International Journal of Radiation Oncology biology • physics

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Clinical Investigation

Efficacy of Dose-Escalated Chemoradiation on Complete Tumor Response in Patients with Locally Advanced Rectal Cancer (RECTAL-BOOST): A Phase 2 Randomized Controlled Trial

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This article was partially supported by the Maag Lever Darm Stichting (MLDS), The Netherlands, Grant FP 1605.

Disclosures: A.M.C., M.P.W.I, and H.M.V. report other grants from Maag Lever Darm Stichting during the conduct of the study.

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

Supplementary material for this article can be found at https://doi.org/10.1016/j.ijrobp.2020.06.013.

Acknowledgments—The authors thank Ann Claessens (clinical trial coordinator, MAASTRO clinic), Marijke van Deursen (clinical research assistant, UMC Utrecht), and Saskia van Amelsvoort (clinical trial coordinator, UMC Utrecht) for their contributions to patient recruitment and data management. Furthermore, they thank the radiation oncologists who were part of the treatment team (Patricia Doornaert, Stella Mook, and Ina Schulz, all members of the radiation oncology staff, UMC Utrecht), Marielle Philippens (MR physicist, UMC Utrecht) for her assistance and input in designing the boost treatment, and Simon Woodings (medical physicist, UMC Utrecht) for reviewing the final draft of the manuscript. Finally, they thank the pathologists Petur Snaebjornsson (The Netherlands Cancer Institute, Amsterdam) and Peter van Zwam (PAMM, Eindhoven) for their contributions to the pathology assessments.

Int J Radiation Oncol Biol Phys, Vol. 108, No. 4, pp. 1008–1018, 2020

https://doi.org/10.1016/j.ijrobp.2020.06.013

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Received Jan 16, 2020. Accepted for publication Jun 4, 2020.

Purpose: Pathologic complete tumor response after chemoradiation in patients with locally advanced rectal cancer (LARC) is associated with a favorable prognosis and allows organ-sparing treatment strategies. In the RECTAL-BOOST trial, we aimed to investigate the effect of an external radiation boost to the tumor before chemoradiation on pathologic or sustained clinical complete tumor response in LARC.

Methods and Materials: This multicenter, nonblinded, phase 2 randomized controlled trial followed the trials-within-cohorts design, which is a pragmatic trial design allowing cohort participants to be randomized for an experimental intervention. Patients in the intervention group are offered the intervention (and can either accept or refuse this), whereas patients in the control group are not notified about the randomization. Participants of a colorectal cancer cohort referred for chemoradiation of LARC to either of 2 radiation therapy centers were eligible. Patients were randomized to no boost or an external radiation boost (5 × 3 Gy) without concurrent chemotherapy, directly followed by standard pelvic chemoradiation (25 × 2 Gy with concurrent capecitabine). The primary outcome was pathologic complete response (ie, ypT0N0) in patients with planned surgery at 12 weeks, or, as surrogate for pathologic complete response, a 2-year sustained clinical complete response for patients treated with an organ preservation strategy. Analyses were intention to treat. The study was registered with ClinicalTrials.gov, number NCT01951521.

Results: Between September 2014 and July 2018, 128 patients were randomized. Fifty-one of the 64 (79.7%) patients in the intervention group accepted and received a boost. Compared with the control group, fewer patients in the intervention group had a cT4 stage and a low rectal tumor (31.3% vs 17.2% and 56.3% vs 45.3%, respectively), and more patients had a cN2 stage (59.4% vs 70.3%, respectively). Rate of pathologic or sustained clinical complete tumor response was similar between the groups: 23 of 64 (35.9%; 95% confidence interval [CI], 24.3-48.9) in the intervention group versus 24 of 64 (37.5%; 95% CI, 25.7-50.5) in the control group (odds ratio [OR] = 0.94; 95% CI, 0.46-1.92). Near-complete or complete tumor regression was more common in the intervention group (34 of 49; 69.4%) than in the control group (24 of 53; 45.3%; (OR = 2.74, 95% CI 1.21-6.18). Grade ≥3 acute toxicity was comparable: 6 of 64 (9.4%) in the intervention group versus 5 of 64 (7.8%) in the control group (OR = 1.22; 95% CI, 0.35-4.22).

Conclusions: Dose escalation with an external radiation therapy boost to the tumor before neoadjuvant chemoradiation did not increase the pathologic or sustained clinical complete tumor response rate in LARC.

Introduction

Chemoradiation before a total mesorectal excision (TME) in patients with locally advanced rectal cancer (LARC) reduces the risk of local recurrence and leads to downsizing of the tumor.[1,2] In 12% to 31% of LARC patients, no residual tumor is found in the resected specimen after chemoradiation, defined as a pathologic complete response (pCR).[3-5] A pCR is associated with a lower risk of recurrence and a longer disease-free and overall survival.[6] Moreover, TME could potentially have been omitted, thereby avoiding postoperative complications and surgery-related morbidity. It has been shown that a watch-and-wait (W&W) approach with regular surveillance in patients with a clinical complete response is a feasible alternative to TME.[7-9]

Higher radiation doses are associated with a higher probability of pathologic tumor regression, as scored with the Mandard tumor regression grade.[10,11] Dose-escalated radiation therapy may therefore enhance tumor downsizing and render more patients eligible for W&W. In a

systematic review on the effect of dose escalation to ≥60 Gy in LARC, a higher pooled pCR rate of 20.4% with acceptable grade ≥3 acute toxicity rate of 10.3% compared with standard chemoradiation.[12] Nevertheless, these results were predominantly based on nonrandomized studies.

In the present trial, the effect of dose-escalated chemoradiation was compared with standard chemoradiation on pathologic or sustained clinical complete tumor response (ie, a combined outcome of pCR and 2-year sustained clinical complete response in organ preservation strategies) in patients with LARC.

Methods and Materials

Study design

RECTAL-BOOST was a pragmatic, multicenter, nonblinded, screening phase 2 randomized controlled trial performed in 2 regional Dutch radiation therapy centers (University Medical Center Utrecht, Utrecht and MAASTRO Clinic, Maastricht), as described previously.[13] RECTAL-BOOST followed the pragmatic trials-within-cohorts design and was conducted within the prospective data-collection initiative on colorectal cancer (PLCRC) cohort.[14,15] In PLCRC, clinical data are collected from adult patients with colorectal cancer of all stages. Participants optionally consent to bio-banking (blood and/or tissue) and questionnaires on patient-reported outcomes and give broad consent for randomization for future experimental interventions, which means that patients can be randomized into trials embedded within the cohort in the (near) future. Only those assigned to the intervention group are informed about the trial and will be offered the intervention, which they can either accept or refuse. Participants assigned to the control group are not notified about the trial and receive treatment as usual, and their clinical data are used comparatively within the trial. The trials-within-cohorts design in the RECTAL-BOOST was evaluated and described in a separate publication.[16] Ethical approval for RECTAL-BOOST and PLCRC was obtained from the institutional review board and the institutional review boards of participating institutions. The study was done in accordance with the trial protocol, Good Clinical Practice guidelines, and Declaration of Helsinki.

Patients

Eligible patients were cohort participants who had given consent to patient reported outcomes and broad randomization for future interventions, and met the following study-specific criteria: diagnosed with LARC (cT4, cT3 with distance to the mesorectal fascia of ≤1 mm and/or cN2 and/or suspicious extramesorectal lymph node metastases), tumor ≤10 cm from the anorectal junction (magnetic resonance imaging [MRI] based), and World Health Organization 0 to 2. All patients were staged with MRI and in accordance with the national guidelines.[17] Patients with oligometastatic disease (cM1) referred for chemoradiation with curative intent were eligible. Exclusion criteria included presence of inflammatory bowel disease, prior pelvic radiation therapy, contraindication for MRI or capecitabine, pregnancy within the last year, and inadequate understanding of the national language. At the beginning of the study, female patients with a rectal tumor in close proximity to the vagina were excluded because of expected low coverage of the target volume. This criterion was removed in December 2015, after further clinical experience with boost planning. All patients provided written informed consent for PLCRC participation. Written informed consent for the RECTAL-BOOST trial was signed by patients in the intervention group who accepted the boost intervention, according to the staged-informed consent procedure.[18]

Randomization

After enrollment in PLCRC, eligible patients were randomly assigned (1:1) to standard chemoradiation (control group) or to a boost before chemoradiation (boost group). Centralized randomization was performed by the study investigators or by an authorized delegate of the Trial Office Imaging Division of the initiating institution. The allocation sequence was concealed. Patients were randomized using block randomization with variable block lengths of 4-6-8 patients, stratified by center. Neither investigators, treating physicians, nor patients were blinded to treatment allocation.

Procedures

Details of the treatment protocol were described previously.[13] In both treatment arms, target volumes were delineated on planning CT scans, aided by T2-weighted MRI and diffusion-weighted imaging (DWI) matched to the planning CT, or positron emission tomography−computed tomography. Radiation therapy was administered using a volumetric modulated arc therapy technique. Chemoradiation consisted of 50 Gy in 25 fractions of 2 Gy, with concurrent capecitabine 825 mg/m^2 twice a day for 5 or 7 days per week. The boost intervention consisted of a sequential, stereotactic boost to the tumor (excluding bowel lumen) of 15 Gy in 5 fractions in 5 consecutive working days without concurrent chemotherapy in the week before the start of chemoradiation.

Delineation of the gross tumor volume (GTV) was based on T2-weighted imaging and DWI. No clinical target volume margin was applied around the GTV. The planning target volume (PTV) included GTV + 11 mm in the anteroposterior direction, GTV + 7 mm in the lateral direction, and GTV + 13 mm in the craniocaudal direction. These margins were derived from in-house observations on tumor movement on daily MRI scans and setup errors. A

cumulative GTV dose of 65 Gy was delivered over the full treatment course of 30 fractions (6 weeks) with an equivalent dose in 2-Gy fractions of 66.3 Gy ($\alpha/\beta = 10$ Gy). The boost dose was aimed at 65 Gy with a maximal point dose of 80 Gy. Organs at risk (OARs) in the boost planning included bowel bag (excluding sigmoid), bladder, vagina, and anal sphincter. OAR constraints took priority over boost dose, resulting in a lower coverage when the tumor was near one of the OARs.

All patients (including controls) were treated according to the same protocol, including target definition, planning and constraints, and treatment delivery. The planning constraints for the combined boost and chemoradiation treatment plan were the same as those for the chemoradiation treatment plan alone. Quality assurance was performed on all radiation therapy plans using standardized methods. Boost planning and delivery were made uniformly between the 2 participating centers. For position verification, a cone beam CT was performed before all boost fractions using the rectal wall as surrogate for tumor position, before the first 3 fractions of chemoradiation, and weekly thereafter. In case of bowel distention, the patient was asked to leave the table and to empty the bowel if possible.

Time-to-response assessment was included in the trial protocol. Response to treatment was evaluated with MRI at 9 weeks after the last treatment fraction. Surgery was considered standard treatment and was planned 12 weeks after completion of chemoradiation. Surgery took place in the institution from where the patients were referred and was performed using the principles of TME, including abdominoperineal resection (APR), low anterior resection (LAR), or a rectosigmoid resection with permanent stoma (Hartmann). Several patients with a (near) complete clinical response, based on MRI and endoscopy, were evaluated for W&W. Adjuvant treatment is not routinely administered in patients with LARC, according to the national guidelines.

Outcomes

The primary endpoint of the first version of the trial protocol was pCR, defined as ypT0N0. However, over time, W&W became more common in patients with a complete clinical tumor response. We therefore changed the primary endpoint into a combined endpoint of pCR in patients with planned TME at 12 weeks after the last radiation therapy fraction and, as surrogate for pCR, a 2-year sustained clinical complete response since the last radiation therapy fraction with absence of locoregional tumor regrowth in patients with W&W management, based on a previous study and the evidence that most regrowths develop within 2 years.[8,19] Patients with a ypT0Nx after local excision and no regrowth/recurrent disease within 2 years were considered complete responders. Patients with progressive disease after chemoradiation who did not receive TME were considered noncomplete responders. This amendment was approved by the ethics committee in March 2017. At the time of the analysis, one patient with W&W had 23 months of follow-up but was considered to be a complete responder.

pCR was assessed by examination of the resected specimen in the referral hospitals of the participating hospitals and performed according to the national guidelines.[17] For patients with pCR, 3 levels were cut on all blocks from the tumor site and examined for presence of tumor cells. Pathologists were unaware of treatment allocation. To confirm protocol adherence, all pathology reports were reviewed by a dedicated pathologist. Follow-up for W&W took place in specialized referral centers.

Secondary outcomes included (near) complete Mandard tumor regression grade (TRG 1-2), (near) complete radiologic MRI response, sphincter preservation, acute toxicity grade $\geq$3, surgical complications grade $\geq$3, and quality of life (QOL) during the first 12 months after randomization. The 5-tier Mandard TRG was assessed according to the publication of Mandard and only presented in patients who received planned surgery at 12 weeks.[11]

Clinical tumor response was assessed by dedicated radiologists using T2-weighted MRI and DWI at 9 weeks after completion of chemoradiation and in accordance with the European Society of Gastrointestinal and Abdominal Radiology guidelines for restaging. Response was classified as clinical complete response, complete/near-complete response, residual mass (ycT1-2, ycT3, or ycT4), and lymph node restaging (ycN0 or ycN+).[20]

Sphincter preservation was defined as patients who received LAR without stoma, had a successfully reversed temporary stoma, or were treated with an organ preservation strategy for 2 years. Toxicity was assessed weekly during treatment and at 4 and 9 weeks after completion of treatment by the radiation oncologist using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Surgical complications were categorized according to Clavien−Dindo classification and included anastomotic leakage, abscess, bleeding, ileus, dehiscent fascia, iatrogenic injury to bowel and ureter/urethra, and other nonspecified complications. QOL was measured with the European Organisation for Research and Treatment of Cancer (EORTC) core cancer questionnaire (QLQ-C30) at baseline (at time of randomization) and at 3, 6, and 12 months.[21] Serious adverse events were registered for patients in the intervention arm from start of radiation therapy until 8 months.

Statistical analysis

We estimated that 30% of the patients in the boost group would achieve a pCR versus 13% in the control group.[10] Patients allocated to the intervention arm may refuse the boost intervention, which would dilute the outcome in an intention-to-treat analysis.[22] The sample size was therefore adjusted for the estimated proportion of patients refusing the intervention, which was in the present trial estimated to

be 20%. Considering this, the estimated sample size was 60 patients per arm, based on a one-sided test ($\alpha = 0.15$, and power = 80%), corrected for a refusal rate of 20%. We used a one-sided test and higher α as recommended for phase 2 screening trials.[23] After enrollment of the 100th patient, the refusal rate in the intervention arm was evaluated.[24] Because the refusal rate was slightly higher than expected, we adapted the sample size from 120 to 128 patients.

The primary outcome was analyzed with a χ^2 test. Logistic regression was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs). Adjusted analysis was performed in case of imbalance in baseline characteristics, as suggested in the literature.[25]

Secondary objectives with a categorical outcome were analyzed with a χ^2 test, and effect sizes were presented in OR with 95% CI. QOL was compared between the treatment groups using the EORTC QLQ-C30 summary score, which is a weighted score based on 13 domains/scales of the questionnaire and captures functioning, global health, and general cancer symptoms.[26] A linear mixed-model was used with a random intercept, an autoregressive covariance structure of the first order, and included time, treatment group, and its interaction. Outcomes were presented in mean differences (MDs) with 95% CI.

Data were analyzed based on the intention-to-treat population. However, for Mandard TRG 1 to 2 and Clavien−Dindo surgical complications we only analyzed the patients who received surgery. Differences with a P value $<.05$ were considered statistically significant, except for the primary endpoint, where $P < .15$ had been prespecified. Data were analyzed with Statistical Package for Social Sciences (SPSS) version 25. An independent data and safety monitoring board periodically assessed safety data, including radiation toxicity and surgical complications. After the first 10 patients treated with dose-escalated chemoradiation followed by LAR, enrollment of patients with a midrectal tumor planned for LAR was paused for 8 months to evaluate safety of the intervention in terms of anastomotic leakage.

The trial was registered with Clinicaltrials.gov, number NCT01951521. The cohort was registered with the number NCT02070146.

Results

Between September 11, 2014 and July 13, 2018, 64 patients were randomly assigned to the control group and 64 to the intervention group (Fig. 1). Of the 64 patients in the intervention group, 51 (79.7%) patients accepted and underwent the intervention. Twelve (18.8%) patients refused to undergo the intervention and received standard chemoradiation. One patient accepted the intervention but did not receive a boost due to a very minimal target coverage because of a small bowel constraint. It was therefore considered unethical to have this patient come to the hospital for 5 additional visits.

Baseline characteristics were well balanced in terms of age, sex, presence of comorbidities, and MRF involvement (Table 1). An imbalance between the control group and boost group was observed in distally located tumors (n = 36, 56.3% vs n = 29, 45.3%, respectively), cT4 stage (n = 20, 31.3% vs n = 11, 17.2%, respectively), and cN2 stage (n = 38, 59.4% vs n = 45, 70.3%, respectively). The prescribed capecitabine dose was similar between the groups (3300 mg/day in each group). Median interval to MRI was 9 weeks, and median interval to surgery was 12 weeks in both groups.

Median tumor volume (based on the number and volume of voxels within the delineated tumor at planning CT) was comparable between the treatment groups (33 mL [interquartile range, 20-47] in the boost arm vs 35 mL [interquartile range, 25-57] in the control arm). Planned mean dose to the PTV of the tumor was 66.8 Gy in the boost group and 50.0 Gy in the control group (Table 2). All patients in the boost group completed the 5 boost fractions. Sixty (93.8%) patients completed the entire radiation schedule and 60 (93.8%) completed the prescribed capecitabine dose versus 63 (98.4%) and 61 (95.3%) in the control arm, respectively. Three patients in the boost arm and 1 patient in the control arm missed the last treatment fraction. One patient in the boost arm missed 2 fractions. In 2 patients (boost arm), missing fractions were related to acute toxicity.

Planned surgery at 12 weeks after completion of CRT was received by 49 (76.6%) patients in the boost group and 53 (82.8%) patients in the control group (Table 2). In the boost group, 28 (43.8%) patients underwent LAR, 18 (28.1%) patients APR, 2 (3.1%) patients a Hartmann, and 1 (1.6%) patient a local excision. In the control group, 32 (50.0%) patients underwent APR, 19 (29.7%) patients LAR, and 2 (3.1%) patients a Hartmann. Three patients in the boost group and 3 patients in the control group with a clinical near-complete response were evaluated for W&W but received delayed surgery because of a residual tumor (none of these patients had a complete response at pathologic assessment). One patient with a W&W approach in each group developed local tumor regrowth, both at 1 year after chemoradiation. The patient in the boost group received salvage APR, and the patient in the control group underwent a salvage local excision (ypT3) followed by completion APR. In total, 9 W&W patients in the boost arm and 5 W&W patients in the control arm had a 2-year sustained clinical complete response. In both groups, 2 patients had distant progressive disease at time of response MRI and received palliative systemic treatment.

Pathologic or 2-year sustained clinical complete tumor response rate was similar between the boost and control group: 23 of 64 (35.9%; 95% CI, 24.3-48.9) in the inter-

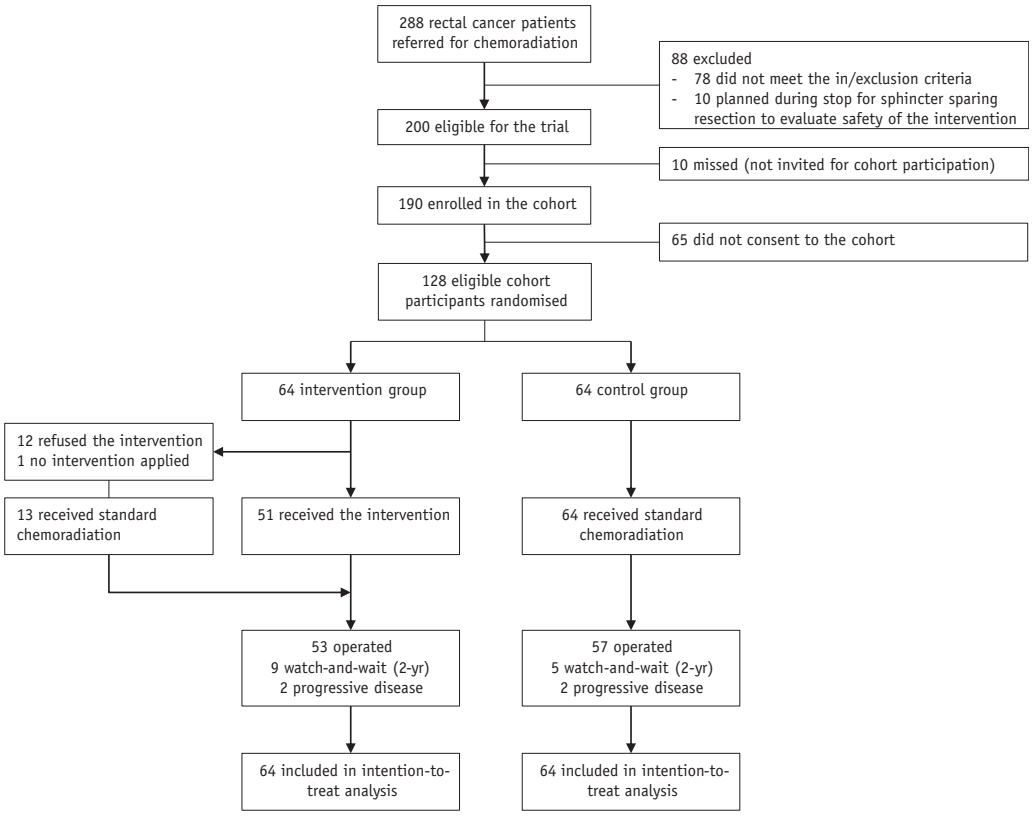

Fig. 1. Flowchart of eligible and randomized patients.

vention group versus 24 of 64 (37.5%; 95% CI, 25.7-50.5) in the control group (OR = 0.94; 95% CI, 0.46-1.92; P = .86). In the boost group, 13 patients had a pCR, 9 patients had a W&W with a 2-year sustained clinical complete response, and 1 patient had a ypT0Nx after a local excision with 2-year freedom from regrowth/recurrent disease. In the control group, 19 patients had a pCR and 5 patients had a W&W with a 2-year sustained clinical complete response.

A multivariable analysis, including treatment allocation and the imbalanced baseline characteristics (ie, cT-stage, cN-stage, and tumor location), showed no significant effect of any of the factors nor a significant primary outcome (Table E1). The per-protocol analysis showed a pathologic or 2-year sustained clinical complete tumor response in 18 of 51 (35.3%) patients treated with dose-escalated chemoradiation and 29 of 77 (37.7%) patients treated with standard chemoradiation (OR = 0.90; 95% CI, 0.43-1.89; P = .79).

Clinical complete/near-complete tumor response (ie, ycT0[near]ycN0) at MRI was not significantly different between the groups: 18 of 64 (28.6%) patients in the boost group versus 12 of 64 (18.8%) in the control group (OR = 1.73; 95% CI, 0.75-3.98) (Table 3, Table E2).

Sphincter preservation was more often achieved in the boost group than in the control group: 36 of 64 (56.3%) versus 22 of 64 (34.4%) (OR = 2.46; 95% CI, 1.20-5.01) (Table 3).

Of all patients who underwent planned surgery, a higher rate of (near) complete tumor regression was observed in the boost group compared with the control group: Mandard TRG 1 to 2 in 34 of 49 (69.4%) versus 24 of 53 (45.3%) in the control group (OR = 2.74; 95% CI, 1.21-6.18) (Table 3, Table E3).

The most common CTCAE acute toxicities included diarrhea/proctitis, fatigue, dermatitis, and cystitis noninfectious (Fig. 2). Grade $\geq$3 toxicity was comparable between the groups: 6 of 64 (9.4%) in the boost group versus 5 of 64 (7.8%) in the control group (OR = 1.22; 95% CI, 0.35-4.22) (Table 3). The proportion of patients with diarrhea/proctitis toxicity grade 1 to 2 in the boost group was higher (57.8% vs 42.4% in the control group). Two patients in the boost arm had grade 4 toxicity. One patient developed capecitabine-related panenteritis and was admitted to intensive care (no DPD deficiency was demonstrated). One patient with mucosal bleeding developed acute renal failure after contrast injection for CT, which was temporarily treated with dialysis. None of the patients in the control arm

Table 1 Baseline characteristics by allocated treatment

Baseline characteristics	Boost group (n = 64)	Control group (n = 64)
Age, y	64.5 (55.0-69.0)	62.0 (56.0-71.0)
Sex		
Male	48 (75.0)	47 (73.4)
Female	16 (25.0)	17 (26.6)
Comorbidities		
None	30 (46.9)	26 (40.6)
1 or more	34 (53.1)	38 (59.4)
Tumor distance*		
≤3.0cm	29 (45.3)	36 (56.3)
3.1-5.0 cm	12 (18.8)	8 (12.5)
5.1-10.0cm	23 (35.9)	20 (31.2)
Tumor stage		
cT2	2 (3.1)	5 (7.8)
cT3	51 (79.7)	39 (60.9)
cT4	11 (17.2)	20 (31.3)
Distance to the mesorectal fascia†		
≤1 mm	42 (65.6)	46 (71.9)
>1 mm	22 (34.4)	18 (28.1)
Nodal stage		
cN0	5 (7.8)	9 (14.1)
cN1	14 (21.9)	17 (26.6)
cN2	45 (70.3)	38 (59.4)
Oligometastatic disease		
No	61 (95.3)	62 (96.9)
Yes	3 (4.7)	2 (3.1)
Capecitabine prescribed dose, mg/d	3300 (3000-3600)	3300 (3000-3300)
Interval to MRI, wk‡	9.0 (8.0-9.0)	9.0 (8.0-9.0)
Interval to surgery, wk	12.0 (12.0-14.0)	12.0 (11.0-13.0)

Data presented as number (%) or median (interquartile range).
* Measured from the anorectal junction on sagittal magnetic resonance imaging.
† Based on the primary tumor.
‡ One patient in the boost group did not undergo the response magnetic resonance imaging because of anxiety symptoms.

Table 2 Treatment course by allocated treatment

Treatment characteristics	Boost group (n = 64)	Control group (n = 64)
Mean PTV_{tumor} dose, Gy*	66.8 (60.1-69.8)	50.0 (49.9-50.2)
Minimum PTV_{tumor} dose, Gy†	58.9 (50.5-64.3)	48.6 (48.3-48.8)
Maximum PTV_{tumor} dose, Gy†	74.0 (65.6-75.1)	51.4 (51.2-51.8)
Radiation therapy fractions completed	60 (93.8)	63 (98.4)
Prescribed capecitabine dose completed	60 (93.8)	61 (95.3)
Planned surgery		
Low anterior resection	28 (43.8)	19 (29.7)
Abdominoperineal resection	18 (28.1)	32 (50.0)
Hartmann resection	2 (3.1)	2 (3.1)
Local excision	1 (1.6)	0
Delayed/salvage surgery‡		
Low anterior resection	1 (1.6)	2 (3.1)
Abdominoperineal resection	1 (1.6)	2 (3.1)
Local excision	2 (3.1)	0
2-y watch-and-wait	9 (14.1)	5 (7.8)
Palliative systemic treatment	2 (3.1)	2 (3.1)

Abbreviation: PTV_{tumor} = planned target volume of the tumor.
Data presented as median (interquartile range) or n (%).
* Planned mean dose to the PTV.
† Minimum dose is the highest dose received by 99% of the PTV (D99) and the maximum dose is the highest dose received by 1% of the PTV (D1).
‡ Includes patients with a (near) complete clinical response after chemoradiation and evaluated for a watch-and-wait strategy but who received surgery because of a nonsustained complete response at first watch-and-wait follow-up assessment (referred to as delayed surgery for near-complete responders), or at later follow-up assessment (referred to as salvage surgery for regrowth).

developed grade 4 acute toxicity. No grade 5 toxicity was observed.

Of all patients who underwent surgery, occurrence of Clavien−Dindo grade >3 surgical complications was not statistically significant between the groups: 14 of 53 (26.4%) in the boost group versus 11 of 57 (19.3%) in the control group (OR = 1.50; 95% CI, 0.61-3.68) (Table 3). One (1.6%) patient in the boost group died of a cardiopulmonary event <30 days after APR with partial sacrum resection, which was judged to be unrelated to the boost intervention.

EORTC QLQ-C30 response rates at the different time points ranged between 68.8% and 92.2% in the boost group and 67.2% and 89.1% in the control group. The summary score showed a significantly lower score in the boost group at 3 months after randomization (MD with the control group = −7.5 [95% CI, 3.0-12.1]; P = .001) (Table 3, Fig. 3). At baseline and 6 and 12 months, QOL was comparable between the groups.

Discussion

This trial may indicate that a radiation therapy boost of 15 Gy to the tumor before standard-dose chemoradiation does not lead to more pathologic or sustained clinical complete tumor responses in patients with LARC. However, significantly more (near) complete tumor regression (Mandard TRG 1-2) and sphincter preservation was observed in the dose-escalated chemoradiation group. Severe acute toxicity and surgical complications were comparable between both groups, but QOL was worse at 3 months after randomization in the boost group.

In a previous publication, a clear dose-response relationship in LARC was demonstrated for tumor regression after preoperative chemoradiation for tumor dose levels in

Table 3 Primary outcome and secondary outcomes by allocated treatment

Outcomes	Boost group (n = 64)	Control group (n = 64)	OR or MD (95% CI) boost vs control	*P* value*
pCR or 2-y cCR	23 of 64 (35.9)	24 of 64 (37.5)	0.94 (0.46-1.92)	.86
ycT0(near)ycN0 at response MRI†	18 of 64 (28.1)	12 of 64 (18.8)	1.73 (0.75-3.98)	.21
Sphincter preservation	36 of 64 (56.3)	22 of 64 (34.4)	2.46 (1.20-5.01)	.01
Mandard TRG 1-2‡	34 of 49 (69.4)	24 of 53 (45.3)	2.74 (1.21-6.18)	.02
CTCAE grade ≥3	6 of 64 (9.4)	5 of 64 (7.8)	1.22 (0.35-4.22)	.75
Clavien–Dindo grade ≥3	14 of 53 (26.4)	11 of 57 (19.3)	1.50 (0.61-3.68)	.50
QoL summary score§				
Baseline	87.7 (1.6)	86.3 (1.6)	1.31 (−5.81 to 3.18)	.57
3 mo	80.8 (1.6)	88.4 (1.7)	−7.54 (−12.09 to −2.99)	.001
6 mo	78.5 (1.7)	82.2 (1.7)	−3.64 (−8.28 to 1.00)	.12
12 mo	87.0 (1.8)	87.5 (1.8)	−0.57 (−5.56 to 4.42)	.82

Abbreviations: cCR = clinical complete response; CI = confidence interval; CTCAE = Common Terminology Criteria for Adverse Events; MD = mean difference; OR = odds ratio; pCR = pathologic complete response; QoL = quality of life; Ref = reference group; TRG = tumor regression grade.

Data presented as n (%) or mean (standard error) for quality-of-life scores.

* Based on χ^2 test.

† One patient in the boost group did not receive a response MRI because of new-onset claustrophobia.

‡ Presented in patients treated with planned surgery at 12 weeks.

§ Presented as mean difference (95% confidence interval).

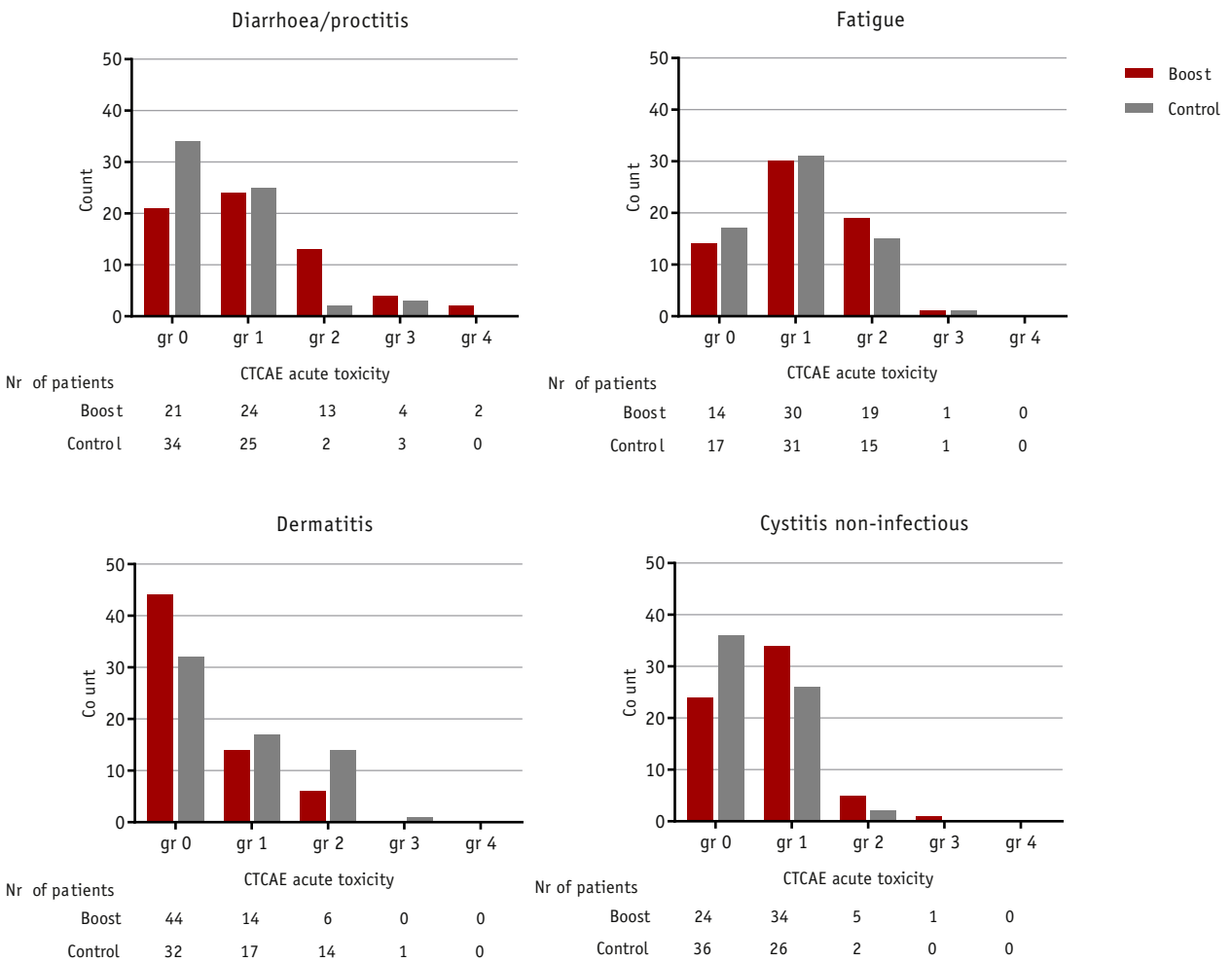

Fig. 2. Common Terminology Criteria for Adverse Events (CTCAE) acute toxicity by allocated treatment. Presented is the highest toxicity grade (gr) per patient during and/or shortly (9 weeks) after chemoradiation.

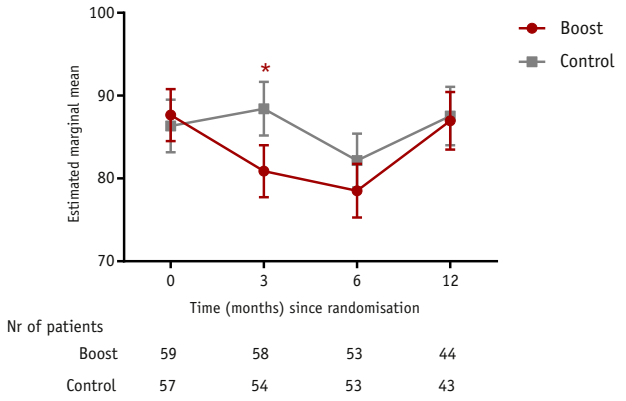

Fig. 3. European Organisation for Research and Treatment of Cancer (EORTC) core cancer questionnaire (QLQ-C30) quality-of-life summary score by allocated treatment at randomization and at 3, 6, and 12 months after. The summary score is a weighted score of 13 items of the questionnaire and captures functioning, global health, and general cancer symptoms. Statistically significant difference between the boost group and control group is denoted with an asterisk.

the range of 50.4 to 70 Gy.[10] In contrast, we observed no increase in complete response rate after dose escalation from 50 to 65 Gy. The study in question was partly based on data from a randomized phase 3 trial, where the addition of brachytherapy boost to standard dose chemoradiation did increase the rate of complete and near-complete response, but not the rate of pCR.[27] The subsequently estimated dose-response curve used ordinal logistic regression for assessing the relationship between dose and TRGs 1 to 4 (not specifically on pCR). The reported dose-response association may thus mainly be driven by TRG 1 to 2, which would support our findings. Yet, it remains unclear why dose escalation leads to more tumor regression but not a complete response. In the present trial, it might partly be explained by the limited boost dose to the PTV of the tumor due to its location near one of the OARs (as shown by the minimum dose), which could have diluted the boost effect. Time between the completion of chemoradiation and (pathologic) response assessment could also play a role, suggesting that near-complete response may become a complete response by awaiting further response, as previously supported.[28,29]

Surprisingly, the rate of complete response after standard chemoradiation that we observed was much higher than reported in literature, especially considering the advanced stage.[3,4] This may partly be explained by tumor size. Tumor volume, as well as nodal stage, has an effect on the dose-response relationship, with smaller-volume tumors and absence of pathologic lymph nodes demonstrating higher probability of tumor regression.[10] In the present trial, patients had a median tumor volume of 35 mL (comparable between the groups), which is relatively small when compared with, for example, the previously discussed phase 3 trial.[27] The national colorectal cancer screening program aims to detect (advanced) tumors earlier, which may have led to smaller tumor volumes compared with those observed in historical cohorts. Nodal stage is rather unlikely to explain the high response rate because most of the patients participating in this trial had node-positive disease. In addition, quality of diagnostic MRI differs among studies and has improved over the past years, which could have resulted in stage migration. The 12-week time interval to surgery may also partly explain the high response rate. Several studies have shown a positive association between time interval and pCR.[3,4] Thus simply on the basis of the 12-week interval from end of radiation therapy to surgery, compared with the 6 to 8 weeks most commonly used, one would expect the complete response rate to be higher than in other trials.[12,30]

Acute toxicity grade 3 to 4 was similar between the treatment arms and comparable with the literature.[12] Nevertheless, more grade 1 to 2 toxicity was observed in the boost arm, which was mainly bowel-related toxicity including proctitis, diarrhea, and mucosal bleeding. Patients in the boost group had a lower QOL at 3 months after randomization. Nevertheless, this effect was temporary, and the 2 groups were equivalent at 6 and 12 months. The effect could have been affected by the nonblinded nature of the trial.

We observed a higher rate of sphincter preservation in the boost group than in the control group. This is a promising finding because a permanent stoma can affect patients' life severely. However, this outcome should be interpreted with caution because there is likely an associated selection bias. At the time of the present trial, organ preservation was not actively offered by all surgeons to all patients with a clinical complete response. As a result, (non)surgical treatment was very much based on preference and not on the effect of the treatment or intervention. Furthermore, the control group was not informed about the present trial and may therefore have had less awareness of the possibility of organ preservation after a clinical complete response.

The results of this trial are aligned with previous randomized trials.[27,31] Published recently, the INTERACT trial was a phase 3 trial investigating the effect of an integrated radiation boost (10 × 1 Gy) during chemoradiation versus chemoradiation with oxaliplatin on Mandard TRG 1 to 2 in LARC. The TRG 1 to 2 rate was significantly higher in the radiation boost group (62% vs 52%), and the pCR rate was similar (24% in both groups). Nevertheless, the INTERACT trial excluded cT4, used a lower boost dose, performed surgery earlier (after 7-9 weeks), and did not include a standard treatment group, which makes the trials less comparable. The previously mentioned Danish phase 3 trial observed a similar pCR rate between the dose-escalated chemoradiation group and the standard arm (18% in both groups), but more TRG 1 to 2 (44% vs 28%).[27] Some nonrandomized studies have shown high

complete response rates in selected LARC patients with endorectal radiation techniques, including high-dose-rate endorectal brachytherapy or x-ray contact therapy.[32,33] This is likely the result of the higher radiation dose achieved within the tumor using these techniques. Unfortunately, endorectal radiation may not be suitable for large tumors and is associated with bleeding toxicity.

This trial has several limitations. Randomization was not stratified by clinical tumor characteristics, which resulted in differences between the groups in cT stage, cN stage, and tumor location, and the choice for adjusted analysis. Furthermore, we redefined the endpoint because progress in organ-sparing treatment approaches had caught up with our primary stated endpoint. However, 2-year freedom from locoregional regrowth may not directly translate into pCR. Patients with a clinical complete response may still have had scattered tumor cells, which are easily missed at response assessment. Instead, a patient-centered outcome should be preferred (ie, clinical complete response leading to organ preservation). This would have required all patients to be evaluated for organ preservation before surgery, which was not the case. These results can therefore not be used to determine the impact of a radiation therapy boost on organ preservation.

Conclusions

The RECTAL-BOOST trial may indicate that dose-escalated chemoradiation with a radiation therapy boost of 15 Gy to the tumor does not lead to more pathologic or sustained clinical complete tumor responses in LARC. We therefore suggest that the investigated dose-escalation strategy currently has no role in the setting of neoadjuvant chemoradiation with planned surgery in LARC patients. However, we showed a high rate of (near) complete tumor regression after dose-escalated chemoradiation, which encourages further investigation into the use of radiation therapy to render more patients suitable for organ preservation.

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