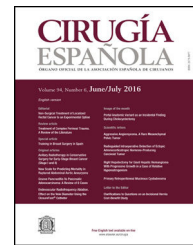




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Editorial

Non Surgical Treatment in Patients With Advanced Rectal Cancer[☆]



Tratamiento sin cirugía en pacientes con cáncer de recto avanzado

Advances made in rectal cancer treatment in recent decades have been aimed at reducing the high rate of local recurrence historically associated with this disease. New imaging studies, preoperative radiochemotherapy, total mesorectal excision and adjuvant chemotherapy have resulted in a substantial reduction in the local recurrence rate in patients with advanced rectal cancer.^{1,2} This multimodal treatment – chemotherapy, radiotherapy and surgery – has succeeded in reducing the local recurrence rate, but it is associated with complications and functional alterations that permanently affect the quality of life of survivors.^{3–7} Each of these therapeutic modalities carries its own risk of side effects that, in the context of multimodal treatment, can accumulate and enhance their negative effects. Unfortunately, currently almost one-third of patients die from metastatic disease. The aim of systemic chemotherapy before surgery (a treatment that has been called total neoadjuvant therapy) is to treat micrometastases earlier, thereby increasing the percentage of patients who complete the treatment in order to reduce the risk of distant metastasis and to improve survival.⁸

The experience of recent years suggests that not all patients obtain the same benefit from each of the components of multimodal treatment. The current challenge is to develop personalized treatment that provides the maximum oncological benefit, while reducing the risk of complications and functional alterations and preserving the patient's quality of life. Several prospective studies attempt to determine the risk/benefit ratio of each therapeutic modality in selected patient groups.^{9,10}

Patients with rectal cancer have variable responses to radiochemotherapy. Those with a higher degree of response — in whom no cancer cells are found in the surgical specimen after total mesorectal excision of the mesorectum — have very low local recurrence rates and very high rates of disease-free survival.¹¹ These findings have contributed to many surgeons

questioning the need to remove the rectum in patients with complete clinical response after neoadjuvant radiochemotherapy.¹² Unfortunately, the clinical response does not perfectly correlate with the pathological response, and some tumors that appear to have disappeared endoscopically and radiologically harbor viable cancer cell nests that can lead to tumor regrowth or even the development of distant metastases. The main barrier to the preservation of the organ in patients with rectal cancer is the difficulty to clinically or radiologically identify those cases in which the tumor has been totally eradicated by neoadjuvant treatment. This barrier has not been an obstacle for certain patients, either because they were not candidates for surgery or because they refused permanent colostomy, have been monitored for years in active surveillance protocols ('wait-and-see'), or have avoided surgery.

In recent years, several hospitals have published their experience with wait-and-see protocols in patients with rectal cancer.¹³ Most are retrospective reviews of selected patients treated with very different neoadjuvant protocols, with no prior definition of response criteria and with disparate follow-ups. Despite their heterogeneity, the results of these series agree that patients with a complete clinical response to radiochemotherapy who are monitored in a wait-and-see protocol have a tumor regrowth rate close to 20%. Most of these patients can be successfully treated by salvage surgery with curative intent, and long-term survival has been comparable to that of patients with a complete pathologic response treated with total mesorectal excision. Likewise, the rate of distant metastasis in these patients has been similar to that observed in patients with a complete pathological response after surgery. As might be expected, the quality of life of patients with a preserved rectum is better than that of patients treated with total mesorectal excision. It is easy to understand that, in view of these results, most patients with locally advanced rectal cancer who are interviewed before

[☆] Please cite this article as: Jiménez-Rodríguez R, García-Aguilar J. Tratamiento sin cirugía en pacientes con cáncer de recto avanzado. Cir Esp. 2021;99:401-403.

starting neoadjuvant therapy would be interested in following a wait-and-see protocol in case of a complete clinic response, as long as the cure rate is not compromised. Although current evidence is inconclusive, the wait-and-see approach has become a viable alternative to immediate surgery for the growing group of patients with complete clinical response to neoadjuvant treatment. In recent years, the wait-and-see strategy has gone from being a forced option in patients who were either not candidates or who refused surgery, to a more intentional attitude in patients who simultaneously aspire to be cured of the disease while still preserving quality of life.

Consequently, one of the priority objectives of rectal cancer research today is to increase the response rate to neoadjuvant treatment and increase the percentage of patients who are able to avoid surgery. In recent years, we have learned that smaller and early-stage tumors tend to respond better to radiochemotherapy. The total dose and the fractionation of radiation therapy also influence the response rate; long-cycle hyperfractionated radiotherapy (56 Gy in fractions of 200 cGy) is associated with higher response rates than short-cycle radiotherapy (25 Gy in fractions of 500 cGy). The response rate is higher when total neoadjuvant therapy is used than when radiochemotherapy is used alone. The order of radiochemotherapy and systemic chemotherapy also influences the response rate: the response is greater when radiochemotherapy is administered before chemotherapy than when chemotherapy is given before radiochemotherapy. Finally, this response rate seems to increase if the time of evaluation or surgery is delayed until 8–10 weeks after the end of neoadjuvant therapy. All these advances have shown that advanced rectal cancer can be eradicated by neoadjuvant treatment in at least one-third of patients.

Faced with this situation, more and more patients diagnosed with rectal cancer come to the consultation well informed about treatment options and are interested in preserving the rectum. The surgeon and patient, in consensus, should consider the wait-and-see option before starting neoadjuvant treatment. We must emphasize the term *consider*, as surgery can only be avoided if the tumor responds completely to treatment. But this response is not guaranteed, and there are no reliable methods to predict it. The first step in a patient with rectal cancer who is interested in preserving the rectum is accurate staging with endoscopy and magnetic resonance imaging. These images are used to determine whether the patient is a good candidate for the wait-and-see protocol, and as a reference to assess tumor response after neoadjuvant treatment. It is important to assess the risk/benefit ratio of wait-and-see strategies by taking into account both the size and location of the tumor, as well as patient characteristics. The ratio will not be the same in a young patient with a proximal tumor who will foreseeably tolerate sphincter-sparing surgery with minimal sequelae as an elderly patient with a distal tumor in whom the only surgical option is abdominoperineal resection and a permanent colostomy. The neoadjuvant protocol should be selected trying to obtain the highest possible response rate. Currently, the protocol associated with the highest complete response rates appears to be radiochemotherapy (56 Gy in fractions of 200 cGy, with 5-fluorouracil or capecitabine for the duration of radiotherapy) followed by 4 months of systemic chemotherapy consisting of CapeOx or FOLFOX.¹⁴ It is recommended to evaluate the tumor at the end of radiochemotherapy and before starting systemic

chemotherapy to ensure that the tumor is responding to treatment. The final evaluation of response, to be performed about 8 weeks after completing systemic chemotherapy, should include a digital rectal examination, flexible sigmoidoscopy, and magnetic resonance imaging.¹⁵ Only those tumors with complete clinical response (disappearance of the tumor on digital rectal examination, whitish scar with no ulcers or nodules on endoscopy, and homogeneous dark scar on T2 sequences, with no diffusion restriction on DWI sequences) should be considered candidates for the wait-and-see protocol. The remainder must undergo surgery.¹⁰

It is evident that some patients who meet the complete response requirements will develop tumor regrowth.^{12,13} The percentage of regrowth will depend on the criteria used by the surgeon to assign the degree of tumor response.^{10,15} If the criteria are very strict, the regrowth rate will be low, but the percentage of patients treated with potentially unnecessary surgery (patients with complete pathological response) will be higher. Conversely, less stringent criteria can lead to the opposite situation of higher regrowth rate and fewer complete pathological responses in patients treated by mesorectal excision. The effect of the regrowth rate on long-term survival is unknown, but it is reasonable to assume that patients who develop tumor regrowth are those who take the most risks and gain the least benefit from the wait-and-see protocol.

Early detection that allows for salvage surgery with curative intent requires patients commit to a rigorous, comprehensive follow-up protocol. As most regrowths are diagnosed in the early years, follow-up visits should be performed every 3–4 months during the first 2 years after completing treatment, and then every 6 months for the next 3 years.^{8,9} What is still unknown is how long we should monitor these patients. The mean follow-up in most published series is no longer than 2 years, so the long-term results are unknown. Therefore, patients should be alerted to possible symptoms indicative of regrowth, and annual check-ups are recommended, possibly for life.

Conclusion

Patients with rectal cancer who develop a complete clinical response after neoadjuvant treatment may benefit from a wait-and-see strategy, whose aim is to avoid the sequelae of surgery. Although some patients develop tumor regrowth and require salvage surgery, the long-term results are probably similar to those of patients with the same degree of response initially treated with surgery. The risk of regrowth requires patients to commit to a thorough follow-up protocol. Finally, it is essential to inform patients that the level of evidence supporting the wait-and-see protocols is currently quite low, and that the long-term results are unknown. It is recommended that patients interested in preserving the rectum should be treated within prospective studies.

Conflict of interests

Dr Garcia-Aguilar has received professional fees from Intuitive Inc, Medtronic, and Johnson & Johnson.

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2173-5077/

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