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TESI DI LAUREA

RESARCH REGISTRY (ReReSARCH):

CONSERVATIVE APPROACH AFTER PREOPERATIVE RADIO AND/OR CHEMOTHERAPY IN PATIENTS WITH RECTAL CANCER

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Abstract

Background. Rectum-preservation for locally advanced rectal cancer (LARC) has been proposed as an alternative to total mesorectal excision (TME) in patients with major (mCR) or complete clinical response (cCR) after neoadjuvant therapy.

Aim. The main objective of the study is to determine the rate of organ preservation and TME-free survival in a real world setting at 3, 5, 10-years in patients with primary rectal cancer treated with neoadjuvant therapy followed by Local excision (LE) or Watch-and-Wait). Secondary objectives are to determine the survival outcomes (OS, DFS, LDFS), the rate of stoma-free patients, the clinical- and tumour-related factors associated with pCR, the association between clinical and pathological response, the morbidity and mortality rates after local excision, the variability between centres with regard to treatment offered and associated results, to determine the ability of MRI after RT and/or CT to identify pCR, to assess the ability of texture analysis of the primary lesion in MRI images before and after RT and/or CT, and the impact on bowel function, faecal continence and QoL.

Methods. This is a prospective, multicenter, observational registry study. The rectum-sparing approach will be considered clinically acceptable if the percentage rate of rectum preservation at two years, in patients treated with rectum-sparing, is not less than 50%. In a registry therefore placed at 50% the expected proportion of rectum-sparing, at 10% the width confidence interval and at 95% confidence level the total number of patients to be enrolled will be at least 384 subjects. The main analysis will be assessment of rectum preservation at 3, 5 and 10 years in patients with rectal cancer after neoadjuvant treatment by rectum-sparing approach. The percentage of rectum preservation will be estimated by the ratio between the number of patients with rectum preservation at 3, 5 and 10 years and the total number of patients who undergo a LE or WW and will be reported with the 95% confidence interval.

Expected results. Based on our previous study, it is expected that more than 50% of patients undergoing local excision can retain their rectum 2 years after the start of treatment.

Sommario

Presupposti dello studio. I trattamenti conservativi in pazienti con carcinoma del retto localmente avanzato (LARC) con risposta clinica maggiore (mCR) o completa (cCR) dopo terapia neoadiuvante, sono stati proposti come alternativa all'escissione mesorettale totale (TME).

Obiettivo. L'obiettivo principale dello studio è determinare il tasso di conservazione d'organo e la sopravvivenza libera da TME in un contesto reale a 3, 5 e 10 anni in pazienti con tumore primario del retto trattati con terapia neoadiuvante seguita da escissione locale (LE) o Watch-and-Wait. Gli obiettivi secondari sono determinare gli esiti di sopravvivenza (OS, DFS, LDFS), il tasso dei pazienti senza stomia, i fattori clinici e tumorali associati alla pCR, la concordanza tra risposta clinica e patologica, la morbilità e mortalità dopo EL, la variabilità tra i centri per quanto riguarda il trattamento offerto e i risultati ottenuti, determinare la capacità della RM dopo la RT e/o la TC di identificare la pCR, valutare la capacità dell'analisi texture della neoplasia primitiva nelle immagini RMN prima e dopo RT e/o TC, l'impatto sulla funzione intestinale, sulla continenza fecale e sulla qualità di vita.

Metodi. Questo è uno studio di registro prospettico, multicentrico e osservazionale. Un approccio rectum-sparing può essere considerato clinicamente accettabile se la frequenza percentuale di conservazione del retto a 2 anni, nei pazienti trattati con rectum-sparing, non è inferiore al 50%. Nell'ambito di un registro, quindi, posta al 50% la proporzione attesa di rectum-sparing, al 10% l'ampiezza dell'intervento di confidenza e a 95% il livello di confidenza il numero totale dei pazienti da arruolare sarà di almeno 384 soggetti. L'analisi principale sarà la valutazione della conservazione del retto a 3, 5 e 10 anni nei pazienti con tumore del retto dopo trattamento neoadiuvante con approccio rectum-sparing. La percentuale di conservazione del retto sarà stimata dal rapporto tra il numero di pazienti con conservazione del retto a 3, 5 e 10 anni e il numero totale di pazienti sottoposti a LE o WW e sarà riportata con l'intervallo di confidenza del 95%.

Risultati attesi. Sulla base del nostro studio precedente, si prevede che più del 50% dei pazienti sottoposti a escissione locale possa conservare il retto a 2 anni dall'inizio del trattamento.

Chapter 1

Introduction

1.1 Neoadjuvant therapy in rectal cancer

Locally advanced rectal cancer (LARC) therapy aims to improve survival and patient-reported outcomes. The former essentially include overall survival (OS), disease-free survival (DFS) and local recurrence-free survival (LRFS), the latter include quality of life (QoL), faecal continence and bowel function.

The multimodal approach, in particular neoadjuvant therapy, has been gaining ground, either according to the classic scheme of long-course pre-operative chemoradiation therapy (CRT), or according to the scheme of short-course radiotherapy (RT), followed by total mesorectal excision (TME) and adjuvant chemotherapy; the latter scheme is prevalent in northern Europe. These treatment schemes resulted in improved local disease control compared to TME alone(1) or surgery followed by postoperative CRT (2). With this strategy, the local recurrence rate decreased to 6% with an estimated 5- and 10-year survival of 75 and 60%, respectively (2,3).

In the most recent version of the National Comprehensive Cancer Network guidelines (4) for LARC patients, the chemotherapy regimen associated with long-course RT includes either Capecitabine or 5-Fluorouracil (5-FU) infusion therapy, while adjuvant chemotherapy is usually given as FOLFOX6 (Oxaliplatin IV, Leucovorin and 5-FU in continuous infusion) for 6 months or CAPOX (Oxaliplatin IV and Capecitabine) for a total of 6 months (4). The administration of chemotherapy before starting CRT it is also acceptable regarding the same guidelines. This approach is called total neoadjuvant therapy (TNT) as all chemotherapy, both sensitising and systemic, is delivered prior to surgery. Within TNT, two treatment algorithms have emerged:

"Induction chemotherapy". The first studies date back to 2006 (5–10). The patient first receives systemic chemotherapy (generally CAPOX and FOLFOX regimens) followed by CRT (RT 45 to 54 Gy and Capecitabine) and finally radical surgery according to the TME technique, 4-8 weeks after the last RT dose. The pathologic complete response (pCR) rate has been reported to range between 11% (9) and 36% (10).

"Consolidation chemotherapy." The scheme involves the administration of systemic chemotherapy (CAPOX or FOLFOX) after CRT and before TME. The first related studies were published in 2013-2015 (11,12). The TIMING study by Garcia-Aguilar et al, compared 4 cohorts of patients, including one control group in which systemic chemotherapy was not administered pre-operatively. This trial showed that the pCR rate increased from 18% to 38% proportionally to the length of the time interval between the end of CRT and surgery and to the increase in cycles of systemic chemotherapy. The trial does not discriminate which parameter influence more the pCR rate, although the hypothesis is that it depends on both factors. In fact, it is commonly believed that the pCR rate is directly proportional to the time interval between the end of neoadjuvant therapy and surgery, reaching a plateau around week 12-13 (13,14). However, a prolonged interval may delay the administration of systemic chemotherapy and it may lead to a higher rate of complications and distant progression. The randomised GRECCAR-6 trial extended the interval between the end of CRT and surgery from 7 to 11 weeks. The results were the increase of the rate of pCR and the negative impact on the complication rate and the quality of mesorectal resection (15). Furthermore, a recent Italian retrospective multicentre study, Deidda et al., showed that in patients in whom neoadjuvant therapy had been poorly effective (non-responders), a time-to-surgery of more than 8 weeks was associated with worse outcomes than an interval of less than 8 weeks (16). These data suggest that increasing the interval between CRT and surgery may positively impact the pCR rate in responders but may have a negative impact on oncological outcomes in non-responders.

The OPRA trial (Organ Preservation in Rectal Adenocarcinoma) compares induction versus consolidation chemotherapy; preliminary results show that the

two approaches have similar outcomes in relation to 3-year DFS rates (Induction 78%, 95%CI 70-87 vs Consolidation 77%, 95%CI 69-86, p=0.9) and distant metastases-free survival (Induction 81%, 95%CI 74-90, vs Consolidation 83%, 95% CI 76.91; p=0.86). Consolidation chemotherapy had a significant advantage in organ preservation rate (43% vs 58%, p=.01) (17). Fokas et al. compared the two treatment regimens. in a multicentre randomised trial with a "pick-the-winner" design based on the hypothesis that after TNT the pCR rate could increase when comparing to the standard preoperative CRT (18). The group receiving consolidation chemotherapy had a pCR rate of 25% compared to 17% in the group receiving induction chemotherapy. Thus, the consolidation chemotherapy group ($P < .001$), but not the induction chemotherapy group ($P = .210$), was able to assess the predefined statistical hypothesis.

After neoadjuvant therapy, the pathological complete response rate (pCR) can now reach values of over 50%, (17) and another 20% or so have a greater response (few residual cells) (19). The wide variability response depends mostly on factors related to the tumor, such as the basal stage, the treatment performed and biological factors. However, it is widely accepted that patients with pCR have significantly better oncological outcomes than patients demonstrating residual disease (20). Despite these advantages, the various combinations of chemoradiation therapy associated with TME are burdened by acute and chronic toxicities, early and late postoperative complications, and negative consequences regarding sexual activity, urinary activity, faecal continence, and bowel function that all together negatively impact patients' quality of life (21).

1.2 Rectum-sparing approach

Considering the high rate of postoperative complications, the relevant functional consequences associated with neoadjuvant therapy followed by TME, and vice versa the excellent outcome found in patients responding to CRT, conservative approaches appear to be appropriate in rectal cancer patients with a major clinical response (mCR) or complete response (cCR). The conservative approach includes simple observation, also called Watch-and-Wait (WW), and Local Excision (LE).

Watch-and-Wait (WW). Dr- Habr-Gama designed and developed the WW strategy in Brazil for patients with cCR after preoperative CRT (22). The encouraging results of the Brazilian experience have been replicated in other centres, stimulating a growing interest in this strategy (23–28). In a recent systematic review, Dattani et al. report an incidence of cCR of 22.4% (95% CI,14.3-31.8), with a regrowth rate (neoplastic regrowth in patients diagnosed with a complete clinical response) of 22.1%, of which 96% in the first 3 years of surveillance (29). The 3-year cumulative risk of regrowth was 21.6% (95% CI, 16.0-27.8) with a salvage surgery rate of 88%. The authors report a distant metastasis rate of 8.2%, of which 60% without synchronous regrowth, and a 3-year OS of 93.5% (95% CI, 90.2-96.2). Based on these results, the authors concluded that the WW approach was feasible provided that close surveillance was implemented to allow a high rate of salvage surgery without increasing the risk of systemic spread of disease. The Italian Association of Medical Oncology (AIOM) panel for guidelines in rectal cancer evaluated nine studies to answer the question whether TME or WW should be used in patients with cCR after neoadjuvant radio chemotherapy (30). The review showed that the overall recurrence rate was higher in the group undergoing the WW approach than in the group undergoing TME (RR = 1.69, 95% CI 1.08, 2.64), and the risk of local recurrence was even higher (RR = 5.37, 95% CI 2.56, 11.27). Having a permanent stoma was a higher risk in patients undergoing TME (RR = 0.15, 95% CI 0.08, 0.29). Unfortunately, the level of the evidence was too low. The authors' conclusion was that WW was correlated with a lower risk of

having a permanent stomia and a higher risk of recurrence which was not associated with a worse OS. The lack of evidence did not allow the panel to make recommendations, and therefore the panel still considered WW to be an experimental approach.

The limitations of the WW approach relate to the high regrowth rate, which in some studies reaches 38%, but generally ranges between 20 and 25% at 3 years (23–28) . The reason for this limitation lies in the suboptimal performance of staging investigations (endoscopy, digital exploration, MRI and endorectal ultrasound) in distinguishing a complete response from an incomplete one. In fact, about 30% of patients who have a cCR still have residual disease. In contrast, most pCR cases do not have a picture of cCR (31). Another critical point of the WW approach concerns the risk, not yet clearly demonstrated, that patients with regrowth are more likely to have distant metastases than those without regrowth(32,33). Smith J et al. found a significantly higher rate of distant recurrence (36% vs 1%, $p<.001$) in subjects who have regrowth than in those who do not (32). The hypothesis that is suggested to explain this finding is that leaving the cancer without systemic treatment for a prolonged time may promote the risk of distant progression.

When comparing to LE, the WW approach avoids intervention and consequently LE-related complications altogether. However, whereas LE appears to be indicated in patients with cCR and mCR, the WW approach is only used in patients with cCR. The reason lies in the fact that the probability of concordance between cCR and pCR is extremely high, whereas the concordance between mCR and pCR is lower.

Local Excision (LE). Historically, LE in chemo- and/or radio-treated patients was only used for those who were unable (age, comorbidities) or refused conventional surgery. Nowadays, LE may be used as an excisional biopsy whose histological outcome decides the subsequent treatment course. When the histological examination documents the absence of tumour or the persistence of minimal residual disease (ypT1 with favourable histological features), a strict follow-up is performed. Patients with ypT1 with unfavourable histological aspects (lymph vascular invasion, LVI; perineural invasion, PNI, G3 G4 differentiation grade, and positive resection margins) and those with ypT>1 are suggested to undergo TME because of the risk of lymph node spread, which is greater than 10% in these individuals, and therefore simple LE cannot be considered an adequate treatment (34). A prospective phase 2 studies and a single randomised prospective study have been published (35–41) (Tab 1) that endorse the hypothesis that LE is a feasible approach with acceptable oncological results and that, compared to standard treatment, with better functional outcomes, thus a better quality of life (42,43).

Author, year	N	T	ypT0-1 %	Local rec. %	Follow – up (months)
ACOSOG, 2011	90	T2	51	ND	ND
Bujko, 2012	89	T2-3	67.2-80	11.8-6.2	24
Lezoche, 2012	50	T2	51	8	60
Pucciarelli, 2013	63	T2-3	68	3	36
GRECCAR, 2015	55	T2-3	61	ND	ND
CARTS, 2015	148	T1-3	56	7.2	17

Table 1: Phase 2 and 3, study on LE after pRT and/or Ct for rectal cancer

Unfortunately, many of the published studies have limitations in terms of sample size, monocentric origin of the data, methodological variability, differences in patient selection and in the definition of major or complete response. A further source of bias is the discrepancy between clinical staging and histopathological

outcome, which may significantly affect the selection of patients who are candidates for organ-sparing approaches. However, despite these limitations and even though organ-sparing approaches are not considered standard of care in rectal cancer, there is an increasing use of these approaches in everyday clinical practice.

Unlike WW, LE is still a surgical procedure that requires hospitalisation, which has its own morbidity that may impact on eventual completion surgery, this may cause re-hospitalizations and re-interventions (35,44). In a 2016 study Habr-Gama et al. reported worse bowel function, faecal continence and QoL in patients undergoing LE compared to patients referred to the WW approach (45).

LE may require salvage surgery, or completion surgery, which is more complex after LE than direct surgery after CRT. Moreover, in most patients there is no tumour, thus making completion surgery an overtreatment. (44). However, compared to WW, LE gives an histological proof of pCR, and subsequentially eliminates the risk of regrowth and allows conservative treatment in patients with pCR who clinically do not show a cCR and would therefore be excluded from a WW approach.

Chapter 2

Objectives

Main Objective.

The study aims to determine the rate of organ preservation and TME-free survival in a real world setting in patients with primary rectal cancer treated with neoadjuvant therapy followed by a rectum-sparing approach (LE or WW).

Secondary objectives.

1. Survival outcomes: overall survival (OS), disease-free survival (DFS) and local recurrence-free survival (LRFS) at 3, 5 and 10 years after the end of neoadjuvant therapy in real-world setting.
2. The frequency of stoma-free patients at 3,5 and 10 years in real-world setting.
3. The clinical factors associated with pathological complete response (pCR).
4. The association between clinical response and pathological response.
5. The morbidity and mortality rates after LE.
6. The impact of LE and WW on bowel function, faecal continence, and quality of life (QoL).
7. The ability of MRI after pRT and/or CT to identify pCR
8. To evaluate the ability of texture analysis of the primary tumour in MRI images before and after pRT and/or CT (high resolution T2 sequences, diffusion-weighted sequences, and contrast medium sequences) in identifying the pCR of the primary tumour (ypT0).

Chapter 3

Materials and Methods

3.1 Study design

This is an extension of the RSARCH observational study (NCT02710812, clinicaltrial.gov) (RESARCH, Rectal Sparing Approach after preoperative Radio- and/or Chemo-therapy). This update of the previous protocol included a prospective, multicenter observational registry with the principal goal to evaluate the efficacy of conservative approaches after neoadjuvant therapy in terms of organ-preserving capacity in a real-world setting.

Patients will be enrolled in the register when they decide to undergo a conservative rectum-sparing approach; no indication is given as to the type of pre-operative radio- and/or chemotherapy treatment.

The collection of data regarding the baseline staging of the tumor (before neoadjuvant therapy) and the therapy regimens used is aimed at identifying which type of tumor and which type of neoadjuvant therapy regimen are associated with a higher number of pathological complete responses (secondary endpoint). Physicians and patients with complete clinical response will discuss the following treatment, local excision, or WW approach.

3.2 Patients' selection

Inclusion and exclusion criteria, definitions of major response and complete clinical and pathological response, definition of adequacy of excision are the same as those used in the two previous works of our research group (35,46). (Flowchart 1 and 2).

Inclusion criteria

- Patients with a histologically proven adenocarcinoma of the rectum, located up to 12 cm from the anal verge at proctoscopy,
- aged ≥ 18 years,
- candidates fit to receive neoadjuvant treatment and able to undergo a TME surgery,
- mCR or cCR following neoadjuvant therapy
- ability to understand the risks and benefits of the trial and to undergo close follow-up.

Informed consent

Informed consent must be signed. The informed consent can be signed after the first or after the second resection following neoadjuvant therapy and in any case before LE if the patient is enrolled in the LE group.
The patient will be adequately informed about the advantages and disadvantages of this approach and about the fact that the gold standard of therapy is, at present, radical surgery (TME).

Exclusion criteria

Patients with an histotype other than adenocarcinoma and patient unable to tolerate TME due to age or severe comorbidities are excluded.

Definitions.

Major clinical response (mCR) is defined as the absence of palpable mass on digital exploration of the rectum, or of pathological lymph nodes (≥ 5 mm in diameter along the short axis) on pelvic magnetic resonance imaging (MRI); or the absence of superficial erosion/ulcer >2 cm in diameter, at proctoscopy.

Clinical complete response (cCR) is defined as the absence of palpable mass on digital exploration of the rectum; the absence of pathological lymph nodes (≥ 5 mm in diameter along the short axis) on pelvic MRI; the absence of any lesion excluding a flat scar.

Pathological complete response (pCR) is defined as the absence of viable cancer cells in the surgical specimen after TME. The term rectum-sparing includes both LE and WW approaches.

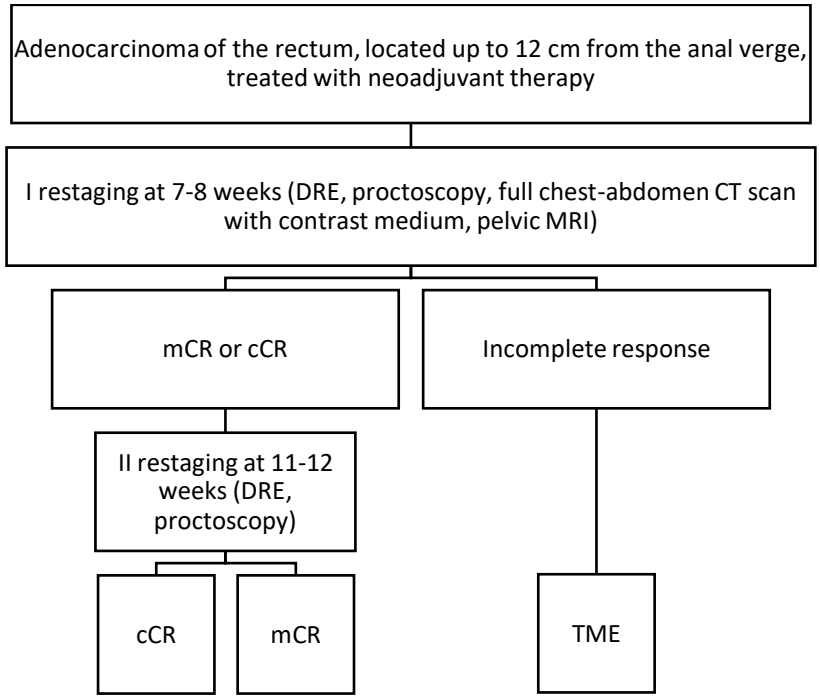

Figure 1: Flow-Chart (1). DRE digital rectal exploration; cCR, clinical complete response ; mCR, major clinical response; TME Total Mesorectal Excision

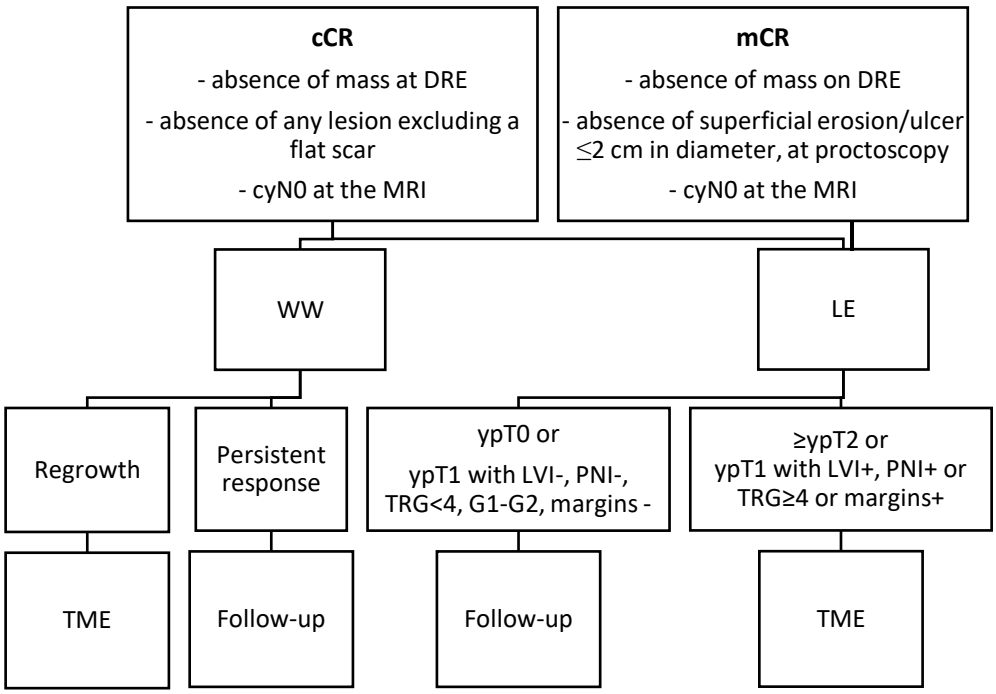

Figure 2: Flow-Chart (2). DRE digital rectal exploration; cCR, clinical complete response; mCR, major clinical response; TME Total Mesorectal Excision; LVI, lymphovascular invasion; PNI perineural invasion; TRG tumor regression grade

3.3 Clinical assessment and staging

Clinical staging and pathological TNM staging are reported according to the American Joint Committee on Cancer 8th Edition (Table 2, 3, 4, 5) The histological grade of adenocarcinoma is reported according to WHO.

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	Non evidence of primary tumor
Tis	Carcinoma in situ, intramucosal carcinoma (involvment of lamina propria with no extension through muscolaris mucosae)
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscolaris propria
T3	Tumor invades trough the muscolaris propria into pericolorectal tissues
T4	Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure
T4a	Tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuos of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades or adheres to adjacent organs or structures

Table 2: Definition for T, AJCC TNM Staging Classification for Rectal Cancer 8th ed., 2017

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic, or perirectal/mesorectal tissues
N2	Four or more regional lymph nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive

Table 3 Definition for N, AJCC TNM Staging Classification for Rectal Cancer 8th ed., 2017

M	M criteria
cM0	No distant metastasis by imaging, etc.; no evidence of tumor in distant sites or orans (this category is not assigned by pathologists)
cM1	Metastasis to 1 or more distant sites or organs or peritoneal metastasis is identified
cM1a	Metastasis to 1 site or organ is identified without peritoneal metastasis
cM1b	Metastasis to 2 or more sites or organs are identified without peritoneal metastasis
cM1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

Table 4: Definition for M, AJCC TNM Staging Classification for Rectal Cancer 8th ed., 2017

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1, T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
Stage IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
Stage IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4a	N1-N2	M0
Stage IVa	Any T	Any N	M1a
Stage IVb	Any T	Any N	M1b
Stage IVc	Any T	Any N	M1c

Table 5: Prognostic Groups, AJCC TNM Staging Classification for Rectal Cancer 8th ed., 2017

Since patients will sign informed consent after neoadjuvant therapy, clinical data prior to neoadjuvant treatment (baseline staging and therapy performed) will be collected retrospectively.

Patients will be resected 7-8 weeks after the end of neoadjuvant therapy. If there is no evidence of response to therapy, standard surgery (TME) will be suggested, while for patients showing mCR or cCR, the interval between neoadjuvant therapy and surgery will be extended by another 4 weeks after which further staging will be performed (see flow-chart 1). At the end of the last staging and if this shows mCR or cCR, the patient can be enrolled in the rectum-sparing protocol, otherwise he/she will be a candidate for conventional surgery (TME).

Baseline clinical staging (cTNM) will correspond to the staging prior to neoadjuvant therapy and will include routine laboratory test, CEA level, pancolonoscopy with biopsies of the rectal lesion, chest and abdomen CT scan with and without contrast medium, pelvic MRI with and without contrast medium. In case of contrast medium allergy, liver ultrasound and chest X-ray may be used. In case of inability to perform pelvic MRI (e.g., incompatible prosthesis, claustrophobia) pelvic CT and transrectal ultrasound will be used.

Post neoadjuvant clinical staging will include routine blood tests, CEA level, proctoscopy, chest and abdomen CT scan with and without contrast medium, pelvic MRI with and without contrast medium. If it is decided to wait a further 4-5 weeks after the first staging, at least the proctoscopy must be repeated. The final staging after neoadjuvant therapy and before the choice of the rectum-sparing approach will be defined as ycTNM.

Re-staging of local pathology (assessment of T and N) is performed with pelvic MRI according to the guidelines(47). Pelvic MRI has a key role in the assessment of lymph node disease status, to define major and complete clinical responses (35,46). However, the accuracy of MRI in identifying residual disease and lymph node metastases is suboptimal (48,49)

In recent years, radiomics has been shown to play a role in predicting the complete response to preoperative CRT (50); Radiomics is understood as the analysis of MRI images to obtain, through mathematical methods and the use of

specific software, quantitative information that cannot be detected by simple evaluation by the radiologist

3.4 Surgical treatment

Local Excision. After neoadjuvant therapy, Local Excision can be performed by conventional transanal excision (TAE) or endoscopic techniques (TEM, TAMIS, TEO etc). The rectum is prepared following standard procedures similar to those used to perform conventional major surgery, including the use of antibiotics. The position of the patient depends on the quadrant where the residual lesion or scar is located. Regardless of the technique performed, the following principles should be respected (35,46): a gross margin of at least 0.5 cm and a full-thickness excision, including mucosa, submucosa, muscularis propria, and perirectal fat was obtained in all patients. Surgical specimens are oriented using a cardboard, helping the pathologist's histological interpretation. The breach in the rectal wall may be closed transversally with resorbable sutures or may be left open at the surgeon's discretion.

The following data will be recorded: duration of hospitalisation, any postoperative complications according to the Clavien-Dindo classification (51) (Table 6), re-interventions, re-hospitalizations within 30 days of discharge, need and reason for completion surgery. If not performed, the reason and viable alternative treatment (re-excision, chemotherapy, radiotherapy or other). If it is performed report the type of surgery, complications and histological examination of the surgical piece.

LE will be considered an adequate treatment and the patient will not undergo further surgical treatment if the histological examination shows that it is a lesion (flowchart two):

- ypT0
- ypT1 with G1-2 degree of differentiation,
- histologically non-infiltrated margins,
- absence of vascular (LVI-) and perineural (PNI-) invasion,
- TRG <4.

LE will be considered an inappropriate treatment if the histological examination shows a lesion with at least one of the following features:

- ypT≥2

- ypT1 with grade G3 differentiation,
- histologically infiltrated margins,
- lymph vascular (LVI+) 0 perineural (PNI+) invasion,
- TRG≥4 In these cases.

In this case, the patient will be advised to undergo a TME which will be referred to as "completion surgery".

Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusionsand total parenteral nutritionare also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications) requiring IC/ICU-management
Grade IIIa	Single organ dysfunction (including dialysis)
Grade IIIb	Multiorgan dysfunction
Grade V	Death of a patient

Table 6: Clavien-Dindo Classification

Completion surgery. This term refers to the use of radical surgery (TME) due to the presence of histopathological features that make LE therapy inadequate. It is performed within about 1 month after LE. However, based on existing publications, about 50% of patients refuse this surgery; sometimes alternative solutions are proposed (e.g., simple local re-excision, chemotherapy). Completion surgery' data will cover the causes of unsuitability of LE, the rate of patients who "should" undergo the surgery and the rate of patients who actually undergo completion surgery, the description of alternative treatments to TME (local re-excision, non-surgical treatments such as radiotherapy) and the histological outcome, morbidity and mortality of completion surgery.

TME will be performed according to the standard technique (52) using the open or minimally invasive approach (laparoscopic or robotic) and includes both anterior resection of the rectum and abdominoperineal resection of the rectum.

3.5 Histological examination

The histological examination of the LE must contain at least the following information: ypT.

If there is persistence of tumour, at least the following features must be described: status of margins; degree of cell differentiation; presence of lymphatic or vascular or perineural invasion; tumour regression grade (TRG) according to Mandard's classification (53) (table 6)

	Mandard's classification
TRG1	Complete regression: fibrosis without detectable tissue of tumor.
TRG2	Fibrosis with scattered tumor cells
TRG3	Fibrosis and tumor cells with preponderance of fibrosis
TRG4	Fibrosis and tumor cells with preponderance of tumor cells
TRG5	Tissue of tumor without changes of regression

Table 7: Mandard's Classification

3.6 Follow-up

Months	3	6	9	12	15	18	21	24	30	36	48	60
Objective examination	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests + CEA	X	X	X	X	X	X	X	X	X	X	X	X
Rectoscopy	X	X	X	X	X	X	X	X	X	X	X	X
Pelvic MRI		X		X		X		X		X	X	X
CT chest-abdomen with contrast medium				X				X		X	X	X
Colonoscopy				X							(X)	

Table 8: Follow-up

Patients will be examined (examination with rectal exploration, proctoscopy, CEA level and routine laboratory tests) every 3 months in the first 2 years, and then every 6 months in the third year, then annually.

MRI will be performed every 6 months for the first 2 years then once a year. Thoraco-abdominal CT scan will be performed annually, unless otherwise clinically indicated. Colonoscopy will be performed at the first year after study enrolment, if negative at 5 years.

Follow-up between 5 and 10 years will be performed as recommended in AIOM guidelines(54).

Definition of recurrence. The diagnosis of recurrence will be determined based on clinical examination, radiological imaging or biopsy. Recurrence shall be distinguished into local and distant. Local recurrence is the recurrence of the disease in the pelvis: endoluminal or extraluminal. Distant recurrence is the presence of the disease at any other site.

3.7 Data collection and Ethics

Data will be collected on the patient's demographic characteristics, performance status (Eastern Cooperative Oncology Group, ECOG), American Society of Anesthesiologists (ASA) score, blood test results and in particular Carcinoembryonic Antigen (CEA), body mass index (BMI). Data on clinical diagnosis and staging before and after neoadjuvant therapy will also be recorded.

Iconographic collection (recording of endoscopic examination and/or photographs of the lesion) will be recommended both before neoadjuvant therapy and at the time of resection. All participating centres will be advised to keep after appropriate anonymisation both the photographic iconography related to the endoscopic examination of enrolled patients and the imaging iconography (thoracoabdominal CT scan and pelvic MRI pre- and post-neoadjuvant therapy).

For the MRI images, after anonymisation of the DICOM files, a centralised collection will be conducted where possible in order to perform:

1. a radiological re-evaluation of the MRIs in order to assess the accuracy of the examination in identifying the pCR after CRT.
2. a texture analysis using specific software on the images available on the main lesion and lymph nodes. MRIs with available high-resolution T2 sequences, diffusion-weighted sequences (in particular ADC maps) and T1 sequences with fat suppression before and after administration of contrast medium will be included, according to the protocol indicated in. It will also be necessary to provide the MRI machine used and the gadolinium-based contrast injected. MRI staging and restaging reports must be prepared.

Data of interest for the study (patient, tumour, treatment, and follow-up) will be prospectively collected and pseudo-anonymised by means of special data collection forms (CRFs) at diagnosis, during and after pRT and/or CT, at surgery and at follow-up for a duration of at least 20 years. The data will be pseudo-anonymised in that the coordinating centre will only have the patient codes while the various participating centres will have a list of names with the corresponding

codes so that they can be traced back to the patients if further information is needed for a specific study. An online Redcap platform will be used, which each centre can access to read its own data while the coordinating centre can access all the data without having the identification codes in addition to those of its patients. All CRFs, which will include clinical, histological and operator data, will have to be sent, also by e-mail, to the trial data manager and entered the online database (REDCAP). The same applies to the centres that will participate in the QoL study.

Ethics

The Institutional Review Board of Padova Hospital has approved the final protocol of the original protocol; the RESARCH study is registered at clinicaltrials.gov (NCT02710812). Moreover, each participating institution obtained a specific approval (44). The RESARCH registry (ReRESARCH) is currently being evaluated by the Institutional Review Board of Padova Hospital.

3.8 Assessment of quality of life, bowel function and faecal continence

Since this is an ancillary study, it will be restricted to only those centres that wish to participate. The evaluation will be longitudinal and will cover QoL, bowel function and faecal continence. The following validated questionnaires will be given in Italian relating to:

- Bowel function:
    - Low anterior resection syndrome (LARS) score (55).
- Quality of life assessment:
    - EORTC QLQ-30 (56).
    - EORTC QLQ-CR29 (57).
    - CPS - Control preference scale (58)
    - SDMQ-9 - Shared Decision-Making Questionnaire (59)
- Faecal continence assessment:
    - Faecal Incontinence Quality of Life scale (FIQL) (60)

The timing of questionnaire administration and collection will be as follows: t1, before LE, or decision for WW option, t2, at 6 months after t1 and t3, at 12 months from the date of t1.

3.9 Statistical analysis

Sample size

The total number of patients to be enrolled will be at least 384 subjects, having set the expected proportion of rectum-sparing at 50%, the confidence interval at 10% and the confidence level at 95.

Definition and analysis for the primary endpoint.

Results will be reported in accordance with the STROBE guidelines (61). All continuous variables will be described using means and standard deviation and measures of position when appropriated. Categorical variables will be described using contingency tables.

The event of this endpoint is removal of the rectum for any cause: the need of completion surgery, surgical complication, bowel function disorders (e.g., incontinence, diarrhoea), recurrence, regrowth.

The main analysis will be assessment of rectum preservation at 3, 5 and 10 years in patients with rectal cancer after neoadjuvant treatment by rectum-sparing approach. The percentage of rectum preservation will be estimated by the ratio between the number of patients with rectum preservation at 3, 5 and 10 years and the total number of patients who undergo a LE or WW and will be reported with the 95% confidence interval.

TME-free survival will be estimated using the Kaplan-Meier method at 3, 5, and 10-years. TME-free survival will be estimated as time interval from the date of enrolment to the date of event (TME) or death, from any cause, or last follow-up.

Definition and analysis of oncological outcomes.

The event is defined as death for any cause, local or distant recurrence, regrowth and a second primary malignancy. Patients alive at the time of analysis will be censored at the date of last assessment. The diagnosis of recurrence is determined by clinical examination, radiological imaging or biopsy. Survival will be estimated by the Kaplan–Meier method and the 3, 5 and 10-year proportions of

surviving patients will be reported with the 95% CI. A Cox model will also be used to obtain an estimate of risk in the LE and WW groups. The following outcomes will be calculated:

Overall survival (OS): time interval from the date of enrolment to the date of death, from any cause, or last follow-up.

Disease-free survival (DFS): time interval from the date of enrolment to the date of the first event (local or distant recurrence or second primary tumour) or death or, in the absence of the former, of the last follow-up.

Local disease-free survival (LDFS): time interval from the date of enrolment to the date of local recurrence (patients undergone LE) or, in patients in WW group when the treatment of the regrowth is not feasible with a R0 or R1 resection, or recurrence following R0-R1 resection, or death or, in the absence of the former, of the last follow-up.

Distant recurrence-free survival (DRFS): time interval from the date of enrolment to the date of distant recurrence or death or, in the absence of the former, of the last follow-up.

Definition and analysis of stoma-free patient rate.

For this endpoint, the event is the presence of stoma. The ratio of the number of patients with stoma at a given follow-up (3, 5, 10 years) to the number of patients at risk will be calculated. Stoma will be defined as present or absent and those present as definitive or temporary.

Definition and analysis of factors associated with pCR.

A multivariate logistic regression model will be used to define this endpoint. Dichotomous variables related to patient, tumour, treatment, and type of surgery will be considered as explanatory variables.

Definition and analysis of concordance between major clinical response (mCR) or complete clinical response (cCR) and pCR.

This will be assessed by estimating the Kappa statistic, which expresses the concordance between two methods not due to chance. Results will be expressed with bootstrap 95% confidence intervals.

Definition and analysis of postoperative mortality and complications.

Mortality will be reported as the number of deaths out of the overall number of patients undergoing LE. For morbidity, the same procedure will be followed, and complications will be reported according to the Clavien-Dindo classification [57] (Table 6). The frequencies of the different preoperative treatments administered, morbidity and packing of a stoma at 2 and 5 years will be described in terms of percentages and reported with 95% confidence intervals; their association with the type of surgical treatment will be verified with the Chi-square test.

Analysis of bowel function, faecal continence, and quality of life (QoL).

The minimally clinically relevant difference defined within various quality of life measures is stable and corresponds to half a standard deviation (62) With this assumption, considering that estimates of standard deviations of published data vary between 15 and 20 points and that the minimally important difference for the EORTC QLQ-C30 questionnaire is approximately 10 points, data collected on at least 130 patients will allow us to verify a 10-point difference between the two conservative approaches with a power of 80%, a 2-tailed alpha error of 0.05 (t-test for independent data).

The scales of the questionnaires on bowel function, faecal continence and quality of life will be constructed using the standard procedures given in the reference manuals. Mean scores and standard deviations will be estimated for each administration of the questionnaires and reported with 95% confidence intervals. The difference in scores between the two conservative approaches will be evaluated at 6 and 12 months after the first administration with a student's t-test or the non-parametric equivalent.

The impact of bowel function on quality of life and faecal continence will be analysed at various times of questionnaire administration using a generalised linear mixed model. Concomitant variables will include the type of conservative approach received and the LARS score categorised into three levels of severity corresponding to no functional impairment (LARS: 0-20), minor impairment (LARS: 21-29) and major impairment (LARS: 30-42).

An initial study will focus on differences in bowel function, faecal continence and quality of life in patients with pathological complete response undergoing WW or LE, respectively. In the light of the minimal or absent invasiveness of the surgical act we could assume a non-inferiority study with the resulting sample size for each of the two groups of at least 69 patients (considering, as above, standard deviation estimates of published data around 20 points, the minimally important difference for the EORTC QLQ-C30 questionnaire at around 10 points and assuming a power of 90%, a 2-tailed alpha error of 0.05 with t-test for independent data). If there is indeed no difference between WW and LE treatment, then 138 patients will be 90% confident that the lower limit of a one-sided 95% confidence interval (or equivalently a bilateral 90% confidence interval) will be above the non-inferiority limit of -10.

Determining the ability of MRI after pRT and/or CT to identify pCR.

The ability of qualitative MRI signs to identify complete response to histopathology for local lesion (ypT0) and lymph node metastases (ypN0) will be assessed by accuracy analysis and Receiver Operating Characteristic curve analysis (ROC).

- To evaluate the ability of texture analysis of the primary lesion in MRI images before and after pRT and/or CT (high-resolution T2 sequences, diffusion-weighted sequences and contrast medium sequences) in identifying the complete tumour mass response after pRT and/or CT (ypT0)
- Determine the ability of texture analysis of mesorectal lymph nodes in MRI images before and after pRT and/or CT to identify the absence of loco-regional lymph node metastases after pRT and/or CT (ypN0 or ycN0 confirmed at follow-up).

For the latter two objectives, specific software will be used to extract first- and second-order texture parameters from MRI images that will be correlated with the complete pathological response and selected (Student/ Mann Whitney test or logistic regression) to create a model for predicting the complete response to CRT of the main lesion (ypT0) and lymph node metastases (ypN0) based on some of them. The available cohort will be divided into a test cohort and a validation cohort.

3.10 Data collection timing

0-3 months: project organisation.

120 months: patient enrolment.

12-120 months: follow-up.

120 months: statistical analysis and drafting of manuscripts on the data obtained.

Chapter 4

Discussion

Total mesorectal excision (TME) after neoadjuvant chemoradiotherapy is correlated with good long-term outcomes. However, considering the high rates of complications, rectum-sparing approaches has been gaining interest in patients with mCR or cCR after neoadjuvant therapy. Rectal-sparing approaches are associated with better bowel function and quality of life compared with TME (43); on the contrary, a higher risk of recurrence has been reported, which may impact on patients' long-term oncologic outcome (63) Although the international guidelines still do not consider rectum-sparing strategies as standard of care, they are increasing in clinical practice. The major concern in performing a non-standard approach (wait-and-see or local excision) is related to the risk of leaving tumor tissue at the site of the primary tumor or in the mesorectum (35). The primary endpoint of the RESARCH trial is to validate the rectal-sparing policy in patients with complete or near-complete clinical response after neoadjuvant chemoradiotherapy (46).

The RESARCH protocol is the first prospective trial that investigates the role of both Local Excision and Watch-and-Wait approach in patients treated with neoadjuvant therapy(46). The aim of the current protocol is to determine the rate of organ preservation and TME-free survival in a real world setting in patients with primary rectal cancer treated with neoadjuvant therapy followed by a rectum-sparing approach (LE or WW). Unfortunately, the implementation of randomised prospective studies is challenging due to the difficulty in enrolling patients. The only prospective randomised study published so far took four years to enroll 150 patients. Given the difficulty of completing randomised prospective studies, the planning of large prospective observational studies (registries) can play a relevant role in the evaluation of new therapeutic strategies. Earlier initiatives of national registries designed with the aim of monitoring the quality of care and surgery for procedures such as TME have indeed proven effective in improving technical and

oncological outcomes. As a result, such strategies qualify as quality-improvement projects (Norwegian Registry & Spanish Viking Project) (64,65)

Based on the above considerations and the European experiences (28,66) , we therefore propose the establishment of a pathology registry to enrol patients with rectal cancer who, after neoadjuvant therapy, show a greater or complete response and who opt for conservative treatment, including both organ-sparing strategies (observation or local excision) currently used in daily clinical practice. The results may provide useful data for a harmonisation of therapeutic procedures in such patients and offer clinically relevant information in clinical practice. Furthermore, it is a common opinion in the scientific community that similar studies are necessary and that from this perspective, the ReRESARCH study has the potential to have scientific relevance and clinical impact of absolute importance

Our study group have published two studies on rectum-sparing treatment after CRT for rectal cancer. The first was a multicentre phase 2 study including patients with cT2-3 medium-low rectal cancer who, following neoadjuvant RT and/or CT, had a major or complete clinical response and therefore underwent LE. At 3-year of follow-up, the local recurrence rate was less than 5% (35). Long-term analysis from this study were recently published (36) and show that at a median follow-up of 108 months, the 5-year OS, RFS, LRFS and DRFS were 87%, 89%, 91%, and 90% respectively. Overall, 78% of patients had their rectum preserved and 84% of patients were stoma-free.

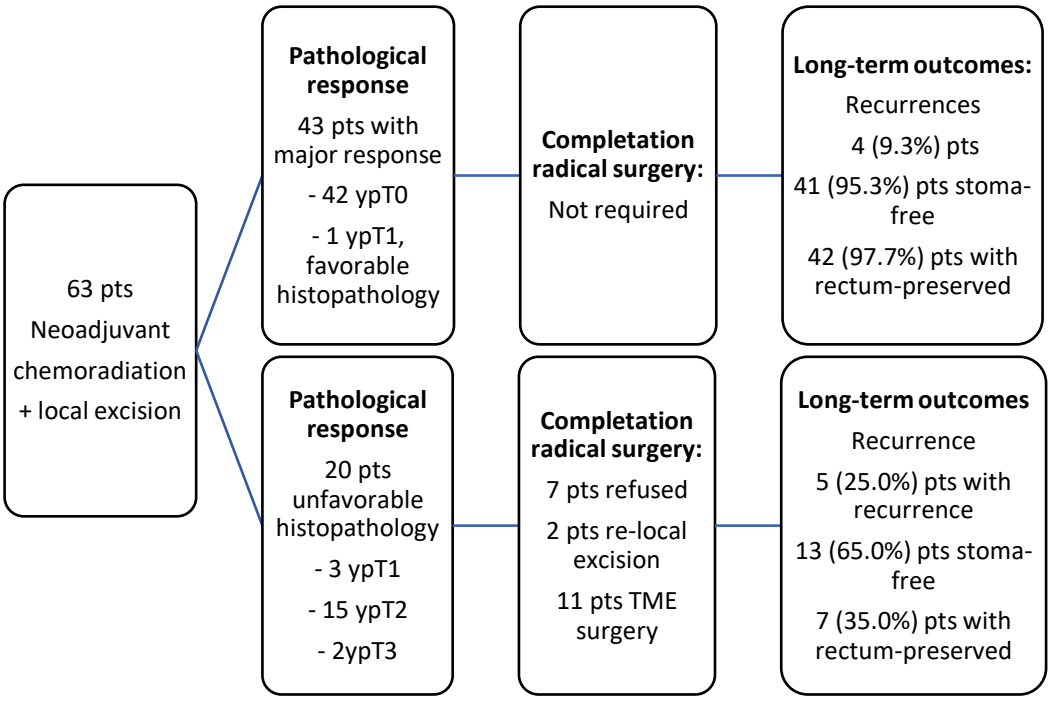

Figure 3:Pathological response, completion radical surgery and long-term outcomes of the study group after a median follow-up of 108 months (36)

Encouraged by these results, we are coordinating a multicentre, prospective, observational study including to patients who, after neoadjuvant therapy, experienced a mCR or a cCR and were treated with a rectum sparing approach (46). Seventeen Italian centres participated in this study. Preliminary results were recently published and showed that out of 160 eligible patients from 17 centres, 98 underwent LE and 62 underwent WW. The rate of major complications in those undergoing LE was less than 3% and, with a median follow-up of 2 years, the regrowth rate in the WW group was 24% (44). Results on outcomes such as organ preservation rate, ostomy-free rate, OS, DFS, LRFS and DRFS with a minimum follow-up of 2 years and median follow-up of 3 years are currently being published (35,46). In this study, 26.5% of patients showed unfavourable histological features after LE, requiring a completion TME. Noteworthy, among patients who agreed to undergo completion TME surgery, only 1 of 11 patients showed residual cancer (lymph node metastasis) at final

histopathology. The clinical implication is relevant as four patients underwent an abdominoperineal resection despite the absence of residual cancer at final histopathology (44)

In our previous study (35), the finding showed that LE in patients with a mCR after CRT is a feasible and safe approach; the expected result from this registry is that more than 50% of patients undergoing local excision can retain their rectum 2 years after the start of treatment.

Limitations

A highly accurate clinical staging after neoadjuvant therapy is pivotal to select the best candidates to rectal sparing approaches. A recent systematic literature review showed that MRI alone has some limitations when it comes to N staging in case of rectal cancer and in discriminating between benign and malignant loco-regional nodes (67). The results of this review suggest that [18F] FDG PET/MRI should be used for rectal cancer restaging after chemoradiotherapy and to select patients for rectum-sparing approaches thanks to its accuracy in T and N staging. For M staging, it should be associated at least with a chest CT scan to rule out lung metastases. (68)

Moreover, the definition of cCR and the follow-up strategies are highly heterogeneous, thus making comparison between the studies difficult; false-positive and false-negative pCR findings should also be taken into account.(30)

Conclusion

The ReRESARCH study protocol aim to create a registry to collect data from different centers, in order to analyze the long-term outcomes of rectal-sparing approach in a real life setting.

Bibliography

1. Kapiteijn E, Marijnen CAM, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative Radiotherapy Combined with Total Mesorectal Excision for Resectable Rectal Cancer. New England Journal of Medicine. 2001 Aug 30;345(9):638–46.
2. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer. New England Journal of Medicine. 2004 Oct 21;351(17):1731–40.
3. Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, et al. Preoperative Versus Postoperative 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. Journal of Clinical Oncology. 2012 Jun 1;30(16):1926–33.
4. National Comprehensive Cancer Network (2022) Rectal Cancer (Version 1.2022). https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. .
5. Calvo FA, Serrano FJ, Diaz-González JA, Gomez-Espi M, Lozano E, Garcia R, et al. Improved incidence of pT0 downstaged surgical specimens in locally advanced rectal cancer (LARC) treated with induction oxaliplatin plus 5-fluorouracil and preoperative chemoradiation. Annals of Oncology. 2006 Jul;17(7):1103–10.
6. Chua YJ, Barbachano Y, Cunningham D, Oates JR, Brown G, Wotherspoon A, et al. Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial. The Lancet Oncology. 2010 Mar;11(3):241–8.
7. Schou JV, Larsen FO, Rasch L, Linnemann D, Langhoff J, Høgdall E, et al. Induction chemotherapy with capecitabine and oxaliplatin followed by chemoradiotherapy before total mesorectal excision in patients with locally advanced rectal cancer. Annals of Oncology. 2012 Oct;23(10):2627–33.
8. Maréchal R, Vos B, Polus M, Delaunoit T, Peeters M, Demetter P, et al. Short course chemotherapy followed by concomitant chemoradiotherapy

and surgery in locally advanced rectal cancer: a randomized multicentric phase II study. Annals of Oncology. 2012 Jun;23(6):1525–30.

9. Dewdney A, Cunningham D, Tabernero J, Capdevila J, Glimelius B, Cervantes A, et al. Multicenter Randomized Phase II Clinical Trial Comparing Neoadjuvant Oxaliplatin, Capecitabine, and Preoperative Radiotherapy With or Without Cetuximab Followed by Total Mesorectal Excision in Patients With High-Risk Rectal Cancer (EXPERT-C). Journal of Clinical Oncology. 2012 May 10;30(14):1620–7.
10. Cercek A, Goodman KA, Hajj C, Weisberger E, Segal NH, Reidy-Lagunes DL, et al. Neoadjuvant Chemotherapy First, Followed by Chemoradiation and Then Surgery, in the Management of Locally Advanced Rectal Cancer. Journal of the National Comprehensive Cancer Network. 2014 Apr;12(4):513–9.
11. Habr-Gama A, Sabbaga J, Gama-Rodrigues J, São Julião GP, Proscurshim I, Bailão Aguilar P, et al. Watch and Wait Approach Following Extended Neoadjuvant Chemoradiation for Distal Rectal Cancer. Diseases of the Colon & Rectum. 2013 Oct;56(10):1109–17.
12. Garcia-Aguilar J, Renfro LA, Chow OS, Shi Q, Carrero XW, Lynn PB, 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. The Lancet Oncology. 2015 Nov;16(15):1537–46.
13. Sloothaak DAM, Geijsen DE, van Leersum NJ, Punt CJA, Buskens CJ, Bemelman WA, et al. Optimal time interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. British Journal of Surgery. 2013 May 3;100(7):933–9.
14. Gambacorta MA, Masciocchi C, Chiloiro G, Meldolesi E, Macchia G, van Soest J, et al. Timing to achieve the highest rate of pCR after preoperative radiochemotherapy in rectal cancer: a pooled analysis of 3085 patients from 7 randomized trials. Radiotherapy and Oncology. 2021 Jan;154:154–60.

15. Lefevre JH, Mineur L, Kotti S, Rullier E, Rouanet P, de Chaisemartin C, et al. Effect of Interval (7 or 11 weeks) Between Neoadjuvant Radiochemotherapy and Surgery on Complete Pathologic Response in Rectal Cancer: A Multicenter, Randomized, Controlled Trial (GRECCAR-6). Journal of Clinical Oncology. 2016 Nov 1;34(31):3773–80.
16. Deidda S, Elmore U, Rosati R, de Nardi P, Vignali A, Puccetti F, et al. Association of Delayed Surgery With Oncologic Long-term Outcomes in Patients With Locally Advanced Rectal Cancer Not Responding to Preoperative Chemoradiation. JAMA Surgery. 2021 Dec 1;156(12):1141.
17. Garcia-Aguilar J, Patil S, Kim JK, Yuval JB, Thompson H, Verheij F, et al. Preliminary results of the organ preservation of rectal adenocarcinoma (OPRA) trial. Journal of Clinical Oncology. 2020 May 20;38(15_suppl):4008–4008.
18. Fokas E, Allgäuer M, Polat B, Klautke G, Grabenbauer GG, Fietkau R, et al. Randomized Phase II Trial of Chemoradiotherapy Plus Induction or Consolidation Chemotherapy as Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer: CAO/ARO/AIO-12. Journal of Clinical Oncology. 2019 Dec 1;37(34):3212–22.
19. Gérard JP, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne PL, et al. Comparison of Two Neoadjuvant Chemoradiotherapy Regimens for Locally Advanced Rectal Cancer: Results of the Phase III Trial ACCORD 12/0405-Prodige 2. Journal of Clinical Oncology. 2010 Apr 1;28(10):1638–44.
20. Maas M, Nelemans PJ, Valentini V, Das P, Rödel C, Kuo LJ, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. The Lancet Oncology. 2010 Sep;11(9):835–44.
21. Pucciarelli S, del Bianco P, Efficace F, Serpentini S, Capirci C, de Paoli A, et al. Patient-Reported Outcomes After Neoadjuvant Chemoradiotherapy for Rectal Cancer. Annals of Surgery. 2011 Jan;253(1):71–7.
22. Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U, Silva e Sousa AH, et al. Operative Versus Nonoperative Treatment for Stage 0 Distal Rectal

Cancer Following Chemoradiation Therapy. Annals of Surgery. 2004 Oct;240(4):711–8.

23. Smith JD, Ruby JA, Goodman KA, Saltz LB, Guillem JG, Weiser MR, et al. Nonoperative Management of Rectal Cancer With Complete Clinical Response After Neoadjuvant Therapy. Annals of Surgery. 2012 Dec;256(6):965–72.

24. Li J, Liu H, Yin J, Liu S, Hu J, Du F, et al. Wait-and-see or radical surgery for rectal cancer patients with a clinical complete response after neoadjuvant chemoradiotherapy: a cohort study. Oncotarget. 2015 Dec 8;6(39):42354–61.

25. Appelt AL, Pløen J, Harling H, Jensen FS, Jensen LH, Jørgensen JCR, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. The Lancet Oncology. 2015 Aug;16(8):919–27.

26. Martens MH, Maas M, Heijnen LA, Lambregts DMJ, Leijtens JWA, Stassen LPS, et al. Long-term Outcome of an Organ Preservation Program After Neoadjuvant Treatment for Rectal Cancer. J Natl Cancer Inst. 2016 Dec 10;108(12):djw171.

27. Renehan AG, Malcomson L, Emsley R, Gollins S, Maw A, Myint AS, et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. The Lancet Oncology. 2016 Feb;17(2):174–83.

28. van der Valk MJM, Hilling DE, Bastiaannet E, Meershoek-Klein Kranenbarg E, Beets GL, Figueiredo NL, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. The Lancet. 2018 Jun;391(10139):2537–45.

29. Dattani M, Heald RJ, Goussous G, Broadhurst J, São Julião GP, Habr-Gama A, et al. Oncological and Survival Outcomes in Watch and Wait Patients With a Clinical Complete Response After Neoadjuvant Chemoradiotherapy for Rectal Cancer. Annals of Surgery. 2018 Dec;268(6):955–67.

30. Capelli G, de Simone I, Spolverato G, Cinquini M, Moschetti I, Lonardi S, et al. Non-Operative Management Versus Total Mesorectal Excision for Locally Advanced Rectal Cancer with Clinical Complete Response After Neoadjuvant Chemoradiotherapy: a GRADE Approach by the Rectal Cancer Guidelines Writing Group of the Italian Association of Medical Oncology (AIOM). Journal of Gastrointestinal Surgery. 2020 Sep 11;24(9):2150–9.
31. Smith FM, Wiland H, Mace A, Pai RK, Kalady MF. Clinical Criteria Underestimate Complete Pathological Response in Rectal Cancer Treated With Neoadjuvant Chemoradiotherapy. Diseases of the Colon & Rectum. 2014 Mar;57(3):311–5.
32. Smith JJ, Strombom P, Chow OS, Roxburgh CS, Lynn P, Eaton A, et al. Assessment of a Watch-and-Wait Strategy for Rectal Cancer in Patients With a Complete Response After Neoadjuvant Therapy. JAMA Oncology. 2019 Apr 11;5(4):e185896.
33. Cotti GC, Pandini RV, Braghiroli OFM, Nahas CSR, Bustamante-Lopez LA, Marques CFS, et al. Outcomes of Patients With Local Regrowth After Nonoperative Management of Rectal Cancer After Neoadjuvant Chemoradiotherapy. Diseases of the Colon & Rectum. 2022 Mar 9;65(3):333–9.
34. Pucciarelli S, Capirci C, Emanuele U, Toppan P, Friso ML, Pennelli GM, et al. Relationship Between Pathologic T-Stage and Nodal Metastasis After Preoperative Chemoradiotherapy for Locally Advanced Rectal Cancer. Annals of Surgical Oncology. 2005 Feb 4;12(2):111–6.
35. Pucciarelli S, de Paoli A, Guerrieri M, la Torre G, Maretto I, de Marchi F, et al. Local Excision After Preoperative Chemoradiotherapy for Rectal Cancer. Diseases of the Colon & Rectum. 2013 Dec;56(12):1349–56.
36. D'Alimonte L, Bao QR, Spolverato G, Capelli G, del Bianco P, Albertoni L, et al. Long-Term Outcomes of Local Excision Following Neoadjuvant Chemoradiotherapy for Locally Advanced Rectal Cancer. Annals of Surgical Oncology. 2021 May 30;28(5):2801–8.
37. Lezoche E, Baldarelli M, Lezoche G, Paganini AM, Gesuita R, Guerrieri M. Randomized clinical trial of endoluminal locoregional resection *versus*

laparoscopic total mesorectal excision for T2 rectal cancer after neoadjuvant therapy. British Journal of Surgery. 2012 Aug 2;99(9):1211–8.

38. Bujko K, Richter P, Smith FM, Polkowski W, Szczepkowski M, Rutkowski A, et al. Preoperative radiotherapy and local excision of rectal cancer with immediate radical re-operation for poor responders: A prospective multicentre study. Radiotherapy and Oncology. 2013 Feb;106(2):198–205.
39. Rullier E, Rouanet P, Tuech JJ, Valverde A, Lelong B, Rivoire M, et al. Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial. The Lancet. 2017 Jul;390(10093):469–79.
40. Verseveld M, de Graaf EJR, Verhoef C, van Meerten E, Punt CJA, de Hingh IHJT, et al. Chemoradiation therapy for rectal cancer in the distal rectum followed by organ-sparing transanal endoscopic microsurgery (CARTS study). British Journal of Surgery. 2015 May 7;102(7):853–60.
41. Garcia-Aguilar J, Shi Q, Thomas CR, Chan E, Cataldo P, Marcet J, et al. A Phase II Trial of Neoadjuvant Chemoradiation and Local Excision for T2N0 Rectal Cancer: Preliminary Results of the ACOSOG Z6041 Trial. Annals of Surgical Oncology. 2012 Feb 14;19(2):384–91.
42. Maas M, Beets-Tan RGH, Lambregts DMJ, Lammering G, Nelemans PJ, Engelen SME, et al. Wait-and-See Policy for Clinical Complete Responders After Chemoradiation for Rectal Cancer. Journal of Clinical Oncology. 2011 Dec 10;29(35):4633–40.
43. Pucciarelli S, Giandomenico F, de Paoli A, Gavaruzzi T, Lotto L, Mantello G, et al. Bowel function and quality of life after local excision or total mesorectal excision following chemoradiotherapy for rectal cancer. British Journal of Surgery. 2016 Dec 21;104(1):138–47.
44. Marchegiani F, Palatucci V, Capelli G, Guerrieri M, Belluco C, Rega D, et al. Rectal Sparing Approach After Neoadjuvant Therapy in Patients with Rectal Cancer: The Preliminary Results of the ReSARCh Trial. Annals of Surgical Oncology. 2022 Mar 2;29(3):1880–9.
45. Habr-Gama A, Lynn PB, Jorge JMN, São Julião GP, Proscurshim I, Gama-Rodrigues J, et al. Impact of Organ-Preserving Strategies on Anorectal

Function in Patients with Distal Rectal Cancer Following Neoadjuvant Chemoradiation. Diseases of the Colon & Rectum. 2016 Apr;59(4):264–9.

46. Barina A, de Paoli A, Delrio P, Guerrieri M, Muratore A, Bianco F, et al. Rectal sparing approach after preoperative radio- and/or chemotherapy (RESARCH) in patients with rectal cancer: a multicentre observational study. Techniques in Coloproctology. 2017 Aug 28;21(8):633–40.
47. Beets-Tan RGH, Lambregts DMJ, Maas M, Bipat S, Barbaro B, Curvo-Semedo L, et al. Magnetic resonance imaging for clinical management of rectal cancer: Updated recommendations from the 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. European Radiology. 2018 Apr 17;28(4):1465–75.
48. Zhuang Z, Zhang Y, Wei M, Yang X, Wang Z. Magnetic Resonance Imaging Evaluation of the Accuracy of Various Lymph Node Staging Criteria in Rectal Cancer: A Systematic Review and Meta-Analysis. Frontiers in Oncology. 2021 Jul 13;11.
49. Kalisz KR, Enzerra MD, Paspulati RM. MRI Evaluation of the Response of Rectal Cancer to Neoadjuvant Chemoradiation Therapy. RadioGraphics. 2019 Mar;39(2):538–56.
50. Miranda J, Tan GXV, Fernandes MC, Yildirim O, Sims JA, Araujo-Filho J de AB, et al. Rectal MRI radiomics for predicting pathological complete response: Where we are. Clinical Imaging. 2022 Feb;82:141–9.
51. Dindo D, Demartines N, Clavien PA. Classification of Surgical Complications. Annals of Surgery. 2004 Aug;240(2):205–13.
52. Heald RJ. A new approach to rectal cancer. Br J Hosp Med. 1979 Sep;22(3):277-81. PMID: 391315.
53. Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer. 1994 Jun 1;73(11):2680–6.
54. Linee guida NEOPLASIE DEL RETTO E ANO, AIOM. 2021.
55. Resendiz A, Martini G, Sensi B, Reddavid R, Marchiori G, Franco C, et al. The Italian version of the LARS score: cross-cultural adaptation and

validation. An Italian Society of Surgical Oncology-Colorectal Cancer Network (SICO-CCN) collaborative study. International Journal of Colorectal Disease. 2021 Aug 11;36(8):1805–10.

56. Sprangers MAG, Cull A, Groenvold M, Bjordal K, Blazeby J, Aaronson NK. The European Organization for Research and Treatment of Cancer approach to developing questionnaire modules: an update and overview. EORTC Quality of Life Study Group. Quality of Life Research. 1998;7(4):291–300.

57. Whistance RN, Conroy T, Chie W, Costantini A, Sezer O, Koller M, et al. Clinical and psychometric validation of the EORTC QLQ-CR29 questionnaire module to assess health-related quality of life in patients with colorectal cancer. European Journal of Cancer. 2009 Nov;45(17):3017–26.

58. Degner LF SJVP. The Control Preferences Scale. Can J Nurs Res. 1997 Fall;29(3):21-43. PMID: 9505581.

59. Kriston L, Scholl I, Hölzel L, Simon D, Loh A, Härter M. The 9-item Shared Decision Making Questionnaire (SDM-Q-9). Development and psychometric properties in a primary care sample. Patient Education and Counseling. 2010 Jul;80(1):94–9.

60. Rockwood TH, Church JM, Fleshman JW, Kane RL, Mavrantonis C, Thorson AG, et al. Fecal incontinence quality of life scale. Diseases of the Colon & Rectum. 2000 Jan;43(1):9–16.

61. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. Declaración de la Iniciativa STROBE (Strengthening the Reporting of Observational studies in Epidemiology): directrices para la comunicación de estudios observacionales. Gaceta Sanitaria. 2008 Mar;22(2):144–50.

62. Norman GR SJWK. interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Medical care:582-592.

63. Bao QR, Capelli G, Spolverato G, Pucciarelli S. ASO Author Reflections: Local Excision Following Neoadjuvant Therapy for Rectal Cancer: A

Compromise Between TME and Watch-and-Wait in Patients with Major Response. Annals of Surgical Oncology. 2021 May 1;28(5):2809–10.

64. Wibe A, Møller B, Norstein J, Carlsen E, Wiig JN, Heald RJ, et al. A National Strategic Change in Treatment Policy for Rectal Cancer—Implementation of Total Mesorectal Excision as Routine Treatment in Norway. A National Audit. Diseases of the Colon & Rectum. 2002 Jul;45(7):857–66.

65. Codina-Cazador A, Espín E, Biondo S, Luján J, de Miguel M, Alós R, et al. Proceso docente auditado del tratamiento del cáncer de recto en España: resultados del primer año. Cirugía Española. 2007 Oct;82(4):209–13.

66. Beets GL, Figueiredo NL, Habr-Gama A, van de Velde CJH. A new paradigm for rectal cancer: Organ preservation. European Journal of Surgical Oncology (EJSO). 2015 Dec;41(12):1562–4.

67. Beets-Tan RGH, Lambregts DMJ, Maas M, Bipat S, Barbaro B, Curvo-Semedo L, et al. Magnetic resonance imaging for clinical management of rectal cancer: Updated recommendations from the 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. European Radiology. 2018 Apr 17;28(4):1465–75.

68. Crimì F, Valeggia S, Baffoni L, Stramare R, Lacognata C, Spolverato G, et al. [18F]FDG PET/MRI in rectal cancer. Annals of Nuclear Medicine. 2021 Mar 31;35(3):281–90.