

REVIEW

What is the watch and wait strategy in the treatment of lower rectal cancer?

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ABSTRACT

Surgery following neo-adjuvant chemoradiotherapy has been the standard in the treatment of lower rectal cancer for some time, providing good oncological outcomes. However, for patients who achieve a clinical complete response, in addition to surgery, the concept of a watch-and-wait (W&W) strategy, has been developed, that is, simply monitoring these patients with no surgical intervention. The W&W strategy can ensure a significantly higher organ preservation rate but with similar oncological outcomes as in patients after total mesorectal excision. Thus, the W&W strategy is considered an attractive treatment choice to avoid major surgery and permanent stoma, in patients with lower rectal cancers. It is also a valid treatment strategy for patients who are willing to accept potentially worse oncological outcomes to achieve this goal.

Keywords: words: watch and wait, rectal cancer, neoadjuvant chemotherapy, neoadjuvant chemotherapy, TME

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Introduction

CNeo-adjuvant chemoradiotherapy (nCRT) followed by TME is now the standard protocol for the treatment of lower rectal cancer¹. It leads to a reduction in the size and staging of the tumor, improvement in the rate of R0 resection and sphincter preservation, a decrease in the chances of local recurrence, and achieves clinical complete response (cCR) or even pathological complete response (pCR) in some patients².

Rectal cancer treatment has become a multidisciplinary challenge with personalized approaches according to individual patients' characteristics³.

The development of high-resolution MRI imaging over the past decade has diversified treatment recommendations, from using the same schedule of neoadjuvant chemoradiotherapy followed by TME surgery and adjuvant chemotherapy for all locally advanced tumors (cT3-4 or N+ M0) toward a variety of more individualized options⁴ (Figure 1).

Surgery following nCRT has been the standard in the treatment of rectal cancer for some time, providing good oncological outcomes. However, the potential sequelae of such radical surgery include long-term urinary and sexual dysfunction, and fecal incontinence. There are also immediate postoperative risks, such as bleeding, infection, and anastomotic leak^{5,6}.

From the patients' perspective, most patients would prefer to avoid the need for a temporary or permanent stoma, maintaining gut function and quality of life⁷.

The Watch-and-Wait (W&W) strategy

It is generally accepted that patients with no clinical, colonoscopic, or imaging evidence of residual tumor after nCRT should be considered as having achieved cCR, while pCR is generally defined as no residual tumor cells or positive lymph nodes (ypT0N0M0) in the resected specimens after nCRT.

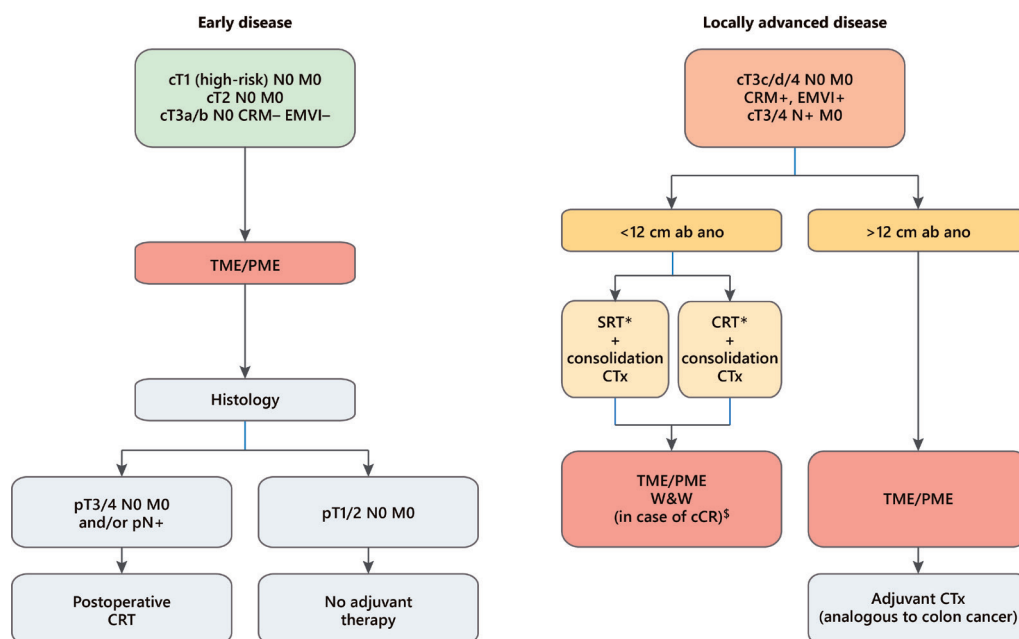


Figure 1. Flowchart of the current treatment standard (with permission)³.

Patients with rectal cancer receiving nCRT have a pathological complete response rate varying from 10 to 20%. In previous studies, approximately 20–30% of rectal cancer patients achieved cCR after nCRT, and 5–44% of patients achieved pCR. Those that achieved pCR had significant benefits in terms of local control and long-term survival⁸.

Currently, there is no standardized definition of cCR, but it can be preliminarily summarized as follows:

- (1) No palpable tumor on digital rectal exam.
- (2) No residual tumor, nodules, or white scar observed on endoscopy, and negative biopsies from the white scar tissue.
- (3) No suspicious lymph nodes on MRI, and substantial downsizing with no residual tumor or residual fibrosis on MRI and CT⁹.

These three modalities: digital rectal examination, endoscopy and MRI, which are considered to be the pillars of assessing response after nCRT, and they have accuracy of 98% to predict the absence of tumor¹⁰.

For patients who achieve a clinical complete response (cCR), the concept of a watch-and-wait (W&W) strategy has developed. The principle of this strategy is the careful monitoring of these patients, without surgical intervention. This concept uses clinical complete response (cCR) as a surrogate marker for pathological complete response (pCR), and in place of this, there is a rigorous follow-up regimen that is required to detect tumor regrowth¹¹.

The W&W strategy can ensure a significantly higher organ preservation rate with similar oncological outcomes as in patients after total mesorectal excision (TME). Thus, the W&W strategy is considered an attractive treatment choice to avoid major surgery and permanent stoma, especially for distal rectal cancers^{5,11}.

The rationale behind the watch-and-wait (W&W) strategy is the knowledge that 20% to 30% of patients receiving neoadjuvant chemoradiotherapy (naCRT) will achieve pCR¹². Furthermore, besides avoiding surgery, patients with pCR have been reported to achieve better outcomes in 5-year disease-free survival and overall survival^{13,14}.

However, despite the strong shift toward personalized medicine, there are currently no reliable methods to identify patients who have achieved a pCR. The challenge with the “watch and wait” approach is therefore identifying the appropriate patients for this strategy^{5,15}.

Follow-up of patients using the watch-and-wait (W&W) strategy

For patients in whom we have decided to apply the watch-and-wait strategy, careful and rigorous follow-up consists of digital rectal examination, CEA, endoscopy, MRI, and PET/CT. The evaluation of cCR should be performed at intervals of 6–8 weeks or longer after nCRT^{5,16}.

The W&W approach is recommended for managing patients who have achieved cCR, and it entails regular physical examination and imaging examinations at intervals of 2–4 months¹⁷.

Digital rectal examination

Clinical examinations are needed every 2 to 4 months for the first 2 years, and imaging every 6 months to detect local regrowth and/or distant recurrence.

The term “tumor regrowth” has been incorporated over time in place of local tumor recurrence in patients with cCR. Tumor regrowth is the preferred term, because any residual tumor not completely eradicated by nCRT has the ability to regrow over time. Other authors have used a set time period to denote tumor regrowth, for example, the reappearance of a tumor within 12 months’ follow-up. The limitation of this definition is that a significant proportion of patients develop tumor regrowth beyond the initial 12 months. Therefore, to ensure that all patients were included, and to prevent bias, any patient in the “watch and wait” group with a tumor identified during the surveillance, regardless of the time point, was included in the analysis⁵.

CEA

It is reported that serum carcinoembryonic antigen (CEA) < 5 ng/dL after nCRT is a good prognostic

factor for rectal cancer, which is related to the complete regression of the tumor after nCRT. Therefore, cCR must be comprehensively evaluated by oncologists, endoscopists, and radiologists^{16,18}.

Endoscopy

The majority of patients with luminal CR (>70%) can be identified by endoscopy, and a flat white scar with or without telangiectasias and the lack of ulceration or nodularity are the most predictive features to identify CR¹⁹.

However, 26 – 36% of patients show other subtle morphological abnormalities, such as small or large flat ulcers, irregular tissue, or residual adenomas, which are more difficult to interpret, leading to a considerable risk of missing residual disease or CRs¹⁰.

New endoscopic techniques with computer aided diagnosis (CAD), using advanced imaging such as narrow band imaging (NBI) or magnifying chromoendoscopy, are designed to aid endoscopists in evaluating the histology of mucosal lesions, for example, by predicting submucosal invasions into advanced adenoma^{20,21}.

Clinical practice is shifting from providing a W&W approach in only typical cCR (a flat white scar without any surface irregularities at the first response assessment) to also selecting patients with a 'near CR' (ulcers, irregularity or adenoma), who may develop a flat white scar at a second reassessment after another interval. The definition of this so-called 'near CR' is unclear, and

the subtle abnormalities are difficult to interpret with endoscopy alone^{20,22}.

MRI

The criteria for assessment of response to post neoadjuvant chemoradiotherapy (NACRT) are MRI using T2-high resolution (T2-HR), MRI based MR-TRG by the MERCURY study group, diffusion weighted imaging (DWI) patterns and their combination²³.

The MRI features of cCR include a scar not thicker than the rectal wall, only a dark T2 signal, no visible lymph nodes, no restricted diffusion, and the lack of or low signal on the apparent diffusion coefficient map²⁵.

The addition of radiological assessment has shown encouraging results in increasing the detection of pCR. Two of the most promising modalities are PET/CT and MRI with diffusion weighted imaging.

PET/CT

PET/CT is used in predicting cCR, reporting an accuracy approaching 91%. When clinical assessment is combined with PET/CT, the accuracy increased to 96%^{5,26}.

Local Resection

All rectal cancer patients treated with the W&W approach who have no evidence of disease progression or recurrence after 1-year follow-up were defined as

Table 1. Criteria for response assessment on post neoadjuvant chemoradiotherapy MRI using T2-high resolution MRI based MR-TRG by Mercury study group, diffusion weighed imaging patterns and their combination²⁴

MR-TRG	T2-HR MRI	DWI	Combination of T2 HR and DWI
1.	Normal rectal wall or thin band of fibrosis	No foci of restricted diffusion	T2 HR 1/2/3 + DW 1
2.	Thick band of fibrosis with doubtful residual tumor	Few scattered foci of restricted diffusion	T2 HR 2/3 + DW 2
3.	Fibrosis/mucin > 50% with tumor	C-shaped band or nodular focus of restricted diffusion	T2 HR 2/3 + DW 3
4.	Little fibrosis, mostly tumor	Smaller than pre-Rx MR	T2 HR 4 + DW 4
5.	No response or progression	No change since previous	T2 HR 5 + DWI 5

sustained cCR, while patients who had not achieved cCR were supplemented with LE or RS.

Local resection should be performed if there are suspicious residual lesions after 10 weeks, and close follow-up is suggested if the pathology of the resected specimen is ypT0¹⁶.

History of the watch-and-wait (W&W) strategy and the problem of this approach

A watch-and-wait (W&W) approach for patients with rectal cancer following clinical complete response (cCR) to NAT is a nonstandard approach, but it has become more widely practiced with the advent of total neoadjuvant therapy, and with increasing demand by patients in the context of a cCR.

In 2002, Nakagawa et al. pioneered the concept of non-surgical treatment for patients who achieve cCR after nCRT²⁷.

In 2004, Habr-Gama et al. introduced a clinical trial with observational management of rectal cancer patients who achieved cCR after nCRT¹¹.

Thereafter, Appelt et al. proposed that high-dose chemoradiotherapy could be used to increase cCR, and the approach was named "Watchful Waiting"²⁸.

Subsequently, Habr-Gama et al. reported that timely salvage surgery was also effective in rectal cancer patients who relapsed during treatment with the W&W modality²⁹.

The basic problem of the published studies on the W&W strategy is that the numbers of reported patients were small. The largest series was reported within the International Watch & Wait database, comprising data of more than 1,000 patients. Their oncological outcome was reported to be similar to standard therapy including TME surgery. However, up to 25% of the initial cCR patients developed a local regrowth within the first 2 years of follow-up. The 5-year overall survival and disease-specific survival were 85% and 94%, respectively³⁰.

Since most tumor regrowth is endoluminal, many patients can be directed to salvage surgery, and it is

speculated that this would not compromise the oncological outcome due to delayed surgical resection³¹. However, long-term data from randomized trials are lacking for this situation³. One reason for the development of tumor regrowth after initial cCR may be explained by the response pattern induced by CRT.

Interestingly, only half of the patients who experienced local regrowth developed distant metastasis. The distant metastasis rate of the watch-and-wait group ranges from 8 to 10%³⁰. This suggests an oncological risk of local regrowth that may not be mitigated by aggressive surveillance and surgical salvage. It is said that the median time for development of distant metastasis in patients in the watch-and-wait group is similar to that of the surgical group. This indicates that distant metastasis may occur before the decision to perform surgery or watch-and-wait.

We have to emphasize that tumors with higher T3 sub-stages often cannot be determined as having cCR after a good response because of the obvious ulceration and residual thickening of the rectal wall³². Furthermore, radiosensitivity increases with less tumor infiltration, and a tumor with a larger volume (or tumor length and circumferential extent) has a very low expected cCR rate³³.

This tells us that there is a strong possibility of achieving empirical cCR in patients who have small or early-stage rectal cancers, determined by baseline MRI as an objective radiological assessment.

At least 5-year survival data is mandatory to preclude late tumor recurrence after TNT and further verify oncological safety.

Although in some patients with cCR after CRT, TME may no be longer necessary, the challenge is still to identify the true responders by clinical assessment. Most of the current evidence for W&W is retrospective, making prospectively collected data of great value.

Ideal proof of the safety of a W&W strategy would come from a prospective study in which patients with cCR would be randomized to W&W or TME. Unfortunately,

it is unlikely that patients with a cCR will accept randomization to such different treatment plans.

Even with the possibility of tumor regrowth and the development of distant metastases, patients are prepared to accept the W&W strategy. In some studies, as many as 83% patients are said to be willing to consider a W&W strategy if they achieved cCR in spite of the higher rate of local regrowth during the first 2 years of follow-up³⁴. More interestingly, up to 30% of patients are willing to sacrifice higher rates of long-term oncological cure in comparison with clinicians³⁵.

Conclusion

The WW strategy can give a significantly higher organ preservation rate but with similar oncological outcomes as in patients after total mesorectal excision.

Thus, the WW strategy is considered an attractive treatment choice to avoid major surgery and permanent stoma, especially for distal rectal cancers. It is also a valid treatment strategy for patients who are willing to accept potentially worse oncological outcomes to achieve this goal. Careful, rigorous follow-up is key in this strategy.

Disclosure of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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