

Tailored Treatment Strategy for Locally Advanced Rectal Carcinoma Based on the Tumor Response to Induction Chemotherapy: Preliminary Results of the French Phase II Multicenter GRECCAR4 Trial

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BACKGROUND: Preoperative radiochemotherapy and total mesorectal excision are the standard-of-care for locally advanced rectal carcinoma, but some patients could be over- or undertreated.

OBJECTIVE: This study aimed to assess the feasibility of radiochemotherapy tailored based on the tumor response to induction chemotherapy (FOLFIRINOX) to obtain a minimum R0 resection rate of 90% in the 4 arms of the study.

DESIGN: This study is a multicenter randomized trial (NCT01333709).

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SETTING: This study was conducted at 16 French cancer specialty centers.

PATIENTS: Two hundred six patients with locally advanced rectal carcinoma were enrolled between 2011 and 2014.

INTERVENTIONS: Good responders ($\geq 75\%$ tumor volume reduction) were randomly assigned to immediate surgery (arm A) or standard radiochemotherapy (Cap 50: 50 Gy irradiation and 1600 mg/m² oral capecitabine daily) plus surgery (arm B). Poor responders were randomly assigned to Cap 50 (arm C) or intensive radiochemotherapy (Cap 60, 60 Gy irradiation, arm D) before surgery.

OUTCOME MEASURES: The primary end point was a R0 resection rate (circumferential resection margin > 1 mm).

STATISTICAL CONSIDERATIONS: The experimental strategies were to be considered effective if at least 28 successes (R0 resection) among 31 patients in each arm of stratum I and 34 successes among 40 patients in each arm of stratum II were reported (Simon 2-stage design).

RESULTS: After induction treatment (good compliance), 194 patients were classified as good ($n = 30$, 15%) or poor ($n = 164$, 85%) responders who were included in arms A and B (16 and 14 patients) and arms C and D (113 and 51 patients). The trial was prematurely stopped because of low accrual in arms A and B and recruitment completion in arms C and D. Data from 133 randomly assigned patients were analyzed: 11, 19, 52, and 51 patients in arms A, B, C, and D. Good responders had smaller tumors than poor responders (23 cm³ vs 45 cm³; $p < 0.001$). The surgical

procedure was similar among groups. The R0 resection rates [90% CI] were 100% [70–100], 100% [85–100], 83% [72–91], and 88% [77–95]. Among the first 40 patients, 34 successes were reported in arms C and D (85% R0 resection rate). The circumferential resection margin ≤ 1 rates were 0%, 0%, 12%, and 5% in arms A, B, C, and D. The rate of transformation from positive to negative circumferential resection margin was 93%.

LIMITATIONS: There was low accrual in arms A and B.

CONCLUSION: Tailoring preoperative radiochemotherapy based on the induction treatment response appears safe for poor responders and promising for good responders. Long-term clinical results are needed to confirm its efficacy. See **Video Abstract** at <http://links.lww.com/DCR/A359>.



KEY WORDS: Early tumor response; Locally advanced rectal carcinoma; Magnetic resonance imaging volumetry; Tailored treatment strategy.

Over the past 2 decades, important progress in the management of locally advanced rectal carcinoma (LARC) has highlighted the key role of multimodal therapeutic strategies that combine surgery, radiotherapy, and chemotherapy. Moreover, preoperative chemoradiotherapy (CRT) was shown to be superior to adjuvant treatment in terms of patient tolerance and compliance, and neoadjuvant CRT based on oral or continuously infused fluoropyrimidine followed by surgery is now considered the standard-of-care for LARC.^{1–3}

This strategy led to decreases in the local recurrence rate to less than 10%, but did not improve overall survival.² Indeed, several studies emphasize the risk of undertreatment of poor responders after preoperative CRT. The lack of tumor response to classical preoperative CRT requires aggressive surgery, but has very limited effect on survival.¹ Specifically, 30% of patients will develop systemic disease. Moreover, the surgery is most often mutilating, and compliance to adjuvant chemotherapy is poor. Conversely, good responders may be overtreated with radiotherapy. Preoperative CRT can negatively affect anorectal function after total mesorectal excision (TME),² and bladder and sexual function, fertility, and bone marrow reserve, as well. At present, induction chemotherapy before CRT is being investigated to determine whether it decreases the risk of distant metastasis and to identify patients who will not respond to CRT. In parallel, new imaging techniques, such as MRI, enable one to define the extent of local tumor involvement, including the circumferential resection margins (CRMs), and to assess the tumor response to neoadjuvant therapy. This enables customization of the surgical technique to each patient. However, the idea of shifting the treatment paradigm (CRT, TME, and adjuvant therapy) to a more individually tailored approach is controversial.⁴

To validate the concept of a more individualized strategy, we conducted a study to determine whether induction chemotherapy can be used to identify subgroups of patients in whom treatments, especially the radiation doses and regimens, could be deescalated or intensified. To accomplish this, we designed a prospective multicenter randomized phase II trial in which treatment was tailored according to the early tumor response to induction chemotherapy. Our primary objective was a minimum 90% R0 resection rate in all arms.

METHODS

Patients and Study Design

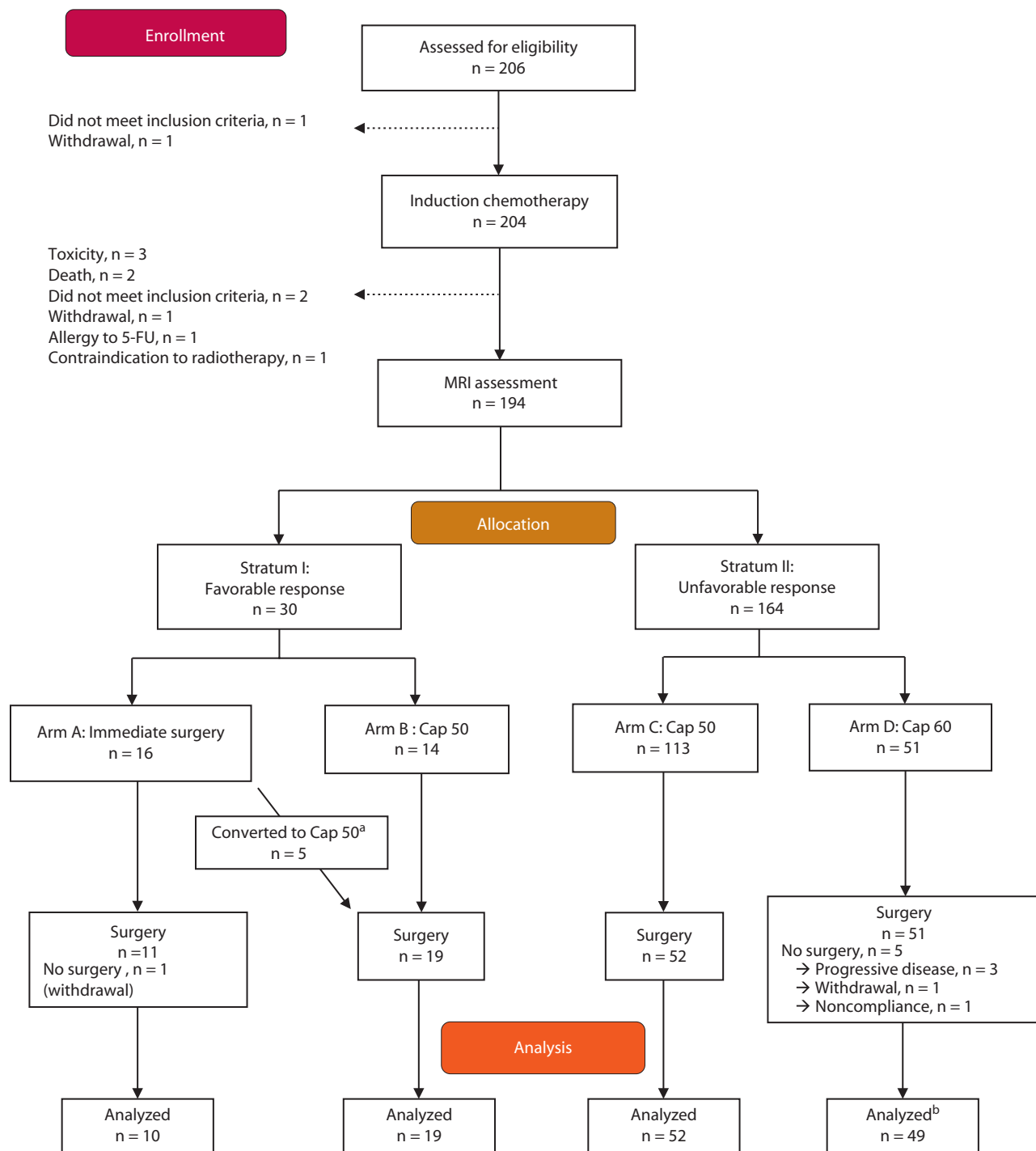
For this national, phase II, multicenter, open-label randomized study (GRECCAR4), patients with nonmetastatic LARC treated at 16 French centers were included. The inclusion criteria were 1) primary tumor evaluated using MRI (initial stage: $\text{mriT3} \geq \text{c}$ or mriT4 ; or the predictive CRM was ≤ 1 mm and the inferior tumor margin was ≥ 1 cm from the anal verge); 2) age ≥ 18 years; and 3) Eastern Cooperative Oncology Group performance status ≤ 2 and adequate hematological, hepatic, and renal function. The main exclusion criteria were 1) an indication for immediate surgery; 2) no MRI evaluation of the primary tumor available before inclusion; and 3) previous pelvic radiotherapy or contraindication to radio- and/or chemotherapy (see complete inclusion and exclusion criteria in the Supplementary Methods, <http://links.lww.com/DCR/A343>).

To determine the early tumor response, 2 weeks after completing the induction chemotherapy, the tumor volume was measured on MRI by using specific software that automatically delineated the tumor. All MRI data were systematically reviewed by 2 radiologists at the coordinator center. Patients were then divided into 2 strata based on the tumor response (Fig. 1). A favorable response (stratum I) was defined as shrinkage $\geq 75\%$ from the initial tumor volume with a predictive CRM > 1 mm. These patients were randomly assigned (1:1 ratio) to receive immediate surgery (experimental arm, arm A) or classical CRT (Cap 50; see Treatments section) followed by surgery (standard arm, arm B). An unfavorable response (stratum II) was defined as shrinkage $< 75\%$ from the initial tumor volume or a predictive CRM ≤ 1 mm. These patients were randomly assigned to receive Cap 50 (standard arm, arm C) or intensified CRT (Cap 60; experimental arm, arm D). Randomization was centralized and stratified by center and initial tumor stage. All patients provided their informed consent before enrollment. The protocol was approved by the local committee and was conducted in accordance with the ethical standards (NCT01333709).

Treatments

Neoadjuvant Treatment

The induction chemotherapy was a FOLFIRINOX regimen entailing 4 cycles of 180 mg/m² irinotecan, 85 mg/m²



^aReasons for conversion:

Investigator's decision (low rectum tumor), n = 3
Patient included before amendment (low rectum tumor), n = 1
Delayed surgery (phlebitis), n = 1

^bThe three patients with progressive disease were considered failure and included in the analysis.

Cap 50 = 50 Gy irradiation with concomitant 1600 mg/m²/day capecitabine; Cap 60 = 60 Gy irradiation with concomitant 1600 mg/m²/day capecitabine.

FIGURE 1. Study flow chart. 5-FU = 5-fluorouracil.

oxaliplatin, 200 mg/m² elvovir, and 5-fluorouracil (400 mg/m² bolus followed by 2400 mg/m² continuous infusion for 46 hours) delivered over 8 weeks (day 1 = day 15). The standard Cap 50 CRT regimen combined a radiation dose of 50 Gy administered as conventional 3D conformal or intensity-modulated radiation therapy (2 Gy/fraction, 5 fractions/week for 5 weeks: 44 Gy as minipelvic radiotherapy with a 6-Gy boost to a reduced target peritumoral volume) with concomitant oral capecitabine (1600 mg/m² daily in 2 identical doses taken during the radiotherapy days). The experimental Cap 60 regimen consisted of 60 Gy irradiation (2 Gy/fraction, 5 fractions/week for 6 weeks: 44 Gy as minipelvic radiotherapy with a 16-Gy boost to a reduced target peritumoral volume) with the same concomitant oral capecitabine intake as in the Cap 50 regimen.

Surgery

Radical proctectomy with TME was performed as laparoscopic or robotic surgery, or conventional laparotomy. Surgical quality was evaluated using the Quirke mesorectum grading system.³

Adjuvant Treatment

The choice of adjuvant treatment was left to the investigators' discretion. Nevertheless, the expert committee suggested no postoperative chemotherapy for tumors with a pathological complete response (pCR) after preoperative treatment (ypCR) or for ypT1N0 tumors, and 6 FOLFOX cycles for ypT ≥ 2 or ypN ≥ 1 tumors.

Outcomes

The primary end point was the R0 resection rate (CRM >1 mm), which was considered to be a surrogate marker of the oncological prognosis. The aim was to confirm the feasibility of tailored management with a 90% R0 resection rate achieved in all arms. The main secondary end points (see Supplementary Methods, <http://links.lww.com/DCR/A343>) were MRI-assessed tumor volume, CRM, and response rate after induction chemotherapy, preoperative treatment toxicity (NCI CTC-CAE v4.0), pCR, peri/postoperative morbidity, and sphincter-saving surgery rates.

Statistical Considerations

The sample size was calculated based on the assumption that 40% of patients would likely show a good response to this therapeutic strategy. For stratum I, a Simon 2-stage optimal design (with $\alpha = 0.10$, $\beta = 0.10$, $p_0 = 80\%$, $p_1 = 95\%$) required a minimum of 14 evaluable patients (7/arm) in the case of early termination after the first stage and a maximum of 62 patients (31/arm) otherwise. The experimental strategy would be considered effective if at least 34 successes among 40 patients in each arm of stratum II were reported, that is, 34 patients achieved R0 resections.

For stratum II, a Simon 2-stage minimax design (with $\alpha = 0.10$, $\beta = 0.10$, $p_0 = 75\%$, $p_1 = 90\%$) required a minimum of 54 evaluable patients (27/arm) in the case of early termination after the first stage and a maximum of 80 patients (40/arm) otherwise. The experimental strategy would be considered effective if at least 28 successes among 31 patients in each arm of stratum I were reported, that is, 28 patients achieved R0 resections.

A maximum of 142 evaluable patients was required: 31 in each arm of stratum I and 40 in each arm of stratum II. After a planned interim analysis, an independent committee (IC) decided to continue including patients until the required number of evaluable patients was accrued in stratum I (ie, 31/arm). For stratum II, randomization was stopped following an amendment after inclusion of 103 evaluable patients. Inclusions continued, but all patients were assigned to arm C and treated with standard Cap 50. Later, a second IC decided to stop inclusions because of the low accrual rate in stratum I.

Statistical analyses were performed on the evaluable population in each arm. Toxicity was evaluated in patients who received at least 1 treatment sequence. Because of the study design, no statistical comparison between arms was performed, with the exception of baseline characteristics and toxicity data during induction chemotherapy. These data were compared among all 4 arms by using the Kruskal-Wallis or Wilcoxon tests for quantitative variables and the χ^2 or Fisher tests for qualitative variables. Data were analyzed by using Stata software, version 13 (College Station, TX).

RESULTS

Between May 2011 and October 2014, 206 patients with LARC were enrolled (Fig. 1). After induction chemotherapy (n = 204), 194 patients were evaluated by using MRI: 30 (15%) were good responders (stratum I: 16 in arm A and 14 in arm B) and 164 (85%) were poor responders (stratum II: 113 in arm C and 51 in arm D). Only 133 randomly assigned patients were analyzed based on the treatment they received: 10 patients in arm A, 19 in arm B (5 patients from arm A were switched to arm B), 52 in arm C, and 49 in arm D (Figure 1). At diagnosis, 89% of patients (119/133) had a predictive positive radial margin status.

The patients' median age was 62 years (range 22–82), and 68% were men. The baseline characteristics were comparable in the 4 arms (Table 1). Patients with lower tumors were found in arms A and B. The median distance between the tumor's inferior pole and the levator ani (ie, tumor topography LP-LA) was 1.5 cm (0–5.8 cm) and 0 cm (0–10 cm) in arms A and B vs 3.3 cm (0–11 cm) and 2.2 cm (0–44 cm) in arms C and D ($p < 0.04$). Bulky tumors were more frequent in arms C and D. The median extramural spread was 6 mm (3–11 mm) and 4 mm (1–16 mm) in arms

TABLE 1. Patient characteristics at baseline

	Good responders (stratum I)		Poor responders (stratum II)	
	Arm A n = 11	Arm B: Cap 50 n = 19	Arm C: Cap 50 n = 52	Arm D: Cap 60 n = 51
Sex, n (%)				
Men	5 (45.5)	11 (57.9)	34 (65.4)	40 (78.4)
Women	6 (54.5)	8 (42.1)	18 (34.6)	11 (21.6)
Age, y				
Median (range)	66.0 (44–78)	63.0 (39–75)	61 (22–82)	62 (22–80)
WHO performance status, n (%)				
0	10 (90.9)	15 (79.0)	40 (76.9)	35 (68.6)
1	1 (9.1)	4 (21.0)	11 (21.2)	14 (27.4)
2	0	0	1 (1.9)	2 (3.9)
BMI, median (range)	25.3 (18.5–33.6)	24.6 (16.9–32.5)	25.4 (16.9–34.0)	25.5 (18.3–41.3)
Missing	0	0	1	1
Tumor topography LP-LA, cm ^a				
Median (range)	1.5 (0–5.8)	0 (0–10)	3.3 (0–11)	2.2 (0–44)
Missing	0	0	2	1
Circumference ≥50%				
n (%)	6 (66.7)	6 (50.0)	35 (94.6)	26 (74.3)
Missing	2	7	15	16
Tumor volume, cm ^{3a}				
Median (range)	23.0 (3.0–148)	22.0 (10.0–57.4)	43.0 (8.3–387)	47.4 (3.3–312)
Missing	0	0	3	1
CRM, mm				
Median (range)	1.0 (0–3)	0 (0–5)	0 (0–20)	0 (0–5)
CRM ≤1 mm				
n (%)	8 (72.7)	18 (94.7)	47 (90.4)	46 (90.2)
EMS, mm ^a				
Median (range)	6.0 (3.0–11.0)	4.0 (1.0–16.0)	10.0 (1.5–40.0)	12.0 (0.5–50.0)
Missing	0	0	3	0
T stage				
T3	11 (100)	19 (100)	40 (76.9)	38 (74.5)
T4	0	0	12 (23.1)	13 (25.5)
N stage				
N0	2 (18.2)	4 (21.0)	2 (3.8)	1 (2.0)
N+	9 (81.8)	14 (73.7)	50 (96.2)	49 (98.0)
Nx	0	1 (5.3)	0	0
Missing	0	0	0	1

WHO = World Health Organization; LP-LA = lower pole-levator ani; CRM = circumferential resection margin; EMS = extramural spread.

^aStatistically significant results: tumor topography LP-LA $p = 0.04$; tumor volume $p < 0.001$; EMS $p < 0.001$.

A and B, 10 mm (1.5–40 mm) and 12 mm (0.5–50 mm) in arms C and D ($p < 0.001$). The median tumor volume also differed between the 2 strata: 23 cm³ (3–148 cm³) and 22 cm³ (10–57.4 cm³) in arms A and B vs 43 cm³ (8.3–387 cm³) and 47 cm³ (3.3–312 cm³) in arms C and D ($p < 0.001$).

Compliance to induction chemotherapy was generally good: 73%, 68%, 73%, and 86% of patients in arms A, B, C, and D had a FOLFIRINOX relative dose-intensity ≥80%. Grade 3 to 4 toxicity was more frequent in arms A and B (63%, 42%) than in arms C and D (36%, 16%). The grade 3 to 4 GI toxicity rate was significantly higher in arm C than arm D (19% vs 6%, Table 2). After induction chemotherapy (Table 3), 12% of patients in stratum II had a tumor volume reduction ≥75% but with a predictive CRM <1 mm; 68% had a volume reduction between 50% and 75%; and 20% had a volume reduction <50%.

Nearly 100% of patients received the full dose of radiotherapy in arms B, C, and D. Of those, 70% received a capecitabine relative dose-intensity ≥80%. Grade 3 to 4 toxicity rates were 26%, 22%, and 24% in arms B, C, and D (Table 2).

After CRT, 57% of patients in arm B had no residual tumor on MRI. Six patients did not undergo surgery because of disease progression ($n = 3$ in arm D, 6%) or withdrawal from the study ($n = 3$). Intersphincteric resection was performed in 34% of patients (both strata), and abdominoperineal resection was done in 6.4% of poor responders (Table 4). The median hospital stay was 12 days (3–78 days). The fistula occurrence rate ranged from 3.9% to 20% (3.9% in arm C, 20% in arm A). One patient died (acute pancreatitis) within 30 days after surgery. The overall postoperative morbidity rates were 50%, 42%, 31%, and 53% in arms A, B, C, and D, and the second surgery rates were 10%, 16%, 12%, and 20%.

TABLE 2. Chemotherapy and radiochemotherapy toxicities

	Good responders (stratum I)		Poor responders (stratum II)	
	Arm A n = 11	Arm B: Cap 50 n = 19	Arm C: Cap 50 n = 52	Arm D: Cap 60 n = 49
Induction chemotherapy				
Grade 3–4 toxicity ^a	7 (63.6)	8 (42.1)	19 (36.5)	8 (15.7)
Cardiac	0	0	1 (1.9)	0
GI	3 (27.3)	4 (21.1)	10 (19.2)	3 (5.9)
Infections	0	0	2 (3.8)	0
Others ^a	6 (54.6)	6 (31.6)	12 (23.1)	7 (13.7)
Radiochemotherapy				
Grade 3–4 toxicity		5 (26.3)	11 (21.6)	12 (23.5)
GI	-	3 (15.8)	8 (15.7)	5 (9.8)
Others		2 (10.5)	4 (7.8)	12 (23.5)
Missing		0	1	0

^aStatistically significant results: overall toxicity $p = 0.004$; others $p = 0.03$.

At the interim analysis, 6 R0 resections were reported among the first 7 patients in arm A, and 7 R0 resections were among the first 7 patients in arm B. Twenty-two R0 resections were reported among the first 27 patients in arm C, and there were 23 R0 resections among the 27 patients in arm D. The IC therefore decided to move to the second step of the study. At the final analysis, there were 10 R0 resections among the 10 evaluable patients in arm A, 19 R0 resections among the 19 evaluable patients and arm B, and 34 R0 resections among the first 40 patients planned for the analysis in each arm of stratum II.

Overall, the R0 resection rates were 100% (90% CI: 74–100) in arm A, 100% (90% CI: 85–100) in arm B, 83% (90% CI: 72–91) in arm C, and 88% (90% CI: 77–95) in

arm D (Table 5). An intention-to-treat analysis gave similar results (data not shown). Pathological assessments were similar in the 4 arms, with 78% overall grade III mesorectum resections and less than 10% grade I resections (Table 6). The pCR rates were 10%, 58%, 13.5%, and 20% in arms A, B, C, and D. CRMs >1 mm were reported for 0%, 0%, 12%, and 5% of patients in arms A, B, C, and D, whereas positive distal margins were reported for 0%, 0%, 6%, and 2% of patients. The median numbers of examined lymph nodes were similar in the 4 arms, and 70% were negative, with the exception of arm C (50% negative). Comparison of the initial MRI-predictive CRM with the histological CRM gave an overall transformation rate (positive to negative) of 93% (103/111). More specifically,

TABLE 3. MRI tumor assessment after induction chemotherapy

	Good responders (stratum I)		Poor responders (stratum II)	
	Arm A n = 11	Arm B: Cap 50 n = 19	Arm C: Cap 50 n = 52	Arm D: Cap 60 n = 51
Tumor topography LP-LA, cm				
Median (range)	4.3 (0–7)	1.3 (0–10)	4.4 (0–22)	3.2 (0–44)
Missing	3	3	3	0
Tumor volume, cm ³				
Median (range)	3.3 (0–28.8)	3.0 (0–13.8)	18.0 (0–217)	17.0 (1.8–159)
Missing	1	0	3	1
CRM ≤1 mm				
n (%)	0	3 (15.8)	31 (59.6)	35 (68.6)
EMS, mm				
Median (range)	0.0 (0–12)	0.0 (0–11)	7.0 (0–20)	6.5 (0–30)
Missing	4	6	5	7
T stage				
≤T2	4 (50.0)	11 (64.7)	1 (2.0)	5 (9.8)
T3	4 (50.0)	6 (35.3)	40 (80.0)	38 (74.5)
T4	0	0	9 (18.0)	8 (15.7)
Missing	3	2	2	0
N stage				
N0	7 (77.8)	14 (73.7)	14 (26.9)	12 (23.5)
N+	2 (22.2)	5 (26.3)	38 (73.1)	38 (74.5)
Nx	0	0	0	1 (2.0)
Missing	2	0	0	0

LP-LA = lower pole-levator ani; CRM = circumferential resection margin; EMS = extramural spread.

TABLE 4. Surgical data and morbidity

	Good responders (stratum I)		Poor responders (stratum II)	
	Arm A n = 10	Arm B: Cap 50 n = 19	Arm C: Cap 50 n = 52	Arm D: Cap 60 n = 46
Delay between neoadjuvant therapy and surgery (weeks), median (range)	4.4 (3.0–6.0)	7.6 (4.4–10.1)	7.0 (0.4–13.3)	7.0 (4.3–24.1)
Length of hospital stay (days), median (range)	11.5 (3–25)	10.0 (6–54)	11.5 (6–50)	13.5 (4–78)
Minimally invasive surgery				
n (%)	7 (77.8)	17 (89.5)	40 (78.4)	29 (64.4)
Missing	1	0	1	1
Abdominoperineal resection				
n (%)	0	0	3 (5.8)	5 (11.1)
Missing	0	0	0	1
Coloanal anastomosis				
n (%)	5 (50.0)	18 (94.7)	32 (64.0)	28 (63.6)
Missing	0	0	2	2
Partial or complete ISR				
n (%)	4 (40.0)	12 (66.7)	14 (28.0)	12 (26.7)
Missing	0	1	2	1
DeFx stoma				
n (%)	7 (70.0)	18 (94.7)	47 (90.4)	41 (93.2)
Missing	0	0	0	2
Surgical morbidity				
Perioperative morbidity				
n (%)	2 (20.0)	2 (10.5)	7 (13.5)	9 (20.0)
Missing	0	0	0	1
Postoperative morbidity				
n (%)	5 (50.0)	8 (42.1)	16 (31.4)	23 (53.5)
Missing	0	0	1	3
Fistula	2 (20.0)	1 (5.3)	2 (3.9)	2 (4.7)
Others	3 (30.0)	7 (36.8)	14 (27.5)	21 (48.8)
Clavien-Dindo grade 3–4				
n (%)	2 (20.0)	5 (26.3)	8 (15.4)	11 (23.9)
Reintervention, n (%)	1 (10.0)	3 (15.8)	6 (11.8)	9 (20.5)
Missing	0	0	1	2

ISR = intersphincteric resection; DeFx = defunctioning.

it was 100% (7/7) in arm A, 100% in arm B (18/18), 87% (40/46) in arm C, and 95% (38/40) in arm D (Table 7).

DISCUSSION

This multicenter phase II trial evaluated the feasibility of tailoring treatment in LARC patients on the basis of the early tumor response (assessed by MRI) to induction chemotherapy. Two experimental arms were studied: CRT deescalation (ie, immediate surgery) for chemosensitive tumors and CRT intensification for chemoresistant tumors. The preliminary results suggest the feasibility of this strategy, although no formal conclusion can be drawn for arms A and B. For arms C and D, however, the results are sufficiently promising to consider moving to a larger trial.

In a phase III randomized study of T4 LARC patients, the standard preoperative chemoradiotherapy (fluorouracil/leucovorin concomitant with 50 Gy radiotherapy) showed a R0 resection rate of 84%, as compared with a rate of 78% among patients receiving preoperative radiotherapy alone.⁵ In our study, although we did not achieve

our 90% R0 resection rate in all 4 arms, our minimum success criteria were met in arms C and D (poor responders), and the resection rate obtained is comparable to that reported in the literature. In the good responders strata (arms A and B), a 100% resection rate was achieved, but because of the low accrual, we cannot draw a formal conclusion regarding these promising results.

The standard preoperative management may expose patients to overtreatment in cases of hypersensitivity to therapy or undertreatment in cases of resistance. Therefore, tailored management is being investigated as a way of avoiding radical surgery in good responders by replacing TME with rectal tumorectomy or no surgery at all.⁶ Another approach to tailored management consists in adapting radiotherapy to the tumor response after treatment with induction chemotherapy and standard TME surgery. Addition of induction chemotherapy, at a full systemic dose, might be more effective against microscopic metastases. Many options are available with regard to the sequence (chemotherapy followed by CRT or vice versa),^{7,8} dose intensity, or drug combinations, including targeted therapies.

TABLE 5. Efficacy: R0 resection rate

	Good responders (stratum I)		Poor responders (stratum II)	
	Arm A n = 11	Arm B: Cap 50 n = 19	Arm C: Cap 50 n = 52	Arm D: Cap 60 n = 51
No surgery				
Progressive disease	0	0	0	3
Patient's withdrawal	1	0	0	1
Noncompliance	0	0	0	1
Resection				
R0				
n (%)	10 (100.0)	19 (100.0)	43 (82.7)	43 (87.8)
90% CI	(74–100)	(85–100)	(72–91)	(77–95)
R1	0	0	9 (17.3)	2 (4.1)
Peritoneal carcinomatosis	0	0	0	1 (2.0)
Progressive disease	0	0	0	3 (6.1)
Resection (first 40 patients)				
R0				
n (%)	NA	NA	34/40 (85.0)	34/40 (85.0)
90% CI			(73–93)	(73–93)

NA = not applicable.

Most phase II studies that assessed induction chemotherapy before CRT used capecitabine or oxaliplatin before standard CRT (Cap 50). The R0 resection rate was high (88%–100%),^{9–11} with a pCR rate ranging from 20% to 40%.^{10,12} The long-term results of a GCR-3 phase II trial that compared preoperative CRT alone and chemotherapy (capecitabine and oxaliplatin, CAPOX) plus CRT showed similar outcomes with both treatments (overall survival: 78% vs 75%, $p = 0.64$).¹² However, the preoperative CAPOX plus CRT was associated with lower acute toxicity and better compliance than CRT alone.

Other studies assessed the addition of targeted therapies as preoperative treatments. They reported pCR rates of 36%, 23%, and 25% and R0 resection rates of 98%, 97%, and 78% for bevacizumab,¹³ cetuximab,¹⁴ and panitumumab.¹⁵ Extension of targeted therapy with bevacizumab^{13,16,17} or anti-epidermal growth factor receptor antibodies^{18,19} during CRT significantly increased postoperative morbidity with no effect on pCR. The Expert-C trial compared 165 patients with LARC (wild-type KRAS/BRAF) who received CAPOX CRT or CAPOX-cetuximab CRT.²⁰ Cetuximab did not improve the pCR (9% vs 11%), R0, sphincter-saving surgery, or surgical complication rate.

The survival plateau in LARC patients and data on the late adverse effects of pelvic radiotherapy raise the question, could systemic chemotherapy without radiotherapy improve the outcomes of these patients, or at least offer a similar outcome with less toxicity and better quality of life?^{24,21,22} A phase II study that assessed neoadjuvant chemotherapy without routine CRT²³ showed that 94% of patients had a R0 resection after FOLFOX and bevacizumab, and pCR was achieved in 25% of patients. Moreover, 93.8% of patients completed the preoperative treatment, and only 6% required CRT. No local recurrence was reported at 4 years, but 12% of patients experienced distal

metastatic relapse. The GEMCAD 0801 trial assessed neoadjuvant capecitabine and oxaliplatin combined with bevacizumab in 46 LARC patients.²⁴ The overall response rate was 78%, and 44 patients had TME with 100% R0 resections. However, a 13% anastomotic leak rate was reported as specific toxicity. A larger ongoing phase II/III study (PROSPECT) is comparing conventional neoadjuvant CRT and neoadjuvant FOLFOX alone in 1060 patients.²⁵ In the experimental arm, if MRI-based restaging suggests a tumor response <20%, CRT is performed before TME.

We included LARC patients presenting large tumors (>40 cm³) or low and aggressive tumors with a predictive CRM ≤1 mm. Lymph node involvement was detected on MRI in more than 90% of these patients, which validates the use of systemic chemotherapy. Compliance to induction chemotherapy was >95%, which is consistent with the literature on neoadjuvant FOLFOX.^{9,11,12,26}

Prognosis prediction using the tumor response to induction chemotherapy was described in 2 earlier studies.^{27,28} In our trial, MRI data were reviewed by 2 experimented radiologists, and the tumor volume was calculated by using dedicated software. The cutoff of 75% reduction in volume to define a favorable response was based on the study by Kang et al²⁹ showing that tumor volume reduction >75% after CRT is significantly associated with high pCR rates. This cutoff appeared high, particularly for arms C and D (65% of patients had a 50%–75% volume reduction and 23% had a <50% volume reduction) and should be lowered in future studies.

A meta-analysis on 4732 LARC patients from phase II/III trials identified factors significantly associated with pCR, in particular, the use of 2 drugs, the fluoropyrimidine administration technique and higher radiotherapy doses.³⁰ Therefore, intensified radiotherapy (60 Gy) appears promising for chemoresistant tumors. Two other meta-analyses confirmed that higher radiation doses are

TABLE 6. Pathological assessment

	<i>Good responders (stratum I)</i>		<i>Poor responders (stratum II)</i>	
	<i>Arm A n = 10</i>	<i>Arm B: Cap 50 n = 19</i>	<i>Arm C: Cap 50 n = 52</i>	<i>Arm D: Cap 60 n = 46</i>
Mesorectum resection (Quirke), n (%)				
Grade I	0	1 (6.3)	1 (2.4)	4 (10.8)
Grade II	2 (22.2)	2 (12.5)	8 (19.5)	5 (13.5)
Grade III	7 (77.8)	13 (81.2)	32 (78.1)	28 (75.7)
Missing	1	3	11	9
Tumor perforation n (%)				
Missing	0	0	3 (6.1)	1 (2.3)
No residual tumor n (%)				
Missing	0	2	3	3
CRM ≤1mm n (%)				
Missing	1 (10.0)	11 (57.9)	7 (13.5)	9 (20.0)
CRM ≤1mm NA	0	0	0	1
Positive distal margin n (%)				
Missing	0	0	6 (11.8)	2 (4.5)
ypT, n (%)				
ypT0	1 (10.0)	0	1	2
ypT1	1 (10.0)	0	6 (11.8)	2 (4.5)
ypT2	2 (20.0)	0	1	2
ypT3	5 (50.0)	0	6 (11.8)	2 (4.5)
ypT4	0	0	3 (5.8)	2 (4.4)
Missing	1	0	0	1
ypN, n (%)				
ypN0	7 (70.0)	16 (84.2)	26 (51.0)	33 (73.3)
ypN1	3 (30.0)	3 (15.8)	25 (49.0)	12 (26.7)
Missing	0	0	1	1
Lymphovascular invasion n (%)				
Missing	3 (30.0)	0	9 (18.0)	2 (4.5)
	0	1	2	2

CRM = circumferential resection margin; NA = not applicable; modified ypN0 = negative node with residual sign of initial positivity.

associated with pCR.^{31,32} Our results in arms C and D show a trend in favor of intensified radiotherapy (arm D) (ypT0: 15% vs 24%; CRM ≤1: 12% vs 4.5%). Conversely, arm C (classical CRT) had the lowest R0 resection rate (83%) among the 4 arms. The mean number of negative lymph nodes was higher in arm D than in arm C (50% vs 70%), which can limit the adjuvant treatment indication. Indeed, the ypN0 status after neoadjuvant CRT is less associated with an adverse prognosis than the pN0 status after primary surgery.³³ These results confirm that, given the lack of effective standardized adjuvant chemotherapy regimens, dose-escalated radiotherapy should be considered as a solution for patients responding poorly to induction chemotherapy. However, long-term oncological and functional results are needed to validate this hypothesis. Indeed, our previous experience with high-dose radiation highlighted the development of sphincter fibrosis that affected the long-term functional results.^{34,35}

Although the population sample was small, the results from arm A suggest that chemosensitive tumors can be safely managed with immediate surgery without neoad-

juvant CRT. But the high rate of vascular lymphatic invasion (30% despite a pN0 rate of 70%) should be carefully monitored. In arm B, the high pCR rate (60%) underlines the possibility of tailoring surgery toward less aggressive approaches, such as tumorectomy or the “watch and wait” strategy.

Our study has several limitations. The lack of a control group (phase II trial design) and the small number of patients, especially in arm A, led to an early arrest of the study. Consequently, no statistical formal conclusion could be drawn for the results from arms A and B. The low accrual in the good responder stratum could have been due to the high cutoff level of the MRI tumor response. Consistent with the findings of Han et al,³⁶ retrospective analysis of stratum II suggests this cutoff could be safely decreased from 75% to 60%. This hypothesis needs be confirmed by a longer follow-up, however. In addition, our study highlights the reluctance to avoid preoperative radiotherapy in patients with low rectal tumors and small CRMs, probably because of the fear of positive margins (3 of the 5 patients randomly assigned in arm A were shifted

TABLE 7. Efficacy: Circumferential resection margin

CRM	Predictive CRM, n	CRM on pathology, n (%)	
		≤1	>1
Arm A			
≤1	7	0	7 (100)
>1	2	0	2 (100)
Arm B			
≤1	18	0	18 (100)
>1	1	0	1 (100)
Arm C			
≤1	46	6 (13)	40 (87)
>1	5	0	5 (100)
Arm D			
≤1	40	2 (5)	38 (95)
>1	4	0	4 (100)
Total			
≤1	111	8 (7)	103 (93)
>1	12	0	12 (100)

CRM = circumferential resection margin.

to arm B for this reason). Ultra-low tumors may be an anatomic contraindication for immediate surgery. Nonetheless, our results confirm the high prognostic value of the early tumor response after induction chemotherapy.

CONCLUSION

Our study, which is one of the first to tailor LARC management based on the early tumor response, has yielded promising preliminary results concerning the R0 resection rate. Although no statistical formal conclusion can be drawn for the good responders' stratum (arms A and B), our results are promising, and we achieved resection rates that favorably compare with rates reported for the standard strategy. With respect to the poor responders, although our 90% objective was not achieved, the minimum success rate was met. However, new therapeutic strategies are still needed for these patients. Tumor responses after induction chemotherapy can be reliably assessed using MRI, which correlates with the pathological assessment. Long-term oncological and functional results are awaited to confirm the safety of this tailored strategy and its impact on patient prognosis.

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