



Watch and wait strategies for rectal cancer

A systematic review

In Ja Park

Department of Colon and Rectal Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Received: October 21, 2021

Revised: November 17, 2021

Accepted: December 6, 2021

Corresponding author:

In Ja Park

Department of Colon and Rectal Surgery, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: +82-2-3010-3937
E-mail: ipark@amc.seoul.kr

ABSTRACT

Watch and wait (WW) strategies have been suggested for patients with clinical complete regression (cCR). The WW approach was first introduced by Habr-Gama in patients with cCR after neoadjuvant treatment. Actually, it is not “no surgery” but “deferral of surgery”; therefore, the WW approach or non-operative management is a representative term currently. The number of publications regarding WW for rectal cancer has increased abruptly. We conducted a systematic review of PubMed for literature published on WW. It is now one of the most interesting issues in rectal cancer treatment. Many studies have reported comparable overall survival with WW and radical resection. However, a high local regrowth rate is a problem, and proper salvage management is the main concern in the WW approach. Adequate patient selection is necessary to achieve favorable oncologic outcomes. However, the appropriate definition and diagnostic method for cCR have not yet been clearly defined. Indeed, advances in local control have not translated into overall survival improvement, and many efforts have been made to improve distant metastasis control and overall survival and improve clinical response to preoperative chemoradiotherapy. In this review, oncologic outcomes, ongoing efforts to improve oncologic outcomes, and limitations for clinical practice were evaluated and described.

Keywords: Clinical complete regression; Neoadjuvant therapy; Rectal neoplasms; Watch and wait

INTRODUCTION

Over the past 100 years, the field of rectal cancer surgery has undergone various surgical developments. In addition, there have been huge changes in technical and oncological aspects accompanied by preoperative chemoradiotherapy (PCRT) during the last 20 years [1-5]. The introduction of PCRT has brought about the most innovative changes in the treatment of rectal cancer. PCRT, which is focused on the reduction of local recurrence, has shown differences in oncological outcomes according to the regression of various tumors after PCRT, which influences the strategy of subsequent surgical treatment.

Total mesorectal excision (TME), an approved standard surgical treatment for rectal cancer, is associated with perioperative morbidity and impaired quality of life [6-9]. Therefore, treat-

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ment strategies that maintain quality of life without compromising oncologic outcomes have gained attention gradually. In patients with complete regression after PCRT (15% to 30% of the patients), organ-preserving approaches, such as local excision and watch and wait (WW), have been attempted based on several studies reporting favorable oncologic outcomes in these patients. Local excision is advantageous in that it confirms the pathologic T stage. Pathologic lymph node metastasis status, however, cannot be detected. Furthermore, some studies have reported that a long interval between completion of PCRT and surgical intervention improved tumor response; therefore, WW, which defers surgery with close surveillance, has recently gained more support [10]. Various efforts, such as total neoadjuvant therapy (TNT), are being attempted to obtain clinical complete regression (cCR) in patients.

However, the diagnostic method to determine whether the patient is suitable for the application of WW is still inaccurate and has limitations in that the standards for subsequent surveillance methods are not clear. In this review, the oncological results of the application of WW to rectal cancer patients who underwent PCRT and the evidence for the applicable patient diagnosis and subsequent surveillance are investigated.

METHODS

The PubMed database was queried using the following search terms: (“rectal cancer”) OR (“rectal neoplasm”) AND (“preoperative chemoradiotherapy”) OR (“neoadjuvant therapy”) OR (“neoadjuvant chemoradiotherapy”) AND (“complete regression”) OR (“good response”) AND (“Watch and wait”) OR (Non-operative management) OR (Deferral of Surgery) OR (“Wait and see”) OR (“Organ preservation”). All literature published prior to September of 2021 was then screened. Articles were excluded if they were not available abstract in English. All articles were screened by one author (IJP). Articles were reviewed and contents were described as five sections based on their reported data.

ONCOLOGIC OUTCOMES OF WW

WW for patients with clinical complete or near-complete regression after PCRT provides the undeniable benefits of avoiding surgical complications and deterioration of quality of life. Though these advantages are important, the oncological outcomes are the prime focus of WW and should not be compromised. Until now, TME is the standard surgery for rectal cancer, so the oncological outcome should not deteriorate compared to that with TME. In the case of pathologic complete regression (pCR) after PCRT, radical resection has

Table 1. Oncologic outcomes of watch and wait approaches for rectal cancer treated with preoperative chemoradiotherapy: comparison with radical resection

Study	Year	Number		FU duration (mo)		Local recurrence (%)		Distant metastasis (%)		Cancer-related death (%)	
		WW	RS	WW	RS	WW	RS	WW	RS	WW	RS
Habr-Gama et al. [18]	2004	71	22	57.3	48	2.8	0	4.2	13.6	0	9.1
Maas et al. [22]	2011	21	20	25	35	4.7	0	0	5	-	-
Smith et al. [24]	2012	32	57	28	43	18.8	0	9.3	5.3	3.2	0
Ayloor Seshadri et al. [16]	2013	23	10	72	72	30.4	0	13	20	-	-
Lee et al. [20]	2015	8	28	41	41	25	3.5	0	10.7	0	10.7
Li et al. [21]	2015	147	51	58	58						
Araujo et al. [15]	2015	42	69	47.7	46.7	19	4.7			62 ^{a)}	82.7 ^{a)}
Renehan et al. [23]	2016	129	109	33	33	-	-	-	-	96 ^{b)}	87 ^{b)}
Lai et al. [19]	2016	18	26	49	42	11.1	0	-	-	-	-
Yeom et al. [26]	2019	15	129	60	60	40	12.4	26.7	3.8	-	-
Beard et al. [17]	2020	53	42	-	-					95 ^{b)}	100 ^{b)}
Wang et al. [25]	2020	59	179	60	60	11.9	0.5	10.2	9.5	-	-

FU, follow-up; WW, watch and wait; RS, radical surgery.

^{a)}Disease-free survival; ^{b)}Overall survival.

been reported to have a very good prognosis [11-14]. Therefore, if CR can be diagnosed clinically, careful implementation of organ-preserving with WW may be attempted.

Many studies compared oncologic outcomes between patients who underwent WW with those who underwent radical resection (Table 1) [15-26].

We cannot discuss WW without mentioning the Habr-Gama series. Habr-Gama, a pioneer in WW, first proposed WW for treating rectal cancer patients with cCR after PCRT in 2004 [18]. With this approach, survival outcomes were found to be comparable to those with radical surgery. The 5-year disease-free survival (DFS) and overall survival (OS) rates after cCR in the WW group were 92% (vs. 83% in the radical surgery group) and 100% (vs. 88% in the radical surgery group), respectively. Habr-Gama obtained the same conclusions from the extended cohort [27-30]. Since then, several other studies have reported similar long-term cancer-related survival or OS with WW in comparison with radical resection.

Smith et al. [31] reported the retrospective data of 113 patients who achieved cCR after PCRT using WW strategies. The 5-year DFS was significantly lower in those who underwent WW (75%) than in those who achieved pCR after TME (92%), but this was mainly due to the high local regrowth rate in the WW group (20%). However, 5-year DFS was not different between WW and TME for pCR (90% vs. 98%), and distant metastasis rate was 8% in WW patients, which was comparable to that reported for patients attaining pCR after TME (4%) in their study and the previous reports. Therefore, we can assume that patients with cCR after PCRT would be willing to accept WW strategies based on the benefit of rectal preservation, and the risk of disease progression was at the expected level. However, a high local regrowth rate is a concern and the strategies for proper surveillance must be actively explored.

Since the number of patients who indicated for WW is small and no definite guidelines regarding when and how to determine cCR with which diagnostic modalities have been provided, conducting randomized controlled trials (RCTs) is challenging for practical and ethical reasons. The supporting data are based mainly on institutional case series and some recent prospective trials implementing various treatment and surveillance strategies. The worldwide interest in WW became the background for the foundation of the International Wait & Watch Database (IWWD). It was established in 2014 and aimed to collect all available data on organ-preserving strategies and evaluate the benefits, risks, and oncologic safety of these approaches [32]. They reported oncologic out-

comes of 880 (87%) patients with cCR among 1,009 patients collected in the database. Distant metastasis was diagnosed in 71 (8%) of 880 patients [33]. The 5-year OS rate was 85% (95% confidence interval [CI], 80.9% to 87.7%) and the 5-year DFS rate was 94% (95% CI, 91% to 96%). The 2-year cumulative incidence of local regrowth was 25.2%. They reported, using conditional survival analysis estimates, that patients who sustained a cCR for 3 years had a less than 2% risk of developing systemic recurrence thereafter during the median long-term follow-up of 55.2 months [34]. Habr-Gama group [35] also studied recurrence risk over time and she reported that recurrence has been known to occur within the first 2 or 3 years after completion of surgery in rectal cancer patients who received PCRT and usually patients who are disease-free for an initial 2 or 3 years, seem disease-free for a long time.

Based on previous reports, it has been proved that WW strategies provide significantly higher sphincter preservation without compromising OS and DFS. However, the high local regrowth rate needs to be improved, and the detection of local regrowth at optimal timing for salvage remains the main challenge.

PATTERN OF FAILURE AFTER WW

When WW fails, we encounter problems that are difficult to handle, such as diagnosing local regrowth and deciding the timing to provide salvage. Indeed, many patients were reluctant to undergo salvage surgery for fear of surgery or stoma. A high local recurrence rate (15% to 30%) is an important oncologic concern in patients with cCR who undergo the WW strategy. Studies comparing radical resection for pCR reported significantly higher local recurrence rates in the WW group. This was mainly due to local regrowth. This might be caused by an inaccurate diagnosis of cCR. The assessment of cCR is usually performed using a combination of digital rectal examination (DRE), flexible endoscopy, and magnetic resonance imaging (MRI) [10,14,18,36-38]. Although the experience and accuracy of these techniques are increasing, the accuracy of diagnosing cCR is not satisfactory because the detection of small foci of residual tumor cells or lymph node involvement is difficult with these techniques.

Little is known about the predictive factors of local regrowth. The InterCoRe consortium evaluated the factors affecting local regrowth after WW for patients with a cCR following chemoradiotherapy in rectal cancer from the data of 11 studies including 605 patients with a median follow-up of 37.6 months [39]. In this meta-analysis, increasing cT stage

was reported to be associated with an increased risk of local regrowth. Predictive factors for local regrowth may be used to set surveillance timely; therefore, we need to try to identify predictive factors of local recurrence in cCR patients using the WW approach.

To detect local recurrence for performing optimal salvage, proper timing and identifying the location of local recurrence is important. The majority of local recurrences occurred within the first 2 to 3 years after the start of the WW strategy, and intraluminal recurrence consisted of 80% to 90% of local recurrences. The IWWD reported that 24% of the cases showed local regrowth and 88% occurred within 2 years. Among regrowth cases, 97% were confined within the bowel wall [33]. Smith et al. [31] reported a 20% local regrowth rate in their retrospective study. Of the 22 regrowths, 19 (86%) had an endoluminal component detectable on DRE and endoscopy in the absence of symptoms. Wang et al. [40] conducted a propensity score matching analysis of WW with radical resection for patients with cCR after PCRT. During the median follow-up of 38.2 months (interquartile range [IQR], 25.9 to 52.4), 14 patients in the WW group had local regrowth, of which 13 (92.9%)

were located in the bowel wall and one (7.1%) was located in the regional lymph nodes. These local recurrence patterns, which are mainly localized to intraluminal growth, would be more eligible than extraluminal pelvic local recurrence.

Unmanageable pelvic recurrence is troublesome and results in frustrating oncological outcomes and poor quality of life [41-43]. The prevalence of the unsalvageable disease is quite low among local recurrences, although the salvage rate varies from 50% to 100% according to the previous studies (Table 2) [14,17,22,23,28,31,33,39,40,42,44-46]. The OnCoRe project [23] also reported a high salvage rate of 88%, which was similar to that described by Chadi et al. [39] (89%) and the Habr-Gama group (90%) [28]. Smith et al. [31] reported that timely surgical salvage could be performed in 20 of 22 (90%) patients with local regrowth and 111 of 113 (98%) overall, with careful surveillance. However, other studies reported salvage rates lower than 70%, with 68.6% as described by On et al. [45] and 69% reported in the IWWD [33]. However, the rate of “technically” unsalvageable disease was quite low in most of the reports, and we need to consider that even radical resection could not guarantee absolute local control even for patients

Table 2. Salvage surgery for patients with local regrowth who undergo watch and wait strategy

Study	Year	Patients	Regrowth (%)	Luminal regrowth only (%)	Salvage surgery (%)	Type of salvage surgery (%)	Disease-free survival (%)
Maas et al. [22]	2011	21	4.7	4.7	100	Transanal endoscopic microsurgery	89 ^{a)}
Habr-Gama et al. [28]	2014	71	31	92.8	89.2	APR (44), AR (28), local excision (28)	88 ^{b)}
Renehan et al. [23]	2016	129	34	93.2	84	APR (49), AR (20), other resection (7)	96 (3-year OS)
Kong et al. [42]	2017	370	28.4	-	83.8	-	-
van der Valk et al. [33]	2018	1,000	25.2	97	86	TME (78), local excision (22.3) ^{c)}	85 ^{d)}
Chadi et al. [39] ^{e)}	2018	602	28	-	89	-	87 ^{d)}
Dattani et al. [44] ^{e)}	2018	692	22.1	-	88	Sphincter preservation (45.3)	93.5 ^{b)}
On et al. [45] ^{e)}	2019	248	12.1	80	83.3	APR (40), LAR(20), other resection (8), local excision (28)	-
Smith et al. [31]	2019	113	19.4	86	100	APR (41), LAR (41), local excision (9), other resection (9)	75 ^{d)}
Park et al. [14]	2019	42	28.2	77.8	88.9	APR (25), sphincter saving resection (37.5), local excision (25)	-
van der Sande et al. [46]	2020	385	23.1	73	94.4	APR (27.4), LAR (40.5), local excision (30.9), induction CTx+CRT+APR (1.2)	90.3 ^{a)}
Beard et al. [17]	2020	53	11.3	-	66.7	APR (50), LAR (50)	95 ^{f)}
Wang et al. [40]	2021	94	14.9	92.9	85.7	APR (41.7)	88 ^{g)}

APR, abdominoperineal resection; AR, anterior resection; OS, overall survival; TME, total mesorectal excision; LAR, low anteriorresection; CTx, chemotherapy; CRT, chemoradiotherapy.

^{a)}2-year; ^{b)}3-year; ^{c)}Surgical information was available in 69% of patients who received salvage surgery; ^{d)}5-year; ^{e)}Systemic review; ^{f)}Cancer specific survival; ^{g)}Non-regrowth free survival.

with pCR, as meta-analysis reported a 2.8% local recurrence rate in this group of patients [47].

In the era of the WW approach, the focus has shifted to local recurrence than distant metastasis. A study comparing local excision with radical resection for T1 rectal cancer reported that the risk of distant metastasis increased in patients who did not receive radical resection [48-51]. Thus, it is likely that the risk of distant metastasis following WW increases. However, in patients with cCR, distant metastasis following WW was reported to be comparable to that after radical resection in patients with pCR in many studies [16,18,22,24,25]. In a recent meta-analysis of 17 reports [52], the pooled data demonstrated a 9.2% risk of distant metastasis in the total group, 23.1% in the local recurrence subgroup, and 5.5% in the non-local recurrence subgroup. The risk of additional distant metastasis attributed to the omission of immediate surgery was low at 3.0%. This might be because selected patients with favorable tumor characteristics would undergo WW strategies.

However, the timing of distant metastasis might be different and related to local recurrence, and we need to consider the relationship between local recurrence and distant metastasis for surveillance.

LIMITATION IN EVALUATION OF TUMOR RESPONSE

Although non-operative management appears attractive in both oncologic and functional aspects, it also has limitations for application in real practice, including diagnostic method of cCR, follow-up guidelines, and lack of evidence in the treatment of failed cases. In many reports, cCR was compatible with pCR in only a small proportion of patients. Imaging modalities, including MRI, computed tomography, and positron emission tomography (PET), do not have sufficient accuracy to diagnose cCR. The best diagnostic test for response assessment after PCRT remains controversial. However, MRI has gained consensus as a standard method among the imaging modalities used for local staging [53].

The role of MRI in evaluating the response to PCRT in rectal cancer has focused on the detection of the clinical complete response of primary tumors. A pooled analysis reported that MRI had 75% accuracy, 95% sensitivity, 31% specificity, 83% positive predictive values, and 47% negative predictive values to detect cCR [54]. Based on these results, we may assume that MRI can be more useful in ruling out cCR rather than determining cCR. To improve the diagnostic accuracy of

cCR using MRI, diffusion-weighted imaging-MRI, which provides a functional assessment of the tissues, was also tested; however, its efficacy in confirming cCR was unclear [38,55-57].

For the evaluation of tumor response to PCRT, two methods are generally used: tumor downstaging based on pre-PCRT clinical stage and MRI-based tumor regression grade (mrTRG) based on morphologic changes (Fig. 1). Tumor downstaging was applied earlier than mrTRG; however, it showed considerable differences with pathologic tumor stage, even only for the primary tumor stage between the clinical and pathological stages because current imaging modalities are not accurate enough for clinical staging and lack of standardization of clinical staging criteria.

Tumor regression does not always result in tumor downstaging. Therefore, TRG was adapted to evaluate the amount of residual tumor. mrTRG was developed to mimic the pathologic TRG. The 5-tier system is usually applied; however, it is difficult to differentiate trivial morphological changes, and the consistency between mrTRG and pathologic TRG was quite variable with differences of 7% to 29% (Fig. 2) [36,58-70]. Therefore, recently, a more simplified form of mrTRG was suggested to discriminate between good and poor responders.

The response evaluation time was also important for detecting cCR. Long-term delay to surgery following the completion of PCRT is associated with an increased likelihood of achieving a pCR. Gambacorta et al. [71]. conducted a pooled analysis of seven international randomized trials to evaluate the optimal time to obtain the highest rate of pCR after PCRT. According to the pooled analysis, the cumulative pCR rate increased significantly when the interval to surgery lengthened, with 95% of pCR events within 10 weeks after completion of PCRT. Therefore, close to 10 weeks after PCRT, more cCR would be detected. MRI findings also showed serial changes according to the increased interval after PCRT. Therefore, we need to standardize the time point of response evaluation to determine the most optimal method to confirm the response to PCRT [72].

Although MRI is widely accepted as the standard method of response evaluation to PCRT for rectal cancer, there are still concerns regarding the advantages and disadvantages of each modality, and how to interpret inconsistency among imaging studies is still required to find a more effective and accurate method to evaluate tumor response. In addition, a combination of physical examination, endoscopy, and MRI findings was used to determine the regression level to overcome the limitations of one diagnostic modality. Ko et al. [73]

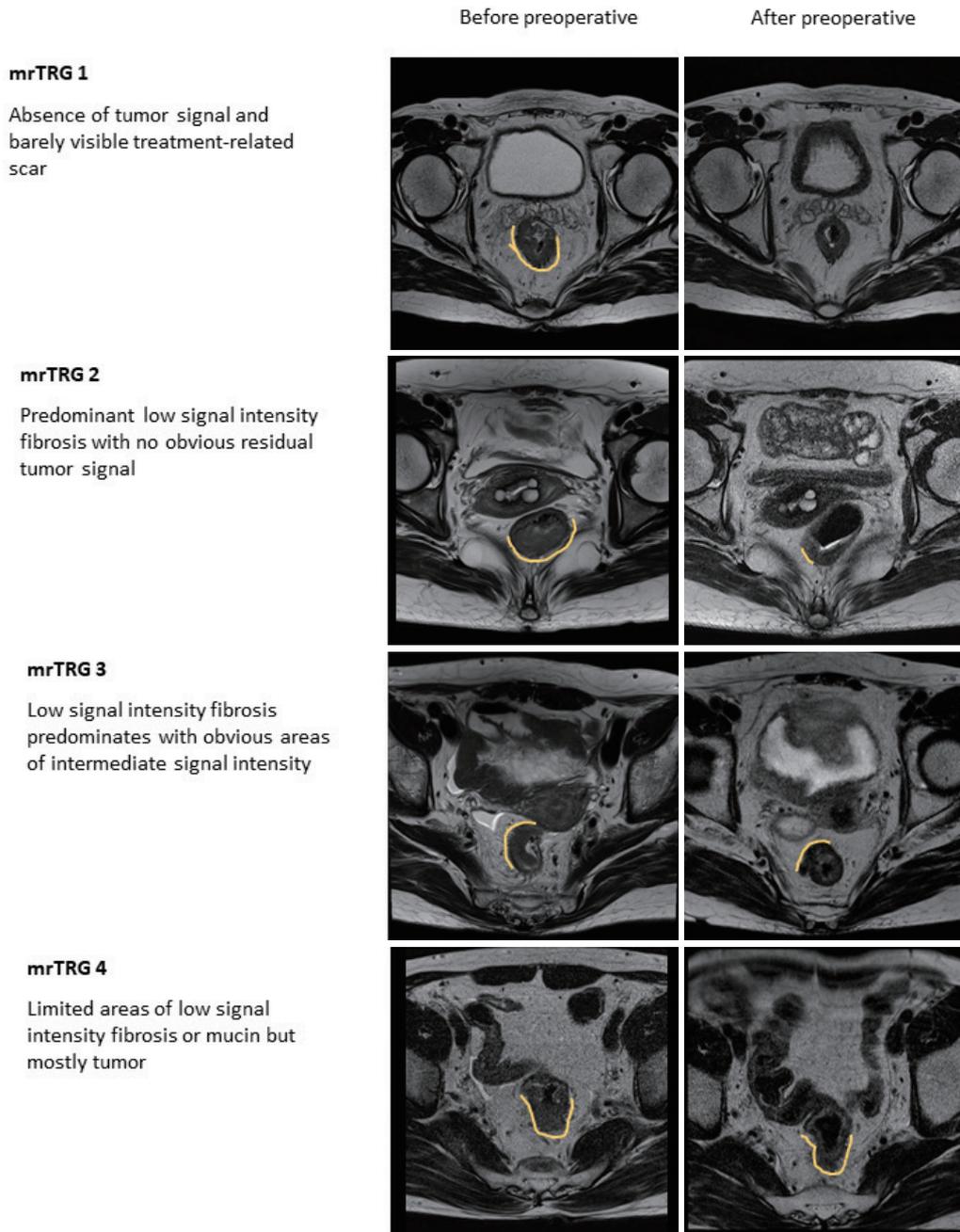


Fig. 1. Magnetic resonance imaging based tumor regression grade (mrTRG). mrTRG categorized tumor regression extent using tumor characteristics and degree of fibrosis, similar to the pathologic tumor regression grade system.

reported that a combination of endoscopy and T2 weighted-MRI increased the identification rate of CR and indicated a 92.6% correction rate in these cases. Crimi et al. [74] attempted to combine morphologic changes identified with MRI and functional information with PET and showed that the mean standardized uptake values of PET had a significant positive correlation with pathologic TRG ($\rho=0.480$; $P=0.037$) and could be used as a complementary method to MRI for response evaluation. There have been studies on the

development of genetic biomarkers for response evaluation [75-78] combined with imaging results.

The rate of lymph node metastasis was up to 16% after PCRT in patients with cCR of the primary tumor [13,41,61,79]. Previously studied methods for response evaluation generally focused on the primary tumor response. The accuracy of lymph node evaluation was much more limited, the optimal criteria for malignant lymph nodes were not clearly defined, and studies were heterogeneous [80-82]. The metastatic lymph

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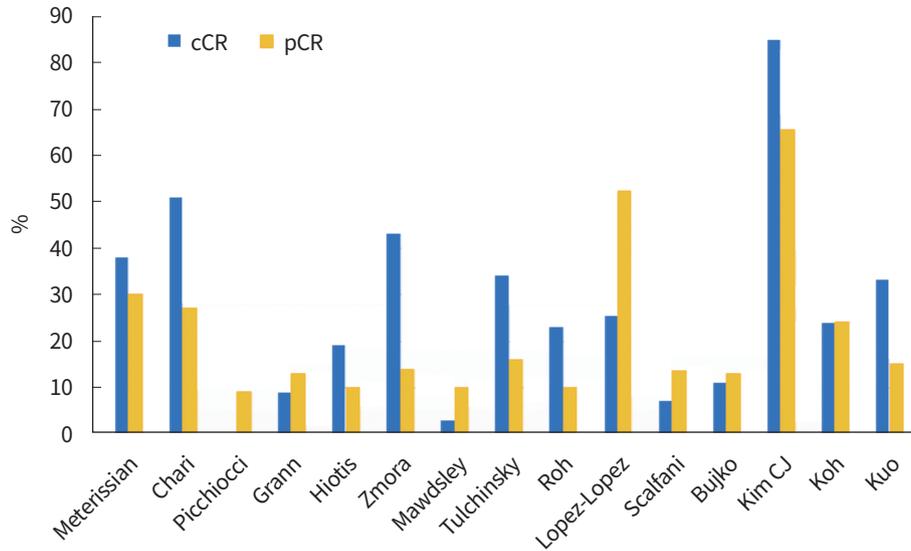


Fig. 2. Consistency between pathologic and clinical complete tumor regression. It showed various discrepancies among studies. cCR, clinical complete regression; pCR, pathologic complete regression.

Table 3. Tumor regression and oncologic outcomes after total neoadjuvant therapy for rectal cancer in prospective trials: comparison with preoperative chemoradiotherapy

Study	Year	Number		TNT type	pCR (%)		Local recurrence (%)		Distant metastasis (%)		Overall survival (%)	
		TNT	PCRT		TNT	PCRT	TNT	PCRT	TNT	PCRT	TNT	PCRT
GCR 3 [96]	2010	56	52	Induction	14	13	5	2	23	22	75 ^{a)}	78 ^{a)}
Bhatti [97]	2015	65	47	Induction	-	-	18.4	23.4	24.6	25.5	70 ^{a)}	47 ^{a)}
POLISH II [94]	2016	261	254	Consolidation	16	12	22	21	30	27	73	65
RAPIDO [93]	2021	462	450	Consolidation	28.4	14.3	8.3	6	20	26.8	89.1	88.8
PRODIGE-23 [95]	2021	231	230	Induction	27.8	12.1	4	6	21.2	28.3	91	88

TNT, total neoadjuvant therapy; PCRT, preoperative chemoradiotherapy; pCR, pathologic complete regression; GCR 3, Grupo Cáncer de Recto 3 Study; RAPIDO, Rectal cancer And Preoperative Induction therapy followed by Dedicated Operation; PRODIGE, Partenariat de Recherche en Oncologie Digestive.

^{a)}5-year overall survival, others are 3-year overall survival.

node is a potent determinant of prognosis. Lymph node metastasis was relatively associated with tumor depth; therefore, patients with pCR would have a low possibility of lymph node metastasis [13,83]. However, many reports have shown worse oncologic outcomes in patients with metastatic lymph nodes, even in pCR patients. Therefore, we must consider lymph node status together to evaluate the response after PCRT. We need to determine how to evaluate lymph node status after PCRT as well as the primary tumor response.

THE ROLE OF TNT IN THE ERA OF WW

Improving the cCR rate has become more interesting as the interest in WW increases. Various methods for improving cCR

have been tested by modifying radiotherapy or chemotherapy. The simplest approach is to extend the time between the completion of PCRT and reassessment. Several studies have shown that extending the interval between chemoradiotherapy and surgery increased pCR rates [65,84-87]. Most patients who were indicated to undergo PCRT had locally advanced recurrent cancer, and the risk of distant metastasis was rather high [88]. Therefore, progression of disease or micrometastasis over a long interval without any treatment was considered. In the patients who did not receive PCRT, delay in adjuvant chemotherapy has been known to adversely impact colonic and rectal cancer survival, whereas completion of PCRT is associated with improved oncologic outcomes [89-91]. In order to reduce distant metastasis in pa-

tients who received PCRT, TNT has emerged and increased because patients who undergo PCRT have the potential to develop WW strategies [34,92-96]. TNT has benefits in terms of improving compliance, better tolerability, and possible earlier treatment of micrometastatic disease.

As the TNT protocol has not yet been established, various methods are being tested (Table 3) [93-97]. Prospective trials combining short-/or long-course radiotherapy and consolidation/induction chemotherapy have been conducted and have reported promising results. Recently, two noticeable RCTs conducted by expert cooperative groups, including the Rectal cancer And Preoperative Induction therapy followed by Dedicated Operation (RAPIDO) and Partenariat de Recherche en Oncologie Digestive (PRODIGE) 23 trials, reported results [93,95]. RAPIDO was an international collaboration driven by the Dutch Colorectal Cancer Group (DCCG) and the Nordic Gastrointestinal Tumour Adjuvant Therapy Group (NGTATG), and PRODIGE was by French national study supported by the Unicancer Gastrointestinal, Fédération Francophone de Cancérologie Digestive (FFCD), Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR), and Groupe Français Chirurgie du Rectum (GRECCAR). The RAPIDO trial compared short-course radiotherapy followed by six cycles of capecitabine and oxaliplatin (CAPOX) to long-cycle CRT with capecitabine, and no adjuvant chemotherapy was administered to the TNT arm. In PRODIGE23, TNT included 12 weeks of upfront triplet chemotherapy (i.e., modified FOLFIRINOX: oxaliplatin, leucovorin, irinotecan, and fluorouracil [mFOLFIRINOX]) followed by CRT, surgery, and 12 weeks of adjuvant chemotherapy (fluoropyrimidines with or without oxaliplatin). The differences between the two trials were the type of neoadjuvant chemotherapy (induction vs. consolidation), duration of radiotherapy (short vs. long-course), and adjuvant chemotherapy.

In the RAPIDO trial [93], disease-related treatment failure including progression, R2 resection, recurrence, new primary colorectal cancer, cancer- or treatment-related death occurring at 3 years in 23.7% of patients treated with TNT and 30.4% of those who had received standard therapy (hazard ratio [HR], 0.75; $P=0.019$). Serious adverse events occurred similarly in both groups. Although local recurrence was reported to be higher in the TNT arm (17% vs. 10%), distant metastasis occurred less frequently in the TNT arm (67% vs. 81%). The PRODIGE 23 set the 3-year DFS rate as the primary endpoint, which was 76% in the TNT group and 69% in the standard-of-care group (stratified HR, 0.69; 95% CI, 0.49 to 0.97; $P=0.034$) at a median follow-up of 46.5 months (IQR,

35.4 to 61.6). Both studies showed consistent results in terms of pCR rate, which was significantly higher in the TNT group than in the control group (28.4% vs. 14.3% in RAPIDO, 27.8% vs. 12.1% in PRODIGE 23) and decreased risk of 3-year distant metastasis rate (7% vs. relative risk 25%). Although many questions about TNT remain unanswered, we assume that TNT would be introduced rapidly in the era of PCRT based on the results from these trials.

Organ Preservation in Rectal Adenocarcinoma (OPRA) phase II trial compared the outcomes between induction and consolidation chemotherapy directly [98]. Patients assigned to the investigation arm received systemic chemotherapy using an induction approach (INCT; before PCRT) or a consolidation approach (CNCT; after PCRT). The decision for TME or WW was based on restaging with DRE, MRI, endoscopy, and/or biopsy, and TME was recommended for patients with no clinical response. In the interim results [99], they found no difference in DFS between patients treated with TNT and selective WW or TME, compared to historical controls treated with CRT, TME, and adjuvant chemotherapy. The order of PCRT and systemic chemotherapy did not affect survival outcomes; the 3-year DFS between the INCT and CNCT arms did not differ (77% vs. 78%, $P=0.63$). However, the time to TME-free period was significantly higher in the CNCT group, and patients who received PCRT followed by systemic chemotherapy were more likely to preserve the rectum compared to patients treated with systemic chemotherapy first. They also categorized patients into three groups according to clinical response (complete, incomplete, and near-complete) and analyzed DFS, OS, and organ preservation. In patients with near-complete response, OS was comparable to that of the patients with clinical complete response, and more than half (52%) achieved organ preservation at 3 years. The OPRA trial suggests the effect of TNT in terms of organ preservation and a more favorable sequence of treatment; however, the survival benefit of TNT remains unclear.

Previously reported and ongoing trials reported the advantage of TNT in terms of organ preservation and distant metastasis control consistently; therefore, TNT would be more popular in applying the WW strategy. However, the treatment sequence, benefit on OS, and detection and management of local regrowth still need to be further evaluated.

SURVEILLANCE

Lack of consensus and expertise in surveillance strategies for patients undergoing WW strategy after PCRT is one of the

major limitations for clinical practice. It is also challenging to make patients adhere to the surveillance. Another barrier in the community is the lack of insurance coverage for interval endoscopy and MRI. Clarification criteria for patient selection and lowering local regrowth rates would improve acceptance and make this approach more generalizable.

Without a clear guideline, most centers performed intensive follow-up in the WW group comparing with patients who underwent radical resection, especially in the first 2 years [22,24,30,84,100,101]. In addition to surveillance of distant metastasis, endoscopy is the main tool for follow-up evaluation for the detection of local regrowth, and MRI has been increasingly used. The utility of performing additional biopsies is highly controversial because the false-negative rate is high and residual disease could not be confirmed with negative biopsy results [37,59,102].

In the initial 1 to 2 years after the WW approach, surveillance was focused on the detection of local regrowth because it was troublesome and caused frequent failures in the WW approach. However, current modalities with endoscopy and MRI have limitations in detecting local regrowth and cannot be compensated with frequent examinations. Therefore, we need to establish a surveillance protocol carefully considering the risk factors of distant metastasis as well as local regrowth and timing of recurrence. We also have to make an effort to find other surveillance methods for complementary imaging modalities, such as genetic biomarkers or combined protocols.

CONCLUSION

WW approaches are an extreme form of treatment for rectal cancer, which can be carefully applied to a subset of patients. Previous evidence has indicated that WW has comparable long-term oncologic outcomes compared with radical resection for patients with cCR or near CR. TNT was successful in achieving cCR/pCR in more patients. Supporting data for WW applications has increased. However, we must consider that we might be deprived of a chance of curative surgical treatment by applying WW in some patients. Radical resection is considered a standard treatment of choice to overcome various limitations in diagnosis, surveillance, or salvage treatment for cCR after neoadjuvant chemoradiotherapy for rectal cancer.

In addition, improving the accuracy of diagnosis of cCR or local regrowth, an efficient biomarker to detect response, and optimal surveillance protocols still need to be solved.

We also tried to determine the treatment sequence that leads to the most effective outcomes and the effect of adjunctive treatments/agents. Furthermore, we keep in mind that TNT has a risk of overtreatment.

Considering the limitations of applying WW, it is not a general treatment for patients who show a good response to PCRT; however, the application of WW would increase, and we have to prepare to adapt WW in clinical practice wisely.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORCID

In Ja Park

<https://orcid.org/0000-0001-5355-3969>

AUTHOR CONTRIBUTIONS

Conception or design: IJP.

Acquisition, analysis, or interpretation of data: IJP.

Drafting the work or revising: IJP.

Final approval of the manuscript: IJP.

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