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EDITORIAL

Neoadjuvant treatment of rectal cancer: Where we are and where we are going

Elísabet González Del Portillo, Felipe Couñago, Fernando López-Campos

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Abstract

Locally advanced rectal cancer requires a multidisciplinary approach based on total neoadjuvant treatment with radiotherapy (RT) and chemotherapy (ChT), followed by deferred surgery. Currently, alternatives to the standard total neoadjuvant therapy (TNT) are being explored, such as new ChT regimens or the introduction of immunotherapy. With standard TNT, up to a third of patients may achieve a complete pathological response (CPR), potentially avoiding surgery. However, as of now, we lack predictive markers of response that would allow us to define criteria for a conservative organ strategy. The presence of mutations, genes, or new imaging tests is helping to define these criteria. An example of this is the diffusion coefficient in the diffusion-weighted sequence of magnetic resonance imaging and the integration of this imaging technique into RT treatment. This allows for the monitoring of the evolution of this coefficient over successive RT sessions, helping to determine which patients will achieve CPR or those who may require intensification of neoadjuvant therapy.

Key Words: Locally advanced rectal cancer; Total neoadyuvant treatment; Radiotherapy; Biomarker; Magnetic resonance imaging; Conservative organ strategy; Watch and wait

Core Tip: The treatment of rectal cancer is well-established, based on total neoadjuvant treatment followed by deferred surgery. However, the development of biomarkers is necessary to predict which patients will achieve a complete pathological response and, therefore, may not require surgical treatment. The advent of new imaging techniques and their morphological, metabolic, and functional information pave the way for defining criteria for patients with locally advanced rectal cancer who are candidates for a conservative strategy.

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INTRODUCTION

Colorectal cancer is the third most common worldwide, accounting for 10% of all diagnosed cancers and standing as the second leading cause of cancer-related deaths globally[1]. Currently, the management of patients with locally advanced rectal cancer (LARC) requires a multidisciplinary approach integrating various treatment modalities such as concurrent and/or sequential neoadjuvant radiotherapy (RT) and chemotherapy (ChT), followed by surgery[2-7].

NEOADJUVANT TREATMENT

The intensification of neoadjuvant treatment, known as total neoadjuvant therapy (TNT), is considered the standard of care for LARC.

TNT is based on ChT and RT. There are two modalities of RT: The short-course and the long-course. Regarding computed tomography (CT), different systemic treatment regimens are being considered[8].

TNT improves compliance rates for ChT treatment compared to adjuvant ChT, with rates of complete pathological responses (CPR) ranging between 10%-30%, depending on the regimen used[2,7,9-13]. Two meta-analyses in recent years have supported that treatment intensification of neoadjuvant TNT therapy in LARC achieved higher CPR rates. One of them is that of Petrelli *et al*[14], that after review of multiple papers and nearly 3000 patients treated with TNT reported CPR rates of 22.4% (95%CI 19.4%-25.7%), concluding that intensification of neoadjuvant LARC treatment achieves higher CPR rates. On the other hand, the meta-analysis by Liu *et al*[15] analyzed the outcome in more than 2000 patients and also concluded that CPR rates were significantly improved with TNT with respect to the standard scheme in LARC. In addition, the CPR variable is considered a prognostic factor that acts as a predictor of local recurrence[3,16,17], possibly impacting overall survival, disease-free survival, and the risk of distant metastasis[15]. Additionally, the interval between RT and surgery becomes crucial in the CPR rates[4,18-20], as indicated by data from the OPRA7 trial[21].

Beyond the combination of RT and ChT in TNT, there is currently debate opening up to consider neoadjuvant monotherapy with ChT or immunotherapy. In this line, the PROSPECT study (NCT01515787) was focused[22]. It compared one arm with the standard treatment of RT and CT against intensified monotherapy CT (FOLFOX). They demonstrated similar short-term oncologic outcomes (disease-free survival, overall survival, and local recurrence). However, they did not conclude that RT could be omitted due to the significantly higher rate of side effects in the experimental arm compared to the standard treatment.

On the other hand, the characterization of the immunological microenvironment tumour may help in the development of new strategies based on immunotherapy. In this regard, tumours with loss of mismatch repair (MMR) protein expression show elevated therapeutic response to PD-1/PD-L1 inhibitors. Nevertheless, those tumours only represent 5%-15% of all colorectal cancers. Although there are no specific publications on rectal cancer, we already have some data on colon cancer, such as the preliminary NICHE study. This study included patients with dMMR or pMMR colon cancers received a single dose of ipilimumab and two doses of nivolumab before surgery, the pMMR group with or without celecoxib. This treatment was safe and feasible, without compromising surgery. Their results showed 100% and 27% pathological response in dMMR and pMMR tumors, respectively[23].

In any case, in the management of LARC, there is a growing interest in the conservative Watch and Wait (WW) strategy, initially proposed by the Habr-Gama *et al*[24] over 20 years ago. The goal is to avoid surgical treatment in selected patients who achieve a complete clinical response after neoadjuvant treatment, opting for close monitoring. The results show survival outcomes similar to those surgically treated with CPR[17,24-27]. Data confirmed in subsequent publications do not show statistically significant differences in terms of local control and overall survival between both treatment approaches. However, differences are observed in quality of life, especially in the physical and cognitive spheres[28], especially in elderly patients and/or those with comorbidities[2,3,7,11] in favour of the conservative strategy However, despite the reported data, prospective studies are still necessary to optimize the management of patients with a WW strategy[7,29-32]. This includes appropriate patient selection, standardization of follow-up strategies, and primarily the identification of applicable biomarkers in clinical practice to help predict which patients would achieve CPR[33]. In this regard, morphofunctional and metabolic imaging, radiomics, and artificial intelligence emerge as elements that open a disruptive and novel research field to define predictive factors for response to RT and ChT treatment.

Some of the biomarkers explored to date include the presence of mutations to assess the response to specific treatments, as mentioned earlier. Additionally, there are groups that have explored the expression of miRNA and found a relationship with resistance to RT[34]. Other studies have examined the expression of specific genes and established a prognostic risk score model to predict the response to ChT[35]. The role of the microbiota has also been analyzed in neoadjuvant treatment response, and the presence of certain bacteria has been associated with a poorer response to treatment[36].

Another area that has been explored as a biomarker is magnetic resonance imaging (MRI). Diffusion-weighted imaging (DWI) sequences characterize the microenvironment and tumour tissues based on the movements of water molecules as a surrogate for the density of the tumour environment, quantified by the apparent diffusion coefficient (ADC). The ADC is inversely proportional to tissue cellularity and has proven capable of distinguishing between tumour recurrence or persistence and inflammation or necrosis with a high level of specificity[2,3,6,37-42].

Several studies propose ADC as a biomarker for CPR in LARC[2,3,9,42-46]. However, to date, there is no well-established relationship between the evolution of this marker and the histopathological response of the surgical specimen. Lambregts *et al*[47] analysed the value of the DWI sequence of MRI in the reevaluation after neoadjuvant treatment to detect patients with a complete response, demonstrating an increase in sensitivity to 52%-64% and a specificity exceeding 90% when adding DWI. This reduced the risk of underestimating residual tumour to below 10%, and these findings were subsequently confirmed[48]. Recently, Azamat *et al*[49] analyzed the response of tumour lesions in patients with LARC after neoadjuvant treatment using the T2 sequence and ADC value by performing an MRI before and after treatment. They concluded that the T2 sequence varied according to whether the response was complete or partial or there was no response, and there is a cut off value of ADC that can be used as a marker for complete response.

A step further has been taken with magnetic resonance-guided RT (MRgRT), allowing for information from morpho-functional imaging and ADC to be obtained throughout successive RT sessions[6]. Cusumano *et al*[50] analyzed data from patients with LARC treated with neoadjuvant MRgRT followed by surgery, studying the early regression index (ERITCP) and correlating it with the rate of pathological responses. They demonstrated that it is a good predictive marker in these patients treated with MRgRT. They obtained combined information on the tumor volume in MRI images at the time of RT treatment planning and the same volume during MRgRT treatment. Moreover, studies suggest that the ADC measured before, during, and after treatment may be useful in predicting pathological response before surgery in LARC, surpassing other classic parameters such as tumor size[2,3]. It positions itself as a potential predictive factor for response in patients undergoing long courses of RT with concurrent CT. In this regard, we will have to await data from ongoing studies like TRIGGER, which will allow us to validate the Magnetic Resonance Tumour Regression Grade as a response marker in the management of LARC with the aim of avoiding surgery, maintaining quality of life in appropriately selected patients without impacting survival rates[13].

CONCLUSION

Taking all of the above into account, we know that the standard TNT has excellent results, but recently, doors have been opened to consider variants based on each patient's characteristics. Predicting the response to TNT remains a challenge. Identifying biomarkers for neoadjuvant treatment response will allow us to determine which patients can safely enter a WW strategy and which patients require an intensification of the treatment.

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