Zusammenfassung


Ergebnisse: 47/87 Patienten (26 low-grade, 21 high-grade) mit 184/1044 Stanzbiopsien (77 low-grade, 107 high-grade) waren positiv für ein Prostatakarzinom. Ein Karzinompatient hatte im Median 3 positive Stanzbiopsien (Spannweite 1 – 12). Die Area under ROC curve für die Detektion des Prostatakarzinoms betrugen 0,65–0,67 und bei ausschließlicher Berücksichtigung der high-grade-Prostatakarzinome zwischen 0,75–0,76. Für die Detektion der Prostatakarzinome/high-grade-Prostatakarzinome ergab sich ein negativer prädiktiver Wert von 87,4–88,2%/92,6–93,1%, eine Spezifität von 72,3–79,4%/71,5–79,8%, eine Sensitivität 49,5–54,8%/62,6–69,2% und ein positiv-prädiktiver Wert von 29,3–34,0%/29,4–34,7%.

Schlussfolgerung: Bei Patienten mit initialem Verdacht auf ein Prostatakarzinom kann ein negativer prädiktiver Wert eine positive Entscheidung unterstützen.

Abstract

Purpose: To evaluate the role of conventional endorectal prostate MRI in patients with initial suspicion of prostate cancer.

Materials and Methods: Ethics board approval was received for this retrospective study of 87 men who underwent 1.5-Tesla conventional prostate MRI with a combination of endorectal and body phased-array coils for suspected prostate cancer before their first systematic 12-core TRUS-guided biopsy. Three radiologists independently analyzed the images, dividing the prostate into 12 regions corresponding to the biopsy schema and scoring each region for the presence of prostate cancer on a 5-point scale. Results were analyzed by prostate region. ROC analysis was done and descriptive statistics were calculated. The negative predictive value, specificity, sensitivity and positive predictive value were calculated using dichotomized scores (benign tissue = scores of 1 and 2; malignant tissues = scores of 3, 4, and 5).

Results: Biopsy revealed cancer in 47/87 patients (26 low-grade, 21 high-grade) with 184/1044 cores (77 low-grade and 107 high-grade) with a median of 3 positive cores per cancer patient (range 1–12). The areas under ROC curves were 0.65–0.67 for cancer detection by region overall and 0.75–0.76 for the detection of high-grade cancer by region. Statistic figures for the detection of all cancers/high-grade cancers by region were as follows: negative predictive value, 87.4–88.2%/92.6–93.1%; specificity, 72.3–79.4%/71.5–79.8%; sensitivity, 49.5–54.8%/62.6–69.2%; and positive predictive value, 29.3–34.0%/29.4–34.7%.

Conclusion: In patients with suspected prostate cancer, negative MRI findings indicate the absence of high-grade prostate cancer on subsequent TRUS-guided 12-core biopsy with high probability. However, agreement between con-
Introduction

Systematic core biopsy guided by transrectal ultrasound (TRUS) is currently the diagnostic test of choice in men with suspected prostate cancer. However, the initial biopsy detects prostate cancer in only 22% of cases [1]. Given the large number of negative biopsies, it is understandable that many men choose not to have a biopsy after weighing the benefits and risks [2]. To overcome this dilemma and avoid unnecessary sampling of normal prostate tissue, it would be highly desirable to have a noninvasive diagnostic tool—preferably an imaging modality—that reliably identifies normal prostate tissue without missing cancer. To meet these needs, a diagnostic modality must combine high negative predictive value with high sensitivity.

In patients with histologically proven prostate cancer, conventional endorectal prostate MRI has shown good sensitivities (61–80%) and good negative predictive values (76–79%) with areas under receiver operating characteristic curves [AUC] of up to 0.79 [3, 4]. High sensitivity (83%), high negative predictive value (89%), and good accuracy (68%) have also been achieved in patients with a persistent suspicion of prostate cancer following at least one negative TRUS-guided biopsy [5]. Only a few published studies have investigated the value of prostate MRI in men scheduled for their first TRUS-guided prostate biopsy. These studies used the entire prostate or the hemi-prostate as the unit of analysis for comparison with the results of sextant or octant TRUS-guided biopsy, did not consistently use an endorectal coil, or included only the peripheral zone in the analysis [6–9].

In a large population of patients scheduled for their first TRUS-guided prostate biopsy, we conducted a study to determine the negative predictive value, sensitivity, specificity, and positive predictive value of conventional prostate MRI performed using the combination of an endorectal coil and a body phased-array coil (conventional endorectal prostate MRI). MRI datasets were retrospectively analyzed independently by three radiologists experienced in prostate cancer imaging, and MRI findings in each patient were correlated to findings from each of the 12 prostatic regions sampled during systematic 12-core biopsy.

Materials and Methods

Patients

This retrospective study was approved by the institutional review board and was compliant with the Health Insurance Portability and Accountability Act. Between July 2003 and February 2008, a total of 92 consecutive patients in whom prostate cancer was suspected due to elevated PSA, abnormal PSA velocity, or suspicious findings on digital rectal exam underwent conventional endorectal prostate MRI at 1.5 Tesla before having their first systematic TRUS-guided 12-core biopsy. The biopsies were obtained in a standardized manner in all patients. At histopathological evaluation, the Gleason grading system was used, and prostate cancer was classified as low grade (Gleason score of 3+3) or high grade (Gleason score of 3+4 or above) [10]. Targeted tissue specimens based on suspicious MRI findings were not obtained. 2 of the 92 patients were excluded because their MR images were non-diagnostic due to motion artifacts. Another 3 patients were excluded because the interval between MRI and biopsy was longer than 6 months. Thus, the study included a total of 87 patients.

MRI Protocol

All patients underwent conventional prostate MRI on a 1.5-Tesla whole-body MR imager (Magnetom Sonata, Siemens, Erlangen, Germany) using the combination of an endorectal coil and a body phased-array coil (conventional endorectal prostate MRI). The body phased-array coil was used for signal transmission, while two elements of a spine-array coil, two elements of a body phased-array coil, and an endorectal coil (Medrad, Pittsburgh, PA) were used for signal reception. Following the acquisition of axial, sagittal, and coronal localizer sequences, the prostate and seminal vesicles were imaged according to a standardized protocol including the following sequences: an axial T2-weighted (w) turbo spin echo (TSE) sequence oriented perpendicular to the longitudinal prostate axis (TR 3720 ms, TE 100 ms, echo train length [ETL] 13, field of view [FOV] 16 × 16 cm), an axial T1w TSE sequence (TR 530 ms, TE 10 ms, ETL 3, FOV 16 × 16 cm) angled in the same way as the T2w sequence, and an angled coronal T2w TSE sequence (TR 3720 ms, TE 100 ms, ETL 13, FOV 16 × 16 cm). All pulse sequences were acquired with a 256 × 256 matrix; 3.0-mm slice thickness, 0.9-mm inter-slice gap, and 100% phase oversampling. Lymph nodes and the bones were assessed using a proton-density (PD) sequence (TR 1200 ms, TE 13 ms, FOV 32 × 24 cm, slice thickness 7 mm). The patients received an intramuscular injection of 20 mg butylscopolamine (Buscopan; Boehringer Ingelheim, Germany) to suppress artifacts caused by intestinal motion.

Interpretation of MR Images

The MRI datasets were randomized and retrospectively evaluated for areas of prostate cancer by three radiologists with 2, 4 and 8 years of prostate MRI experience. The readings were recorded independently. The readers were blinded to PSA levels and biopsy findings. For image evaluation, each prostate was divided into 12 regions corresponding to the sites from which the 12 core biopsies were taken (Fig. 1) after consultation with the urologists who performed the biopsies. Each region was then assessed for the presence of prostate cancer using a 5-point scale (1 = definitely no tumor, 2 = probably no tumor, 3 = possibly tumor, 4 = probably tumor, 5 = definitely tumor) and the corresponding criteria are listed in Table 1 [5, 11, 12]. To ensure their familiarity with the criteria, the three readers underwent brief training, in which datasets from patients not included in the study were used.
Scores were also used to calculate the Cohen $\kappa$ coefficient (benign tissue = scores of 1 and 2; malignant tissue = scores of 3, 4, and 5). The dichotomized scores were performed in MATLAB (version 7.1, Mathworks, Natick, MA) and with commercially available statistical software (SPSS, 11.0; SPSS, Chicago, Ill).

### Results

#### Distribution of Prostate Cancer

Among the 87 patients in the study, the median age was 66 years (range, 48 – 79 years) and the median PSA was 4.6 ng/ml (range, 1.7 – 34.2 ng/ml). The median interval between MRI and biopsy was 19 days (range, 1 – 156 days). Systematic TRUS-guided 12-core biopsy detected prostate cancer in 54 % (47/87) of patients. In the patients with biopsy-proven prostate cancer, the median Gleason score was 3 + 3 (range: 3 + 3 to 4 + 5) (Table 2, Fig. 2). Of the 860 negative biopsy regions, they correctly identified 622 to 683, resulting in sensitivities of 49.5 % (622/1249) to 54.8 % (683/1249) (Table 2). The median number of positive cores was 3 (range, 1 – 12) (Table 3).

#### Detection of All Prostate Cancers

The 47 patients with positive biopsy results had a total of 184 positive cores. Accordingly, 860 biopsy cores were negative for prostate cancer. The three readers correctly identified 91 to 101 of the 184 cancer-positive regions, resulting in sensitivities of 49.5 % (91/184) to 54.8 % (101/184). Out of the 1044 regions biopsied, the three readers scored 705 – 776 as negative on MRI, resulting in negative predictive values ranging from 87.4 % (641/733) to 88.2 % (622/705) (Table 2). Of the 860 negative biopsy regions, they correctly identified 622 to 683, resulting in specificities of 72.3 % (622/860) to 79.4 % (683/860). The positive predictive values ranged from 29.3 % (92/311) to 34.0 % (91/268). The AUCs for prostate cancer detection by MRI ranged from 0.65 to 0.67 (Table 5, 6). The Cohen’s kappa coefficients for inter-reader agreement were fair to moderate (0.35 for reader 1 and reader 2, 0.45 for reader 1 and reader 3, and 0.35 for reader 2 and reader 3).

#### Detection of High-Grade Prostate Cancers

Sensitivities ranged from 62.6 % (67/107) to 69.2 % (74/107) with negative predictive values ranging from 92.6 % (499/539) to 93.1 % (459/493) (Table 3). The AUCs for the detection of high-grade prostate cancer by MRI ranged from 0.75 to 0.76 (Table 6). The Cohen’s kappa coefficients indicated good inter-reader agreement at 0.65 for reader 1 and reader 2, 0.73 for reader 1 and reader 3 and 0.68 for reader 2 and reader 3.

### Statistical Tests

Statistical analysis was performed for each reader on a per-region level. The patients were stratified based on the following groups: all cases, high-grade cancers, and low-grade cancers. Receiver operating characteristic (ROC) curves and the corresponding areas under the curves (AUCs) were estimated non-parametrically for the detection of cancer by each reader for each group. In all statistical methods, a p-value of less than 0.05 was considered to indicate a significant difference. The negative predictive value, sensitivity, specificity, and positive predictive value were calculated using dichotomized scores (benign tissue = scores of 1 and 2; malignant tissue = scores of 3, 4, and 5). The dichotomized scores were also used to calculate the Cohen’s kappa coefficient for the interobserver agreement between the three readers, with 81 – 100 % being classified as very good agreement, 61 – 80 % as good agreement, 41 – 60 % as moderate agreement, 21 – 40 % as fair agreement, and ≤ 20 % as poor agreement. Analyses were performed in MATLAB (version 7.1, Mathworks, Natick, MA) and with commercially available statistical software (SPSS, 11.0; SPSS, Chicago, Ill).

### Table 1

<table>
<thead>
<tr>
<th>peripheral zone</th>
<th>transitional zone/central zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>definitely benign tissue (1)</td>
<td>uniform hyperintense T2 signal</td>
</tr>
<tr>
<td>probably benign tissue (2)</td>
<td>mild hypointensity with diffuse or feathered appearance</td>
</tr>
<tr>
<td>possibly malignant tissue (3)</td>
<td>ill-defined area of diffuse and inhomogeneous mild hypointensity</td>
</tr>
<tr>
<td>probably malignant tissue (4)</td>
<td>mass-like appearance of mild hypointense area</td>
</tr>
<tr>
<td>definitely malignant tissue (5)</td>
<td>definite mass-like region of confluent moderate hypointense area</td>
</tr>
</tbody>
</table>

### Table 2

AUCs for prostate cancer detection by MRI ranged from 0.65 to 0.76. (Table 2). The median number of positive cores was 3 (range, 1 – 12) (Table 3).

### Table 3

Sensitivities ranged from 62.6 % (67/107) to 69.2 % (74/107) with negative predictive values ranging from 92.6 % (499/539) to 93.1 % (459/493) (Table 3). The AUCs for the detection of high-grade prostate cancer by MRI ranged from 0.75 to 0.76 (Table 6). The Cohen’s kappa coefficients indicated good inter-reader agreement at 0.65 for reader 1 and reader 2, 0.73 for reader 1 and reader 3 and 0.68 for reader 2 and reader 3.
Detection of Low-Grade Prostate Cancer

For low-grade prostate cancer, the negative predictive values ranged from 90.5 % (552/610) to 91.7 % (585/638) and the sensitivities ranged from 24.7 % (19/77) to 35.1 % (27/77) (Fig. 7, Tab. 4). The AUCs for the detection of low-grade prostate cancer by MRI ranged from 0.51 to 0.57.

### Table 2

Summary of sensitivity, specificity, negative and positive predictive value to detect all prostate cancers for scores dichotomized as benign (1, 2) vs. malignant (3, 4, 5) for readers 1 – 3 (level of reference: individual biopsy core).

<table>
<thead>
<tr>
<th>Reader</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Negative Predictive Value</th>
<th>Positive Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 1</td>
<td>49.5 % (91/184)</td>
<td>79.4 % (683/860)</td>
<td>88.0 % (683/776)</td>
<td>34.0 % (91/268)</td>
</tr>
<tr>
<td>Reader 2</td>
<td>54.8 % (101/184)</td>
<td>72.3 % (622/860)</td>
<td>88.2 % (622/705)</td>
<td>29.8 % (101/339)</td>
</tr>
<tr>
<td>Reader 3</td>
<td>50.0 % (92/184)</td>
<td>74.5 % (641/860)</td>
<td>87.4 % (641/733)</td>
<td>29.3 % (92/311)</td>
</tr>
</tbody>
</table>

### Table 3

Summary of sensitivity, specificity, negative and positive predictive value to detect high-grade prostate cancer for scores dichotomized as benign (1, 2) vs. malignant (3, 4, 5) for readers 1 – 3 (level of reference: individual biopsy core).

<table>
<thead>
<tr>
<th>Reader</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Negative Predictive Value</th>
<th>Positive Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 1</td>
<td>62.6 % (67/107)</td>
<td>79.8 % (499/625)</td>
<td>92.6 % (499/539)</td>
<td>34.7 % (67/193)</td>
</tr>
<tr>
<td>Reader 2</td>
<td>69.2 % (74/107)</td>
<td>71.5 % (447/625)</td>
<td>93.1 % (447/480)</td>
<td>29.4 % (74/252)</td>
</tr>
<tr>
<td>Reader 3</td>
<td>68.2 % (73/107)</td>
<td>73.4 % (459/625)</td>
<td>93.1 % (459/493)</td>
<td>30.5 % (73/239)</td>
</tr>
</tbody>
</table>

### Table 4

Summary of sensitivity, specificity, negative and positive predictive value to detect low-grade prostate cancer for scores dichotomized as benign (1, 2) vs. malignant (3, 4, 5) for readers 1 – 3 (level of reference: individual biopsy core).

<table>
<thead>
<tr>
<th>Reader</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Negative Predictive Value</th>
<th>Positive Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 1</td>
<td>31.2 % (24/77)</td>
<td>81.8 % (585/715)</td>
<td>91.7 % (585/638)</td>
<td>15.6 % (24/154)</td>
</tr>
<tr>
<td>Reader 2</td>
<td>35.1 % (27/77)</td>
<td>76.4 % (546/715)</td>
<td>91.6 % (546/596)</td>
<td>13.8 % (27/196)</td>
</tr>
<tr>
<td>Reader 3</td>
<td>24.7 % (19/77)</td>
<td>77.2 % (552/715)</td>
<td>90.5 % (552/610)</td>
<td>10.4 % (19/182)</td>
</tr>
</tbody>
</table>

### Discussion

Our results show that if prostate cancer is not detected on a conventional endorectal prostate MRI examination performed before initial systematic TRUS-guided core biopsy, it is highly unlikely that the biopsy will detect cancer. The negative predictive value of MRI was highest for high-grade cancers, at 93 % for each of the three readers.

There is a paucity of data in the literature regarding the use of newer multiparametric MRI techniques incorporating diffusion-weighted imaging (DWI), dynamic contrast-enhanced MRI (DCE-MRI), and/or 1H MR spectroscopy (1H-MRS) before initial TRUS-guided biopsy. One study with 155 patients showed that in patients with a PSA of 4 – 10 ng/ml, the absence of malignant voxels on 1H-MRS was always associated with subsequent negative pro-
tate biopsy results [6]. On the other hand, plenty of studies have shown that patients with at least one negative TRUS-guided biopsy and a persistent clinical suspicion of prostate cancer benefit from multiparametric MRI [5, 16, 17]. Multiparametric MRI has been found to yield a greater negative predictive value than conventional endorectal prostate MRI in such patients and ranged from 78% to 95%, with
highest numbers in studies using a diagnostic 5-point scale [16–18]. The diagnostic benefits of multiparametric MRI techniques are accompanied by some methodological limitations. 1H-MRS requires an acquisition time of at least 9 min. and must be delayed until 6–8 weeks after the last prostate biopsy to prevent hemorrhage-related spectrally degraded voxels [19]. The apparent diffusion coefficient (ADC) calculated from DWI is a function of the signal-to-noise ratio and the applied b-values, which are functions of the diffusion gradients used [15]. As a result, it is difficult to compare ADC values obtained from DWI examinations performed on different scanners and with different b-values. For the analysis of DCE-MRI, several pharmacokinetic models and parameters exist [15, 20, 21]. The application of pharmacokinetic models with different standardized or individualized arterial input functions, as well as the use of different DCE-MRI sequences with different temporal resolutions, has complicated the comparison of DCE-MRI results from different studies [15, 20, 21].

The sensitivities of conventional endorectal prostate MRI (which ranged from 49.5–54.8% for all cancers and 62.6–69.2% for high-grade cancers) were lower than those in most published studies, although the specificities we found were similar to those previously reported. The published sensitivities for prostate cancer detection with conventional endorectal prostate MRI range from 74% to 81% [13, 14]. These higher sensitivities have been achieved in fundamentally different populations, namely patients who had histologically proven prostate cancer at the time of MRI and were scheduled for prostatectomy. In contrast, we investigated patients in whom prostate cancer was suspected based on an abnormal age-related PSA level, abnormal PSA velocity, or suspicious palpation findings. In a study of 40 patients without histologic proof of prostate cancer at the time of MRI, the sensitivity of conventional endorectal prostate MRI was also low, at 43%, despite the fact that only the peripheral zone was analyzed and the hemiprostate was used as the unit of analysis for the results of core biopsy [8]. For the clinically important question whether the patient has prostate cancer or not, the corresponding patient-by-patient analysis lead to much higher sensitivities of 73% to 78% [7, 9]. The newer multiparametric MRI sequences will probably further improve the sensitivity, because already one study with patients with initial suspicion of prostate cancer and several studies with patients with continuous suspicion of prostate cancer after at least one negative biopsy

Fig. 6 Nonparametric receiver operating characteristic (ROC) curves with areas under the curve (AUC) for readers 1–3 for all prostate cancers, high-grade cancers, and low-grade cancers.

Abb. 6 Nicht-parametrische receiver operating characteristic (ROC) curves mit den entsprechenden areas under the curve (AUC) der Reader 1–3 für high-risk-, low-risk- und alle Prostatakzkanome.
showed a considerable improvement of sensitivity and diagnostic accuracy [7, 13, 16, 18].

We found good interobserver agreement for the detection of high-grade prostate cancers by MRI, suggesting that our results are reproducible in this clinical setting. The implementation of multiparametric MRI and structured, standardized reporting could further increase interobserver agreement [22]. It must be noted, however, that all three readers were experienced in interpreting conventional endorectal prostate MRI, and experience has been found to be crucial for the diagnostic accuracy of prostate MRI [23].

It is also important to note that in a study population such as the one investigated here, it is essential to ensure an efficient workflow with prompt reporting of results to referring physicians to minimize any delay in diagnosis that might negatively impact a patient’s prognosis in the screening situation. A report providing information on suspicious MRI findings and their location(s) within the prostate allows the treating urologist to obtain biopsies without delay.

Our study is limited by the fact that we used systematic 12-core transrectal biopsy as the standard of reference. Twelve-core biopsy offers better cancer detection than sextant or octant biopsy, as used in earlier studies investigating the role of prostate MRI before initial biopsy, but in our opinion, it underestimates the extent of cancer, especially in apical and anterior portions of the prostate, resulting in an overestimation of the false-positive rate [24]. This dilemma might be overcome by extended follow-up of patients. In our study, extended follow-up was not possible because of the retrospective design and patients’ increasing tendency to use different healthcare providers at different stages of disease. However, future studies should target longer patient follow-up. Alternatively, transperineal template mapping biopsies should be obtained, as they are the best gold standard in patients with suspected prostate cancer. Transperineal template mapping biopsy, using a line-by-line approach with sampling every 5 mm from the base to the apex of the gland, appears to be comparable in accuracy to pathological analysis of whole-mount prostatectomy specimens. While not detecting every micro-focus of cancer, transperineal template mapping biopsies identify 95% of all significant, life-threatening prostate cancers [25]. Another more practical approach would be targeted transrectal TRUS-guided biopsies of suspicious areas in addition to systematic 12-core transrectal biopsy.

In conclusion, our results suggest that conventional endorectal prostate MRI performed for suspected cancer before initial biopsy has a high negative predictive value, ruling out the detection of high-grade and low-grade cancers by subsequent TRUS-guided core biopsy with probabilities of 93% and 91%-92%, respectively. Based on these data, in patients newly suspected of having prostate cancer who are reluctant to have a biopsy, MRI examination may provide useful information about the likelihood of cancer. However, the sensitivity of conventional endorectal prostate MRI in this subset of patients precludes the use of MRI alone in these patients and makes it necessary to closely monitor (e.g. by PSA testing) those who do not undergo prostate biopsy, regardless of their MRI findings. The sensitivity of conventional endorectal prostate MRI might be improved in the future by the supplementary use of newer techniques such as DWI, DCE-MRI, and 3H-MRS [9, 26, 27]. Once adequate sensitivity can be achieved with MRI, MRI findings can be used to plan targeted biopsies, thus contributing to a marked reduction of core biopsies in the future.

Acknowledgement

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

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Erratum „Franiel T et al. Role of Endorectal Prostate MRI in Patients with Initial Suspicion of Prostate Cancer. Fortschr Röntgenstr 2013; 185: 967–974“

In the above mentioned article the second author name was changed into H. A. Vargas.