BLADDER CANCER – WHAT IS NEW AND CLINICALLY RELEVANT

Canadian Geese - Geist Reservoir (my backyard), Indianapolis, USA

BLADDER CANCER EPIDEMIOLOGY

BLADDER CANCER MODEL

Meyer M. Melicow, 1975

BLADDER CANCER GENETICS

Zieger et al. Int J Cancer 125;2095, 2009
WHO/ISUP 2004 CLASSIFICATION

• NORMAL
• HYPERPLASIA
• FLAT LESIONS WITH ATYPIA
  – Reactive (inflammatory) atypia
  – Atypia of unknown significance
  – Dysplasia (low grade intraurothelial neoplasia)
  – Carcinoma in situ (high grade intraurothelial neoplasia)
• PAPILLARY NEOPLASMS
  – Papilloma
  – Inverted papilloma
  – Papillary neoplasm of low malignant potential
  – Papillary carcinoma, low grade
  – Papillary carcinoma, high grade
• INVASIVE NEOPLASMS

NORMAL UROTHELIUM

Cytokeratin 20
UROTHELIAL HYPERPLASIA

REACTIVE ATYPIA
REACTIVE ATYPIA

DYSPLASIA
DYSPLASIA

Or Incipient Papillary Neoplasia?

CIS WITH UMBRELLA CELLS

Cytokeratin 20
CIS - LARGE CELL

CIS - LARGE CELL
CIS - LARGE CELL

CIS – “SMALL CELL”
CIS - DENUDING

CIS – DENUDING – VON BRUNN’S NESTS
CARCINOMA IN SITU – p53 IHC

~ 80% Positive

CARCINOMA IN SITU

CK20
**UROTHELIAL CARCINOMA IN SITU - LONG TERM OUTCOME**

<table>
<thead>
<tr>
<th>SURVIVAL-TYPE</th>
<th>10-Year</th>
<th>15-Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free</td>
<td>63%</td>
<td>59%</td>
</tr>
<tr>
<td>Cancer-specific</td>
<td>79%</td>
<td>74%</td>
</tr>
<tr>
<td>All-cause</td>
<td>55%</td>
<td>40%</td>
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</tbody>
</table>

*Cheng et al, Cancer 85:2469, 2000*
Canadian geese taking off from ice – Geist Reservoir

PAPILLOMA
52/164 (32%) papillary UC were grade heterogeneous

WHO 1973 vs WHO 2004

Papilloma

Papillary ca, I

Papillary ca, II

Papillary ca, III

Papillary urothelial neoplasm of low malignant potential

Papillary ca, low grade

Papillary ca, high grade
GRADE DISTRIBUTION
WHO 1973 vs WHO 2004

Samaratunga et al. Urology 60:315, 2002

pTa BLADDER CA
LONG TERM OUTCOME

Pan et al, AJCP 133:788, 2010
STAGING OF BLADDER CANCER (2010 TNM)

- **pTa** Non-invasive, papillary
- **pTis** Non-invasive, flat
- **pT1** Invasion of subepithelial connective tissue (lamina propria)
- **pT2** Invasion of muscularis propria
  - **pT2a** inner one-half
  - **pT2b** outer one-half
- **pT3** Invasion of perivesical tissue
  - **pT3a** microscopically
  - **pT3b** macroscopically
- **pT4** Invasion of adjacent structures
BLADDER CANCER: OUTCOME AFTER CYSTECTOMY

N=1,100


TREATMENT OF T1 DISEASE

Understanding Bladder Cancer Death

Tumor Biology Versus Physician Practice

David S. Morris, MD, Alon Z. Weizer, MD, Zaojun Ye, MS, Rodney L. Dunn, MS, James E. Montie, MD, and Brent K. Hollenbeck, MD, MS

"On the basis of clinical and administrative data, we estimate that between 31.2% and 46.8% of deaths potentially were avoidable."

Cancer 115:1011, 2009
TREATMENT OF T1 DISEASE

Seminar article
Optimal timing of radical cystectomy for patients with T1 bladder cancer
Bernard H. Bochner, M.D., FACS*
Urology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY 10017, USA

Invasive T1 bladder cancer: indications and rationale for radical cystectomy
John P. Stein* and David F. Penson
Department of Urology, University of Southern California Keck School of Medicine, Norris Comprehensive Cancer Center, Los Angeles, CA, USA
Accepted for publication 22 February 2004

DIAGNOSIS OF INVASION

Irregular nests
Stromal response
DIAGNOSIS OF INVASION

Increased cytoplasm
Retraction artifact
DIAGNOSIS OF INVAsION

T1 SUBSTAGING

HGPUC T1 ≤ 1mm vs > 1mm
HGPUC Ta vs T1 ≤ 1mm

**T1 SUBSTAGING**

(≤ 1 HPF vs > 1 HPF)

Progression-free survival  
Cancer-specific survival

![Graphs showing survival rates with P-values](image)


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**MUSCULARIS MUCOSAE**
TRIGONE REGION

![Microscopic Image of TRIGONE REGION](image1)

TRIGONE REGION

![Microscopic Image of TRIGONE REGION](image2)
MUSCULARIS MUCOSAE INVASION

MUSCULARIS MUCOSAE INVASION
pT1 – SUBSTAGING: MUSCULARIS MUCOSAE

"pT1a"

"pT1b"

SURVIVAL ACCORDING TO MUSCULARIS MUCOSAE INVASION

• 343 patients - initial treatment
  • 170 pT1
• Cases centrally reviewed
• Substaging possible in 99 (58%)
• Treated by:
  • TURBT with intravesical tx

Angulo et al, J Cancer Res Clin Oncol 119:578, 1993
T1 UC WITH LYMPHANGIOVASCULAR INVASION

- 118 newly diagnosed T1; all with TURBT +/- intra-vesical tx (85%)
- LVI diagnosis based on H&E alone
- LVI diagnosed in 33 cases (28%)

Figure 2. Disease recurrence-free (A), progression-free (B) and metastasis-free (C) survival curves by LVI


CIS WITH LYMPHANGIOVASCULAR INVASION
PROBLEMS WITH IDENTIFICATION OF LYMPHVASCULAR INVASION

“The general use of immunohistochemistry in the routine setting, however, cannot be recommended” Amin et al. Pathology Consensus Guidelines, International Consultation on Urologic Diseases, 2012

UROTHELIAL CARCINOMA - PATTERN OF INVASION

UROTHELIAL CARCINOMA SURVIVAL BY PATTERN OF INVASION


American Coots and a couple of mallards, Geist Reservoir, Indianapolis, IN
UROTHELIAL CARCINOMA
HISTOLOGIC VARIANTS

- Mixed differentiation
  - Nested variant
  - Microcystic variant
  - Micropapillary variant
  - Plasmacytoid variant
  - Inverted growth pattern
    - Clear cell type
    - Lipid-rich
  - Lymphoepithelioma-like variant
    - Lymphoma-like tumors
    - Villoglandular architecture
    - Tumors with HCG production
    - Sarcomatoid carcinoma

UROTHELIAL CARCINOMA
MICROPAPILLARY TYPE

**CLINICAL**
- Similar epidemiology to usual TCC
- High stage, 50% with + LN at diagnosis
- Worse prognosis with high % MP

**PATHOLOGY**
- Small, tight clusters of cells
- Open spaces simulating lymphatic invasion
- Deeply invasive
- Suggested to be a form of glandular differentiation
- Inversion of MUC1 staining to stromal aspect
MICROPAPILLARY VARIANT
MICROPAPILLARY VARIANT

MICROPAPILLARY VARIANT
UC - MICROPAPILLARY VARIANT

UC - MICROPAPILLARY VARIANT: DIAGNOSTIC CRITERIA

• High degree of agreement with “classical cases” (Kappa value 0.79)
• Less agreement for equivocal cases
• Key features for diagnosis included:
  • Extensive retraction artifact
  • Multiple nests within the same lacunar space
  • Epithelial ring forms
  • Peripheral nuclear orientation

UC - MICROPAPILLARY VARIANT
URETER FROZEN SECTION

UC - MICROPAPILLARY VARIANT
UC – MICROPAPILLARY VARIANT: OUTCOME

![Graphs showing Kaplan-Meier plots](image)

*Fig. 2* Kaplan-Meier plots showing bladder cancer-specific mortality probability for conventional urothelial carcinoma compared with invasive micropapillary carcinoma. *P* value based on log-rank test.

*Fig. 5* Percentage of micropapillary carcinoma in the transurethral resections of bladder tumour and disease specific survival (0, < 10%; 1, 10-49%; 2, 50-100% MPC). Time in months.

Lopez-Beltran et al. Hum Pathol 42:1159-1164, 2010

Comperat et al. Pathology 42:650-654, 2010

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**UROTHELIAL CARCINOMA PLASMACYTOID CELL TYPE**

**CLINICAL**
- Described by Saphir in 1955 (“monocytoid SRC”)
- Highly aggressive tumor
- Linitis plastica-like; often no discrete mass but edematous mucosa in many

**PATHOLOGY**
- Sheets of poorly cohesive cells
- Distinct monocytoid/plasmacytoid morphology with variable numbers of true signet-ring cells
- +/- typical UC component
- CK ++ (variable CK7/CK20), p63+, LCA -
Plasmacytoid variant

PLASMACYTOID CARCINOMA
PLASMACYTOID CARCINOMA
PLASMACYTOID CARCINOMA

CD 138

p63

E-cadherin

p63

E-cadherin
PLASMACYTOID VARIANT

CK 7
CK 20
CD 138

PLASMACYTOID CARCINOMA

E-CADHERIN
PATTERN OF SPREAD

Rectum

Pelvic wall

Fallopian Tube

Lymph node

URETER MARGIN
PLASMACYTOID CARCINOMA


PROGNOSTIC SIGNIFICANCE OF VARIANT HISTOLOGY

IMPORTANCE OF PATHOLOGY

New Strategies in Muscle-Invasive Bladder Cancer: On the Road to Personalized Medicine
Jay B. Shah, David J. McConkey and Collin P.N. Dinney
Clin Cancer Res 2011;17:2608-2612. Published OnlineFirst March 17, 2011.

![Image](image1)

Figure 1. MSK Cancer Center research paradigm for patients with invasive bladder cancer. Assignments with invasive urothelial cancer are clinically stratified as either low risk or high risk for biologically advanced disease. Patients in the low-risk category (for whom chemotherapy is not typically administered) are offered enrollment in a single-agent study with a medication such as erlotinib. Distinct is given for 3 days prior to cystoscopy, Pretreatment (biopsies obtained at TURBT) and posttreatment tissue (obtained at cystoscopy) prior for pharmacodynamics and molecular profiling studies. Patients in the high-risk category are offered enrollment in clinical trials that call for the addition of a novel agent (e.g., bevacizumab) to conventional chemotherapy. For all patients with resectable invasive bladder cancer, the research paradigm allows for the testing of novel agents as well as the acquisition of pre- and posttreatment tissue without compromising patient care.

UROTHELIAL LESIONS II: BENIGN MIMICS OF BLADDER CANCER

American Bald eagles “Ice fishing” on Geist Reservoir, Indianapolis, IN