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A COMPREHENSIVE CLINICOPATHOLOGICAL STUDY OF PROSTATE CARCINOMA WITH CORRELATION TO PROSTATE SPECIFIC ANTIGEN (PSA) AND KARNOFSKY PERFORMANCE STATUS (KPS).

Pathology

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ABSTRACT

The present study aims at clinicopathological correlation of prostate carcinoma and correlation of Gleasons grade with preoperative Karnofsky Performance Status (KPS) and preoperative total serum PSA levels.

Total 33 histopathologically confirmed cases of prostate carcinoma were studied and interviewed for determining KPS preoperatively.

All cases in present study showed significantly increased PSA levels with moderate to high grade adenocarcinoma. The most common Gleason's grade and score encountered was 4 and 7 respectively.

No significant correlation found between Gleason's score and KPS. However Age has significant inverse correlation with KPS. Thus patients presenting at relatively early age have better prognosis and treatment tolerance and are candidates for curative therapy.

Thus PSA is reliable tumour marker. Higher grade produce more PSA. Gleason's grading on biopsy helps in definitive diagnosis and predicting prognosis.

KEYWORDS

Prostate, Gleason's grade, PSA, Karnofsky Performance status.

Introduction:

Cancer prostate is most common cancer in men and second most common cause of death due to cancer in men.[1,2] Urinary outflow obstruction is most common presenting symptom in such patients.[1] Many prostatic cancers are relatively slow growing and remain clinically unrecognized. Histological diagnosis of prostate carcinoma on biopsy is a challenging task because of scant tissue availability.[1,2]

Gleason's grading system is universally accepted grading system for prostate carcinoma introduced by Donald F. Gleason in 1966. It is based on low power architectural features of prostate cancer. It has immense prognostic significance and used to determine treatment. [1,5] Serum Prostate Specific Antigen (PSA) is most useful marker in diagnosis and first line of screening test for prostatic cancer. PSA combined with Gleason's score and clinical stage, improves the prediction of pathological stage for prostate carcinoma.[5]

We analyzed histopathological features and Gleasons grading and correlated it with preoperative Karnofsky Performance Status (KPS) which has been used as indicator of quality of life of patients with various malignancies or to determine treatment tolerance.[4]

Methods

The present study was under taken in tertiary care hospital and 33 cases were studied over a period of 1 year (January 2011 to December 2011). Ethical clearance was obtained from ethical committee.

Only histopathologically proven cases of prostate carcinoma were included in study. Preoperative serum total PSA levels (assessed by Chemiluminiscence immunoassay method) along with other concerned clinical data were recorded. Preoperative KPS score was determined by interviewing patients with preformed questionnaire and classified into normal (100-80), reduced (70-50) and severely reduced (40-0).[4,6]

In present study we received 30 needle biopsies and 3 transurethral resection of prostate (TURP). All of them were subjected to standard histopathological processing and stained by Haematoxylin and Eosin stain. The slides prepared were analyzed and graded according to Gleason's grading system.

Serum PSA <4ng/ml was considered normal and Gleason's score then correlated with preoperative PSA levels.

Statistical analysis was done by using mean, rates ,ratios, percentages appropriately. Student 't' test and Chi square test used appropriately for correlation. 'P' value of less than or equal to 0.05 considered statistically significant.

Results

Age group in present study ranged from 55 to 85 years with mean of 67 (SD=± 7.90) years. Carcinoma prostate was most prevalent in age group of 61-70 years accounting for 12 cases (36.36%). Patients presented with lower urinary tract symptoms like frequency, urgency, dysuria. Most common symptom was increased frequency of micturition (90%). Other symptoms were nocturia, hematuria, weight loss, back /bone pain, weakness.

All patients had asymmetric enlargement of prostate on digital rectal examination (DRE). Majority i.e. 26(78%)patients were anemic. Mild to moderate anemia was observed in 10(30%) and 16(48%) cases respectively.

Serum creatinine was elevated in 4 cases of which 2 had primary renal disease. Five cases had evidence of bone metastasis of which 2 had back pain.

The present study on histopathological examination of carcinoma prostate showed presence of 3 Gleason's grades 3, 4 and 5.

The following table shows distribution of grades as primary pattern and secondary pattern. (Table 1)

Table 1 Gleasons grade Primary and Secondary pattern

Primary pattern	Distribution (n=33)	Secondary pattern		Distribution (n=33)	
	Number	Percent		Number	Percentage
Three	7	21.21	Three	11	33.33
Four	15	45.45	Four	16	48.48
Five	11	33.33	Five	6	18.18
Total	33	100	Total	33	100

Most common Gleason's grade observed was 4(84.84%) and most common Gleason's score was 7(45.45%). Gleason's score for each case was calculated by adding primary and secondary pattern.

Fifteen (45.45%) cases showed moderately differentiated carcinoma with score of 7 and 18(54.54%) cases showed poorly differentiated carcinoma with score of 8-10. No case of well differentiated carcinoma (score 2-5) were noted in present study.

Among 15 cases of score 7, six (40%) had pattern of 3+4 while remaining 9 (60%) cases had 4 +3 pattern. Gleason's grade 5A was seen in 4 cases. One case each of clear cell pattern and signet ring cell variant were also noted. Perineural invasion was noted in 30 (90%) cases. Various patterns seen in our study are demonstrated below.

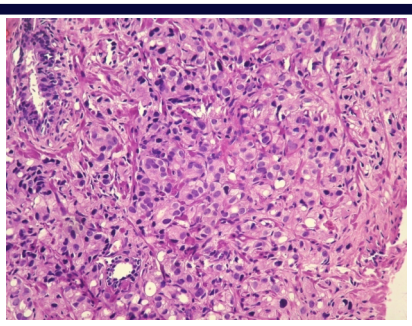


Figure 1: Gleason's Grade 4A showing cells arranged in ill defined glands and sheets with stromal invasion.(H and E: 100X)

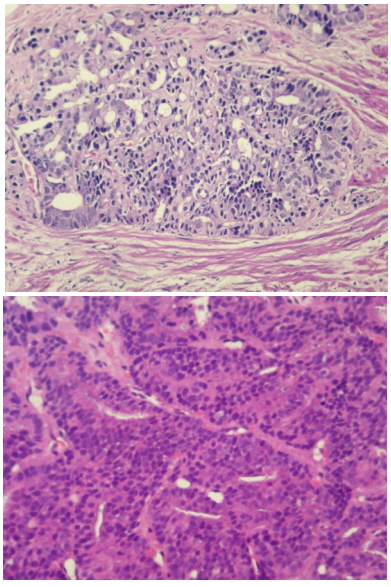


Figure 2: Grade 4A showing cribriform pattern & slit like glands with multilayering of cells. (H and E: 100X)

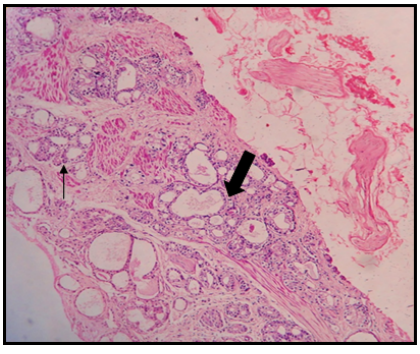


Figure 3: Needle biopsy showing Gleason's score 7 (4+3). Note cribriform pattern of glands with irregular borders (grade 4; thick arrow) and individually placed small glands of equal sizes with back to back arrangement at places (grade 3; thin arrow). (H and E : 40X)

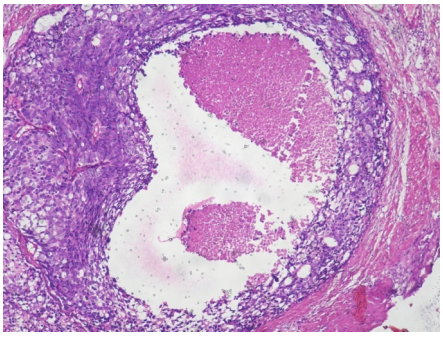


Figure 4: Grade 5A showing tumour cells arranged in glandular pattern with central comedonecrosis. (H and E : 100X)

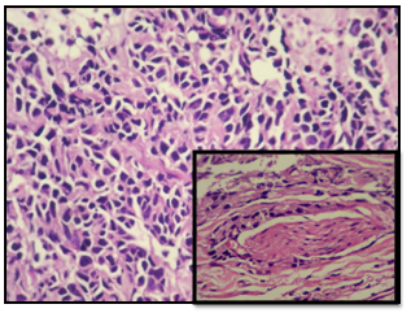


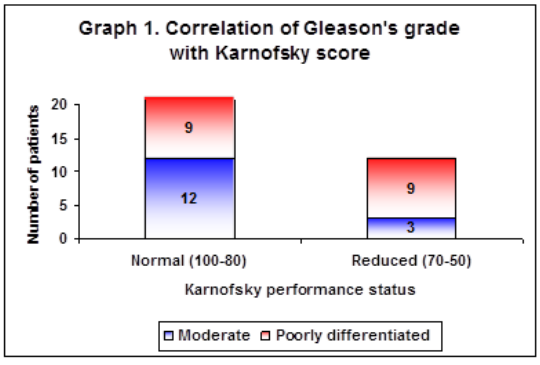
Figure 5: Gleason's grade 5B showing sheets of tumour cells with high N: C ratio invading the stroma. Inset : Perineural invasion. (H and E: 400X)

In present study all cases showed preoperative PSA levels above 20ng/ml and ranged from 21.4 ng/ml to 1014ng/ml with overall mean of 112.4ng/ml. Mean PSA levels for moderately and poorly differentiated carcinomas were 92ng/ml and 129ng/ml respectively, which means PSA values are higher in poorly differentiated than moderately differentiated. However no statistical significance was noted (P value0.57)when student 't' test was applied to analyze correlation between differentiation (grade) and PSA levels (Table 2)

Table 2: correlation of Gleason's grade with preoperative serum PSA levels.

Gleason's grade	Distribution (n=33)	
	Mean	SD
Well differentiated (2 to 5)	-	-
Moderate (6 to 7)	92.05	115.32
Poorly differentiated (8 to 10)	129.44	229.77

p=0.57



p= 0.74 (not significant)

Graph 1: Following graph depicts correlation between KPS and Gleason's Grade

No significant statistical correlation observed between Gleason's grade and KPS by applying Chi square test (p=0.74).

However significant inverse correlation observed between age and KPS score on applying Chi square test (p=0.005), indicating performance decreases with increasing age.

Discussion

The most prevalent age group for carcinoma of prostate in present study was 60-70 years. The mean age at diagnosis was 67 years as compared to 72 years as per western literature and indicates later presentation than Indian population.[789] Other Indian-Asian studies have also shown similar findings with mean age of 67 years.[10,11,12,13,14,15]

All cases in present study exhibited features of adenocarcinoma which is in very close agreemant with studies done by Jackson LA et al (100%), Mawakyoma et al (99%), and Gurumurthy et al (100%).[5,10,12]

In present study majority (54.54%) cases had poorly differentiated

carcinoma followed by moderately differentiated carcinoma(45.45%). No cases of well differentiated carcinoma were noted. This is similar to studies reported by Ctalona WJ et al and shirley SE et al.[16,17] On the contrary several studies reported moderately differentiated carcinoma as predominant type.[10,12,18] Comparison between our study with that of others suggests that, their patients had less aggressive disease and presented later as compared to our region.

Possible contributing factors for above difference are genetic , environmental, socioeconomic, racial, dietary factors and to some extent interobserver variability in Gleason's scoring.[17,19]

We have considered Gleason's score 7 as moderately differentiated as study was carried out in 2011. However as per recent WHO grading it is considered in separate group of moderately to poorly differentiated carcinoma. It was most common score noted (15 cases=45.45%) in our study. Among these 15 cases, 7(40%) cases showed pattern 3+4 while remaining 9(60%) had pattern of 4+3. There is conflicting data on prognostic significance of Gleason's score 7, based on whether primary pattern is 3 or 4.[20,21]

The PSA value in present study ranged from 21.4 to 1014 ng/ml with mean of 112.4 ng/ml. Our analysis of preoperative total serum PSA levels shows interesting differences from reports of non Indian population.Following table compares PSA levels of present study with others.

Table 3: Comparison carcinoma detection rates by PSA levels in various studies

Study	Carcinoma detection rate by PSA levels	
	>20ng/ml	<10ng/ml
Devidson DD et al [22]	12%	61%
Yang WJ et al [23]	66%	15%
Sinha et al [13]	52%	7%
Chavan PR et al [24]	89%	5%
Agnihotri S et al [25]	DRE+ 95% DRE- 62%	DRE+ 59% DRE- 15%

Above table shows that detection rates of prostate carcinoma at low PSA levels are higher in western population than in Indian. Within India this detection rate at low PSA is higher in north India as compared to south and west India. This difference within India can be explained on basis of heterogeneity of population and late presentation of cases due to unawareness about diesease. In our study all cases had PSA more than 100 which is in agreement with most of the studies from India.

Higher PSA levels were observed with poorly differentiated carcinoma than moderately differentiated carcinoma however difference was statisticaly insignificant. The results of various studies on correlation of Gleason's grading and PSA levels are conflicting. Some support positive correlation[10,11,12] like present study saying poorly differentiated carcinomas (high Gleason grade) secrets more PSA, while other studies which proved inverse correlation supports that , the poorly differentiated carcinomas secret low PSA due to loss of PSA encoding gene.[18,26] We support positive correlation however it needs to be further investigated with larger sample size which will consider other factors like tumor volume.

Detection rates of prostate carcinoma in India are very less for PSA value of <10 ng/ml which inturn exposes patients to unnecessary painful biopsy procedure. In present study all cases had PSA more than 20ng/ml hence we support higher cut off value as suggested by Agnihotri S. et al for Indian population provided that cut of value is not impacting the stage at diagnosis and disease specific mortality. Such data is not available currently and hence needs to be studied further before making any recommendation.

The higher PSA levels in India can be attributed to overall low incidence of cancer prostate in asians, indolent nature of disease and unawareness.[27]

Another important point to be noted in various study supporting positive correlation between grade and PSA, that most of such studies lack data regarding tumour volume which has shown strong positive correlation with PSA levels. No information regarding tumour volume is available in present study hence no comment can be made on this issue.

KPS has been related to other prognostic factors like grade, stage, hemoglobin, APACHE score and survival in various malignancies including prostate carcinoma.[29,30]

Our study did not show any significant correlation between Gleason'sgrade and KPS score. Similar findings were observed in a study by Nunez et al.[29] Median KPS score in present study was 80, which means majority cases had normal KPS and hence good quality of life.

Significant inverse correlation of KPS with age was demonstrated by present study, indicating as age increases KPS decreases. Thus patients those who present at early age have better quality of life and better treatment tolerannce. Hence curative treatment should be offered to such patients. However study by Meng T et al suggests that old age and low KPS are not contraindication for curative surgical intervention as KPS is related to general condition of patients which depends on multiple factors. The general condition can be taken care by postoperative monitoring and supportive care.[31]

Perineural invasion was seen in 90% of our cases. In a study by Shirley SE et al, 33.3% and 52 % by Gurumurthy D et al. of the cases showed perineural invasion. Perineural invasion is an established risk factor in other malignancies and a recognized mechanism of metastasis in prostate carcinoma where cancer cells spread by using the rich innervations on the prostate. However, existing views on the significance of perineural invasion are contradictory. Studies by Freedland SJ et al and Ravery V et al found that it was not an independent prognostic factor. On contrary, D'Amico AV et al, Rubin MA et al and Quinn DI et al reported that it was independently prognostic factor. Despite huge data available involving thousands of patients, uncertainty about the prognostic value of perineural invasion has not been addressed yet. [5,17]

Conclusion:

Histopathological examination of prostate with Gleason's grading is most important investigation for definitive diagnosis of prostate carcinoma in era of needle biopsy. In addition it helps in determining prognosis and treatment.

Majority prostate carcinomas present with higher grades, presenting as poorly or moderately differentiated carcinoma and at an early age as compared to western population. Most common Gleason's grade and score observed was 4 and 7 respectively. Though perineural invasion was noted significantly in 90% cases, it lacks consensus on its prognostic value. Gleason's score 7 is a heterogeneous group of carcinoma prostate with primary pattern of either grade 3 or 4 which needs to be evaluated in detail for prognostic purpose.

Preoperative total serum PSA is reliable marker in detecting carcinoma prostate. It is influenced by differentiation of tumour, as higher grades (poor differentiation) present with higher PSA levels though not statistically significant. We suggest that poorly differentiated carcinomas secret more PSA.

KPS decreases with increasing age suggesting that patients presenting at an early age do better those who present at later age. As patients in India present at an early age as compared to western population, they are potential candidates for curative treatment.

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