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SCREENING FOR PROSTATIC TUMORS IN METABOLIC SYNDROME PATIENTS IN ROMANIA

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Abstract

Aims. The aims of our study were to assess the prevalence of prostate tumors in patients with metabolic syndrome.

Material and methods. Subjects were patients recruited from three medical centers in Bucharest, Romania. For this study we selected men over 45 years of age with metabolic syndrome.

The anthropometric measurements included height, weight, waist circumference and hip circumference. We calculated the body mass index (BMI) and measured the blood pressure. Biochemical tests included fasting plasma glucose (FPG), HbA1c, total cholesterol (TC), TG, HDL-C, fasting plasma insulin (FPI), prostate-specific antigen (PSA) and free-PSA. The prostate gland volume was measured by transrectal ultrasound.

The diagnosis of prostatic cancer was based on a positive finding of the histological examination obtained from 14-core biopsy.

Results. There was a high prevalence of prostate tumors (benign and malignant) - 82.85% (n=343). Prostate cancer was diagnosed in 7.9% of patients (n=33) using DRE, PSA, free PSA/PSA ratio and TRUS. The prevalence of BHP was 74.9% (n=310). The results of the present study indicate that PSA detects a significant number of prostate tumors missed in DRE. The use of DRE, PSA and TRUS, in combination, provided the highest rate of detection of prostatic tumors in patients with metabolic syndrome without infectious diseases of the prostate.

Conclusions. The prevalence of prostatic tumors, prostate cancer and benign prostatic hyperplasia in metabolic syndrome patients is high. Due to its increased prevalence, the BPH can be considered as a feature of metabolic syndrome.

Key words: prostate cancer, benign prostatic hyperplasia, insulin resistance, prostate-specific antigen.

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INTRODUCTION

Prostate cancer (PCa) is now recognized as one of the most important public health problems in Europe, being the most common solid neoplasm (202 100 incident cases, 18.1% of all incident cases) outnumbering lung and colorectal cancer (1). The increased incidence of PCa in Europe might be explained by the active screening in these countries.

The prostatic hyperplasia is the most common disorder of the prostate in elderly males, its incidence increases with age, and its prevalence is about 90% in men in their 80s (2).

Age is the only unchangeable and established factor known so far, although androgens and their metabolites strongly influence the growth and development of the prostate gland (3,4). An analysis of autopsy studies has shown that approximately one in three men over the age of 50 years had histological evidence of PCa, up to 80% of these tumors being limited in size and grade and, therefore, being clinically insignificant (5,6). A recent study of incidental PCa diagnosed in organ donors found PCa in 1 of 3 men with an age of 60-69, and this increased to 46% in men over age 70 years (7).

Using data from three U.S. government health surveys, researchers found that obese men generally had lower prostate-specific antigen (PSA) levels on screening exams than thinner men (8).

The metabolic syndrome (MetS) is a cluster of cardiovascular risk factors: diabetes and raised fasting plasma glucose, abdominal obesity, high triglycerides and high blood pressure. The prevalence of the MetS in the general population is estimated to be around 20-25 per cent and increases with age and is higher in men than in women (9,10). Reports about MetS in Romania showed a higher prevalence and varies in men between 28.8%-43.1% (11-13).

The aims of our study were to assess the prevalence of prostate tumors in patients with MetS and also to analyze the sensitivity and specificity of the screening tools. We conducted a screening in a population with MetS because these patients may be diagnosed with PCa less often as they are less likely to have PSA-prompted biopsies than thinner men. Many other investigators have shown that PSA levels are lower in obese men (14-16). Moreover, obesity is a significant risk factor for PCa at the time of biopsy (17).

MATERIALS AND METHODS

Study population and sampling methods

Subjects were patients recruited from three medical centers in Bucharest (two urology clinics and a diabetes and metabolic diseases clinic). We selected men over 45 years of age with MetS who met the inclusion criteria for the study. Patients were made aware of all risks and procedures involved in the study and were included only with written consent.

Inclusion criteria were represented by age over 45 years and presence of MetS according to IDF criteria (central obesity - waist circumference over 94 cm in men or BMI over 30 kg/m^2 plus any two of the following features: 1. triglycerides (TG) $\geq$ 1.695 mmol/lL

(150 mg/dL) or treatment; 2. lower high density lipoprotein-cholesterol (HDL-C) < 40 mg/dL or treatment; 3. blood pressure ≥ 130/85 mmHg or medication; 4. fasting blood glucose ≥ 5.6 mmol/L (100 mg/dL) or medication for diabetes (9).

Exclusion criteria were treatment with testosterone, 5-alpha reductase inhibitors in the last six months (dudasteride, finasteride), infectious diseases of the prostate, the presence of a malignancy other than PCa, participation in other studies simultaneously.

Clinical examination

Clinical examination was performed according to the principles of medical ethics standards and included the following parameters: height, weight, waist circumference (measured at the midpoint between the lower rib margin and the iliac crest), hip circumference (measured as the maximal circumference at femoral trohanters), blood pressure, systolic and diastolic, measured in one arm, after ten minutes rest.

Body mass index (BMI) was calculated (body weight in kilograms divided by the square of height in meters) and categorized based on national guidelines as follows: less than 25 kg/m^2 (normal), 25–29.9 kg/m^2 (overweight), 30–34.9 kg/m^2 (obesity class I), 35-39.9 kg/m^2 (obesity class II), >40 kg/m^2 (obesity class III).

Digital rectal examination was performed in all patients in order to assess the size of the prostate gland, its consistency, the presence of a node, the mobility of the prostate on palpation, the symmetry of the two lobes, noting the characteristics of any asymmetries, palpation of the seminal vesicle.

Laboratory assays

Fasting blood samples were drawn between 7:00 a.m. and 10:00 a.m. The biochemical analyses included fasting plasma glucose (FPG), HbA1c, total cholesterol (TC), TG, HDL-C, fasting plasma insulin (FPI) and prostate-specific antigen (PSA) and free-PSA.

IR (insulin resistance) was determined using Homeostasis model assessment (HOMA-IR) (fasting insulin level (mUI/L)x fasting glucose level (mg/dL)/405 (18); a HOMA-IR index value of more than 2.0 was considered as the criteria of insulin resistance.

The prostate gland volume was measured using transrectal ultrasound (TRUS). TRUS guided prostate needle biopsy was performed in patients with at least one of the following: abnormal DRE, PSA over 3.0 ng/mL, free PSA/PSA ratio <0.2 (RFPSA). TRUS prostatic biopsy was performed in 61 patients; histopathological findings identified 2 patients without prostatic diseases, 26 patients with BPH and 33 patients with PCa.

The diagnosis of PCa was based on a positive finding of the histological examination obtained from 14-core biopsy scheme obtaining 6 far lateral cores (lateral sextant scheme of Stamey – black points) in addition to the 6-core technique plus 2 more in lateral zone.

The diagnosis of benign prostatic hyperplasia (BPH) was based on the prostatic volume (PV) at TRUS (all patients with PV over 30 cm^3 we have considered with BPH); the prostatic size can be also estimated by DRE, even though DRE tends to underestimate the true prostate size compared with TRUS.

Statistical analysis

Statistical analysis was performed

using SPSS 19 (copyright IBM). Results were reported as means and standard deviation for continuous variables normally distributed, and % for dichotomy data. One-way analysis of variance and Chi square and Fisher exact tests analyses were used to compare means and proportions, respectively were used to test differences in proportions. No multiplicity adjustments were used as no intermediate analysis was performed. The independent predictive factors for PCa diagnosis were identified using binary logistic regression analysis. The specificity and sensitivity of the tested equation were defined using the receiver operating characteristics curve. Type I error assumed was 5%.

RESULTS

We have included 414 patients with MetS, with a mean age of 59.5±8.22 years. The prevalence of PCa in our group patients was 7.9% (33 patients) and of the BPH was 74.87% (310 patients); only 17.14% of patients did not have prostatic diseases (p=0.0001).

PCa patients were older than BPH patients or those without prostatic diseases (p=0.045). BMI, SBP, FPI, HOMA-IR, PSA and PV were greater in PCa patients (all p below 0.05). Testosterone level, RFPSA and HbA1c were lower in PCa patients (p=0.045, p=0.0001 respectively p=0.0001). Characteristics of patients are presented in Table 1.

Risk factors for prostatic diseases

As the male population gets older there is a significant increase in prostate disease occurrence. All patients that were 80 and older had prostate disease. We identified more patients with PCa in the age group 60-69 years (11 patients) and 70-79 years (13 patients). The prevalence of the PCa and benign prostatic hyperplasia increased with age (Figure 1).

Another risk factor for PCa is family history; in 15.2% of patients with PCa (five patients) there was presence of family history compared to the group with BPH (3.5% - 11 patients) or healthy people (2.8% - two patients).

In univariate analysis odd ratio of event was 6.11 (CI95% 3.32-11.21, p=0.0001) in patients with advanced age (age over 65 years) and 2.94 (CI95% 1.007-8.63, p=0.049) in patients with family history of PCa.

In univariate analysis for age 60 (<60/>60) OR was 5.5 (CI95% 2.4-12.53, p=0.0001), and for 70 years OR was 5.8 (CI95% 3.1-11.1, p=0.0001).

MetS and prostatic diseases

All patients were stratified according to the MetS components (stratified in 3, 4 or 5 components). 72.72% (n =24) of patients with PCa have 4 or 5 components of MetS; 27.27% (n=9) of patients with PCa have 3 components of MetS. 47.9% (n=34) of patients without prostatic diseases have only 3 components of MetS (Fig.2).

BPH was present in 40.3% (n=125) of the patients presenting 3 components of MetS, 32.3% (n=100) of the patients presenting 4 components of MetS, as well as in 27.4% (n=85) of the patients presenting 5 components of MetS (p=0.023) (Fig.2).

Obesity was present in 81.8% (n=27) patients with PCa, 63.9%

Table 1. Characteristics of the patients

	BPH		Normal		PCa		p value
	Means	SD	Means	SD	Means	SD	
Age (years)	60.4	7.6	52.1	4.7	67.6	8.7	0.0001
Height (cm)	174.0	5.3	176.9	5.9	172.7	4.1	0.0001
Weight (kg)	95.1	11.0	94.3	8.6	94.6	10.4	0.8428
BMI (kg/m^2)	31.4	3.1	30.1	2.2	32.3	2.9	0.0006
WC (cm)	108.5	8.2	106.5	8.0	106.6	7.1	0.0860
HC (cm)	102.9	7.4	100.9	7.0	101.5	7.2	0.0780
SBP (mmHg)	140.0	14.1	134.6	13.0	145.7	14.4	0.0005
DBP (mmHg)	82.4	9.1	79.6	9.6	82.6	9.6	0.0626
TG (mg/dl)	187.6	77.4	201.4	101.0	196.0	55.4	0.3955
HDL-C (mg/dl)	39.9	8.9	40.1	10.0	36.8	6.5	0.1575
TC (mg/dl)	208.3	52.9	205.1	48.0	212.5	35.2	0.7831
FPG (mg/dl)	128.4	52.0	123.1	54.2	106.5	30.7	0.0578
FPI (uU/ml)	16.3	14.6	16.6	19.8	33.6	29.3	0.0001
HOMA-IR	5.6	6.9	5.2	6.3	8.5	7.6	0.0500
HbA1c (%)	7.4	1.7	7.1	1.6	6.0	0.7	0.0001
PSA (ng/dl)	1.2	1.2	0.8	0.8	27.9	30.9	0.0001
FPSA/PSA	0.4	0.1	0.4	0.1	0.1	0.1	0.0001
Testosterone (ng/ml)	3.6	1.3	3.8	1.2	3.1	1.2	0.0451
PV (cm^3)	43.3	9.6	25.8	3.2	54.7	9.9	0.0001

All values are expressed as means±SD

Abbreviations: BMI, body mass index; WC, waist circumference; HC, hip circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HOMA-IR, homeostasis model assessment of insulin resistance; HbA1c, glycated hemoglobin; PSA, prostate-specific antigen; FPSA, free-prostate-specific antigen; PV, prostate volume; BPH, benign prostatic hyperplasia; PCa, prostate cancer.

(n=198) patients with BPH, and 46.5% (n=33) in patients without prostatic diseases (p=0.001). The degree of obesity in PCa patients shows a high percentage of class I obesity (n=20, 60.6%) and class II obesity (n=7, 21.2%). Hypertriglyceridemia was present in 93.9% (n=31) patients with PCa, 67.1% (n=208) patients with BPH and 71.8% (n=51) patients without prostatic diseases (p=0.006).

HypoHDL-cholesterolemia was present in 75.8 % (n=25) patients with PCa, 58.4% (n=181) patients with BPH and 53.5% (n=38) patients without prostatic diseases (p=0.093).

Hypertension was present in 69.7% (n=23) patients with PCa, 66.5% (n=206) patients with BPH and 46.5% (n=33) patients without prostatic diseases (p=0.005). Diabetes was present in 66.7% (n=22) patients with PCa, 77.4% (n=240) patients with BPH and 74.6% (n=53) patients without prostatic diseases (p=0.369).

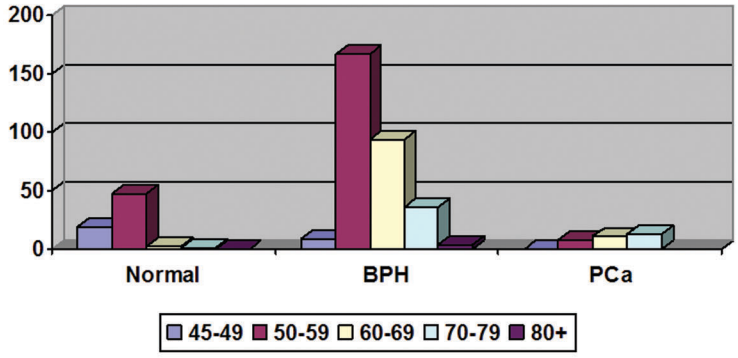


Figure 1. Age groups and prostatic tumors.

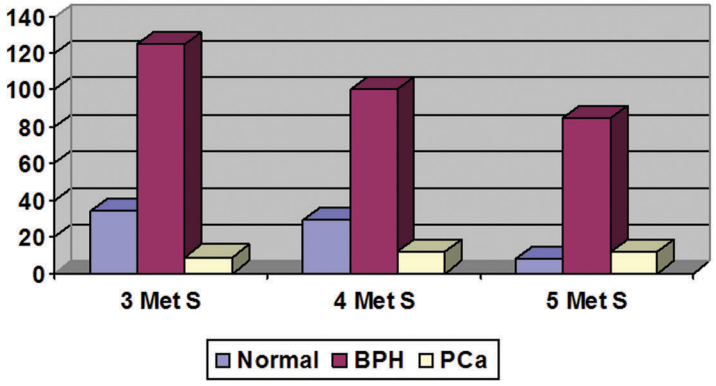


Figure 2. Components of the metabolic syndrome and prostatic tumors.

In univariate analysis increased plasma triglyceride and HOMA-IR levels and low levels of HDL cholesterol were strongly related to the presence of PCa: OR was 5.7 for hypertrigyceridemia (CI95% 2.03-16.35, p=0.0001), 3.6 for low HDL-cholesterol (CI95% 1.7-7.6, p=0.001) and 1.2 for HOMA-IR (CI95% 1.1-1.3, p=0.001).

Multivariate analysis (adjusted for age over 65 years, triglycerides, HDL cholesterol, family history, BMI, hypertension and HOMA-IR) showed that only age over 65 years (OR=7.01, CI95% 3.6-13.4, p = 0.0001), triglycerides (OR=5.28, CI95% 1.7-16.3, p = 0.004) and HDL cholesterol (OR=2.45, CI95% 1.07-5.6, p = 0.023) were independent risk factors for PCa (Fig. 3).

Graphic 3. Independent risk factors for prostate cancer

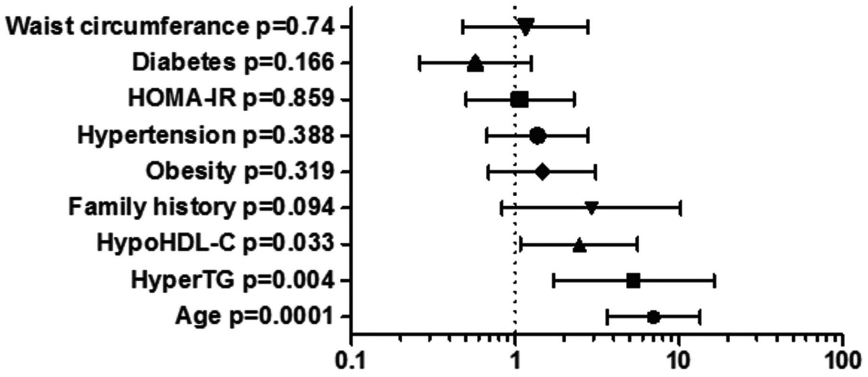


Figure 3. Independent risk factors for prostate cancer.

Diagnosis of prostate tumors

Digital rectal examination

Digital rectal examination was abnormal in 16 patients (5 patients with PCa, 9 patients with BPH, and in 2 patients without prostatic diseases). Only in 15.2% patients with PCa DRE was abnormal.

Among patients with abnormal DRE, 5 patients (31.5%) had PSA level under 3 ng/dL and 11 patients (68.8%) had PSA level over 3 ng/dL. If we used only DRE for screening in patients with MetS the prevalence of PCa would be only 1.2% (5 cases). DRE did not correlate with age or number of MetS components (obesity, hypertension, dislipidemia, diabetes). The validity of DRE in predicting the PCa is 56.1% (SE=5.6%, p=0.242) [CI 95% 45.1-67.2] (Fig. 4).

PSA levels

Median of PSA level was 0.924 ng/dL (CI95% 1.1-13.8) in patients with BPH, 17.5 ng/dL (CI95% 16.9-38.8) in patients with PCa and 0.625 ng/dL (CI95% 0.6-1.02).

Even though transrectal ultrasound guided prostate needle biopsy should be performed in all patients with PSA level over 3 ng/dl (13.3%), it was performed only in 54 of 55 patients (compliance 98.1%).

PSA testing has diagnosis significance/validity in 99.3% of the patients diagnosed with PCa. Optimal threshold for PSA is 3.07 ng/dL, it has a sensitivity of 98.1% and a specificity 95%. Cut-off point 3 ng/dL has a sensitivity of 98.1% and a specificity of 94.5%. Cut-off point 4 ng/dL has a sensitivity of 86.8% and a specificity of 97.9%. PCa is identified using PSA testing at an asymptomatic localized stage.

The validity of PSA measuring in predicting the PCa is 99.3% (SE=0.3%, p=0.0001) [CI 95% 98.6-99.9] (Fig. 4).

Free PSA/PSA ratio

The ratio of free to total PSA may be an important variable for distinguishing between benign and malignant prostate disease.

Free PSA/PSA ratio was under 0.2 in 58 patients (28 patients with BPH, 25 patients with PCa, 5 normal patients); eight patients with PCa have the ratio over 0.2 (p=0.0001).

Free PSA/PSA ratio is valid as a diagnostic tool in 8.2% of the cases (SE=3.2%, p=0.0001) [CI 95% 0.02-0.14] (Fig. 4).

DISCUSSION

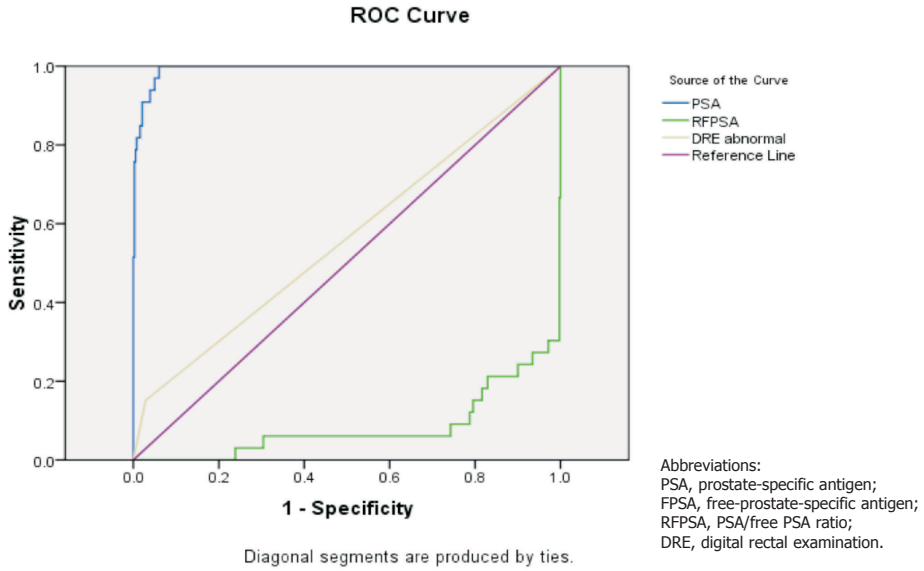
This study is the first screening of prostate tumors in patients with MetS in Romania and the results show the importance of investigation of prostatic disease in this population. In Romania, in our knowledge, this study was the first of this kind to include a combination of DRE, PSA level and TRUS for the diagnosis of prostate tumors.

Prevalence of prostate tumors (benign and malignant) was very high 82.85% (n=343). PCa was diagnosed (using DRE, PSA, free PSA/PSA ratio, TRUS) in 7.9% of patients (n=33). PCa is diagnosed in about 24.2% of men aged 50-59 years, rises in the sixth and seventh decade of life (33.3% respectively 39.4% - the highest incidence). These results are consistent with previously published data.

In our study the prevalence of BHP was higher (74.9%) for at least two reasons: prostatic volume was used as a diagnostic criterion without considering the presence and severity of lower urinary tract symptoms. Secondly, a large number of our patients were obese (63.9%, n=198) (BMI > 30 kg/m^2) which is known to be associated with a higher prostate volume.

Prevalence of prostatic hyperplasia increased with age; 74.9% of the patients aged 51-60 years have BPH, compared to over 70% of those aged 70 to 79 years, and almost 80% of those aged 81 to 90 years. In general population, the prevalence in patients aged 51 to 60 years is smaller - 42% (19).

According to a previous study on PCa in Romania (DRE was used as initial screening tool, performed by highly qualified examiner) the prevalence was 1.6% (11/697) (20).



Abbreviations:
PSA, prostate-specific antigen;
FPSA, free-prostate-specific antigen;
RFPSA, PSA/free PSA ratio;
DRE, digital rectal examination.

Figure 4. ROC curves for PSA, free PSA/PSA ratio and DRE.

Should we have used DRE as the only screening tool, the prevalence of PCa would only be 1.2% (5 cases).

Sensitivity of DRE is extremely low in our study, 15.2%. In another study the sensitivity of DRE was 16.7-21.3% (21).

The sensitivity of PSA depends on the cut-off point for positive and negative results. Sensitivity of PSA is higher than that of DRE in most studies and a combination of the two methods is used in clinical practice. The use of both tests in combination provided the highest rate of detection in all age groups (22,23).

The higher specificity of PSA value, in our study, can be explained by hemodilution of PSA among obese men and the real level of PSA is higher. If we apply the inverse PSA–BMI correlation named Hekal's equation that measures total PSA (ng/ mL) multiplied by age (years) and divided by BMI of the patient then PSA level is higher (24).

The results of the present study as well as recent literature reports indicate that PSA detects a significant number of prostate tumors missed in DRE (25-27).

The correct interpretation of the value of PSA in clinical contexts, in conjunction with active tracking multiple PSA values of patients with infectious disease of the prostate allow a more accurate identification of patients requiring prostate biopsy.

There is some suggestion that PSA testing has led to a reduction in PCa mortality, and most of this evidence is derived from ecological studies. In one study comparing different areas in Austria, men from a region in which PSA testing was free and widely used had a nearly 2-fold reduction in PCa mortality compared with other areas of the country in which PSA testing was not as easily accessible or commonly used (28). Another study using a cross-national comparison also suggested that PSA screening could reduce mortality (29).

New data from a Swedish study show that population screening with PSA in men between 50 and 69 years of age reduced PCa mortality by almost half during a follow-up period of 14 years (30). The ERSPC trial found a significant 20% decrease in the risk for PCa mortality associated with a PSA screening protocol (31).

In the U.S. Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, Andriole *et al*. (31) report no mortality benefit from combined screening with PSA testing and digital rectal examination during a median follow-up of 11 years (32). In Romania, 95% of patients are admitted with T3 or T4 PCa at the time of diagnosis, frequently metastasized. A requirement for active national screening campaign is in this case necessary.

CONCLUSIONS

The prevalence of prostatic tumors, PCa and BPH in MetS patients is high. Due to its increased prevalence, the BPH is discussed by us as a feature of MetS. Based on these results we suggest to determine the PSA value as a screening method for PCa in all patients with MetS.

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