Full Title: 'Watch and wait' after chemoradiotherapy for rectal cancer

Short: 'Watch and wait' for rectal cancer

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No grants or scholarships

Not previously presented

Tables 2 (submitted as supporting information)

Word Count

Abstract 105

Abstract, Body and References 5,082

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as doi: [10.1111/ans.14352](https://doi.org/10.1111/ans.14352)

Abstract

Surgery remains the cornerstone of rectal cancer treatment. However, there is significant morbidity and mortality associated with pelvic surgery, and the past decade has illustrated that a cohort of rectal cancer patients sustain a remission of local disease with chemo-radiation alone. Thus, questions remain regarding the optimal management for rectal cancer; namely, accurately identifying patients who have a complete pathologic response and determining the oncologic safety of the observational approach for this patient group. This review aims to summarise the current evidence to provide an overview to the watch and wait approach in rectal cancer patients with a complete response to neoadjuvant chemoradiation therapy.

Introduction

Following neo-adjuvant chemoradiotherapy (CRT), a proportion (15-27%) of patients experience resolution of disease on histological examination, known as pathologic complete response (pCR)^{1,2}. Patients with pCR appear to have better long-term oncologic outcomes than do partial or non-responders.^{3,4} Thus, surgery may result in overtreatment for some of these patients. However, the reliability of current methods to predict a pCR are variable, and the potential for local recurrence mandates close surveillance. This is an overview of the current understanding of the 'watch and wait' approach in the management of clinical complete response (cCR) after CRT for rectal cancer.

Evolution of Watch and Wait

The classic example of a major shift in treatment was seen with anal squamous cell carcinoma (ASCC). Prior to 1974, ASCC was treated with abdominoperineal resection (APR)⁵. The surgical results were poor and morbidity was significant⁶. Therefore, when Nigro published a case series of 3 patients who received neoadjuvant CRT and had no residual disease at the time of APR⁵, a wave of research was initiated which resulted in a change in approach to ASCC; many patients are now spared the morbidity of surgery and lifelong ostomies since CRT is the mainstay of modern therapy.

Overall morbidity and mortality from rectal cancer surgery is 25-58% and 0.4-3.3% respectively^{7,8,9}. Short-term morbidity includes anastomotic leak (2.4-11%), surgical site infection (1.8-30%), temporary (60-74%) and permanent (7-11%) ostomy formation as well as cardiorespiratory, thrombotic and genitourinary complications^{9,10}. Longer term sexual dysfunction remains a significant issue for approximately a third of both male and female patients^{11,12}.

While the paradigm shift worked well for ASCC, rectal adenocarcinoma is less predictably radio-responsive¹³. In 2002, Nakagawa et al¹⁴ described a series of 52 patients treated with neoadjuvant CRT. Ten patients (19.2%) demonstrated a complete clinical response (cCR) and were watched. Within 8.8 months, 8 of the 10 had developed local regrowth and underwent resection. The study concluded that surveillance was not a safe option for the management of cCR in rectal cancer. In 2004, Habr-Gama et al published a series of 265 patients undergoing CRT for low rectal cancer and found a cCR rate of 26.8% (n=71). These patients were offered an observational approach and only 2 of the 71 patients had local recurrence. The overall survival (OS) and disease free survival (DFS) at 5 years ended up being higher in the observation group than resection group.¹⁵

From these preliminary findings, trials from Denmark¹⁶, the United Kingdom¹⁷, the United States¹⁸ and the Netherlands¹⁹ have emerged. Despite the significant heterogeneity with regard to defining cCR, lack of control groups, and outcome measures, the data can be analysed in order to make some relative conclusions and provide direction for future study.

Prospective Studies

Because the many retrospective reviews are limited by selection bias, heterogeneity within the comparison groups, and small sample size in the observation groups ranging from 12 to 68^{18,20-25}, we chose to focus predominantly on prospective studies. Habr-Gama et al are responsible for a significant proportion of currently available studies and have been following patients since the early 1990s. They report initial cCR rates ranging from 26.8%-68%^{15,26-28} with varying regimens of CRT, including addition of adjuvant chemotherapy during the rest period²⁹ and increases in the radiation dose. The routine interval to reassessment has been extended from the initial reassessment at 8 weeks to beyond 10 weeks³⁰. Local regrowth rates have been reported from 18%-31%, with median follow-up from 36-60 months, although the vast majority of these regrowths were clustered within the first 12 months^{26,30-32}. In 2014, Habr-Gama et al³² described a series of 183 patients, of whom 90 were managed with observation after initial cCR. Twenty-eight patients (31%) experienced local regrowth by 60 months, of whom 26 (93%) were amenable to salvage. Four of the 26 developed local recurrence after salvage and underwent re-salvage. A variety of oncologic outcome measures have since been reported including 5 year cancer specific OS and DFS of 91% and 68%, respectively³², and 3-year OS and DFS of 98% and 72%³⁰.

Interestingly, there is no significant difference in survival outcomes between the 'watch and wait' patients and those who were identified as pCR after resection¹⁵.

A number of series have since been published supporting this approach. Appelt et al¹⁶ performed a prospective study of high dose CRT and demonstrated a 78% cCR rate and 26% local regrowth rate at 2 years, consistent with Habr-Gama's group. The high cCR rate may relate to the relatively high number of T2 tumours and the high radiation dose in this study (60Gy). Of note, all patients were salvageable with DFS and OS of 100% at 2 years. The OnCoRe study¹⁷ from the United Kingdom prospectively observed 31 patients (11% cCR rate) that underwent observational management and another 98 patients with cCR managed observationally who were retrospectively retrieved from a multi-centre database. One hundred and twenty-nine propensity matched patients who underwent surgery for incomplete response were used as the control cohort. Local regrowth rate was 34% at a median of 33 months follow-up.

Thirty-six of the 41 (88%) non-metastatic recurrences were salvageable, and there was no statistical difference between the groups in DFS and OS. In addition, the colostomy free survival was significantly better in the observational group (47% v 74%).

A small prospective cohort study from the Netherlands³³ compared 21 patients with cCR managed with an observational approach to a control group of 20 patients with pCR at time of resection. Two year OS and DFS were not different between the two cohorts. However the morbidity rate for the surgery pCR group was significantly higher, with 35% experiencing major complications, 50% requiring definitive colostomy, and one patient dying from complications of his colostomy reversal. Patients in the pCR group also had significantly increased disruption in functional outcomes requiring more incontinence products, higher incontinence scores, and increased frequency of stool.

Summary of Findings from Both Retrospective and Prospective Studies

Despite the study limitations and heterogeneity, we have attempted to summarise the key findings in order to highlight practice patterns. (Tables S1 and S2)

Neoadjuvant Chemoradiotherapy Regimens

The standard long-course CRT regimen of 45 -50.4 Gy in fractions of 1.8-2Gy over 5 weeks, in combination with 5-FU based chemotherapy, is the model for neoadjuvant treatment. The majority of studies have used this, with some variability in dose of radiotherapy 45-65Gy and chemotherapeutic sensitisers used (5-FU, capecitabine or Tegafur-uracil). There have been attempts to improve cCR rates with higher doses of radiation¹⁶, adding chemotherapeutic agents to neoadjuvant treatments³⁴ and extending the interval to reassessment³⁵. Increasing the radiation dose results in increased response rates at the expense of higher toxicity, although doses of 66-78Gy are used in the management of prostate cancer³⁶.

Oxaliplatin (OX) has been added to intensify the neoadjuvant regimen, however trials have shown mixed results. A recent meta-analysis including 7 randomised controlled trials has shown a slight increase in pCR rate in the combined FU/OX group (RR 1.24), with a more marked increase in grade 3-4 toxicity (RR1.92)³⁷. At present, OX is not a standard component of neoadjuvant regimens.

Interval to reassessment

Traditionally, surgical resection post-LCCRT has been scheduled for 6 weeks from the completion of treatment, based on the Lyon R90-01 study³⁸. More recently, studies have suggested that increasing the interval to surgery further may result in increased downstaging and pCR rate³⁹. Petrelli et al³⁵ performed a meta-analysis of publications looking at the impact of post-CRT interval to surgery on pCR, and found that an interval greater than 6-8 weeks significantly increased pCR rate (from 13.7% to 19.5%; RR 1.42). They did not observe a significant difference in perioperative outcomes or oncologic outcomes (DFS and OS) with this approach. Two large retrospective population based studies have suggested an optimal interval of 9-11 weeks^{40,41}.

The primary concern in increasing the post-CRT interval is disease progression in radio-resistant tumours. Perez et al⁴² suggests the use of positron emission tomography (PET) combined with computed tomography (CT) to identify those that may benefit from an extended interval between treatment and reassessment.

Adjuvant Chemotherapy

Adjuvant chemotherapy is perhaps the most variable treatment component in current 'watch and wait approach' trials. Current guidelines recommend adjuvant chemotherapy for stage III rectal cancer but guidelines for stage II⁴³ remain controversial. So far, the largest trial addressing this (the EORTC 22921 trial)⁴⁴ has not shown a significant benefit to the addition of post-operative chemotherapy in terms of overall, nor disease free survival.

In the context of 'watch and wait' for cCR, one cannot base the decision to give adjuvant chemotherapy on histologic outcome. However, those developing cCR may represent a group with more favourable oncologic outcome and may receive less benefit from adjuvant chemotherapy⁴⁵.

Assessment of Clinical Complete Response

The gold standard to assess complete response is histologic examination of the TME specimen (pCR). However this mandates resection. Without this, assessment is limited and involves a combination of clinical examination with digital rectal examination (DRE), endoscopy and radiologic evaluation using magnetic resonance imaging (MRI) with or without diffusion weighted imaging (DWI)⁴⁶.

Clinical Assessment and Endoscopic Findings

Palpable thickening on DRE is common, however provided the mucosal surface feels regular and smooth, this does not preclude cCR. On endoscopy, whitening of

mucosa, telangiectasia and slight loss of pliability are described as consistent with cCR, whereas residual deep ulceration, irregular superficial ulceration, a palpable nodule, significant stenosis or persistent symptoms mark incomplete response^{47,48}. The positive predictive value of DRE and endoscopy to predict cCR in patients with pCR is controversial. A group from Memorial Sloan Kettering⁴⁹ prospectively evaluated 488 patients and found only 25% of those who had a cCR had pCR at the time of resection, suggesting that clinical assessment underestimates remaining burden of disease. However, more recent studies that retrospectively compared the clinical findings with the pathological results found conversely that clinical assessment may underestimate pCR. The presence of residual ulceration and even exophytic lesions did not preclude pCR^{25,50}.

Radiological Assessment

MRI is standard of care for local staging of rectal cancer, but its role in re-staging is less clear. The usual MRI series are limited in their ability to distinguish persistent tumour from fibrosis and many of the series to date have shown poor correlation between restaging MRI and final pathology^{32,53,34,54,55}. Franklin et al⁵³ retrospectively reviewed the pre- and post-treatment MRI from 20 patients with pCR. Only 7 (35%) had a complete response seen on imaging, consistent with other available studies⁵⁴. The authors find the comparison between MR at completion of treatment and a follow-up MR three months later more discriminatory than isolated scans.

Diffusion weighted imaging (DWI) has increased the positive predictive value of MRI. Curvo Samedo et al⁵⁶ used tumour volume on DWI imaging to predict pCR with sensitivity of 79%, specificity 100% and accuracy 94% in a series of 50 patients.

The role of PET-CT has also been investigated. Perez et al⁵⁷ looked at PET-CT performed 12 weeks after completion of CRT in 99 patients and found a sensitivity of 93%, specificity 53%, and an improvement in the clinical diagnostic accuracy from 91% to 96% in the detection of residual tumour. A systematic review of PET-CT in the prediction of response to CRT showed ability to predict CR with a pooled sensitivity of 71% and specificity of 76%⁵⁸.

The Role of Biopsy

Routine needle biopsy is highly unreliable in the prediction of CR. Perez et al⁵⁹ reviewed 39 patients with incomplete CR who had undergone post-treatment biopsy. Of 14 biopsies negative for tumour, only 3 had sustained a pCR. Thus, routine endoscopic biopsy cannot be relied upon to differentiate tumour from post-treatment change. Unfortunately, excisional biopsy is not significantly

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better⁶⁰⁻⁶². Further, there is a significant rate of functional compromise associated with local tumour excision⁶³. Habr-Gama et al⁶³ compared patients undergoing observational management for cCR with those undergoing local excision for near complete response (T1 and 2) and found inferior anorectal function and quality of life in the local excision group.

Surveillance

Recommended Protocol

The most common protocols involve a combination of clinical examination (DRE, proctoscopy/endoscopy), serum carcinoembryonic antigen (CEA) and cross sectional imaging with MRI and CT. Although the timing of each of these varies between protocols^{16-18,27,64,65}, the authors routinely reassess at 10 weeks to allow for resection at 12 weeks, if indicated. Sammour et al⁴⁶ have collated a summary protocol based on their systematic review of available studies. DRE, endoscopy and CEA should be performed every 3 months for 2 years, with biopsy in the setting of suspicious lesions. Cross sectional imaging includes pelvic MRI every 6 months for the first 2 years, then annually thereafter to 5 years, and chest and abdominal CT every 12 months for the 5 years of follow up.

Salvage Surgery and the Impact on Oncologic Outcomes

Dossa et al⁶⁶ reviewed 867 patients and found a pooled local regrowth rate of 15.7% within 2 years. Surgical salvage was possible for 95%. Of the patients not undergoing salvage, reasons given included patient refusal, comorbidities and pending surgery at time of review. Only 20% of those not receiving surgical salvage, were not suitable on the basis of irresectable local or distant disease.

Similarly, Kong et al⁶⁷ performed a systematic review on salvage surgery following non-operative management of cCR. They found a local regrowth rate of 28.4%, of which 83.8% were salvaged (36% of those for distant recurrence). Both reviews noted a significantly reduced rate of local regrowth with increasing interval from CRT to reassessment^{66,67}.

In terms of oncological outcome, there were no significant differences in cancer specific mortality, DFS nor OS^{66,67}. However, Kong et al reported 3 cases non-salvageable local recurrence after TME resection in the 'watch and wait group' as opposed to 0 in the pCR group (p=0.043). In at least 2 of the 3 cases, patient preference to avoid surgery may have influenced their outcomes. The interpretation of these results is challenging given the low patient numbers and heterogeneity of studies.

Consenting the Patient

The fundamental part of implementing this practice is ensuring informed consent. The decision to undertake an observational approach must balance the potential risks and benefits specific to each patient and their personal priorities. They must understand the current uncertainty and accept the potential for local regrowth and the possibility of unsalvageable disease. To this end, they must be both capable of and willing to undergo the close surveillance recommended.

Future Directions

International Database

Given the obvious difficulties in ethics and recruitment that an approach like this would pose to performing a randomised, controlled trial, we need to look at alternative ways to safely and ethically gather more information. The International Watch and Wait Database (IWWD) (www.iwwd.org) was initiated in 2014 at an international consensus meeting, in order to facilitate the pooling of available retrospective and prospective data from multiple centres. They aim to derive practice guidelines for non-operative management and surveillance on the basis of the prospective data^{68,69}.

Predicting response to CRT

At present, the most consistent predictors of pCR are pre-treatment T stage, N stage, grade, dose or intensification of adjuvant treatment and time to reassessment⁷⁰⁻⁷². Pre-treatment and post-treatment CEA have also been suggested to predict CR⁷³. A large population based study using the National Cancer Database has suggested that smaller, more differentiated tumours with no nodal involvement at diagnosis are more likely to obtain a complete response⁷⁰. This has been supported by smaller retrospective studies^{71,74}. An interval from diagnosis to surgery of greater than 8 weeks is an independent predictor of complete response^{70,71}.

Tie et al⁷⁵ have recently presented their data demonstrating the correlation between post-resection circulating tumour DNA (ctDNA) and recurrence of rectal cancer in the context of pCR. This may lead to the use of ctDNA as a predictive biomarker. The most useful tool would assess the tumour pre-CRT to predict responsiveness to CRT and inform the decision to proceed with observation rather than surgery.

Conclusion

The 'watch and wait' approach to the management of cCR in rectal cancer is gradually gaining momentum and we as clinicians are obliged to discuss these options with our patients. This mandates a comprehensive understanding of the current literature and inherent risks, as well as an approach to protocolised surveillance. While we are implementing these strategies, we should be systematically auditing outcomes to better optimise care.

References

1. Hawkins, A. T. & Hunt, S. R. Watch and Wait: Is Surgery Always Necessary for Rectal Cancer? *Curr. Treat. Options Oncol.* **17**, 22 (2016).
2. Glynne-Jones, R. & Hughes, R. Complete Response after Chemoradiotherapy in Rectal Cancer (Watch-and-Wait): Have we Cracked the Code? *Clin. Oncol.* **28**, 152–160 (2016).
3. Maas, M. *et al.* Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol* **11**, 835–44 (2010).
4. Park, I. J. *et al.* Neoadjuvant treatment response as an early response indicator for patients with rectal cancer. *J. Clin. Oncol.* **30**, 1770–1776 (2012).
5. Nigro, N. D., Vaitkevicius, V. K. & Considine Jr., B. Combined therapy for cancer of the anal canal: a preliminary report. *Dis.Colon Rectum* **17**, 354–356 (1974).
6. Houlihan, O. A. & O'Neill, B. D. P. Chemoradiotherapy for anal squamous cell carcinoma. *Surg.* **14**, 202–212 (2016).
7. Bennis, M. *et al.* Morbidity Risk Factors After Low Anterior Resection With Total Mesorectal Excision and Coloanal Anastomosis. *Ann. Surg.* **255**, 504–510 (2012).
8. Mulrow, J. & Winter, D. C. Sphincter preservation for distal rectal cancer - a goal worth achieving at all costs? *World J. Gastroenterol.* **17**, 855–861 (2011).
9. Fleshman, J. *et al.* Effect of Laparoscopic-Assisted Resection vs Open Resection of Stage II or III Rectal Cancer on Pathologic Outcomes. *Jama* **314**, 1346 (2015).
10. Stevenson, A. R. L. *et al.* Effect of Laparoscopic-Assisted Resection vs Open Resection on Pathological Outcomes in Rectal Cancer: The ALaCaRT Randomized Clinical Trial. *Jama* **314**, 1356–1363 (2015).
11. Hur, H. *et al.* Comparative study of voiding and male sexual function following open and laparoscopic total mesorectal excision in patients with rectal cancer. *J. Surg. Oncol.* **108**, 572–578 (2013).
12. Hendren, S. K. *et al.* Prevalence of male and female sexual dysfunction is high following surgery for rectal cancer. *Ann. Surg.* **242**, 212–23 (2005).
13. Moussata, D. *et al.* XIAP as a radioresistance factor and prognostic marker for radiotherapy in human rectal adenocarcinoma. *Am. J. Pathol.* **181**, 1271–1278 (2012).
14. Nakagawa, W. T. *et al.* Chemoradiation instead of surgery to treat mid and low rectal tumors: is it safe? *Ann. Surg. Oncol.* **9**, 568–573 (2002).
15. Habr-Gama, A. *et al.* Operative Versus Nonoperative Treatment for Stage 0 Distal Rectal Cancer Following Chemoradiation Therapy. *Trans. ... Meet.*

- Am. Surg. Assoc.* **CXXII**, 309–316 (2004).
16. L Appelt, D. A. *et al.* High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study Funding CIRRO—The Lundbeck Foundation Center for Interventional Research in Radiation Oncology and The Danish Council for Strategic Research. *Lancet Oncol* **16**, 919–27 (2015).
 17. Renehan, A. G. *et al.* 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**, 174–183 (2016).
 18. Smith, R. K., Fry, R. D., Mahmoud, N. N. & Paulson, E. C. Surveillance after neoadjuvant therapy in advanced rectal cancer with complete clinical response can have comparable outcomes to total mesorectal excision. *Int. J. Colorectal Dis.* **30**, 769–74 (2015).
 19. Martens, M. H. *et al.* Long-term Outcome of an Organ Preservation Program After Neoadjuvant Treatment for Rectal Cancer. *J. Natl. Cancer Inst.* **108**, djw171 (2016).
 20. Araujo, R. O. C. *et al.* Nonoperative management of rectal cancer after chemoradiation opposed to resection after complete clinical response. A comparative study. *Eur. J. Surg. Oncol.* **41**, 1456–1463 (2015).
 21. Dalton, R. S. J. *et al.* A single-centre experience of chemoradiotherapy for rectal cancer: Is there potential for nonoperative management? *Color. Dis.* **14**, 567–571 (2012).
 22. Lai, C.-L., Lai, M.-J., Wu, C.-C., Jao, S.-W. & Hsiao, C.-W. Rectal cancer with complete clinical response after neoadjuvant chemoradiotherapy, surgery, or ‘watch and wait’. *Int. J. Colorectal Dis.* **31**, 413–9 (2016).
 23. Kuo, L.-J. *et al.* Can we predict pathologic complete response before surgery for locally advanced rectal cancer treated with preoperative chemoradiation therapy? The prediction rates for. *Int J Color. Dis* **27**, 613–621 (2012).
 24. Sanchez Loria, F. *et al.* Non-surgical management (NSM) of rectal cancer. Series of 68 cases, long follow up in two leading centres in Argentina. *Dig. Liver Dis.* **48**, 1372–1377 (2016).
 25. Smith, F. M., Wiland, H., Mace, A., Pai, R. K. & Kalady, M. F. Clinical Criteria Underestimate Complete Pathological Response in Rectal Cancer Treated With Neoadjuvant Chemoradiotherapy. *Dis. Colon Rectum* **57**, 311–315 (2014).
 26. Habr-Gama, A. *et al.* Low rectal cancer: impact of radiation and chemotherapy on surgical treatment. *Dis. Colon Rectum* **41**, 1087–96 (1998).
 27. Habr-Gama, A. *et al.* Watch and Wait Approach Following Extended Neoadjuvant Chemoradiation for Distal Rectal Cancer. *Dis. Colon Rectum* **56**, 1109–1117 (2013).

28. Habr-Gama, A. *et al.* 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.* **88**, 822–828 (2014).
29. Habr-Gama, A. *et al.* Increasing the rates of complete response to neoadjuvant chemoradiotherapy for distal rectal cancer: Results of a prospective study using additional chemotherapy during the resting period. *Dis. Colon Rectum* **52**, 1927–1934 (2009).
30. Habr-Gama, A. *et al.* Watch and Wait Approach Following Extended Neoadjuvant Chemoradiation for Distal Rectal Cancer. *Dis. Colon Rectum* **56**, 1109–1117 (2013).
31. Habr-Gama, A. Assessment and management of the complete clinical response of rectal cancer to chemoradiotherapy. *Colorectal Dis.* **8 Suppl 3**, 21–24 (2006).
32. Habr-Gama, A. *et al.* 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**, 822–828 (2014).
33. Maas, M. *et al.* Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. *J. Clin. Oncol.* **29**, 4633–4640 (2011).
34. Díaz Beveridge, R., Akhoundova, D., Bruixola, G. & Aparicio, J. Controversies in the multimodality management of locally advanced rectal cancer. *Med. Oncol.* **34**, 102 (2017).
35. Petrelli, F., Sgroi, G., Sarti, E. & Barni, S. Increasing the Interval Between Neoadjuvant Chemoradiotherapy and Surgery in Rectal Cancer. *Ann. Surg.* **263**, 458–464 (2016).
36. Wolff, R. F. *et al.* A systematic review of randomised controlled trials of radiotherapy for localised prostate cancer KEYWORDS Brachytherapy Cryotherapy High-intensity focused ultrasound ablation Prostatic neoplasms Prostatectomy Radiotherapy Review Watchful waiting. (2015). doi:10.1016/j.ejca.2015.07.019
37. Yang, Y.-J. *et al.* Fluorouracil-based neoadjuvant chemoradiotherapy with or without oxaliplatin for treatment of locally advanced rectal cancer: An updated systematic review and meta-analysis. *Oncotarget* **7**, (2014).
38. Francois, Y. *et al.* Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. *J. Clin. Oncol.* **17**, 2396 (1999).
39. Wasserberg, N. Interval to surgery after neoadjuvant treatment for colorectal cancer. *World J. Gastroenterol.* **20**, 4256–62 (2014).
40. Kuan, F.-C. *et al.* The survival impact of delayed surgery and adjuvant chemotherapy on stage II/III rectal cancer with pathological complete response after neoadjuvant chemoradiation. *Int. J. Cancer* **140**, 1662–1669

- (2017).
41. Sloothak, D., Geijssen, D. & van Leersum, N. Optimal Timing of Surgery After Chemoradiation for Advanced Rectal Cancer: Preliminary Results of a Multicenter, Nonrandomized Phase II Prospective Trial. *Br. J. Surg.* **100**, 933–39 (2013).
 42. Perez, R. O. *et al.* Optimal Timing for Assessment of Tumor Response to Neoadjuvant Chemoradiation in Patients With Rectal Cancer : Do All Patients Benefit From Waiting Longer Than 6 Weeks ? *Int. J. Radiat. Oncol. Biol. Phys.* **84**, 1159–1165 (2012).
 43. Rectal cancer version 3.2017. *National Comprehensive Cancer Network Guideline* (2017).
 44. Bosset, J.-F. *et al.* Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. *www.thelancet.com/oncology* **15**, (2014).
 45. Maas, M. *et al.* Adjuvant chemotherapy in rectal cancer: Defining subgroups who may benefit after neoadjuvant chemoradiation and resection: A pooled analysis of 3,313 patients. *Int. J. Cancer* **137**, 212–220 (2015).
 46. Sammour, T., Price, B. A., Krause, K. J. & Chang, G. J. Nonoperative Management or 'Watch and Wait' for Rectal Cancer with Complete Clinical Response After Neoadjuvant Chemoradiotherapy: A Critical Appraisal. *Ann. Surg. Oncol.* (2017). doi:10.1245/s10434-017-5841-3
 47. Habr-gama, A. *et al.* Complete Clinical Response After Neoadjuvant Chemoradiation Therapy for Distal Rectal Cancer : Characterization of Clinical and Endoscopic Findings for Standardization. *Dis. Colon Rectum* **12**, 1692–1698 (2010).
 48. Habr-gama, A., São Julião, G. P. & Perez, R. O. Nonoperative Management of Rectal Cancer : Identifying the Ideal Patients. *Hematol. Clin. NA* **29**, 135–151 (2017).
 49. Hiotis, S. P. *et al.* Assessing the Predictive Value of Clinical Complete Response to Neoadjuvant Therapy for Rectal Cancer: An Analysis of 488 Patients. *J. Am. Coll. Surg.* **194**, 131–6 (2002).
 50. Smith, F. M. *et al.* The surgical significance of residual mucosal abnormalities in rectal cancer following neoadjuvant chemoradiotherapy. *Br. J. Surg.* **99**, 993–1001 (2012).
 51. Wotherspoon, A. C. Pathological assessment of rectal carcinoma after preoperative therapy. *Color. Dis.* **8**, 37–39 (2006).
 52. Kuo, L.-J. *et al.* Can we predict pathologic complete response before surgery for locally advanced rectal cancer treated with preoperative chemoradiation therapy? *Int. J. Colorectal Dis.* **27**, 613–621 (2012).
 53. Franklin, J., Anderson, E. & Gleeson, F. MRI features of the complete histopathological response of locally advanced rectal cancer to neoadjuvant chemoradiotherapy.- ClinicalKey. *Clin. Radiol.* **67**, 546 (2012).

54. Van Der Paardt, M. P., Zagers, M. B., Beets-Tan, R. G. H., Stoker, J. & Bipat, S. Patients Who Undergo Preoperative chemoradiotherapy for locally advanced rectal cancer restaged by Using Diagnostic Mr imaging: A Systematic Review and Meta-Analysis 1. *Radiology* **269**, 101 (2013).
55. Nahas, S. C. *et al.* Pathologic Complete Response in Rectal Cancer. *Dis. Colon Rectum* **59**, 255–263 (2016).
56. Curvo-Semedo, L. *et al.* Rectal Cancer: Assessment of Complete Response to Preoperative Combined Radiation Therapy with Chemotherapy—Conventional MR Volumetry versus Diffusion-weighted MR Imaging. *Radiology* **260**, 734–743 (2011).
57. Perez, R. O. *et al.* Accuracy of positron emission tomography/computed tomography and clinical assessment in the detection of complete rectal tumor regression after neoadjuvant chemoradiation: Long-term results of a prospective trial (National Clinical Trial 00254683). *Cancer* **118**, 3501–3511 (2012).
58. Maffione, A. M., Marzola, M. C., Capirci, C., Colletti, P. M. & Rubello, D. Value of ¹⁸F-FDG PET for Predicting Response to Neoadjuvant Therapy in Rectal Cancer: Systematic Review and Meta-Analysis. *Am. J. Roentgenol.* **204**, 1261–1268 (2015).
59. Perez, R. O. *et al.* Role of biopsies in patients with residual rectal cancer following neoadjuvant chemoradiation after downsizing: Can they rule out persisting cancer? *Color. Dis.* **14**, 714–720 (2012).
60. Mignanelli, E. D., Campos-Lobato, L. F., Stocchi, L., Lavery, I. C. & Dietz, D. W. Downstaging After Chemoradiotherapy for Locally Advanced Rectal Cancer: Is There More (Tumor) Than Meets the Eye? *Dis. Colon Rectum* **53**, 251–256 (2010).
61. Berho, M. *et al.* The correlation between tumour regression grade and lymph node status after chemoradiation in rectal cancer. *Color. Dis.* **11**, 254–258 (2009).
62. Hughes, R. *et al.* Can pathological complete response in the primary tumour following pre-operative pelvic chemoradiotherapy for T3-T4 rectal cancer predict for sterilisation of pelvic lymph nodes, a low risk of local recurrence and the appropriateness of local excision? *Int. J. Colorectal Dis.* **21**, 11–17 (2006).
63. Habr-Gama, A. *et al.* Impact of Organ-Preserving Strategies on Anorectal Function in Patients with Distal Rectal Cancer Following Neoadjuvant Chemoradiation. *Dis. Colon Rectum* **59**, 264–269 (2016).
64. Creavin, B. *et al.* Organ preservation with local excision or active surveillance following chemoradiotherapy for rectal cancer. *Br. J. Cancer* **116**, 169–174 (2017).
65. Martens, M. H. *et al.* Long-term Outcome of an Organ Preservation Program After Neoadjuvant Treatment for Rectal Cancer. *J. Natl. Cancer Inst.* **108**, djw171 (2016).

66. Dossa, F., Chesney, T. R., Acuna, S. A. & Baxter, N. N. A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis. *Lancet Gastroenterol. Hepatol.* (2017). doi:10.1016/S2468-1253(17)30074-2
67. Kong, J. C., Guerra, G. R., Warriar, S. K., Ramsay, R. G. & Heriot, A. G. Outcome and Salvage Surgery Following “Watch and Wait” for Rectal Cancer after Neoadjuvant Therapy: A Systematic Review. *Dis. Colon Rectum* **60**, 335–345 (2017).
68. Beets, G. L., Figueiredo, N. L., Habr-Gama, A. & van de Velde, C. J. H. A new paradigm for rectal cancer: Organ preservation: Introducing the International Watch & Wait Database (IWWD). *Eur. J. Surg. Oncol.* **41**, 1562–4 (2015).
69. Van der Valk, M. The International Watch and Wait Database (IWWD) for rectal cancer, an update. *Eur. J. Cancer* **72**, S55–S56 (2017).
70. Al-Sukhni, E., Attwood, K., Mattson, D. M., Gabriel, E. & Nurkin, S. J. Predictors of Pathologic Complete Response Following Neoadjuvant Chemoradiotherapy for Rectal Cancer. *Ann. Surg. Oncol.* **23**, 1177–1186 (2016).
71. Bitterman, D. S. *et al.* Predictors of Complete Response and Disease Recurrence Following Chemoradiation for Rectal Cancer. *Front. Oncol.* **5**, 286 (2015).
72. Sanghera, P., Wong, D. W. Y., Mcconkey, C. C., Geh, J. I. & Hartley, A. Chemoradiotherapy for Rectal Cancer: An Updated Analysis of Factors Affecting Pathological Response. *Clin. Oncol.* **20**, 176–83 (2008).
73. Probst, C. P. *et al.* Watch and Wait?—Elevated Pretreatment CEA Is Associated with Decreased Pathological Complete Response in Rectal Cancer. *J. Gastrointest. Surg.* **20**, 43–52 (2016).
74. Habr-Gama, A. *et al.* Baseline T Classification Predicts Early Tumor Regrowth After Nonoperative Management in Distal Rectal Cancer After Extended Neoadjuvant Chemoradiation and Initial Complete Clinical Response. *Dis. Colon Rectum* **60**, 586–594 (2017).
75. Tie, J. *et al.* The potential of circulating tumor DNA (ctDNA) to guide adjuvant chemotherapy decision making in locally advanced rectal cancer (LARC). *J. Clin. Oncol.* **35**, 3521 (2017).

List of Supporting Information:

Table S1 **Summary of Studies in terms of Design and Protocol**

Table S2 **Summary of Studies in terms of Outcomes**

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Author/s:

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Title:

"Watch and wait' after chemoradiotherapy for rectal cancer

Date:

2018-09-01

Citation:

Mullaney, T. G., Lightner, A. L., Johnston, M., Keck, J. & Wattchow, D. (2018). "Watch and wait' after chemoradiotherapy for rectal cancer. ANZ JOURNAL OF SURGERY, 88 (9), pp.836-841. <https://doi.org/10.1111/ans.14352>.

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