



Magnetic Resonance Imaging and Other Imaging Modalities in Diagnostic and Tumor Response Evaluation

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Functional imaging is emerging as a valuable contributor to the clinical management of patients with rectal cancer. Techniques such as diffusion-weighted magnetic resonance imaging, perfusion imaging, and positron emission tomography can offer meaningful insights into tissue architecture, vascularity, and metabolism. Moreover, new techniques targeting other aspects of tumor biology are now being developed and studied. This study reviews the potential role of functional imaging for the diagnosis, treatment monitoring, and assessment of prognosis in patients with rectal cancer.

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Introduction

Imaging plays a fundamental role in the treatment of rectal cancer. Magnetic resonance imaging (MRI) (and endorectal ultrasound for small tumors) is routinely used for local tumor staging to establish the local tumor extent and evaluate the most important prognostic risk factors to determine the best surgical treatment strategy and the necessity for short-course or long-course neoadjuvant treatment. Imaging is also increasingly adopted to evaluate the treatment response in patients undergoing preoperative chemoradiotherapy (CRT). Until recently, imaging has mainly focused on tumor morphology (size, signal, and shape). However, morphology is no longer sufficient to answer the increasingly complex clinical questions that need to be answered to allow for personalized treatment planning. For example, in patients treated with long-course CRT, it is now of growing importance to know the exact treatment response, as the (near) complete responding patients may be considered for organ-preserving treatment strategies

(local excision or “watchful waiting”) instead of routine surgical resection. Moreover, early prediction of treatment response (ie, before onset or after a few weeks of treatment) may help to identify upfront the patients who are likely to respond well or poorly to treatment, so that treatment may be adjusted and optimized in an early phase to enhance the chance of a good treatment outcome.

Recent innovations in imaging include the use of “functional” imaging techniques that allow for the in vivo evaluation of different biophysiological tissue processes. This functional information can complement the information derived from morphologic imaging and offer whole new insights into tumor biology. The most extensively studied techniques to date are diffusion-weighted imaging (DWI), dynamic contrast enhanced (DCE) or ‘perfusion’ imaging, and positron emission tomography (PET), which are increasingly being shown to be of clinical value. In addition, new methods targeting other aspects of tumor biology are being developed and studied. This review discusses current as well as potential future applications of these functional imaging techniques for the management of rectal cancer patients.

Functional MRI

Diffusion-Weighted MRI

Diffusion-weighted MRI is a noninvasive technique that can be added to any clinical MRI protocol without the need for contrast agents. DWI analyses the random motion (“diffusion”)

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of water protons, which is inversely related to tissue cellularity and the integrity of cell membranes. In tissues with low cellularity (or fluids), water protons can move freely, which induces a loss of signal on DWI. Conversely, in malignant tumors—that are generally hypercellular and contain many intact cell membranes—water diffusion is restricted, resulting in remaining high signal. The sensitivity to diffusion is obtained by applying 2 bipolar diffusion-sensitising gradients to a T2-weighted sequence. The diffusion sensitivity can be varied by adjusting the “b-factor,” which is a combination of the gradient duration, gradient amplitude, and the time interval between the 2 gradients. The higher the b-factor, the greater the signal attenuation from moving water protons. The degree of signal loss as a result of different b-factors can be quantified, a parameter that is called the “apparent diffusion coefficient” (ADC) and provides an indirect measure of tissue cellular structure.

DWI is an established technique for oncologic imaging. In rectal cancer, various applications of DWI have been reported, including primary tumor detection and characterization, lymph node evaluation, and surveillance after treatment. However, the vast majority of articles published on DWI focussed on assessment and early prediction of treatment response to CRT.

There are several ways DWI can be used to evaluate response, including visual evaluation, volumetric assessment, and ADC measurements (Fig. 1). Visual assessment constitutes the most basic approach that is easiest to implement in clinical practice. It entails an assessment of whether or not a high signal (indicating tumor) remains visible at the site of the primary tumor on posttreatment imaging. Visual DWI evaluation has repeatedly been shown to improve the performance of MRI to differentiate between patients with and without residual tumor after CRT^{1,2} and results of a recent meta-analysis indicated that addition of DWI to standard MRI improves the sensitivity for T-staging after CRT from 50% to 84%.³ Another approach is to measure the volume of high-signal areas on DWI. So far 4 reports (including 1 prospective study) measured tumor volumes on DWI and correlated changes in DWI tumor volume as a result of neoadjuvant treatment to the final histopathologic response.⁴⁻⁷ Curvo-Semedo et al⁴ and Ha et al⁵ both reported that DWI tumor volumetry offered the best results to predict which patients would undergo a complete response to CRT, with better results compared with tumor volumetry on morphologic MRI as well as compared with measuring ADC.

Measuring tumoral ADCs (before, during, and after treatment) is by far the most widely studied approach to assess response. Different groups have shown that pretreatment tumor ADC values are typically low in patients who undergo a good response to CRT and high in the poor responders.⁸⁻¹⁰ The hypothesis is that high pretreatment ADC is due to necrosis, which is known to be associated with impaired treatment susceptibility. Low pretreatment ADC values have also been shown in prognostically unfavorable tumors (eg, with higher T-stage, N+, mesorectal fascia invasion, and poor histologic differentiation grade).^{11,12} Pretreatment ADC may thus be used as an imaging marker of therapeutic outcome

and prognosis. As a result of treatment, ADC typically rises, which is believed to be related to loss of cell membrane integrity and ultimately apoptosis, which enlarges the extracellular space. A steep rise in ADC early (ie, 1-2 weeks) after initiation of treatment has also been reported, which may be caused by an early inflammatory response resulting in tumoral edema.⁸ Evidence regarding the use of pretreatment, during treatment, and posttreatment ADC measurements to assess response has so far been inconsistent, which is also related to the fact that ADC measurement are influenced by variations in MRI hardware and field strength, acquisition protocols, and measurement methods.^{13,14} Lack of standardization hampers the implementation of ADC in clinical practice and should be the focus of future studies.

Dynamic Contrast-Enhanced MRI

DCE-MRI is an upcoming technique in rectal cancer. DCE-MRI is based on the fact that tumors release factors that would lead to formation of new vessels, that is angiogenesis. Angiogenesis is necessary for tumors to grow. The process of angiogenesis is disorganized and therefore the formed vessels are of poor quality. Because of the poor vessel quality the perfusion of tumor tissues is less efficient than that of normal tissues. With DCE-MRI, it is possible to evaluate the (change in) perfusion of tumor tissue compared to normal tissues. DCE-MRI uses contrast agents to evaluate perfusion of tissues by measuring inflow of contrast into vessels and permeability of vessels (vessels in tumors are often leaky and would easily leak contrast agents to the extracellular space). These parameters can be assessed in a quantitative manner, by calculating Ktrans, Ve, and Kep. Ktrans is the volume rate constant, which is a measure of leakiness of the vessels. Ve is the volume of the extracellular space, and Kep is constructed by dividing Ktrans by Ve (Ktrans/Ve) and is defined as the constant of flow rate. It is also possible to perform semiquantitative analyses, that is, assessment of the contrast uptake curve in the tumor. For example, steepness of the contrast uptake and area under the contrast uptake curve can then be evaluated.

The main focus of the literature on DCE-MRI is on response prediction and assessment after chemoradiation. An example of a DCE-MRI to assess response in rectal cancer is given in Fig 2. Most of the studies have used quantitative analyses rather than semiquantitative analyses. Regarding early response prediction, conflicting results have been reported. The only pre-CRT DCE parameter that has been repeatedly found as a predictor for response is a high(er) Ktrans.¹⁵⁻¹⁸ A high Ktrans indicates that the tumor is well vascularized and leaky. Increased vascularity leads to high oxygenation that is known to make tumors better responsive to radiotherapy. The increased leakiness is hypothesized to increase accessibility for chemotherapy. For semiquantitative DCE parameters, the late slope of the contrast uptake curve was found to be predictive for response.¹⁹ Several studies have reported that when Ktrans decreases or is low after chemoradiation a good response is to be expected.^{16,18,20,21} This response leads to

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