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MR measurement of Luminal Water in Prostate Gland: Quantitative correlation between MRI and histology

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Abstract

Purpose—To determine the relationship between parameters measured from luminal water imaging (LWI), a new MRI T₂ mapping technique, and the corresponding tissue composition in prostate.

Material and Methods—17 patients with prostate cancer were examined with a 3D multi-echo spin echo sequence at 3T prior to undergoing radical prostatectomy. Maps of seven MR parameters, called N, T_{2-short}, T_{2-long}, A_{short}, A_{long}, geometric mean T₂ time (gmT₂), and luminal water fraction (LWF), were generated using non-negative least squares (NNLS) analysis of the T₂ decay curves. MR parametric maps were correlated to digitized whole-mount histology sections. Percentage area of tissue components, including luminal space, nuclei, and cytoplasm plus stroma, was measured on the histology sections by using color-based image segmentation. Spearman's rank correlation test was used to evaluate the correlation between MR parameters and the corresponding tissue components, with particular attention paid to the correlation between LWF and percentage area of luminal space.

Results—N, T_{2-short}, A_{long}, gmT₂, and LWF showed significant correlation (P<0.05) with percentage area of luminal space and stroma plus cytoplasm. T_{2-short} and gmT₂ also showed significant correlation (P<0.05) with percentage area of nuclei. Overall, the strongest correlation was observed between LWF and luminal space (Spearman's coefficient of rank correlation=0.75, p < 0.001).

Conclusion—Results of this study show that LWF measured with MRI is strongly correlated to the fractional amount of luminal space in prostatic tissue. This result suggests that LWI can potentially be applied for evaluation of prostatic diseases in which the extent of luminal space differs between normal and abnormal tissues.

Keywords

Prostate; Prostatic luminal space; MR T₂ mapping

Introduction

Multiple studies conducted in the past two decades about determination of T₂ relaxation process have indicated that T₂ decay of various animal and human organs can be best described by multi-exponential model (1–7). While in many cases the precise identification of what causes multi exponential relaxation remains unknown, it has been mainly related to the heterogeneity of microscopic water compartments in the tissue. Several studies have shown that quantitative analyses of multi-exponential T₂ relaxation can provide tissue-specific information for diagnostic applications such as: multiple sclerosis (1–2), and cartilage degeneration in osteoarthritis (4–5).

Luminal water imaging (LWI) is a new application of multi-exponential T₂ mapping that has shown promising results for detection and grading of prostate cancer (8). This technique has been developed based on the assumption that glandular tissue of prostate is composed of water compartments of different sizes associated with multiple T₂ relaxation times. It has been demonstrated that T₂ decay curves obtained from prostate are mainly bi-exponential (9–12). One may expect that the bi-exponential T₂ decay of prostate is composed of one term with a longer T₂ attributed to the water protons residing inside the luminal space and another term with a shorter T₂ attributed to the water protons residing within the epithelial and stromal tissue. In LWI, the fractional amount of long component in the T₂ distribution is represented by a parameter called luminal water fraction (LWF), which should be proportional to the fractional volume of luminal space in prostatic tissue. LWF, and in general all LWI measurements are assumed to be related to the morphology and the composition of the underlying tissue, and may provide useful information for diagnostic purposes.

It has been shown that there are differences in distribution of tissue components between normal prostate and prostate affected by diseases such as prostatic adenocarcinoma (PCa) and benign prostatic hyperplasia (BPH) (13–15). Therefore, identification of the relationships between MR parameters and tissue components, and consequently using MR parameters as a surrogate for measurement of the corresponding tissue components, could be of high importance for disease characterization. Particularly, because the fractional cross sectional area of lumen changes significantly with disease progression in PCa (14), identification of the relationship between LWF and the true fractional amount of luminal space in tissue could potentially contribute to disease assessment and grading of PCa.

This study was conducted to evaluate the correlation between LWF and the percentage area of luminal space in tissue through a direct comparison with histology. It was also aimed at

evaluating the correlation between all other MR parameters, measured with this technique, and the percentage area of tissue components, including luminal space, nuclei, and cytoplasm plus stroma.

Materials and Methods

Patient Selection

This study was approved by the institutional human ethics board, and all patients gave informed consent prior to participating in the study. Seventeen patients with biopsy-proven PCa and scheduled for radical prostatectomy were recruited for this prospective study. Participating patients did not have prior treatment for prostate cancer, nor did have any contraindications to MRI. All patients were examined with MR imaging a few days (median 11 days, range 1–41 days) before undergoing radical prostatectomy.

MR Imaging Protocol

All MRI experiments were carried out on a 3T MR scanner (Achieva 3.0T, Philips Medical Systems, Best, The Netherlands). MR signals were acquired with a combination of an endorectal coil (Medrad, Pittsburgh, PA, USA) and a 6 channel cardiac phased-array coil (Philips Healthcare, Best, The Netherlands). Axial images were acquired by tilting the imaging plane to be perpendicular to the rectal wall-prostate interface. Multi-echo data were acquired by using a 3D multi-echo spin echo pulse sequence with TE = 25 ms, developed at the University of British Columbia MRI Research Centre (16) (TR=3073 msec, number of echoes (NE)=64, FOV=240×240×56mm³, voxel size=1×1×4mm³, scan matrix size=240×119, reconstruction matrix size=240×240, slice thickness=4mm, flip angle=90°, number of averages=1, sense factor=2, scan duration=673 sec). During the protocol development, optimized values of the pulse sequence parameters (NE and TE) were calculated with the aid of simulation to maximize the accuracy of T₂ measurements. More details about these simulations are presented in the next section. In addition to the multi-echo images, a set of high resolution T₂-weighted (T2W) images were acquired, with the same orientation, slice thickness, and slice location as multi-echo images, by using a multi-slice Turbo Spin Echo (TSE) sequence (TR=1851 msec, effective TE=80 msec, FOV=140×140×72mm³, voxel size=0.3×0.3×4mm³, scan matrix size=288×228, reconstruction matrix size=512×512, slice thickness=4mm, flip angle=90°, number of averages=3, scan duration=285 sec).

Simulation

It has been shown in previous simulation studies (7, 17) that variation of TR, TE, NE, and signal to noise ratio (SNR) affects the estimation accuracy of T₂ distributions in multi-component T₂ analyses. In this study, the value of TR (3073 msec) was chosen based on previous literature findings (9) such that T₁ contribution was minimized while still maintaining clinically feasible acquisition times. With this TR value, no further improvement in SNR (average SNR within prostate gland from 17 patients: 103, 81–125 95% CI) was achievable by increasing signal averaging as this would require a total scan time of greater than 25 minutes. Such long scan time was avoided as it is not practical in clinical settings. With the set values for TR and SNR, the impact of variations of NE and TE

on the accuracy of T_2 mappings was investigated during the protocol development in this study.

The dependency of multi-component T_2 analysis on variations of TE and NE was investigated through a number of simulations for different values of $T_{2\text{-short}}$ and $T_{2\text{-long}}$ using an in-house program developed in Matlab (The Math Works Inc., Natick, MA, USA). The values for $T_{2\text{-short}}$ (25, 50, 75 msec) and $T_{2\text{-long}}$ (200, 400, 800 msec) were selected based on previously published values (9–10). Images of simulated T_2 signal, $S_s(t)$, were generated in form of simple squares with 64×64 pixels using the following equation:

$$S_s(t) = S_0 e^{\frac{-t}{T_{2\text{-short}}}} + (S_0 F) e^{\frac{-t}{T_{2\text{-long}}}} \quad [1]$$

where t , time, was varied between TE and $NE \times TE$ with intervals of TE, S_0 , the maximum signal of the short component, was set at 10^4 (in accordance with the signal intensity in our actual scan data), and F , the fractional weighting of the long component, was changed linearly from 0 to 0.2 (which is the range for the lowest fraction of long T_2 observed in prostate (10)) through the field of view.

For each set of $T_{2\text{-short}}$ and $T_{2\text{-long}}$ (9 sets in total), images of simulated T_2 signal, $S_s(t)$, were generated for different combinations of TE and NE. The range of TE (7–55 msec) and NE (10–64) was chosen based on practical values for experimental settings. A white Gaussian noise was added to all simulated images to generate an SNR of 100 in similarity with the SNR of our actual data.

Images of simulated T_2 signal, $S_s(t)$, were fitted to a multi-exponential decay function using software written in Matlab which handles regularized Non-Negative Least Squares (NNLS) (18–19) algorithm. From fittings, maps of $T_{2\text{-short}}$, $T_{2\text{-long}}$, and F were generated. More details about the software and fitting procedure are provided in the Data Processing section below. The optimum values of TE and NE (25 msec, and 64) were determined by comparing the calculated and the actual maps of $T_{2\text{-short}}$, $T_{2\text{-long}}$, and F such that the difference between the calculated and the actual maps were minimized.

Whole-mount Histology and Registration to MR images

After the surgery, the excised specimens were immersed in 10% formalin for a minimum of 48 hours, and then dissected and examined histopathologically in a uniform and consistent manner. The seminal vesicles and vas deferens were amputated, and the remainder of the specimen was cut, perpendicularly to the posterior surface of prostate, into 4 mm transverse slices by using a multi-blade cutting device, developed in-house (20). The entire prostate slices and dissected tissues were sent for histological examination and all slices were stained with hematoxylin and eosin (H & E). Areas of prostate infiltrated by tumor were manually identified and marked by an experienced genitourinary pathologist (E.C.J). All stained slides were then digitized with the SL801 autoloader and Leica SCN400 scanning system (Leica Microsystems; Concord, Ontario, Canada) at magnification equivalent to $\times 40$. The images were subsequently stored in the SlidePath digital imaging hub (DIH; Leica Microsystems) of the Vancouver Prostate Centre. Using DIH software, the high resolution histology sections

were examined by an experienced pathologist (L.F), who outlined the tumors and the border between peripheral zone and central gland and assigned the Gleason scores on each slide.

The digitized whole-mount histology sections were registered to MR images by using a software package developed in-house (21) using Matlab. As described before (21), the registration was carried out in three steps. In the first step, histology images were registered to high resolution T2W images. In the second step, multi-echo images were registered to high resolution T2W images and the inverse function of this transformation was determined. In the last step, the inverse transformation of step two was applied to the registered histology from step one, which generated the histology images that were registered to multi-echo images. This approach resulted in deforming the original ROIs, rather than MRI images, resulting in calculation of the ROI averages from non-deformed parametric maps, ensuring their accuracy. Tumor ROIs were manually drawn on the registered histology images, by accurately overlapping the tumor outlines drawn by the pathologist on the non-deformed histology sections. Non-cancerous ROIs were manually drawn on the registered histology images while avoiding the tumor outlines.

Image Segmentation

Identification of tissue components was performed by use of color-based segmentation using DIH software on H&E stained whole-mount histology sections. As depicted in Figure 1, pixels were categorized as luminal space, nuclei, or cytoplasm plus stroma, based on a manually defined set of training data for each component. Any pixel that was not categorized in any of the above classes by the software was referred to as unclassified. For each ROI, the total number of pixels identified for each component was counted, and the percentage area for each component was calculated as the ratio of the segmented pixels to all ROI pixels.

Data Processing

All MR data were processed offline. For each pixel of the multi-echo MR images, that lied within prostate, signal decay curves were fitted to a multi-exponential decay function. Fitting was performed with a software package developed in-house which handles NNLS algorithm using Matlab. The software made no prior assumption about the number of contributing T_2 components in the multi-exponential decay function, and it decomposed each decay curve into multiple T_2 distributions, $S(T_2)$, with distinct peaks as explained by Bjarnason and Mitchell (18) (see Figure 2). Number of the observed peaks for the T_2 distributions in this study ranged from one to three. Since the majority of T_2 distributions were seen to have two peaks, parameterization of the distributions were performed based on a bi-exponential decay modeling with the following parameters: N , gmT_2 , $T_{2-short}$, T_{2-long} , A_{short} , A_{long} , and luminal water fraction (LWF). N was determined by counting the number of peaks in the distribution. gmT_2 which is the mean T_2 time of the entire distribution on a log scale was calculated as explained previously (18) by the following equation:

$$gmT_2 = \exp \left[\frac{\sum_{T_{2-\min}}^{T_{2-\max}} S(T_2) \log T_2}{\sum_{T_{2-\min}}^{T_{2-\max}} S(T_2)} \right] \quad [2]$$

where $T_{2-\min}$ and $T_{2-\max}$ were set at 20 ms and 2000 ms respectively.

$T_{2-\text{short}}$ and $T_{2-\text{long}}$ were defined as geometric mean T_2 of the short and long T_2 components, and were calculated as:

$$T_{2-\text{short}} = \exp \left[\frac{\sum_{T_{2-\min}}^{T_{2-\text{threshold}}} S(T_2) \log T_2}{\sum_{T_{2-\min}}^{T_{2-\text{threshold}}} S(T_2)} \right] \quad [3]$$

$$T_{2-\text{long}} = \exp \left[\frac{\sum_{T_{2-\text{threshold}}}^{T_{2-\max}} S(T_2) \log T_2}{\sum_{T_{2-\text{threshold}}}^{T_{2-\max}} S(T_2)} \right] \quad [4]$$

Where $T_{2-\text{threshold}}$, which was the cut-off T_2 time between the short and long component, was set at 200 ms, based on a graphical analysis of T_2 distributions. From 4700 pixels with two peaks, the geometric mean T_2 value of the short and long components was calculated without setting a cut-off time. For each of the short and long T_2 components, the number of observations per time bin was counted and the corresponding histogram was plotted (See Figure 3). The plots were then fitted using Matlab, and the crossing point of the fits was chosen as the cut-off value between the short and long T_2 components.

A_{short} and A_{long} , were defined as areas under the short and long components (see Figure 2), and were calculated by summing $S(T_2)$ within the region of $[T_{2-\min} - T_{2-\text{threshold}}]$, and $[T_{2-\text{threshold}} - T_{2-\max}]$ respectively; LWF, defined as ratio of area under the long component over the total area under the entire distribution, is equivalent to area function described by Bjarnason and Mitchell (18) and was calculated as:

$$LWF = \frac{\sum_{T_{2-\text{threshold}}}^{T_{2-\max}} S(T_2)}{\sum_{T_{2-\min}}^{T_{2-\max}} S(T_2)} \quad [5]$$

For T_2 distributions with only one peak ($N=1$), depending on the gmT_2 of the distribution compared to the cut-off T_2 , either the pair of $T_{2-\text{short}}$ and A_{short} or $T_{2-\text{long}}$ and A_{long} were set to zero. T_2 distributions with three peaks ($N=3$) were parameterized bi-exponentially where one peak was considered individually and the other two peaks were averaged geometrically.

Maps of these MR parameters were generated for all slices across the entire prostate. Average values of MR parameters were calculated within a total of 359 (263 normal, and 96 tumor) ROIs manually outlined on the registered whole-mount histology images. ROIs were

defined in six types of tissue: cancerous peripheral (PZ) and transition (TZ) zones, non-cancerous PZ and TZ, Anterior Fibromuscular stroma (AFM), and Periurethral Fibromuscular stroma (PFMS).

Statistical Analysis

All statistical analyses were performed using MedCalc (MedCalc Software, Mariakerke, Belgium). Kolmogorov-Smirnov test showed that none of the MR parameters and percentage area of tissue components were normally distributed. Median and ranges of all MR parameters and percentage area of the tissue components were calculated, with each data point corresponding to an ROI averaged value. It should be noted that as each median value was calculated from a large number of ROI averaged data points, a fraction value was obtained for N, while N calculated for each individual pixel had only an integer value.

For evaluating the correlation between MRI measurements and histology data, the whole data set from the entire prostate, regardless of the malignancy status, was used. The correlations between average values of MR parameters and percentage area of tissue components were evaluated with Spearman's rank correlation test. In all analyses $P < 0.05$ was considered statistically significant. For each of the tissue components, the MR parameter with the highest correlation was identified. Scatter plot of each histology-MRI pair (with strongest correlation) was generated and slopes of the regression lines were calculated.

Results

Clinical data for the 17 patients who participated in this study are summarized in Table 1. Median values and ranges of the percentage area of all tissue components and the MR parameters are summarized in Tables 2 and 3, respectively.

Spearman's rank correlation coefficients between MR parameters and tissue components are presented in Table 4. Five MR parameters ($T_{2\text{-short}}$, $\text{gm}T_2$, A_{long} , LWF, and N) showed significant correlation with percentage area of luminal space and percentage area of cytoplasm plus stroma. Two MR parameters ($T_{2\text{-short}}$, $\text{gm}T_2$) also showed significant correlation with percentage area of nuclei. The overall highest correlation coefficient was obtained between percentage area of luminal space and LWF (Spearman's coefficient: 0.75, $P < 0.001$).

Sample histology section and the corresponding LWF map, presented in Figure 4, show good correspondence between LWF and luminal space identified with histology. The highest correlation coefficient between the percentage area of cytoplasm plus stroma and MR parameters was obtained for $\text{gm}T_2$ (Spearman's coefficient: -0.64 , $P < 0.001$), and for the nuclei was obtained for $T_{2\text{-short}}$ (Spearman's coefficient: 0.33 , $P < 0.001$). Scattered plots of these histology-MR pairs are demonstrated in Figure 5.

Discussion

In this study, we investigated the relationship between MR parameters of LWF and the underlying composition of prostatic tissue through a direct comparison with histology. We were particularly interested to verify and establish if there is any relationship between LWF and percentage area of lumen in prostatic tissue. The median values of $T_{2\text{-short}}$, $T_{2\text{-long}}$, and LWF (75, 503, 0.2 in PZ and 83, 551, 0.14 in TZ) measured in normal tissue in this study are comparable to the values of the corresponding parameters previously measured with bi-exponential analyses by Storås et. al (10). In their study, three median values, corresponding to high, intermediate, and low intensity, were reported for each MR parameter in peripheral zone and central gland. Reported median values in their study are as follows: short T_2 : 73, 69, 66 (msec), long T_2 : 837, 470, 325 (msec), long T_2 signal fraction (%): 54, 29, 26 in peripheral zone, and short T_2 : 64, 61, 61 (msec), long T_2 : 502, 450, 456 (msec), long T_2 signal fraction (%): 28, 21, 12 in central gland. The median and range of LWF values in the entire prostate measured in this study are in good agreement with the previously published values for percentage of lumen in the composition of normal prostatic tissue (13). The median value and range of percentage area of luminal space measured in normal and cancerous tissues in PZ are also in good agreement with previously published data (13). However, median values of percentage area of cytoplasm plus stroma and nuclei measured in this study are lower than published values (13) both in normal PZ (42.9, and 7.5 vs. 54.9, and 14.5) and in cancerous PZ (49.0, and 11.5 vs. 61.1, and 23.7). This underestimation could be due to inaccuracy of the segmentation algorithm, since in the calculation of percentage areas for each ROI, an average of 23% of pixels were unclassified. Because luminal space has a simpler color-based pattern (mostly plain white areas in the histology images) in comparison to the rest of the tissue, it is safe to assume that minimum error had occurred in the calculation of luminal space percentage, and that most of the unclassified pixels belonged to cytoplasm plus stroma or nuclei.

Our correlation analyses showed that LWF is positively and significantly related to the percentage area of luminal space. With the exception of fibromuscular stroma, such strong correlation between LWF and luminal space was present in all types of tissue (data not shown).

The slope of the regression line obtained from plot of LWF vs. fractional amount of luminal space was equal to 0.45, rather than 1. This observation implies that LWF, while proportional to the fractional volume of luminal space, is not identical to this histological measure. Several factors could have potentially contributed to this discrepancy between LWF and the fractional volume of luminal space measured with histology. Firstly, LWF measured in this study is likely to be weighted by proton density and T_1 values. In addition, we compared the 2D percentage area of lumen to the 3D fractional volume of the luminal water. Since the glands are ellipsoids, rather than elliptical cylinders aligned in the axial direction, the area of lumen is not linearly proportional to its volume. Simple comparison between the volumes of ellipsoids and elliptical cylinders suggests that the 2D percentage area of luminal space, measured with histology, overestimates the luminal volume by as much as 33%. In reality, this effect is expected to be less than 33%, taking in to account that the glands are not perfect ellipsoids and are not necessarily aligned in the axial direction.

Another contributing factor to be considered is morphological differences between in vivo prostate, imaged with MRI, and excised, fixed prostate, analysed with histology. However, this could make justification of the observed discrepancy even harder. That is because histological processing involves heat-induced dehydration during which the water content is removed. Water-filled cavities are therefore more prone to shrinkage than stromal tissues. Consequently, tissue shrinkage may be non-uniform (22–23). Therefore, luminal space and the luminal water fraction may be smaller in whole-mount histology than in vivo. Although, it is worth to notice that the slopes of the regression lines varied very little between different types of tissue (data not shown), suggesting that the tissue composition is likely not the reason for the LWF underestimating the luminal space. Presumably a systematic error in the histology segmentation procedure resulting in an overall overestimation of percentage area of luminal space might have also been a contributing factor. Finally, water exchange between different compartments within prostatic tissue (e.g. intra-/extra-cellular vs. luminal water) might have resulted in LWF underestimating the volume of luminal space. Determination of the true relationship between LWF and the amount of lumen in prostatic tissue is not trivial and requires further investigations.

The main limitation of this study was related to the segmentation procedure. The software that has been used in this study was not capable of differentiating loose stroma from the epithelial cytoplasm. Therefore, stroma and epithelial cytoplasm were combined into one tissue component in this study. However, according to Langer et al. (13), in cancer there is an increase in percentage area of cytoplasm, and hence in our study measuring the percentage of cytoplasm separate from stroma would be very informative and useful. In order to more accurately investigate the relationship between MR measurements of LWI and percentage area of cytoplasm, a prospective study with a more accurate segmentation algorithm, or better staining techniques, and higher number of patients is required. Another limitation to be noted here is related to the scan time. The relatively long scan time (11 min) of this technique increases the chance of patients' movement during the scan. This may result in a mismatch of data in signal decay curves and consequently the uncertainty of data fitting procedure can be increased. Therefore, a potential future work is to reduce the total scan time of this technique.

The results of this pilot study demonstrate that LWF measured with MRI is significantly correlated with the percentage area of luminal space in the prostatic tissue. This is an important finding, considering that in PCa the amount of luminal space correlates directly to Gleason grade, which is the key prognostic marker. With higher Gleason grade, the glands first coalesce and then disappear in solid sheets of cells (24). Therefore, LWF could potentially differentiate the aggressive forms of PCa from the more biologically benign.

In conclusion, the methodology established for measuring LWF can potentially be used as a surrogate for measurement of fractional amount of lumen in diagnosing various prostatic diseases in which the amounts of lumen differs between normal and abnormal tissues.

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Figure 1. Representative example of segmentation of whole mount histologic images. a) A magnified (20 $\times$) H&E-stained histology section; b) Tissue components are segmented into cytoplasm plus stroma (blue), lumen (yellow), and nuclei (orange).

Figure 2.

H&E-stained histology sections (20×) (top row) and corresponding T₂ distributions (bottom row) obtained from NNLS fitting of multi-exponential T₂ decay curves generated from a single pixel in: a) Gleason 4+4 tumor in peripheral zone (PZ), b) Gleason 3+4 tumor in PZ, and c) normal tissue in PZ. It can be seen that with the progression of malignancy, the fractional amount of luminal space decreases, and so does the area under the second peak, produced by the long T₂ component. While in normal tissue (c) there are two distinct peaks (N=2), in low grade tumor (b) the contribution of the second peak is lessened, and in high grade tumor (a) the second peak is totally absent (N=1).

Figure 3.

Histogram of $T_{2\text{-short}}$ (blue) and $T_{2\text{-long}}$ (orange) for 4700 pixels. Time-axis is shown in logarithmic scale. The solid lines represent the best fit to the data, described in terms of double Gaussian functions ($f(x) = a_1 \times \exp(-((x-b_1)/c_1)^2) + a_2 \times \exp(-((x-b_2)/c_2)^2)$) with the following parameters: $a_1 = 59.89$, $b_1 = 121.8$, $c_1 = 15.21$, $a_2 = 375.8$, $b_2 = 122.2$, $c_2 = 43.29$, and $a_1 = 149$, $b_1 = 597.1$, $c_1 = 181.5$, $a_2 = 167.2$, $b_2 = 943.4$, $c_2 = 442.5$ for $T_{2\text{-short}}$ (dark blue) and $T_{2\text{-long}}$ (red) respectively.

Figure 4. Sample H&E-stained whole-mount histology sections (a,b), with the corresponding LWF map (c), and high resolution T2W image of the same slice (d). In figure (a), color-based segmentation algorithm was applied only for identification of luminal space (shown in green). Notice good correspondence between LWF values (c) and the amount of luminal space (a).

Figure 5.

Regression results and scatter plots of: a) LWF versus percentage area of luminal space (regression line: $y = 0.45x + 0.03$, $P < 0.001$), b) gmT₂ versus percentage area of cytoplasm plus stroma (regression line: $y = -0.2x + 0.19$, $P < 0.001$), and c) T_{2-short} versus percentage area of nuclei (regression line: $y = 0.1x + 0.079$, $P < 0.001$). Each data point on graphs represents average value of MR parameter and corresponding percentage area value for a chosen ROI.

Table 1

Clinical data of 17 patients participating in the study.

Characteristic	Value
Median and range of patient age (y)	66.4 (58–80.3)
Median and range of pre-op *PSA level (ng/mL)	7.9 (1.4–31.6)
Pathologic tumor stage	
pT2a	1
pT2c	4
pT3a	11
pT3b	1
Number of cancerous *ROIs	
*GS=(3+3)	18
GS=(3+4)	24
GS=(4+3)	28
GS=(4+4)	11
GS=(4+5)	8
GS=(5+3)	3
GS=(5+4)	1
GS=(5+5)	3

*PSA = Prostate-specific antigen

*GS = Gleason score

*ROI = Region of interest

Table 2

Percentage area (median values, with ranges in parentheses) of tissue components in different regions derived from histology.

Tissue Component	Non-cancerous *PZ	Non-cancerous *TZ	Normal *AFM	Normal *PFMS	Cancer PZ	Cancer TZ
Luminal space	27.2 ^{a,b,c,d} (13.7–65.4)	33.9 ^{a, b, c, d} (7.2–64.0)	4.8 ^{c, d, e, f} (1.1–21.5)	3.7 ^{c, d, e, f} (0.7–15.6)	11.6 ^{a, b, e, f} (2.8–31.1)	10.8 ^{a, b, e, f} (2.4–26.9)
Cytoplasm plus stroma	42.9 ^{a, b} (5.9–63.2)	40.7 ^{a, b, c} (7.7–63.6)	78.0 ^{c, d, e, f} (34.3–86.3)	68.3 ^{c, d, e, f} (50.8–81.6)	49.0 ^{a, b, f} (21.6–63.2)	47.4 ^{a, b} (23.1–67.2)
Nuclei	7.5 ^{a, b, c, d} (2.3–28.9)	7.3 ^{a, b, c, d} (2.4–18.3)	2.4 ^{c, d, e, f} (1.4–7.6)	4.1 ^{c, d, e, f} (1.5–20.6)	11.5 ^{a, b, e, f} (3.8–38.4)	12.0 ^{a, b, e, f} (6.4–38.4)

*PZ= Peripheral zone, *TZ= Transition zone, *AFM= Anterior Fibromuscular stroma, *PFMS= and Periurethral Fibromuscular stroma.

^aSignificantly different than normal AFM (P<0.01).

^bSignificantly different than normal PFM (P<0.01).

^cSignificantly different than cancer PZ (P<0.01).

^dSignificantly different than cancer TZ (P<0.01).

^eSignificantly different than non-cancerous PZ (P<0.01).

^fSignificantly different than non-cancerous TZ (P<0.01).

Table 3

Average values (median values, with ranges in parentheses) of LWI parameters in cancer and normal tissue in different regions.

MR Measurement	Non-cancerous *PZ	Non-cancerous *TZ	Normal *AFM	Normal *PFMS	Cancer PZ	Cancer TZ
T ₂ -short (msec)	75 ^{a, b, c} (50–152)	83 ^{a, b, c} (49–176)	64 ^{c, d, e, f} (32–80)	69 ^{e, f} (40–111)	72 ^{a, e, f} (25–116)	83 ^a (36–108)
T ₂ -long (msec)	503 ^{a, b, d} (249–904)	551 ^{b, d} (283–948)	617 ^{c, e} (348–1074)	726 ^{c, e, f} (306–1300)	507 ^{a, b, d} (290–923)	722 ^{c, e, f} (249–1135)
gmT ₂ (msec)	114 ^{a, b, c, d} (58–295)	107 ^{a, b, c, d} (57–237)	66 ^{c, d, e, f} (36–86)	74 ^{e, f} (41–120)	84 ^{a, e, f} (30–139)	89 ^{a, e, f} (41–120)
LWF	0.20 ^{a, b, c, d, f} (0.03–0.50)	0.14 ^{a, b, c, d, e} (0.02–0.40)	0.03 ^{c, e, f} (0.02–0.11)	0.03 ^{c, e, f} (0.00–0.13)	0.07 ^{a, b, d, e, f} (0.01–0.18)	0.04 ^{c, e, f} (0.00–0.12)
A _{short} (×105)	159 ^{a, c} (98–290)	164 ^{a, c} (109–268)	138 ^{c, d, e, f} (84–198)	162 ^c (111–211)	185 ^{a, b, c, f} (64–300)	170 ^a (96–219)
A _{long} (×105)	39.2 ^{a, b, c, d, f} (8.0–116.0)	28.2 ^{a, b, c, d, e} (3.5–112.7)	4.3 ^{c, e, f} (2.4–14.6)	5.8 ^{c, e, f} (0.2–26.1)	14.1 ^{a, b, d, e, f} (1.9–59.8)	6.7 ^{c, e, f} (0.1–22.0)
N	2.00 ^{a, b, c, d, f} (1.22–2.47)	1.90 ^{a, b, c, d, e} (1.27–2.61)	1.55 ^{c, e, f} (1.03–2.02)	1.44 ^{c, e, f} (1.01–2.09)	1.82 ^{a, b, e, f} (1.15–2.22)	1.70 ^{e, f} (1.08–2.13)

*PZ= Peripheral zone, *TZ= Transition zone, *AFM= Anterior Fibromuscular stroma, *PFMS= and Periurethral Fibromuscular stroma.

^aSignificantly different than normal AFM (P<0.01).

^bSignificantly different than normal PFM (P<0.01).

^cSignificantly different than cancer PZ (P<0.01).

^dSignificantly different than cancer TZ (P<0.01).

^eSignificantly different than non-cancerous PZ (P<0.01).

^fSignificantly different than non-cancerous TZ (P<0.01).

Table 4

Spearman's rank correlation coefficient (ρ), with 95% confidence intervals in parentheses, between MR measurements and the percentage area of tissue components.

MR Measurement	Luminal Space	Cytoplasm plus stroma	Nuclei
T ₂ -short	0.42 (0.33 to 0.50) P<0.001	-0.50 (-0.57 to -0.42) P<0.001	0.33 (0.23 to 0.42) P<0.001
T ₂ -long	-0.13 (-0.23 to -0.03) P=0.01	0.03 (-0.07 to 0.13) P=0.58	0.06 (-0.05 to 0.16) P=0.27
gmT ₂	0.69 (0.64 to 0.74) P<0.001	-0.64 (-0.70 to -0.58) P<0.001	0.26 (0.16 to 0.35) P<0.001
LWF	0.75 (0.70 to 0.79) P<0.001	-0.52 (-0.59 to -0.44) P<0.001	0.02 (-0.09 to 0.12) P=0.77
A _{short}	-0.11 (-0.26 to -0.01) P=0.03	-0.04 (-0.14 to 0.06) P=0.44	0.13 (0.02 to 0.23) P=0.02
A _{long}	0.71 (0.65 to 0.76) P<0.001	-0.51 (-0.58 to -0.43) P<0.001	0.04 (-0.07 to 0.14) P=0.47
N	0.43 (0.34 to 0.51) P<0.001	-0.26 (-0.35 to -0.16) P<0.001	0.03 (-0.07 to 0.13) P=0.58