

Final Results of the GRECCAR-6 Trial on Waiting Period Following Neoadjuvant Radiochemotherapy for Locally Advanced Rectal Cancer: 5 Years of Follow-up

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BACKGROUND: The potential oncological benefit of extending the waiting period between neoadjuvant radiochemotherapy and surgical resection for rectal cancer is debated.

OBJECTIVE: To evaluate the impact of prolonging this waiting period on the 5-year oncological prognosis and 2-year functional result of locally advanced rectal adenocarcinoma.

DESIGN: Phase III, multicenter, randomized, open-label, parallel-group, controlled trial.

SETTINGS: Patients were enrolled from 24 colorectal centers.

PATIENTS: Patients with nonmetastatic mid or lower cT3/T4Nx or cTxN+ rectal adenocarcinoma who had received radiochemotherapy (45–50 Gy radiation dose with fluorouracil or capecitabine).

INTERVENTION: Patients were randomly assigned to undergo total mesorectal excision either 7 weeks or 11 weeks after radiochemotherapy.

MAIN OUTCOMES MEASURES: Overall survival and disease-free survival at 5-year follow-up and low anterior resection syndrome score assessed after 2 years of follow-up.

RESULTS: Among 265 patients enrolled, 133 were randomized in the 7-week group and 132 in the 11-week group. Twelve patients were excluded because they did not undergo resection. Among 253 patients analyzed, 5-year overall survival was not different between the 2 groups (81.6% in the 7-week group vs 82.6% in the 11-week group, $p = 0.827$), and neither was the 5-year disease-free survival (70.4% in the 7-week group vs 69.5% in the 11-week group, $p = 0.856$). No difference was observed between the 2 groups for distant recurrence (27.4% in the 7-week group vs 25.7% in the 11-week group, $p = 0.777$) or local recurrence (8.4% in the 7-week group vs 10.2% in the 11-week group, $p = 0.543$). The low anterior resection syndrome score was similar between the 7-week (25.0; interquartile range, 15.0–34.0) and 11-week groups (23.0; interquartile range, 14.2–32.0; $p = 0.743$).

LIMITATIONS: The response rate to the low anterior resection syndrome questionnaire was only 52%.

CONCLUSIONS: Extending the waiting period between radiochemotherapy and resection from 7 to 11 weeks does not change the 5-year oncological prognosis in rectal cancer or the 2-year low anterior resection occurrence. See **Video Abstract**.



RESULTADOS FINALES DEL ENSAYO GRECCAR-6 SOBRE EL PERÍODO DE ESPERA TRAS LA RADIOQUIMIOTERAPIA NEOADYUVANTE PARA EL CÁNCER DE RECTO LOCALMENTE AVANZADO: 5 AÑOS DE SEGUIMIENTO

ANTECEDENTES: Se debate el posible beneficio oncológico de prolongar el periodo de espera entre

la radioquimioterapia neoadyuvante y la resección quirúrgica del cáncer de recto.

OBJETIVO: Evaluar el impacto de la prolongación de este periodo de espera sobre el pronóstico oncológico a 5 años y el resultado funcional a 2 años del adenocarcinoma rectal localmente avanzado.

DISEÑO: Ensayo controlado de fase III, multicéntrico, aleatorizado, abierto, de grupos paralelos.

LUGAR: Se reclutaron pacientes de 24 centros colorrectales.

PACIENTES: Pacientes con adenocarcinoma rectal de tercio medio o inferior, no metastásico cT3-4 o TxN+ que habían recibido radioquimioterapia (45 a 50 Gy con fluorouracilo o capecitabina).

INTERVENCIÓN: Se asignaron aleatoriamente a los pacientes para ser sometidos a una escisión mesorrectal total 7 semanas (W7) u 11 semanas (W11) después de la radioquimioterapia.

MEDIDAS DE RESULTADOS PRINCIPALES: Supervivencia global y supervivencia libre de enfermedad a los 5 años de seguimiento y puntuación del síndrome de resección anterior baja evaluada a los 2 años de seguimiento.

RESULTADOS: De los 265 pacientes reclutados, 133 fueron asignados aleatoriamente al grupo de 7 semanas y 132 al grupo de 11 semanas. Doce pacientes fueron excluidos porque no fueron sometidos a resección. Entre los 253 pacientes analizados, la supervivencia global a 5 años no fue diferente entre los dos grupos (81,6% en el grupo de 7 semanas frente a 82,6% en el grupo de 11 semanas, $p = 0,827$), así como para la supervivencia libre de enfermedad a 5 años (70,4% en el grupo de 7 semanas frente a 69,5% en el grupo de 11 semanas, $p = 0,856$). No se observaron diferencias entre los dos grupos en cuanto a la recidiva a distancia (27,4% en el grupo de 7 semanas frente a 25,7% en el grupo de 11 semanas, $p = 0,777$) o la recidiva local (8,4% en el grupo de 7 semanas frente a 10,2% en el grupo de 11 semanas, $p = 0,543$). La puntuación del síndrome de resección anterior baja fue similar entre los grupos de 7 semanas (25,0 IQR [15,0-34,0]) y 11 semanas (23,0 IQR [14,2-32,0], $p = 0,743$).

LIMITACIONES: La tasa de respuesta al cuestionario LARS fue sólo del 52%.

CONCLUSIONES: Ampliar el periodo de espera entre radioquimioterapia y resección de 7 a 11 semanas no modifica el pronóstico oncológico a 5 años en cáncer de recto ni la baja incidencia de resección anterior a 2 años. (Traducción—Dr Osvaldo Gauto)

KEY WORDS: Complete pathological response; MRI; Neoadjuvant radiotherapy; Rectal cancer.

For decades, long-course neoadjuvant radiochemotherapy (RCT) has been a criterion standard for locally advanced rectal cancer, with a time interval between the end of the RCT and the surgery of 6 to 8 weeks.^{1,2} This neoadjuvant treatment significantly reduces the risk of local recurrence.^{1,3} Moreover, for some patients, a pathological complete response (pCR), defined as ypT0N0, can even be observed after RCT with an excellent oncological prognosis.⁴⁻⁶ Following these observations, a more conservative approach can be proposed nowadays for patients with a clinical complete response with a watch-and-wait strategy.⁷ Adjustable factors associated with a good tumoral response were then sought. Besides a small tumor, an extended waiting period between the end of RCT and the rectal resection was suspected to be a relevant factor in improving the rate of clinical complete response.⁸ Several studies have also explored this simple way to improve the rate of pCR.^{9,10} However, some limitations were found in these studies. First, it was not possible to know why a longer waiting period was decided in retrospective studies. Indeed, one could argue that in case of a good initial response, the surgeon may prefer to wait longer. Second, in some publications, chemotherapy was added during the waiting period. Third, the waiting period was wide between studies, ranging from 4 to 16 weeks. To avoid these limitations, a randomized trial was conducted by the GRECCAR to assess the impact of a 4-week-longer waiting period (GRECCAR-6).¹¹ Two hundred sixty-five patients with locally advanced rectal cancer were randomized after completion of the RCT between a 7-week or 11-week waiting period before anterior resection or abdominoperineal resection.¹² The primary end point was the rate of ypT0N0 tumor and no difference was shown between the 2 groups (7-week [W7] group: 15%; 11-week [W11] group: 17.4%; $p = 0.589$). After this publication, a recent meta-analysis reported a contradictory result with a positive impact of a longer waiting period on the pCR rate but without any clinical advantages regarding survival.¹³ Interestingly, post hoc analysis of the FORWARC trial, which used randomization between a long- and short-term interval between RCT and surgery in 157 patients, did not show any difference in the pCR rate.¹⁴ The early oncological results of the GRECCAR-6 trial did not show a difference in the 3-year oncological prognosis between a 7-week and an 11-week waiting period from RCT to the surgery.¹⁵ This study seeks to verify this result after a prolonged 5-year oncological follow-up.

This study aimed to report the long-term outcomes of the GRECCAR-6 trial, including oncological outcomes, and assess the functional results with the risk of low anterior resection syndrome (LARS) when the bowel continuity can be preserved.

PATIENTS AND METHODS

The GRECCAR-6 trial was a phase III, multicenter, randomized, open-label, parallel-group, controlled trial. The design has previously been published.¹¹

Patients

Patients with cT3/T4 or TxN⁺ tumors assessed by radiological examination (MRI and/or endoultrasonography) of the mid or lower rectum who had received RCT (45–50 Gy with intravenous 5-fluorouracil or capecitabine) were included. The exclusion criteria consisted of patients younger than 18 years, patients with upper-third rectal cancer, patients with rectal cancer with synchronous metastasis, patients who did not receive the complete RCT regimen, patients with a previous history of neoplasia (except cutaneous cancer) within the past 5 years, and patients under guardianship or subject to legal protection.

Protocol

Following RCT, patients were randomly assigned in a 1:1 ratio between a 7-week (± 5 -day latency) or an 11-week (± 5 -day latency) waiting period. No specific examination was mandatory during the waiting period, but response assessment by MRI was suggested. At the end of the period, surgical resection of the rectal cancer was planned. The surgery included total mesorectal excision (TME) with either a sphincter-saving procedure or abdominoperineal resection, depending on the height of the tumor and the surgeon's decision. After the exclusion of patients who did not have a TME after the RCT, all randomly assigned patients were included in the modified intent-to-treat (mITT) analysis, whether the timing of their randomization group was respected. In the per-protocol (PP) analysis, only patients who were operated in the exact time frame of the randomized group were considered. Adjuvant chemotherapy was given according to the multidisciplinary meeting decision in each participating center. The GRECCAR-6 protocol was approved by the National IRB (N81-12-19:30/08/12) and was registered on clinicaltrials.gov: NCT01648894.

Outcomes

The current study focuses on secondary outcomes and not on the primary outcome measure, which was the rate of ypT0N0 and on which the sample size calculation was performed.^{11,12} It was planned to include at least 264 patients to detect a difference of at least 14% in pCR occurrence between the 2 groups (2-sided test with an alpha risk of 0.05 and a power of 80%, with a dropout rate of 10%). Secondary end points included overall survival (OS) and disease-free survival (DFS), along with the rate of local and distant recurrence at 5-year follow-up. Distant recurrence was defined as any recurrence in the liver, lung, distant nodes, and/or carcinomatosis. Local recurrence was defined as any pelvic or anastomotic recurrence. After MRI restaging, a good response was defined by a downstaging or a shrinkage in tumoral size of more than 50%. Postoperative complications were defined as the occurrence of surgical or medical complications within 90 postoperative days. Surgical complications included

anastomotic leakage (abscess or peritonitis), abdominal wound complications (infection, hematoma, or dehiscence), perineal wound infection after abdominoperineal resection (infection, hematoma, or dehiscence), bowel obstruction treated with a nasogastric tube, and abdominal bleeding requiring blood transfusion or unplanned reoperation. Medical complications included myocardial infarction, pneumonia, respiratory failure requiring mechanical ventilation, urinary infection, venous thromboembolism (deep vein thrombosis or pulmonary embolism), and myocardial infarction.

Another secondary end point was the LARS score¹⁶ assessed after 2 years of follow-up. The questionnaire was collected during an appointment or by telephone. The surgeon in charge of the patient was responsible for this follow-up. The patient follow-up was to be conducted at 24 ± 4 months. LARS score is a standardized score assessing specifically the bowel function after rectal resection. This score consists of 5 questions, each with 3 to 4 possible answers. This questionnaire was sent to all patients alive and with a bowel continuity preserved 2 years after the randomization. The overall score determines the value of the LARS score, ranging from 0 to 42. This score is categorized into 3 levels: no LARS (score between 0 and 20), minor LARS (score between 21 and 29), and major LARS (score between 30 and 42).

Statistical Analysis

Previous power calculations identified a required sample size of 264 patients. Categorical data were reported as frequencies and percentages and compared with the Pearson χ^2 test or Fisher exact test if the validity conditions were not fulfilled. Quantitative data were expressed as medians and interquartile ranges [IQRs] and compared using the Mann-Whitney *U* test. This test was also used for the comparison of ordinal data. The median follow-up was estimated using the reverse Kaplan-Meier method. OS time was the interval between randomization and death or last follow-up. DFS time was defined as the time from randomization until the first recurrence or death or last follow-up. Patients who did not experience any event and were still alive at 60 months were right censored at this time. Survival curves were plotted using the Kaplan-Meier method. The log-rank test was used to compare survival curves. All tests were 2-sided. A *p* value of <0.05 was considered statistically significant. All analyses were performed using R Software version 4.2.3 (R Core Team, Austria).

RESULTS

Population

A total of 265 patients from 24 participating centers were included between November 2011 and February 2015; of these, 133 were randomized to the W7 group (50.2%) and 132 in the W11 group (49.8%). The main characteristics of

the patients and the postoperative outcomes and pathology are given in Table 1. After excluding 12 patients who did not undergo TME after RCT (Fig. 1), 253 patients had a rectal resection with TME (mITT group). Among them, 201 (79.4%) were operated in the exact time frame of the randomized group (PP group). In the W7 group, 26% of patients had surgery outside the exact time frame (32/125) versus 16% in the W11 group (20/128, $p = 0.05$). Only 1 patient among the 253 included patients (0.4%) experienced a crossover, meaning he was randomized to the W7 group but had the surgical resection within the specified time frame of the W11 group.

OS and DFS

After a median follow-up of 59.5 months, 41 patients (16.2%) died. Five-year OS was 82.1% (95% CI, 77.3%–87.3%). There was no statistical difference regarding OS between the 2 randomization groups (mITT: W7: 81.6% [95% CI, 74.8%–89.1%], vs W11: 82.6% [95% CI, 75.9%–89.9%]; $p = 0.827$; Fig. 2A). Five-year DFS was 69.9% (95% CI, 64.2%–76.0%) and was similar between the 2 groups (mITT: W7: 70.4% [95% CI, 62.5%–79.3%], vs W11: 69.5% [95% CI, 61.8%–78.3%]; $p = 0.856$; Fig. 2B).

Similarly, in the PP analysis, no difference was observed between the 2 randomization groups in OS (W7: 79.4% [95% CI, 71.4%–88.4%], vs W11: 83.7% [95% CI, 76.7%–91.4%]; $p = 0.432$) and DFS (W7: 63.4% [95% CI, 54.0%–74.4%], vs W11: 69.0% [95% CI, 60.5%–78.6%]; $p = 0.389$; see Supplemental Fig. 1 at <http://links.lww.com/DCR/C413>).

Local and Distant Recurrence

Recurrence rates at 5 years were 9.3% (95% CI, 5.4%–13.1%) for local recurrences and 25.6% (95% CI, 20.7%–32.1%) for distant recurrences. The median delay for local recurrences was 17.6 months (IQR, 10.6%–33.4%) and 13.8 months (IQR, 10.4%–24.3%) for distant recurrences.

In the mITT analysis, no difference was found for 5-year local recurrence (W7: 8.4% [95% CI, 3.0%–13.5%], vs W11: 10.2% [95% CI, 4.5%–15.5%]; $p = 0.543$; Fig. 3A) and for 5-year distant recurrence (W7: 27.4% [95% CI, 18.6%–33.2%], vs W11: 25.7% [95% CI, 17.4%–32.2%]; $p = 0.777$; Fig. 3B).

Similar findings were observed in the PP group, with no significant difference identified between the 2 groups for distant or local recurrence ($p = 0.432$ and $p = 0.389$, respectively; see Supplemental Fig. 2 at <http://links.lww.com/DCR/C414>).

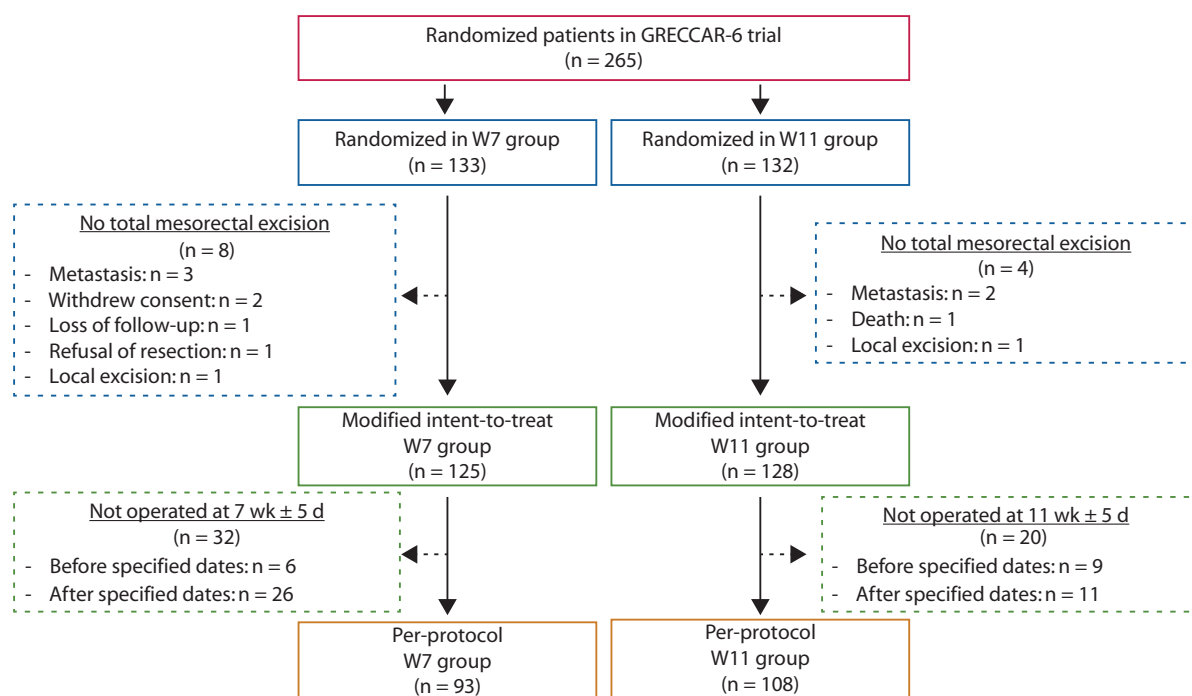
Good Versus Bad MRI Responders

A total of 147 patients (58%) had a restaging MRI after a median time interval from the end of the RCT of 34 days (IQR, 26–44). Fifty-nine patients were considered to be good responders (40%) and 88 patients to

TABLE 1. Population characteristics (7-wk and 11-wk groups)

Variables	Overall (N = 265)	W7 group (N = 133)	W11 group (N = 132)	p
Age, y	64.2 (56.5 to 69.7)	64.5 (57.8 to 69.3)	63.3 (55.4 to 70.0)	0.473
Sex, female	96/265 (36)	49/133 (37)	47/132 (36)	0.834
Initial cT stage				0.457
cT2	13/259 (5.0)	8/128 (6.2)	5/131 (3.8)	
cT3	228/259 (88)	113/128 (88)	115/131 (88)	
cT4	18/259 (6.9)	7/128 (5.5)	11/131 (8.4)	
Initial cN+ stage	200/251 (80)	93/124 (75)	107/127 (84)	0.069
Type of rectal resection				0.726
Anterior resection	227/253 (90)	113/125 (90.4)	114/128 (89)	
Abdominoperineal resection	26/253 (10)	12/125 (9.6)	14/128 (11)	
Postoperative morbidity	93/256 (36)	38/127 (30)	55/129 (43)	0.034
Anastomotic leakage	29/227 (13)	16/113 (14)	13/114 (11)	
ypT stage				0.508
T0	48/254 (19)	20/126 (16)	28/128 (22)	
Tis-T1	21/254 (8.3)	13/126 (10)	8/128 (6.2)	
T2	73/254 (29)	37/126 (29)	36/128 (28)	
T3	99/254 (39)	51/126 (40)	48/128 (38)	
T4	13/254 (5.1)	5/126 (4.0)	8/128 (6.2)	
ypN stage				0.947
N0	174/251 (69)	87/124 (70)	87/127 (69)	0.798
N1a	36/251 (14)	16/124 (13)	20/127 (16)	
N1b	18/251 (7.2)	10/124 (8.1)	8/127 (6.3)	
N1c	9/251 (3.6)	5/124 (4.0)	4/127 (3.1)	
N2a	8/251 (3.2)	3/124 (2.4)	5/127 (3.9)	
N2b	6/251 (2.4)	3/124 (2.4)	3/127 (2.4)	
Adjuvant chemotherapy	67/253 (26)	33/125 (27)	33/128 (26)	

Data are presented as median (interquartile range) or n/N (%).

**FIGURE 1.** CONSORT diagram of the GRECCAR-6 trial. CONSORT = Consolidated Standards of Reporting Trials; W7 = week 7; W11 = week 11.

be bad responders (60%). Five-year OS and 5-year DFS were similar between good and bad responders after MRI restaging ($p = 0.648$ and $p = 0.388$, respectively;

see Supplemental Fig. 3 at <http://links.lww.com/DCR/C415>). A waiting period of 7 weeks compared to 11 weeks between the end of the RCT and the surgery had

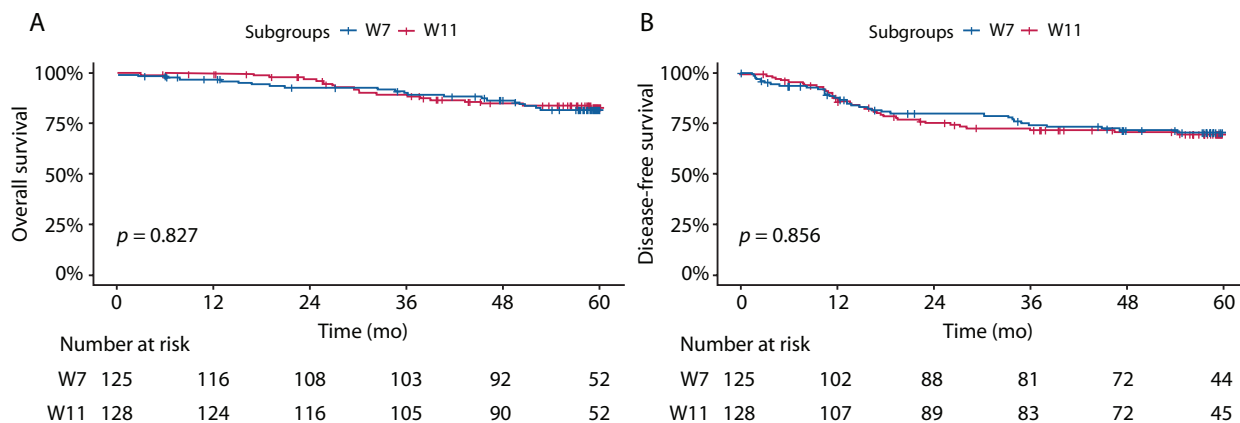


FIGURE 2. Overall survival (A) and disease-free survival (B) between W7 and W11 subgroups (intent-to-treat analysis). W7 = week 7; W11 = week 11.

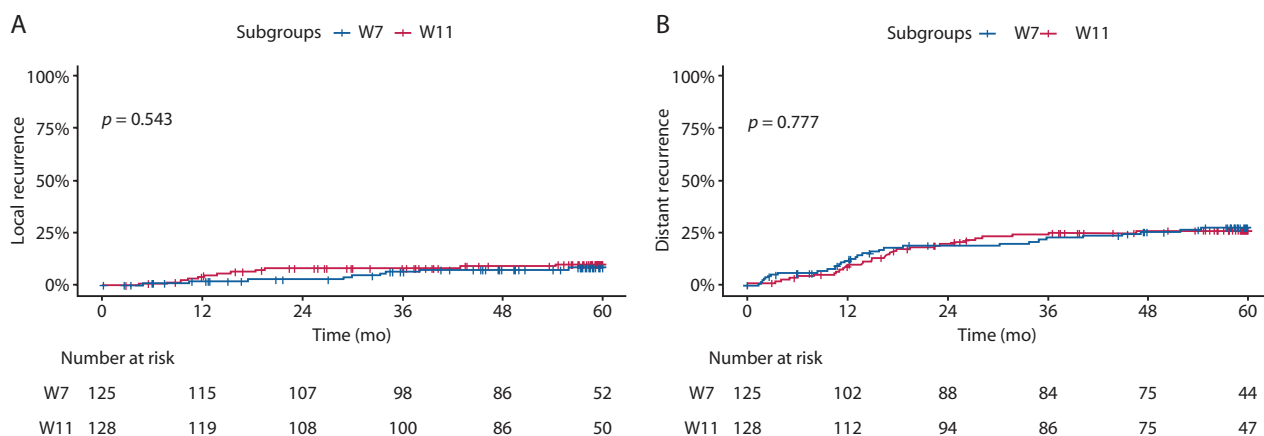


FIGURE 3. Local (A) and distant recurrences (B) between W7 and W11 subgroups (intent-to-treat analysis).

no significant impact on either the OS or DFS among bad responders ($p = 0.125$ and $p = 0.599$, respectively; see Fig. 4), nor among good responders ($p = 0.581$ and $p = 0.598$, respectively; see Supplemental Fig. 4 at <http://links.lww.com/DCR/C416>).

LARS Score: W7 Versus W11 Groups

LARS score was sent 2 years after the surgery to patients who were alive and without a stoma. Among the 253 patients, 54 patients were not eligible for an LARS score assessment (26 patients had an abdominoperineal resection with a definitive stoma, 11 died in the 2 years after the surgery, and 19 had a stoma). Among the 197 patients eligible for a LARS score assessment, 103 patients (52%) answered the questionnaire after a median time interval after the surgery of 24.3 months (IQR, 23.6–25.7). Among eligible patients, a responder was comparable to nonresponder patients to the LARS questionnaire in terms of demographic data, randomization group (W7 vs W11), postoperative morbidity, and adjuvant chemotherapy (see Supplemental Table 1 at <http://links.lww.com/DCR/C417>). The median value

of the LARS score in the entire cohort was 23.0 (IQR, 14.5–33.0). No LARS was found in 45 patients (44%), 21 patients (20%) had minor LARS, and 37 patients (36%) had major LARS. Patients with major LARS were comparable in the 2 groups (see Supplemental Table 2 at <http://links.lww.com/DCR/C418>). Patients in the W7 group had similar LARS occurrence and bowel function characteristics compared to patients in the W11 group (Table 2).

DISCUSSION

This prospective randomized study demonstrates that extending the time interval from 7 to 11 weeks between neoadjuvant RCT and surgical resection for T3/T4-N⁺ rectal cancer does not lead to an improvement in 5-year OS or DFS. Furthermore, this extended time interval does not impact intestinal function in cases of digestive continuity preservation at 2 years.

Our findings regarding the lack of benefit from extending the interval on oncological survival contradict retrospective studies on this subject, some of which have

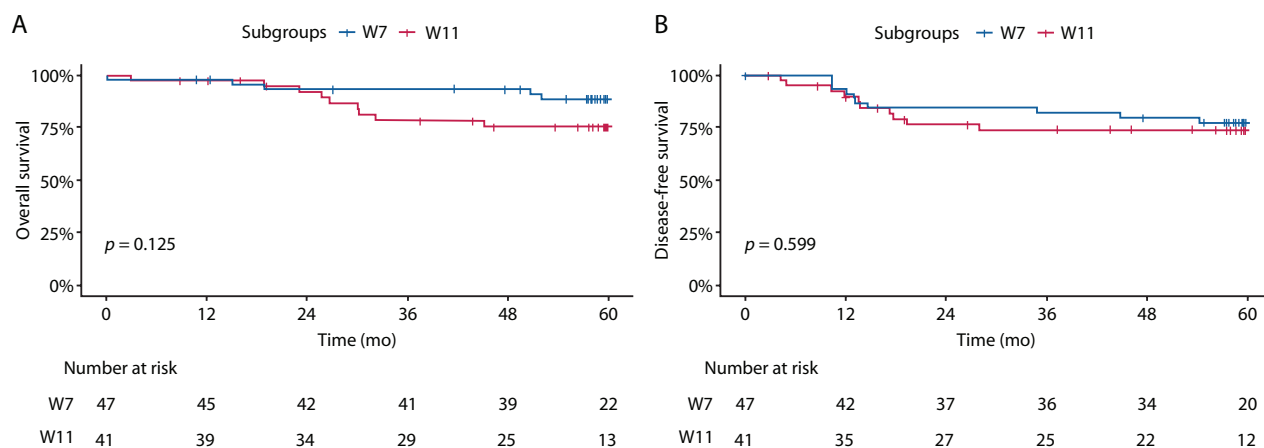


FIGURE 4. Overall survival (A) and disease-free survival (B) between W7 and W11 subgroups among bad MRI responders patients (intent-to-treat analysis).

TABLE 2. LARS score 2 y after the anterior resection: W7 compared with W11 patients

Variables	Overall (N = 103)	W7 (N = 49)	W11 (N = 54)	p ^a
LARS score (/42)	23.0 (14.5–33.0)	25.0 (15.0–34.0)	23.0 (14.2–32.0)	0.743
LARS score				0.889
No LARS (0–20)	45/103 (44)	22/49 (45)	23/54 (43)	
Minor LARS (21–29)	21/103 (20)	9/49 (18)	12/54 (22)	
Major LARS (30–42)	37/103 (36)	18/49 (37)	19/54 (35)	
No LARS or minor LARS	66/103 (64)	31/49 (63)	35/54 (65)	0.870
Do you ever have occasions when you cannot control your flatus (wind)?				0.740
No, never	30/103 (29)	16/49 (33)	14/54 (26)	
Yes, less than once per week	23/103 (22)	10/49 (20)	13/54 (24)	
Yes, at least once per week	50/103 (49)	23/49 (47)	27/54 (50)	
Do you ever have an accidental leakage of liquid stool?				0.084
No, never	41/103 (40)	25/49 (51)	16/54 (30)	
Yes, less than once per week	35/103 (34)	14/49 (29)	21/54 (39)	
Yes, at least once per week	27/103 (26)	10/49 (20)	17/54 (31)	
How often do you open your bowels?				0.166
1–3 times per day	51/103 (50)	25/49 (51)	26/54 (48)	
4–7 times per day	41/103 (40)	18/49 (37)	23/54 (43)	
>7 times per day	3/103 (2.9)	0/49 (0)	3/54 (5.6)	
Less than once per day	8/103 (7.8)	6/49 (12)	2/54 (3.7)	
Do you ever have to open your bowels again within 1 h of the last bowel opening?				0.800
No, never	24/103 (23)	11/49 (22)	13/54 (24)	
Yes, less than once per week	32/103 (31)	14/49 (29)	18/54 (33)	
Yes, at least once per week	47/103 (46)	24/49 (49)	23/54 (43)	
Do you ever have such a strong urge to open your bowels that you have to rush to the toilet?				0.490
No, never	43/103 (42)	19/49 (39)	24/54 (44)	
Yes, less than once per week	34/103 (33)	15/49 (31)	19/54 (35)	
Yes, at least once per week	26/103 (25)	15/49 (31)	11/54 (20)	

Data are presented as median (interquartile range) or n/N (%). LARS = low anterior resection syndrome.

^aWilcoxon rank-sum test, Pearson's χ^2 test, and Fisher exact test.

reported either an oncological advantage in extending this interval,¹⁷ no significant modification in survival,¹⁸ or, conversely, a poorer survival with prolonged delay.¹⁰ Retrospective studies on this topic are inherently biased, particularly due to selection bias in the choice of the interval, as various criteria can influence the clinician's decision, such as the patient's overall condition, the tumor's clinical response to treatment, the distance of the lesion from the

anal sphincter, and whether to pursue an organ preservation strategy. These factors undermine the robustness of the results regarding the impact of the interval. It is noteworthy that the vast majority of published studies on this subject are retrospective and included in meta-analyses without separately analyzing the results of prospective randomized trials.^{9,10} Only 1 prospective randomized controlled trial (phase III) addressing the oncological survival

and with a protocol similar to ours has been published in the literature.¹⁹ A difference worth mentioning is that in this other trial, patients were randomly assigned to an interval between 4 and 8 weeks versus 8 and 12 weeks, slightly differing from our study, in which we compared 7 weeks (± 5 -day latency) to 11 weeks (± 5 -day latency). In this other study, Akgun et al¹⁹ found a significant increase in the pCR rate in the long interval group, whereas in our trial, we did not observe any benefit in the long interval group based on this outcome.¹² Despite these contradictory results on the histological criterion of pCR, long-term oncological outcomes align. Indeed, Akgun et al²⁰ demonstrated equivalent 5-year OS and DFS between short- and long-term interval groups, despite a benefit in distant recurrence with the long interval. This lack of benefit from extending the time interval on OS and DFS is confirmed by our results. The 2 phase III randomized controlled trials on this question are therefore in agreement on this major outcome.

We explored the role of restaging MRI to determine whether this examination may help to stratify patients into the appropriate time interval according to the tumoral response. Although this second MRI was not obligatory in the current study,¹¹ 147 participants underwent this imaging. In the literature, a positive correlation has been reported between the observed tumor response on the restaging MRI and long-term oncological survival after surgical resection in rectal cancer.^{21,22} Our study does not align with this observation, as patients categorized as good or bad responders on the restaging MRI exhibited comparable OS and DFS (see Supplemental Fig. 3 at <http://links.lww.com/DCR/C415>). In addition, a recent report on a large retrospective cohort of 1701 patients undergoing surgery for rectal adenocarcinoma with a poor histological response after neoadjuvant RCT indicated a significantly decreased OS and DFS when the interval between RCT and surgery was prolonged.²³ In our study, within the subgroup of patients identified as bad responders on the MRI, we did not observe any impact on OS or DFS with an extension of the interval from 7 to 11 weeks (Fig. 4). This discrepancy may be partially explained by the limited performance of the restaging MRI in assessing tumor response that will be found on the operative specimen after neoadjuvant RCT.²⁴ Other imaging criteria on MRI, besides a reduction of at least 50% in tumor size, should also be evaluated in the future. A 50% shrinkage on MRI after RCT might be less relevant than other criteria.

The possible impact of the time interval between neoadjuvant RCT and surgery on functional outcomes, including anal continence and stool frequency, has not been explored previously. Neoadjuvant RCT is a determining risk factor for LARS and deterioration of the function result after rectal resection.²⁵ In the GRECCAR-6 trial, we had previously reported a worse quality of mesorectal resection after 11 weeks compared to the

W7 group.¹² It may be an explanation for the RAPIDO trial result, where patients after total neoadjuvant treatment with a longer interval between the end of radiotherapy and surgery (24 weeks on average) compared to patients after conventional neoadjuvant RCT have more often presented with a breached mesorectum on the surgical specimen.²⁶ This observation may be linked to a more challenging pelvic dissection, suggesting that the risk of pelvic nerve injury may be increased when the time interval between radiotherapy and surgery is prolonged. However, our results contradicted this suspected explanation, as the LARS score at 2 years of post-surgical resection was similar between the W7 and W11 groups. This finding is also consistent with recent data on salvage anterior resection performed remotely after RCT failure after a watch and wait strategy (thus a long period since the RCT), which showed equivalent functional outcomes to those of patients operated immediately after RCT.²⁷

Our study has several limitations. First, oncological and functional outcomes were considered as secondary end points, and consequently, the calculation of the patient number was not based on these outcomes. Second, the LARS score only partially reflects long-term functional results and does not encompass all aspects of digestive function. In addition, we did not assess sexual function, urinary function, or quality of life. LARS score was collected only at 2 years, so we cannot assess the evolution of this score over time after the TME; nevertheless, a recent meta-analysis has shown that the LARS score stabilizes from 18 months after TME.²⁸ Finally, the response rate to the LARS questionnaire was 52%.

From the perspective of this study, the neoadjuvant treatment for locally advanced rectal cancer has evolved since the development of the protocol for the GRECCAR-6 trial. The current approach involves total neoadjuvant therapy as proposed in the PRODIGE 23 trial,²⁹ sequentially combining chemotherapy with FOLFIRINOX followed by RCT (50 Gy with capecitabine) and the TME 6 to 8 weeks after the end of the RCT. A recent publication indicated more local recurrence after total neoadjuvant therapy according to the RAPIDO protocol,²⁶ a trend not observed with the PRODIGE 23 protocol,²⁹ leading to a preference for this second protocol. Nevertheless, due to the potential toxicity of the total neoadjuvant treatment, some patients are ineligible for receiving it. For these patients, equivalence between neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy using folinic acid, fluorouracil, and oxaliplatin without radiotherapy has been established, providing a choice between the 2 strategies.³⁰ For patients for whom a neoadjuvant RCT is decided, our study demonstrates that extending the time interval between the end of RCT and surgery from 7 to 11 weeks does not provide a benefit in terms of 5-year oncological

survival and does not alter the functional outcome evaluated by the LARS score at 2 years. The impact of extending the time interval after total neoadjuvant treatment deserves to be evaluated in the future.

These findings were originally presented at the annual meeting of the American Society of Colon and Rectal Surgeons.³¹

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