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Editorial

Selective neoadyuvant therapy in locally advanced rectal cancer: For whom and with what aim?

The criteria for ''generalized'' neoadjuvant treatment for all patients with stage II and III rectal cancer, initially adopted by the National Institutes of Health Consensus Development Conference in 1990,[1] has become completely obsolete after a long process of developments and changes.

Starting in the 1990s, some institutional series and national projects have demonstrated that the implementation of total mesorectal excision (TME) *per se* drastically reduced the local recurrence (LR) rate to below 6%-8%, which casted doubt on the universal need for complementary radiotherapy (RT).[2,3] In contrast, different randomized trials showed that preoperative short-course radiotherapy (SCRT)[4] or long-course chemoradiotherapy (CRT)[5] associated with TME for all tumors considered locally advanced at that time had a positive effect on the reduction of local recurrences, thereby advocating ''generalized'' neoadjuvant treatment.

A key development in the possible indication of ''selective'' neoadjuvant therapy was the unequivocal demonstration of the good prognosis that the absence of tumor involvement in the circumferential resection margin (CRM) has on local recurrence, systemic spread and survival.[3,6] Thus, the absence of CRM invasion detected by high-resolution magnetic resonance imaging (MRI) with an accuracy surpassing 92%[7] makes it possible to select and omit neoadjuvant therapy in up to 40% of tumors in clinical stages II and III, without increasing the LR rate.[8–11] However, other factors associated with a poor prognosis should be considered, such as: fat penetration greater than 5 mm, presence of extramural venous invasion, evident cN2, extramesorectal lymphadenopathies, or tumor location below the *levator ani* muscle plane. Another important change in criteria regarding the need for neoadjuvant therapy occurs when potentially affected lymph nodes are observed. The accuracy of MRI to determine lymph node invasion is limited to 60%, which implies a risk of over-treatment of 40%. Neoadjuvant therapy would be indicated in N2 tumors, weighing the benefits and risks of radiotherapy treatment.[12] Currently, these criteria for ''selective'' neoadjuvant treatment are included in different current guidelines.[13,14]

An important variable to consider in clinical decision-making is the potential adverse effects of neoadjuvant therapy, especially late toxicity and the impact on the patient's functional expectations and quality of life. Although the adverse effects of radiotherapy have decreased in recent years due to better technology and planning, is unfavorable effect on defecation as well as sexual and urological functions must be taken into account, in addition to the effects of TME.[15] Alterations in quality of life as a result of low anterior resection syndrome (LARS) is most severe in tumors of the lower rectum in 45% and 60% of patients, without neoadjuvant RT or with it, respectively.[16] Nonetheless, we must also consider that severe LARS occurs in 33% of non-operated patients, treated only with CRT as part of a watch-and-wait (W&W) strategy.[17]

Along with ''selective'' neoadjuvant treatment, the implementation of multidisciplinary work, MRI staging, and TME surgery audited for quality in the Netherlands have led to an evident progressive reduction in the rate of neoadjuvant RT over the last decade, with no negative impact on the CRM rate.[18] In contrast, according to the results of the Audited Teaching Project of the Spanish Association of Surgeons (*Proyecto Docente Auditado de la Asociación Española de Cirujanos*) on the use of TME, these ''selective'' criteria for neoadjuvant treatment have apparently not been applied since a slight increase was observed in the global rate of neoadjuvant treatment, from 52.8% to 64.9%, during the study period (2006-2016), which paradoxically has also increased in tumors of the upper third, from 31.5% to 38.6%.[19] In the latter, neoadjuvant therapy would be indicated only in those few tumors with poor prognostic factors according to MRI.[13]

With regards to ''generalized'' CRT, the W&W strategy became a part of the therapeutic spectrum for distal rectal cancer at the hands of the Habr-Gama group.[20] The goal is to obtain a long-lasting complete clinical response (CCR), with curative intent and preservation of the rectum. In 880 cases with CCR, the multicenter International Watch & Wait Database has detected 2-year rates of local regrowth and liver metastases of 25% and 8%, respectively, and 5-year rates

of specific and overall survival of 85% and 94%, respectively.[21] However, the notable limitations of the registry include: the variability in the diagnostic imaging studies (MRI in 70%), the types of cT stages included (T1 and T2: 28%; T3: 51%; and T4: 3%), the types of CTx and the different doses of RT (45, 50, 54, 60 Gy) as well as the follow-up methods used. These factors would explain the variability (from 16% to 40%) in the rates of regrowth among the centers with a higher volume of cases.

The W&W strategy has a limited benefit that can be established with current evidence. Thus, if we hypothetically treat 100 cases of locally advanced rectal cancer of the distal third, with a current CRT protocol of maximum efficacy, we will obtain an expected CCR rate of 28% (28 cases).[22] Among these cases, we will observe an expected tumor regrowth rate within the first 3 years of 24% (6-7 cases)[21] and less than 5% (1 case) thereafter.[23] Therefore, the actuarial 5-year rectal preservation rate would be 20% (20 cases), or 1 out of every 5 cases. In addition, it is estimated that 6 out of the 20 patients may present severe LARS.[17] Thus, the crux of the matter is, *how many patients have we overtreated, and what are the consequences?* Among all those treated, only 14% will be ''cured and satisfied'', while 80% will have required a radical intervention with the added effect of radiotherapy, which could have been omitted in an estimated 40%. As Glynne-Jones[24] points out, ''*If the patient fails to respond to CRT, have we actually made them worse? ... the losers may lose as much as the winners gain.*'' Therefore, more long-term prospective observational studies are needed with more uniform inclusion criteria to objectively assess the risks and benefits.

Recently, total neoadjuvant therapy (TNT) has emerged as a strategy that opens new horizons by concentrating CTx preoperatively. The results of 2 recent prospective trials[22,25] (with SCRT and CRT, respectively) demonstrate significant benefits in the overall recurrence rate, disease-free period and increase in CCR, although the results were inconclusive regarding the incidence of LR. Evidently, the increase in CTx and RT doses can have an impact on tolerance and morbidity, especially in frail and elderly patients. All this demonstrates the importance of continuing with new clinical trials or prospective multicenter registries to better define the indications for these new therapeutic strategies.

Based on the above, there seems to be controversy between the ''selective'' CRT strategy to avoid overtreatment versus the ''generalized'' CRT strategies, which can only be resolved in the near future when molecular markers of sensitivity and resistance to neoadjuvant treatment become a predictive reality.[24] In the meantime, the indication for neoadjuvant therapy should be decided individually by the multidisciplinary group, adjusted for patient risk, and the treatment objectives should be defined from the outset according to the characteristics of both the tumor and patient. The main objective may be to reduce the risk of LR, prevent distant metastases, or preserve organs after CCR to avoid potential morbidity from severe LARS or definitive stoma, especially in frail patients with tumors of the lower third. Therefore, it is necessary to individualize the indications and the type of neoadjuvant treatment, while always focusing on *who* it is for and *why*, or *for what purpose*. If we intend to obtain a truly informed consent, it is necessary to know our own results and the patient's expectations, with clearly defined treatment objectives and an explanation of the expected benefits as well as potential adverse effects of the different therapeutic strategies.

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