

Watch and wait for Rectal Cancer: A 9 year Experience

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ABSTRACT:

Background: Neoadjuvant long course chemoradiotherapy has become the standard treatment for locally advanced rectal cancer. It can reduce tumour bulk, downstage, reduce the risk of local recurrence, and increase the possibility of clear resection margins. The aim of our study is to evaluate all patients over a 9 year period who underwent neoadjuvant chemoradiotherapy for rectal cancer and entered our watch and wait programme.

Methods: Data were analysed from a prospective database for all patients diagnosed with rectal cancer over a 9 year period (2011-2019 inclusive).

Findings: Over a 9 year period, 532 patients were treated for rectal cancer, with 180 patients receiving long course chemoradiotherapy. 61 (11%) patients entered a watch and programme as they had a complete clinical and radiological response following chemoradiotherapy. Within this programme, 40 patients (65%) remain disease free over the follow-up period (mean 38 months); 12 (20%) patients had regrowth and proceeded to surgery; and 9 (15%) proceeded to palliation due to being unfit for surgery or had distant metastatic disease. Overall (all cause) mortality was 18% during follow-up period in the watch and wait group.

Conclusions: Neoadjuvant long course chemoradiotherapy is the standard treatment for locally advanced rectal cancer. 34% of our patient group who received long course chemoradiotherapy entered a watch and wait programme with the majority avoiding major rectal surgery.

KEY WORDS: Rectal cancer, watch and wait, long course chemoradiotherapy

INTRODUCTION:

Colorectal cancer treatment and surveillance has undergone changes in the past decade which have resulted in improved outcomes.¹ However, it remains the third most common cancer and the fourth most common cause of cancer death worldwide, accounting for roughly 42,000 new cases and 16,000 deaths in the U.K. per year.² Of these new cases, 32% of male patients and 23% of female patients will have presented with rectal cancer.²

Total mesorectal excision (TME) is the standard surgical procedure for the treatment of rectal cancer. It is the removal *en bloc* of the rectum, mesorectum, and surrounding mesorectal fascia – through either an abdominal or

abdominoperineal approach.¹ TME surgery has significant potential complications – with a 2% risk of peri-operative mortality and a 5% risk of reoperation. Patient reported quality of life is also impacted – those having undergone an abdominoperineal resection will live with a permanent colostomy, and even those who were candidates for sphincter preservation surgery report experiencing bowel dysfunction and low anterior resection syndrome.³

The benefit of TME decreases when the mesorectal fascia surrounding the resected specimen (the circumferential resection margin (CRM)) is threatened or involved by tumour.^{4,5} To combat this, long course neo-adjuvant chemoradiotherapy (LCCRT) was introduced in an attempt to downstage patients whose tumour was radiologically encroaching on the CRM. A sub-group of these patients developed a complete pathologic response to LCCRT, namely that there was no residual tumour in the resected specimen. From this finding, a Brazilian team recognised these patients could potentially avoid surgery.⁶ Their 2004 study (mainly T3 or N1 patients) showed that these complete responders could be recognised clinically, and subsequently radiologically. It was determined with these complete clinical responders, a ‘Watch and Wait’ strategy could be employed. This involved intensive follow up with frequent clinical examination, endoscopy, and MRI imaging of rectum to ensure there was no regrowth of tumour. The outcomes from this watch and wait strategy demonstrated the majority of patients did not have regrowth, allowing them to avoid a TME resection with the associated morbidity and mortality. It was shown that the patients who did have tumour regrowth did not have any decreased disease specific survival compared to standard operative treatment.

Watch and wait has generated significant debate between colorectal surgeons and oncologists. There is now a trend towards organ saving strategies in surgical oncology. Management of anal and several ENT cancers have lead the way with impressive patient outcomes.^{7,8}

Subsequent studies by the Brazilian group continue to display impressive results. However, they have not been consistently replicated by the surgical community.⁹⁻¹¹ Due to uncertainty of safety of this watch and wait strategy, there

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is a paucity of guidance currently published. To attempt to reduce this uncertainty, surgical units have been publishing their results (albeit all with small numbers), cumulating in a meta-analysis.¹² The authors wish contribute their data towards building a consensus within the surgical-oncological community on the validity of watch and wait strategy for complete responders following LCCRT.

Aim

The aim of this study is to add to the evidence of the role of watch and wait in rectal cancer following neoadjuvant long course chemoradiotherapy.

METHODS AND MATERIALS:

Methods

Prospective data collection was performed using the regional "Northern Ireland Electronic Healthcare Record" system. All patients diagnosed with rectal cancer between 2011 and 2019 within the South Eastern Trust were included. Cancers proximal to the rectum were excluded.

ANALYSIS and RESULTS:

Statistics

Categorical and numerical variables were compared by the use of χ^2 and one-way ANOVA and independent t-test respectively. Survival estimations were determined by the use of Kaplan-Meier curves. Comparison was performed with the log rank test. Kruskal-Wallis and Mann Whitney U was used to compare median follow up periods between groups. Differences were considered statistically significant for P values <0.05. IBM SPSS Version 24 was used for statistical analysis.

Comparisons between groups were analysed on an intention to treat basis. Therefore, those patients who were commenced on a definitive treatment plan were analysed within that group regardless of whether their treatment subsequently changed.

Results

Five hundred and thirty-two patients with rectal cancer were treated in the unit between January 2011 and December 2019. Treatment modality information was missing in 5 patients (0.9%). All subjects had a minimum of 12 months follow up data available at the time of analysis.

Overall, the mean age of patients was 67.8 years and 62.4% (n=332) patients were male. During the course of the study, 189 (35.5%) patients died from all causes. Median follow-up was 28 months (IQR 15-45 months). The characteristics of patients in each treatment group are summarised in *Table 1*.

Patients in the palliative care group tended to be older and included a lower proportion of male patients compared to other groups.

Preoperative staging data was available for 54 patients in the watch and wait group, 116 in the straight to surgery group, 34 in the short course radiotherapy group, 164 patients in the long course chemo-radiotherapy group, and 39 patients receiving palliative care from the time of diagnosis.

Survival curves for patients treated by each modality are presented in Figure 1. Mean survival differed significantly between groups ($p < 0.001$). Following exclusion of the patients treated with palliative intent, the only differences in median survival was between the watch and wait group (76 months) and those patients undergoing long course chemoradiotherapy followed by surgery (53 months, $p=0.006$) on pairwise comparison.

Among all of patients who received long course chemoradiotherapy (n=241), 134 (56%) proceeded to surgery, 46 (19%) patients did not undergo surgical excision on account of disease progression during this treatment or because they had been considered fit for surgical treatment initially, became unfit for surgery throughout the course of their treatment. 61 (18%) patients entered the watch and wait programme.

Of the 61 patients involved in the watch and wait programme, 40 are free from disease at median follow up of 38.2 months. Of the 21 patients who developed regrowth, median time to regrowth was 15 months. No rectal cancer regrowth was identified in patients after 34 months of follow-up (See *Figure 2*). Nine regrowth patients proceeded to palliative treatment, four underwent surgery including an APER or anterior resection. One patient had an onward referral to specialist pelvic clearance unit and one underwent a TEMS.

DISCUSSION:

This study demonstrates that for patients with complete clinical response following LCCRT, organ preservation is an option by embarking the watch-and-wait strategy for the well counselled patient. It has shown that a substantial number (40 out of 61) of patients undergoing a watch-and-wait strategy have avoided major rectal surgery with its inherent morbidity and potential permanent stoma, without loss of oncological safety at a median of 28 months follow-up.

After analysis of all subgroups of patients, with removal of those being treated with palliative intent from the outset, there was no significant difference found in all-cause mortality. There was a singular exception – the watch-and-wait group at 70.8 months compared those who had undergone LCCRT, as a pooled group, at a follow-up of 52.6 months showed significantly difference in survival. The wait-and-wait group having greater all-cause survival displayed at this point, but this result wasn't repeated at any other time point. The OnCoRe study and the 2017 meta-analysis also reported non-significance between wait-and-wait and intervention groups.^{12,13}

A recurrence rate of 34% in the watch-and-wait group echo the results of the OnCoRe study (34%) at a similar median follow-up time point (28 vs. 33 months respectively). This falls short of the crude rate of intraluminal regrowth reported after meta-analysis (15.7%), but this crude rate does not take into account variations in follow-up periods in this meta-analysis and has not adjusted for these.

	Watch & Wait n=61 (11.5%)	Straight to Surgery n=160 (30.1%)	Short Course n=37 (7.0%)	Long Course n=180 (33.8%)	Palliative Care n=89 (16.7%)	Overall (n=532)	Test of significance	
Age ^a mean	69.79	66.89	65.64	65.67	73.52	67.88	F = 7.86 4, 522 d.f p = <0.001	
Gender ^b n (%)	M = 43 (70.5) F = 18 (29.5)	M = 96 (60.0) F = 64 (40.0)	M = 28 (75.7) F = 9 (24.3)	M = 117 (65.0) F = 63 (35.0)	M = 41 (46.1) F = 48 (53.9)	M = 330 (62.0) F = 202 (38.0)	$\chi^2 = 15.28$ 4 d.f p = 0.004	
T Stage ^b n (%)	1	1 (1.6)	18 (11.3)	0 (0.0)	2 (1.1)	0 (0.0)	21 (3.9)	$\chi^2 = 79.44$ 12 d.f p = <0.001
	2	21 (34.4)	56 (35.0)	11 (29.7)	38 (21.1)	9 (10.1)	135 (25.4)	
	3	20 (32.8)	35 (21.9)	21 (56.8)	97 (53.9)	20 (22.5)	195 (36.7)	
	4	12 (19.7)	7 (4.4)	2 (5.4)	31 (17.2)	11 (12.4)	64 (12.0)	
	Missing	7 (11.5)	44 (27.5)	3 (8.1)	12 (6.7)	49 (55.1)	117 (22.0)	
N Stage ^b n (%)	0	28 (45.9)	68 (42.5)	18 (48.6)	59 (32.8)	18 (20.2)	191 (35.9)	$\chi^2 = 31.65$ 12 d.f p = 0.002
	1	16 (26.2)	21 (13.1)	11 (29.7)	50 (27.8)	9 (10.1)	107 (20.1)	
	2	9 (14.8)	13 (8.1)	5 (13.5)	55 (30.6)	12 (13.5)	95 (17.9)	
	Missing	8 (13.1)	58 (36.3)	3 (8.1)	16 (8.9)	50 (56.2)	139 (26.2)	
All cause mortality ^b n (%)	11 (18.0)	33 (20.6)	9 (24.3)	69 (38.3)	32 (86.5)	171 (32.1)	$\chi^2 = 35.17$ 4 d.f p = <0.001	
Follow-Up ^c median (IQR)	38.26 (23.50, 46.50)	30.0 (19.00, 44.00)	40.0 (17.5, 63.5)	31.0 (19.00, 50.75)	9.0 (3.50, 20.00)	28.0 (15.00, 45.00)	H = 108.53 4 d.f p = <0.001	

Table 1: Characteristics of patients included in each treatment group.

a. One-way ANOVA b. Chi-squared test c. Kruskal-Wallis test

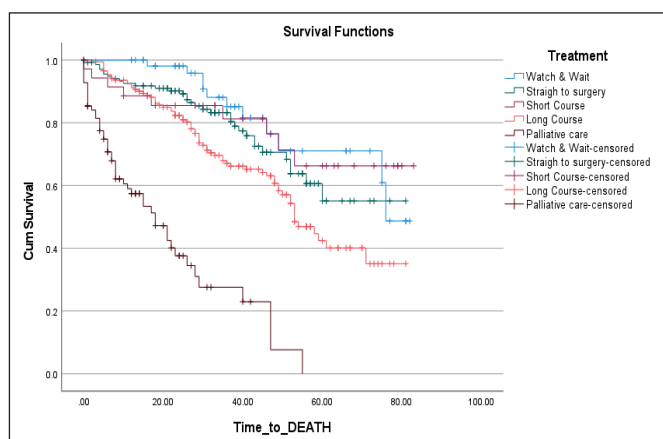


Figure 1: Kaplan-Meier survival curves for patients with rectal cancer treated with watch and wait (blue), straight to surgery (green), short course radiotherapy (purple), long course chemo-radiotherapy (orange) and palliative care (brown). Log rank $\chi^2 = 135.13$, 4 df, p = <0.001.

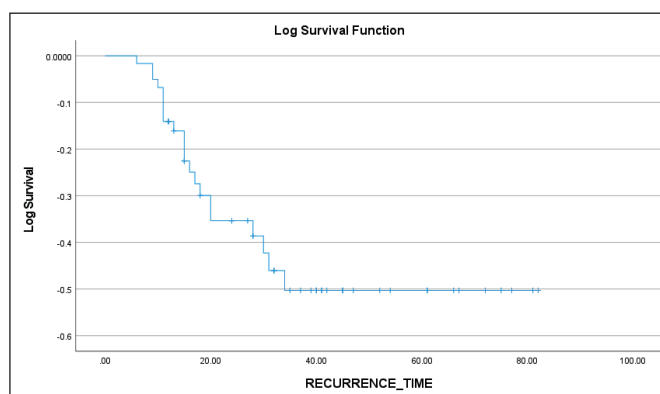


Figure 2: Kaplan-Meier Curve illustrating time to diagnosis of rectal cancer regrowth in patients undergoing “Watch & Wait” management.



Patient characteristics (Table. 1) of the included cohort, when compared to the patient characteristics of studies included in a 2017 meta-analysis and the largest cohort study to date (OnCoRe), appear generally homogenous.^{12,13} Four studies (out of twenty-four) in the meta-analysis presented median ages higher than this cohort and 62% of patients meta-analysed were male, mirroring the 67% in this study. Median follow-up of this study was 28 months – similar comparing to the meta-analysis and the 2015 OnCoRe study (33 months).¹³ The groups which responded to LCCRT, and those who didn't, did not differ in sex, age or tumour characteristics – echoing the results of the OnCoRe study.

The tumours represented in this study were characterised by similar T-stage to in both the OnCoRe study and the meta-analysis, with all having a majority of T3 tumours. Nodal stage differed – 45.9% of those in the watch-and-wait group in this study were N0, compared to 35% in the OnCoRe study, and 48% in the meta-analysis.

Clinical implication and future research

These findings arm the both clinician and patient in deciding the optimum treatment strategy for the patient with rectal cancer who has had a complete clinical response following LCCRT. This allows for full informed consent for a patient entering the watch-and-wait programme. To date, studies suggest upwards of one third of patients will unfortunately require surgery for local regrowth even after LCCRT. Despite this Habr-Gama et al in 2013 showed promising results when watch-and-wait plus salvage strategies were paired together in the setting of local recurrence post LCCRT. They demonstrated a 5 year local recurrence-free survival rate of 94%. Recurrences as a whole were infrequent, with the majority of those who did recur being amenable to salvage surgery. This may help provide reassurance to both patients and clinicians that a watch-and-wait approach with rigorous follow up is a safe and less invasive initial step in the treatment of rectal cancer.¹⁴

Nasir and colleagues in 2018 have suggested local regrowth surgery still has comparable R0 resections to original non-deferred surgical options. It has been shown that the majority of regrowth surgery can still be carried out via a minimally invasive technique (laparoscopic, robotic) without an increase in post-operative morbidity (anastomotic leak, post-op ileus, bleeding) and mortality along with favourable overall oncological outcomes.¹⁵

It is important to emphasise that watch-and-wait requires a strict follow up process, patients must be well informed and be willing to take part. Any institution introducing this method into their clinical practice requires a strong multidisciplinary team commitment to help identify appropriate candidates and have in place a robust follow-up protocol.

There remains no randomised controlled trial (RCT) for watch-and-wait for the complete clinical responder post LCCRT. Recruitment for this may be challenging, with often both clinicians and patients having firm ideas on the

optimum treatment strategy, with the outcomes being vastly different, namely rectal surgery with its morbidity or simply close observation.

Future research may rely on meta-analysis of good quality data and should demonstrate that results are repeatable in all centres, not just highly specialised units.

Limitations

The small number of patients who undergo TME after complete pathological response prevented the authors from using a propensity-score matching method to compare those who chose TME surgery and those who chose watch-and-wait. This method attempts to address the confounding effect of selection bias between patients who choose differing management plans by statistically matching their co-variates. To address this issue, the authors intend to re-examine this data once the sample size grows.

CONCLUSION:

Neoadjuvant long course chemoradiotherapy is the standard treatment for locally advanced rectal cancer. Over a quarter of our cohort who received long course entered the watch and wait programme with the majority of these patients avoiding major rectal surgery.

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