

Does A Longer Waiting Period After Neoadjuvant Radio-chemotherapy Improve the Oncological Prognosis of Rectal Cancer?

Three Years' Follow-up Results of the Greccar-6 Randomized Multicenter Trial

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Objective: The aim of this study was to report the 3-year survival results of the GRECCAR-6 trial.

Summary Background Data: Current data on the effect of an extended interval between radiochemotherapy (RCT) and resection for rectal cancer on the rate of complete pathological response (pCR = ypT0N0) is controversial. Furthermore, its effect on oncological outcomes is unknown.

Methods: The GRECCAR-6 trial was a phase III, multicenter, randomized, open-label, parallel-group, controlled trial. Patients with cT3/T4 or TxN+ tumors of the mid or lower rectum who had received RCT (45–50 Gy with 5-fluorouracil or capecitabine) were included and randomized into a 7- or 11-week waiting period. Primary endpoint was the pCR rate. Secondary

endpoints were 3-year overall (OS), disease-free survival (DFS), and recurrence rates.

Results: A total of 265 patients from 24 participating centers were enrolled. A total of 253 patients underwent a mesorectal excision. Overall pCR rate was 17% (43/253). Mean follow-up from surgical resection was 32 ± 8 months. Twenty-four deaths occurred with an 89% OS at 3 years. DFS was 68.7% at 3 years (75 recurrences). Three-year local and distant recurrences were 7.9% and 23.8%, respectively. The randomization group had no impact on the 3-year OS ($P = 0.8868$) or DFS ($P = 0.9409$). Distant ($P = 0.7432$) and local ($P = 0.3944$) recurrences were also not influenced by the waiting period. DFS was independently influenced by 3 factors: circumferential radial margin

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(CRM) ≤ 1 mm [hazard ratio (HR) = 2.03; 95% confidence interval (CI), 1.17–3.51], ypT3–T4 (HR = 2.69; 95% CI, 1.19–6.08) and positive lymph nodes (HR = 3.62; 95% CI, 1.89–6.91).

Conclusion: Extending the waiting period by 4 weeks following RCT has no influence on the oncological outcomes of T3/T4 rectal cancers.

Keywords: rectal cancer, neoadjuvant radiotherapy, complete pathological response, MRI

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Radiochemotherapy (RCT) is indicated for mid-low T3/T4 or N+ rectal cancers, with 15% to 20% of patients achieving a complete pathological response (ypT0N0).^{1,2} The goal of RCT is to induce downstaging, reduce local recurrence rates, and ultimately achieve a complete pathological response (pCR), which has been associated with significantly improved oncological outcomes.^{3–7}

Since the introduction of organ preservation in rectal cancer, numerous factors associated with good tumoral response have been studied.⁸ Lower T stage ($\leq T2$) and smaller tumors (≤ 4 cm in diameter) have been associated with pCR rates of 40%.^{9,10} However, current guidelines recommend neoadjuvant RCT for larger T3–T4 tumors before resection. In this setting, only a longer waiting period after RCT has been found to be associated with a higher pCR rate.¹ However, results from these studies are influenced by bias and retrospection.¹¹

To assess time interval following RCT on tumor response in rectal cancer, our group conducted the multicenter randomized GRECCAR-6 trial. A total of 265 patients were randomized into a 7- or 11-week interval following neoadjuvant therapy, showing that a longer interval (>7 weeks) was not associated with an increased pCR rate.¹² The oncological effect of this strategy was not reported in the initial study. Although cell death continues after radiotherapy, mainly because of the release of oxygen-free radicals, longer waiting periods may be associated with tumoral regrowth for nonresponding tumors. Ultimately, increasing the interval between RCT and surgery may delay systemic adjuvant chemotherapy for patients with larger nonresponding tumors.¹³

Therefore, the aim of this study was to report the 3-year oncological outcomes of the GRECCAR-6 trial.

PATIENTS AND METHODS

Study Design and Participants

The design, rationale, and primary endpoint of this trial have previously been published.^{5,14} The GRECCAR-6 trial was a phase III, multicenter, randomized, open-label, parallel-group, controlled trial. Patients with cT3/T4 or TxN+ tumors assessed by radiological examination [magnetic resonance imaging (MRI) and/or endo-ultrasound] of the mid or lower rectum who received RCT (45–50 Gy with intravenous 5-fluorouracil or capecitabine) were included. Patients were randomly assigned to groups (ratio 1:1) by an online portal (<http://cleanweb.aphp.fr>). The GRECCAR-6 trial was approved by the National IRB (N° 1–12–19:30/08/12) and was referenced on clinicaltrials.gov: NCT01648894.

Procedures

Patients were randomly included in the 7-week (7w) or 11-week (11w) group. The strict limits for surgery included a ± 5 -day latency around the specified date. No specific examination was mandatory during the waiting period, but response assessment by MRI was suggested. The surgery included total mesorectal excision with either a sphincter-saving procedure or abdominoperineal resection, depending on the height of the tumor and the surgeon's decision.

Pathological Examination

Pathological examination was performed in each center according to the National French Guidelines.¹⁵ The decision regarding pCR was made after examination of the entire macroscopic lesion.

Outcomes

The primary endpoint of the GRECCAR-6 trial was the pCR rate defined as a ypT0N0 specimen confirmed by 2 pathological examinations. Secondary endpoints included overall (OS) and disease-free survival (DFS) along with the rate of local and distant recurrence at 3 and 5 years of follow-up.

After MRI restaging, a good response was defined by a downstaging or a shrinkage in tumoral size of $>50\%$.

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.

Follow-Up

Adjuvant chemotherapy was given according to the MDM decision in each participating centre. According the published protocol, patients were followed up in clinic for 5 years according to the habits of each department.¹⁴ Follow-up was done according to the French Guidelines [clinical examination, computed tomography-scan (or abdominal ultrasound with chest radiography), CEA analysis every 3 to 4 months for 3 years then every 6 months for 2 years].¹⁶

Statistical Analysis

Previous power calculations identified a required sample size of 264 patients.

Qualitative variables were described as number (%) and were compared between groups using Pearson chi-square test or Fisher exact test. Quantitative variables were described as mean $\pm$ SD. Survival curves were plotted using the Kaplan–Meier method. Log-rank test was used to compare survival curves. Potential prognostic factors were evaluated using Cox proportional hazards regression models. Survival time was the interval between the intervention date and a new event or last follow-up. Patients who did not experience any event and were still alive at 36 months were right censored at this time. For each outcome, factors achieving a *P* value <0.20 in the univariate analysis were included in the multivariate model. Hazard ratios were presented with their 95% confidence interval (CI). All statistical tests were 2-sided and performed using SAS software version 9.3; SAS Institute Inc., Cary, NC.

Funding Source

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RESULTS

Patients

A total of 265 patients from 24 participating centers were enrolled between October 2012 and February 2015. Among them, 253 patients underwent a total mesorectal excision. The overall pCR rate was 17% (43/253). Mean follow-up from surgical resection was 32 ± 8 months. The definitive stoma rate was 15.8% ($n = 40$ patients), with abdominoperineal resections ($n = 26$) accounting for the majority of these (Table 1). Among the 227 anterior resections with low anastomosis, the 3 years' definitive stoma rate was 6.2% ($n = 14$). Among the 34 patients who had an anastomotic leakage, the definitive stoma rate was 35.3% ($n = 12$). Adjuvant chemotherapy was given to 67 patients (26.5%), mainly a FOLFOX regimen (77.6%). Indications for adjuvant therapy included positive lymph nodes ($n = 58$), ypT3–T4 tumors ($n = 49$), or R1 resection ($n = 16$).

TABLE 1. Pathological Results After Rectal Resection and Long-Term Follow-Up of Patients in the GRECCAR-6 Trial According to the Randomization Group

Variables	Overall, N = 253	7 wks, N = 125	11 wks, N = 128	P
Pathological results				
ypT0-T2	138 (54.5%)	68 (54.4%)	70 (54.7%)	1
ypT3-T4	114 (45.1%)	57 (45.6%)	57 (44.5%)	
ypTx	1 (0.4%)	0 (0%)	1 (0.8%)	
ypN+	77 (30.4%)	37 (29.6%)	40 (31.3%)	0.878
ypNx	3 (1.2%)	2 (1.6%)	1 (0.8%)	
R1 resection	31 (12.3%)	14 (11.2%)	17 (13.3%)	0.631
Deaths	24 (9.5%)	12 (9.6%)	12 (9.4%)	0.951
Mean time from surgery*	20.3 ± 10.6	17.0 ± 12.2	23.6 ± 7.8	
Anastomotic leakage	2 (8%)	2 (17%)	0 (0%)	
Cancer-related	14 (56%)	5 (42%)	9 (67%)	
Intercurrent disease	4 (16%)	3 (25%)	1 (8%)	
Unknown	4 (16%)	2 (17%)	3 (25%)	
Adjuvant chemotherapy	67 (26.5%)	34 (27.2%)	33 (25.8%)	0.798
FOLFOX	52 (77.6%)	24 (70.6%)	28 (84.8%)	
XELOX	8 (11.9%)	6 (17.6%)	2 (6.1%)	
5-Fluorouracil alone	5 (7.5%)	3 (8.8%)	2 (6.1%)	
Other	2 (3.0%)	1 (2.9%)	1 (3%)	
Local recurrence	18 (7.1%)	7 (5.6%)	11 (8.6%)	0.354
Anastomotic	9 (50%)	4 (57%)	5 (45%)	
Pelvic	9 (50%)	3 (43%)	6 (55%)	
Distant metastasis	55 (21.7%)	25 (20%)	30 (23.4%)	0.507
Liver	25 (44.6%)	13 (52%)	12 (40%)	0.226
Pulmonary	20 (35.7%)	6 (24%)	14 (46.7%)	
Other	10 (19.6%)	6 (24%)	4 (13.3%)	
Definitive stoma	40 (15.8%)	21 (16.8%)	19 (14.8%)	0.670
Abdomino-perineal resection	26 (65%)	12 (57.1%)	14 (73.7%)	
Anastomotic leakage	6 (15%)	3 (14.3%)	3 (15.8%)	
Death before stoma closure	6 (15%)	5 (23.8%)	1 (5.3%)	
Unknown	2 (5%)	1 (4.8%)	1 (5.3%)	

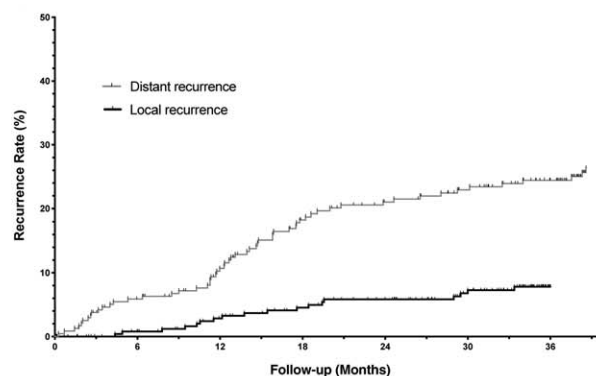
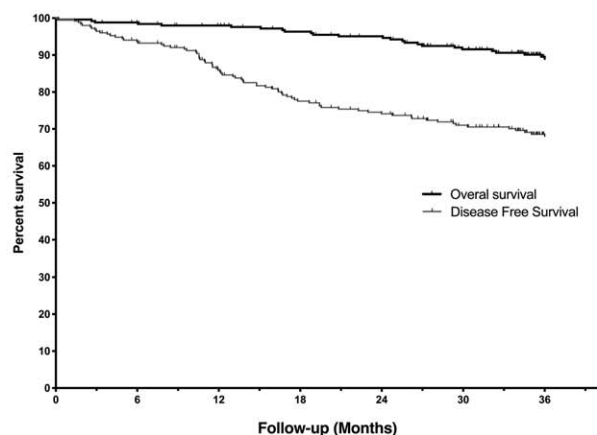
*Months.

In an intention-to-treat analysis, among the 265 included patients, 3-year OS and DFS were 89% and 67.4%. Three-year local and distant recurrence rates were 7.8% and 25.1%, respectively (Fig. 1A and B). Among the 253 patients who undergone a rectal resection and constituted the cohort for further analysis, 3-year OS and DFS were 89.5% and 68.7% (Table 1). Three-year local and distant recurrence rates were 7.9% and 23.8%, respectively. Eight patients had both local and distant recurrences (Table 1). Among the 77 patients

with positive lymph nodes, improved DFS was associated with patients receiving adjuvant chemotherapy (49.2% vs 26.3%, $P = 0.1662$).

Impact of Tumoral Response

Three-year DFS was significantly better in the pCR group (89.6% vs 64.4%, $P = 0.0030$). Only 2 patients (4.7%) with a pCR had a distant recurrence, with no local recurrences encountered.

**FIGURE 1.** OS and DS (A) and distant (DR), local recurrences (LR) (B) of the overall cohort of the GRECCAR6 trial.

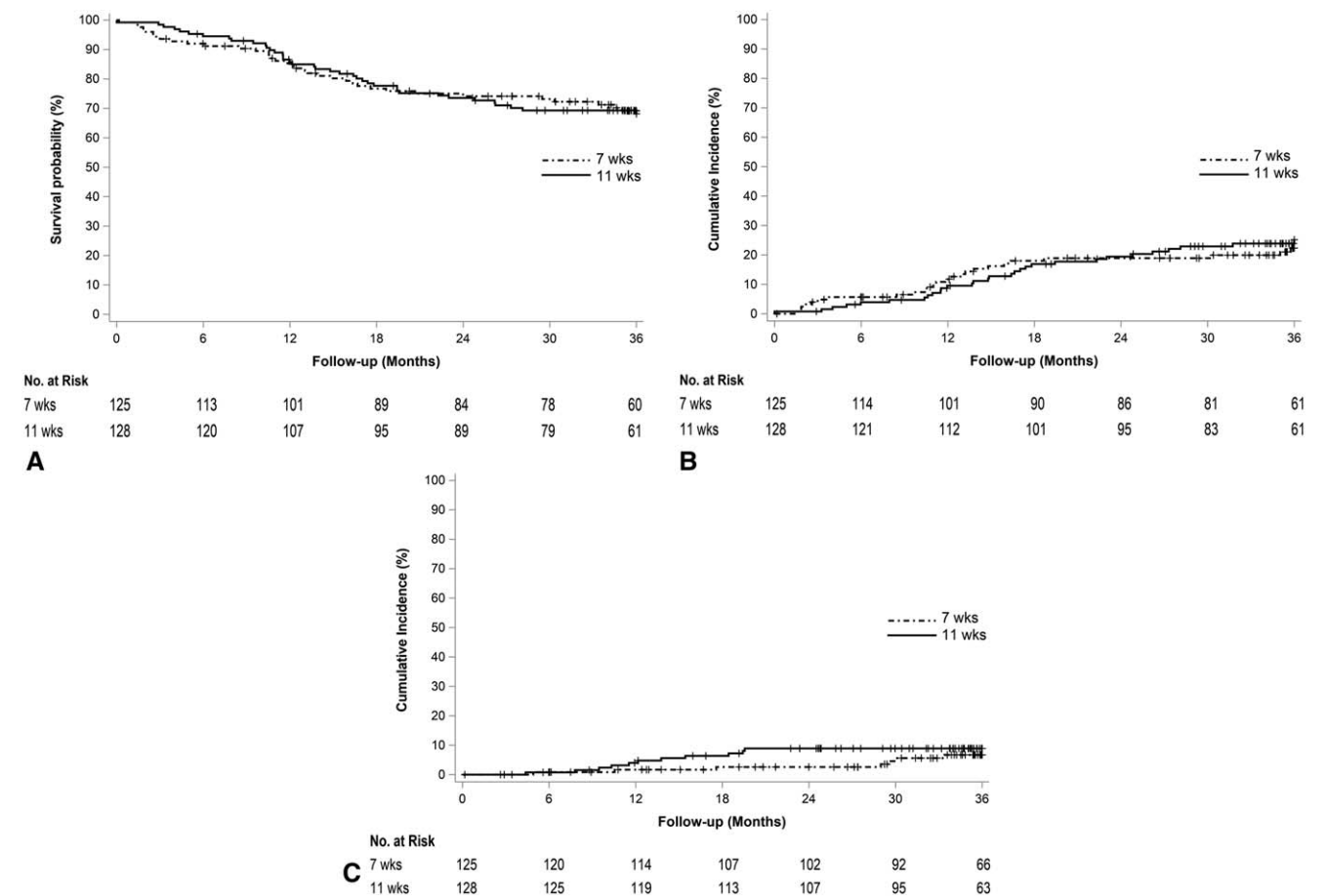


FIGURE 2. Survival curves according to the waiting period after radiochemotherapy (A) DFS (log-rank = 0.9409). (B) Metastatic recurrences (log-rank = 0.7432). (C) Local recurrences (log-rank = 0.3944).

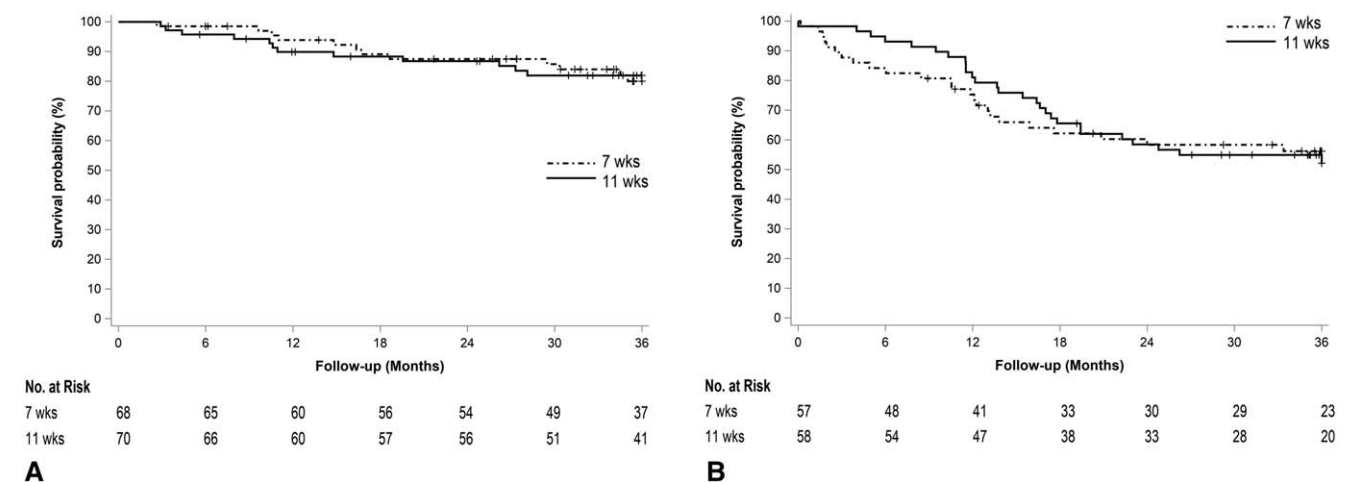


FIGURE 3. Disease-free survival according to the randomization group of: (A) good responders (ypT0-Tis-T1-T2) (log-rank = 0.9509); (b) bad responders (ypT3-T4) (log-rank = 0.9726).

TABLE 2. Univariate and Multivariate Analysis of Factors Influencing the 3-Year DFS Among the Overall Cohort of the GRECCAR-6 Trial

Variable	Univariate		Multivariate		
		Log-Rank	HR	95% CI	P
Sex	Male	0.8411	NI		
	Female				
Age	≤64 y	0.9824	NI		
	>64 y				
Location	Low rectal	0.0819	1.67	0.97–2.87	0.0627
	Mid rectal				
Randomization	7 wk	0.9409	NI		
	11 wk				
Anastomotic leakage	Yes	0.8297	NI		
	No				
ypT	ypT0-T2	0.0001	2.69	1.19–6.08	0.0174
	ypT3-T4				
ypN	ypN0	<0.0001	3.62	1.89–6.91	0.0001
	ypN+				
CRM	CRM >1 mm	<0.0001	2.03	1.17–3.51	0.0114
	CRM ≤1 mm				
Mesorectal quality	Complete	0.9760			
	Incomplete				
Adjuvant chemotherapy	Yes	<0.0001	0.75	0.40–1.40	0.3833
	No				
Resection type	Anterior resection	0.1732	0.99	0.50–1.97	0.9754
	APR				

APR indicates abdominoperineal resection; CRM, circumferential radial margin.

When patients with a good tumoral response to RCT (ypT0-T2, $n = 138$, 54.5%) were compared to tumors with a poor response (ypT3-T4, $n = 115$, 45.5%), a significantly better 3-year DFS was encountered in the good tumoral response group (81.0% vs 54.1%, $P < 0.0001$).

Impact of Waiting Period

The group in which patients were randomized to had no impact on the 3-year OS ($P = 0.8868$) or DFS ($P = 0.9409$) (Fig. 2A). Distant ($P = 0.7432$) and local ($P = 0.3944$) recurrences were also not influenced by the waiting period (Fig. 2B, C).

Subgroup analysis according to the pathological stage have shown that 3-year DFS was not influenced by the waiting period for good ($P = 0.9509$) or bad responder ($P = 0.9726$) (Fig. 3A and B).

Univariate and Multivariate Analysis

DFS was independently influenced by 3 factors: CRM ≤1 mm [hazard ratio (HR) = 2.03; 95% CI, 1.17–3.51], ypT3-T4 (HR = 2.69; 95% CI, 1.19–6.08), and positive lymph nodes (HR = 3.62; 95% CI, 1.89–6.91) (Table 2). Invaded lymph nodes (HR = 2.88; 95% CI, 1.09–7.65, $P = 0.0335$) was independently associated with local recurrences. Distant recurrences were independently influenced by ypT3-T4 (HR = 3.18; 95% CI, 1.11–9.13; $P = 0.0315$) and positive lymph nodes (HR = 3.33; 95% CI, 1.58–7.00; $P < 0.0001$).

Impact of Restaging MRI

A total of 148 patients had a restaging MRI (58.5%) after a mean interval following the end of RCT of 36.3 ± 15.7 days. Patients with restaging MRI had similar characteristics than the 87 patients who did not, except for the rate of mid rectal cancer (41.2% in the restaging group vs 25.3%, $P = 0.01$) (supplementary Table 1, <http://links.lww.com/SLA/B739>). Eighty-eight patients were considered as bad responder (59.7%). Three-year OS and DFS were not influenced by tumoral response after restaging MRI ($P = 0.3081$; $P = 0.1796$, respectively). Three-year DFS was assessed in both good and bad responders in relation to the waiting period. (Fig. 4A and B). Time

between the end of radiation and surgery had no influence on the 3-year DFS in both subgroups. In the good responders, 3-year DFS was 62.7% in the 7-week group and 64.5% in the 11-week group ($P = 0.8866$). In the group of bad responders, 3-year DFS was 79.2% in the 7-week group and 68.6% in the 11-week group ($P = 0.2845$).

DISCUSSION

We have shown in this study that a 4-week increase between the completion of RCT and surgery has no impact on the oncological outcomes of T3/T4-N+ mid-low rectal cancers. The GRECCAR-6 trial therefore shows that both pCR rate and DFS are not influenced by a longer waiting period in contrary to previous retrospective publications.

A 6 to 7-week period of waiting after RCT has become the standard of care after the Lyon trial (39 Gy without chemotherapy) published in 1999.¹⁷ Publication of the long-term results of this trial after 17 years of follow-up did not show any differences in the local recurrence rate or OS between the long-interval group and the short-interval group of 2 weeks.^{18,19}

To date, only retrospective studies and meta-analysis with numerous bias are available, focusing on the pathological examination of the specimen.^{1,20} It is interesting to note that both of these meta-analyses classified patients into only 2 groups: <8 weeks vs >8 weeks. Among patients with a delay >8 weeks, some waited 9 weeks, whereas others waited 14 weeks, which introduces a source of heterogeneity within the same group that should not be overlooked. The relationship between pCR and time delay is sigmoidal, with a maximum effect seen around 6 to 8 weeks.²¹ In a recent meta-analysis of 15 articles including 4431 patients, Wang et al²² observed an increased pCR rate only after 7 or 8 weeks [risk ratio = 1.45 (1.18–1.78), $P < 0.01$].

As there is no improvement in the rate of pCR with a longer waiting period, the role it plays on oncological outcomes is unknown with conflicting results reported in the literature. OS is often not impacted by the waiting period, as radiotherapy has not been shown to impact on OS in randomized trials. The present study

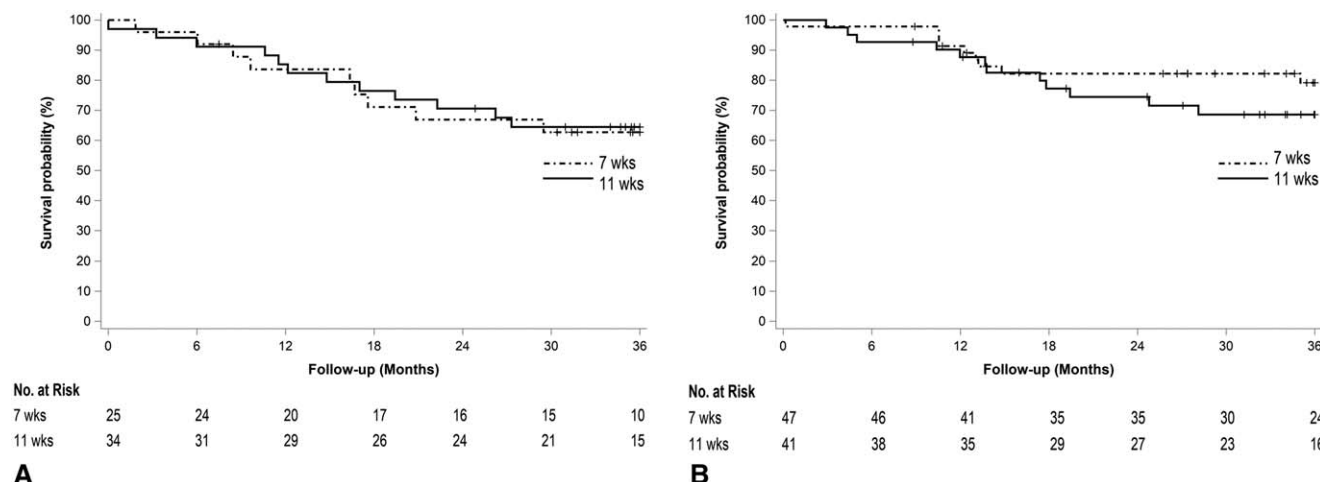


FIGURE 4. Disease free survival according to the randomization group of: (A) good responders on restaging MRI ($P = 0.8866$) and (B) bad responders on restaging MRI ($P = 0.2845$).

reports a 3-year OS of 89%, which is in accordance with previous literature. In the ACCORD 12 trial, 598 patients were randomized with the same clinical characteristics of GRECCAR-6 (T3-T4, Nx) and the 3-year OS of 88%.² The present study also observed the same rate of 3-year DFS, local and distant recurrence rates between a 7w and 11w interval. This result was expected as the pathological results were similar in the 2 groups.¹² However, previous works observed an increase in local recurrences for patient undergoing resection before 7 weeks (10.5% vs 1.2%, $P = 0.04$ ²³ and 12.9% vs 4.8%, $P = 0.025$).²⁴ Tulchinsky reported more distant metastasis also in the group undergoing resection before 7 weeks (19% vs 6%, $P = 0.02$).²⁵ Our rate of 7.9% of local recurrence is higher than recent publications of trials on laparoscopic rectal resection.^{26,27} However, in these trials, only the 2 years rates are given, 17% of included patients had upper third rectal cancer and T4 were excluded. These differences explain that with patients with more advanced and lower rectal cancers, we observed more frequent local recurrences. The worse quality of mesorectal excision observed in the GRECCAR6 trial did not translate into a worse oncological prognosis as seen by Quirke et al.²⁸ However, he included only 42% with neoadjuvant radiotherapy whereas all patients in the GRECCAR6 trial have been irradiated. Moreover, the interpretation of the multivariate analysis of risk factor of local recurrence should be taken with caution. Indeed, with only 18 events, it may be underpowered. Some authors found invaded lymph nodes as risk factors of local recurrence,²⁹ but the majority of publications identified also an invaded CRM or the plane of mesorectal excision.³⁰

As already observed by several authors, patients with a pCR undergoing a rectal resection have an excellent prognosis. Araujo et al³¹ compared 69 pCR specimens to 42 clinical complete responders treated by simple surveillance. They have shown a 1.4% local recurrence and a 10.5% distant recurrence rate in the pCR group. More recently, Marco et al³² observed excellent oncological outcomes in the phase II trial comparing different regimens of consolidation chemotherapy during the waiting period in 58 pCR patients (5-years OS: 98%, 5-years DFS: 94%).

The present study examined the impact of the waiting period in two groups based on the response to radiotherapy. As 89% of the included patients had a mrT3-T4 at initial stage, we defined the group of good responders as patients with a ypT0-T2 tumors. Interestingly, we did not observe any effect of the waiting period on the DFS. This

may be explained by the fact that the tumoral response is observed during the first 7 to 8 weeks as shown by the similar pTNM stage in both groups. No advantage was encountered in delaying the interval from RCT to surgery in the present study, even when tumor response was assessed. The number of patients in each subgroup is low and this study may be underpowered to observe a worse impact for patients with a bad response to radiotherapy with a longer waiting period. Indeed, early adjuvant chemotherapy may have a favorable effect on their DFS. We await the 5-year follow-up of the GRECCAR-6 trial to confirm this hypothesis.

Finally, we looked at the role of restaging MRI that may aid in patient selection according to the tumoral response and stratify patients into the appropriate waiting period. Although a second MRI was not mandatory in the present trial,¹⁴ 151 patients with almost similar initial characteristics had this examination allowing comparison. The MRI was performed between the 5th and 6th weeks following radiotherapy. No effect of the waiting period was observed, although a trend toward a worse DFS was seen for bad responders operated at 11 weeks (66.9% vs 78%). For good radiological responders, no benefit to the existing response was expected with a longer waiting period. For bad radiological responders, either a tumoral regrowth or persistence and absence of adjuvant chemotherapy may be responsible for a worse DFS as observed in the present trial with a reduction of 12% of the DFS. This observation should be confirmed in other trials. We did not have the mrTRG in the present study as described by Patel et al³³ and therefore we used another radiological marker of tumoral response.

Use of adjuvant chemotherapy was limited to patients with positive lymph nodes or R1 resection as recommended by the French guidelines.¹⁶ We observed a favorable effect for the DFS in the subgroup of patients with positive lymph nodes. Only 26.5% of our cohort received adjuvant chemotherapy. This observation limits the comparison with the trial of Marco et al on lengthening the waiting period and adding consolidation therapy as almost 100% of their patients received at least 1 cycle of chemotherapy either before and/or after surgery. In their phase II study, DFS was improved with the lengthening of the waiting period ($P = 0.004$); however, this was associated with the addition of 2 to 6 cycles of FOLFOX before surgery. Five-year DFS was around 80% which is higher than in the present study (3-years DFS: 67.7%). We still need a randomized control trial to confirm that consolidation

chemotherapy improves the tumoral response and DFS and not the period of waiting alone.

We have to report some limitations in this study. First, the oncological outcomes were secondary endpoints and therefore the number of patients included was calculated only for the pCR rates. Second, as previously published in the previous article, some patients (20%) were operated before or after the planned date. However, as the pCR rate was also not different in the per-protocol analysis, it is unlikely that the oncological outcomes should change in this subgroup of patients.

In conclusion, all the findings of the GRECCAR-6 trial confirm that once a 7- to 8-week delay after radiotherapy has been achieved, the majority of the tumoral response has been obtained and no benefit is expected for patients, even good responders on restaging MRI. Delaying the interval between RCT and surgery has no influence on 3-year OS or DFS in the present randomized control trial.

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REFERENCES

- Petrelli F, Sgroi G, Sarti E, et al. Increasing the interval between neoadjuvant chemoradiotherapy and surgery in rectal cancer: a meta-analysis of published studies. *Ann Surg*. 2016;263:458–464.
- Gerard JP, Azria D, Gourgou-Bourgade S, et al. Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. *J Clin Oncol*. 2012;30:4558–4565.
- van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol*. 2011;12:575–582.
- Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol*. 2012;30:1926–1933.
- Lefevre JH, Mineur L, Kotti S, et al. Effect of Interval (7 or 11 weeks) Between Neoadjuvant Radiochemotherapy and Surgery on Complete Pathologic Response in Rectal Cancer: A Multicenter, Randomized, Controlled Trial (GRECCAR-6). *J Clin Oncol*. 2016;34:3773–3780.
- Capirci C, Valentini V, Cionini L, et al. Prognostic value of pathologic complete response after neoadjuvant therapy in locally advanced rectal cancer: long-term analysis of 566 ypCR patients. *Int J Radiat Oncol Biol Phys*. 2008;72:99–107.
- Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol*. 2010;11:835–844.
- Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Ann Surg*. 2004;240:711–717. discussion 717–8.
- Rullier E, Rouanet P, Tuech JJ, et al. Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial. *Lancet*. 2017;390:469–479.
- Garcia-Aguilar J, Renfro LA, Chow OS, et al. Organ preservation for clinical T2N0 distal rectal cancer using neoadjuvant chemoradiotherapy and local excision (ACOSOG Z6041): results of an open-label, single-arm, multi-institutional, phase 2 trial. *Lancet Oncol*. 2015;16:1537–1546.
- Lefevre JH, Parc Y, Tiet E, et al. Increasing the interval between neoadjuvant chemoradiotherapy and surgery in rectal cancer. *Ann Surg*. 2015;262:e116.
- Lefevre JH, Mineur L, Kotti S, et al. Effect of interval (7 or 11 weeks) between neoadjuvant radiochemotherapy and surgery on complete pathologic response in rectal cancer: a multicenter, randomized, controlled trial (GRECCAR-6). *J Clin Oncol*. 2016;34:3773–3780.
- Schaue D, McBride WH. Opportunities and challenges of radiotherapy for treating cancer. *Nat Rev Clin Oncol*. 2015;12:527–540.
- Lefevre JH, Rousseau A, Svrcek M, et al. A multicentric randomized controlled trial on the impact of lengthening the interval between neoadjuvant radiochemotherapy and surgery on complete pathological response in rectal cancer (GRECCAR-6 trial): rationale and design. *BMC Cancer*. 2013;13:417.
- Rullier A, Laurent C. [Recommendations for clinical practice. Therapeutic choices for rectal cancer. What quality criteria are important for surgical excision of rectal cancer?]. *Gastroenterol Clin Biol*. 2007;31:1S34–51. 1S91–5.
- Lakkis Z, Manceau G, Bridoux V, et al. Management of rectal cancer: the 2016 French guidelines. *Colorectal Dis*. 2017;19:115–122.
- Francois Y, Nemoz CJ, Baulieux J, et al. Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. *J Clin Oncol*. 1999;17:2396.
- Glehen O, Chapet O, Adham M, et al. Long-term results of the Lyons R90-01 randomized trial of preoperative radiotherapy with delayed surgery and its effect on sphincter-saving surgery in rectal cancer. *Br J Surg*. 2003;90:996–998.
- Cotte E, Passot G, Decullier E, et al. Pathologic response, when increased by longer interval, is a marker but not the cause of good prognosis in rectal cancer: 17-year follow-up of the Lyon r90-01 randomized trial. *Int J Radiat Oncol Biol Phys*. 2016;94:544–553.
- Du D, Su Z, Wang D, et al. Optimal interval to surgery after neoadjuvant chemoradiotherapy in rectal cancer: a systematic review and meta-analysis. *Clin Colorectal Cancer*. 2018;17:13–24.
- Probst CP, Becerra AZ, Aquina CT, et al. Extended intervals after neoadjuvant therapy in locally advanced rectal cancer: the key to improved tumor response and potential organ preservation. *J Am Coll Surg*. 2015;221:430–440.
- Wang XJ, Zheng ZR, Chi P, et al. Effect of interval between neoadjuvant chemoradiotherapy and surgery on oncological outcome for rectal cancer: a systematic review and meta-analysis. *Gastroenterol Res Pract*. 2016;2016:6756859.
- de Campos-Lobato LF, Geisler DP, da Luz Moreira A, et al. Neoadjuvant therapy for rectal cancer: the impact of longer interval between chemotherapy and surgery. *J Gastrointest Surg*. 2011;15:444–450.
- Zeng WG, Zhou ZX, Liang JW, et al. Impact of interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer on surgical and oncologic outcome. *J Surg Oncol*. 2014;110:463–467.
- Tulchinsky H, Shmueli E, Figer A, et al. An interval >7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer. *Ann Surg Oncol*. 2008;15:2661–2667.
- Stevenson ARL, Solomon MJ, Brown CSB, et al. Disease-free survival and local recurrence after laparoscopic-assisted resection or open resection for rectal cancer: the australasian laparoscopic cancer of the rectum randomized clinical trial. *Ann Surg*. 2019;269:596–602.
- Fleshman J, Branda ME, Sargent DJ, et al. Disease-free survival and local recurrence for laparoscopic resection compared with open resection of stage II to III rectal cancer: follow-up results of the ACOSOG Z6051 randomized controlled trial. *Ann Surg*. 2019;269:589–595.
- Quirke P, Steele R, Monson J, et al. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *Lancet*. 2009;373:821–828.
- Hida K, Okamura R, Park SY, et al. A new prediction model for local recurrence after curative rectal cancer surgery: development and validation as an asian collaborative study. *Dis Colon Rectum*. 2017;60:1168–1174.
- Gietelink L, Wouters MW, Tanis PJ, et al. Reduced circumferential resection margin involvement in rectal cancer surgery: results of the dutch surgical colorectal audit. *J Natl Compr Canc Netw*. 2015;13:1111–1119.
- Araujo RO, Valadao M, Borges D, et al. Nonoperative management of rectal cancer after chemoradiation opposed to resection after complete clinical response. A comparative study. *Eur J Surg Oncol*. 2015;41:1456–1463.
- Marco MR, Zhou L, Patil S, et al. Consolidation mFOLFOX6 chemotherapy after chemoradiotherapy improves survival in patients with locally advanced rectal cancer: final results of a multicenter phase II trial. *Dis Colon Rectum*. 2018;61:1146–1155.
- Patel UB, Taylor F, Blomqvist L, et al. Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience. *J Clin Oncol*. 2011;29:3753–3760.

DISCUSSANTS

Miguel R. Pera (Barcelona, Spain):

Thank you, Dr. Lefevre, for the clear presentation of the long-term results of the GRECCAR-6 study. This is a well-designed randomized controlled trial, which provides level-1 evidence on the effect of the interval between the end of neoadjuvant therapy and surgery (7 weeks vs 11 weeks) on the oncological outcome. I have several questions concerning some points needing clarification.

First, adjuvant chemotherapy was given to only 67 patients (26.5%). This is a very low number, particularly when we bear in mind that patients with T3/T4 or N+ tumors of the mid or lower rectum were included. Could you please comment on this fact as well as its possible effect on the reported outcomes?

Second, one of the strongest predictors of local recurrence is a positive circumferential resection margin. However, the multivariate analysis showed that local recurrences were independently influenced by positive lymph nodes, but not by a positive CRM. Could you explain this finding?

Finally, the analysis of the effect of restaging MRI is interesting because it might aid in patient selection based on tumor response and in stratifying them into the appropriate waiting period. Unfortunately, restaging was performed in <60% of patients, comprising of a selection bias. It is likely that restaging was performed in patients with more locally advanced tumors. For this reason, could you please comment on the real value of this analysis?

Again, your group must be commended for this important work. I would like to thank the Association for the privilege of being the first discussant.

Response From Jérémie H. Lefèvre (Paris, France):

Thank you very much. With regards to adjuvant chemotherapy, it was not mandatory in the trial, as the indications for adjuvant chemotherapy were not strict according to the French guidelines at the time. It was proposed for patients with invaded lymph nodes. Moreover, regarding the T stage, there was no clear indication to give chemotherapy. That's why only 26% of the patients had chemotherapy. If you look at the patients with invaded lymph nodes, three-fourth of them had adjuvant chemotherapy, which is a main indication, as it is in colon surgery. It was a bad prognostic factor to have adjuvant chemotherapy because it was mainly given to N+ patients. In the patients with positive lymph nodes, absence of adjuvant chemotherapy decreased the DFS from 49% to 26%. So, there is a clear beneficial effect of chemotherapy in the case of invaded lymph nodes.

Concerning the CRM, I agree with you. Recently, a Japanese team published a study on 2000 cases of rectal cancers, and observed that local recurrences were influenced by invaded lymph nodes. CRM is usually a risk factor, but as we only had 18 local recurrences, I think that this is not so relevant and we are maybe underpowered.

That's why we only showed the multivariate analysis on the DFS. However, I agree with you.

Concerning the restaging MRI, the characteristics of our 148 patients are almost similar to those of the overall cohort. So, I think that it is sufficient to rely on these data. We still need more data on restaging MRI, especially as we did not have a clear score of MRI restaging after radiochemotherapy at the time of the protocol. However, I think that this can serve as a tool to give proper treatment for patients. If you are in a rectal-sparing strategy and you have a very good response, you can maybe wait longer. However, if you go for a TME because you're, for instance, outside of the GRECCAR-2 trial criteria and you don't want to do rectal-sparing, even if you're a good response, I think you should go for surgery upfront within 7 to 8 weeks. If you have a very bad response on restaging MRI, you should go for something else. I think that there is, perhaps, a place for chemotherapy during the waiting period. However, it is still a work in progress, and I think that these data should serve as a tool for new trials for the role of restaging MRI.

Norbert Senninger (Münster, Germany):

Thank you for your presentation. Please allow me to raise 2 critical questions. First, looking at the hospitals involved, which are all very respected hospitals, each featuring 11 patients per in 30 months. So, this raises the question of whether there was an uneven distribution of the contribution of the centers. Perhaps, one was doing 200 and the others were doing 2 or 3. If there is a significant exclusion rate, why did you not take the patients into account? Perhaps, you cannot draw the conclusions you have drawn.

Second, you said that these are data spanning a period of 3 years, and that the mean follow-up is 32 ± 8 months, which means that some patients were only followed for 24 months. So, it's the actuarial curve. It's not the observed curve. And, we all know that before drawing 2 big conclusions, we have to have the observed curve. So, I would rather go for a 2-year observed curve than an actuarial 3-year curve.

Response From Jérémie H. Lefèvre (Paris, France):

Thank you. For the mean of inclusion of patients by center, it is true that it is 11. However, it is mainly because of the fact that 1 or 2 centers only included 1 patient, and the rest of the teams included a huge proportion of their patients. It's always like that in a multicentric randomized trial. Some teams only included 1 patient, and it is impossible to exclude the team thereafter.

Concerning the 2 years of follow-up results, we of course had them. They were similar, except that we had significantly more local recurrences in the 11 weeks' group. The 2 years' follow-up has so far given results similar to the 3 years' follow-up. However, we are, of course, continuing to follow the patients, even if some have been lost to follow-up, as is the case in every randomized control trial with an oncological purpose. We will definitely present the 5 years' final results of this trial.