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CAN PROSTATE CANCER BE PREDICTED IN BPH PATIENTS WITH ELEVATED SERUM PSA AND NEGATIVE INITIAL SEXTANT BIOPSY? A MULTIVARIATE ANALYSIS STUDY

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Objective To define a predictor of prostate cancer in BPH patients with an intermediate PSA (4.1-10 ng/ml) and a negative initial sextant biopsy.

Patients and Methods During 1999, 193 BPH patients with an intermediate PSA (4.1-10 ng/ml) underwent TRUS and sextant biopsy. The patients whose initial biopsies were negative for prostate cancer were re-evaluated by serum PSA every 6 months. A total of 76 patients were subjected to an extended 11-core biopsy in view of: (1) PSA velocity ≥ 1 ng/ml/year, (2) a PSA rise to > 10 ng/ml and (3) suspicious biopsy findings (atypical adenomatous hyperplasia or high-grade prostatic intra-epithelial neoplasia). Overall, 160 patients were subjected either to TURP (n=127) or open prostatectomy (n=33).

Results On initial sextant biopsy, prostate cancer was diagnosed in 22 out of 193 patients (11.4%). The specificity of the sextant biopsy was 91.8% and its positive predictive value (PPV) was 61.1%. A repeated 11-core biopsy revealed prostate cancer in 11 out of 76 patients (14.5%). The specificity of the 11-core biopsy was 95.4% and its PPV was 78.6%. Three cancers out of 160 (2%) were discovered on definitive pathology. The PSA velocity cut-off point at 1.4 ng/ml/year and the PSA density cut-off point at 0.12 were optimal for the prediction of cancer using receiver operating characteristic curves. The multivariate analysis (stepwise logistic regression) revealed that PSA density (p=0.011), PSA velocity (p=0.002) and age (p=0.021) were the most significant predictors of cancer, when the data were inserted as continuous variables. The sensitivity, specificity and overall accuracy of the model were 80%, 98.7% and 95.9%, respectively. When the data were re-inserted in a coded format, PSA velocity and PSA density were the only predictors. All the analyzed risk factors (age, PSA, DRE, prostate echogenicity and PSA/TZ index) were excluded from the model.

Conclusion PSA velocity and PSA density were the most significant predictors of prostate cancer in BPH patients with an intermediate PSA (4.1-10 ng/ml) and a negative initial sextant biopsy.

Key Words prostate cancer, prostate specific antigen (PSA), 11-core biopsy

INTRODUCTION

Transrectal ultrasound of the prostate (TRUS) and biopsy are often performed to exclude malignancy in men with an elevated serum PSA. However, in many cases prostate cancer is not identified at initial evaluation. A dilemma arises in men with an initially negative biopsy for prostate cancer who subsequently have an abnormally elevated serum PSA. Keetch et al.[1] reported about the results in men undergoing serial prostate biopsies for a persistently elevated serum PSA. The cancer detection rates for biopsies 1, 2, 3 and 4 or more were 34%, 19%, 8%and 6%, respectively. Ellis and Brawer[2] also showed that 20% of men undergoing repeated biopsies after initially negative results had prostate cancer.

The main aim of our study was to define a predictor of prostate cancer in patients with benign prostatic hyperplasia (BPH) with an intermediate PSA (4.1-10 ng/ml) and a negative initial sextant biopsy.

PATIENTS AND METHODS

During 1999, a total of 193 BPH patients with an intermediate serum PSA (4.1-10 ng/ml) underwent TRUS and sextant biopsy. Indications for sextant biopsy were a PSA density ≥ 0.10 in 86% (166/193), an abnormal digital rectal examination (DRE) in 18.1% (35/193) and the presence of hypoechoic nodules at the peripheral zone (PZ) in 16.5% (32/193). The baseline patient characteristics are illustrated in Table 1. PSA testing was performed prior to DRE in all cases (using the IMx assay – normal range from 0 to 4.0 ng/ml). The prostate volume was calculated by planimetry according to the following equation:

prostate volume in cm^3 = (height x width x length) x 0.523.

Patients with negative results on initial biopsy were re-evaluated by PSA and DRE every six months. PSA velocity was calculated in 131 patients who had three separate PSA determinations within at least 18 months. During follow up, a total of 76 patients were subjected to an extended 11-core biopsy of the prostate. The indications for a repeated biopsy are summarized in Table 2.

Eleven-core biopsy incorporated five cores from three alternate sites in addition to conventional sextant biopsy. Two cores were taken from the right and left anterior horns of the peripheral zone (PZ) representing the extreme lateral tissue of PZ in the sagittal plane (Fig. 1). Two cores were taken from the right and left transition zone (TZ) adjacent to the urethra (periurethral biopsies). The last midline biopsy targeted tissue from the distal apical third of the prostate up to the proximal third of the gland base. The midline biopsy of the PZ was usually taken at the midsagittal plane.

None of the patients required sedation. Each patient received 500 mg ciprofloxacin one hour before biopsy and for three days afterwards (500 mg every 12 hours). A neomycin enema (500 mg dissolved in 150 cc normal saline) was routinely administered immediately before the biopsy. Needle biopsies were performed with a spring loaded automatic biopsy device using an 18-gauge Tru-cut needle. Each core was coded to provide an accurate identification of its site of origin.

Overall, 160 patients were subjected either to TURP (n=127) or open prostatectomy (n=33). The results of the initial and repeated biopsies were compared with the results of the definitive pathology.

Table 1: Characteristics of 193 BPH Patients Undergoing Prostate Ultrasound and Initial Sextant Biopsy

	Mean Value ± Standard Deviation (SD)
Patients' age (years)	63.75 ± 8.15
Serum PSA (ng/ml)	6.77 ± 1.71
Prostate volume (cc)	51.18 ± 23.42
Adenoma volume (cc)	26.77 ± 17.12
PSA density	0.15 ± 0.06
PSA/transition zone index	0.35 ± 0.19

For statistical analysis, the coded data were compared using the chi-square test of association. Risk factors (age, serum PSA, DRE, prostate echogenicity, PSA density, PSA/TZ index and PSA velocity) were analyzed by stepwise logistic regression to define the most significant predictors of prostate cancer.

RESULTS

Overall, 36 cancer cases out of 193 patients (18.7%) were identified on initial sextant biopsy, repeat 11-core biopsy and on definitive pathology. The overall cancer detection rate based on the patients' characteristics is illustrated in Table 3.

Initial sextant biopsy revealed prostate cancer in 22 out of 193 patients (11.4%). The specificity of the sextant biopsy was 91.8% and its positive predictive value (PPV) was 61.1%. The results of the initial biopsy are summarized in Table 4. In 9 of 22 patients (41%) in whom cancer was identified, only one biopsy core was positive. The Gleason score was high (7 or more) in 4 out of 22 patients (18.2%).

The repeat 11-core biopsy showed prostate cancer in 11 out of 76 patients (14.5%). Specificity and PPV of the 11-core biopsy were 95.4% and 78.6%, respectively. In 7 of the 11 patients (64%) in whom cancer was identified, only one biopsy core was positive. All cancers diagnosed on repeat biopsy were of low Gleason score (6 or less). The results of the ex-

Table 2: Indications for Repeat 11-Core Biopsy (76 Patients)

	No. of Patients	Percentage (%)
PSA rise to > 10 ng/ml	18/76	23.7%
PSA velocity ≥ 1 ng/ml/year	43/76	56.6%
Suspicious findings on initial biopsy:		
- atypical adenomatous hyperplasia	6/76	7.9%
- high-grade prostatic intra-epithelial neoplasia	5/76	6.6%
Persistently abnormal PSA in patients with chronic prostatitis in spite of appropriate antimicrobial treatment	12/76	15.7%
Abnormal changes in DRE	1/76	1.3%

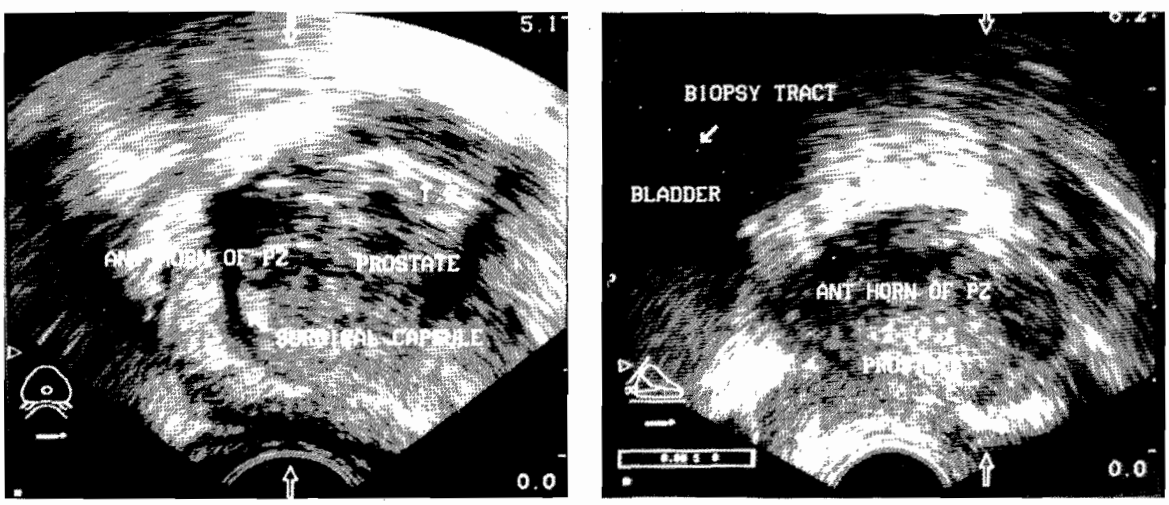

Fig. 1: Anterior horn of the peripheral zone (PZ). It represents the extreme lateral tissue of the PZ in the sagittal plane. **A:** transverse plane, **B:** sagittal plane.

tended 11-core biopsy are summarized in Table 5.

Of the five and six patients in whom a previous sextant biopsy had shown high-grade prostatic intra-epithelial neoplasia (PIN) and atypical adenomatous hyperplasia, respectively, 11-core biopsy revealed prostate cancer in two patients of each group (40% and 33.3%, respectively).

The distribution of positive cores was as follows: sextant biopsy sites only in 18% (2/11), alternate sites only in 64% (7/11), sextant and alternate sites in 18% (2/11). The anterior horn of the PZ was the most frequently positive alternate site (7/9 = 77.8%), followed by the TZ (2/9 = 22.2%), while midline biopsy of the PZ was not involved at all. Overall, a 30.5% (11/36) increase in the cancer detection rate was observed when the biopsy technique included the alternate sites (p=0.0022).

On definitive pathology three cancer patients were discovered out of 160 (2%). Previous needle biopsies of these three patients had shown high-grade PIN in one, atypical adenomatous hyperplasia in another and BPH

Table 3: Overall Cancer Detection Rate Based on the Patients' Characteristics

Patients' characteristics	Cancer Detection Rate [/]*= %		P=Value
Age	< 60	≥ 60	
	[5/59]=8.4%	[31/134]=23%	0.016
DRE	benign	abnormal	
	[20/158]=12.6%	[16/35]=45.7%	<0.001
Echogenicity	homogenous	hypoechoic nodule at PZ**	
	[13/90]=14.4%	[18/32]=56.2%	<0.001
	homogenous	hypoechoic nodule at TZ***	
	[13/90]=14.4%	[5/71]=7%	0.138
PSA density	<0.15	≥ 0.15	
	[11/122]=9%	[25/71]=35.2%	<0.001
PSA velocity♦	<1 ng/ml/year	≥1 ng/ml/year	
	[0/39]=0%	[14/43]=32.5%	<0.001
PSA/TZ index	<0.35	≥0.35	
	[14/116]=12%	[22/77]=28.6%	<0.001

*[/] = proportion [no. of detected cancer cases / total no.]
** PZ = peripheral zone, *** TZ = transition zone
♦ = PSA velocity was calculated in 131 patients (PSA decreased in 49)

Table 4: Results of Initial Sextant Biopsy

	No. of Patients	%
Benign prostatic hyperplasia	130	67.4%
Chronic prostatitis	28	14.5%
Glandular atrophic changes	2	1.0%
Atypical adenomatous hyperplasia	6	3.1%
High-grade prostatic intra-epithelial neoplasia	5	2.6%
Prostatic carcinoma	22	11.4%
Total	193	100%

Table 5: Results of Repeat 11-Core Biopsy

	No. of Patients	%
Benign prostatic hyperplasia	36	47.4%
Chronic prostatitis	22	29.0%
Atypical adenomatous hyperplasia	4	5.2%
High-grade prostatic intra-epithelial neoplasia	3	3.9%
Prostatic carcinoma	11	14.5%
Total	76	100%

Table 6: Results of Definitive Pathology

	No. of Patients	%
Benign prostatic hyperplasia	111	69.4%
Chronic prostatitis	35	21.8%
Glandular atrophic changes	2	1.2%
Atypical adenomatous hyperplasia	4	2.5%
High-grade prostatic intra-epithelial neoplasia	5	3.1%
Prostatic carcinoma	3	2.0%
Total	160	100%

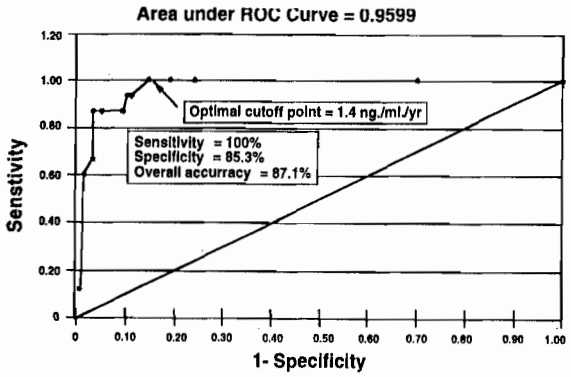

Fig. 2: Receiver operating characteristic curve (ROC) for PSA velocity showing sensitivity graphed against 1-specificity. Arrow indicates optimal cut-off point.

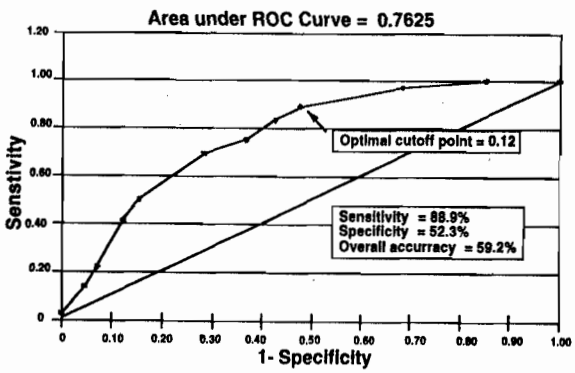

Fig. 3: Receiver operating characteristic curve (ROC) for PSA density showing sensitivity graphed against 1-specificity. Arrow indicates optimal cut-off point.

Table 7: Stepwise Logistic Regression with Data Inserted as Continuous Variables

Preoperative Variable	Regression Estimate (B)	P-Value
PSA density	32.0198	0.011
PSA velocity	2.2520	0.002
Age	0.2458	0.021
DRE		
- benign feeling	0.00	0.149
- firm prostate	-3.8405	0.052
- suspicious nodule	-2.2799	0.673
Constant	-27.6110	0.005

N.B.: Serum PSA, prostate echogenicity and PSA/TZ index were removed from the model

in the third one. On definitive pathology, three additional cases of isolated high-grade PIN and one case of atypical adenomatous hyperplasia were diagnosed. The results of the definitive pathology are summarized in Table 6.

The stepwise logistic regression revealed that PSA density (p=0.011), PSA velocity (p=0.002) and age (p=0.021) were the most significant predictors of prostate cancer when the data were inserted as continuous variables (Table 7). The serum PSA, echogenicity of the prostate and PSA/TZ index were removed from the model. The sensitivity of the model was 80%, while the specificity was 98.7% and the overall accuracy 95.9%. When the data were re-inserted as a coded format, PSA velocity and PSA density were the only relevant predictors of cancer. The significance of the log likelihood ratio (LR) was <0.001 and 0.031 for PSA velocity and PSA density, respectively, when the term was removed from the model. Other risk factors including age, DRE, serum PSA, prostate echogenicity and PSA/TZ index were removed from the model. The sensitivity of the model was 66.7%, while its specificity was 95.7% and its overall accuracy 91.7%.

An optimal prediction of prostate cancer was obtained at a PSA velocity cut-off point of 1.4 ng/ml/year and a PSA density cut-off point of 0.12 using receiver operating characteristic curves (ROC) (Fig. 2, 3).

DISCUSSION

PSA density and PSA velocity have been utilized to increase the specificity of PSA testing in the diagnosis of prostate cancer in men with an elevated serum PSA. Some studies suggest that a PSA density of ≥ 0.15 may be a more reliable predictor in prostate cancer screening than PSA alone[3,4]. However, others could not demonstrate any advantage of PSA density over PSA in early detection of prostate cancer[5,6]. Benson et al.[7,8] reported that PSA density improved specificity while maintaining sensitivity and allowing for the classification of some patients as having a low risk for the development of prostate cancer. Smith and Catalona[9] reported that for PSA velocity calculations to predict cancer reliably at least two, and preferably three PSA measurements within a 1-2 year period were required. Selley et al.[10] reported that an increase in PSA would need to be >30% to be considered significant.

In the study of Keetch et al.[1], a logistic regression analysis revealed that serum PSA alone did not predict the incidence of prostate cancer on subsequent prostate biopsy. In our study, stepwise logistic regression revealed that PSA velocity (P=0.002) and PSA density (P=0.011) were the most significant predictors of prostate cancer in BPH patients with an intermediate PSA (4.1-10 ng/ml) and a negative initial biopsy.

Keetch et al.[11] identified 327 men above the age of 50 with an initially negative prostate biopsy who had a persistent PSA elevation. They compared 70 men with a PSA density ≥ 0.15 and PSA velocity ≥ 0.75 ng/ml/ year to 83 patients with a PSA density < 0.15 and PSA velocity < 0.75 ng/ml/year and found that 46% and 11%, respectively, had prostate cancer on subsequent prostate needle biopsies (P< 0.0001). In a logistic regression analysis PSA density and PSA velocity were predictive of prostate cancer on subsequent biopsy (P= 0.001 and 0.03, respectively). A PSA density ≥ 0.15 alone or a PSA velocity ≥ 0.75 ng/ml/year alone as indicators for a repeated biopsy would have missed 35% and 40% of cancer, respectively.

Catalona et al.[12] analyzed 99 volunteer patients who had a previous negative needle biopsy and a serum PSA level of 4.1 - 10 ng/ml. They found 20% of patients with prostate cancer on their second needle biopsy. This group of patients had significantly lower free PSA

levels and a higher PSA density with an overlap in 83% of the cases. The use of percent free PSA cut-offs of 28% and 30% would have detected 90% and 95% of cancers, respectively, and avoided 13% and 12% of the biopsies, respectively. PSA density cut-offs of 0.10 and 0.08 would have detected 90% and 95% of cancers, respectively and avoided 31% and 12% of biopsies, respectively.

Hayek et al.[13] reported about 149 patients with a serum PSA ranging between 4.1 and 10 ng/ml or an abnormal DRE who had a negative needle biopsy of the prostate. Out of these, 51 (34.4%) had repeated biopsies in view of: (1) a PSA velocity ≥ 1 ng/ml/year (2) a serum PSA rise to greater than 10 ng/ml (3) the development of an abnormal DRE during follow up. Prostate cancer was detected in 8 out of 51 men (15.7%) who had a repeat biopsy. A multivariate analysis failed to identify any significant predictors of prostate cancer in the repeat biopsy group. They concluded in their study that PSA or PSA derivatives (PSA density or free:total PSA) cannot be utilized to determine which patients will be at high risk for requiring repeat prostate biopsy.

Borboroglu et al.[14] reported about extensive transrectal ultrasound-guided biopsies (ranging from 15 to 31 cores depending on the prostate size) in 57 men with a previously negative sextant biopsy. Prostatic carcinoma was identified in 17 out of these 57 men (30%). In 7 of the 17 patients (41%) in whom cancer was identified, only one biopsy core was positive. Of the 15 patients in whom previous sextant biopsy had shown high-grade PIN or atypical small acinar proliferation, extensive needle biopsies revealed cancer in 7 (47%). They also reported that the analysis of clinical factors (PSA, PSA velocity, free:total PSA and previous suspicious biopsy) for the ability to predict a positive biopsy revealed that PSA was the only statistically significant predictor of a positive biopsy ($P < 0.001$). Prostate cancer was noted in 64% of the men with a PSA velocity ≥ 1ng/ml/ year.

Babaian et al.[15] evaluated an 11- core biopsy scheme and conventional sextant biopsies in 362 patients from two institutions. Overall, a 33% increase in the cancer detection rate was observed when the biopsy technique included the alternate areas (P=0.0021). The anterior horn was the most frequently positive biopsy site followed by the TZ and midline sites. In our study, a 30.5% (11 of 36) increase in the overall cancer detection rate was noted when the 11-core biopsy was applied (P=0.0022). It was concluded that the 11-core technique had significantly better cancer detection rates when DRE and TRUS were normal, and in men with a serum PSA between 4.1 - 10 ng/ml[15].

In conclusion, the multivariate analysis revealed that PSA velocity (P=0.002) and PSA density (P=0.011) were the most significant predictors of prostate cancer in BPH patients with an intermediate serum PSA (4.1-10 ng/ml) and a negative initial sextant biopsy. An extended 11-core biopsy is significantly valuable for patients with a persistently abnormal PSA as it increases the overall cancer detection rate by 30.5% (P=0.002).

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RESUME

Le Cancer de la Prostate Peut-Il Etre Prédit chez des Patients Présentant une Hypertrophie Bénigne de la Prostate (HBP) avec un Taux de PSA Elevé et une Biopsie Initiale à 6 Carottes Négative ? Etude par Analyse Multivariée.

Objectifs: Définir un prédicateur de cancer de la prostate chez des patients présentant une HBP avec un taux de PSA intermédiaire (4.1-10ng/ml) et une biopsie initiale à 6 carottes négative. **Patients et Méthode:** Durant l'année 1999, 193 patients présentant une HBP avec un taux de PSA intermédiaire (4.1-10ng/ml) ont bénéficié d'une Résection Trans-Urétrale de la Prostate (RTUP) et d'une biopsie de prostate à 6 carottes. Les patients dont la biopsie initiale était indemne de cancer ont été réévalués par un dosage du taux de PSA tous les six mois. Un total de 79 patients a bénéficié d'une biopsie prostatique à 11 carottes sur la base : (1) d'une vélocité de PSA supérieure ou égale à 1ng/ml/an, (2) d'une élévation du PSA > 10ng/ml et (3) d'une biopsie suspecte (hypertrophie adénomateuse atypique ou haut grade de néoplasie intra-épithéliale prostatique). Au total 160 patients ont bénéficié d'une RTUP (n=127) ou d'une résection prostatique par chirurgie ouverte (n=33). **Résultats :** A l'issu de la biopsie à 6 carottes, le cancer de la prostate a été diagnostiqué chez 22 patients sur 193 (11.4%). La spécificité de cette biopsie était de 91.8% et sa valeur prédictive positive était de 61.1%. La biopsie à 11 carottes avait révélé le cancer de la prostate chez 11 patients sur 76, ce qui représente une spécificité de 95.4% et une valeur prédictive positive de 78.6%. Trois cancers sur 160 (2%) ont été découverts sur l'examen histologique de la pièce opératoire. Les valeurs limites de 1.4ng/ml pour la vélocité du PSA et de 0.12 pour la densité de PSA sont optimales pour la prédiction du cancer de la prostate en utilisant les courbes ROC. L'analyse multivariée utilisant la régression logistique a révélé que la densité de PSA (p=0.011), la vélocité du PSA (p=0.021) et l'âge étaient les plus significatifs prédicateurs de cancer lorsque les donnés étaient introduites selon un format continu. La sensibilité, la spécificité et l'exactitude globale du modèle étaient respectivement de 80%, 98.7% et 95.9%. Lorsque les données sont introduites selon un format codé, la vélocité du PSA et la densité de PSA étaient les seules prédicatrices. Tous les facteurs de risque analysés (age, PSA, toucher rectal, échogénicité, PSA/zone de transition) ont été exclu du modèle. **Conclusion:** La vélocité du PSA et la densité de PSA sont les plus significatifs indicateurs de cancer de la prostate chez les patients présentant 1 HBP avec un taux de PSA allant de 4.1 à 10 ng/ml et une biopsie initiale à 6 carottes négative.

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