BLADDER CANCER: EVOLVING PERSPECTIVES IN ORGAN PRESERVATION AND PELVIC TUMOR CONTROL

OTTAWA REGIONAL CANCER CENTRE

CONTINENT DIVERSION INCREASING # - NODES
SYSTEMIC MICROMETASTASES NEOADJ / ADJUVANT CHEMO

1990
BLADDER CANCER
ORGAN PRESERVATION
ORGAN PRESERVATION

- PATIENT SELECTION
- PATHOLOGY
- TURBT
- URETERIC PATENCY
- BLADDER FUNCTION

- STRATEGY
- BRACHYTHERAPY
- HIGH LET
- ALTERED FRACTIONATION
- CHEMORADIOThERAPY

CHEMORADIOThERAPY

- SINGLE AGENT
  - 5FU
  - CISPLATIN

- COMBINATION
  - CMV-RT MGH
  - RTOG
  - 5FU-PLATIN PARIS
### BLADDER PRESERVATION

<table>
<thead>
<tr>
<th></th>
<th>RT-CMV</th>
<th>RT-PLATIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT ALONE</td>
<td>30-35%</td>
<td>50% COPPIN/NCI SAUER</td>
</tr>
<tr>
<td>LONDON EDINBURGH AUSTRIA</td>
<td>55% HARVARD RTOG</td>
<td>50% COPPIN/NCI SAUER</td>
</tr>
</tbody>
</table>

### ROUTE

<table>
<thead>
<tr>
<th>INTRAVENOUS</th>
<th>INTRAARTERIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEAK EXPOSURE AUC TUMOR CONCENTRATION IV vs IA</td>
<td></td>
</tr>
</tbody>
</table>
INTRAARTERIAL CISPLATIN – CONCURRENT RADIATION
OTTAWA REGIONAL CANCER CENTRE

OBJECTIVES:

INCREASED RATE OF COMFORTABLE BLADDER PRESERVATION

NON COMPROMISE OF SURVIVAL VIS A VIS CYSTECTOMY

ELIGIBILITY CRITERIA

- STATE T2 – T4B
- NON SQUAMOUS HISTOLOGY
- NO HEMATOGENOUS METASTASES (CT ABD/CHEST X-RAY/BONE SCAN)
- NO ENLARGED NODES ABOVE ILIAC BIFURCATION
- NO CONTRAINDICATIONS TO FEMORAL ACCESS
- ADEQUATE RENAL/MARROW FUNCTION
TREATMENT PROTOCOL

- DAY 1  #1 I.A. PLATIN
- DAY 10 RT COMMENCES
  60 GY/30/6WEEKS
- DAY 21  #2 I.A. PLATIN
- DAY 42  #3 I.A. PLATIN
- 6-10 WEEKS
  RESPONSE EVALUATION: CYSTOSCOPY
  BIOPSY
  CYTOLOGY

CHEMOTHERAPY

- INPATIENT – OUTPATIENT
- SALINE HYDRATION
- MANNITOL DIURESIS
- DECADRON – ZOFTRAN EMESIS PROPHYLAXIS
- BILATERAL TRANSFEMORAL INTERNAL
- ILIAC ARTERY CATHETER PLACEMENT
- CISPLATIN 90-120 MG/M² HALVED AND INFUSED
  INTO EACH ARTERY OVER 1 HOUR
- PRESSURE AT CATHETER SITES x 4 HOURS
RADIOTHERAPY

SIMULATION: SUPINE  
PLANNING CYSTO-RECTOGRAM

- VOLUME: PELVIC NODES/BLADDER 40 Gy/20  
- BEAM ARRANGEMENT:  
  4 FIELD BOX  
  L5-S1  
  OBTURATOR FORAMINA –ISCHIAL TUBEROSITIES  
  S2/S3  
  ANT 3CM TO BLADDER. BOOST: 4 FIELD, WHOLE BLADDER 20 Gy/10

PATIENT CHARACTERISTICS

- 1986 – 2003  
- 200 PATIENTS  
- 165 MALES/35 FEMALES  
- AGE RANGE 30 – 88 YEARS  
- MEDIAN: 69 YEARS
PATHOLOGY

TCC 175                      GRADE 1      4
ADENOCA  9                    2          46
MIXED    15                    3         142
NOS      1                     NOS  8

STAGE

• TA   6
• T1   15
• T2   46
• T3A  47  NODE +  14
• T3B  54  - 186
• T4A  15
• T4B  15
• TX   2
UPPER RENAL TRACTS

- NORMAL 137
- UNIL HYDRO 54
- BILAT HYDRO 9 = 32%

SURGICAL DEBULKING

TURBT
- YES 172 = 86%
- NO 28

GROSS RESIDUAL
- YES 157 = 78.5%
- NO 25
- UNCERTAIN 18
TREATMENT DELIVERY/COMPLIANCE

- 196/200 COMPLETED RADIOTHERAPY
- 186/200 COMPLETED CHEMO AS PLANNED
- 7/200 I.A. ←→ I.V. CHEMO

FOLLOW UP

- 2 – 180 MONTHS    MEDIAN 30
RESULTS

COMPLETE RESPONSE

BLADDER STATUS

SURVIVAL

PATTERNS OF FAILURE

TOXICITY

LOCAL RESPONSE

- 185 EVALUABLE/15 NON EVALUABLE
### TABLE 1
**COMPLETE LOCAL RESPONSE**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>ALL PATIENTS</th>
<th>EVALUABLE PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ta=6</td>
<td>5/6</td>
<td>5/6</td>
</tr>
<tr>
<td>T1=15</td>
<td>13/15=86.6%</td>
<td>13/15=86.6%</td>
</tr>
<tr>
<td>T2=46</td>
<td>41/46=89%</td>
<td>41/46=89%</td>
</tr>
<tr>
<td>T3a=47</td>
<td>42/47=89%</td>
<td>42/47=89%</td>
</tr>
<tr>
<td>T3b=54</td>
<td>41/54=76%</td>
<td>41/54=76%</td>
</tr>
<tr>
<td>T4a=15</td>
<td>13/15=86.7%</td>
<td>13/15=86.7%</td>
</tr>
<tr>
<td>T4b=15</td>
<td>9/15=60%</td>
<td>9/15=60%</td>
</tr>
<tr>
<td>Tx=2</td>
<td>2/2</td>
<td>2/2</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>166/200=83%</strong></td>
<td><strong>166/185=90%</strong></td>
</tr>
</tbody>
</table>

**EXCLUDING T4b**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>ALL PATIENTS</th>
<th>EVALUABLE PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ta=6</td>
<td>5/6</td>
<td>5/6</td>
</tr>
<tr>
<td>T1=15</td>
<td>13/15=86.6%</td>
<td>13/15=86.6%</td>
</tr>
<tr>
<td>T2=46</td>
<td>41/46=89%</td>
<td>41/46=89%</td>
</tr>
<tr>
<td>T3a=47</td>
<td>42/47=89%</td>
<td>42/47=89%</td>
</tr>
<tr>
<td>T3b=54</td>
<td>41/54=76%</td>
<td>41/54=76%</td>
</tr>
<tr>
<td>T4a=15</td>
<td>13/15=86.7%</td>
<td>13/15=86.7%</td>
</tr>
<tr>
<td>T4b=15</td>
<td>9/15=60%</td>
<td>9/15=60%</td>
</tr>
<tr>
<td>Tx=2</td>
<td>2/2</td>
<td>2/2</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>157/185=84%</strong></td>
<td><strong>157/173=91%</strong></td>
</tr>
</tbody>
</table>

### Table 3
**BLADDER PRESERVATION (TUMOUR FREE + BCG)**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>ALL PATIENTS</th>
<th>UNKNOWN</th>
<th>EVALUABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ta</td>
<td>5/6</td>
<td>0</td>
<td>5/6</td>
</tr>
<tr>
<td>T1</td>
<td>11/15=73%</td>
<td>0</td>
<td>11/15=73%</td>
</tr>
<tr>
<td>T2</td>
<td>35/46=76%</td>
<td>5</td>
<td>35/46=76%</td>
</tr>
<tr>
<td>T3a</td>
<td>31/47=66%</td>
<td>4</td>
<td>31/47=66%</td>
</tr>
<tr>
<td>T3b</td>
<td>33/54=61%</td>
<td>7</td>
<td>33/54=61%</td>
</tr>
<tr>
<td>T4a</td>
<td>12/13=92.3%</td>
<td>2</td>
<td>12/13=92.3%</td>
</tr>
<tr>
<td>T4b</td>
<td>6/15=40%</td>
<td>4</td>
<td>6/15=40%</td>
</tr>
<tr>
<td>Tx</td>
<td>1/2</td>
<td>0</td>
<td>1/2</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>134/200=67%</strong></td>
<td><strong>22</strong></td>
<td><strong>134/178=75%</strong></td>
</tr>
</tbody>
</table>

**Excluding T4b As per tester**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>ALL PATIENTS</th>
<th>UNKNOWN</th>
<th>EVALUABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ta</td>
<td>5/6</td>
<td>0</td>
<td>5/6</td>
</tr>
<tr>
<td>T1</td>
<td>11/15=73%</td>
<td>0</td>
<td>11/15=73%</td>
</tr>
<tr>
<td>T2</td>
<td>35/46=76%</td>
<td>5</td>
<td>35/46=76%</td>
</tr>
<tr>
<td>T3a</td>
<td>31/47=66%</td>
<td>4</td>
<td>31/47=66%</td>
</tr>
<tr>
<td>T3b</td>
<td>33/54=61%</td>
<td>7</td>
<td>33/54=61%</td>
</tr>
<tr>
<td>T4b</td>
<td>12/13=92.3%</td>
<td>2</td>
<td>12/13=92.3%</td>
</tr>
<tr>
<td>T4b</td>
<td>6/15=40%</td>
<td>4</td>
<td>6/15=40%</td>
</tr>
<tr>
<td>Tx</td>
<td>1/2</td>
<td>0</td>
<td>1/2</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>128/185=69.2%</strong></td>
<td><strong>22</strong></td>
<td><strong>128/167=76.6%</strong></td>
</tr>
</tbody>
</table>
### TABLE 2

<table>
<thead>
<tr>
<th>BLADDER STATUS</th>
<th>NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non evaluable</td>
<td>22</td>
</tr>
<tr>
<td>Tumour free</td>
<td>126</td>
</tr>
<tr>
<td>Tumour free with BCG</td>
<td>8</td>
</tr>
<tr>
<td>Salvage cyst. for invasive</td>
<td>22</td>
</tr>
<tr>
<td>Salvage cyst. superficial</td>
<td>8</td>
</tr>
<tr>
<td>Unsallaged invasive</td>
<td>15</td>
</tr>
<tr>
<td>Unsallaged superficial</td>
<td>0</td>
</tr>
</tbody>
</table>

### TABLE 5

<table>
<thead>
<tr>
<th>STAGE</th>
<th>UNK.</th>
<th>ANED</th>
<th>DNEP</th>
<th>ALIVE</th>
<th>DEAD</th>
<th>A/D LOC ONLY</th>
<th>A/D DIST ONLY</th>
<th>A/D LOC + DIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a=6</td>
<td>6</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0/1</td>
<td>0</td>
<td>0/0</td>
</tr>
<tr>
<td>T1b=15</td>
<td>1</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3/3</td>
<td>0/2</td>
<td>0/1</td>
</tr>
<tr>
<td>T2=46</td>
<td>4</td>
<td>26</td>
<td>5</td>
<td>2</td>
<td>9</td>
<td>9/9</td>
<td>1/0</td>
<td>1/0</td>
</tr>
<tr>
<td>T3a=47</td>
<td>2</td>
<td>19</td>
<td>13</td>
<td>1</td>
<td>12</td>
<td>12/12</td>
<td>0/6</td>
<td>0/6</td>
</tr>
<tr>
<td>T3b=54</td>
<td>6</td>
<td>25</td>
<td>11</td>
<td>1</td>
<td>11</td>
<td>11/11</td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td>T4a=15</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>5</td>
<td>5/5</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>T4b=15</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>11</td>
<td>11/11</td>
<td>1/3</td>
<td>1/3</td>
</tr>
<tr>
<td>Ta=2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0/0</td>
<td>0</td>
<td>0/0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>15</td>
<td>93</td>
<td>35</td>
<td>5</td>
<td>52</td>
<td>52/52</td>
<td>3/7</td>
<td>1/31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1/14</td>
</tr>
</tbody>
</table>
CAUSE SPECIFIC SURVIVAL ALL CASES

Survival Time

Cumulative Proportion Surviving

0.0
0.2
0.4
0.6
0.8
1.0

0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192

T1

T2

CAUSE SPECIFIC SURVIVAL STAGES T1:T2

Time

Cumulative Proportion Surviving

0.0
0.2
0.4
0.6
0.8
1.0

0 12 24 36 48 60 72 84 96 108

T1

T2
ACUTE TOXICITY

2 DEATHS
1 VASCULAR REPAIR FEMORAL PUNCTURE
1 PLASTIC REPAIR GLUTEAL SOFT TISSUE NECROSIS
1 MALLORY-WEISS/M.I.
1 PULMONARY EMBOLUS
35% PATIENTS MEDS FOR G.I. IRRITATION
30% PATIENTS MEDS FOR BLADDER IRRITATION

CHRONIC TOXICITY

1 HEMORRHAGIC CYSTITIS
1 VESICOENTERIC FISTULA
2 RTOG GRADE 1 BLADDER
2 RTOG GRADE 2 BOWEL
1 PELVIC GIRDLE OSTEITIS
SACRAL NEUROPATHY
# NEUROPATHY

<table>
<thead>
<tr>
<th>Grade</th>
<th>Percentage</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>NONE</td>
<td>64%</td>
<td>129</td>
</tr>
<tr>
<td>MILD</td>
<td>20.5%</td>
<td>41</td>
</tr>
<tr>
<td>MODERATE</td>
<td>11.5%</td>
<td>23</td>
</tr>
<tr>
<td>SEVERE</td>
<td>2%</td>
<td>4</td>
</tr>
</tbody>
</table>

NERVE CONDUCTION/FERRET GANGLIA/DOSE

# SUMMARY

WELL TOLERATED OUTPATIENT TREATMENT

COMFORTABLE/FUNCTIONAL BLADDER PRESERVATION

SAFE WITHOUT WORSENING SURVIVAL

CORROBORATES HYPOTHESIS OF 15-25% GAIN IN RADIOSENSITIZATION I.A. VS IV PLATIN
CONTINENT DIVERSION SYSTEMIC MICROMETASTASES

2005
BLADDER CANCER
ORGAN PRESERVATION

LONG TERM ORTHOTOPIC BLADDER FUNCTION BERNE 2002 STUDER

- 83/176 MEN

- DAYTIME INCONTINENCE 2/5/10 YRS
  5 / 5 / 10%

- NIGHT INCONTINENCE 2/5/10 YRS
  20% / 30% / 45%
QUALITY OF LIFE STANFORD-USC 1999 HART-SKINNER

- ILEAL CONDUIT
- KOCK TO SKIN
- KOCK TO URETHRA

- EMOTIONAL/BODY IMAGE/SOCIAL LIMITATION/DAILY ACTIVITIES
- ***** NO DIFFERENCE*****

PELVIC CONTROL MSKCC

- J. UROLOGY 2003 169:177-181
- 214 CYST-ORTHOTOPIC BLADDER
- ****INITIAL RELAPSE PATTERN****
- LOCAL ONLY : LOCAL+DIST 11%:8% OF ALL 214 PATIENTS = 19%
- LOCAL ONLY : LOCAL+DIST 22%:13% OF 103 PT3A/T3B/T4A PATIENTS
- = 35% INITIAL PELVIC FAIL.
SWOG-INTERGROUP NEOADJUVANT MVAC TRIAL HERR JCO JULY/04

- 268 CYSTECTOMY PATIENTS
- 191 ILEAL CONDUIT/ 77 CONTINENT DIVERSION
- BIOPSY CONFIRMED LOC.RECURRANCE
- CRUDE NON ACTUARIAL RATE=
  pT3-T4  27/84 **** 32%****
  UNAFFECTED BY MVAC RX OR NOT

Table 4. Multivariate Logistic Regression Model for Probability of a Local Recurrence

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR*</th>
<th>95% CI</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment RC v MVAC + RC</td>
<td>0.5</td>
<td>0.2 to 1.3</td>
<td>.16</td>
</tr>
<tr>
<td>pT stage 3-4 v 0-2</td>
<td>3.8</td>
<td>1.2 to 12.2</td>
<td>.02</td>
</tr>
<tr>
<td>Node status positive v negative</td>
<td>1.7</td>
<td>0.5 to 5.2</td>
<td>.37</td>
</tr>
<tr>
<td>Margins positive v negative</td>
<td>11.2</td>
<td>3.3 to 37.8</td>
<td>.0001</td>
</tr>
<tr>
<td>Nodes removed &lt; 10 v ≥ 10</td>
<td>5.1</td>
<td>1.8 to 14.7</td>
<td>.002</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odd ratio; RC, radical cystectomy; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin.
*Each OR and P value is adjusted for all other covariates in the model. **P values are two sided and based on the Wald χ² test.
CONTINENT DIVERSION

SYSTEMIC MICROMETASTASES

2005

BLADDER CANCER

ORGAN PRESERVATION
SYSTEMIC MICROMETASTASES

- ADJUVANT
- TO DATE INCREASED DFS WITH NO INCREASE IN OVERALL SURV.
- ?SUBGROUP/P53/PLOIDY CURRENT TRIALS
- NEOADJUVANT
- METAANALYSES SHOW PAN-T STAGE SURVIVAL GAIN OF ***5%***

ISSUES

- EXTRA VESICAL PELVIC CONTROL FOR T3/T4 IS HIGHER WITH CHEMO-RT ORGAN PRESERVATION STRATEGY THAN CYSTECTOMY +/- CHEMO !!!
- IA PLATIN-RT DOES NOT INCREASE SURVIVAL …SYSTEMIC METS
- NEOADJUVANT CHEMO MODEST 5% INCREASE IN SURVIVAL
- INTEGRATING NEOADJUVANT CHEMO AND CHEMO-RT UNSAFE WITH STANDARD RADIOTHERAPY TECHNIQUES
Figure 1. Routine followup CT of 46-year-old asymptomatic patient 4 months after radical cystoprostatectomy. A, 4.5 x 3.0 cm. right pararectal mass (arrow) is visible. B, 4 months after treatment with 3 courses of vinblastine, ifosfamide and gallium, there was stable resolution of disease (arrow).


OTTAWA 05

- USE DOSE SCULPTING AND IMAGE GUIDANCE OF TOMORADIOThERAPY
- INTEGRATE NEOADJ.CHEMO WITH IA PLATIN-RT
- INTEGRATE NEOADJ.CHEMO-PREOP RT WITH CYSTECTOMY
- PHASE 1 STARTED DOSIM/TOXICITY(GEM-CIS)
CONCLUSIONS

- BLADDER CONSERVATION IS SAFELY ACHIEVABLE FOR THOSE WHO WISH IT
- FAILURE TO REDUCE THE UNDERDOCUMENTED PELVIC RECURRENCE RATE POSTCYSTECTOMY IN T3/4 DISEASE NEEDS TO BE ADDRESSED
- THE (TO DATE) MODEST SURVIVAL GAIN WITH CHEMO AWAITS BETTER PELVIC CONTROL AND BETTER AGENTS