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The predictive value of PSA in diagnosis of prostate cancer in non screened population

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INTRODUCION : PSA is the most important tumor marker in all solid tumor, indispensable in the management of prostate cancer. Screening for prostate cancer is still not recomended, although performed in many countries, which introduced questions about the usefulnes of PSA in detection of prostate cancer. The PSA treshold has also been changed, the value of PSA derivatives revised. Whether such changes are applicable in non scrrened population is questionable.

Aim of this study was to evaluate the predictive value of PSA, free/ total PSA and PSA density in our non screened population.

Patients and methods: TRUS guided prostate biopsy was performed in 579 patients. The number of cores was 6-12. Mean age of the patients was 67.5 years (30-90). PSA was ranging from 0.41 to 2250 (mean 38.6ng/ml, median: 11.95, SD 140,45). Digitorectal examination was considered positive in 351 patients. Free PSA was measured in 352 patients with the index ranging from 0.02 to 0.88 (mean free/total PSA: 0.14, median:0.13,). The volume of the prostate was measured in all patients according the prostate ellipsoid model, and PSA density calculated according to the formula PSA/PV. Patients were stratified in 6 groups according to PSA value (I: PSA ng/ml, II: PSA 2.5-4, III: PSA 4-10, IV: PSA 10-20, V: PSA:20 to 50, Group 6: PSA 50).

RESULTS: Non homogenicity of the patients can be seen through the wide range of PSA which was from 0.4 to 2025). Prostate cancer was diagnosed in 233 pts (40.2%). As expected, the probability of detecting cancer was raised with PSA (p), and was extremely rare in pts with PSA below 4 ng/ml. PSA, free/total PSA, volume of the prostate and PSA density were significantly different according to the presence of cancer. Most of our patients had PSA between 4 and 20 ng/ml. Predictive value of PSA was 20.6% for pts with PSA from 4 to 10 and 32.7% for those with PSA from 10 to 20 ng/ml. Sensitivity, specificity, positive and negative predictive values for different cut off's of PSA (4, 10 and 20) was performed. The best results were obtained for PSA cut off of 10 ng/ml. In the group of patient with PSA, PSA density more reliable than free/total PSA index.

CONCLUSION: PSA is still valuable marker for detection of prostate cancer in our non screened population. According to our results PSA treshold should not be lowered below 4 ng/ml. PSA density is a reliable PSA derivative, free/total PSA index having less importance in pts with PSA below 20 ng/ml.

Key words: prostate cancer, diagnosis, PSA value, non screened population

INTRODUCION

PSA PSA testing is responsible for the fact that most prostate cancer are detected in early, curable stages. It is also expected that screening for prostate cancer should be manifested by a reduction in detection rate of aggressive cancers during subsequent screening. PSA testing with early diagnosis should lead to less mortality from prostate cancer, but studies have not proved this theory. Two studies in the United States and Canada showed that regions of these countries with higher rates of PSA testing, prostate cancer diagnosis, and early intervention had prostate cancer mortality rates not significantly lower than those in areas with less intense testing and treatment, so the American College of Preventive Medicine recommends against routine population screening with DRE and PSA. European attitude toward scrrening is similar stressing that there are many arguments against introducing population-based screening for prostate cancer.

PSA is a prostate tissue marker which can be elevated as a result of prostate cancer, but BPH or infection can also cause PSA augmentation. Suspicion of prostate cancer indicates prostatic biopsy. The most universally applied indications include PSA 4.0 or irregular DRE. In all, 22% of

new CaP cases are discovered in men with normal PSA and irregular DRE. Recent studies challenged the PSA treshold of 4 ng/ml. Cancer detection rate can be as high as 22.8% in patients whose PSA ranged from 2 do 4 ng/ml. Stamey suggested that PSA was related to prostate cancer 20 years ago, but that in the last 5 years serum PSA has only been related to benign prostatic hyperplasia. In order to refine the specifity of PSA testing, it is suggested that more frequent use of age-specific PSA reference ranges and isoforms should be encouraged, and the need for biopsy determined on a case-by-case basis.

Most of the studies are from US, were screenig protocols and early detection might have changed the value of PSA testing. It is questionable whether the same trends exists in other regions and other countries since demographic and racial characteristic as well as dietary habits can have influnece on PSA concentration.

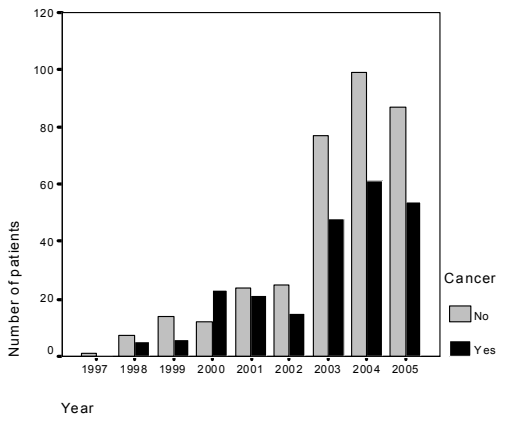
AIM of this study was to evaluate the predictive value of PSA, free/ total PSA and PSA density in our non screened population.

PATIENTS AND METHODS

We analyzed 579 patients in whome transrectal ultrasound guided (TRUS) guided biopsies were performed in the period from 1997 to 200, in the private setting . The patients came for some sort of urinary disturbance or were referred by other urologist for TRUS biopsy. The mean age of the patients was 67,5 years (30 – 90 years). Serum PSA was performed at least once prior to biopsy in all pts (mean PSA:38.6 ng/ml) with Hybritech method of monoclonal immunoassay. Digital rectal examination was classified as positive if any suspicious finding was noted such as induration, palpable node or asymetry of the gland. The description of DRE was available for 559 pts. The description of transrectal ultrasound was available for 481 patients, any abnormal finding were described as positive. Free PSA was measured and F/T index calculated in 351 pts. . Biopsy was performed using transrectal biplanar probe with automatic 18 GA core biopsy system. Biopsies were performed by three urologist and all hystological analysis by two pathologist .

The indication for biopsy was not made according strict criteria but rather on clinical suspicion of prostate cancer considering PSA, free/total PSA, DRE, TRUS. In one patient, adenocarcinoma was found in cervical lymph nodes and prostate biopsy was performed in search for primary tumor.

In most of the patients only one biopsy was done, but in 55 patient the biopsy was repeated. Of these patients, 10 had more than 2 biopsies. Classical sextant biopsy was performed in all patients until 2001, afterwards at least ten cores were obtained, unless the diagnosis of cancer was obvious according to DRE or PSA. In the first years we did not use any anesthetic procedures, afterwards we introduced the use intrarectal Xylocain gel, while instillation of 5 ml of Lidocaine on both sides of the prostate is routinely used in all patients in the last two years, which also made possible the multiple core biopsies.



GRAPH 1

NUMBER OF BIOPSIES

TABLE 1

DIAGNOSIS OF PROSTATE CANCER

Biopsy	Freguency	Percent
Negative	346	59.8
Positive	233	40.2
Total	579	100

For histological processing all cores were divided in six slices and than fixed in 10% phosphate buffered formalin, processed into wax paraffin and stained with haematoxylin-eosin. Biopsy of transitional zone or seminal vesicles was not routinely performed.

RESULTS:

As expected, with the routine use of PSA, the number of biopsies raised each year (Graph 1). The number of positive biopsies lowered with accumulating experience as a result of broadened indicitations.

Prostate cancer was diagnosed in 233 patient (40.2%) which is shown on table 1.

Most of our patients had more than 65 years. PSA , free /total PSA (F/T PSA), volume, and PSA density, were significantly different in patients according to the presecnce of cancer (Table 2)

Non homogenicity of the patients can be seen through a very wide range of PSA which was from 0.4 to 2025 (mean PSA : 38.60, median: 11,9, Standard deviation: 140,47). Digito rectal examination was positive in 352 patient (60,8%). Free / total PSA was done in 351 patients, the mean free / total PSA index beeing 0,14 (median 0,13, range from 0,02- 0,88). The mean volume of the prostate in our patients was 44 ml, the biggest measuring 140 ml.

Since PSA is the most important marker, we grouped patients in 6 groups according to the level of PSA. Group one were patients with PSA less than 2.5 ng/ml, group 2 were formed from patients with PSA between 2.5 and 4 ng/ml, group 3: PSA from 4 to 10, group 4: PSA ranging from 10 to 20, group 5: PSA from 20 to 50 and groupe 6:

TEBLE 2

CHARACTERISTICS OF OUR PATIENT ACCORDING TO THE PRESENCE OF CANCER

/		Ca positive	Ca negative	P value
Age	Mean	69,5	66.1	<0.001
	median	71	67	/
	min	30	38	/
	max	90	85	/
Prostate volume	mean	39.5	47.4	
	median	35.0	44.4	<0.001
	min	10	15	/
	max	127	140	/
PSA	Mean	78.27	12.12	<0.001
	median	23.8	9.22	/
	min	1.5	0.4	/
	max	2025	145	/
F/T PSA	Mean	0.12	0.15	<0.001
	median	0.10	0.14	/
	min	0.02	0.02	/
	max	0.88	0.74	/
PSA density	mean	2.27	0.35	<0.001
	median	0.71	0.21	/
	min	0.04	0.03	/
	max	68.18	18.5	/
DRE	positive	182	170	<0.001
	negative	42	155	/
TRUS	positive	107	162	<0.001
	negative	172	40	/

PSA 50 ng/ml. Most of our patients had PSA between 4 and 20 ng/ml. As expected, cancer detection rate raised with more elevated PSA (table 3), but we can point out to the fact that a cancer detection rate of patients whose PSA was from 4 to 10 was only 20.6%, being slightly bigger for those who had PSA between 10 to 20 ng/ml (32.7%).

Since patients with positive cancer with PSA less than 2.5 ng/ml were extremely rare (only 1 patient out of 19 with PSA less 2.5 had a cancer diagnosed), we analysed the sensitivity, specificity, positive and negative predictive values for PSA with different cutoff posints, the first one being 4, the other 10 and the third one 20 ng/ml. (Table 3a).

We obtained very low specificity with a cutoff of 4 ng/ml; with a cutoff of 10 we still had a good sensitivity with acceptable specificity.

For those different cut off values of PSA , the value of PSA density anf free / total PSA were compared using receiver operating characteristic (ROC) analysis. The area under the curve (AUC) was larger for PSA density than for free/total PSA index which is shown on table 4, making a PSA density more reliable than free/total PSA index. Table 4 :AUC for F/T PSA and PSA density acoording different PSA

Although the possibilty of cancer detection is the most important issue of prostatic biopsy, other pathological findings are of interest suggesting the more or less urgent need need for rebiopsy in cases that cancer was not found on initial biopsy.

Prostatic intraepithelial neoplasia was frequently associated with cancer, 118 patients (50.8%) had PIN along with cancer. PIN as a dominant pathological finding was seen in 95 patient (16.4%). Other pathological findings such as ASAP or PIA were not so frequent. ASAP was present in 25 pts (4.3%), while PIA as a sole finding was diagnosed in only 1 patient. The most frequent benign condition was prostatitis. The PSA distribution according to histological diagnosis was statistically significant (p=0.012), as well as density (p=0.029), while there was not significant difference in the distribution of free/total PSA index.

Gleason score was not done in first 23 patients with cancer, so analysis of grade and gleason score could have been performed in 218 patients. Most of the patients had a Grade 2 cancer, while Gleason score in the majority of patients was 6 or 7. (Table 6)

DISCUSSION:

The pattern of diagnosis of prostate cancer dramatically changed in last ten years. The routine use of PSA as a tool for early diagnosis is essential, although the value of screening programs is doubtful. The pressure to detect more cancers in localised stages led to PSA treshold lowering to 2.6 ng/ml with the detection rate of 15% . On the other side is the concern of over detection, meaning that cancer without potential clinical significance would be diagnosed and treated .

In non screened population, PSA is still a very relaible marker which can be seen through the high detection rate of cancer which in our group of patients is 40.2%. It is striking that very few patients had cancers if PSA was lower than 4ng/ml. This can be explained by the fact that urologist still rely on digitorectal examination. In our patient DRE was estimated positive in 352 pts (60.8%), with more then half (182) having prostatic cancer. In USA, DRE is used as an indication for biopsy if PSA is less than 4 ng/ml, in which cases it has a positive predictive value of 8.8% . The other possible explanation for the low cancer detection with PSA below 4 ng/ml is the age of our patients, the mean age being 67.9 years. Patients under 60 years of age represented only 17.9% of the whole group. This also explaines the low positive predictive value of PSA which is 0.42 for PSA up to 4, and 0.55 for PSA up to 10 ng/ml, while in other studies much more cancer were detected in younger patients with PSA lower than 4 ng/ml

Patients with PSA values between 4 and 20 constituted the majority of our patients (374, 64.6%). Even in those patients the cancer detection rate was low: 25,5% (94 pts). The PSA density was a good predictor of positive biopsy

in those patients while free/total PSA index was not reliable. Free/total PSA index should be more valuable in patients with lower PSA , and can be improved if measurment of testosterone is included .

The volume of the prostate is important in planning the optimal number of cores in the first biopsy set. Prostate volume is also a part of Vienna nomogram which adjust the number of cores according to age of patients, PSA and volume of the prostate. But volume is also important since one of PSA derivative, PSA density is calculated by dividing PSA with gland volume. Benson et all suggested that PSA density over 0.15 may improve the specificity of cancer detection. Our results also showed the superiority of PSA density over F/T PSA. The same result is obtained by Stephan and others . Kobayashi et all found also PSA density to be of value although they pointed out that TRUS measured volume is superior over transabdominal US measurment .

The number of cores is an important factor in detection of prostate cancer. The standard protocol of sextant biopsy is now rarely used, more extended biopsy with 8, 10, 12 or 14 cores are suggested not only for repeated biopsies. Transitional zone might be included. The reason of augmentation of number of cores lies in the fact that more cancers are detected with extended protocols, in lower stages . The use of an extended biopsy protocol at initial biopsy reduces the number of repeat biopsies required and decreases the number of PC detection in the follow-up period. But, the number of cores is also important as more cores improves the accuracy of the biopsy Gleason score in predicting the final Gleason score at RP .

In our patients , we rarely used more than 10 cores, which might also explain the low number of positive biopsies in patients with PSA up to 20 ng/ml.

One of benefits of screening programs is the possibility to diagnose patients with low stage and low grade of PC . Since are patients are not screened we would expect to have more high grade tumors. Still, most of our patients had grade 2 cancer, the most frequent Gleason score beeing 6 or 7.

Findings of PIN (Prostatic intraepithelial neoplasia) or ASAP (Atypical small acinar proliferation) on initial diagnosis is included in the nomogram for repeat biopsy . It was recently published that the detection rate of prostate cancer is higher for PIN (58%) then for ASAP (35%) , although it is pointed from Bostwick laboratories that PIN is declining in it's predictive value .

Prostatis was the most frequent benign condition diagnosed with biopsy. Asymptomatic inflammation of the prostate has been recognized to be an important confounding factor in patients with an elevated PSA . Chronic prostatis has the same effect on PSA as prostate cancer, while free/total PSA might distinguish beetwen two entites according to Stancik et al , although in our patients free/total PSA was not valuable in making such distiction. The use of antibiotics in order to reduce the PSA provoked by infection might be beneficial. It is suggested that infection might contribute to prostate carcinogenesis, so it remains to find out the appropriate way to follow up those patients.

TABLE 3

CANCER DETECTION RATE ACCORDING TO PSA GROUP

PSA Group	Cancer		Total
	No	Yes (%)	
1	17	1(5,5)	18
2	13	2(13,3)	15
3	162	42(20.6)	204
4	115	56(32.7)	171
5	33	66(66.7)	99
6	5	64(92.7)	69
Total	345	231(40.1)	576

TABLE 3A

SENSITIVITY, SPECIFICITY, POSITIVE AND NEGATIVE PREDICTIVE VALUES ACCORDING O DIFFERENT CUT OFF'S OF PSA

	PSA cut off		
	4ng/ml	10 ng/ml	20 ng/ml
Sensitivity	0.98	0.81	0.43
Specificity	0.09	0.55	0.89
Positive predictive V	0.42	0.55	0.72
Negative predictive V	-.80	0.81	0.70
No of pts	34	342	140

TABLE 4

AUC FOR F/T PSA AND PSA DENSITY ACCORDING DIFFERENT PSA

	Area under the curve	
	PSA<10ng/ml	PSA <20ng/ml
F/T PSA	0.42	0.38
PSA density	0.68	0.72

CONCLUSION:

Although there is a tendency to minimise the value of PSA in diagnosis of prostate cancer, it is essential to make difference concerning screening. In developped countries screening program already detected patients having cancer, leaving only younger population in which, of course, lowering of PSA treshold is mandatory.

But what can countries without screeing program learn and accept as a policy ?

According to our results, PSA is PSA treshold should not be lowered under 4, except if digitorectal examination is abnormal. The use of antibiotics in patients with PSA up to 20 might add in discrimination of those having prostatitis or cancer. PSA should be the most important parameter for biopsy; PSA density is a reliable PSA derivative while free /total PSA index is less important and

TABLE 5

PSA ACCORDING TO HISTOLOGICAL DIAGNOSIS

PH	/	PSA	F/T PSA	PSA density
Ca	mean	88.878	0.1507	2.5464
	N	113	45	110
	median	23.300	0.1100	0.7412
PIN	mean	12.084	0.1528	0.5004
	n	94	72	88
	median	10.040	0.1400	0.2629
Ca+PIN	mean	67.596	0.01095	0.2629
	N	119	65	118
	median	24.000	9.000E-02	0.6955
Prostatitis	mean	12.364	0.1507	0.2927
	N	197	137	188
	median	9.100	0.1400	0.2015
BPH	mean	12.222	0.1738	0.3812
	N	41	26	40
	median	7.270	0.1400	0.1953
BPH+ Prostatis	mean	8.304	0.1675	0.1811
	N	10	4	10
	median	7.660	0.1400	0.1568
Total	mean	38.751	0.1454	1,1442
	N	574	349	554
	median	11.900	0.1300	0.2959

as such is not obligatory in patient with PSA up to 20 ng/ml.

SUMMARY

UVOD: PSA je najpozdaniji tumorski marker u onkologiji, neophodan u dijagnostici i terapiji karcinoma prostate. Skrining kod karcinoma prostate nije opšte prihvaćen mada ga mnoge zemlje sprovode. To je ukazalo na nepozdanost PSA u detekcija karcinoma prostate. Do sada prihvaćena granična vrednost PSA je revidirana, kao i vrednost PSA derivata. Da li ove promene imaju implikacija i u našoj populaciji bolesnika je veliko pitanje.

CILJ rada bio je da ispita prediktivnu vrednost PSA, odnosa izmedu slobodnog i totalnog PSA i PSA gustine u našoj grupi bolesnika koji nisu obuhvaćeni skrining programom.

Pacijenti i metode: TRUS vodjena biopsija prostate je učinjena kod 579 bolesnika. Broj uzoraka je bio od 6 do 12. Prosečna starost bolesnika bila je 67.5 godina (30-90). Vrednost PSA kretala se od 0.41 do 2025 (prosečna vrednost: 38.6 ng/ml, mediana: 11.95, SD:140.45). Rektalni pregled je ocenjen kao pozitivan kod 351 bolesnika. F/T PSA je odredjen kod 352 bolesnika i raspon je bio od 0.02 do 0.88 (prosečni F/T PSA:0.14, mediana: 0.13). Volumen prostate je izmeren kod svih na osnovu elipsoidnog modela, a PSA gustina izračunata po formuli PSA/volume prostate. Bolesnici su stratifikovani u 6 grupa u zavisnosti od vrednosti PSA: Grupa 1: PSA , Grupa 2: PSA 2.5-4, Grupa 3: PSA od 4-10, Grupa 4: PSA od 10-20, Grupa 5: PSA 20-50 i Grupa 6: PSA50 ng/ml).

REZULTATI: Na nehomogenost bolesnika ukazuje veliki raspon PSA (0.4- 2025). Karcinom je dijagnostikovan kod njih 233 (40.2%). Očekivano je detekcija karcinoma bila veća ukoliko je PSA bio viši, ali je karcinom bio ekstremno redak ukoliko je PSA bio ispod 4 ng/ml. PSA, F/T PSAi PSA gustina su se bitno razlikovale u zavisnosti od prisustva karcinoma. Najveći broj naših PSA je imao PSA u rasponu od 4- 20 ng/ml. U grupi 3 (PSA od 4-10) prediktivna vrednost PSA je bila samo 20.6%, a u grupi 4 (PSA 10-20 ng/ml): 32.7%. Osetljivost, specifičnost, pozitivna i negativna prediktivna vrednost PSA bile su najbolje pri graničnoj vrednosti PSA od 10 ng/ml. U grupi bolesnika sa PSA ispod 20 ng/ml, gustina PSA je bila pouzdaniji parametar u detekciji karcinoma u odnosu na F/T PSA.

ZAKLJUČAK: PSA predtavlja pouzdan marker u detekciji karcinoma prostate u našoj populaciji koja nije podvrgnuta skrining programom. Na osnovu naših rezultata, granična vrednost PSA ne bi trebalo da bude ispod 4 ng/ml. PSA gustina je pouzdan marker u detekcija karcinoma kod bolesnika sa PSA do 20 ng/ml.

Ključne reči: karcinom prostate, dijagnoza, PSA vrednost

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TABLE 6

GRADE AND GLEASON SCORE

		Gleason score								Total
		3	4	5	6	7	8	9	10	/
Grade	1	1	1	/	/	/	/	/	/	2
	2	/	/	39	58	50	/	/	/	147
	3	/	/	/	/	44	14	10	1	69
Total	/	1	1	39	58	94	14	10	1	218

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