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, Journal-S@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 15–31% 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.7,10 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.21 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 ‘chemoradiation’ 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.22

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 (EH) 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 859 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 trial21 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 1–5 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.

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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, 58 of 248 patients (15.3%) had recurrent disease. In this group, 24 had local recurrence (65.2%), 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
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...
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 5  Follow-up intervals for patients with complete clinical response.

| Study                          | Follow-up intervals                                                                 |
|-------------------------------|-------------------------------------------------------------------------------------|
| Habr Gama et al, 20047        | 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, 20118             | Year 1: 4 × DRE, CEA, endoscopy and MRI; 2 × CT scanYears 2 and 3: 4 × CEA; 2 × DRE, endoscopy and MRI; 1 × CTEars 4 and 5: 2 × CEA, DRE, endoscopy and MRI; 1 × CT |
| Dalton et al, 201215          | EUA at 3 months and 1 yearInitially 6-monthly then yearly PET-CT and MRICEA monitoring |
| Smith et al, 201213           | 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, 201514           | 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, 201524          | Years 1 and 2: clinical, CEA and endoscopy 3-monthlyYears 3–5: clinical, CEA and endoscopy 6-monthly |
| Li et al, 201516              | 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, 2016122            | Years 1 and 2: clinical, CEA and endoscopy (selective biopsies) 3-monthlyYear 3 onwards: clinical, CEA and endoscopy (selective biopsies) 6-monthly; MRI or chest x-ray in the first 6 months then annually |
| Nahas et al, 201623           | 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.
A 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, Hahr-Gama et al have shown that the overall five-year survival for patients who had salvage treatment following recurrent disease was 65.3%, not far off the estimated five-year survival rate for rectal cancer of 60% and 67% in the UK and the United States, respectively.

Although Hahr-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. 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
| Patient no. | Study | Stage | Adjuvant chemotherapy | Recurrence Interval | Type | Salvage | Treatment | Outcome |
|------------|-------|-------|-----------------------|---------------------|------|---------|-----------|---------|
| 1          | Maas et al, 2011<sup>16</sup> | T3 N0 | Yes | 22 months | Local | Yes | TEMS | Alive |
| 2          | Dalton et al, 2012<sup>15</sup> | 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<sup>14</sup> | ? ? ? | 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<sup>7</sup> | ? ? 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<sup>13</sup> | 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 recurrence |
| 20         |           | 3 2 | ? | 14 months | Local | Yes | LAR | Alive |
| 21         | Araujo et al, 2015<sup>4</sup> | ? ? ? | 10 months | Distant | No | Chemotherapy | Alive |
| 22         |           | ? ? ? | 27 months | Distant | No | Chemotherapy | Alive |
| 23         |           | ? ? ? | 43 months | Distant | No | Chemotherapy | Died |
| 24         |           | ? ? ? | 16 months | Distant | No | Chemotherapy | Died |
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                                |
|-----------------------|----------------------------|-------------------------------------------------|----------------------------------------|
| Habr Gama et al, 2004 | +                          | +                                               | -                                      |
| Maas et al, 2011     | +                          | +                                               | -                                      |
| Dalton et al, 2012   | +                          | +                                               | -                                      |
| Smith et al, 2012    | +                          | -                                               | +                                      |
| Araujo et al, 2015   | +                          | -                                               | +                                      |
| Smith et al, 2015    | +                          | -                                               | +                                      |
| Li et al, 2015       | +                          | -                                               | +                                      |
| Lai et al, 2016      | -                          | +                                               | +                                      |
| Nahas et al, 2016    | +                          | +                                               | +                                      |

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