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Outcomes of Postchemoradiotherapy Watch-and-Wait Strategy in Patients With Rectal Cancer: A 20-Year, Single-Center Study

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ABSTRACT

Background and Objectives: The watch-and-wait (WW) strategy is a nonsurgical alternative for patients with rectal cancer exhibiting an excellent response to chemoradiotherapy. Studies on the WW strategy have primarily investigated 5-year oncological outcomes; few have focused on longer-term outcomes or the optimal patient selection approach for this therapeutic strategy.

Methods: This retrospective study enrolled patients with locally advanced rectal adenocarcinoma who had achieved complete response after chemoradiotherapy. Patients who achieved pathological complete response were categorized into a control group ($n = 95$) and those who achieved clinical complete response and were managed using the WW strategy were categorized into a case group ($n = 33$). Kaplan–Meier estimates were calculated for the between-group comparison of survival.

Results: The median follow-up duration was 89 months. Compared with the control group, the case group exhibited improved long-term sphincter preservation, particularly for low-lying tumors ($p = 0.032$), and inferior nonlocal-regrowth disease-free survival ($p = 0.007$). Within the case group, patients achieving a complete response by positron emission tomography exhibited 5-year survival rates similar to those achieving a complete endoscopic response.

Conclusion: The WW strategy is associated with improved sphincter preservation but worse nonlocal-regrowth disease-free survival. The potential of PET in patient selection for this strategy deserves further investigation.

1 | Introduction

Colorectal cancer is the third most common cancer worldwide and the second most common cancer in Taiwan. Rectal cancer accounts for 31% of all cases of colorectal cancer [1, 2]. Surgery has long been the mainstay treatment for rectal cancer [3]. Radical resection often leads to suboptimal functional outcomes and reduced quality of life. It also carries the risk of long-term complications, bowel symptoms, sexual dysfunction, and poor body image [4, 5]. Patients, particularly those with low-lying tumors, may undergo abdominoperineal resection, which is associated with a risk of permanent colostomy [5]. Successful management of

Abbreviations: cCR, clinical complete responses; CEA, carcinoembryonic antigen; CFS, colostomy-free survival; CI, confidence interval; CMR, complete metabolic response; CT, computed tomography; DMFS, distant metastasis–free survival; HR, hazard ratio; IQR, interquartile range; MRI, magnetic resonance imaging; Nonregrowth DFS, nonlocal-regrowth disease-free survival; OS, overall survival; pCR, pathological complete response; PET, positron emission tomography; SUVmax, maximum standard uptake value; WW, watch-and-wait.

rectal cancer necessitates a multidisciplinary approach that integrates surgery, chemotherapy, and radiotherapy [3]. Evidence suggests that long-course preoperative chemoradiotherapy considerably increases the likelihood of a pathological complete response (pCR), with surgical specimens of 15%–20% of all patients exhibiting no viable tumor cells after neoadjuvant therapy [6]. The remarkable oncological outcomes in patients achieving a pCR question the need for radical resection, directing researchers' attention toward an organ-preserving strategy [7].

Over the last decade, nonsurgical management has gained increasing attention as a treatment option in selected cases. In 2004, Habr-Gama et al. confirmed the safety and efficacy of the watch-and-wait (WW) strategy [8]. In this approach, patients exhibiting excellent clinical responses to chemoradiotherapy opt for active surveillance instead of immediate surgery. A series of observational studies have reinforced the potential of the WW strategy to improve patients' quality of life while maintaining acceptable oncological outcomes [9–17]. However, the efficacy of the WW strategy remains debatable because of variations across studies in research design and patient selection. Tools such as endoscopy, computed tomography (CT), magnetic resonance imaging (MRI), and fluorodeoxyglucose–positron emission tomography (PET) have been used to assess a clinical complete response (cCR). The efficacy of fluorodeoxyglucose-PET and intense chemoradiotherapy (additional radiation boost and mitomycin C) in optimizing oncological outcomes of the WW strategy remains underexplored [18, 19].

To address the knowledge gap, we retrospectively reviewed 20 years' worth of data from patients with rectal cancer who had achieved a cCR after long-course chemoradiotherapy and were thus managed using the WW strategy in our tertiary medical center. These patients were compared with those achieving a pCR (a surrogate marker for the most favorable prognosis) after radical surgery to clarify the long-term safety and efficacy of the WW strategy and optimize the patient selection approach for nonsurgical management.

2 | Methods

2.1 | Study Population

We identified patients with locally advanced rectal adenocarcinoma (within 15 cm from the anal verge) who had received long-course chemoradiotherapy at Taipei Veterans General Hospital between 2000 and 2021. Diagnosis was confirmed using endoscopic biopsy, and pretreatment T and N stages were determined using pelvic MRI or CT. Thoracic and abdominal CT scans were performed to assess distant metastases. Patients with metastatic disease, those with concomitant malignancies, and those with a history of pretreatment transanal excision were excluded from this study. For long-course chemoradiotherapy, all patients received three-dimensional conformal radiotherapy, which was administered using linear accelerators (Clinac 2100 C, Varian, Palo Alto, CA, USA). This therapy involved the daily administration of 10 MV X-ray photons, 5 days a week. The total dose was 45 Gy, which was delivered to the entire pelvis in 20–25 fractions. An additional radiation boost to the rectal tumor (5.4–9.0 Gy in three fractions) was optionally delivered by the radiation oncologist. Concurrent oral uracil-tegafur (UFUR, TTY Biopharm, Taipei, Taiwan) and leucovorin (Wyeth Lederle Laboratories, Taipei, Taiwan) were administered at doses of 200 mg/m^2/day in three divided doses and 45 mg/day in three divided doses, respectively. Since 2010, a single dose of mitomycin C (6 mg/m^2; Kyowa Hakko Kirin, Japan) has been intravenously administered at the discretion of the attending oncologist.

Patients were retrospectively divided into case and control groups. The case group comprised patients who had achieved a cCR after long-course chemoradiotherapy and were thus managed using the WW strategy. Treatment decisions were jointly made by the patient, surgeon, radiation oncologist, and medical oncologist after a thorough discussion on therapeutic risks, benefits, and alternatives. The control group comprised patients who had achieved a pCR; these patients underwent curative surgery after chemoradiotherapy, and their surgical specimens exhibited no residual tumors (ypT0N0). Oncological outcomes were assessed using retrospectively collected data. The patients' clinicodemographic characteristics, including age at diagnosis, sex, tumor distance from the anal verge, clinical stage, neoadjuvant therapy, and surgical procedures, were comprehensively analyzed. The distance between the tumor and the anal verge was determined using endoscopic data. The present study was approved by the Institutional Review Board of Taipei Veterans General Hospital, Taiwan (permit number: 2023-12-002BC). The requirement for informed consent was waived by the Institutional Review Board because of the retrospective nature of the study.

2.2 | cCR Assessment

Patients in the case group underwent endoscopic reassessment at least 1 month after the completion of chemoradiotherapy. The endoscopic evaluations were performed by colorectal surgeons, with the same surgeon assessing the patient before and after chemoradiotherapy to ensure consistent evaluation of the clinical response. Clinical responses of regional lymph nodes were evaluated through pelvic MRI or CT performed at least 1 month after chemoradiotherapy. Clinical response was categorized using a 3-tier grading system: cCR was defined as no residual tumor or a flat, white scar; Near-cCR included minor abnormalities, such as small mucosal irregularities, residual erythematous ulcer or irregular wall thickening; Non-cCR indicated the presence of a palpable tumor mass that did not meet the criteria for cCR or near-cCR. Patients with near-cCR upon endoscopy would receive a discretionary PET scan, which was performed at least 3 months after chemoradiotherapy. Patients with negative findings on PET scans (complete metabolic response [CMR]) who did not undergo surgery were also included in the case group. Patients with residual tumors (non-cCR) were strongly advised to undergo surgery and were excluded from subsequent analyses.

2.3 | Follow-Up

Patients were monitored every 3 months during the first 2 years and every 6 months during the subsequent years [20]. The follow-up examination involved serum carcinoembryonic antigen (CEA) measurement, digital rectal examination, endoscopy,

and pelvic CT. Endoscopic and radiological examinations were performed on a semiannual basis. The last date of follow-up was December 31, 2023.

2.4 | Study Outcomes

The primary study outcome was nonlocal-regrowth disease-free survival (DFS; presented as "nonregrowth DFS"), which was defined as the time to the first pelvic recurrence, distant metastasis, or death due to any cause [12]. Pelvic recurrence was defined as tumor recurrence within the pelvis (the radiation field), and distant metastasis was defined as recurrence outside the pelvis. The secondary outcomes were overall survival (OS), distant metastasis–free survival (DMFS), and colostomy-free survival (CFS; an established indicator of patients' quality of life). CFS was estimated as time to permanent colostomy without subsequent reversal. Patients were considered to have achieved sphincter preservation if they were managed using the WW strategy and did not undergo subsequent abdominoperineal resection. All time-to-event variables were calculated from the date of chemoradiotherapy completion in the case group and from the date of surgery in the control group.

2.5 | Statistical Analysis

Categorical variables were compared using the Fisher exact test, and continuous variables were compared using the Mann–Whitney U test. Survival outcomes were compared using the Kaplan–Meier method and a log-rank test. Hazard ratios (HRs) were calculated using Cox proportional hazards models. Univariate and multivariate logistic regression analyses were performed to identify factors influencing sustained clinical response. A two-tailed p value of < 0.05 indicated statistical significance. All statistical analyses were performed using R version 4.2.1 (R Core Team. R Foundation for Statistical Computing, Vienna, Austria).

3 | Results

3.1 | Patient Characteristics

Between July 2000 and December 2021, 1095 patients with nonmetastatic, locally advanced rectal adenocarcinoma received long-course chemoradiotherapy at Taipei Veterans General Hospital (Figure 1). Among them, 33 were managed using the WW strategy (the case group); these patients were selected on the basis of either a complete endoscopic response ($n = 20$) or a CMR ($n = 13$) after chemoradiotherapy. During the same period, 1060 patients underwent radical resection; of them, 95 achieved a pCR (the control cohort). Significant between-group differences were observed in age at diagnosis ($p < 0.05$; Table 1). The median ages were 72 (range: 39–84) and 64 (range: 31–83) years in the case and control groups, respectively. The dose of radiotherapy administered to the entire pelvis to mitigate the risk of local recurrence was higher in

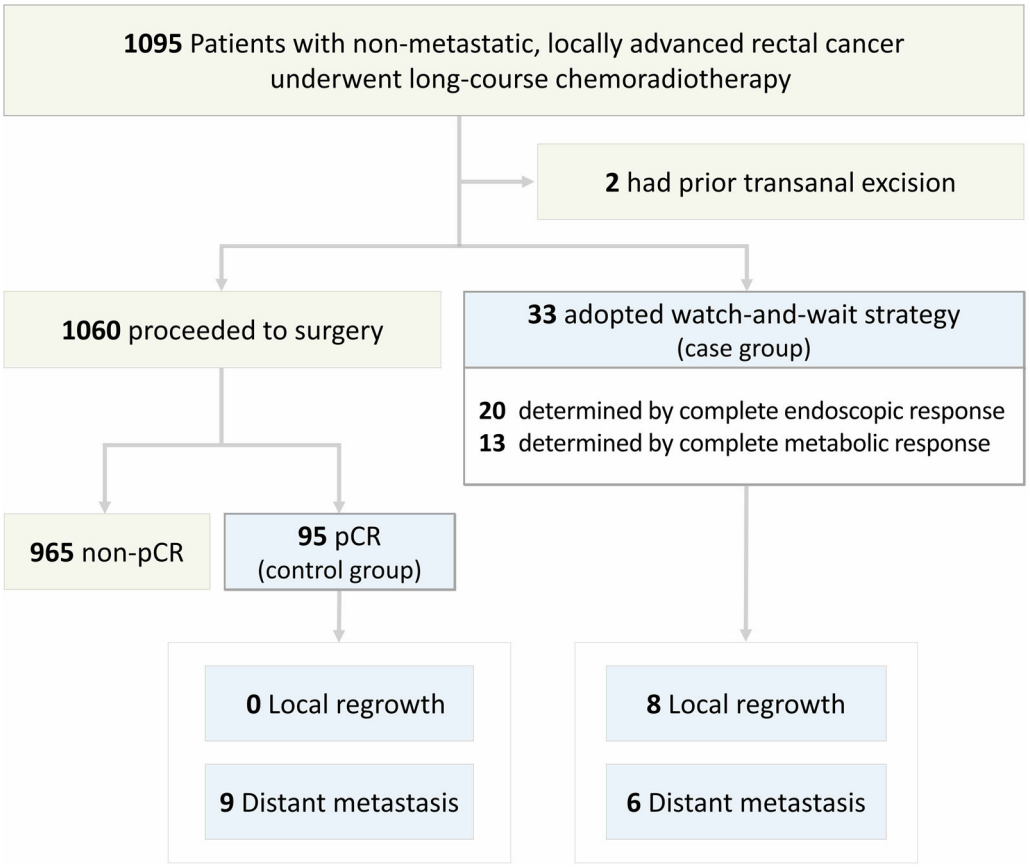

FIGURE 1 | Patient selection methodology. Case group: Patients who were managed using the watch-and-wait strategy after they had achieved a clinical complete response. Control group: Patients who achieved a pathological complete response.

TABLE 1 | Clinicodemographic characteristics of the study cohort.

	Case group ($n = 33$)	Control group ($n = 95$)	p value
Age (years), median (range)	72 (39–84)	64 (31–83)	**0.030**
Sex			0.962
Men, *n* (%)	20 (60.6%)	60 (63.2%)	
Women, *n* (%)	13 (39.4%)	35 (36.8%)	
Distance from anal verge (cm), median (range)	5.0 (1.0–12.0)	5.0 (0.5–14.0)	0.128
Clinical T stage			0.186
cT2, *n* (%)	12 (36.4%)	24 (25.3%)	
cT3, *n* (%)	18 (54.6%)	4 (4.2%)	
cT4, *n* (%)	3 (9.1%)	4 (4.2%)	
Clinical *N* stage			0.293
cN0, *n* (%)	10 (30.3%)	24 (25.3%)	
cN1/2, *n* (%)	23 (69.7%)	71 (74.7%)	
Diagnostic imaging			0.644
CT, *n* (%)	8 (24.2%)	29 (30.5%)	
MRI, *n* (%)	25 (75.8%)	66 (69.5%)	
Pretreatment CEA level (ng/mL), median (IQR)	2.3 (1.98–3.56)	2.8 (2.17–4.75)	0.107
Mitomycin C during radiotherapy, *n* (%)	17 (51.5%)	47 (49.5%)	0.995
Radiotherapy dose (Gy), median (range)	50.4 (45–55)	45 (45–55)	**< 0.001**
Radiotherapy boost, *n* (%)	18 (54.5%)	11 (11.6%)	**< 0.001**

Note: Case group: Patients who were managed using the watch-and-wait strategy after they had achieved a clinical complete response. Control group: Patients who achieved a pathological complete response.
Abbreviations: CEA, carcinoembryonic antigen; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging.

the case group than in the control group (median dose: 50.4 vs. 45 Gy, respectively; $p < 0.001$). Notably, 54.5% and 11.6% of all patients in the case and control groups, respectively, received an additional radiation boost to the rectal tumor ($p < 0.001$). The chemotherapy regimen was similar between the two groups, with 50% of all patients receiving additional mitomycin C. Neither group received induction nor consolidation chemotherapy. No significant between-group differences were observed in sex, tumor distance from the anal verge, clinical tumor and nodal stage, serum CEA level, or imaging modality (Table 1). Diagnostic pelvic MRI was performed in 75.76% and 69.47% of all patients in the case and control groups, respectively. The proportions of pretreatment T- or N-stage were similar between the two groups. The median distance of the tumor from the anal verge was 5 cm. In the control group, the median interval from chemoradiotherapy conclusion to surgery was 49 days (interquartile range [IQR]: 42–59.5 days). The median duration of follow-up was 89 months (IQR: 57.5–133.75 months). A total of 82 patients (64.0%) were monitored for at least 5 years.

3.2 | Local Regrowth

During the follow-up period, 8 of the 33 patients in the case group (24%) had local regrowth, with two patients developing distant metastases before local regrowth. Most cases of local regrowth occurred within the first 2 years after the completion of chemoradiotherapy. The median time to the first occurrence of local regrowth was 20 (IQR: 10.75–24.75) months. The cumulative rates of local regrowth were 8.8% (95% confidence interval [CI]: 0.3–1.8) and 18.9% (95% CI: 4.0–31.5) at the 1- and 2-year follow-ups, respectively. By contrast, no incidence of local regrowth was observed in the control group. In the case group, most cases of local regrowth were salvageable, except in two patients who declined surgery because of multiple comorbidities. Six patients with local regrowth underwent salvage surgery: three underwent abdominoperineal resection, one underwent low anterior resection, one underwent Hartmann's procedure because of metachronous sigmoid cancer, and one underwent transanal excision. The patient undergoing transanal excision achieved a free margin with no further recurrence during the follow-up period. The median interval from local regrowth diagnosis to salvage surgery was 33 days. After salvage surgery, one patient had ypT-stage consistent with pretreatment clinical staging. Furthermore, four patients exhibited downstaging, and one patient exhibited upstaging from T2 to T3 (Supporting Information S1: Table S1). Among patients with isolated local regrowth without synchronous distant metastasis, the rate of 3-year nonregrowth DFS after salvage surgery was 100%.

3.3 | Nonregrowth DFS, DMFS, and OS

Because local regrowth is typically salvageable and rare after radical resection, several studies have used nonregrowth DFS to compare treatment failure between patients who were managed

using the WW strategy and those who had achieved a pCR [12, 16, 17]. In the present study, the rates of 5-year nonregrowth DFS were 80.6% (95% CI: 67.7%–95.9%) in the case group and 88.0% (95% CI: 85.8%–97.3%) in the control group. Long-term nonregrowth DFS outcomes were significantly better in the control group than in case group (HR: 2.55; 95% CI: 1.25–5.17; log-rank $p = 0.007$; Figure 2A). The median durations of nonregrowth DFS in the case and control groups were 112 (95% CI: 80 to not available) and 195 (95% CI: 179 to not available) months, respectively. Age-adjusted multivariate Cox regression revealed that the WW strategy was an independent risk factor for nonregrowth DFS (HR: 0.38; $p = 0.029$). However, no significant associations were noted between nonregrowth DFS and sex, clinical T or N stage, pretreatment CEA level, tumor distance from the anal verge, or additional mitomycin C or radiation boost (Supporting Information S1: Figure S1A).

Distant metastases were the major cause of treatment failure in the case and control groups. During the follow-up period, nine (9.5%) patients in the control cohort developed distant metastases (six patients developed lung metastases and three patients developed liver metastases). Among these nine patients, five underwent metastasectomy. In the case group, six (18.0%) patients developed metastases (five patients developed lung metastases and one patient developed inguinal nodal metastases). In the whole study population, the majority of patients with distant metastases had no concurrent local regrowth. The median interval from the end of chemoradiotherapy to distant metastasis was similar between the case and control groups (23.5 vs. 17.0 months, respectively; $p = 0.862$). The rates of 5-year DMFS were 80.6% (95% CI: 67.7%–95.9%) in the case group and 90.2% (95% CI: 84.2%–96.5%) in the control group (HR: 2.15; 95% CI: 0.76–6.04; log-rank $p = 0.141$; Figure 2B). To identify clinical characteristics influencing DMFS, we analyzed factors such as strategy, age, sex, clinical stage, pretreatment CEA level, neoadjuvant therapy, and tumor distance from the anal verge. However, neither the univariate nor multivariate analyses revealed any significant factor influencing the rate of DMFS (all $p > 0.05$; Supporting Information S1: Figure S1B).

The rates of 5-year OS were 88.2% (95% CI: 76.4%–100%) in the case group and 92.2% (95% CI: 86.9%–97.9%) in the control group; these results are consistent with those of WW-related studies indicating similar outcomes between patients managed using the WW strategy and those achieving a pCR [15]. However, beyond the 5-year timeframe, OS was significantly better in the control group than in the case group (HR: 2.45; 95% CI: 1.16–5.19; log-rank $p = 0.015$; Figure 2C). The median durations of OS in the case and control groups were 112 months (95% CI: 97 to not available) and 195 months (95% CI: 179 to not available), respectively. Age-adjusted multivariate Cox regression revealed that achieving a pCR was independently associated with a reduced risk of mortality (HR: 0.38; $p = 0.033$; Supporting Information S1: Figure S1C).

3.4 | Sphincter Preservation

At the end of follow-up, 6 (18%) patients in the case group and 28 (29%) patients in the control group had a permanent stoma. No significant between-group difference was observed in the rate of sphincter preservation ($p = 0.313$). While previous studies have reported outcomes only up to 5 years [17], our study focused on the long-term results. The rates of 10-year CFS were 72% (95% CI: 52.6%–98.5%) in the case group and 69.3% (95% CI: 60.0%–80.0%) in the control group (HR: 0.63; 95% CI: 0.26–1.53, log-rank $p = 0.340$; Figure 3A). In our case group, the primary reasons for colostomy were salvage abdominoperineal resection and palliative intent. By contrast, in the control group, the primary reasons for colostomy after low anterior resection were postoperative and anastomotic complications, such as fistula formation, leakage, and stricture. These complications

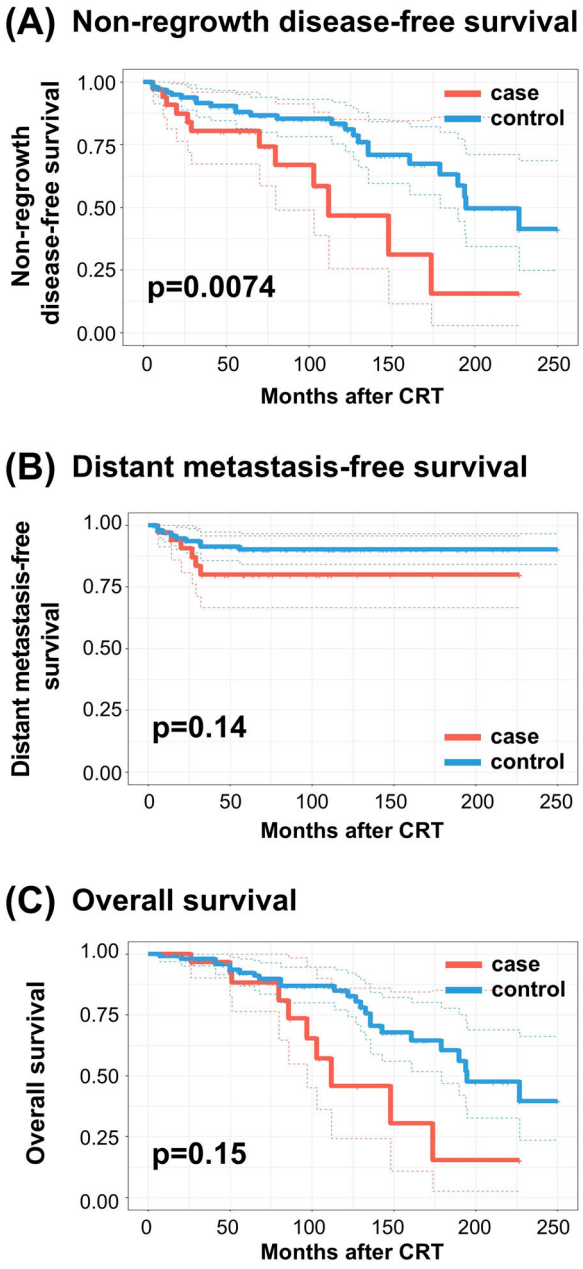

FIGURE 2 | Kaplan–Meier survival estimates for the case and control groups. (A) Nonregrowth disease-free survival. (B) Distant metastasis–free survival. (C) Overall survival. Case group: Patients who were managed using the watch-and-wait strategy after they had achieved a clinical complete response. Control group: Patients who achieved a pathological complete response. CRT, chemoradiotherapy.

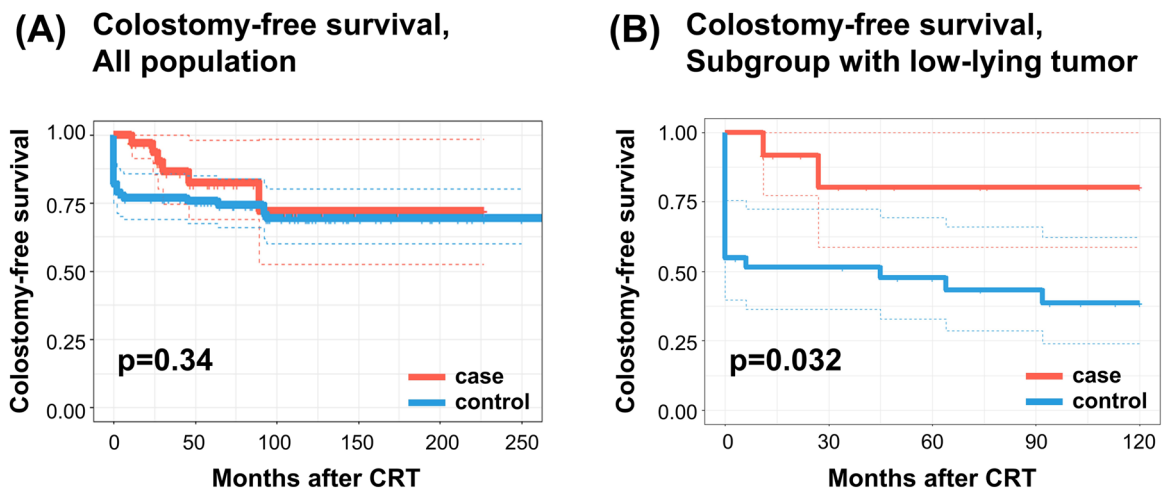

FIGURE 3 | Kaplan–Meier estimates for colostomy-free survival. (A) All patients. (B) Patients with tumors located within 5 cm from the anal verge. CRT, chemoradiotherapy.

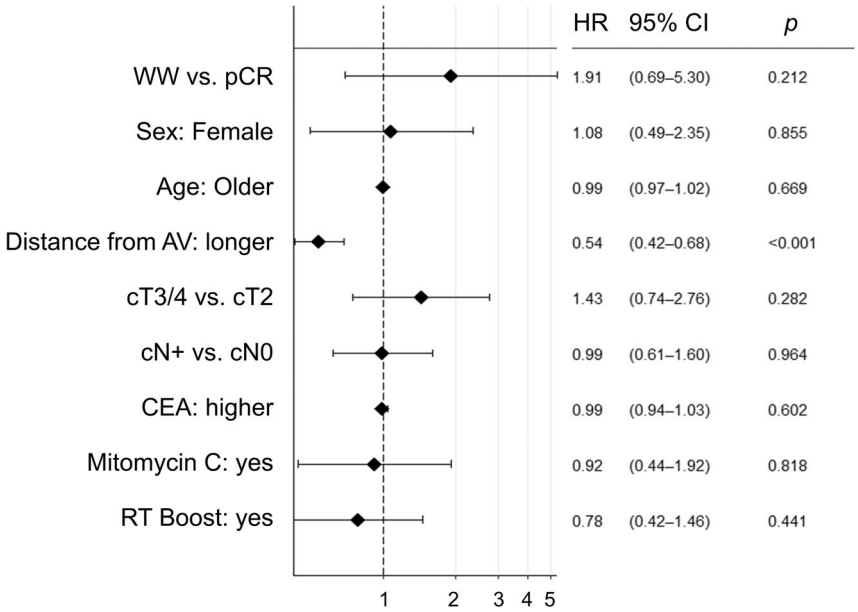

FIGURE 4 | Results of a multivariate Cox regression analysis for colostomy-free survival. AV, anal verge; CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; pCR, pathological complete response; RT, radiotherapy; WW, watch-and-wait.

were observed in two patients who had adhesion ileus and four patients who underwent Hartmann's procedure because of anastomosis stenosis and ischemic bowel. Multivariate Cox regression revealed that a long distance between the tumor and the anal verge was an independent factor associated with a reduced risk of colostomy (HR: 0.54; $p < 0.001$; Figure 4). Notably, for patients with tumors located within 5 cm of the anal verge, the likelihood of long-term sphincter preservation was higher in the case group than in the control group (83.3% vs. 41.9%, respectively; $p = 0.036$). Furthermore, for the aforementioned patients, the rate of 10-year CFS was significantly higher in the case group than the control group (HR: 0.22; 95% CI: 0.05–0.96; log-rank $p = 0.032$; Figure 3B).

Tumor distance from the anal verge exerted no significant effect on the rate of sphincter preservation in the case group ($p = 0.451$). Logistic regression indicated no clinical characteristic as an independent factor associated with the rate of sphincter preservation (all $p > 0.05$). Furthermore, additional radiation boost or mitomycin C exerted no significant effect on CFS in the case group.

3.5 | Nonsurgical Management in Patients Achieving a CMR

All patients in the case group underwent endoscopic reassessments after chemoradiotherapy. The case group included 20 patients who had achieved a complete endoscopic response at the initial assessment (patients selected on the basis of endoscopic findings) and 13 patients with near-cCR upon endoscopy who had achieved a CMR (patients selected on the basis of a CMR). Among patients selected on the basis of a CMR, the residual ulcers usually transformed into scars 8–19 months after chemoradiotherapy. However, one patient with scar formation at 9 months developed inguinal nodal and distant metastases 12 and 32 months, respectively, after chemoradiotherapy. The

median time from chemoradiotherapy to CMR assessment was longer than that from chemoradiotherapy to endoscopy (127 [IQR: 108–266] vs. 83 [IQR: 49–207] days, respectively; $p = 0.020$).

In this study, the proportion of patients with a sustained cCR (for at least 2 years) was higher among patients selected on the basis of a CMR than among those selected on the basis of endoscopic findings (92% vs. 60%, respectively; $p = 0.032$). Logistic regression revealed that a CMR (odds ratio: 8.67; 95% CI: 1.31–173.44) and an increased tumor distance from the anal verge (odds ratio: 2.11; 95% CI: 1.19–4.64) were associated with an increased likelihood of sustained cCR. Multivariate Cox regression indicated no significant effect of additional radiation boost or mitomycin C on the rate of nonregrowth DFS, DMFS, OS, or CFS (all $p > 0.05$). Because the PET scan has recently been included in our protocol for managing patients with rectal cancer, the follow-up period was relatively short for patients with a CMR. During the 5-year period, no significant difference in OS was observed between patients selected on the basis of a CMR and those selected on the basis of endoscopic findings (all $p > 0.05$; Supporting Information S1: Figure S2).

4 | Discussion

Herein, we present our 20-year experience in managing rectal cancer patients who had achieved a cCR and were thus managed using the WW strategy after chemoradiotherapy. The 3-year OS rates were similar between the case (96.6%) and control (97.9%) groups, aligning with the 96% reported in the OnCoRe project [12]. Permanent colostomy could be avoided in > 80% of our case group without compromising oncological safety during the 5-year follow-up period; this finding is consistent with that of MSKCC study (5-year CFS rate: 79%–82%) [15]. Although evidence suggests that the 3-year CFS rate is better in patients managed using the WW strategy than in those achieving a pCR [12, 16, 17], our long-term study revealed no significant between-group difference in the 10-year CFS rate. Nevertheless, for patients with a tumor–anal verge distance of < 5 cm, long-term CFS was superior in our case group than in our control group.

Dose-escalated radiotherapy with additional boost and intense chemotherapy with mitomycin C offered limited survival benefits for patients managed using the WW strategy. Studies have demonstrated that these interventions did not significantly increase the rate of complete response or OS; in fact, the administration of additional mitomycin C was associated with an increased level of toxicity [18, 19]. In our study, the rate of 2-year local regrowth (18.9%) aligns with the range reported in previous meta-analyses and large-scale registries (15.7%–25.9%) [10, 13, 14]. Researchers from MSKCC endorsed the safety of the WW strategy, reporting a 5-year OS rate of 73% and 94% in the WW and pCR group, respectively [15]. These findings are corroborated by our analysis (5-year OS rate: 88.2% in the case and 92.2% in the control group). Nevertheless, the long-term follow-up in the present study revealed significant differences in survival trajectories between the case and control groups (10-year OS: 45.7% vs. 84.8%, respectively). These differences may be due to the older age of the case group, but the survival gap persisted even after adjusting for age. One potential factor for worse OS in the case group is the occult nodal metastases undetected by imaging that might have been addressed by surgery. We further compared the case group with patients who achieved a pCR in the primary tumor but had residual nodal disease after chemoradiotherapy (ypT0N+). While there were no significant differences in non-regrowth DFS or DMFS between these groups, the case group showed better OS (Supporting Information S1: Figure S3). This trend remained consistent when limiting the analysis to patients who were clinically node-positive at initial diagnosis. The finding aligns with prior studies, suggesting that although surgery theoretically addresses residual nodal disease, outcomes of ypT0N+ patients are similar to those of ypT1-2N+ patients [21, 22]. In our study, imaging assessments of nodal response after neoadjuvant CRT may have helped identify true N0 patients in the case group. However, imaging limitations could miss some N+ cases, potentially contributing to the reduced survival in the case group compared to the ypCR group. Caution should be exercised when prescribing the WW strategy to patients achieving a cCR.

A major challenge for the adoption of the WW strategy lies in identifying suitable candidates for nonsurgical management [23, 24]. A complete endoscopic response does not guarantee a pCR; approximately 27% of patients achieving a complete endoscopic response may harbor residual tumors in deeper layers of the rectal wall and mesorectum [25]. Despite the common practice of conducting random biopsies to confirm complete response, current consensus does not support this practice because of a high rate of false-negative results [20]. In our study, thirteen patients in the case group had negative results in initial biopsies, but seven of them experienced local regrowth during the follow-up period. Although MRI remains the primary modality for staging rectal cancer, its accuracy in assessing posttreatment response varies because of the difficulty in differentiating tumors from postradiation inflammation [26]. PET may offer additional insights in this context. Tumors' metabolic characteristics, such as posttreatment maximum standard uptake (SUVmax) and SUV percentage change, are strongly associated with pathological response and DFS [27–29]. A systematic review reported that a > 63% reduction in SUVmax and a posttreatment value of < 4.4 indicated a pCR [30]. In general, posttreatment SUVmax exhibits a strong negative predictive value for pCR, effectively identifying candidates unsuitable for the WW strategy. However, its low positive predictive value for pCR highlights its limited accuracy in safely selecting patients for organ preservation [31]. In our study, some patients with near-cCR upon endoscopy and positive posttreatment PET results were ultimately proved to have residual tumors. On the other hand, among the 13 patients with an initial near-cCR and CMR, three developed local regrowth during the follow-up period. The routine use of PET for rectal cancer surveillance is not endorsed by the current consensus because of its low positive predictive value for responders, high costs, and limited availability [23]. Instead, PET is primarily recommended for patients with suspected distant metastasis or inconclusive findings. Our study validates that PET is useful for patients with near-cCR who opt for organ preservation. Our patients achieving a CMR (as indicated by PET), despite near-cCR endoscopic results, exhibited 5-year survival rates similar to those

in patients achieving a complete endoscopic response. This finding highlights the potential of PET to facilitate patient selection for the WW strategy.

A key factor for the WW strategy is the timing of response assessment after chemoradiotherapy. In our case group, the median interval from chemoradiotherapy completion to a complete endoscopic response was 12 weeks. This duration aligns with the reported duration associated with a high rate of pCR [32, 33], and the global consensus also recommends an initial assessment at 12 weeks from the initiation of treatment, and a repeat assessment at 16–20 weeks if necessary [20]. Notably, this recommendation is based primarily on endoscopic and MRI data; the optimal timing for the PET assessment remains to be determined [34]. Evidence suggests that a prolonged chemoradiotherapy–PET interval (>7 weeks) can improve the accuracy of identifying good responders [29]. In a study by Perez et al., a reduction in SUVmax 12 weeks after treatment was used to predict a complete response [35]. In our cohort, the median interval to PET assessment was 18 weeks. The delayed PET allowed for the evaluation of the comprehensive effect of radiation on tumors and yielded a relatively reliable SUVmax value. These advantages enabled patients with an initial partial response to benefit from organ preservation during an extended wait period [36].

To the best of our knowledge, this study is the first to evaluate the long-term outcomes of patients managed using the WW strategy, particularly those who have achieved a CMR. Our study, which had a median follow-up duration of 89 months, offers longer-term surveillance data than did other studies. However, our study has several limitations. First, the study was limited by its retrospective nature. Because the choice between the WW strategy and the surgery was predominantly driven by the patients, the case group mostly included older patients and those who received a higher RT dose. This higher dose was intended to enhance local control for those opting against surgery. A matched-group design would have facilitated a more robust comparison. Notably, the rates of survival in the present study align with those reported in previous propensity score–matched analyses [12, 17]. Furthermore, the WW strategy remained an independent factor for long-term survival even after age adjustment. Second, our recent incorporation of PET in the WW strategy reduced the duration of follow-up for patients with a CMR. Finally, the off-protocol nature of the WW strategy reduced the sample size and thus statistical power. Large prospective studies are needed to optimize patient selection for the WW strategy.

5 | Conclusion

Our findings suggest that the WW strategy improves the likelihood of long-term sphincter preservation, particularly in patients with low-lying tumors. However, this approach is associated with poor nonregrowth DFS outcomes compared with those in patients achieving a pCR after radical resection. Furthermore, the patients achieving a CMR exhibited 5-year survival rates similar to those in patients achieving a complete endoscopic response. Thus, PET may be useful for patients with near-cCR upon endoscopy.

Author Contributions

S.F.C. and L.W.W. analyzed the data, performed the statistical analyses, and supervised the study. L.W.W., S.H.Y., and J.K.J. contributed to data collection and interpretation. All authors reviewed and approved the final version of the manuscript.

Acknowledgments

The authors have nothing to report.

Ethics Statement

The present study was approved by the Institutional Review Board of Taipei Veterans General Hospital, Taiwan (permit number: 2023-12-002BC).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.