**Grading of TCC**

Murali Varma  
Cardiff, UK  
wptmv@cf.ac.uk

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**Urothelial carcinoma:**  
**Pathologic prognostic factors**

- **Stage**  
  - Most important

- **Grade**  
  - Important only in non-muscle invasive (Ta/T1) tumours  
    - esp. Ta  
    - All T1 treated as high-risk (EAU guidelines)

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**Muscle invasive TCC**  
**Treatment options**

- Radical therapy with/without neoadjuvant chemoRx  
  - Radical radiotherapy  
  - Radical cystectomy

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**Non-muscle invasive TCC:**  
**Prognostic factors**

- Grade  
- Size  
- Number of tumours  
- Number of recurrences  
- Time to first recurrence

*Grade is only of several prognostic factors*

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**Non-muscle invasive TCC:**  
**Risk stratification, treatment and follow-up**

- European Association of Urology (EAU) guidelines  
- [http://www.uroweb.org/guidelines](http://www.uroweb.org/guidelines)  
- European Urology 2013;64:639–653

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**Non-muscle invasive TCC:**  
**Risk group stratification (EAU)**

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk tumours</td>
<td>Primary, solitary, Ta, LG/G1, &lt;3 cm, no CIS</td>
</tr>
<tr>
<td>Intermediate-risk</td>
<td>All tumours not defined in the two adjacent categories (between the category of low and high risk)</td>
</tr>
</tbody>
</table>
| High-risk tumours       | Any of the following:  
  - T1 tumour  
  - HG/G3 tumour  
  - CIS  
  - Multiple and recurrent and large (>3 cm) Ta, G1, G2 tumours (all conditions must be presented in this point) |

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Non-muscle invasive TCC: Treatment recommendations (EAU)

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Treatment recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk tumours</td>
<td>One immediate instillation of chemotherapy</td>
</tr>
<tr>
<td>Intermediate-risk tumours</td>
<td>One immediate instillation of chemotherapy followed by further instillations, either</td>
</tr>
<tr>
<td></td>
<td>chemotherapy for a maximum of 1 yr or 1 yr of full-dose BCG.</td>
</tr>
<tr>
<td>High-risk tumours</td>
<td>Intravesical full-dose BCG instillations for 1–3 yr or cystectomy (in highest risk cases)</td>
</tr>
<tr>
<td>Subgroup of highest risk</td>
<td>Radical cystectomy should be considered</td>
</tr>
</tbody>
</table>

Non-muscle invasive urothelial tumours: Treatment options

- Treatments have significant side effects
- More toxic therapy (BCG) restricted for higher risk disease
- Hence need to identify patients at higher risk of adverse outcome

Non-muscle invasive urothelial tumours: Adverse outcomes

- Recurrence
  - Patient presenting with more tumours
  - Generally recurrence rather than recurrence if original excision complete
    - New tumour
  - May be of same/higher grade and stage
- Progression
  - Grade progression
  - Stage progression

Grading pTa papillary TCC

WHO 1973

- Papilloma – G1 – G2– G3
  - Grade 1: almost normal
  - Grade 3: like carcinoma in situ

Grading pTa papillary tumours

- Established grading system: WHO 1973
- New grading system: WHO 2004 (ISUP)

Grading pTa papillary urothelial tumours: WHO 1973 or 2004?
Grading tumours

- **Groups of patients**
  - Borderline grades cancel each other
  - Inter-observer reproducibility less important
  - Fewer tiers the better?

- **Individual patient**
  - Arbitrary lines in continuum
  - More tiers the better?
  - Inter-observer reproducibility critical

Grading pTa papillary TCC

**WHO 1973**

Papilloma – G1 – G2– G3

<table>
<thead>
<tr>
<th>Benign</th>
<th>Carcinoma TCC</th>
</tr>
</thead>
</table>

**Problems:**

- No criteria defined for various grades

Grading pTa papillary TCC

**WHO 1973**

Papilloma – G1 – G2– G3

**Problems:**

- No criteria defined for various grades
- Large number of tumours end up as G2
- Significant number of G2 tumours progress
- 3 grades of TCC but only 2 Rx options
- “Carcinoma” for non-invasive tumours

Natural History of pTa G1 TCC

- Significant recurrence rate (33%)
- Generally recur as low-grade
- Progression to higher grade/stage rare
- Normal life expectancy
  - Yet classed as cancer (carcinoma)

Grading pTa papillary TCC

**WHO 1973**

• Papilloma – G1 – G2– G3

**ISUP 1998/WHO 2004**

• Papilloma
  • Papillary urothelial neoplasm of low malignant potential (PUNLMP)
  • low-grade carcinoma
  • high-grade carcinoma
When is it a cancer?

**WHO 1973**
- Papilloma
- Grade 1
- Grade 2
- Grade 3
- Invasive

**WHO/ISUP 2004**
- Papilloma
- PUNLMP
- LG
- HG
- Invasive

Severely dysplastic in situ tumour
- Most sites: Carcinoma in situ
- Colon: Adenoma
- Bladder: Carcinoma
  - Urothelial carcinoma!!

Grading pTa papillary TCC

**WHO 2004**
- Papilloma
- Low grade papillary urothelial neoplasm
- High grade papillary urothelial neoplasm

**WHO (1973)**
- Papilloma
- Grade 1
- Grade 2
- Grade 3

**WHO (2004)**
- Papilloma
- PUNLMP
- Low-grade
- High-grade

**WHO/ISUP 2004**
- Provided detailed criteria for each category

**WHO (2004) criteria: Architecture**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Papilloma</th>
<th>PUNLMP</th>
<th>LGPUC</th>
<th>HGPUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Delicate</td>
<td>Delicate, occasionally fused</td>
<td>Fused, branching</td>
<td>Fused, branching</td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Papilloma</th>
<th>PUNLMP</th>
<th>LGUC</th>
<th>HGUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear size</td>
<td>Identical to normal</td>
<td>May be uniformly enlarged</td>
<td>Enlarged with variation in size</td>
<td>Enlarged with variation in size</td>
</tr>
<tr>
<td>Nuclear shape</td>
<td>Identical to normal</td>
<td>Elongated, round-oval, uniform</td>
<td>Round-oval, slight variation in shape and contour</td>
<td>Moderate-marked pleomorphism</td>
</tr>
<tr>
<td>Chromatin</td>
<td>Fine</td>
<td>Fine</td>
<td>Mild variation within and between cells</td>
<td>Moderate-marked variation within and between cells with hyperchromasia</td>
</tr>
<tr>
<td>Nucleoli</td>
<td>Absent</td>
<td>Absent to inconspicuous</td>
<td>Usually inconspicuous</td>
<td>Multiple prominent nucleoli may be present</td>
</tr>
<tr>
<td>Mitoses</td>
<td>Absent</td>
<td>Rare, basal</td>
<td>Occasional, at any level</td>
<td>Usually frequent, at any level, may be atypical</td>
</tr>
<tr>
<td>Umbrella cells</td>
<td>Uniformly present</td>
<td>Present</td>
<td>Usually present</td>
<td>May be present</td>
</tr>
</tbody>
</table>

### WHO 2004 Grading Criteria

- **PUNLMP**
  - Increased thickness but normal polarity
  - Bland cytology: nuclear enlargement
- **Low-grade urothelial carcinoma**
  - *Disturbed architecture* (mild variation in polarity)
  - Bland cytology: mild pleomorphism
- **High-grade urothelial carcinoma**
  - *Disturbed architecture* (marked)
  - Abnormal *cytology* (moderate to severe)

### WHO 2004 Grading Algorithm

1. **Moderate-severe nuclear atypia**
   - Yes
   - Loss of polarity
2. **Yes**
   - High-grade
3. **No**
   - Low-grade
4. **PUNLMP**

### Advantages

- Detailed criteria provided
- Avoids overlap G1-2, G2-3
- Better correlation with urine cytology terminology
- PUNLMP avoids ‘cancer’ label for tumours with excellent prognosis

### 1973

1973

- Grade 1
- Grade 2
- Grade 3

### 2004

- PUNLMP
- Low grade
- High grade
- BCG

- WHO 2004 recommends labelling bad G2 as high-grade and treating them with BCG
- However, BCG therapy has significant unpleasant side effects
WHO(2004)/ISUP

Problems
- Based on expert opinion by consensus
- Bad high-grade tumours have higher risk of progression
  - WHO grade 3?
  - Distinction of these tumours lost in WHO 2004
- A three tier (G1/G2/G3) system may be better than a two tier (LG/HG) system

Grading: 2 tier or 3 tier?
- Reproducibility problem between low-grade and high-grade
  - What is “moderate-marked” cytologic atypia”
  - One persons “bad” low-grade would be another’s “good” high-grade

Grading: 2 tier or 3 tier?
- However it is unlikely that one persons grade 1 would be another’s grade 3 or vice versa
- In WHO 1973, grades 1 and 3 would be distinct
  - But there would be many grade 2 TCCs

WHO 2004: Borderline cases
- Reproducibility issues (inter-observer and intra-observer) would not impact studies on outcome on cohorts
  - Borderline cases likely to be equally distributed among low-grade and high-grade
  - Reproducibility issues would seriously impact individual patient’s management

Which classification (1973/2004)?

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>PUNLMP</td>
<td>Low grade</td>
<td>High grade</td>
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Use both WHO 1973 and WHO 2004?

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<td></td>
</tr>
<tr>
<td>2004</td>
<td>PUNLMP</td>
<td>Low grade</td>
<td>High grade</td>
</tr>
<tr>
<td>Both</td>
<td>G 1 PUNLMP G 1 LG G 2 LG G 2 HG G 3 HG</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Using both 1973 and 2004 provides better stratification
Non-muscle invasive TCC: Risk stratification

- Grade
- Size
- Number of tumours
- Number of recurrences
- Time to first recurrence