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DIAGNOSTIC AND INTERVENTIONAL RADIOLOGY INNOVATIONS IN COLORECTAL CANCER
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The Current Status of Nodal Staging in Rectal Cancer

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Abstract

Purpose of Review To review current practice in MRI-based nodal staging in rectal cancer and assess the associated evidence.
Recent Findings Nodal staging is less accurate than other MRI-detected prognostic markers such as circumferential resection margin status, extramural venous invasion and T stage. Previous research has focused on matching MRI and pathology findings but crucially N stage has never been shown to have prognostic importance on MRI. Recent pathological evidence suggests that tumour deposits may be more important than nodal status and these can be clearly distinguished from nodal metastases on MRI.
Summary Nodal staging on MRI is prognostically inaccurate. MRI staging should move away from TNM to focus on those radiological markers which can be proved to have prognostic accuracy. Tumour deposits should be reported separately to lymph node metastases on both histopathology and imaging. Research is underway confirming their prognostic importance on MRI.

Keywords Rectal cancer · MRI · Staging · Lymph nodes · Tumour deposits · Prognosis

Introduction

Pre-operative staging is an essential aspect of the management of rectal cancer and radiological assessment with magnetic resonance imaging (MRI) plays a key role in this process. As well as defining the anatomy of the tumour and determining surgical strategy by assessing whether safe surgical margins can be achieved, radiological assessment should ideally provide additional prognostic information to separate patients into high- and low-risk groups in order to determine whether they are likely to benefit from neo-adjuvant therapy to reduce their risk of local and distant failure.

Radiological staging currently aims to predict the pathological TNM stage as this is thought to be closely linked to prognosis. The presence of MRI-predicted lymph node metastases (mrLNM) upstages a patient from stage II to stage III and therefore may play a key role in the perception of a 'high-risk' tumour and the decision to utilize pre-operative chemoradiotherapy, although which patients to treat remains controversial and subject to widespread variation in practice.

This article aims to review the evidence surrounding the ability of MRI to accurately diagnose LNM and furthermore outlines our current understanding of the pathways of spread to metastatic disease in rectal cancer which raises questions as to the importance of LNM in this process.

The History of Lymph Node Staging

Current pathological TNM staging appears to be suboptimal as it fails to stratify patients adequately. Several studies have shown that those who are staged as IIB/C (T4a/b,N0) have a significantly worse prognosis than those staged IIIA (T1-2, N1 or T1,N2a) [1–3]. It appears that perhaps LNM are being weighted too heavily when either T stage, or indeed other factors not included in TNM, are better predictors of survival.

The presence of tumour within lymph nodes (LN) was first reported as a marker of poor prognosis by Lockhart-Mummary [4] and later by his colleague Dukes [5], leading to the well-known Dukes staging system. They reported only a 7% survival rate in patients with tumour in the regional lymph nodes (Dukes C) compared with 73% in those without

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(Dukes B) [5]. The AJCC/UICC tumour nodes metastases (TNM) system is an adaptation of this with some modifications and sub-classifications but the same basic principles [6]. TNM previously classified patients as N0, N1 or N2 according to the number of lymph nodes involved [7]; however, with recent TNM editions, this has become more complicated, particularly with the addition of the N1c subcategory [8] which is used for tumour deposits (TD) of non-nodal origin (but rather confusingly is still part of the N stage).

There is currently ongoing controversy amongst the pathology community about the separation of LNM from TD, which are defined as nodules of tumour within the mesorectum without evidence of underlying lymph node architecture. TD have been recognised since the 1930s [5] as a separate entity to LNM but interest in them reignited in the late 1990s when they were first officially recognised in the TNM system [9] and several publications highlighted their importance in predicting poor prognosis [10–12]. Multiple studies, and two recent meta-analyses [13, 14•], have now shown that TD seen on pathology are associated with a worse prognosis than LNM but until recently they have been reported as a single entity and there are significant problems with interobserver variation and widely varying reports of prevalence in the literature [13, 15]. The recognition that TD are prognostically worse than LNM has not yet been reflected in the TNM system, with their presence currently only being reported in node negative cases and with their placement in the prognostic hierarchy below N2 disease.

Assessment of Lymph Nodes on MRI

In the past, nodal staging on MRI has relied on the measurement of LN with the assumption that larger LN would contain tumour. Despite evidence that there is a great degree of overlap in the size of involved and non-involved LN [16–18] and the fact that no cut-off size has ever been universally agreed, a focus on measuring LN still persists within the radiology community. While radiologists regard enlarged LN as an indicator of malignancy, in contrast, in histopathological studies, the presence of numerous large LN has actually been recognised as a good prognostic marker in a number of studies, possibly as a result of an appropriate immune response to the tumour which confers a survival advantage [17–19]. Morphological predictors of nodal involvement, namely mixed signal intensity and irregular borders, have been shown to have greater accuracy than LN size (sensitivity 85% and specificity 97% [16] vs sensitivity 67% and specificity 83% if a 5-mm cut-off is used [20]). However, it is likely that this definition included TD in the past which would also have had irregular borders and were likely to have been classified as LNM on pathology. Figures 1 and 2 show LN which would be classified as benign and malignant respectively using morphological criteria.

Generally, MRI sensitivity and specificity for LNM is only moderate and MRI has a tendency to overstage within the nodal category [20–23] compared with pathology. A recent large retrospective study showed a sensitivity of only 38%, a specificity of 87% and a positive predictive value of 56% for the diagnosis of LNM on MRI compared with pathology, which the authors compared with flipping a coin [24•]. Nodal status is less well seen on MRI than other prognostic markers. A 2012 meta-analysis found a poor diagnostic odds ratio of 8.3 (4.6–14.7) for the detection of mrLNM compared with 20.4 (11.1–37.3) for mrT stage and 56.1 (15.3–205.8) for mrCRM status [25].

Nodal status on MRI has never been proven as an independent marker of poor prognosis in the same way that MRI-detected EMVI and CRM status has been [26, 27]. Multiple studies have examined the diagnostic accuracy of MRI in comparing nodal status on MRI with that of pathology, the gold standard; however, the prognostic accuracy has never been proven. Matching what will be seen on pathology is only useful if this influences survival outcomes.

Separating Lymph Node Metastases From Tumour Deposits on MRI

TD have a very different appearance to LNM on MRI (Fig. 3) and, in our institution, are seen very commonly with a prevalence of around 40%. We define them as nodules of tumour within the mesorectum which appear to directly interrupt the course of a vein (as opposed to lymph nodes which may be located adjacent to veins but will not interrupt their course when seen on two orthogonal views). In our experience, we have observed that TD are very closely related to EMVI but appear to be a more severe manifestation with distinct nodules which are discontinuous from the primary tumour mass. We have observed that they have a particularly poor prognosis. As on pathology, TD are likely to have a prognostic effect which is worse than that of LNM and as such should be reported separately.

Currently, radiologists are required to use the term ‘n1c’ to describe TD seen on MRI in order to fit in with current TNM-based reporting; however, this is confusing and does not reflect their true origin or position in the prognostic hierarchy, as the N1 designation implies that they are prognostically better than N2 disease. Furthermore, if they are only reported in the absence of LNM, as stipulated by TNM, important prognostic information will be lost.

Pathways of Metastatic Spread

The long-recognised correlation between the presence of LNM and poor survival has in the past been assumed to be

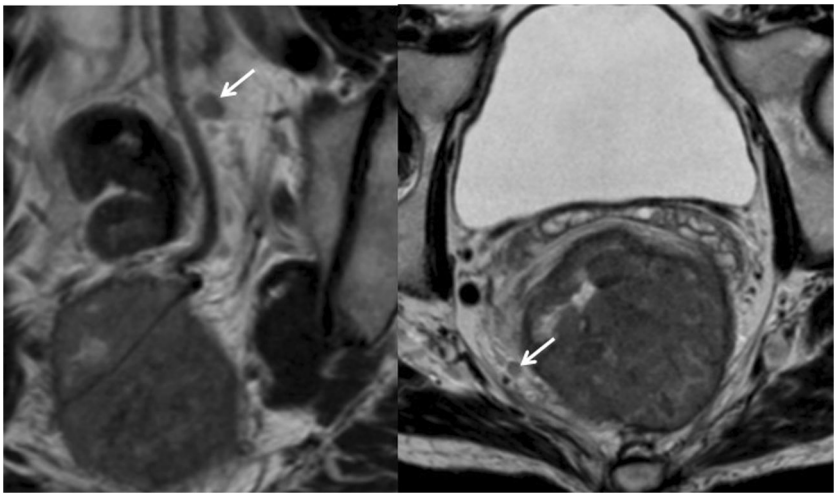

Fig. 1 MRI scan showing benign lymph nodes according to morphological criteria (arrows)

causation. More recently, questions have been raised as to whether this is truly the case. LNM are more common in patients who also have increased depth of invasion and EMVI and, furthermore, nodules previously reported as LNM may in many cases have been TD.

Local recurrence has been a major problem in the past but this has changed considerably following the recognition that the entire mesorectum should be removed en bloc with the tumour with a total mesorectal excision (TME) procedure [28]. Predicting whether surgical margins will be safe using MRI has also been instrumental in reducing local recurrence rates [29]. Accurate pre-operative assessment and high-quality surgery have reduced local recurrence rates from around 20 to around 5% [30]. Furthermore, local recurrence rates are comparable (6% vs 5%) in those with LNM with those who are node negative as long as a good-quality TME is performed [30].

The liver is the most common site of distant metastasis; however, there is no direct route for tumour within LN to gain access to the portal circulation. It seems far more likely that tumour is gaining access via the veins (i.e. EMVI and TD) than taking a circuitous route via the lymphatics and thoracic duct which would not end at the liver. There is increasing evidence to support this hypothesis. Knijn carried out two studies investigating the link between LNM and distant metastases; the first was an autopsy study which showed no association between LNM and liver metastases [31]; the second looked at the KRAS status of primary tumour, LNM and liver metastases and found that while the primary tumour and liver metastases had concordant KRAS mutation status, the tumour in LNM was discordant and therefore was unlikely to be involved in the metastatic pathway [32]. More recently, Naxerova et al. [33•] went a step further and examined the clonal concordance of tumour in these locations. They similarly found that the majority of LNM were of different phylogenetic origin to liver metastases. The simple mechanistic view of primary tumour seeding to LNM and then on to distant metastases is most likely incorrect, and one must therefore question whether LNM are simply a bystander in the metastatic process. LNM may indicate a phenotypically aggressive tumour with the means to spread but may be an end result of this spread rather than a step on the metastatic pathway.

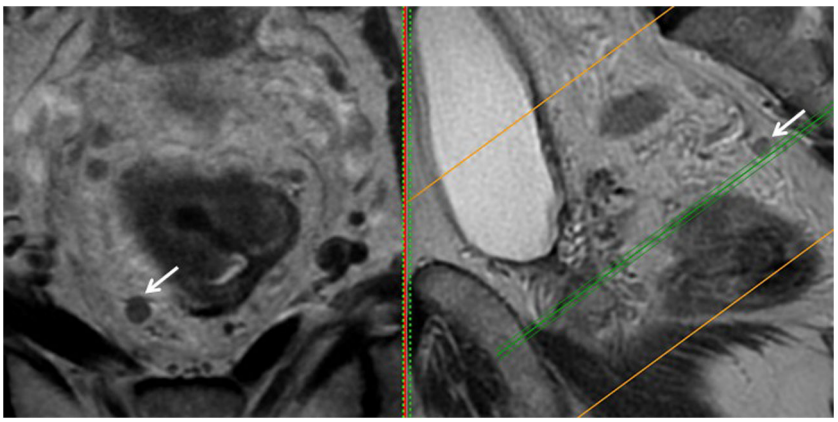

Fig. 2 MRI scan showing malignant lymph nodes according to morphological criteria (arrows)

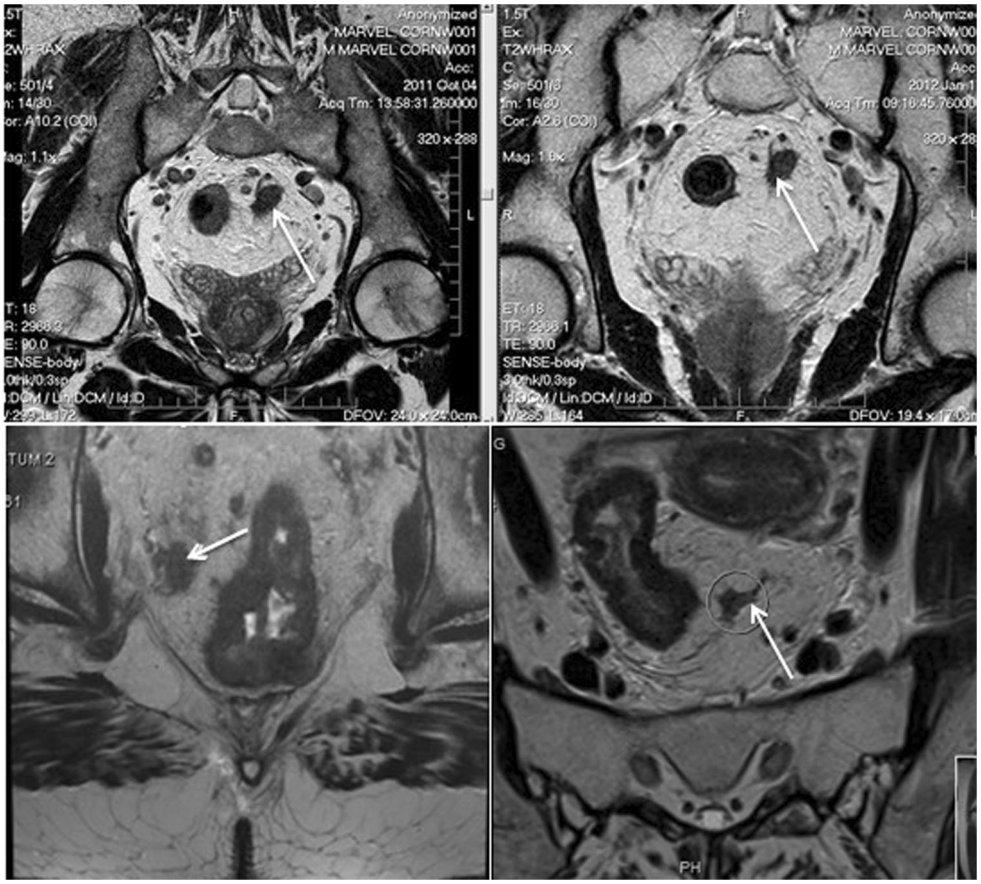

Fig. 3 MRI scans showing the appearance of tumour deposits (arrows)

Discussion

Recently, questions are being raised as to how important LNM really are in the development of recurrence [31, 32, 33•, 34, 35], in particular in the development of distant metastases, and whether other MRI-detected prognostic marker such as extramural venous invasion (EMVI) is more important. The TNM system does not adequately include factors such as the presence of EMVI or the status of the circumferential resection margin (CRM) which have been shown to be extremely important prognostic markers. In contrast, nodal status on MRI has never been proven to have prognostic accuracy but still forms a major part of staging. By using the TNM system, we may be losing prognostic power and we believe that a major reappraisal of MRI staging is needed.

In our practice, we focus on reporting mrEMVI and mrTD rather than mrLNM. We continue to use the term 'mrN1c' as stipulated by the TNM system but this supersedes the presence of mrLNM due to the association with worse prognosis seen on pathology and our own observations that mrTD are associated with very poor prognosis (manuscript submitted). We have observed that if there are nodal metastases in the absence of mrTD or mrEMVI, and the patient is undergoing good-quality TME surgery, this is not a poor prognostic marker. The prognostic significance of TD seen on MRI and the correlation between the diagnosis of TD on MRI and pathology are the subjects of the COMET trial [36] which is currently in progress.

In conclusion, we feel that the radiology community should be focusing on features seen on MRI which can be proven as independent markers of poor prognosis rather than trying to predict pathology findings. The TNM system provides suboptimal prognostic stratification even in pathology and has never truly been evaluated for MRI. Distinguishing the true markers of poor prognosis which allow us to separate patients into high- and low-risk groups on MRI will allow us to make evidence-based treatment decisions and have honest discussions with patients about their level of risk and the potential risks and benefits of neo-adjuvant therapy.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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