International Journal on Oncology and Radiotherapy

Organ Preservation for Rectal Cancer - Are We Any Wiser?

Mini Review

Volume 5 Issue 1- 2024

Author Details

Mohan Hingorani[1], Khaliq Rehman[2] and Nathalie Casanova[3]*

[1]*Consultant Clinical Oncologist, Department of Clinical oncology, Queen Centre of oncology, UK*
[2]*Specialist Grade in clinical Oncology, Department of Clinical oncology, Queen Centre of oncology, UK*
[3]*Consultant Clinical Oncologist, Department of Clinical oncology, St James University Hospital, UK*

*Corresponding author

Mohan Hingorani, Consultant Clinical Oncologist, PhD, FRCR, MRCP

Department of Clinical oncology, Queen Centre of oncology, Cottingham, HU16 5JQ, UK

Article History

Received: March 19, 2024 Accepted: March 20, 2024 Published: March 21, 2024

Abstract

There is considerable interest emerging in the role of organ preservation in rectal cancer and avoiding surgery in patients developing complete clinical response (cCR) after initial chemoradiotherapy. Despite the wider recognition that organ preservation in rectal cancer is reasonable therapeutic paradigm there is still considerable anxiety prevailing regarding the safety and long-term outcomes of adopting such an approach, particularly in younger patients. The purpose of this mini review is to highlight the key evidence regarding organ preservation and define the optimum surveillance protocol.

keywords: Rectal Cancer, Chemoradiotherapy, Radiotherapy

Abbreviations: CCR: Complete Clinical Response; CRT: Chemoradiotherapy; CT: Computed Tomography; DWI: Diffusion Weighted Imaging; EBRT: External Beam Radiotherapy; 5FU: 5 Fluorouracil; FU: Follow Up; MRI: Magnetic Resonance Imaging; TME: Total Mesorectal Excision

Background

Preoperative chemoradiotherapy (CRT) followed by radical surgery is the standard of care for locally advanced rectal cancer resulting in excellent local control rates [1]. However, surgical resection may be associated with morbidity and risk of acute and chronic post-operative complications particularly in elderly patients. Furthermore, there may be long-term and often permanent detrimental effects on quality of life in patients with low rectal tumors who will require abdominal-perineal resection (APR) and permanent stoma. More recently, there is emerging interest in the role of organ preservation in rectal cancer and avoiding surgery in patients developing complete clinical response (cCR) after initial CRT. In those developing a cCR, surgery may be omitted and instead patients are subjected to period of intense surveillance for 2 years to diagnose any tumor regrowth that may be amenable to salvage surgery.

It is now widely recognized that organ preservation in rectal cancer is reasonable therapeutic paradigm but still considerable anxiety prevails regarding the safety and long-term outcomes of adopting such an approach, particularly in younger patients. The purpose of this mini review is to highlight the key evidence regarding organ preservation and define the optimum surveillance protocol. The decision to go down this route will be ultimately influenced by the patient's preferences including acceptance of the uncertainties and possibility of tumor regrowth and commitment to the surveillance protocol.

What is the Evidence?

The Brazilian Experience

In 2014, Habr Gama et al, reported on outcomes of patients with rectal adenocarcinomas (0-7cm anal verge) developing cCR after CRT using 50.4 Gy in 28 fractions with concurrent 5-flourouracil (FU) in week 1 and 5. From the initial cohort (n=183), 90 (49%) patients developed cCR 8 weeks after CRT. The definition of cCR was based on stringent criteria of clinical, endoscopic, and radiologic findings. Briefly, the criteria for considering cCR were the absence of residual ulceration, mass, or mucosal irregularity at clinical/endoscopic assessment. Whitening of the mucosa and the presence of neo-vasculature (telangiectasia) were accepted features of cCR. Patients developing

cCR were managed with active surveillance with clinical visits every 1 to 2 months with a single experienced colorectal surgeon, and underwent clinical and digital rectal examination in addition to rigid proctoscopy. Carcinoembryonic-antigen (CEA) levels were obtained every 2 to 3 months. After 1 year of follow-up, patients were examined every 3 months similarly and every 6 months after 3 years. Radiologic imaging (computerized tomography (CT), magnetic resonance imaging (MRI) was performed after 6 months and yearly thereafter.

There were a total of 28 local or pelvic recurrences (31%) (17 early re-growths within the initial 12 months and 11 late recurrences after 12 months of follow-up). Of the 28 patients with locoregional recurrence, salvage therapy was possible in 26 (93%) patients (local excision=7; major surgical resection=18; brachytherapy =1). The actuarial overall unresected local recurrence-free survival was 94 percent [2]. Habr Gama et al, (2004) reported on subsequent study of 'wait and watch 'strategy' in patients developing cCR after CRT. Two-hundred sixty-five patients with adenocarcinoma of the distal rectum (0-7cm from anal verge) were treated with CRT using 50.4 Gy in 28 fractions combined with concurrent 5-FU during week 1 and 5. Patients were assessed 8 weeks from completion of CRT, to determine tumor response using clinical, endoscopic, and radiologic parameters. In addition, endoscopic biopsies were obtained for pathologic confirmation of complete response. The presence of any significant residual ulcer or positive biopsies was considered incomplete clinical response. Patients with cCR were not operated upon but subjected to intense surveillance program comprised of monthly clinical examinations (including digital rectal examination), CEA levels and proctoscopy. The interval between assessment were increased 2-6 monthly for the second year.

Seventy-one patients had complete clinical response 8 weeks after completion of CRT therapy (26.8%) and were enrolled in the 'wait and watch' protocol. Mean age was 58.1 years, ranging from 35 to 92. Pretreatment mean tumor size was 3.7cm (1-7cm), and initial mean distance from anal verge was 3.6cm (0-7cm). Fourteen patients had a T2 lesion (19.7%), 49 patients had T3 lesions (69%), and 8 had T4 lesions (11.3%). Sixteen patients had radiologic evidence of N+ lesions (22.5%). Two patients (2.8%) developed endoluminal recurrence after 56 and 64 months of CRT completion. One was treated with transanal excision (T1 disease) and the other was treated with salvage brachytherapy with no evidence of further relapse. Three patients developed systemic metastases (4.2%) at 18, 48, and 90 months of follow-up. Five-year overall and disease-free survival rates were 100% and 92%, respectively. Ten-year overall and disease-free survival rates were 100% and 86%, respectively [3].

The International 'Wait and Watch' Database

The International 'Wait and Watch' Database is large scale registry of pooled individual data. All patients with rectal cancer who develop cCR after neoadjuvant therapy and are not considered for surgical resection are eligible to be included in the IWWD. Pooled analysis of 880 patients from the database (47 participating institutes (15 countries)) was reported in Lancet in 2018 after median follow-up of 3.3 years (95% CI 3.1–3.6). Most patients had CRT alone but some patients also received combined modality treatment (e.g. CRT followed by brachytherapy).

The 2-year cumulative incidence of local regrowth was 25.2% and 88% of all local regrowth was diagnosed in the first 2 years, and 97% of local regrowth was located in the bowel wall. Distant metastasis was diagnosed in 71 (8%) patients. 5-year overall survival was 85%, and 5-year disease-specific survival was 94% (91–96%) [4].

The 'OnCoRe' Study

Oncological Outcomes after Clinical Complete Response in Patients with Rectal Cancer (OnCoRe) is a propensity-score matched cohort analysis study, that reported on outcomes of patients developing cCR after neoadjuvant CRT. 259 patients were treated at Christie Hospital between 2011 and 2013 with neoadjuvant CRT from which 31 patients developed cCR and were managed with 'wait and watch' strategy. These were combined with 98 patients with who were managed similarly across 3 other neighboring UK centers between 2005 and 2015. The comparative analyses employed one-to-one paired cohorts of wait and watch versus surgical resection using propensity-score matching (including T stage, age, and performance status).

After median FU of 33 months, local regrowth was detected in 44 patients (34%) and 36 (88%) of 41 patients with non-metastatic local regrowths were salvaged. The 3-year non-regrowth disease-free survival was superior in the watch and wait group compared to surgical resection (88% vs 78%; P=0.043), but not deemed statistically significant as the study used conservative significant P value of less than 0.01. Similarly, 3-year overall survival was superior in the watch and wait group compared to surgical resection [96% vs 87%; P=0.024). Patients managed by watch and wait had significantly better 3-year colostomy-free survival than did those who had surgical resection (74% vs 47%; HR= 0.445 [P<0.0001) [5].

GRECARR 2 Study

The GRECCAR 2 was a randomized Phase III French study of organ preservation in rectal cancer in which patient with cT2/T3 low rectal carcinoma (< 8cm anal verge, of maximum size 4cm), who had a good clinical response (residual tumor < 2cm, no vegetative component and no significant hollow or deep infiltration into the muscular layer) to neoadjuvant chemoradiotherapy were centrally randomly assigned by the surgeon before surgery to either local excision or TME surgery. Patients with ypT0-1 histology after local excision with negative margins were managed with watch and wait and those with ≥ ypT2 disease and positive margins proceeded to TME. The primary endpoint was a composite outcome of death, recurrence, morbidity, and side-effects at 2 years after surgery. The final analysis included 145 patients: 74 in the local excision group and 71 in the TME. In the local excision group, 26 (37%) patients had a completion TME. At 2 years, one or more events from the composite primary outcome occurred in 41 (56%) of 73 patients in the local excision group and 33 (48%) of 69 in the TME group (HR 1.33 (0.62-2.86); P=0.43) [6].

The surgical morbidity was much lower patients undergoing local excision alone compared to TME, but significantly higher in those with local excision proceeding to completion TME. The trial failed to show superiority of local excision over TME, because significant proportion of patients in the local excision group warranted a completion TME that probably increased morbidity and side-effects, compromising the potential advantages of local excision. The important long-term complications in the combined LE and TME groups were faecal incontinence and sexual dysfunction.

Brachytherapy Boost

The role of radiation boost using endo-cavitary contact brachytherapy (Papillon) was evaluated in the Lyon R96-02 randomized trial in which patients with rectal carcinoma cT2/3 Nx located in the lower rectum and not involving more than two-thirds circumference, were randomly assigned to one of two groups: preoperative external-beam radiotherapy (39 Gy in 13 fractions over 17 days) versus the same EBRT with boost (85 Gy in three fractions) using endocavitary contact x-ray treatment. 88 patients were enrolled onto the study. A significant improvement was seen in favor of the contact x-ray boost for complete clinical response (24% v 2%) and for a complete or near-complete sterilization of the operative specimen (57% v 34%). A significant increase in sphincter preservation was observed in the boost group (76% v 44%; P = .004). At a median follow-up of 35 months, there was no difference in morbidity, local relapse, and 2-year overall survival [7].

Definition of Complete Clinical Response

The cCR is defined in accordance with the Response Evaluation Criteria of Solid Tumors (RECIST). This defines cCR as the absence of

tumor on clinical examination and endoscopy at least 4 weeks after completion of neoadjuvant therapy.

Assessment of Response Using Endoscopy and Imaging

This is the most critical part of the assessment of cCR and should be ideally performed by a single and experienced colorectal surgeon for the entire duration (at least the first year) of the surveillance schedule. In the Brazilian cohort, the criteria for considering cCR were the absence of residual ulceration, mass, or mucosal irregularity at clinical/endoscopic assessment. Whitening of the mucosa and the presence of neo-vasculature (telangiectasia) were accepted features of cCR.

Mass and colleagues (2015) published on assessment of clinical response using endoscopy and MRI scanning with diffusion-weighted imaging (DWI). The presence of cCR was defined as the absence of residual tumor with only a flat, white scar with or without telangiectasia. A small, flat ulcer with smooth edges without signs of residual polypoid tissue was considered to be a potential CR. Every other type of ulcer or mass was considered as definite residual tumor. A biopsy was only performed in equivocal cases, both endoscopic assessments and MRI scans were assigned confidence levels (CL) scores ranging from 0-4 where CL0 represented definite residual tumor and CL4 definite cCR. When the confidence levels from all three modalities were combined, the probability for detecting a cCR was 98 percent. The key points and details of the assessment procedure is schematically illustrated in Figure 1.

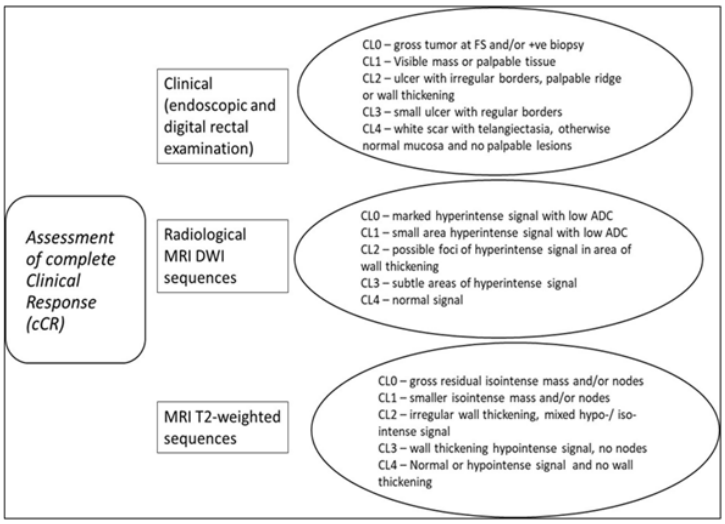

Figure 1: Assessment of complete clinical response (cCR) using endoscopic and imaging techniques. Patients undergo endoscopic assessment combined with digital rectal examination (DRE) and imaging with MRI using diffusion weighted imaging. Each finding is given a confidence level score (CL) and combining CL scores from endoscopic and T2 weighted MRI and DWI-MRI scanning is associated with significant concordance in predicting probability of complete response. For example, score of CL4 for all three modalities indicates 98% probability of complete clinical response. The above algorithm has an excellent applicability for use in the clinic and to facilitate informed decision making in terms of selection of patients suitable for wait and watch strategy.

Surveillance Strategy for Patients Suitable for 'Wait and Watch' Protocol

The assessment of complete clinical response usually incorporates a combination of clinical (endoscopic assessment +/- DRE) and imaging parameters using MRI with T2-weighted sequences and diffusion weighted imaging. The frequence of performing these assessments has varied in different studies but it is generally agreed that all patients should have endoscopic assessments every 3 months and at least 3-6 monthly MRI scans for first two years. There should be clear objective criteria for defining the presence of cCR similar to discussed above. Biopsy should not be routinely performed except in equivocal cases. The essential steps and end points for such a surveillance strategy is summarized in Figure 2.

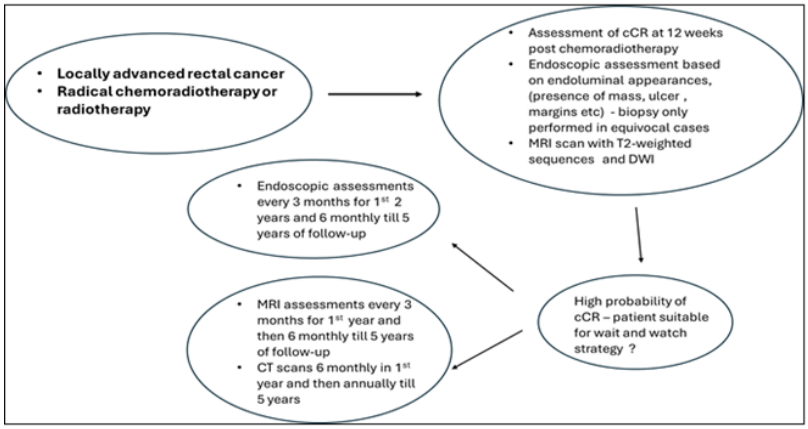

Figure 2: Surveillance Strategy for patients suitable for wait and watch strategy. Patients should undergo endoscopic assessment combined with imaging with MRI using diffusion weighted imaging at 12 weeks post chemoradiotherapy. If assessment indicates high probability of complete clinical response (cCR) they could be potentially suitable for 'Wait and Watch' surveillance strategy. The caveats of adopting such a strategy and the importance of adherence to surveillance protocol should be discussed with all patients. Patients agreeing for surveillance should undergo 3 monthly endoscopic assessments for first two years and 6 monthly thereafter, combined with 3 monthly MRI scans for first year and 6 monthly thereafter, till completion of 5 years of follow-up. Patients should also have 6 monthly CT scans in first year and annually thereafter.

Citation: Hingorani M, Rehman K, Casanova N. Organ Preservation for Rectal Cancer - Are We Any Wiser?. *Int J Onco Radiother*. 2024;5(1):1-4.
DOI: 10.51626/ijor.2024.05.00033

Conclusion

The role of organ preservation in rectal cancer is gaining aider acceptance with recognition of the fact that it may be suitable approach in selected patients. Such patients should have clear objective evidence of cCR at first assessment after chemoradiotherapy and should be motivated to adopt and adhere to strict surveillance protocol. It should be explained to them that there could be up to 50 percent (or higher probability) of subsequent recurrence in which case salvage surgery would be the only curative option. However, it may still offer patients up to 1 in 3 chance of avoiding surgery and organ preservation. In the presence of robust surveillance protocol it is reasonable strategy to discuss with selected and motivated patients with rectal cancer.

Declarations

Acknowledgments

Nil

Author contributions

M Hingorani: Conceptualization, Investigation, Writing-original draft, Writing-review & editing.

Khaliq Rehman: Writing-review and editing

Nathalie Casanova: Writing-review & editing.

All authors read and approved the submitted version."

Conflicts of Interest

"The authors declare that they have no conflicts of interest."

- Ethical Approvals NA
- Consent to participate NA
- Consent to publication NA
- Funding no declaration of any sources of funding

References

1. Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, et al. (2012) Preoperative Versus Postoperative Chemoradiotherapy for Locally Advanced Rectal Cancer: Results of the German CAO/ARO/AIO-94 Randomized Phase III Trial After a Median Follow-Up of 11 Years. Journal of Clinical Oncology 30(16): 1926-1933.
2. Habr Gama A, Gama Rodrigues J, São Julião GP, Proscurshim I, Sabbagh C, et al. (2014) Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. Int J Radiat Oncol Biol Phys 88(4): 822-828.
3. Habr Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U, et al. (2004) Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 240(4): 711-718.
4. Van der Valk MJM, Hilling DE, Bastiaannet E, Meershoek Klein Kranenbarg E, Beets GL, et al. (2018) Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. Lancet 391(10139): 2537-2545.
5. Renehan AG, Malcomson L, Emsley R, Gollins S, Maw A, et al. (2016) Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol 17(2): 174-183.
6. Rullier E, Rouanet P, Tuech JJ, Valverde A, Lelong B, et al. (2017) Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial. Lancet 390(10093): 469-479.
7. Gerard JP, Chapet O, Nemoz C, Hartweig J, Romestaing P, et al. (2004) Improved Sphincter Preservation in Low Rectal Cancer With High-Dose Preoperative Radiotherapy: The Lyon R96-02 Randomized Trial. Journal of Clinical Oncology 22(12): 2404-2409.