Current Superficial (TA,T1, CIS) Bladder Cancer Management

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BCGOncoology.com

Satellite Meeting, 5/22/07, AUA Anaheim, CA
Current Practice

- MMC and BCG: risk factors
- Management of Recurrence: treatment failures
- Biomarkers: research or practice?
- Future Therapies: currently probable?
Key Management Points/Controversies

- TUR: technique and repeat
- Immediate postoperative chemotherapy
- Risk assessment/treatment by risk group
- Low risk: optimal intravesical chemotherapy
- High risk: optimal BCG immunotherapy
- Early Cystectomy rather than BCG for G3,T1
- Recurrence: Definition/management of failures
- What’s new: combo chemo, electomotive/hyperthermic chemo, new/combined IRx
TURBT: Get it all the *Second* Time?

- ~40% (26-83%) have disease at re-TUR and 2-28% are upstaged to T2 (Miladi M: 2003, Eur Urol. 43:241.)
- More extensive resection can reduce disease at re-TUR (Langbein L: 2006, MPP. 15:215.)
- Flamm J: “Residual” disease common even with negative margins at initial TUR (personal communication)
- 10-year disease-specific survival was 76% in 99 T2 pts who received TUR as definitive Rx (Herr HW: 2001, JCO. 19:89.)
- Bottom line: If you can’t get it all the first time, get it the second time!
Randomized Trial of Repeat TUR with Immediate Post op MMC

- 142 T1 TCC randomized re-TUR or not
- All received 40mg MMC after 1\textsuperscript{st} or 2\textsuperscript{nd} TUR 2-6 wks later, then x7
- Recurrence: 19/74 (26\%) group 1 and 43/68 (63\%) group 2
- Median RFS 27 mo (6-48) group 1 vs 12 mo (3-48) in group 2 (p<0.001 for high grade tumors)

Divrik RT: J Urol. 2006 May;175(5):1641
Perioperative Chemotherapy

Forest Plot of Recurrence

* Thiotepa study included dilute, ineffective preparation

Meta-Analysis: Immediate Postoperative Intravesical Chemotherapy

- 1476 patients in 7 randomized clinical trials
- Tumor recurrence reduced from 48.4% to 36.7% (OR 0.61, P<0.0001)
- Effect may be less in multiple than solitary tumors: 65.2% versus 35.8% recurrence.
- Benefit is significant (and cost effective) even in solitary, low-grade tumors.

Sylvester RJ. J Urol. 2004;171:2186-90
Risk Factors in Superficial Bladder Cancer

**Recurrence:** *Multiplicity* is the best predictor
- 51% for solitary
- 91% *multiple*
- As low as 20% @ 5 years if 3 mo. cysto clear

**Progression:** *Lamina propria invasion*
- 4% for Ta, 30% for T1
- 2% for G1,Ta
- 48% for G3,T1

**Mortality:** *Grade* is the best predictor
- 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: Low Grade (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
EORTC Risk Tables for Stage Ta T1 Bladder Cancer

Prior Recurrence Rate
- Primary
- Recurrent ≤ 1 per year
- Recurrent > 1 per year

Number of Tumors
- 1
- 2 to 7
- 8 or more

Tumor Diameter
- < 3 cm
- ≥ 3 cm

T Category
- Ta.
- T1

Grade (WHO 1973)
- G1
- G2
- G3

Concomitant CIS
- No
- Yes

Calculate Probabilities
Clear
Exit

<table>
<thead>
<tr>
<th></th>
<th>1 Year</th>
<th>2 Years</th>
<th>3 Years</th>
<th>4 Years</th>
<th>5 Years</th>
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<td>Probability of Recurrence</td>
<td>0.38</td>
<td>0.51</td>
<td>0.56</td>
<td>0.59</td>
<td>0.62</td>
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<tr>
<td>Probability of Progression</td>
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<td>0.03</td>
<td>0.04</td>
<td>0.05</td>
<td>0.06</td>
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</table>


Programmed by Richard Sylvester, EORTC Data Center, 83 avenue Mounier, 1200 Brussels, Belgium.

Version 1.0, January 2006

http://www.eortc.be/tools/bladdercalculator/
## 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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<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>
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<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>
5 year Tumor Recurrence Curves With Chemotherapy vs Control

EORTC/MRC
Intravesical Chemotherapy Principles:

• *Direct contact* required
• Kill α drug concentration & duration of exposure
• Optimal response occurs with treatment within 6 hours of tumor resection
• Significant improvement with continued treatment or maintenance is difficult to demonstrate
• Low-grade tumors respond best
Improved Mitomycin C Chemotherapy

- 230 randomized Ta, T1 pts.
- *Standard* MMC, 20mg/20cc weekly x6 vs. *Optimized* MMC: 40mg/20cc, NPO overnight, ultrasound confirmed empty bladder, and alkalinization with 1.3gm NaHCO3
- 5 yr recurrence free: *Standard* 24.6% versus 41% with *Optimized* MMC; time to recurrence increased from 11.8 to 29.1 months (P<0.005)
My Recommendation for Ta, T1 TCC

- A Single postop chemotherapy instillation is sufficient for low grade TCC:
  - Thiotepa 30mg/15cc
  - Mitomycin 40mg/20cc
  - Doxorubicin (Adria) 50mg/25cc
Each held for 30 minutes.
- Never give MMC or Adriamycin with perf.
  56 to 58% of postop cytograms show reflux!*  
- Thiotepa can (should?) be given with perf.
- Never give BCG immediately postop!

* Hayek OR, AUA 2007 abstract 338
Risk Groups
Improve Treatment Selection

• Low Risk: Low Grade (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
BCG Versus Doxorubicin: Time to Treatment Failure

BCG Versus Mitomycin-C (SWOG 8795)

Lamm DL. Urol Oncol. 1:119-126, 1995

Percent Recurrence

Time To Recurrence

At Risk Fail Median in Months
BCG 190 44 Not Reached
MMC 187 64 20
## Randomized BCG vs. MMC Studies

<table>
<thead>
<tr>
<th>BCG %</th>
<th>Rec. %</th>
<th>MMC %</th>
<th>Δ BCG</th>
<th>P value</th>
<th>Author/year</th>
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<td>vs</td>
<td>34</td>
<td>+30</td>
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<tr>
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<td>vs</td>
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<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>
</tr>
<tr>
<td>47</td>
<td>vs</td>
<td>42</td>
<td>-5</td>
<td>NS</td>
<td>Witjes '94</td>
</tr>
<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>
<td>43</td>
<td>-3</td>
<td>NS</td>
<td>&quot; '95</td>
</tr>
<tr>
<td>43</td>
<td>vs</td>
<td>56</td>
<td>+9</td>
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<tr>
<td>51</td>
<td>vs</td>
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<td>+15</td>
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</tr>
<tr>
<td>24</td>
<td>vs</td>
<td>29</td>
<td>+5</td>
<td>NS</td>
<td>Krege '96</td>
</tr>
<tr>
<td>38</td>
<td>vs</td>
<td>62</td>
<td>+24</td>
<td>&lt;.001</td>
<td>Ayed '98</td>
</tr>
<tr>
<td>32</td>
<td>vs</td>
<td>54</td>
<td>+22</td>
<td>&lt;.001</td>
<td>Milan '00</td>
</tr>
<tr>
<td>13</td>
<td>vs</td>
<td>26</td>
<td>+13</td>
<td>&lt;.01</td>
<td>Nogueira '01</td>
</tr>
</tbody>
</table>

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.
Management of Recurrence

• Definition of failure:
  – Recurrence after treatment?
  – Early (one year) recurrence after chemo?
  – Late (6 or more months) recurrence after BCG induction or recurrence on 3 week maintenance?

• Chemo failures: BCG appropriate for even for low grade, TA, but long term maintenance may not be indicated.

• BCG Failures: Chemo, repeat BCG, BCG IFn, and novel or experimental therapies
## Second Induction Course of BCG

<table>
<thead>
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<th>N</th>
<th>R</th>
<th>R%</th>
<th>TTR</th>
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<tr>
<td>Bretton</td>
<td>28</td>
<td>18</td>
<td>64%</td>
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<tr>
<td>Hurle</td>
<td>13</td>
<td>6</td>
<td>46%</td>
<td>27 mo</td>
</tr>
<tr>
<td>Kohjimoto</td>
<td>16</td>
<td>6</td>
<td>38%</td>
<td>35 mo</td>
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<tr>
<td>Yamada</td>
<td>31</td>
<td>20</td>
<td>64%</td>
<td>36 mo</td>
</tr>
<tr>
<td>Bui</td>
<td>11</td>
<td>6</td>
<td>54%</td>
<td>84 mo</td>
</tr>
<tr>
<td>O’Donnell</td>
<td>40</td>
<td>19</td>
<td>47%</td>
<td>26 mo*</td>
</tr>
<tr>
<td>Nadler</td>
<td>66</td>
<td>39</td>
<td>59%</td>
<td>45 mo</td>
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<tr>
<td><strong>Total:</strong></td>
<td>205</td>
<td>114</td>
<td>56%</td>
<td>21-84 mo</td>
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</table>

*BCG plus interferon: 53% recurrence free 26 m. vs 36% free (21-84 m) without Ifn*
BCG Maintenance: Not Created Equal

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

Percent Tumor Recurrence

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

Global recurrence

N=385, 3q 3-6 months

N=42 pts

N=93

N=126

Time in months

Years

* Completion of Therapy
* Apparent Increase in Rate of Recurrence
** One Year After Completion of Maintenance
SWOG BCG Arms
Papillary Patients Only

Percent Tumor Recurrence

At Risk Fail Median In Months

At Risk Fail Median In Months

p = 0.001

Months After Registration

3 wk Maint

Monthly M

6 wk Ind

Quarterly M

p = 0.001

Not Reached

63 41 23

120 30 63

191 77 46

BCG8216

BCG8507

BCG8795

BCG8507

BCG8216

BCG8507
3 Week Maintenance BCG

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
Can BCG Delay or Prevent Progression in Superficial Bladder Cancer?

• Meta-analysis of 24 studies, 4863 patients randomized to BCG vs surgery alone (2), BCG maintenance (3), chemotherapy (14), or other immunotherapies (5).
• 2.5 year median follow (max 15)
• 82% Ta, T1, 37% G1, 55% G2, 8% G3; 18% CIS
• 78% received maintenance BCG, 10-30 Rx over 18 weeks to 3 yrs.
<table>
<thead>
<tr>
<th>Study Publ Year</th>
<th>Author and Group</th>
<th>Events / Patients</th>
<th>Statistics</th>
<th>OR &amp; CI</th>
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<td></td>
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<td>BCG</td>
<td>(O-E)</td>
<td>Var.</td>
<td>(BCG)</td>
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<td>Pagano (Padova)</td>
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<td>87</td>
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<td>8.8</td>
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<td>125</td>
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<td>1988</td>
<td>Ibrahim (Egypt)</td>
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<td>5</td>
<td>17</td>
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<td>196</td>
<td>2065</td>
<td>-36.8</td>
<td>80.9</td>
</tr>
</tbody>
</table>

Test for heterogeneity
\( \chi^2 = 9.73, \text{df} = 18: p = 0.9 \)

Treatment effect: \( p = 0.00004 \)

37% ±9 reduction
Early Cystectomy for G3,T1 TCC?

• Survival of patients who come to cystectomy after failing BCG is markedly reduced, *therefore G3,T1 patients should be treated with cystectomy rather than BCG!*

• 40% undergoing immediate cystectomy have T2 or greater disease, ~50% of whom will survive 5 years (20% 5 yr mortality).

• With 88% progression free on BCG at 5 years, if 100% of those progressing died following cystectomy (12% 5 yr mortality), survival would still be *better* (88% versus 80)% than immediate cystectomy!
Understaging of High-Risk T1 Bladder Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>% Understaged</th>
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<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>46%</td>
</tr>
<tr>
<td><strong>Overall Average:</strong></td>
<td><strong>43%</strong></td>
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<td>Author</td>
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<td>Dal Bo '90</td>
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<td>Samodi '91</td>
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<td>Serretta '96</td>
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<td>Brake '00</td>
<td>44</td>
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<tr>
<td>Pansadoro '02</td>
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<td><strong>Total:</strong></td>
<td>796</td>
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BCG Rx G3, T1

- 785 pts superficial TCC, 1982-2000
- 11% (86) G3, T1 treated with maintenance BCG
- 91 month follow up
- Recurrence: 35%, @ mean of 29 months
- Progression: 14%, @ mean of 16 months
- Cancer mortality: 6%, 71 month median follow
- Cystectomy: 9%; 70% alive with intact bladder
- “Cystectomy should not be considered for first line Rx”

Cystectomy or BCG for T1G3?

- 86 pts with \textbf{T1} TCC treated with BCG and followed for 59 (9-149) months.
- 31\% early recurrence, but 91\% overall disease free with additional BCG.
- \textbf{Progression to T2 or higher: 7\%}
- Disease specific survival: 85/86=99\%

Cookson MS: J Urol. 1992;148:797-801. UT San Antonio
Future Therapies

- New treatments are much needed!
- FDA problem: new treatments compared with BCG or BCG refractory
- What’s new: alternative therapy, combo chemo, electomotive/hyperthermic chemo, new/combined IRx
Kaplan Meier Estimate of 5 Year Tumor Free Rate
In Patients Receiving Vitamin Supplement and BCG Therapy
For Bladder Carcinoma


40,000u Vitamin A, 100mg B6, 2gm C, 400mg E: "Oncovite"

\[ p = 0.0014 \]

RDA Vitamins

**Oncovite** (N=35)

**RDA Vitamins** (N=30)
Animal Testing Data

TLT are refractory for treatment with Oncovin.

Untreated Oncovin
CK₃
Oncovin + CK₃

NMR1 mice survivors (%)

Days after i.p. TLT Transplantation

At 40 days, 40% of the animals were still alive.
Single injection murine monotherapy - K652 (human CML) cell line

One injection reduced tumor volume 60-65%
Fluorescence Cystoscopy

Photo by Bart Grossman, 2006
BCG & Electromotive Mitomycin


Slide courtesy of Bart Grossman, MD Anderson
BCG & Electromotive Mitomycin

Disease-free Survival


Progression-free Survival

Slide courtesy of Bart Grossman, MD Anderson
BCG & Electromotive Mitomycin

Overall Survival

Disease-specific Survival


Slide courtesy of Bart Grossman, MD Anderson
Gemcitabine

- **N = 30**
- **BCG Refractory or Intolerant**
- **2 courses 2 g/100 mL twice weekly for 3 weeks separated by 1 week of rest**


Slide courtesy of Bart Grossman, MD Anderson
Other Drugs

• Docetaxel (Taxotere)
  – N = 18
  – 56% short-term DFS
  – 75 mg/100 mL well-tolerated (2 hours)
  – No systemic absorption

• Apaziquone (Eoquin)
  – N = 46, marker lesion study
  – CR in 30 (65%)
  – 4 mg/40 mL (1 hour)
Multi-Agent Intravesical Chemotherapy

- Multidrug regimens: nearly always better in advanced TCC
- Combine to increase cell kill without increased toxicity
- Most frequent DLT for intravesical chemotherapy is cystitis
- Combine drugs with differing mechanisms of action, one or more without vesicant (irritative) side effects

Mike O’Donnell, 2006
Cancer-free Rate for Refractory Patients after Salvage Treatment

UIHC Experience w/ BCG + IFN Failures ‘06 AUA 840 (Maymi)
Alternative Immunotherapy

• KLH: 59% reduction in tumor recurrence with *systemic* administration alone!
• MCC/Regressin/Mycobacterium phlei cell walls: effective in CIS and BCG failures.
• BCG Interferon: 60% protection from recurrence in BCG failure patients.
• Others?
Gene/DNA Therapy

- CG0070: Cell Genesys Rb/GMCSF modified Adenovirus: Phase 1-2
- Schering: promising IFn producing agent
- Biocancel: H19 in clinical trials
Conclusions

• Surgery Counts! Extend resection, send margin, then roller-balling base and edges (?); or re-resect
• Immediate postoperative chemotherapy: standard
• Concentrated chemo for low risk, BCG for high
• 3 week maintenance BCG, not repeated 6 weeks
• High grade: carefully follow upper tracts and prostate. Low threshold for TURP.
• New treatments are greatly needed. Let Andy know and support research.
• BCGOncology.com for slides, handout, questions.
Thanks

For Your Attention!

Extra credit slides follow
PLND and MVAC Improve Survival
Herr HW: JCO, 2004 172:1286

5 yr survival with MVAC plus PLND 52% vs 34% with inadequate or no PLND
Improved Mitomycin C Chemotherapy

• 230 randomized Ta, T1 pts.

• *Standard* MMC, 20mg/20cc weekly x6 vs. *Optimized* MMC: 40mg/20cc, NPO overnight, ultrasound confirmed empty bladder, and alkalinization with 1.3gm NaHCO3

• 5 yr recurrence free: *Standard* 24.6% versus 41% with *Optimized* MMC; time to recurrence increased from 11.8 to 29.1 months (P<0.005)
Perioperative Chemotherapy

Forest Plot of Recurrence

* Thiotepa study included dilute, ineffective preparation
Meta-Analysis: Immediate Postoperative Intravesical Chemotherapy

• 1476 patients in 7 randomized clinical trials
• Tumor recurrence reduced from 48.4% to 36.7% (OR 0.61, P<0.0001)
• Effect may be less in multiple than solitary tumors: 65.2% versus 35.8% recurrence.
• Benefit is significant (& cost effective) even in solitary, low-grade tumors.

Sylvester RJ. J Urol. 2004;171:2186-90
### Muscle Invasive Optimal Therapy

**Current Survival with Cystectomy**

<table>
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<th>Author</th>
<th>%T0</th>
<th>%Mort</th>
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<tr>
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<td>10</td>
<td>-</td>
<td>72</td>
<td>48</td>
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<tr>
<td>Studer</td>
<td>-</td>
<td>4.5%</td>
<td>59</td>
<td>29</td>
<td>25</td>
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<tr>
<td>Grossman</td>
<td>15</td>
<td>0.6%</td>
<td>74</td>
<td>52</td>
<td>36</td>
</tr>
<tr>
<td><strong>Total: 3,220</strong></td>
<td>12%</td>
<td>2.2%</td>
<td><strong>67%</strong></td>
<td><strong>35%</strong></td>
<td><strong>27%</strong></td>
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Herr HW: J Urol. 2007, 177:437
# Understaging of High-Risk T1 Bladder Cancer

<table>
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<tr>
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<td>Amling (1994)</td>
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<tr>
<td>Soloway (1994)</td>
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<tr>
<td>Freeman (1995)</td>
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<tr>
<td>Ghoneim (1997)</td>
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<td>Herr (1999)</td>
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<td>Dutta (2001)</td>
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**Overall Average:** 43%
Maier and Baumgartner: J Urol. 141:529, 1989

- 56 pts post TURBT: 28 with 20mg MMC and 28 with MMC plus 200,000 u hyaluronidase
- Schedule: q 2wks x 6 months, then q 4 wks x2yrs
- No increase observed in toxicity and no serum absorption
- 21 mo follow: 9/28 MMC recurrence (32%) verus 2/28 (7%) MMC + hyaluronidase (P<0.05)