International Journal of Colorectal Disease (2019) 34:2129–2136
https://doi.org/10.1007/s00384-019-03420-0

ORIGINAL ARTICLE

Local excision in rectal cancer patients with major or complete clinical response after neoadjuvant therapy: a case-matched study

M. Bushati[1] · S. Pucciarelli[1] · N. Gennaro[2] · I. Maretto[1] · P. Toppan[1] · A. Perin[1] · E. D. L. Urso[1] · A. Bagatella[1] · G. Spolverato[1]

Accepted: 29 September 2019 / Published online: 14 November 2019

Abstract

Purpose To assess the long-term oncological outcomes in patients with locally advanced rectal cancer who underwent neoadjuvant therapy followed by local or total mesorectal excision.

Methods Patients with locally advanced rectal adenocarcinoma who received neoadjuvant therapy from 2005 to 2017 were evaluated. Those with major or complete clinical response underwent a full-thickness local excision. Kaplan-Meier estimates were used to evaluate overall, disease-free, and local recurrence-free survival of patients who underwent local excision (LE group) and were compared with a matched cohort of patients who underwent total mesorectal excision (TME group).

Results Among 252 patients who received neoadjuvant therapy for rectal cancer, 51 (20.2%) underwent a local excision. At a median follow-up of 61 months, patients who underwent local excision were stoma-free in 88.2% of cases and with rectum preserved in 78.5% of cases, respectively. The estimated 5-year local, disease-free, and overall survival was 91.8% vs 97.6% (95% CI: 79.5–96.8 vs 84.6–99.6), 86.7% vs 86.4% (95% CI: 72.5–93.9 vs 70.1–94.1), and 85% vs 90% (95% CI: 69.0–93.0% vs 75.3–96.2), in the study and matched control group, respectively. None of the differences was statistically significant.

Conclusions One-fifth of patients with locally advanced rectal cancer are manageable with a rectum-sparing approach after neoadjuvant therapy. With this strategy, about 80% patients will have their rectum preserved and 90% will be without stoma at long term.

Keywords Rectal cancer · Neoadjuvant therapy · Local excision · Total mesorectal excision

Abbreviations

LARC	locally advanced rectal cancer
LE	local excision
TME	total mesorectal excision
TEM	transanal endoscopic microsurgery
nCRT	neoadjuvant (chemo)radiotherapy
pCR	pathologic complete response
cCR	complete clinical response
mCR	major clinical response
WW	watch-and-wait
LR	local recurrence
DR	distant recurrence
LAR	low anterior resection
APR	abdominoperineal resection
QoL	quality of life
MRI	magnetic resonance imaging

✉ S. Pucciarelli
puc@unipd.it

[1] 1st Surgical Clinic, Department of Surgery, Oncology and Gastroenterology, University of Padua, Via Giustiniani 2, 35128 Padua, Italy

[2] Regional Health Service, Epidemiology Unit, Veneto Region, Padua, Italy

Introduction

The current standard approach for locally advanced rectal cancer (LARC) is neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME) [1]. This multimodality treatment has been found to reduce local recurrence compared with adjuvant chemoradiotherapy; however, it is associated with significant morbidity, and impairment of bowel function and quality of life (QoL) [2–4]. Interestingly, the patients who show a pathologic complete response (pCR) after neoadjuvant therapy has been found to have significantly better outcomes survival compared with non-responders

[5]. With these findings it is not surprising the increasing interest on rectum-sparing strategies for patients with major (mCR) or complete clinical response (cCR) after neoadjuvant therapy [6–8]. The rectum-sparing approaches include the simple observation (watch and wait, WW) [9], and full-thickness local excision (LE) of the scar or tumor remnant. [10]

Among patients with LARC who receive neoadjuvant therapy, approximately 15–25% show a complete or a major pathologic response [11], and are potential candidates for a rectum-sparing approach. However, the major challenge of this strategy relies on the ability to preoperatively identify patients with pCR [5]. Ideally, organ preservation should preserve the rectum, reduce morbidity, and costs without impairing long-term outcomes such as the rate of local and distant recurrence, and the overall survival.

While several retrospective studies have been published on this issue, the prospective ones are few and most of them do not compare long-term outcomes of TME and transanal LE [10]. [12–17] Since 2005, we started enrolling patients in a multicenter prospective phase 2 trial [10] evaluating the feasibility of LE approach after neoadjuvant therapy in patients with a complete or near complete response to neoadjuvant therapy. We continued thereafter to use the same approach in a systematic and prospective fashion. Therefore, the aim of this study was to compare, long-term outcomes of LARC patients undergoing LE after nCRT with a matched control group who underwent standard TME surgery.

Materials and methods

Patient selection

Between January 2005 and December 2016, a total of 314 patients received neoadjuvant therapy at a single Institution and were included in a prospective maintained database. The flowchart of the study is summarized in Fig. 1.

Treatments

During the study period, radiotherapy was delivered at a dose of 45–50.4 Gy with a standard fractionation (1.8 Gy/fraction) combined with a fluoropyrimidine-based chemotherapy. Surgery was planned at least 6 weeks after the completion of radiotherapy. Neoadjuvant chemoradiotherapy was performed in patients with histologically confirmed rectal adenocarcinoma located up to 12 cm from the anal verge, clinically staged as cT3-4 and/or N positive. Low-lying tumors located within 6 cm from the anal verge, stage cT2N0, likely requiring an abdominoperineal resection, were also included. Patients showing a major or complete clinical response to neoadjuvant therapy underwent a full-thickness transanal LE, while the remaining underwent the standard TME.

LE was performed either with the conventional transanal approach or with transanal endoscopic microsurgery (TEM), at the discretion of the surgeon. In general, LE was performed in low-lying tumors, while TEM in tumors located at > 6 cm from the anal verge. Regardless of the technique performed, the following oncological principles were respected: (1) there was a macroscopic free margin of at least 5 mm around the residual tumor/scar; (2) a full-thickness excision including the perirectal fat was performed. The excised specimen was reoriented on cardboard to facilitate the histological interpretation. Selection criteria for LE and patients' management have been previously reported [10]. Briefly, cCR was defined as no palpable mass at digital rectal examination, no residual tumor or a white scar at proctoscopy, and absence of positive lymph nodes on magnetic resonance imaging (MRI). Patients with the same characteristics at MRI and digital rectal examination, but with a superficial ulcer smaller than 2 cm at proctoscopy, were considered to have a mCR. The clinical response was evaluated at restaging which takes place 6–10 weeks after completion of chemoradiotherapy.

LE was considered to be adequate, and patients were observed if, at histopathology, there were either no viable cells in the surgical specimen (ypT0 or TRG1) or a residual ypT1 with all the following favorable features: well or moderately well differentiated adenocarcinoma, TRG2, and free margins. Subsequent radical TME was recommended, if one of the following features was present: ypT2-3 tumor, TRG3–5, positive margins, lymphovascular invasion, or poor differentiation.

The TME group was selected with a 1:1 ratio. The matching criteria, in order of relevance, included: ypT stage, age (± 3 years) of patients, gender, and duration of follow-up (± 6 months).

Follow-up

Patients with LE were recommended to undergo a strict follow-up which included digital rectal examination, proctoscopy, and Carcinoembryonic Antigen level determination every three months, for the first 2 years; every six months for third year, then yearly. Pelvic magnetic resonance was planned every 6 months, for the first three year, then yearly, and CT scan of the chest and abdomen every year.

Outcomes

Local recurrence (LR) was defined as any recurrence in the pelvis; other locations were defined as distant recurrence (DR). Local and distant recurrences were determined by

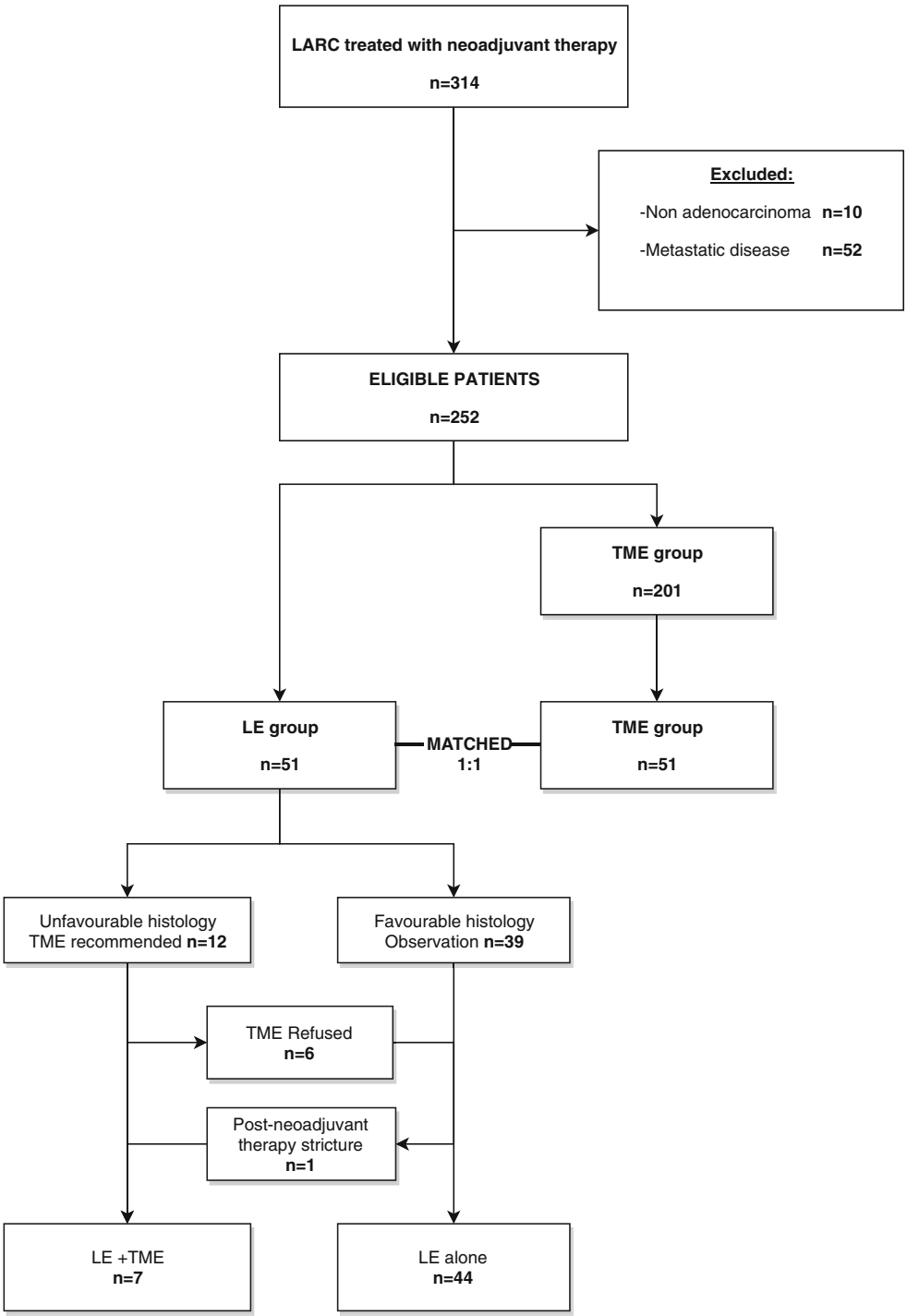

Fig. 1 Flowchart of the study. LARC locally advanced rectal cancer, LE local excision, TME total mesorectal excision

endoscopy, radiological imaging, and/or biopsy. Local recurrence-free survival (LRFS), disease-free survival (DFS), and overall survival (OS) were calculated from the start of chemoradiation to the date of the event (recurrence, death, or last follow-up).

The study was approved by the local ethics committee (Protocol number 4636/AO/18, Ethics Committee, Hospital of Padua).

Statistical analysis

Statistical analyses were performed using SAS® version 9.4 (SAS Institute, Cary, North Carolina, USA). Binary and categorial variables are expressed as number and percentages and continuous variables as median and range. Chi-square test was used for categorical variables. All tests were performed two-sided and $p < 0.05$ was considered statistically

significant. Kaplan-Meier with the log rank comparison test was used to analyze LRFS, DFS, and OS. Patients who underwent a subsequent TME surgery following the LE surgery were included in the LE study group.

Results

Patients

Among 252 eligible patients, 51 (20.2%) underwent LE (LE group). The control group included 51 matched controls (TME group) selected among the remaining 201 patients who received TME. Characteristics of patients are summarized in Table 1. At baseline, the clinical stage was more advanced ($p = 0.003$) and the median distance of the tumor from the anal verge was higher ($p = 0.007$) in the TME than in the LE group.

Time from completion of neoadjuvant treatment and LE was significantly longer to the interval between chemoradiation and TME [70 days (range 41–108 days) vs 52 days (range 46–92 days), $p = 0.0050$], due to the follow-up protocol adopted at our institution.

There was no statistically significant difference between the median follow-up time in the LE and TME groups [61 vs 64 months, $p = 0.544$], respectively.

LE was performed either with the conventional transanal approach ($n = 39$) or with transanal endoscopic microsurgery ($n = 12$).

Based on the histopathological findings, 39 patients of the study group had favorable histopathology features and were observed (ypT0, $n = 35$; ypT1, $n = 4$), one of them underwent a TME due to a post-chemoradiotherapy benign recto-vaginal fistula. Twelve patients showed unfavorable features requiring a completion TME which was refused by six (ypT3, $n = 1$; ypT2, $n = 3$; ypT1TRG > 2, $n = 2$). Of the remaining six (ypT3, $n = 1$; ypT2, $n = 5$), five underwent a completion low anterior and one an abdominoperineal resection. Histopathology of these patients showed ypT3 ($n = 3$), ypT2 ($n = 1$), and ypT0 ($n = 1$). None had positive lymph nodes. Overall, seven patients underwent an early TME out of 51 included in the study group.

Outcomes

Six (7.8%) patients experienced recurrence in the LE group: two local only (3.9%), two distant only, two local and distant. All local recurrences were endo-luminal, detected by proctoscopy, and occurred within 17 months from LE. Three of them were found in patients with ypT0 and, after a salvage TME, none of them had a second recurrence. The only patient with local recurrence who died had also distant recurrence (Table 2). Four patients developed distant recurrence, two of whom died of tumor progression and two are alive without disease.

At a median follow-up of 61 months, 11 patients underwent TME after LE: six had a completion TME, one for a benign rectal stricture, and four for a local recurrence. The rate of

Table 1 Characteristics of patients according to the treatment received

Characteristics	LE group ($n = 51$)	TME group ($n = 51$)	p value
Age, years, median (range)	66 (36–85)	67 (43–84)	0.488
Gender			
Male	34 (66.7%)	32 (62.7%)	0.679
Female	17 (33.3%)	19 (37.3%)	
Pre-treatment CEA (ng/mL)			
< 5	42 (82.3%)	39 (76.4%)	0.138
≥ 5	1 (2%)	6 (11.8%)	
Missing data	8 (15.7%)	6 (11.8%)	
Tumor distance from anal verge, cm, median (range)	4 (2–12)	6 (3–12)	0.007
RT dose (Gy)			
< 50.4	38 (74.5%)	40 (78.4%)	0.257
≥ 50.4	10 (19.6%)	5 (9.8%)	
Missing data	3 (5.9%)	6 (11.8%)	
Oxaliplatin (preoperative)			
Yes	6 (11.8%)	7 (13.7%)	0.767
No	45 (88.2%)	44 (86.3%)	
Clinical T-N stage (%)			
T2 N0	12 (23.6%)	–	0.003
T2 N+	7 (13.7%)	6 (11.8%)	
T3 N0	5 (9.8%)	3 (5.8%)	
T3 N+	18 (35.3%)	32 (62.8%)	
T4 N0	5 (9.8%)	2 (3.9%)	
T4 N+	4 (7.8%)	7 (13.7%)	
Missing data	–	1 (2%)	
Pathological T stage (%)			
ypT0	35 (68.6%)	33 (64.7%)	0.951
ypT1	6 (11.8%)	8 (15.7%)	
ypT2	8 (15.7%)	8 (15.7%)	
ypT3	2 (3.9%)	2 (3.9%)	
Pathological N stage (%)			
ypN0	–	44 (86.2%)	
ypN1	–	6 (11.8%)	
ypN2	–	1 (2%)	
Pathological TRG			
TRG1	35 (68.6%)	33 (64.7%)	0.010
TRG2	11 (21.6%)	5 (9.8%)	
TRG3	3 (5.9%)	13 (25.5%)	
TRG4	2 (3.9%)	0	
LE technique			
TAE	39 (76.5%)	–	
TEM	12 (23.5%)	–	
Surgery			
LE only	44 (86.2%)	–	
LE + completion LAR	1 (2%)	–	
LE + completion APR	6 (11.8%)	–	
LAR	–	44 (86.2%)	
APR	–	7 (13.8%)	
Median follow-up (months)	61 (5–150)	64 (2–158)	$p = 0.544$

Values are presented as median (range) or *n* (%)

LE, local excision; *TME*, total mesorectal excision; *CEA*, carcinoembryonic antigen; *RT*, radiotherapy; *T-N stage*, tumor-nodal stage; *TRG*, tumor regression grade; *TAE*, transanal excision; *TEM*, transanal endoscopic microsurgery; *LAR*, low anterior resection; *APR*, abdominoperineal resection

Table 2 Characteristics, treatment, and outcome of recurrences

Group	Patient age (years)/sex	Local recurrence	Distant recurrence	Baseline cTN	ypTN	TTR (months)	Treatment of recurrence	Outcome
LE	83/female	Yes	No	T2N0	T0NX	4	CTx, APR	NED
	73/female	No	Yes	T2N0	T3NX	34	CTx	DOD
	46/female	Yes	No	T3N1	T1NX	3	CTx, APR	NED
	82/female	Yes	Yes	T3N0	T0NX	17	CTx, APR	NED
	78/male	Yes	Yes	T3N1	T0NX	11	CTx, APR	DOD
	54/male	No	Yes	T4N1	T2NX	9	CTx, Lung resection	NED
TME	66/male	No	Yes	T4N1	T3N1	42	CTx	DOD
	60/male	No	Yes	T4N1	T2N0	41	CTx	AWD
	76/male	No	Yes	T3N1	T3N1	17	CTx	AWD
	67/female	No	Yes	T3N1	T0N0	50	CTx	DOD
	67/male	Yes	No	T3N1	T0N0	18	CTx	DOD

cTN stage, clinical tumor-nodal stage; *ypTN*, pathological tumor-nodal stage after neoadjuvant therapy; *TTR*, time to recurrence; *LE*, local excision; *TME*, total mesorectal excision; *CTx*, chemotherapy; *APR*, abdominoperineal resection; *NED*, nonevidence of disease; *AWD*, alive with disease; *DOD*, died of disease

rectum preservation was 78.5% (40/51) and the rate of patients stoma-free was 88.2% (45/51).

In the matched control cohort, only one (1.9%) patient developed a local recurrence which was presacral and unresectable. The patient died of disease progression. Four patients developed distant recurrence, two of whom died of tumor progression and two are alive with disease. The rate of patients stoma-free was 86.2% (44/51).

There were no statistically significant differences between the LE and the TME groups as concern as the estimated 5-year LRFS [91.8% (95% CI: 79.5–96.8) vs 97.6% (95% CI: 84.6–99.6, log rank test $p = 0.173$)], DFS [86.7% (95% CI: 72.5–93.9) vs 86.4% (95% CI: 70.1–94.1, log rank test $p = 0.143$)], and OS [85% (95% CI:69.0–93.0) vs 90% (95% CI: 75.3–96.2, log rank test $p = 0.637$)] (Fig. 2a–c).

Discussion

The principal aim of this study was to evaluate whether the transanal LE approach is able to increase the rectum preservation without impairing long-term outcomes in rectal cancer patients with a major or complete clinical response after neoadjuvant therapy. The study was performed in a setting of a single Academic Institution where a program of rectum-sparing approach was implemented in 2005. The control group was selected among patients who underwent TME during the same period and the main matching criterion was the ypT stage which is the most powerful prognostic factor after excluding the unavailable N and M status.

The main finding of the study is that, 80% of patients had their rectum preserved without impairing their long-term outcomes.

The rectum-sparing approaches are increasingly used in rectal cancer patients with a major or complete clinical response to neoadjuvant therapy; however, the safety of these approaches is still matter of debate due to the potential increased risk of local and distant recurrences, its timely detection, and successful salvage surgery. Furthermore, the evidences on the feasibility of

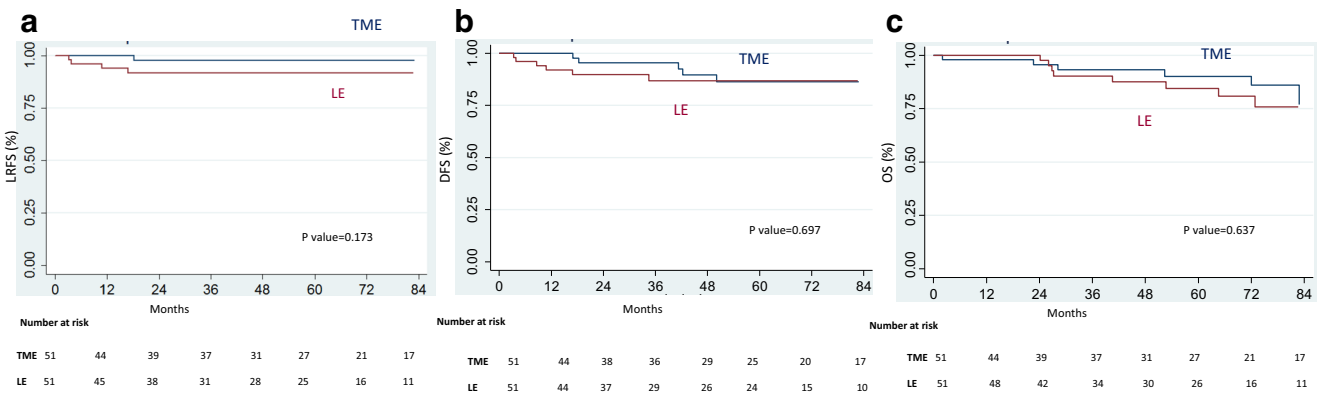

Fig. 2 Kaplan-Meier curves in the LE AND TME groups. **a** Local recurrence-free survival (LRES). **b** Disease-free survival (DFS). **c** Overall survival (OS). *LE*, local excision; *TME*, total mesorectal excision

rectum preserving strategies are still scarce and mainly based on studies underpowered, retrospective, and with a short follow-up period. Moreover, some of the most cited prospective trials include only clinical T2 carcinoma [16, 17] or patients who received neoadjuvant short-course radiotherapy [12]. Thus, the heterogeneity of patient and treatment regimens makes comparison with the present trial difficult. Similarly, our study is not comparable with those that include the Watch and Wait approach. The LE approach is potentially able to increase the proportion of candidates for rectal sparing strategies because it is indicated both in patients with mCR or cCR while the Watch and Wait approach is indicated only in patients with a cCR [14]. A further reason to use the LE approach is related to the wide discrepancy between the clinical and pathological complete response [18]. Drawbacks of LE rely on the postoperative morbidity which is still not irrelevant and may make challenging to perform a sphincter saving surgery in patients who require a TME completion after LE [19, 20]. On the other hand, in the WW strategy there is a delay on the treatment of the false negative patients considered to be complete responders while the response is not complete (patients with regrowth). The effect of this delayed treatment is unknown. In their recent study on 113 patients who underwent a WW strategy, Smith et al. [21] reported a worse survival and a higher incidence of disease progression in patients having a local regrowth compared with those having a sustained cCR (36% vs 1%, $p < 0.001$). Overall, there is still a lack of evidence that one organ-sparing approach is superior to the other, as no comparative studies are available.

The 78.5% of rectal preservation found in our series represents an improvement of previous studies reporting a range of preservation between 66 and 70% [13, 22]. The rate of rectal preservation depends on the ability to correctly select candidates to LE in order to reduce the rate of patients who require completion TME. In a previous multicenter study, we reported that in 31.7% of patients a completion TME was recommended due to unfavorable histopathology features [10]. In the present study this percentage decreased to 23.5%. Likely, the improvement in patients' selection due to the better performance of imaging modalities and to the increasing experience of dedicated surgeons and radiologists might explain the gap. Interestingly, all LR observed in the LE group were resectable, detected within the first 2 years of follow-up, and salvaged by TME. Similar findings have been recently reported by Stijns et al. who found a 9% rate of intraluminal LR, occurred in the first postoperative year, and salvaged [13]. The prospective studies including only clinical T2 rectal cancer quantified LR between 4 and 8% [17, 23]. In our study, the percentage of LR was higher in the LE group than in the TME group (7.8% vs 1.9%), however this difference did not reach a statistical significance. Nevertheless, besides the statistical significance, patients and doctors should be aware that the risk of LR is likely higher after LE than after TME surgery. This risk may be acceptable if is not too high, and if the recurrences are successful managed by salvage surgery. Notably, all patients with LR who underwent salvage TME did not experience any second local recurrence and no positive lymph nodes were detected in the surgical specimen. This seems to confirm either that salvage surgery is successful in patients with LR after LE and that the negative predictive value of MRI is accurate [24]. A further interesting, although not surprising finding, was that three out of four LRs were found in TME patients with a ypT0. In their pooled analysis, Maas et al. [5] reported 12/455 LRs in patients who had a pathologic complete response after neoadjuvant therapy followed by TME surgery. This discrepancy may depend by the fact that the LE is not wide enough to include all the area of the primary tumor or by the inaccuracy of the histopathologic examination. Indeed, an ypT0 after LE does not guarantee an absent risk of LR and outlines that, after the LE, a strict follow-up is mandatory. Surprisingly, 3 out of 6 patients who refused to undergo a salvage TME in the LE group are alive without evidence of disease. We are very cautious to enlarge indications for LE approach and recommend completion TME for ypT2-3 tumors due to the high risk of nodal metastasis which translates in high risk of LR. However, the exact role of completion TME needs to be further investigated and a balance between under- and over-treatment remains a major challenge.

Notably, both disease-free and overall survival were comparable between the LE and TME groups. This is in line with other studies [10, 15, 23] and confirms that a successful salvage TME surgery impacts positively on survival, as well as that a good response to neoadjuvant therapy is able to select patients with a favorable prognosis.

The study do have limitations related to the mono-institutional setting and relatively small sample size, thus the results might not be generalizable. We are aware that a case control design includes some selection bias which is partially mitigated by the fact that the data were prospectively collected. Moreover, few data regarding the radiotherapy dose and the value of pre-treatment CEA were missing. Knowing that radiotherapy is usually delivered at a dose of 45–54.4 Gy with a standard fraction (1.8 Gy/fraction), we did not exclude those in whom the exact dose of radiotherapy was missing, because the missing data do not have a great impact on evaluating the long-term oncological outcomes

of these patients. Similarly, we did not exclude patients with missing pre-treatment CEA value. Although prospective randomized trials might overcome these biases, they are challenging to perform due to the accrual difficulties [15] and ethical concerns [25].

Despite these limitations, the results of this study are valuable because they were obtained within a rectum-sparing program implemented since 2005 and all data were registered prospectively. In addition, the median follow-up is longer than 5 years and, during the study period, the definition of clinical response as well as the treatment schema of neoadjuvant therapy remained unchanged.

In conclusion, the current study confirms that, within a careful and dedicated program of organ preservation for patients with LARC who receive neoadjuvant chemoradiotherapy, the rectum may be preserved and patients will be stoma-free, in about 80% and 90%, respectively, without impairing the oncological and functional outcomes. Both these issues are addressed in an ongoing multicenter observational study [26], which will further help to validate this approach.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Sauer R, Becker H, Hohenberger W et al (2004) Preoperative versus postoperative chemoradiotherapy for rectal cancer. New Engl J Med 35:1731–1740
2. Pucciarelli S, Del Bianco P, Efficace F et al (2011) Patient-reported outcomes after neoadjuvant chemoradiotherapy for rectal cancer: a multicenter prospective observational study. Ann Surg 253:71–77
3. Juul T, Ahlberg M, Biondo S, Espin E, Jimenez LM, Matzel KE, Palmer GJ, Sauermann A, Trenti L, Zhang W, Laurberg S, Christensen P (2014) Low anterior resection syndrome and quality of life: an international multicenter study. Dis Colon Rectum 57: 585–591
4. Smith FM, Waldron D, Winter DC (2010) Rectum-conserving surgery in the era of chemoradiotherapy. Br J Surg 97:1752–1764
5. Maas M, Nelemans PJ, Valentini V, Das P, Rödel C, Kuo LJ, Calvo FA, García-Aguilar J, Glynne-Jones R, Haustermans K, Mohiuddin M, Pucciarelli S, Small W Jr, Suárez J, Theodoropoulos G, Biondo S, Beets-Tan RG, Beets GL (2010) Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol. 11:835–844
6. Perez RO (2016) Complete clinical response in rectal cancer: a turning tide. Lancet Oncol. 17:125–126
7. Gani C, Bonomo P, Zwirner K, Schroeder C, Menegakis A, Rödel C, Zips D (2017) Organ preservation in rectal cancer - challenges and future strategies. Clin Transl Radiat Oncol 3:9–15
8. Smith JJ, Chow OS, Gollub MJ et al (2015) Organ preservation in rectal adenocarcinoma: a phase II randomized controlled trial evaluating 3-year disease-free survival in patients with locally advanced rectal cancer treated with chemoradiation plus induction or consolidation chemotherapy, and total mesorectal excision or non-operative management. BMC Cancer 15:767
9. Habr-Gama A (2006) Assessment and management of the complete clinical response of rectal cancer to chemoradiotherapy. Color Dis 8:21–24
10. Pucciarelli S, De Paoli A, Guerrieri M et al (2013) Local excision after preoperative chemoradiotherapy for rectal cancer: results of a multicenter phase II clinical trial. Dis Colon Rectum 56:1349–1356
11. Aschele C, Cionini L, Lonardi S, Pinto C, Cordio S, Rosati G, Artale S, Tagliagambe A, Ambrosini G, Rosetti P, Bonetti A, Negru ME, Tronconi MC, Luppi G, Silvano G, Corsi DC, Bochicchio AM, Chiaulon G, Gallo M, Boni L (2011) Primary tumour response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol 29:2773–2780
12. Bujko K, Richter P, Smith FM, Polkowski W, Szczepkowski M, Rutkowski A, Dziki A, Pietrzak L, Kołodziejczyk M, Kuśnierz J, Gach T, Kulig J, Nawrocki G, Radziszewski J, Wierzbicki R, Kowalska T, Meissner W, Radkowski A, Paprota K, Polkowski M, Rychter A (2013) Preoperative radiotherapy and local excision of rectal cancer with immediate radical re-operation for poor responders: a prospective multicentre study. Radiother Oncol 106: 198–205
13. Stijns RCH, de Graaf EJR, Punt CJA, Nagtegaal ID, Nuyttens JJME, van Meerten E, Tanis PJ, de Hingh IHJT, van der Schelling G, Acherman Y, Leijtens JWA, Bremers AJA, Beets GL, Hoff C, Verhoef C, Marijnen CAM, de Wilt JHW, CARTS Study Group (2019) Long-term oncological and functional outcomes of chemoradiotherapy followed by organ-sparing transanal endoscopic microsurgery for distal rectal cancer: the CARTS study. JAMA Surg 154:47–54
14. Martens MH, Maas M, Heijnen LA et al (2016) Long-term outcome of an organ preservation program after neoadjuvant treatment for rectal cancer. J Natl Cancer Inst 10:108
15. Rullier E, Rouanet P, Tuech JJ, Valverde A, Lelong B, Rivoire M, Faucheron JL, Jafari M, Portier G, Meunier B, Sileznieff I, Prudhomme M, Marchal F, Pocard M, Pezet D, Rullier A, Vendrely V, Denost Q, Asselineau J, Doussau A (2017) Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial. Lancet. 390: 469–479
16. Lezoche G, Baldarelli M, Guerrieri M, Paganini AM, de Sanctis A, Bartolacci S, Lezoche E (2008) A prospective randomized study with a 5-year minimum follow-up evaluation of transanal endoscopic microsurgery versus laparoscopic total mesorectal excision after neoadjuvant therapy. Surg Endosc 22:352–358
17. Garcia-Aguilar J, Renfro LA, Chow OS et al (2015) Organ preservation for clinical T2N0 distal rectal cancer using neoadjuvant chemoradiotherapy and local excision (ACOSOG Z6041): results of an open-label, single-arm, multi-institutional, phase 2 trial. Lancet Oncol 16:1537–1546
18. Smith FM, Wiland H, Mace A, Pai RK, Kalady MF (2014) Clinical criteria underestimate complete pathological response in rectal cancer treated with neoadjuvant chemoradiotherapy. Dis Colon Rectum 57:311–315
19. Friel CM, Cromwell JW, Marra C, Madoff RD, Rothenberger DA, Garcia-Aguílar J (2002) Salvage radical surgery after failed local excision for early rectal cancer. Dis Colon Rectum 45:875–879
20. Bulut O, Levic K, Hesselfeldt P, Bülow S (2014) The outcome of rectal cancer after early salvage TME following TEM compared with primary TME: a case-matched study. Tech Coloproctol 18:83–84
21. Smith JJ, Strombom P, Chow OS et al (2019) Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. JAMA Oncol. https://doi.org/10.1001/jamaoncol.2018.5896

22. Creavin B, Ryan E, Martin ST et al (2017) Organ preservation with local excision or active surveillance following chemoradiotherapy for rectal cancer. Br J Cancer 116:169–174
23. Lezoche E, Baldarelli M, Lezoche G, Paganini AM, Gesuita R, Guerrieri M (2012) Randomized clinical trial of endoluminal locoregional resection versus laparoscopic total mesorectal excision for T2 rectal cancer after neoadjuvant therapy. Br J Surg 99:1211–1218
24. Maretto I, Pomerri F, Pucciarelli S, Mescoli C, Belluco E, Burzi S, Rugge M, Muzzio PC, Nitti D (2007) The potential of restaging in the prediction of pathologic response after preoperative chemoradiotherapy for rectal cancer. Ann Surg Oncol 14:455–461
25. Glynne-Jones R, Hughes R (2012) Critical appraisal of the 'wait and see' approach in rectal cancer for clinical complete responders after chemoradiation. B J Surg 99:897–909
26. Barina A, De Paoli A, Delrio P et al (2017) Rectal sparing approach after preoperative radio- and/or chemotherapy (RESARCH) in patients with rectal cancer: a multicentre observational study. Tech Coloproctol. 21:633–640