Magnetic Resonance Imaging in Prostate Cancer Diagnosis: Present Role and Future Perspectives

Ressonância Magnética no Diagnóstico de Tumor da Próstata: Papel Atual e Perspectiva Futura

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Resumo

O tumor da próstata (PCa) é o tumor mais comum em homens na Europa. Os meios para avaliação do risco de PCa são o exame físico por toque rectal (DRE) e a determinação da concentração do antigénio específico da próstata (PSA) em análises sanguíneas. O método *gold standard* para o diagnóstico histológico de PCa é a biópsia prostática aleatorizada guiada por ecografia, caracterizada por baixa acuidade.

Os homens com PSA persistentemente elevado após uma biópsia prostática sem neoplasia representam um considerável problema diagnóstico para os urologistas. A repetição de biópsia prostática continua a não diagnosticar tumores clinicamente significativos. Por este motivo, uma maior deteção de tumor da próstata com auxílio de exames de imagem é um tema importante.

Vários estudos sugerem que a combinação de técnicas de Ressonância Magnética (MRI) convencional e funcional (incluem a MRI com imagem de difusão, MRI com perfusão de contraste e MRI por espectroscopia) tem potencial para detetar áreas suspeitas de tumor e permitir a biópsia dirigida, aumentando a exatidão do procedimento, principalmente em doentes com biópsias negativas prévias.

O objetivo deste artigo é rever o papel atual e perspetivas futuras da Ressonância Magnética no diagnóstico de tumor da próstata.

Palavras-chave: Diagnóstico de tumor da próstata, Ressonância Magnética, Ressonância Magnética de difusão, Ressonância Magnética com perfusão de contraste, Ressonância Magnética por espectroscopia.

Abstract

Prostate cancer (PCa) is the most common cancer in men in Europe. The methods for assessing the risk of PCa include the combination of Digital Rectal Examination (DRE) and testing for serum concentration of Prostatic Specific Antigen (PSA). The gold standard method for histological diagnosis of PCa, the random transrectal ultrasound (TRUS) guided biopsy, lacks accuracy. Men with persistently elevated serum PSA levels after negative random TRUS-guided biopsy represent a great diagnostic problem for urologists. Repeating biopsy still misses clinically significant cancers. Therefore, improvement of prostate cancer detection is a main topic of diagnostic imaging.

The data suggest that the combination of conventional and functional magnetic resonance imaging (MRI) techniques (including diffusion-weighted imaging, dynamic contrast-enhanced MRI and MR spectroscopy) has the potential to guide biopsy for cancer foci in patients with previously negative biopsies, increasing the accuracy of the procedure.

The aim of this article is to review the present role and future perspectives of Magnetic Resonance Imaging in prostate cancer diagnosis.

Keywords: *Prostate Cancer Diagnosis, Magnetic Resonance Imaging (MRI), Diffusion-weighted MRI, Dynamic contrast-enhanced MRI, MR spectroscopy*

Introduction

Prostate cancer (PCa) is the fourth most common male malignant neoplasm worldwide[1] and the most common cancer in men in Europe[2]. Among men in Europe, PCa accounts for approximately 11.9% of all cancers and 9% of all cancer deaths[2].

The primary methods for assessing the risk of PCa include the combination of Digital Rectal Examination (DRE) and testing for serum concentration of Prostatic Specific Antigen (PSA), as defined by the 2010 European Association of Urology Guidelines. The gold standard method for histological diagnosis of PCa is random transrectal ultrasound (TRUS) guided biopsy[1, 2 3].

Non-palpable cancers (American Joint Committee on Cancer (AJCC) clinical stage T1c) now account for 75% of newly diagnosed disease[1].

PCa is found in the prostatic peripheral zone in approximately 80%, in the transition zone in 15% and in the central zone in 5%[4].

The systematic biopsy lacks sensitivity, missing cancer in up to 30% of cases, as well as grading accuracy[2, 3 5].

Men with persistently elevated PSA levels after a negative first TRUS guided random biopsy are a well-recognized diagnostic problem in urological practice[6]. For example, a second biopsy detects cancer from 10 to 36% of such men, depending on the aggressiveness of the biopsy technique[1, 6]. Third and even fourth biopsy detect cancer in 5% and 4% of cases, respectively[6, 7].

Repeating biopsy still misses significant cancers, favoring saturation biopsy[8].

The use of Magnetic Resonance Imaging (MRI) for prostate cancer staging has been extensively studied and is showing promising results for tumor localisation[9]. It has the potential to improve the sensitivity and specificity for detecting PCa, to allow targeted prostatic biopsies and to raise the accuracy in the PCa staging. MRI promises to make it a successful imaging tool for improving many aspects of PCa management[3]. It also has the advantage of detecting prostate cancers that might not have been detected, particularly those outside the peripheral zone or in locations not biopsied in normal schemes [10, 11].

Recently, great interest has been shown in multiparametric MRI (mp MRI), which combines anatomic, biologic and functional dynamic information of the prostatic tissue. Mp MRI combines techniques such as anatomic T2-weighted (T2W) imaging with diffusion-weighted imaging (DWI), dynamic contrast-enhanced MRI (DCE-MRI) and MR spectroscopic imaging (MRSI)[2, 3 9].

Accurate characterization of tumor location and extent is vital to ensure optimal delivery of emerging focal therapies and may also impact patient management during active surveillance[9].

The aim of this article is to review the current roles of these advanced MRI imaging techniques and the future perspectives for the detection of PCa.

Methodology

The author's searched the Medline databases (primary fields: prostate cancer, magnetic resonance). The search included articles restricted to English language from January 2001 to February 2012. The selection of the articles was done taking into account the focus of the article on prostate cancer detection using MRI imaging techniques, the number of citations, the date and the type of the articles (recent review articles were preferred).

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Evidence synthesis

In the magnetic resonance community, Tesla (T) is known as the unit of magnetic induction or magnetic flux density in the meter-kilogram-second system (SI)[12].

Conventional MRI at 1.5 or 3.0 T reveals morphological information using T1 and T2 weighted images (T1 and T2-WI)[3,13]. It is recommended to use the endorectal coil with a 1.5 T scanner to improve the detection of PCa and the delineation of the capsule. With the introduction of the higher field strength (3T) and thus higher spatial resolution, the endorectal coil can be used less frequently, which makes MRI more accessible[3,13,14].

The MRI techniques used in PCa detection include conventional MRI and functional MRI. The functional MRI includes MRSI, DWI MRI and DCE MRI. Recommended use of MRI in PCa detection consists of multi-parametric MRI which includes a combination of conventional MRI with at least 2 functional MRI techniques[15, 16].

Conventional MRI

T1-WI is used to detect pelvic bone lesions, lymph nodes and post-biopsy hemorrhage. T2-WI provides high-resolution morphologic imaging of the gland in three planes. Obtaining the standard sequences takes approximately 30 minutes [3, 13, 14]. The peripheral zone is the most common site of prostate cancer, and on T2-WI, cancer is demonstrated as decreased signal intensity within the normal high-signal-intensity peripheral zone[13, 14].

Figure 1: T2 weighted images of normal prostatic peripheric zone, showing hyperintense signal a) axial section b) coronal section

Figure 2: T2 weighted image with hypointense signal (red arrow) suspicious of PCa in a patient with 68 years old and a PSA – 10ng/mL. Biopsy of this area revealed prostatic adenocarcinoma Gleason 7 (3+4)

There has been intense research in the last decade on the use of complementary techniques to improve the detection and staging of PCa by MRI. Mp-MRI combines T2WI, MRSI, DWI and DCE MRI images. T2WI alone is sensitive but not specific for PCa and should be improved using MRI functional techniques. Recommended use of MRI in prostate cancer consists of multi-parametric MRI which includes a combination of high-resolution T2WI images with at least 2 functional MRI techniques as these provide better characterization than T2WI with only one functional technique. In addition to T2WI MRI, which mainly assesses anatomy, diffusion weighted imaging (DWI) and MR spectroscopy imaging (MRSI) add specificity to lesion characterization, while dynamic contrast enhanced MRI (DCE-MRI) has a high sensitivity in cancer detection. According to a recent European Consensus Meeting, mpMRI should include T1-weighted, T2--weighted, diffusion-weighted and contrast-enhanced MRI but not MR spectroscopy. A pelvic phased-array coil is required but not the endorectal coil[16]. Diffusion-weighted imaging (DWI), which shows the motion of extra-cellular water molecules; dynamic contrast material enhanced MRI (DCE-MRI), focusing on tissue vascularity; and MR spectroscopic imaging (MRSI), that allows the detection of metabolites *in vivo* [2, 3 9].

Magnetic Resonance Spectroscopy Imaging

Three dimensional data are acquired from the prostate, with volume elements (voxels) ranging[3] from 0.24 to 0.34cm.

MRSI allows assessment of prostatic tissue metabolism by displaying relative concentrations of chemical compounds with contiguous small volumes of interest (voxels)[5]. The substances measured by MRSI are citrate, creatine and choline[3,14]. Traditionally, prostate MRSI voxels are designated as suspicious for cancer based on the (choline + creatine)/citrate ratio as defined in the literature[14]. In PCa citrate levels are reduced, creatine and choline levels are elevated. Suspicious of cancer is defined as a voxels with (choline + creatine)/citrate ratio > 0,8. Normal peripheral zone tissue is characterized by voxels with a (choline + creatine)/citrate ratio < 0,8[5]. Unfortunately, some benign conditions may also result in an increase of the ratio[3]. Typically, MRSI has high specificity but low sensitivity for PCa detection[17]. MRSI also provides information about lesion aggressiveness. Owing to its poor spatial resolution, it does not give staging information[15].

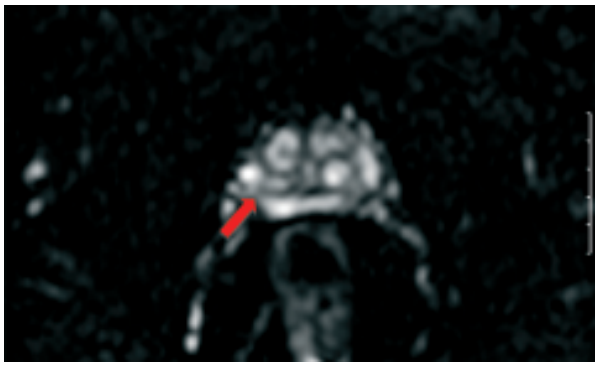

Figure 3: DWI shows decreased diffusion of water molecules in the pointed region (red arrow). MR guided biopsies from this region demonstrated prostate cancer.

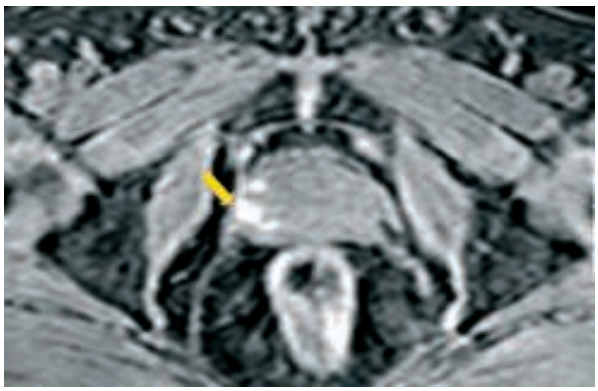

Figure 4: DCE-MRI shows elevated enhancement on the left peripheral zone (arrow). Guided biopsies from this region demonstrated prostate cancer.

Diffusion-weighted imaging

DWI relies on the random movements of water molecules (Known as Brownian motion) in biological tissues. DW MRI derives its image contrast from differences in the motion of water molecules between tissues. DW MRI yields qualitative and quantitative information: qualitative assessment considering the relative tissue signal attenuation for tumor detection and characterization; quantitative analysis of DW MRI is achieved by calculation of the apparent diffusion coefficient (ADC)[13]. The ADC is calculated for each pixel of the image and is displayed as a parametric map. In healthy prostate tissue, ADC are high[3, 13, 14].

Within tumors, the movement rate of water molecules is restricted as compared with normal tissue, probably as a result of many factors as higher cell density and abundance of intra and intercellular membranes in cancer[3, 13, 14].

DWI has advantages such as short acquisition time and no need of contrast medium but also disadvantages as being susceptible to motion and magnetic fields homogeneities[3, 13].

Of all MRI techniques, DWI is the most practical and simple to use[14].

Exam / *Measure*	T2WI MRI plus MRSI	MRSI plus DCE-MRI	MRI plus DWI
Sensitivity	57-100%	93%	81-86%
Specificity	44-96%	89%	84%
Accuracy	67-85%	91%	82%

Table 1 – Advantages and disadvantages of the functional MRI techniques

Dynamic contrast-enhanced magnetic resonance imaging

DCE-MRI consists on the repetitive acquisition of sequential images using T1-weighted sequences during and after intravenous bolus injection of gadolinium-based contrast medium within the prostatic tissue[3, 13, 15].

It allows distinction of malign tissue from benign and normal tissue by assessing tissue vascularity, especially neoangiogenesis, which is an integral feature of tumors. DCE MRI parameters can often be estimated both qualitatively and quantitatively. The parameters frequently reported are onset time of signal enhancement, time to peak, peak enhancement, and washout[3]. Cancers often demonstrate earlier nodular enhancement than the rest of the parenchyma as well as early contrast washout[14].

DCE-MRI is limited by a lack of standardized acquisition protocols and optimal perfusion parameter for differentiating cancer from normal tissue. DCE--MRI has high sensitivity, which can be useful for initial evaluation of potential tumor locations[3, 13, 14].

Advantages and limitations of the different functional MRI are presented at Table 1.

Multi-parametric MRI in prostate cancer diagnosis: recent results

Lawrentchuk et al reviewed all available databases from prospective studies in patients using MRI/ /MRSI and prostate biopsy with previous negative biopsies and persistently elevated PSA levels. Six studies fulfilled the criteria, all of them with limited populations (the largest was 54 cases). For MRI or combined MRI/MRSI, the overall sensitivity for predicting positive biopsies was 57-100%, the specificity 44-96% and the accuracy 67-85%[5, 10].

Sciarra et al performed a prospective study of 180 patients with prior negative random TRUS-guided prostate biopsy and persistent elevated PSA levels. This patients were randomized to a second random prostate biopsy (10 cores) or to a multiparametric 1.5T MRI (MRSI/DCE-MRI) followed by random prostate biopsy with additional samples targeted of suspicious areas described by MRSI and/or DCE-MRI (mean of cores 12.2). At the second biopsy, PCa was found in 24.4% of cases in the first group

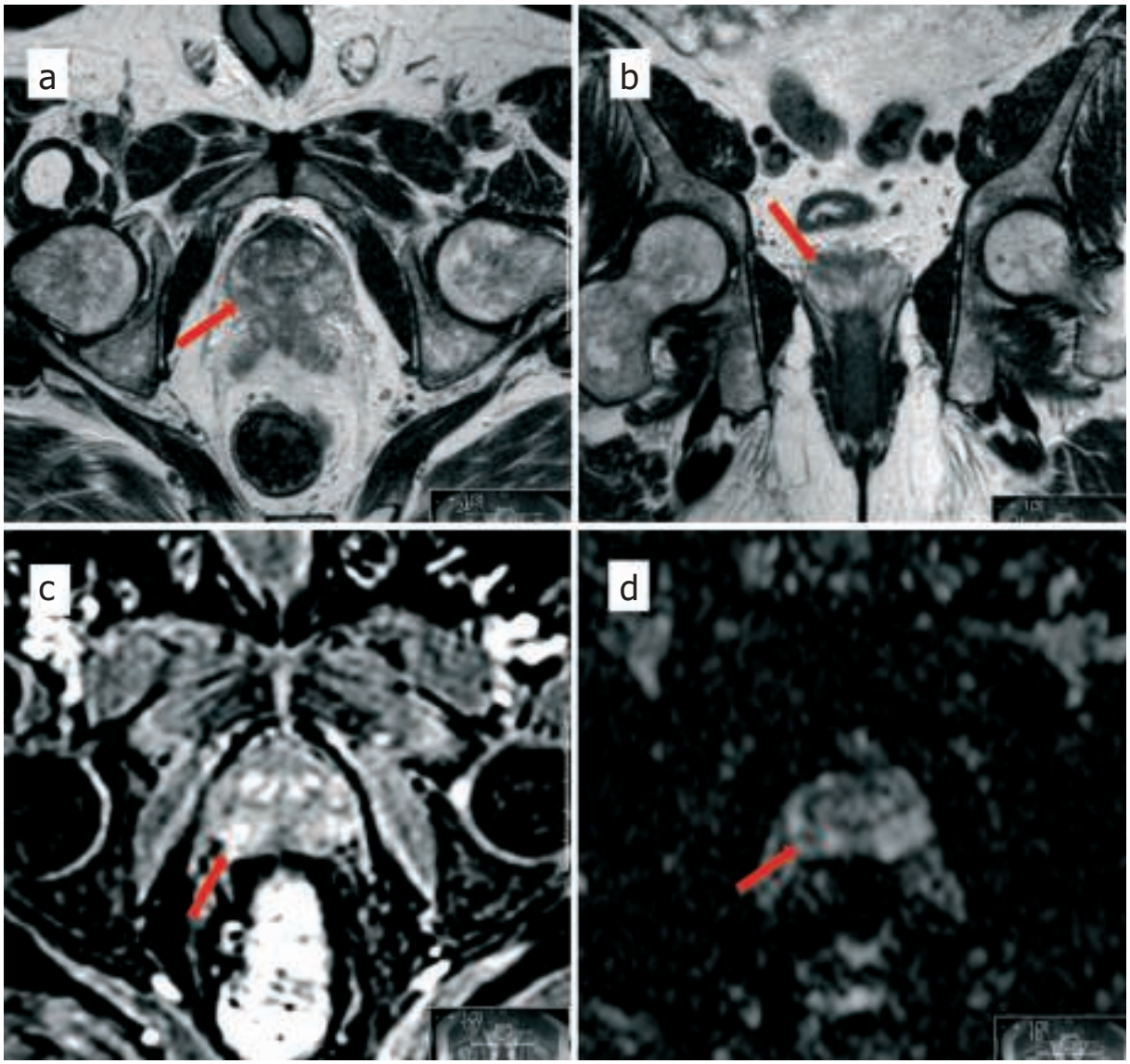

Figure 5: Axial Multiparametric Images of a patient with periferic PCa in the suspicious pointed area (arrow).
a)T2 Weighted axial plane
b)T2 Weighted coronal plane
c)Apparent diffusion coefficient (ADC) map - DWI MRI
d)Dynamic contrast enhanced (DCE) image
The tumor appears dark on the axial T2 weighted image (arrow). The corresponding area shows restricted diffusion on the DWI and ADC images as well as abnormal contrast enhancement on the DCE axial image..

and in 45.5% in the group submitted to mpMRI. In this study, the combination of MRSI plus DCE-MRI had 93% sensitivity, 89% specificity, 89% positive predictive value (PPV), 93% negative predictive value (NPV) and 91% accuracy for predicting PCa detection. Thus, the combination of MRSI and DCE-MRI showed potential to guide biopsy to cancer in patients with previously negative TRUS biopsy[5].

Several studies have evaluated the usefulness of DWI in prostate cancer.

Yoshimitsu et al performed a retrospective study of patients with PCa who had been submitted to radical prostatectomy. For the combined MRI/DWI, this study reported 86% sensitivity, 84% specificity, 90% PPV and 74% NPV for the detection of PCa[13, 14, 18].

Haider at al performed T2WI and DWI MRI to 49 patients before radical prostatectomy using an endorectal coil at 1.5T. T2WI images and T2WI combined with apparent diffusion coefficient maps (T2 + DWI) were scored for the likelihood of tumor and compared with whole-mount histology results. Sensitivity was significantly higher with T2 plus DWI (81%) than with T2 alone (54%), with T2 plus DWI showing a slight loss in specificity compared with T2 imaging alone (84% versus 91%, respectively)[19]. A summary of the sensitivity, specificity and accuracy of the articles mentioned previously is presented in Table 2.

Exam	Advantages	Disadvantages
MRSI	• High specificity	• Long acquisition time • Some benign conditions mimic PCa
DCE-MRI	• High sensitivity • Direct depiction of tumor vascularity	• Unsisfactory depiction of transitional zone cancer in patientes with hypervascular benign prostatic hyperplasia • Difficult to define the best acquisition protocol
DWI-MRI	• Short acquisition time • High contrast resolution between tumors and normal tissue	• Poor spatial resolution and potential risk of image distortion caused by post-biopsy hemorrage

Table 2 – Sensitivity, Specificity and Accuracy of anatomic and functional MRI for prostate cancer detection

Discussion

Experts regard mpMRI of the prostate as promising for the cancer diagnosis of the prostate[16, 20] but there is professional disagreement on its accuracy and usefulness in clinical practice[16, 21]. Variations in technique and the interpretation of images are pointed as the causes for the inconsistency in its reported performance characteristics.

In 2010 a European Consensus Meeting was held with the aim to make recommendations on a standardized method for the conduct, interpretation, and reporting of prostate mpMRI for prostate cancer detection and localization. A consensus was reached on a number of areas related to this. In particular, the panel recommended that all sequences (T2WI, DCE and DWI sequences) except MRSI should comprise the minimum standard. Recent evidence from a large prospective study for 110 patients showing no benefit of spectroscopy for PCa localization compared with T2WI alone supports this recommendation[16, 22].

The ideal population would be men with raised PSA who undergo mpMRI before histologic verification with biopsies. Thus, verification of work-up bias would be limited and the at risk population evaluated. Most studies currently use whole-mount prostatectomy specimens as the reference standard, introducing work-up bias[16].

One of the conclusions of this meeting was that before optimal dissemination of this technology, these outcomes will require formal validation in prospective trials in larger multicentre studies[16, 23].

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