# CHAPTER 11
# Assessment of the Response to Neoadjuvant Treatment

Digital rectal examination (DRE) has been the classic method used by colorectal surgeons to assess not only the clinical staging of lower rectal tumors, but also the response to neoadjuvant treatment. However, an MSKCC study prospectively analyzed the accuracy of digital rectal examination in assessing clinical response to neoadjuvant therapy in 94 patients, and the findings highlighted the shortcomings of this method.[80] The sensitivity of DRE in determining complete or near-complete response (≥90%) was 24%, specificity was 56%, and efficacy 49%. The DRE underestimated the pathological response in 78% of the cases, correctly identifying only 3 of 14 patients (21%) with pCR. This difficulty for the surgeon to reliably determine the safety to perform sphincter-sparing surgery requires preoperative evaluation with endoscopic and imaging methods. However, DRE has a key role, so much so that it is considered essential that the tumor be accessible to this examination to include the patient in a W&W protocol.

In addition to DRE, endoscopy is used to assess response to neoadjuvant therapy. Its findings are obvious to the naked eye and comparison with the endoscopic image prior to treatment is useful. It is somewhat more complex to determine a pCR, since the endoscopic evaluation is limited to luminal vision and does not allow detecting the presence of residual tumor in other layers of the rectal wall or in the lymph nodes. Findings consistent with a pCR have been described in detail, but are summarized in Table 15.

**Images**

To better define the presence of the remaining tumor within the mucosa after treatment, other images are required.

**ERUS**

Although the overall accuracy of ERUS for the initial assessment of the T factor ranges between 62 and 92% and for the N factor between 66-88% and its precision in identifying non-responders to neoadjuvant treatment is similar (82% ), their efficacy in identifying good responders is much lower (29%).[99,185] These limitations are probably attributable to its inability to differentiate between tumor and radiation-induced inflammation and fibrosis.[239] In another study, Pastor et al.[169] used ERUS to assess response to neoadjuvant treatment in 235 patients. Twenty percent were erroneously staged as pCR, with an overall overstaging of 37%, and the authors concluded that this percentage was unacceptably high.

*Due to these limitations, in order to define management ERUS should not be considered to assess the response to preoperative RT or CRT.*

**HR-MRI**

HR-MRI is the most widely used imaging method to restage rectal cancer and assess response after neoadjuvant therapy. This method provides important information to the IDT regarding surgical timing and planning, possible sphincter preservation, postponement of surgery in responders, and intensification of treatment in non-responders. The MERCURY (European Rectal Cancer and Magnetic Resonance Imaging Equivalence Study) group recommends assessment of the following parameters by HR-MRI after neoadjuvant treatment:

- Morphological appearance of the tumor, including any

TABLE 15: FINDINGS CONSISTENT WITH PCR

| | Complete response | Near-complete response | Incomplete response |
|---|---|---|---|
| Endoscopy | White flat scar | Irregular mucosa | Visible tumor |
| | Telangiectasia | Small nodule in the submucosa | |
| | No ulceration or nodularity | Surperficial ulceration | |
| | | Persistent erythema | |
| Digital rectal examination | Normal. | Smooth induration | Palpable tumor |
| | | Surperficial irregularity | |

mucinous or necrotic component.
- Height of tumor from anal margin, compared to height before treatment.
- Tumor length compared to pretreatment length.
- Degree of tumor regression.
- Maximum depth of extramural invasion (distance in millimeters measured from the outermost border of the muscularis propria) of both the tumor and the fibrosis, separately.
- T factor classified according to depth of the extramural invasion from T1 to T4, with subclassification within each factor (e. g., T3a to T3d).
- Distance to the CRM and whether it is threatened or invaded.
- Extramural vascular invasion.
- Lymph node staging, including LLN
- Potential involvement of peritoneal reflection, differentiating distal sigmoid and rectum.

Previous recommendations aimed to reduce the global risk of CRM + to less than 3% and local recurrence to less than 5%, in the population undergoing curative treatment.

HR-MRI has not only been validated as a method for post-adjuvant staging. In addition, the MERCURY group in a prospective study evaluated 111 patients with HR-MRI and histopathology after neoadjuvant treatment and demonstrated the correlation of survival with the response assessed by HR-MRI.[170]

The TRIGGER trial, currently underway, aims to determine whether the degree of tumor regression assessed by HR.MRI (mrTRG) allows the prognosis to be defined with greater precision than the baseline study[7] (Table 16).

*Several studies have confirmed the undoubted value of HR.MRI in the initial staging to decide the indication for neoadjuvant treatment. However, evidence also exists and is being generated about the usefulness of this study in the context of post-neoadjuvant therapy, both to define the surgical strategy and to determine the prognosis and the need for adjuvant treatment.*

TABLE 16: DEGREE OF TUMOR REGRESSION BY HR-MRI

| | |
|---|---|
| mrTRG 1 | Complete radiological response (only linear scar) |
| mrTRG 2 | Good response (dense fibrosis, no tumor signal) |
| mrTRG 3 | Moderate response (fibrosis > 50 % and intermediate signal) |
| mrTRG 4 | Mild response (mostly tumor) |
| mrTRG 5 | No response / tumor regrowth |

## Functional studies

*Perfusion*

Tumor tissues compared to normal tissues show greater vascularization with a rapid peak of enhancement followed by an early washout of contrast. The role of angiogenesis in tumor growth has opened the way to the development of new drugs that act by slowing it down. Tumor angiogenesis and the response to antiangiogenic or antivascular drugs also have applications in imaging techniques. Both perfusion CT (pCT) and dynamic MRI (d-MRI) allow the phenomenon to be studied non-invasively, based on mathematical analysis models that provide the possibility of differentiating, for example, tumor persistence from fibrosis.

*Diffusion*

Diffusion-enhanced MRI (diff-MRI) is a functional technique that uses differences in the extracellular movement of water protons to discriminate between tissues of different cellularity. It provides biological information on various factors such as cell density, the nucleus-cytoplasm relationship, the tortuosity of the extracellular space, the integrity of cell membranes, the organization of tissues (e. g. , gland formation), and tissue perfusion. The degree of restriction to the diffusion of water is directly proportional to the cell density and the integrity of the cell membranes. Thus, the movement of water molecules is more restricted in tissues with high cellularity and intact membranes (e. g, tumor tissue) than in areas of less cellularity or where the membranes have been altered. Another advantage is that diffusion allows a quantitative analysis by calculating the apparent diffusion coefficient (ADC). In general, tumors have low ADC values, while normal tissues and benign lesions usually show high values. Similarly, diffusion could predict the response to neoadjuvant therapy. Tumors with high ADC value tend to present necrosis, which is associated with a poor response to treatment.

A study by the Maastricht group showed that 15% of patients with pCR were lost with the diffusion technique. [8] There is no conclusive evidence that ADC measurement adds value to mrTRG. Furthermore, the results of the Deferral of Surgery Trial suggest that the use of diffusion protocols and PET-CT would have excluded more than 30% and 60% of patients, respectively, who did not

show tumor growth for at least 1 year.[8] At the moment, mrTRG appears to be the best method to identify patients with pCR.

*Multiparametric MRI imaging*

All of these methods constitute a major advance in the field of imaging evaluation in oncology. Recent publications have also established the importance of combining the information obtained with the different techniques for a better understanding of tumor biology. Current technological development allows obtaining multiple data with a single technique or combining multiple imaging modalities to collect more information about the tumor. For example, MRI would allow a single technique to obtain different parameters such as information on morphology and prognostic factors (high resolution sequences), cellularity (diffusion), angiogenesis (perfusion) and tumor metabolism. This could be combined with PET-CT or pCT to achieve the benefits of all these diagnostic modalities.

## PET-CT

Guillem et al.[77] evaluated PET-CT in 121 patients before and after neoadjuvant treatment and compared results with histopathology findings. PET-CT detected pCR in 54% and its absence in 66% of the cases. The authors concluded that PET-CT has limited value in evaluating response to neoadjuvant treatment.

## How to interpret the images?

Only patients classified as cCR are considered candidates for NOT. All of these studies should be repeated every three months for two years and then every six months to complete five years of surveillance. Habr-Gama[85] proposed an intensive follow-up based mainly on endoscopic rectal examination, but complemented with ERUS, CT, HR-MRI and even PET-CT.

As will be seen in developing the topic of TAE, the main obstacle that exists is that pCR can only be determined with certainty with a complete pathological examination of the resected specimen. There is no single study capable of identifying patients with complete tumor regression after neoadjuvant therapy. A combination of clinical and endoscopic findings does not provide enough information and it is well established that cCR is not equivalent to pCR.

Furthermore, the decision to perform surgery should not be based only on the absence of a clinically palpable or visible tumor after neoadjuvant treatment, as the risk of lymph node metastases, which may persist despite complete regression of the primary tumor, must also be considered. Even in pT0 rectal cancers treated with TEM, the risk of to positive lymph nodes or mesorectal tumor deposits is as high as 12%. [81,215,260] The role of imaging for re-staging after neoadjuvant therapy has been the subject of several studies, all of which suggest that neither HR-MRI, nor CT, nor ERUS, nor PET/CT, on their own, are accurate enough to identify true complete responders.[45,75,77,87,122,137,147,171,234,257,259] A major problem with HR-MRI is the difficulty in differentiating areas of small residual tumor from fibrosis, and even the presence of tumor may be overestimated by most trained specialists.[6,49,106] PET/CT findings suggestive of cCR are also associated with a low positive predictive value for pCR (39% in a systematic review).[107] However, HR-MRI together with DRE and endoscopy are the most widely used methods and, in fact, the degrees of tumor regression have been adapted to HR-MRI.[171] The usefulness of diff-MRI is unclear; some studies suggest benefits (particularly a reduction in the number of cases that overestimate the presence of tumor in clinical responders), while others find no additional advantages over standard HR-MRI.[107,118,125,126,134]

*In conclusion, there is no single test capable of identifying patients with complete tumor regression after neoadjuvant therapy. The combination of RT, endoscopy and HR-MRI (through mrTRG), and serial studies when it is decided to postpone surgery, constitute the best method to make decisions after neoadjuvant treatment. According to the guidelines based on the latest NCCN consensus, patients who achieve a cCR, with no evidence of residual tumor on DRE, HR-MRI, and direct endoscopic assessment, can be considered by the IDT for a NOT approach. However, there is still no universally adopted consensus on a standardized follow-up protocol for these patients.*