

**Important imaging considerations in the pre-operative assessment
of rectal cancer**

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Abstract

The role of imaging has become central in the pre-operative decision-making process for patients with rectal cancer. The detailed information which is available from high resolution imaging studies not only provides prognostic information but also allows the surgeon to anticipate potential pitfalls during the operation. The greater the amount of detail known about the tumour, the more selective one can be in the use of pre-operative radiotherapy, which can reduce unnecessary morbidity for minimal gain. Magnetic resonance imaging (MRI) is the most useful modality for the local staging of rectal cancer as it provides the most detail on the important prognostic factors which influence treatment. These include height of tumour from the anal verge, tumour depth of penetration, nodal disease, venous invasion, involvement of the circumferential resection margin. However, endoanal ultrasound (EAUS) is particularly good at staging early tumours and aids in identifying those which are suitable for local excision. We review the important considerations in the pre-operative staging of rectal cancer.

Introduction

Pre-operative investigations have become increasingly important in the optimal management of rectal cancer. Whilst tissue biopsy can confirm the presence of neoplastic disease and histopathological analysis of the resected specimen can influence adjuvant therapy decisions, imaging modalities such as magnetic resonance imaging (MRI), computed tomography (CT) and endoanal ultrasound (EAUS) are able to provide detailed information on both extent of spread as well as specific tumour characteristics at the earliest of stages. As these imaging techniques have become more advanced, there has been less reliance on pathology to influence management strategy and many of the key treatment decisions are now made in the pre-operative setting.

Different imaging modalities have specific advantages depending on the exact information required. For example, MRI may be most accurate in the local staging of advanced rectal tumours due to its ability to delineate the detailed fascial anatomical planes of the pelvis, whereas CT is superior for evaluating distant disease in remainder of the abdomen and chest. However, for optimal, progressive treatment strategies there are certain characteristics which will influence management and it is these factors which must be identified with the greatest accuracy. These include depth of tumour spread through the bowel wall including penetration into the mesorectum, nodal disease (to some extent), and presence of extramural venous invasion (EMVI) and height of tumour from the anal verge. The degree of detail required from imaging modalities is partly determined by the neo-adjuvant treatment policy that is used. More selective policies of neo-adjuvant therapy advocate it for those patients who are most likely to benefit are offered treatment and those who are

unlikely to benefit are not requires a greater detail of tumour behaviour. Conversely, if there is a universal policy to broadly treat all locally advanced tumours with neo-adjuvant therapy, the role of imaging becomes less influential. However regardless of treatment policy, pre-operative imaging also provides the surgeon with a potentially detailed 'roadmap' of the surgical anatomy. Arguably, surgeons do not always utilise the detailed information available from imaging studies which would help identify any potential pitfalls during the procedure.

This article describes the main imaging modalities used in the pre-operative assessment of rectal cancer and follows on to discuss the important tumour characteristics which influence treatment decisions, and the optimal imaging modality to identify them.

Imaging modalities

Magnetic Resonance Imaging (MRI)

MRI has become a central component of the staging process in rectal cancer in UK and many parts of Europe. Results from the MERCURY Study amongst other reports have shown MRI to be able to demonstrate the high-risk features which govern prognosis with accuracy and reproducibility [1-3] . However accuracy is not only dependent on interpretation but more importantly correct technique and image acquisition. For example, correct alignment of the axial images, perpendicular to the long axis of the rectum is essential for accurate assessment of the tumour. The rectum angles posteriorly and inferiorly rather than straight down. Mal-alignment of the imaging field, for example perpendicular to the vertical plane, will lead to

inaccurate staging. Incorrect alignment of the imaging field can have a major influence on pre-operative decision-making.

Recommended Technique

There is no mandatory need for bowel preparation or intra-rectal contrast agent. It is not necessary to use intra-venous antispasmodic agents such as Buscopan but this may be helpful in improving image quality in some patients. Finally, intra-venous contrast enhancement with gadolinium is not recommended for the staging of rectal cancer [4-6]. A 1.5-T (or where possible 3.0T) system is used with phased-array coils that maintain the high signal required but will obtain greater coverage than endorectal coils. It is important that the coil is optimally centred to ensure adequate coverage of the rectum, mesorectum, and anal sphincter complex. It is crucial to cover the lymph node draining territory, which is 5 cm above the tumor [7]; the lower edge of the tumor must lie at least 10 cm below the symphysis pubis and the upper limit of the sacral promontory.

Initial localization images in the coronal and sagittal planes are needed to plan further high-resolution images. A small field of view (160mm x 160mm, 256 x 256 matrix) with a minimum of 4 signal averages to ensure a 0.6 x 0.6 x 3 mm high resolution image (1mm³ voxel size). The first series are T2-weighted sagittal, turbo spin-echo sequences from one pelvic sidewall to the other enable identification of the tumour. The second series consists of large-field-of-view axial sections of the whole pelvis. The third series consists of the high-resolution images that are T2-weighted thin-section axial images through the rectal cancer and adjacent tissues. These sequences must be performed perpendicular to the long axis of the rectum and at

the level of the tumor (3-mm slices); otherwise, the images may be misinterpreted because of partial volume effects. For patients with low rectal cancers, the fourth series consists of high-spatial-resolution coronal imaging that will optimally show the levator muscles, the sphincter complex, the intersphincteric plane, and the relationship to the rectal wall. Zand et al. [8] have described in detail the commonly encountered artifacts and pitfalls in pelvic imaging and recommend several remedies.

Endoanal Ultrasound

Endoanal ultrasound is particularly useful in the local assessment of rectal cancer. However whilst the high spatial resolution of EAUS images is particularly suited to identification of the structure of the bowel wall, the endoanal technique produces inaccuracy with stenosing tumours, polypoidal tumours and high rectal cancer. In addition, it does not demonstrate fully the mesorectal fascia and thus the proximity of tumour to the potential circumferential resection margin. Peri-tumoral inflammation, fibrosis and faecal material can give the appearance of artefact or overcall tumour. Accuracy may be further reduced due to a combination of technical and user errors including incorrect field alignment, improper balloon inflation, physical or refraction artefacts, and if the tumour is close to the anal verge [9].

EAUS identifies different signal characteristics to correspond to the layers of the bowel wall. Five alternate layers of hyper- and hypoechoic rings are produced from the differences in acoustic impedance. A carcinoma is seen as an irregular hypoechoic mass which disrupts the normal anatomical layers. The extent of this disruption determines the depth of invasion and this T-stage. EAUS has increased

accuracy for defining the detail of the bowel wall structure which is particularly useful when planning mucosal resection or transanal excision. Sensitivity and specificity for T1 cancers is 87.8% and 98.3%, respectively [10]. As transanal endoscopic microsurgery (TEMS) and endoscopic submucosal resections become more popular, greater detail of the bowel wall is essential to select appropriate patients. Assessing whether a tumour has breached the submucosa becomes an important decision and other imaging modalities may not be as accurate as EAUS. EAUS may be particularly useful in distinguishing T2 from T3a tumours, more so than MRI. Yet from results of studies looking at the prognostic importance of tumour penetration, it is clear that early T3 tumours and T2 tumours have similar, low rates of disease recurrence [11, 12].

Prognostic factors

Circumferential resection margin

The importance of tumour spread close to, or involving the circumferential resection margin is well known [13, 14]. The CRM is the resection margin used by surgeons to ensure that the specimen is excised en-bloc with its surrounded fascia – the mesorectal fascia. It is the MRF that defines the CRM. Tumour identified to within 1mm of the CRM strongly predicts for local recurrence and poor survival outcomes [15]. Pre-operative knowledge of tumour spread in relation to the CRM not only allows for treatment planning with regards to neo-adjuvant radiotherapy but also informs the surgeon as to the closest margin during resection.

High resolution MRI is the most accurate imaging modality in identifying the mesorectal fascia and thus the CRM. It has been shown to be able to identify potential tumour at the CRM to within 1mm [2, 16-18].

In the MERCURY Study, a total of 349 patients underwent pre-operative MRI assessment followed by TME surgery were predicted to have clear margins. 327 (94%) patients were subsequently found to have clear margins on histopathology [1]. This gave a specificity of 92%. Taylor et al have shown that rates of local recurrence decreased from 53% with tumour less than 1mm from the potential CRM to less than 8% when the tumour distance from the mesorectal fascia was between 1mm and 5mm [18, 19]. A measured distance of 5mm on MRI has been shown to strongly correlate with negative CRM on histology, which led to patients being offered chemoradiotherapy when tumours are within 5mm of the mesorectal fascia. However, this results in substantial overt-treatment of patients with safe margins.

EAUS is unable to identify the mesorectal fascia as an anatomical landmark and thus cannot relate the extent of tumour spread in relation to the CRM. This is an important disadvantage of EAUS compared with MRI, however it is able to evaluate the depth of penetration in relation to the layers of the bowel wall. It is important to appreciate that the CRM and depth of penetration are not synonymous as the mesorectal fascia is not uniform along the entire length of the resection specimen.

The clinical relevance of being able to identify the CRM depends on the management policy with regards to neoadjuvant treatment. Where a more progressive and selective policy is adopted, relation of the tumour margin to the

CRM is imperative for decision-making. In units where such policies are used, involvement of the CRM supercedes all other prognostic indicators for the use of neo-adjuvant chemoradiation.

Extramural venous invasion (EMVI)

EMVI is the presence of tumour cells in the vasculature beyond the muscularis propria [20]. It is a modern term which describes a well-documented tumour phenomenon of vascular invasion. Whilst Warren and Brown's [ref] seminal report in the late 1930s first shed light on the prognostic importance of venous invasion in rectal cancer, it was not until Talbot's studies from St Mark's Hospital, London, that venous invasion was truly recognised as poor prognostic factor associated with the development of metastases and reduced survival outcomes [21, 22]. Up until relatively recently, vascular invasion or EMVI was only reliably detectable on histopathological examination of the resection specimen. As imaging modalities have improved, both CT and MRI have both been shown to be able to identify EMVI with great accuracy. However in the context of local staging it is MRI which is clinically more relevant. EAUS cannot reliably identify vascular invasion and is another limitation of this modality.

Sensitivity and specificity has been reported to be between 62%-100% and 88-89%, respectively [1, 23, 24] although these have been relatively early studies with better scanners now offering higher resolution of detail. A prospective study of 98 patients with biopsy-proven rectal cancer undergoing TME surgery evaluated the accuracy of MRI in identifying EMVI. EMVI was considered present if certain morphological features were seen on 3mm slices – a serpiginous extension of tumour signal within

a vascular structure (defined as a tubular structure containing signal void on T2-weighted images shown in continuity on adjacent slices) [2]. 18 patients had large vessel EMVI visible to the naked eye on H and E stain. 15 of these 18 cases found mrEMVI.

The radiological characteristics of EMVI as seen on MRI have been described in detail [20]. Veins around the rectum are recognised on T2-weighted images as serpiginous or tortuous linear structures. Differentiating between larger and smaller vessels can be difficult and requires a combination of signal characteristics and morphology; that is, there is a signal void in the tubular structures thought to be vessels in addition to changes in contour. Ideal assessment of mrEMVI must include the following: pattern of tumour margin (extension into small veins may produce a nodular border); location of tumour relative to major vessels; vessel calibre (tumour causes vessel expansion and increase in tumour signal in the lumen); and vessel border [20]. Smaller venules can be seen perforating the normal outer rectal wall and produce a low to intermediate signal intensity in tubular structures on T2-weighted images [3]. Venous invasion into these smaller venules can be seen recognised by their expansion and irregularity adjacent to the tumour due to contiguous tumour extension.

Height

Low rectal cancer continues to be the most challenging of the spectrum of disease and management remains controversial. There is some evidence that these tumours

confer a survival disadvantage and further have increased functional consequences - higher rates of permanent stoma, positive CRM, and adverse features compared to more proximal cancers [15, 25, 26]. The distance from the anal verge or height of the tumour is important due to its anatomical relationships as the rectum leaves the peritoneal cavity. It is prognostically significant for local recurrence [19, 27] and anastomotic leak following surgery [28, 29]. Abdominoperineal resection (APER) of rectum has been associated with even higher positive CRM and tumour perforation rates compared to anterior resection with positive margins as high as 30%. Clearly, accurate staging in terms of height is important to offer patients the most appropriate treatment. Surgery of the distal rectum presents specific challenges due to the narrow confines of the pelvis and the important surrounding neurovascular structures which affect function [30]; bowel function is thought to deteriorate where the anastomosis is within 4cm of the anal verge [31]. Thus, in addition to local tumour control, sphincter preservation is an important consideration for patients with low tumours. There is currently no universal consensus on the surgical treatment strategy for low rectal cancers. There are debates surrounding cylindrical versus extra-levator APER, ultralow anterior resection (with or without intersphincteric resection) versus coloanal anastomosis versus APER, and TME versus partial mesorectal excision [32].

The height of rectal cancer is commonly measured from the anal verge and can be based entirely on clinical examination on endoscopy and/or digital rectal examination. Modern series in the English literature arbitrarily define the rectum as composed of three parts: the low rectum (up to 6 cm from the anal verge) the mid rectum (from 7 to 11 cm) and the upper rectum (from 12 to 15 cm) [33].

With preoperative imaging becoming increasingly important in the context of treatment decision making it is important that the language of clinicians is objective and universal – therefore terminology for prognostic factors and definitions must be standardised between all of the disciplines involved in the management of rectal cancer. The clinical approach assesses the intraluminal component of the tumour and its relative subjective mobility in relation to the sphincter complex. Conversely, the radiological assessment involves appreciation of the tumour relative to points of reference external to the rectum. In the upper and mid-rectum the peritoneal reflection may be seen, in the low rectum the sphincter complex can be identified and the distance to the potential surgical resection margin may be accurately assessed [34].

T-stage and tumour penetration

One of the key components of the staging classification is the depth of tumour invasion in relation to the bowel wall. Depth of extramural invasion is recognized as an independent prognostic factor [35, 36]. More recently, certain groups of patients have been identified who are considered high risk and thus may benefit from neo-adjuvant therapy leading to a sub-classification of T-stage. This is determined by the extent of tumour penetration into the fatty lymphovascular envelope of the mesorectum which surrounds the bowel wall. Increasing penetration into the mesorectum is associated with a worse prognosis and increased rates of local recurrence - patients who have tumours which show greater invasion into the mesorectum (>5mm) have been shown to have lower 5-year survival and is independent of lymph node involvement. Those patients whose tumours

demonstrate less than 1mm invasion into the mesorectum have a favourable prognosis [35, 36].

Accurate assessment of this relies on the identification of the layers of the bowel wall which is accurately accomplished by both MRI and EAUS. A meta-analysis of almost 5000 patients comparing accuracy of T-staging between MRI, CT and EAUS showed 84%, 73% and 87%, respectively [37]. EAUS may be more useful for T1 and T2 tumours where accurate identification of the mesorectal fascia has less importance, particularly if the lesion is amenable to local resection however a key factor in decision-making, particular in the selective use of chemoradiotherapy, is identification of the mesorectal fascia so to determine the tumour edge from the CRM in more advanced tumours.

MRI can readily identify the layers of mucosa and muscle through distinct signal characteristics. T2-weighted images are particularly useful for this. The mucosal layer is seen as a very fine line of low signal intensity overlying the much thicker and higher signal of the submucosa. Outside this the muscularis propria can be seen as a dual-layer representing the inner circular and the outer longitudinal muscle layers. The latter has a typically irregular appearance due to vessels traversing the rectal wall. The perirectal fat is identified as a high signal with signal void areas surrounding the relatively low signal intensity of the muscularis. This is all enveloped by the fine layer of low signal intensity representing the mesorectal fascia. Determining the T stage of the tumour depends on careful assessment of the images with respect to the signal characteristics and correct field alignment. Abnormal or unexpected signal intensity in the bowel wall layers defines the T-stage. More

recently, importance has been given to the extent of tumour growth beyond the muscularis into the mesorectal fat.

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T3-substaging

The mesorectum is the lymphovascular envelope which surrounds the rectum to varying degrees. It completely surrounds the middle third of the rectum but is virtually absent in the lower third, and only covers the posterior aspect of the upper third of the rectum. The extent to which tumour penetrates the mesorectal fat is an independent risk factor for recurrence. This is not adequately represented in the traditional staging classifications as the level of penetration into the mesorectum has prognostic implications. T3 tumours are those which have traversed the bowel wall and penetrated into the mesorectum. The majority of patients present with T3 tumours, however there is wide variety in survival rates of these patients. Jass and colleagues were the first to describe the importance of the extent of mesorectal

invasion on prognosis [38]. Further work by Cawthorn and Merkel demonstrated an improvement in 5 year survival in patients who had “slight” mesorectal invasion. Cawthorn described “slight” mesorectal invasion as 4mm or less and found 5 year survival to be 55% compared to 25% when more than 4mm [35, 39]. Another study by Merkel et al studied patient’s survival characteristics with T3 tumours. Those patients with extramural spread of more than 5mm had 5yr survival rate of 54% compared with 85% for those patients whose tumours had extramural spread of less than 5mm [40]. These results were independent of lymph node involvement. These early studies highlight the importance of accurate measurement of tumour penetration into the mesorectum and those tumours with a worse prognosis, namely T3c and T3d. Therefore the distinction between T2 and T3 tumours with less than 5mm mesorectal spread – T3a and T3b; becomes irrelevant as these patients will have minimal benefit from CRT.

Nodes

The prognostic importance of local nodal disease (N1) if optimal total mesorectal excision is performed for rectal cancer is not as clear as previously thought [ref - Chand CD]. However many units continue to irradiate tumours on the basis of N1 disease alone, which makes accurate identification of mesorectal lymph node metastases important to prevent unnecessary morbidity. The “gold-standard” for detecting lymph node metastasis remains histopathological assessment but this information can only influence adjuvant treatment whereas radiotherapy, in particular, is best given pre-operatively [41, 42].

Magnetic resonance imaging (MRI) is the most accurate of the commonly used imaging techniques in identifying local nodal disease in rectal cancer but this is dependent on technique and the criteria used to determine whether a node is malignant or benign [43, 44]. Using incorrect criteria to assess mesorectal nodes may result in under- or over-staging of nodal disease and subsequent poor correlation with histopathology. This is the most likely explanation for the low specificity and sensitivity shown in published reports. Further, the consequences of inaccurate nodal staging can lead to unnecessary treatment and potential morbidity.

Traditionally radiologists have resorted to nodal measurements of varying sizes as a method of determining malignant status but none with any supporting histopathological evidence. A study which matched nodes from in vivo and specimen MRIs with pathology specimens showed that there was no useful size cut-off for predicting nodal status [45]. Further, a histological survey of over 12,000 lymph nodes in rectal cancer showed considerable size overlap between normal or reactive nodes and those containing metastases [46]. A perceived limitation of MRI is the lack of accuracy and ability to detect nodes smaller than 3mm. Yet this may not be as clinically relevant as first appears. Only 2% of nodes which are malignant were of this size.

Lymph node architecture is not commonly assessed using MRI as most radiologists prefer to measure the diameter of nodes instead [47]. As a consequence, the sensitivity and specificity is less than ideal; Bipat and colleagues performed a meta-analysis and reported sensitivity of 66% and specificity of 76% [48]. This paper included studies which gave little information on technique and criteria. Therefore

this lack of consistency makes the conclusion questionable in the context of high resolution imaging.

However when a high resolution MRI technique is used, it is easier to evaluate lymph node architecture and has enabled new criteria for lymph node involvement to be developed. Tumour infiltration into lymph nodes leads to characteristic radiological features which can be readily identified on MRI. Tumour leads to capsular disruption causing the nodal border to become irregular as opposed to the more rounded border of benign nodes. A very small number of lymph nodes with a smooth bordered contour (<6%) have been shown to be malignant whilst those demonstrating irregular outline are malignant in over 90% of cases [45]. Mixed signal intensity occurs due to the heterogeneity of the tumour and necrosis within the node. When using the signal characteristics and border outline together, the sensitivity is much improved.

Technique

Technique is the most important factor when examining for the malignant nodes. It is therefore important to not only use thin slices but also small field of view (FOV) for accurate identification. Many MRI scanners and resultant images are produced with adequate slices of 3mm but with a FOV of 22cm by 22cm and a low matrix resolution. Suspicious lymph nodes can be detected however this is not as accurate as a high matrix resolution of 0.6mm by 0.6mm.

EAUS does not predict lymph node involvement any better. Sensitivity and specificity for detection of cancerous lymph nodes in rectal cancer is 73.2% and 75.8%, respectively [49] although more likely to be accurate in the more proximal parts of

the rectum. Swollen reactive nodes, small blood vessels and even local structure such as the seminal vesicles may mimic malignant nodes.

Conclusion

MRI has several advantages over EAUS. These are due to its ability to accurately delineate the local pelvic anatomy and in particular important fascial planes. EAUS is most suitable for early, flat lesions which are low to mid-rectal. Depth of penetration, height of tumour and loss of resolution are all limitations of EAUS.

With the detailed prognostic information which is now available using high resolution technique for MRI, the surgeon can relay much more precise details of the tumour and the associated risk of disease recurrence to patients prior to surgery. This information ultimately influences management decisions which may include primary surgery versus neoadjuvant treatment; risks of local and distant failure; and potential challenges during surgery.

Unnecessary radiotherapy is associated with increased morbidity and patients should be explained that the risk of pelvic recurrence in early tumours is low; between 0-3% and any benefit from radiotherapy is minimal. The use of MRI can aid in the selective use of radiotherapy pre-operatively. Other prognostic factors such as persistent EMVI are prognostic and may be more relevant in decisions regarding adjuvant therapy. CRM involvement is the greatest risk for local recurrence and this has been shown in multiple studies. And whilst there is some role for EAUS in specific contexts for the local treatment of early cancers, MRI has the overall advantage of providing more information in the local staging of rectal cancer.

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