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Non-surgical "Watch and Wait" Approach to Rectal Cancer

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Abstract

Purpose of Review The standard of care for locally advanced rectal cancer is preoperative chemoradiation (CRT) followed by total mesorectal excision (TME). Patients who achieve a pathologic complete response (pCR) to CRT have favorable oncologic outcomes. Given the significant morbidity and long-term effects on quality of life associated with radical resection, the role of surgery in the subgroup of patients with a clinical complete response (cCR), of whom a significant proportion may have a pCR, is under debate.

Recent Findings An emerging tailored approach to treatment is a "watch and wait" strategy in patients who have a cCR after CRT with the goal of organ preservation. However, concordance between a cCR and pCR is not highly reliable, and improved multimodality prediction algorithms are needed to better predict which patients have achieved a pCR and can therefore safely undergo a "watch and wait" approach.

Summary We review the current data on non-operative management of rectal cancer and ongoing controversies associated with this approach.

Keywords Rectal cancer · Non-operative management · Organ preservation · Watch and wait · Chemoradiation

Introduction

Neoadjuvant chemoradiation (CRT) followed by total mesorectal excision (TME) and adjuvant 5-FU-based chemotherapy has been established as the standard management for locally advanced rectal cancer based on the German CAO/ARO/AIO-94 trial [1]. The prognostic significance of pathologic complete response (pCR) was also demonstrated in this study with a significant improvement in 5-year disease-free survival (DFS) for patients with a pCR or Dworak tumor regression (TRG) grade 4 when compared with TRG 2 + 3 or TRG 0, respectively (86% vs. 75% vs. 63%; $P = 0.006$). None of the pCR patients experience a local relapse [2]. A meta-analysis including 3105 patients corroborated a higher DFS of 83% versus 66% for patients with or without a pCR, respectively [3]. Although excellent oncologic outcomes are seen with this approach, radical surgery can result in significant toxicity. Late sequelae including incisional hernias, urinary incontinence, bowel obstruction/dysfunction, and sexual toxicity have been reported [4–6]. Patients with distal rectal tumors necessitating a permanent colostomy can struggle with body image and poor long-term quality of life [5].

This standard approach carries potential morbidity, resulting in emerging interest in forgoing TME in appropriately selected patients without adverse outcomes on disease control. However, accurately identifying pCR in patients was previously limited to microscopic evaluation of tissue following surgical resection.

Predicting a Pathologic Response After Chemoradiation

The pre-requisite of safely omitting surgery is accurate identification of patients with a pCR prior to surgery. However, clinical assessments based on digital rectal examination (DRE), in conjunction with endoscopic and comprehensive

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radiologic evaluation, are unable to reliably discern post-radiation effects from disease remnant. The lack of direct correspondence between a clinical complete response (cCR) and a pCR has been an obstacle to adopting a "watch and wait" approach. A prospective study of 94 patients with locally advanced rectal cancer demonstrated that DRE at diagnosis and preoperatively cannot reliably distinguish complete responders. Preoperative DRE correctly identified 21% of patients with a pCR likely secondary to confounding effects of post-treatment inflammation and scarring [7]. Endoscopic biopsy or local excision of scar tissue may provide supplementary insight. However, deciphering biopsy results in the post CRT tissue may be difficult, as isolated tumor cells may continue to respond to treatment over time [8]; furthermore, sampling error resulting in false negative results is a legitimate concern. One prospective study evaluating utility of presurgical endoscopic biopsy demonstrated a concordance rate of 59% between biopsy results and final pathologic specimen [9]. In another study, a benign biopsy was predictive of a pCR in 21% of patients [10]. Biopsy in the post CRT setting carries additional risks for complications [11]. Lastly, clinical evaluation of the primary tumor response after CRT does not predict the response in regional lymph nodes. In one series, a pathologic positive mesorectal node was identified in 7% of patients achieving a pCR in the primary tumor [12]. A second study similarly showed an incidence of 9% positive lymph nodes in the ypT0 setting [13].

Inflammation and fibrosis in the post-radiation setting can lead to difficulties with accurate response assessment, leading to over-staging on various imaging modalities. For instance, endorectal ultrasound reliably predicts pCR in 40–50% of patients [14, 15]. In an elegant study, concordance between endorectal ultrasound findings and pathologic T and N staging were 54% and 75%, respectively [16]. The degree of metabolic response on PET generally correlates with treatment response; nonetheless, only 54% of patients with a pCR are correctly categorized as such by preoperative PET scan [17, 18]. More recently, a retrospective study of 125 patients showed that following CRT, SUVmax < 4.3 and percent SUVmax decrease of > 66% were equally predictive of pCR with sensitivity of 65% and specificity of 72% [19].

MRI is routinely employed for rectal cancer staging; however, interpretation of restaging MRI following CRT is challenging [20]. A meta-analysis of 33 studies focused on interim restaging MRI following neoadjuvant CRT described an average sensitivity of 50.4% and specificity of 91.2% to predict tumor stage [21]. The discriminatory power of MRI for pT0 stage had a lower sensitivity of 19%, possibly due to post-treatment fibrosis. MRI functional features such as dynamic contrast enhancement (DCE) or diffusion-weighted imaging (DWI) can further aid in distinguishing pCR. DCE-MRI parameters, such as K(trans), vary greatly between responders and non-responders [22]. MRI during CRT appears to be promising for predicting pCR in primary tumors in ongoing studies [23]. MRI results are less reliable for pretreatment N staging with a mean sensitivity of 76.5% and specificity of 59.8% [21]. Gadofosveset-enhanced MRI read by an experienced radiologist has 80% sensitivity and 97% specificity in nodal staging [24]. A new morphologic "split scar" sign that can be seen on T2-weighted MRI has shown 97% specificity and 52% sensitivity for sustained complete response, defined as pCR or long-term recurrence-free clinical follow-up [25]. A recent study highlights the value of computer-based learning models that can assist clinicians distinguish pathologic responders. An artificial intelligence model employing textural features of T2-weighted MRI showed good discriminatory power for those patients with pCR versus non-responders [26].

Multiple potentially predictive mutations, polymorphisms, chromosomal aberrations, gene expression profiles, and microRNA signatures have previously been described but often lack reproducibility [27]. Finding a molecular signature that predicts for pCR with high degree of sensitivity is possibly within reach in the near future. Exciting results of a small Brazilian study of 30 patients analyzed TYMS (thymidylate synthase) mRNA and TYMS/RAD23B protein expression in circulating tumor cells prior to and after neoadjuvant CRT. Based on this analysis, investigators successfully identified patients exhibiting pCR with 100% sensitivity [28•].

By employing a combination of physical examination, endoscopic examination, imaging, and molecular expression profiles, the ability to accurately predict a pCR to neoadjuvant therapy improves. This in turn allows non-operative management strategies in select group of patients with a more palatable risk of treatment failure.

Time Frame of Pathologic Complete Response

Surgery has historically been performed 6 weeks post completion of CRT. The Lyon R90-01 study revealed improved tumor down-staging with surgery at 6 weeks versus 2 weeks following radiation completion [29]. A meta-analysis of 13 trials grouped 3584 patients into those undergoing TME shorter than 6–8 weeks after CRT and those waiting longer than 6–8 weeks to undergo surgery. A longer interval from CRT completion to surgery was associated with a significant improvement in pCR (19.5% vs. 13.7%) [30]. Caveats of longer intervals between CRT and surgery include concerns for surgical complications resulting from radiation fibrosis and the possibility of disease progression.

Role of Systemic Therapy in Pathologic Complete Response

Delivery of chemotherapy in the interval between CRT and surgery may mitigate risk of disease progression during the

wait time and maximize treatment response. A multicenter, phase II study investigating the addition of chemotherapy in variable intervals between CRT and surgery was comprised of 4 patient groups. The first group underwent TME 6 weeks post CRT, while groups 2–4 received variable cycles of FOLFOX-6 chemotherapy (2, 4, or 6 cycles) followed by TME in 3–5 weeks. Among 259 evaluable patients, the pCR rate was higher with increasing number of chemotherapy cycles and longer wait times (18%, 25%, 30%, and 38% in groups 1–4, respectively) [31, 32]. Another studied treatment approach is induction FOLFOX chemotherapy followed by CRT. In 49 patients receiving induction FOLFOX, consolidative CRT followed by TME, 47% had near complete tumor response (> 90% response), with 27% demonstrating a pCR [33]. The addition of oxaliplatin to standard 5-FU-based CRT regimen was investigated in 4 randomized controlled trials that failed to show improvements in tumor response, with added toxicity [34–37].

The utilization of total neoadjuvant therapy (TNT) may further increase the probability of a pCR. A recent meta-analysis that included 2688 patients treated with TNT and 891 patients treated with neoadjuvant CRT found a higher pCR rate with the addition of consolidative or induction chemotherapy. The pooled pCR was 22.4% in all patients treated with TNT, with an increase in odds of pCR by 39% [38].

A multicenter randomized phase II trial of CRT plus induction or consolidation chemotherapy as TNT has recently been reported (CAO/ARO-AIO-12). Among 306 evaluable patients with stage II or III rectal cancer (156 in the induction arm and 150 in the consolidation arm), pCR was higher in the CRT followed by chemo arm (25% vs. 17%). These findings were despite the decreased compliance with planned chemotherapy among the consolidation group (85% vs. 92%). A longer interval from completion of CRT to surgery in the consolidation arm (median 90 vs. 45 days) and a higher compliance with CRT may in part be responsible for the higher rates of pathologic response in this group of patients [39].

"Watch and Wait" Non-operative Experience

First described by Brazilian investigators, the "watch and wait" strategy for patients achieving a cCR to neoadjuvant CRT is conceptually appealing [40••]. In an updated series, the Habr Gama group reported on 361 patients with low, resectable cT2-4N0/N+ rectal cancers treated with CRT. Repeat endoscopic evaluation of patients was performed 8 weeks after CRT, and patients with mucosal abnormalities or positive biopsies were deemed to have an incomplete response and proceeded to surgical resection. Those found to have a cCR underwent rigorous monitoring and surveillance. Ninety-nine patients with a prolonged cCR greater than 1 year were managed without surgery. Following a 5-year follow-up period, 13 patients experienced recurrences: 5 were endorectal, 7 were distant, and 1 was both. All patients with isolated endorectal recurrences were salvaged successfully. The 5-year OS and DFS were high at 93% and 85%, respectively [41].

A prospective Dutch study of a "watch and wait" approach was previously published [42]. An update of these results with a larger patient population and longer follow-up (median 41 months) was recently published. Between 2004 and 2014, 100 patients with cT1-3 N0-2 who received CRT had a cCR (61 patients) or near cCR (39 patients) and underwent organ preservation. Evaluation of response involved DRE, endoscopy, and MRI. Patients with a cCR underwent watch and wait, while near cCR patients were given the option TME or reassessment at 3 months. Endoscopy and MRIs were performed every 3 months during the first year and every 6 months thereafter. Fifteen patients experienced a local recurrence (12 luminal, 3 nodal), all occurring within 25 months and salvageable. Five patients developed metastases and 5 patients died. Three-year overall survival was high at 96.6% (95% confidence interval (CI) = 89.9 to 98.9%), and colostomy-free survival was 94.8% (95% CI = 88.0 to 97.8%) [43].

Memorial Sloan Kettering published an initial report of stages I–III rectal cancer patients found to have a cCR to CRT, managed non-operatively, and compared with patients treated with radical surgery that had a pCR. Among the 32 patients managed non-operatively, with a median follow-up of 28 months, 6 experienced a local recurrence and were surgically salvaged [44]. In updated results, among 1070 patients with locally advanced rectal cancer treated from 2006 to 2015, 113 (11%) were managed non-operatively after a cCR to CRT. In the same period, 957 patients underwent TME, of which 136 patients had a pCR (13%). With a median follow-up of 43 months, 22 patients in the watch and wait group experienced a local recurrence: 19 were endoluminal/mural and 3 were extraluminal. All local recurrences were salvaged surgically, 2 with a local excision and 22 with a TME. The watch and wait group had a compromised 5-year OS, at 73% (95% CI = 60–89%) compared with 94% (95% CI = 90–99%) in the pCR group. The study also showed higher distant metastasis rate in watch and wait patients who had local regrowth vs those who did not (36% vs 1%, $P < .001$) [45••].

An ongoing multi-institutional randomized phase II study is investigating TNT with CRT and 4 months of FOLFOX either before or after CRT. MRI and endoscopic response assessment will be used to select patients with cCR appropriate for non-operative management [46]. Another multicenter randomized feasibility/embedded phase III TRIGGER trial is underway in the UK. This trial compares outcomes in patients with locally advanced rectal cancer who are randomized (1:2)

Table 1 Summary of studies and ongoing trials employing "watch and wait" approach in LARC

Study	Overview	Design, methods	Main findings
Maas et al. [3]	3105 patients with locally advanced rectal cancer undergoing CRT followed by TME	Meta-analysis (17 datasets)	5-year DFS 83.3% in patients with pCR vs. 65.6% without pCR
Garcia-Aguilar et al. [32]	259 patients treated with neoadjuvant CRT alone or in conjunction with 2, 4, or 6 cycles of FOLFOX-6, followed by TME	Phase 2, non-randomized trial of 4 sequential study groups	pCR rate was higher with increasing cycles of chemotherapy
Petrelli et al. [38]	2688 patients treated with TNT vs. 891 patients treated with neoadjuvant CRT	Meta-analysis (28 studies)	Pooled pCR of 22.4% in TNT group
Habr-Gama et al. [41]	361 patients treated with CRT followed by surgery or surveillance depending on cCR	Retrospective series	5-year OS 93%; 5-year DFS 85%; all patients with isolated endorectal recurrence salvaged
Martens et al. [43]	100 patients treated with CRT with cCR or near cCR, proceeded to organ preservation with rigorous monitoring criteria	Prospective cohort	3-year OS 96.6%, 3-year colostomy-free survival 94.8%; all local recurrences salvaged
Smith et al. [45]	1070 patients managed non-operatively following cCR to CRT and compared with patients who underwent TME with pCR	Retrospective series	5-year OS 73% in watch and wait vs. 94% in pCR
Smith et al. [46]	OPRA Trial: TNT with CRT and 4 months of FOLFOX before or after; patients with cCR will be selected for non-operative management	Randomized phase 2	Ongoing
Battersby et al. [47]	TRIGGER trial: patients randomized to management based on pretreatment MRI vs. response on interim MRI	Randomized feasibility/embedded phase 3	Ongoing
Rombouts et al. [48]	Patients randomized to standard TME, organ-sparing long course RT or short course RT	Randomized phase 2	Ongoing

between management based on pretreatment MRI versus mrTRG score on interval MRI obtained 4–6 weeks after CRT completion. Patients in the control arm undergo surgery after neoadjuvant CRT. In the experimental arm, patients are stratified based on an interval MRI into good responders (mrTRG 1–2) and poor responders (mrTRG 3–5). Good responders are referred for non-operative management receiving 24 weeks of adjuvant chemotherapy (CAPOX or FOLFOX); poor responders receive 12 weeks of consolidation chemotherapy and can proceed with non-operative management if interval MRI shows mrTRG 1–2. Another 12 weeks of adjuvant chemotherapy is given to the initial poor responders either with or without surgery depending on the extent of response [47••].

A 3-arm phase II study enrolling patients up to T3bN0M0 disease will be randomized to standard TME surgery (control) and organ-sparing treatment using long-course CRT or short-course radiation. For patients undergoing the organ-sparing approach, clinical response dictates subsequent steps in therapy. Active surveillance is employed in the case of a complete clinical regression, whereas incomplete clinical regression patients will proceed to local excision [48••]. Results of these ongoing prospective studies will help understand nuances of the watch and wait approach and provide us with evidence-based guidelines for its use. A summary of published work and ongoing studies employing the watch and wait approach is highlighted in Table 1.

Conclusion

While TME is an integral component of rectal cancer treatment, the benefit of rectal resection in complete responders of neoadjuvant CRT may be limited, especially given the potential morbidity of surgery. Results of ongoing prospective studies cited above are eagerly anticipated to establish safety of omitting surgery. Successfully optimizing rates of pCR in the primary tumor and the lymph nodes following CRT would lead to more accurate selection of patients for non-operative management [49]. Ultimately, establishing a comprehensive predictive algorithm incorporating a myriad of molecular, clinical, and radiographic evidence will assist clinicians in successfully tailoring their therapy.

Compliance with Ethical Standards

Conflict of Interest Zahra Ghiassi-Nejad declares no potential conflicts of interest.

Karyn Goodman is on the Advisory Board of RenovoRx.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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