Clinics in Oncology

Case Report
Published: 19 Aug, 2021

Clinical Case: Patient with Locally Rectal Cancer in Watch and Wait Program with Perianal Tumor Fistula

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Abstract

The treatment and management of localized rectal cancer has evolved exponentially in recent years. Thanks to improvements in neoadjuvant treatments and the possibility of close follow-up programs with organ preservation (watch and wait) in patients who acquire clinical complete response their quality of life has improved substantially. We present a clinical case of rectal cancer in neoadjuvant treatment complicated with tumor perianal fistula, its management and impact on its follow-up.

Keywords: Rectal cancer; Watch and wait; Total neoadjuvant treatment; Clinical complete response; Perianal istula

Introduction

Colorectal cancer is the third most diagnosed cancer disease worldwide, with an estimated 1.6 million incidence cases in 2018, making it the fourth leading cause of cancer-associated mortality. Of these, 30% are cases of rectal cancer [1]. Localized rectal cancer is a disease of special interest given the multidisciplinary management it requires, especially in locally advanced stages (LARC) (T3/T4 or N+), a clinical entity with an improvement in terms of increased survival rates free of local relapse, but still with important challenges to solve given that about 30% of patients are not cured by having relapses, especially in the form of distant metastases [2].

Standard multidisciplinary management in patients with LARC consists of long-course fluoropyrimidine based chemoradiation therapy (CTRT) or Short-Course Hypofractionated Radiation Therapy (SCRT) followed by total Mesorrectal Excision (MES) surgery and subsequent adjuvant chemotherapy treatment based on combination of oxaliplatin with fluoropyrimidines FOLFOX/CAPOX [3].

There is great heterogeneity of patients diagnosed with LARC, due to differences in relevant clinical or molecular variables. In this sense, there are data from phase II pilot studies with neoadjuvant chemotherapy treatment of LARC guided by the molecular profile of the tumor where it is objective to increase the rates of pathological response, variable with great impact on the prognosis [4]. Also, thanks to advances in neoadjuvant IMRT techniques in the treatment of LARC, it is possible to increase pathological response rates [5].

Total Neoadjuvant Treatment (administering chemotherapy and chemoradiation therapy prior to surgery) (TNT) has been positioned as a therapeutic alternative to standard treatment in patients with LARC with poor prognostic factors. Recently results of clinical trials published RAPIDO and PRODIGE-23 demonstrated an increase in the rate of disease-free survival greater with this approach, being currently considered the new standard treatment in cases of rectal cancer selected [6,7].

On the other hand, treatment with a close follow-up protocol Watch and Wait ("W&W") is currently being imposed each time as an alternative to surgery in selected patients with localized rectal cancer who achieve clinical complete response (cCR), offering the possibility of a rectum preservation strategy without the need to intervention [8]. They are still about 20% to 30% cCR with the conventional strategy of neoadjuvant chemoradiation therapy. Thanks to the new TNT schemes, these percentages are on the rise. In this sense, there are clinical trials underway, as an

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Received Date: *18 Jul 2021*
Accepted Date: *16 Aug 2021*
Published Date: *19 Aug 2021*

Citation:
Muñoz C, Alvarez-Gallego R, Peinado P, Dueñas V, Saugar ES, Caruso R, et al. Clinical Case: Patient with Locally Rectal Cancer in Watch and Wait Program with Perianal Tumor Fistula. Clin Oncol. 2021; 6: 1847.

ISSN: 2474-1663

example, a multicenter phase II study with 30 patients of localized rectal cancer with a single branch of treatment: TNT with Nal-IRI, 5.FU, Oxaliplatin x 8 cycles followed by conventional chemoradiation therapy and subsequent reassessment at 10 to 12 weeks, whose primary objective is the % rate of cCR obtained (pending results) [9].

Complications in the treatment of LARC, such as tumor perianal fistula, are not common [10], but can have a negative impact on the development of treatment and therefore a negative impact on the cure and survival rates of patients. The management of these cases is not well established due to the few cases published in the literature [11].

We report a clinical case of LARC managed with TNT treatment and W&W strategy, with complication of tumor perianal fistula and its management.

Case Presentation

Male of 57 years of age, without relevant medical history, as a result of hematochia in rectal examination (DRE) is palpated indurated mass in upper anal canal, being diagnosed in colonoscopy of September 10th, 2019 of distal rectum neoplasia in contact with the internal portion of the anal canal, which occupied 70% unobstructed canal, with first biopsy result tubular adenoma with high-grade dysplasia.

Pelvic MRI usual sequences were performed on October 09th, 2019 with data confirming mass in distal rectum of rectoanal junction without solution of continuity with it, with data of invasion of the mesorectal fat, and of the muscles of the elevator of the anus on the left and posterior side and locoregional pathological adenopathies cT4N1 (Figure 1). In low digestive echo endoscopy of November 8th, 2019, endoscopic stage uT4N1 was confirmed due to involvement of the upper anal canal without separation plane of the internal anal sphincter (Figure 2). Body CT and PET CT scans of October 02nd, 2019 and October 18th, 2019 ruled out distant metastatic disease, with 2 liver angiomas confirmed in hepatic MRI on October 23rd, 2019.

In second colonoscopy performed on October 25th, 2019, a second biopsy was taken: Moderately differentiated adenocarcinoma was confirmed in pathological report.

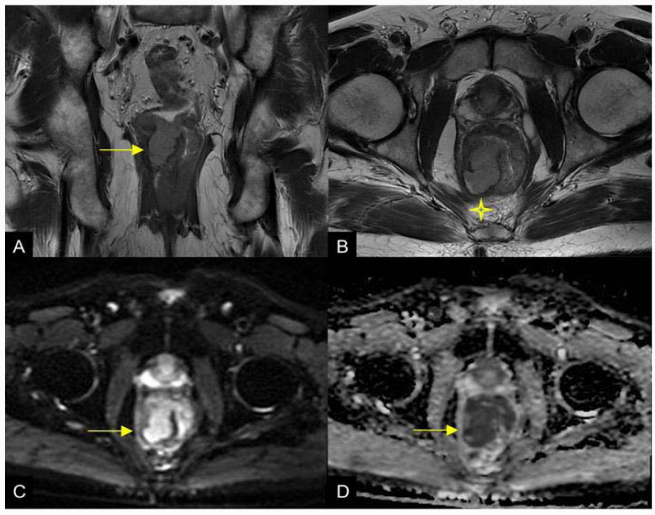

Figure 1: RM to diagnosis. Extensive circumferential tumor in the lower rectum-upper anal canal, with infiltration of the anal sphincter in the right posterolateral hemicircumference (star), well delimited in the morphological sequences TSE T2 (A, B) and with frank restriction in the diffusion sequence (C, D).

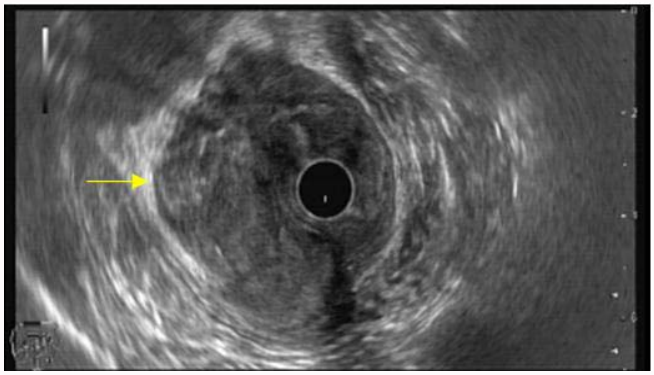

Figure 2: Low digestive echo endoscopy image at diagnosis.

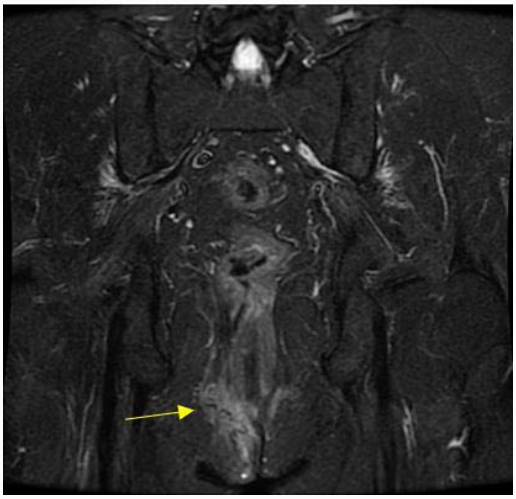

Figure 3: Linear collection of 18 mm × 13 mm × 4 mm located below the right pelvic floor and invading the right pararectal fat and the right gluteal subcutaneous cellular tissue, is regular anfractuous and with hyperintense central area T2, with millimeter enhancement and abscess criteria.

Molecular study confirms MSS, NTRK negative in immunohistochemical study, with NGS panel mutations in TP53, PIK3CA and PTEN genes. KRAS/NRAS/BRAF was WT.

With diagnosis of lower rectum adenocarcinoma G2 cT4N1M0 MSS RAS WT, the patient was offered to participate in clinical study protocol number HM-RE-2017-01 (NCT04009876), (TNT treatment Nal-IRI + 5FU + oxaliplatin x 8 cycles followed by conventional chemoradiation therapy and subsequent assessment to assess whether cCR is obtained and offer organ preservation strategy (W&W)). After resolving doubts, the patient signed informed consent and started chemotherapy cycle 1 on November 14th, 2019.

After the first cycle he was admitted from November 26th, 2019 to December 03rd, 2019 due to febrile syndrome due to perineal abscess. Pelvic MRI was performed on December 02nd, 2019 with findings of linear collection of 18 mm × 13 mm × 4 mm located below the right pelvic quadrant and invading the right pararectal fat and the right gluteal subcutaneous cellular tissue, anfractuous and with hyperintense central area T2, with millimeter enhancement and abscess criteria. There is a junction path with the lowest area of the tumor lesion so it would be an abscessed fistulous path (Figure 3).

As for the aspects derived from the primary tumor and with respect to the previous study, it is objective tumor reduction in more

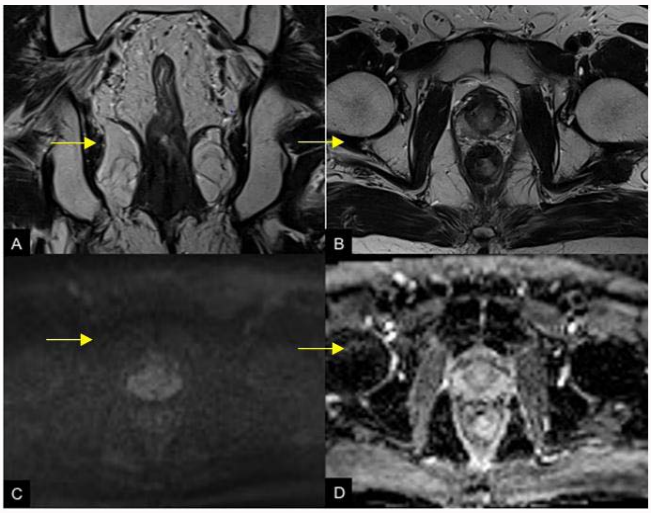

Figure 4: RM post-treatment. Radiological signs of complete response both in the morphological sequences TSE T2 (A,B), with marked hyposignal of the wall of the rectum-anal canal indicative of fibrosis and absence of foci of restriction in the diffusion sequence (C,D).

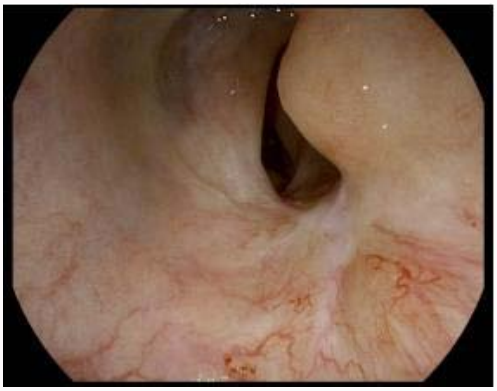

Figure 5: Post-treatment rectoscopy image, where scar lesion in the distal rectum, at 3 cm of anal margin, without signs of recurrence, data of complete endoscopic response of rectal neoplasia is observed.

than 80% of the volume of the rectal tumor mass.

After discussing the clinical case in a multidisciplinary gastrointestinal tumors committee, it was decided to perform discharge colostomy.

Surgery was performed on December 10th, 2019 with discharge on December 13th, 2019: Given the excellent tumor response and resolution of the infectious picture, it continues within the clinical trial, resumes cycle 2 chemotherapy on January 08th, 2020. The patient completed the 8 cycles of neoadjuvant chemotherapy treatment, with good tolerance.

He subsequently completed neoadjuvant treatment with CTRT therapy from April 17th to May 22nd, 2020: Oral Capecitabine 825 mg/m^2 BID Monday through Friday + IMRT: The dose administered to PTV1 was 46 Gy in 23 fractions of 2 Gy, and to PTV2 has been 57.5 Gy in 23 fractions of 2.55 Gy.

At 11 weeks after the end of radiotherapy, the patient came to review in August 2020 with results of complementary tests compatible with cCR data: DRE without tumor, pelvis MRI performed on August 17th, 2020 with absence of macroscopically visible tumor, with negative diffusion sequences (Figure 4); colonoscopy August 18th, 2020 with scar lesion in distal rectum, at 3 cm of anal margin, no signs of recurrence, endoscopic complete response data of rectal neoplasia. Furthermore, biopsy was taken without evidence of malignancy (Figure 5). TAP CT and tumor markers were between normal limits.

Given the cCR and resolution of the infectious complication, reconstruction of the digestive transit was performed on October 29th, 2020.

The patient started the W&W close surveillance protocol, with a final reassessment in June 2021 with no recurrence findings and remaining in cCR today.

Discussion

LARC is a heterogeneous disease, where clinical variables (distance to the anal margin, stage TNM; involvement of the circumferential resection margin, presence of Extramural Venous Invasion (EMVI)) as well as genotypic variables (MSI-H, BRAF status) play a fundamental role in the patient's prognosis. Performing TNT with either Long Course Chemoradiotherapy (LCRT) *vs.* Short-Course Hypofractionated Radiotherapy (SCRT) is critical both to prevent locoregional relapses and to decrease systemic relapse rates (around 8% to 10% of disease frees survival at 3 years). In addition, it helps to increase cCR rates and to be able to select patients with rectal cancer who, without the need for surgery, can have optimal oncological results, with the consequent gain in quality of life. Thanks to the better selection of patients, W&W protocols are increasingly being incorporated into the routine activity of more cancer centers. On the other hand, it remains to define more homogeneous selection strategies, validated in randomized clinical trials and reproducible in different ones. The best neoadjuvant treatment scheme (Induction or consolidation) is not yet defined whether it should be adapted according to the initial clinical stage, how often the optimal follow-up should be carried out [12], etc.

In addition, improvements should be implemented to select patients with cCR for W&W strategy, given that there are about 20% of local recurrences and a sustained risk of distant metastasis persists. One option would be to include the quantification and monitoring of circulating tumor DNA (ctDNA), a technique that has already demonstrated great potential in the detection of Minimal Residual Disease (MRD) [13].

The associated complications such as fistulas/tumor perianal abscess in the context of tumor response, pose a challenge to decide how to complete the neoadjuvant treatment, they can even precipitate changes in the therapeutic strategy of the patient, considering the possible immunosuppression that can produce systemic treatments favoring the risk of infections and the difficulty of scaring of tissues in the course of radiotherapy.

In the clinical case mentioned, we are especially struck by the intense decrease in tumor volume after the first administration of chemotherapy, a fact that could be conditioning the appearance of the fistulous path in the tumor area of the patient or have previous perianal pathology concealed by the tumor that is unmasked.

Despite the limited published evidence, the importance of completing TNT treatment in selected cases of LARC with high risk of relapse such as this case, despite intercurrent complications, impacts on cCR rates, helping to increase progression-free survival

and cure rate. Therefore, conventional surgical treatments of perianal pathology of benign etiology in the context of oncological disease such as LARC should be discussed in multidisciplinary GI committees in order to maximize the possibilities of completing cancer treatment.

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