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SPECIAL ARTICLE

Interdisciplinary Spanish consensus on a watch-and-wait approach for rectal cancer

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Abstract

Watch-and-wait has emerged as a new strategy for the management of rectal cancer when a complete clinical response is achieved after neoadjuvant therapy. In an attempt to standardize this new clinical approach, initiated by the Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD), and with the participation of the Spanish Association of Coloproctology (AECP), the Spanish Society of Pathology (SEAP), the Spanish Society of Gastrointestinal Endoscopy (SEED), the Spanish Society of Radiation Oncology (SEOR), and the Spanish Society of Medical Radiology (SERAM), we present herein a consensus on a watch-and-wait approach for the management of rectal cancer. We have focused on patient selection, the treatment schemes evaluated, the optimal timing for evaluating the clinical complete response, the oncologic outcomes after the implementation of this strategy, and a protocol for surveillance of these patients.

Keywords Rectal cancer · Watch-and-wait · Nonoperative management · Total neoadjuvant treatment · Clinical complete response · Organ preservation

Introduction

In recent years, the management of locally advanced rectal cancer has evolved based on the administration of neoadjuvant therapies (NATs) followed by surgery performed on the principles of total mesorectal excision (TME) proposed by Heald et al. [1]. The administration of NAT provided better results regarding local recurrences with less toxicity than adjuvant treatment [2]. However, TME is a technique associated with high morbidity; a postoperative mortality

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rate at 6 months ranging from 2% to 8% [3]; a high rate of temporary or permanent stomas along with anorectal, urinary, and sexual dysfunction affecting 30–80% of patients [4, 5]; and complications that severely impact patient quality of life. Moreover, compared with TME alone, long-course chemoradiotherapy (CRT) followed by surgical resection is associated with increased long-term morbidity and reduced quality of life [6]. In addition, after the administration of NAT, in the examination of the surgical resection specimen, the disappearance of the tumor and its replacement by fibrosis, necrosis, mucin, angiitis, microcalcifications, etc., can be seen; this is called a pathological complete response (pCR). These patients show better oncological outcomes than those in whom there is a residual tumor. This issue raises the possibility of avoiding surgery in these patients in whom the disappearance of the tumor is assumed based on endoscopic, radiological, and clinical criteria, leading to the concept of clinical complete response (cCR). This strategy is referred to as "watch-and-wait" (W&W) or nonoperative management, and the most relevant clinical guidelines on the management of rectal cancer (RC), such as those from the National Comprehensive Cancer Network [7] and the European Society for Medical Oncology [8], consider W&W if a cCR is achieved after NAT.

In an attempt to standardize this new clinical approach for the management of RC, initiated by the Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD), and with the participation of the Spanish Association of Coloproctology (AECP), the Spanish Society of Pathology (SEAP), the Spanish Society of Gastrointestinal Endoscopy (SEED), the Spanish Society of Radiation Oncology (SEOR), and the Spanish Society of Medical Radiology (SERAM), we present herein a consensus on a watch-and-wait approach for the management of RC.

Patient selection

The W&W strategy offers a noninvasive therapeutic alternative for patients with an RC localized in the low or middle rectum who have achieved a cCR after NAT to avoid morbidity and the sequela of the TME.

Pretreatment evaluation

The initial evaluation should follow a standard RC workup. Endoscopic images must be collected, and magnetic resonance imaging (MRI) is cardinal in this process. The importance of MRI in RC is based on its high accuracy in providing information to guide therapeutic decision-making by assessing not only detailed information on the tumor location, anatomical planes, and baseline local staging but also for risk stratification and obtaining prognostic data [9–11].

Identification of patients before starting treatment is difficult, although it is known that more advanced tumors (i.e., those threatening the circumferential margin, with advanced lymph-node [LN] involvement or extramural venous invasion [EMVI]) have lower cCR rates [12, 13]. These factors may be identified by imaging studies.

MRI is very sensitive in identifying mesorectal fascia involvement [14, 15], and the five-point MRI-EMVI scoring system proposed by Smith et al. [16] has been reported to be reasonably accurate in the detection of EMVI. However, metastatic LN involvement is difficult to determine, with sensitivity ranging between 42 and 89% [17]. Recently, the combination of size and morphological criteria (including a round shape, irregular LN contour, and mixed MRI signal) has been suggested to improve nodal evaluation [17–19].

Finally, rectal adenocarcinoma with mucinous components represents a poor prognostic subgroup of patients with RC. Mucinous adenocarcinoma can be diagnosed, because it typically demonstrates a high signal intensity on T2-weighted (T2w) images [9, 20].

Usefulness of diagnostic biopsy for predicting response to therapy

After anatomopathological confirmation of adenocarcinoma, when a W&W strategy is considered, there is a clear need to acquire as much information as possible from the pretreatment diagnostic biopsy to define which patients are more likely to show a good and sustained response to NAT and can safely avoid radical surgery. Despite several publications on this issue, unfortunately, no robust predictive biomarkers have been found thus far. Several reports on global gene expression profiling on cDNA arrays have defined a gene signature predictive of a good tumor response to neoadjuvant chemoradiotherapy (nCRT). Watanabe et al. [21] described a 33-gene expression signature, while Agostini et al. [22] reported a 19-gene one, both with an accuracy over 90% for predicting tumor response. These signatures mainly include genes involved in DNA replication, the cell cycle, DNA repair, and drug metabolism. Gantt et al. [23] validated a gene signature in the pretreatment biopsy with good results. Additional studies have analyzed the use of several protein biomarkers with promising results. However, no study to date has combined all these potential markers and analyzed whether they can be useful in clinical practice, because such studies have been performed in different hospitals with fairly different therapeutic strategies and sample management [24]. The most promising and robust marker to date is the Immunoscore, which relies on the measurement of CD3- and CD8-positive T cells in the tumor sample. This tool was described in post-therapy specimens, but it has also been validated for pretreatment samples with similar predictive potential. Tumors with high Immunoscore values quantified by digital imaging show a good response to therapy and could be candidates for W&W management with a low risk of recurrence if all the clinical and imaging features are also favorable (i.e., they showed a significantly longer time to relapse compared to tumors with low Immunoscore [HR, 0.21; 95% CI 0.06 to 0.78]) [25].

Posttreatment evaluation

Multidisciplinary management for response assessment after NAT is crucial to identify patients with cCR who may benefit from a conservative strategy. Although some criteria have been proposed, these are not completely adopted. Additionally, the most appropriate time to perform this evaluation is still unknown, especially given the different types of NAT.

Clinical complete response criteria

Radiologic criteria MRI is established as the gold standard technique for restaging RC after NAT [17, 26]. The most commonly used criteria rely on T2W and diffusion-weighted images (DWIs) [27]. Contrast-enhanced sequences are not mandatory. The degree of fibrotic transformation as a measure of response can also be classified using the MRI tumor regression grade (mrTRG), which adapts a similar TRG system used in histopathology. This system shows good interobserver agreement [28], but the agreement between the mrTRG and pathologic TRG is rather low, with limited performance in identifying pCR, showing a sensitivity of 74% and specificity of 63% [29]. The addition of DWI to standard T2w sequences can improve the performance of MRI to differentiate between patients with cCR and those with residual tumor. In a meta-analysis, the pooled sensitivity to predict response was significantly higher for studies including a DWI sequence (84%) than for studies using only standard MRI (50%) [30].

Different groups have developed various MRI criteria to identify a cCR to select patients for W&W management. Maastricht criteria [31, 32], also adopted for the international consensus statement, defined cCR as a significant reduction in tumor size with normalization of the T2w tumoral signal, either with or without residual fibrosis or with edematous wall thickening. On the high b-value DWIs, there should be no signal alterations in the tumoral bed. No suspicious LN should be present. Clinical near-complete response (ncCR) has been fixed for good-responding tumors that do not meet the cCR criteria. The phase III study ACO/ARO/AIO-18.1 [33], a large, multicenter trial, will assess and validate the response to NAT adopted in the Maastricht criteria. The Sao Paulo criteria [34] consider a cCR as occurring when there are no suspicious mesorectal enlarged, irregularly bordered, and heterogeneous nodes besides the presence of fibrotic low signal intensity areas with or without submucosal hypertrophy changes in the tumoral bed. The OPRA trial from the RC consortium [35] proposes similar criteria to define cCR. Thus, a cCR requires only a dark T2w signal without an intermediate signal on T2w MRI, no visible LNs, and no visible signal on high b-value DWIs; an ncCR requires a mostly dark T2w signal with some remaining intermediate signal and/or partial regression of LNs and significant regression of the signal on high b-value DWIs; and an incomplete CR (iCR) requires a more intermediate than dark T2 signal without a T2w scar and/or no regression of LNs and insignificant regression of the signal on high b-value DWIs. Awaiting evidence for the best performance criteria, we recommend using Maastricht criteria, also endorsed by the international consensus recommendations, because they are best suited to define cCR and ncCR (Table 1).

The Lateral Lymph-Node Consortium has evaluated the risk of recurrence for extramesorectal regional LNs, reporting a significantly higher local recurrence rate for suspicious LNs in the pretreatment scan located in the internal iliac and obturator regions that remained larger than 4 and 6 mm, respectively, on posttreatment MRI, with strong advice for LN dissection [27].

Mucinous adenocarcinomas typically show a relatively poor response to NAT with no or little shrinkage. Assessing their response on MRI is difficult, because their high

Table 1 Maastricht criteria for magnetic resonance imaging clinical response evaluation after neoadjuvant treatment

	Clinical complete response (cCR)	Clinical near-complete response (ncCR)	Poor response
T2W	Substantial tumor downsizing. No observable residual tumor or residual fibrosis only. Residual wall thickening due to edema may be present	Obvious downstaging with residual fibrosis but a heterogeneous or irregular aspect and signal	Not fulfilling the criteria for either a cCR or an ncCR
DWI (b = 800–1000)	No signal on a high b-value DWI	Small focal area of high signal on a high b-value DWI	
Lymph nodes	No suspicious lymph nodes: All of them < 5 mm	Obvious downstaging of lymph nodes but remaining node(s) > 5 mm	

DWI diffusion-weighted image

signal intensity remains regardless of the histopathologic degree of viable residual tumor cells within the mucin. As a result, the morphologic response criteria described above are hardly applicable in mucinous tumors. Furthermore, signet-ring tumors typically present with extensive lymphatic and peritoneal tumor spread and are associated with poor overall survival. Therefore, they have a limited role in response evaluation with imaging.

Endoscopic criteria Most studies evaluating the W&W strategy follow the criteria initially described by Habr-Gama et al. [36] for the definition of cCR: absence of residual tumor and presence of a white scar where the tumor previously was, with or without telangiectasias. Of the mucosal alterations possibly predictive of cCR, white scarring has the highest positive predictive value (70–80%) [37]. Other alterations have a lower predictive capacity, although some authors suggest that the presence of a superficial ulcer or some mucosal irregularity would be suggestive of ncCR and that some of these patients could be managed according to the W&W strategy [38].

Biopsies do not seem to improve diagnostic accuracy, because they have a high false-negative rate [39]. There are hardly any studies of endoscopic cCR evaluation with new imaging technologies, although it seems that the evaluation of the crypt pattern with a magnifying endoscope would have a diagnostic reliability of up to 90% [40, 41].

In patients with ulcerated and circumferential tumors, there is a risk of severe scarring and narrowing of the rectal lumen, preventing an appropriate endoscopic follow-up [36].

Endoscopic control should be performed with a high-definition flexible endoscope. The absence of tumor lesions and the presence of a white scar with or without telangiectasias are endoscopic signs of cCR. The existence of a superficial flat ulcer, especially if < 1 cm, is suggestive of ncCR, and these patients could be managed with the W&W strategy, local excision, or TME. The endoscopic criteria for response assessment are summarized in Table 2 and exhibits of the endoscopic images are presented in Figs. 1A, B and C.

Digital rectal examination Digital rectal examination (DRE) is one of the main assessment tools for evaluating the clinical response in tumors of the lower rectum. The tumor regression criteria proposed by the Memorial Sloan Kettering Cancer Center have been accepted by the scientific community. They considered 3 response groups: complete response in which DRE does not palpate any lesion where the original tumor was located; near-complete response, where DRE palpates a small nodularity, ulcer, or some irregularity; and poor or incomplete response, where DRE by palpation clearly indicates the presence of a tumor [42].

Clinical assessment, including DRE and endoscopy, has proven to be the most accurate strategy to select patients who may experience a complete response. Nevertheless, DRE is still a subjective test subject to the interpretation of the evaluator and limited to tumors located in the distal rectum. The addition of MRI increases the identification of complete response to a level that is reliable for clinical decision-making. The combination of radiological (MRI) and clinical (endoscopy and DRE) criteria significantly increased the specificity of the clinical response evaluation, reaching values above 98% of the cases and missing residual tumor in only 2% [42].

Value of rectal biopsy in evaluating tumor response The value of biopsies for the endoscopic assessment of post-NAT in RC is controversial. As reported by van der Sande et al. [37], the addition of biopsies rarely changes the endoscopists' confidence level of response, and the area under the receiver-operating characteristics curve for endoscopy with biopsies is not significantly different from that of endoscopy without biopsies. This may prompt a lack of confidence in biopsy results, because negative biopsies frequently represent sampling errors, supporting the finding

Table 2 Endoscopic criteria for response assessment

Clinical complete response (cCR)	Clinical near-complete response (ncCR)	Poor response
Flat white scar with or without telangiectasia Absence of an ulcer or nodularity	Erythema on the scar Irregular mucosa, small nodules Superficial ulceration	Visible tumor

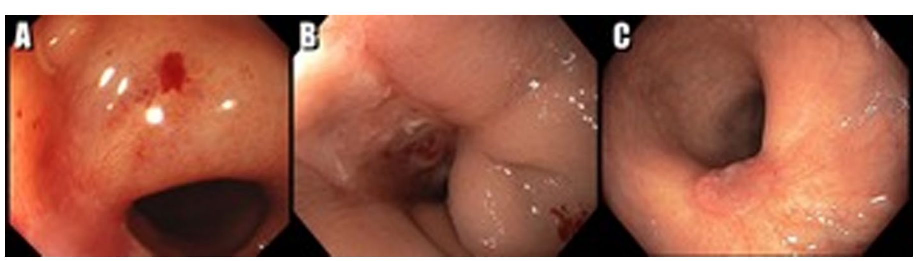

Fig. 1 Exhibits of endoscopic response assessment. **A** Clinical complete response: scar without telangiectasia and absence of ulcer or nodularity; **B** clinical near-complete response: superficial ulceration; **C** poor response: visible tumor

that endoscopic biopsies may have limited clinical use for excluding postneoadjuvant residual tumors. For these reasons, biopsy sampling is not recommended to confirm the response to NAT.

Scheme selection/treatment optimization

Since the W&W approach is based on tumor replacement by fibrosis and the absence of viable residual tumor cells induced by NAT, schemes with high pCR rates will be used.

Standard long-course CRT can achieve pCR rates of approximately 10–20% [43]. Although short-course radiotherapy (SCRT) had shown lower pCR rates, recent data from the Stockholm III trial showed pCR in 10.4% of the patients in whom surgery was delayed by 4–8 weeks [44]. This study demonstrated that delaying surgery after SCRT improves the downstaging of RC with similar oncological results and is a useful alternative to the conventional SCRT with immediate surgery [44]. The results of the Stockholm III study have favored the development of total neoadjuvant treatment (TNT) strategies that combine SCRT and neoadjuvant chemotherapy in an attempt to decrease the rate of distant recurrences. SCRT has the advantage of reduced cost and duration of treatment.

Currently, TNT schemes have shown higher rates of pCR than standard nCRT alone [45]. The PRODIGE 23 trial (induction mFOLFIRINOX followed by nCRT vs. nCRT) showed a higher rate of pCR (27.5% vs. 11.7%) in the experimental arm [46]; a 7-year follow-up analysis of this trial showed that mFOLFIRINOX followed by nCRT significantly improved all outcomes, including OS compared to those who received standard nCRT [47]. Similarly, the RAPIDO trial (SCRT followed by consolidation CAPOX/FOLFOX–18 weeks vs. CRT) and POLISH trial (SCRT followed by consolidation FOLFOX4–3 cycles vs. CRT) showed a higher rate of pCR of TNT compared to CRT (28% vs. 14% and 16% vs. 12%, respectively) [48, 49]. In the STELLAR trial (SCRT followed by four cycles of CAPOX vs. CRT), the total rate of pCR and sustained cCR was significantly higher in the TNT arm (21.8% vs. 12.3%) [50]. A recent update of the RAPIDO trial showed an increased risk of locoregional recurrence, whereas the reduction in disease-related treatment failure and distant metastases remained after 5 years. The experimental treatment, enlarged lateral LN, positive circumferential resection margin, tumor deposits, and node positivity at pathology were significant predictors for developing locoregional recurrence [51]. Further refinement of the TNT schedule in rectal cancer is needed.

A relevant issue is the choice of induction or consolidation chemotherapy. The CAO/ARO/AIO 12 trial showed a higher pCR rate after consolidation chemotherapy than after induction chemotherapy [52]. The OPRA trial is the first randomized phase II study for patients with stage II–III rectal adenocarcinoma treated with induction chemotherapy followed by CRT or CRT followed by consolidation chemotherapy and either TME or W&W management based on the tumor response [53]. The 3-year TME-free survival was 41% in the induction group and 53% in the consolidation group [53]. This higher rate of clinical response after consolidation chemotherapy might be explained based on a long interval after the end of radiotherapy.

Using a similar consolidation approach but with SCRT followed by FOLFOX or CAPOX, Chin et al. [54] showed a TME-free survival rate of 47% (95% CI, 38–59%) at 1 year and 40% (95% CI, 30–52%) at 2 years.

Recently, a 100% cCR has been reported in 12 mismatch repair-deficient RC patients treated with dostarlimab [55] as a new alternative for this type of patient.

Currently, in the setting of W&W management, TNT with consolidation chemotherapy seems to be the better choice for organ preservation. For patients with mismatch repair deficiency, PD-1 blockade is an alternative that requires further confirmation.

Time points for response assessment

Evidence on the optimal timing to assess cCR to treatment is not defined. The optimal timing to surgery after completion of NAT that achieves the highest pCR rate represents a surrogate for the best moment to evaluate the cCR when the W&W strategy is considered. The European Society for Medical Oncology guidelines on RC [8] propose an interval of 12 weeks from the start of treatment to assess cCR in patients treated with neoadjuvant CRT or SCRT. International consensus recommendations [56] propose that time points for response assessment and determining cCR should be selected according to trial design and treatment strategies:

-Standard neoadjuvant CRT or SCRT: initial measurement at 12 weeks from the start of treatment and then, in patients with an ncCR at initial assessment, a repeat assessment at 16–20 weeks to determine a cCR.

-TNT with CRT and either induction or consolidation chemotherapy (duration of 16-20 weeks): the RA should be conducted at 24 weeks after the start of treatment (GRECCARD12, ACO/ARO/AIO-18.1, RAPIDO, and PRODIGE 23).

-TNT with CRT followed by prolonged consolidation chemotherapy (26–34 weeks): the response assessment should be conducted at 34–38 weeks after the start of treatment (OPRA and TRIGGER trials).

One of the main concerns in the evaluation of a delayed response is the early detection of patients refractory to NAT. Currently, no recommendation can be made in this context, although early MRI should be performed on an individual

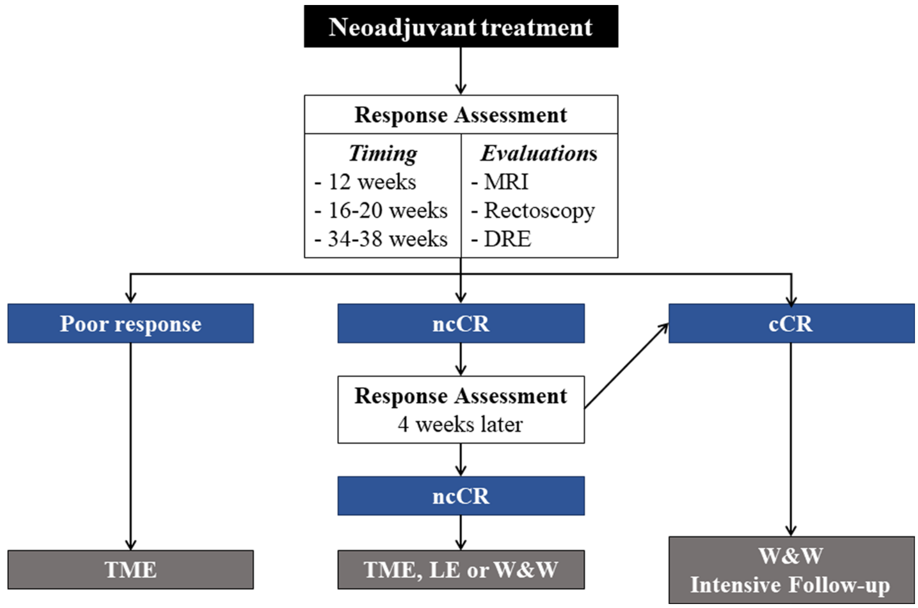

Fig. 2 Algorithm for response assessment. *cCR* clinical complete response, *DRE* digital rectal examination, *LE* local excision, *MRI* magnetic resonance imaging, *ncCR* near-complete clinical response, *TME* total mesorectal excision, *W&W* watch-and-wait, *FU* follow-up

basis if lack of response is suspected to not exclude these patients from a curative surgical approach.

The process for the assessment of response and its implications on treatment decision-making is summarized in Fig. 2.

Oncologic outcomes after a watch-and-wait strategy

The objective of this strategy is to improve the quality of life (QoL) of patients, avoiding sequela from radical surgery.

Quality of life

Data from the Memorial Sloan Kettering experience showed better anorectal function in patients with W&W than in patients with TME [57]. Similarly, Hupkens et al. [58], comparing 47 patients with W&W in front of 41 patients who had neoadjuvant treatment and TME, showed that QoL was better in the W&W cohort. Interestingly, 36% of patients in the W&W arm presented with a major low anterior resection syndrome (LARS) score.

Local regrowth

The counterpart to the improvement of QoL is the possibility of regrowth of the primary tumor. Regrowth is defined as the detection of a tumor involving the bowel wall after an initial cCR is achieved. We can differentiate between local regrowth (detection of a tumor involving the bowel wall only that occurs after an initial cCR and W&W strategy) and locoregional regrowth (detection of a tumor involving either the bowel wall, mesorectum, and/or pelvic organs that occurs after an initial cCR and a W&W strategy) [56]. Typically, this occurs within the first 2–3 years after CRT. A recent review showed regrowth rates ranging between 15.3% and 34% [59]. In 2018, data from 880 patients on the International Watch and Wait database showed regrowth in 25% of the patients in the first two years of follow-up; this regrowth occurs in the lumen of the rectum in most cases. Moreover, 90% of regrowths can be surgically rescued with R0 resections [60]. Although Habr-Gama et al. [61] reported 6.6% of unresectable local failures, more recent reports have shown local failure rates less than 2% [54, 62]. These better local control rates may be related to the new and standardized radiological response criteria.

No marker can predict which tumors are going to regrow, but it has been observed how this occurs more frequently in patients who start NAT with a high initial tumor burden (e.g., deep T3, T4, N2, etc.) and with tumors that later reach a cCR [12, 13]. Circulating tumor DNA determination could play an important role in the detection of recurrence as well as in the evaluation of cCR [63]; however, more studies are needed to position it in this field.

Local excision can be considered an alternative to TME for suspected regrowth in selected patients who wish to preserve their rectum or avoid colostomy in distal RC, although in some studies, this procedure is punished with high morbidity [64].

Possibility of metastases

The appearance of metastases in these patients is another source of concern. Several studies have suggested that patients who develop local regrowth have worse oncological outcomes. In a systematic review with 1,387 patients, the risk of distant metastases in patients with cCR was 5.5%, but in patients with regrowth, it was 23.1% [65]. Recently, data from the International Watch & Wait Database showed metastases in 10.7% of patients; however, 24.1% of patients with regrowth suffered metastases. The development of local regrowth at any time and age was the only factor that remained statistically significant for worse distant metastasis-free survival. Two mechanisms might be involved in metastasis development. An inherent unfavorable biology is collectively responsible for both an incomplete primary tumor response and the development of distant metastases. On the other hand, local regrowth may comprise a second event that increases the risk of metastases by providing a second nidus for potential metastasis not present in patients without regrowth [66].

Overall survival in the setting of W&W

Although high overall survival rates have been reported, the results of the W&W strategy in front of the conventional approach remain unclear. The risk assumed by W&W management could be offset by the short- and long-term mortality of radical surgery. Data from the International Watch and Wait Database show a 5-year overall survival of 85% (95% CI 80·9–87·7%) [60], which is similar to that found by Maas et al. [67] in patients with pCR after NAT (87·6%; 95% CI 83·6–90·7). In a meta-analysis of W&W management versus TME for RC in patients exhibiting cCR after NAT, including 818 patients from nine studies, no differences were found in 5-year overall survival [68]. Since only four were high-quality studies and, surprisingly, the distant metastasis rate was similar in the W&W group and the surgery group, these data should be viewed with caution.

In summary, patients under W&W management have a possibility of local regrowth of 25% with a finally unresectable local failure rate of less than 5%. Local regrowth is related to the appearance of metastases. Long-term survival for all patients in the W&W strategy might be quite similar to those with the conventional management, although this issue remains unclear.

Because of the current uncertainty in the long-term outcomes of W&W management, it is important to consider the patient's opinion, although a few studies have looked at it. In a German study of 49 patients, 83% of patients considered postponing surgery in case of cCR. Quarterly follow-up studies and a local regrowth rate of 25% were considered acceptable by 95% and 94% of the patients, respectively, while 41% were willing to accept a reduced cure rate for a W&W strategy [69]. Another Canadian study analyzed patient and physician preferences for W&W management relative to abdominal perineal resection in the setting of lower RC. Patients were willing to accept a 20% absolute increase in local regrowth (i.e., from 0 to 20%) and a 20% absolute decrease in overall survival (i.e., from 80 to 60%) with nonsurgical treatment compared with abdominal perineal resection, whereas physicians were willing to accept a 5% absolute increase in local regrowth (i.e., from 0 to 5%) and a 5% absolute decrease in overall survival (i.e., from 80 to 75%) with W&W management compared with abdominal perineal resection [70]. Although in general, we would expect broad acceptance of organ-sparing treatment, patient preferences and concerns regarding the various aspects of this strategy vary widely and require specific consideration to assist us in shared decision-making with our patients.

Multidisciplinary follow-up protocol

When a W&W strategy is proposed to the patient, strict multidisciplinary surveillance is necessary to recognize early tumor regrowth and recurrence. Although rectal adenocarcinoma with a cCR usually has an excellent prognosis, patients should know that a small risk of pelvic and metastatic disease exists during follow-up.

The surveillance protocol includes measurements of carcinoembryonic antigen levels in serum; DRE; rectoscopy; MRI for assessment of local disease; and computed tomography of the chest, abdomen, and pelvis for distant metastases. Intensive surveillance is recommended in the first two years following treatment, because most cases of regrowth occur during this period. Between 3 and 5 years post-therapy, monitoring can be less frequent. Based on international consensus recommendations, a follow-up schedule is proposed (Table 3). In addition to rectoscopy, a complete colonoscopy should be performed 1 year, 3 years, and 5 years after the diagnosis of RC. The use of positron emission tomography–computed tomography during surveillance is not recommended; however, if recurrence is diagnosed, it could be helpful to detect metastasis or locoregional disease [8].

Although W&W management avoids surgery complications, CRT may also result in long-term adverse events with a detrimental effect on the patient´s quality of life. High rates

Table 3 Follow-up schedule for patients in a watch-and-wait protocol

	1–2 years	3–5 years	> 5 years
CEA	3 months	6 months	Annually
DRE and visit	3 months	6 months	Annually
Rectoscopy	3–4 months	6 months	Annually
MRI	3–4 months	6 months	Annually
CT	6–12 months	12 months	–

CEA carcinoembryonic antigen, *DRE* digital rectal examination, *MRI* magnetic resonance imaging, *CT* computerized tomography of toxicity are observed in 42% of patients with NAT [71]. Therefore, anorectal, sexual, and urinary function should be monitored in patients receiving W&W management. The Low Anterior Resection Syndrome Score is recommended for measuring anorectal function. The EORTC QLQ-30 (European Organization for the Research and Treatment of Cancer Core Quality of Life Questionnaire) can be useful for the assessment of quality of life, but there are still no specific validated questionnaires for RC patients undergoing organ preservation.

Conclusions

W&W represents an opportunity to avoid major resection surgery in patients who achieve a cCR after NAT with the aim of improving long-term quality of life and functional outcomes. Despite the progressive increase in scientific evidence in recent years, the published studies on this strategy are characterized by marked heterogeneity in the selection criteria, treatment regimens, and response assessment criteria. In this context, there is no standardized approach to applying this strategy. This multidisciplinary consensus aims to help the specialists involved in the management of these patients to advance the implementation of this strategy on an individualized basis without forgetting the importance of including patients in the decision-making process.

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Author contributions Conception and design: MJS and RV. Manuscript writing: all authors. Final approval of manuscript: all authors. Accountable for all aspects of the work: all authors.

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Code availability Not applicable.

Declarations

Conflict of interest MJS has received speaker honorarium from Amgen, Merck, Pierre Fabre, Servier, MSD; travel grants from Amgen, Merck, Pierre Fabre, Servier; advisory honorarium from Amgen, Servier. RJ-R has received funding from JnJ, Abex, and BBraun. MB-B has received research grants from the ESGE/Medtronic. RV has been advisory board member of Roche, Merck, MSD, and AMGEN, and has received speaker honorarium from AMGEN, Roche, Merck, MSD, and Servier. R-GF, OH-R, JL-V, IM, J-RA, MVD-O, JLDT, MJF-A, and JS report no conflict of interest.

Ethical approval Not applicable.

Informed consent Informed consent/ethical approval is not required for this type of project.

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Consent to publish Not applicable.

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