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A practical review of watch-and-wait approach in rectal cancer

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Rectal resection surgery after neoadjuvant treatment has been the mainstay treatment of locally advanced rectal cancer. However, functional outcomes and quality of life after radical resection of the rectum remain suboptimal. The excellent oncologic outcomes in patients who achieved pathologic complete response after neoadjuvant treatment questioned the need for radical surgery. The watch-and-wait approach is a noninvasive therapeutic alternative for organ preservation and avoiding operative morbidity. In the watch-and-wait approach, patients with locally advanced rectal cancer who achieve excellent clinical response after neoadjuvant treatment undergo active surveillance rather than rectal cancer surgery. In this practical review, we summarized the main results of studies on the watch-and-wait approach and provided a practical method for implementing the watch-and-wait approach.

Keywords: Rectal neoplasms, Watch and wait, Non-operative management

Introduction

Neoadjuvant therapy—such as long-course chemoradiotherapy and short-course radiotherapy, surgical resection, and adjuvant chemotherapy—are conventional treatments of locally advanced rectal cancer [1]. Total mesorectal excision has been the mainstay of treatment of locally advanced rectal cancer [2]. However, functional outcomes and quality of life after radical resection remain suboptimal. Rectal surgery is associated with significant morbidity, such as poor body image and gastrointestinal, micturition, and sexual problems. In addition, patients with very low tumors undergo abdominoperineal resection, which results in permanent colostomy [3,4]. The excellent oncologic outcomes in patients who achieved pathologic complete response (CR) after neoadjuvant treatment questioned the need for radical resection surgery [5]. Accordingly, there has been a demand for omitting surgical resection in these patients. The watch-and-wait (WW) approach is a noninvasive therapeutic alternative for organ preservation and avoiding operative morbidity. In the WW approach, patients with locally advanced rectal cancer who achieve excellent clinical response after neoadjuvant treatment undergo active surveillance rather than rectal surgery. Growing evidence has indicated that the WW approach was a safe and effective option in patients who achieved excellent tumor response after neoadjuvant treatment. In this article, we summarized the main clinical results of the WW approach. Clinicians willing to adopt the WW strategy in their routine practice should assimilate the detailed approach. We provided a step-by-step practical review of the WW approach.

Landmark Studies on the WW Approach

Table 1 summarizes the characteristics and outcomes of landmark

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Table 1. Studies on watch-and-wait approach

Study, year	Analysis	Patients	Neoadjuvant therapy		Timing of assessment after neoadjuvant treatment	Outcomes[a]				
			Radiotherapy	Chemotherapy		Local regrowth	Salvage treatment after local regrowth	Distant metastasis	OS	DFS
Habr-Gama et al. [6], 2004	Observational retrospective	71/265 (underwent WW)	50.4 Gy/28 fx	5-FU and leucovorin	8 weeks	2 (2.8%)	2/2 (100%) had transanal resection or brachytherapy	–	5-yr rate: 100%	5-yr rate: 92%
Appelt et al. [7], 2015	Observational prospective	40/51 (underwent WW)	60 Gy/30 fx to tumor, 50 Gy/30 fx to elective lymph node volumes, and 5 Gy endorectal brachytherapy boost	Oral tegafur-uracil	6 weeks	9 (22.5%) 2-yr rate: 25.9%	9/9 (100%) had salvage surgery	3 (7.5%)	2-yr rate: 100% (in full population)	–
Renehan et al. [8], 2016	Observational mixed prospective-retrospective	129 (underwent WW) 31/259 plus 98 from WW registry	45 Gy/25 fx	Fluoropyrimidine-based chemotherapy	8 weeks or more	44 (34%)	32/44 (72.7%) had salvage surgery	4 (3.1%)	3-yr rate: 96%	3-yr non-regrowth rate: 88%
Dossa et al. [9], 2017	Meta-analysis	867 from 23 studies (underwent WW)	Various	Various	Various	2-yr rate: 15.7%	The pooled proportion of patients who had salvage therapy was 95.4%.	–	–	–
van der Valk et al. [10], 2018	IWWD report Observational mixed prospective-retrospective	1,009 (underwent WW)	Various	Various	Various	213/880 2-yr rate: 25.2%	Of 148 patients with information, 46 (31%) had local excision and 115 (78%) had salvage TME.	71 (8%)	5-yr rate: 85%	5-yr rate: 94%
Garcia-Aguilar et al. [11], 2022	OPRA trial Randomized phase II trial prospective	158 (underwent INCT-CRT, of which 105 underwent WW) 166 (underwent CRT-CNCT, of which 120 underwent WW)	45 Gy/25 fx to pelvic nodes and 50–56 Gy to primary tumor and involved nodes	Concurrent capecitabine or 5-FU with 8 cycles of FOLFOX or 5 cycles of CAPEOX before or after chemoradiation	8 ± 4 weeks	42/105 (40%): INCT-CRT 33/120 (27.5%): CRT-CNCT	All patients were recommended for TME.	3-yr distant metastasis-free survival rate: 84% (in full INCT-CRT group) and 82% (in full CRT-CNCT group)	–	3-yr rate: 76% (in full INCT-CRT population) and 75% (in full CRT-CNCT population)

DFS, disease-free survival; OS, overall survival; WW, watch-and-wait; CRT-CNCT, chemoradiotherapy followed by consolidation chemotherapy; FOLFOX, 5-fluorouracil, leucovorin and oxaliplatin; CAPEOX, capecitabine and oxaliplatin; INCT-CRT, induction chemotherapy followed by chemoradiotherapy; TME, total mesorectal excision.

[a] It represents the contents represent the outcomes of patients who underwent WW unless otherwise indicated.

studies. The first report on the WW strategy was published in 2004 by Habr-Gama et al. [6]. In this retrospective study, 71 patients with distal rectal adenocarcinoma who achieved clinical CR after chemoradiation with 5-fluorouracil (5-FU), leucovorin, and 50.4 Gy underwent the WW approach. The survival outcome was excellent, with a 5-year overall survival rate of 100% and disease-free survival rate of 92%.

A prospective observational study including patients with rectal adenocarcinoma (T2-3, N0-1) within the lower third of the rectum (6 cm) was reported in 2015 [7]. The patients received chemoradiotherapy with a high dose of radiation—60 Gy in 30 fractions to tumor, 50 Gy in 30 fractions to elective lymph node volumes, 5 Gy as endorectal brachytherapy boost, and oral tegafur-uracil (300 mg/m^2). Of the 51 patients, 40 (78%) achieved clinical CR and were allocated to the WW approach group. The 1-year local recurrence rate in the observation group was 15.5%. All nine patients who had local recurrence underwent salvage surgery, which was curative with clear resection margins.

A mixed-methods prospective retrospective cohort study including 129 patients managed with the WW strategy was reported in 2016 [8]. Of the 129 patients, 34% had local regrowth, of which 88% having non-metastatic local regrowth were salvaged. The 3-year overall survival rate was 96%, and 3-year non-regrowth disease-free survival rate was 88%. Comparing the outcomes in patients managed with the WW approach with those who underwent surgery using propensity matching analysis, no differences in 3-year non-regrowth disease-free survival and overall survival rates were noted.

A systematic review and meta-analysis assessing the evidence of the WW approach in patients with clinical CR after neoadjuvant chemoradiation was published in 2017 [9]. A pooled analysis of 23 studies including 867 patients showed a 2-year local regrowth rate of 15.7%. Most patients (95.4%) with regrowth underwent salvage treatments. There was no significant difference in overall survival for patients managed with WW after achieving clinical CR compared to patients managed with surgery after achieving clinical CR or patients achieving postoperatively confirmed pathologic CR.

In 2018, an international multicenter registry study conducted by the International Watch & Wait Database (IWWD) reported the results of 1,009 patients managed with the WW approach in 47 institutes from 15 countries [10]. The 2-year cumulative incidence of local regrowth was 25%. Local regrowth was most frequently detected in the first 2 years of follow-up (88%) and located in the bowel wall in most cases (97%). Distant metastases were identified in 71 (8%) of the 880 patients. The 5-year overall and disease-specific survival rates were 85% and 94%, respectively.

The OPRA trial was a prospective, randomized, phase II trial published in 2022. Three hundred twenty-four patients with stage II or III rectal cancer were randomly assigned to either the induction chemotherapy (5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (CAPEOX)) followed by chemoradiotherapy (50–56 Gy with either capecitabine or 5-FU) or vice versa (chemoradiotherapy followed by consolidation chemotherapy) groups [11]. After tumor restaging, patients with clinical or near-CR underwent the WW protocol, whereas those with incomplete response underwent total mesorectal excision. The 3-year disease-free survival rate was 76% in both groups. This finding was comparable to the historical data of patients treated with neoadjuvant therapy and total mesorectal excision, showing a 3-year disease-free survival rate of 75%. The 3-year total mesorectal excision-free survival rate was 41% in the induction chemotherapy followed by chemoradiotherapy groups, and 53% in the chemoradiotherapy followed by consolidation chemotherapy groups. Local recurrence-free survival, distant metastasis-free survival, and overall survival rates were similar between the groups. Thus, the order of chemoradiation and systemic chemotherapy did not change oncologic outcomes. However, chemoradiation followed by consolidation chemotherapy was associated with a higher probability of organ preservation. The OPRA trial suggested that the WW strategy could be safely applied to patients with complete or near-CR after total neoadjuvant treatment.

The WW approach resulted in disease-free survival comparable to that of the standard treatment and gave patients a chance for preserving the rectum. Although there was a chance of local regrowth, most patients who experienced local regrowth underwent successful salvage surgery. However, Smith et al. [12] reported a higher distant metastasis rate among patients who had local regrowth than that among those who did not have local regrowth (36% vs. 1%; $p < 0.001$). The WW approach may be safe in most patients. However, better risk stratification is needed for more precise patient selection.

1. Quality of life

Quality of life is an important aspect when considering the WW approach. In a retrospective case-control study, bowel function was assessed using a questionnaire in 21 patients who underwent the WW approach and 21 matched patients who underwent sphincter-preserving surgery [13]. Patients in the WW arm had better overall bowel function, with the greatest difference on the urgency/soilage subscale. A similar case-control study including 41 patients managed with the WW strategy and 41 matched patients after chemoradiation and surgery showed that patients managed with the WW approach had a better quality of life with fewer defecation and sexual and urinary tract function problems [14].

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2. Who will be the candidate for WW approach?

The inclusion criteria for the IWWD protocol (version 2.1) were as follows [15]. First, patients who achieved clinical CR after neoadjuvant therapy at assessment of tumor response or after local excision (ypT0Nx) following neoadjuvant therapy and underwent a surveillance program with no immediate surgery were included. Second, patients with local clinical CR and M1 disease registered under a separate category were included. Third, these inclusion criteria also comprised patients with a clinical near-CR to neoadjuvant therapy, in whom it was decided to defer surgery, prolong the observation period, and perform reassessment. Patients who subsequently achieved clinical CR within 24 weeks after the last radiotherapy fraction were considered to follow the WW strategy. Fourth, patients who have not achieved clinical CR after neoadjuvant treatment as a result of residual disease but nevertheless received organ-preserving treatment consisting of strict surveillance were also included. These patients may have been included in the registry under different categories. The OPRA study included patients with clinical stage II or III rectal adenocarcinomas. Patients with clinical or near-CR after neoadjuvant treatment participated in the WW protocol. Patients with recurrent rectal cancer, evidence of distant metastasis at diagnosis, or history of pelvic irradiation were excluded from the study. In summary, patients with locally advanced rectal cancer treated with CR or near-CR after neoadjuvant treatment were good candidates for the WW approach.

How to Perform the Neoadjuvant Treatment?

Chemoradiation is the mainstay of treatment before the WW approach. Many series studies including that by Habr-Gama et al. [16] used chemoradiation before the WW approach [16-19]. In the IWWD study, chemoradiation was most commonly used (804/880, 91%) and most patients (781/880, 88.8%) underwent a single therapy, while some (92/880, 10.5%) received a combination modality [10]. Most patients received capecitabine or 5-FU for concurrent chemotherapy. However, the pathologic CR rate was usually less than 15% after standard long-course chemoradiation [20,21]. Several therapeutic strategies have been considered to increase the chance of patients for undergoing the WW approach.

The first strategy was total neoadjuvant therapy. Total neoadjuvant treatment included chemoradiotherapy or short-course radiotherapy and chemotherapy, which were delivered before surgery (or as non-operative management). Total neoadjuvant treatment has been increasingly adopted for the treatment of locally advanced rectal cancers. Recent randomized phase 3 trials have shown the efficacy of total neoadjuvant treatment compared with standard chemoradiation. In the RAPIDO trial, the total neoadjuvant treatment group received short-course radiotherapy (5×5 Gy) followed by six cycles of CAPOX chemotherapy or nine cycles of FOLFOX4 followed by total mesorectal excision. Three years after randomization, the cumulative probability of disease-related treatment failure was 23.7% in the total neoadjuvant treatment group versus 30.4% in the standard care group ($p = 0.019$) [20]. The pathological CR rate doubled in the total neoadjuvant treatment group (28% vs. 14%). In the PRODIGE23 trial, the total neoadjuvant treatment group was administered neoadjuvant chemotherapy with six cycles of fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX), followed by chemoradiotherapy, total mesorectal excision, and adjuvant chemotherapy (six cycles of FOLFOX6 or four cycles of CAPEOX) [21]. The 3-year disease-free survival rates were 76% in the total neoadjuvant treatment group and 69% in the standard-of-care group ($p = 0.034$). Pathologic CR was more than doubled in the total neoadjuvant treatment group (28% vs. 12%). In the CAO/ARO/AIO-12 trial, patients were assigned to receive either three cycles of 5-FU, leucovorin, and oxaliplatin before 5-FU/oxaliplatin chemoradiation or chemoradiation before chemotherapy [22], the pathological CR rates were 17% or 25%, respectively. The 3-year disease-free survival rate was 73% in both groups. These high pathological CR rates in patients treated with total neoadjuvant treatment imply that the use of total neoadjuvant treatment may increase the possibility that patients could undergo the WW approach. In a prospective, randomized phase II OPRA trial, total neoadjuvant treatment and either the WW approach or total mesorectal excision based on tumor response were evaluated [11]. The total neoadjuvant treatment consisted of either induction chemotherapy followed by chemoradiotherapy or chemoradiotherapy followed by consolidation chemotherapy. Approximately half of those receiving chemoradiotherapy followed by consolidation chemotherapy achieved sustained clinical CR and preserved the rectum at 3 years. In a retrospective study, by Chin et al. [23], 90 patients received short-course radiotherapy (25 Gy in 5 fractions) to the pelvic area, followed by consolidation chemotherapy. An optional simultaneous integrated boost dose of 30 Gy was prescribed to the primary and extramesorectal lymph nodes at 35 Gy. Patients with clinical CR ($n = 43$; 47.8%) underwent the WW approach.

The second strategy to enhance tumor response is radiation dose escalation. Radiation dose escalation can be achieved using external-beam radiotherapy or brachytherapy. Habr-Gama et al. [24] conducted a retrospective study, in which patients undergoing standard chemoradiation (50.4 Gy and 2 cycles of 5-FU-based chemotherapy) were compared with those undergoing dose-escalated chemoradiation using external beam radiotherapy (54 Gy and 6 cycles of 5-FU-based chemotherapy). The clinical CR rate was higher

in the dose-escalated chemoradiation group (86% vs. 57%, respectively) compared with those who underwent standard chemoradiation. Patients undergoing dose-escalated chemoradiation were more likely to experience organ preservation and avoid definitive surgical resection at 5 years (67% vs. 30%). In the IWWD study, the standard dose was most frequently used (50 Gy in 354 patients and 45 Gy in 173 patients). However, dose-escalated radiotherapy was used in some patients (54 Gy in 102 patients and 60 Gy in 40 patients).

Brachytherapy is a type of internal radiotherapy. A small radioactive material is put into the body, inside or close to the cancer, or low-energy X-rays (contact X-ray brachytherapy) are used. In brachytherapy, energy is deposited mainly on the surface of tumor and penetrates only a few millimeters of tissue beneath tumor. This treatment delivers a higher dose of radiation directly to tumor than may be possible with external beam radiotherapy. In a prospective observational study conducted by Appelt et al. [7], both external beam radiotherapy and brachytherapy were used for dose escalation. Patients with T2 or T3, N0–N1 adenocarcinoma in the lower third of the rectum (6 cm) were administered chemoradiotherapy (60 Gy in 30 fractions to tumor, 50 Gy in 30 fractions to elective lymph node volumes, 5 Gy endorectal brachytherapy boost, and oral tegafur-uracil) every day for 6 weeks. High rates of clinical CR were achieved (78%). The local recurrence rate at 1 year was 15.5%. Sun Myint et al. [25] evaluated 83 patients who received a contact X-ray brachytherapy boost (mostly 90 Gy/3 fractions/4 weeks) following chemoradiotherapy or radiotherapy (45 Gy). Clinical CR was achieved in 53 patients (63.8%) after brachytherapy boosts. The local recurrence rate after clinical CR was 11.3% with a median follow-up of 2.5 years. In a French multicenter study, patients with rectal adenocarcinoma (T2-3; < 5 cm in diameter) were treated with contact X-ray brachytherapy delivering 90 Gy/3 fractions/4 weeks in combination with chemoradiation (50 Gy) for organ preservation [26]. Among the 74 patients, clinical or near-CR was noted in 71 (95%) at week 14. The 3-year local recurrence and cancer-specific survival rates were 10% and 88%, respectively. In a retrospective study by Garant et al. [27], patients received 40 Gy in 16 fractions of pelvic external beam radiation therapy followed by 3 weekly image-guided adaptive brachytherapy boosts of 10 Gy to the residual tumor for a total of 30 Gy in 3 fractions. With a median follow-up of 1.9 years, the proportion of clinical CR, tumor regrowth rate, and cumulative incidence of local relapse were 86.2%, 13.6%, and 16.8%, respectively, at 2 years. In these brachytherapy studies, rectal bleeding was found to be the main cause of toxicity. Although Sun Myint et al. [25] reported only grade 1 or 2 rectal bleeding, Appelt et al. [7] reported a rate of 7%, Gerard et al. [26] reported 12%, and Garant et al. [27] reported 13% of grade 3 rectal bleeding. In summary, standard long-course chemoradiation could be used for organ preservation. Therapeutic strategies for enhancing tumor response could also be used to increase the chance of undergoing the WW approach. These strategies include total neoadjuvant treatment and radiation dose escalation using either external beam radiotherapy or brachytherapy.

How to Assess Tumor Response after Neoadjuvant Treatment?

Careful reassessment should be performed after neoadjuvant treatment for proper selection of patients who could undergo the WW approach. In the OPRA trial, reassessment was performed using endoscopy, digital rectal examination, magnetic resonance imaging (MRI), and computed tomography (CT) of the chest, abdomen, and pelvis. According to the previously defined schema of endoscopy, digital rectal examination, and MRI in the protocol, tumor response was classified as CR, near-CR, and incomplete CR [28]. For example, CR is defined by endoscopic results of flat, white scar, telangiectasia with no ulcer or nodularity, normal findings on digital rectal examination, MRI results of only dark T2 signal and no visible lymph nodes on T2-weighted MRI, and no visible tumor on B800-B100 signal and/or lack of or low signal on the ADC map on diffusion-weighted MRI. In the IWWD study, reassessment consisted of endoscopy, digital rectal examination, and various imaging modalities, according to each institution's policy [10]. The diagnostic procedures at reassessment were endoscopy (89%), pelvic MRI (71%), pelvic CT (30%), endorectal ultrasound (8%), positron emission tomography scan (4%), carcinoembryonic antigen (CEA, 22%), and local excision (5%).

The timing of the reassessment varied according to the study. In the OPRA trial, reassessment was performed within 8 ± 4 weeks of neoadjuvant treatment. The IWWD protocol indicated that patients with CR after 12 weeks of neoadjuvant treatment would be able to participate. The IWWD protocol also stated that patients with near-CR and those who subsequently achieved clinical CR within 24 weeks could be considered to participate in the protocol. Although there was no consensus on the timing of reassessment, and the timing varied in a range of 4–20 weeks among studies [7,8,16,19,29-32], reassessment was usually performed after 8 weeks in many studies. An early assessment could be misinterpreted as an incomplete response. A sufficient time interval more than 8 weeks from neoadjuvant treatment and reassessment of tumor could allow for maximal tumor regression.

Although there was a good correlation between clinical CR after neoadjuvant treatment and pathologic CR after surgery, some patients still experienced local regrowth after achieving clinical CR

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Table 2. Suggested watch-and-wait protocol

Category	Description
Patients	Patients with locally advanced rectal cancer treated showing CR after neoadjuvant treatment or patients showing near-CR in whom it is decided to defer surgery and prolong the observation period and to perform reassessment
Neoadjuvant treatment	Standard long-course chemoradiation (45–50 Gy with capecitabine or 5-fluorouracil). To enhance tumor response, radiation dose escalation by external beam radiotherapy and/or brachytherapy boost or total neoadjuvant treatment can be used
Reassessment	Reassessment with endoscopy, digital rectal examination, and imaging modalities including pelvic MRI at least after 8 weeks post-treatment
Follow-up	Evaluation with endoscopy, digital rectal examination, and imaging modalities including pelvic MRI at least more than 3 times a year during the first 2 years and then once or twice a year thereafter

CR, complete response; MRI, magnetic resonance imaging.

during the WW duration [33]. Thus, it is important to accurately predict pathologic CR before surgery for the proper selection of patients who could undergo the WW strategy. Promising results have been achieved in studies using cutting-edge technologies. Shin et al. [34] and Bibault et al. [35] developed models to predict pathologic CR after neoadjuvant treatment using radiomics and deep learning technology, If a robust method for predicting pathologic CR is established in the future, the treatment outcome of the WW approach will be further improved.

How to Follow Up in the WW Approach?

A more intensive follow-up protocol was used in the WW approach than in the routine surveillance after standard treatment. The IWWD study emphasized the importance of endoscopic surveillance during the first 2 years because local regrowth occurred mostly in the first 2 years of follow-up (188/213, 88%), with regrowth nearly always located in the bowel wall (206/213, 97%). Heterogeneous surveillance schedules and modalities have been presented in various studies. For example, in the OPRA study, the WW protocol consisted of digital rectal examination and flexible sigmoidoscopy every 4 months for the first 2 years from the time of assessment of response and every 6 months for the following 3 years [11]. Rectal MRI was performed every 6 months for the first 2 years and annually for the following 3 years. In the protocol by Habr-Gama et al. [24], patients were followed up every 6 to 10 weeks during the first 2 years of follow-up, including repeat digital rectal examination, rigid proctoscopy, and CEA level determination. Visits were performed every 12 weeks (3 months) in the third year and every 24 weeks (6 months) thereafter. According to the protocol by Renehan et al. [8], the follow-up protocol consisted of digital rectal examination; MRI (every 4–6 months in the first 2 years); examination under anesthesia or endoscopy; CT scan of the chest, abdomen, and pelvis; and at least two CEA measurements in the first 2 years. In summary, digital rectal examination and endoscopy were the main tools used for follow-up evaluation. Pelvic MRI was another important imaging tool. CT scans of the chest, abdomen, and pelvis; positron emission tomography (PET)-CT scans; or CEA measurements could be used. Visits should be performed at least three times a year during the first 2 years. A summary of the proposed WW protocol is presented in Table 2.

Conclusion

The WW approach has proven its safety and effectiveness in many studies, including a prospective phase 2 randomized study and a large international database study in patients with rectal cancer with clinical or near-CR after neoadjuvant treatment. The WW approach can be a good therapeutic option in patients who do not hope for surgery. Since both surgery and the WW approach have their pros and cons, clinicians should carefully evaluate each patient's goals for treatment and patient's motivation to avoid surgery for maintaining their quality of life or pursue more definite treatment. The optimal intensity of neoadjuvant treatment to maximize tumor response must be determined. Randomized trials on intensive neoadjuvant treatment for undergoing the WW approach are being conducted (NCT02704520 and NCT04095299). A limitation is that no prospective phase 3 clinical study has directly compared between standard treatments and the WW approach. Further randomized controlled trials are required to validate this WW approach. Another limitation is that there was no international consensus regarding the WW protocol. An international consensus needs to be established based on optimal patient selection criteria, neoadjuvant treatment protocols, tumor response assessment criteria, and follow-up protocols.

Statement of Ethics

As this study did not involve any human subjects, Institutional Review Board approval and informed consent were not required.

Conflict of Interest

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

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Author Contributions

Conceptualization, Byun HK, Koom WS. Funding acquisition, Byun HK, Koom WS. Investigation and methodology, Byun HK, Koom WS. Project administration, Byun HK, Koom WS. Resources, Byun HK, Koom WS. Supervision, Koom WS. Writing of the original draft, Byun HK Writing of the review and editing, Byun HK, Koom WS.

Data Availability Statement

Data availability statements provide a statement about where data supporting the results reported in a published article can be found.

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