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ORIGINAL INVESTIGATION

Elderly patients and prostate biopsy. How old is too old?

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Background & aims. Based on autopsy finding that many elderly men bear clinically-insignificant prostate cancer, physicians tend to be reluctant to advise PSA testing in men > 75y and to recommend prostate biopsy, particularly in men who suffer from lower urinary tract symptoms. Herein, we compared the outcome of prostate biopsy in men ≤ 75 and > 75y to determine whether such procedure is worth in the elderly patient.
Methods. We assessed the rates of prostate cancer and of clinically-significant prostate cancer in men ≤ 75 and > 75y who underwent prostate biopsy at our Institution. We also assessed prostate volume, peak flow rate, post-void residual and International Prostate Symptoms Score.
Results. Of 3350 with PSA up to 20 ng/ml, 387 (11.5%) were > 75y. They had higher PSA, similar prostate volume, lower Peak Flow rate and International Prostate Symptoms Score and higher post-void residual than their younger counterpart. Prostate cancer detection rate was 62%, as opposed to 43% in their younger counterpart ($p < 0.0001$); clinically-significant prostate cancer rate was 42.9% as opposed to 24% ($p < 0.0001$). Findings were almost the same in the 2740 patients with PSA up to 10 ng/ml. Multivariate analysis pointed out that all clinical variables independently predicted clinically-significant prostate cancer but elderly patients with PSA up to 10 ng/ml had an almost 5-fold greater risk of such diagnosis than their younger counterpart.
Conclusions. Given their risk of harboring clinically-significant prostate cancer, elderly patients with rising PSA deserve prostate biopsy as early detection may provide significant benefits in terms of disease-free and overall survival.

Key words: Elderly, Prostate cancer, Prostate biopsy, High grade prostate cancer, PSA screening, Early diagnosis

INTRODUCTION

Prostate cancer (PCa) is the most common malignancy in men, with an estimated 1.1 million diagnoses worldwide in 2012, accounting for 15% of all cancers diagnosed [1]. The median age at diagnosis is 66y and, although many elderly men who are diagnosed with PCa will die from other causes, 70% of deaths occur in men older than 75y [2 3].
Since incidence and mortality rise steeply with age, the PCa burden is expected to increase with exponential aging of the population.
Other potential explanations for increasing PCa incidence stay in the increased use of PSA testing, novel imaging techniques and biomarkers [4-7].
Given the risk of overdiagnosis turning into overtreatment, the role of PSA testing in the elderly is a matter of debate. The USPSTF recommends against PSA-based screening for prostate cancer in men 70 years and older [8]. The International Society of Geriatric Oncology (SIOG) guidelines for the management of elderly PCa patients outlines the risks of both over- and under- treatment and the importance of assessing overall health status, comorbidities, and cognitive function

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in personalizing management. Having said this, they conclude that age alone should not preclude initial screening and, in case of a cancer diagnosis, effective treatment [3]. Somewhere in between is the position of current EAU guidelines that recommend to stop early diagnosis of PCa based on life expectancy and performance status; men who have a life-expectancy of < 15 years are unlikely to benefit [1]. This position is likely due to the perception of most PCas in the elderly being clinically insignificant, perception supported by the observation of increasing incidence of PCa with aging at autopsy [9].

In this scenario, physicians tend to be reluctant to advise PSA testing in men > 75y as well as to recommend prostate biopsy (PBx) for increased PSA levels; this is even more true for those with PSA in the grey zone (4-10 ng ml) who suffer from lower urinary tract symptoms (LUTS).

In the present study we compared the outcome of PBx driven by increased PSA and/or abnormal DRE men ≤ 75 and > 75y to determine whether such procedure is worth in the elderly patient.

PATIENTS AND METHODS

Data of patients scheduled for ultrasound-guided transrectal PBx because of increased serum PSA (≥ 4 ng/mL) and/or abnormal digital rectal examination (DRE) were prospectively entered into our dedicated Institutional Review Board-approved database.

All patients underwent PSA measurement before DRE and transrectal ultrasound (TRUS). Uroflowmetry (UFM) was carried out before PBx, waiting for the patient to report a strong sensation to void. Following local non-infiltrative anesthesia [10 11].

TRUS was used to determine prostate and transition zone volume and to guide transrectal prostate sampling according to our systematic 18-core biopsy scheme [12]. Following the procedure Serenoa Repens was given as needed [13].

Men with PSA > 20 ng/ml, men receiving 5 alfa-reductase inhibitors (5-ARIs), or who had previously undergone invasive treatment for benign prostatic hyperplasia, or with dwelling urethral catheters were excluded from the present study.

A senior uropathologist evaluated the specimens according to contemporary diagnostic criteria for high-grade prostatic intraepithelial neoplasia (HGPIN), atypical small acinar proliferation (ASAP) of prostate [14], and PCa. We compared the rates of all PCas and of clinically significant PCas (CSPCa), defined as those with a Gleason Grade Group (GGG) > 1 according to the International Society of Urological Pathology (ISUP) consensus [15] in men ≤ 75 and > 75y. Data were further stratified according to pre-biopsy PSA levels.

Statistical analysis

Continuous variables are reported as medians and interquartile range and analyzed by the Kruskal Wallis test. Categorical variables are reported as frequencies and analysed by the Chi square Test. Multivariate logistic regression analysis was carried out to determine independent predictors of CSPCa. Statistical Analyses were performed using STATA 14 (StataCorp LP, College Station, TX, USA). Significance was set at $\alpha = 0.05$.

RESULTS

Between January 2006 and July 2018, a total of 3820 patients underwent TRUS-guided PBx at our Institution; 3350 met the inclusion criteria. Their clinical characteristics and pathology findings are shown in Table I.

A total of 387 patients (11.5%) were > 75 years and about 18% of them were > 80 years old. Elderly men had higher PSA and higher rates of suspicious DRE than their younger counterpart. As for benign prostatic obstruction (BPO)-related parameters, elderly patients had similar prostate volume (PVol), lower Peak Flow rate (PFR) and International Prostate Symptoms Score (IPSS) and higher post-void residual (PVR) than their younger counterpart.

Most important, cancer detection rate (CDR) was significantly higher in elderly men than in the younger ones (62.01 *vs* 43%, respectively; $p < 0.0001$); the same applied to CSPCa (42.9 *vs* 23.6%, respectively; $p < 0.0001$).

In the sub-analysis of the 2740 patients with PSA up to 10 ng/ml (Tab. II), findings remain the same, as elderly men had higher PSA, higher rates of suspicious DRE, similar PVol, lower PFR and IPSS) and higher PVR than their younger counterpart. Again, cancer detection rate (CDR) was significantly higher in elderly men than in the younger ones (62 *vs* 39%, respectively; $p < 0.0001$) and the same applied to CSPCa (40 *vs* 21%, respectively; $p < 0.0001$).

Multivariate analysis pointed out that all clinical variables independently predicted CSPCa, but age was associated with the greater risk. Specifically, elderly patients had a 4.14-fold greater risk of being diagnosed with CSPCa then their younger counterpart and such risk raised to 4.96 in patients with PSA up to 10 ng/ml (Tab. III).

DISCUSSION

The present study pointed out that, in spite of their BPO-related parameters [16-18], elderly patients had a

Table I. Clinical characteristics and biopsy pathological findings in men with PSA < 20.

	≤ 75 n = 2963	> 75 n = 387	P-value
Age, years	65.0 (60.0, 70.0)	78.0 (76.0, 80.0)	< 0.0001
PSA, ng/ml	6.30 (4.80, 8.79)	7.80 (5.69, 11.20)	< 0.0001
Suspicious DRE, n (%)	1171 (39.9%)	194 (50.2%)	0.003
Prostate volume, cc	52.00 (40.00, 70.00)	52.00 (37.00, 76.00)	0.8
PFR, ml/s	12.40 (9.00, 16.70)	11.00 (7.90, 15.00)	< 0.0001
PVR, ml	30.00 (1.00, 60.00)	40.00 (20.00, 60.00)	0.070
IPSS	10.0 (5.0, 16.0)	12.0 (6.0, 18.0)	0.005
ISUP, n (%)			
0	1704 (58%)	147 (38%)	< 0.0001
ISUP 1	561 (19%)	74 (19%)	
ISUP 2-3	371 (13%)	78 (20%)	
ISUP 4-5	327 (11%)	88 (23%)	

PSA: prostate specific antigen, DRE: digito rectal examination; PFR: peak flow rate; PVR: post voidal residual; IPSS: international prostate symptom score; ISUP: International Society of Urological Pathology

Table II. Clinical characteristics and biopsy pathological findings in men with PSA < 10.

	≤ 75 n = 2472	> 75 n = 268	P-value
Age, years	65.0 (60.0, 69.0)	78.0 (76.0, 80.0)	< 0.0001
PSA, ng/ml	5.75 (4.60, 7.40)	6.24 (5.00, 7.89)	0.001
Suspicious DRE, n (%)	952 (38.5%)	133 (49.7%)	0.005
Prostate volume, cc	51.00 (39.00, 70.00)	50.00 (35.00, 72.00)	0.4
PFR, ml/s	12.60 (9.00, 17.00)	11.80 (8.00, 15.60)	0.010
PVR, ml	30.00 (1.00, 60.00)	40.00 (20.00, 60.00)	0.3
IPSS	10.0 (5.0, 16.0)	13.0 (7.0, 18.0)	0.006
ISUP, n (%)			
0	1477 (60%)	103 (38%)	< 0.0001
ISUP 1	482 (19%)	61 (23%)	
ISUP 2-3	293 (12%)	56 (21%)	
ISUP 4-5	220 (9%)	48 (18%)	

PSA: prostate specific antigen; DRE: digital rectal examination; PFR: peak flow rate; PVR: post voidal residual; IPSS: international prostate symptom score; ISUP: International Society of Urological Pathology

Table III. Multivariate analysis evaluating independent predictors of Clinically significant PCa.

	PSA < 20 AUC = 0.80		PCA < 10 AUC = 0.79	
	OR (95% CI)	P-value	OR (95% CI)	P-value
PSA, per unit	1.15 (1.11, 1.20)	< 0.001	1.08 (1.00, 1.17)	0.06
Suspicious DRE	3.37 (2.57, 4.42)	< 0.001	3.24 (2.39, 4.39)	< 0.001
Prostate volume, per ml	0.97 (0.96, 0.97)	< 0.001	0.96 (0.96, 0.97)	< 0.001
PFR, per ml/s	1.01 (0.99, 1.03)	0.44	1.00 (0.98, 1.03)	< 0.001
Age < 75 years > 75 years	Ref. 4.15 (2.80,6.15)	< 0.001	Ref. 4.96 (3.16, 7.79)	< 0.001

PSA: prostate specific antigen; DRE: digital rectal examination; PFR: peak flow rate

significantly higher risk of being diagnosed with PCa than their younger counterpart. Interestingly, and somehow confuting the assumption that elderly patients tend to harbor clinically-insignificant PCas, elderly men had a

similar rate of low-risk ISUP 1 cancers but a significantly higher rate of CSPCas than their younger counterpart. A novel nomogram based on BPO-related parameters (PFR, PVol, PVR) has recently been shown to predict the risk of prostate cancer at first prostate biopsy with a model predictive accuracy of 0,768 for overall PCa and of 0.8002 for Clinical significant PCa [19]. Question remains whether such clinical factors may impact on treatment outcome, like smoke in bladder cancer [20].

Our findings are consistent with those in literature. Akman et al. [21] analyzed 103 PBxs performed in men aged 75 or more and found that Gleason scores ≥ 7 in 85% and ≥ 8 in 64% of patients. In a larger series of 1446 PBXs, men aged ≥ 75y and with mean serum PSA of 10.4 ng/mL, PCa detection rate was 53%; as much as 78% of these cancers were defined as clinically significant [22].

The increased risk of elderly people harboring aggressive PCas was confirmed also by radical prostatectomy series whereby nearly 90% of men aged > 70y were diagnosed with Gleason score ≥ 7; moreover, they had a significant greater failure rate compared than their matched younger counterpart [23]. The latter finding of elderly people having worse outcome was confirmed also in a large cohort of 12,081 men who underwent active treatment; those ≥ 70y had worse outcomes in terms of biochemical recurrence-free survival as well as cancer specific and overall survival [24].

An interesting finding of our study was that, among tested clinical variables, age was the most significant predictor of harboring CSPCa. It was quite striking that such evidence was even stronger in men with PSA up to 10 ng/ml, who had an almost 5-fold greater risk of being diagnosed with CSPCa than their younger counterpart. Such finding strongly question the assumption that in elderly men with LUTS, a PSA in the grey zone (4-10 ng/ml) in unlikely to be related to the presence of PCa.

The main question however remains whether elderly patients would benefit from an early diagnosis of PCa. Gulati et al. [25] developed 3 models of PCa natural history to project risks of clinical progression events and disease-specific deaths for PSA-detected cases assuming they receive no primary treatment. Among men with PSA detected Gleason score 8-10 disease, the three models project that 29-43% would die of their disease by 10 years after PSA detection in absence of treatment. Of course, question remains regarding the ideal treatment option in such patients. While radical prostatectomy remains the most efficient treatment option, voiding complications remain a key issue though such complication, like for several other surgical procedures, is linked to case volume [26,27].

In conclusion, given their significant risk of harboring PCa and CSPCa, elderly patients with LUTS and rising PSA deserve PBx even when their PSA is just in the grey zone (within 10 ng/ml) and even if their life expectancy is less than 10 years. Evidence suggest that early diagnosis and treatment of clinically significant aggressive PCas may provide significant benefits in terms of disease-free survival and overall survival. Therefore, like for other common benign urological conditions, the final clinical decision has to rely on wise clinical judgment [28-30].

Conflict of Interest

The authors declare no conflict of interest.

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