Interpretation Of Prostatic Biopsies: A Review
A Chitale, S Khubchandani

Citation

Abstract
The incidence of prostatic carcinoma is on the rise in the Indian subcontinent. A definitive diagnosis of this disease is obtained on a TRUS guided needle biopsy. Interpretation of these small biopsies therefore plays a vital role in the management and prognosis of the disease. However every investigation has its limitations. This review is intended to convey the complexities of biopsy interpretation with special emphasis on the problems encountered and need for clinicopathological correlation.

INTRODUCTION
Early detection of cancer is an important issue in the field of oncology. The prostate gland is no exception to this rule. The routine screening of the vulnerable elderly male population with the three pronged approach: digital rectal examination, transrectal ultrasound and estimation of PSA in serum has led to marked increase in the frequency of prostatic biopsies. This surveillance has given rise to detection of many patients with small sized cancers, considered ideal for radical prostatectomy. The pathologist is called upon to report on prostatic biopsy and it can pose many pitfalls in the accurate interpretation. Prostatitis, Benign prostatic hyperplasia and carcinoma cover almost the entire spectrum of prostatic diseases. Virtually all problems in the interpretation of prostatic biopsies pertain to an accurate diagnosis and grading of carcinoma of prostate.

NON-NEOPLASTIC LESIONS
In chronic prostatitis, the inflammatory infiltrate may lead to distortion and atypia of the acini and this glandular abnormality may be misinterpreted as adenocarcinoma. Granulomatous Prostatitis is basically a histiocytic response to destruction of the glandular epithelium and consequent release of secretory products in the stroma. It has to be distinguished from tuberculosis. Squamous metaplasia is often seen near an infarct and this change has no precancerous role.

ADENOCARCINOMA
It is mainly the architectural features that help accurate diagnosis of adenocarcinomas, particularly when it is well differentiated (Fig 1). In these cases, the presence of prominent nucleoli is a very dependable diagnostic criterion. One of the most common grading used is based on degree of nuclear anaplasia (nuclear grade 1,2 and 3 ) and glandular differentiation ( well, moderately and poorly differentiated ). The two parameters, individually or combined, have been found to provide a good prognostic index [1] and this system has been approved by the WHO.

GRADING: GLEASON'S SCORE
There are many grading systems, but the one described by Gleason (1974) [2] is currently the most popular the world over. It is based entirely upon the architectural pattern (Figs 2, 3 & 4) and the grading (grades 1 to 5) is irrespective of nuclear anaplasia. The Gleason's Score includes summation of predominant (primary) and second most prevalent (secondary) grades. If there is only a single pattern in all
parts of cancer bearing biopsy tissue the single grade is doubled to arrive at the score. There are, thus 2-10 scores. Scores 2-4 roughly correspond to well differentiated adenocarcinoma, 5-7 to moderately differentiated adenocarcinoma and 8-10 to poorly differentiated adenocarcinoma. Many investigators are convinced that Gleason’s score is the best predictive prognostic indicator of the biological behavior of this cancer. Fifteen year cancer specific mortality rates with Gleason’s score in 767 men aged 55-74 years at diagnosis managed conservatively (no surgery or radiation therapy) were found to be as under [1]:

**Figure 2**
Figure 2: Adenocarcinoma Gleason Grade 3 H & E x100

**Figure 3**
Figure 3: Adenocarcinoma: Gleason Grade 2 (left upper) and Grade 4 (right lower) H & E x 200

**Figure 4**
Figure 4: Adenocarcinoma: Gleason Grade 5

**Figure 5**
Table 1: Correlation of mortality rate with Gleason’s score (in patients treated conservatively)

<table>
<thead>
<tr>
<th>Gleason's score</th>
<th>Mortality rate</th>
</tr>
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<tbody>
<tr>
<td>2-4</td>
<td>4%-7%</td>
</tr>
<tr>
<td>6</td>
<td>6%-11%</td>
</tr>
<tr>
<td>7</td>
<td>8%-30%</td>
</tr>
<tr>
<td>8-10</td>
<td>42%-70%</td>
</tr>
<tr>
<td></td>
<td>60%-87%</td>
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</tbody>
</table>

Patients with small volume cancer of grade 2-4 have a low mortality (4%-7%) and it is up to the clinician whether to offer conservative treatment. It is evident that there is a steep rise in mortality from grade 7 onwards. Lilleby and others [4] analyzed the grades of 178 cases and compared the three-tier system of WHO with three tier clubbed Gleason’s score and the results were as follows:

**Figure 6**
Table 2: Clubbed Gleason’s scores and corresponding WHO grade

<table>
<thead>
<tr>
<th>Gleason's score</th>
<th>WHO grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason 2-6  44</td>
<td>Grade I  44</td>
</tr>
<tr>
<td>Gleason 7  58</td>
<td>Grade II 130</td>
</tr>
<tr>
<td>Gleason 8-10  76</td>
<td>Grade III 4</td>
</tr>
</tbody>
</table>

Gleason’s grading system became more acceptable because the grades can be stratified into 9 categories as against the three categories (grades) used in the WHO and other grading systems. In the table above, it is clear that Grade II in WHO system contains 130 cases, which include moderate
and also high-grade tumours. These authors, divided the Gleason's system into two tiers:

Gleason 2-6 + Gleason 7a (3+4) = 88 cases, favourable group

Gleason 8-10 + Gleason 7b (4+3) = 90 cases, unfavourable group

Gleason score 7a (3+4) has better prognosis that Gleason score 7b (4+3). It was concluded that two tier Gleason system has more discriminating power in predicting prognosis of prostatic adenocarcinomas.

The histology report should comment upon lymphatic invasion. The latter consists of tumor cells within endothelium lined spaces and has been reported in 35% of radical prostatectomies. The presence of lymphatic invasion indicates extra prostatic extension, (62%) and lymph node metastasis in many cases, (67%). Perineural lymphatic invasion (Fig 5) is a mechanism by which the cancer spreads in periprostatic soft tissues. This has been reported in 38% to 93% of cases of radical prostatectomies, [5]. In a few problematic cases, perineural invasion may be the sole diagnostic criteria but unfortunately it is encountered in as low as 4.7% of prostatic biopsies (Table III) [6]. The presence of blue glandular mucin has been described as a useful parameter although some believe that it is a non-specific finding. Crystalloids, sharp needle-like eosinophilic structures and collagenous micronodules are a specific but infrequent finding in prostatic adenocarcinoma. and we have not encountered any case with these morphological features (Table III).

**Figure 7**

Figure 5: Perineural lymphatic invasion: note neoplastic glands encircling the pale staining nerve twig H & E 400

**IMMUNOHISTOCHEMISTRY**

Immunostaining for high molecular weight keratin is very useful in biopsies suspicious of adenocarcinoma. It specifically stains basal cells that are present in normal glands and not seen in carcinoma. In foci suspicious of carcinoma, demonstration of absence of basal cells (Fig 6) by this stain is diagnostic of adenocarcinoma. In 56% of cases of high grade prostatic intraepithelial neoplasm (PIN) the basal layer is only disrupted but not lacking (Fig 7).[5]

**Figure 8**

Figure 6: Small atypical prostatic glands suspicious of adenocarcinoma not stained with high molecular weight keratin, note the dilated large benign gland showing positive staining. Immunoperoxidase staining with Ck12 x 100

**Figure 9**

Figure 7: Two ducts with intraepithelial high grade neoplasia (PIN) exhibit interrupted basal layer positive for high molecular weight keratin Immunoperoxidase staining with Ck12 x 200

Immunostaining for PSA and PAP is helpful to confirm the prostatic origin of a metastatic adenocarcinoma (Fig 8) and to distinguish between transitional cell carcinoma and
prostatic adenocarcinoma in some situations.

**Figure 10**
Figure 8: Metastatic adenocarcinoma in spine stained strongly positive for PSA Immunoperoxidase x200

**PROSTATIC INTRAEPITHELIAL NEOPLASIA**

Prostatic intraepithelial neoplasia (PIN) is a concept borrowed from the well established and universally accepted term cervical intraepithelial neoplasia. PIN is considered to be the most likely precursor of invasive carcinoma. It is characterized by cellular proliferation within preexisting ducts and glands with cytologic atypical changes bordering on carcinoma (Fig 9) [134]. The precancerous changes were described as mild, moderate and severe dysplasia but currently the moderate and severe grades are combined and referred to as high grade PIN. Mild dysplasia (low grade PIN) is considered clinically insignificant because progression to higher grade has not been reported.

**Figure 11**
Figure 9: Intraductal proliferation of carcinomatous cells (PIN) H & E x100

PIN coexists with cancer in more than 85% of cases. High grade PIN in biopsies generally predicts the presence of cancer in subsequent biopsies. If a biopsy reveals only pure PIN then the patient has to be subjected to repeat biopsies and kept under surveillance. PIN is least likely to be encountered in transurethral resections because 86% of PIN occurs in the peripheral zone. However, the mean incidence of finding PIN in needle biopsies is only 5% to 6%.

The precancerous role of PIN is not universally accepted. Harvei et al [8] believe that there is still lack of proof that PIN is a true premalignant lesion. We reviewed 64 cases of prostatic adenocarcinoma on needle biopsy and found PIN in only 7 cases. No instance of PIN was encountered in noncancerous prostatic biopsies.

**SUSPICIOUS BUT NOT DIAGNOSTIC OF CARCINOMA**

In some biopsies, there is a localized proliferation of small acini that is suspicious for carcinoma but falls just below the diagnostic threshold. The reported incidence is 1.5% to 9% of prostatic biopsies in unselected series [9]. The problem is caused by the small size of the focus and may represent a minimal volume prostatic adenocarcinoma, defined as involving less than 5% of the biopsy tissue. Serial sections need to be studied, as some investigators have shown that the diagnostic yield of additional sections revealed definitive carcinoma in 10% to 36% of cases [10].

Iczkowski and others [9] proposed the term atypical small acinar proliferation. All these patients diagnosed as having small acinar proliferation should be subjected to a repeat biopsy. The likelihood of prostatic cancer on subsequent biopsy in cases with initial suspicious lesion varied from 21%-49% [9,11,12,13,14] in different series. Allen et al reported that cancer was identified on re-biopsy at the same sextant site as the initial atypical biopsy in 48%.

**SUPPORTIVE DIAGNOSTIC CRITERIA IN DIFFICULT CASES OF ADENOCARCINOMA**

We reviewed 127 prostatic biopsies carried out at the Jaslok Hospital in the last two years and looked for the supportive criteria reported by Epstein[6]. In 63 cases there was no malignancy in the biopsy. There were 64 cases of adenocarcinoma and the ages ranged from 40 to 85 years, Epstein (1995) reviewed 434 prostatic biopsies referred to him for diagnostic problems [6]. He described many parameters other than architecture and presence of nucleoli, which are helpful for a definitive diagnosis.
LESIONS MIMICKING ADENOCARCINOMA

ADENOSIS (ATYPICAL ADENOMATOUS HYPERPLASIA)

Adenosis or atypical adenomatous hyperplasia is a benign condition superficially resembling carcinoma. It is commonly found in TUR prostate samples and prostatectomies. It is rarely encountered in biopsies, because the lesion typically occurs in the transitional zone.

ATROPHY & POSTATROPHIC HYPERPLASIA

The biopsies may show atrophic glands and the prevalence is 1.8% to 3.6% in some cases, differentiation from an adenocarcinoma may be difficult and staining for high molecular keratin will resolve the issue.

BASAL CELL HYPERPLASIA

Basal cell hyperplasia consists of a proliferation of basal cells in two or more layers near the basement membrane (Fig 10) of the prostate acini. The cells are immunoreactive for high molecular keratin (34BetaE12 keratin) and this will distinguish the lesion from adenocarcinoma. Other conditions with basal cell proliferation include basal cell adenoma and adenoid basal cell carcinoma, both rather rare.

RARE TYPES OF MALIGNANT TUMORS OF PROSTATE

Some rare types of carcinomas detected in the prostate include ductal adenocarcinoma (“endometrioid” carcinoma) mucinous adenocarcinoma and small cell carcinoma. All these are aggressive tumours in comparison to the conventional adenocarcinoma. A few may respond to hormonal manipulation. Transitional cell carcinomas are also seen in prostatic biopsies but often represent an extension of primary in urinary bladder.

SARCOMAS

Sarcoma of prostate is very rare. Sextan et al. reported 21 cases of adult prostate sarcoma and found leiomyosarcoma in 12 and rhabdomyosarcoma in 4. Sarcomas in children are mostly rhabdomyosarcomas. In our series (Table VI) of 7 cases there was one osteosarcoma, an almost anecdotal occurrence.
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Figure 14
Table 4

<table>
<thead>
<tr>
<th>Lesions of the prostate gland (TOTAL 11,390 CASES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Cumulated series from RN Hospital, Jastok Hospital &amp; Bombay Hospital)</td>
</tr>
</tbody>
</table>

| Normal | 424 |
| Prostatic | 150 |
| Tuberculosis | 16 |
| Granulomatous Prostatitis | 22 |
| Adenomatous Hyperplasia (BPH) | 9102 |
| Suspicious of Adenocarcinoma | 26 |
| Atypical Adenomatous Hyperplasia | 6 |
| Adenocarcinoma, (minimal volume) | 40 |
| Adenocarcinoma (W.D) | 128 |
| Adenocarcinoma (M.D) | 631 |
| Adenocarcinoma (P.D) | 746 |
| TOTAL | 1505 |

Table 5: Carcinoma of Prostate in biopsy & TUR

**Rare Type of Carcinomas**
- Mucinous Adenocarcinoma: 4
- "Endometrioid" Adenocarcinoma: 2
- Neuroendocrine Carcinoma: 3
- Transitional cell Carcinoma: 12

**Sarcomas**
- Leiomyosarcoma: 2
- Rhabdomyosarcoma: 2
- Sarcoma [NOS]: 2
- Osteosarcoma: 1

In our series, WHO grading system was employed in cases of prostatic carcinomas as of 1996. Table V gives the incidence of various grades according to gleason's system in both transrectal biopsies and TUR specimens.

Figure 15
Table 5: Carcinoma of Prostate in biopsy & TUR

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>TUR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason's</td>
<td>No</td>
</tr>
<tr>
<td>Well Differentiated</td>
<td>(2-4) 30</td>
</tr>
<tr>
<td>Moderately Differentiated</td>
<td>(5-7) 82</td>
</tr>
<tr>
<td>Poorly Differentiated</td>
<td>(8-10) 58</td>
</tr>
</tbody>
</table>

The role of prostatic needle biopsy in diagnosis, staging and prognosis

**NEGATIVE BIOPSY IN SUSPECTED CASE OF PROSTATIC CARCINOMA**

USG guided sextant biopsy is now a standard procedure in patients suspected to harbor prostatic cancer. However, the clinician is often faced with a problem of negative needle biopsy in patients having persistent elevated PSA or abnormal rectal digital examination. False negative findings occur in 19% to 23% of initial biopsies in patients with abnormal rectal examination and persistent PSA elevation. In one series dealing with this issue, the repeat sextant biopsy was positive in 19% of cases [17]. Seminal vesicle biopsy is reportedly of value in patients with PSA above 15 and or abnormal seminal vesicles seen on USG. Some urologists routinely advocate a seminal vesicle biopsy for a more realistic assessment of extent of prostate cancer. The yield of seminal vesicle biopsy is approximately 15% in patients with biopsy proven clinically localized cancer and 69% in patients with metastases [18].

**INDICATIONS FOR REPEAT BIOPSIES**

1. presence of high grade PIN
2. small atypical acinar proliferation suspicious but not diagnostic of cancer
3. persistent PSA elevation and abnormal findings on rectal examination or TRUS

The interval at which a biopsy should be repeated may be debatable but Epstein and Potter [3] have recommended an interval of 3 months following the first biopsy.

**ACCURATE EVALUATION OF GRADE & PROGNOSIS ON PROSTATE BIOPSY**

There are studies correlating needle biopsy Gleason score with the Gleason score on study of radical prostatectomy specimens [19]. In one large series, Gleason score of 5-6 on biopsy corresponded to the same grade in the radical prostatectomy in only 64% cases and for scores of 7 or greater on biopsy the agreement was in 88% of cases. Thus, adverse findings on biopsy accurately predict adverse findings on radical specimen. However, it is accepted that Gleason's score is a powerful predictor of prognosis and an important part of histopathology report.

**VOLUME OF CANCER IN THE NEEDLE BIOPSY SPECIMEN**

This assessment may be useful to differentiate organ-confined cancer from one, which has extended beyond the prostate. There are four different ways of assessing the volume of cancer: (1) percentage of biopsy cores involved; (2) percentage of cancer area in each biopsy specimen; (3) millimeters of adenocarcinoma in the entire biopsy; (4) millimeters of adenocarcinoma per core. The most commonly used method is to calculate the percentage of cancer area in all biopsy fragments.
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CLINICALLY SIGNIFICANT CANCER

It is known that a small volume (0.5 cc) of low grade cancer found on needle biopsy may have no potential for progression (clinically insignificant). Some urologists believe that no surgical or hormonal treatment is required in these cases and the patients are to be followed with periodic PSA estimation, DRE and TRUS. How does one differentiate this from the clinically significant cancer? It is easy to assess the tumour volume in TUR samples or radical prostatectomies. However, we believe that, the distinction between clinically significant and clinically insignificant cancer cannot be made on mere biopsy study.

ADJUNCTS TO BIOPSY INTERPRETATION

DNA PLOIDY

Patients with diploid tumours have a more favorable outcome compared to patients with aneuploid tumours. Most low stage tumors are diploid and most high stage tumours non-diploid, but exceptions abound.

MOLECULAR MARKERS

The role of p53 marker in predicting the outcome of prostatic adenocarcinoma is not clear and the results so far are contradictory. However, recent work on staining for bcl-2 has shown that mutation of bcl-2 leads to progression of carcinoma from hormone dependent to hormone refractory state. 

ACKNOWLEDGEMENTS

We wish to thank Dr. S.S. Joshi, Consultant Urologist, Jaslok Hospital & Research Centre for his valuable suggestions.

References

6. Epstein JI. Diagnostic criteria of limited adenocarcinoma of the prostate on needle biopsy Hum Pathol 1995 ; 26 :223- 229
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