USCAP 2018 – Vancouver

HIGHLIGHTS

Bexiga

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INSTITUTO DE ANATOMIA PATOLÓGIA,
Responsável Técnico - Piracicaba/ SBO/Americana
Scientific:
COMPANION MEETING (ISUP)
POSTER SESSION
PLATFORM PRESENTATION

Educational:
EVENING SPECIALTY CONFERENCE
SHORTS COURSES
LONG COURSE
INTERACTIVE MICROSCOPY

General:
EXHIBITORS SEMINARS
HOT TOPICS
SPECIAL LECTURES
The Importance of Pathologic Evaluation in the Management of Non-muscle Invasive Bladder Cancer

Donna Hansel, UCSD
Non-muscle invasive bladder carcinoma

- Broad term that encompasses different grades, stages, molecular profiles and likely different biology
- Grouped together since lower risk of metastasis
- Majority of cases (>90%) are urothelial carcinomas

- Low-grade papillary urothelial carcinoma (Ta, low grade)
- High-grade papillary urothelial carcinoma (Ta, high grade)
- Urothelial carcinoma in situ (Tis)
- Lamina propria-invasive urothelial carcinoma (T1)
....but there are also some diagnostic challenges

• The diagnosis is not always straightforward
  • Grade heterogeneity
  • “Borderline” lesions
  • Limited sampling, cautery artifact, tangential sectioning
  • Mimickers of high-grade and/or invasive disease
  • Variant morphology

• There are a number of lesions that fall below the threshold of “carcinoma”
  • Urothelial proliferation of uncertain malignant potential (UPUMP)
  • Papilloma
  • Papillary urothelial neoplasm of low malignant potential (PUNLMP)
  • Urothelial dysplasia
Distinguishing from LGPUC: Urothelial papilloma

- Thin fibrovascular cores
- Normal urothelium
  - Sometimes with vacuolization of the umbrella cell layer
- Often affects younger patients
- No progression and generally do not recur
  - These are considered benign entities by urologists
Normal urothelium
Polypoid cystitis
Distinguishing from LGPUC: Papillary urothelial neoplasm of low malignant potential (PUNLMP)

- Thin fibrovascular cores
- Thicker urothelial lining (increased proliferation)
- Mitotic figures limited to basal layer of the urothelium
- No atypia
- Can recur in 35-60% of cases

- Low rate of progression
  - 8% progress to invasive carcinoma (up to 13 years)
  - 30-40% progress to LGUCC
Thicker urothelium
No atypia
High-grade papillary urothelial carcinoma

- Thin fibrovascular cores
- Loss of polarity
- Marked atypia of the cells
- Increased mitotic activity that is full thickness
- Loss of cohesiveness
- Denudation may be prominent
- Treatment involves BCG, repeat TUR
Do not use micropapillary CIS as a diagnosis.....
Challenges in getting to a neoplasm: UPUMP and urothelial dysplasia

- Includes both prior “hyperplasia” and “papillary hyperplasia”

- Marked thickening with or without early tenting but no true papillary cores

- Unclear outcomes in the de novo setting

- In the setting of prior neoplasia, may represent an early recurrence
Eixos não arborescentes
Analysis of T1 Bladder Cancer on Biopsy and Transurethral Resection Specimens
Comparison and Ranking of T1 Quantification Approaches to Predict Progression to Muscularis Propria Invasion

Mariah Z. Leivo, MD,* Debashis Sahoo, PhD,† Zachary Hamilton, MD,‡ Leili Mirsadraei, MD,* Ahmed Shabaik, MD,* John K. Parsons, MD, PhD,‡ Andrew K. Kader, MD,‡ Itaaar Derweesh, MD,‡ Christopher Kane, MD,‡ and Donna E. Hansel, MD, PhD*‡

Alleviates many other potential predictors: angiolympathic invasion, muscularis presence, etc.
Is recognizing a variant helpful in determining progression?

- Several categories of urothelial carcinoma variants considered to behave more aggressively
  - Micropapillary and plasmacytoid, among others
  - Early cystectomy and/or modification of chemotherapy based on presence of these variants on pathology report
  - However, some studies suggest stage-for-stage no difference in outcomes

- What can account for these differences in pathology?
  - Does the amount of the variant matter? Maybe
    - Recommendation by WHO to include % of each variant present in the report
  - Can we reliably identify variants? Not always
  - Has the definition changed over time? Yes
  - Is correct terminology being used? Not always
  - Can ancillary testing (including molecular) help us be more objective? Maybe
Conclusions

• Variations in diagnosis based on individual pathologist opinion, changing definitional criteria, sampling variance, terminology inconsistency can all affect outcomes studies

• Additional variations in clinical practice, urologist and oncologist practice and approach also influence outcomes

• More work needs to be done to develop objective markers related to grading, staging and identification of aggressive tumor behavior
CARCINOMA UROTELIAL

POSTERS
Quantidade de trabalhos apresentados como POSTER no USCAP/2018 e sua qualificação quanto ao propósito do estudo

![Bar Chart]

- **PROSTATA**: MOLECULAR - 30, DIAGNÓSTICO/PROGNÓSTICO - 25
- **BEXIGA**: MOLECULAR - 15, DIAGNÓSTICO/PROGNÓSTICO - 25
- **RIM**: MOLECULAR - 15, DIAGNÓSTICO/PROGNÓSTICO - 25
- **PENIS/TESTICULO**: MOLECULAR - 10, DIAGNÓSTICO/PROGNÓSTICO - 15
Distribuição dos 18 trabalhos em bexiga apresentados como POSTER no USCAP/2018 com propósito

**DIAGNÓSTICO/PROGNÓSTICO**

**puramente histológico**

- Diagnóstico: 5
- Estadiamento: 3
- Prognóstico/resposta: 1

**1 a 2 marcadores**

- Diagnóstico: 5
- Estadiamento: 4
- Prognóstico/resposta: 3
Yoga with Dr. Lamps • Abstracts
Platform Presentations • Poster Presentations • Abstract Supplements • iPoster • Poster Guidelines

CLAIM CME/SAM AND VIEW POST MEETING MATERIALS

USCAP Thanks you for attending the 2018 Annual Meeting in Vancouver, British Columbia, Canada.

USCAP's Annual Meeting in Vancouver will exceed your expectations and give you a glimpse of both contemporary and vibrant pathology education at its best. The Academy encourages you to make the most of this conference, designed for a broad spectrum of learning and social opportunities from Hot Topics to social media. Don't miss the Long Courses about "doing more with less."

Augment your general registration by pre-selecting short courses, interactive microscopy sessions, evening specialty conferences and special courses in genomics and leadership. Do this up front when you register for the meeting! Don't wait to secure your place in courses that mean the most to you and which may sell out. Each interactive microscopy session can accommodate only nine learners; so be sure to review the fantastic lineup of teachers and topics. We are hoping to welcome 100 registrants for each Hot Topics session, but seating is limited.

The Academy has received 3,266 abstracts, with top research destined for platform and poster sessions. Dr. Stanley Hamilton of MD Anderson Cancer Center will deliver the Maude Abbott Lecture on "The Pathologist and Individualized Cancer Therapy," and Dr. H. Gilbert Welch of the Dartmouth Institute will discuss "Overdiagnosis and Cancer Screening: Challenges Posed by Birds, Rabbits, and "Surfing" for the Timely Topics lecture. The Generation U party is a celebration of our profession and USCAP's expression of appreciation for attending the meeting.

Vancouver is a special place. Be sure to check Canadian travel instructions on our website and make sure your passport does not expire within six months of this international conference. Please book within the USCAP Hotel Block whenever possible, in order to support the Annual Meeting. Get ready for another unforgettable USCAP experience!

2018 PLATINUM SPONSORS
1. Clinical Significance of Perivesical Lymph Node Metastasis in Radical Cystectomy for Bladder Cancer
2. Refining the Diagnostic Criteria for Flat Urothelial Lesions Using ISUP Imagebase
3. Clinical Utility and Concordance of Upper Urinary Tract Cytology and Biopsy in Predicting Clinicopathologic Features
4. Divergent Histology and Aggressive Pathologic Features at Transurethral Resection of Bladder Tumor Correlate to Response Failure with Neoadjuvant Chemotherapy
5. Microscopic Bladder Neck Invasion Re-Visited: Correlation with Tumor Topography, Staging and Grading
6. An Audit of Pathologic Diagnoses in Urethral Biopsy Specimens
7. Female Urethral Carcinoma: Analysis of 29 Cases and Proposal for a New Staging System
8. A Series of 17 Cases of Primary MALT Lymphoma of the Bladder

1. Immunohistochemical (IHC) Staining Patterns of Ki-67 and p53 in Florid Reactive Urothelial Atypia (RA) and Urothelial Carcinoma In SiTu (CIS) Demonstrate Significant Overlap
3. Dual Staining of Karyopherin Alpha2 and CK20 in the Evaluation of Urothelial Carcinoma in situ of the Bladder
4. PD-L1 Expression Correlates with Lack of Response to BCG Therapy in Non-Muscle Invasive Bladder Cancer
5. PD-L1 Expression Highlights Key Differences in Expression between Urothelial Carcinoma Variants
6. PD-L1 Expression in Upper Tract Urothelial Carcinomas Associated with Higher Pathological Stage
7. Expression of aromatase in tumor-related stroma is associated with human bladder cancer progression
8. COX-2 immunostaining in Urothelial Carcinoma of the Urinary Bladder is associated with Invasiveness and Poor Prognosis
9. Mitotic Index and Recurrence of Non-Invasive Papillary Urothelial Cell Carcinoma.
CARCINOMA UROTELIAL

PODIUM
**Introdução:** Mutações em *FGFR3, HRAS* e *TERT* promoter foram relatados nestas entidades, em frequências variadas, mas não há um estudo molecular compreensivo até o momento.
Conclusão: Diferente do carcinoma urotelial, mutações de ativação do KRAS e HRAS são as mais comuns nos papilomas (e são mutuamente exclusivas). Mutações em FGFR3 e TERT são raras e em genes modificadores de cromatina são pouco comuns.

NGS – 468 genes
13 homens, 3 mulheres

<table>
<thead>
<tr>
<th></th>
<th>9 clássicos</th>
<th>7 invertidos</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRAS</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>KRAS</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>BRAF</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>TERT</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>FGFR3</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
BK Viral integration in Urologic Malignancies
University of Utah, UCSF, Cedars-Sinai

- Expressão de SV40 nas células tumorais em um CDC;
- Ausência de replicação viral no tecido benigno adjacente.
BK Viral integration in Urologic Malignancies
University of Utah, UCSF, Cedars-Sinai

Conclusão: Os sítios de integração do vírus foram clonais, mas não sítio-específico (distribuídos randomicamente nos genomas humano e viral). Significado incerto, porém pode corresponder a uma predisposição à instabilidade genômica e transformação oncogênica.

NGS – 500 genes
PVAUMs = 7 UrCa e 1 CDC

• Polyoma virus associated urologic malignancies (PVAUMs) em pacientes imunocomprometidos.
• Integração viral foi detectada tanto em amostras benignas e malignas.
• Éxons, íntrons, em diferentes genes.
NGS of Primary Adenocarcinoma of the Urinary Bladder
Instituto Português de Oncologia do Porto e Bioptická Laborator (Rep. Tcheca)

Conclusão: Os genes mais frequentemente mutados (>50%) em todos os grupos (*KMT2C, NOTCH1, TP53, BRCA, NF1, ARID2*) não têm overlap e são em linhas gerais diferentes dos genes reportados para adenocarcinoma colônico (*PIK3CA, FBXW7, SMAD4, NRAS, CTNNB1, SMAD2, SOX9*) e carcinoma urotelial (*FGFR3, PIK3CA, HRAS, RB1, TERT*), exceto o *TP53*.

12 Non-urachal Enteric-type Adenocarcinomas
10 Urachal Adenocarcinomas
02 Mucinous Adenocarcinomas
04 Colonic Metaplasias/Adenomas.
Variants and Concomitant Tumor Morphologies Associated with Gene Expression Subtypes of Bladder Cancer in Radical Cystectomy Specimens – University of Chicago

Introdução: Os subtipos Luminal e Basal foram previamente caracterizados geneticamente (BASE47) (Damrauer et al. 2014). Entretanto, histomorfologia detalhada destes diferentes subtipos permanece incompleta e baseada em amostras limitadas.

LUMINAL
GATA3 +
CK5/6 -

BASAL
GATA3 -
CK5/6 +
Conclusão: O estudo identifica novos correlatos morfológicos dos subtipos moleculares em câncer de bexiga. Subtipo não-luminal associa-se a morfologia escamosa, sarcomatoide e pleomorfismo acentuado.

- 48 pT2+, sendo 34/48 (71%) com diferenciação divergente
- Outras variantes, multifocalidade, CIS, LFN+ = sem diferenças entre os subtipos
- Pleomorfismo acentuado, com multinucelação = exclusivo de Basal.

<table>
<thead>
<tr>
<th></th>
<th>Luminal</th>
<th>Basal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escamoso (&gt;1%)</td>
<td>29%</td>
<td>47%</td>
</tr>
<tr>
<td>Escamoso (&gt;30%)</td>
<td>7%</td>
<td>47%</td>
</tr>
<tr>
<td>sarcomatoide</td>
<td>0%</td>
<td>24%</td>
</tr>
<tr>
<td>micropapilífero</td>
<td>6%</td>
<td>12%</td>
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Clinical Significance of Urothelial Carcinoma Ambiguous for Muscularis Propria Invasion on Initial Transurethral Resection of Bladder Tumor – The Johns Hopkins Hospital

**Introdução:** Em alguns casos, a RTU inicial é ambígua para invasão da MP e os pacientes podem ser submetidos a uma re-RTU. O significado clínico do diagnóstico “AMP” ainda não foi objeto de estudo.
Clinical Significance of Urothelial Carcinoma Ambiguous for Muscularis Propria Invasion on Initial Transurethral Resection of Bladder Tumor – The Johns Hopkins Hospital

Conclusão: A maioria dos pacientes com “AMP” na RTU inicial são pT2+ na cistectomia (28/34; 82%), mas menos extensão extravesical, invasão de órgãos pélvicos e linfonodos positivos, com sobrevida mais próxima de pacientes que se apresentaram como pT1 na RTU.

<table>
<thead>
<tr>
<th></th>
<th>pT1 RTU N=127</th>
<th>pT2 RTU N=267</th>
<th>Ambíguo N=34</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT2 na cistectomia</td>
<td>19%</td>
<td>21%</td>
<td>37%</td>
</tr>
<tr>
<td>pT3 na cistectomia</td>
<td>9%</td>
<td>16%</td>
<td>9%</td>
</tr>
<tr>
<td>Linfonodos +</td>
<td>24%</td>
<td>37%</td>
<td>21%</td>
</tr>
<tr>
<td>Sobrevida</td>
<td>86%</td>
<td>59%</td>
<td>82%</td>
</tr>
</tbody>
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Conclusion:

• PD-L1 expression was common (highest in urothelial carcinoma with squamous differentiation), suggesting potential benefit from anti-PD1/PD-L1 therapies.
• SP263 > 22C3 > SP142 with significant correlation among them.

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Escamoso</td>
<td>94%</td>
</tr>
<tr>
<td>Micropapilífero</td>
<td>19%</td>
</tr>
<tr>
<td>Glandular</td>
<td>67%</td>
</tr>
<tr>
<td>Em ninhos</td>
<td>36%</td>
</tr>
<tr>
<td>Plasmocitoide</td>
<td>21%</td>
</tr>
<tr>
<td>Small cell</td>
<td>17%</td>
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A Subset of Lipid-rich Urothelial Carcinoma Show MDM2 Immunostaining and Amplification by FISH
Matoso A et al. The Johns Hopkins Hospital

Introdução: A variante Lipid-rich do carcinoma urotelial é rara e caracterizada por células tipo lipoblastos e prognóstico desfavorável. Há relatos de que apresentam alterações moleculares típicas do carcinoma urotelial, expressão variável de CK e lipídios intacitoplasmáticos ultraestruturalmente. Seriam essas alterações mais próximas de um lipossarcoma?

17 RTU: 8 pT2, 5 pT1 e 6 pT?
10 IHC & 8 FISH
2 a 30% de componente lipid-rich
9/19 eram tumores polipoides
2/19 tinham CIS associado

Courtesy of Dr. Andres Matoso, JHH
GATA3 (+) 100%

HMWCK (+) 86%

P63 (+) 43%

UROPLAKIN2 (+) 0%

Courtesy of Dr. Andres Matoso, JHH
ADIPOPHILIN (+) in 100%

Courtesy of Dr. Andres Matoso, JHH
MDM2 (+) 50%

5/8 FISH+ (4/5 IH+)
3/8 FISH- (3/3 IH-)

Courtesy of Dr. Andres Matoso, JHH
MDM2 was FISH(+) 80% of IHC(+) cases and (-) 100% of IHC(-)

Red is MDM2

Courtesy of Dr. Andres Matoso, JHH
A Subset of Lipid-rich Urothelial Carcinoma Show MDM2 Immunostaining and Amplification by FISH
The Johns Hopkins Hospital

**Conclusão:** Cerca de metade mostram MDM2 por IHC e FISH. Deveriam ser chamados de carcinoma urotelial sarcomatoid com transdiferenciação para lipossarcoma?
Como em contraste com a maioria dos carcinomas sarcomatoides, o componente lipossarcomatoso tende a ser focal, considerou-se melhor a terminologia de variante lipid-rich.
Existe uma busca ativa por refinamentos no diagnóstico do carcinoma urotelial que inclui:

1. Critérios mais objetivos para entidades de conduta potencialmente conservadora;
2. Critérios mais objetivos para variantes que indicam pior prognóstico.
3. Marcadores preditivos de resposta terapêutica e prognóstico e associados aos subtipos luminal e basal, já relativamente bem estabelecidos.
4. Numerosos estudos moleculares direcionados às terapias emergentes para carcinoma avançado, em especial PD-L1, que já está aprovado para uso nos EUA e Brasil.
Obrigada!