Issues in the Management of High Risk Superficial Bladder Cancer

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Carcinoma in situ

pTa (papillary, high grade, non-invasive)

*BUT* 2004 WHO: PUNLMP, PUC-LG, PUC-HC
**SCOPE OF PROBLEM**

- 25-30% of superficial UC (~20% overall)
  - high grade T1/Ta, 50% associated CIS
- Heterogeneous behavior – some prognostic factors
- **RISK OVERTREATMENT** WITH UNNECESSARY LOSS OF BLADDER vs **UNDERTREATMENT** AND FATAL METASTASES

**OBJECTIVE OF TREATMENT**

- TO PREVENT **PROGRESSION** – TO MUSCLE INVASION +/or METASTASES
  - UP TO 50% PROGRESS
  - PROGNOSTIC FACTORS ± CIS, GRADE 3
- TO PREVENT **RECURRENTNESS**
International Consensus 2004
T1 Committee Recommendations

Michael Jewett, Chair, Toronto
Maurizio Brausi, Modena
Don Lamm, Arizona
Alan Nieder, New York
Michael O'Donnell, Iowa
Kyouichi Tomita, Tokyo
Henry Woo, Sydney

T1 Management Algorithm

Urology Dec 2005
2004 International Consensus Conference on Bladder Cancer: T1 Report
CYSTECTOMY

IVe THERAPY

FAILURE O’DONNELL

RECURRENCE/ PERSISTANCE

COMPLETE RESPONSE

2nd LINE IVe THERAPY

FOLLOWUP

British Columbia October 2006

BLADDER CANCER DIAGNOSIS

Not so GOLD Standard CYSTOSCOPY

British Columbia October 2006
HEXVIX FLUORESCENCE CYSTOSCOPY IN DETECTION CIS
Courtesy of Bart Grossman, MDCC

HEXVIX FLUORESCENCE CYSTOSCOPY IN DETECTION Ta
Courtesy of Bart Grossman, MDCC
Technique of Resection for T1 Bladder Tumours

• An initial endoscopic evaluation of patients with documented or suspected bladder cancer should be performed (Grade C)
• A standardized diagram should be used to document individual tumors and biopsy sites and BP (Grade C)
• Resection should include muscle in the specimen for adequate staging (Grade B)
Technique of Resection for Bladder Tumours

• The use of continuous flow resectoscopes should be further evaluated and may provide advantages (Grade C)
• The use of video endoscopy should be further evaluated and may provide advantages (Grade C)
• All visible tumor should be resected (Grade B)
COLD CUP BIOPSY
PITFALLS IN STAGING
SUPERFICIAL DISEASE

• Surgical Pitfalls
  – Endoscopic Morphology
  – Correct Technique
  – Use of Biopsies- Directed, Random
  – Role re-resection
  – Depth resection

VARIABILITY IN RECURRENCE RATE

• VARIED WITH INITIAL NUMBER OF TUMOURS

• VARIED WITH CENTRE UP TO 20%

Brausi et al EORTC Eur Urol 2002
Role of Random and Directed Biopsy for T1

- Multiple random biopsies of normal-looking urothelium should *not* be taken in patients who undergo TUR for low risk superficial bladder cancer (primary single or recurrent single tumors) (Grade B)
- Multiple random biopsies of normal looking urothelium are *always* indicated in high risk tumors (T1G3, multiple tumors, recurrent multiple, CIS) (Grade B)
- The role of multiple random biopsies of normal looking urothelium in intermediate risk tumors remains controversial (Grade B)

ROLE FOR ADJUVANT Rx

- IMMEDIATE POST-OP
- BCG vs CHEMOTHERAPY
- ROLE FOR MAINTENANCE BCG
- BETTER PREDICTION OF RESPONSE
- BCG FAILURE
Role of Immediate Adjuvant Intravesical Therapy for T1

A single dose of chemotherapy should be given at the time of TURBT (ideally within 6 hours but no more than 24 hours) whether or not additional therapy is planned *(Grade A)*

PITFALLS IN STAGING Ta-1G3 DISEASE

- Surgical Pitfalls
- Radiological Pitfalls – risk of overstaging
- Pathology Pitfalls - accuracy
What are the important prognostic factors for T1?

- Clinical and pathological features provide useful prognostic factors for the management of T1 bladder cancer (grade, early recurrence, CIS, size, number, response to IVe Rx) (Grade B)
- A number of biological molecular markers, e.g., P53, have been described, have limited availability, and are not yet established as clinically applicable prognostic factors (Grade C)
PROGNOSTIC FACTORS

- PRESENCE OF CIS, MULTIPLE TUMORS, BLADDER SYMPTOMS, INCOMPLETE RESECTION, RECURRENCE AT 3 MO.

- UROLOGISTS CAN MAKE A REAL IMPACT BY RECOGNIZING PATIENTS AT RISK

PROGRESSION RATES: T1G3

<table>
<thead>
<tr>
<th>SERIES</th>
<th>N</th>
<th>F/U TIME (yrs)</th>
<th>PROGRESSION RATE</th>
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<tbody>
<tr>
<td>Mulders ’94</td>
<td>121</td>
<td>4</td>
<td>43%</td>
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<tr>
<td>Takashi ’91</td>
<td>23</td>
<td>4.3</td>
<td>23%</td>
</tr>
<tr>
<td>Jaske ’87</td>
<td>31</td>
<td>8.8</td>
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<tr>
<td>England ‘81</td>
<td>28</td>
<td>9</td>
<td>39%</td>
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</table>
Upper tract and prostatic/urethral involvement with T1

- Periodic lifelong observation of the upper urinary tract and prostate should be performed in all patients with CIS, high-grade (G3) superficial bladder cancer, or after intravesical chemotherapy failure (Grade B)

- Examination of the upper urinary tract and prostate is recommended in follow-up of all patients with superficial bladder cancer with persistent positive urine cytology (Grade B)
• Upper tract and prostatic/urethral involvement with T1
  • Radical therapy at early stage for patients with relapse in the upper urinary tract or prostate may be curative (Grade C)

• Substaging of T1 Pathology
  • Pathologists are not agreed on the validity or utility of substaging of T1 patients into T1a and T1b (Grade B)
  • There are reports that T1b tumors may be more aggressive with an increased risk of progression (Grade C)
ROLE OF RE-RESECTION

Ex: 2/19
Sc: 1/1
M: 3/6
Mag: 1.0x

W: 256 L: 127
Role of second TURBT for high grade Ta or T1 TCC

- A second TURBT should be performed in all patients with a high grade Ta lesion or any T1 lesion (Grade B)
- The suggested optimal timing of repeat TURBT is within one to four weeks after the first resection (Grade D)
Indications for initial cystectomy versus conservative strategies with bladder sparing for T1 bladder cancer

- Cystectomy and intravesical BCG therapy are both acceptable primary therapies for high grade T1 disease and both options should be discussed (Grade C)

- Initial bladder conservation for T1 disease with intravesical therapy should not be initiated without excluding muscle invasion (Grade B)
Indications for initial cystectomy versus conservative strategies with bladder sparing for T1 bladder cancer

- Cystectomy and intravesical BCG therapy are both acceptable primary therapies for high grade T1 disease and both options should be discussed (Grade C)

- Initial bladder conservation for T1 disease with intravesical therapy should not be initiated without excluding muscle invasion (Grade B)
# BCG FOR T1G3 CANCERS

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>No. Pts.</th>
<th>Recurrence (%)</th>
<th>Progression (%)</th>
<th>Months Follow-up</th>
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<td>24</td>
<td>25</td>
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<td>1992</td>
<td>30</td>
<td>43</td>
<td>7</td>
<td>39</td>
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<tr>
<td>Meng</td>
<td>1995</td>
<td>49</td>
<td>-</td>
<td>16</td>
<td>60</td>
</tr>
<tr>
<td>Pansadoro</td>
<td>1997</td>
<td>50</td>
<td>28</td>
<td>12</td>
<td>42</td>
</tr>
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</table>
MAINTENANCE BCG

Recurrence-Free Survival

0% 20% 40% 60% 80% 100%
0 24 48 72 96 120 140

Maintenance (n=192)
No Maintenance (n=192)

P<0.0001

BCG:MAINTENANCE

Improved therapy

• Maintenance regimen
  - 120 mg X 6 weeks
  - 120 mg X 3 weeks at 3 and 6 months
    and every 6 months for 3 years
• High drop off rate due to toxicity
• Potential efficacy of lower dose BCG
BCG: IMPACT ON PROGRESSION

• META-ANALYSIS OF TRIALS BCG vs OTHER Ive Rx PATIENTS
• SIGNIFICANT REDUCTION IN PROGRESSION

Sylvester RJ, van der Meiijden, Lamm, DL et al J Urol 2002

Initial Bladder Sparing Strategies

• Primary intravesical therapy should be induction BCG immunotherapy with 6 weekly instillations beginning no sooner than 2 weeks after tumor resection (Grade A)
• Cystoscopy with urinary cytology and possible biopsy should be done at 3 months to confirm the absence of recurrence or progression (Grade B)
• Maintenance therapy utilizing the SWOG regimen should be used subsequently used up to 3 weekly instillations at 3, 6 and every 6 months for 3 years (Grade B)
**IMPACT OF BCG**

Herr et al Semin Urol

- Reduces recurrence by 50%
- Risk of invasion @ 5 years 15%
- Risk of invasion @ 10 years 50% (best that can be achieved with surgical management)

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**Classification of BCG Failure for Bladder Cancer**

- BCG refractory: non-improving or worsening disease despite BCG
- **BCG resistant**: disease improves then resolves with further BCG
- BCG relapsing: disease resolves after BCG then returns
- BCG intolerant: recurrent disease in setting of inadequate BCG treatment from drug toxicity
Treatment Options after BCG Failure for Stage T1 Bladder Cancer

- Patients failing induction BCG therapy who recur with high grade disease should be offered cystectomy (Grade C)
- For patients failing initial induction BCG therapy who are unfit, refuse cystectomy or have low/intermediate grade disease, an additional course of a BCG containing intravesical therapy is the preferred option (Grade C)
- Cystectomy is indicated if salvage therapy fails and it should be performed in a timely manner (Grade C)

BCG: COMBINATION WITH IFN-α

For BCG Failure

- REDUCED 1/3-1/10 DOSE BCG + INTERFERON 50x10⁶ units
  - 55 % CR @ 12 MOS
  - DURABLE
- SUPERIOR TO EXISTING, e.g.

O’Donnell, MA et al J Urol 2001
**BCG: COMBINATION WITH IFN-α**

For BCG Failure

- REDUCED DOSE BCG + INTERFERON
  - 45 % CR @ 24 MOS
  - DURABLE
- MAY BECOME 1st LINE

O’Donnell, MA et al J Urol 2004

Joudi, FN et al Urol Oncol 2006 – final report

**Synergy between BCG and IFN-α**
GROUP I
No prior BCG

GROUP II
Prior BCG, Non-intolerant

GROUP III
Prior BCG, Intolerant

INDUCTION
6 weeks of full strength BCG + IFN-α 50 μU; reduce to 1/3 BCG for symptoms if needed

6 weeks of 1/3 strength BCG + IFN-α 50 μU; reduce to 1/9 BCG for symptoms if needed

6 weeks of 1/10 strength BCG + IFN-α 100 μU; reduce to 1/90 BCG for symptoms if needed

CANCER ASSESSMENT
Cysto + cytology + biopsy + 6 weeks after last treatment

MAINTENANCE CYCLES AT 3, 9, 15 MONTHS AFTER LAST INDUCTION
1/3 BCG + IFN-α 50 μU x 1
1/10 BCG + IFN-α 50 μU x 2 (weekly treatments)

1/10 BCG + IFN-α 100 μU x 3 (weekly treatments)

CANCER ASSESSMENT
Cysto + cytology every 3 months for 2 years, then every 6 months

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O’Donnell, MA et al J Urol 2004
EXPERIENCE WITH COMBINATION BCG AND INTERFERON

- 12 patients with superficial transitional cell carcinoma (TCC) of the bladder, refractory to BCG, received combination low dose BCG and Interferon alpha therapy according to the O’Donnell protocol
- Retrospective study using patient charts
- Written consent was obtained for the use of patient files to attain the required data

Induction- 6 weekly instillations of 1/3 dose BCG with 50 million units of Interferon alpha 2b

Maintenance- 3 weekly instillations of combination therapy with 1/3 dose BCG with 50 million units interferon alpha 2b for the first week and 1/10 dose BCG with 50 million units of interferon alpha 2b for the second and third week at 3, 5, 11 and 17 months from induction

Further dose reductions were permitted for intolerable BCG and Interferon alpha toxicity
EXPERIENCE WITH COMBINATION BCG AND INTERFERON

Risk factors in BCG refractory patients

<table>
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<tr>
<th>Risk Factor</th>
<th>No. (%)</th>
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<tbody>
<tr>
<td>BCG refractory with recurrence less than 6 months</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Aggressive histology (CIS, T1, G3)</td>
<td>9 (69)</td>
</tr>
<tr>
<td>Greater or equal to 2 recurrences</td>
<td>10 (77)</td>
</tr>
<tr>
<td>Disease greater than 4 years</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Two or more BCG failures</td>
<td>3 (23)</td>
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</table>

• 75% response rate at 3 month follow-up
• 50% response rate at 12 month follow-up
• Of those that failed combination therapy, 50% had recurrent disease at 3 month follow up
• No progression of disease to muscle invasion or metastases
EXPERIENCE WITH COMBINATION BCG AND INTERFERON

No apparent difference in toxicity with low dose BCG and Interferon alpha combination therapy compared to that of BCG alone

- Consistent with adverse event rate in O'Donnell trial – 5%
- Dose reduction 4% for local and systemic toxicity
- Drop out 6.7% and not clearly related to AE’s/toxicity
- Intolerance about 9%

TOXICITY WITH COMBINATION BCG AND INTERFERON

O'Donnell, MA et al J Urol 2004
**EXPERIENCE WITH COMBINATION BCG AND INTERFERON**

www.projectsinknowledge.com

**FOLLOWUP**

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<tr>
<th>YEAR</th>
<th>MONTH 3</th>
<th>MONTH 6</th>
<th>MONTH 9</th>
<th>MONTH 12</th>
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DISEASE SPECIFIC SURVIVAL w/ CYSTECTOMY: T1 CANCER

<table>
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<tr>
<th>Author</th>
<th>No. Pts.</th>
<th>5 years</th>
<th>10 years</th>
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<tr>
<td>Siref ‘88</td>
<td>32</td>
<td>55%</td>
<td>30%</td>
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<tr>
<td>Malkowicz ‘90</td>
<td>55</td>
<td>78%</td>
<td></td>
</tr>
<tr>
<td>Pagano ‘91</td>
<td>54</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Amling ‘94</td>
<td>91</td>
<td>76%</td>
<td>62%</td>
</tr>
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</table>
• BEST RESULTS AT THE TIME
• PERCEIVED TO BE EXPERT TECHNOLOGY

University of Toronto UroOncology Fellowship

Training program in clinical and research UroOncology

Dr. Antonio Finelli
Dr. Neil Fleshner
Dr. Michael Jewett
Dr. Laurie Klotz
Dr. Rob Nam
Dr. Sharon Sharir
Dr. John Trachtenberg
Dr. Alex Zlotta

Rotations in Medical and Radiation (incl Brachy) Oncology

SUO Approved

One clinical year and up to two research years

Remuneration includes:
Salary
Travel expenses
Tuition if necessary at U of T
Graduate Program encouraged