



ORIGINAL ARTICLE

Selected stage IV rectal cancer patients managed by the watch-and-wait approach after pelvic radiotherapy: a good alternative to total mesorectal excision surgery?

Petra A. Custers^{1,2} | Britt J. P. Hupkens³ | Brechtje A. Grotenhuis¹ |
 Koert F. D. Kuhlmann¹ | Stéphanie O. Breukink⁴ | Geerard L. Beets^{1,2} |
 Jarno Melenhorst⁴ | the Dutch Watch-and-Wait Consortium (collaborators)

¹Department of Surgery, Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, The Netherlands

²GROW School for Oncology and Developmental Biology – Maastricht University, Maastricht, The Netherlands

³Department of Radiotherapy, Maastricht University Medical Centre (MAASTRO), Maastricht, The Netherlands

⁴Department of Surgery, Maastricht University Medical Centre, Maastricht, The Netherlands

Correspondence

Petra A. Custers, Department of Surgery, Netherlands Cancer Institute, Post Box 90203, 1006 BE Amsterdam, The Netherlands.
 Email: pa.custers@nki.nl

Funding information

There has been no financial support for this work.

Abstract

Aim: The aim of this study was to assess the clinical and oncological outcome of a selected group of stage IV rectal cancer patients managed by the watch-and-wait approach following a (near-)complete response of the primary rectal tumour after radiotherapy.

Method: Patients registered in the Dutch watch-and-wait registry since 2004 were selected when diagnosed with synchronous stage IV rectal cancer. Data on patient characteristics, treatment details, follow-up and survival were collected. The 2-year local regrowth rate, organ-preservation rate, colostomy-free rate, metastatic progression-free rate and 2- and 5-year overall survival were analysed.

Results: After a median follow-up period of 35 months, local regrowth was observed in 17 patients (40.5%). Nine patients underwent subsequent total mesorectal excision, resulting in a permanent colostomy in four patients. The 2-year local regrowth rate was 39.9%, the 2-year organ-preservation rate was 77.1%, the 2-year colostomy-free rate was 88.1%, and the 2-year metastatic progression-free rate was 46.7%. The 2- and 5-year overall survival rates were 92.0% and 67.5%.

Conclusion: The watch-and-wait approach can be considered as an alternative to total mesorectal excision in a selected group of stage IV rectal cancer patients with a (near-)complete response following pelvic radiotherapy. Despite a relatively high regrowth rate, total mesorectal excision and a permanent colostomy can be avoided in the majority of these patients.

KEYWORDS

metastatic disease, oncological outcome, organ-preservation, rectal cancer, watch-and-wait

Petra A. Custers and Britt J. P. Hupkens contributed equally.

The members of the Dutch Watch-and-Wait Consortium (collaborators) are listed in the Acknowledgements.

Clinical trial registration: clinicaltrials.gov NCT00939666, NCT02278653 and NCT03426397.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Colorectal Disease* published by John Wiley & Sons Ltd on behalf of Association of Coloproctology of Great Britain and Ireland

INTRODUCTION

Approximately 15%–25% of rectal cancer patients are diagnosed with synchronous stage IV disease [1,2]. This stage encompasses a wide spectrum of metastatic disease, in which various treatment strategies can be applied. In stage IV disease, the primary rectal tumour is often locally advanced, and pelvic radiotherapy can be added early in the treatment to improve local control. In the Netherlands, the so-called M1 schedule is frequently used in patients with limited metastatic disease; this schedule consists of a short-course radiotherapy (5 × 5 Gy) followed by systemic therapy, followed by local treatment of the metastases and rectum [3,4]. In stage IV rectal cancer patients who have been treated with pelvic radiotherapy, a complete response has been reported in up to 26%, usually on histology after total mesorectal excision (TME) [3–5]. Although the watch-and-wait approach could be of value for stage IV rectal cancer patients with a (near-)complete response following pelvic radiotherapy, there are few data available on the outcome of this approach in this patient group.

In nonmetastasized rectal cancer patients, the watch-and-wait approach, first introduced by Habr-Gama in 2004, has emerged as a treatment option for patients with a clinical complete response following neoadjuvant (chemo)radiotherapy to avoid the morbidity and mortality associated with TME surgery [6]. For patients with a clinical complete response, the watch-and-wait approach can be considered oncologically safe, with 5-year disease-specific and overall survival rates of 93.8% and 84.7%, respectively [7]. Patients with a clinical near-complete response at the first assessment are known to have a high likelihood of progressing to a clinical complete response at further follow-up, and can also be offered a watch-and-wait approach [8,9]. In line with the watch-and-wait approach in stage II and III rectal cancer patients, a decrease in the colostomy rate and improved functional outcome and quality of life may be expected in stage IV patients [10–12]. Furthermore, from an oncological point of view, a watch-and-wait approach may be even more justified in stage IV rectal cancer patients because the prognosis of these patients is more defined by the metastatic disease than the primary rectal tumour [2,13].

Previous studies evaluated the oncological outcome of different treatment strategies for stage IV rectal cancer patients [4,5,14]. However, no studies have reported on the watch-and-wait approach in stage IV rectal cancer patients with a (near-)complete response of the rectum following treatment according to these strategies. The aim of the present study was to investigate the clinical and oncological outcome of a selected group of stage IV rectal cancer patients, who after neoadjuvant radiotherapy, show a (near-)complete response of the primary rectal tumour and are managed by the watch-and-wait approach.

What does this paper add to the literature?

This is the first study on the watch-and-wait approach in stage IV rectal cancer patients. This study reveals that the watch-and-wait approach can be considered as an alternative to total mesorectal excision in a selected group of stage IV rectal cancer patients with a (near-)complete response following pelvic radiotherapy.

METHOD

Patient selection

In the Netherlands, since 2004, the majority of rectal cancer patients with a clinical (near-)complete response of the rectal tumour following neoadjuvant (chemo)radiotherapy managed by a watch-and-wait approach have been registered in a trial registry (clinical-trial.gov NCT00939666, NCT02278653 and NCT03426397). The three trial registries are approved by either the local institutional review board of Maastricht University Medical Centre or the medical ethics committee of the Netherlands Cancer Institute and are carried out in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. Currently, 13 hospitals participate in the Dutch watch-and-wait registry, and clinicians can register patients with a clinical (near-)complete response at their discretion. To ensure the quality of the registry, all patients were reassessed by the principal investigator before registration. Clinical data management was carried out by the Clinical Trials Office of the Netherlands Comprehensive Cancer Organisation and local investigators. All patients provided informed consent before registration.

Initially, this trial registry only included nonmetastasized rectal cancer patients managed by a watch-and-wait approach following a (near-)complete response after neoadjuvant (chemo)radiotherapy. At a later stage, the registry was also open for a selected subset of patients with synchronous stage IV disease, when it became clear that some of those patients were also managed by a watch-and-wait approach after a (near-)complete response of the primary tumour following neoadjuvant (chemo)radiotherapy. Metastases were considered synchronous if they were diagnosed at the primary staging or at the restaging 8–12 weeks after the end of (chemo)radiotherapy. Most often the decision by the multidisciplinary team on if and how to treat the rectum was the last step in the long treatment period that was mainly focused on the metastatic disease. In general, in patients with progressive or uncontrolled metastatic disease, the primary tumour is not the main determinant of the outcome, and patients will rarely be subjected to either TME surgery or intensive surveillance (a watch-and-wait approach) of the rectum. Patients who were registered in the watch-and-wait registry mainly had a favourable prognosis, with

limited metastatic disease at diagnosis, or with controlled metastatic disease or the absence of metastatic disease at restaging. For the present study, all patients diagnosed with synchronous stage IV disease who were included in the Dutch watch-and-wait registry between December 2004 and October 2020 were selected.

A clinical complete response of the rectal tumour has been defined as the complete absence of luminal and/or nodal disease on endoscopy, T2-weighted MRI and diffusion-weighted (DWI) MRI, and the absence of palpable residual tumour with digital rectal examination. A near-complete response has been defined as a very good response with no sign of obvious residual tumour that does not meet all the criteria of a complete response but has a high likelihood of progressing to a complete response with further follow-up. The clinical features of a (near-)complete response are provided in Table 1 [12,15,16].

In addition to the standard follow-up with CT and carcinoembryonic antigen (CEA), all patients are monitored for 5 years with a follow-up protocol to detect rectal regrowth: digital rectal examination, endoscopy, MRI and CEA measurements every 4–6 months in the first 2 years and every 6–12 months thereafter.

Data collection

The following data were collected: patient characteristics, characteristics of the rectal tumour and metastases (TNM stage, site of the metastases), treatment details (radiotherapy, systemic therapy, surgery), as well as data concerning the follow-up and survival (rectal regrowth, relapse of distant metastases, death). Additionally, in patients with rectal regrowth, data regarding the treatment of the regrowth (including the type of operation with or without the presence of a permanent colostomy) were collected.

Study outcomes

Study outcomes were defined as: (1) 2-year local regrowth rate, defined as the presence of luminal and/or nodal disease; (2) 2-year

organ-preservation rate (TME-free rate), defined as an in situ resection; (3) 2-year colostomy-free rate, defined as the absence of a permanent colostomy; (4) 2-year metastatic progression-free rate, defined as the absence of progression of the metastatic disease; and (5) the 2- and 5-year overall survival rates, defined as the absence of death.

The study outcomes were calculated from the date of diagnosis until the date of the first evidence of regrowth, surgery, progression of metastatic disease or death to determine the local regrowth rate, organ-preservation rate, colostomy-free rate, metastatic progression-free rate, and overall survival.

Statistics

All statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS version 25.0). Patient and treatment characteristics are reported using descriptive statistics and are presented as percentages or medians with ranges. Kaplan–Meier survival methods were used to analyse the study outcomes. Length of follow-up was calculated from the date of diagnosis until the date of death or the last follow-up date.

RESULTS

Patients

A total of 859 patients have been included to date in the Dutch watch-and-wait registry; 42 patients (4.9%) were diagnosed with synchronous stage IV disease and were included in the present study. Patient and treatment characteristics are shown in Table 2. The median age at diagnosis was 67 years (range 32–79 years), most patients were male (73.8%) and were diagnosed with a cT3 tumour (66.7%). Most metastases were located in the liver (83.4%), followed by the lung (7.1%) or in both liver and lung (7.1%). One patient (2.4%) had metastases located in the lung and adrenal gland. From the patients selected for this study, 81.0% had a clinical complete response

TABLE 1 Clinical features of a complete and near-complete response

| | Complete response | Near-complete response |
|-----------|--|--|
| DRE | Absence of palpable tumour, when initially palpable | Small superficial soft irregularity |
| Endoscopy | White scar without residual tumour | Small residual erythematous ulcer or irregular wall thickening |
| T2W-MRI | Substantial downsizing without residual tumour AND Absence of suspicious lymph nodes | Obvious downstaging with residual fibrosis but heterogeneous or irregular aspect OR Obvious downstaging of lymph nodes but remaining node(s) ≥ 5 mm |
| DWI-MRI | Low signal on high <i>b</i> -value | Small focal area of high signal on high <i>b</i> -value |

Abbreviations: DRE, digital rectal examination; DWI-MRI, diffusion-weighted MRI; T2W-MRI, T2-weighted MRI.

Note: Clinical features of a complete response and near-complete response following neoadjuvant (chemo)radiotherapy were as previously defined [12,15,16].

TABLE 2 Patient and treatment characteristics

| | Total cohort (n = 42) |
|---|--------------------------|
| Median age (years) (range) | 67 (32–79) |
| Sex (n, %) | |
| Male | 31 (73.8) |
| Female | 11 (26.2) |
| Clinical tumour stage (n, %) | |
| cT2 | 4 (9.5) |
| cT3 | 28 (66.7) |
| cT4 | 10 (23.8) |
| Clinical nodal stage (n, %) | |
| cN0 | 8 (19.0) |
| cN1 | 13 (31.0) |
| cN2 | 21 (50.0) |
| Metastases at diagnosis (n, %) | |
| Liver | 35 (83.4) |
| Lung | 3 (7.1) |
| Liver and lung | 3 (7.1) |
| Other | 1 (2.4) |
| Radiotherapy (n, %) | |
| Short-course radiotherapy | 34 (81.0) |
| Chemoradiotherapy | 8 (19.1) |
| Systemic therapy (n, %) | |
| Capecitabine, oxaliplatin and bevacizumab | 25 (59.5) |
| Capecitabine and oxaliplatin | 5 (11.9) |
| Other systemic therapy | 8 (19.0) |
| Median number of cycles (n, range) | 6 (3–9) |
| Local treatment for metastases (n, %) | |
| Surgical resection | 27 (64.3) |
| Surgical resection and ablative technique | 9 (21.4) |
| Ablative technique | 2 (4.8) |
| Clinical complete response | 2 (4.8) |
| Unknown | 2 (4.8) |

and 19.0% a clinical near-complete response of the primary tumour at the time of inclusion.

Treatment details

All patients were treated with pelvic radiotherapy first, with 34 patients (81.0%) receiving short-course radiotherapy (5 × 5 Gy). In the eight remaining patients (19.1%) metastatic disease was first diagnosed at restaging after a long course of chemoradiotherapy (25 × 2 Gy or 28 × 1.8 Gy, with concurrent capecitabine). Following short- or long-course radiotherapy, systemic therapy was given in 38 patients (90.5%) with a median number of six cycles (range three to nine). The majority of patients received capecitabine and oxaliplatin with or without bevacizumab. Thirty-eight patients underwent local

treatment of their metastases: surgical resection and/or an ablative technique (microwave or radiofrequency ablation). In two patients (4.7%), a complete response of the metastases was seen after systemic therapy; therefore, no additional local treatment was performed. Data regarding the local treatment of the metastases were missing in two patients. The median interval between the end of the (chemo)radiotherapy and inclusion in the Dutch watch-and-wait registry was 34 weeks (range 10–54 weeks). The treatment schedule of all 42 patients before entering the watch-and-wait registry is shown in [Figure 1](#).

Outcome

After a median follow-up period of 35 months (range 9–146 months), 25 out of the 42 patients (59.5%) remained regrowth free, in the other 17 patients (40.5%) local regrowth occurred, of which 82.4% occurred in the first 2 years after the primary diagnosis. The 2-year local regrowth rate was 39.9% (see [Figure 2](#)). Local regrowth was located in the bowel wall in 16 patients (94.1%). In three patients, the regrowth was located in the locoregional lymph nodes; two of them also had simultaneous regrowth in the bowel wall. There was no difference in the local regrowth rate between patients with a complete and near-complete response. Follow-up details are shown in [Figure 3](#).

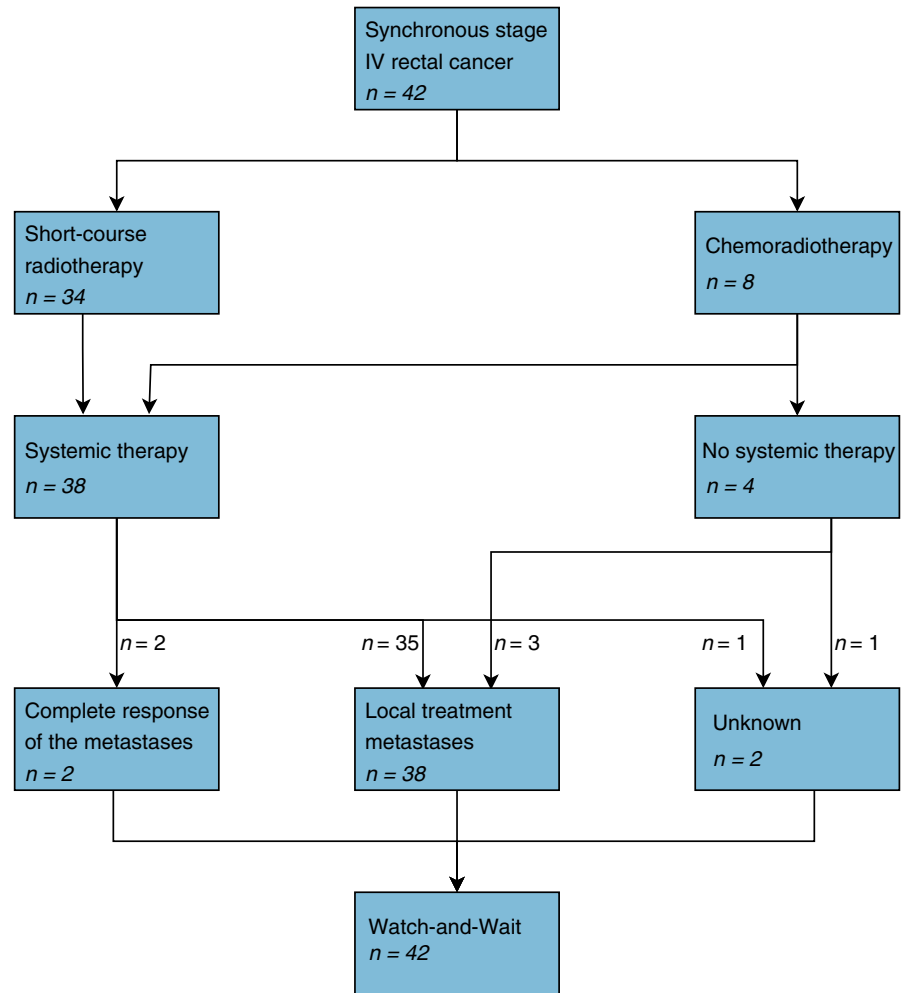
The 2-year organ-preservation and colostomy-free rates were 77.1% and 88.1%, respectively (see [Figure 4](#)). In 9 of the 17 patients with local regrowth (52.9%), subsequent TME surgery was performed: seven patients underwent a low anterior resection and two an abdominoperineal resection. In four patients, TME surgery resulted in a permanent colostomy. In the remaining eight patients with local regrowth (47.0%), TME surgery was not performed; in five of them the regrowth was treated locally (local excision or re-irradiation) and in three the local regrowth remained untreated. In six of these eight patients in whom TME surgery was not performed, progression of distant metastases was reported simultaneously with the detection of regrowth. Treatment details of the regrowth are shown in [Table 3](#).

Of the 42 patients, 25 had progression of the metastatic disease during follow-up and 17 patients were free from progression. The 2-year metastatic progression-free rate was 46.7% (see [Figure 2](#)). Overall, no difference was seen in the metastatic progression-free rate between patients with or without local regrowth. Local regrowth occurred in 6 of the 17 patients (35.3%) without progression of the metastatic disease compared with 11 of the 25 patients (44.0%) with progression of the metastatic disease. Twelve patients (30.2%) died; three patients died during the first 2 years of follow-up. The 2- and 5-year overall survival rates were 92.0% and 67.5%, respectively (see [Figure 2](#)).

DISCUSSION AND CONCLUSIONS

This study reports the clinical and oncological outcomes of a selected group of stage IV rectal cancer patients managed by a

FIGURE 1 Treatment schedule before entering the watch-and-wait registry



watch-and-wait approach after a (near-)complete response following pelvic radiotherapy. The 2-year local regrowth rate was 39.9%, with no difference between patients with a clinical complete response and near-complete response. In the majority of patients (78.6%) TME surgery could be avoided, and 90.5% of patients were colostomy free. Given these benefits, the watch-and-wait approach can be considered as an alternative to TME surgery in this selected group of patients with synchronous stage IV rectal cancer and a (near-)complete response following pelvic radiotherapy.

In nonmetastasized rectal cancer patients managed by a watch-and-wait approach, regrowth rates vary between 16% and 34%, with the variation most likely reflecting the difference in inclusion criteria, whether patients are included after the first or after a second reassessment, and the length of follow-up [7,11,17,18]. Compared with these regrowth rates, the 2-year regrowth rate of 39.9% in the present study is on the high side. This could be related to the short-course radiotherapy schedule that was given in the majority of patients in the present study, whereas a long-course of chemoradiotherapy is much more common in reports on the watch-and-wait approach in nonmetastasized rectal cancer patients. However, there are no studies comparing regrowth rates in patients managed by the watch-and-wait approach following different radiotherapy schedules. Although local regrowth rate is different from local recurrence

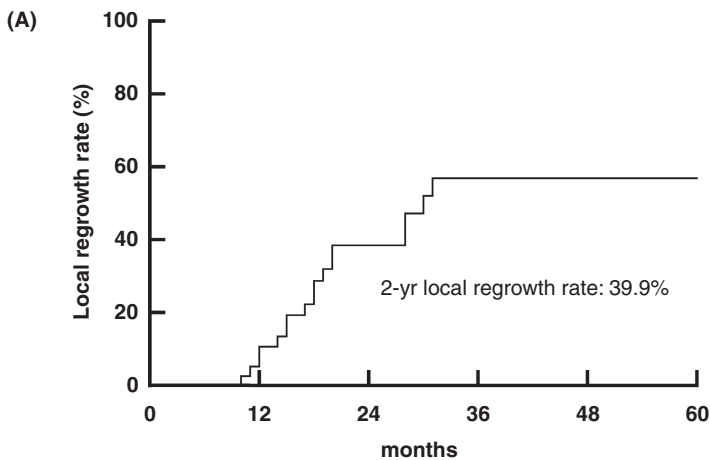
rate, some studies on TME surgery following various radiotherapy schedules report slightly more local recurrences after a short course of radiotherapy compared with a long course of chemoradiotherapy, albeit statistically insignificant [19,20]. An alternative explanation for the higher regrowth rate when compared with nonmetastasized tumours may be a more aggressive tumour biology, that results in both metastatic disease and more hidden residual disease at the primary site, leading to more regrowth. In the present study, the regrowth rate in patients with progression of the metastatic disease was 44.0% compared with 35.3% in patients without progression of the metastatic disease, supporting the idea of a shared unfavourable tumour biology between metastases and regrowth.

The 2-year regrowth rate of 39.9% in the present study could be considered too high for stage II or III rectal cancer patients, especially when it cannot be excluded that a small number of regrowths could give rise to distant metastases [21]. However, in patients with metastatic disease, the prognosis is mainly determined by the behaviour of distant metastases rather than the primary tumour, and the 2-year regrowth rate of 39.9% can be considered oncologically acceptable [2,13].

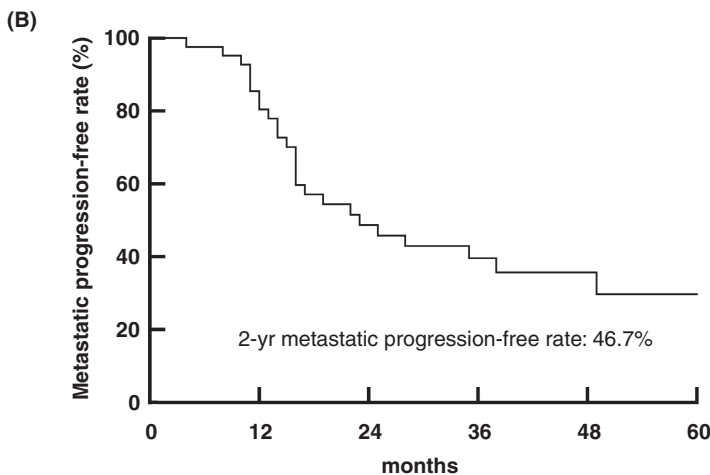
For the treatment of regrowth, TME surgery was performed in about half of patients, considerably lower than the 78% reported by van der Valk et al. in nonmetastasized patients with regrowth



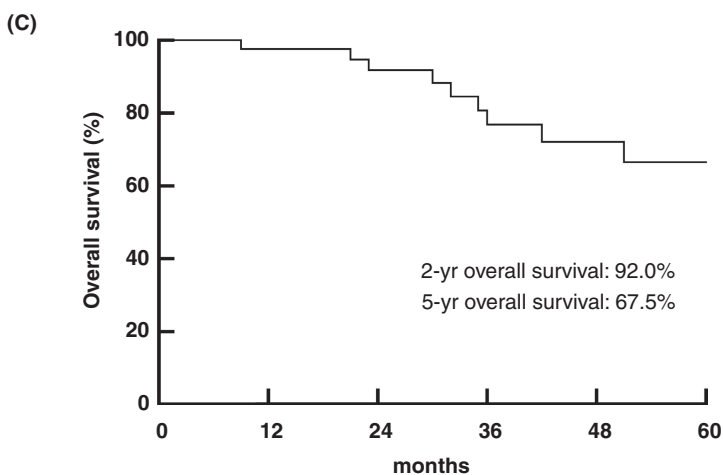
FIGURE 2 Local regrowth rate (A), metastatic progression-free rate (B) and overall survival (C)



Numbers at risk 42 35 14 8 7 5



Numbers at risk 42 33 15 9 6 5



Numbers at risk 42 38 31 21 14 11

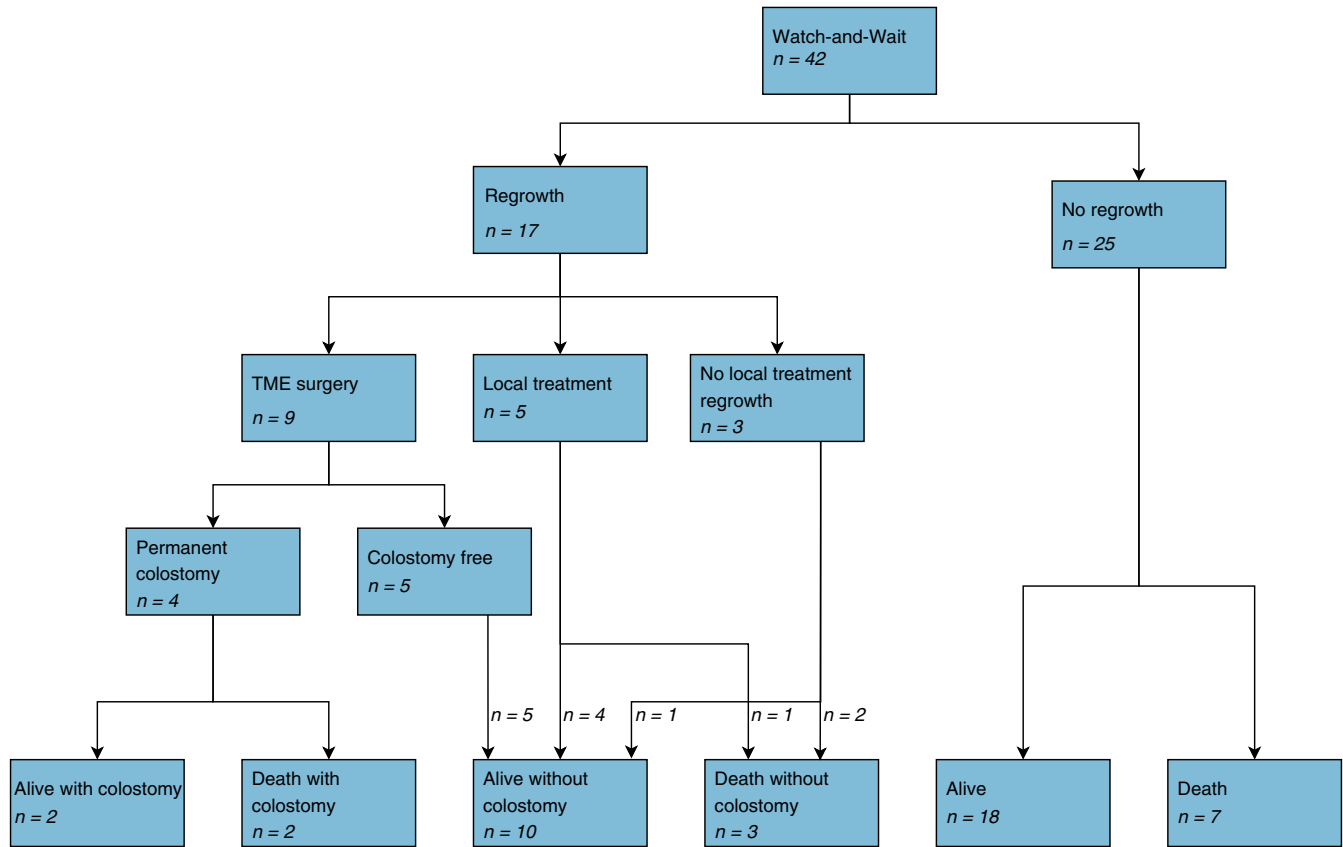


FIGURE 3 Follow-up after entering the watch-and-wait registry (TME, total mesorectal excision)

[7]. This difference is probably related to the high percentages of patients with progression of the distant metastases simultaneously with the detection of regrowth in the present series. Overall, this resulted in a 2-year organ-preservation and colostomy-free rates of 77.1% and 88.1%, respectively. Similar colostomy-free rates of 74% to 95% have been reported in nonmetastasized patients [11,12,17]. In general, avoidance of TME surgery and a colostomy is associated with an improved functional outcome and quality of life, as previously reported [10,22]. Moreover, this has been observed in multiple studies on the preferences of colorectal cancer patients; avoiding a colostomy is valued as one of the most important outcomes by patients, sometimes even more important than being cured from colorectal cancer [22–24]. Although the present study does not report functional outcome, in most patients the rectum is preserved and a colostomy is avoided. This is generally associated with better functional outcome and quality of life, two items that are especially relevant for patients with metastatic disease, who have a more unfavourable prognosis than nonmetastasized patients.

Of the nonmetastasized rectal cancer patients included in the large International Watch-and-Wait Database, the 5-year overall survival rate after a watch-and-wait approach is 84.7% [7]. In the present study, of a selected group of synchronous stage IV rectal cancer patients, the 5-year overall survival is 67.5%, which is much higher than what is generally reported in synchronous stage IV rectal

cancer [3,4,25]. This more favourable survival is due to a number of selection processes in a study that is focusing on the outcome of the treatment of the primary rectal tumour with a watch-and-wait approach, rather than on the treatment and outcome of the metastatic disease. The majority of patients were treated with a short-course of radiotherapy followed by systemic therapy, a schedule that in the Netherlands is often used in patients with limited metastatic disease. In the other patients, the metastatic disease was first diagnosed at restaging after chemoradiotherapy, and was most often limited. Clinicians only included patients in the Dutch watch-and-wait registry when, at the end of a long treatment period, including systemic treatment and local treatment of the metastases, the distant disease was under control and the focus shifted to the treatment of the primary tumour: TME surgery or a watch-and-wait approach. Patients with progressive metastatic disease or patients in a palliative setting are not included in the registry, as the focus is on treatment of the metastatic disease or on symptom control.

The main limitation of this study is the clear selection bias due to a highly selected patient group. The results of this study, especially the overall survival, should therefore be interpreted with caution. The second limitation is the lack of a comparator group, which is similar to most data regarding the watch-and-wait approach in non-metastasized rectal cancer patients in which a comparator group is also missing. A third limitation is the limited availability of data on the metastatic disease, as the registry is focused on the outcome of the

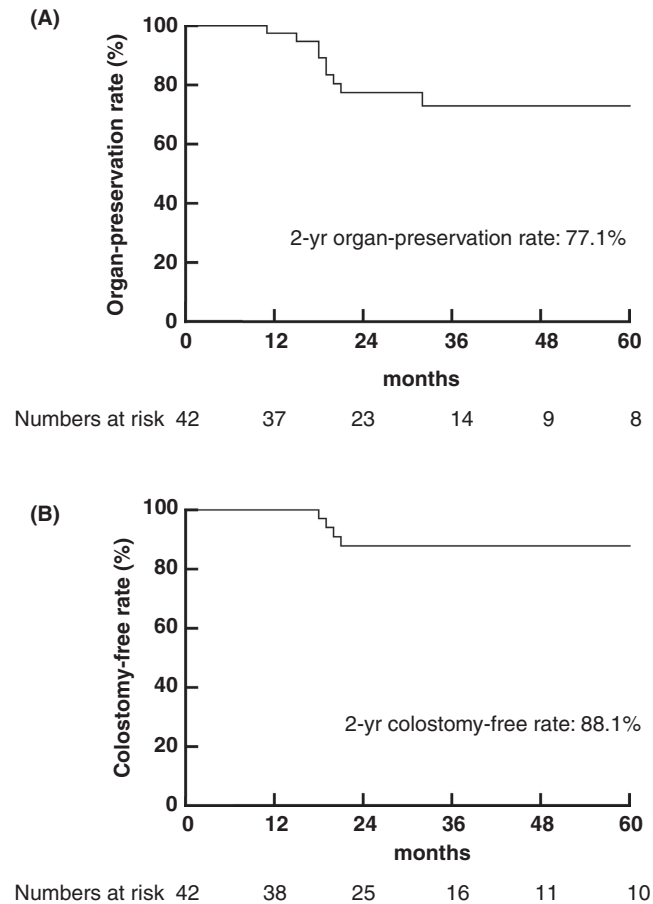


FIGURE 4 Organ-preservation rate (A) and colostomy-free rate (B)

TABLE 3 Treatment details: regrowth

| | Regrowth (n = 17) |
|-------------------------------|----------------------|
| Treatment for regrowth (n, %) | |
| Low anterior resection | 7 (41.2) |
| Abdominoperineal resection | 2 (11.8) |
| Local excision | 3 (17.6) |
| Re-irradiation | 2 (11.8) |
| No treatment for regrowth | 3 (17.6) |
| Permanent colostomy (n, %) | 4 (23.5) |

primary tumour. A fourth limitation of this study is the lack of data on functional outcome and quality of life.

In conclusion, this study evaluates the clinical and oncological outcome of the watch-and-wait approach in a highly selected group of stage IV rectal cancer patients. Although a relatively high regrowth rate is reported, in the majority of patients TME surgery and a colostomy are avoided. This is expected to result in a better functional outcome and quality of life. Therefore, in stage IV rectal cancer patients with good control of the metastatic disease and a (near-) complete response of the rectum following pelvic (chemo)radiation,

the watch-and-wait approach can be considered as an alternative to TME surgery.

ACKNOWLEDGEMENTS

The authors thank the Dutch Watch-and-Wait Consortium (collaborators).

Collaborators: Regina G. H. Beets-Tan, MD, PhD: Netherlands Cancer Institute, Department of Radiology, Amsterdam, The Netherlands; Jeroen Buijsen, MD, PhD: Maastricht University Medical Center, Department of Radiation Oncology (Maastro), Maastricht, The Netherlands and Maastricht University, GROW School for Oncology and Developmental Biology, Maastricht, The Netherlands; Sebastiaan Festen, MD, PhD: Onze Lieve Vrouwe Gasthuis, Department of Surgery, Amsterdam, The Netherlands; Eelco J. R. de Graaf, MD, PhD: IJsselland Hospital, Department of Surgery, Capelle aan de IJssel, The Netherlands; Hester E. Haak, MD: Netherlands Cancer Institute, Department of Surgery, Amsterdam, The Netherlands; Denise E. Hilling, MD, PhD: Leiden University Medical Center, Department of Surgery, Leiden, The Netherlands and Erasmus MC Cancer Institute, University Medical Center Rotterdam, Department of Oncological and Gastrointestinal Surgery, Rotterdam, The Netherlands; Christiaan Hoff, MD: Medical Center Leeuwarden, Department of Surgery, Leeuwarden, The Netherlands; Martijn Intven, MD, PhD: University Medical Center Utrecht, Department of Radiotherapy, Utrecht, The Netherlands; Niels Komen, MD, PhD: Antwerp University Hospital, Department of Abdominal Surgery, Edegem, Belgium and University of Antwerp, Antwerp Surgical Training, Anatomy and Research Center (ASTRAC), Wilrijk, Antwerp, Belgium; Miranda Kusters, MD, PhD: Amsterdam University Medical Centers, Location VUmc, Department of Surgery, Amsterdam, The Netherlands; Monique E. van Leerdam, MD, PhD: Netherlands Cancer Institute, Department of Gastroenterology, Amsterdam, The Netherlands and Leiden University Medical Center, Department of Gastroenterology, Leiden, The Netherlands; Koen C. M. J. Peeters, MD, PhD: Leiden University Medical Center, Department of Surgery, Leiden, The Netherlands; Femke P. Peters, MD, PhD: Netherlands Cancer Institute, Department of Radiotherapy, Amsterdam, The Netherlands and Leiden University Medical Center, Department of Radiotherapy, Leiden, The Netherlands; Apollo Pronk, MD, PhD: Diaconessenhuis, Department of Surgery, Utrecht, The Netherlands; Marit E. van der Sande, MD: Netherlands Cancer Institute, Department of Surgery, Amsterdam, The Netherlands; Wilhelmina. H. Schreurs, MD, PhD: Noordwest Ziekenhuisgroep, Department of Surgery, Alkmaar, The Netherlands; Dirk J. A. Sonneveld, MD, PhD: Dijklander Hospital, Department of Surgery, Hoorn, The Netherlands; Aalbert K. Talsma, MD, PhD: Deventer Hospital, Department of Surgery, Deventer, The Netherlands; Jurriaan B. Tuynman, MD, PhD: Amsterdam University Medical Centers, Location VUmc, Department of Surgery, Amsterdam, The Netherlands; Liselot B. J. Valkenburg-van Iersel, MD, PhD: Maastricht University Medical Center, Department of Internal Medicine, Division of



Medical Oncology, Maastricht, The Netherlands and Maastricht University, GROW School for Oncology and Developmental Biology, Maastricht, The Netherlands; Maarten Vermaas, MD, PhD: IJsselland Hospital, Department of Surgery, Capelle aan de IJssel, The Netherlands; Judith de Vos-Geelen, MD: Maastricht University Medical Center, Department of Internal Medicine, Division of Medical Oncology, Maastricht, The Netherlands and Maastricht University, GROW School for Oncology and Developmental Biology, Maastricht, The Netherlands; Henderik L. van Westreenen, MD, PhD: Isala, Department of Surgery, Zwolle, The Netherlands; Johannes H. W. de Wilt, MD, PhD: Radboud University Medical Center, Department of Surgery, Nijmegen, The Netherlands; David D. E. Zimmerman, MD, PhD: Elisabeth TweeSteden Hospital, Department of Surgery, Tilburg, The Netherlands.

CONFLICT OF INTEREST

The authors have no conflicts of interest associated with this publication, and there has been no significant financial support for this work that could have influenced the outcomes.

AUTHOR CONTRIBUTIONS

Contribution to the conception or design, BJPH, GLB, JM; contribution to the collection of data, PAC, BJPH; contribution to the analysis of the data, PAC; contribution to the interpretation of the data, PAC, BJPH, BAG, KFDK, SOB, GLB, JM; drafting the work, PAC; revising the work, BJPH, BAG, KFDK, SOB, GLB, JM; final approval of the version to be published, PAC, BJPH, BAG, KFDK, SOB, GLB, JM; agreement to be accountable for all aspects of the work, PAC, BJPH, BAG, KFDK, SOB, GLB, JM.

ETHICAL APPROVAL

Patients included in this study are registered in one of the three Dutch watch-and-wait registries approved by either the local institutional review board of Maastricht University Medical Centre or the medical ethics committee of the Netherlands Cancer Institute.








PATIENT CONSENT STATEMENT

All patients provided informed consent prior to study enrolment.

DATA AVAILABILITY STATEMENT

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

ORCID

Petra A. Custers  <https://orcid.org/0000-0003-3298-1045>
 Britt J. P. Hupkens  <https://orcid.org/0000-0002-6849-1948>
 Brechtje A. Grotenhuis  <https://orcid.org/0000-0002-6014-1986>
 Koert F. D. Kuhlmann  <https://orcid.org/0000-0001-6408-5590>
 Stéphanie O. Breukink  <https://orcid.org/0000-0002-5445-4011>
 Geerard L. Beets  <https://orcid.org/0000-0002-1671-9912>
 Jarno Melenhorst  <https://orcid.org/0000-0002-1495-4003>

REFERENCES

- Gatta G, Capocaccia R, Sant M, Bell CM, Coebergh JW, Damhuis RA, et al. Understanding variations in survival for colorectal cancer in Europe: a EURO CARE high resolution study. *Gut*. 2000;47(4):533–8.
- van der Pool AEM, Damhuis RA, IJzermans JNM, de Wilt JHW, Eggermont AMM, Kranse R, et al. Trends in incidence, treatment and survival of patients with stage IV colorectal cancer: a population-based series. *Colorectal Dis*. 2012;14(1):56–61.
- van Dijk TH, Tamas K, Beukema JC, Beets GL, Gelderblom AJ, de Jong KP, et al. Evaluation of short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin and subsequent radical surgical treatment in primary stage IV rectal cancer. *Ann Oncol*. 2013;24(7):1762–9.
- Kok END, Havenga K, Tanis PJ, Wilt JHW, Hagendoorn J, Peters FP, et al. Multicentre study of short-course radiotherapy, systemic therapy and resection/ablation for stage IV rectal cancer. *Br J Surg*. 2020;107(5):537–45.
- Nierop P, Verseveld M, Galjart B, Rothbarth J, Nuytens J, van Meerten E, et al. The liver-first approach for locally advanced rectal cancer and synchronous liver metastases. *Eur J Surg Oncol*. 2019;45(4):591–6.
- 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: long-term results. *Ann Surg*. 2004;240(4):711–7. discussion 7–8.
- 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(10139):2537–45.
- Hupkens BJP, Maas M, Martens MH, van der Sande ME, Lambregts DMJ, Breukink SO, et al. Organ preservation in rectal cancer after chemoradiation: should we extend the observation period in patients with a clinical near-complete response? *Ann Surg Oncol*. 2018;25(1):197–203.
- Habr-Gama A, São Julião GP, Fernandez LM, Vailati BB, Andrade A, Araújo SEA, et al. Achieving a complete clinical response after neoadjuvant chemoradiation that does not require surgical resection: it may take longer than you think! *Dis Colon Rectum*. 2019;62(7):802–8.
- 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(10):1032–40.
- 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(2):174–83.
- 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(12):djw171.
- Afshari K, Chabok A, Naredi P, Smedh K, Nikberg M. Prognostic factors for survival in stage IV rectal cancer: a Swedish nationwide case-control study. *Surg Oncol*. 2019;29:102–6.
- Baltatzis M, Chan AK, Jegatheeswaran S, Mason JM, Siriwardena AK. Colorectal cancer with synchronous hepatic metastases: systematic review of reports comparing synchronous surgery with sequential bowel-first or liver-first approaches. *Eur J Surg Oncol*. 2016;42(2):159–65.



15. Maas M, Beets-Tan RGH, Lambregts DMJ, Lammering G, Nelemans PJ, Engelen SME, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. *J Clin Oncol*. 2011;29(35):4633–40.
16. Habr-Gama A, Perez RO, Wynn G, Marks J, Kessler H, Gama-Rodrigues J. Complete clinical response after neoadjuvant chemoradiation therapy for distal rectal cancer: characterization of clinical and endoscopic findings for standardization. *Dis Colon Rectum*. 2010;53(12):1692–8.
17. Smith JJ, Strombom P, Chow OS, Roxburgh CS, Lynn P, Eaton A, et al. Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. *JAMA Oncol*. 2019;5(4):e185896.
18. 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(7):501–13.
19. Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CAM, Putter H, Kranenbarg E-K, et al. 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. *Lancet Oncol*. 2021;22(1):29–42.
20. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg*. 2006;93(10):1215–23.
21. Socha J, Kepka L, Michalski W, Paciorek K, Bujko K. The risk of distant metastases in rectal cancer managed by a watch-and-wait strategy – a systematic review and meta-analysis. *Radiother Oncol*. 2020;144:1–6.
22. Wrenn SM, Cepeda-Benito A, Ramos-Valadez DI, Cataldo PA. Patient perceptions and quality of life after colon and rectal surgery: what do patients really want? *Dis Colon Rectum*. 2018;61(8):971–8.
23. van der Valk MJM, van der Sande ME, Toebes RE, Breukink SO, Broker MEE, Doornebosch PG, et al. Importance of patient reported and clinical outcomes for patients with locally advanced rectal cancer and their treating physicians. Do clinicians know what patients want? *Eur J Surg Oncol*. 2020;46(9):1634–41.
24. Harrison JD, Solomon MJ, Young JM, Meagher A, Butow P, Salkeld G, et al. Patient and physician preferences for surgical and adjuvant treatment options for rectal cancer. *Arch Surg*. 2008;143(4):389–94.
25. Ayez N, Burger JWA, van der Pool AE, Eggermont AMM, Grunhagen DJ, de Wilt JHW, et al. Long-term results of the 'liver first' approach in patients with locally advanced rectal cancer and synchronous liver metastases. *Dis Colon Rectum*. 2013;56(3):281–7.

How to cite this article: Custers PA, Hupkens BJP, Grotenhuis BA, Kuhlmann KFD, Breukink SO, Beets GL, et al; the Dutch Watch-and-Wait Consortium (collaborators). Selected stage IV rectal cancer patients managed by the watch-and-wait approach after pelvic radiotherapy: a good alternative to total mesorectal excision surgery? *Colorectal Dis*. 2022;24:401–410. <https://doi.org/10.1111/codi.16034>