TRANSANAL MINIMALLY INVASIVE SURGERY PLUS PREOPERATIVE SHORT-COURSE RADIOTHERAPY VERSUS LAPAROSCOPIC TOTAL MESORECTAL EXCISION IN T2N0M0 RECTAL TUMOURS TREATMENT

A RANDOMIZED CLINICAL TRIAL

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Agraeixo la col·laboració i la predisposició d'en Rafael Marcos i la Carme Carmona per proporcionar-me accés a les dades epidemiològiques del càncer.

Vull donar les gràcies al servei de cirurgia colorectal de l'Hospital Josep Trueta per la seva amabilitat i calidesa. Sobretot, agrair al meu tutor, Pere Planellas, la seva ajuda en tot moment i el seu temps dedicat.

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1. ABBREVIATIONS

cCR	Complete clinical response
CEA	Carcinoembryonic antigen
CEIC	Clinical research ethics committee
COREFO	Colorectal functional outcome
CRT	Chemoradiotherapy
CRM	Circumferential resection margin
CT	Computed tomography
ERUS	Endoscopic rectal ultrasound
FISI	Faecal incontinence severity index
FSFI	Female sexual function index
IIEF	International index of erectile function
LC-CRT	Long-course chemoradiotherapy
LE	Local excision
MRI	Magnetic resonance imaging
MRF	Mesorectal fascia
OS	Overall survival
PET	Positron emission tomography
RR	Radical resection
RT	Radiotherapy
SC-RT	Short-course radiotherapy
TAMIS	Transanal minimally invasive surgery
TEM	Transanal endoscopic microsurgery
TME	Total mesorectal excision

2. ABSTRACT

TITLE: Transanal minimally invasive surgery plus preoperative short-course radiotherapy versus laparoscopic total mesorectal excision in T2N0M0 rectal tumours treatment.

BACKGROUND: Colorectal cancer is the third most incident cancer worldwide and the first at Girona province. Radical resection for rectal cancer treatment, such as Total Mesorectal Excision (TME), is accompanied with high morbidity (permanent stomas, bleeding) and poor long term functional outcome (sexual dysfunction, faecal and urinal incontinence), as it involves the dissection of planes closely related to nervous structures in order to excise the mesorectum. The implementation of screening programs will probably show a shift towards more early staged cancers and TME could be seen as an overtreatment for this group of patients, despite its excellent oncological outcomes that had make TME the gold-standard for surgical treatment of late stage I cancers (T2N0M0).
Transanal Minimally invasive surgery (TAMIS) is a new approach for rectal tumours treatment, with excellent functional outcomes. As a local excision procedure it's much less invasive and aggressive than radical resections, but local recurrence rates are much higher than in TME, as it only removes the tumour confined to the rectal wall, while possible nodal metastases undetected by stage methods can remain within the mesorectum. Neoadjuvant treatments like short-course radiotherapy (SC-RT) combined with TAMIS can be a solution to properly treat these early-staged carcinomas.

OBJECTIVE: This study aims to assess if TAMIS plus SC-RT is non-inferior to laparoscopic TME, regarding overall survival. Results over local recurrences, complication rate, cancer-specific survival, quality of life, sexual function and faecal continence will also be assessed.

STUDY DESIGN AND METHODS: In this multicentre trial, patients with clinical staged T2N0M0 rectal cancer will be randomized between TAMIS plus neoadjuvant SC-RT and laparoscopic total mesorectal excision. A sample of 352 patients will enter into the study through a non-probabilistic consecutive recruitment. Data will be collected with questionnaires and tests, preoperatively and postoperatively in each follow-up appointment. Patients who will undergone the experimental approach will be under an extensive follow-up.

KEYWORDS: rectal cancer; transanal minimally invasive surgery; TAMIS; single incision laparoscopic surgery; natural orifice transluminal endoscopic surgery; short-coursed radiotherapy; SC-RT; neoadjuvant treatment; laparoscopic; total mesorectal excision; TME; overall survival; local recurrence; sexual function; faecal incontinence; morbidity.

3. INTRODUCTION

3.1. BASIC ANATOMY OF THE RECTUM

3.1.1. ANATOMIC LANDMARKS

The rectum includes the last 15-20 cm of the digestive tract before the anal canal, communicating the sigmoid colon (at the third sacral vertebrae level) to the anal canal, across the posterior perineum. It is frontally and by his sides covered by peritoneum in the upper third, only frontally covered in its middle third and without peritoneal covering in its lower third (the rectal ampulla).

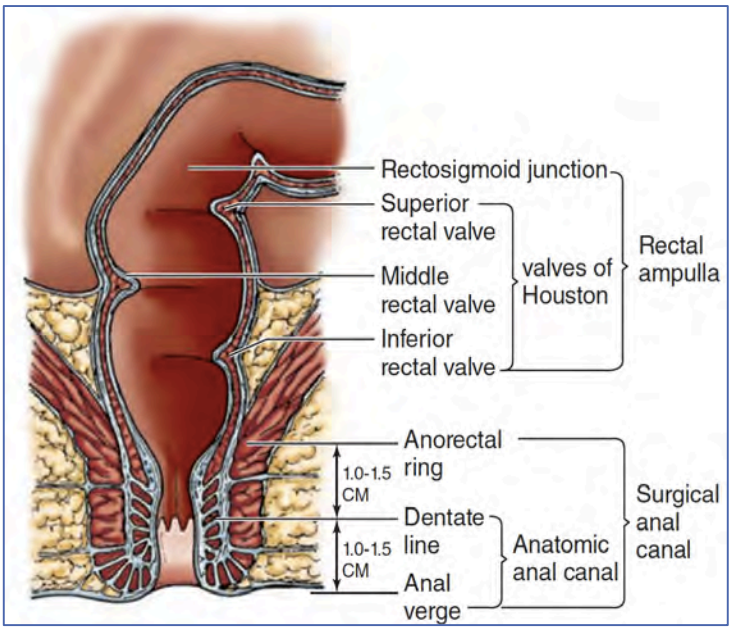

Figure 1. Anatomic landmarks of the rectum and anus. From (3)**.**

Anteriorly we can find the uterine or rectovesical fold (Douglas Pouch) made by the anterior rectal reflection of peritoneum, which contains the urine bladder and feminine genital organs. The Denonvelliers' fascia is a fold of two layers of peritoneum in which the anterior rectum is fixed in men, and separates the rectum from the posterior prostate and seminal vesicles.

Exteriorly, the rectum does not have haustra or omental appendix, and it's quite angulated in its rectosigmoid junction, forming a natural barrier to the stool pass. The mucosa of rectum is similar to colonic one: it is formed by cylindrical epithelium with intestinal glands, lamina propia and muscularis mucosae. It is transversally crossed by the transverse folds of rectum (Houston's valves), which are usually three (superior, mild, inferior), being the Kohlrausch's valve (or mild fold) the most usually found, and the one that limits digital rectal examinations.

3.1.2. VASCULAR SUPPLY

Arterial irrigation of rectum is made by 3 main branches: superior rectal artery (terminal branch of inferior mesenteric artery), mild rectal arteries (branches of intern iliac artery) and low rectal arteries (branches of internal pudendum artery).

Venous drainage of rectum is tributary to portal and inferior cava veins. Pelvian rectum blood is drained by superior rectal veins, part of the inferior mesenteric vein system, which finally joins the portal vein. Mid rectal vein, which is tributary to the internal iliac vein, drain the blood from the rectal ampulla. Inferior rectal veins drain the lower anal canal and are tributary of pudendal veins and finally of the internal iliac vein.

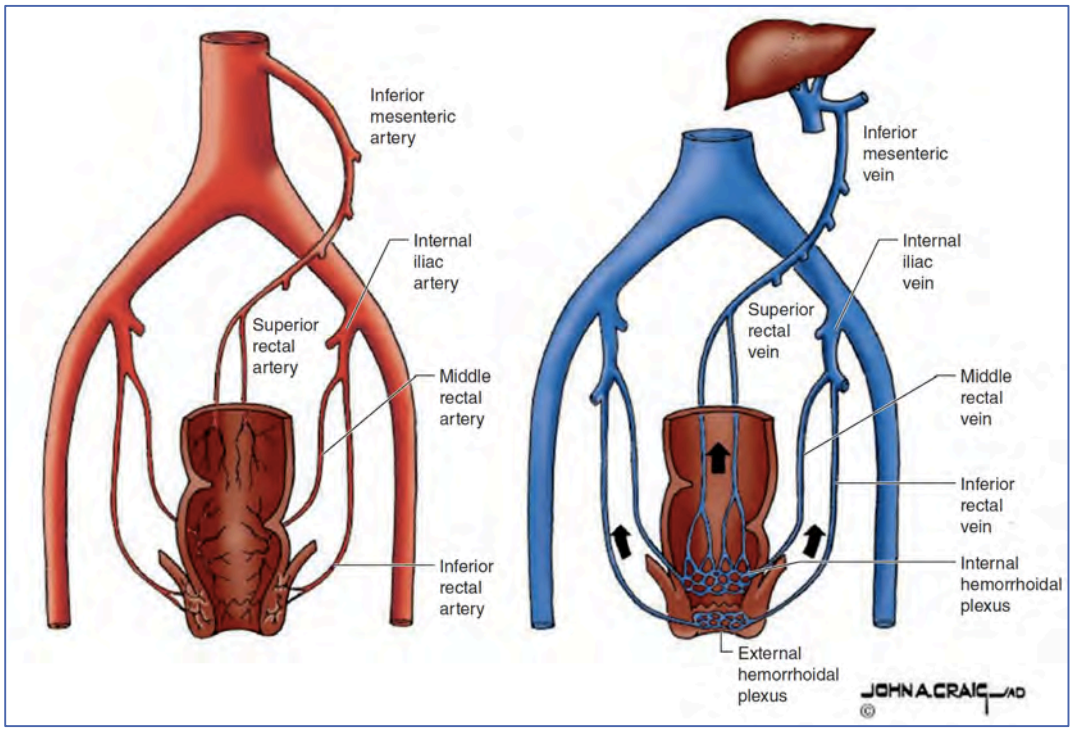

Figure 2. Arterial and venous relationships of the rectum. From (3).

3.1.3. LYMPHATIC DRAINAGE

Lymphatic drainage of the rectum above the dentate line is made by the internal iliac and inferior mesenteric ganglia. Most of the rectal lymph nodes are located within the proximal two-thirds of posterior mesorectum. These lymph nodes are usually little, 80% are smaller than 3 mm in diameter (1), making them difficult to identify without special histopathological preparation and even in image staging.

3.1.4. INNERVATION

The pelvic autonomic nerves consist on the hypogastric, sacral and inferior hypogastric nerves. The first one has sympathetic fibers, which are originated from L1-L3. The sacral nerves have parasympathetic fibers and come from S2-S4, join the hypogastric nerves lateral to the rectum to form part of the pelvic plexus, by ending at the periprostatic plexus. Inferior hypogastric nerve plexus is formed by sympathetic and parasympathetic nerve fibers, and forms a rhomboid on the lateral pelvic sidewall; its fibers innervate the rectum, the bladder, ureter, prostate, seminal vesicles, membranous urethra and penis body.

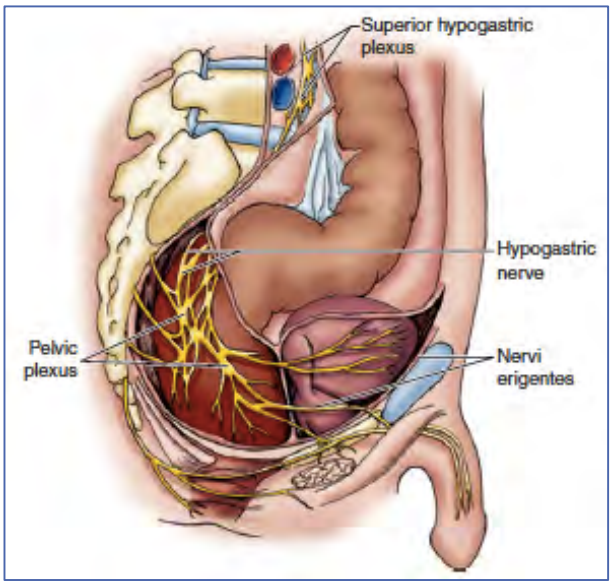

Figure 3. Nerves and plexuses of pelvic area. From (3)**.**

Injury of the pelvic autonomic nerves can cause impotence, loss of normal defecatory mechanisms and bladder dysfunction.

(2–4)

3.2. RECTUM CANCER

3.2.1. EPIDEMIOLOGY

Colorectal cancer is the third cancer in incidence worldwide, with 1,360,000 new cases every year (third most common cancer in men with 746,000 cases and second most common in women with 614,000 cases), which accounts for the 9.7% of cancer cases. Of these patients, 694,000 die annually (8.5% of the total deaths by cancer). (5)

At Girona's province, colorectal cancer had a mean incidence of 518 cases per year in the period from 2010 to 2012. If we add to colorectal cancer the cases of anus cancer (a mean of 6 per year), it becomes the second most incident cancer in each sex and the most incident cancer at Girona province if we sum up both sexes. Of these median of 518 cases per year at Girona province, 160 account for rectal cancer (30.88%). The mean incidence from this period is 102 cases per year in men and 58 in women, with a mean age at diagnostic of 67.9 and 69.4 years respectively. (6)

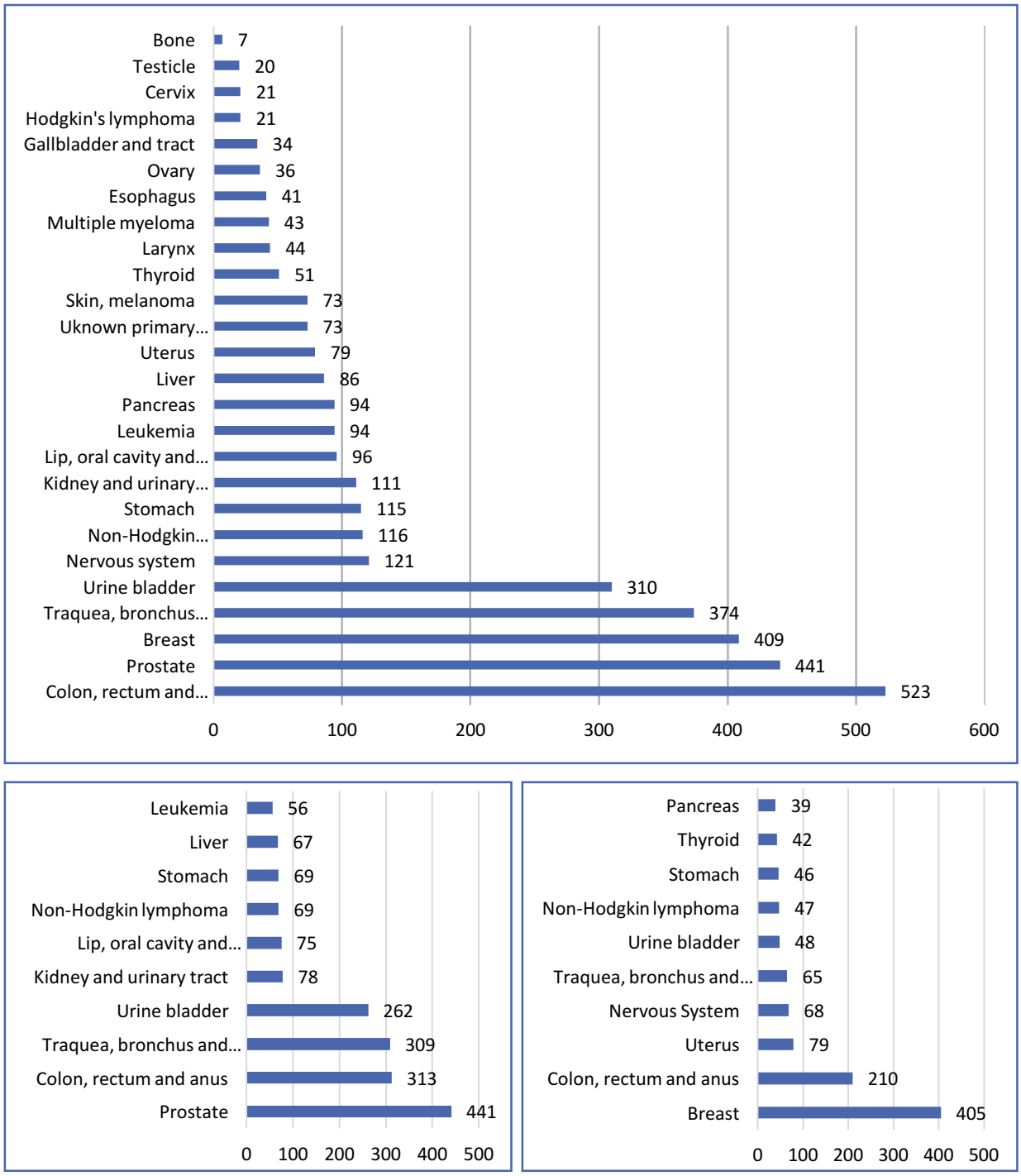

Figure 4. Cancer anual mean incidence in both sexes (up), men (left-down) and women (right-down), Girona province, 2010-2012. From (6).

Data of each colorectal cancer at 2011 was supplied by the Cancer Register of Girona (*Registre del Càncer de Girona, UERCG)*. This data included the staging of each colorectal cancer at Girona province with available data. 547 cases of colorectal and anal cancer were diagnosed at 2011, being more incident in men (340 cases, 62.2%) than in women (207 cases, 37.8%). Of the total cases, they were mostly diagnosed at IIa and IIIc stage (97 cases each), being the stage IVc the less prevalent with one case (*See Annex I*).

Counting each anatomical zone, colon cancer was the most frequent with 418 cases diagnosed. Our cancer of study, rectal cancer, was the second most incident, with 123 cases (23%), and was mostly diagnosed at stage IIIb (40 cases, 32%).

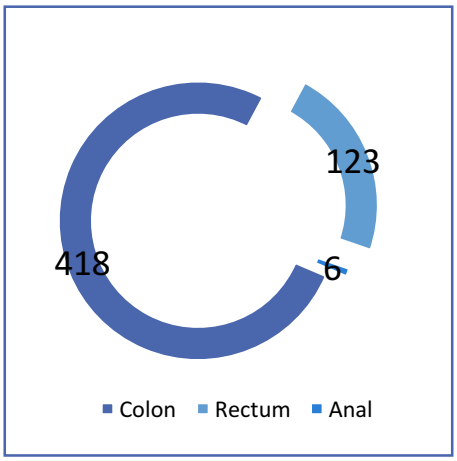

Figure 5. Incident cases of all cancers, by localization. Girona province, 2011. Data supplied by Registre del Càncer de Girona.

This project willing is to propose solutions about T2N0M0 rectal cancer treatment, so further characterization of this cancer stage was made. T2N0M0 tumours are part of stage I cancer as the *American Joint Committee on Cancer* (*AJCC)* establishes. Of the 22 stage I rectum tumours diagnosed at 2011, 13 were cT2N0M0, with a mean age at diagnosis of 75 years (range from minimum of 49 years to a maximum of 93 years). Of these, 3 were women (23,1%) and 10 were men (76,9%).

Clinical staging of rectal cancers was later compared to pathological staging and only 5 of these cancers were pT2N0M0 (38,5%), the other had lower or bigger T (T1, n=3; T3, n=2; T4a, n=1) or/and had nodal metastases (N1a, n=1; N1b, n=1). This data is consistent with some of the concerns that later will be discussed regarding the difficulty of T2N0 correct staging.

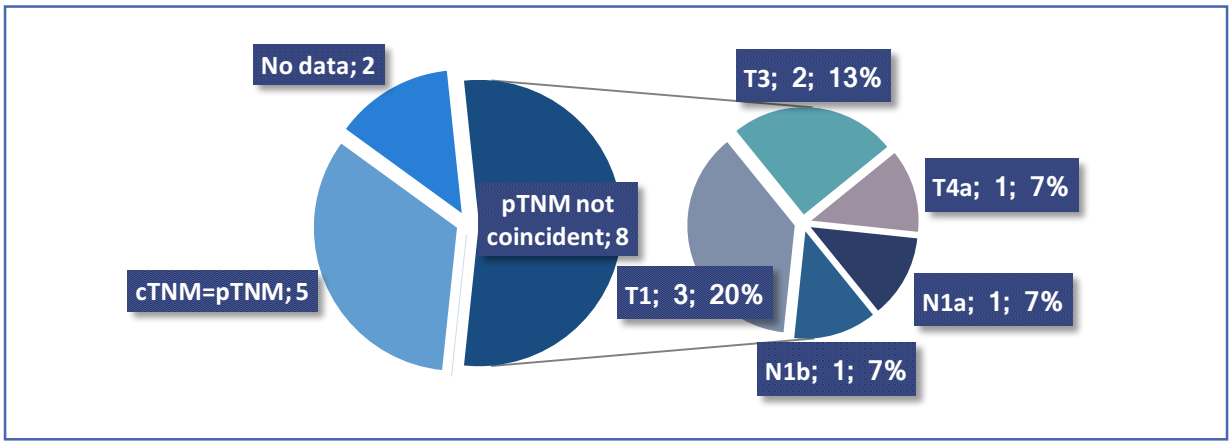

Figure 6. Rectum cancer coincidence of clinical and pathological stage. Data supplied by Registre del Càncer de Girona.

3.2.2. SYMPTOMS

Colorectal cancer symptoms have low specificity. The most common are:

- Changes in depositional habits.
- Blood on stools (dark or fresh-red).
- Diarrhoea or constipation.
- More liquid stool or with less caliber than usual.
- Rectal pain.

- Loss of weight without an apparent cause.
- Asthenia.
- Anaemia.
- Fever.

Usually, these symptoms can be simultaneously present as an anorectal syndrome, with rectal urgency, tenesmus and diarrhoea with blood and mucus. Tenesmus is usually indicative of a large tumour (stage II or III) and possibly fixed. If there is pain with defecation, anal sphincters are probably involved. Also, if cancer trespasses the rectal wall can cause symptoms by invasion of proximal organs, such as vesical invasion with haematuria and urinary frequency; if a rectovesical fistulae is established, pneumaturia and recurrent urinary infections are common problems.

Symptoms of distant metastases can be seen, such as jaundice (liver metastases), bone pain (skeletal metastases), dyspnoea (pulmonary dissemination) and ascites (peritoneal carcinomatosis).

(3,7)

3.2.3. STAGING

(See Annex II for AJCC's TNM and staging tables)

3.2.3.1. TEST AND IMAGING METHODS

Diagnosis is based first on physical examination, including digital rectal examination and a complete history.

- **History**: *see 3.2.2. Symptoms*. Other details, as preoperative sexual function are important to be asked, in order to explain to the patient the possible postoperative diminution of sexual function. Comorbidities such as cardiac, pulmonary and renal ones must be assessed before surgical interventions. Predisposing factors or family history are also important to be detailed.
- **Physical examination**: Digital rectal examination is capital as it is an available and without-cost test that informs tumour size, mobility, fixation, location, relationship to the sphincter mechanism and distance from the anal verge.

  A complete pelvic examination must be assessed in women, to determine vaginal invasion or spread to the ovaries; extension into the prostate and/or bladder must be examined in men. Rigid sigmoidoscopy with biopsy is used for histopathological examination, and also allows us to know proximity to anal verge, circumferential volume, orientation, position and relationship to near structures (vagina, prostate, peritoneal reflection).

- **Complete colonoscopy**: it is very important to be carried on, because 2-8% of the times a synchronous cancer is present. Colonoscopy can help also in assessing localization, volume, in biopsies intake and polyps' excision.
- **Laboratory studies**: complete blood count, electrolytes, liver enzymes (can be normal when there are small hepatic metastases), CEA (preoperative CEA levels greater than 5 ng/ml signify a worse prognosis; postoperative CEA levels non-normalized after surgical resection are a sign of persistent disease; also, if CEA levels are high in controls after a 'curative' resection, we must suspect of recurrent disease).

DISTANT STAGING

Distant staging assesses the extent of metastatic disease. Multiple modalities are used in distant staging. Chest X-ray or computed tomography scan (CT scan) can be used for thoracic distant dissemination, but also abdominal CT scan, magnetic resonance imaging (MRI) or ultrasound of liver and abdomen.

Because of its availability and fast time-of-use, CT is usually the initial staging modality. It can assess in one examination all the abdomen, pelvis and chest.

LOCAL STAGING

For local staging (assessment of mural wall invasion and nodal status) **endoscopic rectal ultrasound (ERUS)** is very useful to determine the depth of tumour invasion, with 69-94% of accuracy. In T2 lesions (because of the difficulty to difference peritumoural inflammation or transmural tumour infiltration) and in bulky, distal or stenotic lesions (because of the inability to overpass the lesion) ERUS can have some difficulties. In the assessment of nodal metastases, rectal MRI, CT and PET/CT are more reliable techniques.

Rectal MRI can be used for all tumours, from the earliest to the latest stages, but distinguishing T2 from borderline T3 tumours is also a common problem. MRI is usually used for assessing the surgical planning and prognosis, by measuring the distance of the tumour from the mesorectal fascia. Comparing ERUS to MRI, ERUS is more specific, but both methods have similar high sensitivities. This tests help on the delimitation and selection of surgical techniques and extent of the surgery.

- At Hospital Universitari Doctor Josep Trueta de Girona, MRI is always done for assessing the local staging and ERUS is recommended to be carried also, especially for assessing the T.

Positron emission tomography-CT (PET-CT) measures and shows the metabolic changes in cancer cells. Using marked glucose (fluorodeoxyglucose) PET-CT can detect reliably colorectal cancer, but not

its depth of invasion. Because of his cost, high radiation exposure and lack of wide availability, PET-CT is usually reserved for identifying patients in which we suspect recurrent lesions after a CEA rinse.

(2,3,8–10)

HISTOPATOLOGICAL

Once the surgery is done, the surgical specimen is examined. Histopathological examination should include surgical specimen with proximal, distal and circumferential margins; also, regional lymph nodes if the specimen includes. Vascular and nerve invasion should be evaluated. Histologic grade can be assessed both in surgical specimen and in biopsy.

AJCC establishes different assessments on histopathological examination, as can be seen in *Annex II*.

3.3. HISTORICAL BACKGROUND AND CURRENT SITUATION ON SURGICAL RECTAL CANCER TREATMENT

3.3.1. ANTIQUITY AND EARLY ATTEMPTS

Rectum cancer has been historically difficult to treat. Since the Ebers medical papyrus (1700 B.C), there have been multiple approaches to treat and cure rectal injuries and diseases. Giovanni Morgagni, at 1739, and Henry Pillore of Rouen (performing the first colostomy at 1776) did their attempts on eighteenth century, but they didn't had success in saving their patients' lives. Starting at 1826, Jacques LisFranc performed five successful resections by everting the rectum and resecting part of it. (11)

At the second half of the 19th century, a big amount of surgeons tried new techniques: Vogel revised more than 1500 cases of resections (from surgeons as Allingham, Billroth, Czerny, Kocher and Kraske) and found that perioperative mortality rate was 20.9% and from the survivors, 80% experienced some local recurrence. (12)

3.3.2. MILES' ABDOMINOPERINEAL RESECTION

A big change occurred at 1908, when William Ernest Miles published on the *Lancet* his findings about the lymphatic spread and noticed that a more aggressive procedure involving the mesenteric lymph nodes could have better outcomes.

His radical abdominoperineal resection involved the rectum and sigmoid, with the mesorectum and the common iliac lymph nodes (Figure 7). He also removed the elevator muscle of anus and made an abdominal colostomy in his procedures. His mortality rate was decreased from a 42% of his original findings to a final 9% in his later papers (due to the advent of anaesthetical and transfusional advances), with a recurrence rate of 29,5%, which was and overall excellent reduction in recurrence and operative mortality, but with a big morbidity in exchange. Nowadays it is still being used, for patients with very low rectal cancers affecting the sphincter or with very poor sphincter's function. (11,12)

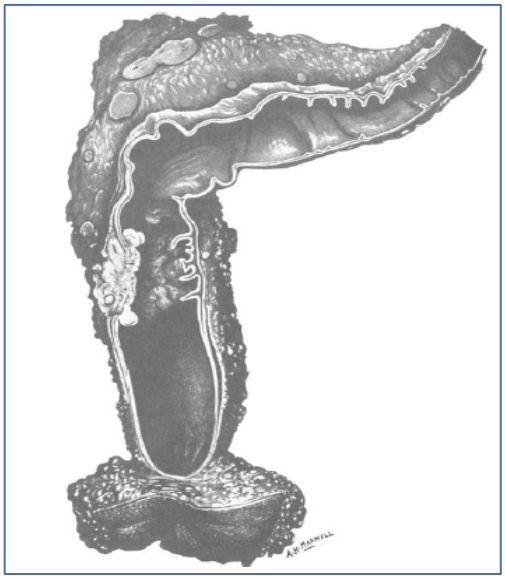

Figure 7. Specimen after Miles' abdominoperineal resection. Lange MM, Rutten HJ, van de Velde CJH. One hundred years of curative surgery for rectal cancer: 1908-2008. Eur J Surg Oncol. 2009;35(5):456–63.

3.3.3. HEALD'S TOTAL MESORECTAL EXCISION

1982 was the year when R.J Heald bring the total mesorectal excision (TME) to light. Using a full length abdominal incision from the xiphisternum to the pubis, he traced carefully a plane (later named by himself the 'Holy Plane') around the rectum, the tumour and all mesorectum (Figure 8), avoiding the digital extraction of the tumour and conserving somatic structures as autonomic nerve plexuses (13). In 1986, he published in the Lancet his total series of 115 patients (7.5 years of length) where he performed TME with a 'curative' surgical intention. The original procedure was applied to his patients, demonstrating that it was surgically possible to excise the mesorectum intact conserving other structures. (14)

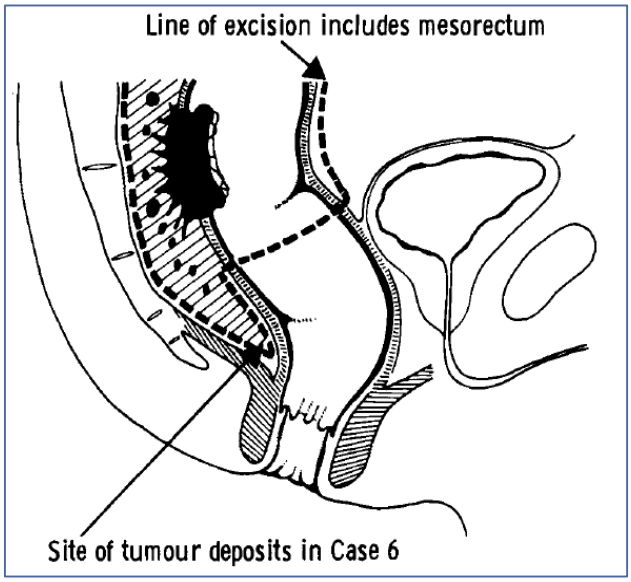

Figure 8. Heald's diagram on TME plane, from (13)**.**

With his findings he reduced the need for abdominoperineal resections, and due to a bigger safety margin left distal to the tumour growth, sphincteral function was better preserved. It was a revolution in terms of better anastomotic and operative result. But the most important thing was his impressive rates of postoperatively mortality (2.6%) and local recurrence at 5 years (3.7%). Heald claimed that

his good results lay in two major findings: the concentration by one surgeon on the technique, and the finding that the **early distal spread of rectal cancer is usually confined to mesorectal tissues**. (12–15)

Later, with the advent of laparoscopic approaches, TME has been performed this way, and it seems to have even better outcomes, as the 2015 COLOR II trial states: Laparoscopic TME is compared to open TME and no differences are seen in local recurrence rate at 3 years (5.0% both groups) and disease-free survival (74.8% vs 70.8%)(16). In fact, the superiority of laparoscopic TME vs open TME is shown in a systematic review of Cochrane library (which includes 14 trials reporting 3528 patients): laparoscopic-TME is non-inferior versus open TME in disease-free survival at 5 years, overall survival, local recurrences, circumferential resection margin positivity, 30-day morbidity and is better in reducing length of hospital stay, wound infection, bleeding (and transfusion requirement), analgesia requirements, and time to first defecation (17). But, in 2016 the ACOSOG Z6051 trial failed in his objective of demonstrating that laparoscopic-assisted TME was non-inferior to open resection in pathological outcomes, which were used as subrogate variables; clinical oncologic outcomes (local recurrence and overall 5-years survival) are pending. (18)

Due to his good outcomes as a curative surgery, TME has become the surgical gold-standard technique in late stage I (T2N0M0) (Figure 9) and locally advanced rectal cancers allowing a radical resection for a better survival (specially in combination with adjuvant therapy). (19)

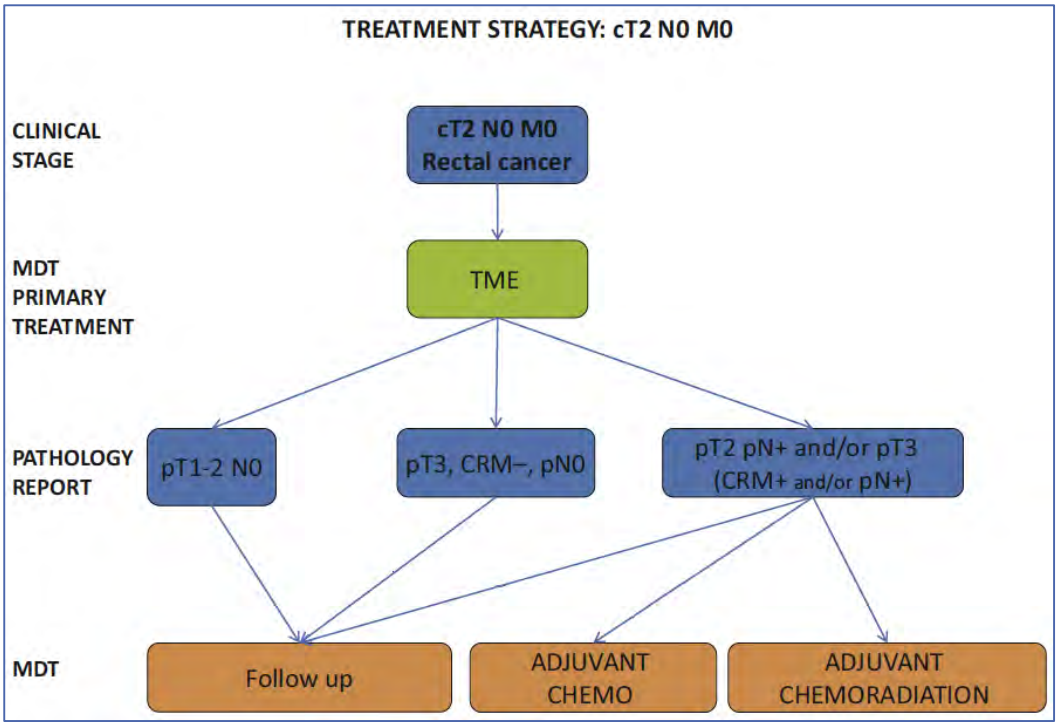

Figure 9. Treatment strategy for cT2 N0 M0. From (19)**.**

COMPLICATIONS RELATED TO TME

Although its good oncological outcomes, morbidity rates are still high, even with the improvement since the first series. Problems such as permanent stomas, anastomosis leakage, sexual dysfunction, faecal and urinary incontinence has been assessed.

Derivative stomas, usually ileostomies (**diverting loop ileostomies**), are used after resections with anastomosis as TME, to protect against an anastomotic dehiscence. The lower the anastomosis, the higher rate of anastomotic dehiscence, so anastomosis around 5 cm or less from the anal verge are always associated to defunctioning stomas that later should be closed. Around a 19% of the primary stomas are finally not closed during follow-up, becoming permanent stomas (20). Postoperative complications, age over 70 years, anastomotic-related complications and tumour recurrence are some of the factors related to stoma final non-closure and the median time to stoma reversal can reach 7.5 months (20,21). Long-term diverting loop ileostomies are related to complications, the most frequent are dermatitis (25%), leakage (18.2%), parastomal hernia (9.1%), peristomal abscess (4.5%) and stenosis (4.5%) (22). Also, stoma closure is related to morbidity and even a small risk of mortality (0.7%). The overall complication rate is around 20% and reoperation is needed in 8% of patients. Small bowel obstruction is the most frequent complication (6.5%); other complications include anastomotic leakage (4.3%), pneumonia (3.6%), urinary tract infection (3.6%), dehydration (2.2%) and intraabdominal abscess (2.2%). (21)

In an exhaustive review (23), major surgical excisions of rectum adenocarcinomas including TME from 1990 to 2008 are analysed. The aggregate **wound infection** rate was 7%, the **anastomotic leak** rate was 11%, the **pelvic sepsis** rate was 12% and the **postoperative death** rate was 2%. Due to the disparity of studies reviewed, some data as **faecal incontinence** results were not fully comparable but pad requirement can be as high as 63% in some studies, and faecal incontinence severity index can reach 31-40 in others[1]. In another review of 2011 sexual function is reviewed in more than 33 articles (24). **Sexual dysfunction** incidence ranged from 23%-69% in men to 19%-62% in women. The study final conclusion states that 'sexual function appears to be poor in patients with rectal cancer and patients with rectal cancer may be informed of the impact that oncological treatment can have'.
Another important fact is that there is more data about men than women, even though, elderly females scored significantly worse in faecal incontinence quality of life subscales of coping and depression than young females and elderly males. (25)

[1] Faecal Incontinence Severity Index (FISI). It assesses the faecal incontinence based in the four types of stool leakage (gas, mucus, liquid and solid) and in five frequencies (one to three times per month, once per week, twice per week, once per day, and twice per day (26). Punctuations higher than 30 are seen as important impairment on quality of life (27).

3.3.4. LOCAL EXCISION

LE is a group of surgical procedures in which tumour removal is done cross anal verge, with theoretically lesser impact in rectal and anal function. These techniques are thought to allow a tumour access with less comorbidity and better quality-of-live outcomes, as the surgical specimen is much smaller, there is no need of mesorectal planes dissection (avoiding potential damage to nervous structures), there is no anastomosis and no derivative stomas are required. Instead, it can only offer a curative resection in tumours confined to the bowel wall, as it is only removed the rectal wall and not all the potentially invaded surrounding tissues like the mesorectum and lymph nodes (Figure 10). For that, local excision procedures are nowadays only feasible for early stage cancers and benign tumours.

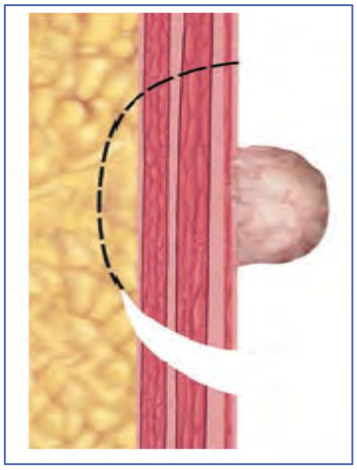

Figure 10. Full-thickness excision of rectal wall, wih little mesorectal fat. From (3).

Two LE procedures will be revised: **Transanal Endoscopic Microsurgery (TEM)** and **Transanal Minimally Invasive Surgery (TAMIS)**.

TRANSANAL ENDOSCOPIC MICROSURGERY (TEM)

TEM was first described in 1983 by Buess as a method for removing polyps and tumours 'in the whole rectum through the anus' (28). A 4-cm-diameter rigid rectoscope is introduced through the anal verge; then, rectal distension is created with CO^2. Patient position depends on the tumour location, so the patient is placed in order to have the tumour visible at the lower part of the rectoscope. (29)

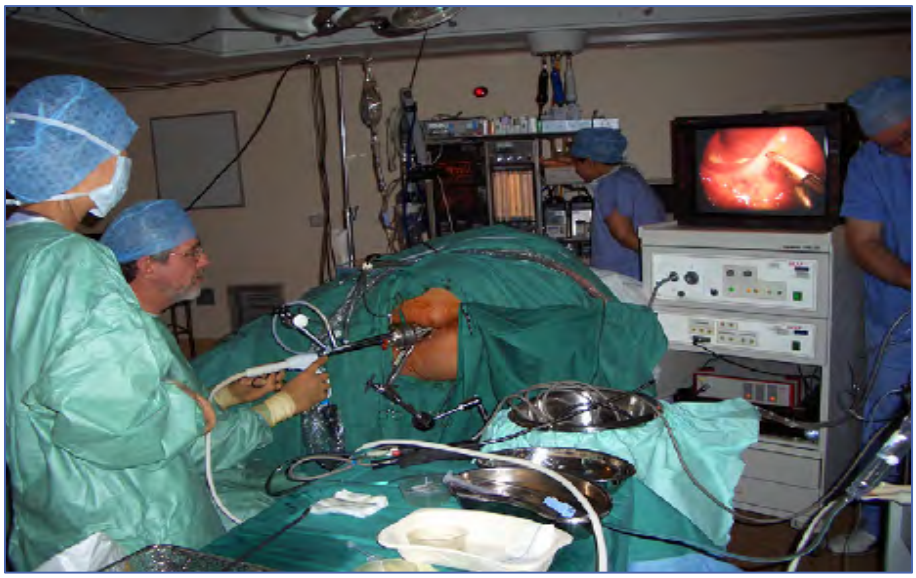

Figure 11. TEM procedure. Sun Myint A, Grieve RJ, McDonald AC, Levine EL, Ramani S, Perkins K, et al. Combined modality treatment of early rectal cancer: the UK experience. Clin Oncol (R Coll Radiol) 2007 Nov;19(9):674–81.

When the tumour is localized, a full-thickness incision of the rectal wall is made around the tumour, keeping a safety margin. Once removed, the defect is usually closed with sutures. Nowadays TEM is an established approach which offers a stable operating platform with magnified stereoscopic view and offers an action range from up to 20 cm. (30)

TRANSANAL MINIMALLY INVASIVE SURGERY (TAMIS)

TAMIS was conceived as a hybrid between TEM and single-port laparoscopy during 2009, by Sam Atallah, Matthew Albert and Sergio Larach. It emerges as a solution to TEM's slow adoption in its more than 20 years, which is caused by two problems: the first, it's steep learning curve; the second, the big amount of money needed to buy such and specialized instrumentation. (31)

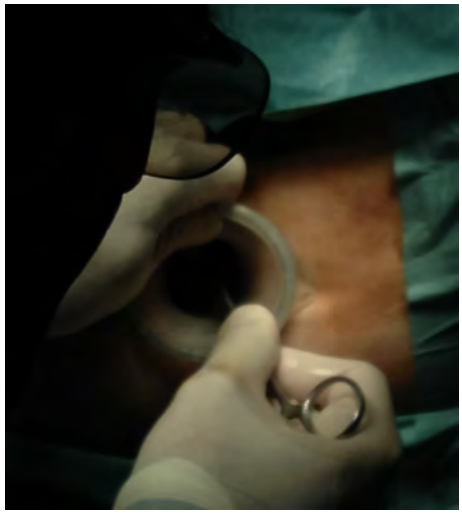

Figure 12. *GelPOINT®* access channel, made of a flexible thermomalleable material, which fits into the anal canal.

For TAMIS, a single-incision laparoscopic port is used (*SILS™ Port, Covidien, Mansfield, MA, USA* or *GelPOINT® Path, Applied Medical, Rancho Santa Margarita, CA, USA*). It is lubricated and introduced into the anal canal with some manual pressure. There, it can be sutured at two points to allow a better stability. The port is made of a flexible material which is ideal for placement into the anal canal without damaging anal structures (in comparison, in TME it's used a 40-mm rigid rectoscope). Three 5-mm cannulas are attached to the gel external cap. A separated insufflation-dedicate access is available, which is used to establish a pneumorectum after the application. Also, one of the 5-mm cannulas can be exchanged for a 12-mm cannula (31). The upper cannula is used to introduce a high-definition flexible camera from a usual laparoscopic video system which allows excellent vision of surgical field. (32)

The first series of patients who underwent a TAMIS surgery was published in 2010. Over a 3-month period all patients with rectal lesions who were candidates for a transanal excision (patients with benign lesions and early-stage adenocarcinomas like Tis and T1N0 lesions) were offered the option to have TAMIS resection. All resections where successful and the defects were closed by suturing the margins. Four patients were discharged at the next day, and two in 48h. A 67% of the surgeries where done in less than 60 minutes (with a mean operating time of 86 minutes, while in TEM it's of 120-140 minutes). There was minimal bleeding, secondary to the tamponing effect on pneumorectum (which can be as high as 18 mm H^20, higher than venous pressure). Another big difference seen between TEM and TAMIS is its range: TEM cannot access low rectum tumours, but TAMIS can. (31)

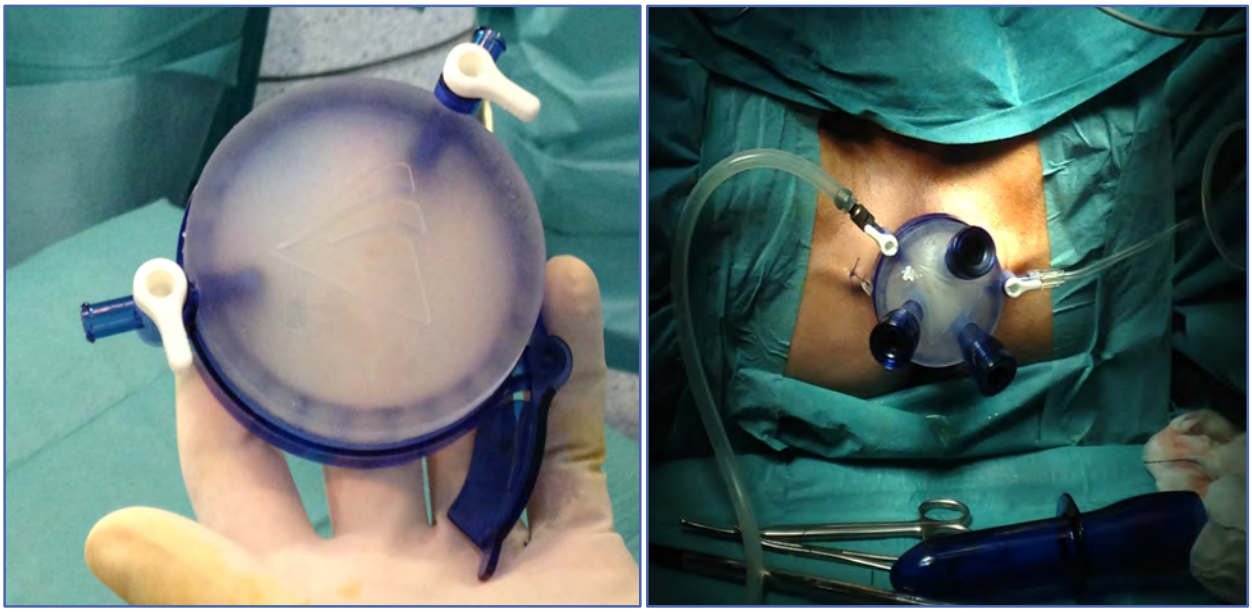

Figure 13. At the left: *GelPOINT®* external cap, which is fixed over the *GelPOINT®* anal part of the path. At the right: external cap final fixation, with valves for CO^2 insufflation and leaking positioned.

After this first contact, TAMIS gained some international interest. A systematic review of 2014 reviewed 390 TAMIS procedures, showing the following data: overall margin positivity rate of 4.36%, tumour fragmentation rate of 4.1%, mean operative time of 76 minutes, minimal blood loss, rate of conversion of 2.31%, average length of stay of 2 days and overall complication rate (Clavien-Dindo classification) of 7.4% (33). TAMIS also seems to improve quality of life and anorectal function based on baseline questionnaires, showing an improvement of continence in 88% of the patients with pre-existent impaired anorectal function and not affecting it in 83% of the patients without preoperative impairment (34,35). Based on anorectal manometry, patients who undergone TAMIS performed normal postoperatively (only minimum rectal sensory volume was significantly less) (36) and comparing this results with others of TEM from similar studies, TEM performed significantly worst by reducing the internal sphincter tone (in some cases with endosonography demonstrating a sphincteral rupture), reducing the anal resting pressure at 3 months, reducing the maximum tolerable volume at 3 months and increasing the number of patients with absent rectoanal inhibitory reflexes (37–39). The presence of significant reduction in anal resting pressure is significantly related with the length of operating time (38) and this is gives us a clue of a possible explanation of why TEM performed worse than TAMIS: the rigid 40-mm rectoscope introduced by the anal margin probably impairs and damages the anorectal muscular fibbers by maintaining them distended the full operative time, while TAMIS flexible port doesn't.

Most of times, TAMIS approaches are done under general anaesthesia, but spinal anaesthesia has also been described, with some better possible outcomes: better pneumorectum due to improved rectal wall relaxation, no needing of anal manual dilation and less postoperative recovery time. (40)

Even so, there aren't any studies directly comparing TEM versus TAMIS for assessing which technique has better oncological and quality-of-life related outcomes. There is only one study comparing TAMIS versus TEM (41), in which 10 surgeons with no experience in transanal surgery performed a dissection plus suture task in experimental artificial models, using both techniques (the sequence was randomly given). They later had to give them subjective impression and objective data also was taken. TEM significantly scored shorter procedural and suturing time. As limitations, this data is collected based on a model-based study and not a clinical-situation or real dissections, it is based on one-time experience and also based on people with no experience at all in transanal surgery. Also, it has to be said that in the procedure that they perform worst (suturing time), in real life situations can be avoided by leaving the defect unclosed, without significantly compromising the bleeding or infection rate and significantly reducing the operating time from a median of 90 minutes to a median of 62 minutes, in exchange of a median of 3 more days of antibiotic therapy. (42)

3.3.5. LOCAL EXCISION PROCEDURES AS AN ALTERNATIVE TO TOTAL MESORECTAL EXCISION

Due to its better complications outcomes, LE has been considered as an alternative to classical more-aggressive procedures, as TME, for treating rectal tumours; but it is known that LE alone is associated with worst oncological outcomes such as inferior survival and higher recurrence rates in locally advanced cancers, as LE techniques don't allow a full lymph node sampling; thus, clinical staging has to be done carefully to ensure that no lymph nodes are affected, in order to assess the needing of further adjuvant therapy. Size of nodal metastasis is related to the T stage, and the actual staging methods perform significantly worse with tinier nodal metastasis. For this reason, early stage tumours (T1 and T2) are more likely to have undetected nodal metastasis than pT3 lesions and unremoved nodal disease by LE can cause local recurrence. (43)

Multiple studies have been searching the feasibility of LE as an option to treat T2N0 tumours. Julio Garcia-Aguilar reviewed 82 patients (T1 n=55, T2 n= 27) who were theoretically the ideal candidates for a LE therapy alone because of his good prognostic factors (no blood or lymphatic vessels affection by the tumour, moderate or well differentiated tumours and not mucinous component). Despite that 5-year survival rates after LE were similar to radical surgery, local recurrence rates were 'alarming high' (T1 n=18% and T2=37%) needing rescuing surgeries, so the recommendation was that T2 tumour shouldn't be excised only with LE alone (44). Later studies followed his steps and tried to assess the feasibility of LE (45–47). These studies encouraged LE even without adjuvant therapy for T1N0 treatment, especially in elder patients or patients not suitable for radical resection, **making LE the preferred choice for low risk patients or patients with comorbidities** (19). T2N0 tumours were

referred to have unacceptable oncological outcomes under LE alone, so TME with/without adjuvant therapy remained the gold-standard for T2N0 tumours.

Despite it all, the role of LE is still a controversial topic when we talk about T2N0 cancers. There is some work made which keeps encouraging further studies (48,49). ACOSOG Z6041 is a trial in which patients with cT2N0 rectal cancer staging (by ERUS or MRI) were administered radiation plus capecitabine and oxaliplatin for 5 weeks; after that, they undergone LE (conventional transanal excision or TEM). The study did not achieve its pre-set goal of 3-years disease-free survival by a tiny margin. Some limitations this trial had is that it was non-randomised, it had a small sample (n=79) and a short follow-up (3 years), there were loses in the return of functional assessment questionnaires and it had very restrictive inclusion criteria (tumours smaller than 4 cm in its greater diameter, involving less than 40% of the circumference and located within 8 cm of the anal verge). Another important fact is that 53 patients received the protocolled chemoradiotherapy but the other 26 received another one due to unexpected toxicity of the protocolled one. Even with all this limitation, differences in rates of recurrence and survival between this trial and the results of other studies in which patients were treated with TME instead of LE, are similar; so results were encouraging to keep further studying. (50)

A 2009 paper (51) compares retrospectively data from the *National Cancer Institute's Surveillance, Epidemiology and End Results* (SEER) of patients with stage I rectal cancer (T1-2N0M0) with tumours under 40 mm, from 1988 to 2003. They compare patients who underwent LE[2] alone, underwent LE plus RT, underwent radical resection (RR)[3] alone or underwent RR plus RT, with the aim of comparing usual treatment (RR without RT) versus treatments which include RT, as a way to test the effectiveness of RT as a treatment modality; for that, hazard ratios (HR) were calculated with RR without radiation as the reference. The first problem seen is that the surgical procedures patients underwent are not homogeneous, with several different procedures which theoretically have different outcomes; the second problem is that SEER database didn't differentiate between clinical and pathological staging, and that's a fact that can bias data against the group of surgical procedure plus RT (as RT can reduce a pTNM staging which was clinically higher before). Regarding overall survival (OS) in T2 tumours, only local excision without radiation HR was statistically significant associated with lower OS [HR 1.40 (1.07-

[2] Local excision procedures they include: 'local cancer destruction without pathology specimen (laser surgery, cryosurgery, electrocautery, or fulguration) (0.1%); local surgical excision with pathology specimen (polypectomy, snare, or laser surgery) (10%); electrocautery, fulguration (0.2%); laser ablation (0.02%); polypectomy (2.9%); excisional biopsy (6.5%).'

[3] Radical resection procedures they include: 'anterior/posterior resection, wedge or segmental resection, trans-sacral rectosigmoidectomy, Hartmann's operation, partial proctectomy, partial proctosigmoidectomy, radical resection non specified (52.8%); pull through with sphincter preservation (colon-anal anastomosis) (1.8%); abdominoperineal resection (14.4%); total proctectomy (9.5%); rectal resection non-specified with partial or total removal of other organs (1.6%).'

1.84), p<0,001]; the other results' differences weren't statistically significant, though RR plus RT had a lower HR [HR=0.94 (0.73-1.22), p=0.09] and LE plus RT had higher HR [1.26 (0.95-1.68), p=0.09]. About HRs on cause-specific survival, statistically significant differences weren't observed. In one hand, one possible explanation to lower OS seen in T2 (also in T1), even if it wasn't statistically significant, was that patients with shorter life expectancy or with more comorbidities were more likely to be treated with LE than with RR. In the other hand, as said before, homogeneity of surgical procedures applied wasn't well specified. Also, in 1988, TME wasn't well spread but neither full-thickness wall LE procedures (like TEM): for that, data of RR and LE cannot be compared with today procedures with guarantees.

ADJUVANT AND NEOADJUVANT THERAPY IN RECTUM CANCER

As we have seen above in some of the studies cited, adjuvant and neoadjuvant therapy can be part of rectum cancer treatment:

- **Adjuvant treatment**, usually chemoradiotherapy is reserved to patients with bad prognosis factors after excision, as positive circumferential resection margins or pN+. (19)
- **Neoadjuvant therapy** is used in >cT2 rectal tumours. Preoperative short-course radiotherapy (SC-RT) is usually reserved to cT3 tumours without nodal involvement (stage IIa), whereas patients staged from IIb to IIIc are preferably treated with preoperative long-course chemoradiotherapy (LC-CRT). (9,19,53)

Table 1. SC-RT and LC-CRT schemes. (9,52)

Short-course radiotherapy (SC-RT)
25 Gy. 5 Gy per fraction in 5 days within a week, followed by immediate surgery (in less than 10 days from the last radiation fraction).
Long-course chemoradiation (LC-CRT)
45-50.4 Gy. 1.8-2 Gy per fraction (6 weeks) with concurrent leucovorin. Concomitant 5-fluorouracil bolus on the first and last 3 days of radiation therapy are administered. Capacitabine schemes have also been used.

The Swedish Rectal Cancer Trial (SRCT) is one of the biggest assessments of SC-RT effectivity on rectal cancer treatment. From 1987 to 1990, 1168 patients from stage I to stage III were randomly assigned to preoperative radiotherapy (SC-RT) followed by surgery within a week or were assigned to surgery alone. Until 2001, patients were followed up, with a total length of follow up of 13 years. Overall survival was found significantly better in patients who received SC-RT (38% vs 30% in surgery alone group, p=0,008); also, cancer-specific survival at 13 years was better (72% vs 62%, p=0,04). Analysing each stage, in spite of better overall survival and cancer-specific survival was observed in RT plus surgery group in each stage, only when all the stages were analysed together and in cancer-specific survival in stage I results were significant. Local recurrences were significant lesser in the preoperative RT group (9% vs 26%, p<0,001), and stratified analysing of each group showed significant reduction of

local recurrence in each stage. No significant differences were seen on groups about distant metastases (34% incidence of distant metastases in each group). So, in conclusion, this study shown a **diminution of local recurrence and a higher overall and specific-cancer survival due to preoperative SC-RT**. At the time of the study (1987), TME was not well spread, so the outcomes must be extrapolate carefully to today clinical practice.(54)

As RT can be a possible solution to diminish LE high recurrence rate with further well designed controlled and prospective studies required to assess it, some concerns still outcropping. Could anorectal and sexual functions after neoadjuvant RT and LE be worse than in patients undergone the accepted low anterior resection with TME alone? For answering that question Gornicki et al. (55) used the data from a previous study (56) in which LE (TEM 41,6%, Kraske procedure 2,2%, transanal excision with the use of retractor 56,2%) plus neoadjuvant RT or CRT was tested to 'assess local control after preoperative radiation and local excision and to determine an optimal radiotherapy regimen'. **No differences were appreciated in the severity of the anorectal symptoms**, except for constipation which occurred significantly more in patients treated with TME alone than in those treated with LE plus RT. **Sexual dysfunction in men was significantly less in LE plus RT group** than in the anterior resection alone group (19% in LE group and 41% on anterior resection group, p=0,031); in woman, no differences in sexual function were observed. Overall, the anorectal functions observed were worse than expected as the authors say; some limitations of the study can explain that: first of all, Kraske procedure and transanal excision with the use of retractors are theoretically more anorectal impairing than TEM and they account for more than a half of the LE procedures made; second, the samples were quite small (LE plus RT group, 44 patients; anterior resection alone group, 38 patients). (55)

It's important to talk about Angelita Habr-Gama's works, when we discuss neoadjuvant treatment in rectal cancer. 'Watch and wait' approach is the maximum expression of neoadjuvant treatment in rectal cancer. Between 2006 and 2010, 70 patients affected by rectal staged as cT2-4 or cN1-2 and M0 with tumours located not below 7 cm from the anal verge participate in the study. All patients received neoadjuvant chemoradiation, consisting in 54 Gy of radiation ('45 Gy with daily doses of 1,8 Gy on weekdays to the pelvis and followed by 9-Gy boost to the primary tumour and perirectal tissue'). At the same time, patients received 3 cycles of bolus 5-fluorouracil and 50 mg of leucovorin for 3 consecutive days every 3 weeks. After radiation was completed, 3 more cycles of chemotherapy were done every 3 weeks. Tumour response assessment were performed 10 weeks after radiation completion, and it included digital rectal examination, proctoscopy and MRI, ERUS and/or PET/CT.

Immediate surgery wasn't offered in patients with a complete clinical response (cCR[4]) and no radiological evidence of residual cancer: these patients enrolled a follow-up program (Figure 14). When a cCR status was maintained after 12 months of CRT completion patients where considered as sustained cCRs. One of the 70 patients died as cause of CRT. The remaining 69 patients completed a minimum follow-up of 12 months from CRT completition. Forty-seven patients (68%) had an initial cCR (at 10th week after CRT), and of these, 39 (51%) developed a sustained cCR (cCR sustained after 12 months after CRT). These patient's three-year overall survival and disease-free survival was 94% and 75% with a median-follow-up of 53 months. On the other side, 33 patients (49%) required immediate or salvage surgery, all of them with R0 margins, showing that immediate radical surgery can be avoided and a potential number of patients can benefit of no surgery (57). With other studies carried on by herself synchronously, these results were confirmed, assessing the 'watch and wait' and the surgical rescue of the non-responders ('watch and wait plus salvage therapy') as a tool to import to our pool of treatments, assessing a 94% of local recurrence free survival and allowing organ-preservation in 80% of the patients if an **extensive follow-up is done**. (52,57)

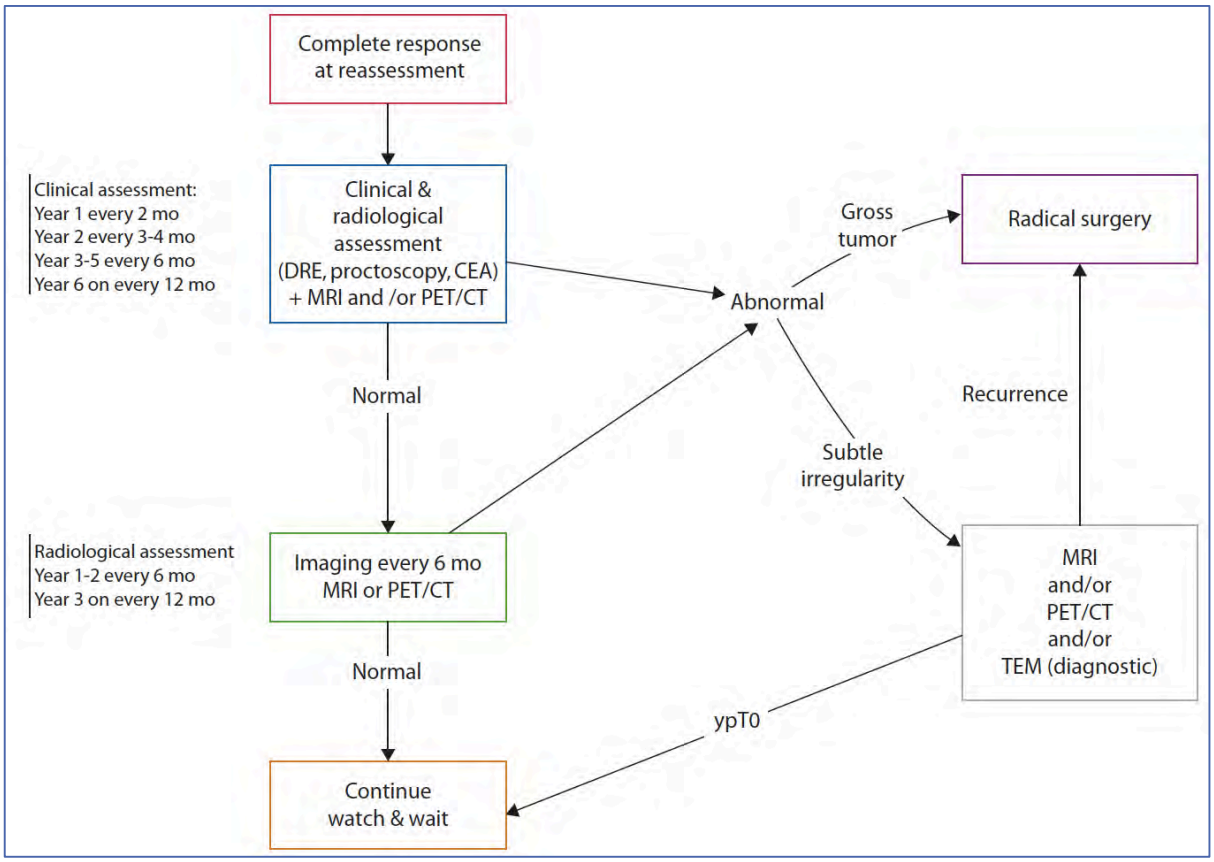

Figure 14. 'Watch and wait' follow-up algorithm. DRE = digital rectal examination.

[4] cCR is defined as absence of residual ulceration, mass, or significant rectal wall irregularity. Radiological features of a complete response were: presence of residual low-signal-intensity areas (on MRI), absence of restriction to diffusion (MRI), absence of residual FDG uptake within the rectal wall (PET/CT). (57)

Between this two different approaches of neoadjuvant treatment (SC-RT or LC-CRT), it seems that not a big consensus is stablished between which is better or whether to use it (19). Bujko et al at 2006 presented the results of his randomized clinical trial in order to know which approach was better (58). A number of 316 patients with T3-4 resectable primary tumour were included, with 48 months of follow-up. Two patients died in the LC-CRT due to cardiac arrest, between the second and the fourth weeks of LC-CRT. The incidence of grade III-IV early adverse effects was 3,2% for the SC-RT and 18,2% for the LC-CRT (p<0,001). Also significantly better compliance was observed for SC-RT (97,9% vs 69,2%). No significant differences were observed on anal sphincter preservation rates, pathological complete response rate, 4-year overall survival, 4-year disease-free survival, late toxicity and the need of a permanent stoma. In order to clarify, a Cochrane Library meta-analysis was made at 2013, reviewing 5 studies. Local recurrence rate was significantly lower in regimes with chemotherapy (OR= 0.39-0.72; p<0,001). No significant differences were observed in five-year overall and disease free survival, but more pronounced grade III and IV acute treatment related toxicity (OR=1.68-10, p=0,002). Summarizing the results, **LC-CRT seems to be more cytotoxic, inducing a bigger complete pathological response,** (OR 3.53, 95%CI 2.12-5.84, p<0,0001), which is translated into a **lower rate of local recurrence, in exchange of more severe toxicity but without significant differences on overall and disease-free survival versus SC-RT.**

3.4. JUSTIFICATION

In order to shed light on the treatment of T2N0M0 rectal neoplasms this protocol is written. Rectal cancer is a current health problem, being the colorectal cancer the most diagnosed in Girona province (6). Bigger local recurrences on T2 rectal cancers are possibly because of the high amount of nodal metastases undetected in preoperative staging. (43)

Based on the evidences and background exposed up to now: on one hand, TME has better survival and lower local recurrences than LE (44,46), inasmuch as it removes all the mesorectal tissue, with small nodal metastases within it (probably undetected by staging methods)(13,14), whereas LE only can remove the tumour confined to the rectal wall (29,31); on the other hand, TME has several complications and impact on quality-of-life, as it involves the dissection of planes which are in close contact to structures as nerves (causing anorectal and sexual dysfunction) and it can require the use of stomas (20–25).

Neoadjuvant treatments (SC-RT and LC-CRT) have shown better results in non-disseminated rectal cancer, leading to a better control and better overall survival respect to surgery alone (52,54). SC-RT is theoretically less toxic but inferior in local recurrence than LC-CRT, while no significant differences

in overall-survival and disease free survival have been assessed.

Adding preoperative SC-RT to LE can be a solution in order to diminish the amount of local recurrences as it can directly treat unseen tiny nodal metastases and can shrink the tumour mass for a further better excision. Data comparing neoadjuvant treatments plus LE versus TME have shown that the differences between the two approaches are minimum or come from retrospective, non-randomized or with small sample studies (48–51), furthermore, the comparisons between the two treatments usually use TEM or theoretically more impairing LE approaches, regarding anorectal and sexual function (55). With the new TAMIS approach, which has shown promising data in overpassing the functional outcomes of TEM and on being more cost-effective (32–36,40), it can change.

In conclusion, due to a shift towards more early staged carcinomas and the high morbidity of TME surgery, there is an increasing need for less invasive treatment approaches with acceptable oncological outcome. After LE alone has revealed to be very risky for T2 tumours, the association of TAMIS with SC-RT could be an oncological safe alternative for radical surgery, with potential improvements in treatment related morbidity, functional outcome and quality of life. This will prospectively be evaluated in this randomised trial.

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5. HYPOTHESIS

5.1. MAIN HYPOTHESIS

Transanal minimally invasive surgery plus a preoperative short-coursed radiotherapy (experimental approach) is non-inferior to laparoscopic anterior resection with total mesorectal excision (standard approach) in overall 5-years survival rate as treatment for patients with rectal cancer staged as cT2N0M0.

5.2. SECONDARY HYPOTHESIS

- The experimental approach is non-inferior to the standard approach in cancer-specific 5-years survival rate as treatment for patients with rectal cancer staged as cT2N0M0.
- The experimental approach is non-inferior to the standard approach in local recurrences rate at 5 years as treatment for patients with rectal cancer staged as cT2N0M0.
- The experimental approach presents lower complications in the postoperative time than the standard approach as treatment for patients with rectal cancer staged as cT2N0M0.
- The experimental approach offers better outcomes to the patients in quality of life after surgery than the standard approach, in patients with rectal cancer staged as cT2N0M0.
- The experimental approach offers better outcomes to the patients in anorectal and bowel function after the surgery than the standard approach, in patients with rectal cancer staged as cT2N0M0.
- The experimental approach offers better outcomes in sexual function after the surgery than the standard approach, in patients with rectal cancer staged as T2N0M0.

6. OBJECTIVES

6.1. MAIN OBJECTIVE

The principal objective is to compare the 5-years overall survival rate between the transanal minimally invasive plus preoperative short-coursed radiotherapy group and the laparoscopic anterior resection with total mesorectal excision group in patients with rectal cancer staged as cT2N0M0.

6.2. SECONDARY OBJECTIVES

- To measure which approach offers better cancer-specific 5-years survival rate to patients with rectal cancer staged as cT2N0M0.
- To compare between the two approaches local recurrences rate at 5 years in patients with rectal cancer staged as cT2N0M0.

- To assess which treatment has a lower rate of complications in the postoperative time in patients with rectal cancer staged as cT2N0M0.
- To define which treatment offers better outcomes to the patients with cT2N0M0 on quality of life during the follow-up after the surgery.
- To review which treatment has better outcomes regarding anorectal and bowel function during the follow-up after the surgery in patients with rectal cancer staged as cT2N0M0.
- To evaluate which treatment is able to maintain a better sexual function after the surgery for patients with rectal cancer staged as cT2N0M0.

7. METHODOLOGY

7.1. STUDY DESIGN

This study is a randomized open-label clinical trial. Each patient will be randomly assigned to one of the two groups in a 1:1 ratio. One group will receive neoadjuvant SC-RT and preferably within a week will undergone LE of the tumour by TAMIS procedure. The other group will be treated with anterior resection with total mesorectal excision by laparoscopic approach. Patients will be followed-up during 5 years in order to assess our stablished objectives.

This study will be carried on in Hospital Universitari Doctor Josep Trueta (Girona), Hospital Clínic de Barcelona (Barcelona), Hospital Universitari Vall d'Hebron (Barcelona), Hospital del Mar (Barcelona), Hospital Universitari de Bellvitge (Barcelona) and Hospital de la Santa Creu i Sant Pau (Barcelona). Hospital Universitari Doctor Josep Trueta will be the reference centre.

7.2. STUDY POPULATION

The population of the study will be every patient with rectum cancer staged as cT2N0M0 in Hospital Universitari Doctor Josep Trueta (Girona), Hopital Clínic de Barcelona (Barcelona), Hospital Universitari Vall d'Hebron (Barcelona), Hospital del Mar (Barcelona), Hospital Universitari de Bellvitge (Barcelona) and Hospital de la Santa Creu i Sant Pau (Barcelona), starting at the day of this project approbation

7.2.1. INCLUSION CRITERIA

- Patients with rectal cancer staged as cT2N0M0, using at least rectal MRI for local staging.
- Patients aged from 18 to 80 years.
- Patients who are able to understand and answer the questionnaires by themselves.
- Patients who have signed the Informed consent form.

7.2.2. EXCLUSION CRITERIA

- Patients not able to undergo surgery due anaesthetical risk.
- Patients with prior pelvic irradiation.
- Patients with tumoral affection of anal sphincter.
- Patients with tumours not excisable by TAMIS: clinically staged tumours bigger than 4 cm or affecting the whole rectal circumference.
- Patients not able to understand and answer the questionnaires.
- Patients with possible high future difficulties to attend control meetings.
- Patients with presence of a synchronous cancer.
- Patients with a short life expectancy due to comorbidities: patients with ASA IV or higher.[5]

7.3. SAMPLING AND SAMPLE SIZE

A consecutive and non-probabilistic sampling will be done, involving every patient with rectal cancer staged clinically as T2N0M0 who comes to a participant hospital.

In the literature, overall 5-years survival rate after radical resection alone in T2N0M0 rectal cancers ranged from 77% of some studies (which used multiple approaches apart from TME)(51) to an 85% of more modern studies, which used a laparoscopic approach but also neoadjuvant therapy (59). An overall 5-years survival rate of 85% will be used as a reference of laparoscopic TME alone, as in this last study named of Marks et al, overall 5-years survival estimation include stage II and stage III besides stage I, and this probably counteracted the use of neoadjuvant therapy. Accepting a beta-risk of 0.2 and a drop-out rate of 0.1, if there is truly no difference between the standard and the experimental treatment, 352 patients (176 patients on each group) are required to be sure that the upper limit of a one sided 95% confidence interval will exclude a difference in favour of the standard group of more than 10%, regarding our main objective. The sample size has been calculated using Sealed Envelope calculator. (60)

7.3.1. TIME OF RECRUITMENT

Knowing that in 2015, Barcelona's province population was 5.523.922 and Girona's one was 753.054, our Hospitals have a potential population of 6.280.732 people (62). In 2011, 13 rectal tumours were

[5] *American Society of Anaesthesiologists' (ASA) Physical Status Classification:*
ASA I: A normally healthy patient. **ASA II**: A patient with mild systemic disease. **ASA III**: a patient with severe systemic disease that is not incapacitating. **ASA IV**: a patient with an incapacitating systemic disease that is a constant threat to life. **ASA V**: A moribund patient who is not expected to survive for 24 hours with or without operation. (61)

staged as cT2N0M0 in Girona's province: assuming that Girona's population in 2011 was of 756.810 people, we can expect to recruit as much as 107,9 cases every year. Knowing that not all the patients diagnosed will meet the specified criteria or will agree to enter into the studio, around 90 patients are expected to be recruited every year of the study. Our estimation with that figure is that recruitment will last 4 years.

7.3.2. RANDOMIZATION

Randomization will be done with IBM's SPSS version 22.0 or higher, after the informed consent form has been signed. Patient's data will be confidentially maintained by assigning every patient an identification number, generated by the same software before randomization.

After randomization, every participant member except for statistician and nurses will know which approach the patient will undergo, as double-blind is not possible in this trial.

Not a single member of the team will be able to modify in which approach the patient is included.

7.4. VARIABLES

7.4.1. INDEPENDENT VARIABLE

Our study independent variable will be the *exposition to preoperative SC-RT plus LE by TAMIS approach* or *exposition to laparoscopic anterior resection with TME approach*. Independent variable's expression will be in proportions or percentages, as it can be defined as a qualitative nominal dichotomic variable.

7.4.2. DEPENDENT VARIABLES

The main dependent variable will be *overall 5-years survival rate*, defined as the *proportion or percentage of patients alive at 5 years after randomisation*. (63)
Survival is a qualitative dichotomic variable, but expressed as a quantitative continuous variable in overall 5-years survival rate.

Secondary dependent variables will be:

- *Cancer-specific 5-years survival rate*, defined as *proportion or percentage of people in a treatment group who have not died from cancer in 5 years* (National Cancer Institute Dictionary of Cancer Terms definition). Survival is a qualitative dichotomic variable, which will be expressed as a quantitative continuous variable.

- *Local recurrence rate at 5 years*, defined as *the proportion or percentage of patients with 'local disease during the follow-up, occurring either alone or in conjunction with generalized recurrence, in patients who have already undergone resection'* (64). Local recurrence is a qualitative dichotomic variable, but it is expressed a quantitative continuous variable.

- *Postoperative complications*, including all the complications occurred from the surgical intervention to the discharge (for as long as a maximum of 90 days). Complications will be defined using the *Clavien-Dindo classification* (*see Annex III*), which include 5 grades (65). It is a quantitative discrete variable, but it will be turned into a categorical ordinal variable to facilitate the analysis: *no complications*, *mild complications* (grade I-II) or *severe complications* (grade III-IV).

- *Quality of life**, measured with the validated SF-36 questionnaire. SF-36 is a validated test which evaluates 9 main items: physical function, physical role, body pain, overall health, vitality, social function, emotional role, mental health and an item which assesses the health versus a year later. Each item is punctuated from 0 to 100, and total punctuation is pondered on a total score of 100 (66). It is a quantitative discrete variable.

- *Sexual function**, measured with the validated *International Index of Erectile Function (IIEF) questionnaire in men* and with the *Female Sexual Function Index (FSFI) questionnaire in women*.
  - *IIEF*: it is a validated questionnaire with 15 items, evaluating 5 main domains (erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. The total score range is 5-75 (67). It is a quantitative discrete variable.
  - *FSFI*: it is a validated questionnaire with 19 questions, evaluating 6 main domains (desire, arousal, lubrication, orgasm, satisfaction, pain). The total score range is 2-36 (68). It is a quantitative discrete variable.

- *Bowel and anorectal function** , assessed with the validated *Colorectal Functional Outcome questionnaire* (COREFO questionnaire) (69). It's a questionnaire with 27 questions, concerning a 2-week period. COREFO questionnaire evaluates incontinence, social impact, frequency, stool-related aspects and need for medication. Score ranges from 27 to 135. It is a quantitative discrete variable.

* Basal score (at first appointment) would be taken and in every meeting as specified in the follow-up.

7.4.3. CO VARIABLES

- *Age*: *55 or younger*; *56 to 69*; *70 or higher*. Age is an important regressor of sexual activity (70). Age have been adapted to a qualitative ordinal variable, using a modification of patterns seen in Nicolosi et al. paper. (71)

- Gender: *woman* or *man*. It is a qualitative nominal dichotomic variable.

- *Bad prognosis factors of rectal cancer*. At least one of the following assessed by the pathological analyses of the surgical specimen: *lymphatic vessel invasion*, *blood vessel invasion*, *tumours bigger than 4 cm in its bigger diameter* or *tumours occupying more than a 40% of the rectum lumen*. It is a qualitative nominal variable.

- *Tumour grade*: *Gx*, *G1*, *G2*, *G4* as stated by *AJCC (see Annex II)*. Preexcisional biopsy or after specimen analysis will be used (the one with biggest grade). It is a qualitative nominal variable.

- *Residual tumour*: *R0*, *R1* or *R2* as defined by *AJCC (see Annex II).* It will be assessed by the pathological analysis of the surgical specimen. It is a qualitative ordinal variable.

- *pTNM*: as defined by *AJCC (see Annex II).* It is a qualitative nominal variable.

- *Tumour position above the anal margin*: *High* (higher than 11 cm from anal verge but not including rectosigmoid union), *mid* (from 11 cm to 5 cm, not including 5), *low* (5 cm or lower). It is a qualitative ordinal variable.

- *Comorbidities*: defined with the validated *Charlson comorbidity index* (72)(*see Annex IX*) . It is originally intended as a way to predict mortality by classifying the comorbidities. The *Charlson comorbidity index* evaluates 20 items, which each one has a punctuation of 1 to 6. It becomes a quantitative ordinal variable as we will define 4 ranges: *0*; *1-2*; *3-4*; *greater or equal to 5*.

- *Rescue treatment*: whether the patient has received or not rescue treatment due to its pTNM or recurrence. The possibilities could be: *TME*, *TME plus adjuvant treatment*, *adjuvant treatment alone*, *metastasectomy* and *metastasectomy plus adjuvant treatment*. It is a qualitative nominal variable.

7.5. MEASURE INSTRUMENTS

- SF-36 questionnaire: a validated Spanish 2.0 version will be used (*see Annex V*) (73). Patient will be given pages from 1 to 5 (of the total of 7). The proceedings needed to final sum of the

score will be done as specified in the instructions stated on the uploaded online questionnaire. If a TeleForm software is available, the printed version given is compatible with it.

- IIEF: a validated Spanish version will be used (*see Annex VI*). As specified before, punctuation ranges from 5 to 75. Each response score is specified in the questionnaire. As a referral to the scores obtained, IIEF punctuation range will be the following: no erectile dysfunction (ED), higher than 25; mild ED, [25, 22]; mild to moderate ED [21, 17], moderate ED [16, 11], severe ED [10, 6].

- FSFI: a validated Spanish version will be used (*see Annex VII*). Punctuation ranges from 2 to 36. Each response has a score, which can be seen in the questionnaire printed (before the checkbox). As a referral to the scores obtained, a score over 20 will be used as normal, and a punctuation of 20 or lower as an abnormal.

- COREFO questionnaire: a validated Spanish version will be used (*see Annex VIII*). As specified, punctuation ranges from 27 to 135. Each of the five possible responses has a score associated from 1 to 5 (first answer = 1, second answer =2, …)

- Charlson comorbidity index: items with its current score, instructions and rules of completion can be seen in *Annex IX*.

7.6. APPROACHES

Preoperative staging will be done as established in every participant hospital's protocol, always ensuring that at least MRI has been used for local staging. Our recommendation is that an ERUS should also be done.

After diagnosis, SF-36, IIEF, FSFI and COREFO questionnaires will be given and Charlson comorbidity index will be assessed by a nurse who won't know in which approach the patient is in. The questionnaires are expected to be given back fulfilled on the same day, as the patients participating on the study will be called to the appointments two hours before the physician visit on each time scheduled.

Prior to the procedures, all patients will receive a full mechanical and antibiotic bowel preparation. Also, thrombotic prophylaxis. For both approaches standard lithotomy position is recommended.

EXPERIMENTAL APPROACH – TAMIS PLUS PREOPERATIVE SC-RT

- **SC-RT** will be given, in a 5 x 5 Gy regime, for a total dose of 25 Gy, delivered within a week. Radiotherapy target volume is defined as: the sacral promontory superiorly, 3-5 cm below the inferior tumour margin, 2-3 cm anterior to the sacral promontory, 1 cm posterior to the anterior sacrum, and 1 cm lateral to the most lateral aspect of the bony true pelvis; anal canal will be spared in every patient whose tumours are not a low rectum tumour.
- **TAMIS:** For being analysed in this project, every TAMIS procedure have to be performed by a surgeon who had made at least 10 TAMIS resections with negative resection margins, as it is a new technique not so well spread as TME by laparoscopic approach. Every patient will undergo TAMIS, preferably and recommended within a week from the last RT fraction. General anaesthesia will be the preferable one; if patients are not healthy enough, spinal anaesthesia will be considered. GelPOINT path will be used as protocolled path. Access channel will be placed into the anal canal gently, after a short heating with warm physiological serum; then, it will be sutured to the perineal skin by the two holes available on this part of the path. After that, external cap will be placed; gas entering and exiting tubes also. Pneumorectum will be stablished and maintained with the gas pressure desired by the surgeon, keeping it in a range from 12 to 18 mmHg.

  TAMIS will be carried on in by a main surgeon (who will work on the two lower ports of the GelPOINT path) and an assistant surgeon, who will handle the camera. Usual laparoscopic instrumentation will be used. Monitor viewing will be the normally used by the hospital; nevertheless, this protocol encourages the use of 3D viewing specially for the suture time. Once the tumour is localized, a circular mark of 2 cm will be made around it with the monopolar hook cautery; then, full-thickness excision of the rectal wall will be done. Suturing of the rectal wall defect will be done whenever possible; if it is not possible, the defect will be left open.

  Preoperative and postoperative antibiotic coverage will be done as stated in each hospitals' protocols. Postoperative coverage will be extended at least two days if the rectal defect is left open.
- **Postoperative care:** *Clavien-Dindo classification* will be assessed during the postoperative caring.
- **Specimen's pathological examination**: After LE, piece will be sent to each hospital's pathologic division in order to assess the resection's margin, tumour grade and final pathological staging. After pathological assessment of the specimen, if pT>2 or resection margins positives, patients will be offered anterior resection with TME due to the big risk of positive ganglia even after preoperative SC-RT.

- **Follow-up**: follow-up schedule can be seen in *7.6.1 Follow-up*. An extended follow-up will be applied in the experimental approach for an early radical rescue treatment in case of local recurrence.
- **Rescue treatment**: patients who experience local recurrences will be treated as specified in Hospital Josep Trueta rectum cancer protocol: surgical treatment will be applied if complete resection is possible. Every case will be studied and evaluated individually. Patients with pulmonary or liver metastases will be tributary of surgical treatment, if complete metastectomy (excision without residual disease) is possible. After that, patients will receive complete chemotherapy with 5-fluorouracile-leucovorine at low doses in 5 cycles. If patient is intolerant to 5-fluorouracile-leucovorine, raltitrexed at low doses will be used.

STANDARD APPROACH – LAPAROSCOPIC ANTERIOR RESECTION WITH TME

Prior to the procedures, patient's abdomen will be marked preoperatively by the enterostomal therapy nurse for potential stoma sites. Also, epidural catheter will be placed by anaesthesia team for postoperative pain control. Preoperatively all lesions may be marked by an injection of India ink.

- **Surgical procedure:** Three surgeons should take part on each surgery, two assistants and one main surgeon. One assistant will work handling the camera. The surgery takes part in 4 steps:
  - Mobilization of the sigmoid colon and rectum: the lateral peritoneal attachment of the sigmoid is divided. Then, the sigmoid is mobilized. The inferior mesenteric artery and vein are separately divided after a hem-o-lok clamping. The division of the inferior mesenteric vessels should be as close to the aorta as possible, by doing a high ligation, to ensure a tension-free anastomosis. Presacral plan must be dissected anterior to the nerves and followed carefully down, until the whole rectum is easily mobilized to the pelvic floor muscles.
  - Mobilization of the distal transverse colon and splenic flexure: starting from the mid-transverse colon, the greater omentum will be gradually peeled off from the transverse mesocolon. The splenic flexure must be gradually taken down and mobilized. Mobilization will be adequate if the sigmoid junction could go to the true pelvis without tension.
  - Exteriorization and resection of the specimen and creation of the pouch: at the left iliac fossa, a 4-6 cm incision is made. Then, it is protected with a plastic bag, the specimen extracted and excised with linear cutter, fashioning a pouch.
  - Intracorporeal anastomosis and creation of covering ileostomy: intracorporeal anastomosis is performed with the circular stapler under laparoscopic view. Finally, a point at least at 20 cm from thte ileocaecal valve is identified for the formation of covering loop ileostomy.

Preoperative and postoperative antibiotic coverage will be done as stated in each hospital's protocol.

- **Postoperative care:** *Clavien-Dindo classification* will be assessed during the postoperative caring. All patients will be under a fast-track protocol.
- **Specimen's pathological examination**: After surgery, the resected piece will be sent to each hospital's pathologic division in order to assess the resection's margin, tumour grade and final pathological staging. After pathological assessment of the specimen, if there are pN+ or/and CRM+, chemoradiotherapy will be done: at first and third week, 5-fluorouracil 500 mg/m2/day plus leucovorin 20 mg/m2/day during 5 days; at the ninth week from the first doses, RT will start, by giving 45 Gy fractioned in 1.8 Gy doses; during the three firsts days of RT and the three lasts days of it, 5-fluorouracile 425mg/m2/day plus leucovorin 20mg/m2/day will be given. After RT completion, two more cycles of chemotherapy will be administered (same doses than the two first cycles).
- **Follow-up**: *see 7.6.1 Follow-up*. These patients will be under the standard follow-up.
- **Rescue treatment**: same as in experimental approach.

7.6.1. FOLLOW-UP

	Time points follow-up										
	Post-operative	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months	48 months	60 months
Clinical evaluation		O	X	O	X	X	X		X	X	X
Analytics (with CEA)		O	X	X	X	X	X	X	X	X	X
MRI			O			O	X		O		O
Sigmoidoscopy			O				O		O		
Chest X-ray							X		X		
Liver ultrasound							X		X	X	
ERUS							X				
Abdominal CT-scan			X			X		X			
Colonoscopy					X						X
Clavien-Dindo classification	X										
SF-36		X	X		X		X		X	X	X
IIEF/FSFI		X	X		X		X		X	X	X
COREFO		X	X		X		X		X	X	X

X = appointments included in normal follow-up.
O = extra appointments only included in the extended follow-up of the experimental group.

7.7. DATA COLLECTION

All the variables and co variables will be collected using the Case Report Form (CRF) (*See Annex X*).

The CRF include different parts, each one is for a specific time:

- First page: identification number of the patient, his initials and the centre number are included. Also, approach assigned after randomisation. There is a part for informed consent in which the person who has given the informed consent form and has explained to the patient his participation in the study must verify that the patient has signed it voluntarily and with enough information.
- Second page: demographic data, in which patient age and sex is stablished. Basal data, where the patient's first scores on the tests and questionnaires are assessed in order to set the basal point from which each patient's scores will be compared. Also entries for Charlson comorbidity index and for the tumour position in rectum are included. Surgical specimen examination data apart is designed to include all the data referring to pathological examination after the excision. In the postoperative time section, the Dindo-Clavien classification will be noted.
- Third and fourth pages: A section for each appointment of the follow-up is included, in order to write down the scores assessed by the tests and questionnaires.
- Fourth and fifth pages: An events section is included for assessing possible event during the follow-up. Finally, the principal investigator's sign off is set as a measure of guarantee to verify the accuracy and veracity of all the data collected.

Data will be collected by at least one surgeon in each participant hospital. Surgeons accredited and designed by the chief investigator will held the responsibility of the veracity of the information directly assessed or transcribed (i. e. by transcribing the inform of the pathologist to the CRF or the Charlson comorbidity index assessed by a nurse).

7.7.1. STUDY SCHEME

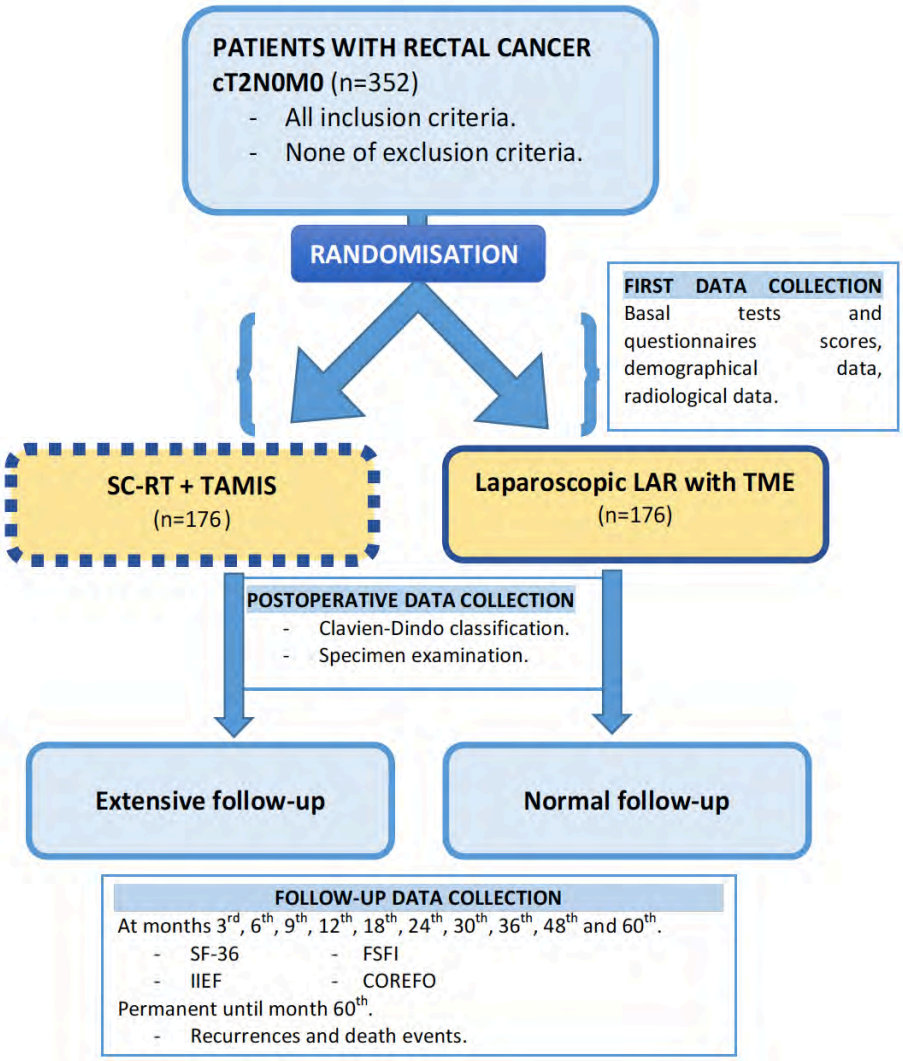

Figure 15. Study scheme.

8. STATISTICAL ANALYSIS

Statistical analyses will be performed using SPSS software v22.0 or higher. All analyses will be on an intention-to-treat basis. Interpretation of the results based on questionnaires and tests (sexual function tests, SF-36 questionnaire and COREFO questionnaire) will be done over patterns of differences between the different approaches and also taking into a consideration the basal data. If the two groups made representing the approaches are not equal attending to the co variables collected, stratified analyses will be done. Kolmogórov-Smirnov test will be applied to determine if the variables follow a normal distribution.

8.1. UNIVARIATE ANALYSIS

- Categorical variables will be described as proportions or percentages.
- Qualitative variables will be described with the mean +/- the standard deviation, presupposing a normal distribution. If the variable is not normally distributed, median and H-spread will be used.

8.2. BIVARIATE ANALYSIS

- Overall 5-years survival rate, cancer-specific 5-years survival rate and local recurrence rate at 5 years will be calculated using the Kaplan-Meier Survival analysis and compared using the log-rank test. Representation with curves will be done. As said before, the experimental treatment will be considered to be non-inferior to the standard treatment group if the one-sided 95% confidence interval excludes a difference equal or smaller than minus 10% in favour of the standard approach in these groups.
- For quantitative discrete variables Mann-Whitney test will be done.
- For categorical variables analyses, chi-squared test will be used.

8.3. MULTIVARIATE ANALYSIS

- For the multivariate analysis, Cox regression will used. Each co variable risk increase respecting the variables will be calculated with hazard rates.

Except in the case of time-to-event bivariate analysis, in every variable studied differences will be calculated over a two-sided 95% confidence interval. Differences with P-values <0.05 will be considered as significant.

9. ETHICAL CONSIDERATIONS

9.1. GENERAL CONSIDERATIONS

Prior to starting the study, the protocol will be presented to Clinical Research Ethics Committee (CEIC) of Hospital Josep Trueta for its approval.

This protocol will be developed in accordance to the Good Clinical Practices Guidelines and following the stablished regulatory law, as it is described in:

- Harmonized Tripartite Rules of the International Conference for Good Clinical Practice Harmonization 1996. Directive 91/507/EECC: Good Clinical Practice Rules for trials with medical products in the European Community.
- Helsinki Declaration of Ethical Principles for Medical Research Involving Human Subjects, last actualization October 2013.
- Spanish 'Law 14/2007, 3rd of July', about biomedical investigation.

Investigators agree, with this protocol signing, to follow the instructions and proceeds written on it and to accomplish the Good Clinical Practice's principles in which it is based.

9.2. INFORMED CONSENT

The investigators have to explain to each patient the study nature, purposes, proceedings, expected time of the study, potential risks, disadvantages and benefits related to the trial participation. Every participant has to be advised that his participation is voluntary and that can exit the study whenever wants, without affectation of his medical treatment or the relationship with his doctor.

Informed consent plus information sheet form is a standard writing, designed to be easy understood and to contain all the needed information. A Catalan version is annexed in this protocol, but Spanish version is also available; for patients with other language requirements, translation will be done. Patients have to write their name and the name of the informant investigator, date the informed consent and sign it in its established fields. Patients have to be given a copy of the signed informed consent form.

Every change in the informed consent form attached in this project must be approved again by the Ethical Committee.

9.3. CONFIDENTIALITY

With this protocol signing, the investigators agree to maintain all the information over the strictest confidentiality, accomplishing the stablished in the Spanish 'Organic Law 15/1999, 13th December', about Personal Data Protection. All the study documentation will be stored ensuring its confidentiality.

10. STUDY LIMITATIONS

1. The study is an open-label trial. Due to the information and the data characteristics, nor the surgeon, the carer, the patient or the pathologist can be blinded. The statistician will be blinded and also the nurses who give and help on questionnaires, tests and assess the Charlson comorbidity index, with the intention to try to reduce a possible observer bias.

2. As we have seen in the epidemiology, presumably our sample won't be homogeneous in terms of sex, as more men are diagnosed of rectal cancer than woman. Same happens with age and comorbidities. In order to avoid a selection bias the most preferable sampling method would have been a stratified consecutive model, but for filling the different stratum the expected time of recruitment would have been ever longer. To solve the problem in some way without affecting the feasibility a stratified data analysis will be done if the two groups are not homogeneously formed.

3. TAMIS is a technique in expansion, not so well spread. For ensuring equal results, some homogenisation acts will be carried on: description of the technique, the first meeting and the need of having performed at least ten prior TAMIS procedures with R0 margins for be a participating surgeon. Also, SC-RT is a technique not well spread in Western-Europe. As the goods used for a normal course and SC-RT are the same, difficulties in application are not expected.

4. Time of recruitment and follow-up is long, as at least nine years are expected. This can difficult the follow-up period. Even the final impact of the study can be handicapped as new approaches could rinse, although it is not very probable. Also, time of recruitment could be lengthen-up if patients refuse entering into the trial.

5. Most of the follow-up appointments are part of the normal medical care that patients receive after a surgery of rectal cancer, and loss of the follow-up is not expected to be very high. Even so, in order to minimise losses as possible, administrative personnel who is part of the study will phone before each appointment. For strengthen the follow-up and make easier the data collection, a CRF has been designed; also, patients will be called up two hours before the surgeon's appointment to fulfil the questionnaires and tests, giving them back on the same day.

6. Most of data collection is based on subjective information, based on questionnaires. Validated Spanish questionnaires will be given in order to achieve the maximum accuracy. There are

available objective examinations to assess anorectal function such as anorectal manometry but it would have significantly increase the budget (an anorectal manometry costs approximately 200€).

11. WORK PLAN

11.1. RESEARCH TEAM

The research team will be formed by:

- *6 surgeons* (S) who accomplishes the expertness criteria (one for each participant hospital), but it is recommended that two surgeons are available per hospital, so more surgeons will be able to participate if match the expertness criteria. If more than one surgeon is available in a centre, one will be designed as 'centre responsible' by the trial coordinator.

  Surgeons' work includes:

  - Inform to the patients and giving them the information sheet.
  - Assessment that signed inform is properly obtained and reflect this on CRF.
  - Surgical procedures.
  - Fulfilment, transcription and verification of CRF's data.
  - Follow-up coordination and attention on the appointments.
  - Introduction to SPSS data base the data collected with CRF.

  Pere Planellas is the *trial coordinator* (Tc), from Hospital Dr. Josep Trueta de Girona. He will be the chief investigator and the highest responsible.

  Trial coordinator's work includes:

  - Setting-up all the meetings required for trial coordination in order to ensure the surgical procedures' homogenisation and teaching the way to fulfil the CRF.
  - Responsibility of writing and communicating the final results whichever they are.
  - To decide the suspension of the trial because of unexpected adverse effects or unacceptable systematically harming.
  - Solve the possible problems and conflicts that can appear during the trial development.
  - Designing a centre responsible in each centre participating.

- At least *6 radiotherapists* (R), one from each centre participant.

  Radiotherapist's work includes:

  - Patient prior specific study on RT fields before SC-RT.

- SC-RT application.

A *chief radiotherapist* (Cr) will be designed, from Hospital Universitari Josep Trueta.

Chief radiotherapist's work includes:

- Coordination and homogenisation of radiotherapies made.
- Specific problem solving about radiotherapy fields.

- *6 nurses* (N), one from each participant centre.

  Nurses' work on the studio includes:

  - Giving to patients the questionnaires and test when they came to the centre two hours before the appointment.
  - Giving all the information needed to respond the questionnaires and tests without influencing patient's answers.
  - Charlson comorbidity index's assessement.

- *6 administrative assistants* (A) coming from the colorectal division's administrative personnel of each centre in the trial.

  Administrative personnel's work includes:

  - Setting-up the appointments of the follow-up.
  - Reminding the follow-up's appointments to the patients.

Not forming part of the research team:

- A *statistician* (St) will be hired in order to manage and make the statistical analyses needed.

  Statistician's work includes:

  - SPSS software's management.
  - Instruction on SPSS software to the other trial staff, in order to show how CRF data has to be introduced.
  - Analyses of the data collected.
  - Graphical representation of the data collected.
  - Problem solving related to SPSS software.

11.2. WORK PLAN

Our study has four phases, each one with a different purpose. Each phase is formed by activities (A). For the Gantt Chart of the project, *see Annex XI.*

Phase I. Coordination and project presentation. Expected time: 2 months.

- **A1**: to obtain the ethical approval from the CEIC. Tc.
- **A2**: First research team meeting. The final protocol will be presented and the proposed chronogram discussed. Each member will be told which is his work. S, Tc, R, Cr, N.
- **A3**: First surgeons meeting. Tc will expose the TAMIS approach in order to achieve homogenisation of the surgeries done. Video examples will be shown. Live surgery will be done if possible. S, Tc.
- **A4**: Second research team meeting. CRF will be explained and training on it will be done. Information entry on the database will be shown by the St. SC-RT fields and procedures will be shown and explained. S, Tc, R, Cr, N, St.

Phase II. Study development. Expected time: 9 years.

- **A5**: Third research team meeting. Possible doubts or errors detected in CRF and/or database will be discussed. Problem solving. S, Tc, R, Cr, N, St.
- **A6**: Consecutive recruitment. S, Tc, R, Cr, N, A, S.
- **A7**: Approaches application. S, Tc, R, Cr, N, A, S.
- **A8**: Data collection. S, Tc, R, Cr, N, A, S.
- **A9**: Annual research team meeting. Every year a meeting will be done in order to assess the situation of the trial. Doubts, problems and conflicts will be discussed. Trial coordinator will have the option to call for a meeting, according to his criteria. S, Tc, R, Cr, N.
- **A10**: Follow-up. S, Tc, R, Cr, N, A, S.

Phase III. Analysis and interpretation. Expected time: 6 months.

- **A11**: Statistical analysis. St, Tc.
- **A12**: Interpretation and discussion of the results. S, Tc.

Phase IV. Results publication. Expected time: 6 months.

- **A13**: Article writing and publication. Our aim will be publication of our results on *Gastroenterology.* S, Tc.
- **A14**: Results diffusion, medical conference's attending. Tc, Cr.

12. FEASIBILITY

This trial will be carried out at six hospitals at the same time: one at Girona, Hospital Universitari Josep Trueta, and five at Barcelona, Hospital Clínic, Hospital Universitari Vall d'Hebron, Hospital del Mar, Hospital de Bellvitge and Hospital Santa Creu i Sant Pau. These six hospitals have been selected because they are accredited centres for rectal cancer treatment and the ones more experienced in laparoscopic and local excision techniques in Catalonia. At least one surgeon is able to perform TAMIS in each of these hospitals; also, SC-RT is available. Means and personnel needed for statistical analyses, data collection and application of the approaches are also available in them all.

Hospital Universitari Josep Trueta has been selected as referral centre because of its Excellence-grade accreditation by the Spanish Association of Coloproctology. The trial coordinator is an experienced surgeon specialist in minimally invasive surgery and in advanced laparoscopic surgery, author of some of the firsts TAMIS resections in our province and country.

Travel expenses are included into the budget in order to not affecting the meeting's attendant

Our estimation is that around 90 patients will be recruited every year, so 4 years of consecutive recruitment are expected to meet our goal. A case report form, instructions about the set-up of the appointments and other measures have been taken for making more feasible data collection, follow-up and minimizing losses on data.

13. BUDGET

Both surgical procedures (TAMIS and LAR with TME) are covered by our national health system, so its costs won't be included in budget's estimation. SC-RT will be included on the budget, as it is not contemplated as a treatment in this cancer stage. Also, extra appointments and tests included in the extensive follow-up group will be added into the budget, as the other test included on standard follow-up are part of the usual medical care.

Surgeons, administrative personnel, nurses and radiotherapist's tasks will be under them working hours, so the only retribution done will be to cover the travel expenses into the meetings, that will be hold in Hospital Universitari Josep Trueta, at Girona. A statistician will be hired for data management, assistance and statistical analysis.

Our aim is to publish on *Gastroenterology*. The publication fees used for budget estimation are the ones set in its site and converted to euros, using the actual dollar exchange rate (0,91 € per dollar).

European Colorectal Congress registration fees are detailed and calculated over the actual prize published online. Transport and accommodation cost's and per diems estimated for conference assistance are calculated to not overpass the maximum established by the Spanish Plan of Project's and Investigation.

Phase I		**Price per unit**	**Units**	
First research team meeting				
	Transport	32 €	15	480 €
	Protocol impression	9,6 €	18	172,8 €
First surgeons meeting				
	Transport	32 €	5	160 €
	Streaming costs	234 €	1	234 €
Second research team meeting				
	Transport	32 €	15	480 €
	Statistician salary	30 €	3	90 €
	Photocopies	0.04 €	300	12 €
Insurance contract		40,000 €	1	40,000 €
			Subtotal	**41,628.8 €**
Phase II				
Third research team meeting				
	Transport	32 €	15	480 €
	Statistician salary	30 €	3	90 €
Study development				
	SC-RT	2,205 €	176	388,080 €
	Sigmoidoscopy	155 €	528	81,840 €
	Analytics with CEA determination	44.18 €	176	7,775.68 €
	MRI	183 €	704	128,832 €
	Clinical appointments	122 €	352	42,944 €
	Tests, questionnaires, CRF,… impression	0.04 €	13,728	549,12 €
Annual meeting				
	Transport	32 €	135	4,320 €
	Photocopies	0,04 €	2,700	108 €
			Subtotal	**655.017,8 €**
Phase III				
	Statistician salary	30 €	30	900 €
			Subtotal	**900 €**
Phase IV				
	Gastroenterology publication fees	3296.71 €	1	3296.71 €
	European Colorectal Congress registration fee	600 €	2	1200 €
	Transport	200 €	2	400 €
	Accommodation's costs	131.94 € / 2 days	2	263.88 €
	Per diem	74.75 € / 2 days	2	149.5 €
			Subtotal	**5,310.09 €**
			Total	**702,855.89 €**

14. IMPACT ON THE NATIONAL HEALTH SYSTEM

As discussed before, colorectal cancer is a current problem on the national health system, as it is becoming the most incident cancer in some regions. With the new screening tests, it is expected that the number of early stage rectal cancers diagnosed will increase, decreasing the mean age of incidence. Actual treatments for these stages offer very good outcomes in survival and local recurrence but the rinse of less impairing approaches is needed in order to avoid the potential

diminution on sexual function and continence, especially if we have in mind that if the incidence age diminishes, people will have to live more years with this kind of impairing problems. Local excision procedures can shift the paradigm of these early-staged tumours, as the actual treatments can be seen too radicals for these patients. If our hypotheses are confirmed, a much less invasive procedure will be able to cure patients without significant postoperative comorbidities and complications. This is important for younger people which wants to maintain his quality-of-live and sexual function, but also for elder people that maybe otherwise won't be able to undergo a radical surgery as TME for its previous comorbidities or for potential postoperative complications.

The early-staged rectal cancer treatment is probably one of the most controversial topic over colorectal surgery, especially the local excision role. If this project confirms its hypothesis, clarification on it will be embraced with open arms.

TAMIS has a big spreading potential, allowing an expected good implementation, as it could be available and affordable to our national health system's hospitals. If our hypotheses are confirmed, TAMIS can displace TEM, which is probably more used even for local excision of polyps and T1 cancers, which material is more expensive and its learning curve is stepper, saving money and offering better postoperative functional outcomes. This will be assessed by one of the biggest consecutive series of TAMIS procedures to the date.

Finally, preoperative SC-RT is not very used in our national health system. At the end of this project, it may become well-spread tool as it is in the USA, Japan or Eastern Europe. SC-RT spread can contribute to minimize the costs derived of neoadjuvant therapies and also to shrink waiting lists.

15. ANNEXES

15.1. ANNEX I: RECTAL CANCER EPIDEMIOLOGIC DESCRIPTION

Table 2. Colon, rectum and anus cancer incidence per stage. Girona province, 2011.

Stage	Frequency	Percentage
No data	41	7,5
I	98	17,9
II	15	2,7
IIA	97	17,7
IIB	16	2,9
IIC	13	2,4
III	7	1,3
IIIA	12	2,2
IIIB	97	17,7
IIIC	35	6,4
IV	11	2,0
IVA	64	11,7
IVB	40	7,3
IVC	1	0,2
Total	**547**	**100**

Table 3. Rectum cancer incidence per stage. Girona province, 2011.

Stage	Frequency	Percentage
No data	3	2,4
I	22	17,9
II	2	1,6
IIA	19	15,4
IIB	2	1,6
IIC	2	1,6
III	2	1,6
IIIA	4	3,3
IIIB	40	32,5
IIIC	8	6,5
IVA	13	10,6
IVB	6	4,9
Total	**123**	**100**

15.2. ANNEX II: AJCC'S TNM

The *American Joint Committee on Cancer (AJCC) Staging Manual* is the main tool used internationally for cancer staging. At the date, its most actual edition is the 7th one. This manual divides cancer in several prognostic stages, based on its TNM staging. TNM staging is based on three items:

- **T**: quantifies depth of tumour invasion into or beyond the colorectum wall or to adjacent organs or structures.
- **N**: accounts for the number of regional lymph nodes with disease.
- **M**: describes the absence or presence of distant metastasis.

TNM classification can be used for clinical (cTNM) or pathologic staging (pTNM , after the surgical specimen is examined). Patients' staging after neoadjuvant treatment is marked as ypTNM. For a recurrent disease, the 'r' prefix is used (rTNM). For colon and rectum, same TNM staging is used. (2)

Table 4. Colorectal TNM. Modified from (2)

Primary Tumour (T)	Regional Lymph Nodes (N)	Distant Metastasis (M)
Tx – Primary tumour cannot be assessed.	**Nx** – Regional lymph nodes cannot be assessed	**M0** – No distant metastasis
T0 – No evidence of primary tumour.	**N0** – no regional lymph node metastasis.	**M1** – Distant metastasis • **M1a** – Metastasis confined to one organ or site. • **M1b** – Metastasis in more than one organ/site or the peritoneum.
Tis – Carcinoma in situ: intraepithelial or invasion of lamina propria.	**N1** – Metastasis in 1-3 regional lymph nodes. • **N1a** – Metastasis in one regional lymph node. • **N1b** – Metastasis in 2-3 regional lymph nodes. • **N1c** – Tumour deposit in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis.	
T1 – Tumour invades submucosa.		
T2 – Tumour invades muscularis propria.	**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.	
T3 – Tumour invades through the muscularis propria into pericolorectal tissues.		
T4a – Tumor penetrates to the surface of the visceral peritoneum. **T4b** – Tumour directly invades or is adherent to other organs or structures.		

Table 5. Colorectal cancer survival. Modified from (2).

Stage		T	N	M	Overall Survival 5-year (%) (based on SEER Data)
0		Tis	N0	M0	Not specified
I		T1	N0	M0	81,4
		T2	N0	M0	75,7
II	IIA	T3	N0	M0	64,0
	IIB	T4a	N0	M0	55,7
	IIC	T4b	N0	M0	44,7
III	IIIA	T1 – T2	N1/ N1c	M0	72,1
		T1	N2a	M0	73,8
	IIIB	T3-T4a	N1/N1c	M0	41,7 - 58,2
		T2-T3	N2a	M0	
		T1-T2	N2b	M0	
	IIIC	T4a	N2a	M0	12,3 – 44,3
		T3-T4a	N2b	M0	
		T4b	N1-N2	M0	
IV	IVA	Any T	Any N	M1a	Not specified
	IVB	Any T	Any N	M1b	

Table 6. Histologic type. Modified from (2).
- Adenocarcinoma *in situ* (high grade dysplasia/severe dysplasia can be used also) (pTis)
- Adenocarcinoma
- Medullary carcinoma
- Mucinous carcinoma
- Signet ring cell carcinoma
- Squamous cell (epidermoid) carcinoma
- Adenosquamous carcinoma
- Small cell carcinoma
- Undifferentiated carcinoma
- Carcinoma, NOS

Table 7. Residual tumour. Modified from (2).	
R0	Complete resection, margins histologically negative, no residual tumour left after resection (primary tumour, regional nodes).
R1	Incomplete resection, margins histologically involved, microscopic tumour remains after resection of gross disease (primary tumour, regional nodes).
R2	Incomplete resection, margins macroscopically involved or gross disease remains after resection (e.g., primary tumour, regional nodes, or liver metastasis).

Table 8. Histologic grade. Modified from (2).	
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

15.1. ANNEX III: CLAVIEN-DINDO CLASSIFICATION

Table 9. Clavien-Dindo Classification of surgical complications. From (69).

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, analgesics, 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 IV	Life-threatening complication (including central nervous system complications: brain haemorrhage, ischemic stroke, subarachnoid bleeding, but excluding transient ischemic attacks), requiring intermediate or intensive care unit aid.
Grade V	Death of the patient.

15.2. ANNEX IV: INFORMATION SHEET AND INFORMED CONSENT FORM

FULL D'INFORMACIÓ AL PACIENT

TÍTOL DE L'ESTUDI: *Cirurgia transanal mínimament invasiva associada a un curs curt preoperatori de radioteràpia v. exèresi total del mesorecte per via laparoscòpica en el tractament de tumors de recte cT2N0M0.*

El seu metge li ha proposat participar en el present estudi d'investigació. Si us plau, llegeixi amb calma la informació que a continuació li proporcionem i que li permetrà decidir si vol o no participar. No és necessari que doni una resposta en aquest moment, pot emportar-se la informació que li proporcionem i valorar-la amb calma. Pot consultar-ho amb els seus familiars, amics o amb altres professionals de la salut, si així ho desitja. Pot fer tantes respostes com vulgui i nosaltres les respondrem. Ha de saber que la seva participació és completament voluntària i que si decidís no participar, la seva decisió no modificarà en absolut la seva relació amb el seu metge ni els tractaments que se li aplicaran ara o en el futur.

Per què és realitza aquest estudi?

El càncer de recte és una malaltia molt comú al nostre entorn. Molta gent el pateix i amb els nous mètodes de cribratge és possible detectar-lo en fases més precoces que abans.

El seu tumor ha sigut diagnosticat en un estadi precoç (cT2N0M0). Aquests tumors solen requerir una cirurgia única en principi (resecció anterior amb exèresi total del mesorecte), en la que una part del recte en la que s'inclou el tumor i un marge de teixit sa s'extirpa, juntament amb ganglis limfàtics (afectats en uns 2 de cada 10 pacients); també inclou tornar a unir (anastomosar) la part de recte que no s'ha extirpat amb la resta d'intestí sa. Aquesta cirurgia es fa per via laparoscòpica, és a dir, a partir de unes 4 incisions a l'abdomen. Amb aquesta cirurgia, el percentatge de curació és molt bo (proper al 85%), però hi ha perill de lesionar estructures nervioses properes que li poden causar problemes com mala funció sexual i incontinència, tant urinària com fecal. També hi pot haver complicacions postquirúrgiques com pèrdua de la unió de l'anastomosis feta, hemorràgies i infeccions. A més, sol requerir fer ileostomies derivatives per tal de protegir la sutura de la unió feta, aquestes ileostomies es solen tancar, però en certes ocasions no és possible (normalment si apareixen complicacions relacionades amb la malaltia). Les complicacions relacionades amb la ileostomia inclouen irritació de la pell del voltant i herniació. Els temps d'alta es situa sobre la setmana.

El nou tractament que vol provar aquest estudi, combina una cirurgia molt menys agressiva, la cirurgia transanal mínimament invasiva (TAMIS) amb un curs curt de radioteràpia (SC-RT) preoperatòria. La radioteràpia és fa en una setmana, amb 5 sessions de radioteràpia i tot seguit, preferiblement en una setmana, el pacient és operat per TAMIS. La TAMIS és una tècnica amb la que, operant a través de l'anus, és a dir, sense fer cap incisió, s'extirpa el tumor sencer amb una vora de teixit sa al voltant, sense necessitat de haver de anastomosar els dos extrems d'intestí ja que el teixit extirpat és molt menor i no inclou tota la circumferència del recte, una sutura simple de pocs centímetres és suficient per reparar el defecte, Aquesta cirurgia té molts millors resultats funcionals, ja que l'impacte sobre la continència i la sexualitat és nul o mínim i limitat als primers dies postoperatori; a més, entre un o dos dies després el pacient pot ser donat d'alta. Els inconvenients que té aquesta cirurgia és que els ganglis que puguin estar afectats i radiològicament no vistos, no serien extirpats, al no permetre-ho la menor incisió de la tècnica quirúrgica. Per tal de contrarestar això, s'afegeix la radioteràpia, per tractar la malaltia que pugui no haver estat detectada amb les proves prèvies a l'operació i així intentar aconseguir la curació amb una experiència molt menys cruenta i menys complicacions.

Quin és l'objectiu de l'estudi?

Els investigadors de l'estudi tenen com a objectiu principal avaluar si la nova tècnica descrita que inclou la TAMIS i la radioteràpia és igual d'eficaç que la tècnica realitzada fins ara en la supervivència dels pacients. També es vol veure si la nova tècnica proporciona millors resultats tant en disminució de complicacions després de

la cirurgia, com en qualitat de vida i funció sexual i intestinal.

Considerarem com que les dues tècniques són equivalents en supervivència si als 5 anys de la cirurgia tenim una supervivència semblant en els dos grups operats. Direm que una tècnica és millor que l'altre en quant a menors complicacions després de la cirurgia si així és vist durant la seva estada a l'hospital després de la cirurgia. Serà millor en qualitat de vida, funció sexual i funció intestinal si les respostes als tests i qüestionaris que els investigadors donen als pacients perquè responguin així ho constaten.

Com es realitzarà l'estudi?

Per a realitzar l'estudi es formaran dos grups, un dels quals rebrà el tractament de TAMIS més radioteràpia i a l'altre grup es farà la resecció anterior del recte amb extirpació total del mesorecte. La assignació dels pacients a un o un altre grup es farà aleatòriament, és a dir, com si tiréssim una moneda a l'aire. Això es fa així per assegurar-nos de que els pacients dels dos grups són semblants. Vostè sabrà el grup al que ha sigut assignat un cop que s'hagi decidit a l'atzar. Ningú pot triar ni modificar el grup al que una persona ha estat assignada per atzar.

Després de les cirurgies i la posterior alta, als dos grups se'ls farà un seguiment, per tal de detectar qualsevol reaparició del tumor. El grup que rep la cirurgia habitual, serà seguit tal com tots els pacients operats d'un tumor al recte; aquest seguiment inclou proves analítiques, proves d'imatge, colonoscòpies i consultes amb el seu cirurgià. El grup que rep el tractament de TAMIS més radioteràpia serà seguit de forma que al seguiment de base realitzat a tots els pacients, se li afegiran més proves d'imatge i més visites amb el seu cirurgià. El seguiment inclòs a l'estudi duraria 5 anys en els dos grups; un cop passats aquests 5 anys, el seu seguiment seguiria tal com es fa habitualment en tot pacient que ha patit la malaltia.

En els dos grups de tractament, en cada una de les visites amb el seu cirurgià se li administrarien uns qüestionaris: un sobre la seva qualitat global de vida, un altre sobre la seva funció sexual i un últim sobre els seus hàbits intestinals. Aquests qüestionaris també s'administrarien abans de la cirurgia. Els pacients seran citats dues hores abans de la seva visita amb el cirurgià per tal de que puguin completar els qüestionaris i ser entregats el mateix dia, per tal d'evitar altres desplaçaments.

La peça quirúrgica extreta amb el tumor, és sempre analitzada pel servei de Anatomia Patològica de forma rutinària, per tal de detectar de forma exacta quina classe de tumor és, classificar-lo i veure si els marges de teixit sà ressecats durant la cirurgia han sigut suficients.

Quins beneficis puc obtenir per participar en aquest estudi?

Amb aquest estudi es pretén obtenir una informació que avui dia no tenim, és a dir, si val la pena o no realitzar la radioteràpia més TAMIS en pacients amb tumors de recte cT2N0M0; per això és necessari demostrar que és al menys tant eficaç com el que ja s'utilitza.

Si el tractament de TAMIS amb radioteràpia preoperatòria fos almenys igual d'eficaç en quant a supervivència i millor en preservar la seva qualitat de vida, funció sexual i funció intestinal que el tractament habitual, vostre podria rebre aquest benefici directe per la seva participació en l'estudi. En qualsevol cas, avui dia no es pot assegurar que vostè rebi aquest benefici per la seva participació en l'estudi. Però és important que sàpiga que amb la seva participació, amb independència del tractament que rebi, pot contribuir a un avenç científic que contribueixi a millorar la qualitat de vida de les persones amb la seva mateixa malaltia.

Cap membre del personal sanitari dels que participen en l'estudi rebran més compensació econòmica per la realització i participació en l'estudi, més enllà de el seu sou com a professionals de salut de l'administració pública.

Quins risc i/o molèsties puc patir per participar en l'estudi?

Tal com hem explicat, la cirurgia habitual (resecció anterior amb extirpació total del mesorecte) inclou els riscos de qualsevol cirurgia major, tal com són els de l'anestèsia, els de l'acte quirúrgic i els del període postoperatori. Aquests riscos inclouen infeccions, hemorràgies, dolor i com a extrem, la mort. Els riscos concrets d'aquesta cirurgia inclouen la dehiscència anastomòtica (descosit de la sutura que uneix els dos extrems d'intestí), incontinència urinària, impotència sexual i incontinència fecal, tant transitòria com permanent. També inclou els

inconvenients de la ileostomia derivativa, com són la irritació de la pell al voltant d'aquesta, herniació o una manca de tancament d'aquesta. El període mig d'ingrés és d'una setmana, però pot ser allargada depenent de l'evolució.

Les complicacions de la cirurgia TAMIS són menys habituals i els més freqüents d'aquesta són la infecció de la ferida i el descosit de la sutura. Temps d'ingrés és d'un o dos dies. Les complicacions relacionades amb la radioteràpia poden incloure fatiga lleu, envermelliment, sequedat i picor en la zona irradiada, irritació important, diarrea, manca de gana, defecació freqüent. Generalment els efectes desapareixen poc després.

Assegurança

El promotor de l'estudi ha contractat una pòlissa d'assegurament de responsabilitat civil que cobrirà els danys inesperats causats per la seva participació en l'estudi i fins a un any després de la finalització d'aquest, sempre que els danys no siguin conseqüència de l'evolució de la malaltia o per ineficàcia del tractament.

Quines dades es recolliran?

Es recolliran dades personals (edat, sexe), dades sobre el càncer (localització del tumor, informació sobre la peça quirúrgica, dades sobre recidives, possibles tractaments rebuts a causa de recidiva) i dades sobre qualitat de vida i funcionalitat recollides en els qüestionaris. Aquests registres es faran a mesura que es recullin les dades.

Els qüestionaris seran entregats dues hores abans de cada visita amb el seu cirurgià. En aquest temps poden ser entregats i contestats sense problemes. Si vostè necessita més temps se li donarà sense inconvenients.

Com es tractaran les meves dades i com es preservarà la meva confidencialitat?

Totes les seves dades es tractaran confidencialment per persones relacionades amb la investigació i obligades pel seu deure personal. També podrien tenir accés les autoritats sanitàries i algun membre designat del Comitè d'Ètica de Investigació Clínica que supervisi l'estudi, si així ho sol·licitaren. Aquest controls es realitzen per garantir que s'hagin respectat els drets dels pacients.

No s'utilitzarà el seu nom ni cognoms per codificar la seva informació registrada; s'utilitzarà un codi que només els investigadors podran relacionar amb el seu nom.
El responsable del registre es el Dr. Pere Planellas, investigador principal de l'estudi.

D'acord amb la Llei Orgànica de Protecció de Dades, ha de saber que té dret a l'accés a les dades de la seva persona que siguin emmagatzemats, a rectificar-los, a cancel·lar-los i a oposar-se al seu ús, sense tenir que donar cap explicació.

Em puc retirar de l'estudi?

La participació en l'estudi és totalment voluntària. Vostè podrà retirar-se en qualsevol moment si ho desitja, sense haver de donar explicacions i sense que això produeixi perjudici en la seva relació amb els metges ni en els cuidats que se li hagin d'administrar.
De la mateixa forma, l'equip d'investigadors pot decidir interrompre l'estudi en qualsevol moment si així fos necessari o si ho exigissin les autoritats sanitàries.

Qui supervisaria l'estudi?

El Comitè d'Ètica d'investigació Clínica de l'Hospital Josep Trueta de Girona, que és l'organisme encarregat d'avaluar la seguretat dels pacients i els aspectes ètics i metodològics d'aquest estudi, ha aprovat l'estudi, així com la present full d'informació i el formulari de consentiment informat.

Amb qui puc contactar en cas de dubte?

Els següent investigador del Servei de cirurgia colorectal de l'Hospital Josep Trueta serà el responsables de l'assaig i d'informar i contestar als seus dubtes i preguntes:

Dr. Pere Planellas Telèfon: XXX XX XX XX

DECLARACIÓ DE CONSENTIMENT DEL PARTICIPANT

Jo ..... , amb DNI ..... ,

a data de __ __ / __ __ / __ __ __ __ declaro que:
(DD / MM / AAAA)

He llegit aquesta fulla d'informació i he tingut temps suficient per considerar la meva decisió;
M'han donat l'oportunitat de formular preguntes i totes elles s'han respost satisfactòriament;
Comprenc que la meva participació és voluntària;
Comprenc que puc retirar-me de l'estudi:

- Quan vulgui,
- Sense haver de donar explicacions,
- Sense que això repercuteixi en les meves cures mèdiques.

Per això, dono lliurement la meva conformitat per a participar en l'estudi i dono el meu consentiment per l'accés i utilització de les meves dades en les condicions que es detallen en la fulla d'informació.
També declaro que he rebut una còpia d'aquest document.

FIRMA DEL PACIENT:	*FIRMA DE L'INVESTIGADOR PRINCIPAL:*
_____	_____
__ __ / __ __ / __ __ __ __ (DD / MMM / AAAA)	__ __ / __ __ / __ __ __ __ (DD / MMM / AAAA)

REVOCACIÓ DEL CONSENTIMENT

Jo ..... , amb DNI ..... ,

a data de __ __ / __ __ / __ __ __ __ , revoco el consentiment donat anteriorment i no desitjo continuar
(DD / MM / AAAA)

participant en l'estudi.

FIRMA DEL PACIENT:	*FIRMA DE L'INVESTIGADOR PRINCIPAL:*
_____	_____
__ __ / __ __ / __ __ __ __ (DD / MM / AAAA)	__ __ / __ __ / __ __ __ __ (DD / MM / AAAA)

15.3. ANNEX V: SF-36

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Datos para el estudio

Día:	Mes:	Año: (20...)	Número identificador:
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ 11 ☐ 12 ☐ 13 ☐ 14 ☐ 15 ☐ 16 ☐ 17 ☐ 18 ☐ 19 ☐ 20 ☐ 21 ☐ 22 ☐ 23 ☐ 24 ☐ 25 ☐ 26 ☐ 27 ☐ 28 ☐ 29 ☐ 30 ☐ 31	☐ Enero ☐ Julio ☐ Febrero ☐ Agosto ☐ Marzo ☐ Septiembre ☐ Abril ☐ Octubre ☐ Mayo ☐ Noviembre ☐ Junio ☐ Diciembre	0 ☐☐ 1 ☐☐ 2 ☐☐ 3 ☐☐ 4 ☐☐ 5 ☐☐ 6 ☐☐ 7 ☐☐ 8 ☐☐ 9 ☐☐	0 ☐☐☐☐☐☐☐☐ 1 ☐☐☐☐☐☐☐☐ 2 ☐☐☐☐☐☐☐☐ 3 ☐☐☐☐☐☐☐☐ 4 ☐☐☐☐☐☐☐☐ 5 ☐☐☐☐☐☐☐☐ 6 ☐☐☐☐☐☐☐☐ 7 ☐☐☐☐☐☐☐☐ 8 ☐☐☐☐☐☐☐☐ 9 ☐☐☐☐☐☐☐☐

Cuestionario de Salud SF-36 (versión 2)

Versión española de SF-36v2™ Health Survey © 1996, 2000 adaptada por J. Alonso y cols 2003.

Este instrumento ha superado los estándares de calidad del **Medical Outcome Trust** y de la Red Cooperativa para la Investigación en Resultados de Salud y Servicios Sanitarios (**Red IRYSS**).
El cuestionario y su material de soporte están disponibles en BiblioPRO, la biblioteca virtual de la Red IRYSS (www.rediryss.net).

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Su Salud y Bienestar

Por favor conteste las siguientes preguntas. Algunas preguntas pueden parecerse a otras pero cada una es diferente.

Tómese el tiempo necesario para leer cada pregunta, y marque con una ☒ la casilla que mejor describa su respuesta.

¡Gracias por contestar a estas preguntas!

1. En general, usted diría que su salud es:

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Excelente	Muy buena	Buena	Regular	Mala

2. ¿Cómo diría usted que es su salud actual, comparada con la de hace un año?:

Mucho mejor ahora que hace un año	Algo mejor ahora que hace un año	Más o menos igual que hace un año	Algo peor ahora que hace un año	Mucho peor ahora que hace un año
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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3. Las siguientes preguntas se refieren a actividades o cosas que usted podría hacer en un día normal. Su salud actual, ¿le limita para hacer esas actividades o cosas? Si es así, ¿cuánto?

	Sí, me limita mucho	Sí, me limita un poco	No, no me limita nada
a Esfuerzos intensos, tales como correr, levantar objetos pesados, o participar en deportes agotadores.	☐ 1	☐ 2	☐ 3
b Esfuerzos moderados, como mover una mesa, pasar la aspiradora, jugar a los bolos o caminar más de 1 hora.	☐ 1	☐ 2	☐ 3
c Coger o llevar la bolsa de la compra.	☐ 1	☐ 2	☐ 3
d Subir varios pisos por la escalera.	☐ 1	☐ 2	☐ 3
e Subir un sólo piso por la escalera.	☐ 1	☐ 2	☐ 3
f Agacharse o arrodillarse.	☐ 1	☐ 2	☐ 3
g Caminar un kilómetro o más	☐ 1	☐ 2	☐ 3
h Caminar varios centenares de metros.	☐ 1	☐ 2	☐ 3
i Caminar unos 100 metros.	☐ 1	☐ 2	☐ 3
j Bañarse o vestirse por sí mismo.	☐ 1	☐ 2	☐ 3

4. Durante las 4 últimas semanas, ¿con qué frecuencia ha tenido alguno de los siguientes problemas en su trabajo o en sus actividades cotidianas, a causa de su salud física?

	Siempre	Casi siempre	Algunas veces	Sólo alguna vez	Nunca
a ¿Tuvo que reducir el tiempo dedicado al trabajo o a sus actividades cotidianas?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b ¿Hizo menos de lo que hubiera querido hacer?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c ¿Tuvo que dejar de hacer algunas tareas en su trabajo o en sus actividades cotidianas?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d ¿Tuvo dificultad para hacer su trabajo o sus actividades cotidianas (por ejemplo, le costó más de lo normal)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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5. Durante las 4 últimas semanas, ¿con qué frecuencia ha tenido alguno de los siguientes problemas en su trabajo o en sus actividades cotidianas, a causa de algún problema emocional (como estar triste, deprimido o nervioso)?

	Siempre	Casi siempre	Algunas veces	Sólo alguna vez	Nunca
a ¿Tuvo que reducir el tiempo dedicado al trabajo o a sus actividades cotidianas por algún problema emocional?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b ¿Hizo menos de lo que hubiera querido hacer por algún problema emocional?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c ¿Hizo su trabajo o sus actividades cotidianas menos cuidadosamente que de costumbre, por algún problema emocional?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. Durante las 4 últimas semanas, ¿hasta qué punto su salud física o los problemas emocionales han dificultado sus actividades sociales habituales con la familia, los amigos, los vecinos u otras personas?

Nada	Un poco	Regular	Bastante	Mucho
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. ¿Tuvo dolor en alguna parte del cuerpo durante las 4 últimas semanas?

No, ninguno	Sí, muy poco	Sí, un poco	Sí, moderado	Sí, mucho	Sí, muchísimo
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. Durante las 4 últimas semanas, ¿hasta qué punto el dolor le ha dificultado su trabajo habitual (incluido el trabajo fuera de casa y las tareas domésticas)?

Nada	Un poco	Regular	Bastante	Mucho
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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9. Las preguntas que siguen se refieren a cómo se ha sentido y cómo le han ido las cosas durante las 4 últimas semanas. En cada pregunta responda lo que se parezca más a cómo se ha sentido usted. Durante las últimas 4 semanas ¿con qué frecuencia...

	Siempre	Casi siempre	Algunas veces	Sólo alguna vez	Nunca
a se sintió lleno de vitalidad?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b estuvo muy nervioso?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c se sintió tan bajo de moral que nada podía animarle?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d se sintió calmado y tranquilo?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e tuvo mucha energía?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f se sintió desanimado y deprimido?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g se sintió agotado?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h se sintió feliz?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i se sintió cansado?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. Durante las 4 últimas semanas, ¿con qué frecuencia la salud física o los problemas emocionales le han dificultado sus actividades sociales (como visitar a los amigos o familiares)?

Siempre	Casi siempre	Algunas veces	Sólo alguna vez	Nunca
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. Por favor diga si le parece CIERTA o FALSA cada una de las siguientes frases:

	Totalmente cierta	Bastante cierta	No lo sé	Bastante falsa	Totalmente falsa
a Creo que me pongo enfermo más facilmente que otras personas	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Estoy tan sano como cualquiera	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Creo que mi salud va a empeorar	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Mi salud es excelente	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Gracias por contestar a estas preguntas

15.4. ANNEX VI: IIEF

INDICE INTERNACIONAL DE FUNCION ERECTIL - IIEF -

Iniciales del paciente _____ Nº identificación _____ Fecha _____

¿Es usted sexualmente activo (definitivo como actividad sexual con pareja o estimulación manual)?

☐ **SI** ☐ **NO**

En caso afirmativo, por favor cumplimente el cuestionario relativo a su actividad sexual. (en cada pregunta, marque sólo una casilla).

	SIN ACTIVIDAD SEXUAL	CASI NUNCA ó NUNCA	MENOS DE LA MITAD DE LAS VECES	LA MITAD DE LAS VECES	MAS DE LA MITAD DE LAS VECES	CASI SIEMPRE ó SIEMPRE
1. Durante las últimas 4 semanas, ¿con qué frecuencia logró una erección durante la actividad sexual[B]?	0	1	2	3	4	5
2. Durante las últimas 4 semanas, cuando tuvo erecciones con la estimulación sexual[D], ¿con qué frecuencia fue suficiente la rigidez para la penetración?	0	1	2	3	4	5
3. Durante las últimas 4 semanas, al intentar una relación sexual[A], ¿con qué frecuencia logró penetrar a su pareja?	0	1	2	3	4	5
4. Durante las últimas 4 semanas, durante la relación sexual[A], ¿con qué frecuencia logró mantener la erección después de la penetración?	0	1	2	3	4	5

	SIN ACTIVIDAD SEXUAL	EXTREMADAMENTE DIFICIL	MUY DIFICIL	DIFICIL	ALGO DIFICIL	SIN DIFICULTAD
5. Durante las últimas 4 semanas, durante la relación sexual[A], ¿Cuál fue el grado de dificultad para mantener la erección hasta completar la relación sexual?	0	1	2	3	4	5

	NINGUNA	1-2 VECES	3-4 VECES	5-6 VECES	7-10 VECES	11 ó MAS
6. Durante las últimas 4 semanas, ¿cuántas veces intentó una relación sexual[A]?	0	1	2	3	4	5

	SIN ACTIVIDAD SEXUAL	CASI NUNCA ó NUNCA	MENOS DE LA MITAD DE LAS VECES	LA MITAD DE LAS VECES	MAS DE LA MITAD DE LAS VECES	CASI SIEMPRE ó SIEMPRE
7. Durante las últimas 4 semanas, cuando intentó una relación sexual[A], ¿con qué frecuencia resultó satisfactoria para usted?	0	1	2	3	4	5

A = Acto sexual;
Se define como la penetración de la pareja.
B = Actividad sexual;
Incluye el acto sexual, caricias juegos anteriores al acto y la masturbación.
C = Eyacular;
Se define como la expulsión de semen del pene (o la sensación de hacerlo).
D = Estimulación sexual;
Incluye situaciones como juegos amorosos con una pareja o mirar fotos eróticas, etc.

INDICE INTERNACIONAL DE FUNCION ERECTIL - IIEF - (cont.)

	NO REALICE EL ACTO	NO DISFRUTE NADA	NO DISFRUTE MUCHO	DISFRUTE ALGO	DISFRUTE BASTANTE	DISFRUTE MUCHO
8. Durante las últimas 4 semanas, ¿cuánto ha disfrutado de la relación sexual[A]?	0	1	2	3	4	5

	SIN ACTIVIDAD SEXUAL	CASI NUNCA ó NUNCA	MENOS DE LA MITAD DE LAS VECES	LA MITAD DE LAS VECES	MAS DE LA MITAD DE LAS VECES	CASI SIEMPRE ó SIEMPRE
9. Durante las últimas 4 semanas, durante la estimulación o la relación sexual[A], ¿con qué frecuencia eyaculó[C]?	0	1	2	3	4	5
10. Durante las últimas 4 semanas, durante la estimulación[C] o la relación sexual[A], ¿con qué frecuencia tuvo una sensación de orgasmo[C] (con o sin eyaculación)?	0	1	2	3	4	5

Las siguientes dos preguntas se refieren al deseo sexual, definido como una sensación que puede ser un deseo de tener una experencia sexual (por ejemplo, masturbación o relación sexual), un pensamiento sobre una relación sexual o un sentimiento de frustración por no tener una relación sexual.

	CASI NUNCA ó NUNCA	EN ALGUNOS MOMENTOS	BUENA PARTE DEL TIEMPO	LA MAYOR PARTE DEL TIEMPO	CASI SIEMPRE ó SIEMPRE
11. Durante las últimas 4 semanas, ¿con qué frecuencia ha sentido un deseo sexual?	1	2	3	4	5

	MUY BAJO ó NULO	BAJO	MODERADO	ALTO	MUY ALTO
12. Durante las últimas 4 semanas, ¿cómo calificaría su nivel de deseo sexual?	1	2	3	4	5

	MUY INSATISFECHO	BASTANTE INSATISFECHO	NI SATISFECHO NI INSATISFECHO	BASTANTE SATISFECHO	MUY SATISFECHO
13. Durante las últimas 4 semanas, ¿cuál ha sido el grado de satisfacción con su vida sexual en general?	1	2	3	4	5
14. Durante las últimas 4 semanas, ¿cuál ha sido el grado de satisfacción con la relación sexual con su pareja?	1	2	3	4	5

	MUY BAJO ó NULO	BAJO	MODERADO	ALTO	MUY ALTO
15. Durante las últimas 4 semanas, ¿cómo calificaría la confianza que tiene en poder lograr y mantener una erección?	1	2	3	4	5

A = Acto sexual;
Se define como la penetración de la pareja.
B = Actividad sexual;
Incluye el acto sexual, caricias juegos anteriores al acto y la masturbación.
C = Eyacular;
Se define como la expulsión de semen del pene (o la sensación de hacerlo).
D = Estimulación sexual;
Incluye situaciones como juegos amorosos con una pareja o mirar fotos eróticas, etc.

15.5. ANNEX VII: FSFI

CUESTIONARIO SOBRE LA FUNCIÓN SEXUAL FEMENINA (Spanish version of FSFI©)

Nº IDENTIFICACIÓN DE LA PACIENTE ☐☐☐

INSTRUCCIONES: Estas preguntas tratan sobre sus sentimientos y respuestas sexuales durante las últimas 4 semanas. Por favor, conteste a las siguientes preguntas con la mayor honestidad y claridad posibles. Sus respuestas serán totalmente confidenciales. Para contestar a estas preguntar, tenga en cuenta las siguientes definiciones:

- Actividad sexual puede incluir caricias, juegos previos, masturbación o coito vaginal.
- Relación sexual se define como penetración del pene en la vagina.
- Estimulación sexual incluye situaciones como los juegos previos con la pareja, la autoestimulación (masturbación) o las fantasías sexuales.

MARQUE SÓLO UNA CASILLA POR PREGUNTA

Deseo o interés sexual es un sentimiento que incluye querer tener una experiencia sexual, sentirse receptiva ante la iniciativa sexual de la pareja y pensar o tener fantasías sobre hacer el amor.

1. Durante las últimas 4 semanas, ¿con qué **frecuencia** ha sentido deseo o interés sexual?

   5☐ Casi siempre o siempre.
   4☐ Muchas veces (más de la mitad del tiempo)
   3☐ Algunas veces (sobre la mitad del tiempo)
   2☐ Pocas veces (menos de la mitad del tiempo)
   1☐ Casi nunca o nunca

2. Durante las últimas 4 semanas, ¿cómo evaluaría su **nivel** (grado) de deseo o interés sexual?

   5☐ Muy alto
   4☐ Alto
   3☐ Moderado
   2☐ Bajo
   1☐ Muy bajo o ninguno

La excitación sexual es un sentimiento que incluye tanto aspectos físicos como mentales. Puede abarcar sensaciones de calor o cosquilleo en los genitales, lubricación (humedad) o contracciones musculares.

3. Durante las últimas 4 semanas, ¿con qué **frecuencia** se ha sentido excitada sexualmente ("caliente") durante la actividad sexual o el coito?

   0☐ No he tenido actividad sexual
   5☐ Casi siempre o siempre
   4☐ Muchas veces (más de la mitad de las veces)
   3☐ Algunas veces (sobre la mitad de las veces)
   2☐ Pocas veces (menos de la mitad de las veces)
   1☐ Casi nunca o nunca

4. Durante las últimas 4 semanas, ¿cómo evaluaría su **nivel** (grado) de excitación sexual ("estar caliente") durante la actividad sexual o el coito?

   0☐ No he tenido actividad sexual
   5☐ Muy alto
   4☐ Alto
   3☐ Moderado
   2☐ Bajo
   1☐ Muy bajo o ninguno

5. Durante las últimas 4 semanas, ¿hasta qué punto se ha sentido **segura** de poder excitarse sexualmente durante la actividad sexual o el coito?

   0☐ No he tenido actividad sexual
   5☐ Segurísima
   4☐ Muy segura
   3☐ Moderadamente segura
   2☐ Poco segura

1□ Muy poco o nada segura

6. Durante las últimas 4 semanas, ¿con qué **frecuencia** se ha sentido satisfecha con su excitación durante la actividad sexual o el coito?

0□ No he tenido actividad sexual
5□ Casi siempre o siempre
4□ Muchas veces (más de la mitad de las veces)
3□ Algunas veces (sobre la mitad de las veces)
2□ Pocas veces (menos de la mitad de las veces)
1□ Casi nunca o nunca

7. Durante las últimas 4 semanas, ¿con qué **frecuencia** ha estado lubricada ("mojada") durante la actividad sexual o el coito?

0□ No he tenido actividad sexual
5□ Casi siempre o siempre
4□ Muchas veces (más de la mitad de las veces)
3□ Algunas veces (sobre la mitad de las veces)
2□ Pocas veces (menos de la mitad de las veces)
1□ Casi nunca o nunca

8. Durante las últimas 4 semanas, ¿hasta qué punto le ha sido **difícil** estar lubricada ("mojada") durante la actividad sexual o el coito?

0□ No he tenido actividad sexual
5□ Extremadamente difícil o imposible
4□ Muy difícil
3□ Difícil
2□ Ligeramente difícil
1□ Nada difícil

9. Durante las últimas 4 semanas, ¿con qué frecuencia **ha mantenido** su lubricación ("humedad") hasta el final de la actividad sexual o el coito?

0□ No he tenido actividad sexual
5□ Casi siempre o siempre
4□ Muchas veces (más de la mitad de las veces)
3□ Algunas veces (sobre la mitad de las veces)
2□ Pocas veces (menos de la mitad de las veces)
1□ Casi nunca o nunca

10. Durante las últimas 4 semanas, ¿hasta qué punto le ha sido **difícil** mantener su lubricación ("humedad") hasta el final de la actividad sexual o el coito?

0□ No he tenido actividad sexual
5□ Extremadamente difícil o imposible
4□ Muy difícil
3□ Difícil
2□ Ligeramente difícil
1□ Nada difícil

11. Durante las últimas 4 semanas, cuando ha habido estimulación sexual o coito, ¿con qué **frecuencia** ha llegado al orgasmo (clímax)?

0□ No he tenido actividad sexual
5□ Casi siempre o siempre
4□ Muchas veces (más de la mitad de las veces)
3□ Algunas veces (sobre la mitad de las veces)
2□ Pocas veces (menos de la mitad de las veces)
1□ Casi nunca o nunca

12. Durante las últimas 4 semanas, cuando ha habido estimulación sexual o coito, ¿hasta qué punto le ha sido **difícil** llegar al orgasmo (clímax)?

0□ No he tenido actividad sexual
5□ Extremadamente difícil o imposible
4□ Muy difícil
3□ Difícil
2□ Ligeramente difícil
1□ Nada difícil

13. Durante las últimas 4 semanas, ¿hasta qué punto se ha sentido **satisfecha** con su capacidad para llegar al orgasmo (clímax durante la actividad sexual o el coito?

0□ No he tenido actividad sexual
5□ Muy satisfecha
4□ Moderadamente satisfecha
3□ Igual de satisfecha como de insatisfecha
2□ Moderadamente insatisfecha
1□ Muy insatisfecha

14. Durante las últimas 4 semanas, ¿hasta qué punto se ha sentido **satisfecha** con la cantidad de intimidad emocional entre usted y su pareja durante la actividad sexual?

    0□ No he tenido actividad sexual
    5□ Muy satisfecha
    4□ Moderadamente satisfecha
    3□ Igual de satisfecha como de insatisfecha
    2□ Moderadamente insatisfecha
    1□ Muy insatisfecha

15. Durante las últimas 4 semanas, ¿hasta qué punto se ha sentido **satisfecha** de su relación sexual con su pareja?

    5□ Muy satisfecha
    4□ Moderadamente satisfecha
    3□ Igual de satisfecha como de insatisfecha
    2□ Moderadamente insatisfecha
    1□ Muy insatisfecha

16. Durante las últimas 4 semanas, ¿hasta qué punto se ha sentido **satisfecha** con su vida sexual en general?

    5□ Muy satisfecha
    4□ Moderadamente satisfecha
    3□ Igual de satisfecha como de insatisfecha
    2□ Moderadamente insatisfecha
    1□ Muy insatisfecha

17. Durante las últimas 4 semanas, ¿con qué **frecuencia** ha experimentado molestias o dolor durante la penetración vaginal?

    5□ Muy satisfecha
    4□ Moderadamente satisfecha
    3□ Igual de satisfecha como de insatisfecha
    2□ Moderadamente insatisfecha
    1□ Muy insatisfecha

18. Durante las últimas 4 semanas, ¿con qué **frecuencia** ha experimentado molestias o dolor después de la penetración vaginal?

    5□ Muy satisfecha
    4□ Moderadamente satisfecha
    3□ Igual de satisfecha como de insatisfecha
    2□ Moderadamente insatisfecha
    1□ Muy insatisfecha

19. Durante las últimas 4 semanas, ¿cómo evaluaría su **nivel** (grado) de molestias o dolor durante o después de la penetración vaginal?

    5□ Muy satisfecha
    4□ Moderadamente satisfecha
    3□ Igual de satisfecha como de insatisfecha
    2□ Moderadamente insatisfecha
    1□ Muy insatisfecha

15.6. ANNEX VIII: COREFO

CUESTIONARIO SOBRE LA FUNCIÓN COLORECTAL (COREFO QUESTIONNAIRE)

Nº IDENTIFICACIÓN DEL PACIENTE ☐☐☐

Instrucciones: Estas preguntas se refieren a las **ÚLTIMAS DOS SEMANAS**. Marque **UNA** sola respuesta.

1. Cuantas deposiciones ha tenido durante el día? (media por día)

   ☐ 0-1
   ☐ 2-4
   ☐ 5-7
   ☐ 8-10
   ☐ 11 veces o más

2. Cuantas deposiciones ha tenido durante la noche? (media por noche)

   ☐ 0
   ☐ 1-2
   ☐ 3-4
   ☐ 5-6
   ☐ 7 veces o más

3. En el caso de que necesitara ir al baño de forma urgente, ha tenido problemas para retener la deposición durante más de quince minutos?

   ☐ No, nunca
   ☐ Sí, menos de una vez por semana
   ☐ Sí, 1-2 días por semana
   ☐ Sí, 3-5 días por semana
   ☐ Sí, 6-7 días por semana

4. Ha tenido alguna falsa alarma? (= ganas de ir al baño sin tener después deposición)

   ☐ No, nunca
   ☐ Sí, menos de una vez por semana
   ☐ Sí, 1-2 días por semana
   ☐ Sí, 3-5 días por semana
   ☐ Sí, 6-7 días por semana

5. Ha tenido dolor durante las deposiciones?

   ☐ No, nunca
   ☐ Sí, menos de una vez por semana
   ☐ Sí, 1-2 días por semana
   ☐ Sí, 3-5 días por semana
   ☐ Sí, 6-7 días por semana

6. Ha experimentado sangrado durante las deposiciones?

   ☐ No, nunca
   ☐ Sí, menos de una vez por semana
   ☐ Sí, 1-2 días por semana
   ☐ Sí, 3-5 días por semana
   ☐ Sí, 6-7 días por semana

7. Ha tenido algún ventoseo sin poder controlar?

   ☐ No, nunca
   ☐ Sí, menos de una vez por semana
   ☐ Sí, 1-2 días por semana
   ☐ Sí, 3-5 días por semana
   ☐ Sí, 6-7 días por semana

8. Se le han escapado heces líquidas durante el día?

   ☐ No, nunca
   ☐ Sí, menos de una vez por semana
   ☐ Sí, 1-2 días por semana
   ☐ Sí, 3-5 días por semana
   ☐ Sí, 6-7 días por semana

9. Se le han escapado heces líquidas durante la noche?

   ☐ No, nunca
   ☐ Sí, menos de una vez por semana
   ☐ Sí, 1-2 días por semana
   ☐ Sí, 3-5 días por semana
   ☐ Sí, 6-7 días por semana

10. Se le han escapado heces sólidas durante el día?

    ☐ No, nunca

- ☐ Sí, menos de una vez por semana
- ☐ Sí, 1-2 días por semana
- ☐ Sí, 3-5 días por semana
- ☐ Sí, 6-7 días por semana

11. Se le han escapado heces sólidas durante la noche?

- ☐ No, nunca
- ☐ Sí, menos de una vez por semana
- ☐ Sí, 1-2 días por semana
- ☐ Sí, 3-5 días por semana
- ☐ Sí, 6-7 días por semana

12. Ha notado algún manchado de heces en su ropa interior durante el día?

- ☐ No, nunca
- ☐ Sí, menos de una vez por semana
- ☐ Sí, 1-2 días por semana
- ☐ Sí, 3-5 días por semana
- ☐ Sí, 6-7 días por semana

13. Ha notado algún manchado de heces en su ropa interior, pijama o camisón al final de la noche?

- ☐ No, nunca
- ☐ Sí, menos de una vez por semana
- ☐ Sí, 1-2 días por semana
- ☐ Sí, 3-5 días por semana
- ☐ Sí, 6-7 días por semana

14. Ha sido difícil para usted distinguir entre una ventosidad y una deposición?

- ☐ No, nunca
- ☐ Sí, menos de una vez por semana
- ☐ Sí, 1-2 días por semana
- ☐ Sí, 3-5 días por semana
- ☐ Sí, 6-7 días por semana

15. Cuando ha ido al váter, hace una deposición le ha costado más de 15 minutos?

- ☐ No, nunca
- ☐ Sí, menos de una vez por semana
- ☐ Sí, 1-2 días por semana
- ☐ Sí, 3-5 días por semana
- ☐ Sí, 6-7 días por semana

16. Ha tenido alguna vez la sensación de no haber vaciado el intestino después de una deposición?

- ☐ No, nunca
- ☐ Sí, menos de una vez por semana
- ☐ Sí, 1-2 días por semana
- ☐ Sí, 3-5 días por semana
- ☐ Sí, 6-7 días por semana

17. Después de una deposición, ha tenido que volver al váter antes de una hora para otra deposición?

- ☐ No, nunca
- ☐ Sí, menos de una vez por semana
- ☐ Sí, 1-2 días por semana
- ☐ Sí, 3-5 días por semana
- ☐ Sí, 6-7 días por semana

18. Ha utilizado medicación para espesar la heces?

- ☐ No, nunca
- ☐ Sí, menos de una vez por semana
- ☐ Sí, 1-2 días por semana
- ☐ Sí, 3-5 días por semana
- ☐ Sí, 6-7 días por semana

19. Ha utilizado medicación para hacer más fluidas las heces?

- ☐ No, nunca
- ☐ Sí, menos de una vez por semana
- ☐ Sí, 1-2 días por semana
- ☐ Sí, 3-5 días por semana
- ☐ Sí, 6-7 días por semana

20. Ha comido ciertos alimentos a propósito para hacer que sus heces fueran más espesas o fluidas?

- ☐ No, nunca
- ☐ Sí, menos de una vez por semana
- ☐ Sí, 1-2 días por semana
- ☐ Sí, 3-5 días por semana
- ☐ Sí, 6-7 días por semana

21. Ha evitado ciertos alimentos a propósito para prevenir que sus heces fueran líquidas o duras?

- ☐ No, nunca
- ☐ Sí, menos de una vez por semana
- ☐ Sí, 1-2 días por semana
- ☐ Sí, 3-5 días por semana
- ☐ Sí, 6-7 días por semana

22. Ha tenido la piel irritada alrededor del ano?

- ☐ No, nunca
- ☐ Sí, menos de una vez por semana
- ☐ Sí, 1-2 días por semana
- ☐ Sí, 3-5 días por semana
- ☐ Sí, 6-7 días por semana

23. Ha tenido que utilizar algo para proteger su ropa interior, como compresas, salva-slips o pañales?

- ☐ No, nunca
- ☐ Sí, menos de una vez por semana
- ☐ Sí, 1-2 días por semana
- ☐ Sí, 3-5 días por semana
- ☐ Sí, 6-7 días por semana

24. Ha tenido que ajustar sus actividades según la disponibilidad de un servicio?

- ☐ No, nunca
- ☐ Sí, menos de una vez por semana
- ☐ Sí, 1-2 días por semana
- ☐ Sí, 3-5 días por semana
- ☐ Sí, 6-7 días por semana

25. Ha tenido que limitar sus actividades diarias (p. Ej. Trabajo o faenas de casa) por problemas con sus deposiciones?

- ☐ No, nunca
- ☐ Sí, menos de una vez por semana
- ☐ Sí, 1-2 días por semana
- ☐ Sí, 3-5 días por semana
- ☐ Sí, 6-7 días por semana

26. Ha tenido que limitar sus actividades sociales (p. Ej. Visitas familiares, visitas al teatro, o comer fuera) por problemas con sus deposiciones?

- ☐ No, nunca
- ☐ Sí, menos de una vez por semana
- ☐ Sí, 1-2 días por semana
- ☐ Sí, 3-5 días por semana
- ☐ Sí, 6-7 días por semana

27. Ha tenido que limitar sus actividades sexuales (con o sin penetración) por problemas con las deposiciones?

- ☐ No, nunca
- ☐ Sí, menos de una vez por semana
- ☐ Sí, 1-2 días por semana
- ☐ Sí, 3-5 días por semana
- ☐ Sí, 6-7 días por semana

15.7. ANNEX IX: CHARLSON COMORBIDITY INDEX

CHARLSON COMORBIDITY INDEX

SUBJECT NO. ☐☐☐

Instructions: please tick the conditions assessed on the patient. Definition of each condition is made below. At the end, sum up every tick after giving them the assigned weights.

1 point	2 points
☐ Myocardial infarct ☐ Congestive heart failure ☐ Peripheral vascular disease ☐ Cerebrovascular disease ☐ Dementia ☐ Chronic pulmonary disease ☐ Ulcer disease ☐ Mild liver disease ☐ Diabetes	☐ Hemiplegia ☐ Moderate or severe renal disease ☐ Diabetes with end organ damage ☐ Any tumour ☐ Leukaemia ☐ Lymphoma
3 points	**4 points**
☐ Moderate or severe liver disease	☐ Metastatic solid tumour ☐ AIDS
SCORE: ☐☐	

Myocardial infarct	History of medically documented myocardial infarction.
Congestive heart failure (CHF)	Symptomatic CHF with response to specific treatment.
Peripheral vascular disease	Intermittent claudication, peripheral arterial bypass for insufficiency, gangrene, acute arterial insufficiency, untreated aneurysm (bigger than 6 cm).
Cerebrovascular disease (except hemiplegia)	History of transient ischemic attack or cerebrovascular accident with no or minor sequelae.
Dementia	Chronic cognitive deficit.
Chronic pulmonary disease	Symptomatic dyspnoea due to chronic respiratory conditions (including asthma).
Ulcer disease	Patients who have required treatment for peptic ulcer disease.
Mid liver disease	Cirrhosis without portal hypertension.
Diabetes	Diabetes with medication, without complications.
Diabetes with end organ damage	Retinopathy, neuropathy, nephropathy.
Hemiplegia (or paraplegia)	Hemiplegia or paraplegia.
Moderate or severe renal disease	Creatinine bigger than 3 mg, dialysis, transplantation, uremic syndrome.
Any tumour	Second solid tumour, non-metastatic, initially treated in the last 5 years. Exclude non-melanoma skin cancers and in situ cervical carcinoma.
Leukaemia	Chronic myelogenous leukaemia, chronic lymphocytic leukaemia, acute myeloid leukaemia, acute lymphoblastic leukaemia, polycythaemia vera.
Lymphoma	Non-Hodgkin's lymphoma, Hodgkin's lymphoma, Waldenström, multiple myeloma.
Moderate or severe liver disease	Cirrhosis with portal hypertension +/- variceal bleeding.
Metastatic solid tumour	Metastatic solid tumour
AIDS	AIDS and AIDS-related complex.

15.8. ANNEX X: CRF

CASE REPORT FORM (CRF)

Project: TRANSANAL MINIMALLY INVASIVE SURGERY (TAMIS) PLUS A PREOPERATIVE SHORT-COURSE RADIOTHERAPY VERSUS LAPAROSCOPIC TOTAL MESORECTAL EXCISION IN T2NOMO RECTAL TUMOURS TREATMENT

- Complete the CRF using a **black ballpoint pen** and ensure that all entries are complete and legible.
- Avoid the use of abbreviations and acronyms.
- The CRF should be completed as soon as possible after the scheduled visit.
- Do not use subject identifiers anywhere on the CRF, such as name, hospital number etc., in order to maintain the confidentiality of the subject.
- Each CRF page should be signed and dated by the person completing the form.
- Ensure that all fields are completed on each page:
  - If a test was Not Done record **ND** in the relevant box(es)
  - Where information is Not Known write **NK** in relevant box(es)
  - Where information is not applicable write **NA** in the relevant box(es)
- **Corrections to entries:** If an error is made, draw a single line through the item, then write the correct entry on an appropriate blank space near the original data point on the CRF and initial and date the change. **Do NOT:** Obscure the original entry by scribbling it out, try to correct/ modify the original entry or use Tippex or correction fluid.

PATIENTS INITIALS ☐☐☐

SUBJECT NO. ☐☐☐

CENTRE NO. ☐☐☐

APPROACH AFTER RANDOMISATION:

☐ TAMIS + SC-RT ☐ TME

INFORMED CONSENT

Did the patient had time to read it? ☐ No ☐ Yes

Did the patient understand the informed consent? ☐ No ☐ Yes

Did the patient sign voluntarily the informed consent form? ☐ No ☐ Yes

.....

Signature of the person taking informed consent

Date participant signed written consent form (equal to date of randomisation):

__/___/_____

(DD / MMM / YYYY)

CRF VERSION 1.0 1

Demographic data	
Date of Birth:	__/____/_____ (DD / MMM / YYYY)
Sex: ☐Male ☐Female	

Basal data	
Date of Assessment: __/____/_____ (DD / MMM / YYYY)	..... Signature of the responsible person
TESTS AND QUESTIONNAIRES	**SCORE**
SF-36	
If male → IIEF	
If female → FSFI	
COREFO	
Charlson comorbidity index	

Tumour position above the anal margin *(radiologically assessed)*	☐High ☐ Mid ☐ Low

Surgical specimen examination data	
Date of Assessment: __/____/_____ (DD / MMM / YYYY)	..... Signature of the responsible person
BAD PROGNOSIS FACTORS	
Lymphatic vessel invasion	☐No ☐ Yes
Blood vessel invasion	☐No ☐ Yes
Tumour >4 in its bigger diameter	☐No ☐ Yes
Tumour occupying more than 40% of rectum lumen	☐No ☐ Yes
OTHER	
Tumour grade	☐Gx ☐ G1 ☐ G2 ☐ G3 ☐ G4
Residual tumour	☐R0 ☐ R1 ☐ R2
pTNM *(write it down)*	☐ ☐ *T* *N*

Postoperative time	
Date of Assessment: __/____/_____ (DD / MMM / YYYY)	..... Signature of the responsible person
DINDO-CLAVIEN CLASSIFICATION	
☐No complications ☐ Grade I ☐ Grade II ☐ Grade III ☐ Grade IV ☐ Grade V	

3rd month	
Date of Assessment: __/____/_____ (DD / MMM / YYYY)	..... Signature of the responsible person
TESTS AND QUESTIONNAIRES	**SCORE**
SF-36	
If male → IIEF	
If female → FSFI	
COREFO score	
6th month	
Date of Assessment: __/____/_____ (DD / MMM / YYYY)	..... Signature of the responsible person
TESTS AND QUESTIONNAIRES	**SCORE**
SF-36	
If male → IIEF	
If female → FSFI	
COREFO score	
12th month	
Date of Assessment: __/____/_____ (DD / MMM / YYYY)	..... Signature of the responsible person
TESTS AND QUESTIONNAIRES	**SCORE**
SF-36	
If male → IIEF	
If female → FSFI	
COREFO score	
24th month	
Date of Assessment: __/____/_____ (DD / MMM / YYYY)	..... Signature of the responsible person
TESTS AND QUESTIONNAIRES	**SCORE**
SF-36	
If male → IIEF	
If female → FSFI	
COREFO score	
36th month	
Date of Assessment: __/____/_____ (DD / MMM / YYYY)	..... Signature of the responsible person
TESTS AND QUESTIONNAIRES	**SCORE**
SF-36	
If male → IIEF	
If female → FSFI	
COREFO score	

48th month	
Date of Assessment: __/____/_____ (DD / MMM / YYYY)	..... Signature of the responsible person
TESTS AND QUESTIONNAIRES	**SCORE**
SF-36	
If male → IIEF	
If female → FSFI	
COREFO score	

60th month	
Date of Assessment: __/____/_____ (DD / MMM / YYYY)	..... Signature of the responsible person
TESTS AND QUESTIONNAIRES	**SCORE**
SF-36	
If male → IIEF	
If female → FSFI	
COREFO score	

Events

DATE OF ASSESSMENT	CAUSE	TREATMENT RECEIVED	SIGNATURE OF THE RESPONSIBLE PERSON
__/____/_____ (DD / MMM / YYYY)	☐ Distant metastases ☐ Local recurrence ☐ Positive ganglia ☐ pT > cT ☐ Death	☐ None ☐ TME plus adjuvanct treatment ☐ TME ☐ Metastasectomy ☐ Adjuvancy ☐ Metastasectomy plus adjuvant treatment	.....
__/____/_____ (DD / MMM / YYYY)	☐ Distant metastases ☐ Local recurrence ☐ Positive ganglia ☐ pT > cT ☐ Death	☐ None ☐ TME + adjuvant treatment ☐ TME ☐ Metastasectomy ☐ Adjuvancy ☐ Metastasectomy plus adjuvant treatment	.....

__/___/____ (DD / MMM / YYYY)	☐ Distant metastases ☐ Local recurrence ☐ Positive ganglia ☐ Death	☐ None ☐ TME + adjuvant treatment ☐ TME ☐ Metastasectomy ☐ Adjuvant treatment ☐ Metastasectomy plus adjuvant treatment	.....
__/___/____ (DD / MMM / YYYY)	☐ Distant metastases ☐ Local recurrence ☐ Positive ganglia ☐ Death	☐ None ☐ TME + adjuvant treatment ☐ TME ☐ Metastasectomy ☐ Adjuvant treatment ☐ Metastasectomy plus adjuvant treatment	.....

PRINICIPAL INVESTIGATOR'S SIGN OFF

Principal Investigator's Signature Statement:

I have reviewed this CRF and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant. All entries were made either by me or by a person under my supervision.

Principal Investigator's Signature:

_____

Principal Investigator's Name:

_____

Date of Signature: __/___/____ (DD / MMM / YYYY)

ONCE SIGNED, NO FURTHER CHANGES CAN BE MADE TO THIS CRF WITHOUT A SIGNED DATA QUERY FORM.

15.9. ANNEX XI: GANTT DIAGRAM