A Randomized Clinical Trial comparing Immediate to MOdified DElayed coloanal anastomosis after total mesorectal excision: the IMODE trial protocol

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Study protocol

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Abstract

Purpose
Immediate coloanal anastomosis (ICA) remains the standard technique for restoring the digestive tract after proctectomy for low rectal cancer. Often, it requires a temporary diversion stoma, thus increasing the risk of complications. Recent data have shown a great potential of the delayed coloanal anastomosis (DCA) both in decreasing anastomosis morbidity and in avoiding ileostomy to the patients. More recently, a modified delayed coloanal anastomosis (mDCA) has been described and seems to have promising results. This study aims to determine whether mDCA is non-inferior to ICA.

Methods
The IMODE trial is a randomized, controlled, non-inferiority trial designed to enroll 70 adults with mid or low rectal cancer. Participants are randomized to ICA or mDCA. The primary endpoint is the anastomotic fistulas (AF) rate at 6 months.

Conclusions
The mDCA can constitute an interesting modality to restore the digestive tract following proctectomy for mid and low rectal cancer; this by decreasing the morbidity of the coloanal anastomosis on the one hand and by avoiding ileostomy on the other hand.

Trial registration
PACTR202209500145137, September 9th, 2022 (retrospectively registered).

Background
In current clinical practice, ICA remains the standard technique for restoring the digestive tract following proctectomy for low rectal cancer [1]. This anastomosis, very often, still requires a temporary diversion stoma [2, 3]. Indeed, ICA is burdened with a significantly high morbidity, mainly represented by AF and pelvic abscesses [4, 5]. To decrease this morbidity, a diversion ileostomy is used by most surgeons after ICA [3, 6]. However, and despite this diversion stoma, the rate of AF remains quite high, varying from 11–15% [6, 7], of whom half will be reoperated and a third will require a permanent colostomy.[8–10] Moreover, this AF represents the third cause of postoperative mortality in rectal surgery after myocardial infarction and bronchopneumonia [11]. On the other hand, it is associated with a high rate of local recurrence [12]. In addition to the morbidity of ICA, there are specific complications related to the ileostomy itself, including postoperative renal failure and intestinal obstruction [13]. Furthermore, ileostomy appears to significantly alter patients' quality of life and self-perception [14, 15]; without
forgetting the complications inherent to the ileostomy closure [16–19]. To overcome the disadvantages of ICA, some authors have suggested as an alternative, a delayed coloanal anastomosis (DCA), where the anastomosis is performed several days after the proctectomy and lowering of the proximal colon through the anus, which is why it is called pull through [20–22]. The delayed approach seems to significantly reduce the morbidity of the coloanal anastomosis [23].

It is clear that there has been renewed interest in DCA over the last few years due to the favorable results of recent studies [24, 25]; especially in the "Redo Rectal Surgery" setting, where DCA seems to play a key role in avoiding a permanent stoma in three out of four patients with a low morbidity rate [26].

In a meta-analysis [27], including 409 patients who had DCA after proctectomy for low rectal cancer from eight observational studies, six of which reported no AF. Postoperative morbidity, particularly pelvic abscesses, ranged from 0 to 25%. In seven studies, the mortality rate did not exceed 3%. Poor fecal continence was recorded in less than 30% of patients. In 2% of cases, a permanent stoma was required. In terms of oncologic outcome at 5 years, between 6% and 38.8% of patients had locoregional recurrence, and overall survival ranged from 63.8–81%. In view of these results, the authors considered DCA as an interesting alternative.

Lin et al. [28] in a recent meta-analysis, showed that after DCA, patients had significantly less stoma compared to ICA (OR = 0.04; CI: 0.02–0.07; P < 0.001). Furthermore, there was no significant difference in terms of overall morbidity or mortality. The rate of AF, postoperative ileus, and pelvic sepsis was comparable in both groups.

In the first multicenter clinical trial, Biondo et al. [29] randomized 92 patients between ICA with diversion ileostomy vs. DCA; 15.2% of patients in the ICA group definitely kept their ileostomy, while 2.2% of patients in the DCA group did not have their anastomosis. In addition, the overall postoperative morbidity rate at 30 days was similar between the two groups (45.7 vs. 34.8%; P = 0.40). On the other hand, the AF rate was clearly lower without reaching significance in the DCA group (13.0% vs. 23.9%; P = 0.28). Moreover, the consequences of anastomotic dehiscence in this same group were definitely benign, since the resulting pelvic abscess was successfully treated in all patients (n = 6) by transanal drainage without the need for laparotomy. Another striking fact of this trial is that the paralytic ileus rate, also favored by the iléostomie [30], was quasi nil after DCA (0% vs. 24%). Although this trial failed to demonstrate the superiority of DCA, the authors nevertheless showed that it is at least as safe and effective as standard coloanal anastomosis, with the advantage of avoiding a diversion ileostomy and its complications.

Recently, Bianco et al. [31] described a new variant of the DCA, called "SHiP" = Short stump and High anastomosis Pull-through procedure. The novelty concerns on the one hand the length of the colonic stump which is shortened to 2cm for better patient comfort, instead of the 8-10cm described by Baulieux et al. [32]; on the other hand, the anastomosis is performed at the upper part of the anal canal, leaving the latter free. According to the authors, this would avoid ischemia of the colonic stump by a "guillotine" effect, which causes fistulas in the early phase and stenosis later on. In the hands of its promoters, this technique is associated with excellent short-term results [31]. Indeed, out of the 37 patients in the series,
the authors reported no AF or stump retraction. Only three patients (8%) had symptomatic stenosis. The functional results were similar to those of ICA. In summary, DCA in its SHiP version allowed the avoidance of ileostomy in all patients in the series with a marked reduction in morbi-mortality.

Based on these findings, we planned to conduct the first randomized controlled trial that compares immediate to modified delayed hand-sewn coloanal anastomosis (mDCA), in other words SHiP procedure, in patients with mid and low rectal cancer. The research question discussed is briefly summarized in Fig. 1. The purpose here is to describe the design of the IMODE trial and justify the design elements included in the study.

**Methods/design**

The study known as IMODE is an open label, non-inferiority randomized single-centre controlled trial, comparing ICA to mDCA following proctectomy with TME for mid and low rectal cancer. The study will be conducted in a University Hospital in Algiers (Algeria). The feasibility of the trial should be ensured, in terms of recruitment and good clinical practices. The study was approved by the local ethical committee. Patient enrolment started in June 2022 and is expected to end in June 2024; Debussy Clinic is the study sponsor. The trial design is summarized in Fig. 2.

**Ethics**

This study will be conducted in accordance with the Helsinki Declaration and the "Good Clinical Practice" guidelines [33]. The study protocol has been approved by the Medical Ethics Committee of the Debussy Clinic. Each patient will be explained the nature of the study, its purpose, the surgical procedures, the expected study duration, the potential benefits and the risks involved. Each participant will be informed that participation in the study is completely voluntary and that he or she may withdraw from the study at any time without affecting his or her therapeutic management. Prior to randomization, written informed consent will be obtained from all patients. The trial protocol has been drafted in compliance with the CONSORT recommendations and SPIRIT guidelines [34, 35]. The results of the study will be presented at national and international conferences in the areas of interest. Written publication of the results is planned in a peer-reviewed medical journal. Authorship for written publications must be confirmed by all principal investigators and will only be granted in the case of substantial contributions as stipulated by the International Committee of Medical Journal Editors [36].

**Hypothesis And Objectives**

The study aims to test the hypothesis that mDCA has advantages in terms of reduced postoperative morbidity compared to ICA with ileostomy.

The main objective of the IMODE trial is to demonstrate the non-inferiority of the mDCA in terms of AF rate compared to ICA following total mesorectal excision (TME) for mid and low rectal cancer.
The primary endpoint is to compare AF rate of the randomized treatment, as defined by the International Study Group of Rectal Cancer (ISREC) \[37\]. The diagnosis of AF will be based on clinical, biological and radiological arguments. Any fever, purulent drainage fluid and/or ascending kinetics of the biomarkers (WBC, CRP) at the 4th postoperative day will motivate a digital exam of the anastomosis as well as an injected CT scan with hydrosoluble opacification. The diagnosis of AF will be retained in the presence of any anastomotic dehiscence, extravasation of the opacifying product, peri-anastomotic abscess or air \[37\].

Secondary endpoints include:

- **Operative time**: number of minutes from incision to operative wound closure.
- **Operative interval** (*mDCA group*): number of days between the 2 stages.
- **Time to ileostomy closure** (*ICA group*): number of days between the 2 procedures.
- **Duration of postoperative ileus**: number of days until transit is re-established.
- **Length of hospital stay**
- **Complete mesorectal rate**: according to Quirke's classification \[38\].
- **R0 surgery rate**: number of specimens with negative resection margins.
- **Postoperative morbidity rate**: number of complications occurring within 90 days postoperatively according to the Clavien-Dindo classification \[39\].
- **Postoperative mortality rate**: number of disease-related deaths occurring within 90 postoperative days.
- **Anastomotic stenosis rate**: number of stenoses requiring dilatation or resection.
- **Readmission rate**: number of re-hospitalizations for complications.
- **LARS score** evaluated at 6 months \[40\].
- **St Marks score** for fecal incontinence assessed at 6 months \[41\].

### Inclusion Criteria

All adults who consult for histologically proven cancer of the mid or low rectum will be assessed for eligibility according to predefined criteria for eventual inclusion in the trial. Eligible patients will be informed of the protocol and invited to participate in the study. Once the informed consent form has been read, approved and signed, patients will be randomized between ICA and mDCA. The key inclusion criteria are male or female, over 18 years old, with cancer of the mid or low rectum (lower part of the tumor located within 10 cm of the anal verge) eligible for R0 proctectomy with TME, patients with or without distant metastases, resectable or not.

### Exclusion Criteria
Will be excluded from the study, all ycT4 tumors invading the external sphincter or levator ani requiring abdomino-perineal resection, fecal incontinence (St Marks score $\geq 6$). Furthermore, altered mental faculties preventing adherence to the study and refusal to participate are considered as exclusion criteria.

**Clinical Management Of Patients**

In accordance with the current guidelines for the treatment of rectal cancer [42], a complete physical exam will be carried out, including a digital rectal exam. Pelvic MRI and thoraco-abdominal CT will determine tumor staging. The 2017 TNM classification will be adopted. The cT3, T4 and/or N+ tumors will receive preoperative chemoradiotherapy. Surgery will be scheduled 6 to 8 weeks after the last course of neoadjuvant therapy.

**Surgical Technique**

Eligible patients will receive a mechanical bowel preparation the day before the surgery using polyethylene glycol (Fortrans®). Under general anesthesia, the procedure will consist of a high tie coloproctectomy with TME by laparotomy or laparoscopy. Following a mucosectomy, the left colon will be lowered trans-anally, and the digestive tract will be restored by either an ICA or mDCA.

**Immediate Coloanal Anastomosis**

It consists of a hand-sewn end-to-end coloanal anastomosis with 000Vicryl®, as described by Parks [43]. Twelve stitches will secure the lowered colon to the anal sphincter. The anastomosis will be protected by a diversion ileostomy; this will be closed during the second stage after 3 to 6 months. A clinical and radiological check of anastomosis integrity is carried out before any closure.

**Delayed Coloanal Anastomosis**

A colonic stump of 2 to 3 cm is left outside. Three stitches with 000Vicryl® are used to anchor the colonic serosa to the upper part of the anal canal on its anterior hemi-circumference (10, 12 and 2 o'clock); and as a marker for the subsequent recutting. The pulled-through colonic stump is inspected daily to ensure its viability. Also, a fat dressing is applied. Patients in this group will be reoperated between the 6th and 10th postoperative day under locoregional anesthesia; where adhesions will be gently released exposing the previously placed sutures. The colonic stump is then cut 1–2 mm from the marker sutures. A high coloanal anastomosis is performed by 12 single stitches with 000Vicryl®.

**Randomization**

The IMODE trial is an unblinded study as participants will know their treatment. Patients who meet the eligibility criteria are randomised to receive either ICA or mDCA. The randomization is performed in 1:1 equal allocation ratio to ensure an adequate comparison of the two groups, an identical number of
participants in each group and to reduce variability. Randomization sequence will be generated by a computer using a variable block size (random block sizes of 4 and 6 participants). Allocation is determined by the holder of the sequence who is situated off site.

**Follow-up**

The inclusion period will be for 18 months, and all patients will be followed up for at least 6 months, through outpatient visits under the responsibility of an attending surgeon other than the principal investigator, according to a predefined schedule (Fig. 3). Postoperatively, all patients will have daily visits where the abdomen will be examined and the drainage checked. A biological workup (WBC, CRP, renal tests) will be systematically performed at day 2 and 4. Patients from the ICA group will be discharged at day 5, if the ileostomy is functional with a normal workup and in the absence of fever, abdominal pain or dietary intolerance. The ileostomy will be electively closed after a 3–6 month interval. Patients in the mDCA group will remain in the clinic until the second stage, and will be discharged at day 5 unless complications occur. All patients will be revisited at 1 month and every 3 months for the first two years, then every 6 months for three years. At each visit, a complete clinical exam will be conducted; in addition to biological (CEA test), radiological (abdominal ultrasound every 3 to 6 months, CT scan every year) and endoscopic (colonoscopy at 3 years) controls. The functional outcomes will be measured via a questionnaire, filled in by the patients at the 6th month visit (Fig. 3). Phone calls from the investigating center are scheduled between visits to ensure their health status. These regular phone calls represent a retention program to minimize the number of patients lost to follow-up.

**Power Of The Study**

This study will be based on the hypothesis that mDCA would not be inferior to ICA in terms of AF rate. The sample size was calculated on the basis of results from previously published studies [29, 31]; reporting AF rate of 0% and 23.9% after DCA "SHiP" and ICA, respectively. To detect a difference between the two proportions with 80% power (risk $\alpha = 0.05$ and $\beta = 0.20$), a one-tailed test determined a requisite number of 35 patients randomized per arm (70 patients in total) accounting for a 20% non-inferiority margin and a 10% dropout rate.

**Statistical analysis**

Baseline demographics, pre-, and postoperative, as well as follow-up data will be compared separately for each group. The analysis will be performed both on an intention-to-treat and per-protocol basis, by an independent statistician after completion of the study. The primary endpoint will be compared between the two groups using the Pearson chi-square test. As for the secondary outcomes, Continuous and categorical variables will be respectively analyzed using the Student t test (or Mann-Whitney U test) and the chi-square test (or Fisher exact test). A two-sided P value < 0.05 will be considered significant.
Data Management

Data will be collected prospectively on case report forms (CRF) specially designed for the trial. The principal investigator will have to collect and check the forms during the monitoring visits. Data entry will be done along the course of the study as visits are made. The investigator will be responsible for the validity of the data reported on the CRF in relation to the source documents. Corrections to the CRF may only be made by the investigator or by other authorized persons. The data will be entered after verification and validation in order to constitute a clean and quality database. SPSS software (IBM SPSS Statistics 22) will be used to build the database, which must comply with the CRFs. The database will be frozen when all data have been entered. At that point, the statistical analysis can begin. All study data will be archived on the server of the Debussy Clinic for a minimum of 10 years after study completion.

Monitoring

An independent specialist in epidemiology and public health will monitor the study. All original data, including all patient records, progress notes, and copies of medical and laboratory test results, will be available for monitoring. Approximately 20% of CRFs and written informed consents will be monitored. Documentation of each site visit will be submitted to the ethics committee. The data will be checked for accuracy by reviewing the above documentation.

Safety And Reporting Of Adverse Events

Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational intervention. All adverse events (AEs) reported spontaneously by the subject or the staff will be collected, fully investigated and reported in the CRF during the entire study period. AEs will be reported to the principal investigator within 24 hours of their detection. If an AE is considered unexpected and related to the study intervention, the principal investigator will submit a report to the ethics committee within three days. This includes the event dates, treatment, resolution, severity rating, and causal relationship to the intervention. In the case of significant differences in AEs between groups, a report will be submitted to the local ethics committee and the trial may be stopped by decision of the principal investigator for unsafety. An interim analysis to ensure safety of mDCA will be performed after randomizing of 50% of the study population. The IMODE trial does not have a stopping rule if non-inferiority is shown before the required number of participants are fully enrolled or if it is determined that non-inferiority cannot be demonstrated in the interim analysis. This is due to the importance of secondary outcomes requiring full recruitment.

Discussion

Colorectal cancer is one of the most common cancers in the world. In terms of prevalence, it ranks third in men with 746,000 cases, after lung and prostate cancer. In women, it ranks second after breast cancer
with 614,000 cases [44]. The treatment of rectal cancer is multi-disciplinary, with surgery playing a key role. Colorectal surgery has been progressing steadily over the decades, from purely palliative procedures to both carcinological and conservative surgery. Thanks to technological advances, patient survival has improved significantly. In fact, the focus today has shifted from carcinological to functional outcomes, making postoperative morbidity, functional results, and quality of life the main endpoints in recent and future studies.

Although the concept of DCA, which aims to spare patients from a diversion stoma, is attractive, and despite the positive findings of this approach, particularly in the treatment of rectal cancers and chagasic megacolon [45], many authors remained sceptical about the need to externalize a colonic stump because of the functional consequences, the constraints related to daily care of the stump for a more or less long time, and finally the difficulty to perform a delayed anastomosis [46]. Moreover, the lack of data as well as the arrival and dissemination of surgical stapling devices have largely limited the spread of this technique and have clearly restricted its indications to Hirschsprung's disease and coloanal anastomosis salvage [47–49].

In the last few years, we have seen a real enthusiasm towards the DCA. The IMODE study is a prospective single-center randomized non-inferiority trial comparing ICA to mDCA after proctectomy for mid and low rectal cancer. In the light of literature data, we wished to conduct this clinical trial in order to determine the real potential of the mDCA since it has never been assessed through a clinical trial. This study was designed to answer the question: is mDCA non-inferior to ICA in terms of anastomotic fistulas rate. We hypothesize that we could decrease both the AF and overall morbidity rates after proctectomy.

As clearly stated in the inclusion criteria, we will perform hand-sewn coloanal anastomosis after proctectomy not only for low but also for mid-rectal tumors. This is mainly for two reasons: The first one is strictly technical; the colo-sus-anal anastomosis can only be performed with surgical staplers, which availability remains unfortunately inconstant here in Algeria. The second concerns the functional and oncological outcomes, which are quite comparable in the short and long term for both approaches [50, 51].

Even though Bianco et al. [31] reported no AF, the rate of anastomotic stenosis remains significant. Consequently, and in the attempt to decrease the rate of stenosis, at least the symptomatic ones, patients will be asked to perform a self digital rectal exam after having ensured the proper healing of the anastomosis without any dehiscence.

Regarding postoperative morbidity and mortality, it seemed to us more relevant and realistic to evaluate it at 90 days.

Finally, here are the expected benefits of this study:

1. To reduce the rate of AF.
2. To decrease the rate of overall morbidity as well as ileostomy-related morbidity.
3. To improve functional outcomes without affecting oncological ones.
4. To reduce costs and save resources, both human and material, by minimizing readmission rates and hospital stay.

Declarations

Authors Contributions: Hani Bendib was involved in conception, trial design and article drafting. Abdelkrim Anou, Nabil Djelali, Hind Oukrine, Said Lahrech, Abdelghani Azzouz, Chemseddine Chekman and Azeddine Djennaoui were involved in critical revision of the article for important intellectual content. All authors were involved in final approval of the article.

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Conflicts of interest/Competing interests: The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethics approval and consent to participate: The study has been approved by the Debussy Clinic medical ethics committee.

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https://doi.org/10.1097/DCR.0b013e3182270c41

https://doi.org/10.1503/cjs.001014


Figures

**Research question:** is mDCA non-inferior to ICA in terms of AF rate?

**Population:** Adults over 18 years old, with histologically proven cancer of the mid or low rectum.

**Intervention:** Patients are randomized to receive either ICA or mDCA.

**Comparison:** Percentage of patients who experienced AF in the ICA versus mDCA group.

**Outcome:** AF rate in randomized treatments.

**Time:** Outcome is measured at the 6th month of follow-up.

**Figure 1**

IMODE research question (PICOT format).
Figure 2

Flowchart of the IMODE trial

Eligible patients
Signed informed consent
Over 18 years old
Mid or low rectal cancer

Exclusion criteria:
ycT4 tumors invading the external sphincter or levator ani, fecal incontinence, mental faculties alteration, refusal

Randomization 1:1

ICA

mDCA

Follow-up
Data collection for primary and secondary outcomes
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**Figure 3**

Schedule of visits.