CIRUGÍA ESPAÑOLA

www.elsevier.es/cirugia

Editorial

Organ preservation in rectal cancer, the desire of a new paradigm☆

Preservación de órgano en cáncer de recto, el deseo de un nuevo paradigma

Locally advanced rectal cancer (LARC) located below the peritoneal reflection, for which in 1982 Bill Heald (Basingstoke, UK) suggested *total mesorectal excision* along embryological planes, remains a problem. Neoadjuvant therapies (chemo-radiotherapy) are particularly indicated, and a derivative stoma is required after surgery, which becomes definitive in a significant percentage. And although the patient can preserve their body image (sphincter preservation), their quality of life is severely affected in terms of defecatory and sexual function.

Tri-modal (neoadjuvant-surgery-adjuvant) therapy is the latest in the treatment of LARC. The standardisation of this therapeutic scheme has drastically reduced local recurrence, but metastatic disease still causes significant mortality (30% metastatic disease with a 10-year cumulative survival of 68%).[1,2] It is clear that better systemic control is needed.

The dilemma has been early "micrometastases", which has led to changes in therapeutic strategy in the period "prior" to the surgical approach, in which delivery of all systemic chemotherapy has already been contemplated. In contrast to colon cancer, it is surprising that adjuvant chemotherapy has not shown a clear survival benefit, and therefore its role in rectal cancer remains controversial.[3–5]

However, there is an important criticism: many of the patients included in these studies "did not receive adjuvant correctly". It is estimated that 30% of elective adjuvant therapy patients will not start adjuvant therapy and of those who do, up to 40% experience some delay in its delivery.[6] Much of the blame for this lies with the morbidity associated with surgery (postoperative complications, delayed recovery, stomas).[7] This lack of CT compliance increases the likelihood of micrometastases, which may explain the lack of improvement in systemic control of the disease,[8,9] with very significant variations in survival ranging from 36% without adjuvant treatment to 76% if adjuvant treatment is started before 6 weeks following surgery. Hence the attitude of delivering all chemotherapy before surgery in what is called "*total neoadjuvant therapy*", a strategy championed by *Memorial* that hypothesises an increase in survival and clinical response rate, opening up the possibility of another therapeutic option: "*non-operative*" *management* of the disease if a complete clinical response (CR) rate has been achieved,[10] an option that has already been accepted by the NCCN as a "viable" therapeutic strategy for rectal cancer in their latest guidelines (version 1. 2021).

This attitude of total neoadjuvant therapy is reinforced by the fact, increasingly supported by the evidence, that a delay in surgical treatment together with the delivery of oncological treatments results in increased pathological responses.[11,12] Pathological complete response (pCR) is currently the most important prognostic marker. The aim of neoadjuvant therapy will therefore be to achieve the best possible clinical response.

There is currently much controversy as to the best neoadjuvant regimen: should it entail radiotherapy "alone" or chemotherapy alone, combined, before radiotherapy or chemotherapy, "short" or "long" cycle radiotherapy, "intensified" radiotherapy, brachytherapy, adding other drugs to pyrimidines in chemotherapy regimens? And then there is "how" and "when" we should assess clinical response.

In terms of "how to assess clinical response", high-resolution MRI with T2- and diffusion- weighted slices is essential for "correct" initial staging of the tumour, which will allow us to "selectively" indicate the patients who would benefit from neoadjuvant therapy. In this initial evaluation, performing anorectal ultrasound together with MRI increases efficacy, especially in earlier stages and more distal tumours.[13] Post-NAD MRI is also essential for assessing clinical response using radiological biomarkers such as mrTRG (regression grade assessed by MRI) which, emulating the histopathological tumour regression grades proposed by Mandar, identifies

☆ Please cite this article as: Domínguez Tristancho JL. Preservación de órgano en cáncer de recto, el deseo de un nuevo paradigma. Cir Esp. 2022. https://doi.org/10.1016/j.ciresp.2021.07.011

"good responders". The Trigger trial evaluates the effectiveness of mrTRG, which attempts to validate the importance of MRI in therapeutic decision-making.[14,15] Clinical response should be assessed, in addition to MRI, by digital rectal examination and endoscopic study with or without biopsy.

With respect to "when to assess response", as we have seen above, there is increasing evidence that the clinical response rate increases as we delay assessment. We should routinely perform a first assessment 6 weeks after the end of neoadjuvant therapy, regardless of the therapeutic regimen used. At this time, we will identify "good responders"; these patients will be able to continue with neoadjuvant therapy. Among the "good responders" we find those who have had a complete CR, who will account for between 10% and 32% depending on the series, and another group that we consider to have had a "near-complete clinical response" (nCR); in the latter it has been observed that 90% will achieve a complete CR 12 weeks after the end of neoadjuvant therapy (late complete response). In patients with "initial" complete CR approximately 12% will have tumour regrowth compared to 28% in patients with "late" complete CR, but in both cases the chance of R0 surgical salvage is higher than 90%. In other words, between 72% and 88% of "good responders" will be able to avoid radical surgery.[16]

Spread of the disease during these waiting times for radical surgery has been a major concern, but this has been observed to be anecdotal in "good responders''.

Neoadjuvant therapy in rectal cancer is therefore presented as a therapeutic tool to achieve the best possible clinical response so that the treatment can be fully delivered prior to radical surgery or radical surgery can be avoided if a complete response is achieved. However, we should not forget that neoadjuvant treatment is associated with toxicity, which becomes particularly evident if the patient eventually must undergo surgery.[17–19] It is therefore appropriate to identify the patients who would be "responders" and those who would be "non-responders" at diagnosis, to avoid the toxicity derived from neoadjuvant therapy. To date, there are no pathognomonic clinical markers predictive of response to neoadjuvant therapy. We will probably have liquid biopsy molecular markers in the future to guide us in this regard.

Another current issue is the implementation of multimodal prehabilitation programmes during neoadjuvant therapy which, despite the scant scientific evidence, seem to have an impact not only on reducing the toxicity derived from neoadjuvant therapy, but which also contribute to an increase in clinical responses.[20,21] We started an observational study in our hospital to examine this phenomenon.[22]

The different neoadjuvant regimens are the subject of research in clinical trials and observational studies and their main objectives are to assess clinical response rate and survival and consider quality of life aspects. There is a huge desire for and interest in organ preservation in rectal cancer, partly due to the patient's need for a decent quality of life without compromising survival, and this goes hand in hand with total neoadjuvant therapy. However, we should not forget that neoadjuvant therapy is not toxicity free, and is fatal in some cases,[23] which is why correct indication for neoadjuvant therapy is required. Everything that has been published suggests that, overall, we are overtreating our patients, and in an era in which total neoadjuvant treatment is being imposed.[24] We must, therefore, find a "balance" between the indication for oncological treatments and the desire for organ preservation.

Conflict of interests

The author has no conflict of interests to declare.

REFERENCES

1. Peeters KC, Marijnen CA, Nagtegaal ID, Kranenbarg EK, Putter H, Wiggers T, et al. The TME trial after a median follow- up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg. 2007;246(5):693–701.
2. Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO- 94 randomized phase III trial after a median follow- up of 11 years. J Clin Oncol. 2012;30(16):1926–33.
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(2):184–90.
4. Breugom AJ, Swets M, Bosset JF, Collette L, Sainato A, Cionini L, et al. Adjuvant chemotherapy after preoperative (chemo)radio- therapy and surgery for patients with rectal cancer: a systematic review and meta- analysis of individual patient data. Lancet Oncol. 2015;16(2):200–7.
5. Bujko K, Glimelius B, Valentini V, Michalski W, Spalek M. Postoperative chemotherapy in patients with rectal cancer receiving preoperative radio(chemo)therapy: a meta-analysis of randomized trials comparing surgery +/- a fluoropyrimidine and surgery + a fluoropyrimidine +/- oxaliplatin. Eur J Surg Oncol. 2015;41(6):713–23.
6. Xu Z, Mohile SG, Tejani MA, Becerra AZ, Probst CP, Aquina CT, et al. Poor compliance with adjuvant chemotherapy use associated with poorer survival in patients with rectal cancer: an NCDB analysis. Cancer. 2017;123:52–61.
7. Khrizman P, Niland JC, ter Veer A, Milne D, Bullard Dunn K, Carson WE 3rd, et al. Postoperative adjuvant chemotherapy use in patients with stage II/III rectal cancer treated with neoadjuvanttherapy: a national comprehensive cancer network analysis. J Clin Oncol. 2013;31(1):30–8.
8. Bos AC, van Erning FN, van Gestel YR, Creemers GJ, Punt CJ, van Oijen MG, et al. Timing of adjuvant chemotherapy and its relation to survival among patients with stage III colon cancer. Eur J Cancer. 2015;51:2553–61. http://dx.doi.org/10.1016/j.ejca.2015.08.016.
9. Petrelli F, Zaniboni A, Ghidini A, Ghidini M, Turati L, Pizzo C, et al. Timing of Adjuvant chemotherapy and survival in colorectal, gastric, and pancreatic cancer, a systematic review and meta-analysis. Cancers (Basel). 2019;11(4):550. http://dx.doi.org/10.3390/cancers11040550.
10. Cercek A, Roxburgh CSD, Strombom P, Smith JJ, Temple LKF, Nash GM, et al. Adoption of total neoadjuvant therapy for locally advanced rectal cancer. JAMA Oncol. 2018.
11. Garcia-Aguilar J, Smith DD, Avila K, Bergsland EK, Chu P, Krieg RM. Optimal timing of surgery after chemoradiation for advanced rectal cancer: preliminary results of a

multicenter, nonrandomized phase II prospective trial. Ann Surg. 2011;254:97–102.
12. Smith J, Chow OS, Gollub MJ, Nash GM, Temple LK, Weiser MR, et al. Organ Preservation in Rectal Adenocarcinoma: a phase II randomized controlled trial evaluating 3-year disease-free survival in patients with locally advanced rectal cancer treated with chemoradiation plus induction or consolidation chemotherapy, and total mesorectal excision or nonoperative management. BMC Cancer. 2015;15:767. http://dx.doi.org/10.1186/s12885-015-1632-z.
13. Detering R, van Oostendorp SE, Meyer VM, van Dieren S, Bos ACRK, Dekker JWT, et al. MRI cT1-2 rectal cancer staging accuracy: a population- based study. Br J Surg. 2020;107:1372–82.
14. Bhoday J, Balyasnikova S, Wale A, Brown G. How should imaging direct/orient management of rectal cancer? Clin Colon Rectal Surg. 2017;30:297–312.
15. Battersby NJ, Dattani M, Rao S, Cunningham D, Tait D, Adams R, et al. A rectal cancer feasibility study with an embedded phase III trial design assessing magnetic resonance tumour regression grade (mrTRG) as a novel biomarker to stratify management by good and poor response to chemoradiotherapy (TRIGGER): study protocol for a randomised controlled trial. Trials. 2017;18(1):394. A description of the TRIGGER trial, an ongoing prospective study including watch-and-wait as a therapeutic strategy.
16. Hupkens BJP, Mass M. ASO author reflections: decision timing for organ preservation in rectal cancer after chemoradiation. Ann Surg Oncol. 2018;5:854–5. http://dx.doi.org/10.1245/s10434-018-7032-2.
17. Rombouts AJM, Al-Najami I, Abbot NL, Appelt A, Baatrup G, Bach S, et al. Can we Save the rectum by watchful waiting or TransAnal microsurgery following (chemo) Radiotherapy versus Total mesorectal excision for early REctal Cancer (STAR-TREC study)?: protocol for a multicentre, randomised feasibility study. BMJ Open. 2017;7e019474. http://dx.doi.org/10.1136/bmjopen-2017-019474.
18. García Aguilar J. Chemoradiotherapy and local excision for organ preservation in early rectal cancer—the end of the beginning? JAMA Surg. 2019;154:54–5.
19. Rullier E, Rouanet P, Tuech JJ, Valverde A, Lelong B, Rivoire M, et al. Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial. Lancet. 2017;390:469–79.
20. Moug S, Mutrie N, Barry SJE, Mackay G, Steele RJC, Boachie C, et al. Prehabilitation is feasible in patients with rectal cancer undergoing neoadjuvant chemoradiotherapy and may minimize physical deterioration: results from The REx trial. Colorectal Dis. 2019;21:548–62.
21. West MA, Astin R, Moyses HE, Cave J, White D, Levett DZH. Exercise prehabilitation may lead to augmented tumor regression following neoadjuvant chemoradiotherapy in locally advanced rectal cancer. Acta Oncologica. 2019;58:588–95.
22. Domínguez Tristancho JL, Hormigo Sánchez AI, Guadalajara Labajo H, García Olmo D. Implantación de un programa de prehabilitación multimodal en pacientes con cáncer de recto electivos de tratamiento neoadyuvante. Madrid, Mayo: Estudio Observacional. Hospital Universitario Fundación Jiménez Díaz; 2020.
23. Fernández-Martos C, Brown G, Estevan R, Salud A, Montagut C, Maurel J, et al. Preoperative chemotherapy in patients with intermediate-risk rectal adenocarcinoma selected by high-resolution magnetic resonance imaging: the GEMCAD 0801 phase II multicenter trial. Oncologist. 2014;19:1042–3.
24. Shi DD, Mamon HJ. Playing with dynamite? A cautious assessment of TNT. J Clin Oncol. 2020;39:103–1060.

José Luis Domínguez Tristancho*
Unidad de Coloproctología y Terapia Celular, Servicio de Cirugía General y del Aparato Digestivo, Hospital Universitario Fundación, Jiménez Díaz, Madrid, Spain

*Corresponding author.
E-mail address: jtristancho@telefonica.net

2173-5077/