Study on Pattern of Different Prostatic Lesions with Reference to Serum Prostate Specific Antigen (PSA) Level among Autopsy Cases

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ABSTRACT

BACKGROUND

Prostatic carcinoma is now recognized as one of the most important causes of morbidity and mortality in the male population. The available statistics on prostatic cancer is based on clinically diagnosed carcinomas and those latent tumours found unexpectedly at prostatectomy and autopsy. The proportion of latent carcinomas among all prostatic cancer-cases depends on the detection rate and varies from country to country, thus casting uncertainty on the comparability of prostatic cancer statistics from different geographic areas. Early diagnosis of prostate cancer is an important issue which needs a multidisciplinary approach using Digital Rectal Examination (DRE), prostate specific antigen assay and transrectal ultrasound with guided biopsy.

METHODS

During the course of medico-legal autopsies on victims dying of unnatural causes, 60 prostates and approx. 5 ml of blood from each of the same 60 cases were collected with the age ranging from 40 to 85 years. This study was conducted in the Department of Pathology, Dept. of Forensic Medicine & Toxicology, Dept. of Biochemistry, R.G. Kar Medical College & Hospital, Kolkata, and at the attached Police Morgue for 1 year during the period of April 2013 to March 2014. No clinical histories were available since these men had not been hospitalized. Cases were selected by random sampling method from all cadavers meeting the inclusion and exclusion criteria on the particular days on which autopsies were conducted.

RESULTS

Definitive histopathological diagnosis was obtained in 46 out of 60 cases with Benign Hyperplasia Prostate (BHP) (60%), prostatitis (8.3%), prostatic adenocarcinoma (8.3%), and corresponding post mortem serum PSA level in benign lesions 0.2-27.6 ng/mL (median value 3.76 ng/mL), in malignancies 3.73-124.1 ng/mL (median value 41.65 ng/mL) while in all 14 normal cases PSA ranges from 0.07 to 2.98 ng/mL.

CONCLUSIONS

Correlation studies of different prostatic diseases with post-mortem serum PSA level are very few. Total PSA level in serum of deceased within 24 hours of death reflects the ante-mortem serum total PSA level. The use of autopsy prostates and PSA data would avoid diagnostic bias from use of clinical material, and permit extensive analysis to be carried out, which is very difficult with live subjects. Incidence of latent adenocarcinoma of prostate as well as nodular hyperplasia of prostate is alarmingly high in men over the age of 50 years. High post-mortem serum total PSA level (cut-off value of 4 ng/mL) is significantly associated with adenocarcinoma of prostate.

KEY WORDS

Prostate Specific Antigen, Nodular Hyperplasia, Autopsy

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BACKGROUND

Prostatic carcinoma is now recognized as one of the most important cause of morbidity and mortality in the male population. The available statistics on prostatic cancer is based on the sum of clinically diagnosed carcinomas and those latent tumours found unexpectedly at prostatectomy and autopsy. The proportion of latent carcinomas among all prostatic cancer cases depends on the detection rate and varies from country to country, thus casting uncertainty on the comparability of prostatic cancer statistics from different areas. Early diagnosis of prostate cancer is an important issue which needs a multidisciplinary approach using Digital rectal examination (DRE), prostate specific antigen assay and transrectal ultrasound with guided biopsy. Despite these efforts, 33% of patients still present with advanced stage of the disease.^[1] Identification of premalignant lesions like prostatic intraepithelial neoplasia (PIN) and atypical adenomatous hyperplasia (AAH) assumes importance in this context and lately, they have been recognized as putative premalignant lesions of prostate.

Measurement of PSA level is an important diagnostic tool in different prostatic diseases including Prostatic Cancer. There is a direct correlation between serum PSA concentration and clinical stage. Irrespective of the treatment modality, PSA reflects accurately the tumour status of the patient and its prognostic outcome.^[2] The post mortem serum PSA level (collected within 24 hours of death) reflects the ante-mortem PSA level.^[3] Study regarding the prevalence of Prostate cancer (including the latent /occult prostatic cancer) and other prostatic pathologies in autopsy cases has not been done so much in India. The use of autopsy of prostates and post-mortem PSA data can avoid diagnostic bias from use of clinical material, and permits extensive analysis, which is very difficult with live subjects.

We wanted to identify different prostatic lesions macroscopically and histopathologically among autopsy cases and evaluate the relation between them with post-mortem serum PSA level using normal prostates as internal control group.

METHODS

This study was a cross sectional study conducted in the Department of Pathology, Dept. of Forensic Medicine & Toxicology, Dept. of Biochemistry, R.G. Kar Medical College & Hospital, Kolkata in the period of April 2013 to March 2014. During the course of medico-legal autopsies on victims dying of unnatural causes, 60 prostates and approx. 5 ml of blood from each of the same 60 cases were collected with the age ranging from 40 to 85 years. The sample was taken based on the convenience of the study. No clinical histories were available since these men had not been hospitalized. Cadavers which are unidentified, decomposed, grossly mutilated or more than 24 hrs old are excluded from the study. Cases were selected by random sampling method, taking all cadavers meeting the inclusion and exclusion criteria on the particular days in which autopsies were conducted by the co-guide in this study, generally on every Monday. The study was approved by the Ethical Committee of the institution. The prostates were

removed en block with seminal vesicles and immediately placed in 10% formalin solution for 2 days at room temperature. After proper fixation, prostates were weighed and measured in three dimensions (width × height × length) and sectioned at 4-mm intervals. Any abnormalities like increase in weight / size and gross features like nodular or cystic changes and presence of calculi were noted. The tissues were processed routinely, embedded in paraffin and conventional sections (4-6 um thick) were stained with Haematoxylin and Eosin (H&E). Deeper sections were examined wherever necessary. It is reviewed that similar procedure was followed for sample removal and tissue processing by Alexandre R.

Zlotta et al. in 2013.^[4] Histopathological examination were done and cancer diagnosed based on the criteria described in the World Health Organization (WHO) classification system.^[5] About 5 ml of blood was collected from the heart of the deceased and serum was separated by centrifuging at 1600-2000 rpm for 10 minutes and its PSA level was measured by standard ELISA method.

Statistical Analysis

The Statistical Package for Social Science (SPSS) Version 20 will be used for Data Analysis. Mean, median, and SD are used to describe quantitative data. Qualitative data are summarized using frequency and percentage.

RESULTS

In the present study, out of 60 cases included, majority of cases 17 cases (28.33%) was in the 50-59 years of age group followed by 60-69 years and minimum 2 cases (3.33%) were above the age of 80 years. The average age of the cases was 58.72 ± 10.62 years (mean $\pm$ SD) with a median of 59 years and range of 40 to 85 years. In terms of religion, only 2 cases were Muslim, constituting 3.33% of total cases. Corresponding change in weight was recorded according to age. An increase in weight was observed with advancing age. Maximum weight of prostate measured was 70 grams and minimum of 13 grams. Mean weight was 35.4 gms with a standard deviation of 13.88 gms. The mean weight in 40-49 age groups was 24.15 gms with a SD of 10.16; 34.88 gms in 50-59 age group with SD of 14.68; 37.87 gms with SD of 11.02; 42.16 gms with SD of 13.9; 52.5 gms with SD of 6.36; in 60-69, 70-79 and 80 & above age groups.

The mean weight of normal prostate is 16.71 gms with a standard deviation of 2.55 gms. The mean weight in different pathological prostates are between 35.33 gms to 50.33 gms and higher than that of normal prostate. NHP cases have a mean weight of 39.9 gms, while PIN cases have 35.33 gms and adenocarcinoma cases have a mean weight of 44 gms. Among 60 autopsy prostates, 14 (23.33%) were found normal out of which 7 (58.3%) were found in 40-49 years with no normal prostate in the ≥ 80 years age group and 46 (76.67%) cases had variable degree of pathology.

Malignant lesion (adenocarcinoma) of prostate was found in 5 (8.33%) cases mostly in 70-79 years group and 3 (5%) cases of premalignant lesion (PIN) were found. Among the 38 (63.33%) benign prostatic lesions, most of the cases i. e. 32 (53.33%) were NHP with distribution in 40-49, 50-59, 60-69

and 70-79 years age groups, 6 (46.2%), 9 (52.9%), 9 (56.3%) and 7 (58.3%) cases, respectively. 2 (3.33%) cases had prostatitis and 3 (5%) had NHP with prostatitis. Only 1 (1.66%) case of basal cell hyperplasia associated with NHP was found in 70-79 years age group.

Age Groups (Years)	Number	Percentage (%)
40-49	13	21.66
50-59	17	28.33
60-69	16	26.66
70-79	12	20
≥ 80	2	3.33
Total	60	100

Table 1. Distribution of Study Population According to Age (n = 60)

Prostatic Lesions	Mean Wt. (gms.)	S.D. (gms)	Range (gms)
Normal (n=14)	16.71	2.55	13-20
Prostatitis (n=2)	43.5	16.26	32-55
NHP (n=32)	39.9	9.9	25-70
NHP/Prostatitis (n=3)	50.33	8.5	44-60
NHP/BCH (n=1)	49	--	--
PIN (n=3)	35.33	6.8	30-43
Adenocarcinoma (n=5)	44	16.1	20-60
Total (n=60)	35.4	13.99	13-70

Table 2. Weight of Prostates in Different Prostatic Lesions (n=60)

Histopathological Diagnosis	Number of Cases	Percentage (%)
Normal	14	23.33
Prostatitis	2	3.33
NHP	32	53.33
NHP with Prostatitis	3	5
NHP With BCH	1	1.66
PIN	3	5
Adenocarcinoma	5	8.33
Total	60	100

Table 3. Distribution of Cases According to Histopathological Diagnosis (n=60)

Cases	Mean	Median	Minimum	Maximum	± SD
Normal (n=14)	0.745	0.425	0.07	2.98	0.81
Prostatitis (n=2)	5.91	5.91	3.6	8.22	3.26
NHP (n=32)	4.65	3.69	0.2	27.6	4.97
NHP/Prostatitis (n=3)	7.66	7	3.92	12.08	4.12
NHP/BCH (n=1)	4.8	4.8	4.8	4.8	--
PIN (n=3)	6.32	3.8	2.1	13.06	5.89
Adenocarcinoma (n=5)	51.27	41.65	3.73	124.1	44.38
All Cases (n=60)	7.9	3.55	0.07	124.1	18.06

Table 4. Distribution of Serum Total PSA Values in Different Prostatic Lesions (n=60)

Maximum number (7, 50%) of all normal prostate were found in 40-49 years age group and with increasing age number of normal prostate was decreasing having no normal prostate in the ≥80 years age group. In this study the serum total PSA level for all 60 cases ranges from 0.07 to 124.1 ng/mL with a mean value of 7.9 ng/mL. and median value of 3.55 ng/mL. For all 14 Normal cases PSA ranges from 0.07 to 2.98 ng/mL. and the mean PSA value for the normal cases is 0.745 ng/mL. with a median value of 0.425 ng/mL. These cases are considered as internal control group in the present study.

Serum total PSA level range for all 5 malignant cases is 3.73 to 124.1 ng/mL with a very high mean of 51.27 ng/mL and median value of 41.65 ng/mL. The lowest PSA value is 0.07 ng/mL. among all the 55 cases not having malignancy with a highest value of 27.6 ng/mL. The mean and median value of the PSA is 3.96 and 3.0 ng/mL., respectively. PSA range for all 38 benign cases is 0.2 to 27.6 ng/mL with mean value of 4.96 ng/mL. and median value of 3.76 ng/mL. PSA range for all 32 cases of Nodular Hyperplasia of prostate 0.2 to 27.6 ng/mL with mean value of 4.65 ng/mL. and median value of 3.69 ng/mL. Within the 3 cases on Prostatic Intraepithelial Neoplasia, the lowest PSA value is 2.1 ng/mL and the highest PSA is 13.06 ng/mL. The mean value is 6.32 ng/mL. and

median is 3.8 ng/mL. PSA for 3 cases of Nodular Hyperplasia of prostate with Prostatitis ranges from 3.92 to 12.08 ng/mL with mean value of 7.66 ng/mL. and median value of 7.0 ng/mL. 2 cases of Prostatitis have PSA values of 3.6 and 8.22 ng/mL. with a mean of 5.91 ng/mL. The only case of Nodular Hyperplasia of prostate with Basal Cell Hyperplasia has a PSA value of 4.8 ng/mL.

DISCUSSION

Autopsy studies that have defined the incidence and morphological evolution of prostatic hyperplasia and carcinoma have been confined largely to hospital autopsy of men with more than 40 years of age. Benign hyperplasia and carcinoma of prostate are increasingly frequent with advancing age. The frequency of incidentally found carcinoma in autopsies of patients with no urological complaints varies from 6.6 to 66.7%.^[6] It is likely that adenocarcinoma of the prostate is the most prevalent cancer in men^[7,8] although it is often discovered incidentally and may remain latent or pursue an indolent clinical course. This prompted us to investigate the spectrum of lesions in routine medicolegal autopsy specimens. Serum PSA level is a good screening test to detect early / latent prostate cancer. Men with organ confined prostatic carcinoma in early stage can be cured by radical prostatectomy and enjoy a survival rate equivalent to that of age-matched men without prostatic carcinoma.

In the present study, a total of sixty (60) autopsy specimens of prostate and their serum PSA levels were studied in the of Department of Pathology, R.G. Kar Medical College & Hospital, during the period from April 2013 to March 2014. The age range of the cases in present study was between 40 years to 85 years with mean age being 58.71 years. Out of 60 autopsy cases 46 cases had some pathology and majority of the cases were encountered in the 6th and 7th decade (58.69% of total cases) with decline in later age group The decline in the number of cases beyond the age 80 years may reflect the average life span of people in our country which rarely exceeds beyond the 6th decade.^[9]

The minimum weight seen in a study done by Pradhan and Chandra.^[10] was 1.6 grams in 1-10 age group; 1.8 grams in study done by Swyer.^[11] and 2.28 grams in study done by Murty and Roy.^[12] for the same age group. Present study showed the minimum weight of 24.15 grams in 40-49 age groups which was higher than other studies as cases below 40 years were not present in the study. But it was similar for the same age group in the studies done by Murty and Roy.^[12]

In the studies done by Murty and Roy and Tornblom et al.^[13] the maximum average weight were 40.3 gm and 34.5 gm respectively, both seen above 71 years. The study by Ghartimagar et al.^[14] showed maximum weight of 60 grams in the only 84 years old subject. The present study showed maximum weight of 52.5 grams in 80+ years age group and it was slightly higher as only 2 cases were present above 80 years. The present study showed 42.16 grams of weight in 71-80 age group correlating well with the study done by Murty and Roy.

The present study showed 5 (8.33%) cases showing inflammation, corroborating with the study done by Men S et al.^[9] in the year 2001 (10.4%). Granulomatous prostatitis was

not seen in this study. Mittal et al.^[8] found only 1.62% of granulomatous inflammation as his number of cases were higher than the present study. Present study showed only 1 (1.66%) case of Basal cell hyperplasia (BCH), observed at 70 years of age. The case was seen associated with NHP. Mittal et al.^[8] found 5.4% of BCH in his study. In the present study, NHP is the most common pathology found in prostate and is seen in a total of 36 (60%) cases, including the 3 (5%) cases associated with prostatitis and 1 (1.66%) case associated with Basal Cell Hyperplasia: the incidence correlating with the autopsy studies done by Ghartimagar et al., Konstantinos et al.^[15], and Men S. et al, the incidence being 55%, 65.5% and 66.4% respectively. The highest percentage of NHP was seen in a study done by Mittal et al. (92.97%), followed by Rekhi et al.^[16] (88.5%) and Ryusei Sasaki et al. in Japan (81%). The percentage was high in these studies as studies were based on prostatectomy done on symptomatic patients.

Present study showed the incidence of Prostatic intraepithelial neoplasia (PIN) in 3 cases (5%), nearer to the incidence shown by Ming Yin et al.^[17] (10.6%) and Ghartimagar et al. (16%). Prostatic adenocarcinoma is the most common form of cancer in men and second leading cause of cancer death.^[1,2]

Comparison of Latent Prostate Carcinoma in Different Studies in India.					
Study		Year	Specimen	No. of Cases	%
Mittal et al. ^[8]		1989	Prostatectomy TRUP & biopsy	13/185	7.02%
Men S. et al. ^[9]		2001	TRUS Biopsy	31/134	23.1%
Neelkamal Kapoor et al. ^[18]		2004	RCP	83/508	16.4%
Rekhi et al. ^[16]		2004	RCP	23/200	11.5%
Desai et al. ^[19]		2004	RCP	3/44	6.8
Present study		2013-2014	Autopsy	5/60	8.33%
Comparison of Latent Prostate Carcinoma in Different Western Countries					
Study		Year	Sample Type	Study Population	% of PCA
Nations/Community	Authors				
Vienna	A.R Rich ^[20]	1935	Autopsy	292	9%
Bristol	G. S. Andrews ^[21]	1949	Autopsy	142	12%
Denmark	B. Hølund ^[22]	1980	Autopsy	223	22%
America (black)	Yatani R. et al. ^[23]	1982	Autopsy	178	36.9%
America (white)	Yatani R. et al. ^[23]	1982	Autopsy	253	34.6%
Colombia	Yatani R. et al. ^[23]	1982	Autopsy	182	31.5%
Hungary	Soos G et al. ^[24]	2005	Autopsy	139	38.8
Pennsylvania	Ming Yin et al. ^[17]	2007	Autopsy	340	12%
Greek	Konstantinos et al. ^[15]	2007	Autopsy	212	18.8%
Present study		2014	Autopsy	60	8.33%
Table 5. Comparison of Latent Prostate Carcinoma in Different Studies in India and Western Countries					

Table 5. Comparison of Latent Prostate Carcinoma in Different Studies in India and Western Countries

Table 5. shows that the incidence of prostatic cancer in this study (8.33%) is corroborating with most of the Indian studies but most of the Western countries showed much higher incidence of latent prostatic carcinoma. The mean age of prostatic carcinoma in the present study (72.6 years) is similar to that shown in the study done by Pan J et al. (70.3 years). All of the cases were found in older ages (>65 years of age) as also shown by Ali Zare-Mirzaie et al.^[25] in 2012, where the tumours were more frequent in >65 years of age. Present study shows that prostatic carcinoma occurs earliest at the age of 65 years. G. S. Andrews^[21] in 1949 and Sakr WA et al.^[26] in 1993, showed that carcinoma was not found before the age of 40. But Shinji Fujikawa et al.^[27] and Soos G et al.^[24] in 2005 showed that

prostatic adenocarcinoma were first detected in the 3rd decade and show a steady increase with age.

This series shows that the incidence of prostatic carcinoma has a tendency towards age- dependent increase and is higher at older age groups. Out of total 5 cases of adenocarcinoma, 1 (6.25%) was found in 60-69 years, 3 (25%) in 70-79 years and 1 (50%) case in ≥ 80 years age group. Same findings were also shown by Alexandre R. Zlotta^[4] in 2013, Ali Zare- Mirzaie et al.^[25] in 2012, Shinji Fujikawa et al.^[27] in 2005 and by almost all other studies in India and other countries. Clareann H. Bunker et al.^[28] (2000) showed a very high age- specific rates of screening detected prostate cancer in West African population: 1%, ages 40- 49 years; 7%, ages 50-59 years; 18%, ages 60-69 years; and 28%, ages 70-79 years.

In the present study, major age specific prevalence of both BPH and LPC is observed in men of the eighth and ninth decade but BPH began to manifest in the male population earlier; as also shown by Konstantinos S et al.^[15] in 2007. Mean age of PIN in present study (61.66 years) is same as in a study by Troncoso et al.^[29] (63.5 years). This study finds 58 years as minimum age of PIN, but many studies showed that PIN can affect prostate at an earlier life, even at third decade as shown by Sakr WA et al.^[26] Muslims may have higher prevalence of prostate cancer. But the present study couldn't able establish relationship of religion with prostatic diseases could not be evaluated in the study because of the very small number of cases in a group. In this study total PSA was measured by ELISA method in the serum prepared from blood collected from the heart of the deceased within 24 hours of death; and this reflects the ante mortem serum total PSA as documented by Richard F. Jones et al. in 2005.

For all 14 normal cases PSA ranges from 0.07 to 2.98 ng/mL and the median PSA value for the normal cases is 0.425 ng/mL. In this study PSA range for all 38 benign cases is 0.2 to 27.6 ng/mL with median value 3.76 ng/mL. Serum total PSA level range for all 5 malignant cases is 3.73 to 124.1 ng/mL with median value 41.65 ng/mL. This value is significantly ($p = 0.0001$) higher than the median PSA value of 3.69 ng/mL in NHP cases (range is 0.2 to 27.6 ng/mL), which is similar to the observed value (3.96 ng/mL) by JM Wolff et al.^[30] in 1996. In spite of a statistically significant difference ($p = 0.0001$), serum PSA values overlapped considerably in both benign and malignant groups in the present study as was found in the study done by JM Wolff et al.^[30] ($p = 0.0001$). Ryusei Sasaki et al.^[31] (2000) also showed that there was a significant difference in total PSA between patients with PCa and BPH ($p < 0.001$).

The presence of isolated PIN does not show a significant elevation of serum PSA (mean PSA of PIN cases is 3.8 ng/mL), as observed by Kim HL, Yang XJ^[32] in 2002 with a mean PSA value of 1.9 ng/mL and by Alexander EE et al.^[33] in 1996, but Brawer MK, Lange PH.^[34] (1989) showed that PIN may be associated with elevation of the serum PSA. Clinically inapparent prostatitis leads to mild increase of PSA (median is 5.91 ng/mL). Out of 2 cases of Prostatitis one showed high level of PSA (8.22 ng/mL), but less than 10 ng/mL. NPH with inflammation leads to increase in PSA-serum levels (median is 7 ng/mL) as compared to serum values of PSA in NHP without any prostatitis (median is 3.69 ng/mL). Out of 3 cases of Nodular Hyperplasia of Prostate with Prostatitis 2 cases (i.e. 66.66%) showed a rise of PSA>4 ng/mL and 1 case (33.33%) showed a PSA level >10 ng/mL. All these findings in this study

is similar to the observations in the study by Block T et al.^[35] in the year 1993 showing 19.5% patients of BPH with prostatitis having serum PSA values of >10 ng/mL.

PSA value of 4 ng/mL as a screening tool and cases are divided according to the total PSA value thus so far obtained and found that 42 (70%) cases have PSA value <4 ng/mL and 18 (30%) cases have PSA >4 ng/mL. having same findings as by Shalini Agnihotri et al.^[36] (2014-June). They found that 70.9 per cent patients had PSA of less than 4 ng/mL and 29.1 per cent had PSA of more than 4 ng/mL.

Present study shows that prostate carcinoma was diagnosed in one (2.38%) case of serum PSA level within the normal range (0-4 ng/mL) and BPH was diagnosed in 14 (77.77%) patients who had serum PSA > 4.0 ng/mL; same findings were shown by HJ Yu et al.^[37] who noticed the prevalence of prostatic carcinoma to be 2.7% in cases having PSA < 4 ng/mL and prevalence of NHP to be 75% of cases who had serum PSA > 4.0 ng/mL.

In the present study, the tests of validity like sensitivity, specificity and positive predictive value of serum total PSA test having a cut-off value of 4 ng/mL to differentiate prostatic carcinoma from benign lesions are 80%, 74.54% and 22.22%. Positive predictive value is similar to that shown by HJ Yu et al.^[37] Crawford ED et al.^[38] and Rashid MM et al.^[39]

CONCLUSIONS

There are plenty of autopsy studies on prostate world-wide, many in India, but studies to correlate different prostatic diseases with post-mortem serum PSA level are very few. Total PSA level in serum of deceased within 24 hours of death reflects the ante-mortem serum total PSA level. The use of autopsy prostates and PSA data would avoid diagnostic bias from use of clinical material, and permit extensive analysis to be carried out, which is very difficult with live subjects. Incidence of latent adenocarcinoma of prostate as well as nodular hyperplasia of prostate is alarmingly high in men over the age of 50 years. Adenocarcinoma of prostate is now the leading cause of cancer death in elderly individuals. High post-mortem serum total PSA level (cut-off value of 4 ng/mL) is significantly associated with adenocarcinoma of prostate. There may be controversies worldwide regarding the value of serum total PSA in the screening of the prostate diseases but the test is a good screening modality which is cost-effective and non-invasive and has high positive predictive value.

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