CHAPTER 1
Introduction

According to US statistics, more than 43,000 new rectal cancers are diagnosed each year in that country alone.[204] Although rectal cancer shares many characteristics with colon cancer, its location within the bony pelvis gives it very special characteristics, since it makes removal with free margins more difficult. Although rectal cancer shares many characteristics with colon cancer, its location within the bony pelvis gives it very special characteristics, since it makes it difficult to remove with free margins. But it also differs in the double lymphatic drainage, especially in the lower rectum, with a direct extension to the systemic circulation through the internal iliac chains, which is added to the portal circulation. Moreover, since the rectum is surrounded by nerves that play important roles in sphincter, urinary and sexual functions, treating its tumors poses a special challenge. In particular, when the necessary precautions for the preservation of the pelvic nerves are not followed, the surgical treatment of rectal tumors can generate functional disorders of all the mentioned areas.

All these differences have caused moderate results with surgical treatment, which motivated interest in associating it with chemotherapy and radiotherapy. On the other hand, specifically in tumors of the lower rectum, the previous difficulties are compounded by the need to resort to an ostomy, which can be overcome with a local resection in early tumors and with multimodal management in advanced ones. Fortunately, the treatment of rectal cancer has undoubtedly evolved in recent years, with a notable reduction in the incidence of local recurrences. This change is attributed both to the refinement of surgical techniques and the improvement of staging methods and the introduction of adjuvant and neoadjuvant (preoperative) treatments, in which radiotherapy (RT) and chemotherapy (ChT) are combined according to different protocols.

To get an idea of the complexity that rectal cancer treatment has acquired, it is enough to list the variants in which it is possible to combine some or all of these therapeutic modalities, considering that ChT and RT can be applied separately and simultaneously or concurrently, the so-called chemoradiotherapy (CRT):

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- ChT - RT

However, the complexity does not end here, since it should be noted that there are variants for each of these forms of treatment.

Surgery, for example, in early stage tumors can take the form of a transanal local excision (TAE) either conventionally or through the endoscopic microsurgical approach, originally known as TEM (Transanal Endoscopic Microsurgery), but which over time was subject to changes and variations that allowed widening its acceptance. In more advanced cases, however, a total mesorectal excision (TME) is necessary, which inevitably requires an abdominal approach. This can take the form of an anterior resection, an intersphincteric resection, or an abdominoperineal resection (APR), either via laparotomy, laparoscopy or robotically-assisted surgery. But more recently this abdominal approach has been complemented with the transanal access, known as taTME (TransAnal Total Mesorectal Excision), in order to complete the most difficult part of the TME, particularly in obese male patients with prostatic hypertrophy, in whom even the most advanced minimally invasive methods do not allow good vision or ease of maneuvering. All these techniques have undergone modifications and changes in recent times, which have made it possible not only to improve oncologic results, but also functional results, which are equally important. Therefore, it is essential that the surgeons who operate on these tumors are trained and up-to-date.

RT for its part, as will be seen later, can be applied in

different ways. If we only consider external RT, a long or short-course regimen can be followed. Moreover, there are new modalities such as three-dimensional image-guided RT and the even more advanced variant, intensity-modulated RT. But in addition, the doses can vary and also the interval in which RT is combined with the surgical approach.

In relation to ChT, various drugs are used, such as 5 Fluoruracil (5-FU), leucovorin (LV), capecitabine, oxaliplatin and irinotecan, which are indicated according to various administration and dose regimens. Furthermore, neoadjuvant regimens have recently been proposed that include molecular therapies such as bevacizumab and cetuximab and the newer nivolumab, ipilimumab and pembrolizumab, in order to increase systemic control in patients at high risk of developing metastatic disease, such as those with extramural vascular invasion, (EMVI) in high resolution magnetic resonance imaging (HR-MRI).[244]

On the other hand, it should be considered that a significant portion of rectal cancers present with metastatic disease, which requires the incorporation of new drugs and the consideration of other strategies, including surgical treatment of metastases simultaneously with excision of the primary tumor, or even before it, a tactic known as a "reverse" approach.[242]

However, the complexity is still not exhausted here, since many variables that influence in one way or another must be carefully evaluated. For example, sex, that is important due to the different anatomical conformation of the pelvis, age and the need to take measures to preserve fertility, history of other neoplasms and as a result, having received RT and even previous surgeries, and the possibility of being faced with a hereditary cancer, among others.

The truth is that a little more than 15 years ago, when the benefit of indicating RT preoperatively and not after surgery was demonstrated, the picture seemed to have cleared up. At that time, rectal cancer was mainly staged with computed tomography (CT) and endorectal ultrasound (ERUS). HR-MRI was not so widespread, and laparoscopic surgery was viewed with caution because its oncologic radicality raised doubts. According to the factors T and N, basically 2 different strategies were adopted. In the cases staged as T3, T4 or N +, RT (or CRT) was started, after which TME was carried out through open surgery, while T1 or T2 were treated only with surgery. ChT, as adjuvant treatment, was only considered at the end of all of the above, which often resulted in patients not receiving systemic treatment until about 6 months after diagnosis.

This approach to the problem seemed simple, but it carried several risks:

- In addition to the fact that HR-MRI was not used and staging was not as accurate as it is today, this strategy implied the possibility of under-treating some patients, exposing them to a poor oncologic result, or over-treating and causing unnecessary complications due to adverse effects of the treatments, or sequelae of unnecessary surgeries, since in a non-negligible number of patients, complete responses to the treatment were found in the histopathology examination.
- On the other hand, the aforementioned delay in establishing a systemic therapy meant that improvements in local control were not accompanied by benefits in terms of survival.

These 2 risks, added to the advances in staging (specifically in the use of MRI), the new RT techniques, the most modern ChT regimens and the advances in minimally invasive surgery, poses today a completely different and much more complex panorama.

While the goal of reducing local recurrences remains of great importance today, two other potential benefits have been added: the possibility of prolonging survival and the goal of rectal preservation. For the first, the therapeutic regimens that indicate ChT prior to surgery, known as total neoadjuvant therapy (TNT) are developed. For the latter, non-operative treatment (NOT) investigations are carried out, following the strategy known as watch and wait (W&W).

The interesting thing is that the results of TNT protocols seem to show better figures in terms of pCR, which in theory would allow increasing the number of patients in whom the organ could be preserved. In this way, the proposed strategy to improve survival also appears to contribute to rectal preservation.

It is clear that in making all these decisions, the different staging methods applied both before and after neoadjuvant treatment play a fundamental role in order to evaluate its effects. Among these methods, proctologic examination, endoscopy and imaging stand out. As already mentioned, in addition to CT and ERUS, HR-MRI has acquired a relevant role. The place of positron emission tomography (PET-CT) is less clear in local staging, and it is used mainly in patients at high risk of metastatic disease. This method also does not appear to have the expected role in evaluating responses to neoadjuvant treatment.

It is desirable, and even essential, that all decisions are made after discussion in interdisciplinary team meetings, a topic that we will delve into during this work. We clarify that despite the fact that the term and abbreviation "interdisciplinary team" (IDT) is less widespread than that of "multidisciplinary team" (MDT), we believe that

the former better reflects the need for interaction between all participants, and so it will be used throughout the work.

We will try to address all these aspects in a simple way, but that allows the specialized surgeon to face the challenge of treating these patients, making the most of the discussion in the context of interdiscipline.

Finally, it should be clarified here that this report will deal with aspects related to daily practice, without dwelling on lines of research that still do not reach clinical utility, such as the prediction of response through genetic studies.