Original Article

Clinicopathological Evaluation of Prostatic Adenocarcinoma: A Unicenter Study

Clement Wilfred D[1]*, Rashmi Krishnappa[1], Sharath Soman[1], Vijaya Viswanath Mysorekar[1], Radhika Kunnavil[2] and Sharon Roshin Reginalt[1]

[1]Department of Pathology, M. S. Ramaiah Medical College, Bangalore, India
[2]Department of Community medicine, M.S. Ramaiah Medical College, Bangalore, India

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ABSTRACT

Background: Prostate cancer is a significant cause of morbidity and mortality. It ranks fifth in cancer incidence and fourth in cancer mortality in India. As the literature on the issue in India is limited, we undertook the study with the objective of evaluating the histopathological features of prostatic adenocarcinoma (PCa) and correlating these with certain clinicopathological variables.

Methods: All the cases of PCa diagnosed on transurethral resection (TURP) specimens and core needle biopsies, over a period of three years (between January 2013 and January 2016), were evaluated. The clinicopathological data obtained was subjected to statistical analysis to discern correlations.

Results: The study included 55 cases of PCa comprised of 29.1% of moderately differentiated, 18.2% of moderate to poorly differentiated and 52.7% of poorly differentiated cases. The mean patient age was 69 years with mean preoperative serum PSA level of 162.9 ng/ml. The three commonest clinical presenting symptoms were increased frequency of micturation (45.5%), incomplete voiding (40%) and dysuria (38.2%). Gleason score 8 was the most frequent [15(27.3%)] followed by Gleason score 9 [13(23.6%)]. The average tumour volume in TURP specimens and needle biopsies was 52.5 % and 58.1% respectively.

Conclusions: A positive correlation was found between high Gleason score and increased PSA levels and tumour volume. Majority of our patients had poorly differentiated PCa with high PSA levels suggesting that the disease is advanced at the time of diagnosis.

***Corresponding author:**
Dr Clement Wilfred D, Associate professor, Department of Pathology, M.S. Ramaiah Medical College, MSR Nagar, MSRIT Post, Mathikere-560054.
Phone: +91 9945226314
Email: clement.wilfred@yahoo.com

Introduction

Prostate cancer is a common malignancy and has become a major health problem in industrialized countries.[1] Globally it is the second most frequent cancer in men and fifth most common cancer overall.[2] An increasing trend in the incidence of prostate cancer has been revealed by several Indian registries.[2] It ranks fifth in cancer incidence and fourth in cancer mortality in India.[3] As the literature on malignant prostatic lesions in India is limited, and as the magnitude of the problem is significant, we conducted the present study with the objective of evaluating the various histopathological features of prostatic adenocarcinoma. Further we correlated the histopathological findings with significant clinicopathologic variables like age, serum PSA (Prostate specific antigen) levels, Gleason score and volume of tumour in the specimen.

Material and Methods

This was a single centre prospective study of all the cases of prostatic adenocarcinoma (PCa) diagnosed on transurethral resection (TURP) specimens and core needle biopsies, conducted in the department of Pathology, M.S Ramaiah Medical College and Hospitals, Bangalore over a period of three years (between January 2013 and January 2016). The formalin fixed prostate specimens were processed as per standard protocol and 4- 5 µm paraffin sections were obtained that were stained with Haematoxylin and Eosin in the standard manner. The sections were viewed in detail and presence of perineural invasion, tumour volume [proportion (%) of prostatic tissue involved by tumour] and Gleason score were determined for each case. Gleason score was determined using the modified Gleason system.[4,5,6] Primary grade (most common) and secondary grade (second most common) patterns were assigned to each case and Gleason score was obtained by summing up the grades. In needle biopsies, when different cores exhibited different Gleason grades, the overall worst Gleason score was given.[5,6] Posthormonal therapy and postradiotherapy cases were excluded. Clinical details and relevant investigations including age, pre-operative serum PSA levels were obtained from the records.

Statistical Analysis: Continuous data was summarised using descriptive statistics. Qualitative variables were summarized using frequency and percentage. One way ANOVA and Kruskal-Wallis followed by post hoc test was employed to test the differences in the mean/median values of variables like PSA, tumour volume and age. Fisher's exact test was used to compare the tumour differentiation across different age groups.

Spearman's correlation was used to find the correlation between Gleason score and other parameters. A level of $p < 0.05$ was considered as statistically significant.

Results

A total of 55 cases of prostatic acinar adenocarcinomas (PCa) from 55 previously untreated patients were diagnosed on prostate specimens comprising of 33 TURP specimens and 22 needle biopsies over a duration of 3 years. Prostatectomy specimens were not received during this period. The mean patient age was 69± **8**.9 years (age range: 52 to 90 years) and the median age was 68 years, with most of the cases occurring in the 6th decade (43.6%) followed by 7th decade (32.7%) [Table 1]. The indications for prostatic tissue sampling were elevated PSA (53%, 29/55), abnormal digital rectal examination (DRE) (20%, 11/55) and abnormal DRE + elevated PSA (27%, 15/55). The clinical presenting symptoms were increased frequency of micturation (45.5%, 25/55), incomplete voiding (40%, 22/55), dysuria (38.2%, 21/55), nocturia (12.7%, 7/55), hematuria (9.1%, 5/55) and acute urine retention (9.1%, 5/55).

Of the 55 cases of PCa, 16 (29.1%) were moderately differentiated (Gleason score 5- 6) (Fig 1), 10 (18.2%) were moderate to poorly differentiated (Gleason score 7) (Fig 2) and 29 (52.7%) were poorly differentiated (Gleason score 8- 10) (Fig 3). There was no statistically significant correlation between the degree of tumour differentiation and age ($p= 0.128$).

The commonest Gleason score was score 8 (27.3%) followed by score 9 (23.6%) [Table 2]. Gleason score 7 was present in 18.2% (10/55) of the cases of which 70% (7/10) had Gleason grade 4+3 and 30% (3/10) had Gleason grade 3+ 4. Gleason pattern 4 was the most frequent primary pattern, occurring in 54.5% (30/55) of the cases. The most common secondary pattern was also Gleason pattern 4 (43.6%; 24/55) [Table 3]. Tertiary pattern was not identified. A higher Gleason score was associated with increased PSA levels ($p= 0.000$) and tumour volume ($p= 0.003$). No correlation was found between age and Gleason score ($p= 0.181$) [Table 4].

37.5% (6/16) of moderately differentiated PCa, 40% (4/10) of moderately to poorly differentiated PCa and 51.7% (15/29) of poorly differentiated PCa exhibited perineural invasion. Overall, 45.5 % (25/55) of the cases showed perineural invasion. High grade PIN was present in 7.3% (4/55) of the cases.

The average volume of TURP specimen was 13.2 ± 9.4 (range: 2 to 40 ml). The average tumour volume in TURP specimen was 52.5± 26.4 % (range: 10 to 95%). The average number of cores in needle biopsies was 7.0 ± 3.2 (range: 2 to 12 cores) and the average tumour volume was 58.1 ± 19.7 with the average number of cores involved being 4.6 ± 2.77. The overall average tumour volume (TURP + needle biopsies) was 54.7± 23.9 %.

Table 1: Age incidence and distribution of prostatic adenocarcinoma.

Age group	No. of cases (%)	Moderately differentiated tumour	Moderate to poorly differentiated	Poorly differentiated tumour
50- 59	6 (10.9%)	5	-	1
60-69	24 (43.6%)	5	7	12
70-79	18(32.7%)	4	3	11
80- 89	6(10.9%)	2	-	4
90- 99	1(1.8%)	-	-	1
	55	16 (29.1%)	10 (18.2%)	29 (52.7%)

Table 2: Distribution of Gleason score, age, tumour differentiation, tumour volume and PSA levels.

Gleason score	No. of cases (%)	Age (mean ± SD)	Tumour differentiation	Average tumour volume (%) ± SD	Mean PSA (ng/ml) ± SD
5	7(12.7%)	67.4 ± 10.2	Moderate	21.4± 10.3	41.3± 9.9
6	9(16.4%)	66.9 ± 10.4	Moderate	55.6± 15.3	65.2± 23.9
7	10(18.2%)	67.5 ± 5	Moderate to Poor	60.2± 21,4	77.4± 33.6
8	15(27.3%)	74 ± 8.7	Poor	62.7± 24.9	178.5± 165.5
9	13(23.6%)	69.2 ± 8.5	Poor	63.6± 21.8	329.3± 242.8
10	1(1.8%)	80.0	Poor	60	310

PSA, Prostate specific antigen.

Table 3: Gleason Pattern.

Gleason pattern	Primary pattern (N= 55) No. of cases (%)	Secondary pattern (N= 55) No. of cases (%)
1	0	0
2	7 (12.7)	0
3	12(21.8)	22 (40)
4	30(54.5)	24(43.6)
5	6(10.9)	9(16.3)

Table 4: Comparison of Gleason score with age, PSA levels and tumour volume.

	Gleason score vs. Age	Gleason score vs. PSA level	Gleason score vs. Tumour volume
Spearman's correlation coefficient	0.183	0.703	0.392
p value	0.181 (not significant)	0.000 (significant)	0.003 (significant)

PSA, Prostate specific antigen

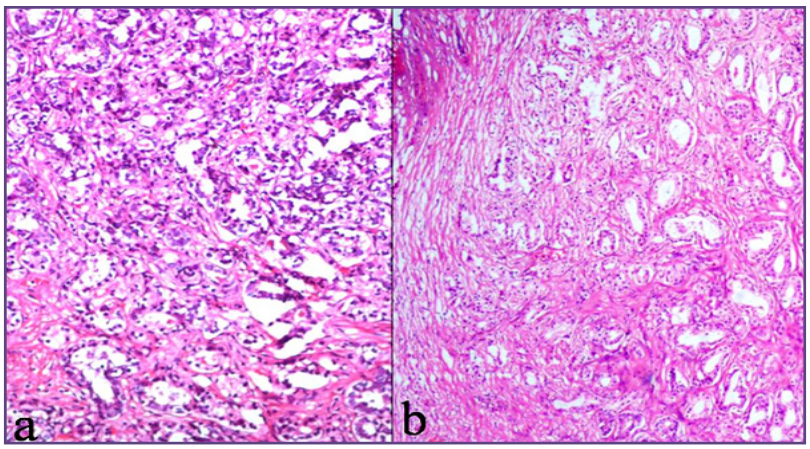

Fig. 1: Prostatic adenocarcinoma, moderately differentiated Gleason score 3+3= 6/10. (a) Pattern 3- single separate very small, small and medium sized glands of variable shape and size with elongated, angular and twisted forms. (b) Pattern 3 with ill-defined infiltrating edges. (H&E, 100X).

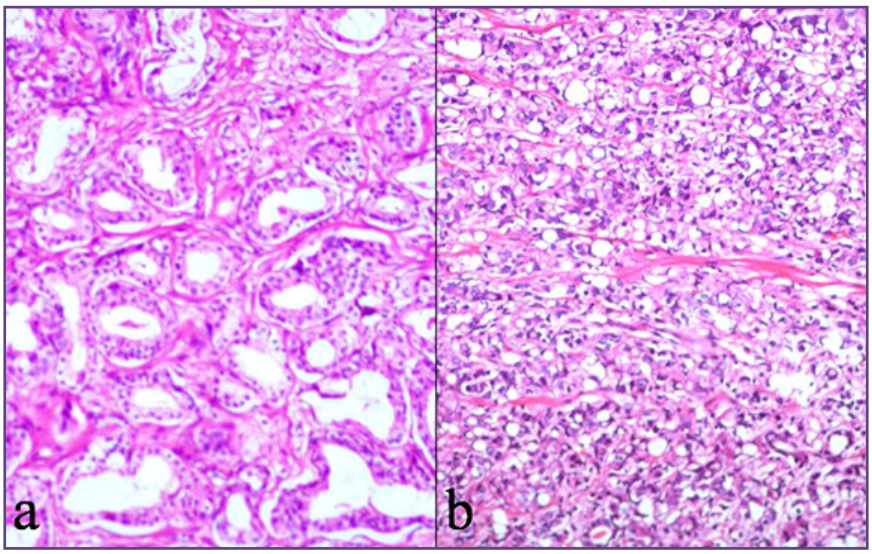

Fig. 2: Prostatic adenocarcinoma, moderate to poorly differentiated Gleason score 3+4= 7/10. (a) Primary pattern 3- single separate small to medium sized glands of variable shape and size. (b) Secondary pattern 4- fused microacinar formations, cords and diffusely permeative tumour cells, many with cleared cytoplasm (hypernephroid pattern). (H&E , 200X).

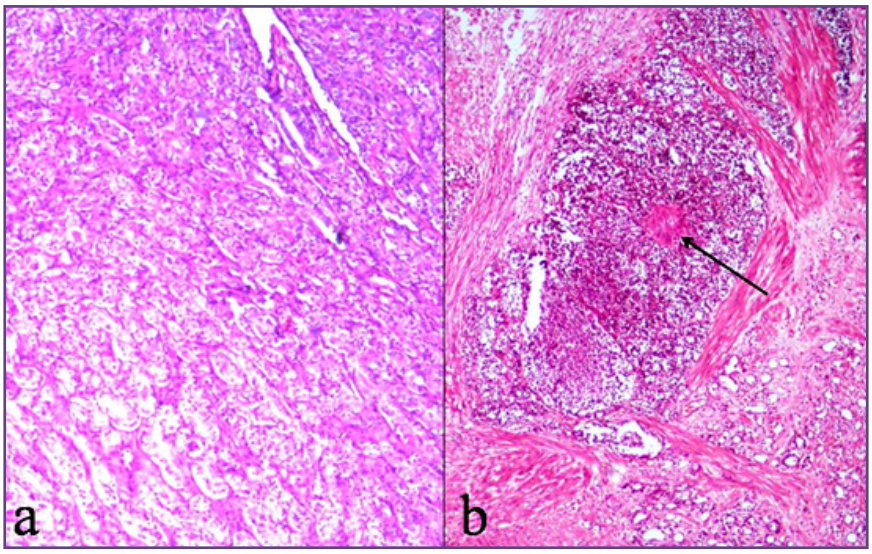

Fig. 3: Prostatic adenocarcinoma, poorly differentiated Gleason score 4+5= 9/10. (a) Primary pattern 4- cords and fused Ill-defined glands with poorly formed glandular lumina . (b) Secondary pattern 5- Expansile solid masses of tumour cells with central necrosis (arrow) (comedocarcinoma) (H&E, 100X).

The mean preoperative serum PSA was 162.9 ng/ml (range: 22 to 800) and median PSA was 85 ng/ml. PSA levels increased with the average tumour volume ($p< 0.0001$).

Discussion

Prostatic adenocarcinoma occurs predominantly in older men. In the present study the mean age was 69 years which is similar to that reported by Jackson et al (68.5 years) and Shirish et al (66.07 years). [7, 8] Majority of our cases (43.6%) occurred in the 6th decade which is similar to that reported by Shirish et al (37%).[7] In studies conducted by Jackson et al and Anushree et al peak incidence of PCa was seen in 7th decade.[3, 7]

A south Indian study conducted by Anushree et al revealed that increased frequency of micturation (38.5%), dysuria (38.5%) and incomplete voiding (38.5%) were the three most common clinical presenting symptom of PCa.[3] Similarly, in another south Indian study by Atchyuta et al, increased frequency (26.7%), dysuria (26.7%) and incomplete voiding (26.7%) were the commonest present symptoms.[8] Our findings are in synchrony with the above studies.

Poorly differentiated PCa comprised the largest group (52.7%) in the present series followed by moderately differentiated PCa (29.1%) and moderate to poorly differentiated PCa (18.2%). A west Jamaican retrospective study on 191 PCa cases found that moderately differentiated PCa was the largest group (35.29%) followed by moderate to poorly differentiated PCa (34.39%).[7] A south Indian study on 17 PCa cases revealed that moderate to poorly differentiated PCa (52.94%) was most frequent followed by poorly differentiated PCa (29.4%).[9] Study conducted in Pakistan on 190 PCa revealed that poorly differentiated PCa (Gleason score 8- 10) (52.7%) was the commonest followed by moderate to poorly differentiated PCa (Gleason score 7) (33.1%) and moderately differentiated PCa (Gleason score 5- 6) (17%).[10] The higher frequency of poorly differentiated PCa in our study is most likely a reflection of the patient's late presentation at the time of diagnosis. Differences in the geographic area, demography and race may possibly have a role in such differences between our study and other studies. Further for needle biopsies, there are several sources of grading discrepancies, including observer variability, pathologist expertise, tissue distortion and sampling error.[11]

Similar to our study none of the other studies quoted above encountered well differentiated PCa.[7,9,10] The possible explanation is that Gleason patterns 1 and 2 are almost never diagnosed on needle biopsy specimens as the calibre of needle cores does not enable the edges of nodules to be seen.[4,5,6,9] These tumours are small, tend to be located anteriorly in the prostate and are usually clinically asymptomatic and thus may not be sampled.[3,9] Well differentiated PCa are rare, exhibit poor diagnostic reproducibility among experts and are often an incidental finding in prostatectomies and TURP specimens performed due to a clinical diagnosis of benign prostatic hyperplasia. [9,11] In a clinicopathological study conducted in Saudi Arabia, which included prostatectomies, well differentiated PCa was found in only 3.8% of the 94 PCa cases and in another study conducted in Sultanate of Oman only 0.08% of the PCa cases were well differentiated with Gleason score between 2 and 4.[12,13]

Gleason grading of PCa is the single most important predictor of biological behaviour and one of the most significant factors determining the therapy of PCa.[14]. Cases with Gleason score 6 or lower are candidates of active surveillance ("watchful waiting therapy"), cases with Gleason score 8- 10 are candidates for radiation therapy or adjuvant therapy and cases with Gleason score 7 usually require some form of definitive therapy.[6] Since its inception by Donald Gleason in 1966, it has remained the cornerstone in the diagnosis and management of PCa and has been endorsed by the World Health Organisation.[6] It is solely based on architectural pattern with all tumours falling into a 5 grade system representing a continuum of progressively complex morphologies.[6,13] Studies have consistently shown that there is a positive correlation of Gleason score to tumour volume, more extensive tumours, positive surgical margins and advanced pathologic stage.[7,10,14] Our experience also is similar in that a higher Gleason score was associated with increased tumour volume (p= 0.003).

PSA is a 33-kd single chain glycoprotein that is a highly sensitive serum biomarker of PCa.[15] Despite debate on the specificity, positive predictive value and utility of PSA in population screening, it still continues to play an indispensible role in the diagnosis and management of PCa.[16] Availability of PSA levels and prostate biopsy has markedly increased the diagnosis of PCa.[7] Further it has a role in determining the long term risk of a particular PCa and monitoring of patients following hormonal/definitive therapy.[16] A study on 67 Nigerian African men with PCa revealed a positive correlation between serum PSA and Gleason grade and score (Spearman's correlation coefficient= 0.40, p= 0.001).[17] Jackson et al, in their study, found that mean PSA of PCa cases with Gleason score of 6 was 50.11ng/ml compared with 70.8 ng/ml, 136.5 ng/ml and 140.5 respectively in Gleason scores 7, 8 and 9.[7] They concluded that PSA levels increases with Gleason score. Another study conducted on 200 PCa patients, in Brazil, revealed positive correlation of high Gleason scores to higher preoperative PSA .[14] These studies are in synchrony with our study, where higher Gleason score was associated with higher PSA levels (Spearman's correlation coefficient= 0.703, p= 0.000). Poorly differentiated PCa tend to be larger and of more advanced stage; thus even though they produce less PSA per cell as compared to well differentiated PCa, they are associated with increased PSA levels.[7,14] Similar to our study (p< 0.0001) other studies have shown that serum PSA levels correlate with tumour volume.[7,14]

Various studies have quoted different incidence of perineural invasion, ranging from 7% to 47%.[7, 8, 9] In the present study the incidence of perineural invasion was 45.6%.

In 7.3% of the our PCa cases, the adjacent prostatic tissue showed high grade PIN which is slightly higher than a west Jamaican study(Jackson et al) (4.7%) and significantly lower than another south Indian study (Anushree et al) (50%). [3, 7]

Conclusion

In the present study we found positive correlation between PSA levels, tumour volume and Gleason score. Majority of

our patients had poorly differentiated PCa with high PSA levels suggesting that the disease is advanced at the time of diagnosis. Serum PSA screening in middle and old age group of men, with skilful clinical examination and prompt prostate biopsy is required to diagnose PCa early enough for a favourable prognosis.

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Competing Interests
Nil

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