Discrimination between clinical significant and insignificant prostate cancer with Apparent diffusion coefficient – A systematic review and meta analysis

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Abstract

Background Multiparametric MRI has become a corner stone in diagnosis of prostate cancer (PC). Diffusion weighted imaging and the apparent diffusion coefficient (ADC) can be used to reflect tumor microstructure. The present analysis sought to compare ADC values of clinically insignificant with clinical significant PC based upon a large patient sample. **Methods** MEDLINE library and SCOPUS databases were screened for the associations between ADC and Gleason score in PC up to May 2019. The primary endpoint of the systematic review was the ADC value of PC groups according to Gleason score. In total 27 studies were suitable for the analysis and included into the present study. The included studies comprised a total of 1633 lesions. **Results** Clinically relevant PCs (Gleason score 7 and higher) were diagnosed in 1078 cases (66.0%) and insignificant PCs (Gleason score 5 and 6) in 555 cases (34.0%). The pooled mean ADC value of the clinically significant PC was $0.86 \times 10^{-3} \text{ mm}^2/\text{s}$ [95% CI 0.83-0.90] and the pooled mean value of insignificant PC was $1.1 \times 10^{-3} \text{ mm}^2/\text{s}$ [95% CI 1.03-1.18]. Clinical significant PC showed lower ADC values compared to non-significant PC. The pooled ADC values of clinically insignificant PCs were no lower than $0.75 \times 10^{-3} \text{ mm}^2/\text{s}$. This value may be proposed as a threshold for distinguishing clinically significant from insignificant PCs. **Conclusions** We evaluated the published literature comparing clinical insignificant with clinically prostate cancer in regard of the Apparent diffusion coefficient values derived from magnetic resonance imaging. We identified that the clinically insignificant prostate cancer have lower ADC values than clinically significant, which may aid in tumor noninvasive tumor characterization in clinical routine.

Background

Multiparametric magnetic resonance imaging (mpMRI) has become a corner stone of diagnosis in prostate cancer (PC) in a cost effective and highly accurate manner [1–4]. A great concern in PC treatment is possible over-diagnosing and over-treatment due to very different biological behaviors of PC, discriminated using Gleason score (GS) [5–7]. GS is still one of the most important prognostic features in prostate cancer [6]. So, a cancer with a GS 6 or lower is considered as a clinically insignificant cancer, which will most likely not result in cancer related death. Therefore, it can be treated in some cases with clinical surveillance [5]. However, PC with a GS of 7 and higher is clinically significant and is associated with tumor related morbidity/mortality [8].

In clinical routine mpMRI is very beneficial due to the high negative predictive value [1]. However, mpMRI can also detect more lesions than conventional diagnostic work flow, which might result in more insignificant cancers [9].

Diffusion-weighted imaging (DWI) is an important sequence of mpMRI. DWI reflects free water movement in tissues [10]. Furthermore, restriction of free water movement in tissues can be quantified by apparent diffusion coefficient (ADC) [10]. ADC is associated with histological features, which restrict diffusion of water molecules, like cell count and protein concentration in the extracellular space [11, 12]. Thus, ADC

may aid in discrimination of several tumors. Previously, numerous studies reported that malignant tumors have significantly lower ADC values compared to benign lesions [13, 14].

PC had also lower ADC values in comparison to benign prostatic tissue [15]. Therefore, DWI is an established technique for detection of PC, especially in the peripheral zone [3].

Besides diagnostic potential, DWI/ADC can also aid characterize prostatic tumors. So far, a recent meta-analysis showed that ADC values correlated inversely with GS [16]. In detail, a correlation coefficient of $r = -0.45$ between ADC and GS was reported in all PCs [16]. Furthermore, it was stronger in PC located in the peripheral zone ($r = -0.48$) in comparison to PCs arose in the transitional zone ($r = -0.22$).

Presumably, ADC may discriminate low risk PCs from high risk tumors. However, published data above are inconsistent and based on small single center studies.

The purpose of the present systematic review and meta-analysis was to compare ADC values between clinically significant and non-significant PCs according to GS in a large patient sample.

Methods

Data acquisition

MEDLINE library and SCOPUS databases were screened for the associations between ADC and Gleason score in PC up to May 2019. The paper acquisition is summarized in Fig. 1.

The following search words were used: “prostate cancer OR prostatic carcinoma OR prostatic cancer OR prostate carcinoma AND DWI OR diffusion weighted imaging OR ADC OR apparent diffusion coefficient AND Gleason score AND Gleason”

The primary endpoint of the systematic review was the ADC value of PC groups according to Gleason score.

Studies (or subsets of studies) were included, if they satisfied all the following criteria: (1) patients with PC confirmed by histopathology, (2) mpMRI with DWI sequence quantified by ADC values, and (3) reported ADC value according to GS.

Exclusion criteria were (1) systematic review, (2) case reports, (3) treatment prediction or histopathology performed after treatment, (4) non-English language, and (5) experimental (xenograft or animals model) studies.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used for the analysis [17]. In total 27 studies were suitable for the analysis and included into the present study [18–41].

Quality-assessment

The methodological quality of the acquired studies was independently evaluated by two readers (A.S. and H.J.M.) using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) instrument [42]. Results of QUADAS-2 assessments are shown in Fig. 2.

Statistical analysis

The meta analysis was performed using RevMan 5.3 (2014; Cochrane Collaboration, Copenhagen, Denmark). Heterogeneity was calculated by means of the inconsistency index I^2 [43, 44]. Finally, DerSimonian and Laird [45] random-effect models with inverse-variance weights were performed without any further correction.

Results

Of the included 27 studies, 9 (33.3%) were of prospective and 18 of (66.7%) retrospective design. Different 1.5T scanners were used in 7 (25.9%) studies and 3T scanners in 20 (74.1%) studies. In 7 studies (25.9%) an additional endorectal coil was used. In 9 studies (33.3%) a bowel preparation was performed.

In all studies, the diagnosis was confirmed by histopathology. The histopathological diagnosis and scoring of PC was made on specimen after radical prostatectomy in 15 studies (55.6%), in 10 studies (37.0%) after transrectal ultrasound guided biopsy, and in 2 studies (7.4%) with both techniques.

The acquired 27 studies comprised a total of 1633 lesions. Clinically relevant PCs (Gleason score 7 and higher) were diagnosed in 1078 cases (66.0%) and insignificant PCs (Gleason score 5 and 6) in 555 cases (34.0%).

The pooled mean ADC value of the clinically significant PC was $0.86 \times 10^{-3} \text{ mm}^2/\text{s}$ [95% CI 0.83–0.90] and the pooled mean value of insignificant PC was $1.1 \times 10^{-3} \text{ mm}^2/\text{s}$ [95% CI 1.03–1.18]. Figure 3 shows the distribution of ADC values divided in clinically significant and insignificant PC.

Thereafter, PCs were divided into subgroups according to the GS as follows: GS 5 and 6 ($n = 555$, 34.0%), GS 7 ($n = 258$, 15.8%), GS 8 ($n = 42$, 2.6%) and GS 9 ($n = 30$, 1.8%). The pooled mean ADC values of the subgroups were as follows: GS 5 + 6 = $1.1 \times 10^{-3} \text{ mm}^2/\text{s}$ [95% CI 1.03–1.18], GS 7 = $0.87 \times 10^{-3} \text{ mm}^2/\text{s}$ [95% CI 0.80–0.94], and GS 8 and 9 = $0.76 \times 10^{-3} \text{ mm}^2/\text{s}$ [95% CI 0.71–0.82].

Furthermore, the GS 7 group was divided into cancers with a primary GS 3 pattern with a sum of 3 + 4 and those with a primary GS 4 pattern with a sum of 4 + 3. GS 3 + 4 were total 7 studies with 170 lesions. The pooled mean ADC value was $0.91 \times 10^{-3} \text{ mm}^2/\text{s}$ [95% CI 0.82–1.01]. GS 4 + 3 were total 4 studies with 88 lesions. The pooled mean ADC value was $0.80 \times 10^{-3} \text{ mm}^2/\text{s}$ [95% CI 0.69–0.91].

Discussion

The present work is the first systematic review and meta-analysis comparing ADC values of clinically significant and insignificant PCs classified according to GS. Because it is based on a large cohort, it provides evident data regarding the quantitative analysis of DWI in distinguishing of different PCs.

GS is still one of the most important prognostic factors in PC to stratify patients employing a robust and durable method [6, 46]. So, GS is significantly associated with biochemical free survival [47]. As already mentioned, there is need to discriminate clinically insignificant PCs (GS 6 and lower), which are in almost every cases sufficiently treated with radical prostatectomy, whereas GS 7 and higher cancers are defined as clinically significant with a possibility of recurrence and tumor related death [46]. To predict GS non-invasively by mpMRI might be crucial because it is increasingly used in clinical routine. Thus, more cancers will be detected, which might result in over-diagnosing and over-treatment, when more clinically insignificant tumors are detected.

As reported previously, DWI/ADC can reflect tissue microstructure in several tumor entities, including PC [11]. In most studies, ADC inversely correlated with cellularity [11]. This is explained by the fact that the extracellular protons are mainly producing the MRI signal. Thus, in cell rich tumors, the extracellular water movement is lowered and correspondingly, the ADC value is also lowered.

Regarding PC, not only cell density is important, but also the glandular structure and formation of the tissue, which is also the most important factor for GS grading [6, 46, 48]. According to the literature, besides cellularity, ADC can also reflect other histopathological features in PC including proliferation index, vascular endothelial expression and hypoxia 1-alpha expression [48, 49]. In fact, it was unambiguously shown that ADC values are positively correlated with amount of glandular lumen with $r = 0.688$ and ADC values are negatively correlated to sole cell count ($r = -0.598$) [48].

Consequently, ongoing research, showed weak to moderate inverse correlations between ADC values and GS, which further strengthened that ADC values are able to reflect tumor microstructure in a non-invasive way with possible translational benefit in daily clinical routine [16].

The present meta-analysis showed that ADC values of different PCs distinct overlapped. However, clinically significant PC defined as PC with GS 7 and higher had lower ADC values than insignificant PCs. Moreover, the pooled ADC values of clinically insignificant PCs were no lower than $0.75 \times 10^{-3} \text{ mm}^2/\text{s}$. Therefore, this value may be proposed as a threshold for distinguishing clinically significant from insignificant PCs. This is the main finding of the present work.

There is recent literature suggesting that GS7 tumors include biological heterogeneous PCs. So far, GS 7 cancers can be estimated as 3 + 4 and 4 + 3 [50–53]. For the first group, the well differentiated cancer pattern is predominant. In contrast, for 4 + 3 lesions, the less differentiated pattern is predominant. This also might reflect different tumor behavior. For example, 4 + 3 cancers are more likely to be tumors with greater pathologic stage, and total tumor volume [50]. Our data corroborate the notion that GS7 cancers

are heterogeneous in terms of their ADC values. In fact, GS 3 + 4 tumors had higher ADC values in comparison to GS 4 + 3 cancers. Presumably, ADC values are able to aid stratify GS 7 cancer, albeit further studies are needed to confirm these results.

Interestingly, some previous studies indicated that conventional imaging analysis by PIRADS scoring, a clinical used scoring system to predict the malignancy possibility, is not capable to discriminate between clinical significant and non-significant PC [54]. In PIRADS scoring, only a qualitative assessment based upon DWI, T2-weighted imaging, and contrast enhanced dynamic MRI [3]. ADC values are not quantitatively assessed in this system. Presumably, ADC values might harbor crucial information regarding GS in PC, which is not currently considered in clinical practice. In fact, Pierre et al. suggested that ADC quantification might aid in diagnosing of PC beyond the qualitative DWI assessment [55].

The present meta-analysis has several limitations to address. Firstly, it is mainly comprised of retrospective studies with possible known bias. Secondly, it was not possible to further stratify the patient samples according to tumor localization. Recently, a meta-analysis showed that cancers arising from transitional zone weaker correlated with GS, which might have an influence on the present analysis. Thirdly, we could not divide the patient sample according to biopsy and radical prostatectomy grading. It was shown that both methods might result in slightly different GS. Fourthly, no exact threshold values and sensitivity/specificity could be established for discrimination of clinical significant and non-significant cancers. This reflects one limitation of ADC values caused by variabilities due to hardware including different MRI scanners, sequence parameters, and interreader variability, which hinders to establish clear threshold values for clinical routine. However, as shown, the pooled ADC values of clinically insignificant PCs were no lower than $0.75 \times 10^{-3} \text{ mm}^2/\text{s}$. Fifthly, our results might be affected by possible publication bias because negative studies, which could not identify an inverse correlation between PC with different GS might not be published.

Clearly, further prospective studies based on large samples are needed to proof and confirm our present results.

Conclusions

Clinical significant PC showed lower ADC values compared to non-significant PC. The pooled ADC values of clinically insignificant PCs were no lower than $0.75 \times 10^{-3} \text{ mm}^2/\text{s}$. This value may be proposed as a threshold for distinguishing clinically significant from insignificant PCs. The quantitative assessment of ADC should be included into the stratification of PCs in clinical practice.

Abbreviations

mpMRI: multiparametric magnetic resonance imaging

PC :prostate cancer

GS: Gleason score

DWI : Diffusion-weighted imaging

ADC: apparent diffusion coefficient

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QUADAS: Quality Assessment of Diagnostic Accuracy Studies

Declarations

Acknowledgements: not applicable

Author Contributions

Alexey Surov had full access to all the data in the study and takes responsibility for the integrity of the data and

the accuracy of the data analysis.

Study concept and design: Hans-Jonas Meyer, Andreas Wienke, Alexey Surov.

Acquisition of data: Hans-Jonas Meyer, Andreas Wienke

Analysis and interpretation of data: Andreas Wienke, Alexey Surov

Drafting of the manuscript: Hans-Jonas Meyer

Critical revision of the manuscript for important intellectual content: Andreas Wienke, Alexey Surov

Statistical analysis: Andreas Wienke

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Figures

PRISMA 2009 Flow Diagram

Figure 1

PRISMA flow chart. An overview of the paper acquisition. Overall, 27 articles comprising 1633 patients were suitable for the analysis.

Figure 2

QUADAS-2 quality assessment of the included studies. Most studies showed an overall low risk of bias.

Figure 3

a Forrest plots of the mean apparent diffusion coefficients of clinical insignificant PC comprising Gleason score 5 and 6. The pooled mean ADC value was $1.10 \times 10^{-3} \text{ mm}^2/\text{s}$ [95% CI 1.03-1.18]. b. Forrest plots of the mean apparent diffusion coefficients of clinically significant PC comprising Gleason score 7 and higher. The pooled mean ADC value was $0.96 \times 10^{-3} \text{ mm}^2/\text{s}$ [95% CI 0.83-0.90].

1.2.6 Gleason 7

Bittencourt 2012b	0.73	0.04	0.9%	0.73 [0.65, 0.81]
Bittencourt 2012c	0.78	0.05	0.9%	0.78 [0.68, 0.88]
Caivano 2013c	1.1	0.04	0.9%	1.10 [1.02, 1.18]
Faletti 2016b	0.74	0.02	1.0%	0.74 [0.70, 0.78]
Faletti 2016c	0.68	0.03	0.9%	0.68 [0.62, 0.74]
Hambrock 2012b	1.07	0.07	0.8%	1.07 [0.93, 1.21]
Li 2014b	0.98	0.02	1.0%	0.98 [0.94, 1.02]
Li 2014c	0.91	0.02	1.0%	0.91 [0.87, 0.95]
Nagarajan 2012b	0.98	0.02	1.0%	0.98 [0.94, 1.02]
Nagarajan 2012c	0.83	0.03	0.9%	0.83 [0.77, 0.89]
Wu 2017b	0.83	0.02	1.0%	0.83 [0.79, 0.87]
Subtotal (95% CI)		10.3%		0.87 [0.80, 0.94]

Heterogeneity: $\tau^2 = 0.01$; $\text{Chi}^2 = 209.30$, $\text{df} = 10$ ($P < 0.00001$); $I^2 = 95\%$
 Test for overall effect: $Z = 23.65$ ($P < 0.00001$)

1.2.3 Gleason 8+

Bittencourt 2012d	0.54	0.12	0.8%	0.54 [0.30, 0.78]
Caivano 2013d	0.92	0.03	1.2%	0.92 [0.86, 0.98]
Chatterjee 2018c	0.61	0.05	1.1%	0.61 [0.51, 0.71]
Faletti 2016d	0.63	0.05	1.1%	0.63 [0.53, 0.73]
Glazer 2017	0.81	0.04	1.2%	0.81 [0.73, 0.89]
Hambrock 2012c	0.94	0.06	1.1%	0.94 [0.82, 1.06]
Li 2014d	0.84	0.01	1.2%	0.84 [0.82, 0.86]
Park 2016c	0.63	0.02	1.2%	0.63 [0.59, 0.67]
Park 2016d	0.64	0.02	1.2%	0.64 [0.60, 0.68]
Sokmen 2018c	0.86	0.04	1.2%	0.86 [0.78, 0.94]
Sokmen 2018d	0.71	0.04	1.2%	0.71 [0.63, 0.79]
Suo 2014c	0.59	0.06	1.1%	0.59 [0.47, 0.71]
Tian 2018c	0.82	0.01	1.2%	0.82 [0.80, 0.84]
Turkbey 2011c	0.9	0.04	1.2%	0.90 [0.82, 0.98]
Turkbey 2011d	0.8	0.05	1.1%	0.80 [0.70, 0.90]
Yagci 2011c	0.84	0.03	1.2%	0.84 [0.78, 0.90]
Subtotal (95% CI)		18.3%		0.76 [0.71, 0.82]

Heterogeneity: $\tau^2 = 0.01$; $\text{Chi}^2 = 235.03$, $\text{df} = 15$ ($P < 0.00001$); $I^2 = 94\%$
 Test for overall effect: $Z = 29.45$ ($P < 0.00001$)

Figure 4

a. Forrest plots of the mean apparent diffusion coefficients of PC with Gleason score 7. The pooled mean ADC value was $0.87 \times 10^{-3} \text{ mm}^2/\text{s}$ [95% CI 0.80-0.94]. b. Forrest plots of the mean apparent diffusion coefficients of PC with Gleason score 8 and higher. The pooled mean ADC value was $0.76 \times 10^{-3} \text{ mm}^2/\text{s}$ [95% CI 0.71-0.82]. c. Box plots of the mean ADC values of clinical insignificant comprising Gleason score

5 and 6, Gleason score 7 and Gleason score 8 and 9 PC groups. There is a clear trend for higher Gleason score PC to have lower ADC values.

Figure 5

a. Forrest plots of the mean apparent diffusion coefficients of PC with Gleason score 3+4. The pooled mean ADC value was 0.91 x10⁻³ mm²/s [95% CI 0.82-1.01]. b. Forrest plots of the mean apparent diffusion coefficients of PC with Gleason score 4+3. The pooled mean ADC value was 0.80 x10⁻³ mm²/s

[95% CI 0.69-0.91]. c. Box plots of the mean ADC values of Gleason score 3+4 and Gleason score 4+3. Gleason 4+3 PC have lower ADC values than Gleason score 3+4.