**T2 Mapping in Prostate Cancer**

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**Objectives:** The aim of the study was to determine the quantitative T2 values in prostate tissue and evaluate them for detection and grading of prostate cancer.

**Materials and Methods:** After approval from the local ethics committee, morphologic T2-weighted (T2w) images, apparent diffusion coefficient (ADC) maps from diffusion-weighted images, quantitative T2 maps, and calculated T2w images from 75 men (median age, 66.3 years; median PSA, 8.2 ng/mL) were acquired at 3 T magnetic resonance imaging (MRI). Data were retrospectively evaluated for their distinction between prostate pathologies.

Eight hundred fifty-seven areas of normal gland (n = 378), prostate cancer (54x Gleason score 6, 98x Gleason score 7, 25x Gleason score 8), benign prostate hyperplasia (BPH) nodes (n = 150), prostatitis (n = 119), and precancerous lesions (n = 33) were determined on calculated and morphologic T2w images. Histological criterion standards were whole gland sections (16 patients), MRI-guided in-bore biopsies (32 patients), MRI/transrectal ultrasound-fusion biopsies (15 patients), and systematic 12-core transrectal ultrasound-guided biopsies (12 patients). Significance was assumed to be P < 0.05.

**Results:** The quantitative T2 values vary significantly between prostate cancer and normal gland tissue or BPH nodes. Similar to the ADC values, the absolute T2 relaxation values in the diagnosis of prostate cancer and to investigate their diagnostic accuracy.

A number of studies have already taken up this approach1–5, however, most of these studies examined the diagnostic accuracy of quantitative T2 values for prostate cancer only in the peripheral zone (PZ). For the transitional zone (TZ), in which the distinction between benign prostatic hyperplasia (BPH) and prostate cancer can be difficult, only limited data are available yet.1,5 For this reason, an absolute parameter that can give indications for or against cancer would be highly beneficial in that case.

Furthermore, there have been indications that the quantitative T2 values correlate with the aggressiveness of the prostate cancer, which can be characterized by the Gleason score.5,6 With regard to this, the question arises of whether T2 maps can be used to differentiate concretely between the individual Gleason scores.

The aim of this work is to determine the quantitative T2 values of prostate cancer with the Gleason score 6, 7, and 8, normal prostate tissue, prostatitis, BPH, and precancerous lesions for PZ and TZ separated, and their evaluation with regard to detection, distinction, and grading of prostate cancer in comparison to the corresponding apparent diffusion coefficient (ADC) values, as well as the suitability of the T2w calculated from quantitative T2 values for diagnosis compared with the acquired morphological T2w images.

**MATERIALS AND METHODS**

**Study Design and Population**

For this retrospective, single-center cohort study, approved by the local ethics committee, 86 men with the following inclusion criteria were consecutively included in our study between January 1, 2015, and January 10, 2016. Inclusion criteria were that first, the patient had received all magnetic resonance imaging (MRI) sequences relevant to the study as part of the multiparametric MRI (mpMRI) examination (T2w, T2 maps, and diffusion-weighted imaging), and second there was a histopathological criterion standard in the form of a biopsy or a prostatectomy. Exclusion criteria were nonrepresentative prostate biopsies (n = 2), a time interval of more than 7 months between biopsy and MRI (n = 8), and an unusable diffusion-weighted imaging sequence (n = 1). Finally, we considered 75 patients to be a study population (Table 1, Fig. 1). They had not been included in any other study published yet.

**Magnetic Resonance Imaging**

All patients received an mpMRI of the prostate at 3 T (MAGNETOM Prisma; Siemens Healthcare Erlangen, Germany) using a body phased array receiver coil (18-channel design with 18 integrated pre-amplifiers, with 3 rows of 6 elements each, dimensions: 385 × 590 × 65 mm [length × width × height]) and into the table integrated 32 channel spine array receiver coil.

Siemens Healthcare supported the study by providing 2 software prototypes such as model-based accelerated T2 mapping and ZoomIT single-shot diffusion epi.7,8 The following sequences were acquired in the study: axial fast spin-echo T2w, axial diffusion-weighted imaging, as well as axial quantitative T2 maps (Table 2). Synthetic T2w images were created based on the T2 maps using the same echo time as the...
morphological T2w. Apparent diffusion coefficient values were used as a reference quantitative parameter, because DWI is well known and routinely used in prostate cancer diagnostic imaging.

**Histopathologic Analysis**

Sixteen (21.3%) of the 75 patients received a DaVinci robot-assisted prostatectomy. The preparations were all cancerous and were processed in exactly the same way as the method published in 2011.9 Thirty-two patients (42.7%) underwent a targeted, MR-guided in-bore biopsy using a 1.5 T MRI in accordance with the previously published method.10,11 Four of these patients had prostate cancer in at least 1 of the 2 to 4 extracted samples. No cancer was found in 28 patients.

The remaining 27 patients (56%) received a transrectal ultrasound-guided biopsy either as a 12-core systematic biopsy (12 of 27) or as an elastic fusion biopsy (15 of 27) with an additional 1 to 3 biopsies from the MR suspected areas.11 Of these 27 patients, 10 (37%) were positive and 17 (63%) negative for prostate cancer.

**Determination of Quantitative T2 and ADC Values for Correlation With Histopathology**

To determine the quantitative T2 and ADC values, lesion-based regions of interest (ROIs) were placed according to the histopathologic reference.12,13

<table>
<thead>
<tr>
<th>TABLE 1. Study Population</th>
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<tbody>
<tr>
<td><strong>Feature</strong></td>
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<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Serum prostate specific antigen, ng/mL</td>
</tr>
<tr>
<td>Time between MRI and MR-guided biopsy, d</td>
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<tr>
<td>Time between MRI and transrectal ultrasound-guided biopsy, d</td>
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<tr>
<td>Time between MRI and prostatectomy, d</td>
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</table>

MRI indicates magnetic resonance imaging.

For the patients with an available whole-mount section, the investigated areas were defined through histopathological findings and then transferred to the T2 maps and DWI sequences (Fig. 2). On average, we placed 23 (7 to 33) ROIs in the whole prostate.

For the other patients who had an MRI-guided in-bore biopsy, fusion biopsy, or systematic TRUS-guided biopsy, both parameters were determined only for the biopsied areas. For the MR-guided biopsies, the precise location of the biopsy was known and documented, and therefore these lesions could be directly transferred to the T2 map and the DWI (Fig. 3). The systematic...
TRUS-guided biopsies were always taken according to a fixed scheme. A peripheral and a medial sample were taken in 3 different craniocaudal directions (apical, medial, and basal) on each side of the prostate and accordingly the ROIs were placed.

For the corresponding ROIs, the mean T2 and ADC values were calculated in the T2 maps and DWI. These mean values were determined in each patient for the following tissue types: prostate cancer of different Gleason scores as well as for normal gland tissue, prostatitis, BPH nodes, and precancerous lesions (atypical small acinar proliferation [ASAP], low- and high-grade prostatic intraepithelial neoplasia [PIN]), in each case separately for the PZ and TZ.

**Image Quality Assessment of Morphological and Calculated T2w**

Two readers (reader 1, radiologist with more than 10 years of experience with prostate MRI; reader 2, 1 year of experience with prostate MRI) assessed both sequences independently in a randomized order and blinded to the indication of mpMRI examination, clinical, and histopathological results. Nine criteria of image quality were rated on a Likert scale of 1, poor, to 5, excellent. These criteria were general image quality, contrast between PZ and TZ, representation of the inner architecture of the PZ as well as the TZ, visibility of the lesion with the highest PIRADS score, presentation of the capsule, presentation of the neurovascular bundle, and the representation of the rectoprostatic angle. Furthermore, in the images we evaluated the risk of extracapsular growth from 1, definitely not present, to 5, definitely present, and the severity of motion artifacts.

**Tumor Detection on the Morphological and Calculated T2w**

With the 36-sector model according to PI-RADS Version 2, a score of 1 (most likely benign) to 5 (most likely malignant) was given for each sector in both image series. Furthermore, each sector was assigned with the respective histopathological criterion standard (normal, BPH, prostatitis, ASAP, PIN, or prostate cancer), if available. The sectors without histology were not considered in the statistical analysis.

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Precancerous tissue and GS = 6 vs GS TZ: GS = 6 vs GS PZ: GS = 6 vs GS PZ: normal vs prostatitis 0.486 (0.416 PZ: prostatitis vs PCA 0.846 (0.790 TZ: PCA vs BPH 0.840 (0.790 − TZ: PCA vs BPH, prostatitis 0.827 (0.776 PZ: PCA vs normal 0.846 (0.804 − PCA vs BPH, prostatitis, normal 0.829 (0.790 − PCA vs BPH, prostatitis, normal 0.829 (0.790 − PCA vs normal 0.846 (0.804 − TZ: PCA vs BPH, prostatitis 0.827 (0.776 − TZ: PCA vs BPH 0.840 (0.790 − PZ: prostatitis vs PCA 0.864 (0.790 − PZ: normal vs prostatitis 0.486 (0.416 − PZ: GS = 6 vs GS ≥ 7 0.742 (0.633 − TZ: GS = 6 vs GS ≥ 7 0.431 (0.312 − Precancerous tissue and GS = 6 vs GS ≥ 7 0.696 (0.621 − Statistical Analysis

The statistical analysis was performed with SPSS 24 (SPSS for Windows, SPSS Inc, Chicago, IL). The mean T2 values were correlated with the mean ADC values using a Spearman correlation. The diagnostic accuracy of T2 and ADC values was determined with receiver operating characteristic curves, binary logistic regression models with the T2 and ADC values as predictors, and DeLong test in SAS 9.4 (SAS Institute, Cary, NC). Significance was assumed to be $P < 0.05$.

RESULTS

Eight hundred fifty-seven ROIs with the respective mean T2 and ADC values from the 75 patients were included in the statistical analysis (Table 3).

Quantitative T2 Values for the Differentiation Between Prostate Cancer and Other Prostate Pathologies

Based on the quantitative T2 values, a significant distinction can be made between prostate cancer and other entities in both PZ and TZ (Table 4). This is best achieved for the distinction between prostate cancer and normal gland tissue (AUC, 0.871 [0.840–0.902]; $P < 0.01$), but also benign altered prostate tissue. For example, a BPH node or prostatitis can be significantly distinguished from prostate cancer (AUC, 0.831 [0.778–0.884]; $P < 0.01$). Normal prostate tissue and benign tissue alterations do not show significant differences in T2 values (Fig. 4). With an 85% sensitivity, this results in a cutoff of 134 milliseconds (specificity 65%) in the PZ, and 104 milliseconds (specificity 68%) in the TZ to differentiate between prostate cancer and normal prostate tissue.

Comparison of the Quantitative T2 Values with the ADC Values

The correlation of the T2 values with the ADC values resulted in a correlation coefficient of 0.772 ($P < 0.01$). The connection does not seem linear (Fig. 5).

The ADC values demonstrate a similar AUC as the T2 values in all questions (Table 4). In the distinction of normal gland tissues and prostate cancer, the AUC for ADC values is slightly lower than for T2 values. These differences are, however, not significant in any of the cases. Therefore, the performance of the T2 values seems to be comparable to the performance of the ADC values in terms of tumor detection and grading. A combination of both parameters yielded a small diagnostic improvement for (1) precancerous lesions versus prostate cancer, (2) prostate cancer versus other, and (3) normal versus prostate cancer, in each case for the whole prostate. This is, however, not significant in any case.

Differentiation of the Cancer Aggressiveness With Quantitative T2 Values and ADC Values

The correlation of the Gleason score with the T2 values showed a significant inverse correlation with $r_S = -0.261 (P < 0.01)$ (Fig. 6). The correlation of the ADC values with the Gleason score also showed a negative correlation with $r_S = -0.160 (P = 0.03)$, that is, however, slightly less significant.

By use of the quantitative T2 values, it is also possible to differentiate between low-grade and intermediate-/high-grade tumors in the PZ ($0.742 [0.633–0.850]; P < 0.01$). This is not possible in the TZ. Despite the correlation, the 95% confidence intervals of the individual Gleason scores overlap (Fig. 6). Because the correlation with $r_S^{(T2)}$ of −0.261 and $r_S^{(ADC)}$ of −0.160 is weak or very weak, the quantitative T2 values and ADC values only allow limited conclusions on the underlying degree of aggressiveness.

Image Quality of the Morphological and Calculated T2w

Reader 1 rated the image quality of the morphological T2w as better in comparison to the calculated T2w image for all nine criteria. Notably, the rating “excellent” was given in most cases for the morphological T2w images.

### Table 3. Number of Examined Areas Divided According to Histological Entity for Peripheral Zone and Transitional Zone

<table>
<thead>
<tr>
<th>Histopathological Areas</th>
<th>Peripheral Zone, n = 539</th>
<th>Transitional Zone, n = 318</th>
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<tbody>
<tr>
<td>Normal</td>
<td>60.67% (327/539)</td>
<td>16.04% (51/318)</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>16.51% (89/539)</td>
<td>9.43% (30/318)</td>
</tr>
<tr>
<td>BPH nodes</td>
<td>0</td>
<td>47.17% (150/318)</td>
</tr>
<tr>
<td>Precancerous lesions</td>
<td>5.01% (27/539)</td>
<td>1.89% (6/318)</td>
</tr>
<tr>
<td>ASAP</td>
<td>1.31% (6/539)</td>
<td>0</td>
</tr>
<tr>
<td>PIN</td>
<td>3.70% (21/539)</td>
<td>1.89% (6/318)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>17.81% (96/539)</td>
<td>25.47% (81/318)</td>
</tr>
</tbody>
</table>

| Gleason score 3 + 3 = 6 | 5.19% (28/539)         | 8.18% (26/318) |
| Gleason score 3 + 4 = 7a| 6.31% (34/539)         | 7.86% (25/318) |
| Gleason score 4 + 3 = 7b| 3.15% (17/539)         | 6.92% (22/318) |
| Gleason score 4 + 4 = 8 | 3.15% (17/539)         | 2.52% (8/318) |

BPH indicates benign prostate hyperplasia; ASAP, atypical small acinar proliferation; PIN, prostatic intraepithelial neoplasia.

### Table 4. AUC of the Receiver Operating Curves for the Respective Questions for Mean T2 Values and Mean ADC

<table>
<thead>
<tr>
<th>AUC Values (Confidence Interval) of ROC Analysis</th>
<th>Quantitative T2 Values</th>
<th>ADC Values</th>
<th>Regression Coefficient T2 + ADC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal vs PCA</td>
<td>0.871 (0.840–0.902)</td>
<td>0.848 (0.814–0.882)</td>
<td>0.877 (0.848–0.907)</td>
</tr>
<tr>
<td>PCA vs BPH, prostatitis, normal</td>
<td>0.829 (0.795–0.862)</td>
<td>0.825 (0.790–0.859)</td>
<td>0.844 (0.812–0.876)</td>
</tr>
<tr>
<td>PZ: PCA vs normal</td>
<td>0.846 (0.804–0.889)</td>
<td>0.831 (0.784–0.877)</td>
<td>0.853 (0.812–0.894)</td>
</tr>
<tr>
<td>TZ: PCA vs BPH, prostatitis</td>
<td>0.827 (0.776–0.877)</td>
<td>0.799 (0.742–0.856)</td>
<td>0.839 (0.791–0.887)</td>
</tr>
<tr>
<td>TZ: PCA vs BPH</td>
<td>0.840 (0.790–0.891)</td>
<td>0.820 (0.765–0.876)</td>
<td>0.859 (0.811–0.906)</td>
</tr>
<tr>
<td>PZ: prostatitis vs PCA</td>
<td>0.864 (0.790–0.902)</td>
<td>0.838 (0.781–0.894)</td>
<td>0.862 (0.811–0.913)</td>
</tr>
<tr>
<td>PZ: normal vs prostatitis</td>
<td>0.486 (0.416–0.555)</td>
<td>0.526 (0.461–0.590)</td>
<td>0.585 (0.512–0.657)</td>
</tr>
<tr>
<td>PZ: GS = 6 vs GS ≥ 7</td>
<td>0.742 (0.633–0.850)</td>
<td>0.746 (0.635–0.858)</td>
<td>0.755 (0.649–0.862)</td>
</tr>
<tr>
<td>TZ: GS = 6 vs GS ≥ 7</td>
<td>0.431 (0.312–0.289)</td>
<td>0.361 (0.221–0.502)</td>
<td>0.645 (0.504–0.787)</td>
</tr>
<tr>
<td>Precancerous tissue and GS = 6 vs GS ≥ 7</td>
<td>0.696 (0.621–0.772)</td>
<td>0.697 (0.620–0.774)</td>
<td>0.705 (0.629–0.782)</td>
</tr>
</tbody>
</table>

AUC indicates area under the curve; ADC, apparent diffusion coefficient; PZ, peripheral zone; TZ, transitional zone; GS, Gleason score; ROC, receiver operating characteristic.
For reader 2, 6 of the 9 criteria showed equally good qualities in the morphological and calculated T2w. The other 3 characteristics (visibility of PZ and TZ, PZ and TZ distinction, visibility of lesions) were rated as better on the calculated T2w by reader 2.

Detection of Prostate Cancer With PIRADS Using Morphological and Calculated T2w

The highest sensitivity and specificity for the differentiation between prostate cancer and noncancer tissue in the PZ results in a PIRADS score of 3 as a cutoff. This is why all lesions with 3 or higher were evaluated as “cancer positive,” and all others as “cancer negative.” The 2 readers evaluated the morphological and calculated T2w in terms of their diagnostic value for the differentiation of prostate cancer versus other entities.

For reader 1, the AUC for morphological T2w was 0.658 (0.597–0.719) and for calculated T2w AUC was 0.682 (0.624–0.740). For morphological T2w reader 2 obtained an AUC value of 0.601 (0.538–0.665) and for calculated T2w AUC of 0.640 (0.581–0.700).

Reader 1 achieved the highest diagnostic accuracy with the calculated T2w. However, the difference between the detection rates in morphological and calculated T2w was not significant for either reader ($P = 0.47$ and 0.28). In addition, the higher diagnostic accuracy of reader 1 in comparison to reader 2 is not significant ($P = 0.14$).

Seminal Vesicle Invasion

The probability of seminal vesicular invasion was determined on both morphological and calculated T2w images. The histologically assessed seminal vesicles of the prostatectomized patients served as a reference. All 16 prostatectomy preparations showed tumor-free seminal vesicles. Reader 2 gave a score of 1 or 2 for all of these patients (seminal vesicle invasion not likely). Reader 1 evaluated the seminal vesicle invasion with a score of 3 in 1 of the 16 patients in both sequences (seminal vesicle invasion possibly present). However, the image quality of these 2 sequences was only moderate in this specific patient. The specificity for the detection of a seminal vesicle invasion based on morphological or calculated T2w alone is 93.8% for reader
Considering this, calculated T2w seems to be equally suitable with an AUC of 0.74 in the PZ, and 0.613 and 0.85 in the TZ. The strong correlation between morphological and calculated T2w for both readers. Sensitivity and specificity show that the diagnosis on the basis of the T2 maps alone is not sufficient. Although reader 1 rated morphological T2w images better in quality, there is no significant difference in the diagnostic accuracy between morphological and calculated T2w for both readers. Sensitivity and specificity show that the diagnosis on the basis of the T2 maps alone is not sufficient.

It has already been shown for some quantitative parameters that they can distinguish prostate cancer from healthy gland tissue. The parameter that can best distinguish alone is the ADC value. The AUC for the differentiation between normal prostate tissue and prostate cancer in the PZ was 0.845; 0.689 and 0.82 in previous studies. Only 2 of these studies also investigated the distinction of the cancer from healthy tissue in the whole gland (AUC, 0.74) (Ref 1, 2).

It has been demonstrated that ADC values as well as quantitative T2 values decrease with increasing Gleason scores. There is only one study known to us, which demonstrated this. Although in our study, we only examined data from one scanner, T2 values are ideally reproducible across scanners. Therefore, here, defined thresholds should be translatable to other systems. However, their diagnostic accuracy must be further investigated. The ratings of morphological and calculated T2w were discrepant for the 2 readers and also their detection rates for prostate cancer in the 2 sequences were different. However, this difference is not significant, and it has already been published, which the evaluation of prostate MRI through PIRADS classification depends on the reader’s experience. Considering this, calculated T2w seems to be equally suitable for cancer detection as morphological T2w. We are not aware of any study, which investigated this approach so far.

Lastly, T2 mapping can give both quantitative and qualitative information about a cancer suspicious area in MRI. In our study, the whole prostate. The AUC values here are comparable with our results (PZ: AUC = 0.846; whole prostate: AUC = 0.871).

In addition, the prevalence of benign prostate hyperplasia tends to increase in old age, which, in an MRI examination, might be identified as a suspected cancer. We demonstrated that it is possible to distinguish between benign changes and prostate cancer using quantitative T2 values. The only study known to us in which PZ and TZ were investigated separately showed that, even in the TZ with an AUC of 0.79, cancer can be distinguished from noncancerous areas. This was also confirmed in our study (AUC = 0.827). We additionally investigated the distinguishability between prostate cancer and other benign pathologies such as prostatitis and also precancerous lesions, which can be significantly differentiated from cancer by T2 values as well.

With regard to the ADC values, a significant inverse correlation with the Gleason score has already been shown. Similarly, the quantitative T2 values decrease with increasing Gleason scores. We were able to demonstrate that the individual tumor grades are distinguishable from each other using the T2 values in the PZ. However, the AUCs of the receiver operating curves were only moderate with 0.718 (Gleason score 6 vs 7) and 0.662 (Gleason score 7 vs 8), which means that T2 mapping can provide evidence of aggressiveness, albeit without allowing a definite conclusion.

In the clinical practice, it is relevant to differentiate low-grade tumors, which are not significant, from higher-grade tumors, which is significantly possible with T2 values. There is only one study known to us, which demonstrated this.

FIGURE 5. Correlation of T2 values in milliseconds and ADC values in $10^{-6} \text{mm}^2/\text{s}$ ($r_S = 0.772$).
detection rate for prostate cancer does not differ significantly between calculated T2w and morphological T2w, and the suspected lesion can additionally be characterized by the quantitative T2 values. Therefore T2 mapping could add a diagnostic gain to the mpMRI protocol. Furthermore, the quantitative T2 values can be included in new approaches in prostate cancer diagnostics such as computer-aided MRI diagnosis. Hereby, some first promising results were published.  

In both studies, they successfully reduced scan times with an equal gain of information, which offers the opportunity to perform sufficient diagnostic within an acceptable time frame. Our study has some limitations. First, a selection bias may have occurred, because it is a retrospective study. Despite the randomization, the evaluation of the image quality of the morphological and calculated T2w can lead to an observation bias as the MR images were not anonymized. As the ROIs on T2w, T2 map, and ADC map were manually plotted, minor inaccuracies may have occurred. Also in histopathology from biopsy samples, there can always occur false-negative results.

In 65 patients (86.7%), there was less than 3 months in between mpMRI and biopsy, in 68 patients (90.7%), less than 4 months, and in 70 patients (93.3%), less than 5 months. There can be small biological changes in the prostate in this time. In addition, in 4 patients, small hyperintense areas occurred in T1w, because they had a TRUS-guided or in-bore biopsy before mpMRI within less than 9 weeks; these patients were however, as the areas were to small and did not result in hypointensities in T2w.

In summary, we can conclude that quantitative T2 values in the PZ as well as in the TZ seem to be suitable to differentiate between prostate cancer and normal gland tissue or BPH nodes, and therefore, the possibility of routinely using T2 mapping should be further investigated.

ACKNOWLEDGMENTS

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REFERENCES