Dynamic Contrast Enhanced MRI of the Prostate: Comparison of Gadobutrol and Gd-DTPA


Material und Methoden: Es wurden insgesamt 53 Patienten mit Prostatakarzinom (PCa) eingeschlossen, welche nach einer multiparametrischen MRT der Prostata mit DCE-MRI prostatektomiert wurden. Jedes PCa > 5 mm (42 PCa in Gd-DTPA-Gruppe, 34 PCa in Gadobutrol-Gruppe) und die gesunde periphere Zone (PZ) wurden in der DCE-MRI qualitativ und quantitativ analysiert. Kurvenverläufe (Typ I, II and III) und pharmacokinetische Parameter wurden analysiert und mit einem linearen Modell verglichen.

Ergebnisse: Die Kurvenverläufe und pharmacokinetische Parameter (Ktrans und kep) waren in PCa und PZ signifikant unterschiedlich. Gadobutrol führte zu einem höheren und schnelleren Peak in der Prostata gegenüber Gd-DTPA. Die Key Points sind:

▶ Gadobutrol bietet einen höheren und schnelleren Peak in der Prostata gegenüber Gd-DTPA.
▶ Es gab keine signifikanten Unterschiede in Kurvenverläufen und pharmacokinetischen Parametern zwischen beiden KM.
▶ Gadobutrol und Gd-DTPA sind geeignet für DCE-MRI der Prostata für die Detektion von PCa.
gemischt linearer Modelle zwischen beiden Gruppen verglichen; zweiseitige p-Werte < 0,05 wurden als signifikant definiert.

**Ergebnisse:** Die Frequenz der Kurventypen I, II und III unterschied sich zwischen den KM weder in der PZ (p = 0,63) noch im PCa (p = 0,75) signifikant voneinander. Pca mit einem Gleason-Score ≥ 7 zeigten im Vergleich zu Gleason-Score ≤ 6 statistisch signifikant häufiger bei beiden KM eine Wash-out-Kurve (Typ III, p = 0,02). Das relative Signalintensitätsmaximum war in der PZ (Gd-DTPA 1,4 a. u. [1,20; 1,59], Gadobutrol 1,58 a. u. [1,37; 1,78]) und im PCa-Gewebe (Gd-DTPA 1,56 a. u. [1,41; 1,71], Gadobutrol 1,76 a. u. [1,59; 1,94]) für Gadobutrol signifikant höher (p = 0,04). Die pharmacokinetischen Parameter Ktrans und kep waren im Tumorgewebe signifikant höher als in der PZ (Ktrans 0,0001; kep p = 0,002). Zwischen den KM fand sich kein signifikanter Unterschied bezüglich der pharmacokinetischen Parameter (p = 0,65)

**Schlussfolgerung:** Diese Arbeit ist der erste systematische Vergleich von Gadobutrol und Gd-DTPA in der DCE-MRI der Prostata. Hierbei konnte gezeigt werden, dass das maximale relative Enhancement mit Gadobutrol im Vergleich zu Gd-DTPA höher ist, wobei Kurventypen und pharmacokinetische Parameter Ktrans und kep weder im PCa noch in der normalen PZ einen statistisch signifikanten Unterschied aufweisen.

**Introduction**

Cancer of the prostate is the most frequent malignant tumor in men, and, after cancer of the lung and colon, has the third-highest mortality rate. The diagnosis of prostate cancer is based on digital-rectal examination, determination of the prostate-specific antigen (PSA) and transrectal ultrasound-guided (TRUS) biopsy. In the case of TRUS-guided biopsy, a total of 10 – 12 samples are taken from both lateral lobes of the prostate following a systematic pattern. Nevertheless, in the case of 20 – 40 % of patients suspected of prostate cancer, a definitive diagnosis of cancer can be ascertained only after repeated biopsy, since a TRUS biopsy is limited by sampling error [1, 2]. This represents a diagnostic problem, since a raised or increasing PSA value raises the suspicion of prostate cancer; however the low negative predictive value of a TRUS biopsy cannot definitively indicate that the patient actually has no cancer. A multiparametric MRI has been shown to be a very sensitive and specific non-invasive method of localization potentially cancerous lesions within the prostate [3, 4]. Multiparametric MRI includes conventional T2- and T1-weighted imaging combined with diffusion imaging and or 1H-magnetic resonance spectroscopy and/or dynamic contrast-enhanced MR imaging (DCE-MRI). Using this approach, T2-weighted imaging is indispensable, especially for interpretation of changes in the transition zone [5]. Compared to T2-weighted imaging alone DCE-MRI provides a diagnostic advantage with respect to prostate cancer detection [6, 7]. Essential in this regard is dynamic information pertaining to contrast medium inflow, since generally T1-weighted gradient echo sequences are used with a brief resolution of < 5 s / measurement [8].

The first approved gadolinium-containing contrast medium for MR diagnosis was gadopentetate dimeglumine (Gd-DTPA; Magnevist, Bayer Healthcare, Berlin, Germany). Consequently, Gd-DTPA was the contrast medium of choice for DCE-MRI of the prostate, as it was for all other organ systems [3, 7, 9]. Since the introduction of Gd-DTPA, a number of additional contrast agents have been approved which are distinguished by their chemical properties. Consequently, studies have been required to test these contrast media and compare them with respect to their relative advantages and disadvantages [10 – 13]. For safety reasons, the occurrence of nephrogenic systemic fibrosis (NSF) accompanying the use of MR contrast media with linear complexes brought to the forefront more thermodynamically stable contrast media with macrocyclic complexes [14, 15]. To date, there has been no systematic comparison of the use of macrocyclic and linear contrast media in prostate DCE-MRI, and therefore no data indicating whether the application of gadobutrol is as reliable as Gd-DTPA in the diagnosis of prostate cancer. Gadobutrol differs from Gd-DTPA by its macrocyclic structure, charge neutrality, its doubled molar mass as well as a higher T1 relativity (Gd-DTPA r1 = 4,1 mmol·s⁻¹, Gadobutrol r1 = 5,2 mmol·s⁻¹) [10, 16]. T1 relativity of a substance is a measure of the signal-increasing effect on T1-weighted sequences, as already demonstrated in numerous studies of various organ systems [17 – 20]. The purpose of this study is to delineate the differences between both contrast media in their enhancement behavior according to contrast medium dosage and the diagnostic value of the prostate DCE MRI based on this comparison, as well as the evaluation of the signal intensity time (SI-t) progression of the macrocyclic contrast medium gadobutrol with the most commonly agent Gd-DTPA in prostate DCE-MRI. Proceeding from results of studies of other organ systems [12, 19, 20], this study is based on the hypothesis that gadobutrol provides a higher relative enhancement in prostate tissue, but that there is no qualitative difference in the enhancement progression.

**Materials and Methods**

**Study Population**

These studies included patients with histologically verified cancer of the prostate who were examined between 1/2009 and 12/2010 with multiparametric MRI of the prostate using Gd-DTPA or gadobutrol with 1,5 T (Magnetom Avanto, Siemens, Erlangen, Germany), and who subsequently underwent prostatectomy. Inclusion criteria in this retrospective study were prostatectomy after histologic verification of prostate cancer, a multiparametric MRI performed according to standardized institute protocol; examination was performed within a week prior to the prostatectomy; dosage of Gd-DTPA at a flow rate of 4 ml/s or gadobutrol at 2 ml/s for the DCE-MRI. An additional inclusion criterion was a carcinoma map created by a consensus of the pathologist and radiologist based upon the pathological prostate sample. After the prostatectomy the entire prostate sample was marked in color (anterior, posterior, left, right) and sliced perpendicular to the longitudinal axis from the apex to the base (5 – 8 slices). The individual slices were quartered into individual slices according to standard protocols, embedded in paraffin and stained with hematoxylin and eosin. All pathologically verified carcinomas > 5 mm as well as areas with a normal peripheral zone were graphically transferred to standardized drawings by the pathologist.
All tumor patterns were assessed using the modified Gleason Scoring System [21]. Then, based upon the consensus of the pathologist and radiologist, the carcinoma foci and normal peripheral zone were separately plotted and coded on printed T2w images. As needed, anatomical landmarks were relied upon for exact identification of the tumor foci on the most closely corresponding MR images; these included zonal structures, prostatic urethra, bladder, ejaculatory duct and seminal vesicles. The serum creatinine and serum PSA values were determined in all patients prior to the MRI examination. The local ethics commission approved this study. Altogether 28 patients were included in the study who had been examined using Gd-DTPA (Magnevist; Bayer Healthcare, Berlin, Germany) – hereafter designated Group A, and 25 patients who had been examined using gadobutrol (Gadovist; Bayer Healthcare, Berlin, Germany) – hereafter designated Group B. A normally classified T2w hyperintense area in the peripheral zone of all patients was previously analyzed in the Pathology department. In addition, 42 cancerous areas in Group A and 34 in Group B were assessed. The median age in Group A (Gd-DTPA) was 62.0 ± 5.9 years, and 62.3 ± 5.7 years in Group B (gadobutrol). The PSA value in both groups was not statistically different (p > 0.05), with an average value of 8.6 ± 4.8 ng/ml for Group A, and 9.7 ± 7.6 ng/ml for Group B. The median Gleason score for prostate cancer was 7 in both groups.

**Multiparametric MRI with Dynamic Contrast Contrast Medium Examination**

Using a combined 6-channel surface coil and an endorectal coil (Medrad Prostate eCoil™, Bayer Healthcare, Berlin, Germany), all patients received a multiparametric MRI of the prostate according to an identical examination protocol by means of a commercially-available MRI unit (1.5 T Magnetom Avanto, Siemens, Erlangen, Germany) – hereafter designated Group A (Gd-DTPA) was 62.0 ± 5.9 years, and 62.3 ± 5.7 years in Group B (gadobutrol). The PSA value in both groups was not statistically different (p > 0.05), with an average value of 8.6 ± 4.8 ng/ml for Group A, and 9.7 ± 7.6 ng/ml for Group B. The median Gleason score for prostate cancer was 7 in both groups.

**Evaluation**

Using evaluation software (syngo Tissue 4 D, Siemens, Erlangen, Germany) the DCE-MRI was registered to the morphological images (T2w) in order to exactly localize the tumor area and normal peripheral zone based on the carcinoma map. Circular fields were used to indicate tumor patterns and normal peripheral zones (BV). The SI-t enhancement curves in the marked fields were calculated as a relative SI-t enhancement of the initial SI without contrast medium, and the individual values were exported over time to an external computer. In addition, the 3-dimensional pharmacokinetic parameter maps of the prostate were calculated using the volume element marking containing the entire prostate. Parameters Ktrans and kep were determined in the previous established fields and likewise exported (Fig. 1).
Based on the values for the relative SI enhancement of the tumors and healthy peripheral zone per time unit, all curves per patient were calculated, blinded and printed out. A radiologist (TD) categorized all curves as Type I, II or III, whereby a Type I curve reflected a steady increase of the enhancement progression; Type II reflected a plateau, and Type III corresponded to a decline in relative enhancement after the peak [25]. These results were then designated (tumor, normal tissue in the peripheral zone, contrast medium) and statistically evaluated [CS, TD].

Statistics
Quantitative data are provided as the average of the least squares from mixed linear models with 95% confidence intervals. Qualitative data are represented as absolute and relative frequencies. The curves between the contrast media were analyzed using multinomial regression analysis in order to compensate for repeated observations of a patient. Relative peak enhancement was defined as the maximum enhancement in the temporal progression of dynamic measurement. Using mixed linear models, this was compared with variance components. Tissue types (tumor, normal peripheral zone), contrast medium and the interaction of both factors served as cofactors. Using the Wilcoxon rank-sum test, the two contrast agents were compared with one another. The temporal curve progressions were compared using linear models including all individual measured values over the entire duration of the measurement. Analogously, the pharmacokinetic parameters $K_{\text{trans}}$ and $k_{\text{ep}}$ were compared between the contrast media. Here again, tissue type and interaction of tissue type and contrast medium served as cofactors. In a further analysis, the tumors were examined under stratification in Gleason score $\leq 6$ and $\geq 7$. All tests were performed bilaterally, p-values $<0.05$ were considered significant. SAS 9.2 (SAS Institute Inc., Cary, NC, USA) was used to perform the analyses.

Results

Qualitative Analysis: Increase (Type I), Plateau (Type II) and Wash-out (Type III)
Statistically, the frequency of curve types between the contrast media did not differ ($p = 0.63$; Table 1). In the normal peripheral zone a Type I curve (steady increase) was shown in 46.4% of cases in Group A, and in 48.0% of cases in Group B. A Type II curve (Plateau) was ascertained among 35.3% (Group A) and 32.0% (Group B). No Type III curve (Wash-out) could be observed in either Group A (Gd-DTPA) or Group B (gadobutrol). In 20.6% of the cases, gadobutrol resulted in a wash-out in the tumor, whereas with Gd-DTPA, a 16.3% rate was not significantly lower. Tumors in Group B (gadobutrol) more frequently demonstrated a Type II curve than in Group A (Gd-DTPA) and correspondingly fewer Type I curves; this was, however, statistically insignificant ($p = 0.75$; Table 1).

In addition, the tumors, based on Gleason scores, were divided into two groups (Gleason score $\leq 6$ and $\geq 7$) in order to evaluate possible differences between the contrast media in relation to Gleason scores. Consequently it was shown that use of both contrast agents achieved a very similar frequency distribution with respect to curve types; there were no significant differences between the contrast media for tumors with a Gleason score of $\leq 6$ or $\geq 7$ (Table 2, $p = 0.43$). Tumors with a Gleason score of $\geq 7$, compared to tumors with a score of $\leq 6$, more frequently demonstrated a statistically significant Type III curve for both contrast media ($p = 0.02$).

Quantitative Analysis: Relative Peak Enhancement and Curve Gradient
The relative SI maximum in normal tissue was 1.4 times [1.20; 1.59] the initial value in the Gd-DTPA group, whereas this value in the gadobutrol group was significantly higher, with 1.58 [1.37; 1.78] ($p = 0.04$). This behavior was similar in tumor tissue. When Gd-DTPA was used, an average peak value of 1.56 [1.41; 1.71] was achieved, whereas with gadobutrol a statistically significant higher value of 1.76 [1.59; 1.94] was achieved ($p = 0.04$, Table 3). These differences were additionally analyzed using a mixed linear model with the inclusion of all measured values in the entire temporal progression. In this case, no distinction could be established between the contrast media in the normal peripheral zone. However, in tumor tissue a trend toward higher relative enhancement values was evident across the entire temporal progression when gadobutrol ($p = 0.05$) was used (Fig. 2). For both tissue types, the shapes of the curves (interaction of contrast agent and time) for Gd-DTPA and gadobutrol varied significantly (peripheral zone $p = 0.003$, tumor tissue $p = 0.0003$). Observation of the resulting curves in the different tissues makes it clear that

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Curve type distribution.</th>
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<tbody>
<tr>
<td></td>
<td>type I</td>
</tr>
<tr>
<td>Gd-DTPA PZ</td>
<td>13 (46.4)</td>
</tr>
<tr>
<td>Gadobutrol</td>
<td>12 (48.0)</td>
</tr>
<tr>
<td>Gd-DTPA PCa</td>
<td>21 (48.8)</td>
</tr>
<tr>
<td>Gadobutrol</td>
<td>12 (35.3)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Distribution of enhancement curves of Type I, II and III in normal peripheral zone (PZ) and prostate cancer (PCa) using Gd-DTPA and gadobutrol; absolute number and percent in parentheses.

<table>
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<th>Table 2</th>
<th>Curve types according to Gleason.</th>
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<tbody>
<tr>
<td>type I</td>
<td>type II</td>
</tr>
<tr>
<td>Gd-DTPA GS $\leq 6$</td>
<td>24 (53.3)</td>
</tr>
<tr>
<td>Gadobutrol</td>
<td>18 (45.0)</td>
</tr>
<tr>
<td>Gd-DTPA GS $\geq 7$</td>
<td>10 (38.5)</td>
</tr>
<tr>
<td>Gadobutrol</td>
<td>6 (31.6)</td>
</tr>
</tbody>
</table>

Frequency of enhancement curve Types I, II and III in prostate cancer of Gleason score (GS) $\leq 6$ and $\geq 7$ using Gd-DTPA and gadobutrol, absolute number and percent in parentheses.
the rise of the enhancement curve when gadobutrol is used is greater than when Gd-DTPA is utilized, although the further progression is the same (except for a parallel shift upward in the case of the gadobutrol tumor enhancement curve), as shown in Fig. 2.

Pharmacokinetic Parameters $K^{\text{trans}}$ and $k_{\text{ep}}$

For all patients the pharmacokinetic parameters $K^{\text{trans}}$ and $k_{\text{ep}}$ were compared between the contrast media. No statistically significant differences for $K^{\text{trans}}$ and $k_{\text{ep}}$ could be determined for the contrast agents ($K^{\text{trans}}$ p-value = 0.41, $k_{\text{ep}}$ p-value = 0.65) (Table 4). The use of Gd-DTPA as well as gadobutrol demonstrated significantly higher pharmacokinetic parameters $K^{\text{trans}}$ and $k_{\text{ep}}$ in tumor tissue than in normal tissue (Table 4, $K^{\text{trans}}$ p-value < 0.0001; $k_{\text{ep}}$ p-value 0.002). Further, when considering the Gleason categories, parameter $K^{\text{trans}}$ for tumors with a Gleason score of ≥7 when Gd-DTPA is used (0.12 [0.09; 0.15]) and gadobutrol (0.14 [0.10; 0.17]) was significantly higher than for tumors with a Gleason score of ≤6 (Gd-DTPA 0.082 [0.04; 0.12] and gadobutrol 0.079 [0.04; 0.12]); p = 0.02; however, once again there was no statistically significant difference between the contrast media (p = 0.60).

Discussion

A comparison of various MR contrast media with respect to SI-t progression and detection of lesions had previously been performed in neuroradiological and cardiovascular magnetic resonance imaging as well as in MR mammography [12, 18–20]. A potential difference of MR contrast agents in DCE-MRI of the prostate had not been previously performed. Therefore, the purpose of this investigation was to analyze the use of gadobutrol and Gd-DTPA in DCE-MRI in order to evaluate possible effects on the resulting curve types and pharmacokinetic parameters.

Several characteristics principally differentiate gadobutrol and Gd-DTPA. While Gd-DTPA is a linear and ionic magnetic resonance contrast medium, gadobutrol has a macrocyclic structure and is charge-neutral [10]. Gd-DTPA has a concentration of 0.5 M, whereas gadobutrol has a 1 M concentration. Thus, examinations using gadobutrol were performed using half the flow compared to DCE-MRI with Gd-DTPA in order to administer the identical volume of contrast medium during the same time period. In addition, gadobutrol has about one-fourth higher T1 relaxivity (1.5 T) compared to Gd-DTPA [16].

Compared to examinations using Gd-DTPA, the current study determined that the gadobutrol-enhanced DCE-MRI demonstrated a higher relative peak enhancement in the healthy peripheral zone of the prostate and tumor tissues. Taking into account all measured values over the entire time progression, a greater increase in the relative enhancement curve was observed in the gadobutrol group, in addition to a trend toward a higher relative enhancement. These differences can be explained by the higher T1 relaxivity of gadobutrol. This had already been described in magnetic resonance mammography, MRI of brain metastases or infectious lesions, as well as in MR imaging using gadobutrol and other extracellular contrast media with higher relaxivity [12, 19, 20]. Additional factors such as charge differences of each contrast medium are also considered as potential influential factors for enhancement behavior. However, charge differences are primarily relevant in so-called delayed imaging, e.g. in cartilage imaging (dGEMRIC) [26].

Within this study we observed SI-t progression of the DCE-MRI for about 5 minutes immediately after administration

<table>
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<th>Table 3</th>
<th>Peak enhancement.</th>
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<tr>
<td></td>
<td>PZ</td>
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<tr>
<td>Gd-DTPA</td>
<td>1.40 [1.20;1.59]</td>
</tr>
<tr>
<td>Gadobutrol</td>
<td>1.58 [1.37;1.78]</td>
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Relative peak enhancement in DCE-MRI using Gd-DTPA and gadobutrol in normal peripheral zone (PZ) and prostate cancer (PCa).

<table>
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<th>Table 4</th>
<th>Pharmacokinetic parameters.</th>
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<tr>
<td></td>
<td>PZ</td>
</tr>
<tr>
<td>Gd-DTPA</td>
<td>$K^{\text{trans}}$</td>
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<tr>
<td>Gadobutrol</td>
<td></td>
</tr>
<tr>
<td>Gd-DTPA</td>
<td>$k_{\text{ep}}$</td>
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<tr>
<td>Gadobutrol</td>
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Pharmacokinetic parameters ($K^{\text{trans}}$ and $k_{\text{ep}}$) in normal peripheral zone (PZ) and prostate cancer (PCa) using Gd-DTPA and gadobutrol.
of the contrast medium. We primarily observed differences in peak enhancement values and increase of the initial enhancement, so that an effect of the charge differences between both contrast agents is probably negligible in this context.

Differences were also found regarding the number of detected lesions during imaging of cerebral lesions of mammary carcinomas [20, 27, 28]. This was not reviewed in the current study. In our opinion, with respect to multiparametric MRI of the prostate, DCE-MRI primarily aids in increasing the specificity as well as the detection and characterization of the most aggressive lesion [29 – 31]. In this investigation we could not establish a difference in frequency among curve types I, II or III. Based on our data, we presume that both contrast media do not qualitatively differ from one another to a clinically relevant extent in either a healthy prostate or tumor tissue with respect to enhancement behavior, since the resulting curve types in both groups exhibit similar frequency. Also in comparing Gleason scores, no statistically significant differences could be determined between the two groups. These results are substantiated by a comparative analysis of the pharmacokinetic parameters. With respect to $K_{\text{trans}}$ and $k_{\text{ep}}$ values, no statistical difference between these contrast agents could be found.

The study additionally showed that 48.8% of tumors in Group A (Gd-DTPA) and 35.3% in Group B (gadobutrol) demonstrated a Type I curve. Of these 38.5% of tumors in Group A and 31.6% in Group B had a Gleason score of ≥ 7. In the recently published ESUR guidelines for structured assessment and classification of prostate carcinomas, suspected tumorous areas are graded from 1 (significant carcinoma highly unlikely) to 5 (clinically significant carcinoma highly likely) [32, 33]. The purpose of this study was not to evaluate the PIRADS criteria. Nevertheless, it should be pointed out that more than 30% of tumors with a Gleason score of ≥ 7 demonstrate a Type I curve, which, according to the current PIRADS classification in DCE-MRI is only assigned a point value of 1. Additional criteria such as focality and asymmetry are only provided for a Type II or Type III curve [32]. During a pending evaluation of PIRADS criteria, therefore, these additional criteria should also be applied to tumors showing a Type I curve, analogously to magnetic resonance mammography [34].

This study is limited by its retrospective approach and interindividual comparison. However, all patients undergoing prostatectomy are treated so that for each carcinoma the best available histological standard is applied with respect to diagnosis and Gleason grading. Due to the required double contrast medium dose and the resulting time delay, interindividual comparison is difficult to perform in the case of patients with histologically verified carcinoma and scheduled prostatectomy.

On the whole it can be concluded that both gadobutrol and Gd-DTPA appear to be highly suitable for DCE-MRI. Relative enhancement in DCE-MRI using gadobutrol tends to be higher; in the course of this study no statistically significant difference could be found with respect to curve type frequencies and the pharmacokinetic parameters $K_{\text{trans}}$ and $k_{\text{ep}}$.

Clinical Relevance

No statistically significant differences were found between both contrast medium types in the curve type frequencies and pharmacokinetic parameters.

Both the macrocyclic gadobutrol and the linear contrast agent Gd-DTPA appear to appear to be well-suited for DCE-MRI of the prostate for the diagnosis of prostate cancer.

Acknowledgement

This manuscript is dedicated to Professor Bernd Hamm for his 60th birthday.

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