Problems and Pitfalls in Urothelial Biopsy Interpretation

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WHO 2004: urothelial neoplasms

Flat urothelial lesions
- Hyperplasia
- Dysplasia
- Carcinoma-in-situ (CIS)

Papillary urothelial tumours
- Papilloma
- Papillary urothelial neoplasm of low malignant potential (PUNLMP)
- Low-grade papillary carcinoma
- High-grade papillary carcinoma

Meaning

Differential diagnosis

Grading 1973
Pitfalls
Invasion
Flat urothelial lesions: **Hyperplasia**

**Hyperplasia**
- Urothelium markedly thickened, without atypia
- Adjacent to low-grade papillary neoplasm
- Also seen alone, without papillary lesion
- Premalignant potential controversial
Flat urothelial lesions: **Dysplasia**

**Dysplasia**
- Atypia, lacking criteria for CIS and not due to inflammation
- Rare diagnosis
- Occurs in 2 clinical setting: 
  - primary: *de novo*
  - secondary: adjacent to papillary tumour
- No subdivision (1-3 or low-severe)

**Histology**
- Comparison with normal urothelium
- Usually, urothelium has normal thickness with umbrella cells
- Loss of polarity with cytologic atypia, not enough for CIS
- Ker20 shows loss of polarity
Flat urothelial lesions: **Dysplasia**

**Problem**
- Dysplasia does not have well-defined, delimited histologic features
- High inter-observer variability (no studies yet)
- Risk of being waste-basket unsure whether CIS or atypia NOS

**Relevance**
- Adjacent to papillary tumour: possibly marker for progression
- *De novo*: premalignant potential (5-19%)
Flat urothelial lesions: **Carcinoma-in-situ**

**Carcinoma-in-situ**

- Thickness urothelium normal or denuded
- Presence of strongly atypical cells (hyperchromasia, pleomorphism, nuclear enlargement) with mitosis
- Adjacent to papillary lesion or *de novo*
- Premalignant potency requires intervention!

**Histologic variants**

- Large cell pleomorphic
- Large cell monomorphic
- Small cell
- Clinging
- Pagetoid
Urothelial CIS, large cell pleomorphic type; 200x
Urothelial CIS, large cell monomorphic type; 200x
Urothelial CIS, small cell type; 200x
Urothelial CIS, Pagetoid type; 200x

p53
Urothelial CIS, glandular luminal differentiation; 200x
Urothelial CIS, squamous differentiation; 200x
Flat urothelial lesions: **Carcinoma-in-situ**

Problem: distinction from normal urothelium

- Identification of atypia might be difficult if normal reference is absent
- Recognition of unusual variants

**Approach**

- Rule of thumb: nuclei larger than 5 mucosal lymphocytes
- Immunohistochemistry helpful:
  - p53 strongly positive
  - Ker20 gradient lost
  - CD44 absent

Do not solely rely on immunohistochemistry!
Flat urothelial lesions: **Carcinoma-in-situ**

**Problem: distinction from reactive atypia**

- Monomorphic nuclear enlargement with prominent nuclei
- Can be very difficult, or even non-conclusive!
- Potential consequence: cystectomy in case of BCG-refractive CIS

**Approach**

- Presence of intra-urothelial inflammation
- Immunohistochemistry helpful:

<table>
<thead>
<tr>
<th>IHC marker</th>
<th>Reactive atypia</th>
<th>CIS</th>
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<tbody>
<tr>
<td>Ker20</td>
<td>Gradient to lumen</td>
<td>No gradient</td>
</tr>
<tr>
<td>p53</td>
<td>Absent to weak</td>
<td>Strong</td>
</tr>
<tr>
<td>CD44</td>
<td>Basal and parabasal</td>
<td>Basal to absent</td>
</tr>
</tbody>
</table>
Reactive urothelial atypia; 200x
Flat urothelial lesions: **Carcinoma-in-situ**

Problem: distinction from atypia due to exogenic causes

Following:
- radiation therapy (cervical cancer)
- bladder instillitation (mitomycine)
- systemic chemotherapy
- Polyoma virus

**Approach**

- Appropriate clinical information!
- Exaggerated atypia
- Abundant cytoplasm, cytoplasmic vacuolisation
Therapy-induced urothelial atypia (chemotherapy bladder ca); 200x
Therapy-induced urothelial atypia (radiation rectal cancer); 100x
Papillary urothelial neoplasms

**WHO 2004/ ISUP classification of papillary neoplasms**

Papilloma

Papillary neoplasm of low malignant potential (PUNLMP)

Low-grade papillary carcinoma

High-grade papillary carcinoma

All urothelial neoplasms can give rise to inverted growth patterns

Use of WHO/ ISUP classification controversial, especially in Europe!
Papillary urothelial neoplasms: **Rationale**

- Normal
- Hyperplasia
- Dysplasia
- CIS

- Papilloma
- PUNLMP
- LG-pUCC
- HG-pUCC
Grading: **Clinical significance**

<table>
<thead>
<tr>
<th>Papilloma</th>
<th>PUNLMP</th>
<th>LG-pUCC</th>
<th>HG-pUCC</th>
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</table>

**Recurrence**

- Papilloma: 10%
- PUNLMP: 30-60%
- LG-pUCC: 60-70%
- HG-pUCC: 50-65%

**Progression (≥pT2)**

- Papilloma: 0%
- PUNLMP: 0-5%
- LG-pUCC: 5-10%
- HG-pUCC: 20-30%
Grading: **Practical histologic criteria**

- **Papilloma**
- **PUNLMP**
- **LG-pUCC**
- **HG-pUCC**

Hyperplasia

Atypia identified at 200x

Atypia identified at 40x
Low-grade pUCC; 200x
High-grade pUCC; 200x
High-grade pUCC; 40x
WHO 2004 versus 1973

Aim WHO/ ISUP 2004:

- Detailed histopathologic definition of tumour grades
- Identification of tumours without progression, which will not have to be labelled as cancer (PUNLMP)
- Reflective of molecular aberrations:
  - FGFR3 mutations: papilloma, PUNLMP, low-grade carcinoma
  - p53 mutations: high-grade carcinoma

ISUP1998 accepted as new WHO classification without validation

Many subsequent studies comparing both systems
**WHO 2004 versus 1973: No improvement**

<table>
<thead>
<tr>
<th></th>
<th>WHO 1973</th>
<th>WHO 2004</th>
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<tr>
<td><strong>Recurrence</strong></td>
<td></td>
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<tr>
<td>G1</td>
<td>63% (56-67%)</td>
<td>LMP 61% (47-69%)</td>
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<tr>
<td>G2</td>
<td>72% (71-75%)</td>
<td>LG 70% (68-73%)</td>
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<tr>
<td>G3</td>
<td>62% (55-65%)</td>
<td>HG 65% (59-71%)</td>
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<tr>
<td><strong>Progression</strong></td>
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<tr>
<td>G1</td>
<td>3% (0-6%)</td>
<td>LMP 1% (0-5%)</td>
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<tr>
<td>G2</td>
<td>12% (7-16%)</td>
<td>LG 8% (1-16%)</td>
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<tr>
<td>G3</td>
<td>26% (25-27%)</td>
<td>HG 23% (20-27%)</td>
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<td><strong>Inter-observer variability</strong></td>
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<td>(\kappa) 0.15-0.41</td>
<td>(\kappa) 0.17-0.58</td>
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WHO 2004 versus 1973: No improvement

Intra- and interobserver variability
No improvement in relation to WHO 1973
Criteria not that "well-defined"?

Recurrence and progression
No improvement in relation to WHO 1973

Avoid nomenclature "cancer" for PUNLMP
Why use term "cancer" for non-invasive disease at all?

Difference in molecular pathways
Valid: FGFR3 versus p53
Papillary urothelial neoplasms: **Pitfalls**

**Differential diagnosis**

- Papillary urothelial hyperplasia
- Papillary/ polypoid cystitis
- Nephrogenic adenoma
Pitfalls: **Papillary urothelial hyperplasia**

**Histology**
- Mossy horizontal growth (instead of vertical 'coral'of papillary cancer)
- Papillae are small, narrow, tent-shaped and non-branching
- Urothelium often hyperplastic
- No atypia

**Relevance**
- Putative precursor of papillary neoplasms
- No large studies available on *de novo* papillary urothelial hyperplasia
Papillary urothelial hyperplasia; 40x
Pitfalls: **Papillary/ polypoid cystitis**

**Histology**
- Broad-based papillae
- Inflammation and edema
- No or reactive atypia
- Urologist notices the difference!

**Relevance**
- Reactive lesion, no neoplasm
Papillary/ polypoid cystitis; 40x
Papillary/ polypoid cystitis; 100x
Pitfalls: Nephrogenic adenoma

Histology
- Papillae, glands and single cells
- Cuboid to columnar single cell layer
- Presence of prominent basal membrane-like material
- No atypia
- No mitoses

Relevance: misdiagnosis if unaware of entity
- Papillary > papillary carcinoma
- Tubular > bladder adenocarcinoma (with signet cells)
- Urethra > prostate adenocarcinoma
- If atypical or solid growth, consider clear cell adenocarcinoma
Nephrogenic adenoma; 40x
Nephrogenic adenoma; 100x
Nephrogenic adenoma; 200x
Intermezzo: **Go on or Questions**

Still awake?

*Time for UCC invasion?*

9:40
Invasion of urothelial carcinoma

Clinical relevance of staging at TURT

- No invasion (pTa-pTis)  Bladder instillations (BCG, mitomycin)
- Lamina propria (pT1)  Bladder instillations, re-TURT
- Detrusor muscle (pT2)  Cystectomy

Detrusor muscle invasion has important therapeutic implications

Invasion beyond detrusor muscle (pT3) not identifiable at TURT

Fat tissue can occur within detrusor muscle and lamina propria
Invasion of urothelial carcinoma

Establishment of invasion
- Irregular nests, dropping off
- Finger-like projections
- Single cell invasion
- Paradoxical differentiation (abundant cytoplasm, abrupt atypia)
- Stromal response (desmoplasia, retraction, inflammation, myxoid)

**Inter-observer variability:** re-staging pT1 to pTa (35-56%) to pT2 (3-13%)

**Substaging:** prognostically significant but poor reproducibility
- No invasion of muscularis mucosae (pT1a) > progression 8%
- Invasion in or through muscularis mucosae (pT1b/c) > progression 34%
Lamina propria invasion (single cells); 100x
Lamina propria invasion (dropping off, retraction); 100x
Lamina propria invasion (dropping off, retraction); 100x
Lamina propria invasion (paradoxical differentiation); 100x
Invasion of urothelial carcinoma: **Pitfalls**

**Benign conditions mimicking UCC invasion**
- Tangential sectioning and thermal damage
- Ureter/ pyelum: distension of lumen with atrophy lamina propria
- Obscuring inflammation
- Pseudo-invasion after radiation therapy
- Inverted urothelial neoplasms
- Proliferation Von Brunn's nests/ cystitis cystica

**Problems in identification detrusor muscle invasion**
- Distinction muscularis mucosae (pT1) and musculus detrusor (pT2)
- Desmoplastic stromal reaction misinterpreted as detrusor muscle
Tangential sectioning; 40x
Obscuring inflammation; 100x
Pseudo-invasion after radiation therapy; 100x
Pseudo-invasion after radiation therapy; 200x
Proliferation Von Brunns nests/ cystitis cystica; 100x
Desmoplastic stromal reaction (Desmin neg.) (pT1); 100x
Muscularis mucosa invasion (pT1); 100x
Thank you!
&
Good luck