**PROBLEMS AND PITFALLS IN THE DIAGNOSIS OF UROTHELIAL LESIONS**

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**UCSF, June 2010**

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**BLadder cancer epidemiology**

- Fourth most common malignancy in the Western world. Second most expensive to treat in the U.S.A.
  - Accounts for 5%-10% of all malignancies among men in Europe and United States
- Risk of developing bladder cancer < age 75:
  - Men 2%-4%
  - Women 0.5%-1%
- More common in European than African ancestry

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**Bladder cancer epidemiology; the tobacco connection**

- Cigarette smoking increases the risk 2-4 fold
  - 30%-50% of cases are attributable to cigarettes
- Latency period is 20-30 years
- Quitting decreases risk to baseline in 20-30 years
- Deep inhalation increases risk 20%-30%
- Unfiltered cigarettes increase risk 35%-50%
- Effect of pipe/cigar smoking is questionable

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**Bladder cancer epidemiology; the occupation connection**

- Second most important risk factor
- Account for up to 20% of all cases
- Workers in the textile and rubber tire industries
  - ß-naphthylamine, 4-aminobiphenyl, benzidine
- Less convincing data on paints, formaldehyde, asbestos, solvents, diesel exhaust, leather workers, steelworkers
**BLADDER CANCER**
epidemiology; the medical history connection

- Chronic urinary tract infection/irritation
  - Schistosomiasis
  - Diverticuli
  - Lithiasis
- Cyclophosphamide
- Radiation therapy
- Coffee
- Artificial sweeteners

**OUTLINE**

- The urothelium; clinical implications of its morphologic plasticity
- “Variants” of urothelial carcinoma that are worth recognizing
- Urothelial carcinoma in situ: morphologic spectrum and differential diagnosis
- The diagnosis of minimally invasive disease
**Intestinal Metaplasia of Bladder Urothelium**

<table>
<thead>
<tr>
<th></th>
<th>Mayo Clinic</th>
<th>Pediatric Hospitals*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases (M:F)</td>
<td>24 (15:9)</td>
<td>29 (15:14)</td>
</tr>
<tr>
<td>Mean Age (range)</td>
<td>38 (3-73)</td>
<td>1.8 (1mo-8yrs)</td>
</tr>
<tr>
<td>Follow-up (median)</td>
<td>14 yrs</td>
<td>13yrs</td>
</tr>
<tr>
<td>A-NED (%)</td>
<td>19 (79)</td>
<td>27 (93)</td>
</tr>
<tr>
<td>D-NED (%)</td>
<td>5 (21)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Local recurrence (%)</td>
<td>1 (4)</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

*Dallas Children’s Hospital and Toronto Hospital for Sick Children
NEPHROGENIC ADENOMA
Immunohistochemistry

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Positive</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>CK-7</td>
<td>40/40</td>
<td>100</td>
</tr>
<tr>
<td>CK-20</td>
<td>23/40</td>
<td>58</td>
</tr>
<tr>
<td>CA-125</td>
<td>32/40</td>
<td>80</td>
</tr>
<tr>
<td>CD-10</td>
<td>9/40</td>
<td>23</td>
</tr>
<tr>
<td>RCC</td>
<td>6/40</td>
<td>15</td>
</tr>
<tr>
<td>Uroplakin*</td>
<td>0/40</td>
<td>0</td>
</tr>
</tbody>
</table>

*membranous or luminal

Oliva E, et al. USCAP 2003(Abs)
UROTHELIAL CARCINOMA OF THE URINARY BLADDER

INCIDENCE

<table>
<thead>
<tr>
<th>Stage at presentation</th>
<th>Percent</th>
<th>Patients per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ta/T1</td>
<td>75</td>
<td>47,625</td>
</tr>
<tr>
<td>T2+</td>
<td>20</td>
<td>12,700</td>
</tr>
<tr>
<td>M+</td>
<td>5</td>
<td>3,175</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>63,500</td>
</tr>
</tbody>
</table>

90% of patients who die of bladder cancer present with a locally advanced tumor.

Natural History of Superficial Bladder Cancer

176 cases (Ta and T1) without adjuvant therapy followed for a least 20 years
- 80% experience recurrence
- 22% died of disease
  - 11% Ta
  - 30% T1

Death from disease was related to:
  Grade
  # of tumors
  # of recurrences


Natural History of Superficial Bladder Cancer

<table>
<thead>
<tr>
<th>Series</th>
<th>Tumor</th>
<th>No. Pts.</th>
<th>% Recur</th>
<th>% Prog</th>
<th>% EVR</th>
<th>DOD</th>
<th>FU Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herr</td>
<td>TaG1*</td>
<td>23</td>
<td>90%</td>
<td>4%</td>
<td>2%</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Holmang**</td>
<td>22</td>
<td>59%</td>
<td>14%</td>
<td>3%</td>
<td>14%</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Holmang</td>
<td>255</td>
<td>71%</td>
<td>2%</td>
<td>-</td>
<td>2%</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Leblanc</td>
<td>152</td>
<td>55%</td>
<td>3%</td>
<td>-</td>
<td>2%</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Haukass</td>
<td>38</td>
<td>56%</td>
<td>7%</td>
<td>3%</td>
<td>1%</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Herr</td>
<td>TaG3</td>
<td>125</td>
<td>95%</td>
<td>39%</td>
<td>33%</td>
<td>26%</td>
<td>15</td>
</tr>
<tr>
<td>Holmang**</td>
<td>55</td>
<td>70%</td>
<td>15%</td>
<td>-</td>
<td>11%</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Haukass</td>
<td>84</td>
<td>67%</td>
<td>11%</td>
<td>-</td>
<td>7%</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Lebret</td>
<td>32</td>
<td>72%</td>
<td>25%</td>
<td>-</td>
<td>12%</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Herr</td>
<td>T1G3</td>
<td>121</td>
<td>90%</td>
<td>52%</td>
<td>39%</td>
<td>31%</td>
<td>15</td>
</tr>
<tr>
<td>Holmang**</td>
<td>99</td>
<td>93%</td>
<td>45%</td>
<td>-</td>
<td>36%</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Haukass</td>
<td>89</td>
<td>79%</td>
<td>29%</td>
<td>-</td>
<td>32%</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

* PUNLMP and LG
** Primary tumor, no CIS. TUR alone
WHO CLASSIFICATION OF UROTHELIAL TUMORS: 2003 “Blue Book”

Histologic variants:
- Invasive UC with squamous differentiation
- Invasive UC with glandular differentiation
- Nested variant
- Microcystic variant
- Micropapillary variant
- Small cell carcinoma
- Lymphoepithelioma-like carcinoma
- Lymphoma-like and plasmacytoid variants
- Sarcomatoid variant (with and without heterologous elements)
- Urothelial carcinoma with giant cells
- Urothelial carcinoma with trophoblastic differentiation
- Clear cell variant
- Lipid cell variant
- Undifferentiated carcinoma

TRANSURETHRAL RESECTION FOR BLADDER CANCER

TUR for urothelial carcinoma 100
- “usual” type 93
- UC with DD 5
- “pure” DD 2

MSKCC
CYSTECTOMY FOR BLADDER CARCINOMA

Residual invasive disease 212
- “usual” carcinoma 154 (73%)
- UC with DD 58 (27%)
  - Squamous 37
  - Glandular 14
  - SMCL/NE 3
  - Squamous, glandular 3
  - SMCL/NE, squamous 1

MSKCC
ADENOCARCINOMA
Mucinous Signet ring cell Papillary NOS

ENTERIC-TYPE ADENOCARCINOMA IMMUNOHISTOCHEMISTRY

<table>
<thead>
<tr>
<th></th>
<th>Bladder</th>
<th>Colon</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK7+/CK20+</td>
<td>24%</td>
<td>8%</td>
</tr>
<tr>
<td>CK7+/CK20-</td>
<td>41%</td>
<td>0%</td>
</tr>
<tr>
<td>CK7-/CK20+</td>
<td>29%</td>
<td>82%</td>
</tr>
<tr>
<td>CK7-/CK20-</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>CDX-2</td>
<td>47-100%</td>
<td>99-100%</td>
</tr>
<tr>
<td>Villin</td>
<td>65-100%</td>
<td>82-98%</td>
</tr>
<tr>
<td>β-catenin</td>
<td>cytoplasm</td>
<td>nuclear</td>
</tr>
</tbody>
</table>

ADENOCARCINOMA OF THE URINARY BLADDER
Grignon et al

<table>
<thead>
<tr>
<th>Stage at Presentation</th>
<th>Cases(%)</th>
<th>Survival(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT1</td>
<td>2 (4)</td>
<td>100</td>
</tr>
<tr>
<td>pT2-pT3a</td>
<td>11 (20)</td>
<td>76</td>
</tr>
<tr>
<td>pT3b</td>
<td>12 (23)</td>
<td>28</td>
</tr>
<tr>
<td>pT4</td>
<td>24 (45)</td>
<td>20</td>
</tr>
</tbody>
</table>

SMALL CELL CARCINOMA
**Small Cell/Neuroendocrine Carcinoma**

**Histologic Subtype**

<table>
<thead>
<tr>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure SCC</td>
</tr>
<tr>
<td>SCC and UC, NOS</td>
</tr>
<tr>
<td>SCC and AC</td>
</tr>
<tr>
<td>SCC and LCNEC*</td>
</tr>
<tr>
<td>SCC, LCNEC and UC</td>
</tr>
<tr>
<td>SCC, AC and SQC</td>
</tr>
<tr>
<td>SCC, UC and AC</td>
</tr>
<tr>
<td>SCC, LCNEC, UC and AC</td>
</tr>
</tbody>
</table>

*These 2 cases were placed into the pure small cell neuroendocrine carcinoma group.

**Small Cell Carcinoma of the Bladder**

Morphologic features

Overall survival in 55 cases

Kaplan-Meier Survival Estimate

**Micropapillary Carcinoma**
MICROPAPILLARY CARCINOMA

20 cases (incidence = 0.7%) Age: mean = 69 M:F = 2.3:1 MPC: 10% = 1 20-95% = 17 >90% = 2
Superficial Component:
- CIS 10/18
- Pap 1/18 grade 3 TCC could not be done
Vascular invasion
- 100% in area of MPC
Stage at Presentation
- T1 = 1
- T2 = 9
- T3 = 6
- T4 = 2

Follow-up: mean 44 mos. (6-96)
- NED = 7
- AWD = 4
- DWD = 7

- Amount of MPC correlated with prognosis (no statistics)
- "...and there was a close correlation between stage and survival, as described by Amin et al"

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Superficial component:
- CIS 13/20 Pap 11/20

Vascular invasion
- 75% (15/20)

Stage at Presentation
- T1 = 3
- T2 = 9
- T3 = 2
- T4 = 6

Follow-up: mean 39 mos (4-156)
- NED = 3
- DOO = 1
- DOD = 19

- Disease specific survival at 5 years: 25%

Amin et al. AJSP 1994;18: 1224
18 cases Age: mean= 67 M:F = 5:1 MPC: <50% = 6
50-90% = 9
>90% = 3
Superficial Component:
- CIS 13/20 Pap 1/20 grade 3 TCC could not be done
Vascular invasion
- 100% in area of MPC
Stage at Presentation
- T1 = 1
- T2 = 9
- T3 = 6
- T4 = 2

Follow-up: mean 44 mos. (6-96)
- NED = 7
- AWD = 4
- DWD = 7

- Disease specific survival at 5 years: 25%

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Micropapillary Variant of Urothelial Carcinoma of the Urinary Bladder:…
Samaratunga et al, Histopathol 45:55-64,2004

- 20 cases diagnosed with a MP component who underwent a cystectomy (1-12mos, mean = 3.3mos)
- correlated the % of MP component on TUR with pT and outcome

FOCAL (<10%)
- pTa = 1
- pT1 = 4
- pT2 = 0
- pT3 = 0
- pT4 = 1

FOLLOW-UP
- NED = 5
- AWD = 0
- DOD = 1

MODERATE (10-50%)
- pTa = 0
- pT1 = 0
- pT2 = 2
- pT3 = 5
- pT4 = 3

FOLLOW-UP
- NED = 4
- AWD = 3
- DOD* = 3

EXTENSIVE (>50%)
- pTa = 0
- pT1 = 0
- pT2 = 0
- pT3 = 1
- pT4 = 3

FOLLOW-UP
- NED = 0
- AWD = 0
- DOD* = 4

* 1 case of DOO in each

---

The Case for Early Cystectomy in the Treatment of Nonmuscle invasive Micropapillary Bladder Cancer
Kamat et al, JUrol, 175:881-885,2006

Of 100 consecutive MPC, 44 were nonmuscle invasive
Tumors with any amount MPC component were included
Not stated if all patients received an initial TUR or Bx
Not stated if any repeat TUR were performed (not likely)
30 patients underwent cystectomy
12 (40%) as initial therapy*
18 (60%) after failed BCG**

* selection criteria? ** time interval to "progression"?

Pathological upstaging at cystectomy: 57% (17/30)

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MICROPAPILLARY CARCINOMA

Interobserver reproducibility study

30 cases reviewed by 14 GU pathologists
-Classic MPC (10)
-UC with retraction artefact (non-classic MPC, 20)

Results:
-Overall kappa: 0.54 (moderate)
-Rate of MPC dx ranged from 9/30 to 20/30 (mean=13/30)
-Classic: all correctly classified at least 8/10 (sensitivity = 93%)
-Non-classic: 6 pathologists, ≤ 2/20 called MPC
5 pathologists, 4-7/20 called MPC
3 pathologists, 9-11/20 called MPC

Conclusion: high sensitivity, rather low specificity

McKenney et al. USCAP 2010
LYMPHOEPITHELIOMA-LIKE CARCINOMA OF THE BLADDER

Cases: 11/1200  
Stage:  T₁ = 1  
  T₂⁺ = 6  
  T₃ = 4  
Follow-up 2-72 mo. (30)  
  NED = 8/10  
  DOD = 2/10  
* 1 pt. died post-op  

*Amin et al. AJSP 1994: 18:466.*

LYMPHOEPITHELIOMA-LIKE UROTHELIAL CARCINOMA

Cases:  9  
Stage:  T₁ = 2  
  T₂ = 2  
  T₃ = 5  
Follow-up: (9-216 mo.)  
Pure or predominant LE:  D-NED = 2/6  
  A-NED = 4/6  
Focal LE:  DOD = 3/3  

### NESTED VARIANT OF UROTHELIAL CARCINOMA

**Clinicopathologic Features**

<table>
<thead>
<tr>
<th>Description</th>
<th>Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>45-97 (68)</td>
</tr>
<tr>
<td>M:F</td>
<td>23:1</td>
</tr>
<tr>
<td>Stage</td>
<td>$T_1$ 12/22, $T_2^+$ 10/22</td>
</tr>
<tr>
<td>Follow-up</td>
<td>1-93 mo (22)</td>
</tr>
</tbody>
</table>

**DECEPTIVELY BENIGN FEATURES OF UROTHELIAL CARCINOMA**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Benign lesion they mimic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nests</td>
<td>Brunn’s nests</td>
</tr>
<tr>
<td>Small tubules</td>
<td>Nephrogenic metaplasia</td>
</tr>
<tr>
<td>Medium-sized glands</td>
<td>Cystitis glandularis</td>
</tr>
<tr>
<td>Cysts</td>
<td>Cystitis cystica</td>
</tr>
<tr>
<td>Inverted growth</td>
<td>Inverted papilloma</td>
</tr>
<tr>
<td>Myxoid stroma</td>
<td>Inflammatory pseudotumor</td>
</tr>
</tbody>
</table>


**UROTHELIAL CARCINOMA IN SITU**

Definition (WHO):
A non-papillary (flat) lesion in which the surface epithelium contains cells that are cytologically malignant.

**Synonym:**
High grade intraurothelial neoplasia

**SCHEMATIC REPRESENTATION OF UROTHELIAL NEOPLASIA**

- Normal
- Dysplasia → CIS → T\textsubscript{1} invasive UC
- Hyperplasia → PUNLMP → PUC-LG / PUC-HG (WHO-G1) (WHO-G2) (WHO-G3)
- T\textsubscript{2+} invasive UC

- PUNLMP = papillary urothelial neoplasm of low malignant potential
- PUC = papillary urothelial carcinoma
- UC = urothelial carcinoma
- LG = low grade
- HG = high grade
UROTHELIAL CARCINOMA IN SITU

Clinical presentation
- Hematuria
- Irritative symptoms

Cystoscopy
- May be difficult to visualize
- Erythematous patch or patches

UROTHELIAL CARCINOMA IN SITU

High grade (by definition)
- >80% positive cytology

Comes in two variations
- In combination with or subsequent to papillary UC (treated or not)
  - Commonly in association with invasive disease
- In a “pure” form
  - Rare (1%)
  - Clinicopathologic entity
  - Commonly multifocal/diffuse

“Erosive” (denuding) cystitis

WHO CLASSIFICATION OF UROTHELIAL TUMORS: 2004 “Blue Book”

Normal urothelium
Reactive atypia
Urothelial atypia of unknown significance
Dysplasia (low grade intraurothelial neoplasia)
Carcinoma in situ
UROTHELIAL CARCINOMA IN SITU
useful criteria

- Pleomorphism (nuclear irregularity) (84%)
- Nucleomegaly (68%)
- Irregular chromatin (47%)
- Loss of polarity (46%)
- Raised nuclear: cytoplasmic ratio (37%)
RELATIVE RISK OF DEVELOPING BLADDER CANCER AFTER RADIATION AND CYCLOPHOSPHAMIDE THERAPY

TRAVIS LB et al. Int J Cancer 1995

Cyclophosphamide therapy
Radiation-induced changes
### RESULTS

<table>
<thead>
<tr>
<th>Subset of interest</th>
<th>Kappa statistic</th>
<th>Degree of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0.484</td>
<td>Good</td>
</tr>
<tr>
<td>Reactive atypia</td>
<td>0.361</td>
<td>Fair</td>
</tr>
<tr>
<td>Atypia ? dysplasia</td>
<td>0.317</td>
<td>Fair</td>
</tr>
<tr>
<td>L.G. dysplasia</td>
<td>0.174</td>
<td>Poor</td>
</tr>
<tr>
<td>H.G.D./CIS</td>
<td>0.653</td>
<td>Excellent</td>
</tr>
</tbody>
</table>

### RESULTS

<table>
<thead>
<tr>
<th>Subset of interest</th>
<th>Kappa statistic</th>
<th>Degree of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-H.G.D. or CIS</td>
<td>0.653</td>
<td>Excellent</td>
</tr>
<tr>
<td>H.G.D./CIS</td>
<td>0.653</td>
<td>Excellent</td>
</tr>
</tbody>
</table>

**THE CONCEPT OF UROTHELIAL ATYPIA AND DYSPLASIA**

- Biologic continuum
- Inflammatory/Reactive changes
- Repair reaction
- Instrumentation
- Psychologic predisposition to find disease
- Kappa statistics
- Supporting clinical and laboratory data?
### FLAT UROTHELIAL LESIONS
#### IMMUNOHISTOCHEMISTRY

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Reactive</th>
<th>CIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK20</td>
<td>umbrella</td>
<td>umbrella</td>
<td>all</td>
</tr>
<tr>
<td>CD44</td>
<td>basal</td>
<td>all</td>
<td>basal or lost</td>
</tr>
<tr>
<td>p53</td>
<td>rare, weak</td>
<td>rare, weak</td>
<td>many, strong</td>
</tr>
<tr>
<td>Ki-67</td>
<td>no to rare</td>
<td>rare, basal</td>
<td>increased, levels</td>
</tr>
</tbody>
</table>
**SUPERFICIAL BLADDER CANCER**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Original Report</th>
<th>Dedicated Pathologist</th>
</tr>
</thead>
<tbody>
<tr>
<td>pTA</td>
<td>46</td>
<td>53 (+7 previously T1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(+1 previously T2+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-1 to T1)</td>
</tr>
<tr>
<td>pT1</td>
<td>24</td>
<td>23 (+1 previously TA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(+5 previously T2+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-7 to TA)</td>
</tr>
<tr>
<td>pT2+</td>
<td>29</td>
<td>23 (-1 to TA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-5 to T1)</td>
</tr>
</tbody>
</table>

**T1 disease paradox:**
- high incidence = high survival
- low incidence = low survival


CRITERIA TO DETERMINE LAMINA PROPRIA INVASION (T₁)

1. Pattern of invasion
   Individual tumor cells or irregularly shaped nests

2. Stromal reaction
   Presence of myxoid, pseudosarcomatous, inflammatory, or sclerotic stromal response

3. Retraction artefact
   Retraction surrounding tumor nests, often suspicious for vascular or lymphatic invasion

4. Morphologic appearance of basement membrane
   Inconspicuous. Loss of regular contour. Loss of parallel array of blood vessels which defines the basement membrane

5. Paradoxical differentiation in early invasive tumor cells
**CARCINOMA OF THE BLADDER**

**Tumor Stage vs Progression**

![Graph showing progression per 100 person/year for Ta and T1 stages.

**SURVIVAL OF STAGE T1 TUMORS, STRATIFIED BY DEPTH OF INVASION ACCORDING TO THE LEVEL OF THE MUSCULARIS MUCOSAE**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Cases</th>
<th>1 year</th>
<th>3 year</th>
<th>5 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>170</td>
<td>100%</td>
<td>92.3%</td>
<td>74.5%</td>
</tr>
<tr>
<td>T1A</td>
<td>50</td>
<td>100%</td>
<td>96.6%</td>
<td>86.4%</td>
</tr>
<tr>
<td>T1B</td>
<td>49</td>
<td>100%</td>
<td>97.2%</td>
<td>51.7%</td>
</tr>
</tbody>
</table>

log rank, P<0.02
