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Rectal Surgery Evaluation Trial (RESET): protocol for a parallel cohort trial of outcomes using surgical techniques for total mesorectal excision with low anterior resection in high-risk rectal cancer patients

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Conflicts of interest

PR, IG, DJ, TR, GS, MGR are proctors for Intuitive Surgical. GS is proctor for Multimed and AB Medica. IG has received an unrestricted research grant from Intuitive Surgical. All other authors have no conflict of interest to disclose.

Abstract

Background. Total mesorectal excision (TME) is the standard of care for rectal cancer, which can be combined with low anterior resection (LAR) in patients with mid-to-low rectal cancer. The narrow pelvic space and difficulties in obtaining adequate exposure make surgery technically challenging. Four techniques are used to perform the surgery: open laparotomy, laparoscopy, robot-assisted surgery, and transanal surgery. Comparative data for these techniques is required to provide clinical data on the surgical management of rectal cancers.

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Methods. The Rectal Surgery Evaluation Trial will be a prospective, observational, case-matched, four-cohort, multicenter trial designed to study TME with LAR using open laparotomy, laparoscopy, robot-assisted surgery, or transanal surgery in high-surgical-risk patients with mid-to-low, non-metastatic rectal cancer. All surgeries will be performed by surgeons experienced in at least one of the techniques. Oncological, morbidity and functional outcomes will be assessed in a composite primary outcome, with success defined as circumferential resection margin ≥ 1 mm, TME grade III, and minimal postoperative morbidity (absence of Clavien-Dindo grade III-IV complications within 30 days after surgery). Secondary endpoints will include the co-primary endpoints over the long-term (2 years), quality of surgery, quality of life, length of hospital stay, operative time, and rate of unplanned conversions.

Discussion. This will be the first trial to study all four surgical techniques currently used for TME with LAR in a specific group of high-risk patients. The knowledge obtained will contribute towards helping physicians determine the advantages of each technique and which may be the most appropriate for their patients.

Keywords: laparotomy; laparoscopy; low anterior resection; rectal cancer; robot-assisted surgery; total mesorectal excision; transanal surgery.

Introduction

Rectal cancer is relatively common, with almost 40,000 new cases estimated for 2017 in the US alone [1]. The standard of care for its treatment is total mesorectal excision (TME), the *en bloc* sharp dissection of the tumour and the mesorectum (the surrounding perirectal lymphatic tissue located within a thin fascial layer) under direct vision [2]. TME has reduced local recurrence rates and improved overall survival [3]. When combined with low anterior resection (LAR), the technique is used to excise tumours in the lower two-thirds of the rectum, a technically challenging surgery due to a narrow pelvis and difficulties in obtaining adequate exposure.

Several surgical techniques are used to perform TME. Dissection using open laparotomy and minimally-invasive laparoscopic or robot-assisted abdominal approach is performed in a ‘top-down’ manner, where the instruments are inserted transabdominally and the procedure progresses from splenic flexure/sigmoid colon mobilization to rectal resection. A transanal approach may also be used, a ‘bottom-up’ procedure where instruments are inserted through the anus to perform rectal resection and TME [4,5]. Minimally-invasive laparoscopy can reduce morbidity compared with open laparotomy and has been increasingly used [6], but high conversion rates from laparoscopy to open surgery have been reported because of technical difficulties in the narrow surgical space [7, 8]. Robotic assistance has the potential to further improve outcomes, including fewer conversions [6, 9-12] and improved potency [9] compared with laparoscopy, with greater benefits reported in male and obese patients and those undergoing LAR [13].

However, comparison of open, laparoscopic and robotic approach is needed, particularly compared with the transanal approach, to help determine which technique may provide optimal outcomes. Inclusion of the most high-risk patients, i.e. those who are most difficult to operate, such as obese patients with narrow pelvis, large mesorectum, large tumor, or bulky prostate [10-15], and consideration of oncological, morbidity, and functional outcomes (i.e. through a co-primary evaluation) should help to achieve this aim. A randomized controlled trial is ethically problematic because of the difficulty in achieving equivalence regarding surgical experience with each technique.

Thus, the prospective, observational rectal surgery evaluation trial (RESET) will aim to study TME with LAR using open laparotomy, laparoscopy, robot-assisted surgery, or transanal surgery in four parallel, case-matched cohorts in centers with expertise in these procedures (Figure 1). The study will be performed in a quality-controlled manner to avoid learning curve concerns while ensuring adequate enrolment for clinical relevance. The primary objective of RESET will be to evaluate each technique in high-surgical-risk, non-metastatic, mid-to-low rectal cancer patients by assessing oncological, morbidity and functional outcomes in a co-primary endpoint comprising three postoperative measures of success: circumferential resection margin (CRM) ≥ 1 mm, TME grade III [16], and minimal postoperative morbidity (absence of Clavien-Dindo grade III-IV complications [14] within 30 days

after surgery). Secondary endpoints will also include the co-primary endpoints over the long-term (2 years), as well as quality of surgery, quality of life (QoL), length of hospital stay, operative time and rate of unplanned conversions.

Methods

Patient recruitment

The study will include male and female adult patients aged ≥ 18 years with rectal adenocarcinoma from the middle and lower third (< 10 cm from the anal verge), who are undergoing a sphincter-saving procedure. Patients will be high-risk from a surgical perspective, presenting with two of the following factors (assessed using MRI): obese patients with body mass index (BMI) > 30 ; narrow pelvis, i.e. inter-tuberous distance < 10 cm; large tumoral volume with suspicion of a close predictive margin (CRM ≤ 1 mm); expected coloanal or ultra-low colorectal anastomosis. Patients will have an adequate functional status, with a score of ≤ 2 on the Eastern Cooperative Oncology Group (ECOG) Scale. All patients will have a voluntarily signed and dated informed consent form approved by the Ethics Committee before inclusion in the study.

Specific exclusion criteria include metastatic disease, T4b tumors that indicate a pelvectomy, the need for abdominal perineal resection, concurrent or previous invasive pelvic malignant tumours (cervical, uterine, or rectal; excluding the prostate) within 5 years before study enrolment, a comorbid illness or condition that would preclude the use of surgery, patients undergoing emergency procedures, and planned rectal surgery along with major concomitant procedures (e.g. hepatectomies, other intestinal resections). No patient will be included if they are pregnant or have a suspected pregnancy or are included in another study which impacts on the surgical technique or its choice; all patients should be willing to comply with all follow-up study requirements.

The sample size was determined based on the incidences of CRM ≥ 1 mm and Clavien-Dindo grade $\geq III$ reported in the literature, and on attaining a success rate of 85% for the primary composite endpoint, with the lower 95% confidence limit being $\leq 4\%$ from the estimated success rate. Assuming

a 2-sided interval, a total of 307 patients will be required within each cohort. Accounting for a 10% loss to follow-up, 1300 patients will be enrolled in the study (325 patients per cohort). All patients during the enrolment period shall be screened and recorded at each site to identify any selection bias.

Study setting

It is expected that this international multicenter trial will take place in 24 sites in 10 countries (France, Spain, Italy, UK, Germany, The Netherlands, Denmark, Sweden, Norway, Belgium), and will begin in September 2018 over a 4-year period, including a 2-year follow-up. The RESET trial is endorsed by the European Society of Coloproctology (ESCP). Participating centers and investigators will be qualified colorectal or general surgeons experienced in the surgical management of patients with rectal lesions and who have a patient population fitting the study requirements. To be eligible for participation in the study, surgeons must have performed 30 procedures for rectal carcinoma <12 cm from the anal verge using one of the study techniques. Surgeons can include patients in any cohort in which they have passed the learning curve of 30 procedures.

Interventions

According to the surgeon's experience, patients undergoing TME with LAR will be included in one of four cohorts. 1) Open laparotomy, a surgical procedure involving a large incision through the abdominal wall to gain access into the abdominal cavity. 2) Laparoscopic surgery, a minimally-invasive technique in which operations are performed via small incisions (usually 0.5–1.5 cm) at a location distant to the site of interest. 3) Robot-assisted surgery using the da Vinci® Surgical System, a minimally-invasive approach that allows good precision, flexibility, and control. 4) Transanal surgery through the anus, where the proctectomy is performed from below upwards up to the pouch of Douglas. If an operation cannot be completed, the patient will be converted to another technique at the discretion of the surgeon.

Outcomes

The primary composite efficacy endpoint will comprise three measures of success: CRM ≥ 1 mm, TME grade III [16], and minimal postoperative morbidity (i.e. the absence of Clavien-Dindo grade III-IV complications [14] within 30 days after surgery). Secondary endpoints will include the above, as well as functional outcome 6 months after stoma closure (low anterior resection syndrome (LARS) score < 30 [17]), oncological results at 1 and 2 years (overall survival, disease-free survival, local pelvic recurrence, metastases rate), rate of unplanned conversions, operative time (minutes), complete TME, a clear distal resection margin (≥ 1 mm), length of stay (days), patient-assessed QoL measures patients (the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires QLQ-C30 and QLQ-CR29) [18], and patient-assessed dysfunction (using the International Prostatic Symptom Score and the International Index of Erectile Function for males [19], and the Female Sexual Functional Index for females [20, 21]). Personnel and resource utilization data and system and instrument use will also be collected. Any technical observations will be reported, and complications will be recorded on the complications case report form (CRF) throughout the duration of the study and followed until they are adequately resolved or explained. No additional risk to those normally encountered from these surgeries in these patients are anticipated, as all techniques are in practice today and only surgeons competent in a given technique will be allowed to perform the surgery.

Data collection and management

Data collected will include the following (Figure 2 and Table 1): patient demographics, characteristics, and preoperative history (age, BMI, cancer treatment, surgical history, comorbid conditions, indication for surgery, baseline QoL and dysfunction); intraoperative assessment (operating room time, estimated blood loss, transfusion, concomitant procedures performed, complications, conversions); postoperative assessment through to discharge (bowel recovery, complications, pathology, patient-reported outcomes during post-surgical recovery until discharge,

QoL, dysfunction); follow-up assessments (complications, procedure-related readmissions, procedure-related reoperations, patient-reported outcomes, QoL) collected during an inpatient visit or via a telephone call. Once a year, for a 1-month period, a complete screening of all rectal procedures of all centers, regardless of the technique used, will be performed, *i.e.* snapshot audits conducted under the control of the European Society of Coloproctology.

Data will be collected pre-operatively, intraoperatively through to discharge, and at 30 days, 6 months, 1 year, and 2 years post-surgery (Figure 2 and Table 1). Data collection forms will be available at <https://ecrfcval.icm.unicancer.fr/CSOnline/>. Primary data collection will be performed by a study coordinator in a study-specific electronic data collection (EDC) system. A dedicated database with the electronic CRF will be used to host the Clinical Trial data for this study. The database has been developed and utilized in accordance with international requirements and standards applicable to clinical investigations, *i.e.* Good Clinical Practice (GCP), and is a GCP-compliant environment that meets applicable 21 CFR Part 11 requirements. Study monitoring will be conducted using a risk-based approach (*i.e.* most of the monitoring activities will be performed using remote monitoring functionality by reviewing the data from the EDC system). The on-site monitoring will be conducted on an as-needed basis in situations including but not limited to protocol compliance issues, major data discrepancies, and safety issues. In general, the study monitoring functions will be performed by the Sponsor or its appointed designee in compliance with recognized GCP, the harmonized standard EN ISO 14155, and local applicable legislation. The major function of the clinical monitor is to observe and assess the quality of the clinical study. It is the responsibility of the site appointed research personnel to complete all CRF and to document conformity to the clinical trial protocol throughout the study.

Patients can choose to withdraw at any time, and the investigator has the right to discontinue patients at their discretion to ensure their well-being. Patients will be evaluated at the time of withdrawal, including the reasons for withdrawal, and no further follow-ups will be performed. If a patient cannot be reached during a visit window, a missed visit will be recorded; after three consecutive missed

visits, a patient will be considered lost to follow-up and a study exit form will be completed in the electronic CRF.

Statistical considerations

The sample size calculation is based on attaining a success rate of 85% for the primary composite endpoint, with the lower 95% confidence limit being no greater than 4% from the estimated success rate. Assuming a two-sided interval, a total of 307 subjects will be required within each cohort. Accounting for a 10% loss to follow up, a total of 1300 subjects will be recruited for this study.

A cohort analysis is planned after inclusion of the first 169 patients in each cohort to verify whether the calibration around a success rate of 85% is correct.

The primary endpoint analysis will be presented by proportions, with 95% confidence intervals (CI) for each cohort, calculated using standard methods based on a binomial distribution for each cohort. Patients from each cohort will be analyzed separately, with the populations defined as intent-to-treat, eligible subjects with no minor or major protocol deviations, and safety. All analyses will be detailed in a statistical analysis plan.

Descriptive statistics will be provided for all discrete variables in the form of rates and proportions with 95% CI. Continuous variables will be described by mean, standard deviation, median and range. Overall survival, disease-free survival, local recurrence rate, and metastasis rate will be estimated using the Kaplan Meier method. Exploratory comparisons of discrete variables will be performed using a Chi-squared test, using continuity correction or Fisher's exact test. Continuous variables will be compared using a Student's t-test, or a non-parametric equivalent (Wilcoxon). Survival statistics will be based on a stratified lo-rank test. All tests will be two sided with a p-value of less than 0.05 considered to indicate statistical significance.

Multivariate analyses will be performed for survival endpoints. A Cox proportional-hazards model will be used to estimate the hazard ratios. Hazard ratios indicating the effects of prognostic factors on the risk of event will be calculated and shown in a forest plot. The interaction test will be used to assess the heterogeneity of treatment effects for subgroup analyses. Analysis of QoL questionnaires (QLQ-C30 and QLQ-CR29) will be performed in accordance with the EORTC guidelines. Time to definitive deterioration in QoL (10-point minimal clinically-important difference) will be analyzed using the Kaplan-Meier method and the log-rank test. Selection bias, often linked to a patient's biological or clinical profile, will be reduced or corrected with multidimensional adjustment methods using a propensity score [22]. This score, which will be calculated after researching the predictive factors of the therapeutic choice by a logistic regression, corresponds to the probability of receiving one of the treatments conditionally to the variable observed before treatment. The score will be integrated as a co-factor in the final multivariate model used to compare the cohorts.

Ethics and dissemination

The trial will be conducted in accordance with applicable European Regulatory requirements, the Declaration of Helsinki, and the principles of GCP Guidelines. Ethics Committee approval was obtained for the study prior to study initiation on site (CPP Ouest II, Angers, France – ID RCB number: 2018-A01293-52). Local country specific approvals will be obtained before setting up of the study in each participating country. Any important protocol modification will be communicated to all participating centers and relevant parties. Patient information will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 and EU2016-679. Access to patient records will be limited to the study investigator, the investigator-delegated study coordinator, and clinical representatives from Intuitive Surgical. The study results will be communicated to the study participating centers and in international meetings or scientific journals.

Trial registration

This study was registered on Clinicaltrials.gov (clinicaltrials.gov identifier: NCT03574493) on the 29th June, 2018.

Discussion

There is a need to provide prospective, comparative data on the different surgical techniques that are currently used for TME with LAR in patients with mid-to-low rectal cancer. Surgery in these patients is technically challenging because of the narrow pelvic space and difficulties in obtaining adequate exposure. This large international study will be the first to evaluate all four techniques: open laparotomy, laparoscopy, robot-assisted surgery, and transanal surgery. A randomized controlled trial is not possible because each surgeon would have to have the same level of surgical experience with each technique at the same time [23], and because they usually have a preference for a given surgical technique. Thus, we have opted for observational assessment of four parallel cohorts in centers with expertise in the procedures. Although there is not expected to be any direct benefit and no additional risk for patients (all surgeons will be experienced in their chosen technique), the research will provide clinical data on the medical care of rectal cancers by surgery. The effectiveness of each technique will be determined, including oncological, morbidity functional outcomes in a composite primary endpoint that will offer greater statistical precision and efficiency [24], as well as the impact on patients' quality of life. Additional measures will be useful to evaluate practical aspects, such as operative time, length of stay, resource utilization, and unplanned conversion to laparotomy for example. Inclusion of patients at high surgical risk (i.e. those who are obese or have a narrow pelvis, large mesorectum, huge tumor, or bulky prostate [25]) will help to determine whether there are advantages to using robotic assistance compared with the other techniques. The data collected should contribute towards the knowledge base that enables physicians to determine which technique will be the most suitable for a particular patient.

Funding

Financial support was provided by Intuitive Surgical, Aubonne, Switzerland.

Roles and responsibilities

PR, IG, DJ, AU, TR, GS and MGR conceptualized the study idea, as the RESET steering committee. AM and NB are the RESET project managers. SG performed the methodological design and statistical analysis plan.

The draft manuscript was prepared by a professional medical writer (Deborah Nock, Medical WriteAway, UK), with full review and approval by all authors.

Trial sponsor and steering committee

The trial sponsor is the Institut du Cancer de Montpellier (ICM), Clinical and Translational Research Department, 208, rue des Apothicaires, 34298 Montpellier Cedex 5, France. The sponsor will manage the overall project conduct and will be responsible for the study monitoring and reporting. The steering committee includes the study investigators and will be responsible for protocol validation, study coordination, regulatory coordination, center selection and publications.

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Table 1. Assessment schedule

	Baseline	Procedure	Discharge	30 days ±3 days	6 months ±14 days	1 year ±30 days	2 years ±30 days	Unscheduled visit
Informed consent	X							
Demographics and medical history	X							
Quality of life: EORTC QLQ-C30 and QLQ-CR29	X			X	X	X	X	
Dysfunction: Males: IPSS, IIEF Females: FSFI	X			X	X	X	X	
Procedure details		X						
LARS (6 months from closure of stoma)					X*	X*		
Pathology			X					
Complications		X*	X*	X*	X*	X*	X*	X*
Study exit forms							X**	

* To be completed if applicable; ** to be completed when lost to follow-up, consent withdrawal, or the patient has completed all study-related visits. EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaires; FSFI, Female Sexual Functional Index; IIEF, International Index of Erectile Function; IPSS, International Prostatic Symptom Score; LARS, low anterior resection syndrome.

Appendice

Information patient note.

Figure 1. Study schematic

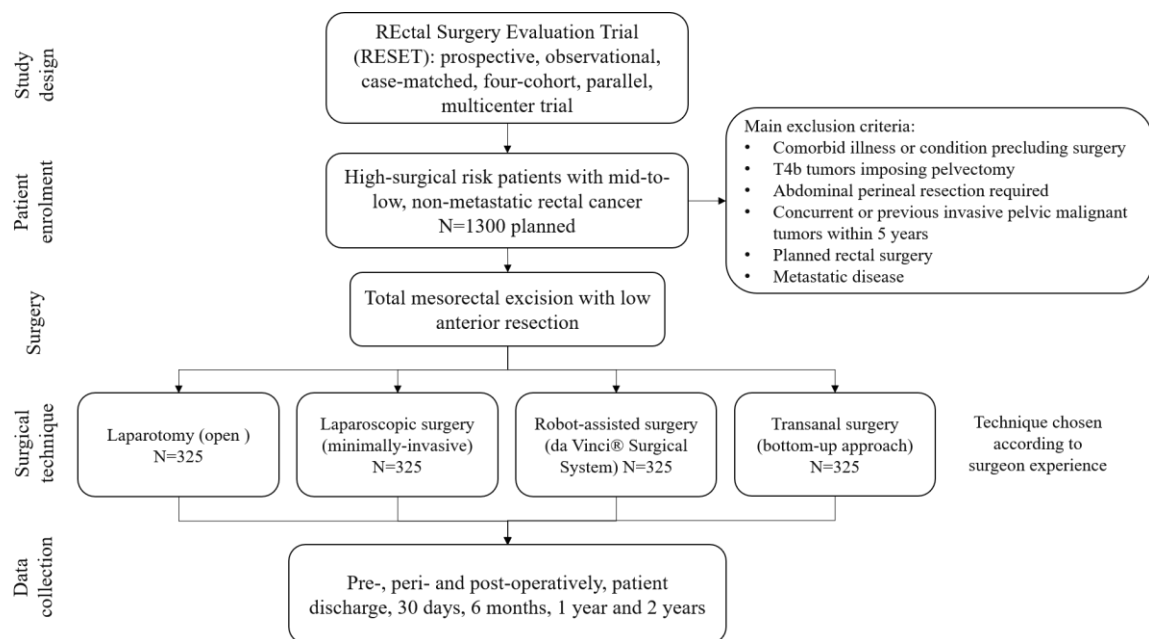
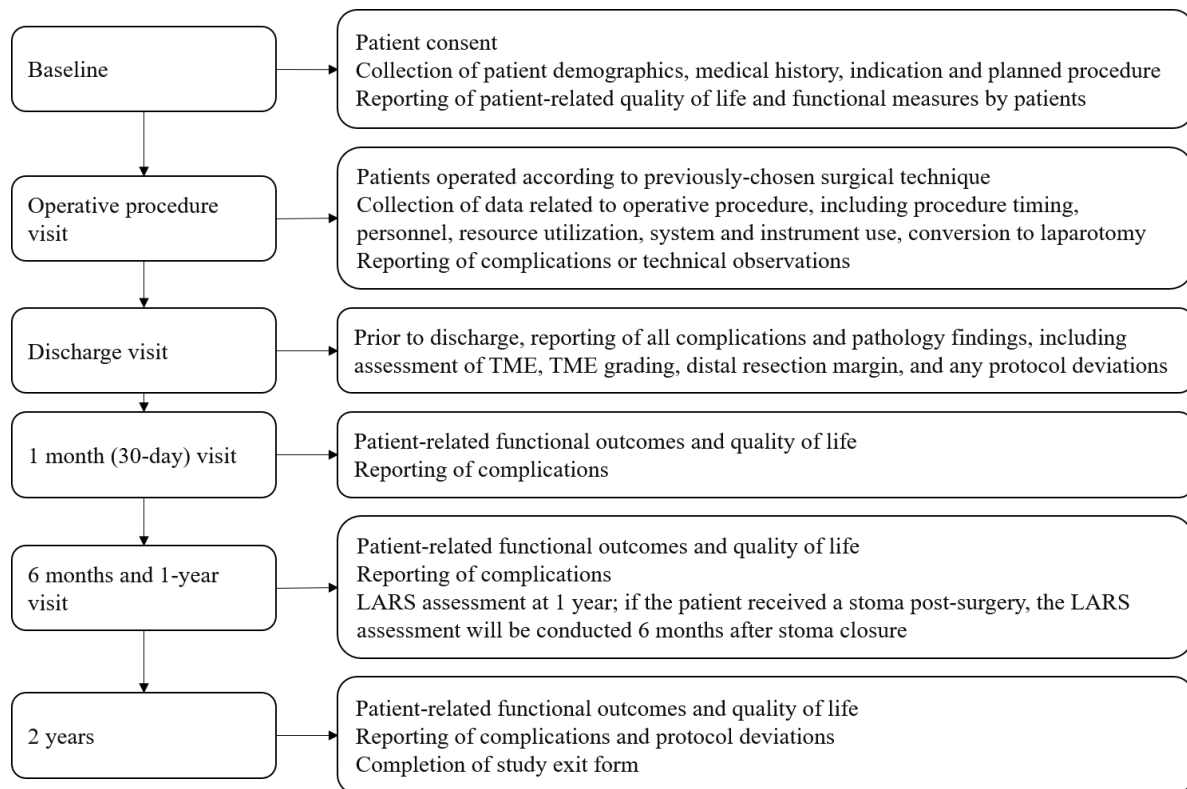


Figure 2. Study schedule



LARS, low anterior resection syndrome; TME, total mesorectal excision.

LAPAROTOMY VS LAPAROSCOPY VS ROBOTIC VS TA-TME RECTAL SURGERY PARALLEL COHORT TRIAL FOR HIGH SURGICAL RISK CANCER PATIENTS.

RESET

N°ICM: **PROICM 2018-03 ORE**

Study sponsor : Institut régional du Cancer de Montpellier (ICM) - Parc Euromédecine,
208 rue des Apothicaires,
34298 Montpellier Cedex 5.

Principal Investigator : Pr ROUANET Philippe
Oncological Surgery, ICM.

Dear Sir/Madam,

Your doctor is suggesting that you participate in an observational research study on rectal cancer surgery. This document is intended to provide you with the necessary information concerning the various aspects of this research.

You will have a period of reflection before making your decision to participate or not in the study. If you do not want to take part in this research, you will continue to benefit from the best medical treatment possible, in accordance with current knowledge of medicine.

Your doctor is also available to answer all your questions and explain anything you may not have understood.

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1. What is the context and objective of the study?

The study which is proposed to you, aims to compare four surgical techniques used to treat rectal cancer.

These 4 techniques are:

- **Laparotomy** (or open): surgical procedure involving a large incision through the abdominal wall to gain access to the abdominal cavity.
- **Laparoscopy** (lap): also called minimally-invasive surgery (MIS), or keyhole surgery; surgical technique in which operations are performed far from their location through small incisions (usually 0.5–1.5 cm) elsewhere in the body.
- **Robotic-assisted surgery** (RAS using the Da Vinci Surgical System): allows many types of complex MIS procedures using the robotic systems to aid the surgical procedures providing more precision, flexibility and control than is possible with the other MIS techniques. All RAS procedures will be performed using a Da Vinci Surgical System.
- **TaTME surgery** (Trans-anal TME) : Type of surgery for rectal cancer that is performed through the anus. This bottom-up surgery performs the proctectomy down to up, until the Douglas pouch.

The ambition of this work is to increase knowledge of all these surgical techniques for rectal cancer management, as to know which is the best surgical technique for a specific patient population.

2. What is the flowchart of the study?

General presentation

This study is an observational prospective, international, multicenter, 4-parallel-cohorts study. Sites or surgeons will select a cohort of the study for which they are qualified.

The expected number of patients is 1300 over 2 years.

Progress of your participation in this study

After reading this information document and discussion with your doctor, if you agree to participate, your clinical data will be recorded in a coded manner in a database.

You will not have any additional medical examinations specific to the study (no additional blood test, imaging, or treatment). The clinical data will simply be recovered from your medical file including your medical history, previous and current treatments and any complications due to your surgery.

Quality of life is an essential parameter for patients operated for a rectal cancer. Quality of life questionnaires will be given to you during your visits before surgery, and 30 days, 1 year and 2 years after your surgery. You will be asked to fill-in these questionnaires. It will take you about 20 to 30 minutes. The questionnaires will evaluate your global health and your overall quality of life and the restoration of your digestive, urinary and sexual functions after surgery.

These questionnaires will be identified by a unique number and will be retrieved by the investigator and entered by computer. These anonymous data may be used for research projects. The information collected will stay strictly confidential.

This study does not prevent you from participating in other research projects that have no impact on the surgical technique chosen and performed.

The expected benefits

Your participation in this study has no direct benefit nor additional risk for your health. However, this research will provide clinical data on the medical care of rectal cancer by robotic surgery. The results of this study will allow increase of our scientific and medical knowledge in this area, and will contribute to improve disease management and patients' care.

3. What are your rights and conditions for participation in the study?

Compensation - support for the costs of the study

You will not receive any financial compensation for your participation in this research.

Regulatory and administrative aspects

Participation in this study is a free and voluntary act. If you refuse to participate, there will be no impact of your refusal on both your treatment and care by your doctor.

If you wish to withdraw from the research, at whatever time and for whatever reason, you will continue to be provided with medical care and follow-up and this will have no effect on your future follow-up.

To participate in this trial, you must: be aged more than 18 years, present with a rectal tumour and consent to participate in the study, *i.e.* have signed this information note. As a precaution, pregnant or suspected pregnant women will not be able to take part in this trial.

The sponsor also reserves the right to terminate the study prematurely at any time. In this case, you will be notified and you will continue to be followed by your doctor without any impact on your treatment and medical care.

Computer processing of personal data

As part of the study, some personal data will be implemented to allow analysis of the results of the research.

All your personal and medical data related to the study will be transmitted to the study sponsor (the Cancer Institute of Montpellier - France), or to the person acting on its behalf. This data will be anonymized and identified by a code number before transmitted to the sponsor. All data may also, under conditions ensuring their confidentiality, be transmitted to the health authorities, or to other entities of the sponsor and used for further research, in your country or abroad.

Who should you contact if you have questions or problems?

In case of problems or questions, you can contact the following people:

Contact details of the patient's referring doctor
Project managers : Name: Mrs Nabila BOUAZZA / Mrs Aurore MOUSSION Phone : +33 (0)4.67.61.30.50 / +33 (0)4.67.61.24.46

<p>Patient name :</p> <p>Date :/...../.....</p> <p>I agree that my clinical data be used for research purposes</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>Signature :</p>
