Prostate cancer pathology—
diagnosis and prognosis

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Prostate cancer (acinar adenocarcinoma)

- Invasive carcinoma composed of neoplastic epithelial cells with secretory differentiation, arranged in a variety of histomorphological patterns, including glands, cords, single cells, sheets.
- Basal cells are absent.
WHO Classification of Tumours of the Urinary System and Male Genital Organs

Edited by Holger Moch, Peter A. Humphrey, Thomas M. Ulbright, Victor E. Reuter

2016
### WHO classification of tumours of the prostate

<table>
<thead>
<tr>
<th>Epithelial Tumours</th>
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</thead>
<tbody>
<tr>
<td>Glandular neoplasms</td>
<td></td>
</tr>
<tr>
<td>Acinar adenocarcinoma</td>
<td>8140/3</td>
</tr>
<tr>
<td>Atrophic pseudohyperplastic</td>
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<tr>
<td>Microcystic</td>
<td>8490/3</td>
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<tr>
<td>Foamy gland</td>
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<tr>
<td>Mucinous (colloid)</td>
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<td>Signet ring</td>
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<tr>
<td>Pleomorphic giant cell adenocarcinoma</td>
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<tr>
<td>Prostatic intraepithelial neoplasia (PIN), high grade</td>
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<tr>
<td>Intraductal carcinoma NOS</td>
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<tr>
<td>Ductal adenocarcinoma</td>
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<tr>
<td>Cillitum</td>
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<tr>
<td>Papillary</td>
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<tr>
<td>Solid</td>
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<tr>
<td>Urothelial carcinoma</td>
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<tr>
<td>Squamous cell carcinoma</td>
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<tr>
<td>Basal cell carcinoma of the prostate</td>
<td>8147/3</td>
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<table>
<thead>
<tr>
<th>Neuroendocrine tumours</th>
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<tbody>
<tr>
<td>Adenocarcinoma with neuroendocrine differentiation</td>
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<tr>
<td>Well differentiated neuroendocrine tumour</td>
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<tr>
<td>Small cell neuroendocrine carcinoma</td>
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<td>Large cell neuroendocrine carcinoma</td>
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<table>
<thead>
<tr>
<th>Mesenchymal Tumours</th>
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<tbody>
<tr>
<td>Stromal tumour of uncertain malignant potential</td>
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<tr>
<td>Stromal sarcoma</td>
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<tr>
<td>Leiomyosarcoma</td>
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<tr>
<td>Rhabdomyosarcoma</td>
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<td>Leiomyoma</td>
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<tr>
<td>Angiosarcoma</td>
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<tr>
<td>Synovial sarcoma</td>
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<tr>
<td>Inflammatory myofibroblastic tumour</td>
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<tr>
<td>Osteosarcoma</td>
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<td>Undifferentiated pleomorphic sarcoma</td>
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<tr>
<td>Haemangioendothelioma</td>
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<td>Granular cell tumour</td>
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<table>
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<th>Haematolymphoid tumours</th>
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<tbody>
<tr>
<td>Diffuse large B-cell lymphoma</td>
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<tr>
<td>Chronic lymphocytic leukaemia / small lymphocytic lymphoma</td>
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<tr>
<td>Follicular lymphoma</td>
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<td>Mantle cell lymphoma</td>
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<tr>
<td>Acute myeloid leukaemia</td>
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<td>B lymphoblastic leukaemia / lymphoma</td>
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<tr>
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<td>Nephroblastoma</td>
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<td>Clear cell adenocarcinoma</td>
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<tr>
<td>Melanoma</td>
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<tr>
<td>Parangangioma</td>
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<tr>
<td>Neuroblastoma</td>
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#### Metastatic Tumours

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<th>Tumours of the seminal vesicles</th>
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<td>Leiomyoma</td>
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<tr>
<td>Schwannoma</td>
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<td>Malignant-type myofibroblastoma</td>
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<td>Gastrointestinal stromal tumour, NOS</td>
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<tr>
<td>Seminoma</td>
<td>9061/3</td>
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<td>Well differentiated neuroendocrine tumour / Carcinoid tumour</td>
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<tr>
<td>Lymphoma</td>
<td>9958/3</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>9364/3</td>
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#### Metastatic Tumours

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O-3) [9734]. Behaviour is coded 0 for benign tumours; 1 for well-differentiated, borderline, or uncertain behaviour; 2 for carcinoma in situ; and grade 3 for malignant neoplasms. All or grade 3. The classification is modified from the previous WHO classification [7564], taking this account changes in our understanding of these lesions.

* These new codes were approved by the IARC/WHO Committee for ICD-O.
Acinar adenocarcinoma
Scope

- Prostate cancer ~
  - Histopathology
  - Grading
- Diagnosis and prognosis ~
  - Core biopsies
  - Transurethral resections
  - Radical prostatectomies
Prostate

Benign acini

Acinar adenocarcinoma

Malignant acini
Prostate Cancer: Gleason grade

- Developed by Dr Donald Gleason in 1966-1974
- Based on glandular pattern of tumour identified at low magnification (*architecture*)
- Sum of the 2 most common grade patterns
Prostate Cancer:  
Gleason grade

- In tumours with 2 distinct histologic patterns, number of observed deaths fell between that expected based on the primary (most common) & that of the secondary (2nd most common) patterns.
- Combined Gleason grade = Gleason score (sum).
- Primary Gleason pattern + secondary Gleason pattern = Gleason score.
Prostate Cancer: Gleason grade

- Gleason score of 2 to 4: low grade.
- Gleason score of 5 to 7*: intermediate grade.
- Gleason score of 8 to 10: high grade.

* Gleason score 7 tumours more aggressive than Gleason 5 to 6.
Convened because:

- Evolution of medical practice and changes in diagnosis of prostate cancer since 1966.
  - Advent of prostate cancer screening.
  - Availability of serum PSA.
  - Use of thin biopsy needles, allowing wider sampling of the prostate.
  - Increasing numbers of radical prostatectomies.
  - Application of immunohistochemistry.
  - Recognition of variants of prostate cancer.
Further modification of Gleason system ~

- Deficiencies in the original Gleason system have impacted on patient care.
- Gleason score 7 can be derived from Gleason 3+4 or Gleason 4+3.
- Lowest combined grade assigned is 6 on a scale of 2 to 10, leading to patients incorrectly assuming that they have a more aggressive cancer when they have good prognostic disease.
Prostate Cancer: Grade groups

- **Grade group 1** ~ Gleason score ≤ 6
  Only individual discrete well formed glands.

- **Grade group 2** ~ Gleason score 3+4=7
  Predominantly well-formed glands with lesser component of poorly formed/fused/cribriform glands.

- **Grade group 3** ~ Gleason score 4+3=7
  Predominantly poorly formed/fused/cribriform glands with lesser component of well-formed glands.

- **Grade group 4** ~ Gleason score 4+4=8; 3+5=8; 5+3=8
  Poorly formed/fused/cribriform glands.
  Predominantly well-formed glands and lesser component lacking glands.
  Predominantly lacking glands and lesser component of well-formed glands.

- **Grade group 5** ~ Gleason scores 9-10
  Lack gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands.
Core biopsy

Radical prostatectomy
Prostate cancer: Adenocarcinoma variants

- Prostatic duct adenocarcinoma
  - Periurethral prostatic ducts, exophytic lesion into urethra, around verumontanum
  - Aggressive, less responsive to hormones
- Mucinous adenocarcinoma
  - Aggressive, bone metastases, advanced disease
- Neuroendocrine differentiation
  - Small cell carcinoma: aggressive
Prostate cancer: Adenocarcinoma variants

- Signet ring adenocarcinoma
- Pseudohyperplastic adenocarcinoma
- Atrophic adenocarcinoma
- Foamy gland adenocarcinoma
Pathologic evaluation of prostate cancer

• Types of prostatic surgical/biopsy specimens:
  – Needle biopsies (TRUS, transperineal).
  – Transurethral resection (TURP).
  – Radical prostatectomy.
Prostate Needle Biopsy:
10 core method, labelled cores
Prostate Needle Biopsy: Core Localisation
Pathologic handling of prostatic needle biopsies

• Location of positive biopsy cores:
  – Predictive of adverse findings at radical prostatectomy.
  – Cancer in multiple biopsy cores predicts multifocal cancer.
Pathologic handling of prostatic needle biopsies

• Location of biopsy cores:
  – Rebiopsy techniques following a diagnosis of atypical glands suspicious for cancer.
  – Increased number of rebiopsy cores from the original and adjacent sites of initial atypical biopsy.
  – Cancer found on rebiopsy in the same site as the initial atypical biopsy in 48% of men (Allen et al. Urology 1998;52:803-807).
1st biopsy

Atypical glands suspicious of cancer in core 9

Repeat biopsy

Cancer in core 10

34βE12
Pathognomonic features of prostatic adenocarcinoma

- Perineural invasion
- Mucinous fibroplasia (collagenous micronodules)
- Glomerulation
Infiltrative architecture
Prominent nucleoli
Luminal crystalloid
Luminal mucin
Luminal eosinophilic secretions
Constellation of histologic features of prostatic adenocarcinoma
Prostate needle biopsies: diagnosis of limited cancer

Use of immunohistochemistry

- High molecular weight cytokeratin
  - 34βE12.
  - Expressed by basal cells in benign glands.
  - Basal cells are absent in prostatic acinar adenocarcinoma.
- p63
  - Nuclear protein encoded by 3q27-29.
  - Regulates growth & development of epithelium of skin, cervix, breast & urogenital tract.
  - Expressed by prostatic basal cells.
- Other basal cell markers
  - CK5/6, CK14.
Basal cells in benign glands:

High molecular weight keratin, 34βE12
Basal cells in benign glands:
p63 immunohistochemistry

H/E  p63
Prostate needle biopsies: *diagnosis of limited cancer*

- **α-methyl-CoA Racemase (AMACR)**
  - Cytoplasmic protein also known as P504S
  - Overexpressed in prostatic adenocarcinoma.
  - > 80% of prostatic adenocarcinomas labelled with antibody against racemase.
  - Not specific, found in:
    - Nodular hyperplasia (12%).
    - Atrophic glands.
    - High grade PIN (>90%).
    - Adenosis.
  - Confirmatory immunostain for prostate cancer in conjunction with light microscopy and basal cell marker.
Prostate needle biopsies: *histologic parameters of importance*

- **Gleason score.**
- **Tumour quantum:**
  - No. of positive cores.
  - Total mm among all cores.
  - %age of each core with cancer.
  - Total % of cancer in entire specimen.
  - Fraction of positive cores.
- **Perineural invasion:**
  - Correlation with extraprostatic extension on RP.
  - Higher incidence of disease progression following RT and RP.
- **Extraprostatic extension**
Prostate needle biopsies:

**grading of cancer**

- **Gleason score 2 to 4?**

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Gleason Score 2–4 Adenocarcinoma of the Prostate on Needle Biopsy

A Diagnosis That Should Not Be Made

*(Am J Surg Pathol 2000; 24: 477-8)*

Jonathan I. Epstein, M.D.
Transurethral resection of prostate

- Incidental discovery of prostate cancer in 8% to 10% cases.
- Transition zone or large peripheral zone cancers.
- Sampling of transurethral resection specimens:
  - Initial random submission of tissue in 8 cassettes:
    - Identifies almost all T1b cancers & about 90% of T1a cancers.
    - Submission of all tissue in younger men (<65 yrs).
    - Remaining tissue submitted if T1a cancer found in the initial 8 cassettes.
Transurethral resection of prostate

- **T1a cancer in younger men:**
  - increased progression risk with long-term follow-up.
  - definitive therapy an option.

- **Submission of remaining tissue if T1a cancer found:**
  - potential of upstaging based on high-grade cancer being found in the additionally submitted tissue.

• **T1a:**
  - tumour occupies \( \leq 5\% \) of the specimen
  - Gleason sum < 7

• **T1b:**
  - higher volume OR
  - higher grade tumour
Radical Prostatectomy

• Complete vs partial sampling:
  – 12% pathologists sample entire prostate gland.
• Whole mount vs routine sections.
• Sections required:
  – Apex (distal margin)
  – Base (proximal margin)
  – Seminal vesicles (base)
  – Vas deferens
  – Rest of prostate gland
Handling of prostatic surgical specimens:
Radical Prostatectomy

• Whole mount sections:
  – Ease of mapping of cancer foci.
  – Aesthetically pleasing.
  – Suitable for teaching and publications.
  – Correlation with imaging techniques.
  – Disadvantages:
    • Thick sections
    • Technically demanding
    • Storage problems
Radical prostatectomy: whole mount sections with cancer foci mapping
Radical Prostatectomy

• Detailed mapping of prostate cancer foci:
  – Biopsies targeted to areas of highest tumour concentration.
  – Optimise locally directed therapies for prostate cancer.

• Correlation with radiology.
Radical Prostatectomy: 
*Pathologic parameters*

- Gleason score.
- Extraprostatic extension.
- Seminal vesicle invasion.
- Lymph node metastases.
- Surgical margin status.
- Perineural invasion.
- Tumour volume.
- Lymphovascular invasion.
Radical Prostatectomy: 
extraprostatic extension

- Tumour extends beyond the outer condensed smooth muscle of the prostate.
- Focal vs established:
  - Focal: only a few glands outside the prostate.
  - Established: non-focal.
Radical Prostatectomy: *seminal vesicle invasion*

- Cancer invades muscle coat of the seminal vesicle.
- Significant prognostic indicator.
Radical Prostatectomy: *lymph node metastases*

- Uniformly poor prognosis in presence of nodal metastases.
- 1% to 2% of patients undergoing RP.
Radical Prostatectomy: surgical margin status

- Positive surgical margins an important prognostic parameter following surgery.
- Equivocal, focal or extensive.
- Site of positive surgical margin is often the site of EPE.
- Positive surgical margin can result from incision into the gland without EPE.
Positive surgical margins in a radical prostatectomy
Radical Prostatectomy: 
perineural invasion

- Found in 75% to 84% of RP.
- Not independently prognostic.
- Largest diameter of nerve with perineural invasion independently related to an increased likelihood of biochemical failure after RP.

(Maru et al. Hum Pathol 2001; 32: 828-33)
Radical Prostatectomy: *tumour volume*

- Total tumour volume is an important predictor of prognosis.
- Not independently prognostic when adjusted for pathologic stage, grade and surgical margins.
Radical Prostatectomy: lymphovascular invasion

- Important in univariate analysis.
- Independent prognostic utility is questionable.
ISUP consensus conference on handling and staging of radical prostatectomy specimens

• WG1: Specimen handling *(Mod Pathol 2011; 24: 6-15).*
• WG2: T2 substaging and prostate cancer volume *(Mod Pathol 2011; 24: 16-25).*
• WG3: Extraprostatic extension, lymphovascular invasion and locally advanced disease *(Mod Pathol 2011; 24: 26-38).*
• WG4: Seminal vesicles and lymph nodes *(Mod Pathol 2011; 24: 39-47).*
• WG5: Surgical margins *(Mod Pathol 2011; 24: 48-57).*
Prostate Cancer: Pathologic T Stage

T1a : ≤5% TURP
T1b : >5% TURP
T1c : cancer on needle biopsy
T2a : ≤half a lobe
T2b : >half a lobe
T2c : both lobes
T3a : extraprostatic extension
T3b : seminal vesicle invasion
Pathologic evaluation of prostate cancer

• Accurate reporting of pathologic parameters of prognostic importance.
• Familiarity with histologic features of cancer.
• Awareness of pitfalls and benign mimics.
• Use of adjunctive diagnostic tools eg. immunohistochemistry.
Thank you