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PI-RADS version 2: optimal time range for determining positivity of dynamic contrast-enhanced MRI in peripheral zone prostate cancer

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AIM: To analyse the optimal time cut-off for determining positivity of dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) in peripheral zone (PZ) prostate cancer (PCa).

MATERIALS AND METHODS: A consecutive series of 89 patients with PZ PCa who had undergone diffusion-weighted imaging (DWI) and subtraction DCE MRI were included. An experienced reader visually analysed the earliest time after contrast medium injection to visualise the best contrast between an index tumour and normal PZ on DCE MRI (i.e., best contrast time). The best contrast time cut-off for clinically significant cancer (csPCa) according to Epstein criteria or International Society of Urological Pathology (ISUP) grade ≥2 was analysed by an experienced reader, and applied to a less-experienced reader. For the index lesion of DWI category 3, the added value of DCE MRI (increased true positive and negative rates of PI-RADSv2 for csPCa) was evaluated using the cut-off time.

RESULTS: The best contrast time cut-off for csPCa was ≤72 seconds for Epstein criteria and ≤56 seconds for ISUP grade ≥2 by an experienced reader. The weighted kappa to determine positivity of DCE MRI was 0.622 for ≤72 seconds and 0.527 for ≤56 seconds between the two readers. The added value of DCE MRI was 55–75% by an experienced reader and 39.1–69.6% by a less-experienced reader.

CONCLUSION: For interpreting PI-RADSv2, imaging findings within 60–72 seconds following contrast media injection seem to reliably determine positivity of DCE MRI in PZ, and have added value for detecting csPCa.

Introduction

According to Prostate Imaging-Reporting and Data System version 2 (PI-RADSv2), findings of dynamic

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contrast-enhanced (DCE) magnetic resonance imaging (MRI) plays a role as a back-up sequence in analysing equivocal peripheral zone (PZ) lesions (i.e., DW category 3).[1,2] DCE MRI is also helpful when the other MRI sequences do not provide acceptable image quality in daily practice (i.e., artefacts from rectal air/motion or metallic device). In addition, recent data suggest that the cancer detection rate of PZ lesions showing DW category 3 is significantly higher when DCE MRI shows positive findings, compared with negative DCE MRI findings.[3,4]

In the current system, positive findings of DCE MRI are defined by the presence of focal earlier or simultaneous enhancement of the lesion corresponding to a suspicious finding on DWI MRI with adjacent normal prostatic tissues.[1] This subjective visual analysis seems to help PI-RADS v2 to be used widely in daily practice because the meticulous process of quantitative or semi-quantitative analysis is not mandatory. Meanwhile, there are risks of inter-reader variability in determining the positivity of DCE MRI.[5,6]

Therefore, the aim of the present study was to analyse the optimal time after contrast medium infection when an index tumour is sufficiently differentiated from the normal PZ tissues of prostate gland. In addition, the added value of the cut-off time of DCE MRI in detecting clinically significant prostate cancer (csPCa) in PZ of the prostate gland was also investigated.

Materials and methods

Study population

The institutional review board approved this study, and the requirement for informed consent was waived. Between January 2016 and July 2016, a consecutive series of 102 patients who met the following inclusion criteria were recruited from the institutional database search: (a) preoperative 3-T MRI including DWI and DCE MRI, (b) surgically confirmed prostate cancer, (c) no preoperative androgen deprivation therapy. Of the 102 patients, 13 patients were excluded because their index tumours were located in the transition zone (TZ). Therefore, 89 patients (median, 66 years; range, 45–78 years) with preoperative 3-T MRI and surgically proven PZ PCa were included in this study (Fig 1).

MRI examination

Prostate MRI including DWI and DCE MRI was conducted using one of three 3-T MRI systems (Discovery MR750, GE Medical Systems; Discovery MR750w, GE Medical Systems; or Achieva, Philips Medical Systems, Milwaukee, WI, USA) with a phased-array body coil. Before the MRI examination, 20 mg butyl scopolamine (Buscopan, Boehringer Ingelheim, Ingelheim am Rhein, Germany) was injected intramuscularly to suppress bowel peristalsis.

The imaging protocols of DWI and DCE MRI are summarised in Table 1. Apparent diffusion coefficient (ADC) maps were generated from DWI data using b-values of 50 and 1000 mm^2/s using the mono-exponential fit. For DCE

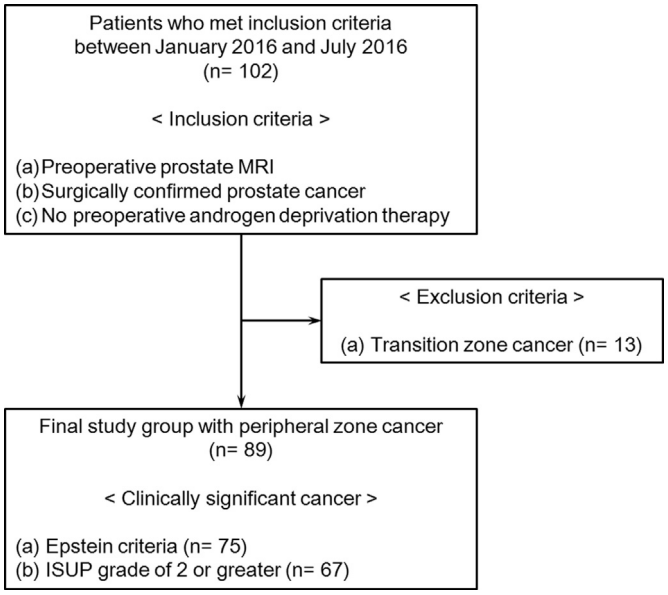

Figure 1 Flowchart of study patients.

MRI, fat-saturated T1-weighted fast-field-echo images with a temporal resolution of <7 seconds (6 seconds for Discovery MR750 and MR750w, and 4 seconds for Archieva) were acquired before and after a bolus injection of gadoterate meglumine (Dotarem; Guerbet, Aulnay-Sous-Bois, France) with a rate of 2–3 ml/s using a power injector at a dose of 0.1 mmol/kg body weight, followed by a 20-ml saline flush.

Histopathological analysis

All surgical specimens were paraffin embedded and submitted for histopathological analysis. Whole-mount serial sections of the specimen were prepared from the apex to the base at 4–5 mm intervals. An experienced genitourinary pathologist with >15 years of experience for prostate cancer (N.H.C.) localised an index tumour using a 24-sector tumour map (PZ or TZ; right or left; base, mid, or apex; and anterior or posterior). The International Society of Urological Pathology (ISUP) grade, tumour volume, and extraprostatic extension (EPE) of an index tumour were

Table 1
MRI protocol.

Parameter	DWI MRI	DCE MRI
Orientation	Axial	Axial
Repetition time (ms)	≥3000	3.3–5.2
Echo time (ms)	≤90	1.6–2.3
Section thickness (mm)	4	3–4
Field of view (mm)	240	240
In plane dimension		
Phase (mm)	≤2.5	<2.0
Frequency (mm)	≤2.5	<2.0
b-Value (s/mm^2)	0, 50, and 1000	NA
Temporal resolution (sec)	NA	4 or 6
Total observation time (min)	NA	≥2

DWI MRI, diffusion-weighted magnetic resonance imaging; DCE MRI, dynamic contrast-enhanced magnetic resonance imaging.

Table 2
Characteristics of study patients.

Parameter	Value
Age (year)	66 (45–78)
PSA (ng/dl)	7.3 (2.5–56.5)
ISUP grade (*n*)	
1	22
2	33
3	15
4	11
5	8
Tumour volume (cm^3)	0.9 (0.1–19.0)
EPE	30.3% (27/89)
csPCa	
Epstein criteria	84.2% (75/89)
ISUP grade ≥2	75.3% (67/89)

Data for age, PSA, and tumour volume are median (range).
PSA, prostate-specific antigen; ISUP, International Society of Urological Pathology; EPE, extraprostatic extension; csPCa, clinically significant prostate cancer.

analysed. The index tumour was determined by EPE or tumour volume.

According to the ISUP grading system, the Gleason score (GS) was classified from the ISUP grade 1 to 5 as follows: grade 1=GS 3+3; grade 2=GS 3+4; grade 3=GS 4+3; grade 4=GS 4+4; and grade 5=GS 4+5 or greater.[7] In this study, two types of definitions for csPCa were utilised as follows: (a) Epstein criteria[8] or (b) ISUP grade ≥2.[9]

Image analysis

Two radiologists (reader 1, S.Y.P., with 6 years of experience in prostate MRI reporting; reader 2, H.B., a third-year resident with experience of >100 cases of prostate MRI reporting) interpreted DWI and DCE MRI retrospectively and independently for the patients who underwent surgery for biopsy-proven PCa. The image viewing software (Myrian®, Intrasense, Montpellier, France) was used for the analysis. In conjunction with the location information of an index tumour from the pathology tumour map, the two independent readers tried to analyse DWI and DCE MRI features of the true cancerous region, while minimising risks of incorrect analysis for benign mimickers; however, they were blinded to the tumour grade, tumour volume, or EPE status.

In terms of DWI MRI, the two readers independently recorded the DWI category of the index tumour per patient. DWI MRI with a b-value of 1000 s/mm^2 and ADC map were used for DWI scoring according to PI-RADSv2.[10] In terms of DCE MRI, the two readers assessed the best time after the

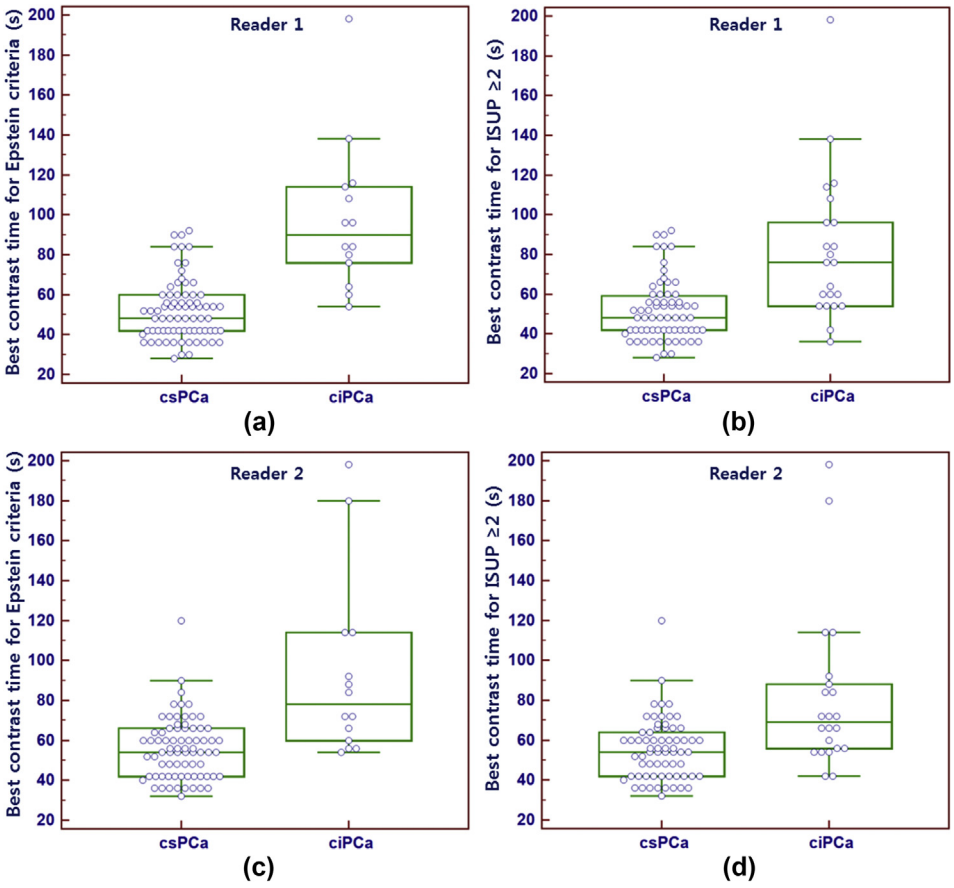

Figure 2 Comparison of the best contrast time for csPCa. The dots represent actual cases and the central box represents the values from the lower to upper quartile (25–75 percentile). The middle line represents the median. The vertical line extends from the minimum to the maximum value, excluding outside and far out values, which are displayed as separate dots. (a,b) For an experienced reader, the best contrast time was significantly earlier in csPCa than in ciPCa according to Epstein criteria (a) or ISUP grade (b), respectively ($p<0.001$). (c,d) For a less experienced reader, the best contrast time was also significantly earlier in csPCa than in ciPCa according to Epstein criteria (c) or ISUP grade (d), respectively ($p<0.001$).

contrast medium injection per patient. The best contrast time was defined by the time interval between the enhanced-image showing the best tissue contrast at the earliest time after contrast injection and the first image of DCE MRI. Here, a DCE image showing the best tissue contrast at the earliest time between an index tumour and benign PZ image was visually selected by two independent readers. For example, when the 10th image after the initiation of contrast medium injection on DCE MRI with the temporal resolution of 6 seconds was subjectively considered to show best tissue contrast by a radiologist, the best contrast time was 60 seconds for the case. Quantitative or semi-quantitative analysis (e.g., enhancement curve typing) was not performed because those methods are not mandatory in PI-RADS v2[1,2] and the purpose of the present study was to suggest a simplified and reproducible guideline to determine the positivity of DCE MRI for csPCa under the principle of PI-RADS v2 interpretation.

Statistical analysis

The Mann–Whitney test was utilised to compare the best contrast time of DCE MRI between csPCa and clinically insignificant prostate cancer (ciPCa) for the two readers, respectively.

Receiver-operating characteristic (ROC) curve analysis was used to evaluate a cut-off of the best contrast time for identifying csPCa according to Epstein criteria or ISUP grade ≥2 or greater, respectively. The cut-off value of the best contrast time interpreted by reader 1 (an experienced reader) was analysed, and it was applied to reader 2 (a less experienced reader). Weighted kappa was investigated to assess the inter-reader agreement in determining the positivity of DCE MRI with the cut-off of the best contrast time derived from reader 1. With the cut-off of the best contrast time derived from reader 1, the area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of the two readers were assessed for csPCa. The PPVs of DCE MRI for csPCa according to various cut-off times were also calculated.

For patients with DWI category of 3, the added value of DCE MRI was calculated using the following equation with a selected cut-off for the best contrast time: added value=the rate of increase in true positive and negative cases of csPCa after adding DCE to DWI MRI. True positive MRI

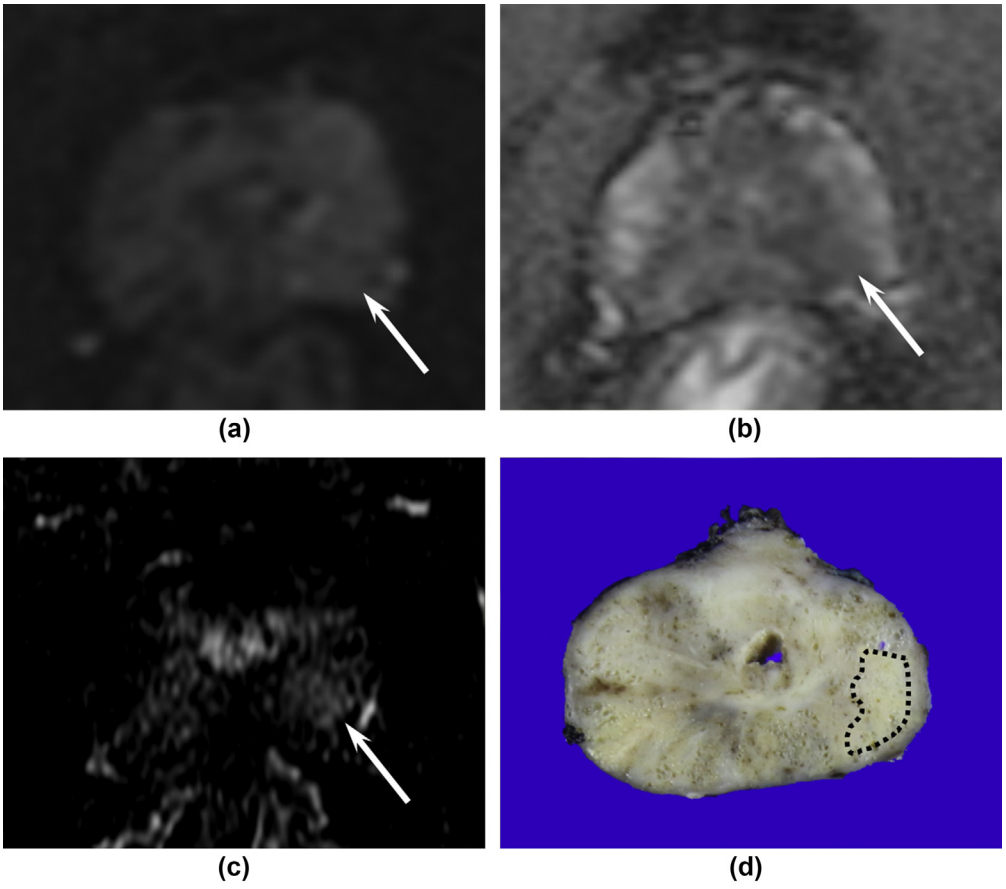

Figure 3 A 67-year-old man with biopsy-proven PCa. (a,b) DWI MRI and ADC map depicted a focal area of mildly or moderately restricted diffusion in left PZ of prostate gland (arrow). The DWI category was 3 for both readers. (c) On DCE MRI, focal enhancement was seen at the corresponding site of the prostate gland (arrow). The best enhancement time was less than 72 seconds (reader 1, 60 seconds; reader 2, 66 seconds), suggestive of positive DCE MRI for Epstein criteria. (d) Radical prostatectomy revealed PCa with ISUP grade 1 and tumour volume of 1.8 cm^3 which met Epstein criteria, but did not meet ISUP grade ≥2 for csPCa.

interpretation of csPCa was defined as a final PI-RADS v2 category ≥4. Additional MRI interpretation was not performed for this sub-analysis.

Statistical analysis was performed using MedCalc (version 13.3, MedCalc Software, Mariakerke, Belgium). A *p*-value of <0.05 was considered statistically significant.

Results

csPCa

The rate of surgically proven csPCa was 84.2% (75/89) for Epstein criteria and 75.3% (67/89) for ISUP grade of 2 or greater (Table 2).

Best contrast time

For reader 1, the best contrast time was significantly earlier in csPCa than in ciPCa according to Epstein criteria (median, 48 versus 90 seconds; $p<0.001$) or ISUP grade (median, 48 versus 76 seconds; $p<0.001$; Fig 2). For reader 2, the best contrast time was also significantly earlier in csPCa than in ciPCa according to Epstein criteria (median, 54 versus 78 seconds; $p<0.001$) or ISUP grade (median, 54 versus 69 seconds; $p<0.001$).

Optimal cut-off to determine positive DCE MRI by an experienced reader

The optimal cut-off time for identifying csPCa was ≤72 seconds for Epstein criteria and ≤56 seconds for ISUP grade ≥2 by reader 1 (Figs 3 and 4).

Application to a less-experienced radiologist

Weighted kappa in determining positivity of DCE MRI was 0.622 (95% confidence interval [CI], 0.412–0.832) for ≤72 seconds and 0.527 (95% CI, 0.355–0.698) for ≤56 seconds between the two readers with different experiences in prostate MRI.

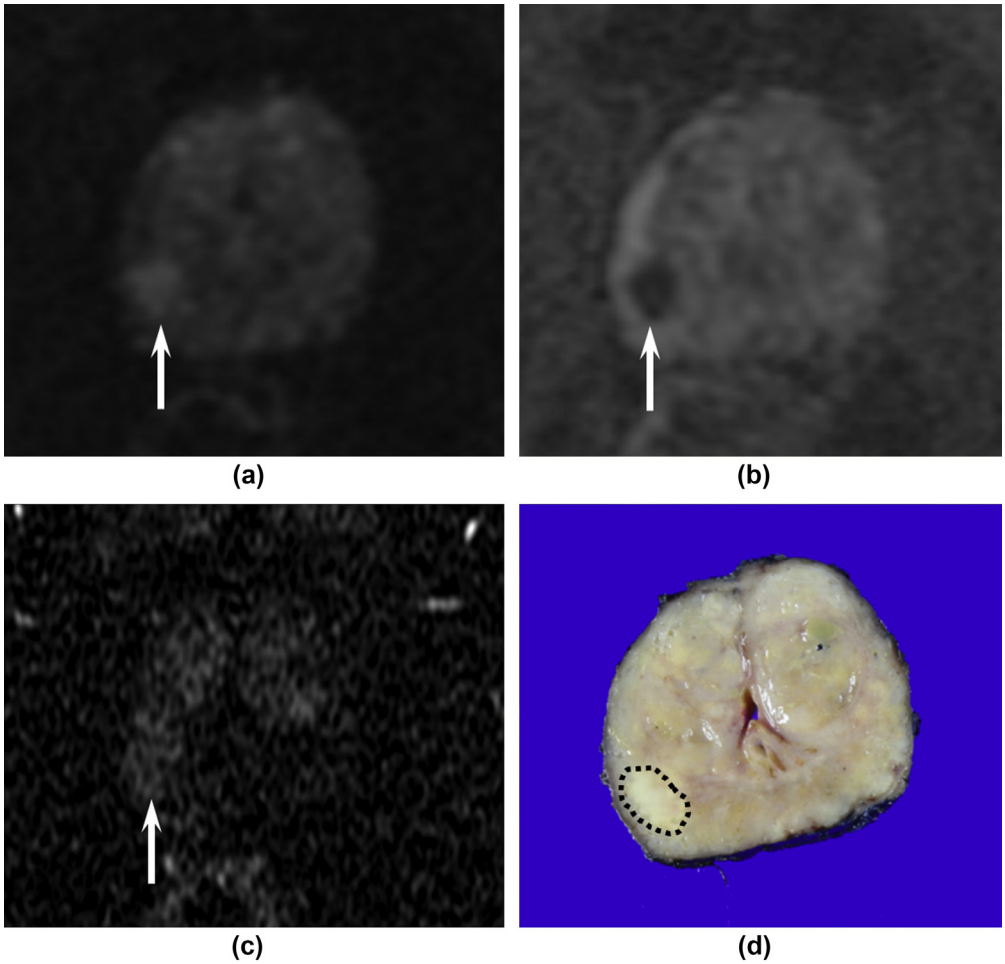

Figure 4 A 65-year-old man with biopsy-proven PCa. (a,b) DWI MRI and ADC map depicted a focal area of markedly restricted diffusion in right PZ of prostate gland (arrow). The DWI category was 4 for both readers. (c) On DCE MRI, focal enhancement was seen at the corresponding site of the prostate gland (arrow). The best enhancement time was less than 56 seconds (36 seconds for both readers), suggestive of positive DCE MRI for Epstein criteria and ISUP grade ≥2. (d) Radical prostatectomy revealed PCa with ISUP grade 3 and tumour volume of 1.2 cm^3, which met both Epstein criteria and ISUP grade ≥2 for csPCa.

With the cut-off, area under the curve of DCE MRI for diagnosing csPCa was 0.922 (0.845–0.968) for Epstein criteria and 0.803 (0.705–0.880) for ISUP grade ≥2 by reader 1, while they were 0.710 and 0.624 by reader 2, respectively. The sensitivity, specificity, PPV, NPV, and accuracy are summarised in Table 3.

The PPV for csPCa was consistently increased as the cut-off time is earlier (Table 4). For the PZ lesions that were enhanced earlier than 60–70 seconds, PPV for csPCa that met Epstein criteria or ISUP were higher than 95% or 85% for reader 1 and 90% or 80–85% for reader 2, respectively.

Added value of DCE MRI for patients with a DWI category of 3

There were 20 and 23 patients with a DWI category of 3, who were interpreted by reader 1 and reader 2, respectively. In terms of Epstein criteria, the number of true positive cases determined by applying the best contrast time of DCE MRI was 12 for reader 1 and 14 for reader 2, while the number of true negative cases was three for reader 1 and two for reader 2. In terms of ISUP grade, the number of true positive cases determined by applying the best contrast time of DCE MRI was six for reader 1 and two for reader 2, while the number of true negative case was five for reader 1 and seven for reader 2. Thus, for patients with a DWI category of 3, the added value of DCE MRI in PI-RADSv2 scoring was 75% (15/20) for Epstein criteria and 55% (11/20) for ISUP grade ≥2 in reader 1. In reader 2, they were 69.6% (16/23) for Epstein criteria and 39.1% (9/23) for ISUP grade ≥2 (Table 5).

Discussion

In the present study, applying the best contrast time of 72 seconds or less to visual analysis of DCE MRI was adequate for the detection of csPCa meeting Epstein criteria (AUC, 0.922 for reader 1 and 0.710 for reader 2). In addition, approximately 90% sensitivity and PPV were attained. Moreover, more than two-thirds of patients with DWI category 3 lesions were correctly diagnosed as csPCa after the chosen best contrast time was used to evaluate DCE MRI (added value, 75% for reader 1 and 69.6% for reader 2).

Greer *et al.* recently reported the addition of DCE to DWI MRI was beneficial in PZ evaluation (Odd ratio, 2.0; p=0.027).[4] In their study, positive DCE MRI findings were associated with the increased cancer detection rate for DWI MRI category 3 lesions. In the present study, using the best contrast time of DCE MRI, two readers correctly diagnosed about 60% of csPCa, which met Epstein criteria and showed DWI category 3. The application of best contrast time of DCE MRI may reliably increase the sensitivity of detecting csPCa for equivocal PZ lesions (i.e., DWI category 3).

In the present study, the best contrast time was significantly earlier in csPCa than in ciPCa. The cut-off of the best contrast time was earlier in lesions with ISUP grade ≥2 than in those satisfying Epstein criteria (≤56 versus ≤72 seconds). Previous study data from semi-quantitative analyses of DCE MRI suggested that high-grade PCa tended to be

Table 3
Application of the best contrast time cut-off for identifying csPCa

	AUC	Sensitivity % (*n*/*N*)	Specificity % (*n*/*N*)	PPV % (*n*/*N*)	NPV % (*n*/*N*)	Accuracy % (*n*/*N*)
Reader 1						
72 s for Epstein criteria	0.922 [0.845–0.968]	89.3 (67/75) [80.1–95.3]	78.6 (11/14) [49.2–95.3]	95.7 (67/70) [88–99.1]	52.6 (10/19) [28.9–75.6]	86.5 (77/89) [77.6–92.8]
56 s for ISUP grade ≥2	0.803 [0.705–0.880]	86.5 (50/67) [77.6–92.3]	72.7 (16/22) [49.8–89.3]	89.3 (50/56) [78.1–96]	48.5 (16/33) [30.8–66.5]	74.2 (66/89) [63.8–82.9]
Reader 2						
72 s for Epstein criteria	0.710 [0.604–0.801]	92.0 (69/75) [83.4–97]	50.0 (7/14) [23–77]	90.8 (69/76) [81.9–96.2]	53.9 (7/13) [25.1–80.8]	85.4 (76/89) [77.6–92.8]
56 s for ISUP grade ≥2	0.624 [0.515–0.725]	56.7 (38/67) [44–68.8]	68.2 (15/22) [45.1–86.1]	84.4 (38/45) [70.5–93.5]	34.1 (15/44) [20.5–49.9]	59.6 (53/89) [48.6–69.8]

Nos. in square brackets are 95% confidence intervals.
csPCa, clinically significant prostate cancer; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; ISUP, International Society of Urological Pathology.

Table 4
PPV changes according to various cut-off time for determining positive DCE MRI.

Parameter	Cut-off time for positive DCE MRI					
	≤90 s	≤80 s	≤70 s	≤60 s	≤50 s	≤40 s
Reader 1						
PPV for Epstein criteria	91.4 (74/81)	93.2 (69/74)	95.7 (66/69)	96.8 (61/63)	100 (38/38)	100 (15/15)
PPV for ISUP ≥2	81.5 (66/81)	82.4 (61/74)	85.5 (59/69)	85.7 (54/63)	94.7 (36/38)	93.3 (14/15)
Reader 2						
PPV for Epstein criteria	89.2 (74/83)	91.1 (72/79)	92.6 (63/68)	93 (53/57)	100 (28/28)	100 (10/10)
PPV for ISUP ≥2	79.5 (66/83)	82.3 (65/79)	83.8 (57/68)	86 (49/57)	92.9 (26/28)	100 (10/10)

PPV, positive predictive value; DCE MRI, dynamic contrast-enhanced magnetic resonance imaging; ISUP, International Society of Urological Pathology.

enhanced earlier than low-grade cancers.[11,12] In Epstein criteria, tumours with ISUP grade 1 (i.e., GS 3+3) are classified as csPCa when the tumour volume is >0.5 cm^3. Different compositions of tumour grade between Epstein criteria and ISUP grade ≥2 might result in differences in best contrast time cut-offs. Therefore, depending on the criteria applied (e.g., Epstein criteria, ISUP grade 2, or ISUP grade 3), the cut-off to determine positive DCE MRI may vary.

Interpreting PI-RADSv2 seems to require a learning curve for accurate and reliable prediction.[13,14] Even amongst experienced radiologists, considerable inter-reader variability in determining the positivity of DCE MRI for PZ lesions was observed (kappa=0.26–0.67).[5,15] In the present study, two independent radiologists with very different levels of experience in interpreting prostate MRI analysed the DCE MRI images using the best contrast time, which resulted in moderate-to-good inter-reader agreement (kappa=0.527–0.622). The application of a certain time point to determine the positivity of DCE MRI may help reduce the inter-reader variability. Multi-institutional studies with different DCE MRI protocols in terms of the temporal resolution are required to establish the optimal time cut-off for csPCa.

In current guideline, DCE MRI requires the image acquisition with a temporal resolution of ≤7–15 seconds, total observation time of ≥120 seconds, and section thickness of ≤3 mm.[1] According to the protocol, hundreds of DCE images covering the whole prostate gland and seminal vesicles are generated. The present results may support further investigations to reduce the image data volume by acquiring enhanced images at effective time ranges such as 30–80 seconds. According to Table 4, evaluating DCE MRI with a cut-off of ≤60–70 seconds after contrast medium injection allowed accurate prediction of csPCa in the PZ (i.e., 85–95%).

Table 5
Application of DCE MRI cut-off to patients with DWI category 3 for PZ.

Parameter	Epstein criteria	ISUP grade ≥2
Rate of csPCa[a]		
Reader 1	80% (16/20)	70% (14/20)
Reader 2	73.9% (17/23)	56.5% (13/23)
Rate of PI-RADSv2 upgrading[b] from 3 to 4		
Reader 1	65% (13/20)	35% (7/20)
Reader 2	78.3% (18/23)	21.7% (5/23)
Added value [c]		
Reader 1	75% (15/20)	55% (11/20)
Reader 2	69.6% (16/23)	39.1% (9/23)

DCE MRI, dynamic contrast-enhanced magnetic resonance imaging; DWI MRI, diffusion-weighted magnetic resonance imaging; csPCa, clinically significant prostate cancer; ISUP, International Society of Urological Pathology.

[a] The number of patients with DWI category 3 was twenty for an experienced reader.

[b] Category upgrading means a condition of DWI category 3 plus positive DCE MRI, leading to PI-RADSv2 category 4.

[c] Added value means accurately predicted cases regarding csPCa or not by incorporating DCE MRI cut-off in patients with DWI category 3. A final PI-RADSv2 category 4 (e.g., DWI category 3 plus positive DCE MRI) indicated a high probability of csPCa.

The present study has several limitations. First, the radiologists were not blinded to the location of the index tumour; however, the aim of the present method was to provide qualitative information regarding the enhancement time of csPCa, while minimising the risks of incorrect analysis of benign mimickers. In addition, the image analysis based on radiology–histopathology correlation of the tumour location was also previously applied to reveal MRI characteristics of an actual tumour.[16,17] The best contrast time in the present study requires prospective studies by blinded readers for practical application. Second, all patients had surgically confirmed PCa, but the prevalence of csPCa in the pre-biopsy setting may lead to changes in the predictive values of DCE MRI. Accordingly, current data should be validated for patients with a suspicion of PCa and pre-biopsy MRI. In the pre-biopsy setting, DCE MRI findings could be correlated with the various pathological conditions proven by the targeted biopsy (i.e., focal prostatitis, insignificant PCa, or csPCa). Third, quantitative or semi-quantitative analysis was not performed. This is because the visual analysis of each MRI sequence is currently accepted in PI-RADSv2, while quantitative or semi-quantitative analyses are not mandatory. In addition, previous meta-analysis demonstrated comparable performance of visual analysis with semi-quantitative analysis with DCE MRI in evaluating prostate cancer.[18] Thus, the aim of the study was to suggest a simple and reliable guideline to determine the positivity of DCE MRI for improving current PI-RADS v2 interpretation. Fourth, higher b-value (e.g., 1400 s/mm^2 or greater) DWI was not used; however, previous studies have reported that a b-value of 1000 s/mm^2 is still useful for prostate DWI or PI-RADS v2 interpretation.[19–21] Nevertheless, combined analysis of the current best contrast time cut-off for DCE MRI with DWI using a higher b-value is necessary. Fifth, according to PI-RADS v2.1, which was released recently, there is a trend to down-score borderline DWI findings in the PZ and

matching these to T2WI (i.e., a wedge-shaped lesion with moderate diffusion restriction is considered as category 2 in version 2.1 because it is more typical of inflammatory changes).[22] Thus, the role of DCE MRI for DWI category 3 should be investigated based on the latest version.

In conclusion, evaluating the radiological findings within 60–72 seconds following contrast media injection may enable reliable interpretation of DCE MRI in PZ, and have added value in differentiating csPCa from ciPCa. Further prospective studies including benign prostatic foci are necessary to confirm the clinical usefulness of the present interpretation method.

Conflicts of interest

The authors declare no conflict of interest.

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