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 is to analyze 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 (cCR) after neoadjuvant therapy were prospectively and retrospectively included in a multicenter watch-and-wait registry between 2004-2018, 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 4 other hypothetical schedules.

Results

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

Conclusion

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

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 two 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 (LR), 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 centers agree on a more frequent surveillance during the first two 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 analyze 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 program

Patients diagnosed with rectal cancer who had a cCR after neoadjuvant therapy who were offered a W&W program 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 2017-2018 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 program if they had a biopsy proven rectal adenocarcinoma without distant metastasis at baseline and received neo-adjuvant treatment with long course chemoradiation consisting of 28x1.8 Gy with 2x825 mg/m^3 capecitabine or short course radiotherapy with 5x5Gy followed by a waiting interval. Patients underwent restaging approximately 8-12 weeks after completion of (chemo)radiation by digital rectal examination (DRE), endoscopy and MRI including diffusion weighted imaging (MRI-DWI). Those who were identified during restaging with a cCR or patients with a 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 (T2W-MRI) with absence of diffusion restriction on MRI-DWI and absence of residual malignant nodes. (5, 6) A 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 T2W-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 (DM) consisted of CT imaging of the chest and liver and 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 program and who developed a 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 (TEM) 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 to also study more intensive hypothetical schedules. 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 two years, all four hypothetical follow-up schedules consisted of less frequent examinations after two years (1-3). For the first two years two schedules tested more frequent, and two schedules less frequent examinations. The hypothetical schedules were as follows:

Schedule 1: 3-monthly endoscopy and MRI in the first year, 3-monthly endoscopy and 6-montly MRI in the second year and yearly endoscopy and MRI thereafter

Schedule 2: 3-monthly endoscopy and MRI in the first year and 4-monthly in the second year and yearly endoscopy and MRI thereafter

Schedule 3: 4-monthly endoscopy and MRI in the first year and 6-monthly in the second year and yearly endoscopy and MRI thereafter

Schedule 4: 6-monthly endoscopy and MRI during the first two years and yearly endoscopy and MRI thereafter

Comparing detection of regrowths in different follow-up schedules

To identify the most 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 is that when the examination with which the LR was actually detected in the series, is left out in a theoretical schedule, the regrowth will be detected at the next scheduled examination. The second assumption is 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, Inc., Chicago, IL). 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 was 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 in- and excluded patients. Fifty (16%) of 304 patients developed a 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 a nCR during restaging but achieved a cCR at second restaging. Median age of LR patients was 64 years (range 43-85). Of the 50 LR patients, 42 (84%) had a distal tumour (≤ 5 cm of the anorectal junction) and 8 (16%) had a mid-rectum tumour (5.1 – 10 cm of 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 a 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 two 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 MR imaging 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 patients (84%), both luminal and nodal in 5 (10%), and in regional lymph nodes only in 3 (6%) (**Figure 2, 3 and 4**). The majority were detected on both endoscopy and MRI (n=32, 64%), in 12 (24%) only on endoscopy and in 6 (12%) LR was only detected on MRI.

Comparing detection of regrowths in different FU 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 five years after the inclusion in the W&W program. Because some patients had more follow-up examinations than required in the standard protocol because of patient preference or logistical planning issue or findings on endoscopy and/or MRI that warranted earlier follow-up, some LRs were actually detected ahead of the standard assessment date. **Supplementary table 1** provides a detailed overview of all patients with a LR and the theoretical difference in detection time-point according to the current and hypothetical schedules. The overall median delay in LR detection was zero (range 0-5) months for the current schedule and zero (range 0-4), zero (range 0-4), two (range 0-4) and two (range 0-5) months for hypothetical schedule 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 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 schedule 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 two years of follow-up. Hypothetical schedule 1 would have zero delays of at least 3 months during the first two 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 two 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 two years (98%), located in the bowel wall (94%) and were visible on endoscopy (88%). The most optimal follow-up schedule focuses on the first two years, with an intensive follow-up including 3-monthly 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 two years (schedules 3 and 4) resulted in more delays. Because very few regrowths became evident after two years, the follow-up interval can be de-intensified in years 3-5, i.e. 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 centers mainly rely on frequent endoscopies during the first two 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 a

standard high-resolution endoscopy with white light. There are several new endoscopic techniques using advanced imaging such as narrow band imaging (NBI) 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 centers is to rely on serial endoscopic assessments, and 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 two years of follow-up has also been noted by others (1-3), and de-intensifying the follow-up interval after two years has been recommended before. (1) Some groups even minimize the follow-up after two 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 to reduce the standard surveillance to regular CEA measurements and only perform CT scans by indication.(18) Considering the low risk of regrowths after two years and only one (late discovered) false negative finding in the current study, some groups may even opt to further reduce the number of examinations after two 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 two years, there is a small number of patients who could benefit from early detection of a late regrowth. While we propose a yearly follow-up after two years of follow-up, some less experienced centers 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 year 4 and 5. The single patient in our study with a late regrowth after two 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

18F-fluorodeoxyglucose PET (PET) 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, e.g. in 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 a 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, due to various reasons, e.g. 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 FU schedule, which leads to measurement bias. Last, patients were included in centers with experience in W&W and caution is required when extrapolating results to those from less experienced centers.

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 two years, followed by a de-intensification after two years of follow-up, which will likely 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 a near CR after 6 months or undergo local excision or contact brachytherapy for a tumour remnant. (22-24) These patients have a higher risk of harboring residual disease in the lumen or regional lymph nodes and should undergo a more intensive follow-up. In less experienced centers physicians might feel

more comfortable with a more gradual de-intensification of the current follow-up schedule, as more assessments compensate for missed detections.

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TABLES

	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)
5x5Gy with a long waiting interval	5% (16/304)	4% (2/50)
Other	1% (3/304)	NA
Adjuvant chemotherapy	16% (47/304)	10% (5/50)

Table 1: Baseline characteristics of W&W patients, and those with a local regrowth included for analyses to evaluate different follow-up schedules. Data are median (range) or %(n/N). LR=local regrowth

FIGURE LEGENDS

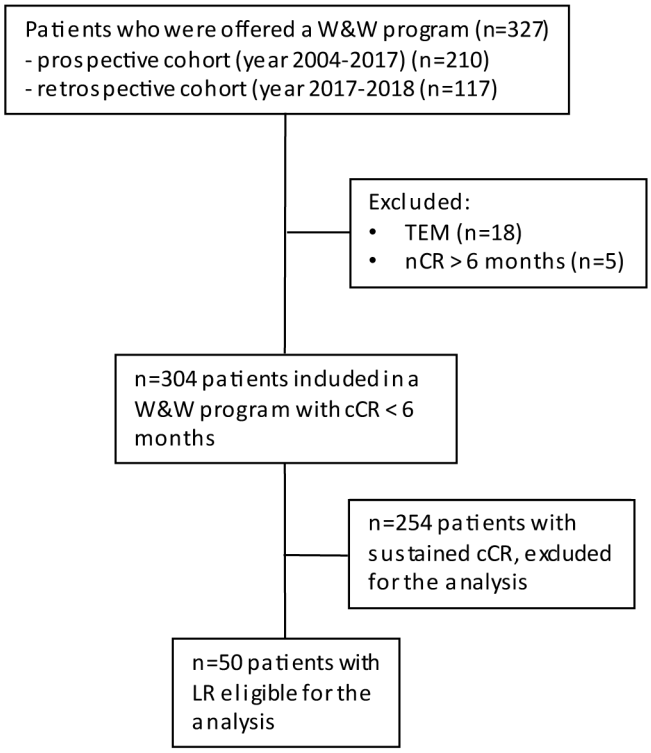
Figure 1. Flowchart with an overview of in- and excluded patients. TEM = transanal endoscopic microsurgery; nCR = near complete response; cCR = clinical complete response; LR = local regrowth

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) shows 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). 6 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 tumor bed with (F) diffusion restriction on diffusion weighted imaging, suspect 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 regrowths; n=number of examinations



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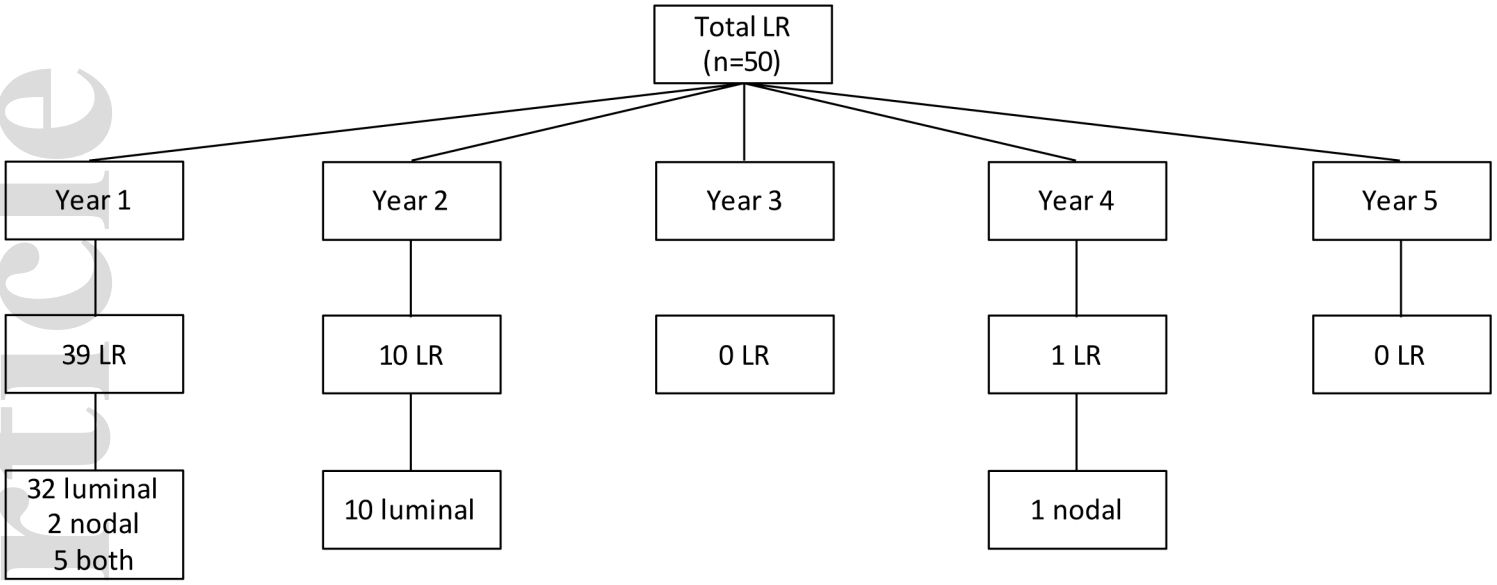

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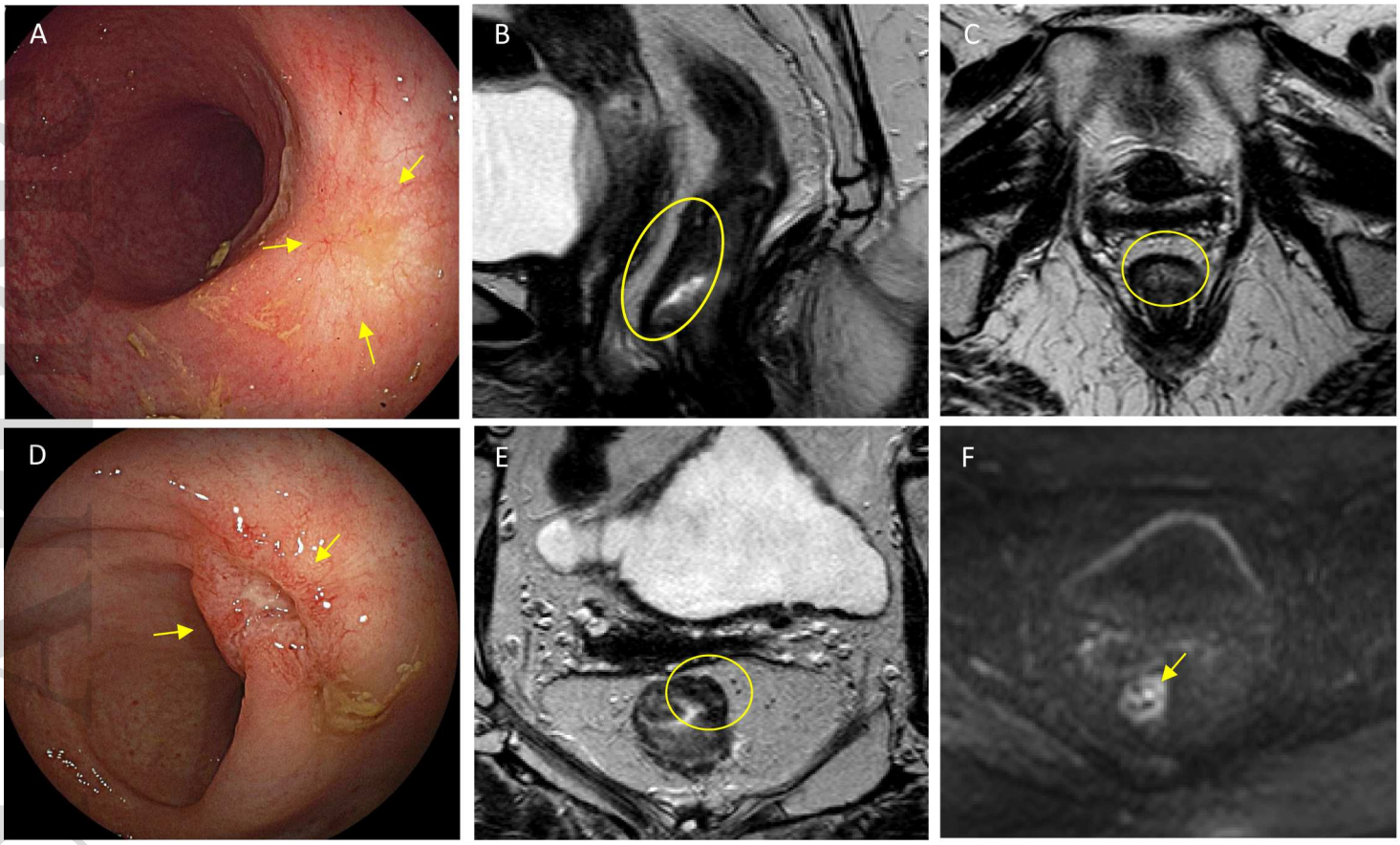

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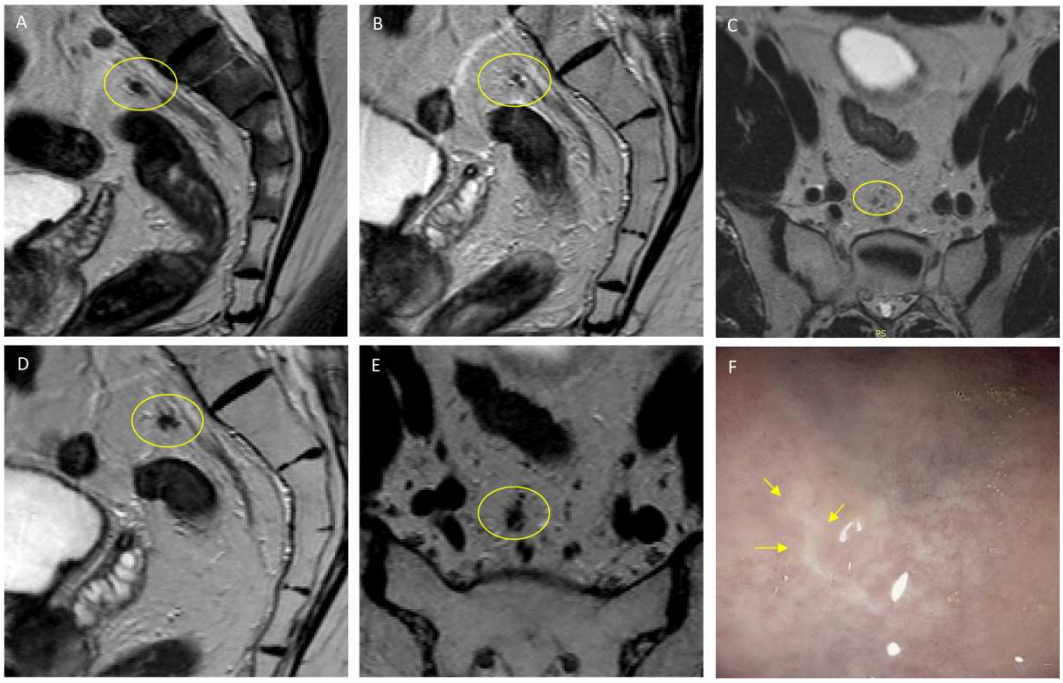

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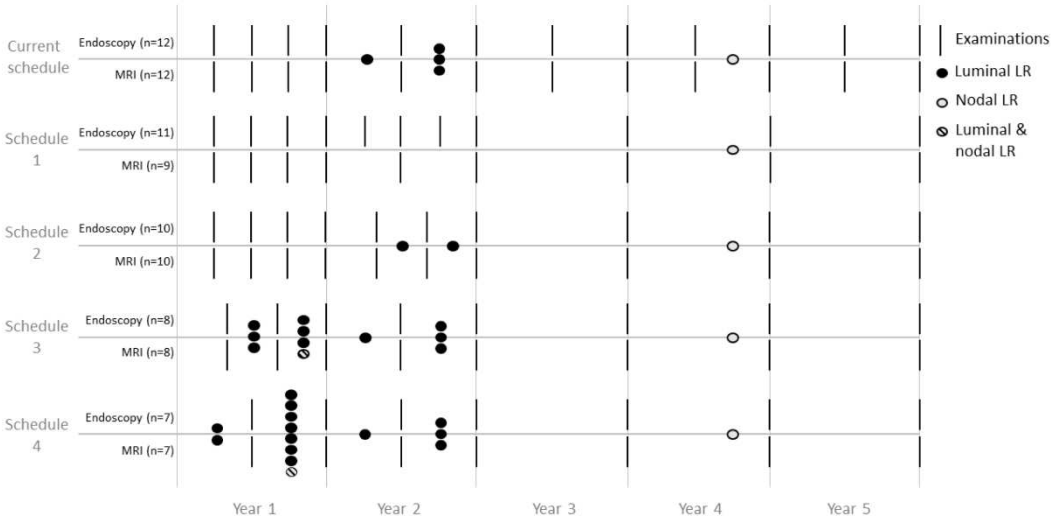

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