PATHOLOGY of urothelial carcinoma in situ

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### WHO classification of tumours of the urothelial tract

#### Urothelial tumours

- **Infiltrating urothelial carcinoma**
- **Nested, including large nested**
- **Microcystic**
- **Micropapillary**
- **Lymphoepithelioma-like**
- **Plasmacytoid / signet**
- **Sarcomatoid**
- **Giant cell**
- **Poorly differentiated**
- **Lipid-rich**

#### Neuroendocrine tumours

- **Small cell neuroendocrine carcinoma**
- **Large cell neuroendocrine carcinoma**
- **Well-differentiated neuroendocrine tumour**
- **Paraganglioma**

#### Non-invasive urothelial neoplasms

- **Urothelial carcinoma in situ**
- **Non-invasive papillary urothelial carcinoma, low-grade**
- **Non-invasive papillary urothelial carcinoma, high-grade**
- **Papillary urothelial neoplasm of low malignant potential**
- **Urothelial papilloma**
- **Inverted urothelial papilloma**
- **Urothelial proliferation of uncertain malignant potential**
- **Urothelial dysplasia**

#### Squamous cell neoplasms

- **Pure squamous cell carcinoma**
- **Verrucous carcinoma**
- **Squamous cell papilloma**

#### Glandular neoplasms

- **Adenocarcinoma, NOS**
- **Enteric**
- **Mucinous**
- **Mixed**
- **Villous adenoma**

#### Urachal carcinoma

- **Clear cell carcinoma**
- **Endometrioid carcinoma**

### Classification and Behaviour

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O). Behaviour is coded 0 for benign tumours, 1 for unexpected, borderline, or uncertain behaviour, 2 for carcinoma in situ, and grade III intraepithelial neoplasia, and 3 for malignant tumours. The classification is modified from the previous WHO classification (756A), taking into account changes in our understanding of these lesions.

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*Eur Urol. 2016 Jul;70(1):106-119*
Urothelial Carcinoma in situ (UCIS)

- A flat urothelial lesion (non-papillary)
  - Surface urothelium contains cytologically malignant cells
  - Synonym: High grade intraurothelial neoplasia

- UCIS - high grade (by definition)
  - No low grade UCIS
Flat Urothelial Carcinoma (in situ)
Histologic criteria and spectrum of morphology

- Normal urothelium
- Nuclear pleomorphism and hyperchromasia, visible mitoses
- Pagetoid/undermining spread
- Discohesive tumor cells
- Involving von Brunn nests
Urothelial Carcinoma *in situ* (UCIS)

- Pure form is rare, 1-3% of newly diagnosed UC
  - *Carcinoma paradoxicum*
  - More common with/adjacent to, or subsequent to papillary UC
    - **Primary CIS**: high grade malignant flat lesion at initial TUR without any prior or concomitant papillary tumor
    - **Secondary CIS**: flat CIS concomitant with or after a prior papillary tumor

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**Table 3. Multivariate analysis of progression to cT1 or higher invasive disease and cT2 or higher muscle invasive disease adjusted for RC before progression**

<table>
<thead>
<tr>
<th>Variables</th>
<th>cT1 or Higher, or RC</th>
<th>cT2 or Higher, or RC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>Primary vs secondary CIS</td>
<td>1.37(1.05–1.81)</td>
<td>0.020</td>
</tr>
<tr>
<td>Age</td>
<td>1.01(0.99–1.02)</td>
<td>0.178</td>
</tr>
<tr>
<td>Gender</td>
<td>1.18(0.86–1.63)</td>
<td>0.300</td>
</tr>
<tr>
<td>BCG response</td>
<td>1.12(0.85–1.46)</td>
<td>0.421</td>
</tr>
</tbody>
</table>

Chade DC et al. *J Urol.* 2010

* Excluding 84 patients due to progression before BCG or missing data.
Urothelial Carcinoma *in situ*
Flat and papillary
Flat Urothelial Carcinoma \textit{(in situ)}, with invasion

UCIS is a documented precursor of invasive cancer
  • Commonly in association with invasive disease (45%-65%)
Role of urine cytology (Paris System)

UCIS is associated with high rate of positive urine cytology (>80%)

I. Adequacy of urine specimen (non-diagnostic or unsatisfactory)

II. Negative for high grade urothelial carcinoma (negative)

III. Atypical urothelial cells

IV. Suspicious for high grade urothelial carcinoma (suspicious) (<10 cells)

V. High grade urothelial carcinoma (HGUC)

VI. Low grade urothelial neoplasia (LGUN)

VII. Other malignancies, primary and metastatic and miscellaneous lesions
Flat Lesions with Atypia: Problems and Pitfalls

- Variability of normal urothelium
- Inflammatory atypia
- Post treatment atypia
- Extensive denudation
**Flat Urothelial Lesions Reproducibility**

<table>
<thead>
<tr>
<th>Subset of interest</th>
<th>Kappa</th>
<th>Degree of Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0.484</td>
<td>Good</td>
</tr>
<tr>
<td>Reactive atypia</td>
<td>0.361</td>
<td>Fair</td>
</tr>
<tr>
<td>Atypia ? dysplasia</td>
<td>0.317</td>
<td>Fair</td>
</tr>
<tr>
<td>L.G. dysplasia</td>
<td>0.174</td>
<td>Poor</td>
</tr>
<tr>
<td>HGD/CIS</td>
<td>0.653</td>
<td>Excellent</td>
</tr>
<tr>
<td>Non-H.G.D./CIS</td>
<td>0.653</td>
<td>Excellent</td>
</tr>
<tr>
<td>H.G.D./CIS</td>
<td>0.653</td>
<td>Excellent</td>
</tr>
</tbody>
</table>

Amin, M.B., et al., *Intraepithelial lesions of the urothelium: an interobserver reproducibility study with proposed terminology and histologic criteria*. Mod Pathol, 1997. 10: p. 69A.

- Role for central pathology review
  - Facilitated by availability of digital pathology capabilities

- Challenging disease for molecular profiling

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Lawless ME et al. *Appl Immunohistochem Mol Morphol*. 2018

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>General Pathologists (N = 127)</th>
<th>GU Pathologist 1 (N = 127)</th>
<th>GU Pathologist 2 (N = 127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive atypia</td>
<td>35 (26)</td>
<td>62 (49)</td>
<td>38 (30)</td>
<td>42 (33)</td>
</tr>
<tr>
<td>Atypia of uncertain significance</td>
<td>35 (26)</td>
<td>13 (12)</td>
<td>18 (14)</td>
<td>15 (12)</td>
</tr>
<tr>
<td>Low-grade dysplasia</td>
<td>17 (13)</td>
<td>7 (5)</td>
<td>15 (12)</td>
<td>15 (12)</td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>40 (31)</td>
<td>43 (34)</td>
<td>60 (47)</td>
<td>54 (42)</td>
</tr>
</tbody>
</table>

GU indicates genitourinary; H&E, hematoxylin and eosin.
Conclusions

• Urothelial carcinoma in situ
  – There is a spectrum of morphologic features
  – Can be pure CIS or associated with papillary UC
    • Primary vs. secondary CIS
      – Not a strictly pathologic diagnosis
    • Implications for management and outcome
      – May be diagnostically challenging
        • Interobserver variability
      – Challenges for molecular studies