Review Article

Correlation between ADC values and Gleason score in evaluation of prostate cancer: multicentre experience and review of the literature

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Abstract: Prostate cancer (PCa) is one of the most common cancers in male population. Multiparametric prostate magnetic resonance imaging (mp-MRI) has assumed a primary role in the diagnosis of PCa, combining morphological and functional data. Among different sequences, functional diffusion weighted imaging (DWI) is a powerful clinical tool which provides information about tissue on a cellular level. However, there is a considerable overlap between either BPH (Benign Prostate Hypertrophy) and prostatic cancer condition, as a different DWI signal intensity could be shown in the normal architecture gland. Apparent diffusion coefficient (ADC) has shown an increasing accuracy in addition to the DWI analysis in detection and localization of PCa. Notably, ADC maps derived DWI sequences has shown an overall high correlation with Gleason score (GS), considering the importance of an accurate grading of focal lesion, as main predictor factor. Furthermore, beyond the comparative analysis with DWI, ADC values has proven to be an useful marker of tumor aggressiveness, providing quantitative information on tumor characteristics according with GS and Gleason pattern, even more strenuous data are needed in order to verify which ADC analysis is more accurate.

Keywords: Prostate cancer (PCa); diffusion weighted imaging (DWI); apparent diffusion coefficient (ADC); multiparametric magnetic resonance imaging (multiparametric MRI); Gleason

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Background

Prostate cancer (PCa) is one of the most common cancer in the male population, with bone metastases in up to 70% of cases, which often require a more aggressive treatment (1-4). The incidence of PCa increases with age, ranging from 34% in the fifth decade, to 70% over the 80 years (5). The increase in survival (about 99%) (5) and the development of minimally invasive procedures in PCa treatment (6) paid attention to improving PCa detection.

Diagnostic imaging has achieved high accuracy in detect tumor and defining their characteristic and aggressiveness (7).

In this regard, MRI has assumed a primary role in the

study of various district and pathologies, thanks to its high contrast resolution (8-17). Notably, in the urogenital pathology management, MRI has become advantageous also in guiding minimally invasive treatment technique (18-20).

These evidences are confirmed by the current role of multiparametric prostate magnetic resonance imaging (mp-MRI), which is the most used instrumental method for the diagnosis of PCa, combining morphological and functional data through which also permits accurate biopsy, increasing its diagnostic yield (21,22).

However, considering the amount of data, the modified version2 of Prostate Imaging Reporting and Data System (PI-RADS), initially published by the ESUR, has been formulated in order to standardize the evaluation and reporting of the mp-MRI interpretation (23), thus providing a system of analysis capable to significantly improve the preoperative detection of PCa. This classification system foresees the use of different sequences (T2-weighted sequences diffusion weighted imaging (DWI) sequences and pre-contrast and post-contrast T1-weighted sequences) which together increase the detective capacity of the magnetic resonance in recognizing PCa.

DWI

Among different multi-parametric sequences, DWI is a powerful clinical tool which provides functional information about tissue on a cellular level (24). Diffusion-weighted sequence exploits the principle of the diffuse motions of the thermally induced free water, called "Brownian" motions, according to which the diffusive properties of tissues are directly related to the amount of free interstitial water and the degree of permeability. In MRI diffusion imaging, the contrast of imaging is based on the intensity of microscopic movements. Two gradients (diffusion gradients) are added before and after a 180° pulse to make a diffusion-sensitive pulse sequence. In the case of stationary spin, the de-phasing of the spin due to the first diffusion gradient is followed by a perfect rephasing by the second gradient. In case of spin in motion, the power factor correction will be incomplete, with the consequent loss of signal inside the voxel (25).

The b value is the measure of the strength and duration of the diffusion gradients, which determines the sensitivity of the DWI sequence in identifying the zones of increased diffusivity (26). Notably, tumor tissue tends to have less diffusivity than normal tissue due to its high cellularity (27). Indeed, the normal glandular architecture is altered in PCa where the large interstitial spaces and the glandular lumens are replaced by nests of tumor cells and fibrous stroma with a consequent reduction in the movements of free water. Therefore, high-intensity signal zone on DWI images is suggestive for clinically significant cancer. However, there is considerable overlap between either BPH and prostatic cancer condition, as a different DWI signal intensity could be shown in the normal architecture gland.

Transitional zone (TZ) and peripheral zone (PZ), indeed, show different structure, with abundant compact fascicles of smooth muscle in the TZ and prevalence of glandular tissue (about the 75% of the total amount of the gland) in the PZ. This different architecture results in different DWI signal intensity, depending on the relative amount of glandular or stromal tissue. Notably, some adenoma could be characterized by high signal intensity on diffusion-weighted MR images and low ADC value, similar to tumor (28) (*Figure 1*). Thus, to increase the accuracy in evaluating DWI, the evaluation should include ADC map and high b-value (23), according to the current guideline for mpMRI interpretation.

The high b-value has shown a high capability in visualize clinically significant cancer by the preservation of signal intensity only in the highly restricted area, especially for subcapsular lesion or those located at the apex or the base of the gland (23). Nowadays, there is no widely accepted "high b-value," even are often used b-value more than 1,000 s/mm^2, with a maximum b-value ranging from 2,000 to 3,000 sec/mm^2 (29). However, even some authors suggest the high b-value the high sensitivity in detecting clinically significant cancer (30), the latter show a significant decrease with b-value higher than 3,200 sec/mm^2 (0.871 to 0.800), considering that signal to noise-ratio decrease as the b-value increase (30).

Apparent diffusion coefficient (ADC)

The ADC has shown an increased accuracy in addition to the DWI analysis in detection and localization of PCa (31). ADC map is a model that expresses the signal decay with increased b-value. Its accuracy widely accepted, with a sensitivity and specificity of 82.6% and 91.3% respectively, and a positive and negative predictive value of 100%, as recently shown (5).

According to the ESUR guidelines, it is advisable to use at least two b-values to obtain ADC map, with the lower at 50–100 sec/mm^2 and the higher ranging from 800–1,000 to 2,000 sec/mm^2 (23). Even no evidence in literature

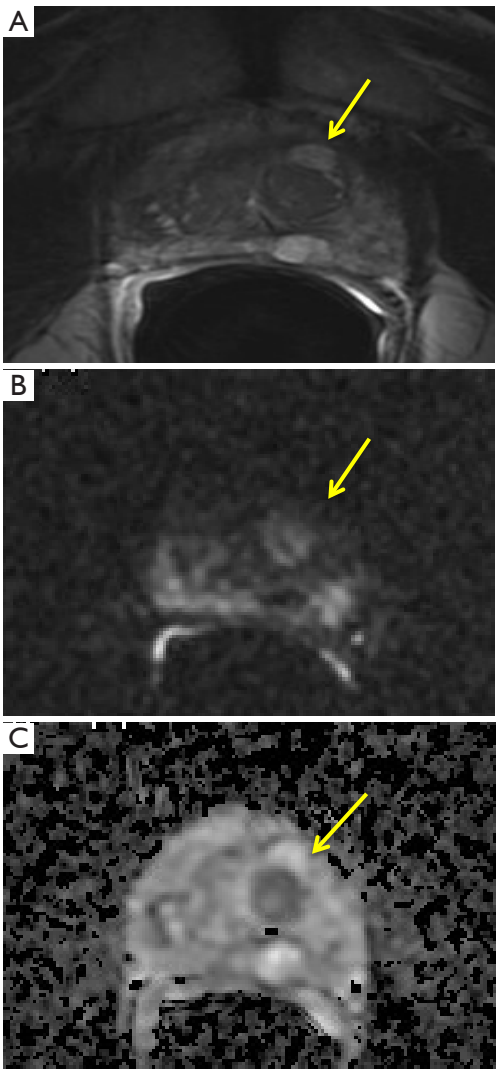

Figure 1 T2 (A), DWI (B) and ADC map (C) in healthy patient. Yellow arrows show central glandular adenoma. DWI, diffusion weighted imaging; ADC, apparent diffusion coefficient.

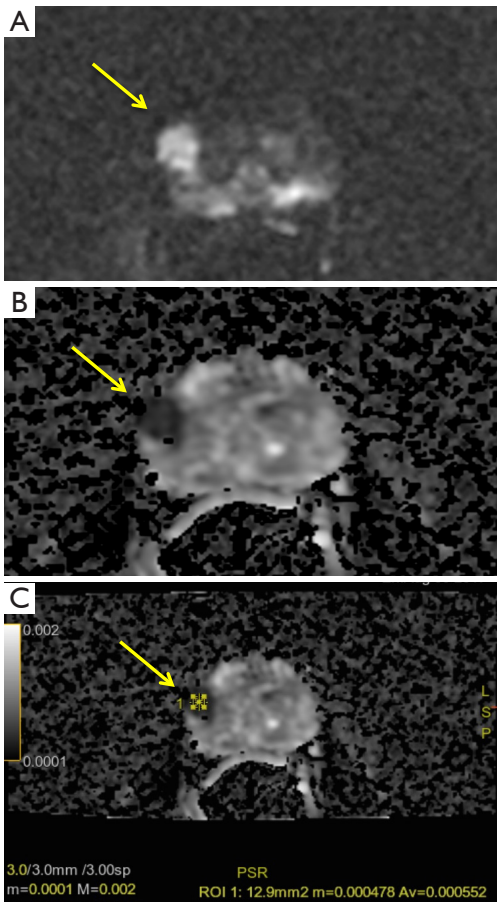

Figure 2 DWI (A) and ADC map (B) in patient with GS 8 prostate cancer (yellow arrow). ADC analysis (*) (C) show a low mean value (0.552×10^{-3}) consistent with the Gleason cancer grading. DWI, diffusion weighted imaging; ADC, apparent diffusion coefficient.

addressed what is the most accurate high b-value to use in ADC computation, higher b-value than 2,000 s/mm^2 has shown significantly lower sensitivity, as demonstrated by the accurate meta-analysis provided by Shaish *et al.* (32), due to the artifacts intrinsically related to the high b-value. However, ADC maps obtained with high b-value has shown high capability in the extracapsular extension of PCa (33).

Other attempts have been made to overcome these technical problems, as shown by Sadinski *et al.*, who used hybrid imaging that produces maps of the changes in ADC and T2 with changing TEs (34). Sadinski *et al.*, indeed, conclude that this approach can potentially display a relatively small signal from cancerous foci within a larger normal glandular tissue. Furthermore, DWI must always be associated with the evaluation of the ADC maps also for the "T2 shine through effect", considering that the long T2-relaxation time of the glandular tissue determines a hyperintensity of PZ in DW images.

Beyond the comparative analysis with DWI, ADC value has proven to be a useful marker of tumor aggressiveness, providing quantitative information on tumor characteristics (24) (*Figure 2*). Furthermore, the assessment of local aggressiveness, through the Gleason score (GS), is the stronger predictor for localized disease. In the last few years, different studies have shown the high correlation between ADC value and GS and Gleason pattern. Indeed, biochemical recurrence rate varies considerably even in

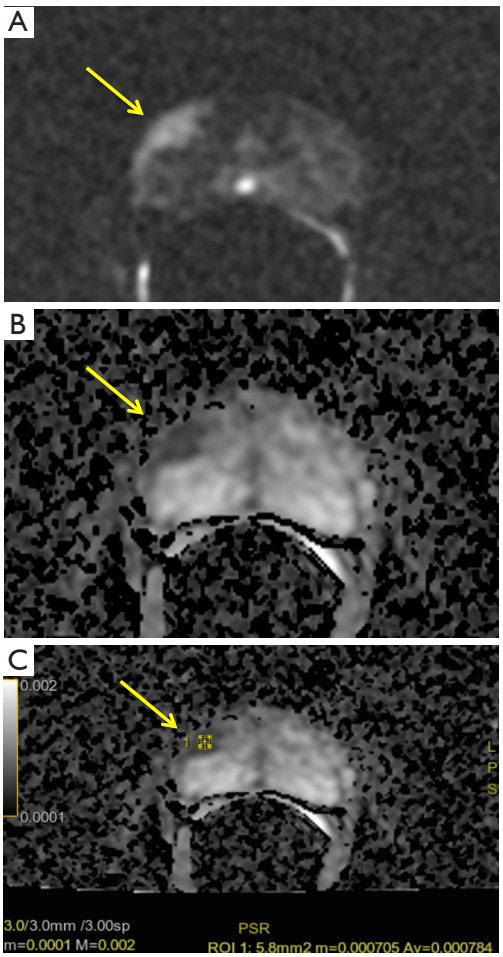

Figure 3 DWI (A) and ADC map (B) in patient with GS 7 prostate cancer (yellow arrow). ADC analysis (*) (C) show a mean value of 0.784×10^{-3}, consistent with the Gleason cancer grading. DWI, diffusion weighted imaging; ADC, apparent diffusion coefficient.

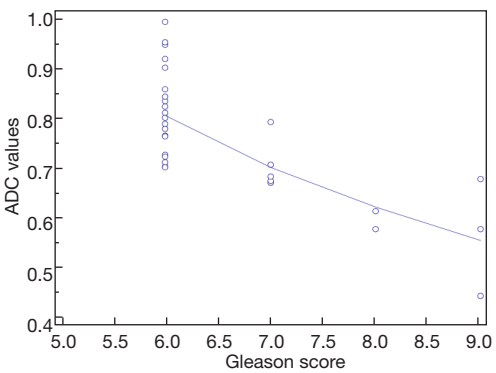

Figure 4 Correlation between ADC values and Gleason score. ADC, apparent diffusion coefficient.

the same GS 7 depending on different Gleason Pattern (GP; 3+4 or 4+3) (31).

By these evidences, our experience shows similar results. Notably, we performed a retrospective analysis on 60 patients (age 45–75 years) who underwent a previous mpMRI with a PI-RADS ≥ 3/5 and a subsequent histological diagnosis of GS ≥6 according to the results of fusion biopsy (Magnetic resonance Imaging-Transrectal Ultrasound Image Fusion Biopsy) or radical prostatectomy. For all of them, it was analyzed the relation between ADC values (mean tumor ADC values) and GS (*Figure 3*). Analysis of data shows a characteristic distribution of value depending on GS (ADC_{mean} $\geq0.702\times10^{-3}$ mm^2/sec for GS 6; ADC_{mean} ranging from 0.672×10^{-3} to 0.795×10^{-3} mm^2/sec for GS 7; ADC_{mean} $\leq0.615\times10^{-3}$ mm^2/sec for GS 8 or 9 and a minimum value of 0.445×10^{-3} mm^2/sec), with all correlation statistically significant (P<0.0001) (*Figure 4*).

However, there is no agreed ADC tumor cut-off value that could be reliably used to determine abnormally low ADC within a lesion (4,5). Nevertheless, in PI-RADS version 2, a threshold of 750–900 mm^2/s is suggested as pathological ADC range value, as in our experience. It is still under debate also which is the most accurate method of measuring the ADC value, considering how absolute ADC values could depend on the selected b-value. Therefore, different options are under investigation beyond ADC tumor mean value, as minimum ADC value (ADC_{min}) and normalized ADC value (ADC_{ratio}: expressed as the ratio between tumor and non-tumor ADC values). ADC_{min}, indeed, is still a valid option as showing in astrocytic brain tumor, with a significant correspondence between lower ADC value and highest cellularity zone, thus improving the tumor grading (35).

ADC_{ratio}, on the other hand, is relatively independent of the b-value used (31). Due to its intrinsic properties, ADC_{ratio} seems to be a more useful and reproducible method (36-38). In fact, among different option, even both ADC_{min} and ADC_{ratio} show a significant correlation with GS in the PZ, only ADC_{ratio} show a significant capability in detecting a clinically significant tumor in TZ tumors, as shown by Wu *et al.* (24). Moreover, many authors affirm that ADC_{ratio} is the only method which shows a significant capability in discriminating GP 3+4 from 4+3 PCa (29,31,39).

ADC maps have shown to be particularly advantageous also in both surgery and radiotherapy follow-up.

Even a relatively low sensitivity (25–29%) in the identification of a loco-regional tumor recurrence in

relation to lower spatial resolution, susceptibility artifacts from surgical clips or gas within the rectum or endorectal coil, and rectal motion, addition of the DWI images and the ADC maps to the T2-weighted sequences has been proven to be useful in identifying a large group of falsely negative patients as the morphological alterations did not correspond to a restricted diffusion area (40). Moreover, ADC values could show significant change also during and after radiotherapy (hypofractionated Proton and Carbon Ion irradiation), due to tumoral cell death and modifications of the local microenvironment; therefore, a finding of ADC values decrease after 18 months from treatment, is suggestive of tumor residual or recurrence (41).

Conclusions

In conclusion, in the last few years, different studies investigated the correlation between ADC derived DWI and tumor alteration. Through the evidence of literature, ADC analysis seems to show a high capability in defining the tumor aggressiveness, as in monitoring radiation therapy effect or surgical recurrence.

In accordance with the current literature, also our unpublished results confirm this strong correlation. However more studies are needed to clarify which ADC value analysis is the more efficient, even ADC_{ratio} seems to show the higher accuracy among different option.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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