Value of Dynamic Contrast-Enhanced (DCE) MR Imaging in Peripheral Lesions in PI-RADS-4 Patients

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ZUSAMMENFASSUNG


Kernaussagen:
▪ 20 % der PI-RADS-4-Patienten wurden durch auffällige, periphere Kontrastmittelanreicherung aus Kategorie 3 aufgewertet.
▪ Klinisch signifikante Prostatakarzinome wurden in fast 40 % der aufgewerteten, peripheren PI-RADS-3-Läsionen gefunden.
▪ 15 % aller signifikanten Karzinome bei PI-RADS-4-Patienten wurden in durch DCE aufgewerteten Läsionen detektiert.
▪ In 7 % aller PI-RADS-4-Befunde wären klinisch signifikante Prostatakarzinome ohne DCE unterschätzt worden.

ABSTRACT
Objective To assess the impact of dynamic contrast-enhanced imaging (DCE) in mp-MRI on prostate cancer (PCa) detection in a large patient cohort assigned to PI-RADS category 4.
Method
This retrospective, single center cohort study includes 193 consecutive patients with PI-RADS assessment category 4 in mp-MRI (T2WI, DWI, DCE) at 3 T with targeted plus systematic biopsy combined as the reference standard. The detection of prostate cancer with and without the use of DCE was compared.

Results
Overall, the PCa detection rate in PI-RADS-4 patients was 62 % (119/193) with DCE and 52 % (101/193) without the inclusion of lesions upgraded on the basis of DCE. 48 % (92/193) had clinically significant PCa (csPCa; Gleason score ≥ 3 + 4 = 7) and 40 % (78/193) without use of DCE. 38 of the 193 patients (20 %) had peripheral lesions upgraded from PI-RADS category 3 to an overall PI-RADS category 4 due to focal positive DCE findings. Of these 38 patients, 18 had PCa including 14 with csPCa. Thus, 15 % (18/119) of the patients with PCa and 15 % (14/92) of the patients with csPCa were detected only based on additional DCE information.

Conclusion
DCE prevents underestimation and misclassification of a significant number of cases of peripheral csPCa and might improve detection rates in PI-RADS-4 patients. The current PI-RADS decision rules regarding upgrading PI-RADS-3 lesions to category 4 due to positive DCE imaging are useful for PCa detection.

Key points:
- Positive peripheral DCE upgraded 20 % of patients in PI-RADS category 4 from category 3.
- Clinically significant PCa was found in almost 40 % of upgraded, peripheral PI-RADS-3 lesions.
- 15 % of all csPCa in PI-RADS-4 patients was detected in DCE-upgraded lesions.
- In 7 % of all PI-RADS-4 cases csPCa would have been underestimated without DCE upgrade.

Introduction
Magnetic resonance imaging (MRI) has become well-established and integrated in many aspects of prostate cancer (PCa) diagnostics [1, 2]. It is able to overcome the well-known limitations of PSA screening and systematic transrectal ultrasound-guided (TRUS) biopsy with respect to missing clinically significant PCa (csPCa) on the one hand and over-detecting low-grade cancer on the other hand [3]. However, the use of dynamic contrast-enhanced imaging (DCE) as an integral part of multiparametric (mp-) MRI of the prostate in addition to T2-weighted imaging (T2WI) and diffusion-weighted imaging (DWI) has been discussed controversially in the recent literature. Several authors report limited value [4, 5] of contrast media application and suggest a biparametric (bp) approach (T2WI, DWI), taking into account the general attempt to minimize costs and measuring time as well as to avoid potential adverse effects like allergic reactions. A recent meta-analysis of 33 single studies revealed high diagnostic accuracy for bp-MRI with respect to the detection of PCa [6]. In the head-to-head comparison, however, mp-MRI (including DCE images) showed a significantly higher pooled sensitivity (0.85; 95 % CI, 0.78–0.93) compared to bp-MRI (0.80; 95 % CI, 0.71–0.90) (p = 0.01), while the specificity did not differ significantly. Other studies also revealed substantial benefits from adding DCE sequences to the MRI protocol in PCa detection especially in the peripheral zone (PZ) [7–9]. In the revised PI-RADS handbook (Prostate Imaging – Reporting and Data System: 2015, Version 2) [10], which constitutes a fundamental guideline for the standardization of mp-MRI protocols and MRI reporting, DCE was assigned a minor role for final PI-RADS classification with a binary evaluation compared to a qualitative assessment in the first version of PI-RADS. Currently, DCE is particularly used to upgrade peripheral PI-RADS category 3 lesions to PI-RADS category 4 if enhancement is focal, earlier or contemporaneous with enhancement of adjacent normal prostatic tissue. PI-RADS-5 lesions are by definition larger and therefore often more obvious compared to PI-RADS-4 lesions. Thus, DCE might be of special advantage in PI-RADS category 4. However, the diagnostic value of contrast media application in prostate MRI remains subject of the current debate and it has to be shown how many additional cases of PCa are found in upgraded PI-RADS-4 lesions. Therefore, this study strives to evaluate the differences in PCa detection with or without DCE imaging in a large cohort of patients assigned to PI-RADS category 4 with targeted MRI/US fusion-guided plus systematic 12-core TRUS-guided biopsy as a reference standard.

Material and Methods
Study population and design
Consecutive patients with clinical suspicion of PCa (elevated PSA values or positive digital rectal examination) assigned to PI-RADS category 4 in standardized mp-MRI and subsequent targeted MRI/US fusion-guided (FUS-GB) plus systematic 12-core transrectal ultrasound-guided (TRUS-GB) biopsy between January 2015 and September 2017 were included in this retrospective single-center cohort study. The patient population was previously evaluated regarding the clinical management of negatively biopsied PI-RADS-4 patients [11]. The study was approved by the local Independent Ethics Committee (IEC) (Medical Faculty, University Düsseldorf) and written informed consent was obtained from all subjects.

Study endpoints
The primary endpoint was PCa detection in patients with PI-RADS category 4 upgraded from PI-RADS category 3 due to positive...
DCE findings according to the current PI-RADS decision rules. Secondary endpoints were overall PCa detection, Gleason distribution and comparison of clinical data of patients with or without PI-RADS upgrade due to positive DCE.

**Image interpretation and data analysis**

Image interpretation was done by two radiologists (T.U., L.S.) with 4 and 9 years of experience reading prostate MRI. Assessment was performed according to PI-RADS v2. Prostate volume was measured by software (DynaCAD, Invivo, Gainsville, USA) and PSA density (PSAD) was calculated by dividing PSA blood levels by prostate volume. Color-coded, parametric maps for additional DCE image evaluation were derived using the same software. Besides standard PI-RADS assessment, PCa detection rates were calculated separately for lesions upgraded from PZ PI-RADS-3 lesions to PI-RADS category 4 due to a positive, suspicious DCE imaging appearance (focal and early/contemporaneous enhancement compared to adjacent normal prostatic tissue) according to the current PI-RADS decision rules. Demographic data (age), clinical data (PSA, PSAD), MRI (prostate volume, longest lesion diameter), and biopsy data were evaluated and described according to the Standards of Reporting for MRI-targeted Biopsy Studies (START) [16].

**Results**

**Patients**

193 patients with PI-RADS category 4 in mp-MRI and subsequent targeted MRI/US fusion-guided (FUS-GB) plus systematic 12-core transrectal ultrasound-guided (TRUS-GB) biopsy were analyzed. 38 patients (20 %) showed peripheral PI-RADS-4 lesions that were upgraded by positive DCE. The baseline characteristics did not differ significantly between patients with PI-RADS upgrade to category 4 and patients without upgraded lesions (Table 1).

**Cancer detection and PI-RADS upgrade**

PCa was detected in 119 of 193 subjects (62 %; 131 PCa-positive lesions) including 92 (48 %) cases of csPCa with GS ≥ 3+4+7. 18 of 38 patients with upgraded PI-RADS-3 lesions had PCa including 14 cases of csPCa. Thus, 15 % (18/119) of all patients with cancer and 15 % (14/92) of patients with csPCa were detected based on DCE information. Without lesions upgraded based on DCE, the overall PCa detection rate would have been 52 % (101/193) for all patients with prostate cancer. The csPCa detection rate would have been 40 % (78/193). Detailed Gleason scores are illustrated in Table 2. On a lesion basis, 92 of a total of 326 PI-RADS-4 lesions were upgraded due to focal, positive DCE (Table 3). Of the upgraded lesions, 38 (41 %) were positive for PCa including 30 lesions with csPCa (33 %). An example of an upgraded PZ PCa lesion is shown in Fig. 1. The median PSAD of patients with upgraded lesions and subsequently verified PCa (0.20; IQR: 0.18–0.22) did not differ significantly from the PSAD of patients with upgraded lesions without PCa (0.16; IQR: 0.11–0.17; p = 0.28).

**Discussion**

This study demonstrates the importance of dynamic contrast-enhanced imaging (DCE) when upgrading peripheral PI-RADS-3 lesions to PI-RADS category 4 in order not to miss clinically significant tumors. 33 % of the peripheral higher-grade PCa lesions would have been underestimated and misclassified as PI-RADS 3 without the help of DCE in this study. The current debate on whether DCE may be omitted in favor of a bi-parametric (T2WI, DWI) MRI protocol, even in the setting of primary tumor detection should, therefore, be held with caution.

In this study we demonstrate high PCa detection rates in PI-RADS-4 patients of 62 % including csPCa rates of 48 % which is...
in line with the findings by Venderink et al. [18] who revealed PCa in 60 % and csPCa in 34 %. Every csPCa with GS ≥ 7 could reliably be detected on mp-MRI in this study. However, the reported PCa detection in PI-RADS category 4 varies greatly in the literature down to 39 % by Mehralivand et al. [19]. Differences in image acquisition, experience of the reader, and subjective interpretation criteria may be responsible for these diverse results. Apart from this, PI-RADS-4 lesions are generally prone to sampling errors due to their smaller size compared to PI-RADS-5 lesions.

15 % of all detected PCa cases in our patient cohort were detected in peripheral lesions upgraded from DWI PI-RADS category 3 to category 4 due to positive DCE findings according to the current PI-RADS decision rules. This corresponds to the results from Rosenkrantz et al. [20] who revealed a csPCa rate of up to 33 % in upgraded PZ lesions and to the findings by Greer et al. [7] who reported improved cancer detection for PI-RADS-3 and 4 lesions in the PZ when DCE imaging is performed.

In recent times the need for DCE as part of the standard prostate MRI protocol has been discussed controversially based on the desire to reduce scanning time and avoid contrast material administration [7, 21, 22]. Some authors suggest bp-MRI in combination with the PSAD level as the diagnostic tool to decide whether a patient needs to be biopsied [5] since the histopatholog-
gic evaluation is still the ultimate gold standard to detect PCa [23]. However, in our study one third of the csPCa lesions would have been misclassified as PI-RADS 3 without the help of DCE and might not have been detected under the assumption that PI-RADS-3 lesions are not biopsied. At our institution, PI-RADS-3 lesions do not get biopsied on a regular basis due to the overall low cancer detection rate in this category and to avoid overdiagnosis of low-risk cancers with the potential for unnecessary adverse effects. Previous studies have revealed that the overall PCA detection rate in PI-RADS category 3 is low and can be managed by follow-up mp-MRI [24] in order to avoid unnecessary biopsies. Fewer biopsies are not only more convenient for the patient but also minimize the risk of complications such as infection [25].

Other authors propose administering contrast media only in doubtful cases (PI-RADS 3) either in a second session or in the same session with the radiologist immediately assessing the MRI images [4]. This requires a highly organized clinical setting. Also, very few patients will profit from such an approach since primarily higher risk patients are referred to mp-MRI and a majority have suspicious lesions.

Besides upgrading PI-RADS-3 to PI-RADS-4 lesions, DCE imaging adds sensitivity by assisting in index lesion selection. Some lesions that might not have attracted attention in the other sequences become suspicious through focal, intense, and early enhancement, considering especially that DWI is more prone to artifacts and can be falsely unremarkable [26]. In our study two patients with upgraded PCa lesions with a Gleason score of 6 showed DWI that was not qualitatively sufficient due to artifacts.

Furthermore, DCE also adds specificity by reducing the number of false-positive results as non-vascularized lesions might be excluded and not get biopsied. DCE imaging is also helpful in tumor detection in the anterior fibromuscular stroma or in the central zone. These aspects were, however, not analyzed in this study. The median PSAD of patients with upgraded PI-RADS-3 lesions and subsequently verified PCa was higher compared to upgraded patients without PCa. However, the effect was not statisti-
cally relevant suggesting that PSAD can give a helpful hint about the PCa risk but cannot be used as a definite predictor.

A potential limitation of this study is the fact that we only included patients with PI-RADS category 4. Thus, PI-RADS 3 lesions with a negative DCE were not assessed, so that there is no data to calculate specificity. We also did not investigate how many cancers would have been missed in complete absence of contrast-enhanced sequences as the basis for calculation of sensitivity. However, several previous studies revealed that a relevant proportion of cases of csPCa will be missed if DCE sequences are not used [27, 28], provided that optimum acquisition and expert evaluation are guaranteed. Unfortunately, DCE images are often not acquired according to current guidelines (MRI parameters, contrast media application), which in turn leads to similar PCa detection rates compared to bp-MRI and complicates the debate. As the study was designed to assess PCa detection in upgraded PZ lesions, other locations and other clinical or MRI morphological data were not evaluated.

In conclusion, DCE prevents the misclassification of a significant number of cases of clinically significant peripheral PCa that would have been underestimated in a bi-parametric protocol. Therefore, DCE plays an important role in primary tumor detection. The current PI-RADS decision rules regarding upgrading PI-RADS-3 lesions to category 4 due to positive DCE imaging are useful. Further studies prospectively investigating a head-to-head comparison of PCa detection with or without DCE imaging are warranted.

**Clinical Relevance**

- Contrast media application can support the detection of clinically significant prostate cancer in mp-MRI of the prostate.
- Dynamic contrast-enhanced sequences might especially be helpful in unclear cases in the setting of primary (early) tumor detection.
- If dynamic contrast-enhanced imaging is used, peripheral PI-RADS-3 lesions might get upgraded to PI-RADS category 4 in 20% of patients.

**Conflict of Interest**

The authors declare that they have no conflict of interest.

**References**


