Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis

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Summary

Background Induction of a clinical complete response with chemoradiotherapy, followed by observation via a watch-and-wait approach, has emerged as a management option for patients with rectal cancer. We aimed to address the shortage of evidence regarding the safety of the watch-and-wait approach by comparing oncological outcomes between patients managed by watch and wait who achieved a clinical complete response and those who had surgical resection (standard care).

Methods Oncological Outcomes after Clinical Complete Response in Patients with Rectal Cancer (OnCoRe) was a propensity-score matched cohort analysis study, that included patients of all ages diagnosed with rectal adenocarcinoma without distant metastases who had received preoperative chemoradiotherapy (45 Gy in 25 daily fractions with concurrent fluoropyrimidine-based chemotherapy) at a tertiary cancer centre in Manchester, UK, between Jan 14, 2011, and April 15, 2013. Patients who had a clinical complete response were offered management with the watch-and-wait approach, and patients who did not have a complete clinical response were offered surgical resection if eligible. We also included patients with a clinical complete response managed by watch and wait between March 10, 2005, and Jan 21, 2015, across three neighbouring UK regional cancer centres, whose details were obtained through a registry. For comparative analyses, we derived one-to-one paired cohorts of watch and wait versus surgical resection using propensity-score matching (including T stage, age, and performance status). The primary endpoint was non-regrowth disease-free survival from the date that chemoradiotherapy was started, and secondary endpoints were overall survival, and colostomy-free survival. We used a conservative p value of less than 0·01 to indicate statistical significance in the comparative analyses.

Findings 259 patients were included in our Manchester tertiary cancer centre cohort, 228 of whom underwent surgical resection at referring hospitals and 31 of whom had a clinical complete response, managed by watch and wait. A further 98 patients were added to the watch-and-wait group via the registry. Of the 129 patients managed by watch and wait (median follow-up 33 months [IQR 19–43]), 44 (34%) had local regrowths (3-year actuarial rate 38% [95% CI 30–48]); 36 (88%) of 41 patients with non-metastatic local regrowths were salvaged. In the matched analyses (109 patients in each treatment group), no differences in 3-year non-regrowth disease-free survival were noted between watch and wait and surgical resection (88% [95% CI 75–94] with watch and wait *vs* 78% [63–87] with surgical resection; time-varying p=0·043). Similarly, no difference in 3-year overall survival was noted (96% [88–98] *vs* 87% [77–93]; time-varying p=0·024). By contrast, patients managed by watch and wait had significantly better 3-year colostomy-free survival than did those who had surgical resection (74% [95% CI 64–82] *vs* 47% [37–57]; hazard ratio 0·445 [95% CI 0·31–0·63; p<0·0001), with a 26% (95% CI 13–39) absolute difference in patients who avoided permanent colostomy at 3 years between treatment groups.

Interpretation A substantial proportion of patients with rectal cancer managed by watch and wait avoided major surgery and averted permanent colostomy without loss of oncological safety at 3 years. These findings should inform decision making at the outset of chemoradiotherapy.

Funding Bowel Disease Research Foundation.

Introduction

Surgical resection, based on the principles of total mesorectal excision,[1] is the mainstay of definitive treatment in patients with rectal cancer, but is associated with a 2–5% risk of perioperative mortality,[2,3] life-threatening early complications, such as anastomotic leak, which occurs in 3–11% of patients,[3,4] long-term bowel, bladder, and sexual dysfunction,[5,6] permanent colostomy, and risk of local recurrence. Preoperative radiotherapy with concurrent chemotherapy (often referred to as long-course chemoradiotherapy) followed by surgical resection improves local control in locally advanced cancers (mainly T3 and T4 tumours) and is recommended in clinical guidelines in many countries, such as the UK,[7] Europe,[8] Japan,[9] and the USA.[10] In patients with locally advanced rectal cancer who have

Research in context

Evidence before this study

In patients with rectal cancer, induction of a clinical complete response to chemoradiotherapy with subsequent watch and wait, and potential avoidance of major surgery, has emerged as a management option. About 15% of patients achieve a clinical complete response after widely used 45–50 Gy doses, but this proportion could be increased with high-dose chemoradiotherapy regimens. However, comparative analyses of oncological safety are scarce, hindering the introduction of this treatment pathway as standard care. We searched PubMed using the terms "complete clinical response" AND "rectal cancer" AND "organ preservation" for articles published in English between Jan 1, 2000, and Aug 27, 2015. We identified several overlapping articles from the Sao Paulo centre in Brazil, where the watch-and-wait policy was pioneered. Of these, the largest series was 99 patients managed by watch and wait. We identified five additional retrospective series, all with fewer than 35 patients managed by watch and wait. Two studies selected patients with a pathological complete response after surgical resection as the comparator; one study compared functional scores between watch and wait and surgical resection, but no study reported comparative permanent colostomy rates. A prospective single-arm study in 55 patients, using high-dose chemoradiotherapy (60 Gy), reported a uniquely high clinical complete response rate of 73%. We found no randomised controlled trials comparing watch and wait versus standard pathway surgical resection.

Added value of this study

The medical literature concludes that more data and long-term outcomes are needed before the strategy of watch and wait might be safely incorporated into clinical practice, as an alternative to major surgery in patients with rectal cancer. In the largest series done so far, our multicentre matched-treatment analysis adds three new findings: more than 60% (85 of 129) patients on the watch-and-wait protocol avoided major surgery; oncological safety is similar to standard-pathway surgical resection; and a quarter (26 of every 100 patients modelled with a 3-year colostomy-free survival of 47% after surgical resection) of patients on watch and wait could avoid a colostomy in the first 3 years of follow-up.

Implications of all the available evidence

Most of the evidence reported so far is from non-comparative single-arm studies. This is the first analysis to deliver sizeable comparative outputs that will inform decision making at the outset of long-course chemoradiotherapy. In this study, oncological safety was achieved in a real-world multicentre setting, thus supporting the establishment of watch and wait with avoidance of major surgery as standard care. Future trials comparing multilevel radiotherapy doses or a radio-sensitising approach to enhance clinical complete response rates, while assessing patient preferences and trade-offs, are worth pursuing.

surgical resection, permanent colostomy is needed in up to 50% of patients.[6] Compared with surgical resection alone, long-course chemoradiotherapy followed by surgical resection is associated with increased long-term morbidity and reduced quality of life.[11]

In the mid-2000s, reports[5] appeared of subgroups of patients with rectal cancer having complete treatment responses after chemoradiotherapy—initially as a pathological complete response and then as a clinical complete response. For patients with a clinical complete response, management by the so-called watch-and-wait approach, with potential avoidance of major surgery and subsequent organ preservation,[5] emerged as a treatment option. Habr-Gama and colleagues[12–16] in São Paulo, Brazil, reported several pioneering institutional-level series with clinical complete response ranging from 26% to 38%. In the largest series[14] of 99 patients managed by the watch-and-wait approach, 6% had local recurrence within the rectal lumen (hereafter referred to as local regrowths, as recommended by the 2014 Champalimaud consensus[17]). Habr-Gama and colleagues' series initially used a chemoradiotherapy regimen of 50·4 Gy (28 fractions) and fluorouracil plus leucovorin,[12–14,18] and later, a more intensive regimen of 54 Gy (32 fractions) and fluorouracil plus leucovorin (six cycles every 21 days).[15] Subsequent studies from centres using radiotherapy schedules of 45–50 Gy, doses widely used in most developed countries, reported clinical complete responses of about 15%, but the proportion of patients with subsequent local regrowth varied widely, ranging from 5% in a Dutch study[19] (one of 21 patients managed by watch and wait) to 19–60% in other series[20–23] (appendix p 1). These inconsistencies raised concerns about the oncological safety of the watch-and-wait approach.[24,25]

See Online for appendix

Appelt and colleagues[26] reported results of an observational study of 55 patients with T2 or T3 N0–N1 adenocarcinomas treated at a Danish tertiary cancer centre by high-dose chemoradiotherapy (60 Gy in 30 fractions) for 6 weeks. They reported that an extraordinarily high proportion (40 [73%] of 55 patients) achieved a clinical complete response. These patients were managed by watchful waiting, and at 1 year 15% of patients had local regrowths. However, in the absence of comparative analyses, the Danish investigators fell short of practice-changing conclusions, stating that "watchful waiting might be a safe alternative" to major surgery.[26] In parallel, the accompanying commentary concluded that "as a randomised controlled trial for watchful waiting is unlikely, analysis of a large prospective [comparative] registry will obtain the best evidence".[27] Two small studies[19,23] have compared oncological outcomes in patients managed by watch and wait versus

those with a reported pathological complete response after surgical resection, but these two categories (pathological complete response and clinical complete response) might not be equivalent (eg, clinicopathological concordance is low[28] and concordance of MRI complete regression with pathological complete response is only moderate[29]), and the analyses do not account for imbalance of key pretreatment confounding factors for survival, such as T stage. Furthermore, some centres advocate the avoidance of chemoradiotherapy (and its concomitant treatment-related morbidities) in most patients with rectal cancer, alternatively favouring meticulous surgical resection guided by discussion with the radiologist in the pretreatment multidisciplinary team meeting, using high-definition MRI, as supported by the MERCURY study.[30]

Since many treatment pathways are available, information is needed about the oncological outcomes following the watch-and-wait approach for patients with a clinical complete response after preoperative chemoradiotherapy. We aimed to address this evidence gap in the OnCoRe (Oncological Outcomes after Clinical Complete Response in Patients with Rectal Cancer) project. We assessed a large region-wide cohort of patients managed by watch and wait, quantifying rates of local regrowth and its subsequent management. Using a matched-treatment analysis, we aimed to compare oncological outcomes and permanent colostomy between patients managed by watch and wait and those who had surgical resection, using date of first chemoradiotherapy as the start time to inform initial decision making.

For more on the **UK National Bowel Cancer Audit project** see http://www.hscic.gov.uk/bowel

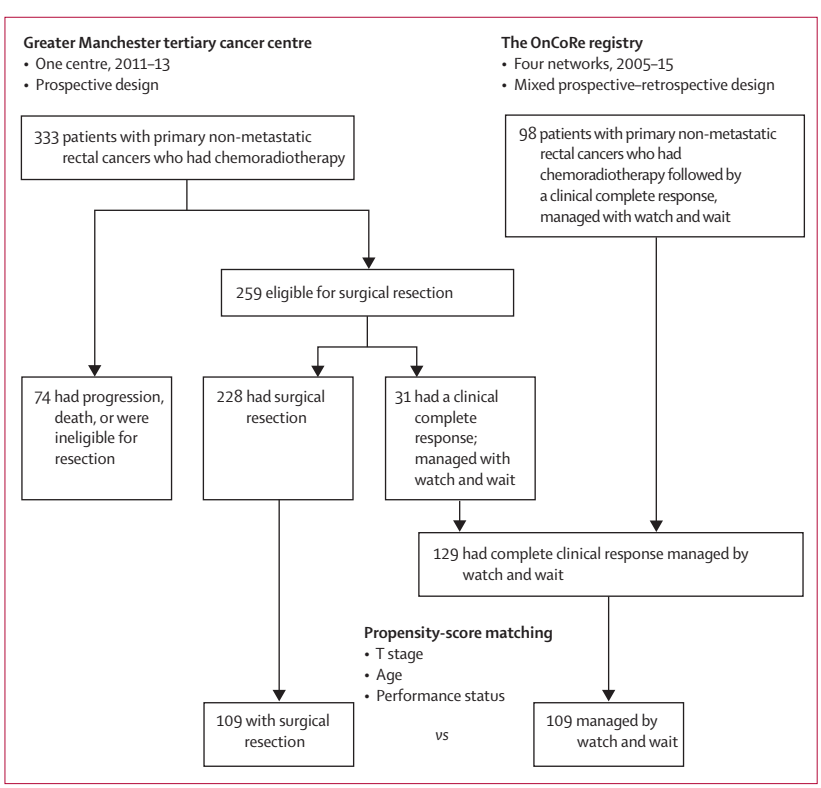

Figure 1: **Study flow diagram**

Methods

Study design and participants

OnCoRe was a propensity-score matched, observational analysis of real-world clinical practice across cancer treatment centres in four neighbouring regions in the UK (Greater Manchester, Lancashire and South Cumbria, Merseyside and Cheshire, and north Wales). We included patients of all ages with a new diagnosis of histologically confirmed rectal adenocarcinoma, without distant metastases (determined by chest, abdomen, and pelvic CT scan), who received preoperative chemoradiotherapy (standard protocol: 45 Gy in 25 daily fractions with concurrent fluoropyrimidine-based chemotherapy for 34 days) through the Christie National Health Service Foundation Trust (Greater Manchester), between Jan 14, 2011, and April 15, 2013. Patients were referred from 13 colorectal cancer regional multidisciplinary team meetings. Inclusion of patients into the study was approved by the Christie clinical audit committee and deemed not to require ethical approval or patient consent.

We also included all patients managed between March 10, 2005, and Jan 21, 2015, collected through the OnCoRe registry, which obtained data from patients with primary non-metastatic rectal cancers who had received chemoradiotherapy followed by a clinical complete response, and were managed by watch and wait. This registry covers Greater Manchester and three neighbouring cancer treatment centres (Lancashire and South Cumbria, Merseyside and Cheshire, and north Wales; figure 1). As this part of the study was also a clinical audit, patient consent was not required. Treatment and follow-up protocols were equivalent across the four regions.

Procedures

In 2010, the study coordinator (based at the Manchester centre) visited each multidisciplinary team to standardise data collection. Clinical, pathological, and treatment-related variables were collected as per the UK National Bowel Cancer Audit project. Pretreatment T and N stages were determined in all patients using MRI. Before treatment, data were collected for body-mass index (BMI), smoking, WHO performance status, baseline serum carcinoembryonic antigen (CEA) concentration, and index of multiple deprivation derived from patient-level postal codes.

All patients, including those in the registry, underwent MRI reassessment after completion of chemoradiotherapy. Those who had an incomplete clinical response were managed by surgical resection—referred to as the standard pathway, whereas those who were regarded by the multidisciplinary team to have a clinical complete response were offered watch and wait using a region-wide clinical protocol agreed in 2009. We used internationally

recognised criteria[31] to define clinical complete response—ie, absence of residual ulceration, stenosis, or mass within the rectum during digital rectal examination and endoscopic examination 8 weeks or more after chemoradiotherapy completion. Classification of clinical complete response required normal radiological imaging of the mesorectum and pelvis. For patients undergoing surgical resection, follow-up was in accordance with national guidelines.[7] For patients managed by watch and wait, a more intensive follow-up protocol was used, consisting of outpatient digital rectal examination, MRI (every 4–6 months in the first 2 years), examination under anaesthesia or endoscopy, CT scan of the chest, abdomen, and pelvis, and at least two CEA measurements in the first 2 years (appendix p 3–4). We also determined the actuarial rate of local regrowth, using the date of the multidisciplinary team decision to watch and wait as the start time. We combined regrowths of mucosal lesions together with the less common submucosal or mesorectum-only regrowth lesions when we calculated regrowths. We followed up patients until Aug 19, 2015.

Outcomes

Because equivalent comparisons of oncological safety between treatment groups were required, we needed to compare equivalent patterns of treatment failure between the groups. Thus, the primary endpoint was non-regrowth disease-free survival, which was the length of time after treatment until death (any cause), local pelvic recurrence, and distant metastasis—not including local regrowths (appendix, p 5). Central to our reasoning for excluding local regrowth events from the disease-free survival analysis is the distinction between local pelvic recurrence and local regrowth; local pelvic recurrence is an oncological treatment failure with a low chance of salvage, but local regrowth is eminently salvageable. Thus, patients following the standard pathway of surgical resection can develop local pelvic recurrence, but they cannot develop a local regrowth (with the rare exception of the primary tumour being transected during surgery), because the local site (the rectum) has been removed (appendix p 5). Secondary endpoints were overall survival and colostomy-free survival, which is an established indicator of reduced quality of life.[32] Events for colostomy-free survival were permanent colostomy and death (any cause).

Statistical analysis

This study was a real-world analysis and our sample size was therefore mainly determined by the number of patients whose data were included in the registry. We compared baseline and matched characteristics using standard tests for continuous variables (Kruskal-Wallis and Wilcoxon signed-rank tests, respectively) and categorical variables (χ^2 and McNemar tests, respectively).

To address the imbalance of potential confounders between the watch-and-wait and surgical resection groups, we matched treatment groups using propensity scores. The propensity score was estimated as the predicted probability of a patient being in the

	Clinical complete response and watch and wait (n=129)	Surgical resection (n=228)	p value
Cancer network			..
Greater Manchester	63 (49%)	228 (100%)	
Lancashire and South Cumbria	37 (29%)	0	
Merseyside and Cheshire	23 (18%)	0	
North Wales	6 (5%)	0	
Sex			0·077*
Men	97 (75%)	151 (66%)	
Women	32 (25%)	77 (34%)	
Age (years)	66·9 (60·8–73·2)	65·0 (57·2–71·6)	0·028†
BMI (kg/m²)	26·5 (23·7–29·3)	25·8 (23·4–29·1)	0·447†
IMD score	16·8 (9·7–37·7)	18·5 (9·7–35·7)	0·592†
Smoking status			0·527*
Never	42 (33%)	65 (29%)	
Ever	51 (40%)	104 (46%)	
Unknown	36 (28%)	59 (26%)	
Performance status			0·028*
0	81 (63%)	130 (57%)	
1	28 (22%)	78 (34%)	
2	9 (7%)	12 (5%)	
Unknown	11 (9%)	8 (4%)	
Pretreatment tumour (T) stage‡			0·001*
cT2	31 (24%)	24 (11%)	
cT3	90 (70%)	154 (68%)	
cT4	8 (6%)	50 (22%)	
Pretreatment nodal (N) status‡			0·003*
N0	45 (35%)	47 (21%)	
N1 and N2	84 (65%)	181 (79%)	
Histological grade¶			0·001*
Well differentiated	5 (4%)	15 (7%)	
Moderately differentiated	86 (67%)	104 (46%)	
Poorly differentiated	2 (2%)	14 (6%)	
Unknown	36 (28%)	95 (42%)	
Serum CEA (μg/L)	3·0 (3·0–4·0)	3·0 (3·0–6·5)	0·0003†
Height from anal verge (cm)	5·0 (4·0–8·0)	6·0 (4·0–8·0)	0·170†
Received radiotherapy dose (Gy)‖	45·5 (45·0–60·0)	44·9 (20·0–54·0)	0·007**
Chemotherapy received			0·834*
Yes	118 (91%)	210 (92%)	
No	11 (9%)	18 (8%)	
Chemotherapy regimen			..
Capecitabine only	106/118 (90%)	208/210 (99%)	
Capecitabine plus other	7/118 (6%)	2/210 (1%)	
Infusional fluorouracil	5/118 (4%)	0	

Data are number (%) and median (IQR), unless otherwise specified. Some totals do not add up to 100% due to rounding. BMI=body-mass index. IMD=Index of Multiple Deprivation. CEA= carcinoembryonic antigen. *χ^2 test or Fisher's exact test. †Kruskal-Wallis test. ‡According to the seventh edition of American Joint Committee on Cancer TNM staging. ¶Based on pretreatment biopsy sample. ‖Data are median (range). **Mean difference between treatment groups is –0·568 Gy; this was statistically significant, but we deemed such a small radiobiological dose difference clinically insignificant, and regarded the radiotherapy doses received to be clinically equivalent.

Table 1: **Patient clinical and demographic characteristics, by treatment group (unmatched)**

watch-and-wait group from a logistic regression model, considering pretreatment variables that were prognostic for non-regrowth disease-free survival. The propensity-score model included T stage, age, performance status (ordinal term), and an interaction term between age and performance status. We did diagnostic tests to assess the goodness of fit of our model and sensitivity analyses of the model assumptions. We then formed matched pairs between patients managed by watch and wait and those who had surgical resection using a one-to-one nearest neighbour calliper of width 0·1 (maximum allowable difference in propensity scores). Only patients matched with propensity scores were included in the time-to-event analyses (full details of principles, variable selection, sensitivity analyses, and paired analyses are shown in the appendix p 6–8).

We constructed Kaplan-Meier curves for all time-to-event endpoints, taking time zero as the date chemoradiotherapy was started, and determined survival estimates with 95% CIs. For the primary endpoint of non-regrowth disease-free survival, and secondary endpoint of overall survival, the hypothesis that watch and wait was non-inferior to the standard pathway in patients matched on equivalent confounding factors was tested with an a-priori margin of 12·5% survival difference, as used previously in equivalent scenarios.[33] If watch and wait seemed to be superior to the standard pathway, we undertook a log-rank test. To account for the observational study design, we used a conservative p value of less than 0·01 to suggest statistical significance in the comparative analyses between treatment groups; we used a p value of less than 0·05 to suggest statistical significance in the logistic regression models informing the propensity-scoring model and in determination of prognosticators for the development of local regrowths.

We used Cox models to assess between-group differences in non-regrowth disease-free survival and overall survival. To take account of the variations in times from start of treatment to either date of surgical resection or date of multidisciplinary team decision for watch and wait, treatment was handled as a time-varying exposure. We included the propensity score, used as the matching variable, as a covariate. We tested the assumptions of proportionality in our Cox models using the Schoenfeld residual test. This assumption was not true for the time-to-colostomy analysis, so we did sensitivity analyses using Royston-Parmar flexible parametric models.[34] We also did sensitivity analyses to test for treatment differences between centres (eg, duration of chemoradiotherapy, and the time to treatment) and restricted our analyses to patients treated within the same time period (treatment start dates between Jan 1, 2011, and Dec 31, 2013) for watch and wait and surgical resection. We also assessed adherence to follow-up protocols in the watch-and-wait group. We did all computations using Stata version 12.1.

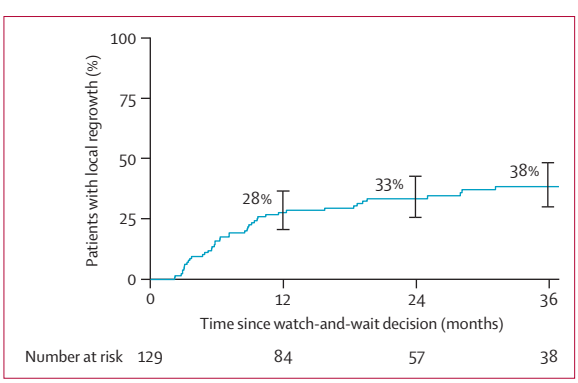

***Figure 2*: Actuarial local regrowth rates in the 129 patients with a clinical complete response managed by watch and wait**
Percentages shown on the graph are actuarial rates at 12, 24, and 36 months after multidisciplinary team decision to watch and wait was made; vertical lines show 95% CI.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author, and LM and RE, had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 14, 2011, and April 15, 2013, 259 patients were included in our Greater Manchester tertiary cancer centre cohort and were eligible for surgical resection (figure 1), 228 of whom underwent surgical resection after chemoradiotherapy (ie, standard pathway). 31 patients were regarded by the multidisciplinary team to have a clinical complete response and offered watch and wait, and a further 98 patients with a clinical complete response were included through the OnCoRe registry, resulting in a total of 129 patients managed with watch and wait in our analysis (figure 1; numbers per centre in appendix p 2). Eight (6%) patients received off-protocol adjuvant chemotherapy as part of the watch-and-wait treatment pathway.

Compared with all patients who received surgical resection, patients managed by watch and wait had tumours that were at an earlier pretreatment T stage (p=0·001), were less likely to have nodal involvement (p=0·003), rarely had poorly differentiated tumours (p=0·001), and had lower mean serum CEA concentrations (p=0·0003; table 1). Radiotherapy doses received were clinically equivalent between treatment groups; 11 (9%) of 129 patients with a clinical complete response did not receive concurrent chemotherapy (for medical reasons, typically existing cardiovascular disease).

After a median follow-up of 33 months (IQR 19–43) from start of chemoradiotherapy, 44 (34%) of the 129 patients with a clinical complete response managed by watch and wait had local regrowths, which

corresponded to a 3-year actuarial rate of 38% (95% CI 30–48; figure 2). 42 (95%) of these 44 regrowths in patients managed by watch and wait were mucosal lesions; two (5%) had submucosal or mesorectal lesions. The following factors affected the risk of developing local regrowths: ever-smoker status (p=0·012) and male sex (p=0·044), but not age, BMI, index of multiple deprivation, performance status, T stage and N stage, baseline serum CEA concentration, or whether concurrent chemotherapy was used (appendix p 9). We noted some evidence of an inverse U-shaped relation between increasing quartiles of time from radiotherapy to multidisciplinary team decision to watch and wait and the subsequent development of local regrowths (appendix p 10).

Of the 41 patients managed by watch and wait with non-metastatic local regrowths, 36 (88%) had salvage therapy: 31 (76%) of 41 underwent subsequent salvage surgery (30 with R0 resections and one with an R1 resection); and five (12%) patients underwent Papillon contact radiotherapy (table 2). Of the 31 patients who underwent subsequent salvage surgery, the post-salvage pathological T and N stages were as follows: five (16%) with ypT1, ten (32%) with ypT2, 16 (52%) with ypT3; and 24 (77%) with ypN0, six (19%) with ypN1, and one (3%) with ypN2.

We derived one-to-one paired cohorts (109 patients in each group) for watch and wait versus surgical resection. These cohorts were well matched for key confounders—ie, age, performance status, and T stage (table 3). After matching, small differences remained for other characteristics not included in the propensity-score matching (appendix p 11). We compared included patients with those who were excluded (20 patients managed by watch and wait and 119 patients with surgical resection) from the matched analysis (appendix p 12–13), and noted that the matched watch-and-wait patients were representative of the whole watch-and-wait cohort. There was wide within-group variation in the time from start of chemoradiotherapy to the multidisciplinary team decision for watch and wait (median 15·6 weeks [IQR 14–18]). As expected, this time was about 2 weeks shorter than the median time from chemoradiotherapy to surgical resection (17·7 weeks [IQR 16–20]; appendix p 14). Duration of chemoradiotherapy and times from chemoradiotherapy to multidisciplinary team watch-and-wait decision did not differ between cancer centres (appendix p 15).

After a median follow-up of 33 months (IQR 24–42) from start of chemoradiotherapy, 40 (18%) of the 218 matched patients had non-regrowth disease events or died. The 3-year non-regrowth disease-free survival for all patients was 83% (95% CI 76–88): 88% (75–94) for the watch-and-wait group and 78% (63–87) for the surgical resection group (log-rank p=0·022; figure 3A). This finding did not violate, and indeed was in the opposite direction to, the a-priori non-inferiority margin.

We tested whether watch and wait was superior to surgical resection in the time-varying Cox model, conditional on the propensity score, and confirmed the difference was non-significant (time-varying p=0·043) at the a-priori p-value cutoff of 0·01. We did sensitivity analyses restricting our treatment groups to the same overlapping time period (2011–13), which included 153 matched patients (76 pairs) derived from 84 patients managed by watch and wait and 228 patients managed by surgical resection, and noted no differences between

	Luminal regrowth only (n=41)	Synchronous luminal regrowth and distant metastasis (n=3)	Distant metastases only (n=4)
Salvage treatments for local regrowth	36 (88%)	1 (33%)	0
Rectal surgery			
Abdominoperineal resection	20 (49%)	1 (33%)*	0
Anterior resection	8 (20%)	0	0
Hartmann's resection	2 (5%)†	0	0
Subtotal colectomy	1 (2%)	0	0
Contact (Papillon) radiotherapy[35]	5 (12%)	0	0
Other treatments	5 (12%)	2 (67%)	4 (100%)
Surgery for distant disease			
Liver resection	0	0	2 (50%)
Inguinal lymphadenectomy	0	0	1 (25%)
Palliative chemotherapy	4 (10%)‡	2 (67%)	1 (25%)
Palliative treatment (no chemo)	1 (2%)§	0	0

Data are number (%). *Plus liver resection. †R0 in one patient; R1 in one patient. ‡Patient choice in two patients; unfit for major surgery in two patients (one patient with advanced lung cancer; one patient with several comorbidities). §Patient unsuitable for chemotherapy or major resection because they had chronic obstructive pulmonary disease, recurrent chest infections, and hypertension.

Table 2: **Subsequent first-disease event and treatment in the 129 patients with a clinical complete response managed by watch and wait**

	Clinical complete response and watch and wait (n=109)	Surgical resection (n=109)	p value
Age (years)	66·4 (60·6–73·2)	67·3 (60·6–72·7)	0·657*
Performance status			0·401†
0	76 (70%)	79 (72%)	
1	25 (23%)	26 (24%)	
2	8 (7%)	4 (4%)	
Pretreatment T stage‡			0·595†
cT2	24 (22%)	20 (18%)	
cT3	77 (71%)	83 (76%)	
cT4	8 (7%)	6 (6%)	

Data are median (IQR) or number (%). *Wilcoxon signed-rank test. †For 2 × N categorical data, where N>2, we used conditional logistic regression on paired data. ‡According to the seventh edition of American Joint Committee on Cancer TNM staging.

Table 3: **Key patient and tumour prognosticators by treatment group after propensity-score matching**

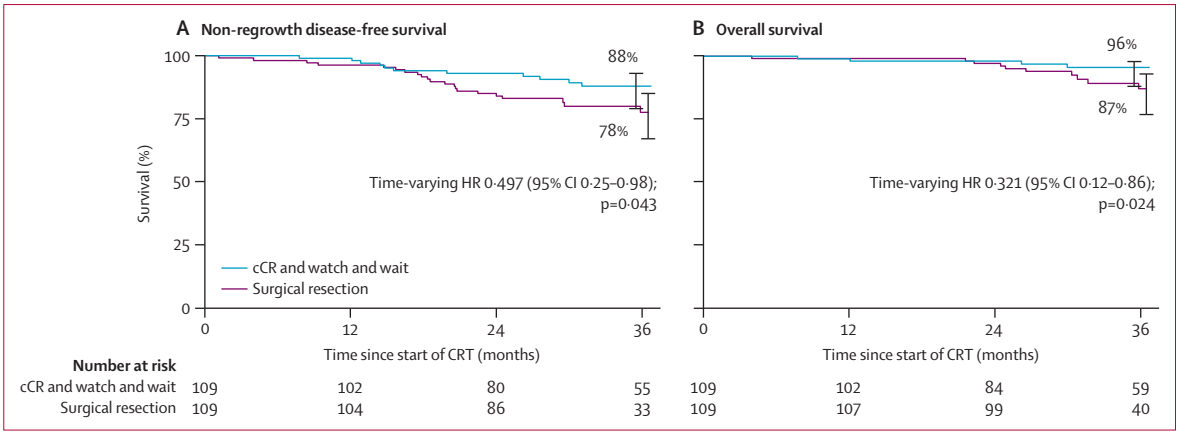

***Figure 3*: Non-regrowth disease-free survival (A) and overall survival (B) in the 218 patients in the matched analysis cohort**
Percentages shown on the graphs are 3-year non-regrowth disease-free survival (A) and 3-year overall survival (B); vertical lines show 95% CIs. We included propensity score as a covariate in the models. cCR=clinical complete response. CRT=chemoradiotherapy. HR=hazard ratio.

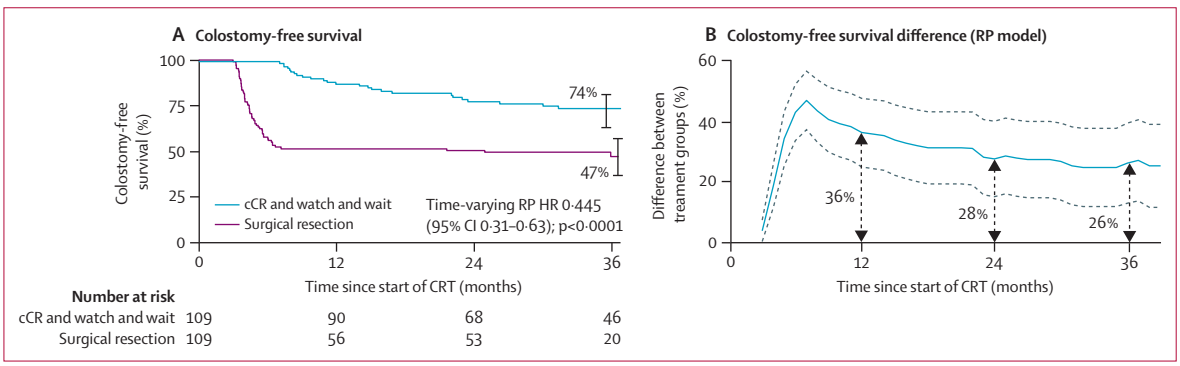

***Figure 4*: Colostomy-free survival for the 218 patients in the matched analysis cohort**
(A) Kaplan-Meier curves of colostomy-free survival with effect modelled in a time-varying covariate RP model; percentages shown on the graph are 3-year colostomy-free survival; vertical lines show 95% CIs. (B) Differences in colostomy-free survival between the two treatment groups with time, based on the RP model; percentages show difference at 12, 24, and 36 months and dotted curves show 95% CI. We included propensity score as a covariate in the models. cCR=clinical complete response. CRT=chemoradiotherapy. HR=hazard ratio based on the time-varying covariate RP model. RP=Royston-Parmar.

groups (3-year non-regrowth disease-free survival was 83% [95% CI 71–90] in the watch-and-wait group *vs* 76% [66–85] in the surgical resection group; log-rank p=0·069; time-varying p=0·137).

Of the 218 matched patients, 21 (10%) died during follow-up. 3-year overall survival was 96% (95% CI 88–98) in the watch-and-wait group versus 87% (77–93) for the surgical resection group (log-rank p=0·015; figure 3B). This result did not violate the a-priori non-inferiority margin. The time-varying Cox model confirmed the difference was non-significant (time-varying p=0·024).

In the matched analysis for watch and wait versus surgical resection, 3-year colostomy-free survival was 74% (95% CI 64–82) and 47% (37–57; log-rank p<0·0001), respectively. In the time-varying Cox model, this difference was significant (p=0·001; figure 4A). However, the assumptions of proportionality were violated (p=0·0043), so as an alternative and preferred approach, we used a Royston-Parmar model and found that the difference remained significant (HR 0·445 [95% CI 0·31–0·63]; p<0·0001). This model afforded the opportunity to test for differences in colostomy-free survival over time. Watch and wait was associated with an absolute difference in patients who avoided permanent colostomy of 36% (95% CI 25–48) at 1 year, 28% (15–40) at 2 years, and 26% (13–39) at 3 years, compared with surgical resection (figure 4B).

Adherence to the region-wide protocol was tested by sampling 40 patients, 20 assigned to watch and wait and 20 assigned to surgical resection, with at least 2 years of follow-up. 16 (80%) of 20 patients managed by watch and wait had at least four MR scans in the first 2 years; 12 (60%) had at least two examinations under anaesthetic or endoscopic examinations in the first 2 years; and 19 (95%) had at least two CT scans in the first 2 years. Of 20 patients undergoing surgical resection, 17 (85%) had at least two CT scans in the first 2 years.

Discussion

In our real-world, multicentre cohort of patients with rectal cancer managed by watch and wait after clinical

complete response, 34% of patients developed local regrowths, mainly in the first 2 years, with most being salvaged. This meant that more than 60% avoided major surgery (ie, organ preservation was maintained), and a quarter could avoid permanent colostomy, without loss of oncological safety in these first 3 years. These findings can inform the decision-making process at the initial treatment stage and support the establishment of the watch-and-wait pathway as standard care.

In the medical literature, the proportion of patients with rectal cancer who develop local regrowths after watch-and-wait management for clinical complete response varies from 5% to 60%.[14,19–23,26] This variation might be a result of different follow-up durations, surveillance intensity, and definitions of time zero in analyses. For example, studies from the São Paulo group[13,14] reported local regrowth rates of less than 10% with a median of 57 months of follow-up, based only on patients who were disease free after an initial 12 months, but in subsequent analyses[15] that included patients with regrowths before and after 12 months, the overall local regrowth rate was 26% with a median of 56 months of follow-up. Data for outcomes after local regrowth are scarce. Four studies have reported numbers of patients who underwent subsequent treatments, ranging from no patients undergoing salvage resection,[21] to 93% in the São Paulo series,[16] to all patients in two studies.[20,23] In our study, 88% of patients in the watch-and-wait group with non-metastatic local regrowths had salvage treatment, consisting of either surgery or Papillon contact radiotherapy. All but two of these 36 patients had mucosal (regrowth) lesions. Compared with surgical resection on a standard pathway, it is unclear whether salvage surgery is technically more challenging (because radiation-related fibrosis might be more established) and whether surgery-related morbidity is increased.

We specifically termed a new oncological endpoint, non-regrowth disease-free survival, arguing that the oncological safety of watch and wait versus surgical resection should be judged by comparing equivalent patterns of treatment failure, thus excluding local regrowths from the disease-free survival analysis. Our overall 3-year non-regrowth disease-free survival rate was 83%. This result is similar to the disease-free survival rates reported in other series—eg, at 5 years disease-free survival was 85% in one study,[14] and at 2 years was 89%[19] and 88%[23] in other series. We suspect that the investigators in these studies excluded local regrowths as disease events, but did not specifically state this. Using non-regrowth disease-free survival and overall survival as endpoints, we showed that management of patients with clinical complete response by watch and wait was oncologically safe. Indeed, our data suggested that patients with a clinical complete response managed by watch and wait survived, on average, for longer (although not significantly so) than those managed by standard surgical resection. Speculation that the cancers of patients with a complete clinical response after chemoradiotherapy (managed by watch and wait) are biologically good tumours with a favourable survival prognosis, equivalent to that reported after complete pathological response in rectal tumours, is tempting.[36] However, assessment of the associations between complete treatment response and prognosis in breast cancer shows that the expected correlation with survival does not universally hold,[37] because factors that determine treatment response might not be those that determine ultimate survival, and vice versa. In turn, this vindicates the choice to use prognostic factors to build our propensity-scoring model rather than factors that only predict clinical complete response.

To our knowledge, this is the first time that colostomy-free survival has been compared between patients managed by watch and wait and those on the standard pathway care. Our modelling suggested that a quarter of patients in the watch-and-wait group could avoid colostomy. Results of a national (UK) survey[32] of colorectal cancer survivors, using patient-reported outcome measures, suggest that colostomy is a clear indicator for reduced quality of life, reporting that the presence of a stoma significantly reduced the proportion of individuals reporting perfect health on the EQ-5D questionnaire, and was associated with higher levels of social distress. For patients with a clinical complete response managed by watch and wait, our data revealed two additional findings. Firstly, about two-thirds of tumours were node positive as assessed by pretreatment MRI, but this did not affect subsequent endpoints, by contrast with some commentaries that have suggested that this feature is a contraindication to watch and wait.[24] Secondly, 9% (11 of 129) watch-and-wait patients did not receive preoperative chemotherapy, suggesting that concurrent chemotherapy per se is not needed to achieve a complete clinical response in all patients, and its absence did not affect study endpoints (3-year non-regrowth disease-free survival among patients without preoperative chemotherapy in the watch-and-wait group was 83% [95% CI 45–95]).

The study has some limitations. First, with a median of 33 months, follow-up was relatively short. For the assessment of local regrowth, most events will be captured within the first 2 years, but locoregional and distant metastatic events might manifest later. Second, we introduced a region-wide follow-up protocol in the patients managed by watch and wait—adherence was moderately good but not complete, representative of real-world off-trial clinical practice. Third, as a patient population following a new treatment pathway, bias—in terms of over-investigation or over-management of patients with disorders or treatments of interest to the treating team—is a risk in patients with a clinical complete response managed by watch and wait, favouring an improvement in general health status. This finding might partly explain the marginally better (but statistically

insignificant) survival in patients managed by watch and wait. Finally, there was an absence of post-treatment functional data. In a Dutch series[19] of 21 patients managed by watch and wait, the data supported the hypothesis that post-treatment function is better in patients managed by watch and wait than in those who have radical surgery. This finding needs to be replicated in larger series.

Our study has several strengths. First, this was the largest reported cohort outside of the São Paulo series[12–15] to be assessed for outcomes after watch and wait for rectal cancer. Our chemoradiotherapy regimens and imaging protocols are similar to those widely used in clinical practice in most developed countries. Second, this cohort is representative of real-world clinical practice, rather than specialist institutional practice, and therefore was generalisable across several treatment centres. Third, we used a standardised definition of clinical complete response. Fourth, we addressed specific challenges with our methods (eg, between-treatment group confounder imbalance, time-varying effects of decision to surgical resection or watch and wait, and the need for a between-treatment-group equivalent survival endpoint for oncological safety assessment), previously incompletely addressed by other investigators in this new clinical setting. Because assessment of oncological safety requires examination of survival outcomes, comparator groups need to be matched for confounding factors, as done in our matched analysis. The choice of the time-varying modelling was vindicated because, in clinical practice, variation in time to surgical resection and time to the watch-and-wait decision is substantial.

Ideally, a watch-and-wait policy after clinical complete response in patients with rectal cancer should be tested against standard total mesorectal excision in a randomised controlled trial assessing both oncological (as an inferiority design) and functional results. However, as pointed out by Maas and colleagues[19] and echoed in a commentary,[27] for many patients who have a clinical complete response, even when explicitly informed about the experimental nature of the watch-and-wait approach, express a strong preference not to undergo major surgery. The next best level of evidence is likely to come through well documented, prospective studies, applying appropriate analytical methods to reduce confounding and biases, in large datasets such as the initiative of the International Watch and Wait database.[27]

For the **International Watch and Wait database** see http://www.iwwd.org/

Our study's findings have shown that continued intraluminal disease control with avoidance of radical surgery might be affected by the time between long-course chemoradiotherapy and the multidisciplinary team decision to watch and wait, for which we saw an inverted U-shaped association (appenidx p 10). We postulate that patients with an early complete response (<14 weeks after start of chemoradiotherapy) and those who take much longer to reach confirmation of clinical complete response (>24 weeks after start of chemoradiotherapy) have fewer regrowths than do those for whom 14–24 weeks lapses between chemoradiotherapy and the watch-and-wait decision. The observed favourable outcome in patients who take more than 24 weeks to achieve a clinical complete response supports the ongoing observational study assessing deferral of surgery (NCT01037049), which includes the promotion of greater refinement of pretreatment T staging (eg, T3a–d) and standardisation of MR-defined tumour regression grading.[38] Finally, the proportion of patients with a clinical complete response after widely used radiotherapy regimens of 45 Gy is 10–15%, whereas high-dose chemoradiotherapy can enhance this proportion to greater than 50%.[15,26] If these high clinical complete response rates can be replicated with acceptable toxic side-effects, both strategies seem to be equivalent in achieving long-term, sustained, complete clinical response. These observations point to a need to design comparative multilevel radiotherapy dose or radio-sensitising trials. These and other future studies need to assess patient preferences and how individuals assess the trade-off between different attributes of treatment and oncological and functional outcome.

Contributors

AGR, AB, NS, MPS, MSW, and STO'D were responsible for the study concept. AGR and RE contributed to the study design. AGR did the scientific literature search, and collated and summarised the identified relevant studies. AGR, SG, AM, ASM, PSR, SS, AB, MPS, MSW, NS, and STO'D were involved in data collection. AGR and LM were responsible for data collection. AGR, LM, and RE analysed the data and wrote the initial draft; all authors contributed to data interpretation and editing, and approved the final draft of the report.

Declaration of interests

AGR reports grants and personal fees from Sanofi Pasteur MPS, outside the submitted work. All other authors declare no competing interests.

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