Utility of reassessment after neoadjuvant therapy and difficulties in interpretation

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Abstract We describe the main tools for MR assessment of the response of rectal cancer tumors after chemotherapy, before surgery. In locally advanced cases of rectal and lower rectal cancer, MR is useful in allowing the treatment strategy to be adjusted, enabling conservative surgery to be performed if the patient responds well. The different types of response (fibrous, desmoplastic and colloid), their appearances and difficulties in MR interpretation are described. We describe the features and performance of MR after neoadjuvant therapy for T and N staging, assessment of circumferential resection margin and diffusion weighted imaging. Quantitative (change in tumor volume) and qualitative (grade of tumor response) MR assessment can distinguish good responders from poor responders.

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Neoadjuvant chemoradiotherapy (CRT) has now become the standard practice to treat local advanced rectal cancers (stages T3c, T3d and T4) [1]. Many trials have shown that these neoadjuvant therapies reduce the risk of local recurrence, enabling complete resection (R0 resection) and achieving better survival [2–5].

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MR has become an essential pretreatment tool, particularly as it provides a detailed assessment of rectal wall extension (T staging) and circumferential resection margins (CRM) which are predictive of complete resection [6,7].

A consensus statement from the European Society of Gastro Intestinal and Abdominal Radiology (ESGAR) was published in 2013, providing MR guidelines for the clinical management of rectal cancer [8]. A reassessment of tumor stage is recommended after chemoradiotherapy and before surgery. It is useful to carry out a local reassessment after neoadjuvant therapy for locally advanced rectal cancers (T3c, T3d and T4) and lower rectal cancers [7]. This reassessment may change the treatment strategy by enabling conservative surgery to replace previously planned abdomino-peritoneal resection for good responders or, conversely, by recommending a more aggressive medical-surgical approach when the tumor remains inaccessible for complete resection.

MR assessment of tumor response was initially based on the tumor response in terms of T stage (downstaging) [6,9,10]. In parallel, other authors have tried to assess changes in the Circumferential Resection Margin (CRM) [11,12]. Several publications have examined volume tumor response (downsizing) [13,14], by recently making use of diffusion weighted images [15].

In addition, qualitative MR response criteria, similar to those used histologically, have been reclassified [16–19].

The aim of this article is to describe the main tools for assessing tumor response after neoadjuvant therapies.

The different types of response after CRT

Changes in treatment after neoadjuvant therapy include fibrotic, desmoplastic, mucinous and inflammatory changes.

Fibrous response

On T2 weighted imaging, areas of fibrosis are hypointense similar to the muscularis propria; conversely, the residual tumor intensity remains the same as that of the initial tumor. Pathologically, the fibrosis is made up of sheets of collagen, fibroblasts and histiocytes.

Desmoplastic response

The desmoplastic response is also called “reactive fibrosis” and consists of collagen deposits within the tumor. On initial MR and after CRT, this reaction appears as thin hypointense spicules on T2 weighted imaging.

Colloid response

This is a necrosis of the tumor with mucinous transformation indicating response to treatment and must not be confused with mucinous adenocarcinomas (10% of tumors), the appearances of which on MR after CRT are unchanged compared to the initial MR. These are tumors with a poor prognosis and increased risk of relapse. Acellular mucinous pools are seen as hyperintensities on T2 weighted images.

The MR technique after CRT

The reassessment MR is performed 6 to 8 weeks after CRT has ended. A T2 weighted sagittal image positions an axial T2 weighted image perpendicular to the long axis of the tumor. This is still a key image with fine sections (1 to 3 mm), and is combined with a coronal T2 weighted image. For lower rectal tumors, an additional T2 image is recommended along the coronal plane of the anal canal. Rectal distension is not mandatory but may be useful (ultrasound gel or a mixture of ultrasound gel and Lumirem®) and should not be excessive (less than 100 ml). Gadolinium chelate injection is not essential, except for lower rectal tumors to better examine extension to the sphincter system. Diffusion weighted images are recommended by the ESGAR consensus statement [8]. It is essential to make a comparison with the initial MR, as identifying the tumor may be difficult if it has reduced greatly in size after CRT [7].

Site of the tumor

It is recommended [8] that the distance between the inferior pole of the tumor and the anorectal junction (lower rectum < 2 cm, middle rectum 2 to 7 cm and upper rectum > 7 cm) be measured along the sagittal plane. The circumferential position of the tumor (lateral, anterior or posterior) and its appearance (polypoid, annular, mucinous or ulcerated) should also be reported. The height of the tumor should appear on the report [8].

T staging after chemoradiotherapy: yT stage

General details

The T staging classification is the same after neoadjuvant therapy [6].

Similarly to the initial pretreatment MR, a tumor extending less than 1 mm beyond the muscularis propria carries exactly the same prognosis as a T2 tumor. It is not therefore clinically useful to clearly distinguish a T2 tumor from a T3a tumor. It is, on the other hand, important to measure the extension of the tumor beyond the muscularis propria, as this is a major prognostic indicator [18].

Reliability of MR

The diagnostic performance of MR before neoadjuvant therapy is excellent (85%) although drops to only around 50% after treatment [20,21] (Table 1).

It is, in reality, difficult to determine whether the tumor is still present after CRT.

The presence of a fibrous inflammatory reaction which accompanies the tumor, in which it is impossible to establish
Reassessment after neoadjuvant therapy and difficulties in interpretation in rectal cancer

Table 1  Accuracy of MR in T staging after chemoradiotherapy (CRT).

<table>
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<th>Year</th>
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<th>n</th>
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whether or not it contains tumor cells, may mimic tumor extension (Fig. 1).

Pitfalls and recommendations

- It is recommended that extension beyond the muscularis propria should only be concluded if an additional nodular appearance is present in the perirectal fat or if a large base is consistent with the tumor [22];
- the tumor generally appears as an intermediate or hyperintense image compared to the muscularis propria, although it is hypointense compared to the submucosa except in cases of mucinous adenocarcinoma (Fig. 2).

Fibrosis is also generally hypointense on T2 weighted images and has a star-shaped retractile appearance [17];
- it is important to be aware of partial volume effects when the section is not perpendicular to the axis of the tumor. It is fundamentally important to use thin 3 mm sections perpendicular to the axis of the tumor [23].

Diffusion weighted imaging

Recent studies have demonstrated the utility of diffusion weighted imaging in detecting residual tumor within the fibrosis, thus improving prediction of complete response [15,24–27]. Areas of fibrosis are generally hypointense on diffusion weighted images with high b values ("T2 black

Figure 1. Rectal tumor initially classified as T3b which became ypT2 after chemoradiotherapy: a: initial pretreatment MR; b: after chemoradiotherapy.

Figure 2. Rectal tumor initially classified as T3a becoming ypT2 after neoadjuvant therapy: a: initial pretreatment MR; b: after chemoradiotherapy: T2 weighted hyperintensity in this mucinous adenocarcinoma.
effect’’ [27]). Conversely, residual tumor exhibits a high cell density and hyperintensity on diffusion weighted images with high b values.

Diffusion weighted images, however, can be difficult to interpret in mucinous adenocarcinoma or in a colloid response (mucin production by the tumor due to the effect of neoadjuvant therapy) responsible for the T2 effect.

According to the ESGAR consensus statement [8], the MR reassessment report should state the presence or absence of residual tumor and/or fibrosis.

**Assessment of the circumferential resection margin (CRM) after CRT**

**General details**

The mesorectal fascia, which is seen as a thin T2 weighted hypointensity surrounding the mesorectal fat, is considered on MR to represent the lateral margins for safe surgical excision. During surgery, the mesorectum is entirely excised, the boundary of which is mesorectal fascia.

A CRM is considered to be positive if any tumor residue is located at least 1 mm from the fascia: this is valid for the initial tumor, for suspicious lymph nodes, and for any vascular invasion or tumor deposition. The MR report [8] should state the shortest distance between the tumor and the mesorectal fascia and its base, and whether or not invasion of the fascia proper remains. MR performs very well in assessing this margin in previously untreated patients, with an overall reliability of between 90 and 95% [28,29]. Accuracy is reduced after chemoradiotherapy, with a reliability of between 66 and 84% [11,12,30] (Table 2).

The tumor response is reflected by a reduction in tumor mass combined with a significant increase in the CRM. Assessment of the CRM after chemoradiotherapy is then straightforward. The CRM assessment is particularly important in lower rectal cancers and occasionally enables the sphincter to be preserved.

In some patients, however, chemoradiotherapy results in a reduction in tumor volume, but also in retraction of pre-existing contacts with the fascia propria (Fig. 3). In these cases, a hypointense T2 area may persist, bridging the tumor and the fascia. It is then difficult to determine whether this area contains tumor cells or, alternatively, whether this fibrous consequence is completely devoid of tumor cells in the histological analysis (Figs. 4 and 5).

**N staging after chemoradiotherapy: yN stage**

The number and size of lymph nodes fall after neoadjuvant therapy, resulting in frequent downstaging in 2/3 of patients [9].

MR after neoadjuvant therapy, however, remains only moderately reliable for staging lymph nodes. The size criterion (small axis of the lymph node over 5 mm in the mesorectum) is the most reliable criterion in reassessment after neoadjuvant therapy according to the ESGAR consensus statement [8]. This may not be enough, however, and a micro-metastasis may be present in a normal sized lymph node [9,31,32]. Reduction in size and a homogeneous

<table>
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**Figure 3.** Lower rectal tumor initially classed as T3 and then pT0 after neoadjuvant therapy: a: initial pretreatment MR; b: after chemoradiotherapy.
Reassessment to chemoradiotherapy market. Response particles contrast node and Over Assessment [34–36] before last treatment, however, shows no reduction in "tumor" volume even though the histological response may be excellent or may even show a specimen devoid of tumor (Fig. 7). This lack of reduction in tumor volume, despite a good histological response, is seen particularly in a colloid response. Following treatment, extensive parts of the tumor become acellular and are replaced by a mucinous material. This colloid response can be suspected when a significant increase in tumor image intensity on T2 weighted sequences after chemoradiotherapy is observed.

Qualitative assessment of response by MR (mrTRG)

The MERCURY group has recently established a tumor response grade (tumor regression grade TRG) by MR (mrTRG) [17–19].

This score is derived from the Dworak and Rodel histological scores [16], and classifies response into 5 stages, from a complete response (TRG 1, genuine restoration of integral rectal wall on MR) to total lack of response (TRG 5).

Like the volumetric assessment, this score separates and distinguishes good responders to neoadjuvant therapies from poor responders.

Assessment of changes in tumor volume before and after treatment

Over the last few years, several groups have examined response to tumor volume as a marker of response to chemoradiotherapy and also as a prognostic indicator (Fig. 6). All of these publications have been consistent in terms of the average reduction in volume after chemotherapy, which ranges between 65 and 73% [13,14,37–41]. Recent publications have shown that the ideal cutoff to separate good responders and poor responders is between 70 and 75%. Using a cutoff of 70%, we have been able to show that good responders, who have a response of over 70%, had very significantly greater progression-free survival than poor responder patients in whom the response was under 70% [14].

Response after chemoradiotherapy in some patients, however, shows no reduction in "tumor" volume even though the histological response may be excellent or may even show a specimen devoid of tumor (Fig. 7). This lack of reduction in tumor volume, despite a good histological response, is seen particularly in a colloid response. Following treatment, extensive parts of the tumor become acellular and are replaced by a mucinous material. This colloid response can be suspected when a significant increase in tumor image intensity on T2 weighted sequences after chemoradiotherapy is observed.

Complete response: yT0 N0

According to the ESGAR consensus statement [8], revascularizing a normal rectal wall consisting of two layers after CRT should be deemed to be a clinical sign of complete response. The use of diffusion weighted and T2 weighted images

Figure 4. The effects of chemoradiotherapy on a rectal tumor and circumferential resection margins (CRM): a: increase in CRM after neoadjuvant therapy (double arrow); b: fibrous retraction of the fascia propria not increasing the CRM.

Consistency of the lymph node signal suggest a disease-free node [8]. The morphological criteria [33] do not enable us to unequivocally establish whether the lymph node is devoid of tumor or not [8].

The use of ultra-small superparamagnetic iron oxide particles (USPIO) provides a negative predictive value of 90% [34–36], which is useful when local incision is intended. This contrast medium, however, is not available on the French market.

Figure 5. False positive tumor-free fibrous band: a: initial pretreatment MR; b: after chemoradiotherapy (fibrous residue (white arrow), in contact with the mesorectal fascia (red arrow)).
improves accuracy of the diagnosis of complete response [24].
Sassen [42] also showed that using these two sequences was of particular benefit, with a high negative predictive value (> 91%) to exclude complete response. The positive predictive value for complete response was inadequate (64 to 80%) to guide minimalist “wait and see approach” management [43].

**Conclusion**

Assessment of the indices which are classically examined in patients suffering from rectal cancer on their initial assessment—T stage and invasion of the fascia (CRM)—is difficult after chemoradiotherapy and less accurate than before treatment. The use of simple quantitative methods, such as tumor volumetry, improves and simplifies this assessment. Qualitative assessment is currently based on the mrTRG score (MR tumor response grade) based on a subjective analysis of response

**Other MR changes after radio- and chemotherapy**

The most common changes seen on MR are fatty transformation of the bone marrow, pre-sacral edema, thickening of rectal and bladder wall, and fatty infiltration of the mesorectum [9].

Figure 6. Volumetry in a good responder patient; a: initial pretreatment MR, the tumor volume is assessed as being 76 cm$^3$; b: after chemoradiotherapy, the tumor volume is assessed as being 13 cm$^3$.

Figure 7. Patient with good histological response (ypT0) in complete response with no reduction in volume (colloid response); a: initial pretreatment MR; b: after chemoradiotherapy.
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via comparison of the pre- and post-chemoradiotherapy MR.

The use of ‘‘functional’’ images, and particularly diffusion weighted images, is useful in looking for residual tumor within the residual mass.

**TAKE-HOME MESSAGES**

- In locally advanced rectal cancers (T3 c and d, T4) and lower rectal cancers, post-neoadjuvant therapy MR is useful for adjusting the treatment strategy, enabling conservative surgery to be performed in cases which respond well.
- Neoadjuvant therapies may cause different types of response: fibrous (hypointense T2 weighted images), desmoplastic (fine spicules which are hypointense on T2 weighted images) or a colloid response (hyperintense on T2 weighted images).
- In T staging and assessment of the CRM, the post-neoadjuvant therapy MR is less accurate than the initial MR, i.e. the MR given before CRT.
- On MR, good responders compared to poor responders to neoadjuvant therapies can be identified from a quantitative assessment (change in tumor volume) if the reduction in tumor volume is over 70% or by a qualitative assessment using a tumor response grade (mrTRG).

**Clinical case**

This 58-year-old male patient presented with a rectal adenocarcinoma and underwent pretreatment rectal MR (Fig. 8a) and then a reassessment MR after 8 courses of chemotherapy and external radiotherapy prior to surgery (Fig. 8b–d).

**Questions**

1. Where is the tumor located?
2. Is residual tumor present after chemoradiotherapy (CRT)?
3. What is the yT, yN stage after chemoradiotherapy?
4. Is the circumferential resection margin (CRM) sufficient?
5. Is a colloid response visible?
6. Is the patient a good or a poor responder?

**Answers**

1. In the middle rectum.
2. Yes.
3. The tumor is classified by MR as stage yT3 yN+ after CRT.
4. Yes, the CRM is 9 mm.
5. No (no T2 weighted hyperintensity).
6. Poor responder as the tumor volume has fallen by 60%.

The surgical treatment involved anterior resection of the rectum. The histological report concluded that a differentiated class pT3N2b adenocarcinoma was present, with a

![Figure 8. MR of a rectal cancer before and after chemoradiotherapy (CRT). Pretreatment sagittal T2 weighted MR (a). Post-chemoradiotherapy sagittal (b) and axial (c, d) MR.](image)
healthy circumferential resection margin, without mucin, and with tumor regression of 10%.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


