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ORIGINAL ARTICLE

Diagnosis of prostate cancer in Serbia

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Summary

Purpose: *A rising incidence of prostate cancer is noticed in USA and Europe, which might be due to better diagnostic procedures and screening programs started in some countries. We still lack epidemiological studies confirming the same trend in our country, but the rising number of patients in whom radical prostatectomy is performed is an indirect proof of bigger recruitment of patients with prostate cancer. The purpose of this study was to establish the most appropriate diagnostic protocol for detection of prostate cancer in our unscreened population.*

Materials and methods: *Transrectal ultrasound (TRUS) -guided biopsies of the prostate were performed in 229 patients. Biplanar transrectal probe with needle channel was used. Six to 10 tissue cores were obtained from each patient.*

Results: *The mean patients' age was 67.12 years (range 42-88). All patients had serum prostatic specific antigen (PSA) estimation before biopsy, which ranged from 0.41 to 1550 ng/ml (mean 50.83), with 146 (63.8%) patients having PSA level greater than 10 ng/ml. Free (F) PSA was performed in 120 (52.4%) patients; the range of F to total (T) PSA ratio was 0.02 to 0.74 (mean > 0.13). Digital rectal examination (DRE) was positive in 65% of the patients. The mean prostate volume was 40.5 ml (range 11-140). Cancer was diagnosed in 99 (43.2%) patients, prostate cancer in situ (PIN) alone was diagnosed in 37 (16.2%), chronic prostatitis in 73 (31.9%), while benign prostatic hyperplasia (BPH) was found in 20 (8.7%) patients.*

Conclusion: *The cancer detection rate in our patients was high. In a lot of patients the biopsy was needed only for histological proof, not as a staging tool, the intention of which is the selection of patients with localized prostate cancer amenable to curative treatment. There is still reluctance to use PSA as a sole indication for biopsy, positive DRE still being mandatory. With such a policy we are missing a lot of curable prostate cancer cases, thus increasing the cost of treatment. A national policy including screening should be considered.*

Key words: diagnosis, free/total PSA, prostate cancer, prostate specific antigen

Introduction

The essential aim of diagnostic and staging procedures is to identify men with prostate cancer in early, potentially curable stage. Different countries have different policies for diagnosing patients with suspected prostate cancer [1,2]. Screening [3] or not screening [4] of male population is a matter of debate. Racial and ethnic variability in detection rates of prostate cancer, although not explained, is well known, implying that geographically and racially different regions might use different diagnostic procedures [5-7]. The cost of diagnostic procedures as well as those of screening programs put a great financial burden [8] and should be taken into account when considering a national policy. In Serbia there is no obligatory protocol concerning patients who might have prostate cancer, so the objective of this study was to compare our results with results from other series in order to establish the most appropriate diagnostic protocol for our patients.

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Materials and methods

From May 1997 to September 2003 TRUS-guided biopsies were performed in 229 patients. All of them were Caucasians, their mean age being 67 years (range 42 - 88). Serum PSA was performed at least once prior to biopsy with the Hybritech method of monoclonal immunoassay, mean PSA being 50.83 ng/ml. The description of DRE was available in 211 patients, estimated as positive in 149 (70.6%) of them. TRUS was available in 194 patients, detecting abnormal findings in 135 (69.6%) of them. Free PSA and F/T ratio were done in 120 patients, with a mean F/T ratio of 0.13. Biopsy was performed using transrectal biplanar probe with automatic 18 G core biopsy system. All biopsies were performed by one urologist, and all histological analyses by one pathologist.

Biopsy was not made according to strict criteria but rather on clinical suspicion of prostate cancer considering PSA, F/T PSA, DRE, and TRUS. In one patient, adenocarcinoma was found in cervical lymph nodes and prostate biopsy was done in search for primary tumor.

Classical sextant biopsy was performed in most patients, but in some cases the number of cores was raised to 8 or 10 (in bigger prostate or younger patients). Biopsy of transitional zone or seminal vesicles was not routinely performed. For histological processing, all cores were divided in 6 slices and then fixed in 10% phosphate buffered formalin, processed into wax paraffin and stained with haematoxylin-eosin. Standard WHO grading was performed in all patients in whom cancer was diagnosed. Gleason scoring was based on the primary and secondary Gleason pattern in 85 patients.

Statistical analysis was done by Statistica for Windows v 5.0 StatSoft Inc. software.

Results

Prostate cancer was diagnosed in 99 out of 229 (43.2%) patients. PIN as a sole histological finding or associated with benign disease such as chronic prostatitis or BPH was found in 37 (16.2%) patients. Chronic prostatitis as the only pathological finding was present in 73 (31.9%) patients, while BPH was diagnosed in 20 (8.7%) patients.

The mean PSA value of the whole group was 51.41 ng/ml, ranging from 0.41 to 1550 ng/ml. Since PSA is considered as the most valuable diagnostic tool, it was stratified in 4 groups (G1. PSA < 4; G2. PSA: 4-10; G3. PSA:10-20; and G4. PSA >20 ng/ml). Most of our patients had PSA values above 10 ng/ml (Table 1).

Table 1. Distribution of patients according to serum PSA and positive cancer biopsy

	Biopsy		
PSA (ng/ml)	*Negative n (%)*	*Positive n (%)*	*Total n (%)*
G 1 (< 4)	19 (14.6)	3 (3.1)	22 (9.6)
G 2 (4-10)	47 (36.15)	14 (14.2)	61 (26.6)
G 3 (10-20)	50 (38.5)	23 (23.2)	73 (31.9)
G 4 (>20)	14 (10.8)	59 (59.6)	73 (31.9)
Total	130 (100)	99 (100)	229 (100)

$p < 0.001$

The PSA distribution according to histological diagnosis (cancer *versus* non-cancer) was statistically significant (Kruskal Wallis rank sum test, $p < 0.01$, Table 2).

Estimation of sensitivity and specificity of different PSA values showed that the best result was obtained for the cut-off value of 10 (Table 3).

PSA was higher with more advanced age ($p = 0.04$), irrespective of the histological diagnosis (Table 4).

The prostatic volume was significantly correlated to the PSA values ($p < 0.01$, Table 5).

F/T PSA ratio was available for 120 patients and ranged from 0.02 to 0.74. The mean F/T PSA ratio was 0.13 and the median 0.12. There was no significant differences in F/T PSA ratio in patients with or without cancer (0.14 and 0.12, respectively).

Table 2. Serum PSA according to histological diagnosis

	No. of patients	*Mean PSA (ng/ml)*	*SD*† *(ng/ml)*	*Median (ng/ml)*	*Min (ng/ml)*	*Max (ng/ml)*
Cancer	99	102	248.38	27.3	2.5	1550
PIN*	37	11.24	4.33	10.5	2.1	20.9
Prostatitis	73	12.49	12.09	9.7	0.5	69.6
BPH§	20	10.27	6.9	8.3	0.4	24.9

Cancer *versus* non-cancer $p < 0.01$

†standard deviation; *prostate cancer *in situ;* §benign prostatic hyperplasia

Table 3. Sensitivity, specificity, positive and negative predictive values according to different serum PSA cut off values

PSA (ng/ml)	*Sensitivity*	*Specificity*	*Pos. predictive value*	*Neg. predictive value*
< 4	0.97	0.15	0.46	0.86
4-10	0.83	0.51	0.56	0.80
10-20	0.60	0.89	0.81	0.74

Table 4. Association of serum PSA and age

PSA (ng/ml)	*n (%)*	*Mean age, years (range)*
< 4	21 (9.2)	62.14 (42-80)
4-10	61 (26.6)	65.64 (42-81)
10-20	74 (32.3)	67.58 (47-80)
< 20	73 (31.9)	69.34 (47-80)

p=0.04

Table 5. Association of serum PSA and prostate volume

PSA (ng/ml)	*No. of patients*	*Mean (cm^3)*	*SD**	*Range (cm^3)*
< 4	22	24.6	14.76	4-67
4-10	53	37.6	15.77	15-86
10-20	68	47.7	18.92	10-140
< 20	66	40.5	22.20	4-99

p <0.01
*standard deviation

DRE was estimated as positive in 149 (65.07%) patients, 85 (57.4%) of whom had also positive histology for prostate cancer.

Cancer was found in only 8 (12.9%) out of 62 patients whose DRE was considered normal ($p < 0.001$). DRE estimated as positive if abnormal or negative if normal, according to histological diagnosis is shown on Table 6.

When TRUS was introduced in the diagnostic work-up of prostate cancer it was expected to add in the accuracy of diagnosis, but in our patients it was not more precise than DRE. Sensitivity, specificity, positive and negative predictive values are shown on Table 7.

Similarly to DRE, TRUS was significantly ($p < 0.01$) correlated with the histological diagnosis (Table 8).

If cancer was histologically diagnosed, PSA values correlated with tumor grade (Table 9). The most raised values were found in patients with grade 3 tumors.

Table 6. DRE in cancer versus non-cancer patients

DRE	*Cancer n (%)*	*Non-cancer n (%)*	*Total n (%)*
Negative	8 (8.08)	54 (41.54)	62 (27.07)
Positive	85 (85.86)	64 (49.23)	149 (65.07)
NA*	6 (6.06)	12 (9.23)	18 (7.86)
Total	99 (100)	130 (100)	229 (100)

p <0.001
*not available

Table 7. Sensitivity, specificity, positive and negative predictive values of TRUS and DRE

	Sensitivity	*Specificity*	*Pos. predictive value*	*Neg. predictive value*
TRUS	0.86	0.44	0.56	0.8
DRE	0.91	0.46	0.57	0.87

Table 8. TRUS according to histological diagnosis

TRUS	*Cancer*	*PIN§*	*Prostatitis*	*BPH†*	*Total*
Negative	12	10	29	8	59
Positive	76	17	33	9	149
NA*	11	10	11	3	18
Total	99	37	73	20	229

p <0.01

Table 9. Serum PSA according to tumor grade

Grade	*No. of patients*	*Mean PSA (ng/ml)*	*SD* (ng/ml)*	*Median (ng/ml)*	*Range (ng/ml)*
1	3	6.97	2.69	8.1	3.9-8.9
2	61	82.72	212.86	27.7	4.2-1550
3	35	156.3	318.16	38.5	2.5-1500

p=0.013
*standard deviation

More than half of our patient had Gleason score more than 5. PSA values raised linearly according to Gleason score from 3 to 7, but decreased in patients with Gleason score 8 and more (Table 10).

Discussion

Despite its limitations, PSA is the most powerful tumor marker which dramatically changed the diag-

Table 10. Serum PSA according to Gleason score

Gleason score	*No. of patients*	*Mean (ng/ml)*	*SD* (ng/ml)*	*Median (ng/ml)*	*Range (ng/ml)*
3	1	3.9	NA	3.9	3.9-3.9
4	1	8.9	NA	8.9	8.9-8.9
5	20	26.72	28.07	19	4.2-132
6	23	124	314	49.3	6.5-1550
7	28	163.1	307.46	40.4	2.5-1500
8	6	42.05	36.82	28.35	10.3-100
9	6	89.87	162	26.8	8-420

p=0.013
*standard deviation

nosis of prostate cancer [9], accounting for a great increase in the incidence of this malignancy [10]. According to our results, the wide use of PSA in our country should increase the rate of early detection of localized prostate cancer. The mean serum PSA value in our group of patients was 50.83 ng/ml, which is an extremely high value, while patients from the CAPSURE study in USA had a median PSA at diagnosis of 7.3 ng/ml. Of course, with such a mean PSA value the cancer detection rate was elevated, being 42%, while other series report a detection rate between 15% and 30% [11-13], or even less in screened population [14]. One of the main reasons for this result is the reluctance of urologists to use PSA as a unique parameter indicating biopsy, relying mostly on DRE, which was estimated as positive in 65% of patients, while in USA and western Europe most of the newly diagnosed patients have nonpalpable tumors (T1c) [15,16].

Recently, Stamey et al. argued the usefulness of PSA as a tumor marker, pointing that in the last 5-year period (since 2000) it mainly reflects the volume of the prostate [17]. We also noticed the correlation between prostate volume and PSA, but still Stamey's et al. statements should be used with caution, since it is applicable, as the authors mentioned, only for USA, where screening programs achieved in previous periods to detect most of the patients with prostate cancer.

The other important issue that can be derived from our results is the high median PSA (9.72 ng/ml) in patients in whom prostate cancer was ruled out. The maximal PSA in this group of patients was 69.6 ng/ml. We can certainly assume that in a next biopsy cancer would be diagnosed, but it is well known from other studies that elevated PSA does not necessarily mean that a cancer is present [18]. These higher values, along with the best specificity and sensitivity obtained for the PSA cut off value of 10 ng/ml, should be taken into account, without forgeting the growing evidence that high grade tumors can be found in patients whose PSA is lower than 4 ng/ml [19,20].

F/T PSA ratio was performed in 120 patients, but no correlation to prostate cancer diagnosis was established. The F/T PSA ratio was reported to aid in the indication for biopsy in patients with intermediate values of PSA [21-23] in order to avoid unnecessary biopsies, but total PSA values in our patients were much higher, which might explain the unreliability of F/T ratio in our group of patients.

TRUS, which is no longer regarded as a diagnostic tool [24], had an important specificity in our patients, but this could be explained by the selection of patients mainly according to DRE, when TRUS was more likely to be positive. In interpreting our findings, the subjective nature of DRE should be stressed.

TRUS is considered as the most appropriate method for measuring the prostatic volume. In our patients the volume was measured either by TRUS or transabdominal US, and in those patients that both methods were used no important differences in the measured volumes were observed. Our data are in correlation with results of other authors [25]. Prostatic volume as well as age have an important impact on the value of PSA [26,27]. As such, they can not be ignored when considering prostate biopsy.

Our patients were a non-screened population of men suspected of having prostate cancer according to symptoms and clinical findings. In this selected population a bigger recruitment of patients having cancer was expected. Our results revealed that in unscreened population more patients were diagnosed in advanced stages. Most of the patients in whom cancer was diagnosed had grade 2 disease, but Gleason score was more than 5 in 2/3 of them. Along with elevated PSA values they should be classified as high risk patients, in whom treatment modalities are restricted [28].

These results call for finding the most appropriate protocol to deal with prostate cancer. Diagnosis is of utmost importance. Specific conditions in different countries concerning the incidence but also socioeconomic status should be taken into consideration. Implanting protocols from more developed countries might not be beneficial. There is still no place for screening, but all efforts should be made in order to diagnose patients in potentially curable stages. PSA has a very important role and might enter as the minimal laboratory requirement for patients referring to general practitioners for lower urinary tract symptoms, bearing in mind its dynamics [29]. The question of what should be the cut off value of PSA that would necessitate a biopsy still remains open. According to our results, lowering the threshold under 4 ng/ml should be exceptional. PSA should not be the only diagnostic parameter; DRE is still mandatory, in order to detect tumors which might have been missed by PSA determination only, since in our patients all 3 with PSA under 4 ng/ml had a positive DRE. Prostate volume assessed by TRUS or transabdominal US is also important, since PSA density might spare men without prostate cancer from unnecessary biopsies.

The other important issue is public awareness of the disease along with treatment options which would also motivate patients to seek early urological examination, while medical professionals should proceed with early diagnostic procedures such as PSA and DRE [30,31].

Our conclusion is that PSA is still the most im-

portant parameter in the diagnosis of prostate cancer. As such, it should be used much more often and biopsy should follow elevated values in order to improve the detection rate, especially in patients with curable stages of prostate cancer. From our group of non-screened patients, the median PSA value was 11.72 ng/ml in those where cancer was ruled out, and that the best results regarding the specificity and sensitivity in detecting prostate cancer were obtained for PSA cut off value of 10 ng/ml.

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