



ORIGINAL ARTICLE

Local excision after neoadjuvant chemoradiotherapy for mid and low rectal cancer: a multicentric French study from the GRECCAR group

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Abstract

Aim: A complete or subcomplete tumour response (CTR) is observed in 10%–25% of patients with mid/low rectal cancer after neoadjuvant chemoradiotherapy (CRT). The aim of our study was to report a multicentric French experience in local excision (LE) after CRT.

Method: All patients who underwent LE for mid/low rectal cancer with suspected CTR after CRT, from 2006 to 2019 in seven GRECCAR centres were included. LE was considered adequate if the specimen showed a ypT0/Tis/T1R0 tumour, otherwise, a completion total mesorectal excision (TME) was discussed. Morbi-mortality, functional results and oncological outcomes were studied.

Results: A total of 257 patients were included. LE specimens showed 36% ypT0, 4% ypTis and 19% ypT1. Thus, 108 patients (42%) had theoretical indication of completion TME, which was performed in only 42 patients. Overall, 30-day morbidity after LE was 11%, including 2% Clavien–Dindo grade III or IV complications. After completion TME, 47% described major low anterior resection syndrome versus 5% after LE alone ($p < 0.001$). After a mean follow-up of 4 years (range 2–6 years), the recurrence rate was 11% after LE, 32% after completion TME and 20% in patients for whom completion TME was indicated but not performed ($p = 0.021$).

Conclusion: TME remains the gold standard for mid/low rectal cancer after CRT. LE in selected patients is safe for operative and functional, but also oncological, results. However, completion TME was indicated in 42% of patients after LE, highlighting the difficulty of the preoperative diagnosis of CTR after CRT.

KEYWORDS

local excision, neoadjuvant treatment, radiochemotherapy, rectal cancer

INTRODUCTION

Current developments in rectal cancer management allow us to consider less and less morbid surgical treatments. Indeed, total mesorectal excision (TME) remains the standard surgical management of mid and

low rectal cancer. This was first described by Heald and Ryall [1] in 1986, who found an overall survival of over 80% and a local recurrence rate below 10% due to *en bloc* excision of the lesion and its mesorectal drainage. However, TME exposes patients to possible severe postoperative complications, such as anastomotic leakage, definitive stoma,

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poor functional outcomes and genitourinary dysfunction [2, 3]. These side effects can be worsened by preoperative radiotherapy [4], which is currently recommended [5] with neoadjuvant chemoradiotherapy (CRT) in cases of locally advanced mid/low rectal adenocarcinoma [6]. Organ preservation strategies have therefore recently been proposed when there is a suspected complete tumour response (CTR) following neoadjuvant CRT. In these selected patients TME remains the standard recommendation, but this can expose a patient with excellent oncological prognosis if the TME specimen shows a CTR to severe morbidity. Thus, local excision (LE) of the residual tumoral scar allows pathological confirmation of CTR or near CTR. In cases of ypT2 or more, completion TME has to be performed because of the risk of mesorectal lymph node involvement; this increases from only 3%–9% in patients with a ypT0/T1 tumour to 25% for a ypT2 tumour [7].

Lezoche et al. [8] designed the first trial randomizing patients with a cT2 low rectal cancer between LE and standard TME after CRT, and showed similar oncological results in both groups after a median follow-up of almost 10 years. A meta-analysis of eight studies [9] confirmed that there was no difference in local recurrence, disease-free survival and overall survival rates between LE after CRT and TME, despite the variability of the included studies. More recently, the GRECCAR 2 trial [10] also showed similar survival in both groups, but a significantly increased morbidity in the completion TME group (46% severe morbidity versus 22% for TME without LE). The rate of definitive stoma was also significantly higher in the completion TME group (25%) when compared with the standard TME group (9%). Therefore, this strategy has so far been recommended by some experts in 'high-risk' patients [e.g. older patients, comorbidities, difficult intersphincteric resection, refusal of abdominoperineal resection (APR)] for whom TME could be detrimental. In a recent case-matched study [11], this strategy showed an excellent rate (72%) of preoperatively diagnosed complete or subcomplete pathological response after CRT and LE, with a significantly lower rate of overall morbidity and better functional outcomes after LE alone when compared with standard TME. This highlights how interesting this strategy could be at a time where neoadjuvant therapies are increasingly performative.

Because only a relatively small number of patients were included in most of these reports, the aim of the present study was to report a large multicentric experience of organ preservation with LE after CRT, and to report oncological and functional outcomes in patients undergoing LE alone versus LE followed by TME.

METHOD

All consecutive patients who underwent LE for mid or low rectal adenocarcinoma with suspected CTR or near CTR after CRT from 2006 to 2019 in seven French tertiary centres were included in the present retrospective study. These patients received long-course preoperative radiotherapy (45 or 50 Gy in 25 fractions over the course of 5 weeks) with concomitant chemotherapy using capecitabine (1600 mg/m² per day of radiotherapy).

What does this paper add to the literature?

Today, organ preservation in management of mid/low rectal cancer is increasingly considered. Our multicentric study reports that local excision after chemoradiotherapy is safe in selected patients. However, 42% of our 257 patients had an indication for completion total mesorectal excision, suggesting that we need to improve the preoperative diagnosis of complete tumour response.

Postirradiation assessment for all patients before LE included a clinical examination, a thoraco-abdomino-pelvic CT scan and a second pelvic MRI, which were performed 5–7 weeks after the end of CRT.

CTR or near CTR was defined as: (1) a normal or subnormal clinical rectal examination, with no mucosal abnormality or only a small residual scar (diameter <2 cm) but without any evidence of ulceration and/or macroscopic rectal tumour and (2) no residual tumour nor involvement of mesorectal lymph nodes on the second MRI.

LE was proposed as an alternative to TME in selected high-risk patients with severe comorbidities (older age, obesity, cardiovascular pathologies, kidney failure, respiratory failure), if the patient refused radical surgery or if an APR or a coloanal anastomosis with intersphincteric resection was required, making the surgery more risky. Patients were informed of the risks of both operations and of the possible indication for completion TME in case of unfavourable pathological results after LE, and all of them consented before surgery.

LE was routinely performed around 6 weeks following the end of CRT and consisted of a complete, *en bloc* and full-thickness technique down to the peri-rectal fat, with 10 mm margins, performed via a standard transanal approach for very low tumours or by transanal endoscopic microsurgery (TEM). A standard transanal approach means LE with a monopolar device and using only an anal retractor (i.e. a Parks or Lone Star retractor). TEM used a stable platform, with insufflation of CO₂ within the rectum, and a camera, similar to a laparoscopic technique [12].

LE was considered adequate if the specimen presented the following pathological features: ypT0/ypTis/ypT1 and R0 resection. On the contrary, a completion TME was proposed quickly following LE if the histological analysis showed yp ≥ T2 and/or R1 resection and/or lymphovascular invasion on the specimen.

All patients were followed every 3 months during the first 2 years after surgery, then every 6 months for 3 years and every year afterwards. Follow-up consisted of clinical examination, thoraco-abdomino-pelvic CT scan and tumour marker dosage (carcinoembryonic antigen and carbohydrate antigen 19.9). Colonoscopy was performed 1 year after surgery, then every 3 years if normal. Furthermore, pelvic MRI was performed at least twice during the first year after LE.



Locoregional recurrence was defined as recurrent disease within the pelvis, including at the site of the anastomosis if a TME was performed. In those cases, a pelvic MRI and a biopsy for histological confirmation was always sought. Metastatic recurrence was diagnosed mainly by the follow-up imaging.

Overall postoperative morbidity concerned all postoperative complications occurring in the 30 days following surgery, and were graded according to the Clavien–Dindo classification [13]. Severe postoperative morbidity concerned all complications of grade III and above. Postoperative mortality was defined as any death occurring within the 90 days following surgery.

Functional outcomes were evaluated at the end of follow-up in stoma-free patients, using the low anterior resection syndrome (LARS) score [14]. This score allows us to grade each patient in three categories: no LARS (LARS score ≤ 20), minor LARS (LARS score between 21 and 29) or major LARS (LARS score ≥ 30). Note that there was no standardization of the use of the LARS score across time, and when several questionnaires had been completed we used the most recent result in our analysis.

Results are presented as the mean $\pm$ standard deviation (range) for continuous variables and number (percentage) for categorical variables. Student's *t*-test was used for continuous variables of normal distribution and the Mann–Whitney and Kruskal–Wallis *U*-tests for nonnormally distributed values. The Fisher exact test was used for categorical variables. All tests with a two-sided *p*-value of less than 0.05 were considered significant. Analyses were performed using the SPSS for Mac OSX computer program (version 26.0, IBM Corp).

This study was approved by our institutional review board, conducted according to the ethical standards of the Committee on Human Experimentation of our institution, and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [15].

RESULTS

Local excision

Between 2006 and 2019, 257 patients underwent LE for mid (21%) or low (79%) rectal cancer with suspected CTR or near CTR after CRT. More than half of them were men (54%), with a mean age of 68 ± 12 years (range 33–93 years). Their characteristics, including clinical TNM staging, are detailed in Table 1.

The mean interval between the end of CRT and LE was 5.6 weeks (range 4.9–6.4 weeks). Most patients underwent LE through a standard transanal approach (71%), whereas 29% had a TEM performed.

Table 2 describes the operative results of LE. Mortality following LE was nil. Overall morbidity at 30 days concerned 28 patients (11%), among whom five patients (2%) had a complication of at least Clavien–Dindo grade III. As for LE-specific morbidity, we noted six patients with postoperative haemorrhage (three needed emergency reintervention, all of them through a transanal approach), six with

TABLE 1 Characteristics of 257 patients undergoing local excision for suspicion of complete tumour response after neoadjuvant chemoradiotherapy for mid/low rectal cancer.

General characteristics	
Gender (male)	138 (54) ^a
Age at LE (years)	68 ± 12 [33–93] ^b
BMI (kg/m ²)	26 ± 5 [16–43]
ASA score 1–2	204 (79)
ASA score 3–4	53 (21)
Cardiovascular risk factors	
High blood pressure	99 (39)
Diabetes	29 (11)
Active smoking	37 (14)
Obesity (BMI ≥ 30 kg/m ²)	52 (20)
Tumour localization	
Mid rectum	54 (21)
Low rectum	203 (79)
Size of the tumour (cm)	3 ± 1 [1–8]
cTNM staging (MRI or ultrasound) ^d	
cT1	4 (1)
cT2	105 (38)
cT3	162 (59)
cT4	5 (2)
cN0	156 (75)
cN+	53 (25)
Delay between end of CRT and LE (weeks)	5.6 [4.9–6.4] ^c

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CRT, chemoradiotherapy; LE, local excision; MRI, magnetic resonance imaging.

^aNumber of patients (percentage of patients).

^bMean $\pm$ standard deviation [range].

^cMedian [range].

^dMissing values.

severe anal pain that resolved under level III analgesics and four with a peri-anal abscess, with a favourable evolution under antibiotics for three of them and transanal drainage for the other.

Histological analysis on the LE specimen showed 36% ypT0, 4% ypTis and 19% ypT1. Resection was complete (i.e. R0) in 89% of the patients. Therefore, after LE, 42% of our cohort ($n = 108$) had a theoretical indication of completion proctectomy with TME.

Completion TME

Among the 108 patients for whom histological features were unfavourable, only 42 (39%) underwent TME following LE. The reasons for this were patient refusal ($n = 9$), comorbidities that were too severe ($n = 18$) and surgeon's discretion ($n = 39$). Their results are shown in Table 3. Completion TME was performed after a median time of 23 days (range 13–43 days) after LE.

TABLE 2 Surgical, histological and morbidity details of 257 patients undergoing local excision for suspicion of complete tumour response after neoadjuvant chemoradiotherapy for mid/low rectal cancer.

Chosen procedure	
Transanal endoscopic microsurgery	74 (29) ^a
Standard transanal excision	181 (71)
Operative time (min)	40 [30–40] ^b
Mortality at 90 days	0
Overall morbidity at 30 days	28 (11)
Clavien–Dindo I–II	23 (9)
Clavien–Dindo III–IV	5 (2)
Postoperative haemorrhage	6 (2)
Needing reintervention	3 (1)
Anal pain	6 (2)
Peri-anal abscess	4 (2)
Length of hospital stay (days)	3 [2–5]
Rehospitalization at 90 days	15 (6)
Histological results	
ypT0	92 (36)
ypTis	11 (4)
ypT1	50 (19)
ypT2	81 (32)
ypT3	23 (9)
Nx	256 (99)
N1	1 (1)
R0	230 (89)

^aNumber of patients (percentage of patients).

^bMedian [range].

Mortality following surgery was nil. Overall morbidity at 30 days was seen in 43% of patients, with 17% having a complication graded Clavien–Dindo III or IV. Five patients (12%) had anastomotic leakage or pelvic abscess following surgery, among whom three needed emergency reintervention for peritonitis.

After pathological analysis, 48% of patients had their completion TME specimen classified as ypT0, 5% as ypT1, 21% as ypT2 and 26% as ypT3. The resection was complete and classified as R0 in 95% of patients.

Oncological results

At the end of a median follow-up of 4.1 years (range 2.4–5.9 years) in 239 patients (18 patients were lost to follow-up), 37 (15%) had a diagnosis of tumour recurrence, among which 17 were local recurrences and 24 metastatic (13 hepatic recurrences, nine pulmonary, two peritoneal, two nodal and one cerebral). Patients who had completion TME had significantly more recurrences than patients undergoing adequate LE ($p=0.012$), especially metastatic ($p=0.006$) but not locoregional ($p=0.846$) recurrences, as shown in Table 4.

TABLE 3 Surgical, histological and morbidity details of 42 patients undergoing completion proctectomy after neoadjuvant chemoradiotherapy and local excision for mid/low rectal cancer. Pathological results are only those after total mesorectal excision.

Chosen procedure	
Colorectal anastomosis	3 (7) ^a
Coloanal anastomosis	24 (57)
Delayed coloanal anastomosis	9 (22)
Abdominoperineal resection	6 (14)
Delay between LE and completion proctectomy (days)	23 [13–43] ^b
Mortality at 90 days	0
Overall morbidity at 30 days	18 (43)
Clavien–Dindo I–II	11 (26)
Clavien–Dindo III–IV	7 (17)
Anastomotic leakage/pelvic abscess	5 (12)
Needing reintervention	3 (7)
Length of hospital stay (days)	13.5 [8–23]
Rehospitalization at 90 days	1 (2)
Histological results	
ypT0	20 (48)
ypT1	2 (5)
ypT2	9 (21)
ypT3	11 (26)
ypT4	0
N0	10 (24)
N1	32 (76)
R0	40 (95)
R1	2 (5)

Abbreviation: LE, local excision.

^aNumber of patients (percentage of patients).

^bMedian [range].

We found no significant difference in the recurrence rate between patients undergoing adequate LE and patients who should have had TME but did not have it performed. The difference between patients who had completion TME and those who should have had it but did not was significant in terms of metastatic recurrence (28% vs. 9%, respectively; $p=0.021$), but not local recurrence (8% vs. 12%, respectively; $p=0.575$).

Overall mortality at the end of follow-up was 19%, and cancer-related mortality was 3%. Likewise, the mortality rate was significantly higher after completion TME when compared with patients with adequate LE ($p<0.0001$) and patients who did not have completion TME although it was indicated ($p=0.002$). No cancer-related deaths occurred in the 'completion TME' group.

Median overall survival was 54 months (range 5–130 months) and median disease-free survival was 17 months (range 0.3–80 months). Moreover, 1-year and 3-year disease-free survival rates were 95% and 88%, respectively.

TABLE 4 Oncological results at the end of follow-up of 239 patients undergoing local excision after neoadjuvant chemoradiotherapy for mid/low rectal cancer.

	Total (N = 239)	LE sufficient (n = 148)	Completion TME performed (n = 25)	Completion TME indicated but not performed (n = 66)
All recurrences	37 (15) ^a	16 (11)	8 (32)	13 (20)
Local recurrence	17 (7)	7 (5)	2 (8)	8 (12)
Metastatic recurrence	24 (10)	11 (7)	7 (28)	6 (9)
Overall mortality	46 (19)	22 (15)	13 (52)	11 (17)
Cancer-related mortality	8 (3)	3 (2)	0	5 (8)

Abbreviations: LE, local excision; TME, total mesorectal excision.

^aNumber of patients (percentage of patients).

Functional results

We were able to analyse functional results in 137 patients from our cohort at the end of follow-up: 118 patients after LE alone (i.e. 55% of all LEs) and 19 after completion TME (i.e. 45% of all completion TMEs).

After LE, 80% of patients reported no LARS versus 47% after completion TME ($p=0.004$). Similarly, major LARS was reported in 5% and 47% ($p<0.0001$) and minor LARS in 14% and 6%, respectively ($p=0.466$).

DISCUSSION

To the best of our knowledge, we report herein the largest series to date on LE after CRT for rectal cancer. The first result of this multicentric study among 257 patients is the rate of correct preoperative diagnosis of CTR or near CTR: 58% ($n=149$) of tumours were effectively classified ypT0-Tis-T1 and R0 after LE. We also observed a rate of severe morbidity of 2%, and most patients (80%) reported no LARS when they only had LE (whether it was adequate or not), making it a safe alternative procedure to TME in selected high-risk patients (i.e. for whom standard TME would be risky) with suspicion of CTR. Moreover, patients who had a CTR and for whom LE was therefore an adequate surgical treatment had satisfactory oncological results, with a 11% overall recurrence rate and 5% local recurrence rate, similar to what is observed after primary TME. Indeed, previous findings had already shown that in well-selected patients oncological prognosis was not modified by a LE first strategy, with Bushati et al. [16], the CARTS trial [17] and the GRECCAR2 trial [18] showing a 5-year local recurrence rate of 7%–8%.

In our study, the rate of theoretical indication of completion TME was high, at 42%, highlighting the difficulty of preoperative diagnosis of CTR. Indeed, despite systematic clinical and radiological examination before LE, we were able to correctly assess only 58% of patients preoperatively, which is in accordance with rates found in the literature (from 53% to 72%) [10, 11, 16, 17, 19]. The GRECCAR

2 trial [10] failed to demonstrate the superiority of LE over standard TME, as nearly half of the patients undergoing LE had indication for a significantly more morbid completion TME, highlighting a defect in patient selection. Preoperative MRI is today the gold standard for tumour assessment of mid and low rectal cancer: it provides the best possible tumour staging, including evaluation of the circumferential margin [20] and the possibility of sphincter preservation [21]. It is also the best imaging technique for evaluation of the response to CRT and should be performed as late as possible after the end of CRT, just before surgery, either TME or LE, around 7 weeks after the end of irradiation [22]. However, both MRI and clinical evaluation seem limited in restaging a rectal tumour after CRT [23–26]. Sclafani et al. [27] showed a poor correlation between the tumour regression grade (TRG) in MRI and the TRG in pathology. Although clinical evaluation is important, Perez et al. [28] showed that residual tumour cells were mainly found in the deepest layers of the rectal wall and not accessible to a clinical evaluation. Finally, it has been found that biopsies are not a good indicator of pathological complete response [29]. Therefore, we believe a pathological CTR can only be suspected after a multistep diagnostic strategy. Another organ preservation strategy described by Dattani et al. [30] is represented by 'watch and wait', also in cases of suspected CTR after CRT. Although promising results have been reported, the international 'watch and wait' database reported a 2-year local regrowth rate of 25%, most of it (88%) occurring during the first 2 years after CRT. Because no randomized study yet exists on this strategy, and following the GRECCAR2 trial, LE is today the preferred strategy for organ preservation in France owing to a low local recurrence rate, as also reported in other papers [17, 18]. We consider that LE is a safe organ preservation strategy allowing confirmation by pathological examination (avoiding under-treated patients) and can be proposed in selected patients after CRT.

Following French recommendations [5], patients in this study received the CAP45/CAP50 protocol as neoadjuvant CRT, comprising irradiation of 45/50 Gy over 5 weeks, with oral capecitabine as concomitant chemotherapy. This design allows complete sterilization in 8% to 27% of the tumour [31], leading to better oncological prognosis [32]. Recently, total neoadjuvant therapy has demonstrated its benefit over CAP50 for locally advanced mid and

low rectal cancer in the PRODIGE 23 randomized trial [33], which adds an induction chemotherapy with FOLFIRINOX to the standard CAP50, and also in the RAPIDO randomized trial [34], which starts with 5×5 Gy short radiotherapy followed by FOLFOX/CAPOX chemotherapy. In addition to an improved disease-free survival, both protocols have shown a significantly higher rate of CTR compared with the control arm (28% vs. 12% and 28% vs. 14%, respectively). Recently, Garcia-Aguilar et al. [35] in their phase II randomized trial reported an interesting TME-free survival of 53% at 3 years using consolidation chemotherapy. Several therapeutic intensification trials, such as OPERA [36] (neoadjuvant CRT with contact X-ray therapy showing an improved 3-year preservation rate in patients with cT2–T3 disease) or the ongoing MORPHEUS trial (endorectal brachytherapy) should continue to help us achieve an even better complete response rate. Finally, another trial from our group, GRECCAR12, has finished recruitment and should soon publicize their results for LE following induction chemotherapy with FOLFIRINOX and standard CRT. According to the GRECCAR2 results, completion TME will be proposed only to patients whose tumour is classified pT2 and cN1, pT3 or R1, to limit the proctectomy-induced morbidity and increase the rate of rectal preservation. It is expected that all these studies will soon allow us to refine our strategies.

Morbidity in the entire cohort after LE was limited (11%, including 2% with severe complications) whereas completion TME led to a higher morbidity rate of 43%, with 17% of complications rated at least Clavien–Dindo grade III. This might have induced a significantly higher noncancer-related mortality after completion TME. GRECCAR2 [18] also showed that both short- and long-term morbidity were significantly higher after completion TME than standard TME. For this reason, a good selection of the patients is mandatory to reduce those requiring completion TME (42% in the present study). Therefore, this strategy could be proposed mainly in selected patients: severe comorbidities that would make radical surgery risky, patient refusal of TME or an excellent response from a tumour that would impose an APR or a difficult coloanal anastomosis with intersphincteric resection. Moreover, we have noted, as in GRECCAR2, that most LEs (>70%) were performed through a standard transanal approach, with the remainder through a TEM, highlighting that this strategy may work mostly in low, or very low, rectal cancers. We also analysed functional results in 137 of our patients, as LARS is a major complication after TME that can occur in up to 60% of patients [14], and is one of the reasons why a conservation strategy is appealing. We report satisfactory results, with 80% of patients after LE alone reporting no LARS and only 5% reporting major LARS (versus 47% after completion TME) at the end of follow-up. These results seem much better than those reported in other studies, as CARTS [17] reported 50% of their 32 patients with major LARS after a similar follow-up. Martens et al. [37] also reported major incontinence in 43% (according to the Vaizey score) of patients after TEM. However, functional results were only reported in seven patients after TEM in that study. Generally, Pucciarelli et al. [38] described a better quality

of life and bowel function in patients undergoing LE versus standard TME.

In conclusion, our study confirms that LE after CRT is a promising technique, with low morbidity and satisfactory oncological outcomes. However, a better selection of patients is needed in the future to lower the number of patients undergoing completion TME, for whom severe morbidity and mortality is significant. Today, standard TME remains the rule after CRT in mid/low rectal cancer, regardless of the tumour response, and pending the results of ongoing randomized trials.

AUTHOR CONTRIBUTIONS

Yves Panis: Conceptualization; methodology; supervision; formal analysis; writing – review and editing; writing – original draft; validation. **Mélanie Calmels:** Conceptualization; investigation; formal analysis; data curation; writing – original draft; writing – review and editing. **Camélia Labiad:** Writing – original draft; writing – review and editing; formal analysis. **Bernard Lelong:** Writing – review and editing; investigation. **Jean-Jacques Tuech:** Investigation; writing – review and editing. **Quentin Denost:** Investigation; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

No conflict of interest from any of the authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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