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Impact of Dose-Escalated Chemoradiation on Quality of Life in Patients With Locally Advanced Rectal Cancer: 2-Year Follow-Up of the Randomized RECTAL-BOOST Trial

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Purpose: Dose-escalated chemoradiation (CRT) for locally advanced rectal cancer did not result in higher complete response rates but initiated more tumor regression in the randomized RECTAL-BOOST trial (Clinicaltrials.gov NCT01951521). This study compared patient reported outcomes between patients who received dose-escalated CRT (5 × 3 gray boost + CRT) or standard CRT for 2 years after randomization.

Methods and Materials: Patients with locally advanced rectal cancer who were participating in the RECTAL-BOOST trial filled out European Organisation for Research and Treatment of Cancer QLQ-C30 and CR29 questionnaires on quality of life (QoL) and symptoms at baseline, 3, 6, 12, 18, and 24 months after start of treatment. Between-group differences in functional QoL domains were estimated using a linear mixed-effects model and expressed as effect size (ES). Symptom scores were compared using Mann-Whitney *U* test.

Results: Patients treated with dose−escalated CRT (boost group, n = 51) experienced a significantly stronger decline in global health at 3 and 6 months (ES −0.4 and ES −0.4), physical functioning at 6 months (ES −1.1), role functioning at 3 and 6 months (ES −0.8 and ES −0.6), and social functioning at 6 months (ES −0.6), compared with patients treated with standard CRT (control group, n = 64). The boost group reported significantly more fatigue at 3 and 6 months (83% vs 66% respectively 89% vs 76%), pain at 3 and 6 months (67% vs 36% respectively 80% vs 44%), and diarrhea at 3 months (45% vs 29%) compared

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M.E. Verweij is responsible for statistical analysis in this study.

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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with the control group. From 12 months onwards, QoL and symptoms were similar between groups, apart from more blood/mucus in stool in the boost group.

Conclusions: In patients with locally advanced rectal cancer, dose-escalated CRT resulted in a transient deterioration in global health, physical, role, and social functioning and more pain, fatigue and diarrhea at 3 and 6 months after start of treatment compared with standard CRT. From 12 months onwards, the effect of dose-escalated CRT on QoL largely resolved.

Locally advanced rectal cancer (LARC) is treated with chemoradiation (CRT) followed by total mesorectal excision (TME).[1,2] Neoadjuvant CRT, which entails radiation therapy of 50 gray (Gy) in 25 fractions with concurrent fluoropyrimidine-based chemotherapy, is administered to facilitate surgery with a clear resection margin and to reduce the risk of local recurrence.[3] This multimodality approach results in 10-year overall survival of approximately 60%,[4,5] but is also associated with impaired quality of life (QoL) and side effects including bowel dysfunction, urinary incontinence, sexual complaints, and stoma-related problems.[6-10] QoL and functional outcomes might be improved by rectum-sparing treatments, such as local excision and active surveillance (also known as watch-and-wait [WW] strategy).[11-14] A WW strategy is feasible in patients with a clinical complete response (cCR) after neoadjuvant treatment.

The randomized RECTAL-BOOST trial investigated whether an additional 15 Gy radiation therapy boost before CRT (boost group) could improve the pathologic complete response (pCR) rate compared with standard CRT (control group) in LARC.[15] The trial did not result in a difference in complete response (36% vs 38%, P = .86), but did show significantly more tumor regression (Mandard 1-2) in the boost group compared with the control group (69% vs 45%, P = .02).[16] Based on this finding, dose-escalated CRT may become a neoadjuvant strategy enabling rectum-sparing treatment in selected rectal cancer patients.

After treatment with dose-escalated CRT, a substantial proportion of patients will experience additional toxicity without achieving cCR. Therefore, the probability of organ preservation needs to be weighed against the effect on QoL. Primary analysis of the RECTAL-BOOST trial showed a significantly lower QoL summary score in the boost group at 3 months after randomization (mean difference [MD] −7.5 [95% confidence interval (CI), −12.1 to −3.0]) and comparable scores at 6 and 12 months (MD −3.6 [95% CI, −8.3 to 1.0] respectively MD −0.6 [95% CI, −5.6 to 4.4]).[16] The current study further investigates the effect of dose-escalated CRT versus standard CRT on different QoL domains, symptoms, and functional outcome. Patient-reported outcomes (PROs) and disease-free survival (DFS) of LARC patients are compared for the first 2 years after the RECTAL-BOOST trial.

Methods and Materials

Patients and treatment

The design of the RECTAL-BOOST trial (Clinicaltrials.gov NCT01951521) has been described in detail.[15] In short, the RECTAL-BOOST trial was a nonblinded, phase II randomized controlled trial performed within a prospective cohort of colorectal cancer patients (Dutch Prospective Colorectal Cancer cohort, PLCRC), according to the Trials within Cohorts (TwiCs) design.[17,18] The RECTAL-BOOST trial was performed in the UMC Utrecht and the Maastro/MUMC+. The institutional review board of the UMC Utrecht approved PLCRC and the RECTAL-BOOST trial. Cohort participants with locally advanced tumors within 10 cm from the anorectal junction and a World Health Organization performance status 0 to 2, who consented to fill out questionnaires and who provided broad consent to randomization to future intervention studies, were eligible. Exclusion criteria were presence of inflammatory bowel disease, prior pelvic radiation therapy, contraindication for magnetic resonance imaging or capecitabine, pregnancy within the last year, and inadequate command of the Dutch language. Patients were allocated to either standard treatment, that is, either CRT that involved 50 Gy in 25 fractions of 2 Gy with concurrent capecitabine 825 mg/m^2 twice daily for 5 or 7 days per week (control group) or dose-escalated CRT including a radiation boost to the tumor of 15Gy in 5 fractions of 3 Gy without concurrent chemotherapy in the week before the start of CRT (boost group).[15,16] TME was performed at 12 weeks after completion of CRT. Several patients who achieved cCR entered active surveillance. Baseline patient, tumor, and treatment characteristics were collected within PLCRC.

Patient-reported outcomes

Patients filled out questionnaires before start of neoadjuvant therapy (baseline) and at 3, 6, 12, 18, and 24 months after start of treatment. Questionnaires were provided online or on paper and collected within the Patient Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship (PROFILES) platform.[19] QoL was assessed with the European Organisation for Research and Treatment of Cancer (EORTC) core and colorectal cancer specific QoL questionnaires (EORTC QLQ-C30 and QLQ-CR29).[20,21] EORTC QLQ-C30 includes a global health

score, 5 functional domains (physical, role, emotional, cognitive, and social functioning), and 9 cancer-related symptoms.[20] The EORTC QLQ-CR29 contains colorectal cancer-specific domains and symptoms.[21] Bowel function was measured with the low anterior resection syndrome (LARS) score in patients without an ostomy at the moment of sending the questionnaire (ie, patients after LARS with restored bowel continuity or on WW).[22] The LARS score contains 5 questions regarding incontinence for flatus, incontinence for liquid stool, stool frequency, re-evacuation, and urgency.

Oncological outcomes

Disease recurrence and survival were obtained from the electronic patient records and the municipality registry up to October 2020. Events for disease-free survival (DFS) included no resection of the tumor due to progression or the patient being unfit for surgery, macroscopic nonradical resection (R2) of the tumor, locoregional recurrence after radical resection of the primary tumor, distant metastatic disease, second primary cancer or death, whichever came first. A local regrowth during WW strategy that was manageable with curative salvage operation (R0 or R1) did not count as an event for DFS.[23]

Statistical analysis

The QoL questionnaires were transformed into scores between 0 and 100 according to their manuals.[21,24] A high score on global health or functional domains represents a high level of functioning or a high QoL. A high score on symptom scales represents a high level of complaints. Only the QoL domains and symptoms that were expected to be affected by dose-escalated CRT were analyzed. For the functional QoL domains, a linear mixed-effects model was applied with a random intercept, time (as factor), interaction between time and treatment, and an autoregressive covariance structure of the first order (assuming that the correlation systematically decreases with increasing distance between timepoints).[25] The estimates of the time and treatment interaction were presented as MD between the treatment groups at each time point with 95% CI. The outcomes were interpreted with the standardized ES, calculated as the MD divided by the pooled standard deviation of the baseline score. ES was categorized into "no change" (ES $<$ 0.2), "small change" (ES, 0.2-0.4), "moderate change" (ES, 0.5-0.7), and "considerable change" (ES $\geq$ 0.8).[26] Symptom scores were presented as proportion of patients experiencing no (0), mild (1-49), moderate (50-99), or severe (100) level of complaints and as MD. Symptom scores were compared using the Mann-Whitney *U* test, because a mixed model was too complex for our data. LARS questionnaires were processed to a weighted sum according to the manual, ranging from 0 to 42. This score is interpreted as "no LARS" (total score, 0-20), "minor LARS" (total score, 21-29), or "major LARS" (total score, 30-42). LARS scores were compared using Mann-Whitney *U* test.[22] Because the number of patients without a (temporary) ostomy at 3 and 6 months was low, LARS scores are presented at 12, 18, and 24 months after start of treatment. Overall survival and DFS times were calculated from start of radiation therapy. Survival probabilities were estimated with the Kaplan-Meier method and compared using log rank test.

Because dose-escalated CRT was expected to unfavorably affect QoL scores and symptoms, intention-to-treat analysis (ie, including patients who did not undergo the boost intervention in the intervention arm) would dilute the real effect estimate. The effect of dose-escalated CRT on PROs was therefore evaluated in the per protocol population, that is, among 64 patients in the control arm who received standard CRT and 51 (of the 64 patients) in the intervention arm who accepted and received dose-escalated CRT. In 2 sensitivity analyses, the mixed-effects model was reapplied to (1) a selection of patients of the per protocol population who were primarily treated with TME (ie, excluding WW and palliative treatment) and (2) the intention-to-treat population. Survival data were analyzed as intention-to-treat because patients who decline the intervention are, in general, more likely to have a worse baseline prognosis. For interpretation of QoL results, survival analyses were repeated in the per protocol population.

The level of significance was set at $P < .05$. Analyses were performed using SPSS Statistics version 25 (IBM) and RStudio version 1.1.442 (RStudio, Inc.).

Results

Between September 2014 and July 2018, 128 patients were included in the RECTAL-BOOST trial. A total of 51 (80%) of 64 patients who were randomized to the intervention group accepted and received the boost intervention (Appendix E1). Thirteen patients refused the intervention and underwent standard CRT. Sixty-four patients were randomized to the control group, and all underwent standard CRT.[16] Most patients were male in both the boost and the control group (75% and 74%, respectively) (Table 1). Median age was 64 and 62 years in the boost and the control group, respectively. Most tumors were located within 3 cm of the anorectal angle in both the boost and the control group (53% and 57%, respectively). The boost group included less cT4 tumors than the control group (18% and 31%, respectively). Patients in the boost group more often underwent low anterior resection (LAR) than patients in the control group (41% and 33%, respectively). Twenty-two percent of patients in the boost group and 14% in the control group entered WW strategy after CRT. At 2 years, 14% (n = 7) and 8% (n = 5) respectively had a sustained cCR.

Response rates for the QLQ-C30 and QLQ-CR29 questionnaires were 92% versus 86% at baseline and 85% versus 74% at 24 months for the boost group and the control group, respectively (Appendix E2). There was a larger decline in global health score, physical functioning, role

Table 1 Patient, tumor, and treatment characteristics of patients with locally advanced rectal cancer included in the per protocol study population of the RECTAL-BOOST trial

	Boost group N = 51	Control group N = 64
Age (y)	64 (26-75)	62 (37-80)
Sex		
Male	38 (74.5)	47 (73.4)
Tumor height*		
≤3.0 cm	27 (52.9)	36 (57.1)
3.1-5.0 cm	8 (15.7)	8 (12.7)
5.1-10.0cm	16 (31.4)	19 (30.2)
Clinical tumor stage		
cT2	2 (3.9)	5 (7.8)
cT3	40 (78.4)	39 (60.9)
cT4	9 (17.6)	20 (31.2)
Distance to the mesorectal fascia		
≤1 mm	33 (64.6)	46 (71.9)
Clinical nodal stage		
cN0	5 (9.8)	9 (14.1)
cN1	12 (23.5)	17 (26.6)
cN2	34 (66.7)	38 (59.4)
Clinical oligometastatic disease		
cM1	3 (5.9)	2 (3.1)
Tumor dose in Gray†	69.2 (54.1-71.3)	50 (49.4-51.5)
Treatment after chemoradiation		
Low anterior resection	21 (41.2)	21 (32.8)
Abdominoperineal resection	17 (33.3)	32 (50)
Watch-and-wait‡	11 (21.6)	9 (14.1)
Palliative systemic treatment	2 (3.9)	2 (3.1)

* Measured from the anorectal angle on sagittal magnetic resonance imaging.
† Mean dose (D95) to the planned target volume of the tumor.
‡ Includes 1 patient in the boost group who entered watch-and-wait after local excision.
Data are presented in number (%) or median [range].

functioning and social functioning in the boost group compared with the control group during the first year after start of treatment (Fig. 1). Based on a linear mixed-effects model, there was a significant between-group difference of small ES in global health at 3 and 6 months (ES −0.4 and ES −0.4, respectively), a considerable difference in physical functioning at 6 months (ES −1.1), a considerable and moderate difference in role functioning at 3 and 6 months (ES −0.8 and −0.6, respectively) and a moderate difference in social functioning at 6 months (ES −0.6) (Table 2). From 12 months onwards, there were no significant differences in functional QoL domains between groups. Sensitivity analysis of patients primarily treated with TME showed comparable results (Appendix E3). In the intention-to-treat population, there was a significant between-group difference of small ES in global health at 3 months (ES −0.4), a moderate difference in physical functioning at 6 months (ES −0.8) and a moderate difference in role functioning at 3 months (ES −0.7) (Appendix E4 and E5).

The boost group reported significantly more often fatigue at 3 (83% vs 66%) and 6 months (89% vs 76%), pain at 3 (67% vs 36%) and 6 months (80% vs 44%), and diarrhea at 3 months (45% vs 29%) compared with the control group. Blood or mucus in stool was more prevalent in the boost group at 6 months (42% vs 20%), 12 months (30% vs 14%), 18 months (23% vs 8%), and 24 months (28% vs 11%). There were no differences in terms of constipation, urinary frequency, or urinary incontinence (Fig. 2, Appendix E6).

Response rates for the LARS questionnaire in patients with bowel continuity at 12 to 24 months were 79% to 88% in the boost and 71% to 75% in the control group, respectively (Appendix E2). Major LARS was reported by 57% in the boost group versus 56% in the control group at 12 months ($P = .8$), 68% versus 58% at 18 months ($P = .9$), and 61% versus 47% at 24 months after start of treatment ($P = .5$, Fig. 3).

At 2 years after start of treatment, 5 of 64 patients in the boost group and 2 of 64 in the control group were deceased. Two-year overall survival was 92% [95% CI, 86-99] and 97% [95% CI, 93-100], respectively ($P = .3$, Appendix E7 and E8). Information on disease recurrence was not available for 1 patient in the boost group and for 2 in the control group. The proportion of patients who experienced an event for DFS at 2 years was 16 of 63 in the boost group and 13 of 62 in the control group. Among them, 1 patient in the boost group and 2 patients in the control group experienced locoregional disease recurrence; 11 and 8 patients, respectively, experienced distant metastatic disease. Two-year DFS was 75% [95% CI, 65-86] in the boost group and 80% [95% CI, 70-90] in the control group ($P = .9$). These results were consistent in the per-protocol population (Appendix E9).

Discussion

Dose-escalated CRT resulted in a significantly stronger decline of small ES in global health at 3 and 6 months, a considerable decline in physical functioning at 6 months, a considerable and moderate decline in role functioning at 3 and 6 months, and a moderate decline in social functioning at 6 months compared with standard CRT. Furthermore, patients treated with dose-escalated CRT reported more pain at 3 and 6 months, more fatigue at 3 and 6 months, and more diarrhea at 3 months. From 12 months onwards, patients treated with dose-escalated CRT reported similar QoL and symptoms as patients treated with standard CRT, apart from more complaints of blood and mucus in stool. Dose-escalated CRT did not influence DFS at 24 months.

Primary results of the RECTAL-BOOST trial showed comparable postoperative complications (26% vs 19%, $P = .5$) and comparable CTCAE grade ≥ 3 toxicity during

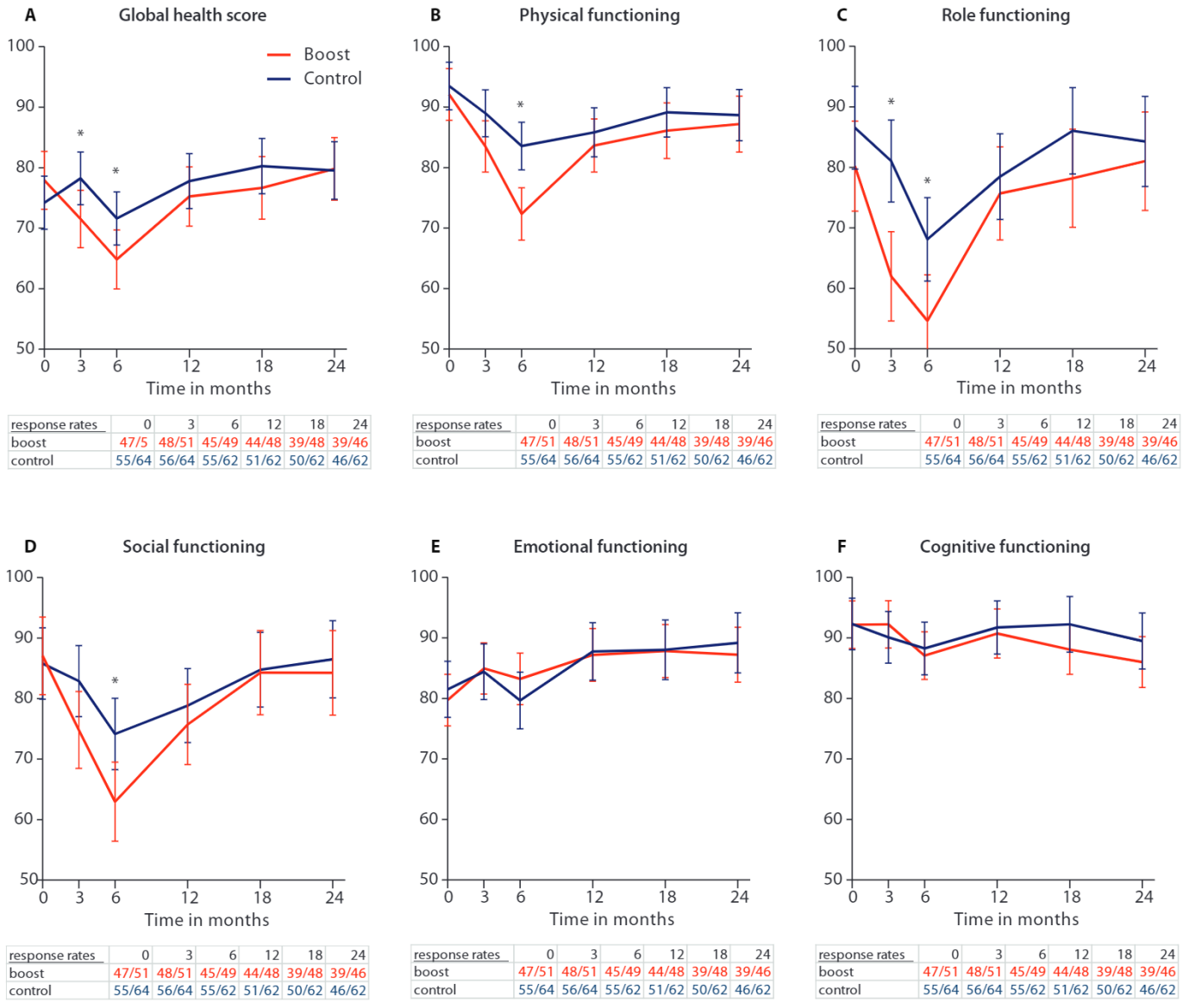


Fig. 1. QLQ-C30 functional quality-of-life domains measured at baseline and at 3, 6, 12, 18, and 24 months after start of treatment in patients treated with dose-escalated chemoradiation (boost group, red) and standard chemoradiation (control group, blue) in the per-protocol population. Scores are presented as means with 95% confidence interval. A higher score indicates better global health or better functioning. Significant between-group differences ($P < .05$), based on a linear mixed-effects model, are marked with an asterisk (*).

and 9 weeks after CRT (9% vs 8%, $P = .75$). Nonetheless, the current study with a focus on PROs found considerable effect of dose-escalated CRT on QoL and symptoms at 3 and 6 months after treatment. This effect remained consistent in sensitivity analysis, including only patients primarily treated with TME. Similar to our results, a previous observational study on QoL after rectal cancer treatment described deterioration in most QLQ-C30 functional domains within 6 months after start of neoadjuvant treatment, with worse deterioration after long-course CRT versus short-course radiation therapy.[27] Our findings underline the importance of collecting PROs in addition to physician reported outcomes such as postoperative complications and severe radiation toxicity, when evaluating a new intervention.

Dose-escalated CRT was administered in the RECTAL-BOOST trial with the aim to increase pCR, which has been suggested to be a surrogate marker for DFS.[28] Because pCR did not differ between groups, no difference in DFS was expected, which was confirmed in the current analysis. In line with our results, comparable DFS at 5 years after treatment was found in the INTERACT trial (preoperative capecitabine-based radiochemotherapy intensified by concomitant boost or oxaliplatin, for cT2 (distal)−cT3 rectal cancer), which compared dose-escalated CRT to chemo-

Table 2 Mean differences in EORTC QLQ-C30 functional quality-of-life domains between the boost and the control group (reference) over time in the per-protocol population.

		Baseline Mean (SD)	3 mo				6 mo				12 mo				18 mo				24 mo			
			MD	95% CI	ES	*P*	MD	95% CI	ES	*P*	MD	95% CI	ES	*P*	MD	95% C.I	ES	*P*	MD	95% C.I	ES	*P*
Global health score	*Control*	74.1 (18.8)	Ref.				Ref.				Ref.				Ref.				Ref.			
	Boost	78.0 (17.3)	−6.7	−13.0 to −0.4	−0.4	.037	−6.8	−13.2 to −0.3	−0.4	.039	−2.5	−9.1 to 4.0	−0.1	.450	−3.6	−10.3 to 3.1	−0.2	.295	0.3	−6.6;7.1	0.0	.935
Physical functioning	*Control*	93.2 (9.0)	Ref.				Ref.				Ref.				Ref.				Ref.			
	Boost	92.8 (11.9)	−5.5	−11.1 to 0.2	−0.4	.058	−11.2	−17.0 to −5.5	−1.1	.000	−2.2	−8.0 to 3.7	−0.2	.461	−3.0	−9.0 to 3.0	−0.3	.326	−1.5	−7.6 to 4.6	−0.1	.631
Role functioning	*Control*	86.4 (20.1)	Ref.				Ref.				Ref.				Ref.				Ref.			
	Boost	81.2 (25.2)	−19.0	−28.9 to −9.2	−0.8	.000	−13.5	−23.4 to −3.4	−0.6	.009	−2.8	−13.0 to 7.4	−0.1	.591	−7.8	−18.4 to 2.7	−0.3	.145	−3.3	−14.0 to 7.5	−0.1	.550
Social functioning	*Control*	85.2 (17.2)	Ref.				Ref.				Ref.				Ref.				Ref.			
	Boost	88.3 (18.0)	−8.1	−16.6 to 0.4	−0.5	.062	−11.2	−19.8 to −2.6	−0.6	.011	−3.1	−11.9 to 5.7	−0.2	.488	−0.5	−9.5 to 8.6	0.0	.919	−2.2	−11.4 to 7.0	−0.1	.637
Emotional functioning	*Control*	79.7 (18.3)	Ref.				Ref.				Ref.				Ref.				Ref.			
	Boost	82.4 (17.7)	−0.5	−6.7 to 5.6	0.0	.862	−3.6	−9.8 to 2.6	−0.2	.259	0.6	−5.7 to 6.9	0.0	.853	0.2	−6.3 to 6.7	0.0	.952	2.0	−4.6 to 8.5	0.1	.557
Cognitive functioning	*Control*	92.4 (12.8)	Ref.				Ref.				Ref.				Ref.				Ref.			
	Boost	93.3 (13.3)	−2.1	−7.8 to 3.5	−0.2	.457	1.2	−4.6 to 6.9	0.1	.691	1.0	−4.9 to 6.8	0.1	.740	4.2	−1.8 to 10.2	0.3	.171	3.5	−2.6 to 9.6	0.3	.263

Abbreviations: CI = confidence interval; ES = effect size; MD = mean difference; EORTC QLQ-C30 = European Organization for Research and Treatment for Cancer Quality of Life Core Questionnaire; SD = standard deviation.

Mean differences were interpreted with the standardized effect size, calculated as the mean difference divided by the pooled standard deviation of the mean quality-of-life score per domain at baseline. Significant between-group differences ($P < .05$), based on a linear mixed-effects model, are bolded.

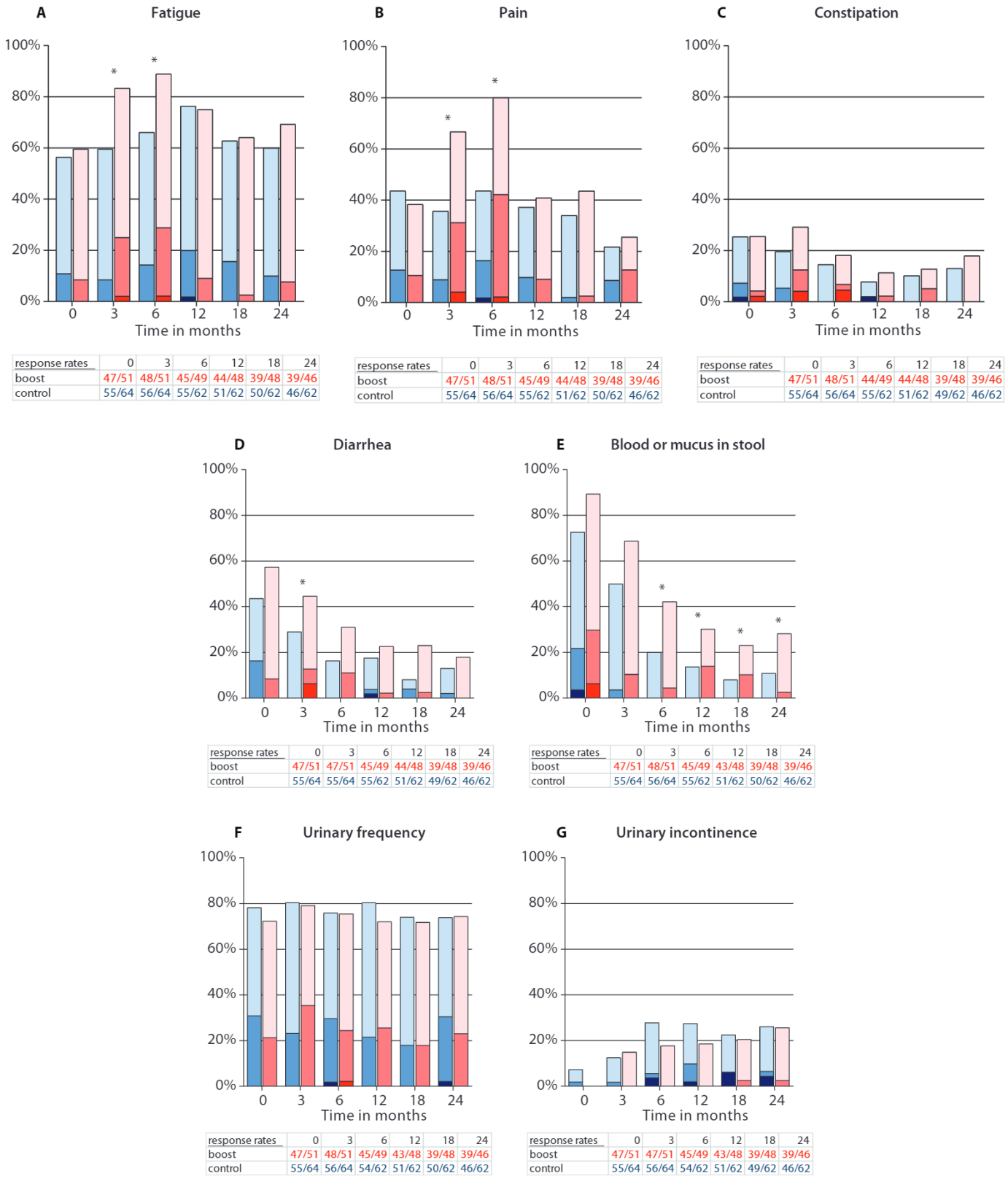
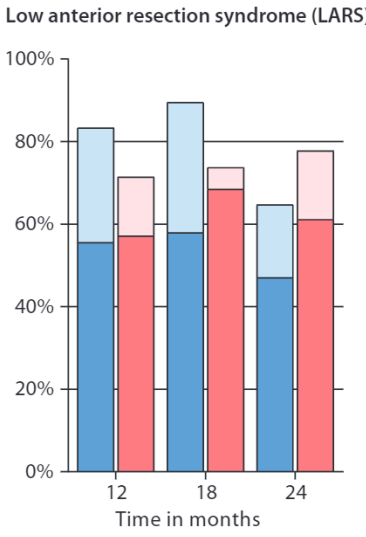


Fig. 2. Proportion of patients reporting symptoms after dose-escalated chemoradiation (boost group, red) and standard chemoradiation (control group, blue) in the per protocol population, as was measured with the quality-of -ife core and colorectal cancer-specific questionnaires (European Organisation for Research and Treatment of Cancer QLQ-C30 and -CR29) at baseline and at 3, 6, 12, 18, and 24 months after start of treatment. Symptom scores were categorized as no (0), mild (1-49), moderate (50-99), or severe (100) level of complaints. Significant between-group differences ($P < .05$), based on the Mann-Whitney U test, are marked with an asterisk (*).



response rates	12	18	24
boost	21/24	19/24	18/24
control	18/24	19/25	17/24

Fig. 3. Proportion of patients reporting minor and major bowel dysfunction after dose-escalated chemoradiation (boost group, red) and standard chemoradiation (control group, blue) as was measured by the low anterior resection syndrome score at 12, 18, and 24 months in patients in the per-protocol population with bowel continuity at the moment of sending the questionnaire.

intensified CRT (75% vs 74%, $P = .4$).[29] Experiencing disease recurrence can severely affect QoL.[30] However, we found no differences in DFS and, therefore, the differences in QoL and symptoms that we observed are not attributable to differences in disease recurrence.

Summarizing the previous and current RECTAL-BOOST results, a boost before CRT administered with conventional radiation therapy did not improve complete response rate nor 2-year DFS in LARC patients and resulted in a transient but considerable effect on QoL. This boost strategy is therefore not recommended. However, dose-escalated CRT initiated more tumor regression than standard CRT, suggesting that dose-escalation may have organ-preserving potential. In the RECTAL-BOOST trial, the minimum dose to the planned tumor volume was limited by nearby organs at risk and their surrounding margins.[16] Margins can be reduced by magnetic resonance-guided radiation therapy, a technique that offers high-precision radiation therapy through daily adaptation to the actual anatomy on magnetic resonance imaging.[31,32] Reduced margins offer better high-dose coverage of the tumor volume, which theoretically results in an increased chance on a complete response. Furthermore, radiation therapy with reduced treatment margins delivers a decreased dose to the surrounding healthy tissue, theoretically resulting in less radiation-induced toxicity. Clinical trials are needed to confirm whether magnetic resonance −guided dose-escalated chemoradiation therapy effectively increases probability of rectum-preserving treatment with acceptable effect on QoL and symptoms. Patients willing to participate in trials on dose-escalated chemoradiation therapy for rectal cancer should be counseled on the transient but considerable effect on QoL and symptoms.

Total neoadjuvant therapy, that is, addition of chemotherapy to standard 5-FU based CRT, could be an alternative neoadjuvant strategy enabling rectum-sparing treatment. A recent meta-analysis showed that addition of chemotherapy before or after CRT led to similar pCR rates, but intensification of chemotherapy during CRT led to significantly higher pCR rates compared with standard CRT.[33] Intensification of CRT by addition of oxaliplatin in the German CAIRO-4 trial (Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy for locally advanced rectal cancer) and ACCORD 12/0405-Prodige 2 (Comparison of Two Neoadjuvant Chemoradiotherapy Regimens for Locally Advanced Rectal Cancer) trial had limited effect on QoL after treatment, but increased grade ≥ 3 toxicity during treatment.[34,35]

Blood and/or mucus in stool was the only symptom that remained more prevalent in the boost than in the control group from 6 months onwards. In a phase II trial on high-dose chemoradiotherapy and watchful waiting for T2-3 distal rectal cancer, predominantly mild bleeding from the rectal mucosa also was the most common physician-related toxicity, with a prevalence of 78% beyond 1 year of treatment (n = 21 of 27).[36] Rectal bleeding is the main sign of radiation proctitis, which may occur in patients treated with LAR or in a WW strategy. Chronic radiation proctitis has been consistently associated with the volume of rectum receiving ≥ 60 Gy.[37] Bleeding occurs because of radiation-induced vessel damage, which causes ischemia and formation of new vessels that are prone to bleeding.[38] In most cases, the bleeding is mild and no treatment is required. For more severe cases, treatment that aims to protect the mucosa (eg, sucralfate enemas and oral metronidazole) or reduce ischemia (eg, hyperbaric oxygen) might mitigate the bleeding.[38,39] In our study population, 1 patient of the boost group received treatment with sucralfate enema for rectal bleeding.

When administering dose-escalated radiation therapy aiming for rectum-sparing treatment, it is important to protect bowel function.[12,40] A higher irradiation dose to the rectum and the anorectal complex has been associated with deteriorated anorectal function.[10,41] In our results, there was no indication for increased bowel dysfunction after dose-escalated CRT compared with standard CRT. Most patients with bowel continuity in both the boost and the control group reported major LARS at 12, 18, and 24 months after treatment, which is comparable to earlier studies that found approximately 65% major LARS among LARC patients treated with CRT and LAR.[12,42] Most cases of bowel dysfunction develop within the first 2 years after treatment.[43]

However, our data do not exclude increased late-onset LARS after dose-escalated CRT. In line with our results, the HERBERT study—a phase I dose-escalation study on a brachytherapy boost after external beam radiation therapy (EBRT) in rectal cancer patients unfit for surgery—found a significant increase in patient-reported bowel symptoms during EBRT and during brachytherapy until 2 weeks after end of treatment but similar patient-reported bowel symptoms to baseline at 2, 6, and 12 months after treatment.[44] Because bowel continuity was preserved in a low number of patients, our LARS data are based on small patient numbers and need to be interpreted with caution.

The RECTAL-BOOST was a pragmatic trial within PLCRC according to the TwiCs design, which has specific strengths and risks of bias. According to the TwiCs design, randomized trials are implemented within a cohort, which promotes efficiency and limits selective patient inclusion. A previous publication showed good comparability of the RECTAL-BOOST participants to LARC patients in the National Cancer Registry, supporting generalizability of our results.[45]

In TwiCs, like in classic randomized controlled trials, the effect of the intervention may be diluted when many patients do not receive the assigned treatment. In TwiCs, patients are given the option to refuse the experimental intervention, which may lead to more dilution in the intervention arm than in the control arm (where patients are unaware of being part of a trial and all undergo the standard treatment). In the RECTAL-BOOST trial, the intervention acceptance rate was reasonably high (n = 51 of 64, 80%). To prevent underestimation of the effect of dose-escalated CRT on QoL, per protocol analysis was performed for PRO comparison.

The RECTAL-BOOST trial was not blinded. Owing to the inherent subjective nature of PROs, QoL of the boost group could have been affected by patient perception of the treatment (ie, information bias).[46] Control patients were not notified of being in the control group, so PROs of the control group could not have been affected by information/disappointment bias.[47] The boost group may have expected more toxicity, which could have led to overestimation of the effect of dose-escalated CRT on QoL.

Despite randomization, a bigger proportion of patients had LAR (41% vs 33%) or a WW strategy (22% vs 14%), and a smaller proportion of patients had abdominoperineal resection (33% vs 50%) in the boost compared with the control group. Because abdominoperineal resection has been associated with a bigger (negative) effect on QoL than LAR, this imbalance could have led to underestimation of the effect of dose-escalated CRT on QoL.[48,49]

Lastly, the responses to the sexuality items of the EORTC CR-29 were too low to be presented. Those results would have been of interest because sexual dysfunction is a possible late toxicity of rectal cancer treatment.[8] Otherwise, our response rates were reasonably high. By applying a mixed model, only the few patients who replied to none of the questionnaires (n = 4 of 115, or 3% of the per protocol population) were excluded from PRO analysis, minimizing the risk of bias due to missing data.[50]

Conclusions

Our results show that dose-escalated CRT has a considerable effect on QoL and symptoms at 3 and 6 months after treatment, that largely resolves thereafter. Dose-escalated CRT did not affect DFS at 2 years.

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