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Research Article

# Therapeutic Results of Rectal Cancer in Southern Tunisia

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## Abstract

**Introduction:** Multimodal treatment made of radio chemotherapy and surgery has improved the local control rate of rectal cancer but the metastatic relapse rate and overall survival remain stable.

**Patients and Methods:** Our work was a retrospective study of patients with locally advanced non-metastatic rectal cancer treated with radio-chemotherapy at Habib Bourguiba Sfax University Hospital in the period from January 2009 to December 2017. A descriptive analysis and a study of the survivals was done.

**Results:** We collected 66 patients. The tumor was in the lower rectum in 46 patients. According to the 2017 TNM classification, the tumors were classified as T3 in 49 cases. The disease was classified as N0 in 20 cases. Eleven patients had immediate surgery and 55 patients had received neoadjuvant therapy. The neoadjuvant treatment consisted of preoperative Radiotherapy concomitant with Chemotherapy for 53 patients. Ten patients did not undergo surgery. The predominant histological type was lieberkühnian adenocarcinoma in 47 cases. A T3 tumor was found in 24 patients operated after neoadjuvant treatment and 6 patients operated immediately. Lymph node involvement was observed in 25 patients. The clearance was less than 1 mm in 12 cases. For patients operated after neoadjuvant treatment, a complete histological response was obtained in six patients (13.3%). The adjuvant treatment consisted of adjuvant RT-CT for the eleven patients operated on immediately. Adjuvant Chemotherapy was administered in 29 patients operated after neoadjuvant treatment. It was associated with adjuvant RT in four cases. At the first post-treatment evaluation, 43 patients (65.1%) were in complete remission. Thirteen relapses were recorded after a median delay of 17 months (11 - 72 months). The 5-year OS and SES were 53% and 60% respectively, and the 5-year DFS was 82%. DFS at 5 years was 73%.

**Conclusion:** The prognosis of rectal cancers remains reserved. Accurate pre-therapeutic evaluation and optimization of neoadjuvant treatment according to prognostic factors of the disease could improve oncological results while preserving a good quality of life.

***Keywords:*** *Rectal Cancers; Neoadjuvant Treatment; Radiotherapy; Chemotherapy*

## Introduction

Rectal cancer is the 2nd leading cause of cancer death in the world with nearly 880792 deaths per year [1]. In Tunisia, the incidence rate is about 1865 new cases per year. This cancer is the fourth most common among men and the second most common among women Diagnosis at the locally advanced stage is observed in about two thirds of cases [2].

Enormous progress has been made in the management of rectal cancer. Radiation therapy (RT) decreases the local relapse rate by more than 50% [3-5]. The administration of chemotherapy (CT) concomitantly with RT further decreases the local relapse rate (17 versus 8%) and increases the complete tumor response on the surgical specimen compared to RT alone (8% versus 16%) [6,7]. Nevertheless, the distant progression and overall survival rates remain stable and the probability of survival at 5 years is about 70% [8,9].

Very few Tunisian series have been interested in the evaluation of the therapeutic results of rectal cancer treatment in Tunisia.

## Objective of the Study

The objective of this work was to evaluate the therapeutic management of patients with non-metastatic rectal cancer and to study the evolutionary profile of patients treated with concurrent radio-chemotherapy (RT-CT) for non-metastatic rectal cancer.

## Patients and Methods

This is a retrospective study, conducted at the Habib Bourguiba University Hospital in Sfax, Tunisia, of patients treated for nonmetastatic rectal cancer between January 2009 and December 2017. All patients with non-metastatic rectal cancer who had concomitant RT-CT for curative purposes were included.

Preoperative 3D RT (45-50.4 Gy) combined with CT was indicated for tumors of the middle and lower rectum classified as T3-T4 and/or with lymph node involvement (N1-3). For subperitoneal upper rectal tumours of stages II and III whose lower pole invades the mesorectum, and for those of stage T2N0 of the lower rectum, the indication was discussed in a multidisciplinary consultation meeting. In case of surgical contraindication or refusal of the patient, an exclusive irradiation, with or without CT, was delivered.

For patients operated immediately, in case of underestimation during the initial staging and in case of invaded margins, postoperative RT was proposed in association with CT in the presence of anatomo-pathological risk factors: p T4, invaded lymph nodes, positive circumferential margin and/or positive distal margin.

The modalities of rectal resection varied according to the location of the tumor, its possible extension to neighboring organs, the patient's terrain, and the state of the sphincter.

The type of surgery was decided in the multidisciplinary consultation meeting before and after evaluation of the clinical response to preoperative treatment by clinical examination, rectoscopy and pelvic CT and/or MRI.

The surgery consisted of a total or partial removal of the rectum and the entire mesorectum by laparotomy or laparoscopy.

A post-treatment evaluation of the response to the treatment was scheduled after 2 to 3 months from the end of the treatment. It was performed by clinical and endoscopic examination, as well as abdominal and pelvic imaging.

Further monitoring was quarterly for 2 years and semi-annually for 3 years, then annually.

Data analysis was done with SPSS 23 software.

Descriptive statistical analysis was performed for epidemiological and therapeutic data. Quantitative variables were expressed with means and medians with the two extremes. The qualitative variables were expressed as numbers and percentages.

The analysis of the different survival curves (recurrence-free survival, metastasis-free survival, event-free survival, overall survival) was performed using the Kaplan-Meier method.

## Results

Between January 2009 and December 2017, 66 patients were managed by the digestive oncology committee of the Habib Bourguiba University Hospital in Sfax, Tunisia.

The median age was 55 years [34 - 83]. The sex ratio was 0.8.

The tumor was located in the lower rectum in 35 patients (53%), in the middle rectum in 27 patients (40.9%) and in the upper rectum in 4 patients (6.1%). The tumor was circumferential non-stenosing in 26 cases (41.4%) and circumferential stenosing in 6 cases (7.1%) and non-circumferential in 29 cases (43.9%).

All patients had a pelvic CT scan. Abdominal-pelvic MRI was performed in only 33 (50%).

According to the 2017 TNM classification, the tumors were classified as T2 in 8 cases (12.1%), T3 in 49 cases (74.2%), and T4 in 9 cases (13.6%). The disease was classified as N0 in 20 cases (30.3%). Tumors were stage III in 46 cases (69.7%), stage II in 22.7% and stage I in 7.5%.

### Treatment

Eleven patients had primary surgery, of which 8 patients had an anterior resection (AR) followed by adjuvant RT-CT within a median of 14 weeks (7 - 24 weeks). The other had three abdominoperineal amputation.

Fifty-five patients had received neoadjuvant treatment followed by surgery such as RA in 25 patients (55.8%), PAA in 17 patients (37.8%) and total coloproctectomy in 2 patients.

The median time from the end of RT to surgery was 8 weeks with extremes from 4 to 100 weeks. Four patients were lost to follow-up after RT-CT and had reconsulted with recurrence of rectal bleeding at 7, 8, 24 and 25 months respectively, remaining non-metastatic and were therefore operated.

For the patients who had already neoadjuvant RT-CT, four had received an additional dose of 20 Gy of RT postoperatively for invaded margins and 29 patients had received adjuvant CT (Table 1).

The predominant histological type was lieberkühnian adenocarcinoma, which was present in 47 cases (84%), of which 18 cases (32%) were well differentiated. Eight patients had mucinous carcinoma (14.2%). Among the patients operated firstly, six patients (54.5%) had a tumor classified as pT3 with lymph node involvement in 10 cases.

Among the patients operated after neoadjuvant treatment, 24 patients (53.3%) had a tumor classified as ypT3 with lymph node involvement in 15 patients. A complete histological response (pCR) was obtained in 6 patients (13.3%) and a tumor remnant (Dworak 0-3) was found in 39 patients (86.7%).

Distal resection margins were not invaded in all patients. The average margin was 3 cm [0.8 - 7 cm]. Four patients had a margin of less than 1 cm. They had undergone PAA.

The mean clearance was 4.1 mm [0 - 15 mm]. It was less than 1 mm in 16 cases (28.4%) of which four were operated firstly, indicating adjuvant radiochemotherapy.

Vascular and lymphatic emboli were found in 15 cases (26.8%) and peri-neural sheathing in 25 cases (44.6%), indicating adjuvant chemotherapy.

| | Number | Percentage |
|---|---|---|
| **Type of concomitant chemotherapy** | | |
| Fufol | 44 | 83% |
| LV5FU2 | 2 | 3.7% |
| 5FU en continu | 4 | 7.5% |
| Capecitabine | 3 | 5.6% |
| **Concomittant RT dose** | | |
| 44 Gy | 2 | 3.6% |
| 50.4 Gy | 2 | 3.6% |
| 45 Gy | 49 | 89% |
| 64 Gy | 2 | 3.6% |
| **Adjuvant CT** | | |
| Folfox | 29 | 74% |
| LV5FU2 | 3 | 7.6% |
| XELOX | 3 | 7.6% |
| Capécitabine | 1 | 2.5% |
| Fufol | 3 | 7.6% |
| **Adjuvante RT dose** | | |
| 45 Gy | 7 | 46% |
| 64 Gy | 4 | 26% |
| 20 Gy | 4 | 26% |

***Table 1:*** *Radiotherapy and chemotherapy received by patients.*

## Post-treatment evaluation

At the end of the therapeutic procedure, 43 patients (65.1%) were in complete remission (Figure 1). Twenty patients (30%) were in progressive of their disease and three were lost to follow-up.

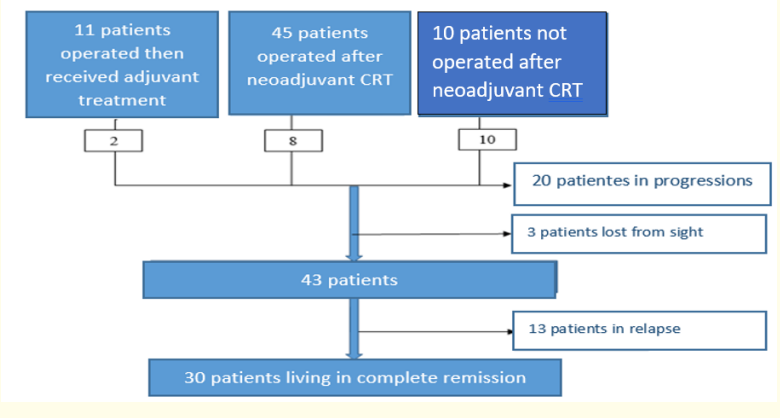


***Figure 1:*** *Evolution of patients after treatment.*

All the non-operated patients had pelvic locoregional progression associated with metastatic progression in seven cases.

For the operated patients, three patients had isolated local progression, four patients had metastatic progression, and three patients had local and metastatic progression. The mean time to progression was 2.4 months (1 - 4 months) since the end of treatment for six patients.

The site of local progression was pelvic in two cases, at the anastomosis in two cases and at the presacral level in two cases. The sites of metastatic progression were lung in 5 cases, liver in 3 cases, bone in 2 cases and one case of brain metastasis.

### Evolution

The median follow-up was 52 months [1 - 116 months]. All patients (20 cases) who were in progression died after a mean overall survival of 17 months (6 - 30 months).

Thirteen relapses (30% of patients who were in complete remission at evaluation) were reported after a median time of 17 months (11 - 72 months). These were isolated local relapse in five cases (11.6%) (3 pelvic and 2 anastomotic relapse), local and metastatic relapse in two cases (4.6%), and metastatic relapse in 6 cases (13.9%). The lung was the primary site of metastasis. The majority of recurrences (75%) occurred within the first two years.

Treatment of local recurrences was surgery in 2 patients (PAA combined with prostatectomy in 1 patient and vaginal recurrence removal in 1 patient). An additional 20 Gy of RT was delivered for one patient who refused to be reoperated. Two patients had undergone palliative CT. Only the patient operated for a pelvic recurrence localized at the vaginal level had in complete remission (Table 2).

| Patients | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Age (years) | 66 | 71 | 53 | 48 | 53 |
| Distance tumor- anal margin | 5 cm | 1 cm | 5 cm | 12 cm | 2 cm |
| C TNM | T2N1 | T3N1 | T3N1 | T3N1 | T3N1 |
| Surgery | RA | RT-CT+ APA[2] | RT-CT+ RA | RA | RT[1] -CT + AAP |
| p TNM | pT2N1 | ypT4N0 | ypT3N0 | pT3N1b | ypT4N0 |
| CRM | | CRM < 1 mm | CRM < 1 mm | | CRM < 1 mm |
| Adjuvant treatment | RT[1] -CT | (No adjuvant treatment because of the delays) | CT | RT-CT | CT+RT* |
| Relapse time (months) | 24 | 24 | 11 | 16 | 72 |
| Relapse site | anastomosis | Vagina | Anastomosis | Pelvis (ant) | Pelvis (ant+lat) |
| Relapse treatment | Abstention: hematological problem | Surgery: colpectomy | CT: folfox+avastin+ RT: 20Gy | Surgery: APA+. prostatectomy +CT: folfox | Palliative care OMS = 3 |
| Response | Death | Remission | Progression | Progression | Progression |
| Survival (months) | 32 | 124 | 31 | 24 | 80 |

***Table 2:*** *Clinical and evolutive characteristics of local relapses.*

*RT: Radiotherapy; CT: Chemotherapy; AR: Anterior Resection; APA: Abdominoperineal Amputation; *: RT Complement; 1: Interruption of RT > 7 days; 2: surgery delays >12 weeks, CRM: Circumferential Resection Margin.*

For metastases, surgery was indicated for 2 patients with pulmonary metastasis, associated with adjuvant CT. These 2 patients are alive in remission of their diseases with a follow-up of 18 months and 14 months since the treatment. Palliative CT was administered to 6 patients. Palliative care was decided for the remaining patients (Table 3).

| cTNM | Treatment | pTNM | CRM | Adjuvant therapy | Relapse time (months) | Relapse type | Relapse site | Relapse treatment | Response | Survival (Months) |
|---|---|---|---|---|---|---|---|---|---|---|
| T3N1 | RT-CT+ RA | ypT0N0 | Good | CT | 24 | Metastatic | Lungs | Surgery: Wedge | Remission | 46 |
| T2 N0 | Primary RA | pT4N1 | Good | RT | 37 | Metastatic | Liver | Abstention : OMS = 3 | Progression | 50 |
| T3N2 | RT-CT+ RA | ypT3N2 | Good | CT | 12 | Metastatic | Lungs | Surgery: CT: capox | Remission | 49 |
| T3N0 | RT-CT+ AAP | ypT3N2 | Good | CT | 30 | Metastatic | Lungs | CT: folfox | Progression | 68 |
| T3N0 | RT-CT+ RA | ypT3N0 | Good | | 17 | Local + metastatic | Anastomosis lungs | CT: folfox | Progression | 11 |
| T4N1 | RT[1] -CT + AAP | ypT4N0 | CRM < 1 mm | CT | 11 | Local+ metastatic | Pelvis + lungs | CT: folfiri | Progression | 17 |
| T2N0 | AAP d'emblée | pT3N1 | CRM < 1 mm | RT-CT | 14 | Metastatic | Peritoneal | CT: folfox | Progression | 38 |
| T3N1 | RT-CT+RA | ypT3N0 | Good | | 16 | Metastatic | Lungs | CT: folfox | In the course of CT | 62 |

***Table 3:*** *Clinical and evolutionary characteristics of metastatic relapse.*
*RT: Radiotherapy; CT: Chemotherapy; AR: Anterior Resection; AAP: Abdominoperineal Amputation; L: Local; M: Metastatic; MA: Anal Margin; CRM: Circumferential Resection Margin; 1: Interruption of RT > 7 days.*

Overall survival and event-free survival at 5 years were 53% and 60%, respectively. Locoregional recurrence/progression-free and metastasis-free survival at 5 years were 82% and 73% respectively.

## Discussion

Preoperative RT has played an important role in the treatment of rectal cancer since 1995 [5]. Two randomized Dutch and German trials have demonstrated the benefit of RT followed by surgery on the local relapse rate compared to surgery alone [3,5]. This benefit is maintained even in the long term. The local relapse rate at 5 years was 5% versus 11% ($p < 0.001$) in the surgery alone group whatever the tumor location and stage but it seems maximal for stage III tumors and minimal for stage I tumors. However, there was no difference in OS between the 2 groups (62.2% vs 62.6% at 5 years with and without RT respectively) [5].

Several trials have investigated the combination of concomitant CT with preoperative RT [7,10-12]. These studies have shown that RT-CT is superior to RT in terms of local control even though the surgery does not fully meet the quality criteria (Local recurrence at 5 years

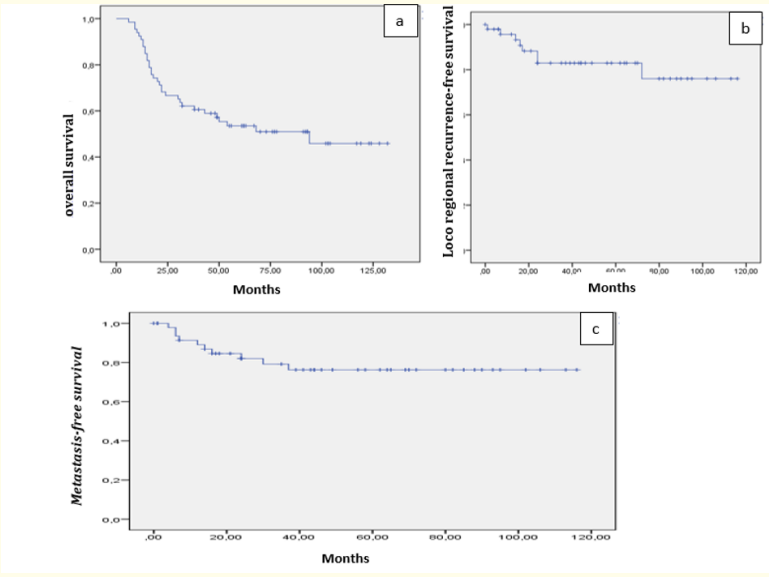


***Figure 2:*** *Overall survival (a), locoregional recurrence-free survival (b), metastasis-free survival (c).*

was 16.5% in the RT alone group versus 9.4% in the RT-CT group) but without clear benefit on disease-free survival and OS. A systematic review of several trials showed that CT increases the pCR rate (11.8% in RT-CT versus 3.5% for RT alone) [9]. This is put forward as a strong argument in favor of RT-CT because it is hoped to obtain a negative CRM or sphincter preservation.

The Tunisian series that studied the therapeutic results of this regimen were old and did not detail the protocols of RT-CT and relatively [13,14]. The ISA study published in 2021 had the primary objective of evaluating histological response after neoadjuvant therapy [15]. The recurrence-free survival (RFS) rate in this study was equivalent to our series (81% versus 82% at 5 years). However, the OS rate was better (72% versus 53% at 5 years). This difference can be attributed to the fact that all patients included had neoadjuvant RT-CT followed by surgery. Metastatic relapse was lower in our series (DFS at 5 years was 63% versus 73% in our series).

In an Algerian series, including 58 patients with non-metastatic rectal adenocarcinoma (stage II (18.61%), stage III (53, 44%)), the OS at 3 and 5 years was 70% and 55% respectively. Ten patients (18.86%) had recurrence with a mean time of 18.90 with extremes of 6 and 36 months [16].

In a large Korean series including 1232 patients with stage II-III rectal cancer treated with RT-CT followed by surgery adjuvant CT was given to 962 patients (78.1%). The 5-year OS and SES rates were 84.1% and 71.1%, respectively [17].

In the different Western series the 5-year SES ranged from 63% to 79% and the 5-year OS ranged from 68% to 71%. Table 4 summarizes the results of the different series.

Relapse after curative surgery is one of the major factors affecting long-term survival. Its frequency is estimated at 22.5% at 5 years, including 12% of local recurrence. The OS in case of recurrence is about 11% at 5 years.

According to Mesli., *et al*. patients with tumor recurrence had a poor survival rate at 3 years compared to those without tumor recurrence (30.85% vs. 64.30%) [16].

| Study | Number | Stage | neoadj/adj RT-CT (%) | Surgery | RT dose (Gy) | Adj CT | Neoad CT Protocol | EFS at 5 years | OS at 5 years |
|---|---|---|---|---|---|---|---|---|---|
| Mzoughi and al 2016 [14] | 154 2000-2009 | II-III-IV (26%) | 70%/- | 90% | -- | - | - | 69% | 42% |
| Farhat and al 2019 [13] | 188 2000-2015 | I-II-III | 64%/34% | 100% | 45 | - | 5FU | 56% | 54% |
| Mesli and al 2016 [16] | 58 2009-2015 | I-II-II IV (7%) | 24%/41% | 100% | - | - | - | | 55% |
| Song and al 2019 [17] | 1232 2005-2014 | II-III | 100% | 100% | 50.4 | 78% | 5FU(90%) cap(10%) | 71% | 84% |
| Karagkounis and al 2019 [18] | 545 1995-2012 | II-I-III IV (7%) | 100% | 100% | 50.4 | - | - | 63% | |
| Lescut and all 2015 [19] | 17 1993-2008 | II-III | 100% | 970% | 45 | 45% | 5FU (56%) Cap (28%) Capox (15%) | 74% | 68,8% |
| Castillego and al 2017 [20] | 115 2007-2014 | II-III | 100% | 100% | 45-50.4 | 64% | 5FU (73%) Cap (26%) | 79% | 71% |
| Hajer and al 2020 [15] | 70 2010-2016 | I II III | 100% | 100% | 45 50.4 (12%) | 45% | Cap (97%) Folfox (3%) | SSR: 81% SSM: 63% | 72% |
| Sahnoun and al [21] | 30 2004-2014 | All pT3 | 72%/26% | 100% | 45 (85%) 25 (14%) | 83% | Fufol (30%) 5FU (16%) Folfox (4%) | 39% | 33,5% |
| Our study | 66 | I-II-III | 83%/16,6% | 84% | 45 Gy | 43% | Fufol (83%) 5FU (7.5%) | 60% | 53% |

***Table 4:*** *Characteristics and results of the different study.*
*RT: Radiotherapy; CT: Chemotherapy; neoadj: Neoadjuvant; adj: Adjuvant; EFS: Event-Free Survival; OS: Overall Survival; FU: Fluorouracil; Capecitabine.*

Locoregional recurrences usually occur 1 to 3 years after completion of treatment of the primary rectal cancer. They are usually associated with synchronous metastatic localizations in 40 to 50% of cases [22], slightly more frequent than in our series. Indeed, 2 out of 7 patients (28%) had an associated metastatic location. Pre-sacral and lateropelvic recurrences were the most frequent localizations. For our patients, the recurrences were located at the anterior pelvic level (2 cases) and at the anastomosis level (3 cases).

The place of re-irradiation of recurrent rectal cancer remains unclear in the literature. The evaluation of tumor responses to RT concluded that recurrent tumors had a minimal response suggesting radioresistance [22]. The doses used ranged from 27 to 40 Gy (1.7 to 2.2 Gy per session) in combination with CT. However, the therapeutic results were controversial in terms of R0 resection rate but without improvement in survival rates or local control and significant postoperative complications. Surgery is important in case of local recurrence but only 18 to 30% of rectal recurrences were considered resectable at the time of diagnosis. Indeed, the bony involvement and the proximity of the vasculo-nervous structures frequently encountered in posterior and lateral recurrences indicate against resection.

In specialized centers, pelvic exenteration could be performed but with a very high morbidity of about 76% [23]. Anterior or anastomotic recurrences are more accessible to R0 surgery. For unresectable tumours the treatment would be RT and palliative CT which could improve pelvic pain [22].

The prognosis of locoregional recurrence depends on the rate of R0 resection, the stage of the initial disease and the presence of synchronous metastases. Overall survival at 2 years varies between 50% and 70%. The 5-year OS varies between 17% and 42%.

In our series, only one patient among five was alive in complete remission 5 years after treatment of the recurrence. She had a colpectomy for her vaginal recurrence.

For metastatic recurrence, the liver is the most common site of metastatic recurrence for rectal cancer (7%) followed by the lung (5%). Brain and peritoneal metastases are uncommon and are associated with a worse prognosis [24]. In our series, pulmonary progression was the most frequent (6 among 8 cases).

Surgery remains the best treatment for these metastatic relapses with a 5-year OS that can reach 50% after metastasectomy [25]. In our series, only patients operated for their pulmonary metastases were alive and in complete remission.

Several CT protocols are used depending on the patient's condition and the drugs previously used. This CT can be combined with targeted therapies with antiagiogenic (anti-VEGF) or anti-EGFR tumor action.

This study has several strengths: the management of the patients included was fairly uniform, recognizing an expected low degree of variation based on the length of the study period (9 years). Long-term follow-up, with a median duration of 4 years. However, some limitations should be recognized: Because this is a retrospective study, there is a risk of bias in the availability of follow-up data and in the assessment of treatment outcomes. Multicentricity of surgical management was a source of missing data especially regarding clinical and radiological assessment data of response to neoadjuvant therapy. The non-routine practice of MRI in the context of locoregional extension assessment due to the lack of availability of this examination

## Conclusion

The management of locally advanced non-metastatic rectal cancer treated with concurrent RT-CT at our institution resulted in a satisfactory local control rate, while the distant recurrence rate remained high but comparable to published studies. The overall survival was lower than in some published series due to the proportion of patients not operated. An improvement in the management of patients with this type of tumor is necessary. This requires early control of metastatic disease, which is the leading cause of death in rectal cancer. There is currently a growing interest in delivering the full course of planned CT as neoadjuvant rather than adjuvant therapy. This emerging approach called "total neoadjuvant therapy" is being studied in several trials as either induction CT before RT-CT or consolidation CT after RT-CT. These trials have shown a benefit in recurrence-free survival and metastasis-free survival as well as an increase in pCR.

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