Detection of prostate cancer using IVIM model

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Aims and objectives

In developed countries, prostate cancer account up to 20% of new cases of cancer diagnosed in males being considered a rising health problem. Therefore, there is a growing interest in the early diagnosis of this entity.

Prostate is a glandular structure with a wide extracellular space. The central gland shows different components, such as stroma, ductal structures, and smooth muscular fibers. Besides, the peripheral zone is less structured, meanwhile prostate cancer shows high cellularity and several inter and intracellular membranes. Most of prostate cancer (75-85%) occurs in the peripheral zone, but it is also the most common site of chronic prostatitis. The transition zone, whereas the benign prostatic hyperplasia occurs, surrounds the urethra. The central zone holds most of the remaining glands. However, it has been shown that the transition zones and central gland presents cancer in up to 25% of radical prostatectomy specimens.

MRI is usually used for locorregional staging of prostate cancer. In addition, MRI applications in other clinical scenarios are growing, such as nodule characterization or detection of cancer in patients with negative biopsy and high clinical suspicion (persistent elevated PSA and/or PSA ratio). MRI protocols have expanded from morphological sequences to include functional ones. Between them, Diffusion Weighted Imaging (DWI) has converted in the most accepted one. Furthermore, in the PIRADS system, DWI has been recognized as the most useful between all functional sequences in the differentiation between cancer and normal prostate [1].

Most of the experience has been accumulated using a monoexponential signal decay analysis of DWI, which is quantified by means of Apparent Diffusion Coefficient (ADC), [2-5]. However, this approach is limited because of the superposition of vascular flow, tubular flow, and passive diffusion, being ADC significantly affected by perfusion phenomena.

Intravoxel incoherent motion (IVIM) model described by Le Bihan [7] has been shown more suitable than monoexponential analysis to several well vascularized organs in the body, such as kidney, liver, pancreas and prostate.

Le Bihan and coworkers developed intravoxel incoherent motion (IVIM) model of diffusion signal decay, also known as bicompartimental model, and demonstrated that pure molecular diffusion and microcirculation can be distinguished. The blood perfusion inside the vessels shows a random movement that can be modeled as pseudodiffusion, and
detected at low b values (under 100 s/mm$^2$) (Fig. 1 on page 3). As this pseudo diffusion is b value dependent, it accounts only a very small proportion of the measured signal on each voxel at higher b values. In order to partially avoid perfusion contamination, a valid approach is to exclude of the ADC quantification, all b values under 100 s/mm2, which allows obtaining ADC$_{\text{high}}$ also known as ADC$_{\text{free perfusion}}$.

IVIM-model separates the diffusion signal decay in two different diffusion compartments. For low b values, between 0 and 100 s/mm$^2$, the diffusion signal experiments a fast decay due to the blood flow along the microvasculature, while for higher b values, over 100 s/mm2 the signal decay is related to pure diffusion characteristics of the tissue (without perfusion effects), as it shows a more progressive decay (Fig. 2 on page 4).

In prostate, recent reports have shown a significant difference between cancer and normal peripheral zone for IVIM-derived parameters demonstrating lower $D$ and $f$ values in cancer tissue than in health peripheral zone. [8-11]

Our aim is to analyze the capabilities of IVIM-derived parameters ($f$: perfusion fraction and $D$: tissue diffusion coefficient) to detect prostate cancer and differentiate it from normal prostate and also, to compare the results obtained with this approach with the ADC quantifications obtained using a conventional monoexponential analysis of diffusion signal decay.

**Images for this section:**
Fig. 1: Bicompartimental ivim signal decay analysis scheme

\[
\frac{S_b}{S_0} = (1-f) \cdot \exp(-bD) + f \cdot \exp[-b(D+D^*)]
\]

Fig. 2: Bicompartimental signal decay in prostate cancer
Methods and materials

Population:

Between June 2011 and October 2013, 130 consecutive MRI prostate studies were performed in patients with suspicion of prostate cancer or with confirmed prostate cancer for locoregional staging. All studies include a DWI sequence. Only patients (n: 42) with confirmed prostate cancer by TRUS biopsy were included in the final analysis. Six studies were excluded due to poor image quality. 30 patients presented only one cancerous nodule at peripheral zone, 4 patients presented one malignant nodule on each side of peripheral zone and 2 patients presented the cancer in central gland. The final population included were 36 males, with age range of 56-75 years-old (mean age: 66.3) with 40 nodules confirmed as prostate cancer.

MRI protocol:

All studies were performed in a 3T magnet with a 6 elements phase-array, including: high resolution TSE T2-weighted image in sagittal and coronal planes, 3D with isotropic voxel (VISTA) TSE T2-weighted sequence, axial TSE T1-weighted image, DWI and DCE-MRI. The diffusion-weighted sequence was performed in a total scan time of 4 minutes and 30 seconds, using aSSh SE EPI diffusion-weighted sequence with spectral fat suppression and a SENSE factor of 2, pixel resolution of 2.5 x 2.5 x 7 mm with a minimum gap slice of 3.5 mm and TR/TE of 5000/54 ms.

Four low b values were acquired below 100 s/mm² (0, 20, 40, 100) and 4 high b values over 100 s/mm² (300, 500, 1000, 2000). This sequence was fitted to the IVIM model of diffusion signal decay using a PRIDE Philips research software tool. D and f were calculated for all nodules and normal contralateral peripheral zone.

An elliptic region of interest (ROI) was place within the suspicious node trying to avoid contamination from normal tissue. Areas of necrosis, haemorrhage and susceptibility artefact were excluded of measurements. The ROI extension was between 20 and 60 mm² for all nodules, using the same ROI size for contralateral peripheral zone measurements. Fig. 3 on page 6 and Fig. 4 on page 6 represent examples of peripheral and central prostatic malignant nodes respectively with the bicompartimental signal decay analysis and the data collected for each parameter (Fig. 5 on page 7 and Fig. 6 on page 7).
In addition, ADC according to a monoexponential model of diffusion was calculated using all b values (ADC total) and all b values > 100 s/mm² (ADC free perfusion) for both tumor and normal prostate tissue at peripheral zone.

**Statistical analysis:**

Commercially available statistical software was used to perform normal distribution analysis (Kolmogorov-Smirnov), paired Student T - test for evaluating the differences at f, D, ADCtotal and ADC free of perfusion between prostate cancer and health peripheral contralateral zone. Dispersion diagram were generated using mean and standard deviation with a confidence interval of 95%. Receiver Operating Characteristic (ROC) curves were also calculated to determine sensitivity and specificity for each parameter (f, D, ADCtotal and ADC free of perfusion). For this analysis, a p value of less or equal than 0.05 was considered statistically significant.

**Images for this section:**

![Images](image-url)

**Fig. 3:** Example of peripheral zone prostate cancer with DWI (b2000), f and D IVIM derived maps, T2W TSE and ADC maps derived from DWI with and without low b values.
**Fig. 4:** Example of central zone prostate cancer with DWI (b2000), f and D ivim derived maps, T2W TSE and ADC maps derived from DWI with and without low b values.

<table>
<thead>
<tr>
<th>PERIPHERAL CANCER</th>
<th>Perfusion fraction</th>
<th>Tissue diffusion coefficient (x10^-3 mm²/s)</th>
<th>ADC total (x10^-3 mm²/s)</th>
<th>ADC free of perfusion (x10^-3 mm²/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral zone</td>
<td>0.44 +/- 0.41</td>
<td>0.95 +/- 0.10</td>
<td>1.25 +/- 0.64</td>
<td>1.16 +/- 0.90</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.17 +/- 0.08</td>
<td>0.41 +/- 0.65</td>
<td>0.48 +/- 0.84</td>
<td>0.42 +/- 0.08</td>
</tr>
</tbody>
</table>

**Fig. 5:** Data and bicompartimental signal decay curve of figure 3 nodule.
<table>
<thead>
<tr>
<th></th>
<th>Perfusion fraction</th>
<th>Tissue diffusion coefficient (x10⁻³ mm²/s)</th>
<th>ADC total (x10⁻³ mm²/s)</th>
<th>ADC free of perfusion (x10⁻³ mm²/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral zone</td>
<td>0.47 +/- 0.07</td>
<td>1.01 +/- 0.10</td>
<td>1.27 +/- 0.64</td>
<td>1.09 +/- 0.90</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.22 +/- 0.07</td>
<td>0.49 +/- 0.11</td>
<td>0.58 +/- 0.84</td>
<td>0.47 +/- 0.08</td>
</tr>
</tbody>
</table>

**Fig. 6:** Data and bicompartimental signal decay curve of figure 4 nodule.
Results

Both, ADC total and ADC free perfusion of prostate cancer calculated according to the monoexponential analysis of DWI were significantly lower compared to normal peripheral zone one (p<0.001) (Fig. 7 on page 10 and Fig. 8 on page 10 ). The biexponential model showed also significant differences (p<0.001) between cancer and healthy peripheral zone tissue, with lower values of both $f$ and D within prostatic tumor. (Fig. 9 on page 11 and Fig. 10 on page 11 )

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Perfusion fraction</th>
<th>Tissue diffusion coefficient (x$10^{-3}$ mm$^3$/s)</th>
<th>ADC total (x$10^{-3}$ mm$^3$/s)</th>
<th>ADC free of perfusion (x$10^{-3}$ mm$^3$/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral zone</td>
<td>0.42 +/- 0.01</td>
<td>0.89 +/- 0.25</td>
<td>1.11 +/- 0.38</td>
<td>0.98 +/- 0.36</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.25 +/- 0.01</td>
<td>0.59 +/- 0.16</td>
<td>0.74 +/- 0.25</td>
<td>0.64 +/- 0.19</td>
</tr>
</tbody>
</table>

Fig. 13: Table 1. Resume of mean and standard deviation of $f$, D, ADC total and ADC free perfusion for peripheral zone and tumoral nodules.

References: MRI UNIT, CLINICA LAS NIEVES - Jaen/ES

ROC curve demonstrated elevated accuracy with high sensitivity and specificity for all calculated parameters obtaining the highest area under the curve for parameters derived from biexponential model: D (0.95) and $f$ (0.93). (Fig. 11 on page 12 )

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Perfusion fraction</th>
<th>Tissue diffusion coefficient (x$10^{-3}$ mm$^3$/s)</th>
<th>ADC total (x$10^{-3}$ mm$^3$/s)</th>
<th>ADC free of perfusion (x$10^{-3}$ mm$^3$/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutoff value</td>
<td>0.34</td>
<td>795.8</td>
<td>955.7</td>
<td>839.9</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>87.5%</td>
<td>95%</td>
<td>92%</td>
<td>87.5%</td>
</tr>
<tr>
<td>Specificity</td>
<td>80%</td>
<td>75%</td>
<td>83%</td>
<td>80%</td>
</tr>
<tr>
<td>AUC</td>
<td>0.93</td>
<td>0.95</td>
<td>0.92</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Fig. 14: Table 2. Resume of sensitivity, specificity and AUC as its cut-off values for each parameter.

References: MRI UNIT, CLINICA LAS NIEVES - Jaen/ES

D, ADC total and ADC free perfusion performed similarly to distinguish, in a statistically significant manner, between cancer and normal prostate tissue. Also, a positive relation between D and ADC free of perfusion was found (Pearson correlation coefficient of 0.87) without significant difference between those parameters, as they measure the same physiological process, the pure diffusion of water within prostate tissue.
The statistical analyses for all patients showed that the mean of perfusion fraction in tumor regions was significantly lower ($p < 0.001$) than that from normal prostatic tissue (Fig. 12 on page 13). Similarly to other published data [8-11], $f$ in prostate cancer is lower than in normal prostate. This fact is not completely well understood yet, and it has been related to the TE of the sequence or to the histological heterogeneity of prostate cancer, as it presents not only vessels but also glandular secreting tissue.

**Images for this section:**

![Graph showing ADC total values distribution of cancer (left column) and peripheral health zone (right column)](image_url)

**Fig. 7:** ADC total values distribution of cancer (left column) and peripheral health zone (right column)
Fig. 8: ADC free perfusion values distribution of cancer (left column) and peripheral health zone (right column).

Fig. 9: ADC total values distribution of cancer (left column) and peripheral health zone (right column).
**Fig. 10:** D values distribution of cancer (left column) and peripheral health zone (right column)
Fig. 11: ROC curves for $f, D$, ADC total and ADC free perfusion.
Fig. 12: Dispersion diagram for D and f in tumor and health nodules
Conclusion

Bicompartimental IVIM diffusion approach is able to differentiate bening prostate tissue and cancer. D value correlates properly with ADC generated without the influence of perfusion (ADC_{free of perfusion}). ADC_{total} is also able to differentiate accurately prostate cancer from normal peripheral zone. D and f values have high accuracy for the detection and characterization of malignant prostatic nodules.

Personal information

References


