Preoperative Imaging Staging of Rectal Cancer

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Abstract
Carcinomas of the rectum are associated with a significant local and distant recurrence rate. Not all patients are appropriate candidates for preoperative radiation therapy. Preoperative identification of those most likely to benefit from neoadjuvant therapy is important. There is no general consensus on the role of endorectal ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) in staging patients with rectal cancer. Although the tumor stage is an important prognostic factor, preoperative assessment is associated with prediction of the circumferential resection margin. Newer developments such as coils, sequences and gradients in MRI, evolution of multidetector CT and new contrast media, allow for an algorithm selection aiming at the best diagnostic options for patients. The present review will discuss the current role of the various imaging modalities in staging carcinomas of the rectum.

Introduction

Rectal cancer is a common malignant disease in Western countries with a high rate of mortality. Numerous improvements in the surgical, radiologic, and oncologic treatment have been made over the past two decades. Poor prognosis of rectal cancer is associated with its high risk of metastases and local recurrence.

Total mesorectal excision (TME) is defined as the resection of both the tumor and the surrounding mesorectal fat and currently is the surgical treatment of choice for rectal carcinoma. This treatment has been shown to reduce the mortality rate from 16 to 9% [1]. In addition, TME is associated with a recurrence rate of less than 10% when used as an isolated treatment option [2]. Inadequate surgical excision with microscopically infiltrated resection margins may result in a local recurrence rate of up to 83% [3]. Incomplete removal of the lateral spread of the tumor seems to be responsible for the majority of these recurrences [4]. The use of preoperative radiation therapy in patients with involvement of the mesorectal fascia at the time of diagnosis has been shown to reduce the recurrence rate from 8.2 to 2.4% at 2 years [2, 5]. The indications for preoperative radiation therapy vary between USA and Europe [6, 7]. Prerequisites for this treatment option include accurate preoperative tumor staging with regard to tumor detection, mesorectal fat infiltration, mesorectal fascia status, nodal involvement and distal metastatic disease. The contribution of imaging in
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Preoperative T staging of a rectal tumor is not a simple process. Digital examination is considered unreliable [6], whereas the results of computed tomography (CT) are variable, particularly for early tumors [8]. At present, there is no widely accepted protocol on the role of diagnostic imaging in the preoperative T staging of rectal cancer. In one study, a survey in 142 departments in UK showed that only 50% of rectal cancer cases do have access for transrectal ultrasonography (TRUS) or magnetic resonance imaging (MRI) [9].

CT has been used widely for preoperative assessment of disseminated disease but its role in local staging is limited with reported accuracies ranging from 33 to 82% [10, 11]. In a recent meta-analysis of 78 studies in 4,897 patients with rectal cancer, CT showed an accuracy of 73% for T staging [12]. Multidetector technology allows for a multiplanar imaging, but there are limited prospective studies to address a newer role for CT in this respect [13]. Although spatial resolution has improved considerably with multidetector CT, its limitation remains the inherent low contrast resolution. Carcinomas of the rectum are demonstrated as focal, irregular wall thickening lesions on CT. For small tumors without any associated wall thickening, contrast enhancement in the arterial phase may be the only indicator of tumor growth [14].

TRUS is helpful in determining the depth of invasion of early-stage disease with a reported accuracy of 64–96% [15, 16]. The outermost hypoechoic layer corresponds to the muscularis propria. Carcinomas are hypoechoic, and the degree to which they disrupt and penetrate the rectal wall layers suggests the local stage. T1 tumors do not penetrate the muscularis propria and the preservation of a bright sonographic layer medial to the muscularis, represents an intact submucosa. T2 tumors penetrate the muscularis propria and so merge with it (fig. 1). T3 tumors proceed beyond the muscularis propria infiltrating the perirectal fat to a variable degree. TRUS however cannot reliably visualize the mesorectal fascia and thus cannot indicate whether the planned surgical circumferential resection margin (CRM) will be successful. Other limitations of TRUS are the operator-dependent quality of the examination and the inability to pass the probe through obstructing tumors. The proportion of early-stage disease in which local excision is the treatment of choice is only 5%. For all the above reasons, TRUS has not been adopted as the imaging modality of choice for preoperative local staging of rectal cancer.

The main challenge for radiological staging today is to address accurately the relationship of the tumor and the mesorectal fascia. A recent study of 686 patients undergoing TME showed that local recurrence was only 5% in those with a disease-free CRM as opposed to 22% if infiltrated [17]. MRI has been applied from its early days for staging rectal cancer, with a limited accuracy originally [18]. The development of endorectal coils improved the accuracy [19]. Further developments in phased-array coils, gradients and pulse sequences obviated the need of endorectal coils since accuracy increased up to 100% [20]. MRI with phased-array coils is able to provide detailed anatomy of the rectum and perirectal structures (fig. 2). In a study though of 76 patients, Beets-Tan et al. [21] found a moderate prediction of T stage by MRI with considerable interobserver variability (67 and 83% for two readers). In the same study, the prediction of mesorectal fascia involvement was much higher with excellent interobserver agreement, thus allowing an MRI disease-free distance of 5 and 6 mm to correspond to a histopathological disease-free margin of 1 and 2 mm, respectively.

Fig. 1. TRUS in a patient with rectal carcinoma shows that the hypoechoic tumor invades the muscular wall (arrows).
One study in 98 rectal cancer patients showed 92% agreement between MR images and histologic findings for prediction of the CRM [22]. Another study in 43 patients not only confirmed a high accuracy (95%) for prediction of CRM but in addition proved in cadavers that the thin linear structure seen on MRI indeed corresponds to the mesorectal fascia (fig. 2) [23]. Therefore, although the accuracy of MRI in local staging remains controversial, its efficiency in estimating the carcinoma infiltration of the mesorectal fascia is widely accepted. The differentiation between stage T2 and T3 tumors will not affect or modify the overall preoperative or operative management of the patients. The clinically relevant benefit of MRI is the assessment of the distance from the tumor to the CRM which will predict local recurrence [17, 24].

An optimized MRI technique employed should include pelvic phased-array coils, sagittal T2-w turbo spin-echo sequences through the pelvis to detect the tumor, and then high-resolution T2-w examinations perpendicular to the tumor’s long axis and in coronal plane, using FOV of 16–18 cm, thin sections of 3–4 mm and high matrix of up to 512 × 512. Axial T1-w images of the entire pelvis are always used for detecting lymphadenopathy. Routine use of intravenous contrast does not seem to increase accuracy [25]. On T2-w images, carcinomas appear as wall lesions exhibiting signal intensity slightly higher than the muscularis propria. High signal intensity of the tumor on T2-w images suggests the presence of mucinous carcinoma which has a worse prognosis compared to the non-mucinous one [26]. The outermost margin of the muscularis propria will remain intact with stage T2 tumors or less (fig. 3). Differentiation between T2 and T3 tumors may be difficult with MRI and overstaging is often caused by perirectal desmoplastic reactions which do not contain tumor cells [20, 21].

For T3 tumors with disease-free circumferential margins, it was shown that >5 mm spread of tumor beyond the bowel wall predicts a significantly poorer survival than <5 mm spread (fig. 4–6) [27]. A possible limitation of MRI, not addressed so far, is the converging of the muscularis propria and the mesorectal fascia anteriorly and towards the anal canal where a very early T3 lesion can still theoretically infiltrate the mesorectal fascia [28].

Fig. 2. Normal MRI anatomy in a 72-year-old male patient. The axial T2-w turbo spin-echo MR image shows the high signal intensity of the rectal mucosa (white arrow), the intact mesorectal fat (asterisks) and the normal appearance of the mesorectal fascia (black arrows).

Fig. 3. Stage T1 rectal carcinoma. The axial T2-w turbo spin-echo MR image shows the small intraluminal polypoid lesion (arrow) with no disruption of the muscular layer.
bone marrow [32, 33]. In patients with advanced disease, a baseline MRI before radiotherapy should be performed because it is not easy to differentiate post-radiation fibrosis from viable tumor within fibrosis [34].

**N Stage**

Evaluation of lymph node metastatic involvement is a difficult task for radiologists. Lymph node neoplastic infiltration has been assessed for a long time by using morphological criteria such as the size and shape. A node measuring >8 mm in the short axis is probably malignant [35]. Enlarged nodes however may be benign and reactive whereas small nodes may be infiltrated. For rectal cancer in particular, over half of the metastatic nodes secondary to rectal cancer are <5 mm and are located within 3 cm of the primary tumor [36, 37]. In a large trial, lymph node metastatic disease was shown to predict local recurrence [2]. In this study, patients with stage III had a 10- and 3-fold higher risk for local recurrence than did those with stage I and II, respectively. Recent studies with TME as the treatment of choice showed that there is no association of nodal involvement and rate of local recurrence [12, 38, 39]. Therefore, nodal involvement might be clinically irrelevant if an adequate disease-free margin exists. TME however does not remove the internal iliac nodes. Lower rectal cancer is associated with internal iliac nodes involvement in 28%, and in 6% of cases those lateral nodes seem to be the only lymph nodes involved [40]. MRI depiction of the nodes lateral to mesorectal fascia is clinically important since if detected they must be included in the radiation field. Extended removal is not indicated as it results in significant urinary and sexual dysfunction.

There is a wide variation in accuracy for metastatic nodal detection with TRUS (62–87%), CT (22–73%) and MRI (39–95%) [12, 15, 41–46]. TRUS applies the criteria of lack of ovoid morphology and central echogenic nidus, but its inherently limited field of view is a major limitation. CT is based on size alone and therefore is not reliable. High-resolution MRI with the inherent contrast between fat and lesions predicts nodal involvement most accurately when the morphological features, such as a spiculated or indistinct border and a mottled heterogeneous appearance, are used rather than the size alone [35, 47] (fig. 4–6). The use of size therefore as a criterion for determining nodal involvement in rectal cancer is not recommended. Invisible lymph nodes preoperatively are a highly specific MRI indication of disease-free nodal status [35]. The rate
and degree of nodal enhancement has not been yet addressed in the literature to provide any additional information (fig. 8). The recent development of lymph node-specific contrast agents will aid in detecting tumorous involvement in normal-sized nodes [48]. A node with mixed or increased signal intensity will be probably malignant, whereas a node with central or uniform low signal intensity at T2*-w MR images non-malignant.

Fig. 6. T3 rectal carcinoma in a 53-year-old male patient. a Sagittal T2-w MR image shows the neoplastic wall thickening (arrows). b Coronal T2-w MR image shows lymph nodes (white arrows) lateral to the mesorectal fascia (black arrows) with sharp margins suggesting reactive status. A tubular structure (long white arrow) represents vascular invasion. c Axial contrast-enhanced T1-w MR image shows anterior extension of the tumor, in close proximity to the mesorectal fascia (short arrow). Vascular invasion is demonstrated with the presence of tubular structures (long arrows).

Fig. 7. Stage T4 rectal cancer. Sagittal T2-w (a) and contrast-enhanced T1-w (b) MR images show a mucinous rectal carcinoma (long arrow) extended anteriorly to invade the posterior myometrium (short arrow).

Fig. 8. Stage T3 rectal cancer. The axial contrast-enhanced fat-suppressed T1-w MR image shows the intense enhancement of the tumor (thick arrows), and two nodes in the perirectal fat with intense (thin arrow) and moderate (short arrow) enhancement, of unclear predictive value.
Recently, the application of diffusion-weighted imaging, a relatively old idea that proved to be very successful in detecting acute brain ischemia, has shown to be feasible in abdominal areas [49]. According to this technique, it is possible to detect early changes in the architecture of tissue and differentiate malignant from benign lesions on the basis of hypercellularity commonly found in malignancies. The signal in diffusion-weighted images strongly depends on the diffusion of water molecules, mainly located in the extracellular space. Whenever there is an alteration in the size of the extracellular space, the diffusion pattern is directly affected. It has been shown that increased cellularity causes a reduction in size of the extracellular space, therefore diffusion is restricted in such a case and the corresponding quantitative parameter, namely the apparent diffusion coefficient (ADC) is reduced. On the contrary, whenever there is an increase in the size of extracellular space due to increased water content, there is an elevation of the ADC. In this content, malignant lymph nodes might be possible to be differentiated from inflammatory due to lower ADC values that may exhibit (fig. 9, 10). In addition, it has been shown that ADC measurements may also help in assessing post-radiation fibrosis [50].

**M Stage**

Distant metastatic disease in patients with rectal carcinoma is most commonly located in the liver. Studies have shown that patients who die of cancer are found at autopsy to have liver metastases with a frequency of 25–
50%. In patients with colorectal cancer, 40% on average develop liver metastases [51]. Hepatic metastatic disease is associated with poor prognosis.

The liver is a unique organ with regard to its dual blood supply pattern (arterial and portal) and its vulnerability to metastatic disease. It is reported that hepatic metastases undergo a complex process regarding the development of their vasculature and particularly the relative contribution of the portal vein and the hepatic artery in the blood supply [52–56]. Thus, tumor vascularity is a continuously changing phenomenon. In the very early phase, the neoplastic cells are expected to receive nourishment by diffusion from surrounding vessels. This happens until the metastatic focus reaches a size of 150–200 mm [57]. As tumor grows, angiogenesis occurs with vessels arising either from arterial or portal components. The portal contribution seems to decline as the tumor exceeds 2 mm in size and the arterial role predominates [54]. An additional characteristic of importance is that metastases, unlike the normal liver parenchyma, lack Kupffer cells. In general, most metastases from rectal carcinoma are hypovascular receiving blood supply from the hepatic artery whereas normal liver parenchyma receives 60–70% of its blood supply from the portal vein.

The progress that has been achieved in the past two decades in medical imaging has offered the ability to visualize small-sized metastatic lesions (<1 cm) achieving a sensitivity of as high as 90% [58]. Unfortunately, the ability of an imaging modality to depict a parenchymal focal lesion does not depend solely on size. Other factors relative to the biological stage of the metastatic process (i.e. tumor vascularity) seem to influence the depiction ability of modern imaging modalities [59, 60]. Subsequently, neither of the imaging tests in their conventional versions could provide negative predictive values greater than 70% [61]. Newer developments are currently being assessed clinically including multidetector CT scanners, high-field MR scanners with fast MR sequences and phased-array coils, use of superparamagnetic or hepatocyte-specific MR contrast agents and ultrasound contrast agents, and PET-CT.

**Ultrasonography**

Ultrasonography (US) is currently the most commonly applied imaging modality for assessing hepatic metastases. Baseline gray-scale US is the first-line technique exhibiting a sensitivity ranging from 40 to 80% depending on the diameter of the lesions and the experience of the sonologist [62].

![Ultrasound liver scan](image)

**Fig. 11.** Ultrasound liver scan of a 64-year-old female with rectosigmoid colon adenocarcinoma and a metastatic lesion located at segment V of the liver parenchyma (arrows). a At baseline scan the lesion is hyporeflective with some degree of echogenic center. b At the arterial phase there is a ring-like peripheral enhancement with the rest of the lesion remaining hypovascular. c At the sinusoidal phase, the metastasis remains hypovascular and is clearly depicted from the surrounding enhanced normal parenchyma. Thick arrows in b and c denote time counter in seconds after intravenous contrast injection.

The introduction of US contrast agents and the advances in ultrasound apparatuses, able to detect these agents in real time, have improved the overall accuracy of baseline US in liver metastatic disease, both for detection and monitoring the effect of therapy [63–67]. There are no reports yet to describe the performance of the newer systems exclusively on patients with colorectal cancer liver metastases. A recent work from Quaia et al. [68] compared prospectively contrast-enhanced ultrasound versus baseline ultrasound and contrast-enhanced spiral CT in metastatic disease of the liver in general. This is the
only study on the topic and contrast-enhanced US was found to show an 83% sensitivity, 84% specificity and a high accuracy as shown by a 0.929 ROC under the curve analysis. Sonographically, after the intravenous contrast administration, the colorectal hepatic metastases present a hypovascular pattern as early as the arterial phase with a perilesional enhancing rim. They remain hyporeflective at the portal phase compared to the surrounding liver parenchyma (fig. 11). The gold-standard reference in US fields is the intraoperative examination of the liver which is widely accepted to approach a 100% sensitivity in detecting metastatic disease.

**Computed Tomography**

CT is generally considered the primary imaging modality for diagnosis and preoperative staging in patients suffering from primary cancers of the abdomen. It provides wide availability and simultaneous evaluation of primary cancer, as well as metastatic disease. However, the reported sensitivity of single-detector row helical CT for the detection of hepatic metastases, as compared with other recently established liver imaging modalities, remains unsatisfactory [69–71]. Furthermore, the accurate characterization of small hepatic metastases with helical CT alone is often difficult, since small hepatic cysts are the most frequently encountered cause of low attenuation focal lesions on CT [72]. A recent meta-analysis comparing imaging modalities in colorectal liver metastasis showed that contrast-enhanced CT shows sensitivity ranging from 70 to 85%, or even lower for lesions <1 cm in diameter [73]. Higher sensitivity (87.1%) has been reported for CT arterial portography, but this technique,
although still favored by some institutions, relies on interventional angiographic procedures and is usually related to high rates of false-positive diagnoses [74]. Metastatic lesions in CT may be hypodense or isodense to the normal parenchyma. Contrast-enhanced CT scanning is performed as a standard portal venous (hepatic) phase study utilizing a minimum 42-gram iodine load modified according to patient weight. The lesions appear hypodense for reasons discussed previously (fig. 12, 13). In patients who are potential surgical candidates, an additional arterial-phase CT series is acquired for accurate arterial and portal branches mapping.

**Magnetic Resonance Imaging**

Colorectal hepatic metastases most commonly appear as lesions that are moderately hyperintense on T2-w images and hypointense on T1-w images. Gadolinium-based intravenous contrast agents can improve the sensitivity of MRI in detecting metastases. During dynamically enhanced scanning, metastases may be of increased signal during the arterial phase and decreased signal in the portal phase, but as a general rule they are usually hypovascular in arterial phase. They may also show peripheral washout with the periphery of the metastasis being of lower signal than the center and adjacent liver. On delayed scanning, metastases may have increased signal [75, 76] (fig. 14). The absence of Kupffer cells in the metastatic foci is exploited by MRI using iron oxides. This superparamagnetic agent is taken up in Kupffer cells resulting in a lower signal in normal liver but no change in the signal of the metastasis on T2-w images, thus increasing overall conspicuity (fig. 15).

In a recent study that compares 16-row multidetector CT versus SPIO-enhanced MRI, the sensitivity was 80 and 94.5%, respectively (p < 0.05) [77]. In the aforementioned meta-analysis study, SPIO-enhanced MRI was the most accurate modality (p < 0.001) [73].

Diffusion-weighted imaging has been proposed as an alternative source of contrast to differentiate more accurately malignant from benign focal liver lesions [48]. As explained previously, malignant lesions present with increased cellularity therefore exhibit restricted diffusion, in contrast to benign lesions where increased extracellular space is resulting in free diffusion. In case of colorectal metastasis, diffusion-weighted images show a characteristic imaging pattern of a bright focal area that corresponds most probably to necrosis surrounded by a high intensity rim that reflects an area with restricted diffusion (fig. 16).

**Fig. 14.** MRI scan of the same patient as in figure 11. a T1-w transverse scan with fat suppression. The hepatic metastasis at segment V is hypointense (arrow). b Post-contrast transverse scan at arterial phase shows a hyperintense ring-like enhancement of the lesion (arrow), which is centrally hypovascular. c Post-contrast transverse scan at portal venous phase illustrates washout of the peripheral enhancement of the metastasis (arrow), which remains hypovascular compared to the rest of the normally enhanced liver parenchyma.
Positron Emission Tomography

The role of positron emission tomography (PET) or PET/CT is currently limited to assessing hepatic metastatic disease and, although sensitive, it should be used mainly as an additional imaging modality for detection of extrahepatic disease [73]. False-positive results occur secondary to inflammatory or granulomatous lesions and false-negative in cases with small tumors. PET/CT is widely accepted as a highly sensitive and specific technique in assessing local recurrence.

Detecting the Occult Colorectal Liver Metastases

Major efforts have been made thus far to establish an efficient diagnostic approach, in order to achieve the earliest possible detection of liver metastatic disease. For several years, interest has been focused on investigating the hemodynamic changes provoked by the presence of secondary neoplastic lesions of the liver. The two major fields of those studies include dynamic scintigraphic examinations and more recently color Doppler US. The former is systematically described in the works of Leveson et al. [78, 79]; the latter is extensively presented in the studies published by Leen et al. [80]. Although the concept of hemodynamic changes due to the presence of hepatic metastases was confirmed experimentally, reproducibility of these techniques was not universally proven [81, 82]. Hence the issue of occult hepatic metastases detection is still a major challenge that remains under investigation in the field of ongoing research.

Conclusions

With the newer treatment options in rectal cancer, such as preoperative radiation, preoperative chemotherapy and TME, there is an increased demand for accurate depiction by imaging the high-risk patients for local recurrence. For superficial tumors which are treated with surgery alone, TRUS is able to assess the muscular involvement. For the vast majority of rectal carcinomas, MRI will detect accurately the mesorectal fascia and the CRM. MRI is superior to CT for assessing invasion of the surrounding organs and structures. Nodal disease remains a difficult radiological diagnosis, although nodes as small as 2–3 mm can now be depicted with high-resolution MR images. For hepatic metastatic disease, the highest sensitivity (95–99%) is provided with intraoperative US, superparamagnetic iron oxide (SPIO) or gadoxenate dimeglumine (Gd-BOPTA)-enhanced MRI and contrast-enhanced CT during arterial portography. The choice between portal phase helical CT performed with >45 g of iodine and MRI with a gadolinium-based contrast agent or SPIO should depend on availability and ex-
pertise and not on literature-based diagnostic accuracy alone. The contrast-enhanced ultrasound technique is the fastest emerging imaging approach, but more clinical series are expected to define its exact role. The role of multidetector CT has to be set, but for distant metastatic disease it remains the first option. Further studies should address the establishment of preoperative MRI as a useful clinical tool, the role of diffusion and perfusion imaging for preoperative staging of the primary tumor, the role of newer contrast media for detecting metastatic nodal disease and the relative accuracy of US, MRI and multidetector CT for distant metastatic disease.

References


