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Evaluation of the complications after early closure of derivative ileostomy: a controlled randomized clinical trial

FINAL DEGREE PROJECT

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I would like to express my most sincere gratitude to the department of General and Digestive Surgery of Hospital Universitari Josep Trueta for welcoming me in the service and for letting me learn and love the clinical practice day after day.

Specially, I would like to dedicate this work to Dr. Franco Marinello. Thank you for your patient and great attention, this project would not have been possible without your help.

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1. ABBREVIATIONS

APR: abdominoperineal resection

AL: anastomotic leak

C-DCSC: Clavien-Dindo Classification for surgical Complications

CRC: colorectal cancer

CT: computed tomography

FAP: familial adenomatous polyposis

HNPCC: hereditary non-polyposis colorectal cancer

IBD: inflammatory bowel disease

LAR: low anterior resection

LARS score: Low Anterior Resection Syndrome score

LE: local excision

NSAID: nonsteroidal anti-inflammatory drugs

PET-CT: positron emission tomography – computed tomography

PSC: primary sclerosing cholangitis

QOL: quality of life

TAE: transanal excision

TEM: transanal endoscopic microsurgery

TME: total mesorectal excision

UC: ulcerative colitis

2. ABSTRACT

Background: Patients undergoing surgery for low rectal cancer often receive a simultaneous construction of a temporary ileostomy, and most of them keep their stoma for at least 8-12 weeks. Late reversal of a temporary ileostomy is associated to low mortality, but up to 20-33% of morbidity. Some of the most common complications are small bowel obstruction (0- 15%), wound infections (0-18.3%), anastomotic leaks (0-8%) and stoma site hernias (5%). A few prospective studies have investigated the morbidity and mortality of an early closure of the ileostomy, which is considered to be 2 weeks after the first surgery. Even though it did not seem to be associated with higher rates of neither of them, it is still unknown when the best moment for the closure is.

Objective: The aim of this study is to evaluate the complications related to the closure of the ileostomy, both in the stoma site and the rectum. We will also collect data and compare the quality of life of patients during a year after closure surgery.

Design: A randomized, controlled clinical trial which will be carried out in Hospital Universitari Josep Trueta from January 2017 until 2023.

Method: We will need a sample of 63 patients and a non-probabilistic, consecutive method of recruitment will be used. They will be randomly assigned to one of the treatment groups. Non parametric U-Mann Whitney test will be used for the statistical analysis of the primary and secondary endpoints, and a confidence interval of 95% will be assumed.

Key words: Ileostomy closure, ileostomy reversal, complications, quality of life, morbidity rate.

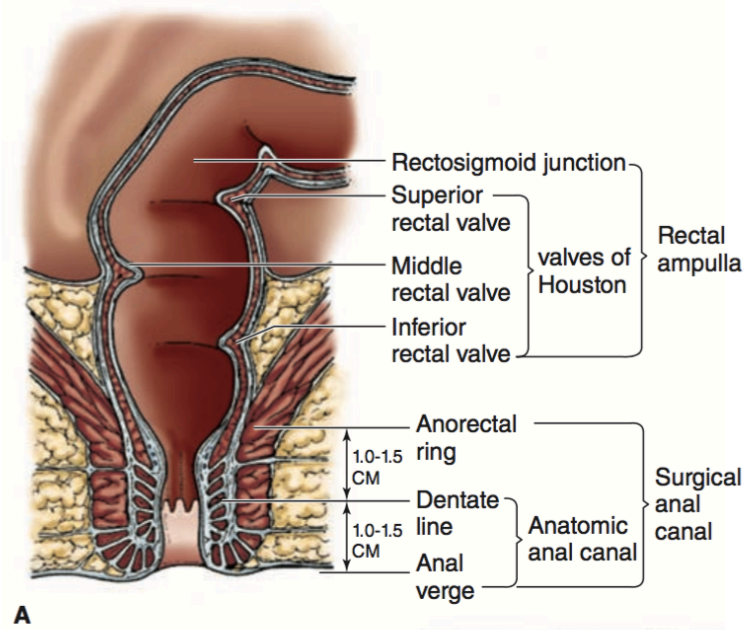
3. INTRODUCTION

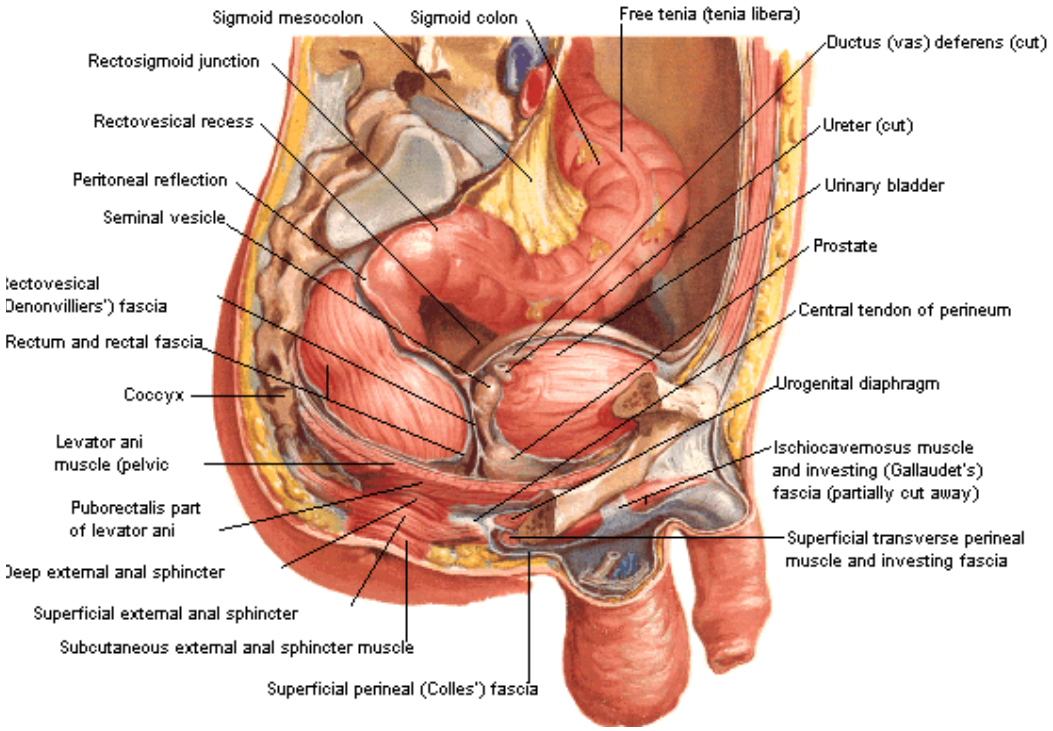
3.1 ANATOMY SUMMARY

The rectum has usually 15–20 cm in length, and it extends from the rectosigmoid junction, to the anal canal. It is "fixed" posteriorly by Waldeyer's fascia and laterally, by the lateral stalks. In male patients, the anterior rectum is fixed to Denonvilliers' fascia, a fold of two layers of peritoneum that separates the rectum from the prostate and seminal vesicles. In female patients, the peritoneal cavity descends to the pouch of Douglas. When seen endoscopically, the rectum has three valves (known as Houston valves), the middle of which corresponds to the anterior peritoneal resection (Fig 1).

An accurate description for distal rectal cancer (palpable lesions) is the distance above the anorectal ring as palpated by the examining surgeon. For nonpalpable lesions, a rigid sigmoidoscope is used to localize the lesion and then define the distance from the anal verge to the mass. The anal canal starts at the top of the "high-pressure zone", which is the proximal side of the anorectal ring, a muscular structure consisting of the internal sphincter, external sphincter, and puborectalis. Therefore, in order to achieve an adequate distal margin (>2 cm) with sphincter preservation, the lower border of a tumour must be located above the top of the anorectal ring. If curative resection compromises perfect function of the sphincter apparatus, or if an adequate distal margin cannot be obtained while preserving the anorectal ring, an APR with a permanent colostomy should be constructed.

The type of therapy offered to a patient with rectal cancer depends not only on the stage of the tumour but also on its location within the pelvis, its relation to the anal sphincters and the peritoneal reflexion (1).


Rectosigmoid junction
Superior rectal valve
Middle rectal valve
Inferior rectal valve
valves of Houston
Rectal ampulla
Anorectal ring
1.0-1.5 CM
Dentate line
1.0-1.5 CM
Anal verge
Anatomic anal canal
Surgical anal canal
A


Sigmoid mesocolon
Sigmoid colon
Free tenia (tenia libera)
Ductus (vas) deferens (cut)
Rectosigmoid junction
Rectovesical recess
Ureter (cut)
Peritoneal reflection
Urinary bladder
Seminal vesicle
Prostate
lectovesical Denonvilliers') fascia
Central tendon of perineum
Rectum and rectal fascia
Urogenital diaphragm
Coccyx
Levator ani muscle (pelvic
Ischiocavernosus muscle and investing (Gallaudet's) fascia (partially cut away)
Puborectalis part of levator ani
Superficial transverse perineal muscle and investing fascia
Deep external anal sphincter
Superficial external anal sphincter
Subcutaneous external anal sphincter muscle
Superficial perineal (Colles') fascia

3.2 EPIDEMIOLOGY

Colorectal cancer represents almost the 10% of the total cancers and was the third most frequent in 2012 worldwide with a total of 1,360,500 new cases. Among these, 746,000 cases were diagnosed in men and 614.000 in women (2). Almost 55% of the cases occur in more developed regions. 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). Despite the lower incidence, mortality is higher (52%) in the less developed regions of the world, reflecting a poorer survival in these regions. 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). (3).

In Europe, and taking both genders into account, it occupied the second position after breast cancer, but it was first in Spain, where 39,553 new cases were diagnosed in 2014, 23,482 in men and 16,071 in women. Moreover, the world adjusted rate is 49,8 for men and 27,7 for women. Therefore, colorectal cancer is more frequent in men both worldwide and specifically in Europe and Spain (4)(Annex 1).

Furthermore, in Spain, the evolution of this cancer has been at the expense of a constant increase, mostly among men and more intense around the past decades, but not due to the systematic screening, which was implemented in 2000 in some regions of Catalonia. Nowadays it is more extended. Therefore, the increase of the incidence should respond to the influence of different risk

factors, which we will explain later (5).

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. If we analyse the data more concretely, CRC occupies the third place in men and second in women, representing the 14,6% and the 15,1%, respectively, of all the malignant neoplasms diagnosed and with an approximate survival of 50% in five years (6).

3.3 ETIOLOGY AND RISK FACTORS (7)

3.3.1 Dietary Constituents and Supplements

The relationship between diet and CRC risk is unclear:

- **Red Meat**

Dietary iron may increase free-radical production in the colon, and these free radicals may cause chronic mucosal damage or promote other carcinogens. Alternatively, dietary heme, present in red meat, may have a cytotoxic effect on colonic surface epithelium, resulting in rebound inhibition of apoptosis and crypt hyperplasia.

It 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. Genetics may also play a role.

- **Fruit and vegetable intake**

There is the hypothesis that vegetable intake reduces the risk of CRC, however, the evidence for an association between fruit and vegetable intake and the risk of CRC is inconsistent (8).

- **Fiber**

Dietary fiber was one of the first dietary components thought to have a protective role in carcinogenesis. Despite that, a meta-analysis with the data from 13 prospective cohort studies concluded that this association did not hold when adjusted for other dietary risk factors (9).

3.3.2 Alcohol

Alcohol ingestion has a possible role in colorectal carcinogenesis (10).

3.3.3 Aspirin and Nonsteroidal Anti-inflammatory Drugs

A consistent reduction in the risk of colorectal neoplasia in NSAID users was identified in studies of various designs (11). Overall, data evaluating the effect of nonaspirin NSAIDs is more limited than that for aspirin. NSAIDs and aspirin may play an important role in secondary chemoprevention of colorectal adenomas and cancer (12).

3.3.4 Obesity

Obesity appears to increase the risk of colorectal cancer in men and premenopausal women, although this association is controversial (13).

3.3.5 Smoking

A meta-analysis of 106 studies revealed a positive dose–response relationship between increased cigarette consumption and CRC risk. The risk increased by 7.8 % for every 10 additional cigarettes per day or by 4.4 % for every additional 10 pack-years (14).

3.3.6 Inflammatory Bowel Disease

Patients with long-standing inflammatory bowel disease (IBD) are known to be at an elevated risk of CRC, although it is difficult to precisely estimate the risk.

In series published of IBD patients, more specifically UC, the cumulative probability of CRC was of 2 % after 10 years of disease, 8 % after 20 years, and 18 % after 30 years. The risk of CRC varied geographically and was higher in studies conducted in the USA (15) .

3.3.7 Family History

Individuals with a family history of CRC are at an increased risk of developing CRC. In a recent meta-analysis including 59 studies, the relative risk of developing CRC with one affected first-degree relative was 2.24 (95 % CI, 2.06– 2.43) and 3.97 if more than two first-degree relatives were affected. This corresponds to a pooled lifetime risk of a 50-year-old of 1.8 % with no family history, 3.4 % with one affected first-degree relative, and 6.9 % with two or more first-degree relatives (16).

Some of the increased risk attributed to family history is due to inheritance of known susceptibility genes, such as mutations in the APC gene, p53 gene, or in MMR genes, particularly MSH2, MLH1, and MSH6 (17) (7).

3.3.8 Coffee intake

Coffee intake (decaffeinated coffee as well) could be associated with the colorectal cancer, being a protective factor, but with no clear evidence (18) (19) (20).

3.4 CLINICAL PRESENTATION

Colorectal cancers diagnosed in patients who are asymptomatic and undergoing screening or surveillance have a very favourable prognosis.

The patient with rectal cancer usually presents to the surgeon after a definitive endoscopic diagnosis. The patient's initial complaint may include rectal bleeding or occult blood in the stool (25%), a change in bowel habits or stool caliber, rectal pain, a sense of rectal "fullness," weight loss, nausea, vomiting, fatigue, or anorexia. The bleeding may be of varying intensity and colour, but generally right red rectal bleeding is more consistent with a more distal location of a cancer.

Symptoms depend on the location of the tumour and are more frequently associated with a more advanced tumour. Moreover, larger masses cause obstruction with crampy, colicky pain, associated with or after meals (1).

In addition, specific symptoms may assist the surgeon in deciding on the optimal approach to therapy. Tenesmus, the constant sensation of needing to move one's bowels, usually is indicative of a large and possibly fixed stage II or III cancer. Pain with defecation suggests involvement of the anal sphincters; cancers growing directly into the anal sphincter usually are not amenable to sphincter-sparing procedures. Information pertaining to anal sphincter function is invaluable when one is

contemplating a low anastomosis. If patients are incontinent, they are better candidates for an ostomy. Preoperative sexual function is important to know because of the risks of possible postoperative diminution of sexual function.

A comprehensive medical history should be aimed at identifying other medical conditions, such as cardiopulmonary, renal, and nutrition, that may require additional evaluation before surgical intervention and allow appropriate risk stratification. For patients with a cardiac history or symptoms, a stress test and cardiology evaluation should be performed.

Family history or factors predisposing the patient to rectal cancer, such as FAP, HNPCC, and IBD, are important to take into account as one plans the operative procedure (21).

3.5 DIAGNOSIS AND PREOPERATIVE STAGING

Treatment decisions in patients with rectal cancer can be influenced by the presence of synchronous tumours, by the locoregional extension of the disease, and by the presence of distant metastasis. Therefore, every patient should undergo a complete evaluation before outlining a treatment plan.

First, a complete colonoscopy is important to exclude synchronous polyps and cancers, but loco-regional staging is essential to guide the initial therapy. A digital rectal examination (DRE) provides useful information because the mobility of the tumour in relation to the rectal wall is an indication of the depth of tumour invasion. The DRE is particularly useful in assessing the relationship of the tumour to the elevator muscle and the external anal sphincter, and deciding between the different treatment options. Apart from this, a proctoscopic examination is the best method to assess the distance of the tumour from the anal verge, the only anatomical landmark that can be seen

simultaneously with the distance marks of the rigid scope (1).

In addition to a thorough clinical examination, every rectal cancer patient should undergo adequate local and regional staging with the help of the best available imaging technology (22):

- Endorectal ultrasound (ERUS) is a useful technique for staging early rectal cancer as it provides detailed images of the different layers of the rectal wall and demonstrates the disruption of those layers by the tumour.
- Magnetic resonance imaging (MRI) is most useful for staging locally advanced rectal cancer because it provides a broader view of the pelvis and the best images of the fascia propria of the rectum and mesorectal fascia involvement, which indicates the need of preoperative therapy.
- The new CT scanners also provide high-resolution cross-sectional images of the rectum, the mesorectum, and surrounding pelvic structures, and can be used for the loco-regional staging of rectal cancers when high-quality MRI is not available.
- A chest x-ray and a CT scan of the abdomen and pelvis are also commonly included in any patient assessment to diagnose metastatic disease, although these test are not routinely done nowadays.

Occasionally, other tests such as a triple-phase CT of the liver or a PET-CT may be necessary to confirm the diagnosis of liver or pulmonary metastasis.

3.6.1 TNM Staging

The purpose of staging any cancer is to describe the anatomic extent of the lesion. Staging by clinical examination, radiology, and pathology aids in planning treatment, evaluating response to treatment,

comparing the results of various treatment regimens, and determining prognosis. Currently, the most widely accepted staging system for rectal cancer in the United States and Europe is the 7th edition of the TNM classification system(annex 1) (23)(24).

3.6 TREATMENT: CHOOSING THE SURGICAL APPROACH

Surgical and oncologic management varies greatly depending on the stage and location of the tumour within the rectum. Superficially invasive, small cancers may be managed effectively with local excision. However, most patients have more invasive tumours that require major surgery, such as low anterior resection (LAR) or abdominoperineal resection (APR). Yet others present with locally advanced tumours adherent to adjacent structures such as the sacrum, pelvic sidewall, vagina, uterus, cervix, prostate, or bladder, requiring an even more extensive operation.

After establishing the diagnosis and completing the staging workup, a decision is made whether to pursue immediate resection or administer preoperative chemoradiotherapy. For patients with stage II and III rectal cancer the authors advocate for combined preoperative chemoradiotherapy. The authors recommend this for all stage II and III patients with tumours located in the distal two-third of the rectum. For patients with rectal cancer in the proximal one-third of the rectum, the authors use preoperative chemoradiotherapy by case basis depending on the size and bulkiness of the tumour as well as the patient's medical and surgical history. Furthermore, other publications state that upper-third tumours behave like colon tumours, suggesting that preoperative radiotherapy is not needed in most cases, saving up ileostomy taxes. (25).

Overall, there is an important controversy regarding the use of preoperative chemoradiation in upper

rectal tumours. Most trials reporting the effectiveness of TME and neoadjuvant therapy consider the rectum as a single unit. Consequently, there is a lack of specific evidence on this issue for upper rectal cancer (26).

The primary goal of surgical treatment for rectal cancer is complete eradication of the primary tumour along with the adjacent mesorectal tissue and the superior haemorrhoidal artery pedicle. Although reestablishment of bowel continuity at the time of surgery has become routine, cancer removal should not be compromised in an attempt to avoid a permanent colostomy (27).

At the completion of the evaluation, the surgeon must decide whether the patient requires a TME (total mesorectal excision) or can be treated with a local form of therapy, such as local excision (LE) or transanal microscopic surgery. To make the right choice, the surgeon should take into consideration both the location and characteristics of the tumour and the overall status of the patient.

LOCAL EXCISION (28) (29)	Early stage cancer not penetrating the muscularis propria. N0. M0 *Conventional transanal excision* (TAE) or *transanal endoscopic microsurgery* (TEM)
TOTAL MESORRECTAL EXCISION	Tumours penetrating the muscularis propria. Mesorectal N+. In upper rectal cancer, a subtotal mesorectal excision including 5cm below the distal margin can be an option (26)
ABDOMINOPERINEAL RESECTION	Tumours penetrating the muscularis propria and infiltrating the muscle or external anal sphincter.

3.7 INTESTINAL STOMAS (30)

Intestinal stomas have long been used by surgeons for faecal diversion and they are considered a vital element as either a permanent means for stool evacuation or as a temporary bridge in order to treat complicated abdominal complications or to heal more distal anastomoses.

An ostomy is a surgically created opening between a hollow organ and the body surface or between any two hollow organs, and it is named by the organ involved. For example, an *ileostomy* is an opening from the ileum to the skin, a *colostomy* is from the colon, a *gastrostomy* is from the stomach, and so forth (Fig. 31.2). When two organs are joined the descriptive term incorporates both. For instance, an anastomosis between the small bowel and colon might be called an *ileocolostomy*, between colon and the rectum, a *colorectostomy* or *coloproctostomy*.

There are many indications for a stoma (Table 31-1). Permanent stomas are fashioned when there is a need for removal of the anus along with its associated musculature. This procedure may be necessary in patients with distal rectal cancers who require an APR or those individuals with severe IBD with involvement of the sphincter mechanisms, among others such as acute colon perforations due to diverticulitis or trauma. Besides, an ostomy should be considered when the patient is under unstable conditions which could compromise anastomotic healing.

Stomas may also be used on a temporary basis, which are indicated in cases of intra-abdominal catastrophes and may act as a lifesaving bridge in critically ill patients. Perhaps one of the most common indications for the creation of a temporizing stoma is for patients undergoing deep pelvic dissections, total mesorectal excisions, a low-lying ileo-anal or colo-anal bowel anastomosis, or in patients who undergo a high-risk distal bowel anastomosis. These stomas serve as a protection for

anastomotic dehiscence.

Moreover, temporary stomas may be created as either an ileostomy or a colostomy, with the type of stoma used, dictated by the circumstances found at the time of the initial surgery as well as the preference of the surgeon.

Stomas may be created as either a loop stoma or an end stoma. Loop stomas are often used when they are intended to be temporary since such a creation will often facilitate reversal. Alternatively, an end stoma with a distal mucous fistula may be created in order to provide distal bowel decompression. These stomas are often smaller and easier to manage. They are rarely associated with stomal prolapse and may have a lower incidence of parastomal hernia formation. However, if the end stoma is done on a temporary basis, they often require more extensive surgery for reversal since the other end of the bowel is often buried within the abdominal cavity.

Many surgeons prefer a protective loop ileostomy for low-lying anastomoses because of the relative ease of reversal, easier stoma management by the patient, lower incidence of parastomal hernia formation, and a lower incidence of peristomal sepsis.

Finally, it is important to know that the physiological changes that occur in patients with ostomies are primarily related to the loss of continence and reduced colonic absorptive surface area. These affect fluid and electrolyte balance and lifestyle but generally have little effect on nutrition. However, if more than 50 cm of terminal ileum is removed or taken out of continuity, nutritional consequences are likely to occur.

A diverting loop ileostomy should be considered in any low anastomoses (<5 cm) from the dentate line, which are associated with anastomotic leak rates of up to 17%. Other risk factors for

anastomotic breakdown include a history of radiation, perioperative steroid use, malnutrition, elderly women with a thin rectovaginal septum, or elderly patients undergoing preoperative combined-modality therapy with planned postoperative chemotherapy. Additionally, if there is any question regarding the integrity of the anastomosis, an ileostomy should be created.

Ileostomies can be closed within 8 weeks but often are left in place until the patient completes adjuvant chemotherapy. A Gastrografin (diatrizoate meglumine) enema is used to check the patency and integrity of the anastomosis prior to takedown of the anastomosis.

TABLE 31-1. Indications for a stoma

- Protection of distal anastomosis
- Treatment of anastomotic leak
- Large bowel obstruction
- Bowel perforation
- Abdominal or perineal trauma
- Rectal injury
- Diverticular disease
- Complex anorectal disease
- Complications from radiation
- Fecal incontinence
- Inflammatory bowel disease
- Motility and functional disorders including idiopathic megarectum and megacolon
- Infections – necrotizing fasciitis, Fournier's gangrene
- Congenital disorders – imperforate anus, Hirschsprung's disease, necrotizing enterocolitis, intestinal atresias

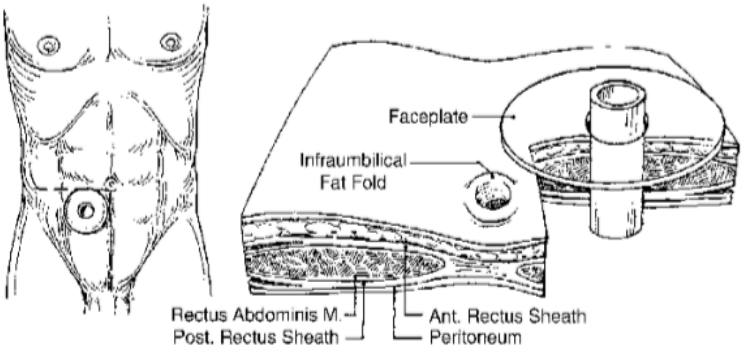


FIGURE 31-2. Stomal placement. The site is selected to bring the stoma through the rectus abdominus muscle (with permission from Beck DE. Intestinal stomas. In: Beck DE, editor. Handbook of colorectal surgery. 2nd ed. Taylor and Francis; 2003).

3.8 STOMAL COMPLICATIONS

Stoma complications should not be underestimated. The true incidence of stoma-related complications is unknown since there is great debate as to what actually them. Most patients will experience some sort of skin irritation due to faeces contact or the stoma appliance, representing the largest subset of stoma-related issues.

The prevalence of intestinal stoma complications was assessed by colorectal group in Chicago. They reported the incidence of stoma complications in 1,616 patients. A total of 34.2% of these individuals suffered a complication related to their stoma, 27.7% of those individuals had an early complication, and only 6.5% suffered a late complication. The authors noted that the highest complication rate was in patients with a loop ileostomy (31).

3.10.1 Skin irritation and leakage

While many surgeons consider skin irritation and leakage commonplace issues relating to stomas, most of them consider this a complication only if it requires surgical correction. But most of the skin issues related to the stoma do not require surgery.

Many of the skin problems from a stoma are due to poor site selection in the first place, specially by placing the stoma under a skin crease (Fig. 31.6). One study showed that 51% of patients questioned, reported problems with a rash and 36% had experienced leakage (32).

When this complication occurs, if the stoma was used on a temporary basis, then it should be reversed as soon as it is feasible. If, however, the stoma was created on a permanent basis, then stoma revision may need to be performed, and the patient should undergo a secondary surgery for reposition.

3.10.2 Parastomal hernia

Parastomal hernia remains a major problem following stoma creation. The true incidence of parastomal hernia is unknown, because of the lack of concept and diagosis standardization. In addition, many patients with parastomal hernia often have some disability related to this problem, such as skin breakdown near the stoma site or an inability to fit an appliance around the stoma, or something as devastating as incarceration of a loop of bowel within the hernia and requiring emergency surgery for resection and repair.

A recent prospective audit of parastomal hernias found that the overall rate was of 33%. Furthermore, they found that for every additional millimeter increase in aperture size there was a

10% increase in risk of developing a hernia and for every additional year of patient age the risk increased by 4%. Also, the same study reported that colostomies were at higher risk for hernia formation than ileostomies (33).

Parastomal hernia prevention is perhaps the best method of treatment. As a general rule, stomas should be placed through the rectus sheath for additional muscular support, fascial openings should be of the appropriate size for the portion of exteriorized bowel, prophylactic use of mesh may be considered for those patients requiring a permanent stoma, and extraperitoneal tunneling of the bowel may also be considered. Moreover, many surgeons have advocated prophylactic mesh placement at the time of the stoma creation in order to prevent parastomal hernias.

3.10.3 Stone formation

Another problem in patients with an ileostomy is the development of urinary stones. It has been estimated that up to 12% of patients with an ileostomy may develop urinary stones and the numbers seem to be higher in those patients who have had small bowel resected in addition to having an ileostomy. While serum calcium, Vitamin D, and urinary calcium are often normal in these patients, it appears that a high level of uric acid is the main cause of the stone formation. Therefore, serum uric acid levels should be monitored in these patients and they should be started on allopurinol prophylactically if the levels remain high.

3.10.4 Intestinal obstruction

Intestinal obstruction may occur after any abdominal surgical procedure. Therefore, the true incidence of intestinal obstruction after stoma formation is not really known. In addition, how many obstructions are directly related to the stoma itself is not clear. As in most cases, adhesions are

probably the most common cause, but small bowel volvulus, internal hernia, or even incarcerated parastomal hernias may also be contributing factors.

This complication is handled as in any other case of bowel obstruction; patients should be supported with intravenous fluids and nasogastric tube decompression of the bowel with serial abdominal exams and X-rays. Unresolving obstructions will need operative exploration and lysis of adhesions.

Mention must be made of food bolus obstruction. Many patients with an ileostomy will develop signs and symptoms of bowel obstruction due to the accumulation of poorly masticated or digested food (e.g., popcorn, peanuts, fresh fruits, meat, and vegetables). A careful history may reveal dietary indiscretions. Further, the possibility of a food bolus obstruction should be considered in any patient with an ileostomy who has radiologic evidence of a distal obstruction.

3.10.5 Ischemic stomas

Early stomal ischemia has been reported in 1–10% of colostomies and 1–5% of ileostomies (34).

Many stomas may initially appear oedematous and congested after stomal creation due to mechanical trauma and the compression of the small mesenteric vessels but this often resolves within a few days to weeks after surgery. However, true stomal ischemia is a much more serious condition and often occurs due to tension of the mesentery as the bowel exits the abdominal wall. It may also be related to the exteriorized portion of bowel being excessively stripped of its mesentery.

If there is concern about bowel viability after surgery, one can simply insert a glass test tube or sigmoidoscope into the stoma in order to determine if the bowel is viable beneath the tip of the stoma. If the stoma is viable at the fascial level, then the patient may be carefully observed (35).

3.10.6 Stomal prolapse

Stomal prolapse is a more common complication of loop than end stomas. This problem often occurs in patients with redundant segments of bowel and in those with a large enough fascial opening to permit such prolapse and intussusception. These patients commonly have parastomal hernias associated with the prolapse. A suggestion of fixating the bowel to the fascia may prevent this complication (36).

The best way to treat a stomal prolapse is to reverse the stoma (37).

3.9 STOMA REVERSAL

Stoma reversal may be either one of the easiest or most challenging procedures to perform depending on the type of stoma and the length of time the stoma has been in place. The procedure may be associated with significant morbidity as well. While most patients recover well from such surgery, severe complications can result in death. A recent systematic review of 48 studies of ileostomy reversal included over 600 patients from 18 countries. The overall morbidity after loop ileostomy reversal was 17.3% with a mortality rate of 0.4%. The most common postoperative complications were small bowel obstruction (7.2%) and wound infection (5.0%). The authors of this review concluded that while stoma creation may be considered necessary for anastomotic protection, the reversal is certainly far from a risk-free procedure (38). Another study confirmed these same results reporting complications in as many as one-third of the patients who underwent ileostomy reversal with 3% of the patients dying after the surgery (35). The most common complications following reversal of stoma are:

- **Hernias:** it occurs when the bowel protrudes through the muscles of your abdomen causing a bulge beneath the skin. The risk of a hernia formation is small but is more likely in frail, older and overweight patients. Moreover, it's also seen more frequently in those who have strained their bodies or have undertaken too much exercise in the first few weeks following surgery. Management includes supporting your hernia with a belt or binder, or surgery.

- **Anastomotic leak**: it is a leak from the stitching where the bowel is joined back together. This happens approximately in 1 in 250 cases of stoma reversals, and is therefore one of the most dreaded complications following reversal surgery, with reported rates ranging from 3 to 26%.(39) Early diagnosis of an AL is crucial for the prevention of mortality. The signs and symptoms can be subtle or obvious and include the presence of fever, oliguria, ileus, diarrhoea, leucocytosis, and peritonitis (40). Once suspicion is raised, if the anastomosis is in the low pelvis, one can consider a digital rectal examination with the intent of feeling any defect. Otherwise, physical examination is generally nonspecific except in the setting of enteric contents draining from the wound or a drain. Water-soluble contrast enema, traditionally the first test used to evaluate a higher anastomosis, has been largely supplanted by a computed tomographic (CT) scan.

  Clearly, the best time to detect and even prevent a possible AL is at the time of its creation while still in the operating room. *Beard et al* performed a randomized, prospective study looking at intraoperative air testing versus not testing anastomoses for leaks. The patient's pelvis was filled with saline and air was introduced through a proctoscope, and if air bubbles were seen in the fluid an air leak was present. If the site of leakage was found, sutures were placed to repair the site of leakage. They found a higher clinical leak rate (14% versus 4%) in

the patients who were not air tested. In addition, the radiographic leak rates in patients who were not air tested were significantly higher (29% versus 11%). Thus, air testing of the anastomosis is recommended intraoperatively. However, it is notable that even with testing and repair, this did not completely prevent an AL (41). An alternative to air testing is to use intraluminal instillation of a dilute solution of povidone-iodine after the bowel is occluded above the anastomosis with finger pressure.

When an AL has been diagnosed, there are four main treatment options: antibiotics, drainage of the leak or abscess percutaneously or surgically, laparotomy with diversion, and laparotomy with takedown of the anastomosis. If a patient has clinical diffuse peritonitis, a laparotomy should be performed. However, if there is localized sepsis or peritonitis, antibiotics with or without percutaneous drainage can be considered, with the hope of avoiding a reoperation and likely stoma (39).

- **Abdominal collection**: this refers to a collection of infected fluid inside the abdomen and presents as worsening pain and bloating. The management of this condition involves antibiotics and drainage of the collection using either an ultrasound or CT scan.

- **Ileus and bowel obstruction**: this is because of a delay in the bowel movement or contractions known as peristalsis. The cause of this condition is generally due to the handling of the bowel during the surgery and bruising which creates swelling. If an ileus or bowel obstruction occurs and the bowels temporarily stop working the patient may experience increased bloating, abdominal pain, nausea and vomiting. This can be managed by stopping dietary intake and allowing the bowel to rest. Furthermore, it may also be necessary to pass

a nasogastric tube to relieve the symptoms. Keeping mobile and chewing gum may prevent an ileus.

Similar symptoms may occur in patients who develop a bowel obstruction, which is generally caused by adhesions or kinking of the bowel. In most cases the initial management is the same as described above for an ileus and in the majority of cases the bowel obstruction will also settle down on its own. A small percentage of patients will require a further operation or intervention.

- **Fistula formation:** it is an abnormal connection between two parts of the body, in this case it is often from the bowel to the surface of the skin. In rare cases problems from the join made during the first operation can occur once the stoma is reversed and continuity of the bowel is restored. The most common problem is caused from an infection around the rectal anastomosis (join) which can present as a fistula. Some fistulas can heal on their own but surgery may be considered if the fistula does not close within a few months.

Apart from the complications, possible side effects of the stoma reversal are:

- **Diarrhoea**: from the first few days up to a few weeks before it settles down. In a small percentage of patients, it can take up to 6 months before the bowel motions become more consistent. The main treatment consists on adjusting the food the patient eats and taking antidiarrhoeals such as loperamide.

- **Frequency and urgency**: this can be more of a problem for those who have had a low join or anastomosis in the bowel and for those who have had pelvic radiotherapy and/or were

already suffering from a weak sphincter muscle

The easiest stomas to reverse are traditionally the loop stomas. As discussed previously, both limbs of bowel are present and as such they simply need to be reanastomosed and returned to the abdominal cavity.

Therefore, end stoma reversal is often more challenging. The abdominal cavity must be explored in order to locate the distal portion of the bowel. The distal bowel is often atrophied and may be friable from long standing diversion. This may make it difficult to use staplers especially circular stapling devices. Care must be taken in order not to tear or injure the serosa of the distal limb of bowel.

3.9.1 Time to reverse a derivative ileostomy after rectal resection

Nowadays, patients with a temporary stoma tend to keep it for at least 12-24 weeks before the reversal, and around 20% of them will never have it closed, mainly because of the complications after rectal excision surgery. Timing of stoma closure has been previously investigated in a few prospective studies that mainly focused on morbidity and mortality, concluding that it is associated with a low mortality, but more than 20% of morbidity for the ones closed after 8-12 weeks (42). For that reason, studies have been carried out lately for the evaluation of an early closure of the stoma, and results have been promising. Some of them concluded that the number of complications can be reduced if the closure is done 2 weeks after the stoma creation surgery (43)(44).

The time for reversal of the stoma is an issue of central importance, but there is not enough evidence yet to make reliable recommendations about when the best timing is.

3.9.2 LARS: Low anterior resection syndrome

Low anterior resection syndrome (LARS) is a change in bowel habits that may happen after surgery for rectal cancer. It includes a wide range of issues that can have a great impact on people's quality of life.

To treat cancer that affects the proximal 2/3 of the rectum, part of it is removed and the colon is anastomosed to the part of rectum that is still in place, or even colon can be anastomosed to the anal canal. Removing part of the rectum decreases the body's ability to store stool and changes the way that the bowels work. Therefore, most patients who have rectal cancer surgery usually develop LARS, but changes can be mild for some of them and more severe for others. Symptoms of LARS may include:

- Frequency and urgency
- Clustering of bowel movements
- Faecal incontinence
- Ileus
- Flatulence
- Bowel fragmentation

Symptoms usually start after the ostomy is closed, and for most patients they improve after 1 or 2 years. However, some of them can stay with LARS symptoms forever (45). In order to evaluate these symptoms, an internationally validated and reliable quality of life test has been developed, called the LARS score. It is a simple self-administered questionnaire measuring bowel dysfunction after rectal cancer surgery (46).

4. JUSTIFICATION

Patients undergoing surgery for low rectal cancer often receive a simultaneous construction of a temporary ileostomy, which is done to limit the consequences of anastomotic leakage such as abscess formation, peritonitis, and poor neorectal function (38). One can anticipate that anastomotic leakage occurs in a medically fragile patient, in patients who received preoperative radiotherapy after a technically difficult operation, or if intraoperative adverse events were present. However, anastomotic leakage could also occur in patients with no obvious risk factors. The difficulty in predicting anastomotic leakage, including patients considered to be at low risk, has generated several studies in recent years with the aim of identifying risk factors. They have concluded after multivariable analysis that the most common risk factors for leakage are low anastomosis, preoperative radiation and male gender (47).

Most of the patients keep their stoma for at least 8-12 weeks, allowing enough time for recovery from the first resection and resolution of the abdominal inflammation, however, it is not unusual that the stoma is left in place much longer, after finishing adjuvant chemotherapy. Even for some patients it becomes permanent (>20% of the them) (44) (39)

Stoma creation affects patients differently, but studies have shown that those carrying stomas have a lower quality of life compared to those who underwent similar procedures without the stoma formation (43). That is to say, they have been shown to negatively influence quality of life and body image. Despite prior counselling, many patients remain distressed with the thought of having a stoma and are keen to get it closed as early as possible. Hence, both surgeons and patients look forward to an early closure of the stoma (48).

Late reversal of a temporary ileostomy is associated to low mortality (0,1-4%) (35), but up to 20-33% of morbidity. Some of the most common complications are small bowel obstruction (0- 15%), wound infections (0-18.3%), anastomotic leaks (0-8%) and stoma site hernias (5%) (38). Moreover, a recently published review found major complications ranging from 0% to 7-9% and minor complications varying from 4-5% to 30% (49).

A few prospective studies have investigated the morbidity and mortality of an early closure of the ileostomy, which is considered to be 2 weeks after the first surgery. Even though it did not seem to be associated with higher rates of neither of them, it is still unknown when the best moment for the closure is. That is to say, all these findings point to the obvious: this issue requires further investigation in a randomised clinical trial in order to be able to make reliable recommendations.

The aim of this study is to analyse the number and severity of the complications in the early closure compared to the late closure of the ileostomy after rectal cancer resection. There are still no solid recommendations for the timing of closure, and most of the studies published so far are retrospective case-control studies or based on day-case experiences. Therefore, randomized clinical trials are needed in order to confirm the benefits of an early closure of ileostomies and to set the proper time for the stomal reversal.

5. HYPOTHESIS AND OBJECTIVES

5.1 HYPOTHESIS

Patients who undergo early closure of derivative ileostomy (2-3 weeks) after rectal cancer resection with low colorectal anastomosis have fewer complications compared to those who undergo later closure (3-6 months)

5.2 OBJECTIVES

5.2.1 Primary objective

The primary aim of the study is to register and compare the number of postoperative complications of the control (late closure) group and the experimental (early closure) after the closure surgery, both in the rectum and stoma site.

5.2.2 Secondary objectives

- To analyse the severity (major or minor) of the complications in each group with the Clavien-Dindo Classification for Surgical Complications (Table 1) and compare the results in the two groups (50). This classification has been used in several clinical studies and it is internationally validated.
- To analyse of the quality of life in the two groups before the closure surgery, and 1 and 12 months after it with specific and validated questionnaires: Lars Score. (Annex 3), COREFO score (Annex 4) and SF-36 (Annex 5).

6. MATERIAL AND METHODS

6.1 STUDY DESIGN

This is a non-placebo controlled, opened, prospective randomized controlled clinical trial which aims to compare the complications in the stoma site and rectum in two groups, including patients with ileostomy reversal two weeks after rectal resection (early closure) and the other one 3-6 months after its creation (late closure). Patients will be followed up from the moment they enter the study, that is to say, after the rectal surgery and ileostomy creation, until 12 months after the stoma closure. They will be randomized (simple) in a 1:1 ratio in two groups, the intervention group will have their stomas reversed within 2 weeks, and the control group between 3-6 months after surgery. In addition, subjects will receive oral and written information about the trial, and the consent has to be signed by all of them to be part of the trial.

Hospital Universitari Josep Trueta will be the reference centre in which the patients will be selected.

6.2 STUDY POPULATION

The target population of the study will be adult patients (+18 years) who underwent a surgical treatment for rectal cancer with low colorectal anastomosis and a construction of a protective ileostomy. No restrictions or stratification for age and gender will be made. Patients will be placed in either of both groups randomly in a 1:1 ratio.

6.2.1 Patient exclusion criteria

- Patients under 18 years old.

- Patients who refuse to sign the informed consent.
- Patients who suffer from other comorbidities after the first surgery, which hamper a new intervention in the convalescence.
- Patients with clinical or radiological signs of suture dehiscence within the first 14 days after surgery.

6.3.2 Participant withdrawal or termination

An intention-to-treat analysis will be used in this study, so if a patient leaves 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.

6.3 SAMPLE

6.3.1 Sample selection

A non-probabilistic consecutive sampling method will be used; patients who undergo a low rectal resection with the creation of an ileostomy in the General Surgery department of Hospital Universitari Josep Trueta will be selected and will be offered to enter the study according to inclusion criteria. The patient selection will take as long as needed until the sample size is complete.

6.3.2 Sample size

The sample size estimation is based on literature review. Studies showed a rate between 20-45% of postoperative complications in the control group, and 15-30% of postoperative in the intervention group. They all had very severe inclusion and exclusion criteria. Therefore, to prove our hypothesis,

we have used the power calculator GRANMO. Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, with an anticipation of a 5% drop-out rate, and assuming a 30% of complications in the control group and a 10% in the intervention group, we need a total sample of 126 patients (63 for each group) to recognize a statistical difference. ARCISNUS approximation has been used.

6.3.3 Estimated time of recruitment and enrolment

It has been estimated that 126 patients are needed for this study. By analysing the data from the database of Hospital Universitari Josep Trueta, the number of patients who were operated at this centre last year and met the inclusion criteria for the study have been calculated, which is 40. Since this is a monocentric study, it has been estimated that at least 3 and a half years will be needed to recruit the whole sample. Candidates will be informed (annex 7) and invited to participate voluntarily, having to sign the informed consent (annex 8).

6.3.4 Randomization

Statistician expert will create a database containing the participants. Each patient will have an ordered code. With a simple 1:1 randomization, patients will be assigned either to the early closure group (1) or to the late closure group (2), so neither the statistician, the surgeon or the patient will decide it. This randomization will be created by the SPSS software.

6.3.5 Masking techniques

Studies that apply surgical techniques have a detection bias because it is not possible to blind the surgeon or the patient. In this case, both the surgeon and the patient will know when the stoma is going to be reversed, and therefore it will not be a double-blinded study.

Despite that, the main endpoint (number of complications) is a hard variable, it is objective and easy to diagnose, so the detection bias for the primary and the first of the secondary endpoints will not be troublesome.

6.4 STUDY VARIABLES

In order to assess the proposed objectives, the variables are the following:

6.4.1 Independent variable

The independent variable of this study is the time of closure of the ileostomy (2 weeks versus 3-6 months). It will be defined as a categorical nominal variable.

6.4.2 Dependent variables

Primary dependent variable

The main dependent variable of this study will be the number of complications related to the stoma site and rectum in each group. The surgeon will register the number of complications of each patient immediately after the surgery, and after discharge. It will be defined as a quantitative discrete variable.

Secondary dependent variables

Number of major and minor complications according to the Clavien-Dindo Classification for Surgical Complications, measured in both groups (Table 1). This classification score classifies complications according to their necessary treatment, and it is therefore an objective measure, based on

standardized criteria. Annex 4 and table 2 show how the data is going to be collected. Every complication of each patient will be collected and categorized from I to V, depending on its severity and, therefore, treatment. It will be defined as a quantitative discrete variable (Table 2).

For the comparison of the quality of life the patients will be provided with different questionnaires, before the closure surgery and at 1 and 12 months after surgery:

- **LARS score** (annex 3): the LARS score is a simple self-administered questionnaire measuring bowel dysfunction after rectal cancer surgery. It consists of 5 questions, and each answer has a number (the biggest the number the worst the condition). The interpretation of the test is the following: 0-20 no LARS, 21-29 minor LARS, 30-42 major LARS. It will be defined as a quantitative discrete variable.
- **COREFO score** (annex 4): this is also a self-administered questionnaire measuring colorectal functional outcome after a rectal surgery. It assesses faecal incontinence, frequency, social impact and the need for medication. Each question is graded from 1 to 5, the bigger the number the worst the condition. It will be defined as a quantitative discrete variable (51).
- **SF-36 questionnaire** (annex 5): it is a self-administered questionnaire containing 36 items which takes about 35 minutes to complete. It measures health on eight multi-item dimensions covering functional status, well-being, and overall evaluation of health. For each dimension, items scores are coded, summed and transformed on to a scale from 0 (worst health) to 100 (best health)(52).

TABLE 1. Classification of Surgical Complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications
	Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

Table 2

	EARLY CLOSURE		LATE CLOSURE	
	n	%	n	%
GRADE I				
GRADE II				
GRADE IIIA				
GRADE IIIb				
GRADE IVa				
GRADE IVb				
GRADE V				

6.5. DATA COLLECTION

For the process of data collection, it is vital that the abdominal surgery department is aware that this study is being carried out; the surgeon in charge will inform the rest of the members of the unit about it. Moreover, patients will also play an important role in our study since they will have to fill in the QOL questionnaires.

For the purpose of gathering the needed information, a flowchart was created (figure 2) (table 3):

- **Trial entry (day 1 to 15)**

Patients who underwent a surgical resection of a rectal tumour and the creation of a protective ileostomy who meet the inclusion criteria will be asked if they want to participate in the trial. They will be orally informed about the different procedures and timing of treatments, but they will also be provided with an information sheet (annex 7).

If they agree to participate, they will be asked to sign the informed consent (annex 8). If they don't agree to sign it, they will be excluded from the trial.

If the patient has signed the informed consent, he or she will be randomly placed in one of the two treatment groups (early reversal or late reversal), and it will be written down and formally documented.

- **Stoma creation postoperative stage (day 1-15)**

The signs and symptoms of suture dehiscence will be checked during the early postoperative period (the first 14 days). As these we consider: open wound, broken sutures, pain at wound site, wound bleeding and pus or frothy drainage in infected wounds. It will be assessed by the surgeon with

physical examinations and radiological procedures. As stated before, if this happens in the first 14 days after surgery, the patient will be excluded from the trial.

Before the stoma reversal surgery, the patient will fill the QOL (LARS score) questionnaire.

- **Stoma reversal (2 weeks versus 3-6 months after stoma creation)**

Patients will undergo another surgery for the reversal of the ileostomy, one group after 2 weeks and the other after 3-6 months. The intervention procedure will be described in the next section.

- **Follow up: 1 and 12 months after stoma reversal**

We will assess the general condition of the patient, and also the complications of the stoma closure immediately after the surgery while the patient is at the hospital, and after discharge. We will document them and also classify them with the Clavien-Dindo Classification for Surgical Complications (table 1). Annex 6 and table 2 show how complications data is going to be collected: each patient will have a number of identification, and every complication will be recorded saying which type of complication it is, a description if needed and the grade (I-V). If a patient has more than one complication, we will underline the most severe one.

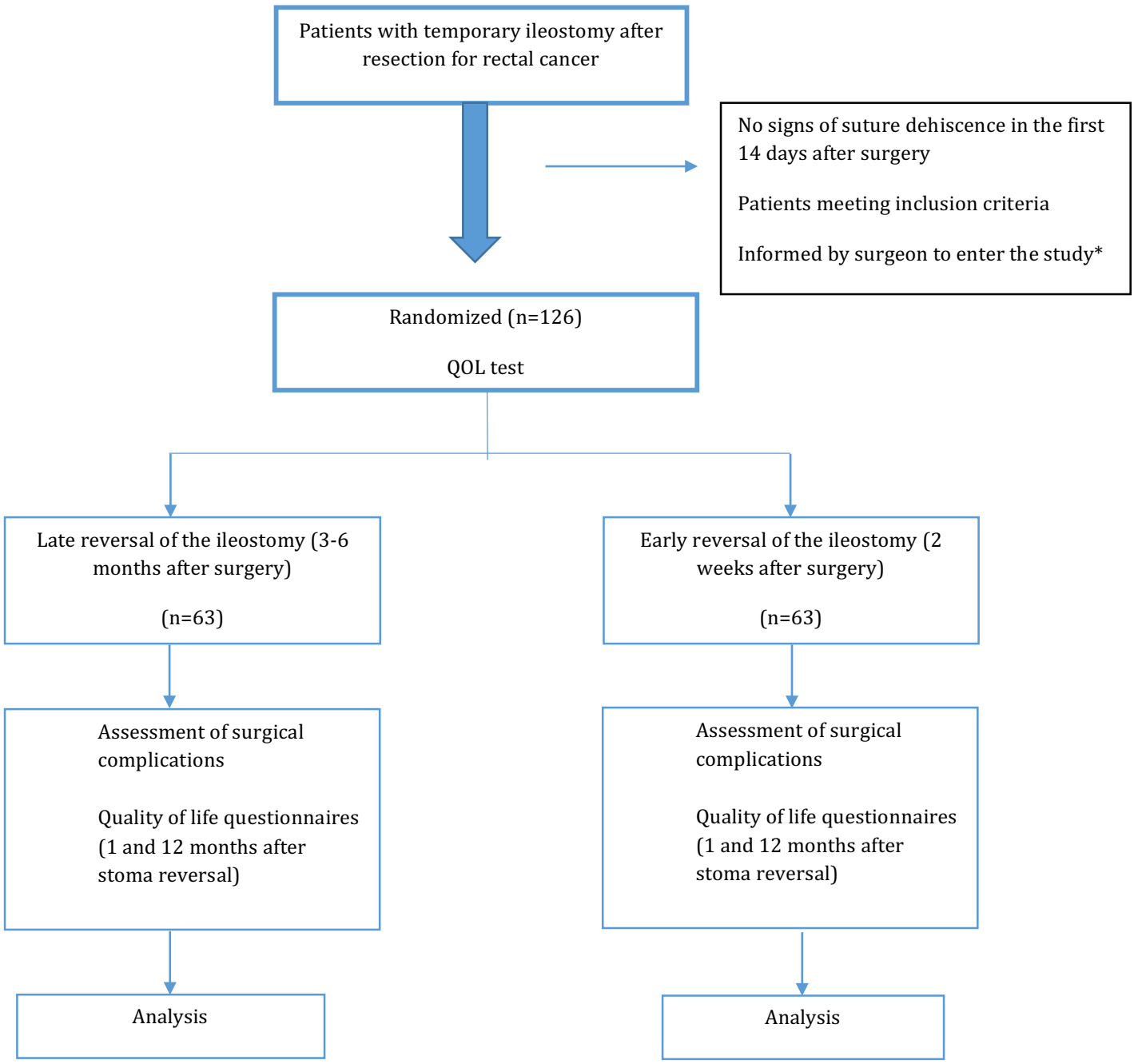
Patients will also receive the QOL tests again to fill them (table 3).

Table 3.

	Postop. Assessment by the surgeon	CT scan of the pelvis	**Early reversal of the stoma**	**Late reversal of the stoma**	C-DCSC registration	QOL LARS score
Day 1-5 after ileostomy creation						
Day 14 after ileostomy creation						
INCLUSION/ RANDOMIZATION **1st-2nd week**						
Before closure surgery						
2 weeks after ileostomy creation						
3-6 months after ileostomy creation						
1 month after closure surgery						
12 months after closure surgery						

Complications and QOL registration – Surgical procedures – General and radiological assessment – Informed consent

Figure 2.


Patients with temporary ileostomy after resection for rectal cancer
No signs of suture dehiscence in the first 14 days after surgery
Patients meeting inclusion criteria
Informed by surgeon to enter the study*
Randomized (n=126)
QOL test
Late reversal of the ileostomy (3-6 months after surgery)
(n=63)
Early reversal of the ileostomy (2 weeks after surgery)
(n=63)
Assessment of surgical complications
Quality of life questionnaires (1 and 12 months after stoma reversal)
Assessment of surgical complications
Quality of life questionnaires (1 and 12 months after stoma reversal)
Analysis
Analysis

6.5.1 Intervention

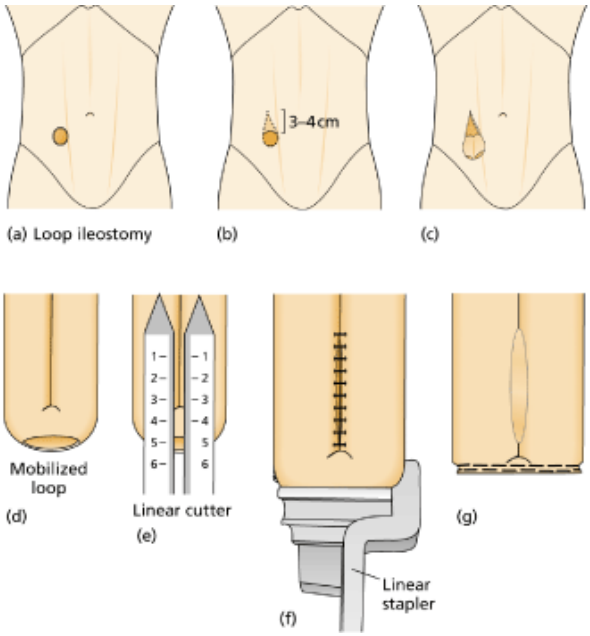
Closure of the loop can be a difficult and tedious procedure. It is important that all adhesions involving both limbs be divided and that sufficient length allow enough mobilization for anastomosis closure.

In the case of a loop ileostomy, it has to be dissected down to the peritoneal level. It is helpful to extend the circular defect vertically for a distance of 3-4cm, and it should be done full thickness including the anterior abdominal wall and the skin. A 'mini laparotomy' is created which facilitates easy and full dissection of the loop (figure 4). Closure of the bowel defect by hand is difficult and produces a narrow lumen; it is recommended that the closure then proceeds as a stapled, side-to-side anastomosis of at least 7-cm length, using a linear cutter and a straight linear stapler (figure 4.) (53). Despite that, it can also be closed with simple sutures inside the abdominal cavity, without having to use staples.

Reversal of an end ileostomy is more difficult, as one end of the bowel has to be rejoined within the abdomen. This usually means that the surgeon will have to open the abdomen via the old scar to be able to safely access the bowel. As a result of the increased surgery, compared to the closure of a loop stoma, there will be a longer stay in hospital and a greater recovery time before normal activities can be resumed.

End ileostomies can also be reversed laparoscopically, it depends on the training of the surgeon. Even if this is attempted it may be necessary to convert to the open operation, as the aforementioned adhesions can cause severe problems laparoscopically. That said, if this type of surgery is carried out then it is likely there will be less post-operative pain and a shorter stay in hospital.

Figure 4.


3–4cm
(a) Loop ileostomy
(b)
(c)
Mobilized loop
(d)
Linear cutter
(e)
Linear stapler
(f)
(g)

6.6 STATYSTICAL ANALYSIS

A detailed statistical analysis plan will be made on all randomized patients using an intention to treat analysis (ITT). This will be performed with the Statistical Package for the Social Science (SPSS) software for Windows®.

For primary objective, the independent variable was defined as a categorical nominal variable and the dependent variable as a quantitative discrete variable. Therefore, the U-Mann-Whitney test or Wilcoxon rank sum test will be used. Even so, if the dependent variable is defined as a percentage of complications, the Chi-squared test could be used.

For the first of the two secondary objectives, the number of complications were classified in 5 different subgroups with the Clavien-Dindo Classification for Surgical. The dependent variable is quantitative discrete again, so the U-Mann-Whitney test will be used, unless it is defined as a percentage, in that case the Chi-square test could be performed.

Finally, for analysing the quality of life, non-parametric test will be used in all analyses, that is to say, the U-Mann-Whitney test or Wilcoxon rank sum test, where necessary. Moreover, variations over time within the same patient group will be analysed with the Friedman analysis of variance.

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

6.7 WORK PLAN AND CHRONOGRAM

This study is expected to last 7 years plus 4 months for protocol elaboration and coordination. The activities carried out during this time will be organized in 5 phases which are detailed below (annex 9):

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

In this first phase, from September to December 2016, the study protocol 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, methods will be discussed. The chronogram will also be arranged at this point.

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

2. **Field work**

- Sample recruitment (3.5 years): patients who undergo a low resection of a rectal tumour and the creation of a temporary ileostomy, and who meet the inclusion criteria for the study will be collected and distributed randomly into two different groups (early reversal and late reversal of the ileostomy). Since there are around 40 cases like this per year at the Hospital Universitari Josep Trueta it will take three and a half years to recruit all the needed patients. It is important to remember that the informed consent must be signed by the patient.
- Intervention and follow up (4.5 years): patients incorporated in the study will go through their assigned interventions, depending on the group, in 2 weeks or 3-6 months.

Each patient will be followed during a year after the closure of the temporary ileostomy, providing the QOL tests and evaluating the surgical complications, more exactly, 1 and 12 months after the intervention.

3. Data collection (6 years)

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

4. Statistical analysis and interpretation (1 year)

After all the data is collected it will be analysed using the appropriate statistical tests set in the protocol for each objective. This will be performed by the blinded statistician.

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

5. Publication (1 year)

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

7. ETHICAL AND LEGAL ASPECTS

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.

Our ethical code is reflected on the great respect about all basic ethic principles according to the World Medical Association Declaration of Helsinki (2013) which also rules the principles of human experimentation. Moreover, the committee will also ensure that the study respects all these ethical principles.

Previous to the inclusion, participants will be properly informed about the interventions and the clinical trial with an information sheet (annex 7), where the risks, the benefits and the alternatives of the different interventions will be reflected. They will participate voluntarily, therefore, they must understand and sign the informed consent (annex 8) 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. In particular the section II, where it specifies the basic principles, requirements, authorization and security of the studies in which a human being undergoes an invasive procedure.

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 21th 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.

8. STRENGTHS AND LIMITATIONS

First of all, the main limitation of this clinical trial is that it is an open label trial, and therefore it is not possible to design a double blind study, 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 a non-probabilistic recruitment 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 inference is 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 complications due to other comorbidities after the ileostomy creation surgery. Loses and withdrawals during the follow up can also cause a selection bias. In order to reduce it, we will calculate the sample size with expectations of future loses (5% in this case). Withdrawals will be registered in the study and described in the results.

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.

Another strength is that sample size and methods are designed to study the main objective but also the secondary objectives, so they will all have a definitive result.

9. FEASIBILITY

This study 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, statistician) is well trained and has experience on this field.

The hospital will provide all the necessary means such as personnel salaries, surgeries, cures and radiological procedures. Computer devices and programs to elaborate the database and to carry out the statistical analysis will also be provided.

We estimated that in the Hospital Universitari Doctor Josep Trueta de Girona around 40 patients undergo a rectal surgery with the creation of a temporary ileostomy per year. To find the main hypotheses relevant, we explained before that the sample size should be 63 patients per group, so we expect that in 6 years (starting January 2017) of patient recruitment, follow up and data collection, we will have the final results of the study (annex 9).

10. BUDGET

The realization of this study does not include an increase of the costs of the surgical intervention, nor the necessity of additional radiological tests or personnel. The main reason is because it is the procedure used in the clinical practice nowadays, where a CT scan is performed to rule out subclinical anastomotic complications.

Nevertheless, further support is needed in order complete some of the tasks:

- Development of the database, data collection and the realization of the statistical analysis.
- Assistance to scientific meetings, congresses, and diffusion of the results.
- Elaboration and translation of the scientific work for international publications.

Some of the extra costs are the following:

1. Hiring of a technician for the data collection and support of the follow up: 5000€ per year.
2. Hiring of a statistical consultancy firm through the Instituto de Investigación Biomédica de Girona (IDIBGI): 300€ for each of the planned publications. Total 600€.
3. Attendance of National and International Congresses for the broadcasting of the results:
    - Inscription and trip to the National Congress of Coloproctology: 450€ each year for three years. Total 1350€.
    - Inscription and trip to the congress of the European Association of Coloproctology: 1000€ each year for three years. Total 3000€.
4. Translation services: 200€ for each of the two publications. Total 400€.
5. Publication expenses in international journeys: 100€ for each of the two publications. Total 200€.

6. Material expenses included in table 3.

A responsibility assurance will not be hired because the interventions that patients will go through for this clinical trial represent an equal risk as the one they would go through in the usual clinical practice. As described before, the surgical interventions analysed in this study are the same as the ones performed in the Hospital Universitari Dr. Josep Trueta, and they are thoroughly described and accepted by the scientific community.

BUDGET

	Description	**Total Cost**
STAFF		
Technician for data collection/follow up	5000€per year x 6 years	30.000€
Statistical consultancy firm	300€ x 2 publications	600€
Translation services	200€ x 2 publications	400€
MATERIAL		
IBM SPSS Statistics license	300€ per year x 2 years	600€
External hard drive 1TB	60€ per unit	60€
Pen-drive	14€ per unit x 5 units	70€
Stapler	10€ per unit x 3 units	30€
Folder	2,5€ per unit x 4 units	10€
Paper punch	15€ per unit x 2 units	30€
Pen	0,3€ per unit x 50 units	15€

Folio package	3,5€ per unit x 50 units	35€
Box of 250 envelopes	40€ per unit	40€

PUBLICATION AND DISSEMINATION

National congress	450€ per year x 3 years	1350€
International congress	1000€ per year x 3 years	3000€
Publication expenses	100€ x 2 publications	200€

TOTAL

		36.440€

11. IMPACT

The main aim of this project is to study the benefits and safety of an early closure of a protective ileostomy, including the patient's quality of life.

Due to the quite high frequency of complications after the creation of a stoma and after its late closure, and the worse quality of life of patients living with it, we consider that there is a necessity to assess an alternative treatment for them. Although studies have been carried during the past years, it is evident that further investigation is needed in order to make reliable recommendations, and that is the reason why we decided to propound this protocol.

If our hypothesis is validated and the results obtained are relevant, we will be confident to implement this new timing of ileostomy closure for the benefit of our patients. Firstly, because the rates of complications will be lower and secondly because the quality of life of the patients will improve. Moreover, since our sample has very few exclusion criteria and it's similar to the reference population, we could extrapolate the results and make reliable recommendations.

As a whole, it will be a positive change in the way we treat these patients, and we could potentially reduce the amount of them who never undergo the ileostomy closure in the end (around a 20% at this moment) (54) (44)

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ANNEX 1

Tabla 2. Estimaciones de la incidencia de cáncer en España para el año 2014 por tipo tumoral. Mujeres

Tipo tumoral	N Casos	IC 95%	TB	IC 95%	TAm	IC 95%	TAe	IC 95%
Labio, Cavidad oral y Faringe	1.671	(1.473 - 1.886)	7,1	(6,2 - 8,0)	3,4	(3,0 - 3,9)	4,8	(4,2 - 5,4)
Esófago	387	(302 - 488)	1,6	(1,3 - 2,1)	0,7	(0,6 - 0,9)	1,1	(0,8 - 1,4)
Estómago	3.248	(2.924 - 3.598)	13,8	(12,4 - 15,3)	5,3	(4,8 - 5,9)	8,0	(7,2 - 8,8)
Colon	11.687	(10.529 - 12.934)	49,5	(44,6 - 54,8)	19,8	(17,9 - 21,9)	29,5	(26,7 - 32,6)
Recto	4.384	(3.515 - 5.450)	18,6	(14,9 - 23,1)	7,9	(6,3 - 9,8)	11,6	(9,3 - 14,4)
Colorectal	16.071	(14.623 - 11.712)	68,1	(62,0 - 75,1)	27,7	(25,2 - 30,5)	41,1	(37,4 - 45,3)
Hígado	1.552	(1.288 - 1.848)	6,6	(5,5 - 7,8)	2,3	(2,0 - 2,8)	3,6	(3,0 - 4,2)
Vesícula y vías biliares	1.033	(874 - 1.212)	4,4	(3,7 - 5,1)	1,4	(1,2 - 1,6)	2,2	(1,9 - 2,6)
Páncreas	3.183	(2.836 - 3.562)	13,5	(12,0 - 15,1)	4,9	(4,4 - 5,5)	7,5	(6,7 - 8,4)
Laringe	295	(127 - 663)	1,3	(0,5 - 2,8)	0,7	(0,3 - 1,7)	1,0	(0,4 - 2,3)
Pulmón	5.404	(4.856 - 6.003)	22,9	(20,6 - 25,4)	11,8	(10,6 - 13,2)	16,6	(14,8 - 18,5)
Melanoma cutáneo	2.352	(2.038 - 2.695)	10,0	(8,6 - 11,4)	5,7	(4,9 - 6,6)	7,5	(6,5 - 8,7)
Mama	26.354	(22.991 - 30.117)	111,7	(97,5 - 127,7)	63,0	(54,5 - 72,4)	85,0	(73,8 - 97,6)
Cuello uterino	2.375	(1.969 - 2.839)	10,1	(8,3 - 12,0)	6,3	(5,2 - 7,6)	8,2	(6,7 - 9,9)
Cuerpo uterino	5.963	(5.232 - 6.759)	25,3	(22,2 - 28,7)	13,0	(11,3 - 14,9)	18,5	(16,1 - 21,1)
Ovario	3.276	(2.904 - 3.681)	13,9	(12,3 - 15,6)	7,4	(6,5 - 8,3)	10,2	(9,0 - 11,5)
Riñón	1.854	(1.600 - 2.139)	7,9	(6,8 - 9,1)	3,9	(3,4 - 4,5)	5,4	(4,7 - 6,3)
Vejiga urinaria	3.498	(2.989 - 4.059)	14,8	(12,7 - 17,2)	5,9	(5,0 - 6,8)	8,8	(7,5 - 10,2)
Encéfalo y SNC	1.646	(1.443 - 1.866)	7,0	(6,1 - 7,9)	4,0	(3,5 - 4,5)	5,2	(4,5 - 5,9)
Tiroides	2.417	(2.252 - 2.590)	10,2	(9,5 - 11,0)	6,6	(6,1 - 7,0)	8,9	(8,2 - 9,5)
Linfoma de Hodgkin	669	(582 - 765)	2,8	(2,5 - 3,2)	2,6	(2,2 - 3,0)	2,7	(2,4 - 3,1)
Linfomas no hodgkinianos	3.315	(2.944 - 3.716)	14,1	(12,5 - 15,8)	6,9	(6,1 - 7,7)	9,5	(8,4 - 10,6)
Mieloma	1.233	(862 - 1.751)	5,2	(3,7 - 7,4)	2,0	(1,4 - 2,8)	3,0	(2,1 - 4,3)
Leucemias	2.615	(2.199 - 3.090)	11,1	(9,3 - 13,1)	5,7	(4,9 - 6,7)	7,3	(6,2 - 8,5)
Otros cánceres	5.060	(4.302 - 5.882)	21,4	(18,2 - 24,9)	9,0	(7,8 - 10,3)	12,8	(11,1 - 14,6)
Total exc. piel no melanoma	95.471	(91.414 - 100.025)	404,7	(387,5 - 424,0)	200,3	(190,8 - 210,9)	278,8	(266,0 - 293,2)

TB: Tasa bruta. TAm: Tasa ajustada a la población estándar mundial. TAe: Tasa ajustada a la población estándar europea
Fuente: Red Española de Registros de Cáncer

Tabla 1. Estimaciones de la incidencia de cáncer en España para el año 2014 por tipo tumoral. Hombres

Tipo tumoral	N Casos	IC 95%	TB	IC 95%	TAm	IC 95%	TAe	IC 95%
Labio, Cavidad oral y Faringe	4.961	(3.884 - 6.193)	21,8	(17,1 - 27,2)	12,7	(9,8 - 15,9)	17,8	(13,8 - 22,3)
Esófago	1.960	(1.736 - 2.209)	8,6	(7,6 - 9,7)	4,8	(4,2 - 5,4)	6,8	(6,1 - 7,7)
Estómago	5.106	(4.649 - 5.601)	22,4	(20,4 - 24,6)	11,0	(10,0 - 12,0)	16,4	(14,9 - 18,0)
Colon	15.198	(13.121 - 17.522)	66,8	(57,7 - 77,0)	31,5	(27,2 - 36,3)	48,0	(41,5 - 55,4)
Recto	8.284	(7.377 - 9.264)	36,4	(32,4 - 40,7)	18,3	(16,2 - 20,5)	27,2	(24,2 - 30,4)
Colorectal	23.482	(21.216 - 26.004)	103,2	(93,2 - 114,3)	49,8	(45,0 - 55,1)	75,2	(68,0 - 83,2)
Hígado	4.078	(3.496 - 4.709)	17,9	(15,4 - 20,7)	9,5	(8,1 - 11,0)	13,8	(11,8 - 16,0)
Vesícula y vías biliares	1.081	(861 - 1.336)	4,8	(3,8 - 5,9)	2,1	(1,7 - 2,6)	3,3	(2,6 - 4,1)
Páncreas	3.405	(3.060 - 3.781)	15,0	(13,5 - 16,6)	7,5	(6,7 - 8,3)	11,1	(10,0 - 12,4)
Laringe	3.442	(3.003 - 3.918)	15,1	(13,2 - 17,2)	8,9	(7,7 - 10,2)	12,5	(10,9 - 14,3)
Pulmón	22.455	(19.952 - 25.212)	98,7	(87,7 - 110,8)	51,7	(45,8 - 58,2)	75,8	(67,3 - 85,2)
Melanoma cutáneo	2.517	(2160 - 2905)	11,1	(9,5 - 12,8)	6,1	(5,2 - 7,1)	8,6	(7,3 - 9,9)
Próstata	32.641	(26.966 - 38.998)	143,5	(118,5 - 171,4)	67,6	(55,5 - 81,2)	103,4	(85,2 - 123,7)
Testículo	997	(893 - 1.109)	4,4	(3,9 - 4,9)	4,3	(3,8 - 4,8)	4,4	(3,9 - 4,9)
Riñón	3.523	(3.128 - 3.952)	15,5	(13,8 - 17,4)	8,5	(7,6 - 9,6)	12,2	(10,8 - 13,7)
Vejiga urinaria	16.756	(15.091 - 18.534)	73,7	(66,3 - 81,5)	36,7	(32,9 - 40,7)	54,9	(49,4 - 60,7)
Encéfalo y SNC	2.317	(2.078 - 2.578)	10,2	(9,1 - 11,3)	6,5	(5,8 - 7,2)	8,4	(7,5 - 9,3)
Tiroides	801	(709 - 902)	3,5	(3,1 - 4,0)	2,3	(2,0 - 2,6)	3,0	(2,6 - 3,4)
Linfoma de Hodgkin	923	(819 - 1.035)	4,1	(3,6 - 4,5)	3,7	(3,2 - 4,1)	3,9	(3,5 - 4,4)
Linfomas no hodgkinianos	4.185	(3.666 - 4.752)	18,4	(16,1 - 20,9)	10,8	(9,5 - 12,3)	14,6	(12,8 - 16,5)
Mieloma	1.466	(1.013 - 2.110)	6,4	(4,5 - 9,3)	3,0	(2,1 - 4,3)	4,6	(3,2 - 6,6)
Leucemias	3.633	(3.044 - 4.306)	16,0	(13,4 - 18,9)	9,4	(8,0 - 11,1)	12,4	(10,4 - 14,6)
Otros cánceres	6.084	(5.205 - 7.049)	26,7	(22,9 - 31,0)	14,3	(12,3 - 16,5)	20,3	(17,4 - 23,4)
Total exc. piel no melanoma	145.813	(138.709 - 153.734)	641,0	(609,8 - 675,8)	331,0	(315,4 - 348,4)	483,3	(460,2 - 509,1)

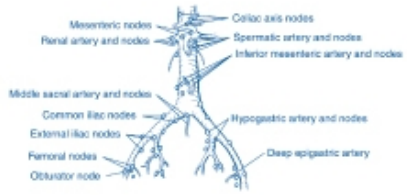
N Casos: Número de casos. TB: Tasa bruta. TAm: Tasa ajustada a la población estándar mundial. TAe: Tasa ajustada a la población estándar europea.
Fuente: Red Española de Registros de Cáncer

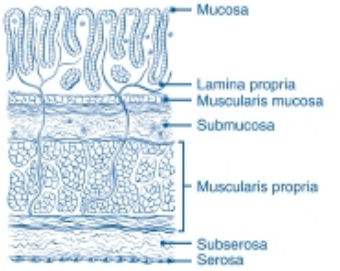
ANNEX 2

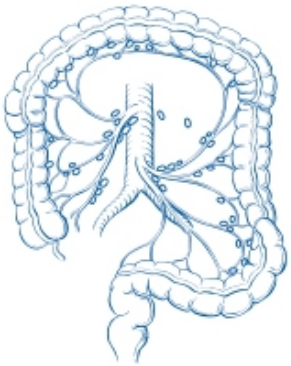
American Joint Committee on Cancer

Colon and Rectum Cancer Staging

7th EDITION







Definitions

Primary Tumor (T)

- **TX** Primary tumor cannot be assessed
- **T0** No evidence of primary tumor
- **Tis** Carcinoma in situ: intraepithelial or invasion of lamina propria[1]
- **T1** Tumor invades submucosa
- **T2** Tumor invades muscularis propria
- **T3** Tumor invades through the muscularis propria into pericolorectal tissues
- **T4a** Tumor penetrates to the surface of the visceral peritoneum[2]
- **T4b** Tumor directly invades or is adherent to other organs or structures[2,3]

Regional Lymph Nodes (N)[4]

- **NX** Regional lymph nodes cannot be assessed
- **N0** No regional lymph node metastasis
- **N1** Metastasis in 1–3 regional lymph nodes
- **N1a** Metastasis in one regional lymph node
- **N1b** Metastasis in 2–3 regional lymph nodes
- **N1c** Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
- **N2** Metastasis in 4 or more regional lymph nodes
- **N2a** Metastasis in 4–6 regional lymph nodes
- **N2b** Metastasis in 7 or more regional lymph nodes

Distant Metastasis (M)

- **M0** No distant metastasis
- **M1** Distant metastasis
- **M1a** Metastasis confined to one organ or site (for example, liver, lung, ovary, nonregional node)
- **M1b** Metastases in more than one organ/site or the peritoneum

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage	T	N	M	Dukes*	MAC*
0	Tis	N0	M0	–	–
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1–T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3–T4a	N1/N1c	M0	C	C2
	T2–T3	N2a	M0	C	C1/C2
	T1–T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3–T4a	N2b	M0	C	C2
	T4b	N1–N2	M0	C	C3
IVA	Any T	Any N	M1a	–	–
IVB	Any T	Any N	M1b	–	–

NOTE: cTNM is the clinical classification, pTNM is the pathologic classification. The y prefix is used for those cancers that are classified after neoadjuvant pretreatment (for example, ypTNM). Patients who have a complete pathologic response are ypT0N0cM0 that may be similar to Stage Group 0 or I. The r prefix is to be used for those cancers that have recurred after a disease-free interval (rTNM).
* Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (any T N1 M0 and any T N2 M0). MAC is the modified Astler-Coller classification.

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Financial support for AJCC 7th Edition Staging Posters provided by the American Cancer Society

Notes

1 Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or mucosal lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.

2 Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (that is, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina).

3 Tumor that is adherent to other organs or structures, grossly, is classified (T4b). However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classifications should be used to identify the presence or absence of vascular or lymphatic invasion, whereas the Pn site-specific factor should be used for perineural invasion.

4 A satellite peritumoral nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule may represent discontinuous spread, venous invasion with extravascular spread (V1/2), or a totally replaced lymph node (N1/2). Replaced nodes should be counted separately as positive nodes in the N category, whereas discontinuous spread or venous invasion should be classified and counted in the Site-Specific Factor category Tumor Deposits (TD).

ANNEX 3

LARS-score - Scoring Instructions

Add the scores from each 5 answers to one final score.

Do you ever have occasions when you cannot control your flatus (wind)?

☐ No, never	**0**
☐ Yes, less than once per week	**4**
☐ Yes, at least once per week	**7**

Do you ever have any accidental leakage of liquid stool?

☐ No, never	**0**
☐ Yes, less than once per week	**3**
☐ Yes, at least once per week	**3**

How often do you open your bowels?

☐ More than 7 times per day (24 hours)	**4**
☐ 4-7 times per day (24 hours)	**2**
☐ 1-3 times per day (24 hours)	**0**
☐ Less than once per day (24 hours)	**5**

Do you ever have to open your bowels again within one hour of the last bowel opening?

☐ No, never	**0**
☐ Yes, less than once per week	**9**
☐ Yes, at least once per week	**11**

Do you ever have such a strong urge to open your bowels that you have to rush to the toilet?

☐ No, never	**0**
☐ Yes, less than once per week	**11**
☐ Yes, at least once per week	**16**

Total Score: _____

Interpretation:

0-20:	**No LARS**
21-29:	**Minor LARS**
30-42:	**Major LARS**

ANNEX 4

COREFO: Colorectal Functional Outcome Questionnaire

Score each question:

1: No, Never **2**: Yes, less than once per week **3**: Yes, 1-2 days per week **4**: Yes, 3-5 days per week **5**: Yes, 6-7 days per week

Part A: Incontinence	Score (1-5)
Have you unintentionally passed wind?	
Have you unintentionally passed liquid stools during the day?	
Have you unintentionally passed liquid stools during the night?	
Have you unintentionally passed solid stools during the day?	
Have you unintentionally passed solid stools during the night?	
Have you had a smear of feces in your underwear during the day?	
Have you had a smear of feces in your underwear, pajamas or nightgown at the end of the night?	
Was it difficult to distinguish between passing wind and a bowel movement?	
Have you used something to protect your underwear, such as sanitary towels, panty liners, or nappies?	
Total:	

Part B: Social Impact	Score (1-5)
If you needed to go urgently, did you have trouble stopping your bowel movement for longer than 15 minutes?	
Have you had a false alarm? (i.e. a need to go without a bowel movement)	
When you went to the toilet, did your bowel movement require more than15 minutes?	
Did you feel that your bowels were not empty after your bowel movement?	
After your bowel movement, did you have to return to the toilet within 1 hour for a bowel movement?	
Did you adjust your activities to the availability of a toilet?	
Were you limited in your daily activities (i.e. work or housework) due to problems with your bowel movements?	
Were you limited in your social activities (i.e. family visits, visits to the theater, or eating out) due to problems with your bowel movements?	
Were you limited in your sexual activities (with or without sexual intercourse) due to problems with your bowel movements?	
Total:	
Part C: Frequency	Score (1-5)
How many bowel movements have you had during the day?	

How many bowel movements have you had during the night?	
Total:	
Part D: Stool-related Aspects	Score (1-5)
Have you had pain during your bowel movements?	
Have you experienced blood loss during your bowel movements?	
Have you had irritated skin around your anus?	
Total:	
Part E: Need for Medication:	Score (1-5)
Have you used medicine to thicken your stools?	
Have you eaten certain foods on purpose to make your stools thicker or thinner?	
Have you purposely avoided certain foods to prevent your stools from becoming loose or hard?	
Total:	

ANNEX 5

SF36 Health Survey

INSTRUCTIONS: This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question please give the best answer you can.

1. In general, would you say your health is: (Please tick **one** box.)
   - Excellent ☐
   - Very Good ☐
   - Good ☐
   - Fair ☐
   - Poor ☐

2. Compared to one year ago, how would you rate your health in general now? (Please tick **one** box.)
   - Much better than one year ago ☐
   - Somewhat better now than one year ago ☐
   - About the same as one year ago ☐
   - Somewhat worse now than one year ago ☐
   - Much worse now than one year ago ☐

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? **(Please circle one number on each line.)**

	Activities	Yes, Limited A Lot	Yes, Limited A Little	Not Limited At All
3(a)	**Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
3(b)	**Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
3(c)	Lifting or carrying groceries	1	2	3
3(d)	Climbing **several** flights of stairs	1	2	3
3(e)	Climbing **one** flight of stairs	1	2	3
3(f)	Bending, kneeling, or stooping	1	2	3
3(g)	Waling **more than a mile**	1	2	3
3(h)	Walking **several blocks**	1	2	3
3(i)	Walking **one block**	1	2	3
3(j)	Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? **(Please circle one number on each line.)**

		Yes	No
4(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
4(b)	Accomplished less than you would like	1	2
4(c)	Were **limited** in the **kind** of work or other activities	1	2
4(d)	Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (e.g. feeling depressed or anxious)? **(Please circle one number on each line.)**

		Yes	No
5(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
5(b)	Accomplished less than you would like	1	2
5(c)	Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? (Please tick **one** box.)

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

7. How much physical pain have you had during the past 4 weeks? (Please tick **one** box.)

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Very Severe ☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Please tick **one** box.)

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

9. These questions are about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that is closest to the way you have been feeling for each item.

	(Please circle one number on each line.)	**All of the Time**	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
9(a)	Did you feel full of life?	1	2	3	4	5	6
9(b)	Have you been a very nervous person?	1	2	3	4	5	6
9(c)	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
9(d)	Have you felt calm and peaceful?	1	2	3	4	5	6
9(e)	Did you have a lot of energy?	1	2	3	4	5	6
9(f)	Have you felt downhearted and blue?	1	2	3	4	5	6
9(g)	Did you feel worn out?	1	2	3	4	5	6
9(h)	Have you been a happy person?	1	2	3	4	5	6
9(i)	Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc.) (Please tick **one** box.)

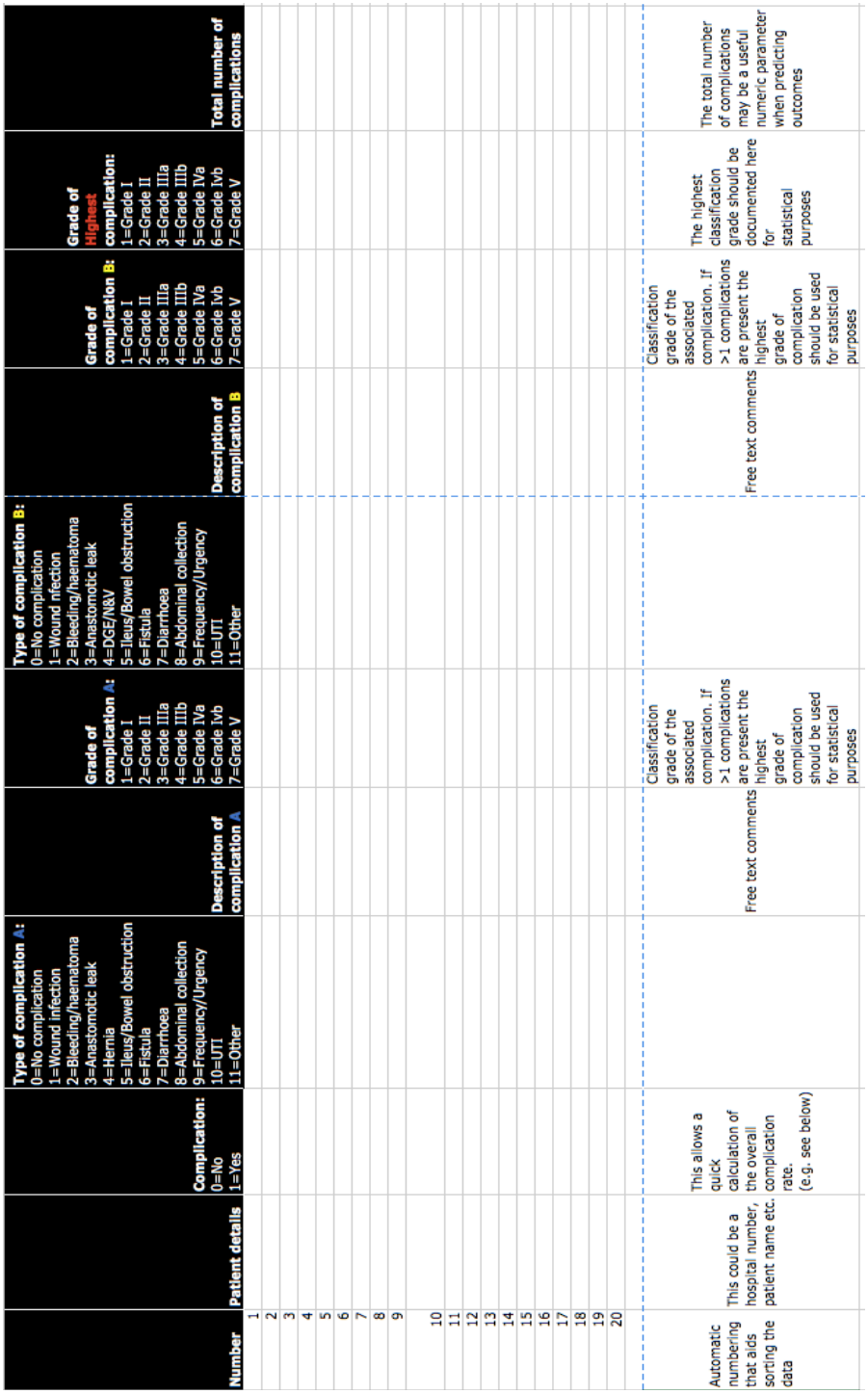
- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

11. How TRUE or FALSE is each of the following statements for you?

	(Please circle one number on each line.)	**Definitely True**	**Mostly True**	**Don't Know**	**Mostly False**	**Definitely False**
11(a)	I seem to get sick a little easier than other people	1	2	3	4	5
11(b)	I am as healthy as anybody I know	1	2	3	4	5
11(c)	I expect my health to get worse	1	2	3	4	5
11(d)	My health is excellent	1	2	3	4	5

Thank You!

ANNEX 6



Number	Patient details	Complication: 0=No 1=Yes	Type of complication A: 0=No complication 1=Wound infection 2=Bleeding/haematoma 3=Anastomotic leak 4=Hernia 5=Ileus/Bowel obstruction 6=Fistula 7=Diarrhoea 8=Abdominal collection 9=Frequency/Urgency 10=UTI 11=Other	Description of complication A	Grade of complication A: 1=Grade I 2=Grade II 3=Grade IIIa 4=Grade IIIb 5=Grade IVa 6=Grade IVb 7=Grade V	Type of complication B: 0=No complication 1=Wound infection 2=Bleeding/haematoma 3=Anastomotic leak 4=DGE/N&V 5=Ileus/Bowel obstruction 6=Fistula 7=Diarrhoea 8=Abdominal collection 9=Frequency/Urgency 10=UTI 11=Other	Description of complication B	Grade of complication B: 1=Grade I 2=Grade II 3=Grade IIIa 4=Grade IIIb 5=Grade IVa 6=Grade IVb 7=Grade V	Grade of Highest complication: 1=Grade I 2=Grade II 3=Grade IIIa 4=Grade IIIb 5=Grade IVa 6=Grade IVb 7=Grade V	Total number of complications
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
15										
16										
17										
18										
19										
20										
Automatic numbering that aids sorting the data	This could be a hospital number, patient name etc.	This allows a quick calculation of the overall complication rate. (e.g. see below)	Free text comments	Classification grade of the associated complication. If >1 complications are present the highest grade of complication should be used for statistical purposes	Free text comments	Classification grade of the associated complication. If >1 complications are present the highest grade of complication should be used for statistical purposes	The highest classification grade should be documented here for statistical purposes	The total number of complications may be a useful numeric parameter when predicting outcomes	

ANNEX 7

Hospital Dr. Josep Trueta, Av. França s/n 17007 Girona	HOJA DE INFORMACIÓN	Evaluación de las complicaciones del cierre precoz de la ileostomía protectora: un ensayo clínico controlado aleatorizado.

TÍTULO DEL ESTUDIO: Evaluación de las complicaciones del cierre precoz de la ileostomía protectora: un ensayo clínico controlado aleatorizado.

INVESTIGADORES: Dr. Franco Marinello, Janire Rojo Zarragoitia

LOCALIZACIÓN: Hospital Universitari Doctor Josep Trueta

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.

DESCRIPCIÓN DEL ESTUDIO

El objetivo principal de este estudio es comparar las complicaciones del cierre precoz (2 semanas) de la ileostomía de protección versus la tardía (3-6 meses). Esto significa que los participantes serán asignados aleatoriamente a uno de los dos grupos, y a usted se le facilitará un test de calidad de vida antes de la cirugía del cierre, y 1 y 12 meses después. Aparte de eso, el cirujano llevará a cabo un seguimiento de las complicaciones que puedan surgir después de la cirugía.

Por lo tanto, usted será seguido y visitado durante un año tras la operación de cierre de la ileostomía. 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 ha sometido a una resección de un tumor rectal asociado a una ileostomía de protección y por lo tanto temporal. Además, cumple los criterios de inclusión de este ensayo clínico.

PARTICIPACIÓN VOLUNTARIA

Su participación en este estudio es totalmente voluntaria. Es usted libre de decidir si quiere formar parte de él o no, y puede abandonar el mismo en cualquier momento y por cualquier razón. La decisión que tome no afectará el tratamiento y asistencia sanitaria que merece y necesita. Si decide participar en el estudio tendrá que firmar el consentimiento informado después de leer esta hoja de información.

A pesar de ser voluntario, usted podrá ser excluido del estudio si los investigadores lo consideras estrictamente necesario porque en un momento del proceso cumple alguno de los criterios de exclusión. En cualquier caso, recibirá a información adecuada de por qué ha sido apartado del estudio en curso.

BENEFICIOS Y RIESGOS EN LA PARTICIPACIÓN DEL ESTUDIO

Su ileostomía temporal debe ser cerrada ya sea en un corto tiempo tras la cirugía de resección del recto y creación del estoma o varios meses después. El procedimiento quirúrgico será igual para los dos grupos. Por lo tanto, el tipo de complicaciones que puedan surgir serán similares, por ejemplo, obstrucción intestinal (0-15%), infecciones de la herida (0-18,3%), fugas anastomóticas (0-8%) o hernias del estoma, entre las más comunes. La tasa de mortalidad es muy baja, entre 0,1-4% en los últimos estudios publicados, sin diferencias estadísticamente significativas entre los grupos de cierre precoz y tardío.

Usted no tendrá que seguir llevando una bolsa de estoma tras esta cirugía, por lo tanto los beneficios del cierre de la ileostomía es evidente en cuanto a la mejoría de la calidad de vida, pero además el objetivo de este estudio es evaluar si se podrían disminuir el número de complicaciones de esta cirugía.

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

Los datos de cada paciente están guardados en una base de datos informatizada y protegida por contraseña. La información será confidencial de acuerdo con la Ley Orgánica Española (15/1999) sobre la protección de datos.

Sólo los investigadores y colaboradores tendrán acceso a esta información recopilada durante el estudio. Su identificación personal no será pública en ningún momento

COMPENSACIÓN ECONÓMICA

Su participación en el estudio no incluye ningún coste adicional y usted no tendrá que pagar los tratamientos recibidos durante el estudio.

CONTACTO: Si tiene alguna duda durante el estudio por favor contacte con los investigadores: Dr. Franco Marinello y Janire Rojo Zarragoitia

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.

Hospital Dr. Josep Trueta, Av. França s/n 17007 Girona	INFORMARTION SHEET	Evaluation of the complications after early closure of derivative ileostomy: a controlled randomized trial

TITLE OF THE STUDY: Evaluation of the complications after early closure of protective ileostomy: a controlled randomized trial.

INVESTIGATORS: Dr. Franco Marinello, Janire Rojo Zarragoitia

LOCATION: Hospital Universitari Doctor Josep Trueta

We would like to provide you with the information about a research that is being carried out in our centre, which you are invited to participate. We would like you to consider this research study and then decide whether or not you wish to take part in it. Please read carefully the following information before decide whether or not to take part.

DESCRIPTION OF THE STUDY

The main objective of this study is to compare the complications after an early closure (2 weeks) of a protective ileostomy versus its late closure (3-6 months). That means that participants will be randomly assigned to one of the two groups, and you will be provided with a quality of life test (QOL)

before the ileostomy closure, and 1 and 12 months after it. Apart from that, the surgeon will assess the surgery complications after the ileostomy closure.

Therefore, you will be followed up during one year after the ileostomy closure. If you need extra visits due to any complication an appointment can be scheduled at any time.

WHY HAVE YOU BEEN INVITED?

You have undergone a rectal surgery and a protective ileostomy, meeting the inclusion criteria for this trial.

VOLUNTEER PARTICIPATION

Your participation in the study is totally voluntary. You are free to decide whether to participate or not and you are able to withdraw the study at any time without any reason. The decision will not affect the treatment or healthcare assistance you deserve and receive. If you decide to participate you will have to sign an informed consent after reading this information sheet.

Despite being voluntary, you can be excluded from the study if investigators consider it strictly necessary because you may meet the exclusion criteria at one point. In any case you will receive a proper explanation why have you been withdrawn from the study.

BENEFITS AND RISKS OF PARTICIPATION ON THE STUDY

Your temporary ileostomy has should be reversed, either soon after the stoma creation surgery or after several months. The surgical procedure will be the same for both groups, so the type of complications of the closure are the same; such as bowel obstruction (0- 15%), wound infections (0-

18.3%), anastomotic leaks (0-8%) and stoma site hernias (among the most common ones). Mortality rates are very low, between 0.1-4% in the last studies, and no significant differences have been found between early and late closure surgeries.

You will not have to wear a stoma bag any longer so he benefits of both an early or late closure in regards to the quality of life are evident. In regards to the complications, the aim of the study is to evaluate if they can be reduced.

RESPONSIBILITY AND INSURANCE

You are insured for any damage you may suffer as a result of your participation on this trial, in accordance with the law.

CONFIDENTIALITY

All patient data is recorded on a password protected computer database. The information will be confidential according to the Spanish Organic law (15/1999) on personal data protection.

Only the researchers and collaborators will be able to access this information and data collected during the study. Your personal identification will not be disclosed.

ECONOMIC COMPENSATION

Your participation in the study will not include any additional cost and you will not pay the treatments received during this study.

CONTACT: If any doubt or problem during the trial occurring during period please contact the researchers: Dr. Franco Marinello and Janire Rojo Zarragoitia

Hospital Universitari Dr. Josep Trueta

Av/ de França, s/n. 17007 – Girona

Thank you for reading this. Try to keep this information sheet until your participation in the study is finished. Any queries, questions or doubts do not hesitate to ask us.

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

ANNEX 8

Hospital Dr. Josep Trueta, Av. França s/n 17007 Girona	CONSENTIMIENTO INFORMADO	Evaluation of the complications after early closure of protective ileostomy: a controlled randomized trial

Hospital Universitari de Girona
Doctor Josep Trueta

CONSENTIMIENTO POR ESCRITO DEL PARTICIPANTE

TITULO DEL ESTUDIO: Evaluation of the complications after early closure of protective ileostomy: a controlled randomized trial.

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, y que puedo retirarme del estudio cuando quiera, sin que ello repercuta en los cuidados médicos y sin dar explicaciones.

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 de los 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: ----------

Fecha: __ __ / __ __ / __ __

Hospital Dr. Josep Trueta, Av. França s/n 17007 Girona	INFORMED CONSENT	Evaluation of the complications of the early closure of a temporary ileostomy: a controlled randomized trial

WRITTEN INFORMED CONSENT FOR THE PATIENT

TITLE OF THE STUDY: Evaluation of the complications of the early closure of a temporary ileostomy: a controlled randomized trial.

I……

Confirm that: have been informed by the investigator about the purpose of the study

- 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 understand that my participation is entirely voluntary and I can withdraw this study any moment I wish, for any reason and without any consequences for the healthcare I receive.
- I give permission to collect my data and analyse it. I have been informed that all my data will be kept confidential.

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

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.

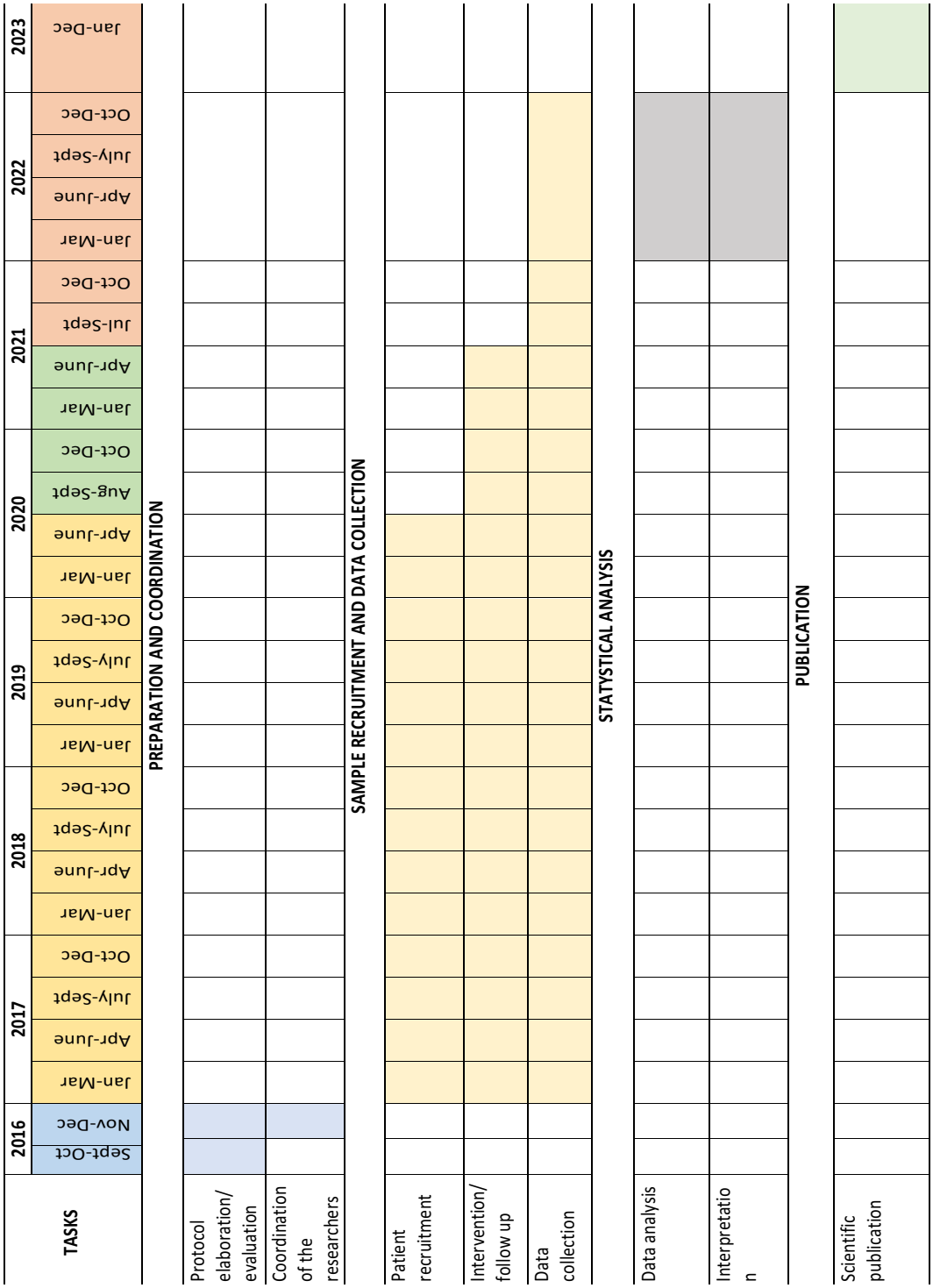
Yes---------- No----------

Signature of the participant: ----------

Signature of the investigator: ----------

Date: __ __ / __ __ / __ __

ANNEX 9


2016
2017
2018
2019
2020
2021
2022
2023
Sept-Oct
Nov-Dec
Jan-Mar
Apr-June
July-Sept
Oct-Dec
Aug-Sept
TASKS
PREPARATION AND COORDINATION
SAMPLE RECRUITMENT AND DATA COLLECTION
STATYSTICAL ANALYSIS
PUBLICATION
Protocol elaboration/ evaluation
Coordination of the researchers
Patient recruitment
Intervention/ follow up
Data collection
Data analysis
Interpretatio n
Scientific publication