Total Neoadjuvant Therapy in Locally Advanced Rectal Cancer: A New Approach

Tratamento Neoadjuvante Total no Cancro do Reto Localmente Avançado: Uma Nova Abordagem

Ana João Pissarra[1], Joana Luís[1], Daniela Macedo[1], Pedro Chinita[2], Nuno Figueiredo[3]

***Corresponding Author**/Autor Correspondente
Ana João Pissarra [anajoaopissarra@gmail.com]
Hospital Lusíadas Lisboa, Rua Abílio Mendes 12, 1500-458 Lisboa, Portugal
ORCID iD: https://orcid.org/0000-0001-5649-4271

https://doi.org/10.48687/lsj.186

Abstract

Locally advanced rectal cancer (LARC) is a relatively common disease, with a poor prognosis because of its high metastatic potential. Gold standard in the treatment for LARC includes concurrent chemoradiotherapy (CRT) followed by surgery and adjuvant chemotherapy. An alternative strategy known as total neoadjuvant therapy (TNT) involves administration of CRT plus neoadjuvant chemotherapy before surgery with the goal of delivering uninterrupted systemic therapy to eradicate micrometastasis. Recent data suggests that TNT delivers superior rates of pathologic complete responses with similar disease-free and overall survival, compared to standard approach. Additionally, it may allow an increased number of patients entering organ preservation programs. In light of a clinical case, the authors review this controversial but very contemporary issue.

Keywords: Neoadjuvant Therapy; Neoplasm Staging; Rectal Neoplasms/therapy; Watchful Waiting

Resumo

O cancro do reto localmente avançado (LARC) é uma doença relativamente comum, com um mau prognóstico dado o seu elevado potencial metastático. O tratamento *gold standard* para o LARC inclui quimiorradioterapia (QRT) seguida de cirurgia e quimioterapia adjuvante. Uma estratégia alternativa designada de tratamento neoadjuvante total (TNT) consiste na administração de QRT seguido de quimioterapia neoadjuvante antes da cirurgia, com o objetivo de dar a terapêutica sistémica de forma ininterrupta para irradicar possíveis micrometastases. Dados recentes sugerem que a estratégia TNT oferece taxas de respostas patológicas completas superiores, com sobrevida livre de doença e sobrevida global semelhante, em comparação com a abordagem padrão. Além disso, pode permitir que um número maior de doentes entre em programas de preservação de órgão. À luz de um caso clínico, os autores revêm esta questão controversa, mas muito contemporânea.

Palavras-chave: Conduta Expectante; Estadiamento de Neoplasias; Neoplasias do Reto/tratamento; Tratamento Neoadjuvante

1. Centro de Oncologia, Hospital Lusíadas Lisboa, Lusíadas Saúde, Lisboa, Portugal **2.** Serviço de Radioncologia, Hospital Lusíadas Amadora, Lusíadas Saúde, Amadora, Portugal **3.** Serviço de Cirurgia, Hospital Lusíadas Lisboa, Lusíadas Saúde, Lisboa, Portugal

Recebido/Received: 15/11/2023 **– Aceite/Accepted:** 07/12/2023 **– Publicado online/Published online:** 29/12/2023 **Publicado / Published:** 29/12/2023

Introduction

The authors present the case of a male patient, 66 years old, presented with a 3-month history of rectal bleeding, in which the colonoscopy revealed a rectal adenocarcinoma at 3cm from the ano-rectal ring.

Local staging with high-resolution, multiparametric, pelvic magnetic resonance imaging (MRI) confirmed the lesion of the lower rectum, with irregular parietal thickening involving the anterior and right half of the rectal circumference, focal loss of muscle layer hyposignal, mesorectal fascia, peritoneal reflection or anal sphincter were clear and several small but suspicious nodes in the mesorectum - mrT3aN+. Computed tomography of thorax-abdomen-pelvis did not show distant disease and carcinoembryonic antigen (CEA) and carbohydrate antigen (Ca19.9) were within the normal range.

The patient was discussed at a colorectal cancer multidisciplinary team meeting and was decided total neoadjuvant therapy (TNT) followed by reassessment of tumor response. He initiated chemoradiotherapy (CRT) with capecitabine and completed 54 Gy of radiotherapy (RT) in 30 fractions, followed by consolidation chemotherapy (CT) with CAPOX (capecitabine and oxaliplatin) for 6 cycles. At 8 weeks after CRT, a re-staging with pelvic MRI, digital rectal examination and flexible rectosigmoidoscopy demonstrated a white scar with telangiectasia, no palpable nodules and radiological evidence of tumor regression grade (mrTRG) 1/2. After a shared-decision process the patient understood the risks and benefits of his condition – clinical complete response – and agreed to enter a non-operative management pathway.

The patient is symptom-free, with no evidence of local or distant disease and under a Watch & Wait (W&W) surveillance protocol at 22 months after treatment.

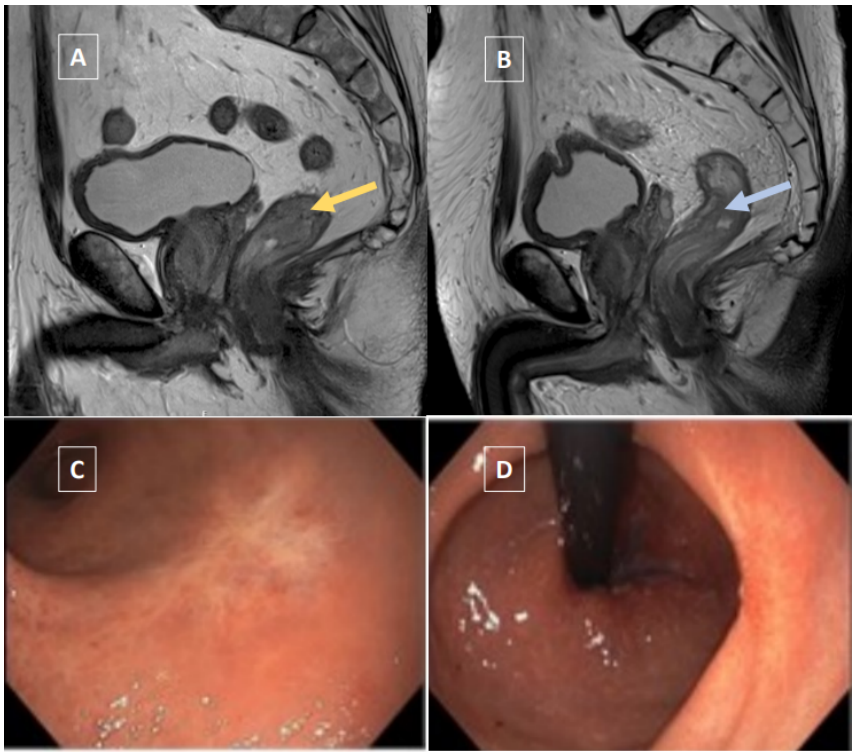

Figure 1. A) Sagittal image of pre-treatment pelvic MRI (low rectal cancer – yellow arrow); B) Sagittal image of post-treatment pelvic MRI (hypointensity fibrotic scar at the tumor site – blue arrow); C) Endoscopic image of the white scar with telangiectasia, at the tumor location; D) Endoscopic image of the scar in retroflexion

Discussion

Colorectal cancer remains a deadly disease, is the second cause of cancer-related deaths worldwide and accounts for 10% of all cancer types.[1]

For patients with locally advanced rectal cancer (LARC), multimodal treatment consisting of neoadjuvant CRT followed by total mesorectal excision (TME) surgery and adjuvant computed tomography (CT) has been the standard of care for many years.[2] In recent years, this paradigm has been challenged, as local control is no longer an issue (with local recurrences <5%) but distant disease rates remain high (29% - 39%).[3]

Doubts have been raised of the effective benefit of adjuvant chemotherapy, after CRT and good-quality TME surgery.[4] Despite the guidelines recommendations that TME should be

followed by adjuvant treatment, less than 50% of eligible patients receive their scheduled adjuvant chemotherapy due to treatment compliance, post operative complications and delays.[5]

TNT, a therapeutic strategy that incorporates CT with CRT prior to surgery, is now recognized by many centers as the preferred standard for the treatment of LARC.[6] Using this approach, multiagent CT and RT, are administered before surgical resection or the decision on nonoperative management.

Accumulating evidence shows that TNT prevent the onset of micrometastasis, reduce distant metastasis via systemic CT and improve survival. TNT has also been associated with better compliance, a decrease in toxicity, a reduced need of ileostomy and its duration, and increased rates of complete clinical response (cCR).[7] These patients may enter an organ preservation strategy, namely W&W or even local excision after downstaging, in order to improve quality of life (QoL) low anterior resection syndrome (LARS), urinary and sexual dysfunctions.[8,9]

TNT is a promising treatment for LARC and has been explored in previous single-arm trials, and recently in randomized controlled trials evaluated different TNT strategies compared with standard CRT therapy, in terms of CRT and CT sequencing, systemic chemotherapy, and radiotherapy modality. There are two important recent phase 3 trials that investigated the usefulness of TNT for LARC.

The RAPIDO trial that compared 25 Gy of RT followed by 18 weeks of CT with CAPOX/FOLFOX versus 50 or 50.4 Gy of conventional long-course CRT (LC-CRT), which enrolled high-risk patients with T4, N2, EMVI, positive MRF involvements, or positive lateral nodes. The primary endpoint was 3-year disease--related failure, which reached significance at 23.7% versus 30.4% ($p = 0.019$) as well as pCR.[10] In five-year follow-up of the RAPIDO trial, 12% of locoregional failure (LRF) was detected in experimental arm versus 8% in standard arm (p=0.07).[11]

The PRODIGE 23 trial compared 12 weeks of CT with mFOLFOX-IRI followed by 50 Gy of RT and 12 weeks of CT with FOLFOX/capecitabine at adjuvant setting versus 50 Gy of LC-CRT followed by 24 weeks of FOLFOX or capecitabine at adjuvant setting. The primary endpoint was 3-year disease-free survival (DFS), which had a statistically significant difference at 75.7% vs 68.5% (p = 0.034).[12] The 7-year follow-up confirmed the benefit in survival endpoints with DFS 62.5% vs 67.6% and overall survival 76.1% vs 81.9% in standard arm versus experimental arm respectively.[13]

However, many critical limitations were raised in PRODIGE 23, that could hamper the interpretation of its exceptional long--term oncological outcomes, as the trial's population correlates poorly with our real-world cohort of patients: young population (less than 13% were >70 years); not so locally advanced disease (only 13% of cT4 and 27% of MRF involved patients were included); and there were no data related to EMVI positivity or lateral pelvic side-wall lymph node involvement.[14]

Both trials showed benefits over standard neoadjuvant therapy, but the inclusion criteria, the chemotherapy drugs, dosages and the radiation fractionation were very diverse. Therefore, direct comparison between these studies is challenging. These outcomes demonstrated that TNT is a promising strategy with superior rate of pCR and DFS compared with standard treatments such as LC-CRT and adjuvant CT.

In TNT strategy, the question remains of which is the better option between induction or consolidation CT. CAO/ARO/AIO-12 trial is a phase 2 trial of CRT plus induction or consolidation CT as TNT for LARC. Patients were assigned to received induction CT using 3 cycles of mFOLFOX6 before fluorouracil/oxaliplatin CRT (50.4 Gy) or for consolidation CT after CRT. The primary endpoint was pCR rate, and the secondary endpoints were DFS and toxicity. The results showed a higher pCR in the consolidation group (25% vs 17%). In contrast, no differences in long-term outcomes and chronic toxicity or QoL were observed between consolidation CT and induction CT.[15]

Nowadays, organ preservation strategies (namely W&W and Local Excision after TNT) are burning issues in the research field of LARC, trying to avoid operative morbidity, fecal incontinence / definitive colostomies and sexual & urinary dysfunction.

The OPRA trial, a recent trial that incorporates W&W, was a prospective, randomized phase 2 trial that tested the hypothesis of a rectum-preserving treatment approach for locally advanced rectal cancer could achieve similar oncological outcomes to those of standard resection-based treatment. Primary end-point was DFS, and the probability of achieving clinical complete response (cCR) or near-cCR (ncCR), and therefore the likelihood of avoiding TME, according to the sequence of administration of systemic CT and CRT in the two TNT arms was examined as a secondary end point. Patients were eligible for enrollment if they had confirmed clinical stage II ou III adenocarcinoma of the rectum and was treated with induction CT followed by LC-CRT or LC-CRT followed by consolidation CT and either TME or W&W on the basis of tumor response. Salvage TME was recommended during W&W for patients who experienced tumor regrowth. The outcomes demonstrated that DFS was not different between two groups (76% vs 76%). The 3-year TME-free survival was 41% and 53%, indicating that consolidation CT is better when aimed at the WW approach than induction chemotherapy.[16]

Ongoing trials with circulating tumor DNA (ctDNA), are trying to identify biomarkers to predict response to neoadjuvant therapy, improving patient selection for a non-surgical, active surveillance approach. The ctDNA can be detected in about 75% of patients with LARC at the baseline and in about 15%–20% of patients in the post-neoadjuvant, or postoperative setting. ctDNA clearance rate after delivering neoadjuvant CRT, or integrating baseline ctDNA with other conventional markers of clinical response can be a promising marker to select and monitor patients on the WW approach.[17]

In addition to CT and CRT, some trials try to investigate the role of other therapies like target therapies and immunotherapy in the neoadjuvant setting of LARC. The molecular target agents like anti-EGFR or anti-VEGF did not show benefit in response or survival when associated with CT.[18] In relation to immunotherapy, mismatch repair-deficient (dMMR) colorectal cancer is responsive to programmed death 1 (PD-1) blockade in the context of metastatic disease, and checkpoint blockade could be effective in dMMR LARC.[19] A phase 2 trial in patients with stage II or III rectal cancer demonstrated higher rate of major pathological response or pCR after sequentially combined CRT, 5 cycles of nivolumab, and radical surgery.[20] About 9% of rectal cancer was diagnosed as dMMR, and those patients would dramatically change their treatment strategies with immunotherapy.

Multiple ongoing, and future trials, may assist the clinical decision of which modality treatment could benefit the individual patient thus minimizing morbidity from futile treatments while improving survival and preserving the QoL of our patients.

Conclusion

TNT is a therapeutic strategy that deliver full dose of CT and RT with good compliance, and has the potential to reduce the risk of micrometastasis, overall recurrence and improve the survival in LARC. Because of decreased QoL after TME, organ preservation and W&W approach must be evaluated. Due to expect high pCR, TNT with CRT followed by consolidation CT seems to be the best strategy. Additionally, selected patients have great advantage by using anti-PD-1 monoclonal antibody, and in the future the use of ctDNA will help us to decide the better approach.

In conclusion, patients with clinically advanced disease should be presented in multidisciplinary tumour boards for multimodality care with medical oncology, radiation oncology, surgery, gastroenterology, radiology and pathology input.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship.

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Patient Consent: Consent for publication was obtained.

Provenance and Peer Review: Commissioned; without external peer review

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Consentimento: Consentimento do doente para publicação obtido.

Proveniência e Revisão por pares: Comissionado; sem revisão externa por pares.

Contributorship Statement

AJP, JL, DM, PC and NF: Drafting and review of article
All authors approved the final version.

Declaração de Contribuição

AJP, JL, DM, PC e NF: Redação e revisão do artigo
Todos os autores aprovaram a versão final.

References

1. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71:209-49. doi: 10.3322/caac.21660.
2. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rodel C, Cervantes A, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28: iv22–iv40. doi:10.1093/annonc/mdx224
3. Bosset JF, Calais G, Mineur L, Maingon P, Stojanovic-Rundic S, Bensadoun RJ, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol. 2014;15:184-90. doi: 10.1016/S1470-2045(13)70599-0.
4. Breugom A, Swets M, Bosset JF, Collette L, Sainato A, Cionini L, et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. Lancet Oncol. 2015;16:200-7. doi: 10.1016/S1470--2045(14)71199-4.
5. Rodel C, Liersch T, Becker H, Fiektau R, Hohenberger W, Hothorn T, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: Initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol. 2012; 13: 679–87. doi: 10.1016/S1470--2045(12)70187-0.
6. National Comprehensive Cancer Network: Clinical Practice Guidelines in Oncology: Rectal Cancer. Version 5.2023 [accessed Jan 2022] Available at: https://fascrs.org/news/nccn-new-rectal-cancer-guideline-important--points
7. Petrelli F, Trevisan F, Cabiddu M, Sgroi G, Bruschieri L, Rausa E et al. Total neoadjuvant therapy in rectal cancer: A systematic review and

meta-analysis of treatment outcomes. Ann Surg. 2020; 271: 440–8. doi: 10.1097/SLA.0000000000003471.

8. Calmels M, Labiad C, Lelong B, Lefevre J H, Tuech JJ, Benoist S et al. Local excision after neoadjuvant chemoradiotherapy for mid and low rectal cancer: a multicentric French study from the GRECCAR group. Coloretal Dis. 2023;25:1973-80. doi: 10.1111/codi.16742
9. Contin P, Kulu Y, Bruckner T, Sturm M, Welsch T, Muller-Stich BP, et al. Comparative analysis of late functional outcome following preoperative radiation therapy or chemoradiotherapy and surgery or surgery alone in rectal cancer. Int J Coloretal Dis. 2014;29:165-75. doi: 10.1007/s00384-013--1780-z.
10. Bahadoer RR, Dijkstra EA, van Etten B, Marijnen C, Putter H, Kranenbarg E, et al. RAPIDO collaborative investigators. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open--label, phase 3 trial. Lancet Oncol. 2021;22: 29-42. doi: 10.1016/S1470--2045(20)30555-6.
11. Dijkstra E, Nilsson P, Hospers G, Bahadoer R, Kranenbarg E, Roodvoets A et al. Locoregional failure during and after short-course radiotherapy followed by Chemotherapy and surgery compared with long-course chemoradiotherapy and surgery: a 5-year follow-up of the RAPIDO Trial. Ann Surg. 2023;278:e766-72. doi: 10.1097/SLA.0000000000005799.
12. Conroy T, Bosset JF, Etienne PL, Rio E, François E, Mesgouez-Nebout N, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER--PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2021; 22: 702-15. doi: 10.1016/S1470-2045(21)00079-6.
13. Conroy T, Etienne PL, Rio E, François E, Mesgouez-Nebout N, Bosset JF, et al. Total neoadjuvant therapy with mFOLFIRINOX versus preoperative chemoradiation in patients with locally advanced rectal cancer: 7-year results of PRODIGE 23 phase III trial, a UNICANCER GI trial. J Clin Oncol. 2023;41:LBA3504. doi:10.1200/JCO.2020.38.15_suppl.4007
14. Giunta E F, Bregni G, Pretta A, Deleporte A, Liberale G, Bali A M, et al. Total neoadjuvant therapy for rectal cancer: Making sense of the results from the RAPIDO and PRODIGE 23 trials. Cancer Treat Rev. 2021 May:96:102177. doi: 10.1016/j.ctrv.2021.102177.
15. Fokas E, Schlenska-Lange A, Polat B, Klautke G, Grabnbauer G, Fietkau R, et al. Chemoradiotherapy plus induction or consolidation chemotherapy as total neoadjuvant therapy for patients with locally advanced rectal cancer: long-term results of the CAO/ARO/AIO-12 randomized clinical trial. JAMA Oncol. 2022; 8: e215445. doi: 10.1001/jamaoncol.2021.5445.
16. Garcia-Aguilar J, Patil S, Gollub MJ, Kim J, Yuval J, Thompson H, et al. Organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy. J Clin Oncol. 2022; 40: 2546-56. doi: 10.1200/JCO.22.00032.
17. Pezeshki PS, Ghalehtaki R. The clinical application of ctDNA to predict response to neoadjuvant chemoradiotherapy in patients with locally--advanced rectal cancer. Biomark Res. 2023;11:81. doi: 10.1186/s40364--023-00521-5.
18. Beppu N, Ikeda M, Kataoka K, Kimura K, Ikeuchi H, Uchino M, et al. Total Neoadjuvant Chemotherapy in Rectal Cancer: Current Facts and Future Strategies. J Anus Rectum Colon. 2023; 7: 1–7. doi: 10.23922/jarc.2022-060.
19. Cercek A, Lumish M, Sinopoli J, Weiss J, Shia J, Lamendola-Essel M, et al. PD-1 blockade in mismatch repair-deficient, locally advanced rectal cancer. N Engl J Med. 2022; 386: 2363-76. doi: 10.1056/NEJMoa2201445.
20. Bando H, Tsukada Y, Inamori K, Togashi Y, Koyama S, Kotani D, et al. Preoperative chemoradiotherapy plus nivolumab before surgery in patients with microsatellite stable and microsatellite instability-high locally advanced rectal cancer. Clin Cancer Res. 2022; 28: 1136-46. doi: 10.1158/1078-0432.CCR-21-3213.