WHO Classification of Tumors: Tumors of the Urothelial Tract
an update on the 4th edition

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Disclosure

Dr. Victor Reuter has nothing to disclose.

WHO Classification of Tumors: Tumors of the Urothelial Tract
an update on the 2016 4th edition

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J. Cheville P. Tamboli T. Tsuzuki E. Oliva
K. Trpkov J. Eble A. Folpe A.O. Osunkoya
P. Humphrey

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Infiltrating urothelial carcinoma</td>
<td>Infiltrating urothelial carcinoma</td>
</tr>
<tr>
<td>with squamous differentiation</td>
<td>with divergent differentiation</td>
</tr>
<tr>
<td>with glandular differentiation</td>
<td></td>
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<tr>
<td>with trophoblastic differentiation</td>
<td></td>
</tr>
<tr>
<td>Nested</td>
<td>Nested, including large nested</td>
</tr>
<tr>
<td>Microcystic</td>
<td>Microcystic</td>
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<tr>
<td>Micropapillary</td>
<td>Micropapillary</td>
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<td>Lymphoepithelioma-like</td>
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<td>Plasmacytoid/signet ring cell/diffuse</td>
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<td>Plasmacytoid</td>
<td>Sarcomatoid</td>
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<tr>
<td>Sarcomatoid</td>
<td>Giant cell</td>
</tr>
<tr>
<td>Giant cell</td>
<td>Poorly differentiated</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>Lipid rich</td>
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<tr>
<td></td>
<td>Clear cell</td>
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</tbody>
</table>
WHO Classification of Tumors: Tumors of the Urothelial Tract
Differences between the 3rd and 4th editions

Third edition: urothelial tumors
Non-invasive urothelial neoplasias
Urothelial carcinoma in situ
Papillary urothelial carcinoma, low grade
Papillary urothelial carcinoma, high grade
Papillary urothelial neoplasm of low malignant potential
Urothelial papilloma
Inverted urothelial papilloma

Fourth edition: urothelial tumors*
Non-invasive urothelial neoplasias
Urothelial carcinoma in situ
Papillary urothelial carcinoma, low grade
Papillary urothelial carcinoma, high grade
Papillary urothelial neoplasm of low malignant potential
Urothelial papilloma
Inverted urothelial papilloma
Urothelial proliferation of uncertain malignant potential (hyperplasia)*
Urothelial dysplasia**

Fourth edition:
Urachal Carcinoma
Tumours of Müllerian type
Clear cell carcinoma
Endometrioid carcinoma
Neuroendocrine tumors
Small cell neuroendocrine carcinoma
Large cell neuroendocrine carcinoma
Well differentiated neuroendocrine carcinoma
Paraganglioma

Fourth edition:
Mesenchymal tumors
Inflammatory myofibroblastic tumor
Perivascular epithelioid cell tumor
Solitary fibrous tumor
Granular cell tumor
Miscellaneous tumors
Tumors of the upper urinary tract
Tumors arising in a diverticulum
Urothelial tumors of the urethra

WHO Classification of Tumors: Tumors of the Urothelial Tract
an update on the forthcoming 4th edition

Outline
• Molecular taxonomy of urothelial neoplasia
  • Classification
  • Therapeutics
• Divergent differentiation in urothelial neoplasia
• Tumours of Müllerian type
• Grading of papillary urothelial tumors
• Substaging tumors invading the lamina propria

Comprehensive molecular characterization of urothelial carcinoma of the bladder
Expression characteristics of bladder cancer

Towards a molecular classification of bladder cancer

Comprehensive molecular characterization of urothelial bladder carcinoma

Somatic mutation of fibroblast growth factor receptor-3 (FGFR3) defines a distinct morphological subtype of high-grade urothelial carcinoma

Targetable aberrations...

Neratinib study - any solid tumor with HER2 mutations
Anti-HER2 immunotherapy (DN24-02)
RTOG 0524 trial (Her2)
BKM10 trial for bladder cancer patients with alterations within the PI3K/Akt/mTOR pathway
Mocetinostat (histone deacetylase [HDAC] inhibitor) for UC with CREBBP and/or EP300 alterations
Other potential targets: FGFR3, EGFR, ERBB3, etc.
Genome sequencing identifies a basis for everolimus sensitivity

Fig. 1 (A) Computed tomography images of the index patient demonstrating complete resolution of metastatic disease (arrows).

The many faces of divergent differentiation in urothelial carcinoma

UROTHELIAL CARCINOMA WITH DIVERGENT DIFFERENTIATION

CYSTECTOMY FOR BLADDER CARCINOMA
300 consecutive cases

Residual MP invasive disease 212
- Conventional UC 154 (73%)
- UC with DD 58 (27%)
  - Squamous 37
  - Glandular 14
  - SMCL/NE 3
  - Squamous, glandular 3
  - SMCL/NE, squamous 1

Dalbagni et al, J Urol 2001;165:1111-1116
Reclassification after pathology re-review - radical cystectomy (n=1,211)  
Mayo Clinic experience (Linder et al. J Urol 2013) 

THE CLINICAL RELEVANCE OF VARIANT HISTOLOGY IN UROTHELIAL CARCINOMA AFTER RADICAL CYSTECTOMY  
Soave A et al, Urol Oncol 2015;33:ePub  
Non-squamous variant histology is associated with inferior survival but are not independent predictors of survival  
Variant histology is associated with established predictors of aggressive tumor biology  
Xylinas A et al, Eur J Cancer 2013;49:1889-1897  
While variant UCB histology was associated with worse outcomes on univariate analysis, this effect did not remain significant on multivariable analyses 

THE IMPACT OF OF SQUAMOUS AND GLANDULAR DIFFERENTIATION ON SURVIVAL AFTER RADICAL CYSTECTOMY FOR UROTHELIAL CARCINOMA  
Kim SP et al, J Urol 2012;188:405-409 

Nested variant of urothelial carcinoma, including large nested  
• Cytologically bland variant of invasive urothelial carcinoma  
• Disorderly proliferation of discrete to confluent crowded small nests beneath the urothelium  
• Nuclei generally show little or no atypia  
• Variations include the presence of tubules, microcystic features, and large nests  
• The stroma is typically myxoid, focally desmoplastic, or lacking a response.  
• Large nested carcinoma is distinguished from an inverted growth pattern of non-invasive urothelial carcinoma by muscularis propria invasion, irregularly infiltrating nests, or a stromal reaction
Infiltrative border deep
Stromal reaction deep
Tubular and microcystic variants

Deceptively bland cytology

ADENOCARCINOMA
Mucinous Papillary NOS

ADENOCARCINOMA OF THE URINARY BLADDER
Grignon et al

<table>
<thead>
<tr>
<th>Stage at Presentation</th>
<th>Cases(%)</th>
<th>Survival(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT1</td>
<td>2 (4)</td>
<td>100</td>
</tr>
<tr>
<td>pT2-pT3a</td>
<td>11 (20)</td>
<td>76</td>
</tr>
<tr>
<td>pT3b</td>
<td>12 (23)</td>
<td>28</td>
</tr>
<tr>
<td>pT4</td>
<td>24 (45)</td>
<td>20</td>
</tr>
</tbody>
</table>

Cancer 1991;67:2165-2172
Mucinous adenocarcinoma with signet ring cells

PLASMACYTOID UROTHELIAL CARCINOMA
(signet ring cell / diffuse)

Diffuse infiltrative growth
Non-gland/nest-forming
Poorly cohesive
Plasmacytoid cells predominate
Variable # of signet ring cells
No extracellular mucin

Plasmacytoid urothelial carcinoma

Figure 2.
(A) Overall survival (OS) for all patients (n=31) was 17.7 months. (B) OS by stage (I-III [45.8 months] vs. IV [13.4 months]; P<0.001).

Somatic CDH1 loss-of-function mutations are pathognomonic of plasmacytoid-variant bladder cancer

Modified figure

Somatic CDH1 loss-of-function mutations are pathognomonic of plasmacytoid-variant bladder cancer

SF-1

MICROPAPILLARY UROTHELIAL CARCINOMA
MICROPAPILLARY CARCINOMA
Interobserver reproducibility study

30 cases reviewed by 14 GU pathologists
- Classic MPC (10)
- UC with retraction artifact (non-classic MPC, 20)

Results:
- Overall kappa: 0.54 (moderate)
- Rate of MPC dx ranged from 9/30 to 20/30 (mean=13/30)
- Classic: all correctly classified at least 8/10 (sensitivity = 93%)
- Non-classic: 6 pathologists, ≤ 2/20 called MPC
  5 pathologists, 4-7/20 called MPC
  3 pathologists, 9-11/20 called MPC

Conclusion: high sensitivity, rather low specificity


The Case for Early Cystectomy in the Treatment of Nonmuscle invasive Micropapillary Bladder Cancer
Kamat et al, JUrol, 175:881-885, 2006

Of 100 consecutive MPC, 44 were nonmuscle invasive
Tumors with any amount MPC component were included
Not stated if all patients received an initial TUR or Bx
Not stated if any repeat TUR were performed (not likely)
30 patients underwent cystectomy
  12 (40%) as initial therapy*
  18 (60%) after failed BCG**
* selection criteria? ** time interval to “progression”?

Pathological upstaging at cystectomy: 57% (17/30)

Figure 1. Kaplan-Meier estimated cumulative CSM in patients treated with early cystectomy (dashed curve) and conservative therapy (solid curve).

Impact of micropapillary urothelial carcinoma variant histology on survival after radical cystectomy


Table 3
Multivariable analysis examining predictors of survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall survival</th>
<th>Recurrence-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>MUC</td>
<td>0.91 (0.55, 1.49)</td>
<td>&lt;0.01 (0.70 (0.55, 1.73)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt;65</td>
<td>1.39 (1.41, 2.22)</td>
<td>&lt;0.01 (1.09 (0.88, 1.31)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Female</td>
<td>1.08 (0.91, 1.29)</td>
<td>0.39 (1.11 (0.88, 1.41)</td>
</tr>
<tr>
<td>Pathologic TNM stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2N0M0</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt;T3N0M0</td>
<td>2.16 (1.77, 2.65)</td>
<td>&lt;0.01 (2.86 (2.17, 3.42)</td>
</tr>
<tr>
<td>Urothelial histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low grade</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>High grade</td>
<td>1.42 (1.32, 1.40)</td>
<td>&lt;0.01 (1.65 (1.14, 2.38)</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>1.38 (1.16, 1.65)</td>
<td>&lt;0.01 (1.40 (1.27, 2.81)</td>
</tr>
<tr>
<td>Histologic grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low grade</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>High grade</td>
<td>1.42 (1.32, 1.40)</td>
<td>&lt;0.01 (1.65 (1.14, 2.38)</td>
</tr>
<tr>
<td>Adjacent chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>0.68 (0.36, 0.98)</td>
<td>&lt;0.01 (0.56 (0.44, 0.73)</td>
</tr>
</tbody>
</table>

Plasmacytoid variant of bladder cancer defines patients with poor prognosis if treated with cystectomy and adjuvant cisplatin-based chemotherapy

Keck et al. BMC Cancer 2013, 13:71

Müllerian-type tumors

- Arise from pre-existing Müllerian precursors within the bladder
  - Endometriosis, rarely Müllerianosis
- Tumour types*:
  - Clear cell carcinoma (F:M, 2:1)
  - Endometrioid carcinoma (only females)
  - Histopathology – identical to those seen in the female genital tract
- Clear cell carcinoma:
  - Tubulocystic, papillary, diffuse
  - Basophilic or eosinophilic secretions
  - Tumor cells flat, cuboidal or columnar
  - Hobnail cells common
  - Nuclear enlargement and hyperchromasia
  - Brisk mitotic activity
- Immunohistochemistry
  - PAX8, HNF81, CA-125, p53 positive and high Ki-67
  - Endometrioid carcinoma express ER and PR

*Similar morphologies may be seen in urothelium-derived tumours

Clear Cell Carcinoma of the Urinary Bladder

Cases 13
M:F 2:11
Age 22-83 (57)
Endometriosis 2
Müllerian-type cysts 2

Clear cell carcinoma associated to Müllerian rests

Müllerian and mucinous metaplasia

Clear cell carcinoma

Müllerian rests

ER

HNF-ß1

p53

Glypican

AFP

HCG
ADENOCARCINOMA OF THE UROTHELIAL TRACT: why is it included in multiple sub-sections?

<table>
<thead>
<tr>
<th>Bladder</th>
<th>Urachus</th>
<th>Müllerian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteric features</td>
<td>Enteric features</td>
<td>Clear cell and endometrioid features</td>
</tr>
<tr>
<td>predominate</td>
<td>predominate</td>
<td>predominate</td>
</tr>
<tr>
<td>Mixed histology</td>
<td>Mixed histology</td>
<td>Mixed histology</td>
</tr>
<tr>
<td>common</td>
<td>less common</td>
<td>rare</td>
</tr>
<tr>
<td>Arises from</td>
<td>Arises from urachal</td>
<td>Arises form Müllerian rests</td>
</tr>
<tr>
<td>surface urothelium</td>
<td>epithelium (urothelium)</td>
<td>within or outside the bladder</td>
</tr>
<tr>
<td>*mucinous cystic</td>
<td>category</td>
<td></td>
</tr>
<tr>
<td>Standard bladder</td>
<td>staging</td>
<td>Not well defined</td>
</tr>
<tr>
<td></td>
<td>staging varies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>depending on site of urachal remnant</td>
<td></td>
</tr>
</tbody>
</table>

Why is the WHO/ISUP classification sensible?

• Uniform terminology and definitions based on the level of cytological and architectural abnormalities (order and disorder) as well as establishment of detailed criteria for various preneoplastic conditions and tumor grades.
• Definition of a group of lesions (high grade) with a high risk of progression that may be candidates for adjuvant therapy.
• Elimination of ambiguity in diagnostic categories in the 1973 WHO system (grade 1-2, grade 2-3)
• Inclusion of a category of papillary neoplasm (PUNLMP) that is not associated with invasion at the time of diagnosis and has a negligible risk of progression, although the potential for recurrence requires clinical surveillance

WHO/ISUP CLASSIFICATION OF UROTHELIAL TUMORS (2004 and 2010)

PAPILLARY NEOPLASMS
• Papilloma
• Inverted papilloma
• Papillary urothelial neoplasm of low malignant potential
• Papillary urothelial carcinoma, low grade
• Papillary urothelial carcinoma, high grade

ASSESSMENT OF PAPILLARY UROTHELIAL NEOPLASMS

- At medium magnification, the tumour pattern gives a predominant impression of:
  - ORDER: Of architectural and cytological features
  - DISORDER: Of architectural and cytological features

- If PUNLMP or Papillary Urothelial carcinoma, low grade:
  - If architectural and cytological features are mostly normal:
    - YES
  - If architectural and cytological features are not normal:
    - NO

- If PUNLMP:
  - Urothelial carcinoma, low grade
- If architectural and cytological features are mostly normal:
  - Urothelial carcinoma, high grade
Papillary Urothelial Neoplasm of Low Malignant Potential

A: interval to first recurrence


B: interval to progression


How much HG do you need?
....any, 5%, 10%?
Combining molecular and pathologic data to prognosticate non-muscle-invasive bladder cancer

Bas W.G. van Rhijn

**MOLECULAR AND CLINICAL PATHWAYS OF BLADDER CANCER**

Figure 1: Simplified two-pathway model for disease pathogenesis of BC. This figure shows the combination of molecular and pathologic data in non-muscle-invasive BC. Arrow thickness is indicative for the percentage of tumors. The NF1 deletion is largely responsible for the favorable molecular pathway in NMIBC. Among many others, PI3K and Akt alterations are examples of unfavorable NMIBC. Molecular alterations, not included in the figure in the interest of clarity, are represented by the horizontal arrow. NF1 = neurofibromatosis 1; FGFR3 = fibroblast growth factor receptor 3; T = mutated expression (p.T547A); U = urothelial hyperplasia.
In T1 disease, several substaging strategies have been proposed to improve outcome prediction, but have been difficult to adopt due to......

...Based on the available data, it is recommended to provide an assessment of the depth and/or extent of sub-epithelial invasion in T1 cases.

• ≤ 0.5 mm single focus (pT1m) versus
  > 0.5 mm or multifocal (pT1e)
• Doesn’t need MM/VP landmark
• Showed pT1m/e significant for PFS and DSS but not the pT1a/b/c system

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