HANDLING AND REPORTING OF CANCER CONTAINING BLADDER SPECIMENS
Conflict of Interest Disclosure

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The individual below has responded that he has no relevant financial relationship with commercial interest to disclose:

David Grignon, MD
BLADDER CANCER EPIDEMIOLOGY

![Estimated New Cases and Estimated Deaths](image)

*Estimates are rounded to the nearest 10 and exclude basal and squamous cell skin cancers and in situ carcinoma except urinary bladder.

REPORTING OF BLADDER BIOPSIES/TURBT TUMOR CONTAINING SPECIMENS

- Histologic type
  - For UC, morphologic variant if present
- Grade (ISUP/WHO 2004)
- *Papillary or non-papillary type
- Microscopic extent of tumor
- If invasion – involvement of muscularis propria present or absent
  - In all specimens document the presence or absence of muscularis propria
REPORTING OF BLADDER BIOPSIES/TURBT TUMOR CONTAINING SPECIMENS

- *For T1 tumors:
  - Depth of invasion – focal or extensive
  - Involvement of muscularis mucosae
- Lymph-vascular invasion
- Associated epithelial lesions
- *Additional pathologic findings
- Based on College of American Pathologists guidelines (2011)
- *optional elements
9q-/9p-; FGFR3/HRAS

Papilloma—papillary carcinoma

Flat noninvasive carcinoma

Invasive papillary carcinoma

Flat invasive carcinoma

9q-/9p-; p53, RB, 8p-, 8p+, 17p-
SURVIVAL BY ARCHITECTURAL PATTERN

- 537 cases
- mean 9 year fu
- Ta/T1: TURBT +/- IV therapy
- T2/T3: TURBT +/- IV therapy, part or rad cyst
- all cases classified by a single reviewer

Lipponen et al, Int J Cancer 51:396, 1992
UROTHELIAL CARCINOMA
SIGNIFICANCE OF GROWTH PATTERN

Angulo et al, J Cancer Res Clin Oncol 119:578, 1993
PAPILLARY CARCINOMA
PREDICTORS OF RECURRENCE

- Number of tumors
- Size of tumor (s)
- Histologic grade
- Stage (Ta vs T1)
- Concurrent CIS
- Prior recurrence (s)

Most important in EORTC risk model (Babjuk et al. Eur Urol 59:997, 2011)
PAPILLARY CARCINOMA
PREDICTORS OF PROGRESSION

- Number of tumors
- Size of tumor(s)
- Histologic grade
- Stage (Ta vs T1)
- Concurrent CIS
- Prior recurrence(s)

Most important in EORTC risk model (Babjuk et al. Eur Urol 59:997, 2011)
CLASSIFICATION OF UROTHELIAL NEOPLASMS

“Members of the jury, have you reached a verdict?”
The Jury

WHO Classification of Tumours of the Urinary System & Male Genital Organs
IARC, Lyon, 14-18 December 2002
CURRENT CLASSIFICATION
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
PAPILLOMA
PUNLMP
LOW GRADE
HIGH GRADE
52/164 (32%) papillary UC were grade heterogeneous

pTa BLADDER CA
LONG TERM OUTCOME

Progression in stage

PUNLMP  LPUC pTa  HPUC pTa
N=175    N=483    N=129

Pan et al, AJCP 133:788, 2010
pTa BLADDER CA
LONG TERM OUTCOME

Cancer-specific mortality

N=175
N=483
N=129

Pan et al, AJCP 133:788, 2010
215 patients with low grade non invasive papillary tumors (pTa)
All treated by TURBT alone
Followed by cystoscopy q6 months
Follow up of 6 – 10 years (median 8 years)
143 (67%) had at least 1 recurrence
17 (8%) had stage or grade progression
1 (0.5%) died of bladder cancer
Recommended reduced frequency of follow up “less is more”

For Index Patient No. 2: A patient with small volume, low-grade Ta bladder cancer.

Recommendation: An initial single dose of intravesical chemotherapy may be administered immediately postoperatively.
[Based on review of the data.]

For Index Patient No. 4: A patient with initial histologically confirmed high-grade Ta, T1 and/or Tis bladder cancer.

Standard: For patients with lamina propria invasion (T1) but without muscularis propria in the specimen, repeat resection should be performed prior to additional intravesical therapy.
[Based on review of the data and Panel consensus.]
UROTHELIAL HYPERPLASIA
DYSPLASIA
DYSPLASIA

Or Incipient Papillary Neoplasia?
CIS WITH UMBRELLA CELLS
CIS - PAGETOID
CARCINOMA IN SITU – p53 IHC

~ 80% Positive
CARCINOMA IN SITU

CK20

P53
REACTIVE ATYPIA

CK20

p53
UROTHELIAL CARCINOMA IN SITU - LONG TERM OUTCOME

<table>
<thead>
<tr>
<th>Survival-Type</th>
<th>10-Year</th>
<th>15-Year</th>
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<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>
</tr>
</tbody>
</table>

Cheng et al, Cancer 85:2469, 2000
### STAGING OF BLADDER CANCER (2009 TNM)

<table>
<thead>
<tr>
<th>pT Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>pTa</td>
<td>Non-invasive, papillary</td>
</tr>
<tr>
<td>pTis</td>
<td>Non-invasive, flat</td>
</tr>
<tr>
<td>pT1</td>
<td>Invasion of subepithelial connective tissue (lamina propria)</td>
</tr>
<tr>
<td>pT2</td>
<td>Invasion of muscularis propria</td>
</tr>
<tr>
<td>pT2a</td>
<td>Inner one-half</td>
</tr>
<tr>
<td>pT2b</td>
<td>Outer one-half</td>
</tr>
<tr>
<td>pT3</td>
<td>Invasion of perivesical tissue</td>
</tr>
<tr>
<td>pT3a</td>
<td>Microscopically</td>
</tr>
<tr>
<td>pT3b</td>
<td>Macroscopically</td>
</tr>
<tr>
<td>pT4</td>
<td>Invasion of adjacent structures</td>
</tr>
</tbody>
</table>
BLADDER CANCER STAGING
THE TERMINOLOGY ISSUE

• To the pathologist “invasive” means extension through the epithelial basement membrane to involve the lamina propria

• To the urologist “invasive” may mean involvement into the muscularis propria
HISTOLOGIC FEATURES OF INVASION

- Loss of smooth BM outline
- Single cells or irregular clusters of cells haphazardly extending from surface
- Invading cells with more abundant eosinophilic cytoplasm than non-invasive
- Retraction artifact
- Stromal edema - myxoid, desmoplasia or fibrosis
- Inflammation
DIAGNOSIS OF INVASION

Irregular nests
Stromal response
DIAGNOSIS OF INVASION

Increased cytoplasm
Retraction artifact
DIAGNOSIS OF INVASION
RETRACTION ARTIFACT
DIAGNOSIS OF INVASION
DIAGNOSIS OF INVASION
DIAGNOSIS OF INVASION
DIAGNOSIS OF INVASION
SURVIVAL ACCORDING TO PATHOLOGIC T-category (AJCC - 1987)

- 343 patients - initial treatment
- M:F, 6.6:1
- Age, mean 66 yrs
- Treated by:
  - TUR (59%)
  - cyst (14%)
  - RT (15%)

P<0.001

Angulo et al, J Cancer Res Clin Oncol 119:578, 1993
### 15-Year Follow Up of “Superficial” Bladder Cancer

<table>
<thead>
<tr>
<th>Category</th>
<th>Progression free survival</th>
<th>Disease specific surv.</th>
</tr>
</thead>
<tbody>
<tr>
<td>pTa – LG</td>
<td>95%</td>
<td>100%</td>
</tr>
<tr>
<td>pTa – HG</td>
<td>61%</td>
<td>74%</td>
</tr>
<tr>
<td>pT1</td>
<td>44%</td>
<td>62%</td>
</tr>
</tbody>
</table>

_Herr HW, J Urol 163:60, 2000_
UROTHELIAL CARCINOMA
“MICROINVASION”

- 68 cystectomies for CIS
- microinvasion (<5 mm) identified in 23 (34%)
- bladder cancer deaths in:
  - 1/46 (2%) without microinvasion
  - 3/22 (14%) with microinvasion

Farrow and Utz, Clin Oncol 1:609, 1982
MICROMETER-BASED T1 SUBSTAGING

# MUSCULARIS MUCOSAE DEVELOPMENT IN THE NORMAL URINARY BLADDER

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Continuous</td>
<td>3%</td>
<td>13%</td>
</tr>
<tr>
<td>Interrupted</td>
<td>20%</td>
<td>45%</td>
</tr>
<tr>
<td>Scattered</td>
<td>71%</td>
<td>43%</td>
</tr>
<tr>
<td>Absent</td>
<td>6%</td>
<td>0%</td>
</tr>
</tbody>
</table>
MUSCULARIS MUCOSAE
TRIGONE REGION
MUSCULARIS MUCOSAE INVASION
MUSCULARIS MUCOSAE INVASION
pT1 - SUBSTAGING BASED ON 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

P<0.02
SURVIVAL ACCORDING TO MUSCULARIS MUCOSAE INVASION

• 151 patients – pT1 on TUR
• Cases centrally reviewed
• 97 included in study
  • All high-grade with mp in specimen
• Substaging possible in 85 (88%)
• Treated by:
  • TURBT +/- intravesical BCG

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 10021, 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 2008
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
MUSCULARIS PROPRIA INVASION
MM vs MP INVASION: SMOOTHELIN
MM vs MP INVASION: SMOOTHHELIN
MM vs MP INVASION: SMOOTHHELIN

Desmin

Smoothelin
MP INVASION vs DESMOPLASIA

TRICHRHE

DESMIN
PERIVESICAL FAT INVASION (?)

FINAL DIAGNOSIS:
BLADDER NECK AND LEFT TRIGONE, TUR:
- HIGH-GRADE UROTHELIAL CARCINOMA DEEPLY INVADING MUSCULAR WALL OF BLADDER, WITH FOCAL EXTRAMURAL INVASION AROUND A NERVE. APPROXIMATELY ONE-HALF OF ALL TISSUE CONSISTS OF TUMOR.
PERIVESICAL FAT INVASION
UROTHELIAL CARCINOMA ANGIOLUMPHATIC INVASION

- **McDonald and Thompson (1948)**
  - with: 12% 5-year survival
  - without: 38% 5-year survival

- **Bell et al (1971)**
  - with: 29% 5-year survival
  - without: 51% 5-year survival
BLADDER CANCER
ANGIOLYMPHATIC INVASION

• 170 T1 patients on phase III clinical trial
• TURBT + adriamycin or mitomycin C
• minimum 18 months follow up
• angiolympathic invasion determined by H&E combined with factor VIII IHC
• unequivocal invasion in 17 cases (10%)
• 5 year survival: 44% with vs 81% without angiolympathic invasion (P<0.02)

Lopez & Angulo, Histopathology 27:27, 1995
ANGIOLYMPHATIC INVASION
CIS WITH ANGIOLYMPHATIC 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, 2011
GRADE AS A PREDICTOR OF OUTCOME IN T1 CA TREATED BY TURBT

Reviewed all T1 G1 cases reported to Swedish Urinary Bladder cancer registry, 2000 – 2003

Of 97 cases: 55 reported incorrectly, 20 restaged as pTa, 29 upgraded

Concluded “that G1 urothelial carcinoma has no propensity for infiltrative growth”
INVASIVE CARCINOMA GRADING

- 201 consecutive newly diagnosed invasive bladder carcinomas
  - Grade 1: 0 0%
  - Grade 2: 7 3%
  - Grade 3: 194 97%

Jordan et al, Cancer 60:2766-2774, 1987
UROTHELIAL CARCINOMA
NODULAR INVASION

UROTHELIAL CARCINOMA
TRABECULAR INVASION

UROTHELIAL CARCINOMA
INFILTRATIVE INVASION

UROTHELIAL CARCINOMA
SURVIVAL BY PATTERN OF INVASION

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
MICROPAPILLARY VARIANT
The Case for Early Cystectomy in the Treatment of Nonmuscle Invasive Micropapillary Bladder Carcinoma

Ashish M. Kamat,*† Jason R. Gee,‡ Colin P. N. Dinney,§ H. Barton Grossman,¶ David A. Swanson,‖ Randall E. Millikan,** Michelle A. Detry,‡ Tracy L. Robinson‡ and Louis L. Pisters††

From the Departments of Urology (AMK, JRG, CPND, HBG, DAS, TLR, LLP), Genitourinary Medical Oncology (REM), and Biostatistics and Applied Mathematics (MAD), The University of Texas M. D. Anderson Cancer Center, Houston, Texas

Fig. 1. Overall survival of patients with nonmuscle invasive micropapillary urothelial carcinoma.

Fig. 3. Cancer specific survival of patients treated with cystectomy stratified by timing of cystectomy.

J Urol 175:881-885, 2006
PLASMACYTOID VARIANT
PLASMACYTOID VARIANT
PLASMACYTOID VARIANT
PATTERN OF SPREAD

- Rectum
- Fallopian Tube
- Pelvic wall
- Lymph node
LYMPH NODE STATUS

When Does Lymphadenectomy Improve Survival of Patients With Genitourinary Malignancies?


Extent of Pelvic Lymph Node Dissection During Radical Cystectomy: Where and Why!

Harry W. Herr

Department of Urology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021-6007, USA
LYMPH NODES IN BLADDER CA

• Improved survival with increased number of lymph nodes resected
• Improved survival with extended lymph node dissection
• Lymph node density (proportion of nodes positive)
• Optimal number of lymph nodes – 9, 16, 20, 24, more?
IMPORTANCE OF PATHOLOGY

New Strategies in Muscle-Invasive Bladder Cancer: On the Road to Personalized Medicine

Jay B. Shah, David J. McConkey and Colin P.N. Dinney

Clin Cancer Res 2011;17:2608-2612. Published OnlineFirst March 17, 2011.
New Strategies in Muscle-Invasive Bladder Cancer: On the Road to Personalized Medicine

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Figure 1. MD Anderson Cancer Center neoadjuvant paradigm for patients with invasive bladder cancer. All patients with invasive urothelial cancer are clinically stratified as either low risk or high risk for locoregionally advanced disease. Patients in the low-risk category (to whom chemotherapy is not typically administered) are offered enrollment in a single-agent study with a medication such as erlotinib. Erlotinib is given for 5 days prior to cystectomy. Pretreatment tissue (obtained at TURBT) and posttreatment tissue (obtained at cystectomy) are then used for pharmacodynamic 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 neoadjuvant paradigm allows for the testing of novel agents as well as the acquisition of pre- and posttreatment tissue without compromising patient care.
CLASSIFICATION OF RENAL NEOPLASMS