



SEOM-GEMCAD-TTD clinical guidelines for localized rectal cancer (2025)

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Abstract

This guideline provides a comprehensive overview of the management of localized rectal cancer, highlighting recent major advances in therapeutic strategies. Accurate staging remains essential, as it informs treatment decisions and facilitates risk assessment. A pivotal development in rectal cancer treatment is the adoption of total neoadjuvant therapy (TNT), which has demonstrated improved tumor response, reduced risk of systemic recurrence, and enhanced survival outcomes. This approach enables a “watch-and-wait” strategy and conservative management that may render surgery unnecessary and preserves rectal function in patients who achieve a complete clinical response. By emphasizing a structured approach to staging, multidisciplinary evaluation, and innovative treatment pathways, this guideline aims to improve outcomes while minimizing the morbidity associated with rectal cancer treatment.

Keywords Rectal cancer · Total neoadjuvant treatment · Watch and wait

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Introduction

The Spanish Society of Medical Oncology (SEOM) Clinical Guidelines for localized rectal cancer aim to provide oncologists with evidence-based, practical recommendations for the diagnosis, treatment, and follow-up of localized rectal cancer, drawing on the latest scientific advances and clinical consensus in Spain.

Developed by a multidisciplinary panel of experts from SEOM, these guidelines integrate current international evidence with national clinical experience to support personalized, high-quality care for patients with rectal cancer.

Methods

This guideline is based on a systematic review of the literature and combines the latest available evidence with expert consensus. Recommendations are ranked using the Infectious Diseases Society of America–US Public Health Service Grading System for clinical guidelines. This system assigns levels of evidence and grades of recommendation to ensure that oncologists can apply evidence-based interventions when treating RC [1] (Table 1). Evidence-based recommendations are summarized in Table 2.

Incidence and epidemiology

Colorectal cancer (CRC) is the most common cancer in Spain, with an estimated 44,573 new cases expected in 2025, of which 14,646 will be rectal cancer (RC). The annual incidence of CRC stands at 85 new cases per 100,000

inhabitants, with a slight annual increase of 0.2%. CRC affects men more frequently than women, at a ratio of 3:2, and is a substantial cause of cancer mortality. In 2022, CRC was responsible for 15,198 deaths, corresponding to 13.7% of all cancer-related deaths in Spain [2].

Key risk factors for RC include advanced age, inflammatory bowel disease, and family history of CRC or adenomas. Lifestyle factors such as smoking, excessive alcohol consumption, a diet rich in red and processed meats, type II diabetes, scant physical activity, and obesity also play a significant role in RC development.

Most RC is sporadic, arising via the chromosomal instability (CIN) pathway. However, around 5–10% of cases are associated with deficient mismatch repair (dMMR), although hereditary conditions such as Lynch syndrome and familial adenomatous polyposis also contribute to the risk of RC. An increase in RC cases in individuals under the age of 50 has been noted; however, underlying causes remain unclear [3].

Diagnosis, pathology, and molecular biology

Clinical presentation and definition

RC commonly presents with rectal bleeding, altered bowel habits, and tenesmus. Most cases are adenocarcinomas. RC is defined as a tumor located within 15 cm of the anal margin, as measured by rigid sigmoidoscopy or magnetic resonance imaging (MRI). Depending on its location, RC is categorized into:

- Low: Up to 5 cm from the anal margin.
- Middle: 5 to 10 cm from the anal margin.
- High: 10 to 15 cm from the anal margin.

Table 1 Levels of evidence and grades of recommendation [1]

Levels of evidence	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts' opinion
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit; does not outweigh risk or disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally, not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Table 2 SEOM recommendations for the management of localized rectal cancer

	LE, GoR
<i>Diagnosis, pathology and molecular biology</i>	
MRI is the standard test to define locoregional clinical staging and predict the risk of recurrence	I, A
Multidisciplinary teams are mandatory to customize treatment	I, A
Universal MMR or MSI testing is mandatory in all newly diagnosed individuals with rectal cancer	I, A
<i>Staging and risk assessment</i>	
MRI reports should include tumor stage (T), nodal stage (N), tumor deposits, circumferential resection margin (CRM), mesorectal fascia (MRF) status, extramural venous invasion (EMVI), and tumor location	III, A
Accurate identification of all risk factors for rectal cancer is essential to predict local and/or distant recurrence and inform individualized treatment	III, A
<i>Management of local disease</i>	
Incidental pT1 rectal adenocarcinoma with favorable histologic characteristics may be managed with endoscopic polypectomy	III, A
For cT2-3 c N0-1 non-distal rectal cancer, TME remains the preferred strategy <i>although</i>	I, A
CRT followed by local excision techniques make organ preservation possible in many cases	I, A
Intensification of radiotherapy may increase CR rates, enabling more patients to pursue organ-preserving strategies	I, A
<i>Classic neoadjuvant strategies, total neoadjuvant treatment, and options without preoperative radiotherapy</i>	
cT3a-bN0 tumors located in the upper and middle rectum with no risk factors of local or distant relapse: TME surgery upfront	I, A
cT3a-bN1 tumors located in the upper and middle rectum: PROSPECT trial vs neoadjuvant CRT vs TNT	I, A
T2 N+, T3 b-c with no threat to the circumferential margin and eligible for sphincter-sparing surgery: PROSPECT trial vs neoadjuvant CRT vs TNT (RAPIDO trial, PRODIGE23 trial, or consolidation arm in OPRA trial)	I, A
T3N0 distal tumors: PROSPECT trial vs neoadjuvant CRT vs TNT	I, A
High risk for local recurrence: TNT (RAPIDO trial, PRODIGE 23 trial, or consolidation arm in OPRA trial)	I, A
High risk for distal relapse: TNT (RAPIDO trial, PRODIGE 23 trial, both arms of TNT in OPRA trial)	I, A
<i>Adjuvant chemotherapy</i>	
Consider adjuvant chemotherapy in individuals with rectal cancer treated with preoperative CRT in high-risk stages II and III; the level of evidence is low and provides benefit limited in DFS rather than OS	II, C
Decisions should involve patient–doctor discussions weighing benefits and potential toxicities	V, A
<i>Immunotherapy</i>	
Six months of treatment with dostarlimab is recommended for MSI-H/dMMR locally advanced rectal cancer	II, A
<i>Elderly and frail patients</i>	
Decisions in these cases should be made on an individual basis by a multidisciplinary committee with all the specialists involved in treatment	III, A
Local excision is a viable treatment option for small tumors after SCRT or CRT	II, B
<i>The watch-and-wait strategy</i>	
The W&W strategy should be agreed upon with the patient and discussed in a multidisciplinary committee	III, A
Based on current evidence, for individuals with well-documented cCR, W&W yields comparable oncological outcomes to surgery and should be presented as a therapeutic option	II, A
For subjects with ncCR, a delayed re-evaluation should be considered to determine if W&W is appropriate	III, B
Intensive follow-up with MRI and sigmoidoscopy is essential for W&W patients	I, A
<i>Follow-up, long-term implications, and survivorship</i>	
Clinical assessment and CEA determination should be performed every 3–6 months for the first 2 years, and then every 6 months for a total of 5 years	II, A
Yearly CT of the chest, abdomen, and pelvis should be performed for 5 years. More frequent testing should be contemplated for high-risk patients	I, A
A complete colonoscopy is recommended 1-year post-resection (or at 3–6 months if not performed preoperatively). Repeat colonoscopy is recommended at 3 years, and then every 5 years or more frequently depending on the findings	III, A
Recommendations as to healthy lifestyles, particularly with respect to diet and physical exercise, improved outcomes and quality of life should be made after treatment for rectal cancer	II, A

MRI, magnetic resonance imaging; MMR, mismatch repair; MSI, microsatellite instability; TME, total mesorectal excision; CRT, chemoradiotherapy; CR, complete response; TNT, total neoadjuvant treatment; DFS, disease-free survival; OS, overall survival; SCRT, short-course radiotherapy; W&W, watch and wait; ncCR, nearly complete clinical response; CT, computerized tomography

Diagnostic procedures

The initial diagnostic workup includes [4]:

- Complete history and physical examination.
- Laboratory tests, including a full blood count, liver and renal function tests, and serum carcinoembryonic antigen (CEA).
- Thoracic and abdominal computed tomography (CT) with intravenous contrast to assess metastatic disease.

A complete colonoscopy with biopsy is mandatory to confirm the diagnosis and exclude the presence of synchronous colonic tumors. In cases where obstruction prevents full colonoscopy, virtual colonoscopy is recommended. If neither colonoscopy nor virtual colonoscopy is possible, completion colonoscopy should be performed at 3–6 months post-surgery.

In early-stage disease (cT1–cT2), rectal endoscopic ultrasound (EUS) can be useful to determine tumor depth, though MRI remains the most accurate test to establish locoregional stage and predict the risk of local recurrence (LR) or metastasis [5]. MRI is crucial to guide treatment decisions. Positron emission tomography (PET) is not routinely indicated, although it may be worthwhile in tumors with a greater risk of distant metastases at diagnosis, such as those with elevated CEA or extensive extramural vascular invasion (EMVI) on MRI. In addition, it may be beneficial when delineating areas for radiotherapy in certain cases.

Pathology

Histopathological evaluation is necessary for precise tumor characterization. Initial endoscopic biopsy should collect information regarding the type of adenocarcinoma (intestinal, mucinous, signet-ring cells), histological grade (G1–G4), and status of DNA repair proteins. The endoscopic resection of polyps or small tumors can be both diagnostic and therapeutic, if it is performed en bloc to assess both the degree of invasion and margin status. In addition to the data required in the initial biopsy, the presence of budding and lymphovascular infiltration should be described to evaluate the risk of lymph node involvement and the need for surgery.

For mesorectal resections, the pathology report should include: classification of the total mesorectal excision (TME) quality; tumor grade (G); T stage (depth of tumor penetration); number of regional lymph nodes (N) examined and involved; proximal, distal, as well as circumferential margins; lymphovascular and perineural invasion; extranodal tumor deposits; tumor budding; and response to neoadjuvant therapy if applicable, using systems such as the Mandard TRG or AJCC that categorize the degree of fibrosis and tumor viability [6, 7].

Molecular biology

MMR testing is crucial to identify dMMR tumors. It has prognostic and therapeutic implications, particularly when neoadjuvant immunotherapy could become standard practice [8].

While it is necessary to analyze specific genomic alterations such as *RAS*, *BRAF V600E*, *NTRK*, and *HER2* in advanced tumors, as they may influence subsequent therapeutic decisions, such testing is not recommended in localized tumors [9]. After diagnosis, all cases must be discussed by a specialized, multidisciplinary team (MDT) to individualize treatment.

Staging and risk assessment

Pelvic MRI is the gold standard for locoregional staging and provides essential information for surgical planning (III, A) [10–12]. MRI is used to determine tumor depth (T), involvement of regional lymph nodes (N), circumferential resection margin (CRM), distance from the mesorectal fascia (MRF), extramural vascular invasion (EMVI), and invasion of adjacent structures, such as the anal sphincter complex in low tumors [11].

T1 tumors must be classified according to Haggitt and Kudo–Kikuchi stages, based on polyp morphology [6, 7].

The subdivision of category T3 RC into two subgroups of extramural spread (≤ 5 mm or > 5 mm) resulted in significant different overall survival (OS) and LR rates [13].

Testing for molecular biomarkers, such as MMR/MSI status, has likewise made it possible to establish different prognoses and levels of therapeutic response according to the presence/absence of said biomarkers. CEA levels and liquid biopsy can also guide monitoring and treatment decisions, in particular when assessing for minimal residual disease after local treatment [14].

The 8th edition of the TNM staging system for RC should be used for clinical and histopathological staging [15]. Nevertheless, all the above-mentioned factors, as well as MRI findings, must be pondered individually to assess the risk of both local and distant recurrence, and thus define the best treatment strategy.

Management of local disease (Fig. 1)

For early-stage RC (cT1–2N0), radical resection should ensure cure. Endoscopic polypectomy may be considered in cases of an incidental pT1 rectal adenocarcinoma finding with favorable histologic characteristics (absence of mucinous features or signet-ring cells, low grade, negative margins, absence of lymphovascular or perineural invasion,

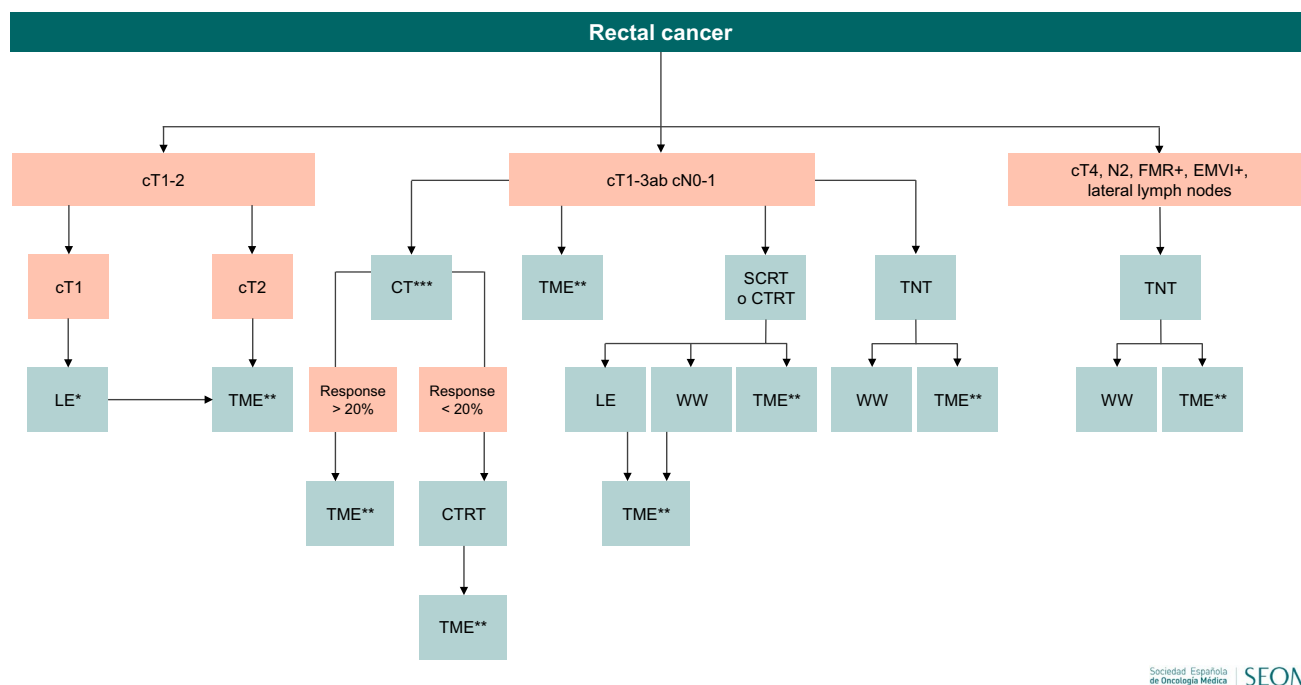


Fig. 1 Rectal cancer treatment algorithm. LE, local excision; TME, total mesorectal excision; CT, chemotherapy; CRT, concomitant chemoradiotherapy; SCRT, short-course radiotherapy; WW, watch and wait; TNT, total neoadjuvant therapy; MRF, mesorectal fascia;

EMVI, extramesorectal venous invasion. *If high-risk features, proceed to TME. **Consider adjuvant QT if high-risk stage II or stage III after surgery. ***If tumors are located in the upper and middle rectum

submucosal invasion depth < 1–2 mm and low-grade budding) [16].

In cT1 rectal adenocarcinoma with the previously described favorable histological criteria, local excision (LE) techniques, such as transanal endoscopic microsurgery (TEM) or transanal minimally invasive surgery (TAMIS), offer a less invasive option compared to radical resection. These approaches reduce morbidity, including sexual and urinary dysfunction, and reduce the likelihood of a permanent stoma in distal tumors. However, these techniques are associated with higher rates of LR compared to radical resection, although OS rates remain comparable [17].

Patients with cT1 tumors with adverse histological features, including lymphovascular invasion, high histologic grade, signet-ring cells, mucinous features, submucosal invasion depth > 2 mm, or positive margins, should undergo radical surgery with TME, given the elevated risk of LR [18, 19].

Stage cT2N0M0 tumors have a significant risk of occult nodal metastases (10–25%), and TME remains the preferred strategy, as local excision alone is associated with unacceptable LR rates of between 26 and 47% [20].

For smaller, early-stage, low RC (cT1–T3, cN0–1), neoadjuvant short-course radiotherapy (SCRT) or chemoradiotherapy (CRT), followed by LE or non-surgical management if complete clinical response (cCR) is achieved, can help

preserve rectal function and decrease TME morbidity (II, B). Trials report organ preservation rates of 70% in subjects with T1–T2N0 tumors receiving SCRT followed by LE [21, 22].

For T2–T3abN0–1 low RC with a favorable response to CRT, studies suggest similar outcomes in terms of LR, distant metastasis-free survival (DMFS), and OS compared to CRT followed by LE with TME. The phase 3 TAU-TEM trial yielded promising results, with 44.5% pathological complete response (pCR) and 82.7% organ preservation in the experimental arm, as well as reduced morbidity [23]. The intensification of RT in selected individuals can improve outcomes based on the results of trials such as MORPHEUS and OPERA. Both studies suggest that higher dose or longer duration RT could enhance tumor response, potentially leading to better rates of cCR. This intensified approach could make it possible for more patients to be eligible for conservative management (67% vs 99% 3-year organ preservation when tumors were < 3 cm and treated with contact X-ray brachytherapy in the OPERA trial). Long-term follow-up of ongoing trials will elucidate the full impact of such strategies [24, 25].

Management of locally advanced disease (Fig. 1)

Classical neoadjuvant strategies

Historically, preoperative CRT or RT was typically administered in stage II–III RC considering the observed decrease in LR rates, although these strategies have failed to prove a survival benefit. Moreover, tumors with no risk of LR are often overtreated. At present, a selective approach is preferred based on the risk of systemic and/or LR as shown by MRI. Tumors staged as cN2, MRF involvement, EMVI positive, or with lateral node involvement have a high risk of systemic recurrence, while tumors staged as cT4, with MRF involvement, requiring abdominoperineal amputation, or with the risk of anal sphincter involvement are at greater risk for LR. On the other hand, there is a clear consensus regarding the surgical indication for lateral lymph nodes. Lateral lymph nodes should be resected with a short-axis diameter ≥ 7 mm following neoadjuvant therapy, given the increased risk of locoregional and metastatic recurrence if left in situ [9].

Preoperative CRT was based on the German study that demonstrated less toxicity and better locoregional outcomes compared to postoperative CRT [26]. Concomitant 5-FU with preoperative RT (50.4 Gy) was administered in this trial. Concomitant capecitabine is not inferior to 5-FU and is now regarded as standard [27]. Oxaliplatin or targeted drugs combined with fluoropyrimidines have yet to demonstrate a clear benefit, although some studies report higher rates of pathological responses [28, 29].

In contrast, treatment consisting solely of SCRT has demonstrated a decreased rate of LR versus surgery alone [30]. No differences in LR or OS have been detected when comparing both strategies, notwithstanding more tumor downstaging in favor of CRT [31, 32].

Total neoadjuvant treatment

Given that preoperative CRT may be associated with better treatment compliance, allows full systemic doses of CT to be delivered, and can treat micrometastases early, the addition of preoperative CT to standard neoadjuvant CRT has been evaluated through several randomized trials; unfortunately, inclusion criteria were not homogeneous.

The PRODIGE 23 trial enrolled patients with stage II–III RC and displayed a benefit of induction TNT in 3-year disease-free survival (DFS), 3-year DMFS, and pCR compared to routine treatment [33]. Furthermore, at 7-year follow-up, the difference in OS in favor of the TNT arm was statistically significant [34]. The RAPIDO

trial studied patients with high-risk RC, defined as cT4ab, EMVI, cN2, involved MRF, or enlarged lateral nodes. The results revealed a benefit in 3-year disease-related treatment failure (DRTF), 3-year DMFS, and pCR with consolidation TNT [35]. The POLISH study reported that TNT improved 3-year OS rates in individuals with primary or locally recurrent RC involving adjacent organs (cT4) or a palpably fixed cT3 [36]. Finally, the STELLAR trial, a non-inferiority study of consolidation therapy in cT3–4 and/or N+ RC established that the TNT group had better 3-year OS, pCR, and cCR (21.8% versus 12.3%; $p=0.002$) [37]. These results prove that the benefit derived from TNT is associated with a reduced rate of distant metastases and an increased rate of pCR.

Despite these encouraging results, some concerns remain. A subsequent analysis of the RAPIDO trial showed a higher local recurrence rate in the R0 subgroup of the TNT arm (7.2% vs 3.9%; $p=0.049$) [38], raising legitimate questions. However, the proportion of patients undergoing surgery with curative intent was nearly significantly higher in the TNT group (92% vs 89%; $p=0.089$) [35], although this benefit was offset by the increased local recurrence rate.

Few studies have explored the benefits of consolidation over induction CT in the context of TNT. The OPRA study compared both TNT strategies in participants with stage II–III RC and found that consolidation therapy achieved greater rates of organ preservation. The results showed that both TNT strategies followed by non-surgical management in cases with a cCR enabled approximately 50% of patients to avoid surgery (TME-free survival 39% (95% CI, 32–48) in the INCT-CRT group and 54% (95% CI, 46–62) in the CRT-CNCT group ($p=0.012$)). In addition, no significant differences were detected in DFS or DMFS between patients managed with observation and those who underwent surgery, suggesting that TNT with consolidation may be an effective approach to avoid radical resection. A pooled analysis of the OPRA and CAO/ARO/AIO 12 randomized phase 2 trials demonstrated higher rates of CR with the consolidation strategy, with no differences in DFS [39]. The authors suggest that this should be regarded as the preferred TNT sequence if organ preservation is a priority (Table 3).

Options without preoperative radiotherapy

In cT3a-b, N0-1, and RC located in upper or middle rectum, the risk of local and systemic recurrence is low; therefore, neoadjuvant RT may be omitted and TME surgery should be proposed.

Recently, the PROSPECT trial has proven the non-inferiority of preoperative FOLFOX to preoperative CRT with respect to DFS with similar OS and LR rates in RC staged as T2N+, T3N0, or T3N+ in subjects eligible for sphincter-sparing surgery [40]. This strategy spares patients with low

Table 3 Randomized trials of total neoadjuvant therapy

Study	N	Eligibility	Treatment strategy	Primary endpoint	Primary outcome	pCR	DFS
POLISH II ³⁶	515	Fixed cT3 or cT4	SCRT-FOLFOX4×3-TME vs. CRT (FOLFOX)-TME	R0 resection	77% vs 71%	16% vs 12%	43% vs. 41%
STELLAR ³⁷	599	Distal or middle third T3–T4 and/or N+	SCRT-CAPOX×4-TME±CAPOX×2 vs CRT TME±CAPOX×6	3-year DFS	64% vs 62.3%	22.5% vs 12.6%	64% vs. 62.3%
RAPIDO ³⁸	912	cT4a/b, EMVI, cN2, CRM+ or enlarged lateral lymph nodes	SCRT-CAPOX×6/FOLFOX4×9-TME vs CRT-TME-CAPOX×8/FOLFOX4×12	3-year disease-related treatment failure	23.7% vs 30.4%	28% vs 14%	23.7% vs 30.4%
PRODIGE 23 ³³	461	cT3–T4	mFOLFIRINOX×12-CRT-TME-mFOLFOX×6/Cape×4 vs. CRT-TME-mFOLFOX6×12/Cape×8	3-year DFS	76% vs 69%	28% vs 12%	76% vs. 69%

EMVI, extramural venous invasion; CRM, circumferential resection margin; SCRT, short-course radiotherapy; TME, total mesorectal excision; CRT, chemoradiotherapy; R0, radical resection; DFS, disease-free survival; pCR, pathological complete response

risk of LR the toxicity of RT with early treatment of micro-metastases. Tumor site may guide neoadjuvant treatment, with the possibility of choosing preoperative CRT or TNT for tumors located in the lower rectum or that threaten the MRF, while opting for preoperative CT for tumors in other locations.

Adjuvant chemotherapy

Adjuvant chemotherapy is clearly recommended in patients with high-risk stage II and stage III colon cancer; however, the benefit of completing adjuvant therapy based on post-surgical pathological stage in rectal cancer has yet to be well defined. A benefit (OS, DFS) has been demonstrated with adjuvant 5FU-based chemotherapy following surgery in rectal cancer [41], albeit of less magnitude than in colon cancer, although it should be remembered that very few studies include TME and/or CRT/RT. More recent studies and meta-analyses that include CRT/SCRT have not confirmed any benefit with 5FU in monotherapy [42]. The combination of oxaliplatin with 5FU has demonstrated inconsistent benefit in DFS and no improvement in OS. Only two studies have revealed a benefit in PFS, the phase 3 AIO-04 study [29], which evaluated the addition of oxaliplatin as neoadjuvant and adjuvant therapy, and the phase 2 ADORE study [43], displaying a benefit in PFS, limited to OS in cases of ypN+.

With the positioning of TNT as the predominant strategy in the treatment of locally advanced RC, adjuvant CT following neoadjuvant CRT or upfront surgery has taken a secondary role.

Immunotherapy

There is preclinical and clinical evidence of the benefit of immunotherapy in dMMR or MSI-high colon and rectal tumors; in rectal cancer, dMMR accounts for 5–10% of the population [44].

The clinical evidence is supported by a phase 2 study with 16 participants with locally advanced stage II–III rectal cancer (75% cT3–4, 94% cN+) with dMMR, who received a total of 6 months of dostarlimab every 3 weeks [44]. Patients who achieved CR were allowed to undergo a watch-and-wait period, whereas those whose response was incomplete finished their treatment with CRT. At the time of publication, 12 of the 16 subjects who had completed treatment were in complete response (CR) (defined by MRI, endoscopic ultrasound, and DRE). These results can be confirmed by other studies in localized colon cancer (NICHE-1, NICHE-2), in which the combination of nivolumab and ipilimumab achieved complete pathological response rates of between 95 and 97% [45]. Regardless of these spectacular results, more mature follow-up and survival data are necessary. The role of RT (SCRT/LCRT), chemotherapy, duration of treatment with immunotherapy, and sequence of treatment are questions that remain to be answered in the dMMR and pMMR populations.

Exceptional, patient-specific situations

Although TME surgery is the optimal curative approach, elderly and frail individuals with RC may not always be able to undergo a surgical procedure. No standardized treatment regimen or guidelines are available for these people, and some patients receive no treatment at all, resulting in debilitating symptoms with impaired quality of life. Although survival has improved significantly among elderly patients, clinicians should bear in mind that overall 1-year mortality is around 10–15% [46] and, among the frailest, risks of surgical treatment are even higher and may outweigh benefits, with 2-year mortality rates exceeding 40% [47] and undesirable functional outcomes that reduce quality of life (bowel, urinary and sexual dysfunction) in more than 50% [48]. Data from the literature reveal that 30% of older patients

(> 70 years) who did not undergo surgery received no treatment at all; this percentage rose to 41% in those over the age of 80 years and in those with multimorbidity, with a 3-year OS of 9% [49].

Considering the lack of scientific evidence endorsing a specific type of treatment, we propose that these cases be addressed on an individual basis by a MDT (including surgeons, oncologists, radiotherapists, anesthesiologists, and geriatricians) with the aim of prioritizing quality of life and functional recovery over oncological results, using tools such as patient prehabilitation prior to deciding which therapy to prescribe. A comprehensive geriatric assessment or frailty screening should be performed prior to treatment in patients over 70 years of age, given their higher risk of toxicity and early mortality [9].

Regarding different treatments, bibliographic data are controversial insofar as radiotherapy is concerned. Preliminary results from the NACRE randomized trial indicate that all patients over 75 years of age completed a SCRT regimen, while 14% did not complete the CRT regimen; the number of adverse effects was higher than in the SCRT regimen. CRT regimens in patients fit to receive them have demonstrated better disease control with subsequent surgery [50].

Local excision is a reasonable option (low morbidity and mortality, good functional results) for treating small residual tumors after performing CRT or SCRT in the elderly and frail individuals unable to undergo complete TME.

Watch and wait strategy for rectal cancer

The watch and wait (W&W) strategy for RC has become a major alternative to traditional surgical resection, especially in patients achieving a cCR following neoadjuvant therapy. This approach focuses on monitoring patients closely after treatment, delaying or avoiding surgery unless tumor regrowth or recurrence is observed.

Scientific evidence

The Habr-Gama group pioneered the W&W approach in RC management. In 2009, they reported that adding CT after neoadjuvant CRT raised cCR rates to 65% in people with distal RC, making it possible for many to avoid surgery. A 2014 follow-up study demonstrated that 30% of these patients experienced regrowth. Nevertheless, most were successfully treated with salvage surgery, maintaining high local control rates and OS and DFS comparable to those who underwent immediate surgery [51].

In 2021, Jiménez-Rodríguez et al. demonstrated that using TNT resulted in cCR rates of 50–60%, thereby significantly augmenting the likelihood of avoiding surgery. The authors suggested that TNT might be a better option for

more advanced tumors, offering greater local control without the need for surgical resection [52].

In 2019, the International Watch & Wait Database (IWWD) provided robust, multicenter evidence that 25–30% of subjects managed with W&W suffer LR within the first 3 years of follow-up [53]. Most of these recurrences can be treated with salvage surgery, achieving R0 resection rates of approximately 90%. Moreover, the 5-year OS for W&W patients is comparable to those who undergo immediate surgery, with survival rates exceeding 80%, underpinning the oncological safety of this approach.

Meanwhile, Garcia-Aguilar et al. published the only prospective, randomized study that incorporates the WW strategy based on response to TNT in 2022 [54]. The study sample comprised 324 patients with stage II/III RC who were randomly assigned to two TNT strategies: induction CT followed by CRT (INCT-CRT) or CRT followed by consolidation CT (CRT-CNCT). Participants achieving cCR or near-complete response (ncCR) were eligible for W&W, while those with incomplete responses (iCR) underwent TME. Individuals treated with W&W after TNT exhibited comparable 3-year DFS and MDFS to those undergoing immediate surgery. After 5 years, the organ preservation rate was higher in the CRT-CNCT group (54%) compared to the INCT-CRT group (39%), suggesting that consolidation CT improves organ preservation. Tumor regrowth occurred in 36% of subjects undergoing W&W, primarily within the first 2 years, and was more common in cases of ncCR versus cCR. Despite these differences, DFS rates were similar, with 5-year DFS at 71% for INCT-CRT and 69% for CRT-CNCT, displaying comparable oncological control [55].

A secondary analysis of the OPRA trial explored the relationship between tumor response grade and oncological outcomes. Participants were divided into three categories: cCR, ncCR, and iCR. At 3 years, 77% of the cCR cohort maintained organ preservation compared to 40% of the ncCR group. The risk of tumor regrowth was higher among ncCR patients (51.1%) in contrast to cCR patients (22%). Nevertheless, most ncCR cases were successfully managed with salvage surgery, without affecting OS [56].

Timing of tumor response evaluation

The timing of response evaluation post-TNT remains controversial. International consensus recommendations propose that time points for response assessment and cCR determination should be selected in keeping with the trial design and treatment strategies [57]. After TNT with CRT and either induction or consolidation CT, response assessment should be conducted 34–38 weeks after treatment initiation (OPRA study) [58].

An analysis of 1,010 patients from IWWD categorized them into those who achieved cCR at the first evaluation and

those who did so at subsequent evaluations. Organ preservation rates were comparable between both groups: 77.8% for initial cCR and 79.3% for delayed cCR. Furthermore, 5-year OS rates were 92.2% for early cCR and 86.0% for delayed cCR, i.e., with no statistically significant differences, endorsing the option to extend observation periods to maximize organ preservation in initially partial responders [59].

Follow-up protocols for W&W

In W&W patients, intensive follow-up is essential. Recommended surveillance involves MRI and sigmoidoscopy every 3 months during the first 3 years, followed by semi-annual evaluations for the next 3 years. CT scans should be performed semiannually in the first 3 years and annually thereafter to monitor the progression of distant disease. High-definition endoscopes should be used for these imaging techniques, and routine biopsies are not necessary unless clinically indicated.

Gollub et al. (2023) published an introductory guide on MRI as a critical tool in W&W, particularly in cases in which cCR is not initially achieved [60]. This imaging technique enables tumors to be re-assessed after prolonged surveillance, which may lead to late cCR in some people. It can also predict local recurrence before it becomes clinically evident, making it possible to perform early interventions and potential salvage surgeries. However, interpreting MRI images poses challenges; for instance, scar tissue can mimic residual tumors, leading to false positives. This underscores the need for standardized protocols to improve diagnostic accuracy.

Follow-up, long-term implications, and survivorship

Post-treatment surveillance of CRC should be conducted to evaluate possible therapeutic complications, discover recurrences that are potentially eligible for curative resection, and identify new metachronous neoplasms at a preinvasive stage.

It has been well documented that 25–40% of cases of stage II or III RC will recur. Patients with locally advanced RC have a higher risk of recurrence (around 80% within the first 3 years after surgery and 95% within the first 5 years) and benefit more from follow-up. In addition, approximately 7% of subjects will present with metachronous colon tumors.

Long-term follow-up care for RC patients is indispensable, given the potential side effects of curative treatments, such as chemoradiotherapy and surgery. These therapies, while effective in controlling cancer, can lead to bowel, urinary, and sexual dysfunction, significantly impacting quality of life. Regular monitoring helps to identify and manage

these issues early, providing interventions that can improve functional outcomes.

Debate persists as to the selection of optimal surveillance strategies after potentially curative CRC surgery. Meta-analyses conclude that more intensive surveillance results in earlier detection of recurrence with the possibility of local salvage, with no effect on survival [61]. In line with most expert groups and published guidelines [9, 62], we recommend intensive postoperative surveillance for individuals with resected stage II or III RC who would be regarded as candidates for curative-intent surgery. Surveillance testing should not be performed in people with severe comorbid conditions or advanced age [63].

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Data availability Data sharing is not applicable to this article as no datasets were generated or analyzed.

Declarations

Conflict of interest Maria José Safont Aguilera: fees for attendance at conferences and courses from Amgen, BMS, Merck, Sanofi, Servier, and fees as a speaker or consultant: Amgen, Bayer, BMS, GSK, Merck, Pierre Fabre, Sanofi, Servier, and Takeda. Rosario Vidal Tocino reports speaker and other fees from Servier, BMS and Merck; advisory board from GSK and Bayer; advisory board, speaker and other fees from MSD and Amgen; other fees from Roche and Speaker from Astellas and Pierre Fabre. Vicente Alonso Orduña: fees for advisory board from AMGEN and speaker fees from Novartis, Merck and Servier. Ferrán Losa Gaspá, Encarna González-Flores, María Luisa Limón Mirón, José Luis Manzano Mozo, María del Carmen Riesco Martínez, Elena Asensio Martínez, and Ruth Vera García have nothing to disclose.

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