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Markers For Significant or High-Grade Prostate Cancer in Patients Over 75 Years Undergoing Prostatic Biopsy

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Abstract

Purpose: To show the increased necessity of routine prostate biopsy in men older than 75 years and to identify markers, which reliably indicate the presence of a prostate cancer (PCa), we evaluate several different parameters from elderly patients.

Methods: 196 patients over 75 years were included in the study, inclusion criteria for the biopsy were: PSA levels >4 ng/ml and/or a suspicious finding on dig ital rectal examination (DRE). The parameters analyzed included: age, prostate size, PSA levels, DRE findings, American Society of Anesthesiologists (ASA) PCa detection rate, Gleason score, clinically significant PCa detection rate and type of therapy once PCa had been detected (curative intent or palliative intent).

Results: PCa was detected in N=115 patients (59%), with 84.3% of them being defined as clinically significant ($p<0.05$) and 60.8% ($p<0.05$) as high grade. Only a PSA level > 10 ng/ml with a simultaneous positive DRE finding was a marker for high-grade or significant PCa ($p< 0.001$) in patients >70 years.

Conclusions: Our findings demonstrate that the prevalence of significant and high-grade PCa in the elderly patients is high raised (~60%). We identified two significant markers for patients over the age of 75, namely an increased high PSA level (PSA>10 ng/ml) and positive DRE. The combination of both markers indicates that the patient is suffering under a significant and high-grade PCa. In our opinion, every patient showing a combinational increase of both markers should be biopsied in order to receive an adequate therapy.

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Introduction

With the aging of the population and the fact that over 70% of all PCa are diagnosed in men over 65 years, it seems that most patients over the age of 70 years will present with PCa [1]. Between 2000 and 2050, the number of men over 65 years is expected to increase 4-fold worldwide. By 2030, the percentage of men older than 65 years will increase to 19.6% of the population compared with 12.4% of the population in 2000 [1-3]. Taking this into account and the fact that elderly men will suffer from PCa, the early detection of PCa is necessary.

The choice of PCa treatment regime for elderly patients is complex. Published data suggest that older men with localized PCa may not receive potentially life prolonging treatment since they will not benefit from these therapies [4]. The upper age limit for radical prostatectomy (RPE) as a curative treatment for localized PCa is controversial. Historically, RPE was rarely offered to patients older than 70 years due to the probably shorter life expectancy and poor functional outcome.

Nevertheless, according to the US Preventive Services Task Force screening for PCa in men younger than age 75 years is necessary due to a clearly defined benefit. However, in the Task Force's opinion and due to insufficient data, the screening of elderly patients (>75 years) is deemed not necessary [5]. They hypothesised that most of these patients will have a PCa of lowergrade with minimal clinical impact.

Chodak et al. performed a meta-analysis of 828 men with clinically localized PCa and a median age of 69 years who were treated with watchful waiting or hormone therapy [6]. They concluded that mortality rate matched with Gleason grade was not affected by age and for patients with poorly differentiated PCa watchful waiting is not appropriate. They identified that patients with with high grade PCas and

Furthermore, side effects of hormone therapy include: hot flashes, osteoporosis, loss of libido or impotence, and psychological effects, such as depression, memory difficulties, or emotional lability, are quite common. For the evaluation of competitive therapies, the palliative nature of hormone therapy is of great importance in regard to the quality of life of the patient.

The upper age limit for RPE as a curative treatment for localized PCa is controversial. A curative treatment is currently discussed because of the increasing age of the population. Minino et al. showed that the overall survival of RPE patients older than 70 years is 13 years [7]. Several different studies demonstrated adequate oncological outcomes, as well as a statistically significant and clinically important improvement in the disease-specific mortality rate of patients undergoing RPE [8-10]. Nevertheless, selecting appropriate candidates for surgical treatment of PCa is critically important in the elderly population. Studies show that surgical treatment of PCa in elderly patients (>65 years) offers comparable outcomes to those in younger ones, with significant gains in life expectancy and quality of life [11].

Alibhai et al. reported the effect of RPE on life expectancy and quality-adjusted life expectancy in elderly men [12].

During recent years robot-assisted laparoscopic radical prostatectomy (RARP) has become popular among urologists for the treatment of localized PCa. RARP is a well-tolerated treatment option for localized PCa due to fast recovery, less blood loss, improved cosmetics and surgical outcomes, in comparison to RPE. Due to these factors RARP is frequently chosen for the treatment of localised PCa [13,14].

The term significant PCa determines prostate cancers with a volume of less than 0.5 cm^3 and which will not become significant within the patient's life span. These tumors are usually left untreated [15]. In contrast the significant tumors are the high-grade PCas which are extremely aggressive and grow and spread quickly (according to the staging, every tumor > Stage IIB is a high grade PCa [15]).

In general, PCas were categorized according to their Gleason Score. The Gleason Score classifies prostate tumors according to their aggressiveness. The grading system is a numbered from 2 to 10, high Gleason grade numbers indicating greater risks and a higher mortality rate for the patient. The first half of the score is based according to the microscopic appearance, tissue samples which look more like normal prostate tissue receive a lower Gleason number (Gleason grade 2) than tissue samples with predominantly representing

cancer (Gleason grade 5). The second half of the Gleason grade is based on the second most common cell morphology (grade 1-5). Both numbers in combination produce the total score of the cancer [16] .

To the best of our knowledge, this is the first publication identifying two already pre-operativechracteristic markers, which are significantly positive in patients over 75 years suffering under a significant or high grade PCa.

Patients and Methods

A retrospective review of 196 patients, aged over 75 years, underwent a prostate biopsy between April 2004 and April 2010. Patient data was collected from both institutions according to the same inclusion criteria (see below). An informed consent was obtained and signed by the patient.

Ethnic origin was not documented in this study, including patients from Europe while the number of patients from other ethnic backgrounds was negligible.

Inclusion criteria for the biopsy were PSA levels >4 ng/ml or a suspicious finding on digital rectal examination (DRE). A multivariate analysis was conducted in order to detect potential markers for high grade or significant PCa. The parameters analyzed included: age, prostate size, PSA levels, DRE findings, American Society of Anesthesiologists score rate (ASA) [17] [18], Gleason score [16], clinically significant PCa detection rate (according to the Epstein criteria [19]), PCa in at least 3 biopsy needle cores or present in > 50% of any one biopsy needle core, Gleason score > 6 or PSA density > 0.15 or free PSA < 15 %), high grade PCa detection rate (defined as Gleason score 8-10) or type of therapy once PCa has been detected (Curative intent or palliative intent). It is important to mention that the ASA score is necessary to evaluate the condition of the patient's health and his ability to survive surgery. We used for the comparison between 2 groups the Student-*t*-student test, for comparison between 3 or more groups the one-way ANOVA with the Tukey correction, and for comparison of binomial values the Chi-square test. Simple linear regression was employed to test the effect of one continuous parameter against another. A p-value of <0.05 was considered statistically significant. TRUS prostate biopsies were performed with a Siemens Allegra ultrasound machine with a 6.5 MHz sector probe in both studies. The 18 core TRUS guided prostate biopsy was performed according to the following scheme: one biopsy each of the median peripheral zone at the base, mid gland and apex of both lobes (biopsies 1-3 and 10-12). One biopsy sample each of the medial-lateral peripheral zone at the base, mid gland and apex of both lobes (biopsies 4-6 and 13-15) and one biopsy sample each of the lateral peripheral zone at the base, mid gland and apex of both lobes (biopsies 7-9 and 16-18).

Results

Table 1 presents all patients' parameters which are necessary for evaluation. ,

The median age was 79 years (75-87) the median PSA levels were 22.1 ng/ml (3.7-233 ng/ml), and the median ASA score was 1.8 (1-3). 156 patients (79.5%) were thought to have a positive DRE. PCa was detected in 115 patients (59%), from this 84.3% being defined as clinically significant ($p<0.05$) and 60.8% ($p<0.05$) as high-grade PCa. A Gleason score of 6 was evident in 45 patients (39.1%), a Gleason 7 in 23 patients (20%), a Gleason 8 in 25 patients (21.7%) and a Gleason score of 9 in 22 patients (19.9%). On multivariate analysis, we found that an increased PSA level > 10 mg/dl ($p<0.05$) and a positive DRE finding ($p<0.05$) were independent markers for high-grade or significant PCa ($p< 0.001$). After diagnosis, patients underwent therapy (N=56) with a curative intent (48.6%).- Therefore, 30 patients underwent radiation therapy (26.1%) and 26 RPE (22.5%). 49 patients (42.6%) who underwent therapy with a palliative intent were treated as follows:, 30 patients (26.1%) hormonally , 7 patients (6.1%) with bilateral orchiectomy, 5 patients (4.6%) with green light laser and 7 patients (6.1%) with transurethral resection of the prostate (TUR-P). 10 patients (8.6%) did not undergo any kind of therapy. In summary most of the patients with curative intent were treated with radiation therapy (26.1%), and most of the patients with palliative intent received a hormonal therapy (26.1%).

Patients with a negative biopsy [42 patients (50.6%)], did not undergo further treatment, while 29 patients (34.9%) underwent TUR-P, 7 patients (8.4%) green light laser treatment, and 5 patients (6.1%) underwent prostatectomy (Data not listed in table 1).

Discussion

The diagnosis and treatment of PCa in elderly

patients is frequently discussed. Published data suggest that men aged over 75 should not be routinely screened for PCa [19-22]. Therefore, less than 50% of urologists routinely perform PSA tests in healthy men over the age of 75 years [23]. This might be due to the fact that they believe either most of these men will have cancer of a lower grade and stage with minimal clinical impact or that they have high grade PCa and would suffer from treatment problems due to their increased age. Nevertheless, Mistry et al. analysed 1446 needle biopsies of the prostate in men aged 75 or older, and found that 53% were positive for PCa, of which 78% would be defined as clinically significant cancer [11]. They argued that the potential benefit of identifying patients with aggressive PCa even older than 75 years is of great importance. They concluded that the treatment, once the PCa is diagnosed, is dependent on the patients' life expectancy, preference and general condition [11]. These results were similar to our own. As shown, PCa was detected in =115 of patients (59%), with 84.3% of them being defined as clinically significant ($p<0.05$) and 60.8% ($p<0.05$) as high-grade PCa. Possibly the situation is different, even if the patients were examined before the age of 75 years and the cancer is possibly detected earlier. Most of the institutions do not have information about prior examinations of the patients and therefore finding of a characteristic marker is essential.

In our case the patients received different treatments, shown in table 1, indicating that most of the patients were under therapy or at least under control.

Furthermore, it is important to consider that men who are 75 years old today are different from the 75-year-olds alive half a century ago : they are physically younger, and, in many cases, still sexually active [11]. Furthermore, diagnosis of PCa does not automatically mean invasive therapy. Large retrospective studies have shown similar 10-year survival rates between watchful waiting and radical prostatectomy in patients with well to moderately differentiated PCa [19-22]. Therefore, according to our data, while the age of diagnosis is unimportant, the early diagnosis PCas is of great importance. Indeed, recent studies have demonstrated that in patients with poorly differentiated PCa, potentially curative therapy can result in life expectancy and quality adjusted life expectancy gains in patients diagnosed up to age 80 years [23].

In a recent study, we evaluated the surgical, the oncologic and the functional outcome in men ≥75 years undergoing robot-assisted laparoscopic radical prostatectomy (RARP) [24]. RARP has become profoundly popular among urologists for the treatment of localized PCa as it is a well-tolerated, safe, and efficacious intervention for the management of localized PCa [13,14].

We identified 45 patients and evaluated various parameters including: minor and major postoperative complications, postoperative Gleason score, pathological stage, positive-margin status, continence and potency in 12 months, disease-specific mortality, and presence of biochemical progression at the follow-up period. Major complications were noted in 2.2% of cases. Organ-confined disease was noted in 68.8%, extra prostatic extension in 31.2%, and a positive surgical margin status was encountered in 11.1% of cases. At 12 months, 86.9% of patients were continent and 39.6% were potent. After a median follow-up of 17.2 months no disease-specific mortality was evident and 95.5% were free of biochemical progression. We demonstrated that RARP in patients ≥75 years of age is a safe surgical procedure with limited complications, excellent oncologic and continence outcome as well as acceptable potency. There are certain limitations that should be addressed regarding our study. The first one is that the retrospective and non-controlled design of our work limits our ability to generalize our findings. The second one is that although after diagnosis was made 56 patients underwent therapy with a curative intent (48.6%), 30 patients underwent radiation therapy (26.1%), and 26 RPE (22.5%). As yet, we have no long term follow-up data on these men to evaluate the impact of PCa and its treatment on the quality and longevity of their lives. However, patients with high grade PCa suffer more than those with lower grade, since the tumor is more aggressive and they have metastases. It could be shown that elderly patients with high grade PCa receiving curative therapy had better outcomes and a higher life quality [25]

Nevertheless, in a further effort to improve personalized treatment,

we show in this study the importance of screening of patients over the age of 75 years with our defined markers.

Table 1: The parameters analyzed included: age, prostate size, PSA levels, DRE findings, ASA score PCa detection rate, Gleason score, clinically significant PCa detection rate, high grade PCa detection rate and type of therapy once PCa had been detected (Curative intent or palliative intent). BPH (Benign Prostatic Hyperplasia).

Parameters	All patients	Prostate cancer patients	BPH patients
Patients	N=196 (100%)	N=115 (59%)	N=83 (41%)
Age 75-87	Median 79	Median 79	Median 78
ASA score 1-3	Median 1.8	Median 2.03	Median 1.5
PSA 3.7 -233 ng/ml	Median 22.1	Median 30.5	Median 10.3
Positive DRE	N=156 (79.5%)	N=88 (76.6%)	N=68 (81.9%)
Significant PCa	N=97 (84.3%)	High-grade PCa	N=70 (60.8%)
Gleason score		Therapy:	
Gleason 6:	N=45 (39.1%)	Curative Intent:	N=56 (48.6%)
Gleason 7:	N=23 (20%)	Palliative Intent:	N=49 (42.6%)
Gleason 8:	N=25 (21.7%)	No intervention:	N=10 (8.6%)
Gleason 9:	N=22 (19.9%)		
Curative Intent:			
	Radiation:	N=30 Patients	(26.1%)
	ASA: 2.1	PSA 33.2 ng/ml	Age 79
	RPE:	N=26 Patients	(22.5%)
	ASA: 1.4	PSA 10.6 ng/ml	Age 77
Palliative Intent:			
	Hormonal:	N=30 Patients	(26.1%)
	ASA: 2,6	PSA 36.6 ng/ml	Age 79
	Orchidectomy	N= 7 Patients	(6.1%)
	ASA: 2.1	PSA 127.3 ng/ml	Age 82
	Green light laser	N=5 Patients	(4,6%)
	ASA: 2,2	PSA 12,4 ng/ml	Age 86
	TUR-P	N=7 Patients	(6,1%)
	ASA: 1,8	PSA 26,5 ng/ml	Age 82

Conclusion

We show that elderly patients (>75 years) suffer under significant and high grade PCas more frequently than previously suspected. We chose the evaluation of the correlation between PSA and DRE, as marker for significant or high grade PCa, since these two factors are well characterised. The PSA level is usually established in every routine laboratory and the routine diagnose of PSA is even more prostate specific than the analysis of other markers such as CA 19-9 or CA 50, which are considered to be more general tumor biomarkers [26] . On the other hand one can argue that it is reasonable for urologists to avoid biopsy of the prostate in the elderly due to concerns about "overdiagnosis and overtreatment" of clinically insignificant PCa.

Nevertheless, as seen in our retrospective study, prostate biopsy should be performed in patients in whom high PSA levels (PSA > 10 ng/ml) and a positive DRE are found simultaneously, since they have an increased chance of exhibiting significant and high-grade PCa and could benefit from curative therapy. Finally, we believe that all patients over the age of 75 years with an increased PSA over 10 ng/ml and a positive DRE should be biopsied for adequate therapy and to increase the patient's survival rate.

Ethical Standards

This retrospective study was approved by the ethics committee of the Medical Faculty of the University of Cologne, which met the requirement to prove informed consent. Since the study is retrospective, no further ethics considerations apply.

Research involving Human Participants

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Author's Contribution:

V Zugor: Project development, Data Collection, Interpretation of the data

M von Brandenstein: Manuscript writing, Data Analysis

A Tok: Manuscript writing, Data Collection

AP Labanaris: Project development, Interpretation of the data, critical reading of the manuscript

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