Characterization of prostate cancer using T2 mapping at 3 T: A multi-scanner study

A. Hoang Dinh\textsuperscript{a}, R. Souchon\textsuperscript{a}, C. Melodelima\textsuperscript{b,c}, F. Bratan\textsuperscript{a,d,e,f}, F. Mège-Lechevallier\textsuperscript{g}, M. Colombel\textsuperscript{e,f,h}, O. Rouvière\textsuperscript{a,d,e,f,*}

\textsuperscript{a} Inserm, U1032, LabTau, Lyon 69003, France
\textsuperscript{b} Université Joseph-Fourier, laboratoire d’écologie Alpine, BP 53, Grenoble 38041, France
\textsuperscript{c} CNRS, UMR 5553, BP 53, Grenoble 38041, France
\textsuperscript{d} Hospices civils de Lyon, department of urinary and vascular radiology, hôpital Édouard-Herriot, Lyon 69437, France
\textsuperscript{e} Université Lyon, Lyon 69003, France
\textsuperscript{f} Université Lyon 1, faculté de médecine Lyon Est, Lyon 69003, France
\textsuperscript{g} Hospices civils de Lyon, department of pathology, hôpital Édouard-Herriot, Lyon, 69437, France
\textsuperscript{h} Hospices civils de Lyon, department of urology, hôpital Édouard-Herriot, Lyon, 69437, France

KEYWORDS
Prostate cancer; Prostate multiparametric MRI; T2; Prostate cancer aggressiveness

Abstract
Rationale and objectives: To assess the prostate T2 value as a predictor of malignancy on two different 3 T scanners.

Patients and methods: Eighty-three pre-prostatectomy multiparametric MRIs were retrospectively evaluated [67 obtained on a General Electric MRI (scanner 1) and 16 on a Philips MRI (scanner 2)]. After correlation with prostatectomy specimens, readers measured the T2 value of regions-of-interest categorized as ”cancers”, ”false positive lesions”, or ”normal tissue”.

Results: On scanner 1, in PZ, cancers had significantly lower T2 values than false positive lesions ($P=0.02$) and normal tissue ($P=2 \times 10^{-5}$). Gleason $\geq 6$ cancers had similar T2 values than false positive lesions and significantly higher T2 values than Gleason $\geq 7$ cancers ($P=0.009$). T2 values corresponding to a 25% and 75% risk of Gleason $\geq 7$ malignancy were respectively 132 ms (95% CI: 129–135 ms) and 77 ms (95% CI: 74–81 ms). In TZ, cancers had significantly lower T2 values than normal tissue ($P=0.008$), but not than false positive findings. Mean T2 values measured on scanner 2 were not significantly different than those measured on scanner 1 for all tissue classes.

* Corresponding author. Service de radiologie urinaire et vasculaire, pavillon P, hôpital É.-Herriot, 5, place d’Arsonval, 69437 Lyon cedex 03, France.
E-mail address: Olivier.rouviere@netcourrier.com (O. Rouvière).

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Multiparameric MRI (mp-MRI) has yielded good results in prostate cancer detection and localization [1,2], but its interpretation is still limited by a lack of standardization. Indeed, characterization of focal lesions seen on prostate mp-MRI remains difficult because of the overlap between the appearance of cancers and benign conditions and because the different pulse sequences that compose mp-MRI may yield discordant results [2,3]. As a consequence, the good results published by specialized institutions may not be reproduced by less-experienced radiologists [4].

There are three ways to improve the standardization of mp-MRI interpretation. The first one is to establish a diagnostic score that could be easily used by all readers. The European Society of Urogenital Radiology has recently proposed the so-called PIRADS score [5], but two recent studies have shown that inter-reader agreement remained poor to moderate, even with the PIRADS score [6,7]. The second solution is to develop computer-aided diagnosis (CAD) systems that could assist the radiologist [8,9]. However, these systems are developed only in specialized institutions and are not widely available. The third solution would be to use a quantitative approach for mp-MRI interpretation, by defining thresholds for quantitative parameters that could help assess the risk of malignancy of a given focal lesion. However, quantification in MRI may be influenced by the imaging parameters and the scanner calibration and settings. As a result, it is not sure that one can define quantitative thresholds that may be reproducible form one scanner to another.

To date, little has been published on the role of the measurement of the T2 value in prostate cancer characterization at 3 T [10,11]. The purpose of this study was to assess whether the T2 value was a significant predictor of malignancy and to evaluate the robustness of its measure on two different scanners at 3 T.

**Material and methods**

**Patient population**

At our institution, prostate mp-MRI is part of the usual workup before radical prostatectomy. Since September 2008, all patients treated by radical prostatectomy who had undergone a preoperative mp-MRI at our institution were offered to have their data entered in a prospective radio-pathological correlation database [Corrélations Anatomoradiologiques en IRM de Prostate (CLARA-P) database]. All patients entered in the database gave written consent for the use for research purposes of their MR and pathological data and signed the Institutional Review Board-approved consent form. The database was also registered with the appropriate administrative authority (Commission Nationale de l’Informatique et des Libertés, no 08-06).

For the present study, we selected from the database the patients who had been imaged in two departments of radiology. Department 1 used a 3 T General Electric scanner (MR 750, Milwaukee, WI, USA) and department 2 a 3 T Philips MR scanner (Achieva Xseries, Best, The Netherlands). At our institution, most prostate mp-MRIs are performed in department 1. However, some patients were imaged in department 2, mostly for practical and organizational reasons. The CLARA-P database contained a total of 158 consecutive patients imaged at 3 T on scanner 1 or 2. Seventy-five patients were excluded because the multi-echo sequence for T2 mapping had not been acquired (n = 60) or because T2 maps were of poor quality (n = 15). This left a study population of 83 patients. **Table 1** shows their mean age and PSA level.

**MR protocol**

For both scanners, mp-MR protocols included T2-weighted (T2w), diffusion-weighted (Dw) and dynamic contrast-enhanced (DCE) sequences, as well as a multi-echo sequence for T2 mapping (**Table 2**). T2 maps were calculated from monoeponential decay fitting of the multi-echo datasets using dedicated vendors’ software.

T2w, Dw, DCE and T2 maps axial images were acquired with the same position and slice thickness to allow direct comparison between sequences.

**MR image analysis**

The mp-MRIs of the patients included in the CLARA-P database were reviewed by two independent radiologists with 11 years and 1 year of experience at the start of the database in 2008. They delineated all suspicious lesions visible in the prostate using the Osirix freeware (Osirix, Switzerland). Suspicious lesions were defined in the peripheral zone (PZ) as any focal lesion showing hypointensity on T2w images and/or restriction of diffusion on apparent...
Table 2 Imaging parameters.

<table>
<thead>
<tr>
<th>Scanners</th>
<th>1</th>
<th>2</th>
</tr>
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<tbody>
<tr>
<td>Manufacturer, field strength</td>
<td>General Electric Medical System, 3 T</td>
<td>Philips Medical Systems, 3 T</td>
</tr>
<tr>
<td>Model name</td>
<td>Discovery MR750</td>
<td>Achieva 3 T Xseries</td>
</tr>
<tr>
<td>Receive coil type</td>
<td>32-channel PPA coil</td>
<td>16-channel PPA + endorectal coil</td>
</tr>
<tr>
<td>Sequence</td>
<td>T2w, Dw, DCE</td>
<td>T2w, Dw, DCE</td>
</tr>
<tr>
<td>TR (ms)</td>
<td>5000, 5000, 3.9</td>
<td>5021, 3925, 4, 4950</td>
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<tr>
<td>TE (ms)</td>
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<td>120, 70, 2.3, 25, 50, 75, 100, 125</td>
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<tr>
<td>FOV (mm)</td>
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<td>180 × 180, 180 × 180, 180 × 180</td>
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<td>Acquisition matrix</td>
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<td>344 × 255, 116 × 103, 100 × 100</td>
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<tr>
<td>b-values (s/mm²)</td>
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<td>0, 800, 2000</td>
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<tr>
<td>Flip angle (degrees)</td>
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<td>90/180, 90, 8, 90/180</td>
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<tr>
<td>Slice thickness (mm)</td>
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<td>3, 3, 3</td>
</tr>
<tr>
<td>Number of temporal acq.</td>
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<td>50</td>
</tr>
<tr>
<td>Temporal resolution (s)</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>

Coefficients (ADC) maps, and/or early enhancement on DCE images. In the transition zone (TZ), only lesions with homogeneous hypointensity, no capsule, lenticular or amorphous shape and involving the anterior third of TZ on T2w images were taken into consideration [12–15].

Histopathological analysis

Whole-mount sections were obtained according to the Stanford method [16] every 3 mm, to match MR slice thickness. Pathological analysis was done by an uropathologist with 10 years of experience at the start of the database in 2008. All tumors with in-plane dimensions > 2 × 2 mm² and a Gleason score ≥5 were delineated on the whole-mounts glass cover. The Gleason score of all individual cancer foci was assessed.

MR histological correlation

MR images and whole-mounts were prospectively compared by the uropathologist and the two radiologists, using side-by-side comparison. These readers reviewed all suspicious lesions in mp-MRI and defined those that matched cancer foci (true positives), and those that corresponded to benign conditions (false positives). Then, they delineated in consensus ROIs that were as close as possible to the histological truth. To do so, they modified, when needed, the delineation of true positives so that their volume and shape correspond to those of histological cancers. They also delineated the missed cancers that were retrospectively seen on mp-MRI images and all the false positives noted by at least one reader of the CLARA-P database. All the ROIs were labelled as per their histological nature (cancer or false positive).

Then, one researcher with one year of experience in prostate imaging retrieved the delineations of cancers and false positive lesions and copied them on T2 maps images using the Osirix freeware. He delineated the rest of PZ and TZ that did not contain cancer at pathology and had been judged as normal on mp-MRI by the two radiologists. These ROIs will be referred to as PZ and TZ normal tissue in the rest of the paper. The anterior fibromuscular stroma was excluded from the delineation of the TZ normal tissue.

Computation of T2 values

The mean T2 value was then calculated for each ROI. When a given ROI was present on several slices, the mean T2 value was computed as the average value weighted by the area of the ROIs delineated on each individual axial slice.

Thus, the study database was composed, for each patient, of one T2 value for PZ normal tissue, TZ normal tissue, and each cancer and benign false positive lesion that had been delineated.
Statistical analysis

Statistical analysis was performed using the R software (http://cran.r-project.org/). Generalized linear mixed models (GLMM) were used to quantify the ability of T2 value to discriminate cancers from false positive lesions and Gleason ≥ 7 cancers from other abnormal mp-MRI findings (i.e. false positive lesions + Gleason ≤ 6 cancers). Individual random effects were used in order to take into account the intra-patient correlation structure. The likelihood ratio was applied to determine the significance of the model. Regression coefficient significance was tested using the Wald test. GLMM models were calculated using package lme4. The accuracy of the model was measured by the area under the ROC curve (AUC). GLMM predictions and AUC were calculated using package ROCR. Measures obtained on scanners 1 and 2 were compared with the Wilcoxon non-parametric test that is suitable for small samples. A P value < 0.05 was considered statistically significant and all interval estimations given in this paper are 95% confidence intervals (CI).

Results

T2 values of the different types of prostate tissue measured on scanner 1

In total, 288 ROIs corresponding to cancers (n = 99), benign false positive lesions (n = 55) and normal tissue (n = 134) were delineated in patients imaged on scanner 1.

Table 3 shows the mean T2 values measured in cancers, false positive lesions and normal tissue in PZ and TZ. In PZ, the mean T2 value was significantly lower in cancers than in normal tissue (P = 2 × 10⁻⁴) and false positive lesions (P = 0.02). In TZ, the mean T2 value was also significantly lower in cancers than in normal tissue (P = 0.008). TZ cancers and TZ false positive lesions were not compared due to the small number of TZ false positive lesions.

Table 4 shows the AUCs for discriminating, using the mean T2 value, cancers from normal tissue, false positive lesions and the overall group of benign tissue (normal tissue + false positive lesions), in PZ and in TZ.

Table 5 shows the mean T2 values in cancers as a function of their Gleason score and location. In PZ, Gleason ≥ 7 cancers had significantly lower mean T2 than Gleason ≤ 6 cancers (P = 0.009) and false positive lesions (P < 0.0003). In contrast, the mean T2 value was not significantly different in Gleason ≤ 6 cancers and in false positive lesions (P = 0.73). The AUCs for discriminating, using the mean T2 value, Gleason ≥ 7 cancers among all cancers and among all
suspicious lesions visible on mp-MRI (i.e. cancers + false positive lesions) were respectively 0.67 (95%CI: 0.65–0.7) and 0.68 (95%CI: 0.65–0.72; Fig. 1).

Figs. 2 and 3 respectively show the overall risk of malignancy and the risk of Gleason ≥ 7 malignancy expressed as a function of the T2 value in the population of suspicious lesions on mp-MRI (i.e. cancers + false positive lesions) in PZ. The T2 values corresponding to an overall risk of malignancy of 25% and 75% were respectively 176 ms (95%CI: 162–183 ms) and 85 ms (95%CI: 80–90 ms). The T2 values corresponding to a risk of Gleason ≥ 7 malignancy of 25% and 75% were respectively 132 ms (95% CI: 129–135 ms) and 77 ms (95% CI: 74–81 ms).

In PZ, the mean T2 value was significantly lower in cancers than in normal tissue ($P = 0.006$) and false positive lesions ($P = 0.045$). In TZ, it was lower in cancers than in normal tissue, but not significantly ($P = 0.07$; Table 3).

The mean T2 values measured on scanner 2 in cancers, false positive lesions and normal tissue were similar and not significantly different than those measured on scanner 1, neither in PZ nor in TZ (Table 3). The mean T2 values measured on both scanners in Gleason ≤ 6, Gleason 7 and Gleason ≥ 8 cancers were similar (Table 5); the difference was not statistically tested due to the small number of cancers imaged on scanner 2.

**Discussion**

Ideally, a quantitative MR parameter used for prostate cancer detection should have three characteristics. First, it should significantly discriminate prostate cancer from benign tissue. Second, it should distinguish aggressive from less aggressive tumors. Finally, it should show little...
dependency on MR protocol settings and MR vendors so that reliable inter-institutions thresholds could be defined between malignant and benign tissues or between aggressive and less aggressive tumors. In this study, we assessed whether the T2 value fulfilled these three conditions.

First, in agreement with several other studies performed at 1.5 T [17–20] or at 3 T [10], we found the T2 value to be significantly lower in PZ cancers than in normal PZ. However, to be useful in daily practice, the T2 measurement must discriminate malignant from benign tissue in the subgroup of areas appearing suspicious on mp-MRI. Liu et al. assessed 18 patients with 31 suspicious lesions detected on 3 T mp-MRI and that were targeted on biopsy [11]. The T2 values of areas positive at biopsy (85–124 ms) were significantly lower than that of suspicious areas with negative biopsy findings (83–168 ms, \( P < 0.05 \)). Our results, based on a larger population and using prostatectomy specimens as gold standard, confirm that the T2 value can significantly discriminate cancers within the group of PZ lesions appearing suspicious at mp-MRI.

Second, we found the T2 value to be significantly lower in Gleason \( \geq 7 \) than in Gleason \( \leq 6 \) cancers in PZ. Only one study evaluated the potential role of T2 measurement in assessing tumor aggressiveness. Gibbs et al. showed a trend for decreasing T2 with increasing Gleason score in 20 patients treated by radical prostatectomy [10]. However, the difference was not significant, probably due to the small number of patients evaluated. Interestingly, in our series, we found a complete overlap between the T2 values measured in Gleason \( \leq 6 \) cancers and in benign false positive lesions. Taken together, our results suggest that the T2 value could be used, in the group of PZ suspicious areas seen on mp-MRI, as an indicator of aggressive tumors rather than as an indicator of mere malignancy. This finding is particularly interesting in the current context of emphasis on the non-invasive assessment of prostate cancer aggressiveness in order to reduce over-detection and over-treatment of indolent cancers [21].

However, T2 measurement will be useful in clinical practice only if it is possible to define quantitative thresholds between tissue classes. For that purpose, T2 measurement needs to be robust to changes in imaging parameters and to be reproducible from one scanner to another. Little has been published on the subject. In one study, a second T2 map was acquired at 3 T in 8 patients thirty minutes after a first scan. Reproducibility was good, with differences between the two measurements being, on average, less than 2% [11]. In another one, performed at 1.5 T, 13 patients underwent two prostate MRIs, a median of seven days apart. T2 measurements were found to be highly reproducible, with a within-patient coefficient of variation of less than 4% [22]. In those two studies, however, the imaging parameters and the scanners were the same for the two measurements. Our study brings indirect evidence that T2 measurements are relatively insensitive to changes in imaging protocols or MR scanners. First, the mean T2 values measured on our two scanners were very similar for all the tested classes of tissue, despite the fact that the two scanners were from different vendors and that the TE selections used for the multi-echo sequences were different. Second, these mean T2 values were also similar to those published at 3 T in PZ by Liu et al. using accelerated T2 mapping on a Philips scanner (normal PZ: 149 ± 49 ms; benign suspicious lesions: 114 ± 32 ms; cancer: 100 ± 10 ms) and by Gibbs et al. using fast spin echo on a GE scanner (normal PZ: 142 ± 24 ms; cancer: 109 ± 20 ms) [10,11]. However, comparisons of mean values obtained in different patients may underestimate the variability of T2 measurement. Only a comparison of T2 values obtained on the same patients with two different scanners could assess whether meaningful inter-vendor T2 thresholds could be used to discriminate benign and malignant prostate tissue or aggressive and less
aggressive tumors. To our knowledge, such a study has not been done yet.

Even if the T2 value is proved in the future to be insensitive to the imaging parameters, our study suggests that its use will not be sufficient by itself to adequately characterize focal abnormalities of the PZ. Indeed, modeled T2 thresholds for a 25% risk of cancer and of Gleason ≥ 7 cancer were 176 and 132 ms, respectively. This is within the range of T2 values measured in normal PZ. Similarly, the modeled risk of cancer and of Gleason ≥ 7 cancer does not reach 90% in the range of observed T2 values (Figs. 2 and 3). This indicates that the use of the T2 value as a stand-alone cannot definitively ascertain or definitively rule out cancer or even Gleason ≥ 7 cancer. This is in line with the abundant body of literature that shows that a multiparametric approach is necessary for prostate MRI [5,23]. Thus, other quantitative parameters are necessary in addition to the T2 value if one wants to exclusively use a quantitative approach to characterize prostate cancer. The apparent diffusion coefficient (ADC), some semi-quantitative enhancement parameters (e.g., peak enhancement, wash-in and wash-out rates) or some pharmacokinetic parameters (e.g., Ktrans and Kep) have been shown to be significant indicators of malignancy or even aggressive malignancy [24–31]. However, they depend on many factors related to the imaging protocol (e.g. b-values selection or TE for ADC, temporal resolution for enhancement and pharmacokinetic parameters), the model used for analysis or even the patient (e.g., cardiac output or hematocrit) for pharmacokinetic parameters [27,32–35]. Thus, it remains unclear whether it will be possible or not to use reliable diagnostic thresholds for these parameters, even with standardized protocols. Nonetheless, we have started at our institution a systematic study of all factors that could influence diffusion and enhancement parameters in order to further explore this possibility.

The T2 values measured in suspicious benign lesions and in cancers in T2 were similar, suggesting that the T2 will not be a useful predictor of malignancy in T2. Fortunately, recent works showed that T2 cancer appearance tended to be monomorphic on T2w imaging with homogeneous hypointensity, lack of capsule, ill-defined boundaries, amorphous or lenticular shape and anterio-apical location [12–15,36]. These simple criteria provide an efficient characterization of T2 nodules [15] even if measuring the ADC and Ktrans may also be useful [14].

Our study has some limitations. First, our conclusions are limited by the small number of patients imaged on scanner 2. Second, matching mp-MRI focal lesions with corresponding regions on whole-mounts remains difficult due to the difference in angle section between MR images and whole-mounts. Thus, some mismatches might have occurred. Third, the study population was made of patients treated by radical prostatectomy. Although we paid attention to take into account all suspicious lesions visible at mp-MRI, extrapolation of our results to other populations (e.g., candidates to biopsy or patients under active surveillance) may not be appropriate.

In conclusion, we found the T2 value to be a significant predictor of aggressive (Gleason ≥ 7) tumors at 3 T. We also observed similar mean T2 values for all tested tissue classes on two different MR scanners from different vendors using non-standardized imaging protocols for T2 mapping. This suggests that the T2 value may be robust to changes in protocols and MR vendors. However, it does not seem possible to definitively ascertain or rule out the presence of cancer (or Gleason ≥ 7 cancer) using the T2 value as a stand-alone. Thus, any quantitative approach for diagnosing prostate cancer and evaluating its aggressiveness will need to be multiparametric and use other quantitative parameters.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


