

review

# Multiparametric MRI - local staging of prostate cancer and beyond

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**Background.** Accurate local staging is critical for treatment planning and prognosis in patients with prostate cancer (PCa). The primary aim is to differentiate between organ-confined and locally advanced disease with the latter carrying a worse clinical prognosis. Multiparametric MRI (mpMRI) is the imaging modality of choice for the local staging of PCa and has an incremental value in assessing pelvic nodal disease and bone involvement. It has shown superior performance compared to traditional staging based on clinical nomograms, and provides additional information on the site and extent of disease. MRI has a high specificity for diagnosing extracapsular extension (ECE), seminal vesicle invasion (SVI) and lymph node (LN) metastases, however, sensitivity remains poor. As a result, extended pelvic LN dissection remains the gold standard for assessing pelvic nodal involvement, and there has been recent progress in developing advanced imaging techniques for more distal staging.

**Conclusions.** T2W-weighted imaging is the cornerstone for local staging of PCa. Imaging at 3T and incorporating both diffusion weighted and dynamic contrast enhanced imaging can further increase accuracy. "Next generation" imaging including whole body MRI and PET-MRI imaging using prostate specific membrane antigen (<sup>68</sup>Ga-PSMA), has shown promising for assessment of LN and bone involvement as compared to the traditional work-up using bone scintigraphy and body CT.

Key words: multiparametric MRI; prostate cancer; staging

## Introduction

Accurate staging of prostate cancer is essential to inform prognosis and to stratify patients for appropriate management. MRI affords excellent soft tissue differentiation making it the most accurate modality for preoperative local T-staging of prostate cancer.<sup>1</sup> According to European Association of Urology (EAU) guidelines, local staging investigations are only indicated for intermediate and high-risk patient groups.<sup>1</sup> The high accuracy of multiparametric MRI (mpMRI) for detection of index lesions can aid T-staging, and can also identify tumours

that may be missed by systematic biopsies, enabling early re-biopsy and accurate risk stratification.<sup>2</sup>

For the purposes of prognosis and management the primary aim is to differentiate organ-confined disease from locally advanced disease. Extracapsular disease and seminal vesicle invasion carry a worse prognosis due to a greater risk of positive surgical margins leading to biochemical recurrence<sup>3,4</sup> and an increased risk of lymph node (LN) metastases, respectively.<sup>5</sup> Nodal disease on its own is associated with a higher risk of progression to metastatic disease and thus a higher rate of cancer specific mortality.<sup>6-8</sup>

Traditionally, staging of prostate cancer has been performed using nomograms such as Partin tables which are based on digital rectal examination (DRE), prostate-specific antigen (PSA) levels, Gleason score and percentage core involvement as a surrogate of lesion volume.<sup>9-11</sup> This approach often underestimates the true stage of the disease and has been shown to be inferior to MRI<sup>12</sup>, with the combination of MRI findings and nomograms showing significant added value for predicting adverse pathology in prostate cancer.<sup>13</sup> In addition to improving accuracy, MRI also provides information on the site and extent of disease, which helps surgical planning, informing decision making on taking wider surgical margins to decrease the rate of positive margins, or performing nerve-sparing surgery to decrease morbidity. In case of a gross extracapsular extension or seminal vesicle invasion on MRI, external beam radiotherapy is a recom-

mended approach over brachytherapy or surgery, to avoid under dosing or positive surgical margins, respectively.<sup>14</sup> As MR imaging currently does not offer sufficient diagnostic performance, extended pelvic lymph node dissection (ePLND) remains the gold standard for N-staging.<sup>1</sup> However, ePLND has its own disadvantages including higher morbidity, with worse intraoperative and perioperative outcomes, and may result in under-sampling, thus its direct therapeutic effect is equivocal.<sup>15</sup>

This review aims to summarize the role of MRI in staging prostate cancer and focuses mainly on exploring the current evidence and providing a practical approach to assessment of extracapsular extension, seminal vesicle invasion and nodal disease.

## Staging of prostate cancer

The most widely used system for staging of prostate cancer is the tumour, nodes, and metastases (TNM) staging system developed by the American Joint Committee on Cancer (AJCC). The current version of the TNM staging of prostate cancer (8th edition) was implemented in January 2018 introducing grade groups and simplifying organ-confined disease to pathological stage pT2 and omitting pT2a–pT2c, however, this sub-classification is retained for clinical staging (Table 1).<sup>16</sup> In addition, Cancer-group staging of prostate cancer (stage I–IV) is determined by TNM, PSA levels at diagnosis, and histologic Grade Groups.<sup>17</sup>

Locally confined disease (T1–T2) is further divided into stage T1a and T1b tumours which are not apparent clinically and are found incidentally, typically at transurethral resection. From the radiological standpoint, the more relevant categories are stage T1c and T2 (a–c) as histologically they both represent a biopsy proven carcinoma albeit with an important difference: T1c cancer is by definition not visualised at MRI. This is relevant to active surveillance studies (AS) cohorts, with the term “non-visible lesion” (T1c) being introduced, based on the predictive nature of this feature, with a significantly increased progression free survival for non-visible lesions when compared with the MRI-visible lesions (T2).<sup>18</sup>

Locally advanced prostate cancer carries a worse prognosis than organ-confined disease. T3a disease describes extraprostatic extension, T3b seminal vesicle invasion, and T4 disease direct invasion of adjacent organs/structures (Table 1). In clinical practice those undergoing prostate mpMRI will

TABLE 1. Summary of TNM guidelines for the staging of prostate cancer

Category	Definition
<b>Tumour</b>	
Tx	Primary tumour cannot be assessed (e.g. CT study, severe artefacts on MRI)
T1a–T1b	Tumour incidental histologic finding
T1c	Tumour identified by needle biopsy but not visible by imaging
T2	Organ confined disease
T2a	The tumour involves up to one half of 1 side of the prostate
T2b	The tumour involves more than one half of 1 side of the prostate
T2c	The tumour involves both sides of the prostate
T3	Extraprostatic extension
T3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of the bladder neck
T3b	Tumour invades seminal vesicle(s)
T4	Tumour invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
<b>Node</b>	
Nx	Regional lymph nodes were not assessed
N0	No positive regional lymph nodes
N1	Metastases in regional lymph node(s)
<b>Metastasis</b>	
Mx	M staging not assessed (e.g. MRI with pelvic only coverage)
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bones
M1c	Other site(s) with or without bone disease

have at least one sequence where the field of view covers the pelvis to the level of aortic bifurcation<sup>19</sup> in order to evaluate the common iliac and bifurcation nodes (M1a) and from which partial M staging of the bony pelvis (M1b) can be performed.

## MR imaging

### MRI scanners

The Prostate Imaging-Reporting and Data System (PI-RADS) guidelines<sup>19</sup> are aimed at standardizing MRI acquisition and interpretation and recommend MRI to be performed at 3T in order to increase signal-to-noise ratio (SNR) and spatial resolution, and decrease acquisition times.<sup>20,21</sup> If acquisition protocols are optimized and contemporary technology is employed, then 1.5T scanners are also able to provide sufficient diagnostic performance. 1.5T scanning may also be preferential when a patient has an implant non-compatible at higher field strengths, or with bilateral hip replacements in order to minimise artefact.<sup>22,23</sup> The routine use of an endorectal coil (ERC) is no longer recommended.<sup>19</sup> 3T scanners or contemporary 1.5T scanners can provide sufficient imaging quality and although ERC increases SNR bring disadvantages, including deformation of the gland contour, near field coil flare, increased cost and time of examination as well as higher patient discomfort.<sup>19,21</sup>

### MRI protocol

Standard prostate MRI protocols should incorporate anatomical T1W and T2W imaging in combination with the two functional sequences of diffusion weighted imaging (DWI) and dynamic contrast enhanced imaging (DCE).<sup>24</sup> A set of minimal technical parameters for each of these sequences is outlined in Table 2<sup>25</sup>, although institutions are encouraged to optimize imaging protocols based on their own equipment, capacity and expertise. It is mandatory for axial T2W, DWI and DCE to be acquired in the same location, angle, slice thickness and gap to allow for synchronous scrolling through the images and direct evaluation of suspicious findings between the sequences. Axial T1W1 is essential to assess post-biopsy haemorrhage, and is typically employed as the sequence to cover the pelvis to the aortic bifurcation to enable bone and nodal assessment.

T2W imaging is the key sequence for local T-staging of the prostate. The high in-plane spatial resolution allows for accurate evaluation of extra-

TABLE 2. PI-RADS v2.1 recommended MR imaging protocols

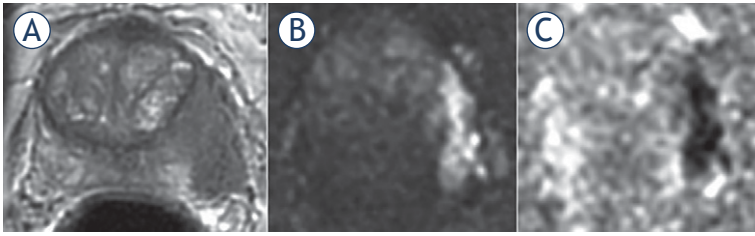
Imaging sequence	Technical parameters
<b>T2 imaging</b>	<p>Axial plane and a minimum of one additional orthogonal plane (either sagittal or coronal)</p> <p>Straight axial plane to the patient or to the long axis of the prostate</p> <p>FOV: 12-20 cm to image the entire prostate gland and seminal vesicles</p> <p>Section thickness/gap: 3 mm/0 mm</p> <p>In-plane resolution: <math>\leq 0.7</math> mm (phase) x <math>\leq 0.4</math> mm (frequency)</p>
<b>DW imaging</b>	<p>Axial plane (same locations as for T2WI)</p> <p>Free-breathing spin echo EPI sequence combined with spectral fat saturation is recommended</p> <p>Section thickness/gap: 3 mm/0 mm</p> <p>TE: <math>\leq 90</math> ms; TR: <math>&gt; 3000</math> ms</p> <p>FOV: 16-22 cm</p> <p>In plane dimension: <math>\leq 2.5</math> mm phase and frequency</p> <p>ADC map calculation: low b-value should be set at 0–100 s/mm<sup>2</sup>, high b-value should be <math>&lt; 1000</math> s/mm<sup>2</sup></p> <p>"High b-value": b-value of <math>\geq 1400</math> sec/mm<sup>2</sup>; it can be acquired by scanning or calculated</p>
<b>DCE</b>	<p>Axial plane (same locations as for T2WI)</p> <p>Fat suppression and/or subtraction is recommended</p> <p>2D or 3D T1 GRE sequence (preferred)</p> <p>Section thickness/gap: 3 mm/0 mm</p> <p>Injection rate: 2-3 ml/s</p> <p>TR/TE: <math>&lt; 100</math> ms/ <math>&lt; 5</math> ms</p> <p>In-plane dimension: <math>\leq 2</math>mm X <math>\leq 2</math>mm</p> <p>Temporal resolution: <math>\leq 15</math> s</p> <p>Total observation: <math>&gt; 2</math>min</p>

2D = two-dimensional; 3D = three-dimensional; ADC = apparent diffusion coefficient; EPI = echo planar imaging; DW = diffusion weighted; FOV = field of view; GRE = gradient echo T2W = T2 weighted; TE = echo time; TR = repetition time

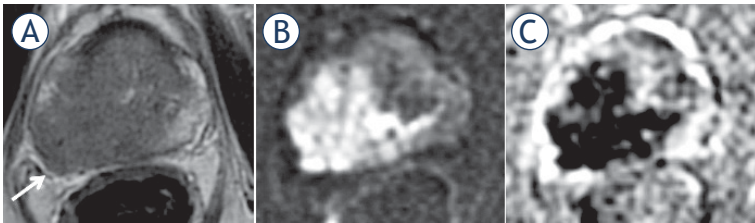
capsular extension, neurovascular bundle assessment and seminal vesicle invasion. Fast-spin-echo (FSE) or turbo-spin-echo (TSE) imaging should be obtained in the axial plane and in at least one additional orthogonal plane (sagittal or coronal) with the highest quality possible and thin slices at 3 mm with no gap.<sup>25</sup> 3D T2 weighted imaging with isotropic voxels and slice thickness at 1 mm may be obtained, with evidence suggesting utility for assessment of extraprostatic extension<sup>26</sup> and for nodal and bone staging when combined with DWI of the entire pelvis (b-values 0–1000 s/mm<sup>2</sup>).<sup>27</sup>

### Limitations

*Motion artefact.* Bowel peristalsis is a well-known cause of motion artefact in abdominal imaging,



**FIGURE 1.** 65-yr-old man with PSA 19.5 ng/ml. Invasion of the periprostatic fat and neurovascular bundle (NVB) infiltration at the left midgland consistent with T3a disease. Biopsy showed Gleason score (GS) 4 + 4 = 8. Radical retropubic prostatectomy (RRP) confirmed GS 4 + 4 = 8 and showed established T3a disease with a clear surgical margin (at least 1 mm).



**FIGURE 2.** 77-yr-old man with PSA 38.2 ng/ml. (A) T2 weighted (T2W) imaging; (B) diffusion weighted (DW) imaging; (C) apparent diffusion coefficient (ADC) map. T3a at the right mid gland with bulging and asymmetrical thickening of the right neurovascular bundle (arrow). Gleason score (GS) = 9 with extracapsular extension and clear surgical margins was confirmed at radical prostatectomy.

but the relatively low position of the prostate, remote from small bowel combined with limited evidence prior to PIRADS version 2 means that anti-spasmodic agents are not recommended in current guidelines. However, recent studies have shown use of anti-peristaltic agents significantly improves image quality of T2W imaging<sup>28, 29</sup> with better depiction of anatomical details (e.g. prostatic capsule and neurovascular bundles) as well as reducing non-diagnostic MRI to < 1%.<sup>29</sup> Routine use of antiperistaltic agents (recommended dose 20 mg HBB *i.v.* or 1 mg glucagon) prior to prostate mp-

**TABLE 3.** PI-RADS v2 criteria for predicting extraprostatic extension

Capsular abutment
Capsular irregularity, spiculation or retraction
Neurovascular bundle asymmetry or thickening
Obliteration of the rectoprostatic angle
Tumour-capsular contact > 10 mm
Bulge or loss of capsule
Measurable extracapsular disease

MRI may therefore be beneficial for optimisation of T2W image quality, a key sequence of mpMRI for local staging.<sup>30</sup> The risk of side-effects with these agents is low and these are usually minor and self-limiting.<sup>31</sup>

## T-staging

### T3a disease

Extension of the tumour into the periprostatic fat is defined as T3a disease, termed extracapsular extension (ECE). Of note, however, in a strict sense the prostate lacks a true capsule as an anatomic structure that encloses the gland but has rather an outer fibromuscular layer which is inseparable component of the prostatic stroma.<sup>32,33</sup> T3a disease also incorporates invasion into the neurovascular bundle, internal sphincter and bladder neck.<sup>1</sup> Histopathologically, extracapsular extension (ECE) is sub-classified into focal and established with the latter carrying a worse prognosis.<sup>34</sup> However, there is currently no clear consensus on the exact definitions of these, which can vary from a few glands beyond the capsule to cancer extending up to 0.5 mm radially from the capsule.<sup>1</sup> In addition, focal ECE cannot be detected by MRI due to inherent resolution limits.<sup>35</sup>

Extracapsular extension has traditionally been evaluated by clinical criteria and nomograms such as Partin tables, which are based on PSA, DRE and Gleason score at biopsy.<sup>36</sup> However, nomograms represent a patient level risk score alone, have been shown to be inferior to MRI<sup>11,37</sup>, and unlike MRI offer no information on location and extent of ECE. A meta-analysis by de Rooij *et al.* in 2016 showed MRI to have a high specificity of 91% but only moderate sensitivity at 57% in diagnosing ECE. Of note, this analysis included studies with both uni- and multiparametric protocols at both 1.5T and 3T, and sub-analysis of 3T studies improved overall performance with specificity 86% and sensitivity 68%.<sup>38</sup> The main reasons for improvement being higher spatial resolution at 3T and improved lesion identification with a multiparametric approach, allowing interrogation of the capsule and neurovascular bundle in the adjacent region (Figure 2).<sup>39</sup>

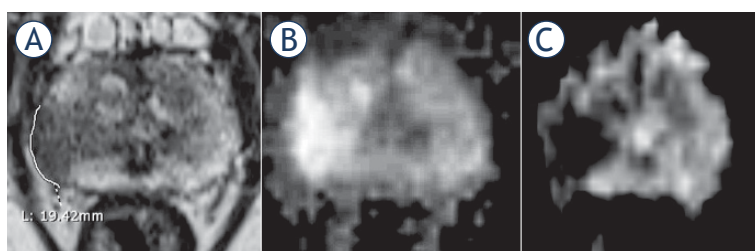
Several approaches have been proposed and explored in order to increase diagnostic accuracy for the evaluation of ECE. Prostate imaging-reporting and data system (PI-RADS) guidelines recommends various morphologic criteria (Table 3).<sup>19</sup> These have been evaluated and demonstrated sensitivity and specificity between 60%–81% and



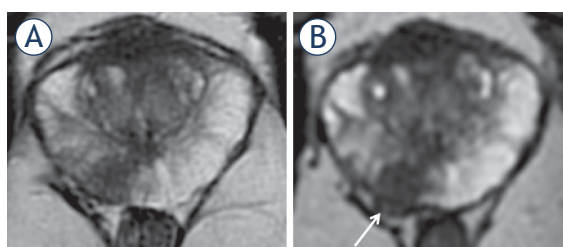
75%–78%, respectively, and showed moderate inter-reader agreement ( $K = 0.45$ ) for the prediction of T3a disease.<sup>40,41</sup>

In addition, the length of tumour contact with the capsule at MRI (Figure 3) has also been shown to be a strong predictor of ECE<sup>35,42,43</sup> with good to excellent inter-reader agreement<sup>26,35</sup> (Figure 3).<sup>26,35</sup> However, a reliable threshold is yet to be established, with reported rates varying from 6–20 mm, the PI-RADS v2 guidelines recommend an arbitrary threshold of 10 mm<sup>19</sup>, which pre-dates many of these studies. The reason for variability is likely multifactorial with different methodology employed and variations in scanner strength, vendor and protocols. For instance, Rosenkrantz *et al.* measured the length in a linear rather than curvilinear fashion which likely explains their lower reported threshold of 6 mm.<sup>35</sup> In addition, a more recent study suggests that thresholds differ between low- (Grade Group 1–2) and high-grade (Grade Group 3–5) cancers, with the former having a positive predictive values (PPV) of 90.4% for ECE at 12.5 mm and the optimal cut-off for the latter being 5 mm.<sup>26</sup> This finding was further confirmed by Matsuoka *et al.* who reported significantly increased upstaging in low- versus high-grade cancers when the same threshold (10 mm) was applied.<sup>44</sup> Given that lower apparent diffusion coefficient (ADC) values in prostate cancer correlate with higher Gleason score<sup>45,46</sup>, this could potentially be exploited as an adjunct for more accurate diagnosis of T3a disease prior to biopsy results. To date however, there have been mixed results when applying ADC values for stage assessment, which may relate to difficulties in applying uniform quantitative values.<sup>39,47–50</sup>

Another potential approach to improve sensitivity is utilisation of an isovolumetric 3D T2 imaging sequence to acquire thinner slices with less partial voluming and reformatting of isotropic images in multiple planes. Studies using 3D-T2 sequence have reported encouraging results with sensitivity and specificity ranging from 58.3%–84% and 73.1%–89%, respectively.<sup>44,51–53</sup> In addition, Caglic *et al.* proposed a new criterion of 3D Contact which significantly improved detection of ECE (sensitivity, specificity: 73.7% and 87.8%) when compared to the length of capsular contact measured on conventional T2 imaging in axial plane (sensitivity, specificity: 59.6%, 87.8%).<sup>26</sup> This approach exploited the reduced partial voluming due to thinner slices (Figure 4) and reconstruction of images in multiple planes in order to measure the more representative a truer length of capsular contact. Although not supported by work of Jäderling *et*



**FIGURE 3.** 74-yr-old man with PSA 35.2 ng/ml. (A) T2 weighted (T2W) imaging, (B) diffusion weighted (DW) imaging, (C) apparent diffusion coefficient (ADC) map. T3a at the right mid gland as suggested by a broad capsular contact at 19.4 mm. Biopsy showed Gleason score (GS) 4 + 4 = 8 disease. Patient underwent radiotherapy.



**FIGURE 4.** 57-yr-old man with PSA 26 ng/ml. (A) Axial T2 weighted imaging (T2WI) shows mid gland right peripheral zones (PZ) lesion (arrow) with capsular contact but no tumour extension beyond it. (B) axial thin-sliced cube reformat suggests capsular breach and right neurovascular bundle involvement (arrow). Prostatectomy showed tumour in the right mid gland, Gleason score 4 + 5 = 9, with established extracapsular extension (ECE) (pT3a).

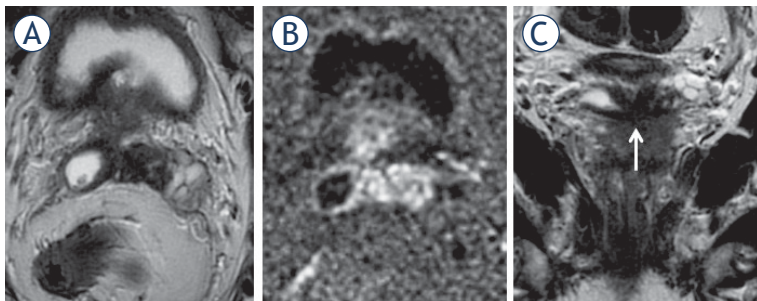
*al.* using 3D-T2 reconstructions, it should be noted that their analysis was based on morphological criteria and not on quantifying capsular contact.<sup>54</sup>

Although diagnostic accuracy for early ECE is improving, sensitivity remains relatively poor, and it should be noted that these results come from experienced centres, utilizing modern equipment and optimised protocols. As a result, equivocal MRI findings should not change the planned treatment course, but rather ensure discussion between radiologists and urologists at multidisciplinary meetings on a case-by-case basis. Practical advice would be to flag indeterminate features of ECE, to allow wider surgical margins to be taken in the corresponding region.<sup>10</sup> Furthermore, reporting the exact location of T3a disease is important, as clear margins are harder to obtain at the apex whereas tumours remote from the neurovascular bundle (NVB) such as in the anterior location will allow nerve sparing surgery and reduce resultant morbidity from urinary incontinence or erectile dysfunction.

### T3b disease

T3b disease is defined as involvement of one or both seminal vesicles (SV) by prostate cancer, with the prevalence of SV invasion in surgical series being reported at 4–23%.<sup>55,56</sup> Patients with T3b disease carry an increased risk of lymph node involvement, local recurrence and distant metastases<sup>57</sup>, making preoperative identification of SV involvement an important factor for prognosis and treatment planning. Patients with T3b disease are typically not offered radical prostatectomy or brachytherapy unless as part of a multimodal approach, and are usually offered external beam radiotherapy (EBRT) and androgen deprivation therapy (ADT).

MRI has been shown to outperform clinical risk assessment tools such as Kattan nomogram and Partin tables in predicting SV involvement<sup>13,58</sup>, with meta-analyses showing moderate sensitivity of 73% and specificity of 95% for multiparametric MRI studies at 3T.<sup>38</sup> Recent work by Grivas *et al.* including 527 patients at 3T mpMRI achieved similar results with sensitivity, specificity, PPV and negative predictive values (NPV) at 75.9%, 94.7%, 62% and 97%, respectively.<sup>59</sup>

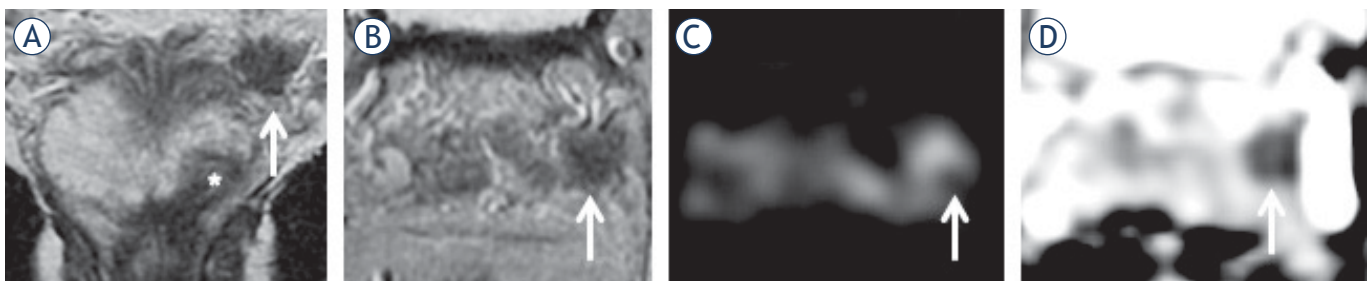


**FIGURE 5.** 65-yr-old-man with PSA = 15.3 ng/ml and Gleason score 4 + 4 = 8 at biopsy. Axial (A) and coronal (C) T2 weighted imaging (T2WI) and diffusion weighted imaging (DWI) (B). T3b involving both seminal vesicles via ejaculatory ducts, shown in the coronal plane (arrow).

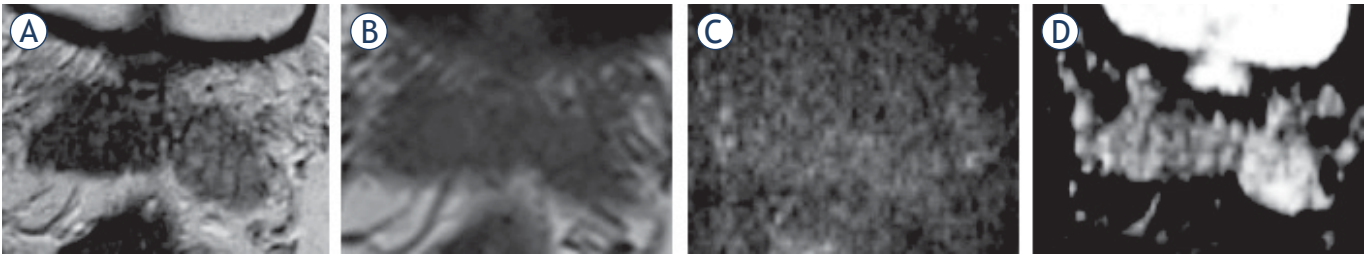
Histopathologically, SV invasion is defined as prostate cancer penetrating the SV muscular wall, with tumour involving the extraprostatic portion of the vesicles rather than the intraprostatic ejaculatory ducts.<sup>57</sup> Three routes of invasion have been described, Type I: direct spread via the ejaculatory duct complex (Figure 5), Type II: extracapsular spread of disease with invasion via the outer seminal vesicle wall and type III: metastatic involvement from a remote intraprostatic lesion (Figure 6). The first two types individually or in combination account for more than 95% of cases, with type III spread being extremely rare.<sup>60,61</sup>

Seminal vesicles are best evaluated on T2W imaging in combination with functional imaging. Coronal or sagittal reformats are especially useful in demonstrating the type of spread. In Type I invasion, invasion *via* the erectile dysfunction (ED) causes SV expansion with a low signal intraluminal mass and may cause diffuse or focal wall thickening. In Type II involvement, there is obliteration of the angle between the base of the prostate and SV.<sup>60</sup> In addition, in 2009 Jung *et al.* proposed a novel six-tier classification system for SV invasion based on morphological appearance of SV on T2W imaging (Class 0 = normal SV appearance, Class 5 = apparent mass lesion with destructive architecture) showing sensitivity and specificity of 71.4 and 96.6%, respectively.<sup>62</sup> More recent work incorporating functional sequences has further increased accuracy, with DWI proving to be of more incremental value than DCE.<sup>56,63</sup>

There are known pitfalls to be aware of when assessing for SV involvement, such as diffuse wall thickening due to SV atrophy or asymmetry. In addition, there can be large variation with a mean right - left asymmetry of 20% and surgical series suggesting SV length between sides can vary up to 9-fold.<sup>64</sup> Post-biopsy haemorrhage can mimic the low T2 signal of prostate cancer and review



**FIGURE 6.** 67-yr-old man with raising PSA = 12.7 ng/ml. (A) (coronal) and (B) (axial) T2 weighted (T2W) imaging shows index lesion in the left apex (\*) and a low signal focus in the left seminal vesicle (arrow) with corresponding restricted diffusion on diffusion weighted imaging (DWI) ((C); arrow) and apparent diffusion coefficient (ADC) map ((D); arrow).



**FIGURE 7.** 55-yr-old-man with PSA 32 ng/ml. (A) T2 weighted (T2W) imaging, (B) T1 weighted (T1W) imaging, (C) diffusion weighted (DW) imaging, (D) apparent diffusion coefficient (ADC) map. Low T2 signal in the right seminal vesicle is mimicking prostate cancer (D), however, there is no restricted diffusion. Biopsy of the right seminal vesicle showed amyloidosis which was confirmed at radical prostatectomy. Index tumour with Gleason score 4 + 3 = 7 was in the left peripheral zone.

of T1W imaging for high signal within the SV is therefore essential. Another important mimic of prostate cancer is amyloidosis which exhibits low T2 signal but does not show diffusion restriction (Figure 7). In cases with equivocal SV findings on prebiopsy MRI, patients can undergo subsequent targeted biopsy in order to correctly stage the disease (Figure 7).<sup>65</sup>

Although PI-RADS v2 does not recommend abstinence from ejaculation prior to prostate mpMRI<sup>19</sup>, some centres require patients to refrain from ejaculation prior to imaging in order to achieve maximal distension. Recent studies suggest 72 hours abstinence as the recommended interval to achieve maximal seminal vesicle distension.<sup>66-69</sup> This may be beneficial in evaluation of seminal vesicle invasion but further prospective studies including patients with prostate cancer are required to determine the effect on local staging accuracy.

## N-Staging

EAU guidelines recommend N-staging should be performed on prebiopsy MRI in patients from all risk groups.<sup>1</sup> This is in line with PI-RADS v2 guidelines which recommend that the prostate MRI protocol, which is primarily aimed at evaluating gland-confined and locally advanced disease, should also incorporate an additional sequence for the purpose of pelvic nodal staging from the level of aortic bifurcation.<sup>24</sup> PCa spreads primarily to four pelvic nodal stations, considered regional nodes: the obturator, internal and external iliac and presacral LNs. Involvement of any regional node is classified as N1 stage, whilst involvement of non-regional stations (para-aortic or paracaval LNs) represents M1a disease.<sup>17,70</sup> Nodal mapping studies have shown that approximately 75% of pelvic nodal metastases are distributed between the ob-

turator fossa, internal and external iliac chain and the remaining 25% between the presacral, common iliac or aortic bifurcation group.<sup>71,72</sup>

MRI has traditionally relied on size and morphological criteria in LN assessment including an enlarged size (> 8 mm), loss of fatty hilum, rounded shape, low T2W signal similar to primary tumour, or an irregular border. This is of limited diagnostic accuracy mainly due to low sensitivity, with a meta-analysis from 2008 incorporating anatomical imaging studies alone (T2W and T1W) reporting a sensitivity of only 39% (specificity 82%).<sup>73</sup> Size criteria in isolation is unhelpful, with a recent study showing the majority (68%) of metastatic nodes to have a short axis diameter < 5 mm.<sup>27</sup> More recent studies have tried to establish whether an ADC threshold can be applied for discrimination of benign from malignant LNs.<sup>27,74-78</sup> Although malignant LNs typically exhibit lower ADC values, there is significant overlap between normal and pathological LNs as well as large variation in the reported thresholds, limiting the value of quantitative ADC measures at an individual patient level.<sup>79</sup> Reasons for poor discrimination include micro metastasis being unlikely to lower the overall ADC value of a node, whilst some benign conditions (lipomatosis, sinus histiocytosis, and follicular hyperplasia)<sup>27</sup> as well as inflammation (sarcoidosis and catch scratch disease) can also result in restricted diffusion within LNs.<sup>80,81</sup> In addition, reproducibility of ADC measurements in small structures such as LNs may be insufficient and differences in acquisition protocols between centres further inhibits establishment of an absolute threshold.<sup>82-85</sup> Consequently, some studies have focused on qualitative assessment of DWI using high b-value imaging in combination with anatomical T2W and reported improved performance with sensitivities of 55–73% and specificities of 86–90%.<sup>27,86</sup> Normal LNs have an inherent relatively long T2 relaxation time and will there-



fore appear as high signal intensity structures on high b-value imaging (Figure 8), which is especially useful in depicting LNs as a “nodal map” when these do not meet size criteria. Detected nodes should then be carefully evaluated on T2W imaging in order to avoid false positive results due to structures which also appear bright on high b-value DWI (bowel mucosa, vessels, nerves)<sup>87</sup> and to assess morphological features of malignancy.

Current diagnostic performance of MRI in nodal staging is sub-optimal, thus ePLND remains the gold standard. Due to the limited sensitivity (high false negative rate) of MRI, negative findings should not deter surgeons from performing lymphadenectomy in patients with a high clinical risk for LN involvement. Conversely, the specificity of MRI is high (low false positive rate) and LNs considered to be suspicious at MRI warrant resection.

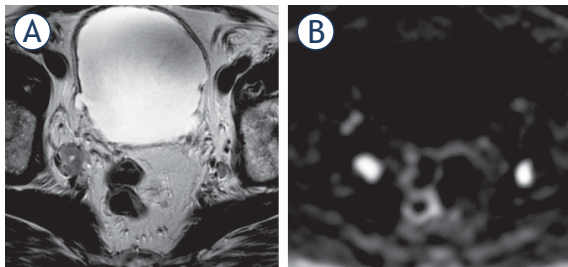
Further work and development of imaging techniques with a high diagnostic performance is needed in order to more efficiently and less invasively identify patients with metastatic LNs. Initial clinical trials with prostate specific membrane antigen (<sup>68</sup>Ga-PSMA) PET-MRI have shown promising results for detection of LN metastases<sup>88,89</sup>, resulting in change of treatment (either to systemic treat-

ment or active surveillance) in approximately one third of patients.<sup>90</sup> MR lymphangiography (MRL) with ultra-small superparamagnetic iron oxide (USPIO) has also demonstrated encouraging results with studies reporting sensitivity of 65–100% and specificity of 93–100% on a per patient basis.<sup>91–93</sup> However, USPIO is currently not licenced for general clinical use, with only the Netherlands producing it (commercially known as Combidex) and licensing it mainly for the research purposes in patients with PCa.<sup>94</sup>

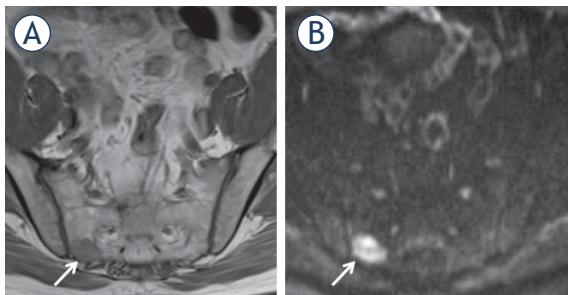
## M-Staging

EAU guidelines recommend staging for metastatic disease (M1a–M1c) in patients with unfavourable intermediate (International Society of Urological Pathology [ISUP] grade group 3) or high-risk (ISUP grade group 4–5) disease.<sup>1</sup> Current guidelines recommend evaluation of non-regional LNs and visceral metastases (M1a and M1c disease, respectively) by CT abdomen/pelvis imaging, combined with bone scintigraphy (BS) for evaluation of bone metastases (M1b disease) (Figure 9).<sup>95</sup>

Several studies have shown MRI (either whole-body MRI or axial skeleton only MRI) to significantly outperform BS for assessment of M1b disease, with a thorough meta-analysis from 2014 reporting MRI sensitivity and specificity to be 97% and 95% compared to BS at 79% and 82%, respectively.<sup>96</sup> MRI is not incorporated into current guidelines mainly due to its limited availability and lower cost effectiveness.<sup>96</sup> However, over the last decade whole body MRI (WB-MRI) has been gradually gaining attention due to its ability to detect bone marrow infiltration by malignant cells before bone remodelling occurs and therefore becomes visible on BS.<sup>97</sup> The METastasis Reporting and Data System for Prostate (MET-RADS-P) is aimed at practical guidance for acquisition, interpretation, and reporting of WB-MRI in advanced prostate cancer.<sup>98</sup> The recommended protocol consists of a combination of anatomical and functional sequences (T1W, short tau inversion recovery [STIR] or fat suppressed T2W and DW imaging). Bone metastases appear as low signal on T1W imaging, bright on STIR or fat suppressed T2W and with restricted diffusion. Beside bone assessment, WB-MRI can also provide N-staging and assess for involvement of visceral organs.<sup>99,100</sup> Whilst the diagnostic potential of WBMRI is promising, there are barriers to widespread adoption, including additional coils required, increased scanning time, the



**FIGURE 8.** 77-yr-old man with PSA = 38.2 ng/ml. Enlarged nodes bilaterally consistent with metastatic involvement on T2 weighted imaging (T2WI) (A), more conspicuous on diffusion weighted imaging (DWI) (B).



**FIGURE 9.** 61-yr-old man with PSA = 12.7 ng/ml. Bone metastasis (arrow) in the right sacrum shown as low signal on T1 weighted (T1W) imaging (A); more conspicuous as high signal on diffusion weighted imaging (DWI) (B).



need for sub-specialised knowledge, and increased reporting time. A recent study from 2018 by Larbi *et al.* has shown a possible means of overcoming some of these disadvantages by demonstrating that the combination of either T1-DWI or T1-STIR is non-inferior to a full protocol (Figure 9), whilst at the same time showing good interobserver agreement.<sup>101</sup>

## Conclusions

MpMRI is the recommended modality for the local staging of prostate cancer. It has shown superior performance compared to traditional staging based on clinical nomograms, and provides additional information on the site and extent of disease. T2W-weighted imaging remains the cornerstone for ECE and SV invasion assessment, however, improved accuracy can be achieved by scanning on 3T devices with the incorporation of diffusion weighted and dynamic contrast enhanced imaging. Whilst its role in nodal and bone staging outside academic centres is currently limited, there are emerging “next generation” imaging modalities including <sup>68</sup>Ga-PSMA-PET/MRI and whole-body MRI offer potential to become the future standard of care for evaluation, having shown superior results for distal staging in comparison to the traditional work-up with bone scintigraphy and body CT. Despite the advantages of mpMRI there remain limitations which should be known to radiologists and other members of the multidisciplinary team in order to jointly decide on the best treatment options for prostate cancer patients on an individual basis.

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