ORIGINAL ARTICLE

Relationship between prostate volume and Gleason score of prostatic adenocarcinoma on prostate biopsies: a prospective analysis from a developing country

Bilal Masood, Murli Lal, Muhammed Mubarak, Altaf Hashmi, SAA Naqvi, SAH Rizvi, Rehan Mohsin

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Sindh Institute of Urology and Transplantation (SIUT), Karachi.
B Masood
M Lal
M Mubarak
A Hashmi
SAA Naqvi
SAH Rizvi
R Mohsin

Correspondence:
Prof Dr. Muhammed Mubarak, Professor of Pathology, Javed I. Kazi Department of Histopathology, Sindh Institute of Urology and Transplantation (SIUT), Karachi-74200, Pakistan
Cell: + 92-21-99215752
Email: drmubaraksiut@yahoo.com

Abstract

Introduction: Prostate cancer (PCa) is the most common solid organ cancer in men throughout the world. We conducted this study to find out the prevalence of high grade PCa in our population and to find out the relationship between prostate volume (PV) and Gleason score (GS) on needle biopsies.

Subjects and methods: This is a cross-sectional, observational study carried out at the Department of Urology, from October 2014 to June 2015. A total of 74 patients with newly diagnosed PCa underwent assessment for PV. GS was calculated on prostate needle biopsies. Eight cores of needle biopsies were obtained in each patient. PV was classified into low and high PV and the relationship between PV and GS of PCa was assessed. The SPSS version 16.0 was applied for data analysis.

Results: The mean age of all patients was 65.34±4.40 years. Majority of patients (54.1%) were >65 years old. The mean total serum prostate specific antigen (sPSA) was 212.9±339.3 ng/ml and median sPSA was 82.5 ng/ml (Interquartile range [IQR]: 20.9-224.1). The frequency of high grade PCa in new patients was 75.7%. There was statistically significant relationship between high grade PCa and high PV (p=0.03). The PV also correlated with total sPSA (r=0.501, p=0.01).

Conclusion: The frequency of high grade PCa is very high in our patients and the higher PV is associated with higher grades of PCa. More studies are needed to further investigate this relationship.

Keywords: Prostatic Cancer, Gleason Score, Prostate Volume, Grading prostatic specific antigen

Introduction:

Prostate carcinoma (PCa) is the most common solid cancer in men and it represented around 29% of the incident cancers in United States in 2007.[1] Out of these, 91% were at local or regional stage for which the 5-year survival is excellent approaching around 100%.[2] The treatment of prostatic carcinoma depends upon the risk of progression of the disease.[3] Depending on the risk of progression, the physician with the consent of the patient, may choose to only observe the cancer at one spectrum and intervene early, on the other hand. PCa is risk stratified in three categories of low, intermediate and high risk for progression depending on the clinical stage, prostate specific antigen (PSA) level and Gleason score (GS). Out of these, the GS is best correlated to disease outcome making it an important factor in making treatment decision and counseling the patient.[4] The GS acquired through needle biopsy has a shortcoming that it is often underscored.[5] In some series, it has been observed that the actual GS post-prostatectomy has been higher as compared to the biopsy GS. The implication of this can be severe for patients with low scores on biopsy, opting for active surveillance as the treatment choice. Numerous efforts have been made to identify variables that can predict this discrepancy prior to decision making.[6] Prostate volume (PV) has also been

implicated as a predictor of higher grades in biopsies.[7] It was during the prostate cancer prevention trial (PCPT) that it was implicated that patients on anti-androgen drugs with smaller prostates have a higher frequency of high grade PCa.[8] It was inferred that due to the smaller size of the prostate, there were higher chances of catching a high grade PCa on needle biopsy as compared to finding high grade tumor in a larger prostate. Investigators found that this relationship also holds true in patients not on anti-androgen drugs.[6] Mir et al. in their study described an inverse relationship between PV and GS,[6] i.e. the lower the volume the higher the grade of PCa. In their series, they found that 52% of the biopsy samples with GS of over 7 had a PV of 30 ml or less, and prostates with volumes of 50 ml or greater had only 26% high grade tumors (GS, 7 or more).[9]

We conducted this study to find out the prevalence of high grade PCa in our population treated at our clinics and to find out the relationship between PV and GS on needle biopsies.

Materials and methods:
This is a cross-sectional, observational study carried out at the Department of Urology, Pakistan from October 2014 to June 2015. By taking the least percentage i.e. (26%),[7] confidence interval of 95%, margin of error 10%, the sample size was calculated to be 74 patients. The sampling technique was non-probability and consecutive.

All patients of newly diagnosed PCa on transrectal ultrasound (TRUS)-guided biopsy aged ≥50 years were included. Eight cores were obtained from all patients as described in our earlier study.10 Patients with history of 5 α-reductase inhibitor use for enlarged prostate were excluded.

This study was conducted after taking institutional and ethical review committee approval. A total of 74 patients presenting to the prostate clinic, with newly diagnosed PCa, fulfilling the inclusion criteria, were included in the study. Informed consent was taken from each patient to participate in this study.

Patients were assessed for their PV by TRUS examination. In TRUS examination of the prostate, scanning began in the axial plane, and the base of the prostate and seminal vesicles were visualized first. A small amount of urine in the bladder facilitates the examination; therefore, all patients were asked to hold urine to have a full bladder before the examination was carried out. The patients were explained the procedure and a consent taken.

Pre-procedure the patients were changed into the hospital gown. The patients were placed on a comfortable couch in the left lateral position. The right thigh was flexed and the left was kept straight. For the patients' comfort a pillow was placed beneath to protect pressure points.

For the purpose of this examination, a 7 MHz transducer with endorectal probe was used. Once the patient was in position, the probe was well lubricated with xyloclane jelly and inserted per rectally after informing the patient. Seminal vesicles were then identified bilaterally, with the ampullae of the vas deferens on either side of the midline. The seminal vesicles are convoluted cystic structures that are darkly anechoic making it a mark for their identification.

Next, the base of the prostate was visualized. The different zones and borders of the prostate was localized according to standard TRUS criteria. Volume assessment of the prostate was then carried out. Of the several formulas that have been developed for this purpose, the most commonly used is the ellipsoid formula, which requires measurement of 3 different prostate dimensions and the same was used in this study.

First, the transverse dimension and the anteroposterior dimension at the estimated point of the widest transverse dimension were measured in the axial plane. Next, the longitudinal dimension was measured in the sagittal plane just off the midline (because the bladder neck often obscures the cephalad extent of the gland). The

Table 1:Age distribution (n=74)

Age of patients	Number	Percentage
< 65 years	34	45.9
≥65 years	40	54.1

Table 2:Relation of prostatic volume with cancer grade (n= 74)

Prostatic volume	High grade cancer		P value
	Yes	No	
High	35 (62.5)	06 (33.3)	0.03
Low	21 (37.5)	12 (66.7)	

Data is shown in frequency follows by percentages in parenthesis.

Table 3:Relation of prostatic volume with cancer grade, stratified according to age (n= 74)

Age of patients	Prostatic volume	High grade cancer		P value
		Yes	No	
< 65years	High	16 (80.0)	04 (20.0)	0.15
	Low	08 (57.1)	06 (42.9)	
≥65years	High	19 (90.5)	02 (9.5)	0.08
	Low	13 (68.4)	06 (31.6)	

ellipsoid volume formula was then applied, as follows:

Volume = height × width × length × 0.52.

The probe was withdrawn and the patient cleaned and covered. Post procedure all the patients received prophylactic dose of ciprofloxacin 500 mg twice daily for three days if they were not previously on any antibiotic therapy.

For the purpose of elimination of bias, all the ultrasounds were carried out by the same sonologist under the supervision of consultant radiologist having more than five years of experience. Similarly, all the biopsies were assessed by the same urological pathologist with 15 years of experience. A pre-designed structured proforma was used to document all the data. The proforma included patients name, age, registration number, histological grade, GS and PV. The low volume was defined arbitrarily (taking value close to the mean volume of the whole cohort) as volume of < 50 ml and high volume as ≥50 ml. High grade PCa was defined as GS ≥7 and low grade PCa as GS <7.

Data Analysis:
Data was analyzed by using SPSS version 16 (SPSS Inc., Chicago, IL, US). Mean and standard deviation (SD) was computed for numerical variables like age, GS and PV. Frequency and percentages were applied to assess categorical data like high grade PCa, and high and low PVs. Chi square test was used to compare the frequency of high grade cancer in patients with high and low PVs. A p-value of < 0.05 was taken as significant. To control for the effect modifiers, stratification was done with regards to age and GS. Chi square test was used to assess the stratification for age. While unpaired student's t test was used to assess the stratification of GS and PV and p value of <0.05 was taken as significant.

Results:
Between October 2014 to June 2015, 74 patients with PCa and with low and high PV were identified and were included in the study. Assessment of the relationship between PV and grade of the cancer was then carried out.

The mean age ± SD of all patients was 65.34±4.40 years. The age range was between 60 to 75 years. Majority of the patients (54.1%) were > 65 years of age. The mean total serum prostate specific antigen (sPSA) was 212.9±339.3 ng/ml and median sPSA was 82.5 ng/ml (Interquartile range [IQR]: 20.9-224.1). The mean GS of the 74 patients in this study was 7.74 ± 1.304 and the mean PV of all patients was 52.53 ± 22.96 ml.

The high grade PCa was found in 56 (75.7%) patients, while 18 (24.3%) had low grade cancers. In this study, 41 (55.4%) patients had a high PV and 33 (44.6%) had a low PV.

On exploring the relationship between GS and PV, it was observed that 35 (62.5%) patients with high grade cancer had high PV, while 21 (37.5%) patients of these had low PV. The association of the high grade cancer with high PV was statistically significant (p=0.03). This

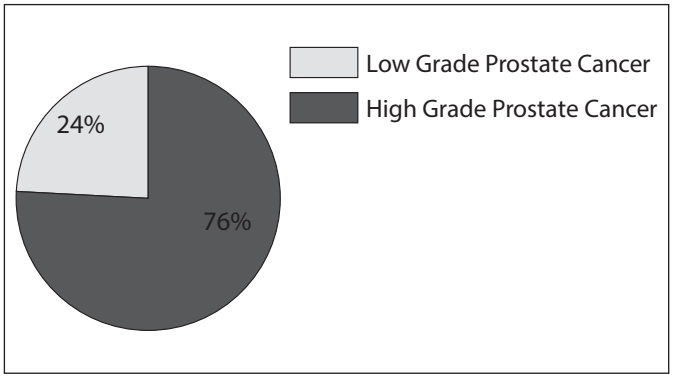

Figure 1: Frequency of high grade prostatic cancer among 74 men

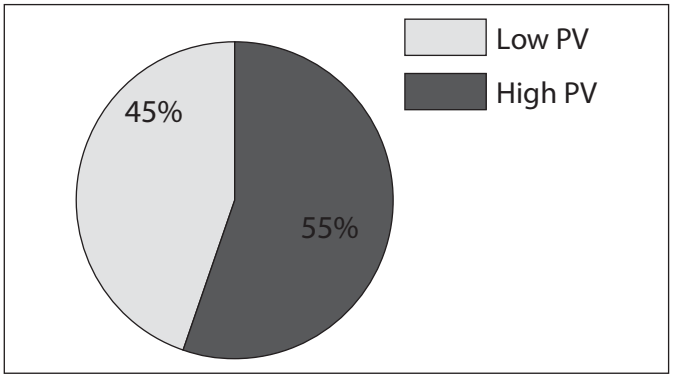

Figure 2: Frequency of high and low prostatic volumes (n= 74)

relationship was independent of the patients' age. The PV also correlated with total sPSA (r=0.501, p=0.01).

Discussion:

The aim of any oncological practice, whether medical or surgical, is to provide the best possible treatment for the patient concerned. This makes the pre-treatment selection extremely important with regards to patient counseling, treatment options forwarded and the patient making educated and informed decision.

Since most of the urological centers around the world are experiencing an increase in the number of patients with PCa owing to the overall increase in life expectancy and health awareness, the question of risk stratification has become increasingly important. To date, most centers use a combination of PSA, digital rectal examination (DRE) and the GS to stratify their patients.[10] Upon the finding of these investigations, the patients are placed into palliative or curative treatment regimes.

Of the above findings, the best parameter which correlates with the outcome of the patients is the GS.[11] Especially, biopsy GS is used for predicting a clinically insignificant PCa, which can be considered a target of active surveillance or watchful waiting rather than definite therapy.[12]

As GS is the fundamental method of grading the PCa, the question of its relationship to PV is of paramount importance. Small PVs are usually not a high alert for further investigations. Therefore, when the issue was raised by Mir et al.[7] that small volume prostates have higher grades of cancer as their retrospective analysis showed, the optimal timing and interpretation of the biopsy result needed further investigation. This became more pertinent to the Asian population as it has been reported to have a lower volume prostate on average when compared with the Western population.[6,13]

The results of our study demonstrate that the frequency of high grade cancers in the newly diagnosed PCa patients is very high, i.e., 75.7%. The frequency calculated from a retrospective data of Chung and colleagues is 55.8%.[6] This shows a relatively higher frequency in our population. This is most likely due to late presentation of our cases, but this may be multifactorial and needs further investigation.

This study showed that the higher volume prostates had higher grades of prostatic cancers. This is in contrast to the findings of Mir et al[7] who showed that the two had an inverse relationship. The difference may be accounted for by the difference in sample size; however, results of recent studies have shown that there is usually upgradation of GS of the same patient after prostatectomy.[13] They also included only patients with PSA level less than 10 ng/ml. In contrast, our patients usually have very high PSA values on presentation.[10] This together with a high prevalence of larger prostates in our patients may partly explain the discrepant results in our study. The PV correlated well with total sPSA values in our study.

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There are some limitations in the study too. This is a single center based study and of short duration. Only prostate biopsy data were used for exploring the relationship between prostate grades and prostate volumes. Radical prostatectomy specimens were not available in these patients. No data on the treatment or follow-up of patients is included. Despite, the above shortcomings, we believe that this study is of crucial importance as it is the first study from Pakistan exploring the potential relationship between PCa grades and prostate volumes. It will serve as a baseline study for further research on this important topic.

Conclusion:
Our data suggest that there is a higher frequency of high grade PCa in our newly diagnosed patients and that the larger prostates have higher grades of PCa. Further studies are warranted which should preferably be multi-centric to further investigate this relationship.

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Role and contribution of authors:
Dr Bilal Masood, Conception and designing, collection and analysis of data, primary drafting of the paper

Dr Murli lal, Conception and designing, collection and analysis of data, primary drafting of the paper.

Dr Muhammad Mubarak, Conception and designing, collection and analysis of data, primary and final drafting of the paper

Dr Altaf Hashmi, Acquisition of data, critical review and final approval of the paper.

Dr SAA Naqvi, Critical review and final approval of the manuscript.

Dr SAH Rizvi, Critical review and final approval of the manuscript.

Dr Rehan Mohsin, Acquisition of data, critical review of the paper.

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