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Could the conservative approach be considered safe in the treatment of locally advanced rectal cancer in case of a clinical near-complete or complete response? A retrospective analysis

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ABSTRACT

Background: Conservative approach has emerged as an option for the management of rectal cancer (RC) patients with a near or complete clinical response after neoadjuvant chemoradiotherapy (nCRT). The aim of this study is to assess the impact of the conservative approach by comparing patients' survival outcomes and quality of life with those who had surgical resection.

Methods: A single-institution and retrospective study including RC patients who reached a near complete or complete clinical response after nCRT from January 2010 to September 2019. Conservative approaches included local excision or watch and wait strategy; surgery approaches included anterior resection or abdominal-perineal resection.

Local regrowth (LR), overall survival, disease free survival, metastasis free survival and colostomy free survival were evaluated through Kaplan-Meier curves and compared trough log-rank tests. Quality of life was measured by the following validated questionnaires: EORTC QLC30, EORTC QLQ – CR29 and Fecal Incontinence Quality of Life scale.

Results: Overall 157 patients were analyzed: 105 (66,9%) underwent radical surgery and 52 (33,1%) had a conservative approach. With a median follow-up of 51 months, 2 patients in the surgical group had a local recurrence and 8 in the conservative group had a LR, respectively. Distance metastasis occurred in 7 and 1 patients of surgical and conservative group, respectively. No differences were detected in terms of survival outcomes except for colostomy free survival (p: 0,01). The conservative group showed better intestinal ($p < 0.01$) and sexual (p: 0,04) function and emotional status (p: 0,02).

Conclusions: Conservative approach seems to be safe in terms of survival outcomes with a significant advantage on quality of life in RC patients who achieved clinical complete response after nCRT.

1. Introduction

The management of locally advanced rectal cancer (LARC) has evolved significantly over the past decades, improving survival outcomes, especially local control and, recently, disease-free survival (DFS) [1,2]. Currently, the gold standard of treatment for low-medium LARC is neoadjuvant chemo-radiotherapy (nCRT) or, alternatively, short course radiotherapy (SCRT) followed by total mesorectal excision (TME) [3–5]. After nCRT, a pathological complete response (pCR) was achieved in about 15–40% of patients [6–8]. Furthermore, although surgery after nCRT has been the cornerstone in the treatment of rectal cancer, it is still associated with a 2–5% risk of perioperative mortality [9] and long-term complications occurring in 6–35% of cases [10] with a significant impact on quality of life (QoL) [11]. A watch-and-wait (WW) strategy for LARC patients with a clinical complete response (cCR) after

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nCRT is currently a non-standard approach, but has become more widely practiced [12–14]. Recent studies have supported a conservative approach, with similar survival outcomes compared to the patients undergoing surgery [15–17]. However, there is no lack of conflicting voices regarding the efficacy and safety of these approaches. The percentage of patients with local regrowth (LR) varies widely, from 6% in a Dutch study [18] to 19–69% in other studies [19–22]. Tumor regrowth also appears to correlate with an increased risk of distant metastases (DM) [23]. These inconsistencies have raised concerns about the oncologic safety of the conservative approach.

The aim of this study is to evaluate the safety and benefits of the conservative strategy for patients with cCR or near clinical complete responses (near cCR) after nCRT with regard to survival outcomes and QoL compared with patients who achieved a pCR after TME surgery.

2. Materials and methods

2.1. Patients' selection criteria and study design

This retrospective study enrolled all LARC patients treated consecutively from January 2010 to September 2019. Inclusion criteria were at least 18 years at the time of diagnosis, a biopsy-proven adenocarcinoma of the rectum with no evidence of distant metastases on radiological staging examination. The study was approved by the ethics committee of our institution, and informed consent was obtained from patients when applicable.

In this study oncologic outcomes were evaluated for LARC patients treated by a conservative off-protocol strategy. This was a non-randomised comparison study between patients who underwent TME surgery with pCR and patients who achieved a cCR or near cCR after nCRT. Surgical patients were used as the standard group. These two groups were not directly compared because the retrospective study design.

Patients from the INTERACT study treated from 2010 to 2013 who met the inclusion criteria were included in this study [24].

2.2. Clinical workflow

All patients were staged by pelvic magnetic resonance imaging (MRI) and contrast-enhanced thoracic and abdominal Computed Tomography (CT) scan.

All cases were discussed during the multidisciplinary tumor board (MTB) of rectal cancer, composed by radiation oncologists, medical oncologists, radiologists, anatomo-pathologists, and surgeons, in order to share the best treatment options.

All patients underwent a long course chemo-radiotherapy. The total radiotherapy (RT) dose on the pelvis was 45 Gy in 25 fractions of 1.8 Gy/die, while the dose on the gross tumor volume (GTV) was 55 Gy in 25 fractions (with a concomitant boost of 2 Gy per week) or in 25 fractions of 2.2 Gy/die with simultaneous integrated boost [24,25]. Radiotherapy was delivered by three-dimensional conformational RT (3D-CRT) or intensity modulated RT (IMRT) or Volumetric Modulated Arc Therapy (VMAT) techniques.

Concomitant chemotherapy consisted of oral capecitabine or continuous infusion of 5-fluorouracil with or without oxaliplatin [26], depending on the clinical presentation.

The response was based on digital rectal examination (DRE) and pelvic MRI. Endoscopic examination was not always performed. In some cases of near cCR or cCR, a second re-evaluation with MRI and rectoscopy was performed at 12–14 weeks after the end of nCRT. The final assessment of cCR or near cCR was based on clinical judgments and decisions of the MTB.

A visible residual lesion with 30% or greater reduction in its largest diameter [27] was considered as clinical partial response.

Near clinical complete response was defined as a soft superficial irregularity at DRE, and a small residual flat ulcer with smooth edges with no signs of residual polypoid tissue at endoscopy. At pelvic MRI, near cCR was defined as an obvious down-staging with/without residual fibrosis, but with a heterogeneous or irregular aspect on MRI and/or a small focal area of high signal on b1000 DWI-MRI [28,29].

Clinical complete response was defined by the absence of a palpable mass at DRE and of any mucosal irregularity at endoscopy. At MRI, the rectal wall appeared normal or showed only a thin hypointense thickening of the wall. Futhermore, no suspicious lymph nodes were involved and low signal on b1000 images or low ADC at the previous tumor site [29].

Surgery was performed by TME technique at least 10–12 weeks after the end of nCRT. Post-operative complications were evaluated during the hospitalization period and during a 30-days follow-up [8,30].

The conservative approach group included LARC patients undergoing both local excision (LE) or vigilant WW. Local excision included transanal endoscopic microsurgery (TEM), transanal minimally invasive surgery (TaMIS) and excisional biopsy.

Patients considered high risk (cT4 or cT3 with cN2, extramesorectal lymph nodes involvement, mucinous component or extramural vascular invasion) received adjuvant systemic treatment [26,31].

The assessment of QoL in terms of bowel, sexual, rectal continence and quality of life in general was recorded through the administration of questionnaires: the European Organization for Research and Treatment of Cancer (EORTC) models Quality of life-Core (QLQ-C) 30, QLQ Colorectal Cancer Module-29, Fecal Incontinence Quality of Life (FIQL) scale [32,33]. Answers to questions relating the same broad category (intestinal function, sexual function, habits, and relational aspect) were aggregated, analysed, and presented together. Quality of life questionnaires were administered within 12 months after surgery in surgical patients and 12 months after the end of nCRT in the conservative approach group.

For surgical patients, follow-up was according to national guidelines, whereas in case of cCR after WW or pT0 after LE, a more intensive follow-up protocol consisting of outpatient DRE, MRI every 6 months, rectoscopy every 3 months in the first 2 years and annual CT scan of the chest, abdomen, and pelvis was used.

Local recurrence, for surgery patients, was defined as the evidence of recurrent disease in the pelvis, rectal wall or mesorectum confirmed by histological exam in surgical patients. Local regrowth (LR) was actually considered in patients managed with a conservative strategy as any sign of tumor recurrence in the rectal wall at DRE or endoscopy or imaging [34]. Suspected cases of local recurrence or LR were discussed during MTB to evaluate the indication for salvage surgery with TME. Local regrowths were confirmed histologically in all cases.

2.3. Endpoint

The primary endpoint was to compare survival outcomes such as overall survival (OS), disease-free-survival (DFS), metastasis-free-survival (MFS), colostomy-free-survival (CFS) between the surgical and conservative approach groups.

Furthermore, QoL was compared between the two groups in terms of bowel, bladder and sexual function, rectal continence and QoL in general.

2.4. Statistical analysis

The statistical analysis was performed by Python 3.7 with relevant modules to the single tasks (i.e. Lifelines, SciPy, Statmodels, Pandas) with a constant underlying confidence interval of 95%, as such all p values below 0.05 were considered statistically relevant. Overall survival, DFS, MFS and CFS were evaluated through Kaplan-Meier curves and compared through log-rank test. The date of diagnosis or treatment was used as the initial date with either the event date or the last follow up date as the final censoring date. Overall survival means the time elapsing between the date of diagnosis of the neoplasm and last follow-up date or death from any cause; DFS was defined as the time from the date of treatment to the detection of recurrent disease or death, whichever occurred first; MFS was defined as the time elapsed between the moment of treatment and the appearance of disease at a distance; the CFS was defined as time interval between the date of histological diagnosis and the date of colostomy.

Median follow-up times were calculated with Reverse Kaplan-Meier curves. Where appropriate, the effects of single descriptors on the selected outcomes were analyzed through univariate Ordinary Least Squares or univariate logistic regressions. The QoL questionnaires were processed by comparing the means of the scores given by the two patients groups and evaluating the results with two-tailed t-tests. Where appropriate, p values for relevant comparisons were calculated through Chi-square, Kruskal-Wallis tests, Mann Whitney tests or Fisher's exact tests.

3. Results

From January 2010 to September 2019, 757 LARC patients were treated in our division: total of 157 (20,7%) patients obtain pCR or cCR after nCRT. Of these, 93 (59,2%) were men and 64 (40.7%) were women with a median age of 65.5 years (range 26–80). Clinical characteristics are reported in Table 1. Significant statistical differences were observed between the surgical and conservative approach groups. In particular for cT ($p < 0.01$), cN ($p < 0.01$), tumor location ($p < 0.01$) and neoadiuvant concomitant chemotherapy type ($p < 0.01$), and adjuvant CT ($p < 0,01$).

Table 1
Clinical and Demographic Characteristics by Patient Cohort.

Characteristic	Conservativeapproach groupN: 52 (%)	Surgical groupN: 105 (%)	p value
median age (range)	65.5(42–82)	65(26–80)	0,16 [a]
sex			
Male	31 (59,6%)	62 (59%)	0,93*
Female	21 (40,4%)	43 (41%)	
median distance from anal verge (range), mm	20(0–70)	41(0–120)	**<0.001** [a]
clinical tumor			
cT1	1 (1,9%)	0 (0%)	**<0.001***
cT2	21 (40,4%)	4 (3,8%)	
cT3	23 (44,2%)	73 (69,5%)	
cT4	7 (13,5%)	28 (26,7%)	
clinical node			
cN0	20 (38,5%)	9 (8,6%)	**<0.001***
cN+	32 (61,5%)	95 (90,5%)	
grading			
NOS	11 (21,1%)	30 (28,6%)	0.26*
Gx	25 (48,1%)	43 (40,9%)	
G1	2 (3,8%)	6 (5,7%)	
G2	13 (25%)	15 (14,3%)	
G3	1 (1,9%)	8 (7,6%)	
median RT Dose (range) (Gray)	55 (48,6–55)	55 (35,2–55)	0,73 [a]
neoadjuvant CT			
Cap/5Fu	42 (80,8%)	60 (57,1%)	**<0.001***
Oxa based	10 (19,2%)	45 (42,9%)	
adjuvant CT	7 (13,5%)	33 (31,4%)	**0,01***

RT: Radiotherapy; CT: Chemotherapy; Cap: Capecitabine; 5Fu: 5-fluorouracil; Oxa: oxaliplatin *Fisher's Exact Test; a Mann–Whitney test.

The median RT dose was 55 Gy (range 35,2–55 Gy) in both groups: all patients received a boost on GTV and in 55 patients (35%) the neoadiuvant concomitant chemotherapy was intensified with oxaliplatin.

The mean time between the end of nCRT and the first restaging was 7,8 weeks (range 2–17).

At the first restaging 52 patients (33,1%) obtained a partial clinical response, 54 (34.4%) a near cCR and 51 (32.5%) a cCR. Thity-two (20,4%) patients underwent endoscopy at restaging.

In the conservative approach group, 29 (55.8%) patients had a "near cCR" at first evaluation based on either inconclusive endoscopy such as a small red/ulcer lesion, residual on DRE, or equivocal MRI immaging and underwent immediate LE (22 TEM and 12 other techniques). All patients showed ypT0 with negative margins, except in 5 cases where margin status was not available (Fig. 1).

Only 2 (3.9%) patients with a cCR at first evaluation were immediately managed with WW. The remaining 21 (40.4%) patients after the first evaluation underwent a second re-assessment that confirmed in 14 and 2 patients a cCR and near cCR, respectively, while in 5 an evolution from near cCR to cCR. Five patients were managed with EL (ypT0) and 16 patients were included in a WW policy (Fig. 1).

The mean time between nCRT and the second restaging was 21 weeks (range 12,5–33).

When preferred, the surgery was performed with an interval from nCRT of 16,4 weeks (range 7–38).

105 (66,8%) patients underwent surgical approach, in particular 79 (75.23%) anterior resection (AR) and 26 (24.7%) abdominal-perineal resection (APR).

Among patients treated with a conservative approach, 36 (69%) initially had distally localized tumors that would have required APR with positioning of a permanent colostomy: of these, only 2 patients had LR for which one underwent APR and one died for simultaneous severe metastatic disease.

In the surgical group, 20 patients (19%) had post-operative complications: 4 (20%) surgical wound dehiscence, 4 (20%) wound infection, 3 (15%) intra-abdominal or presacral abscesses, 5 (25%) perianal fistulas and 4 (20%) recurring intestinal sub-occlusions. These events required new hospitalizations for medical therapies and surgical procedures.

Forty patients (32,5%) received a systemic adjuvant treatment: 33 (82,5%) in the surgery group and 7 (17,5%) in the conservative approach group. Thirty-one (77,5%) patients received a chemotherapy regimen with oxaliplatin. The median number of adjuvant chemotherapy cycles was 8 (range 2–12) and 36 (90%) patients completed at least 8 cycles.

The median follow-up was 51 months (range 43–59) for all patients: 54 months (range 39–58) and 67 months (range 30–70) for the surgical and conservative approach group, respectively.

The LR occurred in 8 patients (15,4%) and in all cases was an intraluminal LR. Two (1,9%) surgical patients developed local recurrence. The median interval from the end of treatment to the appearance of LR was 21,4 months (range 6,5–63,6), 15,2 months (range 6,5–56,5) and 47,6 months (range 31,7–63,5) in the conservative approach and surgical group, respectively (Fig. 2).

Local regrowth in patients with conservative approach was treated in 3 (37,5%) patients with APR while in 2 (25%) with a LE; one patient (12,5%) unfit for surgery underwent brachytherapy treatment, 1 (12,5%) was not treated because of concomitant severe metastatic disease and finally 1 (12,5%) was lost to follow-up

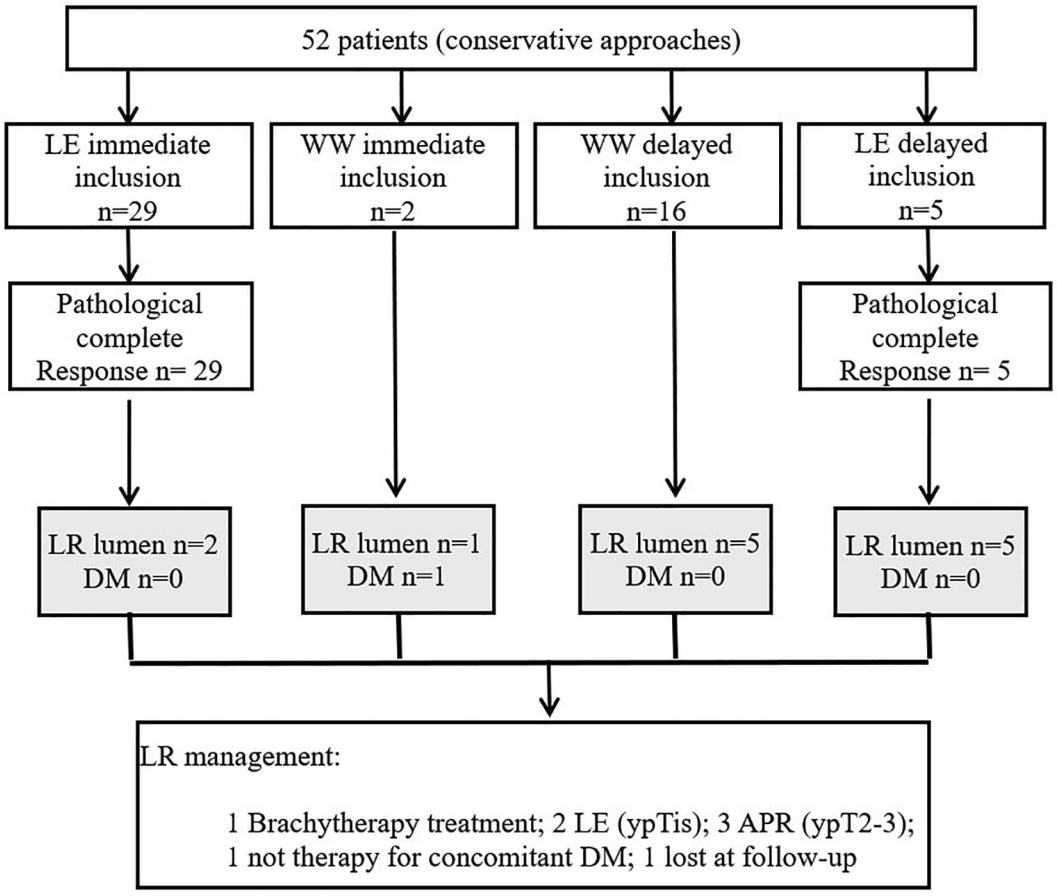

Fig. 1. Flowchart of patient's treatment. LE: local excision; WW: watch-and-wait; LR: local regrowth; DM: distant metastasis; APR: abdominal-perineal resection.

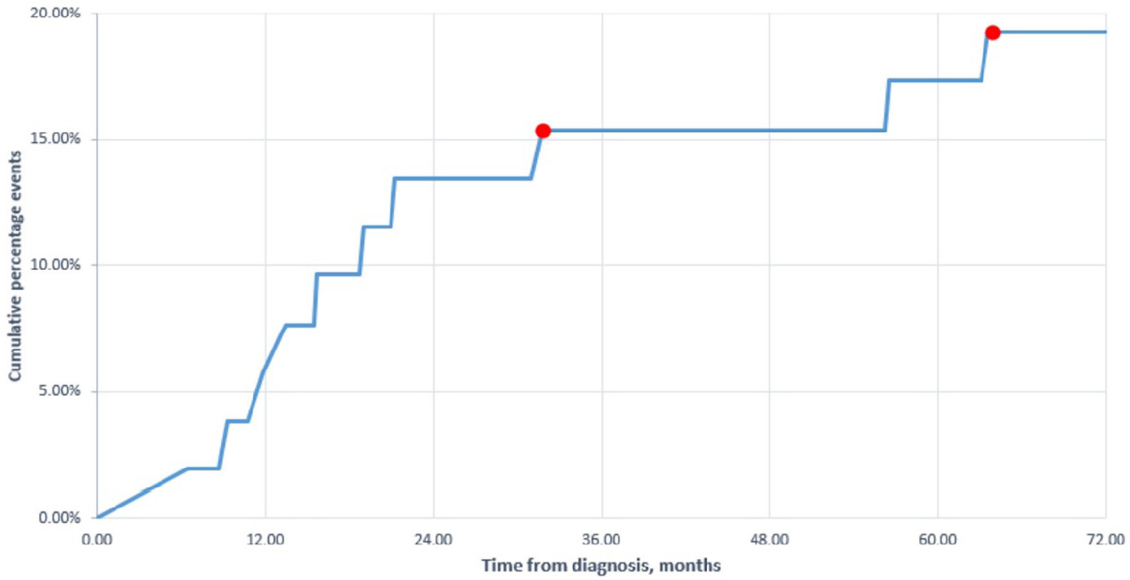

Fig. 2. cumulative local regrowth and local recurrence rate. The red points corresponded to surgical patients. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(Fig. 1). Pathological specimens showed residual pathology (ypT2-3) in the 3 patients undergoing APR while a ypTis in the LE cases. The local recurrence in the surgical group underwent a new segmental colon resection surgery.

The 3-years-OS was 95% and 98% for the surgical and conservative approach groups, respectively (p = 0.67). Nine (6%) patients died: 2 and 7 in the conservative approach and surgical group, respectively. Only 2 patients died of rectal cancer, 1 of

another primary cancer, and the remaining of other causes (Fig. 3A).

The 3-years-MFS was 94% and 100% for the surgical and conservative approach groups, respectively (p = 0.24). Metastasis events occurred in 8 patients (5%): 7 (87.5%) and 1 (12.5%) in the surgical and conservative approach group, respectively (Fig. 3B).

The 3-years-DFS was 95% and 87% for the surgical and conservative approach group, respectively (p = 0.81) (Fig. 3C).

The 3-years-CFS was 75% and 93% for the surgical and conservative approach group, respectively (p = 0.01) (Fig. 3D).

3.1. Quality of life

Overall, 76 (48.4%) patients completed QoL questionnaires, 43 (56,7%) in the surgical group (9 APR, 34 AR) and 33 (43,3%) in the CA group (7 EL, 11 TEM, 15 WW).

Compliance was good, although some individual items had slightly lower data compliance, particularly for questions about sexual function to which 18 patients (24.6%) did not respond. Evaluating the QoL questionnaires, there were statistically significant differences between the two groups in terms of bowel function influenced by food (p < 0.01) and drink (p < 0.01), incomplete emptying (p < 0.01), ability to contain the defecatory urge (p = 0.02) and retain air (p < 0.01). A particularly sensitive aspect concerns the problem of incontinence, which represents a significant problem for patients undergoing surgery (p = 0.01) with a higher frequency in involuntary loss of stool (p < 0.01) with an impact on the organization of daily activities

(p = 0.04). Finally, erection activity (p = 0.03) is reduced in the surgical group while the desire for sexual activity is maintained (Fig. 4) (Supplemental Materials).

4. Discussion

Since the pioneering work of Habr-Gama et al, the conservative approach is ~~was~~ considered safe for patients who achieve a cCR or near cCR after nCRT for LARC [15]. However, this conservative strategy requires that complete responses ~~are~~ be accurately identified ~~from~~ by clinical and radiological features.

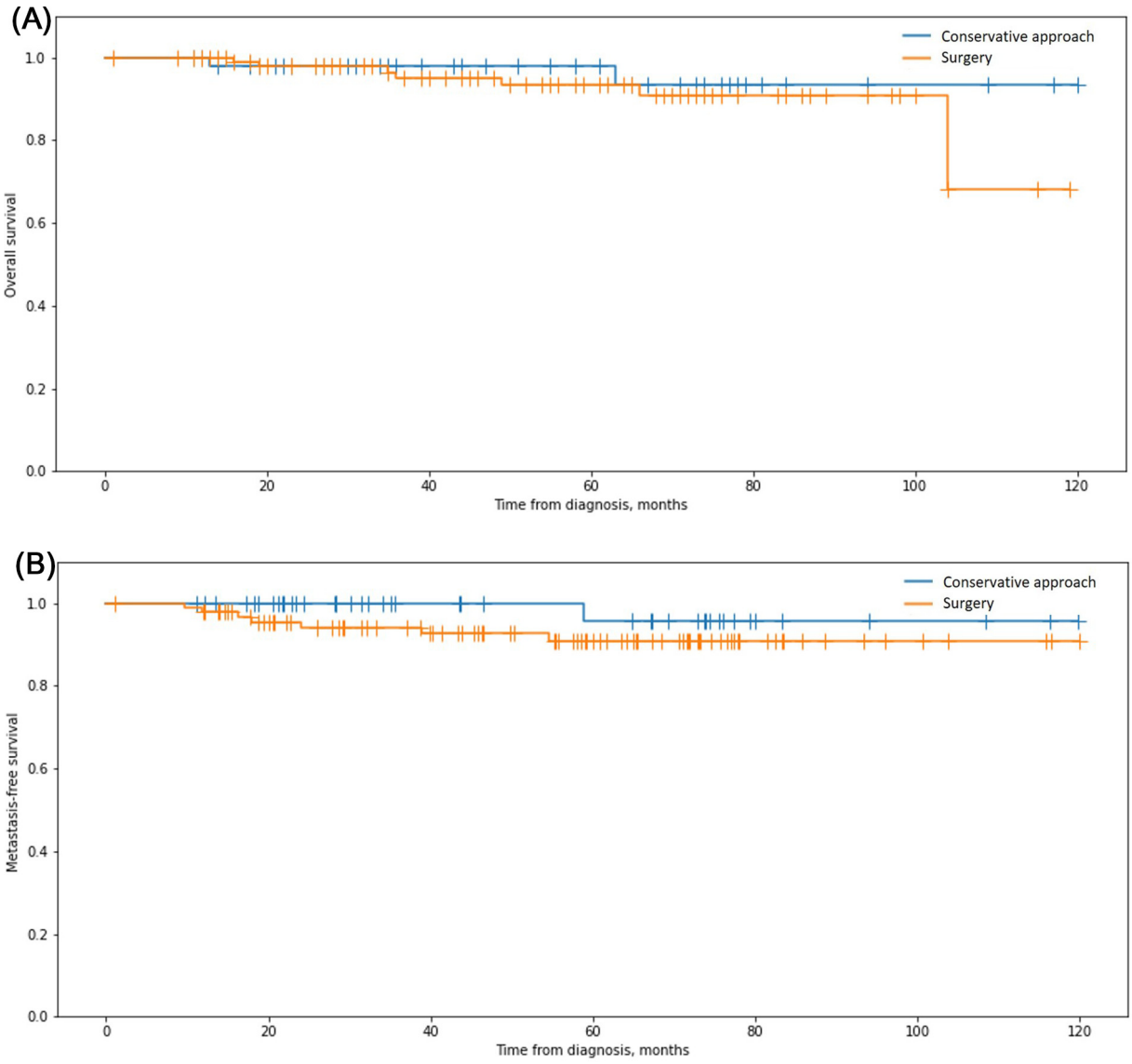

Fig. 3. Kaplan-Meier curves of (A) Overall Survival, (B) Metastasis-free survival, (C) Disease-Free Survival, (D) Colostomy-free survival in the conservative approach and surgical group. The log-rank test was used to compare outcomes between the two groups.

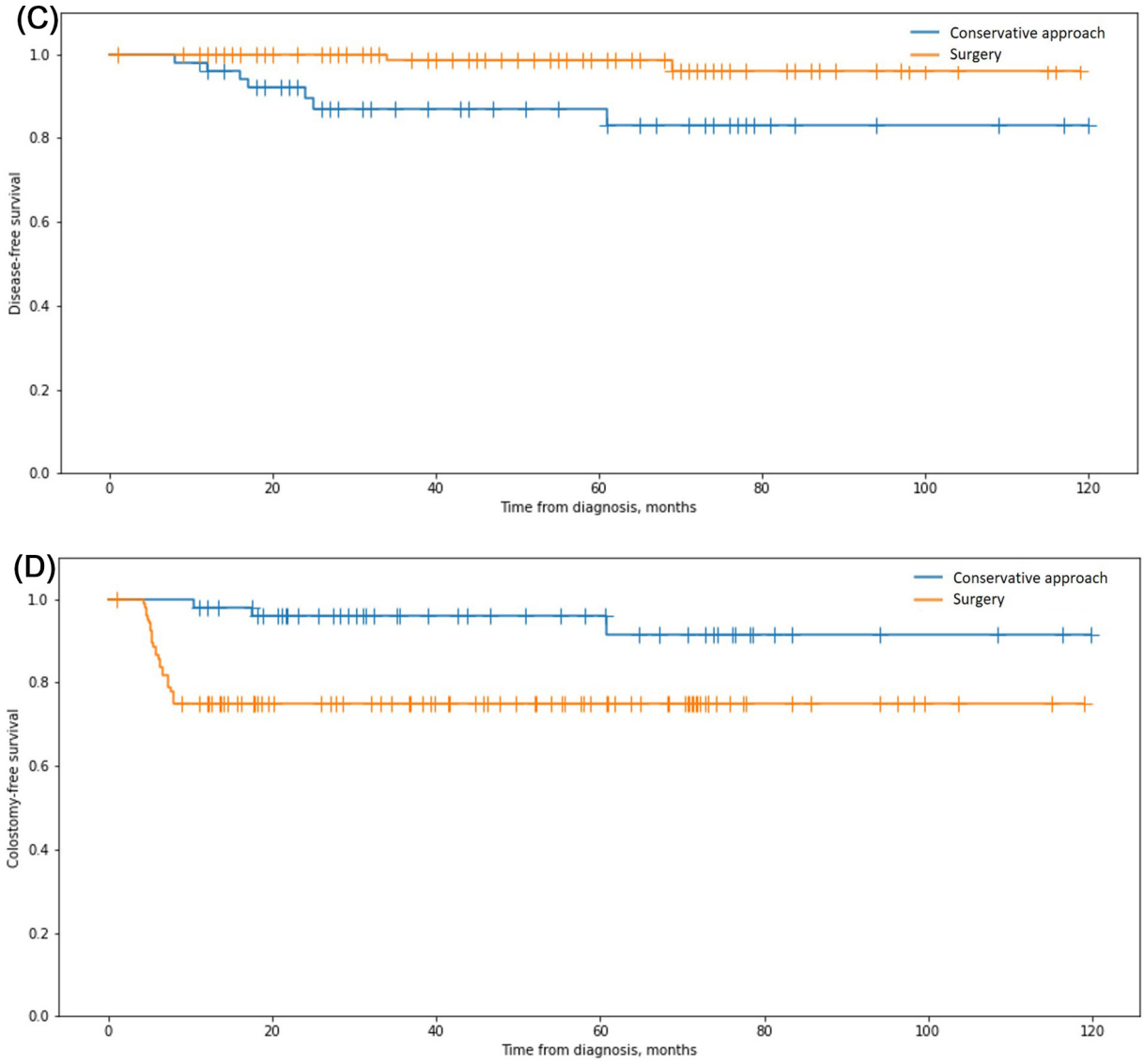

Fig. 3 (*continued*)

Our retrospective study supports the conservative approach with oncological outcomes comparable to the surgical group and better functional outcomes.

These findings are in line with the recent evidence from the Greccar-2 randomized trial, where in selected patients with a good response after nCRT, no differences were reported between the groups undergoing LE and TME in survival outcomes [35]. In addition, the TREC study demonstrates the feasibility and the organ preservation benefits of a multimodal organ-preservation strategy in early-stage rectal cancer, incorporating SCRT and TEM, compared with radical surgery without radiotherapy [36].

However, one of the most important issues in the conservative treatment strategy is the occurrence of LR: a rate between 19 and 25% of LR has been reported in LARC patients managed with a conservative approach. Nevertheless, salvage surgery with R0 resection is possible while preserving local disease control [13,21]. In our analysis, LR occurred in 8 patients (15,4%) in the conservative approach group with a median interval from the end of nCRT of 15,2 months and 95% of LR events occurred within 24 months. This result supports the need for more intensive follow-up in the first 2 years, when most events occur [34,37–38], allowing salvage surgery in approximately 90% of LRs [34,39]. In our series, 2 patients underwent LE because of ypTis-1 while 3 patients required APR with permanent colostomy.

However, although LR was associated with a higher number of distant metastatic events [23,34–36], in our experience, metastasis seems to be infrequent especially in the conservative approach group (2%), showing no significant differences with surgical patients; only one patient with LR died for several simultaneous distant metastases.

Moreover, the strategy of organ preservation, in selected patients, seem increasingly feasible to ensure better management of daily life. Considering CFS as an indicator of QoL with a lower level of social distress [38], patients undergoing a conservative approach benefited in about 25% of cases. In our series, more than half of patients with neoplasia of the lower rectum were managed with a conservative approach, avoiding permanent colostomy.

Overall, LARC patients managed with a conservative approach had a better functional outcome than those operated on, those operated on, particularly in terms of defecation, sexual and urinary tract function, as reported in previous studies [40,41]. Even with the limitations associated with an incomplete collection of QoL questionnaires, significant differences were recorded between the two groups, particularly on bowel function. Indeed, the greatest

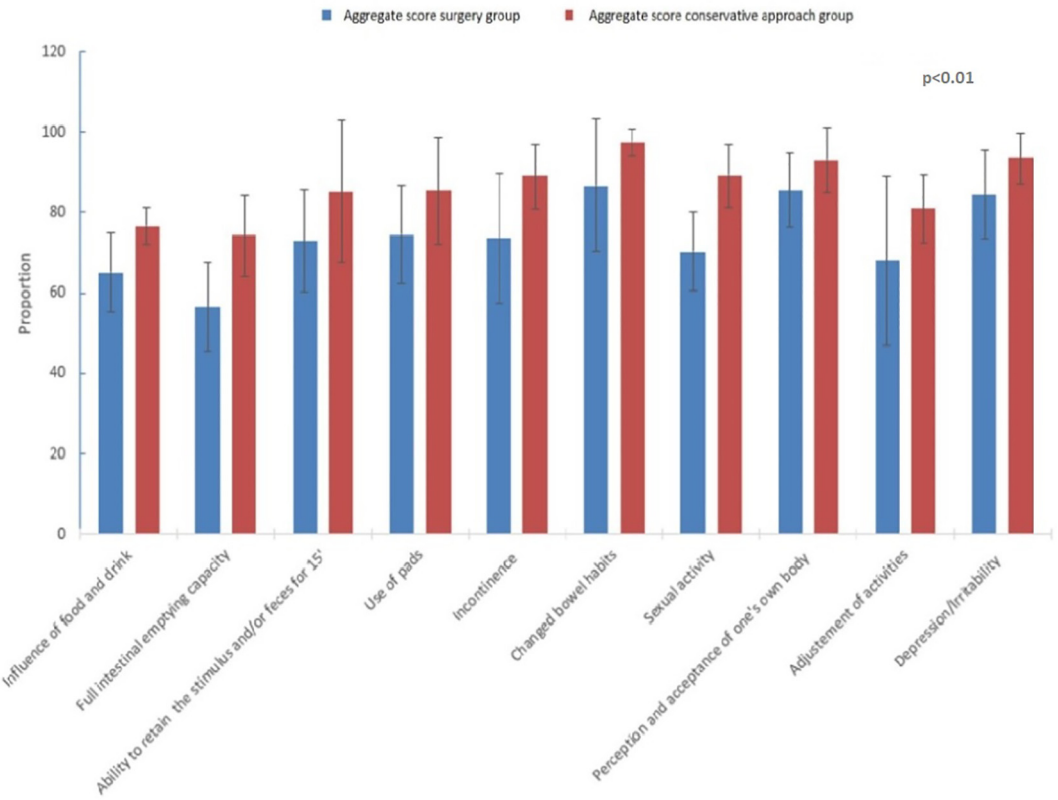

Fig. 4. aggregate outcomes of quality of life surveys based on several items from EORTC QLQ and FiQL questionnaires, as submitted by surgery and conservative approach patients within 12 months after surgery or the end of nCRT, respectively. Results on single question were assessed with two-tailed t-tests, while aggregates where tested by first calculating the pooled standard deviation, the standard error between the two means and then calculating the corresponding p-value. The individual scores have been scaled from their original grades to a 0 to 100 scale, with higher values always indicating a more positive quality of life rating. Multiple questions pertaining to the same broad category were average out and presented together. The graph reported the outcomes with a statistical difference between the two groups (p value < 0.01).

discomfort was related to bowel dysfunctions mainly associated with surgery [42–43], particularly in the control of flatus and defecatory urge and for the change in bowel and eating habits. In addition, the surgical group more significantly reported fecal incontinence with a negative impact on daily life, affecting social relationship, habits and emotional status of the patient.

Finally, collaterally, this study evaluated the impact of lengthening the surgical interval on pCR [8,30]: 21 patients underwent a second instrumental re-evaluation at 12 weeks with an evolution from near cCR to cCR in 5 patients, suggesting that, in selected cases, the use of the second re-evaluation could be useful for a consolidation of the response [38].

There are some limitations to this study. It is a single-institution study with a discrete, but not large, number of patients followed for a sufficient follow-up, covering an observation period of about 10 years with differences in the radiotherapy technique, chemotherapy regimens associated with nCRT, clinical restaging strategy and surgical interval. In fact, endoscopy, generally considered the most relevant study to assess response, in our case series it was performed in only 20.4%. Study weaknesses included those inherent in retrospective studies including selection bias and recall bias. Indeed, in the conservative approach group tumors were lower, representing ~~a~~ potentially different biology that could alter survival outcomes. The two groups were imbalanced in terms of cT and cN, in favour of the conservative approach group, and inhomogeneous concerning the type of concomitant chemotherapy. In addition, about half of the patients responded to the QoL questionnaires: the difficult collection of information, subjectivity or complacency of patients in answering the questionnaires may make some assessment less accurate and influence the outcome. Finally, in the conservative approach group, we included patients managed with both WW and LE, and therefore no distinction was made between these two approaches in the evaluation of the LR and QoL. In any case, in our study, we did not find worse anorectal function after the conservative approach in patients treated with LE as described in a previous study [43].

5. Conclusions

In conclusion, the conservative approach seems to be feasible and safe and should be considered in case of cCR or near cCR after nCRT. However, rigorous selection criteria and ~~a~~ careful clinical-instrumental follow-up are required to ensure its success. In particular, to avoid the bias on the imbalance between the two groups, the different initial clinical characteristics such as cT, cN, and distance from anal verge could be considered among the selection criteria of the treatment choice in case of almost clinical near complete or complete response.

In our study, rectal preservation was achieved in 94% of LARC patients managed conservatively. The outcomes are comparable to those of pCR patients after surgery with a significant benefit on bowel function and social and relational aspects.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2021.02.009.

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