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Rapid Quantitative T$_2$ Mapping of the Prostate using 3D Dual Echo Steady State (DESS) MRI at 3T


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ABSTRACT

Purpose: To develop and evaluate a rapid 3D quantitative $T_2$ mapping method for prostate cancer imaging using Dual Echo Steady State (DESS) MRI at 3T.

Methods: In simulations, DESS-$T_2$ mapping in the presence of $T_1$ and $B_1^+$ variations was evaluated. In a phantom and healthy volunteers ($n = 4$), 3D DESS-$T_2$ mapping was compared to a 2D turbo spin echo (TSE) approach. In volunteers and a pilot patient study ($n = 29$), quantitative $T_2$ in normal prostate anatomical zones and in suspected cancerous lesions was evaluated.

Results: The simulated bias for DESS-$T_2$ was less than 2% (5%) for typically observed $T_1$ ($B_1^+$) variations. In phantoms and in vivo, high correlation of DESS-$T_2$ and TSE-$T_2$ ($r^2 = 0.98$ and $0.88$, p-value < 0.001) was found. DESS-$T_2$ in the normal peripheral zone (PZ) / transition zone (TZ) was $115 \pm 26$ ms / $64 \pm 7$ ms in healthy volunteers and $129 \pm 39$ ms / $83 \pm 12$ ms in patients. In suspected cancerous lesions, DESS-$T_2$ was $72 \pm 14$ ms, which was significantly decreased from normal PZ (p < 0.001), but not from TZ.

Conclusion: Rapid 3D $T_2$ mapping in the entire prostate can be performed in one minute using DESS.

Keywords: Prostate Cancer Imaging, $T_2$ mapping, Dual Echo Steady State (DESS) MRI, and 3T MRI.
INTRODUCTION

Prostate cancer is the second leading cause of cancer related death in men in the U.S. (1). Conventionally, prostate cancer is diagnosed and monitored using transrectal ultrasonography (TRUS)-guided systematic needle biopsy to obtain tissue samples, which are assigned a Gleason Score (GS) indicating the aggressiveness of cancer. However, due to sampling bias this approach might miss clinically significant cancer and it is an uncomfortable, invasive procedure that some patients undergo repeatedly in conventional active surveillance. Magnetic Resonance Imaging (MRI) is a promising, non-invasive tool to detect and monitor prostate cancer (2). Prostate MRI relies on multi-parametric (mp) T2-weighted (w), diffusion and dynamic contrast-enhanced imaging. However, qualitative analysis of mp-MRI alone performs suboptimally in distinguishing indolent from aggressive cancers. Le et al found that ~30% of clinically significant tumors (GS > 7 on whole-mount histopathology) were missed by multi-parametric MRI (mp-MRI) (3). Therefore, systematic biopsy is still considered the gold standard for assessing prostate cancer aggressiveness (4).

Quantitative MRI has shown promise for assessing tumor aggressiveness (5–9). Further, quantitative as opposed to qualitative MRI can reduce subjectivity in the assessment, which is important for long-term monitoring of patients such as men on active surveillance, as well as to improve uniformity of reporting across readers and institutions. However, the implementation of quantitative methods is technically challenging and thus far limited to research settings. One quantitative MR parameter, T2 relaxation, reflects the interaction of water molecules on a cellular level and is therefore potentially highly sensitive to detect pathological tissue alterations. However, current methods to reliably measure T2, such as single spin-echo (SE), acquire multiple image sets to map T2. This results in compromises between spatial resolution, 3D coverage, and scan time. The impractically long scan times associated with SE-T2 mapping, which might be on the order of tens of minutes, also make scans highly vulnerable to motion artifacts. Further, extracting T2 from multi-contrast images is limited in accuracy due to potential mis-registration between images. Multi-echo SE sequences, such as turbo spin echo (TSE), are commonly used to speed up the acquisition. However, quantification is limited
because of contributions of stimulated and indirect echoes to the multi-echo signal, which depends on a variety of parameters including $T_2$, $T_1$, $B_0$, $B_1^+$ and diffusion. The accuracy of TSE-$T_2$ mapping can be improved by using a more complicated fitting approach, which accounts for all above-mentioned echo contribution effects, e.g. stepwise Bloch simulations, but this requires the pre-computation of a signal data base for fitting (10).

Alternatively, three-dimensional (3D) dual echo steady state (DESS) MRI (11–13) has shown its potential for $T_2$-mapping in the knee (14–16). DESS acquires two images (“FID” and “Echo”) with distinct contrast in a single scan. This feature of DESS allows for both morphological $T_2$-weighted ($T_2$-w) and quantitative $T_2$ imaging in a single scan. Even though a simple exponential fit can yield quantitative $T_2$ if a flip angle (FA) of 90° is used, to achieve sufficient SNR, DESS is typically performed at lower FA. As a consequence, $T_2$ mapping requires detailed modeling of the DESS signals (14–18).

We propose the application of DESS to achieve rapid 3D $T_2$ maps of the entire prostate. In this work, we aim to evaluate quantitative $T_2$ mapping with 3D DESS applied to the prostate in simulations, phantoms, healthy volunteers and a pilot patient study.

**METHODS**

This research was approved by the local institutional review board and all human subjects gave written, informed consent prior to scanning. MRI experiments were performed on a 3T MRI system (TIM Trio or Skyra, Siemens Healthcare, Erlangen, Germany) using a body matrix and a spine array coil. DESS was acquired in addition to standard $T_2$ mapping reference sequences (TSE in volunteers) and in addition to standard clinical sequences for prostate mp-MRI (in patients).

**DESS Acquisition and $T_2$ Mapping**

The DESS sequence is a steady-state free precession (SSFP) sequence, which acquires two signals in each TR: 1) “FID” with mixed $T_2 / T_1$ contrast and 2) “Echo” with primarily $T_2$ contrast (Figure 1). The ratio of these two signals was fitted to a signal model to obtain quantitative $T_2$ values for each image voxel (17). Detailed sequence
parameters are listed in Table 1. Quantitative T\textsubscript{2} mapping was performed in MATLAB R2013b (MathWorks, Natwick, MA, USA).

The signal ratio of DESS Echo and FID (S) shows a strong T\textsubscript{2} dependence (14–17,19), which is used to fit quantitative T\textsubscript{2}. Since it also depends on T\textsubscript{1} and B\textsubscript{1}\textsuperscript{+}, these parameters need either be measured to be included on a per voxel basis in the data fitting algorithm, or, in a simplified approach, a global (fixed) estimate for T\textsubscript{1} and B\textsubscript{1}\textsuperscript{+} can be used (16):

\[ T_{2,\text{fit}} = \arg\min_{T_2 \in T_{2,\text{range}}} \| S_{\text{meas}}(T_1, B_{1}^{+}, T_2) - S(T_{1,\text{fix}}, B_{1,\text{fix}}^{+}, T_2) \|_2 \] (1)

Where \( S_{\text{meas}}(T_1, B_{1}^{+}, T_2) \) is the measured signal ratio and \( S(T_{1,\text{fix}}, B_{1,\text{fix}}^{+}, T_2) \) are calculated from the signal model for each candidate T\textsubscript{2} in a predetermined range (\( T_{2,\text{range}} \)).

**Simulations**

In simulations, we sought to quantify the bias of fitted T\textsubscript{2} with respect to T\textsubscript{1} and B\textsubscript{1}\textsuperscript{+}, if these were implemented as a fixed global estimate in a parameter range typically observed in prostate MRI. For the global estimate, we used \( T_{1,\text{fix}} = 2200 \) ms based on a recent study, which measured average T\textsubscript{1} in the prostate in 108 patients (20). We set relative B\textsubscript{1}\textsuperscript{+},fix = 1. Simulations were performed over a physiologically relevant parameter space. We assumed a range of \( T_{1,\text{true}} = [1500 \text{ to } 3000 \text{ ms}] \) and initially set \( T_{2,\text{true}} = 150 \) ms:

\[ T_{2,\text{fit}}(T_{1,\text{true}}) = \arg\min_{T_2 \in T_{2,\text{range}}} \| S_{\text{sim}}(T_{1,\text{true}}, B_{1,\text{fix}}^{+}, T_2, T_{2,\text{true}}) - S(T_{1,\text{fix}}, B_{1,\text{fix}}^{+}, T_{2,\text{true}}) \|_2 \] (2)

Minimizing the cost function yields the result for fitted T\textsubscript{2} ("T\textsubscript{2,fit}"). The normalized difference between T\textsubscript{2,fit} and T\textsubscript{2,true} corresponds to the bias in the fitted T\textsubscript{2} estimate due to using a fixed T\textsubscript{1}, which deviates from the true T\textsubscript{1}:

\[ T_{2,\text{bias}}(T_{1,\text{true}}, T_{2,\text{true}}) = \frac{T_{2,\text{fit}}(T_{1,\text{true}}) - T_{2,\text{true}}}{T_{2,\text{true}}} \] (3)
This simulation was expanded for a range of $T_{2,\text{true}}$ values ($T_{2,\text{true}} = [50$ to $250 \text{ ms}]$) to obtain the $T_2$ bias over a range of $T_{1,\text{true}}$ and $T_{2,\text{true}}$. Similarly, simulations were also performed to study the $T_2$ bias due to relative $B_1^+$ variations over a range of 0.5 to 1.5.

**Phantom Study**

To verify our simulation results and to evaluate DESS-$T_2$ mapping performance in the presence of $T_1$ variations, we designed a phantom with 16 5-ml tubes filled with specific concentrations of Gd-DTPA and CuSO$_4$ to adjust the $T_1$ and $T_2$ relaxation times. The tubes were placed in a container filled with water and arranged in a 4x4 grid to comprise a range of $T_1$ values with variation along the column dimension and $T_2$ along the row dimension in a parameter range typically observed in the prostate: $T_1 = 900$ – 2000 ms, $T_2 = 100$ – 300 ms. We acquired 3D DESS and for reference $T_2$ mapping using 2D turbo spin echo with 9 TE values ranging from 12 to 270 ms. We also acquired a $T_1$ map using an inversion recovery turbo spin echo (IR TSE) sequence with 9 IR times ranging from 150 to 6000 ms to evaluate $T_{1,\text{true}}$ vs a global estimate $T_{1,\text{fix}}$ in the fitting algorithm. Other imaging parameters were identical to the volunteer study (Table 1). Quantitative $T_2$ maps were calculated from DESS as described above and from TSE data using a simple exponential fit. Similarly, quantitative $T_1$ was obtained from a simple exponential fit to the IR data. DESS $T_2$ fits were obtained in two ways: 1) using a global estimate for $T_{1,\text{fix}} = 2200 \text{ ms}$ and 2) using a voxel based $T_1$ ($T_{1,\text{true}}$) derived from the IR $T_1$-map. For quantitative evaluation, ROIs were drawn in each tube. Median ROI values for DESS-$T_2$ were compared to TSE-$T_2$. Further, DESS-$T_2$ using $T_{1,\text{fix}}$ vs. a voxel-based $T_1$ map was compared. For repeatability analysis a second DESS-$T_2$ acquisition was obtained 90 minutes later.

**Volunteer Study**

To evaluate prostate DESS $T_2$ mapping in vivo, four healthy male volunteers ($27 \pm 4 \text{ years}$) were scanned. To assess repeatability, three serial 3D DESS acquisitions (TA ~ 1 min each) were acquired. For reference, 2D turbo spin echo (TSE)-$T_2$ mapping was performed over a range of TE values (12 to 160 ms, total TA ~ 9 min). Detailed MR protocol parameters are listed in Table 1. Image analysis was performed in MATLAB.
For quantitative data analysis, ROIs were drawn in prostate peripheral zone (PZ), transition zone (TZ) and muscle (M) on three consecutive central image slices. ROIs were drawn on DESS-T2 maps and copied to TSE-T2 maps. If necessary, i.e. if the volunteer shifted between DESS-T2 and TSE-T2 acquisitions, ROIs were manually adjusted in 2 out of 4 volunteers by 1-2 pixels on TSE-T2 to match DESS-T2 ROI location using anatomical landmarks. Combining ROI data from all four volunteers and three image slices resulted in a total of n = 12 ROIs per zone. Median ROI values were compared between DESS-T2 and TSE-T2. Repeatability was assessed on serial DESS-T2 scans.

**Prostate Cancer Patient Study**

As a clinical proof-of-principle study, 29 consecutive patients (58 ±18 years) were prospectively scanned with DESS after urologist referral for prostate mp-MRI. Men with elevated serum prostate-specific antigen (PSA) were referred for lesion detection prior to biopsy, or active surveillance (in men with biopsy proven low-grade cancer). Patient scans were conducted between June 2014 and March 2015. After obtaining informed consent, patients were scanned using the clinical standard mp-MRI protocol, and the DESS-T2 mapping sequence was added (two serial 3D DESS scans, acquisition time for each scan was 1 min 3 s). In one patient, additionally, a high-resolution 3D DESS acquisition with image resolution matched to clinically acquired 3D T2w TSE was added to show the clinical potential of DESS to replace T2w-MRI. Table 1 lists the detailed MR protocol parameters of sequences relevant for this study. As part of clinical routine in our institute, a board-certified, experienced radiologist (>2000 cases read) identified suspected cancerous lesions on multi-parametric MRI based on criteria employed at our institute for prostate MRI readings (21): For T2-w, ADC and DCE MRI, first an individual score for each of the three modalities ranging from 1-5 was assigned to a suspected MRI lesion (for scoring criteria see supporting Table S1). Finally, the overall suspicion level combining all three modalities was determined by the following formula: weighted average for final score = (2·ADC score + T2w score + DCE score)/4. If the combined score was 3 or greater, the lesion was termed “suspected cancerous lesion”.

For quantitative analysis, suspected cancerous lesion (SL) ROIs were drawn on clinical protocol 3D T₂-w TSE and re-drawn on DESS-T₂ maps matching the spatial ROI shape and location using anatomical landmarks. In addition to the SL ROI, ROIs were also drawn in normal peripheral zone (PZ), transition zone (TZ) and muscle (M). Similar to healthy volunteers, repeatability of the DESS-T₂ maps was also assessed by comparing serial DESS acquisitions. Further, to evaluate the dependence of DESS-T₂ on T₁ variations, DESS-T₂ obtained by using a fixed T₁ estimate (T₁,fix = 2200 ms (20)) in the fitting algorithm was compared to DESS-T₂ using a pixel-based T₁ map (calculated from variable flip angle (VFA) T₁ mapping, MR protocol parameters see Table 1). An additional feature of the DESS acquisition is that by combining the quantitative T₂-map and the DESS-FID acquired image with appropriate weighting factors, “synthetic” T₂-weighted images with any desired contrast weighting (TE_eff) can be calculated:

\[
I_{\text{TE}_{\text{eff}}} = I_{\text{DESS-FID}} \cdot e^{-\left(\frac{\text{TE}_{\text{eff}}}{\text{DESS-T}_2}\right)}
\] (4)

**Statistical Analysis**

All statistical analysis was performed in MATLAB. All ROI results are presented as median ± standard deviation. Pooling ROI results for all volunteers or patients together, the mean ± standard deviation from all median ROI values was used. Linear regression and Pearson’s correlation coefficient ρ was used to 1) compare DESS-T₂ to reference T₂ mapping (TSE), 2) assess repeatability on serial DESS-T₂ acquisitions and 3) evaluate the use of a global T₁ vs. pixel-based T₁ map. Differences between T₂ values in different ROI zones were tested with one-way analysis of variance and zone pairs were compared in a multiple comparison test with Bonferroni correction. A p-value of < 0.05 was considered significant.
RESULTS

Simulations

Our simulations showed that DESS-T2 fitting using a global estimate for $T_1$ and $B_1^+$ is robust in the presence of $T_1$ and $B_1^+$ variations typically observed in prostate MRI. If the true $T_1$ or $B_1^+$ is smaller (larger) than the global $T_1$ or $B_1^+$ estimate, DESS-T2 is under-(over) estimated (Figure 2a, c). The bias in $T_2$, due to $T_1$ or $B_1^+$ variations is more severe for larger $T_2$ (Figure 2b, d). However, results from a recent analysis of $T_1$ and $B_1^+$ in a representative patient population showed that over the whole prostate, $T_1$ variations were within 250 ms and $B_1^+$ variations were within 10% (20). These observed parameter variations for $T_1$ ($B_1^+$) would translate to a bias in DESS-T2 measurements of less than 2% (5%) (indicated by a red box in Figure 2).

Phantom Study

Quantitative IR TSE-$T_1$, TSE-$T_2$ and DESS-$T_2$ maps of the 4x4 $T_1/T_2$ phantom are shown in Figure 3 a-c. As intended by design, $T_1$ in the tubes was approximately constant along rows, but varied along the column dimension and vice versa for $T_2$. Assessing the $T_1$ dependence, phantom experiments confirmed our simulations results that using a fixed $T_1$ resulted in a bias in DESS-$T_2$ estimates (if $T_1$ true (from $T_1$ map) < $T_1$ fix (assumed) resulted in underestimation of DESS-$T_2$). This bias was increased for larger $T_2$ but within only a few percent over typical $T_1$ variations (Figure 3d). ROI analysis showed that DESS-$T_2$ was highly correlated to reference TSE-$T_2$ ($r^2 = 0.99$, p-value < 0.001) over a range of $T_1$ values (Figure 3e). Repeatability for DESS-$T_2$ in a scan-rescan experiment (after 90 min) was excellent ($r^2 = 0.99$, p-value < 0.001) (Figure 3f). The coefficient of variation was slightly higher for DESS-$T_2$ compared to TSE-$T_2$, however the difference was not significant (p-value = 0.23).

Volunteer Study

3D DESS images in a healthy volunteer exhibited distinctly different image contrast in the FID and Echo images (Figure 4a, b). From these images quantitative 3D DESS-$T_2$
maps were obtained (Figure 4c) and compared to reference 2D TSE-T\(_2\) maps (Figure 4d). ROI analysis yielded DESS-T\(_2\) of 115 ± 26 ms (mean ± SD of all volunteer ROI median values) in the PZ and 64 ± 7 ms in the TZ (Table 2, Figure 5a). A high correlation of DESS-T\(_2\) and TSE-T\(_2\) (\(r^2 = 0.88\), p-value < 0.001, Figure 5b) was found. However, DESS-T\(_2\) values were lower compared to TSE-T\(_2\) values. This can be explained by the fact that our TSE-T\(_2\) values were not corrected for contributions from stimulated echoes and achieving flip angles of less than 180° for the refocusing pulses in the multi-echo train. Both effects are known to result in T\(_2\) overestimation on multi-echo based SE T\(_2\) mapping (10). A high correlation of DESS-T\(_2\) on serial scans (\(r^2 = 0.95\), p-value < 0.001, Figure 5c) indicated high repeatability.

Prostate Cancer Patient Study

In 29 scanned patients, 23 suspected cancerous lesions were identified on standard mp-MRI in 17 patients. Only these men were included in further analysis. High-resolution DESS-Echo (Figure 6c) showed very similar T\(_2\)-w contrast compared to clinical standard T\(_2\)-w 2D TSE MRI (Figure 6b). DESS-FID and DESS-Echo images in patients showed clear depiction of morphological prostate zones, such as a distinction of PZ and TZ, on both contrast weightings (Figure 6c-f). These zones were also reflected in quantitative DESS-T\(_2\) maps (Figure 6g). Quantitative ROI analysis yielded DESS-T\(_2\) of 129 ± 39 ms (mean ± SD of all patient ROI median values) in the normal PZ and 83 ± 12 ms in the TZ (Table 2). DESS-T\(_2\) in SL (72 ± 14 ms) was significantly different from normal PZ (p < 0.001, Figure 7a), but not from TZ T\(_2\). DESS-T\(_2\) on serial scans was highly correlated (\(r^2 = 0.79\), p-value < 0.001, Figure 7b), even though the correlation was less than in healthy volunteers. We observed a very high correlation (\(r^2 = 0.99\), p-value < 0.001, Figure 7c) of DESS-T\(_2\) using a fixed T1 estimate (T\(_1\)_fix = 2200 ms) compared to DESS-T\(_2\) using a pixel-based T1-map. From the quantitative DESS-T\(_2\) map, we obtained flexible T\(_2\)-w contrast by calculating “synthetic” T\(_2\)-w images with TE\(_{eff}\) = 100 ms (Figure 6h).
DISCUSSION

Our results demonstrate that 3D quantitative T2 mapping can be performed rapidly in the entire prostate using DESS at 3T with a spatial resolution of 1.1 x 1.1 x 3.5 mm³ in about 1 min. We found a high correlation between DESS-T2 and standard TSE-T2 mapping approaches. There is a clear advantage using DESS with regard to total acquisition time, since a conventional T2 mapping approach required about 9 min scan time.

Quantitative in vivo mapping of T2 relaxation is still a challenge due to long scan durations. Multi-echo based T2 mapping (e.g., TSE) sequences are practical solutions to shorten the scan time, but they can be biased if stimulated echo contributions are not considered in the fitting algorithm and have considerably longer scan time than the DESS approach. Recently, acceleration techniques for multi-echo TSE have been proposed to reduce acquisition time three-fold from ~ 9 min to 2.8 min (22). Agarwal et al, combined k-t-T2 with partial Fourier MRI and SENSE reconstruction to achieve 7.9 fold acceleration to obtain 0.60 mm in-plane 2D T2 maps in a total acquisition time of 5 min 55 s to cover the whole prostate (23). For comparison, using 3D DESS to obtain the same image resolution would require 4 min 46 s without any acceleration techniques. Further, SAR is less of a concern for 3D DESS (FA=30°) compared to SE-type sequences, especially at 3 T.

Even though in this study we found in simulations and in vivo, that the bias in DESS-T2 estimates due to “normal” T1 variations over the prostate is small, this might not be the case for larger T1 variations, for example present in hematoma, i.e. bleeding after biopsy. However, this residual bias can be eliminated by using voxel-based T1 mapping, which is already part of clinical mp-MRI protocols because of its key role for quantitative DCE data analysis.

The prostate can be divided into different anatomical zones, which exhibit distinct tissue properties (24). The noncancerous, noninflamed peripheral zone is characterized by high macromolecular and free water content in luminal space, leading to longer T2. Noncancerous central gland, including the transition zone has often a more heterogeneous appearance, especially when involved by benign prostatic hyperplasia, with overall
shorter T2. This is reflected in our study results. We observed longer T2 in the PZ as compared to the TZ for volunteers and patients using DESS-T2. Further, our results using DESS-T2 (129 ± 39 / 83 ± 12 ms in patient PZ and TZ) were in the same range as previously published T2 values using TSE-T2 mapping approaches at 3T (6,7,23,25,26). In addition, our result for muscle DESS-T2 (38 ± 4 ms) compares well to muscle T2 measured by Stanisz et al (40 ± 4 ms) at 3T (27). Cancerous tissue consists of highly compacted cells resulting in decrease in T2. We found a significantly lower DESS-T2 in suspected cancerous lesions (72 ± 14 ms) as compared to normal PZ tissue. Similarly, decreased T2 in lesions was previously observed using spin echo mapping approaches (6,7,23,26). However, as it was recently pointed out by Langer et al. (28), although T2 may help distinguish dense tumors from normal PZ tissue, bulk T2 of sparse tumors (defined as intermixed prostate cancer with normal tissue) may not be significantly different from surrounding normal tissue. Therefore, the presence of normal PZ components in prostate cancer places inherent limitations on the ability of T2 (and similarly to ADC within the mp-MRI protocol) to fully characterize PZ tumors.

The consensus for clinical prostate MRI interpretation recommends reviewing multi-parametric images in conjunction, including T2-w, diffusion and dynamic contrast enhanced T1-w images (29). The diagnostic performance of this multi-parametric approach may be potentially improved by the addition of a quantitative T2 map. If done correctly, quantitative imaging yields a direct and repeatable assessment of tissue properties. The apparent diffusion coefficient (ADC) obtained from diffusion weighted imaging already adds a quantitative parameter to most clinical prostate MRI protocols and has been proven to be of great value in clinical prostate MRI (7,8,30–32). Quantitative T2 may further enhance conventional multi-parametric quantitative analysis. Recent studies showed that quantitative T2, similar to quantitative ADC, negatively correlated to cell density (12), however to a lesser extent as ADC. Therefore quantitative T2 may facilitate noninvasive assessment of prostate cancer aggressiveness. For example, Wang et al found a correlation between signal intensity on T2-w images with Gleason grade at whole mount pathologic evaluation after radical prostatectomy (33).
Even though the primary objective of this study was to present quantitative $T_2$ mapping, to be clinically relevant, the presented 3D DESS sequence must have potential to replace current $T_2w$ imaging in the standard clinical protocol. This has already been demonstrated in an early study at 1.5 T (34). Also in our study, the “Echo” image showed similar contrast to current $T_2w$ imaging. Further, using the DESS approach, any desired $T_2$ weighted image contrast can be retrospectively reconstructed using the quantitative DESS-$T_2$ map. A potential application of a “tunable” $T_2$ contrast image might be in post-processing algorithms such as automatic segmentation of the prostate as is required for studies comparing imaging results to whole-mount specimen analysis after prostatectomy.

Our study had several limitations. First, we only considered a single $T_2$ component in our analysis. However, recent studies have shown that prostate tissue in healthy volunteers can exhibit at least two $T_2$ components (35,36). DESS-$T_2$ mapping can be extended to a multi-component $T_2$ analysis if multiple DESS acquisitions, are acquired, thereby yielding more than two DESS-images for data fitting. Second, in our study we found significantly different $T_2$ in suspected cancerous lesion compared to PZ $T_2$. This might be important since most cancers are found in the PZ. On the other hand, we did not observe a significantly different mean $T_2$ in lesion compared to $T_2$ in the TZ. However, our patient population was small, potentially too small to lead to significant differences. Wang et al (33) found that lesions in the TZ classified as Gleason grade 3 had a significantly lower $T_2w$ signal intensity ratio than did lesions in the PZ classified as the same Gleason grade. As noted above, TZ prostate tissue appears more heterogeneous which potentially might hinder lesion detection based on quantitative imaging. Third, an important limitation of the DESS approach is the motion sensitivity of the acquisition sequence. This especially affects the “Echo” signal, which is lower in SNR. Our patients received Glucagon injection to reduce bowel movement. DESS $T_2$-mapping could potentially greatly benefit from motion correction techniques. Finally, we did not correlate our quantitative $T_2$ results to histopathology or clinical outcome in this proof-of-principle patient study. This needs to be a topic of future research in large-scale patient studies, which could be accomplished using the fast 3D DESS $T_2$ mapping sequence as an add-on to standard prostate mp-MRI.
CONCLUSION
In conclusion, we have demonstrated that rapid one-minute 3D T₂ mapping of the entire prostate can be performed using DESS at 3T. Our results showed that DESS-T₂ was not sensitive to T₁, B₁⁺ in a range typically observed in the prostate and has excellent repeatability. In an initial proof-of-principle patient study we have shown that DESS-T₂ in suspected cancerous lesions was significantly lower than in normal peripheral zone tissue. Based on our technique, the potential clinical impact of quantitative T₂ needs validation in further large-scale patient studies with multi-reader analysis and cross validation to histopathologic Gleason score and clinical outcomes.

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**Figure 1.** The DESS pulse sequence is a steady-state gradient echo sequence. In each TR two echoes with distinct image contrast are acquired, called the “FID” and the “Echo”. A small spoiler gradient is applied between the FID and Echo signal to suppress banding artifacts.
**Figure 2:** Simulations show that using a fixed $T_1$ estimate ($T_{1,\text{fix}} = 2200$ ms) in the data fitting routine results in $T_2$ under- (over-) estimation ($T_{2,\text{true}} = 150$ ms), if the true $T_1$ is lower (higher) than the $T_1$ estimate (a). If the true $T_1$ deviates from the $T_1$ estimate, the bias observed in the fitted $T_2$-values is larger for increasing $T_2$ (b). Similar observations hold for $B_1^+$ variations (c,d). The simulated bias is within 2% (5%) for variations in $T_1$ ($B_1^+$) typically observed in the prostate (red box).
Figure 3: A phantom with $T_1$ / $T_2$ variations primarily along columns / rows was imaged using 2D Inversion Recovery (IR) turbo spin echo (TSE) $T_1$ mapping (a), 2D TSE-$T_2$ mapping (b) and 3D DESS-$T_2$ mapping (c). Using a fixed $T_1$ estimate ($T_1 = 2200$ ms) in the fitting routine, deviations in fitted $T_2$ values were found that were increased for larger $T_2$, consistent with simulation results (d). DESS-$T_2$ measurements were highly correlated with TSE-$T_2$ ($r^2 = 0.98$) over a range of $T_1$ values, using the $T_1$ map in the fitting routine (e). Scan-scan DESS-$T_2$ measurements showed excellent repeatability (f). The coefficient
of variation (CV) was higher for DESS-T₂ compared to TSE-T₂, however the difference was not significant (p-value = 0.23) (g).

**Figure 4:** Representative DESS images from a healthy volunteer are shown: DESS-FID (a), DESS-Echo (b), DESS-T₂ map (c) and for comparison a TSE-T₂ map (d). DESS-FID and DESS-Echo are displayed at same window level settings. ROIs were drawn for further quantitative data analysis as shown in (a) in the peripheral zone (PZ), transition zone (TZ) and in muscle (M).
Figure 5: Results of quantitative analysis in healthy volunteers. Median T2 values for the different ROI zones are shown for TSE-T2 and 3 consecutive DESS-T2 measurements (scan #1 to #3) (a). DESS-T2 in all zones was significantly different from each other (p-value < 0.001), with larger DESS-T2 in the PZ as compared to TZ. DESS-T2 values (scan #1) were highly correlated with TSE-T2 measurements ($r^2 = 0.88$, p-value < 0.001). Correlation of T2 measurements obtained by two sequential DESS acquisitions was high ($r^2 = 0.95$, p-value < 0.001).
**Figure 6:** Representative DESS images from a prostate cancer patient compared to clinical standard T2-w MRI: 3D T2-w TSE (a) and 2D-TSE T2-w (b) showed very similar T2-w contrast as high-resolution (0.66x0.66x1.5mm³) 3D DESS-Echo (c). Simultaneously acquired high-resolution 3D DESS-FID (d) provided one additional contrast image. For T2-mapping, low-resolution (1.1x1.1x3.5 mm³) 3D DESS-Echo (e) and DESS-FID (f) was fitted to obtain 3D DESS-T2 map (g). DESS-FID and DESS-Echo are displayed at same window level settings. Retrospectively, using the DESS-T2 map and the DESS-FID, 3D T2-w images with desired “effective” TE contrast can be generated: e.g. TE_{eff} = 100 ms (h). A suspected cancerous lesion (indicated by a yellow arrow) identified by a radiologist on the clinical T2-w images (a and b) is visually apparent in DESS images (c-h) and has low T2-values (g). Note that a water excitation only pulse was used in low-resolution DESS (e,f) for fat suppression. For imaging parameters see Table 1.
**Figure 7**: Results of quantitative analysis in prostate cancer patients. Median $T_2$ in SL ROIs was significantly different from PZ ROIs ($p < 0.001$) and but not from ROIs in the TZ (a). ROI $T_2$ values in repeated DESS scans were correlated ($r^2 = 0.79$, $p$-value $< 0.001$ (b)). There were no significant differences in $T_2$ if using a fixed T1 estimate (2200 ms) or a pixel-based T1 map ($r^2 = 0.99$, $p$-value $< 0.001$ (c)).
### TABLES

**Table 1: MR protocol parameters.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient, Volunteer and Phantom: 3D DESS</th>
<th>Patient: high-resolution 3D DESS</th>
<th>Patient: 2D T2w imaging</th>
<th>Patient: 3D T2w imaging</th>
<th>Phantom and Volunteer: 2D T1 mapping</th>
<th>Patient and Volunteer: T1 mapping</th>
<th>Phantom: T1 mapping</th>
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<tr>
<td>Sequence</td>
<td>DESS&lt;sup&gt;a&lt;/sup&gt; (low-res)</td>
<td>DESS (high-res)</td>
<td>T2w -TSE</td>
<td>3D T2w-TSE</td>
<td>T2 –TSE&lt;sup&gt;c&lt;/sup&gt;</td>
<td>T1-VIBE-Dixon&lt;sup&gt;d&lt;/sup&gt;</td>
<td>T1 –TSE&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>2D</td>
<td>3D</td>
<td>2D</td>
<td>3D</td>
<td>2D</td>
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<td>Fat Suppression</td>
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<td>Inversion Recovery Time</td>
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<td></td>
<td></td>
<td>variable&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>170x170</td>
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<td>170x170</td>
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<td>260x260</td>
<td>220x220</td>
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<td>1.1x1.1&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0.66 x 0.66&lt;sup&gt;g&lt;/sup&gt;</td>
<td>0.6x0.6</td>
<td>0.66 x 0.66&lt;sup&gt;g&lt;/sup&gt;</td>
<td>1.1x1.1</td>
<td>1.6x1.6</td>
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<td>461&lt;sup&gt;h&lt;/sup&gt;</td>
<td>651&lt;sup&gt;h&lt;/sup&gt;</td>
<td>328&lt;sup&gt;h&lt;/sup&gt;</td>
<td>192 (phantom), 308&lt;sup&gt;h&lt;/sup&gt; (volunteer)</td>
<td>207&lt;sup&gt;h&lt;/sup&gt;</td>
<td>192</td>
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<td>Parallel Imaging (R)</td>
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<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Slice Thickness [mm]</td>
<td>3.5&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1.5&lt;sup&gt;g&lt;/sup&gt;</td>
<td>3.6</td>
<td>1.5&lt;sup&gt;g&lt;/sup&gt;</td>
<td>3.5</td>
<td>3.6</td>
<td>3.5</td>
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<td>4000</td>
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<td>4000</td>
<td>4.17</td>
<td>10500</td>
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<td>201</td>
<td>variable&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>30</td>
<td>30</td>
<td>160</td>
<td>110</td>
<td>180</td>
<td>variable&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
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<td>Echo Train Length</td>
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<td>25</td>
<td>-</td>
<td>22</td>
<td>2</td>
<td>22</td>
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<td>Bandwidth [Hz/px]</td>
<td>160</td>
<td>160</td>
<td>200</td>
<td>315</td>
<td>130</td>
<td>895</td>
<td>130</td>
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<td>Acquisition Time [min: sec]</td>
<td>1:03</td>
<td>7:26</td>
<td>3:20</td>
<td>7:00</td>
<td>0:31 (phantom), 1:02 (volunteer)</td>
<td>0:35</td>
<td>1:24</td>
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</tbody>
</table>

<sup>a</sup>DESS was acquired 3x (2x) in volunteers (patients) to assess repeatability.

<sup>b</sup>The resolution and FOV coverage of the high-resolution 3D DESS acquisitions were matched to clinically acquired 3D T2w TSE.
cT₂-TSE method for T₂ mapping: Sequence was repeated 9 times with TEs of [12, 25, 37, 61, 74, 09, 111, 135, 160] ms, total time ~ 9 min
dVariable Flip Angle (VFA) method for T₁ mapping: Sequence was repeated 4 times with a flip angle of 2°, 5°, 10° and 15°
eInversion Recovery (IR)-TSE method for T₁ mapping: Sequence was repeated 9 times with inversion times of [50, 100, 150, 300, 500, 1000, 2000, 4000, 6000] ms
fFor low resolution DESS, this is the acquired, raw image resolution, no interpolation.
gFor high resolution DESS, matched to 3D T2-w imaging, this is the interpolated resolution (0.66 x 0.66 x 1.50 mm³); the acquired resolution was (0.74 x 0.66 x 2.25 mm³)
hOversampling along phase-encode (right-left) dimension to avoid fold-over artifacts
Table 2: Quantitative DESS-T₂ values in healthy volunteers and patients (Median ± SD).

<table>
<thead>
<tr>
<th>ROI zone</th>
<th>TSE-T₂ [ms]</th>
<th>SL</th>
<th>PZ</th>
<th>TZ</th>
<th>M</th>
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<tr>
<td>Volunteer</td>
<td>TSE-T₂ [ms]</td>
<td>138 ± 23</td>
<td>92 ± 11</td>
<td>49 ± 5</td>
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<tr>
<td></td>
<td>DESS-T₂ [ms]</td>
<td>115 ± 26</td>
<td>64 ± 7</td>
<td>37 ± 2</td>
<td></td>
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<tr>
<td>Patient</td>
<td>DESS-T₂ [ms]</td>
<td>72 ± 14</td>
<td>129 ± 39</td>
<td>83 ± 12</td>
<td>38 ± 4</td>
</tr>
</tbody>
</table>

a For ROI location see Figure 4 and 6, SL = suspected cancerous lesion, PZ = peripheral zone, TZ = transition zone, M = muscle

b 12 ROIs were analyzed in healthy volunteers (n = 4, 3 image slices each)

c 23 ROIs were analyzed in prostate cancer patients (n = 17 patients, 1 slice per lesion)
Supporting Table S1:

<table>
<thead>
<tr>
<th>Score</th>
<th>T2-w TSE</th>
<th>ADC (x 10^3 mm²/s)</th>
<th>DCE</th>
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<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>&gt; 1.4</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>Faintly decreased signal</td>
<td>1.2 – 1.4</td>
<td>Early or intense enhancement</td>
</tr>
<tr>
<td>3</td>
<td>Distinct low signal</td>
<td>1.0 – 1.2</td>
<td>Early and intense enhancement or early enhancement with washout</td>
</tr>
<tr>
<td>4</td>
<td>Distinct low signal with ill-defined margins</td>
<td>0.8 – 1.0</td>
<td>Early and intense enhancement with washout</td>
</tr>
<tr>
<td>5</td>
<td>Focal low signal with mass effect</td>
<td>&lt; 0.8</td>
<td>Early enhancement is intense with immediate washout</td>
</tr>
</tbody>
</table>

Scoring criteria (1) for multi-parametric prostate MRI at our institution: T2-weighted turbo spin echo (T2-w TSE), apparent diffusion coefficient (ADC) mapping, dynamic contrast enhanced (DCE) MRI. First an individual score for each of the three modalities ranging from 1-5 was assigned to a suspected MRI lesion. The overall suspicion level combining all three modalities was determined by the following formula: weighted average for final score = (2·ADC score + T2w score + DCE score – TZ)/4 where “TZ” is 1 if the lesion lies in the transition zone and 0 otherwise. If the combined score was 3 or greater the lesion was termed “suspected cancerous lesion” and included in study.