UNIVERSITÀ DEGLI STUDI DI PADOVA

UNIVERSITÀ DEGLI STUDI DI PADOVA

Corso di Laurea Magistrale in Medicina e Chirurgia

Dipartimento di Scienze Chirurgiche, Oncologiche e Gastroenterologiche

Direttore: Ch.mo Prof. Fabio Farinati

Unità Operativa Complessa di Chirurgia generale 3

Direttore: Ch.mo Prof. Salvatore Pucciarelli

TESI DI LAUREA

Long and short-term outcomes of completion and salvage total mesorectal excision after rectal-sparing approaches

Relatore: Prof.ssa Gaya Spolverato

Correlatore: Dott. Quoc Riccardo Bao

Laureanda: Sara Codato

ANNO ACCADEMICO 2022-2023

Ai miei genitori, a nonna Mimma e a Davide
che hanno sempre creduto in me, dall'inizio alla fine.
E a te, nonna Lisa, che più di chiunque altro avresti voluto esserci.

"Senza fretta, ma senza tregua"
-Lev Tolstoj-

Contents

Abstract

Background. Patients with mid-low rectal cancer enrolled in a rectal-sparing approach may require Total mesorectal excision (TME) due to high-risk histopathological features, local regrowth or recurrence, and may have a compromised surgical outcomes and survival.

Aim. This study aims to evaluate the short- and long-term outcomes of patients undergoing completion or salvage TME after a rectal-sparing approach.

Methods. This is a sub-analysis of the ReSARCh study (NCT02710812, clinicaltrials.gov), which is a multicentre, prospective, observational study including patients with complete or major clinical response after neoadjuvant treatment for locally advanced rectal cancer. Patients were treated with local excision (LE) in case of complete or major response, or with Watch-and-wait (WW) in case of complete response, at the discretion of the clinicians/patients. Patients who required a completion TME for unfavourable histopathology after LE or a salvage TME for local recurrence or local regrowth, were included in this analysis. Stoma rate, 30-day complications and 30-day mortality after TME were collected. An intention-to-treat analysis of patients who required TME was performed and overall survival (OS), disease-free survival (DFS), local recurrence-free survival (LRFS) and distant recurrence-free survival (DRFS) were estimated using the Kaplan-Meier method.

Results. Between April 2016 and April 2023, a total of 299 patients were enrolled in the ReSARCh study and a total of 190 patients were available for analysis. Of these, 66 (34.7%) were selected for this study. Of them, 45 (68.2%) initially underwent LE, while the other 21 (31.8%) followed WW approach. Completion TME was necessary in 36 (54.5%) patients, while salvage TME was required in 9 (13.6%) patients for local recurrence after LE and in 21 (31.8%) patients for local regrowth after WW approach. A total of 40 (60.6%) TMEs were performed, including 28 low anterior resections, 11 abdominoperineal resections and 1 pelvic exenteration. The overall 30-day post-operative complications rate was 32.5%, of which 6 (15.0%) were major (Clavien-Dindo≥3), and the 30-day mortality was 2.5%. At a median follow-up of 38 (31.2-48.7) months, the stoma-free rate was 87.5% and the 1-, 3- and 5-year OS and DFS were 100%, 98.5%, 94.0% and 87.7%,

77.9%, 64.6%, respectively, while the 1-, 3- and 5-year LRFS and DRFS were 93.9%, 86.0%, 83.5% and 97.0%, 93.3%, 93.3%, respectively.

Conclusions. About one third of the patients required TME after an initial rectal-sparing approach. TME after a rectal-sparing approach is safe and feasible, as the rate of major post-operative complications and mortality are acceptable. Survival of patients requiring TME after LE or WW is not compromised and is characterized by a low recurrence rate. Most patients treated with cTME showed no residual tumour on histopathological analysis and had no recurrence. The criteria for recommending completion surgery should be redefined.

Sommario

Presupposti. I pazienti con cancro del retto medio-basso sottoposti ad approcci conservativi del dell'organo potrebbero necessitare di un'escissione totale del mesoretto (TME) per caratteristiche istopatologiche ad elevato rischio o per recidiva locale, e potrebbero avere una compromissione sia degli esiti chirurgici sia della sopravvivenza.

Obiettivo. L'obiettivo di questo studio è di valutare gli esiti di lungo e breve termine nei pazienti che si sono sottoposti a una chirurgia di completamento o di salvataggio dopo un approccio conservativo del retto.

Metodi. Lo studio rappresenta una sub-analisi del protocollo ReSARCh (registrato come NCT02710812, clinicaltrials.gov), uno studio multicentrico, prospettico e osservazionale che include pazienti con una risposta clinica completa (cCR) o maggiore (mCR) al trattamento neoadiuvante per il cancro del retto localmente avanzato. I pazienti sono stati trattati con escissione locale (LE) in caso di risposta clinica completa o maggiore, o con regime di sorveglianza (WW) in caso di risposta clinica completa, a discrezione del medico e del paziente. I pazienti che hanno richiesto una TME di completamento per caratteristiche istopatologiche sfavorevoli dopo LE, o che hanno richiesto una TME di salvataggio dopo recidiva locale sono stati inclusi nell'analisi. I dati raccolti riguardavano il tasso di stomia, le complicanze post-operatorie a 30 giorni e la mortalità a 30 giorni dalla TME. È stata eseguita un'analisi intention-to-treat dei pazienti che necessitavano di una TME, e la sopravvivenza globale (OS), la sopravvivenza libera da malattia (DFS), la sopravvivenza libera da recidiva locale (LRFS) e la sopravvivenza libera da recidiva a distanza (DRFS) sono state stimate attraverso l'utilizzo delle curve di Kaplan-Meier.

Risultati. Tra aprile 2016 ed aprile 2023, un totale di 299 pazienti sono stati inclusi nel protocollo ReSARCh, e di questi, 190 erano congrui per l'analisi. 66 (34.7%) pazienti sono stati selezionati per lo studio. Di questi, 45 (68.2%) si sono sottoposti a LE, i restanti 21 (31.8%) hanno seguito un regime di WW. La TME di completamento è stata richiesta in 36 (54.5%) pazienti, mentre la TME di salvataggio è stata richiesta in 9 (13.6%) pazienti nel gruppo LE e in 21 (31.8%) pazienti nel gruppo WW a seguito di una recidiva. In totale sono state eseguite 40 (60.6%) TME, includendo 28 resezioni anteriori di retto, 11 resezioni addomino-

perineali e 1 exenteratio pelvica. Il tasso di complicanze post-operatorie a 30 giorni è stato di 32.5%, di cui 6 (15.0%) sono state complicanze maggiori (secondo la classificazione Clavien-Dindo≥3), e la mortalità è stata del 2.5%. Al follow-up medio di 38 mesi (31.2-48.7), il tasso di pazienti senza stomia è stato dell'87.5% e l'OS a 1, 3 e 5 anni è stata rispettivamente del 100%, 98.5%, 94.0%; la DFS del 87.7%, 77.9%, 64.6%; mentre la LRFS e la DRFS a 1, 3 e 5 anni sono state rispettivamente del 93.9%, 86.0%, 83.5% e del 97.0%, 93.3%, 93.3%.

Conclusioni. Circa un terzo dei pazienti selezionati per un approccio conservativo del retto hanno richiesto una TME durante il follow-up. La TME dopo un approccio conservativo del retto è sicura e attuabile, poiché le complicanze post-chirurgiche maggiori e la mortalità risultano essere accettabili. La sopravvivenza dei pazienti che hanno richiesto una TME dopo LE o WW non è stata compromessa ed è caratterizzata da un basso tasso di recidiva. La maggior parte dei pazienti trattati con TME di completamento, all'analisi istopatologica, non ha riportato la presenza di tumore e, inoltre, non ha avuto recidiva. I criteri per raccomandare la chirurgia di completamento dovrebbero essere, quindi, ridefiniti.

INTRODUCTION

The standard treatment of locally advanced rectal cancer is actually neoadjuvant chemoradiotherapy (nCRT) followed by Total mesorectal excision (TME)[1]. This approach have achieved a 5- and 10-year overall survival (OS) of approximately 75% and 60% [2,3] respectively. However, there are several disadvantages for the patient's quality of life.[4]

According to recent studies, approximately 15-27% of patients have a complete clinical response (cCR)[5]. Although clinical and pathological response are not always concordant[6], clinical response can be used as an indication for a rectal-sparing approach. Local excision (LE) and Watch and Wait (WW) have been proposed as rectal-sparing approaches in selected patients who have a cCR or major complete clinical response (mCR) after nCRT. On the one hand, LE is a full-thickness excisional macro-biopsy of the residual tumour or scar performed with transanal approach, offering the advantage of a histopathological evidence of cCR or mCR. On the other hand, WW strategy consists of a rigorous follow-up after a cCR, avoiding surgical treatment which would be lately considered in case of local regrowth [7].

Nevertheless, histopathological analysis of the surgical specimen in patients treated with LE may show some high-risk features, such as ypT≥2, positive margins, TRG≥ 3 and/or poor grade of differentiation (G3). [17] In this case, there is a substantial risk of disease persistence or early recurrence, so a completion TME (cTME) should be recommended. This may reflect the poor accuracy of restaging after nCRT. [19] Similarly, in patients enrolled in a WW programme, the rate of local tumour regrowth at 2 years is about 25%[21] during the follow-up period and 77.7% of them required a salvage TME (sTME). In both cases, there is a risk of local recurrence after LE, which also requires a sTME.

Interest for rectal-sparing approaches has increased in recent years, and so have the outcomes of cTME or sTME compared to the standard of care. Two studies show that there are no significant differences between patients undergoing cTME and those undergoing primary TME in terms of surgical and oncological outcomes [8,9].

In the study by *Levic et al*, no significant differences were found between standard and salvage TME in terms of intra- and post-operative complications [8]. The systematic review and meta-analysis by *Mohamed et al* found that early cTME did not worsen mortality, morbidity, stoma rate, local and distant recurrences, although the quality of surgical specimens was lower than that of primary TME [9]. In contrast to previous studies, some authors found that cTME after LE could worsen both surgical and oncological outcomes, such as recurrence.[11-12] On the other hand, after a WW approach, in the majority of patients (≈90%)[13] cTME was a possible treatment for local tumour regrowth, with adequate disease control.[14] Similar to other studies, curative salvage surgery in patients who had tumour regrowth was possible in 83% of patients, with no difference in distant recurrence. Furthermore, OS and DFS were equivalent in the WW group and in patients undergoing immediate surgery[15] and no significant differences were found in tumour-specific mortality[16].

Patients requiring a completion or salvage TME may have a reduced survival due to clinical failure. The aim of this study is to evaluate the long- and short-term outcomes of patients requiring a TME after an initial rectal-sparing approach. The primary endpoints are overall survival (OS), disease-free survival (DFS), local recurrence-free survival (LRFS) and distant recurrence-free survival (DRFS). Secondary endpoints are 30-day post-operative complications rate, 30-day mortality and morbidity.

METHODS

2.1 Study design

This study represents a sub-analysis of the ReSARCh study (protocol registered on clinicaltrials.gov, registration number NCT02710812). The ReSARCh study is a prospective, multicentre, observational, phase 2 study that enrolled patients with medium and low rectal cancer treated with LE or WW rectal-sparing approach. The protocol and preliminary results have been published previously. [17,20]

Criteria for inclusion were as follows:

- age≥18 years,
- biopsy to confirm the presence of rectal adenocarcinoma, up to 12 cm from the anal verge,
- patients who had receive neoadjuvant treatment and had cCR or mCR,
- patients eligible for radical TME surgery,
- patients able to understand the risks and benefits of the protocol.

Exclusion criteria were: patients with partial or no clinical response, patients ineligible for TME with metastatic lymph nodes on MRI.

The study was approved by the Ethics Committee of the coordinating centre, and then approved by the local Ethics Committee of each participating centre. Patients provided written informed consent to participate in this study after an adequate explanation of the study.

2.2 Data collection and staging

Gender, age, American Society of Anaesthesiologists (ASA) score, Eastern Cooperative Oncology Group (ECOG) performance status scale, Body Mass Index (BMI), clinical history, digital rectal examination, colonoscopy, CEA levels, chest/abdomen CT and pelvic MRI were the baseline check-ups. Data were collected by every participating centre using the RedCAP database.

Clinical and pathological stages were determined according to the American Joint Committee on Cancer (8th Edition) for rectal cancer.

Baseline clinical staging were assessed with digital rectal examination, rectoscopy or colonoscopy, pelvic MRI for loco-regional metastases (or in singular cases with pelvic CT or endorectal ultrasound), chest-abdominal CT for distant metastases, CEA levels and questionnaires (QoL and functional assessment).

The first restaging was performed 7-8 weeks after completion of neoadjuvant therapy with the same diagnostic work-up, except for colonoscopy. If there was no evidence of response or partial response, patients were recommended to TME. In case of mCR or cCR, patients underwent an additional proctoscopy after 11-12 weeks after completion of nCRT (second restaging). If the patient showed a mCR or cCR, a rectal-sparing approach was proposed. In case of mCR, LE was proposed, whereas in case of cCR, LE or WW was proposed at the discretion of clinicians.

2.3 Definitions of response

A cCR has been defined when there is:

- absence of palpable mass at digital rectal exploration,
- absence of mucosal abnormalities at endoscopy,
- absence of metastatic lymph nodes at MRI.

A mCR has been defined as:

- absence of palpable mass at digital rectal exploration,
- presence of small mucosal irregularity or superficial ulcer no more than 2 cm in diameter at endoscopy,
- absence of metastatic lymph nodes at MRI.

A pathologic complete response (pCR) was defined as the absence of viable tumour cells in the specimen (ypT0NX) following LE, and a ypT0N0 after TME.

2.4 Local Excision

LE was performed by TAE (transanal excision), TEM (transanal endoscopic microsurgery), TAMIS (transanal minimally invasive surgery) or TEO (transanal endoscopic operation). Regardless of the surgical technique used, a full thickness excision including all layers of the rectal wall with a gross free margin of at least 0.5 cm was recommended. The surgical specimens were oriented on a cardboard before fixation.

LE was considered curative if histological assessment documented pCR (ypT0) or ypT1 with TRG<3 and G1-2 or negative margins. In case of high-risk histopathological features including ypT≥2, high-grade (G3) ypT1, positive margins (<1mm), lympho-vascular or perineural invasion and tumor regression grade (TRG) ≥3 according to Mandard's classification, a completion surgery was recommended.

2.5 Follow-up

The follow-up is within the framework of current national guidelines (AIOM follow-up in rectal cancer). After LE or WW, patients will be visited every 3 months in the first two years, and then every 6 months in the following three years. During each follow-up, the following exams will be performed:

- Digital rectal examination;
- Rectoscopy;
- CEA and routine haematochemical examinations;
- MRI every 6 months up to 5 years;
- Chest-abdominal CT (annually unless otherwise clinically indicated);
- Colonoscopy (at 1 year, if negative at 3 years, if still negative at 5 years);
- Completion questionnaires (optional at 6 and 12 months after surgery).

2.6 Inclusion criteria

For this sub-analysis, patients were retrospectively selected from the ReSARCh database. Inclusion criteria were the need to perform a cTME or a sTME for oncological reasons, namely:

- patients with high-risk features on histopathological analysis after an LE (cTME);
- patients who developed a local recurrence after LE (sTME);
- patients who developed local tumour regrowth during WW strategy (sTME).

Patients who required rectal resection for other reasons (i.e. post-LE complications) were excluded from this analysis.

2.7 Endpoints and outcome measures

The primary endpoint of this study was the impact of cTME and sTME on long- and short-term oncological outcomes.

The outcome measures were OS, DFS, LRFS, DRFS. Secondary endpoints included 30-day post-operative complications and 30-day mortality. Major post-operative complications were defined as grade≥3 according to the Clavien-Dindo score.[26]

2.8 Statistical analysis

The sample was subjected to a descriptive statistical analysis that considered the dependent and independent variables. The analysis was conducted using the following numerical indices: median, quartiles and interquartile range (IQR).

An intention-to-treat analysis was performed in the entire cohort to define the survival of patients requiring TME after a rectal-sparing approach, and OS, DFS, LRFS, DRFS were estimated by using the Kaplan-Meier method. Each outcome

was calculated from the date of surgery or its refusal to the date of the event (local or distant recurrence, death or last follow-up). Analyses were performed using R software (version 4.0.4, available at https://www.R-project.org) with the gtsummary package (available at https://CRAN.R-project.org/package=gtsummary). P-value <0.05 was considered statistically significant.

RESULTS

3.1 Patients' characteristics

A total of 299 patients were extracted from the ReSARCh study database, and, after excluding lost-to-follow-up patients, unavailable data or follow-up<24 months, 190 patients were extracted. Of these, 66 (34.7%) were selected for this study. Selection criteria were as follows (*Fig.1*):

- request for cTME for radicalization (high-risk pathological features) after LE (*n*=36, 18.95%);
- request for sTME for tumour recurrence in LE approach (*n*=9, 4.7%);
- request for sTME for tumour regrowth in the WW approach (*n*=21, 11.0%).

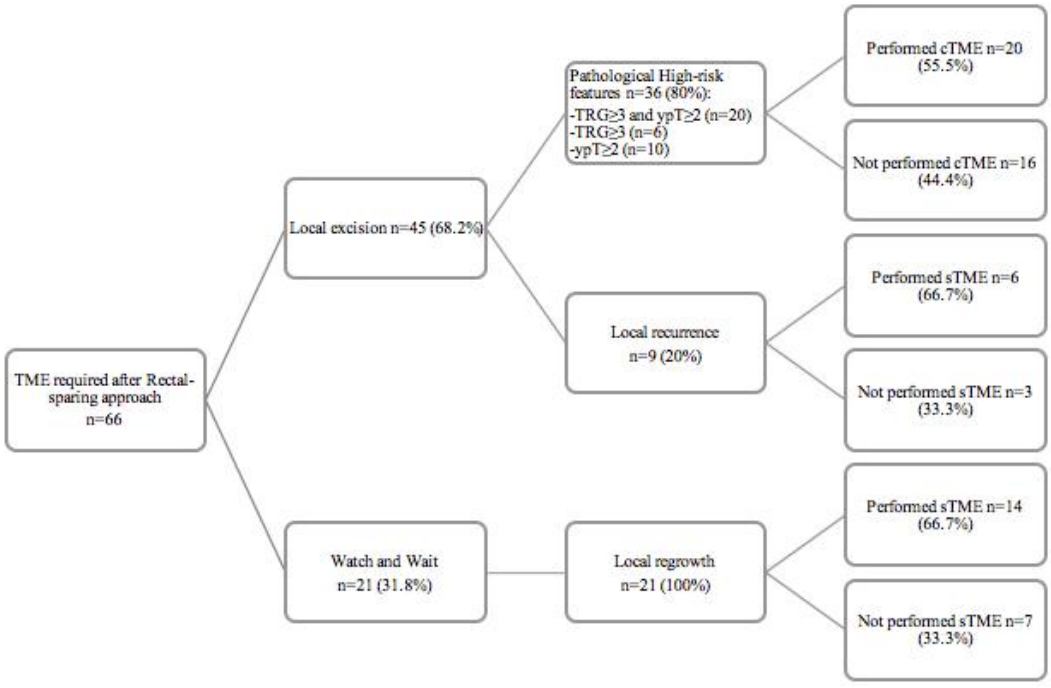


Fig.1: Indications for total mesorectal excision (TME) after local excision and watch and wait.

Baseline characteristics of the patients and the tumours are summarised in *Table 1*. Overall, 42 (63.6%) were male and the median age was 66 (61-75) years. Most patients had an ASA score≤ 2 (*n*=51, 77.3%), and an ECOG performance status 0 (*n*=44, 66.7%).

The median distance to the anal verge was 4 (1-12) cm, clinical T stage was cT1 (*n*=1, 1.5%), cT2 (*n*=16, 24.2%), cT3 (*n*=46, 69.7%), cT4 (*n*=3, 4.5%). Lymph nodes were clinically positive in 45 (68.2%) patients. Overall, 57 (86.4%) patients received standard long-course chemoradiotherapy, 4 (6.1%) received a short-course radiotherapy, and only 5 (7.6%) received total neoadjuvant therapy. In patients who received nCRT, the most common chemotherapy regimens included capecitabine alone (*n*=53, 85.0%). After preoperative treatment, characteristics of tumours were: ycT0 (*n*=27, 40.9%), ycT1(*n*=27, 40.9%), ycT2 (*n*=6, 9.1%), ycT3 (*n*=3, 4.5%). At first restaging, a cCR was achieved in 17 (25.8%) patients, while the other 49 (74.2%) had a mCR. At second restaging, 30 (45.4%) patients had a cCR, while 34 (51.5%) had a mCR.

LE was performed in 45 (68.2%) patients, and 21 (31.8%) were followed up in a WW programme.

TABLE 1 Baseline characteristics of patients and tumours.

		Local Excision (N=45)	**Watch and Wait (N=21)**	**Total (N=66)**
		N (%) or Median (IQR)	N (%) or Median (IQR)	N (%) or Median (IQR)
Sex	Female	15 (33·0)	9 (43·0)	24 (36·4)
	Male	30 (67·0)	12 (57·0)	42 (63·6)
Age	Years	67·0 (60·0-75·0)	65·0 (61·0-73·0)	66 (61·0-75·0)
ASA score	1	10 (23·0)	10 (48·0)	20 (30·3)
	2	23 (52·0)	8 (38·0)	31 (47·0)
	3	8 (18·0)	3 (14·0)	11 (16·7)
	4	3 (6·8)	0 (0·0)	3 (4·5)
	NA	1 (2·2)	0 (0·0)	1 (1·5)
ECOG performance status	0	27 (60·0)	17 (80·9)	44 (66·7)
	1	5 (11·1)	3 (14·3)	8 (12·1)
	2	0 (0·0)	0 (0·0)	0 (0·0)
	4	1 (2·2)	0 (0·0)	1 (1·5)
	NA	12 (26·7)	1 (4·8)	13 (19·7)
BMI	Kg/m^2	26·7 (24·2-30·8)	22·7 (21·2-27·1)	25·5 (23·2-29·0)
CEA	ng/mL	1·9 (1·4-3·8)	2·2 (1·8-3·5)	2·1 (1·5-3·8)
Distance from anal verge	Cm	4·0 (3·0-6·0)	7·0 (3·0-9·0)	4·0 (3·0-7·0)
Clinical T stage	1	0 (0·0)	1 (4·8)	1 (1·5)
	2	11 (24·0)	5 (24·0)	16 (24·2)
	3	31 (69·0)	15 (71·0)	46 (69·7)
	4	3 (6·7)	0 (0·0)	3 (4·5)

Clinical N stage	N0	12 (27·0)	9 (43·0)	21 (31·8)
	N+	33 (73·0)	12 (57·0)	45 (68·2)
Neoadjuvant treatment	Chemotherapy only	0 (0·0)	0 (0·0)	0 (0·0)
	Long-course CRT	38 (84·4)	19 (90·5)	57 (86·4)
	Short-course RT	3 (6·6)	1 (4·8)	4 (6·1)
	TNT	4 (8·8)	1 (4·8)	5 (7·6)
Radiotherapy dose	Gray	50 (46·0- 55·0)	50 (50·0-55·0)	50 (46·0-55·0)
Neoadjuvant Chemotherapy	5FU-Oxaliplatin	0 (0·0)	1 (5·0)	1 (1·6)
	Capecitabine	36 (80·0)	17 (81·0)	53 (80·3)
	CAPEOX	3 (6·6)	0 (0·0)	3 (4·8)
	Capecitabine concomitant RT	1 (2·2)	2 (10·0)	3 (4·8)
	Xelac	1 (2·2)	0 (0·0)	1 (1·5)
	CT concomitant RT	1 (2·2)	0 (0·0)	1 (1·5)
	No chemotherapy	3 (6.6)	1 (4·0)	4 (6·1)
ycT stage at second restaging	0	13 (28·9)	14 (67·0)	27 (40·9)
	1	21 (46·6)	6 (29·0)	27 (40·9)
	2	5 (11·1)	1 (4·8)	6 (9·1)
	3	3 (6·7)	0 (0·0)	3 (4·5)
	X	0 (0·0)	0 (0·0)	0 (0·0)
	NA	3 (6·7)	0 (0·0)	3 (4·5)
ycN stage at second restaging	N0	45 (100·0)	21 (100·0)	66 (100)
	N+	0 (0·0)	0 (0·0)	0 (0·0)
Tumour response at first restaging	Complete	3 (6·7)	14 (67·0)	17 (25·8)
	Major	42 (93·0)	7 (33·0)	49 (74·2)
Tumour response at second restaging	Complete	9 (20·0)	21 (100·0)	30 (45·4)
	Major	34 (75·5)	0 (0·0)	34 (51·5)
	NA	2 (4·4)	0 (0·0)	2 (3·0)
Patient's status at last follow up	NED	41 (91·1)	18 (85·7)	59 (89·3)
	AWD	2 (4·4)	3 (14·2)	5 (7·6)
	DOD	2 (4·4)	0 (0·0)	2 (3·1)

Abbreviations: ASA American Society of Anesthesiologists, BMI Body Mass Index, CEA Carcinoembrionic antigene, CRT Chemoradiotherapy, ECOG Eastern Cooperative Oncology Group, NA Not available, TNT Total Neoadjuvant Therapy, NED No Rvidence of Disease, AWD Alive with disease, DOD Dead of disease

3.2 Outcomes of local excision

The outcomes of LE were summarized in *Table 2*.

The most frequent LE techniques were TAE (*n*=17, 25.7%) and TEM (*n*=18, 27.3%), while TAMIS and TEO were performed in 5 (7.6%) and 5 (7.6%) patients, respectively.

Patients undergoing LE had a median inhospital length-of-stay of 3 (0-13) days, and surgery was performed at a median of 15 (12-18) weeks after completion of neoadjuvant therapy. The majority of patients had no complications (*n*=37, 82.2%), while 8 (17.8%) had post-operative complications. Of these, 7 (87.5%) had a Clavien-Dindo≤2, and only 1 patient required further surgery.

On histopathological analysis, the tumour regression grade (TRG) were TRG1 (*n*=6, 9.1%), TRG2 (*n*=13, 19.7%), TRG3 (*n*=15, 22.7%) and TRG4 (*n*=11, 16.7%). The pathological T stage of 45 patients was as follows: ypT0 (*n=7,* 15.5%), ypT1 (*n*=8, 17.7%), ypT2 (*n*=27, 60.0%), ypT3 (*n*=3, 6.7%). In almost all surgical specimens after LE, margins were negative (*n*=40, 88.9%) and, interestingly, 7 (15.5%) patients had no evidence of tumour.

Completion surgery was required in 36 (80.0%) of the patients and was performed in 20 after LE. The reasons for completion surgery were as follows: both TRG≥3 and ypT≥2 were *n*=20 (two patients also had a G3 tumour), only TRG ≥3 were *n*=6 and only ypT≥2 were *n*=10. In patients undergoing cTME, LAR was performed in 15 (75.0%), and APR in 5 (25.0%). Out of 5, 2 APRs were performed with an open technique, whereas a laparoscopic approach was chosen for the remaining patients undergoing cTME (*n*=18, 90.0%).

sTME was required in 20% of patients (*n*=9) with evidence of local recurrence. Of these, only one did not undergo cTME and had local recurrence. Among the 9 patients with local recurrence, 8 were treated with surgery (of these 6 with sTME), the other one with chemotherapy. Four of these recurrences were intraluminal tumours and one was a mesorectal recurrence. Two patients, however, had distant recurrences, both in the lungs.

TABLE 2. Characteristics Local excision (N=45)

	Local excision (N=45)
	N (%) **or**

		Median (Interquartile Range)
Local excision technique	Transanal excision (TAE)	17 (25·7)
	Transanal minimally invasive surgery (TAMIS)	5 (7·6)
	Transanal endoscopic microsurgery (TEM)	18 (27·3)
	Transanal endoscopic operation (TEO)	5 (7·6)
30-day complications	No	37 (82·2)
	Yes	8 (17·8)
Clavien-Dindo Classification	1	2 (25·0)
	2	5 (62·5)
	3	1 (12·5)
	4	0 (0·0)
Time from completion neoadjuvant therapy to surgery	Weeks	15·6 (12·6-18·3)
Length-of-stay	Days	3·4 (2-4)
Tumour Regression Grade (TRG)	1	6 (9·1)
	2	13 (19·7)
	3	15 (22·7)
	4	11 (16·7)
ypT stage	0	7 (15·5)
	1	8 (17·7)
	2	27 (60·0)
	3	3 (6·7)
ypN stage	N0	22 (48·9)
	N+	3 (6·6)
	NA	20 (44·4)
Reasons for requiring TME after LE	Completion surgery	36 (80·0)
	Salvage surgery	9 (20·0)
Completion surgery (n=36)	Not performed	16 (44·4)
	Performed	20 (55·5)
Surgery after recurrence (n=9)	Not performed	1 (11·1)
	Performed	8 (88·9)
Type of surgery (n=28)	Abdominoperineal resection	10 (35·7)
	Low anterior resection	16 (57·1)
	Re-LE	2 (7·2)
30-day complications after completion surgery (n=28)	No	19 (67·8)
	Clavien-Dindo 1	3 (10·7)
	Clavien-Dindo 2	3 (10·7)
	Clavien-Dindo 3	2 (7·1)
	Clavien-Dindo 5	1 (3·6)
Distant recurrence (DR)	No	43 (95·5)
	Yes	2 (4·5)

3.3 Outcomes Watch-and-wait

The characteristics of patients who required a TME after a WW approach were summarised in *Table 3*. At baseline staging, patients enrolled in a WW protocol had cT1(*n*=1, 4.8%), cT2 (*n*=5, 23.8%) or cT3 (*n*=15, 71.4%), cN0 (*n*=9, 42.8%) and cN+ (*n*=12, 57.1%). Overall, 19 (90.5%) received long-course chemoradiotherapy with capecitabine, one (4.8%) patient received long-course chemoradiotherapy with 5FU-oxaliplatin and one received short-course radiotherapy. The median time to local regrowth was 15 (9-19) months after the completion of nCRT.

The following salvage operations were performed: LAR (*n*=12), APR (*n*=1), pelvic exenteration (*n*=1), LE (*n*=5, one subsequently underwent LAR after two months). A laparoscopic approach was chosen for sTME in 7 patients, while an open or combined (*n*=1) approach for 6. Four patients had post-operative complications (Clavien-Dindo≥3, *n*=2). Of the remaining 2 patients, 1 continued to refuse sTME, and the last was treated with chemotherapy.

On histopathological examination of specimen, 3 patients had no evidence of tumour, while the other 14 had evidence of adenocarcinoma, with a mean diameter of 3.1 cm. The tumours grading was G1 (*n*=2, 14.2%), G2 (*n*=6, 42.8%), G3 *(n*=3, 21.4%), Gx (*n*=1, 7.14%), and was not available in 2 patients. The following ypT stage was found: ypT0 (*n*=4, 21.0%), ypT1 (*n*=2, 10.5%), ypT2 (*n*=8, 42.1%), ypT3 (*n*=3, 15.8%), NA (*n*=2, 10.5%). Lympho-vascular invasion was present in 4 patients (23.5%), and perineural invasion in 2. The median number of lymph nodes analysed was 12 (1-30). Lymph nodes metastases were found in one patient.

Of the 21 patients who had local regrowth, only 1 had a local recurrence 17 months after sTME. In addition, in 2 patients (9.5%) there was distant recurrence with liver and lungs involvement, while one patient developed a new primary thyroid tumour that was treated surgically.

TABLE 3. Characteristics Watch-and-wait (N=21)

		Watch-and-wait (N=21)
		N (%) or Median (Interquartile Range)
Time to regrowth	Months	14·6 (9-19)

Salvage surgery	Performed	19 (90·4)
Type of surgery (n=19)	Abdominoperineal resection	1 (5·2)
	Low anterior resection	12 (63·1)
	LE	5 (26.3)
	Pelvic exenteration	1 (5·3)
ypT stage (n=19)	0	4 (21·0)
	1	2 (10·5)
	2	8 (42·1)
	3	3 (15·8)
	NA	2 (10·5)
ypN stage (n=19)	N0	12 (63·1)
	N+	1 (5·3)
	NA	6 (31·6)
Tumour grading (n=14)	G1	2 (14·3)
	G2	6 (42·8)
	G3	3 (21·4)
	Gx	1 (7·1)
	NA	2 (14·3)
30-day complications (n=19)	No	15 (78·9)
	Yes	4 (21·1)
Clavien-Dindo Classification (n=4)	1	0 (0·0)
	2	2 (50·0)
	3	2 (50·0)
	4	0 (0·0)
Recurrence	Local recurrence	1 (4·7)
	Distant recurrence	2 (9·5)

3.4 Analysis of TME

Of the 66 patients who required TME after a rectal-sparing approach, TME was actually performed in 40 (60.6%) patients, LE in 6 (9.1%), and 20 patients did not undergo any completion or salvage surgery. The informations are summarised in *Table 4*. The most common reason for not performing TME was patient refusal (*n*=11, 16.7%). Of the 36 patients in the LE group who were recommended a cTME, 10 (27.7%) refused the surgical procedure. A further 2 patients had a higher surgical

risk that did not allow cTME to be performed, 1 was treated by chemoradiotherapy and 3 patients did not undergo the procedure for unknown reasons.

The most common surgical procedures were LAR (*n*=28, 42.4%) and APR *(n*=11, 16.6%), performed in the most cases by laparoscopic technique (*n*=26, 65%). Of the 40 patients who underwent TME, 35 (87.5%) required a stoma, which 14 (35.0%) were definitive. Of the remaining patients, at last follow-up, 6 (15.0%) had a temporary stoma that was not reversed, and 15 (37.5%) had reversed stoma.

A total of 13 (19.7%) patients experienced complications after the TME procedure and the Clavien-Dindo classification was ≥3 in 6 (15.0%) of them. Specifically, complications were wound dehiscence (*n*=2), anastomotic leak (*n*=3), fever (*n*=2), diarrhoea (*n*=1), occlusion (*n*=2) and 2 were unspecified. Only one patient died from post-operative complications.

At the final histopathological analysis of the specimen, adenocarcinoma was found in 22 (47.8%) patients, while no tumour was found in 24 (52.2%) patients undergoing TME surgery. The tumour grade was G2 in 13 (32.4%), surgery was radical (R0) in 38 patients (95.0%) and ypT stage was ypT0 (*n*=20, 50.0%), ypT1 (*n*=3, 7.5%), ypT2 (*n*=9, 22.5%), ypT3 (*n*=6, 15.0%), ypT4 (*n*=1, 2.5%), not available (*n*=1. 2.5%). The median number of lymph nodes examined was 12.0 (5.0-17.5), and lymph node metastases were found in four patients. The final ypTNM stage was as follows: stage 0 (*n*=18, 45.0%), stage I (*n*=9, 22.5%), stage II (*n*=8, 20.0%), stage III (*n*=4, 10.0%) and 1 (2.5%) not available.

TABLE 4. Characteristics cTME or sTME (N=66)

		cTME or sTME (N=66)
		N (%) or Median (Interquartile Range)
Indication for TME	Completion surgery (LE only)	36 (54·5)
	Local regrowth (WW only)	21 (31·8)
	Local recurrence	9 (13·6)
Type of surgery	LAR	28 (42·4)
	APR	11 (16·6)
	Re-LE	6 (9.1)
	Pelvic exenteration	1 (1·5)
	Not performed	20 (30·3)
Surgical approach (n=40)	Open	12 (30·0)

	Laparoscopic Combined NA	26 (65·0) 1 (2·5) 1 (2·5)
Stoma at last follow-up (n=40)	Temporary Definitive Reversed Not performed	6 (15·0) 14 (35·0) 15 (37·5) 5 (12·5)
30-day complications after surgery (n=40)	No Yes	27 (67·5) 13 (32·5)
Clavien-Dindo Classification	≥3	6 (15·0)
Mortality	30-days	1 (2·5)
ypT stage (n=40)	T0 T1 T2 T3 T4 NA	20 (50·0) 3 (7·5) 9 (22·5) 6 (15·0) 1 (2·5) 1 (2·5)
ypN stage (n=40)	N0 N+ NA	34 (85·0) 4 (10·0) 2 (5·0)

3.5 Long-term outcomes

The median time of follow-up was 38.0 months (31.2-48.7). At last follow-up, 59 (89.4%) patients had no evidence of disease, 5 (7.6%) were alive with disease, and 2 (3.0%) had died of disease. In the intention-to-treat analysis, OS at 1-, 3- and 5-year was 100% (95% CI 100-100), 98.5% (95% CI 100-95) and 94.0% (95% CI 100-84), respectively (*Fig.1*).

A total of 10 patients experienced a recurrence, while 4 patients had a new primary tumour, including haematological malignancy (*n*=1), lungs (*n*=1), thyroid (*n*=1), and uterus (*n*=1). To note, only one sTME-treated patient had another local recurrence, and 2 patients (LE *n*=1, WW *n*=1) had a further distant recurrence. The estimated 1-, 3- and 5-year DFS was 87.7% (95% CI 96-80), 77.9% (95% CI 88-68), and 64.6% (95% CI 90-46), respectively (*Fig.2*).

Overall, 10 (15.5%) patients had a local recurrence within the first 3 years of follow-up. Four of these were endoluminal, two extra-luminal, and four were not specified. In the LE group, 9 (20.0%) patients had a recurrence, of which 1 patient did not undergo cTME although it was required after LE. In the WW group, only

one patient had a local recurrence after sTME. The estimated 1-, 3- and 5-year LRFS was 93.9% (95% CI 99-88), 86.0% (95% CI 94-77) and 83.5% (95% CI 93-74) respectively (*Fig.3*).

Four patients (6.0%) had distant recurrences within the first 3 years of follow-up, involving lungs and liver. Two of these were treated surgically and the others were treated with chemotherapy. One patient, who had both local and distant recurrence, died. The estimated 1-, 3- and 5-year DRFS was 97.0% (95% CI 100-92), 93.3% (95% CI 99-87), and 93.3% (95% CI 99-87) (*Fig.4*).

When comparing patients initially treated with LE and those who underwent a WW approach, the estimated cumulative DFS 1-, 3- and 5-year in the LE group was 89.0% (95% CI 80-99), 77.0% (95% CI 66-91) and 49.0% (95% CI 22-100) respectively, while in the WW group was 85.0% (95% CI 71-100), 80.0% (95% CI 64-100) and 80.0% (95% CI 64-100 with a log-rank test, p=0.55). (*Fig.5*).

Fig.1 *Kaplan-Meier estimate OS*

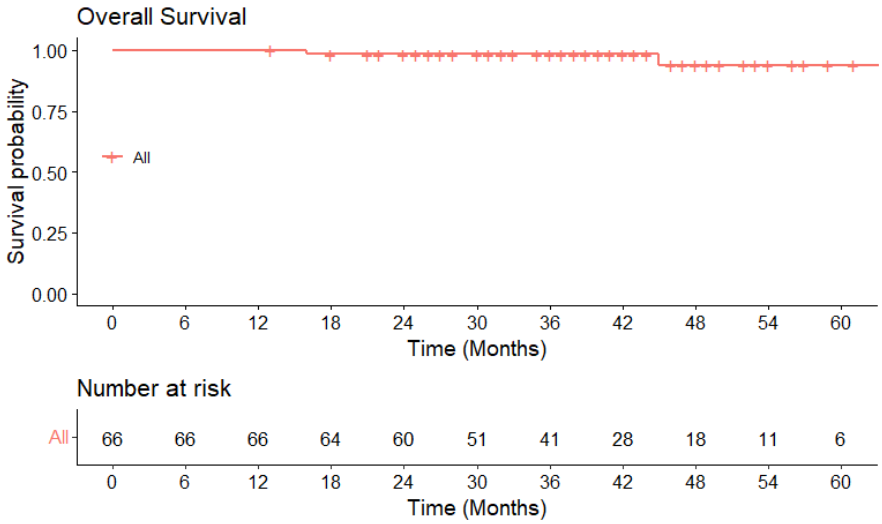


Fig.2 *Kaplan-Meier estimate DFS.*

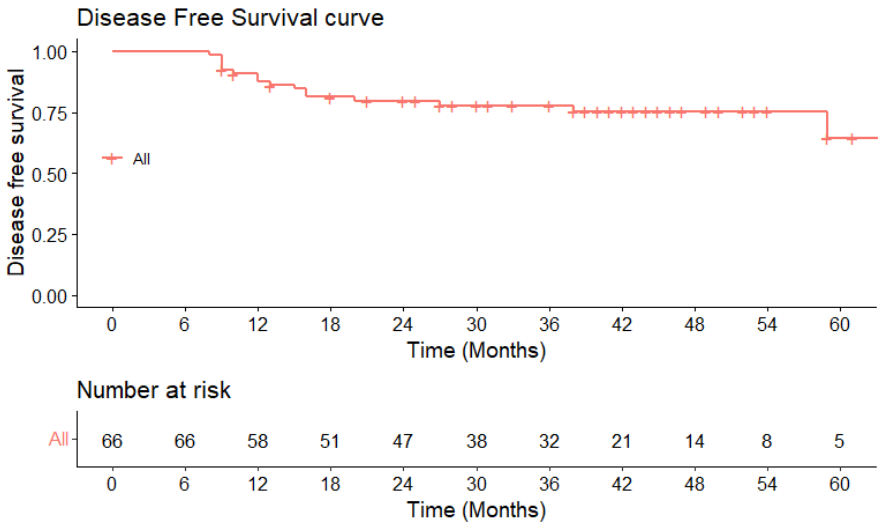


Fig.3 *Kaplan-Meier estimate LRFS*

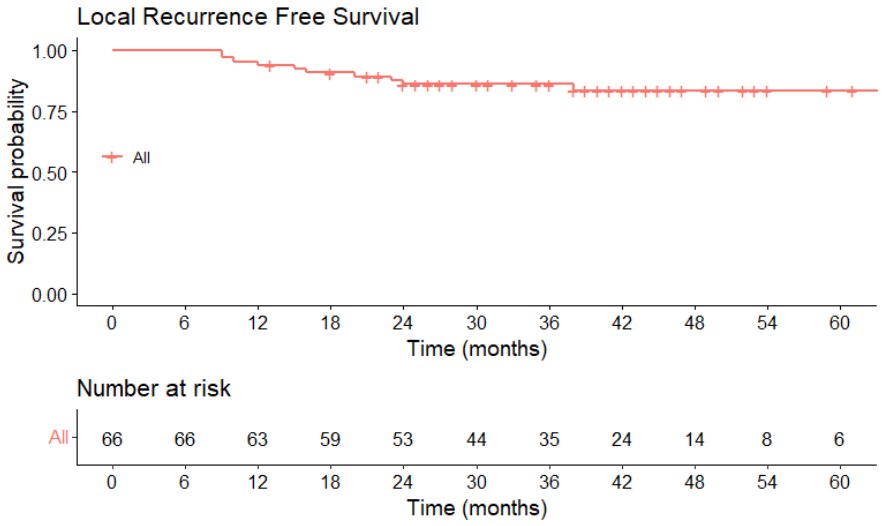


Fig4. *Kaplan-Meier estimate DRFS*

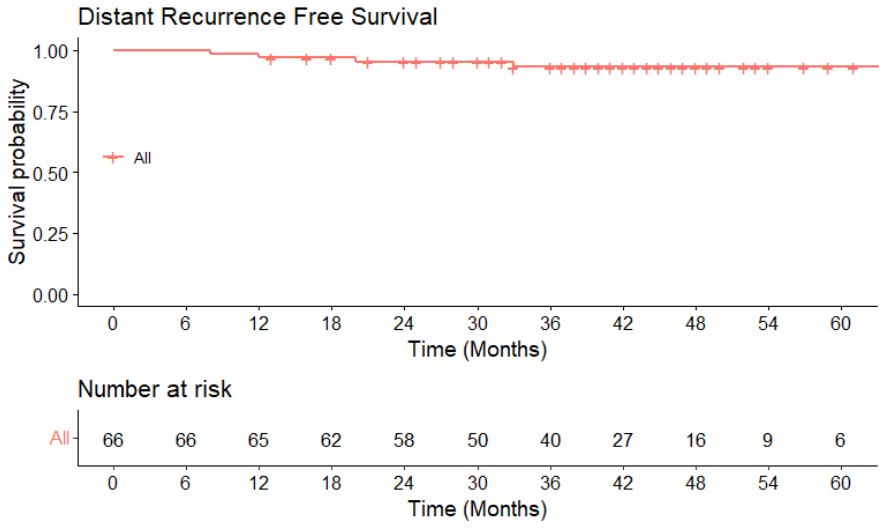
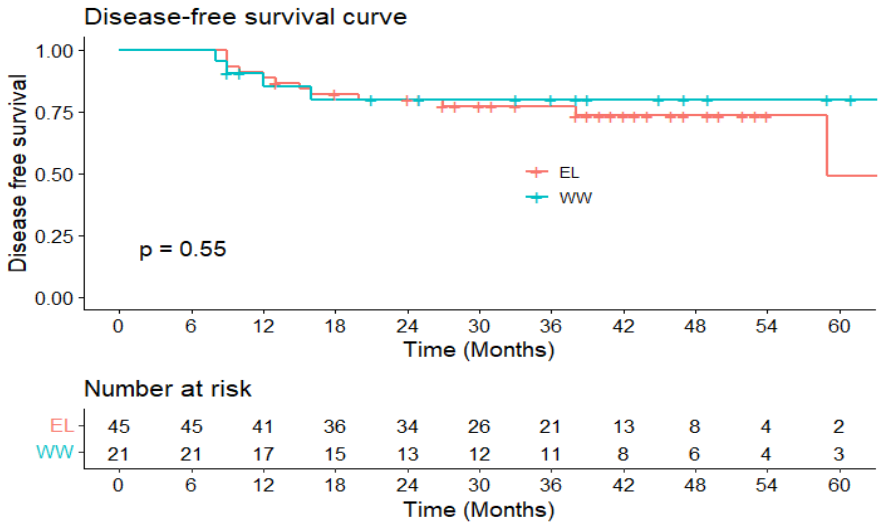


Fig.5 *Kaplan-Meier estimate DFS in the LE and WW groups.*



DISCUSSION

The aim of the study was to analyse the outcomes of patients with rectal cancer who required completion and salvage TME after a rectal-sparing approach. Rectal-sparing approaches avoid compromising quality of life, but may require TME in case of recurrence or regrowth. These patients may represent a failure in the rectal-sparing approaches, mainly due to a staging error and poor accuracy of restaging after neoadjuvant treatment, which may lead to persistent disease or early recurrence, and ultimately reduced survival. Furthermore, completion or salvage surgery may be technically more difficult and affected by a higher rate of post-operative complications.

In our study, a total of 20 (30.3%) patients underwent cTME, and 20 (30.3%) underwent sTME (6 in the LE group and 14 in the WW group). Of these, 13 had post-operative complications. The rate of major complications was approximately 15.0% and the 30-day mortality was 2.5%. In the study by *Levic et al* [8], comparing patients who underwent primary TME with those who underwent sTME after TEM, although none received preoperative chemoradiotherapy, they found that there were no differences in terms of postoperative complications, while the mortality after sTME was 8%. In terms of mortality, their results differ from ours, probably because the patients did not receive neoadjuvant chemoradiotherapy. However, the effect of cTME after LE on post-operative complications is still controversial. In fact, some authors have found that cTME surgery after LE may worsen surgical outcomes: *Morino et al* [11] found that a previous TEM was a risk factor for APR rate, while 30-day morbidity was similar in the primary TME and TEM-TME groups (p=0.463). Regarding sTME after the WW approach, studies are still scarce and focused on local/distant recurrences during the follow-up or on the feasibility of surgery: for example, *Habr-Gama et al* [14] claimed that the WW strategy allowed a technically unimpaired TME in case of regrowth thanks to an intact surgical field.

A total of 36 patients in the LE group required cTME. Of these, 20 patients underwent completion surgery, while the other 16 did not undergo cTME, mainly because of their refusal. To note, most patients (90%) treated with cTME showed

no residual tumour on histopathological analysis of the specimen. On the other hand, the goal of completion surgery is to prevent future recurrences or persistence of disease. Indeed, in our study, cTME showed excellent results in terms of local control of disease, and none of the patients treated with cTME developed recurrence. In the GRECCAR2 study[22], a prospective, randomized, open-label, multicentre, phase III trial, *Rullier et al* reported similar local recurrences rate between TME and LE, while completion surgery was required in approximately 1/3 of patients initially treated with LE. In this study, the criteria for cTME were less strict than ours, including only ypT2-3 or R1 resection. However, outcomes after cTME were not reported. The concordance between histopathological analysis of LE and clinical staging is still poor, reflecting the still inaccurate staging after neoadjuvant treatment. Our group has previously reported that the current clinical criteria for defining pathological response are still poor, with a sensitivity in detecting cCR and mCR of 37.5% and 59.3% respectively [19]. Most interestingly, of the 19 (42.2%) patients who did not receive TME in the LE group, none died and only one had a local recurrence treated with chemotherapy. This result is interesting and highlights the possibility that cTME may have been over-recommended in some case. All these considerations emphasize the need to redefine the criteria for completion surgery after LE.

In the 21 patients of the WW group who required sTME for local regrowth, sTME was performed in 14 (66.6%) of them, and R0 resection was achieved in 13 (92.8%) cases. After sTME, only one patient had a local recurrence 23 months later and was treated with chemotherapy; another, however, had a distant recurrence involving the liver. Previous studies have reported that sTME was possible in at least 83-90% of patients[13-14-15]. This finding is also supported by other authors, such as *Cotti et al* [13] in whom pelvic control is feasible in 85% of cases after sTME in patients with WW strategy. *Cotti et al* reported a sphincter-sparing surgery rate of 75%, whereas in our study, in 12 of 14 patients (85.7%) sphincter-sparing procedure was feasible. Note that the inclusion criteria of *Cotti's* work were similar to ours in terms of initial staging (they considered stage II/III or cT2N0M0) and neoadjuvant treatment (long-course chemoradiotherapy). Their lower rate of sphincter preservation is probably due to the retrospective, single-institution nature of the study.

Moreover, after salvage surgery for local regrowth, only one (7.1%) patient develop a recurrence. *Kong et al* [15] reported a total of 370 patients who followed a WW approach. Among those who subsequently underwent salvage surgery (*n*=88) for tumour regrowth, only 3 (3.4%) patients developed local recurrence. These results are reassuring for the safety role of WW strategy, however, data on local recurrence after sTME are still limited and insufficient to draw a firm conclusion. Considering the rarity of the local recurrences after treatment, only analyses with longer follow-up and a larger study cohort could give us insight into this subject.

One of the controversies in the current WW literature is the impact of local regrowth on distant recurrence. In this analysis, only 2 (9.5%) patients developed distant metastases, within a median time of 10 months. Of these, one had previously undergone sTME. Similar observations were presented in IWWD: although our sample size is significantly smaller than in IWWD, approximately 10% of patients developed distant recurrence within the first year[21]. The authors suggest that distant recurrences are related to tumour biology rather than to the omission of immediate surgery[14], while other authors such as *Smith et al,* support the hypothesis that distant recurrence may be associated with local regrowth[24]. *Fernandez et al* found a five-fold higher risk to developing distant recurrence in patients who had local regrowth[27]. Since distant recurrence is a rather rare event even in large multicentre databases, in our opinion only larger prospective studies could properly analyze this aspect.

Good results in terms of OS and DFS were found in our study. The 5-year OS and DFS was 94% and 65%, respectively. In the GRECCAR2 study[24], the 5-year OS and DFS in LE group were 84% and 70%, respectively. Of note, only high-risk patients who required a completion or salvage surgery were included in this analysis, although shorter follow-up and smaller sample size were reported in our study. However, the estimated intention-to-treat DFS was similar (78%). Regarding WW, in the OPRA trial, 62 patients required a salvage surgery for local regrowth. Of these 9 (15%) patients had local recurrence after sTME and 6 (10%) had both local and distant recurrence. However, the comparison of the DFS of patients who were recommended sTME and TME for partial or absent response after restaging was similar.[18] Overall, these results underlined good results of sTME and the oncologic safety of a rectal-sparing approach, balancing the risk of delaying TME in case of local regrowth or recurrence.

Finally, in comparison with the intention-to-treat analysis, the DFS of patients initially undergoing LE and WW was similar. Note that the groups compared are likely dishomogeneous due to the study's inclusion criteria, which allowed patients with mCR to undergo LE only, and patients with cCR to undergo both LE and WW. Therefore, the comparative analysis is limited and subjected to bias. However, although this analysis included only patients with high-risk recurrence, no difference was found between LE and WW. Considering that patients with a cCR are also included in LE group, the DFS are not dissimilar to those of WW, probably because of the impact of cTME on eventual recurrence. This observation underlines that, although there is not always concordance between clinical and pathological staging of the tumour, LE has the advantage of histopathological proof of response to neoadjuvant treatment, also allowing patients to be enrolled in a rectal-sparing approach in case of mCR. Again, on the other hand, these data suggest that a redefinition of patients requiring cTME is needed and that the actual restaging after neoadjuvant treatment should be improved.

4.1 Limitation of the study

Our study has some limitations that need to be considered. First, it is a retrospective analysis of a multicentre, observational study. This analysis was not planned in the original protocol, data on TME are lacking and some information was not available, either because some centres did not update patient information in the database or because there was heterogeneity in surgical techniques, based on surgeon preferences. Second, the limited number of events could not be considered representative of the population. The rate of patients needing cTME after LE, of patients needing sTME for local regrowth after WW or for local recurrence, varied between 20 and 30% of the cohort. In addition, the number of patients actually undergoing TME was also limited by a high number of patient refusals. Probably only by using large registry database with longer follow-up, could the outcome data of patients with local recurrence suggest some conclusions. Finally, the short median follow-up time does not allow accurate assumptions about long-term outcomes for all patients.

CONCLUSIONS

About one third of the patients required TME after an initial rectal-sparing approach. TME after a rectal-sparing approach is safe and feasible, as the rate of major post-operative complications and mortality are acceptable. Survival of patients requiring TME after LE or WW is not compromised and is characterized by a low recurrence rate. Most patients treated with cTME showed no residual tumour on histopathological analysis and had no recurrence. The criteria for recommending completion surgery should be redefined.

Bibliography

1. National Comprehensive Cancer Network (2022) Rectal Cancer (Version 1.2022).
2. R. Sauer, T. Liersch, S. Merkel, et al. "Preoperative versus post- operative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years", *J Clin Oncol*. (2012);30(16):1926–33.
3. R. Sauer, H. Becker, W. Hohenberger, et al. "Preoperative versus postoperative chemoradiotherapy for rectal cancer". *N Engl J Med.* (2004);351(17):1731–40.
4. S. Pucciarelli, F. Giandomenico, A. De Paoli, et al. "Bowel function and quality of life after local excision or total mesorectal excision following chemoradiotherapy for rectal cancer." *Br J Surg* (2017) 104 (1):138-147. DOI:10.1002/bjs.10318
5. M. Maas, P.J. Nelemans, V. Valentini, et al. "Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data." *Lancet Oncol (*2010); 11: 835–44.
6. J.G Guillem, D.B Chessin, J. Shia, et al. "Clinical examination following preoperative chemoradiation for rectal cancer is not a reliable surrogate end point", *J Clin Oncol (*2005); 23: 3475–79.
7. L. D'Alimonte, Q.R Bao, G. Spolverato, G. et al. "Long-Term Outcomes of Local Excision Following Neoadjuvant Chemoradiotherapy for Locally Advanced Rectal Cancer". *Ann Surg Oncol* (2020) DOI:10.1245/s10434-020-09243-6
8. K. Levic, O. Bulut, P. Hesselfeldt, et al. "The outcome of rectal cancer after early salvage TME following TEM compared with primary TME: a case-matched study" *Tech Coloproctol.* (2013) DOI: 10.1007/s10151-012-0950-2
9. M.A Chaouch, J. Khan, G. Talvinder Singh, et al. "Early salvage total mesorectal excision (sTME) after organ preservation failure in rectal cancer does not worsen postoperative outcomes compared to primary TME: systematic review and meta-analysis", *International Journal of Colorectal Disease* (2021), DOI: 0.1007/s00384-021-03989-5
10. G. Piessen, C. Cabral, S. Benoist, et al. "Previous transanal full-thickness excision increases the morbidity of radical resection for rectal cancer", *The Association of Coloproctology of Great Britain and Ireland* (2011) 14, 445–452; DOI:10.1111/j.1463-1318.2011.02671
11. M. Morino, M. Ettore Allaix, S. Arolfo, et al. "Previous transanal endoscopic microsurgery for rectal cancer represents a risk factor for an increased abdominoperineal resection rate" *Surg Endosc* (2013) 27:3315–3321, DOI 10.1007/s00464-013-2911-x
12. W. van Gijn, V. Brehm, E. de Graaf, et al. "Unexpected rectal cancer after TEM: Outcome of completion surgery compared with primary TME" *EJSO* (2013) vol 39 p.1225e1229; DOI: 10.1016/j.ejso.2013.08.003
13. G.C. Cotti, R.V. Pandini, O. Braghiroli, et al. "Outcomes of Patients With Local Regrowth After Nonoperative Management of Rectal Cancer After Neoadjuvant Chemoradiotherapy", *Dis Colon Rectum* (2022); 65: 333–339, DOI: 10.1097/DCR.0000000000002197
14. A. Habr-Gama, J. Gama-Rodrigues, G.P. Sao Juliao, et al. "Local Recurrence After Complete Clinical Response and Watch and Wait in Rectal Cancer After Neoadjuvant Chemoradiation: Impact of Salvage Therapy on Local Disease Control" *Int J Radiation Oncol Biol Phys* (2013), Vol. 88, No. 4, pp. 822e828; DOI: 10.1016/j.ijrobp.2013.12.012
15. J.C. Kong, G.R. Guerra, S.K. Warrier, et al. "Outcome and Salvage Surgery Following "Watch and Wait" for Rectal Cancer after Neoadjuvant Therapy: A Systematic Review." *Dis Colon Rectum* (2017); 60: 335–345, DOI: 10.1097/DCR.0000000000000754

16. F. Dossa, T.R. Chesney, S.A. Acuna, et al. "A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis",*Lancet Gastroenterol Hepatol*; (2017) 2: 501–13; DOI:10.1016/ S2468-1253(17)30074-2
17. A. Barina, A. De Paoli, P. Delrio, et al. "Rectal sparing approach after preoperative radio- and/or chemotherapy (RESARCH) in patients with rectal cancer: a multicentre observational study", *Tech Coloproctol*. (2017); 21(8):633–40.
18. J. Garcia-Aguilar, S. Patil, M.J. Gollub, et. al., "Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy (OPRA)", *Journal of Clinical Oncology* (2022), vol 40 DOI: 10.1200/JCO.22.00032
19. S. Deidda, G. Spolverato, G. Capelli, et al. **"**Limits of Clinical Restaging in Detecting Responders After Neoadjuvant Therapies for Rectal Cancer.*" Diseases of the Colon & Rectum* (2022), DOI:10.1097
20. F. Marchegiani, V. Palatucci, G. Capelli, et al. *"*Rectal Sparing Approach After Neoadjuvant Therapy in Patients with Rectal Cancer: The Preliminary Results of the ReSARCh Trial*", Ann Surg Oncol* (2022) 29:1880–1889 https://doi.org/10.1245/s10434-021-11121-8
21. M.J.M. van der Valk, Hilling, E. Bastiaannet, et al., "IWWD Consortium. Long-term outcomes of clinical complete responders a er neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study." *Lancet (*2018); 391:2537–2545.
22. E. Rullier, P. Rouanet, J.J. Tuech, et al. "Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial" *Lancet* (2017), 390 (10093), pp.469-479, DOI: 10.1016/S0140-6736(17)31056-5
23. J. Garcia-Aguilar, L.A. Renfro, O.S. Chow, et al. "Organ preservation for clinical T2N0 distal rectal cancer using neoadjuvant chemoradiotherapy and local excision (ACOSOG Z6041): results of an open-label, single-arm, multi-institutional, phase 2 trial", *Lancet Oncol* (2015); 16: 1537–46.
24. E. Rullier, V. Vendrely, J. Asselineau, et al, "Organ preservation with chemoradiotherapy plus local excision for rectal cancer: 5-year results of the GRECCAR 2 randomised trial", *Lancet Gastroenterol Hepatol* (2020)*,* DOI*:* 10.1016/ S2468-1253(19)30410-8
25. S. Pucciarelli, F. Giandomenico et all, "Bowel function and quality of life after local excision or total mesorectal excision following chemoradiotherapy for rectal cancer" *British Journal of Surgery* (2017); 104(1):138-147. doi: 10.1002/bjs.10318. Article. IF 5,899
26. D. Dindo, "The Clavien–Dindo Classification of Surgical Complications"; In: Cuesta, M., Bonjer, H. (eds) "Treatment of Postoperative Complications After Digestive Surgery". *Springer, London*. (2014), https://doi.org/10.1007/978-1-4471-4354-3_3.
27. L.M Fernandez, G.P Sao Juliao, N.L Figueredo, et al. "Conditional recurrence-free survival of clinical complete responders managed by watch and wait after neoadjuvant chemoradiotherapy for rectal cancer in the International Watch & Wait Database: a retrospective, international, multicentre registry study." *The Lancet Oncology* 22.1 (2021): 43-50.