

Clinicopathological View of Prostate Biopsy: A Literature Review.

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Abstracts: The prostate is a wall-nut sized organ in the male located at the neck of the bladder. In the prostate, there are three common group of diseases. They include: inflammatory lesions, benign enlargement, neoplastic lesions/tumour-like lesions. Adenocarcinoma of the prostate is the commonest form of cancer in men.

Prostate biopsy refers to taking of tissue from the prostate gland and examining them under the microscope for the presence of any pathological lesion. Types of prostate biopsy include: Transurethral biopsy, transrectal biopsy and transperitoneal biopsy. The laboratory handling of prostate biopsy depends on the type of biopsy done. Generally, this include – Fixation: To prevent decomposition of the tissue; dehydration: using graded concentration of alcohol; clearing: using xylene; infiltration: using paraffin wax to replace the water that was removed from the tissue; embedding: to orient the tissue properly in paraffin wax; microtomy: involving sectioning of the tissue; staining: using haematoxylin and eosin; mounting: using destyrene, plastisizer, xylene; microscopy: done using a microscope by the pathologist to make a diagnosis of an inflammatory, nodular hyperplasia or neoplastic lesion depending on the microscopic findings. However sometimes ancilliary investigations may need to be done to help the pathologist in arriving at a reasonable conclusion such as immunohistochemistry.

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I. Background

The prostate is a wall-nut sized organ in the male located at the neck of the bladder. The normal gland weighs about 20 g, measuring 4cm x 3cm x 2cm and is enclosed in a fibrous capsule. The prostatic parenchyma can be divided into four biologically and anatomically distinct zones or regions: the peripheral, central, and transitional zones, and the region of the anterior fibromuscular stroma.¹ As men get older, the prostate gland enlarges due to hyperplasia and may become symptomatic in some person resulting in benign prostatic hyperplasia which is the commonest prostatic lesion observed in men.² Adenocarcinoma of the prostate is the commonest form of cancer in men, accounting for 29% of all cancers in the United States in 2007.³ Benign prostatic hyperplasia or fibromuscular hyperplasia is a very common disorder in men over 50 years of age. Galic et al in a study in Croatia in 2008 found that the prevalence of benign prostate hyperplasia was 23.1%, of prostatitis was 5.1% and of prostate cancer 3.7%.⁴

In the prostate, there are three common group of diseases. They include: inflammatory lesions, benign enlargement, neoplastic lesions, tumour-like lesions

II. Prostatitis

Inflammatory lesions of the prostate include:

1. Acute bacterial prostatitis: It is caused by infection by bacteria, usually gram negative rods such as *Escherichia Coli* and *Staphylococcus aureus* following a lower urinary tract obstruction, instrumentation involving the prostate or by seeding through lymphohaematogenous route. The patient may have fever, chills and dysuria. The prostate is usually tender and boggy.
2. Histologically, acute bacterial prostatitis maybe characterised by presence of minute, disseminated abscesses; as large, coalescent focal areas of necrosis; or as diffuse edema, congestion and suppuration of the entire gland may be seen.
3. Chronic bacterial prostatitis: It is caused by similar organism as in acute bacterial prostatitis. They present with dysuria, low back pain and perineal discomfort or could be asymptomatic. The patients often have a history of recurrent urinary tract infections (cystitis, urethritis) caused by the same organism. The prostatic secretion show leukocytosis and positive bacterial culture. The condition is usually difficult to treat.

4. Chronic abacterial prostatitis: This is the commonest inflammatory lesion of the prostate. It has similar clinical findings as in chronic bacterial prostatitis. There is no history of recurrent urinary tract infection, prostate secretion shows leukocytosis and bacterial culture is negative.
5. Granulomatous prostatitis : This is characterised by formation of granulomas in the prostate. It could be specific when the aetiologic agent is known such as *Mycobacterium tuberculosis* and fungi or non-specific when no microbe can be isolated.
6. Autoimmune prostatitis: Histologically typical characterised by a mixed inflammatory infiltrate rich in eosinophils is seen, accompanied by fibrosis and obliterative phlebitis and characterized by elevated serum IgG4 levels.

III. Benign Prostatic Hyperplasia/Nodular Hyperplasia

Benign enlargement of the prostate gland is referred to as benign prostatic hyperplasia or more appropriately as proposed by Moore, nodular hyperplasia. Nodular hyperplasia represents a nodular enlargement of the prostate gland caused by hyperplasia of the stromal and glandular components. Hormonal imbalance, FGF-7 and PDGF play a role in causing the hyperplasia, impaired cell death and accumulation of senescent cells within the gland resulting in the disease. The process of prostatic hyperplasia occurs mostly in men after age 50. The process usually begins at about age 30 years and becomes symptomatic at an older age reaching upto 75% at age greater than 70years.

Clinically, patients present with symptoms of urinary tract irritation and obstruction including frequency, dysuria, urgency, hesitancy and dribbling.

Grossly in nodular hyperplasia the prostate is enlarged and histological sections show proliferation of glands and fibromuscular stroma.

IV. Carcinoma Of The Prostate

Prostatic adenocarcinoma is the commonest internal malignancy in male. It is the second commonest cause of cancer death in males. The risk factors for this condition include age, hormonal imbalance, black race, genetic and hereditary factors. About 75% of men beyond 65years of age would develop prostatic adenocarcinoma. It is considered a disease of men greater than 50years. Genetic mutations involving various genes including androgen receptor gene, ETS, TRPMSS2, PTEN, BRCA1/2, RB, p16/INK4a, MLH1, MSH2, APC, EZH-2 (enhancer of zeste-2), alpha-methylacyl-CoA racemase (AMACR), and *PCA3* gene. Morphologically, in approximately 70% of cases, carcinoma of the prostate arises in the peripheral zone of the gland, usually in a posterior location. It may be palpable on digital rectal examination. The neoplastic tissue is gritty and firm, but when embedded within the prostatic substance it may be extremely difficult to visualize and more readily apparent on palpation.

Histologically, most lesions are adenocarcinomas that produce well-defined, readily demonstrable gland patterns. The glands are typically smaller than benign glands and are lined by a single layer of cuboidal or low columnar epithelium. In more advanced cases the glands are angulated, fused and may be forming sheets. About 80% of cases, prostatic tissue removed for carcinoma harbors precursor lesions, referred to as high-grade prostatic intraepithelial neoplasia (PIN). PIN consists of benign prostatic acini lined by cytologically atypical cells with prominent nucleoli. Prostatic adenocarcinoma is graded using the Gleason's grading system. Grading and staging of prostate cancer aids in prognostication of the disease(see table 1)

Patients with prostate adenocarcinoma usually would have an elevated prostate specific antigen (PSA) level, elevated PSA velocity and PSA density.

There are rare tumour of the prostate which include- ductal adenocarcinoma, adenosquamous carcinoma, squamous carcinoma, colloid adenocarcinoma, mesenchymal tumours and lymphomas.

Tumour like lesions of the prostate include:

- Squamous metaplasia - This may follow hormonal manipulations, transurethral resection or surrounds an area of infarct.
- Basal cell hyperplasia – It is characterised by solid nest of benign looking basal cells and may accompany benign prostatic hyperplasia.
- Postatrophic hyperplasia: Characterised histologically by presence of atrophic glands with large areas composed of fibrous tissue.
- Melanosis of the prostate refers to the presence of elongated cells in the prostatic stroma containing melanin. The histology is similar to that of blue nevus.

Prostate biopsy is the taking of tissue from the prostate gland and examining them under the microscope for the presence of any pathological lesion.⁵

Table1: Showing staging of prostatic adenocarcinoma

The staging of prostate adenocarcinoma can be done using the TNM system as follows:
Staging of Prostatic Adenocarcinoma Using the TNM System

TNM Designation	Anatomic Findings
Extent of Primary Tumor (T)	
T1	CLINICALLY INAPPARENT LESION (BY PALPATION/IMAGING STUDIES)
T1a	Involvement of ≤5% of resected tissue
T1b	Involvement of >5% of resected tissue
T1c	Carcinoma present on needle biopsy (following elevated PSA)
T2	PALPABLE OR VISIBLE CANCER CONFINED TO PROSTATE
T2a	Involvement of ≤5% of one lobe
T2b	Involvement of >5% of one lobe, but unilateral
T2c	Involvement of both lobes
T3	LOCAL EXTRAPROSTATIC EXTENSION
T3a	Extracapsular extension
T3b	Seminal vesical invasion
T4	INVASION OF CONTIGUOUS ORGANS AND/OR SUPPORTING STRUCTURES INCLUDING BLADDER NECK, RECTUM, EXTERNAL SPHINCTER, LEVATOR MUSCLES, OR PELVIC FLOOR
Status of Regional Lymph Nodes (N)	
N0	NO REGIONAL NODAL METASTASES
N1	METASTASIS IN REGIONAL LYMPH NODES
Distant Metastases (M)	
M0	NO DISTANT METASTASES
M1	DISTANT METASTASES PRESENT
M1a	Metastases to distant lymph nodes
M1b	Bone metastases
M1c	Other distant sites

PSA, prostate-specific antigen.

V. Types Of Prostate Biopsy

The transrectal prostate biopsy is guided by the transrectal ultrasound scan through the anus into the rectum guiding the doctor and thus the biopsy gun to the right site for biopsy. It may cause small bleeding from the rectum and blood/urine in the semen. The transrectal route has been used for finger guided prostate biopsy since the mid-1950s. The gold standard of transrectal biopsy is now transrectal ultrasound scan guided biopsy after Hodge et al demonstrated higher detection rates for sextant transrectal biopsy of ultrasound (TRUS)-guided prostate biopsy than for sextant finger-guided analog sampling.^{6,7} The indications for a TRUS include an elevated PSA and abnormal digital rectal examination suggestive of prostate cancer.

5.1 Preparation of patients for transrectal prostate biopsy: Antibiotics prophylaxis is given to patients to reduce the risk of infection, drugs that increase the risk of bleeding such as aspirin are contraindicated. An enema before the biopsy maybe necessary to empty the faeces and gas in the rectum for patients undergoing a transrectal prostate biopsy. The doctor may repeat a biopsy in six months if he believes that the biopsy missed a tumour based on family history, rising PSA density or a findings from a digital rectal

examination.

5.2 Transurethral prostate biopsy is performed using a lighted cystoscope passed through the urethra so that one can look directly at the prostate and collect tissue through a small incision. This prostatectomy procedure is usually performed under local anaesthesia. This procedure is the gold standard for the operative management of benign prostatic hyperplasia.⁸

5.3 Transperineal prostate biopsy involves collection of the prostate tissue through small incision in the perineum. This could be performed under general or local anaesthesia depending on what the patient wants.⁵ Transperineal prostate biopsy is re-emerging after decades of being an underused alternative to transrectal biopsy guided by transrectal ultrasonography (TRUS). The rising incidence of antimicrobial resistance and diabetics who are at high risk of infection favours transperineal biopsy as a sterile alternative to standard TRUS-guided biopsy.⁹

A study done by Efesoy et al show that the complications of transrectal ultrasound scan of the prostate include- haematuria in 66.3% of cases, haematospermia in 38.8% of cases, rectal bleeding in 28.4%, vasovagal episodes in 7.7% and genitourinary tract infection in 6.1%, urosepsis in 0.5%, acute urinary retention in 0.3%, haematuria requiring transfusion in 0.05%, Fournier' gangrene in 0.05% and myocardial infarction in 0.05% of cases.¹⁰ the study by Rassweiler et al show the prevalence of complication from transurethral resection of the prostate (TURP) to be highest in urinary retention(9%), urinary tract infection(8.2%), transfusion rate(7.1%), clot retention(5%) and TUR syndrome.⁸ TUR syndrome caused by dilutional hyponatraemia due to early perforation of capsular veins with consecutive influx of hypotonic irrigating fluid is characterised by mental confusion, nausea, vomiting, hypertension, bradycardia and visual disturbance.¹¹ The study by Webb et al show that patient who had transperineal biopsy had the following complication - haematuria (42%), pain (31%), haemospermia (13%) and less than 1% had septicaemia and acute urinary retention. They concluded that this method was suitable for patients that are susceptible to infective complication.¹²

VI. Adequacy Of Prostate Biopsy

Virtually no data exist as to what constitutes adequate sampling at core needle biopsy.^{13, 14} The needle that is currently being use is the 18 gauge needle. Transrectal Biopsy: An adequate transrectal biopsy is composed of 12-core biopsy referred to as the sextant biopsy. Two core biopsies are collected from the base, middle and apex region of prostate on the left and the right. There may be an extended sextant biopsy with 14-core biopsies. There have been no proven benefit of excessively sampling the prostate which may result in discovery of indolent cancer that would otherwise not have been a health issue for the patient. Transperineal Biopsy: In this biopsy 14-core biopsies is considered adequate. Depending on the approach/technique used, between 12-26 core biopsies or upto 50 core biopsies could be collected.¹³ A study by Emilliozi et al show that if adequately biopsied, there is a higher chance of detecting prostate cancers in biopsies when compared to the traditional TRUS.¹⁵ Different authors have also carried out a scheme with the combination of transrectal and transperineal 6-core prostate biopsy simultaneously. They have shown that the two approaches combined were better than a single approach.^{16,17,18,19} Transurethral Biopsy: The specimen is usually a prostatectomy specimen requiring proper sampling by the pathologist.

VII. Handling Of Prostate Biopsy In The Histopathology Laboratory

Tissue Fixation: The prostate tissue can be adequately fixed using 10% neutral buffered formalin. Bouin's solution could be used to fix core biopsy specimen in order to colour the tiny core biopsy tissue yellow from the picric acid. This enhances visibility of the sample during processing. However in some centres the visibility of the formalin-fixed samples can be enhanced by the introduction of eosin into the sample.

Tissue Processing: Core biopsy specimens are processed as all in one cassette or each core biopsy in separate cassette. The processing involves dehydration using graded concentration of alcohol, clearing with a clearing agent such as xylene or limonene and infiltration using paraffin wax.

Tissue Embedding: The tissue is embedded in paraffin wax

Sectioning: The tissue is sectioned at 2-5 micrometers using a rotary, semi-automated or automated microtome. After which it is put on water in a water bath at 40°C and it is then put on a glass slide coated with albumin.

Staining: The tissue is routinely stained using haematoxylin and eosin stain. Histochemistry could be done depending on what is needed. Phosphotungstic acid haematoxylin and periodic acid Schiff/ mucicarmin could help in identifying skeletal muscle and mucin.

Mounting: The section is mounted using destyrene plasticizer xylene.

Microscopy: This is done by the pathologist with the aid of a microscope as follows

The number of strands is noted and any lesion present in the tissue is noted whether inflammatory, hyperplastic, atrophic or malignant. Prostate cancers are reported using the Gleason's system as stated above.

VIII. Immunohisto chemistry

There are several immunohistochemical antibodies that can be used to detect specific antigen. Immunohistochemistry done for prostate cancer include: Alpha-methylCoA racemase (AMACR) which stains positive for malignant epithelial cell of the prostate gland.

P63, Cytokeratin 34beta E12 and 5/6 are positive for the basal epithelial cells and thus negative for prostate adenocarcinoma neoplastic cells but positive in benign prostate glands containing basal epithelial cells.²⁰

IX. Conclusion

The prostate is an organ that can be affected by a wide variety of lesions especially nodular hyperplasia and adenocarcinoma. The ability of health care givers to recognise and manage these lesions is of immense benefit to the patients.

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