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Watchful Waiting: A prospective study of chemoradiotherapy as definitive treatment of low rectal cancer

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Summary

Background

Abdominoperineal resection is a standard treatment for patients with distal T2-3 rectal cancers. This is an extensive and mutilating procedure, and, consequently, alternative treatment strategies are actively being explored. This prospective trial studied high dose radiotherapy with concomitant chemotherapy for non-surgical management of low rectal cancer.

Methods

Patients with primary, resectable T2-3, N0-1 adenocarcinoma in the lower 6 cm of the rectum were treated with chemoradiotherapy: 60 Gy/30 fractions to the tumour, 50 Gy/30 fractions to elective lymph nodes, 5 Gy endorectal brachytherapy boost, and daily peroral tegafur-uracil 300 mg/m^2. Patients with complete clinical tumour regression, negative tumour site biopsies, and no nodal or distant metastases on CT and MRI 6 weeks after treatment were allocated to observation ("watchful waiting"). All other patients were referred for standard surgery. Patients under observation were followed closely, with surgical resection in case of local recurrence. Primary trial endpoint was local recurrence in the observation group within the first year, assessed using clinical examinations, endoscopies with biopsies and PET-CT. Quality of life (QoL) and functional outcome in the observation group was evaluated using the EORTC colorectal cancer specific QoL module (QLQ-CR29) and physician-evaluated Jorge-Wexner score. Analyses were based on data for all patients correctly enrolled on trial. This study is registered with ClinicalTrials.gov, identification number NCT00952926. Enrolment is closed, but follow-up is ongoing with regards to secondary trial endpoints.

Findings

51 patients were enrolled and fulfilled the inclusion criteria; 40 patients demonstrated clinical complete response and were allocated to observation. Local recurrence in the observation group at one year was 15•5% (95% CI 3•3%–26•3%), translating into 58% (95% CI 41%–73%) of all treated patients with local control with chemoradiotherapy alone two years after treatment. Current median follow-up with respect to local recurrence in the observation group is 23•9 months (IQR 15•3 – 31•0 months). Patients with local recurrence all underwent standard surgical resection. The most common acute grade 3 adverse event was diarrhea, which affected 4/51 (8%) of patients. Sphincter function in the observation group was excellent, with 18/25 (72%) of patients at one year and 11/16 (69%) at two years reporting no faecal incontinence at all, and median Jorge-Wexner score 0 at all time points. The most common late toxicity was bleeding from the rectal mucosa; grade 3 bleeding was found in 2/30 (7%) and 1/17 (6%) of patients at one and two years, respectively. No unexpected serious adverse reactions or treatment related deaths were seen.

Interpretation

High dose chemoradiotherapy allowed a high proportion of patients to avoid permanent colostomy. The results indicate that this treatment strategy may represent a safe alternative to abdominoperineal resection for patients with distal rectal cancer.

Funding

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Background

Cancer in the distal part of the rectum constitutes a distinct therapeutic challenge. Very small tumours can often be managed with local excision,[1,2] but larger tumours are mainly treated with abdominoperineal resection (APR) and a permanent stoma or ultra-low anastomosis, both of which may have serious consequences.[3-6]

Preoperative radiotherapy improves local control, even with optimal surgical techniques,[7,8] and is thus employed for a considerable proportion of patients. If neoadjuvant chemoradiotherapy (CRT) with delayed surgery is used, as is the case in many countries, most patients will present with some degree of tumour regression at the time of surgery. A group of patients will have complete response to the neoadjuvant therapy, i.e. no remaining tumour cells in the pathological specimen.[9] Considerable interest has therefore risen as to whether a faction of patients can be identified for whom tumour control can be achieved with CRT alone. A small number of studies, mainly retrospective, have reported encouraging outcomes with careful patient selection and close follow-up (watchful waiting),[10-12] although others have been unable to reproduce these results.[13] If this approach can be realised in prospective series, then it represents an attractive alternative to extensive surgery and permanent stoma for patients with distal rectal cancer.[14] Important open questions, however, concern the fraction of patients for whom this will be an option as well as the safety of salvage surgery in case of local tumour recurrence after clinical complete response.

The current prospective observational trial was thus designed to determine the proportion of patients with low rectal cancer who can be managed with high dose radiotherapy and concomitant chemotherapy alone. Furthermore, we wanted to examine the overall outcome (survival and disease-free survival) for a cohort of patients where watchful waiting constituted a central part of the general treatment strategy.

Methods

Study design and participants

This was a prospective observational trial. Patients were referred from surgical departments nationwide but were treated in a single, tertiary Danish cancer centre and enrolled in the study prior to initiation of CRT. See Figure a1 (Appendix 1, supplementary material online only) for an overview of the treatment and assessment process. Patients who were candidates for the trial had primary resectable T2-3 adenocarcinoma of the rectum within six centimetre of the anal verge, i.e. they were patients who were planned for an abdominoperineal resection or an ultra-low resection of the rectum. Additional eligibility criteria included performance status as well as liver, kidney, and bone-marrow function allowing for long-course CRT, age ≥18 years, and no distant metastases. Normal bone marrow function was defined as leukocytes ≥ 3 x 10^9/liter, thrombocytes ≥ 100x10^9/liter; normal liver function as alanine transaminase < 2.5 x upper normal level (UNL), bilirubin < 2.5 x UNL; and normal renal function as serum creatinine < 1.5 x UNL. The initial trial protocol specified no lymph node involvement (N0, all lymph nodes <5mm), but early clinical experience revealed a substantial proportion of patients with small tumours in the distal part of the rectum where negative lymph node status could not be definitively determined on magnetic resonance imaging (MRI) or with a limited number (1-3) of lymph nodes in close proximity to the primary tumour. Thus a protocol amendment allowing for enrolment of these (N1) patients was approved by the ethics committee shortly after trial initiation (after enrolment of five patients). Baseline workup required pelvic MRI, transrectal ultrasound imaging, computed tomography (CT) of the thorax and abdomen, whole body PET-CT, as well as endoscopy (with biopsy) and clinical examination. The trial protocol was approved by the Regional Scientific Ethical Committee for Southern Denmark (protocol ID S-20090063), and all patients provided oral and written informed consent for experimental treatment.

Procedures

Chemoradiotherapy

Treatment consisted of long-course radiotherapy with concomitant chemotherapy and brachytherapy tumour boost. External beam radiotherapy was 60 Gy in 30 fractions to the tumour and 50 Gy in 30 fractions to the elective lymph node volumes, delivered once daily on weekdays. All patients were treated with intensity modulated radiotherapy (IMRT) using a concomitant boost technique; technical details and volume definitions can be found in Appendix 2 (supplementary material). Chemotherapy was peroral tegafur-uracil (UFT) 300 mg/m^2 daily on radiotherapy treatment days; pausation or discontinuation was allowed in case of excess toxicity, at the discretion of the treating physician, but no dose reductions were allowed. An endorectal brachytherapy tumour boost of 5 Gy was delivered in the final week of external beam treatment (see Appendix 2 for details). Acute toxicity was recorded by treating physician weekly during treatment. Patients were to be withdrawn from the study in case of distant metastases detected during the treatment course, less than 30 Gy (50%) of the planned radiation dose delivered, or less than 50% of the planned UFT dose given.

Response assessment

Endoscopies with selected site biopsies of the tumour were performed at baseline, throughout the course of treatment (weeks two, four and six) and six weeks after the end of treatment. Ink tattoos surrounding the tumour were placed in the rectal wall at baseline (see Figure a2, Appendix 3), to allow for continuous assessment of tumour regression. At least four biopsies were performed within the ink-marked area at 3, 6, 9 and 12 o'clock, and if necessary at points of interest. Final evaluation of tumour response to CRT was six weeks after treatment completion. Patients were allocated to observation ("watchful waiting") if they had no signs of remaining disease. This decision was based on clinical examination, endoscopy with negative biopsies from the primary tumour site and pelvic MRI. Clinical complete response on endoscopy was defined as a small, white scar in the rectal wall or a superficial erosion/ulceration without palpable tumour. If an ulcer or erosion persisted, additional biopsies were taken at the edge (i.e. the potentially invasive front). Figure a2 in Appendix 3 contains representative examples of response as seen on endoscopy. MRI was primarily used to evaluate the status of regional lymph nodes after CRT: Suspect lymph nodes were considered malignant if their diameter was >5mm; and no heterogeneity criteria were used. Primary tumour regression on MRI, while available, was not part of the formal response assessment, and no scoring of imaging response (e.g. "magnetic resonance imaging tumour regression grade", mrTRG, or similar[15]) was reported. No patient was allocated to surgery solely due to unclear response of primary tumour on MRI. Additionally, CT (not PET-CT) was used to screen for distant metastases. See Appendix 3 for further details on the response assessment procedure. All patients with incomplete response were referred for surgery.

Follow-up: Patients allocated to observation

Patients in the observation group were followed with clinical examinations and endoscopies every two months for the first year, every three months the second year, half-yearly the third year, and after four and five years. Biopsies were performed if suspicious lesions in the rectal wall were detected at endoscopy; generally, at least two biopsies were taken from or near the centre of the lesion. PET-CET was performed thrice the first year, twice the second year, and yearly thereafter. No adjuvant chemotherapy was given. Patients with local tumour recurrence were referred for surgical treatment; distant disease progression was evaluated and treated on an individual patient basis.

Late toxicity and functional outcome in the observation group was primarily evaluated using patient-reported Quality-of-Life (QoL). The European Organisation for Research and Treatment of Cancer (EORTC) colorectal cancer specific QoL module (QLQ-CR29)[16] was completed prior to and at the end of CRT, at six

months and twelve months in the follow-up period, and yearly thereafter. Physician-evaluated faecal incontinence using the Jorge-Wexner scale[17] was recorded at every visit. Bleeding from the rectal mucosa was scored retrospectively from patient charts using the Common Terminology Criteria for Adverse Events (CTCAE) v4•0.

Follow-up: Patients referred to early surgery

Patients referred for surgery due to incomplete tumour response were recommended full excision. Patients refusing surgery at this point left the trial. Adjuvant chemotherapy was given in case of negative prognostic features in the surgical specimen (T4 tumours, R1 resection, venous and/or perineural invasion, poor differentiation, lymph node metastases), as specified in the national Danish guidelines.[18] Patients were followed after surgery according to the standards of the treating surgical department.

Early and salvage surgery

Surgery was performed according to national Danish guidelines for colorectal cancer surgery.[18] Salvage surgery in case of local tumour recurrence in the observation group was based on the same principles as primary rectal cancer surgery. Evaluation of the pathological specimens included ypTpN grading, resection margin involvement (positive if ≤1 mm distance from tumour to margin), and tumour regression grade (TRG) according to the Mandard scale.[19] Length of hospital stay and post-operative complications were recorded.

Outcomes

Primary trial outcome was local tumour recurrence one year after allocation to the observation group. Secondary endpoints were cumulative local recurrence, distant metastases, and overall survival (OS), all in the full trial population. Data from all patients correctly enrolled on trial were used for analyses for primary and secondary outcomes.

Statistical analysis

The trial was planned with a two-phase design (based on a modified Simon's two stage approach):[20] A local recurrence rate of ≤30% was deemed clinically acceptable, and the initial phase of 30 patients thus required fewer than 16 local recurrences in the first year of follow-up. The second phase planned for a total number of 100 patients, in order to establish a 20 percentage point width of the 95% confidence interval (CI) for the primary outcome measure.

Cumulative incidences of local recurrence and distant metastases were calculated using the Kaplan-Meier estimator. Patients were recorded as failed locally when biopsies confirmed tumour recurrence in the rectal wall and were censored in case of non-cancer death or new primary cancer, but not if distant metastases occurred. Time to local recurrence was calculated from allocation to observation. Distant metastases were all biopsy confirmed; patients were censored in case of non-cancer death or new primary cancer, but not at local recurrence in the observation group. Time to distant metastases was calculated from date of trial enrolment. Median follow-up times were calculated using the Kaplan-Meier estimator of potential follow-up.[21] Additional details regarding statistical considerations can be found in Appendix 4. All statistical analyses were conducted using R (version 3.1.2).

The study is registered with ClinicalTrials.gov, identifier NCT00952926.

Role of the funding source

This study was partly funded by CIRRO - The Lundbeck Foundation Center for Interventional Research in Radiation Oncology and The Danish Council for Strategic Research. The funding parties had no influence on the study design and collection, analysis, and interpretation of data; in the writing of the report; or the

decision to submit the paper for publication. The corresponding author (ALA) had full access to all study data and held the final responsibility for the decision to submit for publication.

Results

The study was initiated in October 2009, with first patient enrolled Oct 20 2009. Patient accrual proved considerably slower than expected, and a decision was made in December 2013 to close the trial prematurely; at this point 55 patients had been enrolled. Final patient was enrolled Dec 23 2013. Data collection for the current report was done in December 2014, at which point the median time-from-enrolment was 34•5 months (inter-quartile range, IQR, 22•1 – 44•4 months).

Fifty-five patients were registered on trial, but four were deemed ineligible during baseline workup (see Figure 1). Thus 51 patients were correctly enrolled, were treated on trial, and constituted the study population. See Table 1 for an overview of patient characteristics and details of treatment delivered.

Treatment compliance, acute toxicity and treatment response

All but one patient received radiotherapy according to protocol; all patients completed their planned radiotherapy schedule. Forty-three patients completed full dose chemotherapy. The remaining eight patients received a median 70% (IQR, 57% – 83%) of the planned chemotherapy dose. Seven of those patients discontinued chemotherapy partway through the treatment course due to toxicity, while one patient paused treatment for 6 days. Acute grade 1-2 toxicity was experienced by 41 out of 51 (80%) patients: Most common (≥10%) toxicities were diarrhea, nausea, anaemia, leukopenia, neutropenia, and thrombocytopenia. Four patients had grade 3 diarrhea, two patients grade 3 nausea, one patient grade 3 anaemia, and one patient grade 3 leukopenia. No grade ≥4 toxicity, serious adverse reactions, or treatment related deaths were seen. Table a1 (Appendix 5, online only) contains more details on acute treatment toxicity.

The majority of patients had tumour site biopsies done according to protocol; see Table a2 (Appendix 5, online only) for overview of biopsy results. A small number of patients had unusually good response to the CRT, with no clear target for biopsies at the evaluation 6 weeks after treatment. For these patients, negative biopsies at week 6 of treatment were used for evaluation of local response. Forty patients (16 cT2N0, 7 cT2N1, 7 cT3N0, 10 cT3N1) were ultimately classified as clinical complete responders and were allocated to observation (Figure 1). See Figure a2 (Appendix 3, online only) for representative examples of complete and incomplete responders, as observed at endoscopies. No patient with complete primary tumour response had positive lymph nodes on MRI at the time of response assessment.

Patients allocated to observation

Median follow-up in the observation group was 23•9 months (IQR 15•3 – 31•0 months). Nine patients presented with local tumour recurrence and were referred for salvage surgery. Cumulative local recurrence at one year was 15•5% (95% CI 3•3% – 26•3%) and 25•9% (95% CI 9•3% – 42•8%) at two years, see Figure 2. Median time from allocation to observation until local recurrence was 10•4 months. Patients had clearly visible and palpable tumour at the time of recurrence (six patients) and/or positive biopsies (eight patients). See Appendix 3 for examples of local recurrence as seen at endoscopies. No local recurrences were detected by imaging alone, and only a single patient had local recurrence diagnosed at a non-scheduled clinical examination. Three patients presented with distant metastases, one of those prior to local recurrence. So far, no patients have had local tumour recurrence after the two year follow-up point; i.e. local recurrence seems to occur within the first two years of allocation to observation.

Salvage surgery was curative, with clear resection margins, for all nine patients. Post-surgical complications as well as length of hospital stay were comparable to the group undergoing early surgery after incomplete response (see Table 2). No patient undergoing salvage surgery has so far presented with local recurrence after surgery.
Patient reported functional outcome was good, with mild faecal incontinence in a few patients only (Figure 3a). Physician-scored sphincter function (Jorge-Wexner score) was likewise very low (median 0, IQR 0–0 at all time points); Figure 3b illustrates the change in Jorge-Wexner score over time. The predominant late toxicity proved to be bleeding from the rectal mucosa, reported in approximately 80% of patients followed for at least a year, although mild in the majority of cases (see Figures 3c-d). Only 2/30 (7%) and 1/17 (6%) of patients had grade 3 bleeding at one and two years, respectively. Overall scores on the QLQ-CR29 symptom scales (i.e. all questions except no. 56 (males) or 58 (females)) showed little variation over time: Median baseline score was 9•7 (IQR 6•9 – 14•3, n=38), median score at 12 months 10•1 (IQR 5•6- 16•2, n=27), and median score at 24 months 13•8 (IQR 6•6-19•4, n=16).

Patients referred to early surgery due to incomplete response

11 patients had incomplete response and were referred for resection, but only seven underwent surgery as recommended. All had clear resection margins, and two patients had no remaining tumour cells in the pathological specimen; further details can be found in Table 2. All but one patient had APRs with complete resection of the sphincter musculature. Median follow-up after surgery was 19•3 months (IQR 13•0 – 35•5 months), during which no local recurrences were detected.

Overall survival, distant metastases and local control in all patients

After a median 26•7 months (IQR 18•2 – 38•0 months) of follow-up, five patients in the full study population developed metastatic disease, corresponding to a 6•5% (0% – 15•0%) incidence at two years. Three of those were in the observation group (all lung metastases) and two in the surgery group (one lung, one liver). Three lung metastases were curatively resected, with no evidence of recurring disease so far; the remaining two patients underwent chemotherapy. Two patients died from new primary cancers (one in each group), but none from rectal cancer. Two-year overall survival was 100%. The total proportion of patients treated on trial who had local tumour control at two years with CRT alone was 58% (95% CI 41% - 73%). No patients had uncontrolled local disease at the time of data collection.

Discussion

This trial examined the use of high dose CRT for low T2-3 rectal cancer, with deferral of surgery (“watchful waiting”) for clinical complete responders. The trial was able to reach its primary endpoint by demonstrating a local recurrence rate within the first year of 15•5% (95% CI 3•3% – 26•3%). Perhaps more intriguingly, the two-year rate of patients who had local tumour control with CRT alone was 58%. These patients all avoided major, potentially harmful surgery, with apparent excellent functional outcome. The incidence of distant metastases so far seems acceptable for T2-3, N0-1 low rectal cancer. This is, to the best of our knowledge, the first fully prospective trial to report on the use of definitive CRT for low rectal cancer, and thus the first trial to allow for estimation of the proportion of patients who can be managed non-surgically.

The option of ”watchful waiting” for rectal cancer patients with complete clinical response to CRT was first introduced in a seminal paper by Habr-Gama et al,[10] who reported a 88% five-year survival rate for patients with sustained response allowed to undergo observation instead of surgery. These impressive results have since been corroborated by a case series from Maas et al[12] as well as a number of follow-up publications by the Brazilian group.[11,22-24] The proportion of patients manageable by CRT alone varies between reports, as

does the incidence of local recurrence for patients followed without surgery. This is at least to some extent likely due to differences in criteria for clinical complete response: The Mass et al series of 21 patients represented merely 11% of all rectal cancers treated with CRT in the study period, but only one of those 21 patients presented with an endoluminal recurrence during a median 15 months of follow-up. The publications from the Habr-Gama group vary somewhat, depending on groups of patients reported on, but several of the observation cohorts constitute over half of the treated patients. With approximately 25% local tumour recurrence, 30-50% of patients treated showed long-term control of their primary cancer with non-surgical management. It should be recognised, though, that comparisons between series are complicated by disparities in the use of supplementary chemotherapy, e.g. after CRT but prior to response evaluation[23] or after allocation to observation.[12] Overall, the results of the current study are comparable to the Brazilian reports, in terms of proportion of patients classified as complete responders as well as in incidence of local recurrence in the observation group.

A high rate of clinically complete responders (78%) was observed, even compared to the Habr-Gama reports. This might be partially explained by patient selection: Tumours were generally small (more than half cT2), and the study cohort contained patients referred by outside departments, preselected by their primary surgeon as likely to benefit from the trial treatment strategy. However, the high response rate may also be due to the high dose of radiotherapy delivered: The prescribed radiation dose to the tumour from external beam and brachytherapy combined was 66 Gy. A previously published study[25] by our group indicated the likely existence of a dose-response relationship for pathologically assessed regression of rectal tumours following CRT, and while this is not guaranteed to hold true for clinical tumour regression and local control as well, it supports the use of high dose CRT for definitive treatment. A substantial number of patients with cT3 or cN1 had clinical complete response, and this suggests that the relevance of this treatment strategy is not restricted to patients with very early (T2N0) disease.

It is worth remembering, when evaluating the results of studies of observation for complete responders after CRT, that ”local recurrence” after non-surgical management is generally not comparable to local recurrence after conventional, TME-based surgical treatment. Tumour re-growth in the rectal lumen can be handled with salvage surgery, the outcome of which does not appear to differ substantially from primary surgery for non-responders,[11] unlike local recurrence after primary surgery. It has previously been argued that primary local recurrence after “watchful waiting” may not be an optimal endpoint for evaluation of organ preserving treatment strategies; local recurrence after salvage surgery may ultimately be a better outcome measure for comparison with conventional treatment.[14]

Despite the high radiation doses, the observed toxicity was relatively mild and functional outcome good. Possibly, the highly conformal radiotherapy techniques used may explain this. IMRT is especially well suited for irradiation of concave targets, such as the nodal regions involved in rectal cancer radiotherapy, and the steep dose gradients delivered with endorectal brachytherapy allow for very selective tumour boosting. Still, the good functional outcome may seem surprising, based on historical experience from curative radiotherapy of anal cancer. For anal cancer, though, tumour involvement of sphincters often hinders optimal preservation of sphincter function, even after full tumour regression has been achieved. This is not the case for T2-3 primary resectable rectal cancer. The one major late toxicity observed, bleeding from the rectal mucosa, can presumably be explained by the steep dose gradient from the brachytherapy boost. The rectal mucosa received over 300% of the prescribed brachytherapy dose,[26] resulting in a total “equivalent dose in 2 Gy fractions” to the mucosa of well over 100 Gy. This unexpected toxicity may force a re-evaluation of the use of brachytherapy for tumour boosting, and a recently initiated multicentre study (ClinicalTrials.gov identifier NCT02438839) will examine if external beam boosting alone can replace brachytherapy. Any radiation-induced toxicity should, though, be weighted against the potential morbidity from surgical tumour control.

The current study closed earlier than initially planned, due to slow patient accrual, mainly resulting from fewer outside institutions actively referring patients than originally anticipated. Additionally, we suspect that the centralised treatment, and the resulting logistical challenges for patients, might have proved restrictive for optimal enrolment. The early termination limits the impact of the study, especially due to the relatively small number of patients treated. However, our prospectively collected data confirms previously published reports. Another weakness of the study is the somewhat short follow-up. The primary trial endpoint was local control at one year; hence the reporting of trial results at the current time. Nonetheless, concerns might remain regarding late local recurrences. We find it reassuring, though, that none of the patients followed for over two years have had local recurrence so far; i.e. it seems unlikely that the estimate of the incidence of local recurrence is going to change substantially with longer follow-up. On the other hand, the incidence of distant metastases (6•5% at two years) will likely increase at later time points. Distant metastases (and overall survival) were examined in the full study population, to allow for evaluation of the full treatment strategy, as compared to standard management. With standard surgical treatment, patients do relapse distantly well past two years, and we expect this to be the case with the current treatment strategy as well. Thus patients will need to be followed longer for evaluation of secondary study endpoints.

Follow-up for the group of patients undergoing early surgery due to incomplete response to CRT was, although conducted according to protocol, suboptimal: These patients were not followed as closely as patients allocated to observation, particularly with regards to late toxicity and patient-reported QoL. Patients with cT2 cancer will not typically be offered preoperative CRT, and therefore T2 patients without complete response could, with the treatment strategy studied, be exposed to treatment with potential late side effects without substantial estimated benefit. The lack of toxicity and QoL evaluation for these patients prevents examination of any negative impact of the CRT on patient outcome.

Additional drawbacks of the study include limited details and uncertainties in the clinical staging: Enrolled patients with T3 disease did not have T3 subclassification recorded, as this was only introduced after the initiation of the trial (2009); and clinical nodal stage assessment in rectal cancer is notoriously difficult and thus associated with substantial uncertainty, even when MRI is used. Furthermore, the use of UFT in the preoperative setting for rectal cancer – while standard in many Danish centres – is internationally far less common than e.g. 5-FU, and this might raise concerns regarding the generalizability of the study results. Available, though limited, evidence points towards UFT being at least as effective as 5-FU in the preoperative setting;[27] thus we believe that our results should be indicative of what might be achievable with fluorouracil or other pro-drugs.

In conclusion, this prospective trial indicates that a treatment strategy for low rectal cancer consisting of high dose CRT combined with “watchful waiting” for clinical complete responders might be a safe and effective alternative for selected patients with low rectal cancer. Patients with local recurrence all underwent standard surgical resection, and the incidence of distant metastases is in agreement with current literature reporting on patients undergoing primary surgery.[28] Ultimately, 58% (95% CI 41% - 73%) of all patients were managed non-surgically, with good functional outcome. This is clearly a realistic treatment option for low rectal cancer that should be prospectively explored in a multicentre setting to see whether the results can be reliably reproduced outside of individual, eminence-based groups.

Conflicts of interests

The authors declare no conflicts of interest.

Author contributions

AJ and JP designed and planned the study. All authors obtained data: JP, AJ, LHJ, JCRJ, HH, and FSJ assessed patients for eligibility; JP, AJ, LHJ and JCRJ evaluated response and saw observation patients at follow-up; HH and FSJ followed surgical patients and oversaw treatment of local recurrences; JL did analysis of biopsies; SRR was responsible for radiological assessment; and ALA for radiotherapy treatment data. ALA performed data analysis and wrote the first draft of the manuscript. All authors participated in interpretation of the results and critically revised the manuscript, and all authors have approved the final version of the manuscript.

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Research in context (panel)

Evidence before this study

The strategy of "watchful waiting" rather than surgery for rectal cancer patients with clinical complete response after chemoradiotherapy (CRT) has been a topic of intense discussion often more based on difference in opinions than solid data from prospective trials. At the time of writing, the number of reviews and opinion pieces published on the topic well exceeds the number of clinical studies. A systematic search of papers on non-surgical management of rectal cancer using CRT was conducted prior to the design (early 2009) and initiation of the study here presented. The Pubmed database was searched using combinations of the terms "rectal cancer", "chemoradiotherapy", "non-surgical management" and "watch-and-wait" (as well as variations thereof). A later systematic review[13] includes all studies located in this search. The major patient series reported at the time were from the Habr-Gama group in Brazil. These papers, while seminal, represented retrospective reports of a single centre experience, with non-stringent patient selection and variations in workup, treatment, and response evaluation. No data from registered, prospective trials were available at the time.

Added value of this study

This prospective trial examined the use of high dose CRT for low T2-3 rectal cancer, with deferral of surgery ("watchful waiting") for clinical complete responders. The results indicate that a high proportion of selected rectal cancers may potentially be managed with CRT alone, i.e. a group of patients may be able to avoid major surgery. The large fraction of patients responding to CRT treatment, compared with results in previously published reports, may be due to the high dose radiation delivered.

Implications of all the available evidence

This trial, as well as evidence from previous (mainly retrospective) studies, supports the notion that a treatment strategy for low rectal cancer consisting of high dose CRT combined with "watchful waiting" for clinical complete responders may be a safe alternative to standard treatment, with excellent functional outcome. However, validation in a multicenter setting is mandatory before the approach can be integrated into daily clinical practice.

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Figure legends

Figure 1: Overview of patients enrolled and treated on trial.

Figure 2: Cumulative incidence of local tumour recurrence in patients allocated to observation.
Time calculated from date of allocation to observation. Dashed lines indicate 95% confidence interval, markers indicate censored patients.

Figure 3: Functional outcome and late toxicity in patients allocated to observation
Patient numbers in figures indicate how many had data available at any given time point. a) Patient response to question 50 ("Have you had leakage of stools from your back passage?") on the QLQ-CR29 questionnaire. White "Not at all"; blue "A little"; green "Quite a bit"; red "Very much". b) Physician-scored sphincter incontinence, using the five-item Jorge-Wexner scale (maximum possible score: 20). Lines indicate changes over time (e.g. from baseline to six-months follow-up) for individual patients; line width is proportional to number of patients for a given change. c) Patient response to question 38 ("Have you had blood in your stools?") on the QLQ-CR29 questionnaire. White "Not at all"; blue "A little"; green "Quite a bit"; red "Very much". d) Physician-scored rectal bleeding, using CTCAE v4.0 item "Rectal hemorrhage".