The Electromagnetic Detection of Prostatic Cancer: Evaluation of Diagnostic Accuracy

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OBJECTIVES To evaluate the accuracy of the TRIMprob in the diagnosis of prostate neoplasm.

METHODS Consecutive patients referred for prostate biopsy were prospectively enrolled. Patients had history taken, physical examination by digital rectal examination (DRE) of the prostate, assessment of total and free serum prostate-specific antigen (PSA) levels, prostate transrectal ultrasonography (TRUS), and TRIMprob test. Indications for prostate biopsy included one or more of the following conditions: total serum PSA levels of 4.0 ng/mL or more, free/total serum PSA ratio of 0.18 or less, positive results on DRE, and suspicious findings on TRUS. Twelve-core, TRUS-guided biopsies were performed with local anesthesia. A blinded investigator performed the TRIMprob test; the lowest value of the signal at 465 MHz was looked for and recorded, although data of the electromagnetic signal at 930 and 1295 MHz were also recorded.

RESULTS One hundred eleven patients (aged 64.9 ± 8.1 years, mean ± standard deviation), enrolled between November 2004 and August 2005, were analyzed. Total serum PSA level was 8.4 ± 3.6 ng/mL, and free/total serum PSA ratio was 0.15 ± 0.7. TRIMprob sensitivity for the diagnosis of prostate cancer was 0.86%; specificity and positive and negative predictive values were 0.60 and 0.88; accuracy was 72%. TRIMprob accuracy outperformed any other diagnostic parameter considered, including the rule of chance. The association of TRIMprob and DRE offered a sensitivity and a negative predictive value of 0.86% or greater.

CONCLUSIONS TRIMprob had the highest accuracy rate, among all other tests, for the diagnosis of prostate cancer. Electromagnetic detection with the TRIMprob test seems to be a promising technology and a useful additional tool for the early detection of prostate cancer. UROLOGY 72: 340–344, 2008. © 2008 Elsevier Inc.

Prostate cancer is the most common neoplasm of adult men in the United States. Recent data suggest that 230,460 new cases will occur in the year 2006, with 27,350 estimated deaths in the United States.[1,2] Prostate-specific antigen (PSA) assay and digital rectal examination (DRE) are used to detect the presence of prostate cancer, but the final diagnosis requires histologic examination of biopsy specimens. The introduction of the PSA assay considerably improved the detection of prostate cancer, and it is extensively used for early diagnosis and screening programs.[3–6] The marker is not disease specific, and several conditions affecting the prostate gland, including ejaculation, physical activity, cystoscopy, DRE, and prostate biopsy, may result in elevated PSA levels.[7]

In 1992 Clarbruno Vedruccio, an Italian physicist, patented a maser for the electromagnetic detection of biologic tissue anomalies.[8] The equipment, named TRIMprob (TRIMprobe; Finmeccania, Rome, Italy), is composed of a nonlinear oscillator disposed into a cylindrical probe, a radiofrequency spectrum analyzer, and dedicated computer software. In 2004 Vedruccio and Meessen modeled TRIMprob function from a mathematical standpoint, and Bellorofonte published the first article on the electromagnetic diagnosis of prostate cancer in 2005.[9,10] The TRIMprob consists of a battery-operated probe, a receiver, and a control computer (Fig. 1). The probe emits electromagnetic radiation with three frequency components (465, 930, and 1395 MHz); a spectrum analyser, fed by a receiving antenna, measures signal intensities that are displayed on a computer screen. The interaction between the electromagnetic field emitted by the probe and cancerous tissue results in a significant decrease of the signal intensity at 465 MHz, whereas the signal at 930 and 1395 remains unchanged.[9,10] In a previous study, reduction of the signal intensity at 465 MHz below 50 U (on an arbitrary scale between 255 and 0) provided the best diagnostic accuracy for prostate cancer.[10] Preliminary evaluation of TRIMprob accuracy showed a sensitivity of 95.5% and a specificity of 42.7%,

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Figure 1. The TRIMprob system is composed of the exploratory probe, the receiver (a spectrum analyzer), and a laptop computer with dedicated software to manage patient information and store TRIMprob data.

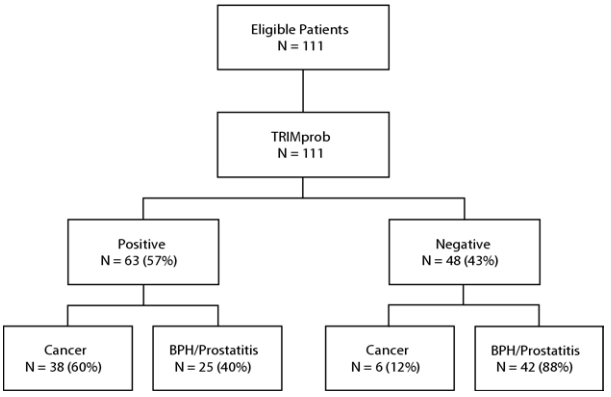

Figure 2. Flow diagram of patients undergoing prostate biopsy. Patients with a significant decrease of the electromagnetic signal at 465 MHz were labeled as "positive," and those without any significant decrease were described as "negative."

with a positive predictive value (PPV) of 63.6% and a negative predictive value (NPV) of 89.8%.[10]

Our prospective study aimed at verifying the experience of Bellorofonte *et al*. The objective of the study was to evaluate the accuracy of the TRIMprob test, total PSA, free/total PSA ratio, DRE, and transrectal ultrasonography (TRUS) in the diagnosis of prostate neoplasm in a prospective study.

MATERIAL AND METHODS

Patients referred to our outpatient clinic for early diagnosis of prostate cancer between November 2004 and August 2005 were consecutively enrolled after receipt of informed consent. Study parameters included medical history, physical examination with DRE, TRUS evaluation (5 to 10 MHz bi-convex endocavitary probe [ref. 8808] and Falcon ultrasound equipment [BK Medical, Milan, Italy]), total and free serum PSA values, and TRIMprob evaluation. Prostate-specific antigen was measured with the IMMULITE DPC system (Medical System SPA, Genoa, Italy). Inclusion criteria for prostate biopsy consisted of one or more of the following conditions: total PSA level 4.0 ng/mL or greater, free/total PSA ratio 0.18% or less, abnormal results on DRE (presence of a palpable nodule and/or increased firmness), and abnormal results on TRUS (hypoechogenic lesion). Exclusion criteria included prior diagnosis of prostate cancer, prior prostate surgery, and treatment with 5-alpha reductase inhibitors. The TRIMprob room was free from relevant electromagnetic interference; no other electrical devices, including mobile telephones or medical devices, were allowed. The TRIMprob test was performed by a single operator (C.D.N.) blind to patient status according to the technique described by Bellorofonte *et al.*[10] The prostate gland was explored with a transperineal approach with the patient normally dressed, standing 2 m in front of the receiver with the legs slightly apart[10]; when the lowest signal intensity at 465 MHz was measured, signal intensity values at 465, 930, and 1395 MHz were recorded by the TRIMprob computer software and data stored in the patient file.

Prostate biopsy was performed under local anaesthesia (10 mL of 1% lidocaine and a 22-gauge needle) with a TRUS-guided approach.[11] All patients underwent 12-core biopsy with a 16-gauge needle (Magnum 1000; BARD, Rome, Italy) and a spring-loaded biopsy gun (MG1522; BARD). Each biopsy core was individually processed according to standard histologic procedures and stained with hematoxylin and eosin.

The study was designed and carried out according to the criteria of the Standards for Reporting of Diagnostic Accuracy initiative.[12] A coin toss was used as reference for the rule of chance in the evaluation of diagnostic accuracy.

Data were analyzed with SPSS 12.0 software (SPSS, Milan, Italy); sensitivity, specificity, accuracy, and positive and negative predictive value of the TRIMprob test, total PSA, free/total PSA ratio, DRE, and TRUS for the detection of prostatic cancer were calculated. Analysis of variance for independent variables was performed with the Student *t* test and the Mann-Whitney test when appropriate. Correlation between study parameters and biopsy outcome was calculated with the chi-square test. Multivariate analysis was performed, evaluating the TRIMprob dichotomic results, associated to the results of the other examinations (total PSA, free/total PSA ratio, DRE, TRUS), and the diagnostic accuracy of associated diagnostic tests was calculated. An alpha value of 0.05 was used as the threshold for significance.

RESULTS

Characteristics of the study cohort are summarized in Table 1. A total of 111 subjects were evaluable for analysis. Mean (± standard deviation) patient age was 64.9 ± 8.1 years, total serum PSA level was 8.4 ± 3.6 ng/mL, and free/total serum PSA ratio was 0.15 ± 0.7. TRIMprob test results were abnormal in 63 patients (57%), and 38 patients had a positive biopsy (11 had a Gleason score of 6, 24 a Gleason score of 7, 2 a Gleason score of 9, and 1 a Gleason score of 10). Forty-eight patients had normal TRIMprob test results, and 42 had negative results on biopsy, whereas 6 were diagnosed with prostate cancer (2 patients had a Gleason score of 6 and 4 a Gleason score of 7). Overall, 44 prostate cancers were detected (Fig. 2).

Chi-square test of individual parameters versus the outcome of prostate biopsy showed a significant correla-

Table 1. Characteristics of patients undergoing prostate biopsy (categories are not mutually exclusive)

	Total PSA ≥4 ng/mL	Free/total PSA ratio ≤0.18	Abnormal results on DRE	Abnormal results on TRUS	Patients, n (%)
	√				28
	√	√			28
	√	√	√		7
	√	√	√	√	6
	√		√		7
	√		√	√	3
		√			6
		√	√		1
		√	√	√	0
			√		1
			√	√	0
	√			√	6
	√	√		√	11
		√		√	1
				√	6
Patients, n (%)	96 (86.5)	60 (54)	25 (22.5)	33 (29.7)	111 (100)

PSA = prostate-specific antigen; DRE = digital rectal examination; TRUS = transrectal ultrasound.

TABLE 2. Sensitivity, specificity, positive and negative predictive value, and accuracy of individual and associated diagnostic parameters

Parameter	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
Individual parameters					
TRIMprob	0.86	0.63	0.60	0.88	0.72
Total PSA (≥4.0 ng/mL)	0.90	0.16	0.41	0.73	0.45
Free/total PSA (≤0.18)	0.78	0.34	0.35	0.72	0.50
DRE	0.40	0.88	0.69	0.69	0.69
TRUS	0.36	0.79	0.69	0.48	0.55
Coin toss	0.45	0.54	0.36	0.63	0.55
Associated parameters					
TRIMprob + DRE	0.96	0.57	0.59	0.95	0.72
Total PSA + DRE	0.96	0.13	0.42	0.82	0.46
Free/total PSA + DRE	0.81	0.53	0.51	0.82	0.64

PSA = prostate-specific antigen; DRE = digital rectal examination; TRUS = transrectal ultrasound.

tion between results of TRIMprob plus DRE and biopsy outcome, with a Cramer's V of 0.508 ($P < 0.001$) and 0.337 ($P < 0.001$), respectively. No significant correlation was found for total PSA level and PSA ratio. Analysis of TRIMprob data showed a sensitivity of 86% and specificity of 63%. The accuracy rate was 72%; a PPV of 60% and a NPV of 88% were calculated. Diagnostic accuracy of TRIMprob, total serum PSA level, free/total PSA ratio, DRE, and TRUS are summarized in Table 2.

Chi-square test for associated parameters versus the outcome of prostate biopsy resulted in a significant correlation between TRIMprob plus DRE and free/total PSA ratio plus DRE and biopsy outcome, with a Cramer's V of 0.532 ($P < 0.001$) and 0.337 ($P < 0.001$), respectively. Evaluation of diagnostic accuracy for associated diagnostic parameters confirmed that the association of TRIMprob and DRE produced the best diagnostic accuracy (Table 2).

COMMENT

Studies of diagnostic accuracy are not without bias, and results remain valid for the observed population, particularly in prostate cancer studies, for which the source of error is fourfold. As long as the use of prostate biopsy is restricted to patients at risk for prostate cancer, the study cohort is inevitably characterized by a higher incidence of disease compared with the general population (40% versus 15% to 20%). Furthermore, false-negative biopsy results inevitably occur notwithstanding the increasing number of cores obtained in each patient. Inclusion criteria for the present study can be considered conservative because patients with a total PSA value of 4.0 ng/mL or lower could only be included in case of a low free/total PSA ratio, positive results on DRE, or suspicious results on TRUS. The negative predictive value of TRIMprob analysis seems to be high, and the evaluation of its accuracy in patients with PSA levels below 4.0 ng/mL is currently underway. The TRIMprob was able to identify prostate cancer irrespective of Gleason score (patients with Gleason scores from 6 to 10 were correctly identified by the TRIMprob), and false-negative cases were in the Gleason 6 and 7 range. No correlation was found between TRIMprob signal and the number of positive cores and/or the extent of their

involvement (data not shown). Analysis of the relationship between TRIMprob signal and prostate cancer volume or location is beyond the scope of this study and will be the subject of a future report. Another unresolved problem is the availability of "true negative" cases from the patient cohort as long as only patients at risk for prostate cancer were included. In a previous study a cohort of young male patients referred to the outpatient clinic for infertility was used; a very high intensity of the signal at 465 MHz was found in this patient cohort, which proved to be significantly different from results in patients with prostate cancer.[10]

The results of this study confirm the data previously published by Bellorofonte.[10] Comparison of the accuracy data obtained in the two studies is reassuring; the slight decrease in the TRIMprob sensitivity (from 95% to 86%) is compensated by a larger increase in specificity (from 43% to 63%). The observed differences in the accuracy of the remaining parameters depend on the different subject populations and chance. In both studies electromagnetic analysis provided the best NPV, which may reduce unnecessary biopsies in patients with very low risk. The different results obtained with TRUS may depend on interpretation of the ultrasound picture; in Bellorofonte's study a high sensitivity was compensated by a low specificity, whereas a more conservative approach was used in the present study and the very high specificity was balanced by a significant reduction of sensitivity.[10] Overall we are very satisfied with our results; electromagnetic analysis of the prostate in more than 1150 patients enabled us to achieve a level of accuracy that seems to be of clinical value. Interestingly, TRIMprob was the only test that outperformed the "rule of chance" in both sensitivity and specificity. The association of TRIMprob and DRE provided the best diagnostic accuracy among the various combinations of diagnostic tests, with a sensitivity and negative predictive value of 95% or greater, which may be of interest from a clinical standpoint.

After the initial article from Bellorofonte, three additional articles were published in the peer-review literature showing the diagnostic potential of the TRIMprob in breast, thyroid, and bladder cancer.[13–15] An article on the use of "intelligent probes" for the electromagnetic diagnosis of cancer recently appeared in the peer-reviewed literature,[16] and the TRIMprob is just one of these new probes.

The TRIMprob device is not without limitations because the probe is manually operated, but the results of a multicenter study conducted in Italy confirmed the diagnostic accuracy and have recently been accepted for publication. Scanning of the prostate is performed blindly, and the system is not fused with an imaging device; the availability of fusion software may help address this problem in the future. Possible interference caused by the presence of cancerous tissue in other pelvic organs (rectum and bladder) is theoretically possible but did not seem to be a problem in this case series (all enrolled patients are still followed up in our outpatient clinic, and no evidence of bladder or rectum/colon cancer has appeared to date).

TRIMprob analysis is not yet included in the diagnostic algorithm of prostate cancer, and further research is required to corroborate current data.

Electromagnetic detection of cancer is a fascinating subject that is finally turning from a hypothesis into a real possibility. The incomplete understanding of the physical rules governing the nonthermal interactions of electromagnetic radiation with biological tissues disturbs us all, but the subject goes well beyond the understanding of the average urologist. Analysis of TRIMprob performance in experimental prostate, melanoma, and breast tumors implanted in nude mice has been completed, and data will be submitted for publication shortly.

CONCLUSIONS

The TRIMprob device opened a new perspective in the management of prostate cancer, but a new culture and a new language must be developed to fully exploit its possibility. Research programs on electromagnetic detection of cancer are finally taking off, and we expect an exponential growth of the research in this area. Urology is again facing the challenge of opening a new field; the ultimate role of electromagnetic diagnosis of prostate cancer is yet to be defined, but we would like to believe that we have already entered a new era.

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