

Early and late morbidity of local excision after chemoradiotherapy for rectal cancer

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Abstract

Background: Local excision (LE) after chemoradiotherapy is a new option in low rectal cancer, but morbidity has never been compared prospectively with total mesorectal excision (TME). Early and late morbidity were compared in patients treated either by LE or TME after neoadjuvant chemoradiotherapy for rectal cancer.

Method: This was a *post-hoc* analysis from a randomized trial. Patients with clinical T2/T3 low rectal cancer with good response to the chemoradiotherapy and having either LE, LE with eventual completion TME, or TME were considered. Early (1 month) and late (2 years) morbidities were compared between the three groups.

Results: There were no deaths following surgery in any of the three groups. Early surgical morbidity (20 per cent LE versus 36 per cent TME versus 43 per cent completion TME, $P=0.025$) and late surgical morbidity (4 per cent versus 33 per cent versus 57 per cent, $P<0.001$) were significantly lower in the LE group than in the TME or the completion TME group. LE was associated with the lowest rate of early (10 versus 18 versus 21 per cent, $P=0.217$) and late medical morbidities (0 versus 7 versus 7 per cent, $P=0.154$), although this did not represent a significant difference between the groups. The severity of overall morbidity was significantly lower at 2 years after LE compared with TME or completion TME (4 versus 28 versus 43 per cent grade 3–5, $P<0.001$).

Conclusion: The rate of surgical complications after neoadjuvant chemoradiotherapy in the LE group was half that of TME group at 1 month and 10 times lower at 2 years. LE is a safe approach for organ preservation and should be considered as an alternative to watch-and-wait in complete clinical responders and to TME in subcomplete responders.

Introduction

Organ preservation is a relatively new approach to the management of rectal cancer. Several studies have reported encouraging results ranging from 22–100 per cent organ preservation and 72–100 per cent 5-year overall survival, with the use of local excision (LE) or a watch-and-wait approach in patients with T2/T3 low rectal cancer demonstrating good clinical response to neoadjuvant chemoradiotherapy^{1–10}. The morbidity of LE with conventional transanal endoscopic microsurgery (TEM) or transanal minimally invasive surgery (TAMIS) ranges from 6–12 per cent, when used in isolation in patients with early-stage disease^{11–13}. Conversely, the morbidity of LE after neoadjuvant

chemoradiotherapy, which impairs healing and is known to induce significant morbidity itself, is not well documented.

Four prospective multicentre studies of LE following neoadjuvant therapy have reported overall early morbidity ranging from 26–31 per cent^{2–5}. A single-institution study compared LE with total mesorectal excision (TME) after chemoradiotherapy and reported no difference in early morbidity¹. Late morbidity of LE after chemoradiotherapy remains largely unknown.

The randomized trial undertaken by the present investigators demonstrated the oncological safety of LE in organ preservation for selected patients with T2/T3 low rectal cancer who were good responders to chemoradiotherapy. That study found no

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difference in local recurrence or survival at 5 years between patients allocated to the LE or TME groups¹⁴, noting that some patients in the LE group required TME at a later date (completion TME). The objective of the present study was to compare early and late morbidity between the three surgical techniques, LE, TME and completion TME, in patients treated initially with neoadjuvant chemoradiotherapy for low rectal cancer.

Methods

Study design

Patients enrolled in the randomized multicentre GRECCAR2 trial comparing LE with TME in downstaged tumours following neoadjuvant chemoradiotherapy for low rectal cancer, were considered. Inclusion criteria were low rectal carcinoma (8 cm or less from the anal verge), largest diameter 4 cm, clinically staged T2 or T3, and N0–1, with endorectal ultrasonography, pelvic MRI, and CT scan. Good clinical responders (residual tumour 2 cm or less, irrespective of N status) were randomized between LE (experimental arm) and TME (control arm). In the LE group, patients with a good pathological response (ypT0–1) underwent follow-up, while those whose resection specimen showed a poor pathological response (ypT2–3) or R1 resection underwent a completion TME.

Patients were classified according to the 7th TNM staging system¹⁵.

Treatments

Radiotherapy consisted of three-dimensional 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/day, 5 days/week, and oxaliplatin 50 mg/m²/week, were administered during radiotherapy. Digital examination and pelvic MRI were performed 6–8 weeks after chemoradiotherapy to restage the tumour. A good clinical response was defined as a residual tumour scar 2 cm or less, suggesting complete or substantial response.

Surgery was performed 8 weeks after chemoradiotherapy. Transanal LE involved a full-thickness excision of the rectal wall, with a 1-cm margin, performed conventionally with anal retractors or by TEM. In the TME group, surgery was performed transabdominally via a laparoscopic approach. A protecting diverting stoma was used.

Outcome measurements

The primary objective of this *post-hoc* study was to report specific and general morbidities of each of the three surgical techniques, LE, TME, and completion TME after neoadjuvant therapy. All morbidity was graded from 1–5 according to the Clavien–Dindo classification¹⁶. Patients were included in the three groups according to treatment received, irrespective of the initial randomization arm. Rates of early and late surgical and medical morbidity between the three groups were evaluated. A secondary objective of the study was to compare the severity of treatments needed to deal with surgical complications and the lengths of hospital stay in the different groups. Early morbidity was defined as morbidity up to 30 days from the surgery and late morbidity from 1 month to 2 years from surgery. Among patients initially treated by LE, those who underwent completion TME were excluded from the analysis at 2 years.

Statistical analysis

Data were analysed from a prospectively developed database at day 30 and up to year 2 in all patients by the Clinical Epidemiology Unit and the Health Vigilance Unit of CHU of Bordeaux. General and specific complications, including all Clavien–Dindo grades 1–5, were reviewed and analysed from 1 March to 30 April 2020 by two independent observers. In cases of disagreement, consensus was obtained from a third investigator. Qualitative variables were expressed in proportions and compared with the χ^2 test or Fisher's exact test when appropriate. Quantitative variables were expressed as median with range and compared with the t test or the Wilcoxon test when appropriate. All analyses were performed with a two-sided 5 per cent type 1-error rate, using the software SPSS, version 20.0.

Results

Population

From March 2007 to September 2012, 186 patients with a low rectal cancer stage T2/T3 were enrolled at 15 French institutions and 148 clinically good responders were randomized resulting in 74 in the LE group and 74 in the TME group. Of these, three patients were excluded (1 high rectal cancer, 1 metastatic disease, 1 withdrew consent) and 145 were analysed in the intention-to-treat analysis (74 LE, 71 TME) (Table 1). Cross-over occurred in one patient in the LE group (1 TME for technical reasons), and in 11 patients in the TME group (8 LE, 3 watch and wait due to patient or surgeon preference). This meant that 81 patients effectively underwent LE, 61 had TME and 28 had a completion TME after LE. LE was performed conventionally in 58 patients and by TEM in 23, of whom 86 per cent (70 of 81 patients) had closure of the rectal defect.

Early morbidity

Overall morbidity is summarized in Fig. 1. There was no death due to neoadjuvant chemoradiotherapy or surgery in either LE (0 of 81 patients) or the TME group (0 of 89). The details of early complications are presented in Table 2. Early surgical morbidity

Table 1: Patient characteristics, intention to treat

Characteristic	LE(n = 74)	TME(n = 71)	P
Age (years)*	61 (35–84)	64 (40–88)	0.177
Gender			0.379
Male	50 (68)	43 (61)	
Female	24 (32)	28 (39)	
ECCO status			0.333
0	68 (92)	68 (96)	
1–2	6 (8)	3 (4)	
Tumour stage			0.571
T2	41 (55)	36 (51)	
T3	33 (45)	35 (49)	
Nodal stage			0.178
N0	42 (57)	48 (68)	
N1	32 (43)	23 (32)	
Tumour size (cm)*	3.0 (1.3–4.0)	3.0 (2.0–4.0)	0.464
Distance from anal verge (cm)*	4.0 (2.5–8.0)	4.0 (2.5–7.0)	0.462
Surgery performed			<0.001
LE	47 (64)	6 (8)	
LE + cTME	26 (35)	2 (3)	
TME	1 (1)	60 (85)	
No surgery	0 (0)	3 (4)	

Values in parentheses are percentages unless indicated otherwise; *values are median (range). LE, local excision; TME, total mesorectal excision; ECCO, Eastern Cooperative Oncology Group; cTME, completion total mesorectal excision.

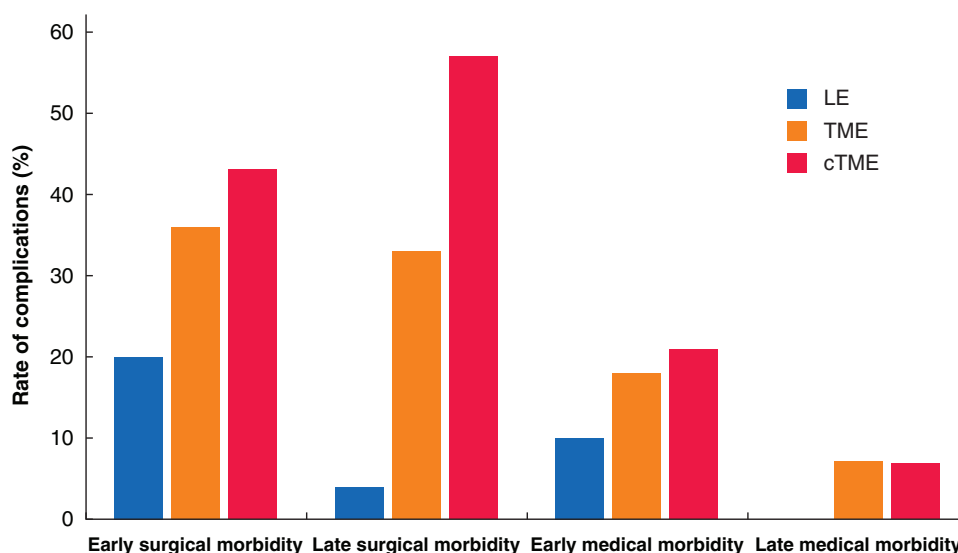


Fig. 1 Rate of complications following local excision and total mesorectal excision after neoadjuvant therapy

Early surgical morbidity, $P=0.025$; late surgical morbidity $P<0.001$; early medical morbidity, $P=0.217$; late medical morbidity, $P=0.154$. LE, local excision; TME, total mesorectal excision; cTME, completion total mesorectal excision

Table 2: Early morbidity (1 month) in patients treated by local excision and total mesorectal excision following radiochemotherapy for rectal cancer

Morbidity	Local excision (n = 81)	TME [†] (n = 61)	cTME [‡] (n = 28)	P
Surgical morbidity				
Rectal bleeding	8 (10)	0 (0)	0 (0)	
Pelvic pain	4 (5)	1 (2)	0 (0)	
Pelvic abscess	4 (5)	2 (3)	4 (14) [§]	
Rectovaginal fistula	1 (1)	1 (2)	0 (0)	
Anastomotic leakage	0 (0)	4 (7)	2 (7)	
Colonic ischaemia	0 (0)	4 (7)	0 (0)	
Bowel obstruction	0 (0)	5 (8)	3 (11) [§]	
Stoma complication	0 (0)	3 (5)	0 (0)	
Parietal abscess	0 (0)	3 (5)	2 (7) [§]	
Perineal abscess	0 (0)	0 (0)	2 (7) [§]	
Total number of complications	17 (NA)	23 (NA)	13 (NA)	
Number of patients with complications	16 (20)	22 (36)	12 (43)	0.025
Medical morbidity				
Urinary infection	3 (4)	2 (3)	2 (7) [§]	
Urinary retention	1 (1)	5 (8)	4 (14) [§]	
Prostatitis	1 (1)	0 (0)	1 (4)	
Cardiac complication	1 (1)	1 (2)	0 (0)	
Pneumonia	1 (1)	0 (0)	2 (7) [§]	
Anaemia	1 (1)	0 (0)	0 (0)	
Dehydration	0 (0)	4 (7)	0 (0)	
Pleural effusion	0 (0)	1 (2)	0 (0)	
Total number of complications	8 (NA)	13 (NA)	9 (NA)	
Number of patients with complications	8 (10)	11 (18)	6 (21)	0.217
Hospital stay (days)*	3 (2–4)	10 (7–13)	16 (11–33)	<0.001

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). [†]All low anterior resection (LAR). [‡]Only morbidity of completion total mesorectal excision (cTME) itself: 23 LARs and 5 abdominoperineal resections (APRs). [§]One patient with APR. TME, total mesorectal excision.

was significantly lower after LE (16 of 81 patients, 20 per cent) compared with TME (22 of 61, 36 per cent) or completion TME (12 of 28, 43 per cent) ($P=0.025$). The types of surgical complication differed between the groups. Rectal bleeding (8 of 81 patients, 10 per cent) and rectal pain (4 of 81, 5 per cent) were the most frequent complications after LE, whereas anastomotic complications, involving leakage, colonic ischaemia, abscess and vaginal fistula (17 of 89 patients, 19 per cent), along with bowel obstruction (8 of 89, 9 per cent), were the most frequent complications following TME or completion TME (Table 2). There was no

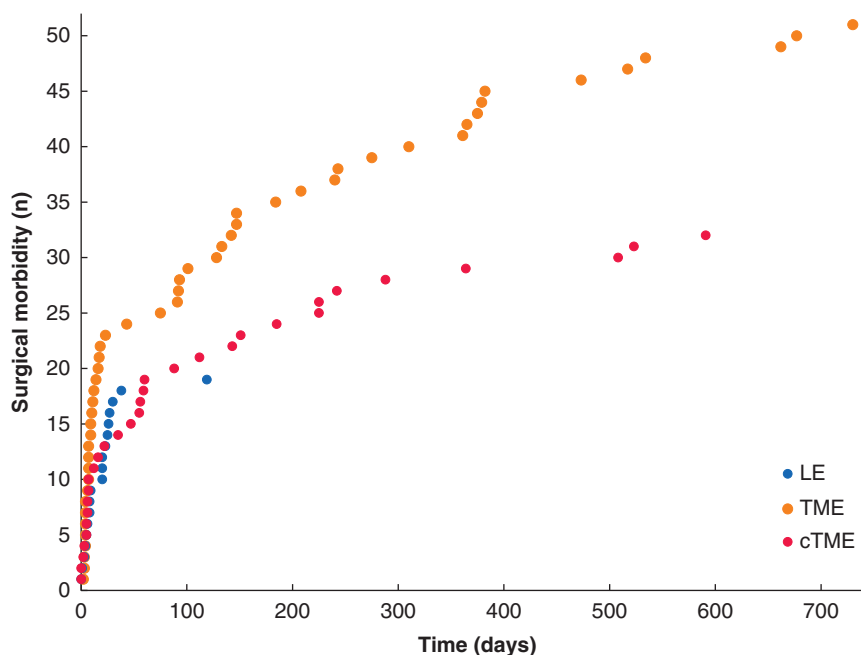
difference in rate or type of early complications between the TME and completion TME groups.

Early medical morbidity was also lower after LE (8 of 81 patients, 10 per cent) than after TME (11 of 61, 18 per cent) or completion TME (6 of 28, 21 per cent) although this difference was not statistically significant ($P=0.217$). The most frequent complications were urinary infection (3 of 81 patients, 4 per cent) after LE, and urinary retention (9 of 89, 10 per cent) and dehydration due to protecting ileostomy (4 of 89, 4 per cent) after any TME (Table 2). Hospital stay was significantly shorter after LE

Table 3: Late morbidity (2 years) in patients treated by local excision and total mesorectal excision following radiochemotherapy for rectal cancer

	Local excision(n = 53)	TME*(n = 61)	cTME†(n = 28)	P
Surgical morbidity				
Anorectal stenosis	1 (2)	9 (15)	4 (14)	
Rectovaginal fistula	1 (2)	2 (3)	1 (4)	
Anastomotic leak or pelvic abscess	0 (0)	4 (7)	4 (14)	
Bowel obstruction	0 (0)	3 (5)	4 (14)	
Stoma complication	0 (0)	2 (3)	1 (4)	
Wound abscess	0 (0)	1 (2)	1 (4)	
Abdominal hernia	0 (0)	7 (11)	4 (14)	
Total number of complications	2 (NA)	28 (NA)	19 (NA)	
Number of patients with complications	2 (4)	20 (33)	16 (57)	<0.001
Medical morbidity				
Cerebral haemorrhage	0 (0)	2 (3)	0 (0)	
Cardiac arrhythmia	0 (0)	1 (2)	0 (0)	
Pneumonia	0 (0)	1 (2)	1 (4)	
Urinary retention	0 (0)	0 (0)	1 (4)	
Total number of complications	0 (NA)	4 (NA)	2 (NA)	
Number of patients with complications	0 (0)	4 (7)	2 (7)	0.154

Values in parentheses are percentages. *All total mesorectal excisions (TMEs) were low anterior resections. †Completion total mesorectal excision (cTME) included 23 low anterior resections and 5 abdominoperineal resections.

**Fig. 2 Delay of occurrence of complications in the local excision and total mesorectal excision groups**

LE, local excision; TME, total mesorectal excision; cTME, completion total mesorectal excision

(3 days), than after TME (10 days) or completion TME (16 days) ($P < 0.001$).

Late morbidity

Late morbidity was analysed for 53 patients who underwent LE alone, 61 patients with TME and 28 patients who had completion TME. The details of late morbidity are presented in [Table 3](#). Events continued to be noted in the TME group up to 2 years ([Fig. 2](#)). Late surgical morbidity was significantly lower after LE (2 of 53 patients, 4 per cent) compared with TME (20 of 61, 33 per cent) or completion TME (16 of 28, 57 per cent) ($P < 0.001$). In the TME group, the most frequent late surgical complications were anastomotic stenosis (13 of 89, 15 per cent), anastomotic leakage

(11 of 89, 12 per cent) and abdominal hernia (11 of 89, 12 per cent). In the LE group only two patients had a late surgical complication (1 rectal stenosis, 1 rectovaginal fistula) ([Table 3](#)). Late medical morbidity was lowest after after LE (0 of 53 patients) compared with TME (4 of 61, 7 per cent) or completion TME (2 of 28, 7 per cent), although this did not reach statistical significance ($P = 0.154$).

Severity of complications

Details of the overall severity of complications (surgical and medical) are presented in [Table 4](#). Only one patient in the LE group required admission to the intensive care unit for haemorrhagic shock. Overall, two-thirds of patients in each group had minor or

Table 4 Severity of overall complications

Severity	Early			P	Late			P
	LE(n = 81)	TME(n = 61)	cTME(n = 28)		LE(n = 53)	TME(n = 61)	cTME(n = 28)	
Clavien–Dindo grade				0.218				<0.001
Grade 0–1	59 (73)	36 (59)	15 (54)		51 (96)	37 (61)	12 (43)	
Grade 2	17 (21)	16 (26)	8 (29)		0 (0)	7 (12)	4 (14)	
Grade 3	4 (5)	9 (15)	5 (18)		2 (4)	17 (28)	12 (43)	
Grade 4	1 (1)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
Grade 5	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	

Values in parentheses are percentages. LE, local excision; TME, total mesorectal excision; cTME, completion total mesorectal excision.

Table 5 Treatment of patients with surgical complications

Treatment	Early			Late		
	LE(n = 16)	TME(n = 22)	cTME(n = 12)	LE(n = 2)	TME(n = 20)	cTME(n = 16)
No treatment	5 (31)	2 (9)	0 (0)	0 (0)	2 (10)	0 (0)
Medical treatment	7 (38)	11 (50)	7 (58)**	0 (0)	2 (10)	3 (19)***
Interventional (radiology or endoscopy)	2 (13)*	2 (9) [§]	0 (0)	0 (0)	3 (15) ^{§§}	3 (19) ^{†††}
Minor surgery	1 (6) [†]	1 (5) [¶]	0 (0)	2 (100) ^{††}	4 (20) ^{¶¶}	2 (12) ^{†††}
Major surgery	1 (6) [‡]	6 (27) [#]	5 (42) ^{††}	0 (0)	9 (45) ^{##}	8 (50) ^{§§§}

Values in parentheses are percentages. Early: *endoscopic rectal haemostasis; †rectal examination under general anaesthesia for ulceration and pain; ‡colostomy for rectovaginal fistula; §radiological pelvic abscess drainage; ¶suture of rectovaginal fistula; #abdominal drainage for anastomotic leak (n = 2), colectomy for colonic ischaemia (n = 3), stoma prolapse (n = 1); **pelvic abscess (n = 1), perineal abscess (n = 2), bowel obstruction (n = 1), colonic abscess (n = 1), wound abscess (n = 2); ††pelvic abscess (n = 1), anastomotic leak (n = 2), bowel obstruction (n = 2). Late: ††suture of rectovaginal fistula (n = 1) and surgical anal dilatation (n = 1); §§endoscopic anal dilatation; ¶¶surgical anal dilatation; ##colectomy for bowel obstruction (n = 1), definitive colostomy for anastomotic leak (n = 2), redo coloanal anastomosis for anal stenosis or chronic leakage (n = 2), transabdominal hernia repair (n = 2); ***rectovaginal fistula (n = 1), anastomotic leak (n = 1), bowel obstruction (n = 1); †††endoscopic bowel obstruction (n = 1), radiological pelvic abscess drainage (n = 2), radiological pelvic abscess drainage; †††anal stenosis; §§§anastomotic leak (n = 1), bowel obstruction (n = 2), haemorrhage (n = 1), wound dehiscence (n = 4). LE, local excision; TME, total mesorectal excision; cTME, completion total mesorectal excision.

no complications (grade 0–1). Severity of overall morbidity was lower after LE than after TME or completion TME. Although not statistically significant 1 month after surgery (grade 3–5: 6 versus 15 versus 18 per cent, $P=0.218$), there was a significant difference at 2 years (grade 3–5: 4 versus 28 versus 43 per cent, $P < 0.001$).

Treatment of surgical complications

During the first month, management of surgical complications included medical treatment and interventional therapy (radiological or endoscopic) in at least two-thirds of the patients in both the LE and TME surgery groups (Table 5). During the overall period of follow-up, major surgery was required significantly less frequently after LE (1 of 18 patients, 6 per cent) than after TME (15 of 42, 36 per cent) and completion TME (13 of 28, 46 per cent) ($P=0.014$).

Discussion

This study demonstrated a significantly lower rate of early and late surgical morbidity after LE compared with primary or completion TME. Globally the rate of surgical complications was halved at 1 month and 10 times lower at 2 years in the LE group than in the TME group. Late surgical complications were less severe, hospital stay was shorter, and the lowest rates of early and late medical morbidity all occurred in the LE group. The most frequent complications reflected the different approaches: rectal bleeding and pain being most common after LE, and anastomotic leakage and bowel obstruction following TME. These findings suggest that LE is superior to TME regarding morbidity after neoadjuvant chemoradiotherapy in patients who have had a good local response.

LE alone is an alternative to TME in the surgical treatment of early rectal cancer. The US national cancer database reported 765 LE and 1359 TME for stage I rectal cancer treated by surgery alone and showed no difference in 5-year overall survival for T1 lesions and a lower 30-day morbidity after LE versus TME (6 versus 15 per cent, $P < 0.001$)¹¹. The Swedish rectal cancer registry including 643 LE and 7891 TME had similar outcomes, again with much lower rates of 30-day morbidity following LE (11 versus 36 per cent)¹². In patients undergoing surgery alone, the two largest studies comparing LE and TME showed that the morbidity of LE is two- to three-fold lower than TME^{11,12}.

LE following neoadjuvant chemoradiotherapy is a relatively new option in rectal cancer and its advantage over TME in terms of morbidity is not yet established. Four prospective multicentre studies^{2–4} and one single-centre randomized study¹ involving patients with T1–T3 low rectal cancer, found local recurrence rates in LE patients of between 3 and 8 per cent, with disease-free survival between 82 and 91 per cent at 3–5 years, suggesting neoadjuvant therapy and LE to be a safe oncological alternative to TME in selected patients. On the other hand, 30-day surgical morbidity was reported to be between 26 and 31 per cent^{2–4}, about three times higher than that observed with LE alone and close to the 36 to 40 per cent seen after laparoscopic or open TME^{17,18}. Only the single-institution study which prospectively compared LE and TME after neoadjuvant therapy demonstrated no difference in morbidity between the two procedures (14 versus 20 per cent, $P=0.42$)¹.

GRECCAR 2 was a national multicentre phase 3 trial based on the hypothesis of superiority of LE over TME in patients treated with neoadjuvant chemoradiotherapy for T2/T3 low rectal cancer¹⁷. The study reported the occurrence of one or more events

from the composite primary outcome (death, recurrence, severe morbidity or side effects) at 2 years in 56 per cent of patients in the LE group and 48 per cent in the TME group ($P = 0.43$), suggesting no superiority of LE. However, one-third of the patients in that study treated with LE went on to have a completion TME, which possibly compromised any advantages of LE. Because the role of completion TME is questionable^{3,14}, the present study focused on the details of surgical morbidity including this particular subset of patients and confirmed superiority of LE over both TME and completion TME. TME without neoadjuvant therapy is a safe option for early/small rectal cancer and this alternative merits consideration so that the patient is fully informed of all choices prior to making a decision. The other major finding of the present study was the high rate of late surgical morbidity following TME. In contrast to existing literature focused on short-term morbidity^{18,19}, late complications were seen at up to 2 years in one third of patients in the present study, suggesting that late morbidity of TME and its impact on long-term quality of life has previously been underestimated.

As in other studies, the nature of early complications differed between the LE and TME groups. Rates of early complications were similar in the present study to those reported elsewhere, both for LE and TME following chemoradiotherapy^{1–4,20}. It seems likely that rates of late complications would therefore be similar to those found in the present study.

Late morbidity after neoadjuvant therapy and LE has been reported in only one prospective study using short-course radiotherapy (25 Gy) followed by LE⁴. At 1 year after treatment, six of 62 patients had complications mainly due to the side effects of pelvic irradiation, in line with 4 per cent morbidity at 2 years in the LE group in the present study. In contrast, late morbidity in the present study after TME was much higher, affecting more than a third of patients in the early postoperative period and a similar proportion at 2 years. This included patients with delayed complications (pelvic abscess), recurrent complications (chronic anastomotic leakage), as well as new complications (late fistula, anastomotic stenosis, bowel obstruction and hernia). A German trial (CAO/ARO/AIO-94) reporting long-term outcomes at 10 years observed that patients with any surgical complication after TME had impaired overall survival (47 versus 64 per cent, $P < 0.001$) and an increased incidence of local recurrence (15 versus 6 per cent, $P < 0.001$)²¹.

The present study has limitations. The sample size was relatively small and *post-hoc* analysis should be interpreted with caution. The study compared surgical techniques and not the strategies. The results, nevertheless, may be useful for decision making regarding strategies for organ preservation. Due to its low morbidity and its potential advantages in terms of quality of life²², LE can be considered as an alternative to watch and wait^{14,23}. With a significantly low morbidity profile, LE can also be used as an alternative to TME in patients with incomplete responses to treatment. The new knowledge about the differences in the nature and evolution of long-term morbidities with these different approaches and how they impact on patients' lives merits further investigation.

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