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Original Article

A Study of Adenocarcinoma Prostate, It's Correlation with Prognostic Factors and Gleason Score

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Abstract

Needle core biopsies or Tru cut biopsies are the commonly used diagnostic tool in detection of prostatic cancers. It also poses as a major diagnostic challenge in tumour detection in prostate as the diagnosis depends on the size and number of adequate cores. This study conducted at a tertiary care centre in kerala, aims to identify adenocarcinomas of prostate in needle core biopsies received in the department of pathology in a time period of two years, determining its Gleason's score and correlating it with age of the patients and serum PSA levels. Gleason's scoring system has evolved over many years and this study is based on the 2005 ISUP Modified Gleason Score. The conduct of this study also was restricted to core biopsies of prostate in indicated patients. The advent of needle core biopsies has brought about a revolution in detecting carcinomas of prostate at an early stage and which can also be attributed to the increasing rate of detection of prostatic malignancies worldwide.

Context: In view of increasing incidence of prostatic tumours in men in India, this study was conducted in needle core biopsies of prostate at a Tertiary Care Centre in Mid Kerala.

Aims:

1. To identify adenocarcinomas of prostate in needle core biopsies and classify according to its Gleason score.
2. To correlate Gleason's score with age of the patients and Serum PSA levels.

Settings and Design: Department of Pathology,Government TD Medical College, Alappuzha, Prospective Study.

Methods and Material: All needle core biopsies of Prostate with a histological diagnosis of Adenocarcinoma of Prostate were included in this study during a period of two years. All tissue cores were processed and H & E stain was done to evaluate and score the tumour according to 2005 ISUP Modified Gleason score. Age and Serum PSA levels were also correlated with the Gleason score.

Statistical analysis used: Descriptive Analysis

Results: 40 cases of adenocarcinoma prostate in needle core biopsies were studied in a time period of 2 years. Gleason's score was determined for each patient and they were grouped as Group A,B,C with Gleason score ≤6,7 and ≥8 respectively. 36 out of 40 patients were in the age group of >60 years and they had a higher Gleason's score as compared to patients who were <60 years of age. Serum PSA levels were available in 29 cases.

A serum PSA level of ≥10ng/ml were noted in 79% of cases and these patients had a statistically significant correlation with higher Gleason's score. In our study 5 cases showed associated Prostatic Intraepithelial Neoplasia(PIN) and 1 case with perineural invasion was noted out of the 40 biopsies.

Conclusions

1. The mean age of the patients in our study was 70 years
2. The mean Gleason score was 7.1, with a range of 5 to 9.
3. Linear regression analysis of age with Gleason score showed a correlation coefficient (r^2) of 0.01.
4. Patients with a serum PSA of >10ng/ml was found to have a higher Gleason score compared to those with serum PSA of ≤10ng/ml which was statistically significant (P = 0.0001).

Key-words: Prostate Adenocarcinoma, Prostate carcinoma.

Key Messages: Carcinomas of Prostate is increasing in incidence worldwide and with the advent of needle core biopsies the rate of detection is gradually increasing. The study could identify a significant correlation with high serum PSA levels and high Gleason score. Also increasing age is highly correlated with a higher Gleason score.

Introduction

Prostate cancers stands as the second most commonly diagnosed malignancy in men worldwide. Very few studies have been conducted in this part of Kerala on cancers of Prostate. In India, the true data regarding the incidence of prostate cancer is limited. This is mainly due to the fact that prostatic carcinomas are not a notifiable disease and it becomes symptomatic at late stages. In India, population-based and community-based studies on prostate cancer are also limited.[1] The definitive diagnosis of malignancy based on a minimal or limited amount of carcinoma in needle biopsy prostate is a major challenge for the pathologist. There are some guidelines and constellation of findings with a combination of the major and minor diagnostic criteria which permit a definitive diagnosis of focal or minimal adenocarcinoma in prostatic cores. Some of the features in major criteria for identifying prostatic adenocarcinoma are infiltrative glandular growth pattern, absence of basal cells and nuclear atypia with nucleomegaly. Minor criteria includes intraluminal wispy blue mucin, amorphous pink secretions, intraluminal crystalloids mitotic figures, adjacent high grade prostatic intraepithelial neoplasia, amphophilic cytoplasm and hyperchromasia of nuclei.[2] The differential diagnosis of adenocarcinoma of prostate in needle biopsy tissue may include many benign entities like atypical adenomatous hyperplasia and glandular atrophy. Grade 3 prostatic intraepithelial neoplasia and focal glandular atypia or atypical small acinar proliferation also should be considered before diagnosing minimal adenocarcinoma. The most valuable supporting evidence for the diagnosis of minimal adenocarcinoma is immunohistochemistry using antibody 34 betaE12 or P63 which are the basal cell markers. Most cases can be diagnosed based on H&E-stained sections without these immunostain. The diagnosis of adenocarcinoma of prostate in needle core biopsy specimens presents few set of challenges. Firstly, early detection efforts, including screening with the prostate-specific antigen (PSA) and digital rectal examination, have resulted in identification of lower-stage and smaller-volume carcinomas of the prostate.[3,4,5,6]

Individual cancers show substantial variation in its outcome and it becomes important to stage the disease due to its variable biological potential. The various prognostic indicators include clinical staging, serum PSA levels, percentage of biopsy core involved and histological grade. The histolopathological Gleason grade and score correlates both with local invasiveness and its potential to metastasize. In some subsets of cancers, both confined to prostate and locally advanced, the existing markers are often unable to differentiate poor from good outcome cancers.[7]

Diagnosing Prostate Cancer

Symptoms related to prostate cancers rarely become evident until it is advance. Positive findings in digital rectal examination (DRE) or elevated levels of serum prostate-specific antigen (PSA) can be considered in recommending a prostatic biopsy. Even then there still remains controversy regarding the benefits of early diagnosis in prostatic cancers. It has been demonstrated that an early diagnosis of prostate cancer is best achieved using a combination of DRE, PSA and Needle core biopsies for confirmation. The most reliable method in diagnosis is by a Transrectal ultrasound (TRUS)-guided needle biopsy and in general, a safe procedure. Apart from infectious complications and pain, the majority of complaints center on the issues of urethral and rectal bleeding, as well as hematospermia. A TRUS-guided biopsy using an 18-gauge needle to obtain a tissue core is universal for obtaining biopsy of prostate. A minimum of 10-12 systemic, laterally directed cores is recommended on initial biopsy, with more cores in larger glands.

A core directed more laterally directed core at the lateral horn along with medially directed towards the apex can also show better cancer detection rates without increasing adverse events. Biopsies from transition zone are not recommended in the first set as it owes to low detection rates.

A repeat biopsy is always warranted in patients with persistent indication. ≥20 cores which is considered as saturation biopsy should be only reserved for repeat biopsy in patients who have negative results in initial biopsy but who are still strongly suspected to have prostate cancer.[8]

Serum PSA: The high sensitivity and low specificity of PSA testing in the diagnosis of prostate cancer is a problem in clinical practice.[9-12] The general cutoff for the PSA level is 4.0 ng/mL. With the use of this cutoff, the cancer detection rate ranges from 35% to 42.3% for 10 to 12 core biopsy.[13,14] If serum PSA (ng/ml) is <4, patients are not followed up. If the values are 4-10, PSA density (serum PSA per gland volume) is calculated for further management. A prostatic needle biopsy is done in patients with serum PSA values >10, a PSA density >1.5 and a hard prostate on digital rectal examination. A high serum PSA level may be attributed to higher chances of positive tissue diagnosis, a higher Gleason score, and a greater likelihood of bone metastasis.

2005 ISUP Modified Gleason score

Gleason's microscopic grading system for prostatic carcinoma

Grade	Description
1	Single, separate, uniform glands in closely packed masses with a definite, usually rounded, edge limiting the area of tumour
2	Single, separate, slightly less uniform glands, loosely packed with less sharp edge.
3a	Single, separate, much more variable glands, may be closely packed but usually irregularly separated, ragged, poorly defined edges.
3b	Like 3a, but very small glands or tiny cell clusters.
3c	Sharply and smoothly circumscribed rounded masses of papillary or loose cribriform tumour ('papillary intraductal tumour')
4a	Raggedly outlined, raggedly infiltrating, fused glandular tumour.
4b	Like 4a, with large pale cells ('hypernephroid')
5a	Sharply circumscribed, rounded masses of almost solid cribriform tumour, usually with central necrosis ('comedocarcinoma')
5b	Ragged masses of anaplastic carcinoma with only enough gland formation or vacuoles to identify it as adenocarcinoma.

Materials and Methods

A total of 40 cases of prostatic adenocarcinomas were studied over a period of 2 years at a tertiary care centre in mid kerala. Routine formalin fixation, histopathology processing, paraffin wax embedding, sectioning and H& E staining was done in all cases. The H&E sections positive for carcinoma prostate were graded and scored as per the 2005 ISUP modified Gleason's score. All the H&E sections were examined independently and patients were catergorised according to the Gleason's score. The number of cores were not considered in the study and a global Gleason score was given for each case. Table.1 shows the categorization of patients based on their Gleason scores.

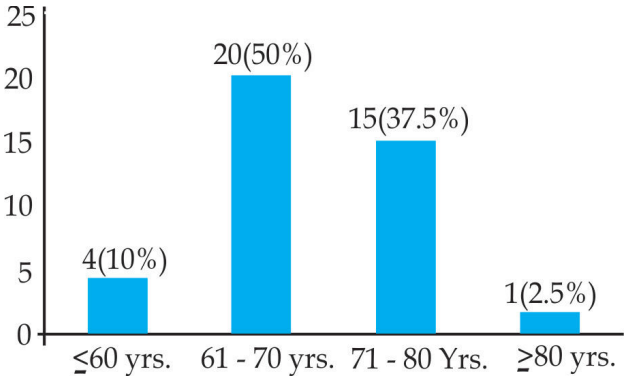
Table 1: Categorisation of patients based on Gleason score.

Category	Gleason's Score
A.	≤ 6
B.	7
C.	≥ 8

Results

The age group of patients ranged from 57-93 years with a mean age of 70 years. 36 out of 40 patients were in the age group above 60 years and 4 patients were below 60 years of age. The age groups and percentage of patients are given in Chart 1. The range of Gleason score in our study was between 5 to 9 and 7.1 was the mean Gleason score.

Chart 1 : Age group of patients.



12 patients (30% cases) had a Gleason score of ≥8 while 11 patients had a score of ≤6. Figure 1 shows Gleason score 3. Most of the patients (42.5%) had a Gleason score of 7(3+4 and 4+3). Figure 2 and 3 shows Gleason score 4. The age was compared with the Gleason score of patients and it was found that the higher the age, greater was the Gleason score.

Linear regression analysis of age with Gleason score showed a correlation coefficient (r^2) of 0.01. The comparison of age groups and the Gleason score of the patients is given in Table 2.

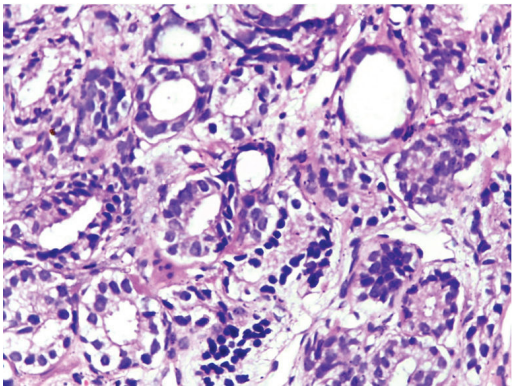


Fig. 1: Gleason score 3, small, uniform glands.

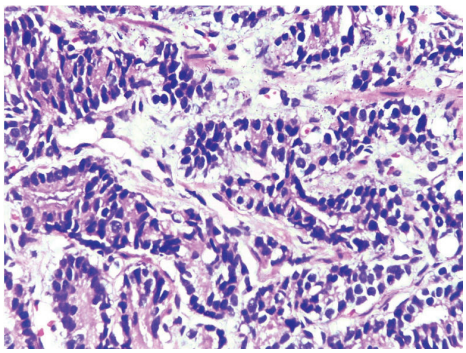


Fig. 2: Gleason score 4, raggedly infiltrating and fused glands.

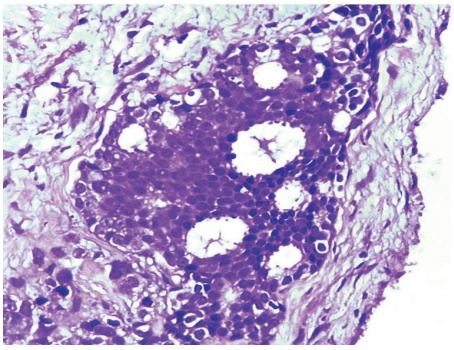


Fig. 3: Gleason score 4, cribriform pattern of glands.

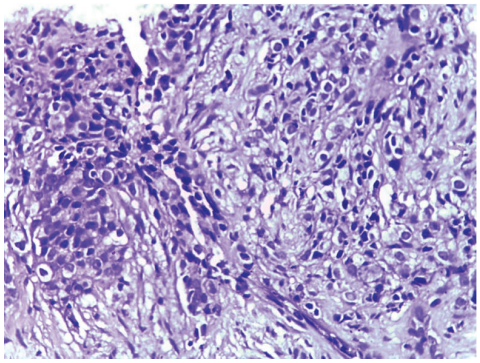


Fig. 4: Gleason score 5, infiltrating glands and tumour cells.

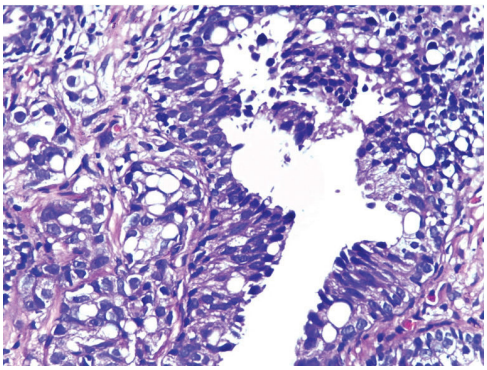


Fig. 5 : High grade PIN.

Table 2: Comparison of age groups with Gleason score.

Age group	Gleason score ≤6	Gleason score 7	Gleason score ≥8
≤60	0	3	1
61-69	8	5	7
≥70	3	9	4

Table 3: Comparison of serum PSA with Gleason score.

Serum PSA	Gleason score ≤6	Gleason score 7	Gleason score ≥8	P value
≤10ng/ml	7	0	0	<0.00001
>10ng/ml	4	17	1	

Table 4: Associations with carcinoma prostate.

Associations	No. of Cases	Percentage
PIN 2	3	8.3%
PIN 3	1	2.7%
Perineural invasion	1	2.7%

32 out of 36 cases were in the age group of above 60 years and they had higher Gleason score as compared to those less than 60 years of age(P=<0.0001). Figure 4 shows Gleason score 5. Among the biochemical parameters, serum PSA levels were measured in our study since it has a significant role in the management protocol of carcinoma prostate. Serum PSA values were obtained in 29 of our 40 cases and 75% of the cases had a level of >10ng/ml. A comparison of serum PSA value and the Gleason score was done and the patients with a serum PSA of >10ng/ml was found to have a higher grade of tumour compared to those with serum PSA of ≤10ng/ml as shown in Table 3. This difference was statistically significant (P=<0.00001).4 of our cases were associated with Prostatic intraepithelial neoplasia (PIN) of which 3 was PIN grade 2 and one PIN grade 3 as in figure 5. One of our cases also showed perineural invasion as given in the Table 4.

Discussion

The burden of prostate cancer falls disproportionately on men who are elderly or black. The median age at diagnosis is approximately 71 years, and the median age at death is 78 years. More than 75% of all cases of prostate cancer are diagnosed in men older than 65 years of age, and 90% of deaths occur in these patients. Incidence is approximately 60% higher and mortality rate is 2 times higher in black than in white men.[15] Asian-American men and Hispanic men have lower incidence rates than non-Hispanic white men.[16] The mean age of the 40 cases in our study was 70 years with a range of 57 to 93 years. 50% of the patients were in the age group of 61–70 years and 75% of cases were above the age of 65 years. There were 3 cases below the age of 60 years. Prostatic carcinoma is a tumour of old age and our results were comparable with other studies. Two Indian studies on prostatic cancer showed a lower mean age of the patients compared to our study. The hospital based study conducted in Tata Memorial hospital, Mumbai in 2011 showed a mean age of 64 years.[17] While the one conducted in Nizam's Institute of Medical Sciences in 2006 was only 43.5 years.[18] In a study by Morgan et al., a total of 371 patients with ductal adenocarcinoma were identified along with 442,881 patients with acinar adenocarcinoma.[19] Ductal cases were more commonly seen in men over 70-years as compared to acinar adenocarcinoma (54% vs. 44%, p<0.001), and there were no differences in the distribution by race. However, all our cases were acinar adenocarcinoma.

Gleason Score and Age

Gleason score is an individual prognostic factor in prostatic adenocarcinoma. In the year 2003, recognizing the importance of the Gleason grading system, the World Health Organization (WHO) adapted Gleason grading as the standard for prostate carcinoma. The Gleason grading system continues to play a crucial and critical role in the management and treatment stratification of patients with prostate cancer. It is sometimes difficult to perform Gleason grade assessment on a minimal focus of adenocarcinoma. In the 40 cases of adenocarcinoma prostate in our study, there were 12 cases having a high score of 8 or more and of which 50% were of age more than 70 years. 17 cases (42%) were grouped under the intermediate category of Gleason score 7. Our study was conducted on needle biopsies and follow up of the patients were not received to evaluate for stage or grade migration. A comparison of age with Gleason score showed a positive correlation with a correlation coefficient (r^2) of 0.01. The higher the age the higher was the Gleason score. 32 out of 36 cases were in the age group of more than 60 years and they had higher Gleason score as compared to those less than 60 years of age(P=<0.0001). There is data suggesting that older men have higher proportion of Gleason scores of 8–10. Russo et al showed that the prostate cancer-specific mortality (PCSM) increases with advancing age in men with Gleason score of 6 or 7 but not in Gleason score 8-10.[20] None of the needle biopsies were given a score of less than 3 in our study.

Serum PSA

Men with prostate carcinoma have a greater increase in PSA level over time than men without cancer.[21] It is unclear whether examining the annual rate of change in PSA level (PSA velocity) improves health outcomes or reduces unnecessary biopsies. Because of the individual variation and intra individual variation, PSA velocity is useful only in men who have three or more tests of PSA level done over a period of 1 to 3 years.[22,23]

An analysis from the Physicians Health Study used longitudinal follow-up instead of biopsy.[24] In this study, they used a PSA cut-point of 4.0 ng/mL or higher and the sensitivity for detecting cancer appearing within 2 years after screening was 73.2%. Although the study calculated sensitivity separately for aggressive (that is, extracapsular or higher grade) and nonaggressive (that is, intracapsular and lower grade) cancer (sensitivity, 91% vs. 56%), it is not clear that these categories corresponds to clinically important and clinically unimportant tumors. Among men who did not receive a diagnosis of prostate cancer in those 2 years, 14.6% had an initial PSA level of 4.0 ng/mL or greater, corresponding to a specificity of 85.4%. In our study serum PSA was obtained in only 29 out of 40 cases. In rest of the cases the PSA levels were either not estimated or were unavailable. Of the 29 cases, following a clinical protocol as mentioned earlier in the results, a level of more than 10ng/dl was considered significantly high. There were 22 patients who had a high value of serum PSA which contributed to 75% of cases. The PSA values were compared with the Gleason score in our study.

The serum PSA levels together with the Gleason score and clinical findings are required for prognostication in prostatic carcinomas. The majority of cases included in our study had a serum PSA of >10ng/ml, which was an indication for needle biopsy of prostate. But also some cases

with a serum PSA <10ng/ml were also obtained as the clinical findings were highly suggestive of malignancy. In an Indian study by Singh and Dogra et al, serum PSA correlated with histopathology. He found that with increasing serum PSA, the organ confinement of disease decreases linearly, reaching upto 60% in patients with PSA more than 20 ng/ml (P=0.03).[25] Seminal vesicle involvement also increases linearly in a significant manner (P=0.02) with increase in serum PSA levels. Similarly, capsular infiltration and lymph node involvement increased with increase in serum PSA levels but not in linear or a significant manner. Importantly, there were 9 cases in the group with PSA more than 20 ng/ml that had both seminal vesicle involvement and capsular infiltration suggesting poorer histopathological and possibly poorer long-term oncological outcome for this group. In our study 22 cases (75%) had a serum PSA level of >10ng/ml and 11 cases (38%) of the 22 had a Gleason score of ≥8, while there were 3 cases with a Gleason score of >8 and serum PSA level <10ng/ml. This shows that even a lower level of PSA can be seen in carcinoma which may go undetected if the biochemical parameter alone is considered. Serum PSA must be always combined with the digital rectal examination findings and clinical symptoms of the patient for making an appropriate diagnosis in case of prostatic adenocarcinomas. A comparison of serum PSA value and the Gleason score was done in our study and the patients with a serum PSA of >10ng/ml was found to have a higher grade of tumour compared to those with serum PSA of ≤10ng/ml. This difference was statistically significant (P=<0.00001).

Perineural Invasion (PNI)

We had a case in which perineural invasion (PNI) was noted in needle biopsy associated with adenocarcinoma. The finding of PNI at biopsy is a potential preoperative predictor of extraprostatic tumor extension. PNI is defined as the presence of prostate cancer tracking along or around a nerve within the perineural space. Although the finding of PNI on histological sections of a radical prostatectomy specimen has no significance, the importance for treatment planning of PNI found on prostate needle biopsy has been a source of debate. PNI is a major mechanism of prostate cancer extension from prostatic parenchyma to periprostatic soft tissue and so PNI extensive enough to be sampled on needle biopsy may signal an increased likelihood of extraprostatic extension of cancer or cancer recurrence. The detection of PNI has lately decreased due to the early diagnosis of prostatic carcinomas with S.PSA, DRE and needle biopsy.

Conclusion

The aim of the study was to diagnose prostatic adenocarcinomas of prostate in needle core biosies and its correlation with serum PSA and Gleason score which was conducted in a tertiray care centre in Kerala. The mean age of the patients in our study was 70 years and the mean Gleason score, 7.1. A Linear regression analysis of age with Gleason score showed a correlation coefficient (r^2) of 0.01. Patients with a serum PSA of >10ng/ml was found to have a higher Gleason score compared to those with serum PSA of ≤10ng/ml which was statistically significant (P = 0.0001). This study intends to throw light on the fewer number of studies being done in prostatic needle core biopsies in this part of India. Prostatic tumours are on the rise and earlier detection is always a challenge to the pathologist all over the globe. A complete evaluation with clinical history, digital rectal examination, serum PSA levels and Gleason's scoring of histopathological sections can help arrive at an accurate diagnosis and achieve adequate cure for the patients.

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Conflict of Interest: Nil

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