

Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial

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Summary

Background Organ preservation is a concept proposed for patients with rectal cancer after a good clinical response to neoadjuvant chemotherapy, to potentially avoid morbidity and side-effects of rectal excision. The objective of this study was to compare local excision and total mesorectal excision in patients with a good response after chemoradiotherapy for lower rectal cancer.

Methods We did a prospective, randomised, open-label, multicentre, phase 3 trial at 15 tertiary centres in France that were experts in the treatment of rectal cancer. Patients aged 18 years and older with stage T2T3 lower rectal carcinoma, of maximum size 4 cm, who had a good clinical response to neoadjuvant chemoradiotherapy (residual tumour ≤ 2 cm) were centrally randomly assigned by the surgeon before surgery to either local excision or total mesorectal excision surgery. Randomisation, which was done via the internet, was not stratified and used permuted blocks of size eight. In the local excision group, a completion total mesorectal excision was required if tumour stage was ypT2–3. The primary endpoint was a composite outcome of death, recurrence, morbidity, and side-effects at 2 years after surgery, to show superiority of local excision over total mesorectal excision in the modified intention-to-treat (ITT) population (expected proportions of patients having at least one event were 25% vs 60% for superiority). This trial was registered with ClinicalTrials.gov, number NCT00427375.

Findings From March 1, 2007, to Sept 24, 2012, 186 patients received chemoradiotherapy and were enrolled in the study. 148 good clinical responders were randomly assigned to treatment, three were excluded (because they had metastatic disease, tumour >8 cm from anal verge, and withdrew consent), and 145 were analysed: 74 in the local excision group and 71 in the total mesorectal excision group. In the local excision group, 26 patients had a completion total mesorectal excision. At 2 years in the modified ITT population, one or more events from the composite primary outcome occurred in 41 (56%) of 73 patients in the local excision group and 33 (48%) of 69 in the total mesorectal excision group (odds ratio 1.33, 95% CI 0.62–2.86; $p=0.43$). In the modified ITT analysis, there was no difference between the groups in all components of the composite outcome, and superiority was not shown for local excision over total mesorectal excision.

Interpretation We failed to show superiority of local excision over total mesorectal excision, because many patients in the local excision group received a completion total mesorectal excision that probably increased morbidity and side-effects, and compromised the potential advantages of local excision. Better patient selection to avoid unnecessary completion total mesorectal excision could improve the strategy.

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Introduction

The standard treatment for rectal cancer is total mesorectal excision with or without neoadjuvant chemoradiotherapy according to initial staging definition.^{1,2} Surgery is associated with complications, including death during the operation for 2% of patients,³ and early or late morbidity in 25–50% of patients.^{4,6} However, neoadjuvant radiotherapy leads to tumour sterilisation in 16% of patients and is associated with a good prognosis for the disease.⁷ These findings allow the possibility of saving the rectum in the case of an excellent response after neoadjuvant chemoradiotherapy. Saving the rectum would be revolutionary, especially in

locally advanced rectal cancer, where it would be associated with a dramatic improvement of quality of life, mainly because most postoperative complications due to surgery will disappear, as well as later complications, such as a definitive colostomy, urogenital dysfunctions, or gastrointestinal disorders.⁵ Saving the rectum would also be an opportunity to save costs for health-care systems because smaller tumours, which are good candidates for rectum preservation, are increasingly found now because of national bowel cancer screening programmes.

Organ preservation is a new concept for patients with rectal cancer treated by neoadjuvant therapy.⁸ For

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Research in context

Evidence before this study

Neoadjuvant chemoradiotherapy for locally advanced rectal cancer at tumour stages T3T4 induces 16% of tumour sterilisation. Organ preservation, by use of observation or local excision, is a new concept proposed for good clinical responders to avoid morbidity and side-effects of rectal excision.

We searched PubMed and ClinicalTrials.gov for English-language articles published between January, 2000, and January, 2017, using the terms “rectal cancer” and “organ preservation” or “watch and wait” or “local excision”. We identified a few studies, mostly about the “watch and wait” strategy, which were either single institution (from a pioneering Brazilian team), or multicentre trials (Danish, British, and Dutch studies), but included only a few participants (55–109); one included a comparative, retrospective analysis. Moreover, patient selection criteria in these studies were unclear. Studies that investigated local excision for organ preservation also included few participants. Investigators from the ACOSOG Z6041 phase 2 trial reported a national experience with 5% local recurrence and 88% survival at 3 years; however, they only included patients with T2, nodal stage (N) 0 tumours in their study and did not report long-term side-effects. Finally, a systematic research published in January, 2017, did not identify any phase 3, randomised trials in the setting of organ preservation for rectal cancer treated by neoadjuvant chemoradiotherapy.

Added value of this study

We reported the first phase 3, multicentre, national randomised trial comparing local excision and rectal excision in clinical good responders after chemoradiotherapy for patients

with T2T3N0–1 low rectal cancer, with the objective to assess both oncological and non-oncological issues. Results from our study confirmed those from the ACOSOG Z6041 trial by showing 40% pathological response ypT0 and showed that patients with rectal cancer tumour stage T2 and even T3, but with tumours of no more than 4 cm, are good candidates for organ preservation. By using a three-step strategy including clinical staging, clinical response, and pathological response, organ preservation could occur in 46% of patients without risk of missing positive mesorectal lymph nodes. The strategy seemed oncologically safe because 3-year local recurrence and disease-free survival did not differ between the local excision and total mesorectal excision groups. Globally, the strategy of local excision was not superior to conventional surgery, because of a high rate of completion surgeries, which increased morbidity and side-effects at 2 years. The findings also showed that few positive lymph nodes (8%) occurred in such small irradiated tumours, indicating that completion surgery should be limited to less than 10% of patients (at stages ypT2/N1 and ypT3).

Implications of all the available evidence

Our study supports the strategy of organ preservation for rectal cancer treated by chemoradiotherapy. Patients with small T2T3 rectal tumours are the best candidates for this strategy. Completion surgery could even be restricted further to patients with high-risk ypT2–3 tumours after local excision. Using our three-step strategy is oncologically secure and offers a promising new standard in patients treated by chemoradiotherapy for rectal cancer.

patients with a complete or subcomplete clinical response, the strategies of observation (watch-and-wait) or transanal local excision are available. Single-institution,⁹ retrospective,¹⁰ and prospective cohort studies^{11,12} have reported findings from use of the observation strategy (15% to 30% of local recurrence usually controlled by curative radical surgery and 58% to 92% stoma-free with survival up to 80% in most studies at 2 or 3 years of follow-up).^{9–12} Local excision has been assessed in single-institution¹³ and multicentre studies^{14–17} (but not comparative studies), all of which included very few patients. Only one phase 2 US trial has reported the experience of organ preservation at a national level, including low rectal cancer at stage T2N0 treated by local excision after chemoradiotherapy.¹⁸ Results were promising with less than 5% local recurrence and 88% survival at 3 years; however, this study could not change standard practice of total mesorectal excision because there was no comparative group. Moreover, only patients with stage I (T2N0) tumours were included.

We therefore did a randomised clinical trial comparing local excision with total mesorectal excision in patients who were good responders after chemoradiotherapy for

T2T3N0–1 (stage I–III) lower rectal cancer. The primary objective of the study was to test the overall superiority of local excision compared with total mesorectal excision with regards to a composite endpoint of efficacy and safety (death, recurrence, major surgical morbidity, and severe side-effects at 2 years after surgery); secondary objectives were assessment of the tumour response and whether the strategy was safe from an oncological perspective up to 3 years after surgery.

Methods

Study design and participants

We did a prospective, randomised, open-label, multicentre, phase 3 trial at 15 tertiary centres in France expert in the treatment of rectal cancer, comparing local excision and total mesorectal excision in patients with downstaged lower rectal cancer. The study was approved by the ethics committee (CPP southwest of France number 3).

Inclusion criteria were patients aged 18 years or older able to receive radiochemotherapy and major surgery, having lower rectal infiltrating carcinoma (≤ 8 cm from the anal verge), greatest diameter 4 cm, clinically

staged T2 or T3, and N0-1 (none to three nodes ≤ 8 mm involved). Exclusion criteria were metastatic disease, anal sphincter involvement, contraindication for chemotherapy, previous pelvic radiotherapy, history of other cancer and tumours presenting with major adenoma component. Investigations included colonoscopy and biopsy, endorectal ultrasound, pelvic MRI, abdominal and thoracic CT scan, allowing Union for International Cancer Control/Tumour Node Metastase (UICC/TNM) classification of the tumour.¹⁹ Patients' written informed consent was obtained before inclusion.

Randomisation

Patients were included before or after neoadjuvant chemoradiotherapy after confirmation of inclusion criteria and were randomly assigned before surgery, centralised via the internet (figure 1). Randomisation was not stratified and used permuted blocks of size eight. No masking was implemented. Good clinical responders to neoadjuvant chemoradiotherapy (residual tumour ≤ 2 cm) were randomly assigned by the surgeon to either local excision or total mesorectal excision. In the local excision group, patients with a good pathological response (ypT0-1) had a follow-up, while those with a poor pathological response (ypT2-3 or R1) had a completion total mesorectal excision.

Procedures

Radiotherapy consisted of 3D conformal pelvic radiotherapy delivering 50 Gy with high-energy (18 MV) photons in fractions of 2 Gy, 5 days a week over 5 weeks. Capecitabine 1600 mg/m² per day, 5 days per week, and oxaliplatin 50 mg/m² per week, were administered during radiotherapy. In January, 2009, oxaliplatin was stopped because of results from phase 3 trials showing increased toxicity without increased response when oxaliplatin was added to conventional chemoradiotherapy.²⁰ Restaging was done 6–8 weeks after chemoradiotherapy by pelvic MRI. A good clinical response was defined as a residual tumour scar of 2 cm or less, with no vegetative component and no significant hollow or deep infiltration into the muscular layer.²¹ Both patients with complete and subcomplete clinical responses were therefore admitted.

Surgery was done 8 weeks after irradiation. Local excision was a full thickness excision of the rectal wall, with a bowel margin of 1 cm, performed conventionally or with transanal endoscopic microsurgery. Identification of the residual scar was obtained by visualisation of abnormal mucosal (white colour with telangiectasies), residual ulcers, or superficial hollows. In the total mesorectal excision group, sphincter preservation was anticipated because inclusion criteria were small rectal tumours without anal sphincter involvement and experienced surgeons trained in the intersphincteric resection technique did the surgery. A completion total mesorectal excision was recommended at 1–4 weeks after

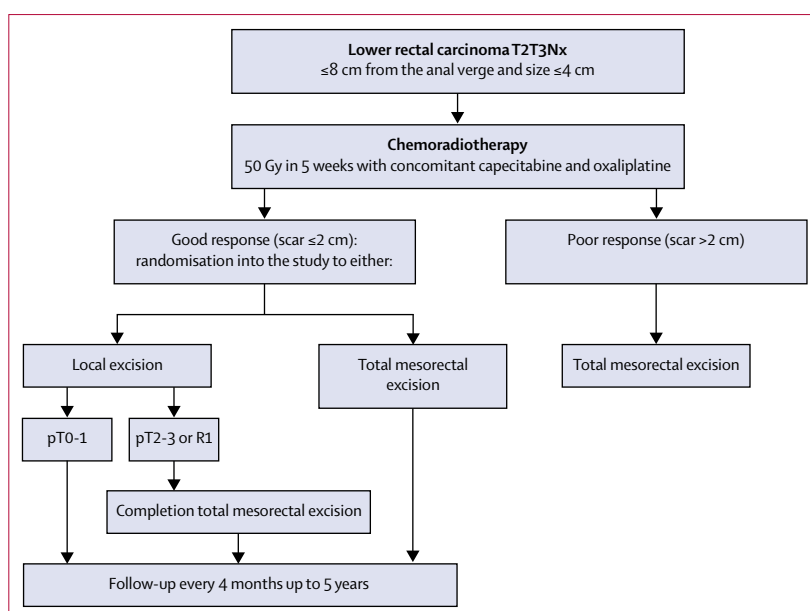


Figure 1: Study design

T=tumour stage. N=nodal stage. p=pathological stage.

local excision for patients with a bad pathological response after local excision (ypT2–3 or R1).

The rectal specimens were examined following the US pathological guidelines.²² Tumours were classified using the 7th UICC/TNM staging system.¹⁹ A complete pathological tumour response (ypT0) was defined as the absence of cancer cells in the tumour area included in its entirety, regardless of the presence of acellular mucin pools. R0 resection included surgical margin of at least 1 mm for both local excision and total mesorectal excision specimens. The tumour regression was graded as described by Rödel and colleagues.²³

Patients were followed up every 4 months for 2 years, then every 6 months for up to 5 years, by using clinical examination with rectal digitation by the surgeon, thoracoabdominal CT scan, and endorectal ultrasound and pelvic MRI in patients who received local excision. Any patient with suspected local recurrence had a biopsy before receiving salvage total mesorectal excision.

Outcomes

The primary endpoint was a composite outcome with four components: death, recurrence (local or distal), major surgical morbidity (grades III–V of Dindo's classification²⁴), and severe complications (definitive colostomy, anal incontinence, or impotence) at 2 years after randomisation. Secondary endpoints were local recurrence, metastatic recurrence, disease-free and overall survival at 3 years, and clinical and pathological tumour response. Anal incontinence was defined as a Wexner score of more than 10.²⁵ Impotence was defined as worse sexual activity by using the validated questionnaire QLQ C30-CR38 in all patients. Patients who were not sexually active before

treatment were considered as no worse function and missing data were obtained by phone interview.

Statistical analysis

We hypothesised that the incidence of each event of the composite endpoint after local excision versus total mesorectal excision for downstaged rectal cancer would be the following: operative death 0 versus 2%, major morbidity 5% versus 20%, severe complications 5% versus 25–50%, and we expected local recurrence (5%) and metastatic recurrence (10%) to be similar in both groups, assuming that local excision would be as successful as total mesorectal excision on those oncological endpoints.²⁶ The proportion of patients having at least one event was therefore expected to be 25% versus 60% (for superiority); 46 patients per group were required ($\alpha=0.05$, power=90%, two-sided χ^2 test). Assuming 10% of patients in the local excision group would have a poor pathological response and require a completion total mesorectal excision, 120 patients (60 in each group) were required. After

inclusion of 60 patients, the independent data monitoring committee recommended to increase inclusions up to 72 per group due to an estimate of 20% of patients having a poor pathological response after local excision.

Qualitative variables were compared at 2 years with the χ^2 test or Fisher's exact test when appropriate. The composite endpoint and each of its components were compared at 2 years after surgery between groups using logistic mixed models adjusted on centres, tumour, and nodal stages, in a modified intent-to-treat analysis (some patients were excluded from analysis for eligibility criteria or consent withdrawal). Missing data were replaced by occurrence of the event. We also did a sensitivity analysis excluding patients with missing outcome data. Kaplan-Meier method or adapted Kaplan-Meier method handling deaths as a competing risk were used for the estimation of 3-year disease-free and overall survival, 3-year local, uncontrolled local, and metastatic cumulative incidence rates. Patients were all censored at 3 years for these survival analyses. Comparisons of survival and cumulative incidence rates between groups

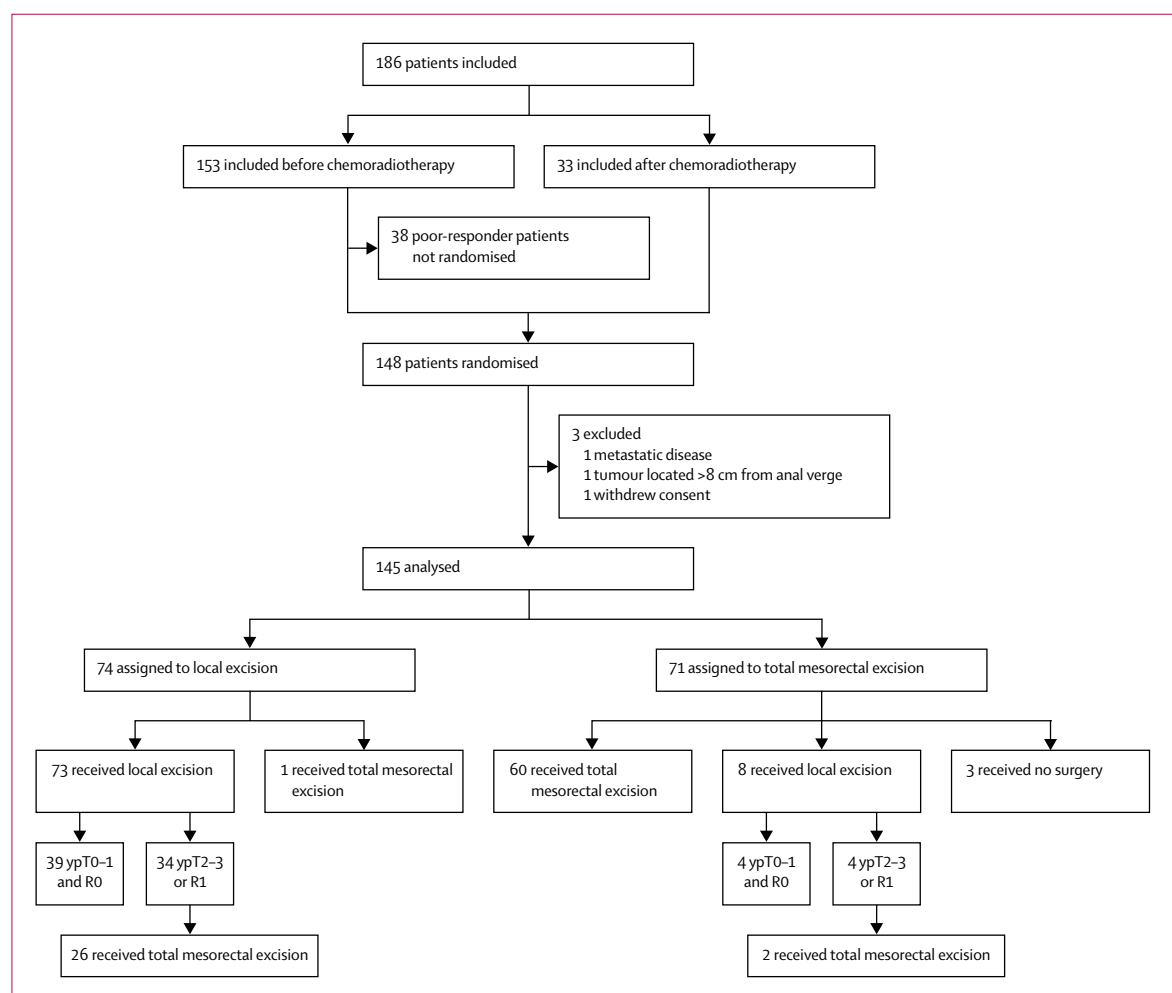


Figure 2: Trial profile

were analysed with modified intent-to-treat and per-protocol (patients analysed according to the strategy they actually received) approaches. Proportional hazard models were used, adjusted on centres, tumour, and nodal stages. Adjustment on pathological tumour response was also considered in the per-protocol analyses because of the potential imbalance between groups. Models assumptions were checked with cumulative sums of martingale-based residuals. The safety analysis was presented in three groups, according to the surgery (local excision alone, total mesorectal excision alone, and local excision and completion total mesorectal excision), because a post-hoc exploratory analysis that was meant to explore how the new strategy might have been affected in patients receiving completion total mesorectal excision and local excision alone. All analyses were done with a 5% type 1 error rate. Statistical analyses used SAS software (SAS version 9.3) and were done at the Clinical Epidemiology Unit of the University Hospital of Bordeaux, France. The trial was registered with ClinicalTrials.gov, number NCT00427375.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author, AD, and JA had full access to all the data in the study and had final responsibility with AR, VV, and QD for the decision to submit for publication.

Results

Between March 1, 2007, and Sept 24, 2012, 186 patients were enrolled at 15 French institutions: 153 were included before, and 33 after chemoradiotherapy (figure 2). Among the 153 patients included before treatment, 115 (75%) had a good clinical response. Overall, 148 patients who were clinically good responders were randomly assigned to surgery, three were excluded, and 145 were analysed: 74 in the local excision group and 71 in the total mesorectal excision group in the modified intent-to-treat analyses (81 and 61 patients in both groups received local excision and total mesorectal excision, respectively, and were included in the per-protocol analyses). The two groups were balanced in terms of patient demographic characteristics, tumour characteristics, and neoadjuvant therapy (table 1). The date for final follow-up was Feb 28, 2015.

No deaths occurred after neoadjuvant therapy. Grade 3 toxic effects were present in 15 (10%) of 145 patients. The most frequent toxicities were diarrhoea (eight [6%]), nausea (one [1%]), asthenia (one [1%]), and rectitis (two [1%]). Grade 3 toxic effects were greater after oxaliplatin plus capecitabine compared with capecitabine alone, but the difference was not significant (10 [15%] vs five [6%]; $p=0.103$).

The median interval between chemoradiotherapy and surgery was 60 days (range 34–132; IQR 51–67).

Compliance to surgery is summarised in table 1 and figure 2. In the local excision group one patient had total mesorectal excision because of technical difficulties, whereas in the total mesorectal excision group 11 patients did not have total mesorectal excision because of patient refusal ($n=6$) or surgeon discretion ($n=5$). The median interval between local excision and completion total mesorectal excision was 28 (range 2–88; IQR 15–49) days.

In the per-protocol population, among 81 patients in total treated by local excision, 58 had a conventional transanal local excision and 23 had transanal endoscopic microsurgery; monobloc excision was done in 80 patients (one had missing data), and rectal closure by suturing was done in 70 patients. Among 61 patients in total treated by total mesorectal excision, ten had a low anterior resection, 22 had a coloanal anastomosis, and 29 had a intersphincteric resection. In 28 patients in the per-protocol population who had a completion total

	Local excision (n=74)	Total mesorectal excision (n=71)
Age (years)*	61 35–84; 55–71	64 (40–88; 53–72)
Sex		
Male	50 (68%)	43 (61%)
Female	24 (32%)	28 (39%)
ECOG performance status		
0	68 (92%)	68 (96%)
1 or 2	6 (8%)	3 (4%)
Distance from anal verge (cm)*	4.0 (2.5–8.0; 3.0–6.0)	4.0 (2.5–7.0; 3.0–5.0)
Distance from anal ring (cm)*	1.5 (0.0–5.0; 1.0–3.0)	1.0 (0.0–4.5; 1.0–2.0)
Tumour size (cm)*	3.0 (1.3–4.0; 3.0–4.0)	3.0 (2.0–4.0; 3.0–4.0)
Tumour location		
Anterior	23 (31%)	22 (31%)
Posterior	34 (46%)	31 (44%)
Lateral	17 (23%)	18 (25%)
Tumour stage		
T2	41 (55%)	36 (51%)
T3	33 (45%)	35 (49%)
Nodal stage		
N0	42 (57%)	48 (68%)
N1	32 (43%)	23 (32%)
Surgery undertaken		
Local excision	47 (64%)	6 (8%)
Local excision plus completion total mesorectal excision*	26 (35%)	2 (3%)
Total mesorectal excision†	1 (1%)	60 (85%)
No surgery	0	3 (4%)

Data are n (%) or median (range; IQR). *Five abdominoperineal resections, all in the local excision group. †No abdominoperineal resections.

Table 1: Baseline characteristics of the modified intent-to-treat population

	Local excision (n=74)*	Total mesorectal excision (n=71)*	Odds ratio (95% CI)	p value†
Primary outcome: composite of death, tumour recurrence, morbidity, and side-effects at 2 years				
One or more events present	41/73 (56%)	33/69 (48%)	1.33 (0.62–2.86)	0.43
Details of composite outcome				
Death	4/74‡ (5%)	4/71‡ (6%)	0.98 (0.18–5.24)	0.98
Tumour recurrence	11/71 (16%)	14/70 (20%)	0.81 (0.32–2.03)	0.63
Major morbidity	17/70 (24%)	15/69 (22%)	1.18 (0.51–2.72)	0.68
Side-effects total	24/69 (35%)	19/65 (29%)	1.29 (0.53–3.14)	0.54
Colostomy	9/70 (13%)	5/68 (7%)	1.76 (0.61–5.02)	0.27
Faecal incontinence§	3/62 (5%)	9/65 (14%)	0.60 (0.20–1.82)	0.34
Sexual dysfunction	17/73 (23%)	12/67 (18%)	1.10 (0.46–2.64)	0.81

*Frequency varies because proportions in the two groups are based on available data. †p values were based on a modified intention-to-treat comparison, in which missing data were replaced by occurrence of the event (missing=failure) and adjusted on centres, tumour, and nodal stages. ‡No postoperative deaths. §Assessed in patients without previous colostomy.

Table 2: Primary composite outcome at 2 years (modified intention-to-treat analysis)

	Local excision n=74	Total mesorectal excision n=71	Hazard ratio (95% CI)	p value*
Modified intention-to-treat population			NA	NA
Local recurrence†	4 (5%)	4 (6%)	0.74 (0.18–3.07)	0.68
Metastatic recurrence†	9 (12%)	12 (17%)	0.68 (0.25–1.82)	0.44
Uncontrolled local recurrence†	1 (1%)	3 (4%)	0.24 (0.02–2.30)	0.21
Disease-free survival‡	58 (78%)	54 (76%)	0.75 (0.35–1.60)	0.45
Overall survival‡	68 (92%)	65 (92%)	1.06 (0.30–3.71)	0.92
Per-protocol population	n=81	n=61	NA	NA
Local recurrence†	5 (6%)	2 (3%)	1.58 (0.25–9.77)	0.63
Metastatic recurrence†	12 (15%)	8 (13%)	0.68 (0.24–1.93)	0.47
Uncontrolled local recurrence†	1 (1%)	2 (3%)	0.34 (0.03–4.44)	0.41
Disease-free survival‡	61 (75%)	50 (82%)	0.92 (0.40–2.12)	0.84
Overall survival‡	72 (89%)	58 (95%)	1.82 (0.46–7.26)	0.40

NA=not applicable. *Comparisons adjusted for centres, tumour, and nodal stages for modified intention-to-treat analyses and further adjustments for pathological tumour response for per-protocol analyses. †Absolute numbers correspond to occurrence of the event at 3 years. ‡Absolute numbers correspond to absence of the event at 3 years.

Table 3: Oncological outcomes at 3 years (Kaplan Meier)

mesorectal excision, one had a low anterior resection, 15 had coloanal anastomoses, seven had intersphincteric resections, and five had abdominoperineal resections. No patients (of 61) had an abdominoperineal resection at initial total mesorectal excision, but five (18%) of 28 had one for completion total mesorectal excision.

In the modified intention-to-treat analysis 74 (100%) of 74 in the local excision group and 67 (94%) of 71 in the total mesorectal excision group had an R0 resection ($p=0.055$). 57 (40%) patients had tumours defined as ypT0, 29 (20%) as ypT1, 44 (31%) as ypT2, and 12 (9%) as ypT3. 86 (61%) of 142 patients had a good pathological response (ypT0–1), which was higher in patients with cT2 than cT3 tumours: 52 (69%) versus 34 (51%; $p=0.026$). From 89 total mesorectal excision specimens seven (8%) of 89 had positive lymph nodes. These were identified in no patients (of 30) with ypT0 tumours and none of 13

with ypT1, three (8%) of 36 with ypT2, and four (40%) of ten with ypT3. Pathological positive lymph nodes (ypN1) were found in one (2%) of 55 patients with cN0 versus six (18%) of 34 with cN1 rectal tumours ($p=0.007$).

28 rectal specimens after completion total mesorectal excision had a similar number of lymph nodes retrieved to 61 specimens after a primary total mesorectal excision: median 12 (range 1–28; IQR 8–16) versus 10 (1–26; IQR 8–14; $p=0.63$). Residual tumours were found in the bowel wall of one patient staged ypT2 after local excision and ypT3 after a completion total mesorectal excision. All patients had an R0 resection. Two (7%) of 28 patients who had a completion total mesorectal excision had positive lymph nodes.

One or more event from the composite outcome occurred in 74 of 145 randomly assigned patients at 2 years' follow-up. In the modified intention-to-treat analysis, one or more events occurred in 41 (56%) of 73 patients in the local excision group and 33 (48%) of 69 patients in the total mesorectal excision group (odds ratio 1.33, 95% CI 0.62–2.86; $p=0.43$). There was no operative mortality in either group. The modified intention-to-treat analysis did not show superiority of local excision over total mesorectal excision in all components of the composite outcome (table 2).

All patients had a 3-year follow-up, except those who died. Median follow-up was 36 months (range 11–36; IQR 36–36). In the modified intention-to-treat analysis, the difference between groups for oncological outcomes at 3 years was not significant (table 3, figure 3). Per protocol analysis supported these results with no difference between groups for all oncological endpoints (table 3).

Overall, eight local recurrences occurred in the 145 randomly assigned patients: two after a primary total mesorectal excision, five after local excision, and one after no surgery. The median time to local recurrence was 8.5 months (range 4–26; IQR 7–12); six (75%) of eight occurred in the first year. Local recurrence occurred in two patients with tumour stage ypT0R0, two with ypT1R0, and one with ypT2R0 after local excision; one with ypT1N0R0 and one with ypT3N1R1 after total mesorectal excision, and in one patient who had no surgery.

Management of local recurrence was achieved with salvage total mesorectal excision (one low anterior resection, one abdominoperineal resection [two were R1 resections]) in the two patients treated with a primary total mesorectal excision, and four salvage total mesorectal excisions (three low anterior resections, one abdominoperineal resection; all R0) after local excision. Two patients had no surgery, one because he refused, and one had diffuse metastases.

Among the eight patients who refused the completion total mesorectal excision in the local excision group (eight had ypT2), one had local recurrence alone treated by curative salvage total mesorectal excision, two had

metastatic recurrence (one with local recurrence), and two died (one from secondary cancer and one from cardiac disease). At the date of analysis, six were alive, five free from disease and one with metastatic disease.

Among the 38 patients diagnosed as non-responders at imaging, 20 had a residual tumour that was greater than 2 cm (of these, 19 had total mesorectal excision, one had local excision), 16 had a residual tumour of 2 cm or less with suspicion of infiltration (of these, 11 had total mesorectal excision, five had local excision), and two were lost to follow-up. Of the 33 specimens analysed (three were missing data), there were five at stage ypT0, eight at ypT1, 14 at ypT2, and six at ypT3; five were ypN1 (five [18%] of 28 were from a total mesorectal excision) and one had an R1 resection. 13 (39%) of 33 had a good pathologic response of ypT0-1.

The sensitivity analyses excluding missing data presented similar results to those obtained for the primary endpoint. However, the exploratory analysis showed variability in morbidity and severity of complications according to type of surgery: the more aggressive the surgery, the higher the complication rates (table 4). The severity of complications was also influenced by surgery; patients with local excision had minor complications requiring medical or endoscopic treatment mainly for rectal bleeding, whereas patients with total mesorectal excision or completion total mesorectal excision had severe complications requiring reoperation for pelvic abscess, peritonitis, small bowel obstruction, or colonic ischaemia. Three (6%) of 53 patients had early complications specifically related to local excision alone, and one (2%) of 53 had late complications related to local excision alone; all were minor. The major complications occurring after local excision alone (two pelvic abscess of 53) were due to salvage total mesorectal excision for local recurrence. Exploratory analyses according to the type of surgery showed that cumulative 3-year local recurrence occurred in five (9%) of 53 patients after local excision alone, two (3%) of 61 patients after total mesorectal excision, and in no patients after local excision plus completion total mesorectal excision; metastatic recurrence was noted in eight (15%) of 53, eight (13%) of 61, and four (14%) of 28 in the local excision, total mesorectal excision, and local excision plus completion total mesorectal excision groups, respectively. At 3 years, 37 (70%), 50 (82%), and 24 (86%) in these groups, respectively, were alive and free from disease.

Discussion

This trial was designed to compare organ preservation (local excision) and radical surgery (total mesorectal excision) in patients treated with chemoradiotherapy for lower rectal cancer. Considering the composite endpoint, the results of the study failed to show superiority of local excision compared with total mesorectal excision; however, the findings suggest the oncological safety of

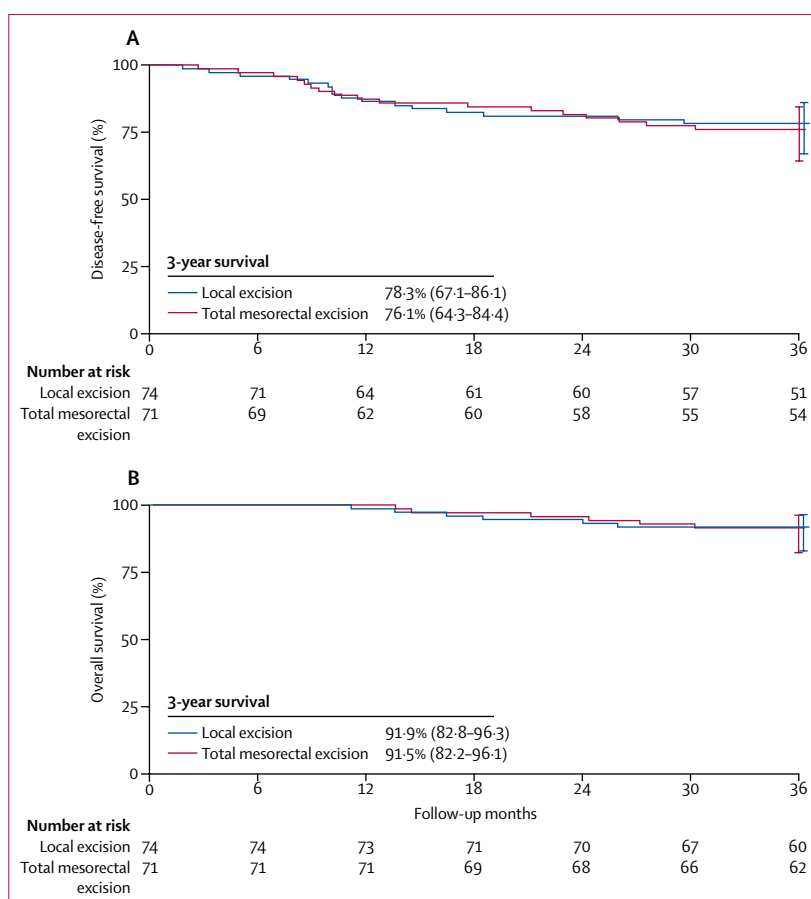


Figure 3: Survival after local excision versus total mesorectal excision

local excision, with no significant difference of local recurrence and disease-free survival at 3 years between the two groups. The absence of superiority of local excision in our trial was due to a high number of completion total mesorectal excisions undertaken, which significantly increased the morbidity and complications of the procedure and therefore compromised the potential advantages of local excision. On the other hand, the large number of nodal responses in patients with ypT0-1 and in most with ypT2 tumours suggests that a completion total mesorectal excision was not necessary in most cases.

Organ preservation is a new concept for locally advanced rectal cancer, which was introduced by Habr-Gama in 2004.⁹ However, over the past decade, only retrospective or non-comparative studies of this strategy have been reported.⁹⁻¹⁸ Our study is the first phase 3 multicentre trial in this setting. We used a composite endpoint, including both oncological and non-oncological outcomes, because we considered that the high morbidity of total mesorectal excision³⁻⁶ was an important aspect for which we expected a benefit with local excision, and that the oncological outcomes would not be affected, mostly because of the good prognosis of complete responders;⁷

	Local excision (n=53)*	Total mesorectal excision (n=61)*	Local excision plus completion total mesorectal excision (n=28)*	p value†
Major morbidity or side-effects total	14/48 (29%)	22/58 (38%)	21/27 (78%)	0.0001
Major morbidity (Dindo III-V)	6/48 (12%)	13/60 (22%)	13/28 (46%)	0.0031
Early morbidity (1 month)	3/53 (6%)	6/61 (10%)	7/28 (25%)	0.0291
Late morbidity (up to 2 years)	3/48 (6%)	10/60 (17%)	8/28 (29%)	0.0322
Side-effects	9/48 (19%)	17/57 (30%)	16/27 (59%)	0.0013
Definitive colostomy	2/48 (4%)	5/59 (9%)	7/28 (25%)	0.0178
Faecal incontinence‡	0	9/56 (16%)	3/22 (14%)	0.0056
Sexual dysfunction	7/53 (13%)	10/58 (17%)	11/27 (41%)	0.0113
Details of major morbidity				
Pelvic abscess or leakage	2 (4%)§	6 (10%)	8 (29%)	NA
Pelvic haematoma	0	0	1 (4%)	NA
Small bowel obstruction	0	1 (2%)	3 (11%)	
Colonic ischaemia	0	3 (5%)	0	NA
Vaginal stenosis	0	1 (2%)	0	NA
Rectal bleeding after local excision	2 (4%)	0	0	NA
Anastomotic coloanal stenosis	0	1 (2%)	1 (4%)	NA
Prolapse of ileostomy	0	1 (2%)	0	NA
Late rectal stenosis after local excision	1 (2%)	0	0	NA
Cardiac arrhythmia	1 (2%)	0	0	NA
Cerebrovascular accident		1 (2%)		
Pulmonary embolism	0	0	1 (4%)	NA
Overall major morbidity (number)	6 (11%)	13 (21%)	13 (46%)	NA
Overall major morbidity (number/total number)	6 (11%)	14 (23%)	14 (50%)	NA

NA=not applicable. *Proportions in the two groups based on available data. †p values based on a per-protocol comparison without replacement of missing data or adjustments. ‡Assessed in patients without previous colostomy for another cause of incontinence. §Complications after salvage total mesorectal excision.

Table 4: Morbidity and side-effects at 2 years according to type of surgery (post-hoc exploratory analysis)

however, we considered it important to assess the procedure overall with a measure combining all clinical outcomes.

Our study showed that patients favoured the organ preservation approach because they valued a possible better quality of life associated with less invasive surgery, as underlined by the lower compliance to the allocated surgery in the total mesorectal excision group than in the local excision group in case of good clinical response. Furthermore, some patients in the local excision group refused to undergo a completion total mesorectal excision. The originality of our study is the three-step strategy, which included three criteria for patient selection for organ preservation: clinical staging, good clinical response to chemoradiotherapy, and pathological response. One of our main findings was that after chemoradiotherapy for small T2T3 rectal carcinomas (≤ 4 cm), 75% of patients had a good clinical response (carcinoma ≤ 2 cm), which was associated with 61% of good pathological tumour response (ypT0-1) that correlated with a low risk of positive lymph nodes (100% ypN0). This strategy theoretically translates to

organ preservation in 46% of patients without the risk of positive mesorectal lymph nodes being missed in an assessment. The advantage of our strategy is therefore to propose and predict the chance of organ preservation in selected patients with a low oncological risk.

The number of patients with morbidity and complications was similar in both groups, which did not enable us to show an advantage of the local excision strategy. This high morbidity is due to the higher than anticipated number of completion total mesorectal excisions, and to that the morbidity of completion total mesorectal excisions was twice as high after a primary total mesorectal excision. An exploratory analysis according to the type of surgery undertaken suggested that local excision was associated with less morbidity than total mesorectal excision, which in turn was less morbid than local excision plus completion total mesorectal excisions. Additionally, the types of complications after local excision appeared to be less severe than after total mesorectal excisions or completion total mesorectal excisions, although they were considered as a major morbidity according to Dindo's classification. Thus, although we were not able to show a difference between the groups, we hope for a potential advantage of local excision in the future, if modifying the screening and surgical indication criteria enables inclusion of a population with a lower risk of requiring completion total mesorectal excisions.

Pathological data showed a low rate of positive lymph nodes, 8% for the overall population, suggesting that completion total mesorectal excision was overused in our study. Positive lymph nodes occurred in 0, 0, 8%, and 40% of patients with ypT0, ypT1, ypT2, and ypT3 tumours, respectively, after chemoradiotherapy for small T2T3 rectal cancer. These numbers are lower than the 5%, 8%, 26% and 55% usually reported after chemoradiotherapy for more advanced T3T4 disease,²⁷ and might be attributed to the smaller size of the tumours in our trial (maximum diameter 4 cm). Indeed, tumour and nodal responses are correlated with the clinical tumour stage and tumour size.²⁸ In our study, the lower number of positive pathological lymph nodes in patients clinically staged N0 than in those staged N1 suggests that patients with ypT2 and cN0 tumours, conventionally treated with completion total mesorectal excision, might not require completion total mesorectal excisions in the future. This finding is in accordance with the results of the ACOSOG Z6041 trial.¹⁸

Results from the non-randomly assigned patients (ie, those considered as clinically inadequate responders), showed that 39% had a good pathological response (ypT0-1), suggesting that the method of assessment of the response in our study was not optimum and that some clinically inadequate responders could have benefited from organ preservation. Improved imaging, particularly pelvic MRI,²⁹ and a delay before making a decision, might improve the diagnosis of response.

The American ACOSOG Z6041 phase 2 trial included 79 patients with T2N0 lower rectal cancer treated with chemoradiotherapy (54 Gy, capecitabine and oxaliplatin) followed by local excision.¹⁸ 4% of patients had local recurrence and 88% were alive and free from disease at 3 years, and the investigators concluded that local excision after chemoradiotherapy was an alternative to major surgery in unfit patients. Our finding of 5% local recurrence occurring in the local excision group confirms the results of ACOSOG Z6041. Although we included more patients with advanced tumours (T3 and N1), we believe that local recurrence remained low in our trial because only good clinical responders were considered for local excision and completion total mesorectal excision was recommended for patients with ypT2-3 tumours. The proportion of patients alive and disease-free at 3 years was lower in our study compared with the ACOSOG Z6041 (78% vs 88%) probably because we included patients with stages II and III disease, as well as those with stage I disease. Therefore, metastatic disease could be a problem if patients with more locally advanced tumours are considered for organ preservation programmes. Indeed, after local excision or watch-and-wait strategies, adjuvant chemotherapy is not conventionally used.^{11,12,18}

A Dutch observational study¹² reported results from 100 patients with T1-4/N0-2 rectal tumours located between 0 and 15 cm from the anal verge, treated with chemoradiotherapy (50 Gy) or radiotherapy (5×5 Gy): 61 had an immediate complete clinical response, 24 had delayed complete clinical response 3 months later, and 15 had local excision for near complete clinical response.¹² Most patients had no surgery at all, and at 3 years, 85% were recurrence-free and 81% were alive and disease-free. This study supported the previous results of a Brazilian team (Gama and colleagues⁹), and was able to improve the diagnostic performance of complete clinical response after neoadjuvant therapy by using high quality MRI.²⁹ Findings from a Danish trial proposed high dose chemoradiotherapy alone (external beam 60 Gy plus brachytherapy 5 Gy) in patients with T2-3/N0-1 lower rectal tumours.¹¹ The trial stopped after the first 55 patients because of accrual difficulties. Of 40 patients with complete clinical response, 26% had local recurrence at 2 years; all local recurrences were treated by curative radical surgery.

The OnCoRe Manchester registry study¹⁰ compared retrospectively 109 patients with T2-4 rectal cancers treated by chemoradiotherapy and observation (watch-and-wait) with 109 matched patients treated by chemoradiotherapy and total mesorectal excision. Although survival was not compromised in the observation group, 38% of patients had local recurrence at 3 years, and most patients (24 [65%] of 37) treated for local recurrence received abdominoperineal resection or Hartmann's.

In the future, there is no doubt that observation, as proposed in previous studies, will become a standard in

good clinical responders after chemoradiotherapy for rectal cancer, especially for patients with a complete clinical response. Indeed, observation alone is less invasive than surgery, even local excision. However, given the findings from our trial, especially the high morbidity and number of complications at 2 years in the less invasive local excision group with no advantage compared with standard surgery, it seems necessary to investigate long-term non-oncological outcomes in any type of organ preservation programme. In particular, investigations should include the effect of salvage total mesorectal excision, and to compare this in intention-to-treat populations with standard of care.

Organ preservation after neoadjuvant chemoradiotherapy for rectal cancer includes a risk of overtreatment, where total mesorectal excision alone would be a safe possibility. The response is stage-dependent with 58% of T1, 28% of T2, 16% of T3, and 12% of T4 tumours reaching stage ypT0.⁷ Big tumours theoretically are exposed to a high risk of overtreatment if organ preservation is anticipated, because the chance of sterilisation is low. Conversely, small tumours can be overtreated, especially for patients who will require a completion total mesorectal excision. Our study reporting 40% of patients with ypT0 tumours, similar to the 44% of patients with ypT0 tumours in ACOSOG Z6041,¹⁸ suggests that small T2T3 tumours less than 4 cm are good candidates for organ preservation because of the high chance of complete or subcomplete pathological response. Furthermore, our data suggest that most completion total mesorectal excisions could be avoided. Finally, close follow-up with MRI to detect lymph node recurrences could also be an alternative to completion total mesorectal excisions.

Our clinical trial had several limitations. First, the sample size was small—however, our study included ultra-selected patients with small T2T3 low rectal tumours, which represents 20% of rectal cancers. The anticipated number of patients required to test our hypothesis was obtained and we do not think that inclusion of more patients would have changed the conclusions.

Second, we used a non-usual composite primary endpoint. This strategy might have induced difficulties for interpretation of the results because no weighting was used for each component. However, we believe that the composite outcome was representative of what is expected from a patient with rectal cancer and good clinical response, because it included oncological, toxicity, and functional issues. Also this study was not masked, because of the different surgical procedures in the two groups.

Third, we did not show the superiority of local excision over total mesorectal excision, and furthermore the width of the CIs of the comparative analysis showed the limited precision of the estimates, preventing any argument that the local excision approach was non-inferior (or equivalent)

to total mesorectal excision. Fourth, we also explored and described morbidity and oncological outcomes in the local excision, local excision plus completion total mesorectal excision, and total mesorectal excision groups; although this analysis was exploratory and does not correspond to comparable groups as per randomisation, it might implicate some important features for the future of research on this procedure such as a close follow up to screen for local recurrences in patients undergoing local excision, and also informing patients who undergo local excision that, would a completion total mesorectal excision be necessary in the future, the morbidity after both procedures seems higher than after traditional total mesorectal excision. Finally, interpretation of the final results needs caution because of the protocol deviation of nine of 71 patients assigned to total mesorectal excision not receiving total mesorectal excision. This protocol deviation might have produced less morbidity in the total mesorectal excision group, suggesting underestimation of morbidity occurred in this group; however, this possibility was explored in the per-protocol analysis, and the conclusions were not affected. By contrast, the choice of Dindo stages III–V to define surgical morbidity suggests overestimation of morbidity in the local excision group because severity of complications was higher after total mesorectal excision than after local excision. Indeed, rectal bleeding after local excision treated by endoscopy was defined as grade 3, similar to that noted with laparotomy for peritonitis after total mesorectal excision. Thus, there is a potential for overestimation of morbidity after local excision alone and in the local excision group, although this was not shown in the study.

In conclusion, local excision was not superior to total mesorectal excision in patients with T2T3 small rectal cancers with good response after chemoradiotherapy; however, 3-year local recurrence and disease-free survival did not differ significantly between groups (although the study was not powered to test formally whether local excision was oncologically safe). The absence of superiority of local excision might have been due to a high occurrence of completion total mesorectal excisions that probably increased morbidity and complications. However, pathological data showed a low occurrence of positive lymph nodes in such small, irradiated tumours, suggesting that most completion total mesorectal excisions were not necessary. We hypothesise that, similar to ypT0-1/Nx tumours, the subgroup of ypT2/N0 tumours might not require completion total mesorectal excisions either, and only high-risk patients with ypT2N1 and pT3 tumours will require this surgery. A new trial, GRECCAR 12, will test this hypothesis and will serve to optimise the response by using neoadjuvant chemotherapy plus chemoradiotherapy. In the future, watch-and-wait studies, as well as local excision studies, will contribute together to study the efficacy and safety of strategies aimed at increasing the chances of organ preservation in complete or subcomplete responders

after neoadjuvant therapy for rectal cancer. By using such strategies, we expect around 20% of patients with rectal cancer could avoid radical surgery.

Contributors

ER, AD, and JA conceived the idea and designed the study, and analysed and interpreted the data. ER, PR, J-JT, AV, BL, MR, J-LF, MJ, GP, BM, IS, MP, FM, MPo, and DP provided study materials or patients. GRECCAR 2 investigators and research assistants obtained and assembled the data. ER, AD, JA, AR, VV, and QD wrote the report. All authors contributed to data interpretation and approved the manuscript.

Declaration of interests

We declare no competing interests.

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References

- 1 Van Gijn W, Marijnen CAM, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre randomised, controlled TME trial. *Lancet Oncol* 2011; **12**: 575–82.
- 2 Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006; **355**: 1114–23.
- 3 Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet* 2009; **373**: 811–20.
- 4 Pahlman L, Bohe M, Cedermark B, et al. The Swedish rectal cancer registry. *Br J Surg* 2007; **94**: 1285–92.
- 5 Peeters KCMJ, van de Velde CJH, Leer JWH, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients—a Dutch colorectal cancer group study. *J Clin Oncol* 2005; **23**: 6199–206.
- 6 Marijnen CAM, van de Velde CJH, Putter H, et al. Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial. *J Clin Oncol* 2005; **23**: 1847–58.
- 7 Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol* 2010; **11**: 835–44.
- 8 Baxter N, Garcia-Aguilar J. Organ preservation for rectal cancer. *J Clin Oncol* 2007; **25**: 1014–20.
- 9 Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long term results. *Ann Surg* 2004; **240**: 711–18.
- 10 Renehan AG, Malcomson L, Emsley R, et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. *Lancet Oncol* 2016; **17**: 174–83.
- 11 Appelt AL, Pløen J, Harling H, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. *Lancet Oncol* 2015; **16**: 919–27.
- 12 Martens MH, Maas M, Heijnen LA, et al. Long-term outcome of an organ preservation program after neoadjuvant treatment for rectal cancer. *J Natl Cancer Inst* 2016; **108**: djw171.
- 13 Lezoche E, Baldarelli M, Lezoche G, Paganini AM, Gesuita R, Guerrieri M. Randomized clinical trial of endoluminal locoregional resection versus laparoscopic total mesorectal excision for T2 rectal cancer after neoadjuvant therapy. *Br J Surg* 2012; **99**: 1211–18.
- 14 Bujko K, Richter P, Kołodziejczyk M, et al. Preoperative radiotherapy and local excision of rectal cancer with immediate radical re-operation for poor responders. *Radiother Oncol* 2009; **92**: 195–201.

- 15 Pucciarelli S, De Paoli A, Guerrieri M, et al. Local excision after preoperative chemoradiotherapy for rectal cancer: results of a multicenter phase II clinical trial. *Dis Colon Rectum* 2013; **56**: 1349–56.
- 16 Verseveld M, de Graaf EJR, Verhoef C, et al. Chemoradiation therapy for rectal cancer in the distal rectum followed by organ-sparing transanal endoscopic microsurgery (CARTS study). *Br J Surg* 2015; **102**: 853–60.
- 17 Smart CJ, Korsgen S, Hill J, et al. Multicentre study of short-course radiotherapy and transanal endoscopic microsurgery for early rectal cancer. *Br J Surg* 2016; **103**: 1069–75.
- 18 Garcia-Aguilar J, Renfro LA, Chow OS, et al. Organ preservation for clinical T2N0 distal rectal cancer using neoadjuvant chemoradiotherapy and local excision (ACOSOG Z6041): results of an open-label, single-arm, multi-institutional, phase 2 trial. *Lancet Oncol* 2015; **16**: 1537–46.
- 19 Edge SB, Byrd DR, Carducci MA, Compton CC, eds. AJCC cancer staging manual, 7th edn. New York: Springer; 2009.
- 20 Gérard JP, Azria D, Gourgou-Bourgade S, et al. Comparison of two neoadjuvant chemotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCOR 12/0405-Prodige 2. *J Clin Oncol* 2010; **28**: 1638–44.
- 21 Schell SR, Zlotecki R, Mendenhall WM, et al. Transanal excision of locally advanced rectal cancers downstaged using neoadjuvant chemoradiotherapy. *J Am Coll Surg* 2002; **194**: 584–91.
- 22 Washington MK, Berlin J, Branton P, et al. Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum. *Arch Pathol Lab Med* 2009; **133**: 1539–51.
- 23 Rodel C, Martus P, Papadopoulos T, et al. Prognostic significance of tumour regression after preoperative chemoradiation for rectal cancer. *J Clin Oncol* 2006; **24**: 8688–96.
- 24 Dindo D, Demartines N, Clavien PA, et al. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205–13.
- 25 Jorge JM, Wexner SD. Etiology and management of fecal incontinence. *Dis Colon Rectum* 1993; **36**: 77–97.
- 26 Rullier E, Vendrely V. Can mesorectal lymph node excision be avoided in rectal cancer surgery? *Colorectal Dis* 2011; **13** (suppl 7): 37–42.
- 27 Bujko C, Nowacki MP, Nasierowska-Guttmejer A, et al. Prediction of mesorectal nodal metastases after chemoradiation for rectal cancer: results of a randomised trial. Implication for subsequent local excision. *Radiother Oncol* 2005; **76**: 234–40.
- 28 Gérard JP, Chamoire E, Gourgou-Bourgade S, et al. Clinical complete response (cCR) after neoadjuvant chemoradiotherapy and conservative treatment in rectal cancer. Findings from the ACCORD 12/PRODIGE 2 randomized trial. *Radiother Oncol* 2015; **115**: 246–52.
- 29 Maas M, Lambregts DM, Nelemans PJ, et al. Assessment of clinical complete response after chemoradiation for rectal cancer with digital rectal examination, endoscopy, and MRI: selection for organ-saving treatment. *Ann Surg Oncol* 2015; **22**: 3873–80.