __ / __ __ / __ __ Date: __ __ / __ __ / __ __

ANNEX 6

Hospital Universitari de Girona Doctor Josep Trueta

Institut Català de la Salut

CONSENTIMIENTO INFORMADO PARA RESECCIÓN SEGMENTARIA DE COLON

DECLARO: Que el/la Doctor/a _____me ha explicado que es conveniente proceder, en mi situación, a RESECCIÓN SEGMENTARIA DE COLON.

1 - Mediante este procedimiento se pretende extirpar la parte del intestino que está enfermo, evitando las complicaciones derivadas del mismo (sangrado, perforación, obstrucción, fístula...) que precisarían intervención urgente. La realización del procedimiento puede ser filmada con fines científicos o didácticos.

2 - El médico me ha advertido que el procedimiento requiere la administración de anestesia y que es posible que durante o después de la intervención sea necesaria la utilización de sangre y/o hemoderivados, de cuyos riesgos me informarán los servicios de anestesia y de hematología.

3 - Se me va a extirpar la parte del intestino grueso que está enfermo, para posteriormente suturarlo y restaurar la continuidad del tubo digestivo. Se me ha adverrtido que en ocasiones puede ser necesario ampliar la extirpación a otros órganos y que, a veces, por cuestiones técnicas hay que realizar un ano artificial que, en la mayoría de los casos, es provisional. También sé que cabe la posibilidad de que durante la cirugía haya que realizar modificaciones del procedimiento por los hallazgos intraoperatorios para proporcionarme el tratamiento más adecuado.

4 - Comprendo que a pesar de la adecuada elección de la técnica y de su correcta realización pueden presentarse efectos indeseables, tanto los comunes derivados de toda intervención y que pueden afectar a todos los órganos y sistemas, como otros específicos del procedimiento ; poco graves y frecuentes: infección o sangrado de la herida, retención aguda de orina, flebitis, aumento del número de deposiciones, dolor prolongado en la zona de la operación, o poco frecuentes y graves: dehiscencia de la laparotomía (apertura de la herida), fístula de la anastómosis por alteración en la cicatrización que en la mayoría de los casos se resuelve con tratamiento médico (medicamentos, sueros, etc), pero que a veces precisa intervención con la realización de un ano artificial, sangrado o infección intraabdominal, obstrucción intestinal o reproducción de la enfermedad. El médico me ha explicado que estas complicaciones habitualmente se resuelven con tratamiento médico (medicamentos, sueros, etc.), pero pueden llegar a requerir una reintervención, generalmente de urgencia, incluyendo un riesgo mínimo de mortalidad.

5 - El médico me ha indicado que para la realización de ésta técnica puede ser necesaria una preparación previa (aunque puede ser posible su realización sin una preparación completa).

También me ha indicado la necesidad de advertir de mis posibles alergias medicamentosas, alteraciones de la coagulación, enfermedades cardiopulmonares, existencia de prótesis, marcapasos, medicaciones actuales o cualquier otra circunstancia.

Por mi situación vital actual (diabetes, obesidad, hipertensión, anemia, edad avanzada...) puede aumentar la frecuencia o la gravedad de riesgos o complicaciones

6 - El médico me ha explicado que en mi caso no existe una alternativa eficaz de tratamiento.

He comprendido las explicaciones que se me han facilitado en un lenguaje claro y sencillo, y el facultativo que me ha atendido me ha permitido realizar todas las observaciones y me ha aclarado todas las dudas que le he planteado.

También comprendo que, en cualquier momento y sin necesidad de dar ninguna explicación, puedo revocar el consentimiento que ahora presto.

Por ello, manifiesto que estoy satisfecho con la información recibida y que comprendo el alcance y los riesgos del tratamiento.

Y en tales condiciones CONSIENTO que se me realice una RESECCIÓN SEGMENTARIA DE COLON.

En Girona, __/__/____

Fdo.: El/la Médico Fdo.: El Paciente Fdo.:El representante legal, familiar o allegado.

REVOCACIÓN

D./Dña. (Nombre y dos apellidos del paciente): . . . . . de . . . . . años de edad, con domicilio en . . . . . y D.N.I. nº . . . . . .

D./Dña. (Nombre y dos apellidos): . . . . . de . . . . años de edad, con domicilio en . . . . . y D.N.I. nº . . . . . en calidad de (Representante legal, familiar o allegado) . . . . . .de (Nombre y dos apellidos del paciente) . . . . . .

REVOCO el consentimiento prestado en fecha. . . . . , y no deseo proseguir el tratamiento, que doy con esta fecha por finalizado.

En . . . . . (Lugar y fecha)

Fdo.: El/la Médico Fdo.: El Paciente Fdo.: El representante legal, familiar o allegado.

INFORMATION CONSENT FOR THE SEGMENTARY RESECTION OF THE COLON

DECLARE: That the Doctor _____ explained me that it is convenient to proceed, in my situation, to SEGMENTARY RESECTION OF COLON.

1 - This procedure is intended to remove the part of the intestine that is sick, avoiding complications derived from it (bleeding, perforation, obstruction, fistula ...) that would require urgent intervention. The procedure can be filmed for scientific or didactic purposes.

2 - The doctor has warned me that the procedure requires the administration of anaesthesia and that it is possible during or after the intervention to use blood and / or blood products, whose risks will inform me of the anaesthesia and haematology services.

3 – The part of the bowel that is sick will be removed, and then it will be sutured and restored continuity of the digestive tract. I have been warned that sometimes it may be necessary to expand the extirpation to other organs and that, sometimes, for technical reasons an artificial anus must be made, which in most cases is provisional. I also know that it is possible that during the surgery it is necessary to make modifications of the procedure by the intraoperative findings to provide the most appropriate treatment.

4 - I understand that despite the proper choice of technique and its correct implementation, undesirable effects can occur, both common ones resulting from any intervention and that can affect all organs and systems, as well as specific ones of the procedure; Not very serious and frequent: infection or bleeding of the wound, acute retention of urine, phlebitis, increased number of stools, prolonged pain in the area of the operation, or infrequent and serious: laparotomy dehiscence (opening of the wound), anastomosis fistula due to alteration in healing which in most cases is resolved with medical treatment (medicines, serum, etc.), but sometimes requires intervention with the completion of an artificial anus, bleeding or intra-abdominal infection, intestinal obstruction or reproduction of the disease. The doctor has explained to me that these complications usually resolve with medical treatment (medicines, serums, etc.), but may require a re-operation, usually of an emergency, including a minimum mortality risk.

5 - The doctor has told me that for the preparation of this technique may be necessary a prior preparation (although it may be possible to perform without a complete preparation).

I also indicated the need to warn of my possible drug allergies, coagulation disorders, cardiopulmonary diseases, existence of prosthesis, pacemakers, current medications or any other circumstance.

Because of my current vital situation (diabetes, obesity, hypertension, anemia, old age ...), it can increase the frequency or severity of risks or complications

6 - The doctor has explained that in my case there is no effective alternative treatment.

I have understood the explanations given me in clear and simple language, and the doctor who has attended me has allowed me to make all the observations and has clarified all the doubts I have raised.

I also understand that, at any time and without the need to give any explanation, I can revoke the consent I now provide.

I hereby state that I am satisfied with the information received and that I understand the scope and risks of the treatment.

And in such conditions I CONSENT that I realize a SEGMENTARY RESECTION OF COLON.

In Girona, __ / __ / ___

Signed: The Doctor | Signed: The Patient | Signed: legal representative, family member or relative.

REVOCATION

D./D. (Name and two surnames of the patient):. . . . . from . . . . . Years of age, domiciled in. . . . . And D.N.I. . . . . .

D./D. (Name and two surnames):. . . . . from . . . . . Years, domiciled in. . . . . And D.N.I. . . . . (Legal representative, family member or relative). . . . . .de (Name and two surnames of the patient). . . . . .

I RETURN consent given on date. . . . . , And I do not want to continue the treatment, which I give with this date for finished.

In . . . . . (Place and date)

Signed: The Doctor | Signed: The Patient | Signed: legal representative, f family member or relative.

ANNEX 7

FULL INFORMATIU

HOSPITAL UNIVERSITARI DE GIRONA DOCTOR JOSEP TRUETA

PREPARACIÓ DEL COLON A DOMICILI

Servei de cirurgia general i digestiva

La preparació del colon ha de ser molt bona per poder realitzar una intervenció quirúrgica de l'aparell digestiu. Per això és important que segueixi les següents intruccions:

4 DIES ABANS D'INGRESSAR A L'HOSPITAL

- Durant tot el dia haurà de fer una dieta pobre en residus.
  - ***POT PRENDRE:*** Arròs i pastes, brous, carn i peix a la planxa o bullit, formatges, biscots o galetes sense fibra, pa torrat, sucs filtrats, infusions, te, cafè i begudes sense gas.
  - ***NO POT PRENDRE:*** Amanides, verdures i llegums, fruites, patates, carns i peixos amb salsa, embotits, llet, greixos, pastissos ni begudes amb gas.

1 DIA ABANS D'INGRESSAR A L'HOSPITAL

- L'esmorzar i el dinar hauran de seguir la mateixa dieta pobre en residus que els dies anteriors.
- Per sopar haurà de fer una dieta líquida:

POT PRENDRE: Aigua, brous filtrats, sucs colats, infusions, te, cafè i begudes sense gas.

MEDICACIÓ A PRENDRE EL DIA ABANS D'INGRESSAR

- Ha de seguir prenent la medicació habitual, excepte si el metge la suspèn.
- A les 20 h s'ha de posar una injecció subcutània de Fragmin 5000UI
- Abans d'anar a dormir ha de prendre:
  - Diazepam 5mg VO (Valium®)
  - Omeprazol 20mg VO

DIA D'INGRÉS

- Higiene
  - Dutxeu-vos amb sabó de Clorhexidina
- Preneu un got d'aigua amb dos cullerades de sucre abans de sortir de casa
- Hora d'ingrés: 7.30 h. matí.

La medicació que ha de prendre el dia abans d'ingressar i el sabó de clorhexidina li serà lliurat a la consulta d'anestèsia

Generalitat de Catalunya
Departament de Salut

Hospital Universitari de Girona Doctor Josep Trueta

Pàgina 1 de 1

Aprovació Comissió de Qualitat: 08/09/2010 FI-CGD-001:CATALÀ

INFORMATION SHEET

HOSPITAL UNIVERSITARI DE GIRONA DOCTOR JOSEP TRUETA

PREPARATION OF THE COLON AT HOME

Digestive and General Surgery Unit

The preparation of the colon should be very good to perform surgery of the digestive system. It is therefore important to follow these instructions:

4 DAYS BEFORE THE HOSPITALADMISSION

- During the day you must follow a poor residue diet.

  - YOU MAY TAKE:
  Rice and pasta, broth, grilled or boiled meat or fish, cheese, crackers or non-fibre biscuits, toasted bread, strained fruit juices, herbal tea, tea, coffee and non-carbonated beverages.
  -YOU MAY NOT TAKE:
  Salads, vegetables, legumes, fruit, potatoes, meat or fish with sauces, sausages, milk, fats, cakes and pastries, carbonated drinks.

1 DAY BEFORE THE HOSPITALADMISSION

- For breakfast and lunch you must follow the same low residue diet as the previous days.
- For dinner you must follow a liquid diet:
  - YOU MAY DRINK:
  Water, strained broth, strained juices, herbal tea, tea, coffee and non-carbonated drinks.

MEDICATION YOU NEED TO TAKE THE DAY BEFORE THE HOSPITALIZATION

- You may continue to take your medikations,unless you are told otherweise
- At 20.00hrs you have to give yourself a subcutaneous injection of Fragmin 5000UI
- Before you going to sleep you have to take:
  - Diazepam 5mg VO(Valium)
  - Omeprazol 20mg VO

THE DAY OF THE HOSPITALADMISSION

- Hygiene
  - Take a shower and use Clorhexidina soap
- You should take a glass of water with two spoonfuls of sugar before leaving your house.
- Time of hospitalization: 07.30hrs (AM)

- ❖ The medication and the soap will be given to you at the **consulting room of anaesthesia**

Generalitat de Catalunya
Departament de Salut

Hospital Universitari de Girona Doctor Josep Trueta

Registre d'aprovació per la Comissió de Qualitat: 08/09/2010

ANNEX 8

Hospital Universitari de Girona Doctor Josep Trueta

Hospital Universitari de Gir Doctor Josep Trueta

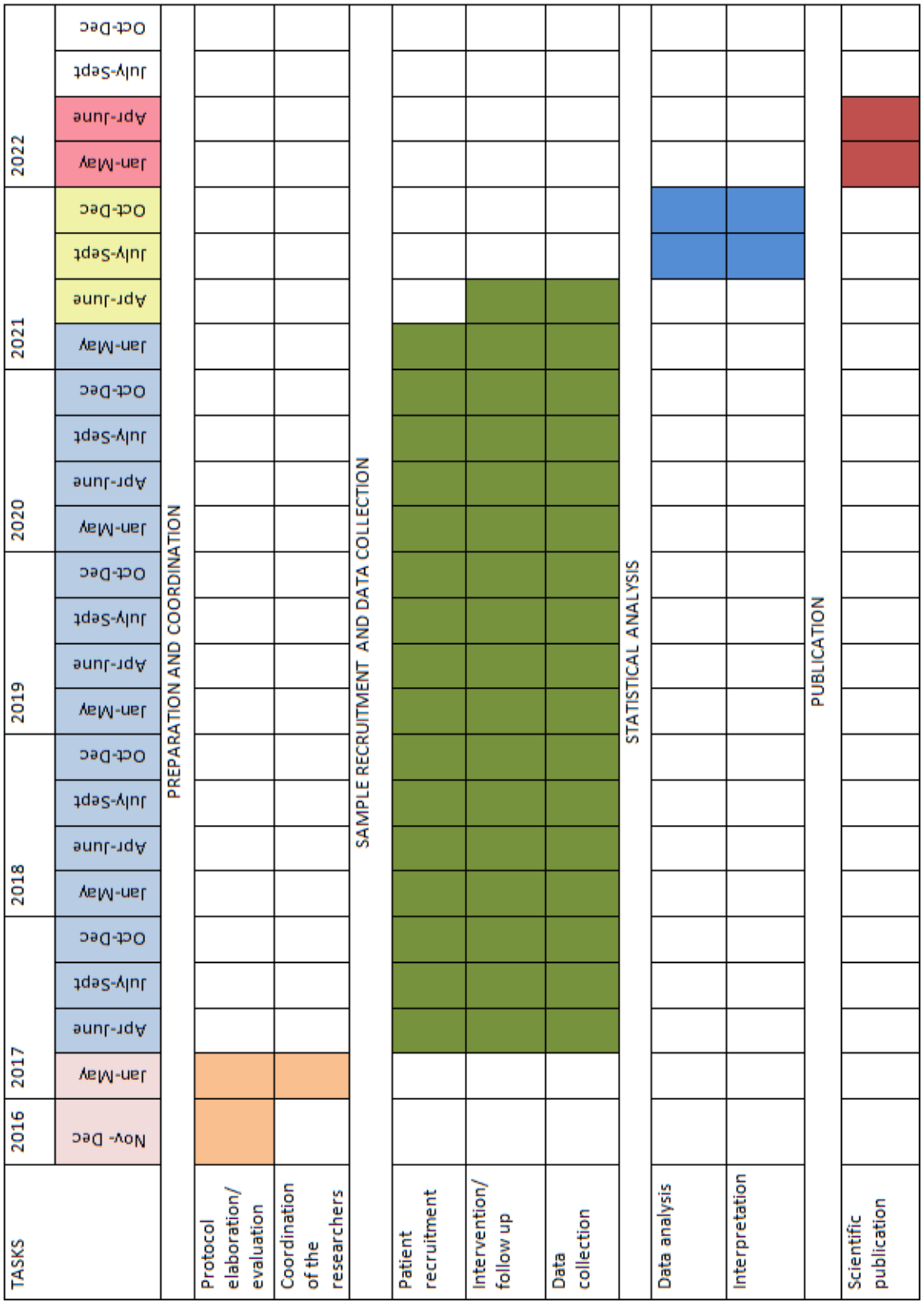
PARTICIPANT DATA SHEET

Patient's code number:
Date of birth: __/__/____
Sex:
BMI:
ASA score:
Current diagnosis and TNM stage:
Surgical technique group:

HOSPITAL EVALUATION		
Time to recovery the bowel function: _____h for the first flatus. _____h for the first dejection.		
COMPLICATIONS	**YES**	**NO**
- Anastomotic leakage		
- Wound infection		
- Ileus		
ORAL FEEDING TOLERATION: _____days post-operatory		
AMBULATION RECOVERY: _____days post-operatory		
TOTAL DAYS OF HOSPITALIZATION:		

AMBULATORY EVALUATION		
7 DAYS POST-OPERATORY		
COMPLICATIONS	**YES**	**NO**
- Anastomotic leakage		
- Wound infection		
- Ileus		
30 DAYS POST-OPERATORY		
COMPLICATIONS	**YES**	**NO**
- Anastomotic leakage		
- Wound infection		
- Ileus		

ANNEX 9


TASKS
2016
2017
2018
2019
2020
2021
2022
Nov- Dec
Jan-May
Apr-June
July-Sept
Oct-Dec
PREPARATION AND COORDINATION
Protocol elaboration/ evaluation
Coordination of the researchers
SAMPLE RECRUITMENT AND DATA COLLECTION
Patient recruitment
Intervention/ follow up
Data collection
STATISTICAL ANALYSIS
Data analysis
Interpretation
PUBLICATION
Scientific publication