WHO'S WHO IN THE NEW WHO CLASSIFICATION OF UROLOGIC CANCER?

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WHO (2015) BLUE BOOK COMMITTEE

Diagnosis, Prognosis, Prediction, Prevention
PROSTATE CANCER

What is new in the WHO 2016:

• Topic 1:
  Grading of prostate tumors
WHO/ISUP 2014 MAJOR RECOMMENDATION

- Report percent pattern 4 Gleason score 7 in both needle biopsies and radical prostatectomies.

All of these are now Gleason pattern 4

All glomeruloid glands should be graded as Gleason pattern 4 regardless of morphology.
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

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

ORIGINAL ARTICLE

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 L. Epstein, MD* Lars Egevad, MD, PhD † Mohar R. Amin, MD ‡ Beat Delahaye, MD ‡ John R. Scardino, MD † Peter A. Humphrey, MD ‡ Am J Surg Pathol 2016
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,† Mahdi R. Amii, 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


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

Reporting of Gleason score Prognostic Grade Groups

<table>
<thead>
<tr>
<th>Gleason score ≤ 6:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade Group I</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gleason score 3 + 4 = 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade Group II</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gleason score 4 + 3 = 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade Group III</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gleason score 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade Group IV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gleason score 9-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade Group V</td>
</tr>
</tbody>
</table>

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


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+3, 5+4, 5+5
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: 76.1%
- Grade Group 4: 63.3%
- Grade Group 5: 48.9%

2005 2014

What is new in the WHO 2016:

- Topic 2: Intraductal cancer
HG-PIN

CONVENTIONAL (MICROACINAR) CARCINOMA

PROSTATIC DUCTAL CARCINOMA
Intraductal Carcinoma of the Prostate

- Late event in P Ca evolution, with intraductal spread of aggressive P Ca and cancerization of preexisting ducts and acini by high-grade P Ca.
- 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
Grading of Intraductal Prostate cancer

Pure Intraductal Carcinoma Should not be Graded
Topic 3: Classification of neuroendocrine differentiation in prostate

What is new in the WHO 2016:

- 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?

**EMERGENCE OF NE PHENOTYPE WITH MOLECULAR CORRELATES**

**Classification of Tumors Along**

<table>
<thead>
<tr>
<th>USUAL PCA</th>
<th>PCA with NED</th>
<th>SMALL CELL CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR++</td>
<td>AR -</td>
<td>AR -</td>
</tr>
<tr>
<td>PSA++</td>
<td>PSA -</td>
<td>PSA -</td>
</tr>
<tr>
<td>REST++</td>
<td>REST low</td>
<td>REST -</td>
</tr>
<tr>
<td>MYC Amplif +/-</td>
<td>MYC Amplif -/+</td>
<td>MYC Amplif -/+</td>
</tr>
<tr>
<td>TMPRSS2 ERG +/-</td>
<td>PTEN Loss -/+</td>
<td>AURKA Amplif +/-</td>
</tr>
<tr>
<td>PTEN Loss +/-</td>
<td>anti-apoptotic factors &amp; neuronal genes</td>
<td>anti-apoptotic factors &amp; neuronal genes</td>
</tr>
</tbody>
</table>

**AR**, **PSA**, **REST**, **MYC Amplification**, **TMPRSS2-ERG**, **PTEN Loss**, **anti-apoptotic factors**, **neuronal genes**
Proposed Morphologic Classification of Prostate Cancer with Neuroendocrine Differentiation

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

*co-first authors

- 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.
Carcinoid Tumor - WDNET

- Definition: A well differentiated NE tumor occurring primarily in the prostate gland, showing the classic morphology of carcinoid tumor at other sites such as the lung, but which is not closely associated with usual prostate carcinoma or which does not arise from the urethra or extend from the bladder.

- In younger patients, screening for stigmata of MEN may be considered.

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)
What is new in the WHO 2016:

• Topic 4:
  Classification of renal tumors

Will be covered tomorrow
What is new in the WHO 2016:

• Topic 5: Grading of renal tumors

GRADING OF RCC (2016)

• WHO/ISUP SYSTEM – modified from Fuhrman system
• To factor in necrosis for clear cell RCC
• Recommended to be used in all types of RCC though not validated beyond clear cell RCC

RCC - FUHRMAN GRADING

1 2

3 4
WHO/ISUP grade 1

Nucleoli are inconspicuous or absent at low and high power.

WHO/ISUP grade 2

Grade 2: nucleoli are clearly visible at high-power magnification but are not prominent.

WHO/ISUP grade 3

Grade 3: nucleoli are prominent and are easily visualized at low-power magnification.
WHO/ISUP grade 4

Grade 4: presence of tumor giant cells and/or marked nuclear pleomorphism; sarcomatoid carcinoma; carcinoma showing rhabdoid differentiation

WHO/ISUP grade 3 with coagulative necrosis

ISUP grade 3 with necrosis
NEW IN BLADDER: WHO 2016

VI. Flat lesions –
- Atypia urothelial proliferation of unknown significance

VII. Classification of variants – large nested, signet ring/plasmacytoid, chordoid

VIII. Urachal carcinoma including low grade cystic tumors

IX. Emerging Molecular subtypes

CLASSIFICATION OF BLADDER EPITHELIAL TUMORS

FLAT LESIONS

PAPILLARY LESIONS

INVERTED LESIONS

INVASIVE LESIONS
THE WHO (2016) / ISUP CLASSIFICATION
OF UROTHELIAL (TRANSITIONAL CELL)
NEOPLASMS OF THE URINARY BLADDER

- Normal
- Urothelial proliferation of uncertain malignant potential
- Flat lesions with atypia
  - Dysplasia
  - CIS (high-grade intraurothelial neoplasia)
Grading of Non-Invasive Urothelial Neoplasms of the Bladder

<table>
<thead>
<tr>
<th>Flat Lesions</th>
<th>Papillary Tumors</th>
<th>Inverted Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Urothelial Papilloma</td>
<td>Inverted Papilloma</td>
</tr>
<tr>
<td>Urothelial Hyperplasia</td>
<td>PUNLMP</td>
<td>Inverted PUNLMP</td>
</tr>
<tr>
<td>Urothelial Dysplasia</td>
<td>Papillary UCa, Low Grade</td>
<td>Inverted Papillary UCa, Low grade</td>
</tr>
<tr>
<td>Urothelial CIS</td>
<td>Papillary UCa, High Grade</td>
<td>Inverted Papillary UCa, High Grade</td>
</tr>
</tbody>
</table>

* PUNLMP: papillary urothelial neoplasm of low malignant potential.
CLASSIFICATION OF BLADDER LESIONS WITH INVERTED GROWTH PATTERN

- Inverted papilloma
- Inverted urothelial neoplasm of LMP
- Inverted urothelial carcinoma, low grade, non-invasive
- Inverted urothelial carcinoma, high grade, non-invasive
- Inverted urothelial carcinoma, high grade, invasive
All invasive urothelial CA is graded as high grade.

Classification of invasive bladder CA:

- Urothelial carcinoma
  - Squamous cell Ca
    - conventional
    - verrucous
    - basaloid
  - Adenocarcinoma
    - mucosal based
    - urachal
- Variants of urothelial Ca
  - nested (incl. large nested)
  - microcystic
  - micropapillary
  - lymphoepithelioma-like
  - sarcomatoid
  - diffuse/plasmacytoid
  - signet ring cell
  - giant cell
  - lipid-rich
  - clear cell
  - undifferentiated
- Neuroendocrine carcinoma
  - Small cell
  - Large cell
  - Well differentiated tumor
  - Paraganglioma

Classification of invasive bladder CA will be covered tomorrow.
PRIMARY ADENOCARCINOMA OF THE BLADDER

Anatomic:
• Urachal
• Bladder mucosa

Histology:
• Adenocarcinoma NOS
• Enteric
• Mucinous
• Signet ring
• Clear cell
• Hepatoid
• Combined (from above)

Rule out:
• Urothelial Ca with glandular features
• Metastasis

Mucosal based

Adenocarcinoma in situ

Urachal
URACHAL CARCINOMA

Clinicopathologic diagnosis

• Criteria:
  • Dome or anterior location
  • Absence of cystitis glandularis or intestinal metaplasia
  • Absence of primary elsewhere
  • Epicenter of mass in bladder wall
Non-invasive and low grade mucinous cystic tumors of urachus

Survival of noninvasive mucinous cystic tumors of urachus

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TESTIS CANCER

What is new in the WHO 2016:

• **Topic 10**: Precursor lesion nomenclature for germ cell tumor of the testis

• **Topic 11**: Revised Classification for germ cell tumors
GERM CELL TUMORS

ITGCN = GCNIS (Germ Cell Neoplasia in Situ)

• ASSOCIATED WITH GCNIS
• NOT ASSOCIATED WITH GCNIS
• ASSOCIATED WITH GCNIS
  - Similar epidemiologic associations
  - Arise from maturation delayed germ cells arising in a damaged testicular milieu: impaired spermatogenesis, tubular shrinkage, peritubular sclerosis, immature Sertoli cells, interstitial widening, hyalinized tubules, and microlithiasis
  - Isochromosome 12 p

HISTOGENESIS

WHO 2015 CLASSIFICATION OF GERM CELL TUMORS OF TESTIS

• ASSOCIATED WITH GCNIS
  - Classic seminoma
  - Pure or Mixed (non-seminomatous) tumor
    - Embryonal carcinoma
    - Yolk sac tumor
    - Choriocarcinoma & other trophoblastic tumors
    - Teratoma, post-pubertal type
    - Mixed – combinations of above incl. Seminoma
REGRESSED GERM CELL TUMOR
(Germ cell tumor of unknown type)

- Spontaneous regression first presents with metastasis
  - Scar – band like or stellate
  - Cysts
  - Calcification

Regression:
Vascularized scar

Regression: Coarse intratubular calcifications
Regression: Lymphoplasmacytic infiltrate & scar

Hyalinized tubules
Intratubular germ cell neoplasia, unclassified

LESSONS FROM REGRESSION: when to look for signs of regression

- Patient presents with widespread metastatic choriocarcinoma
- Patient presents with retroperitoneal GCT
- Patient with unusual tumor in retroperitoneum – Wilms’, PNET
- Orchiectomy in a young patient for pain or non-specific symptoms and scar in first few sections
- Patient with germ cell tumor in spermatic cord but none in testis
- Histology of the primary and mets does not match

METASTATIC GERM CELL TUMOR WITH NEPHROBLASTOMA (WILMS-LIKE TUMOR)
METASTATIC GERM CELL TUMOR WITH (WILMS-LIKE
HISTOLOGY: second bx

TROPHOBLASTIC TUMORS OF
TESTIS

• Choriocarcinoma (including monophasic CC)
• Placental site trophoblastic tumor (HPL+, p63 -)
• Epithelioid trophoblastic tumor (HPL -, p63 +)*
• Cystic trophoblastic tumor*
  * Frequently at metastatic sites

WHO 2016 CLASSIFICATION OF
GERM CELL TUMORS OF TESTIS

• NOT ASSOCIATED WITH GCNIS
  - Spermatocytic tumor
  - Yolk sac tumor, prepubertal type
  - Teratoma, prepubertal type (all age groups)
    - Epidermoid and Dermoid cyst
    - Well differentiated neuroendocrine
tumor (monodermal teratoma)
    - Mixed teratoma and Yolk sac tumor,
      prepubertal type
SPERMATOCYTIC TUMOR (2016 WHO NOMENCLATURE)

Unique
• Older age group (average age 52 yrs; 19-92 range)
• Not associated with GCNIS/ITGCN
• Not associated with cryptorchidism
• Not associated with 12p abnormalities – gains of Chr 9 and 1: FGFR3 & HRAS mutations or gene amplifications
• Not associated with other germ cell components
• No ovarian counterpart or extragonadal location
• Clinically benign, rare metastasis. Death if associated with sarcomatous transformation
PEDIATRIC YST

- Unlike Adult YST
  - No racial or geographic predilection
  - Stable incidence
  - Not associated with GCNIS/ITGCN
  - Always pure
  - 16-20 months age
  - Low incidence of advanced and metastasis
  - Responds to chemotherapy
  - Survival approaches 100%

TERATOMA

"Prepubertal"
- Teratoma in prepubertal age
  Teratoma without ITGCN/GCNIS
- Teratoma in postpubertal age
  Teratoma without ITGCN/GCNIS

"Postpubertal"
- Teratoma in postpubertal age
  with ITGCN/GCNIS

PEDIATRIC TERATOMA

- No association with GCNIS, dysgenetic gonadal changes, scarring or 12p
- Tumors with this histology occur in post-pubertal age – "benign prepubertal teratoma" designation encompasses all ages
- Distinct differences from adult teratoma:
  - Calcification, hair follicles frequent; may have other endodermal, mesenchymal or ectodermal components
  - Smooth muscle tends to envelop epithelium
  - Salivary gland, pancreas etc

In postpubertal setting: Lack scar, tubular atrophy, necrosis, microlithiasis – consider 12p study
TERATOMA – POST PUBERTAL TYPE

- Young adults
- 3-7% pure
- Almost 50% of mixed GCT contain teratoma
- Immaturity in epithelial or mesenchymal elements no impact on prognosis – **atypia is not graded**
- Cytologic atypia with architectural overgrowth – x4 – low power field - “malignant transformation in teratoma”

TERATOMA, “prepubertal type” - EPIDERMOID CYST - BENIGN

- Lacks ITGCN
- Look for GCNIS
TERATOMA “prepubertal type”, - DERMOID CYST

Lacks GCNIS

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PENILE CANCER

What is new in the WHO 2016:

• Topic 11: Classification of Intraepithelial lesions

CLASSIFICATION OF PENILE SCC

Non HPV-related

HPV-related

INTRAEPITHELIAL LESIONS

INVASIVE LESIONS

INTRAEPITHELIAL LESIONS

INVASIVE LESIONS
Penile intraepithelial neoplasia (PeIN)

**Historical nomenclature**
- Erythroplasia of Queyrat (glans)
- Bowen’s disease (shaft)
- Bowenoid papulosis
- Dysplasia (Mild, moderate, and severe)
- Carcinoma in situ
- Squamous intraepithelial lesion (SIL); low and high grade
- Penile intraepithelial neoplasia (PeIN 1, 2, 3)

**Penile intraepithelial neoplasia (PeIN)**

**HPV-UNRELATED**
- DIFFERENTIATED (Simplex) PeIN

**HPV-RELATED**
- UNDIFFERENTIATED PeIN
  - Basaloid
  - Warty
  - Warty/basaloid

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Differentiated PeIN</th>
<th>Undifferentiated PeIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>&gt;60</td>
<td>40-50</td>
</tr>
<tr>
<td>Location</td>
<td>Foreskin</td>
<td>Glans</td>
</tr>
<tr>
<td>Color</td>
<td>White/gray</td>
<td>Red</td>
</tr>
<tr>
<td>Multifocal</td>
<td>Sometimes</td>
<td>Often</td>
</tr>
<tr>
<td>HPV-related</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>p16</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>LS</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Associated SCC</td>
<td>Usual Verrucous Sarcomatoid</td>
<td>Warty Basaloid Warty-Basaloid</td>
</tr>
</tbody>
</table>
PeIN differentiated

Normal epithelium
Bimodal pathway of 
ca progression

HPV-related

40%

Warty Ca (100%)
Basaloid Ca (80%)

HPV-unrelated

60%

Keratinizing SCC (>65%)
Verrucous Ca (>65%)
Pseudohyperplastic Ca (100%)

What is new in the WHO 2016:

Topic 12: Classification & Grading of Squamous cell carcinoma

WHO CLASSIFICATION OF PENILE SQUAMOUS CELL CA

Non HPV related:
SCC:
- usual
- pseudoglandular
- Pseudohyperplastic

Verrucous:
- pure
- cuniculatum

Papillary NOS
Adenosquamous
Sarcomatoid
Mixed

HPV related

Basaloid
- classical
- papillary variant

Warty
- classical
- warty-basaloid
- clear cell

Lymphoepithelioma like

Other rare
SQUAMOUS CELL CARCINOMA

PSEUDOHYPERPLASTIC SQUAMOUS CELL CARCINOMA ASSOCIATED WITH BXO

- Foreskin mucosal lesions, frequently multicentric
- Background of balanitis xerotica obliterans
- Very well-differentiated squamous cell carcinoma with features resembling pseudoepitheliomatous hyperplasia
- Carcinoma – pushing invasion beyond lamina propria into dartos or corpus spongiosum
  - Marked asymmetry of pushing edges of neoplasm
  - Nests may show keratinization at base
  - Destructive invasion below
VERRUCOUS CARCINOMA OF PENIS

exophytic component

endophytic component

Carcinoma Cuniculatum of Penis
Carcinoma Cuniculatum of Penis

Courtesy Dr. Velasquez

WARTY (CONDYLOMATOUS) CARCINOMA

- Complex undulating appearance
- Long papillae - fibrovascular cores
- Deeper - burrowing into lamina propria and corpus spongiosum
- Hyperkeratosis, parakeratosis, HPV changes
- Obvious cytologic atypia (well to moderately differentiated)
**WHO/ISUP Grading in penile SCC.**

- Gr I, well differentiated
- Gr II, moderately differentiated
- Gr III, poorly differentiated