Original Research Article

Nonoperative versus operative approach according to the response to neoadjuvant chemoradiotherapy for rectal cancer: A prospective cohort study

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ABSTRACT

Purpose: To report on organ preservation following chemoradiotherapy (CRT) in a prospective cohort of locally advanced rectal cancer patients.

Methods and materials: Fifty-two patients received CRT. MRI and 18F-FDG-PET/CT were performed prior to CRT. Response assessment was done 6 and 12 weeks after CRT using digital rectal examination, MRI, 18F-FDG-PET/CT and endoscopy. For clinical complete response or minimal residual disease, a watch-and-wait (W&W) protocol was started.

Regrowth-free survival (ReFS), Total Mesorectal Excision-free disease-free survival, distant metastasis-free survival (DMFS) and overall survival (OS) were evaluated using Kaplan-Meier method. Functional outcome was compared with the Wilcoxon signed-rank test using EORTC QLQ-C30, MSKCC BFI, LARS and IIEF-5/FSFI-5 questionnaires. A previously developed prediction model performance was tested using receiver operating characteristic analysis.

Results: 29/52 patients entered a W&W protocol. There was no difference in two-year DMFS (81.1 % vs 78.8 %, p = 0.82), two-year OS (96.4 % vs 100 %, p = 0.38) and two-year DFS (77.5 % vs 78.8 %, p = 0.87) between W&W patients and those who underwent surgery at 12 weeks after CRT. Two-year DMFS differed between W&W with local regrowth, W&W with sustained response and patients who had surgery (66.7 % vs 88.0 % vs 78.8 %; p = 0.04). At 6 and 12 months, W&W patients reported good QoL and bowel function. The model validation reached an AUC of 0.627.

Conclusion: Good functional outcome in patients with rectal cancer allocated to surveillance after CRT needs to be balanced against potentially worse DMFS in a subset of patients without sustained clinical complete response. Reliable prediction of patients eligible for surveillance programs needs further investigation.

Introduction

Since 2004, the interest in surveillance programs for patients with rectal cancer with a clinical (near-)complete response following chemoradiotherapy (CRT) has steadily increased [1]. As patients with a pathologic complete response (pCR) have good oncological outcome,
omission of total mesorectal excision (TME) following CRT emerged as an alternative [2,3]. In both physicians and patient advocate groups this approach is appraised with great enthusiasm as this could spare patients from additional bowel, urinary and sexual dysfunction [4-6].

To implement organ preservation, oncological safety needed to be proven. This was shown in a prospective cohort for patients with a clinical complete response (cCR) who followed a surveillance program [7]. However, in a retrospective analysis, worse survival was reported for patients in a surveillance protocol [8]. This was attributed to the higher incidence of distant progression among patients who developed local regrowth.

Detection of patients eligible for surveillance following CRT relies on the combination of digital rectal examination (DRE), endoscopy and T2-weighted and diffusion-weighted (DW)-MRI [9]. Patient selection should be improved to reduce the risk of developing local regrowth and/or distant metastasis. Significant changes in tumor volume on T2-MRI, apparent diffusion coefficient (ADC) values on DW-MRI, and standardized uptake values on 18F-FDG-PET/CT were used in a prediction model to better identify well-responding patients [10].

The aim of this study was to prospectively evaluate survival outcome and patient-reported functional outcome in patients with locally advanced rectal cancer undergoing surgery vs surveillance following CRT. We report on 52 patients in a prospective cohort to whom surveillance was offered in case of a (near-)complete clinical response 12 weeks following CRT.

Methods and materials

Study design and participants

Fifty-two patients enrolled in a prospective mono-center cohort study between February 2016 and June 2019. A sample size of 100 was calculated to validate the prediction model of Joyce et al [10]. However, due to slow patient accrual and novel insights in the treatment [8], the cohort was closed after 52 patients. The study was approved by the institutional Ethical Committee in accordance with European Regulations and conducted in accordance with the Declaration of Helsinki (October 2000). Written informed consent was obtained from all participants.

Inclusion criteria were adenocarcinoma of the rectum, cT2-3 N0-2 M0, scheduled for CRT, WHO PS < 3, adequate bone marrow, hepatic and renal function & adequate contraception in fertile patients. Exclusion criteria were previous (<5 years) or concurrent malignancies except for adequately treated carcinoma in situ of the cervix and non-melanoma skin cancer, prior chemotherapy or radiotherapy for rectal cancer, pregnant or breastfeeding women, significant impairment of intestinal resorption, allergy to intravenous contrast, contra-indications for MRI, history of uncontrolled seizures, central nervous system disorders or psychiatric disability and any condition hampering compliance with the protocol. Pretreatment investigations included colonoscopy and biopsy, CEA, T2- and DW-MRI and 18F-FDG-PET/CT.

After inclusion, patients underwent CRT. Tumor response was assessed six and twelve weeks after completion of CRT. Non-responding or progressing patients six weeks after CRT underwent TME. Responding patients were re-assessed at twelve weeks. Good responders were assigned to surveillance with strict follow-up, poor responders underwent surgery. (Sup Fig. 1).

Procedures

Radiotherapy consisted of volumetric modulated arc therapy of 50 Gy in 25 fractions. The clinical target volume was delineated according to Valentini et al. [11]. Organs at risk were delineated according to the RTOG consensus guideline [12]. Concomitant chemotherapy was a continuous infusion of 5-fluorouracil (225 mg/m²/d) or capecitabin bid (825 mg/m²).

Intermediary response assessment was done six weeks after CRT by MRI to identify poor responders. At twelve weeks, final response assessment was done using DRE, rectoscopy and MRI. At six and twelve weeks, 18F-FDG-PET/CT was done for study purposes. Clinical complete remission (cCR) or minimal residual disease (MRD) were considered a good clinical response. cCR was defined as absence of any irregularity on DRE, whitening of the mucosa or telangiectasia with mucosal integrity on rectoscopy, combined with absence of diffusion restriction in the fibrotic area on MRI [13,14]. MRD or near-cCR was defined as a small residual mass or ulcer on DRE/rectoscopy and/or a small area of diffusion restriction on MRI. For both cCR and MRD, absence of suspect lymph nodes on MRI was needed.

TME was omitted when achieving good response, with strict follow-up to detect local regrowth (Supplementary Table 1). MRD was eligible for W&W as further evolution to complete response is possible [15]. Salvage TME was performed for local regrowth. In poor responders, TME was performed. No adjuvant chemotherapy was given in the W&W arm. After surgery, chemotherapy was given according to the decision of the multidisciplinary tumor board (MDT).

Patient-reported functional outcome assessment was done using the EORTC QLQ-C30 questionnaire, Low Anterior Resection Syndrome (LARS) questionnaire, MSKCC Bowel Function Instrument, International Index of Erectile Function (IIEF-5) and Female Sexual Function Index (FSFI) [16–20].

Outcome definition

Two years after CRT we reported local recurrence-free survival (LRFS), distant-metastasis-free survival (DMFS), disease-free survival (DFS) and overall survival (OS). For the W&W group, regrowth-free survival (ReFS) and TME-free disease-free survival (DFS) were reported. Additional endpoints were quality of life (QoL) and bowel and sexual functional outcome of patients 3, 6, 12, 18 and 24 months after CRT. We reported the performance of the model of Joyce et al. [10], although validation was powered at 100 patients. The endpoint for this model was sustained cCR or ypT0-1 N0.

Statistical analysis

Patient and tumor characteristics and functional outcome parameters were compared using the Wilcoxon signed-rank test. Survival outcomes were measured in an intention-to-treat analysis from the completion of CRT and censored at last follow-up. Survival was estimated using the Kaplan-Meier method. A p-value < 0.05 was used. For model validation, the prediction classifier was calculated using the formula and respective parameter weights as described [10]. The performance was expressed using the area under the curve (AUC) of the receiver operating characteristic (ROC) analysis. Statistical analyses were performed in the statistical language R version 3.5.1 [21].

Results

Patient and tumor characteristics

Patient and tumor characteristics are listed in Table 1. Patients in the surveillance cohort had significantly more cT2 tumors (31.7 % vs 13.0 %, p = 0.024) (Table 1). Age, sex, distance to the mesorectal fascia (MRF) and CEA did not differ.

Response assessment

One out of 52 patients did not complete CRT due to severe toxicity (CTCAE grade 3 diarrhoea). All patients underwent response assessment at 6 weeks. Nineteen out of 52 patients (36.5 %) had a cCR on MRI. Three out of 33 patients (9.1 %) without cCR on MRI had poor response and therefore underwent immediate TME. As such, 49 patients were...
available for response assessment at twelve weeks. Twenty-one of 49 (42.9%) patients had cCR as observed from DRE, endoscopy and MRI findings and 10/49 (20.4%) had MRD. These 31 patients were eligible for surveillance. However, 1/31 patients (who had cCR) developed a fistula due to tumor necrosis and underwent surgery. For another patient (who had MRD), surgery was preferred at the MDT. In summary, 29/52 (55.8%) patients started surveillance whereas 23/52 (44.2%) underwent immediate TME (Fig. 1).

Survival outcomes
Median follow-up was 26 months (5–38 months). Six of 29 W&W and 4/23 surgery patients developed distant metastases. Two-year DMFS was 81.1% (95% CI 67.3% – 97.6%) and 78.8% (95% CI 62.1% – 100%) respectively (p = 0.82). Similarly, there were no differences in two-year OS (96.4% (95% CI 89.8% – 100%) vs 100% (95% CI 100% – 100%), p = 0.38), DFS (77.5% (95% CI 63.1% – 95.3%) vs 78.8% (95% CI 62.1% – 100%), p = 0.59) nor LRFS (90.1% (95% CI 90.1% – 100%) and 95.0% (95% CI 85.9% – 100%), p = 0.87) for W&W versus surgery (Fig. 2A-D).

Nine W&W patients (31%) developed local regrowth, all during the first year after CRT (median 7 months). Seven of them had MRD and not cCR. Given 9 patients with MRD entered the surveillance protocol, 7/9 (78%) of patients with MRD developed a local regrowth. In contrast, only 2/20 (10%) of patients with cCR at twelve weeks developed a local regrowth. Two-year ReFS in the W&W cohort was 68.2% (95% CI 53.1% – 87.8%) (Sup Fig. 2A), subdivided in 89.5% (95% CI 76.7% – 100%) for cCR and 22.2% (95% CI 6.6% – 75.4%) (p < 0.0001) (Fig. 3).

Table 1
Baseline patient and tumor characteristics – By treatment decision 12 weeks after CRT. Abbreviations: CEA = carcinoembryonic antigen; IAS = internal anal sphincter; MRF = mesorectal fascia. Tumor location: low < 5 cm; mid 5 & <10 cm; high > 10 cm from anal verge.

|                | Surgery | Watch and Wait | p    |
|----------------|---------|----------------|------|
| n              | 23      | 29             |      |
| age (median [IQR]) | 60 [51, 65] | 60 [54, 67] | 0.501|
| sex (%)        | F 7 (30.4) | 6 (20.7) | 0.629|
|                | M 16 (69.6) | 23 (79.3) |      |
| Clinical T-stage (%) | 2 3 (13.0) | 15 (51.7) | 0.024|
|                | 3a 10 (43.5) | 7 (24.1) |      |
|                | 3b 7 (30.4) | 3 (10.3) |      |
|                | 3c 2 (8.7) | 4 (13.8) |      |
|                | 3d 1 (4.3) | 0 (0.0) |      |
| Clinical N-stage (%) | 0 7 (30.4) | 7 (24.1) | 0.971|
|                | 1a 6 (26.1) | 9 (31.0) |      |
|                | 1b 4 (17.4) | 5 (17.2) |      |
|                | 2a 3 (13.0) | 5 (17.2) |      |
|                | 2b 3 (13.0) | 3 (10.3) |      |
| Tumor Location high (median [IQR]) | 0.0 | 2.6 | 0.425|
|                | low 19 (82.6) | 25 (79.3) |      |
|                | mid 4 (17.4) | 4 (13.8) |      |
| IAS Invasion (%) | 0 1.0 [0.0, 3.0] | 2.9 [0.0, 5.0] | 0.157|
|                | 1 6 (26.1) | 4 (13.8) |      |
| Distance to MRF (mm) (median [IQR]) | 1.0 | 2.9 | 0.015|
|                | CEA (median [IQR]) | 2.7 [1.6, 4.9] | 2.6 [1.4, 3.8] | 0.634|

Fig. 1. Flow of Trial Participants. Abbreviations: cCR = Clinical Complete Response; CRT = Chemoradiotherapy; MRD = Minimal Residual Disease; MRI = Magnetic Resonance Imaging.
These nine patients underwent salvage TME. There were no significant differences in pathological tumor characteristics for salvage surgery versus planned per-protocol surgery (Table 2). Six patients (21%) developed distant metastases in the W&W group. The two-year TME-free disease-free survival was 59.9% (95% CI 43.9% – 81.7%) (Sup Fig. 2B).

Seven out of 9 patients with a local regrowth had MRD on response assessment 12 weeks after CRT. Given the differential prognosis for patients with sustained cCR versus patients with local regrowth [8], we compared the survival of these W&W subgroups with the surgery patients. Four out of 9 patients with a local regrowth and 2/20 with sustained cCR developed distant metastasis versus 4/23 surgery, with respective two-year DMFS of 66.7% (95% CI 42% – 100%), 88.0% (95% CI 73.5% – 100%) and 78.8% (95% CI 62.1% – 100%) (p = 0.04) (Sup Fig. 3A). One out of 9 patients with a local regrowth died due to surgical complications after salvage TME. No other deaths were observed. The two-year OS for the aforementioned groups was 88.9% (95% CI 70.6% – 100%), 100% (95% CI 100% – 100%), 100% (95% CI 100% – 100%) respectively (p = 0.10; Sup Fig. 3B).

**Functional outcomes**

EORTC QLQ-C30 (Sup Fig. 4A-D) response rate was 71.2% at baseline, 80.8% at 3, 82.7% at 6, 79.6% at 12, 72.3% at 18 and 72.5% at 24 months after CRT. Global health score improved from 66.7% at baseline to 83.3% at 24 months (Supplementary Table 2) and at 6 months it was higher for surveillance patients compared to the surgery cohort (83.3% vs 66.7%, p = 0.01). Physical function of W&W patients was better at 6 (100.0% vs 80.0%, p = 0.01) and at 18 months (86.7% vs 93.3%, p = 0.04), as was role function at 6 (100% vs 66.7%, p < 0.01) and 12 months (100% vs 83.3%, p = 0.02). At 24 months no differences persisted. No differences between the surgery and W&W group were observed for other QLQ-C30 scores (Supplementary Table 3).

MSKCC-BFI and LARS questionnaires were analyzed in patients without stoma as it might influence results. Questionnaire completion rate in stoma-free patients was 71.2% at baseline, 88.9% at 3, 57.4% at 12, 78.0% at 18 and 66.7% at 24 months. Total MSKCC BFI score was worse at 12 and 18 months for operated patients (76.5 vs 52.0 (p < 0.01) and 78.0 vs 57.5 (p = 0.01)), but this difference disappeared at 24 months (Sup Fig. 5A). Similarly, no other BFI subscale differences were present 24 months after CRT (Supplementary Table 4). Twelve months
after treatment, 67% of stoma-free surgery patients reported major LARS vs 17% in W&W patients (Sup Fig. 5B) (Supplementary Table 5).

W&W patients were more sexually active, although not statistically significant (Supplementary Table 6). In sexually active patients, sexual interest and sexual arousal was non-different for W&W versus surgery (Supplementary Table 7 & 8). Too few data were available to report on female sexual function. In men no differences in erectile function were observed (Supplementary Table 9).

Prediction model

For 49/52 patients, 5 parameters were derived from imaging in order to calculate the prediction model for response [10] (Supplementary Table 10). For 3/52 patients imaging was lacking or qualitatively insufficient (e.g. interference due to hip prosthesis). For the model validation, we analyzed available data of 28 W&W patients and 21 surgery patients.

Twenty-four out of 49 (49.0%) patients achieved the composite outcome of either ypT0-1 N0 after surgery or sustained cCR after W&W, for which the model of Joye et al. predicts. The model predicted tumor response correctly in 30/49 cases, with 61.2% accuracy (Supplementary Table 11). The area under the ROC curve was 0.627 (95% Confidence Interval 0.464 – 0.790) (Sup Fig. 6).

Discussion

In this cohort 29/52 patients had (near-)complete response and underwent surveillance. The functional outcome and two-year LRFS, DMFS and OS confirmed the benefit of organ preservation in patients with sustained cCR. Unfortunately, a subset of patients is at risk of local regrowth and/or distant metastases. For them, CRT was not sufficient notwithstanding the initial response. It is thus necessary to further optimize and tailor CRT. If a sustained response is anticipated, treatment optimization should focus on minimizing morbidity by offering organ preservation. In contrast, for patients at risk for recurrent disease, treatment optimization should focus on enhancing survival. A total neoadjuvant treatment strategy holds promise to serve both aims, although the optimal sequence of such regimen could vary [22–24]. Better patient selection could guide the tailoring of treatment.

For patients with cCR, the goal of surveillance is to improve the patient’s functional outcome, at least if a non-operative approach is oncologically safe. Our findings confirmed oncological safety in case of a sustained cCR [15]. Additionally, patient-reported functional outcome proved that organ preservation is an appropriate strategy. In our cohort, W&W patients had higher QoL 6 months after CRT although this difference disappeared at later time points, which could be due to some patients needing salvage TME. Indeed, better QoL was seen in patients with sustained cCR versus patients who underwent surgery after CRT [25]. Also, 12 and 18 months after CRT, W&W patients rated bowel function better, although this difference did not hold at 24 months after CRT. Nevertheless, non-operated patients reported less soiling and were less affected by LARS. Concordant with Hupkens et al., W&W patients were more sexually active 12 months after CRT although sexual interest and arousal and, for male patients, erectile function were similar [25].
Notwithstanding these data showing better patient-reported functional outcome when omitting surgery, limiting surgical morbidity through W&W was never an option for the patients in our cohort who needed surgery given the absence of cCR or MRD. Future trials should focus on comparing patients with sustained cCR vs pCR after CRT as this could demonstrate the clinical benefit for functional outcome [26].

Unfortunately, two-year local regrowth rate of 31.8 % was higher than 15.7 % – 25.2 % in other series and the International Watch-and-Wait Database (IWWD) [27–30], which is probably related to inclusion of patients with MRD for surveillance. Tumor response reaches a plateau of patients with MRD for surveillance. Tumor response reaches a plateau 12 weeks after CRT, but it is debated whether further extension of the interval is possible, as residual tumor at endoscopy, T2-MRI irregularities or diffusion restriction at DW-MRI might not be definitely associated with residual tumor [31,32]. Potentially, there is a place for local excision in patients with MRD [33]. Local regrowth mainly occurs in the bowel wall, which can be salvaged by surgery with excellent local control [29]. In our study excellent pelvic control was observed without any local recurrences. Notwithstanding excellent local control and the suggestion that interval extension does not impact oncological outcome [34], concerns have been raised about the development of metastases in patients with local regrowth due to survival of resistant cancer cells that disseminate or due to inherently more aggressive tumor biology [8]. We share this concern based on our results comparing DMFS between patients with a local regrowth vs patients with sustained cCR or operated patients. Conceivably, patients in our study were deferred from systemic treatment which could have been administered if they underwent surgery and no pCR was found, although the benefit of adjuvant chemotherapy is debated [35,36]. The better DMFS observed for patients with sustained cCR highlights the need for improved response prediction.

Table 2
Surgical outcome parameters of patients who underwent salvage surgery versus patients who were planned for surgery 6 or 12 weeks after CRT.

|                          | Salvage Surgery | Surgery after CRT | p    |
|--------------------------|-----------------|-------------------|------|
| n                        | 9               | 23                |      |
| Type of operation (%)    |                 |                   |      |
| APR                      | 1 (11.1)        | 5 (21.7)          | 0.85 |
| TME                      | 8 (88.9)        | 18 (78.3)         |      |
| Interval from CRT to surgery (days) (median [IQR]) | 279.0 [227.0, 429.0] | 109.0 [105.5, 318.0] | <0.01 |
| Max tumor diameter in mm (median [IQR]) | 22.5 (15.0, 27.8) | 20.0 (13.5, 28.8) | 0.83 |
| Tumor grade (%)          |                 |                   |      |
| 1                        | 0 (0.0)         | 2 (8.7)           | 0.57 |
| 2                        | 7 (27.8)        | 13 (56.5)         |      |
| 3                        | 0 (0.0)         | 2 (8.7)           |      |
| NA                       | 2 (22.2)        | 6 (26.1)          |      |
| ypT (%)                  |                 |                   |      |
| 0                        | 1 (11.1)        | 3 (13.0)          | 0.21 |
| 1                        | 0 (0.0)         | 3 (13.0)          |      |
| 2                        | 1 (11.1)        | 8 (34.8)          |      |
| 3                        | 5 (55.6)        | 8 (34.8)          |      |
| X                        | 2 (22.2)        | 1 (4.3)           |      |
| 1                        | 6 (66.7)        | 16 (69.6)         | 0.63 |
| 3                        | 3 (33.3)        | 6 (26.1)          |      |
| 2                        | 0 (0.0)         | 1 (4.3)           |      |
| Lymphovascular Invasion (%) | 5 (55.5)        | 18 (78.3)         | 0.21 |
| 0                        | 1 (22.2)        | 4 (17.4)          |      |
| 1                        | 2 (22.2)        | 1 (4.3)           |      |
| NA                       | 2 (22.2)        | 1 (4.3)           |      |
| Perineural Invasion (%)  | 0               | 6 (66.7)          | 0.19 |
| 0                        | 6 (66.7)        | 16 (69.6)         |      |
| 1                        | 1 (11.1)        | 6 (26.1)          |      |
| NA                       | 2 (22.2)        | 1 (4.3)           |      |
| Positive section margin (%) | 8 (88.9)        | 22 (95.7)         | 1.00 |
| 0                        | 8 (88.9)        | 22 (95.7)         |      |
| 1                        | 0 (0.0)         | 1 (4.3)           |      |
| Distance to MRF in mm (median [IQR]) | 7.0 (2.8, 11.8) | 3.0 (1.0, 6.5) | 0.13 |
| pCR (%)                  | 0               | 8 (88.9)          | 0.01 |
| 0                        | 8 (88.9)        | 20 (87.0)         |      |
| 1                        | 1 (11.1)        | 3 (13.0)          |      |
| ypT0-I N0 (%)            | 0               | 8 (88.9)          | 0.72 |
| 0                        | 8 (88.9)        | 17 (73.9)         |      |

chemotherapy prior to expected surgery, thereby enhancing the compliance up to 94 % [40]. Early introduction of chemotherapy might be beneficial to treat undetectable micrometastases which could evolve to detectable macrometastases [41]. Two randomized trials demonstrated that additional chemotherapy before surgery reduces disease-related treatment failure, mainly driven by a better [22,23]. It was also shown that TNT increased tumor response rate (i.e. pCR), potentially enlarging the patient group that could benefit from organ preservation [42]. Whether chemotherapy should be delivered prior to or following radiotherapy is currently unclear and probably depends on the aim one wishes to achieve [43]. A head-to-head comparison demonstrated an increased pCR rate when radiotherapy was given first [44], without compromising disease-free survival and distant metastases. If organ preservation is desired, CRT followed by consolidation chemotherapy is the preferred TNT sequence [45].

Choosing the optimal treatment and sequence will gain importance in the future. Clinical factors might guide treatment selection, although prediction tools could be useful. We tested a prediction model based on MRI and 18F-FDG-PET/CT imaging [10]. Unfortunately, the model could not be validated.

The strength of this cohort lies in the prospective data collection and the patient-reported outcome measures, and in standardized CRT. Several limitations should be discussed. First, this is an analysis of a limited number of patients with relatively short follow-up. This is foremost a limitation when assessing patient-reported bowel and sexual function and for prediction model validation. Second, an inherent bias in defining both groups exists, as a good responder (with good prognosis [2]) is more likely to be in the W&W group. Third, the treatment paradigm has changed in recent years with the adoption of TNT strategies. Last, we analyzed functional outcome in an intention-to-treat manner comparing patients in a W&W protocol versus patients who underwent surgery. There were however 9/29 patients with a local regrowth in the W&W group, which might significantly impact the functional outcome measures as these patients eventually underwent salvage surgery. However, a post-hoc analysis on functional outcome comparing W&W with sustained cCR vs W&W with regrowth vs surgery patients would even further decrease the patient numbers in each group.

Conclusion

From this prospective cohort analysis, we conclude that functional outcome in a W&W protocol is favorable. This needs to be balanced against more distant metastases in a subset of patients without sustained cCR. Strict follow-up in a surveillance protocol is necessary to rapidly identify patients in need for salvage TME. Future studies need to improve selection of patients with rectal cancer eligible for a surveillance program following CRT.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
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Appendix A. Supplementary data

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