Review – Prostate Cancer

Advances in Magnetic Resonance Imaging: How They Are Changing the Management of Prostate Cancer

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Abstract

Context: Although magnetic resonance imaging (MRI) is emerging as the most commonly used imaging modality for prostate cancer (PCa) detection, treatment planning, and follow-up, its acceptance has not been uniform. Recently, great interest has been shown in multiparametric MRI, which combines anatomic T2-weighted (T2W) imaging with MR spectroscopic imaging (MRSI), dynamic contrast-enhanced MRI (DCE-MRI), and diffusion-weighted imaging (DWI).

Objective: The aim of this article is to review the current roles of these MR techniques in different aspects of PCa management: initial diagnosis, biopsy strategies, planning of radical prostatectomy (RP) and external radiation therapy (RT), and implementation of alternative focal therapies.

Evidence acquisition: The authors searched the Medline and Cochrane Library databases (primary fields: prostatic neoplasm, magnetic resonance). The search was performed without language restriction from January 2008 to November 2010.

Evidence synthesis: Initial diagnosis: The data suggest that the combination of T2W MRI and DWI or MRSI with DCE-MRI has the potential to guide biopsy to the most aggressive cancer foci in patients with previously negative biopsies, increasing the accuracy of the procedure. Transrectal MR-guided prostate biopsy can improve PCa detection, but its availability is still limited and the examination time is rather long. Planning of RP: It appears that adding MRSI, DWI, and/or DCE-MRI to T2W MRI can facilitate better preoperative characterization of cancer with regard to location, size, and relationship to prostatic and extraprostatic structures, and it may also facilitate early detection of local recurrence. Thus, use of these MR techniques may improve surgical, oncologic, and functional management. Planning of external RT and focal therapies: MR techniques have similar potential in these areas, but the published data remain very limited.

Conclusions: MRI technology is continuously evolving, and more extensive use of MRI technology in clinical trials and practice will help to improve PCa diagnosis and treatment planning.

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1. Introduction

At present, the evaluation of prostate cancer (PCa) is based mainly on parameters such as the serum prostate-specific antigen (PSA) level, clinical stage, pathological findings at biopsy or after surgery [1,2]. The three cross-sectional imaging modalities—computed tomography (CT), ultrasonography, and magnetic resonance imaging (MRI)—have been tested in PCa patients, and they all have substantial limitations [3]. Recently, great interest has been shown in multiparametric MRI, which combines anatomic T2-weighted (T2W) imaging with MR spectroscopic imaging (MRSI), diffusion-weighted imaging (DWI), and/or dynamic contrast-enhanced MRI (DCE-MRI). The combination of anatomic, biologic, and functional dynamic information offered by multiparametric MRI promises to make it a successful imaging tool for improving many aspects of PCa management. There is a real need for clinicians to base therapeutic decisions not only on predictive methods and nomograms that include PSA, digital rectal examination (DRE) findings, and transrectal ultrasound (TRUS) biopsy findings, but also on imaging.

2. Evidence acquisition

The aim of this article is to review the current roles of multiparametric MRI techniques in different phases of PCa diagnosis and management and to suggest how these MR techniques may help address clinicians’ questions. We searched the Medline and Cochrane Library databases (primary fields: prostatic neoplasm, magnetic resonance; secondary fields: humans, spectroscopy, dynamic contrast, diffusion, early diagnosis, prostate biopsy, radical prostatectomy [RP], external radiation therapy [RT], focal therapies, recurrence). The search was performed without language restriction from January 2008 to November 2010. The search was limited to those 3 yr to produce an up-to-date article focused only on very recent studies.

3. Evidence synthesis

3.1. Technical aspects

Traditionally, MRI for PCa has been performed with a 1.5-Tesla (1.5T) scanner and endorectal coil. With the introduction of a higher field strength (3T), and, thus, higher spatial resolution, the endorectal surface coil can be used less frequently, which makes MRI more accessible [4,5]. Intense research has focussed on the use of complementary techniques to improve the detection, characterization, and staging of PCa by MRI. Proton MRSI provides metabolic information, DWI shows the Brownian motion of extracellular water molecules, and DCE-MRI visualises tissue vascularity, especially neoangiogenesis [6,7].

3.1.1. Magnetic resonance spectroscopic imaging

With MRSI, three-dimensional (3D) data are acquired from the prostate, with volume elements (voxels) ranging from 0.24 cm³ to 0.34 cm³ [8]. MRSI shows the relative concentrations of certain metabolites within voxels. In the prostate, the substances analyzed by MRSI are citrate, creatine, and choline. In PCa, citrate levels are reduced; creatine and choline levels are elevated. PCa can be distinguished from healthy peripheral zone tissue on the basis of the choline plus creatine-to-citrate ratio [9]. Unfortunately, some benign conditions, such as prostatitis and postbiopsy changes, may also result in an increase of the ratio [3,8]. MRSI is an accurate technique to localise and characterise PCa, and to monitor changes indicating progression or treatment response. MRSI requires a longer acquisition time and more expertise than other functional MRI techniques.

3.1.2. Diffusion-weighted imaging

In DWI, proton diffusion properties within water are used to obtain image contrast. The extracellular and intraductal water molecules move freely; therefore, in healthy prostate tissue within the peripheral zone, the so-called apparent diffusion coefficient (ADC) values are high. PCa tissue destroys the normal glandular structure of the prostate and also has a higher cellular density than healthy prostate tissue, resulting in decreased extracellular space. Therefore, the water molecule movement is restricted in PCa, and PCa shows lower ADC values than surrounding, healthy, peripheral-zone prostate tissue [6,8]. DWI examination can be obtained rapidly without the use of contrast medium. Thus, of all the functional MRI techniques, DWI is the most practical and simple to use. DWI has the disadvantages of being susceptible to motion and magnetic-field homogeneities.

3.1.3. Dynamic contrast-enhanced magnetic resonance imaging

DCE-MRI consists of the acquisition of sequential images using T1-weighted sequences during the passage of a contrast agent (gadopentetate dimeglumine) within the prostatic tissue. The pharmacokinetics of gadolinium-based contrast agents in the prostate produce different enhancement patterns in PCa and benign tissues. The technique is based on the assessment of neoangiogenesis, which is an integral feature of tumours. DCE-MRI parameters can often be estimated both qualitatively and quantitatively, and the parameters frequently reported are onset time of signal enhancement, time to peak, peak enhancement, and washout [3]. DCE-MRI is limited by a lack of standardised acquisition protocols and analytic models. DCE-MRI has high sensitivity, which can be useful for initial evaluation of potential tumour locations.

3.2. Initial diagnosis and biopsy strategies

3.2.1. Initial diagnosis and indication for prostate biopsy

As defined by the 2010 European Association of Urology guidelines [1], the primary methods for diagnosing PCa include DRE, testing for serum concentration of PSA, and TRUS-guided prostate biopsy.

Individually, the functional MRI techniques (MRSI, DWI, and DCE-MRI) have shown the potential to add value to conventional anatomic MRI in PCa detection (Fig. 1) [10–14]. Because they have relatively high specificity in
comparison with PSA, their use could prevent unnecessary, systematic, random biopsies and delay of diagnosis and treatment (Table 1). It is essential to know if combining more than one functional MR technique could improve results even further. In a small prospective study (19 cases), which used prostatectomy as the standard of reference, the combination of DWI with either MRSI or DCE-MRI (1.5T MRI) increased area under the curve (AUC) values for detection of PCa tumours from 0.65–0.71 to 0.94. Adding a third functional MRI technique did not further improve detection (the AUC value for DWI, DCE, and MRSI together was 0.95) [11]. In a recent logistic regression analysis (42 cases with prostatectomy as the standard of reference), the ADC value at DWI (AUC = 0.69) was the best performing single parameter for PCa detection when compared with T2-weighted imaging and DCE-MRI parameters [10]. Because the clinical significance of PCa is related to Gleason grades, Villeirs et al. [15] investigated in 356 subjects (mean serum PSA = 11.5 ng/ml) the ability of MRSI (1.5T MRI) to predict the presence or absence of high-grade (Gleason score ≥4 + 3) PCa in men with elevated PSA. They found MRSI had significantly higher sensitivity for high-grade PCa (92.7%) than for lower grade tumours (67.6%) and a 7.4% false-positive rate.

Multiparametric MRI techniques may also contribute to the detection of transition-zone PCa. In a retrospective

| Table 1 – Initial diagnosis and determination of need for prostate biopsy |
|---------------------------------|---------------------------------|
| Actual diagnostic tools         | Digital rectal examination      |
|                                 | Prostate-specific antigen and its derivatives |
|                                 | Prostate cancer antigen 3 gene (PCA3) |
|                                 | Nomograms                       |
| What MRI could offer            | Reduction of indications for nonuseful biopsy procedures |
|                                 | Identification of patients at risk for clinically significant prostate cancer |
| Potential limits of MRI         | The difficulties of merging multiparametric MRI with TRUS to direct TRUS-guided biopsies |

MRI = magnetic resonance imaging; TRUS = transrectal ultrasound.
study of 23 patients, the addition of DWI and DCE-MRI to T2-weighted MRI increased accuracy in the detection of transition-zone cancer from 64% to 79% [16]. However, additional research is needed to confirm these initial results.

3.2.2. Biopsy strategies

Random TRUS-guided biopsy is now the preferred method for histologic diagnosis of PCa. However, sextant biopsies have been reported to miss up to 30% of cancers, and when compared with RP for tumour localization, biopsy results had a positive predictive value (PPV) and a negative predictive value (NPV) of 83% and 36%, respectively [17,18]. Although MRSI is not used at this time as a first approach to diagnose PCa, it can be useful for directing targeted biopsies, especially for patients with PSA levels suggestive of cancer and negative previous biopsies (Table 2). Men with persistently elevated serum PSA levels after a negative random TRUS-guided biopsy represent a great diagnostic problem for urologists. Biopsy strategies with an increased number of cores have also been proposed to reduce false-negative rates. However, such saturation biopsies can be associated with increased patient morbidity, and controversy persists over whether taking more cores results in the detection of more tumours with low-risk characteristics.

In a limited population of 54 men with elevated PSA levels and previous negative biopsy results, Cirillo et al. [14] found that the use of MRSI combined with MRI at 1.5T had 100% sensitivity, 51.4% specificity, 48.6% PPV, 100% NPV, and 66.3% accuracy in indicating sites of PCa. Sciarra et al. [18] performed a prospective study of 180 patients with prior negative random biopsy results and persistently elevated PSA levels. Patients were randomised to a second random prostate biopsy or to multiparametric 1.5T MRI (MRSI/DCE-MRI) followed by random prostate biopsy with additional targeted sampling of suspicious areas identified on multiparametric MRI (Fig. 2). At the second biopsy, PCa was found in 24.4% of cases in the first group versus 45.5% in the group that underwent multiparametric MRI. The combination of MRSI plus DCE-MRI had 93% sensitivity, 89% specificity, 89% PPV, 93% NPV, and 91% accuracy for predicting PCa detection. Thus, the combination of MRSI and DCE-MRI has the potential to guide biopsy to cancer foci in patients with negative prior biopsy results. To avoid interferences caused by postbiopsy changes, the MRI examination should be performed successfully as early as 60 d after the first biopsy. Laurentschuk and Fleshner [19] reviewed all available databases from prospective studies of patients with previous negative biopsy results and persistently elevated PSA levels who underwent MRSI and repeat prostate biopsy. Among the six studies that fulfilled the criteria, MRSI had sensitivity of 57–100%, specificity of 44–96%, and accuracy of 67–85% in the prediction of positive repeat-biopsy results [19].

Recently, some studies have also analysed the practicability of MR-guided biopsy (Fig. 3). Hambrock et al. [20] tested the feasibility of translating maps of potential areas of tumour in the prostate, obtained from multiparametric 3T MRI data (including T2W MRI, DWI, and DCE-MRI), for directing MR-guided biopsies. Results from 21 patients with elevated PSA levels and negative previous biopsy results were analysed. All areas of suspected tumour identified on multiparametric MRI were translated to 3T T2W MRI and biopsied under MR guidance. MR-guided biopsy procedure time was 35 min.

In 68 patients with similar characteristics, Hambrock and colleagues [21] analyzed the results of multiparametric 3T MR-guided biopsy and compared them with results from a matched population of patients who underwent multi-session TRUS-guided biopsy. The tumour detection rate for MR-guided biopsy was 59% using a median of four cores, and it was significantly (p < 0.001) higher than that of TRUS-guided prostate biopsy. Yakar et al. [22] and Pondman et al. [23] have provided additional data showing that, in patients with prior negative TRUS-guided biopsy results, 3T MR-guided prostate biopsy is feasible and has a higher rate of PCa detection than does repeat TRUS-guided biopsy. MR-guided biopsies of the prostate are becoming more and more available, but there is currently no consensus on the optimal technique.

**Table 2 – Biopsy strategy**

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MRI = magnetic resonance imaging; TRUS = transrectal ultrasound.

Fig. 2 – Biopsy scheme of the entire gland volume. Note potential biopsy sites based on magnetic resonance imaging morphologic, metabolic, and vascularisation changes in the medial and lateral left peripheral zone (planes IV, V, VI; gland area between 4 and 5).
In conclusion, in the initial diagnosis of PCa, the use of multiparametric MRI combining T2W imaging, MRSI, DCE-MRI, and DWI can potentially reduce the rate of false-negative biopsies and decrease the need for more extensive or repeat biopsy procedures by allowing biopsies to be targeted with substantial specificity and sensitivity.

3.2.3. Clinical relevance and potential limits of magnetic resonance imaging in the initial diagnosis

The level of evidence to support the use of multiparametric MRI in the initial diagnosis of PCa is particularly significant in cases with persistently elevated PSA levels and previous negative biopsies. Different prospective studies and one randomised study [14,18,19] have been conducted.

Of the available multiparametric MRI techniques, T2W MRI, DWI, and DCE-MRI are, at present, the most practical and relevant for clinical practice. The use of MRI for directing targeted biopsies is limited by the difficulties of merging multiparametric MRI with real-time TRUS to direct TRUS-guided biopsies and the lack of equipment for MR-guided biopsy at most centres.

3.3. Oncologic and functional implications in the planning of radical prostatectomy

To obtain the best results with RP, from either an oncologic or functional point of view, meticulous preoperative selection of cases and planning of surgery are crucial. Often used for treatment selection and planning are predictive instruments such as nomograms, which typically include PSA and pathologic findings at biopsy [1,24]. Imaging-derived preoperative information concerning the risk of extracapsular disease and the locations of tumour foci in the prostate can help clinicians select and plan surgical treatment appropriately (Table 3).

3.3.1. Preoperative local staging

The literature shows a wide range (50–92%) in the accuracy of local staging by MRI [17]. It has been suggested that the addition of volumetric data from MRSI or DCE-MRI to MRI significantly improves local staging and, in particular, reduces interobserver variability [17]. However, the findings still need to be validated in larger studies. Seiz et al, in their collaborative review article [8], underlined that
sensitivity, specificity, and accuracy in tumour staging were higher with DCE-MRI than with MRSI. In a limited population of 64 cases, Kim et al. [25] analysed the role of a combined DWI and DCE-MRI technique (at 1.5T) in predicting the local stage, using pathologic results obtained at RP as the reference standard. In detecting extraprostatic extension, the combination of DWI and DCE-MRI displayed 82.4% sensitivity, 87.2% specificity, 70% PPV, and 93.2% NPV. Higher values (92.3%, 93.1%, 85.7%, and 96.7%, respectively) were found when only cases with clinically high-risk disease features (cT3, PSA ≥20 ng/ml, or Gleason score ≥8) were analysed. In 158 patients with clinical stage T1c disease, Zhang et al. [26] analysed the role of preoperative combined MRI/MRSI (at 1.5T) in predicting the pathologic stage of PCa. The overall accuracy of PCa staging by MRI/MRSI was 80%; staging accuracy was highest for the smallest tumour volumes (91% for tumour volumes <0.5 cm³ vs 75% for tumour volumes >2.0 cm³). In the detection of extracapsular disease, MRI/MRSI had an AUC of 0.74. In a limited population of 27 patients considered for RP, Augustin et al. [27] compared the accuracy of 3T MRI with the Partin tables in predicting pathologic stage. In the detection of extracapsular extension, MRI had an accuracy of 85.2%, sensitivity of 66.7%, and specificity of 100%. The Spearman ρ for correlation with extracapsular extension was higher for MRI findings (0.780) than for the Partin tables (0.363). Overall, 3T MRI was significantly more accurate than the Partin tables in predicting the final pathologic stage.

3.3.2. Preoperative localization and mapping of tumour foci
Better characterization of PCa is necessary to improve surgical, oncologic, and functional outcomes. MR techniques can provide needed information about the location and size of PCa, as well as its relationship to prostatic and extraprostatic structures (Fig. 4).

Katahira et al studied 201 patients with PCa who underwent DWI before RP [28]. Each prostate was divided

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<td>Potential limits of MRI</td>
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MRI = magnetic resonance imaging; NVB = neurovascular bundle.

Fig. 4 – Patient (age: 65 yr) with a prostate-specific antigen level of 9.5 ng/ml; digital rectal examination identified no suspicious areas; transrectal ultrasound-guided biopsy showed prostate adenocarcinoma Gleason 6 (3 + 3) in left and right samples. Histology at radical retropubic prostatectomy showed a Gleason 6 (3 + 3) tumour with Gleason 7 (4 + 3) focal hot spots (pT2b). (A) Axial T2-weighted magnetic resonance image (MRI) shows low signal intensity tumour in peripheral zones (PZ) (white area). (B) Axial dynamic contrast-enhanced MRI shows increased contrast leakage in tumour and benign prostatic hyperplasia areas. (C) Axial apparent diffusion coefficient (ADC) map from diffusion-weighted imaging shows low signal throughout the entire tumour, with two focal low signal intensity hot spots (yellow areas). These findings may reflect the fact that the tumour is predominantly Gleason score 6 (3 + 3), with focal areas of Gleason score 7 (4 + 3). (D) Histopathology map after radical retropubic prostatectomy shows Gleason 6 (3 + 3) prostate cancer (PCA) area identical to the low signal intensity area in (A), and Gleason 7 (4 + 3) PCA in focal hot spots identical to areas of restrict diffusion on ADC map in (C).
into eight segments; on the basis of 1.5T MRI results, the probability of the presence of PCa in each segment was estimated using a five-point rating scale. Results were compared with those of whole-mount, step-section, histopathologic examination. The sensitivity, specificity, and AUC of DWI for the localization of PCa were 73%, 89%, and 0.842, respectively. In a study of 83 patients who underwent RP, Puech et al. [29] analysed the performance of DCE-MRI (at 1.5T) in identifying and localizing intraprostatic cancer foci in relation to cancer volume at histology. At MRI, the prostate was divided into eight segments and results scored on a five-point scale. The sensitivity and specificity of DCE-MRI for identification of PCa foci of any volume were 32% and 95%, respectively. For identification of cancer foci >0.5 ml, the sensitivity and specificity were 86% and 94%, respectively, and the AUC was 0.874. In their study of 158 patients with clinical stage T1c PCa, Zhang et al. [26] assessed the accuracy of MRI/MRSI in predicting PCa in 12 prostate regions, using whole-mount, step-section pathologic maps as the reference standard. The results of combined MRI/MRSI were relevant, but their accuracy did not differ significantly among the different areas of the prostate (AUC = 0.71 for the base, 0.61 for the midgland, and 0.69 for the apex). Weinreb et al. [30] published the results of a prospective multicentre study conducted by the American College of Radiology Imaging Network to assess the incremental value of MRSI to MRI in the sextant localization of peripheral-zone PCa. Authors analysed imaging results for 134 patients with PCa who underwent combined MRI/MRSI at 1.5T. Eight readers independently rated the likelihood of the presence of PCa in each prostate sextant by using a five-point scale, and histopathologic results at RP were used as the reference standard. The accuracy of combined MRI/MRSI (AUC = 0.58) was equivalent to that of MRI alone (AUC = 0.60). This negative result for MRSI may have been partly related to the fact that the study population consisted predominantly of patients with low-risk, small-volume disease: Most of the cases were clinical stage T1c, the mean PSA was 5.9 ng/ml, and the mean tumour volume was 2.75 cm³.

### 3.3.3. Functional evaluation

The decision to preserve or resect the neurovascular bundles (NVBs) at RP is often difficult and based on preoperative clinical characteristics and intraoperative findings. MRI techniques can help predict the absence of tumour in the areas of the NVBs (Fig. 5). In a study of 75 patients with PCa scheduled for RP, Labanaris et al. [31] analysed the value of conventional and functional 1.5T MRI in predicting the risk of extracapsular extension in relation to NVBs. Cases were considered appropriate for nerve-sparing surgery if the tumour did not extend outside the capsule in the posterolateral region of the prostate as assessed by imaging. Based on MRI findings, the operative strategy was changed in 44% of cases. Among these, the findings favoured NVB preservation in 67% of cases with high clinical probability of extracapsular extension and opposed NVB preservation in 33% of cases with low clinical probability of extracapsular extension. Based on the final histopathologic findings, the sensitivity, specificity, and accuracy of MRI in predicting seminal-vesicle invasion, extracapsular extension, or NVB involvement, and thereby obtaining a correct preoperative decision, were 92%, 100%, and 100%, respectively. In a population of 62 patients who underwent RP, Brown et al. [32] evaluated the impact of preoperative staging with 1.5T MRI on NVB-sparing aggressiveness and surgical margin positivity. They concluded that unenhanced MRI is of limited usefulness in detecting extracapsular extension and therefore carries the risk of leading to inappropriate nerve-sparing surgery and possible positive surgical margins. MRSI, DWI, and DCE-MRI were not performed in the study.

The probability of recovering erectile function after RP is associated inversely with patient age and comorbidity, and directly with the extent and number of NVBs preserved. In patients reported to have undergone nerve preservation, poor recovery of erectile function after surgery raises several questions. In a study of 53 patients with PCa who
underwent bilateral nerve-sparing RP, Sciarra et al. [33] analysed the capability of a dedicated 3D, isotropic, MRI T2-weighted sequence to depict postsurgical changes in the NVBs. Postoperative MRI examinations were compared with the International Index of Erection Function five-item (IIEF-5) questionnaire, which served as the reference standard. The authors developed a relative five-point system for classifying MRI findings on the basis of anatomic course delineation for each or both NVBs. In all cases the correlation and regression analysis between MRI and IIEF-5 findings resulted in high coefficient values ($r = 0.45; p = 0.001$). The imaging protocol and the NVB-change classification system proposed in this study can be applied successfully as early as 40 d after RP. Together, they could provide an additional diagnostic tool in the postoperative evaluation and treatment of erectile dysfunction (Fig. 6).

3.3.4. Early detection of local recurrence after radical prostatectomy
The crucial point in the evaluation of biochemical progression after RP is the differentiation between local and distant disease. Often this evaluation is based on clinical parameters (PSA, PSA doubling time, and the interval between surgery and PSA relapse), pathologic stage, resection margins and grade at surgery, or nomograms. Casciani et al. [34] analysed a limited population of 51 PCa patients with biochemical progression after RP who underwent MRI and DCE-MRI (1.5T MRI) before TRUS-guided biopsy of the prostatic fossa. When compared with biopsy results, MRI alone achieved an accuracy of only 48%; combined MRI/DCE-MRI had an accuracy of 94%. Cirillo et al. [35] analysed the roles of MRI and DCE-MRI (at 1.5T) for diagnosing local recurrence of PCa in 72 patients with biochemical progression (mean PSA = 1.23 ng/ml) after RP. Imaging results were compared with prostatectomy-bed biopsy findings or PSA reduction after RT. Sensitivity, specificity, PPV, NPV, and accuracy were 61.4%, 82.1%, 84.4%, 57.5%, and 69.4%, respectively, for unenhanced MRI, and 84.1%, 88.3%, 92.5%, 78.1%, and 86.1%, respectively, for DCE-MRI. Sciarra et al. [36] analysed findings from combined MRSI and DCE-MRI (at 1.5T) in 70 PCa patients with biochemical progression after RP. The reference standard was a biopsy-proven cancer recurrence (mean PSA = 1.26 ng/ml) in 50 patients and a reduction in PSA level >50% following RT (mean serum PSA = 0.8 ng/ml) in 20 patients. The sensitivity, specificity, PPV, and NPV of combined MRSI and DCE-MRI were 87%, 94%, 96%, and 79%, respectively, in the first group, and 86%, 100%, 100%, and 75%, respectively, in the second group. Receiver operating characteristic
analysis showed that MRSI performed less well in the second group than in the first group; this difference may reflect the fact that the required voxel size for spectroscopic imaging is larger than that for DCE-MRI, an issue that may be especially relevant in patients with small-volume disease, such as the second group in the Sciarra et al study.

These analyses suggest that the use of combined MRSI and DCE-MRI can improve the detection of local recurrence after RP, including in patients with low PSA values and low-volume recurrence (Fig. 7).

3.3.5. Clinical relevance and potential limits of magnetic resonance imaging in radical prostatectomy planning

The level of evidence to support the use of multiparametric MRI in this field starts to be significant, particularly for preoperative localization and mapping of the tumour and an early diagnosis of local recurrence. Different prospective studies on a significant population have been presented (26,28–30,35,36). The possibility of improving the planning of a nerve-sparing RP, combining an oncologic and functional evaluation, is also clinically suggestive. A 3T MRI evaluation can be sufficient, but the combination of at least two (DCE-MRI and MRSI) multiparametric techniques can improve results, particularly for an early diagnosis of local recurrence [36]. In addition, MRSI and DWI can distinguish the presence of recurrence from healthy residual prostate tissue. Limitations are mainly related to possible artefacts due to structure modification after the biopsy or the surgical procedure that can influence a correct analysis of the prostate or of a possible recurrence.

Fig. 7 – Patient (age: 58 yr) with prostate-specific antigen (PSA) progression, from 0.1 to 0.7 ng/ml, 8 mo after radical retropubic prostatectomy (RRP). At RRP, prostatic adenocarcinoma of Gleason 7 score (4+3) and stage pT2b was found. Locally recurrent prostate cancer was confirmed on the basis of a PSA decrease (PSA = 0.1 ng/ml) after external beam radiation therapy. (a) T2-weighted magnetic resonance imaging (MRI) shows 5-mm intermediate signal intensity nodule (arrow) in a perianastomotic location. (b) MR spectroscopic imaging analysis with reference images on the nodule shows two consecutive voxels with reduced citrate (Ci) signal and increased choline (Cho) plus creatine (Cr) to citrate ratio (>1). (c) Dynamic contrast-enhanced (DCE) MRI shows a hypervascular lesion (arrow) and malignant patterns. (d) DCE-MRI intensity/time curve of the same area shown in (c) demonstrates a hypervascular lesion. (e) Axial diffusion-weighted imaging shows restriction (high signal intensity on T2 native image) of the nodule.
3.4. Oncologic implications in the planning of radiation therapy

Treatment of PCa with external RT has evolved. However, it is known that poor treatment coverage at RT is associated with an increased risk of local and distant progression [37].

The major obstacle to achieving sufficient coverage is the limited ability of CT, the modality typically used for RT planning, to delineate tumour (Table 4). In patients undergoing external-beam radiation therapy (EBRT), three possible indications for MRI techniques have been considered: (1) localization of the tumour before and during RT, (2) prediction of the risk of progression after RT, and (3) detection of local recurrence after RT.

### 3.4.1. Localization of the tumour before and during radiation therapy

Before RT, MRI has much greater soft-tissue contrast than CT and better delineates the extent of PCa in the prostate and periprostatic structures, especially at the apex close to the bulb of the penis. This leads to a more accurate delineation of the irradiation field, which allows reduction of the dose to the periprostatic tissue and urethra, along with delivery of the maximum dosage to

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**Table 4 – Planning for external-beam radiation therapy**

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MRI = magnetic resonance imaging; RT = radiation therapy.

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**Fig. 8** – Patient (age: 69 yr) with prostate-specific antigen (PSA) progression (PSA = 2.0 ng/ml) 3 yr after external-beam radiation therapy (RT) (primary prostatic adenocarcinoma: Gleason score 7 (4 + 3), right peripheral zone [PZ]). Magnetic resonance imaging (MRI) and transrectal ultrasound (TRUS)-guided biopsy of this area confirmed Gleason score 8 (4 + 4) recurrence after RT at right PZ (same primary tumour location). (A) Axial T2-weighted MRI shows low signal intensity in the prostate due to previous RT. Therefore, tumour (arrow) is difficult to see. At arrow there is some bulging. (B) Axial dynamic contrast-enhanced MRI shows increased contrast leakage at right PZ (circle) that is highly suspicious for prostate cancer. (C) Axial apparent diffusion coefficient map from diffusion-weighted imaging shows restriction (low signal intensity) (circle). TRUS-guided biopsy of this area confirmed Gleason score 8 (4 + 4) recurrence.
the target within the prostate [37]. The recent literature does not include any relevant studies on the use of MRI parameters for monitoring tissue changes during RT [38].

3.4.2. Prediction of the risk of progression

McKenna et al. [39] suggested that pretreatment endorectal MRI findings are predictive of outcomes after external RT. In a study of 40 patients with PCa, they showed that the mean diameter of extracapsular extension was an independent predictive variable for progression (hazard ratio [HR] = 2.06; 95% confidence interval [CI], 1.22–3.48). They also suggested that patients with extracapsular extension >5 mm on MRI may be potential candidates for more aggressive therapies, such as radiation dose escalation or combining therapy with androgen deprivation. In a study of 67 men who underwent EBRT for PCa, Joseph et al. [40] showed that preoperative evaluation of 1.5T MRSI data could be used to predict outcomes after RT. In particular, the volume of malignant metabolism on MRSI was an independent predictor of biochemical failure (HR = 1.63; 95% CI, 1.29–2.06; p < 0.001).

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**Fig. 9** – Patient (age: 67 yr) with prostate-specific antigen level of 15 ng/ml; histology at biopsy showed prostatic adenocarcinoma of Gleason score 6 (3 + 3) in the right peripheral zone (PZ). The patient chose high-intensity focussed ultrasound (HIFU) treatment. (a) Pretreatment axial dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) (arrow); (b) perfusion map, and (c) intensity/time curve show pathologic enhancement in the right PZ. (d–f) At MR spectroscopic imaging, the spectrum of metabolites shows an increase of choline (circles on spectra) in the same site combined with an increase of creatine (rectangle in [e]); the pattern is consistent with tumour-associated prostatitis. (g) Post-HIFU (1 mo) analysis: axial DCE-MRI, (h) perfusion map, and (i) intensity/time curve show absence of angiogenesis and a wide zone of coagulative necrosis.
3.4.3. Detection of local recurrence after radiation therapy

After RT, the prostate is characterised by a diffuse low signal. For this reason, MR T2W imaging is less helpful in localizing PCa recurrence (Fig. 8). In a limited population of 64 patients who underwent EBRT for PCa, Westphalen et al. [37] compared the role of combined MRI/MRSI with MRI (at 1.5T) alone in detecting local recurrence. Results from TRUS-guided biopsies were used as the reference standard. The combined MRI/MRSI analysis, when compared with MRI alone, had a greater percentage of true-positive results (59% vs 41%) without an important change in the percentage of false-positive results (10% vs 7%). Therefore, the addition of MRSI to T2W MRI alone significantly improved the detection of local recurrence after RT.

Studies evaluating DCE-MRI after RT report sensitivities of 70–74% and specificities of 73–85% [41]. In 172 patients with PCa treated with EBRT, Kara et al. [42] compared the role of DCE-MRI (1.5T MRI) with TRUS in follow-up (18 mo from RT). Using biopsy results as the reference standard, the sensitivity and specificity of TRUS in the detection of tumour recurrence after RT were 53.3% and 60%, respectively. The sensitivity and specificity of T2W MRI were 86% and 100%, respectively; the sensitivity and specificity of DCE-MRI were 93% and 100%, respectively. DCE-MRI was significantly more accurate than T2W MRI for the detection of PCa recurrence after RT.

3.4.4. Clinical relevance and potential limits of magnetic resonance imaging in radiation therapy planning

The level of evidence to support the use of multiparametric MRI in this field is still low and further prospective studies are necessary. Multiparametric MRI is very accurate in showing normal and abnormal prostate tissue and therefore could be important for enabling optimal intensity-modulated RT planning. Although T2W and DWI MRI are limited in the detection of local recurrence after RT, DCE MRI or MRSI can be used to accurately identify the presence of such recurrence [37,42].

Limitations are mainly related to possible artefacts due to structure modification during RT that can influence a correct analysis of treatment response or recurrence identification.

3.5. Oncologic implications in the planning of focal therapies

Besides RP and EBRT, different focal therapies, such as brachytherapy (a well-established treatment for PCa), cryosurgical ablation, and high-intensity focussed ultrasound (HIFU), have emerged as alternative therapeutic options in patients with PCa [1]. The efficacy and safety of these procedures are strongly influenced by the accuracy of PCa localization and tumour volume prediction [43]. A second important issue is the ability to characterise morphologic changes induced by focal therapies inside the tumour mass to better assess treatment efficacy in the individual patient (Table 5). Multiparametric MRI has the potential to localise primary or recurrent PCa accurately, to describe tumour volume, and to show morphologic changes during and after treatment (Figs. 9 and 10) [44]. Changes in MRSI findings during different focal therapies have been described: An initial phase with an increase in choline or in all metabolites detected has been reported, and a second phase of metabolic atrophy (ie, detection of no metabolites) has been considered evidence of complete response [43]. With DWI, a reduction of ADC is considered the most important signifier of local recurrence after focal treatment; however, fibrosis can produce similar ADC values, limiting the usefulness of DWI in the evaluation of focal therapy [43]. DCE-MRI shows changes in vascularity and contrast enhancement that correlate well with inflammation, necrosis, devascularisation, and fibrosis induced by focal therapies [43].

Three possible indications for MRI techniques in patients undergoing focal therapies have been suggested: (1) localisation and identification of the tumour before treatment, (2) guidance of focal treatment, and (3) identification of morphologic changes as measures of response.

However, to date, most published studies have focussed primarily on the feasibility of using MRI in the setting of focal therapy rather than on results in terms of oncologic control, and data are very limited.

Table 5 – Planning for focal therapies

<table>
<thead>
<tr>
<th>Actual diagnostic tools</th>
<th>Prostate-specific antigen</th>
<th>Computed tomography scan</th>
<th>Transrectal ultrasound-guided biopsy</th>
<th>Nomograms</th>
</tr>
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<tbody>
<tr>
<td>What MRI could offer clinics</td>
<td>Mapping of the prostate for tumor sites</td>
<td>Guide for focal therapy performance</td>
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<td>Potential limits of MRI</td>
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MRI = magnetic resonance imaging.

3.5.1. Brachytherapy

Transperineal brachytherapy is considered a safe and effective technique mainly for the treatment of localised (cT1b-T2a), low-risk (Gleason score <6, PSA <10 ng/ml, <50% of biopsy cores involved) PCa [1]. It is performed under TRUS guidance, and a prostate volume <50 cm³ is considered necessary for successful implantation [1]. The benefits of image-guided brachytherapy using MRI and the feasibility of targeting the peripheral zone with good dosimetric coverage have been described [45]. In brachytherapy, the current standard for post-plan dosimetry is CT imaging performed either immediately after the procedure or 1 mo later. In a cohort of 131 men receiving iodine-125 prostate brachytherapy, Crook et al. [46] used 1.5T MRI at 1 mo postimplantation to determine the treatment margins. They reported satisfactory use of MRI to cover a 2- to 3-mm periprostatic margin. Similarly, Acher et al. [47] compared 1.5T MRI with CT as a method for the dosimetric analysis of permanent prostate brachytherapy implants. In 30 cases, four observers agreed significantly more closely on the prostate base and apex positions, as well as the outlining contours, when reading MR images than when reading CT images. These studies suggest that MRI-based dosimetry offers an alternative to CT-based dosimetry, allowing better prostate delineation and more confident 3D reconstruction of the implant.
3.5.2. High-intensity focussed ultrasound

In a study of 10 patients, Cirillo et al. [48] assessed the roles of MRI and MRSI (1.5T MRI) in evaluating changes in the prostate after HIFU for PCa, correlating imaging findings with histology at biopsy. At 4 mo, there was a statistically significant difference ( \( p = 0.015 \)) between patients responding to treatment and those with persistent disease by combining negative MRI with PSA level \(< 0.5 \text{ ng/ml}\). MRSI data were suitable for analysis only in three cases with partial necrosis and provided no additional value.

In a study of 15 patients treated with HIFU for PCa, Ben Chiekh et al. [49] used T2W MRI and DCE-MRI at 1.5T for the detection of local tumour recurrence. At biopsy, tumour recurrence was found in 13 of 15 cases. On T2W MRI, the treated prostate tissue was diffusely hypointense, which interfered with interpretation. Only 3 cases had suspicious areas at MRI, whereas all 15 cases had suspicious areas at DCE-MRI. Sensitivity, specificity, PPV, and NPV of T2W MRI were 0.13, 0.98, 0.60, and 0.81, respectively, and 0.70, 0.85, 0.55, and 0.91, respectively, for DCE-MRI. DCE-MRI was strongly predictive of positive biopsy results, but T2W MRI was not. Kim et al. [50] used DCE-MRI and the combination of T2W MRI and DWI (1.5T MRI) in 27 patients with increased PSA levels after HIFU. Biopsy detected local tumour progression in 54 (33%) of 162 sextants in 18 cases. Sensitivity, specificity, and accuracy values achieved by two independent readers were 80–87%, 63–68%, and 71–72%, respectively, with DCE-MRI, and 63–70%, 74–78%, and 73%, respectively, with combined T2W MRI and DWI.

3.5.3. Cryotherapy

The literature search did not reveal any articles on the use of MRI in patients undergoing cryotherapy for PCa.
3.5.4. Clinical relevance and potential limits of magnetic resonance imaging in focal therapies planning

The level of evidence to support the use of multiparametric MRI in this field is still low, and only the feasibility has been demonstrated.

4. Conclusions

The standard tests and predictive models that clinicians use to choose diagnostic and therapeutic strategies for PCa have considerable limitations, and a valid imaging tool is needed to improve all stages of PCa management. Published data indicate an emerging role for MRI (particularly multiparametric MRI combining T2W imaging, DWI, DCE, and MRSI) as the most sensitive and specific tool available for imaging PCa. Multiparametric MRI can provide metabolic information; characterise tissue and tumour vascularity, as well as tissue cellularity and integrity; and correlate with tumour aggressiveness [51]. It appears to be the most accurate imaging method for localising primary PCa and staging primary or recurrent PCa.

The available literature suggests that multiparametric MRI is helpful and clinically relevant for the following tasks at minimum: (1) detection of PCa in patients with previous negative prostate biopsies and persistently elevated serum markers, in whom it reduces the need for additional and more extensive biopsies and identifies suspicious areas for targeted sampling; (2) characterization of PCa to facilitate appropriate treatment selection; and (3) early identification of local recurrence in patients with biochemical recurrence after primary therapy. Two other potential applications of MRI for PCa include MR-guided prostate biopsy and MR-guided focal therapy; however, for these, only feasibility has been demonstrated and data on the significance of clinical results are needed.

Larger multicentre studies are needed to confirm the initial promising results and validate the use of multiparametric MRI for all the indications previously discussed here. Before such studies can be performed, however, more research is needed to standardise imaging protocols and determine reproducible quantitative parameters and thresholds for identifying and evaluating PCa with multiparametric MRI.

The development of prostate MRI has been limited by obstacles to its dissemination and implementation. Although MRI of the prostate can be mastered [52], experienced radiologists who are trained appropriately to read it are still lacking. Furthermore, even in centres where MRI technology is present, its availability for PCa imaging is often limited. Pressure from referring physicians (e.g., urologists, radiation oncologists, and medical oncologists) is needed to ensure the availability of MRI expertise, as well as MRI time, for the indications noted in this review.

Finally, efforts to evaluate the cost effectiveness of multiparametric MRI will also be needed. Although there are no recent studies on this topic, it seems likely that the use of multiparametric MRI to achieve more accurate initial diagnoses will lead to more effective and tailored therapies with lower costs.

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Study concept and design: Sciarra.

Acquisition of data: Sciarra.

Analysis and interpretation of data: Barentsz, Bjartell, Eastham, Hricak, Panebianco, Witjes.

Drafting of the manuscript: Sciarra.

Critical revision of the manuscript for important intellectual content: Barentsz, Bjartell, Eastham, Hricak, Panebianco, Witjes.

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