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Systematic review and meta-analysis on outcomes of salvage therapy in patients with tumour recurrence during 'watch and wait' in rectal cancer

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ABSTRACT

INTRODUCTION The 'watch and wait' approach has recently emerged as an alternative approach for managing patients with complete clinical response in rectal cancer. However, less is understood whether the intervention is associated with a favourable outcome among patients who require salvage therapy following local recurrence.

MATERIALS AND METHODS A comprehensive systematic search was performed using EMBASE, PubMed, MEDLINE, Journals@Ovid as well as hand searches; published between 2004 and 2018, to identify studies where outcomes of patients undergoing watch and wait were compared with conventional surgery. Study quality was assessed using the Newcastle–Ottawa assessment scale. The main outcome was relative risks for overall and disease specific mortality in salvage therapy.

RESULTS Nine eligible studies were included in the meta-analysis. Of 248 patients who followed the watch and wait strategy, 10.5% had salvage therapy for recurrent disease. No statistical heterogeneity was found in the results. The relative risk of overall mortality in the salvage therapy group was 2.42 (95% confidence interval 0.96–6.13) compared with the group who had conventional surgery, but this was not statistically significant ($P > 0.05$). The relative risk of disease specific mortality in salvage therapy was 2.63 (95% confidence interval 0.81–8.53).

CONCLUSION Our findings demonstrated that there was no significant difference in overall and disease specific mortality in patients who had salvage treatment following recurrence of disease in the watch and wait group compared with the standard treatment group. However, future research into the oncological safety of salvage treatment is needed.

KEYWORDS
Rectal cancer – Watch and wait – Non-operative management – Salvage treatment

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Introduction

The management of rectal cancer has seen several milestones over the twentieth century,[1] with a growing interest in newly emerging approaches in rectal cancer surgery such as extra-levator abdominoperineal resection of rectum (ELAPE)[2] and transanal total mesorectal excision (TaTME).[3] However, these treatment advancements still fail to address the issue of considerable morbidities associated with surgical resection in rectal cancer treatment despite improvements in minimally invasive techniques.[4,5] Short-term morbidities include anastomotic dehiscence, bleeding and pelvic sepsis, while long-term morbidities may involve urinary and sexual dysfunction, which compromise quality of life.[5,6]

Following the pioneering work of Habr-Gama *et al*,[7] there has been a gradual paradigm shift towards organ preservation in the treatment of rectal cancer in patients who had a complete clinical response after neoadjuvant chemoradiotherapy. This group of patients with complete clinical response are subjected to intensive follow-up for disease recurrence. The watch and wait approach has emerged as an alternative option to immediate surgery for the management of patients who have a complete clinical response following chemoradiotherapy, minimising the risk of overtreatment.[7–16]

Approximately 13–31% of patients experience local recurrence following complete clinical response and will require salvage therapy either in the form of anterior resection or abdominoperineal resection of the rectum to obtain disease control.[17,18] Habr-Gama *et al* have shown that salvage therapy is possible in over 90% of recurrences.[18] However, long-term outcomes in this group of

patients who require salvage therapy are not as well understood as in the watch and wait group.

In the absence of randomised controlled trials, a systematic review and meta-analysis of the available data might help better understand the outcomes of this group of patients who underwent salvage therapy while being managed under the watch and wait protocol. Previous systematic reviews and meta-analyses have mainly focused on the outcomes of watch and wait for rectal cancer.[19,20] This systematic review therefore aimed to compare the outcomes of those who had salvage therapy for tumour regrowth following watch and wait with conventional gold standard surgery.

Materials and methods

Search strategy

The following electronic databases were searched: Embase (1996 to third week March 2018), Medline (1996 to third week March 2018), PubMed (2004 to third week March 2018) and Journals@Ovid (2004 to third week March 2018).

The appropriate medical subject heading terms were used in the databases. The terms 'rectal cancer', 'watch and wait' and 'chemoradi*' were used. Additional records were identified and added from hand-searching. Additional terms 'rectal carcinoma', 'rectal neoplasm', 'active surveillance' and 'organ preservation' were used. The conduct and reporting of this review is in keeping with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[21]

Inclusion and exclusion criteria

Studies eligible for inclusion included studies that reported survival data of patients who underwent salvage therapy following disease recurrence under watch and wait and that of a control group (e.g. surgical resection with or without neoadjuvant chemo-radiotherapy). Salvage therapy was not restricted only to surgical treatment as long as the intention was to cure the patient of disease. Randomised controlled trials, retrospective and prospective cohort studies that looked at the survival of patients who had the watch and wait strategy for rectal cancer management following chemoradiotherapy were also included. Full-text articles in English were included. Where appropriate, authors were contacted to request additional data.

Studies were excluded if the necessary information needed to calculate a relative risk (RR) were not provided. Therefore, observational studies which had data on salvage therapy but no control group were excluded. Abstracts of conference proceedings were also excluded because they often do not provide sufficient information.

Study selection and quality assessment

Two authors (JO and JS) appraised the studies extracted from the databases. The Newcastle–Ottawa scale was used to assess the quality of the studies. Disagreements or uncertainties about satisfaction of quality criteria were discussed with a third reviewer (EHA) and consensus was achieved.

Data extraction

Two reviewers (JO and JS) extracted data on the articles which met initial quality assessment. Data on the type of study, characteristics of the study population, sample size, types of treatments, duration of follow-up and the survival rates were extracted systematically and tabulated.

Outcomes

The primary outcome for these analyses was the relative risk of overall mortality for patients who underwent salvage therapy following recurrence under the watch and wait approach. Mortality in the treatment group was defined as death following salvage intervention in patients who had recurrence subsequent to neoadjuvant chemoradiotherapy. Therefore, patients in the watch and wait group who died without receiving any intervention would not have been included in this analysis. We also compared the disease specific mortality of patients who had salvage treatment with patients who had standard treatment.

Statistical methods

Main results were expressed as relative risks with 95% confidence intervals (CI). Individual estimates of relative risks of the studies were then combined in a meta-regression analysis to give a pooled relative risk, which represents the overall risk of mortality in the salvage therapy group compared to the standard care group (control).

Heterogeneity was assessed using Pearson chi-squared test and value of I2.[22] The value of I2 describes the percentage of variation across studies due to heterogeneity rather than chance. Depending on the statistical heterogeneity observed, fixed or random effects models were carried out as appropriate. Results were reported graphically using forest plots (with relative risks at 95% confidence intervals). All analyses were performed using STATA software version 14.0.

Results

The search strategy yielded 839 articles in total and, after removing duplicates, a total of 720 articles were eligible for screening. Of the 720 articles screened, 40 full text articles were assessed for eligibility for this systematic review and meta-analysis. Nine studies were included; one randomised controlled trial[25] and eight observational cohort studies.[7,8,12–16,24] Several papers by Habr-Gama *et al* were excluded as they included the same cohort of patients.[17,18] In such instances, we selected the most relevant paper published. Full details of this screening process is shown in Figure 1.

Studies and study population

Tables 1–3 describe the characteristics of the included studies and patient demographics. Across the nine studies, a total of 248 patients had undergone the watch and wait approach and 324 patients were in the control group. Sample size of studies ranged from 6 to 122 patients. The majority of the included studies were retrospective

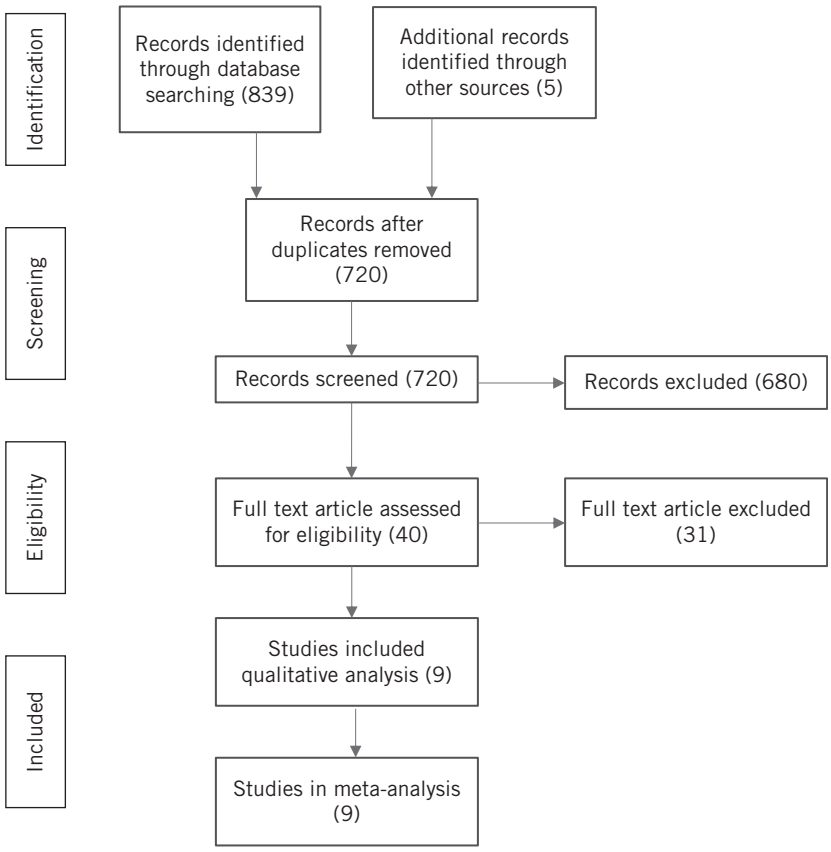

Figure 1 PRISMA diagram.

cohort studies. Age range of the study populations varied from 54 to 70 years. Generally, the patients in the watch and wait group were older than the patients in the control group.

In five studies, the decision to treat with watch and wait was reportedly based on several factors, which include patients' preference and presence of multiple co-morbidities,[8,13,14,16,24] while patients in three studies were actively recruited into the watch and wait group.[7,12,23]

Of the 568 patients (248 watch and wait group and 320 controls) that provided complete T and N staging data, majority of the patients had T3 tumour (54% vs 41%, watch and wait vs control) and node-negative disease (41% vs 30%; Table 2). However, it was not possible to extract individual T and N stage data in patients who had salvage therapy as a result of disease recurrence. There was also lack of data on comorbidities and we could only assume that patients were fit for major surgery.

All of the patients included in the watch and wait group had complete clinical response. However, studies did not always provide clear standardised criteria for complete clinical response and various modalities were used in the assessment of complete clinical response as shown in Table 4. The mean time to response evaluation post-neoadjuvant chemoradiotherapy were between 6 and 12 weeks. Follow-up intervals also varied (Table 5). The overall follow-up period in the watch and wait cohort, which included patients who had salvage therapy ranged from 25 to 68.4 months. A follow-up period of 28 months or less reported in three of the studies might have been inadequate owing to the possibility of recurrence after follow-up.[8,13,15]

Disease recurrences following 'watch and wait

Figure 2 and Table 6 summarise the outcomes of patients who had recurrent disease. Overall, 38 of 248 patients (15.3%) had recurrent disease. In this group, 24 had local recurrence (63.2%), six had both local and systemic recurrence (15.8%) and eight had systemic recurrence only (21%). The timing of local recurrence varied from 5 to 60 months. Seven of the nine patients who developed distant metastasis survived; one patient was considered to have had salvage therapy in the way of a pulmonary wedge resection for a single pulmonary metastasis, three patients had systemic chemotherapy, and the remaining three patients received no treatment.[7,14,16,24]

Table 1 Summary of patient demographics comparing surgical resection with watch and wait in rectal cancer.

Study	Design	Mean time (weeks)[a]	Patients		Age (years)		Male : Female		Mean follow-up (months)	
			W&W (*n*)	Control (*n*)	W&W (*n*)	Control (*n*)	W&W	Control	W&W (*n*)	Control (*n*)
Maas *et al*, 2011[8]	Prospective	6.5	21	20	65	64	14 : 7	16 : 4	25	35
Dalton *et al*, 2012[15]	Retrospective	6								
Smith *et al*, 2015[14]	Retrospective	12	18	30	62.3	60.4	15 : 3	20 : 10	68.4	46.3
Habr Gama *et al*, 2004[7]	Prospective	8	71	22	58.1	53.6	12 : 10	18 : 14	48	28
Smith *et al*, 2012[13]	Retrospective	4–10	32	57	70	60	18 : 14	27 : 30	42	47.7
Araujo *et al*, 2015[24]	Retrospective	12	42	69	63.6	60.1	17 : 25	34 : 35	46.7	49.9
Lai *et al*, 2015[12]	Retrospective	n/a	18	26	67.6	63.8	15 : 3	12 : 14	49.4	42.3
Li *et al*, 2015[16]	Retrospective	n/a	30	92	62	56	18 : 12	60 : 32	58	58
Nahas *et al*, 2016[23]	RCT	8.7	4	2	n/a	n/a	n/a	n/a	33.2	28.2

[a] Mean time to response evaluation.
W&W, watch and wait.

Table 2 Summary of tumour staging comparing surgical resection with watch and wait in rectal cancer.

Study	Distance from ARJ (cm)		T1 (*n*)		T2		T3		T4		T missing		N +ve		N –ve		N missing	
	W&W	Cont.	W&W	Cont.	W&W	Cont.	W&W	Cont.	W&W	Cont.	W&W	Cont.	W&W	Cont.	W&W	Cont.	W&W	Cont.
Maas *et al*, 2011[8]	2.9	3.4	1	0	5	1	13	17	2	2	0	0	15	17	6	3	0	0
Dalton *et al*, 2012[15]	3.3	n/a	0	n/a	1	n/a	4	n/a	1	n/a	6	6	5	n/a	1	n/a	6	6
Smith *et al*, 2015[14]	4.1	6	1	2	1	16	16	12	0	0	0	0	7	12	11	18	0	0
Habr Gama *et al*, 2004[7]	3.6	3.8	0	0	14	1	49	19	8	2	0	0	16	6	55	16	0	0
Smith *et al*, 2012[13]	6	7	0	n/a	10	11	22	n/a	0	n/a	0	46	18	n/a	14	20	0	37
Araujo *et al*, 2015[24]	n/a	n/a	3	0	12	15	12	36	1	2	14	16	n/a	n/a	n/a	n/a	42	69
Lai *et al*, 2015[12]	3.4	4.8	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	18	26	n/a	n/a	n/a	n/a	18	26
Li *et al*, 201516	3.5	3.8	3	10	5	14	15	48	7	20	0	0	16	53	14	39	0	0
Nahas *et al*, 2016[23]	n/a	n/a	0	0	1	2	3	0	0	0	0	0	3	2	1	0	1	–

AJR, anorectal junction; Cont., control; W&W, watch and wait.

Of the 38 patients who had recurrent disease, 26 of these patients (68.4%) had some form of salvage therapy with a curative intent; 25 patients had surgical resection (abdominoperineal excision/resection, Hartmann's, transanal endoscopic microsurgery, local excision) and one patient had brachytherapy for local recurrence. Two patients who had salvage therapy died during the follow-up period from cardiac arrest post-surgery,[24] and systemic re-recurrence 12 months after salvage abdominoperineal resection of rectum, respectively.[13]

Overall, the rate of local and systemic re-recurrence post salvage therapy was 16%; 14.3% of patients who had only local recurrence experienced re-recurrence. Re-recurrence post-salvage therapy in patients who initially developed both local and distant disease occurred in 33% of patients.

Overall risk of mortality

Seven studies provided information on overall mortality in salvage therapy group following watch and wait. The

Table 3 Chemoradiotherapy regimen and outcomes comparing surgical resection with watch and wait in rectal cancer

Study	Salvage (*n*)	Salvage treatment in W&W group (*n*)	Chemotherapy regimen
Maas *et al*, 2011[8]	1	TEMS (1)	28 fractions of 1.8 Gy combined with 2 × 825 mg/m^2 capecitabine
Dalton *et al*, 2012[15]	6	APER (5) Hartmann's (1)	45 Gy in 25 fractions over 5 weeks with concurrent capecitabine (825 mg/m^2)
Smith *et al*, 2015[14]	2	TEMS (positive margin) followed by APER and subsequent cyberknife radiation due to pelvic recurrence (1) Pulmonary wedge resection (1)	Radiotherapy ?? + 5-FU or capecitabine. 11 had 'adjuvant' 5-FU
Habr Gama *et al*, 2004[7]	5	TEMS (1) Brachytherapy (1) Systemic chemotherapy (3)	5040 cGy given at 180 cGy/day for 6 consecutive weeks. 5-fluoracil and folinic acid administered intravenously for 3 consecutive days on the first and last 3 days of radiation therapy
Smith *et al*, 2012[13]	6	Anterior resections (3) APER (3)	5040 cGy followed by 5-FU or capecitabine
Araujo *et al*, 2015[24]	4	Anterior resections (1) APER (3)	45.0 Gy to 50.4 Gy. A bolus of 5-FU and leucovorin during the first and last week of radiotherapy. In a minority, capecitabine was orally administered during all 5 weeks of radiotherapy
Lai *et al*, 2015[12]	2	Transanal wide excision (2)	5-FU was administered as a bolus with a low-dose leucovorin bolus for 5 days on days 1–5 and 29–33 in combination with radiotherapy (45 Gy in 25 fractions or 54 Gy in 30 fractions)
Li *et al*, 2015[16]	2	TME (1) Local excision (1)	50 Gy/25 f/2 Gy, capecitabine, 825 mg/m^2 bid, concurrently
Nahas *et al*, 2016[23]	1	LAR (1)	5-FU with leucovorin by IV bolus on days 1–5. Radiation in weeks 1 and 5. Total pelvic dose radiation was 5040 Gy in 30 sessions

APER, abdomen-perineal excision of rectum; FU, fluorouracil; IV, intravenous; LAR, low anterior resection; TEMS, transanal endoscopic microsurgery; TME, total mesorectal excision; W&W, watch and wait.

pooled overall risk of mortality after salvage therapy was 2.42 (95% CI 0.96–6.13), although difference between the salvage therapy group and the control group was not statistically significant (Fig 3). Two studies were excluded because there were no events in both treatment arms and therefore, do not provide any indication of neither direction nor magnitude of the relative treatment effect. This is in keeping with standard practice by the Cochrane Review Group.[25]

Disease-specific mortality

We also assessed disease-specific mortality of patients in the salvage group compared with those who had received standard treatment. Overall pooled results of five studies showed a 2.63 increased risk of disease specific mortality in the salvage therapy group (95% CI 0.81–8.53; Fig 4).

Quality of studies

According to the Newcastle–Ottawa scale, studies were subjected to significant bias, in terms of the selection criteria, as well as short follow-up periods. Figure 5 shows the summary of the scores for each of the papers included in this study. Generally, there were clinical heterogeneity in terms of assessing complete clinical response, chemoradiotherapy regimen and length of follow-up. In some of the studies, the follow-up period could be deemed inadequate due to the possibility of disease recurring beyond the intended follow-up period.[8,13,15] There was also variability in the type of salvage treatment ranging from standard surgical procedures to local excision. All the papers had outcomes of patients undergoing the watch and wait management strategy as their primary aim. One of the papers did not report on the TNM staging of their patients.[12]

Discussion

Our findings indicate that the likelihood of mortality between patients who had salvage therapy and those who received conventional surgery are not significantly different. Findings were consistent across the different studies. We found that 68.4% of patients who developed recurrences had salvage therapy with a curative intent. In this

Table 4 Methods used to define complete clinical response by various studies.

Study	Method
Habr Gama *et al*, 2004[7]	Assessed using the same pretreatment clinical, endoscopic and radiologic parameters (CT).Proctoscopy: no significant residual ulcer or positive biopsies
Maas *et al*, 2011[8]	Imaging with MRI: Downsizing with no residual tumour or residual fibrosis only (with low signal on high B-value DWI). No suspicious lymph node.Endoscopy: no residual tumour or only a small residual erythematous ulcer or scar. Negative biopsies from scar, ulcer or former tumour location.Digital rectal examination: no palpable tumour.
Dalton *et al*, 2012[15]	Imaging with MRI: significant tumour regression with little evidence of residual tumour.Examination under anaesthesia: residual mucosal ulcers are considered to be residual tumour even if biopsies are benign.FDG-PET if no evidence of tumour clinically and on biopsies.
Smith *et al*, 2012[13]	Digital rectal examination: no palpable tumour.Endoscopy: no visible pathology other than a flat scar with selective biopsies.
Smith *et al*, 2015[14]	Not standardised but based upon digital rectal examination, rigid proctoscopy, endorectal ultrasound, axial imaging and selective endoscopic biopsies.
Araujo *et al*, 2015[24]	No clear criteria but based on digital rectal examination, endoscopy and MRI.
Li *et al*, 2015[16]	No clear criteria but based on digital rectal examination, CT, MRI, endoscopy with biopsy and transrectal ultrasonography.
Nahas *et al*, 2016[23]	Digital rectal examination: no residual deep ulceration with or without a necrotic centre; no superficial ulcer or irregularity even in presence of mucosal ulceration; no palpable nodule even in presence of mucosal integrity; no significant stenosis that impedes protoscope sliding through.Imaging with MRI: shrinkage of tumour with homogenous low signal intensity on T2 images characterising fibrosis and no residual tumour. No lymph node involvement and no extramural vascular invasion.
Lai *et al*, 2016[12]	Digital and endoscopic examination: absence of residual ulceration, mass or mucosal irregularity. Whitening of the mucosa and the presence of neovasculature (telangiectasia).Imaging: CT, transrectal ultrasonography or MRI without evidence of residual extra-rectal disease.

CT, computed tomography; DWI, diffusion-weighted imaging; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.

Table 5 Follow-up intervals for patients with complete clinical response.

Study	Follow-up intervals
Habr Gama *et al*, 2004[7]	Year 1: monthly DRE, proctoscopy ± biopsies, CEA; CT and chest x-ray 6-monthlyYear 2: 2-monthly follow-up as aboveYear 3: 6-monthly follow-up as above
Maas *et al*, 2011[8]	Year 1: 4 × DRE, CEA, endoscopy and MRI; 2 × CT scanYears 2 and 3: 4 × CEA; 2 × DRE, endoscopy and MRI; 1 × CTYears 4 and 5: 2 × CEA, DRE, endoscopy and MRI; 1 × CT
Dalton *et al*, 2012[15]	EUA at 3 months and 1 yearInitially 6-monthly then yearly PET-CT and MRICEA monitoring
Smith *et al*, 2012[13]	Year 1: clinical examination and endoscopy every 3 months; imaging 6-monthlyYear 2 onwards: clinical examination and endoscopy every 4–6 months; imaging 6-monthly
Smith *et al*, 2015[14]	Year 1: proctoscopy (selective biopsies), CEA 3-monthly; CT or PET 6-monthly; colonoscopy 6-monthlyYears 2 and 3: proctoscopy (selective biopsies), CEA 6-monthly; CT or PET annually; colonoscopy annuallyYear 4 onwards: annual proctoscopy (selective biopsies), CEA, CT or PET and colonoscopyNote: CT or PET and ERUS or MRI if changes in proctoscopy or rise in CEA
Araujo *et al*, 2015[24]	Years 1 and 2: clinical, CEA and endoscopy 3-monthlyYears 3–5: clinical, CEA and endoscopy 6-monthly
Li *et al*, 2015[16]	Year 1: monthly DRE and CEA; 3-monthly endoscopy with biopsies and ERUS; 6-monthly CT, MRI and chest x-rayYear 2: 6-monthly follow-upYear 3 onwards: annual follow-up
Lai *et al*, 2016[12]	Years 1 and 2: clinical, CEA and endoscopy (selective biopsies) 3-monthlyYear 3 onwards: clinical, CEA and endoscopy (selective biopsies) 6-monthlyCT, MRI or chest x-ray in the first 6 months then annually
Nahas *et al*, 2016[23]	Year 1: 3-monthly DRE, proctoscopy, CEA, CT and MRI; annual colonoscopyYears 2 and 3: 3-monthly DRE, proctoscopy, CEA; 6-monthly MRI and CT; annual colonoscopyYears 4 and 5: 6-monthly DRE, proctoscopy, CEA, MRI and CT; annual colonoscopy

CEA, carcinoembryogenic antigen; CT, computed tomography; DRE, digital rectal examination; DWI, diffusion-weighted magnetic resonance imaging; ERUS, endorectal ultrasound; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.

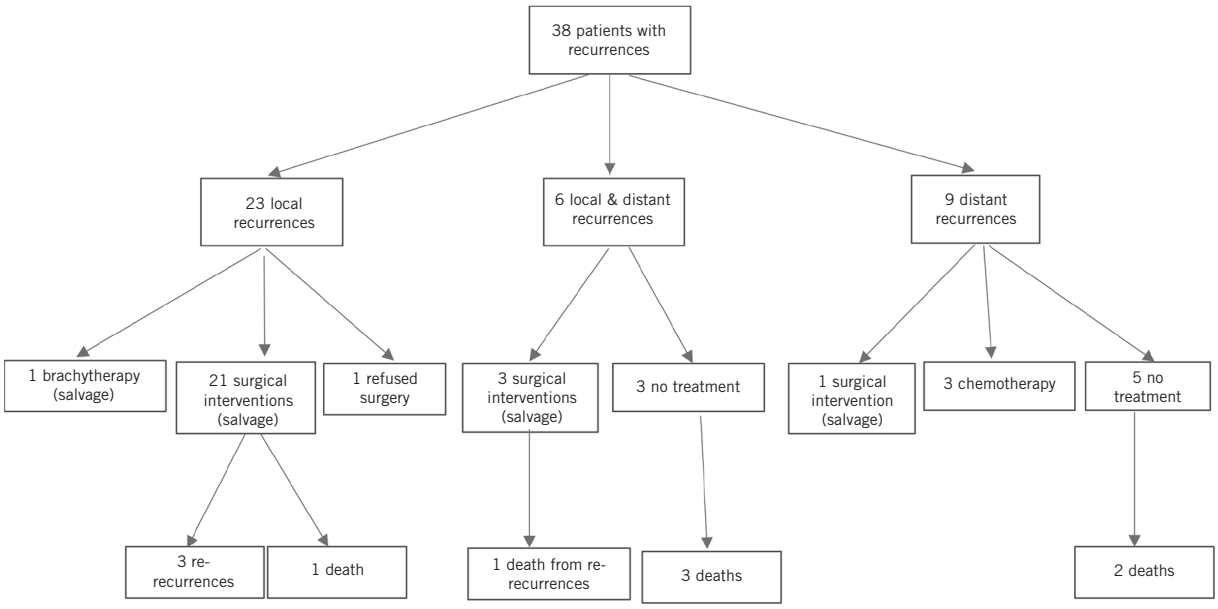

Figure 2 Outcomes of patients who had recurrences in the watch and wait group.

cohort of only patients who had salvage therapy, survival rate was 92.3% compared with 92.9% in the control group.

To the best of our knowledge, this is the first meta-analysis focused on outcomes of post-salvage therapy in patients with recurrent rectal cancer managed by the watch and wait strategy. Although we limited our search to articles published from 2004, the risk of omitting older articles is low because watch and wait in rectal cancer was only introduced in clinical practice over the past decade.

Despite the delay of surgery-related morbidity in the watch and wait approach, there is a clear trade-off with a local recurrence rate of 15.3%, which might seem high compared with no local recurrence reported in studies of patients treated with radical surgery who had pathological complete clinical response. That said, Habr-Gama *et al* have shown that the overall five-year survival for patients who had salvage treatment following recurrent disease was 63.3%,[26] not far off the estimated five-year survival rate for rectal cancer of 60% and 67% in the UK[27] and the United States,[28] respectively.

Although Habr-Gama *et al* have shown that salvage was possible in 90% of their cases, which is higher than the 68.4% reported in our study, this could be explained by a multitude of factors including the variation in patient selection, treatment strategies and surveillance modalities.[18] Their study also reported a high loss to follow-up of nearly 30% over five years. Studies included in our review were conducted in the early stages of the development of watch and wait strategy. Hence, it is possible that with better understanding of watch and wait, improvement in the recognition of complete clinical response, and advances in imaging technology, timely treatment of any disease recurrence could be initiated with the inference that salvage treatment is possible in a higher proportion of patients than demonstrated by our results.

It is emphasised that our data should be interpreted with caution, owing to the general lack of standardisation in the definition of complete clinical response, chemotherapy regimen, follow-up protocols, and salvage therapy for the treatment of recurrence. Clinical and methodological heterogeneity was high among studies included in this review. To address this, a random effects model for the meta-analysis was carried out. We also carried out sensitivity analyses where studies of small sample size and high heterogeneity were excluded from the meta-analysis and found no effect to the outcomes (data not shown).

It is also worth noting that the literature on outcomes of salvage therapy was scarce and consisted of mostly small retrospective cohort studies, which precluded the generalisation of risks and formulation of firm conclusions. While the watch and wait approach has been offered for some time to a selected group of patients in clinical practice, the quality of data on the outcomes of the cohort of patients who require subsequent salvage therapy as a result of disease recurrence remains poor. Existing systematic reviews and meta-analysis assessing the overall survival of watch and wait for rectal cancer, which combined a proportion of patients who subsequently underwent salvage therapy have demonstrated that the majority of patients who

Table 6 Summary of the timing of recurrence, type of recurrence, salvage treatment and outcomes of all patients who developed recurrence in the watch and wait group.

Patient no.	Study	Stage		Adjuvant chemotherapy	Recurrence		Salvage	Treatment	Outcome
		T	N		Interval	Type			
1	Maas *et al*, 2011[8]	T3	N0	Yes	22 months	Local	Yes	TEMS	Alive
2	Dalton *et al*, 2012[15]	2	1	?	15 weeks	Local	Yes	Hartmann's	Alive. Re-recurrence after 6 months. Pelvic exenteration (R0), developed lung metastases
3		2	0	?	25 weeks	Local	Yes	APER	Alive. Re-recurrence. Liver metastases after 52 weeks.
4		?	?	?	?	Local	Yes	APER	Alive
5		?	?	?	?	Local	Yes	APER	Alive
6		?	?	?	?	Local	Yes	APER	Alive
7		?	?	?	?	Local	Yes	APER	Alive
8	Smith *et al*, 2015[14]	?	?	?	9.4 months	Local	Yes	TEMS	Alive. Re-recurrence. Positive margins so had APER, developed presacral recurrence and had cyberknife radiation. Had another local recurrence 4 months later but patient refused surgery
9		?	?	?	32 months	Distant	Yes	Pulmonary wedge resection	Alive
10	Habr Gama *et al*, 2004[7]	?	?	No	56 months	Local	Yes	TEMS	Alive
11		?	?	No	64 months	Local	Yes	Brachytherapy	Alive
12		?	?	Yes	18 months	Distant	No	Chemotherapy	Alive
13	?	?	Yes	48 months	Distant	No	Chemotherapy	Alive	
14	?	?	Yes	90 months	Distant	No	Chemotherapy	Alive	
15	Smith *et al*, 2012[13]	2	0	?	11 months	Local and distant	Yes	APER	Alive with disease
16		3	0	?	12 months	Local and distant	Yes	APER	Alive with disease
17		3	1	?	13 months	Local	Yes	LAR	Alive
18		2	x	?	10 months	Local	Yes	LAR	Alive
19		3	1	?	7 months	Local and distant	Yes	TEMS	Died. APER (R1 resection). Local re-recurrence
20		3	2	?	14 months	Local	Yes	LAR	Alive
21	Araujo *et al*, 2015[24]	?	?	?	10 months	Distant	No		Alive with disease
22		?	?	?	27 months	Distant	No		Alive with disease
23		?	?	?	43 months	Distant	No		Died
24		?	?	?	16 months	Distant	No		Died

25		?	?	?	8 months	Local and distant	No		Died
26		?	?	?	25 months	Local and distant	No		Died
27		?	?	?	29 months	Local and distant	No		Died
28		?	?	?	16 months	Local	Yes	APER	Alive
29		?	?	?	30 months	Local	Yes	LAR	Alive
30		?	?	?	32 months	Local	No (refused)		Alive with disease
31		?	?	?	19 months	Local	Yes	APER	Alive
32		?	?	?	24 months	Local	Yes	APER	Died. Cardiac arrest 2 months postoperatively at home
33	Lai *et al*, 2016[12]	?	?	?	14 months	Local	Yes	TEMS	Alive
34		?	?	?	36 months	Local	Yes	TEMS	Alive
35	Li *et al*, 2015[16]	?	?	?	18 months	Local	Yes	TME	Alive
36		?	?	?	26 months	Local	Yes	TEMS	Alive
37		?	?	?	50 months	Distant	No	Alive with disease	
38	Nahas *et al*, 2016[23]	3	2	?	6 months	Local	Yes	LAR	Alive

APER, abdomen-perineal excision of rectum; LAR, low anterior resection; TEMS, transanal endoscopic microsurgery.

developed local recurrence after watch and wait can be salvaged with surgery.[19,20,29]

A survival meta-analyses was not feasible in this review because of the lack of clear follow-up data. Pooling survival rates (survival over time) without adjusting for the duration of follow-up is not considered to be appropriate as it can lead to spurious conclusions, especially when the statistical power is low.

Clinical implications

Rectal resection continues to be associated with significant morbidity despite advancement in treatments with minimally invasive rectal surgery.[5] In the current era following the Montgomery ruling and in accordance with the General Medical Council guidance on consent, it is probably in the best interest of patients to be informed of the various options available including watch and wait should they achieve a complete clinical response after neoadjuvant chemoradiotherapy for rectal cancer. The results of our study provides cautious optimism for patients who wishes to know the outcomes following salvage treatment should a recurrence occur. It should be stressed that the current evidence on the oncological safety of salvage treatment is not conclusive. However, the appeal of organ preservation by avoiding major surgery with its associated morbidity may be sufficient for some patients to consider watch and wait.

Recommendations for future research

There is lack of assessment of quality of life in all the studies for patients in the watch and wait intervention group. This is an important clinical issue to consider as some of these patients will have short and long-term complications related to neoadjuvant therapy. None of the current studies compared the quality of life between watch and wait and patients who had surgical resection. Future studies should explore these issues.

The need for a standardised protocol for the assessment of complete clinical response, follow-up and salvage treatment is also highlighted. Future studies should equally assess the outcomes of salvage treatment in recurrent disease in watch and wait just as previous studies have justified adopting watch and wait as a management strategy within a strict clinical study for complete clinical response in rectal cancer studies. For this, we need larger prospective studies with longer term follow-up.

Conclusion

While our findings suggest that there is no statistically significant difference in overall risk of mortality in patients who had local recurrence following salvage treatment compared with patients who had standard treatment, a firm conclusion that salvage treatment is oncologically as safe as standard treatment cannot be made. Larger studies with a standard protocol need to be conducted to address this issue in light of the growing popularity of the watch and wait approach.

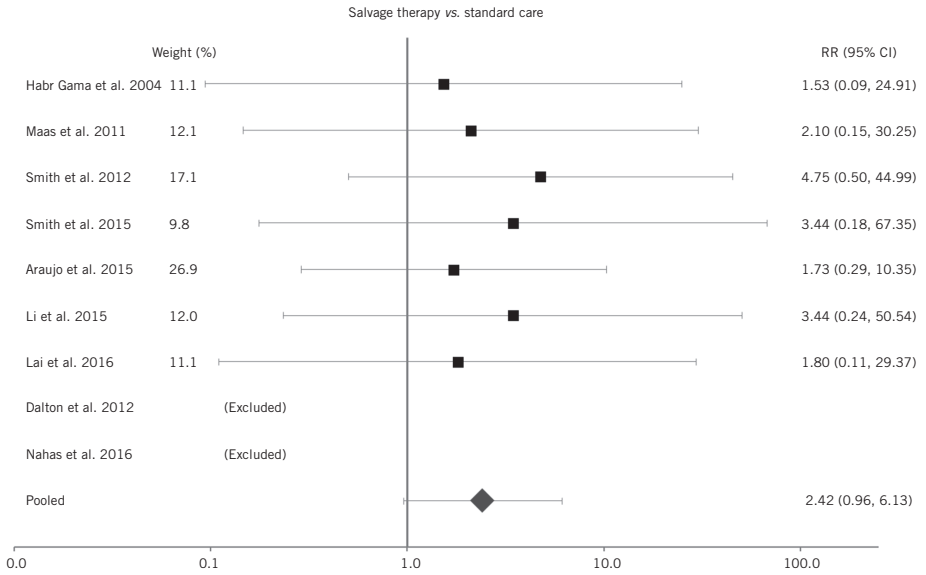

Figure 3 Forest plot of random effects meta-analysis demonstrating the overall risk of mortality in patients who had salvage therapy versus patients who had standard treatment. Overall effect size is not statistically significant ($P = 0.06$).

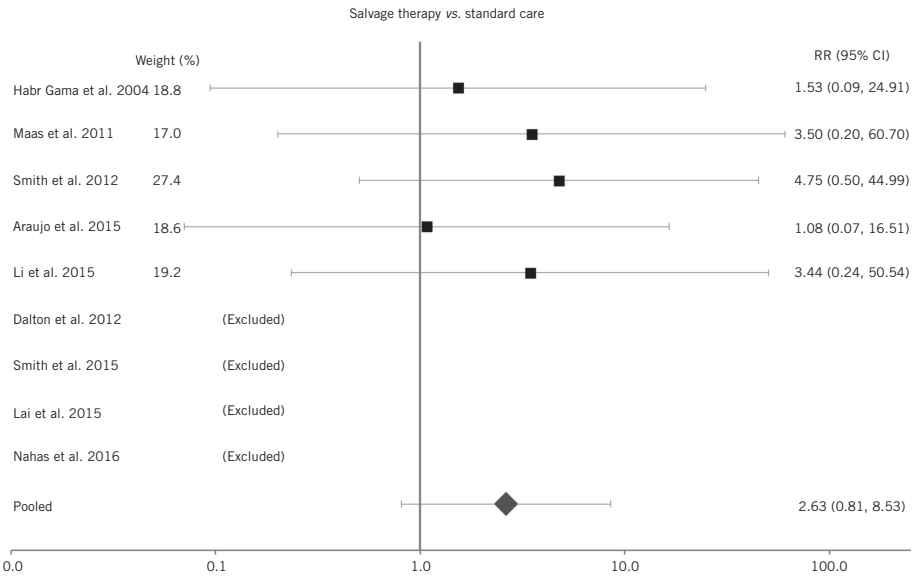

Figure 4 Forest plot of random effects meta-analysis demonstrating disease specific mortality in patients who had salvage therapy compared with patients who had standard treatment. Overall effect size is not statistically significant ($P = 0.11$).

Study	Selection			Comparability			Outcome		
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome was not present at onset	Comparability of cohorts at most important factor	Comparability of cohorts additional factors	Assessment of outcome	Length of follow-up	Adequacy of follow-up
Habr Gama *et al*, 2004[7]	⊕	⊕	⊕	⊕	⊕	⊖	⊕	⊕	⊕
Maas *et al*, 2011[8]	⊕	⊕	⊕	⊕	⊕	⊖	⊕	⊖	⊕
Dalton *et al*, 2012[15]	⊕	⊕	⊕	⊕	⊕	⊖	⊕	⊖	⊕
Smith *et al*, 2012[13]	⊕	⊕	⊕	⊖	⊕	⊕	⊕	⊖	⊕
Araujo *et al*, 2015[24]	⊕	⊕	⊕	⊕	⊕	⊖	⊕	⊕	⊕
Smith *et al*, 2015[14]	⊕	⊕	⊕	⊕	⊕	⊖	⊕	⊕	⊕
Li *et al*, 2015[16]	⊕	⊕	⊕	⊖	⊕	⊖	⊕	⊕	⊕
Lai *et al*, 2016[12]	⊖	⊕	⊖	⊕	⊕	⊖	⊕	⊕	⊕
Nahas *et al*, 2016[23]	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕
	Selection			Comparability			Outcome		

Figure 5 Newcastle–Ottawa score for assessment of quality of the studies included.

References

1. Aly EH. Time for a renewed strategy in the management of rectal cancer: critical reflection on the surgical management of rectal cancer over 100 years. *Dis Colon Rectum* 2014; **57(3)**: 399–402.
2. Anderin C, Martling A, Lagergren J *et al.* Short-term outcome after gluteus maximus myocutaneous flap reconstruction of the pelvic floor following extra-levator abdominoperineal excision of the rectum. *Colorectal Dis* 2012; **14(9)**: 1,060–1,064.
3. Koedam TWA, van Ramshorst GH, Deijen CL *et al.* Transanal total mesorectal excision (TaTME) for rectal cancer: effects on patient-reported quality of life and functional outcome. *Tech Coloproctol* 2017; **21(1)**: 25–33.
4. Aly EH. Have we improved in laparoscopic resection of rectal cancer: critical reflection on the early outcomes of COLOR II. *Transl Gastrointest Cancer* 2013; **2(4)**: 175–178.
5. Shearer R, Gale M, Aly OE, Aly EH. Have early postoperative complications from laparoscopic rectal cancer surgery improved over the past 20 years? *Colorectal Dis* 2013; **15(10)**: 1,211–1,226.
6. Glynne-Jones R, Hughes R. Complete response after chemoradiotherapy in rectal cancer (watch-and-wait): have we cracked the code? *Clin Oncol* 2016; **28 (2)**: 152–160.
7. Habr-Gama A, Perez RO, Nadalin W *et al.* Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Ann Surg* 2004; **240(4)**: 711–718.
8. Maas M, Beets-Tan RGH, Lambregts DMJ *et al.* Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. *J Clin Oncol* 2011; **29(35)**: 4,633–4,640.
9. Appelt AL, Pløen J, Harling H *et al.* High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. *Lancet Oncol* 2015; **16(8)**: 919–927.
10. Renehan AG, Malcomson L, Emsley R *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* 2016; **17**(2):174–183.
11. Sanchez Loria F, Iseas S, O'Connor JM *et al.* Non-surgical management of rectal cancer: series of 68 cases, long follow up in two leading centres in Argentina. *Dig Liver Dis* 2016; **48(11)**: 1,372–1,377.
12. Lai C-L, Lai M-J, Wu C-C *et al.* Rectal cancer with complete clinical response after neoadjuvant chemoradiotherapy, surgery, or 'watch and wait.' *Int J Colorectal Dis* 2016; **31(2)**: 413–419.
13. Smith JD, Ruby JA, Goodman KA *et al.* Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. *Ann Surg* 2012; **256(6)**: 965–972.
14. Smith RK, Fry RD, Mahmoud NN, Paulson EC. Surveillance after neoadjuvant therapy in advanced rectal cancer with complete clinical response can have comparable outcomes to total mesorectal excision. *Int J Colorectal Dis* 2015; **30(6)**: 769–774.
15. Dalton RSJ, Velineni R, Osborne ME *et al.* A single-centre experience of chemoradiotherapy for rectal cancer: is there potential for nonoperative management? *Colorectal Dis* 2012; **14(5)**: 567–571.
16. Li J, Liu H, Yin J *et al.* Wait-and-see or radical surgery for rectal cancer patients with a clinical complete response after neoadjuvant chemoradiotherapy: a cohort study. *Oncotarget* 2015; **6(39)**: 42,354–42,361.
17. Habr-Gama A, Perez RO, Proscurshim I *et al.* Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy. *J Gastrointest Surg* 2006; **10(10)**: 1,319–1,329.
18. Habr-Gama A, Gama-Rodrigues J, São Julião GP *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* 2014; **88(4)**: 822–828.
19. Kong JC, Guerra GR, Warrier SK *et al.* Outcome and salvage surgery following 'watch and wait' for rectal cancer after neoadjuvant therapy: a systematic review. *Dis Colon Rectum* 2017; **60(3)**: 335–345.
20. Sammour T, Price BA, Krause KJ, Chang GJ. Nonoperative management or 'watch and wait' for rectal cancer with complete clinical response after neoadjuvant chemoradiotherapy: a critical appraisal. *Ann Surg Oncol* 2017; **24 (7)**: 1,904–1,915.
21. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6(7)**: e1000097.
22. Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Smith GD, Altman DG, eds. *Systematic Reviews in Health Care*. London: BMJ Publishing Group; 2001. pp. 285–312.
23. Nahas SC, Rizkallah Nahas CS, Sparapan Marques CF *et al.* Pathologic complete response in rectal cancer: can we detect it? Lessons learned from a proposed randomized trial of watch-and-wait treatment of rectal cancer. *Dis Colon Rectum* 2016; **59(4)**: 255–263.
24. Araujo ROC, Valadão M, Borges D *et al.* Nonoperative management of rectal cancer after chemoradiation opposed to resection after complete clinical response: a comparative study. *Eur J Surg Oncol* 2015; **41(11)**: 1,456–1,463.
25. Higgins JPT, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.1.0. London: Cochrane Collaboration; 2011.
26. Habr-Gama A, Sao Juliao GP, Gama-Rodrigues J *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* 2017; **60(6)**: 586–594.
27. Cancer Research UK Bowel cancer survival. 2018. www.cancerresearchuk.org/about-cancer/bowel-cancer/survival (cited February 2019).
28. Siegel RL, Miller KD, Fedewa SA *et al.* Colorectal cancer statistics, 2017. *CA Cancer J Clin* 2017; **67(3)**: 177–193.
29. Dossa F, Chesney TR, Acuna SA, Baxter NN. 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; **2(7)**: 501–513.