Short Communication

Tissue Resonance Interaction Method (TRIMprob) has the potential to be used alongside the recognized tests in the screening protocols for prostate cancer

Ozgur Gokce,[1] Oner Sanli,[1] Artur Salmaslioglu,[2] Atadan Tunaci,[2] Cavit Ozsoy[1] and Faruk Ozcan[1]

Departments of [1]Urology and [2]Radiology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

Abstract: The objective of this study was to evaluate the accuracy of the magnetic induction technique with a nonlinear tunable oscillator (the Tissue Resonance Interaction Method [TRIMprob]) in the diagnosis of prostate cancer (CaP). Overall, 148 men were split into two groups (patients at risk of CaP [Group 1] and controls [Group 2]) and evaluated with the TRIMprob. Group 1 consisted of 100 patients (mean age: 63.8 ± 7.2 years) with elevated prostate-specific antigen (>4 ng/mL) levels and/or abnormal digital rectal examination. Eleven patients (Group 2a, mean age: 59.5 ± 7.3) with previously biopsy-proven CaP served as positive controls. In addition, 37 voluntary men (Group 2b, mean age: 39.8 ± 10.4) with normal prostate-specific antigen and digital rectal examination without lower urinary tract symptoms served as negative controls. Non-linear resonance was analyzed at 465 MHz and a cut-off value of 40 units was detected as the resonance value for the best threshold to distinguish benign conditions from CaP after transrectal ultrasonography-guided biopsy with a standard 10–12 core technique in Group 1. Mean resonance values (±standard deviation) with the TRIMprob examination for patients in Groups 1 and 2b were 36.72 ± 22.35 and 73.64 ± 10.06, respectively, whereas for patients in Group 2a, it was 13.73 ± 12.12 ($P < 0.01$). Sensitivity, specificity, positive and negative predictive values of the TRIMprob using the study cohort of Group 1 were found as 76%, 61.3%, 39.6% and 88.5%, respectively. Despite some technical limitations, the non-invasive TRIMprob examination may have a role in screening protocols for CaP.

Key words: electromagnetism, prostate cancer, prostate-specific antigen.

Introduction

Biomagnetism is the study of bioelectric processes in living organisms as reflected by their associated magnetic fields.[1] The magnetic fields related to these bioelectric interactions in living organisms may be detected by non-invasive techniques called 'biomagnetometric methods'.[2–4] Briefly, coupling of the oscillations of the probe with those from the biological tissues produces the remarkable phenomenon of 'nonlinear resonance interaction,' which is detected by the receiver of the measuring system.[5–7]

The aim of the present study was to evaluate the accuracy of this method (magnetic induction technique with nonlinear tunable oscillator) in the detection of carcinoma of the prostate (CaP) and address its drawbacks.

Methods

The study cohort ($n = 148$) was evaluated in two groups as follows: Group 1 ($n = 100$): patients at risk of harboring CaP; and Group 2: controls to validate the methodology for discriminating CaP from benign prostatic hyperplasia and other benign conditions. Ethical approval was obtained from the local ethics committee before the initiation of the study and informed consent was obtained from each of the participants.

Group 1 was evaluated in three subgroups as patients with elevated prostate-specific antigen (PSA >4 ng/mL) (Group 1a, $n = 45$), suspicious digital rectal examination (DRE) (Group 1b, $n = 14$) or elevated PSA and suspicious DRE (Group 1c, $n = 41$), respectively.

Correspondence: Oner Sanli MD, Department of Urology, Istanbul Faculty of Medicine, 34390 Capa – Istanbul, Turkey. Email: sanlio@istanbul.edu.tr

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Group 2 was evaluated in two subgroups. Group 2a ($n = 11$) consisted of patients with previously known biopsy proven CaP (positive controls). Group 2b was consisted of 37 men with normal PSA (≤4 ng/mL) and DRE without lower urinary tract symptoms (LUTS) (negative controls). These above-mentioned control groups were also used to compare the 'resonance values' of patients who were supposed to have statistically significant benign (Groups 2b) and malignant conditions (Group 2a).

All patients (before biopsy in Group 1) underwent analysis of tissue resonance with a nonlinear tunable oscillator (the Tissue Resonance Interaction Method [TRIMprob] system, Galileo Avionica, Turin, Italy) and the non-linear resonance was analyzed at 465 MHz. Resonance values are representative of power measured on a logarithmic scale but expressed in arbitrary units ranging between 0 and 255. After completion of the study, when data obtained from transrectal ultrasonography (TRUS)-guided-biopsy (Group 1) was plotted on a receiver operating characteristics (ROC) curve, a cut-off resonance value of 40 units was found as the best value for differentiating non-cancerous lesions and CaP.

The examination with the TRIMprob was performed as has been previously described.[6–8] Abnormal values were accepted as lower than 40 units while scanning the six standard conventional positions. In addition to the detected resonance values, a typical pattern of signal reduction at 465 MHz band below a threshold amplitude was taken into consideration while deciding if CaP was present or not. Intraobserver and interobserver variability was assessed in 10 patients from each of the groups at 24 h after the initial scanning and revealed 100% consistency for intraobserver and 10% discrepancy for interobserver variability.

All patients had their free and total PSA measurements before biopsy. Cut-off values of 4.0 ng/mL and 18% were used for total serum PSA and free/total (f/t) PSA ratio, respectively. Meanwhile, prostate volume was determined and PSA density (PSAD) was calculated using

Table 1 Data regarding the individual parameters of the patients

	Group 1 ($n = 100$)		Group 2a ($n = 11$)		Group 2b ($n = 37$)		*P*-value
	Mean	SD	Mean	SD	Mean	SD	
Age	63.89	7.29	59.55	7.38	39.86	10.45	0.000
Total PSA	8.8	0.09	7.51	4.15	0.76	0.36	0.000
Free PSA	1.518	1.312	1.172	0.824	0.21	0.11	0.000
f/t PSA (%)	20.02	8.90	15.27	7.91	28.73	4.21	0.000
Volume (mL)	56.67	30.02	38.45	12.01	24.84	7.54	0.000
PSAD	16.7	13.15	20.73	10.07	3.05	0.74	0.000

f/t, free/total; PSA, prostate-specific antigen; PSAD, PSA density; SD, standard deviation.

Table 2 Sensitivity, specificity, PPV, NPV and overall accuracy of individual diagnostic parameters (Group 1, $n = 100$)

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Overall accuracy (%)
TRIMprob	76.0	61.3	39.6	88.5	65.0
TPSA (>4 ng/mL)	88.0	21.3	27.2	84.2	38.0
F/T PSA (<18%)	64.0	52.0	30.8	81.3	55.0
PSAD	56.0	69.3	37.8	82.5	66.0
DRE	84.0	54.7	38.2	91.1	62.0
TRUS findings	84.0	56.0	38.9	91.3	63.0

DRE, digital rectal examination; f/t, free/total; NPV, negative predictive values; PPV, positive predictive values; PSA, prostate-specific antigen; PSAD, PSA density; TPSA, total PSA; TRIMprob, nonlinear tunable oscillator; TRUS, transrectal ultrasonography.

TRUS. PSAD >0.15 ng/mL/mL was accepted as suggestive of CaP. Prostate biopsies (Group 1) were done including 10–12 cores according to the prostate weight.

Statistical analyses

The Student's *t*-test, the Mann–Whitney *U*-test, one-way ANOVA and the Kruskal–Wallis test were used where appropriate. Calculation of the area under the ROC curves for total PSA, f/t PSA ratio, PSAD and evaluation with TRIMprob were performed using statistical software. ROC analysis was done post-hoc and the ROC curve was graphed as the false-positive rate versus sensitivity and summarized by the area under the ROC curve. For these analyses, SPSS 10.0 for Windows was used.

Results

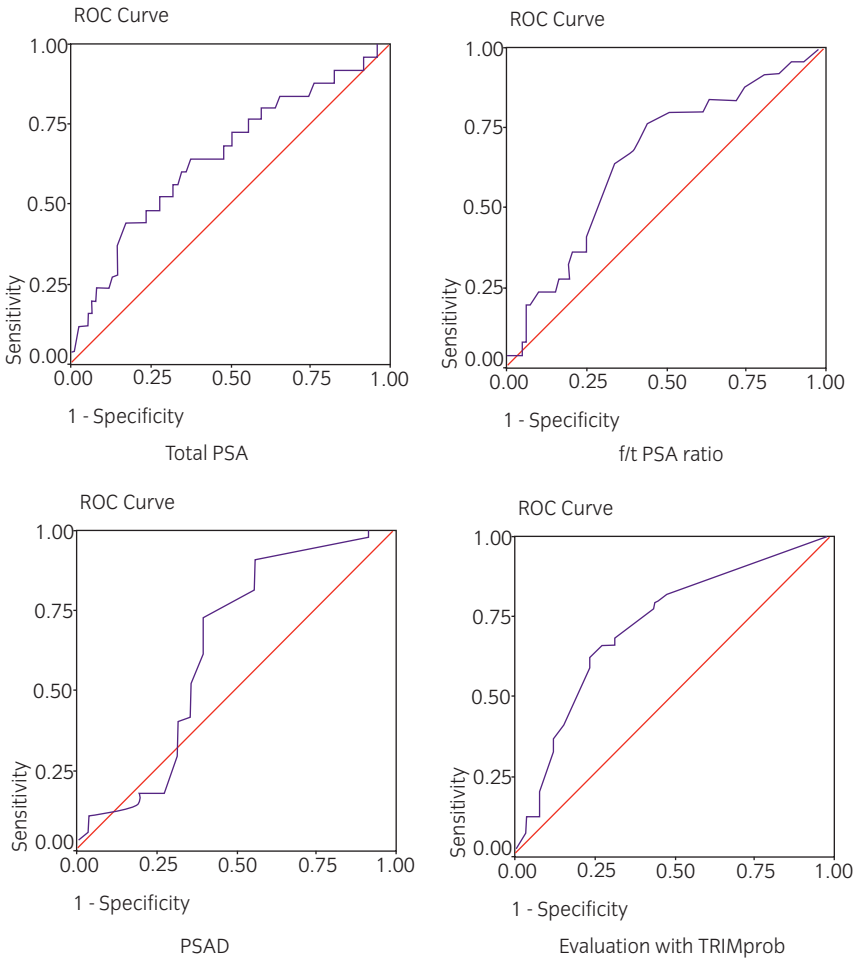
Table 1 presents the mean ages, mean serum total and free PSA values, free/total PSA ratios, mean prostate volumes and mean PSA densities for all groups. The mean resonance values according to the TRIMprob examination for patients in Groups 1 and 2b were 36.72 ± 22.35 and 73.64 ± 10.06, respectively; whereas for patients in Group 2a, this value was 13.73 ± 12.12 ($P < 0.01$). Meanwhile, Group 1c (27.41 ± 24.69) had significantly lower mean resonance values compared to Group 1a (45.23 ± 22.15) and Group 1b (38.36 ± 23.48), respectively ($P < 0.01$).

Biopsy-proven CaP was detected in Groups 1a ($n = 4$; 8.8%), 1b ($n = 2$; 14.2%) and 1c ($n = 19$; 46.3%), respectively. This outcome revealed that the patients with a higher risk of CaP had resonance values closer to the values obtained for CaP than benign prostatic conditions. Using the study cohort of Group 1, a sensitivity of 76% and specificity of 61.3% for the diagnosis of CaP with positive predictive values (PPV) and negative predictive values (NPV) of 39.6% and 88.5%, respectively, was found. In addition, the overall diagnostic accuracy of this method was found as 65%. The sensitivity, specificity, positive and negative predictive values of individual diagnostic parameters are summarized in Table 2.

In addition, the area under the ROC curve was greater for resonance values according to the TRIMprob compared to the serum total PSA, the f/t PSA ratio, and the PSAD (Fig. 1). Our comparison of the area under the ROC curves indicated that evaluation with TRIMprob and f/t PSA ratios were statistically different from the total PSA and PSAD.

Discussion

In the first prospective study evaluating the role of TRIMprob, Bellorofonte *et al.* evaluated 757 patients including control groups comprising patients with normal DRE and PSA.[6] The authors found a sensitivity of 95.5% and a specificity of 42% for the diagnosis of CaP with a PPV and NPV of 63.6% and 89.8%, respectively, when the cut-off resonance value was chosen as 50 units. In a multicenter prospective study, Da Pozzo *et al.* evaluated 188 patients with this technique who were candidates for TRUS biopsy and reported the sensitivity and specificity of this technique for detecting CaP as 80% and 51%, respectively.[7] Similarly, Tubaro *et al.* reported the same parameters as 89% and 62% in 111 patients undergoing TRUS biopsy.[8] Our data is in accordance with the aforementioned series. However, one should note that the TRIMprob has missed 5.6–13.3% of cancer patients in the studies mentioned



	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
TOTAL PSA	0.649	0.066	0.027	0.520	0.777
F/T PSA %	0.623	0.076	0.067	0.475	0.771
PSAD	0.655	0.062	0.020	0.533	0.778
TRIMPROB	0.715	0.061	0.001	0.595	0.834

Fig. 1 Comparison of receiver operating characteristics (ROC) curves of 100 (Group 1) patients with biopsy for total prostate-specific antigen (PSA), free/total (f/t) PSA ratio, PSA density (PSAD) and nonlinear tunable oscillator (TRIMprob).

above.[6–8] This outcome may be attributed to the lack of a comparison of TRIMprob with the gold standard technique (prostatectomy specimen) for determining its efficacy. However, we believe that the high NPV associated with this method suggests that this new technology might be shown to reduce repeated series of biopsies. Thus, larger series are needed to confirm this assumption.

The TRIMprob procedure has some drawbacks that should be addressed. Firstly, the technique suggested by the manufacturer is highly dependent on the examiner. Moreover, the imaging technique is challenging and unclear for general use. In a similar study, Bellorofonte *et al.* found the resonance cut-off value of 50 units is the best criterion differentiating between non-cancerous lesions and CaP.[6] This discrepancy between the two studies may lead to a 'gray zone' that makes this test less valuable. Moreover, like other studies evaluating the sensitivity of an imaging modality, it is not possible to discriminate clinically significant and insignificant cancers. As information about the relationship between signal amplitude and cancer volume is still obscure, the sensitivity of this technique might be overestimated. In addition, it is not clear if the specificity of this technique is adversely affected by coexisting comorbidities of the scanned organ (prostatitis, previous surgery etc.) or organs neighboring the prostate (cystitis etc.). However, these problems arise more or less in almost every imaging study and molecular marker to be used for selecting candidates for definitive treatment alternatives for localized disease.[9] Therefore, with the aid of improving technology this non-invasive technique may have a role in the screening of CaP.

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