Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO) a randomised, open-label, phase 3 trial

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Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial

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Summary

Background Systemic relapses remain a major problem in locally advanced rectal cancer. Using short-course radiotherapy followed by chemotherapy and delayed surgery, the Rectal cancer And Preoperative Induction therapy followed by Dedicated Operation (RAPIDO) trial aimed to reduce distant metastases without compromising locoregional control.

Methods In this multicentre, open-label, randomised, controlled, phase 3 trial, participants were recruited from 54 centres in the Netherlands, Sweden, Spain, Slovenia, Denmark, Norway, and the USA. Patients were eligible if they were aged 18 years or older, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, had a biopsy-proven, newly diagnosed, primary, locally advanced rectal adenocarcinoma, which was classified as high risk on pelvic MRI (with at least one of the following criteria: clinical tumour [cT] stage cT4a or cT4b, extramural vascular invasion, clinical nodal [cN] stage cN2, involved mesorectal fascia, or enlarged lateral lymph nodes), were mentally and physically fit for chemotherapy, and could be assessed for staging within 5 weeks before randomisation. Eligible participants were randomly assigned (1:1), using a management system with a randomly varying block design (each block size randomly chosen to contain two to four allocations), stratified by centre, ECOG performance status, cT stage, and cN stage, to either the experimental or standard of care group. All investigators remained masked for the primary endpoint until a prespecified number of events was reached. Patients allocated to the experimental treatment group received short-course radiotherapy (5×5 Gy over a maximum of 8 days) followed by six cycles of CAPOX chemotherapy (capecitabine 1000 mg/m² orally twice daily on days 1–14, oxaliplatin 130 mg/m² intravenously on day 1, and a chemotherapy-free interval between days 15–21) or nine cycles of FOLFOX4 (oxaliplatin 85 mg/m² intravenously on day 1, leucovorin [folinic acid] 200 mg/m² intravenously on days 1 and 2, followed by bolus fluorouracil 400 mg/m² intravenously and fluorouracil 600 mg/m² intravenously for 22 h on days 1 and 2, and a chemotherapy-free interval between days 3–14) followed by total mesorectal excision. Choice of CAPOX or FOLFOX4 was per physician discretion or hospital policy. Patients allocated to the standard of care group received 28 daily fractions of 1·8 Gy up to 50·4 Gy or 25 fractions of 2·0 Gy up to 50·0 Gy (per physician discretion or hospital policy), with concomitant twice-daily oral capecitabine 825 mg/m² followed by total mesorectal excision and, if stipulated by hospital policy, adjuvant chemotherapy with eight cycles of CAPOX or 12 cycles of FOLFOX4. The primary endpoint was 3-year disease-related treatment failure, defined as the first occurrence of locoregional failure, distant metastasis, new primary colorectal tumour, or treatment-related death, assessed in the intention-to-treat population. Safety was assessed by intention to treat. This study is registered with the EudraCT, 2010-023957-12, and ClinicalTrials.gov, NCT01558921, and is now complete.

Findings Between June 21, 2011, and June 2, 2016, 920 patients were enrolled and randomly assigned to a treatment, of whom 912 were eligible (462 in the experimental group; 450 in the standard of care group). Median follow-up was 4·6 years (IQR 3·5–5·5). At 3 years after randomisation, the cumulative probability of disease-related treatment failure was 23·7% (95% CI 19·8–27·6) in the experimental group versus 30·4% (26·1–34·6) in the standard of care group (hazard ratio 0·75, 95% CI 0·60–0·95; p=0·019). The most common grade 3 or higher adverse event during preoperative therapy in both groups was diarrhoea (81 [18%] of 460 patients in the experimental group and 41 [9%] of 441 in the standard of care group) and neurological toxicity during adjuvant chemotherapy in the standard of care group (16 [9%] of 187 patients). Serious adverse events occurred in 177 (38%) of 460 participants in the experimental group and, in the standard of care group, in 87 (34%) of 254 patients without adjuvant chemotherapy and in 64 (34%) of 187 with adjuvant chemotherapy. Treatment-related deaths occurred in four participants in the experimental group (one cardiac arrest, one pulmonary embolism, two infectious complications) and in four participants in the standard of care group (one pulmonary embolism, one neutropenic sepsis, one aspiration, one suicide due to severe depression).

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See Online for appendix

Interpretation **The observed decreased probability of disease-related treatment failure in the experimental group is probably indicative of the increased efficacy of preoperative chemotherapy as opposed to adjuvant chemotherapy in this setting. Therefore, the experimental treatment can be considered as a new standard of care in high-risk locally advanced rectal cancer.**

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Introduction

Standard of care for locally advanced rectal cancer consists of chemoradiotherapy followed by surgery according to total mesorectal excision principles after 6–8 weeks. In several countries, adjuvant chemotherapy is also part of the standard of care. Preoperative chemoradiotherapy aims to downstage tumours, leading to improved locoregional control with local recurrence rates of approximately 5–9%.[1,2] However, unfortunately the occurrence of distant metastases has not decreased accordingly.

Downstaging also occurs after short-course radiotherapy followed by delayed surgery, as found in the Stockholm III trial.[3] Although the evidence is not entirely conclusive, many centres administer adjuvant chemotherapy intended to reduce systemic relapses, but compliance is suboptimal.[2,4,5] Surgery can safely be delayed after short-course radiotherapy, creating a window of opportunity to deliver chemotherapy preoperatively instead of postoperatively—an approach that is expected to increase compliance.[6,7] We hypothesised that this approach might result in a decreased number of distant metastases without increasing the risk of locoregional failure, ultimately improving survival outcomes.

The Rectal cancer And Preoperative Induction therapy followed by Dedicated Operation (RAPIDO) trial is based on the Dutch M1-trial[8] in which patients with metastatic primary rectal cancer received short-course radiotherapy,

Research in context

Evidence before this study

On May 15, 2020, we searched PubMed, without any language or date restrictions, using terms related to rectal cancer, short-course radiotherapy, and preoperative chemotherapy. We found no randomised trials that used the approach of 5 × 5 Gy radiotherapy followed by 18 weeks of preoperative chemotherapy and curative surgery in patients with locally advanced rectal cancer. Research in the past two decades has resulted in improved categorisation of rectal cancer, especially by MRI. More precise surgery and appropriate use of preoperative radiotherapy or chemoradiotherapy have yielded considerably lower rates of local recurrence than has been seen before. However, distant metastases have not decreased and, as a result, overall survival has not improved proportionally. By contrast with its successful use in colon cancer, adjuvant chemotherapy, although used extensively in many countries, has not convincingly affected rates of recurrence or survival in rectal cancer. Randomised trials have shown poor tolerability for adjuvant chemotherapy, possibly explaining the absence of effect. Therefore, we hypothesised that delivering preoperative chemotherapy after radiotherapy would increase compliance, reduce distant metastases, and ultimately improve survival. This approach, called total neoadjuvant therapy, resulted in the initiation of several phase 2 trials, with favourable outcomes.

Added value of this study

The experimental treatment of the RAPIDO trial decreased the rate of disease-related treatment failure compared with standard of care, mainly due to fewer distant metastases. Moreover, this approach doubled the rate of pathological complete response compared with the standard of care treatment. No differences regarding locoregional failure and overall survival after 3 years of follow-up were observed. The results also suggested that the experimental treatment could have additional benefits, such as fewer visits to specialised health-care facilities, a prominent advantage in the context of the COVID-19 pandemic.

Implications of all the available evidence

Preoperative short-course radiotherapy followed by chemotherapy and total mesorectal excision could be considered as a new standard of care. The PRODIGE 23 trial has also reported improved results with a total neoadjuvant therapy approach compared with a similar standard of care treatment as used in the RAPIDO trial, although with a more demanding experimental treatment with triplet chemotherapy and conventional chemoradiotherapy. These trials add strong evidence to support the proposal that total neoadjuvant therapy should replace the current standard treatment since it decreases the risk of systemic relapse and could potentially improve overall survival. In future research, data from the RAPIDO trial will be used to explore dose-effect associations for tumour control and toxicity of the radiotherapy and chemotherapy regimens, quality of MRIs, quality of life, local recurrence, and metastatic patterns. Furthermore, in the context of the growing interest in organ preservation in rectal cancer treatment, the high rate of pathological complete response observed in the experimental treatment group of RAPIDO is encouraging.

followed by six cycles of capecitabine, oxaliplatin, and bevacizumab, and surgery after 6–8 weeks. High chemotherapy compliance (42 [84%] of 50 patients received six cycles) and primary tumour downstaging in 20 (47%) of 43 patients were reported. Moreover, a pathological complete response of the primary tumour occurred in 11 (26%) of 43 patients.[8] Similarly, favourable experiences of combining short-course radiotherapy and subsequent chemotherapy have been reported in Sweden.[6]

The main objective of the RAPIDO trial was to reduce disease-related treatment failure at 3 years with short-course radiotherapy followed by chemotherapy and total mesorectal excision compared with standard chemoradiotherapy, total mesorectal excision, and optional adjuvant chemotherapy (predefined by hospital policy). Data on compliance, toxicity, and postoperative complications in the RAPIDO trial have been published previously.[9] Here we present the primary endpoint after a median follow-up of 4·6 years.

Methods

Study design and participants

The RAPIDO trial was an investigator-driven, open-label, randomised, controlled, phase 3 trial, done at in 54 hospitals and radiotherapy centres in seven countries (the Netherlands, Sweden, Spain, Slovenia, Denmark, Norway, and the USA). The study was coordinated by the Clinical Research Center (Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands), including randomisation, trial and database management, quality assurance, and quality control (EM-KK and AGHR).

Patients were eligible for inclusion if they were aged 18 years or older, with a biopsy-proven, newly diagnosed, primary, locally advanced rectal adenocarcinoma with distal extension less than 16 cm from the anal verge. A pelvic MRI with at least one of the following high-risk criteria was required: clinical tumour (cT) stage cT4a or cT4b, extramural vascular invasion, clinical nodal (cN) stage cN2, involved mesorectal fascia (tumour or lymph node ≤1 mm from the mesorectal fascia), or enlarged lateral lymph nodes considered to be metastatic. For all staging, the TNM-5 classification was used.[10] Other inclusion criteria were that the patient must be mentally and physically fit for chemotherapy, have an Eastern Cooperative Oncology Group (ECOG) performance score of 0–1, be assessed for staging within 5 weeks before randomisation, be available for follow-up, and provide written informed consent. Additionally the following laboratory results were required: a white blood cell count of $4·0\times10^9$ cells per L or higher, platelet count of 100×10^9 per L or higher, a clinically acceptable haemoglobin level, a creatinine level indicating renal clearance of 50 mL/min or higher, and bilirubin level below 35 µmol/L. Comorbidities were permitted. Exclusion criteria included extensive growth of the rectal tumour into the cranial part of the sacrum or the lumbosacral nerve roots indicating that surgery will never be possible even if substantial tumour downsizing is seen and presence of metastatic disease or recurrenct rectal cancer. Full exclusion criteria are provided in the appendix (p 53).

The trial was carried out in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. Surgery was mandatory; therefore, a watch-and-wait strategy was considered a protocol violation. After central evaluation by the medical ethics committee of University Medical Center Groningen (Groningen, Netherlands [2011/098]), the boards of directors or local ethics committees of all participating centres approved the protocol. The protocol is included in the appendix (pp 24–137).

Randomisation and masking

Patients were recruited at the participating hospitals before commencement of any treatment and randomly assigned (1:1) by use of the ProMISe data management system (version 4.0) using a stratified and randomly varying block design (each block size was randomly chosen to contain two to four allocations), to either the experimental group or standard of care group. Stratification factors were institution, ECOG performance status (0 or 1), cT stage (cT2–cT3 or cT4), and cN stage (cN– or cN+). Randomisation was coordinated by the Clinical Research Center. All investigators remained masked to treatment assignment for the primary endpoint until the prespecified number of events was reached. Due to the nature of the intervention, patients and clinical staff were not masked to group assignment.

Procedures

A high-resolution, three-dimensional T2-weighted sequence MRI was mandatory before and after preoperative treatment. The protocol specified details on MRI reporting (appendix pp 24–137). MRI reports minimally included the following details: tumour height from the anorectal junction, morphology of the tumour, depth of extramural spread, presence or absence of extramural vascular invasion, mesorectal fascia involvement, breach of the peritoneal reflection by the tumour, presence or absence of mesorectal or extra-mesorectal lymph node metastases, and, at restaging, the response to preoperative treatment. Mesorectal lymph nodes with a short axis diameter of more than 10 mm and round shape, and those with a short axis of 5–9 mm and meeting at least two criteria of round shape, irregular border, or heterogeneous signal intensity on MRI were defined as metastatic.[11] Extra-mesorectal lymph nodes with an irregular border or heterogeneous signal intensity, or both, or round lymph nodes with a short axis diameter of more than 10 mm, or a combination of these factors, were considered to be metastatic.

An overview of both treatment regimens is provided in the appendix (p 7). Patients in the experimental group were assigned to short-course radiotherapy (5×5 Gy),

administered over a maximum of 8 days. Chemotherapy was preferably started within 11–18 days after the last radiotherapy fraction, but within at least 4 weeks. Chemotherapy consisted of six cycles of CAPOX (capecitabine 1000 mg/m² orally twice daily on days 1–14, oxaliplatin 130 mg/m² intravenously on day 1, and a chemotherapy-free interval between days 15–21) or nine cycles of FOLFOX4 (oxaliplatin 85 mg/m² intravenously on day 1, leucovorin [folinic acid] 200 mg/m² intravenously on days 1 and 2, followed by bolus fluorouracil 400 mg/m² intravenously and fluorouracil 600 mg/m² intravenously for 22 h on days 1 and 2, and a chemotherapy-free interval between days 3–14). After completion of chemotherapy, surgery according to total mesorectal excision principles was planned after 2–4 weeks. The choice of CAPOX or FOLFOX4 was determined by the treating physician and according to hospital policy.

In the standard of care group, patients received radiotherapy in 28 daily fractions of 1·8 Gy up to 50·4 Gy or 25 fractions of 2·0 Gy up to 50·0 Gy, as per the decision of the treating physician and hospital policy, with concomitant twice-daily oral capecitabine 825 mg/m². Optional field reduction was recommended after 45 Gy (1·8 Gy schedule) or 46 Gy (2·0 Gy schedule), with the last fractions delivered to the tumour bed. Surgery according to total mesorectal excision principles was planned 6–10 weeks after the last radiotherapy fraction. If protocolised by the participating centre, adjuvant chemotherapy was administered within 6–8 weeks using eight cycles of CAPOX or 12 cycles of FOLFOX4.

In both groups, the clinical target volume for radiotherapy included the entire mesorectum with the primary tumour and relevant regional lymph nodes; an additional boost dose was optional. The clinical target volume of the boost was the assessable tumour with a 1 cm margin within the same anatomical compartment as where the tumour is located. In case of toxicity (according to Common Terminology Criteria for Adverse events [CTCAE] version 4) a dose reduction of 25% or more (relative to the previous chemotherapy cycle) was protocolised (appendix p 8). Laboratory and adverse event monitoring during preoperative therapy was done before all cycles in the experimental group and weekly in the standard of care group. Adverse events related to preoperative and adjuvant therapy were assessed and graded by the local investigator using CTCAE version 4 and postoperative complications using the Clavien-Dindo classification.[12] Surgery was done according to total mesorectal excision principles; a partial mesorectal excision was accepted for proximal tumours. Open and laparoscopic approaches were allowed and at the surgeon's discretion. The completeness of resection was assessed using the residual tumour classification.[13] Pathological assessment of the resected sample was done according to national guidelines of each participating country and included standardised work up and reporting. The involvement of circumferential resection margins, quality of the sample, and complete tumour response (yes or no) were recorded. Quality of the resection was assessed at two different levels for abdominoperineal excision (mesorectum and anal canal) and at one level for anterior resection (mesorectum). A serious adverse event was defined as any untoward medical occurrence or effect that at any dose: results in death; is life threatening (at the time of the event); requires admission to hospital or extension of ongoing hospital stay; results in persistent or clinically significant disability or incapacity; is a congenital anomaly or birth defect; or is a new event of the trial likely to affect the safety of the participants, such as an unexpected outcome of an adverse reaction, lack of efficacy of a study drug used for the treatment of a life threatening disease, and major safety finding from a newly completed animal study.

A standardised, minimal follow-up schedule was defined, with clinical assessments at 6, 12, 24, 36, and 60 months after surgery, including carcinoembryonic antigen measurement. Total colonoscopy was obligatory within the first year unless done preoperatively. The study protocol mandated chest x-ray or CT of the thorax and liver ultrasound or CT of the abdomen at 12 and 36 months as a minimum. A colonoscopy was mandatory 60 months postoperatively. On indication, other diagnostics (eg, PET CT scan) were allowed, to confirm or detect recurrent disease. Functional outcome and health-related quality of life of patients who did not have a disease-related treatment failure event within 36 months after surgery were measured once, using three European Organisation for Research and treatment of Cancer (EORTC) questionnaires: the quality-of-life questionnaire for patients with cancer (QLQ-C30), the quality-of-life questionnaires for patients with colorectal cancer (QLQ-CR29; supplemented with questions related to sexual functioning from the prostate cancer [QLQ-PR25] and endometrial cancer [QLQ-EN24] modules) and the quality-of-life questionnaire to assess chemotherapy-induced peripheral neuropathy (QLQ-CIPN20). The low anterior resection syndrome (LARS) scores, regarding bowel function, were also measured.[14] These questionnaires were available in the official languages of each country, except Slovenian. Hence patients from Slovenia were not assessable for the 3-year endpoint of quality of life.

Outcomes

The primary endpoint was disease-related treatment failure, defined as the first occurrence of locoregional failure, distant metastasis, a new primary colorectal tumour, or treatment-related death. Locoregional failure included locally progressive disease leading to an unresectable tumour, local R2 resection, or local recurrence after an R0–R1 resection. Locoregional regrowth after a clinical complete response and a watch-and-wait period was not considered a locoregional failure when

followed by an R0–R1 resection. Disease-related treatment failure events were not centrally reviewed. Data collection continued after the first disease-related treatment failure event for separate analyses of locoregional failure and distant metastases. Although these were not protocolised secondary endpoints, the stated aim of RAPIDO to reduce systemic relapses without compromising local control justifies these analyses as separate outcomes. Other secondary endpoints were completion rate of neoadjuvant treatment, toxicity, R0 resection rate (resection margin of >1 mm), pathological complete response rate (no residual tumour at pathological assessment after surgery), surgical complications within 30 days, quality of life (in patients alive without disease-related treatment failure, 3 years after surgery), functional outcome, overall survival (time from randomisation to death from any cause), and local recurrence. Toxicity and surgical complications within 30 days have been reported elsewhere.[9] Quality-of-life outcomes will be reported in depth elsewhere.

Statistical analysis

After two protocol amendments, the primary endpoint was changed from disease-free survival to disease-related treatment failure. Around 1 year before the end of the inclusion period, it became apparent that disease-free survival, commonly used in adjuvant trials, was an inappropriate endpoint in a neoadjuvant trial, because patients are not disease free at randomisation and some will never become disease free. For this reason, the protocol was amended (version 3.1; Jan 8, 2016) and a new primary endpoint was formulated: time to disease-related treatment failure. The change to this new endpoint was approved by the medical ethics committee and data safety monitoring board (DSMB), which did ongoing safety surveillance and evaluated interim analyses. The first planned and blinded efficacy interim analysis was done on Oct 17, 2017, after 226 disease-related treatment failure events. The second interim analysis was planned after 339 events. However, after a median follow-up exceeding 3 years, the total number of events (for which investigators were masked to treatment group assignment) was lower than anticipated and the required number of events (n=452) was expected to never be reached. Potential reasons for this situation are as follows: alteration of the endpoint (death due to other reasons and a new primary tumour, other than colorectal, are not events), a finite period of follow-up (statistical programs assume endless follow-up), and possibly better overall outcomes than projected. Therefore, the hypothesis changed from a decrease in events from 50% to 40%, to a decrease in the probability of disease-related treatment failure events from 30% to 22·5% with the experimental treatment, approved by the medical ethics committee and DSMB (protocol version 3.2; June 13, 2019; appendix pp 24–137).

To detect a decrease in 3-year cumulative probability of disease-related treatment failure from 30% to 22·5%, corresponding to a hazard ratio (HR) of 0·715, a two-sided log-rank test with 280 events would achieve 80% power at a two-sided α significance level of 0·05.

The primary analysis and the secondary endpoint analysis of overall survival were done in the intention-to-treat population (all patients randomly assigned to treatment, excluding those who withdrew informed consent or were ineligible), as were the analyses of locoregional failure and distant metastases. The secondary endpoints of R0 resection and pathological complete response were analysed in patients who had a resection; surgical complications were analysed in patients who had surgery with curative intent within 6 months; quality of life was assessed in patients who had resection, did not already develop a disease-related treated failure event, and responded in full to the questionnaires; and toxicity was analysed in all patients who started on their allocated treatment.

Using IBM SPSS Statistics (version 25.0), we compared proportions using the χ^2 test and continuous data, depending on the distribution, with Student's *t* test or the Mann-Whitney *U* test. All calculated median values are accompanied by an IQR and means with SDs. Using R (version 3.6.1), we did all survival analyses using the Kaplan-Meier method on an intention-to-treat basis. We calculated HRs and 95% CIs using Cox regression. Visual inspection of the cumulative hazards showed no evidence of violation of the proportional hazards assumption. For our separate analyses of locoregional failure, all patients, with and without distant metastases, were included, and for the separate analyses of distant metastases all patients, with and without locoregional failure, were included. Patients who were alive and disease free at last follow-up were censored. We used the reverse Kaplan-Meier method to calculate median follow-up. We calculated cumulative incidence of disease-related treatment failure accounting for non-treatment-related death as a competing risk. For distant metastases and locoregional failure, we calculated cumulative incidences accounting for all causes of death as a competing risk. For all competing risks analyses, we calculated and report cause-specific HRs. We calculated p values for all survival analyses on the basis of (cause-specific) log-rank tests.[15,16] For pathological complete response, we calculated odds ratios (ORs) and 95% CIs.

To assess whether the main results were robust, we did sensitivity analyses to study the effect of timing of disease staging (ie, time-related bias), and to adjust for stratification factors. Additionally, in sensitivity analyses, we analysed the influence of hospital policy on adjuvant chemotherapy within the standard of care group on the endpoints of disease-related treatment failure, distant metastases, and locoregional failure using the Kaplan-Meier method. We did subgroup analyses on associations between the primary endpoint and baseline characteristics and present these analyses in a forest plot.

We did a post-hoc analysis of disease-free survival from surgery. Additionally, we calculated disease-free survival,

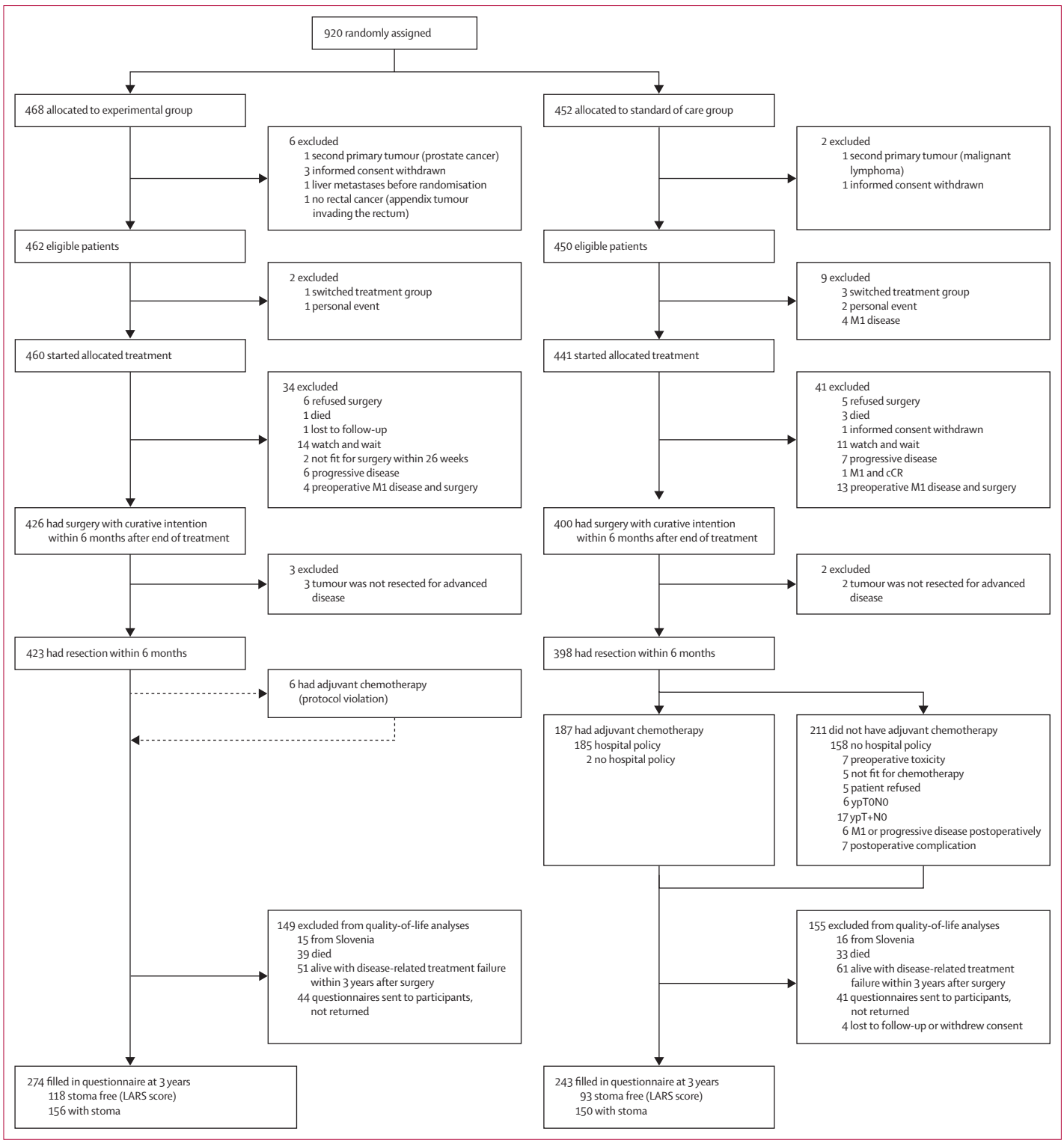


Figure 1: **Study profile**
cCR=clinical complete response. LARS=low anterior resection syndrome. M1=metastatic disease.

as defined by Fokas and colleagues,[17] which is similar to our definition of disease-related treatment failure but includes a second primary cancer, other than colorectal, and death from all causes as events. According to this definition, patients are not disease free at the start of the curves; rather they are event free.

The starting point for all analyses was date of randomisation. The significance threshold for all p values was 0·05.

The RAPIDO trial is registered with EudraCT (2010-023957-12) and ClinicalTrials.gov (NCT01558921).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

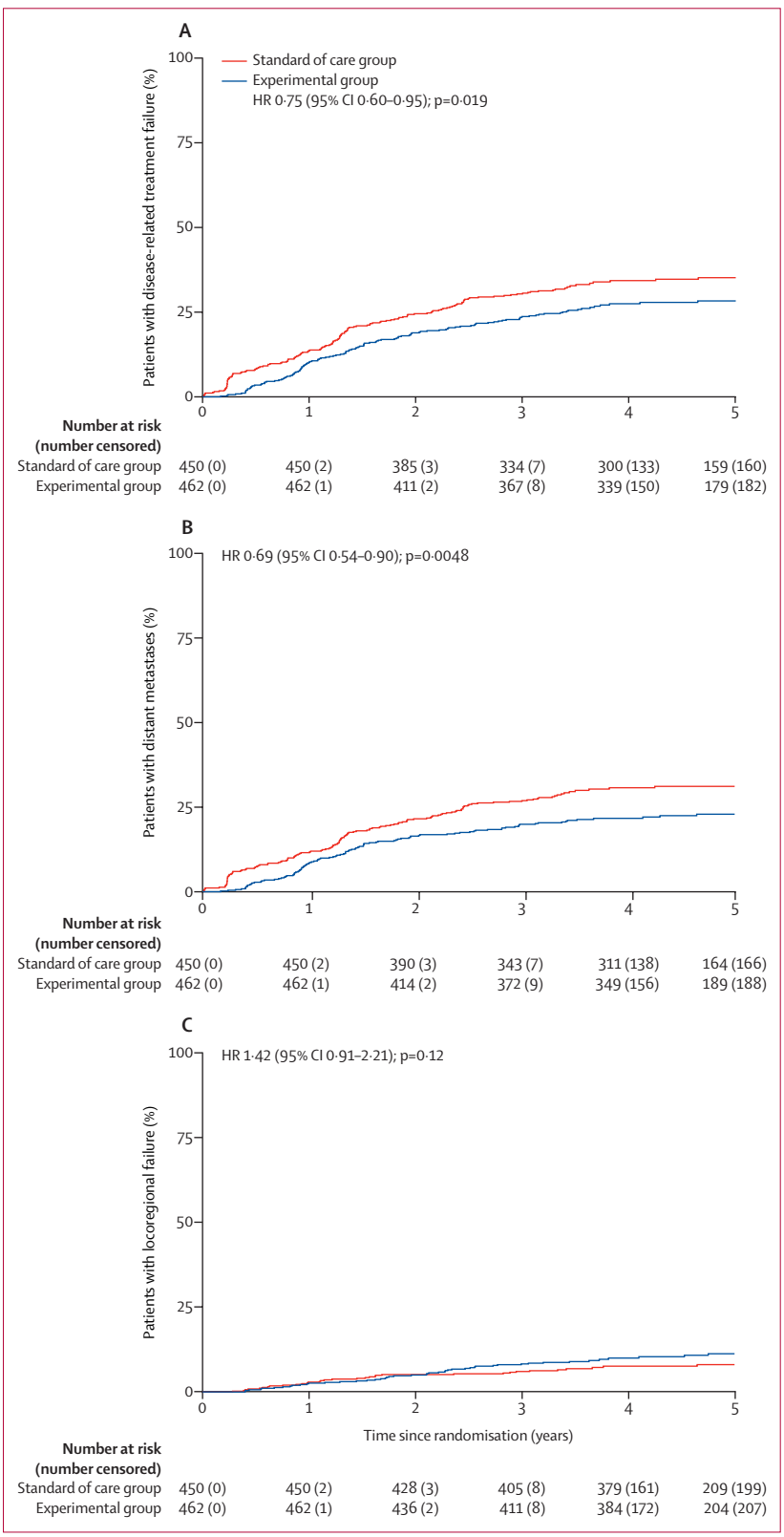
Between June 21, 2011, and June 2, 2016, 920 patients were randomly assigned to the experimental group (468) or standard of care group (452), of whom 912 (99%) were eligible (462 in the experimental group and 450 in the standard of care group; figure 1). Baseline characteristics of eligible participants are shown in table 1. Information on the proportion of participants in each group by year and country of inclusion is provided in the appendix (p 9). At the time of analyses (database lock was on June 19, 2020), median follow-up was 4·6 years (IQR 3·5–5·5). The median time between randomisation and surgery was 25·5 weeks (IQR 24·0–27·9) in the experimental group and 15·9 weeks (14·6–17·6) in the standard of care group.

After reaching 128 disease-related treatment failure events in the experimental group and 152 events in the standard of care group, the difference between groups in disease-related treatment failure at 3 years was significant, with fewer disease-related treatment failure events in the experimental group than in the standard of care group (3-year cumulative probability of 23·7% [95% CI 19·8–27·6] *vs* 30·4% [26·1–34·6]; HR 0·75 [95% CI 0·60–0·95]; p=0·019; figure 2). Distant metastasis caused most disease-related treatment failures (table 2). At 3 years, the cumulative probability of distant metastases was 20·0% (95% CI 16·4–23·7) in the experimental group compared with 26·8% (22·7–30·9) in the standard of care group (HR 0·69 [95% CI 0·54–0·90]; p=0·0048; figure 2). The cumulative probability of locoregional failure at 3 years was 8·3% (95% CI 5·8–10·8) in the experimental group compared with 6·0% (3·8–8·2) in the standard of care group (HR 1·42 [95% CI 0·91–2·21]; p=0·12; figure 2). The post-hoc subgroup analysis of disease-free survival from surgery, in patients with an R0 (>1 mm) resection within 6 months after the end of preoperative treatment is provided in the appendix (p 10). Notably, randomisation in this subgroup comparison (743 of 902 eligible patients) is no longer guaranteed to be balanced with respect to important prognostic factors. Therefore, the comparison could be biased due to possible differences in type of resection and approach, resection rate, pathological response, and other factors, between the treatment groups. The adjusted disease-free survival according to a different definition by Fokas et al,[17] which was similar to our definition of disease-related treatment failure but included a second primary cancer,

	Experimental group (n=462)	Standard of care group (n=450)
Sex		
Male	300 (65%)	312 (69%)
Female	162 (35%)	138 (31%)
Age at randomisation, years		
Median (IQR)	62 (55–68)	62 (55–68)
Range	31–83	23–84
Age category		
<65	280 (61%)	270 (60%)
≥65	182 (39%)	180 (40%)
Clinical T stage*†		
cT2	14 (3%)	14 (3%)
cT3	301 (65%)	299 (66%)
cT4	147 (32%)	137 (30%)
Clinical N stage*†		
cN0	42 (9%)	35 (8%)
cN1	118 (26%)	120 (27%)
cN2	302 (65%)	295 (66%)
Other high-risk criteria†		
Enlarged lateral nodes	66 (14%)	69 (15%)
Extramural vascular invasion positive	148 (32%)	125 (28%)
Mesorectal fascia positive	285 (62%)	271 (60%)
Number of high-risk criteria per patient†		
1	158 (34%)	168 (37%)
2	160 (35%)	146 (32%)
3	98 (21%)	96 (21%)
4	39 (8%)	29 (6%)
5	7 (2%)	11 (2%)
ECOG performance status		
0	369 (80%)	365 (81%)
1	93 (20%)	85 (19%)
Distance from anal verge on endoscopy, cm		
<5	103 (22%)	115 (26%)
5–10	181 (39%)	153 (34%)
≥10	146 (32%)	151 (34%)
Unknown	32 (7%)	31 (7%)
Treated in a hospital with policy for adjuvant chemotherapy		
Yes	273 (59%)	265 (59%)
No	189 (41%)	185 (41%)

Data are n (%), unless otherwise indicated. Percentages might not equal 100% due to rounding. cN=clinical nodal. cT=clinical tumour. ECOG=Eastern Cooperative Oncology Group. N stage=nodal stage. T stage=tumour stage. *According TNM-5. †MRI defined.

Table 1: **Baseline characteristics of eligible patients**



other than colorectal, and death from all causes as events, had a hazard ratio of 0·75 (95% CI 0·60–0·93; p=0·010). However, according to this definition, patients are not disease free at the start of the curves, rather they are event free. Sensitivity analyses adjusting for possible time-related bias and separately for stratification factors showed similar results as the original analyses (appendix pp 12–13). Local recurrence in each group is shown in table 2.

In the experimental group, median time between conclusion of radiotherapy and start of chemotherapy was 14 days (IQR 12–17) in patients who started allocated treatment. In the standard of care group, the optional field reduction after 45 or 46 Gy, as described in the protocol, was done for 102 (23%) of 441 patients who started treatment. Among patients who started allocated treatment, one (<1%) of 460 patients in the experimental group and ten (2%) of 441 in the standard of care group were given an external beam boost. Dose reduction of chemotherapy occurred in 201 (44%) of 460 patients in the experimental group, in 25 (6%) of 441 patients in the standard of care group during preoperative therapy, and in 64 (34%) of 187 patients during adjuvant chemotherapy in the standard of care group. Of the patients who started allocated treatment in the experimental group, 454 (99%) of 460 started with CAPOX. In the experimental group, 71 (15%) of 460 patients prematurely stopped preoperative chemotherapy. In the standard of care group, 40 (9%) of 441 patients prematurely stopped chemotherapy during preoperative (neoadjuvant) treatment and 69 (37%) of 187 who started adjuvant chemotherapy prematurely stopped chemotherapy during adjuvant treatment. Thus, in the experimental group, 389 (85%) patients completed preoperative chemotherapy compared with 401 (90%) patients in the standard of care group who completed chemotherapy. Reasons for stopping chemotherapy were toxicity (in 65 [14%] patients in the experimental group, 32 [7%] in the standard of care group during preoperative treatment, and 60 [32%] in the standard of care group during adjuvant therapy), disease progression (in one [<1%] in the experimental group, two [<1%] in the standard of care group during preoperative treatment, and one [1%] in the standard of care group during adjuvant therapy), and other (in one [<1%] in the experimental group, one [<1%] in the standard of care group during preoperative treatment, and three [2%] in the standard of care group during adjuvant therapy). Additional reasons in the experimental group were non-compliance (one [<1%]), patient withdrew from study (two [<1%]), and unknown (one [<1%]). In the standard of care group, during preoperative treatment the

Figure 2: **Cumulative probability of disease-related treatment failure (A), distant metastases (B), and locoregional failure (C)**
HR=hazard ratio.

reasons for prematurely stopping chemotherapy were unknown (five [1%]) and during adjuvant chemotherapy reasons were non-compliance (two [1%]), patient withdrew from study (two [1%]), and unknown reasons (one [1%]).

Overall, 426 (92%) of 462 patients in the experimental group and 400 (89%) of 450 patients in the standard of care group (p=0·086) had surgery with curative intent within 6 months from the end of preoperative treatment. No differences were seen between the groups regarding type of approach (p=0·31) or type of resection (p=0·56; appendix pp 14–15). The proportion of patients with R0 resection was high and similar in the two groups (table 2). Of the 826 patients who had surgery with curative intent, the tumour was unresectable in five (1%) patients (three in the experimental group and two in the standard of care group), leading to exclusion of these patients from pathological analyses. 120 (28%) of 423 patients in the experimental group had a pathological complete response compared with 57 (14%) of 398 in the standard of care group (OR 2·37 [95% CI 1·67–3·37]; p<0·0001; table 2). 3-year overall survival was 89·1% (95% CI 86·3–92·0) in the experimental group and 88·8% (85·9–91·7) in the standard of care group (HR 0·92 [95% CI 0·67–1·25]; p=0·59; figure 3).

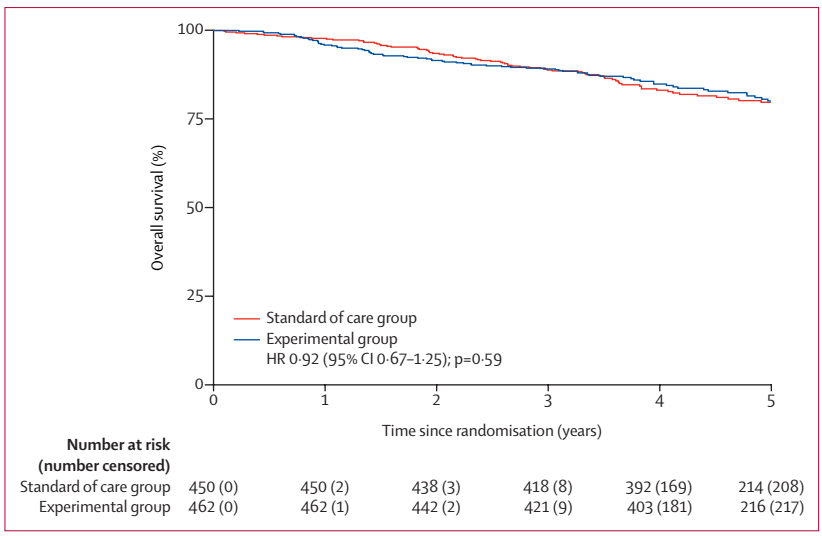
An overview of adverse events is provided in table 3. Grade 3 or higher adverse events during preoperative treatment occurred in 219 (48%) of 460 patients in the experimental group, compared with 109 (25%) of 441 patients in the standard of care group and during adjuvant chemotherapy in 63 (34%) of 187 patients in the standard of care group. The most common grade 3 or higher adverse event was diarrhoea in both treatment groups (table 3). Serious adverse events occurred in the experimental group in 177 (38%) of 460 patients and, in the standard of care group, in 87 (34%) of 254 patients without adjuvant chemotherapy and in 64 (34%) of 187 with adjuvant chemotherapy (appendix pp 16–19). Diarrhoea was the most common serious adverse event in the experimental group during preoperative chemotherapy (41 [9%] of 460) and in the standard of care group during preoperative chemoradiotherapy (11 [3%] of 441). During adjuvant chemotherapy, the most common serious adverse event in the standard of care group was infectious complications (eight [4%] of 187). Postoperatively, the most common serious adverse events in both groups were wound-related events (appendix p 18).

At the time of database lock, 161 patients had died, including 80 (17%) of 462 patients in the experimental group (four [5%] deaths were treatment related [one cardiac arrest, one pulmonary embolism, two infectious complications]; 63 [79%] were rectal cancer related; six [8%] were due to a second primary tumour; four [5%] were due to other causes; and three [4%] were due to unknown reasons) and 81 (18%) of 450 patients in the standard of care group (four [5%] were

	Experimental group	Standard of care group	p value
All eligible patients			
Surgery with curative intent within 6 months after the end of preoperative treatment			
Yes	426/462 (92%)	400/450 (89%)	0·086*
No	36/462 (8%)	50/450 (11%)	..
Disease-related treatment failure, first occurring	128 (23·7%)†	152 (30·4%)†	0·019†
Locoregional failure			
Local progression, unresectable tumour	1/128 (1%)	1/152 (1%)	..
R2 resection	0	0	..
Local recurrence	22/128 (17%)	13/152 (10%)	..
Locoregional failure and distant metastasis‡			
Local progression, unresectable tumour	4/128 (3%)	2/152 (1%)	..
R2 resection	1/128 (1%)	0	..
Local recurrence	7/128 (5%)	4/152 (3%)	..
Distant metastasis	86/128 (67%)	123/152 (81%)	..
New primary colorectal tumour	3/128 (2%)	5/152 (3%)	..
Treatment-related death	4/128 (3%)	4/152 (3%)	..
Patients with a resection within 6 months after the end of preoperative treatment			
Residual tumour classification			
R0 >1 mm	382/423 (90%)	360/398 (90%)	0·87*
R1 ≤1 mm	38/423 (9%)	37/398 (9%)	..
R2	3/423 (1%)	1/398 (<1%)	..
Circumferential resection margin			
>1 mm	385/423 (91%)	363/398 (91%)	0·92*
≤1 mm	38/423 (9%)	35/398 (9%)	..
Differentiation grade during pathological assessment			
Well differentiated	62/423 (15%)	82/398 (21%)	0·09*§
Moderately differentiated	167/423 (39%)	189/398 (47%)	..
Poorly differentiated	44/423 (10%)	35/398 (9%)	..
No tumour	129/423 (30%)	69/398 (17%)	..
Not assessed	21/423 (5%)	23/398 (6%)	..
Pathological complete response			
Yes	120/423 (28%)	57/398 (14%)	<0·0001*
No	303/423 (72%)	341/398 (86%)	..
Pathological T stage¶			
ypT0	129/423 (30%)	69/398 (17%)	<0·0001*
ypTis	2/423 (<1%)	1/398 (<1%)	..
ypT1	17/423 (4%)	17/398 (4%)	..
ypT2	82/423 (19%)	96/398 (24%)	..
ypT3	157/423 (37%)	190/398 (48%)	..
ypT4	36/423 (9%)	25/398 (6%)	..
Pathological N stage¶			
ypN0	317/423 (75%)	273/398 (69%)	0·017*
ypN1	75/423 (18%)	78/398 (20%)	..
ypN2	31/423 (7%)	47/398 (12%)	..
Postoperative M stage¶			
ypM0	420/423 (99%)	396/398 (99%)	0·70*
ypM1	3/423 (1%)	2/398 (1%)	..

Data are n (%). Proportions might not equal 100% due to rounding. M stage=metastasis stage. N stage=nodal stage. R0=clear resection margins. R1=resection margin of 0–1 mm. R2=macroscopic residual tumour. T stage=tumour stage. *p value calculated using χ^2 test. †3-year cumulative probability; p value calculated using the log-rank test. ‡Locoregional failure and distant metastasis diagnosed simultaneously within 30 days of each other. §p value calculated on the basis of well, moderately, and poorly differentiated. ¶According to TNM 5.

Table 2: **Number of surgeries with curative intent, disease-related treatment failures, and pathological outcomes**



Number at risk (number censored)						
Standard of care group	450 (0)	450 (2)	438 (3)	418 (8)	392 (169)	214 (208)
Experimental group	462 (0)	462 (1)	442 (2)	421 (9)	403 (181)	216 (217)

Figure 3: **Overall survival**
HR=hazard ratio.

treatment related [one pulmonary embolism, one neutropenic sepsis, one aspiration, one suicide due to severe depression]; 66 [82%] were related to rectal cancer; seven [9%] were due to a second primary tumour; and four [5%] were due to other causes; appendix p 20).

Analyses of quality-of-life data are to presented in a subsequent publication; here, we present the number of respondents. 3 years after resection, 602 (73%) of 821 patients received quality-of-life questionnaires (318 in the experimental group and 284 in the standard of care group; figure 1). Responses were obtained from 517 (86%) of 602 patients (274 in the experimental group and 243 in the standard of care group), of whom four (1%) did not respond in full. Among 211 (26%) of 821 patients who did not have a disease-related treatment failure and who did not have a stoma, 207 (98%) responded to the LARS questionnaire on bowel function (116 in the experimental group and 91 in the standard of care group). In total, 402 (78%) of 517 patients completed the QLQ-CIPN20 questionnaire on neurotoxicity (217 in the experimental group, 109 in the standard of care group without adjuvant chemotherapy, and 76 in the standard of care group with adjuvant chemotherapy). The questionnaire responses are to be reported in a subsequent publication.

Subgroup analyses of disease-related treatment failure according to baseline characteristics were consistently in favour of the experimental group (appendix p 21). Of the 54 participating centres, 28 (52%) opted to administer adjuvant chemotherapy in the standard of care group. In sensitivity analyses, within the standard of care group, hospital policy on adjuvant chemotherapy did not affect the probability of disease-related treatment failure at 3 years (HR 1·18 [95% CI 0·85–1·64]; p=0·32). Comparing hospitals with and without adjuvant chemotherapy policies in the standard of care group, similar probabilities of distant metastases (28·5% [95% CI 23·1–34·0] *vs* 24·4% [18·2–30·6]; p=0·34) and locoregional failure (7·2% [4·1–10·4] *vs* 4·3% [1·7–7·3]; p=0·20) were seen.

Among the 912 eligible patients, 25 (3%) were followed up according to the watch-and-wait strategy due to a clinical complete response (14 in the experimental group and 11 in the standard of care group). In the experimental group, two (14%) of 14 patients developed distant metastasis and one (7%) developed local regrowth; and in the standard of care group, one (9%) of 11 patients developed distant metastasis, one (9%) developed local regrowth, and one (9%) simultaneously developed distant metastasis and local regrowth (appendix p 22).

Discussion

In this study, we found that patients treated with short-course radiotherapy followed by 18 weeks of systemic chemotherapy before surgery have a significantly lower probability of disease-related treatment failure at 3 years after randomisation than do patients undergoing standard of care chemoradiotherapy followed by optional adjuvant chemotherapy after surgery. Hospital policy regarding the use of adjuvant chemotherapy did not affect disease-related treatment failure in the standard of care group. Additionally, with the experimental treatment, the pathological complete response rate was double that in the standard of care group. Given the increased tendency to refrain from surgery in patients with a clinical complete response after preoperative treatment, the experimental treatment offers the potential opportunity for patients seeking organ preservation.

The lower probability of disease-related treatment failure in the experimental group than in the standard of care group can mainly be attributed to a decreased rate of distant metastases. A possible explanation for this reduction in distant metastases might be better compliance to preoperative chemotherapy in the experimental group than with adjuvant chemotherapy when offered in the standard of care group;[9] patients are generally in better condition before than after surgery. Fewer weeks of chemotherapy (18 weeks preoperatively *vs* 24 weeks postoperatively) could also have contributed to better compliance in the experimental group than in the standard of care group, and did not result in reduced efficacy. Justification for a reduced number of chemotherapy cycles has emerged in several adjuvant colon cancer trials, showing that 3 months of CAPOX is non-inferior to 6 months of CAPOX in terms of disease-free survival.[18,19] Predefined hospital policy regarding the use of adjuvant chemotherapy did not affect disease-related treatment failure in the standard of care group, suggesting that the efficacy of postoperative chemotherapy might be low.[20,21] Systemic chemotherapy in the experimental group started approximately 18 weeks earlier than in the standard of care group, potentially leading to more effective eradication of possible micrometastases. Although some guidelines exclude proximal rectal

cancers from preoperative radiotherapy or chemoradiotherapy, we believe exceptions exist (eg, in the presence of high-risk criteria).

The randomised Polish II study,[22] which included 515 patients with locally advanced rectal cancer, also compared preoperative short-course radiotherapy followed by chemotherapy with chemoradiotherapy. No significant difference in the 3-year cumulative incidence of distant metastases between the experimental (30%) and standard groups (27%) was reported (relative risk 1·21 [95% CI 0·59–1·15] p=0·25).[22] In the RAPIDO trial, the rate of distant metastases (20·0%) was lower in the experimental group than in the standard of care group (26·8%), which was similar to the standard group in the Polish II study. Although MRI was not mandatory in the Polish II study, this similarity in outcome indicates that the two trials enrolled similar patient populations. An explanation for the difference between the two experimental groups in these two studies might be the duration of preoperative chemotherapy: six cycles of CAPOX or nine cycles of FOLFOX4 in the RAPIDO trial versus three cycles of FOLFOX4 in the Polish II study. Further insight into how the number of chemotherapy cycles affects this outcome will come from the ongoing randomised STELLAR trial.[23] In the STELLAR trial, patients with MRI-staged non-metastatic locally advanced rectal cancer are given six cycles of CAPOX, divided into four preoperative cycles after short-course radiotherapy and two adjuvant chemotherapy cycles.[23]

The overall probability of locoregional failure in the RAPIDO trial at 3 years is similar to previously published data.[1,2,4,24] A longer period between radiotherapy and surgery in the experimental group than in the standard of care group might have led to increased downstaging, and possibly a higher proportion of patients with a pathological complete response. However, for patients who had little or no response to therapy, the extended interval between randomisation and surgery in the experimental group compared with the standard of care group (median time 25·5 weeks [IQR 24·0–27·9] *vs* 15·9 weeks [14·6–17·6]) might be disadvantageous. The higher number of residual pathological T4 (ypT4) tumours in the experimental group than in the standard

	Experimental group				Standard of care group						
	During preoperative therapy (n=460)				During preoperative therapy (n=441)				During adjuvant therapy (n=187)		
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4
General adverse events											
Allergic reaction	19 (4%)	5 (1%)	1 (<1%)	0	3 (1%)	0	0	0	6 (3%)	1 (1%)	0
Alopecia	9 (2%)	0	0	0	6 (1%)	0	0	0	3 (2%)	0	0
Cystitis	38 (8%)	1 (<1%)	0	0	97 (22%)	0	0	0	9 (5%)	0	0
Fatigue or lethargy	297 (65%)	14 (3%)	0	0	255 (58%)	6 (1%)	0	0	118 (63%)	10 (5%)	0
Febrile neutropenia	0	5 (1%)	0	0	0	1 (<1%)	0	1 (<1%)	0	1 (1%)	0
Hand-foot syndrome	134 (29%)	8 (2%)	0	0	77 (17%)	5 (1%)	0	0	68 (36%)	4 (2%)	0
Neurological toxicity	362 (79%)	19 (4%)	1 (<1%)	0	30 (7%)	1 (<1%)	0	0	119 (64%)	16 (9%)	0
Radiation dermatitis	24 (5%)	2 (<1%)	0	0	112 (25%)	14 (3%)	0	0	1 (1%)	0	0
Rash maculopapular	18 (4%)	0	0	0	16 (4%)	2 (<1%)	0	0	5 (3%)	0	0
Weight loss	78 (17%)	3 (1%)	0	0	48 (11%)	1 (<1%)	0	0	22 (12%)	0	0
Other*	266 (58%)	111 (24%)	20 (4%)	1 (<1%)	235 (53%)	46 (10%)	8 (2%)	2 (<1%)	106 (57%)	26 (14%)	7 (4%)
Gastrointestinal toxicity											
Abdominal pain†	213 (46%)	25 (5%)	2 (<1%)	0	161 (37%)	6 (1%)	2 (<1%)	0	40 (21%)	4 (2%)	0
Diarrhoea	225 (49%)	75 (16%)	6 (1%)	0	220 (50%)	40 (9%)	1 (<1%)	0	95 (51%)	13 (7%)	0
Faecal incontinence	37 (8%)	0	0	0	43 (10%)	0	0	0	2 (1%)	0	0
Nausea	232 (50%)	16 (3%)	0	0	139 (32%)	3 (1%)	0	0	90 (48%)	4 (2%)	0
Oral mucositis	49 (11%)	3 (1%)	0	0	23 (5%)	0	0	0	21 (11%)	0	0
Proctitis	44 (10%)	4 (1%)	0	0	48 (11%)	6 (1%)	0	0	3 (2%)	0	0
Rectal bleeding	103 (22%)	1 (<1%)	0	0	93 (21%)	3 (1%)	0	0	2 (1%)	1 (1%)	0
Rectal mucositis	43 (9%)	3 (1%)	0	0	53 (12%)	3 (1%)	0	0	5 (3%)	0	0
Rectal pain	106 (23%)	4 (1%)	0	0	135 (31%)	5 (1%)	0	0	22 (12%)	0	0
Vomiting	99 (22%)	9 (2%)	0	0	38 (9%)	3 (1%)	0	0	38 (20%)	3 (2%)	0

In the standard of care group, no grade 5 adverse events occurred during adjuvant chemotherapy. *According to Common Terminology Criteria for Adverse events version 4.0 (ear and labyrinth disorders, endocrine disorders, eye disorders, general disorders and administration site conditions, hepatobiliary disorders, immune system disorders, injury, poisoning and procedural complications, investigations, metabolism and nutrition disorders, musculoskeletal and connective tissue disorders, neoplasms benign, malignant and unspecified [including cysts and polyps], nervous system disorders, psychiatric disorders, renal and urinary disorders, reproductive system and breast disorders, respiratory, thoracic and mediastinal disorders; and skin and subcutaneous tissue disorders). †Due to constipation, obstruction, or other causes.

Table 3: **Adverse events**

of care group (9% *vs* 6%) could indicate the presence of a small proportion of non-responding tumours that might actually progress during preoperative treatment. Hence, early response imaging could be advocated, enabling alterations in therapeutic approach.

In the Stockholm III trial,[25] with less advanced tumours than in our study population, pathological complete response was seen in 29 (10·4%) of 285 participants following short-course radiotherapy with delayed surgery compared with two (2·2%) of 94 participants after long-course radiotherapy.[25] In the experimental group of the RAPIDO trial, the pathological complete response rate was 28%. Apart from the longer interval between radiotherapy and surgery in RAPIDO than in Stockholm III (>18 weeks *vs* 4–8 weeks), the addition of chemotherapy in RAPIDO is likely to have contributed to the higher rate of pathological complete response. In a study with four consecutive series of patients with intermediate-risk rectal cancer, pathological complete response rates increased from 18% (95% CI 10–30) after chemoradiotherapy alone to 38% (27–51) in patients receiving six cycles of modified FOLFOX6 in the interval between chemoradiotherapy and surgery.[26] Delivering additional cycles of chemotherapy and extending the interval between chemoradiotherapy and surgery seems to have added value in achieving pathological complete response, and is associated with a survival benefit.[27] A pooled analysis showed that patients with a pathological complete response after chemoradiotherapy have favourable outcomes regarding local control and overall survival.[28] Although no studies have yet shown that a pathological complete response achieved by the additional effect of chemotherapy is associated with improved prognosis, this outcome seems possible. Additionally, an adequately assessed clinical complete response followed by a watch-and-wait strategy is increasingly being used as an alternative to major surgery.[29] The experimental RAPIDO regimen resulted in a high rate of pathological complete response and could potentially be used to initiate a watch-and-wait strategy.

After a median follow-up of 4·6 years, no difference in overall survival was observed, but might be revealed with longer follow-up that will continue until 10 years after randomisation, according to the trial protocol.

The optimal timing of chemotherapy in a total neoadjuvant approach remains a matter of debate. The fear of local progression could justify a radiotherapy-first approach, whereas prioritising the early control of potential micrometastases would justify a chemotherapy-first strategy. The chemotherapy-first strategy is under investigation in the PRODIGE 23 trial[30] (preoperative chemotherapy before chemoradiotherapy, followed by total mesorectal excision and adjuvant chemotherapy). The initial results showed significantly increased 3-year disease-free survival, metastasis-free survival, and pathological complete response rate compared with chemoradiotherapy followed by total mesorectal excision and adjuvant chemotherapy.[30] An obvious advantage of short-course radiotherapy as part of a total neoadjuvant approach is its short duration with minimal delay between the end of radiotherapy and start of systemic chemotherapy. To our knowledge, optimal timing for chemotherapy has been investigated in only one published randomised study so far.[31] In that study, patients having preoperative chemotherapy after chemoradiotherapy had fewer adverse events, better compliance to chemoradiotherapy, and higher pathological complete response rates than did patients who started with preoperative chemotherapy.[31] The long-term results on oncological outcomes are awaited.[31] Currently, chemoradiotherapy before preoperative chemotherapy appears to be the preferred option.

To exclude the potential bias of recurrent disease and treatment thereof, only patients without disease-related treatment failure at 3 years will be analysed in the RAPIDO trial with respect to quality of life, results of which will be published elsewhere.

In the experimental group of the RAPIDO trial, more serious adverse events of diarrhoea and neurological toxicity occurred than in the standard of care group, probably due to preoperative treatment with CAPOX. Another possible contributing factor to diarrhoea could be the longer period between diagnosis and removal of the tumour. Despite differences in toxicity between treatment groups during preoperative treatment, no effect on surgery was observed in our previous report of compliance, toxicity, and post-operative complications in the RAPIDO trial.[9]

Concerns have been raised about short-course radiotherapy having lower efficacy than conventional chemoradiotherapy; however, to our knowledge, no randomised trials have compared the anti-tumour or downstaging effect of short-course radiotherapy and delayed surgery to chemoradiotherapy with a similar delay. Therefore, we cannot draw firm conclusions about relative efficacy between short-course radiotherapy and chemoradiotherapy. In the Stockholm III trial,[25] more downstaging and a higher pathological complete response rate were observed after short-course radiotherapy than after long-course radiotherapy, indicating that the tumour-cell kill effect is probably higher from five fractions of 5 Gy than from 25 fractions of 2 Gy, and not less, as the commonly used coefficients in the linear-quadratic formula indicate.[32] Additionally, the long-term consequences of short-course radiotherapy are under debate. Evidence indicates that short-course radiotherapy results in long-term morbidity.[33] However, the long-term morbidity caused by chemoradiotherapy is less studied than short-course radiotherapy, making a comparison difficult. Moreover, at least two randomised trials indicate no differences in late complications (ie, at 3–5 years) between the two treatments.[34,35] Notably, most data on long-term consequences originate from trials using either two anterior-posterior portals or the conventional three

dimensional-conformal radiotherapy technique instead of the currently used intensity-modulated radiation therapy or volumetric modulated arc therapy techniques. Furthermore, the target volumes have been reduced compared with the many studies on which our present knowledge of radiotherapy-induced late effects (ie, at 4–10 years) after rectal cancer radiotherapy has been based.[33] With these newer techniques and the possibilities of daily adaptive therapy, doses to relevant organs at risk are substantially reduced. Therefore, the ultimate effects on long-term functional outcomes and morbidity require careful assessment in the coming years.

Our study has several limitations. Alteration of the primary endpoint during a trial is undesirable but was considered necessary because disease-free survival was inappropriate in a neoadjuvant trial on patients with high-risk locally advanced rectal cancer. Another potential limitation was the absence of a central review of baseline MRIs. Patients could have been under-staged or over-staged, although over-staging was most probably predominant.[36] However, bias towards one group is unlikely to have occurred because randomisation was stratified.

A prominent benefit of the experimental treatment reported here, especially in the context of the COVID-19 pandemic, is the decrease in the number of treatment days spent in health-care facilities, 12 days in the experimental group versus 25–28 days in the standard of care group for the preoperative period on the basis of typical treatment regimens. If adjuvant chemotherapy is given (8 treatment days in 24 weeks if CAPOX, 24 days if FOLFOX4), the reduction is even more pronounced. This reduction in time spent in hospital minimises the risk for these susceptible patients and improves hospitals' ability to implement physical distancing during the COVID-19 pandemic situation.[37]

In summary, in patients with high-risk locally advanced rectal cancer, the RAPIDO trial shows that short-course radiotherapy followed by 18 weeks of chemotherapy before surgery decreases the probability of disease-related treatment failure compared with chemoradiotherapy with or without adjuvant chemotherapy, mainly by reducing the probability of distant metastases. Additionally, the high rate of pathological complete response in the experimental group can potentially contribute to organ preservation. Supported by previously reported high compliance and tolerability,[9] this treatment could be considered as a new standard of care for patients with high-risk locally advanced rectal cancer. Future research could focus on assessing tumour response to preoperative treatment at an early stage and improving the efficacy of systemic therapy with the aim of decreasing distant metastases even further.

Contributors

BvE, CAMM, PJN, BG, CJHvdV, and GAPH designed the study. BvE, CAMM, EM-KK, AGHR, IDN, RGHB-T, LKB, TF, AJtT, JC, MPH, IE, AC, PJN, BG, CJHvdV, GAPH, and collaborative investigators provided the data. EM-KK and AGHR coordinated the trial at the Clinical Research Center (Department of Surgery, Leiden University Medical Center, Leiden, Netherlands). RRB and EAD did the literature search. RRB, EAD, and HP analysed the data and designed the figures. RRB, EAD, BvE, CAMM, EM-KK, PJN, BG, CJHvdV, and GAPH interpreted the results. RRB and EAD wrote the manuscript equally. BvE, CAMM, HP, EM-KK, AGHR, IDN, RGHB-T, LKB, TF, AJtT, JC, MPH, IE, AC, PJN, BG, CJHvdV, and GAPH read and reviewed the manuscript. All authors approved the final version of the manuscript.

Declaration of interests

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Data sharing

A data sharing statement is provided in the appendix (p 23).

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