CHAPTER 15
Adjuvant Chemotherapy After Neoadjuvant Treatment

The indication of adjuvant ChT after surgery in patients who were treated with neoadjuvant therapy is a subject of some controversy. The possibility of downstaging rectal cancers after neoadjuvant treatment poses situations for which there is no definitive answer in terms of scientific evidence. Such is the example of cases in which after preoperative CRT indicated for a locally advanced tumor, even with frankly suspicious lymphadenopathies in the previous images, histopathology reports negative lymph nodes. The discussion that usually arises in these cases is whether or not adjuvant ChT should be indicated, something that does not generate much discussion when these nodes are positive.

Current recommendations suggest 4 months of adjuvant ChT after treatment with long-course CRT or short-course RT. However, the indication in patients with pCR is controversial. The evidence for this recommendation comes from experiences in which adjuvant ChT and RT were indicated for 4 months after surgery. A Cochrane review that included 20 randomized studies, of which only one administered preoperative CRT, concluded that adjuvant ChT with 5-FU significantly reduces the risk of recurrence and death.[176] But the truth is that the indication for adjuvant ChT in patients who received RT or CRT preoperatively lacks conclusive scientific evidence.

- In 2001, a clinical trial was published in Italy that randomized 653 patients with T3-T4 tumors operated on after CRT, to receive adjuvant ChT with 5-FU versus observation. Overall survival at 5 years was 68% in the ChT group and 64% in the control group.[38]
- In 2014 this same group compared patients operated after CRT, treated with 6 cycles of adjuvant ChT with 5-FU with controls[197]. No differences were found in the recurrence rate or OS, even when it was calculated in patients with stage ypN +. This study did not comply with the protocol, since 28% of the patients who were to receive adjuvant ChT did not.
- In 2006, Fietkau et al.[56] published their experience with 95 patients treated with CRT based on 5-FU. They had no distant disease and their resections were considered R0. Sixty-five of these patients (68.4%) received adjuvant ChT. The risk factors for 3-year DFS were evaluated by univariate and multivariate analysis and the only significant prognostic factor was stage N. In cases staged as ypN0, DFS was 87.5% in those who received adjuvant ChT and 87% in controls. In contrast, DFS was 30% in patients with ypN2 tumors. These data suggest that adjuvant ChT could be avoided in node-negative patients, while perhaps it should be intensified in ypN2.
- In the EORTC22921 study, 1011 patients with T3-T4 tumors located up to 15 cm from the anal margin, randomly assigned to receive short-course RT or long-course CRT, were again randomized into 2 arms to receive or not 5-FU based adjuvant ChT.[43] ChT improved local control, especially after CRT, but there were no differences in OS or DFS. The 5-year DFS was 58% in the ChT group and 52% in the control group (p = 0.13), while OS was 6 7% and 6 3% with and without ChT, respectively (p = 0,12). The problem with this study is that adherence to adjuvant ChT was 43%, so results are difficult to interpret.
- In the Netherlands, a multicenter trial known as PROCTOR/SCRIPT was conducted, in which a group of patients initially treated with short-course RT were randomized to adjuvant ChT vs. observation.[17] The regimen used was 5-FU in 177 patients (PROCTOR) and capecitabine in 292 patients (SCRIPT). Neither study recruited the expected number of cases, but even when analyzed together, the benefit of ChT was not demonstrated.
- Finally, the UK Chronicle study compared adjuvant ChT with fluopyrimidine vs. control in a group of patients operated on after CRT.[73] This study planned to recruit 800 patients but closed with only 113 cases. While 3-year DFS was higher in the group treated with ChT, although not significantly, OS was practically identical.
- Finally, a systematic review of these 4 studies was published, but it also failed to demonstrate differences in favor of systemic ChT in terms of OS, DFS, or the appearance of metastases.[16]

An important problem with adjuvant ChT lies in the difficulties in its administration, either due to delayed initiation or discontinuation. This issue is particularly complex in lower rectal tumors, as the ostomy often complicates management of nutrition and water-electrolyte imbalance. In general, it is recommended to start adjuvant ChT between 4 and 12 weeks after surgery. However, if its administration is delayed for more than 4 wee-

ks, there is data suggesting a 14% increase in mortality for every 4 elapsed weeks.[9]

Although the evidence regarding the benefit of adjuvant ChT in the context of neoadjuvant treatment is scarce and poor, its indication only seems useful in cases with nodal disease persistence, especially in stage ypN2. All this, added to the difficulties and the frequent delay in its application due to the postoperative consequences, only highlights the interest in TNT.

Benefit of adjuvant ChT in patients with pCR

Given all these difficulties, it has been questioned whether pCR to neoadjuvant therapy could be a predictor of the benefit of adjuvant therapy. There is much evidence from retrospective series, registry reports and even a meta-analysis, demonstrating the good prognosis of patients with pCR, which has raised doubts about the risk of overtreatment that the indication of adjuvant therapy could imply in this context.[91,135,145] However, several retrospective series reported benefits in overall survival.[47,103,124,179,228] It should be noted that these are retrospective data and have some inconsistencies. In fact in some of these series the benefits seem exaggerated.

Although the indication for adjuvant ChT is an IDT decision, it is generally not recommended in the context of pCR, except in cases with unfavorable characteristics or poor clinical staging prior to neoadjuvant treatment.

Benefit of adjuvant ChT in patients who do not respond to neoadjuvant treatment

A study that analyzed data from European studies concluded that adjuvant h provides greater benefits to patients who do not respond to neoadjuvant therapy, compared to those who reach pCR.[13,22,71,197,198]

The phase II study, known as ADORE Trial, demonstrated that patients with minimal response or ypN2 benefit from higher intensity ChT with the addition of oxaliplatin, compared to conventional treatment with fluopyrimidines.[99]

Given this scant evidence, it is not surprising that there is not even consensus among the most widely used international guidelines:

- The NCCN guidelines recommend that all of these patients receive ChT, even with a pRC after neoadjuvant therapy.
- ESMO guidelines suggest that adjuvant ChT be considered in stage III and high-risk stage II patients, although they emphasize that the level of scientific evidence is much lower than for colon cancer and is likely limited to a benefit in DFS and not OS.
- In contrast, the EURECCA experts concluded that there is insufficient evidence to recommend its use in this context.

This is also a decision of the IDT, but adjuvant treatment is generally recommended in the context of lack of response to neoadjuvant therapy, except in cases with very favorable histological characteristics and good clinical staging before neoadjuvant therapy, for example in low tumors whose indication was the preservation of the organ or the sphincter.

Adjuvant ChT after TNT

In patients who received TNT with at least 4 months of ChT, adjuvant ChT is not recommended.

ChT regimen of choice

Possible options for adjuvant ChT in patients who have received neoadjuvant therapy, with either CRT or short-course RT include leucovorin-modulated 5-FU bolus, leucovorin-modulated 5-FU continuos infusion, leucovorin-modulated 5-FU continuos infusion plus oxaliplatin (FOLFOX), or capecitabine plus oxaliplatin (CAPOX). Some groups routinely use an oxaliplatin-based regimen for all neoadjuvant patients, regardless of the pathology report of surgical resection (yp). However, a risk-adapted treatment strategy seems more reasonable. This implies the selection of an oxaliplatin-containing regimen in those patients with a lower degree of response, either ypT3-4 or N +. The latest results of the ADORE trial support the indication of oxaliplatin in patients with stage ypN2.[100] In addition, other factors such as performance status, presence of comorbidities and patient preference must be considered.

There are few randomized phase III trials comparing different postoperative regimens after neoadjuvant CRT and, although there is also no consensus, a 5-FU regimen modulated by leucovorin or capecitabine is uually indicated, extrapolating from experience in adjuvant colon cancer treatment. As with colon cancer, irinotecan-containing regimens cannot be recommended.

The role of higher intensity oxaliplatin-containing regimens (such as FOLFOX and CAPOX) has not yet been fully defined by phase III trials, but the following data are

available:

- The ADORE trial included 321 stage II and III patients treated with neoadjuvant CRT.[100] Randomization between the traditional 5-FU/leucovorin and FOLFOX regimens was performed after surgery, which reduced desertion. The oxaliplatin arm showed a significant benefit in DFS at 74 months, but not in OS, in exchange for greater toxicity. This DFS benefit was even more important in patients with stage ypN2 or very poor response to treatment.
- At least five published trials have examined the contribution of oxaliplatin to neoadjuvant CRT, but only two, PETACC and CAO/ARO/AIO-04, compared oxaliplatin with a ChT regimen without this drug, both during CRT and after surgery.[188,200] Although there were no significant differences in OS in either of these two studies, CAO/ARO trial reported a significant improvement in 3-year DFS with oxaliplatin, both for preoperative CRT and in the adjuvant setting.
- A meta-analysis that included the previously reported trials (PETACC-6, CAO/ARO/AIO-04 and ADORE), also concluded that an oxaliplatin-containing regimen could improve DFS, albeit with a higher incidence of Grade 3 or 4 nausea and vomiting.[258] There were no significant differences in terms of OS, hematologic toxicity, and diarrhea.

Expert group recommendation guidelines

- NCCN guidelines, based on the 2021 consensus, for adjuvant ChT after neoadjuvant treatment are based on initial clinical staging and can be summarized as follows:[159]
  - Clinical stages T1-2N0 would not require adjuvant ChT.
  - For patients without lymph node metastases in clinical staging, options include 5FU plus leucovorin, CAPOX, or FOLFOX. This includes T3N0 tumors with negative CRM, tumors with involved or threatened CRM, T4 or locally unresectable tumors, or medically inoperable patients. However, in all cases, oxaliplatin-containing regimens are preferred. An oxaliplatin-based regimen is recommended for patients with suspicious lymph nodes on clinical staging.
- The ESMO guidelines, by contrast, are based on pathological staging (yp). These guidelines emphasize that adjuvant ChT regimens based exclusively on fluopyrimidines has no demonstrated benefit in the context of neoadjuvant treatment and, conversely, the addition of oxaliplatin may improve DFS, although without benefits in OS. The recommendation is to treat patients with stage ypIII and those with high-risk stage ypII. The decision to indicate an oxaliplatin regimen must be made jointly by the IDT and the patient, considering the expected toxicity in each particular case and the risk of relapse.

Given the limited evidence and the disparity in recommendations, the decision to use or not an oxaliplatin-based ChT regimen after surgery should be based on yp staging, performance status, existence of comorbidities, and also patient's decision.