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Non-Operative Management of Rectal Cancer: A Critical Review

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Abstract

Neoadjuvant chemoradiotherapy followed by a total mesorectal excision is the standard of care for patients with locally advanced rectal cancer. This trimodality approach achieves excellent local tumour control and improves patient survival. However, it is accompanied by severe morbidity and long-term functional consequences that can affect the quality of life emphasizing non-operative approach. Non-operative management of rectal cancer is a treatment approach in which patients who achieve a complete clinical response to chemoradiotherapy are closely monitored. Even though it is not a standard of care, preliminary findings indicate that it is a viable option for patients with advanced stage rectal cancer who achieve a complete response to chemoradiation and are compliant with surveillance strategies. This review aims to provide insight into literature review, timing, modalities of treatment response and ongoing studies that may support expanded use of non-operative management of rectal cancer.

Keywords: Complete clinical response; Neoadjuvant chemoradiotherapy; Rectal cancer; Treatment response assessment

Introduction

According to Indian GLOBOCAN data 2020, colorectal cancer is the 5th most frequently diagnosed cancer in both sexes, with an annual incidence of 28260 cases and an annual mortality of 16149 cases.[1] Pre-operative chemoradiotherapy (CRT) followed by a total mesorectal excision (TME) is the standard of care for patients with locally advanced rectal cancer (LARC). Numerous complications have been reported with TME, including infection, wound complications, vascular injury, presacral bleeding, ureteral injury, urinary and sexual dysfunction.[2-4] Neoadjuvant chemoradiotherapy (NCRT), when combined with surgery achieves excellent local tumour control and improves patient survival. However, it is accompanied by severe morbidity and long-term functional consequences that can affect the quality of life (QOL). Therefore it is crucial to optimize non-operative strategies without compromising oncologic outcomes.

Non-operative management of rectal cancer is a treatment approach in which patients who achieve a complete clinical response (cCR) to NCRT are closely monitored, with surgery reserved for salvage purposes. Treatment de-escalation can be considered for lower-risk patients to maintain disease control while avoiding the toxicity and poor QOL associated with combined-modality therapy. It may be an appropriate option for certain patients who have multiple comorbidities, who cannot tolerate radical surgery or wish to avoid the potential complications of TME.

Literature Review

The German rectal trial established pre-operative CRT as a standard of care in 2004.[5] This study demonstrated pathological complete response (pCR) rates to the tune of 8%.[5] Subsequently, several other studies reported pCR rates as high as 20% following NCRT.[6-9] The non-operative management of rectal cancer was pioneered in 2004 at the University of Sao Paulo School of Medicine by Dr Habr-Gama and her group.

Retrospective Studies

Dr Habr-Gama and her group retrospectively evaluated 265 patients with resectable distal rectal cancer treated with NCRT [50.4 Gy dose of radiotherapy (RT) along with 5-Fluorouracil (5-FU), Leucovorin]. 22 patients (8.3%) with incomplete clinical response treated by surgery who achieved pCR were compared to 71 patients (26.8%) with cCR at 8 weeks treated by non-operative strategy with close surveillance program of monthly evaluation with a digital rectal examination (DRE), proctoscopy, biopsy and carcinoembryonic antigen (CEA) testing. 5-year overall survival (OS) and disease-free survival (DFS) rates were similar in both groups. Long term analysis revealed that 10-year OS and DFS rates were 100% and 86%, respectively, in the non-operative cohort. [10]

In an updated series published in 2006, Habr-Gama et al.[11] reported on 361 patients with low, resectable cT2-4N0/N+ rectal cancers treated with NCRT (50.4Gy RT along with concurrent leucovorin, and bolus 5-FU administered intravenously for 3 consecutive days on the first and last 3 days of CRT). Tumour response was evaluated 8 weeks after CRT. Patients who experienced a cCR were not operated on immediately and were continuously monitored. Following the initial tumour response assessment, 122 patients were considered to have a cCR. Only 99 patients (27.4 %) out of 122 patients sustained a cCR for at least 12 months and were managed non-operatively. There were 13 (13.1%) recurrences at a mean follow-up of 59.9 months: 5 (5%) endorectal, 7 (7.1%) systemic, and 1 (1%) combined recurrence. All 5 isolated endorectal recurrences were salvaged. 5-year OS and DFS were 93% and 85%, respectively.

Lim et al.[12] performed a retrospective analysis of 48 patients with rectal cancer who are treated with RT or CRT alone because of excessive operative risk or patient refusal of surgery. A cCR was documented in 27 patients (56%), with 14 patients (30%) having a partial response. Patients with a cCR had a median progression-free survival (PFS) of 65 months.

Smith et al.[13] conducted a retrospective analysis of 32 stage I-III rectal cancer patients. Patients with cCR after CRT and subsequently managed non-operatively were compared to 57 patients with a pCR after radical rectal resection. After a median follow-up of 28 months for the non-operative group, 6 recurred locally (3 of them also had a concurrent distant recurrence). All 6 local failures were controlled by salvage rectal resection with no further local recurrence of disease at a median follow-up of 17 months. In pCR group, there were no local failures. The 2-year distant DFS (88% vs 98%, P = 0.27) and OS (96% vs 100%, P = 0.56) were similar for non-operative and pCR groups. Hence, rectal resection was successfully avoided in 81% of patients selected for non-operative management. When combined with salvage surgery, the non-operative cohort appears to achieve similar local and distant disease control compared with patients with a pCR treated by rectal resection.

Lai et al.[14] compared the outcomes of rectal cancer patients treated with CRT with cCR followed by either a "watch and wait" strategy or TME. They concluded that watch and wait policy avoids the morbidity associated with radical surgery and preserves oncologic outcomes, and can be considered a therapeutic option in patients with LARC following CRT with cCR.

Araujo et al.[15] conducted a retrospective analysis of disease recurrence in rectal cancer patients. 42 patients who were managed non-operatively compared to 69 patients who had pCR following surgical resection. With a follow-up of 47 months, overall recurrence rates were 12 (28%) in the non-operative group and 8 (11.5%) in the surgical group. Isolated local recurrence rates were 5 (11%) and 1 (1.4%), respectively, in the non-operative and surgical groups. No difference in OS was found (71.6% vs 89.9%, p = 0.316), but there was a higher DFS favoring surgical group (60.9% vs 82.8%, p = 0.011).The non-operative group achieved OS comparable to surgical treatment and spared patients from surgical morbidity, but it resulted in more

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recurrences, prompting the caution against routine use of non-operative management of rectal cancer outside of clinical trials.

Prospective Studies

Most of the data related to non-operative management of rectal cancer are from retrospective, single-institutional, or non-comparative studies. Limited prospective studies are summarized here.

A small prospective study was done by Maas et al. [16] from Maastricht University Medical Center in the Netherlands evaluated the feasibility and safety of a wait-and-see policy with strict selection criteria and follow-up. Between 2004 - 2010, 192 patients with cT1-3N0-2 were treated with CRT (50.4 Gy RT over 28 fractions with concurrent capecitabine). 21 patients with rectal cancer who achieved cCR following NCRT were selected for the wait-and-see policy with magnetic resonance imaging (MRI) and endoscopy plus biopsies. The wait and see group's functionality and outcomes were compared to those of a control group of 20 patients who achieved pCR following NCRT and TME. At a mean follow-up of 25 ± 19 months, in the wait and see group, 20 (95%) patients remained disease-free; 1 patient developed a local recurrence and was surgically salvaged. The cumulative probability of 2-year DFS and OS were 89% and100% respectively for wait and see group. The control cohort had a 2-year OS of 91% and DFS of 93%, similar to patients with cCR on the "wait and see" protocol. As expected, bowel function, as measured by the Memorial Sloan-Kettering Cancer Center (MSKCC) Bowel Function Index, was significantly superior in patients who were managed non-operatively.

Habr-Gama et al. [17] conducted a prospective single-arm analysis of 70 patients with distal rectal cancer to describe the outcomes of non-operative management. The NCRT regimen included delivering 54 Gy of RT and six cycles of 5-FU/leucovorin (with three cycles delivered concurrently and three cycles delivered after RT). Ten weeks after completion of RT, patients were evaluated for tumour response. Initially, 47 (68%) patients had cCR. However, 8 (17%) experienced early tumour regrowth within the first 12 months of follow-up. Finally, 39 (57%) patients maintained a sustained cCR for at least 12 months. Late recurrences occurred in 4 (10%) cases, all of which were successfully salvaged through surgery. Three-year OS and DFS for patients with sustained cCR was 94% and 75%, with a median follow-up of 53 months.

A Dutch study by Appelt et al. [18] evaluated the use of dose-escalated RT (60Gy to the primary tumour) followed by a 5 Gy endorectal brachytherapy boost in 51 eligible patients with T2-T3 rectal tumours. The 1-year local recurrence rate was 15.5 %, with a median follow-up of 24 months. Sphincter function in the non-operative group was excellent, with 18 (72%) of 25 patients at 1-year and 11 (69%) of 16 patients at 2-years reporting no faecal incontinence. Grade-3 proctitis was reported in 2 (7%) of 30 patients at 1-year and 1 (6%) of 17 patients at 2-years. While these results are promising, larger studies with longer follow-up are needed to evaluate the long-term effects on bowel function after high-dose irradiation.

Renehan et al. [19] from the United Kingdom (UK) sought to prospectively assess oncologic outcomes of non-operative rectal cancer management in patients achieving cCR. Their OnCoRe study analyzed patients with non-metastatic rectal cancer treated with NCRT using a propensity score-matched cohort analysis (45 Gy in 25 fractions with concurrent fluoropyrimidine-basedchemotherapy).Non-operative management was offered to 129 patients who attained cCR following CRT, and they were compared one-to-one to paired cohorts of patients who underwent surgical resection. At 3-year follow-up, the rate of local recurrence was 34% in patients managed non-operatively, and 88% of non-metastatic locally recurrent tumours were salvageable. There were no significant differences in OS (96 % vs 87%) or 3-year DFS (88% vs 78%). However, non-operatively managed patients had a higher rate of colostomy-free survival than surgical patients, with a 26 % absolute difference in avoiding permanent colostomy at 3 years. This matched cohort investigation of the UK population confirmed that many patients with rectal cancer treated non-operatively could avoid major surgery and permanent colostomy without compromising local control.

Recently, a similar study was done by Wang et al. [20] investigated the long-term clinical outcomes of wait and watch strategy in comparison to surgical resection. They demonstrated that the watch-and-wait strategy was safe, with similar survival outcomes but a superior sphincter preservation rate as compared to

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surgery and could be offered as a promising conservative alternative to invasive radical surgery.

Systematic Review And Meta-Analysis

Dossa et al. [21] systematically reviewed 23 studies of patients with rectal adenocarcinoma managed by watch-and-wait after cCR to NCRT. The researchers interpreted that most patients treated by watch-and-wait avoid radical surgery. Patients who have regrowth almost all underwent salvage therapy, and no significant differences in OS or non-regrowth cancer recurrence in patients treated with watch-and-wait versus surgery.

In summary, the studies mentioned above suggest that non-operative management may be an alternative approach to TME in highly selected patients with LARC who achieve a cCR to NCRT.

Timing Of Treatment Response Assessment

Tumour assessment six to eight weeks after completion of CRT is currently established standard of care for patients with rectal cancer. [22,23] The lack of agreement on the optimal timing of response assessment stems from retrospective data indicating that longer time intervals between the completion of treatment and the initial post-treatment patient assessment may be associated with higher pCR rates. [24-29] cCR has been assessed at various time points in the studies conducted till date to evaluate the non-operative strategy. The time period ranges from 4 to 20 weeks after completion of NCRT. Various timing of assessment post-NCRT described in table 1.

Given these findings, it appears that treatment response assessment to determine the cCR should be performed around week 8 following completion of NCRT. This criterion, however, may need to be adjusted based on the patient's initial tumour stage, as more advanced tumours require a longer time interval to achieve a cCR. The initial reassessment should not be excessively delayed because early detection of inadequate response to NCRT can help in proceeding to surgery.

Modalities Of Treatment Response Assessment

The success of non-operative rectal cancer management depends upon an accurate tumour response assessment following CRT. DRE, endoscopic procedures, imaging and tumour markers are proposed to be employed to assess tumour response. DRE is an essential tool for assessing primary tumour response, as it may reveal findings not visible on radiographic imaging. DRE has a relatively low sensitivity of 24% for predicting complete response but has a very high specificity of 56%. One prospective study demonstrated that only 21% of patients with pCR had a negative DRE before surgery. On the other hand, there were no instances in which DRE findings were negative, and subsequent pathology revealed residual tumour. [34]

Habr-Gama et al.[35] first published guidelines on the standard findings of cCR on proctoscopy and DRE. A whitened scar, telangiectasia, palpable stiffness of the scar, and a lack of visible tumour or palpable nodule were all indicators of cCR. Nodularity, ulceration, or severe stenosis suggested an incomplete clinical response. The finding of any irregularity, residual superficial ulceration, or nodule should prompt surgical attention, including transanal full-thickness excision or even a radical resection with TME. The drawback of DRE and endoscopy is the inability to evaluate nodal response. Endoscopic ultrasound has been reported to be accurate in restaging nodal involvement following CRT in a range of 39% to 83%.[36]

A retrospective study by Perez et al. [37] assessed the role of biopsies in patients with residual rectal cancer following NCRT after downsizing. They concluded that in patients with distal rectal cancer undergoing NCRT, post-treatment biopsies are of limited clinical value in ruling out persisting cancer. A negative biopsy result after a near-cCR should not be considered sufficient for avoiding a radical resection.

According to Smith et al. [38] 74% of patients with residual mucosal abnormality like visible ulceration or mass had no sign of residual malignancy on proctectomy specimens, whereas 27% of patients with mucosal cCR still had the residual disease. This emphasized the significance of using different approaches, such as imaging, to assess CRT response.

There is uncertainty regarding the most appropriate diagnostic modalities for evaluating tumour response following NCRT. Positron emission tomography-Computed tomography (PET- CT) and MRI are the most frequently used imaging modalities. Radiographic imaging can be used to evaluate both the primary site and any nodal disease in a potentially

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non invasive manner. PET-CT imaging has garnered considerable interest due to its theoretical advantage of detecting metabolically active disease and differentiating it from post-treatment tumour changes.

Guillem et al. [39] conducted a prospective study to assess its utility in this setting but concluded that neither PET nor CT have adequate predictive value for differentiating pCR from an incomplete response. The investigators demonstrated that PET and CT accurately detected complete response in 54% and 19% of patients and incomplete response in 66% and 95% of patients, respectively.[39] Maffione et al.[40] reported that PET-CT was generally accurate with a sensitivity and specificity rate of 73% and 77%, respectively and supported its use for restaging LARC. A study examining the use of PET to assess response to NCRT in rectal cancer demonstrated that patients who developed an increase in SUVmax after 6 weeks were less likely to develop significant tumour downstaging. Early-late SUVmax variation at 6-week PET-CT may help identify these patients and allow tailored selection of CRT-surgery intervals for individual patients.[41]

MRI, when combined with diffusion-weighted imaging (DWI), holds significant promise for detecting complete response accurately. Lambregts et al.[42] illustrated that the addition of DWI to standard MRI sequences increased the sensitivity for selection of complete responders from 0% - 40% to 52 - 64% while maintaining a range of high specificity 89-98%.These findings were validated in a larger multi-institutional study, which found that post-CRT DWI volumetry offers the best results for detecting patients with a complete response after CRT with a sensitivity of 70% and specificity of 98%.[43]

The reported overall accuracy of MRI using standard imaging sequences in predicting the pathologic stage of irradiated rectal cancer is 47%–54% for T staging and 64%–68%forN staging [44]. Van Heeswijk et al.[45] demonstrated that restaging MRI with DWI sequences could reliably differentiate between yN0 and yN-positive patients following CRT with a sensitivity of 100%, a specificity of 14%, a positive predictive value of 24%, and a negative predictive value of 100%. In general, imaging studies are beneficial for restaging primary tumours and nodal lymph nodes following NCRT.

The "magnetic resonance tumour regression grade" (mrTRG) has been described based on the degrees of low signal intensity, intermediate signal intensity, and tumour signal intensity present on MRI after neoadjuvant treatment.[46] According to Bhoday et al.[47] mrTRG was ten times more likely to detect cCR than clinical assessment, allowing a significant number of patients to forgo immediate surgery and instead adopt a watch-and-wait approach.

The utility of tumour markers, particularly CEA, in rectal cancer was investigated. Perez et al.[48] examined the prognostic value of serum CEA levels before and post NCRT and elucidated that post-CRT CEA level <5ng/ml is a favourable prognostic factor for rectal cancer and is associated with increased rates of earlier disease staging and complete tumour regression. Post-CRT CEA levels may be helpful in decision making for patients who may be candidates for alternative treatment strategies.[48] Although low CEA levels following CRT may indicate a greater likelihood of pCR, this test result should be interpreted in conjunction with clinical and imaging data to guide management decisions.

Maas et al.[49] demonstrated that combining T2-weighted and diffusion-weighted MRI, endoscopy, and DRE (triple assessment) led to a post-test probability for predicting a complete response of 98 %.The studies mentioned above suggest that multiple modalities should be used to assess patients with cCR following CRT accurately.

Ongoing Trials

Several clinical trials are now being conducted to explore various strategies to enhance cCR rates. Various ongoing trials related to non-operative management are discussed here in Table 2.

Conclusion

Non-operative management is a potential alternative for rectal cancer treatment. The objective is to spare selected patients from the morbidity associated with radical surgical resection while retaining the excellent tumour control rates associated with standard combined modality therapy. The preliminary results of non-operative management for a subset of rectal cancer patients are encouraging. Critically, patient selection depends upon close and careful surveillance after a favourable response to CRT. Even though non-surgical management of

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rectal cancer with close-monitoring is not a standard of care for rectal cancer, initial findings indicate that it is a viable option for patients with LARC who achieve a complete response to CRT and are compliant with surveillance strategies. Patients should be informed in detail about the possibility of unsalvageable recurring disease resulting from non-surgical management, and a clear understanding of possible outcomes should be ensured.

Table 1 : Timing between NCRT and first reassessment in non-operative management of rectal cancer"

Study	Year of study	NCRT schedule	Timing of assessment after NCRT
Dalton et al [30]	2012	45 Gy/25# with concurrent Capecitabine	8 weeks
Smith et al [13]	2012	50.4 Gy/28 # with concurrent 5-FU or Capecitabine	4 – 10 weeks
Habr Gama et al [17]	2013	54Gy/30# with concurrent 5-FU/Leucovorin followed by 3 cycles adjuvant chemotherapy with 5-FU/Leucovorin	10 weeks
Appelt et al [18]	2015	60 Gy/30# to tumour + 50 Gy/30 to LNs along with Tegafur-uracil	6 weeks
Renehan et al [19]	2016	45 Gy/25# with concurrent 5-FU or Capecitabine	≥ 8 weeks
Vaccaro et al [31]	2016	50.4 Gy/28# with concurrent 5-FU/Leucovorin	8-12 weeks
Lai et al [14]	2016	45 Gy/25# or 54 Gy/30# with concurrent 5-FU/Leucovorin	8-12 weeks
Martens et al [32]	2016	50.4 Gy/28# or 5 Gy/5# with concurrent 5-FU	8-20 weeks
Creavin et al [33]	2017	50-54 Gy/30 # with concurrent 5-FU	6-8 weeks

: Number of fractions, Gy : Gray, 5-FU : 5-fluorouracil

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"Table 2 : Ongoing trials related to non-operative management of rectal cancer"

Clinical trials.gov identifier (NCT number)	Type of study	Title	Planned enrollment	Primary Outcome
NCT03402477	Observational Prospective	"Watch and Wait" in Patients With Complete Clinical Response (cCR) After Neo-adjuvant Chemoradiotherapy for Primary Locally Advanced Rectal Cancer.	100	Local relapse rate
NCT03426397	Observational Prospective	Multicentre Evaluation of the "Wait-and-see" Policy for Complete Responders After Chemoradiotherapy for Rectal Cancer	220	2-year non-regrowth DFS
NCT03125343	Interventional Non-Randomized	A Multicenter Prospective National Cohort Study for Patients With Advanced Rectal Cancer - is it Possible to Induce Remission and Avoid Surgery - Watch and Wait?	200	3-year DFS
NCT04095299	Interventional Randomized	Randomized Trial of Standard Dose Versus High Dose of Radiotherapy in Rectal Preservation With Chemo-radiotherapy to Patients With Early Low and Mid Rectal Cancer: The Watchful Waiting 3 Trial	111	2-year rectal preservation
NCT03846726	Observational Retrospective	Watch-and-wait Approach Versus Surgical Resection for Rectal Cancer Patients With Complete Clinical Response After Chemoradiotherapy: a Multi-center Cohort Study	513	PFS
NCT03001362	Interventional Non-Randomized	Radical External Beam Chemoradiation in Patients With Rectal Cancer: a "Wait-and-see" Approach	48	Feasibility of a "wait and see" approach

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