The Paris System for Reporting Urinary Cytopathology

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The Paris System (TPS) for reporting urinary cytopathology

- Joint initiative of the American Society of Cytopathology (ASC) and the International Academy of Cytology (IAC)
- Led by Dr Dorothy Rosenthal (Johns Hopkins, Baltimore) and Dr Eva Wojcik (Loyola, Chicago)
- Further developed by members of the ASC and IAC at the International Congress of Cytology meeting held in Paris in May 2013
- Echoes Bethesda terminology for reporting cervical and thyroid cytology
TPS: Categories

• I. Non-diagnostic or Unsatisfactory
• II. Negative for High Grade Urothelial Carcinoma
• III. Atypia
• IV. Suspicious for High Grade Urothelial Carcinoma
• V. Low Grade Urothelial Neoplasia (LGUN)
• VI. High Grade Urothelial Carcinoma (HGUC)
• VII. Other malignancies, primary and metastatic
Histopathological terminology of urothelial neoplasia

- **WHO 1973**: Grades 1, 2 and 3
- **ISUP/WHO 2004**: Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP)
  - Low grade urothelial carcinoma (LGUC)
  - High grade urothelial carcinoma (HGUC)
- Use of the term carcinoma for low grade tumours (PUNLMP & LGUC) needs revision
- *The Paris system of reporting urinary cytology is leading the way in guiding histopathological terminology of urothelial neoplasia*
I. Non-diagnostic or Unsatisfactory

• Cellularity and cell content varies widely
• Unsatisfactory or unsuitable when sample quality is compromised due to degenerative changes due to overgrowth of contaminant microbes or cells obscured by blood, exudate or other artefacts
• 20 cells/10 hpf in bladder washings (LBC).

JASC 2015,4;57-62
II. Negative for HGUC

- Implies absence of atypical, suspicious or malignant cells in an adequate sample
- Features attributable to inflammation may be referred as ‘reactive changes’ but reported as negative for HGUC. The word ‘atypia’ should not be used in this setting
- Treatment effect and BK virus effect may be reported as Negative for HGUC
Negative for high grade urothelial carcinoma
Reactive Urothelial Cells (Negative for HGUC)

- Uniform size
- Fine chromatin
- Round nuclei
- Smooth borders
- Small nucleoli
III. Atypia

- Atypia should be reminiscent of HGUC but in very small numbers
- Does not include papillary clusters suggestive of LGUN
Criteria for Atypia

• Non-superficial and non-degenerated urothelial cells with a high N/C ratio > 0.5 (required) and one of the following:
  • **Hyperchromasia** (compared to the umbrella cells or the intermediate squamous cell nucleus)
  • Irregular clumped chromatin
  • Irregular nuclear membranes
Atypia
Atypia
Atypia
Atypical cytology and ancillary testing: UroVysion FISH

Mix of 4 probes labelled with fluorochromes

Courtesy: Dr Michael Neat, Chief Cytogeneticist, Viapath, London
Analysis and criteria for classification of UroVysion FISH results

- Initially select morphologically abnormal cells
  - Large nuclear size/irregular shape
  - Patchy DAPI stain
  - Cell clusters (non-overlapping)
  - If no morphologically abnormal cells present, scan all cells

- Minimum analysis of 25 cells

- FISH positive if:
  - ≥4 cells showing gain of at least 2 of #3, #7 & #17
  - ≥12 cells showing homozygous deletion of $p16$ i.e. no $p16$ signals
Potential issues with analysis/interpretation of the assay

False positives

- **BK polyoma virus (rare)**
- **Benign/reactive cells**
  - 27/77 (35.1%) benign with reactive changes were FISH+
- **Tetraploidy**
  - ? less specific predictor of malignancy
  - dividing cells, polyploidy in normal cells
  - ? >10 cells to define FISH+ result

Savic et al Int J Cancer. 2009;124:2899-2904
False negatives

- low-grade neoplasms
- non-exfoliating - representative cells not shed into the urine sample
- Lack of atypical cells on the slide used for FISH

Highlights importance of correlation with cytomorphology and clinical context
Potential of UroVysion FISH

Useful adjunctive test, improves sensitivity of urine cytology

- Does earlier detection translate into decreased mortality?

- Is negative predictive value sufficient to decrease the need for or frequency of cytoscopic follow-up?

- Is there a cost benefit - can/does incorporation of FISH results reduce no. of biopsies performed?
IV. Suspicious for HGUC

- Non-superficial and non-degenerated urothelial cells with a high **N/C ratio > 0.7** (required)
- **Hyperchromasia** (compared to the umbrella cells or the intermediate squamous cell nucleus) (required)

*and one of the following:*

- Irregular clumpy chromatin
- Irregular nuclear membranes
Suspicious for HGUC
Suspicious for HGUC
V. Low grade urothelial neoplasm (LGUN)

• LGUN - combined cytologic term for low grade papillary urothelial neoplasms (LGPUN) (which include urothelial papilloma, PUNLMP and LGPUC) and flat, low grade intraurothelial neoplasia

• Three-dimensional cellular papillary clusters (defined as clusters of cells with nuclear overlapping, forming "papillae") with fibrovascular cores with capillaries (esp if cell block is examined)

• Diagnosis of LGUN may be made in correlation with cystoscopic or biopsy findings
VI. High grade urothelial carcinoma (HGUC)

• “The number of atypical urothelial cells is an important criterion to classify urine cytology specimens into the ‘positive’ or the ‘suspicious’/AUC-H categories. A cut off number of **>10 cells** to render a definitive diagnosis of HGUC seems valid from the clinical standpoint.”

Urine Cytology: Does the Number of Atypical Urothelial Cells Matter for distinguishing the “high-grade urothelial carcinoma” from the “suspicious for HGUC” cytological categories? (Brimo et al. USCAP 2015)
### The Paris System: criteria for HGUC, Suspicious & Atypia*

<table>
<thead>
<tr>
<th>Category Criteria</th>
<th>HGUC</th>
<th>Suspicious for HGUC</th>
<th>Atypia</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of atypical cells</td>
<td>&gt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>N:C ratio</td>
<td>&gt;0.7</td>
<td>&gt;0.7</td>
<td>0.5-0.7</td>
</tr>
<tr>
<td>Hyperchromasia</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Clumped chromatin / Irregular nuclear borders</td>
<td>Either one of the two criteria</td>
<td>Either one of the two criteria</td>
<td>Any one of the three criteria</td>
</tr>
</tbody>
</table>

*In conjunction with explanatory notes for each category*
TPS categories: Risk of malignancy & clinical management

- Unsatisfactory/Non-diagnostic (?<5%) Repeat cytology, cystoscopy in 3 months if high clinical suspicion
- Negative for Malignancy (0-2%) Clinical follow up as needed
- Atypical Urothelial Cells (8-35%) Clinical follow up as needed. Use of ancillary testing
- Suspicious for HGUC (50-90%). More aggressive follow up, cystoscopy, biopsy
- Low Grade Urothelial Neoplasm LGUN (~10%). Need biopsy to further evaluate grade and stage
- High Grade UC (>90%). More aggressive follow up, cystoscopy, biopsy, staging
- Other malignancy (>90%). More aggressive follow up, cystoscopy, biopsy, staging
Further work

• The Paris system aims to standardize reporting of urinary tract cytology
• Published range of atypia 1.9% to 23.2% (suggested limit atypical and suspicious categories to <10%)
• Outcome data, reporting rates of categories, Atypia:HGUC ratio etc.
• Potential use of UroVysion FISH in Atypia cases


References
