Updates in bladder cancer including RCPath dataset, subtypes of bladder cancer and molecular developments

Dr Jonathan H Shanks

The Christie NHS Foundation Trust, Manchester, UK
RCPath dataset and beyond: grading bladder cancer
NICE guidance
International Consultation on Urologic Disease guidance
Forthcoming publications
Meetings held by consensus groups on bladder cancer grading

- October 1997 - Washington (Urologists/pathologists/oncologists/scientists) - initial meeting organised by Dr Mostofi. Term ‘PUNLMP’ first proposed at this meeting

- March 1998 - Boston (at USCAP Meeting) (Pathologists - members of ISUP)
WHO/ISUP consensus classification of urothelial neoplasms

Epstein JI, Amin MB, Reuter VR, Mostofi FK and the Bladder Consensus Conference Committee
Re: use of term “low malignant potential” in bladder neoplasms

“I personally was not a strong advocate of this change although I have no serious issue with it”

RH Young (Professor of Pathology, Harvard Medical School)

March 1999 (Handout USCAP Meeting)
The Christie NHS Foundation Trust

WHO 1973 and 2004 compared

<table>
<thead>
<tr>
<th>WHO 1973</th>
<th>Grade 1 (G1)</th>
<th>Grade 2 (G2)</th>
<th>Grade 3 (G3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO 2004</td>
<td>PUNLMP</td>
<td>Low grade (LG)</td>
<td>High grade (HG)</td>
</tr>
<tr>
<td>WHO 1973 + WHO 2004</td>
<td>G 1 PUNLMP</td>
<td>G 1 LG</td>
<td>G 2 LG</td>
</tr>
</tbody>
</table>

Low grade papillary urothelial carcinoma (all images from Epstein JI; Amin MB; Reuter VE; Mostofi F American Journal of Surgical Pathology. 22:1435-1448, 1998.)
High grade papillary urothelial carcinoma (all images from Epstein JI; Amin MB; Reuter VE; Mostofi F American Journal of Surgical Pathology. 22:1435-1448, 1998.)
Papillary urothelial carcinoma: low grade versus high grade


Low grade:
- Predominantly ordered, yet minimal crowding and minimal loss of polarity, cohesive
- Nuclei round to oval; slight variation in nuclear shape and contour
- Mild variation in nuclear chromatin within and between cells
- Nucleoli usually inconspicuous
- Mitosis occasional at any level
- Umbrella cells usually present

High grade:
- Predominantly disordered with frequent loss of polarity, often discohesive
- Moderate-marked nuclear pleomorphism
- Moderate-marked chromatin variation with hyperchromasia
- Multiple prominent nucleoli may be present
- Mitoses usually frequent at any level
- Umbrella cells may be absent
Bladder biopsy: isolated lesion (10 year old boy)
Same patient (10 year old boy): re-resection specimen
- The [WHO 2004] high-grade group contains a much broader spectrum of tumours than grade 3 in WHO 1973

- Only 4.5% of cases were classified as grade 3, [in WHO 1973] whereas 21.6% of the same group of cases were classified as high-grade carcinoma using WHO/ISUP criteria by one expert group

Dataset for tumours of the urinary collecting system (2nd edition)
[April 2013]

Shanks JH, Chandra A, McWilliam LJ, Varma M

WHO 1973 and 2004 compared

<table>
<thead>
<tr>
<th>WHO 1973</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (G1)</td>
<td>Grade 2 (G2)</td>
<td>Grade 3 (G3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHO 2004</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PUNLMP</td>
<td>Low grade (LG)</td>
<td>High grade (HG)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHO 1973 + WHO 2004</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>G 1 PUNLMP</td>
<td>G 1 LG</td>
<td>G 2 LG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>G 2 HG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>G 3 HG</td>
</tr>
</tbody>
</table>
“The published comparisons, however, have not clearly confirmed that the WHO 2004 classification has better reproducibility than the 1973 classification.

The prognostic value of both grading systems (WHO 1973 and 2004) has been confirmed. Attempts to demonstrate better prognostic value of one of the systems, however, have yielded controversial results.

The majority of clinical trials published to date on TaT1 bladder tumours have been performed using the 1973 WHO classification, and therefore, the following guidelines are based on this version.

Until the prognostic role of WHO 2004 is validated by more prospective trials, both classifications should be used.”
Update for the practicing pathologist: the international consultation on urologic disease-European association of urology consultation on bladder cancer


“The grading system of choice for papillary and flat non-invasive urothelial neoplasia is the WHO 2004/ISUP system”
A four-tiered grading system for bladder cancer based on the WHO 1973 and 2004 classifications van Rhijn et al. 2015

Tier 1
- Tier 2
- Tier 3
- Tier 4

WHO 1973
- Grade 1 (G1)
- Grade 2 (G2)
- Grade 3 (G3)

WHO 2004
- PUNLMP
- Low grade (LG)
- High grade (HG)

WHO 1973 + WHO 2004
- G 1 PUNLMP
- G 1 LG
- G 2 LG
- G 2 HG
- G 3 HG
Molecular abnormalities in bladder cancer  
(reviewed in *Hum Pathol* 2010;41:155-162 and 2011;42:455-81)

LOH chromosome 9q  
*FGFR3* activating mutations  
(the most frequently mutated oncogene in bladder cancer)  
[gene on chromosome 4]

Growth advantage but cell cycle regulation and apoptosis mechanisms intact/genetically stable

*TP53* mutations  
Loss of *RB1*

Disruption of apoptosis  
Genetically unstable
Activating \textit{FGFR3} mutations are found in up to 80\% of grade 1/low grade papillary Ta urothelial carcinomas. \textit{TP53} is typically wild type (lacking mutation). Genetically stable
The aim of any grading system should be to provide the clinician an accurate indication of where a particular tumour lies in the morphological and clinical continuum. In clinical practice, tumour grade is used in conjunction with clinical prognostic factors such as [stage], size and multiplicity of tumours, number of recurrences and interval to first recurrence.

- First published NICE guidelines for bladder cancer
- Covers patient information and support recommendations, diagnosis, risk stratification and staging and recommendations on patient management
- Covers management of locally advanced and metastatic bladder cancer and palliative care for patient with incurable bladder cancer
- Pathology lead: Dr Ashish Chandra (Guys and St Thomas, London)
Risk stratification [for bladder cancer not invading muscularis propria] (NICE Guideline development group) [from NICE guidelines NG2. Feb 2015 http://www.nice.org.uk/guidance/ng2]

**Low risk:**

Urothelial cancer with any of:

- solitary pTaG1 with a diameter of less than 3 cm
- solitary pTaG2 (low grade) with a diameter of less than 3 cm
- any papillary urothelial neoplasm of low malignant potential
Intermediate risk:
Urothelial cancer that is not low risk or high risk, including:
- solitary pTaG1 with a diameter of more than 3 cm
- multifocal pTaG1
- solitary pTaG2 (low grade) with a diameter of more than 3 cm
- multifocal pTaG2 (low grade)
- pTaG2 (high grade)
- any pTaG2 (grade not further specified)
- any low-risk non-muscle-invasive bladder cancer recurring within 12 months of last tumour occurrence
High risk:

Urothelial cancer with any of:

- pTaG3
- pT1G2
- pT1G3
- pTis (Cis)
- aggressive variants of urothelial carcinoma, for example micropapillary or nested variants
Aspects of the NICE guidance pertinent to diagnosis/staging [from NICE guidelines NG2. Feb 2015 http://www.nice.org.uk/guidance/ng2]

- “Obtain detrusor muscle during TURBT”
- “Do not take random biopsies of normal-looking urothelium during TURBT unless there is a specific clinical indication (for example, investigation of positive cytology not otherwise explained)”
- “Record the size and number of tumours during TURBT”
- “Offer people with suspected bladder cancer a single dose of intravesical mitomycin C given at the same time as the first TURBT”
- “Consider further TURBT within 6 weeks if the first specimen does not include detrusor muscle”
- “If the first TURBT shows high-risk non-muscle-invasive bladder cancer, offer another TURBT as soon as possible and no later than 6 weeks after the first resection”
International consultation on urologic disease [ICUD]: approach to grade heterogeneity

Amin MB et al. Mod Pathol 2015;28:612-630

- Assign by highest grade component
- In equivocal cases, consider key cliniopathologic data, including focality/multifocality, previous grade, size, frequency of recurrence, presence/absence of CIS, cytology in deciding whether to ‘upgrade’ an equivocal lesion
- No role for immunohistochemistry or molecular assays in grading

“Currently there are no prognostic immunohistochemical or molecular studies that are recommended to be routinely performed on biopsy or resection specimens”

- Classification of inverted lesions given
- Incipient papillary lesions
- Micropapillary carcinoma (selected aspects)
- Variants of urothelial carcinoma not reviewed by WHO 2004
- Recommended terminology for urine cytology
International consultation on urologic disease [ICUD]: classification of inverted urothelial neoplasia  Amin MB et al. Mod Pathol 2015;28:612-630

- Inverted papilloma
- Inverted PUNLMP
- Inverted urothelial carcinoma, low grade, non-invasive
- Inverted urothelial carcinoma, high grade, non-invasive
- Inverted urothelial carcinoma, high grade, invasive
Inverted urothelial carcinoma, grade 2/low grade, pTa
Urothelial carcinoma with an inverted growth pattern can be distinguished from inverted papilloma by fluorescence in situ hybridisation, immunohistochemistry and morphologic analysis


- 15 inverted papillomas and 29 inverted urothelial carcinomas studied
- MiB-1, p53 and CK20 + UroVysion FISH
- None of the inverted papillomas were positive for MiB-1 or CK20
- 1 inverted papilloma was positive for p53
- For inverted carcinoma 66% were MiB-1+ve, 59% CK20 +ve and 59% p53 +ve
- 3 inverted carcinomas were negative for all 3 markers
- All inverted papillomas had normal UroVysion FISH
- 72% carcinomas had abnormalities by FISH
Telomere shortening distinguishes inverted urothelial neoplasms

- Inverted urothelial carcinoma, inverted papilloma and cystitis glandularis compared (>25 cases of each)
- Quantitative FISH using telomere-specific probe on interphase nuclei
- Telomere lengths in 3 above conditions were 29%, 84% and 91% respectively relative to normal control urothelium
<table>
<thead>
<tr>
<th>Degree of atypia</th>
<th>Exophytic papillary lesion</th>
<th>Flat lesion</th>
<th>Endophytic/inverted lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Papilloma</td>
<td>Normal</td>
<td>Inverted papilloma</td>
</tr>
<tr>
<td>Minimal</td>
<td>PUNLMP</td>
<td>Hyperplasia</td>
<td>Inverted PUNLMP</td>
</tr>
<tr>
<td>Distinct, mild-mod</td>
<td>Pap urothelial carcinoma, low grade</td>
<td>Dysplasia</td>
<td>Inverted pap uro ca, low grade Ta</td>
</tr>
<tr>
<td>Moderate-severe</td>
<td>Pap urothelial Ca, high grade, Ta</td>
<td>CIS</td>
<td>Inverted pap Uro ca, high grade, Ta</td>
</tr>
<tr>
<td>Severe</td>
<td>Pap uro ca HG invasive</td>
<td>HG invasive</td>
<td>Inverted HG invasive</td>
</tr>
</tbody>
</table>
Follow up recommended with rebiopsy of any visible lesions
Papillary urothelial hyperplasia is a clonal precursor to papillary transitional cell carcinoma

Chow N-H et al. *Int J Cancer* 2000;89:514-518

- 15 cases of papillary hyperplasia (PH) examined for LOH at 17 microsatellite markers on chromosome 9
- 53% of PH were clonal
- 9q most frequently lost
- 1 case had identical LOH patterns in PH and papillary carcinoma occurring 3 years later
International consultation on urologic disease [ICUD]: classification incipient papillary lesions  Amin MB et al. Mod Pathol 2015;28:612-630

- Dysplasia with early papillary formations
- Carcinoma in situ with early papillary formations

Such lesions are often seen in patients under surveillance for urothelial neoplasia

Similar changes may be seen following treatments (“truncated papillae of treated papillary carcinoma”)

Correlation with cystoscopic findings is a pre-requisite
Case with conventional invasive urothelial carcinoma and invasive micropapillary carcinoma.