What’s New in Pathology of Genitourinary Tumors

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Kidney Tumors

- Multilocular cystic renal neoplasm of low malignant potential
  - Old name: Multilocular cystic renal cell carcinoma
  - No death or metastasis
Multilocular cystic renal neoplasm of low malignant potential
Multilocular cystic renal neoplasm of low malignant potential
Hereditary leiomyomatosis and RCC-associated RCC

- Rare tumor
- Characteristic morphology
- Germline mutation in *FH* (encoding fumarate hydratase) at 1q42.3-q43
- Poor prognosis with early metastasis
MiT family translocation carcinoma

- Harbor gene fusion involving \( TFE3 \) (Xp11 translocation) or \( TFEB \) (6:11 translocation)
- Originally discovered in young patients.
- Present in adults as well
- IHC or break-apart FISH
MiT family translocation carcinoma
• Xp11 translocation RCC is similar to clear cell RCC in survival (worse than papillary RCC)
• Distant metastasis and older age predicts death
• ASPSCR1-TFE3 RCCs more likely to have regional nodal mets than PRCC-TFE3 RCCs
• Most nodal+ ASPSCR1-TFE3 RCC patients remain disease-free without adjuvant therapy
• T(6:11) RCCs are more indolent that Xp11 RCCs
Succinate dehydrogenase-deficient RCC

• Very rare. Between 14 and 76 years old (mean age=38; median age=35). M:F=1.8:1. Majority low grade.
• Hereditary, with mutation in a SDH gene (SDHB>SDHC>SDHA or SDHD)
• Personal or family history of SDH-deficient RCC, paraganglioma, GIST or pituitary adenoma may be present (autosomal dominant tumor syndrome)
• All patients should be offered genetic testing
• Confirmed by loss of SDHB expression on IHC
Tubulocystic RCC

- Uncommon cystic renal epithelial malignancy
- Most incidentally discovered, 70% in left kidney
- Most present as a solitary, well-circumscribed multicystic mass.
- Gain of chromosome 7 and 17, and loss of the Y chromosome (close relationship with papillary RCC)
- Majority behave indolently.
Acquired cystic disease-associated RCC

- In the background of end stage renal disease and acquired cystic disease (long term hemodialysis).
- Variable architecture, microcysts and intratumoral oxalate crystals. Often multifocal and bilateral.
- Most are indolent.
Clear cell papillary RCC

- Typically detected incidentally.
- Morphologic overlap with clear cell RCC and papillary RCC. Molecular profile is distinct.
- Typically indolent.
Clear cell papillary RCC
Prostate Cancer: Prognostic grouping

- Divide prostate cancer into 5 different prognostic groups (Groups 1-5)
- Not a new grading system
- Re-grouping of Gleason grading system
- Group I (3+3), II (3+4), III (4+3), IV (4+4), and V (Combined score of 9 or 10)
- The premise is that indolent tumor would be group 1 instead of having 6 points
Measuring cancer length and percentage on biopsy cores
Measuring cancer length and percentage on biopsy cores
Metastatic Prostate Cancer

- Cancer kills patients by metastasis
- Bone, lymph nodes, visceral organs and soft tissue
- Little is known about metastatic tumors
SU2C/AACR/PCF West Coast Dream Teams

- UCLA, UCSF, UC Davis, UC Santa Cruz, OHSU, University of British Columbia
- Team consists of basic researchers, translational scientists, interventional radiologists, urologists, medical oncologists and pathologists.
• Plan is to biopsy metastatic tumors from 300 men who have failed medical therapy.
• Tumor tissue is subjected to histologic examination, RNAseq (after LCM) and Iron Torrent study with a pre-determined panel (whole exome sequencing planned).
West Coast Dream Team Biopsy Trial

- Metastatic Prostate Cancer
- Testosterone <50 ng/dL
- Progressing after AR-targeting or microtubule targeting drugs (e.g. abiraterone acetate, MDV3100, docetaxel, cabazitaxel, etc)
- Ability to tolerate radiologically-guided biopsies

Every 3 Month Clinical Assessment

Treatment(s)

Serum, Plasma, and Blood for CTC’s collected at baseline, 3 months after therapy begins, and at progression.

n = 300
<table>
<thead>
<tr>
<th>Anatomic Site</th>
<th>Biopsies Processed (n)</th>
<th>Positive Biopsies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>134</td>
<td>94 (70%)</td>
</tr>
<tr>
<td>Liver</td>
<td>26</td>
<td>24 (92%)</td>
</tr>
<tr>
<td>Node</td>
<td>66</td>
<td>60 (91%)</td>
</tr>
<tr>
<td>Other Soft Tissue</td>
<td>21</td>
<td>19 (90%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>247</strong></td>
<td><strong>197 (80%)</strong></td>
</tr>
</tbody>
</table>
Metastatic CRPC (Adenocarcinoma)
Metastatic CRPC (Adenocarcinoma)
Small cell carcinoma
<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Adenocarcinoma</th>
<th>IAC</th>
<th>SCNC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytoplasm</td>
<td>Abundant</td>
<td>Moderate to abundant</td>
<td>Scant</td>
</tr>
<tr>
<td>Nuclear chromatin</td>
<td>Clumpy, vacuolated, open chromatin pattern</td>
<td>Fine homogeneous chromatin pattern</td>
<td>Fine homogeneous chromatin pattern</td>
</tr>
<tr>
<td>Nuclear staining</td>
<td>Light</td>
<td>Dark</td>
<td>Dark</td>
</tr>
<tr>
<td>Nuclear shape</td>
<td>Some degree of irregularity</td>
<td>Round and regular</td>
<td>Irregular</td>
</tr>
<tr>
<td>Nuclear molding</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Nucleoli</td>
<td>Prominent macronucleoli</td>
<td>Absent or central small nucleolus</td>
<td>No nucleoli</td>
</tr>
<tr>
<td>Crush artifact</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Mitotic figures</td>
<td>Rare</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Glandular formation</td>
<td>Obvious</td>
<td>Vague</td>
<td>No</td>
</tr>
</tbody>
</table>
A novel histologic variant of metastatic prostate cancer

Adenocarcinoma

IAC

Small cell carcinoma
<table>
<thead>
<tr>
<th></th>
<th>Pure Adeno (N = 53)</th>
<th>Pure IAC (N = 40)</th>
<th>Pure SCNC (N = 16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AR amplification by FISH (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>28 (53%)</td>
<td>22 (55%)</td>
<td>8 (53%)</td>
<td>0.886</td>
</tr>
<tr>
<td>Negative</td>
<td>25 (47%)</td>
<td>16 (40%)</td>
<td>7 (44%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>2 (5%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Median log AR transcript reads (range)</strong></td>
<td>15.11 (1.97-20.13)</td>
<td>14.83 (9.31-18.03)</td>
<td>15.05 (2.50-17.99)</td>
<td>0.183</td>
</tr>
<tr>
<td><strong>Median AR pathway activity signature score (range)</strong></td>
<td>-0.06 (-1.83-2.42)</td>
<td>-0.09 (-3.82-5.891)</td>
<td>-1.58 (-2.76-0.49)</td>
<td>0.034*</td>
</tr>
<tr>
<td><strong>AR nuclear expression by IHC (%)</strong></td>
<td>N = 31 cases evaluable</td>
<td>N = 24 cases evaluable</td>
<td>N = 9 cases evaluable</td>
<td>0.749</td>
</tr>
<tr>
<td>Positive</td>
<td>27 (87%)</td>
<td>21 (88%)</td>
<td>7 (78%)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>4 (13%)</td>
<td>3 (12%)</td>
<td>2 (22%)</td>
<td></td>
</tr>
</tbody>
</table>

* Overall p-value = 0.034 across the three histologic subtypes. Adeno vs. non-adeno p-value = 0.132; SCNC vs. non-SCNC p-value = 0.024.*
IAC carries a poor prognosis despite bland cytology

Log rank $P = 0.132$

Survival Probability

Adeno: 25.8 m
IAC: 19.1 m
SCNC: 12.8 m
Overal Survival of Adeno vs Non-Adeno (SCNC+IAC)

Log rank P = 0.018

Adeno: 25.8 m
Not-adenocarcinoma (SCNC + IAC)
Median = 11.1 m
IAC vs. Adeno 50-gene Signature (AUC = 0.802)
<table>
<thead>
<tr>
<th>Signature</th>
<th>5-MR</th>
<th>360-MR</th>
<th>50-gene</th>
<th>Dense</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Cell vs Not</td>
<td>0.801</td>
<td>0.847</td>
<td>.755</td>
<td>.894</td>
</tr>
<tr>
<td>Small Cell vs IAC</td>
<td>0.682</td>
<td>0.788</td>
<td>.682</td>
<td>.879</td>
</tr>
<tr>
<td>Small Cell vs Adeno</td>
<td>0.780</td>
<td>0.811</td>
<td>.879</td>
<td>.902</td>
</tr>
<tr>
<td>IAC vs Adeno</td>
<td>0.405</td>
<td>0.541</td>
<td>.802</td>
<td>.620</td>
</tr>
<tr>
<td>Adeno vs Not</td>
<td>0.509</td>
<td>0.705</td>
<td>.764</td>
<td>.575</td>
</tr>
</tbody>
</table>

As few as 5 regulators often accurate enough
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