‘Patient Reported Outcomes following Cancer of the Rectum’ (PROCaRe)

Version 1.2: June 2021

clinicaltrials.org NCT04936581

Título del estudio	'Patient Reported Outcomes following Cancer of the Rectum'
Título corto	PROCaRe
Registro	NCT04936581
Versión	1.2 – June 2021
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2. Brief summary

The surgical management of rectal cancer includes a Total Mesorectal Exicison (TME); depending on the height of the tumor, the problem of preservation of the anal sphincter arises, being able to perform a low anterior resection, an ultra-low anterior resection (RAUB) or an intersphincteric disscetion. In some cases invading the sphincters or the puborectalis muscle, an abdominoperineal resection needs to be performed, being the gold standard in this particular situation so far.

TME can be performed by open, laparoscopic, robotic or transanal approaches, as long as the oncological principles for the resection are achieved. Unfortunately, up to 90% of these patients will present a change in bowel habit, ranging from an increased frequency of bowel movements to the degree of fecal incontinence or evacuation dysfunction. Of these patients, 25-50% will have a severe alteration in the quality of life. This wide spectrum of symptoms has been called «low anterior resection syndrome» (LARS). Other collateral damage is the change in sexual and urinary function, due to hypogastric plexus injury. There is a significant lack of multicenter prospective studies that provide evidence, and that reveal the functional results and quality of life of these techniques available to date for the management of rectal cancer.

The study is set up as a prospective multicentre observational study. Inclusion criteria are: 1) patients over 18 years old, 2) diagnosed with rectal cancer located below the peritoneal reflection, defined by pereoperative MRI, 3) undergoing Open, laparoscopic, robotic or Transanal Total Mesorectal Excision (taTME) approaches, 4) with/withou derivative stoma and 5) with/without neoadjuvant treatment. Exclusion criteria are: 1) Upper rectal cancer, located above the peritoneal reflection, 2) previous radical prostatectomy, 3) previous pelvic radiotherapy, 4) rectal resection without primary anastomosis, 5) intraoperative findings of peritoneal carcinomatosis, 6) stage IV disease, 7) multivisceral or en-bloc resection, which includes uterus, prostate, vagina or bladder, 8) rectal resection due to a benign condition, 9) rectal resection due to a recurrence of rectal cancer (previous anterior resection or another pimary neoplasm), 10) rectal resection following a ‘watch & wait’ program, 11) emergency surgery, 12) previous derivative colostomy 13) inflammatory bowel disease.

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 45 subjects are necessary in first group and 45 in the second to recognize as statistically significant a difference greater than or equal to 2 units. The common standard deviation is assumed to be 3. It has been anticipated a drop-out rate of 20%

Primary outcomes are LARS and Vaizey score. Secondary outcomes included are QLQ C30 and CR29, sexual function questionnaire (female/male), urinary function questionnaire and postoperative complications (Clavien-Dindo classification)

Data will be collected in an online secure and protected repository (Castor edc). The planned study period is 2 years (September 2021 – September 2023).

It is essential to have a validated instrument that allows us to assess sphincter function and the different aspects of quality of life in operated patients, since increased survival in this pathology has led to greater importance in the evaluation functional outcome and quality of life; Furthermore, there are recent studies that speak of the direct relationship between these factors.

3. Background

TÍTULO: Patient Reported Outcomes following Cancer of the Rectum (PROCaRe)

BACKGROUND

The rectum is located in a narrow space, limited by the bone and surrounded tissues, in a very complex and narrow pelvic space. It necessarily implies greater difficulty in achieving tumour-free margins[3], and preserving sexual, urinary and fecal continence functions[4]. Depending on the height of the tumor, the difficulty of preserving the anal sphincter arises, being able to perform a low anterior resection (LAR), an ultra-low anterior resection (RAUB) or an intersphincteric ultra-low anterior resection (ISR). Finally, if it is not impossible to preserve the sphincters or to make an anastomosis, an abdominoperineal resection (APR) is needed, being the gold standard in this particular situation.

In order to perform a correct surgery, all the previous alternatives must follow the principle of Total Mesorectal Excision (TME) described by Heald in 1982.[1] There is no consensus nowadays regarding the ideal approach for this procedure, and it can be performed using open or minimally invasive surgery, including laparoscopy, transanal approach (taTME), and robotic surgery.

Laparoscopic surgery has shown great advantages over open surgery, such as less postoperative pain, shorter hospital stay and early recovery.[2] However, this approach has some technical difficulties, especially when it comes to tumours located at the mid-low

rectum, in male and obese patients, which leads to a higher conversion rate for this subgroup of patients.[3] This is why this laparoscopic procedure is considered highly demanding, and the 'European Society of Coloproctology' published in a cross-sectional study only 20% of laparoscopic surgery in such cases.[4]

Robotic surgery then emerged with the idea of overcoming these technical difficulties. It has shown better results in terms of conversion to open surgery, despite an increase in operative time and higher economic costs. Some studies showed an improvement in erectile function after robotic surgery compared to laparoscopy,[5-7] as well as a trend towards better functional results.[8] However, its adoption worldwide is slow due to a lack of availability in most of centers.[9]

Due to this controversy, a new approach that combines laparoscopic abdominal and transanal dissection has emerged in the last decade, the taTME.[10] To date, several retrospective and prospective studies have been published, which show similar short and long-term results between techniques. However, after ensuring oncological results, we must also focus on sphincter and bowel function, and patients' quality of life after surgery.

Anal sphincter sparing surgery is currently the most commonly performed in rectal cancer patients. Unfortunately, up to 90% of these patients will present a change in bowel habit, ranging from an increased frequency of bowel movements to the degree of fecal incontinence or evacuation dysfunction, after rectal resection and reconstruction. Of these patients, 25-50% will have severe changes in quality of life.[11] This wide spectrum of symptoms has been called 'Low Anterior Resection Syndrome' (LARS) [12] Another collateral damage caused during surgery affects to sexual and urinary function,[13] due to hypogastric nerves damage. There is an important lack of multicenter prospective studies providing evidence, and showing pateints' functional results and quality of life after all these techniques available for the management of rectal cancer.

RATIONALE

For these reasons, it is essential to have a validated instrument that allows us to assess sphincter function and the different aspects of quality of life in patients undergoing surgery for rectal cancer, since increased survival in this pathology has led to greater importance in the evaluation functional outcome and quality of life. Moreover, there are some recent studies showing a direct relation between these factors.

4. Objectives

Main objective:

- To analyse patients' sphincter function following surgery for rectal cancer
- To compare results regarding sphincter function between different surgical approaches

Secondary objectives:

- To analyse sexual function following surgery for rectal cancer and to compare results between different surgical approaches
- To analyse urinary function following surgery for rectal cancer and to compare results between different surgical approaches
- To analyse quality of life following surgery for rectal cancer and to compare results between different surgical approaches

5. Hypothesis

- Damage to the sphincter function in patients who undergo surgery for rectal cancer is multifactorial, and it is not related to the surgical approach performed

6. Methods

Multicentre, prospective, observational study, which aims to analyse the objectives using questionnaires of sphincter function, sexual and urinary function and quality of life.

- Sample size: Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 45 subjects are necessary in first group and 45 in the second to recognize as statistically significant a difference greater than or equal to 2 units. The common standard deviation is assumed to be 3. It has been anticipated a drop-out rate of 20%
- Population:
    - Patient selection: Participants that meet the criteria will be identified in each centre
    - Patient information sheet (Appendix 1) will be given in clinic and informed consent (Appendix 2) will be obtain before including the patient in the study

- Selection criteria:
  - Inclusion criteria
    - Patients over 18 years old
    - Informed consent
    - Diagnosed with rectal cancer located below the peritoneal reflection, defined by pereoperative MRI
    - Open, laparoscopic, robotic or Transanal Total Mesorectal Excision (taTME) approaches
    - Patinets with/withou derivative stoma
    - Patients with/without neoadjuvant treatment
  - Exclusion criteria:
    - Upper rectal cancer, located above the peritoneal reflection
    - Previous radical prostatectomy
    - Previous pelvic radiotherapy
    - Rectal resection without primary anastomosis
    - Intraoperative findings of peritoneal carcinomatosis
    - Stage IV disease
    - Multivisceral or en-bloc resection, which includes uterus, prostate, vagina or bladder
    - Rectal resection due to a benign condition
    - Rectal resection due to a recurrence of rectal cancer (previous anterior resection or another pimary neoplasm)
    - Rectal resection following a 'watch & wait' program
    - Emergency surgery
    - Previous derivative colostomy
    - Inflammatory bowel disease

- Follow-up: The questionnaires will be given in the preoperative outpatient clinic. After the surgical intervention, patients will have their usual follow-up clinic and the same questionnaires will be given 6, 12 and 24 months after the initial intervention or the stoma reversal if present (appendix 3). Questionnaires can be answered via phone call if desired.
- Data collection: Data will be collected in an online secure and protected repository (Castor edc).
- Sampling method: probability sample
- Duration of the study: Preliminary results will be analysed at 1 year follow-up, 24 months after the start of the recruitment. Total duration of the study will be 48 months, so 24 months of follow-up can be completed for every case included in the study.

- Outcomes: A detailed description of the outcomes is presented in the Appendix 4
  - Primary outcomes
    - Tripartite (Appendix 5)
    - LARS score (Appendix 6)
    - Vaizey scroe (Appendix 7)
  - Secondary outcomes
    - QLQ C30 and CR29 (Appendix 8 and 9)
    - Sexual function questionnaire (female/male) (Appendix 10 and 11)
    - Urinary function questionnaire (Appendix 12)
    - Postoperative complications (Clavien-Dindo classification)

	Cavien-Dindo Classification
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
II	Requiring pharmacological treatment with drugs other tan such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
III	Requiring surgical, endoscopic or radiological intervention.
a	Intervention not under general anesthesia.
b	Intervention under general anesthesia.
IV	Life-threatening complication requiring ITU management.
a	Single organ dysfunction (including dialysis).
b	Multiorgan dysfunction.
V	Death of a patient

- Anastomotic leak defined as ‘a breach in a surgical join between two hollow viscera, with or without active leak of luminal contents’ [Peel 1991].
- Length of hospital stay
- 30 and 90-day mortality
- Readmission rate
- Reintervention rate
- 6/12/24 months free-stoma survival
- Total time with stoma

- List of study parameters:
    - Tripartite (Appendix 5)
    - LARS score (Appendix 6)
    - Vaizey scroe (Appendix 7)
    - QLQ C30 and CR29 (Appendix 8 and 9)
    - Sexual function questionnaire (female/male) (Appendix 10 and 11)
    - Urinary function questionnaire (Appendix 12)
    - Postoperative complications (Clavien-Dindo classification)
    - Patient and tumour's features
    - Treatment characteristics:neoadjuvant therapy, timing to surgery, mechanical or oral bowel preparation, approach to surgery, beyond TME surgery, anastomosis construction, high of the anastomosis, air leak test.
    - Anastomotic leak, time to leak, treatment, ITU admission, evaluation and healing, permanent stoma.
    - Stoma reversal.
    - Complications (Clavien-Dindo)
    - Length of stay, readmission, mortality.

7. Data collection and analysis

Prospective observational study. Data will be collected in an online secure and protected repository (Castor edc).

A flow chart will be used to summarize trial participation, with reasons for ineligibility, refusal, drop-out, and loss to follow-up recorded as far as possible. Baseline characteristics will be described as means and standard deviations (continuous variables) or counts and percentages (categorical variables). A p value of <0.05 will be considered significant.

SPSS V21 will be used for the statistical analysis.

8. Participating centres

The list of participating centres is shown in appendix 13. The study will remain open for more participating centres, but local ethical approval is required.

9. Ethical and regulatory considerations

9.1. Data protection and patient confidentiality

All investigators and study site staff must comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Data will be protected by:

- The creation of coded, depersonalised data where the participant's identifying information is replaced by an unrelated sequence of characters.
- Secure maintenance of the data and the linking code in separate locations using encrypted digital files within password protected folders and storage media.
- Limiting access to the minimum number of individuals necessary for quality control, audit, and analysis. Only the CI and co-ordinator will have access.

- Data will be stored for 5 year after completion of the study.
- Data custodian will be the chief investigator.

9.2. Access to the final study dataset

- Individuals involved in the study who will have access to the full dataset: chief investigator and co-ordinator.
- Only the steering group has access to the full study dataset in order to ensure that the overall results are not disclosed by an individual study site prior to the main publication.
- The study will allow site investigators to access the full dataset if a formal request describing their plans is approved by the steering group.

10. Dissemination policy

- The chief investigator and the associate PI own the data arising from the study.
- On completion of the study, the data will be analysed and tabulated and a Final Study Report prepared.
- All participating investigators will have rights to publish any of the study data, previous approval by the steering group.
- There are no time limits or review requirements on the publications.
- No funding or supporting body needs to be acknowledged within the publications and whether they have reviewed and publication rights of the data from the study.
- There are no plans to notify the participants of the outcome of the study, either by provision of the publication, or via a specifically designed newsletter, presentation etc.

10.1. Authorship eligibility guidelines and any intended use of professional writers

- Guidelines on authorship on the final study report.
    - Every associate PI will be part of the authorship list

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12. Appendix

- 12.1 Patient information sheet
- 12.2 Informed consent
- 12.3 Flow-chart
- 12.4 Dataset
- 12.5 Tripartite questionnaire
- 12.6 LARS score
- 12.7 Vaizey score
- 12.8 EORTC QLQ-C30
- 12.9 EORTC QLQ-CR29
- 12.10 Sexual function questionnaire (female) (FSFI)
- 12.11 Sexual function questionnaire (male) (IIEF)
- 12.12 Urinary function questionnaire (IPSS)
- 12.13 List of participating centres
- 12.14 Certificate of approval CRF (Castor EDC)