WHO/ISUP classification of urothelial carcinoma

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Triggers for the 1998 ISUP/WHO classification proposal (2004 WHO classification)

1. Grading criteria of the 1973 WHO classification “poorly defined”
   • *Intra- and inter-observer variation*

2. 1973 WHO: subset of non-invasive papillary carcinomas with no progression and low recurrence rate
   • *Not all are “carcinomas”*

3. Need for better identification of patients with risk of progression
   • *Improved risk assessment*

Montironi R et al, JCP 2008;61:3-10
2004 WHO classification

• *International standard*:  
  – International Society of Urologic Pathologists (ISUP)

• *Endorsed by*:  
  1. WHO 2004 Blue Book
  2. 4th Series Armed Forces Institutes of Pathology Fascicle on Bladder
  4. 2011 ICUD on bladder cancer
Flat neoplasms

1. **Without atypia**
   - Flat urothelial hyperplasia

2. **With atypia**
   - Urothelial dysplasia (*Low-grade intraurothelial neoplasia*)
   - Urothelial carcinoma in situ (*High-grade intraurothelial neoplasia*)
   - Reactive atypia
   - Atypia of unknown significance
Flat neoplasms

1. Flat urothelial hyperplasia
   • *Precursor lesion for a subset of papillary urothelial neoplasms*

2. Urothelial dysplasia
   • *Few studies, most dated: 5% to 19% risk of developing cancer*

3. Urothelial carcinoma in situ
   • *Development of invasion is seen in 20 to 30% of the cases*

Montironi R et al, JCP 2008;61:3-10
Papillary neoplasms
( other than papilloma )

1. PUNLMP*  →  flat hyperplasia
2. LG papillary UC  →  flat dysplasia
3. HG papillary UC  →  CIS

* Papillary urothelial neoplasm of low malignant potential
Normal Urothelium

PUNLMP

LG UPC

HG UPC
## Papillary neoplasms: prognosis

<table>
<thead>
<tr>
<th></th>
<th>Papilloma</th>
<th>PUNLMP</th>
<th>LG Pap UC</th>
<th>HG Pap UC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recurrence</strong></td>
<td>9-18%</td>
<td>17-62 (34)</td>
<td>34-78 (50)</td>
<td>34-74</td>
</tr>
<tr>
<td><strong>Grade progression</strong></td>
<td>2</td>
<td>11</td>
<td>7-12</td>
<td>-</td>
</tr>
<tr>
<td><strong>Stage progression</strong></td>
<td>0</td>
<td>0-4</td>
<td>3-18</td>
<td>27-61</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td>100</td>
<td>93-100</td>
<td>82-96</td>
<td>65-90</td>
</tr>
</tbody>
</table>

Does not predict risk at individual patient level
Contributions of the 2004 WHO classification

1. Establishment of detailed criteria of various preneoplastic conditions and various grades of tumor

2. Identification of a distinct group of patients (HG papillary UCa) who would be ideal candidates for intravesical therapy

3. Creation of a category of tumor that identifies a tumor with a negligible risk of progression (PUNLMP), whereby patients avoid the label of having cancer which has psychosocial and financial implications

<table>
<thead>
<tr>
<th></th>
<th>% of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>PUNLMP</td>
<td>48%</td>
</tr>
<tr>
<td>LG papillary Ca</td>
<td>73%</td>
</tr>
<tr>
<td>HG papillary Ca</td>
<td>92%</td>
</tr>
</tbody>
</table>

“The new proposed classification system for noninvasive urothelial neoplasms does not increase the reproducibility”
Grading papillary urothelial neoplasms with histologic heterogeneity

• Grade heterogeneity is not uncommonly encountered in papillary urothelial neoplasia.

• There are studies showing that pure HG papillary UC has a higher disease progression rate than tumors with mixed high grade and low-grade areas.

• The 2004 WHO classification recommends grading of heterogeneous tumors to be based on the highest grade present in a tumor.
Grading papillary urothelial neoplasms with histologic heterogeneity
# Grade heterogeneity of urothelial neoplasms

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PUNLMP</td>
<td>PUNLMP</td>
<td>19 (76)</td>
</tr>
<tr>
<td>PUNLMP</td>
<td>Low grade</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Low grade</td>
<td>PUNLMP</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Low grade</td>
<td>Low grade</td>
<td>79 (73)</td>
</tr>
<tr>
<td>Low grade</td>
<td>High grade</td>
<td>23 (21)</td>
</tr>
<tr>
<td>High grade</td>
<td>Low grade</td>
<td>16 (53)</td>
</tr>
<tr>
<td>High grade</td>
<td>High grade</td>
<td>14 (47)</td>
</tr>
</tbody>
</table>

*Adapted from Cheng L, et al. Cancer 2000; 88: 1663-1670*
Grading papillary urothelial neoplasms with histologic heterogeneity

• There is no current widely acceptable definition or criteria to provide quantitative estimate of size of smallest focus required to “upgrade” a lesion

• Studies are needed to establish quantitative/semi-quantitative criteria that need to be present to alter assignment of grade in tumors with grade heterogeneity
1. PUNLMP has been shown to be the least reproducible component of a combined scoring system even among experienced observers.

2. Exclusion of PUNLMP from grading scheme seems to improve interobserver variability.

3. The clinical management of patients with PUNLMP or LGPUC is currently similar, if not identical.
What is missing in the 2004 WHO classification

- Lesions with architectural pattern intermediate between flat and fully developed papillary neoplasms

- Morphologic spectrum similar to that of the flat neoplasms:
  1. Papillary urothelial hyperplasia (2004 WHO)
  2. Dysplasia with early papillary formation
  3. CIS with early papillary formation
## Post-2004 WHO classification

<table>
<thead>
<tr>
<th>Group No 1. Flat</th>
<th>Urothelial hyperplasia</th>
<th>Urothelial dysplasia</th>
<th>Urothelial carcinoma in situ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group No 2a. Papillary, precursors</td>
<td>Urothelial papillary hyperplasia</td>
<td>Dysplasia with early papillary formation</td>
<td>Carcinoma in situ with early papillary formation</td>
</tr>
<tr>
<td>Group No 2b. Papillary</td>
<td>Papillary urothelial neoplasm of low malignant potential</td>
<td>Low-grade papillary carcinoma</td>
<td>High-grade papillary carcinoma</td>
</tr>
</tbody>
</table>
What is missing in the 2004 WHO classification

1. Early phases of fully developed papillary neoplasms
2. Usually occur in the backdrop of treatment setting (followup)
3. These terms are only descriptive diagnosis and outcome studies are not available
Inverted neoplasms (other than inverted papilloma)

- The urothelial neoplasms with an inverted growth pattern show a spectrum of architectural and cytological features

- Three subgroups could be defined:
  1. neoplasms that have the least degree of cytological atypia
  2. neoplasms with the most severe degrees of cytological atypia
  3. those that lie in between
Inverted neoplasms

• A classification and terminology consistent with those of the flat and papillary urothelial lesions and neoplasms should be adopted (staging: pTa)

• Scant molecular and clinical studies on the urothelial carcinoma with an inverted growth pattern have been published, mainly focusing on the differences with the inverted urothelial papilloma
Inverted neoplasms

1. Inverted urothelial neoplasm of low malignant potential
2. Low-grade inverted UC
3. High-grade inverted UC
# Post-2004 WHO classification

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<td></td>
<td></td>
</tr>
<tr>
<td>Group No 2b. Papillary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group No 3. Inverted</td>
<td></td>
<td></td>
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</tbody>
</table>
Conclusions

1. 1973 → 2004 a step forward
2. Towards a revised 2004?
3. The success of clinical detection methods is basically hampered by the "incomplete" description of the morphology of the non-invasive neoplasms before, under and following treatment