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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Low rectal cancer treatment strategies: a cohort study assessing watch and wait

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Abstract

Purpose Treatment strategies for low rectal cancer have been evolving toward achieving less treatment morbidity with the same oncological success—we aimed to assess the results of the new watch and wait (W&W) strategy in our cohort.

Methods A tertiary care cohort study was conducted. New patients with rectal adenocarcinoma up to 6 cm from the anal margin, cM0, locally staged higher than cT1N0, evaluated between November 2014 and October 2018, were included. All 93 patients received neoadjuvant radiotherapy ± chemotherapy. Re-evaluation was planned 8–12 weeks after the end of treatment. Patients showing clinical complete response (cCR) were given the choice of either to proceed to surgery or to enter W&W.

Results Of the 93 patients, 82.8% were re-evaluated and 20.8% had cCR. Patients in clinical stages II/III were significantly less likely to achieve cCR than those in stage I ($p = 0.017$).

After a mean follow-up of 17.44 months, there were 4 regrowths in the 16 patients under W&W, all submitted to R0 surgery, ypN0; there were no deaths or local recurrences; one patient with regrowth had distant recurrence.

Sixty patients underwent direct surgery after a mean follow-up of 16.23 months; 3 patients had local and distant recurrences; 7 others had only distant recurrences; there were 8 deaths.

There were no statistically significant differences between patients under W&W and patients who underwent direct surgery regarding local or distant recurrences, or death ($p > 0.9$; $p = 0.44$; $p = 0.19$, respectively).

Conclusion The W&W strategy for low rectal cancer achieved the same oncological outcomes as the traditional strategy while sparing some patients from surgery.

Keywords Rectal cancer · Watch and wait · Treatment · Gastrointestinal oncology

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Introduction

In the twenty-first century, neoadjuvant chemoradiation (CHRT), followed by surgery with total mesorectal excision (TME) and completed by adjuvant chemotherapy (CH) has been the standard treatment for locally advanced [American Joint Committee on Cancer (AJCC) stages II-III] (Edge et al. 2010) rectal adenocarcinoma (ADC), (Sauer et al. 2004) achieving excellent oncological outcomes. However, these results happen at the expense of a 2.4% peri-operative mortality rate and very high morbidity—22.8% (Bosset et al. 2006). More than one-third of the patients end up with urinary or fecal incontinence and/or sexual disfunction in the long run (Milgrom and Goodman 2014), and in the case of low rectal tumors (lower limit at less than 6cm from the anal margin), the risk of a permanent colostomy adds to these negative outcomes, impacting on the quality of life (Grumman et al. 2001).

Several studies have demonstrated that after CHRT, rectal surgical specimens show no evidence of residual cancer in around 20% of cases—pathological complete response (pCR) cases (Campos-Lobato et al. 2011). Patients with pCR have been shown to have better prognosis than those with residual tumor after CHRT (Campos-Lobato et al. 2011). Other authors have shown that the post-CHRT T stage (ypT) correlates with the post-CHRT N stage (ypN) (Pucciarelli et al. 2005), with rare (0–7%) node metastasis in patients with no residual primary tumor (Habr-Gama et al. 2010). Together, these data ended up questioning the absolute need for surgery for all rectal cancer patients.

The first results proving that radiotherapy (RT), either isolated or with added CH, can be curative for some rectal ADC cases came from a series of patients who had refused surgery or who had been deemed unfit for surgery due to severe comorbidity (Wang et al. 2005). Later, Habr-Gama et al. developed a therapeutic strategy, called «watch and wait» (W&W), in which rectal ADCs are restaged after CHRT and deferral of surgery with intensive surveillance for regrowths is offered to patients in whom a clinical complete response (cCR) is found (Habr-Gama et al. 2014). This group's data showed no significant differences in either overall or disease-free survival at 5 years between patients under W&W and those undergoing surgery after CHRT (Habr-Gama et al. 2014). In later years, groups from the Netherlands (Maas et al. 2011), UK (Dalton et al. 2011) and the USA (Smith et al. 2012) also published results from similar therapeutic strategies that corroborate the low local recurrence rate found by the Brazilian group, with disease-free and overall survival numbers that are identical to those of the standard therapeutic strategy.

In 2018, the first results from the International Watch & Wait database, where groups worldwide voluntarily register their patients' data, were published, giving increased strength and credibility to the W&W strategy (2018). However, the limited patient number and short follow-up of some of the published patient series and the wide protocol variation between groups included in the international database, along with the lack of a randomized controlled trial, still keep W&W as an experimental therapeutic strategy.

Our group started a W&W program in 2014, after taking into account the published data and having considered that a randomized controlled trial in this field might not be easily feasible—patients would have to agree on giving up the choice of undergoing surgery or not. Our data are included in the International Watch & Wait database, but we aimed to assess our series' specific results regarding local and distant recurrences and mortality.

Materials and methods

Study design and recruitment

This was an inception cohort study—all patients with a new diagnosis of rectal ADC with lower limit at or below 6cm [by magnetic resonance imaging (MRI) and/or rigid rectosigmoidoscopy] from the anal margin evaluated at the Colorectal Cancer Multidisciplinary Team (GMCCR) of the Instituto Português de Oncologia de Lisboa, Francisco Gentil, EPE (IPOLFG) between November 2014 and October 2018 were screened for the study.

Data regarding patient gender, age at rectal cancer diagnosis, diagnosis at screening examinations versus symptom-driven, familial and personal history of colorectal cancer (CRC) or other Lynch syndrome-associated tumors, previous abdomino-pelvic surgeries and/or radiotherapy and comorbidities were collected. Patients with contraindications for pelvic RT and those with synchronous tumors other than CRC were excluded from the study.

Rectal ADCs (classified according to the WHO Classification of Tumors of the Digestive System) (Bosman et al. 2010) were staged (AJCC staging) (Edge et al. 2010) using thoracic computerized tomography (CT), abdominal CT or MRI and pelvic MRI (patients with contraindications or intolerance to MRI underwent pelvic CT), plus endorectal ultrasound at clinicians' choice. Patients staged cT1N0 and all those staged cM1 were excluded from the study.

Neoadjuvant treatment and reassessment protocol

All the remaining low rectal ADC patients received neoadjuvant CHRT (50.4 Gy in 28 fractions at 1.8 Gy per fraction over 5.5 weeks plus 5-fluorouracil or capecitabine) or neoadjuvant isolated RT (25 Gy in 5 fractions at 5 Gy per

fraction administered during 1 week). Short-course RT was given when patients were 80 years or older and/or had other contraindications to chemotherapy.

Patient re-evaluation was planned at 8-12 weeks after the end of neoadjuvant treatment and included a proctological clinical examination performed by expert rectal surgeons, a flexible sigmoidoscopy performed by a dedicated gastroenterologist and a pelvic MRI (CT when MRI was contraindicated) assessed by an expert radiologist—all doctors performing the examinations were part of the study team.

Reassessment results' definitions

A cCR to CHRT was defined as: (Habr-Gama et al. 2010; Wang et al. 2005; Habr-Gama et al. 2014; Maas et al. 2011; Dalton et al. 2011; Smith et al. 2012; Patel et al. 2011) pelvic MRI with no evidence of residual tumor in the rectal wall (fibrosis or edema might be present), or any suspected lymphadenopathies;

– no palpable lesions at rectal examination (a subtle decrease in pliability in the scar area was acceptable); and

– flexible sigmoidoscopy with no evidence of residual lesion (a white scar or telangiectasia was acceptable).

Patients were defined as having a near-complete clinical response when they were found to have: (Habr-Gama et al. 2010; Wang et al. 2005; Habr-Gama et al. 2014; Maas et al. 2011; Dalton et al. 2011; Smith et al. 2012; Patel et al. 2011)

– pelvic MRI with a significant reduction of the tumor [Tumour Regression Grade (TRG) (Patel et al. 2011) 2] and

– flexible sigmoidoscopy with a white scar, telangiectasia or mild mucosal irregularity/ erythema.

Patients' allocation to W&W or traditional strategy groups

Patients without complete or near-complete response at 8–12 weeks were submitted to surgery within 2 weeks. Patients with a near-complete response at 8–12 weeks post-neoadjuvant treatment were re-evaluated with the same protocol 4 weeks later (at 12–16 weeks). At this time point, patients were submitted to surgery if they did not show a cCR. These patients who underwent surgery following the neoadjuvant therapy comprise the traditional strategy group.

All patients with a cCR were offered the choice of proceeding to surgery or entering a W&W strategy. In those who gave informed consent for the W&W strategy, surgery was deferred, and regular surveillance was initiated.

W&W strategy

Surveillance protocol:

– Pelvic MRI, flexible sigmoidoscopy, proctological examination every 3 months in the first 2 years and then every 6 months until the fifth year.

– CEA every 3 months in the first 3 years and then every 6 months until the fifth year.

– Thoraco-abdominal CT every 6 months in the first year and then annually for 4 more years.

– Colonoscopy 1 year after the end of treatment and then 3 years after and every 5 years from then on, if no high risk adenomas (1cm or larger, high-grade dysplasia or villous component) were found.

Regrowths were defined as the reappearance of any lesion in the rectal wall and/or of pathologic mesorectal lymph nodes in patients who previously had a cCR.

Whenever evidence of regrowth was found on any of the examinations, surgery with TME was performed.

Follow-up and recurrences

Local disease recurrence was defined as any pelvic recurrence found after surgery with TME.

Distant and local disease recurrences were managed according to the usual GMCCR protocol. All distant and/or local recurrences found during follow-up were considered for the analysis.

End of follow-up was defined as the date of death or the last registered clinical assessment of the patient. Follow-up was assessed from the GMCCR meeting in which cCR was assumed for patients under W&W strategy and from the date of surgery for patients without cCR.

For the Kaplan–Meier analysis, time from diagnosis to the first recurrence (either local or distant) or to the end of follow-up was used for both groups of patients.

Ethical and regulatory statements

The study was approved by IPOLFG's Ethics Committee and Investigation Unit (Approval 119/2014) and developed according to the Helsinki Declaration principles.

Statistical analysis

Statistical analysis was done using SPSS Statistics 24 (IBM®).

Continuous variables were expressed as means, medians and standard deviations. Qualitative variables were expressed as absolute and/or relative frequencies and associations were tested by Chi-square or Fisher's exact tests. Binary logistic regression was used for multivariate analysis (Enter method).

The Kaplan–Meier method was used to assess disease-free survival (defined as the time from diagnosis to the first disease recurrence) and a log rank test was run to

determine if there were differences between the two treatment strategies.

A significance level of 0.05 for bilateral testing was accepted.

Results

Population characterization

From November 2014 to October 2018, 93 new patients with low rectal cancer staged higher than cT1N0 and with no metastatic disease at diagnosis were evaluated by the IPOLFG Colorectal Cancer Multidisciplinary Team—52.7% were male; the mean age at diagnosis was 64.74 years (± 12.44).

Most cases (90.3%) were diagnosed after symptoms and only 7.5% of the diagnosis came from colorectal cancer screening examinations.

In 43% of cases, the tumor's lower margin was within 2cm from the anal verge; in 31.2% of cases it was between 2 and 4cm and in the remaining 25.8% it was between 4 and 6cm.

Staging was done with thoracic CT and abdominal CT/MRI in all cases, plus pelvic MRI in 90.3% of patients and pelvic CT in the remaining ones (with contraindications to MRI). In 31.2% of cases, endorectal ultrasound was also included for the pelvic staging.

Clinical staging showed most patients (79.6%) were stage III at diagnosis, with only 11.8% of stage I patients.

Due to staging and/or attempting to preserve sphincteric function or to achieve a cCR, all patients received neoadjuvant RT (long course CHRT in 92.5% of patients, isolated short-course RT in the remaining 7.5%).

Re-evaluation results

Most patients (82.8%) were re-evaluated after the end of the neoadjuvant therapy (the final re-evaluation happened 10.24 ± 4,7 weeks after the end of neoadjuvant treatment). In 15 patients, the final re-evaluation was done 3.13 ± 2.88 weeks after an initial re-evaluation that showed a near-complete clinical response.

Reasons for not being re-evaluated were synchronous colorectal cancer or colonic polyposis (6 cases), death or severe disability (4 cases), large volume cT4 tumor at diagnosis (2 cases) or logistic reasons (4 cases).

There were no significant differences between patients who were re-evaluated or not regarding gender, age at diagnosis, reason for diagnosis or stage at diagnosis (Table 1). Patients who received isolated short-course RT were less frequently re-evaluated after treatment than those who received long course CHRT ($p = 0.001$) and this difference remained significant in multivariate analysis ($p = 0.003$) (Table 1).

Table 1 Population characterization according to the post-neoadjuvant therapy re-evaluation status

Variables	Re-evaluation after chemoradiation (number of patients)		Significance	
	Yes	No	Univariate analysis*	Multivariate analysis**
Gender				
Male	39	10	$p = 0.388$	$p = 0.588$
Female	38	6		
Age at diagnosis				
Under 65	41	6	$p = 0.284$	$p = 0.568$
65 or more	36	10		
Reason for diagnosis				
Screening/ surveillance	7	2	$p = 0.650$	$p = 0.739$
Symptoms	70	14		
Stage at diagnosis				
Stage I	9	2	$p > 0.9$	$p = 0.461$
Stage II or III	68	14		
Short-course RT				
Yes	2	5	$p = 0.001$	$p = 0.003$
No	75	11		

RT radiotherapy

*Chi-square or Fisher's exact test

**Binary logistic regression

The final assessment of all 77 re-evaluated patients showed a cCR in 20.8% of them (16 patients). One patient who did not show cCR died of unrelated causes before undergoing surgery and was excluded from further analysis.

In the 76 patients who remained for analysis, there were no significant differences between patients with or without cCR regarding gender, age at diagnosis, reason for diagnosis or type of neoadjuvant treatment (Table 2). Patients who were clinically staged as stage II or III were significantly less likely to achieve a cCR than those in stage I ($p = 0.017$). This association remained statistically significant in multivariate analysis ($p = 0.009$) (Table 2).

Patients undergoing W&W

The 16 patients who had a cCR agreed to enter a W&W surveillance program and had a mean follow-up of 17.44 months (2–44 months) at the time of the analysis. The median follow-up was 12 months. Of these patients, 31.3% received adjuvant CH (all cT3 and/or cN+ patients except those older than 80 and patients who had severe side-effects to neoadjuvant CH).

Table 2 Population characterization according to the post-neoadjuvant therapy re-evaluation results

Variables	Clinical complete response (number of patients)		Significance	
	Yes	No	Univariate analysis*	Multivariate analysis**
Gender				
Male	6	33	$p = 0.266$	$p = 0.289$
Female	10	27		
Age at diagnosis				
Under 65	8	33	$p = 0.782$	$p = 0.227$
65 or more	8	27		
Reason for diagnosis				
Screening/surveillance	3	4	$p = 0.157$	$p = 0.256$
Symptoms	13	56		
Stage at diagnosis				
Stage I	5	4	$p = 0.017$	$p = 0.009$
Stage II or III	11	56		
Short-course RT				
Yes	0	2	$p > 0.9$	$p > 0.9$
No	16	58		

RT radiotherapy

*Chi-square or Fisher's exact test

**Binary logistic regression

Regrowths were found in four patients (25%) during surveillance (all in the first 12 months of surveillance); in three cases, the clinical examination detected the regrowth and in one case it was detected by endoscopy. MRI and endoscopy confirmed the findings in all cases. These four patients were submitted to surgery (abdomino-perineal resection in 2, low anterior resection in 2, without stoma reversal in one). The pathological examination showed ypT2 in two cases, ypT1 in one and ypT3 in the remaining case. All patients were ypN0 and all resections were R0. None of these patients had received adjuvant CH [due to clinical staging at diagnosis (cT2N0) in 2 patients or to bad tolerance to neoadjuvant CH in the 2 other patients, who were initially staged as cT3N0]. Adjuvant CH was given to three of them after surgery for the regrowth. The patient who did not receive adjuvant CH was initially staged cT2N0 and the pathological examination of the surgical specimen after regrowth surgery showed ypT2N0.

There were no deaths and no local recurrences in this group of patients during follow-up. One of the patients who had surgery for a regrowth and then received adjuvant CH had a distant recurrence, diagnosed 14 months after surgery.

Patients undergoing the traditional treatment strategy

From the 60 patients who were re-evaluated, did not show cCR, and were submitted to surgery, 58.3% were submitted to low anterior resections and 38.3% to abdomino-perineal resections (2 other patients were submitted to extended surgeries due to synchronous lesions or T4 cancers). The surgical specimen showed that 28.3% of the patients were ypN positive. Pathological complete responses were found in eight patients (13.3%). After surgery, 78.3% of the 60 patients received adjuvant CH.

After a mean follow-up of 16.23 months (median: 16 months), local recurrence was found in three patients (5%), along with distant recurrence in all of them. A further seven patients had distant recurrence (16.7% in total).

There were eight deaths during follow-up in this group of patients (3 of the deaths were related to treatment, 3 were due to disease progression and 2 others were due to unrelated causes).

Comparison between strategies

There were no statistically significant differences between patients who entered a W&W strategy and patients who were directly submitted to surgery regarding local or distant recurrences, or death ($p > 0.9$; $p = 0.44$; $p = 0.19$, respectively, Table 3). There were also no statistically significant differences in any of these three outcomes between patients who entered a W&W strategy

Table 3 Oncological results according to the treatment strategy (and in the subgroup of patients found to have pCR)

Variables	Treatment strategy (number of patients)		Significance
	Watch and wait	Traditional (pCR)	Univariate analysis*
Local recurrence			
Yes	0	3 (1)	$p > 0.9$ ($p = 0.33$)
No	16	57 (7)	
Distant recurrence			
Yes	1	10 (1)	$p = 0.440$ ($p > 0.9$)
No	15	50 (7)	
Death			
Yes	0	8 (1)	$p = 0.191$ ($p = 0.33$)
No	16	52 (7)	

pCR patients with a pathological complete response

*Chi-square or Fisher's exact test

and the subgroup of patients under the traditional strategy who were found to have a pCR ($p = 0.33$; $p > 0{,}9$; $p = 0.33$, respectively) (Table 3).

There was no statistically significant difference in the disease-free survival distributions for the two strategies [$X^2(1) = 1.244$, $p = 0.265$) (Fig. 1).

Discussion

TME rectal surgery (Hill and Rafique 1998) revolutionized the CRC clinical field, dramatically improving rectal ADC patients' outcomes (Ross et al. 1999; Bjerkeset and Edna 1996). However, especially when added to neoadjuvant pelvic RT, this success comes at the cost of significant morbidity (Peeters et al. 2005). If some patients can avoid surgery without compromising their oncological outcome, this will improve their bowel function and quality of life (Habr-Gama et al. 2016; Bernier et al. 2018).

Although Habr-Gama's group data (Habr-Gama et al. 2010; Habr-Gama et al. 2014) and more recently the International Watch & Wait Database's results (2018) support the W&W strategy's safety and benefit, it is still considered experimental, mainly due to the lack of a randomized control trial and to the heterogeneity between published patient series, both in terms of patient selection and of proposed evaluations (Bernier et al. 2018).

In 2014, our GMCCR considered scientific data was enough to allow us to offer W&W as a valid option to our patients. After Ethics Committee's approval, we started a structured program, with a prospective data registry.

Our data are in agreement with Habr-Gama's group (Habr-Gama et al. 2017) in showing that stage I patients, who traditionally might not receive CHRT, may especially benefit from the W&W strategy, by being the most likely to achieve cCR, consequently avoiding surgery.

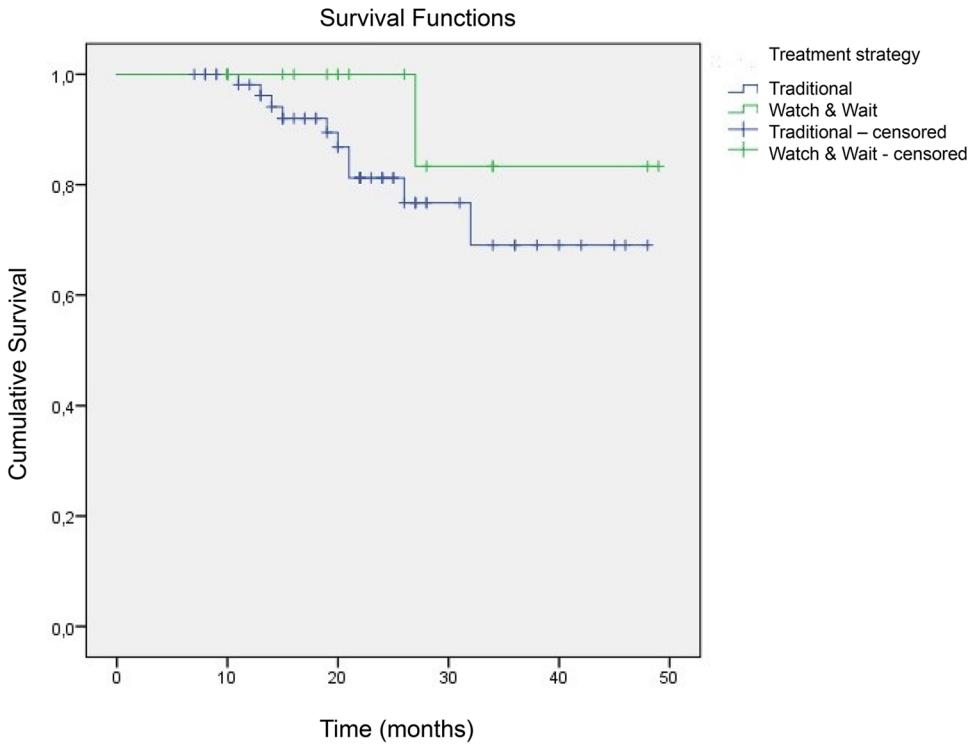

Fig. 1 Disease-free survival functions plot for the two treatment strategies (Kaplan–Meier method)

Regarding the percentage of patients achieving cCR, however, our results (20.8%) are closer to those of other groups (24% in the United Kingdom group (Dalton et al. 2011), for instance), most likely due to the different CHRT scheme used by the Brazilian group, which is not standard in Europe. The 13.3% of pCR still found in patients classified as not having a cCR are also in accordance with other published results and show that there are still limits to our ability to assess response to CHRT. In the future, adding positron-emission tomography-CT to the evaluation protocol (Perez et al. 2012) may help to identify cCR more accurately.

In our series, there was no statistically significant difference in the achievement of cCR between patients who received short-course RT or CHRT ($p > 0.9$, Table2), but this result may be affected by a selection bias, since patients who received short-course RT were significantly less likely to be re-evaluated ($p = 0.001$, Table 1).

Most importantly, as shown in the largest patient series, the International Watch & Wait Database (2018), our W&W patients achieved the same oncological outcomes as those in the traditional therapeutic strategy, with no significant increases in either death or disease recurrences.

Patients who underwent surgery straight after CHRT/RT are theoretically those with a worse prognosis, because they did not achieve cCR to neoadjuvant therapy. It may be argued that patients under W&W should therefore be expected to have better oncological outcomes. However, the traditional strategy group also includes patients who were later found to have pCR and these have been shown, in previous studies, to have the best prognosis (Campos-Lobato et al. 2011). Although the numbers are small, when patients under W&W were compared to the subgroup with pCR, there were no statistically significant differences in outcomes either.

Our series is limited by the small number of patients and the yet short follow-up. This short follow-up implies that results regarding recurrences must be seen with caution, namely in the case of distant recurrences that tend to occur later, especially when patients receive multimodality treatment.

Despite these limitations, the standardized patient selection and treatment/follow-up protocols, with prospectively collected data, give our results a robustness that is lacking in some of the early trials.

In the future, the results of randomized controlled trials like the TRIGGER trial (Battersby et al. 2017) that includes a «Deferral of Surgery» arm, similar to W&W, may further define if this new strategy should become a new standard of care.

Conclusion

In our series, there were no statistically significant differences between patients under W&W and patients who underwent direct surgery regarding local or distant recurrences, or death ($p > 0,9$; $p = 0.44$; $p = 0.19$, respectively). Therefore, as expected, we achieved the same oncological outcomes with W&W as with the traditional strategy, while sparing some patients from surgery.

By continuing to collaborate with the International Watch & Wait Database, our group hopes to contribute to the definition of common standards for the W&W strategy and to the achievement of robust follow-up results to clarify its validity and safety.

Author contributions All authors participated in the conception and design of the study; all authors collected and analyzed data for the study and performed the treatments and/or the diagnostic examinations on the study patients, according to their medical specialty; João Cortez Pinto and Isadora Rosa drafted the article. All authors revised the article critically for important intellectual content and gave approval of the final version to be submitted.

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Compliance with ethical standards

Conflict of interest Isadora Rosa reports grants, personal fees or non-financial support from ABBVIE, FERRING, MSD, TAKEDA, PHARMAKERN, JANSSEN, and DR FALK PHARMA, outside the submitted work; the remaining authors have nothing to disclose.

Ethics approval The study was approved by IPOLFG's Ethics Committee and Investigation Unit (Approval 119/2014) and developed according to the Helsinki Declaration principles.

Consent to participate All patients gave informed consent for every diagnostic and/or therapeutic procedure/strategy.

Consent for publication All authors approved the final version of the manuscript for publication.

Availability of data and material All data and material are held by the authors' institution and may be available upon request.

References

Battersby NJ, Dattani M, Rao S et al (2017) A rectal cancer feasibility study with an embedded phase III trial design assessing magnetic resonance tumour regression grade (mrTRG) as a novel biomarker to stratify management by good and poor response to chemoradiotherapy (TRIGGER): study protocol for a randomised controlled trial. Trials 18:394

Bernier L, Balyasnikova S, Tait D et al (2018) Watch-and-wait as a therapeutic strategy in rectal cancer. Curr Colorectal Cancer Rep 14:37–55

Bjerkeset T, Edna TH (1996) Rectal cancer: the influence of type of operation on local recurrence and survival. Eur J Surg 162:643–648

Bosman FT, Carneiro F, Hruban RH, et al. WHO Classification of Tumours of the Digestive System. IARC Press, 2010:134-146.

Bosset J, Collette L, Calais G et al (2006) Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 355:1114–1123

Dalton R, Velineni R, Osborne M et al (2011) A single-center experience of chemoradiotherapy for rectal cancer: is there potential for nonoperative management? Colorectal Dis 14:567–571

de Campos-Lobato L, Stocchi L, da Luz Moreira A et al (2011) Pathologic complete response after neoadjuvant treatment for rectal cancer decreases distant recurrence and could eradicate local recurrence. Ann Surg Oncol 18:1590–1598

Edge S, Byrd DR, Compton CC, et al. (eds) (2010) AJCC Cancer Staging Manual and Handbook. Springer-Verlag, New York

Grumman M, Noack E, Hoffmann I et al (2001) Comparison of quality of life in patients undergoing abdominoperineal extirpation or anterior resection for rectal cancer. Ann Surg 233:203–213

Habr-Gama A, Perez R, Wynn G et al (2010) Complete clinical response after neoadjuvant chemoradiation therapy for distal rectal cancer: characterization of clinical and endoscopic findings for standardization. Dis Colon Rectum 53:1692–1698

Habr-Gama A, Gama-Rodrigues J, São Julião G et al (2014) Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local diseases control. Int J Radiation Oncol Biol Phys 88:822–828

Habr-Gama A, Lynn PB, Jorge JM et al (2016) Impact of Organ-Preserving Strategies on Anorectal Function in Patients with Distal Rectal Cancer Following Neoadjuvant Chemoradiation. Dis Colon Rectum 59:264–269

Habr-Gama A, São Julião GP, Gama-Rodrigues J et al (2017) Baseline T classification predicts early tumor regrowth after nonoperative management in distal rectal cancer after extended neoadjuvant chemoradiation and initial complete clinical response. Dis Colon Rectum 60:586–594

Hill GL, Rafique M (1998) Extrafascial excision of the rectum for rectal cancer. Br J Surg 85:809–812

Maas M, Beets-Tan R, Lambregts D et al (2011) Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol 29:4633–4640

Milgrom S, Goodman K (2014) Non-operative management of locally advanced rectal cancer. Seminars Colon Rectal Surg 25:22–25

Patel U, Taylor F, Blomquist L et al (2011) Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: mercury experience. J Clin Oncol 29:3753–3760

Peeters KC, van de Velde CJ, Leer JW et al (2005) Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients—a Dutch colorectal cancer group study. J Clin Oncol 23:6199–6206

Perez RO, Habr-Gama A, Gama-Rodrigues J, et al (2012) Accuracy of positron emission tomography/computed tomography and clinical assessment in the detection of complete rectal tumor regression after neoadjuvant chemoradiation: long-term results of a prospective trial (National Clinical Trial 00254683) Cancer 118:3501–3511.

Pucciarelli S, Capirci C, Emanuele U et al (2005) Relationship between pathologic T-stage and nodal metastasis after preoperative chemoradiotherapy for locally advanced rectal cancer. Ann Surg Oncol 12:111–116

Ross A, Rusnak C, Weinerman B et al (1999) Recurrence and survival after surgical management of rectal cancer. Am J Surg 177:392–395

Sauer R, Becker H, Hohenberger W et al (2004) Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 324:709–715

Smith J, Ruby J, Goodman K et al (2012) Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. Ann Surg 256:965–972

van der Valk MJM, Hilling De, Bastiaannet E et al (2018) 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 391:2537–2545

Wang Y, Cummings B, Catton P et al (2005) Primary radical external beam radiotherapy of rectal adenocarcinoma: long term outcome of 271 patients. Radiother Oncol 77:126–132