Bladder Cancer Statistics, 2006

- New Cases: 61,460
  - 44,690 Men - 16,730 Women
- 3:1 Men to Women
  - 50% over age 73
- Estimated Deaths: 13,060
  - Men: 8,990 - Women: 4,070
- Incidence/Mortality: 20.8%
  - Men: 20% - Women: 24%
- Prevalence: More than 500,000 in US
Bladder Cancer Etiology

- Initial link - aniline dyes made in 1895
- Industrial exposure - rubber & textiles
- Aromatic amines - 30 x risk
- Tobacco - 3 x increased risk - 60% of cases
- Treatment Complication - 9 x risk with cyclophosphamide or ifosfamide - 4 x RT
- Schistosoma hematobium, infection, foreign body: squamous cell carcinoma
Diet and Bladder Cancer Risk: A Meta Analysis

- 40% increased risk for diets low in fruit: (HR 1.40, 95%: 1.08-1.83)
- 16% increased risk for diets low in vegetables: (HR 1.16, 95%: 1.01-1.34)
- 37% increased risk for diets high in fat: (HR 1.37, 95%: 1.16-1.83)
- No increased risk for increased meat or reduced Vitamin A

Diet and bladder cancer: a meta-analysis of six dietary variables.
Bladder Cancer Pathology

- Transitional Cell: 94%
- Squamous Cell: 5%
- Adenocarcinoma: <1%
- Rhabdomyosarcoma: <1%
Bladder Cancer
Signs and Symptoms

• 85% present with gross or microscopic hematuria
  • Bleeding is typically intermittent and not related to grade/stage
• 20% have irritative voiding symptoms burning, frequency
  • More commonly associated with CIS and high grade tumors
Diagnosis

• Cystoscopy is key
  • Papillary tumors are easily seen
  • High grade, solid, flat or in situ tumors may not be seen
• Urinary Cytology
  • 80% + sensitivity in high grade tumors with 95% specificity
  • Sensitivity improved with FISH
• IVP, CT scan for upper tract evaluation
Cystoscopy showing bladder tumor
Bladder Cancer: Natural History

• About 70% present with resectable, superficial tumors
  • but up to 88% recur within 15 years
• Patients can and should be monitored with cystoscopic examination at regular intervals to directly assess disease status
• Accessible for disease assessment
  • Topical and systemic treatment
BCG
1800-1900
- Majority of adults infected with tuberculosis - 25% mortality

1884
- Kock demonstrates M. tuberculosis causes TB

1894
- Calmette & Guerin begin race for vaccine in Lille, France at Institute Pasteur

1904
- Nocard isolates virulent bovine tuberculosis strain that is to become BCG

1921
- 13 years and 231 passages later- avirulence
- July given to newborn infant born to mother with active TB
BCG Past

1929
• Pearl in autopsy studies notes protective effect of TB against cancer

1935
• Holmgren in Sweden is first to treat cancer in humans with some success in 28 pts.

1936
• Rosenthal - BCG stimulates reticuloendothelial system

1959
• Old/Clarke (US) and Halpern (France) - BCG inhibits experimental tumors in animals
BCG Past
Lubeck, Germany BCG Tragedy

1930

- 70 infants died in Lubeck, Germany
- BCG implicated in deaths
- Doctors accused; later proven to be cross contamination with wild tuberculosis
BCG Past

1972
- Rosenthal - significant reduction in leukemia mortality in BCG vaccinated babies

1970’s
- multiple claims of success, but controlled trials fail to confirm efficacy in advanced disease, but...

1976
- Morton- 91% CR with BCG injected melanoma nodules
# Intralesional BCG Cell Wall Injections

<table>
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<th>Controls – Oil Injection</th>
<th>Sensitized</th>
<th>Unsensitized</th>
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<tbody>
<tr>
<td>N = 16</td>
<td>N = 10</td>
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</tbody>
</table>
BCG in Bladder Cancer

1976
• Morales - 12 fold reduction in recurrence in nine bladder cancer patients

1977
• Lamm reports success in controlled animal studies of bladder cancer

1980
• Lamm reports successful randomized clinical trial

80’s-90’s
• Multiple comparison studies show BCG to be superior to chemotherapy
Percent Tumor Free

Months

BCG

Control

P = 0.014

Tumor Recurrence

Time in Months

Percent Tumor Free

Combined BCG

Combined Control

Disease Free Interval for Patients Without CIS and With Prior Chemotherapy – Protocol 8216

- At Risk BCG 20, Relapses 2
- At Risk Adriamycin 18, Relapses 11

Southwest Oncology Group
Southwest Oncology Group – Disease Free Interval for Patients Without CIS – Protocol 8216

At Risk BCG 28, Relapses 6
At Risk Adriamycin 26, Relapses 16
Progress in Bladder Cancer

- Incidence up from
  - 14.6/100,000 in 1973 to 16.5 in 1997 (adjusted to 1970 population)
- Mortality down: 4.2/100,000 in 1973 to 3.2 in 1997
  - 5 yr survival 53% in 1950, 82% in 1997
- One of only 5 cancers with *increased* incidence and *reduced* mortality

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Percentage Change</th>
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<tbody>
<tr>
<td>Testis</td>
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<tr>
<td>Bladder</td>
<td>-1.3</td>
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<tr>
<td>Breast</td>
<td>-.3</td>
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<tr>
<td>Ovary</td>
<td>-.5</td>
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<tr>
<td>Thyroid</td>
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</table>

*Seer, 2000*
Risk Factors in Superficial Bladder Cancer

Recurrence
- 51% for solitary
- 91% multiple
- As low as 20% @ 5 years if 3 mo. cysto clear

Progression
- 4% for Ta, 30% for T1
- 2% for G1,Ta
- 48% for G3,T1

Mortality
- 6% G1, 21% G3
- CIS: 52% progression T2 or higher if untreated
- T2(+): 45% 5yr survival with cystectomy
Risk Groups
Improve Treatment Selection

• Low Risk: G1,Ta solitary tumor with no recurrence at 3 months
• Intermediate Risk: Multiple or recurrent G1,Ta; G2,Ta
• High Risk: Any G3, Lamina propria invasion (T1), CIS, or 3 month recurrence
Mechanisms of Tumor Recurrence

- Implantation at the time of tumor resection
- Incomplete resection
- Stimulation by growth factors induced by surgery and the healing process
- Growth of transformed cells or CIS
- Continued induction and promotion due to continued carcinogen exposure
Principles of Intravesical Chemotherapy

- Direct contact with cancer cells is required
- Tumor kill is proportional to duration of exposure and drug concentration
- Optimal response occurs with treatment within 6 hours of tumor resection
- Significant improvement with continued treatment or maintenance not reported
- Low-grade tumors respond best
## Thiotepa: Controlled Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Control</th>
<th>Thio</th>
<th>% Δ</th>
<th>P</th>
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<tbody>
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<td>51</td>
<td>97%</td>
<td>58%</td>
<td>39%</td>
<td>0.001*</td>
</tr>
<tr>
<td>Byar</td>
<td>86</td>
<td>60%</td>
<td>47%</td>
<td>13%</td>
<td>0.016</td>
</tr>
<tr>
<td>Nocks</td>
<td>42</td>
<td>64%</td>
<td>65%</td>
<td>-1%</td>
<td>NS</td>
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<tr>
<td>Asahi</td>
<td>134</td>
<td>41%</td>
<td>40%</td>
<td>1%</td>
<td>NS</td>
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<tr>
<td>Schulman</td>
<td>209</td>
<td>69%</td>
<td>59%</td>
<td>10%</td>
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<tr>
<td>Koontz</td>
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<td>39%</td>
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<td>Zincke</td>
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<td>71%</td>
<td>30%</td>
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<tr>
<td>Prout</td>
<td>90</td>
<td>76%</td>
<td>64%</td>
<td>12%</td>
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<tr>
<td>MRC</td>
<td>367</td>
<td>37%</td>
<td>40%</td>
<td>-3%</td>
<td>NS</td>
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<tr>
<td>Netto</td>
<td>34</td>
<td>80%</td>
<td>43%</td>
<td>37%</td>
<td>NS</td>
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<tr>
<td>Hirao</td>
<td>93</td>
<td>46%</td>
<td>15%</td>
<td>31%</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td>1257</td>
<td>60.6%</td>
<td>44%</td>
<td>16.6%</td>
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</table>
Single Immediate Post op Chemotherapy Reduces Tumor Recurrence in Ta,T1 TCC: Meta analysis of Randomized Trials

- 7 trials, 1476 patients, median follow 3.4 years (max 14.5)
- Recurrence: reduced from 362/748 (48.4%) with TUR alone to 267/728 (36.7%) with one postoperative dose epirubicin, MMC, thiotepa or pirarubicin
- 39% reduction in the odds of recurrence with chemotherapy (OR = 0.61, p < 0.0001)
- Both single (OR = 0.61) and multiple tumors (OR = 0.44) benefited
- 65.2% with multiple tumors recurred vs. 35.8% with single tumors
- One instillation may be insufficient with multiple tumors

Sylvester R: J Urol abstr. 270, 2004
## Mitomycin C: Controlled Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>C</th>
<th>MMC</th>
<th>% Δ</th>
<th>P</th>
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<tr>
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<td>52%</td>
<td>10%</td>
<td>42%</td>
<td>0.01</td>
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<tr>
<td>Niijima</td>
<td>278</td>
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<td>57%</td>
<td>5%</td>
<td>NS</td>
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<tr>
<td>Kim</td>
<td>43</td>
<td>82%</td>
<td>81%</td>
<td>1%</td>
<td>NS</td>
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<tr>
<td>Tolley</td>
<td>452</td>
<td>60%</td>
<td>41%</td>
<td>19%</td>
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<tr>
<td>Krege</td>
<td>234</td>
<td>46%</td>
<td>27%</td>
<td>19%</td>
<td>0.04</td>
</tr>
<tr>
<td>Akaza</td>
<td>298</td>
<td>33%</td>
<td>24%</td>
<td>9%</td>
<td>NS</td>
</tr>
<tr>
<td>Total:</td>
<td>1384</td>
<td>51.5%</td>
<td>37.6%</td>
<td>13.9%</td>
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</table>
# Summary of Controlled Chemotherapy Trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Series/N</th>
<th>% Δ</th>
<th>(range)</th>
<th>P&lt;0.05</th>
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<tbody>
<tr>
<td>Thiotepa</td>
<td>1257/11</td>
<td>16.6%</td>
<td>(-3-41)</td>
<td>6/11</td>
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<tr>
<td>Doxorubicin</td>
<td>1751/8</td>
<td>16.2%</td>
<td>(5-39)</td>
<td>4/8</td>
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<tr>
<td>Mitomycin</td>
<td>1384/6</td>
<td>13.9%</td>
<td>(1-42)</td>
<td>3/6</td>
</tr>
<tr>
<td>Ethoglucid</td>
<td>226/1</td>
<td>20.0%</td>
<td>(NA)</td>
<td>1/1</td>
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<tr>
<td>Epirubicin</td>
<td>985/6</td>
<td>19.6%</td>
<td>(9-26)</td>
<td>3/6</td>
</tr>
<tr>
<td>Total:</td>
<td>2297/32</td>
<td>17%</td>
<td>(-3-42)</td>
<td>17/32</td>
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</table>
# Controlled BCG Trials

<table>
<thead>
<tr>
<th>Author</th>
<th>No.</th>
<th>NoRx</th>
<th>BCG</th>
<th>Ben.</th>
<th>P</th>
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<td>Lamm ‘85</td>
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<td>20%</td>
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<td>&lt;.001</td>
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<tr>
<td>Herr ‘85</td>
<td>86</td>
<td>95%</td>
<td>42%</td>
<td>53%</td>
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<tr>
<td>Yamamoto ‘90</td>
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<td>67%</td>
<td>17%</td>
<td>50%</td>
<td>&lt;.0.05</td>
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<td>Pagano ‘91</td>
<td>133</td>
<td>83%</td>
<td>26%</td>
<td>57%</td>
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<tr>
<td>Mekelos ‘93</td>
<td>94</td>
<td>59%</td>
<td>32%</td>
<td>27%</td>
<td>&lt;0.02</td>
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<td>Krege ’96</td>
<td>224</td>
<td>48%</td>
<td>29%</td>
<td>24%</td>
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<td>Kolodziej ’02</td>
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<td>55%</td>
<td>19%</td>
<td>36%</td>
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<tr>
<td><strong>Total:</strong></td>
<td>798</td>
<td>66%</td>
<td>26%</td>
<td>40%</td>
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Meta-Analysis of BCG vs. TUR Alone

- 26 publications reviewed
- 6 acceptable trials with 585 patients
- Mean log hazard ratio for recurrence -.83, P<0.001
- 56% reduction in hazard attributable to BCG
- Manageable toxicity: cystitis 67%, hematuria 23%, fever 25%, frequency 71%
- Conclusion: BCG provides significantly better prophylaxis of tumor recurrence in Ta, T1 TCC
## Randomized BCG vs. Chemotherapy Studies

<table>
<thead>
<tr>
<th></th>
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<th>Doxorubicin</th>
<th>Epirubicin</th>
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<td><strong>Rec</strong></td>
<td><strong>Chemo</strong></td>
<td><strong>Adv.</strong></td>
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<tr>
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<tr>
<td>7%</td>
<td>vs</td>
<td>43%</td>
<td>+35</td>
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<td>vs</td>
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<td>+26</td>
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<tr>
<td>53%</td>
<td>vs</td>
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<td>vs</td>
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<td>+30</td>
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<td>24%</td>
<td>vs</td>
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<td>+18</td>
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<td><strong>Epirubicin</strong></td>
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<tr>
<td>33%</td>
<td>vs</td>
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## Randomized BCG vs. MMC Studies

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<th>MMC</th>
<th>( \Delta ) BDG</th>
<th>P Value</th>
<th>Author/Year</th>
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<tr>
<td>4%</td>
<td>vs</td>
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<tr>
<td>28%</td>
<td>vs</td>
<td>62%</td>
<td>+34</td>
<td>&lt;.001*</td>
<td>Finnblad ‘89</td>
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<tr>
<td>61%</td>
<td>vs</td>
<td>80%</td>
<td>+19</td>
<td>NS</td>
<td>Lee ‘92</td>
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<tr>
<td>47%</td>
<td>vs</td>
<td>42%</td>
<td>-5</td>
<td>NS</td>
<td>Witjes ‘94</td>
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<tr>
<td>64%</td>
<td>vs</td>
<td>42%</td>
<td>-21</td>
<td>NS</td>
<td>Vegt ‘95</td>
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<tr>
<td>46%</td>
<td>vs</td>
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<td>vs</td>
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<td>Krege ‘96</td>
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<tr>
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<td>vs</td>
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<td>+24</td>
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<tr>
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<td>vs</td>
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<td>14%</td>
<td>vs</td>
<td>26%</td>
<td>+13</td>
<td>&lt;.01</td>
<td>Nogueira ‘01</td>
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36.7% of 781 vs 53.8% of 771 (+17%) in maintenance BCG studies. 6/6 maintenance BCG studies significant vs 1/5 non-maint.
BCG Versus Mitomycin-C
(SWOG 8795)

Time To Recurrence
Percent Recurrence

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<th>Median in Months</th>
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<td>64</td>
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<tr>
<td>Reached</td>
<td>190</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>187</td>
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</table>

Lamm DL
Urol Oncol
1:119-126, 1995

• “This is the highest level of evidence-based medicine and the results presented here suggest that intravesical BCG is superior to mitomycin C.”

• “A subgroup analysis of 3 trials that included only high-risk Ta and T1 patients indicated no heterogeneity (P>0.25) and a LHR for recurrence of -0.371 (0.012). With MMC used as the control in the meta-analysis, a negative ratio is in favour of BCG and, in this case, was highly significant (P<0.001).”
Optimal Intravesical Chemotherapy

• Immediate postoperative treatment is best, confirmed by meta-analysis (Sylvester, 2004)

• *Concentration* is more important than dose: 40mg MMC/20ml water, 30mg thiotepa/15cc, 50mg Adra/25cc all for 30 minutes within 6 hours post op

• MMC: 40mg/20ml, dehydration, ultrasound confirmed bladder drainage and 1.3g bicarb. HS, AM and at time of instillation doubles protection from recurrence (Au, JNCI, 2001)
BCG Versus Doxorubicin: Time Without Treatment Failure

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>5-year RFS</th>
</tr>
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<tbody>
<tr>
<td>BCG CIS</td>
<td>64</td>
<td>45%</td>
</tr>
<tr>
<td>BCG Ta, T1</td>
<td>63</td>
<td>37%</td>
</tr>
<tr>
<td>Doxorubicin Ta, T1</td>
<td>67</td>
<td>18%</td>
</tr>
<tr>
<td>Doxorubicin CIS</td>
<td>68</td>
<td>17%</td>
</tr>
</tbody>
</table>

5 Year Tumor Recurrence Curves With Chemotherapy vs Control

EORTC/MRC

Percent Tumor Free

Time (Years)

Chemotherapy
Control
BCG vs Chemo For CIS: Meta-Analysis

Sylvester: J Urol. 174:86, 2005

- 9 randomized trials including 700 pts. with CIS
- Chemo: MMC, Epi, Adria, or sequential MMC/Adria
- BCG: 68% CR vs Chemo: CR 52%; P=0.0002
- 3.6 year follow: 47% BCG vs 26% Chemo NED
- 26% reduction in disease progression with BCG
- “BCG reduces the risk of short and long-term treatment failure compared with chemotherapy… agent of choice in the treatment of CIS.”
Principles of BCG Immunotherapy

- Minimize tumor burden ($10^3$ cells, mouse)
- Juxtapose BCG and tumor cells
- Use sufficient but not excess BCG (Dose-Response curve is Bell-shaped). Excess BCG (e.g., repeated 6 week courses) suppresses the immune response
- Initial immune stimulation peaks at 6 weeks, subsequently at 3 weeks
- Immune stimulation wanes with time
- TH1 immune competent host & antigenic tumor
Dose-Response Curve to BCG (in mice)

Individual responses and preparations vary, but too little or too much BCG reduces effect.

Low-Dose Versus High-Dose BCG


- BCG, 75 mg (n=90)
- BCG, 150 mg (n=93)

Proportion disease free vs. Time since start of treatment, months
Why Maintenance BCG?

• The risk of tumor recurrence is lifelong

• The immune stimulation and protection from tumor recurrence induced by BCG wanes with time
Three Week Maintenance BCG
SWOG 8795: 385 Evaluable, NED

Recurrence -free Survival

Worsening -free Survival

Survival

Lamm DL et al, J Urol 163, 1124, 2000

p < 0.0001

p = 0.04

p = 0.08
Figure 1

Percent Tumor Recurrence

Years

M: Three Week Maintenance BCG
I: Induction Only

* Completion of Therapy
** Apparent Increase in Rate of Recurrence
One Year After Completion of Maintenance
Results

• With 10 year follow-up, recurrence reduced from 52% to 25% (P<0.0001)
• Recurrence-free survival increased from 30% to 48% (P<0.0001)
• Worsening-free survival increased from 52% to 60% (P<0.04)
• Overall survival increased from 51.5% to 57.8% (P=0.08, NS)
BCG Maintenance: Not Created Equal

Completion of Therapy * Apparent Increase in Rate of Recurrence ** One Year After Completion of Maintenance

N=385, 3q 3-6 months

N=385, 3q 3-6 months

N=126, 6q 6mo.

N=42 pts. 1q 3mo.

N=93 pts. 1q 1mo.

Global recurrence

% Tumor Recurrence

% Disease Free

N=93 pts. 1q 1mo.

N=385, 3q 3-6 months

N=126, 6q 6mo.

M, TaT1, 3wk maintenance BCG
M, CIS, 3wk maintenance BCG
I, CIS, 6wk induction BCG
I, TaT1, 6wk induction BCG

* Completion of Therapy
** One Year After Completion of Maintenance
Progression All Studies With Maintenance

| Study Publ Year | Author and Group | Events / Patients | Statistics | OR & CI | |1-OR| % ± SD |
|-----------------|------------------|-------------------|------------|---------|----------------|-------------|
| 1991 Pagano (Padova) | 11 / 63 3 / 70 | -4.4 3.1 | | | | |
| 1987 Badalament (MSKCC) | 6 / 46 6 / 47 | -0.1 2.6 | | | | |
| 2000 Lamm (SW8507) | 102 / 192 87 / 192 | -7.5 24.1 | | | | |
| 2001 Palou | 2 / 61 3 / 65 | 0.4 1.2 | | | | |
| 1996 Rintala (Finnbl 2) | 3 / 90 3 / 92 | 0 1.5 | | | | |
| 1995 Rintala (Finnbl 2) | 4 / 40 2 / 28 | -0.5 1.3 | | | | |
| 1995 Lamm (SW8795) | 24 / 186 15 / 191 | -4.8 8.8 | | | | |
| 1999 Malmstrom (Sw-N) | 22 / 125 15 / 125 | -3.5 7.9 | | | | |
| 2001 Nogueira (CUETO) | 8 / 127 10 / 247 | -1.9 3.9 | | | | |
| 1991 Rintala (Finnbl 1) | 2 / 58 3 / 51 | 0.7 1.2 | | | | |
| 2001 de Reijke (EORTC) | 18 / 84 10 / 84 | -4 5.9 | | | | |
| 2001 vd Meijden (EORTC) | 19 / 279 24 / 558 | -4.7 9.1 | | | | |
| 1982 Brosman (UCLA) | 0 / 22 0 / 27 | 0 0 | | | | |
| 1990 Martinez-Pineiro | 4 / 109 1 / 67 | -0.9 1.2 | | | | |
| 1999 Witjes (Eur Bropir) | 2 / 25 1 / 28 | -0.6 0.7 | | | | |
| 1997 Jimenez-Cruz | 7 / 61 6 / 61 | -0.5 2.9 | | | | |
| 1994 Kalbe | 2 / 35 0 / 32 | -1 0.5 | | | | |
| 1991 Kalbe | 2 / 17 0 / 21 | -1.1 0.5 | | | | |
| 1993 Melekos (Patras) | 7 / 99 2 / 62 | -1.5 2 | | | | |
| 1988 Ibrahim (Egypt) | 12 / 30 5 / 17 | -1.1 2.6 | | | | |

| Study Publ Year | Author and Group | Events / Patients | Statistics | OR & CI | |1-OR| % ± SD |
|-----------------|------------------|-------------------|------------|---------|----------------|-------------|
| 1988 Ibrahim (Egypt) | 12 / 30 5 / 17 | -1.1 2.6 | | | | |

Test for heterogeneity
$\chi^2=9.73$, df=18: $p=0.9$

Total 257 / 1749 196 / 2065 -36.8 80.9 37% ± 9 reduction

BCG better | No BCG better

Treatment effect: $p=0.00004$
Kaplan Meier Estimate of 5 Year Tumor Free Rate
In Patients Receiving Vitamin Supplement and BCG Therapy
For Bladder Carcinoma

p=0.0014
Natural and Chemotherapy Treated History of T1, G3, TCC

<table>
<thead>
<tr>
<th>Author</th>
<th>No.</th>
<th>Progr.</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heney ‘83</td>
<td>27</td>
<td>48%</td>
<td>36 mo.</td>
</tr>
<tr>
<td>Rutt ‘85</td>
<td>430</td>
<td>31%</td>
<td>60 mo.</td>
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<tr>
<td>Malmstrom ‘87</td>
<td>7</td>
<td>43%</td>
<td>60 mo.</td>
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<tr>
<td>Jakse ‘87</td>
<td>31</td>
<td>33%</td>
<td>60 mo.</td>
</tr>
<tr>
<td>Kaubisch ‘91</td>
<td>18</td>
<td>50%</td>
<td>36 mo.</td>
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<tr>
<td>Mulders ‘94</td>
<td>48</td>
<td>27%</td>
<td>48 mo.</td>
</tr>
<tr>
<td>Klan ‘95</td>
<td>17</td>
<td>65%</td>
<td>72 mo.</td>
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<tr>
<td>Holmang ‘97</td>
<td>58</td>
<td>48%</td>
<td>84 mo.</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td>519</td>
<td>33%</td>
<td></td>
</tr>
</tbody>
</table>
## BCG in Grade 3, Stage T1  TCC

<table>
<thead>
<tr>
<th>Author</th>
<th>No.</th>
<th>Prog. %</th>
<th>Followup</th>
<th>Author</th>
<th>No.</th>
<th>Prog %</th>
<th>Follow-up</th>
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<tbody>
<tr>
<td>Boccon - Gibod ’89</td>
<td>47</td>
<td>12</td>
<td>-</td>
<td>Vicente ’96</td>
<td>95</td>
<td>11</td>
<td>46</td>
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<tr>
<td>Dal Bo ’90</td>
<td>24</td>
<td>25</td>
<td>22</td>
<td>Lebret ’98</td>
<td>35</td>
<td>12</td>
<td>45</td>
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<tr>
<td>Samodi ’91</td>
<td>62</td>
<td>0</td>
<td>46</td>
<td>Baniel ’98</td>
<td>78</td>
<td>8</td>
<td>56</td>
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<tr>
<td>Cookson ’92</td>
<td>86</td>
<td>7</td>
<td>59</td>
<td>Klan ’98</td>
<td>109</td>
<td>13</td>
<td>78</td>
</tr>
<tr>
<td>Eure ’92</td>
<td>30*</td>
<td>7</td>
<td>39</td>
<td>Gohji ’99</td>
<td>25</td>
<td>4</td>
<td>63</td>
</tr>
<tr>
<td>Pfister ’95</td>
<td>26</td>
<td>27</td>
<td>54</td>
<td>Brake ’00</td>
<td>44</td>
<td>16</td>
<td>43</td>
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<tr>
<td>Hurle ’96</td>
<td>51</td>
<td>14</td>
<td>33</td>
<td>Pansadoro ’02</td>
<td>86</td>
<td>14</td>
<td>71</td>
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<tr>
<td>Zhang ’96</td>
<td>23</td>
<td>35</td>
<td>45</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Sereretta ’96</td>
<td>50</td>
<td>12</td>
<td>52</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td>871</td>
<td>12</td>
<td></td>
<td></td>
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</tbody>
</table>
Clinical v. Pathologic Staging
Stage T1 TCC

Cystectomy in 101 Clinical State T1 patients
Final Pathologic States

<table>
<thead>
<tr>
<th>Stage</th>
<th>Count</th>
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<tbody>
<tr>
<td>pTO</td>
<td>19</td>
</tr>
<tr>
<td>pTIS</td>
<td>4</td>
</tr>
<tr>
<td>pTa</td>
<td>0</td>
</tr>
<tr>
<td>pT1</td>
<td>47</td>
</tr>
<tr>
<td>pT2</td>
<td>10</td>
</tr>
<tr>
<td>pT3a</td>
<td>2</td>
</tr>
<tr>
<td>pT3b</td>
<td>8</td>
</tr>
<tr>
<td>pT4</td>
<td>11</td>
</tr>
</tbody>
</table>

Amling, J. Urol, 1991
# Understaging of High-Risk Superficial Bladder Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>% Understaged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pagano</td>
<td>35%</td>
</tr>
<tr>
<td>Amling</td>
<td>37%</td>
</tr>
<tr>
<td>Soloway</td>
<td>36%</td>
</tr>
<tr>
<td>Freeman</td>
<td>34%</td>
</tr>
<tr>
<td>Ghoneim</td>
<td>62%</td>
</tr>
<tr>
<td>Herr</td>
<td>49%</td>
</tr>
<tr>
<td>Dutta</td>
<td>64%</td>
</tr>
</tbody>
</table>

**Overall Average:** 45%
Cystectomy is The Gold Standard for Invasive TCC
How Good is Gold?

- Pelvic recurrence: 5-30%
- Overall 5 yr survival: 42-60%
- Morbidity and mortality (0.3-6%)
Current Survival with Cystectomy


269 patients at MSK 1990-3; 45% 5yr survival, 67% DSS
Current Survival with Cystectomy


- 5 yr survival: 64% for TIS, TA, T1;
- 59% for T2
TUR for Muscle Invasive TCC

- Barnes: 40% 5 yr survival when confined to bladder
- Solsona: 59 pts, 75% 10 yr DFS, 80% bladder preservation
Partial Cystectomy for Muscle Invasive Bladder Cancer

- 37 patients, 1982-2003 followed for 73 months (6-217).
- 51% had no tumor recurrence.
- 9 (24%) superficial and 9 (24%) invasive or advanced recurrence.
- 6 (16%) died of bladder cancer.
- 5 year overall and DSS: 67% and 87%

Kassouf W: J Urol. 2006;175:2058-62. MD Anderson
463 Muscle-Invasive TCC Patients

463 patients
1979 - 1989
reTUR
432 pts

T2
281 pt (65%)
Cystectomy
+/- CT

T0 or T1
151 pts (35%)

52 pts
Immediate Cystectomy
(23 T0, 29 T1)

99 pts
TUR*
(73 T0, 26 T1)

Followup: 10 yrs > 20 years
*+/- IVT, salvage cystectomy for rec tumor invasion
TUR vs. Cystectomy for T2 ⇒T0 TCC


151 non-randomized pts, 99 TUR only, 52 immediate cystectomy

TUR: 82% surv. 18% DOD

Cystectomy: 65% surv. 35% DOD
Superficial Recurrence: No Effect on Survival
### TUR and BCG in Invasive TCC

<table>
<thead>
<tr>
<th>Author/yr</th>
<th>N</th>
<th>%NED</th>
<th>Follow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netto ‘84</td>
<td>10</td>
<td>60%</td>
<td>32 mo</td>
</tr>
<tr>
<td>Lamm ‘84</td>
<td>17</td>
<td>41%</td>
<td>24 mo</td>
</tr>
<tr>
<td>Pansadoro ‘87</td>
<td>41</td>
<td>24%</td>
<td>18 mo</td>
</tr>
<tr>
<td>Rosenbaum ‘96</td>
<td>13</td>
<td>15%</td>
<td>60+mo</td>
</tr>
<tr>
<td>Volkmer ‘03</td>
<td>22</td>
<td>46%</td>
<td>60 mo*</td>
</tr>
</tbody>
</table>

*69% 5yr survival, P0 2nd TUR
Neo Adjuvant Chemotherapy: Meta Analysis

- 10 randomized clinical trials, 2688 patients
- 13% reduction in bladder cancer death (hazard ratio 0.87, P=0.016)
- 5 yr overall survival increased from 45 to 50%
- No significant benefit for platinum alone

Adjuvant Chemotherapy Post Cystectomy or RT: Meta-Analysis

- 491 patients in 6 randomized trials
- 25% reduction in mortality (HR 0.75; 95%: 0.061-0.09, P=0.019)
- Overall 3 yr survival increased from 45% to 54% with adjuvant chemotherapy

ABC Meta-analysis Collaboration: Cochrane Database of Systematic Reviews. 2006, Issue 2
Surgery versus Radiation Therapy
For Muscle Invasive TCC: Meta-Analysis

• Only 3 quality randomized trials; 493 patients
• 3 yr survival increased from 28% with radiation to 45% with surgery
• 5 yr survival increased from 20% to 36% (OR 2.17, 95% 1.39-3.38)

Shelley MD. Surgery versus radiotherapy for muscle invasive bladder cancer. Cochrane Database of Systematic Reviews. 2001 Issue 4
Lymphadenectomy in Bladder Cancer

• Skinner/Stein: Dissection to include common, presacral, and distal para caval and para aortic nodes
• N1 outcome nearly as good as N0; N3 poor
Survival with Positive Nodes

- 150 N+, M0 patients; 108 without prior CRx
- Median N+ nodes: 2; 12 on average removed
- 70% received adjuvant chemotherapy (P<.01)
- 5 yr OS: 30.9%, DSS: 45.5% and RFS: 29.7%
- <25% Density: OS: 37.3% v 18.7%; RFS: 38.1% v. 10.6% for >25% (P<.02)


• 1,359 patients median age 67 (47-78)
• Operative Mortality: 2% (27 patients)
• Overall survival 10 yrs for T2: 47%
• Recurrence free survival, T2: 72%

J Urol. 2006;175:886-9
Limited Node Dissection:
Cleveland Clinic Experience

- 385 pts, mean age 62 (31-84) with negative cystectomy margins, 1987-2000
- Obturator and external iliac nodes only
- 12 (2-32) nodes removed
- 45 mo median follow; no neo RT or CRx
- 12% (45) had positive nodes: only 9% overall and recurrence free survival at 5 yr

Dhar NB: BJU Int. 2006 Sep 6; E pub ahead of print
Delay in Cystectomy:  
Keep it Less Than 12 Weeks

• 13 papers, only 3 (23%) failed to show worse prognosis with delay in surgery
• Increase in stage and/or mortality found in 10 papers
• Consensus: cystectomy should be accomplished in less than 12 weeks from the diagnosis of muscle invasive disease

Conclusions

• Bladder cancer is more common than generally appreciated

• Multiple models are available to test novel treatments

• Translational research is facilitated by the propensity for bladder cancer to recur and the ability to treat and follow bladder cancer transurethrally

• Bladder cancer is responsive to many types of treatment
Conclusions

• Early detection and effective treatment appear to be lowering the mortality of bladder cancer

• Low risk (solitary Ta, G1) patients are best treated with a single instillation of chemo post TUR

• Intermediate risk patients can be treated with chemotherapy (immediate) or BCG

• BCG is never given immediately post op!

• High risk (G3, T1, or CIS) patients are best treated with BCG
Conclusions

- BCG provides superior protection from tumor recurrence
- While BCG is highly effective, it has significant and even life-threatening toxicity, and 50% or more of patients eventually fail treatment.
- Side effects of BCG can be reduced with careful catheterization, dose reduction (x3) and delay
- New, less toxic, more effective bladder cancer treatments are needed
Conclusions

• Patients failing BCG with muscle invasive disease/late cystectomy patients have reduced survival.
• Immediate cystectomy for G3,T1: 45% unsuspected T2 or greater disease.
• Cystectomy for T2 or greater: 45% 5 yr surv.
• BCG for G3, T1: 12% delayed progression.
• Repeat resection of T2 disease: 35% T1 or T0; Cystectomy for these: 65% survival, compared with 82% survival for noncystectomy.
Thank You!

for your attention

BCGOncology.com
Combination Vitamins (Oncovite) in Bladder Cancer

- 65 patients post bladder tumor resection randomized to RDA vitamins vs high dose:
  - 40,000 IU Vitamin A
  - 100mg Vitamin B6
  - 2,000mg Vitamin C
  - 400 IU Vitamin E plus 90 mg Zinc

- Tumor recurrence reduced from 91% RDA to 41% at 5 years with Oncovite