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ORIGINAL CONTRIBUTION

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

Running head: oncological impact of interval after radio-chemotherapy.

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ABSTRACT

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 non-metastatic mid or lower cT3-4 or TxN+ rectal adenocarcinoma who had received radio-chemotherapy (45 to 50 Gy with fluorouracil or capecitabine).

INTERVENTION: Patients were randomly assigned to undergo total mesorectal excision either 7 weeks (W7) or 11 weeks (W11) after radiochemotherapy.

MAIN OUTCOMES MEASURES: Overall survival and disease-free survival at 5 years of 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 as they did not undergo resection. Among 253 patients analyzed, 5-year overall survival was not different between the two groups (81.6% in 7-week group versus 82.6% in 11-week group, $p = 0.827$), as well as for the 5-year disease-free survival (70.4% in 7-week group versus 69.5% in 11-week group, $p = 0.856$). No difference was observed between the two groups for distant recurrence (27.4% in 7-week group versus 25.7% in 11-week group, $p = 0.777$) or local recurrence (8.4% in 7-weeks group versus 10.2% in 11-week group, $p = 0.543$). Low anterior resection syndrome score was similar between the 7-week (25.0 IQR [15.0-34.0]) and 11-week groups (23.0 IQR[14.2-32.0], $p = 0.743$).

LIMITATIONS: The response rate to the LARS questionnaire was only 52%.

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

Spanish abstract

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

INTRODUCTION

For decades, long course neoadjuvant radiochemotherapy (RCT) has been a gold 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 has proven to reduce significantly the risk of for 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. Beside a small tumor, an extended waiting period between the end of RCT and the rectal resection was suspected to be a relevant factor to improve 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 good initial response, the surgeon may prefer to wait longer. Secondly, in some publications a chemotherapy was added during the waiting period. Thirdly, the waiting period was wide between studies ranging from 4 weeks to 16 weeks. To avoid these limitations, a randomized trial was conducted by the GRECCAR to assess the impact of a 4 weeks longer waiting period (GRECCAR-6).[11] Two hundred sixty-five patients with a locally advanced rectal cancer were randomized after completion of the RCT between a 7 weeks or 11 weeks 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 two groups (W7: 15%; W11: 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 the survival.[13] Interestingly, post-hoc analysis of the FORWARC trial, which consisted in a randomization between long and short time interval between RCT and surgery in 157 patients did not show any difference in the pCR rate.[14] The early oncological results of the GRECCAR6 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. The aim of this study was to report the long-term outcomes of the GRECCAR 6 trial, including oncological outcomes and also to assess the functional results with the risk of low anterior resection syndrome (LARS) when the bowel continuity can be preserved.

MATERIAL 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 endoultrasound) of the mid or lower rectum who had received RCT (45-50 Gy with intravenous 5-FU or capecitabine) were included. The exclusion criteria consisted of patients <18 years of age, patients with upper-third rectal cancer, rectal cancer with synchronous metastasis, patients who did not receive the complete RCT regimen, a previous history of neoplasia (except cutaneous cancer) within the last 5 years, and patients under guardianship or subject to legal protection.

Protocol

Following RCT, patients were randomized in a 1:1 ratio between a 7 week (± 5-day latency) or a 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 exclusion of patients who did not have a TME after the RCT, all randomized patients were included in the modified intent-to-treat (mITT) analysis, whether the timing of their randomization group was respected or not. In the per-protocol analysis (PP) only patients who were operated in the exact timeframe of the randomized group were considered. Adjuvant chemotherapy was given according to the MDM 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 upon which the sample size calculation was done.[11,12] It was planned to include at least 264 patients to detect a difference of at least 14% in pCR occurrence between the two groups (two-sided test with an alpha risk of 0.05 and a power of 80%, with a dropout rate of 10%). Secondary endpoints included overall survival (OS) and disease-free survival (DFS) along with the rate of local and distant recurrence at 5 years of 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 >50%.

Postoperative complications were defined by 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 nasogastric tube, 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 endpoint was the LARS score[16] 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 months +/- 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 three 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. Categorial data were reported as frequencies and percentages and compared with the Pearson chi square test or Fisher's exact test if the validity conditions were not fulfilled. Quantitative data were expressed as medians and interquartile range [IQR] and compared using the Mann-Whitney U test. This test was also used for the comparison of ordinal data. Median of 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 define as the time from randomization until the first recurrence or death or last follow-up. Patients who did not experience any event and still alive at 60 months were right censored at this time. Survival curves were plotted using the Kaplan–Meier method. Log-rank test was used to compare survival curves. All tests were two-sided. A p value of <0.05 was considered statistically significant. All analyses were performed using the R Software version 4.2.3 (R Core Team, Austria).

RESULTS

Population

A total of 265 patients from 24 participating centers were included between the November 2011 and February 2015, 133 were randomized in the W7 group (50.2%) and 132 in the W11 group (49.8%). The main characteristics of the patients as the post-operative outcomes and pathology are given in Table 1. After excluding 12 patients who did not undergo TME after the RCT (Fig. 1), 253 patients had a rectal resection with TME (mITT group). Among them, 201 (79.4%) were operated in the exact timeframe of the randomized group (PP group). In the W7 group, 26% of patients had surgery outside the exact timeframe (32/125) versus 16% in the W11 group (20/128, p = 0.05). Only one 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 timeframe of the W11 group.

Overall and Disease-Free Survival

After a median follow-up of 59.5 months, 41 (16.2%) patients have died. Five-year OS was 82.1% (95% CI: 77.3-87.3). There was no statistical difference regarding OS between the two 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 two 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 two 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); $p = 0.389$) (Supplementary 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. 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 two groups for distant recurrence nor for local recurrence ($p = 0.432$ and $p = 0.389$, respectively, Supplementary 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 as good responders (40%) and 88 patients as 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,

Supplementary 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 has 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 Supplementary 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 stoma. Among the 253 patients, 54 patients were not eligible to a LARS score assessment (26 patients had an abdominoperineal resection with a definitive stoma, 11 died in the 2 years following the surgery and 19 had a stoma). Among the 197 patients eligible to a LARS score assessment, 103 patients have answered to the questionary (52%) after a median time interval following the surgery of 24.3 months (IQR: 23.6-25.7). Among eligible patients, responder was comparable to nonresponder patients to LARS questionnaire in terms of demographic data, randomization group (W7 versus W7), post-operative morbidity, and adjuvant chemotherapy (Supplementary Table 1 at http://links.lww.com/DCR/C417). Median value of LARS score in the entire cohort was 23.0 (IQR: 14.5-33.0). No LARS was found in 45 patients (44%), 21 patients had a minor LARS (20%) and 37 patients a major LARS (36%). Patients with major LARS were comparable in the two groups (supplementary Table 2 at http://links.lww.com/DCR/C418). Patients in the W7 group had a 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 weeks 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 reported either an oncological advantage in extending this interval,[17] or 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 or not to pursue an organ preservation strategy. These factors undermine the robustness of the results on the impact of the interval. It is noteworthy that the vast majority of published studies on this subject are retrospective and included in meta-analysis without separately analyzing the results of prospective randomized trials.[9,10] Only one 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 randomized to an interval between 4 to 8 weeks versus 8 to 12 weeks, slightly differing from our study where we compared 7 weeks (± 5-day latency) to 11 weeks (± 5-day latency). In this other study, Akgun *et al.* found a significant increase in the pCR rate in the long interval group,[19] 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 al.* demonstrate equivalent 5-year OS and DFS between short and long interval groups, despite a benefit in distant recurrence with the long interval.[20] This lack of benefit from extending the time interval on OS and DFS is confirmed by our results. The two phase III randomized controlled trials on this question are therefore in agreement on this major outcome.

We explored the role of re-staging MRI to determine if this exam may help to stratify patients into the appropriate time interval according to the tumoral response. While 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 re-staging 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 re-staging MRI exhibited comparable OS and DFS (see Supplementary Fig. 3 at http://links.lww.com/DCR/C415). Additionally, 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 partly explained by the limited performance of the restaging MRI in assessing tumor response that will be find 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 following rectal resection.[25] In 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 to 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 postsurgical 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 following a watch and wait strategy, so after a long period of time from the RCT, which showed equivalent functional outcomes to those of patients operated immediately after RCT.[27]

Our study has several limitations. Firstly, oncological and functional outcomes were considered as secondary endpoints, and consequently, the calculation of the patient number was not based on these outcomes. Secondly, the LARS score only partially reflects long-term functional results and does not encompass all aspects of digestive function. Additionally, we did not assess sexual function, urinary function, and 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] Lastly, the response rate to the LARS questionnaire was 52%.

With 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 (50Gy with capecitabine) and the TME 6-8 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 FOLFOX without radiotherapy has been established, providing a choice between the two 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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LEGENDS

Figure 1: CONSORT diagram of the GRECCAR6 trial.

Figure 2: Overall survival (1-A) and disease-free survival (1-B) between W7 and W11 subgroups (intent-to-treat analysis).

Figure 3: Local (1-A) and distant recurrences (1-B) between W7 and W11 subgroups (intent-to-treat analysis).

Figure 4: Overall survival (1-A) and disease-free survival (1-B) between W7 and W11 subgroups among bad MRI responders patients (intent-to-treat analysis).

Table 1: Main population, 7 weeks and 11 weeks groups characteristics

Variables	Overall[1] N=265	W7 group[1] N=133	W11 group[1] N=132	P-value
Age (years)	64.2 (56.5-69.7)	64.5 (57.8-69.3)	63.3 (55.4-70.0)	*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+	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)	
Post-operative 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)	

Variables	Overall[1] N=265	W7 group[1] N=133	W11 group[1] N=132	P-value
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)	

[1]Median (25%-75%); n/N (%)

Table 2: LARS score 2-year after the anterior resection between W7 and W11 patients.

Variables	Overall[1] N=103	W7[1] N=49	W11[1] N=54	p-value[2]
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)	
More than 7 times per day	3/103 (2.9)	0/49 (0)	3/54 (5.6)	

Variables	Overall[1] N=103	W7[1] N=49	W11[1] N=54	p-value[2]
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 one hour 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)	

[1] Median (25%-75%); n/N (%)

[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Figure 1

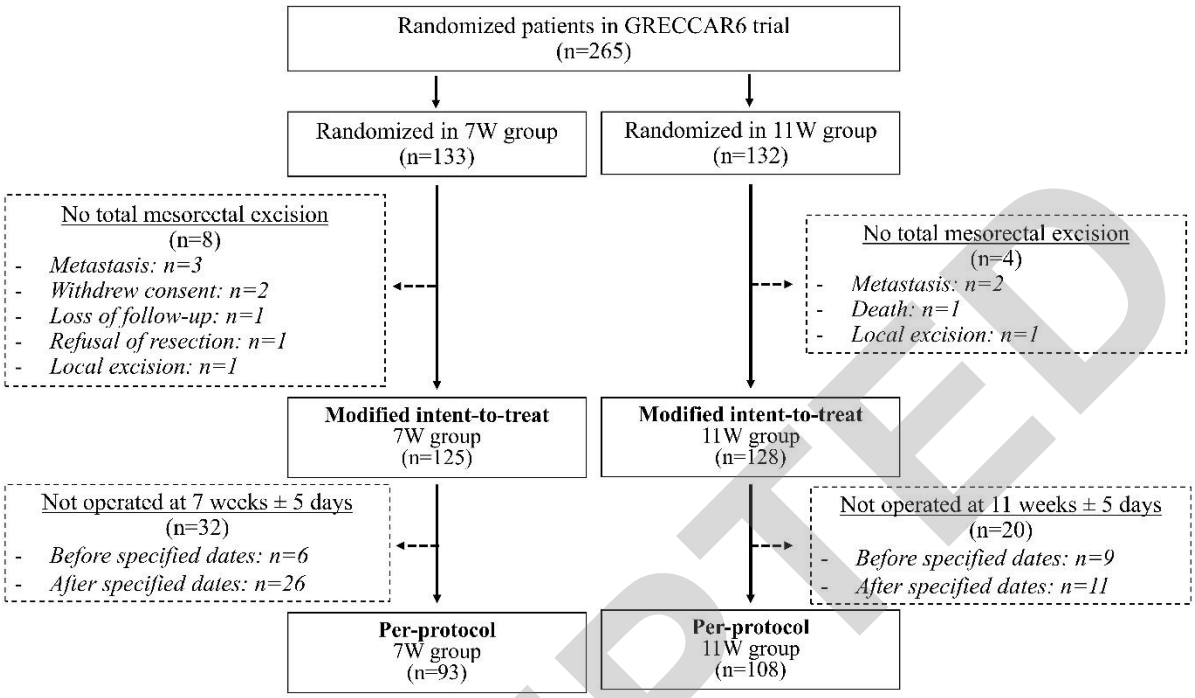

Figure 2

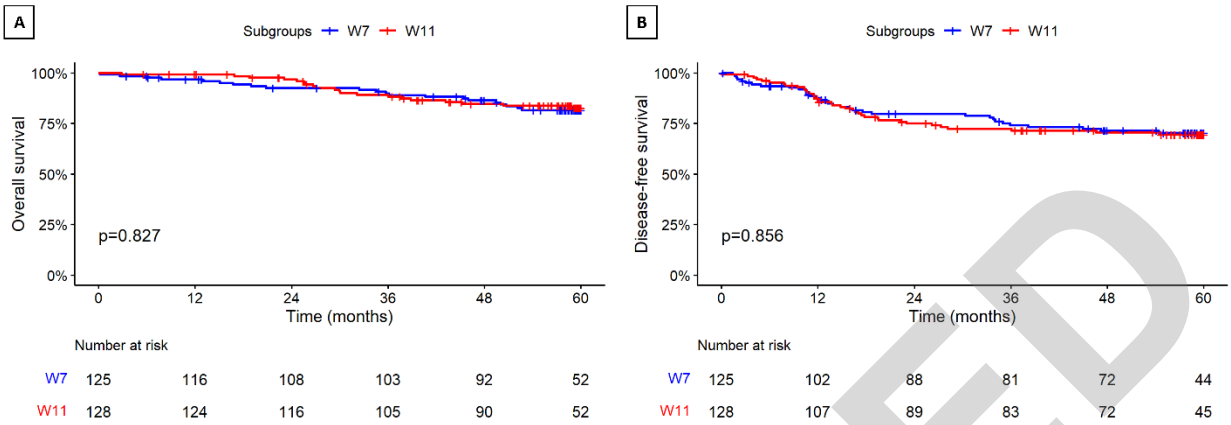

Figure 3

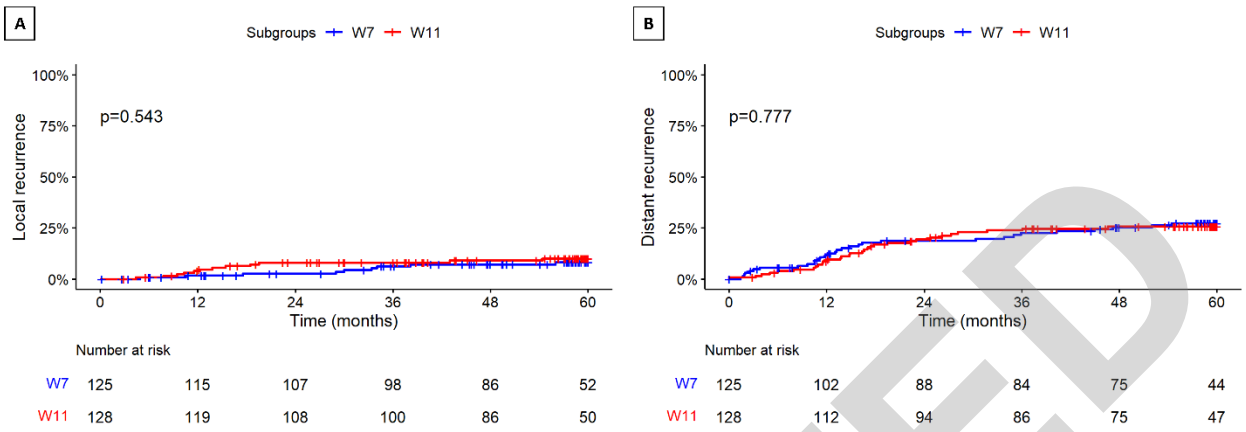

Figure 4