Acta clin Croat 2004; 43:379-383 Professional Paper

DIAGNOSTIC VALUE OF AGE SPECIFIC PROSTATE SPECIFIC ANTIGEN IN PROSTATE CANCER PATIENTS

Ante Reljić[1], Igor Tomašković[1], Ana-Marija Šimundić[2] and Božo Krušlin[3]

[1]Department of Urology, [2]Clinical Department of Chemistry, [3]Ljudevit Jurak Department of Clinical Pathology, Sestre milosrdnice University Hospital, Zagreb, Croatia

SUMMARY – The aim of the study was to analyze age distribution in patients undergoing early diagnosis procedures within the scope of the prostate cancer program, and to compare diagnostic accuracy of total prostate specific antigen (tPSA) test and age specific PSA range test in differentiating prostate cancer from benign prostate hyperplasia in order to reduce the number of unnecessary biopsies. Age distribution was analyzed in 394 patients with negative digitorectal examination, and diagnostic accuracy was analyzed in 80 patients with negative digitorectal and tPSA of 4.0-9.9 ng/mL. All 80 patients underwent prostate biopsy under transrectal ultrasound guidance obtaining at least six cores. Statistical analysis included t-test, Mann-Whitney rank sum test, specificity and sensitivity, positive and negative predictive value, and detection rate. The patient mean age was 67.0 years. Only *22%* were self referred to the early diagnosis program seeking PSA and urologist consultation while being free from any other urologic difficulties. This population was significantly younger in comparison with patients referred to urologist by general practitioner for their micturition difficulties (Mann-Whitney test, $p<0.001$). Total PSA differentiated significantly prostate cancer from benign prostate hyperplasia ($p=0.007$, t-test). Positive predictive value for tPSA and age specific PSA range test did not differ significantly (16.2 *vs.* 17.6%). The sensitivity and specificity of age specific PSA range test was 92.3% and 16.41%, respectively. It is concluded that there is the need of additional public health education about prostate cancer since only *22%* of the respective population seek urology consultation and PSA testing, being aware of the benefits of the early diagnosis of prostate cancer. Up to 38% of patients included in the early diagnosis program are beyond target population since no curable treatment could be offered to them even if the diagnosis of prostate cancer was established. Although age specific PSA range test reduces the rate of biopsies by 16.4%, 7.6% of prostate cancers are thus missing, whereas false positive results account for as many as 83.58% of cases, clearly calling for search for the potentially better ways of reducing the number of unnecessary prostate biopsies.

Key words: *Prostatic neoplasms – diagnosis; Prostate specific antigen; Prostati neoplasms – pathology; Neoplasms staging – methods*

Introduction

Prostate cancer (PC) is the fourth most common malignancy (immediately following pulmonary, colorectal and stomach cancer) in Croatia with an incidence of 7%. From 1968 till 1997, the number of newly diagnosed PC patients increased by 82%, while PC mortality increased by 238%[1]. In 1980, only 12% of PC patients had localized disease[2]. According to reports from the large urology departments in Croatia, presented at the Croatian Urologic Society Symposium on Prostate Cancer in Zagreb in 1996, as many as 85% of newly diagnosed patients had been diagnosed with incurable disease (unpublished data). At our Department of Urology we had defined methods and goals of early diagnosis program for prostate cancer[3]. In the next few years, the rate of localized prostate cancer (T1 and T2 as potentially curable) diagnosis increased resulting in an ever growing number of radically treated patients.

Analyzing biopsy material we observed a great proportion of negative histologic reports, especially in the group of patients with negative digitorectal finding and prostate

Correspondence to: *Ante Reljić, M.D.*, Department of Urology, Sestre milosrdnice University Hospital, Vinogradska c. 29, HR-10000 Zagreb, Croatia
E-mail: ???

Received April 22, 2004, accepted September 30, 2004

specific antigen (PSA) between 4 and 9.9 ng/mL (84%)[4]. The reason for that could be inadequate specificity of total PSA (tPSA), primarily inpatients. Other authors report on the same problem[5,6]. Among many different methods used to improve tPSA specificity, age specific PSA based on PSA elevation with age is especially interesting[7]. Oesterling *et al*. classified patients according to age into age specific PSA ranges. Thus, age specific PSA is considered normal if 2.5 ng/mL or less in patients aged 40-49; 3.5 ng/mL or less in patients aged 50-59; 4.5 ng/mL or less in patients aged 60-69; and 6.5 ng/mL or less in patients aged 70-79[7]. Partin *et al.*[8] and Reissigl *et al.*[9] independently report on increased sensitivity of age specific PSA in younger men and increased specificity in older ones in comparison to tPSA at a cutoff value of 4 ng/mL. In contrast, Catalona *et al.*[10] state that age specific PSA increases the number of unnecessary biopsies in younger men while postponing the diagnosis of cancer at the age of 60-73 when patients are still eligible for radical treatment. Littrup *et al.*[11] reached the same conclusion stating that a cutoff at 4 ng/mL remains the most effective value for screening. Clinicians have been warned to use age specific PSA with caution, since Food and Drug Administration has not approved its utility[12].

Facing contradictory results of age specific PSA utility, we found it potentially useful to determine its value on our own material. In the present study we analyzed general population descriptors of patients enrolled in the study and compared diagnostic utility of age specific PSA with tPSA in patients with negative digitorectal examination and PSA between 4 and 9.9 ng/mL. The objective of the analysis was to allow for the number of unnecessary biopsies to reduce using age specific PSA, and to assess the utility of this test in clinical practice.

Material and Methods

From April 2001 till September 2002, negative digitorectal findings were recorded in 388 patients aged 46-85. Total PSA was determined before or at least 7 days of the examination using DPC Immulite monoclonal assay. PSA below 4 ng/mL and above 10 ng/mL was recorded in 274 and ten patients, respectively, leaving the remaining 89 patients in the range between 4 and 9.9 ng/mL. Patients with positive or suspect digitorectal finding, patients previously diagnosed with prostate cancer, and patients on medicamentous or previous surgical therapy for benign prostate hyperplasia (BPH) were excluded from the study. All patients underwent transrectal ultrasound examination (TRUS) (/7/9 Hz Siemens Sonoline Prima or, Siemens SI-400, Tübingen, Germany). According to Oesterling's age specific PSA categorization, patients were stratified as "positive" if actual PSA was higher than expected for the age, or "negative" if actual PSA was within the range expected for the age. Eighty-nine patients with PSA between 4 and 9.9 ng/mL underwent prostate biopsy (automatic Bard Magnum TM device and 18 gauge needle). Six to 10 biopsy cores were obtained from each of them, depending on prostate volume and suspect lesions on TRUS. Every set of biopsies contained at least two cores from the transition zone of the prostate. Biopsy cores were separately placed in containers and fixed with 10% formaldehyde. Classic hemalum eosin staining was used before pathohistologic analysis. Additional immunohistochemical staining (p-63 and high molecular weight cytokeratin HMW-CK) was used if necessary. Nine patients were diagnosed with high grade prostatic intraepithelial neoplasia (HG-PIN) or atypical small acinar proliferation (ASAP) necessitating repeat biopsies and they were excluded from the study.

Statistical analysis

A series of 394 patients with negative digitorectal finding were analyzed with respect to age distribution. Statistical analysis included t-test, Mann-Whitney rank sum test, specificity and sensitivity, detection rate (DR), positive and negative predictive value (PPV, NPV) for age specific PSA and its diagnostic utility in reducing prostate biopsies.

Results

Out of 394 patients with negative digitorectal examination, 274 (69.50%) had total PSA below 4 ng/mL and 31 above 10 ng/mL. The largest proportion of patients in the early diagnosis of prostate cancer program were aged 60-69 (n=173 or 43.90%) and 70-79 (n=138 or 35.02%), followed by those aged 50-59 (n=65 or 16.49%). The number of patients aged 80 and more enrolled in the early diagnosis of prostate cancer program was twofold that of patients aged 50 or less (3.04% *vs.* 1.53%).

There were 244 (61.92%) patients examined at the age of 70 or less, whereas 150 (38.07%) patients were older than 70. Age range was 46-87 (mean 66.72) years. As many as 308 (78.17%) patients were referred to urologist by their general practitioner for urination difficulties, and 86 (21.82%) were self-referred demanding urologist consultation and PSA testing. Age range in patients referred by

their physician was 57-87 (median 72.82) and in self-referred population 46-68 (median 59.78; Mann-Whitney test, $p<0.00001$).

Out of 80 patients with negative digitorectal examination and PSA of 4-9.9 ng/mL, 13 (16.25%) were diagnosed with prostate cancer and 67 (83.75%) with BPH on biopsy. Those with prostate cancer had PSA of 4.43-9.97 (mean 7.71) ng/mL and those with BPH had PSA 4.28-9.63 (mean 6.63) ng/mL (t-test, $p=0.007$). Positive predictive value (PPV) for total PSA (tPSA) was 16.25% (16/80 patients), representing detection rate in this material.

Actual tPSA was elevated in respect to age specific cutoff in 12 of 13 (92.30%) patients with prostate carcinoma and in 56 of 67 (82.35%) patients with negative prostate biopsy, yielding age specific PSA sensitivity of 92.30% and specificity of 16.41%. PPV of age specific PSA range test was 12/68 (17.64%), and negative predictive value (NPV) 11/12 (91.66%), and detection rate 15.00%.

Discussion

During the last 6 years of the early diagnosis of prostate cancer program, we noted serious changes in the diagnosis and treatment of prostate cancer. There has been a shift towards a greater proportion of patients at an early (curable) stage of the disease, which could primarily be attributed to PSA testing of each man above 50 years of age who presented for urologist consultation, irrespective of his difficulties. Total PSA in 394 study patients was comparable to the results of Cooner who differentiates the screening and referred population of patients[5]. Analysis of our data indicated that we had the "clinical" but not the "screening" population. This defines the purpose of this approach, which is not to reduce mortality (since we do not conduct screening) but to make early diagnosis of prostate cancer at a curable, earlier stage in younger men. We proved that the self-referred population without urinary difficulties represented significantly younger men in comparison to those referred to urologist by their general practitioner (Mann-Whitney test, $p<0.001$). This is a clear effect of the public health actions taken in previous years. Although encouraging, we cannot be fully satisfied with these effects since only 21.82% of study patients were self-referred. On the contrary, 38.07% of the subjects were older than 70, when we usually do not conduct any radical (curable) treatment. In our opinion, it is counterproductive to follow the principles of early diagnosis of prostate cancer in men not eligible for radical treatment. Our results suggest that there is a need of further continuous public education of male population as well as of health professionals to achieve a larger proportion of younger, asymptomatic men enrolled in the early diagnosis program who would, if found affected, be eligible for efficacious treatment. Such experiences exist in Great Britain with a particular emphasis on the education of lower social classes[13]. On the other hand, greater involvement of younger men in the program brings the issue of unnecessary biopsies into focus.

tPSA is one of the best known tumor markers[14,15]. Total PSA differs significantly prostate cancer from BPH in patients with negative digitorectal examination and PSA between 4 and 9.9 ng/mL (t-test; $p= 0.007$). For the same group of patients, Catalona *et al.* report on tPSA PPV of 20.7% in screening population, which is comparable with our results[16]. Cooner reports on a lower PPV of only 5.5% in his clinical population[5]. This discrepancy could be explained by the fact that Cooner performed sextant biopsies in all patients, whereas we adjusted the number of biopsies to the prostate size, visible lesions on TRUS in peripheral zone and obligate sampling of transition zones with at least 2 cores.

Anticipating the above mentioned problem of the large proportion of unnecessary biopsies, we analyzed diagnostic accuracy of age specific PSA range test as a rapid and simple method that causes no extra costs and cannot be neglected in medical practice in Croatia. This parameter has been used in daily practice to interprete PSA values and to indicate prostate biopsy. Our results yielded no statistically significant difference in PPV for age specific PSA range in comparison to total PSA (17.64 *vs.* 16.25%). Since PPV depends on disease prevalence we considered it more appropriate to compare the sensitivity and specificity of these tests. Age specific PSA range test had a sensitivity of 92.30%, missing 7.7% of prostate cancers. The proportion of 7.7% of false negative results meets the needs of early diagnosis of prostate cancer, since missed patients with prostate cancer can be diagnosed at an early stage at further regular annual controls. Mettlin *et al.* report on a lower sensitivity of 67.3% of the same test, however, measured in a screening population[17]. The specificity of age specific PSA range test in our material was 16.41%. Using this test we could reduce the number of unnecessary biopsies by 16.41% in comparison to tPSA test without reducing significantly the test sensitivity. Catalona *et al.* report on the reduction of prostate biopsies with the same test by 15%, missing 8% of prostate cancer cases[10]. In the study of Mettlin *et al.* in a screening population, the specificity was favorable (90.9%) leading to a significant reduction in the number of biopsies[17]. Reissigl *et al.* describe a

21% reduction in biopsies in patients older than 60, missing only 4% of organ-confined cancers[9]. It should be emphasized that Oesterling *et al.*[7] and Dalkin *et al.*[18] have defined the criteria for age specific PSA range in Caucasian population with negative digitorectal examination, PSA<4ng/mL, and negative TRUS where prostate cancer has been excluded by clinical and/or histologic methods. Morgan *et al.* proved the Oesterling's age specific PSA range to miss as many as 40% of prostate cancers in blacks[19]. Racial differences have been established in age specific PSA range utility[19]. In spite of a 16% reduction of biopsies, age specific PSA leaves 83.58% (56/67) of false positive results. There is a growing number of reports that the use of free/total PSA ratio and transition zone PSA density (TZ density; PSA/volume of transition zone ratio) results in an even better reduction of unnecessary biopsies by 19%-95%[12,15,20,21]. The European Association of Urology Guidelines suggest repeat biopsies if there is a persistent indication in spite of negative result in the first biopsy. Namely, Keetch *et al.*[22] and Roerhborn *et al.*[23] report on 20% of prostate cancers found on repeat biopsies. Moreover, repeat biopsies are advocated if first biopsy has revealed high grade prostatic intraepithelial neoplasia or atypical small acinar proliferation. Other authors give similar recommendations[24]. The European Guidelines do not specify what "persistent indication" does imply in particular. In our opinion, there is a substantial collision in trying to reduce the number of unnecessary biopsies and to perform repeat biopsies shortly after the initial negative biopsy[25]. Having in mind the slow course of the natural history of prostate cancer, we recommend regular follow up in patients with negative digitorectal examination and PSA of 4-9.9 ng/mL.

In conclusion, we can state that age specific PSA range in comparison to tPSA enables a 16% biopsy reduction, missing not more than 8% of prostate cancers. We believe this represents an improvement in the early diagnosis of prostate cancer. Nevertheless, we consider it necessary to compare diagnostic accuracy of age specific PSA range tests with other PSA related tests such as transition zone-density PSA or free total PSA ratio[12,15].

References

1. STRNAD M, ZNAOR A. Epidemiologija raka prostate. In: ŠAMIJA M, OREŠIĆ V, SOLARIĆ M, editors. Rak prostate. Zagreb: Medicinska naklada, 2002:9-11.
2. Croatian Health Care Institute Cancer Registry. Cancer incidence in 1980. Zagreb, 1986; Bulletin No. 5:1-11.
3. RELJIĆ A, KRALJIĆ I. Early diagnosis of prostate cancer: where do we stand?. Acta Clin Croat 1997;36:49-54.
4. RELJIĆ A. Biopsija prostate. In: ŠAMIJA M, OREŠIĆ V, SOLARIĆ M, editors. Rak prostate. Zagreb: Medicinska naklada, 2002:55-9.
5. COONER WH. Prostate-specific antigen, digital rectal examination, and transrectal ultrasonic examination of the prostate in prostate cancer detection. Monogr Urol 1991;12:3-7.
6. EPSTEIN JI. Diagnosis adenocarcinoma of the prostate on needle biopsy. In: SILVERBERG SG, editor. Prostate biopsy interpretation. Philadelphia-New York: Lippincott-Raven, 1995:87-132.
7. OESTERLING JE, JACOBSEN SJ, CHUTE CG, GUESS HA, GIRMAN CJ, PANSER IA, *et al.* Serum PSA in community-based population of healthy men. JAMA 1993;270:860-4.
8. PARTIN AW, CRILEY SR, SUBONG ENP, ZINCKE H, WALSH PC, OESTERLING JE. Standard *versus* age-specific prostate specific antigen reference ranges among men with clinically localized prostate cancer: a pathological analysis. J Urol 1995;155:1336-40.
9. REISSIGL A, POINTNER J, HORNINGER W, ENNEMOSER O, STRASSER H, KLOCKER H, BARTSCH G. Comparison of different prostate-specific antigen cutpoints for early detection of prostate cancer: results of a large screening study. Urology 1995;46:662-7.
10. CATALONA WJ, HUDSON MA, SCARDINO PT, RICHIE JP, AHMANN FR, FLANIGAN RC, *et al.* Selection of optimal prostate specific antigen cutoffs of early detection of prostate cancer: Receiver operating characteristic curve. J Urol 1994;154:2037-42.
11. LITTRUP PJ, KANE RA, METTLIN CJ, MURPHY GP, LEE F, TOI A, *et al.* Investigators of the American Cancer Society National Prostate Cancer Detection Project: Cost-effective prostate cancer detection. Reduction of low-yield biopsies. Cancer 1994;74:3146-52.
12. POLASCIK TJ, OESTERLING JE, PARTIN AW. Prostate specific antigen: a decade of discovery – what we have learned and where we are going. J Urol 1999;162:293-306.
13. FITZPATRICK P, CORCORAN N, FITZPATRICK JM. Prostate cancer: how aware is the public? Br J Urol 1998;82:43-8.
14. YAGODA A, OLSSON C. Prostate cancer. In: CALABRESI P, SCHEIN PS, editors. New York: McGraw-Hill, Inc., 1993:910-25.
15. CARTER HB, PARTIN AW. Diagnosis and staging of prostate cancer. In: WALSH PC, editor. Campbell's urology. Philadelphia, PA: Saunders, 2002;3056-64.
16. CATALONA WJ, RICHIE JP, AHMANN FR, HUDSON MA, SCARDINO PT, FLANIGAN RC, *et al.* Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. J Urol 1994;151:1283-90.
17. METTLIN C, LITTRUP PJ, KANE RA, MURPHY GP, LEE F, CHESLEY A, *et al.* Relative sensitivity and specificity of serum prostate specific antigen (PSA) level compared with age-referenced PSA, PSA density, and PSA change. Cancer 1994;74:1615-20.
18. DALKIN BL, AHMANN FR, KOPP JB. PSA levels in men older than 50 years without clinical evidence of prostatic carcinoma. J Urol 1993;150:1837-9.
19. MORGAN TO, JACOBSEN SJ, McCHARTY WF, JACOBSON DJ, McLEOD DG, MOUL JW. Age-specific reference ranges for prostate-sprecific antigen in black men. N Engl J Med 1996;335:304-7.

20. DJAVAN B, BRAWER MK, MARBERGER M. Molecular forms of prostate-specific antigen for prostate cancer detection. In: HOFMANN R, HEINDENREICH A, MOUL JW, editors. Prostate cancer. Berlin: Springer, 2003:55-65.
21. WOODRUM DL, BRAWER MK, PARTIN AW, CATALONA WJ, SOUTHWICK PC. Interpretation of free prostate specific antigen clinical research studies for the detection of prostate cancer. J Urol 1998;159:5-12.
22. KEETCH DW, CATALONA WJ, SMITH DS. Serial prostate biopsies in men with persistently elevated serum prostate specific antigen levels. J Urol 1994;151:1571-4.
23. ROERHBORN CG, PICKERS GJ, SANDERS JS. Diagnostic yield of repeated ultrasound guided biopsies stratified by specific histopathologic diagnosis and prostate specific antigen levels. Urology 1996;47:347-52.
24. HUGOSSON J. Early diagnosis: state of the art in clinical routine and screening studies. In: KURTH KH, MISCKISCH GM, SCHROEDER FH, editors. Renal, bladder, prostate and testicular cancer – an update. New York: The Parthenon Publishing Group, 2000:91-5.
25. The European Urology Association. Prostate Cancer Guidelines. Arnheim: EAU Health Office, 2001.

Sažetak

DIJAGNOSTIČKA VRIJEDNOST ZA DOB SPECIFIČNOG ANTIGENA SPECIFIČNOG ZA PROSTATU U BOLESNIKA S RAKOM PROSTATE

A. Reljić, I. Tomašković, A-M. Šimundić i B. Krušlin

Cilj rada bio je analizirati dobnu strukturu populacije u koje se provodi rana dijagnostika raka prostate te usporediti dijagnostičku vrijednost ukupnog antigena specifičnog za prostatu (tPSA) i referentnog raspona PSA specifičnog za dob u razlikovanju raka prostate i dobroćudne hiperplazije prostate, kako bi se smanjio broj nepotrebnih biopsija prostate. Dobna struktura analizirana je u 394 bolesnika s negativnim digitorektalnim nalazom, a dijagnostička vrijednost navedenih parametara uspoređena je s onima zabilježenim u 80 bolesnika s negativnim digitorektalnim nalazom i tPSA od 4,0-9,9 ng/mL. U svih 80 bolesnika učinjena je biopsija pod kontrolom transrektalnog ultrazvuka uzimajući najmanje 6 biopsijskih uzoraka. Preparati su analizirani rutinskim metodama, a prema potrebi je imunohistokemijski (p63, HMW-CK) postavljena i patohistološka dijagnoza. Prosječna dob ispitanika u programu rane dijagnostike je 67 godina. Samo 22% ispitanika samoinicijativno traži pregled i test na PSA, bez prisutnosti tegoba mokrenja, ali je ta populacija značajno mlađa u usporedbi s bolesnicima koje upućuje liječnik opće prakse zbog mikcijskih smetnja (Mann-Whitney, $p<0,001$). Serumska vrijednost tPSA u ispitanoj skupini značajno je razlikovala bolesnike s rakom prostate od onih s dobroćudnom hiperplazijom prostate (t-test, $p=0,007$). Nije bilo razlike u pozitivnoj prediktivnoj vrijednosti za tPSA i raspon za dob specifičnog PSA (16,2% prema 17,.6%). Osjetljivost raspona za dob specifičnog bila je 92,3%, a njegova specifičnost 16,41%. Zaključeno je kako treba i dalje sustavno raditi na javnozdravstvenoj izobrazbi muške populacije u Hrvatskoj, budući da samo 22% ispitanika traži pregled i PSA test svjesni potrebe za ranom dijagnostikom. Načela rane dijagnostike provode se, najvjerojatnije nepotrebno, u čak 38% ispitanika koji ne predstavljaju ciljnu populaciju za ranu dijagnostiku. Prilikom indiciranja biopsije prostate, služeći se kriterijima za raspon za dob specifičnog PSA može se smanjiti broj nepotrebnih biopsija za 16,4%, dok se dokazivanje raka prostate propušta u 7,6% slučajeva. Razmjer lažno pozitivnih nalaza raspona za dob specifičnog PSA i dalje je 83,58%, pa se drži potrebnim ispitati potencijalno bolje načine smanjenja broja nepotrebnih biopsija.

Ključne riječi: *Neoplazme prostate – dijagnostika; Antigen specifičan za dob; Neoplazme prostate – patologija; Određivanje stadija neoplazme – metode*