Management of Superficial Bladder Cancer

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Clinical Director, Urologic Oncology
Weill Medical College-Cornell University
Estimated new cancer cases.
10 leading sites by gender, US, 2000

- Prostate: 29%
- Lung & Bronchus: 14%
- Colon & Rectum: 10%
- Urinary Bladder: 6%
- Non-Hodgkin’s Lymphoma: 5%
- Melanoma of Skin: 4%
- Oral Cavity & Pharynx: 3%
- Kidney & Renal Pelvis: 3%
- Leukemia: 3%
- Pancreas: 2%
- All Other Sites: 19%

- Breast: 30%
- Lung & Bronchus: 12%
- Colon & Rectum: 11%
- Uterine Corpus: 6%
- Ovary: 4%
- Non-Hodgkin’s Lymphoma: 4%
- Melanoma of Skin: 3%
- Pancreas: 2%
- Thyroid: 2%
- All Other Sites: 22%

38,300 (men) + 14,900 (women) = 53,200
Estimated cancer deaths.
10 leading sites by gender, US, 2000

<table>
<thead>
<tr>
<th>Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; Bronchus</td>
<td>31%</td>
</tr>
<tr>
<td>Prostate</td>
<td>11%</td>
</tr>
<tr>
<td>Colon &amp; Rectum</td>
<td>10%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>5%</td>
</tr>
<tr>
<td>Non-Hodgkin's Lymphoma</td>
<td>5%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>3%</td>
</tr>
<tr>
<td>Liver &amp; Intrahepatic Bile Duct</td>
<td>3%</td>
</tr>
<tr>
<td>Urinary Bladder</td>
<td>3%</td>
</tr>
<tr>
<td>Stomach</td>
<td>3%</td>
</tr>
<tr>
<td>All Other Sites</td>
<td>22%</td>
</tr>
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<table>
<thead>
<tr>
<th>Site</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Lung &amp; Bronchus</td>
<td>25%</td>
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<tr>
<td>Breast</td>
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<tr>
<td>Colon &amp; Rectum</td>
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</tr>
<tr>
<td>Pancreas</td>
<td>5%</td>
</tr>
<tr>
<td>Ovary</td>
<td>5%</td>
</tr>
<tr>
<td>Non-Hodgkin's Lymphoma</td>
<td>5%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
</tr>
<tr>
<td>Uterine Corpus</td>
<td>2%</td>
</tr>
<tr>
<td>Brain &amp; Other Nervous System</td>
<td>2%</td>
</tr>
<tr>
<td>Stomach</td>
<td>2%</td>
</tr>
<tr>
<td>Multiple Myeloma†</td>
<td>2%</td>
</tr>
<tr>
<td>All Other Sites</td>
<td>21%</td>
</tr>
</tbody>
</table>
Epidemiology

• 5\textsuperscript{th} most common cancer in men

• 12,000 cancer related deaths/year

• 70% present as superficial TCC

• “Superficial” = Ta, Tis, T1

• Men>Women
Epidemiology

- 2.8% lifetime risk in caucasian men
  0.9% lifetime risk in African American men

- 1% risk in caucasian women
  0.6% African American women

- Carcinogens implicated in bladder cancer
  – could have 40 year latency period
Risk Factors for Superficial TCC

• Cigarette smoking: 2-4 fold increase risk
  4-Aminobiphenyl
  O-toluidine

• Arylamine exposure
  2-Naphthylamine
  Benzidine
  4-Aminobiphenyl

• Chemotherapy – cyclophosphamide

• Pelvic radiation therapy
Pathology of Superficial Bladder Cancer

- 90% **Transitional Cell Carcinoma** (TCC)

- 5% **squamous cell** - more common in middle east – schistosomiasis
  - also seen in chronic catheterization

- 0.5%-2% **Adenocarcinoma** - urachal
## Bladder Cancer

<table>
<thead>
<tr>
<th>Grade</th>
<th>Rec %</th>
<th>Prog %</th>
<th>Death %</th>
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</thead>
<tbody>
<tr>
<td>Papilloma</td>
<td>10</td>
<td>0-1</td>
<td>0</td>
</tr>
<tr>
<td>PUNLMP</td>
<td>20</td>
<td>3</td>
<td>0-1</td>
</tr>
<tr>
<td>TaG1</td>
<td>20</td>
<td>5-10</td>
<td>1-5</td>
</tr>
<tr>
<td>TaG3</td>
<td>30</td>
<td>15-40</td>
<td>10-25</td>
</tr>
<tr>
<td>T1G3</td>
<td>40-60</td>
<td>30-52</td>
<td>33</td>
</tr>
<tr>
<td>CIS</td>
<td>10 (focal)</td>
<td>50-75</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>90 (diffuse)</td>
<td></td>
<td></td>
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</tbody>
</table>

WHO, International Society of Urological Pathology
Consensus Classification of Urothelial Neoplasms
Ta Tumors

- Account for 70% of superficial TCC
- Typically low grade – fibrovascular core, confined to mucosa, basement membrane intact
- 50-70% recurrence but 5% chance of progression
Tis Tumors

- Carcinoma in situ – replaces entire urothelial mucosa with high grade, anaplastic cells

- Often diffuse process and multicentric

- Often not visible cystoscopically
T1 Tumors

- Invades into lamina propria
- Often high grade
Papilloma of Low Malignant Potential (PLMP)

- No more than 8 cell layers thick
- Cytologically normal epithelium
Diagnosis of Superficial TCC

“Hematuria”

• Hematuria – most common – present 80%

• Degree of hematuria not related to stage or grade of disease

• 13% of population has microhematuria

• >3-5 RBC/HPF should undergo evaluation
Diagnosis of Superficial TCC Imaging and Cystoscopy

- IVP or CT scan with hematuria protocol preferred
- Retrograde pyelogram used to further evaluate suspicious findings on IVP/CT
- Ultrasound inadequate to visualize collecting system
- CT scan with late phase images and CT urograms ideal
- Cystoscopy is gold standard – flexible instruments helpful – could obtain bladder wash
Urinary Cytology

• Voided or urine washing

• 40-60% sensitivity (as high as 90% in G3 Lesions)

• Dependent on grade of tumor

Incidence of + urine cytology according to grade

<table>
<thead>
<tr>
<th>Grade</th>
<th># patients</th>
<th>Negative (%)</th>
<th>Positive (%)</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>68</td>
<td>62(91)</td>
<td>6(9)</td>
</tr>
<tr>
<td>II</td>
<td>60</td>
<td>41(68)</td>
<td>19(32)</td>
</tr>
<tr>
<td>III</td>
<td>20</td>
<td>6(30)</td>
<td>14(70)</td>
</tr>
</tbody>
</table>

Potential Diagnostic Markers

- S phase (Ki67)
- P53
- P21 – downstream of p53 – if + favorable outcome
- Rb
Natural History

Ta Tumor

- Recurrence and Progression

- Overall 60-70% recurrence rate

- Progression based on Grade:
  - Low grade – 4-5% progression
  - High grade – 39% progression (26% died of TCC)

Natural History
T1 Tumor

• Most often high grade

• 30-50% progression rate

• Depth of lamina propria prognostic

• 70% associated with Cis

• Size of tumor predictive of recurrence
Natural History

Tis

- 54% progress to muscle invasive disease

- If diffuse and associated with symptoms – progression rate higher

- Worse prognosis if associated with papillary tumor

Herr et al, J Urol, 147: 1020, 1992
## Long term survival of patients with CIS

<table>
<thead>
<tr>
<th></th>
<th>10 years</th>
<th>15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>63%</td>
<td>59%</td>
</tr>
<tr>
<td>CSS</td>
<td>79%</td>
<td>74%</td>
</tr>
<tr>
<td>All cause</td>
<td>55%</td>
<td>40%</td>
</tr>
</tbody>
</table>

High risk superficial disease-treated natural history

Cookson et al, J. Urol 1997
Factors Predicting Recurrence and Progression

• Pathology
  Stage, Grade, Presence of CIS

• Cystoscopy Findings
  Tumor size, tumor #, Structure (Papillary vs. sessile)

• Treatment Response – Recurrence at first cysto

• Biologic Markers – p53
Natural History
T1, GIII TCC

• Natural history of T1, G3:
  - 69-80% recurrence rate
  - 33-48% progression rate

• “Rule of 30%”
  a.) 30% never recur
  b.) 30% die of metastatic TCC
  c.) 30% require deferred cystectomy
AUA Bladder Cancer Clinical Guidelines Panel

• Standard vs. Guideline vs. Opinion

• 3 index patients

  a.) Index patient 1: abnormal urothelial growth but no diagnosis of cancer
  b.) Index patient 2: Ta, T1 tumor of any grade, with or without Cis, no prior intravesical therapy
  c.) Index Patient 3: Cis or T1, GIII with 1 prior course of intravesical therapy
AUA Bladder Cancer Guidelines

Index Patient 1

- Biopsy
- Cytology

- It is agreed that adjuvant intravesical therapy decreases recurrence but does NOT prevent progression.
AUA Bladder Cancer Guidelines

Index Patient 2

• Complete TUR if feasible

• Option – Electrocautery vs. fulguration vs. laser can be used

• Option – post TUR for Ta intravesical chemo or immuno is an option (supported for multiple recurrences)

• Guideline – BCG or Mitomycin should be given for T1, G3 Ta, or Cis

• Option – Cystectomy can be considered in select patient as initial therapy
AUA Bladder Cancer Guidelines

Index Patient 3

- Option – cystectomy performed in Cis or G3, T1 after primary intravesical tx.

- Option – Second course intravesical tx an option
Treatment of Superficial TCC

TURB

- Electrosurgical resection
- Complete resection and deep biopsies ensure adequate staging
- Random biopsies controversial
- Prostatic urethral sampling
TUR vs. TUR + BCG
T1, GIII

- 153 patients (92 TUR+BCG, 61 TUR alone)
  23% in BCG arm had co-existing CIS compared with 10% in TUR alone arm (p=0.04)
- 5.3 year median follow up
- Recurrence rate:
  a.) BCG: 70%
  b.) TUR alone: 75%
- Time to recurrence:
  a.) BCG: 38 months
  b.) TUR alone: 22 months
- Progression Rate:
  a.) BCG: 33%
  b.) TUR alone: 36%
- Cystectomy Requirement:
  a.) BCG: 29%
  b.) TUR alone: 31%
- Overall Survival: No significant difference

Overall Survival

Recurrence Free Survival

Time to cystectomy

Progression Free Survival

Intravesical Therapy

Indications

- Large tumor (>5cm) at presentation
- Multiple papillary tumors
- Grade III, Ta tumors
- Any T1 tumor
- CIS
- Positive cytology after resection
- Early tumor recurrence after TURB
Intravesical Agents

- Thiotepa
- Doxorubicin
- Mitomycin-C
- Epirubicin
- Ethoglucid
- Bacille Calmette-Guerin (BCG)
- Interferon
- Gemcitabine
Thiotepa

- 1st intravesical chemo used
- Alkylating agent
- 30-60mg in 30-60cc H2O – given in 6 weekly instillations
- Leukopenia/thrombocytopenia can develop – 25%
- Questionable efficacy – 35-45% response rate although overall benefit when compared with control groups is <20%
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th># Pts.</th>
<th>TURB alone</th>
<th>TURB+Thiotepa</th>
<th>Benefit (%)</th>
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<tbody>
<tr>
<td>Burnand et al</td>
<td>1976</td>
<td>51</td>
<td>97</td>
<td>58</td>
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<td>Byar and Blackar</td>
<td>1977</td>
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<td>Nocks et al</td>
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<td>Asahi et al</td>
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<td>Koontz et al</td>
<td>1981</td>
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<td>Schulman et al</td>
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<td>209</td>
<td>69</td>
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<tr>
<td>Zincke et al</td>
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<td>Prout et al</td>
<td>1983</td>
<td>90</td>
<td>76</td>
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<tr>
<td>Medical Research Council</td>
<td>1985</td>
<td>243</td>
<td>37</td>
<td>40</td>
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<td>Hirao et al</td>
<td>1992</td>
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<td>15</td>
<td>31</td>
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<tr>
<td>TOTAL</td>
<td></td>
<td>1073</td>
<td>63</td>
<td>46</td>
<td>17</td>
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</table>

\[ P < 0.05 \]
Doxorubicin (Adriamycin)

- Anthracycline antibiotic
- Systemic absorption rare
- Dose of 30-100mg in conc. of 1mg/ml
- Maintenance therapy not supported in literature
- Side effect – chemical cystitis (28%)
- Decreases recurrence but does not prevent progression
### Doxorubicin

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th># Pts.</th>
<th>TURB alone</th>
<th>TURB+Doxorubicin</th>
<th>Benefit (%)</th>
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<tr>
<td>Niijima et al</td>
<td>1983</td>
<td>436</td>
<td>62</td>
<td>45</td>
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<td>Zincke et al</td>
<td>1983</td>
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<tr>
<td>Akaza et al</td>
<td>1987</td>
<td>457</td>
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<td>25</td>
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<tr>
<td>Rubben et al</td>
<td>1988</td>
<td>220</td>
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<td>56</td>
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<tr>
<td>Obata et al</td>
<td>1994</td>
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<tr>
<td>Kurth et al</td>
<td>1997</td>
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<tr>
<td>Ali-el Dein et al</td>
<td>1997</td>
<td>121</td>
<td>66</td>
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<td><strong>Total</strong></td>
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<td>1694</td>
<td><strong>61</strong></td>
<td><strong>43</strong></td>
<td><strong>18</strong></td>
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</table>

*P*<0.05
Mitomycin C

- Alkylating agent
- Minimal systemic absorption
- Typical dose 40mg/40cc – given weekly x8 followed by maintenance monthly for year
- Chemical cystitis and allergic reactions (skin)
- Most effective when given immediately post-TURB
# Mitomycin C

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th># pts.</th>
<th>TURB alone</th>
<th>TURB+mitomycin C</th>
<th>Benefit</th>
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<tr>
<td>Huland and Otto</td>
<td>1983</td>
<td>79</td>
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<td>Niijima et al</td>
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<td>Akaza et al</td>
<td>1987</td>
<td>298</td>
<td>33</td>
<td>24</td>
<td>9</td>
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<td>Kim and Lee</td>
<td>1989</td>
<td>43</td>
<td>82</td>
<td>81</td>
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<tr>
<td>Tolley et al</td>
<td>1996</td>
<td>452</td>
<td>60</td>
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<td>Krege et al</td>
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<td>234</td>
<td>46</td>
<td>27</td>
<td>19</td>
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<tr>
<td><strong>Total</strong></td>
<td></td>
<td>1384</td>
<td><strong>56</strong></td>
<td><strong>40</strong></td>
<td><strong>16</strong></td>
</tr>
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</table>

P<0.05
BCG

Immunotherapy

Most common agent for superficial TCC

Unknown mechanism of action

Side-effects a potential problem
BCG

- Large studies by Lamm and Herr have demonstrated decrease in recurrence and delay in progression

- Does not prevent progression

- Theracys – live attenuated Mycobacterium Bovis from Connaught strain of Bacillus Calmette and Guerin
High grade, cT1 treated with BCG

• At 15 years
  – 52% progression (35% within 5 years)
  – 31% DOD (25% within 5 years)
  – 35% alive with intact bladder

• Delay in progression with BCG at 10 years but no difference at 15 years

BCG
Two Methods for Therapy

• Second induction course

• Maintenance Therapy
BCG
Second Induction Course

• Second course of BCG warranted in patients with initial prolonged response to induction therapy

• Also indicated in a select group of patients who fail a single course of BCG

• BCG Failure = + cytology or biopsy after 6 months

• 32% of patients with a + biopsy at 3 months were NED at 6 months  Herr et al.  J Urol, 141: 22-29, 1989.

## Maintenance BCG

<table>
<thead>
<tr>
<th>Author</th>
<th># Patients</th>
<th>Follow-up</th>
<th>Maintenance protocol</th>
<th>Randomized</th>
<th>Toxicity</th>
<th>Recurrence</th>
<th>Progression</th>
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<tbody>
<tr>
<td>Bedalame et al.</td>
<td>93</td>
<td>22 mos.</td>
<td>Monthly x 2 years</td>
<td>yes</td>
<td>increased</td>
<td>No change</td>
<td>No change</td>
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<tr>
<td>Hudson et al.</td>
<td>80</td>
<td>14 vs. 17</td>
<td>Quarterly BCG x 2 years</td>
<td>yes</td>
<td>increased</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Witjes et al.</td>
<td>49</td>
<td>43 mos.</td>
<td>6 biw + 8 monthly</td>
<td>yes</td>
<td>Yes</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Lamm et al. SWOG</td>
<td>384</td>
<td>91 vs. 87 mos</td>
<td>Tiw BCG @3,6,12,18, 24,30,36 mos.</td>
<td>yes</td>
<td>Decreased</td>
<td>Yes</td>
<td>Yes</td>
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</tbody>
</table>
Maintenance BCG

SWOG 8507

BCG given weekly for 3 Weeks at 3,6,12,18,24,30,36 months

Recurrence free survival
P<0.0001

Worsening free Survival
P=0.04

Survival
P=0.08

Lamm et al. J Urol, 163: 1124-29, 2000
BCG vs. Mitomycin

- Meta analysis – 11 trials (1421 patients-BCG and 1328 – Mitomycin)
- 26 mos median follow-up
- BCG: 38.6% recurrence
  Mitomycin: 46.4% recurrence
- BCG superior to Mitomycin in preventing recurrence
- Superiority of BCG over Mitomycin in preventing recurrence mostly seen in maintenance BCG trials

# BCG vs. Chemotherapy

<table>
<thead>
<tr>
<th>Author</th>
<th># pts.</th>
<th>Follow-up</th>
<th>Chemotherapy</th>
<th>CIS</th>
<th>Non-CIS</th>
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</thead>
<tbody>
<tr>
<td>Lamm et al. SWOG 8216</td>
<td>262</td>
<td>65 mos</td>
<td>doxorubicin</td>
<td>70% CR BCG vs. 34% Doxorubicin</td>
<td>63% recurrence BCG vs. 82% doxorubicin</td>
</tr>
<tr>
<td>Finnbladder Group</td>
<td>91</td>
<td>6</td>
<td>Mitomycin C</td>
<td>58% CR with Mitomycin C vs. 40% with BCG</td>
<td>70% CR with Mitomycin vs. 88% BCG at 6 mos and 79 vs. 97% at 12 mos.</td>
</tr>
<tr>
<td>Dutch Southeast Cooperative Urological Group</td>
<td>469</td>
<td>36</td>
<td>Maintenance Mitomycin C</td>
<td>67% CR with Mitomycin vs. 74% with Tice BCG vs. 60% with RIVM-BCG</td>
<td>43% RR mitomycin vs. 64%RR with Tice BCG vs. 46% RR with RIVM BCG</td>
</tr>
</tbody>
</table>
BCG + Interferon

• O’Donnel et al. - effect in BCG-refractory patients

• 5/99-1/01 – 1100 patients
  460 failed BCG 2 or more times
  50%Ta, 22%T1, 21%CIS, 7% mixed

• 1/3 dose BCG+50 million U Interferon-alpha2B (Intron A)
BCG and Interferon

- 45% NED at 24 months
- 28% NED if re-induction necessary
BCG + Interferon
Factors that Influence Outcome

- Papillary vs. Flat CIS - no difference
- Ta and T1 had same results (even if G3)
- # BCG failures not significant
- Low grade tumors did worse
- Small tumors (<2.5cm) do better
- >5 TURB do worse
- Residual disease do worse
- Multifocal tumors do worse
- Longer duration of cancer do worse
- Failure of 3 or more courses of chemo do worse
- Those who fail initial BCG<6 mos do worse
Conclusion

• 92% of all bladder cancer is Ta/T1 – 15% deaths

• 8% of all TCC is T2 – 85% deaths

• BCG effect in delaying progression

• BCG + Interferon may have role

• Molecular biology will further define bladder cancer