Prostate cancer ~ diagnosis and impact of pathology on 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.
Prostate cancer

• How do pathologists diagnose prostate cancer?
  – Core biopsy
  – Transurethral resection
  – Radical prostatectomy

• What are important pathological parameters that impact prognosis?
Prostate

Acinar adenocarcinoma

Benign acini

Malignant acini

PZ

CZ

Seminal vesicle

Ejaculatory duct

Proximal urethra

Anterior fibromuscular stroma

Periurethral zone

Distal urethra

p63/34βE12

Basal cells

No basal cells
Diagnosis of prostate cancer

• Architecture, *at low magnification*
  – Defines Gleason grade
• Cytonuclear features, *at high magnification*
• Absence of basal cells, *corroborated using immunohistochemistry*
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.
Gleason Grading System

Gleason 1

Gleason 2

Gleason 3

Gleason 4

Gleason 5
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:
    • 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

Epstein et al

*BJU Int.* 2013 May; 111(5): 753–760.
Gleason grade grouping of prostate cancer is of prognostic value in Asian men

Joe Yeong, Rehena Sultana, Jonathan Teo, Hong Hong Huang, John Yuen, Puay Hoon Tan, Li Yan Khor

J Clin Pathol. 2017 Sep;70(9):745-753.
Cytonuclear features

Prostate cancer

p63/34βE12

Absence of basal cells
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
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).
1\textsuperscript{st} biopsy

Atypical glands suspicious of cancer in core 9

Cancer in core 10

Repeat biopsy

34\textbeta E12
Prostate needle biopsies: histologic parameters of importance

- Gleason score/grade group.
- 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.
- For Gleason score 7, to provide the % Gleason pattern 4.
- Perineural invasion:
  - Correlation with extraprostatic extension on RP.
  - Higher incidence of disease progression following RT and RP.
Prostate needle biopsies: grading of cancer

• **Gleason score 2 to 4?**

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**Editorial**

**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:
  – 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 (grade group).
• Extraprostatic extension.
• Seminal vesicle invasion.
• Lymph node metastases.
• Surgical margin status.
• Perineural invasion.
• Tumour volume.
• Lymphovascular invasion.

Pathologic stage
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.
- Diameter of tumour in node.
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.
- Record length of positive margins – add all the lengths of positive margins.
- Threshold of 3mm to separate focal vs non-focal/extensive involvement of margins.
- Report grade of tumour at margin.
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)

• Not necessary to report its presence.
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.
- Maximal dimension of tumour in the largest tumour slice.
Radical Prostatectomy: lymphovascular invasion

- Important in univariate analysis.
- Independent prognostic utility?
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).*
SUMMARY ~
Pathologic evaluation of prostate cancer

- Accurate reporting of pathologic parameters of importance in different prostate specimens.
- Familiarity with histologic features of cancer.
- Awareness of pitfalls and benign mimics.
- Use of adjunctive diagnostic tools eg. immunohistochemistry.
Thank you!