Histopathological Features of MRI-Invisible Regions of Prostate Cancer Lesions

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ABSTRACT

BACKGROUND:

Previous studies have reported tumor volume underestimation with multiparametric (mp)MRI in prostate cancer diagnosis.

PURPOSE:

To investigate why some parts of lesions are not visible on mpMRI by comparing their histopathology features to those of visible regions.

STUDY TYPE:

Retrospective.

POPULATION:

Thirty-four patients with biopsy-proven prostate cancer scheduled for prostatectomy (median 68.7 years).

FIELD STRENGTH/SEQUENCE:

T₂-weighted, diffusion-weighted imaging, T₂ mapping, and dynamic contrast-enhanced MRI on two 3T systems and one 1.5T system.

ASSESSMENT:

Two readers delineated suspicious lesions on mpMRI. A pathologist delineated the lesions on histopathology. A patient-customized mold enabled the registration of histopathology and MRI. On histopathology we identified mpMRI visible and invisible lesions. Subsequently, within the visible lesions we identified regions that were visible and regions that were invisible on mpMRI. For each lesion and region the following characteristics were determined: size, location, International Society of Urological Pathology (ISUP) grade, and Gleason subpatterns (density [dense/intermediate], tumor morphology [homogeneous/heterogeneous], cribriform growth [yes/no]).

STATISTICAL TESTS:

With generalized linear mixed-effect modeling we investigated which features explain why a lesion or a region was invisible on MRI. We compared imaging values (T_2 , ADC, and K^{trans}) for these features with one-way analysis of variance (ANOVA).

RESULTS:

Small, anterior, and ISUP grade 1-2 lesions ($n = 34$) were missed more frequent than large, posterior, ISUP grade ≥ 3 lesions ($n = 35$). Invisible regions on mpMRI had lower tumor density, heterogeneous tumor morphology, and were located in the transition zone. Both T_2 and ADC values were higher in "intermediate" compared with "dense" regions ($P = 0.002$ and < 0.001) and in regions with heterogeneous compared with homogeneous morphology ($P < 0.001$ and 0.03). K^{trans} was not significantly different ($P = 0.24$ and 0.99).

DATA CONCLUSION:

Regions of prostate cancer lesions that are invisible on mpMRI have different histopathology features than visible regions. This may have implications for monitoring during active surveillance and focal treatment strategies.

KEYWORDS:

Gleason subpatterns; multiparametric MRI; prostate cancer; tumor delineation; volume assessment

The current definition of clinically significant prostate cancer is based on a combination of criteria including prostate-specific antigen level, clinical stage, Gleason score, number of positive cores, and extent of prostate cancer involvement of the biopsy [1]. The latter two parameters are indirect measures of prostate tumor volume and therefore are not precise. Accurate and robust volume assessment of prostate cancer lesions is becoming more important to guide treatment decisions [2] in particular for eligibility assessment and monitoring of patients in active surveillance [2, 3], as well as for guidance in focal treatment options [4].

As multiparametric magnetic resonance imaging (mpMRI) is currently being used in the diagnostic work-up of prostate cancer [5, 6], it would be practical if mpMRI could also be used for assessment of tumor volume [2]. Multiparametric MRI is useful to identify whether a patient has clinically significant prostate cancer: sensitivity values of 93% and 96% have been reported from two large trials based on patients with suspected prostate cancer [7, 8]. However, the sensitivity on a lesion basis is much lower: about half of the individual tumor foci appears to be not visible on mpMRI [9, 10]. Moreover, mpMRI tends to underestimate the size of large lesions [11-13]. Bratan et al identified that the accuracy of volume assessment is influenced by the size of lesions, Gleason score, and tumor Likert score [13]. For these reasons, tumor volume estimation with mpMRI should be considered with care in clinical practice [13], because this could have consequences for risk stratification [11].

To be able to improve volume assessment of lesions with mpMRI, we first need to understand why parts of lesions are not visible. Based on histopathology a single lesion can consist of a combination of Gleason patterns (GPs) and even within a single GP multiple architectural subpatterns can be present [14]. Langer et al indicated that there is a significant relation between histological features of normal and malignant prostate tissue and mpMRI parameters [15]. Moreover, different Gleason subpatterns have different signal intensities on T₂-weighted (T₂W) images [16]. Therefore, we hypothesized that the underlying intratumor histopathology heterogeneity may impact the visibility of a lesion on mpMRI. Thus, the purpose of this study was to investigate why some parts (ie, regions) of lesions are not visible on mpMRI by comparing their histopathology features to those of visible regions.

Materials and Methods

Patients

Retrospective analysis was performed of prospectively collected data of 34 biopsy-proven prostate cancer patients (median 69 years, range 54–76 years). The patients were consecutively included (October 2014 to April 2016) in three centers after Institutional Review Boards approval and written informed consent. Exclusion criteria were contraindications for MRI, prior treatment of prostate cancer, and transurethral resection of the prostate.

Imaging

The pretreatment mpMRI exam consisted of T₂W images in three directions, fat-saturated 3D T₁-weighted images, diffusion-weighted imaging (DWI), T₂ mapping, and dynamic contrast-enhanced (DCE) MRI. Patients were scanned with one 1.5T system and two 3.0T systems (Philips Healthcare, Best, Netherlands). Details of the scanning parameters are presented in Table 1. An apparent diffusion coefficient (ADC) map was calculated from DWI using a semilogarithmic linear fit through the data of b-values 200 and 1000 s/mm². A T₂ map was created from multiecho spin echo data by fitting a monoexponential decay function as implemented in the scanner software [17]. For quantitative analysis of the DCE data, the signal intensities were converted to concentration values using a baseline T₁ map generated from a variable flip angle series acquired (3D spoiled gradient echo sequence, repetition time [TR] 20 msec, echo time [TE] 4 msec, flip angles of 3, 6, 10, 20, and 30°) [18]. The standard Tofts model was applied to estimate K^{trans} using a deconvolution implementation [19]. As input for the model we used patient-specific arterial input functions derived from the magnitude data for the 1.5T system, whereas the arterial input functions were derived from the complex data for the data from the 3T systems [20]. All quantitative maps were rigidly registered to the axial T₂W image. When scanned with an endorectal coil, the T₂W image with endorectal coil was deformable registered to the T₂W image without endorectal coil. Before the start of patient inclusion, calibration measurements were performed to check consistency in the quantitative MRI parameters between the three institutes.

Two urogenital radiologists with 14 (S.W.T.P.J) and 6 years (I.G.S.) experience delineated suspicious lesions with a Prostate Imaging Reporting and Data System (PI-RADS) score of 3 and higher on the registered images [5]. Data of two test patients outside this cohort were used to reach agreement about the way they delineated: lesion border was based on low signal intensity on T2W MRI, high signal intensity on the DWI image with highest b-value, and low signal intensity on the ADC map. If the delineations of the two radiologists did not overlap, this patient was discussed to reach a consensus delineation. The peripheral zone (PZ), transition zone (TZ), and posterior and anterior sectors were segmented on T2W scans according to the prostate sector map [5].

Histopathology

Patient-customized 3D-printed molds were created using the transversal T₂W images [21]. Specimens were fixated (10% formalin) in the mold and sliced in 3-mm slices parallel to the MRI slices. Hematoxylin and eosin-stained wholemount slices were digitized (Aperio Technologies, Vista, CA). Lesions and GP 3, 4, and 5 were manually segmented (resolution 0.5 μm/pixel).

Imaging-Histopathology Interpretation

To link the delineations made by the readers on MRI to the lesions in histopathology, the histopathology slices were registered to the T₂W images using a registration method based on anatomical landmarks visible on the T₂W and the histopathology slices [22]. The error in the registration was assessed by independent observers (Supporting information).

The concordance between mpMRI delineations and histopathology lesions was evaluated on three levels using the histopathology as ground truth: patient-level, lesion-level, and region-level (Fig. 1). *Patient-level*: As all patients included in this study had known biopsy-proven prostate cancer, a patient was classified with visible cancer when both readers identified on mpMRI at least one suspicious lesion in the prostate with PI-RADS ≥ 3 , whereas a patient was classified with "invisible cancer" in the absence of suspicious lesions. *Lesion-level* (Fig. 1d): Lesions were identified on histopathology. Lesions were considered separate when the distance between the closest borders of the lesions was more than 3 mm [24]. A lesion, identified on histopathology, was classified as visible on mpMRI when both readers made a delineation in the same prostate zone, sector, and laterality as on histopathology [23]. A lesion was called invisible on mpMRI when it was missed by both readers. *Region-level* (Fig. 1e): Region-level analysis was carried out only for lesions that were classified as visible. Regions were identified per histopathology slice to be able to take the histopathology heterogeneity into account. If a lesion was present in multiple slices, this resulted in multiple regions per lesion. A region was classified as visible when it was delineated by both readers and invisible when it was not delineated by any. A region was classified as inconsistently delineated when delineated by only one of the readers. As for these regions it was unclear if they were visible or not, they were not further analyzed.

Both at the lesion- and at region-level we assessed several characteristics: size, location, and histopathology features. For lesions, their size was calculated with the ellipsoid volume formula [5]. For regions, their size (ie, surface area) was calculated from the number of voxels inside a region. For location, the zone (PZ or TZ) and sector (anterior or posterior) were determined in which the majority of the voxels of a lesion or region were located. From the histopathology data, first the International Society of Urological Pathology (ISUP) grade 1–5 were determined from the percentage of GP within a lesion or region [25]. In addition, several subpatterns were assessed [14] (Fig. 2). The density of neoplastic glands was either identified as "dense" or "intermediate" (Fig. 2a) [16]. A GP 4 region was classified as having cribriform growth if a part consisted of expansile rounded tumor areas with a cribriform pattern, large-sized glands with glomeruloid features showing a cribriform pattern, or complex fused glands with irregular cribriform areas (Fig. 2b) [14]. In addition to the subpatterns classification suggested by Kweldam et al [14], a lesion or a region was classified as having homogeneous morphology when the morphology of all tumor cells was the same, and heterogeneous morphology when more than one type of morphology was present; for instance, if both acinar and foamy tumor cells were present (Fig. 2c). Histopathology analyses were based on consensus between a trained researcher (G.G.) and a uropathologist with more than 6 years of experience (J.d.J.).

Statistical Analyses

Sensitivity of mpMRI was calculated on a patient-, lesion-, and region-level. Univariate and multivariate generalized linear mixed-effect modeling (GLMM) was used to investigate whether size,

location, or histopathology features explain why a lesion or region was not visible on mpMRI (RStudio, Boston, MA, v. 1.1.383, 2017, lme4 package) [26]. For ISUP grade, the lesions and regions were divided into two groups: ISUP grade 1 and 2 vs. ISUP grade 3 or larger. Size was classified as smaller or larger than 0.5 cm^3 for lesions, and smaller or larger than 0.5 cm^2 for regions. For the lesion-level GLMM, patients and lesions were added as random effects. For the region-level GLMM, regions were also added to the random effects to take into account that multiple regions could relate to the same lesion. In a forward approach, we investigated which combination of factors resulted in the best model fit using analysis of variance (ANOVA). To understand how location and the histopathology features affect the visibility on mpMRI, the median mpMRI values (T_2 map, ADC, and K^{trans}) of the lesions and regions were compared for each of these characteristics using one-way ANOVA with a statistical significance level of 0.05 (SPSS, Chicago, IL, v. 22, 2013).

Due to the unavailability of (parts of) wholemount slices, delineations and the imaging data were not taken into account for which histopathology information was not available. For one patient, missing DCE-MRI data were substituted with the median values of the K^{trans} from all other patients.

Results

Four out of 34 patients were excluded from analysis due to insufficient quality and slice orientation of the histopathology slides ($n = 3$) and hormonal therapy between the MRI and the prostatectomy ($n = 1$) [27]. The clinical characteristics of the remaining 30 are presented in Table 2.

The sensitivity for prostate cancer detection with mpMRI at the patient level was 0.97 (Supplemental Table S1). In total, 69 lesions were identified on histopathology with a median size of 0.3 cm^3 (range $0.0\text{--}16.8 \text{ cm}^3$). From these lesions 13 had ISUP grade ≥ 3 , of which two were not visible. The sensitivity for detecting all lesions on mpMRI was 0.51, whereas the sensitivity for detecting lesions with ISUP grade ≥ 3 was 0.85 (Table S1). Anterior location, small size, and ISUP grade 1–2 increased the chance of missing lesions on mpMRI (Table S2). Lesions smaller than 0.5 cm^3 had a $\beta = 4.1$ times higher chance of being missed than lesions larger than 0.5 cm^3 . A similar result was found for anterior lesions compared with posterior lesions ($\beta = 3.8$). ISUP grade 1–2 lesions had a $\beta = 3.0$ times higher chance of not being detected compared with ISUP grade ≥ 3 lesions. Figure S1 shows the imaging characteristics of the lesions with different location and histopathology features.

At the region level we investigated possible explanations why some regions of a visible lesion were invisible on mpMRI. Figure 3a shows an example of a visible ISUP grade 4 lesion with almost overlapping delineations by both readers. Figure 3b shows an example of a visible lesion with ISUP grade 1, but a large region of the lesion was not delineated by the readers. In total, the characteristics of 83 visible regions (surface area range $0.01\text{--}4.4 \text{ cm}^2$) and 36 invisible regions (surface area range $0.06\text{--}2.7 \text{ cm}^2$) were analyzed (Table 3). A median of 14% (range 6–41%) of the volume of a lesion was inconsistently delineated by the two readers and not taken into account in

further analyses. The sensitivity of visible regions in TZ was lower than regions in PZ (0.56 vs. 0.76). The sensitivity of visible regions with ISUP grade 1–2 was not different from the sensitivity of delineating ISUP grade ≥ 3 regions, as the confidence intervals overlapped. The sensitivity for regions with intermediate density was lower compared with dense regions (0.35 vs. 0.78). The same was true for regions with heterogeneous morphology compared with regions with homogeneous morphology (sensitivity = 0.44 vs. 0.72).

Multivariate analysis showed that the regions with intermediate density, heterogeneous tumor morphology, and location in TZ were more likely to be invisible on mpMRI (Table 4). The intermediate density regions had a $\beta = 3.2$ times higher chance of being invisible compared with dense regions. Low ISUP grade, small size, anterior location, and presence of cribriform growth did not have a significant influence on missing a region. This is in contradiction to the results on the lesion level, where ISUP grade was an explaining factor for missing an entire lesion. However, we did not observe a relation between ISUP grade and intermediate density and heterogeneous morphology: in ISUP grade 1–2 regions 20% had an intermediate density, while in ISUP grade ≥ 3 regions 16% had an intermediate density. Similarly, in ISUP grade 1–2 regions 9% had heterogeneous morphology, which was comparable for ISUP grade ≥ 3 regions with 6% heterogeneous morphology. This illustrates that the intermediate density and heterogeneous morphology were independent from ISUP grade. In addition, in four patients for whom regions with ISUP grade ≥ 3 were invisible, these regions had either intermediate density or heterogeneous morphology, whereas the visible regions for those patients were dense and had homogeneous morphology.

To understand how the different tested factors affect mpMRI data, their imaging characteristics were analyzed (Fig. 4). No significant differences in T_2 , ADC, and K^{trans} were observed for regions in different zones and sectors ($P = 0.14, 0.33, 0.57$, and $P = 0.23, 0.72, 0.17$). In regions with ISUP grade ≥ 3 , the ADC values were significantly lower and K^{trans} was significantly higher than in regions with ISUP grade 1–2 ($P = 0.02$ and 0.007). No significant difference was found for the T_2 values ($P = 0.19$). In regions with intermediate density T_2 and ADC values were significantly higher than in dense regions ($P = 0.002$ and < 0.001), while K^{trans} was not different ($P = 0.24$). In addition, in regions with heterogeneous morphology T_2 and ADC values were significantly higher than for regions with homogeneous morphology ($P < 0.001$ and 0.03), while K^{trans} was not different ($P = 0.99$). ADC values in regions where cribriform growth was present were significantly lower than the regions without cribriform growth ($P = 0.03$), while T_2 and K^{trans} were not different ($P = 0.33$ and 0.07).

Figure 5 shows the histopathology features and imaging characteristics of delineated and missed regions of the lesions for four patients. In all cases, the delineated areas on mpMRI were dense on histopathology, had homogeneous morphology, and were located in the PZ. The signal intensities of T_2W and ADC values were low in these regions. In the first two cases (Fig. 5a & b), large regions of ISUP grade ≥ 3 were missed by both readers on T_2W and ADC. These regions had an intermediate

density and homogeneous morphology and were located either in PZ or TZ. In the third example (Fig. 5c), the area that was missed was dense, but with heterogeneous morphology. The fourth example (Fig. 5d) shows a large missed region that had both intermediate density and heterogeneous morphology.

Discussion

Accurate tumor volume assessment is necessary for treatment decision and monitoring strategies in prostate cancer. Tumor volume may be underestimated on mpMRI [11]. In this proof-of-principle study, we linked the delineations by readers on mpMRI to detailed histopathology characteristics to identify reasons for this underestimation. Although the characteristics of invisible lesions and invisible regions were not compared directly, from our results we observed that the factors for missing an entire lesion were different from missing a part of it: while size and ISUP grade were important for lesion detection, other histopathological features explain why a part (ie, a region) of this lesion was invisible. Specifically, a region of a lesion was more likely to be missed on mpMRI when it had intermediate density, heterogeneous tumor morphology, and was located in TZ.

The per-lesion sensitivity of our data was in the same range as reported by other studies [10]. The detailed histopathology analysis led to segmentation of many small low-grade lesions that were all invisible on mpMRI. This may explain why this study showed lower sensitivity for lesion detection than Borofsky et al [11]. Like other studies, size, ISUP grade, and location were important factors for missing entire lesions [10, 28-31]. Rosenkrantz et al found that visible and invisible lesions have a different density [31]. In our study, this was only true in univariate analysis.

Of the visible lesions, some regions were not visible, which will result in underestimation of tumor volume. The invisible regions have different histopathology characteristics than visible regions, confirming previous results that a prostate lesion consists of a combination of multiple subpatterns that represent themselves differently on mpMRI [14, 16]. Bratan et al also looked at density as an influencing factor for the accuracy of volume assessment: from their analysis the Gleason score, size, and Likert score were significant predictors for accurate volume assessment [13]. The discrepancy could be explained by the study design, as their study was performed on a lesion level, while our study was performed on a region level.

The imaging values of visible and invisible regions did not differ between different prostate locations (ie, PZ vs. TZ and anterior vs. posterior). This suggests that the conspicuity of lesions in different locations of the prostate is affected by differences in tissue surrounding the prostate cancer lesion rather than differences in tumor characteristics. This hypothesis arises from studies reporting on the normal zone imaging characteristics showing that the T_2 and ADC values of lesions are more similar to those in normal TZ than in the normal PZ [32, 33]. Our data confirmed previous studies showing that ADC and K^{trans} values were significantly different in regions with low- and high-grade cancer [34,

35]. In addition, we showed that regions with intermediate density had higher T_2 and ADC values than the dense regions, consistent with other studies [16, 36]. Regions with heterogeneous morphology also had higher T_2 and ADC values than the homogeneous regions. As the readers based their delineations on the T_2W images and DWI, this could explain why regions with intermediate density and heterogeneous morphology were missed. Interestingly, K^{trans} was not different for any of these features. Although the role of DCE-MRI is limited for lesion detection in the PI-RADS v2 guidelines, for tumor volume assessment this role should be further evaluated. This is in line with the findings of Bratan et al indicating that the combined volume delineated on individual T_2W , ADC, and DCE images resulted in a better volume estimation [13].

Most lesions with cribriform growth were detected in our study, consistent with Prendevill et al [37]. This is promising, as cribriform growth is a prognostic factor for disease-specific mortality [38]. These lesions with cribriform growth were mainly mixed with poorly formed/fused morphology, which have a better mpMRI conspicuity than lesions with pure cribriform morphology [39]. In contrast, there were many regions with intermediate density in our study population and those were often missed. Therefore, we expect that this will also often occur in clinical practice and will result in underestimation of tumor volume. In this study we investigated all histopathology lesions. However, not all of them will have the same importance for the diagnosis and prognosis of a patient. In addition, the clinical relevance of invisible regions with intermediate density and heterogeneous morphology remains unclear and warrants further investigation by studying their genetic background. With a growing population choosing active surveillance, we need to be aware of this error, especially when mpMRI is propagated as a monitoring tool without any biopsy procedure [40]. Focal treatment plans may be expanded by margins beyond the visible lesion on mpMRI [11] at the cost of increasing the treated healthy volume. Therefore, we recommend developing guidelines for more accurate lesion delineation.

Although we analyzed a considerable number of lesions and regions and applied GLMM to account for the interdependence at the patient-, lesion-, and region-level, still the small number of patients may have led to some factors being not significant and may not represent the true variability of the disease. Because of the size of our study, we limited the histopathology analysis to a few subpatterns. Our cohort consisted of prostatectomy patients, as this is necessary for histopathology-imaging interpretations, but this limits the generalizability of the results. Another limitation is the way tumors were delineated on mpMRI. As there is currently no consensus about prostate cancer delineation, differences with other studies [13] may exist. Furthermore, image quality, and therefore tumor detection and delineation, could have been affected by image registration. Another factor that could have influenced tumor conspicuity is the use of a 1.5T system at one of the institutes. However, we investigated the effect of different MR systems by adding institute as a random effect to the mixed modeling and observed that this did not improve the model performance. Data analysis was limited to the availability of histopathology slices.

In conclusion, regions of prostate cancer lesions that are not visible on mpMRI have different histopathology features than regions that are visible. Regions with intermediate density and heterogeneous tumor morphology are likely to be missed on prostate mpMRI. This could explain tumor volume underestimation of prostate cancer lesions with mpMRI and may have implications for monitoring during active surveillance and focal treatment strategies in prostate cancer management.

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Table 1: Details of Scanning Parameters

	Parameter	System A ^a	System B ^b	System C ^c
No. of patients		<i>n</i> = 12	<i>n</i> = 7	<i>n</i> = 3
Turbo spin echo T2-weighted	FOV (mm ³)	280x350x120	240x240x176	140x140x75 (with endo)
				200x282x75 (without endo) ^d [140x140x75]
	Acquired voxel size (mm ³)	1.1x1.1x3	0.8x0.8x3	0.46x0.58x3 (with endo)
				0.7x0.7x3 (without endo) ^d [0.7x0.7x3]
	Reconstructed voxel size (mm ³)	0.6x0.6x3	0.4x0.4x3	0.27x0.27x3 (with endo)
				0.4x0.4x3 (without endo) ^d [0.4x0.4x3]
	TR/TE (msec)	Range 2500–5000/80	Range 2500–5000/95	Range 2500–5000/120
Single-shot EPI DWI	FOV (mm ³)	262x415x120	262x262x66	160x180x63 [256x256x66]
	Reconstructed voxel size (mm ³)	1.3x1.3x5	1.4x1.4x3	1.1x1.1x3 [1.3x1.3x3]
	TR/TE (msec)	3500/67	3500/65	3500/59 [3600/57]
	b-values (s/mm ²)	0 (1), 200 (4), 600	0 (5), 200 (5), 500	0 (1), 200 (4), 600 (4), 1000
	(averages)	(4), 1000 (8)	(5), 1000 (5)	(8)
	Parallel imaging factor	3	3	2
Multi-echo spin echo T2 mapping	FOV (mm ³)	262x262x60	262x262x60	170x170x60
	Acquired voxel size (mm ³)	2.3x2.3x3	1.5x1.5x3	0.8x0.8x3 [1x1x3]
	Reconstructed voxel size (mm ³)	1.4x1.4x3	0.8x0.8x3	0.4x0.4x3 [0.6x0.6x3]
	TR/TE /ΔTE (msec)	Range 2000–5000/30/15	Range 2000–5000/30/15	2459/32/16
	No. echoes	10	10	12
	Parallel imaging factor	2	3	2 ^e
3D spoiled gradient echo DCE	FOV (mm ³)	262x262x60	262x262x60	360x520x60
	Acquired voxel size (mm ³)	2.5x2.5x6	2x2x3	1.8x1.8x6 [2.3x2.3x6]
	Reconstructed voxel size (mm ³)	1.4x1.4x3	1.2x1.2x3	1.2x1.2x3 [1.3x1.3x3]
	TR/TE (msec)	5/1.9	4/1.9	4/1.9 [5/1.9]
	Flip angle (degrees)	30	13	20
	Parallel imaging factor	3	4	4
	Dynamic scan time (sec)	2.4	2.5	2.7 [2.9]
	No. of dynamics	120	120	110
	Contrast agent	15 mL of 0.5 mM Dotarem	15 mL of 0.5 mM Dotarem	15 mL of 0.5 mM Dotarem
	Injection rate (mL/s)	3	2	3

- a 1.5T Ingenia scanner using a dStream Torso coil.
- b 3T Ingenia system using a 16-channel anterior and 12-channel posterior coil.
- c 3T Achieva system using a 6-channel cardiac coil in combination with an endorectal coil. Three patients were scanned on an upgraded system (Achieva dStream) where we used a 16-channel anterior and 12-channel posterior coil. The parameters that were different at the upgraded system, are given between square brackets.
- d For those patients scanned with an endorectal coil an additional T2W scan was acquired without endorectal coil to facilitate registration with histopathology.
- e In addition to standard parallel imaging a k-t undersampling scheme was applied for further acceleration of the sequence (Van Houdt et al, Magn Reson Med. 2018;79).

Table 2: Patient Characteristics (n = 30)

Patient characteristic		Median (range)
Age		69 years (54–76)
Prostate-specific antigen		7.8 ng/mL (3.7–40.0)
Time between MRI and prostatectomy		18.5 days (5–65)
		No. of patients
T stage	cT1	9
	cT2	13
	cT3	6
unknown	2	
Gleason score		
Pre-operative biopsy	3 + 3	11
	3 + 4	13
	3 + 5	2
	4 + 3	2
	4 + 4	1
	4 + 5	1
Prostatectomy specimen*	3 + 3	7
	3 + 4	12
	3 + 5	4
	4 + 3	5
	4 + 5	2

* This was retrieved from patients' pathology report at each center.

Table 3: Sensitivity at the Region Level

Characteristic	Subtype		Visible	Invisible	Sensitivity	95% confidence interval
Location	Zone	PZ	61	19	0.76	0.65–0.85
		TZ	22	17	0.56	0.40–0.72
	Sector	Posterior	66	24	0.73	0.63–0.82
		Anterior	17	12	0.59	0.39–0.76
Size	Surface area (cm ²)	≥ 0.5	45	21	0.68	0.55–0.79
		< 0.5	38	15	0.72	0.57–0.83
		≥ 3	31	7	0.82	0.65–0.92
		2	4	1	0.80	0.30–0.99
		1	48	28	0.63	0.51–0.74
Sub-patterns	Density	Dense	75	21	0.78	0.68–0.86
		Intermediate	8	15	0.35	0.17–0.57
	Tumor morphology	Heterogeneous	4	5	0.44	0.15–0.77
		Homogeneous	79	31	0.72	0.62–0.80
	Cribriform growth	Yes	24	4	0.86	0.66–0.95
		No	59	32	0.65	0.54–0.74

ISUP grade = International Society of Urological Pathology; PZ = peripheral zone; TZ = transition zone.

Table 4: Results From the Best-Performing Generalized Linear Mixed-Effect (GLMM) Model to Indicate Which Factors Most Likely Explain Why a Region Is Invisible on mpMRI

Fixed effects	β	Std. error	P-value
Intermediate density (ref = dense)	3.2	0.9	< 0.001
Heterogeneous morphology (ref = homogeneous morphology)	1.9	0.9	< 0.05
TZ (ref = PZ)	1.7	0.8	< 0.05
Intercept (β_0)	-4.9	3.7	0.18
Residuals (ϵ_0)	Median	1 st quartile	3 rd quartile
	-0.23	-0.42	0.40

β = regression coefficients; TZ = transition zone; PZ = peripheral zone; ref = reference in GLMM.

Supplementary Table 1 : Sensitivity at patient- and at lesion-level

Level	Subtype	Visible	Invisible	Sensitivity	95% Confidence Interval
Patient-level	All Patients	29	1	0.97	0.86-1.00
	ISUP grade ≥ 3	6	0	1.00	0.52-1.00
	1-2	23	1	0.96	0.77-0.99
Lesion-level	All lesions	35	34	0.51	0.38-0.63
	<i>Location</i> Zone PZ	28	27	0.51	0.37-0.64
	TZ	7	7	0.50	0.24-0.76
	Sector Posterior	28	13	0.68	0.52-0.81
	Anterior	7	21	0.25	0.11-0.45
	<i>Size</i> Volume (cm ³) ≥ 0.5	20	5	0.80	0.59-0.92
	< 0.5	15	29	0.34	0.21-0.50
	<i>ISUP grade</i> ≥ 3	11	2	0.85	0.54-0.97
	2	4	1	0.80	0.30-0.99
	1	20	31	0.4	0.26-0.54
	<i>Structure/texture</i> Density Dense	27	18	0.60	0.44-0.74
	Intermediate	8	16	0.33	0.16-0.55
	Tumor morphology Heterogeneous	5	2	0.71	0.30-0.95
	Homogeneous	30	32	0.48	0.36-0.61
	Cribriiform growth Yes	9	1	0.90	0.54-0.99
	No	26	33	0.44	0.31-0.57

Abbreviations: ISUP = International Society of Urological Pathology; PZ = peripheral zone; TZ = transition zone

Supplementary Table 2: Multivariate analysis for the best performing generalized linear mixed-effect model for missing a lesion.

Fixed effects	β	Std. error	p-value
Size < 0.5 cm³ (ref size ≥ 0.5 cm ³)	4.1	1.7	0.016
Anterior sector (ref posterior sector)	3.8	1.2	0.002
ISUP grade 1-2 (ref ISUP Grade ≥ 3)	3.0	1.5	0.055
Intercept (β_0)	0.2	0.8	0.73
Residuals (ϵ_0)	Median	1 st quartile	3 rd quartile
	-0.01	-0.30	0.32

β , regression coefficients

Figure 1

An example illustrating the lesion- and region-level analysis. (a) Both readers delineated a suspected lesion in this patient. The delineations are on the right side of the prostate, in the PZ, and posterior sector. (b) Histopathology slice with manual GP segmentations. There are two lesions on the histopathology slice: lesion 1, ISUP grade 3, located posteriorly in the PZ, and lesion 2, ISUP grade 1, anteriorly in TZ. (c) Registered histopathology to T2W image. Lesion 1 coincides with the delineations of both readers, unlike lesion 2 that was not delineated by any of them. (d) Lesion-level analysis: lesion 1 was classified as a visible lesion, whereas lesion 2 was classified as an invisible lesion. (e) For region-level analysis, lesion 1 was subsequently divided in different regions: visible for the area that was delineated by both readers, invisible for the parts that were missed by both readers, and undefined when the area was only delineated by one of the readers.

Figure 2

Three histopathology subpatterns to describe the density, architecture, and morphology of a lesion or region: (a) density, (b) cribriform growth for GP 4, and (c) tumor morphology. Scale bar = 900 μ m

Figure 3

Two examples of patients with GP segmentations on the registered histopathology slice and the delineations of readers shown on the corresponding axial mpMRI images. (a) An example of two lesions on the histopathology slice, one was visible and almost completely delineated, and the other one invisible on mpMRI for the readers. (b) An example of a visible lesion that was partially delineated by the readers. For DWI an image of b -value of 1000 s/mm^2 is shown, whereas for DCE one of the dynamic scans at 90 sec is shown. The T_2 maps are scaled between 0 and 300 msec, the ADC maps are scaled between 0 and $2.4 \cdot 10^{-3} \text{ mm}^2/\text{s}$, and K^{trans} maps are scaled between 0 and 0.8 min^{-1} .

Figure 4

Imaging characteristics of all regions (median T_2 , median ADC, and median K^{trans}) for location and histopathology features. Asterisks indicate statistical significance between the two groups ($P < 0.05$).

Figure 5

The histopathology features and imaging characteristics of visible (green delineation) and invisible regions (red delineation) are illustrated in four patients. Each row represents one patient. The ADC maps are scaled between 0 and $2.4 \times 10^{-3} \text{ mm}^2/\text{s}$, and K^{trans} maps are scaled between 0 and 0.8 min^{-1} . (a) A patient with ISUP grade 4 lesion with homogenous morphology and cribriform growth located in PZ. The invisible region had intermediate density, whereas the visible region was dense. (b) A patient with ISUP grade 4 lesion. The visible region was dense, with cribriform growth and located in PZ, whereas the invisible region had intermediate morphology, without cribriform growth and located in TZ. (c) A patient with ISUP grade 2, dense lesion in PZ. The visible region had homogeneous morphology, whereas the invisible region was heterogeneous. (d) A patient with ISUP grade 2 lesion in PZ. The visible region was dense and had homogenous morphology, whereas the invisible region had intermediate density and heterogeneous morphology.

Figure S1

Imaging characteristics of all lesions (median T2, median ADC, and median K^{trans}) for location and histopathology features. Asterisks indicate statistical significance between the two groups ($p < 0.05$).

Supporting information

Assessment of qMRI performance

In this study, quantitative MRI was acquired at three systems. Prior to start of the patient study, the MR protocols were checked for consistency using calibration phantoms. For T2 the Eurospin II test object 5 (Diagnostic Sonar LTD, Livingston, Scotland) was used, whereas for ADC an ice-water phantom was used [1]. As there is no direct way to validate K^{trans} we checked two aspects that are important in the analysis pipeline with the Eurospin II phantom: accuracy of baseline T1 mapping and stability of DCE signal during the acquisition. The accuracy of T2, ADC, and T1 was expressed as the

$$\text{systematic error} = \frac{\bar{X} - X_{true}}{X_{true}} \cdot 100\%$$

(1)

Where X_{true} is the true value known for the sample in the phantom and $\bar{X}$ the measured value averaged over voxels inside a region. Systematic error was calculated per sample in the phantom. Median and range were calculated.

Table 1 Systematic error for T2, ADC, and T measured on the three different systems. For T2 and T1 median and range are reported for the twelve samples in the phantom. For ADC only one sample was available. Values for the center slice were used.

Systematic Error (%)	System A	System B	System C
	Median (range)	Median (range)	Median (range)
T2	-7% (-11 to -1)	2% (-2 to 8)	-2% (-7 to 2)
ADC	4%	3%	-1%
T1	-7% (-16 to -7)	-14% (-21 to -3)	-9% (-21 to 13)

To estimate the stability of the DCE signal, the coefficient of variation was calculated from the signal intensities in an ROI during the acquisition. The CV was similar for the three institutes with an overall average CV of $1.5 \pm 0.6\%$.

Assessment of registration errors

We estimated the accuracy of the registration between histopathology and the T2-weighted MRI by measuring the Euclidean distance between landmarks placed in the histopathology and T2-weighted slices. For this we selected one slide per patient and asked two independent observers with different levels of experience in image-histopathology registration to place at least three landmarks. These were different landmarks as used for the registration. We found an average of 2.5 ± 1.2 mm landmark distance for an inexperienced observer and 1.8 ± 0.8 mm for the experienced observer.

For six patients we estimated the angle between the histopathology and the MRI slices to verify whether the slice-by-slice correspondence as introduced by the mold was correct. We observed a median angle of 3° (range 1° - 9°).

References

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