



Magnetic resonance fingerprinting based comprehensive quantification of T1 and T2 values of the background prostatic peripheral zone: Correlation with clinical and demographic features

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ABSTRACT

Purpose: To quantify and assess the distribution of MR fingerprinting (MRF)-derived T1 and T2 values of the whole prostatic peripheral zone (PZ), and perform subgroup analyses according to clinical and demographic features.

Method: One hundred and twenty-four patients with prostate MR exams and MRF-based T1 and T2 maps of the prostatic apex, mid gland, and base were identified from our database and included. Regions of interest encompassing the right and left lobes of the PZ were drawn for each axial slice on the T2 map and copied to the T1 map. Clinical data were obtained from medical records. Kruskal-Wallis test was used for assessing differences between subgroups and the Spearman coefficient was used for assessing any correlations.

Results: Mean T1 and T2 values were 1941 and 88 ms, respectively, for the whole-gland, 1884 and 83 ms for the apex, 1974 and 92 ms for the mid-gland, 1966 and 88 ms for the base. T1 values were weakly negatively correlated with PSA values, while T1 and T2 values were weakly positively correlated with prostate weight and moderately positively correlated with PZ width. Finally, patients with PI-RADS 1 scores had higher T1 and T2 values of the whole PZ, compared with those with scores 2–5.

Conclusion: Mean T1 and T2 values of the background PZ of the whole gland were 1941 ± 313 and 88 ± 39 ms, respectively. Among clinical and demographic factors, there was a significant positive correlation between T1 and T2 values and PZ width.

1. Introduction

Prostate cancer (PCa) is the second most common malignancy in men, with an estimated 1.4 million new cases and over 375,000 deaths annually worldwide [1]. Multiparametric magnetic resonance imaging (MRI) has emerged as a crucial tool for the detection, localization, and evaluation of PCa, and is endorsed by worldwide guidelines [2–6].

The prostate is usually divided into four zones: the peripheral zone (PZ), central zone, transition zone, and anterior fibromuscular stroma [7,8]. Over 70 % of detected clinically significant PCa (csPCa) is located in the PZ, and the MRI appearance is commonly described as a discrete hypointense lesion on T2-weighted images (T2WI), contrasting with a predominantly homogeneous T2-hyperintense background [8,9].

However, in real-world scenarios, it is much more common to observe background signal changes that appear as a diffusely T2-hypointense PZ or a multitude of heterogeneous T2-hypointense areas in the PZ [10]. Those heterogeneous confounders include, among others, age-related changes, chronic and acute prostatitis, atrophy/scar tissue, post-biopsy and post-radiation changes, and effects of hormones or other drugs, although 5-alpha-reductase inhibitors in special do not seem to affect lesion conspicuity on T2WI [11–13]. Importantly, previous studies showed that prominent background signal changes were associated with higher odds for a false negative PI-RADS 1 MRI [14], lower MRI sensitivity to detect csPCa [15] and lower concordance between MRI and biopsy findings for csPCa [16]. Nonetheless, to this date, studies on this topic were based on qualitative scoring methods, with only moderate

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interobserver reproducibility [10,15]. Therefore, quantitative assessment of the background PZ may add value for a better accuracy in biopsy decision making and better concordance with biopsy findings, with better reproducibility and granularity compared to traditional qualitative methods.

MR Fingerprinting (MRF) is an MRI quantification technique that has been validated in both phantom and human-based studies. Importantly, MRF was shown to be capable of differentiating csPCa from non-cancer lesions in both the PZ and transition zone, when combined with apparent diffusion coefficients [17–19]. However, previous studies did not allow for a comprehensive assessment of the PZ background, as the reported T1 and T2 values of the PZ related to only small and predefined regions of interest (ROIs) of T2-hyperintense normal-appearing PZ, which did not capture the heterogeneity of the whole PZ background compartment [18,19]. Therefore, the goal of our study is to quantify and assess the distribution of MRF-derived T1 and T2 values of the whole PZ and perform subgroup analyses according to clinical and demographic features.

2. Materials and methods

2.1. Study population

This HIPAA-compliant retrospective study was performed under approval by the local Institutional Review Board, with a waiver for the need of obtaining informed consent.

A retrospective search was performed on our institutional database for consecutive patients that underwent a PI-RADS v2.1 compliant prostate MRI, and MRF-based T1 and T2 maps including the apex, mid gland, and base from October 2017 to June 2019. Those patients were referred to a clinical MRI due to elevated prostate-specific antigen (PSA), including biopsy-naïve patients ($n = 57$) and those with one or more prior biopsies ($n = 66$, at least 8 weeks before the MRI examination). Demographic and clinical data were obtained from the electronic medical record whenever available, including age, race/ethnicity, patient weight, PSA levels, prostate weight, and the PI-RADS scores from the MRI reports. Of note, the PI-RADS component of the assessment included only information related to the PZ, and 21 patients with transition zone focal lesions were excluded from this sub-analysis. Data about biopsy status and ethnicity was not available for one patient, while PSA values were missing for 14 patients.

2.2. Magnetic resonance imaging

The MRI exams were obtained on three 3 T scanners (Scanner 1: Magnetom Verio, Siemens Healthineers, Scanner 2: Magnetom Verio, Siemens Healthineers and Scanner 3: Magnetom Skyra, Siemens Healthineers), using standard body and spine array coils for both standard MRI and MRF acquisitions, in compliance with PI-RADS v2.1 guidelines. These included high-resolution multiplanar T2WI (FOV: 16 cm, slice thickness: 3.0 mm), diffusion-weighted imaging (FOV: 24 cm, slice thickness: 3.0 mm, b-values: 50, 500, 1000, 1400 s/mm²) and dynamic contrast enhancement assessment (8 s per phase, 3:00 min total running time). For the current study, only the T2WI axial images were analysed in combination with MRF data. MRF images were obtained through a FISP-MRF sequence, as illustrated in the literature [20]. Three axial images representative of the apex, mid-gland, and base were obtained and analysed per patient, matching the position of axial T2WI slices as much as possible. The imaging parameters included: matrix size: 400x400; FOV: 40x40 cm²; TR: 13–15 ms; flip angle: 5–75°; slice thickness: 6 mm. The acquisition time for each 2D MRF slice was ~40 sec. To extract quantitative tissue properties from the MRF data, an MRF dictionary was generated for the T1 range of 20–2950 ms and the T2 range of 9–500 ms, and pattern matching was performed using MATLAB (MathWorks, Natick, MA). Fully quantitative T1 and T2 maps were generated as a result of this post-processing.

2.3. Image analysis

All studies were reviewed and annotated by one radiologist with 14 years of experience in prostate imaging (L.K.B.). The T1 and T2 maps were used for annotation, in correlation with available axial T2WI. Two ROIs, encompassing the whole visualized right and left lobes of the PZ, were manually annotated per axial slice on the T2 map, and automatically copied to the T1 map. Thus, a total of six T1 and six T2 ROIs were generated per patient. Care was taken to include the whole visible PZ on each lobe/slice while excluding from the ROIs any evident PI-RADS ≥ 3 focal lesions mentioned on the original reports and visualized on T2WI. Each ROI provided means of T1 and T2 values (in ms), as well as standard deviations (SD), which were recorded. For each patient, the whole gland PZ T1 and T2 values were obtained by averaging out all of the 6 available ROIs on each map. Finally, the PZ width, also referred as PZ thickness, was measured as the maximum PZ width in 3 representative slices of the apex, mid gland, and base on T2WI, and then averaged for further analysis as an additional variable. Fig. 1 exemplifies the annotation methods above in patients with and without a visible lesion.

2.4. Statistical analysis

Statistical analysis was performed using SPSS statistical analysis software (IBM). Continuous variables were expressed as mean and SD. Clinical variables including prostate weight, PSA values, biopsy status, average PZ width, patient age, patient weight, race/ethnicity, and PI-RADS score of the original MRI report were categorized into subgroups. The whole PZ background mean T1 and T2 values were presented on histograms, with the SD recorded. Kruskal-Wallis test was used to test for significant differences between groups. Pairwise comparisons were done using the Dunn's post hoc test and significance values were adjusted by the Bonferroni correction for multiple tests. The Spearman coefficient was used for assessing the correlation between continuous variables and T1 and T2 values. A linear regression test was used to estimate the relationship between PZ width and T1 and T2 values. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Study population

A total of 129 patients were identified through the retrospective search. Three patients were excluded due to the presence of significant motion artefacts in their MRI, while two MRIs were excluded to avoid duplication, as the respective patient had been included in this study with a previous MRI scan. This resulted in a sample size of 124 patients, with a mean age of 64.80 ± 7.70 years, body mass index of 29.4 ± 5.0 kg/m², PSA level of 8.04 ± 6.31 ng/mL, and prostate weight of 57.60 ± 35.80 g. Seventy-nine percent were Caucasian, 17 % were African American, 2 % were Hispanic, 1 % Asian, and 1 % unknown. The distribution of the remaining clinical and demographic features can be found in Tables 1 and 2.

3.2. T1 relaxation time

The mean T1 value of the whole PZ background was 1941 ± 313 ms, and the T1 distribution is detailed in Fig. 2A. Mean T1 values were similar among the 3 scanners used in this study (Scanner 1: 1926 ± 328 ms; Scanner 2: 1991 ± 202 ms; Scanner 3: 1949 ± 325 ms; $p = 0.65$). There was a significant difference between mean T1 values of the PZ background of the base of the gland, mid-gland, and the apex compared with the average T1 value of the whole PZ (1966 ± 338 ms; 1974 ± 335 ms and 1884 ± 317 ms, respectively, $p < 0.01$ for all comparisons) (Fig. 3A). However, the percentage difference between the mean T1 values of these segments and the whole PZ was 1.25 % for the base, 1.68 % for the mid-gland, and 3 % for the apex. Moreover, considering the

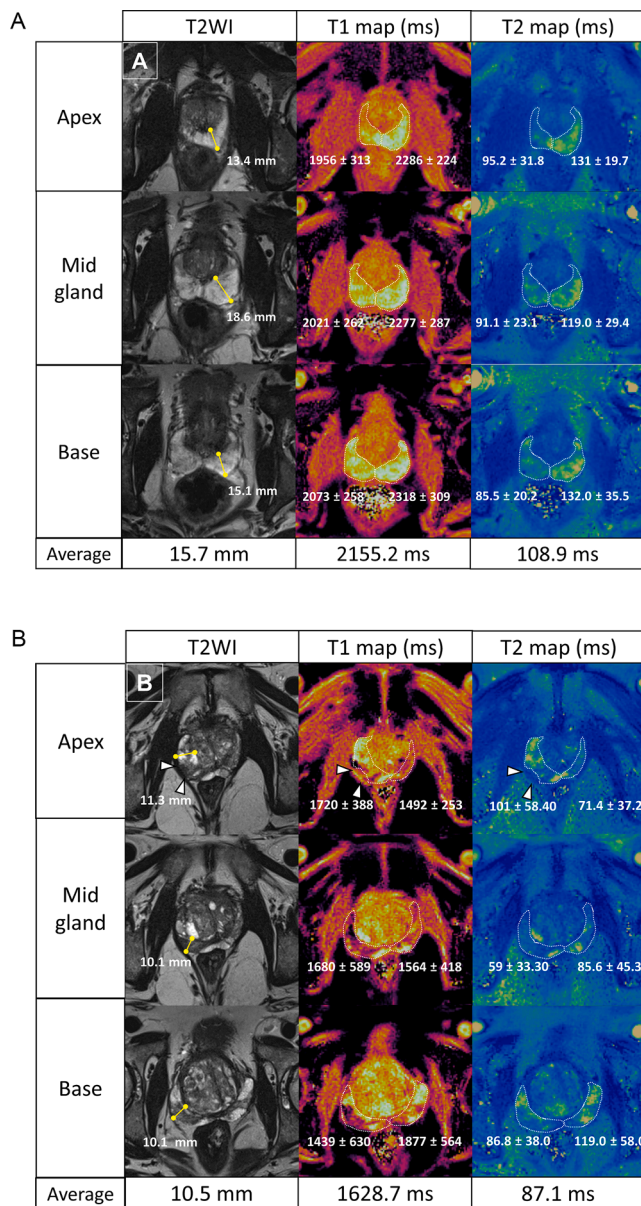


Fig. 1. A (Coloured). Annotation of ROIs of the background PZ and measurement of PZ width in a patient without a focal suspicious lesion. Peripheral zone width was measured as the largest radial width of the background PZ on the apex, mid-gland, and base of the prostate, on axial T2-weighted images. Those 3 measurements were then averaged out for analysis in the study as the average PZ width (bottom row). Two regions of interest encompassing respectively the right and left lobes of the background peripheral zone were manually drawn per axial slice on the MRF-T2 map (white dotted lines in the third column) and copied to the corresponding MRF-T1 maps (white dotted lines in the second column). This was done in representative slices of the apex, mid gland, and base, and the resulting 6 ROIs for both T1 and T2 were then averaged out to compose the average T1 and T2 values of the whole peripheral zone (bottom row). MRF: MR fingerprinting; PZ: peripheral zone; ROI: region of interest. (B) (Coloured). Annotation of ROIs of the background PZ and measurement of PZ width in a patient with a focal suspicious lesion. This figure illustrates the annotation in a patient with a suspicious lesion (arrowheads), which was excluded from the ROI segmentation. PZ: peripheral zone; ROI: region of interest.

three slices/segments, there was only a significant ($p < 0.01$) pairwise difference between the T1 values of the apex-mid gland and apex-base pairs.

There was a significant difference in mean T1 values among the PZ

width groups, with higher T1 values noted with larger PZ width categories ($p < 0.01$) (Fig. 4A). There was also a moderate correlation of T1 values with the continuous variable of PZ width (Spearman's $\rho = 0.44$, $p < 0.01$). In a regression analysis, each mm unit increase in the average PZ width was associated with a 56.9 ms increase in the mean T1 value of the whole gland. Patients with PI-RADS 1 scores had higher T1 values than other PI-RADS scores at pairwise comparisons ($p < 0.01$ for all comparisons) (Fig. 5A), but there was no significant difference in the background PZ T1 values among the remaining patients with PI-RADS 2–5 scores. T1 values were not significantly different between PSA groups, although they were weakly negatively correlated with continuous PSA values (Spearman's $\rho = -0.19$, $p = 0.04$). T1 values were weakly correlated with continuous prostate weight (Spearman's $\rho = 0.18$, $p = 0.04$), but showed no significant difference among weight groups. Finally, there was no significant difference in T1 values between classes of biopsy status, age, patient weight, and ethnicity, nor correlation with the continuous variables of age and patient weight. Average T1 values for the whole PZ background, apex, mid-gland, and base and their correlation with clinical and demographic features are detailed in Table 1.

3.3. T2 relaxation time

The mean T2 value of the whole PZ background was 88 ± 39 ms, and the distribution of mean T2 values of the whole PZ background is detailed in Fig. 2B. Mean T2 values were similar among the three scanners used in this study (Scanner 1: 93 ± 38 ms; Scanner 2: 80 ± 22 ms; Scanner 3: 82 ± 44 ms; $p = 0.06$). There was a significant difference between mean T2 values of the PZ background of the base of the gland, mid-gland, and the apex compared with the whole PZ (88 ± 46 ms; 92 ± 40 ms and 83 ± 35 ms, respectively, p -value < 0.01 for all comparisons) (Fig. 3B). However, the percentage difference between the mean T2 values of segments and the whole PZ was 0.54 % for the base, 4.39 % for the mid-gland, and 5.18 % for the apex. Further, among the three slices/segments, there was only a significant ($p < 0.02$) pairwise difference between the T2 values of the apex-mid gland and apex-base pairs.

There was a significant difference in mean T2 values among the PZ width groups, with higher T2 values noted with larger PZ width categories ($p = 0.01$) (Fig. 4B). There was also a moderate correlation of T2 values with the continuous variable of PZ width (Spearman's $\rho = 0.36$, $p < 0.01$). Notably, each mm unit increase in the average PZ width was associated with a 6.20 ms increase in the T2 value for the whole PZ. There was no significant difference between mean T2 values and prostate weight groups, but T2 values were weakly positively correlated with prostate weight (Spearman's $\rho = 0.20$, $p = 0.03$). Similarly to the T1 analysis above, patients with PI-RADS 1 scores had higher T2 values than other PI-RADS scores at pair-wise comparisons ($p < 0.01$ for all comparisons) (Fig. 5B), but there was no significant difference in the PZ background T2 values among patients with PI-RADS 2–5 scores. Additionally, mean T2 values did not differ among PSA, biopsy status, age, patient weight, and ethnic groups and had no correlation with the continuous variables of PSA, age, and patient weight. Average T2 values for the PZ background of the whole gland, apex, mid-gland, and base and their correlation with clinical and demographic features are described in Table 2.

4. Discussion

To the best of our knowledge, this is the first study to comprehensively assess the T1 and T2 values of the whole PZ background with its different segments, using MRF and correlating those with clinical and demographic features. Mean T1 and T2 values were, respectively, 1941 ms and 88 ms for the whole PZ, with variations of up to 3 % between the whole PZ and prostatic base, mid gland or apex alone on T1 measurements, and of up to 5.18 % on T2 measurements. Furthermore, the range

Table 1

Average T1 values of the background peripheral zone of the whole gland and stratified by segment and clinical features.

Feature	N	Average T1 (ms)	SD T1	P-value for Difference	Correlation	P-value for Correlation
Whole Gland	124	1941	313			
Apex	124	1884	317	<0.01	–	–
Mid Gland	124	1974	335	<0.01		
Base	124	1966	338	<0.01		
Prostate Weight (g)	124			0.17	0.18	0.04
<25 g	8	1861	232			
25–45	50	1874	276			
45–65	27	2048	352			
65–85	22	1942	329			
>85 g	17	2006	338			
PSA values (ng/mL)				0.33	– 0.19	0.04
<2.5	8	2144	376			
2.5–4.0	12	2007	197			
4.0–10.0	65	1949	337			
>10	25	1876	280			
Biopsy Status				0.77	–	–
Biopsy Naive	57	1958	324			
Previous biopsy	66	1933	304			
PZ Width (mm)				<0.01	0.44	<0.01
<6.0	3	1690	182			
6.0–9.0	34	1848	243			
9.0–12.0	52	1920	279			
12.0–15.0	25	2138	356			
>15.0	4	2340	125			
Age (Years)				0.51	– 0.11	0.24
<50	4	1868	400			
50–60	27	2010	311			
60–70	62	1920	301			
70–80	29	1945	343			
>80	2	1773	65			
Patient Weight (kg)			0.95	0.02	0.82	
<70	9	1948	185			
70–90	50	1930	304			
90–110	47	1973	337			
110–130	13	1936	388			
>130	5	1908	190			
Ethnicity				0.47	–	–
Caucasian	98	1948	287			
African American	21	1972	416			
Hispanic	3	1739	320			
Asian	1	1631	–			
Other	0	–	–			
PI-RADS				0.02	– 0.27	<0.01
1	3	2557	263			
2	67	1971	287			
3	4	1716	405			
4	15	1864	269			
5	14	1847	297			

N - number; PI-RADS - Prostate Imaging Reporting and Data System; PSA - Prostate-Specific Antigen; PZ – peripheral zone; SD – standard deviation.

of T1 and T2 values obtained by the MRF technique was robust among the three scanners used in this study. Patients with PI-RADS 1 scores showed overall higher T1 and T2 values than other PI-RADS scores, whereas no significant difference was found in T1 and T2 values of the PZ background among patients with PI-RADS scores from 2 to 5 for PZ lesions.

Unlike previous studies that reported T1 and T2 values from limited and pre-selected ROIs [18,19], this study used large ROIs encompassing the entire PZ regions for a representative slice at each level, which provided a robust and comprehensive assessment of T1 and T2 values for the whole PZ and its segments, especially accounting for the heterogeneity of the PZ background. Previous MRF investigations using 3 T MRI scanners reported normal-appearing PZ mean T1 values ranging from 1875.7 to 2367 ms and mean T2 values varying from 95 to 598.2 ms [17–19,21–23], as detailed in Table 3. Significantly, the mean T1 value found in our study (1941 ms) was similar to the one reported by Han et al. [22] (1875.7 ms), which was based on ROIs covering the entire normal-appearing PZ on a single slice, although the mean T2 values were considerably lower in our study (88 ms vs 173.4 ms). It is indeterminate whether this discrepancy in T2 values may be due to the use of

a three-dimensional MRF technique by Han et al. [22], as opposed to the two-dimensional technique used in our study. Furthermore, our findings were also similar to the study by Shiradkar et al. that showed mean T1 and T2 values of 1913 and 95 ms, respectively, based on limited ROIs determined on whole mount histology and then mapped onto MRF [23]. Remarkably, Panda et al. reported a normal PZ mean T1 value of 2240 ms and mean T2 value of 146 ms [19], considerably different from our study. Of note, those ROIs were drawn over limited normal-appearing areas of the PZ on the same slices as the PCa lesions, and the higher T1 and T2 values obtained may have been influenced by the selection of the most homogeneous areas to represent the normal PZ. Nonetheless, in this same study, the biopsy-proven benign prostatic tissue mean T1 and T2 values were 1810 and 71 ms [19], fairly similar to our findings, and likely more representative of the heterogeneity of the normal PZ background.

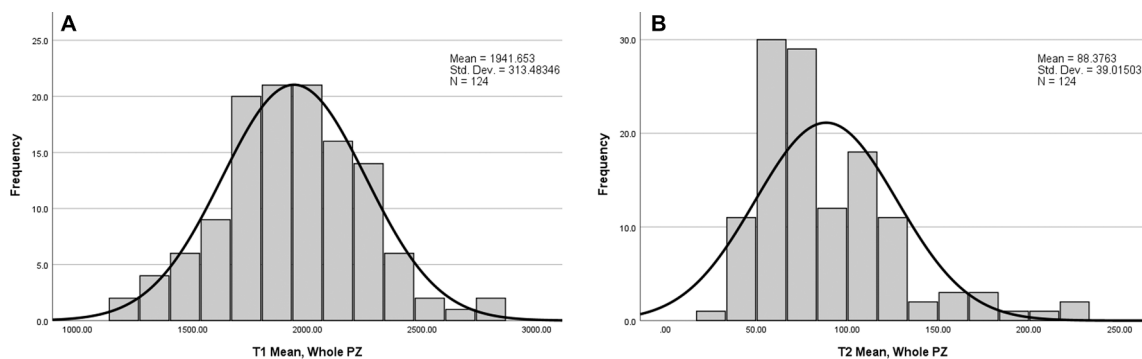
Previous studies have also employed other MRI quantification techniques (e.g. dual acquisition fast spin-echo and dual-echo steady state), to study T2 relaxation times in the normal appearing peripheral-zone, with reported values ranging from 115 to 122 ms for healthy volunteers [24,25] and one study reporting a mean T2 relaxation time of

Table 2

Average T2 values of the background peripheral zone of the whole gland and stratified by segment and clinical features.

Feature	N	Average T2 (ms)	SD T2	P-value for Difference	Correlation	P-value for Correlation
Whole Gland	124	88	39			
Apex	124	83	35	<0.01	–	–
Mid Gland	124	92	40	<0.01		
Base	124	88	46	<0.01		
Prostate Weight (g)	124			0.13	0.20	0.03
<25 g	8	70	25			
25–45	50	79	24			
45–65	27	96	45			
65–85	22	89	44			
>85 g	17	108	51			
PSA values (ng/mL)				0.78	– 0.17	0.08
<2.5	8	100	53			
2.5–4.0	12	96	40			
4.0–10.0	65	89	38			
>10	25	84	37			
Biopsy Status				0.64	–	–
Biopsy Naïve	57	90	40			
Previous Biopsy	66	86	37			
PZ Width (mm)				0.01	0.36	<0.01
<6.0	3	65	20			
6.0–9.0	34	77	26			
9.0–12.0	52	84	33			
12.0–15.0	25	112	52			
>15.0	4	125	49			
Age (Years)				0.84	– 0.06	0.50
<50	4	79	39			
50–60	27	92	35			
60–70	62	87	40			
70–80	29	90	41			
>80	2	68	5			
Patient Weight (kg)			0.87	– 0.01	0.91	
<70	9	94	39			
70–90	50	83	35			
90–110	47	90	43			
110–130	13	93	38			
>130	5	78	17			
Ethnicity				0.55	–	–
Caucasian	98	88	33			
African American	21	96	60			
Hispanic	3	71	33			
Asian	1	52	–			
Other	0	–	–			
PI-RADS				0.03	– 0.22	0.02
1	3	197	36			
2	67	90	35			
3	4	76	50			
4	15	86	30			
5	14	75	27			

N - number; PI-RADS - Prostate Imaging Reporting and Data System; PSA - Prostate-Specific Antigen; PZ - peripheral zone; SD - standard deviation.

**Fig. 2.** Histograms of mean T1 (A) and T2 (B) values of the whole-gland background peripheral zone of the study population. MRF – MR fingerprinting; N- number; PZ – peripheral zone; Std. Dev. - standard deviation.

129 ms for patients [25]. Nonetheless, the study population of these investigations were mostly comprised of healthy volunteers [24,25]. Significantly, the study that reported T2 relaxation times for patients

included only 29 patients that underwent mpMRI prior to biopsy or active surveillance [25].

Additionally, our work highlighted the association of clinical and

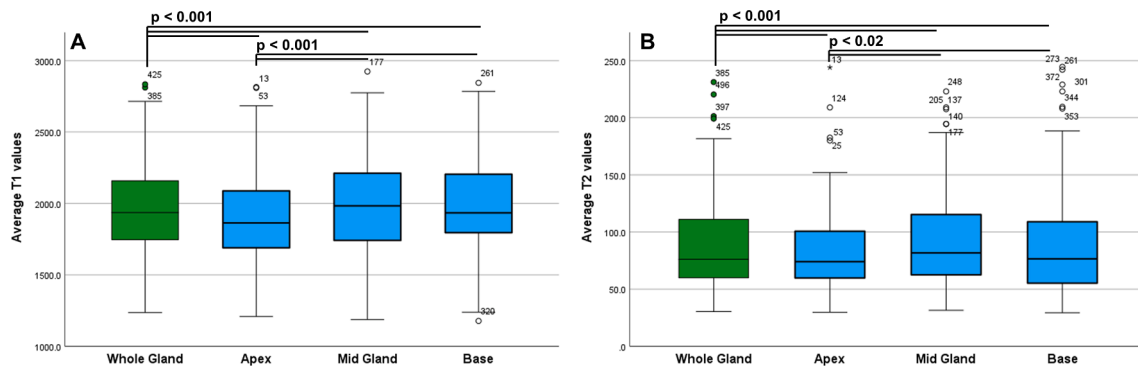


Fig. 3. Box plots of mean T1 (A) and T2 (B) values of the peripheral zone of the whole gland, apex-only, mid-gland-only, and base-only. Horizontal connecting lines, with their respective p-values, illustrate significant differences between the variables. (A) Y-axis was truncated at 1000 ms for better visualization. Circles below and above the error bars represent outliers. MRF – MR fingerprinting; PZ – peripheral zone.

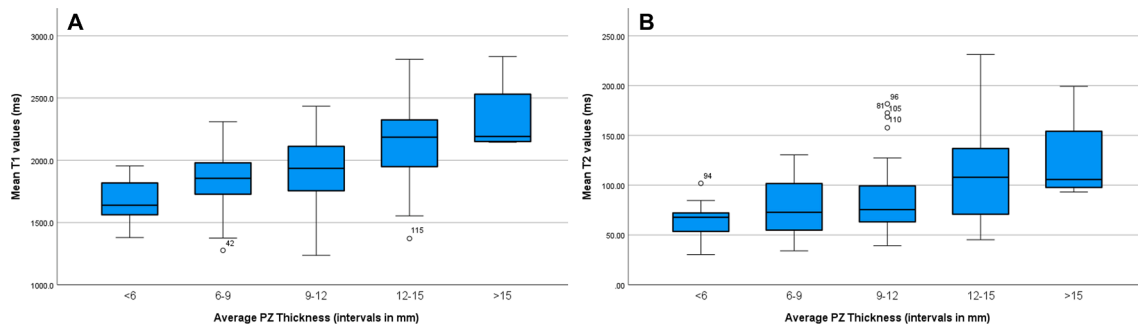


Fig. 4. Box plots of mean T1 and T2 values of the background peripheral zone according to peripheral zone width groups. (A) shows progressively increasing mean T1 values for higher peripheral zone width groups. Pairwise comparisons were statistically significant ($p < 0.05$) for every group comparison, except for the following: 6 mm vs 6–9 mm, 6–9 mm vs 9–12 mm, and 12–15 mm vs > 15 mm. (B) also shows progressively increasing mean T2 values for higher peripheral zone width groups. Pairwise comparisons were statistically significant ($p < 0.05$) for every group comparison, except for the following: 6 mm vs 6–9 mm, 6 mm vs 9–12 mm, 6–9 mm vs 9–12 mm, and 9–12 mm vs > 15 mm. (A) Y-axis was truncated at 1000 ms for better visualization. Circles below and above the error bars represent outliers. PZ – peripheral zone.

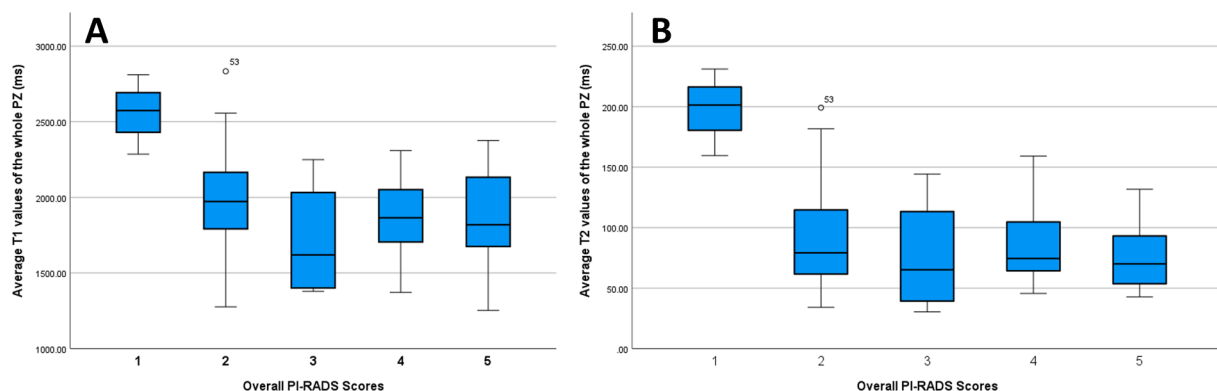


Fig. 5. Box plots of mean T1 and T2 values of the whole gland background peripheral zone associated with the overall PI-RADS scores of the PZ on the patient level. Only the PI-RADS 1 groups had significantly ($p < 0.001$) higher mean T1 and T2 values compared to other groups. (A) Y-axis was truncated at 1000 ms for better visualization. Circles below and above the error bars represent outliers. PI-RADS - Prostate Imaging Reporting and Data System; PZ – peripheral zone.

demographic features with T1 and T2 values of the PZ background. As the most relevant example, there was a significant positive correlation between the average PZ width and both T1 and T2 values. A possible explanation for this fact includes a higher percentage of luminal components, compared with epithelial and stromal components on the histologic level; however, the assessment of features of tissue compartment ratio [26] is beyond the scope of the current study. Moreover, PZ width can be influenced by prostate volume and/or by PZ compression from benign prostate hyperplasia of the transition zone [27], and studies

utilizing volumetric analysis would enable further insights into this possible correlation.

Furthermore, although T1 and T2 values were similar across the 3 scanners, it is possible to notice a non-statistical difference among T2 values between the 3 scanners (Scanner 1: 93 ± 38 ms; Scanner 2: 80 ± 22 ms; Scanner 3: 82 ± 44 ms; $p = 0.06$). Nonetheless, we previously demonstrated that MRF values are reproducible and repeatable across different scanners from different institutions [17]. Thus, we believe this non-statistical difference in T2 values could be attributed to different

Table 3

Previous studies on MR Fingerprinting quantitative values of the background peripheral zone.

Study	Subanalysis	N	T1 value		T2 value		ROI selection and drawing method
			Mean or Median	SD or IQR	Mean or Median	SD or IQR	
Yu et al. [14]	Dataset A	120	2247	450	169	61	Drawn in normal-appearing PZ. The minimum ROI sizes ranged from 7 to 174 mm ²
	Dataset B	43	2367	295	193	68	
Sushentsev et al. [17]		10	2041.0	209.4	598.2	218.5	Drawn using T2WI as reference and then transposed to the MRF T1 map
Panda et al. [15]	–	82	2240	360	146	61	Drawn on visually normal-appearing PZ contralateral to PZ lesions
Shiradkar et al. [19]	–	24	1913	350	95	28	Delineated by a pathologist on whole mount slide and then mapped on to a single MRF slice
Han et al. [18]	–	90	1875.7	323.2	173.4	50.7	Covered the entire normal PZ in a single slice with the largest area of normal-appearing prostate gland tissue
Lee et al. [8]	NE	57	1906.1	1711.9–2306.7	179.8	138.0–244.9	ROI covering the entire normal-appearing PZ in the section where the PZ appeared largest
Lo et al. [13]	CE	57	880.5	483.0–624.4	185.7	125.3–242.4	ROIs of 10 pixels in size drawn in normal appearing regions with no specific findings
	Centre 1	7	2551.8	409.7	164.1	73.9	
Current Study	Centre 2	6	2153.4	331.1	115.4	48.7	Drawn on the T2 map encompassing the right and left lobes of the PZ per axial slice (apex, mid-gland and base) and automatically copied to the T1 map
	Centre 3	11	2257.6	378.9	146.0	59.4	
	All Scanners	124	1941	313	88	39	
	Scanner 1	69	1926	328	93	38	
	Scanner 2	15	1991	202	80	22	
	Scanner 3	40	1949	325	82	44	

CE - contrast-enhanced; IQR – interquartile range; MRF - MR fingerprinting; N - number; NE – non-contrast enhanced; PZ - peripheral zone; ROI - region of interest; SD - standard deviation.

clinical characteristics amongst patients scanned on Scanner 2 compared to Scanners 1 and 3. Nonetheless, this study lacks sufficient statistical power to examine this hypothesis, given that only 15 patients were scanned on Scanner 2.

Surprisingly, there was no statistical difference found between T1 and T2 values across age categories in our study, as it is widely known that younger patients more frequently present with T2-hypointense signal intensities in the PZ [10]. However, this finding probably relates to the low number of subjects younger than 50 years old included ($n = 4$). Therefore, future investigations with a younger patient population would contribute to determining whether quantitative T1 and T2 values vary significantly by age.

Finally, we analysed whether the average T1 and T2 values of the PZ background varied among patients with different overall PI-RADS scores for PZ lesions. As expected, PI-RADS 1 scores, albeit with very low prevalence in our population ($n = 3$), were associated with significantly higher T1 and T2 values of the PZ background, when compared with patients with PI-RADS scores 2 to 5. This is partly in alignment with the PI-RADS guidelines [9] definitions, as score 1 represents a homogeneously T2-hyperintense PZ. Conversely, there was no difference in the T1 and T2 values of the PZ background among the remaining PI-RADS categories. Importantly, the slightly lower mean values on PI-RADS 3 patients, although not statistically significant, due to the low prevalence of PI-RADS 3 patients ($n = 4$) in our study population. However, this raises the question as to whether a more heterogeneous PZ background would contribute to adding uncertainty to radiologists reading prostate MRIs, by leading to a higher likelihood of finding a PI-RADS 3 lesion, which stands as an equivocal/indeterminate finding. This statement remains largely speculative, and few previous studies proposed to investigate this association, however only with qualitative techniques, not allowing for robust assessment of prostate tissue composition, and with only moderate interobserver agreement [10,15]. The ability to quantify background signal changes of the prostate with tools such as MRF may allow for the investigation of the effects of PZ heterogeneity and composition on lesion detection, and on the negative predictive value of prostate MRI.

4.1. Limitations

Our study had several limitations. This was a retrospective study from a single institution and, therefore, was limited to the available cases. In addition, there might be potential differences in body transmit coils as well as transmit modes between the two types of MR scanners used and their impact on MRF quantification needs to be evaluated in the future. Importantly, our study originated in the same department where previous prostate MRF studies were performed, and part of the study populations may have overlapped [17–19,23]. However, our study included a larger database than any of the preceding and was based on a different, comprehensive ROI annotation approach. Moreover, additional quantification methods were not assessed in this study. Additionally, our study was limited by the lack of histologic confirmation of the drawn ROIs of the background PZ, which were assumed to represent non-cancerous PZ. Furthermore, since our study excluded transition zone lesions and lacked the availability of follow-up histology results, it is not possible to rule out that the presence of PCa outside the PZ may also have affected T1 and T2 values. While care was taken to exclude obvious lesions from the ROI segmentation, it was not possible to exclude the possibility of MRI invisible PCa in the included background PZ, nor to correlate our findings with the presence of benign entities such as chronic prostatitis or scar tissue/atrophy. However, we believe the chosen approach more closely emulates clinical practice and helps to inform future studies aiming to address tumor visibility in light of MRF measurements. Finally, describing only means and SDs, we did not explore the regional heterogeneity of the PZ nor any kind of texture analysis of the quantitative data. Future studies with voxel-wise analyses and the use of radiomics techniques are ongoing in our group, and may further detail the nature and composition of the background PZ on MRI.

5. Conclusions

We provided a comprehensive analysis of the quantitative T1 and T2 values of the background PZ of the prostate using MRF. Mean T1 and T2 values of the background PZ of the whole gland were 1941 ± 313 and 88 ± 39 ms, respectively. Among clinical and demographic factors, there

was a significant positive correlation between T1 and T2 values and PZ width. This data can serve as a reference standard for future studies based on prostate MRF, and points to directions for further assessing the effects of background signal changes of the prostate on the determination of the prostate composition and the detection of csPCa.

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CRediT authorship contribution statement

Eduardo Thadeu de Oliveira Correia: Data curation, Formal analysis, Methodology, Writing – original draft. **Peter L. Qiao:** Investigation, Writing – original draft, Writing – review & editing. **Mark A. Griswold:** Resources, Writing – review & editing. **Yong Chen:** Methodology, Writing – review & editing. **Leonardo Kayat Bittencourt:** Data curation, Formal analysis, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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