



RANDOMISED CONTROLLED TRIAL

A randomized phase III trial of structured tumour response surveillance and shared decision-making for organ preservation in rectal cancer – PRODIGE 101-GRECCAR 20-EVAREC trial protocol

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Abstract

Aim: Standard management with chemoradiotherapy (CRT) or total neoadjuvant therapy (TNT) followed by total mesorectal excision (TME) reduces local recurrence but often is associated with significant long-term functional impairment. Organ preservation (OP) has become a key therapeutic goal in rectal cancer to reduce surgery-related morbidity without compromising oncological outcomes. Three main OP strategies have been developed: Watch and Wait (W&W) strategy, Local Excision (LE) and Contact X-ray Brachytherapy (CXB), both applicable in patients showing a favourable tumour response after neoadjuvant therapy. The current challenge is defining the optimal timing and modalities for response assessment to accurately identify complete clinical response while balancing oncological control, functional outcomes and patient preferences. This trial evaluates whether a structured tumour response surveillance program combined with shared decision-making (SDM) can safely increase OP rates.

Methods: GRECCAR 20 is a multicentre, randomized, open-label, phase III trial enrolling patients with cT2-T3N0-1 rectal adenocarcinoma ≤ 8 cm from the anal verge and ≤ 4 cm in length, without involvement of the anal canal. Across the French GRECCAR and PRODIGE network, 270 patients will be recruited over 36 months. After neoadjuvant treatment (CRT or induction chemotherapy followed by CRT), participants are randomized to either a structured tumour response surveillance strategy with SDM over 8 to 24 weeks (experimental arm) or standard response assessment without SDM at 8 weeks (control arm). In the experimental arm (Arm A), reassessments at 2-, 4- and 6-month post-treatment will guide management decisions—W&W, LE, CXB or TME—through a collaborative process between patient and clinician. In the control arm (Arm B), treatment decisions at 2 months will be made solely by the clinician, between LE or TME, based on clinical, endoscopic and radiological assessment. The primary outcome is the OP rate at 2 years. Secondary endpoints include disease-free survival, TME-free survival, functional outcomes, quality of life (QoL) and patient-reported outcome measures (PROMs).

Conclusion: GRECCAR 20 is the first randomized trial to assess a structured tumour response surveillance program incorporating SDM in rectal cancer. By prioritizing patient values and QoL, this trial aims to improve OP rates without compromising oncological safety, potentially establishing a new standard of personalized, patient-centred care.

KEYWORDS

endocavitary radiotherapy, local excision, organ preservation, shared decision-making, total mesorectal excision, watch and wait

INTRODUCTION

The treatment of rectal cancer has evolved significantly over the past decades, becoming a truly multidisciplinary approach focused on optimizing both oncological control and functional preservation. For patients with locally advanced rectal cancer (LARC), the standard strategy – neoadjuvant treatment followed by total mesorectal excision (TME) – has significantly reduced local recurrence (LR) [1–5]. However, this strategy is associated with substantial long-term morbidity, including sexual, urinary or digestive dysfunction [6–9].

In this context, organ preservation (OP) has emerged as a major goal in selected patients, aiming to avoid radical surgery without compromising oncological outcomes. Two OP strategies have been developed: an opportunist approach with Watch and Wait (W&W) strategy and a selective approach with local excision (LE). Both strategies aim to preserve anorectal function in patients showing a favourable tumour response after neoadjuvant therapy. [10–12] The W&W strategy, pioneered by Habr-Gama et al. [10] involves intensive surveillance in patients achieving a clinical complete response (cCR) following chemoradiotherapy (CRT) based on clinical, endoscopic and radiological criteria, whatever the initial staging. This strategy has shown comparable oncological outcomes in selected patients, with reduced morbidity [13]. Alternatively, LE provides a minimally invasive surgical option for patients with near-complete (nCR) or clinical complete response (cCR) following neoadjuvant therapy. Several studies have evaluated this approach in patients with T1-T3aN0M0 tumours treated with CRT or total neoadjuvant treatment (TNT), reporting OP rates between 50 and 80% [11, 12, 14–17]. In the GRECCAR 2 trial, patients with cT2-T3 tumours <4 cm and favourable response to CRT were randomized to LE or TME [12]. Nearly 60% achieved OP with similar oncological outcomes, and LE significantly reduced low anterior resection syndrome (LARS) (5% vs. 47%, $p < 0.001$) [18].

To enhance tumour response, several strategies have been proposed: [1] intensifying the type and sequence of chemotherapy administration with TNT; [2] extending the interval between CRT and surgery; and [3] increasing radiation dose with endorectal brachytherapy. First, phase III trials such as RAPIDO and PRODIGE 23 demonstrated higher pathological complete response (pCR) rates with TNT. RAPIDO showed an increased pCR (28.4% vs. 14.3%) using short-course radiotherapy and consolidation chemotherapy [19], while PRODIGE 23 reported improved disease-free and

overall survival (DFS and OS) with induction triplet chemotherapy, along with higher pCR rates (28% vs. 12%) [20, 21]. Two phase II trials, CAO/ARO/AIO-12 and OPRA, compared TNT sequencing. Both found higher OP rates with consolidation chemotherapy (CRT-CNCT) versus induction-first (INCT-CRT) [22, 23]. By contrast, the phase III GRECCAR 12 trial (NCT02514278) tested INCT-CRT against standard CRT and reported a significantly higher pCR rate with a non-significant but higher OP rate in the experimental arm (71.3% vs. 63.6%) [24]. Second, delaying surgery after CRT has also improved OP rates, as seen in CAO/ARO/AIO-12 [22] and OPRA trial [23] with longer intervals between treatment and surgery in consolidation chemotherapy group (45 vs. 90 days for the induction and consolidation group in the German trial, 8 vs. 28.5 weeks for the induction and consolidation group in OPRA trial, respectively). Finally, radiotherapy intensification strategies, such as adding contact X-ray brachytherapy (CXB), have also been effective. The OPERA trial evaluated the addition of contact X-ray brachytherapy (CXB) to CRT in patients with cT2-T3bN0-1 tumours, reporting significantly improved 3-year OP rate (81% vs. 59%) particularly in tumours <3 cm [25] with sustained benefit at 5 years [26]. Based on these findings, current French national guidelines now support OP strategies, including LE and radiotherapy boost, in expert centres for selected patients with small (≤ 4 cm), cT2-T3, N0 or limited N1 (≤ 3 mesorectal nodes) rectal tumours, following CRT or TNT [27].

Accurate assessment of tumour response in LARC remains the cornerstone of any OP strategy. We have previously demonstrated the feasibility of a structured tumour response surveillance program, integrating standardized clinical, radiological and metabolic assessments [28]. Good responders (nCR or cCR at 8 weeks after neoadjuvant treatment) were enrolled in a 2-monthly surveillance program, achieving an 88% OP rate at 6 months with either LE or W&W without compromising oncological safety (median follow-up 32 months).

Thus, the current challenge lies in defining the optimal timing and modalities for response assessment to identify cCR, while balancing oncological control, functional outcomes and patient preferences. Before OP strategies can be widely adopted, integrating shared decision-making (SDM) into the therapeutic process is crucial to align treatment with individual patient values. SDM is a medical decision-making model aimed at promoting patient autonomy. It is based on a structured exchange of information—often supported by dedicated decision-support tools—and a shift in the patient-physician relationship toward balanced collaboration in reaching a consensual decision. SDM is particularly appropriate in clinical

situations where multiple treatment options are available, each with very different implications for the patient in terms of side effects, practical constraints or risks. In these situations, the patient's preferences are essential in determining which option best aligns with their goals and circumstances.

The aim of this trial is to evaluate the safety and effectiveness of a Response Surveillance Program, already defined in a monocentric pilot study performed by our team, incorporating SDM, for guiding OP strategies, in patients with LARC after neoadjuvant therapy.

METHODS

Trial design

GRECCAR 20 is a multicentre, prospective, open-label, two-parallel arm randomized controlled phase III trial comparing the tumour response surveillance program with SDM, versus standard

tumour response assessment in OP strategies in patients with T2-T3N0-1 rectal cancer (≤ 8 cm from the anal margin) (Figures 1, 2). In summary, the control arm reflects the current French standard of care, limited to LE or TME according to tumour response, while the experimental arm evaluates a structured tumour response surveillance program incorporating all available organ preservation strategies (LE, W&W, CXB). This design allows comparison between national practice and a broader international approach and assesses whether such strategies can be safely generalized in France.

Trial setting

This trial will take place in surgical and oncological departments with a special interest in colorectal oncology. All French hospitals participating in the GRECCAR and PRODIGE research group network will be eligible and invited to participate.

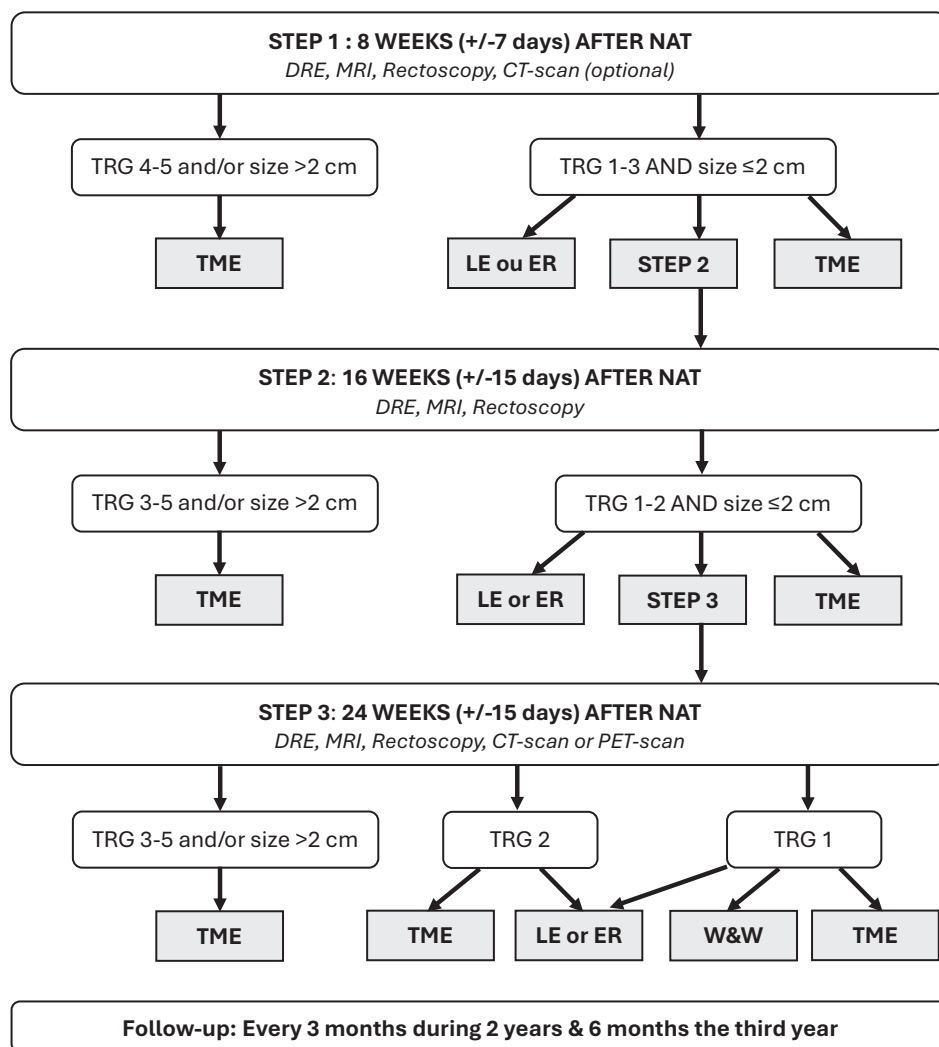


FIGURE 1 Experimental arm protocol schema. DRE, digital rectal examination; ER, endocavitary radiotherapy; LE, local excision; NAT, neoadjuvant treatment; TME, total mesorectal excision; W&W, watch and wait.

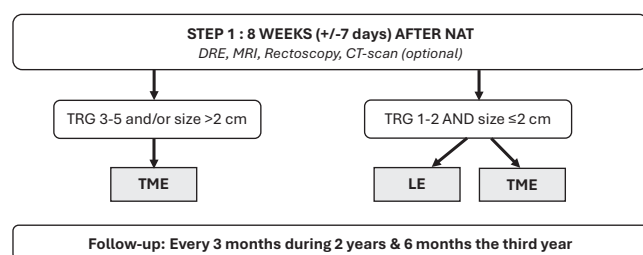


FIGURE 2 Control arm protocol schema. DRE, digital rectal examination; LE, local excision; NAT, neoadjuvant treatment; TME, total mesorectal excision.

TABLE 1 Inclusion and exclusion criteria for GRECCAR 20 trial.

Inclusion Criteria

- Age 18–80 years old
- Histologically confirmed rectal adenocarcinoma, MSS
- Neoadjuvant therapy (CRT with 50 Gy or induction chemotherapy with CRT)
- Initial characteristics of primary rectal cancer before neoadjuvant therapy:
 - Stage c T2–3
 - c N0–1 (≤ 3 lymph nodes)
 - No distant metastasis (M0)
 - Tumour size ≤ 4 cm, lower than the hemi-circumference of the rectum
 - Location ≤ 8 cm from the anal verge
 - No involvement of the canal anal and/or the internal/external sphincters
- Operable patient
- Compliance with the study protocol and follow-up schedule
- Person affiliated with or beneficiary of a social security scheme
- Informed consent

Exclusion Criteria

- Contra indication to pelvic MRI
- Patients with previous pelvic radiotherapy or chemotherapy
- Patients with MSI status and immunotherapy
- Patients with other concomitant cancer, or medical history of cancer other than treated in situ cervical carcinoma or basocellular carcinoma or spinocellular carcinoma
- Pregnant or active breast-feeding woman
- Persons deprived of liberty or under guardianship or incapable of giving consent
- All conditions including familial, sociological or geographical condition that could hinder adherence to the study protocol or follow-up scheduled

Eligibility criteria

An extensible list of inclusion and exclusion criteria is summarized in Table 1. Adult patients (18–80 years old) are eligible to participate if they have histologically proven MSS lieberkuhnian adenocarcinoma of the rectum, within 8 cm from the anal margin (confirmed by digital rectal examination or MRI if the digital examination is not possible), length of tumour ≤ 4 cm without involvement of the anal canal and/or the internal/external sphincters. Inclusion required either prior or planned neoadjuvant treatment with 6 cycles of (m) FOLFIRINOX or FOLFOX chemotherapy followed by CRT (CAP

50), or CRT alone, according to MDT decision. This design ensures that TNT is not mandated for all patients, particularly those with early-stage tumours, thereby avoiding unnecessary overtreatment or side effects. Moreover, the choice of induction chemotherapy before CRT reflects the current French national guidelines [27], which are based on the results of the PRODIGE 23 trial [20, 21]. Before the initiation of any neoadjuvant therapy, MRI staging had to confirm a T2–T3 tumour, with nodal status classified as N0 or N1 (defined as ≤ 3 suspicious lymph nodes). Absence of distant metastases (M0) was required, as demonstrated by CT scan or PET-CT. Further exclusion criteria will include previous chemotherapy or pelvic radiotherapy, any contraindication to pelvic MRI and the presence of another active malignancy or a history of cancer within the past 5 years (except for adequately treated in situ cervical carcinoma, non-melanoma skin cancer or any other in situ carcinoma considered cured). Patients must be willing and capable of providing written informed consent and must be willing to comply with scheduled visits, treatment plans, radiological assessments and other trial-related procedures.

Recruitment and randomization

Eligible patients will be identified through multidisciplinary meetings and preoperative clinic attendances where they will be invited to participate in this trial. Pre-inclusion visit may take place before, during or after neoadjuvant treatment. Eligibility, especially radiological criteria, is reviewed, and a centralized pre-treatment MRI review is performed by an expert radiologist within 24–72 h via the KEOSYS platform. If there is disagreement between the centre and central review, a third radiologist expert reassessment is conducted. All participants identified as suitable for inclusion will be provided with a detailed written patient information sheet and have a face-to-face discussion with a member of the research team. Following receipt of written informed consent and confirmation of eligibility, all patients will be centrally randomized using an on-line randomization system on a 1:1 basis to receive the tumour response surveillance program with SDM (experimental arm) versus standard tumour response assessment (control arm). Patients will be stratified according to centre and neoadjuvant treatment. Randomization is performed centrally at or just before the first reassessment visit (i.e. at 8 weeks ± 7 days after the last radiotherapy session). Concretely, this occurs once completion of neoadjuvant therapy has been confirmed.

TRIAL INTERVENTIONS

Management of patients will begin at 2-month post-treatment evaluation (+/7 days), following randomization and treatment arm allocation. In both arms, the timing of response assessment will be defined from the completion of neoadjuvant treatment, irrespective of whether patients received CRT alone or induction chemotherapy followed by CRT. The end of neoadjuvant treatment (last radiotherapy session)

therefore served as the reference point for the 2-, 4- and 6-month reassessments in the experimental arm and the 8-week reassessment in the control arm. Each MRI reassessment will be reviewed by an expert radiologist via the KEOSYS platform. For every reassessment, in case of a discrepancy between clinical, endoscopic and radiological reassessment that could impact patient management, the case will be discussed in the OP multidisciplinary team (MDT). All participating clinicians were trained in structured SDM and provided with decision aids, which are used exclusively in the experimental arm.

Experimental arm (Arm A)

In the experimental arm (Arm A), patients will undergo a three-step reassessment (2-, 4- and 6-month post-treatment). Depending on the tumour response, several management options may be proposed to the patient. For poor responders, TME is required, ensuring oncological safety. For good responders, OP options are then discussed according to predefined tumour response criteria and within a structured SDM process, allowing the final decision to reflect both oncological safety and patient preferences. Each consultation will be conducted by a surgeon, and an oncologist or a nurse to review and discuss the different treatment strategies. SDM will be grounded in the multidisciplinary consultation and supported by decision aids developed specifically for the study in collaboration with patient representatives.

First step

The primary reassessment will be performed at 2-month post-treatment with digital clinical examination, rectoscopy and pelvic MRI (thoraco-abdominopelvic CT scan is optional). According to defined clinical, endoscopic and radiological criteria, if the tumour response is:

- **TRG 1–3 and size tumour ≤ 2 cm:** the patient and clinician may choose between three possible management options through SDM.
 - The patient will continue in the close tumour response surveillance program, with the next consultation planned for 4 months after the end of treatment.
 - Local excision or contact X-ray
 - TME
- **TRG 4–5 and/or size tumour > 2 cm:** the clinician should perform TME.

Second step

A second reassessment will be performed at 4-month post-treatment with digital examination, rectoscopy and pelvic MRI. According to defined clinical, endoscopic and radiological criteria, if the tumour response is:

- **TRG 1–2 and size tumour ≤ 2 cm:** the patient and clinician may choose between three possible management options through SDM.
 - The patient will continue in the close tumour response surveillance program, with the next consultation planned for 6 months after the end of treatment.
 - Local excision or contact X-ray.
 - TME
- **TRG 3–5 and/or size tumour > 2 cm:** the clinician should perform TME.

Third step

A third reassessment will be performed at 6-month post-treatment with digital examination, rectoscopy, pelvic MRI, thoraco-abdominopelvic CT scan or PET scan (according to centre practices). According to defined clinical, endoscopic and radiological criteria, if the tumour response is:

- **TRG 1 and size tumour ≤ 2 cm:** the patient and clinician may choose between three possible management options through SDM.
 - Watch and Wait strategy
 - Local excision or contact X-ray
 - TME
- **TRG 2 and size tumour ≤ 2 cm:** the patient and clinician may choose between two possible management options through SDM.
 - Local excision or contact X-ray
 - TME
- **TRG 3–5 and/or size tumour > 2 cm:** the clinician should perform TME.

Control arm (Bras B)

In the control arm, a reassessment will be performed at 2-month post-treatment with digital clinical examination, rectoscopy and pelvic MRI (thoraco-abdominopelvic CT scan is optional). The clinician will decide the following treatment solely on oncological and clinical outcomes (no SDM). According to defined clinical, endoscopic and radiological criteria, if the tumour response is:

- **TRG 1–2 and size tumour ≤ 2 cm:** The two therapeutic options will be determined by MDT. As with any treatment, patients will retain the right to accept or decline the therapeutic proposal recommended by the MDT.
 - Local excision.
 - TME
- **TRG 3–5 and/or size tumour > 2 cm:** the clinician should perform a TME.

TABLE 2 Classification of tumour response: clinical, radiological and endoscopic criteria.

Grade	Response	Definition
Clinical assessment		
Grade 1	Complete	No nodule, ulcer or induration, normal mucosa
Grade 2	Sub-complete	Superficial induration or ulcer ≤ 2 cm
Grade 3	Partial (Moderate)	Tumour regression $< 50\%$ with exophytic tumour
Grade 4	No response	Tumour volume and appearance identical to the initial tumour
Radiological assessment		
Grade 1	Complete	No residual tumour
Grade 2	Good	Dense hypo-intense fibrosis, minimal residual tumour
Grade 3	Moderate	50% fibrosis/mucin, with intermediate signal indicating residual tumour
Grade 4	Slight	Minor fibrosis or mucin, predominantly residual tumour
Grade 5	No response	Tumour identical to the initial tumour

Response	Definition
Endoscopic assessment	
Complete	No nodule, no ulceration; flat, white scar with or without superficial telangiectasia. No residual mucosal abnormality or submucosal irregularity.
Sub-complete	Presence of any of the following: (a) residual mucosal irregularity, (b) flat residual ulcer or (c) submucosal irregularity or swelling.
Incomplete	Definite residual tumour or marked ulceration with: (a) $< 50\%$ reduction in tumour size, or (b) residual tumour diameter > 20 mm (not attributable to inflammation/oedema)

Tumour response assessment

Clinical assessment

Tumour response will be assessed by clinical digital examination classified according to the tumour regression grade (Table 2). Clinical reports should include tumour size, localization of the tumour (anterior, posterior, circumferential, lateral), the distal tumour boundary relative to the anal margin and the anal canal, and tumour regression grade (TRG) according to Habr Gama et al. [29].

Radiological assessment

Once the patient is included, tumour response will be assessed by MRI. A centralized review by a radiologist will be carried out for each re-evaluation to validate tumour response (tumour size and TRG), according to Table 2. Good responders are defined as a downsizing of

the tumour $> 50\%$ and fibrosis $> 50\%$, which correspond to residual tumour ≤ 2 cm and ymrTRG1-3. Bad responders are defined as residual tumour > 2 cm or ymrTRG4-5 (regardless of size).

Endoscopic assessment

Tumour response will be assessed by rectoscopy with the following definitions (Table 2):

- Complete response: no nodule, no ulceration, a flat and white scar with or without superficial telangiectasia at the site of the initial tumour. There should be no residual mucosal abnormality, nor any suggestion of submucosal irregularity.
- Sub-complete response: Identification of one of the following: residual mucosal irregularity, flat residual ulcer, submucosal irregularity or swelling.
- Incomplete response: Positive identification of a residual tumour or marked ulceration with either: less than 50% reduction in tumour size, or residual tumour diameter > 20 mm (when the residual mass cannot reasonably be attributed to inflammation/oedema).

Each expert will indicate the grade of endoscopic tumour response (retrospectively) after reviewing the images and videos.

Surgery

According to the tumour response and the selected treatment strategy:

- Total Mesorectum Excision (TME) with or without sphincter preservation. The operative approach will be at the discretion of the operating surgeon.
- Local Excision (LE) with a distal margin of 1 mm. Based on the pathological results, the recommendations are as follows: Surveillance if ypT0-1 or ypT2 Nx/cN0 or Completion TME if ypT2 Nx/cN1, ypT3 or R1 resection (to be performed within 4 weeks).

Quality assurance

Each centre will be required to undergo initial and ongoing training on tumour reassessment and SDM before participating in the study. Quality assurance will be ensured through this training program, centralized case review and patient decision-support materials. Only qualified centres will be allowed to participate in the study.

Outcome assessment

The primary outcome is the 2-year organ preservation (OP) rate, comparing the effectiveness of 'Tumour Response Surveillance

Program in Rectal Cancer with Shared Medical Decision-Making with Patients' (experimental arm) compared with 'Standard Tumour Response Assessment in Rectal Cancer without Shared Medical Decision-Making with Patients' (standard arm).

The following secondary outcomes will also be assessed and reported in both strategies:

- Patient compliance with the tumour response surveillance program
- Disease-free survival and overall survival at 3 years
- Local recurrence-free survival at 3 years
- Regrowth-free survival at 3 years
- Total mesorectal excision (TME)-free survival at 3 years
- Surgical morbidity and mortality at postoperative day 90
- PROMs (Patient-Reported Outcome Measures): Quality of life (EQ-5D-5L, EORTC QLQ-CR29 and EORTC QLQ-C30)
- Digestive function scores (LARS and Wexner questionnaires)
- Urinary function score (USP questionnaire)
- Sexual function scores (FSFI and IIEF-5 questionnaires)
- Proportion and time to return to work among employed patients.

Assessment schedule and follow-up

All patients will be followed up at 3-monthly intervals in the first two years postoperatively and at 6-monthly intervals in the third postoperative year. Patients in Arm A will have their first follow-up 9 months after completion of neoadjuvant treatment for patients who have completed all three stages of Arm A, and patients in Arm B will also have their first follow-up at 6 months (Table 3).

This follow-up visit will include the following examinations:

- Contact X-ray or W&W: digital clinical examination, thoraco-abdominopelvic CT scan, pelvic MRI and rectoscopy (every 6 months for 2 years and then once a year in the third year).
- Local excision: digital clinical examination, thoraco-abdominopelvic CT scan, pelvic MRI, annual rectoscopy
- TME: digital clinical examination, thoraco-abdominopelvic CT scan

All questionnaires will be administered to patients in both groups at 12 and 24 months.

Sample size calculation and statistical analysis

The organ preservation rate is estimated at 60% in the standard arm, according to GRECCAR 2 trial [12]. We hypothesize that the new strategy will increase this rate to 80%. Using a two-sided type I error rate of 5%, a power of 90%, and a Z-test (Chi-squared), a sample size of 106 patients

per group is required. Accounting for 10% loss to follow-up and 15% protocol deviations, the final sample size is set at 135 patients per arm.

Statistical analysis will be conducted in accordance with a pre-specified statistical analysis plan. The primary analysis will be based on an intention to treat (ITT) where all patients are analysed according to their randomized treatment, regardless of protocol adherence. A modified ITT will also be undertaken, including all randomized patients without major protocol deviations. Efficacy analyses (primary and secondary endpoints) will be performed on the ITT and mITT populations.

Baseline characteristics will be performed on the entire randomized population. Quantitative variables will be summarized using mean, standard deviation, median, interquartile range and range and compared using a Student's test or a non-parametric test of Wilcoxon. Categorical variables will be presented as frequencies and percentages and compared by a chi-squared test, a corrected chi-squared test or a Fisher exact test, as appropriate. Time-to-event endpoints such as OS, DFS will be analysed using Kaplan-Meier estimates, with comparisons between arms made using the log-rank test. Hazard ratios (HR) and 95% confidence intervals will be estimated using Cox proportional hazards models, both unadjusted and adjusted for stratification variables. If the proportional hazards assumption is violated, restricted mean survival time (RMST) methods can be applied. RMST represents the expected survival time over a specific time horizon and offers an alternative measure to summarize the survival profile. QoL outcomes will be analysed in the ITT population, including patients with at least one baseline questionnaire.

For each variable, the number of missing data will be described. The reason for being missing will be documented as much as possible in order to interpret the results.

Trial management

The trial will be led by the principal investigator QD. A trial management group comprising the principal investigator, trial assistants, coordinators and co-applicants will be established to implement and manage the clinical and practical running of the trial. Data management, trial coordination, data management and statistical input will be provided by the project team of Bordeaux Colorectal Institute and FFCD (Fédération Francophone de Cancérologie Digestive).

Serious adverse events

Patient safety monitoring is carried out in accordance with standard clinical care practices and the procedures in effect at the participating institution.



TABLE 3 Assessment schedule and follow-up.

Follow-up First follow-up at 6 months (± 15 days) after the end of radiation, EXCEPT for patients who have completed all 3 stages of arm A (first follow-up at 9 months) Every 3 months for 2 years Every 6 months in the 3rd year									
	Screening	Inclusion/ Randomization	Assessment of tumour response				IF W&W	IF LE	IF TME
			ARM A	ARM B					
Information patient and consent	✓								
Consent signed	✓	✓							
Eligibility	✓	✓							
Medical and surgical history	✓								
Professional activity	✓								
Biopsy	✓								
Treatments	✓	✓							
B-HCG	✓		✓ ^a			✓			
			STEP 1 2 months after RCT	STEP 2 4 months after RCT	STEP 3 6 months after RCT	2 months after RCT			
SDM			✓	✓	✓				
Clinical examination ^b	✓		✓	✓	✓	✓	✓	✓	✓ (If Applicable)
MRI	✓(Before Treatment)		✓	✓	✓	✓	✓	✓	
Rectoscopy			✓	✓	✓	✓	✓(Every 6 months and one a year the third year)	✓Annual	
CT Scan	✓		✓ (optionnal)		✓ Or TEP-Scan (centre decision)	✓	✓	✓	✓
Strategy			TRG 1-3: - LE or RE (if sizes≤2 cm) - continuation of the EVAREC program - TME TRG-4-5: TME	TRG 1-2: - LE or RE (if sizes≤2 cm) - continuation of the EVAREC program - TME TRG-3-5: TME	TRG 1: - LE or RE (sizes≤2 cm) - continuation of the EVAREC program - TME TRG 2: - LE or RE (sizes≤2 cm) - TME TRG-3-5: TME	TRG 1-2: - LE or RE (sizes≤2 cm) - TME TRG-3-5: TME			
Questionnaires ^c			✓		TRG-3-5: TME 2713	✓	✓ 12 & 24 months	✓ 12 & 24 months	✓ 12 & 24 months
Morbidity & mortality (DINDO)				✓	✓	✓			
AE/SAE		✓	✓	✓	✓	✓	✓	✓	✓

^aβ-HCG: Serum β-HCG levels must be assessed at baseline and repeated in cases of surgical intervention or endocavitary radiotherapy.

^bClinical examination: Rectal examination, Size, Weight, ECOG, comorbidity and treatments.

^cQuestionnaires: QLQ-C30-CR29, LARS score & WEXNER score, IIEF-5/FSFI, USP, EQ-5D-5L, activity professional, Decisional conflict scale (DCS), Regret Conflict Scale (RCS).

Ethics and regulatory considerations

The PRODIGE 101 – GRECCAR 20 – EVAREC trial has received approval from the French ethics committee (CPP), and ANSM has been informed of the approval of CPP. It will be conducted in accordance with standard principles of good clinical practice for conducting clinical trials and all recommendations from the World Medical Association Declaration of Helsinki and the European Union Regulation 2016/679. The trial has been registered on [ClinicalTrials.gov](https://clinicaltrials.gov) website under the identification number NCT06740357. The trial will be sponsored by Dijon University Hospital with appropriate provisions made for public liability insurance policy in accordance with the French Public Health Code.

Dissemination

The results of the trial will be presented at national and international scientific meetings and formal publications will be published in peer-reviewed journals.

DISCUSSION

OP has become a key objective in the management of rectal cancer, aiming to reduce surgery-related morbidity without compromising oncological outcomes. Several trials have demonstrated the feasibility of OP strategies through W&W or LE in carefully selected patients with complete or near-complete response after neoadjuvant therapy. Reported OP rates range from 50 to 80% [11, 12, 14–17] and our own structured tumour response surveillance program has achieved an OP rate of 88% at 6 months through W&W or LE [28].

GRECCAR 20 is the first randomized phase III trial designed to assess the efficacy of a defined Response Surveillance Program, applying a tailored and dynamic approach to OP, either with W&W strategy, LE or CXB. We hypothesize that this personalized strategy will further increase OP rates at 2 year post-neoadjuvant treatment. Moreover, secondary endpoints, including OS, DFS, regrowth-free survival and TME-free survival, will evaluate the oncologic safety of this approach.

Beyond oncological outcomes, GRECCAR 20 trial addresses a critical gap in the current OP research by integrating patients' perspectives into treatment decisions. Unlike previous studies that used a paternalistic decision-making model, GRECCAR 20 is the first phase III trial to evaluate a structured tumour response surveillance program incorporating SDM. This collaborative approach ensures that the final decision between clinician and patient reflects not only oncological outcomes but also individual patient values, particularly regarding digestive, sexual or urinary function as well as QoL expectations.

SDM is a collaborative and bidirectional process and emphasizes active patient involvement [30]. The process involves three key steps: [1] presenting the clinical decision and outlining evidence-based

options with their risks and benefits; [2] exploring the patient's values, preferences and lifestyle; and [3] jointly deciding on the most appropriate strategy [31]. The widely adopted “three-talk model” by Elwyn et al.—comprising ‘team talk’, ‘option talk’ and “decision talk”—serves as the conceptual framework [32]. The concept of SDM has been widely studied and used in other fields of medicine. In urology, particularly for the management of localized prostate cancer, SDM has become a standard, allowing patients to choose between active surveillance, surgery or radiotherapy with a clear understanding of functional trade-offs [33]. A Cochrane systematic review confirmed that the use of decision aid with SDM improves patient knowledge, increases alignment between choices and patients' values, and reduces decisional conflict [34]. However, direct patient involvement in the decision-making process does not eliminate the risk of decisional regret and may generate a sense of personal responsibility, which clinicians must be mindful of. The SDM framework implemented in this trial aims to standardize shared decision-making practices and provide structured support to patients throughout the process.

Despite this widespread integration in other specialties, SDM remains underutilized in colorectal oncology [35]. GRECCAR 20 aims to challenge this approach by integration SDM at each follow-up visit, where TME, LE and W&W or CXB are discussed based on tumour response and evolving patient priorities. The trial will evaluate whether SDM, combined with close follow-up at 2, 4 and 6 months, can safely increase OP rates without compromising oncological safety. Compliance to the response surveillance program will be also assessed to validate the feasibility of SDM.

Another important strength of the GRECCAR 20 trial is its strong evaluation of long-term functional outcomes. While several studies have focused on OP with oncological outcomes, GRECCAR 20 incorporates validated patient-reported outcome measures (PROMs) to assess digestive, urinary and sexual function but also QoL and work integration. By collecting standardized PROMs (LARS, Wexner, FSFI, IIEF-5, USP, EQ-5D-5L, EORTC QLQ-C30/CR29) at key time points, GRECCAR 20 allows a robust evaluation at predefined timepoints to assess the full impact of each OP strategy. These data will enhance understanding of how OP and SDM influence not only survival but also patient QoL and satisfaction.

CONCLUSION

GRECCAR 20 represents a critical step forward in the evolution of rectal cancer management. By combining structured tumour surveillance with SDM, this trial seeks to increase OP while establishing patient-centred care as a central position of clinical practice. Its results may offer a new paradigm where oncological control, functional outcomes, quality of life and individual preference are all considered essential endpoints.

AUTHOR CONTRIBUTIONS

Barbara Noiret: Conceptualization; investigation; writing – original draft; writing – review and editing; visualization; validation.

Véronique Vendrely: Conceptualization; investigation; validation. **Alexis Delattre:** Conceptualization; validation; methodology; formal analysis. **Adrien Vavasseur:** Conceptualization; investigation; writing – review and editing. **Hélène Maillou-Martinaud:** Writing – review and editing; investigation. **Stéphanie Nougaret:** Conceptualization; investigation; writing – review and editing; validation. **Jeremie Jacques:** Conceptualization; investigation; writing – review and editing; validation. **Thibaud Haaser:** Conceptualization; investigation; validation; writing – review and editing. **Côme Lepage:** Funding acquisition; project administration. **Quentin Denost:** Conceptualization; investigation; funding acquisition; writing – original draft; methodology; validation; visualization; writing – review and editing; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ETHICS STATEMENT

The study was approved by the French ethics committee (CPP) and the French regulatory authority (ANSM). It was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All participants provided written informed consent prior to inclusion.

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