CHAPTER 5
Treatment Regimens

Once the indication for neoadjuvant treatment in the IDT has been decided, a wide range of possibilities opens up when defining the most appropriate treatment regimen for the case in question. This is a truly complex decision, as the regimens are subject to the continual emergence of clinical trials providing new alternatives, and the fact that the variables related to the patient and his/her history and tumor characteristics are endless. This makes it difficult to establish protocols in advance, and reinforces the importance of the IDT. However, there are some general guidelines that we will try to clarify:

- It is important to note that, since there is no definitive evidence, the best treatment regimen depends in part on the experience of the team and its results. Thus, in the USA there is a greater inclination towards long-course CRT regimens (fractionated RT concurrent with fluoropyrimidine-based ChT) than in Europe. This is especially recommended for bulky tumors, in which it is important to reduce tumor mass.
- In other cases, for example when neoadjuvant treatment has been decided in smaller tumors but with suspicious lymph nodes, or even in T3 tumors but with clearly negative CRM, the short-course RT regimen could be considered. This could also be an option in patients with co-morbidities that advise against a long-course regimen, or in stage IV cases in order not to delay an adequate ChT regimen.
- Patients with high metastatic risk, on the other hand, appear as good candidates for a TNT regimen (it will be developed in detail later), since one of the advantages of this strategy is precisely the greater compliance of ChT regimens with relation to those indicated after surgery. Among these cases are patients with obvious lymph node metastases, EMVI +, but it can also be considered in those cases with threatened or compromised CRM. On the contrary, it would not make sense in high T3 or low T1-T2 tumors, but perhaps consolidation ChT could be considered in the event of an almost complete response in order to preserve the sphincter or even the organ. Although some studies, such as OPRA and Prodige,[23] included low T3 N0 tumors, the indication of TNT in these cases is debatable.[41,65] It would only make sense if you were looking for a complete response to start a W&W protocol. Given that there are patients with poor response to ChT (particularly patients with high levels of microsatellite instability or defects in DNA repair), if TNT with induction ChT is indicated, it would be prudent to evaluate the response 2 months after the start of ChT, and in cases with poor or no results, go directly to CRT.
- Although short-term RT is not widely accepted in our environment, the experiences reported with short-term and long-wait RT, in the manner of CRT regimens, pose a new paradigm since responses comparable to those of the classical long-course regimen are obtained, reducing times. The results of the RAPIDO trial, which will be discussed in detail later, are a clear example.

Long-course regimen

From the clinical trial of the German Group for the Study of Rectal Cancer, it has been clearly demonstrated that preoperative CRT is superior to postoperative RT in terms of local relapses and preservation of sphincters, although without advantages in survival.[198] The German study clearly demonstrated the downstaging effect and benefits of giving RT before surgery rather than after. The addition of ChT concurrent with RT has also been widely shown to be beneficial, and this is one of the reasons that has led many specialists to favor long-course CRT over short-course RT.[12,14,28,72,146] Some randomized studies confirmed the ineffectiveness of oxaliplatin in radiosensitization and the increased toxicity implied by its concurrent use with RT.[3,69] However, the long-term results are not so well evaluated, so a benefit cannot be ruled out in the reduction of distant relapses in higher risk patients.

Short-course regimen

In opposition to the long-course regimen, more widespread in the US and Argentina, in other countries the short-course RT is preferred, supported by some studies that show similar results between both regimens.

As already mentioned, many studies have been published that demonstrated the superiority of the short-course regimen compared to surgery alone after the implementation of TME[10,140,141,173,183,202,212,251] (Table 9).

Short-course vs. long-course RT regimen

However, there are situations in which each of these two policies appears more reasonable.

- The long-course regimen is the choice in voluminous

TABLE 9: RESULTS OF TME WITH OR WITHOUT PREOPERATIVE RT

	n	LR (%)		OS/DFS (%)		Long-term results
		TME	TME+RT	TME	TME+RT	
Sweden, 2009	1168	27	11*	48	58*	RT > gastrointestinal disorders
Canada, 2010 (includes stage I)	1350	11	4.4*	79/72	80/78*	RT < quality of life and > sexual disorders
Holland, 2002	1861	10.9	5.6*	64	64*	RT > sexual disorders, fecal incontinence and perineal wound complications

**Significant difference*

lesions, or cT4 stage, as well as in those cases in which CRM involvement is suspected or R0 resectability is in doubt.

- On the contrary, the short-course regimen would be more indicated in patients not suitable for receiving a CRT regimen or in those with metastatic disease in whom it would not be desirable to delay the start of ChT.
- Finally, in patients with T3 tumors and free CRM, or T1-2 N1-2 tumors, both regimens are equally acceptable options.

Of course there are also trials that compared the short-course with the long-course regimen. Below we describe the findings of what we consider the most important:

- A study carried out in Poland randomized 312 patients with a 48-month follow-up and compared short-course RT with one-week surgery with a long-course regimen.[20] In the long-course group, pCR was 16% vs. only 1% in the short-course group, and this difference was significant. The difference in the number of patients with positive CRM was also significant, in favor of the long-course regimen. However, there were no differences in the number of local relapses or in survival. In favor of the short-course regimen, there was a lower incidence of early toxicity episodes (Table 10).
- Another study conducted in Australia randomly compared these 2 regimens in a population of 326 patients.[160] In this study, there was also a significant difference in the number of pCR, 15% with the long-course vs. 1% with the short-course regimen, but there were no differences in the incidence of CRM involvement or in sphincter preservation. Regarding local relapses, at 3 years there were 4.4% with the long-course and 7.5% with the short-course regimen, but without statistical significance. There were also no differences in metastatic relapses, survival, or toxicity.
- The same year, EORTC22921 study was published, in which 1011 patients with T3-T4 tumors were randomized into 4 arms:

RT + surgery
RT + surgery + adjuvant ChT

TABLE 10: COMPARISON OF SHORT-COURSE RT VS. LONG-COURSE CRT OUTCOMES

	RT + Surgery	QRT + Surgery	p
Local relapses	9 %	14.2 %	0.17
OS (4 years)	67.2 %	66.2 %	0.96
DFS	58.4 %	55.6 %	0.82
CRM +	13 %	4 %	0.017
Early toxicity	3.2 %	18.2 %	< 0.001
Late toxicity	10.1 %	7.1 %	0.36

TABLE 11: LOCAL RECURRENCE: EORTCC22921 TRIAL RESULTS

	RT + Surgery	CRT + Surgery	RT + Surgery + QT	QRT + Surgery + ChT	p
LR	17.1 %	8.7 %	9.6 %	7.6 %	0.002

CRT + surgery
CRT + surgery + adjuvant ChT

RT consisted of 45Gy for all groups, and the adopted ChT was 5-FU + LV. There were no differences in OS or DFS for any of the groups, but a lower number of local relapses were observed in the CRT + surgery + adjuvant ChT group in relation to the other 3 arms[13] (Table 11).

- Finally, a meta-analysis analyzed the incidence of local relapses in tumors located less than 5 cm from the anal margin and found no differences between these 2 regimens.[210]

These studies show the obvious downstaging effect that is obtained when the wait is prolonged after treatment with RT, something that also occurs when an identical waiting period is adopted with the short-course regimens. However, long regimens seem to lead to greater toxicity without such clear benefits in terms of local relapses.