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Multimodal imaging evaluation in staging of rectal cancer

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Abstract

Rectal cancer is a common cancer and a major cause of mortality in Western countries. Accurate staging is essential for determining the optimal treatment strategies and planning appropriate surgical procedures to control rectal cancer. Endorectal ultrasonography (EUS) is suitable for assessing the extent of tumor invasion, particularly in early-stage or superficial rectal cancer cases. In advanced cases with distant metastases, computed tomography (CT) is the primary approach used to evaluate the disease. Magnetic resonance imaging (MRI) is often used to assess preoperative staging and the circumferential resection margin involvement, which assists in evaluating a patient's risk of recurrence and their optimal therapeutic strategy. Positron emission tomography (PET)-CT may be useful in detecting occult synchronous tumors or metastases at the time of initial presentation. Restaging after neoadjuvant chemoradiotherapy (CRT) remains a challenge with all modalities

because it is difficult to reliably differentiate between the tumor mass and other radiation-induced changes in the images. EUS does not appear to have a useful role in post-therapeutic response assessments. Although CT is most commonly used to evaluate treatment responses, its utility for identifying and following-up metastatic lesions is limited. Preoperative high-resolution MRI in combination with diffusion-weighted imaging, and/or PET-CT could provide valuable prognostic information for rectal cancer patients with locally advanced disease receiving preoperative CRT. Based on these results, we conclude that a combination of multimodal imaging methods should be used to precisely assess the restaging of rectal cancer following CRT.

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Key words: Rectal cancer; Multimodality; Imaging; Staging; Restaging

Core tip: In rectal cancer, accurate staging and circumferential resection margin assessment are essential for stratifying the risks of recurrence and determining the optimal therapeutic strategy for individual patients. In the preoperative setting, a combination of multimodal imaging methods, including endorectal ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI), can be used to precisely assess the preoperative staging of rectal cancer. However, restaging after neoadjuvant therapy remains a challenge with all of these modalities. Recently, high-resolution MRI with diffusion-weighted imaging and/or positron emission tomography-CT imaging methods have been developed to precisely assess the restaging of rectal cancer following neoadjuvant chemoradiation therapy.

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INTRODUCTION

Rectal cancer is a tumor that arises from the rectum within 15 cm of the anal verge^[1]. In 2013, there were an estimated 40340 new cases of rectal cancer in the United States, and rectal cancer is a major cause of cancer-related deaths in the developed world^[2]. The prognosis of rectal cancer patients depends on the disease stage at the time of diagnosis^[3-5]; thus, accurate disease evaluation is necessary to properly treat rectal cancer.

Rectal cancer prognosis is largely determined by tumor-node-metastasis staging, which evaluates the depth of tumor invasion into the rectal wall as well as the presence of lymph node (LN) and other distant metastases (Table 1)^[3,4]. Again, accurate staging is crucial to determine the optimal treatment strategy, including selecting the appropriate surgical procedure. For example, early-stage (T1 and some T2) tumors may be suitable for local excision or trans-anal endoscopic microsurgery, whereas more advanced lesions (T3-4 and/or N1-2) may merit neoadjuvant chemoradiation therapy (CRT) followed by total mesorectal excision [TME; the surgical removal of the rectum and mesorectum enveloped by the mesorectal fascia (MRF)]^[5,6]. In cases requiring TME, the status of the circumferential resection margin (CRM; defined by the spreading of the tumor to the MRF) is an important prognostic factor for predicting survival and local recurrence^[1,5,7-9].

Because neoadjuvant CRT is the standard treatment for locally advanced rectal cancer, assessing tumor response using conventional imaging methods has been challenging^[10-15]. The goal of neoadjuvant CRT is to preserve sphincter function while improving tumor resectability and reducing tumor mass prior to surgery^[5]. Therefore, a more reliable imaging method would facilitate the design of more effective pre- and post-operative treatment strategies. Moreover, an effective assessment method would allow stratification of patients according to the risk of recurrence using preoperative and post-CRT assessments of the depth of tumor invasion and nodal status as well as of CRM involvement^[16,17].

Currently, several imaging modalities, including endorectal ultrasound (EUS), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) or PET-CT, are used to assess preoperative staging and therapeutic response. This review will address the advantages and limitations for each of these imaging modalities in the context of staging and assessing therapeutic response in rectal cancer patients.

IMAGING MODALITIES FOR PREOPERATIVE STAGING

The preoperative staging of a rectal cancer tumor has been correlated with the patient's long-term prognosis^[3-5].

Table 1 Tumor nodes metastasis staging of rectal cancer based on the American Joint Committee on Cancer 7th edition

Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma <i>in situ</i>
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria and into perirectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum
T4b	Tumor directly invades or is adherent to other organs or structures
Regional lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases in 1-3 regional lymph nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastases in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, pericolic, or perirectal tissues without regional nodal metastasis
N2	Metastases in 4 or more regional lymph nodes
N2a	Metastases in 4-6 regional lymph nodes
N2b	Metastases in 7 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to 1 organ or site (<i>e.g.</i> , liver, lung, ovary, non-regional node, external iliac lymph node)
M1b	Metastases in > 1 organ/site or the peritoneum

Note-Adapted from the American Joint Committee on Cancer staging system^[9].

In particular, tumor staging facilitates the formulation of a structured multidisciplinary approach to manage the disease and assess a patient's prognosis over the course of treatment. Preoperative staging of rectal cancer can be divided into either local or distant staging. Local staging primarily involves assessment of mural wall invasion and nodal status for metastasis as well as CRM involvement, while distant staging assesses the extent of metastatic disease. Currently, several modalities are used for the preoperative staging of rectal cancer (Table 2).

EUS

EUS is performed by introducing a water-filled balloon containing a high-frequency transducer and trans-anal probe into the rectum. This approach can delineate the five layers of the rectal wall as alternating hyper-echoic and hypo-echoic bands^[18,19]. EUS is particularly effective for assessing the depth of tumor invasion into the rectal wall, with 69%-94% accuracy (Figure 1)^[20-23]. EUS can accurately distinguish between early- and advanced-stage rectal lesions with sensitivity, specificity and accuracy rates of 96%, 85% and 94% respectively^[6]. EUS is more specific in evaluating local tumor invasion when compared to MRI imaging (86% *vs* 69% specificity rates respectively), although both methods have similar high sensitivities for evaluating the depth of tumor penetration into the muscularis propria (94%)^[24].

A recent meta-analysis of 5039 patients from 42 studies carried out between 1980 and 2008 supports

Table 2 Advantages and disadvantages of imaging modalities in preoperative staging

Imaging modalities	Advantages	Disadvantages
Preoperative staging		
EUS	Depth of tumor invasion in early rectal cancer	Limited field of view Perirectal invasion and LN metastasis
CT	Wide availability Fast scanning time	Local staging and CRM involvement in lower rectal cancer
MRI	High soft tissue resolution Local staging and CRM involvement	Distant metastasis
PET/CT	Distant metastasis	Poor spatial resolution Perirectal invasion and CRM involvement
Post-therapeutic restaging		
EUS	None	Low accuracy of T staging and LN staging
CT	Relatively high accuracy of CRM status	Relatively low accuracy of T staging and LN staging
MRI	High specificity of therapeutic response assessment High accuracy of CRM involvement	Relatively poor sensitivity
PET/CT	Distant metastasis	No standard parameter and follow-up protocol

MRI: Magnetic resonance image; EUS: Endorectal ultrasonography; CT: Computed tomography; PET: Positron emission tomography; CRM: Circumferential resection margin; LN: Lymph node.

the accuracy of EUS for determining T stages, with pooled sensitivity and specificity rates of approximately 81%-96% and 91%-98%, respectively^[25]. However, the accuracy of EUS in assessing the depth of invasion into the rectal wall appears to vary with the tumor stage, with lower accuracy in T2 lesions, compared with that in early-(T1) and advanced-(T3-T4) stage lesions^[25]. Furthermore, EUS cannot reliably distinguish between peritumoral inflammation or transmural tumor infiltration, which may lead to over-staging of T2 tumors as T3 tumors and subsequent overtreatment^[21,26,27]. The staging of bulky, distal and/or stenotic lesions with EUS can also be challenging due to the limited field of view and the inability of probes (especially rigid probes) to traverse the lesion^[19,23].

Lymph node (LN) staging with EUS remains difficult and is less accurate than T staging, with reported accuracy rates of 64%-83%^[20,21,23,28]. Although EUS-detected morphological characteristics, including a round shape, peritumoral location, size, and hypo-echogenicity) could be associated with malignant LNs, these features are neither sensitive nor specific^[10,19,29]. Moreover, EUS can evaluate only perirectal or mesorectal LNs, thereby limiting the screening capacity of this method. In contrast, other imaging modalities such as CT, MRI and PET/CT can visualize the iliac and mesenteric or retroperitoneal nodes, allowing for more comprehensive LN staging.

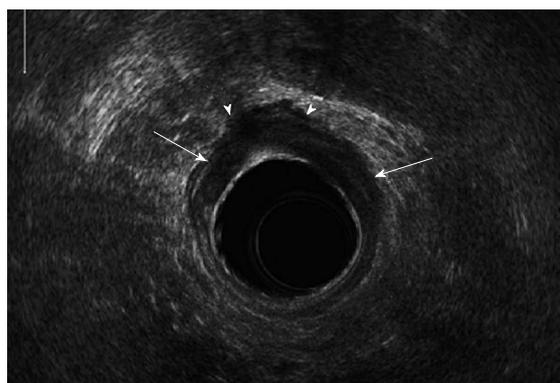


Figure 1 Endorectal ultrasound image of T3 rectal cancer. Endorectal ultrasonography image shows a hypo-echoic mass (arrows) that extends into the echogenic mesorectal fat (arrowheads).

Recent developments in 3-dimensional EUS technology, with enhanced resolution and a multi-planar display, have resulted in improved T- and LN-staging accuracy rates compared to 2-dimensional EUS^[30]. Nevertheless, an assessment of the MRF remains impossible and the accuracy of the procedure is largely dependent on the experience of the operator^[19,21,30]. Thus, the major role of EUS in rectal cancer staging is for assessment of tumor invasion depth, particularly in early-stage rectal tumors, for which EUS can be used to evaluate whether tumors are suitable for treatment by trans-anal or local excision^[6,17,25].

CT

CT is commonly used as the initial staging modality for rectal cancer because of its wide availability and fast scanning times. In a single examination, CT can also assess the entire abdomen, pelvis and chest, allowing for both local staging and distant metastases evaluations^[17,31]. Initial studies using conventional CT to assess locally advanced rectal cancers (*i.e.*, \geq T3) reported T staging accuracy rates of 79%-94%^[32-34]. The technical advances in multi-detector CT (MDCT) have provided enhanced spatial resolution through thin-collimation scanning and multi-planar reformation, and have improved the accuracy rates to greater than 90%^[35]. Nevertheless, MDCT has shown limited value for early-stage lesions confined to the rectal wall (*e.g.*, differentiation between T1 and T2 tumors), for which EUS may be more effective. Furthermore, the lower resolution of MDCT is unable to reliably distinguish the layers of the rectal wall and to differentiate between desmoplastic or peritumoral inflammatory reactions and tumor infiltration into the perirectal fat^[24,36]. These limitations lead to a tendency to over-stage T1 or T2 tumors as T3 tumors when using MDCT.

LN staging is predominantly based on the size criterion and, to a lesser extent, on morphology^[17]. One study suggests that a LN with axis above 4.5 mm in diameter is usually considered malignant, but such size criteria are not generally considered to be accurate^[37]. The lack of a clear cut-off diameter to determine whether a LN is metastatic

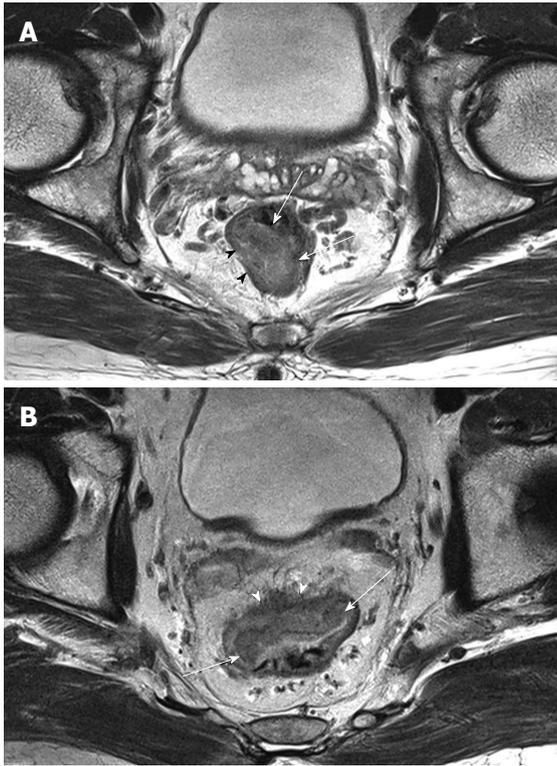


Figure 2 Stage T2 and T3 rectal cancer detected by magnetic resonance imaging. A: T2-weighted magnetic resonance image shows an intraluminal polypoid mass (arrows) confined to the intact, hypo-intense muscularis propria (arrowheads), suggestive of a T2 cancer; B: T3 lesion is seen as a tumor (arrows) that extends through the hypo-intense muscle layer into the perirectal fat (arrowheads).

has led to wide variability in LN-staging sensitivity and accuracy using CT, with respective rates of 25%-86% and 35%-84%^[17,37]. Moreover, even with the enhanced resolution of MDCT, accurate assessment of the nodal status remains challenging because microscopic metastases in normal-sized LNs cannot be depicted on CT.

Regarding assessments of CRM involvement, in a multicenter study of 250 patients^[38], MDCT showed overall sensitivity and specificity rates of 76% and 96%, respectively for mid to upper rectal cancer patients. This result suggests that CT may be an alternative to MRI to predict CRM involvement in such patients. In lower rectal cancer, however, CT is less accurate and inconsistently predicts CRM involvement^[39,40]. Thus, in a preoperative setting, CT is best suited for evaluations of distant metastases, as this modality is limited with regard to local staging and CRM status determinations.

MRI

Since 1986, MRI has been used to delineate rectal tumors and locally stage rectal cancers. Initial MRI studies using a body coil have reported overall accuracy rates ranging from 59% to 88%, similar to the accuracy range for CT^[41-43]. Recently, rectal MRI has been performed with either an endorectal coil or a phased-array surface coil. Several studies with phased-array MRI showed accuracy rates of 65%-86%, and studies with an endorectal coil

reported slightly improved T staging rates (71%-91%)^[43,44]. Although the endorectal coil permits a more detailed differentiation of the rectal wall, its routine use in clinical practice is controversial due to some limitations of the technology. Specifically, it is difficult to clearly differentiate between the mucosa and submucosa, to access high and/or stenotic rectal lesions, and to completely evaluate the mesorectum and surrounding structures due to the limited field of view^[10,17,45]. However, in a comparative study on endorectal and phased-array coils, both techniques yielded similar diagnostic accuracy rates (80%) for the depth of tumor invasion^[46].

In addition, recent studies have shown that the use of 3.0-T MRI improves the overall T staging accuracy for rectal cancer with accuracy rates of 86%-95%^[47-49]. This represents a significant improvement over 1.5-T MRI, which has T staging accuracy rates of 67%-86%^[50-52]. Moreover, improvements in scanner gradients and dedicated external coils have allowed rectal MRI to be successfully performed with phased-array surface coils; allowing high-resolution imaging with thin-sections and an enhanced field of view, and providing a more comfortable patient experience^[43].

The use of rectal MRI techniques for clinical decisions regarding bowel preparation, the use of antispasmodic agents, and the use of rectal gel can vary according to the preference of the radiologists^[53]. Although the use of gadolinium contrast enhancement rarely improves rectal cancer staging *via* MRI, many centers still acquire images both before and after gadolinium administration^[54,55].

To identify and stage rectal cancers with MRI, high-resolution T2-weighted image with thin-sections is the primary approach used to differentiate between the tumor, mucosal and submucosal layers, muscular layer, perirectal fat, and MRI^[56]. However, because the submucosal layer is not always efficiently visualized on MRI^[6], the ability to differentiate between T1 and T2 lesions may be limited. Using MRI, a T3 lesion is defined as a tumor that extends through the hypo-intense muscle layer into the hyper-intense perirectal fat with a bulging or nodular appearance, whereas a T2 tumor is confined to the hypo-intense muscle layer (Figure 2)^[56]. In prospective comparative studies with histopathology, MRI-based staging strongly correlated with the depth of tumor invasion (82%)^[56] and agreed with the extramural depth of invasion (95%)^[57]. However, staging failures commonly occur when differentiating T2 from borderline T3 tumors, as it is difficult to distinguish direct tumor infiltration (T3) from speculated structures in the perirectal fat due to fibrosis or peritumoral inflammation (T2)^[58]. In contrast, MRI is particularly accurate when identifying T3 and T4 tumors, with a sensitivity of 80%-86% and specificity of 71%-76% for T3 tumors^[59].

Regarding LN assessments with MRI, a size cut-off of 5 mm in diameter is the most commonly used criterion. However, 15%-42% of patients with rectal cancer have metastatic perirectal LNs that are smaller than 5

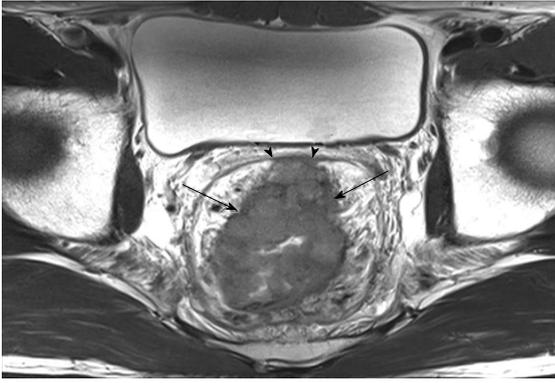


Figure 3 Mesorectal fascia invasion detected by magnetic resonance imaging. T2-weighted magnetic resonance image shows a T3 tumor (arrows) with involvement of the mesorectal fascia (arrowheads).

mm^[60,61], indicating that this criterion is not accurate enough for reliable assessment. Using a combination of other criteria, including an irregular border and/or a mixed signal intensity, MRI for nodal staging shows an accuracy of 85%, with a moderate sensitivity of 75% and high specificity of 98%^[61]. However, a recent meta-analysis of 1249 patients from 23 data sets showed that the ability to assess LN involvement was consistently poor with a pooled sensitivity of 77% and specificity of 71%^[62]. Similarly, in another meta-analysis study, MRI showed poor accuracy when compared with EUS and CT^[24]. With improvements to MRI scanners and techniques, the nodal staging accuracy has increased to 91%, with a high sensitivity of 89%^[47]. High-resolution MRI with thin-sections has enabled evaluations of the detailed characteristics of LNs. Nevertheless, it remains challenging to detect micro-metastases in small or normal-sized LNs using MRI.

MRI is a reliable imaging modality for CRM status assessments, making the technique an important element of surgical planning and prognosis. Most commonly, MRI is used to measure the distance of a tumor from the MRF, as the MRF is observed as a thin hypo-intense line that envelops the perirectal fat and rectum. In a prospective study by the Magnetic Resonance Imaging and Rectal Cancer European Equivalence (MERCURY) study group, which defines CRM involvement as a tumor within 1 mm of the MRF, MRI showed 92% specificity for preoperative predictions of a clear CRM (Figure 3)^[63]. This 1 mm threshold is the most commonly used criterion to assess CRM involvement, although Beets-Tan *et al.*^[58] reported that a 5 mm cut-off on MRI could also predict CRM involvement with a high degree of certainty. Published data have shown that MRI has a high accuracy rate of 86% for predicting CRM involvement, with good intra- and inter-observer agreement^[17,58,64]. Thus, MRI is a powerful method for preoperatively assessing both local staging and CRM involvement with high accuracy and reproducibility, effectively identifying patients who require preoperative CRT in order to minimize incomplete tumor resections and local recurrences^[63].

PET-CT

PET enables the measurement and visualization of metabolic changes within cancer cells. Fluorodeoxyglucose (FDG) is the most common PET tracer used, as its uptake is increased in tumors due to increased metabolic activity in the tumor cells, which facilitates efficient radiolabelling. Studies have shown that PET-CT can reliably detect colorectal cancer but not its depth of tumor invasion^[65,66]. The poor spatial resolution and lack of detailed anatomy provided by FDG-PET make the determination of the degree of local tumor spread, LN involvement, CRM status, or relationship to the sphincter complex difficult.

The utility of PET-CT scanning for initial staging of rectal cancer remains unclear^[14]. While PET-CT is capable of detecting occult synchronous tumors or metastases at the time of initial presentation, the detection rate is too low to justify the costs and radiation exposure for its routine use. In addition, PET is limited to the identification of non-mucinous tumors because FDG uptake is hampered by the presence of mucin^[67]. Currently, PET-CT is reserved for the staging of patients prior to surgical removal of recurrent lesions or distant metastases and to identify recurrent lesions in patients with an unexplained rise in serum carcinoembryonic antigen. PET-CT may be particularly useful for the staging of distant metastatic spread, particularly if radical surgery is being considered but no local staging information is available using other imaging methods^[14].

One recent study demonstrated that preoperative PET altered the treatment strategy in 17% of patients, including 13% for whom surgery was cancelled and 4% for whom the radiotherapy field was changed^[68]. One explanation for this finding is that PET-CT frequently yields additional staging information in patients with low rectal cancer. Thus, PET-CT could be used to improve the accuracy of pretreatment imaging, thereby allowing for more appropriate stage-specific therapy^[69].

IMAGING MODALITIES FOR EVALUATION OF POST-TREATMENT RESPONSES

Preoperative CRT has been widely adopted for the management of patients with locally advanced rectal cancers because it can facilitate tumor downsizing and downstaging, leading to increased rates of sphincter-sparing surgeries and pathologic complete response^[5]. If tumor responses to neoadjuvant CRT could be assessed before surgery, patients could receive appropriately tailored treatments. For example, patients who respond well to the CRT could be offered less radical treatments, whereas those who fail to respond could be identified as candidates for more radical surgeries or second-line therapies^[14]. Traditionally, tumor response assessments are achieved by measuring the percentage of the tumor size reduction according to the Response Evaluation Criteria in Solid Tumors criteria, as the change in tumor size is generally thought to correlate with treatment efficacy^[70]. However,

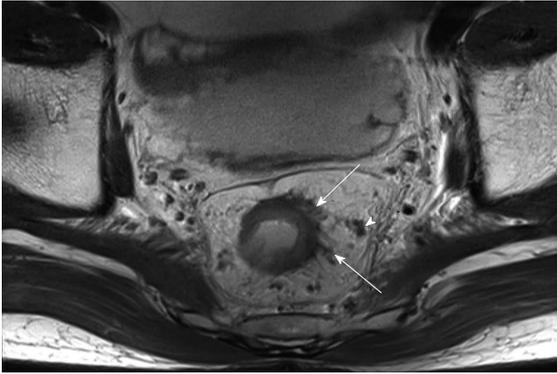


Figure 4 Over-staging due to post-chemoradiotherapy changes. T2-weighted image obtained after chemoradiotherapy shows hypo-intense infiltration (arrows) to the perirectal fat and a spiculated lymph node (arrowheads), which was misinterpreted as a remnant T3 lesion and metastatic node. However, there was neither a residual tumor nor metastatic lymph node on the pathological examinations after surgery.

this assessment approach is insensitive to early treatment changes, and it can be difficult to distinguish between viable tumors and CRT-associated non-tumoral masses (*e.g.*, inflammation, necrosis, or fibrosis)^[11]. Given these limitations, the response of locally advanced rectal cancers should be addressed not only by tumor size, but also by additional prognostic factors, including the extramural depth of invasion, nodal status, and CRM involvement, as well as the relationship with pelvic structures (Table 2). Thus, it is important to determine which imaging modalities can provide accurate and reliable information regarding these criteria to accurately assess tumor responses.

Efficacy of EUS for assessing post-CRT rectal cancer response

EUS does not appear to play a role in post-therapeutic response assessments because it cannot reliably differentiate between post-radiation edema, inflammation, fibrosis, and viable tumors^[19]. Due to this limitation, the accuracy of EUS for rectal cancer restaging after radiation therapy is markedly low (47%)^[71]. In locally advanced rectal cancers, the T staging accuracy rates for EUS, when performed at 4–6 wk after the completion of CRT, were 29% in responsive patients and 82% in nonresponsive patients, with a high misinterpretation rate (71%) in responsive patients^[72]. In the same study, the overall accuracy of EUS for LN involvement after CRT was 57%^[72]. Thus, EUS is not recommended for restaging after radiotherapy or CRT.

Efficacy of CT for assessing post-CRT rectal cancer response

CT is most commonly used to evaluate treatment responses in solid tumors. However, in CRT-treated rectal cancer, the utility of CT is limited for identifying and following-up metastatic lesions. In a recent study to correlate tumor responses measured by CT in accordance with the histopathology, the overall accuracy rates of T and N restaging were 65% and 67%^[73] respectively, which

represents an improvement over a previous study (reporting T restaging of 37% and N restaging of 62%)^[13]. However, the tumor over-staging and under-staging rates after CRT were 23% and 12% respectively, because rectal wall thickening caused by CRT-induced fibrosis can be misidentified as residual tumors on CT^[73]. In CRM status assessments after CRT, CT accurately predicted a negative CRM in 71% of cases^[13]. Nevertheless, it remains unclear whether CT would have a clinical impact on the therapeutic outcome of local staging in patients with locally advanced, CRT-treated rectal cancer because of its poor resolution, further studies are necessary to evaluate the efficacy of this approach^[14].

With the recent advances aimed at reducing radiation exposure, perfusion CT is an emerging and noninvasive technique that permits measurements of tumor vascularity and perfusion changes, allowing measurements of CRT response. In rectal cancers, perfusion CT has been shown to differentiate rectal cancer from the normal rectal wall^[74,75]. In addition, perfusion CT could be useful for predicting tumor responses and clinical outcomes of CRT, as it can differentiate between tumors with normal *vs* low blood flow, as low blood flow before CRT is associated with a poor response^[74,75].

Efficacy of MRI for assessing post-CRT rectal cancer response

As in preoperative evaluation, T2-weighted MRI plays a major role in rectal cancer restaging after CRT. The concordance between the post-CRT MRI and the histological T stage was only fair to moderate ($\kappa = 0.40$), suggesting rather low accuracy^[76]. However, when a morphological response assessment (*e.g.*, responder *vs* non-responder) was used, the overall accuracy rate improved to 79%^[77]. High-resolution MRI with thin-sections yielded an improved T staging accuracy rate after CRT, with good concordance ($\kappa = 0.64$)^[78]. Despite these improvements, a recent meta-analysis showed that MRI-mediated rectal cancer restaging after preoperative CRT remains challenging, with poor sensitivity (50.4%) due to the difficulty of differentiating tumor changes from the residual tumor (Figure 4) using MRI^[79]. In cases of mucinous tumors, which are hyper-intense on T2-weighted images, stage prediction errors can also arise, making it difficult to distinguish between a remnant tumor and a mucin pool^[76,80]. However, the pooled specificity rate was as high as 91.2%, which suggests that positive MRI results can accurately identify CRT-responsive patients; however, negative MRI results may not similarly identify non-responsive patients^[79].

To determine the LN status after CRT, the same pre-CRT morphological criteria (*i.e.*, size, irregular borders, and signal homogeneity) are applied. This assessment method has a reported overall accuracy rate of 64%–68%^[76,81,82]. Moreover, recent studies of MRI assessment of post-CRT LN status reported high accuracy rates of 87%–88%^[77,78]. However, changes in morphological appearances after CRT, including high-signal interfer-

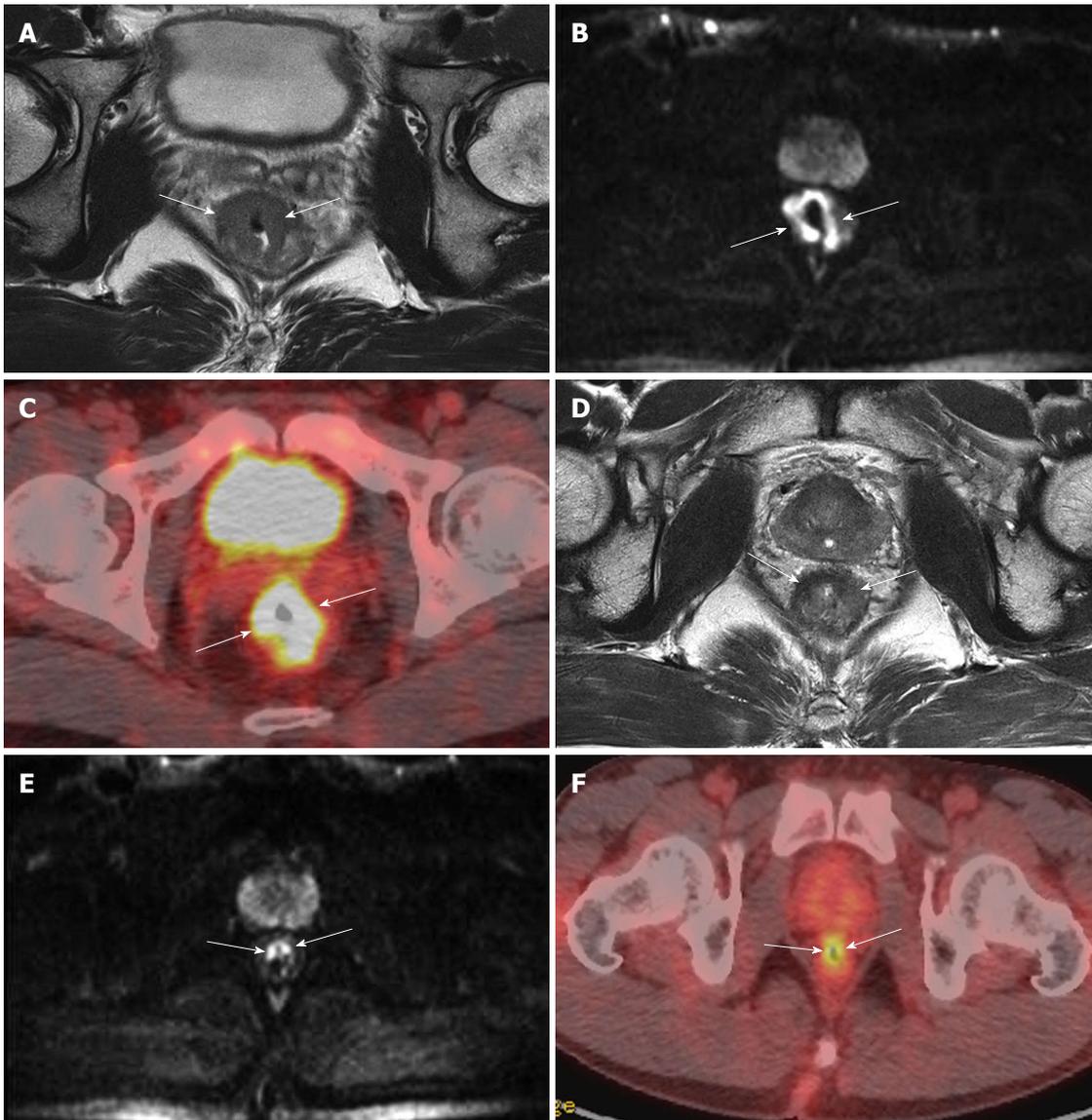


Figure 5 Combination of high-resolution magnetic resonance imaging with diffusion-weighted imaging and positron emission tomography/computed tomography for assessing tumor response after neoadjuvant chemoradiotherapy. A-C: T2-weighted magnetic resonance image (MRI) (A), diffusion-weighted imaging (DWI) (B), and positron emission tomography (PET)/computed tomography (CT) (C) obtained before chemoradiotherapy (CRT) shows a T3 tumor (arrows) with the restricted diffusion and intense hyper-metabolism; D-F: After CRT, T2-weighted MRI (D) shows a marked decrease in the tumor size. DWI (E) shows the focal diffusion restriction confined to the rectal wall, corresponding to histological proven T2 lesion. PET/CT (F) also demonstrates the good tumor response to CRT.

ence from mucin pools or spiculated LN margins, can make MRI assessments prone to over-staging (Figure 4)^[12,77,78].

According to a prospective study by the MERCURY group, the accuracy rate and negative predictive value for identifying CRM involvement in 97 CRT-treated patients were 77% and 98% respectively, whereas the same values were 91% and 93% in 311 patients who underwent primary surgery^[63]. A recent meta-analysis study reported a similar result, with a mean sensitivity of 76.3% and mean specificity of 85.9%^[79]. However, it should be noted that CRM involvement errors frequently occur in MRI assessments because of diffuse hypo-intense infiltration into the perirectal fat or MRF after CRT^[63,83]. Nevertheless, MRI assessment is considered effective for restaging tumors after CRT, particularly with respect to potential

CRM involvement.

Use of diffusion-weighted imaging in MRI for assessing post-CRT rectal cancer response

Diffusion-weighted imaging (DWI) is a newly emerging, functional MRI technique that can supplement conventional MRI assessment and enable the noninvasive characterization of biological tissues based on the properties of water diffusion. Thus, DWI can provide microstructural information, including changes in cellularity and integrity of cellular membranes, which often precede conventional morphological alterations. DWI has been used to detect and characterize tumors and distinguish between necrotic and viable solid portions within tumors by quantifying apparent diffusion coefficient (ADC) values^[84,85]. The ADC value decreases with increasing cell

density due the restricted diffusion of water molecules, which tends to increase in necrotic regions^[84,86].

The ADC values of tumors with good or complete responses were significantly higher than those of tumors with poor responses, and the presence of higher pre-CRT ADC values reflected necrotic CRT-resistant tumors^[86,87], suggesting that this approach is useful for predicting CRT response ahead of treatment. In contrast, the post-CRT ADC values of rectal cancers were lower than those of the pre-CRT tumors; a difference that was attributed to fibrosis or scar tissue formation and was not correlated with tumor response. These results indicate that the addition of DWI to standard MRI may facilitate the detection of viable tumors and identify CRT-responsive patients (Figure 5)^[88-90]. Moreover, in a recent meta-analysis, restaging with DWI showed good pooled sensitivity (83.6%) and specificity rates (84.8%)^[79]. Thus, DWI can provide a useful biomarker to assess and monitor treatment responses to CRT^[86,91].

Efficacy of PET-CT for assessing post-CRT rectal cancer response

PET-CT is a promising modality for identifying recurrent rectal cancer and distant metastasis. A significant reduction of standardized uptake values on post-CRT PET of responders compared with non-responders has been noted by a number of studies (Figure 5), suggesting that this approach can effectively assess CRT response^[15,92,93]. However, the efficacy of PET-CT for the prediction of tumor response remains controversial, especially for assessing pathological complete response to CRT in rectal cancer due to several limitations of the technology. One limitation is the variation in definitions and parameters used for defining a good *vs* a poor response. Another limitation is the uncertainty regarding the timing of PET imaging after the completion of radiotherapy. The optimal time to carry out PET assessment after the completion of CRT remains unclear, with initial studies suggesting an interval of only 6 wk being too soon to confirm metabolic response^[93]. Therefore, at present, the role of PET-CT in post-CRT restaging is not well established. It is possible that PET-CT may provide additional information in assessing response; however, PET-CT needs to be formally compared with existing methods to properly evaluate its efficacy.

FUTURE DIRECTIONS FOR MULTIMODAL IMAGING EVALUATION IN RECTAL CANCER STAGING

Multimodal imaging assessments in rectal cancer facilitate the design of treatment strategies and predict patient prognosis. Continued improvement of imaging techniques will provide superior image resolution, three-dimensional viewing, and decreased image acquisition times, and may provide new functional qualities. The use of EUS is likely to increase in future staging inves-

tigations, which will be complementary to the management of rectal cancer. DWI has been applied as a useful biomarker, which could be used to assess and monitor treatment responses to CRT, although protocol standardization and experienced radiologists are required to maximize the efficacy of this approach. Although the role of PET-CT needs to be formally compared with existing methods, PET-CT could provide additional valuable information for the assessment of post-CRT response. Restaging using a combination of imaging methods including high-resolution MRI, DWI and PET-CT will provide valuable prognostic information before definitive surgery. Despite these improvements, determination of the LN metastasis remains challenging in rectal cancer staging. LN research is further needed.

CONCLUSION

In preoperative settings, EUS is suitable for assessing the depth of tumor invasion, particularly in superficial and early-stage rectal tumors. CT imaging is a common method for evaluation of distant metastases. MRI is a useful and reliable modality for assessing preoperative staging and CRM involvement, allowing physicians to stratify the risks of recurrence and determine the optimal therapeutic planning for individual patients. PET or PET-CT assessment is recommended when there is clinical, biochemical or radiological suspicion of systemic disease.

Restaging after neoadjuvant therapy, particularly CRT, is challenging with all modalities because it is difficult to reliably differentiate between radiation-induced changes and the tumor itself. However, recent data suggest that a combination of high-resolution MRI with DWI, and PET-CT could provide valuable prognostic information before surgery for patients who were treated with preoperative CRT for locally advanced rectal cancer.

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