Multimodal Treatment of Rectal Cancer. Vision of the Oncologist

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Since the recommendations of the National Cancer Institute (NCI) in 1990,[1] that introduced postoperative chemoradiotherapy (CRT) in the interdisciplinary management of patients with rectal cancer, enormous advances have been consolidated in the different disciplines involved in the diagnosis and treatment of this disease. Currently, there is an imperative conviction about the development of more integrative and transversal work modalities for the benefit of these patients. These advances have managed to substantially improve local control of the disease. However, with the best version of all disciplines, in three decades the impact on increasing the overall survival of patients with locally advanced rectal cancer (LARC) has been almost nil. Thus, with standard treatment, CRT followed by total mesorectal excision (TME), the risk of developing distant metastases remains unchanged in 20-30% of cases.[2] This low impact on long term outcome, probably is the consequence of strategies that have been, and continue to be, deeply empirical in the design of the treatments and that have been limited only to changing the place of the pieces or "the disciplines". Even in 2020, we cannot specify which is the best sequence for more satisfactory a strategy. However, there is congruence through the different alternatives of a "tetris-like" approach, in that in the face of a total neoadjuvant treatment (TNT) strategy the place of surgery or the decision to omit it would constitute the last link in the therapeutic sequence.

With the aim of achieving an impact on distant recurrence, the first and still current model of TNT with initial or "induction" QT with oxaliplatin, followed by long-course CRT and TME (designated TNT1) showed that: 1) a greater interval from diagnosis to surgery was feasible, 2) toxicity was acceptable, 3) R0 resection rates were satisfactory (> 90%), 4) objective responses with tumor regression between 88 and 97% were obtained, 5) rapid symptom control and greater adherence to treatment were achieved and 6) the percentage of the planned dose of CT received was higher when administered preoperatively than when it was given as adjuvant therapy, without compromising, although unfortunately also without increasing disease-free survival (DFS) and overall survival (OS).[3-7] This model also allowed to identify subgroups of patients responding to induction QT who can undergo surgery omitting radiotherapy and triggered the possibility of testing this hypothesis prospectively.[8,9] Another additional advantage of this strategy , perhaps of greater interest to patients, is the possibility of performing a closure of the ostomy generated in the TME surgery earlier than indicated in the standard treatment. Furthermore, by increasing the degree of tumor regression, this model has established the interest in achieving: a) a clinical complete response (cCR), an encouraging endpoint for sphincter preservation and/or b) a higher complete pathological response rate (pCR) in LARC trials, as a surrogate for better OS.[5] In the United States, induction with FOLFOX for 4 months followed by CRT is already a recommended preoperative option for high-risk patients.[10] Finally, it should be noted that TNT1 has been adopted in the context of prospective translational research as a model to achieve a better molecular understanding of the effect of QT and RT.[11] However, the aforementioned results were obtained through phase 2 clinical trials (only one randomized with the standard treatment) and large-volume retrospective series with the usual biases in patient selection and incomplete clinical staging by high-resolution magnetic resonance imaging (HR-MRI), not considering extramural vascular invasion in any of the series as a risk factor. At ASCO 2020, the first prospective trial based on induction QT with the FOLFIRINOX scheme followed by a long course of concurrent RT with fluoropyrimidines with an interval to surgery of eight weeks, compared with a long-course standard treatment and surgery was presented. In both arms, adjuvant treatment was mandatory. PRODIGE 23 met its primary objective, showing in the experimental arm a greater benefit in DFS and distant metastasis-free survival (HR: 0.69; p = 0.034 and HR: 0.64; p = 0.017, respectively). Furthermore, it was not associated with greater postoperative complications and there were no

The author declare the absence of conflicts of interest.

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Received: *May, 2020.* ***Accepted:*** *June, 2020.*

differences in the assessment of quality of life between both arms. The pCR rate was 27% compared to 12% for the standard treatment. It is the first trial that prospectively demonstrated greater systemic control of the disease, probably at the expense of using a higher intensity induction treatment than previous trials. On the other hand, the response rate of the primary tumor to the effect of CT before RT was not mentioned, which would be of interest to take into account in tumors of the middle or upper rectum without RT criteria and with systemic risk. In any case, this CT triplet is being studied in this setting in the FOBEAR study, but also in a different context in GRECCAR 12, with the aim of evaluating the effectiveness for the preservation of the organ in patients with cancer of the lower rectum.[12]

By better understanding the effect of the time interval after CRT on the response, leaving aside the dichotomy between good and bad responders and adding a third category (the "slow responders"), it was proposed to fill the longest interval between CRT and surgery with CT, moving the place of the pieces. Thus, a second approach to TNT was generated, the initial long-course TNT2: CRT, followed by CT and finally TME. This other extended neoadjuvant model, filling the interval to response with CT, initially with capecitabine,[13] followed by the addition of oxaliplatin as “consolidation” CT, always after CRT, achieved higher rates of cCR and pCR and a higher compliance to CT, as previously mentioned.[13] In TNT2, the consolidation CT by prolonging the interval between the CRT and the evaluation of the response, allowed to postpone the surgical decision according to the response achieved and promoted the strategy of omission of surgery not only within clinical practice but also as an experimental option within clinical trials.[14] Leaving aside the excitement produced by achieving the primary endpoint, such as obtaining higher percentages of cCR and/or pCR, TNT2 has not yet been shown to improve long-term cancer outcomes. With this strategy there appears to be a greater DFS, but this benefit was obtained in a prospective non-randomized trial. It is appropriate to be cautious with its results since this study could have an initial clinical understaging, due to only a low percentage of cases had HR-MRI[14] despite its indisputable role in documenting tumor involvement beyond the mesorectum. Faced with either of the two aforementioned approaches, opponents of TNT base their rejection on a possible risk of over-treatment. They argue that as experience grows, familiarity and feasibility have lowered the threshold for offering TNT (initially intended for patients with LARC) to patients with earlier or lower-risk stages.[15]

On the other hand, the controversy about a possible greater surgical morbidity due to the development of fibrosis, potentially increasing as we move away from the completion of RT, is still glowing.[16]

There are also data that TNT2 compared to TNT1 would be associated with lower toxicity, higher compliance during RT, and a higher pCR rate.[17] Although this randomized phase 2 trial (AIO-12) achieved its primary endpoint by demonstrating a higher pCR rate with TNT2, the interval to surgery was 6 weeks with TNT1 vs. 12 weeks with TNT2. This imbalance, due to the effect of the post-CRT time, could explain the differences in tumor regression in each arm. Perhaps, with another similar design that also compared induction vs. consolidation in patients treated with QTRT, but with DFS as the endpoint, it could be answered whether there are unbiased differences between the two strategies.[14] The OPRA clinical trial also compared the effectiveness of the two TNT modalities but specifically in the context of lower rectal cancer, with the aim of demonstrating differences in the effectiveness to achieve cCR and therefore a higher percentage of patients who are candidates for the non-surgical strategy. However, the primary objective was to demonstrate a better DFS. This was not reached, since there was no difference between the two arms of TNT. What it did show was that the strategy of initiating neoadjuvant treatment with long-course CRT followed by CT (FOLFOX/CAPOX) during the interval to response was superior in TME-free survival, compared with the induction strategy with the same CT scheme ($p = 0.007$). The percentage of patients assigned to the organ preservation strategy was 58% in the consolidation arm vs. 43% in the induction arm ($p = 0.01$). Beyond these robust results for intentionally selecting “watch and wait” patients, the TNT2 arm received a higher dose of radiation therapy and, of course, the interval to evaluation of response was longer.[18] The results of this study are in line with the AIO12, in both prospective trials it was observed that waiting longer, associated with consolidation CT, allow achieving a greater degree of tumor regression.

Finally, an adaptation of TNT2 consisting of short-course RT followed by CT (extrapolated from the benefit obtained with short-course RT in metastatic patients),[19] has led to the development of different randomized trials. Unfortunately, they have different primary endpoints and CT schema duration. In the RAPIDO trial, short-course RT followed by consolidation CT compared with standard long-course CRT did not increase the percentage of R0 resections, which was its primary endpoint, although it was associated with less toxicity. On the other hand, the longer interval until surgery did not have impact on surgical morbidity and mortality.

In agreement with the previous strategies, it had no greater benefit in DFS or OS.[20]

The effectiveness and safety results of short-course RT followed by XELOX plus bevacizumab in patients with metastatic rectal cancer in the DUTCH M1 study[21] also prompted the development of the RAPIDO study, designed for adenocarcinoma of the rectum with one or more worse prognostic factors, selected in all cases by HR-MRI: mrT4a/b, EMVI +, N2, involvement of the mesorectal fascia and/or lateral lymph nodes. The multicenter trial, primarily from European centers, included more than 900 patients with these characteristics. It was the first randomized trial where patients received the longest duration of systemic treatment before surgery: 6 courses of CAPOX or 9 of FOLFOX. On the one hand, this duration would imply a greater systemic control, but on the other, a longer interval until surgery (24 weeks after RT). The control arm was the standard long-course treatment followed by surgery at 8-10 weeks. In this group, 40% of the patients did not receive adjuvant treatment with oxaliplatin, perhaps one of the most relevant biases. The primary endpoint was disease-related treatment failure, an endpoint combining local recurrence, distant metastasis, treatment-related death, etc. Disease-related treatment failure was 7% higher in the control arm (HR: 0.75, p = 0.019), probably at the expense of the higher percentage of patients who developed distant metastases in this arm (27 vs. 20 %, HR: 0.69, p = 0.005). No differences were observed in OS or local recurrence when comparing standard treatment with short-course RT followed by consolidation CT for 4-5 months. It was also shown that a longer waiting time until surgery is not associated with greater postoperative complications and, again, that a longer interval associated with consolidation CT significantly achieves a greater degree of tumor regression, 28 vs. 14% (p = 0.001).[22]

To increase the complexity of the analysis of the evidence, it should be noted that in all TNT models mentioned there are discrepancies in CT treatment schemes, either CAPOX or FOLFOX, and in their duration. In studies investigating the ideal duration of adjuvant CT in colon cancer, CT for 6 months with FOLFOX demonstrated a benefit in DFS equivalent to CT with CAPOX. However, when CT was investigated for 3 months, benefit was only seen with the CAPOX scheme and only for low-risk stages III.[23]

Thus, considering these data specifically in the LARC trials, the duration of induction or consolidation CT could have been insufficient, since it has not been longer than 3 months even with the FOLFOX-based regimens. On the other hand, in these LARC trials, the decision to complete adjuvant CT was not mandatory and was left to the discretion of the investigators. This decision is usually complex in clinical practice, since the tools to assess the prognosis of patients and predict the benefit of adjuvant CT in the context of TNT are controversial. On the one hand, in the 7th edition of the TNM (AJCC v7) a pathological tumor regression score (CAP) was introduced that has been shown to be superior to the systems used previously.[24-26] Patients with pCR (CAP: 0) have excellent long-term outcomes, with a very low risk of local or distant recurrence.[27] In contrast, those with moderate, minimal, or no response (CAPG2 -G3) have a significantly higher risk of recurrence.[28,29] However, to establish the prognosis, this score does not consider the status of the lymph nodes (not even those involved in the surgical specimen) or other systemic risk factors that are generally considered in the pathological report. Another tool with prognostic intent is the NAR score[30] that has been incorporated as an end point in some modern clinical trials.[11] This formula contemplates the initial clinical staging of the tumor and not only the pathological report, but it has a certain degree of ambivalence. The NAR score follows the assumption that the prognosis improves with further tumor regression. However, in some analyzes, when there is pCR, the score results in higher scores (associated with a worse prognosis) in tumors clinically staged in early stages. There is a contradiction: the pCR of initially small tumors have a worse prognosis than the pCR of initially more advanced tumors.[31] NAR also does not include initial lymph node staging (subject to imperfect sensitivity on HR-MRI). Thus, the response to treatment does not have any sufficient clinical, morphological or pathological evaluation to correctly verify the success of neoadjuvant therapy.

It is the biological characteristics of the tumor that may be relevant to predict therapeutic success, allow molecular risk stratification, and facilitate better clinical decision-making. In the last decade, different approaches have been published to identify a holy grail or molecular biomarkers as possible candidates for response prediction, still without consistent results.[32-35] This inconsistency is related, at least in part, to differences in the selection of patients, the size of the sample, the different treatments indicated and, most importantly, the definitions used to classify the tumor response. Tumor heterogeneity and the absence of an integrative analysis that includes the role of the microenvironment under CRT treatment are also reasons for these inconsistencies. A comprehensive understanding of the biological factors that generate a given neoadjuvant response is required. A rigorous evaluation of the response must be done to identify effective and sensitive predictive biomarkers that allow us to redefine and direct neoadjuvant strate-

gies. Thus, it will be possible to identify those who would be harmed by being exposed to a treatment that is increasingly extensive and may be associated with complications, some irreversible, which affect the quality of life of patients in different aspects.

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