CHAPTER 2
Historical Context

Influence of surgical technique

The anatomical definition of the rectum is itself controversial; the accuracy of this definition is important, because the recommended treatment modalities for the rectum, colon, and anus differ significantly.

In 2000, the rectum was defined as the last part of the digestive tract up to 12 cm from the anal margin as determined by rigid proctoscopy. This definition was based on a study that showed differences in local recurrence rates for lesions located above 12 cm from the margin (9.6%) compared to those located below that height, in the middle and lower rectum (30.1 and 30.7%, respectively). Although this definition has been used commonly it is imprecise, since it is not the same in patients of 1.5 or 1.9 meters of height, for example.

Based on these discussions, the NCCN guidelines in version 6.2020 have defined the rectum by placing it below a virtual line that runs from the sacral promontory to the superior border of the symphysis pubis as determined by the HR-MRI, and ending at the superior border of the functional anal canal, defined as the palpable superior border of the anal sphincter and the puborectal muscles at the level of the anorectal ring. Likewise, the rectum can be divided into superior, middle, and inferior based on the location of the anterior peritoneal reflection as determined by CT or HR-MRI. Accordingly, the upper rectum is above the anterior peritoneal reflection, the middle rectum at the level of it, and the lower rectum below. The length of the anal canal is also variable, and usually longer in men than in women. Tumors located in the proximal rectum, at the level of the sacral promontory, behave similarly to colon cancers and therefore, the therapeutic strategy is assimilated to tumors of the distal sigmoid. They are commonly referred to as rectosigmoid junction tumors. On the contrary, it should be taken into account that low tumors may involve the anal canal, the internal and external sphincters, or the levator ani muscles.

The details related to surgical treatment are not the object of this report, but it should be mentioned here that rectal cancer surgery is one of the surgical areas in which it has been shown that specialization and the volume of patients treated contribute significantly to improving the results, both in morbidity and mortality and in oncologic prognosis. As an example, in 1998 Porter et al, published that a specialized surgeon who performs more than three operations per year for rectal cancer has 10% local recurrences, compared to 45% obtained by a surgeon who does not have this experience.[180]

Heald's detailed description and bibliographic spread of the TME technique is another factor that definitely contributes to the reduction of local recurrences throughout the world.[92,93] So much so that at present, incidences of recurrence above 10% are not considered acceptable, when previously figures above 30% were reported. Kockerling et al.[120] published how the implementation in Sweden of the technique according to Heald's teachings, in a series of more than 1500 patients operated on consecutively with a follow-up of more than 13 years, allowed diminish significantly the recurrence rate from 39.4 to 9.8% and also increased global survival (Table 1).

TABLE 1: CHANGE IN OUTCOME AFTER IMPLEMENTATION OF TME IN SWEDEN.

	Local relapses	Overall survival (5 years)	p
Pre TME	39.4%	50%	< 0.0001
Post TME	9.8%	71%	

TME is recommended for all tumors located in the middle and lower rectum. For tumors of the upper rectum, a 5 cm resection of the mesorectum below the lower limit of the tumor is sufficient.

In any case, the complexity in decision-making, as well as the continuous innovation in the different techniques for the treatment of these tumors, make their management essential by surgeons not only specialists in coloproctology, but perhaps also super specialized in this disease.

Adjuvant treatment

The two main components of adjuvant therapy for rectal cancer, and when we talk about adjuvant we talk about postoperative treatment, are RT to the pelvis and ChT regimens based on 5-FU.

Adjuvant chemotherapy

The main objective of ChT is to decrease the probability

of distant relapses. Its indications in rectal cancer are not different from those considered for colon cancer, that is, to increase survival time by reducing the possibility of metastatic relapses. However, the same type of drugs can be used concurrently with RT for rectal cancer, and in this case is intended to increase the sensitivity of the tumor to radiation. In the course of this report we will see that ChT can also precede surgery beyond its radiosensitizing effect.

We will not deepen into aspects related to adjuvant ChT outside the neoadjuvant context, since not only is it beyond the scope of this report, but in that situation it does not offer differences in relation to the management of any colorectal cancer.

Postoperative radiation therapy

The objective of adjuvant RT is to increase local control in stages II and III, but as we will see throughout this report, when it is indicated preoperatively as neoadjuvant treatment, it also aims to increase the rates of negative circumferential resection margin (CRM), the preservation of the sphincter, and even more, the preservation of the rectum.

Three randomized clinical trials have been conducted comparing surgery alone with surgery plus postoperative RT for T3 or N1-N2 rectal cancer. The only one showing a decrease in the local recurrence rate was the NSABP R-01 trial.56 Local recurrences decreased from 25% in the surgical arm to 16% in the postoperative RT arm (p = 0.06). Several clinical studies have shown a decrease in local recurrence rates to the level of 6 to 8%. Differences among these trials may reflect patient selection and radiation therapy dosage. These studies reported that postoperative RT could reduce local recurrence, but the technique and the total dose were important to achieve this effect. Despite these results in terms of local recurrence, neither survival nor distant recurrences improved with RT at doses of 45 to 50 Gy. This was one of the reasons that led to the consideration of adding ChT to RT in the postoperative period.

Currently, as we will see later, adjuvant RT should be an exception, since tumors that benefit from this treatment to improve local control would have to be identified before surgery.

Postoperative chemoradiotherapy

As already mentioned, the addition of ChT to RT has been used to improve the sensitivity of tumors to radiation and reduce distant relapses. Several studies have shown to improve local control and survival.

The Gastrointestinal Tumor Study Group trial compared the following treatment arms:[222]

A. Surgery alone
B. Surgery followed by postoperative RT (40-48 Gy)
C. Surgery followed by postoperative ChT (bolus of 5-FU and semustine)
D. Surgery followed by concurrent RT and ChT

This study demonstrated a decrease in pelvic failure for the group treated by surgery and postoperative CRT (11 vs. 24% for surgery alone). In addition, a statistically significant 7-year survival advantage was found using the combination of resection, RT and ChT.

The NCCTG subsequently conducted a randomized clinical trial in which 204 patients were assigned to RT (45-50.4 Gy in 25-28 fractions) with or without concurrent ChT (5-FU bolus).123 There was a significant decrease in pelvic recurrence (14 vs. 25%) and a significant decrease in cancer-related deaths for the group treated by resection, RT, and ChT compared to the group treated with resection and RT.

Findings from these studies prompted publication of a recommendation at a National Cancer Consensus Conference Institute (NCI) in 1990, establishing the indication of adjuvant treatment for patients with rectal carcinoma T3-T4 N0, or N1-N3 (stages II-III) consisting of six cycles of ChT based on 5-FU and concurrent RT to the pelvis.162 This regimen became the standard against which all adjuvant treatment protocols for rectal cancer are compared. In fact, in the United States, postoperative CRT became the most common mode of offering adjuvant therapy, generally administered as a continuous infusion of 5-FU and approximately 50.4 Gy of pelvic RT in daily fractions of 1.8 to 2.0 Gy (6-week treatment).

Although the trend in Europe was to treat with RT without ChT, the strategy used in the US adding ChT showed better distant control and fewer metastases. Furthermore, a 10-15% survival advantage was demonstrated. Intergroup trial 0114 was designed to study the effects of using immunomodulators in combination with ChT during RT.[206,220] It failed to demonstrate advantages with the use of levamisole and / or LV as an addition to the 5-FU bolus in this instance. The NCCTG study, for its part, did show that 5-FU in infusion compared to bolus administration improved DFS and overall survival (OS).[163]