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Original Article

Quality of life and late toxicity after short-course radiotherapy followed by chemotherapy or chemoradiotherapy for locally advanced rectal cancer – The RAPIDO trial

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ABSTRACT

Background and purpose: The RAPIDO trial demonstrated a decrease in disease-related treatment failure (DrTF) and an increase in pathological complete responses (pCR) in locally advanced rectal cancer (LARC) patients receiving total neoadjuvant treatment (TNT) compared to conventional chemoradiotherapy. This study examines health-related quality of life (HRQL), bowel function, and late toxicity in patients in the trial.

Materials and methods: Patients were randomized between short-course radiotherapy followed by pre-operative chemotherapy (EXP), or chemoradiotherapy and optional post-operative chemotherapy (STD). The STD group was divided into patients who did (STD+) and did not (STD−) receive post-operative chemotherapy. Three years after surgery patients received HRQL (EORTC QLQ-C30, QLQ-CR29 and QLQ-CIPN20) and LARS questionnaires. Patients who experienced a DrTF event before the toxicity assessments (6, 12, 24, or 36 months) were excluded from analyses.

Results: Of 574 eligible patients, 495 questionnaires were returned (86%) and 453 analyzed (79% completed within time limits). No significant differences were observed between the groups regarding QLQ-C30, QLQ-CR29 or LARS scores. Sensory-related symptoms occurred significantly more often in the EXP group compared to all STD patients, but not compared to STD+ patients. Any toxicity of any grade and grade ≥ 3 toxicity was comparable between the EXP and STD groups at all time-points. Neurotoxicity grade 1–2 occurred significantly more often in the EXP and STD+ group at all time-points compared to the STD− group.

Conclusion: The results demonstrate that TNT for LARC, yielding improved DrTF and pCRs, does not compromise HRQL, bowel functional or results in more grade ≥ 3 toxicity compared to standard chemoradiotherapy at three years after surgery in DrTF-free patients.

Several studies demonstrated substantial late toxicity, compromised health-related quality of life (HRQL), and low anterior resection syndrome (LARS) after rectal cancer treatment [1,2]. Impairment is more often reported in patients who underwent pre-operative treatment and surgery compared to surgery alone [3–6]. Pre-operative short-course radiotherapy (scRT) with

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immediate surgery and chemoradiotherapy (CRT) (with delayed surgery) are associated with comparable late toxicity [7]. Post-operative chemotherapy, having the aim to decrease systemic recurrences, further adds morbidity [8].

Total neoadjuvant treatment (TNT) has gained increased interest under the assumption of improved systemic control by pre-operative chemotherapy compared to post-operative chemotherapy [9–11].

The RAPIDO trial aimed to decrease disease-related treatment failure (DrTF) after scRT followed by systemic chemotherapy compared to CRT and optional post-operative systemic chemotherapy. The primary endpoint demonstrated a significant difference in DrTF events in favor of the experimental group compared to the standard-care group, 23.7% *vs.* 30.4%; $p = 0.019$, respectively [12]. Furthermore, the pathological complete response (pCR) rate was doubled in the experimental group (28% *vs.* 14%; $p < 0.0001$) [12]. The similarly designed STELLAR trial failed to demonstrate this advantage of TNT (pCR rate 17% after scRT with CAPOX pre- and post-operatively compared to 12% after CRT and post-operative CAPOX, $p = 0.134$) [13]. The current study aims to assess HRQL, bowel function, and late toxicity following TNT with scRT compared to standard CRT with or without post-operative chemotherapy in patients participating in the RAPIDO trial.

Material and methods

Patient selection

The RAPIDO trial was an investigator-initiated, international, multicenter, phase III, randomized trial. It was centrally evaluated by the medical ethics committee of University Medical Center Groningen, the Netherlands (2011/098) and locally approved by all participating centers. Inclusion and exclusion criteria have been described [9,12,14]. In short, patients of 18 years or older were randomized (1:1) in case they had biopsy-proven, newly diagnosed rectal cancer less than 16 cm from the anal verge at endoscopy and at least one high-risk feature on MRI (cT4a/b, cN2, extramural vascular invasion, involved mesorectal fascia or enlarged lateral lymph nodes considered to be pathological). All RAPIDO trial patients who underwent a resection and were free from a DrTF event (defined as distant metastasis, locoregional failure, second primary (colorectal) tumor or treatment-related death) at three years after surgery were invited to participate in the HRQL analysis. The LARS questionnaire was completed by DrTF-free patients who underwent an anterior resection and did not have a remaining diverting stoma three years after surgery. Due to the unavailability of questionnaires in the Slovenian language, patients from Slovenia were excluded. During follow-up, toxicity assessments according to the CTCAE version 4 were performed by the treating physician at 6, 12, 24, and 36 months. Toxicity was recorded for all resected patients without a DrTF at each time point. Patients in whom a DrTF event was detected within three months after toxicity assessment or questionnaire completion were excluded from further analyses.

Treatments

Patients were randomized to receive the experimental (EXP) or the standard-care (STD) treatment. The EXP treatment consisted of 5x5 Gy radiotherapy followed by six cycles of CAPOX or nine cycles of FOLFOX4 and surgery according to total mesorectal excision (TME) principles 2–4 weeks after the last chemotherapy. The STD treatment entailed long-course radiotherapy (28–25 × 1.8–2.0 G y) and concurrent capecitabine followed by surgery after eight ± two weeks. Details of the treatments have been published [9,12,14]. According to hospital policy, patients in the STD group should or should not receive eight cycles of CAPOX or twelve cycles of FOLFOX4 post-operatively. To determine the effect of post-operative chemotherapy on HRQL, LARS, and late toxicity, the STD group was split into two subgroups: a group without (STD−) and a group with post-operative chemotherapy (STD+). All patients who started post-operative chemotherapy were assigned to the STD+ group, irrespective of the number of cycles they received.

Questionnaires

The following questionnaires, developed by the European Organization for Research and Treatment of Cancer (EORTC), were used: QLQ-C30 [15], QLQ-CR29 [16] and QLQ-CIPN20 [17]. To improve the evaluation of the sexual function in male patients, the QLQ-CR29 questionnaire was supplemented by questions 51, 52, 54, and 55 of the QLQ-PR25 [18]. For female patients, question 59 was replaced by question 53, and questions 50–52 and 54 of the QLQ-EN24 [19] were added. In addition, bowel function was scored by the LARS questionnaire [20,21]. Information on the EORTC and LARS questionnaires is provided in the appendix pp. 17–20. The distribution of patient-specific questionnaires was centrally managed by the Clinical Research Center of the LUMC, Leiden, the Netherlands. All participating centers received the questionnaires approximately 2 months in advance for further distribution to study participants. In case of a non-responding participating center, one reminder by e-mail was sent from the Clinical Research Center approximately one month after the anticipated response time. All completed questionnaires were returned to the Clinical Research Center for further central analysis. All questionnaires filled in 2.75–3.25 years after surgery by eligible patients were included in the analyses.

Toxicity according to the treating physician

Only the highest score of any toxicity at each measurement was included in the analyses. Toxicities were pooled in the following groups: blood and lymphatic, gastrointestinal, fatigue, allergic reaction, weight loss, nervous system, respiratory, renal and urinary, skin, sexual, or other toxicities. For each time-point of toxicity assessment, a window of +/− 3 months was accepted.

Statistical analysis

The HRQL scores and missing data of the QLQ-C30, QLQ-CR29 and QLQ-CIPN20 questionnaires were analyzed and interpreted according to EORTC guidelines [22]. The questionnaires consisted of single items, of which some were aggregated into multi-item scales. When responses were available for at least half of the items on a scale, all completed items were used for calculation. When more than 50% of responses on an item were lacking, the scale score was set to missing. Scoring ranges from 0 to 100 where a higher score represents a better function in functional scales and a lower score represents fewer symptoms in a symptom scale or item. Differences of 5–10 points on an EORTC HRQL function scale/item/symptom were considered a small clinically meaningful difference (hereafter small), 10–20 points a moderate clinically meaningful difference (hereafter moderate), and >20 points a large clinically meaningful difference (hereafter large) [23]. All items or symptoms with both clinical meaningfulness and statistically significant differences are reported here. All other items or symptoms with clinical meaningfulness which are not statistically significant are highlighted in grey in the supplementary appendix. Descriptive statistics were used to calculate means, frequencies, and percentages. Differences in means between the two (EXP and STD) and three groups (EXP, STD− and STD+) were tested by the independent t-test and ANOVA test, respectively. The Chi-square test was

used to compare proportions. When significant differences between the three groups were revealed, post-hoc Bonferroni analyses were performed for pairwise comparisons between the group means. Multiple testing was corrected by considering a two-sided *p*-value of ≤0.01 to be statistically significant. SPSS for Windows (version 23.0, SPSS, Chicago, IL) was used for the statistical analyses.

Results

In total, 920 patients were randomized in the RAPIDO trial. Of the 468 patients in the EXP group, 420 patients underwent surgery with curative intent. In the STD group, 396 out of 452 patients underwent surgery with curative intent. Reasons for exclusion of patients is provided in Fig. 1. Of the patients who underwent curative surgery, 15 patients were from Slovenia in the EXP group and 16 patients in the STD group. After exclusion of patients from Slovenian institutions and patients who had a treatment failure, questionnaires were sent to 574 patients alive, three years after surgery. Of those, 453 (78.9%) completed and returned the questionnaires within the set time limits. Of the 300 patients who were free of a stoma at three years and therefore eligible to receive the LARS questionnaire, 175 patients (58.3%) returned the questionnaire. Reasons for ineligibility and exclusions are provided in Fig. 1. For the toxicity analyses Slovenian patients were included, resulting in 706, 655, 590, and 560 evaluable patients (alive without a DrTF event) at 6, 12, 24, and 36 months after surgery, respectively (Fig. 1).

Of the 453 responders, 243 patients received the EXP and 210 the STD treatment, of whom 99/210 patients (47.1%) started post-operative chemotherapy. One patient in the EXP group received post-operative chemotherapy but was not excluded for further analyses. Non-responders to the questionnaire were significantly younger compared to analyzed patients. Other baseline and treatment characteristics were equally balanced between analyzed patients and non-responders (Table S1). Table 1 provides the clinicopathological characteristics of the 453 evaluable patients who returned the HRQL questionnaires. Compliance to radiotherapy and chemotherapy is reported in Table S2.

No statistically significant and clinically meaningful differences regarding the EORTC QLQ-C30 and EORTC QLQ-CR29 scores were observed between the two (EXP *vs.* STD) (Tables S3 and S4) or three (EXP *vs.* STD+ *vs.* STD−) groups (Figs. 2 and 3, detailed information in tables S3 and S4).

The EORTC QLQ-CIPN20 questionnaire revealed statistically significant and clinically meaningful differences with worse scores for the EXP group compared to the whole STD group for the sensory

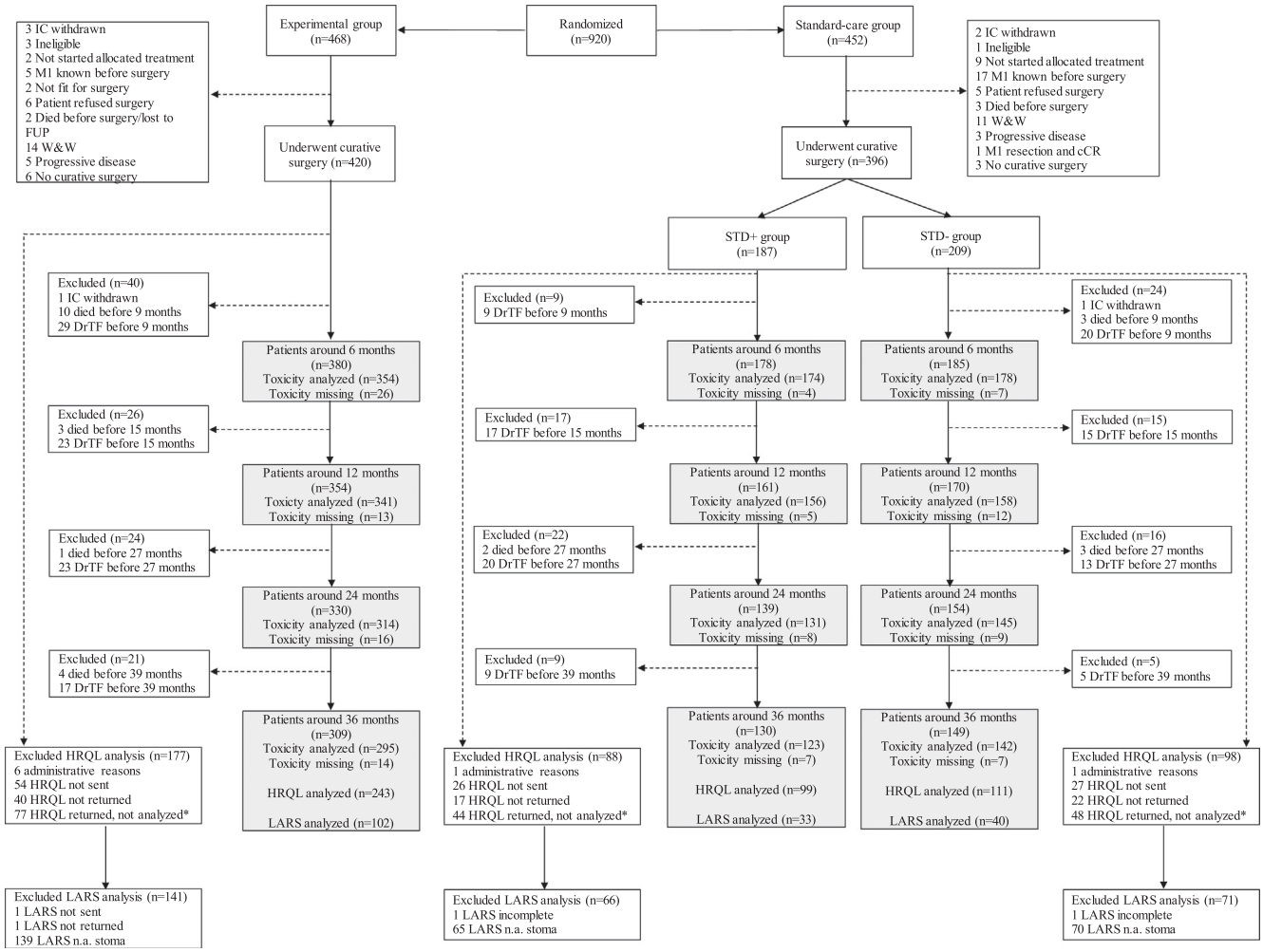

Fig. 1. Consort diagram. *STD+* standard-care with post-operative chemotherapy; STD− standard-care without post-operative chemotherapy; *IC* informed consent; *DrTF* Disease-related Treatment Failure; *LARS* low anterior resection syndrome. EXP: 77 HRQL returned, not analyzed included 56 DrTF before 3 years, 17 Filled in, out of window and 4 DrTF within 3–3.25 years patients. STD+: 44 HRQL returned, not analyzed included 36 DrTF before 3 years, 6 Filled in, out of window, 2 DrTF within 3–3.25 years patients. STD−: 48 HRQL returned, not analyzed included 35 DrTF before 3 years, 12 Filled in, out of window, 1 DrTF within 3–3.25 years patients.

Table 1
Clinicopathological characteristics of analyzed patients.

	EXP (*n* = 243)		STD (*n* = 210)		*p*-value	STD+ (*n* = 99)		STD− (*n* = 111)		*p*-value[§]
Gender					0.08					0.22
Male	144	−59.3	141	−67.1		66	−66.7	75	−67.6	
Female	99	−40.7	69	−32.9		33	−33.3	36	−32.4	
Age at randomization (years)					0.75					0.07
(median, IQR)	63	(55–68)	62	(54–69)		60	(52–67)	65	(57–69)	
Distance from anal verge on endoscopy (cm)					0.62[†]					0.65[†]
<5 cm	46	−18.9	50	−23.8		19	−19.2	31	−27.9	
5−10 cm	102	−42	73	−34.8		36	−36.4	37	−33.3	
≥10 cm	79	−32.5	71	−33.8		41	−41.4	30	−27	
Unknown	16	−6.6	16	−7.6		3	−3	13	−11.7	
Type of approach					0.19					<0.0001
Laparoscopic	100	−41.2	98	−46.7		32	−32.3	66	−59.5	
Open	119	−49	100	−47.6		63	−63.6	37	−33.3	
Laparoscopic converted to open	24	−9.9	12	−5.7		4	−4	8	−7.2	
Type of surgery					0.44					0.16
(Low) Anterior resection	148	−60.9	121	−57.6		64	−64.6	57	−51.4	
Abdominoperineal resection	86	−35.4	84	−40		35	−35.4	49	−44.1	
Hartmann's procedure	7	−2.9	5	−2.4		–		5	−4.5	
Other	2	−0.8	–			–		–		
Pathological T-stage *					<0.0001					<0.0001
ypT0	96	−39.5	42	−20		17	−17.2	25	−22.5	
ypTis	2	−0.8	1	−0.5		–		1	−0.9	
ypT1	13	−5.3	10	−4.8		7	−7.1	3	−2.7	
ypT2	45	−18.5	59	−28.1		24	−24.2	35	−31.5	
ypT3	72	−29.6	91	−43.3		47	−47.5	44	−39.6	
ypT4	15	−6.2	7	−3.3		4	−4	3	−2.7	
Pathological N-stage *					0.03					0.002
ypN0	203	−83.5	165	−78.6		73	−73.7	92	−82.9	
ypN1	35	−14.4	28	−13.3		13	−13.1	15	−13.5	
ypN2	5	−2.1	17	−8.1		13	−13.1	4	−3.6	
Stoma 3 years after surgery					0.11					0.25
No stoma	104	−42.8	75	−35.7		34	−34.3	41	−36.9	
Stoma	139	−57.2	135	−64.3		65	−65.7	70	−63.1	

Data are presented as n (%). Percentages may not equal 100% due to rounding.
EXP experimental; *STD* standard-care; *STD+* standard-care with post-operative chemotherapy; *STD-* standard-care without post-operative chemotherapy; *SD* standard deviation.
§ p-value represents the difference in mean scores between the EXP, STD- and STD+ groups.
† p-value calculated in patients in which the distance to the anal verge was known.
* According TNM 5.

scale (EXP 20.1 *vs*. STD 11.0; $p < 0.0001$), but not for the motor (EXP 11.7 *vs*. STD 8.5; $p = 0.11$) or the autonomic scales (EXP 7.9 *vs*. 7.2; $p = 0.61$) (details in Table S5). Clinically and statistically significant differences between the EXP and STD groups, in favor of the STD group were seen in tingling fingers or hands (small), tingling toes or feet (large), numbness toes or feet (moderate), pain in toes or feet (moderate) and trouble standing or walking (moderate). Comparison of the three groups for the items in the sensory score is displayed in Fig. 4, demonstrating that the EXP group experienced significantly more often pain in toes or feet ($p = 0.004$, moderate) than the STD+ group. For most items, the STD− group experienced fewer symptoms than either the EXP or the STD+ group (Fig. 4). Other than the items of the sensory score, clinically (all small) and statistically differences between the EXP and STD− in favor of the STD− group were seen in trouble handling small objects, overall QLQ-CIPN20 score and, the motor scale. Besides, a small clinically and statistically difference between the STD+ and STD− in favor of the STD− group was seen in the overall QLQ-CIPN20 score.

Major LARS occurred more frequently in the STD than in the EXP group (76.4% *vs.* 58.8%), but this difference was not statistically different ($p = 0.02$) (Table S6). Major LARS in the STD+ and STD− was similar (73% *vs.* 78%, Table S6).

Late toxicity over time regarding the EXP and STD group is summarized in Table S7 and Fig. S4. Significant differences in all combined toxicity between the two groups were not found at any time point. At 6 months approximately 56% of patients in both groups experienced any toxicity and this declined over time to 28% and 29% for EXP and STD groups, respectively, at 36 months (Table S7). Neurotoxicity was the most frequently reported toxicity. Grade 1–2 neurotoxicity was reported significantly more often in the EXP group at all time-points but toxicity grade 3 or higher did not differ significantly between the groups at any time-point (Table S7 and Fig. S1). Concerning other grade 1–2 toxicities, some statistically significant differences were observed at 6 months: fatigue (9% *vs*. 17%) and skin toxicity (3% *vs*. 9%) for EXP *vs.* STD, respectively, but none of these differences remained statistically significant at 12, 24 or 36 months (Table S7).

Late toxicity over time regarding the EXP, STD+ and STD− groups are summarized in Fig. 5a, 5b, and Table S8. The total toxicity rate at 6 months was 55%, 67%, and 45% for the EXP, STD+ and STD− group, respectively. At 12 months after surgery, the corresponding figures were 51%, 46%, and 35%, respectively. At 36 months, inter-group differences have disappeared with 28%, 28%, and 30% of patients experiencing any toxicity, respectively. Neurotoxicity was reported most in the EXP and STD+ group and mainly concerned grade 1–2 toxicity. At 6 months after surgery, 34%, 43%, and 2% of patients experienced any grade of neurotoxicity for EXP, STD+ and STD-, respectively. Only 5 patients (1%) in the EXP group experienced grade 3 toxicity at this time-point (Fig. 6 and Table S8). At 12 and 36 months, the frequency of neurotoxicity for EXP *vs.* STD+ was 29% *vs.* 27% and 14% *vs.* 11%, respectively. Grade ≥ 3 toxicity did not significantly differ between the three groups and was 9%, 9%, and 11% for EXP, STD+ and STD-, respec-

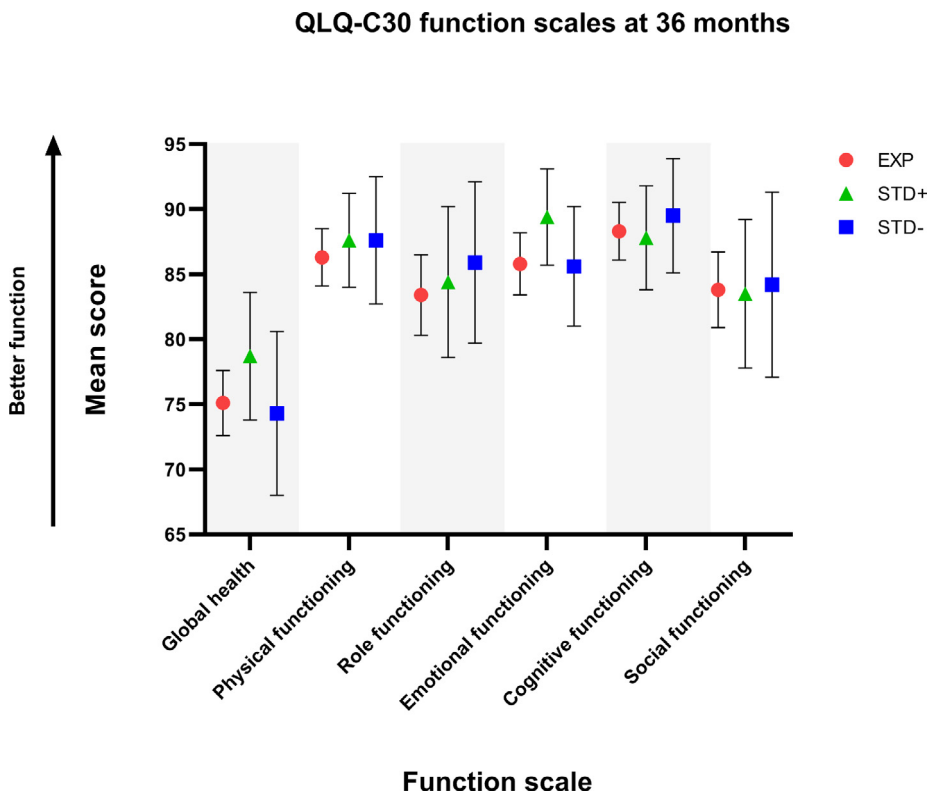

Fig. 2. EORTC QLQ-C30 function scales, provided as mean and 99% confidence interval. A higher score represents a better function. *EXP* experimental; *STD+* standard-care with post-operative chemotherapy; STD− standard-care without post-operative chemotherapy.

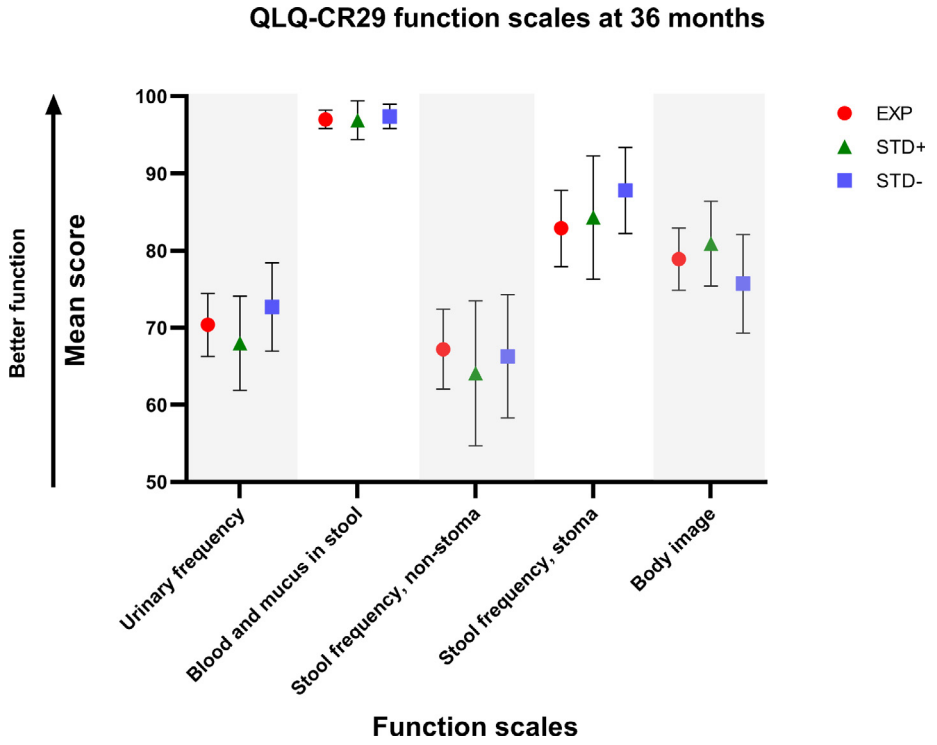

Fig. 3. EORTC QLQ-CR29 function scales, provided as mean and 99% confidence interval. A higher score represents a better function. *EXP* experimental; *STD+* standard-care with post-operative chemotherapy; STD− standard-care without post-operative chemotherapy.

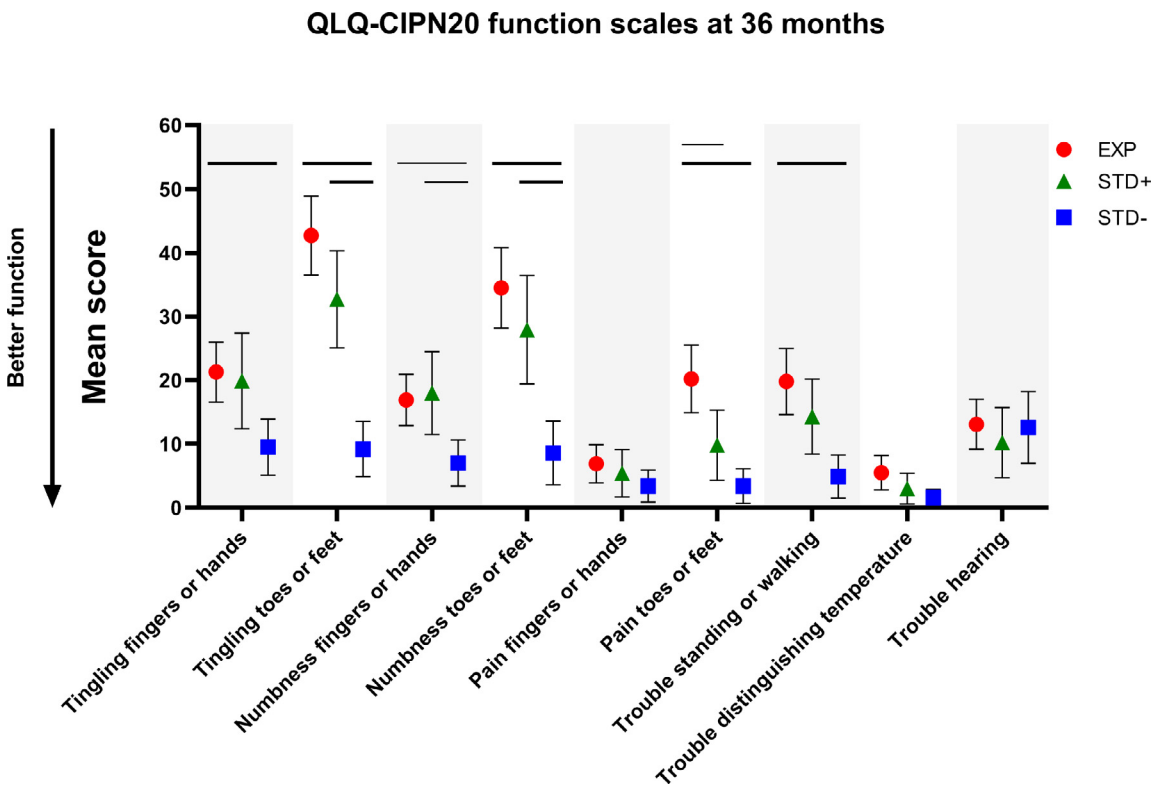

Fig. 4. EORTC QLQ-CIPN20 sensory scale, provided as mean and 99% confidence interval. A lower score represents a better function. The horizontal lines represent statistically significant differences between the groups; non-bold line $p < 0.004$ and bold line $p < 0.0001$. *EXP* experimental; *STD+* standard-care with post-operative chemotherapy; STD− standard-care without post-operative chemotherapy.

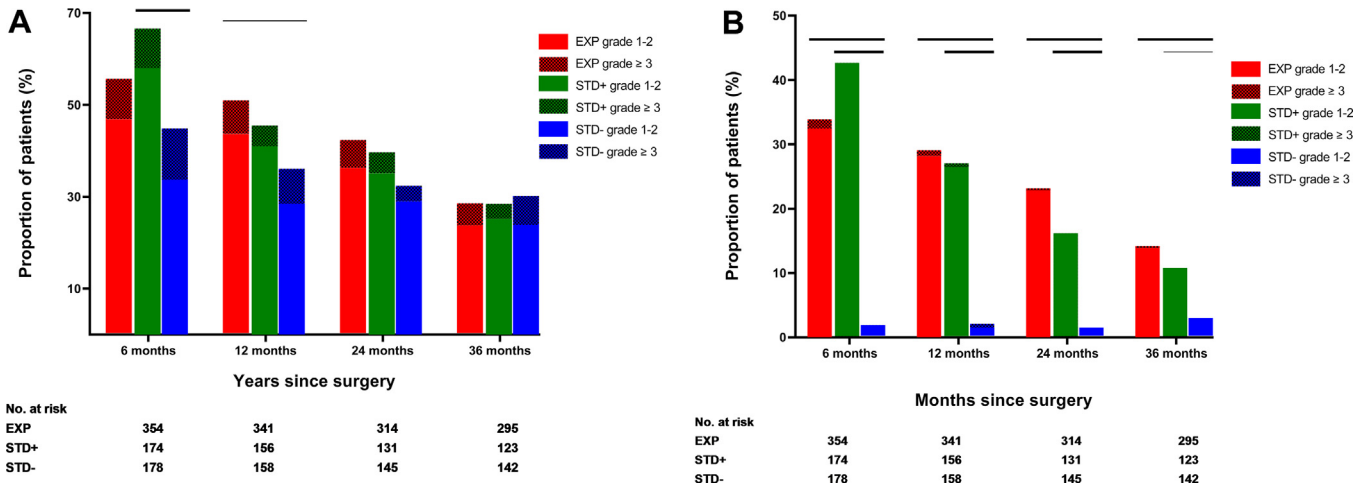

Fig. 5. (A) Toxicity and (B) neurotoxicity per follow-up moment regarding three subgroups. *n* represents the number of evaluable patients (excluding missing). Toxicity was scored with a range of 3 months at 6, 12, 24, and 36 months. The horizontal lines represent statistically significant differences in any toxicity grade between the groups; non-bold line $p = 0.002$ (in A) and $p = 0.010$ (in B) and bold line $p < 0.0001$. *EXP* experimental; *STD+* standard-care with post-operative chemotherapy; STD− standard-care without post-operative chemotherapy.

tively at 6 months (Table S8). However, some differences were observed for grade 1–2 toxicity. In Table S8, grade 1–2 toxicities at 6 months in the three groups are presented.

Discussion

The HRQL and long-term toxicity analyses of the RAPIDO trial reported here demonstrate that no significant differences are reported for either HRQL, bowel function, or late toxicity between the patients receiving TNT or standard CRT. In subgroup analyses, neurological toxicity and patient-reported neurological complaints were more often observed in patients receiving oxaliplatin, either in the pre- or post-operative settings.

The RAPIDO trial demonstrated that scRT followed by pre-operative chemotherapy results in improved oncological outcomes, including increased pCR rates, compared to standard CRT [12]. This report on HRQL, toxicity, and functional outcome, demonstrates that scRT and pre-operative chemotherapy can also be delivered without increasing adverse long-term effects for patients.

Three years after surgery, most patients experienced major LARS in both groups, with 59% in the EXP and 75% in the STD group. These figures underline the need for other strategies, such as non-operative management for complete responders. However, one must be cautious to extrapolate functional outcome after surgery towards the outcome in a non-operative setting, given that the current figures are influenced by both the (neo)adjuvant treatment and by surgery. Given the relatively high pCR rate of 28% after scRT followed by chemotherapy [12] this treatment is a better alternative than CRT, when the aim is to avoid surgery. Despite that the LARS is not a validated questionnaire for bowel function after organ preservation, non-randomized studies demonstrate that organ preservation is associated with better bowel function compared to pre-operative CRT and surgery [24,25]. Surgery and radiotherapy are both contributing to the development of major LARS [26,27]. The use of oxaliplatin did most probably not have an effect on LARS since patients in the experimental group, all receiving oxaliplatin, experienced less often major LARS. The experimental approach results in at least similar, and possibly even better bowel function than standard CRT at three years after surgery. Deterioration of bowel function beyond 3–4 years after surgery is caused by aging of the patients [28].

In general, pre-operative RT followed by surgery is accompanied by increased late toxicity compared to surgery alone [29]. The comparison of scRT with immediate surgery and CRT, as has been done in the Polish and TROG trials, demonstrated no difference in late toxicity between the two groups [30,31]. Prolonging the interval between scRT and surgery did not change the risk of late toxicity, being about 40% in the Stockholm III trial (median follow-up 5.2 years) [32]. Despite the introduction of systemic chemotherapy after scRT, we noted less late toxicity three years after surgery (28%), which can possibly be explained by the introduction of more advanced radiation and surgical techniques compared to the Stockholm III trial [32]. An important note is that the late toxicity numbers in the Stockholm III trial represent any reported late toxicity at any time post-operatively, making a direct comparison between the two trials difficult. Late toxicity results presented here are in line with the findings in the Polish II trial, with a similar design as the RAPIDO trial [33]. From this, we can again conclude that scRT combined with pre-operative chemotherapy can be considered as a safe treatment strategy.

As expected, the neurological toxicity was predominantly observed in patients receiving oxaliplatin-containing chemotherapy (either pre- or post-operatively). Recently published adjuvant trials in colon cancer [34] have demonstrated that reducing the number of CAPOX cycles from eight to four (or from twelve to six using FOLFOX), resulted in less toxicity without compromising oncological outcomes, at least for most subgroups. Extrapolating data from the colon cancer trials could lead to the assumption that the number of courses of CAPOX could be reduced from the six cycles used in the RAPIDO trial leading to reduced toxicity without compromising oncological outcomes. However, this assumption must be tested in trials.

The implementation of pre-operative chemotherapy inevitably leads to overtreatment for those who do not benefit from systemic chemotherapy. Further refinement of patient selection is therefore warranted. A more personalized approach based on imaging characteristics or biomarkers is not yet available. A careful weighing of expected benefits and harms should therefore be discussed with the patient in a shared decision-making process. The increasing interest in organ preservation makes this trade-off even more complicated; even though most patients will not develop distant metastases, they may benefit from an increased response with a subsequent greater chance for organ preservation.

It could be argued that a possible limitation of our study is that it is based on a subset of patients who were disease-free at time of analysis and underwent a curative resection. Since recurrence-related symptoms may blur HRQL and toxicity analyses, we feel this subset is justified. Besides, the RAPIDO trial cannot confirm nor refute this thought as patients with a recurrence did not receive HRQL questionnaires. The design of the trial included an optional post-operative chemotherapy policy in the CRT group. The decision to administer post-operative chemotherapy was indicated by center before the start of the trial, enabling us to compare the results of the group of patients who received post-operative chemotherapy and those who did not. However, some confounding may still be present, especially since patients who were unable to start with chemotherapy were included in the STD− group. A more favorable pathological stage may result in the omission of post-operative chemotherapy even if the policy for post-operative chemotherapy was present. However, additional intention-to-treat analyses did not demonstrate an influence of hospital policy on HRQL, bowel function, and late toxicity (data not shown). Another possible confounder is that compliance to the questionnaire was 79%, with non-responders being younger. Still, given that non-responders were equally divided over the two treatment groups, we feel this will not influence the results.

In conclusion, the RAPIDO trial is the largest randomized study comparing TNT with conventional CRT with or without post-operative chemotherapy in patients with locally advanced rectal cancer and high-risk features for recurrence. Despite the lack of overall survival benefit yet, we believe that the reduced DrTF and increased pCR rates, combined with similar HRQL, bowel function and (late) toxicity profiles up until three years after surgery, support the preference for TNT.

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Declaration of interests

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Appendix A. Supplementary data

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