CHAPTER 3
Rationality of Neoadjuvant Therapy

As already described, in 1990 the consensus of the National Cancer Institute in the USA established that combined postoperative ChT and RT improve local control and survival in stages II and III and should be recommended.

Simultaneously, in Europe, the EORTC publishes a series of 341 patients operated with curative intent in which the addition of preoperative 34.5Gy of RT allowed a significant reduction in local relapses, although with no changes in 5-year OS70 (Table 2).

Some years later, the Swedish Rectal Cancer Trial shows how a RT regimen of 25Gy delivered preoperatively in 5 to 7 days, followed by surgery one week after completing RT, allowed in 1168 patients a significant reduction in local recurrences and an improvement in 5-year survival. This is the first study that shows any influence of RT not only in terms of local control, but also in survival, but it should be mentioned that this experience was carried out in previously to the dissemination of the TME technique in that country[217] (Table 3).

In the USA, the group from the Memorial Sloan Kettering Cancer Center (MSKCC) publishes a series of 32 patients with stage T3 tumors who undergo a preoperative regimen of 5040 cGy associated with ChT with 5-FU and LV.[76,151] After a short follow-up of 22 months, no local relapses were found, but what is interesting is that the sphincter was preserved in 85% of cases and in 9% of the specimens no residual tumor was found on microscopic examination.

Some years later, this same group published a series of 297 patients with T3-T4 or N1 tumors located up to 15 cm from the anal margin treated with 1900 to 5040 cGy + 5-FU followed by surgery at 6 weeks.[79] With an average follow-up of 44 months, they obtained 4% local recurrences (Table 4).

Thus, in Europe and the United States, two different regimens of neoadjuvant treatment are being developed in parallel, mainly based on RT. In Europe, the most widely adopted protocol, known as "short-course RT", consists of 2,500 cGy delivered on 5 days followed by surgery after a period of 5 to 14 days. While in the USA, the "long-course RT" regimen is applied, which consists of a total dose of 5040 cGy (daily fractions of 1.8 to 2 Gy) for about 5 weeks, associated with ChT based on fluoropyrimidines with the aim of increasing radiosensitivity, followed by surgical treatment after a period of no less than 4 weeks.

TABLE 2: SURGERY ALONE VS. SURGERY + PREOPERATIVE RT.

	RT + Surgery	Surgery	p
Local relapses	15%	30%	0.003
Overall survival (5 years)	69.10%	59.10%	0.08

TABLE 3: SURGERY ALONE VS. SURGERY + PREOPERATIVE RT (SWEDISH RECTAL CANCER TRIAL).

	RT + Surgery	Surgery	p
Local relapses	11%	27%	0.001
Overall survival (5 years)	58%	48%	0.04

TABLE 4: PREOPERATIVE CRT. MSKCC´S EXPERIENCE.

Type of relapse	N
Local only	7 (2%)
Local and distant	5 (2%)
Distant only	55 (19%)
Total	67 (23%)

Given the spread of these two currents of treatment, both opposed to the concept of adjuvant (postoperative) RT or CRT, a controversy arises as to when treatment with RT or CRT should be applied.

Table 5 summarizes the advantages and disadvantages of preoperative or postoperative radiotherapy.

This controversy seems to have come to an end with the publication in 2004 in the New England Journal of Medicine of the study conducted by Sauer, known as the German Trial.198 This study showed that the indication of preoperative RT reduced significantly the number of pelvic relapses from 13 to 6%. There were no differences in survival, but it was possible to increase sphincter preservation significantly and the anastomotic strictures were reduced (Table 6).

TABLE 5: ADVANTAGES AND DISADVANTAGES OF PRE AND POSTOPERATIVE RT

	Advantages	Disadvantages
Preop.	More oxygenated tissues	Over-treatment (Role of HR-MRI)
	Less possibility of intraoperative tumor spread	Disappearance of metastases (CRT)
	Less toxicity on the small bowel and the anastomosis	
	Downstaging and sphincter preservation	
	Greater local control	
	Degree of response can predict survival	
	Treatment delay due to surgical complications is avoided	
	Better functional results by not irradiating the colon to be anastomosed	
Postop.	It is performed after histopathological staging	Delay or inability of application due to postoperative complications
		Irradiation of anastomosis
		Less sphincter preservation

The theoretical advantage of irradiating tissue not affected by postoperative hypoxia, the possibility of reducing the size of some tumors, facilitating the operation and even hypothetically increasing sphincter preservation, the lower probability of actinic enteritis and the execution of the anastomosis in a non-irradiated colon are the reasons that motivate the current preference for neoadjuvant therapy, instead of postoperative RT as previously used. On the other hand, the risk of overstaging and unnecessarily treating a group of patients with RT is compensated for and even lower than the risk of understaging and forcing a postoperative treatment that can lead to worse oncological outcomes and greater complications.[78] Moreover, as mentioned among the advantages of neoadjuvant treatment and confirmed by Sauer's study by demonstrating greater sphincter preservation, the beneficial effect in terms of local control is added to the effect known as downsizing (decrease in tumor size), which facilitates the surgical technique and even allows considering a change in the previously proposed tactic.

Besides the downsizing of the primary tumor, a similar effect is produced in the involved nodes, and has been verified a smaller number of nodes in surgical specimens.

At present, there is another reason in favor of neoadjuvant CRT, which appears with the experience obtained after years of its application. This is based on the fact that the prognosis of patients with rectal cancer operated after neoadjuvant treatment is more related to postoperative pathologic staging (yp) than to preoperative clinical staging (c), which suggests that response or non-response is in some way a determining factor of tumor biology, very useful to define the need to add ChT to treatment. In particular, patients staged with ypN2, given their poor prognosis, are clear candidates for adjuvant treatment.[31,119,168,254]

TABLE 6: SUMMARY OF GERMAN TRIAL RESULTS

Pelvic recurrence	6	13	0.006
Distant recurrence	36	38	0.84
Overall survival	68	65	0.32
Disease-free survival	76	74	0.8
Sphincter preservation	39	19	0.004
Anastomotic stenosis	4	12	0.003

On the other hand, short-course RT would allow the application of this therapeutic modality in a more rapid way and thus intensify ChT in patients with rectal cancer at risk of compromised CRM and potentially resectable synchronous metastases.[18,89,177,203]

Neoadjuvant therapy has definitely established itself as a therapeutic strategy based on its obvious benefits that far outweigh the eventual risk of overtreatment, which is decreasing in light of improvements in staging.

Is neoadjuvant treatment necessary in the era of TME?

Since many studies demonstrating the benefits that RT adds to surgery were conducted in the days before the spread of the TME technique, several studies subsequently attempted to establish whether the addition of RT improves the results of rectal cancer resection performed following the precepts of Heald. The Swedish study that demonstrates the advantages of short-course RT in the stage prior to the diffusion of the TME technique in that country has already been mentioned.

Thus, in 2000, Cammà et al.[25] published in JAMA a systematic review that included 14 randomized clinical trials, with 6,426 patients. This meta-analysis showed that the addition of RT favored patients in terms of global mortality, cancer-associated mortality, and local recurrences.

In 2001, a clinical trial carried out in the Netherlands was published, in which surgery with strict application of TME as the only treatment was compared with the same surgery associated with preoperative RT, at a dose of 25 Gy according to the short-course strategy.[108] Special attention was paid to the surgical technique, specifically respecting the TME technique. Local relapses were analyzed in 1,653 M0 cancers with complete resection and a mean follow-up of 25 months. Both at 2 and 4 years the number of local recurrences was lower in the group that received preoperative RT (Table 7).

The sample was stratified according to tumor height and TNM stage. This benefit was found to be greater in tumors of the middle rectum than in those of the lower rectum, and that it does not occur in upper third rectal tumors. Likewise, it was found that RT did not improve the results in stages I and IV, but it did in stage II and even more so in stage III. In 2007, the results were published after 6 years of follow-up, and the advantages of RT were maintained.[172] Although, they were not found to be evident in low and stage II tumors, they were evident in the middle rectum and stage III tumors. On this occasion, recurrences in tumors with and without CRM were also analyzed. Unsurprisingly, RT was found to provide no benefit when it fails to make this margin negative (Table 8).

TABLE 7: DUTCH TME TRIAL RESULTS (TME VS. TME + PREOPERATIVE SHORT-COURSE RT

	Local relapses (2 years)	Local relapses (4 years)	p
TME	8.2%	10%	
TME + RT	2.4%	3%	< 0.001

TABLE 8: LOCAL RELAPSES ACCORDING TO CRM INVOLVEMENT WITH OR WITHOUT PREOPERATIVE SHORT-COURSE RT

CRM	TME + RT		TME		p
	n	RL (%)	n	RL (%)	
+	136	19.7	144	23.5	0.393
-	715	3.4	717	8.7	< 0.001

With this study, it was definitively concluded that although TME alone had significantly improved rectal cancer treatment outcomes, RT provides in certain cases an additional benefit that should not be overlooked.