EFFICACY OF DELAYED COLOANAL ANASTOMOSIS FOR MEDIUM AND LOWER RECTUM CANCER TREATMENT. PHASE 2 CLINICAL TRIAL

CASCADOR Protocol

SYNOPSIS

National multicentre trial

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SPONSOR **INSTITUT BERGONIÉ**

SYNOPSIS

Title of study	**Efficacy of delayed coloanal anastomosis for medium and lower rectum cancer treatment. Phase II clinical trial.** **CASCADOR Protocol**
Acronym	**CASCADOR**: **C**olo**A**nale **S**imple vs **C**olo**A**nale **D**ifférée en **O**ncologie **R**ectale (*Simple Coloanal vs. Delayed Coloanal in Rectal Oncology*)
Sponsor	Institut Bergonié Centre Régional de Lutte Contre le Cancer de Bordeaux et du Sud-Ouest (*Regional Cancer Centre of Bordeaux and the South-West*) 229, cours de l'Argonne 33076 Bordeaux Cedex FRANCE
Coordinator	Prof. Serge EVRARD, Gastrointestinal Tumours Unit
Number of centres	**7 centres** **ACAD** (delayed coloanal anastomosis) group: 3 centres - FCCC *(French Comprehensive Cancer Centre)* Institut Bergonié, Bordeaux, France - Hôpital de la Croix-Rousse, CHU *(University Hospital Centre)* Lyon, - CHU Grenoble, **ACAI** *(immediate coloanal anastomosis)* group**:** 4 centres - FCCC Léon-Bérard, Lyon, France, - Hôpital d'Adultes de Brabois, CHU Vandoeuvre-lès-Nancy, - Centre Alexis Vautrin, Vandœuvre-lès-Nancy, France - CHU Bordeaux
Indications	Medium and lower rectal cancer.
Study design	National multicentre phase II clinical trial
Number of patients	116 patients to be recruited (58 per group, see statistical analysis section).
Study duration	Enrollment begins: 2nd quarter 2010 Enrollment ends: 30 April 2017 Patient follow-up period: 2 years Study duration 9 years: 7 years of recruitment + 2 years of follow-up.
Primary objective	The aim of this study is to evaluate the efficacy of delayed coloanal anastomosis (ACAD) in the treatment of medium and lower rectal cancers at 30 days, in terms of symptomatic anastomotic fistula requiring a bypass stoma.
Secondary objectives	▪ Evaluation of the efficacy of immedite coloanal anastomosis (ACAI) in the treatment of medium and lower rectal cancers at 30 days, in terms of symptomatic anastomotic fistula requiring a bypass stoma. ▪ According to the surgical technique used (ACAD or ACAI): ○ Evaluation of the number of patients with a stoma (at 30 days, 1 year, and 2 years), ○ Evaluation of postoperative morbidity associated with coloanal anastomosis (at 30 days), ○ Evaluation of pre- and post-operative mortality (at 30 days), ○ Evaluation of progression-free survival (at 1 and 2 years), ○ Functional evaluation (quality of life, continence) (at 6 months, 1 year, and 2 years), ○ Evaluation of the duration of hospitalisation and economic impact (immediate or deferred costs, at 30 days, 1 year, and 2 years). ▪ Evaluation of the potential predictive role of the type of surgery on the occurrence of fistulas.
Inclusion criteria	1. Histologically proven rectal adenocarcinoma. 2. Medium or lower rectum tumour requiring removal of the entire rectum and its mesorectum. 3. T1 N+ or T2 N+ or T3 N+ or T3 N0 **and** M0 tumour. 4. Aged between 18 and 75 years inclusive. 5. ASA ≤ 2. 6. Sphincter continence compatible with coloanal anastomosis.

	7. Patients who received preoperative radiotherapy alone or chemotherapy and radiotherapy. 8. Patient registered with a social security system. 9. For patients of childbearing age: use of contraception. 10. Patient information and signed and dated informed consent.
Exclusion criteria	1. Other histology of rectal cancer. 2. T1 N0 or T2 N0 or T4 tumour. 3. Metastatic disease M1. 4. History of cancer except cervical carcinoma in situ or basal cell carcinoma of the skin. 5. Patients who for psychological, social, family or geographical reasons could not be treated or followed up regularly according to the study criteria; patients deprived of liberty or under guardianship. 6. Pregnant or nursing women.
Evaluation criteria	**<u>Primary evaluation criteria</u>** The efficacy of each surgical procedure (ACAD and ACAI) will be evaluated in terms of patients with no symptomatic anastomotic fistula requiring a bypass stoma (ileostomy or colostomy, whether preventive or curative) for treatment in the first 30 days after surgery. An anastomotic fistula is defined by: ▪ the escape of faeces through a drainage system, if one is present, or ▪ a set of clinical signs (fever, subocclusion, etc.) requiring confirmation by pelvic scan (collection of fluid plus gas in the perianastomal area). **<u>Secondary evaluation criteria</u>** ▪ The number of bypass stomas (preventive or therapeutic) will be evaluated. ▪ Morbidity will be assessed in terms of grade 3 and 4 surgical complications according to the Dindo classification of surgical complications and the NCI-CTCAE V3 toxicity scale. ▪ Post-operative mortality will be assessed during the first 30 days after the date of surgery. ▪ Progression-free survival will be assessed at 1 and 2 years. This is defined as the time between the date of the surgery and the date of the earliest of the following events: ○ The patient's death, whatever the cause, ○ Local or distant progression. ▪ A functional assessment will be conducted in the month prior to surgery and at 6 months, 1 year, and 2 years after surgery: ○ Quality of life will be assessed using self-administered EORTC QLQ-C30 questionnaire and its colorectal module QLQ-CR38. ○ Digestive functions, in particular anal incontinence, will be evaluated using the 5-item Jorge and Wexner scale. ○ An economic impact study will be conducted. Economic impact (hospitalisation, re-hospitalisation) will be evaluated using data from the French hospital discharge database (PMSI). The use of consumables during the operation and the fitting of temporary or permanent colostomy bags or ileostomy bags (loss of sphincter on fistula) until the eventual restoration of intestinal continuity will be evaluated.
Description of treatments	Whatever the mode of continuity restoration used, resection is the same in the two groups. It consists of total excision of the rectum and its mesorectum, whether the procedure is performed by laparotomy or laparoscopy. • **ACAD group (Delayed Coloanal Anastomosis)** After surgical resection, the colon is exteriorised through the anus and attached to the buttock with two stitches. On or around day 6, the exteriorised colon is resected and the coloanal anastomosis is performed without a preventive bypass stoma. • **ACAI group (Immediate ColoAnal Anastomosis)** After surgical resection, coloanal anastomosis is usually performed after creation of a J-pouch, when possible. In most cases, a preventive stoma is created.

<table>
<tr><td></td><td>If there is no fistula, the patient will undergo another surgery for closure of the bypass stoma.</td></tr>
<tr><td>Monitoring methods and duration</td><td>A 30-day complications assessment will be done at the postoperative consultation (i.e. approximately 40-45 days after surgery, in practice).
6 months after surgery, functional results will be assessed using quality of life questionnaires.
Patients will be seen again at the 1- and 2-year postoperative marks to assess the functional outcome of their digestive system, using quality of life questionnaires. Their final recovery status will also be recorded.
Patients will be monitored according to the usual follow-up of each surgeon.</td></tr>
<tr><td>Study timeline</td><td>
<table>
<tr><th></th><th>Inclusion</th><th></th><th>40-45 days post-op</th><th>6 months after surgery</th><th>1 year after surgery</th><th>2 years after surgery</th></tr>
<tr><td>Inclusion/exclusion criteria</td><td>X</td><td rowspan="7">SURGERY</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Informed consent signed</td><td>X</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Pre-anaesthetic assessment</td><td>X</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Quality of life questionnaires</td><td>X</td><td></td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Assessment of complications</td><td></td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>Functional digestive outcomes (stoma)</td><td></td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
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</td></tr>
<tr><td>Statistical analysis</td><td><u>Determining the number of patients</u>
▪ ACAD group
The primary judgement criterion was the efficacy of ACAD surgery as measured by the absence of fistula requiring a bypass stoma. We wish to demonstrate that the rate of patients with a fistula requiring a bypass stoma is less than 15%, i.e. the efficacy rate of ACAD is greater than 85%. Based on a one-sided binomial test with null and alternative hypotheses of 85% and 95% respectively, <u>53 eligible and evaluable ACAD patients</u> will be required (one-sided type I error of 5% and power of 80%). If 49 or more patients (out of 53) have no fistula requiring a bypass stoma, then we will conclude that ACAD is effective. In order to anticipate possible non-evaluable patients, we plan to recruit <u>58 ACAD patients</u>.
▪ ACAI group

In parallel, we plan to recruit <u>58 ACAI patients</u>.
<u>Statistical analysis</u>
▪ Quantitative variables: number of values, number of missing data, mean, standard deviation, 95% confidence interval, median, 1st and 3rd quartiles, minimum and maximum.
▪ Qualitative variables: number of values, number of missing data, frequency, percentage for each variable modality and exact confidence interval of each modality.
▪ Survival data: Kaplan-Meier method, median survival times with 95% confidence interval, median follow-up (follow-up) using the reverse Kaplan-Meier method,</td></tr>
<tr><td>Benefits</td><td>Putting forward a surgical technique associated with low morbidity for patients treated for medium and lower rectal cancer.</td></tr>
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