

Chapter 2

The Important Radiological Prognostic Factors that Influence Neoadjuvant Treatment in Rectal Cancer

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Abstract

Modern management of rectal cancer requires detailed staging of both local and distal disease. Identification of specific tumour characteristics that influence prognosis and survival outcome can now be detected using an array of imaging modalities. This information allows for the most appropriate treatment options to be used to help improve clinical outcomes for patients. Morphological characteristics such as tumour depth, mesorectal spread, local nodal involvement, extramural venous invasion and proximity of tumour edge to the circumferential resection margin are important predictors of local and distant disease recurrence. High resolution MRI can accurately stage locoregional disease. MRI can provide detailed anatomical information required for surgical planning and can identify tumour features that confer poor prognosis. CT imaging remains the most optimum imaging modality for assessing distal disease. Advances in imaging technology such as the use of PET-CT may be increasingly used to further risk-stratify patients with rectal cancer in the future.

Introduction

Rectal cancer staging provides critical information regarding the extent of disease. The information gained from staging forms the basis for determining prognosis and informing treatment decisions. Accuracy of staging is therefore of paramount importance to guide treatment appropriately and ensure optimal patient outcomes. Man-

agement decisions are no longer based solely on histopathology alone but guided by information regarding extent of disease and tumour behavior gained from preoperative imaging. This is particularly the case for neoadjuvant treatment decisions.

Multimodal imaging now plays a key role in the staging of rectal cancers. Information regarding tumour characteristics and behavior can now be obtained from high quality imaging techniques such as Magnetic Resonance Imaging (MRI), influencing treatment type and timing. Detailed evaluation of the tumour is required to identify key features that are associated with poor prognosis and early recurrence. Assessment of these features is often not readily available from initial tissue biopsy results but relies on their detection from staging imaging. This leads to a high level of reliance on the accuracy of the imaging modalities chosen. A shift toward selective neoadjuvant treatment means that initial treatment decisions are now the most important in terms of clinical outcomes for patients.

Whilst the use of Computerised Tomography (CT) imaging of the chest, abdomen and pelvis has become routine for assessing distal metastases, the imaging modality of choice for locoregional assessment remains contentious. MRI and Endoanal Ultrasound (EAUS) both offer advantages for staging local disease. More complex imaging such as positron emission tomography (PET) and contrast enhanced MRI may be required for the assess-

ment of indeterminate distal lesions. Ultimately, the aim of any combination of imaging methods is to provide the maximum amount of information regarding tumour location, spread and behavior. This should in turn influence treatment and impact on improved clinical outcomes.

This chapter will cover the preoperative staging imaging modalities used to assess both local and distal disease that can influence treatment decisions. Important prognostic features and their detection on different types of imaging will also be discussed.

Local Staging

MRI and EAUS are the two common imaging modalities used for local staging. MRI is thought to provide the best overall detailed picture of the pelvic anatomy and identify prognostic features of rectal cancer that influence treatment decisions. Information regarding tumour height and depth, infiltration of the mesorectum, circumferential resection margins, nodal disease and extramural venous invasion (EMVI) are required to inform decisions regarding the use of neoadjuvant therapy and type of surgical resection required.

Tumour Depth, Mesorectal Spread and Circumferential Resection Margin (CRM)

One of the main constituents of the TNM staging classification of rectal cancer is the assessment of tumour penetration through the individual layers of the bowel wall. Depth of tumour penetration influences the use of preoperative chemoradiotherapy (CRT) and the type of surgical resection required. MRI and EAUS are both able to accurately identify the layers of the bowel wall and therefore assess tumour depth. Early T-stage tumours (T1 and T2), where the tumour is confined to the bowel wall, commonly requires surgical resection alone and usually only requires preoperative therapy if adverse features are identified [1]. The risk of recurrence of T1 and T2 tumours independent of lymph node involvement is 5% and 10%, respectively [2]. A proportion of these early stage tumours may be amenable to alternative surgical treatments. Some T1 tumours, that do not demonstrate adverse features, may be treated with local excision. This can be performed by transanal endoscopic microsurgery (TEMS), thereby avoiding the morbidity associated with the more invasive total mesorectal excision (TME) approach [3,4]. EUAS is thought to be particularly useful in assessing early tumours. However, recent studies suggest it may not be as accurate as previously thought [5]. The lack of penetration

of the high resolution probe means that it has poor accuracy in distinguishing between early villous lesions larger than 5mm height [6]. The TREC – Transanal Endoscopic Microsurgery and Radiotherapy in Early Cancer trial is currently assessing whether short course neoadjuvant treatment and local excision produces better outcomes than TME for these early cancers. The trial is also focusing on the role of MRI in the detection and decision making for treatment of early rectal cancers.

The majority of patients will present with T3 rectal cancer [7]. These tumours invading the muscularis propria and mesorectum have an overall recurrence rate of 25% and often require neoadjuvant therapy to minimise the risk of local recurrence [2,8]. The use of selective neoadjuvant treatment now relies on improved accuracy of staging tumour depth, specifically relating to tumour penetration of the mesorectum. The mesorectum surrounds the rectum along its length and acts as an oncological barrier to tumour spread. The gold standard for oncological clearance of rectal cancer is total mesorectal excision, whereby the rectum and mesorectum are removed en bloc [9,10]. The introduction of TME has dramatically reduced local recurrence rates. The mesorectal fascia forms the outmost part of the mesorectum therefore defining the circumferential resection margin (CRM). Surgical resection aims to have clearance at the CRM and is an important determinant of prognosis. If this is not achieved, and there is

tumour present at the CRM, this is a positive predictor of local tumour recurrence and not compensated for by the use of radiotherapy [8,11]. Identification of the mesorectal fascia is therefore essential for treatment planning. If the CRM is threatened by tumour penetration selective neo-adjuvant chemoradiotherapy may be indicated [8].

Although EAUS is very accurate for assessment of local disease in early rectal cancer, its use is limited as it is unable to identify the mesorectal fascia. However, MRI can clearly identify the CRM and is able to identify tumour penetration of the mesorectum to within millimetres [8,12]. To provide optimal treatment it is imperative that tumour penetration is neither under or over estimated. The accuracy of MRI relies on the correct field alignment, which is made in relation to the long axis of the rectum. If this is not achieved then the tumour penetration may be under or over estimated. The different layers of the bowel wall are distinguishable as they have unique signal characteristics, which are best appreciated with T2 weighted images [13]. The depth of tumour penetration is detected by disruption of these normal signal characteristics, with the depth of spread into the mesorectum being of particular importance. Increasing accuracy of staging, through improvements in imaging, has led to the subclassification of T3 tumours relating to the depth of extramural spread. Minimal penetration of the mesorectum is associated with better patient outcomes. Stage T3a tu-

mours that breach the mesorectum by less than 1mm have similar outcomes to T2 tumours [14]. The differences in survival for patients with T3 tumours relates to depth of mesorectal infiltration, first described by Jass [7]. Further work by Cawthorn confirmed this by reporting 5 year survival rates of 55% with tumour penetration less than 4mm compared with 25% if the mesorectum was penetrated by greater than 4mm [15]. Meckel also described 5 year survival of 54% for patients with extramural spread of 5mm compared to 85% if the mesorectal invasion was less than 5mm [14]. Early T3 tumours (T3a and T3b) confer a better prognosis, providing no adverse features are present, and show little benefit from chemoradiotherapy. This highlights the importance of not only identifying the CRM but also the extent of mesorectal invasion within millimetres. The accuracy of MRI in assessing this has been demonstrated by the MERCURY Study Group. Preoperative imaging and histological specimens of 295 patients who had undergone surgical resection were compared. The correlation between MR and histological assessment of tumour spread was to within 0.5mm [16,17].

One of the most important factors accounting for local failure of surgical resection is tumour presence at the CRM. Tumour presence within 1mm of the surgical resection margin is considered to represent a pathologically involved margin. This has been shown to be the single most important predictor of local disease recurrence and poor prognosis [18]. Results from the MERCURY trial showed

that rates of local recurrence decreased with increasing distance from the potential CRM. Local recurrence was seen in 53% of cases with tumour penetration less than 1mm from the CRM and less than 8% when that distance was between 1mm and 5mm [19]. The study also found that using a cut off greater than 1mm was not useful in identifying patients at higher risk of local recurrence. This has important implications for the use of neoadjuvant CRT in this high risk group. Previous work demonstrated that MRI was only able to predict tumor presence to within 5mm of the mesorectal fascia with good correlation with histological specimens [20]. Therefore patients with tumour penetration within 5mm of the CRM would have been offered CRT, resulting in substantial over treatment.

Tumour Height

Assessing the height of the tumour is important when planning surgical resection and the use of neoadjuvant therapy. Low rectal cancers are considered to be within 6cm of the anal verge and carry a worse prognosis compared to upper and mid rectal tumours. Treatment of low rectal cancers is challenging both in terms of the difficulties of resection within the rigid confines of the pelvis, higher rates of positive resection margins and higher local recurrence rates [21,22]. Assessing the height of these tumours was traditionally performed by rigid sigmoidoscopy and digital rectal examination. However, tumour height and surgical planes relating to the levators and sphincter com-

plex can now be accurately assessed using high resolution MRI. Operative decisions can therefore be made based on the MRI predictive planes of excision such as low anterior resection, intersphincteric resection or extralevator abdominoperineal resection (APR)[23]. Tumours extending into the intersphincteric plane are most likely to lead to local recurrence and have positive resection margins, which can be demonstrated by MRI [22]. These tumours would most benefit from neoadjuvant treatment to down stage disease. There is also evidence demonstrating higher recurrence rates for low rectal tumours treated with APR compared to low anterior resection [24-27]. As a consequence of this the Low Rectal Cancer Study (MERCURY II) was designed. The study aims to assess the use of MRI and selective neoadjuvant therapy to accurately identify the surgical planes and stage low rectal cancers to reduce the rates of positive resection margins and increase survival.

Results from a small retrospective study have already demonstrated the potential for MRI to predict the plane of excision in order to achieve negative circumferential margins. The reported positive predictive and negative predictive values were 57 % and 96%, respectively [28].

Nodal Disease

Assessment of tumour spread to locoregional lymph nodes forms part of the local staging of rectal cancer and is a component of the TNM classification. Presence of tu-

mour spread to local lymph nodes informs decisions regarding use of neoadjuvant chemoradiotherapy. Involvement of local lymph nodes confers a poorer prognosis and as nodal disease burden increases overall survival decreases [29,30]. Gunderson demonstrated 5 year survival rates for patients with rectal cancer in a large population-based analysis of 64%, 52.4%, and 37.5% for N0, N1, and N2 disease, respectively [31].

Traditionally, accurate identification of nodal disease has been challenging. Whilst lymph nodes can be visualised on both EAUS and MRI the difficulty lies in assessing the presence of metastatic disease within these nodes. With improvements in the accuracy of MRI adverse features of lymph nodes can now be assessed. Histopathological analysis of resected specimens remains the gold standard for assessment of local nodal disease. However, as the results are only available post operatively they cannot inform the decisions regarding neoadjuvant treatment. Size of lymph nodes alone has poor concordance with disease presence and can lead to overstaging of disease. MRI is unable to clearly detect lymph nodes smaller than 3mm. However, less than 2% of nodes this size are thought to be malignant [32]. There appears to be no cut off value of node size to assess presence of metastases. A histological survey by Dworak looking at 12,000 lymph nodes in rectal cancer demonstrated that there was significant overlap between normal or reactive nodes and nodes containing metastases

based on size alone [33]. Other features such as nodal morphology must therefore be assessed.

Features such as nodal border and signal characteristics detected on MRI may help to differentiate between normal and abnormal nodes. Nodes with an irregular border have been shown to be malignant in over 90% of cases, whereas at least 94% of those with a smooth regular outline are benign [32]. Mixed signal characteristics are seen in nodal metastases and show good correlation with histological analysis. Areas of necrosis within the lymph nodes account for the mixed signal detected by MRI. Nodes that display homogenous hypo or hyper dense signal are less likely to be malignant. When nodal border, contour and signal characteristics are assessed together the sensitivity and specificity of MRI is increased to 85 and 97%, respectively [28]. The sensitivity and specificity of EAUS for assessing local lymph node involvement is only 73% and 75%, respectively [34]. EAUS is likely to be more accurate when detecting nodes in the proximal rectum. However, it is unable to detect nodes less than 5mm in size and due to limitations of visualising the whole mesorectum positive lymph nodes in this area may be missed. Therefore using EAUS alone to assess nodal disease may under stage the rectal cancer.

In addition to mesorectal nodes, lateral pelvic sidewall nodes must also be assessed. Spread to these lymph nodes is thought to be through extramural vasculature. This is

more frequently seen in advanced and often low rectal cancers with an incidence ranging between 8.6% and 24% [35-37]. The presence of metastases in these nodes is associated with increased risk of positive mesorectal nodes and extramural venous invasion [39]. MRI is the modality of choice for assessing disease burden in this area as these nodes are difficult to assess on EAUS [39]. Presence of nodal disease in lateral lymph nodes is treated differently across the world. In countries such as Japan they are aggressively treated with surgical resection whereas in the West presence of disease is treated with CRT. The optimum treatment remains unknown. The results of a small randomized control trial of 51 patients demonstrated that preoperative radiotherapy produced similar oncological outcomes as pelvic sidewall dissection without the implications of post surgical urinary and sexual dysfunction [38].

The presence of positive lymph nodes in close proximity to the mesorectal fascia poses further diagnostic uncertainty. Previously, disease presence in lymph nodes within 1mm of the CRM had been reported to increase the risk of local recurrence and be an indication for neoadjuvant CRT [39]. However, more recent results from analysis of the MERCURY trial data by Shihab and colleagues do not support this. 31 patients were identified with suspicious lymph nodes within 1mm of the circumferential resection margin on preoperative MRI. None of these patients

had an involved CRM [40]. This would suggest that positive nodes detected by MRI within close proximity of the CRM are unlikely to increase risk of tumour recurrence and therefore this group of patients is unlikely to benefit from neoadjuvant therapy.

Extramural Venous Invasion (EMVI)

Extramural venous invasion (EMVI) is defined as the presence of tumour cells in the vasculature beyond the muscularis propria in the mesorectum. It is an adverse prognostic indicator, independent of tumour stage. It is associated with increased risk of distant metastases and local recurrence [41,42]. EMVI is seen in up to 50% of patients with rectal cancer, almost exclusively in stage T3 and T4 tumours [43]. Patients with EMVI positive tumours have a 50% greater chance of developing distal metastases compared to 12% in EMVI negative patients.

MRI is able to detect EMVI with precision unlike EAUS, which is unable to detect the subtle changes in signal cause by tumour infiltration of vessels [43]. High resolution MRI can demonstrate the characteristic serpiginous extension of tumour signal into the perirectal or pericolic fat, best seen on T2 weighted images [44]. Smith et al defined the four criteria by which EMVI should be assessed on MRI. These include the following: the pattern of tumour margin, which gives the appearance of nodularity; location of tumour to relevant vessels, which makes

tumour invasion more likely; calibre of vessel as tumour infiltration can cause an increase in luminal size; and vessel border if the tumour disrupts the vessel itself [44]. This morphological feature plays a role in decision making for the use of neoadjuvant treatment. MRI can be further used to assess EMVI response to treatment, demonstrated by fibrosis of infiltrated vessels. A recent retrospective study demonstrated improved disease free survival in patients who had MRI evidence of EMVI response to chemoradiotherapy [45].

Chemoradiation causes significant changes in the tumoural architecture which makes identification of specific tumour characteristics more challenging. This is the case for EMVI where pathologists rely on these 'landmarks' to detect the presence of venous involvement. The fibrosis caused by the radiation component of the neo-adjuvant treatment disrupts the normal micro-anatomy [46]. Detection rates are improved by using specific stains which are directed to the elastin component of the vessel but MRI has been shown to be particularly useful in these cases [47]. A recent study by Chand et al, has shown the advantage of using MRI in detecting more cases of EMVI compared to pathology following CRT [48].

Positron Emission Tomography (PET)

The use of positron emission tomography in cancers patients has increased significantly over the last few years.

This functional imaging can identify areas of increased cellular activity, such as malignancy, infection and inflammation, using radio-labelled tracers. The most frequently used radiopharmaceutical is fluorine-18-labelled deoxyglucose (FDG). Following intravenous administration cells with increased glucose metabolism, such as cancers cells, take up FDG as it acts as an analogue to glucose. These areas of pathologically increased cellular activity are then identified on imaging. This alteration in biological activity of cells occurs in the earliest stages of cancer, often before structural or anatomical changes are apparent on other imaging modalities. PET alone is unsuitable for staging due to limited spatial resolution. However, PET and CT in combination has been demonstrated to have improved accuracy than either modality in isolation [49]. There remains little evidence to support its use in routine staging [50].

There may be a role for PET/CT in initial staging in high risk patients. In a study by Hunter patients were stratified into high risk (presence of EMVI, extramural spread of >5mm, T4 tumours, an involved CRM, intersphincteric plane involvement in low rectal tumours) or low risk of developing distal metastases. Synchronous distal metastases were detected in 20.7% of high risk patients compared to only 4.2% in the low risk group on PET-CT and contrast enhanced MRI [51]. This demonstrates that high risk patients may benefit from this additional preop-

erative imaging to tailor the use of selective neoadjuvant CRT. PET/CT has demonstrated increasing usefulness in radiotherapy planning for patients with rectal cancer [52]. Gross tumour volume appears to be better predicted on PET/CT than CT alone, which may lead to more accurate targeting of radiotherapy [52,53]. The real impact of PET/CT in this regard requires further investigation and larger scale studies to influence existing clinical practice.

The main role of PET appears to be emerging predominantly in assessing response to neoadjuvant treatment. Several small studies and recent systematic reviews assessing the use of PET to detect tumour response to CRT have demonstrating promising results [54-56]. The optimum timing of follow up PET imaging remains unknown. However, the most reliable results appear to be from PET performed during or immediately following CRT [56]. The histological correlation with tumour response on PET has yet to be confirmed with variable results from small studies [57,58]. A recent meta-analysis by Rymer et al has shown the potential of PET-CT in assessing treatment response and the utility of standard uptake values (SUV) to predict outcomes [59]. Further prospective trials assessing the clinical value of PET are still required.

Distal Staging

Assessment of potential metastatic spread is vital, as the presence of distal disease will impact on the timing and type of treatment used. There is little debate that com-

puterised tomography of the chest, abdomen and pelvis is the imaging modality of choice to assess distal spread of rectal cancer. The location of the rectal cancer may influence distant spread due to the variation in lymphatic drainage along its length. For example, low rectal cancers are more likely to drain to the lateral pelvic sidewall compared with tumours of the upper and mid rectum. This lymphatic drainage pathway differs from the more common route of following the inferior mesenteric vessels. Common sites of metastasis for rectal cancer are the liver and lungs and CT is highly accurate in identifying metastases in these areas.

Distal metastases to the lungs are more frequently seen in rectal cancer compared to colon cancer [60]. UK national guidelines advise preoperative CT of the chest as part of staging rectal cancer. However, there remains debate as to whether preoperative CT staging of the chest is mandatory for early colorectal cancers. The occurrence of pulmonary metastases is much more likely in the presence of nodal disease and hepatic metastases [61,62]. One advantage of CT over plain chest radiography is the ability to detect smaller lesions. However, CT is more likely to identify benign radiological abnormalities than chest radiography, resulting in false positive findings and potential delays in treatment [63]. For indeterminate lesions functional imaging techniques such as PET in conjunction with CT may be useful. If pulmonary metastases are present it is vital to ascertain the relation of these to the

lung anatomy. Patients with unilobar single metastases are less likely to have undetected irresectable disease compared with patients with multilobar lesions.

Liver metastases are frequently encountered in patients with rectal cancer. These can be commonly identified on CT imaging. However, other imaging modalities such as MRI, ultrasound and PET can offer advantages and disadvantages over each other. A single optimal imaging strategy for assessing liver metastases has yet to be designed. To fully characterise a liver lesion its precise location and relation to local vasculature and anatomical landmarks must be accurately assessed. Ideal imaging should be able to detect micrometastases and distinguish benign lesions from malignant. This is of particular importance in selecting patients who may benefit from liver resections and assessing response to preoperative chemotherapy. Hepatic metastases are relatively hypovascular compared to normal liver parenchyma, which can be detected by helical CT portal venous phase imaging with up to 85% accuracy [64]. Arterial phase imaging using helical CT can help to further characterise lesions if required. Liver metastases typically appear hypodense with circumferential ring enhancement as opposed to haemangiomas that have a nodular peripheral enhancement pattern [65]. For indeterminate lesions contrast enhanced MRI with gadolinium or ferumoxides may be useful. Liver specific contrast mediums can target functioning Kupffer cells or hepatocytes to produce characteristic appearances on

MRI. This results in MRI being extremely accurate at differentiating between benign and malignant liver lesions. PET imaging is also highly accurate at identifying hepatic and extrahepatic metastases with a sensitivity and specificity of 94.6% and 75.9%, respectively, demonstrated in a large meta analysis [66]. Although for smaller lesions, less than 10mm, contrast MRI remains superior to PET [67].

Summary

The identification of tumour characteristics that strongly influence prognosis and risk of recurrence on staging imaging now plays an important role in treatment planning for patients with rectal cancer. There has been a shift away from the singular reliance of pathology for all treatment decisions. MRI has proven to be the most accurate in identifying key local tumour characteristics that influence the use of preoperative oncological therapy and dictate the type of surgical resection performed. Based on these prognostic markers patients can now be better risk-stratified and preoperative therapy used more selectively in the high risk patient groups. MRI is able to accurately detect involvement of the CRM and tumour spread into the mesorectum thereby identifying patients with high risk of local recurrence. CT remains the imaging of choice for distal staging of disease with the use of PET and MRI to characterize indeterminate lesions. There is now an emerging role for the use of PET-CT and MRI to assess response to neoadjuvant therapy and disease recurrence.

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