What is new in Prostate Cancer?

Mahul B. Amin
Professor and Chairman,
Gerwin Endowed Professor for Cancer Research
Department of Pathology & Lab Medicine
Professor, Department of Urology
University of Tennessee Health Science Center,
Memphis, TN
mamain5@uthsc.edu
<table>
<thead>
<tr>
<th>WHATS NEW IN PROSTATE CANCER</th>
<th>IMPLICATIONS FOR PATHOLOGISTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low risk disease</strong></td>
<td><strong>Low risk disease</strong></td>
</tr>
<tr>
<td>- Active Surveillance</td>
<td>- Understand important role of</td>
</tr>
<tr>
<td>- Multiparametric MRI guided</td>
<td>pathologist in P Ca reporting</td>
</tr>
<tr>
<td>biopsies</td>
<td>parameters important for</td>
</tr>
<tr>
<td></td>
<td>treatment stratification</td>
</tr>
<tr>
<td><strong>Intermediate and high risk</strong></td>
<td><strong>Intermediate and high risk</strong></td>
</tr>
<tr>
<td>disease</td>
<td>disease</td>
</tr>
<tr>
<td>- Robotic RP, Focal (non-</td>
<td>- Accurate grading and</td>
</tr>
<tr>
<td>whole gland treatments),</td>
<td>staging</td>
</tr>
<tr>
<td>advances in RT &amp; hormonal</td>
<td>- Understanding treatment</td>
</tr>
<tr>
<td>therapy</td>
<td>effects</td>
</tr>
<tr>
<td><strong>Metastatic Cancer</strong></td>
<td><strong>Metastatic Cancer</strong></td>
</tr>
<tr>
<td>Castrate Resistant Prostate</td>
<td>- Classification of NE PCa</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
</tr>
</tbody>
</table>
WHO (2015) BLUE BOOK COMMITTEE

Diagnosis
Prognosis
Prediction
Prevention

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
Creating the Bridge from a “Population Based” to a More “Personalized” Approach
WHAT'S NEW IN PROSTATE CANCER

PATHOLOGY

Gleason Grading and Prognostic Grade Groups – Implementation - Feb 2017

Intraductal Cancer – WHO 2016

Variants of P Ca – microcystic, PIN-like and aberrant p93 positive - accepted WHO 2016

Classification of P Ca with neuroendocrine differentiation PCF 2014 & WHO 2016 -

Staging of P Ca – Implementation - Jan 2018
TOPIC I

GLEASON GRADING AND PROGNOSTIC GRADE GROUPS
The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

Jonathan I. Epstein, MD,* William C. Allsbrook, Jr, MD,† Mahul B. Amin, MD,‡ and Lars L. Egevad, MD, PhD,§ and the ISUP Grading Committee‖
Impact of 2005 Gleason Consensus conference

Approved that the diagnosis of Gleason pattern 1 and Gleason pattern 2 should almost never be made in needle bxs.

**Impact:** In Gleason’s original data – patterns 2-5 accounted for 28% of cases. Gleasons 2-5 now virtually disappeared from clinical practice, 1.6% in recent biopsy series.
Impact of 2005 Gleason Consensus conference

- Poorly formed glands were classified as Gleason pattern 4
- Stricter definitions for cribriform pattern 3 vs. cribriform pattern 4
- Donald Gleason’s own grading classification: 3.7% (10/270 cases) had primary pattern 4, and (7.4%) (20/270 cases) with a secondary pattern 4
- In 2014, the diagnosis of pattern 4 much more prevalent due to the ISUP
The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

Definition of Grading Patterns and Proposal for a New Grading System

Jonathan I. Epstein, MD,* Lars Egevad, MD, PhD,† Mahul B. Amin, MD,‡ Brett Delahunt, MD,§ John R. Srigley, MD,‖ Peter A. Humphrey, MD, PhD,¶ and and the Grading Committee

Contemporary Gleason Grading of Prostatic Carcinoma

An Update With Discussion on Practical Issues to Implement the 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

Jonathan I. Epstein, MD,* Mahul B. Amin, MD,† Victor E. Reuter, MD,‡ and Peter A. Humphrey, MD, PhD§

**Issues pertaining to implementation in clinical practice**

- reporting of cancer per specimen/cores etc.
- reporting of different foci in RP

Why the Need for Yet Another Consensus Conference in 2014

• Changes in prostate cancer practice has led some clinicians to challenge the existing grading system

• Important for the pathology community to respond

67 pathology experts & 18 clinicians, from 17 different countries participated
Why the Need for Yet Another Consensus Conference in 2014

ISUP wanted to update issues that in since 2005 which were

- Not discussed
- Lacked consensus
- New observations and issues
- New data

Proactive stance:
- AJCC/UICC staging (2016) – implementation 2017
The Diagnosis of “Cancer” Drives Overtreatment

• Fear of death from cancer likely plays some role, and removing the label “cancer” could reduce unnecessary treatment of low grade disease.

• Proposed name: IDLE (indolent lesion of epithelial origin) (Esserman, Lancet Oncol et al., 2013)

“...The problem for the public is you hear the word cancer, and you think you will die unless you get treated. We should reserve this term, ‘cancer,’ for those things that are highly likely to cause a problem.”
“We need a 21st-century definition of cancer instead of a 19th-century definition of cancer, which is what we’ve been using,” said Dr. Otis W. Brawley, CMO for Am Cancer Society.

Gleason 6 is cancer based on

• Morphological features

• Molecular characteristics

• 20% undersampling of higher grade cancer with Gleason 6 on biopsy

• Patients will be lost to follow-up if low grade PCa is called IDLE tumor – designate as cancer & inform urologist to counsel patients accordingly of prognosis.
Reporting of Gleason score Prognostic Grade Groups

- **Gleason score ≤ 6:**
  - Grade Group I
  - Grade Group II

- **Gleason score 3 + 4 = 7**
  - Grade Group III
  - Grade Group IV

- **Gleason score 4 + 3 = 7**
  - Grade Group IV
  - Grade Group V

- **Gleason score 8**
  - Grade Group V

- **Gleason score 9-10**
  - Grade Group V

Gleason scores can be grouped and range from Grade Group I (most favorable) to Grade Group V (least favorable).

INCORPORATION OF PROGNOSTIC GROUPS ENDORSED BY THE ISUP (2105) & WHO (2016)
Probability of recurrence-free progression for different prognostic grade groups

Approx. 20,000 pts treated at 4 institutions

5 yr Biochem Risk free Surv.

- Grade Group 1: 97.5%
- Grade Group 2: 93.1%
- Grade Group 3: 78.1%
- Grade Group 4: 63.3%
- Grade Group 5: 48.9%

Years Since Surgery
Implications of Reporting of Gleason score Prognostic Grade Groups

**Group 1**: lowest grade, possible candidates for active surveillance; 20% cases may have higher unsampled grade; makes distinction between Gleason 2+2, 2+3, 3+3 irrelevant

**Group 2**: Good prognosis, rare metastasis

**Group 3**: Worst prognosis than Group 2

**Group 4**: Not nearly considered high-grade, has significantly better prognosis than Group 5

**Group 5**: Worst prognosis, obviates need to distinguish 4+5, 5+4, 5+5
Contemporary Gleason Grading of Prostatic Carcinoma
An Update With Discussion on Practical Issues to Implement the 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

Jonathan I. Epstein, MD,* Mahul B. Amin, MD,† Victor E. Reuter, MD,‡ and Peter A. Humphrey, MD, PhD§

Issue pertaining to implementation in clinical practice
- reporting of cancer per specimen/cores etc.
- reporting of different foci in RP
- future directions

Approach to application of Gleason Grading

• Gleason grading should be performed first at 4X and 10X magnifications

• If gland fusion or necrosis are suspected – only then go to 20X to confirm

• Do not use 20X & 40X to find poorly formed glands or single cells
GLEASON PATTERN 3

NO MORE:
Cribriform glands
Poorly formed glands & rare single cells

3A SINGLE, SEPARATE, VARYING GLANDS, SCATTERED
3B SINGLE, SEPARATE, VERY SMALL GLANDS, SCATTERED
3C PAPILLARY/CRIBRIFORM MASSES. SMOOTHLY CIRCUMSCRIBED
Gleason grade 3
Case 21

Gleason grade 3
Gleason grade 4; Fused

Gleason Grading in Needle Biopsy

Gleason Grade 4

Gland fusion
Hypernephroid pattern
Irregular cribriform

Poorly formed glands with ill-defined lumina
“POORLY FORMED GLANDS”
Tangential Sectioning: Making a 3D structure 2D

Courtesy of J. McKenney
Gleason grade 4; ill defined
Case 13

Gleason grade 4; ill defined
Case 39

Gleason grade 4; ill-defined

ALL OF THESE ARE NOW GLEASON PATTERN 4
All cribriform glands should be graded as Gleason pattern 4 regardless of morphology.
All glomeruloid glands should be graded as Gleason pattern 4 regardless of morphology.
• Report percent pattern 4 Gleason score 7 in both needle biopsies and radical prostatectomies.
Gleason Grading in Needle Biopsy

Gleason Grade 5

Solid, fused sheets, single cells
Cribriform or papillary with necrosis
Rosette-like structures – Gleason 5
Gleason grade 5
Case 44

Gleason grade 5
GLEASON GRADING OF VARIANTS OF PROSTATE CANCER

- Ductal Ca. - Gleason 4 or 5 (if necrosis)
- Signet ring cell Ca. - Gleason 4 or 5
- Small cell Ca. - do not grade
- Sarcomatoid Ca. - do not grade
GLEASON GRADING OF VARIANTS OF PROSTATE CANCER

NEW

- Mucinous carcinoma behaves more indolently than previously believed – recommendation: subtract the mucin and grade the tumor – not all mucinous carcinomas are Gleason pattern 4

- PIN-like carcinoma is a Gleason pattern 3
GRADE GROUPS IN PROSTATE CANCER

ACCEPTED

- 2016 World Health Organization (WHO) Pathology & Genetics: *Tumours of the Urinary System and Male Genital System*
- College of American Pathologists (CAP) Checklists
- NCCN Guidelines (2017)
TOPIC III

NEWLY DESCRIBED HISTOLOGIC VARIATIONS IN PROSTATE CANCER
DOUBLE-LAYER PATTERN
PIN – LIKE PCa
PIN – LIKE P Ca
PIN – LIKE P Ca
Nodularity with papillary infolding: most often a sign of benignity.
Papillary infoldings

Pseudohyperplastic PCa
Pseudohyperplastic PCa
Cystic Change: most often a sign of benignity
Microcystic PCa

Cystic Change
Am J Surg Pathol
2010: Vol 34
Microcystic PCa
Microcystic Change
Microcystic PCa
Microcystic PCa

HMCK
Abberant expression p63 in Prostate cancer
p63, HMWCK and AMACR cocktail
TOPIC II

• INTRADUCTAL CARCINOMA OF PROSTATE
CONVENTIONAL (MICROACINAR) CARCINOMA
PROSTATIC DUCTAL CARCINOMA

PAPILLARY GROWTH
PROSTATIC DUCTAL CARCINOMA
DUCTAL CANCER OF PROSTATE

HG-PIN

Invasive cancer

Intraductal cancer
Acinar carcinoma (pure or >80%) is most common.

Acinar carcinoma with ductal histology is occasional.

Ductal carcinoma (pure or >80% in RP) is very rare.

most common

occasional

most common histology when ductal pattern is present
Intraductal Carcinoma of the Prostate

- Late event in PCa evolution, with intraductal spread of aggressive PCa and cancerization of preexisting ducts and acini by high-grade PCa.
- In a minority of cases, may be precursor lesion because in approximately 10% of RP cases following a NBx dx of IDC, IDC in the whole prostate gland is found in pure form, without associated invasive carcinoma.
Intraductal Carcinoma of the Prostate

Criteria

- Marked expansile growth of atypical cells
  - Large cribriform/solid architecture
  - Occasionally spans the width of the core

- Lesion within native prostate glands
  - Basal cell layer at least partially preserved
  - Complete or partial involvement of involved glands

- Prominent cytologic atypia, mitoses, comedonecrosis may be present
12 cores, only 1 positive core with 2 atypical
Intraductal Carcinoma of the Prostate

Molecular Aspects

• ERG gene fusion in 58-75% IDC-P; 100% concordance between IDC-P and adjacent PCa
• PTEN (cytoplasmic) loss in 84% IDC-P; 92% concordance between IDC-P and adjacent PCa
• ERG and PTEN IHC may help distinguish IDC-P from its mimics
Atypical large acinar proliferation suspicious for intraductal carcinoma
Atypical large acinar proliferation suspicious for intraductal carcinoma.
Atypical Large Acinar Proliferation, suspicious for IDC:

- **Comment:** Falls short of intraductal carcinoma and exceeds HG-PIN – has strong implications for need to rebiposy
Reporting of Intraductal Carcinoma

**With invasive carcinoma:**
- Invasive acinar adenocarcinoma (+/- IDC)
- Invasive ductal carcinoma (+/- IDC)

**Without invasive carcinoma:**
- Intraductal carcinoma; no evidence of invasive carcinoma (use strict criteria). IDC is not graded
- Atypical large acinar proliferation suspicious for intraductal carcinoma (falls short of diagnostic criteria)
Pure Intraductal Carcinoma - Provide comment:

• The intraductal growth exceeds HGPIN
• There is no diagnostic invasive carcinoma
• Immediate rebiopsy is recommended as in the vast majority of cases, this pattern is seen in invasive cancer and when cancer is present, signifies aggressive tumor
• Some experts in the literature have proposed definitive treatment in the absence of invasive cancer
TOPIC IV

NEUROENDOCRINE CARCINOMA OF PROSTATE
Recent Experiences

Cornell Experience – Molecular

• Beltran et al. *Cancer Discovery* 2011
• 7 NEPC, 30 PCa and 5 benign
  • *Expression: Next-Gen RNA seq*
  • *Copy Number: Affymetrix Oligo Arrays*
• Integrated datasets, screened for targetable molecular lesions
• Aurora Kinase A (AURKA) and n-Myc (MYCN) over-expression and amplification
Increased NE Differentiation: Why are we seeing more of it?

- Patients living longer
- Higher potency antiandrogens
  - Abiraterone
  - Enzalutamide
- Emergence of androgen independent clones of PCa – NE phenotype
- Increased awareness
- Metastatic biopsy protocols

deBono et al. NEJM; Scher et al. NEJM 2012
PCa with neuroendocrine differentiation

- Usual PCa
- Poorly diff PCa with expression of NE markers
- NECa

• How do we characterize lesions along this spectrum
• At what point in this continuum is the NE marker expression clinically significant?
Proposed Morphologic Classification of Prostate Cancer with Neuroendocrine Differentiation

Epstein*, Amin*, Beltran, Lotan Mosquera, Reuter, Robinson, Troncoso, Rubin

* Co-first authors

PCF 2013 Classification for PCa with Neuroendocrine Differentiation

- Usual PCa with Neuroendocrine (NE) Differentiation
- PCa with Paneth Cell NE Differentiation
- Carcinoid Tumor
- Small Cell NE Carcinoma
- Large Cell NE Carcinoma (LCNEC)
- Mixed (Small or Large Cell) NE Carcinoma - Acinar Adenocarcinoma

- PCa with overlap features of small cell and acinar adenocarcinoma – Provisional Category
- Castration resistant PCa with small cell carcinoma-like clinical features – Clinical Category
Usual PCa with NE Differentiation

**Definition:** Morphologically typical, usual acinar or ductal adenocarcinoma of the prostate in which NE differentiation is demonstrated by immunohistochemistry alone.
Usual PCa with Focal Neuroendocrine Differentiation
Usual PCa with NE Differentiation

- **Recommendation:** Since clinical significance is uncertain, it is not recommended to employ IHC stains to detect NED in otherwise typical primary PCa
Adenocarcinoma with Paneth Cell-like NED

**Definition:**
Histologically typical PCa containing varying proportions of cells with prominent eosinophilic cytoplasmic granules on routine light microscopy (Paneth cell-like change) which are NE marker-positive.
Small Cell Carcinoma

- **De novo cases**
  - 50% pure, 50% mixed

- **Metastatic cases**
  - Increasingly detected through biopsy
  - 40-50% of cases have history of usual Pca
  - Interval: 1-300 months, median 25 months
  - Aggressive disease with frequent visceral metastases
  - Rarely associated with paraneoplastic syndromes (ACTH)
Small Cell Carcinoma – Special Studies

- Synaptophysin, chromogranin, CD56: 90%
- PSA, p501S etc. 17-25%
- p63 (24%), HMWCK (35%)
- Cyclin D1 loss
- TTF-1 50%
- ERG Rearrangements
  - RT-PCR or FISH, 50%
Small Cell – “Oat Cell”
Small Cell – “Intermediate”
Large Cell NE Carcinoma

**Definition:** High grade tumor with
- NE architecture (organoid nests, palisading, rosettes, trabeculae, sheets)
- Non-small cell NE carcinoma cytology (prominent nucleoli, vesicular clumpy chromatin and/or large cell size and abundant cytoplasm)
- Expression of at least one neuroendocrine marker (excluding neuron specific enolase)
Large Cell NE Carcinoma

- Largest series by Evans et al. (n=7)
- One de novo
- 6 progression typical PCa following longstanding ADT
- Rapid disease dissemination, mean 7 mo
- Consensus classification recommends strict criteria and requirement of nested architecture and/or peripheral palisading
- Rare diagnosis
- Further study is needed
TOPIC V

STAGING OF PROSTATE
AJCC 8E, IMPLEMENTATION
JAN 1, 2018
Definition of primary tumor

ALL pT2

Change: Pathologically organ-confined disease is considered pT2 and no longer subclassified by extent of involvement or laterality (III)
PROSTATE: SUMMARY OF CHANGES

• Histologic Grade
  – The Gleason score (2014 criteria) and the Grade Group should both be reported (II)

<table>
<thead>
<tr>
<th>Grade Group</th>
<th>Gleason Score</th>
<th>Gleason Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≤6</td>
<td>≤3+3</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>3+4</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>4+3</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>4+4</td>
</tr>
<tr>
<td>5</td>
<td>9 or 10</td>
<td>4+5, 5+4, or 5+5</td>
</tr>
</tbody>
</table>
PROSTATE: SUMMARY OF CANCES

• **AJCC Prognostic Stage Group**
  – Stage III includes select organ-confined tumors based on PSA and Gleason/Grade Group status (II)

<table>
<thead>
<tr>
<th>When T is...</th>
<th>And N is...</th>
<th>And M is...</th>
<th>And PSA is...</th>
<th>And Grade Group is...</th>
<th>Then the stage group is...</th>
</tr>
</thead>
<tbody>
<tr>
<td>cT1a-c</td>
<td>N0</td>
<td>M0</td>
<td>&lt;10</td>
<td>1</td>
<td>I</td>
</tr>
<tr>
<td>pT2</td>
<td>N0</td>
<td>M0</td>
<td>&lt;10</td>
<td>1</td>
<td>I</td>
</tr>
<tr>
<td>cT1a-c</td>
<td>N0</td>
<td>M0</td>
<td>&gt;= 10 &lt;20</td>
<td>1</td>
<td>IIA</td>
</tr>
<tr>
<td>cT2b-c</td>
<td>N0</td>
<td>M0</td>
<td>&lt;20</td>
<td>1</td>
<td>IIA</td>
</tr>
<tr>
<td>T1-2</td>
<td>N0</td>
<td>M0</td>
<td>&lt;20</td>
<td>2</td>
<td>II B</td>
</tr>
<tr>
<td>T1-2</td>
<td>N0</td>
<td>M0</td>
<td>&lt;20</td>
<td>3</td>
<td>IIC</td>
</tr>
<tr>
<td>T1-2</td>
<td>N0</td>
<td>M0</td>
<td>&lt;20</td>
<td>4</td>
<td>IIC</td>
</tr>
<tr>
<td>T1-2</td>
<td>N0</td>
<td>M0</td>
<td>&gt;= 20</td>
<td>1-4</td>
<td>II A</td>
</tr>
<tr>
<td>T3-4</td>
<td>N0</td>
<td>M0</td>
<td>Any</td>
<td>1-4</td>
<td>II B</td>
</tr>
<tr>
<td><strong>Any T</strong></td>
<td>N0</td>
<td>M0</td>
<td>Any</td>
<td>5</td>
<td>III C</td>
</tr>
<tr>
<td><strong>Any T</strong></td>
<td>N1</td>
<td>M0</td>
<td>Any</td>
<td>Any</td>
<td>IVA</td>
</tr>
<tr>
<td><strong>Any T</strong></td>
<td>N0</td>
<td>M1</td>
<td>Any</td>
<td>Any</td>
<td>IV B</td>
</tr>
</tbody>
</table>

• Precedence liver, bone, and gastrointestinal stromal tumors (GIST) (e.g., mitotic rate in GIST, and location/ multifocality in bone and hepatocellular carcinoma)
Thank you!