Prostate Cancer Detection with Multiparametric MRI: A Comparison of 1 M-Concentration Gadobutrol with 0.5 M-Concentration Gadolinium-Based Contrast Agents

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Abstract
Introduction: Gadobutrol (Gd-DOTA-butrol) (Gadovist®) is a macrocyclic gadolinium-based contrast agent for magnetic resonance imaging (MRI) formulated at 1.0 mmol Gd/ml. Gadobutrol's higher concentration compared to other contrast agents (0.5 mmol Gd/ml) is associated with higher T1 relaxivity. We examined whether gadobutrol increases the accuracy of prostate cancer detection using dynamic contrast-enhanced MRI. Materials and Methods: Multiparametric MRI was performed in 379 patients: 94 patients received 1 M gadobutrol while 285 randomly received equivalent doses of 0.5 M gadoterate meglumine or gadopentetate dimeglumine. MRI images were retrospectively and blindly assessed for the presence of cancer by comparing them with prostate biopsy findings. Results: The specificity and accuracy were significantly higher with 1 M gadobutrol than 0.5 M of the other contrast agents. There were no significant differences in the sensitivity, or positive and negative predictive values. Conclusion: Multiparametric MRI using 1 M gadobutrol may improve the accuracy of prostate cancer detection.
be accurate for detecting prostate cancer [3–17]. The Prostate Imaging Reporting and Data System version 2 states that DCE imaging should always be interpreted along with T2WI and DWI, as its role is felt to be secondary to that of T2WI imaging and DWI [18]. Others reported that DCE-MRI plays a complementary role with DWI in the detection of prostate cancer [9]. DCE-MRI was also reported to provide better detail than T2WI obtained with a pelvic phased-array coil [7]. A previous report on prostate MRI which compared 1 M gadobutrol with 0.5 M concentrations of other GBCAs found no significant differences among the enhancement profiles. The authors did note, however, that gadobutrol yielded higher and faster peak enhancement in prostate cancer and in the normal peripheral zone than gadolinium diethylenetriamine pentaacetic acid [19]. However, the ability to accurately detect prostate cancer in multiparametric MRI using 1 M gadobutrol is unknown.

The purpose of this study was to evaluate whether MRI before prostate biopsy using 1 M gadobutrol is more accurate than MRI using an equivalent dose of 0.5 M concentrations of other GBCAs.

**Materials and Methods**

This single-center retrospective study was approved by our institutional review board. Informed consent was obtained from all individual participants included in the study.

**Subjects**

The study enrolled 415 consecutive patients who underwent systematic prostate biopsy and multiparametric MRI at admission to our acute care hospital between April 2013 and August 2016. We excluded 27 patients who had undergone prostate biopsy within 6 months before MRI, 8 patients who did not undergo prostate biopsy within 12 months after MRI, and 1 who had a history of transurethral prostate surgery, leaving 379 for inclusion. Among the study patients, 94 underwent MRI using the 1 M concentration of gadobutrol (Gd-DO3A-butrol) (Gadovist®; Bayer Healthcare, Berlin, Germany) (used after 5 Nov. 2015) while 285 underwent MRI using the 0.5 M concentrations (equivalent doses) of other GBCAs, with 125 receiving the macrocyclic agent gadoterate meglumine (Gd-DOTA) (Magnescope®, Fuji Pharma, Tokyo, Japan) (not used after 5 Nov. 2015) and 160 receiving the linear agent gadopentetate dimeglumine (gadolinium diethylenetriamine pentaacetic acid) (Magnevist®, Bayer Healthcare, Berlin, Germany) (used throughout), chosen at random. Overall patient characteristics and among GBCA groups are shown in table 1 and 2.

**Table 1. Patient characteristics**

|                          | 1 M gadobutrol (n = 94) | 0.5 M GBCA (n = 285) | p (t-test) |
|--------------------------|-------------------------|----------------------|-----------|
| Mean age                 | 71                      | 70                   | 0.27      |
| Mean PSA level \(\text{ng/dl}\) | 35.42                   | 52.57                | 0.54      |

PSA = Prostate-specific antigen.

**MRI Protocol**

Patients were scanned using a 1.5 T (Ingenia 1.5 T®; Philips, Amsterdam, Netherlands) or a 3.0 T MR scanner (Ingenia 3.0 T®; Philips) with an anterior phased-array coil (Philips) before undergoing biopsy.

In 1.5 T MR scanning, the following images were acquired.

**Table 2. MRI approaches**

|                          | 1 M gadobutrol | 0.5 M GBCA | Total |
|--------------------------|---------------|------------|-------|
| 1.5 T scanner            | 36            | 122        | 158   |
| 3 T scanner              | 58            | 163        | 221   |
| Total                    | 94            | 285        | 379   |

Transverse spin-echo T2WI of the prostate and seminal vesicles were acquired using the following parameters: TR/TE 4229/100, section thickness 3 mm, field of view 220 mm, matrix 304, and acquisition time 3 min 6 sec.

Transverse T1-weighted images (T1WI) of the pelvic region from the aortic bifurcation to the symphysis pubis were acquired using the following parameters: TR/TE 557/8, section thickness 5 mm, field of view 320 mm, matrix 352, and acquisition time 3 min 6 sec.

Sagittal spin-echo T2WI of the prostate and seminal vesicles (+ SPAIR) were acquired using the following parameters: TR/TE 3321/100, section thickness 3 mm, field of view 220 mm, matrix 288, and acquisition time 2 min 36 sec.

Coronal spin-echo T2WI of the prostate and seminal vesicles (+ SPAIR) were acquired using the following parameters: TR/TE 3000/80, section thickness 3 mm, field of view 220 mm, matrix 256, and acquisition time 3 min.

DWIs were acquired with a single-shot echo-planar imaging technique using the following parameters: TR/TE 6250/81, field of view 220 mm, section thickness 3 mm, matrix 96, acquisition time 4 min 3 sec, and b values 0, 1000, and 2000 s/mm².

DCE-MRI images were acquired with enhanced T1-weighted high resolution isotropic volume excitation using the following parameters: TR/TE 4.7/2.3, flip angle 10°, section thickness 4 mm, field of view 220 mm, matrix 240, and scan performed before and 30, 60, and 120 s after the administration of gadobutrol, gadoterate meglumine, or gadopentetate dimeglumine at a dose of 0.1 mmol/kg through a peripheral vein at a rate of 2 ml/s.

In 3.0 T MR scanning, the following images were acquired.

Transverse spin-echo T2WI of the prostate and seminal vesicles were acquired using the following parameters: TR/TE 6000/100, section thickness 3 mm, field of view 220 mm, matrix 320, and acquisition time 3 min 36 sec.
Transverse T1WI of the pelvic region from the aortic bifurcation to the symphysis pubis were acquired using the following parameters: TR/TE 593/17, section thickness 5 mm, field of view 320 mm, matrix 336, and acquisition time 2 min 46 sec.

Sagittal spin-echo T2WI of the prostate and seminal vesicles were acquired using the following parameters: TR/TE 4162/90, section thickness 3 mm, field of view 220 mm, matrix 320, and acquisition time 2 min 36 sec.

Coronal spin-echo T2W images of the prostate and seminal vesicles (+ SPAIR) were acquired using the following parameters: TR/TE 5000/75, section thickness 3 mm, field of view 220 mm, matrix 272, and acquisition time 2 min 50 sec.

DWIs were acquired with a single-shot echo-planar imaging technique using the following parameters: TR/TE 7500/84, field of view 220 mm, section thickness 3 mm, matrix 96, acquisition time 4 min 52 sec, and b values 0, 1000, and 2000 s/mm².

DCE-MRI images were acquired with enhanced T1-weighted high resolution isotropic volume excitation using the following parameters: TR/TE 3.6/1.82, flip angle 10°, section thickness 3 mm, field of view 220 mm, matrix 256; and scan performed before and 30, 60, and 120 s after the administration of gadobutrol, gadoterate meglumine, or gadopentetate dimeglumine at a dose of 0.1 mmol/kg through a peripheral vein at a rate of 2 ml/s.

### Image Interpretation

The images were retrospectively and blindly read by one radiologist with 17 years of experience. The reader interpreted all the images, and recorded the presence or absence of cancer.

### Biopsy

Cancer presence was determined according to the pathological findings on ultrasound-guided biopsies, or, if ultrasound did not reveal a nodule, ultrasound-guided systematic 10-core biopsies were performed using a one-handed biopsy needle (Primecut II®, Boston Scientific, Marlborough, MA, USA) by urologists unaware of the MRI findings.

### Statistical Analysis

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of diagnostic imaging using MRI were calculated for the group receiving gadobutrol and the group receiving the more dilute agents. Additionally, the sensitivity, specificity, PPV, NPV, and accuracy were calculated for the different scanner groups (1.5 T and 3 T MRI). Fisher’s exact test was used to compare the MRI diagnostic performance for each group. A p value < 0.05 was considered statistically significant. All analyses were performed using R version 3.3.0 (The R Foundation for Statistical Computing, Vienna, Austria).

### Results

According to the histopathological diagnoses, 227 patients had a malignancy and 152 did not. A representative case is shown in figure 1.

The sensitivity, specificity, PPV, NPV, and accuracy in the 1 M gadobutrol and 0.5 M GBCA groups are shown in table 3. The specificity and accuracy were significantly higher in the 1 M gadobutrol group than in the 0.5 M GBCA group (0.87 vs. 0.68, p = 0.034 and 0.89 vs. 0.80, p = 0.043, respectively). There were no significant differences in the sensitivity (p = 0.63), PPV (p = 0.15), or NPV (p = 0.42) between the groups.

The sensitivity, specificity, PPV, NPV, and accuracy in the 1.5 T MRI and 3.0 T MRI groups are shown in table 4. There were no significant differences in the sensitivity (p = 0.29), specificity (p = 0.13), PPV (p = 0.59), NPV (p = 1), or accuracy (p = 0.78).

### Discussion

This was a single-center retrospective study. The specificity and accuracy were significantly higher with the 1 M concentration of gadobutrol than with the equivalent doses of 0.5 M concentrations.

The sensitivity, specificity, and accuracy in this study were comparable to those in a previous report on diagnostic ability using 3.0 T multiparametric MRI without an endorectal coil [10]. The differences between these and the present groups involved the physicochemical properties of contrast agents and differences in concentration. In another study, the T1 relaxivity of gadobutrol was slightly higher than that of gadoterate meglumine and gadopentetate dimeglumine [1, 2]. Additionally, in the study by Kramer et al. [20], a higher Gd concentration (1 M gadobutrol) showed a higher signal-to-noise ratio and better image quality on dynamic magnetic resonance angiography of the carotid arteries at the time of

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**Table 3. Detectability of prostate cancer on multiparametric MRI**

| GBCA Concentration | Sensitivity | Specificity | PPV | NPV | Accuracy |
|--------------------|-------------|-------------|-----|-----|----------|
| 1 M                | 0.91        | 0.88        | 0.63|     |          |
| 0.5 M              | 0.88        | 0.68        | 0.034|    |          |

**Table 4. Detectability of prostate cancer (1.5 T MRI vs. 3 T MRI)**

| MRI Type | Sensitivity | Specificity | PPV | NPV | Accuracy |
|----------|-------------|-------------|-----|-----|----------|
| 1.5 T    | 0.86        | 0.90        | 0.29|     |          |
| 3 T      | 0.80        | 0.69        | 0.13|     |          |

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the early phase, despite the shortened bolus due to the same injection rate regardless of concentration, as in our study. Therefore, it is possible that these factors contributed to the differences.

In Iwazawa et al.’s [9] study, DWI alone and DWI combined with DCE-MRI were significantly more sensitive than DCE-MRI alone. In our study, there was no significant difference in sensitivity between 1 M gadobutrol and 0.5 M of other GBCAs. It seems that DEC-MRI contributed little to improving the sensitivity. On the other hand, the specificity and accuracy using the 1 M concentration of gadobutrol were significantly higher than that for equivalent doses of 0.5 M concentrations of other GBCAs.

Our results suggest that detection of prostate cancer with multiparametric MRI might be more accurate using a 1 M concentration of gadobutrol than an equivalent dose of a 0.5 M concentration of other GBCAs.

This study has several limitations. We compared interpretation reports and pathological reports of biopsies, and saw no distinctions between cancer in the peripheral zone and transitional zone. Because we had no proof that the nodule identified on MRI was the same nodule evaluated by pathology, we could not compare tumor size and staging. Thus, a comparison with the pathological specimen of the entire prostate and evaluation of gadobutrol’s accuracy in detecting prostate cancer in D’Amico intermediate and high-risk nodules is required. This was a
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Gadobutrol might contribute to a more accurate detection of prostate cancer.

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