"A Coin Has Two Sides", The Duality Of Male Pathology

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I am Colombian and speak English with a Spanish accent!
Ultrasound-guided biopsy following a specified grid pattern of biopsies remains the standard of care. This approach misses 21% to 28% of prostate cancers.


**Inflammation / granulomas**

**Benign**
- Adenocarcinoma, radiation, atrophy seminal vesicle

**HGPIN**
- Hyperplasia glands

**Malignant**
- Sarcomas, lymphomas
- Other malignancies
- Basal, Gleason, fat invasion, vascular invasion

Remember Malignant Glands Lack Basal Cells
Atrophy

Acute inflammation

Corpora amylacea (secretions)

Granulomas
coccidiomycosis

Basal cell hyperplasia (BPH)

GMS

Benign Prostatic Lesions

1. Prostate cancer is the most common, noncutaneous cancer in men in the United States.
2. In 2017, approximately 160,000 men will be diagnosed with prostate cancer.


The indolent course of many tumors and the potential for adverse treatment effects have generated controversy regarding the utility of screening and early detection.

The diagnosis of prostate cancer is based on the microscopic evaluation of prostate tissue obtained via needle biopsy.

Prostate Carcinoma

Mimics of Prostate Carcinoma

Atrophy. Benign

Carcinoma with atrophic features

How To Make The Histologic Diagnosis Of Prostate Carcinoma

Carcinoma involving 5% of the biopsy

High power

Prominent nucleoli

The Histologic Features of Prostate Carcinoma

<table>
<thead>
<tr>
<th>Architecture</th>
<th>Small glands</th>
<th>Sometimes large</th>
<th>infiltrating glands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gland Appearance</td>
<td>Round or angulated glands</td>
<td>rigid lumen</td>
<td>blue mucin</td>
</tr>
<tr>
<td>Cytology</td>
<td>Large nuclei and nucleoli</td>
<td></td>
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<tr>
<td>Tumor extension</td>
<td>Invasion perineural, vascular, fat, and other organs</td>
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</table>

Remember in difficult lesions:
1. Levels
2. Immunohistochemical stains (IHC) (judicious application)
3. Consultation (second opinion)

Terminology

1. Gland
2. Lumen
3. Nuclei
4. Nucleoli
5. Stroma
**Prostate Carcinoma**

- Rigid lumen
- Blue mucin
- Malignant gland invading a nerve
- Common finding seen in 11—37% of biopsies

**Nerve**

- Common finding seen 11—37% of biopsies

**Vascular Invasion**

- Prostate Carcinoma
  - Stain: Pin 4 cocktail immunostain
  - Stain: High molecular weight cytokeratin

**Special Stains Are Helpful in a Difficult Diagnosis**

- Stain: High molecular weight cytokeratin
  - Basal cells stain brown, secretory cells and stroma without staining (blue)

**The Precursor: High Grade Intraepithelial Neoplasia (HGPIN)**

- Incidence in biopsies 7%
- Does not raise PSA
- Higher risk for carcinoma if HGPIN involves several cores

- Remember: Carcinoma lacks basal cells and HGPIN has basal cells
  - The cells contain large nuclei with nucleoli similar to carcinoma

- The precursor hinders early detection with traditional prostatic biopsy.
### Reporting Discontinuous Focus of Prostate Carcinoma

- **Discontinuous involvement by prostate carcinoma is common.**
- **Two methods for measuring the discontinuous focus:**
  1. Adding each focus
  2. Assessing discontinuous focus as a single focus

**Reported as % and mm of tumor**

*Report includes a diagram*

*Source: Dr. Ming Zhou, USCAP Conference, San Antonio, March 2017.*

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### The Gleason Grading System: A Practical Approach

The Gleason score assigned to a case of prostate cancer is an important prognostic indicator that guides therapeutic decisions.

- Prostate carcinoma usually has two patterns.

#### Steps:
1. **Confirm the histologic diagnosis of cancer**
2. **Match the pattern(s) with a specific Gleason grade**
3. **Decide which pattern is more common (primary pattern) and the second most common pattern (secondary pattern)**
4. **Add the primary and secondary pattern (Gleason score)**
5. **Assign the Gleason group**

Prostate carcinoma usually has two patterns.

#### Original (initial) by Dr. Gleason

#### Modified 2015

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### Gleason Clinical Significance

- Grade is a strong predictor of aggressiveness and metastatic potential.
- Not reliable when used alone to predict outcome.
- Clinically, needle biopsy Gleason grade is usually combined with other pretreatment factors, such as serum total PSA, % free PSA, local clinical T stage, and amount of tumor in needle biopsy, to predict pathologic stage.

The new grading system is based on the modified (2005 and 2014) Gleason score groups, resulting in 5 prognostically distinct GRADE GROUPS.

<table>
<thead>
<tr>
<th>Grade Group</th>
<th>Possible Gleason grade combinations</th>
<th>Example 1</th>
<th>Example 2</th>
<th>Example 3</th>
<th>Example 4</th>
<th>Example 5</th>
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<tbody>
<tr>
<td>3+3</td>
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New Grading System: Why?
1. Gleason scores 2 to 5 are currently no longer assigned.
2. In practice, the lowest score now assigned is 6. This results in a logical yet incorrect assumption on the part of patients of an expectation that definite treatment is always necessary.
3. Separate 3+4 vs 4+3

Grading Subjectivity
Gleason grading has an inherent level of subjectivity, depending on individual interpretations.

Studies of intraobserver variability demonstrate agreement in up to 78% of cases; therefore, at least 22% of cases may be reread by the same pathologist as a different Gleason score.

Multiple Biopsy Cores With Different Gleason Grade
Assign a composite Gleason to all positive biopsy cores submitted in the same container.

Assign individual Gleason to different cores as long as cores are submitted in separate containers.

Prostatectomy With Multiple Tumor Nodules Showing Different Gleason
1. Always report the dominant nodule.
2. Report the secondary nodule only if it contains a high-grade Gleason grade.

The Stage

Gross bladder neck involvement T4

Microscopic: bladder involvement
Presence of cancer glands within smooth bundles of bladder neck without benign glands
Staged as pT3a no pN0
Staging Radical Prostatectomy (AJCC 8th)

Summary Of Changes Between 7th And 8th AJCC Cancer Staging:

1. Pathologically confined disease is pT2 and no longer subclassified by extent or laterality
2. The Gleason score and grade group are reported
3. Stage III includes select confined disease based on PSA and Gleason group status

Source: http://www.avidphone.com/change‐part‐i/

Bladder neck

Anterior part is rounded

Posterior part is flat

Apex is cone shape

Submit The Entire Gland

Serially section the remaining prostate from apex to base, in 3 mm sections perpendicular to urethral axis. Identify where cancer (firm, yellow, indurated) comes closest to capsule or margins. Submit every other slice in halves, quarters, sixths, or eighths, depending on the size of the cross section. Serially section and submit representative bilateral seminal vesicles and vas deferens.

https://grosspathology.sites.uchicago.edu/page/prostate
Extraprostatic Extension (EPE) (T3)

- Prostate has no true capsule
- At the periphery has a condensed fibromuscular layer
- EPE is defined as cancer beyond confines of prostate gland (at the level or beyond fat)
- Location and extent should be documented (focal and non-focal)

EPE: Prostate tumor in adipose tissue
Positive margin carcinoma at ink margin
Only in prostatectomies

Ink the margins
Different colors

If tumor is not seen in the sections from a prostatectomy, what to do?
1. Don't panic
2. Make sure all tissue is submitted
3. Confirm there is no patient misidentification
1. Perform a single deep H&E recut from each block
2. Cut several levels from the positive area (left lateral apex)
3. Review the initial biopsy

Risk Stratification Schema for Prostate Cancer
National Comprehensive Cancer Network Risk Stratification

- Very low risk
  - Clinical stage of T1c, Gleason score of 6 or less, prostate-specific antigen (PSA) level of less than 10 ng/mL, less than 3 biopsy cores with cancer presence of 50% or less in each core, and PSA density of less than 0.15 ng/mL/g

- Low risk
  - Clinical stage of T1 to T2a, Gleason score of 6 or less, and PSA level of less than 10 ng/mL

- Intermediate risk
  - Clinical stage of T2b to T2c, Gleason score of 7, or PSA level of 10 to 20 ng/mL

- High risk
  - Clinical stage of T3a, Gleason score of 8 to 10, or PSA level greater than 20 ng/mL

- Very high risk
  - Clinical stage of T3b to T4, primary Gleason pattern 5, or greater than 4 biopsy cores with Gleason score of 8 to 10

Prostate Cancer Nomograms
- Calculates probability (0%–100%) of extent of disease, biochemical recurrence, cancer-specific survival based on: age, PSA level, clinical stage, Gleason score, percentage of biopsy cores involved with cancer

Cancer of the Prostate Risk Assessment
- Scoring system from 0 to 10 based on age, PSA level, Gleason pattern 4 or 5, clinical stage, percentage of biopsy cores involved with cancer

- Low risk score:
  - 0–2

- Intermediate risk score:
  - 3–5

- High risk score:
  - 6–10

Pathologic Grading System of the International Society of Urological Pathology
- Groups 1 to 5
Eligible For Active Surveillance (AS)

**VERY LOW RISK**
1. cT1c (non-palpable)
2. Gleason score ≤6
3. Serum PSA <10 ng/ml
4. Fewer than 3 prostate biopsy cores positive, ≤50% cancer in each core

**LOW RISK**
1. cT1 to cT2a
2. Gleason score ≤6
3. Serum PSA <10 ng/ml

A finding of upgrading cancer on repeat biopsy commonly prompts treatment. Beyond grade, other biopsy parameters used to signify progression include an increase in the volume of prostate cancer based on the percentage of involved cores and percentage of involvement within an individual biopsy core.

Most current programs use an increase in Gleason score to 7 or more as one of the criteria to recommend interventional therapy for men on AS.

Reference: Archives of Pathology & Laboratory Medicine 2014 138:10, 1387-1405

Testicular Pathology

Testis Anatomy

Source: Meditation garden.net "Meditation"

Source: StatPearls.com "Testis Anatomy"
Testicular Histology/Adnexal Structures

- Rete testis: epithelium lines spaces that drain through the efferent tubules into the epididymis

- Epididymis

- Vas Deferens

Spermatogenesis

- Spermatogonia
- Secondary spermatocyte
- Primary spermatocyte
- Spermatids
- Sperm cell

Sertoli and Leydig cells

- Sertoli cells
- Leydig cells
- Seminiferous tubules
- Leydig cells (testosterone)
1. The tunica albuginea is the fibrous covering of the testis.
2. The tunica albuginea is covered by the tunica vaginalis.

The testes are wrapped by two sheets:

- Tunica albuginea
- Tunica vaginalis

The Testis is Opened Like a Book

Grossing the Testis

There are two major categories of testicular tumors:

<table>
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<tr>
<th>Germ Cell Derived</th>
<th>Non-Germ Cell Derived</th>
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<td>&gt;95% testicular tumors</td>
<td>2-5% (in adults)</td>
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</table>

- Sex cord-stromal tumors (Sertoli cell tumors, Leydig cell tumors, Granulosa cell tumors [adult and juvenile])
- Ovarian type testicular tumors
- Hemangiomatos
- Hematolymphoid tumors
- Metastatic tumors

Classification of Germ Cell Tumors

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Germ Cell Tumors Derived From Germ Cell Neoplasia In Situ

- Germ cell neoplasia in situ (GCNIS)
- Tumor one histologic type (40%)
  - Seminoma
  - Embryonal carcinoma
  - Yolk sac tumor (YST) postpubertal type
  - Teratoma postpubertal
  - Choriocarcinoma
- Tumors of more than one histologic type (60%)
  - Mixed germ cell tumors
  - Regressed germ cell tumors

Germ Cell Tumors Unrelated to Germ Cell Neoplasia In Situ

- Spermatocytic tumor
- Seminoma prepubertal type
- Teratoma prepubertal
- Choriocarcinoma
- Mixed teratoma and yolk sac tumor prepubertal
- Yolk sac tumor prepubertal

World Health Organization (WHO) Classification of Germ Cell Tumors

The five germ cell tumors to remember:
1. Seminoma
2. Embryonal Carcinoma
3. Yolk Sac Tumor
4. Teratoma
5. Choriocarcinoma

Epidemiology of Germ Cell Tumors

1. 1% of male carcinomas worldwide
2. Most common cancer for white males between puberty and 40s in industrialized nations
3. USA: incidence 6/100,000 (whites), 1.2/100,000 (blacks)
4. The incidence has increased in the last 40 years worldwide

Risk Factors

1. Family history
2. Previous Germ cell tumor
3. Undescended testis
4. Occupational (pesticides)
5. Marijuana use (frequent)

CONCLUSIONS:

The strongest association was found for non-seminoma development— for example, those using cannabis on at least a weekly basis had two and a half times greater odds of developing a non-seminoma.

Reference:
Gurney et al. BMC Cancer 2015, 15
Facts to know:
1. Precursor to all germ cell tumors (exception spermatocytic seminoma and prepubertal teratoma)
2. Present in most germ cell tumors
3. Progression to invasive disease is 5 years (?)

References:

Germ Cell Neoplasia In Situ (GCNIS)
The tubules contain abnormal cells replacing the normal cells.

Facts to know:
1. 70% of germ cell tumors
2. Most common combination: embryonal carcinoma with teratoma, seminoma and yolk sac tumor
3. Any combination can be seen
4. Average presentation is 30 years old
5. Percentages of different elements in mixed germ cell tumors should be reported

Teratoma
Yolk sac tumor
Embryonal

One Histologic type (Pure)
1. Seminoma
2. Embryonal carcinoma
3. Yolk sac tumor
4. Teratoma
5. Choriocarcinoma

Source: PubMed

Seminoma
- Most common pure tumor is seminoma
- Occasionally embryonal carcinoma
- Pure postpubertal yolk sac very rare (0.6%)

Facts to know:
1. Makes 40% of all germ cell tumors
2. Presents in the 4th decade
3. 10‐20% contain syncytiotrophoblast with mild elevation of serum HCG
4. NO AFP production

Seminoma with syncytiotrophoblast that produces HCG

Pure Tumors
1. Seminoma
2. Embryonal carcinoma
3. Yolk sac tumor
4. Teratoma

Facts to know:
1. Makes 40% of all germ cell tumors
2. Presents in the 4th decade
3. 10‐20% contain syncytiotrophoblast with mild elevation of serum HCG
4. NO AFP production
2. Embryonal Carcinoma

**FACTS TO REMEMBER**

1. Age: 20s-30s
2. Rare as a pure tumor; frequently mixed with other GCT's (40%)
3. Poorly demarcated, variegated with areas of hemorrhage
4. Cells are large and hyperchromatic
5. More aggressive than seminoma (10% patients present with metastatic disease)
6. Retroperitoneal LN involvement is common.

3. Yolk Sac Tumor

**FACTS TO REMEMBER**

1. Most common testicular tumor of infants and children (up to 3 years)
2. In children has a good prognosis
3. Pediatric are predominantly pure
4. In adults the pure form is rare and is frequently seen mixed with embryonal carcinoma
5. Alpha Fetoprotein elevated

4. Teratoma

**FACTS TO REMEMBER**

1. Contain elements derived from different embryologic origins
2. This means it can make any tissue found in the human body (cartilage, epithelium, fat, bone, neural elements)
3. Well differentiated, are referred to as mature
4. Incompletely differentiated (fetal tissues) are referred to as immature
5. Prepubertal: always benign, pure not associated with GCNIS
6. Postpubertal: always mixed, malignant and associated with GCNIS

5. Choriocarcinoma

**FACTS TO REMEMBER**

1. Most aggressive germ cell tumor
2. Early metastases, many to the brain
3. Elevated HCG (no AFP)
4. Pure is rare, seen in mixed tumors
5. Has two types of cells: syncytiotrophoblasts and cytotrophoblasts
6. Hemorrhage background

Regressed tumor "burn out"

**FACTS TO REMEMBER**

1. Germ cell tumors that have undergone partial or complete regression leaving behind a nodular focus of scar
2. Less than 5% undergo regression
3. Presentative manifestations or pain
4. Histology: fibrotic nodule, calcifications
5. Most important differential is non neoplastic scar
6. Detection of GCNIS is crucial for the diagnosis
7. Present as high stage tumors
Artifacts that can alter the staging of testicular tumors

True pT2

- The assessment of vascular invasion is often difficult. The problem is not whether the tumor is in a vessel, but whether it is an artifactually displaced tumor or genuine.

False pT2

1. Tumor in external surface of the tunica vaginalis (False positive margin, pT2?)
2. Due to dull blade and excessive force during grossing

References

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