

Prostate Cancer

Assessment of Prostate Cancer Aggressiveness Using Dynamic Contrast-enhanced Magnetic Resonance Imaging at 3 T

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Abstract

Background: A challenge in the diagnosis of prostate cancer (PCa) is the accurate assessment of aggressiveness.

Objective: To validate the performance of dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) of the prostate at 3 tesla (T) for the assessment of PCa aggressiveness, with prostatectomy specimens as the reference standard.

Design, settings, and participants: A total of 45 patients with PCa scheduled for prostatectomy were included. This study was approved by the institutional review board; the need for informed consent was waived.

Outcome measurements and statistical analysis: Subjects underwent a clinical MRI protocol including DCE-MRI. Blinded to DCE-images, PCa was indicated on T2-weighted images based on histopathology results from prostatectomy specimens with the use of anatomical landmarks for the precise localization of the tumor. PCa was classified as low-, intermediate-, or high-grade, according to Gleason score. DCE-images were used as an overlay on T2-weighted images; mean and quartile values from semi-quantitative and pharmacokinetic model parameters were extracted per tumor region. Statistical analysis included Spearman's ρ , the Kruskal-Wallis test, and a receiver operating characteristics (ROC) analysis.

Results and limitations: Significant differences were seen for the mean and 75th percentile (p75) values of wash-in ($p = 0.024$ and $p = 0.017$, respectively), mean wash-out ($p = 0.044$), and p75 of transfer constant (K^{trans}) ($p = 0.035$), all between low-grade and high-grade PCa in the peripheral zone. ROC analysis revealed the best discriminating performance between low-grade versus intermediate-grade plus high-grade PCa in the peripheral zone for p75 of wash-in, K^{trans} , and rate constant (K_{ep}) (area under the curve: 0.72). Due to a limited number of tumors in the transition zone, a definitive conclusion for this region of the prostate could not be drawn.

Conclusions: Quantitative parameters (K^{trans} and K_{ep}) and semi-quantitative parameters (wash-in and wash-out) derived from DCE-MRI at 3 T have the potential to assess the aggressiveness of PCa in the peripheral zone. P75 of wash-in, K^{trans} , and K_{ep} offer the best possibility to discriminate low-grade from intermediate-grade plus high-grade PCa.

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1. Introduction

Prostate cancer (PCa) is the most common malignancy in the Western male population and the third leading cause of cancer-related death in developed countries [1]. Primary methods to diagnose PCa are prostate-specific antigen (PSA) and digital rectal examination (DRE), usually followed by transrectal ultrasound (TRUS) systematic biopsy. Histopathology of the biopsy ultimately confirms the presence and the Gleason score (GS) of PCa. Characterization of PCa based on the combination of PSA level, DRE findings, and the GS from TRUS biopsy are used for the choice of treatment. However, both PSA and DRE have a low specificity and a low sensitivity [2]. In addition, TRUS biopsies are invasive, have a relatively low sensitivity, and tend to underestimate the GS and thus aggressiveness [3,4]. Because not all PCas are life-threatening, accurate assessment of aggressiveness is essential to prevent overdiagnosis and thus overtreatment of indolent cancers [5].

Magnetic resonance imaging (MRI) will play an important upcoming role in the diagnosis and management of PCa. In addition to T2-weighted (T2w) imaging for detailed anatomical information, functional MRI techniques for additional information such as diffusion-weighted imaging (DWI), MR spectroscopic imaging (MRSI), and dynamic contrast-enhanced (DCE) MRI have already proved their usefulness in the detection of PCa [6].

DCE-MRI is based on the permeability of blood vessels and extravasation of contrast agent into the surrounding tissue. In PCa, fast angiogenesis results in the formation of leaky endothelia with a higher permeability than normal vessels. When a contrast agent is administered into the vessels it will leak out of the capillaries into tissue, where it temporarily changes the T1 relaxation time. A straightforward way of representing contrast-related signal intensity changes is with semi-quantitative parameters. These parameters are derived from a signal intensity-time curve and are relatively easy to calculate, but they may not accurately reflect the contrast concentration in tissue. Quantification of contrast leakage by pharmacokinetic modeling represents direct vascular information by estimating the concentration of contrast leakage into tissue. This is challenging, though, because multiple approaches for calibration and modeling exist, and each model makes its own assumptions that may not be valid for every tissue or tumor type.

In a recent discussion about the value of MRI in PCa, authors proposed the need for implementing multiparametric MRI assessment with defined thresholds that should contribute to the prevention of overdiagnosis and overtreatment of indolent PCa [7]. A few studies have already shown that DWI and MRSI have the potential to assess the aggressiveness of PCa [8–10]. For DCE-MRI at 1.5 Tesla (T), results are inconsistent regarding correlations with aggressiveness and GS [11–15]. Literature about the use of DCE-MRI for assessing PCa aggressiveness at 3 T is lacking. Before a full multiparametric MRI protocol can be implemented for the characterization of PCa, each technique has to be evaluated for its value prior to combining all the techniques together.

Our purpose was to validate retrospectively the performance of semi-quantitative parameters and pharmacokinetic model parameters derived from DCE-MRI of the prostate at 3 T for assessing PCa aggressiveness, with the GS of cancer foci from prostatectomy specimens as the reference standard.

2. Materials and methods

2.1. Patient characteristics

The institutional review board waived the need for informed consent. Between 2007 and 2009, all patients with newly biopsy-proven organ-confined PCa who had undergone a 3 T MR examination with the use of an endorectal coil including DCE-MRI prior to radical prostatectomy (RP), without any previous therapy for PCa, were enrolled in the study.

2.2. Data acquisition

All imaging was performed using a 3 T whole-body system (Magnetom Trio, Siemens, Erlangen, Germany). An endorectal coil (MEDRAD Inc, Pittsburgh, PA, USA) filled with approximately 40 ml of perfluorocarbon and a pelvic phased-array coil were used for signal reception. Peristalsis was suppressed with an intramuscular injection of 1 mg glucagon (GlucaGen, Nordisk, Gentofte, Denmark) and 20 mg butylscopolamine bromide (Buscopan, Boehringer-Ingelheim, Ingelheim, Germany) prior to the examination.

The in-house clinical protocol was performed including high-resolution T2w turbo spin-echo imaging in three orthogonal directions, in accordance with recently published guidelines [16]. DCE-MRI was acquired by using turbo fast low-angle shot three-dimensional spoiled gradient-echo imaging with the following parameters: TR 2.4–2.9 ms, TE 1.35–1.51 ms, flip angle 10–14°, partition thickness 3.0–4.0 mm, in-plane resolution 1.8×1.8 – 1.5×1.5 mm, and a temporal resolution of 3 s before, during, and after a 15 ml intravenous bolus injection of gadolinium chelate (Dotarem, Guerbet, France), which was administered with a power injector (Spectris Solaris, Medrad Inc, Indianola, PA, USA) and followed by a 20 ml saline flush. Minor differences in parameters were due to a clinical protocol change during the study.

2.3. Histopathology analysis

All RP specimens were processed and completely embedded according to a standard protocol as previously described [9]. PCa was categorized in three different aggressiveness levels according to GS: low-grade with only Gleason grades (GGs) 2 or 3 present, intermediate-grade with a secondary or tertiary GG of 4 but no 5 component, and high-grade with a primary GG of 4 and/or any 5 component.

2.4. Magnetic resonance imaging analysis

PCa was indicated on T2w images by one radiologist based on the histopathology results and blinded to the DCE-MRI data. Because it remains a challenge to correctly register pathology findings with MR images, we tried to overcome this by slicing the resected prostate with similar angulation with respect to the rectal wall surface as the slices of MRI. Subsequently, a region of interest (ROI) of the histopathologic size of the cancer focus was drawn on the anatomical T2w images based on the histopathology results (Fig. 1a and 1b), taking into account the deformation of the prostate on MR images due to the use of an endorectal coil and shrinkage of the prostate after removal from the body. Anatomical landmarks such as benign prostatic hyperplasia nodules

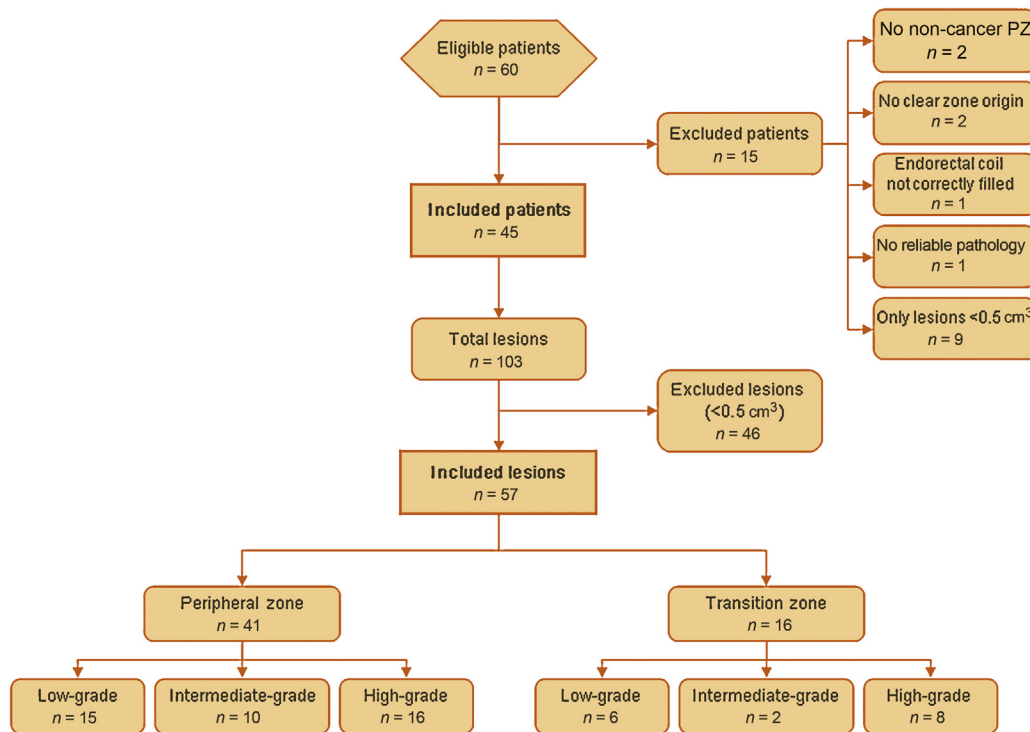


Fig. 1 – Flow diagram of inclusion and exclusion criteria and classification of patient subcohorts.

and urethra were also used for reference. A non-cancer part of the peripheral zone (PZ) was used for patient-specific calibration of pharmacokinetic modeling, which was done according to a permeability-limited two-compartment model [17] and a reference tissue method to estimate a patient-dependent arterial input function (AIF) [18–20]. Our in-house software was used to calculate statistics of the ROIs from semi-quantitative parameters wash-in (slope of the wash-in phase of the curve), time to peak (time between start of enhancement and maximum enhancement), wash-out (slope of the late-wash phase of the curve), relative enhancement (signal intensity of peak enhancement divided by signal intensity at start of enhancement), and pharmacokinetic model parameters transfer constant (K^{trans}), rate constant (K_{ep}), and extravascular extracellular space (v_e).

2.5. Statistical analysis

PZ and transition zone (TZ) cancer were evaluated separately. For all parameters the mean values of each cancer ROI were determined. To incorporate possible heterogeneity within tumors, we additionally determined the 75th percentile (p75) for wash-in, relative enhancement, K^{trans} , K_{ep} , and v_e . For time to peak and wash-out, an inverse correlation with tumor aggressiveness was expected, so for these the 25th percentiles (p25s) were calculated.

All parameters were tested for correlation with aggressiveness and lesion size using Spearman's ρ . Only for parameters that correlated significantly with aggressiveness, the median values of all data in each aggressiveness level were compared with each other using the Kruskal-Wallis test with the Dunn multiple comparison posttest. Finally, the area under the curve (AUC) of receiver operating characteristics (ROC) analysis was determined to study the performance of discriminating low-grade from intermediate-grade plus high-grade PCa.

GraphPad Prism v.5.0 (GraphPad Software, San Diego, CA, USA) and MATLAB R2012a (MathWorks, Natick, MA, USA) were used to perform

statistical analyses. For all statistical tests, a p value <0.05 was considered significant.

3. Results

A total of 15 patients were excluded from the analysis because the entire PZ consisted of PCa and thus did not contain non-cancer PZ tissue as a reference for calibration ($n = 2$); cancer covered both PZ and TZ, so a clear distinction of origin could not be made ($n = 2$); no reliable pathology results ($n = 1$) were available; patients only had lesions of insignificant size ($<0.5 \text{ cm}^3$; $n = 9$); or the endorectal coil was not filled with perfluorocarbon ($n = 1$).

Overall, 57 clinically significant cancer foci $>0.5 \text{ cm}^3$ according to histopathology were present in the remaining 45 patients (Table 1; Fig. 1). In a typical example, a large tumor enhanced clearly with contrast agent administration (Fig. 2).

A significant correlation with aggressiveness in the PZ was found for wash-in (mean: $\rho = 0.43$, $p = 0.006$; p75: $\rho = 0.45$, $p = 0.004$), K^{trans} (mean: $\rho = 0.38$, $p = 0.01$; p75: $\rho = 0.41$, $p = 0.008$), K_{ep} (mean: $\rho = 0.43$, $p = 0.006$; p75: $\rho = 0.45$, $p = 0.004$) and a significant negative correlation for wash-out (mean: $\rho = -0.39$, $p = 0.01$; p25: $\rho = -0.33$, $p = 0.04$). Only wash-in correlated significantly with lesion size (mean: $\rho = 0.36$, $p = 0.02$; p75: $\rho = 0.37$, $p = 0.02$). Wash-out and K^{trans} only just approached significance with lesion size in the PZ.

In the TZ, only the p75 of K^{trans} correlated significantly with aggressiveness ($\rho = 0.52$, $p = 0.04$). All other parameters did not show any correlation with aggressiveness. For lesion

Table 1 – Characteristics of patients and tumors

No. of patients	45		
PSA level, mg/ml, median (range)	6.90 (2.08–40.96)		
Age, yr, median (range)	64 (48–70)		
Gleason score		No. of tumors	
PZ:			
2 + 3	Low*	1	Low: 15
3 + 2	Low	1	Intermediate: 10
3 + 3	Low	13	High: 16
3 + 3 + 4	Intermediate	1	Total: 41
3 + 4	Intermediate	9	
3 + 4 + 5	High	3	
4 + 3	High	8	
4 + 3 + 5	High	1	
4 + 4	High	1	
4 + 5	High	2	
5 + 3	High	1	
TZ:			
2 + 3	Low	2	
3 + 2	Low	3	Low: 6
3 + 3	Low	1	Intermediate: 2
3 + 2 + 4	Intermediate	1	High: 8
3 + 4	Intermediate	1	Total: 16
2 + 4 + 5	High	1	
4 + 2	High	1	
4 + 3	High	1	
4 + 3 + 5	High	4	
4 + 5	High	1	

PSA = prostate-specific antigen; PZ = peripheral zone; TZ = transition zone.
* Cancers are classified in classes according to their aggressiveness, solely based on the localized Gleason score rather than the full D'Amico risk classification.

size, p75 of K^{trans} showed a significant correlation as well ($\rho = 0.54$, $p = 0.03$) while the mean only just approached significance ($\rho = 0.48$, $p = 0.06$).

Comparison of the medians of the aggressiveness levels revealed a significant difference for the semi-quantitative parameters wash-in (mean: $p = 0.024$; p75: $p = 0.017$) and wash-out (mean: $p = 0.044$) for the PZ (Fig. 3, Table 2). For the quantitative parameters, only the p75 of K^{trans} ($p = 0.035$) showed a significant difference for the PZ (Fig. 4, Table 2). All differences were found between the low-grade and high-grade level.

Although K^{trans} did show a correlation with aggressiveness in the TZ, no statistically significant differences were found between the medians of the aggressiveness levels (Fig. 5). Table 2 lists the median values and interquartile ranges for the parameters per aggressiveness level for both zones.

With the use of ROC analysis, the highest discriminating performance between low-grade versus intermediate-grade plus high-grade PCa was seen for the p75 of wash-in, K^{trans} , and K_{ep} (all with AUC: 0.72) in the PZ and for the p75 of K^{trans} (AUC: 0.75) in the TZ (Table 3).

4. Discussion

This study showed that both quantitative (K^{trans} and K_{ep}) and semi-quantitative (wash-in and wash-out) parameters derived from DCE-MRI can be helpful tools to assess PCa

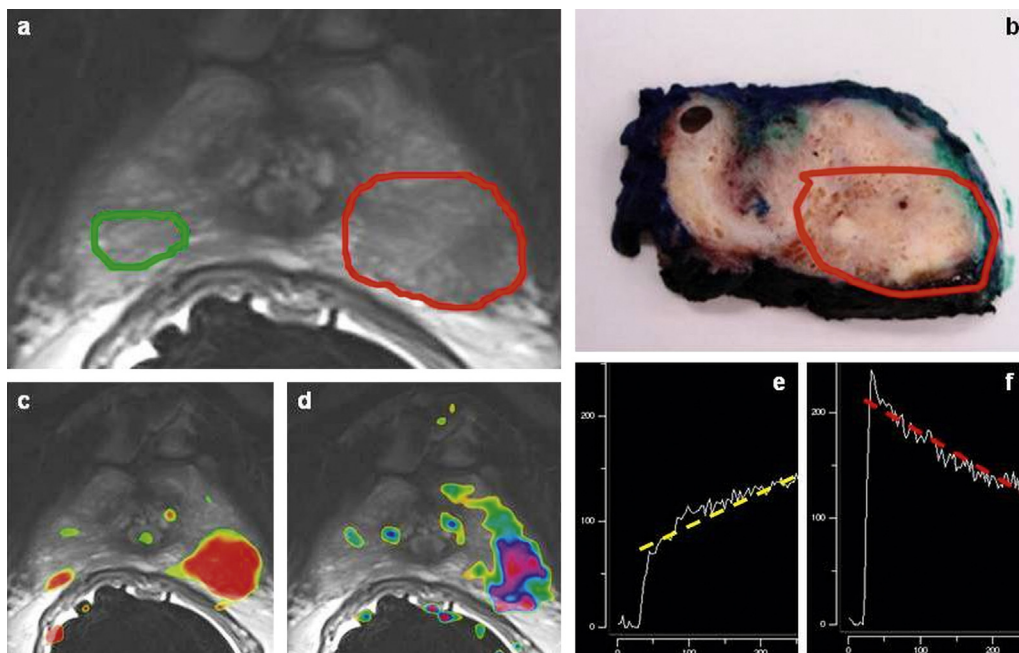


Fig. 2 – Dynamic contrast-enhanced magnetic resonance imaging of a 66-yr-old patient with Gleason 4 + 3 prostate cancer (PCa) in the left peripheral zone: (a) T2-weighted (T2w) image with a region of interest of PCa (left peripheral zone, red outline) and non-cancer tissue (right peripheral zone, green outline, used as reference tissue for calibration), based on (b) the histopathologic results of the prostatectomy specimen (cancer region in red outline, indicated by the pathologist on the photographed slice). An overlay of (c) the wash-out (late-wash phase) and (d) the transfer constant (K^{trans}) on the T2w image shows wash-out and enhancement of the cancer region, respectively. Qualitative signal-intensity curves over time of (e) non-cancer and (f) high-grade cancer: The curve of non-cancer tissue shows slow wash-in and continuing wash-in during the late-wash phase (yellow dashed line), the curve of the high-grade cancer tissue shows rapid wash-in (steeper slope of the wash-in phase than for non-cancer tissue) and fast wash-out in the late-wash phase (red dashed line).

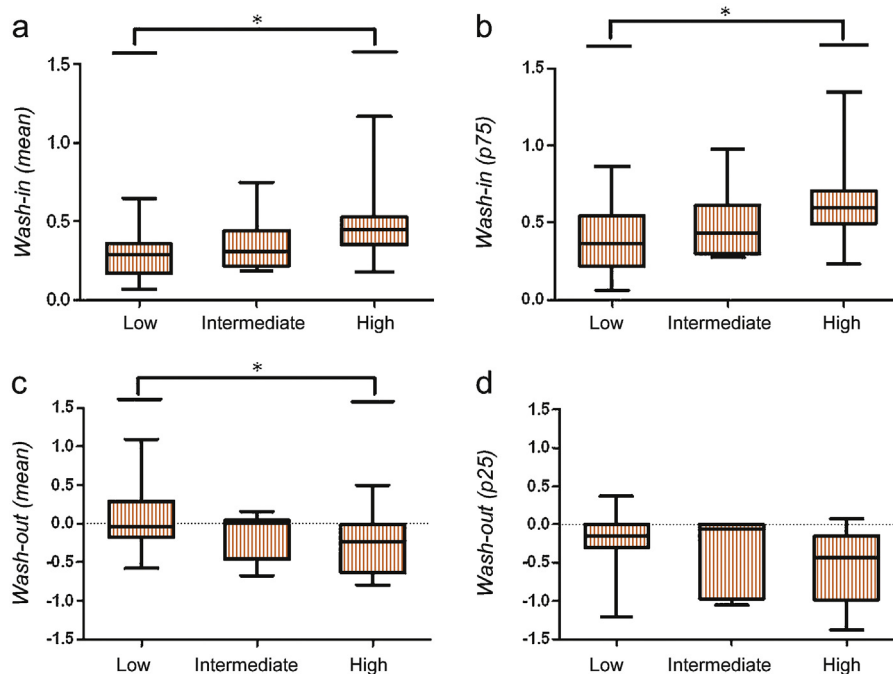


Fig. 3 – Semi-quantitative parameters for the peripheral zone. Box-and-whisker plot (range: 5–95th percentile) of (a) the mean and (b) the 75th percentile (p75) of wash-in values and (c) mean and (d) 25th percentile (p25) of wash-out values per cancer aggressiveness class. A significant difference between low-aggressive and high-aggressive prostate cancer was found for both the mean and the p75 values of wash-in ($p = 0.024$ and $p = 0.017$, respectively) and for the mean values of wash-out ($p = 0.044$).

aggressiveness in the PZ. For the parameters that either positively or negatively correlated with aggressiveness, differences in median ranks between low-grade and high-grade PCa were found, but not with intermediate-grade PCa. Although there is a significant difference between low-grade and high-grade PCa in the PZ, considerable

overlap exists. According to the recent literature, it is of great importance to recognize indolent PCa to prevent overtreatment of these low-grade tumors [5,7]. Therefore, not only a correlation with aggressiveness is interesting, but it is of clinical value to separate low-grade from all higher grade PCa. Our results revealed that discriminating

Table 2 – Median values (with interquartile range) for all dynamic contrast-enhanced parameters that correlated with aggressiveness, for each aggressiveness class

		Peripheral zone		
		Low-aggressive (n = 15)	Intermediate-aggressive (n = 10)	High-aggressive (n = 16)
Wash-in	Mean [§]	0.29 (0.17–0.36)	0.31 (0.22–0.44)	0.45 (0.35–0.53)
	p75 [†]	0.37 (0.22–0.55)	0.43 (0.30–0.61)	0.60 (0.50–0.71)
Wash-out	Mean [*]	−0.04 (−0.17 to 0.29)	0.00 (−0.46 to 0.05)	−0.23 (−0.64 to −0.01)
	p25	−0.15 (−0.31 to 0.01)	−0.06 (−0.97 to 0.01)	−0.44 (−0.98 to −0.15)
K^{trans}	Mean	0.81 (0.65–0.98)	0.86 (0.63–1.34)	1.25 (1.02–1.44)
	p75 [‡]	0.94 (0.24–1.40)	1.05 (0.99–1.96)	1.68 (1.31–20.4)
K_{ep}	Mean	2.40 (1.63–3.11)	3.02 (2.56–3.91)	3.41 (2.79–4.21)
	p75	2.87 (0.70–4.43)	4.23 (3.14–5.83)	4.31 (3.36–6.20)
		Transition zone		
		Low-aggressive (n = 6)	Intermediate-aggressive (n = 2)	High-aggressive (n = 8)
K^{trans}	Mean	0.85 (0.47–1.11)	0.90 (0.86–0.94)	1.26 (0.92–1.54)
	p75	1.06 (0.67–1.51)	1.15 (1.06–1.24)	1.55 (1.24–2.21)

K_{ep} = rate constant; K^{trans} = transfer constant; p25 = 25th percentile; p75 = 75th percentile.

[§] Significant difference ($p = 0.024$), posttest: low- and high-aggressive cancer.

[†] Significant difference ($p = 0.017$), posttest: low- and high-aggressive cancer.

^{*} Significant difference ($p = 0.044$), posttest: low- and high-aggressive cancer.

[‡] Significant difference ($p = 0.035$), posttest: low- and high-aggressive cancer.

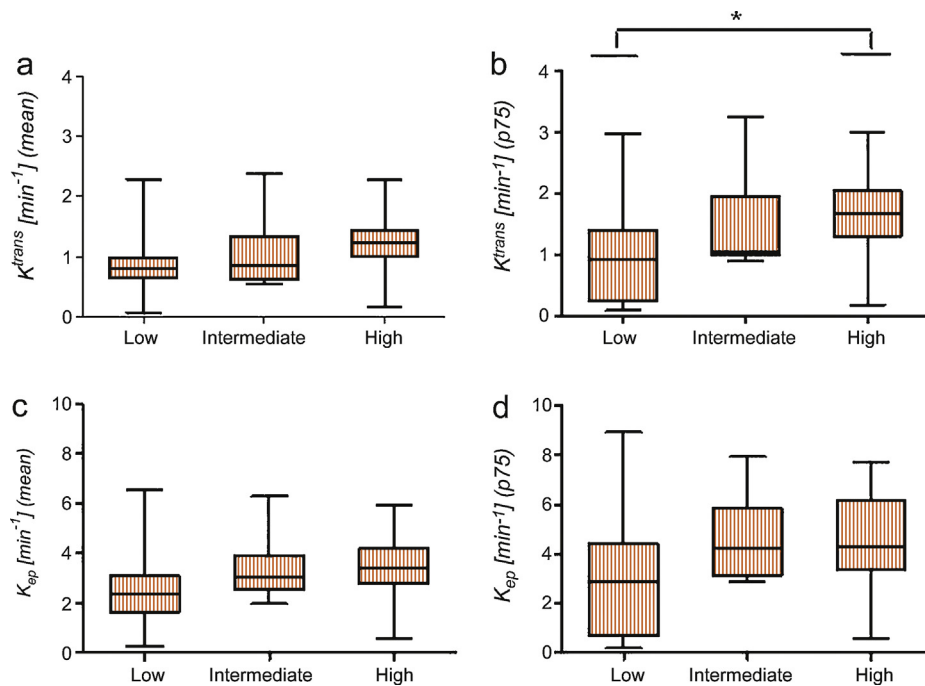


Fig. 4 – Quantitative parameters for the peripheral zone. Box-and-whisker plot (range: 5–95th percentile) of (a) the mean and (b) the 75th percentile (p75) values of the transfer constant (K^{trans}) and (c) the mean and (d) the p75 values of the rate constant (K_{ep}) per cancer aggressiveness class for the peripheral zone. A significant difference was found for the p75 values ($p = 0.035$) between low-grade and high-grade class, where the mean only just approached significance ($p = 0.050$). For K_{ep} , no significant differences were found.

low-grade from intermediate-grade plus high-grade PCa is possible with a fair performance with quartile values of the parameters wash-in (p75), wash-out (p25), K^{trans} , and K_{ep} (both p75) in the PZ, and p75 of K^{trans} in the TZ. Perhaps the more heterogeneous vascularization pattern of TZ tumors [21] could explain the lack of more than one parameter correlating with aggressiveness, although our number of TZ tumors in this work could be too small to conclude this conclusively. The plausible hypothesis of a relation between DCE-MRI and microvascular density has been confirmed in PCa [13,22], although conflicting results of a correlation between microvascular density and GS have been found [23,24].

At 1.5 T, a significant correlation of wash-out and GS was previously found [15], although other studies concluded that

both semi-quantitative and pharmacokinetic parameters of DCE-MRI were only useful for the detection of PCa [11–14]. At 3 T, few studies exist, most with the main objective to detect PCa rather than to analyze for a correlation with GS [25–27]. Turkbey et al. [28] suggested that sensitivity for the detection of PCa increases with higher GS when using DCE-MRI next to T2-weighted imaging, but here K^{trans} and K_{ep} maps were evaluated visually instead of quantitatively. Moradi et al. [29] did find a positive correlation between GS and DCE-MRI, although they did not quantify the pharmacokinetic parameters. Our use of a higher temporal resolution, probing the first phase of enhancement more accurately, and the use of a patient-specific AIF instead of a population-based AIF contribute to a better signal enhancement curve and improved pharmacokinetic modeling. Together with the use

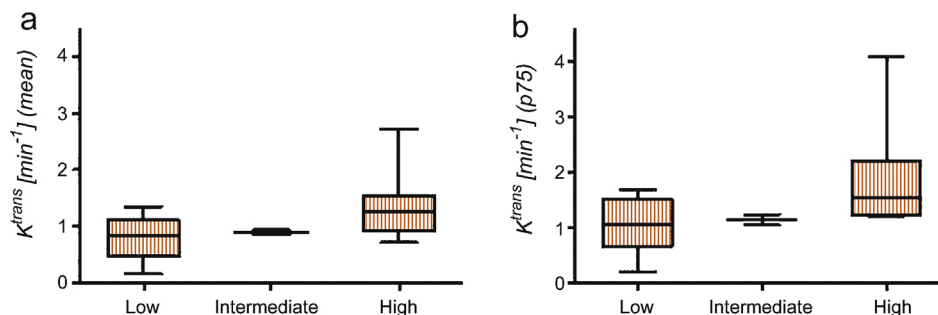


Fig. 5 – Quantitative parameters for the transition zone. Box-and-whisker plot (range: 5–95th percentile) of (a) the mean and (b) the 75th percentile (p75) values of the transfer constant (K^{trans}) per cancer aggressiveness class. No significant differences were found between medians of the low-, intermediate-, or high-grade cancer class.

Table 3 – Areas under the receiver operating characteristic curves for studying the performance of discriminating low-grade from intermediate-grade plus high-grade prostate cancer^a

Peripheral zone		AUC	p
Wash-in	Mean	0.71	0.03
	p75	0.72	0.02
Wash-out	Mean	0.65	0.03
	p25	0.70	0.11
K^{trans}	Mean	0.68	0.06
	p75	0.72	0.02
K_{ep}	Mean	0.70	0.03
	p75	0.72	0.02
Transition zone		AUC	p
K^{trans}	Mean	0.72	0.18
	p75	0.75	0.12

AUC = area under the curve; K_{ep} = rate constant; K^{trans} = transfer constant; p25 = 25th percentile; p75 = 75th percentile.
^a The p value indicates whether there is a significant difference between both groups, with $p < 0.05$ considered statistically significant.

of whole-mount histopathology as the reference standard, this could explain our correlations of multiple DCE parameters with GS.

We used a permeability-limited two-compartment model based on the Tofts model, with a per-patient calibrated AIF and non-cancer PZ as reference tissue. With this model the intravascular space is considered as one compartment and the interstitial space as the second compartment, so one assumes that an exchange of contrast agent will take place between those two compartments with permeability as the limiting step. Some authors argue that a blood flow-limited model is preferred in cancer tissue or that the use of a three-compartment model, which comprises the vascular volume as one compartment with the addition of two sequential interstitial compartments with slow and fast exchange, better represents the distribution of contrast agents [30]. We assumed that in PCa a permeability-limited model is a better way of representing the spread of contrast agent because the prostate is a highly vascularized organ and thus blood flow as the limiting step is less plausible. We decided not to further expand the number of pharmacokinetic parameters by keeping the number of modeled compartments at two.

This study had several limitations. First, this was a validation study with a limited number of patients; therefore confirmation of these findings and the performance in a prospective predictive setting is essential before it can be implemented in clinical practice. Because of the limited number of cancers in the TZ, we cannot draw a definitive conclusion for this region. Second, because we used prostatectomy specimens as the gold standard, there might be some selection bias because patients with a very low or a very high GS and extracapsular extension usually do not undergo a prostatectomy. Third, our method for pharmacokinetic calibration is impossible in the cases of complete fill of the PZ area with tumor because there would be no non-cancer PZ tissue as reference available for our specific calibration method of the pharmacokinetic model parameters. Fourth, in this study design, only

histopathologically proven cancer areas were assigned on anatomical MR images, and non-cancer areas were not assessed (only for patient-specific pharmacokinetic calibration). Therefore, negative predictive values of parameters derived from DCE-MRI cannot be calculated and should be determined in a prospective predictive study.

Our results could be of important clinical relevance. DCE-MRI can be a valuable tool in the diagnostic process for differentiating low-aggressive from higher-aggressive PCa within the PZ, so that overtreatment of indolent types of organ-confined PCa can be prevented by selecting suitable patients for active surveillance and those that will need immediate treatment can be identified. However, too much overlap in both semi-quantitative and pharmacokinetic model parameters exists to use DCE-MRI as a sole technique. In studies by Hambrock et al. [8] and Kobus et al. [9], DWI and MRSI, respectively, were correlated with aggressiveness. Subsequently, Kobus et al. combined the two functional techniques to evaluate if both techniques have complementary value for the assessment of PCa localization and aggressiveness [31]. In a next step, the combination of all parameters from a full multiparametric MRI examination needs to be validated for its performance in PCa characterization, followed by a predictive study to confirm its true prognostic value. DCE-MRI can contribute best to this analysis with the use of quartile values of wash-in, wash-out, K^{trans} , and K_{ep} . Pharmacokinetic modeling can only be performed in specialized institutions with dedicated software programs, so for institutions that do not have this expertise the use of the semi-quantitative parameters wash-in and wash-out might be sufficient.

5. Conclusions

Quantitative parameters (K^{trans} and K_{ep}) and semi-quantitative parameters (wash-in and wash-out) derived from DCE-MRI have the potential to assess PCa aggressiveness in the PZ at 3 T, despite overlap between aggressiveness classes. P75 of wash-in, K^{trans} , and K_{ep} offer the best possibility to discriminate low-grade from intermediate-grade plus high-grade PCa. These initial results are preliminary but promising for selecting those patients with organ-confined low-aggressive PCa suitable for active surveillance and thus preventing overtreatment.

Author contributions: Eline K. Vos 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: Vos, Litjens, Kobus, Scheenen.

Acquisition of data: Hambrock, Hulsbergen-van de Kaa.

Analysis and interpretation of data: Vos, Scheenen.

Drafting of the manuscript: Vos, Scheenen.

Critical revision of the manuscript for important intellectual content: Litjens, Kobus, Hulsbergen-van de Kaa, Barentsz, Huisman, Scheenen.

Statistical analysis: Vos, Kobus, Scheenen.

Obtaining funding: Barentsz, Scheenen.

Administrative, technical, or material support: Litjens, Huisman.

Supervision: Scheenen.

Other (specify): None.

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