The evaluation of follow-up strategies of watch-and-wait patients with a complete response after neoadjuvant therapy in rectal cancer

Received: 16 December 2020 | Revised: 19 January 2021 | Accepted: 5 March 2021

DOI: 10.1111/codi.15636

ORIGINAL ARTICLE

The evaluation of follow-up strategies of watch-and-wait patients with a complete response after neoadjuvant therapy in rectal cancer

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ABSTRACT

Aim: Many of the current follow-up schedules in a watch-and-wait approach include very frequent MRI and endoscopy examinations to ensure early detection of local regrowth (LR). The aim of this study was to analyse the occurrence and detection of LR in a watch-and-wait cohort and to suggest a more efficient follow-up schedule.

Method: Rectal cancer patients with a clinical complete response after neoadjuvant therapy were prospectively and retrospectively included in a multicentre watch-and-wait registry between 2004 and 2018, with the current follow-up schedule with 3-monthly endoscopy and MRI in the first year and 6 monthly thereafter. A theoretical comparison was constructed for the detection of LR in the current follow-up schedule against four other hypothetical schedules.

Results: In all, 50/304 (16%) of patients developed a LR. The majority (98%) were detected at ≤2 years, located in the lumen (94%) and were visible on endoscopy (88%). The theoretical comparison of the different hypothetical schedules suggests that the optimal follow-up schedule should focus on the first 2 years with 3-monthly endoscopy and 3–6 monthly MRI. Longer intervals in the first 2 years will cause delays in diagnosis of LR ranging from 0 to 5 months. After 2 years, increasing the interval from 6 to 12 months did not cause important delays.

Conclusion: The optimal follow-up schedule for a watch-and-wait policy in patients with a clinical complete response after chemoradiation for rectal cancer should include frequent endoscopy and to a lesser degree MRI in the first 2 years. Longer intervals, up to 12 months, can be considered after 2 years.

KEYWORDS
chemoradiotherapy, clinical complete response, follow-up, organ preservation, rectal cancer, watch-and-wait

*See the Acknowledgements for the members of the Dutch Watch-and-Wait Consortium.

What does this paper add to the literature?

Although the importance of good follow-up in watch-and-wait patients is evident, the current schedules may be more intensive than required. This study shows that intensity of follow-up can be markedly reduced after an intensive surveillance in the first 2 years.

INTRODUCTION

During the last decade, the watch-and-wait (W&W) approach has been accepted as an alternative treatment in rectal cancer patients with a clinical complete response (cCR) after neoadjuvant therapy [1–3]. Adequate follow-up in W&W patients is essential for early detection and treatment of local regrowths (LRs), in order to achieve similar long-term outcomes compared to patients who undergo a standard rectal resection. It has been widely accepted that a three-modality approach has the highest accuracy to detect complete responders with frequent digital rectal examination (DRE), endoscopy and MRI with diffusion-weighted imaging (DWI) [1]. Most centres agree on a more frequent surveillance during the first 2 years, but there is a marked difference in the schedules regarding frequency and use of MRI and endoscopy [1,4]. Intensive follow-up visits and examinations can be a burden for patients, especially the frail and elderly. In addition, there is little information on the efficiency of frequent follow-up examinations, and on the value of MRI and endoscopy in detecting LR. In order to improve W&W follow-up, there is a need to balance between optimal LR detection, burden and efficiency. The current intensive follow-up protocol in the Dutch W&W network was based more on safety concerns than on evidence. The aim of this study is to analyse the occurrence and detection of LR in a W&W cohort and to suggest a more efficient follow-up schedule.

METHOD

Details of the W&W programme

Patients diagnosed with rectal cancer who had a cCR after neoadjuvant therapy who were offered a W&W programme between 2004 and 2017 were prospectively included in a local study from the Maastricht University Medical Center, approved by the local institutional review board and registered in clinicaltrials.gov since 2009 (NCT00939666 and NTC02278653), and provided informed consent. W&W patients from 2017 to 2018 were retrospectively included in a quality-controlled national registration of W&W patients, for which informed consent was waived by the local institutional review board. Patients were included in a W&W programme if they had a biopsy proven rectal adenocarcinoma without distant metastasis at baseline and received neoadjuvant treatment with long course chemoradiation consisting of 28 x 1.8 Gy with 2 x 825 mg/m^3 capecitabine or short course radiotherapy with 5 x 5 Gy followed by a waiting interval. Patients underwent restaging approximately 8–12 weeks after completion of (chemo)radiation by DRE, endoscopy and MRI including DWI (MRI-DWI). Those who were identified during restaging with a cCR or patients with a near complete response (nCR) were included in W&W. A cCR was defined as (1) no residual tumour felt on DRE, (2) white scar and/or telangiectasia of the mucosa on endoscopy and (3) low signal intensity at the original tumour site on T2-weighted MRI with absence of diffusion restriction on MRI-DWI and absence of residual malignant nodes [5,6]. An nCR was defined as (1) minor soft mucosal abnormality or irregularity felt on DRE, (2) superficial ulceration and/or mild persisting erythema of the scar and (3) intermediate or low residual signal on T2-weighted MRI and/or small foci of diffusion restriction on MRI-DWI [5,6]. All patients included for W&W were informed of the experimental nature of the study and were aware that the W&W approach was an alternative treatment and deviated from current guidelines. The current follow-up schedule in the Dutch hospital network consists of 3-monthly endoscopy and MRI in the first year and 6-monthly thereafter [7]. Standard follow-up methods for distant metastasis consisted of CT imaging of the chest and liver and carcinoembryonic antigen (CEA) blood levels for 5 years, according to national guidelines [8].

Study cohort for the analysis of detection of regrowths

First, we analysed the timing and modality of regrowths. Patients who were included in the W&W programme and who developed an LR during follow-up were eligible for the analysis of detection of regrowths. In order to provide a strictly selected study cohort, W&W patients who developed a typical cCR on MRI and endoscopy at first or second restaging (after another 6- to 12-week interval) were selected and W&W patients with a persisting nCR at second restaging or patients with local excision (transanal endoscopic microsurgery) prior to inclusion for W&W were excluded. Although it was intended that patients followed the advised current follow-up schedule (3-monthly endoscopy and MRI in the first year and 6-monthly thereafter), in reality some patients had fewer examinations while others had more frequent examinations because of patient preference, logistical planning issues or findings on endoscopy and/or MRI that warranted earlier follow-up. These variations could be used to evaluate the delay of LR detection in the current follow-up schedule and allowed more intensive hypothetical schedules also to be studied. The detection of LR with the actual follow-up schedule in the study cohort was compared with the estimated timing of regrowth detection if the current follow-up schedule would have been followed and in four additional hypothetical follow-up schedules. At the start of the study, before any analysis

was performed, the study group agreed on the four hypothetical schedules, based on literature and own experience. Because many studies have shown a low incidence of LRs after 2 years, all four hypothetical follow-up schedules consisted of less frequent examinations after 2 years (1–3). For the first 2 years two schedules tested more frequent and two schedules less frequent examinations. The hypothetical schedules were as follows.

1. Schedule 1: 3-monthly endoscopy and MRI in the first year, 3-monthly endoscopy and 6-monthly MRI in the second year and yearly endoscopy and MRI thereafter.
2. Schedule 2: 3-monthly endoscopy and MRI in the first year and 4-monthly in the second year and yearly endoscopy and MRI thereafter.
3. Schedule 3: 4-monthly endoscopy and MRI in the first year and 6-monthly in the second year and yearly endoscopy and MRI thereafter.
4. Schedule 4: 6-monthly endoscopy and MRI during the first 2 years and yearly endoscopy and MRI thereafter.

Comparing detection of regrowths in different follow-up schedules

To identify the optimal schedule, the actual LR detection, defined as the LR detection according to the actually performed evaluations in the study cohort, was compared with the estimated LR detection in the current and hypothetical schedules. Delay in LR detection was calculated as the difference between the actual LR detection and LR detection in the current and hypothetical schedules. For the analyses, there were two assumptions. The first was that when the examination with which the LR was actually detected in the series was left out in a theoretical schedule, the regrowth would be detected at the next scheduled examination. The second assumption was that in a theoretical schedule a regrowth cannot be detected earlier than when it was actually detected in the series.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 25.0). Baseline data were collected for all patients and included age, sex, baseline clinical staging, neoadjuvant therapy, type of surgical procedure, adjuvant chemotherapy and median follow-up time. Quantitative data were expressed as median with a range of minimum and maximum values. Categorical data were reported as the number of patients with percentages. LR was defined as tumour regrowth in the lumen or in mesorectal lymph nodes. Duration of follow-up and interval to event were calculated from the date of restaging MRI to the event of interest or last follow-up date that was used as a date of censoring.

RESULTS

Demographics

Figure 1 shows a flowchart with an overview of included and excluded patients. Fifty (16%) of 304 patients developed an LR during follow-up with a 2-year LR rate of 17%. 23 (46%) of 50 LR patients had a cCR during restaging and 27 (54%) had an nCR during restaging but achieved a cCR at second restaging. The median age of LR patients was 64 years (range 43–85). Of the 50 LR patients, 42 (84%) had a distal tumour (≤ 5 cm from the anorectal junction) and eight (16%) had a mid-rectum tumour (5.1–10 cm from the anorectal junction). Median follow-up time was 30 months (9–115) and median time from end of radiotherapy to date of restaging MRI was 9 weeks (5–18) . A more detailed overview of baseline characteristics of W&W patients and those who developed an LR and who were eligible for the analysis are shown in Table 1.

Patients with a local regrowth

The majority of LRs were diagnosed within 2 years (n = 49, 98%). The only patient with a regrowth later than 2 years had a nodal regrowth along the superior rectal vessels at the level of L5 diagnosed after 3 years and 8 months. In retrospect this was missed at MRI and the node was already visible 21 months earlier on MRI after 23 months of follow-up (i.e., this was in fact also a recurrence within 2 years). LRs were located luminal-only in 42 (84%) patients, both luminal and nodal in five (10%) and in regional lymph nodes only in three (6%) (Figures 2, 3 and 4). The

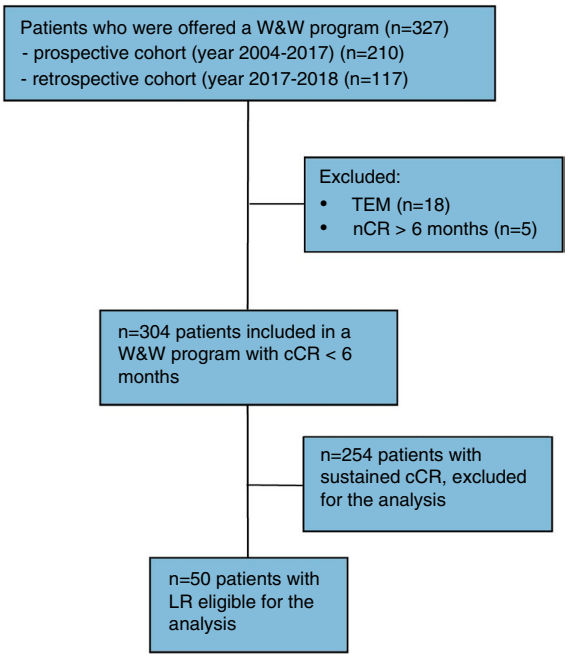

FIGURE 1 Flowchart with an overview of included and excluded patients. cCR, clinical complete response; LR, local regrowth; nCR, near complete response; TEM, transanal endoscopic microsurgery; W&W, watch-and-wait

TABLE 1 Baseline characteristics of W&W patients, and those with a local regrowth included for analyses to evaluate different follow–up schedules

	W&W patients (*n* = 304)	Patients with LR (*n* = 50) eligible for analysis
Median age (years)	66 (33–87)	64 (43–85)
Sex (male)	67% (204/304)	72% (36/50)
Clinical T stage		
T1	1% (2/304)	0% (0/0)
T2	21% (66/304)	10% (5/50)
T3	69% (209/304)	74% (37/50)
T4	9% (27/304)	16% (8/50)
Clinical N stage (N+)	73% (222/304)	68% (34/50)
Distance anal verge (cm)		
≤5	78% (237/304)	84% (42/50)
>5	22% (67/304)	16% (8/50)
Neoadjuvant therapy		
CRT	94% (285/304)	96% (48/50)
5 × 5 Gy with a long waiting interval	5% (16/304)	4% (2/50)
Other	1% (3/304)	NA
Adjuvant chemotherapy	16% (47/304)	10% (5/50)

Note: Data are median (range) or % (*n*/*N*).

Abbreviations: CRT, chemoradiotherapy; LR, local regrowth; W&W, watch-and-wait.

majority were detected on both endoscopy and MRI (*n* = 32, 64%), in 12 (24%) only on endoscopy and in six (12%) LR was only detected on MRI.

Comparing detection of regrowths in different follow-up schedules

The current follow-up schedule used in the Dutch hospital network consists of 24 examinations (12 endoscopy with DRE and 12 MRI-DWI) in 5 years after the inclusion in the W&W programme. Because some patients had more follow-up examinations than required in the standard protocol because of patient preference or logistical planning issues or findings on endoscopy and/or MRI that warranted earlier follow-up, some LRs were actually detected ahead of the standard assessment date. Table S1 provides a detailed overview of all patients with an LR and the theoretical difference in detection time-point according to the current and hypothetical schedules. The overall median delay in LR detection was 0 (range 0–5) months for the current schedule and 0 (range 0–4), 0 (range 0–4), 2 (range 0–4) and 2 (range 0–5) months for hypothetical schedules 1, 2, 3 and 4, respectively.

Figure 5 provides an overview of all patients with at least 3 months of delay in LR detection with both the current follow-up schedule and the hypothetical schedules. In addition to the current follow-up schedule (24 examinations), the four hypothetical schedules consisted of 20, 20, 16 and 14 examinations for schedules 1, 2, 3 and 4, respectively. With the current follow-up schedule, four patients with at least 3 months of delay in detection of LRs occurred in the first 2 years of follow-up. Hypothetical schedule 1 would have zero delays of at least 3 months during the first 2 years of follow-up, schedule 2 would have two delays of at least 3 months, schedule 3 would have 11 delays of at least 3 months and schedule 4 would have 14 delays of at least 3 months. In both the current schedule and the hypothetical schedules, one delay of at least 3 months in LR detection occurred after 2 years of follow-up in the patient described above with a nodal regrowth that was detected at 3 years and 8 months but that was in retrospect visible at 21 months.

DISCUSSION

The majority of the LRs in a W&W approach for a complete response after neoadjuvant therapy of rectal cancer were detected within 2 years (98%), located in the bowel wall (94%), and were visible on endoscopy (88%). The optimal follow-up schedule focuses on the first 2 years, with an intensive follow-up including 3-monthly

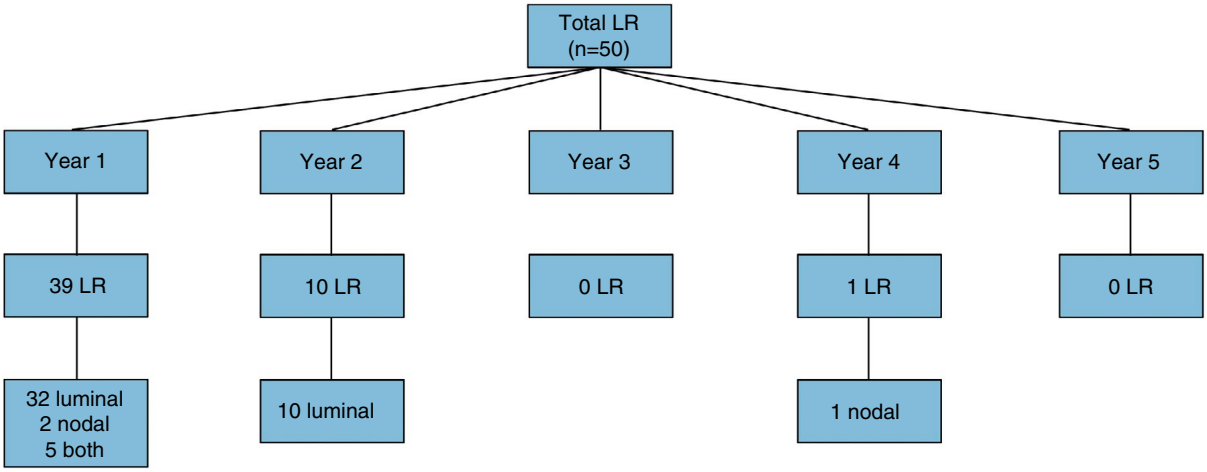

FIGURE 2 Flowchart of local regrowths. LR, local regrowth

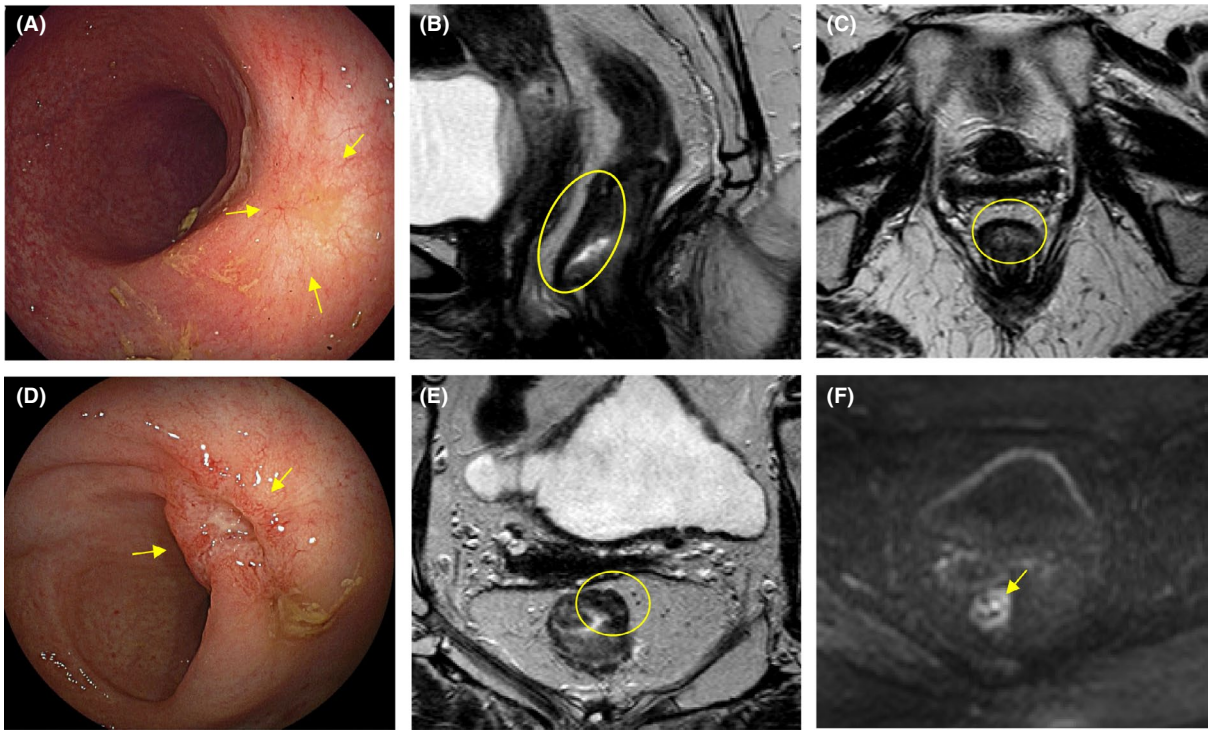

FIGURE 3 Example of patient with rectal cancer with a clinical complete response after neoadjuvant treatment. (A) White scar tissue and telangiectasia (yellow arrows) on endoscopy and (B) corresponding fibrotic wall on sagittal and (C) transversal T2-weighted MR images (indicated in yellow). Six months later, (D) there is an ulcer with elevated edges on endoscopy (yellow arrows) and (E) tumour mass is visible on transversal T2-weighted MR images within the fibrotic tumour bed with (F) diffusion restriction on diffusion-weighted imaging, suspicious for a local regrowth

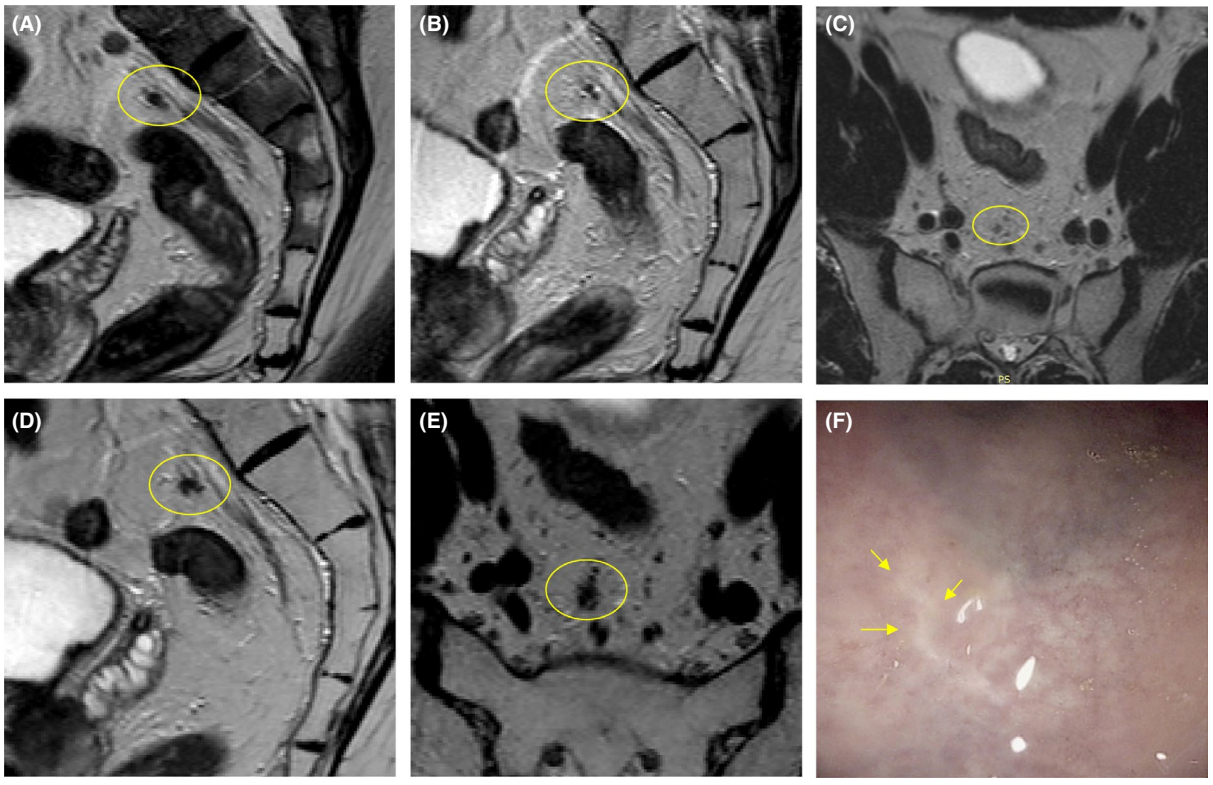

FIGURE 4 Example of a patient with rectal cancer with a malignant lymph node on (A) sagittal T2-weighted MR images before chemoradiation treatment. After chemoradiation treatment (B), (C) the lymph node decreased in size and was considered as no longer suspect. 12 months later (D), (E) the lymph node has grown, suggestive of nodal regrowth, while maintaining a luminal complete response on endoscopy (yellow arrows) (F)

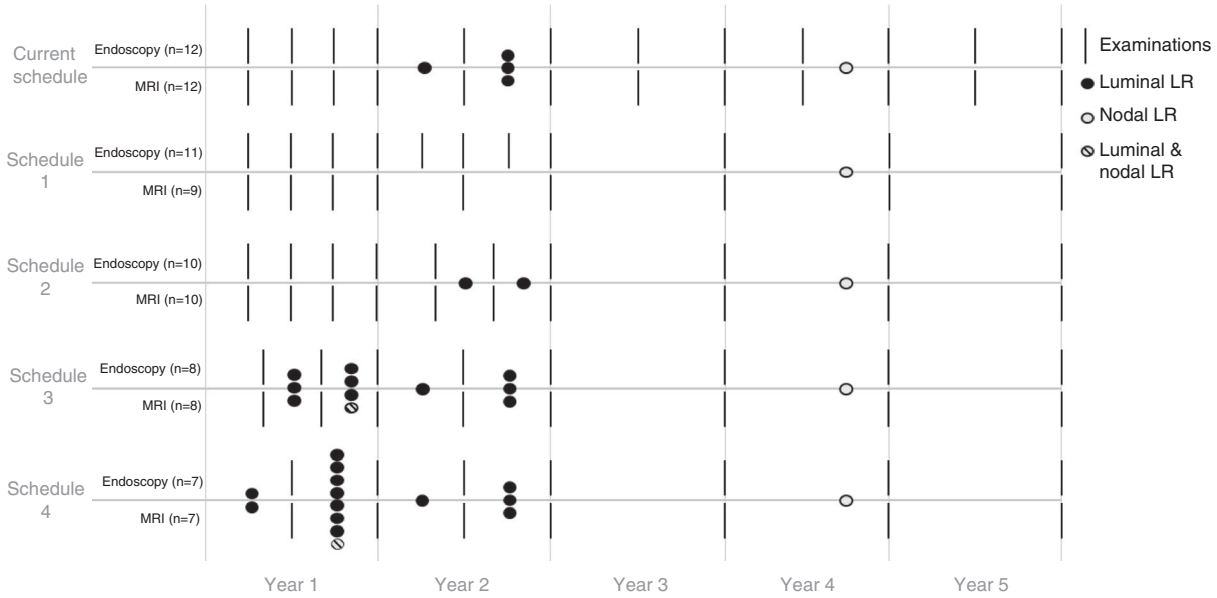

FIGURE 5 Overview of all patients with at least 3 months of delay in LR detection with both the current follow-up schedule and hypothetical schedules. LR, local regrowth; *n*, number of examinations

combined endoscopy and MRI assessment in the first year. In the second year the MRI can be performed at a 6-monthly interval combined with endoscopy every 3 months. This schedule minimizes the delay in detection of regrowths based on the available outcome data in the current series. Moreover, this schedule de-intensified the current follow-up schedule from 24 examinations to 20 examinations. De-intensifying the follow-up examinations in the first 2 years (schedules 3 and 4) resulted in more delays. Because very few regrowths became evident after 2 years, the follow-up interval can be de-intensified in years 3–5, that is, to 12-monthly follow-up, with no extra delay in detection.

Other studies also reported that most regrowths are luminal [1,3], and a number of W&W centres mainly rely on frequent endoscopies during the first 2 years [9–11]. It is known that clinical assessment with DRE and endoscopy is the single most accurate modality for identification of complete responders [4]. The most commonly used endoscopic technique is standard high-resolution endoscopy with white light. There are several new endoscopic techniques using advanced imaging such as narrow band imaging and chromoendoscopy which may improve the diagnostic accuracy of endoscopy in the future [12,13]. However, more studies need to confirm its added value before these techniques will be implemented in a W&W follow-up. The policy in most centres is to rely on serial endoscopic assessments and to perform targeted biopsies of any changes in the scar. When adenocarcinoma is found the interpretation is easy, but there is always the risk of a false negative biopsy through sampling error, and adenomatous changes and high-grade dysplasia can be difficult to interpret [5,14,15].

Our finding of the vast majority of regrowths occurring in the first 2 years of follow-up has also been noted by others [1–3], and de-intensifying the follow-up interval after 2 years has been recommended before [1]. Some groups even minimize the follow-up after 2 years to standard surveillance with regular CT scans and CEA measurements and omission of specific W&W follow-up [16,17]. Moreover, recent updated Dutch guidelines even recommend reducing the standard surveillance to regular CEA measurements and only performing CT scans by indication [18]. Considering the low risk of regrowths after 2 years and only one (discovered late) false negative finding in the current study, some groups may even opt to further reduce the number of examinations after 2 years which will increase the cost-effectiveness. Although it is clear that the efficiency of regular follow-up with MRI and endoscopy is lower after 2 years, there are a small number of patients who could benefit from early detection of a late regrowth. While we propose a yearly follow-up after 2 years of follow-up, some less experienced centres may feel more comfortable with a more gradual decrease as more assessments can compensate for missed detections, for example by maintaining a 6-monthly interval in year 3 and going to a 12-monthly follow-up in years 4 and 5. The single patient in our study with a late regrowth after 2 years had a high nodal deposit while the luminal tumour was still in complete remission. In retrospect the growing node was already visible on MRI scans more than a year earlier (after 23 months of follow-up) and the nodal regrowth was visible at CT as well, highlighting the importance of both the technical quality of the MRI as well as attentive reading by radiologists. The field of view of the MRI (both sagittal and axial) has to be wide enough to encompass the lateral nodal area as well as the proximal nodal area at the level of the promontory. Even though ^{18}F-fluorodeoxyglucose positron emission tomography might help in detection of malignant nodes, its use as part of the standard routine is unlikely, given the costs and availability. It can be an adjunct when in doubt about nodes or other potential tumour metastases, for example in the case of an increased CEA [19–21]. In addition, as late nodal regrowths are

rare, standard follow-up with CT for distant metastasis also aids in detecting these regrowths, which makes the risk of missed regrowths due to de-intensification of follow-up schedules small.

This study has several limitations. First, the number of LRs was relatively small. Second, although the majority of patients were prospectively registered, some of the details of the endoscopy and MRI reports, such as modality of detection of an LR and the interpretation by the clinician, had to be identified and interpreted retrospectively, which could have caused minor issues in determining the exact timing and modality of diagnosis of the regrowth. Third, it has to be noted that duration of follow-up and interval to event was calculated from date of restaging MRI. This has to be taken into account when comparing the results to studies with different starting points, such as the start or end of radiotherapy. Fourth, for various reasons, for example findings that needed short follow-up (e.g., change on MRI), some patients had more frequent examinations. Patients who correctly followed the current protocol could not be taken into account to evaluate this more intensive follow-up schedule, which leads to measurement bias. Last, patients were included in centres with experience in W&W and caution is required when extrapolating results to those from less experienced centres.

This study provides an overview of LRs during W&W that can be used to adapt the current strict follow-up protocol for W&W. The results support an intensive follow-up in the first 2 years, followed by a de-intensification after 2 years of follow-up, which will probably result in a lower burden for patients and a better efficiency. However, this follow-up protocol may not be adequate for patients at a higher risk for regrowth, such as patients who have an nCR after 6 months or undergo local excision or contact brachytherapy for a tumour remnant [22–24]. These patients have a higher risk of harbouring residual disease in the lumen or regional lymph nodes and should undergo a more intensive follow-up. In less experienced centres physicians might feel more comfortable with a more gradual de-intensification of the current follow-up schedule, as more assessments compensate for missed detections.

ACKNOWLEDGEMENTS

The authors thank the Dutch Watch-and-Wait consortium: Stephanie O. Breukink, MD, PhD, Department of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands; Sebastiaan Festen, MD, PhD, Department of Surgery, OLVG West, Amsterdam, The Netherlands; Eelco J. R. de Graaf, MD, PhD, Department of Surgery, IJsselland Hospital, Capelle aan de IJssel, The Netherlands; Brechtje A. Grotenhuis, MD, PhD, Department of Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands; Denise Hilling, MD, PhD, FEBS, Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands; Christiaan Hoff, MD, Department of Surgery, Medical Center Leeuwarden, Leeuwarden, The Netherlands; Martijn Intven, MD, PhD, Department of Radiotherapy, University Medical Center Utrecht, Utrecht, The Netherlands; Niels Komen, MD, PhD, Department of Surgery, University Hospital Antwerpen, Antwerpen, Belgium; Koen CMJ Peeters, MD, PhD, Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands; Apollo Pronk, MD, PhD, FEBS, Department of Surgery, Diakonessenhuis, Utrecht, The Netherlands; W.H. (Hermien) Schreurs, MD, PhD, Department of Surgery, Northwest Clinics, Alkmaar, The Netherlands; Dirk J.A. Sonneveld, MD, PhD, Department of Surgery, Dijklander ziekenhuis, Hoorn, The Netherlands; Koen Talsma, MD, PhD, Department of Surgery, Deventer Hospital, Deventer, The Netherlands; Jurriaan B. Tuynman, MD, PhD, Department of Surgery, Amsterdam University Medical Centres, Location VUmc, Amsterdam, The Netherlands; Miranda Kusters, MD, PhD, Department of Surgery, Amsterdam University Medical Centres, Location VUmc, Amsterdam, The Netherlands; Henderik L. van Westreenen, MD, PhD, FEBS, Department of Surgery, Isala, Zwolle, The Netherlands; Johannes H. W. de Wilt, MD, PhD, Department of Surgery, Radboud UMC, Nijmegen, The Netherlands; David D.E. Zimmerman, MD, PhD, FEBS, Elisabeth-Tweesteden Hospital, The Netherlands.

CONFLICT OF INTERESTS

None declared.

ETHICAL STATEMENT

Patients between 2004 and 2017 were prospectively included in a local study from the Maastricht University Medical Center, approved by the local institutional review board and registered in clinicaltrials.gov since 2009 (NCT00939666 and NTC02278653), and provided informed consent. W&W patients from 2017 to 2018 were retrospectively included in a quality-controlled national registration of W&W patients from the Netherlands Cancer Institute, for which informed consent was waived by the local institutional review board.

AUTHOR CONTRIBUTIONS

The authors HEH, JZ, DMJL, RGHBT, JM, GLB and MM made substantial contributions to: conception, design, acquisition of data, analysis and interpretation of data; drafting the article and revising it critically for important intellectual content; and gave final approval of the version to be published.

FUNDING

None declared.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Haak HE, Žmuc J, Lambregts DM, et al. The evaluation of follow-up strategies of watch-and-wait patients with a complete response after neoadjuvant therapy in rectal cancer. *Colorectal Dis.* 2021;23:1785–1792. https://doi.org/10.1111/codi.15636