BJS Open, 2025, zraf136
https://doi.org/10.1093/bjsopen/zraf136
Original Article

Watch-and-wait approach in high-risk locally advanced rectal cancer: outcomes after complete response to total neoadjuvant therapy

Evi Banken[1,2,3,*], Barbara M. Geubels[2,4,3], Fleur E. C. Vande Kerckhove[2,3], Davy M. J. Creemers[2,3], Stijn H. J. Ketelaers[2,5], Joost Nederend[6], Heike M. U. Peulen[7], Irene E. G. van Hellemond[1], Harm J. T. Rutten[2,3] and Jacobus W. A. Burger[2,3]

[1]Department of Medical Oncology, Catharina Hospital, Eindhoven, The Netherlands
[2]Department of Surgery, Catharina Hospital, Eindhoven, The Netherlands
[3]GROW Research Institute for Oncology and Reproduction, Faculty of Health, Medicine and Life Science, Maastricht University, Maastricht, The Netherlands
[4]Department of Surgery, Antoni van Leeuwenhoek, Amsterdam, The Netherlands
[5]Department of Surgery, Maastricht Academic Medical Center, Maastricht, The Netherlands
[6]Department of Radiology, Catharina Hospital, Eindhoven, The Netherlands
[7]Department of Radiotherapy, Catharina Hospital, Eindhoven, The Netherlands

Correspondence to: Ms.Evi Banken, Department of Medical Oncology and Surgery, Catharina Hospital Eindhoven, Michelangelolaan 2, EJ Eindhoven 5623, The Netherlands (e-mail:evi.banken@catharinaziekenhuis.nl)

Abstract

Background: In patients with the most advanced stages of high-risk locally advanced rectal cancer (LARC), extensive resections often lead to morbidity and functional impairment. It is unclear whether these patients, despite poor prognosis, are suitable candidates for a watch-and-wait (W&W) approach in cases of a clinical complete response (cCR).

Methods: Consecutive patients with high-risk LARC who underwent total neoadjuvant therapy (TNT), followed by surgery or a W&W approach between January 2016 and February 2023, were retrospectively analysed. High-risk features included tumour invasion into the mesorectal fascia, grade 4 extramural venous invasion, enlarged lateral lymph nodes, or tumour deposits. Patients were categorized into complete response (CR) or non-CR, and stratified by W&W and surgically treated. Outcomes were regrowth, local recurrence, distant metastases (DM), regrowth-free survival, organ survival, local recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), recurrence-free survival (RFS) (all death-censored), and overall survival.

Results: Of 135 patients, 29 (21.5%) achieved a cCR and entered W&W. A total of 103 patients (78.0%) underwent immediate surgery, including 15 (11.1%) with a pathological CR. Median follow-up was 42 months (range 9–76) for CR patients *versus* 42.5 months (range 7–82) for non-CR patients. Local recurrence and DM occurred in 1 (2.3%) and 7 patients (15.9%) in the CR group, respectively, *versus* 14 (15.9%) and 21 patients (23.9%) in the non-CR group, respectively. Three-year death-censored LRFS and DMFS rates were 97.6% and 82.7% in the CR group, respectively, *versus* 85.8% and 76.0% in the non-CR group, respectively ($P = 0.016$, $P = 0.273$). Five-year overall survival was 89.5% in the CR group *versus* 84.0% in the non-CR group ($P = 0.131$). Median follow-up was 44 months (range 16–71) in W&W patients and 42 months (range 7–82) in surgically treated patients. Among W&W patients, regrowth occurred in seven patients (24.1%) and the 3-year death-censored regrowth-free survival was 79.2%. Three-year death-censored RFS and 5-year overall survival were 71.9% and 90.9% in W&W patients, respectively, *versus* 72.3% and 84.2% in surgically treated patients, respectively ($P = 0.680$, $P = 0.115$).

Conclusion: A W&W approach can be considered safe and feasible for patients with high-risk LARC. Achieving a CR after TNT is associated with favourable oncological outcomes.

Introduction

Standard treatment for locally advanced rectal cancer (LARC) currently consists of neoadjuvant chemoradiotherapy followed by surgery. Despite this treatment, 5–10% of patients develop local recurrence, and 25–40% develop distant metastases[1–3]. High-risk tumour characteristics in patients with LARC, such as mesorectal fascia (MRF) invasion, extramural venous invasion (EMVI), tumour deposits (TDs), and pathological lateral lymph nodes are associated with a 20–50% increased risk of local and systemic recurrence, and worse survival when compared with patients without these features[4–10]. Surgery in these high-risk patients mostly requires extensive procedures with additional resections, and is associated with significant morbidity, functional impairment, and poor quality of life[11–13]. As a result, there has been growing interest in organ-preserving strategies as an alternative to surgery. The feasibility of a watch-and-wait (W&W) approach in the most extensive and aggressive tumours remains uncertain, given that these tumours have a higher tendency to invade surrounding organs, cause obstructive symptoms, and are associated with a poorer prognosis[14].

Keywords: induction chemotherapy, radiotherapy, response assessment, organ preservation, rectal cancer management
Received: May 14, 2025. **Revised:** September 17, 2025. **Accepted:** September 28, 2025

Multiple studies have examined the association of MRF invasion, EMVI, TDs, and pathological lateral lymph nodes with local recurrence, distant metastases, and survival rates. A study by Nagtegaal *et al*[4]. demonstrated that patients with MRF involvement had significantly higher rates of local recurrence (16.4% *versus* 5.8%) and distant metastases (37.6% *versus* 12.7%) compared with those without involvement. The Multicenter Lateral Node Study[6] reported a high recurrence rate (19.5%) in patients with pathological lateral lymph nodes. Similarly, the presence of EMVI was linked to an increased risk of metachronous metastases (odds ratio 3.91; $P < 0.001$)[8]. In a large cohort of 4455 patients, Agger *et al.*[15] found that patients with TD-positive tumours had local recurrence and distant metastases rates of 6.3% and 38.9% compared with 2.7% and 14.3%, respectively, in patients with TD-negative tumours. These high-risk features, collectively referred to as the 'MEND-criteria', define high-risk LARC in the ongoing MEND-IT trial[16].

A W&W approach can be considered in cases of a complete response (CR) after neoadjuvant therapy, allowing patients to avoid surgery while being closely monitored. Several studies[17–23] have demonstrated that organ-preserving strategies are safe and result in good oncological outcomes in patients with rectal cancer . Recently, there has been an increasing shift towards total neoadjuvant therapy (TNT) in patients with LARC, which incorporates chemotherapy into the neoadjuvant regimen with the goal of improving oncological outcomes. Large randomised clinical trials have shown that TNT is very effective in increasing CR rates compared with chemoradiotherapy alone, suggesting that it could be an effective strategy when aiming for organ preservation[24–28]. The Organ Preservation in Patients with Rectal Adenocarcinoma trial[29] evaluated organ preservation rates after TNT, comparing induction chemotherapy *versus* consolidation chemotherapy, and reported organ preservation rates of 39–54% at 5 years. However, this study included all T3-category and N + category tumours and therefore primarily consisted of lower-risk tumours.

Currently, there are lack of data on W&W strategies and associated oncological outcomes in patients with high-risk LARC achieving a CR after TNT. The feasibility and safety of the W&W approach in this population remain controversial, primarily due to concerns about an increased risk of local recurrence and distant metastases. This study aimed to evaluate oncological outcomes of patients with high-risk LARC who achieved a CR after TNT and to compare outcomes of W&W patients with surgically treated patients.

Methods

Patients

All consecutive patients with high-risk LARC without distant metastases, who were treated with TNT and surgery or W&W at the Catharina Hospital, Eindhoven, between January 2016 and February 2023, were retrospectively selected. All baseline magnetic resonance imaging (MRI) scans were assessed by one experienced radiologist specialised in rectal cancer. Patients were included if at least one 'high-risk' tumour characteristic was present (*Fig. 1*):

(a) Tumour invasion into the MRF; and/or
(b) EMVI grade IV; and/or
(c) TDs; and/or
(d) Lateral lymph nodes with a short-axis ≥ 7 mm.

The presence of only a threatened MRF (distance ≤ 1 mm) without invasion was considered insufficient for inclusion. Patients lacking a response MRI scan or with less than 1 year of follow-up after surgery or the last chemoradiotherapy fraction (W&W patients) were excluded.

The MRI scans met the following requirements:

- 1.5 or 3 Tesla MRI scanner.
- Phased-array receiver coil for pelvic imaging.
- High-resolution T2-weighted imaging in three planes (sagittal, coronal, and transverse), maximum slice thickness 3 mm, no fat suppression.
- Diffusion-weighted imaging (DWI) with b-value ≥ b800 and apparent diffusion coefficient maps.
- T2 and DWI must cover the entire tumour area.
- No endorectal filling.

Imaging quality was deemed sufficient by the study radiologist (JN, 13 years of experience). MRI assessment was performed in accordance with the Dutch and ESGAR guidelines[30,31].

Patients with a clinical CR (cCR) or pathological CR (pCR) after neoadjuvant therapy were categorized as the CR group and patients with partial response or no response were categorized as the non-CR group. cCR was defined as the absence of residual disease on clinical evaluation, using digital rectal examination, endoscopy, and pelvic MRI with DWI. pCR was defined as the absence of vital tumour cells in the resected specimen (Mandard 1, pT0N0).

This study was approved by the Dutch Medical Research Ethics Committees United—Nieuwegein (registration number AW23.041/W23.008.) and exempt from the Medical Research Involving Human Subjects Act. Written informed consent was waived due to the retrospective design.

Treatment

During the study period, TNT was given in selected patients with poor prognostic features and locally advanced tumours, based on multidisciplinary team discussions, and was primarily delivered as induction chemotherapy.

Neoadjuvant chemotherapy generally consisted of doublet chemotherapy: four 3-weekly cycles of CAPOX (capecitabine 1000 mg/m^2 orally twice daily for 14 days with oxaliplatin 130 mg/m^2 intravenously on day 1), or six 2-weekly cycles of FOLFOX-6 (5-fluorouracil 400 mg/m^2 intravenously on day 1 followed by continuous infusion of 2400 mg/m^2 over 44 hours, plus oxaliplatin 85 mg/m^2 intravenously and leucovorin 400 mg/m^2 intravenously, both on day 1), or triplet chemotherapy: six 2-weekly cycles of FOLFOXIRI (irinotecan 165 mg/m^2 body surface area (BSA) intravenously, followed by oxaliplatin 85 mg/m^2 BSA intravenously with leucovorin 400 mg/m^2 BSA on day 1, followed by 3200 mg/m^2 BSA of continuous 5-fluorouracil intravenously on days 1–2).

Neoadjuvant chemoradiotherapy consisted of external beam radiotherapy (from January 2016 to June 2019, Intensity Modulated Radiotherapy; since June 2019, Volumetric Modulated Arc Therapy technique) with a cumulative dose of 50.0–50.4 Gray in 1,8–2 Gray fractions with concomitant chemotherapy (capecitabine 825 mg/m^2 twice daily on radiotherapy days).

Response to TNT was evaluated with MRI-DWI and computed tomography scans 6–8 weeks after treatment. For (near) cCR, digital rectal examination and endoscopy were performed to confirm a CR. If uncertain, restaging with MRI, endoscopy, and

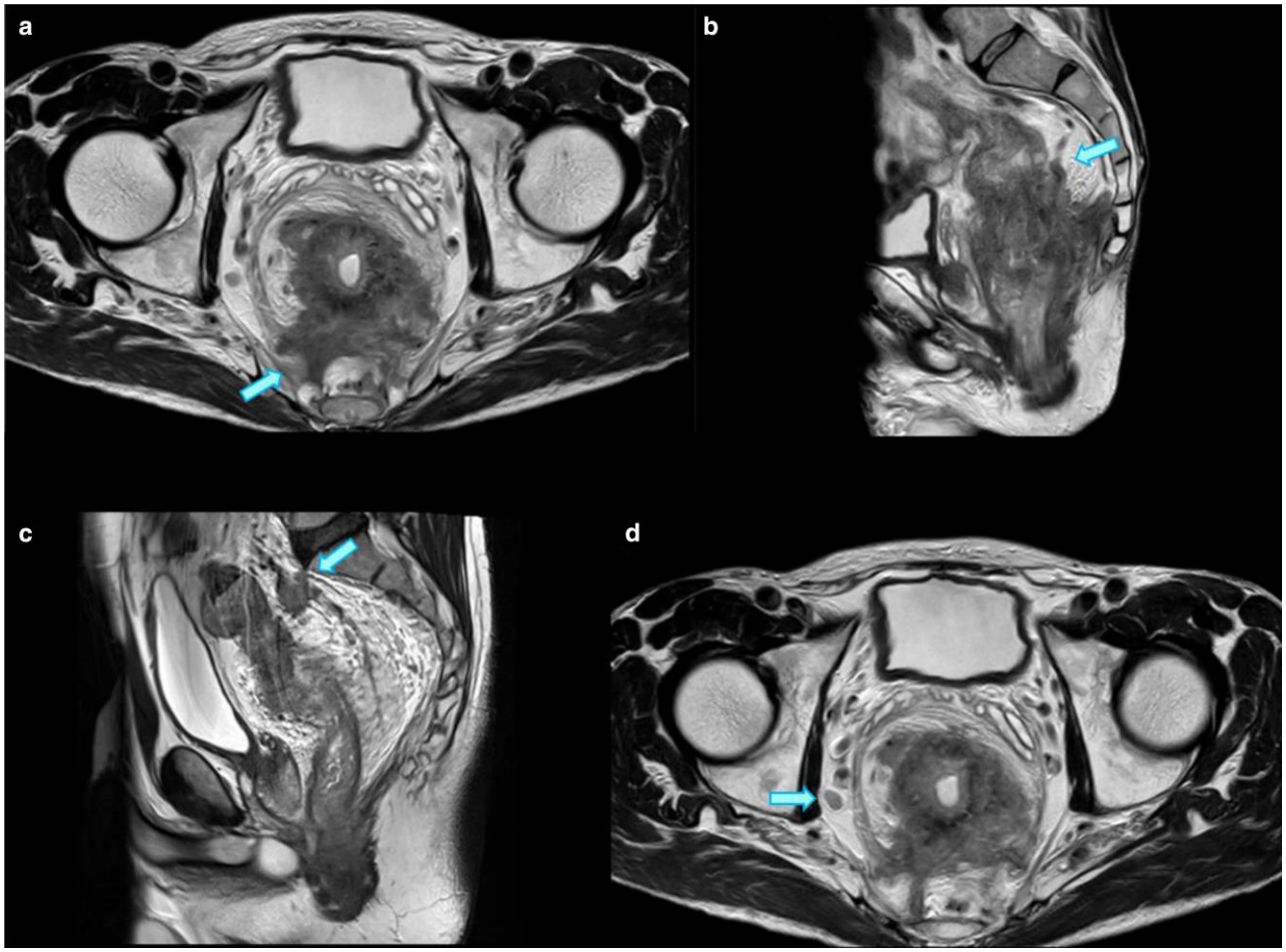


Fig. 1 High-risk criteria ('MEND-criteria')
a Mesorectal fascia invasion, **b** extramural venous invasion grade IV, **c** tumour deposit, **d** pathological lateral lymph node.

digital rectal examination was conducted after 12 weeks. Upon confirming cCR, a W&W approach was considered in consultation with the patient, following standard guidelines[32]. Patients without a CR were advised to proceed to total mesorectal excision (TME) surgery.

Outcomes

The primary outcome was 3- and 5-year OS. Secondary outcomes were regrowth rate, death-censored regrowth-free survival, organ-preservation rate, death-censored organ survival, local recurrence rate, death-censored local recurrence-free survival (LRFS), distant metastases rates, death-censored distant metastasis-free survival (DMFS) and death-censored recurrence-free survival (RFS). Local regrowth was defined as the reappearance of vital tumour tissue on MRI-DWI and/or endoscopy in cCR patients. Organ preservation was defined as sustained cCR without subsequent radical surgery due to a residual tumour or a stenosis. Local recurrence was defined as histopathological or clinical (imaging in combination with clinical findings, with consensus in the multidisciplinary team) evidence of recurrent disease within the pelvis after TME surgery.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics® version 25.0 (IBM, Armonk, New York, USA). Continuous data were reported as mean(standard deviation (s.d.)) or as median (range), and categorical data as counts with percentages. Group differences in categorical data were assessed using the χ^2 test or Fisher's exact test; continuous variables were compared using the independent samples *t* test. A two-sided *P*-value < 0.05 was considered statistically significant. Kaplan–Meier survival analyses evaluated overall survival (OS), death-censored regrowth-free survival, death-censored organ survival, death-censored LRFS, death-censored DMFS, and death-censored RFS. OS was calculated from the date of diagnosis until the date of death, with censoring at last follow-up for patients still alive. Death-censored regrowth-free survival was calculated from restaging MRI after TNT until the date of regrowth, with censoring at last follow-up or death. Death-censored organ survival was calculated from restaging MRI after TNT until the date of surgery; patients without surgery were censored at death or last follow-up. Death-censored LRFS, DMFS, and RFS were calculated from the date of diagnosis until date of event, that is, the date of regrowth, local recurrence, or distant metastases, with censoring at death or last follow-up. Follow-up time was defined as the time from diagnosis to the last reported clinical follow-up.

Results

Study population

A total of 135 patients with high-risk LARC were treated with TNT during the study period. Three patients (2.2%) died during or short after neoadjuvant treatment: one due to progressive disease

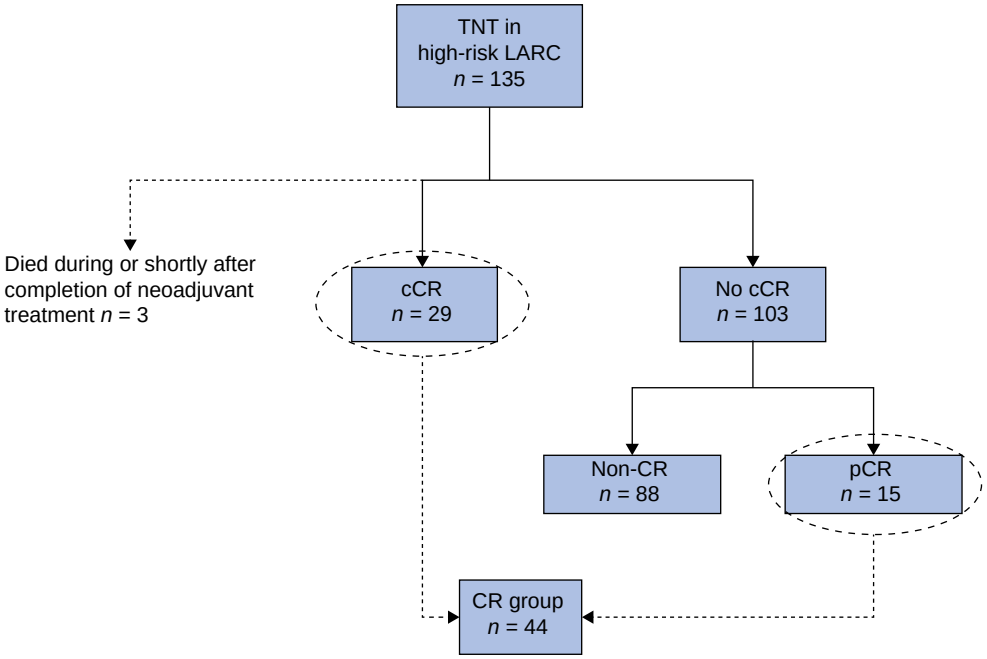


Fig. 2 Study flowchart of included patients

TNT, total neoadjuvant therapy; LARC, locally advanced rectal cancer; cCR, clinical complete response; pCR, pathological complete response; non-CR, non-complete response; CR, complete response.

during induction chemotherapy, one due to progressive disease after completion of TNT, and one due to an out-of-hospital cardiac arrest, most likely caused by sepsis due to tumour abscess formation, which was already present at diagnosis. Of the 132 remaining patients, 29 (21.5%) achieved a cCR after TNT. The remaining 103 patients (76.3%) without cCR underwent surgery. Among those who underwent surgery, 15 of 103 (14.6%) had a pCR. Retrospective review demonstrated that 10 of 15 of these patients with pCR demonstrated a radiological partial or good response at restaging. Due to uncertainty regarding a cCR, surgery was performed. In another 3 of 15 patients with pCR, a radiological CR was documented; in one case surgery was pursued due to a persistent stenosis, whereas in the other two the indication was unclear, although patient preference may have contributed. Lastly, in the remaining 2 of 15 patients with pCR, restaging assessment was limited by mucinous tumour and motion artifacts.

When combining cCR and pCR, 44 patients (32.6%) achieved a CR (*Fig. 2*). Baseline characteristics of the CR group and the non-CR group are presented in *Table 1*. No significant differences for age, sex, tumour category, and MEND-criteria were found between the groups.

Total neoadjuvant therapy

The majority of patients (95.5%) were treated with induction chemotherapy. Four patients (3.0%) received neoadjuvant consolidation chemotherapy after chemoradiotherapy. In three cases, consolidation chemotherapy was administered due to persistent, possibly irresectable disease. In one case, the patient was referred after initiation of chemoradiotherapy elsewhere, and consolidation chemotherapy was subsequently administered. Additionally, two patients received consolidation chemotherapy in addition to induction chemotherapy during the waiting period before surgery due to an excellent response. Treatment regimens are presented in *Table 1*. In those treated with triplet chemotherapy (36 of 132, 27.3%), a CR (pCR or cCR) was achieved in 18 patients (50%). In comparison, for patients treated with doublet chemotherapy (96 of 132, 72.7%), a CR was observed in 26 patients (27.1%) ($P = 0.013$).

Oncological outcomes

The median follow-up of all patients was 42.5 months (range 7–82). The median follow-up time of all patients in the CR group was 42 months (range 9–76) compared with 42.5 months (range 7–82) in the non-CR group. Dividing the cohort based on treatment strategy, the median follow-up time in all W&W patients was 44 months (range 16–71) compared with 42 months (range 7–82) in all surgically treated patients.

Local regrowth and local recurrence

Local regrowth was observed in 7 of 29 patients (24.1%) who entered a W&W approach. The median time to regrowth was 7 months (range 3–37). The 1- and 3-year death-censored regrowth-free survival rates were 79.2% and 79.2% (95% confidence interval (c.i.) 64.3 to 94.1; *Fig. 3*). Radical salvage TME surgery was performed in all patients with regrowth.

A total of 110 patients (81.5%) underwent surgery, either after neoadjuvant treatment or after regrowth. In the CR group, one patient (2.3%) developed a local recurrence after 24 months, and was one of the cCR patients who underwent salvage TME surgery after regrowth and developed a local recurrence thereafter. In the non-CR group, 14 patients (15.9%) developed local recurrence, occurring after a median 16.5 months (range 11–57). The 1- and 3-year estimated death-censored LRFS rates were 100% and 97.6% (95% c.i. 92.9 to 100) in the CR group, respectively, compared with 98.8% (95% c.i. 96.4 to 100) and 85.8% (95% c.i. 78.0 to 93.6), respectively, in the non-CR group ($P = 0.016$) (*Fig. 4*).

Organ preservation in W&W patients

Organ preservation was achieved in 21 of 29 patients (72.4%) who entered a W&W approach. Surgery was required in seven patients

Table 1 Baseline characteristics of the CR group and non-CR group

	CR ($n = 44$)	non-CR ($n = 88$)	P*
Age (years), mean(s.d.)	57.98(10.8)	59.73(10.3)	0.367†
Sex			0.358
Male	32 (72.7%)	57 (64.8%)	
Female	12 (27.3%)	31 (35.2%)	
T category			0.085
T3	26 (59.1%)	38 (43.2%)	
T4	18 (40.9%)	50 (56.8%)	
N category			0.553
N0	3 (6.8%)	3 (3.4%)	
N1	15 (34.1%)	28 (31.8%)	
N2	26 (59.1%)	57 (64.8%)	
EMVI grade IV			0.277
Yes	22 (55.0%)	54 (61.4%)	
No	22 (50.0%)	34 (38.6%)	
MRF invasion			0.572
Yes	21 (47.7%)	37 (42.0%)	
No	23 (52.3%)	51 (58.0%)	
Tumour deposits			0.079
Yes	29 (65.9%)	68 (77.3%)	
No	15 (34.1%)	17 (19.3%)	
Missing	0 (0%)	3 (3.4%)	
Lateral lymph nodes			0.596
Yes	11 (25.0%)	26 (29.5%)	
No	33 (75.0)	62 (70.5%)	
Chemotherapy			0.675
ICT	41 (93.2%)	85 (96.6%)	
ICT + CCT	1 (2.3%)	1 (1.1%)	
CCT	2 (4.5%)	2 (2.3%)	
Type of chemotherapy			0.045
CAPOX	24 (54.5%)	65 (73.9%)	
FOLFOX	2 (4.5%)	5 (5.7%)	
FOLFOXIRI	18 (40.9%)	18 (20.5%)	
Chemoradiation			
Yes	44 (100%)	88 (100%)	
No	0 (0%)	0 (0%)	

Values are *n* (%) unless indicated otherwise. CR, complete response;. non-CR, non-complete response; EMVI, extramural venous invasion; MRF, mesorectal fascia; ICT, induction chemotherapy; CCT, consolidation chemotherapy; CAPOX, capecitabine, oxaliplatin; FOLFOX, 5-fluorouracil, oxaliplatin, leucovorin; FOLFOXIRI, 5-fluorouracil, oxaliplatin, irinotecan, leucovorin. *χ^2 test, except †independent samples *t* test.

due to tumour regrowth, whereas one patient required surgery due to a persistent stenosis. In one patient, stoma formation was required due to a stenosis, although the rectum remained *in situ*. Consequently, this patient was classified as having organ preservation. The 1- and 3-year death-censored organ survival rates were 82.6% (95% c.i. 68.7 to 96.5) and 75.4% (95% c.i. 59.5 to 91.3), respectively.

Distant metastases

Distant metastases occurred in 7 patients (15.9%) in the CR group and 21 patients (23.9%) in the non-CR group. The median time to occurrence of distant metastases was 22 months (range 12–29) in the CR group and 17 months (range 11–53) in the non-CR group. Among the W&W patients, four patients (13.8%) developed distant metastases, occurring after a median 22.5 months (range 12–26). Of the seven patients with local regrowth, two developed distant metastases (28.6%). The 1- and 3-year estimated death-censored DMFS rates were 97.7% (95% c.i. 93.2 to 100) and 82.7% (95% c.i. 70.9 to 94.5), respectively, in the CR group compared with 97.6% (95% c.i. 94.3 to 100) and 76.0% (95% c.i. 66.2 to 85.8), respectively, in the non-CR group ($P = 0.273$) (Fig. 4).

Recurrence-free survival

The 1-year estimated death-censored RFS was 90.7% (95% c.i. 82.1 to 99.3) in the CR group *versus* 97.6% (95% c.i. 94.3 to 100) in the non-CR group ($P = 0.847$). The 3-year estimated death-censored RFS was 73.6% (95% c.i. 60.1 to 87.1) in the CR group *versus* 71.4% (95% c.i. 61.2 to 81.6) in the non-CR group ($P = 0.847$) (Fig. 4).

Overall survival

The median follow-up time of all patients for the OS analysis was 44.5 months (range 19–99) in the CR group and 55.5 months (range 18–89) in the non-CR group. The 3- and 5-year estimated OS rates were 100% and 89.5% (95% c.i. 75.8 to 100), respectively, in the CR group compared with 84.0% and 84.0% (95% c.i. 76.0 to 92.0), respectively, in the non-CR group, ($P = 0.131$) (Fig. 5).

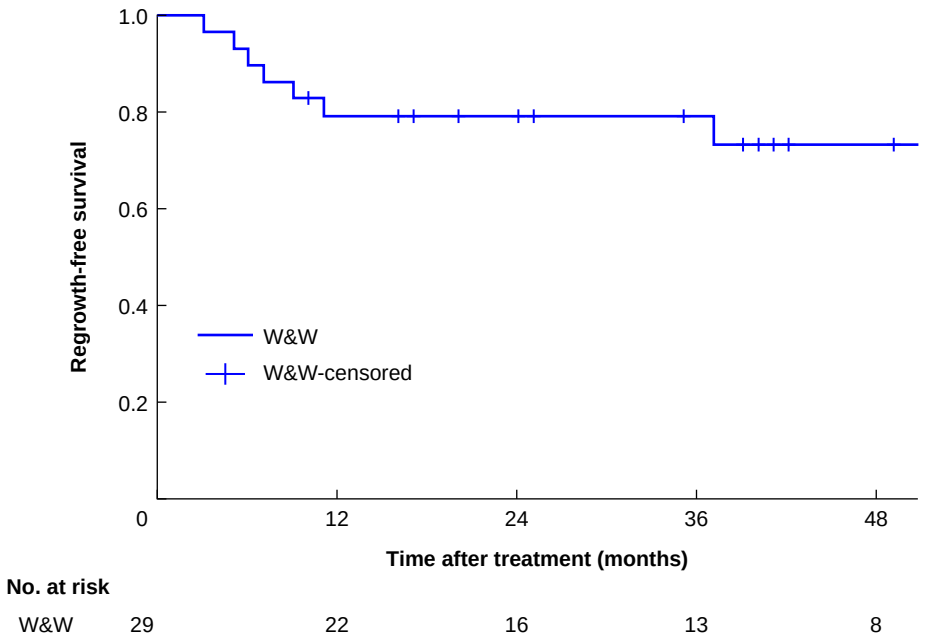


Fig. 3 Kaplan–Meier estimates of regrowth-free survival in patients managed with W&W

W&W, watch-and-wait.

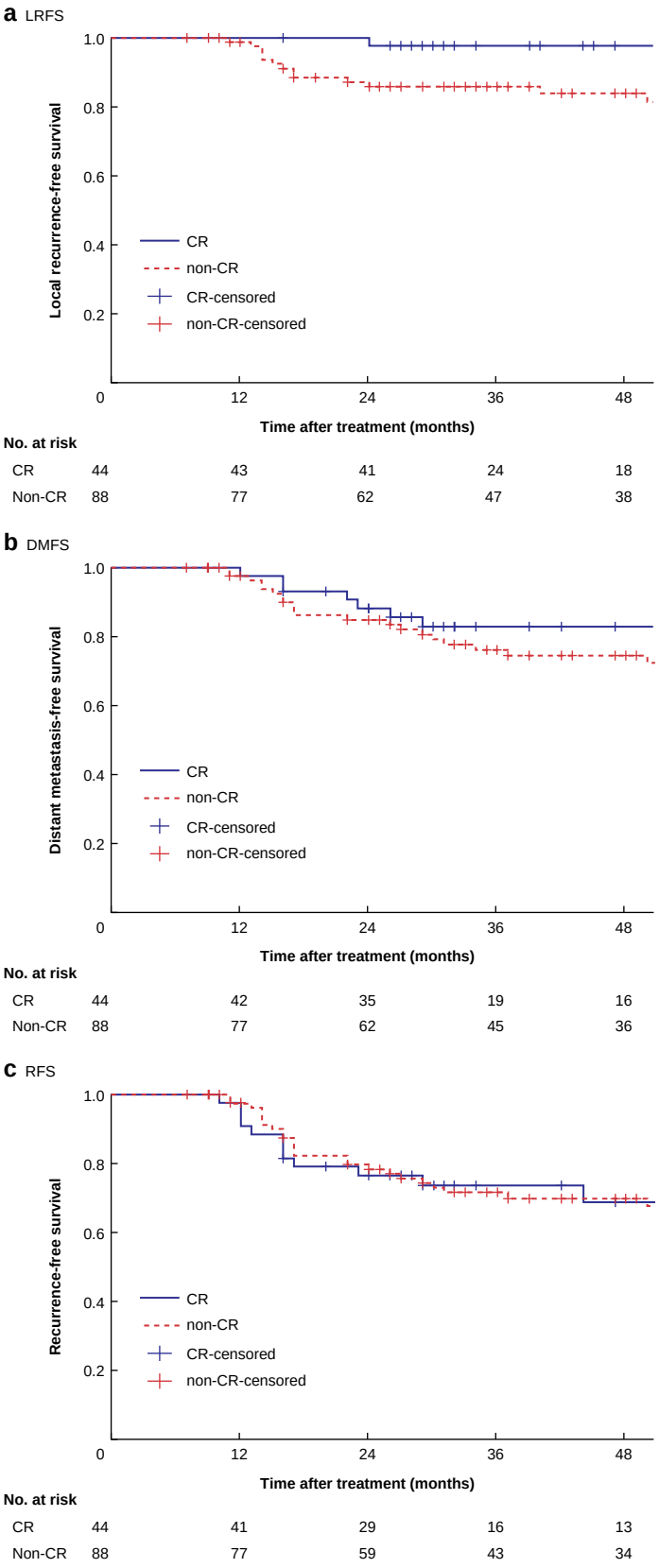


Fig. 4 Kaplan–Meier estimates of LRFS, DMFS, and RFS in patients with CR *versus* patients with non-CR

a LRFS; log rank, $P = 0.016$, **b** DMFS; log rank, $P = 0.273$, **c** RFS; log rank, $P = 0.847$. LRFS, local recurrence-free survival; CR, complete response; non-CR, non-complete response; DMFS, distant metastasis-free survival; RFS, recurrence-free survival.

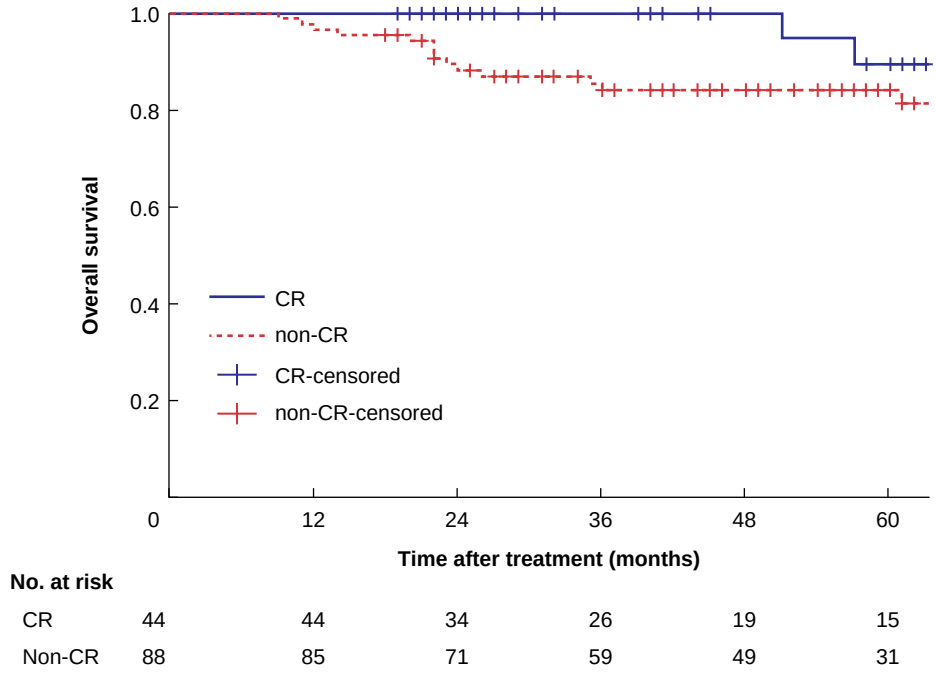


Fig. 5 Kaplan–Meier estimates of overall survival in patients with CR *versus* patients with non-CR

CR, complete response, non-CR, non-complete response. Log rank, $P = 0.131$.

Oncological outcomes in W&W patients

The estimated 3- and 5-year OS rates for W&W patients were 100% and 90.9% (95% c.i. 73.8 to 100) compared with 86.1% (95% c.i. 79.0 to 93.2) and 84.2% (95% c.i. 76.4 to 92.0) for patients who underwent immediate surgery ($P = 0.115$) (*Fig. 6*). The estimated 1- and 3-years RFS rates for W&W patients were 86.2% (95% c.i. 73.7 to 98.7) and 71.9% (95% c.i. 55.4 to 88.4), respectively, compared with 97.9% (95% c.i. 95.0 to 100) and 72.3% (95% c.i. 63.1 to 81.5), respectively, for surgically treated patients ($P = 0.680$) (*Fig. 7*).

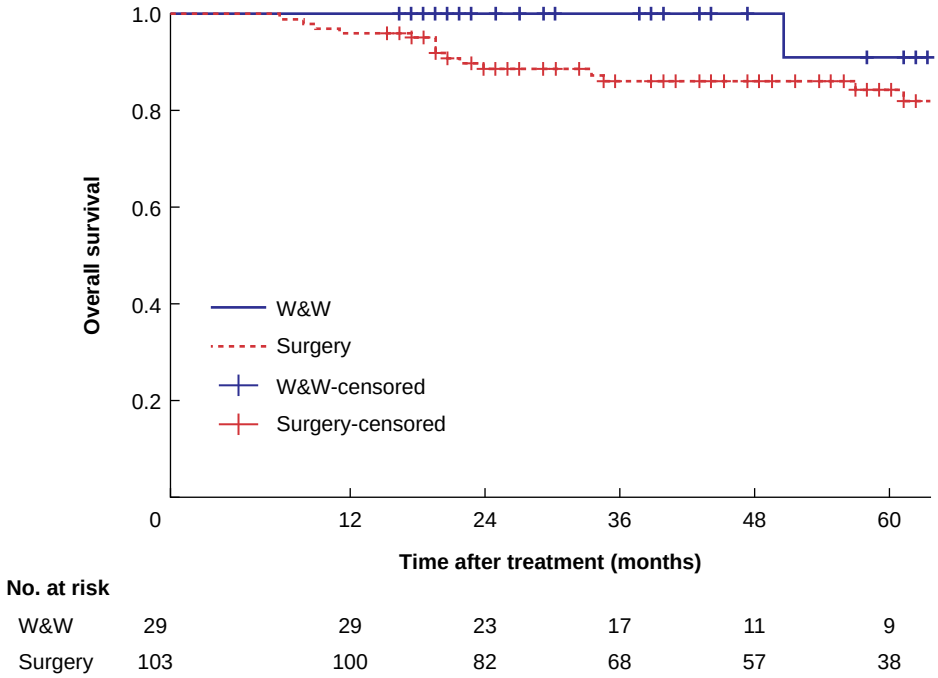
Discussion

The present study evaluated patients with LARC with specific high-risk tumour characteristics associated with a poor prognosis who achieved a pCR or cCR after TNT. The authors demonstrated a CR rate of 32.6% after TNT in patients with high-risk LARC. These patients have a favourable 5-year OS of 89.5%. Local regrowth was observed in seven patients (24.1%) with cCR after a median follow up time of 44 months (range 16-71). Patients managed with a W&W approach were not associated with increased risk for local recurrence and distant metastases, or worse survival, compared with the patients who underwent immediate surgery.

In the present study, the incidence of regrowth among W&W patients was comparable to previous studies[17,23,33–35] on W&W strategies in rectal cancer, despite the selection of patients with high-risk LARC. A large cohort study[23] involving 1009 patients similarly reported a 2-year cumulative regrowth incidence of 25.2%, whereas Fernandez *et al.*[18] observed regrowth in 26.7% of patients. Importantly, all patients with regrowth in the cohort were successfully treated with radical salvage TME surgery, consistent with findings by van der Valk *et al.*[23], who also demonstrated high success rates for salvage TME surgery after regrowth. In the present study, patients managed with a W&W approach were not associated with worse oncological outcomes compared with the surgically treated patients (3-year RFS 71.9% *versus* 72.3%, respectively, and 5-year OS 90.9% *versus* 84.2%, respectively). These findings align with the results from the Manchester Tertiary Cancer Centre[36], which reported similar DFS and OS rates between W&W and surgically treated patients with rectal cancer, despite the cohort including more high-risk LARC tumours. In the context of local recurrence, the CR patients had a significantly lower risk of local recurrence compared with non-CR patients (3-year death-censored LRFS 97.6% *versus* 85.8%, respectively; $P = 0.016$).

Estimated organ preservation survival at 3 years was 75.4% in patients who entered a W&W approach. Other studies[36,37] focusing on organ preservation reported comparable organ preservation rates. The lower adoption of the W&W approach in the early years of the study period likely explains why 14.6% of the surgically treated patients had a pCR. Most of these patients underwent restaging 4 weeks after the last fraction of chemoradiotherapy. In retrospect, nearly all of these patients demonstrated a good response on imaging, and none developed a local recurrence. Therefore, it is important to consider delaying surgery and awaiting the maximum therapeutic effect before deciding to operate. With a favourable response on the first restaging, prolonging the waiting interval to 12 weeks can be considered in order to avoid unnecessary surgery.

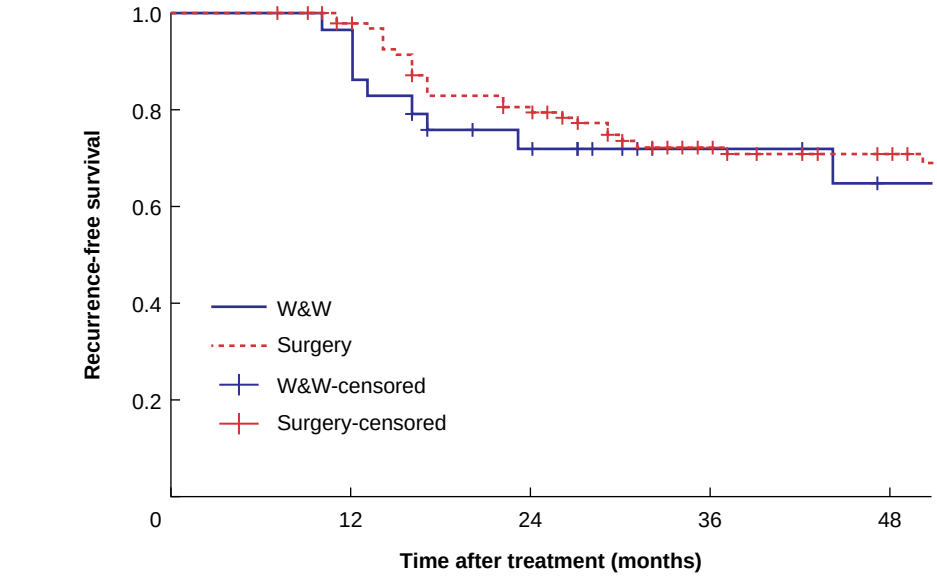
This study suggests that, even in patients with high-risk LARC, 5-year OS can be favourable when a CR is achieved after TNT. Moreover, survival outcomes are comparable to those reported in earlier studies[23,38] on patients with a CR, despite the fact that those studies included fewer tumours with high-risk criteria. The beneficial 5-year OS of the CR group supports the hypothesis that a good response to neoadjuvant therapy is a sign of favourable tumour biology, and can serve as a prognostic factor for oncological outcomes[39–41]. The risk of developing



No. at risk

W&W	29	29	23	17	11	9
Surgery	103	100	82	68	57	38

Fig. 6 Kaplan–Meier estimates of overall survival in patients managed with W&W *versus* surgical resection
W&W, watch-and-wait. Log rank, $P = 0.115$.



No. at risk

W&W	29	25	18	11	8
Surgery	103	91	71	48	39

Fig. 7 Kaplan–Meier estimates of recurrence-free survival in patients managed with W&W *versus* surgical resection
W&W, watch-and-wait. Log rank, $P = 0.680$.

distant metastases in the CR patients of this cohort is relatively low compared with what is generally known from patients with LARC, also suggesting favourable tumour biology in those achieving a good response[42–44]. When considering only the W&W group (cCR), and comparing it with all patients who underwent immediate surgery (pCR and non-CR), the present study showed that a W&W approach in patients with high-risk LARC does not result in poorer survival rates (5-year OS 90.9% *versus* 84.2%, respectively).

The findings suggest a realistic chance of achieving a CR after TNT (32.6%), particularly with triplet induction chemotherapy, which showed significantly higher CR rates compared with doublet induction chemotherapy (50.0% *versus* 27.1%, respectively; $P = 0.013$). However, triplet chemotherapy was introduced later in the study period, coinciding with increased adoption of the W&W approach. Evidence supporting the superiority of triplet chemotherapy over doublet chemotherapy in achieving CR in rectal cancer is limited. A meta-analysis[45] by

Moretto *et al.* showed that induction chemotherapy with FOLFIRINOX had better OS and pCR rates than induction chemotherapy with CAPOX. Currently, the JANUS trial[46] is exploring outcomes of chemoradiotherapy with triplet *versus* doublet consolidation chemotherapy in patients with LARC. Furthermore, the MEND-IT trial[16] is studying the effect of FOLFOXIRI and chemoradiotherapy on CR rates in patients with high-risk LARC. Further research is needed to evaluate whether triplet *versus* doublet induction chemotherapy provides superior long-term organ-preserving and oncological outcomes in patients with high-risk LARC.

This study is the first to evaluate a W&W approach in patients with high-risk LARC. Its strength lies in the selection of patients with LARC with high-risk tumour characteristics associated with poorer prognosis, demonstrating that, even in this group, a W&W approach is safe. However, limitations include its retrospective design and relatively small study population. As this study only included patients treated with TNT, selection bias may have played a role, favouring fitter patients. Additionally, the present study lacks detailed data on induction chemotherapy and chemoradiotherapy induced toxicity, and functional outcomes after W&W and TME surgery. Lastly, this study combined cCR and pCR outcomes, as both are associated with similar oncological outcomes and likely reflect beneficial tumour biology[37]. However, the authors acknowledge that cCR is determined clinically and therefore carries the risk of local regrowth, whereas pCR is pathologically confirmed after surgery and does not bear this risk. In contrast, patients who did not undergo surgery were not at risk of local recurrence, as local recurrence is defined as occurring only following surgical resection. Therefore, whereas combining these groups is appropriate for evaluating the prognostic value of CR, caution is warranted when interpreting outcomes such as regrowth and local recurrence.

A W&W approach can be considered safe and feasible for patients with high-risk LARC in whom a CR is achieved. In case of a good response to neoadjuvant treatment, prolonging the waiting interval may prevent unnecessary surgery resulting in a pCR. Favourable long-term oncological outcomes were observed in patients with high-risk LARC who achieved a CR after TNT, suggesting that tumour response may be a more reliable predictor of oncological outcomes than baseline clinical tumour stage.

Funding

This study was funded by Netherlands Organisation for Health Reserach and Development (ZonMW), project number 10070012010003. The funding sources had no role in study design, data collection, data analysis, data interpretation, or writing the paper.

Author contributions

Evi Banken (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing—original draft), Barbara M. Geubels (Conceptualization, Data curation, Methodology, Writing—review & editing), Fleur E. C. Vande Kerckhove (Conceptualization, Writing—review & editing), Davy M. J. Creemers (Conceptualization, Writing—review & editing), Stijn H. J. Ketelaers (Conceptualization, Writing—review & editing), Joost Nederend (Conceptualization, Data curation, Methodology, Writing—review & editing), Heike M. U. Peulen (Conceptualization, Writing—review & editing), Irene E. G. van Hellemond (Conceptualization, Methodology, Supervision, Validation, Writing—review & editing), Harm J. T. Rutten (Conceptualization, Methodology, Supervision, Validation, Writing—review & editing), and Jacobus W. A. Burger (Conceptualization, Methodology, Supervision, Validation, Writing—review & editing)

Disclosure

The authors declare no conflict of interest.

Data availability

Data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C *et al.* Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol* 2012;**30**:1926–1933
2. van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EMK, Putter H, Wiggers T *et al.* Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* 2011;**12**:575–582
3. van der Meij W, Rombouts AJM, Rütten H, Bremers AJA, de Wilt JHW. Treatment of locally recurrent rectal carcinoma in previously (chemo)irradiated patients. *Dis Colon Rectum* 2016;**59**:148–156
4. Nagtegaal ID, Marijnen CAM, Kranenbarg EK, van de Velde CJH, van Krieken JHJM. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma. *Am J Surg Pathol* 2002;**26**:350–357
5. Schaap DP, Voogt ELK, Burger JWA, Cnossen JS, Creemers GJM, van Lijnschoten I *et al.* Prognostic implications of MRI-detected EMVI and tumor deposits and their response to neoadjuvant therapy in cT3 and cT4 rectal cancer. *Int J Radiation Oncol Biol Phys* 2021;**111**:816–825
6. Ogura A, Konishi T, Cunningham C, Garcia-Aguilar J, Iversen H, Toda S *et al.* Neoadjuvant (chemo)radiotherapy with total mesorectal excision only is not sufficient to prevent lateral local recurrence in enlarged nodes: results of the multicenter lateral node study of patients with low cT3/4 rectal cancer. *J Clin Oncol* 2019;**37**:33–43
7. Nagtegaal ID, Knijn N, Hugen N, Marshall HC, Sugihara K, Tot T *et al.* Tumor deposits in colorectal cancer: improving the value of modern staging—a systematic review and meta-analysis. *J Clin Oncol* 2017;**35**:1119–1127
8. Siddiqui MRS, Simillis C, Hunter C, Chand M, Bhoday J, Garant A *et al.* A meta-analysis comparing the risk of metastases in patients with rectal cancer and MRI-detected extramural vascular invasion (mrEMVI) vs mrEMVI-negative cases. *Br J Cancer* 2017;**116**:1513–1519
9. Lord AC, D'Souza N, Shaw A, Rokan Z, Moran B, Abulafi M *et al.* MRI-diagnosed tumor deposits and EMVI status have superior prognostic accuracy to current clinical TNM staging in rectal cancer. *Ann Surg* 2022;**276**:334–344

10. Miyoshi M, Ueno H, Hashiguchi Y, Mochizuki H, Talbot IC. Extent of mesorectal tumor invasion as a prognostic factor after curative surgery for T3 rectal cancer patients. *Ann Surg* 2006;**243**:492–498
11. Hendren SK, O'Connor BI, Liu M, Asano T, Cohen Z, Swallow CJ *et al.* Prevalence of male and female sexual dysfunction is high following surgery for rectal cancer. *Ann Surg* 2005;**242**:212–223
12. Pappou EP, Temple LK, Patil S, Smith JJ, Wei IH, Nash GM *et al.* Quality of life and function after rectal cancer surgery with and without sphincter preservation. *Front Oncol* 2022;**12**:944843
13. Steffens D, Solomon MJ, Young JM, Koh C, Venchiarutti RL, Lee P *et al.* Cohort study of long-term survival and quality of life following pelvic exenteration. *BJS Open* 2018;**2**:328–335
14. Jankowski M, Pietrzak L, Rupiński M, Michalski W, Hołdakowska A, Paciorek K *et al.* Watch-and-wait strategy in rectal cancer: is there a tumour size limit? Results from two pooled prospective studies. *Radiother Oncol* 2021 Jul;**160**:229–235
15. Agger E, Jörgren F, Jöud A, Lydrup ML, Buchwald P. Negative prognostic impact of tumor deposits in rectal cancer. *Ann Surg* 2023;**278**:e526–e533
16. van den Berg K, Schaap DP, Voogt ELK, Buffart TE, Verheul HMW, de Groot JWB *et al.* Neoadjuvant FOLFOXIRI prior to chemoradiotherapy for high-risk ("ugly") locally advanced rectal cancer: study protocol of a single-arm, multicentre, open-label, phase II trial (MEND-IT). *BMC Cancer* 2022;**22**:957
17. Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U, Silva e Sousa AH *et al.* Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy. *Ann Surg* 2004;**240**:711–718
18. Fernandez LM, São Julião GP, Figueiredo NL, Beets GL, van der Valk MJM, Bahadoer RR *et al.* Conditional recurrence-free survival of clinical complete responders managed by watch and wait after neoadjuvant chemoradiotherapy for rectal cancer in the International Watch & Wait Database: a retrospective, international, multicentre registry study. *Lancet Oncol* 2021;**22**:43–50
19. Martens MH, Maas M, Heijnen LA, Lambregts DMJ, Leijtens JWA, Stassen LPS *et al.* Long-term outcome of an organ preservation program after neoadjuvant treatment for rectal cancer. *J Natl Cancer Inst* 2016;**108**:djw171
20. Smith JD, Ruby JA, Goodman KA, Saltz LB, Guillem JG, Weiser MR *et al.* Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. *Ann Surg* 2012;**256**:965–972
21. Appelt AL, Pløen J, Harling H, Jensen FS, Jensen LH, Jørgensen JCR *et al.* High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. *Lancet Oncol* 2015;**16**:919–927
22. Hupkens BJP, Martens MH, Stoot JH, Berbee M, Melenhorst J, Beets-Tan RG *et al.* Quality of life in rectal cancer patients after chemoradiation: watch-and-wait policy versus standard resection—a matched-controlled study. *Dis Colon Rectum* 2017;**60**:1032–1040
23. van der Valk MJM, Hilling DE, Bastiaannet E, Meershoek-Klein Kranenbarg E, Beets GL, Figueiredo NL *et al.* Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. *Lancet* 2018;**391**:2537–2545
24. Dijkstra EA, Nilsson PJ, Hospers GAP, Bahadoer RR, Meershoek-Klein Kranenbarg E, Roodvoets AGH *et al.* Locoregional failure during and after short-course radiotherapy followed by chemotherapy and surgery compared with long-course chemoradiotherapy and surgery. *Ann Surg* 2023 Oct;**278**:e766–e772
25. Jin J, Tang Y, Hu C, Jiang LM, Jiang J, Li N *et al.* Multicenter, randomized, phase III trial of short-term radiotherapy plus chemotherapy versus long-term chemoradiotherapy in locally advanced rectal cancer (STELLAR). *J Clin Oncol* 2022;**40**:1681–1692
26. Cercek A, Roxburgh CSD, Strombom P, Smith JJ, Temple LKF, Nash GM *et al.* Adoption of total neoadjuvant therapy for locally advanced rectal cancer. *JAMA Oncol* 2018;**4**:e180071
27. Kasi A, Abbasi S, Handa S, Al-Rajabi R, Saeed A, Baranda J *et al.* Total neoadjuvant therapy vs standard therapy in locally advanced rectal cancer. *JAMA Netw Open* 2020;**3**:e2030097
28. Conroy T, Bosset JF, Etienne PL, Rio E, François É, Mesgouez-Nebout N *et al.* Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2021;**22**:702–715
29. Verheij FS, Omer DM, Williams H, Lin ST, Qin LX, Buckley JT *et al.* Long-term results of organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy: the randomized phase II OPRA trial. *J Clin Oncol* 2024;**42**:500–506
30. Federatie Medisch Specialisten. Colorectaal Carcinoom, 2020. Locoregionale stadiëring rectumcarcinoom. Cited 2025 Feb 19. Available from: https://richtlijnendatabase.nl/richtlijn/colorectaal_carcinoom_crc/diagnostiek_bij_crc/locoregionale_stadi_ring_rectumcarcinoom.html
31. Beets-Tan RGH, Lambregts DMJ, Maas M, Bipat S, Barbaro B, Curvo-Semedo L *et al.* Magnetic resonance imaging for clinical management of rectal cancer: updated recommendations from the 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. *Eur Radiol* 2018;**28**:1465–1475
32. Federatie Medisch Specialisten. Colorectaal Carcinoom. 2020. Watchful waiting na neoadjuvante therapie met resectie als aanvankelijk intentie bij CRC. Cited 2025 Feb 19. Available from: https://richtlijnendatabase.nl/richtlijn/colorectaal_carcinoom_crc/primaire_behandeling_rectumcarcinoom_bij_crc/watchful_waiting_na_neoadjuvante_therapie_met_resectie_als_aanvankelijke_intentie_bij_crc.html
33. Dattani M, Heald RJ, Goussous G, Broadhurst J, São Julião GP, Habr-Gama A *et al.* Oncological and survival outcomes in watch and wait patients with a clinical complete response after neoadjuvant chemoradiotherapy for rectal cancer. *Ann Surg* 2018;**268**:955–967
34. Chadi SA, Malcomson L, Ensor J, Riley RD, Vaccaro CA, Rossi GL *et al.* Factors affecting local regrowth after watch and wait for patients with a clinical complete response following chemoradiotherapy in rectal cancer (InterCoRe consortium): an individual participant data meta-analysis. *Lancet Gastroenterol Hepatol* 2018;**3**:825–836
35. Dossa F, Chesney TR, Acuna SA, Baxter NN. A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2017;**2**:501–513
36. Renehan AG, Malcomson L, Emsley R, Gollins S, Maw A, Myint AS *et al.* Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. *Lancet Oncol* 2016;**17**:174–183
37. Cotti GC, Pandini RV, Braghiroli OFM, Nahas CSR, Bustamante-Lopez LA, Marques CFS *et al.* Outcomes of

patients with local regrowth after nonoperative management of rectal cancer after neoadjuvant chemoradiotherapy. *Dis Colon Rectum* 2022;**65**:333–339

38. Zorcolo L, Rosman AS, Restivo A, Pisano M, Nigri GR, Fancellu A *et al.* Complete pathologic response after combined modality treatment for rectal cancer and long-term survival: a meta-analysis. *Ann Surg Oncol* 2012;**19**:2822–2832
39. Park IJ, You YN, Agarwal A, Skibber JM, Rodriguez-Bigas MA, Eng C *et al.* Neoadjuvant treatment response as an early response indicator for patients with rectal cancer. *J Clin Oncol* 2012;**30**:1770–1776
40. Beddy D, Hyland JMP, Winter DC, Lim C, White A, Moriarty M *et al.* A simplified tumor regression grade correlates with survival in locally advanced rectal carcinoma treated with neoadjuvant chemoradiotherapy. *Ann Surg Oncol* 2008;**15**:3471–3477
41. Wei IH, Garcia-Aguilar J. Non-operative management of rectal cancer: understanding tumor biology. *Minerva Chir* 2018;**73**:601–618
42. Bahadoer RR, Hospers GAP, Marijnen CAM, Peeters KCMJ, Putter H, Dijkstra EA *et al.* Risk and location of distant metastases in patients with locally advanced rectal cancer after total neoadjuvant treatment or chemoradiotherapy in the RAPIDO trial. *Eur J Cancer* 2023;**185**:139–149
43. Glimelius B, Myklebust TÅ, Lundqvist K, Wibe A, Guren MG. Two countries—two treatment strategies for rectal cancer. *Radiother Oncol* 2016;**121**:357–363
44. Osterman E, Hammarström K, Imam I, Osterlund E, Sjöblom T, Glimelius B. Recurrence risk after radical colorectal cancer surgery—less than before, but how high is it? *Cancers (Basel)* 2020;**12**:3308
45. Moretto R, Vetere G, Carullo M, Ciracì P, Masi G, Cremolini C. Induction treatment with FOLFIRINOX or oxaliplatin-based doublet followed by long-course chemoradiotherapy and surgery in locally advanced rectal cancer. A systematic review and pooled analysis from phase II and III trials. *Cancer Treat Rev* 2024;**130**:102829
46. Alvarez JA, Shi Q, Dasari A, Garcia-Aguilar J, Sanoff H, George TJ, *et al.* Alliance A022104/NRG-GI010: the Janus Rectal Cancer Trial: a randomized phase II/III trial testing the efficacy of triplet versus doublet chemotherapy regarding clinical complete response and disease-free survival in patients with locally advanced rectal cancer. *BMC Cancer* 2024;**24**:901.