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# CHAPTER 16
# Neoadjuvant Treatment in Stage IV Tumors

To the complexity that the management of rectal tumors implies, it is not uncommon for the IDT to add an additional element, which is given by the possible coexistence of metastatic disease, which in turn can be resectable (or potentially resectable) or directly unresectable.

As if this were not enough, given the infinity of variables that influence the results of treatment in this context, the evidence is practically non-existent. We will not delve into decisions related to surgical management (whether it should be synchronous or staged, or whether the reverse approach should be considered, starting with liver resection before removal of the primary tumor) since it is not the objective of this report. However, as a general guideline, also from the surgical point of view it is preferable to initially focus on the control of metastatic disease (reverse approach), since the prognosis will depend on it to a greater extent. Instead, an attempt will be made to analyze the possible strategies of ChT added to neoadjuvant therapy in both contexts, depending to whether or not the metastatic disease is resectable. In any case, the criteria to indicate neoadjuvant treatment do not change, that is, it will be indicated based on the same parameters related to the primary tumor, regardless of the presence or absence of metastases.

**Resectable metastases**

The NCCN guidelines consider that systemic ChT should always be indicated in these cases, either before or after neoadjuvant therapy, for which long-course CRT or short-course RT are equally acceptable. In all cases, staged or synchronous surgery will follow systemic ChT and neoadjuvant therapy. Beyond the fact that both neoadjuvant regimens are included in the guidelines, short-term RT is preferred, since the duration of the long-course regimen with low-intensity ChT places patients at risk of spreading their systemic disease. It is evident that in this circumstance systemic ChT is essential and should be started as soon as possible, unless the symptoms of the primary tumor force us to act differently.

An interesting option proposed by a Korean group suggests starting with systemic ChT and continuing with short-course RT, but scheduling surgery after a long waiting period of 6 weeks, during which another 4 cycles of systemic ChT are applied. The objective is to intensify the treatment of the systemic disease, which will ultimately determine the prognosis of patients.[116]

In any case, in this complex context the only possibility of achieving cure is related to the possibility of resecting the entire disease with negative margins. However, the indications for neoadjuvant treatment of the primary tumor should not be neglected, since pelvic relapse is described in up to 34% of cases and there are even situations in which metastatic disease is controlled but locoregional relapse occurs with its associated morbidity.[24,117]

**Unresectable metastases**

In this situation, the primary objective is systemic control, so ChT is always indicated as the main and, sometimes, the only treatment. In fact, in cases where the primary tumor causes no symptoms, systemic CT is the only treatment to consider. In contrast, in symptomatic tumors, a short-course RT regimen could be indicated to avoid occlusion and the need for urgent surgical intervention.[44,238] This problem was addressed in a phase II study, in which 40 patients with symptomatic tumors and unresectable synchronous metastases received short-course RT (5 x 5 Gy) and oxaliplatin-based systemic ChT. The median survival was 11.5 months and only 8 (20%) patients required surgery during their disease. Symptoms resolved completely in 30%, and another 35% had significant improvement.[229] In the case of frankly obstructive lesions, a decompressive ostomy can be performed before ChT. The placement of stents constitutes an alternative and perhaps it is currently the best indication for the use of these devices. However, it is not always possible to use them in tumors affecting the lower rectum due to the risk of migration.

*In conclusion, in stage IV the main objective is systemic control, to which the indications for neoadjuvant treatment are subordinated, since the initial focus is placed on ChT.*