Organ preservation with chemoradiotherapy plus local excision for rectal cancer: 5-year results of the GRECCAR 2 randomised trial

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Summary

Background GRECCAR 2 was the first multicentre, randomised trial to compare local excision with total mesorectal excision in downstaged low rectal cancer. Encouraging oncological results were noted at 3 years' follow-up but needed to be corroborated with longer follow-up. In this study, we aimed to report the 5-year oncological outcomes, including local recurrence, metastatic disease, and survival.

Methods Patients age 18 years and older with T2T3 low rectal cancer, of maximum size 4 cm, who were clinically good responders after chemoradiotherapy (residual tumour ≤2 cm) were randomly assigned before surgery to either local excision or total mesorectal excision. Randomisation was centralised and not stratified and used permuted blocks of size eight. In the local excision group, a completion total mesorectal excision was performed if pathological tumour stage was ypT2–3. The primary objective of this study was to assess the 5-year oncological outcomes of local recurrence, metastatic disease, disease-free survival, overall survival, and cancer-specific mortality, which were the secondary endpoints of GRECCAR 2. We used Kaplan-Meier estimates and Cox modelling to estimate and compare recurrence and survival in modified intention-to-treat and as-treated populations. This trial was registered with ClinicalTrials.gov, number NCT00427375.

Findings Between March 1, 2007, and Sept 24, 2012, 148 patients who were good clinical responders were randomly assigned to treatment, three patients were excluded after randomisation (because they had metastatic disease, tumour >8 cm from anal verge, or withdrew consent), leaving 145 for analysis: 74 in the local excision group and 71 in the total mesorectal excision group. Median follow-up was 60 months (IQR 58–60) in the local excision group and 60 months (57–60) in the total mesorectal excision group. 23 patients died and five were lost to follow-up. In the local excision group, 26 had a completion total mesorectal excision for ypT2–3 tumour. In the modified intention-to-treat analysis, there was no difference between the local excision and total mesorectal excision groups in 5-year local recurrence (7% [95% CI 3–16] *vs* 7% [3–16]; adjusted hazard ratio [HR] 0·71 [95% CI 0·19–2·58]; p=0·60), metastatic disease (18% [CI 11–30] *vs* 19% [11–31]; 0·86 [0·36–2·06]; p=0·73), overall survival (84% [73–91] *vs* 82% [71–90]; 0·92 [0·38–2·22]; p=0·85), disease-free survival (70% [58–79] *vs* 72% [60–82]; 0·87 [0·44–1·72]; p=0·68), or cancer-specific mortality (7% [3–17] *vs* 10% [5–20]; 0·65 [0·17–2·49]; p=0·53).

Interpretation The 5-year results of this multicentre randomised trial corroborate the 3-year results, providing no evidence of difference in oncological outcomes between local excision and total mesorectal excision. Local excision can be proposed in selected patients having a small T2T3 low rectal cancer with a good clinical response after chemoradiotherapy.

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Introduction

Organ preservation is a new concept in treatment of rectal cancer.[1–3] Compared with standard rectal excision, organ (rectal) preservation offers the opportunity to avoid the operative mortality, significant morbidity, and digestive and urogenital dysfunction often associated with major surgery.[4–6] However, these advantages should not be compromised by a poorer oncological outcome in terms of local recurrence or metastatic disease and survival. Two approaches have been developed for organ preservation in rectal carcinoma treated by neoadjuvant chemoradiotherapy: watch and wait, and local excision. Watch and wait is an observational concept, based on the treatment of squamous cell anal cancer.[7] After neoadjuvant chemoradiotherapy, patients are clinically observed and surgery is done only in cases of incomplete response or local regrowth. The term local regrowth is usually used following tumour reappearance after watch and wait, whereas the term local recurrence is used after surgery. Although the advantage of watch and wait is

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Research in context

Evidence before this study

We searched PubMed and ClinicalTrials.gov for English-language articles published between Jan 1, 2000, and Sept 30, 2019, using the terms "rectal cancer" and "organ preservation" or "watch and wait" or "local excision" or "chemoradiotherapy". Several prospective studies including between 50 and 79 patients reported local excision after chemoradiotherapy for cT1–T3N0 rectal tumour and showed 3–8% local recurrence and 72–95% overall survival. Two meta-analyses and one international database of watch and wait included between 692 and 880 patients with cT1T4Nx tumours and reported local regrowth in 16–25% of patients, with 88–95% success of salvage surgery in those with local regrowth, and 3-year overall survival of 85–93%. To our knowledge, GRECCAR 2 is the only multicentre, randomised phase 3 trial to compare organ preservation with radical surgery, but only short-term results have been previously published.

Added value of this study

The 5-year results of the GRECCAR 2 trial comparing local excision and total mesorectal excision in patients with a good clinical response after chemoradiotherapy for small T2T3 low rectal cancer showed no significant difference between groups in local recurrence, metastatic disease, overall survival, disease-free survival, or cancer-specific mortality. These findings corroborate the 3-year results and provide no evidence of difference in oncological outcomes between local excision and radical surgery in selected patients with a small low rectal cancer and good response after chemoradiotherapy. The low frequency of 5-year local recurrence (7%) is because of patient selection and completion surgery in bad pathological responders, although the role of the latter needs further investigation. The proportion of patients with metastatic disease (nearly 20%) observed in our trial underlines that metastases have been underestimated in the literature of organ preservation and suggests adjuvant chemotherapy could be used when organ preservation is planned.

Implications of all the available evidence

To our knowledge, this is the first phase 3 trial reporting long-term outcomes of organ preservation for rectal cancer. It provides a high level of evidence suggesting the oncological safety of organ preservation in selected low rectal cancers.

the potential avoidance of surgery, the disadvantage is leaving the tumour scar in place, which requires radical surgery in a third of cases.[8,9] Local excision is a different concept in which, 6–8 weeks after chemoradiotherapy, transanal surgery is done to remove the residual tumour scar while leaving the rectum in place. The disadvantage to this approach is the requirement for systematic surgery, although this is minor surgery,[10] whereas the advantage is limiting the risk of local recurrence by removing the tumour.[3,10]

Since the first reports of watch and wait,[1,2,11–13] two meta-analyses of watch and wait have been reported.[14,15] One was a pooled analysis of 692 patients showing 22% had local regrowth, 8% had metastases, and 88% required salvage surgery, and 3-year overall survival was 93%, and concluded that watch and wait seems feasible and safe.[14] The second meta-analysis included 867 patients and showed no significant difference in overall survival between watch and wait and rectal excision, but better disease-free survival in the surgery group.[15] The authors concluded that few patients have been compared and more prospective studies are needed to confirm the long-term safety of watch and wait. More recently, a retrospective observational study pointed out worse disease-free survival and disease-specific survival after watch and wait compared with standard rectal excision, and a higher incidence of metastasis in patients with local regrowth compared with those without local regrowth in the watch-and-wait group (eight [36%] of 22 *vs* one [1%] of 91),[8] although this difference was smaller in the recent and large cohort from the International Watch & Wait Database (38 [18%] of 213 *vs* 33 [5%] of 634).[16] Thus, the oncological safety of watch and wait is unclear and still debated.[17]

Local excision after neoadjuvant chemoradiotherapy has been investigated by several prospective trials including patients mainly with early-stage or small rectal tumours.[10,18–20] The biggest phase 2 single-arm trial included 79 patients with T2N0 tumours and showed 4% local recurrence and 88% disease-free survival at 3 years.[3] We did a phase 3 trial (GRECCAR 2) comparing local excision versus total mesorectal excision in T2T3N0–1 low rectal cancers treated with neoadjuvant chemoradiotherapy and reported no significant differences between groups in death, disease recurrence, morbidity, or side-effects at 2 years.[21] We also reported that some patients with a bad pathological response did not receive the completion surgery required by the protocol. Long-term oncological outcomes after organ preservation with either watch and wait or local excision have yet to be reported from a multicentre randomised trial.

The main objective of the study was therefore to compare the 5-year oncological outcomes between local excision and total mesorectal excison in the GRECCAR 2 trial, in terms of local recurrence, pelvic control (also known as uncontrolled local recurrence), metastatic disease, and survival.

Methods

Study design and participants

GRECCAR2 was a prospective, randomised, open-label, multicentre, phase 3 trial done at 15 centres in France. The protocol has been previously reported.[21] Eligible patients were aged 18 years or older, able to receive

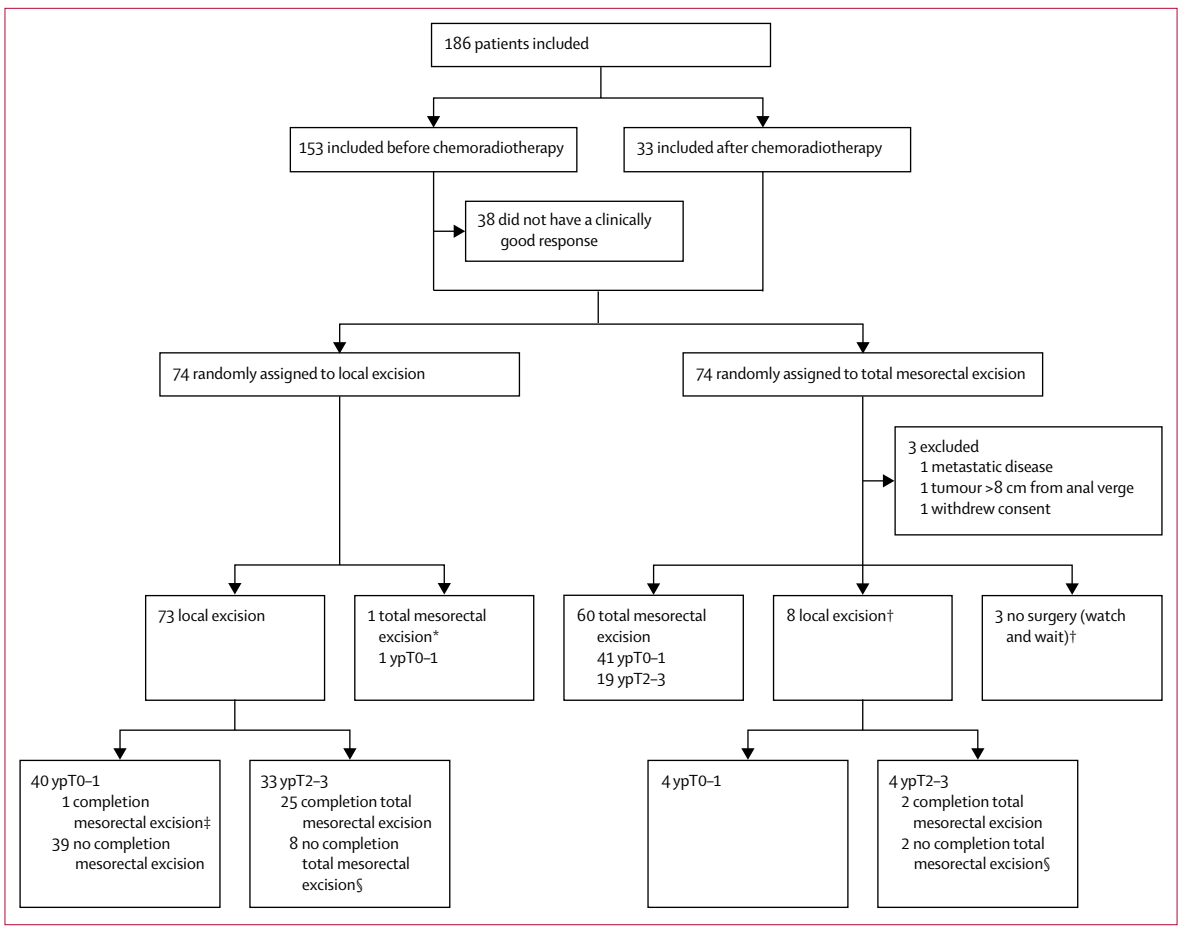

Figure 1: **Trial profile**
*Protocol deviation because of technical difficulties. †Protocol deviation because of patient refusal or surgeon discretion. ‡For R1 resection. §Protocol deviation.

chemoradiotherapy and major surgery, had a low rectal cancer carcinoma (≤8 cm from the anal verge), maximum size 4 cm, clinically staged T2 or T3, and N0–1 (with up to three nodes ≤8 mm involved). Non-eligible patients had anal sphincter involvement, previous pelvic radiotherapy, contraindication for chemotherapy, and metastatic disease. We used the Union for International Cancer Control Tumour Node Metastasis[22] classification for tumour staging after colonoscopy, endorectal ultrasound, pelvic MRI, and abdominal and thoracic CT scan. Patients were included before or after neoadjuvant chemoradiotherapy (figure 1). The trial protocol was approved by the scientific ethical regional committee (CPP southwest of France number 3), and all patients provided written informed consent. A list of participating centres is shown in the appendix.

Randomisation and masking

GRECCAR 2 was an open-label study. Good clinical responders to neoadjuvant chemoradiotherapy (residual tumour ≤2 cm) were randomly assigned (1:1) to either local excision or total mesorectal excision.[21] Randomisation was centralised and not stratified, and used permuted blocks of size eight.

Procedures

Neoadjuvant treatment consisted of long-course chemoradiotherapy, 50 Gy in 25 fractions of 2 Gy, 5 days a week over 5 weeks, in association with fluorouracil based chemotherapy as previously described.[21] Pelvic MRI was used at 6–8 weeks after chemoradiotherapy for tumour restaging. A good clinical response was a complete or subcomplete response, 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. Nodal response at MRI was not used for decision making.

Surgery was done 8 weeks after chemoradiotherapy. Local excision was a surgical transanal traditional or endoscopic full thickness rectal wall excision, with a bowel margin of 1 cm. Total mesorectal excision included removal of the rectum and the whole of the mesorectum. In the local excision group, patients with a good pathological response (ypT0–1) were followed up, and those with a poor

See Online for appendix

	Local excision (n=74)	Total mesorectal excision (n=71)
Median age (years)	61 (35–84)	64 (40–88)
Sex		
Male	50 (68%)	43 (61%)
Female	24 (32%)	28 (39%)
ECOG status		
0	68 (92%)	68 (96%)
1–2	6 (8%)	3 (4%)
Median distance from anal verge (cm)	4·0 (2·5–8·0)	4·0 (2·5–7·0)
Median distance from anal ring (cm)	1·5 (0·0–5·0)	1·0 (0·0–4·5)
Median tumour size (cm)	3·0 (1·3–4·0)	3·0 (2·0–4·0)
Tumour size <2 cm	4 (5%)	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 actually performed		
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 median (range) or n (%). ECOG=Eastern Cooperative Oncology Group.
*Five abdominoperineal resections, all in the local resection group.
†No abdominoperineal resections.

Table 1: **Baseline characteristics of the intention-to-treat population**

pathological response (ypT2–3 or R1) had a completion total mesorectal excision (figure 1). Completion total mesorectal excision, if required, was done 1–4 weeks after local excision.

Patients with positive lymph nodes (ypN1) after total mesorectal excision could receive adjuvant chemotherapy (FOLFOX for 6 months) at discretion of the oncologists. No patient treated by local excision alone received adjuvant chemotherapy. Follow-up after surgery included digital rectal examination, endorectal ultrasound, pelvic MRI, and thoracoabdominal CT scan every 4 months for 2 years, then every 6 months for up to 5 years.

Outcomes

The primary endpoint of the GRECCAR 2 trial was a composite outcome including death, recurrence, severe morbidity, and side-effects at 2 years and findings for this outcome have been published.[21] In this study, we aimed to report the 5-year oncological outcomes, including local recurrence, uncontrolled local recurrence, metastatic disease, overall survival, disease-free survival, and cancer-specific mortality (death due to rectal cancer).

Statistical analysis

To show the superiority of local excision versus total mesorectal excision for the primary endpoint of GRECCAR 2, 144 patients (72 in each group) were required.[21] In this study, no sample size was calculated to analyse the oncological outcomes at 5 years. We used the Kaplan-Meier method to estimate 5-year disease-free survival and overall survival. We used a cumulative incidence competing risks method to estimate the 5-year oncological outcomes of local recurrence, uncontrolled local recurrence, metastatic disease, and cancer-specific mortality. We compared survival and cumulative incidence between groups in a modified intention-to-treat analysis (ie, excluding patients who were ineligible after randomisation or who withdrew consent) and an as-treated analysis (patients analysed according to the surgery they actually received). We used proportional hazard models, adjusted by centre, tumour stage, and nodal stage to control for potential between-centre heterogeneity in patient care and strong prognostic factors of oncological outcomes. Further adjustment by pathological tumour response was done in the as-treated analyses because of the potential imbalance between groups. Models assumptions were checked with cumulative sums of martingale-based residuals. We also did a post-hoc subgroup analysis, comparing strategies according to pathological tumour response. All analyses were done with a 5% type I error rate. Statistical analyses were performed at the Clinical Epidemiology Unit of the University Hospital of Bordeaux, France, using SAS software (version 9.4; SAS Institute, Cary, NC, USA). GRECCAR 2 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 members of the scientific committee had access to all the data, contributed to data interpretation, and shared the responsibility for the final decision to submit the report for publication.

Results

Between March 1, 2007, and Sept 24, 2012, 186 patients were enrolled and treated by chemoradiotherapy. 148 patients had a clinically good response and were randomly assigned to surgery. Three patients were excluded, all in the total mesorectal excision group (one patient had metastatic disease, one had a tumour located >8 cm from the anal verge, and one withdrew consent), and 145 were therefore included in the modified intention-to-treat analysis: 74 in the local excision group and 71 in the total mesorectal excision group. The two groups were balanced in terms of patient

	Local excision	Total mesorectal excision	Unadjusted hazard ratio (95% CI)	Unadjusted p value	Adjusted hazard ratio (95% CI)	Adjusted p value
Modified intention-to-treat analysis	n=74	n=71	NA	NA	NA	NA
Local recurrence	5 (7%); 95% CI 3–17	5 (7%); 95% CI 3–16	0·96 (0·28–3·31)	0·95	0·71 (0·19–2·58)	0·60
Uncontrolled local recurrence	2 (3%); 95% CI 1–12	3 (4%); 95% CI 1–13	0·63 (0·10–3·76)	0·61	0·48 (0·08–2·90)	0·42
Metastatic disease	13 (18%); 95% CI 11–30	13 (19%); 95% CI 11–31	0·95 (0·44–2·06)	0·90	0·86 (0·36–2·06)	0·73
Overall survival	63 (84%); 95% CI 73–91	59 (82%); 95% CI 71–90	0·87 (0·39–1·98)	0·75	0·92 (0·38–2·22)	0·85
Disease-free survival	52 (70%); 95% CI 58–79	52 (72%); 95% CI 60–82	1·11 (0·60–2·06)	0·73	0·87 (0·44–1·72)	0·68
Cancer-specific mortality	4 (7%); 95% CI 3–17	7 (10%); 95% CI 5–20	0·54 (0·16–1·85)	0·33	0·65 (0·17–2·49)	0·53
As-treated analysis	n=81	n=61	NA	NA	NA	NA
Local recurrence	6 (8%); 95% CI 4–17	2 (3%); 95% CI 1–13	2·34 (0·47–11·58)	0·30	1·96 (0·34–11·45)	0·45
Uncontrolled local recurrence	2 (3%); 95% CI 1–11	2 (3%); 95% CI 1–13	0·76 (0·11–5·37)	0·78	0·57 (0·08–4·40)	0·59
Metastatic disease	16 (20%); 95% CI 13–32	8 (13%); 95% CI 7–25	1·53 (0·65–3·68)	0·33	0·94 (0·36–2·46)	0·90
Overall survival	66 (80%); 95% CI 69–88	53 (87%); 95% CI 76–93	1·45 (0·61–3·42)	0·40	1·10 (0·42–2·91)	0·84
Disease-free survival	54 (66%); 95% CI 54–75	49 (80%); 95% CI 68–88	1·77 (0·90–3·49)	0·10	1·08 (0·50–2·33)	0·84
Cancer-specific mortality	5 (7%); 95% CI 3–17	6 (10%); 95% CI 5–21	0·64 (0·20–2·10)	0·46	0·36 (0·09–1·38)	0·14

Percentages correspond to 5-year survival estimates derived from Kaplan-Meier and cumulative incidence methods.

Table 2: **5-year oncological outcomes**

demographic characteristics, tumour characteristics, and neoadjuvant therapy (table 1). In the local excision group, 26 (35%) of 74 patients had a completion total mesorectal excision for ypT2–3 tumour. Protocol deviations from randomisation occurred in one patient of the local excision group (one total mesorectal excision because of technical difficulties) and in 11 patients in the total mesorectal excision group (eight local excisions and three watch and wait because of patient refusal or surgeon discretion). Overall, 81 patients received local excision and 61 a received total mesorectal excision (as-treated analysis population; figure 1). A subsequent protocol deviation occurred in ten patients who received local excision (eight in the local excision group and two in the total mesorectal excision group); these patients did not receive the planned completion total mesorectal excision after local excision for ypT2 tumours. Overall, six patients received adjuvant chemotherapy: three after completion total mesorectal excision in the local excision group and three in the total mesorectal excision group, all for ypN1 stage disease. The median follow-up was 60 months (IQR 58–60) in the local excision group and 60 months (57–60) in the total mesorectal excision group. All patients had a follow-up of 60 months, except 23 who died and five who were lost to follow-up at 38, 43, 49, 55, and 57 months.

Overall, ten (7%) patients had local recurrence (five in the local excision group and five in the total mesorectal excision group). Five (3%) of 145 patients had local recurrence alone and five (3%) had local recurrence with metastases. The ten local recurrences were endoluminal, and there was no pelvic lymph node recurrence. The median time for diagnosis of local recurrence was 12 months (range 5–59; IQR 10–26); five (50%) of ten recurrences occurred in the first year, two (20%) in the second year, one (10%) in the third year, one (10%) in the fourth year, and one (10%) in the fifth year of follow-up. Patients with local recurrence (n=10) had a primary rectal tumour staged ypT0 (n=2), ypT1 (n=3), ypT2 (n=2), ypT3 (n=1) and two patients had no surgery. Salvage surgery with curative intent—ie, macroscopic removal of the disease—was possible in (70%) of the ten patients (rectum in all cases and hepatectomy in two cases), whereas three (30%) of ten patients with local recurrence had palliative chemotherapy for unresectable metastatic disease. All patients with local recurrence alone after local excision (n=4) had salvage R0 resection.

The 5-year cumulative incidence of local recurrence did not differ between the local excision group and the total mesorectal excision group (table 2). In the modified intention-to-treat analysis, 5-year local recurrence was 7% (95% CI 3–16) for local excision versus 7% (3–16) for

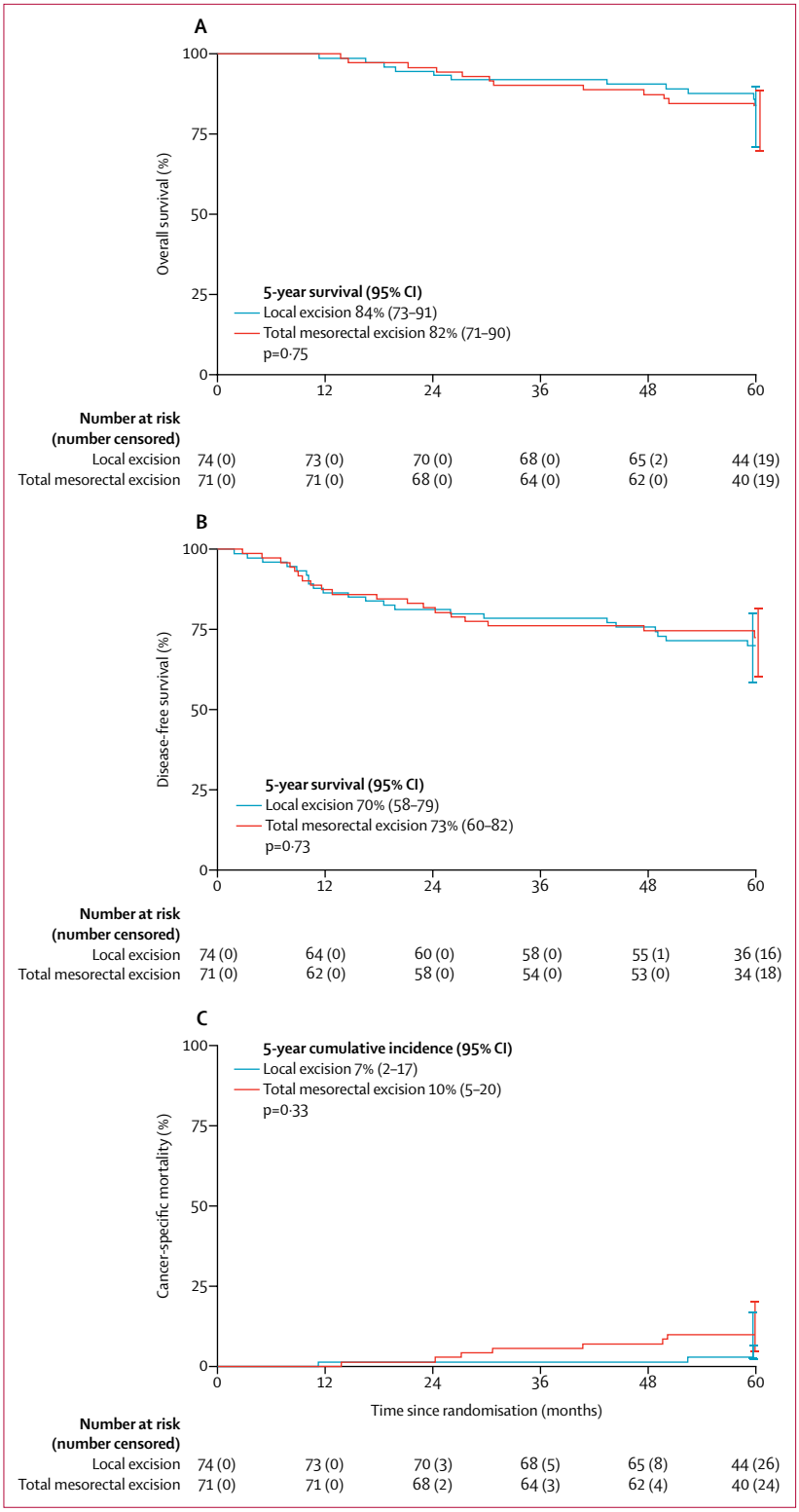

Figure 2: **Kaplan-Meier estimates of survival and mortality in the modified intention-to-treat population**
Non-adjusted estimates of (A) overall survival, (B) disease-free survival, and (C) cancer-specific mortality.

	Local excision (n=11)	Total mesorectal excision (n=12)	Total (n=23)
Rectal cancer	4 (36%)	7 (58%)	11 (48%)
Second cancer*	3 (27%)	1 (8%)	4 (17%)
Cardiovascular	3 (27%)	2 (17%)	5 (22%)
Infection	0	1 (8%)	1 (4%)
Accident	1 (10%)	0	1 (4%)
Unknown	0	1 (8%)	1 (4%)

*Not a new primary or recurrent rectal cancer.

Table 3: **Causes of death**

total mesorectal excision (adjusted hazard ratio [HR] 0·71 [95% CI 0·19–2·58]; p=0·60). 5-year uncontrolled local recurrence did not differ between groups (3% [95% CI 1–12] *vs* 4% [1–13]; adjusted HR 0·48 [95% CI 0·08–2·90]; p=0·42). The as-treated analysis showed no significant difference in local outcomes between groups (table 2).

Overall, 26 (18%) of 145 patients had metastatic disease (n=13 in each group). There were 28 sites of metastases in the local excision group and 29 in the total mesorectal excision group. Metastases were present more frequently in lung (14 in the local excision group *vs* nine in the total mesorectal excision group) and liver (five *vs* 12), than in lymphatic (five *vs* three), peritoneum (one *vs* one), brain (none *vs* four), and bone (three *vs* none). Three (12%) of 26 patients with metastatic disease had previously received adjuvant chemotherapy after total mesorectal excision, all for ypN1 stage disease.

In the modified intention-to-treat analysis, the proportion of patients with metastatic disease at 5 years did not differ between the local excision group (18% [95% CI 11–30]) and total mesorectal excision group (19% [11–31]; adjusted HR 0·86 [95% CI 0·36–2·06]; p=0·73). In the as-treated analysis, there was no significant difference in incidence of metastatic disease between groups (table 2). Notably, the 5-year cumulative incidence of metastatic disease was three times higher in the patients with bad pathological response (ypT2–3; 28% [95% CI 18–43]) compared with the patients with a good pathological response (ypT0–1; 10% [6–19]; risk ratio 2·78, 95% CI 1·22–6·35; p=0·02).

In the modified intention-to-treat analysis, 5-year survival and cancer-specific mortality did not differ between groups: 5-year overall survival was 84% (95% CI 73–91) in the local excision group versus 82% (71–90) in the total mesorectal excision group (adjusted HR 0·92 [95% CI 0·38–2·22]; p=0·85), disease-free survival was 70% (95% CI 58–79) versus 72% (60–82; adjusted HR 0·87 [0·44–1·72]; p=0·68), and cancer-specific mortality was 7% (3–17) versus 10% (5–20; adjusted HR 0·65 [0·17–2·49]; p=0·53; figure 2). In the as-treated analysis there were no significant differences in outcomes between groups (table 2).

In the modified intention-to-treat population, 23 (16%) patients had died at 5 years (11 in the local excision group

	ypT0–1				ypT2–3			
	Local excision	Total mesorectal excision	HR (95% CI)	p value	Local excision	Total mesorectal excision	HR (95% CI)	p value
Modified intention-to-treat analysis (n=142)*	n=41	n=45	NA	NA	n=33	n=23	NA	NA
Local recurrence	3 (7%); 95% CI 3–22	2 (4%); 95% CI 1–17	1·34 (0·19–9·31)	0·77	2 (7%); 95% CI 2–27	1 (4%); 95% CI 1–30	2·03 (0·08–53·53)	0·67
Uncontrolled local recurrence	0	1 (2%); 95% CI 0–15	NA	NA	2 (7%); 95% CI 2–27	1 (4%); 95% CI 1–30	2·03 (0·08–53·53)	0·67
Metastatic disease	4 (10%); 95% CI 4–25	5 (11%); 95% CI 5–25	1·20 (0·18–8·21)	0·85	9 (29%); 95% CI 17–51	6 (26%); 95% CI 13–52	0·95 (0·31–2·89)	0·93
Overall survival	35 (85%); 95% CI 70–93	39 (87%); 95% CI 73–94	1·36 (0·36–5·17)	0·65	28 (83%); 95% CI 69–93	17 (72%); 95% CI 48–87	0·37 (0·09–1·43)	0·15
Disease-free survival	31 (76%); 95% CI 59–86	36 (80%); 95% CI 65–89	1·20 (0·40–3·63)	0·74	21 (62%); 95% CI 42–76	15 (63%); 95% CI 39–80	0·84 (0·32–2·18)	0·72
Cancer-specific mortality	2 (5%); 95% CI 1–19	3 (7%); 95% CI 2–20	1·96 (0·15–26·17)	0·61	2 (8%); 95% CI 2–31	4 (17%); 95% CI 7–42	0·24 (0·04–1·49)	0·13
As-treated analysis (n=142)	n=44†	n=42	NA	NA	n=37	n=19	NA	NA
Local recurrence	4 (9%); 95% CI 4–23	1 (2%); 95% CI 0–17	2·53 (0·25–25·66)	0·43	2 (6%); 95% CI 2–25	1 (5%); 95% CI 1–36	1·97 (0·07–52·97)	0·69
Uncontrolled local recurrence	0	1 (2%); 95% CI 0–17	NA	NA	2 (6%); 95% CI 2–25	1 (5%); 95% CI 1–36	1·97 (0·07–52·97)	0·69
Metastatic disease	6 (14%); 95% CI 7–29	3 (7%); 95% CI 2–21	2·70 (0·26–27·80)	0·40	10 (29%); 95% CI 17–49	5 (26%); 95% CI 12–56	0·88 (0·27–2·87)	0·83
Overall survival	36 (82%); 95% CI 67–90	38 (90%); 95% CI 77–96	1·64 (0·37–7·27)	0·51	30 (78%); 95% CI 59–89	15 (79%); 95% CI 53–92	0·64 (0·16–2·47)	0·51
Disease-free survival	31 (70%); 95% CI 55–82	36 (86%); 95% CI 71–93	1·99 (0·58–6·83)	0·27	23 (59%); 95% CI 41–74	13 (68%); 95% CI 43–84	0·91 (0·32–2·62)	0·87
Cancer-specific mortality	3 (7%); 95% CI 2–21	2 (5%); 95% CI 1–18	1·07 (0·05–21·73)	0·96	2 (7%); 95% CI 2–28	4 (21%); 95% CI 9–50	0·21 (0·04–1·26)	0·09

Percentages correspond to 5-year survival estimates derived from Kaplan-Meier and cumulative incidence methods. Comparisons (hazard ratio and p values) are adjusted by centre, tumour stage, and nodal stage. NA=not applicable. *Excluding three patients who had watch and wait. †Four patients were from the total mesorectal excision group and three had an event (metastasis, death, or both)

Table 4: **5-year oncological outcomes by pathological tumour stage**

and 12 in the total mesorectal excision group; table 3). There were no deaths in either group due to surgery or neoadjuvant therapy.

In the post-hoc subgroup analysis of patients with good pathological responses (ypT0–1), there was no difference in 5-year oncological outcomes in patients who received local excision or total mesorectal excision, in both the modified intention-to-treat and as-treated analyses (table 4). No patient had uncontrolled pelvic recurrence after local excision for ypT0–1.

In the post-hoc subgroup analysis of patients with bad pathological response (ypT2–3), there were also no differences in 5-year oncological outcomes between groups in both the modified intention-to-treat and as-treated analyses (table 4). The proportion of patients with metastatic disease at 5 years, although higher in patients with bad pathological response than in those with good pathological response, did not differ between the local excision group and the total mesorectal excision group.

Overall, eight patients randomly assigned to the local excision group received a local excision alone for ypT2 tumour, without completion total mesorectal excision (figure 1). One of these eight patients had a local recurrence alone treated by curative rectal excision and two patients had metastatic disease, one treated by curative surgery and one by palliative chemotherapy (one associated with local recurrence). 5-year cancer-specific mortality in these patients was 14% (95% CI 2–89).

Discussion

There was no significant difference in long-term oncological outcomes between patients who had a good clinical response after chemoradiotherapy for small T2T3 low rectal cancer, who were treated by either local excision or total mesorectal excision. 5-year local recurrence, uncontrolled local recurrence, metastatic disease, disease-free survival, overall survival, and cancer-specific mortality did not differ between the two groups. Our data therefore suggest local excision is a potential option in patients who have a good clinical response after neoadjuvant chemoradiotherapy for small T2T3 rectal cancer. The post-hoc subgroup analyses suggest the safety of the rectal preservation strategy, with no significant differences of oncological outcomes in

patients with good pathological response (ypT0–1) treated by local excision alone or total mesorectal excision. Completion total mesorectal excision does not seem to be required in these patients. For patients with a bad pathological response (ypT2–3), the absence of difference between the two groups also suggests the safety of the strategy, although the role of the completion total mesorectal excision is unclear.

To our knowledge, this is the first prospective multicentre study reporting the long-term outcomes at 5 years in the setting of organ preservation after neoadjuvant chemoradiotherapy for rectal cancer. In our first reported findings at 3 years follow-up,[21] we observed local recurrence in four (5%) of 74 patients in the local excision group versus four (6%) of 71 patients in the total mesorectal excision group. At 5 years, local recurrence was observed in five (7%) patients in each group. The 5-year findings therefore support the preliminary results of the GRECCAR 2 trial, suggesting the oncological safety of local excision in term of local control. Moreover, all patients treated with curative intent for local recurrence were able to benefit from radical salvage surgery. This outcome suggests the relevance of the study follow-up schedule, which included digital rectal examination, pelvic MRI, endorectal ultrasound, and thoracoabdominal CT scan every 4 months for 2 years, then every 6 months for up to 5 years. The fact that seven (70%) of ten local recurrences occurred during the first 2 years underlines the necessity of a close follow-up during this period.

Metastatic disease is one of the main issues of rectal cancer. The preliminary 3-year results of the GRECCAR 2 study reported that nine (12%) of 74 patients had metastatic disease after local excision versus 12 (17%) of 71 patients after total mesorectal excision. The 5-year results from the modified intention-to-treat analysis (18% *vs* 19%) support the absence of difference between groups with a longer follow-up. This high proportion of patients with metastases, compared with the 10% observed in patients with complete pathological response after chemoradiotherapy and rectal excision,[23] might be due to the fact that our study included patients with complete and subcomplete pathological responses. The 5-year incidence of metastatic disease (nearly 20%) is also higher than the 8% reported in the literature of watch and wait.[14,16] We believe the incidence of metastatic disease was underestimated in watch-and-wait studies because these studies included patients with complete and incomplete pathological responses, as we did in GRECCAR 2. This underestimation is probably due to the retrospective nature of the studies, their small sample size, and the lack of 5-year follow-up.[14–16] In this study, the relatively high incidence of metastases at 5 years questions testing chemotherapy in strategies of organ preservation for rectal cancer. At present, the evidence of adjuvant chemotherapy after radiochemotherapy for rectal cancer is scarce. The ongoing GRECCAR 12 trial (NCT02514278) aims to evaluate induction chemotherapy with four cycles of FOLFIRINOX plus chemoradiotherapy versus chemoradiotherapy, with the hypothesis of increasing the rate of organ preservation and survival in rectal cancer by adding neoadjuvant FOLFIRINOX to chemoradiotherapy.

The concept of organ preservation for rectal cancer, using chemoradiation plus local excision is well accepted in cases of ypT0–1 tumour status because the risk of positive mesorectal lymph nodes is low: less than 10% in T3T4 tumours[23] and nearly zero in small T2T3 tumours.[21] By contrast, leaving in place the rectum and mesorectum after local excision for ypT2 tumour is still debated.[24,25] The first reason for this debate is the 20–30% incidence of positive mesorectal lymph nodes reported from conventional irradiated T3T4 tumours.[23] The second is the 23% rate of local recurrence after neoadjuvant therapy and local excision in ypT2 rectal tumour from a pooled analysis of 1068 patients selected by both clinical response and prohibitive comorbidity.[25] However, the GRECCAR 2 study, which included a very selected population of small T2T3 and N0–1 rectal tumours, with a good clinical response, reported new findings.[21] Pathology data from the original study showed seven (8%) of 89 specimens had positive lymph nodes,[21] suggesting that the nodal response is dependent of the initial tumour size. The smaller the tumour, the higher the response. Second, tumour cells were found in a limited number of completion specimens: one (4%) of 28 in the bowel and two (7%) of 28 in mesorectal lymph nodes.[21] Third, eight (24%) of 34 patients with bad pathological response did not receive the completion total mesorectal excision (violating the protocol) and this did not seem to compromise the oncological outcomes (there was no difference between groups in both modified intention-to-treat and as-treated analyses). Finally, 5-year cancer-specific mortality in this subgroup of eight patients was similar to that of the controlled total mesorectal excision group (14% *vs* 10%). Therefore, these findings support a new concept: in case of initial small irradiated rectal tumour, (with a maximum size of 4 cm), the mesorectum could be left in place after local excision for ypT2 tumour, especially if the initial tumour was staged N0 with MRI. Our findings are in accordance with the ACOSOG phase 2 trial,[3] which showed 4% local recurrence in patients treated by local excision after neoadjuvant chemoradiotherapy for small T2N0 rectal cancer, and a study of the US National Cancer Database[26] that showed similar 5-year overall survival between patients who received radical surgery and those who had local excision with neoadjuvant or adjuvant chemoradiotherapy in stage I rectal cancer. However, although promising, omitting radical surgery after local excision for ypT2 tumours after neoadjuvant therapy for primary small rectal tumours needs confirmation by the ongoing GRECCAR 12 trial, which is testing this new strategy.

The 5-year results of modified intention-to-treat analyses in the local excision group (7% local recurrence

and 84% overall survival) are concordant with mid-term or long-term outcomes of phase 2 trials, which showed an incidence of local recurrence of 3–8% and overall survival of 72–95% at 3 to 5 years after local excision following chemoradiotherapy for T1–T3 low rectal cancer.[3,10,18,19] These findings are also concordant with watch-and-wait series reporting local regrowth in 15–38% of patients, with 88–95% success of salvage surgery in those with local regrowth, and overall survival of 73–96% after an intermediate follow-up of 24–43 months.[1,8,11,13–16,22] The role of watch and wait in organ preservation for rectal cancer treated by neoadjuvant therapy is still debated.[27] The advantage of watch and wait is that having no surgery might preserve bowel function and improve quality of life. It has been shown that anorectal function is better after watch and wait than after local excision.[28] The disadvantage of watch and wait is the potential residual cells left in place that are not diagnosed by the actual imaging, requiring radical surgery in a third of patients.[14] Salvage surgery, although oncologically safe (with around 90% achieving R0 resection), is associated with 50% of patients requiring abdominoperineal excision and definitive colostomy, which compromises quality of life.[14] The effect of local regrowth on metastatic disease has not been solved[8] because comparative studies are lacking.[14–16] By contrast, local excision exposes patients to a risk of local recurrence of less than 10%,[3,10,18,19] and we noted in our findings that the long-term oncological outcomes did not differ between local excision and radical surgery, whatever the pathological response. The main disadvantage of local excision is potential completion total mesorectal excision because it is associated with twice as much morbidity and side-effects than a primary total mesorectal excision.[21]

There are limitations in comparing the two approaches of local excision and watch and wait in term of efficacy and side-effects. There are no studies prospectively comparing the two strategies. Watch-and-wait series also include more advanced tumours than local excision studies, because 67–69% of patients in watch-and-wait studies have T3-stage disease.[14,15] More advanced tumours are more heterogeneous, and potentially more aggressive and resistant to chemoradiotherapy, facilitating both lack of tumour regression and the development of metastases.[8,17] The UK trial STAR-TREC (NCT02945566) is focusing on organ preservation by using watch and wait and includes a control arm with radical surgery, and the findings will help clarify the differences in outcomes between watch and wait and radical surgery.

This study has some limitations. First, the long-term oncological outcomes were secondary endpoints of the GRECCAR 2 trial; therefore it was not designed as a non-inferiority trial and no margin was predefined to explore 5-year oncological safety of local excision versus total mesorectal excision. Likewise, the sample size was not calculated specifically for these comparisons. This design precludes the interpretation of the reported absence of differences between groups as a definitive confirmation of the oncological safety of local excision, because we cannot rule out that the study was underpowered to detect clinically significant differences. However, the target population includes patients with a good clinical and pathological response to neoadjuvant treatment, representing a limited proportion of the overall population of patients with rectal cancer. As such, this study of 145 patients is a unique phase 3 trial in this setting. Moreover, data were exhaustive and completed up to 5 years in most patients, and results were similar for all the oncological outcomes in both modified intention-to-treat and as-treated analyses. Second, protocol deviations (randomisation and completion surgery) tended to bias toward the null the comparison between groups. This is a theoretical consideration: the protocol deviations observed in the study are expected to decrease the differences in outcomes of both groups, and thus to bias the comparison between groups towards the null. But we cannot compare the observed results to the true results (ie, if no deviation was observed). However, as-treated analyses permitted attenuation of this bias, although these analyses might fail to completely account for residual confounding bias. In the subgroup of patients with ypT0–1 tumours, small differences in disease-free and overall survival between study groups were noted in the as-treated analyses and could be partly explained by these deviations (three [75%] of four patients who refused total mesorectal excision for local excision had an event: metastatic disease, death, or both). It is unclear whether having a total mesorectal excision would have changed the outcome in these three patients because only one of them died from rectal cancer and the cancer-specific mortality seems similar between groups. Conversely, the large confidence intervals preclude claiming either oncological safety or absence of oncological safety.

The 5-year results of the GRECCAR 2 trial support the preliminary results: we did not provide evidence of a difference in local and metastatic disease, survival, and cancer-specific mortality between treatment groups. Local excision might therefore be a safe option in selected patients with a small low rectal cancer and a good response after chemoradiotherapy. The 20% incidence of metastases observed in our trial underlines proposing chemotherapy when a rectal preservation strategy is planned. The role of completion surgery after local excision in patients with ypT2 tumour is questionable because tumour cells are present in a very limited number of completion specimens. Close follow-up by MRI and endoscopy could be an alternative to completion surgery in such patients. Our results and recommendations are limited to small T2T3 low rectal tumours and therefore cannot be translated to more locally advanced tumours. Further studies need to determine the role of chemotherapy (including GRECCAR 12)[29] and high-dose irradiation (including the OPERA study, NCT02505750)[11] to increase the chance of organ preservation by treating

the primary tumour; must investigate how best to manage patients with a subcomplete response; explore how to reduce the risk of local recurrence; and must also include patients with more advanced tumours. These studies will also serve to determine the role of local excision and completion surgery.

Contributors

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

Declaration of interests

We declare no competing interests.

Data sharing

Individual participant data will not be available. The study protocol will be available on request to eric.rullier@chu-bordeaux.fr.

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