CHAPTER 9
Neoadjuvant Treatment Indications

Due to the great heterogeneity that occurs in patients with rectal cancer, when defining the indication and the neoadjuvant treatment strategy, some general guidelines should be considered:

- On the one hand, the obvious need to stratify risk according to clinicopathological factors (e. g., T and N staging and perhaps histological grade) and preoperative staging by HR-MRI (e. g., CRM involvement), in order to adapt and individualize the indication.
- Second, a specific goal for treatment must be set. As an example, if the preservation of the organ is sought, it is preferable to indicate the prolonged regimen of CRT, although the most recent evidence also shows good results in this regard with regimens of short-duration and long-wait RT or TNT consolidation.

The main indication for neoadjuvant treatment, supported by results of randomized trials, is the presence of a tumor staged as T3 or T4, prior to any treatment. Preoperative long-course CRT or short-course RT is classically recommended for these patients, followed by surgical resection and subsequent adjuvant ChT.

A relative indication is the presence of nodes suspected of being positive on HR-MRI or ERUS. However, determining the positivity of the nodes can be particularly difficult. Most of the involved lymph nodes are smaller than 1 cm and furthermore, not all lymph nodes seen with ERUS or HR-MRI represent metastatic disease.

Objections to these indications

The reality is that the review of some studies allows us to infer that the presence of invasion of the perirectal fat, as well as the existence of metastatic lymph nodes by themselves, does not imply a mandatory need to indicate neoadjuvant treatment:

- In 1999 Willett et al.,[250] from the Massachusetts General Hospital in Boston, in patients with low-grade T3 N0 tumors with invasion of the mesorectal fat < 2 mm and without vascular or lymphatic invasion obtained 5% of local relapses without RT, in contrast to 29% in tumors of the same stage but with the aforementioned risk factors that were irradiated.
- In 2005, an experience from the Cleveland Clinic in Ohio was published, showing that the addition of postoperative RT has no effect in reducing local or distant recurrences in patients with T1 or T2 tumors, N1.[111]

From these two experiences, it could be assumed that in T3N0 or T1-T2N1 tumors a correct surgery with an adequate TME should be sufficient.

On the other hand, a study published by Simunovic et al.,[205] in 2003, showed that the indication of preoperative RT in high-risk tumors due to their size, fixity and proximity to the anal margin and the rectal fascia, did not prevent recurrences from being greater than in patients with tumors without these risk factors who had not received neoadjuvant treatment. This result was one of the reasons that strengthened the idea that there is a subgroup of patients in whom it is necessary to take one more therapeutic step, with the aim of improving cancer outcomes.

As early as 2001, Myerson et al.,[158] in a series of 384 patients treated with neoadjuvant RT, analyzed the number of recurrences according to the presence of 4 risk factors (distance to the anal margin <5 cm, circumferential, fixed or occlusive tumor). They verified that 2% recurrences in patients without risk factors, 10% when there were up to 2 factors and 26% when there were 3 or 4 factors. They suggested that in this group of patients some form of ChT should be added to neoadjuvant RT, and not only as a radiosensitizer. In some way, this was a thought that strengthened the spread of long-course CRT to the detriment of short-course RT and was also a precursor to the induction ChT and TNT regimens.

Based on the favorable rates of local recurrence after TME alone in the Dutch trial and in several other retrospective studies and a prospective observational study, the usefulness of neoadjuvant therapy has also been questioned in patients with T3N0 tumors without mesorectal fascia involvement, particularly those located in the upper part of the rectum.[30,108,161,172,194]

On the other hand, in a review of 188 patients with cT3N0 tumors by ERUS and HR-MRI who received neoadjuvant CRT, the histopathology of the specimen showed that 41 (22%) had positive mesorectal lymph nodes at the time of surgery.[78] Given the downstaging effect of CRT, it is likely that an even larger number of patients could have had lymph node disease and perhaps required preoperative treatment, had initial surgery been indicated.

It is evident that management of T3 or N + tumors has been and continues to be highly controversial topic, so various groups consider it necessary to make their decisions based on some additional staging. The different pu-

blished international guidelines have some variants for the T factor depending on the depth of mesorectal invasion (levels T3a, T3b, T3c and T3d), since some studies have shown a low risk of recurrence in superficial T3 tumors. Likewise, importance has been given to the number of lymph nodes described (levels N1a, N1b, N2a, N2b and N3), due to the fact that in reality lymph node involvement fundamentally implies a systemic rather than locoregional risk.

In particular, the ESMO guidelines base the indication on the size of the node (> 5 mm). Several studies have shown that T3 tumors with invasion > 5 mm have a higher rate of lymph node involvement and lower cancer-specific survival compared to tumors with a penetration depth ≤ 5 mm.[182,148] These findings have led to some suggest that the distinction between T2 and T3 tumors is not as necessary as the identification of high-risk T3 tumors with a depth of invasion > 5 mm.[52] In fact, ESMO guidelines suggest that patients with a depth of invasion ≤ 5 mm are appropriate candidates for initial surgery rather than neoadjuvant therapy, even if they have positive nodes, as long as neither the levator muscles nor the mesorectal fascia are threatened and the surgeon has the ability to perform a correct TME by applying the principles stipulated by Heald.

Although HR-MRI can accurately subclassify those patients with T3 tumors, this subclassification was not incorporated into TNM staging and has not yet been validated as a prognostic factor, thus the possibility of defining the indication for neoadjuvant treatment based on the depth of invasion is not yet standard, at least in the United States.[218]

To date, given the limitations of the images, various groups in the United States consider that all patients with adenocarcinoma of the rectum cT3N0 by ERUS or HR-MRI are suitable candidates for neoadjuvant treatment, since it is estimated that around 20% of patients may be understaged.

Other indications

A finding that is generally accepted as an indication for neoadjuvant treatment is the presence in imaging studies of an invaded or threatened CRM, due to the reduced probability of achieving a negative CRM in surgery, which is associated with a high risk of local recurrence.

The presence of EMVI, although it is a factor more associated with systemic disease, is also considered an important finding when evaluating the indication for neoadjuvant treatment.

Beyond its prognostic implications, the presence of extramesorectal lymph node disease, in particular the presence of LLN, is another indication for neoadjuvant treatment.

Tumor height is also an important factor since low tumors are known to have higher local recurrence rates. But to be more specific, the need to avoid APR in patients with correct sphincter function has recently been added as a neoadjuvant treatment indication, even in patients with T1 or T2 tumors but with a high surgical risk or who refuse a definitive ostomy. However, the use of neoadjuvant treatment in stage I tumors (T1-T2 N0) is controversial and has not yet been approved as a standard. Both the American (NCCN) and the European (ESMO) guidelines consider transabdominal surgery as the approach of choice in these cases. Neoadjuvancy in early stages was evaluated in order to achieve sphincter preservation, but this has not been demonstrated. Furthermore, it is doubtful whether these patients benefit in terms of local control. Despite this, it is important to note that, for many patients in whom surgery is contraindicated or refused, RT or CRT may be the only available treatment regimen.

In the particular case of cT2N0 tumors, in which transanal resections have an unacceptable local recurrence rate, new alternatives have been proposed based on the appearance of some studies. In the phase II ACOSOG Z6041 trial, patients with T2N0 rectal tumors received CRT with capecitabine plus oxaliplatin followed by local resection. After a 56-month follow-up, local recurrence rate was 4% and DFS at 3 and 5 years was 86.9 and 80.3%, respectively. These results suggest that neoadjuvant treatment followed by local resection may be an alternative treatment to radical surgery in selected patients with T2N0 tumors as a way of achieving sphincter preservation and avoiding a definitive ostomy.

The same approach could be adopted in order to avoid a coloanal anastomosis in patients with poor sphincter function and at high risk for major surgery or who refuse it. This would be a case where the goal is clearly the preservation of the organ. Although some recent studies have shown good rates of cCR with a short-course RT regimen and delay in surgery, the regimen chosen in these cases should be long-course CRT, or even more, as will be discussed later, preferably consolidation TNT.

Neoadjuvant treatment followed by TAE could be feasible as an alternative to TME in distal T2N0 tumors with good response, although not necessarily cCR.[186,191,246] However, this is not yet a standard strategy, especially when there is direct invasion of the sphincter. The NCCN and ESMO guidelines consider transabdominal surgery the approach of choice in this si-

tuation, except in patients with high surgical risk due to age or comorbidities, or who refuse transabdominal surgery. In this case, they should be warned about the possible complications of TAE in the context of neoadjuvant treatment and the difficulties of performing TME if the definitive histopathology reveals that TAE was not enough.

Beyond the different opinions, the lack of absolutely conclusive evidence and the existence of innumerable additional factors, the findings related to the tumor that should make the IDT evaluate the indication for neoadjuvant treatment are:

- *Tumor invasion beyond the muscularis propria.*
- *Suspicious mesorectal lymph nodes.*
- *CRM involvement.*
- *EMVI +.*
- *Suspicious LLN.*
- *Indication of APR.*
- *To avoid a coloanal anastomosis (high risk or patient refusal).*

The role of HR-MRI in the indication of neoadjuvant treatment

Currently, no one doubts that HR-MRI is the quintessential staging method for rectal cancer. Bernier et al.[8] describe the therapeutic management of rectal cancer patients at the Royal Marsden Hospital, where decisions are made based on the findings of this study. At this center, the following patients are included in the good prognosis group:

- T3a-b tumors of the upper and middle third of the rectum.
- Any N (but negative N1c).
  CRM and EMVI negative.

These cases have an indication for TME without neoadjuvant therapy. In contrast, patients with T3c-d, EMVI +, N1c, or involved CRM are selected for neoadjuvant CRT.

We will summarize some studies that demonstrate the fundamental role of HR-MRI in the indication of neoadjuvant treatment:

The Mercury group published a prospective and multicenter study, which demonstrated the efficacy of HR-MRI for the adequate staging of patients, which allows differentiating those who will have a good evolution with primary surgery as the only treatment from those who should receive neoadjuvant treatment.[218] Thirty-three percent of patients (122/374) with stages I, II or III by HR-MRI were considered to have a good prognosis. In this group of patients, OS and DFS was 68 and 85%, respectively and the local recurrence rate was 3%.

The criteria for a good prognosis were the following:

- T1-T2 or T3a-b tumors (extramural depth of invasion < 5 mm) with potentially negative CRM (tumor >1 mm from the mesorectal fascia) and any N stage.
- Absence of EMVI.
- Lack of involvement of the intersphincteric space or the levator muscles.

The findings considered to be of poor prognosis were:

- T3c-d (extramural extension > 5 mm) or T4 tumors.
- CRM + (<1 mm) or involvement of intersphincteric space
- Presence of EMVI.

Of the 122 patients with a good prognosis by HR-MRI, only 8 (6.5%) had 4 or more involved lymph nodes (N2) in the histopathology. The important thing is that no patient had to receive postoperative RT. The centers participating in the study do not routinely indicate neoadjuvant treatment to those patients with T3 tumors with a good prognosis, regardless of factor N. The results validate this strategy that, due to the adequate selection of tumors with a good prognosis by means HR-MRI and the performance of quality TEM prevented neoadjuvant treatment in 30% of patients.

The QuickSilver Clinical Trial is a phase 2 study that evaluated the safety and feasibility of using HR-MRI in order to select patients with rectal cancer with a good prognosis for primary surgery.[113]

The following criteria were considered to have a good prognosis:

- T2, T3 tumors with an extramural depth of tumor invasion < 5 mm.
- Distance to the mesorectal fascia > 1 mm.
- Absence of EMVI.

The rate of compromised CRM was 4.9% (4/82), also suggesting that CRT may not be necessary for all patients with stage II and III rectal cancer.

These studies and experiences show that HR-MRI is an essential study in the clinical staging prior to any treatment of rectal cancer, especially in locally advanced tumors. In our opinion and experience, the presence in the IDTof the specialized radiologist exponentially increases the value of this study.

What do the guidelines say?

There are considerable variations in management among

different countries or regions of the world. As is often the case in such a complex entity, these differences have motivated the grouping of experts in panels or consensus groups and the creation of guidelines. However, we will never stop repeating that beyond the recommendations that emerge from the guidelines, these are only general recommendations to be taken into account during the discussion in the IDT, since each patient must be considered and discussed individually.

The variability in the guidelines is not only observed among the different continents as it happens between the American guidelines of the National Comprehensive Cancer Network (NCCN), the European guidelines of the European Society for Medical Oncology (ESMO) or the Japanese guidelines of the Japanese Society for Cancer of the Colon and Rectum (JSCCR). There are also differences even among countries in the same region. A clear example of this situation occurs between the UK guidelines and those of other European countries.

The preference of American groups for the long-course CRT regime is widely known, while in some European countries such as the Netherlands and Sweden, short-course RT is mainly used, except for locally advanced tumors with a high risk of recurrence (CMR +, T4b) or with criteria of unresectability at the time of staging, in which they also recommend long-course CRT. In fact, in these two countries only 15 to 23% of the patients receive long CRT scheme. On the other hand, and in accordance with the NCCN guidelines, the Canadian guidelines recommend the administration of long-course CRT, excluding patients not suitable for receiving CT, who receive only preoperative radiotherapy.

The EURECCA consensus arises with the purpose of unifying criteria among different European societies and providing updated support to IDTs across Europe.237 Its name is the acronym for EUropean REgistry of Cancer CAre or EURopEan CanCer Audit. This panel of experts was made up of delegates from different societies related to the management of rectal cancer, such as the European Society for Oncological Surgery (ESSO), the European Society for Therapeutic Radiotherapy and Oncology (ESTRO), the European Society for Pathology (ESP), the European Society for Clinical Oncology (ESMO), the European Society for Radiology (ESR), the European Society for Coloproctology (ESCP), the European Cancer Organisation (ECCO), the European Oncology Nursing Society (EONS) and the European Organization for Patients with Colorectal Cancer (EuropaColon). Consensus was achieved using the Delphy method, and the final document is the result of the first multidisciplinary consensus conference on colon and rectal cancer care, held in December 2012, in Perugia, Italy.

Below we will try to summarize the most important guidelines available.

ESMO

In Europe and the Scandinavian countries, rectal cancer is classified into different categories based on risk factors assessed in the HR-MRI. The European Society for Medical Oncology (ESMO) suggested this modality for the first time in 2013, incorporating the risk of local recurrence as a pillar in the choice of the different treatment regimenes in the clinical practice guidelines. Multivariate analyzes demonstrate that certain risk factors assessed by HR-MRI, such as the distance from the tumor to the anal margin, the depth of tumor invasion in the rectal wall (T stage), and the degree of tumor response to neoadjuvant treatment are considered independent risk factors that affect the rate of sphincter preservation. But the number of positive lymph node (stage N), the depth of tumor extension through the mesorectal fat, the involvement of the mesorectal fascia, and the presence of EMVI are predictive factors of local recurrence and also of the appearance of distant metastases and the OS. For this reason, the European guidelines base the indication of neoadjuvant treatment on the findings of the HR-MRI, mainly on the identification of extramural extension and the subclassification of T3 tumors (from T3a to T3d). These findings determined that for many it was not so necessary to differentiate T2 from T3 tumors and the differentiation of low-risk T3 tumors (T3a and T3b) from high-risk ones (T3c and T3d) began to be considered. This is due to the fact that HR-MRI has a low sensitivity to differentiate T2 from borderline T3a tumors, mainly due to overstaging caused by the desmoplastic reaction of the peritumoral tissue. ESMO and RSNA (Radiological Society of North America) take into account the subclassification of T3 tumors in their guidelines. ESMO divides tumors into T3a <1 mm, T3b ≥ 1-5 mm, T3c > 5-15 mm, T3d > 15 mm, while RSNA in T3a < 5 mm, T3b ≥ 5-10 mm, T3c > 10 mm. ESMO is more accurate but creates difficulties in measurement and is not very reproducible, while RSNA has a higher application value. However, subclassification of T3 tumors based on the depth of extramural tumor invasion has not yet been incorporated into TNM staging and therefore, has not been adequately validated as a prognostic factor. Thus, as we will see, the indication for neoadjuvant therapy based on the depth of extramural invasion is not standard in the American guidelines.

ESMO divides rectal tumors into 5 risk groups based on clinical staging, and establishes different lines of treatment in each of these groups.

- Ultra-low risk group includes:

- T1 sm1 N0 tumors.

Surgery can be performed directly without neoadjuvant therapy regardless of the location of the tumor. However, ESMO considers that RT or CRT could be an alternative to surgery and that TAE, TEM or TAMIS could be complemented with perioperative CRT, if adverse pathological characteristics are present.

- Low-risk cancers include:
  - T1-T2 or high T3a-T3b tumors, N0 or high N1 tumors, with uninvolved mesorectal fascia and without EMVI.

In these cases surgery can be performed directly. If a positive CRM is reported on histopathology, CRT should be added (this should be avoided as much as possible) and if metastatic lymph nodes are found, adjuvant ChT should be indicated. In this low-risk group, neoadjuvant therapy could be performed in order to preserve the organ in high-risk patients, poor candidates for surgery, or those who reject it.

- Intermediate-risk group includes:
  - T3a tumors or low T3b tumors but without levator muscles involvement, with negative CRM.
  - T3a tumors or T3b tumors in the middle or upper rectum, N1-2, without EMVI.

In this group, TME might also be sufficient, although short-course RT or long-course CRT is recommended if a good quality TME cannot be assured. There is controversy in the selection of long or short-course treatment, but since long-course CRT can achieve a higher rate of pCR, it is currently the first choice of most radiotherapy centers.

The routine preoperative administration of CRT or short-course RT to all patients at risk for metastatic mesorectal lymph nodes on imaging remains controversial due to the poor diagnostic accuracy of lymph node positivity on HR-MRI, especially if the size of the node is the only criterion considered, and the consequent lack of prognostic relevance of supposedly positive nodes in this study on local recurrence. Data suggest a low risk of local recurrence if the surgeon routinely performs good quality TME and removes mesorectal nodes en bloc. However, it is the surgeon's responsibility to demonstrate and audit the quality of the resected specimen. If histopathology reports adverse prognostic factors, including metastatic lymph nodes or CRM +, postoperative ChT or CRT should be added. Given the results of the German study, there is no doubt that the latter should be avoided and that it is always preferable to administer RT or CRT preoperatively.

High-risk group (locally advanced tumors) includes:

- T3c-d tumors with negative CRM, without involvement of the levator ani muscles.
- T3c-d, N1-2, EMVI + tumors.

The recommended treatment modality is short-course RT or long-course CRT. The first regimen, particularly indicated in elderly patients or those with a contraindication to tolerate CRT, is followed by TME. In high-risk patients who received CRT and achieved cCR NOT can be considered.

- Very high-risk group (advanced disease) includes:
  - T3 tumors with CRM +
  - T4b tumors, involvement of the levator ani muscles.
  - LLN +.

This group has a precise indication of a long-course CRT regimen, although short-course RT with a delay in surgery also appears as an option.

Of the preoperative factors related to the tumor, CRM has emerged as one of the most important predictors of results. The anal sphincter is an important repair because the mesorectal fascia does not extend beyond the puborectalis muscle. Since several studies have shown that preoperative RT or CRT is more efficient and less toxic than postoperative therapy, it is increasingly important to assess the risk of CRM involvement to determine treatment and HR-MRI is the most accurate imaging modality for this evaluation. In the case of CRM + post TME, if preoperative RT was not administered, adjuvant CRT should be suggested. However, this situation should not arise.

In summary, for ESMO, assessing the relationship between the tumor and the mesorectal fascia is crucial and even more important than lymph nodes status in deciding the indication for neoadjuvant therapy. ESMO considers short-course RT the standard regimen, with the option of long-course CRT if the CRM, or an R0 resection is at risk.

NCCN

NCCN guidelines are based primarily on TNM classification. Thus, NCCN guidelines recommend neoadjuvant therapy in those patients with a high risk of local recurrence. This includes stages II (T3-T4 N0, that is, tumors that infiltrate beyond the muscularis propria) and stages III (any T with N + and no distant metastasis).

In both stages II and III, with negative CRM, NCCN recommends neoadjuvant treatment, considering both short and long-course RT, and even induction or consolidation TNT combined with both forms of RT. The indication of a short-course RT regimen should be discussed in the IDT, according to the need to achieve

downstaging and the possibility of long-term toxicity.

In cases with involved CRM, T4 or unresectable tumors, the recommendation is TNT in any of its forms (induction or consolidation).

In both situations, if a cCR is achieved, NOT can be decided after discussion in the IDT and with the patient, although the probability of distant metastasis should be pointed out.

In potentially resectable synchronous metastatic disease, when the CRM is negative, the primary treatment is ChT followed by short-course RT or long-course CRT. On the contrary, in cases with CRM involved, initial ChT should be followed by a long-course CRT regimen. However, the possibility of starting treatment with any RT regimen and then continuing with ChT is also being considered.

Finally, when faced with unresectable metastatic disease, the treatment is always systemic ChT. In the event that after this therapy the disease became resectable, the options described in the previous paragraph would be used.

The most commonly used neoadjuvant regimen in the US is long-course CRT, with conventional daily fractions of 1.8 to 2 Gy for 5 to 6 weeks for a total dose of 45 to 50.4 Gy and concurrent ChT based on 5- FU. On the other hand, short-course RT with 5 Gy daily for 5 days without ChT is a less widely used alternative regimen. In that country, the benefit of short-course RT is considered greater for tumors at 5 to 10 cm from the anal margin with negative CRM and involved lymph nodes. Converserly, this treatment is considered not effective in reducing local recurrence in low tumors with positive CRM. A meta-analysis from the Cochrane database showed that patients treated with short-course RT followed by surgery had reduced local recurrence compared to those who underwent surgery alone, but they did not achieve a significant increase in sphincter preservation. Since short-course RT appears to provide effective local control and the same OS as CRT regimens, it is currently considered a valid option for patients with T3N0 or T1-3, N1-2 tumors with negative CRM. But it is not recommended for T4 or CRM + tumors.

The NCCN guidelines are based on TNM and recommend neoadjuvant stages II and III.

Japanese guidelines

Interestingly, neoadjuvant ChT was not described by the Japanese guidelines (JSCCR), although its favorable results have been widely demonstrated.[88] These guidelines largely focus on the extent of lymph node dissection, since lymph node metastatic spread and tumor invasion depth are considered the most important prognostic factors. Therefore, they recommend lymph node dissections from so-called D1 for pTis tumors to D3 dissections (lateral pelvic lymphadenectomy) for cT3-4 or cN + tumors.

ERECCA

In this consensus the following indications were defined:

- T3N0, negative CRM and upper rectum:
  - Direct TME.
  - Short-course RT and immediate surgery.
  - CRT and surgery after 6-8 weeks.
- T3N0, negative CRM and lower rectum:
  - Short-course RT and immediate TME.
  - Long-course CRT and TME at 6-8 weeks.

(Short-course RT has the advantages of lower cost and lower risk of acute toxicity).

- T3, N1-2 and negative CRM:
  - Short-course RT and immediate TME.
  - Long-course CRT and TME at 6-8 weeks.
- T3, N1-2, positive CRM and T4
  - Long-course CRT and TME at 6-8 weeks.

(Short-course RT with delayed surgery may be an option in patients with poor conditions to receive CRT).

- Stage IV
  - Short-course RT is preferred given the little systemic effect of CRT.

ASCRS

The American Society of Colon and Rectal Surgeons, through its Committee on Clinical Practice Guidelines, evaluated the evidence related to rectal cancer and established recommendations regarding all instances of its management, based on the best available evidence.[255] The following are the recommendations related to the indication of neoadjuvant treatment:

- Neoadjuvant treatment should be recommended for patients with clinical stage II/III rectal cancer. This has a high grade of recommendation based on level of evidence 1A.
- The treatment decision must be discussed in the IDT, on an individual basis. High grade of recommendation, with level of evidence 1A.
- The response to neoadjuvant treatment should be evaluated prior to surgical treatment. High grade of recommendation with level of evidence 1B.

Spanish Society of Medical Oncology (acronym in Spanish: SEOM)

The SEOM developed its guidelines in 2010 in which

it recommended neoadjuvant CRT in T3-T4 or N + tumors.[27]

National Institute for Health and Care Excellence (NICE)

The NICE guidelines define three risk groups for local recurrence based on HR-MRI findings:

- High risk

Threatened (<1 mm) or invaded CRM, or low tumors invading the intersphincteric plane or the levator muscles.

- Moderate risk

Any cT3b or greater, in which the MRC is not threatened, or any suspicious lymph nodes that do not threaten the MRC or the presence of EMVI.

- Low risk

T1, T2, or T3a tumor, and no suspicious lymph nodes.

EMVI is also associated with a high risk of systemic recurrence.

In patients whose primary rectal tumor appears resectable at presentation, the following points are recommended:

- Risk of local recurrence, short and long-term morbidity, and late effects of treatments should be discussed in the IDT and with the patient.
- Short-course RT and long-course CRT should not be offered to patients with operable low-risk rectal cancer except in the context of a clinical trial.
- Consider short-course RT and immediate surgery in patients with moderate-risk operable rectal cancer.
- Consider long-course CRT followed by surgery after a period that allows downstaging in borderline (between moderate and high risk) tumors
- Long-course preoperative CRT should be offered to patients with high-risk operable rectal cancer.
- Preoperative CRT should not be offered solely to facilitate sphincter-preserving surgery.
- Neoadjuvant CT alone should not be indicated except in the context of a clinical trial.

In summary, NICE guidelines recommend offering short-course RT or long-course CRT to patients with rectal tumors in stages T1-T2, N + or T3-T4, with any N substaging.

Association of Coloproctology of Great Britain and Ireland (ACPGBI)

The ACPGBI established the following recommendations in 2017:[74]

- Local resection after short-course RT or long-course CRT may be considered in patients with early rectal cancer in whom cCR is not achieved and who are unsuitable or reject radical surgery. Grade C recommendation.
- With optimal staging by HR-MRI, patients with tumors that do not involve the mesorectal fascia (cT2-4a, N0-2, negative CRM) can be treated with surgery alone. Grade B recommendation.
- Patients with tumors that do not involve the mesorectal fascia (cT2-4a, N0-2, and negative CRM) with HR-MRI features suggesting an increased risk of local recurrence (T3c, N +, or EMVI +) may be considered for preoperative RT. In this situation, both short-course RT and long-course CRT are acceptable. Grade A recommendation.
- In patients receiving short-course RT, surgery should be performed within 11 days after the first fraction of radiotherapy to minimize the risk of complications. If surgery cannot be performed within this interval, surgery should be delayed beyond 4 weeks. Grade B recommendation.
- In patients receiving long-course CRT, surgery should be scheduled 6 to 10 weeks after completion. A dose of at least 45 Gy in 25 fractions with infusion of 5-FU or oral capecitabine is recommended. Grade B recommendation.
- If a patient requires RT in addition to surgery, it should be administered preoperatively. Patients who have undergone initial surgery and have an involved CRM should be treated with adjuvant CRT postoperatively. A dose of at least 45 Gy in 25 fractions along with 5-FU is recommended. This situation should be avoided. Grade A recommendation.
- Patients with tumors that threaten or involve the mesorectal fascia should be treated with preoperative RT. In this situation, the most effective strategy is long-course CRT, followed by surgery 8 to 12 weeks later. A dose of at least 45 Gy in 25 fractions with 5-FU infusion or oral capecitabine is recommended. Grade B recommendation.
- Patients with tumors that threaten or involve the mesorectal fascia and are unable to tolerate long-course CRT should be offered short-course RT followed by surgery 8 to 12 weeks later, to allow time for maximum tumor shrinkage. Grade C recommendation.
- Patients should be re-staged with pelvic HR-MRI and CT of the chest, abdomen, and pelvis toward the end of the 8-12 week interval between completion of RT and surgery. Grade C recommendation.
- The overall strategy for the treatment of lower rectal cancers should be defined on the basis of the HR-MRI report. Grade B recommendation.

- In selected patients with cCR after long-course CRT, NOT may be considered. A clearly defined surveillance protocol is necessary to identify eventual local re-growth of the tumor as early as possible. Grade C recommendation.

What do we do in our IDT?

The main objective of our IDT is the correct selection of patients who will benefit from neoadjuvant treatment by identifying with preoperative staging those with a higher risk of developing local or distant recurrence. There is a variable percentage of patients who can be successfully treated by primary surgery, without significant risk of local recurrence or systemic disease. To stratify patients into risk groups we give preponderance to HR-MRI. This imaging study provides the necessary data to establish whether the patient can be considered to have a good or bad prognosis. This division is made based on the following information:

- CRM involvement
- Extramural tumor invasion.
- Nodal involvement.
- Presence of EMVI.
- Puborectalis muscle involvement.

Tumors of the upper rectum or those without involvement of the levator muscles are considered to have a good prognosis when they present:

- Potentially free CRM (> 1 mm).
- Stages T1-T2 or T3 with extramural invasion < 5 mm.
- Absence of EMVI.
- N0/N1.

These patients will be selected for TME without prior treatment.

Among the cases considered to have a poor prognosis are two other groups of patients:

First of all, patients at increased risk of systemic failure:

- T3 tumors with extramural invasion > 5 mm.
- N2 lymph node involvement.
- Suspicious LLN.
- Presence of EMVI.

Second, patients at increased risk of local recurrence:

- Probable involvement of the CRM.

These patients, as well as all those with tumors stage cT2 or higher, located at the level of the puborectalis muscle, will be selected for some form of neoadjuvant treatment, which will be defined in the context of interdiscipline.

In summary:

- The indication for neoadjuvant treatment is undoubted in tumors located less than 12 cm from the anal margin that:
  - Involve the CRM or its resectability is in doubt
  - Invade neighboring organs (T4).
- T3, N1 and EMVI + tumors in the HR-MRI, have risk criteria for local recurrence with evidence not as clear as in the previous ones, so the indication will be discussed in the interdisciplinary meeting. It is necessary to insist that this interaction is a mandatory circumstance before defining the therapeutic tactic for rectal cancer.
- Furthermore, it is essential to explain to the patient the possibility of a cCR and a pCR if surgery is undertaken. But also that the potential benefits of NOT must be balanced with the potential increased risk of distant relapses, something that requires further study.
- Finally, factors that can jeopardize the achievement of quality TEM, either by the patient or the tumor, should always be considered in the IDT discussion. Among the former, a difficult pelvis, in male patients, obese, with prostatic hypertrophy and bulky tumors, always implies a challenge beyond the surgeon's experience and the chosen approach, be it conventional, laparoscopic, robotic, or transanal (taTME). Among the latter, the TNM stage and the size, height, and location of the tumor (anterior, lateral, or posterior) are important.