Innovations in Renal Cell Carcinoma and Urothelial Cancer
Florida Society of Clinical Oncology Fall General Session 2023

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Recent suggestion for staging of bladder cancer

Subcategorization of pT1

Extent of lamina propria invasion (pT1) in transurethral specimens has prognostic value.
Subcategorization of pT1

• Approaches for subcategorization of pT1
  1. *Micrometric measurements* (microscopic vs extensive invasion)
  2. *Histoanatomical landmarks* such as the muscularis mucosae and the vascular plexus of the lamina propria

• Higher subcategories (both approaches) correlate with recurrence and stage progression.

• Micrometric pT1 approach may better predict outcome.

• Pathologists are strongly encouraged to convey the extent of lamina propria invasion using any of the proposed approaches (2022 WHO GU tumors).
  • Example: urothelial carcinoma focally (*micrometric*) and superficially (*histoanatomically*) invades lamina propria.
Heterogeneity in grade of papillary urothelial carcinoma

- Heterogeneity in grade is characteristic of non-invasive papillary urothelial carcinoma.
- Heterogeneity in grade occurs in one third of tumors and may impact outcome.
- It is recommended to grade the tumor based on its highest-grade component (WHO GU tumors 2022).
  - If high grade component $\geq 5\%$, High grade
  - If high grade component < 5\% with < 5\% high-grade component, Low-grade
Application of AI (Artificial Intelligence) for evaluation of heterogeneity of urothelial carcinoma

Predicting tumor recurrence of low grade papillary urothelial carcinoma

28.5% recurrence rate

87.5% recurrence rate

HR: 5.43 (95% CI 1.1, 26.27)
Molecular Pathways in Bladder Cancer
Molecular Subtypes of muscle invasive urothelial carcinoma (transcriptomic profile classification)
Basal and Luminal subtypes of muscle invasive urothelial carcinoma

Possible origin and transcriptional control of basal and luminal MIBC

Immunohistochemistry

Molecular Subtype Of Muscle Invasive Urothelial Carcinoma

<table>
<thead>
<tr>
<th>Class Name</th>
<th>Luminal Papillary (LumP)</th>
<th>Luminal Non-Specified (LumNS)</th>
<th>Luminal Unstable (LumU)</th>
<th>Stroma-rich</th>
<th>Basal/Squamous (Ba/Sq)</th>
<th>Neuroendocrine-like (NE-like)</th>
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<tbody>
<tr>
<td>% of MIBC</td>
<td>24%</td>
<td>8%</td>
<td>15%</td>
<td>15%</td>
<td>35%</td>
<td>3%</td>
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**Oncogenic mechanisms**
- **Luminal / Luminal**
  - FGFR3 + PPARγ + CDKN2A -
  - PPARγ + E2F3 +, ERBB2 +, Genomic instability, Cell cycle +

**Mutations**
- FGFR3 (40%), KDM6A (38%)
- ELF3 (35%)
- TP53 (76%), ERCC2 (22%), TMB +, APOBEC +
- TP53 (61%), RB1 (25%)
- TP53 (94%) RB1 (39%)*

**Stromal infiltrate**
- Fibroblasts
- Fibroblasts, Myofibroblasts
- Fibroblasts Myofibroblasts
- CD8 T cells, NK cells

**Immune infiltrate**
- B cells

**Histology**
- Papillary morphology (59%)
- Micropapillary variant (36%)
- Squamous differentiation (42%)
- Neuroendocrine differentiation (32%)

**Clinical**
- T2 stage +
- Older patients + (80+)
- Women + T3/T4 stage +
- Median overall survival (years) 4

* 94% of these tumors present either RB1 mutation or deletion.
Clinical Application Of Molecular Subtypes Of Urothelial Carcinoma

- lowest rate of upstaging was seen in patients with luminal tumors without systemic therapy as compared with non-luminal tumors (34% versus 51%)
- The luminal-papillary subtype was strongly associated with FGFR3 alterations $\rightarrow$ FGFR3 inhibitor
- The luminal-infiltrated subtype featured PD1 and PD-L1 and expression of other immune cell-related genes
- Basal subtype was enriched in PD-L1 expression tumor cells.
- Basal subtypes of MIBC tumors show the best overall survival benefit from NAC (77.8% versus 49.2%) at 3-year follow-up.
Summary

• Available data support combining pathology reports incorporating both standardized pathologic data, such as histologic grade, AJCC/TNM stage, and other risk parameters, with relevant molecular information.

• Providing luminal-basal phenotype may provide data on the need to perform additional testing, such as PD-L1 or FGFR3 mutation/translocation analysis, thus serving as quick screening of cases necessitating extra workup.
WHO Classification of Tumors / International Society of Urological Pathology (WHO/ISUP)

histological grading

Grade 1

Grade 2

Grade 3

Grade 4
Survival outcome of RCC bases on WHO Classification of Tumours / International Society of Urological Pathology (WHO/ISUP) histological grading

Clear cell renal cell carcinoma, grade 4 with sarcomatoid and rhabdoid feature showed response to immune checkpoint inhibitor (pembrolizumab)
Radical nephrectomy (4/2018)
Clear Cell Renal Cell Carcinoma
Tumor Necrosis

Sarcomatoid RCC (Grade 4)
Perinephric Invasion (pT3a)
PDL1 Immunostain
Combined Positive Score (CPS) : 5