ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4

Journal of Coastal Life Medicine

Current Practice of Diagnosis and Reporting of Prostatic Intraepithelial Neoplasia

Received: 18 October 2022, **Revised:** 19 November 2022, **Accepted:** 21 December 2022

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Keywords

Intraepithelial, prospective, manifestations, surveillance

Abstract

Background - Prostatic intraepithelial neoplasia is the histological term for a precancerous disorder of the prostate gland. It can be identified by the presence of abnormal cells in the prostatic ducts and acini, which may be a precursor to prostate cancer. Prostate biopsies performed to evaluate an increase in prostate-specific antigen or suspect results from digital rectal examinations frequently reveal prostate intraepithelial neoplasia.

Methods: In the Department of Pathology at the Karad Institute of Medical Sciences, 127 people with prostatic intraepithelial neoplasia underwent prospective cross-sectional research from January 2017 to May 2019. Patient demographics, clinical presentation, diagnostic strategies, reporting norms, and management strategies were all gathered. Prostatic Intraepithelial Neoplasia was determined by histological examination of prostate biopsy tissues.

Results: The 127 patients in the study ranged in age from 50 to 80 years, with an average age of 65. The majority of clinical manifestations were associated with elevated Prostate Specific Antigen levels (87.4%) and abnormal digital rectal test findings. The diagnostic procedures utilized to confirm Prostatic Intraepithelial Neoplasia were targeted biopsy, Magnetic Resonance Imaging, and transrectal ultrasound-guided biopsy.

Conclusion: This study highlights the current approaches for prostatic intraepithelial neoplasia diagnosis and reporting. The methods used by pathologists for reporting varied greatly. Active surveillance is a common therapy strategy for patients with Prostatic Intraepithelial Neoplasia. Uniform standards for the diagnosis, reporting, and therapy of prostatic intraepithelial neoplasia must be established in order to enhance patient outcomes. Additional investigation and reaching an agreement are necessary.

1. Introduction –

Premalignant lesions known as atypical adenomatous hyperplasia and prostate intraepithelial neoplasia were long believed to be the most likely precursors of prostate cancer. (Ayala & Ro, 2007). A premalignant condition known as prostate glandular epithelium aberrant cellular alterations is known as prostate intraepithelial neoplasia. It is regarded as a lesion that occurs before prostate cancer and raises the possibility of invasive carcinoma. (Humphrey, 2003)

Prostate cancer is the leading cause of death and morbidity worldwide. Longer life expectancies and advancements in early detection methods and testing equipment are the main causes of the rising prevalence of prostate cancer. As a result, it is projected that the number of clinically significant prostate cancers will rise throughout the ensuing decades. (Joniau et al., 2005)

Therefore, if one is to prevent an equal increase in mortality owing to prostate cancer, early detection of prostate cancer as well as the identification of any putative precursor lesions, specific histological abnormalities, and associated prognostic indicators are essential. For proper patient management and prompt intervention to stop or identify the progression of prostate cancer, accurate diagnosis and reporting are essential. (Hirachand et al., 2017)

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Prostatic Intraepithelial Neoplasia is currently diagnosed and reported using a multidisciplinary approach that includes clinical assessment, imaging methods, and histological analysis. Imaging tests including transrectal ultrasonography (TRUS) and magnetic resonance imaging (MRI) assist visualize the prostate gland and find problematic areas, while clinical examination aids in identifying related symptoms and risk factors. However, a biopsy-derived sample of prostate tissue is histopathologically examined to determine the precise diagnosis of Prostatic Intraepithelial Neoplasia. (Epstein, 1999)

Therefore, in this era of increasing knowledge about prostatic diseases, both neoplastic and non-neoplastic, it is necessary to periodically analyze the known premalignant lesions and reassess their correlation or influence with benign and malignant prostatic disorders. Prostate Specific Antigen is the most established and well-liked serum test for the early detection and monitoring of prostate cancer patients..

The architectural and cytological characteristics of the biopsy samples are evaluated by pathologists in order to determine the existence and severity of Prostatic Intraepithelial Neoplasia. Prostatic Intraepithelial Neoplasia is divided into low-grade and high-grade patterns by the International Society of Urological Pathology (ISUP), which provides important information regarding the severity and propensity for development to prostate cancer. (Rubin, 2004)

The pathology report is an essential tool for doctors to use in communication since it gives them a thorough explanation of the Prostatic Intraepithelial Neoplasia findings, including its extent and location inside the prostate gland. Clinical decision-making is influenced by these data, including if additional assessment, surveillance, or therapy choices are necessary. To increase the accuracy and reliability of the diagnosis of Prostatic Intraepithelial Neoplasia and patient outcomes, it is imperative to continually improve diagnostic methods and reporting processes. (Amin, 2005, Humphrey, 2003)

Therefore, the objective of the current study is to assess the histomorphological characteristics of prostate lesions, namely Prostatic Intraepithelial Neoplasia. Also assessed will be the value of estimating serum Prostate Specific Antigenlevels in the diagnosis of various prostatic lesions.

2. Materials and Methodolgy -

A prospective cross-sectional study had 127 patients with prostatic lesions. It was conducted at the department of Pathology, Karad Institute of Medical Sciences, over the course of two years, from June 2017 to May 2019.

The inclusion criteria for the study were - All surgical specimens of the prostate from our hospital as well as referrals from other institutions were included in the study. These specimens included transurethral resection of the prostate (TURP) and prostatic biopsies.

Specimens without any clinical information and those whose serum Prostate Specific Antigen levels were unknown were eliminated.

The institutional ethical committee granted the study its ethical approval.

Method of collection of data -

On a predesigned and pretested proforma, the patient's age, comprehensive history, including any complaints and previous examinations, and preoperative serum Prostate Specific Antigen values were all documented.

Quantitative assessment of total serum Prostate Specific Antigen was carried out in the Department of Biochemistry using the Immuno Enzymatic Assay, and Prostate Specific Antigen values of the patients were recorded before the surgical procedure.

Procedure –

COLLECTION OF SPECIMENS AND GROSSING TECHNIQUES

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Prostate biopsy and transurethral resection of prostate (TURP) samples were the two types of histopathological specimens that were received. For 12 to 24 hours, all of the specimens were fixed in 10% formalin. Prostate specimens from transurethral resection were weighed and the full specimen, weighing up to 10 grams, was taken in 4 cassettes.

(A) **(B)**

Figure 1: Gross specimen of TURP(A) and prostatic biopsy (B).

Diagnosed and categorized as inflammatory, Benign Prostatic Hyperplasia, premalignant, and malignant lesions, respectively. In order to diagnose Benign Prostatic Hyperplasia, prostatitis, Prostatic Intraepithelial Neoplasia, and adenocarcinoma, WHO recommendations from 2016 were adhered to. For grading and grading prostatic adenocarcinoma patients, the Gleason's grade and score established by WHO (2016) was used. By combining the dominating pattern with the most frequent pattern, the Gleason score of was created.

Diagnostic criteria used for Prostatic Intraepithelial Neoplasia were

Low degree Prostatic Intraepithelial Neoplasia features include uneven cell spacing, cellular crowding, modest nuclear enlargement, and epithelial proliferation with nuclear stratification.

Epithelial cells with nuclear expansion, hyperchromasia, and the presence of one or more sizable, noticeable nucleoli are considered to have high-grade Prostatic Intraepithelial Neoplasia.

In-depth research was done on each case to determine whether Prostatic Intraepithelial Neoplasia with Benign Prostatic Hyperplasia and prostatic cancer was present.

The sensitivity and specificity of the serum Prostate Specific Antigen assay were evaluated by comparing the histopathological diagnosis with Prostate Specific Antigen levels.

3. Results –

The current study was a two-year prospective study conducted in the Pathology department. 127 cases of prostatic lesions in all, spanning the months of June 2017 and May 2019, were examined.

In the present study, patients ranged in age from 45 to 98 years old, with a mean age of 68.37 years. The age range from 61 to 70 years was the most common, accounting for 62 instances. In our analysis, increased frequency of urination was the most frequent presenting symptom, occurring in 40.2% of patients, while pathological fracture/bone pain only occurred in one case, or 0.7% of cases. Only 9 of the 127 total specimens were prostatic biopsies, and 118 instances were transurethral resections of the prostate.

According to the standards, each rectal examination's findings were categorized into 4 grades. The most frequent finding was grade I prostatomegaly, which occurred in 59 instances. Grade II prostatomegaly occurred in 47 cases. The results of the Ultrasonography and the digital rectal examination

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were compared, as shown in the table.

Table 1: Distribution of prostatic lesions on basis of prostatomegaly

	Prostatomegaly		**Distribution**	
	DRE	**USG**	**Number**	**Percent**
Grade I	3 to 3.8 cms	upto 30 gms	59	46.5
Grade II	3.8 to 4.5 cms	30 to 50 gms	47	37
Grade III	4.5 to 5.5 cms	50 to 80 gms	20	15.7
Grade IV	>5.5 cms	> 80 gms	1	0.8
Total			127	100

In the current study, 127 total cases were obtained, of which 116 cases of Benign Prostatic Hyperplasia, 10 cases of prostate cancer, and 1 biopsy of High grade Prostatic Intraepithelial Neoplasia were histopathologically determined to be true. For Benign Prostatic Hyperplasia cases, the mean Prostate Specific Antigen was 4.46 ng/ml, ranging from 0.01 to 33.13 ng/ml. 50 cases of Benign Prostatic Hyperplasia had normal Prostate Specific Antigen levels, or up to 4 ng/ml, while 66 cases had Prostate Specific Antigen levels above 4 ng/ml.

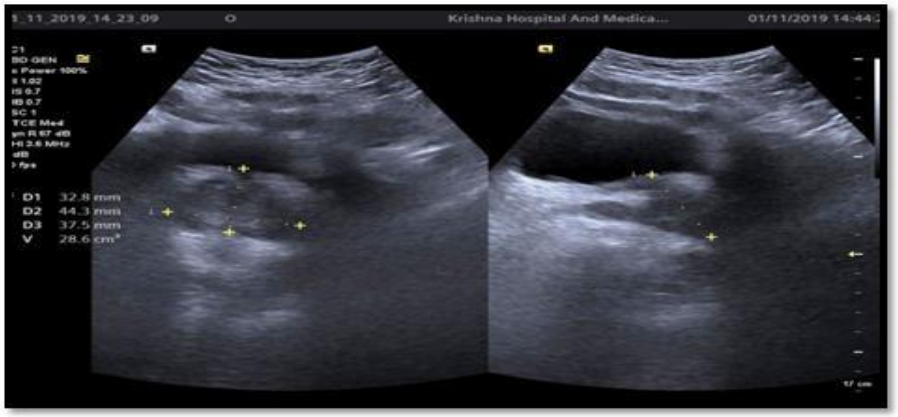

Figure 2: Ultrasonography showing prostatomegaly

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ISSN: 2309-6152 (Online)
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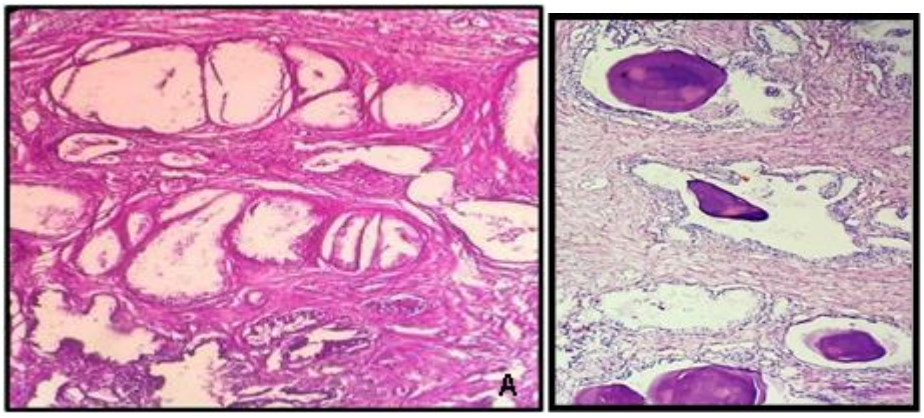

Figure 3: Benign Prostatic Hyperplasia, cystically dilated glands with stromal hyperplasia (A) and showingcorpora amylacea in the lumina(B) (H&E,400X)

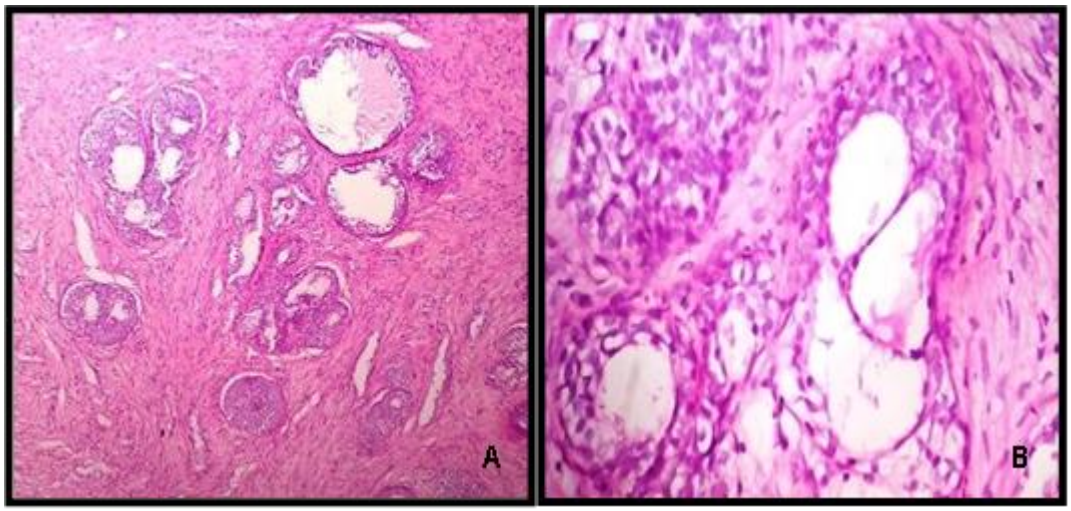

Figure 4 (A&B) : Benign Prostatic Hyperplasia with associated basal cell hyperplasia.(H&E,100X & 400X)

In the current study, 60 patients (47.2%) had Prostatic Intraepithelial Neoplasia found. These Prostatic Intraepithelial Neoplasia cases ranged in age from 50 to 95, with a mean age of 69. These had Prostate Specific Antigen levels ranging from 0.01 to 271 ng/ml. Out of 60 instances, 39 cases of low-grade Prostatic Intraepithelial Neoplasia and 21 cases of high-grade Prostatic Intraepithelial Neoplasia were found.

Out of 60 cases, 50 (83.3%) had Benign Prostatic Hyperplasia as a contributing factor. Age for these ranged from 50 to 85 years, with a mean of 67.5 years; Prostate Specific Antigen levels ranged from 0.0 to 33.1 ng/ml, with a mean of 4.71 ng/ml. Digital rectal examination and Ultrasonography results, which were presented as complaints, matched the clinical presentation of Benign Prostatic Hyperplasia cases.

Tufting was the most frequent pattern among architectural variations, showing up in 8 examples (53.3%), followed by cribriform, flat, and micropapillary pattern.

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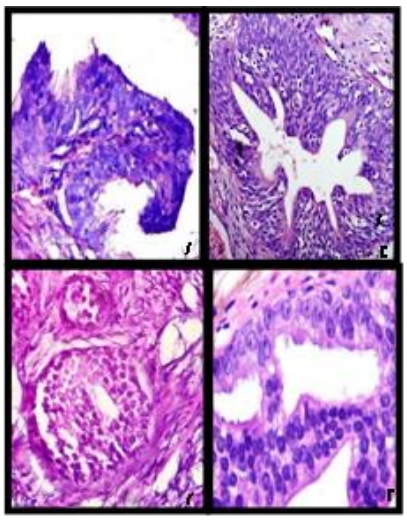

Figure 5: Foci of HGPI A -Micropapillary, B-Tufting,Cribriform, D-Flat patterns of High grade Prostatic Intraepithelial Neoplasia (H&E, 400X)

In our analysis, a total of 10 cases (7.9%) of prostatic cancer were found. Malignant patients ranged in age from 54 to 95, with a mean age of 74.5 years. Incidence of carcinoma peaked in the seventh decade.

90% of the cases of prostate cancer were prostatic adenocarcinomas. The prostate was involved in one case of bladder urothelial cancer. The range of Prostate Specific Antigen levels was large, from 0.59 to 271 ng/ml, with a mean of 132.08 ng/ml. Prostate Specific Antigen values were above 100 ng/ml in 7 instances (or 70%).

The prostate was involved in one case of transitional cell carcinoma of the bladder in a 70-year-old man with a Prostate Specific Antigen level of 3.2 ng/ml.

Four patients (40%) had grade 1 prostatomegaly, five cases (50%) had grade III, and one case (10%) had grade IV prostatomegaly, according to Digital rectal examination and Ultrasonography findings.

According to the prevalent development pattern, the 9 instances of prostatic adenocarcinoma were categorized and evaluated using the Gleason score and Gleason grade group. Out of the nine instances, Gleason scores 7 and 10 were detected in four (44.4%) and two (22.2%), respectively. Scores 6, 8, and 9 were found in one (11.1%) case

Table 2: Grades of prostatomegaly in Benign Prostatic Hyperplasia and malignant prostatic lesions

Prostatomegaly	**Benign Prostatic Hyperplasia**	**Malignancy**	**Total**
Grade I	54 (46.6%)	4 (40%)	58 (46%)
Grade II	47 (40.5%)	0	47 (37.3%)
Grade III	15(12.9%)	5 (50%)	20 (15.9%)
Grade IV	0	1 (10%)	1 (0.8%)
Total	116	10	126

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In terms of mean ages, there was no statistically significant difference between instances of Benign Prostatic Hyperplasia, Prostatic Intraepithelial Neoplasia, and cancer. (p value 0.001). Similar to this, there was no discernible difference between the mean Prostate Specific Antigen values of Prostatic Intraepithelial Neoplasia and Benign Prostatic Hyperplasia cases. However, the p value in cases of prostate cancer was significant (0.001).

The specificity and positive predictive value increased to 100% with the Prostate Specific Antigen cutoff value raised to 50 ng/ml, but the sensitivity remained same in our study.

4. Discussion –

The 127 cases of prostate lesions that were diagnosed in our department between June 2017 and May 2019 made up the subjects of the current study. Prostatic intraepithelial neoplasia, one of many histological abnormalities of the prostate, was the focus of the examination of the specimens.

In our analysis, the 61-70 age group was the most common, followed by 71-80 years. The average age was 68 years. The median age in several previous Indian studies has been found to be consistent with our findings.

Clinical presentation:

In our analysis, frequency was the most prevalent clinical complaint, accounting for 40.2% of patients, similar to findings from studies by Puttaswamy. et al. and Londhe and Shah et al. (Puttaswamy et al., 2016, Londhe & Shah, 2018)

With only 0.8% of instances, bone pain/pathological fracture was the least prevalent.

Both benign and malignant prostatic tumors presented with comparable obstructive urinary symptoms. Our investigation found no differences between the clinical characteristics of prostate cancer cases that were malignant and those that were not; similar findings have been reported in the literature and in studies by Hirachand S. et al. and Kumar R. et al. (Kumar & Ahmad, 2019)

Type of specimen received:

In our study, 127 prostatic specimens, of which 92.9% were Transurethral Resection of Prostate and 7.1% were prostatic biopsies, were received for our investigation. This result was consistent with research conducted by Shah, Puttaswamy, and Vidyasagar M. Salve, among others. (Puttaswamy et al., 2016, Evangalin, 2018, Karki et al., 2019)

Serum Prostate Specific Antigen levels:

All 127 subjects' total serum Prostate Specific Antigen levels were measured before surgery and reported. In our investigation, the Prostate Specific Antigen concentrations ranged from 0.01 ng/ml to 271 ng/ml. 13.5 ng/ml was the overall mean value.

The majority of cases (53.5%) with various prostatic lesions had Prostate Specific Antigen levels within the normal range, while 34.6% had levels between 4 and 10 ng/ml, 6.3% had levels between 10 and 100 ng/ml, and 5.5% had levels above 100 ng/ml.

Both the Mainali N et al. (Mainali et al., 2018) and Alpesh M Maru et al. (Maru et al., 2014) studies revealed elevated Prostate Specific Antigen levels. According to a study by Zivkovic S., patients with Benign Prostatic Hyperplasia, prostatitis, Prostatic Intraepithelial Neoplasia, and cancer may have Prostate Specific Antigen readings between 4 and 10 ng/ml. (Zivkovic, 2004)

Benign Prostatic Hyperplasia:

The most prevalent prostatic lesion detected was Benign Prostatic Hyperplasia, which was similarly noted in other studies by Bhat et al and Banerjee et al. (90,106).

Our study and the reported incidence of Benign Prostatic Hyperplasia in India are both around 92.9%. A similar incidence was also documented by Deshmukh et al in their investigation. In line with findings from earlier studies, in our study was linked to other disorders such squamous metaplasia, basal cell hyperplasia, Benign Prostatic Hyperplasia and cribriform hyperplasia.

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In line with findings from earlier studies, Benign Prostatic Hyperplasia in our study was linked to other disorders such squamous metaplasia, basal cell hyperplasia, and cribriform hyperplasia.

In cases of Benign Prostatic Hyperplasia, low grade Prostatic Intraepithelial Neoplasia was the most frequently seen grade, whereas high grade Prostatic Intraepithelial Neoplasia was more frequently seen in situations of adenocarcinoma. Similar conclusions were made in a study by Muthuvel et al., Rekhi et al., and others. (Rekhi et al., 2004)

Prostate carcinoma:

Similar to the findings of Muthuvel et al., Mittal BV et al., and Yadav et al., 7.8% of the cases in this investigation were identified as malignant. ("Study of Various Histopathological Patterns in Prostate Biopsy," 2017)

Only one incidence of transitional cell carcinoma involving the prostate was recorded, and 90% of all prostatic malignancies were primary prostatic adenocarcinomas.

According to Rajan Shah et al.'s study, (Karki et al., 2019) adenocarcinomas account for more than 95% of instances of prostate cancer. Similar results were found in studies conducted by Bhat et al. and Arya et al. (Bhat et al., 2019)

Prostate adenocarcinoma was observed in men who were ten years older than those with Benign Prostatic Hyperplasia. Other investigations, including those by Jayapradeep and Hirachand et al., reported similar outcomes.

Our study's 74.5-year average patient age for those with adenocarcinoma of the prostate was consistent with studies by Shah et al., Mir A Khan et al. and Kumar et al. (Kumar & Ahmad, 2019, Karki et al., 2019, Jang et al., 2016)

Six of the nine instances (66.6%) in this group exhibited a stronger correlation with High grade Prostatic Intraepithelial Neoplasia. Similar results (61.4%) were found in a study conducted by Horninger W et al.

Studies by Alpesh et al., McGuire BB et al., and Mainali et al., respectively, found that 8%, 17.5%, and 26.6% of prostatic cancer cases had Prostate Specific Antigen levels below 10ng/ml. Additionally, according to research by Thompson et al., prostate cancer can be identified at lower Prostate Specific Antigen levels.

The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) and the European Randomized Study of Screening for Prostate Cancer (ERSPC) reported doubts about the value of Prostate Specific Antigen screening for prostate cancer.

These high-grade low Prostate Specific Antigen tumours actually have a worse prognosis, according to a study by McGuire BB et al. Similarly, one case of prostatic adenocarcinoma with a Gleason grade 4 was found in our Prostatic Intraepithelial Neoplasia investigation.

In our analysis, a 7 was the most frequent Gleason's score. Similar findings were found in investigations conducted by Satyasri K et al and Kusuma et al.

Similar to a study by Londhe et al., our analysis for the Gleason Grade Group indicated that Grades 5 and 2 were identified in equal frequency (33.3%), followed by 1 instance for each of Grade Groups 1, 3, and 4 (11.1%). (Londhe & Shah, 2018)

Sensitivity and specificity of serum PSA:

In our investigation, the Prostate Specific Antigen cutoff of 20 ng/ml had a sensitivity of 77.8% and a specificity of 97.5%. In our analysis, specificity reached 100% with a cut of 50 ng/ml while sensitivity stayed the same.

Similar results were seen in the study by Salve et al., who found that raising the cutoff for Prostate Specific Antigen levels decreased sensitivity while raising specificity (Evangalin, 2018). Udeh et al. also noted a statistical difference between instances of Benign Prostatic Hyperplasia and prostate cancer in the serum Prostate Specific Antigen levels.

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5. Conclusion -

Benign prostatic hyperplasia is the most frequent cause of low grade prostatic intraepithelial neoplasia. High grade prostatic intraepithelial neoplasia is seen to be more frequently associated with adenocarcinoma. Prostatic cancer manifests later in life while benign prostatic hyperplasia and prostatic intraepithelial neoplasia show no discernible difference in age distribution. However, elevated serum Prostate Specific Antigen levels can result from both benign and malignant prostate tumours. Although clinical examination, assessment of preoperative serum Prostate Specific Antigen values, and Ultrasonography are realistic preliminary diagnostic techniques, they cannot provide a conclusive diagnosis of some prostatic abnormalities, particularly prostatic intraepithelial neoplasia. Prostate Specific Antigen 's value in the early identification of prostate cancer is debatable due to its limited sensitivity and specificity. However, with increasing cut off values of serum Prostate Specific Antigen, its specificity increases for detection of prostatic carcinoma.

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