Diffusion-weighted Magnetic Resonance Imaging in Characterization and Staging of Rectal Cancer

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ABSTRACT

Rectal cancer is one of the most common clinical malignant tumors, which accounts for about 15% of all malignant tumors (1). It is the third most common cancer in men and the second most common cancer in women (2). Adenocarcinomas compromise approximately 96% of all colorectal cancers, whereas the uncommon malignancies include lymphoma, gastrointestinal stromal tumors and carcinoid (3). The prognosis of rectal cancer is directly related to tumor infiltration into the mesorectum and the ability to surgically achieve negative circumferential resection margins (CRMs) (4).

The use of total mesorectal excision (TME) as the standard treatment of rectal cancer and the adoption of neoadjuvant chemoradiotherapy for patients with locally advanced rectal cancers, diagnosed on the basis of MRI features, has led to substantial improvement in local disease control (5). There is a need for an accurate clinical staging of rectal cancer to optimize individualized treatment (6).

Rectal cancer is staged based on TNM classification system where T stage refers to local tumor extent, N stage refers to regional lymph node status, and M stage refers to the presence or absence of distant metastatic disease (7). Currently, MRI is the preferred imaging modality for local staging of rectal cancer (8).

High-resolution T2-weighted images are the gold standard for evaluating rectal cancer. Proper planning of high resolution T2 imaging sequences is essential in staging accuracy (9). However, structural imaging techniques have shown clear limitations in tumor evaluation. Different functional and molecular imaging techniques such as DWI and dynamic contrast enhanced (DCE) imaging are useful tools for providing insights into tumor phenotype and improving the assessment of tumor response to treatment (10, 11).

DW-MRI enables a noninvasive characterization of biologic tissues on the basis of their water diffusion properties (12).
Pathology Rectal Cancer

Colorectal cancer is the third most common cancer and a major cause of morbidity and mortality throughout the world (13). Successful multimodal treatment of rectal cancer requires accurate diagnosis and staging, which guides optimal treatment strategies (14).

The diagnosis is usually established by means of clinical examination (rectal digital examination), endoscopy (sigmoidoscopy and colonoscopy), double-contrast barium enema examination and histologic confirmation, supplemented by biochemistry (tumor markers eg, blood carcino-embryonic antigen measurement). All of these techniques are poor indicators of the depth of invasion and lymph node involvement, which are both important features for prognosis (14, 15).

Accurate preoperative assessment of these prognostic factors is an important first step in assigning patients to one of the available treatment strategies which include surgical excision or course of preoperative chemotherapeutic and radiation therapy aimed at downstaging the tumor and decreasing the risk of post-operative tumor recurrence (16).

Histologic Types:

Most primary rectal cancers are adenocarcinomas, of which most are conventional gland-forming tumors. However, other special types need to be addressed as they exhibit different behavior and/or molecular phenotype such as mucinous adenocarcinoma with more than 50 % of the lesion composed of pools of extracellular mucin, signet-ring cell carcinoma, medullary carcinoma, adeno-squamous carcinoma and undifferentiated carcinoma (17).

Tumor grading: Histopathologic

Adenocarcinomas are graded predominantly based on the extent of glandular appearance.

Grade 1: (well-differentiated): Lesions exhibit glandular structures in >95 % of the tumor.

Grade 2: (moderately differentiated): Adenocarcinoma has 50–95 % glands).

Grade 3: (poorly differentiated): Adenocarcinoma has 5–50 % glands.

Grade 4: (undifferentiated): < 5 % of tumor with glandular differentiation (17).

Staging of Rectal Cancer with MRI:

In the context of primary tumor staging, performing rectal MRI is important for the evaluation of tumor location and morphology, T category, anal sphincter complex involvement, circumferential resection margin status (CRM Status), involvement of the pelvic sidewall, extramural vascular invasion (EMVI), and N category. These features should be included in the rectal MRI report (8) (Table1).
Standardized reporting template for dictation MRI studies for rectal cancer:

Table (1): Standardized reporting template for MRI studies for rectal cancer (18).

<table>
<thead>
<tr>
<th>Size Appearance</th>
<th>-x-x- cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumferential? Ulcerating</td>
<td></td>
</tr>
<tr>
<td>Signal intensity</td>
<td>T1, T2, T3, fat suppression</td>
</tr>
<tr>
<td>Distance of lower edge of tumor from anal verge</td>
<td>......cm</td>
</tr>
<tr>
<td>T stage</td>
<td>T1, T2, T3, T4a, T4b</td>
</tr>
<tr>
<td>Lymph nodes involvement</td>
<td>Describe all regional and non-regional lymph nodes if present, define N stage as described in TNM staging.</td>
</tr>
<tr>
<td>Minimum distance of tumor and lymph nodes from CRM</td>
<td>Mm</td>
</tr>
<tr>
<td>Relationship of the tumor to the anterior peritoneal reflection</td>
<td>For upper and middle third rectum</td>
</tr>
<tr>
<td>Is the mesorectum intact</td>
<td></td>
</tr>
<tr>
<td>Evidence for EMVI</td>
<td>Positive or negative</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>M0, M1, Mx</td>
</tr>
</tbody>
</table>

Location and Morphology:

It is crucial to describe the tumor location in the craniocaudal direction (upper, middle, or lower rectum) and in the circumferential plane, as well as its length, relationship to the anterior peritoneal reflection, and distance from the inferior border of the tumor to the anal verge and the anorectal junction. This information is important to determine the best surgical approach (8).

The location of the tumor is categorized as low (0–5 cm from the anal verge), middle (5.1–10 cm from the anal verge), and high (10.1–15 cm from the anal verge) (Fig.1). Tumors located above 15 cm from the anal verge are treated as colon cancer and, consequently, their staging and treatment differ from those of rectal cancer (8).

The tumor’s morphologic pattern (polypoid, ulcerating, circumferential, or semicircumferential) and especially its appearance (mucinous or nonmucinous) should also be described (Fig. 2). Mucinous tumors show high signal intensity at T2-weighted MRI and have a
worse prognosis than that of nonmucinous tumors, with a higher metastatic propensity and often a higher stage at the time of diagnosis.

**Fig. (1):** Tumor location in the craniocaudal direction. (a) Illustration depicts the sagittal view of the rectum and provides the measurements of the tumor from the anal verge, which help categorize tumor location. Blue lines separate the low, mid, and high rectum. (b–d) Sagittal T2-weighted MR images show tumors (arrow) in the high (b), mid- (c), and low (d) rectum. Dotted line = measurement from the rectum entrance to the tumor location.
Fig. (2): Mucinous and nonmucinous tumors. Axial oblique T2-weighted MR images in two different patients show a mucinous tumor (arrow in a) and a nonmucinous tumor (arrow in b). Mucinous tumors typically show high signal intensity, and nonmucinous tumors show intermediate signal intensity.

Mid- and high rectal cancer tumor staging (TNM staging system):

T category is characterized by the depth of tumor penetration into the rectal wall and extramural spread into the mesorectum and adjacent structures. It is important to identify the most invasive portion of the tumor, corresponding to the area of deepest infiltration (Fig 3). The T category is better applied to mid- and high rectal cancers and differs from that of low rectal cancer, especially owing to the narrowing of the mesorectum, which is a barrier to circumferential tumor spread.

T1 tumors infiltrate the submucosa.

= T2 tumors extend into but not beyond the muscularis propria (Fig. 4).

Rectal MRI does not provide a reliable distinction between these two categories.

Therefore, patients should undergo endorectal US owing to its superior diagnostic performance in these cases.

= T3 tumors are characterized by a discontinuity of the muscularis propria, with extension of the tumor into the mesorectum without infiltration of the mesorectal fascia or adjacent organs.

Spread into the mesorectum can be depicted as spicules of low signal intensity in the hyperintense mesorectal fat or distortion of the hypointense muscularis propria.

T3 tumors are classified into four categories dependent on the distance between the outermost edge of the muscularis propria and the maximum extramural spread of the tumor (Fig. 5, 6).

T3a: tumour extends <1 mm beyond muscularis propria.

T3b: tumour extends 1-5 mm beyond muscularis propria.

T3c: tumour extends 5-15 mm beyond muscularis propria.

T3d: tumour extends > 15 mm beyond muscularis propria.
Lastly, T4 tumors: (T4a) those that infiltrate the peritoneal reflection (Fig 7) or (T4b) tumor that invades the surrounding structures such as pelvic wall, vagina, prostate, bladder or seminal vesicles (8) (Fig 8).

Tumor invasion is defined as loss of the intervening fat plane and corresponding T2 signal abnormality within the involved surrounding structure.

**Fig. (3):** Illustration depicts the anatomy of the rectum and the possible locations of rectal cancer along with corresponding T categories and potential tumor sizes for each location (8).

**Fig. (4):** Axial T2-weighted MR images shows tumor of intermediate signal intensity, it does not invade the T2 hypointense muscularis layer (white arrow), findings characteristic of a T1 or T2 tumor (25).
Fig. (5): Oblique axial T2-weighted MR image shows a tumor infiltrating 10 mm beyond the muscularis propria (T3c), with positive MRF infiltration.

Fig. (6): Two examples of (T3d) tumors. (a) Circumferential rectal wall thickening with extramural invasion of 16 mm beyond muscularis propria at maximum thickness. (b) Tumor infiltrating muscularis propria and the whole thickness of perirectal fat opposite 8 O’clock with involvement of mesorectal fascia.
Fig. (7): Oblique axial T2-weighted MR image shows a tumor invading the anterior peritoneal reflection (arrowhead), a characteristic finding of a (T4a) tumor.

Fig. (8): (a) Axial and (b) Sagittal plane reformatted images from original sagittal three-dimensional (3D) T2-weighted images, show a rectal cancer (white arrow) growing into an adjacent small bowel loop (black arrow) (T4b).

Low rectal cancer and anal sphincter complex status: Tumors in the lower rectum are in close proximity to the anal sphincter complex and are more likely to invade the MRF and adjacent organs, owing to the narrowing of the mesorectum in this location.

A specific staging system on the basis of invasion of the anal sphincter complex was reported for staging of low rectal cancer. The report should describe if the tumor invades the internal sphincter, intersphincteric plane, and external sphincter and/or levator ani (Table2). The coronal oblique plane is the best plane for this evaluation at T2-weighted MRI.
Table (2): Showing stages of low rectal cancer seen on MRI \(^{(24)}\).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Tumor confined to bowel wall but does not extend through full thickness; intact outer muscle coat.</td>
</tr>
<tr>
<td>2</td>
<td>Tumor replaces muscle coat but does not extend into intersphincteric plane.</td>
</tr>
<tr>
<td>3</td>
<td>Tumor invades intersphincteric plane or lies within 1mm of levator muscle.</td>
</tr>
<tr>
<td>4</td>
<td>Tumor invades external anal sphincter and is within 1mm and beyond levators with or without invading adjacent organs.</td>
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**Circumferential resection margin (CRM Status):**

Circumferential resection margin is the surface of the non-peritonealized part of the rectum that is resected during surgery. MRI is the most reliable imaging modality to determine potential CRM involvement \(^{(30, 31)}\). At MRI, CRM status can be obtained by measuring the shortest distance between the outermost part of the rectal tumor and the MRF \(^{(32)}\). The circumferential resection margin status is potentially positive if this measurement is less than 1 mm \(^{(33)}\). A tumor–mesorectal fascia distance of more than 1 mm is a reliable predictor for negative margins after total mesorectal excision (Fig 9). A positive circumferential resection margin status is the most important predictor of local recurrence and poor survival \(^{(24)}\). Therefore, every report should include the circumferential resection margin status and the location of potential involvement (clock-wise method) \(^{(8)}\).

![Fig. (9): CRM status. (A) Axial T2-weighted HR MRI shows negative CRM (41 mm) (arrow). (B) Axial T2-weighted HR MRI shows that the tumor clearly extending beyond the mesorectal fascia (arrow) positive CRM \(^{(24)}\).](image-url)

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Extra Mural Vascular Invasion (EMVI):

Vascular invasion is a condition in which tumor cells are present in the blood vessels that are beyond the muscularis propria in the tumor area. The identification of blood vessel invasion is critical, as blood vessels are one of the main routes of tumor metastasis. Local and distant metastasis, recurrence and the overall survival rate of the patient depend on the extent of venous invasion (35).

MRI can depict extra mural vascular invasion with moderate to high sensitivity and specificity (36). It provides additional information for staging, showing evidence of vascular invasion that cannot be recognized by histopathology due to destruction of the vessel walls (37). Extra mural vascular invasion results in wall irregularity, focal enlargement, and/or signal intensity of the tumor (intermediate at T2-weighted imaging) within the vessel (38) (Fig 10).

![Fig. (10):](a, b) Sagittal T2-weighted MR images in two different patients show signs of EMVI, characterized by focal enlargement of the vessel, signal intensity of the tumor replacing the flow void, and wall irregularity (arrow) (8).

Peritoneal Reflection:

Upper rectal tumors can penetrate the peritoneum. In high resolution MRI, the typical appearance is nodular extension through the peritoneal reflection at or above the level of the anterior fixation in the rectum, which is better demonstrated in the axial plane (Fig.11), peritoneal infiltration is an important prognostic factor for local recurrence (39).
Lymph node involvement (N stage):

The incidence of lymph node metastasis is 6-14% in T1 tumors, 17-23% in T2 tumors and 49-66% in T3 tumors (40, 41).

Many studies have looked at whether MRI can detect the presence of lymph node metastasis (N0 versus other N-stages). These studies, based primarily on lymph node size, have not shown very high accuracy rates for the diagnosis of presence of malignant lymph nodes (42). Lymph node size, by itself, is poorly predictive of nodal status as there is overlap in the size of normal and pathologic lymph nodes (43).

Evaluation of lymph node size in combination with lymph node morphology is important to optimize interpretation accuracy.

Morphologically abnormal lymph nodes that seem heterogeneous or demonstrate irregular margins are considered diseased (43, 44) (Fig.12).

** Lymph node can be categorized as positive based on one of 3 criteria:

1) Short axis equal to or greater than 9 mm.

2) Short axis 5 to 9 mm and at least 2 abnormal morphologic features (heterogeneous signal intensity, irregular border, or round shape);

3) Short axis less than 5 mm and all 3 abnormal morphologic features (heterogeneous signal intensity, irregular border, and round shape).

N stage: N0 disease is defined as no pathologic regional lymph nodes.
N1 disease is defined as 1 to 3 pathologic regional lymph nodes.

N2 disease is defined as 4 or more pathologic regional lymph nodes.

For MRI staging purposes, differentiating between N0 and N1 disease is important because patients with pathologic lymph nodes typically undergo preoperative neoadjuvant chemoradiation before resection regardless of T stage.

Perirectal and internal iliac lymph nodes are considered regional lymph nodes in the setting of rectal cancer, whereas inguinal, external iliac, common iliac, and periaortic lymph nodes are considered non-regional lymph nodes (45).

Extramesorectal nodes are important to describe, including those along the pelvic sidewall, as they are a negative prognostic predictor and are not routinely resected (46). Lesions that infiltrate the presacral space can manifest with retroperitoneal lymph nodes; therefore, those chains are also important to evaluate (8).

Fig. (12): Axial T2WI images (1.5 T) of a rectal cancer originating from the right rectal wall. There is a malignant lymph node (black arrow) in the obturator fossa on the left side (28)

Rectal Cancer Imaging

It is essential in treating rectal cancer to have an adequate pre-operative imaging. In the last twenty years, endorectal ultrasound (ERUS) has become the primary method for locoregional staging of rectal cancer. ERUS is a very useful modality for assessing local depth of invasion of rectal carcinoma into the rectal wall layers (T stage) (47).

EUS is superior to MRI in early lesions assessment as differentiating between T1 and T2 lesions is challenging with MRI due to limited visualization of the rectal submucosa. MRI is preferred over EUS in locally advanced cases (T3/T4) which require a more detailed evaluation of the resection plane and the circumferential margin resection status. ERUS is also useful for detection of local recurrence at the anastomosis site, which might require fine-needle aspiration of the tissue (48).

MR Imaging Technique
Technique:

MR images were obtained with a 1.5 or 3T whole body system and a phased array body coil.

Patient Preparation:

Examination is performed for all patients (with histologically proven rectal cancer as part of their staging process before initiating treatment).

Bowel preparation, filling of the rectum with contrast agents, or air insufflation are not recommended. IV or intramuscular antispasmodic agents are also not mandatory but can be helpful in improving image quality.

IV contrast enhancement with gadolinium is not recommended for staging of rectal cancer (51, 52).

Coil positioning: The coil may need repositioning depending on the location of tumor seen on sagittal sequences. The cranial border of the coil should not be higher than L5 and the caudal border of the coil should be 10 cm below the symphysis pubis in low rectal tumors (53).

MRI sequences:

Initial localization images in the coronal and sagittal planes are needed to plan the high-resolution images. The first series is the sagittal T2-weighted, fast (turbo) spin-echo sequence from one pelvic sidewall to the other, which enables identification of the primary tumor. It helps to locate the distance of the tumour from the anal verge and defines its cranio-caudal extension (Fig 13). The second series consists of large-field-of view axial sections of the whole pelvis. The scan protocol for these sequences was TR 3000–4000ms, TE 70–90ms, field of view (FOV) 28–32cm×28–32cm, matrix 276×384, slice thickness 5mm and gap 1mm (54).

The third series consists of the high-resolution images that are T2-weighted thin-section axial images through the rectal cancer and adjacent tissues, to demonstrate the parietal extension of the tumour through the rectal wall and any contact with the mesorectal fascia. These sequences must be performed perpendicular to the long axis of the rectum and at the level of the tumor (3-mm slice thickness); otherwise, the images may be misinterpreted because of partial volume effect.

For patients with low rectal cancers, the fourth series consists of high-spatial-resolution coronal imaging parallel to the anal canal. It will optimally show the levator muscles, the sphincter complex, the intersphincteric plane, and the relationship to the rectal wall (54).

High-resolution T2W protocol (TR 4200–5000ms, TE 108 ms, slice 3 mm, 210–300s acquisition time, FOV 180–240 mm).

T1-weighted imaging seldom leads to increased information for experienced radiologists. Its use, however, does not increase imaging time considerably and may occasionally help with other diagnoses. Mucin-producing tumours might be better visualised with T1-weighted imaging compared with T2-weighted imaging (28).

Axial DW images were obtained using a single-shot echo-planar imaging sequence. The scan protocol was TR 3200ms, TE 74ms, field of view (FOV) 300 mm×244 mm, matrix 128×128, slice thickness 7mm, gap 2.1mm, b factor 0 and 1000s/mm². All patients held their breath while the DW images were being acquired (55).
Contrast-enhanced imaging with gadolinium does not improve the diagnostic accuracy of local staging of cancer rectum, however, particularly at restaging, the use of intravenous contrast material may help to identify local recurrence (8, 28).

Diffusion Weighted Imaging:

At present, the use of diffusion-weighted imaging incorporated into a standard MR protocol is gradually increasing because of its proven benefit not only for tumor detection/characterization but also for monitoring treatment response (56, 57). Diffusion weighted imaging measures water diffusion characteristics, which are dependent on multiple factors such as cell density, vascularity, viscosity of extracellular fluid, and cell membrane integrity (56). By quantifying these properties and expressing them as an apparent diffusion coefficient (ADC), DWI could potentially be used as an imaging biomarker to better select patients with poor prognosis who will truly benefit from a more aggressive neoadjuvant treatment (58).

Mean ADC was calculated from a sample of three round/oval-shaped regions of interest (ROIs) that were manually placed within solid tumor parts (as identified as focal masses showing intermediate signal intensity on the anatomical T2-weighted images and bright signal intensity on DWI) of three independent tumor-containing slices. The size and position of the ROIs was chosen to include as much of the solid tumor area as possible (59) (Fig 14).

It is used as an imaging biomarker. This could be beneficial in clinics to predict prognostic factors such as nodal stage, mesorectal fascia (MRF) involvement, and histological differentiation grade (60, 61). Moreover, ADC may have value to predict therapeutic response, which (in the future) could impact treatment stratification (62).

It may predict cell death, which can be predicted as an increase in ADC value, which precedes alterations in tumor size (63).
Fig. (14): Example of manual placement of an oval-shaped ROI for measurement of the ADC values for each tumor on the ADC map (a). High b-value (1000 s/mm²) DWI (b) and T2W (c) images provided respectively functional and anatomical reference \(^{(59)}\).

**Diffusion weighted imaging physics:**

Conventional imaging detects cancer by identifying anatomical distortion or altered tissue appearances. However, identification of small volume active tumour, either at presentation or at early disease relapse remains challenging because small volume disease may not result in detectable structural or morphological change on conventional imaging. Furthermore, the effects of therapy and complications may obscure or mimic recurrent disease \(^{(64)}\). DW-MRI can be a useful tool to detect malignant transformation within nonspecific mural wall thickening or small rectal cancers whose location is not mentioned by the referring physician, or in case of specific pathologic conditions such as desmoplastic reaction, fibrotic or inflammatory changes due to radiotherapy \(^{(65)}\).
One of the simplest methods of obtaining DW images is to apply pairs of opposing and balanced magnetic field gradients (but of different durations and amplitudes) around a spin-echo refocusing pulse of a T2 weighted sequence. Stationary water molecules are unaffected by the paired gradients, and thus retain their signal. Non-stationary water molecules acquire phase information from the first gradient, but are not rephased by the second gradient, leading to an overall loss of the MR signal. The signal reduction on the DW image is proportional to the amount of diffusion water motion occurring during the pulse sequence. Hence, on DWI, there is usually less signal attenuation (i.e. higher signal intensity) of tumour compared with normal tissue due to the restricted diffusion of water molecules in tumours, which is presumed to be due to an increased cellular density (65) (Fig. 15).

The strength of diffusion-weighting applied is referred by the b-value (measured in s mm$^{-2}$), which indicates the magnitude and duration of the applied gradients and time between the paired gradients. DWI using a larger b-value (e.g. b-value = 500 s mm$^{-2}$) is more sensitive to the slower motion of water molecules and smaller diffusion distances (64).

With all functional imaging techniques, DWI information should be interpreted with information from conventional imaging to improve disease assessment. DWI is emerging as a powerful, new diagnostic tool which will be increasingly applied to the evaluation of tumors (64).

![Fig. (15): Mucinous rectal cancer in a 76-year-old male patient. (A) Axial T2WI show high focal signal intensity of the upper rectal wall (arrow), which confused with residual water in the rectum. (B) Axial DWI of the same plane demonstrate focal markedly hyperintense tumor (arrow) and the residual water is hypointense. Right seminal vesicles are hyperintense (arrowhead) (65).](image-url)
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