High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study

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Summary

Background Abdominoperineal resection is the standard treatment for patients with distal T2 or T3 rectal cancers; however, the procedure is extensive and mutilating, and alternative treatment strategies are being investigated. We did a prospective observational trial to assess whether high-dose radiotherapy with concomitant chemotherapy followed by observation (watchful waiting) was successful for non-surgical management of low rectal cancer.

Methods Patients with primary, resectable, T2 or T3, N0–N1 adenocarcinoma in the lower 6 cm of the rectum were given chemoradiotherapy (60 Gy in 30 fractions to tumour, 50 Gy in 30 fractions to elective lymph node volumes, 5 Gy endorectal brachytherapy boost, and oral tegafur-uracil 300 mg/m²) every weekday for 6 weeks. Endoscopies and biopsies of the tumour were done at baseline, throughout the course of treatment (weeks 2, 4, and 6), and 6 weeks after the end of treatment. We allocated patients with complete clinical tumour regression, negative tumour site biopsies, and no nodal or distant metastases on CT and MRI 6 weeks after treatment to the observation group (watchful waiting). We referred all other patients to standard surgery. Patients under observation were followed up closely with endoscopies and selected-site biopsies, with surgical resection given for local recurrence. The primary endpoint was local tumour recurrence 1 year after allocation to the observation group. This study is registered with ClinicalTrials.gov, number NCT00952926. Enrolment is closed, but follow-up continues for secondary endpoints.

Findings Between Oct 20, 2009, and Dec 23, 2013, we enrolled 55 patients. Patients were recruited from three surgical units throughout Denmark and treated in one tertiary cancer centre (Vejle Hospital, Vejle, Denmark). Of 51 patients who were eligible, 40 had clinical complete response and were allocated to observation. Median follow-up for local recurrence in the observation group was 23·9 months (IQR 15·3–31·0). Local recurrence in the observation group at 1 year was 15·5% (95% CI 3·3–26·3). The most common acute grade 3 adverse event during treatment was diarrhoea, which affected four (8%) of 51 patients. Sphincter function in the observation group was excellent, with 18 (72%) of 25 patients at 1 year and 11 (69%) of 16 patients at 2 years reporting no faecal incontinence at all and a median Jorge-Wexner score of 0 (IQR 0–0) at all timepoints. The most common late toxicity was bleeding from the rectal mucosa; grade 3 bleeding was reported in two (7%) in 30 patients at 1 year and one (6%) of 17 patients at 2 years. There were no unexpected serious adverse reactions or treatment-related deaths.

Interpretation High-dose chemoradiotherapy and watchful waiting might be a safe alternative to abdominoperineal resection for patients with distal rectal cancer.

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Introduction

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

Preoperative radiotherapy improves local control, even with optimal surgical techniques,[7,8] and is thus used in many patients. If neoadjuvant chemoradiotherapy with delayed surgery is used, as is the case in many countries, then most patients will have some degree of tumour regression at the time of surgery. A group of patients will have complete response to the neoadjuvant therapy—no remaining tumour cells in the pathological specimen.[9] Much interest has therefore risen as to whether some patients can be identified for whom tumour control can be achieved with chemoradiotherapy alone. Investigators of a few 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 shown successful in a prospective series, watchful waiting would be an attractive alternative to extensive surgery and permanent stoma for patients with distal rectal cancer.[14] However, questions remain as to 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.

We designed this prospective observational trial to establish the proportion of patients with distal rectal cancer who can be managed with high-dose radiotherapy and concomitant chemotherapy alone. Furthermore, we wanted to examine the overall outcome (survival and

Research in context

Evidence before this study

The strategy of watchful waiting rather than surgery for patients with rectal cancer with clinical complete response after chemoradiotherapy has been intensely debated, often due to difference in opinions rather 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. We did a systematic search of papers on non-surgical management of rectal cancer using chemoradiotherapy before design (early 2009) and initiation of the study. We searched PubMed for papers in English and using combinations of the terms "rectal cancer", "chemoradiotherapy", "non-surgical management", and "watch-and-wait" (as well as variations thereof). Glynne-Jones and Hughes (2013) later did a systematic review that 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, although seminal, represented retrospective reports of a single centre experience, with non-stringent patient selection and variations in work-up, treatment, and response evaluation. No data from registered, prospective trials were available at the time of initiation.

Added value of this study

Our prospective trial examined the use of high-dose chemoradiotherapy for low T2 and T3 rectal cancer, with deferral of surgery (watchful waiting) for clinical complete responders. The results indicate that a high proportion of selected rectal cancers could potentially be managed with chemoradiotherapy alone—a group of patients might be able to avoid major surgery. Most patients responded to chemoradiotherapy treatment in our study compared with results in previously published reports, which could be due to the high-dose radiation delivered.

Implications of all the available evidence

Findings from this trial, as well as evidence from previous (mainly retrospective) studies, support the notion that this treatment strategy might be a safe alternative to standard treatment, with excellent functional outcome. However, validation in a multicentre setting is needed before the approach can be integrated into daily clinical practice.

disease-free survival) for a cohort of patients in whom watchful waiting was a central part of the general treatment strategy.

Methods

Study design and participants

For the **protocol** see http://www.sygehuslillebaelt.dk/dwn462996

See Online for appendix

This was a prospective observational trial. The protocol is available online. Patients were referred from surgical departments throughout Denmark but were treated in a tertiary Danish cancer centre (Vejle Hospital) and enrolled in the study before the start of chemoradiotherapy (appendix p 1). Eligible patients had primary resectable T2–T3 adenocarcinoma of the rectum within 6 cm of the anal verge—ie, patients who were planned for an abdominoperineal resection or an ultra-low resection of the rectum. Diagnosis was confirmed with pelvic MRI, transrectal ultrasound imaging, CT of the thorax and abdomen, whole body fluorodeoxyglucose-PET-CT, endoscopy (with biopsy), and clinical examination. Additional eligibility criteria included performance status that allowed for long-course treatment with curative intent as well as liver, kidney, and bone marrow function that allowed for long-course chemoradiotherapy, older than 18 years, and no distant metastases. We defined normal bone marrow function as leucocyte count 3×10^9 cells per L or higher and thrombocytes 100×10^9 cells per L or higher; normal liver function as alanine amino-transferase less than 2·5 times the upper limit of normal (ULN), bilirubin less than 2·5 times the ULN; and normal renal function as serum creatinine less than 1·5 times ULN. The initial trial protocol specified no lymph node involvement (N0, all lymph nodes <5 mm), but early clinical experience showed many patients with small tumours in the distal rectum in whom negative lymph node status could not be definitively established with MRI, or with a few (one to three) lymph nodes in close proximity to the primary tumour. Thus we made a protocol amendment to allow enrolment of these patients with N1. This amendment was approved on May 26, 2010, by the ethics committee shortly after trial initiation (after enrolment of five patients). 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

Eligible patients were given 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 a day on weekdays (Monday to Friday) for 6 weeks. All patients were treated with intensity modulated radiotherapy using a concomitant boost technique; technical details and volume definitions in appendix p 2–3. Chemotherapy was peroral tegafur-uracil (UFT) 300 mg/m² every day on radiotherapy treatment days; chemotherapy could be interrupted or discontinued in case of excess toxicity by the discretion of the treating physician, but no dose reductions could be made. An endorectal brachytherapy tumour boost of 5 Gy was delivered in the final week of external-beam treatment (appendix p 3). Acute toxicity was recorded according to Common Terminology

Criteria for Adverse Events (CTCAE) version 4.0 by treating physicians every week during treatment. Patients were to be withdrawn if distant metastases were detected during the treatment course, less than 30 Gy (50%) of the planned radiation dose was delivered, or less than 50% of the planned chemotherapy dose given.

We did endoscopies with selected-site biopsies of the tumour at baseline, throughout the course of treatment (weeks 2, 4, and 6), and 6 weeks after the end of treatment. We placed ink tattoos surrounding the tumour in the rectal wall at baseline (appendix p 4) to allow for continuous assessment of tumour regression. At least four biopsies were done within the ink-marked area at the positions 3, 6, 9, and 12 o'clock, and if necessary, at points of interest. Final evaluation of tumour response to chemoradiotherapy was done 6 weeks after treatment completion. Patients were allocated to observation (watchful waiting) when they had no signs of remaining disease. We based this decision on clinical examination, endoscopy with negative biopsy results from the primary tumour site, and pelvic MRI. We defined clinical complete response on endoscopy as a small, white scar in the rectal wall or a superficial erosion or ulceration without palpable tumour. If an ulcer or erosion persisted, we took additional biopsies at the edge (ie, the potentially invasive front; appendix p 4). We mainly used MRI to evaluate the status of regional lymph nodes after chemoradiotherapy (suspect lymph nodes were considered malignant if their diameter was larger than 5 mm) and no heterogeneity criteria were used. Primary tumour regression on MRI, although available, was not part of the formal response assessment, and no scoring of imaging response (eg, MRI tumour regression grade or similar[15]) was reported. No patient could be 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 (appendix p 4). All patients with incomplete response were referred for surgery.

Patients in the observation group were followed with clinical examinations and endoscopies every 2 months for the first year, every 3 months the second year, every 6 months the third year, and 12 months in the fourth and fifth year. Biopsies were taken when 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-CT was done three times the first year, twice the second year, and every year thereafter. No adjuvant chemotherapy was given. We referred patients with local tumour recurrence to surgical treatment; distant disease progression was assessed and treated on an individual patient basis.

We assessed late toxicity and functional outcome in the observation group with patient-reported quality-of-life (QoL) scores. The European Organisation for Research and Treatment of Cancer (EORTC) colorectal cancer specific QoL module (QLQ-CR29)[16] was completed before and at the end of chemoradiotherapy, at 6 months and 12 months in the follow-up period, and every year 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 CTCAE version 4.0.

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 or perineural invasion, poor differentiation, any 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. Surgery was done according to national Danish guidelines for colorectal cancer surgery.[18] Salvage surgery for 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 according to the Mandard scale.[19] We recorded length of hospital stay and postoperative complications.

Outcomes

The primary endpoint was local tumour recurrence 1 year after allocation to the observation group. We calculated time to local recurrence from allocation to observation group. Secondary endpoints were cumulative local recurrence (time from trial enrolment to death from any cause), distant metastases (defined as time to distant metastases from date of trial enrolment), and overall survival, all in the full trial population.

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 in the first year of follow-up of 30% or lower was deemed clinically acceptable, and so the first phase of 30 patients thus required fewer than 16 local recurrences in the observation group. The second phase planned for a total number of 100 patients to establish a 20 percentage point width of the 95% CI for the primary endpoint measure.

We calculated cumulative incidences of local recurrence and distant metastases with the Kaplan-Meier estimator. Bounds of the CIs for local recurrence and distant metastases were calculated from the SEs of the cumulative incidence curves. For the lower bounds, a standard log-transformation approach was used. The upper bounds were estimated using the Peto method, which takes into account the increase in uncertainty of the incidence estimate with the decrease in numbers at risk at later timepoints—ie, a more

conservative estimate so as to not underestimate the upper bounds of the recurrence incidence. Estimates of follow-up times were calculated using the Kaplan-Meier estimator of potential follow-up[21]—ie, the Kaplan-Meier estimator with the status indicator reversed. Patients were recorded as having had local failure 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. Distant metastases were all confirmed by biopsies; patients were censored in case of non-cancer death or new primary cancer, but not at local recurrence in the observation group. We used data for all patients correctly enrolled on trial for analyses of primary and secondary outcomes. We did all statistical analyses with R (version 3.1.2). The study is registered with ClinicalTrials.gov, identifier NCT00952926.

Role of the funding source

The funders 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 had final responsibility for the decision to submit for publication.

Results

We enrolled the first patient Oct 20, 2009. Patient accrual was considerably slower than expected, and on Dec 23, 2013, the principal investigator (AJ), in consultation with the rest of the protocol group, decided to close the trial prematurely. At this point 55 patients had been enrolled. The 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 (IQR 22·1–44·4 months). 55 patients were registered on trial, but four were not eligible during baseline investigation (figure 1). 51 patients from three centres were enrolled and were treated on trial (study population; table 1).

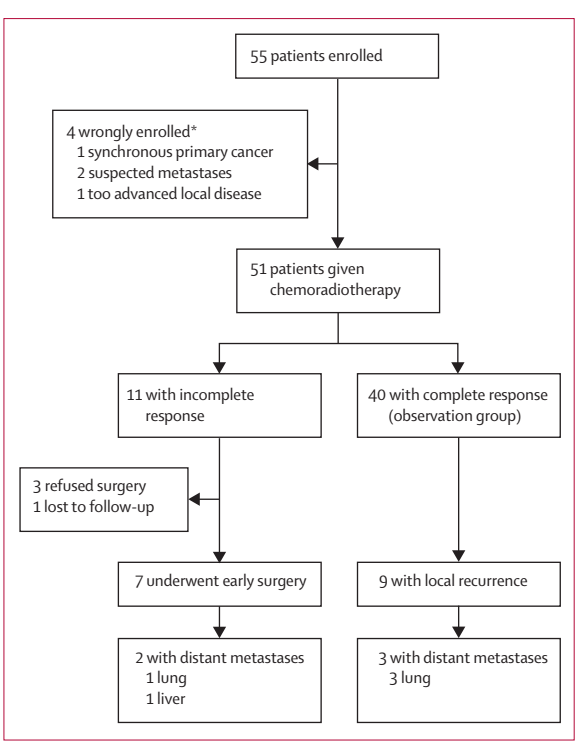

***Figure 1*: Study population**
*All patients deemed ineligible during baseline assessment.

50 patients (98%) received radiotherapy according to protocol; all patients completed their planned radiotherapy schedule. 43 (84%) patients completed full-dose chemotherapy. The remaining eight patients received a median 70% (IQR 57–83) of the planned chemotherapy dose. Seven of these patients discontinued chemotherapy partway through the treatment course due to toxicity, whereas one patient paused treatment for 6 days. Table 2 shows adverse event data; no grade 4 or 5 toxicity, serious adverse reactions, or treatment-related deaths were noted.

45 (88%) of 51 patients had all tumour site biopsies done according to protocol (appendix p 5). 4 (8%) had unusually good response to the chemoradiotherapy, 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. We ultimately classified 40 patients (16 cT2N0, seven cT2N1, seven cT3N0, and ten cT3N1) as clinical complete responders and allocated them to the observation group (figure 1). No patient with complete primary tumour response had positive tests for lymph nodes on MRI at the time of response assessment.

11 patients had incomplete response to chemoradiation and were referred for resection, but only seven underwent surgery as recommended (three refused surgery, and one was lost to follow-up; figure 1). All had clear resection margins, and two patients had no remaining tumour cells in the pathological specimen (table 3). All but one patient had abdominoperineal resections with complete resection of the sphincter musculature. Median follow-up after surgery was 19·3 months (IQR 13·0–35·5), during which no local recurrences were detected.

Median follow-up in the observation group was 23·9 months (IQR 15·3–31·0). In this time, nine patients had local tumour recurrence and were referred for salvage surgery. Cumulative local recurrence at 1 year was 15·5% (95% CI 3·3–26·3), and 25·9% (9·3–42·8) at 2 years (figure 2). Median time from allocation to observation until local recurrence was 10·4 months (IQR 8·0–13·6). Patients who had local recurrence had clearly visible and palpable tumour at the time of recurrence (n=6) or positive biopsies (n=8) or both (appendix p 4). We detected no local recurrences by imaging alone and only one patient had local recurrence diagnosed at a non-scheduled clinical examination. Three patients had distant metastases, of

which one was detected before identification of local recurrence. At the time of data cutoff for this analysis, no patients have had local tumour recurrence after the 2 year follow-up point—ie, local recurrence seems to occur within the first 2 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 similar to the group who had early surgery after incomplete response (table 3). No patient who had salvage surgery has so far presented with local recurrence after surgery.

Patient-reported functional outcome was good, with no faecal incontinence reported by 18 (72%) of 25 patients at 1 year, and 11 (69%) of 16 patients at 2 years (figure 3A). Physician-scored sphincter function (Jorge-Wexner score) was likewise good (median 0 [IQR 0–0] at all timepoints; figure 3B). The main late toxicity was bleeding from the rectal mucosa, with bleeding of any severity reported by 21 (78%) of 27 patients followed-up for at least 1 year, although was mild in most patients (figure 3C, 3D). Two (7%) of 30 patients had grade 3 rectal bleeding at 1 year as did one (6%) of 17 at 2 years. Overall scores on the QLQ-CR29 symptom scales (ie, all questions except number 56 [men] or 58 [women]: to what extent were you interested in sex) showed little variation over time: median score at baseline (n=38) was 9·7 (IQR 6·9–14·3), median score at 12 months (n=27) was 10·1 (5·6–16·2), and at 24 months (n=16) was 13·8 (6·6–19·4).

After a median of 26·7 months (IQR 18·2–38·0) of follow-up, five (10%) of 51 patients in the full study population developed metastatic disease, corresponding to a 6·5% (0–15·0) incidence at 2 years. Three patients 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 at the time of this analysis; the remaining two patients were treated with chemotherapy. Two patients died from new primary cancers (one in each group; one after 48 months, one after 33 months), but none from rectal cancer. 2 year overall survival was 100%. The estimated total proportion of patients treated on trial who had local tumour control at 2 years with chemoradiotherapy alone was 58% (95% CI 41–73). No patients had uncontrolled local disease at the time of data collection.

Discussion

In this trial, we examined the use of high-dose chemoradiotherapy for low T2 and T3 rectal cancer, with deferral of surgery (watchful waiting) for patients who had complete clinical response to treatment. We reached our primary endpoint by showing a local recurrence rate within the first year of 15·5% (95% CI 3·3–26·3). Perhaps more intriguingly, 58% of patients had local tumour control at 2 years with chemoradiotherapy alone. These patients all avoided major, potentially harmful surgery, with apparent excellent functional outcome. The incidence of distant metastases so far seems acceptable for T2 and T3 N0–N1 low rectal cancer. This is, to the best of our knowledge, the first fully prospective

	Total population (n=51)
Disease stage	
T2N0	18 (35%)
T2N1	9 (18%)
T3N0	10 (20%)
T3N1	14 (27%)
Median age (years)	67 (58–75)
Men	39 (76%)
Women	12 (24%)
Tumour size*	
n	47*
Diameter (cm)	2·8 (2·1–3·5)
Length (cm)	3·4 (2·7–4·3)
Distance from sphincter (cm)*	
n	48*
Median distance	4·8 (4·0–5·2)
Radiotherapy according to protocol	
Yes	50 (98%)
No†	1 (2%)
Radiotherapy treatment volumes (cm^3)	
CTV-T	45·5 (34·8–60·5)
PTV-T	172·8 (141·0–201·0)
CTV-N	627·0 (552·8–670·5)
PTV-N	1363 (1276–1462)
Full-dose chemotherapy	
Yes	43 (84%)
No	8 (16%)

Data are n (%) or median (IQR). CTV=clinical target volume. PTV=planning target volume. T=tumour volume. N=elective lymph node volume. *Data not available for all tumours. †The one patient who did not receive radiotherapy according to protocol had bilateral hip alloplastics, which complicated the planning of concomitant boost intensity-modulated radiation therapy; instead, a single-dose-level plan to 50·4 Gy was given and supplemented with two 5 Gy brachytherapy boosts.

Table 1: **Patient and treatment characteristics**

	Grade 0	Grade 1–2	Grade 3	Grade 4	Grade 5	ND
Nausea	31 (61%)	17 (33%)	2 (4%)	0	0	3 (6%)
Vomiting	44 (86%)	4 (8%)	0	0	0	3 (6%)
Diarrhoea	22 (43%)	23 (45%)	4 (8%)	0	0	2 (4%)
Anaemia	24 (47%)	25 (49%)	1 (2%)	0	0	1 (2%)
Leucopenia	36 (71%)	13 (25%)	1 (2%)	0	0	1 (2%)
Neutropenia	44 (86%)	6 (12%)	0	0	0	1 (2%)
Thrombocytopenia	36 (71%)	14 (27%)	0	0	0	1 (2%)
Other	9 (18%)	38 (75%)	2 (4%)	0	0	2 (4%)
Worst grade of toxicity	2 (4%)	41 (80%)	6 (12%)	0	0	2 (4%)

Shows the distribution of peak scores during treatment. "Other toxicity" was typically from either skin or bladder. All side-effects scored using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. ND=not assessed.

Table 2: **Adverse events during chemoradiotherapy**

	Early surgery after incomplete response (n=7)	Surgery at local recurrence (n=9)*
Surgery type		
Abdominoperineal resection	6 (86%)	9 (100%)
Other	1 (14%)	0 (0%)
Pathological evaluation		
Primary tumour		
pT0	2 (29%)	0
pT1	2 (29%)	2 (22%)
pT2	2 (29%)	3 (33%)
pT3	1 (14%)	4 (44%)
Node		
pN0	6 (86%)	9 (100%)
pN1	1 (14%)	0
Tumour regression grade†		
1	2 (29%)	..
2	0	..
3	4 (57%)	..
4	1 (14%)	..
Complications		
Infection	1 (14%)	2 (22%)
Wound infection	1 (14%)	1 (11%)
Delayed healing	1 (14%)	3 (33%)
Pelvic abscess	0 (0%)	0 (0%)
Bleeding	0 (0%)	0 (0%)
Blood transfusion	0 (0%)	0 (0%)
Days admitted to hospital	9 (8–9)	10 (8–11)

*One patient in the observation group had a transanal endoscopic microsurgery due to high-grade dysplasia, and later had a transanal excision showing carcinoma, followed by a full abdominoperineal resection. Data for the above refers to the abdominoperineal resection procedure. †Tumour regression grade assessment is only well defined for evaluation of primary tumour regression at surgery shortly after chemoradiotherapy, not for tumour regrowths in a previously treated volume; hence grade is not reported for patients with local recurrence.

Table 3: **Details of early and salvage surgery**

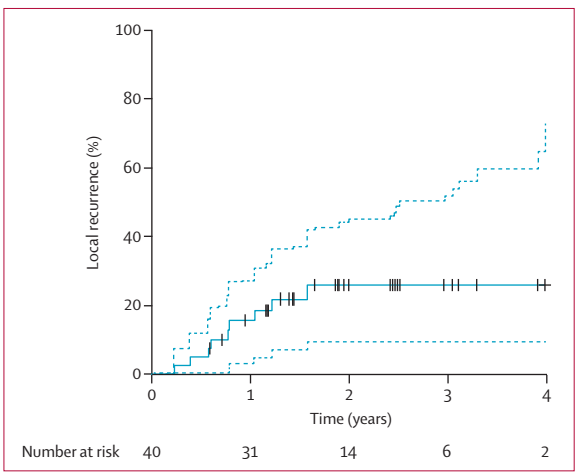

Figure 2: **Cumulative incidence of local tumour recurrence in patients allocated to observation**
Time calculated from date of allocation to observation. Dashed lines are 95% CIs; markers indicate censored patients.

trial to report on the use of definitive chemoradiotherapy for low rectal cancer, and thus the first study to allow for estimation of the proportion of patients who can be managed without surgery.

The option of watchful waiting for patients with rectal cancer with complete clinical response to chemoradiotherapy was first introduced by Habr-Gama and colleagues,[10] who reported that 88% of patients with sustained response given observation instead of surgery were alive after 5 years. These impressive results were supported by a case series from Maas and colleagues[12] as well as several follow-up publications by Habr-Gama's group.[11,22–24] The proportion of patients successfully managed by chemoradiotherapy alone varies between reports, as does the incidence of local recurrence for patients observed after not receiving surgery. This scarcity is at least somewhat due to differences in criteria for clinical complete response: Maas and colleagues' series of 21 patients represented only 11% of all rectal cancers treated with chemoradiotherapy in the study period, but only one of those 21 patients presented with an endoluminal recurrence during a median 15 months of follow-up. Findings in publications from Habr-Gama's group vary somewhat, depending on groups of patients reported on, but several of the observation cohorts constitute over half of the treated patients. With about 25% of patients having local tumour recurrence, 30–50% of patients treated had long-term control of their primary cancer with non-surgical management. However, comparisons between series are complicated by disparities in the use of supplementary chemotherapy (eg, after chemoradiotherapy but before response evaluation,[24] or after allocation to observation[12]). Overall, our results are similar to those in the Habr-Gama's reports, in terms of proportion of patients classified as complete responders as well as in incidence of local recurrence in the observation group.

We observed a high proportion of clinically complete responders (78%), even higher than that in reports from Habr-Gama and colleagues. This finding might be partially explained by patient selection: tumours were generally small (more than half were cT2), and the study cohort contained patients referred by outside departments, preselected by their main surgeon as likely to benefit from the trial treatment strategy. However, the high proportion of patients with complete response could also be due to the high dose of radiotherapy—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 probable existence of a dose–response relationship for pathologically assessed regression of rectal tumours after chemoradiotherapy, and although this relation is not guaranteed to hold true for clinical tumour regression and local control too, it supports the use of high-dose chemoradiotherapy for definitive treatment. Many patients with cT3 or cN1 had clinical complete response, suggesting that the relevance

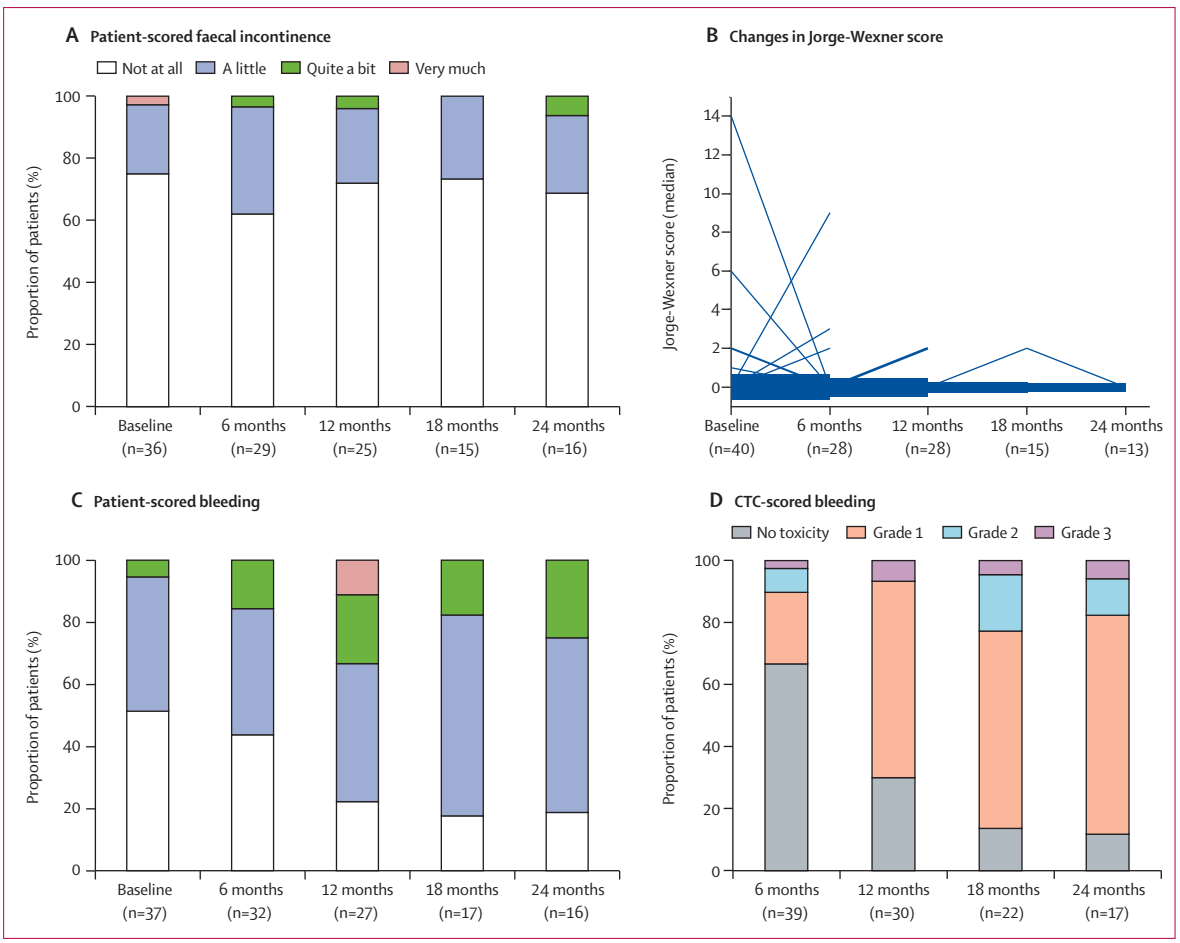

***Figure* 3: Functional outcome and late toxicity in patients allocated to observation**
n=patients with data available at that timepoint. (A) Patient response to question 50 ("Have you had leakage of stools from your back passage?") on the QLQ-CR29 questionnaire. (B) Physician-scored sphincter incontinence, using the five-item Jorge-Wexner scale (maximum score 20). Lines indicate changes over time 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. (D) Physician-scored rectal bleeding, using Common Terminology Criteria for Adverse Events version 4.0 item rectal haemorrhage: grade 0 (no toxicity), grade 1 (mild; intervention not indicated), grade 2 (moderate symptoms; medical intervention or minor cauterisation indicated), and grade 3 (transfusion, radiological, endoscopic, or elective operative intervention indicated).

of this treatment strategy is not only for patients with very early (T2N0) disease.

Local recurrence after non-surgical management is generally not comparable to local recurrence after conventional, total mesorectal excision-based surgical treatment. Tumour regrowth in the rectal lumen can be handled with salvage surgery, the outcome of which does not seem to differ substantially from primary surgery for those who do not respond,[11] unlike management of local recurrence after primary surgery. Primary local recurrence after watchful waiting might not be an optimum endpoint for evaluation of organ-preservation treatment strategies; local recurrence after salvage surgery could ultimately be a better outcome measure for comparison with conventional treatment.[14]

Despite the high radiation doses, observed toxicity was relatively mild and functional outcome was good. The highly conformal radiotherapy techniques that we used might explain this finding. Intensity modulated radiotherapy 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. Nevertheless, the good functional outcome might seem surprising because of historical experience from curative radiotherapy of anal cancer. Involvement of sphincters in anal cancer tumours often hinders optimum preservation of sphincter function, even after full tumour regression. This is not the case for T2 or T3 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 more than 300% of the prescribed brachytherapy dose,[26] resulting in a total equivalent dose in 2 Gy fractions to the mucosa of more than 100 Gy.

This unexpected toxicity could cause a re-evaluation of the use of brachytherapy for tumour boosting, and a recently initiated multicentre study (NCT02438839) will examine if external-beam boosting alone can replace brachytherapy. However, any radiation-induced toxicity should be weighed against the potential morbidity from surgical tumour control.

Our study closed earlier than was initially planned because of slow patient accrual, mainly resulting from fewer outside institutions actively referring patients than was originally anticipated. Additionally, we suspect that the centralised treatment, and the resulting logistical challenges for patients, might have proved restrictive for optimum enrolment. The early termination limits the impact of the study, especially due to the relatively few 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 1 year; hence the reporting of trial results at the current time. Nonetheless, concerns about late local recurrences might remain. We find it reassuring that none of the patients followed for longer than 2 years have had local recurrence so far (ie, it seems unlikely that the estimate of the incidence of local recurrence is going to change substantially with longer follow-up). However, the incidence of distant metastases (6·5% at 2 years) will likely increase at later timepoints. We examined distant metastases (and overall survival) in the full study population to allow for evaluation of the full treatment strategy, as compared with standard management. With standard surgical treatment, patients do relapse distantly well after 2 years, and we expect this to be the case with the current treatment strategy. Therefore, patients will need to be observed longer for evaluation of secondary study endpoints.

Follow-up for the group of patients undergoing early surgery due to incomplete response to chemoradiotherapy was, although conducted according to protocol, suboptimum; these patients were not investigated as closely as patients allocated to observation, particularly with regards to late toxicity and patient-reported quality of life. Patients with cT2 tumours will not typically be offered preoperative chemoradiotherapy, and therefore patients with T2 tumours without complete response could, with the treatment strategy studied, be exposed to treatment with potential late side-effects without substantial estimated benefit. The limited assessment of toxicity and quality of life for these patients prevents examination of any negative effect of the chemoradiotherapy on patient outcome.

Additional drawbacks of the study include incomplete details and uncertainties in the clinical staging. Enrolled patients with T3 disease did not have T3 subclassification recorded because this was only introduced after the start 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 tegafur-uracil in the preoperative setting for rectal cancer, although standard in many Danish centres, is far less common internationally than, for example fluorouracil, raising potential concerns about the generalisability of the study results. Available, although limited, evidence points towards tegafur-uracil being at least as effective as is fluorouracil 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, findings from our prospective trial indicates that watchful waiting for patients with low rectal cancer who have complete clinical response to high-dose chemoradiotherapy might be a safe and effective alternative for some individuals. Patients with local recurrence all underwent standard surgical resection, and the incidence of distant metastases is in agreement with current published work reporting on patients undergoing primary surgery.[28] Ultimately, more than half 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 groups.

Contributors

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; and SRR was responsible for radiological assessment and ALA for radiotherapy treatment data. ALA analysed data 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.

Declaration of interests

We declare no competing interests.

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