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Rectal Cancer: Watch and Wait

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Key Concepts

- Pathologic complete treatment response following neoadjuvant chemoradiation therapy and surgery for rectal cancer is associated with favorable prognosis.
- Pathologic complete treatment response is observed in approximately 15–20% of rectal cancer patients following chemoradiation therapy.
- Clinical and radiographic assessment of neoadjuvant therapy treatment response is suboptimal, and remains a primary challenge for safe implementation of watch and wait strategies.
- Approximately one in three patients exhibiting clinical complete response will develop tumor regrowth.
- At present, watch and wait should be offered to patients only in the context of a clinical trial.
- Local excision following neoadjuvant chemoradiation therapy is associated with significant risk for pain and poor wound healing.

Introduction

Over the past few decades, the management of rectal cancer has become increasingly complex. What was once a disease with high mortality and limited treatment options that typically necessitated a permanent colostomy has become a model for multidisciplinary evaluation and treatment and surgical advancement. For over a century, surgical resection has remained the cornerstone of curative treatment of rectal cancer. The principles of treatment include complete *en bloc* resection of the tumor-bearing rectum and mesorectum with clear margins along with clearance of pelvic lymphadenopathy and, when possible, restoration of intestinal continuity [1]. However, because of the historically high risk of local failure after surgery alone, clinicians have utilized neoadjuvant radiotherapy or chemoradiation therapy (nCRT) which has improved the rate of local tumor control [2]. Now the oncologic outcomes following treatment of rectal cancer in the modern era can equal outcomes following treatment of colon cancer [3]. Despite these advances, the multimodal treatment for rectal cancer is associated with a significant impact on long-term functional and quality of life outcomes including risks for bowel, bladder, and sexual dysfunction, pain, and potential need for permanent colostomy. Therefore there is great interest in strategies to decrease the toxicity of treatment, including strategies that employ the selective use of radiation, chemotherapy, or even surgery.

The modern concept of selective use of surgery following chemoradiation therapy for patients with rectal cancer are based on the fact that pathologic complete response (pCR) is observed in approximately 10–20% of patients following long course chemoradiation therapy. In 2004, Habr-Gama and her group first reported outcomes for selective surgery with a nonoperative (a.k.a. "watch and wait" or "wait and see") strategy in select patients who achieved a clinical complete response (cCR) following chemoradiation therapy [4]. In the decade since that initial report, a number of other investigators have attempted to bring further light to understanding the potential for a selective surgical approach. They have also highlighted a need for considering a number of important factors including assessing and improving the effectiveness of neoadjuvant therapy, predicting pCR prior to pathologic evaluation, determining the true risk for locoregional failure following a watch-and-wait approach, and understanding the potential for salvage surgical treatment and subsequent long-term survival outcome following treatment failure. While definitive surgical resection remains the standard of care for all patients with non-metastatic rectal cancer, a growing number of studies are providing supportive evidence for a watch and wait, organ-preserving approach in highly selected patients with rectal cancer.

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Neoadjuvant Chemoradiation Therapy

For patients with locally advanced rectal cancers, traditionally considered as clinical stage II and III, neoadjuvant therapy has been administered to improve local control. Building upon the demonstrated oncologic benefit of total mesorectal excision (TME) surgery by Heald, the Dutch Colorectal Cancer Group randomized patients to preoperative radiotherapy (5×5 Gy) followed by immediate TME surgery to TME surgery alone [5, 6]. This demonstrated that preoperative radiotherapy, when compared to TME surgery alone, was associated with a significant reduction in local recurrence although no improvement in overall survival could be demonstrated [7]. Meanwhile, the EORTC 22921 and FCCD 9203 studies demonstrated that addition of concurrent chemotherapy administered over a 5–6 week duration followed by delayed surgery demonstrated improvement in local recurrence free survival when compared to preoperative radiotherapy alone [8, 9]. However, the landmark study of the German Rectal Cancer Study Group definitively established the superiority of preoperative (neoadjuvant) vs. postoperative chemoradiation therapy, followed by surgery 6–8 weeks later, with improved local control and sphincter preservation [2].

Preoperative chemoradiotherapy is typically administered in "long course" fashion, with radiotherapy and a radiosensitizing chemotherapeutic agent administered over a 5–6 week period with a 6–10 week treatment break prior to proctectomy. This extended period of time allows for tumor regression, if the tumor is sensitive to the therapy [10]. This may facilitate more optimal surgery, including sphincter preservation, by reducing the tumor bulk and permitting surgery to be safely conducted in previously uninvolved but inaccessible adjacent tissue planes [11]. It also provides potential clearance of microscopic tumor spread, safely permitting a closer distal margin at resection with subsequent restoration of intestinal continuity [12, 13]. The surgeon should be cautious, however, not to leave tissue in situ that was previously involved with tumor, as radiotherapy does not induce tumor kill in a "wave front," and residual nests of tumor cells can be found spread throughout the initial volume of tissue involved by the tumor. Lastly, studies demonstrating improved sphincter preservation must be taken with a grain of salt, as estimation of whether a surgeon will be able to perform restorative proctectomy or not based on initial clinical examination is subjective.

As one would expect, similar responses to pelvic short-course preoperative therapy were previously not observed, as proctectomy was typically performed within a week or 2 of short-course radiotherapy, prior to the development of radiation induced inflammation, and too short a time to allow for significant tumor regression [14]. More recent trials in which proctectomy was delayed 4–8 weeks after short course radiotherapy reveal that tumor regression and relatively high rates of complete pathologic response do occur [15]. In addition, oncologic outcomes following short course radiotherapy and long course chemoradiotherapy for patients with locally advanced rectal cancer have been demonstrated to be similar in prospective randomized trials [14, 16]. Thus, it is likely that significant tumorcidal effect can be achieved with either regimen, but the added time delay prior to proctectomy with long course chemoradiotherapy results in more tumor involution seen on histologic evaluation of the proctectomy specimen. Furthermore, the potential systemic effects of the concurrent chemotherapy are not well understood.

Response to treatment has been an important observation, and following completion of CRT up to 50% of patients will experience a cCR as defined by replacement of the tumor bed by scar or normal appearing mucosa on clinical and endoscopic examination [17]. Pathologic complete response (specimen without evidence of residual tumor cells) or pathologic near-complete response (specimen with only single or small groups of tumor cells) can be observed in 10–40% of patients following neoadjuvant chemoradiation therapy (nCRT) [18, 19]. Complete clinical response, however, is not necessarily predictive of pathologic response. It is now widely recognized that tumor regression in response to neoadjuvant treatment is an important prognostic indicator of long-term outcome. It can be associated with tumor volume reduction, down-staging and nodal sterilization and a number of pathologic grading systems now exist to describe the extent of response (Table 30-1). It is a pathologic biomarker of the effectiveness of local and systemic tumor control and major response with complete or near complete resolution is

Table 30-1. Tumor Regression Grading Systems

TRG	Mandard [22]	Dworak [23]	Rödel [10]	Ryan [24]	CAP [25]
0		No regression	No regression		No residual tumor cells
1	No residual cancer cells	Dominant tumor mass with obvious fibrosis and/or vasculopathy	Fibrosis <25% of tumor mass	No residual cancer cells or single cells	Single or small groups of cancer cells
2	Rare residual cancer cells	Dominantly fibrotic changes with few tumor cells or groups	Fibrosis 25–50% of tumor mass	Residual cancer outgrown by fibrosis	Residual cancer outgrown by fibrosis
3	Fibrosis greater than residual cancer	Very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucous substance	Fibrosis >50% of tumor mass	Significant cancer outgrown by cancer or no fibrosis with extensive residual cancer	Minimal evidence of fibrosis
4	Residual cancer greater than fibrosis	Complete regression	Complete regression		
5	No regression				

highly associated with a favorable prognosis [20]. In a large study of 725 patients treated with neoadjuvant chemoradiation and total mesorectal excision for locally advanced rectal cancer at The University of Texas, MD, Anderson Cancer Center, local recurrences were virtually absent and systemic recurrences occurred in fewer than 10% of patients exhibiting complete response or major downstaging to ypT0-2 N0 disease [21]. In fact in the modern era of TME surgery, distant, rather than local, disease recurrence has emerged as the primary concern.

Surgery for Rectal Cancer

The principles for surgical curative treatment for rectal cancer have been established since the beginning of the twentieth century with Ernest Miles' description of abdominoperineal excision (APE) with end colostomy for carcinomas of the rectum and pelvic colon [26]. Since then, a number of surgical and multidisciplinary advances as outlined above have improved treatment outcomes, reduced operative mortality, and offered the potential for sphincter preservation. However, for patients with distal rectal cancer, the excellent oncologic outcomes of nCRT and surgery can be associated with the need for permanent colostomy or with significant risk for bowel dysfunction including fecal incontinence and soiling following coloanal reconstruction.

Quality of life among rectal cancer patients undergoing surgical resection with or without a permanent colostomy was compared in a systematic review of 5127 patients from 35 non-randomized studies. Fourteen of the studies reported that APE was not associated with poorer quality of life measures than low anterior resection among patients with rectal cancer. The remaining studies found some difference, although it was not always in favor of non-stoma patients. These results may in part reflect underlying bowel dysfunction among patients undergoing TME surgery with sphincter preservation, so-called low anterior resection syndrome (LARS) [27]. In a long-term follow-up study at 14 years of patients randomized to preoperative radiotherapy followed by proctectomy with TME to proctectomy with TME alone in the Dutch trial, 56% of the patients randomized to preoperative radiotherapy followed by proctectomy and 35% of the patients randomized to proctectomy alone reported major LARS [28].

Finally the prevalence of male and female sexual dysfunction is high after surgery for rectal cancer and up to one-half of the patients undergoing surgery with rectal cancer will report a deterioration in sexual function, and a third of patients will report the development of urinary dysfunction [29, 30]. While some of these effects may be attributed to pelvic autonomic injury from radiation therapy, the majority of the effect is caused by nerve injury at surgery. This is a particular concern among distal rectal cancer patients undergoing APE. While the case can be made that these effects are exacerbated when surgery is performed by less experienced surgeons, these issues remain significant problems that impact quality of life following even among patients undergoing sphincter preserving rectal cancer surgery. Thus there is a need for approaches to treating rectal cancer that can also safely preserve functional and quality of life outcomes.

The Watch and Wait Approach

Based on these concerns, the appeal of a watch and wait, organ preserving, nonoperative approach is obvious. If radical surgery to resect rectal cancer could be avoided, then patients would not be subject to the associated surgical morbidity and potential long-term effects on quality of life. However before such a strategy can be more broadly applied, it is important to ensure that oncologic outcomes are not being compromised, particular for this group of patients who are expected to have excellent outcomes, with an extremely low risk for either local or distant disease recurrence, with proctectomy. What is also unknown is if response to chemoradiotherapy is just a biologic response indicator of favorable tumor biology, or if similarly good outcomes can be achieved by increasing the rate of pCR. In light of the fact that nCRT has been associated with improvement in pelvic control, but not overall survival suggests that the former may be true. However, the body of evidence regarding the prognostic value of even an intermediate response indicates that tumor behavior is a continuum from favorable to poor. Moreover, it is now recognized that the interval from the completion of chemoradiation therapy to clinical or pathologic assessment can impact the rate of complete response as ongoing regression can be observed well beyond the traditional 6–8 week interval to assessment.

Following Habr-Gama's original report, other investigators initially reported a wide range of success with an initially nonoperative approach, including a locoregional treatment failure rate of up to 50–60%, much higher than the 3% failure rate initially reported by Habr-Gama [31, 32]. While not fully explained, the reasons for this discrepancy may have included differences in initial tumor burden, selection of patients for a watch and wait approach following neoadjuvant therapy, method and timing of assessment, or the neoadjuvant treatment regimen. In addition the method of selection of patients for nonoperative therapy in Habr-Gama's initial report may have played a major role [4]. Specifically, patients were not included in the study (observation) group until they had been followed for 12 months following chemoradiotherapy. Put another way, patients initially selected for nonoperative therapy who failed in the first 12 months were excluded from analysis. This has the potential to bias the results heavily in favor of the observation group.

Recent data, including from an updated report by Habr-Gama, indicates that the true risk for locoregional treatment failure is approximately 30% [17, 33]. This suggests that a

Table 30-2. Comparison of selected modern studies

Series	Number of patients observed	Number of patients operated	Median follow-up (months)	cCR	Local regrowth	Outcome
Mass 2011 [36]	21	20	15 (observed)	100%	1 patient	2-year OS 100%
			35 (operated)			2-year DFS 89%
Dalton 2012 [31]	12	37	25.5 (mean)	24%	50%	Disease free at follow-up
Habr-Gama 2014 [17]	93	90	60	49%	31%	5-year OS 91%
						5-year LRFS 69%
						5-year DFS 68%
Smith 2015 [34]	73	72			26%	4-year OS 91% (obs) vs. 95% (surg)
						4-year DSS 91% (obs) vs. 96% (surg)
Smith 2015 [37]	18	30	68.4 (mean)		1 patient	Alive with pelvic disease at 54 months

number of patients initially thought to have a pCR based on clinical assessment of complete response actually had undetected viable tumor, highlighting one of the major challenges and pitfalls of the watch and wait approach. One potential solution to the challenge of clinically identifying patients with a pCR is to ensure a close follow-up strategy. This will only be effective, however, if salvage treatment is proven to be effective. We recommend that patients be monitored with digital rectal and endoluminal examination every 3 months along with carcinoembryonic antigen level determination and biopsy of any suspicious lesions. The majority of tumor regrowth will be detected within the first 12 months, in which case patients may be eligible for curative resection with the possibility for coloanal reconstruction for tumors without anal canal involvement precluding partial sphincter resection with anastomosis. There is concern that a longer delay to surgery will result in making the salvage resection more difficult. Although it has been reported that salvage surgical resection after nonoperative management is feasible, longer delays in identification of regrowth has been associated with more than a 50% decrease in the ability to perform sphincter preserving salvage surgery [17, 33]. Tumor regrowth occurring deep to the mucosa may be difficult to identify before more extensive sphincter involvement and the addition of radiation-induced posttreatment fibrosis along the pelvic floor or anal sphincter complex may also preclude subsequent sphincter-preserving resection.

Thus when tumor regrowth occurs, subsequent sphincter preservation cannot be assured. In fact this is quite understandable and reasonable if patients are indeed selected for a watch and wait approach based on distally located tumors. Finally, what remains to be settled is if leaving the rectum containing residual viable tumor in patients with cCR but not pCR increases the risk for distant failure. Recent data regarding 73 patients from Memorial Sloan Kettering suggest that there is the potential for increased risk of distant metastasis among patients undergoing watch and wait when compared to those with pCR, but the sample size was relatively small and the difference did not achieve statistical significance ($p = 0.09$) [34].

Despite these concerns the evidence in support of a watch and wait approach is growing. A limited number of prospective series have reported on nCRT followed by observation (Table 30-2). A review of the wait and see approach published in 2012 identified 30 publications from 9 series including 650 patients. While demonstrating proof of principle, significant heterogeneity of the studies in staging, inclusion criteria, study design, and follow-up rigor limit our ability to draw firm conclusions [35].

Clinical Assessment of Treatment Response

The clinical assessment of treatment response is difficult and is perhaps the greatest challenge and limiting factor for safe implementation of the watch and wait approach. A number of different strategies have been considered including clinical assessment, full-thickness local excision, metabolic imaging, and high-resolution pelvic MRI imaging.

The concordance between clinical and pathologic evaluation has traditionally been poor both in terms of sensitivity (~25%) for detecting pCR, and specificity (~60–90%) for excluding residual disease [38, 39]. Moreover, there has not existed a standard method for the clinical evaluation of complete response. Investigators have advocated for a combination of digital rectal examination and endoluminal visualization to identify residual mass, ulceration, nodularity, or stenosis, all of which may suggest persistent tumor [40]. Findings in support of a complete response include regular and smooth mucosa, and changes such as whitening or presence of telangiectasias. However, in a recent study, the false-positive rate for pCR based on preoperative clinical assessment was 27% [41]. Improvement in the clinical detection of pCR may be possible with a higher pretest probability of complete response, as demonstrated by the ACoSOG Z6041 trial of nCRT with concurrent capecitabine and oxaliplatin followed by local excision for cT2N0 rectal cancers that observed a sensitivity of 85% for detection of pCR based on

digital rectal examination and proctoscopy. However even in the setting of a prospective trial with a primary endpoint of pCR, the false positive rate was 33% [42]. These data suggest that while the detection of pCR can be improved, the risk for false-positivity remains a significant concern.

Given the challenges for clinical assessment of residual disease within the bowel wall, a number of investigators have considered local excision of the tumor bed as both a diagnostic test to assess pathologic treatment response and a therapeutic maneuver to excise any residual tumor cells residing within the bowel wall. Endoscopic biopsy alone has the obvious limitation of being able to provide only a superficial sampling of the tumor bed that can miss residual disease that may be present more deeply within the bowel wall or away from the site of biopsy. Among 39 patients exhibiting clinical response to nCRT but not meeting clinical criteria for pCR, endoluminal biopsies were associated with a negative predictive value of only 11% [43].

Full thickness excision of the entire tumor bed may be performed through a variety of approaches including transanal excision, transanal endoscopic microsurgery (TEM), or transanal minimally invasive surgery (TAMIS). However, while complete pathologic assessment of the bowel wall can be performed, it still cannot provide information regarding the status of the unresected lymph nodes, which may contain viable tumor in up to 9.1% of patients who achieve ypT0 status and 17.1% of patients with ypT1 disease [18, 44, 45]. However, the presence of ypN+ status may be influenced by pretreatment patient selection and ypT0 status among patients with earlier stage initial disease may be associated with a relatively low risk for ypN+ disease [46]. Another major limitation of full-thickness excision following nCRT is that it is associated with significant treatment associated toxicity including poor healing and pain. In fact the risk for wound dehiscence has been reported to be 26–70% following nCRT [47, 48]. Consistent with these single institutional findings, the multicentered ACoSOG Z6041 study reported a 54% overall rate of perioperative complications following local excision [42]. Moreover, local excision following nCRT is still associated with a significant risk for anorectal and sexual dysfunction. In a study of 44 patients, 51% and 46% reported incontinence of flatus and loose stool, respectively, and 59% reported clustering and 49% reported urgency. In addition, 19% of men and 20% of women reported negative impacts on sexual quality of life [49]. Finally, the watch and wait strategy may perhaps have the greatest appeal for patients whose tumors involve the anal sphincter for whom sphincter preservation would be impossible. Full-thickness excision in this circumstance would necessitate at least partial resection of the internal sphincter. Thus the role for full-thickness excision in a watch and wait approach remains limited.

Two primary approaches to radiologic imaging for the assessment of treatment response have been investigated. Despite its utility in signaling response to systemic therapy for a variety of malignant diseases, metabolic imaging with ^{18}fluorodeoxyglucose positron emission computed tomography (PET) has not been shown to be reliable for the identification of complete responders (AUC 0.57–0.73) [50]. Although comparing the change in baseline with 12-week posttreatment standardized ^{18}FDG uptake values may provide some improvement in test performance [51].

Table 30-3. MRI tumor regression grade (mrTRG) [54]

mrTRG	Description
1	Tumor bed with low signal intensity signaling fibrosis with no residual intermediate tumor signal
2	Tumor bed with predominance of fibrosis with minimal residual intermediate tumor signal
3	Substantial intermediate intensity tumor signal present, but does not predominate over low intensity fibrosis
4	Minimal fibrosis
5	No change from baseline

Perhaps one of the most useful imaging tests is high-resolution MRI. Areas of treatment response and fibrosis are characterized by low signal intensity on T2 weighted imaging. The presence of uniform low signal intensity with the absence of areas of intermediate signal intensity within it is suggestive of a pCR. Based on these findings and a comparison to pretreatment MRI, a tumor regression grade has been proposed by the Mercury Study investigators (Table 30-3) [52]. The so-called mrTRG of 1–3 correlated with better survival outcomes when compared to mrTRG 4–5, comparable to the difference in survival observed when comparing ypT0-3a vs. ypT3b or greater [52]. There is currently great interest in the potential for the addition of diffusion weighting or functional dynamic contrast enhanced MRI to improve the detection of response, and other technologies may still be on the horizon [53]. In the meantime, MRI may play an important role in identifying patients with significant treatment response and more favorable prognosis who may be eligible for a watch and wait approach. Such a strategy was employed by a group from Maastricht University in the Netherlands to identify 21 patients for a wait and see approach that were compared to 20 matched control patients exhibiting pCR treated with surgery. They utilized strict selection criteria requiring evidence of cCR, including by posttreatment high-resolution magnetic resonance imaging (MRI) and then MRI-based follow-up every 3 months for the 1st year and biannually thereafter. With their approach, 75% of the pCR patients who had undergone resection were classified by MRI incomplete responders. After a median follow-up of 15 months (vs. 35 months in the surgery group), only 1 patient experienced a local recurrence in the study arm [36]. The TRIGGER trial lead by investigators at the Royal Marsden and the Pelican Cancer Foundation in the United Kingdom will randomize patients to deferral of surgery with watch and wait for good (mrTRG 1–2) and systemic therapy for poor (mrTRG 3–5) responders based on MRI with an opportunity for the poor responders to be converted to complete response vs. immediate surgery in the control arm.

Increasing the Rate of Complete Response

Based on the presumption that patients with pCR are eligible for an organ-preserving watch and wait approach, a number of investigators have tried to improve the rate of PCR with neoadjuvant therapy. These can broadly be categorized as (1) radiotherapy dose intensification including contact radiation; (2) utilization of more active chemotherapeutic regimens; (3) increase in the time interval from chemoradiotherapy to surgery; and (4) a combination of these approaches.

Perhaps the most common strategy for radiotherapy dose escalation is local boost therapy to the tumor volume. This approach has the advantage of increasing the delivered dose to the tumor volume without increasing toxicity to uninvolved surrounded bowel and can be achieved through IMRT or contact therapy [55]. In a randomized trial of external beam radiotherapy to 39 Gy in three fractions with endocavitary boost to 85 Gy compared to external beam radiotherapy alone, there was significant increase in complete or near-complete sterilization (57% vs. 34%, respectively) [56]. Unfortunately, while boost therapy to the primary tumor bed can increase the rate of response within the bowel wall, the lymph nodes may remain unaddressed; however these strategies appear to be well tolerated and remain the subject of further investigation.

A number of studies have attempted to increase the treatment response by incorporating more highly active concurrent chemotherapy regimens. Indeed, it has been reported that systemic chemotherapy alone may be associated with pCR in up to 25% of patients with relatively early rectal cancers [57]. Unfortunately, after several randomized studies of concurrent fluoropyrimidine-based oxaliplatin containing regimens, an increase in pCR has been observed only in the German CAO/ARO/AIO-04 randomized trial at the cost of increased toxicity as demonstrated in NASBP R-04 and STAR-01 [58–61].

The time interval between nCRT and surgery is another important factor associated with pCR. The Lyon R90-01 trial randomized patients to an interval of 6–8 weeks vs. <2 weeks and found a higher rate of complete response (26% vs. 10.3% $p = 0.005$) following the longer interval [62]. However, subsequent long-term follow-up after a median 6.3 months demonstrates no difference in local recurrence or survival [63]. Thus while it is well recognized that a longer treatment interval is associated with a higher rate of pCR, it has not been demonstrated that patients exhibiting pCR after a longer treatment interval have the same good prognosis of those who were more rapidly sterilized. Thus tumor cell death is initiated immediately (during neoadjuvant therapy), but the pCR rate can be manipulated by changing the duration of delay prior to proctectomy. Therefore, one cannot assume that one neoadjuvant therapy regimen is superior to another based on pCR rate if proctectomy occurs at different intervals following neoadjuvant therapy.

Additional strategies for improving treatment response while providing systemically active therapy include induction and consolidation chemotherapy. Induction chemotherapy has the potential to improve survival outcomes by improving tumor regression and the ability to deliver systemic chemotherapy with a lower rate of associated toxicity. The EXPERT and EXPERT-C phase II studies of pretreatment capecitabine with oxaliplatin and with cetuximab in patients with high-risk rectal cancers showed that a high rate of R0 resection could be achieved although there was not a remarkable increase in the rate of pCR [64]. The addition of the EGFR inhibitor resulted in greater rates of radiographic response, although not in the rate of pCR [65].

Capitalizing on the potential for improved tumor regression with increased time interval to surgery, the Timing of Rectal Cancer Response to Chemoradiation trial, delivering up to six cycles of mFOLFOX6 after standard CRT was associated with an increase in pCR to 38% vs. 18% with standard nCRT alone [66]. The rate of surgical complications was not increased and no increased risk for progression was observed. Others have reported have provided supportive evidence for consolidation chemotherapy, but its potential role in improving durability of treatment response for patients undergoing a watch and wait strategy is unknown [67]. And the Rectal cAncer and Preoperative Induction therapy followed by Dedicated Operation (RAPIDO) trial is currently randomizing patients to short-course (5×5 Gy) pelvic radiation followed by six cycles of capecitabine and oxaliplatin and TME vs. standard nCRT and TME with the goal of improving disease-free and overall survival without compromising local control [68]. There is also an ongoing randomized study of induction vs. consolidative chemotherapy for patients with rectal cancer undergoing nCRT that is intended to improve disease-free survival when compared to standard CRT (NCT02008656). While these studies are not designed to investigate a strategy of watch and wait, it may shed new light on the role of consolidative chemotherapy in patients with high-risk rectal cancer.

Finding the Way Forward

The management of rectal cancer has become increasingly complex. While currently most patients with clinical stage II or III disease are treated with neoadjuvant chemoradiotherapy or short course radiotherapy followed by proctectomy, there is increasing recognition of the potential to avoid radiation therapy associated toxicity, as excellent results can be achieved with high-quality resection in appropriately selected patients without high-risk features on initial evaluation [69]. We also continue to learn about the role of neoadjuvant chemotherapy alone for treatment of intermediate-risk mid-rectal cancers [57]. Patients with intermediate-risk dis-

tal rectal cancers in whom a permanent colostomy will be required may be the optimal candidates in whom to study a watch and wait approach. These patients with small tumors close to or involving the sphincters are most likely to both require permanent colostomy at surgery and to achieve a complete response to chemoradiation therapy.

However a number of unresolved questions remain. The long-term oncologic efficacy of the watch and wait approach still requires validation, especially given the high cure potential associated with definitive surgery in this patient population. While it appears that surgical salvage for tumor regrowth is feasible, it is unknown if the delay can lead to lost window of opportunity for patients with distal cancers who were otherwise candidates for coloanal reconstruction. The potential that the risk for distant recurrence may be increased with a nonoperative approach must also be examined. Finally, there exists no reliable method for identifying patients with pCR who may then be eligible for a watch and wait approach and local tumor excision still carries significant morbidity risk without providing complete information regarding the status of the regional lymph nodes. Currently, the most objective method for identifying potential candidates for a watch and wait approach seems to be comparison of pre- and posttreatment high-resolution MRI imaging to assess response. Using MRI response to clinical response criteria with a strict protocol for follow-up may be the most reliable way of implementing a watch and wait strategy but it is far from a perfect test. Systemic chemotherapy, either as induction or consolidation, is another approach to increasing the likely of achieving pCR and identifying the low-risk in whom selective surgery can be considered and may play a role in reducing the risk for distant recurrence [66]. Finally, while there is great interest in molecular analysis that should be incorporated into all future trials, as of yet there are no molecular signatures that can predict the likelihood of achieving a pCR.

Until recently, most surgeons would have been reluctant to consider a nonoperative approach for rectal cancer, but the increasing emergence of data may have turned the tide on opinion [70]. As of yet there is no evidence from randomized controlled trials to support nonoperative strategies for patients with rectal cancer. Questions regarding patient selection, optimal method for inducing pCR, methods for assessing treatment response, and adequacy of follow-up remain unanswered.

Given the infrequent primary outcome of recurrence in this patient population, a randomized non-inferiority study is likely not feasible. But there is a critical need for evidence, perhaps through well-conducted prospective cohort studies, so that the watch and wait strategy can be safely incorporated into the overall management strategy for patients with rectal cancer. For now, radical surgery should remain standard treatment for rectal cancer, and watch and wait should only be performed in the context of clinical trials.

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