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Contribution of Radiology to Staging of Prostate Cancer

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Accurate tumor detection and establishment of disease extent are important for optimal management of prostate cancer. Disease stage, beginning with identification of the index prostate lesion, followed by primary tumor, lymph node, and distant metastasis evaluation, provide crucial clinical information that not only have prognostic and predictive value, but guide patient management. A wide array of radiological imaging modalities including ultrasound, computed tomography, and magnetic resonance imaging have been used for the purpose of prostate cancer staging with variable diagnostic performance. Especially, the last years have seen remarkable technological advances in magnetic resonance imaging technology, enabling referring clinicians and radiologists to obtain even more valuable data regarding staging of prostate cancer. Marked improvements have been seen in detection of the index prostate lesion and evaluation of extraprostatic extension while further improvements are still needed in identifying metastatic lymph nodes. Novel approaches such as whole-body MRI are emerging for more accurate and reproducible assessment of bone metastasis. Post-treatment assessment of prostate cancer using radiological imaging is a topic with rapidly changing clinical context and special consideration is needed for the biochemical setting, that is, the relatively high serum prostate-specific antigen levels in studies assessing the value of radiological imaging for post-treatment assessment and emerging therapeutic approaches such as early salvage radiation therapy. The scope of this review is to provide the reader insight into the various ways radiology contribute to staging of prostate cancer in the context of both primary staging and post-treatment assessment. The strengths and limitations of each imaging modality are highlighted as well as topics that warrant future research.

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Tumor Detection and Primary Staging

Primary staging of prostate cancer can be applied to several clinical scenarios that include the following: (1) detecting abnormal lesions in biopsy-naïve patients with clinical suspicion of prostate cancer (eg, elevated serum prostate specific antigen [PSA] levels or a positive digital rectal exam); (2) detecting cancer in patients who had negative biopsy results despite persisting clinical suspicion of prostate cancer (eg, rising PSA); or (3) staging in patients with biopsy-proven prostate cancer.[1]

Identification of Index Lesion

The overarching goal in this context is to identify the presence of clinically significant prostate cancer, as not all cancers lead to adverse outcomes such as cancer-related deaths. In fact, it is well known based on clinical and autopsy studies that a significant proportion of prostate tumors grow at a rate so slow that patients will often die from other causes even before the prostate cancer starts to manifest with any clinical symptoms or signs.[2] Several radiological imaging modalities have been used for detecting prostate cancer, including US, CT and MRI. Although there have been several reports showing that US (especially with advanced US technology such as elastography and contrast-enhanced US) and CT can be helpful, these modalities have inherent pitfalls

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such as high inter-operator variability (for US) and limited capability for soft tissue contrast, which hinders their application in clinical practice.[3-6] Currently, MRI is accepted as the conventional imaging method that can be used to detect the index primary prostatic lesion with the highest accuracy and reproducibility. A multiparametric (mp) imaging approach is recommended, which includes anatomical sequences of T1-weighted (T1W) and T2-weighted (T2W) images and also functional sequences such as diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) MRI.[1] Magnetic resonance spectroscopy has been advocated in the past[7]; but is currently deemed optional and no longer required as part of the contemporary mpMRI protocol due to low spatial resolution and long acquisition time of the commonly used acquisition protocols.[8] For standardization and optimization of image acquisition and interpretation of mpMRI, one of the most up-to-date trends is to use the Prostate Imaging Reporting and Data System (PIRADS) version 2.[9] Based on a recent meta-analysis, PIRADS version 2 shows relatively good diagnostic performance for detecting prostate cancer with a pooled sensitivity of 0.89 (95% confidence interval [CI] 0.84-0.92) with specificity of 0.73 (95% CI 0.46-0.78) based on 21 studies.[10]

Primary Tumor Staging

After initial detection of the index prostate lesion, the next step is "staging". Primary tumor staging, or T staging, can be done in terms of various aspects using radiological imaging modalities. There has been attempt to use MRI for determination of tumor size, but MRI can substantially under- or over-estimate the size of the tumor specimens with wide variability.[11,12] One of the most important roles of imaging in T staging is assessment of the presence of extraprostatic extension (EPE) (Fig. 1). Extraprostatic extension refers to either local extension beyond the prostatic capsule (ECE), into the seminal vesicles (SVI), or to adjacent organs. Identifying the presence of EPE is of utmost importance in that if present, it is associated with an increased likelihood of adverse outcomes (eg, postoperative biochemical recurrence) and that is crucial in optimizing patients' management strategies.[13] Despite advances in MRI technology, T2WI remains the main MRI sequences for evaluating EPE as it has inherently high spatial resolution (for outlining the margin of the tumor and prostate) and relatively high-contrast resolution between tumor and the normal prostatic tissue. Specific imaging findings on T2WI such as broad tumor contact, bulging of the capsule, obliteration of the rectoprostatic angle, and

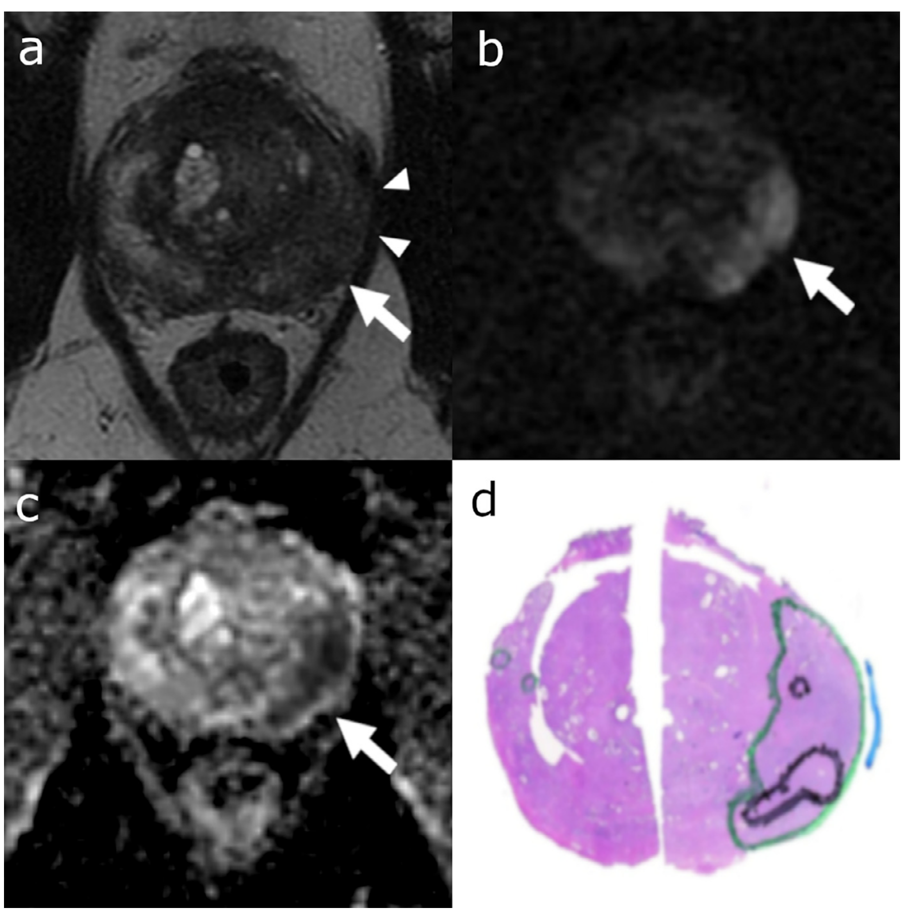

Figure 1 Axial T2 weighted (a), DWI (b) and ADC (c) MRI images and correlating representative pathology tumor map (d) from whole-mount slide. Colored ink outlines tumor location (green = Gleason pattern 3, black = Gleason pattern 4 or 5, blue = areas of extracapsular extension). A 58-year-old patient with a left posterolateral peripheral zone base to mid gland dominant lesion on T2 weighted images (arrows in a-c), diffusion restriction with broad capsular abutment suspicious for extracapsular extension (arrowheads in a, blue ink in d).

asymmetry of the neurovascular bundle have been shown to be associated with ECE.[14] In addition, low signal intensity within the seminal vesicle with loss of its normal architecture on T2WI is highly predictive of SVI and MRI has been shown to improve the performance in predicting SVI when added to clinical nomograms (eg, Kattan nomogram).[15,16] Based on a meta-analysis of 38 studies including 4001 patients, the pooled sensitivity and specificity for overall detection of stage T3 prostate cancer was 0.61 (95% CI 0.54-0.67) and 0.88 (95% CI 0.85-0.91), respectively.[17] As such, albeit the relatively high specificity, there is much room for improvement with regard to the sensitivity for determining EPE. Until now, assessment of EPE has mostly been done on subjective analysis like the Likert scale for likelihood of EPE and there has been criticism about the level of experience potentially altering the diagnostic performance.[14,18] Therefore, more recent efforts focus on finding ways to potentially improve diagnostic accuracy and to reduce interobserver variability. Some examples of these are quantitative biomarkers such as tumor size/volume,[19] length of capsular contact, ADC calculated DWI, and DCE parameters. Larger tumor size and greater length of contact between the tumor and prostatic capsule (>12-14 mm),[20] either measured on cross-sectional imaging or US,[21] have been shown to independently significant predictive factors of EPE. Lower tumor ADC values have also been shown to improve the prediction of EPE compared to T2WI alone in numerous studies.[22,23] Several DCE MRI variables such as plasma flow (PF) and mean transit time (MTT) have also shown ability to predict EPE.[24] These functional MRI sequences are thought to be of incremental value as they indirectly provide information associated with tumor aggressiveness (ie, Gleason score, cellularity, and angiogenesis). In addition, standardized image interpretation (ie, PIRADS) should contribute to improving diagnostic performance and leveling out the differences between readers with different levels of experience.[25]

Lymph Node Staging

Lymph node staging has been an area of interest for the use of radiological imaging. However, as of now, no single modality has shown an optimal diagnostic performance to detect or rule out metastatic lymph nodes. While US has virtually no role in this area, radiologists have traditionally used certain size- and shape-specific criteria on CT and MRI to assess lymph node metastasis. For example, one of the most commonly used criteria for metastatic lymph nodes from prostate cancer is a round lymph node with short axis diameter greater than 8 mm or an oval node with larger than 10 mm.[26] With use of such criteria, both the sensitivity and specificity are low with reported pooled estimates of 0.42 (95% CI, 0.26-0.56) and 0.82 (95% CI, 0.8-0.83), respectively according to a meta-analysis of 24 studies based on CT and MRI.[27] The low sensitivity of using cross-sectional imaging, arises from the fact that LNs that harbor only microscopic metastasis do not show significant changes in size and shape (Fig. 2); while benign processes such as reactive hyperplasia can also lead to enlarged LNs, and in turn,

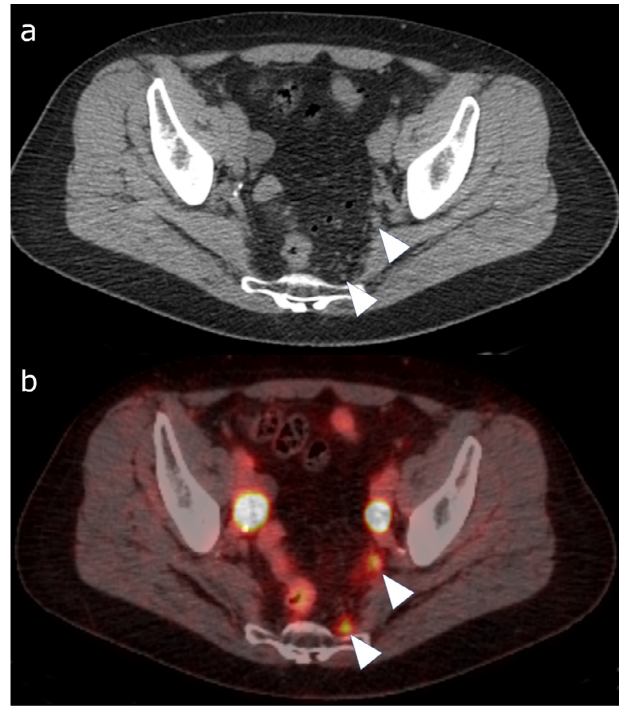

Figure 2 Gallium-68 PSMA PET/CT study with the CT (a) and fused PET/CT (b) image. A 67-year-old patient with biochemical recurrence following radical prostatectomy, pelvic lymph node dissection, and radiation. The CT image shows punctate pelvic lymph nodes, not suspicious based on morphology (arrow heads in a). The fused image shows uptake within small left internal iliac and presacral lymph nodes (arrowheads in b), suspicious for metastasis.

false-positive results for metastatic LNs.[28] Therefore, in clinical practice, routine or extended pelvic lymph node dissection is commonly practiced with up to one third of patients without suspicious looking LNs on cross-sectional imaging found to have metastatic LNs (Fig. 2).[29]

In the recent years, intensive efforts to improve the diagnostic performance of CT and MRI for detecting LN metastasis have been carried out. Up to now the most promising technique seems to be the use of a lymphotropic MRI contrast agent, ultrasmall superparamagnetic particles of iron oxide (USPIO). Several studies have shown that using USPIO even microscopic metastasis can be identified with high accuracy in patients with prostate cancer.[30-35] In addition, a recent meta-analysis demonstrated that although there has not been a substantial improvement in the diagnostic performance of MRI in LN staging (pooled sensitivity and specificity of 0.56 and 0.94, respectively, in 24 studies with 2928 patients), studies using USPIO had significantly greater sensitivity of 0.84 (0.71-0.97) than those that did not use USPIO (0.46, 95% CI 0.34-0.58) which is comparable to the performance of prostate-specific membrane antigen PET/CT (0.86 95% CI 0.37-0.98).[36,37] This improved capability of USPIO in detecting micrometastasis seems to stem from its unique characteristics. After USPIO injected, it leaks into the extravascular space, is taken up by the lymphatics to the lymph nodes and then is internalized by macrophages. As USPIO is superparamagnetic, accumulation of the contrast agent leads to T2 shorting and in turn decreased signal intensity (SI) on T2WI and T2*WI. However, LNs harboring metastasis may have areas having no or few normal macrophages, and therefore will not show decreased SI.[38] Nevertheless, there are still obstacles for the translation of USPIO from the research realm into real-life clinical practice. The most important factor is the lack of commercial availability and regulatory approvals of USPIO agents. Ferumoxtran-10, the USPIO agent used in the studies above, is currently only manufactured privately in the Netherlands. Agents with similar properties such as Ferumoxytol, which was originally approved for iron replacement therapy in anemia associated with renal failure are being tested as an alternative with better availability.[39] Other drawbacks include the need for two separate image interpretation sessions (baseline and 24-36 hours after injection of USPIO),[38] inter-reader variability associated with level of reader experience,[32,40] and potential adverse reactions (eg, back pain, hypersensitivity reactions, hypotension, and chest pain).[41]

Based on the published literature, other advanced MRI sequences do not seem to provide substantial incremental value in the N staging of prostate cancer either due to lack of studies testing the MRI sequence (eg, DCE-MRI) or due to absence of improved diagnostic performance when additionally using the MRI sequence (eg, DWI).[36] Although DWI may not directly contribute to prediction of metastatic LNs, studies have shown that DWI used in conjunction with USPIO may not only improve diagnostic performance, but also shorten interpretation time and reduce inter-reader variability.[34,35]

Distant Metastasis Staging

Distant metastasis (M) staging for patients with prostate cancer typically focuses on detecting bone metastasis, which is the most common site of initial metastasis. Metastasis to other visceral organs can occur and is particularly important in certain situations, for example: (1) the presence of visceral metastasis precluding radionuclide therapy (ie, alpha-particle emitter, radium-223) for metastatic bone lesions[42]; and (2) brain imaging to detect subclinical metastases in atypical prostate cancer histologies (eg, small cell or cribriform histological subtypes).[43]

Radiological imaging is important to identify bone metastasis, especially in patients with high-risk or locally-advanced prostate cancer. At present, bone scans and CT are recommended by guidelines for detection of metastatic bone disease, but due to their low sensitivity and specificity, it is generally recognized that more advanced techniques are needed for this purpose.[44] Although in general, PET/CT using different radiopharmaceuticals (PSMA, choline, and fluciclovine) is considered to be the primary next generation imaging method for bone metastasis by experts,[45] whole body MRI could also play a role in this area (Fig. 3). A recent meta-analysis of 10 studies with 1031 patients demonstrated that pooled sensitivity and specificity of MRI for detection of

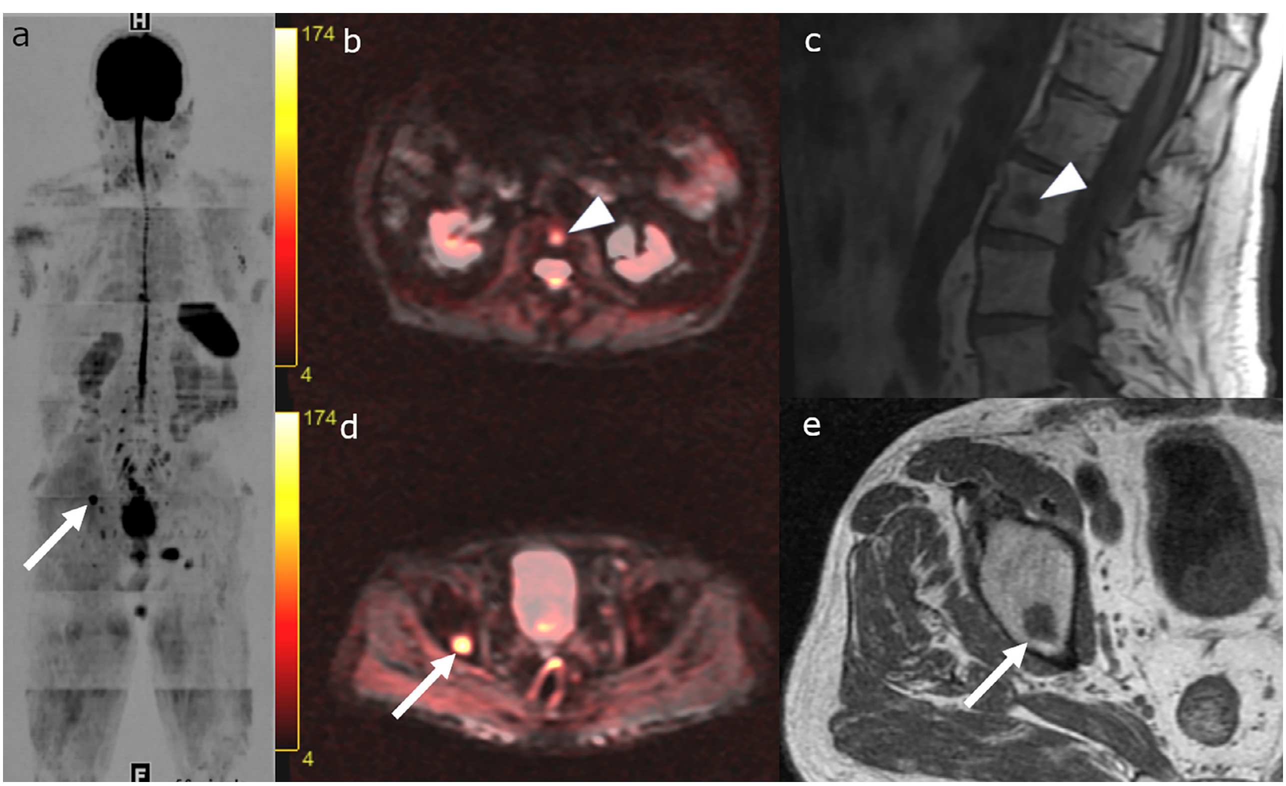

Figure 3 Whole body MRI with grey scale inverted DWI image (a), axial T1-weighted and DWI fused images (b and d), sagittal (c) and axial (e) T1 weighted images. A 79-year-old patient with metastatic Gleason 8 Prostate Cancer. T1 hypointense lesions with diffusion restriction in the right superior acetabulum (arrows in a, d-e) and L2 vertebral body (arrowheads in b-c), consistent with metastases.

bone metastasis in patients with prostate cancer were 0.96 (95% CI 0.87-0.99) and 0.98 (95% CI 0.93-0.99) on a per-patient basis.[46] Nevertheless, there has been concern on issues regarding verification bias (ie, not all bone lesions can be confirmed as metastasis pathologically), the fact that previous studies are based on per-patient analysis but not per-lesion analysis, and that routine prostate MRI does not cover all areas of potential bone metastasis (eg, cervicothoracic spine, ribs, and appendicular skeleton).[47,48] To this end, whole body MRI could play a key role in not only bone metastasis imaging, but also may be the solution for "one size fits all" approach for detecting and monitoring metastasis in general (ie, bones, lymph nodes, and visceral metastases).[49] Sequence components for whole body MRI generally require the following: (1) whole spine sagittal T1WI, (2) whole spine sagittal STIR or fat saturated T2WI, (3) whole body axial or coronal T1WI, and (4) whole body axial DWI with calculation of ADC values.[50] However, based on a consensus meeting by a multidisciplinary panel of experts in prostate cancer, a consensus for using whole body MRI has not been achieved yet, and this is thought to have arisen from lack of standardization for acquisition and interpretation of whole body MRI and experience in this area.[51] Recent efforts to overcome these hurdles include the METastasis Reporting and Data System for Prostate Cancer (MET-RADS-p) which aims for standardization and decreasing variability of whole body MRI, and in turn is anticipated to act as a catalyst for increased use and verification of whole body MRI for potential contribution in patients with prostate cancer.[50]

Post-treatment Assessment

Post-treatment assessment refers to detection of local recurrence or metastasis in patients with rising PSA levels or other clinical suspicion of prostate cancer recurrence after primary treatment (eg, radical prostatectomy or radiotherapy). This is an area of rapidly changing clinical context due to accumulating evidence of imaging modalities and treatment methods.

MRI has been the mainstay of the contemporary approach for detecting locally recurrent prostate cancer among all conventional imaging modalities. Bone scans and CT are commonly used in this clinical setting despite of their low yield for detecting recurrence or metastasis, at least partly due to easier accessibility. For example, in a previous study including 93 patients with PSA relapse after radical prostatectomy, it was shown that the bone scans were of limited value as the probability of a positive scan was <5%, unless PSA levels were very high (>40-45 ng/ml).[52] In addition, another study assessing CT in patients with biochemical recurrence, it was found that the positivity of CT was 0% in patients with low PSA levels (<10 ng/ml).[53] On the other hand, there does seem to be improved diagnostic performance when using MRI. Especially when using multiparametric MRI, relatively high pooled sensitivities and specificities of 0.84 and 0.85 for detection of locoregional recurrences in patients with biochemical recurrence after radical prostatectomy have been reported (Figs. 4 and 5).[54] Furthermore, multiparamateric MRI using T2WI, DWI and DCE MRI has been shown to demonstrate moderate sensitivity and high specificity of 0.71 and 0.94, respectively, for detection of locally recurrent prostate cancer after radiation therapy.[55] However, interpretation of these studies using MRI needs to be done with caution. The mean PSA levels of the study populations at the time of MRI in available studies range between 0.71 and 5.26 ng/ml with upper limits ranging from 1.7 to 68.3 ng/ml, which is considered to be above what would be clinically acceptable today without intervention.[56-63] Contemporary guidelines suggest that patients receive salvage radiation therapy before PSA levels rise over 0.5 ng/ml.[64] Therefore, more recent efforts focus on assessing the performance of MRI in patients experiencing early post-prostatectomy PSA elevation. For example, in a study of 142 patients with PSA elevation of ≤1

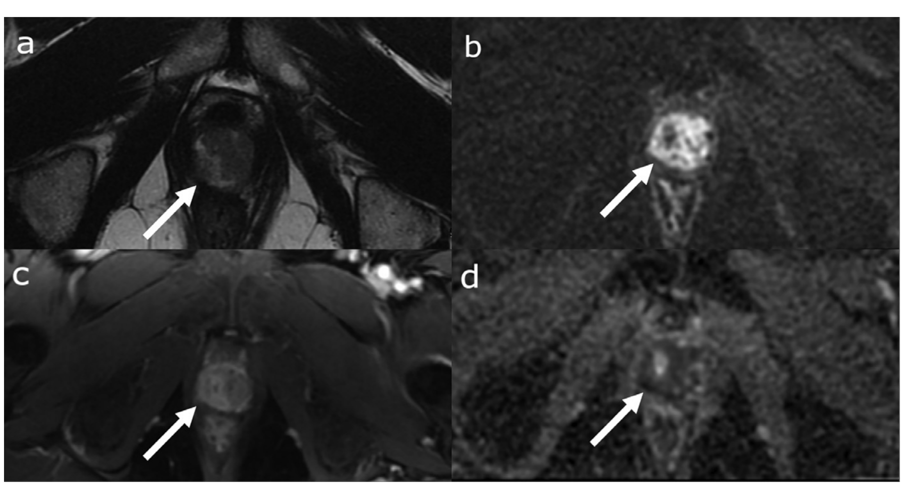

Figure 4 Multiparametric prostate MRI with axial T2 weighted image (a), DWI (b), dynamic contrast enhanced image (c) and ADC (d). A 63-year-old patient with rising PSA 10 years after radical prostatectomy. MRI shows a new mass at the site of the vesicourethral anastomosis (arrow in a) with diffusion restriction (arrows in b and d) and avid enhancement (arrow in c).

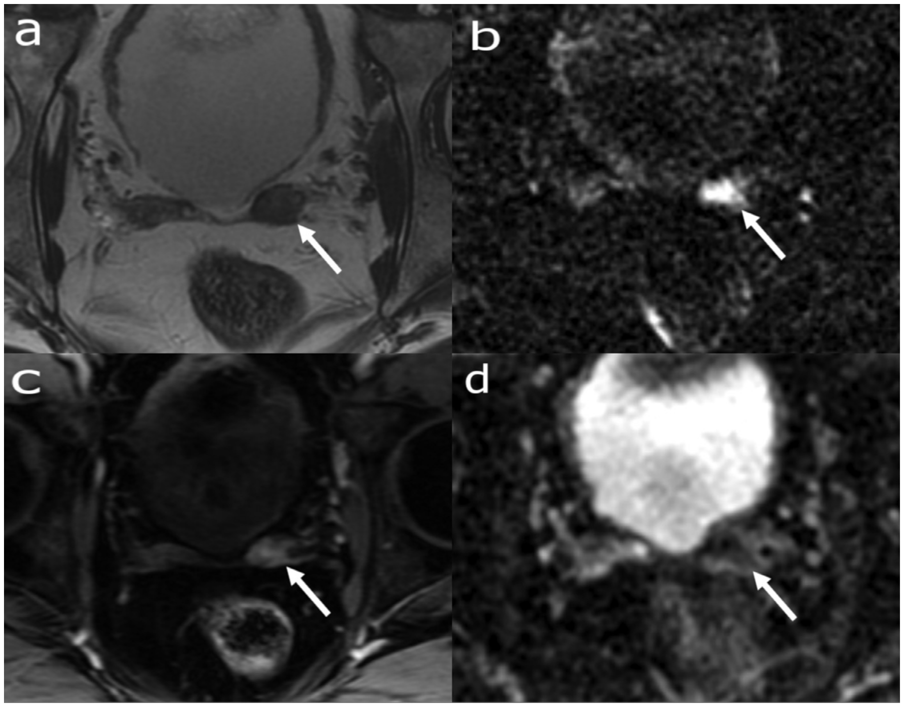

Figure 5 Multiparametric prostate MRI with axial T2 weighted image (a), DWI (b), dynamic contrast enhanced image (c) and ADC (d). A 72-year-old patient with biochemical recurrence with a T2 intermediate nodular mass (arrow in a) with diffusion restriction (arrows in b and d) and early avid enhancement (arrow in c) in the left seminal vesicle surgical bed suspicious for recurrent tumor.

ng/ml after radical prostatectomy, pelvic MRI was only positive in 11% of the patients, predominantly in the form of local recurrence.[65] Based on these studies, it may be premature to strongly advocate the use of conventional radiological imaging modalities to guide management in all patients with biochemical recurrence. Not only is salvage radiation therapy is commonly performed empirically without confirmation on imaging or pathology, but there is available evidence indicating that many patients with biochemical recurrence without detectable lesions on multiparametric MRI, show response to salvage radiation therapy.[66] Additional evidence shows that "early" or "very early" salvage radiation therapy, with variable definitions of PSA levels <0.5 ng/ml,[67,68] <0.2 ng/ml,[69] or even at the very first sign of PSA rise improves outcomes.[70]

Conclusion

The role of radiological imaging modalities in staging of prostate cancer is continuously evolving. Currently, multiparametric MRI is the accepted modality of choice, especially for detecting the index prostate lesion and evaluation of extraprostatic extension. Areas of further improvement include N and M staging. While MRI has shown some value in the context of post-treatment assessment, future studies including patients with low PSA levels are needed to meet the shifting paradigm of early salvage therapy initiation. Knowledge of the strengths and limitations of each imaging modality is crucial for accurate imaging interpretation and understanding the role of their contribution to prostate cancer staging.

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