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

Ante Reljić1, Igor Tomašković1, Ana-Marija Šimundić2 and Božo Krušlin3

1Department of Urology, 2Clinical Department of Chemistry, 3Ljudevit 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; Prostatic 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 disease2.

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 cancer3. 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
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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 4.9-9.9 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 4.9-9.9 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.

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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 interpret 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. 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. In the study of Mettlin et al. in a screening population, the specificity was favorable (90%) leading to a significant reduction in the number of biopsies. Reissigl et al. describe a
21% reduction in biopsies in patients older than 60, missing only 4% of organ-confined cancers. It should be emphasized that Oesterling et al. and Dalkin et al. have defined the criteria for age specific PSA range in Caucasian population with negative digitorectal examination, PSA < 4 ng/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. Racial differences have been established in age specific PSA range utility. 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%.

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. and Roehrborn et al. 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. 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. 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.

References


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 dobrozdravne 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 opæe prakse zbog mikcijskih smetnja (Mann-Whitney, p<0,001). Serumska vrijednost tPSA u ispitanoj skupini značajno je razlikovala bolesnike s raku prostate od onih s dobrozdravnom hiperplazijom prostate (t-test, p=0,007). Nije bilo različite 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 rano dijagnostikom. Načela rane dijagnostike provode se, najvjerojatnije nepotrebno, u čak 38% ispitanika koji ne predstavljaju ciljnu populaciju za rano 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. Razmjera 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