Enhancing diagnostic accuracy for prostate cancer in multiparametric MRI: current Diffusion Weighted Imaging (DWI) techniques and future perspectives

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Abstract

Introduction and objectives. Multiparametric MRI of the prostate is considered the most efficient imaging technique for prostate cancer diagnosis, with overall detection rates of up to 60%. Diffusion Weighted Imaging (DWI) is a functional sequence that gained the dominant role in the prostate MRI protocol, as stated in the second version of the Prostate Imaging - Reporting and Data System (PI-RADS). We aimed to perform a systematic review of the literature concerning DWI, its technique, pitfalls, clinical efficiency and future perspectives.

Materials and methods. We performed a systematic review of the PubMed database using specific keywords both directly and using the Medical Subject Headings (MeSH) system. Priority was given to systematic reviews and clinical trials published in the last 5 years.

Results. DWI is clearly depicted in both versions of the PI-RADS system, and is universally deployed as an Echo-Planar Imaging technique. Classic DWI has a dual interpretation system: qualitative (direct signal intensity assessment) and quantitative (thru the Apparent Diffusion Coefficient - ADC and the ADC maps) that is used simultaneously. However, the poor spatial resolution (mainly at high b values of 1000 and 2000 s/mm²) can be a serious impediment for lesion identification thus enhancing techniques like DWI/T2 image fusions and computed DWI images were developed. A novel interpretation system for DWI data is Diffusion tensor Kurtosis Imaging that assesses kurtosis in the distribution of water molecules across the lesion. All these techniques provided promising results in the feasibility studies.

Conclusions. DWI is a multivalent technique, with a complex interpretation system and an improved clinical efficiency that could facilitate the progression to contrast-free multiparametric MRI.

Keywords: diffusion, DWI, Image fusions, Kurtosis Tensor Imaging, multiparametric MRI prostate cancer

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Introduction and objectives
Prostate cancer (PC) is the most frequent cancer in men living inside the EU, with an incidence rate of 70.4/100000 and a corresponding mortality rate of 10.9/100000, following lung and colo-rectal cancers[1]. In current clinical practice, PC diagnosis is based on the triad: PSA level, Digital Rectal Examination (DRE) and the histopathological exam after prostate biopsy. However, it has a low detection rate of up to 40% [2,3].

The introduction of MRI in PC diagnosis increased the overall detection rates up to 60% and is currently performed in a complex multi-sequence protocol („multiparametric”). Apart from the classic anatomical high-resolution T1 and T2, functional imaging had a determinant role by the means of Diffusion Weighted Imaging (DWI)[4].

The European Society of Genitourinary Radiology introduced guidelines for both performing and interpreting prostate MRI in 2012 called PI-RADS (Prostate Cancer Reporting and Data System) [5]. The second version of the PI-RADS was issued two years later, in 2014, and largely emphasized the role of DWI within the multiparametric prostate MRI protocol, finally resulting in a DWI-oriented diagnosis, followed by T2 and Dynamic Contrast-Enhanced T1 (DCE)[6,7].

We aimed to perform a systematic review of the literature concerning DWI, its examination technique, current pitfalls and their solutions, as well as its clinical efficiency in PC diagnosis and future perspectives.

Materials and methods
We performed a thorough PubMed search using the following keywords: MRI, diffusion weighted imaging, DWI, DWI/T2, image fusions, kurtosis, Diffusion tensor Kurtosis Imaging. A separate search was performed using the terms „prostate cancer”, „Multiparametric MRI”, „prostate”. Then a third search was performed using the terms combined with the „AND” connector. The most generic search (MRI AND prostate cancer) returned a series of 4679 articles. It was later refined using the specific DWI and DWI/T2 fusion terms. Restricting the search to clinical trials, the resulting list contained 266 items. Similar results were obtained with the other terms.

A series of filters were applied. Articles were limited to clinical trials and reviews, written in English or French and published in the last 5 years. The lot was subjected to a series of strict inclusion and exclusion criteria. Reviews had to be systematic, well documented, with recent studies included and a proper methodology. For clinical trials, priority was given to large, multi-center, randomized controlled trials. Articles with inconclusive abstracts were discarded. Where available, full-text versions were analyzed and processed for the remaining lot.

Results and discussions
Basic DWI principles
DWI is a novel imaging technique that studies the diffusibility of water molecules within biological tissues. In prostate cancer diagnosis, it is characterized by a 10 to 15% increase in PC detection rate when compared to the other diagnostic sequences (T2, DCE and spectroscopy) [8,9]. DWI images express the degree of movement of water molecules in tissues, called Brownian motion. Diffusivity of a lesion is inversely correlated to the compactness of the inner cellular micro-environment. Cancer lesions generally show high cellularity with an increased nuclear: cytoplasmic ration, resulting in an increased restriction when compared to the surrounding tissues. When examining the lesion at low b-values (<100 s/mm²) as well as high b-values (e.g. 1000s/mm²), the lesion appears hyperintense on the native DWI images and hypointense on the ADC maps. In case of fluid-containing lesions with fluid centers like necrotic or cystic cancers, the lesion will appear hyperintense at low b-values but with a significant signal drop in the high b-valued images and hyperintense on the ADC maps. Fast-moving cells (as blood cells) experience signal loss at all b-values creating the „dark-blood” effect [4].

Benign lesions, such as abscesses can also show diffusion restriction and mimic cancer. Differential diagnosis is done by correlating the aspect of the lesion on the other sequences. E.g. a hyperintense peripheral zone in the prostate will be „carried” upon the corresponding DWI image and mimic (or obscure) cancer (T2 „shine-through” effect). The true diffusivity will be revealed on the ADC maps [4].

Examination technique
According to the ESUR guidelines, DWI should be acquired in the axial plane using an echo-planar sequence and parallel imaging techniques. Gradients and diangiagnosis is done by correlating the aspect of the lesion on the other sequences. E.g. a hyperintense peripheral zone in the prostate will be „carried” upon the corresponding DWI image and mimic (or obscure) cancer (T2 „shine-through” effect). The true diffusivity will be revealed on the ADC maps [4].
intensities would enable calculation of the ADC in relation to the b=0 s/mm² images. For optimum DWI, examiners should use the 0, 100, 500 and 800-1000 s/mm² b values. The TE values should be kept to a minimum (typically<90ms) [5]. Examinations can be performed both on 1.5 and 3 Tesla machines, with a necessity for an endorectal coil the 1.5 while for the 3 T, a standard phased array torso coil would suffice. For comparison purposes, the section plane should be set perpendicular to the long axis of the prostatic gland [4].

**Diagnostic efficiency for prostate cancer**

Synthesizing the overall diagnostic efficiency of DWI for prostate cancer is difficult, mainly because of the large inhomogeneity of the reported results. According to different authors, reporting is performed to the different stages of prostate cancer, starting from indolent disease and expanding towards the locally-advanced cases.

**Predicting aggressiveness**

Considering that a high ADC value would be found more likely in a less aggressive lesion, Kim et al used the $0.830 \times 10^{-3}$ mm²/sec ADC as cut-off value for predicting the less aggressive forms of PC and subsequently enrolled those patients for Active Surveillance rather than radical therapy. They demonstrated that a high ADC value would be a predictor of organ-confined Gleason<=6 PC (odds ratio = 2.43, p = 0.011 and odds ratio = 2.74, p = 0.009, respectively) [10].

In order to reduce overdiagnosis of clinically-insignificant PC, Pokorny et al performed a broad study comparing the PC detection rates both for conventional transtrectal echo-guided prostate biopsy (TRUS-GB) and for magnetic resonance-guided transtrectal biopsy (MR-GB). They included 223 patients with clinical suspicion of PC (abnormal PSA and/or abnormal DRE) that were subjected to TRUS-GB alone. In the whole lot, suspicious lesions (PI-RADS 3,4 and 5) were found in 143 cases (sensitivity of 63%) which were subjected to TRUS-GB along with the rest that were subjected to TRUS-GB alone. The authors stated that conventional TRUSGB identified more low-risk patients 47(37.3%) when compared to 6(6.1%) patients in the MRGB group. However, this group could have been influenced by selection bias (these patients already had suspicious lesions on MRI, resulting in a low probability for low-risk disease [3].

Several studies suggested that the ADC value in DWI for PC could be a prediction score for tumor aggressiveness, particularly the Gleason score of the lesion. De Cobelli et al performed DWI on 72 biopsy-proven PC patients and found that the ADC values as well as the ADC rates of the analyzed lesions decreased as the Gleason score increased, with ADC values of 1.47, 0.96, 0.80, and $0.78 \times 10^{-3}$ mm²/s, for the following Gleason categories: normal tissue and biopsy Gleason scores of 6, 7, and 8-10 (p < 0.001). In conclusion they suggested that a decreased ADC value could suggest the presence of an aggressive PC [11].

**Predicting extracapsular extension**

Considering patients with extracapsular invasion, Woo et al performed DWI and T2 sequences and analyzed the concordance rates between different interpreters using the PI-RADS scores for both sequences. They found that in patients with average PI-RADS scores less that equal to three on T2 images, the mean ADC values were significantly lower in case of extracapsular extension than in the patients with organ-confined disease (mean ± SD, 0.794 ± 0.116 and 1.027 ± 0.339, respectively) (p < 0.001). They concluded that the ADC had an incremental value in patients without a high suspicion for extracapsular extension on T2-weighted imaging [12].

A similar study was performed by Kayat Bittencourt et al who explored the overall efficiency for predicting extracapsular extension on multiparametric MRI (DWI, T2 and DCE) in PC patients using the PI-RADS system. The authors included 133 PC patients prone to radical prostatectomy and found extraprostatic extension in 60 patients (45%). After analysis of the individual ROC curves for optimum efficiency in each parameter, they reported that extracapsular extension was predicted with a sensitivity of 63%, a specificity of 78%, positive likelihood ratio of 3.77 and a negative likelihood ratio of 0.56. They concluded, however that the PI-RADS criteria showed a moderate accuracy for the prediction of extraprostatic extension [13].

**Table I: Synthesis of the most recent trials concerning the clinical efficiency of classic DWI.**

<table>
<thead>
<tr>
<th>Author / Year</th>
<th>Study / Population</th>
<th>Staging parameters</th>
<th>Number of patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scher 2015</td>
<td>TRUS-GB alone</td>
<td>TRUS-GB alone</td>
<td>207</td>
<td>Increased ADC (Gleason score 6,7,8) (p &lt; 0.001)</td>
</tr>
<tr>
<td>De Cobelli et al 2015</td>
<td>ADC and/or PI-RADS</td>
<td>ADC and/or PI-RADS</td>
<td>72</td>
<td>ADC values decreased with increasing Gleason score (p &lt; 0.001)</td>
</tr>
<tr>
<td>Nasoni et al 2015</td>
<td>MR and/or T2</td>
<td>MR and/or T2</td>
<td>117</td>
<td>PI-RADS increased, ADC decreased with Gleason score (p &lt; 0.001)</td>
</tr>
<tr>
<td>Kayat Bittencourt et al 2015</td>
<td>MR and/or T2</td>
<td>MR and/or T2</td>
<td>119</td>
<td>Increased ADC values with increasing Gleason score (p &lt; 0.001)</td>
</tr>
</tbody>
</table>
New perspectives in DWI

Introducing Diffusional Kurtosis Tensor Imaging (DKI)

DKI is an alternative interpretation and quantification model of diffusion data that was demonstrated to fit DWI better than the monoexponential ADC which is routinely used in prostate MRI. According to Jensen et al, DKI should be performed using at least three b-values and at least 15 different gradient directions, in order to have a precise assessment, in comparison to standard DWI with 3 directions [14,15].

Starting from these principles, Quentin et al performed multiparametric prostate MRI on 31 patients (21 with abnormal PSA levels) and performed biopsies for 29 lesions in 14 patients. All-in-all, histopathology confirmed 17 cancer lesions in 9 patients. DKI was interpreted separately on a special workstation. After statistical analysis, the authors reported that the axial (Kax) and mean kurtosis (Kmean) values were significantly different in the tumor (Kax 1.78 ± 0.39, Kmean 1.84 ± 0.43) compared with the normal peripheral zone (Kax 1.09 ± 0.12, Kmean 1.16 ± 0.13; p < 0.001) or the central zone of the gland (Kax 1.40 ± 0.12, Kmean 1.44 ± 0.17; p = 0.01 respectively). They also reported a minor correlation between axial kurtosis (Kax -r = 0.19) and the Gleason score [16].

Improving DWI accuracy using digitally calculated high b-valued images

DWI can increase its diagnostic efficiency by using high b-values during image acquisition. However, the increase in B-value also results in a decrease in signal-to-noise ratio with poor image quality. Thus, alternative techniques were developed for obtaining these special images using computed post-processing techniques (like DKI and IntraVoxel Incoherent Motion - IVIM). Grant et al performed such a study where they compared lesion visibility and image quality both native and calculated (using IVIM and DKI) high b-valued images (at 0, 1000 and 2000 s/mm²) for 106 PC patients. They identified, mapped and compared the suspicious lesions across these images. They reported that the overall lesion number was greater in the b=2000 images, while image quality was similar for both native and calculated b=1000 images while for the b=2000 ones, the native images proved better quality. Concerning the calculation models, more lesions were visible in the IVIM model when compared to the DKI[17].

Introducing fusion imaging

Fusion imaging is a revolutionary post-processing technique that obtains hybrid morphological and functional images by digitally overlapping a high-resolution T2 image and its corresponding DWI one taken at the same level. The DWI/T2 image fusions and particularly their ability of detecting PC in prostate MRI was researched in 2011 by Rosenkrantz et al on a series of 42 PC patients that underwent radical prostatectomy after MRI. They reported statistically significant improvements in terms of accuracy and sensitivity for both readers using the fused images while for the specificity differences were present but non-significant (Reader 1: Accuracy +5.9%, Sensitivity +10%; Reader 2: Accuracy +7.1%, Sensitivity +14.2%, p<0.05) [18].

Fig. 1. Multiparametric MRI of the prostate in a 46-year-old prostate cancer patient (PSA 6ng/ml, a right-sided cancer with a Gleason score of 3+4=7). The target lesion has a discrete hyposignal in T2 (A) and an increased signal intensity in DWI (B) and the DWI/T2 fusion (C), suggestive for malignancy.
the Radiant® software. Interpretation was performed blinded using the PI-RADS score for T2 and DWI while for the DWI/T2 fusions we made an adapted variant of the score. To the present day the study is ongoing and preliminary results are promising.

Fig. 2. Multiparametric MRI of the prostate in a healthy 30-year-old control patient. The prostate is homogeneous in T2 (A), DWI (B) and DWI/T2 fusion (C).

Conclusions
1. DWI is generally accepted and performed according to the PI-RADS recommendations by the majority of authors;
2. Clinical efficiency of DWI is difficult to assess without the presence of the T2 sequence;
3. DWI could be used as a predictor of tumor aggressiveness (by appreciation of the Gleason score) and extracapsular extension;
4. Novel adjuvant techniques are being developed for improving diagnostic accuracy in DWI, with promising results.

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