

# Tissue-resonance interaction method for the noninvasive diagnosis of prostate cancer: analysis of a multicentre clinical evaluation

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Level of Evidence 2b

## OBJECTIVE

To determine, in a multicentre prospective study, the accuracy of the tissue-resonance interaction method (TRIMprob, new technology developed for the noninvasive analysis of electromagnetic anisotropy in biological tissues) in the diagnosis of prostate cancer.

## PATIENTS AND METHODS

Two hundred patients (mean age 67.4 years) scheduled to have prostatic biopsies (because of a prostate-specific, PSA, antigen level of

≥4 ng/mL or a suspicious digital rectal examination, DRE) were preliminarily examined while unaware of their clinical details using TRIMprob in five different centres. The final diagnosis obtained with TRIMprob was compared with the final histological diagnosis after extended biopsies.

## RESULTS

Of the 188 evaluable patients (mean PSA level 9.3 ng/mL, SD 8.8; mean prostate volume 62.0 mL, SD 32.4), 61 (32.4%) had a positive biopsy for adenocarcinoma of the prostate. The overall sensitivity, specificity, positive predictive value, negative predictive value (NPV) and accuracy of TRIMprob were 80%, 51%, 44%, 84% and 60%, respectively. The prostate cancer detection rate after biopsy was significantly higher in patients with a

positive examination (49/111, 44%) than in patients with a negative TRIMprob (12/77, 15%;  $P < 0.001$ ). When TRIMprob results were combined with DRE findings the sensitivity and NPV both increased to 92%.

## CONCLUSION

TRIMprob seems to be a useful tool in the diagnosis of prostate cancer and can increase the accuracy of PSA or DRE results. The high NPV suggests that this new technology might be useful to reduce the indications for prostatic biopsy or repeated series of biopsies in patients suspected of having prostate cancer.

## KEYWORDS

prostate, cancer, PSA, DRE, diagnosis, tissue-resonance method

## INTRODUCTION

Prostate cancer represents a major health problem worldwide and is the second leading cause of death from cancer in the USA [1]. PSA is the one test with the highest positive predictive value (PPV) for prostate cancer, but when used as a screening method it is not an ideal tumour marker; the specificity of PSA at >4 ng/mL is 60–70% [2,3]. The PPV of a DRE is low and a recent meta-analysis reported it to be ≈18% [4].

At present the most effective method for the early detection of prostate cancer is the combined use of a DRE and PSA [4]. As prostate cancer screening programmes presently result in many negative prostatic biopsies, new tumour markers or technologies

are urgently needed to give a more accurate indication of when prostatic biopsies are necessary.

A new device for the noninvasive analysis of electromagnetic anisotropy in biological tissues (the tissue-resonance interaction method, TRIMprob; TrimProbe SpA, Turin, Italy) has been developed and introduced in clinical practice to detect prostate cancer [5]. The physical principles of this new technology were summarized by Vedruccio and Meessen [6]. Briefly, an alternating electromagnetic field interacts with charged particles (molecules, ions, electrons, nuclei) in a target tissue and provokes a secondary radiation. Normal and neoplastic biological tissues interact with electromagnetic waves differently, and the detection and recording of

specific changes in the level of electromagnetic fields that irradiate a target tissue can hypothetically be used in clinical practice to predict cancer. A frequency of 465 MHz seems to be best suited for such an analysis [5].

Preliminary results in prostate cancer detection with TRIMprob have been encouraging, but were only obtained in one institutional clinical series [5]. The primary objective of the present open-label, prospective, multicentre study was to assess the diagnostic accuracy of TRIMprob for detecting prostate cancer compared with the results obtained from a series of prostatic biopsies. The secondary objective was to compare the agreement between the diagnosis provided by TRIMprob and that

provided, respectively, by PSA, the percentage of free PSA (%fPSA) and a DRE.

## PATIENTS AND METHODS

The clinical study was approved by the Ethical Committees of all the involved institutions; 200 patients (mean age 67.4 years, range 49–80) who were due to have random prostatic biopsies were included in the study in five different urological departments. The inclusion criteria were a PSA level of  $\geq 4$  ng/mL (obtained within 60 days of the date of enrolment) and/or the presence of one or more nodules on DRE; all patients had to be aged 45–80 years. Exclusion criteria were: the presence of a pacemaker and/or any other active implantable device; coexistent pelvic neoplasm; a previous diagnosis of prostate cancer; previous prostate biopsy; or treatment with 5 $\alpha$ -reductase for BPH.

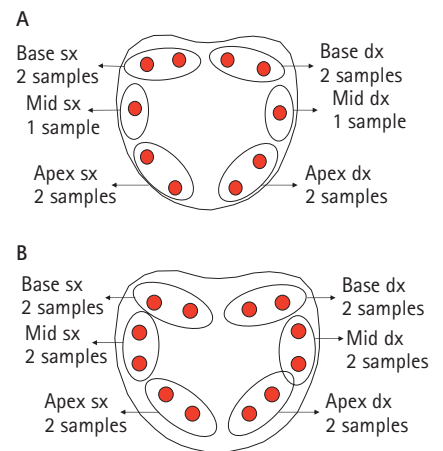
Once a patient was enrolled and had given written informed consent to participate in the study, he had the following examinations that were exclusively conducted by medical personnel from the five departments participating in the study. An investigator, with no access to any clinical information, assessed the patient with the TRIMprob system on an outpatient basis. TRIMprob investigations were conducted by five urologists, one from each centre participating to the study. This device was described in detail previously [5]. Briefly, the system consists of a battery-operated detection probe, a receiver and a computer console that displays the information obtained. The probe is  $\approx 30$  cm long and can easily be held in one hand. It contains a tuneable, autonomous oscillator and an antenna which emits a very weak electromagnetic wave at several frequencies (465, 930 and 1395 MHz). The penetration of the electromagnetic wave depends on its frequency and the dielectric properties of the target tissues. Theoretically, the 465 MHz frequency has a plane wave penetration for tissue thicker than 4 cm and is therefore best suited for analysis of the perineal region. The prostate gland is therefore irradiated through the perineal region by the resulting field from the TRIMprob antenna. When a resonance is stimulated the changes in the electromagnetic pattern emitted by the probe are detectable. The receiver is situated  $\approx 1.5$  m from the probe, acting as a multifrequency radiation pattern analyser, and displays the

three different frequencies. When the probe is brought close to the patient, the biophysical interaction causes changes in one or several frequency amplitudes depending on the pathological state of the tested tissue. These changes are shown on a logarithmic scale and are expressed in arbitrary units of 0–255. A negative signal variation is the result of the interaction of the emitted field with prostatic tissue, and constitutes the basis for diagnosing the irradiated tissues. These measurements are shown on a computer display during the examination and saved for analysis.

A standard method for the TRIMprob investigation of the prostate was defined and used in the present study, according to preliminary experience reported previously [5,13]. In the present study the active part of the probe was positioned at the perineal level with the patient looking at the receiver of the system. The operator was positioned behind the patient and to the side, to avoid interference with the electromagnetic signal emitted by the probe. Well-defined movements of the probe, i.e. transverse, perineal and rotational, were necessary to conduct a complete examination of the prostate, always ensuring that the probe radiating part maintained good contact with the patient's perineum. For each patient the probe was moved in six standard conventional positions, termed posterior median, posterior left, posterior right, anterior median, anterior left and anterior right. For the detection of anterior positions the patient was asked to turn his back towards the receiver. The amplitude values corresponding to the six prostate areas were saved on the receiver. The suspected presence of prostate cancer was based on evaluating the three spectral lines displayed in each of the three anterior and three posterior positions. According to previous clinical experience an examination was considered suspect for cancer when it was possible to detect a reduction of the 465 MHz band below a threshold (10% of its normal amplitude) in at least two saved projections, the latter for confirmation purposes. On the basis of the results obtained, the investigator indicated whether cancer was present or not (TRIMprob positive or negative).

A second urologist, who had no information about the result of the TRIMprob examination, carried out the following examinations: a blood sample was taken from each patient enrolled in the study for central analysis of

FIG. 1. Systematic schemes for prostatic biopsies. At least 10 biopsy cores were taken for prostates of  $< 50$  g (A), and at least 12 for prostates of  $\geq 50$  g (B).



total PSA, fPSA and PSA ratio; a DRE, considering the overall prostate consistency and presence/absence of nodules, and if present, an indication of their location (one side/both sides), and any prostate asymmetry; TRUS, considering the prostate volume and weight, and the presence of hypoechoic/hyperechoic areas. When such areas were identified, the dimension and location of each area and the presence of calcifications was noted; TRUS-guided biopsies, collecting information for each of the biopsy cores, i.e. the presence or absence of tumour, and if there was tumour, an indication of the percentage of specimen positive for cancer, histology of the tumour, and cancer grade according to the five point Gleason scale. The TRUS-guided biopsies were taken according to a systematic prostate scheme (Fig. 1). At least 10 biopsy cores were taken for a prostate of  $< 50$  g and at least 12 for prostates of  $\geq 50$  g; one additional core was taken in the area of each nodule discovered.

Pathologists were unaware of the TRIMprob findings but not, as in usual clinical practice, of other clinical data, e.g. PSA level and DRE findings. A central pathological review of prostatic biopsies was not considered in the study.

## RESULTS

The final dataset included 188 patients who were evaluable for analysis; 12 patients were excluded because of protocol violation (five refused to have prostatic biopsies after

Variable	Patients		P (chi-square)	
	Total	+ve biopsy		-ve biopsy
Overall	188	61	127	
Age				<0.001
45-54	8	2 (3)	6 (5)	
55-59	23	3 (5)	20 (16)	
60-64	52	13 (21)	39 (31)	
65-69	43	19 (31)	24 (19)	
70-74	39	18 (30)	21 (16)	
75-85	23	6 (10)	17 (13)	
PSA, ng/mL				<0.001
<4.1	25	7 (11)	18 (14)	
4.1-9.9	100	30 (49)	70 (55)	
10-19.9	52	18 (30)	34 (27)	
≥20	11	6 (10)	5 (4)	
%fPSA				<0.001
<18	119	48 (79)	71 (56)	
≥18	69	13 (21)	56 (44)	
Prostate volume, mL				<0.001
1-40	55	28 (46)	27 (21)	
40-70	76	27 (44)	49 (39)	
70-220	57	6 (10)	51 (40)	
TRIMprob				<0.001
Positive	111	49 (80)	62 (49)	
Negative	77	12 (20)	65 (51)	
DRE				<0.001
Positive	39	25 (41)	14 (11)	
Negative	149	36 (59)	113 (89)	

**TABLE 1**  
The clinical characteristics of 188 patients referred for prostatic biopsy because of an abnormal DRE or elevated PSA level

Characteristic	TRIMprob		P
	positive	negative	
Mean (SD):			
age, years	66 (7.2)	66 (7.0)	0.377
PSA, ng/mL	10 (10.8)	8 (4.3)	0.760
Prostate volume, mL	62 (34.8)	62 (28.5)	0.984
DRE +ve, n	27	12	0.146
DRE -ve, n	84	65	

**TABLE 2**  
Clinical characteristics of the 188 patients according to TRIMprob results

TRIMprob evaluation and seven were not biopsied according to the above-described standard). Table 1 summarizes the descriptive characteristics of the patients; there was a wide range of PSA values (1-108 ng/mL), although 90% of the patients had a PSA level of < 20 ng/mL (mean 9.3, SD 8.8). The mean (SD, range) volume of the examined prostates was 62.0 (32.4, 10-220) mL. There were no significant differences among centres in age, PSA level and DRE findings ( $P=0.42, 0.55$  and  $0.28$ , respectively).

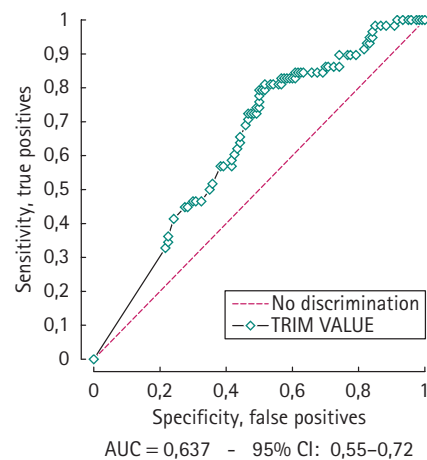
Of the 188 patients, 61 (32.4%) had a positive biopsy for adenocarcinoma of the prostate; of the 127 with a negative biopsy for cancer, 12 (10%) were diagnosed with atypical small

acinar proliferation or high-grade prostatic intraepithelial neoplasia, and these were considered as negative cases in the statistical analysis. The mean (range) Gleason score of the diagnosed cancers was 6.4 (4-9) and the mean number of positive cores was 4.2 (1-8).

A univariate analysis showed that patients with positive biopsies were older than those with negative biopsies, at 67.4 (6.4) vs 65.2 (7.2) years ( $P=0.03$ ), while mean PSA values were not significantly different in the two groups, at 10.0 (5.7) vs 9.0 (9.9) ng/mL ( $P=0.45$ ).

Patients with a negative biopsy had a significantly higher prostate volume than

**FIG. 2.** Receiver operating characteristics curve: TRIMprob (465 MHz) diagnosis of prostate cancer in 188 patients referred for prostatic biopsy because of an abnormal DRE or elevated PSA level.



those with a positive biopsy, at 69.6 (31.8) vs 49.3 (29.5) mL ( $P<0.001$ ). The cancer detection rate was significantly higher in patients with a positive DRE (25/39, 64%) than in patients with a negative DRE (36/149, 24%,  $P<0.001$ ). The patient characteristics according to biopsy findings are also reported in Table 1.

TRIMprob investigations were positive in 111/188 patients (59%) and negative in the remaining 77/188 (41%). There were no significant differences in TRIMprob performance among the centres. TRIMprob correctly detected 49/61 patients (80%) with prostate cancer and gave a false-positive result in 62/127 patients (48%). Assuming that an extended series of positive biopsies is the reference standard for detecting prostate cancer, the overall sensitivity, specificity, PPV, negative PV (NPV) and accuracy of TRIMprob were 80%, 51%, 44%, 84% and 60%, respectively. The prostate cancer detection rate on biopsy was significantly higher in patients with a positive examination (49/111, 44%) than in patients with a negative TRIMprob (12/77, 15%;  $P<0.001$ ). The performance of TRIMprob for detecting prostate cancer is shown schematically in Fig. 2.

None of the evaluated variables (PSA level, age, prostatic volume) was statistically different between the groups of patients with a positive and negative TRIMprob result (Table 2). The mean PSA level, Gleason score and mean number of positive cores were not

significantly different between the true-positive and false-negative patients on TRIMprob analysis ( $P = 0.469, 0.640$  and  $0.499$ , respectively).

The sensitivity, specificity, PPV, NPV and accuracy of TRIMprob were also compared with those of DRE and %fPSA (threshold 18%) and are summarized in Table 3. While the specificity of DRE was higher than that of TRIMprob (89% vs 51%,  $P < 0.001$ ), the sensitivity and the NPV of TRIMprob were higher than those of DRE (80% vs 41%, and 84% vs 75%, both  $P < 0.001$ ). When the TRIMprob result was combined with DRE findings, the sensitivity and NPV both increased to 92%. Figure 3 presents the probability of a positive or negative biopsy in patients with positive and negative TRIMprob results, stratified first according to the DRE result (normal or abnormal). The probability of a positive biopsy in the presence of a positive TRIMprob varied significantly depending on the DRE. The positive biopsy rate was as low as 8% in patients with a negative TRIMprob and DRE, and as high as 67% in patients with both positive findings.

## DISCUSSION

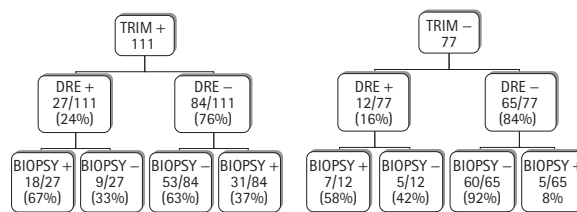
An increased PSA value and/or an abnormal DRE are the two major indications for a TRUS-guided prostatic biopsy, which is the standard method for detecting prostate cancer. Unfortunately, the specificity of PSA at levels of  $>4.0$  ng/mL is only 60–70% and thus up to 40% of prostatic biopsies are unnecessary [2]. Moreover, the false-negative rate of TRUS-guided biopsy is high (30%–40%), and biopsies must therefore often be repeated [7,8]. In this situation it is reasonable to seek other techniques which can be used to reveal prostate cancer [9,10].

TRIMprob is a new technology which has the great advantages of being noninvasive and easily reproducible [5]. Published data on prostate cancer detection with TRIMprob suggest that the nonlinear resonance interaction at 465 MHz is the most relevant in distinguishing cancerous from benign prostate tissue [5], and for this reason we focused on this frequency in the present clinical study, designed to confirm preliminary published data. No consensus has yet been reached as to why the 465 MHz frequency is more specific for detecting cancer tissue than 930 and 1395 MHz.

TABLE 3 The sensitivity, specificity, PPV, NPV and accuracy of TRIMprob, DRE, %fPSA in the 188 patients

Test	Sensitivity	Specificity	PPV	NPV	Accuracy
TRIMprob	80	51	44	84	60
DRE	41	89	64	75	73
%fPSA (threshold 18)	79	46	79	46	58
Trimprob + DRE	92	47	46	92	61

FIG. 3. The probability of a positive or negative biopsy in patients with positive and negative TRIMprob results, stratified according to the DRE result (normal or abnormal), in 188 patients referred for prostatic biopsy because of an abnormal DRE or elevated PSA level.



Previous single-institution results also showed that this device seems to have clinical utility [11,12]. The present study provides the first multicentre demonstration of the clinical utility of this noninvasive technology for detecting prostate cancer.

The present patients were due to have a prostate biopsy because of suspected cancer. According to published data, two-thirds would have had a negative biopsy which was therefore unnecessary. This was confirmed, as only 61 of 188 patients had a histological diagnosis of prostatic cancer. The prostate cancer detection rate on biopsy was significantly higher in patients with a positive TRIMprob examination (44%) than in those with a negative result (15%;  $P < 0.001$ ). None of the evaluated variables (PSA level, age, prostatic volume) was statistically different between groups of patients with a positive and negative TRIMprob result.

In the present study the TRIMprob method was confirmed to be highly sensitive for diagnosing prostate cancer, but lacked specificity; the sensitivity was 80% when used to detect prostate cancer by different investigators who had no access to the clinical information of the patient. In association with the DRE findings the sensitivity of TRIMprob increased from 80% to 92%, but the specificity did not change (remaining stable at 47%) and the overall accuracy increased only slightly (60.6 to 61.7%). At present the major limitation of this device is thus the many false-positive results.

As we have no clear reason to explain this lack of specificity, we only have hypotheses. It is likely that the nonlinear resonance at 465 MHz, as used in this clinical trial to distinguish between cancerous and benign tissue, might also be generated by other biological tissue, e.g. prostatic calcifications or inflammatory infiltration, which are relatively frequent in patients with BPH. Moreover, prostatic biopsies, even if extensive, might have failed to detect some prostate cancer. As the present cancer detection rate decreased progressively as the prostate volume increased, it is possible that we missed some cancers in larger prostates. It was already reported that most missed cancers at initial biopsy are in large prostates [13]. Unfortunately, repeat biopsies were not taken in the present study and thus we do not know how many cancers were missed in the first series of prostate biopsies. The specificity of the TRIMprob method might also be improved by using a different method to assess a positive TRIMprob scan.

We used a standard method for the TRIMprob investigation of the prostate, and to assess a positive scan, as already described [5]. However, TRIMprob performance might be improved in the future by defining other methods, and these need to be investigated further.

In a recent preliminary series of patients we were able to increase the sensitivity of the method with no effect on specificity simply by considering as positive a TRIMprob

examination of the prostate that could reproduce a positive signal not only in two different sites but also at two different distances.

We were also unable to clarify the reasons for the false-negative cases, as the pathological characteristics of the true-positive and false-negative cases were not significantly different.

In conclusion, TRIMprob seems to be a useful tool in the diagnosis of prostate cancer and can be used to increase the accuracy of PSA and DRE results. In our opinion, and at the present level of understanding, it is unsuitable as a single investigative tool for screening, due to its low specificity. However, the high sensitivity and NPV might be considered its present strength, and we suggest that this new technology might be useful in clinical practice to reduce the rate of negative biopsies typically associated with PSA screening programmes, and to avoid repeated series of biopsies in patients suspected of having prostatic cancer. Data reported in this study need to be confirmed by other multicentre and larger clinical series.

#### CONFLICT OF INTEREST

None declared.

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Abbreviations: (P)(N)PV, (positive) (negative) predictive value; TRIMprob, tissue-resonance interaction method; %fPSA, percentage free PSA.