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BRIDGE −1 TRIAL: BReak Interval Delayed surgery for Gastrointestinal Extraperitoneal rectal cancer, a multicentric phase III randomized trial

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ABSTRACT

Design: Neoadjuvant chemoradiotherapy (nCRT) followed by surgery is the standard of care for locally advanced rectal cancer (LARC).
Several studies have shown a correlation between a longer interval between the end of nCRT and surgery (surgical interval - SI) and an increased pathological complete response (pCR) rate, with a maximum obtained between 10 and 13 weeks.
The primary endpoint of this multicenter, 2-arm randomised trial is to investigate SI lengthening, evaluating the difference in terms of complete response (CR) and Tumor Regression Grade (TRG)1 rate in the two arms. Secondly, the impact of SI lengthening on survival outcomes and quality of life (QoL) will be investigated.
Methods: Intermediate-risk LARC patients undergoing nCRT will be prospectively included in the study. nCRT will be administered with a total dose of 55 Gy in 25 fractions on Gross Tumor Volume (GTV) plus the corresponding mesorectum of 45 Gy in 25 fractions on the whole pelvis. Chemotherapy with oral capecitabine will be administered continuously.
The patients achieving a clinical major or complete response assessed at clinical-instrumental re-evaluation at 7–8 weeks after treatment completion, will be randomized into two groups, to undergo surgery or local excision at 9–11 weeks (control arm) or at 13–16 weeks (experimental arm). Pathological response will be assessed on the surgical specimen using the AJCC TNM v.7 and the TRG according to Mandard. Patients will be followed up to evaluate toxicity and QoL.
The promoter center of the trial will conduct the randomization process through an automated procedure to prevent any possible bias.

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For sample size calculation, using CR difference of 20% as endpoint, 74 patients per arm will be enrolled.
Conclusions: The results of this study may prospectively provide a new time frame for the clinical re-evaluation for complete/major responders patients in order to increase the CR rate to nCRT.
Trial registration:
ClinicalTrials.gov Identifier: NCT03581344.

Introduction/rationale

Preoperative chemoradiotherapy (CRT) followed by surgery is the standard treatment in locally advanced rectal cancer (LARC) [1], since it has been demonstrated to significantly increase local control (LC) [2–4]. Neoadjuvant CRT (nCRT) treatment leads to a high response rate, characterized by a pathological complete response (pCR) rate of about 15%- 38 [5,6]. Several *meta*-analyses and pooled analyses have shown a clear correlation between pCR and long-term clinical outcomes such as LC, metastasis free survival (MFS), disease free survival (DFS) and overall survival (OS) [7–9].

Several factors may influence pCR after neoadjuvant treatment: among these, studies have particularly examined chemotherapy (CHT) intensification with the addition of a second drug to fluoropyrimidines during nCRT [10–12], the impact of the radiotherapy (RT) boost on the macroscopic tumor lesion [5,13–15] and the interval between the end of neoadjuvant treatment and surgery [6,16,17].

CHT intensification has been investigated in several phase 2 studies, while randomized trials have evaluated the combination of 5-fluoracil (5-FU) and oxaliplatin concomitance with preoperative RT [5,12,18–20].

The CAO/ARO/AIO-04 is the only study that demonstrated an increase in DFS with the addition of oxaliplatin to CRT treatment [10].

Dose escalation, especially after the introduction of intensity-modulated radiotherapy (IMRT) and the growing interest in protocols based on the introduction of brachytherapy, has been tested in several phase 2 studies. Data from the Italian multicenter INTERACT study showed that intensified RT (55 Gy in 5 weeks + 5FU) produced the same results in terms of pCR as intensified CHT (50.4 Gy in 5 weeks and 3 days + 5FU and oxaliplatin), but with statistically lower toxicity [5]. A dose–response model developed by Appelt et al. showed a clear correlation between the RT dose and tumor response [13]. In support of this model, a *meta*-analysis confirmed that a significant increase in pCR is obtained with RT doses greater than or equal to 60 Gy, without a significant increase in toxicity [14].

Finally, the surgical interval (SI), also explored in a randomized trial [16], allows the tumor to respond to treatment and surgery to be performed when the treatment- related inflammation is no longer present and the late fibrotic processes caused by RT have not yet developed. The standard interval between the end of CRT and surgery currently is about 6–8 weeks. Phase II, retrospective studies, *meta*-analyses and pooled analyses report that extending the SI beyond 12 weeks leads to an increase in pCR without a corresponding increase in perioperative morbidity [6,17,21,22], with the exception of the GRECCAR 6 trial, which showed no benefit in oncological outcomes after extension of SI by an additional 4 weeks compared to standard [23]. The impact of SI was evaluated in an Italian pooled analysis conducted by the AIRO Study Group for Gastro-Intestinal Diseases, conducted on>2000 patients, which showed a significantly higher pCR rate in patients undergoing surgery after 13 weeks [17].

A prospective non-randomized phase II study investigated the effect of increasing cycles of CHT in the pause between CRT and surgery on SI prolongation [6]. After undergoing CRT, patients were divided into 4 groups. Group 1 underwent total mesorectal excision (TME) at 6–8 weeks after CRT while patients in groups 2–4 received two, four, or six cycles of mFOLFOX6 in the pre-surgical break, respectively. The authors reported an increasing pCR rate from group 1 to group 4, with a statistically significant difference between group 1 and group 4, (18% vs 38% $p = 0.01$). This result confirms that lengthening with the addition of CHT in the pre-surgical break increases pCR rates, but leaves the question of whether this result can be attributed to lengthening time or to the addition of neoadjuvant CHT.

Furthermore, a recent pooled analysis of 3085 patients from 7 randomised trials investigated the optimal SI to achieve the highest rate of pCR and the impact on survival outcomes [24]. This interval was found to be 10 weeks and to have no detrimental effect in terms of local recurrence (LR), distant metastasis (DM), DFS and OS.

The possibility of increasing complete response (CR) rates through different strategies makes it possible to implement personalized approach for organ preservation strategies. Conservative surgical approaches, such as full-thickness local excision (LE) of the scar or tumor remnant and watch and wait (W&W), have recently been applied in patients who achieve clinical major (cMR) or clinical complete response (cCR) after nCRT [25,26]. This approach appears to be feasible and advantageous for the reduction of morbidity and toxicities that may result from TME after successful nCRT. Currently there are no studies of the superiority of one approach over the other in case of cCR. The most recent studies compare both approaches with TME, demonstrating the advantages of organ preservation and organ function with comparable oncological outcomes [25,27,28].

Taking into account the evidence reported in the literature derived from retrospective or non-randomized trials, the present study aims to compare in a prospective scenario the impact of SI on CR. This will be carried out by randomizing a selected group of LARC patients, without high risk factors, who have achieved cCR or cMR at 7–8 weeks after nCRT to undergo surgery or a conservative approach, at 9–11 weeks (control arm) or at 13–16 weeks (experimental arm). The exclusion of LARC patients with high-risk features who achieve partial response, stable disease or disease progression after nCRT may provide a different perspective compared to the design and results provided by the GRECCAR-6 trial, based on the assumption that these types of patients could not benefit from an organ-preservation approach [29].

The results of the BReak Interval Delayed surgery for Gastrointestinal Extraperitoneal rectal cancer (BRIDGE −1) trial could prospectively confirm a new SI after nCRT in LARC patients, in order to detect the highest response rate. Furthermore, based on the data reported in the literature [24], the evidence obtained will be able to clearly define the characteristics of patients who can benefit from this approach. Collaterally, the correlation between clinical and pathological response and the impact of SI lengthening on survival outcomes and quality of life (QoL) will be investigated.

Design

The proposed study is a multicentre randomised phase III trial. The study design is reported in Fig. 1.

All patients included in the study will receive nCRT.

Patients will undergo clinical-instrumental restaging at 7–8 weeks and, in case of major or complete clinical response, will be randomized into two groups:

1. surgery or LE at an interval of 9–11 weeks after completion of nCRT;
2. clinical-instrumental re-evaluation at 11–12 weeks followed by surgery or LE at 13–16 weeks after the end of nCRT.

Treatment description

Patients selection

The inclusion and exclusion criteria are presented in Table 1.

Clinical evaluation, staging and re-staging

The treatment strategy of all patients will be discussed in the context of the multidisciplinary tumor board (MDT), consisted of core group of surgeons, radiation oncologists, medical oncologists, radiologists, pathologists to share the best therapeutic options, both at the diagnosis and at presurgical restaging. Table 2 shows the schedule and procedures used for initial staging and restaging. TNM clinical and pathological stage are determined according to the American Joint Committee on Cancer [30], and the histological grade of adenocarcinoma according to WHO.

Definition of response

Clinical complete response [31] is defined when all of the criteria listed below are present:.

- objective examination: no palpable mass on digital rectal examination (DRE);
- magnetic resonance imaging (MRI) [32]: no evidence of lymph nodes or lymph nodes with short axis less than 5 mm. No detectable residual tumor on either morphological examination or diffusion weighted imaging (DWI) sequences with re-appearance of rectal wall layers. Hypointense parietal thickening in T2-weighted (T2w) sequences with no evidence of residual, hyperintense in DWI sequences/hypointense in apparent diffusion coefficient (ADC) map.
- endoscopy: absence of any endoscopic lesions. A flat scar should be considered as absence of endoscopic lesion.

Clinical major response [33] is defined when 1 or more of the above criteria are present:

- objective examination: palpable mass at DRE
- MRI [32]: no evidence of residual lymph nodes or residual lymph nodes with short axis less than 5 mm. Hypointense parietal thickening in T2w sequences but with small residual hyperintense areas in DWI sequences.
- endoscopy: absence of deep or superficial ulcer > 2 cm in diameter.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	
General	ECOG 0–1 Age over 18 years Written informed consent
Primary tumor characteristics	Histological proven adenocarcinoma of the rectum located between 0 and 12 cm above the internal anal sphincter Clinical stage cT2N1-2, M0; cT3, N0-N2, M0 cMR or cCR
Exclusion criteria	
General	Contraindications for MR and/or endoscopy Pregnancy or lactating female patients Psychological, familial, sociological or geographical condition potentially hampering compliance with the oncological treatment, the study protocol and follow-up schedule No other malignancies in the last 5 years of previous history (except skin and initial cervical cancer) Absolute contraindications to RT, CHT and surgery. Patients discontinuing treatment.
Primary tumor characteristics	Mesorectal fascia involvement for tumor Clinical stage cT4 Extramesorectal nodes involvement Extramural venous invasion (EMVI) Tumor located at a distance > 12 cm from the internal anal sphincter Presence of distant metastases Partial response, no-change or disease progression at re-evaluation 7–8 weeks after completion of nCRT

ECOG: Eastern Cooperative Oncology Group; MR: Magnetic Resonance; cMR: clinical major response; cCR: clinical complete response; RT: radiation therapy; CHT: chemotherapy; nCRT: neoadjuvant chemoradiotherapy.

Pathological Complete response is defined as anatomo-pathological absence of tumor cells in the rectum and mesorectal lymph nodes examined on the surgical specimen [7].

Radiotherapy: Treatment volumes

Gross tumor volume (GTV) includes clinically evident disease (both T and N) on clinical and instrumental diagnostic examinations.

The CTV1 includes the GTV and the corresponding mesorectum, defined as the axial section of mesorectum extending from the cranial to the caudal pole of the tumor.

The CTV2 includes the CTV1, the total mesorectum and selected lymphatic drainage stations, which will be delineated manually

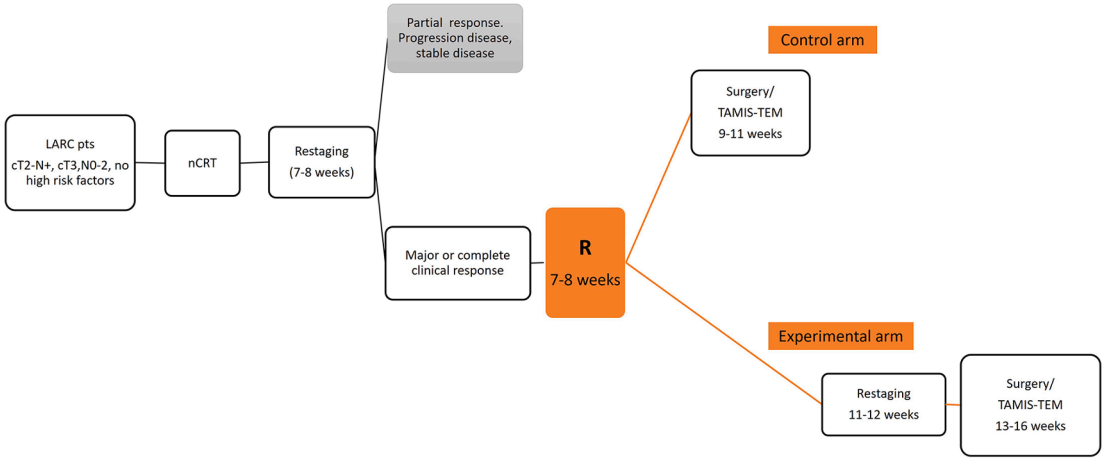

Fig. 1. Study design. LARC: locally advanced rectal cancer; nCRT: neoadjuvant chemoradiotherapy; R: randomization; TAMIS transanal minimally invasive surgery; TEM: transanal endoscopic microsurgery.

Table 2
Staging and re-staging procedures.

	Staging and baseline clinical assessment	Restaging at 7–8 weeks (control arm)	Re-staging at 11–12 weeks (experimental arm)
Medical history	x		
DRE	x	x	x
Recto-colonoscopy + biopsy*	x		
Pelvic MR	x	x	x
Thorax-abdominal CT	x		
18F-FDG PET-CT	optional	if previously performed	if previously performed
Proctoscopy		in case of major or complete clinical response	x

DRE: digital rectal examination; MR: magnetic resonance; CT: computed tomography; 18F-FDG PET-CT: 18F-fluorodeoxyglucose Positron Emission Tomography/Computed tomography.
* if colonoscopy cannot be performed because the lesion is stenosing, rectoscopy + biopsy and double contrast opaque enema or colon CT scan or colonoscopy within 6 months of surgery is recommended.

according to the international guidelines for rectal cancer [34].

Planning target volume (PTV) 1 and 2 will correspond to CTV1 and CTV2 respectively with a variable margin at the discretion of the center and image guided RT (IGRT) technique used.

The organs at risk (OARs) will be bladder, small bowel (as bowel bag), single intestinal loops in particular clinical conditions (loops with diverticula or fixed loops in the Douglas cavity or posterior pelvi), anal canal and femoral heads.

In the case of IMRT: bone marrow in the pelvis, penile bulb, vagina (at least the lower 1/3), testes, uterus and ovaries (pre-menopausal women) should be considered.

Technique and treatment doses

The prescribed dose is 55 Gy at the level of PTV1 with a daily fractionation of 2.2 Gy and 45 Gy at the level of PTV2 with a daily fractionation of 1.8 Gy, over 5 weeks.

In case of 3D treatment: the 55 to PTV1 dose will be given with a concomitant boost of 1 Gy twice a week (total dose/fraction on PTV1 twice a week of 2.8 Gy) and 45 Gy to PTV2 with daily fractionation of 1.8 Gy/day, over 5 weeks.

A linear accelerator with minimum energy of 6MV is required and image verification, with digitally reconstructed radiography (DRR) or cone beam computed tomography (CBCT) should be performed prior to treatment.

The simulation CT can be performed with different patient positioning (supine vs prone +/- bowel loop dislocators) according to the Centre's discretion. Pelvic organ filling protocols are recommended for greater reproducibility of the treatment.

In case of IMRT technique, the dose should be reported according to the ICRU (International Commission on Radiation Units and Measurements) report 83 [35].

In case of 3D technique, the dose should be reported according to the ICRU report 50–62 recommendations and a treatment with 3 or more beams is recommended [36].

The dose to OARs will be assessed according to the dose constraints reported in the QUANTEC report [37].

In case of grade $\geq$ 3 gastro-intestinal toxicity (excluding stomatitis which is exclusively due to CHT) or $\geq$ 3 grade hematological toxicity (excluding the combination white blood cells G3 and neutrophils $<$ G3), radiation treatment will be discontinued until toxicity decreases to a grade G2 or lower.

The fraction dose and total dose will not be reduced. In case of RT interruption, concomitant CHT will be stopped accordingly.

Concomitant chemotherapy

Two concomitant CHT schedules are allowed: oral chronomodulated capecitabine 1650 mg/m^2 (25% h 8:00, 25% h 18:00, 50% h 23:00) or oral capecitabine 825 mg/m^2 twice daily.

Surgical treatment and anatomopathological assessment

Surgery will be performed according to standard technique using the open, laparoscopic or robotic approach, at the surgeon's discretion. It includes either anterior resection of the rectum, abdominoperineal resection of the rectum using the TME technique, or conservative surgery approaches, such as transanal minimally invasive surgery (TAMIS) or transanal endoscopic microsurgery (TEM). These evaluations will be shared within the multidisciplinary team.

The histopathological assessment of the response will be graded according to the following classifications: Mandard [38]; Washington MK et al/College of American Pathologists [39]; in case of positive lymph nodes, the Nottingham Rectal Cancer Prognostic Index (NRPI) score [40] will also be used.

Toxicity and quality of life assessment

Acute and late toxicity and QoL, bowel function, rectal continence and sexual activity will be assessed as part of the study.

Grading of acute and late toxicity will be performed using the Common Terminology Criteria for Adverse Events (CTCAE) 4.0 scale [41].

These assessments will be performed by administering grading scales and questionnaires at various times:

T0: before the start of radiation treatment.
T1: at first restaging.
T2: after surgery.
T3: at 6 months follow-up.
T4: at 12 months follow-up.

QoL questionnaires will be: Memorial Sloan Kettering Cancer Centre (MSKCC) bowel function instrument [42], Fecal Incontinence Quality of Life scale (FIQL) [43], European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 [44] and EORTC QLQ-CR29 [45].

Adjuvant chemotherapy

The protocol does not include criteria for the administration of adjuvant systemic treatment. The choice is at the discretion of the individual center in relation to clinical and pathological features.

Follow-up

The follow up surveillance will be performed with clinical and instrumental assessment; toxicity, and QoL will be evaluated during follow-up as reported in Table 3 and 4.

Endpoints

The primary endpoint of this phase III trial is to evaluate the difference in terms of CR rate, reported as pCR (ypT0ypN0) in case of TME, or ypT0ycN0 in case of LE and Mandard's TRG1, in the two arms.

The secondary endpoints are the differences in terms of OS, DFS, local recurrence free survival (LCFS), colostomy-free survival and MFS, in the two arms. Furthermore, the concordance between cMR or cCR and pCR will be assessed.

Table 3
Follow-up after neoadjuvant treatment in case of total mesorectal excision (TME).

	Follow up time (months)												
	1	3	6	9	12	18	24	30	36	42	48	54	60
Objective examination and DRE	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood sample and CEA	x	x	x	x	x	x	x	x	x	x	x	x	x
Thorax-abdomen-pelvis CT		x		x		x		x		x		x	
Colonoscopy					x				x				x
QoL questionnaires	x		x		x								
Abdomen US			x		x		x		x		x		x

DRE: Digital rectal examination; CT: Computed tomography; QoL: Quality of life; US: Ultrasound.

Table 4
Follow-up after neoadjuvant treatment in case of minimally invasive surgery approach.

	Follow up time (months)														
	1	3	6	9	12	15	18	21	24	30	36	42	48	54	60
Objective examination and DRE	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood sample and CEA	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Proctoscopy		x	x	x	x	x	x	x	x	x	x	x	x	x	x
MRI			x		x		x		x		x		x		x
Thorax-abdomen-pelvis CT					x				x		x		x		x
Colonoscopy					x						x				
Abdomen US		x		x		x		x		x		x		x	
QoL questionnaires	x				x										

DRE: Digital rectal examination; MRI: Magnetic resonance imaging; CT: Computed tomography; QoL: Quality of life.

Statistics

Sample size

CR difference has been used as the end-point for sample calculation.

In order to achieve a sensitivity of 95% and a study power of 80% and considering in the experimental arm the expected CR rate is 35%, compared to 15% in the control arm, the number of patients in each arm was 70 [46].

Considering a difference in CR of 20% (15% to 35%) and a patient dropout of 5%, the sample enrolment considered 74 patients in each arm.

Randomization procedures

Patients achieving cMR or cCR at 7–8 weeks after the end of neoadjuvant CRT will be included in the study. Patients undergoing surgery 9–11 weeks after the end of nCRT represent the control arm of the BRIDGE-1 study. Patients who underwent surgery 13–16 weeks after the end of nCRT (Fig. 1) represent the experimental arm of the BRIDGE-1 study. These patients, prior to delayed surgery, will be re-evaluated clinically and instrumentally at 11–12 weeks after the end of neoadjuvant CRT.

Patients will be assigned to one of the arms according to a random assignment. Randomization will be stratified according to gender, age (≤65 years old), stage (stage II, or III) and tumor site (low and medium/high). When a patient is assigned to one arm, randomization will allow a patient with the same characteristics to be enrolled in the other arm.

The randomization process will be conducted by the promoter center through an automated dedicated in-house software by Knowledge Based Oncology (KBO) labs. These procedures should prevent any possible bias related to an unbalanced selection, even if involuntary by the researcher.

Statistical analysis

The statistical comparison of the primary endpoint between the two groups will be carried out using Fisher's non-parametric test.

Regarding the secondary endpoints:

1. Survival will be estimated using the Kaplan-Meier curve. Comparison of the curves will be statistically evaluated using the log-rank test.
2. Concordance between cMR or cCR and pCR will be determined using Fisher's non-parametric test.
3. Colostomy-free survival will be estimated using the Kaplan-Meier curve. Comparison of the curves will be statistically evaluated using the log-rank test.

Data collection procedure

Data from each center will be collected in electronic case report forms (CRFs) using BOA (Beyond Ontology Awareness) software [47], which will automatically anonymize and transfer the data into a single cloud-based database. Subsequently, the aggregated data will be processed by the promoter center.

Planned timeline

0–3 months: project organization; 18–36 months: patient enrolment; 36–48 months: statistical analysis and publication of data about primary end-point;48–60 months: statistical analysis and publication of data on survival outcomes.

Ethics committee approval for ongoing research

The protocol has been written according to the principles of good clinical practice (GCP). This study is conducted in accordance with the most recent version of the Declaration of Helsinki and with the Italian laws and regulations. The study protocol was approved by the ethics committee of promoter center (ethics committee identifier code 1908). Approval by the respective ethics committee relevant to each site will be collected before opening new sites. Written informed consent, signed and personally dated is obtained from each patient before inclusion in the trial.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2022.03.002.

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