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Magnetic resonance imaging for prostate cancer before radical and salvage radiotherapy: What radiation oncologists need to know

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Abstract

External beam radiotherapy (EBRT) is one of the principal curative treatments for patients with prostate cancer (PCa). Risk group classification is based on prostate-specific antigen (PSA) level, Gleason score, and T-stage. After risk group determination, the treatment volume and dose are defined and androgen deprivation therapy is prescribed, if appropriate. Traditionally, imaging has played only a minor role in T-staging due to the low diagnostic accuracy of conventional imaging strategies such as transrectal ultrasound, computed tomography, and morphologic magnetic resonance imaging (MRI). As a result, a notable percentage of tumours are understaged, leading to inappropriate and imprecise EBRT. The development of multiparametric MRI (mpMRI), an imaging technique that combines morphologic studies with functional diffusion-weighted sequences and dynamic contrast-enhanced imaging, has revolutionized the diagnosis and management of PCa. As a result, mpMRI is now used in staging PCa prior to EBRT, with possible implications for both risk group classification and treatment decision-making for EBRT. mpMRI is also being used in salvage

radiotherapy (SRT), the treatment of choice for patients who develop biochemical recurrence after radical prostatectomy. In the clinical context of biochemical relapse, it is essential to accurately determine the site of recurrence - pelvic (local, nodal, or bone) or distant - in order to select the optimal therapeutic management approach. Studies have demonstrated the value of mpMRI in detecting local recurrences - even in patients with low PSA levels (0.3-0.5 ng/mL) - and in diagnosing bone and nodal metastasis. The main objective of this review is to update the role of mpMRI prior to radical EBRT or SRT. We also consider future directions for the use and development of MRI in the field of radiation oncology.

Key words: Prostate cancer; Staging; Radical radiotherapy; Multiparametric magnetic resonance imaging; Biochemical failure; Radical prostatectomy; Salvage radiotherapy

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Core tip: Multiparametric magnetic resonance imaging (mpMRI) has revolutionized the management of prostate cancer, including external beam radiotherapy (EBRT). mpMRI has also improved local staging and recurrence detection after radical prostatectomy, even in patients with low prostate-specific antigen levels, and it has increased the accuracy of EBRT, potentially improving survival outcomes while reducing side effects. For these reasons, mpMRI is an essential tool in the evaluation and treatment of prostate cancer.

Couñago F, Sancho G, Catalá V, Hernández D, Recio M, Montemuiño S, Hernández JA, Maldonado A, del Cerro E. Magnetic resonance imaging for prostate cancer before radical and salvage radiotherapy: What radiation oncologists need to know. *World J Clin Oncol* 2017; 8(4): 305-319 Available from: URL: <http://www.wjgnet.com/2218-4333/full/v8/i4/305.htm> DOI: <http://dx.doi.org/10.5306/wjco.v8.i4.305>

INTRODUCTION

In the last decade, the growing use of multiparametric magnetic resonance imaging (mpMRI) in the diagnosis and treatment of prostate cancer (PCa) has revolutionized patient management. Numerous studies confirm the emerging and increasingly important role of mpMRI in PCa in a wide range of clinical contexts, including: Tumour screening and detection^[1]; prostate biopsy guidance^[2]; staging^[3]; assessment of tumour aggressiveness^[4]; active surveillance protocols^[5]; treatment planning (surgery, radiotherapy, and focal therapies)^[6-8]; and detection of recurrence after radical prostatectomy (RP) or external beam radiotherapy (EBRT)^[9,10].

There are two main indications for radiotherapy in PCa: (1) the initial treatment of patients with a recent

diagnosis of Pca; and (2) salvage treatment in patients with recurrent disease after RP. In both of these clinical scenarios, conventional diagnostic strategies [digital rectal examination (DRE), transrectal ultrasound (TRUS) with "blind" biopsies, computed tomography (CT), and bone scintigraphy] all have a low yield for establishing the T stage and in detecting recurrences post RP, all of which could result in undertreatment. In this context, the objective of this review is to update the role of mpMRI in the radical treatment of PCa with EBRT and in salvage radiotherapy (SRT) after RP. In addition, we discuss future directions for the use and development of MRI in the field of radiation oncology.

WHAT IS PROSTATE MPMRI?

mpMRI is an imaging technique that allows for the non-invasive assessment of the prostate gland. It is called multiparametric because various pulse sequences (*i.e.*, multiple parameters) are used to help detect and characterize the prostate lesions. Currently, mpMRI includes both morphologic (T1 and T2) and functional sequences [diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) imaging with gadolinium]. Spectroscopy no longer plays an important role and is thus not included in current MRI guidelines^[11,12].

MORPHOLOGIC IMAGING

T1-weighted pulse sequence

The T1 sequence consists of a T1-weighted (T1W) Fast Spin Echo (FSE) from the aortic bifurcation to the symphysis pubis, assessed on the axial plane (Figure 1). The T1W sequence cannot discriminate various prostate gland zones and therefore its main utility is in detecting the presence of post-biopsy bleeding (a common cause of false positives in PCa diagnosis) (Figure 2), nodal disease, and bone metastasis^[13].

T2-weighted pulse sequence

The T2 sequence consists of a T2-weighted (T2W) FSE sequence that includes the prostate gland and seminal vesicles (Figure 1B-D). The T2W sequence is normally performed in three spatial planes (axial, coronal, and sagittal). T2W sequence is capable of discriminating various anatomic zones of the prostate, including the peripheral, central, and transitional zones, as well as the anterior fibromuscular stroma, neurovascular plexus, surgical pseudocapsule, and the prostate capsule. In normal prostates, the peripheral zone is homogeneous and hyperintense on MRI (Figure 1B). In adults, the transitional zone is larger, with a heterogeneous signal and hyperplastic nodules of varying appearance, thus this zone can sometimes present diagnostic difficulties^[13].

Cancerous prostate lesions usually appear as nodules or hypointense areas on T2W images, with less well-defined margins at the transitional zone. A

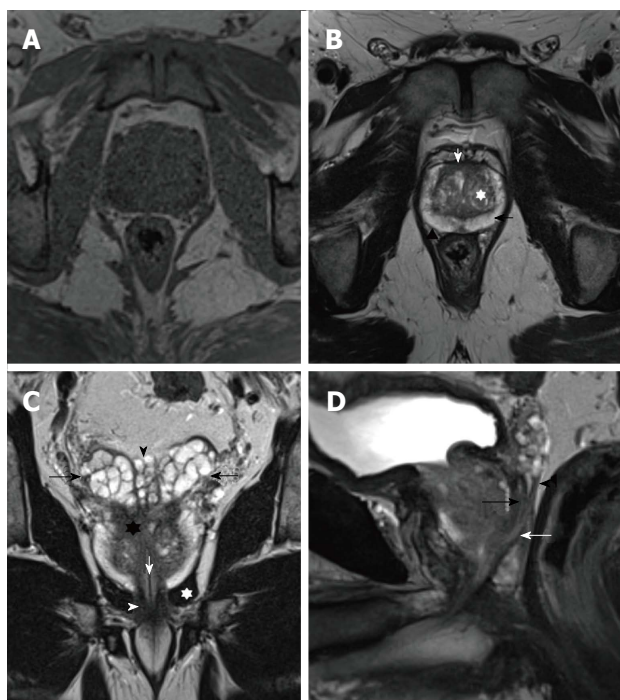


Figure 1 Normal prostate anatomy on magnetic resonance imaging - T1 and T2-weighted images. A: T1-weighted axial image of a normal prostate: Homogeneous gland, isointense to the adjacent pelvic muscles. It is not possible to differentiate any anatomical detail; B: Axial image of the prostate shows peripheral zone (PZ - black arrow) as a hyperintense area with a U-shape. The transitional zone (TZ - white asterisk) has a hypointense multinodular pattern ("organized chaos"). Anterior fibromuscular stroma (white arrow) is seen as a hypointense area anterior to the TZ and medial to both anterior PZ horns. The "capsule" (arrowhead) is seen as a hypointense rim surrounding the gland; C: Coronal image shows the hyperintense seminal vesicles located cephalad to the base of the prostate (black arrows). Ampulla of vas deferens (VD - black arrowhead) can be seen as paired structures medial to both seminal vesicles (SV). Prostate central zone (asterisk) is seen as a hypointense area located in the base of the prostate gland. Urethra (white arrow), levator ani muscle (white asterisk) and external sphincter (white arrowhead) are also shown; D: Sagittal image shows the vas deferens (black arrow), seminal vesicles (arrowhead) and the ejaculatory duct (white arrow).

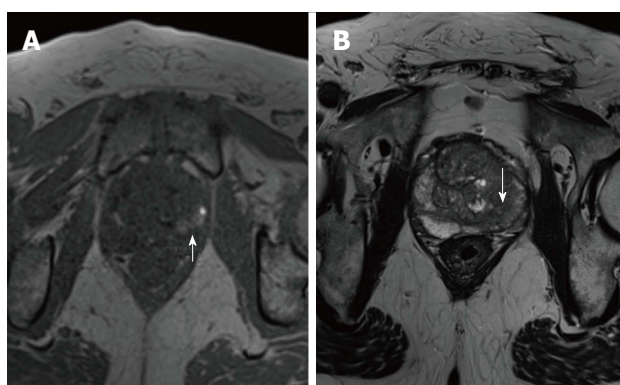


Figure 2 T1 (A) and T2-weighted images (B) of the midgland of the prostate. The left peripheral zone has a hyperintense area (white arrow, A) in T1-weighted image that correlates with a hypointensity (white arrow in B) in T2-weighted image, suggestive of bleeding in a patient with a recent transrectal ultrasound prostate biopsy.

limitation of the T2W sequence is that benign and malignant alterations often overlap. According to the Prostate Imaging Reporting and Data System (PIRADS)

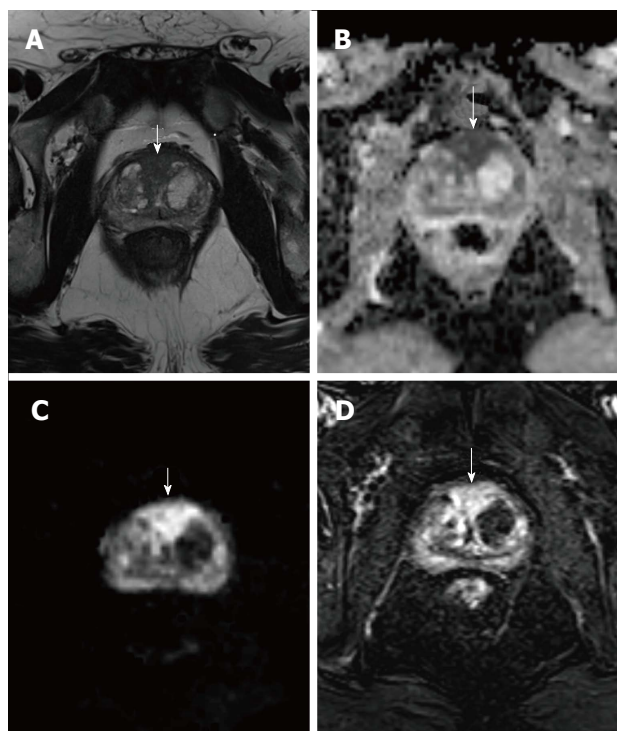


Figure 3 A 71-year-old patient. A: T2-weighted axial image at the level of the midgland of the prostate shows a hypointense nodular lesion at the transitional zone/anterior fibromuscular stroma, with a diameter of 26 mm (arrow); B and C: ADC map (B) and DWI image (C) show a marked hypo- and hyperintensity, respectively, in relation to restriction of diffusion (white arrows); D: DCE image with significant enhancement of the lesion (arrow). The characteristics of the nodule are compatible with a PIRADS 5 lesion and the marked restriction of the diffusion suggests a high-grade clinically significant prostate carcinoma, confirmed by the results of a MRI-guided transrectal ultrasound prostate biopsy (Gleason 4 + 4).

v2 model (see PIRADS reporting and interpretation model, version 2), the T2W sequence is key to the diagnosis of PCa in the transition zone^[11] (Figure 3A). It is also useful in the diagnosis of local dissemination^[14].

FUNCTIONAL SEQUENCES

Diffusion sequences

Diffusion sequences [diffusion-weighted MRI (DW-MRI) and apparent diffusion coefficient (ADC)] are performed in the axial plane and include the prostate and seminal vesicles (Figure 3B and C). These sequences are used primarily to evaluate the movement of the free water molecules in the interstitial space and through the cellular membrane. The behavior of lesions on DW-MRI and ADC is conditioned by cell density, the extracellular space, the integrity of cell membranes, and the extent of glandular organization. A correct assessment is based on a qualitative (high *b*-value DWI) and quantitative (ADC map) evaluation of the images. In PCa, the presence of impeded diffusion appears as a high signal intensity on the DWI and low intensity on the ADC map^[13].

PCa presents architectural changes that restrict water diffusion. The more aggressive the tumour, the more pronounced these changes tend to be. For this

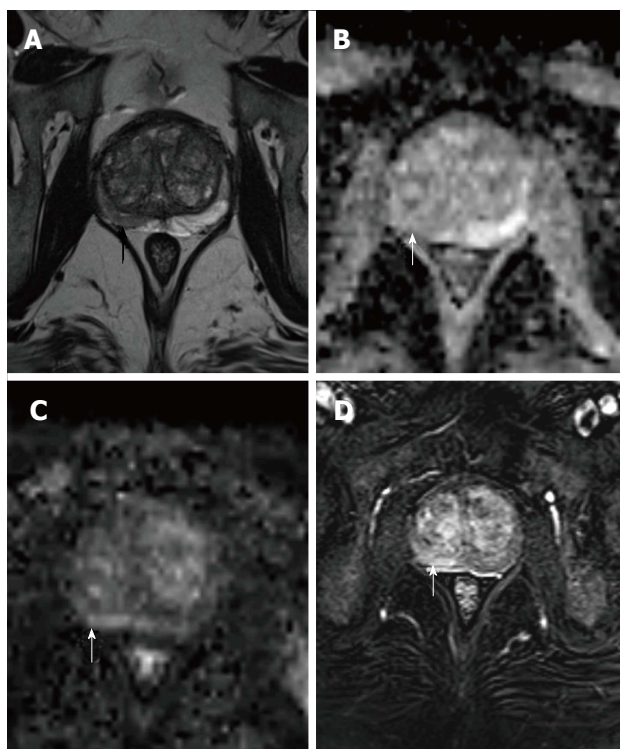


Figure 4 Prostate magnetic resonance imaging of a 64-year-old patient. A: T2-weighted image shows an area of hypointensity in the right peripheral zone of the midgland of the prostate (black arrow); B: A discrete restriction of diffusion in ADC map (white arrow); C: DWI image (white arrow); D: Enhancement on DCE image (white arrow), suggestive of prostatitis, confirmed by transrectal ultrasound biopsy.

reason, diffusion sequences are valuable not only to characterise lesions likely to be malignant, but also to help to predict the Gleason score of the lesions^[15,16] (Figure 3). Benign lesions, such as those occurring secondary to prostatitis, usually present less diffusion restriction (Figure 4)^[17].

According to the PIRADS v2 model, diffusion sequences are crucial to the diagnosis of PCa in the peripheral zone and in characterising indeterminate lesions in the transition zone^[12] (Figure 5B and C).

Dynamic contrast-enhanced sequences

Dynamic contrast-enhanced (DCE)-MRI is performed in the axial plane and includes the prostate and seminal vesicles. This sequence is performed prior to endovenous gadolinium administration and up to 4 min afterwards (Figure 5D).

In malignant lesions, the most common phenomenon observed on DCE-MRI is early uptake of the contrast material and early washout (Figure 5D). However, this behaviour is relatively variable and sometimes overlaps with that of benign lesions. According to PIRADS v2, although DCE sequences have a secondary value, their main value is in their contribution to the characterization of indeterminate lesions in the peripheral zone^[12].

Pharmacokinetic models of DCE-MRI perfusion allow us to quantify various parameters to evaluate contrast perfusion, including k^{trans} (the volume transfer

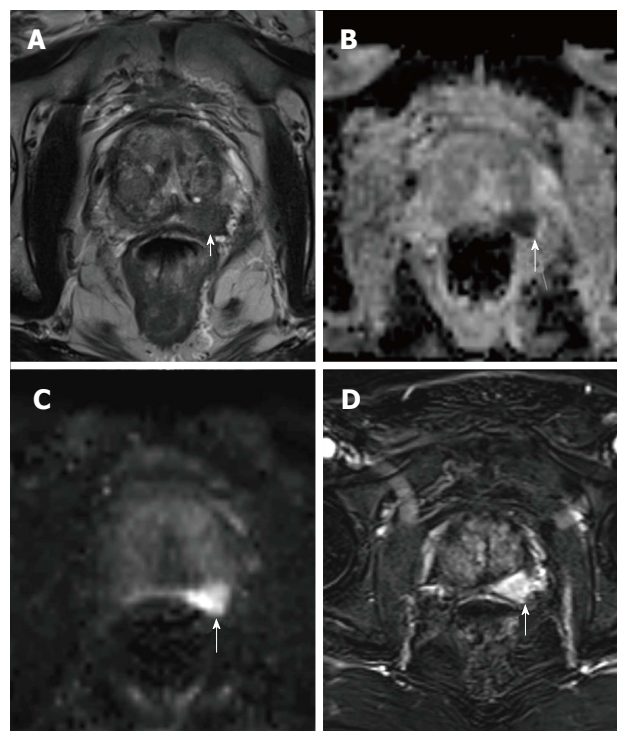


Figure 5 An 82-year-old patient with PIRADS 5 lesion in the basal left peripheral zone showing hypointensity (white arrows) in T2-weighted image (A), restriction of diffusion in apparent diffusion coefficient map (B) and diffusion-weighted magnetic resonance image (C), DCE shows significant early enhancement of the suspicious area (D). MRI-guided transrectal ultrasound biopsy confirmed a clinically significant prostatic carcinoma (Gleason 5 + 4). DCE: Dynamic contrast enhancement; MRI: Magnetic resonance imaging.

constant, which reflects the efflux rate of gadolinium contrast from the vascular compartment through the endothelium to the interstitial space), k_{ep} (rate of return to the vascular space), and V_e (the fractional volume of the extracellular tumour space). Using these data, it is possible to build parametric maps that represent the intratumoral heterogeneity of the spatial distribution of these parameters. However, at present, no conclusive results are available to support the use of these parameters for diagnostic purposes.

PIRADS ACQUISITION, INTERPRETATION, AND REPORTING MODEL, VERSION 2.0

A consensus-based model - PIRADS v2 - has been developed for interpreting and scoring mpMRI results. Several organizations, including the European Society of Urogenital Radiology (ESUR), American College of Radiology (ACR), and the AdMeTech Foundation, participated in the development of this model. The main objective of the model - aside from standardizing acquisition, interpretation and reporting protocols - is to predict the probability of clinically significant PCa by hierarchically organizing the information obtained in each MRI sequencing modality according to whether the lesion is located in the peripheral or transitional zone^[11,12]. Although this model has some limitations, its implementation has served to reduce intra- and inter-

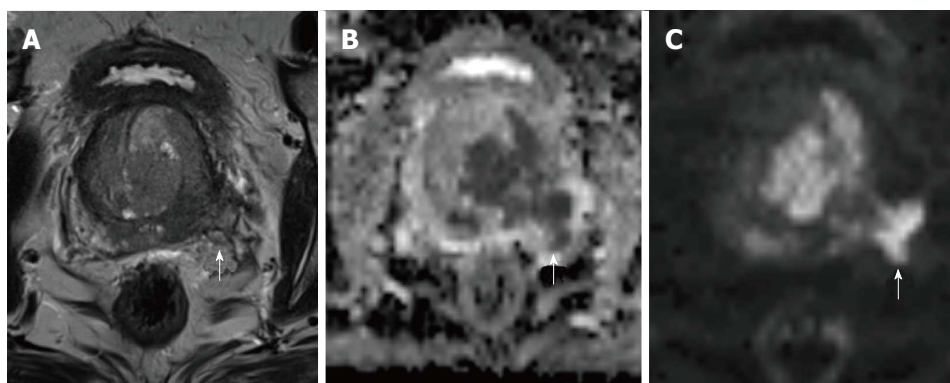


Figure 6 Prostate carcinoma with extracapsular extension in a 72-year-old patient. A: T2-weighted axial image of the pelvis at the level of midgland of the prostate shows a marked hypointensity in the left peripheral zone and disruption of the "capsule", distorting the normal anatomy of the left neurovascular bundle with measurable extracapsular extension (ESUR Score 5); B and C: ADC map (B) and DWI-images (C) demonstrate a significant restriction of diffusion, with hypointensity in the ADC and hyperintensity in the DWI-images that extend beyond the prostate "capsule" (arrows). Surgical specimen confirmed a pT3a prostate carcinoma. ADC: Apparent diffusion coefficient; DWI: Diffusion-weighted magnetic resonance imaging.

Table 1 European Society of Urogenital Radiology scoring of extracapsular extension in prostate cancer

Findings	Score
Abutment	1
Irregularity	3
Neurovascular bundle thickening	4
Bulge, loss of capsule	4
Measurable extra-capsular disease	5

observer variability as well as to increase the diagnostic yield of mpMRI.

EQUIPMENT

The minimum technological requirements necessary to guarantee that mpMRI assessment is performed to an acceptable quality standard have been defined by consensus agreement^[11]. This consensus establishes, as a minimum requirement, that MRI equipment should be at least 1.5T magnetic field strength. The use of endorectal coil is only essential in older 1.5T equipment because newer MRI equipment at 1.5T and 3T are both capable of obtaining reliable image quality without the need for coils. The elimination of the need for endorectal coils is beneficial because it reduces imaging time, thus increasing patient comfort^[11].

STAGING

Local staging

MRI is the imaging technique of choice to determine whether the tumor is organ-confined or extra-glandular. In the year 2012, the ESUR proposed a 5-point scale to establish the probability of extracapsular extension (ECE) based on direct and indirect signs^[14] (Table 1 and Figure 6).

Schieda *et al.*^[18] evaluated the ability of this 5-point scoring system to predict ECE compared to a "non-standardized" reporting modality. Those authors

concluded that the optimal sensitivity/specificity was achieved with a score of " ≥ 3 ". In addition, the scale was more sensitive than the non-standardized modality (59.5% vs 24.5%, $P = 0.01$) without significant differences in specificity (68.0% vs 75.0%, $P = 0.06$).

Several clinical nomograms are available to predict the likelihood of ECE. The two most common nomograms are the Partin tables (which include several variables: PSA, biopsy-based Gleason score, and clinical stage)^[19] and the nomogram developed at the Memorial Sloan-Kettering (MSK) Cancer Center (which adds prostate biopsy results - specifically, the percentage of positive cylinders)^[20]. Recently, Feng *et al.*^[21] conducted a retrospective study of 112 patients who underwent mpMRI prior to RP to determine if mpMRI could improve the predictive capacity of the Partin tables and the MSK nomogram for ECE. The authors found that the area under the curve (AUC) for the Partin and MSK nomograms for predicting ECE was 0.85 and 0.86, respectively. When mpMRI was added, the AUC increased, respectively, to 0.92 and 0.94.

In the most recent guidelines published by the European Society of Urology, mpMRI has been included as a local staging technique in the following patient risk groups: High-risk disease; intermediate risk disease with predominantly Gleason pattern 4; and low-risk disease if mpMRI is considered necessary for treatment planning^[11].

Staging of distant disease

The diagnosis of metastatic disease is essential to ensure proper therapeutic management and MRI has proven its value as a diagnostic tool for metastasis (Figure 7). In a recently published meta-analysis, Shen *et al.*^[22] compared the relative utility of choline PET/CT, MRI, and bone scintigraphy in the diagnosis of bone metastasis in patients with PCa. The authors reported sensitivity values, respectively of 91%, 97%, and 79% and specificity values of 99%, 95%, and 82%. These differences between these imaging modalities

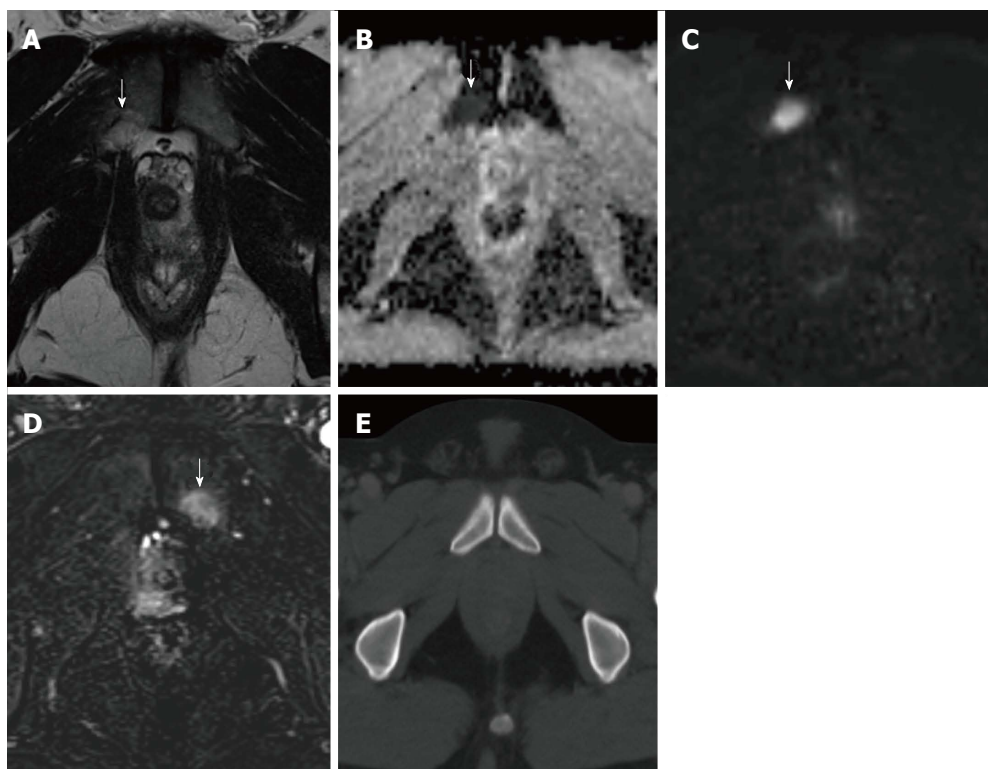


Figure 7 A 54-year-old patient with recently diagnosed prostate carcinoma. A: T2-weighted axial image of the pelvis shows an ill-defined hyperintense area in the right pubis (arrow); B and C: ADC map (B) and DWI images (C) show restriction of diffusion in the same area (arrow); D: DCE image presents enhancement of the lesion after IV gadolinium (arrow). MRI findings were suspicious for pelvic bone metastasis, with no evidence of such lesion on staging abdomino-pelvic CT scan performed a week earlier (E) and in a previous bone scintigraphy (not shown). Bone metastasis was confirmed on clinical evolution. MRI: Magnetic resonance imaging; DCE: Dynamic contrast-enhanced; CT: Computed tomography.

were statistically significant, with bone scintigraphy significantly less sensitive and less specific than the other two techniques. By contrast, MRI presented the highest diagnostic sensitivity for detecting metastasis.

Lecouvet *et al.*^[23] evaluated 100 patients at a high risk of metastasis to compare the diagnostic yield of whole-body DW-MRI vs CT and bone scintigraphy with Technetium Tc 99m (supported by simple X-ray when necessary) in the diagnosis of bone and nodal metastasis. Bone scintigraphy (\pm X-ray) plus CT had a sensitivity of 84% vs 91%-94% for whole-body DW-MRI ($P < 0.05$); specificity values were, respectively, 94%-97% vs 91%-96% ($P > 0.05$). The authors conclude that one-step, whole-body MRI can effectively assess nodal and bone metastasis in patients with high-risk PCa, thus eliminating the need for multimodal diagnosis (Figure 8).

Conde-Moreno *et al.*^[24] compared whole-body DW-MRI to choline PET/CT in the diagnosis of metastatic disease, finding that choline PET/CT had a greater sensitivity whereas whole-body DW-MRI had a greater specificity. Given these findings, the authors conclude that these techniques are complementary.

The value of MRI in the diagnosis of bone and nodal metastasis has been recognized by the ESUR^[14]. The European Society of Urology also contemplates the use of MRI as an alternative technique to detect possible metastasis in intermediate and high-risk patients^[11].

Re-staging following recurrence after radiotherapy

Reported 5-year biochemical relapse rates after radiotherapy range from 15% in low-risk patients to 67% in high-risk cases^[9]. Both DW-MRI and DCE-MRI allow us to detect recurrences after radiotherapy. In a group of 24 patients who developed biochemical relapse following radiotherapy, Kim *et al.*^[25] performed prostate mpMRI at 3T (phased array coil), followed by TRUS-guided biopsy. They assessed the diagnostic performance of both DW-MRI and DCE-MRI to detect recurrent disease. The sensitivity, specificity, and diagnostic accuracy of DW-MRI were 49%, 93%, and 82%, respectively, vs 49%, 92% and 81% for DCE-MRI. Combined DW-MRI and DCE-MRI resulted in a sensitivity, specificity, and diagnostic accuracy of 59%, 91% and 83%, respectively.

Tamada *et al.*^[26] demonstrated the diagnostic value of mpMRI to assess recurrence after brachytherapy, reporting a sensitivity of 77%, specificity of 92%, and diagnostic accuracy of 90%.

IMPACT OF MPMRI ON TREATMENT DECISIONS FOR RADIOTHERAPY

Impact on the therapeutic strategy (EBRT)

Several studies have evaluated the impact of mpMRI staging on PCa risk group classification and on treatment decisions for EBRT (Table 2). Couñago *et al.*^[6] assessed

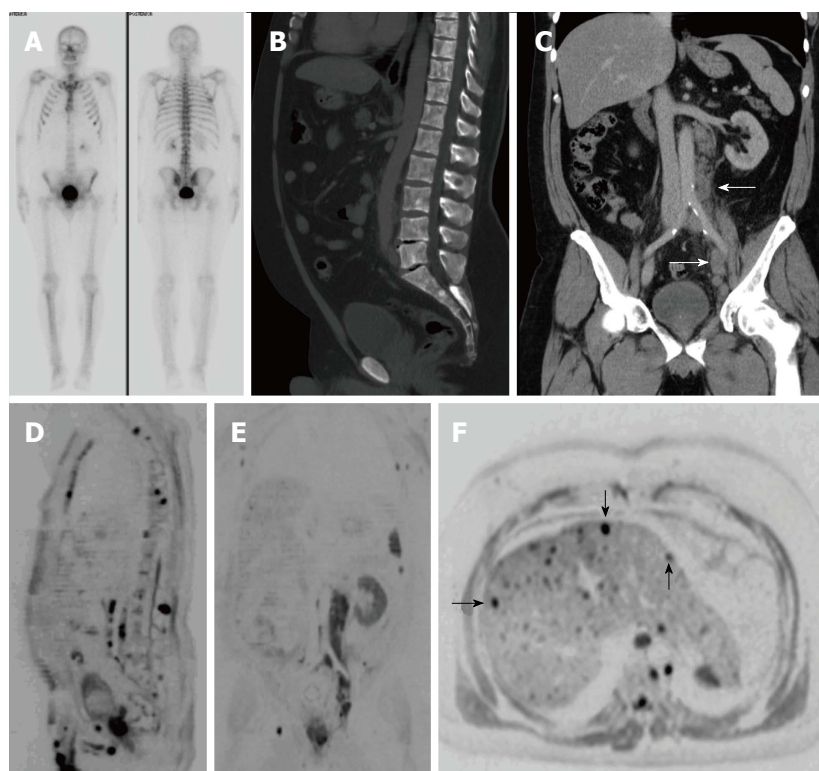


Figure 8 A 51-year-old patient with a history of Gleason 4 + 5 prostate carcinoma treated with hormone therapy. A: Re-staging bone scintigraphy was negative for bone metastases; B and C: Sagittal (B) and coronal (C) images of abdominal CT scan show a diffuse axial bone altered density that could not rule out bone metastases, along with multiple retroperitoneal and pelvic enlarged nodes suggesting malignant adenopathies (white arrows in C); D and E: Sagittal (D) and coronal (E) whole-body MRI images clearly show multiple bone metastases and adenopathies, along with hepatic nodules (black arrows in F, axial abdominal MRI) suspicious for metastatic disease. MRI: Magnetic resonance imaging.

274 patients staged initially by DRE and TRUS and subsequently by 3T mpMRI prior to the final EBRT treatment decision. The risk group classification shifted after mpMRI in 32.8% of cases after all factors (PSA, Gleason score and T-stage) were considered. In addition, in 43.8% of cases (52.5% depending on criteria used to indicate or not ADT in intermediate-risk patients), this led to a change in some aspect(s) of the radiotherapy treatment (treatment volume, dose, and ADT). Finally, the mpMRI results were validated in the subgroup of surgical patients, showing a 70.0% sensitivity and 93.8% specificity for ECE.

Panje *et al*^[8] evaluated 122 patients staged using 1.5T or 3T (38% of sample) phased-array-body coil MRI. Most (53.3%) patients had received ADT prior to the mpMRI. The authors found that the use of mpMRI resulted in risk group modification in 28.7% of cases. Because the influence of 1.5T MRI and the use of ADT prior to mpMRI on the results is not known, it is difficult to perform a direct comparison with other studies.

Liauw *et al*^[27] evaluated the role of endorectal coil mpMRI at 3T prior to EBRT in a group of 122 PCa patients, finding that mpMRI resulted in a change in therapeutic approach (indication for active surveillance, brachytherapy in monotherapy and dose modification, treatment volume, and use of ADT in EBRT) in 18% of patients. Recently, Pullini *et al*^[28] prospectively evaluated 44 patients with PCa to determine the impact of mpMRI at 3T on staging and treatment decisions for EBRT, finding that staging by mpMRI resulted in a change in risk group classification in 41% of patients, thus potentially impacting the EBRT treatment decision.

Based on the studies described above, it is clear that

mpMRI staging has a significant impact on radiotherapy treatment decisions, with risk group modifications ranging from 18% to 41% of patients, depending on the study. This wide variability may be attributable to numerous different factors, including the following: The MRI (magnet and coil, protocol used, experience of the radiologist); the initial clinical staging (experience of the clinician with DRE/TRUS, the use of CT to evaluate pelvic lymph nodes, *etc.*); the clinical characteristics of the patient cohort; the treatment protocol at each centre (dose, fractionation, target volume, indication for ADT, use of brachytherapy, *etc.*); the use of ADT prior to MRI; and finally the inclusion (or not) of metastatic patients in the final results.

Despite this heterogeneity, one finding common to all these studies is that a large percentage of patients staged by mpMRI are upstaged compared to conventional clinical staging. As a consequence, mpMRI staging implies that more patients will be classified as intermediate risk, high-to-very high risk, or metastatic patients. Nevertheless, it is worth noting that risk group downgrading has been reported in a small percentage (4%-12%) of patients^[8,28].

Despite the clear influence of mpMRI staging on EBRT treatment decisions, numerous questions remain unresolved. For instance, we do not know which patient groups would benefit most, in terms of cost-effectiveness, from mpMRI staging. Nor is it clear if changes in therapeutic management based on MRI findings will increase survival and/or quality of life in these patients. The clearest example of this can be seen in low-risk patients in which upstaging after mpMRI is common (20%-50%) even though long-term biochemical control

Table 2 Studies evaluating the impact of the staging using magnetic resonance imaging in prostate cancer patients treated with radiotherapy

Ref.	Year	Type of MRI	No. of patients	Field strength	Coil	Tumor stage shift (%)	Risk group changes (%)	Change in RT (CTV, doses, HT) (%)	Technique validation
Jackson <i>et al</i> ^[75]	2005	Morphological	199	1.5T	PAB	55	NR	32.6 ²	No
Couñago <i>et al</i> ^[76]	2014	Multiparametric	103	3T	PAB	94.1	33.9	33.9	Yes
Chang <i>et al</i> ^[77]	2014	Morphological	115	1.5T	PAB	68.6	7	20 ¹	No
Panje <i>et al</i> ^[8]	2015	multiparametric	122	1.5T and 3T	PAB	55.7	28.7	30	No
Horsley <i>et al</i> ^[78]	2015	Morphological	509	1.5T	PAB	20	9	18	No
Yamaguchi <i>et al</i> ^[79]	2015	Morphological	157	1.5T	PAB	25	9	8 ¹	No
Couñago <i>et al</i> ^[6]	2015	Multiparametric	274	3T	PAB	90.4	32.8	43.8 or 52.5 ³	Yes
Pullini <i>et al</i> ^[28]	2016	Multiparametric	44	3T	PAB	65.9	40.9	NR	No
Liauw <i>et al</i> ^[27]	2016	Multiparametric	122	3T	PAB	NR	18	22	No

¹Exclusive assessment of the CTV change; ²Data from T1-T2 to T3-T4 upstaging; ³Values according to the HT criteria in intermediate-risk patients. PAB: Phased-array-bodycoil; NR: Not reported; CTV: Clinical target volume; HT: Hormonal therapy.

in this risk cohort (staged exclusively by conventional DRE) and treated with EBRT is excellent (93% at 10 years' follow up)^[29]. Therefore, we must exercise caution with regard to the changes in tumour stage that can result from the use of these newer, more precise imaging tests. In this sense, more prospective, multicentric studies are needed to better clarify the role of mpMRI prior to EBRT.

Contouring and treatment planning in EBRT

MRI has proven to be highly useful in radiation oncology in improving the accuracy of treatment volume delineation. The use of MRI allows for more precise identification of the prostate gland location and thus more accurate contouring, especially of the prostate apex, which can help to avoid over- or under-estimation of the microscopic volume that commonly occurs with CT-based contouring^[30].

mpMRI can also help to rule out the presence of high-grade disease in the transition zone at the anterior base, thus allowing for lower doses to the bladder neck. In addition, MRI is highly useful in identifying the anatomic structures involved in erections: The internal pudenda artery, the periprostatic nerve fibers, and the penile bulb. The improved anatomic definition of these structures with mpMRI could help to limit the radiation dose to these areas, which could potentially lead to higher rates of erectile function preservation and, consequently, better quality of life^[30]. Therefore, compared to CT-based treatment volumes, MRI allows for the delineation of a smaller clinical target volume (CTV), distinguishing the CTV from normal tissue, suggesting that MRI-based contouring can reduce treatment-related toxicity in PCa^[8].

The reliability of mpMRI in tumour staging plays an increasingly important role in advanced radiotherapy techniques such as intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT). In these highly-conformal techniques with narrow treatment margins, it is vitally important to accurately detect the presence of extracapsular disease or seminal vesicle invasion and to include these areas within

the treatment volume to avoid geographic loss and, consequently, underdosing^[8].

DETECTION OF RELAPSE AFTER RADICAL PROSTATECTOMY

PSA levels become undetectable after RP; however, depending on the pathological stage and other risk factors, up to 60% of patients with PCa will eventually develop biochemical relapse (defined as PSA > 0.2 ng/mL with two consecutive rises)^[31].

Current cancer treatment guidelines recommend SRT after RP if the PSA remains elevated or if biochemical relapse is detected during follow-up^[32]. In both of these clinical scenarios, the elevated PSA may be secondary to local disease (associated or not with a significant risk of metastasis) and/or distant disease. Although SRT is one of the potentially curative treatments in these cases, with cause-specific survival rates up to 3 times greater than observation alone^[33], up to 50% of patients will develop a recurrence in the 10 years following SRT. These poor outcomes may be due to a variety of factors, including: (1) tumour-related factors associated with a greater risk of biochemical progression and worse disease-free survival, including the following: Initial PSA; Gleason 8; involvement of the seminal vesicles; infiltrated resection margins; early biochemical relapse; and PSADT; (2) delayed initiation of SRT when the PSA is > 1 ng/mL and palpable disease is evident on DRE; and (3) SRT-related factors (which merit more research to define the optimal therapeutic strategy for disease control): If the exact location of the relapse site is unknown, this can result in an inadequate CTV, underdosing, and the need for systemic treatment.

SRT is most effective when administered before the PSA reaches 0.5 ng/mL^[34]. However, with such low PSA levels, conventional imaging tests - TRUS, bone scintigraphy, and CT - are of little use in detecting the recurrence. In recent years, mpMRI has become more widely used in the detection of local recurrences. Indeed, it is the only imaging technique recommended by the ESUR to evaluate pelvic recurrences in patients

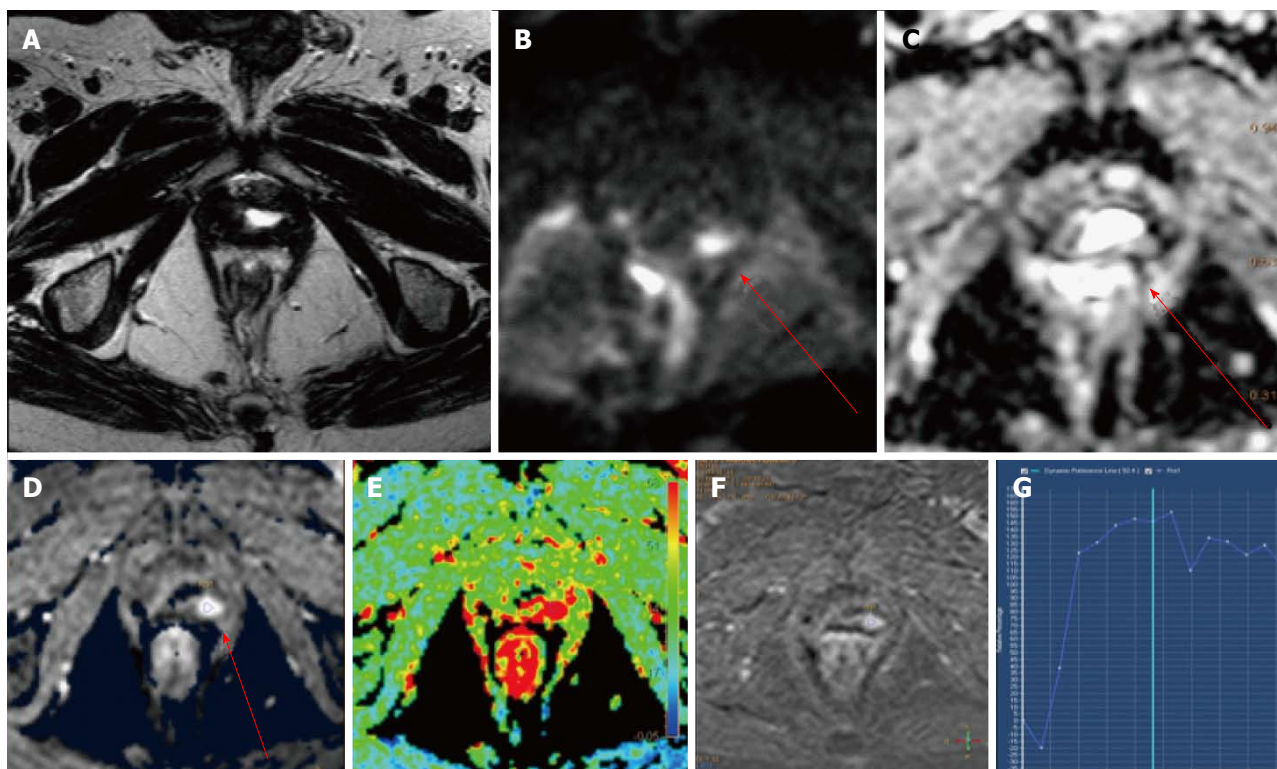


Figure 9 Multiparametric magnetic resonance imaging of local recurrence. A: Morphological study: Axial T2-weighted fast-spin echo image. No recurrence is detected; B-F: Functional study; B and C: Axial diffusion sequences showing restricted diffusion in ADC map (arrow); D-G: Axial gradient-echo T1-weighted images showing focal enhancement in dynamic study (D) (arrow), color map (E) and curve (G).

with low (0.2-2 ng/mL) PSA levels^[14].

Although no protocol has yet been established for the use of MRI in SRT, in most published studies the approach does not differ from that used to assess the prostate in cases with a suspected tumour or local dissemination.

In local relapse, the most common patterns observed on MRI are slightly hyperintense lesions on T2W sequences and hypervascular lesions on the DCE-MRI. Cirillo *et al.*^[35] showed that adding DCE to T2W sequences improved detection rates for local relapse after RP: Unenhanced and contrast-enhanced MRI yielded, respectively, the following outcomes: Sensitivity (61.4% vs 84.1%), specificity (82.1% vs 89.3%), positive predictive value (84.4% vs 92.5%), negative predictive value (57.5% vs 78.1%), and accuracy (69.4% vs 86.1%). In diffusion imaging, the radiological appearance of local recurrence may be similar to the tumour, with high signals in the diffusion sequences and low signals in the ADC map (Figure 9). PIRADS v2 is not applicable in local relapses, although it may be in the future.

Incidence of recurrences detected by mpMRI

Multiple authors have investigated the capacity of mpMRI to detect post-prostatectomy relapses, with detection rates ranging from 84%-95% in series that use endorectal coil MRI in patients with median PSA > 1 ng/mL, many of whom also had palpable disease

on DRE^[9,35,36]. Other studies carried out in patients with lower PSA levels (median PSA, 0.3-0.59 ng/mL) by endorectal coil MRI^[37,38] and/or pelvic MRI have reported recurrence rates ranging from 24%-91%^[39-42] (Table 3). This variability among studies is likely due to several factors, including: Retrospective study design; sample size and sample heterogeneity; differences in the radiologists' experience level; the use of different MRI sequencing modalities; and difference in relapse criteria.

Results from a retrospective study^[43] and from a meta-analysis^[44] suggest that the ¹¹C or ¹⁸F-choline PET/CT has a higher detection rate for local, nodal, or metastatic recurrences post RP when the PSADT is < 6 mo and PSA values are > 1 ng/mL. By contrast, in patients with lower PSA values, mpMRI has proven to be more sensitive in detecting local recurrences^[22,45-48] and in small-sized (< 10 mm) local relapses^[47]. Other authors have found that diagnostic rates for visible pelvic relapses are higher when mpMRI and PET/CT are combined vs MRI or choline PET/CT alone^[49-51]. Recently, studies that investigated the use of PET/CT with PSMA (prostate-specific membrane antigen) ligands have reported higher detection rates for local relapse compared to choline PET/CT, even in cases with low PSA levels^[52]. However, other authors, including Freitag *et al.*^[53], have found that adding MRI to PET provides additional value even when ⁶⁸Ga-PSMA-11 is used as a tracer in PET/CT.

Table 3 Studies on multiparametric magnetic resonance imaging with low prostate-specific antigen levels for the diagnosis of local recurrence after radical prostatectomy

Ref.	Year	Desing	Coil and Magnet	No. of patients	PSA (mean or median)	Mean or median lesion size	Reference standard	% rRL	MRI sequences, Se, Spe, PPV, NPV, Acc
Linder <i>et al</i> ^[38]	2007	Retrospective	PAC + ERC 1.5T and 3T	187	0.59 ng/mL	10 mm	TRUS biopsy, PSA reduction after SRT or increased lesion size on serial imaging	91	T2 + DCE Se: 91% Spe: 45% PPV: 85% NPV: 60%
Rischke <i>et al</i> ^[39]	2012	Retrospective	PAC 1.5T	33	0.30 ng/mL	11 mm	PSA reduction after SRT and changes in MRI after SRT	67	T2 + DCE Se: 67% Spe: 100% PPV: 100% NPV: 83% Acc: 83%
Liauw <i>et al</i> ^[37]	2013	Retrospective	ERC 1.5T and 3T	88	0.30 ng/mL	0.26 cc	None	24	T2 + DCE + DWI
Park <i>et al</i> ^[56]	2014	Retrospective	PAC 1.5T and 3T	113	0.43 ng/mL	12 mm	TRUS biopsy	NR	T2 + DCE
Verma <i>et al</i> ^[42]	2014	Retrospective	PAC 3T	90	0.20 ng/mL negative MRI 0.40 ng/mL positive MRI	NR	None	22.2	T2 + DCE + DWI
Couñago <i>et al</i> ^[40]	2015	Retrospective	PAC 3T	57	0.40 ng/mL	15.2 mm	None	24.6	T2 + DCE + DWI
Hernandez <i>et al</i> ^[41]	2015	Retrospective	PAC 3T	70	0.38 ng/mL	8.5 mm	None	47 (local + lymph nodes) 38.6 (local)	T2 + DCE + DWI

mpMRI: Multiparametric MRI; RP: Radical prostatectomy; rRL: Radiographic local recurrence; T2: T2-weighted imaging; DCE: Dynamic contrast-enhanced imaging; DWI: Diffusion-weighted imaging; Se: Sensitivity; Spe: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; Acc: Accuracy; PAC: Phased-array coil; ERC: Endorectal coil; NR: Not reported, SRT: Salvage radiation therapy.

Clinical factors associated with mpMRI findings

Several factors, including PSA levels at recurrence, the PSADT, and the presence of compromised resection margins, have all been significantly associated with mpMRI findings. Several authors have defined pre-radiotherapy PSA cut-off values, ranging from $> 0.3^{[37]}$ to $> 0.5^{[40]}$ or $\geq 0.54^{[39]}$ ng/mL, as clinical predictors of MRI positivity. Eifler *et al*^[19] reported a higher probability of visible local relapse in patients with PSADT > 14 mo. In addition, a PSADT < 6 mo has been associated with higher incidence of nodal relapse, even with PSA levels < 1 ng/mL. Hernández *et al*^[41] reported a median PSADT of 5.12 mo in patients with nodal recurrence vs 12.7 mo in patients without evidence of nodal disease on MRI ($P = 0.17$). Finally, a study that used MRI lymphography (ferumoxtran-10) to assess nodal involvement found that patients with positive lymphography presented a median PSADT of 3.8 mo^[54].

Topography of recurrences

Most local recurrences occur in the peri-anastomotic and retrovesical regions^[41,55,56], although up to 22% of recurrences have been diagnosed at the resection site of the vas deferens^[57].

Efficacy of mpMRI to detect nodal relapse

Data on the efficacy of MRI to detect nodal relapses after RP are scant, particularly in patients with low PSA

values. However, an incidence between 5%-10% has been estimated^[37,41], most commonly involving the external iliac lymph node chains. It has been suggested that DW-MRI could increase the detection of nodal relapses, with a reported 90% efficacy rate in nodes < 1 cm^[58] (Figure 10).

The two studies that used MRI with ferromagnetic contrast (ferumoxtran-10) to evaluate patients with biochemical relapse after RP reported positive nodes (< 1 cm) in 72% and 20% of patients, respectively, even with low PSA levels^[54,59]. The main limitation of these studies is that ferumoxtran-10 was authorized only for research purposes.

Detection of bone metastasis

Recent research suggests that the use of whole-body MRI (WB-MRI), together with WB-DW-MRI, may allow assessment of nodal recurrence and bone metastasis with a single imaging modality. These approaches show greater sensitivity and specificity than conventional imaging and will facilitate the evaluation and monitoring of response to systemic treatments^[60].

IMPACT OF MPMRI ON SRT TREATMENT DECISIONS

The impact of mpMRI on the efficacy of SRT is not known, but use of mpMRI is becoming increasingly

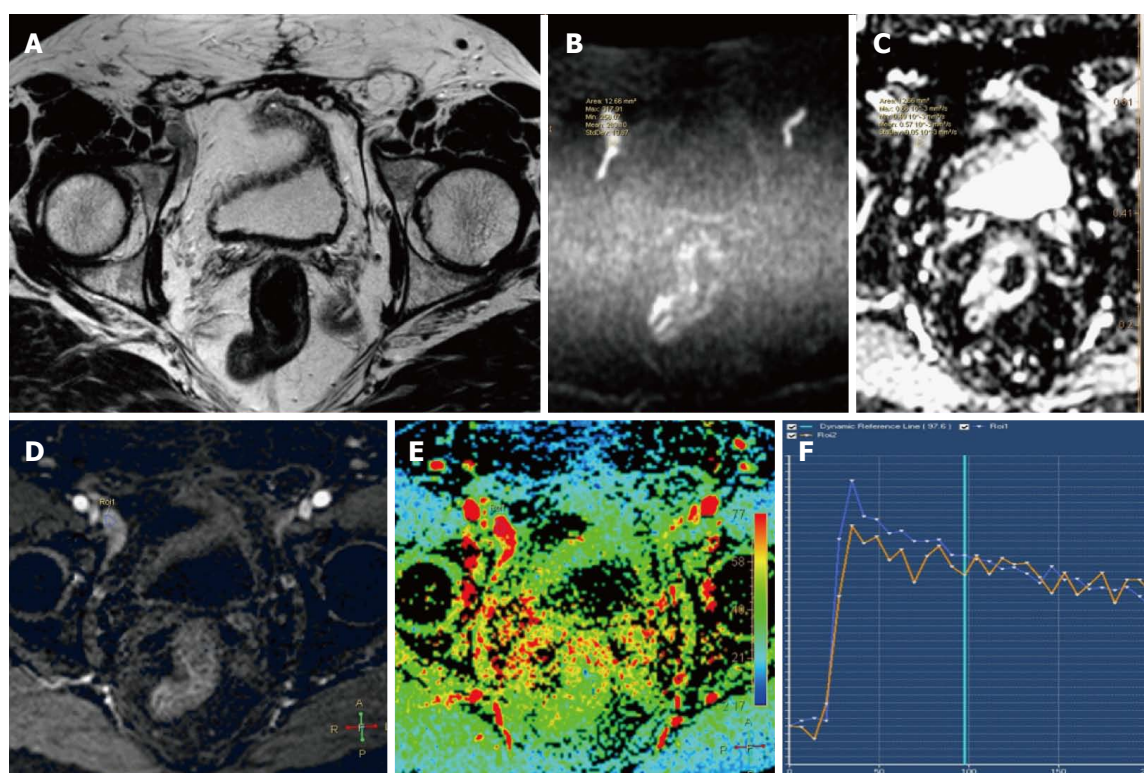


Figure 10 Lymph node study. A: Axial T2-weighted fast-spin echo image shows right external iliac lymph nodes; B and C: Axial diffusion sequences; C: Restricted diffusion in ADC map; D: Axial gradient-echo T1-weighted perfusion image showing a high peak enhancement; E: Color map; F: Curve; ADC: Apparent diffusion coefficient.

common in the evaluation of disease dissemination in patients with biochemical relapse after RP. The information provided by mpMRI is integrated into the decision-making process for SRT planning, as follows.

Definition of the CTV

Individualized treatment planning should assure that the relapse site is included within the CTV in accordance with published guidelines.

Irradiation (or not) of the lymph node stations:

The benefits of elective pelvic irradiation in SRT is controversial since currently available data include only retrospective studies; however, findings from those studies suggest that pelvic irradiation increases both biochemical control^[61] and biochemical relapse-free survival^[62]. It has been suggested that RP may lead to changes in the lymphatic drainage pattern and that these are not adequately included in the CTV when contoured according to current recommendations^[63,64].

Irradiation of oligometastatic bone disease:

Currently, the decision to irradiate oligometastatic bone lesions is considered on an individual basis by consensus at multidisciplinary urological tumour boards, or in the context of a clinical trial.

It would be interesting to investigate the impact of irradiating only the nodal stations in patients with a short PSADT whose mpMRI images indicate the presence of nodal disease without prostate bed

involvement. Similarly, it would also be interesting to conduct a study in which patients with a long PSADT (> 10 mo) and local disease alone received irradiation only to the local disease site. In both of these scenarios, the impact of ablative RT techniques such as stereotactic body radiotherapy (SBRT) should be investigated.

Dose escalation

We hypothesize that treating the prostatectomy bed at conventional doses while simultaneously increasing the dose to the relapse site detected on MRI could improve outcomes without increasing toxicity^[65]. In fact, high dose irradiation delivered exclusively to the relapse site could be curative and this approach would also minimize irradiation of healthy tissue, thus reducing the risk of side effects.

Adjuvant systemic treatment

The addition of hormone therapy to SRT remains controversial. In clinical practice, the trend is to administer combined treatment in patients with high-risk disease and/or poor prognostic factors. The RTOG 9601 study showed a significant increase in overall survival at 10 years in patients with post-RP biochemical relapse who were treated with SRT (64.8 Gy) plus bicalutamide 150 mg for 2 years vs patients who received RT alone [82% vs 78%, hazard ratio: 0.75 (95%CI: 0.58-0.98), $P = 0.036$]^[66]. The results of studies currently underway, such as RADICALS and RTOG 0534, should definitively determine the benefit of hormone therapy in patients

who undergo postoperative radiotherapy. However, it should be pointed out that none of the aforementioned trials have included mpMRI or PET/CT for the purpose of diagnosing and locating tumour recurrences. As we have suggested above, more intensive treatment at the relapse site could improve SRT outcomes, with or without hormone therapy.

FUTURE DIRECTIONS

The future of MRI in radiotherapy includes the following:

Monitoring response to radiotherapy

Various studies have shown the potential utility of ADC and K^{trans} to monitor response to radiotherapy in patients with PCa^[67,68]. This application of MRI could be used to investigate the impact of new focal therapies administered early in patients with persistent disease or local relapse.

Technological advancements that increase detection rates [PET/MRI and new radiotracers (PSMA)]

PET/MRI is a new multimodal imaging technique that improves diagnostic imaging, with a promising future in the evaluation of PCa. In addition to diagnosis and staging, PET/MRI plays an important role in detecting recurrences in patients with biochemical relapse. In bone metastasis, the use of PET/MRI improves the detection and characterization of bone lesions, especially with the use of new radiotracers (¹⁸F-FNa, PSMA, choline), providing functional information as well as greater anatomic information due to the incorporation of MRI^[50,69,70]. These data are essential for ablative radiotherapy.

The future of imaging in PCa will be marked by improvements in equipment and in the sequences and antennas used, especially 3T equipment, diffusion sequences, and multichannel surface coils (≥ 128 channels).

Implementation of MRI in the workflow of radiation oncology departments

It is worth highlighting the incipient but growing use of MRI in radiation oncology departments. MRI is used not only for simulations, workflow, and treatment planning, but it is also being incorporated into linear accelerators to guide radiotherapy treatment^[71].

Genetic testing and MRI

At least one study has been conducted showing that MRI and genetic testing can improve the reliability for risk stratification in patients with PCa^[72].

Guidelines for focal treatments

Several studies have assessed the role of MRI-guided dose escalation (EBRT or brachytherapy) to the dominant intraprostatic lesion^[73,74].

CONCLUSION

The data obtained from mpMRI imaging are increasingly being integrated into PCa staging, recurrence detection, and therapeutic management. mpMRI is also being incorporated into the workflow of radiation oncology departments due to its capacity to help define target volumes for radical radiotherapy and SRT after prostatectomy. Technological advances, such as PET/MRI combined with new radiotracers such as PSMA, can improve staging and recurrence detection, and assist in planning more accurate treatments.

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