Usefulness of ADCratio (rADC) for prostate cancer aggressiveness assessment in patient treated with 5-alpha-reductase inhibitors (5-ARI) for benign prostate hypertrophy (BPH)

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Authors: L. Basso, S. Migone, C. bergaglio, F. Rosa, V. Prono, L. Secondini, I. Verardo, G. Perugin, C. E. Neumaier; Genoa/IT  
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Aims and objectives

Benign Prostatic Hypertrophy (BPH) is the most common benign prostatic pathology and is symptomatic in about 50% of patients [1][2][3]. EAU guidelines published in 2015 recommend 5#-Reductase Inhibitors (5-ARIs) (Finasteride and Dutasteride) for the management of lower urinary tract symptoms (LUTS) as a first-line therapy [4]. These drugs reduce Prostate Specific Antigen (PSA) levels by 50% after 6-12 months of therapy. Prostate cancer (PCa) is the most common malignant neoplasm in male population [5] [6] and several studies recently examined the incidence of PCa in patients treated for BPH with 5-ARIs.

Different studies showed controversial results: the Prostate Cancer Prevention Trial (PCPT) and the REDUCE (Reduction by Dutasteride of Prostate Cancer Events) both demonstrated a decrease in the incidence of PCa (18.4% and 22.8% respectively), but an increased incidence of high-grade PCa (Gleason Score > 7) among the group of patients treated with Finasteride in PCPT [7] and a significant increase of high-grade PCa (GS>8) in the 3rd and 4th year of therapy with Dutasteride in REDUCE [8]. According to these studies, in 2011 FDA made a safety announcement about the risk of an increase of high-grade PCa (GS>8) among patients treated with 5ARIs [9] and did not approve these drugs for the prevention of PCa.

However, a revision of PTCP results carried out in 2008, pointed out that the correlation of high-grade PCa (defined as GS>7) in patients under therapy with Finasteride was not statistically significant [10].

Moreover, also other studies carried out many years later and investigating the relationship between Dutasteride and high-grade PCa, as The Reduction by Dutasteride of Clinical Progression Events in Expectant Management of Prostate Cancer (REDEEM) study [11] and the study published by Andriole and colleagues [12], did not reveal any increase in high-grade PCa among the group of treated patients.

Although the well-established role of Diffusion Weighted Imaging (DWI) in the multiparametric protocol for the diagnosis of peripheral PCa [13], and the inverse correlation between Apparent Diffusion Coefficient (ADC) and GS as an important predictive tool for tumor aggressiveness [14], ADC values are known to be widely variable in relation to several factors, like field strength, acquisition parameters and prostate zones.
PI-RADS v2 guidelines suggest an ADC threshold of $0.9 \times 10^{-3} \text{ mm}^2/\text{s}$ to help discrimination between PCa and normal tissue in the Peripheral Zone (PZ) [13]. However, Langer and colleagues find out that small, low-graded PCa of the PZ, called "sparse tumors", have an ADC value similar to the ADC value of normal tissue [15]. In order to solve this problem, many studies were conducted on ADC ratio, defined as the ratio between the ADC value measured in cancerous tissue (ADC cancer or cADC) and the ADC value measured in normal tissue (ADC normal or nADC) [16][17][18]. Boesen and colleagues demonstrated that ADC ratio shows a better correlation to GS than cADC and is more accurate in discriminating between clinically significant and not-significant cancer [19].

The aim of this retrospective and monocentric study is to compare the changes of the ADC values measured in cancerous tissue between a group of patients treated with Finasteride or Dutasteride and a group of untreated patients and, secondarily, to investigate the correlation between Gleason Score (GS) and ADC values, expressed both as the ADC value measured in cancerous tissue (cADC) and as the ADC ratio (rADC).
Methods and materials

Patient selection

43 patients who underwent a Multiparametric Magnetic Resonance Imaging (mpMRI) and a Transrectal Ultrasound biopsy (TRUS-bx) with Transperineal Prostate Mapping (TPM-bx) or Radical Prostatectomy (RP) from June 2013 to November 2015 were retrospectively enrolled in this study. 21 of enrolled patients were under pharmacological treatment for BPH with 5ARIs, as Finasteride (Finasterid 5 mg, PharmaCoDane, Herlev, Denmark) or Dutasteride (Avodart, PharmaCoDane, Herlev, Denmark) since at least one year, and 22 patients were under no therapy. The patients were identified through our RIS/PACS (Radiology Information System/Picture Archiving and Communication System).

All recruited patients underwent a mp-MRI and a TRUS-biopsy was performed with a time gap not exceeding 2 months or within at least 6 weeks before mp-MRI.

No one of the enrolled patients had a MRI/TRUS-fusion biopsy. Patients treated with focal therapy, Radical Prostatectomy (RP), LHRH agonist or chemotherapy were excluded. They were also excluded if the images were not satisfactory (e.g. multiple artifacts from total hip replacements or patient movements).

 Acquisition Protocol

Each patient underwent mp-MRI on a 3T MRI scanner (Signa EXCITE®HDxT, GE, Milwaukee, USA) according to Prostate Imaging and Reported Data System Version 2 (Pi-RADS v2) guidelines of 2015 with a pelvic coil (Phased Array, 8 channels). To suppress peristalsis of the bowels, intravenous injection of hyoscine butylbromide (Buscopan®, 20 mg, Boehringer, Taiwan) was administered immediately before the examination started.

All patients underwent para-axial T2-WI (Fast Recovery Fast Spin Echo-XL 90) parallel to the short axis of prostate and sagittal and paracoronal T2-WI parallel to the long axis. The diffusion study was then done by acquiring a single-shot echoplanar imaging sequence (DWI-EPI) using two different b values (50, 1000) in a single acquisition. T1 Spoiled Gradient Echo was acquired before and after contrast administration.
Bolus injection of Gd-DTPA (Prohance® 279.3 mg/ml, flac. 15 ml i.v., Bracco, Italy) was performed by a power injector (Medrad®) with an injection rate of 4 ml/sec. followed by a 20 ml flush with saline.

All data are resumed in Table 1 on page 8.

Image analysis

Two Radiologists with 15 and 3 years of experience in prostatic MRI retrospectively and together reviewed the images and placed the Regions of Interest (ROIs) on the main cancerous lesion reported by biopsy.

ADC maps were generated from the MRI-workstation software using $b$ values of 100-1000 s/mm$^2$.

A ROI was drawn in the slice of ADC map where the suspicious area was best visible.

Another ROI of the same area was placed in the contralateral portion of peripheral gland, symmetrically to the suspicious area, radiologically rated PI-RADS 2 and reported as normal at biopsy.

In patients without suspicious lesions, ROIs were drawn in the most homogeneous portion of the peripheral gland.

The mean cADC and nADC values were obtained by the mean of three ROIs for each measurement and were recorded for analysis. rADC was obtained by the ratio between the mean cADC and the mean nADC. Some example are reported in Fig. 1 on page 8, Fig. 2 on page 9 and Fig. 3 on page 9.

Statistical analysis

The statistical analysis was performed using software MedCalc v14 and a $p$ value<0.05 was considered significant. ANOVA test was used to assess the correlation between clinical and histological characteristics of cancer and ADC values. The correlation between cADC and GS and between ADC ratio and GS has been studied with ANOVA test and receiver operating characteristic (ROC) curves.
ROC curves were generated and Area Under the Curve (AUC) was calculated to assess the ability of the ADC values to discriminate between GS<6 and GS#6. The ADC value with the highest AUC was recorded.
**Table 1**: Acquisition Protocol.

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![Images](image1.jpg)

![Images](image2.jpg)
Fig. 1: Patient treated with 5ARIs presenting a suspicion for PCa seen by mpMRI (PI-RADS 5) and confirmed by biopsy (GS 4+5). A. Axial T2-WI: hypointense area in right posterolateral zone (PZpl Mid) suspicious for PCa. B. Axial T1-WI C. DWI D. ADC map E. ADC map with settled ROIs on suspicious lesion and contralateral tissue

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Fig. 2: Untreated patient with a suspicious area for PCa (PI-RADS 4) confirmed by biopsy (GS 3+3). A. Axial T2-WI: hypointense area in right posterolateral zone (PZpl Mid) suspicious for PCa. B. DWI C. ADC map D. ADC map with settled ROIs on suspicious lesion and contralateral tissue

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**Fig. 3:** Patient under therapy with 5ARIs, without any suspicious findings described at the mpMRI (PI-RADS 2) and with a prior negative biopsy. A. Axial T2-WI: hypointense area in right posterolateral zone (PZpl Mid) suspicious for PCa. B. DWI. C. ADC map. D. ADC map with settled ROIs on PZ.

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Results

A total of 43 patients (21 treated with 5ARIs and 22 untreated) with a mean age of 70.1 (range 63.7-75.7) and a mean PSA of 7.3 ng/ml (range 4.2-11) was analyzed in this study. No statistically significant difference (p=0.02) was observed neither between the mean age of patients in the two groups (mean age of treated patients 68.7 years [range 62.8-74.5]; mean age of untreated patients 74.5 years [range 64.2-77.3]), nor between the PSA levels in the two groups (mean PSA of treated group 5.9 ng/ml [range 3.7-10.1] and mean PSA of untreated group 7.8 ng/ml [range 6-11]). All data are resumed in Table 2 on page 13.

Since this study is retrospective, we decided to select the same number of patients for each GS, in order to make the statistical analysis more homogeneous and comparable. 20 patients with a biopsy positive for prostate cancer and 23 patients with a negative biopsy were chosen.

Table 2 on page 13 shows the distribution of GS in the two groups. 6 tumors had a 3+3 GS, 2 tumors had a 3+4 GS; 8 tumors had a GS of 4+3; 2 tumors had a 4+4 GS and 2 tumors had a 4+5 GS.

Table 3 on page 13 shows that cADC values are significantly higher in 5ARIs group than in untreated group (p=0.05): the mean value of cADC is 1.3 x10^{-3} mm2/s (range 0.8-1.6 x10^{-3} mm2/s) in treated patients, while is 1 x10^{-3} mm2/s (range 0.6-1.5 x10^{-3} mm2/s) in untreated patients.

nADC values as well are significantly (p=0.01) higher in the treated group: the mean nADC value in the treated group is 1.6 x 10^{-3} mm2/s (range 1.5-1.8 x 10^{-3} mm2/s) versus 1.4 x 10^{-3} mm2/s (range 1.3-1.6 x 10^{-3} mm2/s) in the untreated group.

rADC values, instead, did not revealed any statistically significative difference (p=0.4) between the two groups. The mean ADC ratio value is 0.9 (range 0.6-1) in the treated group and 0.8 (range 0.4-1) in the untreated group.

Using ANOVA test, a significant correlation (p<0.001) between cADC and GS was demonstrated among both groups.
Table 4 on page 14 reports the inverse correlation between cADC and GS among the treated group (red line) and the untreated group (green line).

ANOVA test demonstrated the same significant inverse correlation (p<0.001) between ADC ratio and GS in the two groups (Table 5 on page 15).

ROC analysis showed an AUC of 0.975 (confidence interval [CI] 0.874-0.999) for the cADC value and an AUC of 0.987 ([CI] 0.894-1) for the ADC ratio in the ability to distinguish between Gleason Score <6 and Gleason Score #6. (Table 6 on page 15).

The cut-off value of 0.733 for ADC ratio showed a sensitivity of 95%, a specificity of 100%, a PPV of 100% and a NPV of 92%.

It is remarkable that for a higher cut-off value, as 0.9167, the sensitivity was 95% while the specificity was decreased by 73%.

ROC analysis also revealed that for a GS#7, the cut-off value is #0.6667 with an Odds Ratio of 125,2 (6.4-2438.2) and a p value<0.0001. The sensitivity is 100%, the specificity is 83%, the PPV is 72% and the NPV is 100%.
Table 2: Patient data and distribution of GS between the two groups.

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Table 3: cADC, nADC and ADC ratio (rADC) values in the two groups of patients.
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Table 1: Acquisition Protocol.

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Table 4: ANOVA test showing the correlation between cADC and GS in patients treated with 5ARIs (red line) and in untreated patients (green line).

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Table 5: ANOVA test showing the correlation between ADC ratio and GS in patients treated with 5ARIs (red line) and in untreated patients (green line).

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Table 6: ROC analysis shows the Sensitivity and Specificity of cADC and rADC in the discrimination between cancerous tissue (GS #6) and normal tissue.

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Conclusion

This study revealed that cADC and nADC are significantly higher in patients treated with 5ARIs than in untreated patients.

From a clinical and a radiological point of view, these results reveal that a correct diagnostic overview with mpMRI can be arduous in patients under therapy with 5ARIs: Radiologists should be always informed about patient’s therapy with Finasteride and Dutasteride to interpret correctly the mpMRI findings.

As suggested by Giganti et al. [20], these drugs can make small and low-grade tumors less visible in mpMRIs performed during active surveillance (AS) protocols.

The significant correlation with GS has been demonstrated for both cADC and ADC ratio. As Hambrock and colleagues [21] previously affirmed, we observed an inverse correlation between cADC and GS in the two study groups. The same inverse correlation is confirmed, also, in the analysis of ADC ratio, as already shown by Boesen and colleagues [2][19]. Their study examined a cohort of untreated patients, while our study presents similar results both in the group of untreated patients and in the group of patients undergoing 5ARIs therapy. Moreover, as already mentioned, several studies demonstrated the best correlation of ADC ratio with GS and its ability to standardize the difference in cADC values between peripheral and transitional zones [19]. In our study, ADC ratio did not show a significant difference between the two groups, probably because the difference in cADC values between the two groups is normalized by the ratio with nADC. This result is crucial to demonstrate that the use of the ratio could improve the discrimination and the identification of suspicious lesions even in patients undergoing 5ARIs.

ROC analysis pointed out the superiority of ADC ratio in the discrimination between cancer (GS#6) and normal tissue (GS<6) in both groups, with a cut-off value of 0.733.

We tested a cut-off value of 0.6667 to distinguish between clinically significant prostate cancer (GS#7) and clinically non-significant prostate cancer (GS<7): in this case the sensitivity of rADC improved if compared to cADC, but the specificity decreased.

However, some limits have to be considered in our study. First of all, ADC is influenced by the magnetic field strength, the b-value chosen, the acquisition parameters, the prostatic zones analyzed and the patient variability. Second, patients treated with
5ARIs underwent mpMRI with a different time period of therapy. Third, the histological confirmation of PCa in some patients was obtained by TRUS biopsy, that represents the real GS only in 30-50% of patients. Despite the low diagnostic accuracy, it must be considered that the biopsy GS remains one of the most important decision factor for the diagnostic and therapeutic iter.
Personal information

Luca Basso, MD
lukabasso89@gmail.com
References

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