**2016 WHO CLASSIFICATION OF TUMOURS OF THE PROSTATE**

Peter A. Humphrey, MD, PhD
Yale University School of Medicine
New Haven, CT

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**WHO “BLUE BOOKS” ON PATHOLOGY AND GENETICS**

- Standard classifications worldwide for all malignancies
- Last WHO book on classification of Tumors of the Urinary System and Male Genital Organs published in 2004
- Many evidence-based changes in the 2016 volume

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**WHO Blue Books : History**

- “In 1956 the WHO passed a resolution to explore the possibility that the WHO might organize centers … whose main purpose was to develop histological definitions of cancer types and to facilitate wide adoption of uniform nomenclature.”

2016 WHO CLASSIFICATION OF TUMOURS OF THE PROSTATE

AUTHORS: PROSTATE CHAPTER
- 36 authors from 16 countries

OUTLINE
- New Entity: Intraductal Carcinoma
- New Variants of Acinar Adenocarcinoma of the Prostate
- New Variant of Neuroendocrine Tumors of the Prostate: Large Cell Neuroendocrine Carcinoma
- Immunophenotype of Acinar Adenocarcinoma
- Grading of Adenocarcinoma
- Risk Stratification and Active Surveillance
- Genetic Profile and Molecular Classification
INTRADUCTAL CARCINOMA OF THE PROSTATE

- An intra-acinar and/or intraductal neoplastic proliferation that has some features of high-grade prostatic intraepithelial neoplasia but exhibits much greater architectural and/or cytological atypia.

HISTOLOGICAL FEATURES OF INTRADUCTAL CARCINOMA OF THE PROSTATE

- Malignant cells filling large acini and prostatic ducts, with preservation of basal cells, and either:
  - A solid or dense cribriform pattern or
  - A loose cribriform pattern with either:
    - Marked nuclear atypia (nuclear size 6x normal or larger) or
    - Comedonecrosis

Intraductal Carcinoma of Prostate: Spectrum of Presentation

- A. Loose cribriform
- B. Dense cribriform
- C. Solid
- D. Comedonecrosis
- E.F. Nuclear pleomorphism

GENETIC PROFILE OF INTRADUCTAL CARCINOMA OF THE PROSTATE

- Intraductal carcinoma in most cases represents a late event in prostate cancer evolution.
- Genetically, intraductal carcinoma is different from high grade PIN with greater loss of heterozygosity, including loss of heterozygosity of TP53 and RB1, and with a greater frequency of ERG rearrangement.
- Cytoplasmic PTEN loss is common in intraductal carcinoma, but not high grade PIN.

Proposed Model of Retrograde Glandular Colonization


INTRADUCTAL CARCINOMA OF THE PROSTATE: OUTCOME

- Associated with high-grade and high-volume prostate cancer at radical prostatectomy
- Independent predictor of clinical outcome
- Isolated intraductal carcinoma in prostate needle biopsy: Definitive therapy may be indicated although 10% of patients will have intraductal carcinoma at radical prostatectomy so repeat biopsy is also an option.
VARIANTS OF ACINAR ADENOCARCINOMA OF THE PROSTATE

- Variants of acinar adenocarcinoma of the prostate may be of significance due to difficulty in diagnosis and due to prognostic and/or therapeutic differences compared to usual acinar adenocarcinoma of the prostate.

HISTOLOGICAL VARIANTS OF ACINAR ADENOCARCINOMA

- Atrophic variant
- Pseudohyperplastic variant
- **Microcystic variant: NEW**
- Foamy gland variant
- Mucinous variant
- Signet ring-like variant
- **Pleomorphic giant cell variant: NEW**
- Sarcomatoid variant

ATROPHIC VARIANT

- Malignant glands with cytoplasmic volume loss (WHO 2016 definition)
- May be found sporadically or post-treatment (radiation or hormonal therapy)
- Incidence: 2% of needle core cases and 16% of whole glands
PSEUDOHYPERPLASTIC ADENOCARCINOMA

PSEUDOHYPERPLASTIC ADENOCARCINOMA: PAPILARY PATTERN

NEW: MICROCYSTIC VARIANT OF ACINAR ADENOCARCINOMA

- Cystic change in prostatic adenocarcinoma glands seen in 11% of RP cases; may be confused with cystic change in benign glands, which is common
- Dilated glands 10-fold larger diameter compared to usual small gland adenocarcinoma
MICROCYSTIC ADENOCARCINOMA IN NEEDLE BIOPSY

Foamy gland adenocarcinoma

- First formally described in 1996
- Incidence in needle biopsy: 17% (2% pure)
- Incidence in radical prostatectomy: 15% to 23%

INITIAL DEFINITION: FOAMY GLAND ADENOCARCINOMA

- Infiltrative small acini with characteristic xanthomatous cytoplasm without nuclear enlargement or nucleolar prominence in most cases
- Intraluminal pink secretions in about one-half of cases

Am J Surg Pathol 34:556, 2010

AJSP 20:419, 1996
NUCLEAR ATYPIA IN USUAL ACINAR VERSUS FOAMY GLAND ADENOCARCINOMA

p63 AND AMACR IMMUNOHISTOCHEMISTRY IN DIAGNOSIS OF MINIMAL FOAMY GLAND CARCINOMA

FOAMY GLAND ADENOCARCINOMA, GLEASON GRADE 5 + 5 = SCORE OF 10
UNUSUAL PSEUDO BENIGN VARIANT ADENOCARCINOMAS OF THE PROSTATE

- Diagnose with great caution in pure form in needle biopsy tissue
- Search for continuity with usual adenocarcinoma
- Apply markers: basal cell stains (high molecular weight cytokeratin, p63) and AMACR

NEW: PLEOMORPHIC GIANT CELL ADENOCARCINOMA

- Rare
- Admixed with high Gleason score (9 to 10)
- Some cases emerge after hormonal or radiation treatment of acinar adenocarcinoma
- Outcome poor

NEUROENDOCRINE TUMOR CLASSIFICATION

- Adenocarcinoma with neuroendocrine differentiation
- Well-differentiated neuroendocrine tumour (carcinoid tumor)
- Small cell neuroendocrine carcinoma
- Large cell neuroendocrine carcinoma: NEW
**LARGE CELL NEUROENDOCRINE CARCINOMA OF THE PROSTATE**

- Rare; largest series = 7 cases (Evans AJ, et al. AJSP 30:684, 2006)
- In 6/7 cases there was a history of prior hormonal therapy of adenocarcinoma
- Large cells, low N/C ratio, coarse chromatin, prominent nucleoli, high mitotic activity, necrosis, and immunohistochemical or EM evidence of neuroendocrine differentiation
- Outcome poor, even after chemotherapy: 7 months survival

**IMMUNOPHENOTYPE OF ACINAR ADENOCARCINOMA**

- 2004 Blue Book: Commonly utilized markers in immunohistochemistry:
  - PSA
  - PSAP
  - High molecular weight cytokeratins
  - p63
  - AMACR (P504S)

**IMMUNOPHENOTYPING IN SPECIFIC DIAGNOSTIC SCENARIOS**

- Diagnosis of limited (minimal) adenocarcinoma on needle biopsy
- Poorly-differentiated prostatic adenocarcinoma versus urothelial carcinoma
- High-grade adenocarcinoma of the prostate versus granulomatous prostatitis/xanthoma
- High-grade adenocarcinoma of the prostate versus urinary bladder adenocarcinoma
- Diagnosis of metastatic adenocarcinoma of the prostate
DIAGNOSIS OF LIMITED (MINIMAL) ADENOCARCINOMA ON NEEDLE BIOPSY
- p63
- High molecular weight cytokeratins (using 34betaE12)
- AMACR
- ERG not recommended

ISUP recommendations: AJSP 38: e6, 2014

POORLY-DIFFERENTIATED PROSTATIC ADENOCARCINOMA VERSUS UROTHELIAL CARCINOMA
- ISUP recommendation: PSA and GATA3 (right) to start
- 2nd line urothelial markers: p63 and high molecular weight cytokeratins
- 2nd line prostatic markers: NKX3.1 and prostein (P501S)

Diagnosis of metastatic adenocarcinoma of the prostate
- New prostatic markers since 2004:
  - NKX3.1 (top right) – a homeobox containing transcription factor
  - Prostein (P501S) (below right) – distinctive granular Golgi-type signal
- Can provide added value beyond PSA and PSAP
PROSTATE CANCER GRADING

- Gleason grading system remains the standard approach: Most of the text and all images are devoted to ISUP modified Gleason grading.
- The 2014 ISUP modified system is described (AJSP 40: 244, 2016) and the new 2015 ISUP modified Gleason grading schematic diagram is presented.
- Recommendation: Report % Gleason pattern 4 when the highest grade is Gleason score 7
- Grade groups introduced

EVOLUTION OF GLEASON GRADING

NEW 2015 ISUP MODIFIED GLEASON GRADING DIAGRAM IN WHO 2016
All cribriform adenocarcinomas are high-grade pattern 4
Glomeruloid carcinoma is high-grade pattern 4
Mucinous adenocarcinoma may be 3 or 4
Do not grade intraductal carcinoma
Additional details on morphologies within Gleason patterns

GLEASON GRADE PATTERN 4: ALL CRIBRIFORM GLANDS

CRIBRIFORM ADENOCARCINOMA

Outcome: independently associated with biochemical failure after radical prostatectomy, with metastasis after radical prostatectomy, and with metastasis-free and disease-specific survival.

Mod Pathol 28:457, 2015
GLEASON GRADE PATTERN 4: GLOMERULOID STRUCTURES

In the past: Some have graded as 3. Now: 4 uniformly

GLEASON GRADING OF MUCINOUS ADENOCARCINOMA OF PROSTATE

GLEASON PATTERN ARCHITECTURAL ARRANGEMENTS SPECIFIED

- **Gleason pattern 3**: Discrete, well-formed, variably sized glands
- Variably sized glands include microcystic and pseudohyperplastic glands
- vs. WHO 2004: No cribriform glands
GLEASON PATTERN ARCHITECTURAL ARRANGEMENTS: PATTERN 4

- **Gleason pattern 4:** Cribiform, poorly-formed, fused, or glomeruloid glands
- Poorly-formed glands were not recognized in the WHO 2004 book, but were in the 2005 ISUP paper

Need “cluster of poorly formed glands” to be certain of pattern 4 rather than tangentially sectioned pattern 3

GLEASON PATTERN ARCHITECTURAL ARRANGEMENTS: PATTERN 5

- **Gleason pattern 5:** Sheets, individual cells, cords, linear arrays, and solid nests
- Linear arrays and solid nests not recognized in WHO 2004 blue book or 2005 ISUP paper.

GLEASON GRADING DIAGRAM

WHO 2004 VS. ISUP/WHO 2016
WHO 2016 RECOMMENDATION:
REPORT % GLEASON GRADE PATTERN 4

- Percentage of high-grade pattern 4/5 proposed as a significant prognosticator (JAMA 281;1395, 1999)
- Mainly tested in radical prostatectomy cases
- Not established: increments to use
- Previously viewed as experimental, with optional reporting
- May have implications for active surveillance and radiation therapy

% 4/5 GLEASON GRADE IN RELATION TO FAILURE AFTER SURGERY

JAMA 281:1395, 1999
IMPACT OF % GLEASON PATTERN 4 ON OUTCOME AFTER RADICAL PROSTATECTOMY (n =12, 823)


% GLEASON PATTERN 4 IN NEEDLE BIOPSY TISSUE

- G4% in multivariate analysis was a significant predictor of adverse pathology and time to biochemical recurrence.
- Can improve risk assessment even in 3+4 versus 4+3 subsets of Gleason score 7.

IMPACT OF LOW % GLEASON GRADE 4 IN 3+4 = SCORE OF 7 PROSTATE CANCERS IN NEEDLE BIOPSY

- Several studies suggest no/minimal impact of less than 5% or 10% Gleason grade 4 in 7s:
- Lack of significant risk of adverse pathology among Gleason 7 patients when G4% is 5% or 10%; however it is markedly different when G4% reaches 20% (J Urol Feb 2016)
- 3+3=6 vs. 3+4=7 with 5% or less Gleason grade 4: No difference in pathologic findings in radical prostatectomy tissue (AJSP 38:1096, 2014) and biochemical recurrence (Ann Diagn Pathol 20:48, 2016)
# Prognostic Grade Groups

- **Group I**: Gleason score < 7
- **Group II**: Gleason score 3 + 4 = 7
- **Group III**: Gleason score 4 + 3 = 7
- **Group IV**: Gleason score 8
- **Group V**: Gleason score 9-10


*BJU Int* 111:753-760, 2013

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## Prognostic Grade Groups: Initial Data for Needle Biopsy and Radical Prostatectomy

<table>
<thead>
<tr>
<th>Group</th>
<th>Needle Biopsy</th>
<th>Radical Prostatectomy</th>
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<tbody>
<tr>
<td>I</td>
<td>&lt; 3.5</td>
<td>&lt; 3.5</td>
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<tr>
<td>II</td>
<td>&gt; 3.5</td>
<td>&gt; 3.5</td>
</tr>
<tr>
<td>III</td>
<td>&lt; 4.5</td>
<td>&lt; 4.5</td>
</tr>
<tr>
<td>IV</td>
<td>&gt; 4.5</td>
<td>&gt; 4.5</td>
</tr>
</tbody>
</table>

Surgical risk p = 0.001

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## Outcome for 20,845 Men Based on Grade Groups


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GRADE GROUPS

- “These grade groups should be reported in conjunction with the 2014 WHO/International Society of Urological Pathology (ISUP) modified Gleason scores.”
- Reporting Example: Adenocarcinoma, Gleason grade 3 + 3 = score of 6 (grade group 1)

RISK STRATIFICATION AND ACTIVE SURVEILLANCE FOR ACINAR ADENOCARCINOMA

- The vital importance of risk stratification is highlighted in a section on prognosis and predictive factors.
- Details on pathologic prognostic factors provided for different types of tissue samples – needle biopsy, transurethral resection, and radical prostatectomy tissues

RISK CATEGORIES

- Tables or nomograms that utilize patient age, clinical stage, measures of serum PSA, number of cores with cancer, linear extent of cancer, and Gleason score
- Table in WHO 2016 blue book: National Comprehensive Cancer Network (NCCN) risk groups
NCCN GUIDELINES 2015

NCCN LOW RISK GROUPS

VERY LOW RISK
- cT1c (non-palpable)
- Gleason score ≤ 6
- Serum PSA < 10 ng/ml
- Fewer than 3 prostate biopsy cores positive, less than or equal to 50% cancer in each core

LOW RISK
- cT1 to cT2a
- Gleason score ≤ 6
- PSA < 10 ng/ml

INTERMEDIATE RISK ALLOWED IN SOME ACTIVE SURVEILLANCE COHORTS
- cT2b – cT2c
- Gleason score of 7 (usually 3+4=7)
- PSA 10 -20 ng/ml
**INCLUSION CRITERIA FOR ACTIVE SURVEILLANCE**

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Patients</th>
<th>Clinical stage</th>
<th>PSA</th>
<th>Gleason score</th>
<th>Cancer extent</th>
<th>Other</th>
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<tbody>
<tr>
<td>Cooperberg and Glass 640</td>
<td>≤ T2</td>
<td>≤ 10</td>
<td>≤ 6</td>
<td>≤ 50% any one core</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klotz et al 453</td>
<td>≤ 15</td>
<td>≤ 3+4</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Schulz et al 403</td>
<td>≤ T2a</td>
<td>≤ 15</td>
<td>≤ 50% any one core</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bul et al 2494</td>
<td>≤ T2</td>
<td>≤ 10</td>
<td>≤ 6</td>
<td>≤ 2 cores positive</td>
<td>PSAD ≤ 0.2</td>
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</tr>
<tr>
<td>Patel et al 870</td>
<td>T1c</td>
<td>≤ 6</td>
<td>≤ 2 cores + ≤ 50% cores any core</td>
<td>PSAD ≤ 0.15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Arch Pathol Lab Med 138: 1390, 2014

**GENETIC PROFILE OF PROSTATE CANCER**

- Since 2004 there has been a remarkable expansion of knowledge on the genetics of prostate cancer.
- *ETS* gene fusions and the *TMPRSS2-ERG* fusion described in 2005 (Science 310:644, 2005).
- Next-generation sequencing technologies have revolutionized our understanding of the molecular basis of prostate cancer and its significant genetic heterogeneity.

**ETS Gene Fusions Discovered in 2005 :**

- The most common mutations in both primary and metastatic prostate cancer are fusions of the androgen-regualted promoters with *ERG* and other members of the *ETS* family, particularly *TMPRSS2-ERG*.
The Prostate Cancer Genome Undergoes Frequent Large-scale Genomic Rearrangements Detected by Whole Genome Sequencing

- Median of 90 rearrangements per genome (range 43-213). 7 cases of high-grade prostate cancer characterized. (Nature 470:244, 2011).
- Rearrangements, not single base pair substitutions, as in colon and breast cancer, are dominant.
- Abundant DNA translocations and deletions that arise in a highly interdependent manner = chromoplexy, a process that commonly disrupts cancer genes. (Cell 153:666, 2013).

Landscape of Prostate Cancer Mutations: Rearrangements

Landscape of Prostate Cancer Mutations: Significantly Mutated Genes in Primary Prostate Cancer
Genomic Copy Number Alterations Increase with Gleason Scores

Mutations in Genes in the PI3K/PTEN/AKT and AR Pathways are Common

MUTATIONAL PROFILES: PRIMARY VS. METASTATIC PROSTATE CANCER

TCGA: Cell 16A, 1011, 2015
MOLECULAR CLASSIFICATION OF PROSTATE CANCER

- Major advances have been made in cataloguing the genomic alterations in prostatic carcinoma
- Objective is subclassification of acinar adenocarcinoma
- Not currently used

ONE FUTURE

- Integration of genomic profiles such as whole genome or whole exome or targeted gene sequence data, or epigenetic alterations, or specific RNA expression panels into predictions of prostate cancer outcome and response to treatment
- Structure = histomorphology will remain important as anatomic structure, genomic structure, and functional parameters of prostate cancer are synthesized