Pergamon

European Journal of Cancer Vol. 31A, No. 1, pp. 12–14, 1995

0959–8049/95 $9.50+0.00

0959-8049(94)00309-2

Volume Adjustment for Intermediate Prostate-specific Antigen Values in a Screening Population

Chr.H. Bangma, D.E. Grobbee and F.H. Schröder

In a screening population of 812 men, between the ages of 55 and 77 years, and prostate-specific antigen (PSA) below 10.0 ng/ml (Hybritech), digital rectal examination (DRE) and transrectal ultrasonography of the prostate (TRUS) were performed. Seventeen prostate carcinomas were detected. Four methods of prostate volumetry were used to determine volume-adjusted PSA levels. These were PSA density for the total gland volume (PSAD), for the inner zone volume (PSAT) and population-specific excess PSA values. There was a significant difference between the benign and the malignant population for age, PSA, PSAD, PSAT and excess PSA values. The maximal discriminatory potential, analysed by the area under receiver ROC curve, was 0.90, reached for prolate spheroid determined excess PSA. For PSA alone this was 0.86. Volume-adjusted PSA values have no additional benefit beyond unadjusted values in screening for prostate carcinoma in this study.

Key words: prostatic carcinoma, screening, PSA, ultrasonography
Eur J Cancer, Vol. 31A, No. 1, pp. 12–14, 1995

INTRODUCTION

SCREENING FOR prostate carcinoma (PCa) might provide a means of detecting confined prostate carcinoma at a treatable stage [1]. While digital rectal examination (DRE) and serum prostate-specific antigen (PSA) determination have a limited positive predictive value (PPV) [2], especially in the intermediate range of PSA values between 4 and 10 ng/ml, their combined application was shown to be more effective. Transrectal ultrasonography (TRUS) of the prostate in combination with PSA and DRE may increase PPV and negative predictive values (NPV) for detection of PCa.

Volumetric parameters have been thought to limit the number of transrectal biopsies of the prostate without increasing the number of false negatives. In this study, ultrasonic volumetry was performed to determine volume-adjusted PSA values, for example, prostate-specific antigen density (PSAD), which indicates abnormal PSA production in the body. Several formulae of PSA density have been reported, including PSAD (PSA/total gland volume [3]) and PSAT (PSA/inner zone volume [4]). In this Rotterdam feasibility study for screening prostate carcinoma, new volume-adjusted PSA values were evaluated for their use in selecting participants for further diagnostic examinations and/or prostate biopsy.

Correspondence to Chr.H.Bangma.
Chr.H. Bangma and F.H. Schröder are at the Department of Urology and D.E. Grobbee is at the Department of Epidemiology & Biostatistics, Erasmus University and Academic Hospital, Rotterdam, The Netherlands.
Revised 22 Jul. 1994; accepted 1 Aug. 1994.

PATIENTS AND METHODS

Of a screening population of 1739 males, between the ages of 55 and 77 years, 812 participants were randomly chosen for diagnostic examinations by DRE and TRUS, if PSA was below 10.0 ng/ml (monoclonal Hybritech Tandem-R Stratus). DRE and TRUS were performed by four urological residents with a 1846 Bruel and Kjaer 7.0 MHz biplanar ultrasound probe. Four different methods of prostate volumetry of total gland and inner zone were used: 5 mm step-section planimetry, prolate spheroid volume (0.524 × transverse × transverse × anteroposterior diameter), elliptical volume (0.524 × cephalocaudal × transverse × anteroposterior diameter), and the semiplanimetric ellipsoid volume (8 × [area of largest ultrasonic transverse section]*2/3π × cephalo-caudal diameter [5]). Males with suspicious DRE findings and hypoechoic TRUS lesions larger than 7 mm in diameter were biopsied under ultrasound guidance.

From the relationship between serum PSA and inner zone volume, a set of formulae for predicted PSA values was obtained for correction of inner zone volume for each volumetric method, as illustrated in Figure 1 for planimetry. The slope of the regression formula represents the mean PSA production/ml tissue of inner zone. Extrapolation of the inner zone volume to nil shows the intercept of the regression formula, which represents the mean PSA production of a peripheral zone of mean volume. Excess PSA values were calculated by subtracting the predicted PSA from the serum PSA.

Using logistic regression analysis the relative risk of presence of PCa was estimated for each diagnostic marker separately and combined. Various contributions of PSA and measures of prostate volume were used to arrive at the model that predicted best the presence of PCa. Relative discriminatory potential of

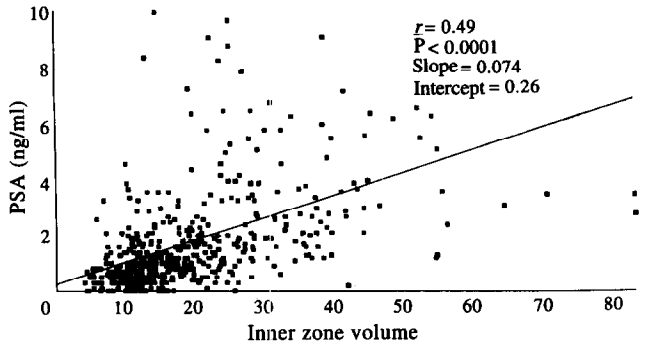

Figure 1. Serum PSA as a function of planimetric inner zone volume. The linear regression line between inner zone volume and serum PSA indicates the formula for predicted PSA. Predicted PSA = 0.26 + 0.074 × inner zone volume.

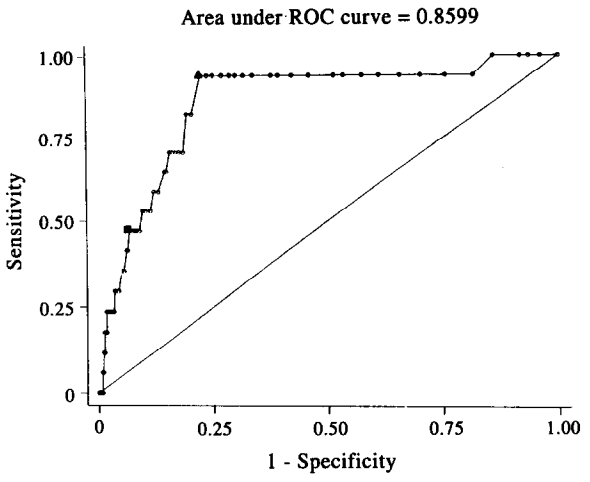

Figure 2. ROC curve of serum PSA for detection of prostate carcinoma; serum PSA values of 2.3 (▲) and 4.0 (■) ng/ml are indicated.

the different models was assessed by calculating the area under the receiver operator characteristic (ROC) curve [6], of each model.

RESULTS

For the 812 participants, the mean age was 64.5 years (S.D. 5.3, range 55–77), and the mean body weight 78.3 kg (S.D. 10.2, range 51–116). Mean values of volumetric measurements were 35.5 ml (S.D. 14.5, range 7.7–117.0) for total gland planimetric volume, and 18.4 ml (S.D. 11.1, range 1.7–82.9) for inner zone planimetric volume. The mean serum prostate specific antigen was 1.7 ng/ml (S.D. 1.7), and the mean PSAD 0.045 ng/ml/g (S.D. 0.040). Bilateral biopsies were performed in 74 participants, and 17 prostate carcinomas were found. There was a significant difference between the benign and the malignant population for age, total gland height, serum PSA, PSAD, PSAT and population-derived excess PSA values. The discriminatory potential to detect prostate carcinoma of each parameter was determined by the area under ROC. For PSA alone the area was 0.86, for PSA in combination with age 0.88, PSA and prostatic height 0.86, and PSA with both age and height 0.86. The ROC areas of some of the significant volumetric parameters by four different methods are noted in Table 1. In the ROC curve of serum PSA, several PSA values are indicated (Figure 2). At a cut-off PSA level of 4.0 ng/ml, sensitivity of PSA to detect PCa was 0.47 and its specificity was 0.91. For a cut-off level of 2.3 ng/ml this was 0.94 and 0.78, respectively.

DISCUSSION

Compared to serum PSA values, volumetric adjustments of those in the intermediate and low range do not improve the selection of males either at risk from prostate carcinoma or for prostate biopsy in a screening population. When the volumetric corrections made by the PSAD, the PSAT and the excess PSA were compared, the best method of volumetric correction of serum PSA to maximise the diagnostic capacity for detecting PCa appeared to be the excess PSA, increasing the area under the ROC curve from 0.86 to a maximum of 0.90 (prolate spheroid volumetry). For screening purposes, however, this slight improvement by volumetric measurements hardly offers an attractive procedure, as TRUS is expensive and time consuming, even when performed by skilled technicians instead of physicians. The correction of the serum PSA by the volume of the prostate or parts of it are based on the idea that PSA production of normal or adenomatous prostatic tissue in the inner zone may conceal the abnormal PSA production in malignant tissue. The contribution of the PSA production of the peripheral zone, as illustrated by the intercept of the formula calculating excess PSA (Figure 1), is limited. The value of 0.26 ng/ml, however, is a median value, correlated to a peripheral zone of median volume (16.4 ml). The median PSA production per gram of peripheral zone tissue would be 0.016 ng/ml/g, which is far less than the PSA production in the inner zone of 0.074 ng/ml/g, illustrated by the slope of the formula. Therefore only correction of the serum PSA for the inner zone volume seems to be justified.

Table 1. Area under ROC curve for volume-adjusted PSA

	PSA density	PSAT	Excess PSA
Planimetric	0.88	0.85	0.87
Prolate spheroid	0.86	0.87	0.90
Elliptical	0.86	0.83	0.89
Ellipsoid	0.81	0.82	0.88

Volume-adjusted PSA values are influenced by the method of prostate volumetry. Reproducability of inner zone and total gland volumetry is best in planimetry [7], and improvement is not expected [8]. The serum PSA concentration is influenced by various biochemical and biological factors, several of which are still poorly understood. Values of PSA production in adenomatous tissue might be dependent on the epithelial fraction [9], and leaking of PSA from epithelial cells to the serum is increased in malignancy [10], but these values show a wide variation. The mathematically derived value of PSA production in the inner zone of 0.074 ng/ml/g in our study corresponds well with the clinically determined value in the study of Mandell and colleagues [9].

In other studies, selection of males at risk for prostate carcinoma or for prostate biopsy in a screening population has been performed using PSA, DRE and TRUS as discriminative parameters [11,12]. The partial detection rates for PCa in the PSA range between 0 and 10 ng/ml in these studies were 3.7 and 1.5%, respectively. By choosing a prescreen level of 2.0 ng/ml for performing DRE and TRUS, 11% of cancers would have been missed in both studies, this is 15–17% of cancers with a

PSA between 0 and 10 ng/ml. By introduction of the prescreen level of 2.0 ng/ml as a cut off-value for doing DRE and TRUS, Lee and colleagues calculated that the biopsy percentage would have been reduced by 50% [12]. The percentage of participants with a PSA smaller than 2.0 ng/ml was 69% [11]. In our study, the partial detection rate for PSA values up to 10 ng/ml was 2.1%. Only 1 of the 17 detected carcinomas had a PSA below 2.0 ng/ml, while 70% of men had a PSA below 2.0 ng/ml. Using a prescreen level of 2.0 ng/ml, the number of biopsies would have been reduced from 74 (9.1%) to 39 (4.3%).

A correlation of serum PSA with age, which may be of importance to discriminate between participants with and without prostate carcinoma in screening populations, has been reported ([11], $r = 0.18$; [13], $r = 0.43$). In the Rotterdam study, the correlation of PSA with age was 0.25. Adjustment of the serum PSA for age resulted in a slight improvement of the diagnostic capacity as expressed by the area under ROC from 0.86 to 0.88. Although more easy than correction by prostatic volume, the improvement is considered too small to be worth persuing. Diagnostic use of TRUS in screening for prostate carcinoma might increase the detection rate of prostate carcinoma [14]. In his study, 42% of detected tumours were in the PSA range below 4.0 ng/ml. In 41% of patients, who underwent a radical prostatectomy for prostate cancer, the lesion was only detected by TRUS. Of these tumours, 68% appeared histologically organ-confined. In the study of Catalona and colleagues [15] in 79% of males with a prostate carcinoma and a PSA below 10.0 ng/ml, the malignancy was histologically organ-confined, while in the group with a PSA of more than 10.0 ng/ml, this number was 13%.

According to Lee and colleagues [16], this implies that in order to detect non-palpable and curable (confined) carcinomas, TRUS has to be performed particularly in the group with intermediate and low PSA values. Unfortunately, this is also the largest group. In the Rotterdam study, all detected cancers in this group were organ-confined [17], and detected by TRUS in 100% and DRE in 82%. Limiting TRUS for screening participants with a PSA between 2.0 and 10.0 ng/ml would have reduced TRUS performance by 70%, only missing one of 17 carcinomas.

In conclusion, volumetric adjustments of PSA values up to 10.0 ng/ml have no additional benefit beyond unadjusted values for selection of males at risk of prostate carcinoma or for prostate biopsy in a screening population. A prescreen level of 2.0 ng/ml selects 30% of the screening population in which 94% of prostate cancers detectable by TRUS or DRE are found.

1. Catalona WJ, Smith DS, Ratliff TL, Basler JW. Detection of organ confined prostate cancer is increased through prostate specific antigen screening. *JAMA* 1993, **270**, 948–954.
2. Bentvelsen FM, Schröder FH. Modalities available for screening for prostate cancer. *Eur J Cancer* 1993, **29A**, 804–811.
3. Benson MC, Whang IS, Pantuck A, *et al.* The use of prostate specific antigen density to enhance the predictive value of intermediate levels of serum prostate specific antigen. *J Urol* 1992, **147**, 817–821.
4. Kalish J, Adams JA, Cooner WH, Graham SD. Comparison of PSAD and PSAT in benign and malignant prostatic disease. *J Urol* 1993, **149**, (suppl.), 414A.
5. Littrup PJ, Kane RA, Williams CR, *et al.* Determination of prostate volume with transrectal ultrasonography for cancer screening. *Radiology* 1991, **179**, 49–53.
6. Green D, Swets J. *Signal Detection Theory and Psychognosics*. New York, John Wiley and Sons, 1966, 45–49.
7. Niemer AQHJ, Davidson PJT, Bangma Chr H, Hop WCJ, Schröder FH. Observations on the reliability and reproducibility of transrectal ultrasonic volume measurements of the prostate: the effect of equipment and observers (presented at the annual meeting 1992 of the B.A.U.S.-congress). *Br J Urol* submitted.
8. Bangma Chr H, Hengeveld EJ, Niemer AQHJ, Schröder FH. Errors in transrectal ultrasonic planigraphy of the prostate. *Ultrasound Med Biol*, accepted, 1994.
9. Mandell K, Partin A, Hill G, *et al.* PSA density in BPH: correlation with stromal epithelial ratios and influence of age. *J Urol* 1993, **149**, 448A.
10. Stamey TA, Yang N, Hay AR, *et al.* Prostate specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med* 1987, **317**, 909–916.
11. Labrie F, Dupont A, Suburu R. Serum prostate specific antigen as pre-screening test for prostate cancer. *J Urol* 1992, **147**, 846–852.
12. Lee F, *et al.* Predicted prostate specific antigen results using transrectal ultrasound gland volume. *Cancer* 1992, **70** (suppl.) 211–220.
13. Oesterling JE. Serum prostate-specific antigen in a community-based population of healthy men: establishment of age-specific reference ranges. *JAMA* 1993, **270**, 860–864.
14. Mettlin C, Lee F, Drago J, Murphy GP. The American Cancer Society National Prostate Cancer Detection Project, findings on the detection of early prostate cancer in 2425 men. *Cancer* 1991, **67**, 2949–2958.
15. Catalona WJ, Smith DS, Ratliff TL, *et al.* Measurement of prostate-specific antigen as a screening test for prostate cancer. *N Engl J Med* 1991, **324** 1156–1161.
16. Lee F, Litrrup PJ, Torp-Petderson S, *et al.* Prostate cancer: comparison of transrectal ultrasound and the digital rectal examination for screening. *Radiology*, 1988, **168**, 351–354.
17. Kirkels WJ, Schröder FH, Damhuis RS, Nijs HGT, Roobol-Bouts M. A European study for screening of adenocarcinoma of the prostate. Report of a pilot study. *J Urol* 1993, **149** (suppl.) 289A.