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Original Article

Compliance and tolerability of short-course radiotherapy followed by preoperative chemotherapy and surgery for high-risk rectal cancer – Results of the international randomized RAPIDO-trial

Maxime J.M. van der Valk [a,*], Corrie A.M. Marijnen [b,c,3], Boudewijn van Etten [d,3], Esmée A. Dijkstra [e], Denise E. Hilling [a], Elma Meershoek-Klein Kranenbarg [a], Hein Putter [f], Annet G.H. Roodvoets [a], Renu R. Bahadoer [a], Tone Fokstuen [g], Albert Jan ten Tije [h], Jaume Capdevila [i], Mathijs P. Hendriks [j], Ibrahim Edhemovic [k], Andrès M.R. Cervantes [l], Derk Jan A. de Groot [e], Per J. Nilsson [m,2,3], Bengt Glimelius [n,2,3], Cornelis J.H. van de Velde [a,2,3], Geke A.P. Hospers [e,2,3,*], Collaborative investigators [1]

[a] *Department of Surgery;* [b] *Department of Radiotherapy;* [c] *Department of Radiotherapy, Netherlands Cancer Institute, Amsterdam;* [d] *Department of Surgery, University of Groningen, University Medical Center Groningen;* [e] *Department of Medical Oncology, University of Groningen;* [f] *Department of Medical Statistics, Leiden University Medical Center, The Netherlands;* [g] *Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden;* [h] *Department of Medical Oncology, Amphia Hospital, Breda, The Netherlands;* [i] *Department of Medical Oncology, Vall Hebron University Hospital, Vall Hebron Institute of Oncology (VHIO). Barcelona, Spain;* [j] *Department of Medical Oncology, Northwest Clinics, Alkmaar, The Netherlands;* [k] *Department of Surgical Oncology, Institute of Oncology Ljubljana, Slovenia;* [l] *Department of Medical Oncology, Hospital Clínico Universitario de Valencia, Spain;* [m] *Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden;* [n] *Department of Immunology, Genetics and Pathology, Uppsala University, Sweden*

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Background: Preoperative chemoradiotherapy (CRT) followed by total mesorectal excision is widely accepted as the standard of care for high-risk rectal cancer. Adjuvant chemotherapy is advised in several international guidelines, although the survival benefit remains unclear and compliance is poor. The current multidisciplinary approach has led to major improvements in local control, yet the occurrence of distant metastases has not decreased accordingly. The combination of short-course radiotherapy (SCRT) and chemotherapy in the waiting period before surgery might have several benefits, including higher compliance, downstaging and better effect of systemic therapy.
Methods: This is an investigator-initiated, international multicentre randomized phase III trial. High-risk rectal cancer patients were randomized to SCRT followed by chemotherapy (6 cycles CAPOX or alternatively 9 cycles FOLFOX4) and subsequent surgery, or long-course radiotherapy (25–28 $\times$ 2–1.8 Gy) with concomitant capecitabine followed by surgery and optional postoperative chemotherapy (8 cycles CAPOX or 12 cycles FOLFOX4) according to local institutions' policy. The primary endpoint is time to disease-related treatment failure. Here, we report the compliance, toxicity and postoperative complications in both study groups.
Findings: Between June 2011 and June 2016, 920 patients were enrolled. Of these, 901 were evaluable (460 in the experimental arm and 441 in the standard arm). All patients in the experimental arm received 5 $\times$ 5 Gy radiotherapy, and 84% of all patients received at least 75% of the prescribed chemotherapy. In the standard arm, the compliance for CRT was 93% and 58% for postoperative chemotherapy. Toxicity $\geq$grade 3 occurred in 48% of patients in the experimental arm, compared to 25% of patients in the standard arm during preoperative treatment and 35% of patients during postoperative chemotherapy. No statistically significant differences in surgical procedures or postoperative complications were observed.

* Corresponding authors at: Hanzeplein 1, P.O. Box 30.001, 9700 RB Groningen, The Netherlands (G.A.P. Hospers). Albinusdreef 2, P.O. Box 9600, 2300 RC Leiden, The Netherlands (M.J.M. van der Valk).
E-mail addresses: mvandervalk@lumc.nl (M.J.M. van der Valk), g.a.p.hospers@umcg.nl (G.A.P. Hospers).
[1] Full list displayed in Appendix, Table 1.
[2] Principal investigators of the RAPIDO-trial.
[3] Shared senior authorship.

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Interpretation: High compliance (84%) of preoperative systemic treatment could be achieved with the experimental approach. Although considerable toxicity was observed during preoperative therapy, this did not lead to differences in surgical procedures or postoperative complications. Longer follow-up time is needed to assess the primary endpoint and related outcomes.

Over the past decades, preoperative radiotherapy has been integrated as an essential part of the treatment of intermediate and high-risk rectal cancer. Long-course radiotherapy with concomitant 5FU-based chemotherapy (chemoradiotherapy, CRT), and total mesorectal excision (TME) after a period of 6–10 weeks is currently widely accepted as the standard of care for high-risk rectal cancer. Although this approach has led to remarkably low rates of local recurrence, the occurrence of distant metastases has not decreased accordingly.

In high-risk colon cancer, adjuvant chemotherapy has a beneficial effect on the risk of recurrence and survival [1,2]. For high-risk rectal cancer patients, the role of adjuvant chemotherapy after preoperative radiotherapy and curative resection is still under debate since several clinical trials have reported negative or inconclusive results [3]. Multiple possible explanations for the absence of a clear survival benefit have been suggested, including poor compliance, and postoperative complications causing delay or omission of adjuvant treatment [4]. Although the exact benefit remains unclear, adjuvant chemotherapy is advised for high-risk rectal cancer in several guidelines [5,6].

The rationale for preoperative long-course CRT in patients with high-risk rectal cancer, in addition to reducing the risk of local recurrence, is to induce locoregional tumour downsizing and thereby increase the chance of radical (R0) total mesorectal excision [7,8]. Short-course radiotherapy (SCRT) followed by immediate surgery is currently generally indicated to reduce the risk of local recurrence in intermediate risk resectable rectal cancer, where tumour downsizing is not required. However, similar downsizing effects as compared to CRT can be expected if a prolonged waiting period before surgery is handled. The recently reported Stockholm III trial suggests that the chances of a radical resection and risk of postoperative complications are not compromised by delaying surgery after SCRT [9–11]. Moreover, oncological outcomes after SCRT and delayed surgery were not inferior to long-course radiotherapy [12].

In the RAPIDO-trial, the rationale of the experimental treatment was to achieve better compliance and systemic effects by giving full-dose chemotherapy prior to surgery, after SCRT has been applied to induce locoregional tumour cell kill. The goal is to reduce the risk of distant metastases and improve survival while maintaining locoregional control. For the present report, we examined the safety of the experimental treatment, expressed as compliance, treatment-induced toxicity and postoperative complications compared to standard treatment and optional postoperative chemotherapy.

Methods

Study design

The 'RAPIDO'-trial (Rectal cancer And Preoperative Induction therapy followed by Dedicated Operation, ClincialTrials.gov identifier NCT01558921) is an investigator-initiated, international multicentre phase III two-arm randomised study. The details of the study protocol have been published previously [13]. In short, patients diagnosed with rectal cancer, less than 16 cm from the anal verge at endoscopy and with high-risk features on MRI were randomised with a 1:1 ratio to either the experimental treatment consisting of SCRT (5x5 Gy in one week), followed by 18 weeks of chemotherapy and subsequent TME; or the standard treatment arm, consisting of long-course radiotherapy (25–28 × 2–1.8 Gy) with concomitant capecitabine followed by TME after a 6–10 week waiting period, and subsequently optional 24 weeks of postoperative chemotherapy according to the local institutions' policy (Fig. 1).

Participants were recruited in the participating hospitals directly after diagnosis and before the start of any treatment. Inclusion criteria were histologically proven rectal adenocarcinoma with at least one of the following high-risk criteria on pelvic MRI: cT4a/b, cN2, extramural vascular invasion, involved mesorectal fascia and enlarged lateral lymph nodes considered to be metastatic. Additional criteria were age ≥18 years; ECOG performance score ≤1; staging within 5 weeks prior to randomisation; mentally and physically fit for chemotherapy; adequate potential for follow-up and written informed consent. Main exclusion criteria were extensive tumour growth into the sacrum above S3 or tumour

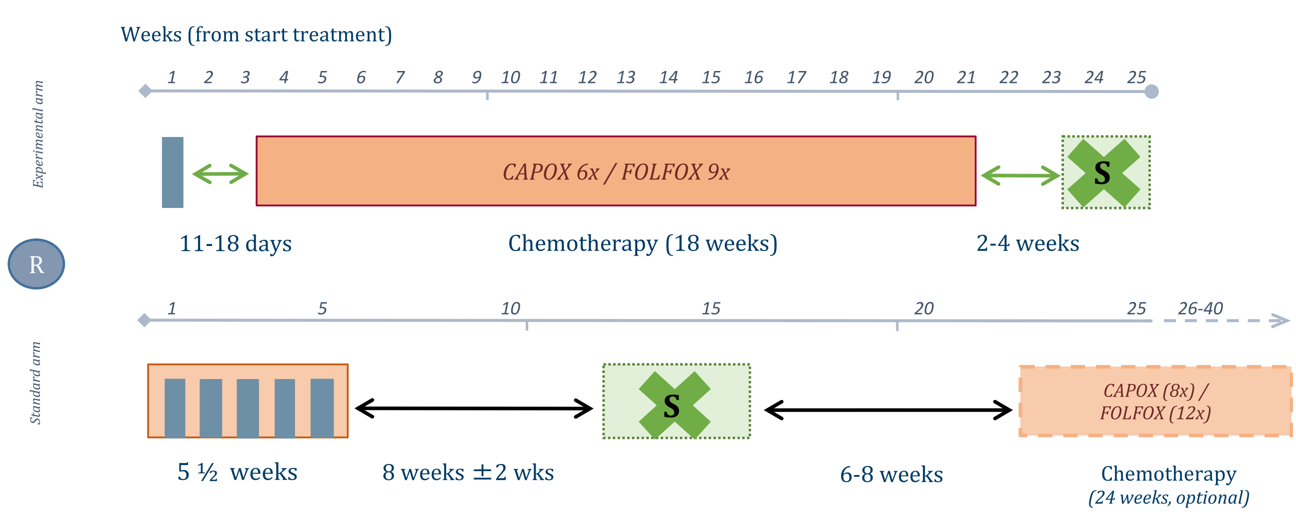

Fig. 1. Study protocol treatment for the experimental arm and standard arm per week.

involvement of the lumbosacral nerve roots; distant metastases at baseline; recurrent rectal cancer, active inflammatory bowel disease or known syndrome with predisposition for colorectal cancer, concomitant active other malignancy; known DPD deficiency and contraindications for MRI.

Randomisation and masking

Randomisation was performed centrally through the ProMISe randomisation program with stratification for institution, performance status (0/1), clinical T-stage (cT3/cT4) and clinical nodal status (cN−/cN+) (Clinical Research Center, Dept. of Surgery, Leiden, The Netherlands). Treatment groups were not masked throughout the trial. As advised by the data safety monitoring board after an interim analysis in 2017, the investigators and outcome adjudicators remain blinded for the primary outcome and all related outcomes until the data has matured.

Procedures

In the experimental arm, radiotherapy consisted of a total dose of 25 Gy in 5 daily fractions to the pelvis including the gross primary tumour volume with a margin and mesorectal and presacral lymph nodes. The lateral obturator and internal iliac nodes were included in the target volume for rectal tumours below the peritoneal reflection. Subsequent chemotherapy consisted of 6 cycles of capecitabine 1000 mg/m^2 twice daily on day 1–14; and oxaliplatin 130 mg/m^2 I.V. on day 1 (CAPOX); or alternatively 9 cycles of oxaliplatin 85 mg/m^2 I.V. on day 1, leucovorin 200 mg/m^2 I.V. on day 1 and 2; followed by a loading dose of 5-fluorouracil (5-FU) 400 mg/m^2 I.V. bolus; and 5-FU 600 mg/m^2 for a period of 22 hours on day 1 and day 2 every 2 weeks (FOLFOX4). In case of radiation-induced toxicity, the start of chemotherapy could be delayed by a maximum of 4 weeks. In case of chemotherapy-related $\geq$grade 3 toxicities, the dose of oxaliplatin and/or capecitabine was adapted for the next cycle according to protocol. Surgery was scheduled after a 2–4-week recovery period after the last chemotherapy cycle, at approximately 22–24 weeks after the start of radiotherapy (Fig. 1).

In the standard arm, patients received 28 fractions of 1.8 Gy or 25 fractions of 2.0 Gy (total 50–50.4 Gy), with similar target volumes as in the experimental group. Concomitant capecitabine 825 mg/m^2 was given twice daily on day 1 to 33–38, depending on the number of fractions. Approximately 8 weeks (±2 weeks) after the last radiotherapy fraction surgery was scheduled. Postoperative chemotherapy was optional and given according to the policy of individual institutions at the start of the institute's participation (either 8 cycles of CAPOX or max. 12 cycles FOLFOX4, Fig. 1). Toxicity was evaluated weekly during (chemo-)radiotherapy, and per cycle (2 or 3 weeks) during preoperative and postoperative chemotherapy.

Outcomes

After a protocol amendment in 2016, the primary endpoint of the RAPIDO-trial was changed from disease-free survival (DFS) to 'Disease-related Treatment Failure' (DrTF), which is a more appropriate endpoint for this neoadjuvant study setting, as some patients will never become disease free. DrTF is defined as the time between randomisation and either local or distant relapse, disease progression, resection with macroscopically involved margins (R2), rectal cancer-specific or treatment-related death, or diagnosis of a new colorectal cancer. Secondary endpoints are overall survival, the rates of R0 resection and negative circumferential margins, pathological complete response (pCR) rate, quality of life and functional outcomes. For the current compliance and safety analyses, all eligible patients who started the allocated treatment were included. Compliance for radiotherapy was defined as at least 25 Gy for patients in the experimental arm, and $\geq$45 Gy for patients in the standard arm with concurrent capecitabine for at least 25–28 days (depending on the number of radiotherapy fractions). Based on the results of previous studies, the definition of compliance for chemotherapy was met when a patient received at least 75% of the prescribed courses [14,15]. In case of toxicity, dose reductions were allowed as described in the protocol. When one of the study drugs was discontinued due to toxicity, this was considered a course modification. For patients in the experimental arm, this means at least 5 courses of CAPOX, 7 courses of FOLFOX4 or alternatively at least 4 courses of CAPOX and $\geq$1 capecitabine or at least 7 courses of chemotherapy in total in case of switch from CAPOX to FOLFOX4. For postoperative chemotherapy, the same definition was used.

The Common Terminology Criteria of Adverse Events classification (CTCAE, version 4.0) was used to report the highest grade of adverse events per patient during preoperative treatment and postoperative chemotherapy. Postoperative complications were classified according to the Clavien-Dindo classification [16]. In analyses regarding postoperative complications, all patients who underwent surgery with curative intent within 26 weeks of the last chemotherapy were evaluated. Surgical complications included surgical site-infections, intra-abdominal infections, wound dehiscence, anastomotic leak, postoperative bleeding, or other surgery-related complications. The occurrence of complications and death during pre- and postoperative therapy and within 30 days of surgery or postoperative admission were reported.

Statistics

Sample size calculations were based on the expected difference of 10% in the primary endpoint [13]. After a protocol amendment in June 2019, the difference was changed to 7.5%. For the secondary endpoints toxicity, compliance and postoperative complications, no formal power calculations were made. Data was used as available after a data lock January 16th 2020. In the current manuscript, it was our aim to describe the compliance and toxicity in both groups. We also examined if there were any differences in surgical procedures and postoperative complications. For these analyses, chi-square tests were used to compare proportions, whereas t-tests or Mann–Whitney U tests were used for comparison of continuous parameters, depending on the distribution of the data. A two-sided p-value of <0.01 was considered statistically significant. All analyses were performed in IBM SPSS Statistics (version 24.0).

Role of the funding source

The funders were not involved in the study design, data collection, data analysis, interpretation and writing of the report. MV, CM, GH, EM, AR had full access to the raw data. All authors have seen and approved the final manuscript and share responsibility for the decision to submit for publication.

Results

Between June 21th 2011 and June 2nd, 2016, 920 patients were randomised from 7 countries and 54 institutions. Of these, six patients were considered ineligible, because of a concurrent active malignancy (n = 2), no rectal cancer (n = 1), not mentally and physically fit (n = 2) or distant metastases before randomisation (n = 1) (Consort, please see supplementary material). Four patients had withdrawn their consent before the start of the allocated treatment; and 9 patients were excluded from the analyses since the allocated treatment was never started. In total, 901 patients were included in the safety and compliance analyses, of whom 460 in the experimental arm and 441 in the standard arm. Patient characteristics are reported in Table 1.

The compliance for radiotherapy in the experimental arm was 100%. All patients started chemotherapy, of whom 455 started with CAPOX and five with FOLFOX4. Twenty patients switched from CAPOX to FOLFOX4 during treatment. In 48 patients oxaliplatin was omitted for one or more courses and capecitabine monotherapy was given (10.4%). Three hundred and five patients completed all six courses of CAPOX and four patients completed nine cycles of FOLFOX4 (67%). In total, chemotherapy was delivered for at least 75% of the prescribed courses in 84% of all patients (387/460, Fig. 2).

In the standard arm, 62% of patients ($n = 275$) received fractions of 1.8 Gy, 37% ($n = 165$) received fractions of 2.0 Gy and the fraction dose was unknown in 1 patient. In total, 98% of all patients received a total irradiation dose of at least 45 Gy (433/441). Seven patients received less than 45 Gy and in one patient the total dose was unknown. Reasons for discontinuation radiotherapy before the threshold of 45 Gy were precordial pain ($n = 2$), ventricular fibrillation ($n = 1$) and colonic obstruction ($n = 3$), and one patient died during CRT. Capecitabine was started in 440 out of 441 patients and one patient started 5-FU. Capecitabine was continued for at least 5 weeks in 94% (413/441, Fig. 3A), with dose reductions due to toxicity in 25 patients (5.7%). In total, 93% (412/441) completed CRT according to protocol.

Two hundred and forty two out of 400 (60%) patients who underwent surgery with curative intent within 26 weeks were from an institution with a local policy for postoperative chemotherapy. Of these, 23% ($n = 55$) never started postoperative chemotherapy for various reasons: pathological node negative disease (ypT + N0, $n = 17$), pathological complete response ($n = 6$), patient refusal ($n = 5$), toxicity during CRT ($n = 7$), progressive disease ($n = 8$) and postoperative complications ($n = 7$) or patients not fit to receive chemotherapy ($n = 5$). Eventually, 187 patients (77%) started postoperative chemotherapy of whom 47% (89/187) completed at least 6 full cycles of CAPOX (Fig. 3B). In total, 58% (108/187) received at least 75% of the protocolled chemotherapy courses. The main reasons for stopping chemotherapy were toxicity or patient-reported poor compliance.

During preoperative therapy, grade ≥3 adverse events occurred in 48% of patients in the experimental arm, and in 25% of the standard arm (Table 2). Diarrhoea was the most common adverse event during preoperative therapy in both groups. During postoperative chemotherapy in the standard arm, 35% of patients experienced a grade ≥3 adverse event. Vascular disorders and neurological toxicity were the most commonly observed side-effects during systemic treatment with oxaliplatin (preoperative chemotherapy in the experimental arm and postoperative chemotherapy in the standard arm). In total four patients died (grade 5) during preoperative treatment. In the experimental arm, one patient died of a cardiac arrest in the presence of electrolyte disturbances. In the standard arm, one patient died due to neutropenic sepsis, one died of aspiration after a fall and one patient developed severe depression and committed suicide. No treatment-related deaths were reported during postoperative therapy. The total number of reported serious adverse events was similar in both arms (Appendix A).

In total, 826 patients (90%) went for curative intent surgery within 26 weeks according to protocol, 426 (91%) in the experimental arm and 400 (88%) in the standard arm. Reasons for exclusion from the analyses of surgical procedures and postoperative complications were progressive disease, watch and wait policy, and patients who refused surgery or who were unfit to undergo surgery (consort, please see supplementary material). In the experimental arm, 6 patients (1%) were diagnosed with progressive disease in the time before surgery, compared to 18 (4%) patients in the standard arm ($p < 0.01$). Details of the surgical procedures are reported in Table 3A. Surgery was performed at median 3.4 (IQR 2.3–5.1) weeks after the final chemotherapy cycle and median 23.6 weeks after the last radiotherapy in the experimental arm. Eight weeks after the final chemotherapy cycle and 27.5 weeks after the last radiotherapy, 90% of all patients had undergone surgery. In the standard arm, surgery was performed at median 8.9 (IQR 8.0–10.4) weeks after the last dose of capecitabine and radiotherapy, and after 12 weeks 90% of patients had undergone surgery.

Postoperative complications occurred in 50% and 47% of patients in the experimental arm and the standard arm, respectively ($p = 0.411$, Table 3B), with major postoperative complications (Clavien-Dindo grade III or higher) in 15% and 14% of patients, respectively ($p = 0.670$). In total, four patients died in-hospital or within 30 days after surgery. In the experimental arm, one patient died of a pulmonary embolism, five days postoperatively and two patients died of infectious complications 16 and 41 days after surgery, respectively. One patient in the standard arm died of a pulmonary embolism 11 days post-surgery.

Table 1
Patient characteristics of all patients that started allocated treatment.

	Experimental arm ($n = 460$) *n, (%)*	Standard arm ($n = 441$) *n, (%)*
Age at randomisation		
[mean, range]	61 [31–83]	61 [23–84]
Gender		
Male	299 (65)	304 (69)
BMI		
[mean, SD]	26.2 [4.4]	26.2 [4.4]
ECOG performance status		
0	368 (80)	358 (81)
1	92 (20)	83 (19)
Clinical T-and N-status		
cT2-3N0	24 (5)	19 (4)
cT2-3N+	289 (63)	278 (63)
cT4N0	23 (5)	23 (5)
cT4N+	124 (27)	121 (27)
High-risk criteria		
cT4 disease	151 (33)	144 (33)
cN2 disease	312 (68)	299 (68)
Lateral nodes	65 (14)	64 (15)
EMVI+	147 (32)	122 (28)
MRF+	284 (62)	263 (60)
Distance from anal verge (endoscopy)		
<5 cm	103 (22)	114 (26)
5–10 cm	180 (39)	148 (34)
≥10 cm	145 (32)	148 (34)
Unknown	32 (7)	21 (5)
Year of randomisation		
2011	7 (2)	10 (2)
2012	34 (7)	29 (7)
2013	95 (21)	106 (24)
2014	128 (28)	101 (23)
2015	148 (32)	139 (32)
2016	48 (10)	56 (13)
Country		
Denmark	16 (3)	11 (2)
The Netherlands	180 (39)	179 (41)
Norway	11 (2)	11 (2)
Slovenia	18 (4)	16 (4)
Spain	57 (12)	57 (13)
Sweden	168 (37)	157 (36)
United States	10 (2)	10 (2)

Data are presented as number of patients (%), unless indicated otherwise. BMI: body mass index; ECOG: Eastern Cooperative Oncology group; T-stage: Tumour stage; N-stage: Nodal stage; EMVI: Extramural vascular invasion; MRF: Mesorectal fascia; MRI: Magnetic Resonance Imaging.

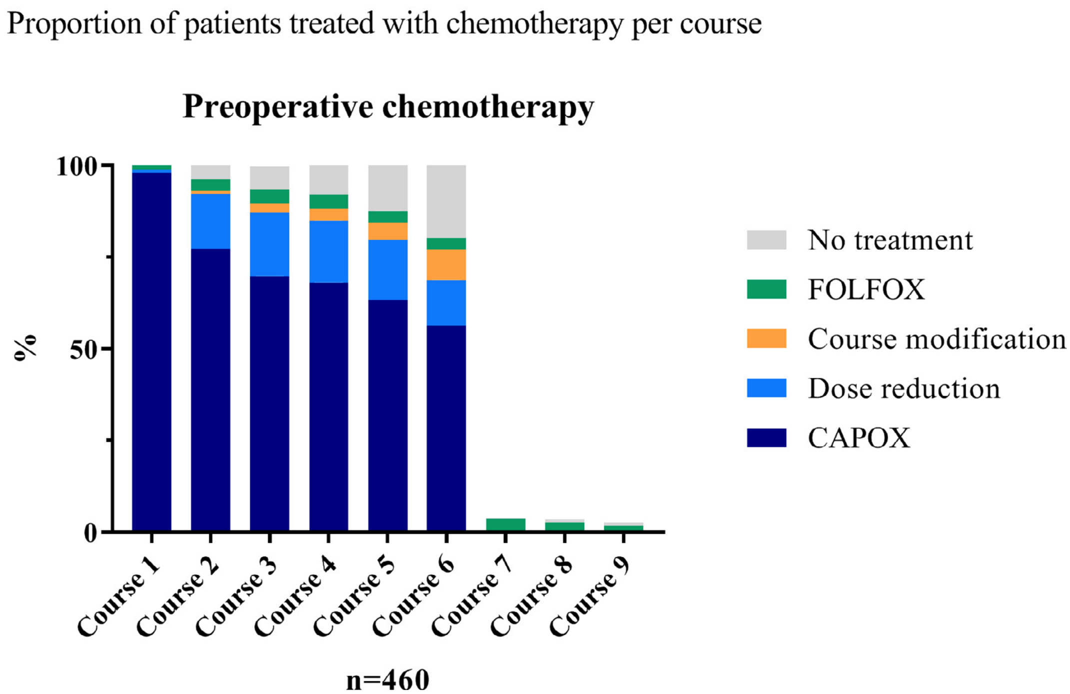

Fig. 2. Compliance in experimental arm. Proportion of patients treated with chemotherapy per course.

Discussion

The RAPIDO-trial was initiated to investigate the role of SCRT followed by 18 weeks of preoperative chemotherapy and surgery for patients with rectal cancer at high risk of systemic disease. Here, we report the compliance, toxicity and details of surgical complications in both study groups. We hypothesised that the experimental treatment would result in higher compliance of systemic treatment compared to postoperative treatment, without compromises in surgical procedures. Nearly all patients received the full dose of radiotherapy; 100% and 98% in the experimental and standard treatment arm respectively, with concurrent capecitabine in concordance with the protocol in 94% of patients receiving CRT. The compliance for oxaliplatin-containing chemotherapy before surgery was 84% for patients in the experimental arm, compared to only 58% postoperatively in the standard arm.

The occurrence of distant metastases is now the most common cause of uncontrollable disease in rectal cancer [17]. While it is established that adjuvant chemotherapy after curative resection improves disease-free and overall survival in patients with high-risk colon cancer, several trials and meta-analyses have failed to show a similar effect in rectal cancer patients who have already undergone neoadjuvant (chemo-)radiotherapy and curative surgery [3,18]. One of the possible explanations for the absence of a clear benefit is the low compliance rates reported for postoperative treatment in rectal cancer (43–74%), while compliance in patients with colon cancer is reported to be 70–86% [4]. Additionally, a large meta-analysis including mostly colon cancer patients, showed that the effect of systemic therapy appears to diminish if adjuvant chemotherapy is postponed [19]. By administering chemotherapy before surgery, significantly more patients received adequate systemic therapy compared to the conventional approach.

In addition, recent evidence has changed the views on the optimal duration of adjuvant therapy for patients with stage III colon cancer. A pooled analysis of four trials has shown very similar DFS at least in low risk patients (pT1-3N1) treated with 3 *versus* 6 months of oxaliplatin-containing chemotherapy [20]. Based on these findings, it appears that 3 months adjuvant therapy may be sufficient. For patients with high risk disease (cT4 and/or N2), this is less clear. In our data, 84% of all patients received at least 3 months of oxaliplatin-based chemotherapy in the preoperative setting, compared to 57% receiving this as postoperative treatment. However, it is uncertain whether these results and recommendations can be extrapolated to rectal cancer patients.

Some observational studies initially reported on the feasibility of 5x5 Gy and delayed surgery [9,10]. The Dutch "M1" study, including primary stage IV rectal cancer patients, was the first to incorporate preoperative chemotherapy after SCRT. In this phase II study, 90% of patients received at least 4 courses of preoperative CAPOX and bevacizumab after SCRT, and 84% received the full dose of 6 courses [15]. No tumour progression was observed in the interval between radiotherapy and surgery and a R0 resection could be accomplished in 72%. Bevacizumab was added to CAPOX in the "M1" study, but since there is no evidence that bevacizumab improves oncological outcome in stage II-III colon cancer, this was omitted in the RAPIDO-protocol [21]. It is widely accepted that preoperative CRT is superior to postoperative CRT in terms of local control, compliance and survival [7]. However, systemic treatment is still deferred until patients have recovered from surgery. Given the known limitations of postoperative chemotherapy, others have suggested to intensify CRT by adding oxaliplatin to preoperative CRT. The German CAO/ARO/AIO-04 study showed that the addition of oxaliplatin improved pCR rates and DFS, but an overall survival benefit was not detected [22]. Other trials have failed to reveal any gain [23–25]. A different strategy is to combine CRT and chemotherapy in the preoperative setting [26], either by adding preoperative chemotherapy in the waiting period between CRT and surgery, or alternatively start with chemotherapy followed by CRT and subsequent surgery [27,28]. The Spanish GCR-3 trial showed that with this approach, the compliance of systemic therapy is superior when delivered preoperatively compared to postoperatively. Although the rationale for these approaches is clear, the aforementioned trials demonstrated that the summed toxicity

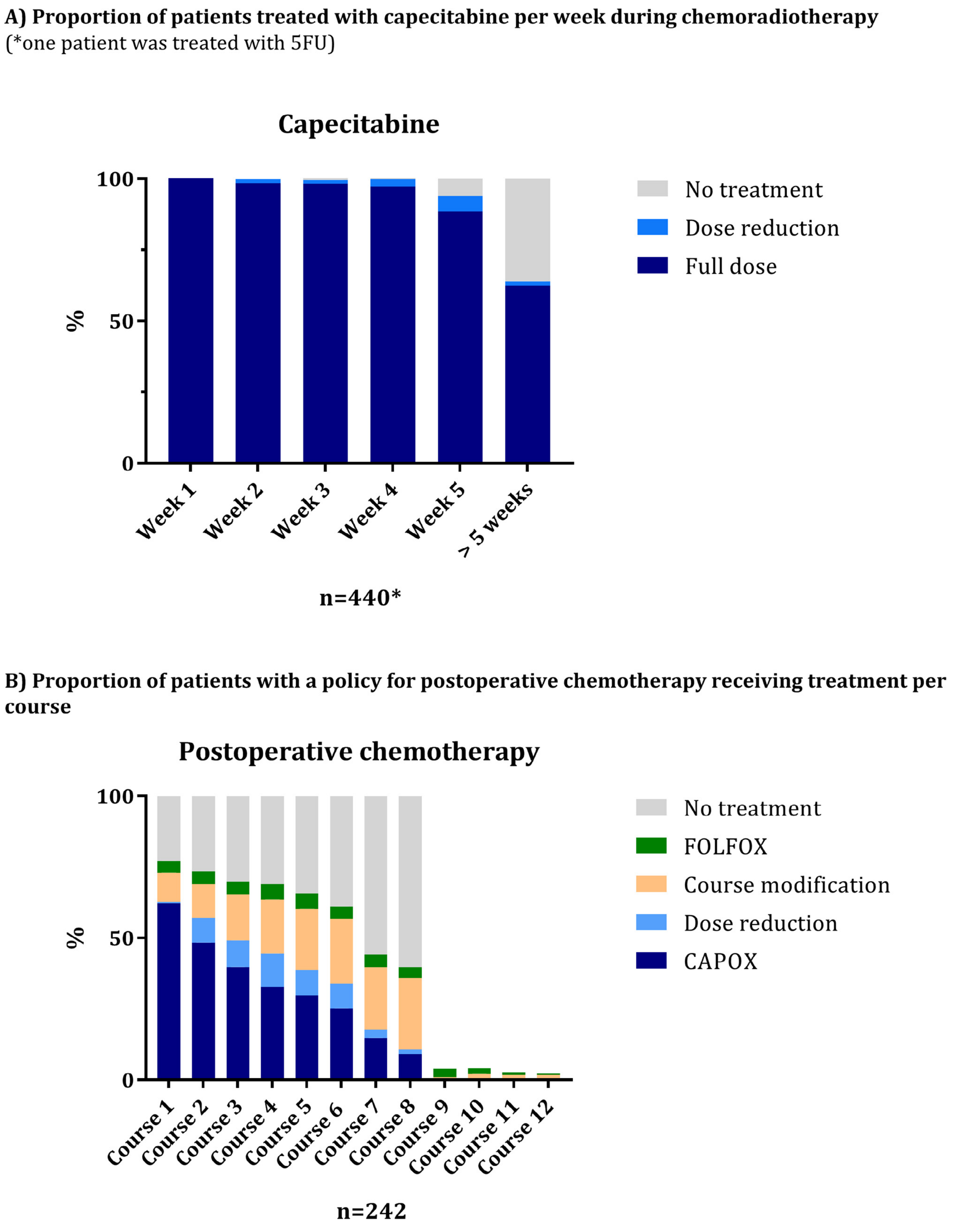

Fig. 3. Compliance in standard arm. (A) Proportion of patients treated with capacitabine per week during chemotherapy. (B) Proportion of patients with a policy for postoperative chemotherapy receiving treatment.

of CRT and chemotherapy can be extensive. To replace CRT by SCRT when full-dose systemic chemotherapy is administered preoperatively may therefore be a good alternative. The Polish II trial comparing CRT with concomitant oxaliplatin and SCRT followed by 3 courses of preoperative FOLFOX reported lower acute toxicity in the SCRT arm, and no differences were found in R0 resection rates

Table 2
Toxicity.

	Experimental arm	Standard arm	
	During preoperative therapy (n = 460) n (%)	During preoperative therapy (n = 441) n (%)	During postoperative therapy (n = 187) n (%)
Highest grade adverse event reported by patient			
Grade 1–2	238 (52)	323 (74)	119 (64)
Grade 3	191 (41)	98 (23)	58 (31)
Grade 4	30 (7)	10 (2)	7 (4)
Grade 5	1 (<1)	3 (<1)	0
Adverse events ≥CTCAE Grade 3			
General			
Febrile neutropenia	5 (1)	2 (<1)	1 (<1)
Mucositis	3 (<1)	–	–
Weight loss	3 (<1)	1 (<1)	–
Fatigue/Lethargy	14 (3)	6 (1)	10 (5)
Hand–foot syndrome	8 (2)	5 (1)	4 (2)
Neurological toxicity	20 (4)	1 (<1)	16 (9)
Blood and lymphatic system	5 (1)	4 (<1)	4 (2)
Cardiac disorders	7 (2)	10 (2)	–
Infections and infestations	18 (4)	7 (2)	6 (3)
Vascular disorders	39 (8)	18 (4)	1 (<1)
Gastro-intestinal toxicity			
Nausea or vomiting	19 (4)	5 (1)	5 (3)
Diarrhoea	81 (18)	41 (9)	13 (7)
Obstruction/constipation	15(3)	5 (1)	2(1)
Proctitis, rectal bleeding	8(2)	14(3)	1(1)
Abdominal pain	15 (3)	4 (1)	3 (2)
Other	20(4)	11(2)	3(2)

Toxicity was graded according to the Common Terminology Criteria for adverse events (CTCAE) version 4.0.

Table 3A
Surgical procedures. Surgical procedures in patients undergoing standard surgery with curative intention. Data are presented as n (%) or median (IQR). *Irresectable tumour or distant metastasis detected at surgery.

	Experimental arm (n = 426)		Standard arm (n = 400)		p
Type of approach					
Laparoscopic	178	(42%)	182	(46%)	0.310
Laparoscopic converted to open	42	(10%)	29	(7%)	
Open	206	(48%)	189	(47%)	
Type of resection					
No resection*	3	(<1%)	2	(<1%)	0.562
Hartmann procedure	22	(5%)	12	(3%)	
Abdominoperineal resection	147	(34%)	157	(39%)	
(Low) Anterior resection	246	(58%)	219	(55%)	
of which without stoma	*25*	*(10%)*	*27*	*(12%)*	
Other type of resection	9	(2%)	10	(3%)	
Duration of surgery					0.607
in minutes (median, IQR)	245 (198–330)		245 (185–324)		
missing	n = 27		n = 21		
Blood loss					0.007
in ml (median, IQR)	300 (150–650)		250 (100–500)		
missing	n = 83		n = 89		
Mesorectal plain as assessed by surgeon					0.032
Intact	334	(78%)	342	(85%) (6%)	
Breached	40	(9%)	23	(9%)	
Missing	52	(12%)	35		

and oncological outcomes between the treatment arms in this study [29]. Other benefits of SCRT include logistic simplicity, it is less demanding for patients and a reduction of the number of fractions can lead to cost-savings [30].

In the present study, the preoperative toxicity was higher in the experimental group compared to the standard arm, yet comparable to the toxicity of oxaliplatin-containing chemotherapy in the postoperative setting. Furthermore, the toxicity of the preoperative therapy did not lead to an increase in postoperative complication rates. It was observed that surgery could be performed within 8 weeks after the last course of chemotherapy in more than 90% of patients in the experimental arm. More importantly, there was no indication that the preoperative toxicity had any impact on resection rate, choice of surgical approach or type of surgery. No statistically significant differences between the two study arms with respect to rate or severity of postoperative complications were observed. Furthermore, treatment-related and postoperative mortality was low in both groups.

Table 3B
Surgical complications. Surgical complications within 30 days of surgery were reported, and graded according to the Clavien-Dindo classification. Data are displayed as n (%) or median (IQR). *Highest grade reported per patient. **Postoperative death <30 days or in-hospital death.

	Experimental arm (n = 426)	Standard arm (n = 400)	p
Hospital admission after surgery in days	9 (7–14)	8 (7–12)	
(median, IQR)			0.023
Readmissions after surgery	58 (14%)	61 (15%)	0.504
Total hospital admission			
including readmissions (median, IQR)	10 (7–15)	9 (7–14)	0.091
Any postoperative complication	215 (50%)	189 (47%)	0.411
CD classification*			
Grade I	58 (14%)	58 (15%)	
Grade II	84 (20%)	67 (17%)	
Grade III	62 (15%)	61 (15%)	
Grade IV–V	11 (3%)	3 (1%)	0.224
Patients with 1 or more general postoperative complication	79 (19%)	60 (15%)	0.174
≥CD grade II			
Cardiovascular	13 (3%)	10 (3%)	
Neurological	8 (2%)	4 (1%)	
Urological	10 (2%)	13 (3%)	
Pneumonia	23 (5%)	10 (3%)	
Sepsis	14 (3%)	6 (2%)	
Other infection	29 (7%)	18 (5%)	
Other	6 (1%)	8 (2%)	
Patients with 1 or more surgical complication	63 (15%)	55 (14%)	0.670
≥CD grade III			
Intra-abdominal infection	21 (5%)	18 (5%)	
Wound complications	13 (3%)	17 (4%)	
Ileus	17 (4%)	7 (2%)	
Anastomotic leakage	14 (3%)	9 (2%)	
(out of n patients with a primary anastomosis)	*246*	*219*	
Stoma related problems	3 (1%)	8 (2%)	
(out of n patients with a stoma)	*400*	*372*	
Other surgical complication	11 (3%)	7 (2%)	
Reoperations	42 (10%)	31 (8%)	0.286
Reasons			
Intra-abdominal infection/wound dehiscence	13 (3%)	13 (3%)	
Anastomotic leakage	10 (2%)	5 (1%)	
Bleeding	2 (<1%)	2 (<1%)	
Stoma complications	3 (<1%)	2 (<1%)	
Ileus	9 (2%)	6 (2%)	
Other reason	5 (1%)	3 (<1%)	
Postoperative mortality**	3 (<1%)	1 (<1%)	0.347

Another concern of replacing CRT by SCRT in locally advanced rectal cancer patients is related to the efficacy of 25 Gy in one week compared to more than 45 Gy with chemotherapy (CRT) in 5–6 weeks, and the impact on local control. The two RCTs comparing SCRT to long-course CRT did not show differences in surgical procedures or local control, despite a difference in pCR rates in favour of the CRT arm [31,32]. The absence of downstaging after SCRT in these two studies can be explained by the short interval between SCRT and surgery. Several other studies have demonstrated that 5 $\times$ 5 Gy induces downstaging and downsizing when the interval between RT and surgery is prolonged [9,10,33]. In the Stockholm III trial, the downstaging effect was more pronounced after 5x5 Gy with delayed surgery than after long-course radiotherapy (25 $\times$ 2Gy) without chemotherapy [11], giving an indication that the cell kill effect of SCRT should not be a major concern even for locally advanced cancers, particularly not if effective systemic chemotherapy is added. In the SCRT with delay group of the Stockholm III trial, surgery was performed 4–8 weeks after termination of radiotherapy, and this did not lead to inferior local control or more postoperative complications compared to long-course radiotherapy or SCRT and immediate surgery [12]. An interval of more than 20 weeks between radiotherapy and surgery in the experimental arm in the present study did not lead to differences in the details of surgical procedures or postoperative complications. Moreover, progressive disease was observed less frequently than in the standard arm with an interval of only 6–10 weeks.

Due to an unexpected overall low event rate, a protocol amendment has been approved for the event-driven primary endpoint of the RAPIDO trial. As the aim of the present report was to describe the tolerability of the experimental treatment rather than to detect or exclude any differences between the study groups, no pairwise comparison of the toxicity rates was performed. Moreover, as postoperative chemotherapy was optional for patients randomized to the standard arm, there were considerable differences in the denominator of preoperative and postoperative therapy and the latter group is possibly influenced by selection of patients fit for chemotherapy after surgery. Furthermore, we did not collect patient-reported outcomes for toxicity, which could have led to underestimation of the toxicity profiles. However, the use of the CTCAE classification makes underestimation of the incidence of ≥grade 3 toxicity unlikely. With regards to the generalisability of the results, the median age of 61 year and exclusion of patients with ECOG performance score > 1 indicate a study population of young and fit patients, while toxicity profiles may be more serious in elderly or frail patients.

In conclusion, high compliance of systemic therapy could be achieved with the experimental schedule of SCRT followed by preoperative systemic chemotherapy. Although considerable preoperative toxicity was reported compared to CRT, no differences were found in the details of surgical procedures, the proportion of patients undergoing surgery and the rate or severity of postoperative complications. The final results of the RAPIDO-trial on the oncological and health-related quality of life outcomes of this approach are awaited.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.03.011.

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