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Editorial

The Controversy of Neoadjuvant Therapy in Rectal Cancer[☆]



Controversia en neoadyuvancia y cáncer de recto

Rectal cancer accounts for approximately 35% of all colorectal cancers. In patients with localized rectal cancer, neoadjuvant treatments (prior to surgery) with short radiotherapy (5×5) or chemoradiotherapy (CHT-RDT) with fluoro-pyrimidines are considered standard treatment.^{1,2} When accompanied by total mesorectal excision, these 2 treatment options significantly reduce local recurrence rate, which is below 5%. The 2 strategies have recently been compared, and similar efficacy was found in terms of local and systemic control of the disease.³ Despite this, 30% of operated patients presented recurrence of their disease, mainly at a distance. Different groups, including ours, have associated the post-CHT-RDT pathological response with a risk of 3-year and 5-year recurrence.^{4,5}

In order to reduce the risk of distant progression, several studies have evaluated the benefit of adjuvant chemotherapy after CHT-RDT. With the exception of the ADORE⁶ randomized phase II study, the remaining studies demonstrated a benefit of adjuvant chemotherapy in 3-year disease-free survival (DFS) (with oxaliplatin-fluoro-pyrimidines versus fluoro-pyrimidines,^{7,8} oxaliplatin-fluoro-pyrimidines versus placebo⁹ or fluoro-pyrimidines versus placebo^{10,11}) at less than 5%. Recently, Carvalho and Glynne-Jones have suggested that to demonstrate statistically significant differences between the 2 strategies (control versus oxaliplatin-fluoro-pyrimidines) with an expected difference of 5% and a power of 80%, more than 2000 patients would be required.¹² With the current evidence, the authors concluded that adjuvant chemotherapy cannot be considered standard treatment after neoadjuvant CHT-RDT.

Neoadjuvant chemotherapy and CHT-RDT has shown a better tolerance and compliance than adjuvant chemotherapy after CHT-RDT, with a similar efficacy,¹³ so it has been proposed as a new therapeutic option in rectal cancer. In spite of the use of neoadjuvant chemotherapy with oxaliplatin and

fluoro-pyrimidines followed by CHT-RDT±cetuximab or FOLFOX±afibercept ‘followed by CHT-RDT, the percentage of patients with complete pathological response (ypT0N0) is between 10% and 25%,^{14,15} and the 3-year DFS is between 65% and 75%, suggesting that patients resistant to CHT-RDT could also be resistant to induction chemotherapy±directed therapies. Recently, a study by the Polish Group has been published comparing short RDT followed by FOLFOX (3 cycles) and then surgery versus CHT-RDT followed by surgery in patients with high-risk rectal tumors. No differences were found in 3-year DFS rates (53% vs 52%).¹⁶ The RAPIDO study comparing short RDT followed by CAPOX (6 cycles) versus CHT-RDT with capecitabine will definitely answer whether induction chemotherapy is superior to CHT-RDT. This study has included more than 800 patients and has sufficient power to demonstrate a benefit of more than 10% in 3-year DFS rates with the strategy of short RDT followed by CAPOX versus conventional CHT-RDT.¹⁷

In most of the previously mentioned studies, magnetic resonance imaging (MRI) was not used for the staging of patients. MRI provides optimal staging of rectal cancer and predicts the risk of distant recurrence with extramural vascular invasion (EMVI) and local recurrence (mesorectal fascia of the middle and upper rectum and invasion of the sphincter in lower-third tumors).¹⁸ It is also a useful technique to identify patients with middle or upper-third involvement without invasion of the mesorectal fascia, who are candidates for clinical trials with systemic treatment without radiotherapy. MRI with neoadjuvant post-treatment diffusion also makes it possible to select patients with tumors of the lower third of the rectum with optimal radiological response, who are candidates for a “watch-and-wait” strategy.¹⁹

The characterization of the immunological component of the microenvironment has allowed new therapeutic strategies to be developed. In this sense, PD-1/PD-L1 checkpoint

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inhibitors are especially relevant. Tumors with loss of “mismatch repair” (MMR) protein expression show high levels of lymphocyte infiltration²⁰ and present an elevated therapeutic response to PD-1/PD-L1 inhibitors.²¹ However, tumors with MMR only account for 5%–15% of all colorectal cancers. An immunoscore has recently been proposed for the rectum, in which the high density of CD3 and CD8 correlate with better clinical evolution.²² Nevertheless, preliminary results of our group show the presence of 3 clusters in metastatic colon cancer, based on the analysis of immune-related gene expression signatures using NanoString technology.

After 20 years of studies with adjuvant and neoadjuvant chemotherapy (including targeted therapies) in rectal cancer, progress in DFS and overall survival has been very modest at best. Although the results of the RAPIDO study have not yet been published, it seems unlikely that they will demonstrate a benefit of neoadjuvant therapy compared to conventional chemo-radiotherapy treatment of more than 10%. In the current era of MRI and potential immune signatures, the design of adaptive studies in neoadjuvant therapies would make it possible to select the most favorable patients for combinations of immunotherapy versus standard treatment. This strategy would represent a radical but necessary change in the design of rectal neoadjuvant therapy studies and would replace the current “chemotherapy-radiotherapy for all” with “personalized immunotherapy combinations”.

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