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Review

An Evidence-Based Review of Watch-and-Wait Strategy in Locally Advanced Rectal Cancer Achieving Complete Response After Neoadjuvant Chemoradiotherapy

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Abstract

To compare the clinical outcomes of the W&W strategy and surgery in locally advanced rectal cancer patients who achieved a clinical complete response (cCR) status post-neoadjuvant therapy.

We searched for meta-analyses, clinical trials, and observational studies comparing two treatment strategies up to May 2023 in several databases, including PubMed, Embase, and Cochrane Library. We reported the article selection process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and appraised the studies using the Oxford Center for Evidence-Based Medicine criteria.

From 164 articles, we included two meta-analyses, one clinical trial, and four observational studies that met the criteria of validity, importance, and applicability. These studies indicated that the proportion of patients adopting the W&W strategy was limited. Most studies showed that the W&W group had a higher local recurrence rate than the surgery group. However, there was no significant difference in metastasis rates, disease-free survival (DFS), and overall survival (OS).

The W&W strategy could be decided upon by a multidisciplinary approach in rectal cancer patients achieving cCR status after neoadjuvant therapy. Despite the higher local recurrence rate in the W&W group, strict surveillance and salvage therapy could provide a similar outcome.

Keywords: Chemoradiotherapy, neoadjuvant therapy, rectal neoplasms, treatment outcome, watch-and-wait

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Colorectal cancer remains one of the cancers with the highest incidence in the world.[1,2] Approximately thirty percent of colorectal cancer cases occur in the rectum. Surgery has been the primary treatment for rectal cancer.[3] However, some cases with locally advanced stages cannot be treated with surgery alone, requiring neoadjuvant therapy to downsize the tumor before surgery.[4] Providing radiotherapy, chemotherapy, or a combination of both has proven effective in reducing tumor size, even in achieving a complete clinical response (cCR).[4]

Several guidelines for rectal cancer management still recommend total mesorectal excision (TME) after neoadjuvant chemoradiation therapy as the standard treatment for locally advanced rectal cancer.[5–7] However, this procedure carries a risk of complications, such as bleeding, intestinal obstruction, and anastomotic leakage, and has a negative impact on defecation, urinary tract, and sexual function.[8–10] Therefore, the importance of TME in cases of locally advanced rectal cancer that achieve cCR after neoadjuvant therapy has become controversial.

First introduced through a case series study in 2004, the W&W strategy was considered safe and effective in patients who achieved a complete response after neoadjuvant therapy, with better organ preservation outcomes.[11] Several studies have supported this, some of which are reflected in rectal cancer management guidelines by the National Comprehensive Cancer Network (NCCN), which mention the W&W strategy.[7,8,11,12] The W&W strategy has been considered in the NCCN guidelines since 2018.[5,7] In line with the development of research findings, the NCCN guidelines

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in 2023 explained the principles of non-operative management of rectal cancer patients who achieve cCR after neoadjuvant therapy, including the criteria for patients who are suitable for non-operative management and the recommendations for surveillance.[13]

On the other hand, some studies remain skeptical about this approach.[14] Other studies have also shown higher local recurrence rates in patients undergoing the W&W strategy after achieving cCR post-neoadjuvant therapy.[15–17] Thus, this study aims to compare the outcomes of the W&W strategy with surgery in patients with locally advanced rectal cancer who achieved cCR after neoadjuvant chemoradiation therapy, including the rate of local recurrence and metastasis.

Methods

Literature Search Strategy

According to the Centre for Evidence-Based Medicine (CEBM), University of Oxford, we conducted this evidence-based case report. We reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched for articles using several online databases, including PubMed, Embase, and Cochrane Library (Table S1) on May 6, 2023, using the PICO criteria:

- **Population:** Patients with locally advanced rectal cancer (LARC) achieving cCR after neoadjuvant chemoradiotherapy.
- **Intervention:** Watch-and-wait strategy.
- **Comparator:** Surgery.
- **Outcome:** Recurrence rate and survival.

After searching for articles, we screened for similar articles in each database. The screened articles were selected using the eligibility criteria determined by the title and abstract.

Eligibility Criteria

We included meta-analyses, randomized controlled trials, and observational studies comparing the watch-and-wait (W&W) strategy with surgery in patients with LARC achieving cCR after neoadjuvant chemoradiotherapy. Literature reviews, case reports, and conference proceedings were excluded from this study.

Risk of Bias Assessment

We critically appraised the included articles using the Centre for Evidence-Based Medicine (CEBM), University of Oxford guidelines. We used a critical appraisal tool from CEBM for therapy studies and a FAITH instrument for meta-analyses. Critical appraisal assessed the validity, importance, and applicability of the included studies.

Results

We searched for literature in three databases: PubMed, Embase, and Cochrane Library. We used "rectal cancer," "watch-and-wait strategy," "surgery," and "recurrence or metastasis," as well as synonyms, as keywords (Table S1). We found 164 articles from a literature search (Fig. 1). We removed the duplicate articles, obtaining 140 articles. We screened the articles that met the eligibility criteria, resulting in 10 articles included for full-text review. Finally, we included two meta-analyses[18,19], one clinical trial[20], and four observational studies[21–24] for critical appraisal. Critical appraisal was conducted according to the Centre for Evidence-Based Medicine (CEBM). The level of evidence (LoE) was also determined based on Oxford CEBM 2011. We assessed each study's validity, importance, and applicability (Tables 1, 2).

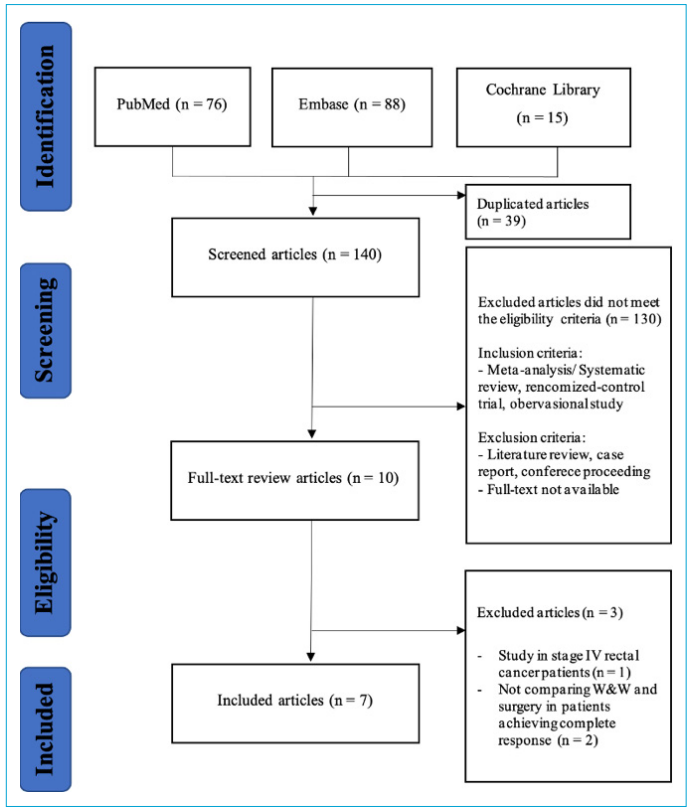

Figure 1. Results of literature search.

Table 1. Critical appraisal of meta-analysis

Study/Level of evidence	Validity						Importance	Applicability
	Question	Find	Appraise	Include	Total up	Heterogeneity		
Yu et al.[18], 2021/1	+	+	+	+	+	+	+	+
Kim et al.[19], 2017/1	+	+	+	?	+	+	+	+

Table 2. Critical appraisal of therapy study

Study/Level of evidence			Validity					Importance			Applicability		
	Study design	Sample size	Randomization	Drop out <20%	Similar subject characteristics	Equal treatment	Blinding	Domain	Determinant	Outcome	Patient preferences
Garcia-Aguilar et al.[20], 2022/2	Randomized phase II trial	324	+	+	-	+	-	+	+	+	+
Han et al.[21], 2022/3	Prospective cohort	84	-	+	+	+	-	+	+	+	+
Zhang et al.[22], 2021/3	Retrospective cohort	212	-	N/A	?	+	-	+	+	+	
Smith et al.[23], 2019/3	Retrospective cohort	249	-	N/A	+	+	-	+	+	+	+
Yeom et al.[24], 2019/3	Retrospective cohort	144	-	N/A	-	+	-	+	+	+	+

Characteristics of the Included Studies

We found six articles that met the eligibility criteria. Tables 3–6 show the characteristics of the included studies based on the study design. Most of the included studies showed that the number of patients in the surgery group was higher than in the W&W group.[18,19,22–24] Meanwhile, the study by Garcia-Aguilar et al.[20] and Han et al.[21] recruited more subjects in the W&W group because the study was conducted prospectively. Habr-Gama (2004) first introduced the W&W strategy in patients with rectal cancer post-chemoradiation.[11] However, it remained controversial due to the different results from other studies. The NCCN initially recommended the W&W strategy in rectal cancer patients achieving cCR post-neoadjuvant therapy in 2018.[7] It has been constantly updated, with the surveillance protocol quoted in NCCN 2022.[5] This was led by the results of a trial by Garcia-Aguilar et al.[20] conducted multicentrally. Therefore, the W&W strategy was rarely performed in retrospective studies.

Age was also related to the treatment decision after nCRT. Some studies showed that the patients in the W&W group were older than those in the surgery group.[21,23,24] The study by Smith et al.[23] and Yeom et al.[24] showed that there was a significant difference in age between the two groups. The patients in the W&W strategy in the study by Jimenez-Rodriguez[9] were also significantly older than surgery patients. The age might be related to the patients' conditions; older patients have a higher risk for surgery regarding comorbidity, frailty, and complication.[9,25,26] This led to clinicians' tendency to perform the W&W strategy in elderly patients.[25] The difference in age between groups also affected the results of the included studies. The study by Smith et al.[23] and Yeom et al.[24] reported that the DFS and OS in the W&W group were lower than in the surgery group.

Moreover, the study by Jimenez-Rodriguez[9] also reported that the treatment decision considered tumor location. The location of the tumor in patients who chose the W&W strategy was closer to the anal verge due to the difficulty of sphincter preservation, leading to selection bias in the study.

The included studies also showed a higher proportion of male patients than female patients in both groups.[20–24] This was consistent with the data from GLOBOCAN 2020, which reported that the incidence of rectal cancer was higher in men, almost twice as high as in women.[27] Moreover, colorectal cancer was the cause of death in 0.66% of men and 0.44% of women.[28]

Six studies corresponded to the clinical question, involving only locally advanced rectal cancer before nCRT. The regimen of nCRT varied in each included study, as shown in Tables 3–6. LCCRT was the most common regimen given to the patients, with a total radiation dose of 45–56 Gy, concur-

Table 3. Characteristics of meta-analysis studies

No.	Study	Design	Objective	Population (n)	Age (years)	Sex (male; %)	Clinical stage pre nCRT	nCRT regimen	Follow-up period (months)
1.	Yu et al.[18], 2021/1	Meta-analysis (9 articles)	To determine the safety and efficacy of the W&W strategy with compared to TME for rectal cancer patients achieving cCR after nCRT.	818 TME: 479 W&W: 339	TME: 53.6 - 69 W&W: 50 - 67.5	NI	Stage I - III T3-4: 86.4% N1-2: 63.9%	IMRT 45 - 50.4 Gy/ 25 - 28 fx with oral sensitizer (capecitabine oral 825 mg/m^2/bid)	TME: 35 - 72 W&W: 25 - 72
2.	Kim et al.[19], 2017/1	Meta-analysis (4 articles)	To compare oncological outcomes (recurrence, DFS, and OS) between the W&W and TME groups in rectal cancer patients achieving pCR or cCR post nCRT.	313 TME: 215 W&W: 98	NI	NI	Stage II - III	Radiation dose ranged 45 - 50.4 Gy, concurrent with 5-FU IV or oral capecitabine	NI

cCR: clinical complete response; DFS: disease-free survival; FU: fluorouracil; fx: fractions; IMRT: intensity modulated radiotherapy; nCRT: neoadjuvant chemoradiation therapy; NI: no information; OS: overall survival; pCR: pathological complete response; TME: total mesorectal excision; W&W: watch-and-wait strategy.

Table 4. Characteristics of clinical trial.

No.	Study	Design	Objective	Population (n)	Age (years)	Sex (male; %)	Clinical stage pre nCRT	nCRT regimen	Follow-up period (months)
1.	Garcia-Aguilar et al.[20], 2022/2	Randomized phase II trial	To evaluate the efficacy of the W&W strategy for organ preservation in patients with local stage rectal cancer who have undergone total neoadjuvant therapy, as well as determining the rate of organ preservation in patients who underwent INCT-CRT with CRT-CNCT	324 INCT-CRT (146) Surgery: 41 W&W: 105 CRT-CNCT (158) Surgery: 38 W&W: 120	INCT-CRT: 59 (IQR 51-68) CRT-CNCT: 56 (IQR 49-67)	INCT-CRT: 65 CRT-CNCT: 61	Stage II (T3-4, N0) or Stage III (T1-4, N1-2) INCT-CRT Tumor: T1-2 (7%); T3 (78%); T4 (15%) Nodal: N- (30%); N+ (70%) CRT-CNCT Tumor: T1-2 (13%); T3 (76%); T4 (11%) Nodal: N- (28%); N+ (72%)	Radiotherapy (IMRT/ 3D-CRT 45 Gy/25 fx + local booster up to total dose of 50-56 Gy) + capecitabine (825 mg/m^2, bid) or FU (225 mg/m^2/day) Induction or consolidation chemotherapy (FOLFOX or CapeOx)	36 (IQR 22.1-48.7)

cCR: clinical complete response; CRT-CNCT: chemoradiotherapy-consolidation chemotherapy; FU: fluorouracil; fx: fractions; INCT-CRT: induction chemotherapy-chemoradiotherapy; IQR: inter-quartile range; nCRT: neoadjuvant chemoradiation therapy; TME: total mesorectal excision; W&W: watch-and wait strategy.

Table 5. Characteristics of observational studies.

No.	Study	Design	Objective	Population (n)	Age (years)	Sex (male; %)	Clinical stage pre nCRT	nCRT regimen	Follow-up period (months)
1.	Han et al.[21], 2022 / 3	Prospective cohort	To compare long-term outcomes between the W&W strategy and surgery in patients with locally advanced rectal cancer.	84 TME: 26 W&W: 58	57.9±1.18 TME: 58.4 (±1.70) W&W: 57.6 (±1.54)	66.7 TME: 65.4 W&W: 67.2	Locally advanced stage (cT3-4, N0 and any T, N + cM0) Tumor: T2 (7.1%); T3 (83.3%); T4 (9.5%) Nodal: N1 (78.6%); N2a (17.9%); N2b (3.6%)	SCRT (30 Gy/ 10 fx) or LCCRT (50.6 Gy/ 22 fx), with capecitabine oral 825 mg/m2 bid, day 1-5 weekly. (a) 50.6 Gy/22 fx + capecitabine (84.5%) (b) 51 Gy/34 fx + capecitabine (8.3%) (c) 30 Gy/10 fx + capecitabine (7.1%)	TME: 35 - 72 W&W: 25 - 72
2.	Zhang et al.[22], 2021/3	Retrospective cohort	To identify the criteria of rectal cancer patients who would benefit from surgery after achieving cCR following nCRT. - Low risk patient (CA19-9<35 U/mL and CEA<5 ng/mL) - High risk patient (CA19-9>35 U/mL or CEA>5 ng/mL)	212 TME: 160 W&W: 52	58 (IQR 47 - 65)	62.3	Locally advanced stage (T1-4 N1-2 M0 and T3-4 N0 M0) Tumor: T2 (7.1%); T3 (68.9%); T4 (24.1%) Nodal: N0 (25.5%); N1 (48.1%); N2 (26.4%)	IMRT 50 Gy/25 fx + capecitabine 1000 mg/m2 bid, 14 days, 3-weekly + oxiplatin 100 mg/m2, 1 day), followed by 1 cycle of CapeOx (optional) 3 - 4 cycles neoadjuvant chemotherapy: CapeOx (capecitabine 1000 mg/m2 bid, 14 days, 3-weekly + oxiplatin 130 mg/m2, 1 day)	NI

cCR: clinical complete response; fx: fractions; IMRT: intensity modulated radiotherapy; IQR: inter-quartile range; LCCRT: long-course chemoradiotherapy; nCRT: neoadjuvant chemoradiation therapy; NI: no information; SCRT: short-course radiotherapy; TME: total mesorectal excision; W&W: watch-and-wait strategy.

rently with oral capecitabine or 5-fluorouracil.[18–24] Induction or consolidation chemotherapy with the FOLFOX or CapeOx regimen was tentatively given in some studies.[20–23]

The NCCN recommended the use of LCCRT or SCRT for total neoadjuvant therapy for inoperable locally advanced rectal cancer.[5] SCRT was administered at a total dose of 25 Gy in 5 fractions, while LCCRT was administered at a total dose of 44–50 Gy in 25–28 fractions.[5] The guideline by EURECCA also recommended neoadjuvant chemoradiotherapy with a total dose of 50–54 Gy, concurrently with 5-FU, to escalate resectability.[6] The highest radiation dose was given in the study by Garcia-Aguilar et al.,[20] with a total dose of 50–56 Gy to the gross tumor and gross nodes. The study by IWWD (2018) also administered a total dose of 45–60 Gy concurrently with capecitabine or 5-FU.[17]

A prospective observational study by Appelt et al.[10] also administered radiotherapy in 51 patients with escalated doses up to 60 Gy in 30 fractions to the tumor, 50 Gy in 30 fractions in regional lymph nodes, and 5 Gy of endorectal brachytherapy, concurrently with oral tegafururacil 300 mg/m^2. It reported that the local recurrence rate in one year reached 15.5% (95% CI 3.3–26.3), with the most common grade-3 acute toxicity being diarrhea (8%) and grade-3 late toxicity being rectal bleeding (7%) in one year.[10] The study proved that the W&W strategy had better sphincter preservation without fecal incontinence reported.[10]

The follow-up period of the included studies varied. Due to prospective data collection, Han et al.[21] showed no significant difference in the follow-up period between the two groups. Meanwhile, the retrospective studies by Smith et al.[23] and Yeom et al.[24] showed that the median follow-up period in the W&W group was shorter than in the surgery group. This might affect the results of the studies, leading to a higher risk of bias in retrospective studies.

Discussion

The clinical practice guideline for rectal cancer by the NCCN in 2023 included the non-operative management (NOM) protocol.[13] It featured multidisciplinary team collaboration as crucial for

Table 6. Characteristics of observational studies. (cont.)

No.	Study	Design	Objective	Population (n)	Age (years)	Sex (male; %)	Clinical stage pre nCRT	nCRT regimen	Follow-up period (months)
3.	Smith et al.[23], 2019 / 3	Retrospective cohort	To analyze the outcomes of W&W strategy in rectal cancer patients who achieved cCR after nCRT	249 TME: 136 W&W: 113	TME: 57.3 (25.0 - 87.9) W&W: 67.2 (32.1 - 90.9) TME vs W&W: P < 0.001	TME: 58 W&W: 59 TME vs W&W: P = 0.90	TME Tumor: T2 (20%); T3 (76%); T4 (4%) Nodal: N0 (32%); N1-2 (68%) W&W Tumor: T2 (20%); T3 (80%); T4 (0%) Nodal: N0 (35%); N1-2 (66%) TME vs W&W Tumor (P = 0.13); Nodal (P = 0.63)	(a) LCRT 45 - 54 Gy/ 25 - 28 fx + 5-FU IV/ capecitabine oral (most common) (b) Induction chemotherapy (8 cycles of FOLFOX), followed by LCRT (c) LCRT followed by consolidation chemotherapy (8 cycles of FOLFOX) (d) 8 cycles of FOLFOX + bevacizumab (most infrequent)	43 (IQR 27-43) TME: 55 W&W: 33
4.	Yeom et al.[24], 2019 / 3	Retrospective cohort	To investigate the W&W protocol outcomes in rectal cancer patients who achieved cCR post nCRT	169 RS: 129 LE: 25 W&W: 15	RS: 63.8 (33 - 83) LE: 73.0 (44 - 81) W&W: 74.0 (39 - 89) P < 0.001	RS: 72.9 LE: 60 W&W: 53.3 P = 0.167	RS: Tumor: T1-2 (6.2%); T3-4 (93.8%) Nodal: N0 (58.1%); N+ (41.9%) LE: Tumor: T1-2 (8.0%); T3-4 (20.0%) Nodal: N0 (76.0%); N+ (24.0%) W&W: Tumor: T1-2 (20.0%); T3-4 (80.0%) Nodal: N0 (33.3%); N+ (66.7%) TME vs W&W Tumor: P = 0.029 Nodal: P = 0.104	LCRT 50.4 Gy/ 28 fx + 5-FU chemotherapy	RS: 48 (5-100) LE: 30 (2-93) W&W: 20 (2-56) P < 0.001

cCR: clinical complete response; FU: fluorouracil; fx: fractions; IMRT: intensity modulated radiotherapy; IQR: inter-quartile range; IV: intravenous; LCRT: long-course radiotherapy; LE: local excision; nCRT: neoadjuvant chemoradiation therapy; RS: radical surgery; TME: total mesorectal excision; W&W: watch-and-wait strategy.

treatment decisions. The patients also had to commit to following the surveillance protocol intensively.[13] The surveillance protocol for patients committed to NOM consisted of history taking, physical examination, and CEA examination every 3–6 months for two years, followed by every six months for five years; endoscopy, as well as proctoscopy or sigmoidoscopy, every 3–4 months for two years, followed by every six months for five years; rectal MRI every six months for at least three years; thoracoabdominal CT every 6–12 months for five years; and pelvic CT if MRI was not performed.[13,20,29,30] Colonoscopy was performed one year after the completion of therapy. If an adenoma was found, a colonoscopy had to be repeated after a year. If an adenoma was not found, a colonoscopy could be performed after three years, followed by every five years.[13,20,29,30]

The criteria for cCR after neoadjuvant therapy were also determined using high-definition endoscopy, digital rectal examination, and MRI.[13] Biopsy and tumor DNA examination were not recommended if the patients had met those criteria.[8,13] The criteria for cCR were determined one month after the completion of chemotherapy for patients who had undergone CRT-CNCT or eight weeks after the completion of radiotherapy for patients who had undergone INCT-CRT while waiting for the late radiation response.[13,20]

The comparison of oncological outcomes between included studies is shown in Tables 7–10. Two meta-analyses showed that the local recurrence rate in the W&W group was significantly higher compared to the TME group.[18,19] Similar results were shown in clinical trials and observational studies.[20–24]

The results of a multicenter study by IWWD (2018)[17] in 880 patients reported that the incidence of local regrowth in two years reached 25.2% (95% CI 22.2–28.5%), with 88% occurring in the first two years, and 97% located in the bowel. The significant difference in LRFS in the study by Zhang et al.[22] was found in low-risk patients with low levels of CA19-9 and CEA, while the LRFS was not significantly different in high-risk patients.

Moreover, the study by Garcia-Aguilar et al.[20] showed that the recurrence rate was higher in patients with the INCT-CRT protocol (40%) compared to the CRT-CNCT protocol (27%), with TME-free survival in three years in the INCT-CRT and CRT-CNCT groups reaching 47% (95% CI 39–56%) and 60% (95% CI 52–68%), respectively (p=0.02). The study by Asoglu et al.[15] reported that TME-free DFS and organ preservation rates in five years in the W&W group reached 77.5% (95% CI 63.2–91.8%) and 85.0% (95% CI 72.3–97.8%), respectively.

Patients who experienced local regrowth during the W&W strategy were advised to undergo surgery. The study by Garcia-Aguilar et al.[20] reported that local regrowth would occur in 33% of patients in the W&W strategy, and TME was recommended within approximately 30 (IQR 20–103) weeks after restaging post-neoadjuvant therapy. The study by IWWD showed that 213 out of 880 patients with the W&W strategy post-neoadjuvant therapy would experience local regrowth. Among them, 148 patients underwent surgery, including 31% local excision and 78% TME. It also stated that local regrowth rarely could not be salvaged.[17] Of 115 patients with curative resection, 88% achieved a negative surgical margin.[17] Salvage surgery had a favorable outcome if local regrowth was detected early through a committed surveillance protocol.[15]

In contrast to the local recurrence rate, the included studies reported that the rate of distant metastasis, DFS, and OS in the W&W group was not significantly different compared to the surgery group.[18–24] The study by IWWD[17] reported that distant metastasis occurred in 71 of 880 patients with the W&W strategy, with the distant metastasis rate in three years reaching 8.1% (95% CI 6.2–10.5). Distant metastasis commonly occurred in the lung (62%), liver (41%), distant lymph nodes (11%), and peritoneum (6%). Of patients with local regrowth, 18% developed distant metastasis.

Based on the study by IWWD,[17] the DFS and OS rates in patients with the W&W strategy reached 93.8% (95% CI 90.9–95.9) and 84.7% (CI 80.9–87.7), respectively. DFS and OS declined in patients with local regrowth, reaching 84.0% (95% CI 75.0–89.9) and 75.4% (95% CI 66.2–82.4), respectively.[17] However, the study by Garcia-Aguilar et al.[20] showed that there was no significant difference in DFS rate and sphincter-saving surgery rate between patients undergoing TME at restaging post-neoadjuvant therapy and those undergoing TME for local regrowth in the W&W group.[20] The study by Asoglu et al.[15] also showed that the DFS and OS rates in patients who underwent salvage surgery after local regrowth reached 80% and 94.9%, respectively.

Additionally, Zhang et al.[22] showed that there was a significant difference in DMFS and DFS rates between the W&W group and TME group in low-risk rectal cancer patients, characterized by a baseline level of CA19-9 < 35 U/mL and CEA < 5 ng/mL. Therefore, the study stated that TME was more beneficial for low-risk rectal cancer patients.[22]

Table 7. Comparison of results, strengths, and weaknesses between the included meta-analysis studies.

No	Study	Local recurrence	Distant metastasis	Disease-free survival	Overall survival	Strengths	Weaknesses
1.	Yu et al.[18], 2021 / 1	TME: 0.8% W&W: 10.8% TME vs W&W: OR 8.54, 95% CI 3.52 – 20.71, P < 0.001	TME: 8.6% W&W: 10.2% TME vs W&W: OR 1.12, 95% CI 0.68 – 1.84, P = 0.67	TME: 96.3% W&W: 96.9% DFS 5 years TME vs W&W: OR 1.79, 95% CI 0.27 – 11.80, P = 0.54	TME: 92.4% W&W: 93.2% OS 5 years TME vs W%W: OR 1.03, 95% CI 0.39 – 2.75, P = 0.95	- The study answered the clinical question. - Critical appraisal was conducted using Newcastle-Ottawa scale (NOS) criteria, including high quality studies. - It compared characteristics of subject between included studies. - It combined the results of included studies, reported as a forest plot. - It analyzed the heterogeneity and consistency of data, reported as a funnel plot.	- No RCT and limited number of studies were included. - Some of included studies did not report clinical data in detail. - Chemoradiation regimens were not described in detail. - The detail data of T and N stages was lacking
2.	Kim et al.[19], 2017 / 1	TME: 1.9% W&W: 11.2% TME vs W&W: RR 0.18; 95% CI: 0.06 – 0.55	TME: 6.0% W&W: 5.1% TME vs W&W: RR 1.0; 95% CI: 0.37 – 2.70	TME vs W&W: HR 0.59; 95% CI: 0.32 - 1.10	TME vs W&W: HR 0.76; 95% CI 0.47 - 1.23	- The study answered the clinical question. - Critical appraisal was conducted using Newcastle-Ottawa scale (NOS) criteria. - It combined the results of included studies, reported as a forest plot. - It analyzed the heterogeneity and consistency of data	- No RCT and limited number of studies were included. - The number of subjects in TME group was twice greater than W&W group. - There was no data regarding time, methods, and effectiveness of salvage therapy. - Characteristics of subject from included studies was not reported. - Neoadjuvant chemoradiation regimens in each included study were not described in detail. - The quality of studies and the risk assessment of bias were not conducted.

cCR: clinical complete response; DFS: disease-free survival; HR: hazard ratio; nCRT: neoadjuvant chemoradiation therapy; OS: overall survival; OR: odds ratio; RCT: randomized-controlled trial; TME: total mesorectal excision; W&W: watch-and-wait strategy.

Table 8. Comparison of results, strengths, and weaknesses of the included clinical trial.

No	Study	Local recurrence	Distant metastasis	Disease-free survival	Overall survival	Strengths	Weaknesses
1.	Garcia-Aguilar et al.[20], 2022/2	TME at restaging: 8.9% Local regrowth pada W&W: 33.3% TME after local regrowth: 12%	TME at restaging: 20.3% TME after local regrowth: 18.7%	DFS 3 years INCT-CRT: 76% (95% CI, 69 - 84) CRT-CNCT: 76% (95% CI, 69 - 83)	NI	- The study answered the clinical question. - The study was conducted prospectively randomized in multicenter, avoiding the risk of bias. - The number of subjects was sufficient. - Study was implemented the intention-to-treat principle, with dropout rate < 20%. - The regimens of nCRT were reported. - The characteristics of subject was reported.	- The primary outcome of study was not to analyze the outcomes of W&W and surgery but comparing the regimen of neoadjuvant therapy. - The characteristics of subjects in W&W group and TME group were not compared. - The follow-up period had not reached 5 years. - Surgery was performed if there was residual tumor post nCRT, either at restaging or local regrowth in W&W group. - The trial was not blinded.

CRT-CNCT: chemoradiotherapy-consolidation chemotherapy; DFS: disease-free survival; INCT-CRT: induction chemotherapy-chemoradiotherapy; nCRT: neoadjuvant chemoradiation therapy; TME: total mesorectal excision; W&W: watch-and-wait strategy.

Limitations

This study has several limitations. First, there were limited RCTs comparing the W&W strategy with TME in patients with LARC who achieved cCR after neoadjuvant therapy. This might be due to the unfeasibility of conducting a double-blinded trial. The current RCTs conducted randomization to determine the regimen of neoadjuvant treatment. The strategy after neoadjuvant therapy was determined according to the clinical response after neoadjuvant therapy. Second, this study did not compare the outcomes and toxicity for each radiation dose in the range of 45–60 Gy, nor did it compare the chemotherapy regimens. Third, there are limited studies analyzing the criteria for patients who were not suitable for the W&W strategy.

Conclusion

This study compares the advantages and disadvantages of W&W strategies and surgery in patients with locally advanced rectal cancer achieving cCR after neoadjuvant therapy. Despite the higher rate of local recurrence, the W&W strategy could be considered through a multidisciplinary approach to improve organ preservation and avoid the risks and complications of surgery. An appropriate surveillance protocol according to practical guidelines should be implemented to detect local regrowth as early as possible so that salvage surgery can be performed immediately.

The rates of metastasis, DFS, and OS in patients who underwent the W&W strategy were not significantly different from those in patients who underwent surgery after neoadjuvant therapy. Local regrowth could degrade OS and DFS. However, if the patient immediately undergoes salvage surgery, the DFS rate of patients undergoing TME while experiencing local regrowth was not significantly different from that of those undergoing TME during restaging after neoadjuvant therapy. Therefore, with a surveillance protocol during the W&W strategy and salvage treatment, the W&W strategy can improve quality of life and achieve good clinical outcomes.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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Table 9. Comparison of results, strengths, and weaknesses between the included observational studies.

No	Study	Local recurrence	Distant metastasis	Disease-free survival	Overall survival	Strengths	Weaknesses
1.	Han et al.[21], 2022/3	TME: 3.8% W&W: 15.5% TME vs W&W: P = 0.127	TME: 11.5% W&W: 6.8% TME vs W&W: P = 0.477	DFS 3 years TME: 84.6% W&W: 81.1% TME vs W&W: P = 0.819	OS 3 years TME: 92.3% W&W: 96.6% TME vs W&W: P = 0.403	- The study answered the clinical question. - Study was conducted prospectively. - The characteristics of subject was not significantly different between two groups. - The regimen of nCRT was reported. - All subjects were included in statistical analysis, with dropout rate < 20%	- Small sample size - The study was not randomized and not blinded.
2.	Zhang et al.[22], 2021 / 3	LRFS 5 years Low risk group TME: 99.0% W&W: 82.0% TME vs W&W: P < 0.001 High risk group TME: 100% W&W: 94.1% TME vs W&W: P = 0.072	DMFS 5 years Low risk group TME: 95.9% W&W: 84.3% TME vs W&W: P = 0.028 High risk group TME: 77.9% W&W: 94.1% TME vs W&W: P = 0.143	DFS 5 years Low risk group TME: 95.9% W&W: 75.3% TME vs W&W: P < 0.001 High risk group TME: 72.3% W&W: 94.1% TME vs W&W: P = 0.152	OS 5 years Low risk group TME: 99.0% W&W: 92.3% TME vs W&W: P = 0.050 High risk group TME: 89.8% W&W: 87.5% TME vs W&W: P = 0.899	- The study answered the clinical question. - Sample size was sufficient. - Univariate and multivariate analysis were conducted. - The regimen of nCRT was reported. - The study analyzed the criteria of patients obtaining benefit of surgery after nCRT, considering the morbidity and risks of TME.	- Data was collected retrospectively without randomization and blinding, increasing the risk of bias. - The number of subjects in TME group was twice more than W&W group. - The characteristics of subject was not compared between groups. - Other factors which might be related, such as extramural vascular invasion and circumferential margin, was not analyzed.

cCR: clinical complete response; DFS: disease-free survival; DMFS: distant metastasis-free survival; LRFS: local recurrence-free survival; nCRT: neoadjuvant chemoradiation therapy; OS: overall survival; TME: total mesorectal excision; W&W: watch-and-wait strategy.

Table 10. Comparison of results, strengths, and weaknesses between the included observational studies. (cont.)

No	Study	Local recurrence	Distant metastasis	Disease-free survival	Overall survival	Strengths	Weaknesses
1.	Smith et al.[23], 2019/3	TME: 0% W&W: 19.5% TME vs W&W: not analyzed	TME: 3.7% W&W: 7.9% TME vs W&W: not analyzed	DFS 5 years TME: 92% (95% CI, 87 - 98%) W&W: 75% (95% CI, 62 - 90%) TME vs W&W: not analyzed	OS 5 years TME: 94% (95% CI, 90 - 99%) W&W: 73% (95% CI, 60 - 89%) TME vs W&W: not analyzed	- The study answered the clinical question. - Sample size was sufficient. - The characteristics of subject was compared between two groups. - The regimen of nCRT was reported. - Treatment for tumor recurrence after W&W was reported.	- Data was collected retrospectively without randomization and blinding, increasing the risk of bias, including selection and recall biases. - In W&W group, the median of age was significantly older, with smaller tumor size compared to surgery group. - Oncological outcome was not analyzed between two groups.
2.	Yeom et al.[24], 2019 / 3	RS: 12.4% LE: 20% W&W: 40% P = 0.019	RS: 68.8% LE: 20.0% W&W: 33.3% P = 0.096	DFS 5 years RS: 85.9% LE: 72.9% W&W: 27.8%	NI	- The study answered the clinical question. - The characteristics of subject was compared between two groups. - The regimen of nCRT was reported. - Salvage therapy in each group was reported.	- Data was collected retrospectively without randomization and blinding, increasing the risk of bias. - The number of subjects in W&W group was not comparable to other groups. - Age, tumor stage, and follow-up period was significantly different between groups. - OS was not analyzed.

cCR: clinical complete response; DFS: disease-free survival; LE: local excision; nCRT: neoadjuvant chemoradiation therapy; NI: no information; OS: overall survival; RS: radical surgery; TME: total mesorectal excision; W&W: watch-and-wait strategy.

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Table S1. Literature searching from online databases.

Database	Keywords	Hits
PubMed	((((Rectal Neoplasms[MeSH Terms]) AND (Neoadjuvant Therapy[MeSH Terms])) AND ((((((watch[Title/Abstract] AND wait[Title/Abstract]) OR (watch-wait[Title/Abstract])) OR (watch wait strategy[Title/Abstract])) OR (watch-and-wait strategy[Title/Abstract])) OR (watch-and-wait [Title/Abstract])) OR (watch-and-wait approach[Title/Abstract])))) AND (((((total mesorectal excision[Title/Abstract]) OR (TME[Title/Abstract])) OR (mesorectal excision[Title/Abstract])) OR (rectal surgery[Title/Abstract])) OR (rectal excision[Title/Abstract])))) AND ((((((((((Neoplasm Recurrence, Local[MeSH Terms]) OR (Recurrence[MeSH Terms])) OR (Recurrence[Title/Abstract])) OR (Relapse[Title/Abstract])) OR (recidivism [Title/Abstract])))) OR (Metastasis[Title/Abstract])) OR (Neoplasm Metastasis[MeSH Terms])) OR (Disease-Free Survival[MeSH Terms])) OR (Disease-Free Survival[Title/Abstract]))	61
EMBASE	('rectum cancer'/exp OR 'cancer of the lower rectum' OR 'cancer of the rectum' OR 'cancer of the upper rectum' OR 'cancer, rectum' OR 'malignancies of the rectum' OR 'malignancy, rectum' OR 'rectal cancer' OR 'rectal carcinogenesis' OR 'rectal malignancies' OR 'rectal malignancy' OR 'rectum cancer' OR 'rectum malignancy') AND ('watch-and-wait strategy':ti,ab OR 'watch and wait':ti,ab OR 'watch-and-wait approach':ti,ab OR 'wait and see':ti,ab) AND ('total mesorectal excision':ti,ab OR 'mesorectal excision'/exp OR 'rectal excision':ti,ab) AND ('recurrence risk'/exp OR 'recidivation risk' OR 'recidivism risk' OR 'recurrence rate' OR 'recurrence risk' OR 'relapse rate' OR 'risk recidivism' OR 'risk, recurrence' OR 'disease free survival':ti,ab OR 'metastasis'/exp OR 'cancer cell dissemination' OR 'cancer cell metastasis' OR 'cancer cell spread' OR 'cancer dissemination' OR 'cancer metastasis' OR 'cancer spread' OR 'carcinoma metastasis' OR 'disseminated tumor cell' OR 'disseminated tumour cell' OR 'metastases' OR 'metastasic type' OR 'metastasis' OR 'metastasis formation' OR 'metastatic cancer' OR 'metastatic cancers' OR metastatic carcinoma' OR 'metastatic carcinomas' OR 'metastatic disease' OR 'metastatic tumor' OR 'metastatic tumors' OR 'metastatic tumour' OR 'metastatic tumours' OR 'neoplasm metastasis' OR 'neoplastic cell dissemination' OR 'sarcoma metastasis' OR 'secondary cancer' OR 'secondary carcinoma' OR 'tumor dissemination' OR 'tumor metastasis' OR 'tumor migration' OR 'tumor spread' OR 'tumour dissemination' OR 'tumour metastasis' OR 'tumour migration' OR 'tumour spread')	88
Cochrane Library	#1 : MeSH descriptor: [Rectal Neoplasms] explode all trees #2 : (Rectal cancer):ti,ab,kw OR (Rectal malignancy):ti,ab,kw OR (Rectum cancer):ti,ab,kw OR (Rectum malignancy):ti,ab,kw #3 : #1 OR #2 #4 : (watch and wait approach):ti,ab,kw OR (watch and wait strategy):ti,ab,kw OR (watch and wait):ti,ab,kw OR (wait and see):ti,ab,kw #5 : (total mesorectal excision):ti,ab,kw OR (mesorectal excision):ti,ab,kw OR (rectal excision):ti,ab,kw #6 : MeSH descriptor: [Recurrence] explode all trees #7 : MeSH descriptor: [Neoplasm Metastasis] explode all trees #8 : (recurrence risk):ti,ab,kw OR (recurrence rate):ti,ab,kw OR (relapse):ti,ab,kw OR (disease free survival):ti,ab,kw OR (metastasis):ti,ab,kw #9 : #6 OR #7 OR #8 #10 : #3 AND #4 AND #5 AND #9	15