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Is clinical complete response as accurate as pathological complete response in patients with mid-low locally advanced rectal cancer?

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Purpose: The standard treatment for locally advanced rectal cancer involves neoadjuvant chemoradiation followed by total mesorectal excision surgery. A subset of patients achieves pathologic complete response (pCR), representing the optimal treatment outcome. This study compares the long-term oncological outcomes of patients who achieved pCR with those who attained clinical complete response (cCR) after total neoadjuvant therapy, managed using a watch-and-wait approach.

Methods: This study retrospectively evaluated patients with mid-low locally advanced rectal cancer who underwent neoadjuvant treatment from January 1, 2005, to May 1, 2023. The pCR and cCR groups were compared based on demographic, clinical, histopathological, and long-term survival outcomes.

Results: The median follow-up times were 54 months (range, 7–83 months) for the cCR group (n = 73), 96 months (range, 7–215 months) for the pCR group (n = 63), and 72 months (range, 4–212 months) for the pathological incomplete clinical response (pICR) group (n = 627). In the cCR group, 15 patients (20.5%) experienced local regrowth, and 5 (6.8%) developed distant metastasis (DM). The pCR group had no cases of local recurrence, but 3 patients (4.8%) developed DM. Among the pICR patients, 58 (9.2%) experienced local recurrence, and 92 (14.6%) had DM. Five-year disease-free survival rates were 90.0% for cCR, 92.0% for pCR, and 69.5% for pICR (P = 0.022). Five-year overall survival rates were 93.1% for cCR, 92.0% for pCR, and 78.1% for pICR. There were no significant differences in outcomes between the cCR and pCR groups (P = 0.810); however, the pICR group exhibited poorer outcomes (P = 0.002).

Conclusion: This study shows no significant long-term oncological differences between patients who exhibited cCR and those who experienced pCR.

Keywords: Rectal neoplasms; Neoadjuvant chemoradiation therapy; Pathological complete response

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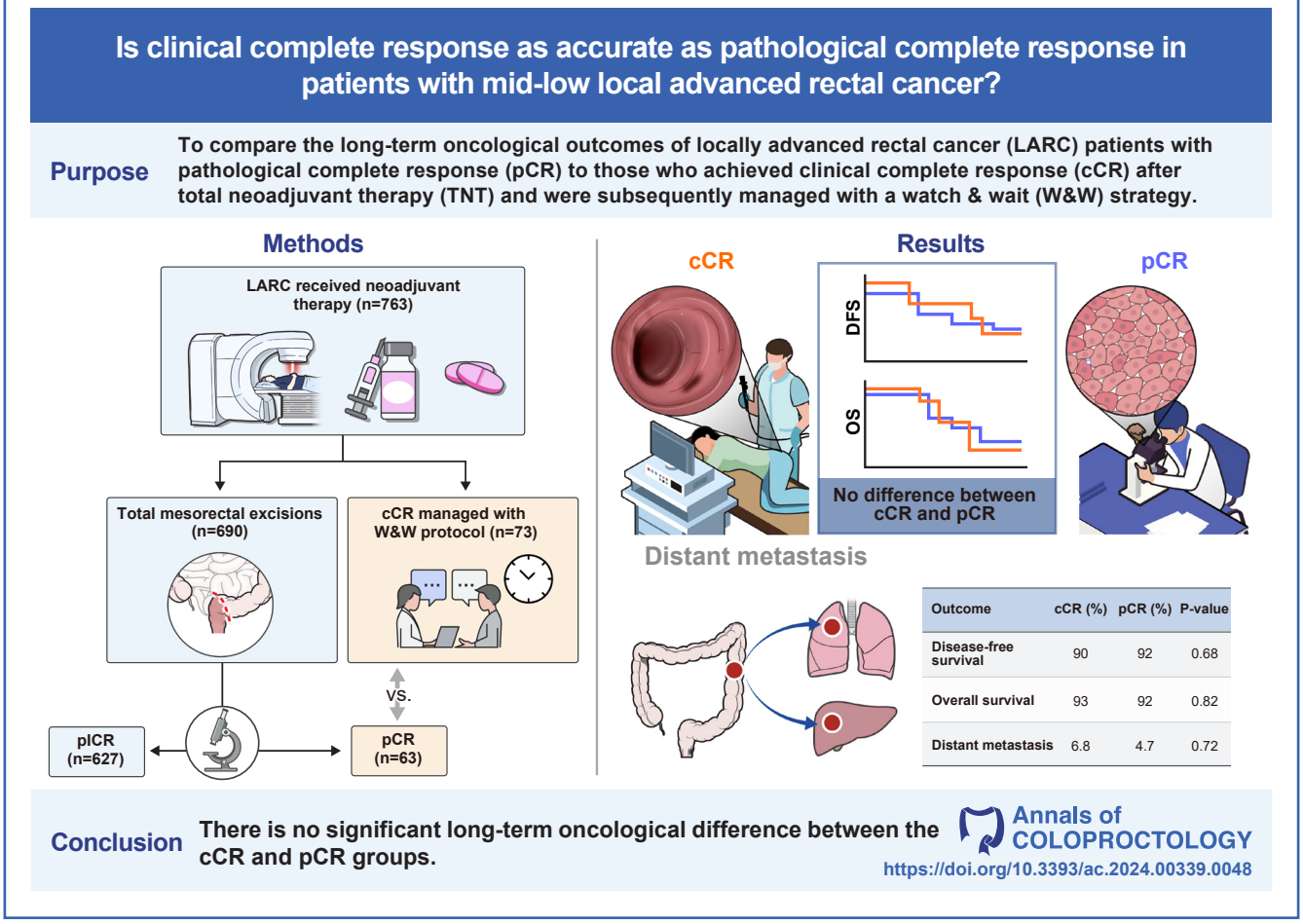
Graphical abstract



INTRODUCTION

Total mesorectal excision (TME) is the gold standard for treating rectal cancer [1]. The widespread adoption of TME has decreased the global rate of local recurrence (LR) to between 4% and 10% [2–7]. Neoadjuvant therapy (NAT) has been shown to further reduce the incidence of LR in cases of locally advanced rectal cancer (LARC) [8]. The use of NAT has also introduced the concepts of clinical complete response (cCR) and pathological complete response (pCR) [9].

In TME specimens, achieving a pCR represents the most favorable response to NAT, whereas incomplete responses indicate reduced treatment efficacy. More specifically, favorable long-term oncological outcomes are consistently linked to achieving pCR [10]. However, pCR can only be determined after the surgical procedure and subsequent specimen assessment.

Rectal cancer surgery is technically challenging and carries significant risks, including the possibility of requiring a stoma. Complications such as anastomotic leak can lead to sepsis, and there is an elevated risk of nerve damage that may result in sexual and urinary dysfunction [11–13]. Furthermore, this surgery often results in suboptimal sphincter function, increasing the likelihood of developing low anterior resection syndrome (LARS) following sphincter-preserving resections. Notably, between 50% and 90% of patients who undergo a low anterior resection report symptoms of LARS [7, 14]. Within this subgroup, approximately 5% may require a permanent stoma [15].

Over the past 2 decades, there has been a growing focus on improving quality of life and functional outcomes for patients undergoing rectal cancer resection [16]. The watch-and-wait (W&W) approach has attracted significant interest due to its potential to obviate the need for surgery, thereby sparing patients from associated complications and facilitating organ preservation. Habr-Gama et al. [9, 17] demonstrated that selected patients with a cCR could be safely managed without immediate surgical intervention, providing evidence for the safety and efficacy of the W&W strategy, which not only improves quality of life and functional outcomes but also reduces the risk of surgical morbidities

associated with rectal cancer, emphasizing the importance of careful patient selection to optimize long-term outcomes.

The International Watch & Wait Database (IWWD) has further validated the W&W approach by providing robust data on long-term outcomes, thereby supporting its use in clinical practice. According to the IWWD, patients managed with a W&W strategy after achieving cCR have demonstrated promising oncological outcomes. These include low rates of regrowth and overall survival rates comparable to those of patients who undergo immediate surgery [18].

This study aimed to compare oncological outcomes between 2 groups of patients with LARC: those who achieved pCR following NAT and surgical intervention, and those who achieved cCR after total neoadjuvant therapy (TNT) and were subsequently managed with a W&W strategy. Additionally, we investigated whether patients with a pathological incomplete clinical response (pICR), who did not achieve either cCR or pCR after neoadjuvant therapy, exhibit worse oncological outcomes than those who responded to treatment.

METHODS

Ethics statement

The study was approved by the Institutional Review Board of Acıbadem University (No. 2019-02/4). Informed consent for publication of the research details and clinical images was obtained from each patient. This study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement principles for cohort studies [19].

Study population

This study retrospectively evaluated a consecutive series of patients with mid-low LARC who underwent NAT between January 1, 2005, and May 1, 2023. The patients were divided into 2 groups: those who achieved cCR after TNT and were subsequently managed with a W&W strategy, and those who underwent surgery after NAT (TNT or chemoradiotherapy [CRT] ± oxaliplatin-based consolidation chemotherapy) and achieved pCR. Data were extracted from a prospectively maintained surgical database.

The inclusion criteria were as follows: (1) adenocarcinoma confirmed by biopsy; (2) mid-low LARC, endoscopically determined to be within 12 cm of the anal verge (AV); (3) clinical TNM stage II–III; (4) absence of distant metastases and concurrent malignancies; and (5) NAT, which includes CRT or TNT. The exclusion criteria were the following: (1) proximal rectal cancer, defined endoscopically as more than 12 cm from the AV; (2) early rectal cancer surgery (stage I); (3) metastasis during or following NAT; (4) short-course radiotherapy regimen; and (5) patients who underwent local excision (LE) after NAT.

Staging for patients in both groups was conducted using digital rectal examination (DRE), biopsy, total colonoscopy, thoracic/abdominopelvic computed tomography (CT), and pelvic magnetic resonance imaging (MRI).

NAT involved the following protocols [20]:

1. Standard CRT: oral capecitabine (825 mg/m^2 twice daily) combined with 28 sessions of concurrent prolonged radiation therapy at 50.4 Gy.
2. TNT (standard CRT and consolidation chemotherapy): prolonged CRT followed by consolidation chemotherapy (6 cycles of FOLFOX [fluorouracil, leucovorin, and oxaliplatin]). This involved administering leucovorin (400 mg/m^2) and oxaliplatin (85 mg/m^2) in tandem every 2 weeks, then injecting a bolus of 5-fluorouracil (5-FU; 400 mg/m^2) and infusing 5-FU (2,400 mg/m^2). In June 2018, the consolidation regimen changed to once-daily doses of capecitabine (1,000 mg/m^2) and oxaliplatin (130 mg/m^2) on days 1 to 14, repeating every 3 weeks for 8 cycles.

Restaging after NAT was conducted between 4 and 26 weeks, depending on the specific neoadjuvant treatment protocol. Following consolidation chemotherapy, assessments including DRE, sigmoidoscopy, and pelvic MRI were repeated. The criteria for cCR aligned with the MRI tumor regression grade (TRG) score defined by the MERCURY group [21], and the endoscopic criteria established by Habr-Gama et al. [22]. Additionally, high b-value (b1000) diffusion-weighted MRI sequences were considered by the radiologist. Positron emission tomography (PET)/CT scans were meticulously examined to identify any unusual uptake in distant regions, lymph nodes, and the primary tumor.

The follow-up protocols for the W&W strategy included DRE and endoscopy every 2 months, along with measurements of carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) every 3 months over a 2-year period. MRI scans were conducted every 4 months, and PET/CT scans were performed every 6 months for the first 3 years. After this period, pelvic MRI was scheduled every 6 months, thoracoabdominal CT annually, and DRE and endoscopy every 4 months. Following the 5th year, thoracoabdominal CT was planned for the 10th year, pelvic MRI examinations were conducted annually, and DRE and endoscopies were carried out every 6 months. The follow-up regimen for the NAT+surgery group involved annual thoracoabdominal CT scans, quarterly assessments of oncological markers (CEA, CA 19-9), and colonoscopies at postoperative 1, 3, 5, and 10 years.

Definitions

Clinical complete response

The definitive assessment of cCR was based on the clinical judgment of the attending surgeon following TNT. DRE findings were characterized by the presence of a plain white scar, which may or may not include telangiectasia, but excluded any signs of ulceration or nodularity during endoscopic examination. Additionally, cCR was indicated by the absence of a contrast-enhancing lesion, an MRI TRG between 3 and 5, and no evidence of positive lymph node involvement on pelvic MRI [9].

Pathological complete response

According to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th Edition and the College of American Pathologists, pCR was defined as ypT0N0, indicating no residual tumor (T0) and no regional lymph node metastasis (N0) following NAT [10].

Pathological incomplete response

The pICR was defined as the presence of viable residual cancer cells in the resected specimen following NAT for rectal cancer. In contrast to pCR, where no cancer cells are found, pICR signifies that the tumor has not been completely eliminated by the preoperative treatment [23].

Disease-free survival

For patients with pCR, disease-free survival (DFS) was defined as the time from the date of surgery to either tumor recurrence or death from any cause. In patients with cCR, DFS was calculated from the completion of CRT and encompassed locoregional recurrence, distant metastasis, and death from any cause, while local regrowth (LRG) was excluded.

Overall survival

For patients with pCR, overall survival (OS) was defined as the time from the date of surgery to death from any cause. In patients with cCR, OS was calculated from the completion of of CRT to death from any cause.

TME-free survival

TME-free survival was defined as the time from after CRT was completed to the first occurrence of any of the following events: radical TME due to an incomplete response at restaging, any locoregional regrowth after an initial cCR that requires salvage TME, any nonsalvageable regrowth where an R0 resection cannot be achieved, the development of distant metastases, or death from any cause, whichever comes first [24].

Organ preservation–adapted survival

Organ preservation–adapted survival was defined as the time from the completion of CRT to the occurrence of one of the following events: failure to resect the primary tumor due to local disease progression or the patient being unfit for surgery, nonradical resection (R2 resection), locoregional recurrence after R0/1 resection, nonsalvageable local regrowth where only an R2 salvage resection is possible in nonoperative management, any distant metastatic disease, the development of a second primary colorectal or other cancer, treatment-related death, or death from any cause [24].

Statistical analysis

Data were analyzed using IBM SPSS ver. 27 (IBM Corp), with a 95% confidence level. Statistical analyses assessed differences in demographic and clinical characteristics between groups, employing the Mann-Whitney test for nonparametric pairwise comparisons, and either the one-way analysis of variance or Kruskal-Wallis test for intergroup comparisons. The chi-square test was used to evaluate associations between categorical variables. Survival and recurrence rates were analyzed using the Kaplan-Meier method, with log-rank tests comparing oncological outcomes across groups. P-values less than 0.05 were considered statistically significant, supporting the reliability of the observed differences in survival and recurrence outcomes.

RESULTS

Clinical findings

Between January 1, 2005, and May 31, 2023 a total of 763 patients diagnosed with mid-low LARC and subsequently treated with NAT were included in the study. Among these patients, 560 (73.4%) underwent CRT alone, 99 (13.0%) underwent TNT, and the remaining 104 (13.6%) patients received CRT along with 2 or 3 cycles of either CAPEOX (capecitabine and oxaliplatin) or FOLFOX. Of the 99 patients who underwent TNT, 73 (73.7%) achieved cCR and were managed with the W&W strategy. However, 26 patients did not achieve cCR and therefore underwent TME surgery. In the group of 690 patients who underwent TME, 63 (9.1%) achieved a pCR, defined as ypT0N0. Notably, only 12 of these 63 pCR patients (19.0%) received TNT (Fig. 1).

Comparison of cCR and pCR included demographic characteristics, LR and distant metastasis (DM) rates, and 5-year DFS and OS. Notably, the average age of patients in the cCR group was higher than that in the pCR group (56.7±12.85 years vs. 51.4±12.64 years, $P<0.022$). However, there were no significant differences between the groups in terms of sex, body mass index, distance from the AV, clinical tumor stage, or nodal stage. The

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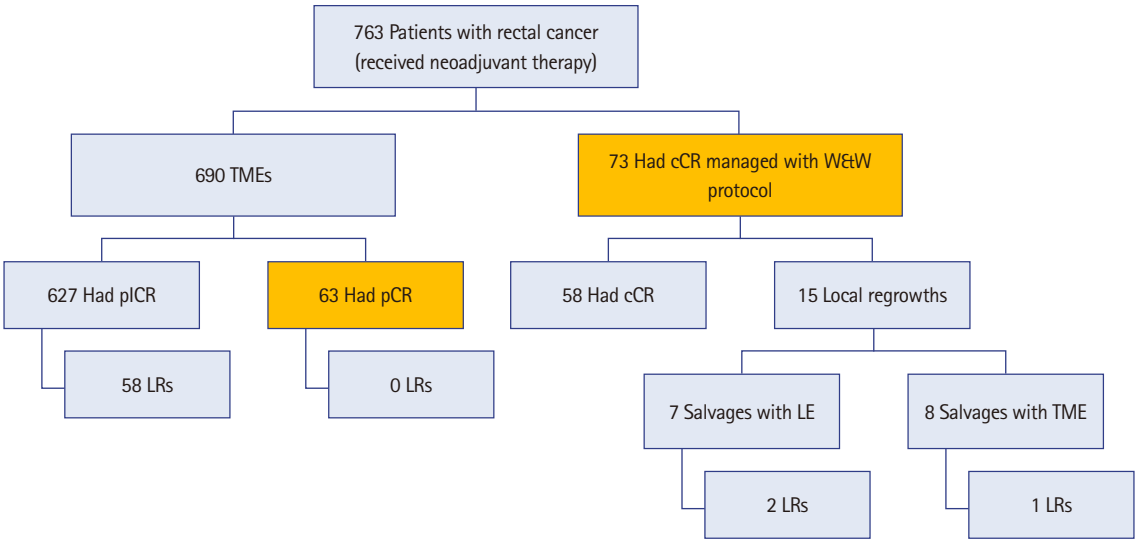

Fig. 1. Selection of patients. TME, total mesorectal excision; cCR. clinical complete response; W&W, watch-and-wait; pICR, pathological incomplete clinical response; pCR, pathological complete response; LE, local excision; LR, local recurrence.

majority of patients in both groups were classified as cT3 (cCR, 79.5%; pCR, 88.8%; P = 0.703) and cN positive (cCR, 69.9%; pCR, 61.9%; P = 0.683) (Table 1). While all patients in the cCR group received consolidation chemotherapy, only 12 of the 63 patients (19.0%) in the pCR group underwent this treatment (P = 0.022).

The study included 627 patients who achieved pICR following NAT for rectal cancer. The average age of these patients was 55 ± 10.57 years. Among those who experienced pICR, 365 (58.2%) were male and 262 (41.8%) were female. The median body mass index was 26.6 kg/m^2 (range, 18–45 kg/m^2). The tumors were located at a median distance of 4.3 cm (range, 0–10 cm) from the AV. Clinical tumor classification among the patients was distributed as follows: 73 (11.6%) were classified as cT2, 458 (73.0%) as cT3, and 96 (15.4%) as cT4. Regarding clinical nodal classification, 173 (27.6%) were cN negative, while 454 (72.4%) were cN positive.

The median follow-up duration after NAT was 54 months (range, 7–83 months)for the cCR group (W&W), 96 months (range, 7–215 months) for the pCR group, and 72 months (range, 4–212 months) for the pICR group.

Table 1. Clinical and demographic characteristics

Characteristic	cCR group (n = 73)	pCR group (n = 63)	P-value
Age (yr)	56.7 ± 12.85	51.4 ± 12.64	0.022[a]
Sex			0.694[b]
Male	43 (58.9)	35 (55.6)	
Female	30 (41.1)	28 (44.4)	
Body mass index (kg/m^2)	26.3 ± 3.68	27.1 ± 2.92	0.138[a]
Distance from AV (cm)	3.0 (0–8)	3.2 (0–10)	0.578[a]
Pretreatment T category			0.703[c]
T2	5 (6.8)	3 (4.8)	
T3	58 (79.5)	56 (88.8)	
T4	10 (13.7)	4 (6.4)	
Pretreatment N category			0.683[c]
N negative	22 (30.1)	24 (38.1)	
N positive	51 (69.9)	39 (61.9)	
Consolidation treatment	73 (100)	12 (19.0)	0.022[c]
Follow-up (mo)	54 (7–83)	96 (7–215)	0.012[a]

Values are presented as mean ± standard deviation, number (%), or median (range).
cCR, clinical complete response; pCR, pathological complete response; AV, anal verge.
Calculated using [a]t-test, [b]Kruskal-Wallis test, or [c]z-test.

Oncological outcomes

In the W&W group, 15 out of 73 patients (20.5%) exhibited evidence of LRG, as detailed in Table 2. The median time to LRG occurrence was 18.8 months (range, 8–36 months). Salvage treatments were administered as follows: 7 patients (46.6%) received LE, one of whom also underwent additional brachytherapy; 8 patients (53.4%) underwent TME, which included 4 low anterior resections (LARs) and 4 abdominoperineal resections (APRs). Table 2 provides detailed information on the patients who required salvage surgery due to LRG.

One patient developed LRG at 18 months after LE (ypT2) and underwent APR in a second salvage operation (ypT2N0). This patient had no evidence of disease for 56 months after APR. Another patient developed LRG at 17 months after LE (ypT3) and

Table 2. Clinical characteristics of patients with local regrowth and subsequent salvage surgery

Patient no.	Clinical stage	Regrowth time (mo)	Salvage operation	Surgical pathology	After salvage pelvic recurrence	Distant metastasis	Status
1	T4N+	19	APR, PE	ypT3N1	Yes	Liver, bone	DOD
2	T3N–	17	LE	ypT3	Yes	No	DOD
			LAR	ypT3N0			
			APR	ypT3N1			
3	T3N+	13	LE	ypT3	No	Liver, lung	NED
4	T3N+	35	APR	ypT3N2	No	Lung	DOD
5	T3N+	24	LAR	ypT2N0	No	No	NED
6	T2N–	24	LE	ypT2	No	No	NED
7	T3N+	18	LE	ypT2	Yes	No	NED
			APR	ypT2N0			
8	T2N+	8	LE	ypT2	No	No	NED
9	T3N+	36	APR	ypT4N0	No	No	NED
10	T4N+	20	LE	ypT1	No	No	NED
11	T3N–	10	LAR	ypT2N0	No	No	NED
12	T3N+	13	APR	ypT2N0	No	No	DOD
13	T3N+	16	LAR	ypT2N0	No	No	NED
14	T3N+	11	LE	ypT2	No	No	NED
15	T3N+	20	LAR	ypT3N1	No	No	NED

APR, abdominoperineal resection; PE, pelvic exenteration; DOD, dead of disease; LE, local excision; LAR, low anterior resection; NED, no evidence of disease.

was treated with laparoscopic LAR (ypT3N0). Eight months later, LRG developed again, and APR was performed (ypT3N1). This patient died 60 months later due to acute kidney failure.

One patient developed liver and lung metastases 10 months after LE (ypT3) and underwent metastasectomy. At the 45-month follow-up, there were no signs of LR or systemic metastasis.

In the patient who missed follow-up appointments for 2 years due to the COVID-19 pandemic, LRG was detected during the 36-month follow-up. Subsequently, APR (ypT4) was performed. The patient showed no evidence of disease for 32 months following APR.

Another patient developed LRG at 19 months and underwent APR (ypT3N1). At the 27-month follow-up, LR was detected, prompting pelvic exenteration. Bone and lung metastases were identified at the 48-month follow-up, and the patient unfortunately passed away at the 66-month follow-up.

A total of 6 patients (8.2%) in the cCR group underwent APR. Among those who underwent salvage surgery, 3 patients (20%) developed DM.

Two patients without LRG experienced systemic metastases. The first patient developed lung metastasis at the 19th month of follow-up and underwent metastasectomy. By the 78th month of follow-up, there were no signs of LR or systemic metastasis. The second patient was found to have liver metastasis at the 18th month of follow-up and received radiofrequency ablation. At the 38th month of follow-up, there were no signs of LR or systemic metastasis. Consequently, DM was detected in 5 patients in the total cCR group.

In the pCR group, LR was not detected. Consequently, APR was performed in 4 patients (6.3%) from this group. DM were identified in 3 patients (4.8%): 1 had lung metastasis at postoperative 26 months, another developed bone metastasis at postoperative 48 months, and the third experienced liver metastasis at postoperative 16 months.

In the pICR group, LR was detected in 58 patients (9.2%), and DM was identified in 92 patients (14.6%). Thirty-eight patients had liver metastases, 34 had lung metastases, 16 had both liver and lung metastases, 2 had peritoneal carcinomatosis, and 2 had para-aortic lymph node recurrences. APR was performed on 72 patients of the 627 total (11.4%), while the others underwent sphincter-sparing TME.

There was no statistically significant difference between cCR and pCR in terms of DM (P = 0.624). In comparison to the other 2 groups, the pICR group had a considerably lower rate of DM-free survival (P = 0.018) (Fig. 2A). The 5-year DFS was 90.0% in the cCR group and 92.0% in the pCR group (P = 0.689). The 5-year DFS was 69.5% in the pICR group, which was statistically lower than that of the other 2 groups (P = 0.022) (Fig. 2B, C).

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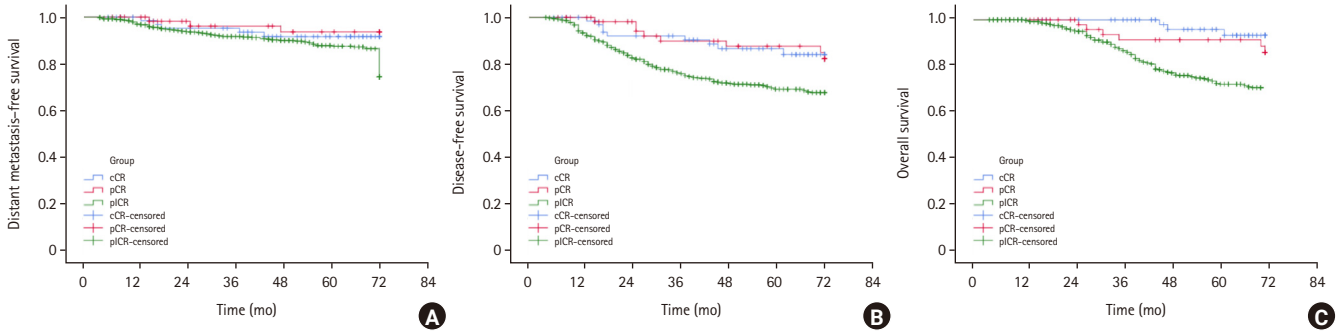

Fig. 2. Oncologic outcomes according to tumor response. (A) Distant metastasis–free survival. (B) Disease-free survival. (C) Overall survival. cCR, clinical complete response; pCR, pathological complete response; pICR, pathological incomplete clinical response.

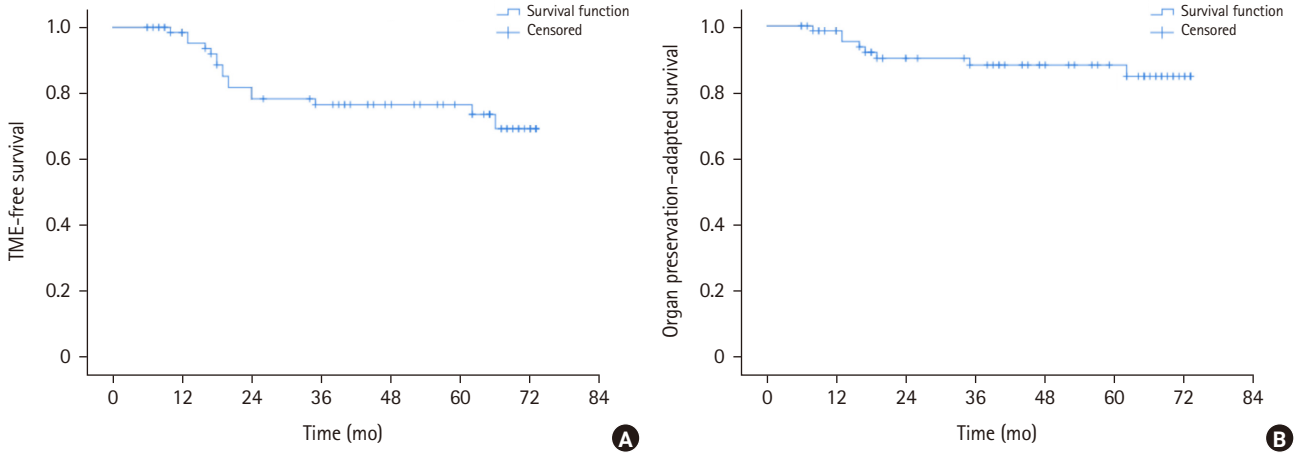

Fig. 3. Disease-free survival in patients with clinical complete response following the watch-and-wait protocol. (A) Total mesorectal excision (TME)-free survival. (B) Organ preservation–adapted survival.

In the cCR group, 5 patients died: 3 from the disease, 1 from COVID-19, and 1 from kidney failure. In the pCR group, 5 patients also died, with 3 succumbing to the disease and 2 to cardiac causes. Consequently, the 5-year OS was 93.1% for cCR and 92.0% for pCR, showing no statistical difference (P=0.810). Patients in the pICR group had a significantly lower OS of 78.1% (P=0.002) (Fig. 2). Among cCR individuals following the W&W strategy, the 5-year TME-free survival rate was 78.0%, while the rate for organ preservation–adapted survival was 89.0% (Fig. 3).

DISCUSSION

The W&W strategy has emerged as a distinctive and promising alternative treatment modality, exemplifying organ preservation in the treatment of LARC [25]. The integration of TNT has led to a significant increase in cCR rates, paving the way for the broader adoption of the W&W strategy. This is supported by literature showing a median cCR rate of 65% (ranging from 55.0% to 75.0%) [20, 25–27]. The primary concerns associated with the W&W approach include the potential for LRG, the development of DM, and generally poor oncological outcomes, which could potentially degrade the quality of life for patients who achieve cCR and cause anxiety among protocol participants. It is an undeniable fact that patients achieving pCR, indicative of the maximal response to NAT, experience better long-term oncologic outcomes [10]. However, few studies have compared the long-term oncological outcomes between patients achieving cCR and those achieving pCR [18, 28]. This study aimed to demonstrate the safety of the W&W strategy by comparing patients who achieved pCR, representing the optimal treatment response, with those showing pICR, indicating a less favorable response, and patients exhibiting cCR, in terms of their long-term oncologic outcomes.

The LRG rate among patients achieving a cCR has been reported to range from 19.0% to 31.0% [18, 27–31]. Consistently, our study found that 15 patients (20.5%) in the W&W group experienced regrowth. These patients underwent salvage surgery, with a

significant number (46.6%) opting for LE as the surgical approach. These rates are in line with global findings, which vary from 1.0% to 44.0% [29–34]. LR necessitating secondary surgery was observed in 2 of these patients, as well as in 1 patient (4.0%) who underwent TME. This case series demonstrates a notably high local control rate of 96.0%, achieved through effective management of salvage LRG.

Regrowth represents a critical vulnerability in the W&W approach, primarily due to its potential to initiate systemic metastasis. In the cCR group, DM was detected in 5 patients (6.8%). Of these, 3 underwent salvage surgery after experiencing LRG. Notably, the incidence of DM was higher in patients with LRG compared to those without (20.0% vs. 3.4%). Similar trends were observed by Smith et al. [28], who compared cCR and pCR patients, and found significantly higher rates of DM in those with LRG (36.0% vs. 1.0%)]. Comparable results were reported in the IWWD study (24.1% vs. 6.0%) [18] and in the meta-analysis by Socha et al. [35] (23.1% vs. 5.5%), attributing these findings to either tumor biology or the tumor's response to NAT, which is influenced by intratumoral heterogeneity. This phenomenon could be explained by the possible presence of multiple subpopulations of cancer cells within a tumor, each varying in their sensitivity and resistance to treatment. Consequently, while sensitive clones may diminish, resistant clones can survive and multiply, potentially leading to a more aggressive progression of the disease [36].

In a study conducted by Maas et al. [37], which analyzed 3,105 cases across 14 studies, 484 cases (15.0%) achieved pCR. During the 5-year follow-up, the LR rates were 2.8% in the pCR cohort compared to 9.7% in the pICR group. Notably, the current study found no instances of LR in the pCR group, while the LR rate was 9.2% among patients with pICR. Although the DM rate was slightly higher in the cCR group than in the pCR group (6.8% vs. 4.7%), this difference was not statistically significant. In contrast, a significantly higher incidence of DM, at 14.6%, was observed in patients with pICR. Smith et al. [28] reported similar DM rates in their single study comparing cCR and pCR cohorts, with rates of 8% and 4%, respectively. Their research also indicated 5-year OS rates of 73% in the W&W group and 94% in the pCR group, with corresponding 5-year DFS rates of 75% and 92%. Additionally, disease-specific survival in the W&W group was 90%. Our study reports 5-year OS rates of 93.0% for the cCR group, 92.0% for the pCR group, and 78.0% for the pICR group. The respective DFS rates during the same period were 90.0%, 92.0%, and 69.5%. Similarly, Maas et al. [37] highlighted DFS and OS rates for the pICR group at 65.6% and 76.4%, respectively, showing a notable similarity.

The present study summarizes an evolutionary journey [13, 19, 38–40], commencing with long-term chemotherapy combined with oral capecitabine, initially at intervals of 4 weeks, which were then extended to 6, 8, and 10 weeks. This progression ultimately leads to the inclusion of 2 chemotherapy cycles, culminating in the adoption of the W&W strategy. We firmly believe that the tumor response induced by NAT is the ultimate prognostic indicator. The regression of tumors following radiation treatment has a temporal aspect, with the maximum response developing over several months [40]. Our previously published data shows a cCR rate of 65.0%, which starkly contrasts with the near-cCR rate of 10.0% observed in cases undergoing LE [19, 41]. Notably, Garcia-Aguilar et al. [42] reported TNT achieving a pCR of up to 28%, while the OPRA trial reports cCR rates reaching 41% [25]. Given the favorable prognosis associated with both cCR and pCR, the goal is to achieve a strong tumor response. The level of response induced by NAT appears to be a critical determinant of disease prognosis. For patients achieving cCR, delaying surgery is a viable option. Enhancing the NAT response could be achieved through more frequent assessments, increased radiation doses, enhanced systemic chemotherapy in conjunction with radiotherapy during the neoadjuvant phase, and a shift from induction to consolidation chemotherapy [7, 19, 26, 41].

Within the limits of our study, we found no significant differences in DM, OS, and DFS between cases of cCR and pCR. However, the pICR group demonstrates significantly worse outcomes. This suggests that the surgical risks may outweigh the dangers of tumor regrowth when considering the W&W strategy. The implications are significant, as foregoing TME surgery could lead to substantial benefits, including lower morbidity and improved quality of life. Therefore, the primary objective of NAT should focus on achieving a strong tumor response.

This study has several limitations. First, it is a single-center retrospective study, which carries a risk of inclusion bias and may not yield results that are generalizable to other centers. Consequently, broader, prospective, multicentric studies are necessary. Second, although the study includes a relatively large number of patients, the size of the groups is still too small to provide definitive data on LR. Third, the extended timeframe of the study could introduce biases related to changes in treatment modalities and waiting times. Despite this, the primary objective of the study remains to compare the pCR (ypT0N0) achieved through neoadjuvant therapy with the cCR (ct0N0) obtained through an intentional W&W strategy.

Despite these limitations, this study presented long-term oncological outcomes of cCR following NAT, which have been rarely reported in the literature. Additionally, this study details the experience with NAT at a tertiary referral center known for its exper-

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tise in the W&W strategy.

In conclusion, this study demonstrates that there is no significant long-term oncological difference between the cCR and pCR groups. The W&W strategy provides the benefit of organ preservation for patients who achieve cCR, ensuring an oncologically safe quality of life. Therefore, optimizing NAT strategies could improve complete responses, potentially allowing many patients to avoid unnecessary surgery.

ARTICLE INFORMATION

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

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Conceptualization: all authors; Formal analysis: NS, VA, OA; Investigation: NS, OA; Methodology: all authors; Supervision: OA; Writing–original draft: all authors; Writing–review & editing: all authors. All authors read and approved the final manuscript.

Additional information
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