CONSERVATIVE MANAGEMENT OF BLADDER CANCER

Madhur K Garg, MD
2007 ESTIMATED US CANCER CASES*

Men 766,860

Women 678,060

- Prostate 29%
- Lung & bronchus 15%
- Colon & rectum 10%
- Urinary bladder 7%
- Non-Hodgkin lymphoma 4%
- Melanoma of skin 4%
- Kidney 4%
- Leukemia 3%
- Oral cavity 3%
- Pancreas 2%
- All Other Sites 19%

Women:

- 26% Breast
- 15% Lung & bronchus
- 11% Colon & rectum
- 6% Uterine corpus
- 4% Non-Hodgkin lymphoma
- 4% Melanoma of skin
- 4% Thyroid
- 3% Ovary
- 3% Kidney
- 3% Leukemia
- 21% All Other Sites

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
# 5-Year Relative Survival (%)*
## During 3 Time Periods by Cancer Site

<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>50</td>
<td>53</td>
<td>66</td>
</tr>
<tr>
<td>Breast (female)</td>
<td>75</td>
<td>79</td>
<td>89</td>
</tr>
<tr>
<td>Colon</td>
<td>51</td>
<td>59</td>
<td>65</td>
</tr>
<tr>
<td>Leukemia</td>
<td>35</td>
<td>42</td>
<td>49</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>13</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Melanoma</td>
<td>82</td>
<td>86</td>
<td>92</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>48</td>
<td>53</td>
<td>63</td>
</tr>
<tr>
<td>Ovary†</td>
<td>37</td>
<td>40</td>
<td>45</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Prostate</td>
<td>69</td>
<td>76</td>
<td>100</td>
</tr>
<tr>
<td>Rectum</td>
<td>49</td>
<td>57</td>
<td>66</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>73</td>
<td>78</td>
<td>82</td>
</tr>
</tbody>
</table>

*5-year relative survival rates based on follow up of patients through 2003.
†Recent changes in classification of ovarian cancer have affected 1996-2002 survival rates.
PATHOLOGY

- *Transitional cell carcinoma*: accounts for 92% of all bladder cancers
- *Squamous cell carcinoma*: accounts for 6% of all bladder cancers
- *Adenocarcinoma*: accounts for 1% of all bladder cancers
- *Other histologic types*: account for 1% of all bladder cancers
  - include sarcomas, pheochromocytomas, lymphomas, small cell tumors, and carcinoid tumors
TRANSITIONAL CELL CARCINOMA

- Pleomorphic
- Unequal sizes of cells
- Unequal sizes of nuclei
- High nuclear to cytoplasm ratio
- papillary (80%) vs solid (20%)
- 70% superficial, 25% invasive, 5% metastatic
DISEASE AT PRESENTATION

NATURAL HISTORY

- **Lymphatic invasion:**
  - 5% for pT1
  - 30% for pT2-3a
  - 60% for pT3b-pT4

- **Hematogenous invasion:**
  - 5–20% of all patients present with *de novo* metastases.
  - *most common distant sites:* lung, bone, and liver
MANAGEMENT BY DEPTH OF INVASION

*1. Superficial

*2. Muscle-invasive*

*3. Highly advanced, high-grade, multiple tumors, or metastatic
SUPERFICIAL BLADDER CANCER (TA, T1, TIS)

75% superficial
75% chance of recurrence

3 critical components of treatment
- Cystoscopic resection
- Intravesical BCG, thiotepa, doxorubicin, mitomycin-C
- Surveillance
# Superficial Bladder Cancer

<table>
<thead>
<tr>
<th>Stage, Grade</th>
<th>Recurrence After TURBT</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ta, G1</td>
<td>50% @ 1yr</td>
<td>2% @ 5yr</td>
</tr>
<tr>
<td></td>
<td>75% @ 2yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100% @ 5yr</td>
<td></td>
</tr>
<tr>
<td>Ta, G2-3</td>
<td>50% @ 1yr</td>
<td>20% @ 5yr</td>
</tr>
<tr>
<td></td>
<td>100% @ 3yr</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>50% @ 1yr</td>
<td>50% @ 5yr;</td>
</tr>
<tr>
<td></td>
<td>80% @ 3yr</td>
<td>80% if</td>
</tr>
<tr>
<td></td>
<td>90% @ 5yr</td>
<td>associated Tis</td>
</tr>
</tbody>
</table>

Fitzpatrick, Journal of Urology, 1986
INVASIVE BLADDER CANCER (T2-T4)
<table>
<thead>
<tr>
<th>T0</th>
<th>n (clinical)</th>
<th>n (pathological)</th>
<th>OS (%)</th>
<th>LF (%)</th>
<th>DM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>5</td>
<td>6</td>
<td>--</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>T1</td>
<td>20</td>
<td>18</td>
<td>56</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>T2</td>
<td>43</td>
<td>25</td>
<td>50</td>
<td>6</td>
<td>27</td>
</tr>
<tr>
<td>T3</td>
<td>12</td>
<td>26</td>
<td>23</td>
<td>32</td>
<td>40</td>
</tr>
<tr>
<td>T4</td>
<td>--</td>
<td>5</td>
<td>--</td>
<td>20</td>
<td>40</td>
</tr>
</tbody>
</table>

**Greven, Cancer 69: 2767-70; 1992**

- **SWOG**
  - Natale et al.
  - Cystectomy
  - 303
  - 49%

- **USC**
  - Stein et al.
  - Cystectomy
  - 633
  - 48%

- **Italy**
  - Sternberg and Parmar
  - Cystectomy
  - 303
  - 49%
SURGERY

- **TURBT**  
  *Trans Urethral Resection of Bladder Tumor:*  
  - *Ta/is/1 bladder cancer*  
  - *initial therapy in bladder conservation therapy.*  

- **Radical Cystectomy:**  
  *Muscle invasion bladder cancer, salvage after RT failure.*  

- **Technique:** En bloc resection of bladder, peritoneal covering, perivesical fat, lower ureters, bil. pelvic LNs, prostate, seminal vesicles, pelvic vas deferens, proximal urethra (men), entire urethra (all women, men with CIS / multicentric tumors / involvement of bladder neck or prostatic urethra), uterus, fallopian tubes, ovaries, anterior vaginal wall.

- **Pelvic lymphadenectomy:** common iliac, external iliac, hypogastric, obturator.
SURGERY

- **Toxicity:** impotence (unless nerve sparing), incontinence.
- **Urinary diversions:**
  - Ileal conduit
  - Continent diversion (cecoappendicostomy, ileostomy aka Kock pouch, cecoleostomy aka Indiana pouch).
- **Toxicity of pouches:** 2% mortality, 5% metabolic disturbances, 30% re-operation rate.
- **Relative contraindications for continent diversion:** increased age, intercurrent disease, poor renal function, bowel disease, urethrectomy.
NEOADJUVANT CHEMOTHERAPY

• No value of neoadjuvant chemo in OS in any of 6 RCT’s

**TABLE 57.11. PROSPECTIVE RANDOMIZED TRIALS COMPARING NEOADJUVANT CHEMOTHERAPY AND DEFINITIVE LOCAL TREATMENT ALONE**

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Standard Arm</th>
<th>Neoadjuvant Arm</th>
<th>Survival p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crawford et al (28)</td>
<td>298</td>
<td>Cystectomy</td>
<td>M-VAC/cystectomy</td>
<td>NS</td>
</tr>
<tr>
<td>Wallace et al (209)</td>
<td>296</td>
<td>Radiotherapy</td>
<td>CDDP/radiotherapy</td>
<td>NS</td>
</tr>
<tr>
<td>Martinez-Pineiro et al (107)</td>
<td>122</td>
<td>Cystectomy</td>
<td>CDDP/cystectomy</td>
<td>NS</td>
</tr>
<tr>
<td>Hall (62)</td>
<td></td>
<td>Cystectomy</td>
<td>CMV/cystectomy</td>
<td>NS</td>
</tr>
<tr>
<td>Bassi et al (2)</td>
<td>206</td>
<td>Cystectomy</td>
<td>M-VAC/cystectomy</td>
<td>NS</td>
</tr>
<tr>
<td>Mainstrom et al (103)</td>
<td>317</td>
<td>Cystectomy</td>
<td>MTX/CDDP/cystectomy</td>
<td>NS</td>
</tr>
</tbody>
</table>

M-VAC, methotrexate, vinblastin, doxorubicin, and cisplatin; CDDP, cisplatin; CMV, cisplatin, methotrexate, and vinblastin, MTX, methotrexate.

• International Trialist’s Group RCT
  • 976 pts; T2G3–T4a Nx N0/Nx M0
  • Cisplatin + mtx + vinblastine x 3 cycles then cystectomy or RT
  • 3-yr OS 55.5% for neoadjuvant chemo vs 50.0% for primary treatment alone (p=.08); improved CR w/ neoadjuvant
ADJUVANT CHEMOTHERAPY

- 4 RCT’s, all with major methodological flaws.
  - Possibly with benefit, but lack of convincing evidence.
BLADDER PRESERVATION THERAPY

- Avoid effects of radical cystectomy including urinary incontinence, erectile dysfunction, dyspareunia.
EXTERNAL BEAM RT AS PRIMARY THERAPY

• EBRT alone used for curative intent from 1950s-1980s
• Comparisons between RT and radical cystectomy difficult
  • inferior survival results or toxicities with RT alone
• CR in approximately 40-50%
• Distant metastatic disease

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Mean Age (Yrs)</th>
<th>Radiation Dose (Gy)</th>
<th>Tumor Stage</th>
<th>5 Years</th>
<th>10 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duncan &amp; Quilty (37)</td>
<td>963</td>
<td>66</td>
<td>55b</td>
<td>T1–T4</td>
<td>30</td>
<td>18</td>
</tr>
<tr>
<td>Blandy et al (8)</td>
<td>704</td>
<td>68</td>
<td>55b</td>
<td>T1–T4</td>
<td>40</td>
<td>--</td>
</tr>
<tr>
<td>Goffinet et al (55)</td>
<td>384</td>
<td>60</td>
<td>70</td>
<td>T1–T4</td>
<td>30</td>
<td>--</td>
</tr>
<tr>
<td>Goodman et al (56)</td>
<td>470</td>
<td>66</td>
<td>50b</td>
<td>T2–T3</td>
<td>38</td>
<td>22</td>
</tr>
<tr>
<td>Quilty &amp; Duncan (138)</td>
<td>333</td>
<td>67</td>
<td>55b</td>
<td>T3</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>Gospodarowicz et al (57)</td>
<td>121</td>
<td>70</td>
<td>60</td>
<td>T2–T4b</td>
<td>32</td>
<td>--</td>
</tr>
<tr>
<td>Hayter et al (69)</td>
<td>1,372</td>
<td>70</td>
<td>60</td>
<td>T2–T4</td>
<td>28</td>
<td>--</td>
</tr>
<tr>
<td>Johnson et al (82)</td>
<td>319</td>
<td>~70</td>
<td>64</td>
<td>T1–T4</td>
<td>28</td>
<td>8</td>
</tr>
<tr>
<td>Daehlin et al (31)</td>
<td>90</td>
<td>71</td>
<td>64</td>
<td>T1–T4</td>
<td>29</td>
<td>14</td>
</tr>
<tr>
<td>Fossa et al (44)</td>
<td>271</td>
<td>73</td>
<td>60</td>
<td>T2–T4</td>
<td>22</td>
<td>--</td>
</tr>
<tr>
<td>Bell et al (4)</td>
<td>120</td>
<td>70</td>
<td>50</td>
<td>T1–T4</td>
<td>50</td>
<td>--</td>
</tr>
<tr>
<td>Mooney et al (117)</td>
<td>379</td>
<td>73</td>
<td>60</td>
<td>T2–T3</td>
<td>22</td>
<td>--</td>
</tr>
<tr>
<td>Total</td>
<td>5,526</td>
<td>70</td>
<td>60</td>
<td>T1–T4</td>
<td>31</td>
<td>15</td>
</tr>
</tbody>
</table>

EBRT, external beam radiation therapy.
*In 250-cGy daily fraction.
University of Erlangen study phase I/II

- 67 pts; T1-4 N0-2 M0
- TURB → 50.4/1.8 + concurrent cisplat (25/d * 5d 1st and last week of RT)
- CR in 75% of pts (75% in T3, 25% in T4)
- Better CR/local control than historical control with TURB+EBRT only
- 18% of CR pts w/ local recurrence @ 18mos
- 3-yr OS 66% in both chemoRT and RT

MASSACHUSETTS GENERAL HOSPITAL: PHASE I-II

- n=106 enrolled from 1986-1993

- Single institution prospective non-randomized study

- Diagnosis of muscle-invading clinical stage T2 to T4aNXM0

- Induction:
  - TURBT
  - 2 cycles of MCV chemotherapy (methotrexate, cisplatin, and vinblastine)
  - 39.6 Gy pelvic irradiation with cisplatin

Journal of Clinical Oncology, 1997
SCHEMA

TURBT

106 patients

Neoadjuvant MCV* 2 cycles

99 patients

Cisplatin + 4000 cGy

97 patients

urologic evaluation

19 patients

Radical Cystectomy

13 < a T0** response
6 not able to tolerate induction therapy

76 patients

Consolidation with C + 2480 cGy

70 with a T0** response
6<T0, unsuited for surgery

* MCV = Methotrexate, Cisplatin, Vinblastine
** T0 = re-biopsy negative and cytology negative
RESULTS

- 70 patients (66%) received consolidation therapy
  - 64/70 with T0 response
  - 6 with <T0 response who could not tolerate or refused radical cystectomy

- 36 patients (34%) ultimately underwent cystectomy
  - 17 with evidence of tumor before completing induction
  - 13/19 with <T0 response to induction therapy
  - 6/70 with T0 response

- 5-year actuarial overall survival and disease-specific survival rates of all patients were 52% and 60%, respectively, and 43% surviving with bladder
  - T2: 63%
  - T3-T4: 45%
RESULTS (CONTINUED) – CONSOLIDATION THERAPY BLADDER MORBIDITY

- No patient required cystectomy for treatment-related bladder morbidity

- 8/70 patients developed symptoms that may have resulted from consolidation therapy
  - 7 developed transient hematuria
  - 1 developed mild incontinence (dribbling, without need for a pad)
RTOG 89-03

Phase III Trial of Neo-adjuvant Chemotherapy in Patients with Invasive Bladder Cancer Treated with Selective Bladder Preservation by Combined Radiation Therapy and Chemotherapy: Initial Results of Radiation Therapy Oncology Group 89-03

WU Shipley, KA Winter, DS Kaufman, WR Lee, NM Heney, WR Tester, BJ Donnelly, PM Venner, CA Perez, KJ Murray, RS Doggett, and LD True

Massachusetts General Hospital, Radiation Therapy Oncology Group Headquarters, Albert Einstein Cancer Center, Wake Forest University School of Medicine, Washington University School of Medicine, Medical College of Wisconsin, Radiation Oncology Center, University of Washington Medical School, University of Alberta

Journal of Clinical Oncology, 1998
METHODS

- n=123 with T2 to T4aNXM0 bladder cancer
- Multi-center prospective study

Arm 1, n=61
2 cycles MCV $\rightarrow$ 39.6 Gy pelvic irradiation + cisplatin for 2 courses

Arm 2, n=62
39.6 Gy pelvic irradiation + cisplatin for 2 courses
## RESULTS (CONTINUED) – ARM 1 VS. ARM 2

<table>
<thead>
<tr>
<th></th>
<th>Arm 1</th>
<th>Arm 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed protocol</td>
<td>67%</td>
<td>81%</td>
<td>74%</td>
</tr>
<tr>
<td>5-yr survival</td>
<td>48%</td>
<td>49%</td>
<td>49%</td>
</tr>
<tr>
<td>Distant mets at 5 yrs</td>
<td>33%</td>
<td>39%</td>
<td>35%</td>
</tr>
<tr>
<td>Functioning bladder at 5 yrs</td>
<td>36%</td>
<td>40%</td>
<td>38%</td>
</tr>
<tr>
<td>Treatment-related deaths</td>
<td>4/61</td>
<td>1/62</td>
<td>5/123</td>
</tr>
</tbody>
</table>

No differences are statistically significant
## RESULTS (CONTINUED) – TREATMENT-RELATED TOXICITY

<table>
<thead>
<tr>
<th></th>
<th>Arm 1 (MCV)</th>
<th>Arm 2 (no MCV)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>During neoadjuvant MCV, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>21</td>
<td>—</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td>Neutropenic fever</td>
<td>23</td>
<td>—</td>
</tr>
<tr>
<td>Infection</td>
<td>8</td>
<td>—</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>23</td>
<td>—</td>
</tr>
<tr>
<td><strong>Late morbidity, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Renal</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Neurologic</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Bladder</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Intestinal</td>
<td>8</td>
<td>5</td>
</tr>
</tbody>
</table>
International Phase III Trial Assessing Neoadjuvant Cisplatin, Methotrexate, and Vinblastine Chemotherapy for Muscle-Invasive Bladder Cancer: Long-Term Results of the BA06 30894 Trial

This article presents the long-term results of the international multicenter randomized trial that investigated the use of neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) chemotherapy in patients with muscle-invasive urothelial cancer of the bladder treated by cystectomy and/or radiotherapy. Nine hundred seventy-six patients were recruited between 1989 and 1995, and median follow-up is now 8.0 years.
Randomly Allocated (N = 976)

Allocated to no CMV (n = 485)

Allocated to CMV (n = 491)

- Received allocated intervention of 3 cycles (n = 392)
- Did not receive allocated intervention (n = 99)
- Received 2 cycles (n = 37)
- Received 1 cycle (n = 33)
- Received 4 cycles (n = 1)
- Received 0 cycles (n = 28)
- Reasons
  - Renal toxicity effect/impaired function (n = 23)
  - Other toxicity effects of chemotherapy (n = 18)
  - Disease progression or early death (n = 14)
  - Refusal to continue treatment (n = 21)
  - Protocol errors/unspecific reason (n = 23)

Lost to follow-up
- (n = 2)

Still on therapy
- (n = 0)

Analyzed
- (n = 485)

Lost to follow-up
- (n = 4)

Still on therapy
- (n = 0)

Analyzed
- (n = 491)
The previously reported possible survival advantage of CMV is now statistically significant at the 5% level. Results show a statistically significant 16% reduction in the risk of death (hazard ratio, 0.84; 95% CI, 0.72 to 0.99; P=.037, corresponding to an increase in 10-year survival from 30% to 36%) after CMV.

This was a randomized phase III trial of either no neoadjuvant chemotherapy or three cycles of CMV. Local therapy was left to the treating physician and they do not state that their data differentiate between RT and surgery.
<table>
<thead>
<tr>
<th>RTOG Protocol</th>
<th>Reference</th>
<th>ChemoRT after TURBT</th>
<th>#</th>
<th>OS</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>95-06</td>
<td>Kaufman et al.</td>
<td>5-FU, CP + BID hypofractionated XRT</td>
<td>34</td>
<td>(83%) (3yr)</td>
<td>67%</td>
</tr>
<tr>
<td>97-06</td>
<td>Hagan et al.</td>
<td>CP + BID XRT; adj MCV</td>
<td>52</td>
<td>(61%) (3 yr)</td>
<td>74%</td>
</tr>
<tr>
<td>99-06</td>
<td>Parliament et al.</td>
<td>TAX, CP + BID XRT; adj CP + GEM</td>
<td>84</td>
<td>56% (5 yr)</td>
<td>81%</td>
</tr>
<tr>
<td>02-33</td>
<td>Zietman et al.</td>
<td>5-FU vs TAX + CP + BID XRT; adj GEM, TAX, CP</td>
<td>97</td>
<td>72% (4 yr)</td>
<td>73%</td>
</tr>
<tr>
<td>University of Paris</td>
<td>Houssset et al.</td>
<td>CP, 5FU + hypofractionated BID split course RT</td>
<td>120</td>
<td>63% (5 yr)</td>
<td>77%</td>
</tr>
</tbody>
</table>
BC2001 – NEJM

A 2x2 factorial randomised phase III study comparing standard versus Whole bladder radiotherapy with tumour boost with and without synchronous chemotherapy in muscle invasive bladder cancer

Radiotherapy with or without Chemotherapy in Muscle-Invasive Bladder Cancer


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE
BC2001

- Primary EP:
  - Loco regional & DF survival
- Secondary EP:
  - Toxicity at 1 & 2 years
- Tertiary EP
  - Acute toxicity
  - Cystoscopic control at 3 months, 1 & 2 years
  - Salvage cystectomy rate
  - OS
BC2001

- 360 Patients in 7 years; Median age of 73; 80% male
- TURBT ~55% in each group
- Incomplete resection in ~30%
- Residual palpable mass also similar with ~20% in each group/arm
- Treatment completion rates ~80%
BC2001

T2-T4a TCC
WHO PS 0-2
No previous chemo or RT

Mitomycin C 12 mg/m2 Day 1
5 FU 500mg/m2 fractions 1-5 & 16-20
RESULTS

- Higher Overall Grade 3-5 toxicity (p=0.07) with Chemo-RT
- Significantly greater GI toxicity (p=0.007) with Chemo-RT
- Improvement in Loco-regional Disease Free Survival (p=0.03)
- Overall Survival with 5FU+MMC (50% Vs 34%) is currently not statistically significant (p=0.16)
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of radiotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole-bladder</td>
<td>63</td>
<td>0.78 (0.33–1.60)</td>
<td>0.66</td>
</tr>
<tr>
<td>Modified-volume</td>
<td>58</td>
<td>1.02 (0.37–2.79)</td>
<td></td>
</tr>
<tr>
<td>Elective whole-bladder</td>
<td>239</td>
<td>0.62 (0.40–0.95)</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy dose fractionation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55 Gy in 20 fractions</td>
<td>142</td>
<td>0.77 (0.43–1.36)</td>
<td></td>
</tr>
<tr>
<td>64 Gy in 32 fractions</td>
<td>217</td>
<td>0.63 (0.41–0.98)</td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>118</td>
<td>0.62 (0.35–1.13)</td>
<td>0.72</td>
</tr>
<tr>
<td>No</td>
<td>242</td>
<td>0.71 (0.46–1.10)</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>360</td>
<td>0.68 (0.48–0.96)</td>
<td></td>
</tr>
</tbody>
</table>

Chemoradiotherapy Better vs. Radiotherapy Better
**Overall Survival (%)**

- Chemoradiotherapy
- Radiotherapy

Hazard ratio, 0.82 (95% CI, 0.63–1.09)

P=0.16

**Locoregional Disease–free (%)**

- Chemoradiotherapy
- Radiotherapy

Hazard ratio, 0.68 (95% CI, 0.48–0.96)

P=0.03
RADIATION THERAPY SIMULATION

- Oral contrast is administered 45-60 minutes before simulation to permit small bowel visualization.
- Patient is asked to void prior to simulation.
- Supine position, a Foley catheter is placed, and a post-void residual (X cc) is obtained.
- 25 cc of air and X cc of contrast (~ 25cc) is placed into the bladder, and a cystogram is performed.
- Air in the bladder rises to the top and helps define the anterior bladder extent.
- Cystogram contrast material cannot be less than the post-void residual because this is amount of urine is present in the bladder during treatment.
- CT Simulation done.
- **Bladder is full for boost sim**
RADIATION THERAPY

- **GTV 1** = Tumor

- **PTV 1** = **GTV 1** + 1.5cm Dose 64Gy in 32fx or 55Gy in 20 Fx

- **CTV 2** = Residual Bladder

- **PTV 2** = **CTV 2** + 1.5cm Dose 80% of PTV 1

- This can be done SIB or sequentially
RADIATION THERAPY FIELDS

- Initial fields are treated with four-field technique (alternatively AP and Laterals)
  
  - Initial field weighting: anteroposterior portals deliver 70% and lateral portals deliver 30% of the initial field dose – this permits the boost treatment to be delivered with lateral portals only without overdosing the femoral heads (i.e., maintaining femoral head dose < 5000 cGy).
  
  - in the lateral portals, the entire anal canal and posterior rectum should be blocked

- Boost fields are treated with opposed lateral technique to limit small bowel exposure. Patients should have a full bladder, to protect part of the bladder.
“BOTTOM LINE”
RADIOLOGIC RESPONSE

Pre treatment CT scan

CT Scan at 6 weeks
CONTRA-INDICATIONS TO BLADDER PRESERVATION

- + node above common iliac bifurcation
- Diffuse involvement of bladder mucosa or bladder neck
- T4 disease with stromal invasion
- Hydronephrosis 2/2 tumor
- Poor renal function (serum creatinine > 150-200 µmol/l)
- Poor hepatic function
- Small bladder capacity
- IBD
Large population based studies examining symptoms experienced by patients who received high dose bladder radiotherapy

- Over 74% report good long-term urinary function
- Comparable to cystectomy patients in urinary, rectal, and sexual function

QOL

- MGH study examining quality of life and urodynamics in stage T2-4a bladder conservation patients
  - Normal bladder function was preserved in the majority of patients with an intact bladder (75%)
  - 20% with mild to moderate bowel symptoms
  - 20% with occasional urinary incontinence
  - 59% satisfied with sexual function

- Zietman et al, 2003
FUTURE....

- **Genetics:**
  - Deletions involving $17p$, $18q$, and **RB gene locus** are seen with muscle-invasive disease only.
  - Deletions involving $3p$ and $11p$ are seen in both superficial and muscle-invasive disease.
  - Poor prognostic factors: Over expression of p53, EGFR2 or her2/neu, Hyper diploid Ch7, 11, 17.
  - MRE11-protein associated with treatment response.
MRE 11: EXPRESSION IS PREDICTIVE OF CAUSE-SPECIFIC SURVIVAL FOLLOWING RADICAL RADIOTHERAPY FOR MUSCLE-INVASIVE BLADDER CANCER


- New ways to help select between RT and cystectomy for muscle invasive bladder cancer

- Prospective trial needed for further evaluation – data on the next slide.
Radiation Cohort \( P < 0.001 \)

Log-rank \( P < 0.001 \)

<table>
<thead>
<tr>
<th>Survival from RT (mo)</th>
<th>Low MRE11</th>
<th>High MRE11</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>44</td>
<td>134</td>
</tr>
<tr>
<td>25</td>
<td>15</td>
<td>88</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
<td>54</td>
</tr>
<tr>
<td>75</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>100</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>125</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

HR = 0.43 (95% CI: 0.26–0.71)

Cystectomy Cohort \( P < 0.48 \)

Log-rank \( P = 0.46 \)

<table>
<thead>
<tr>
<th>Survival from cystectomy (mo)</th>
<th>Low MRE11</th>
<th>High MRE11</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>22</td>
<td>68</td>
</tr>
<tr>
<td>25</td>
<td>15</td>
<td>35</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>75</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>100</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>125</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

HR = 1.30 (95% CI: 0.65–2.64)

High MRE11 Patients \( P < 0.02 \)

Log-rank \( P = 0.021 \)

<table>
<thead>
<tr>
<th>Survival from treatment (mo)</th>
<th>RT (High MRE11)</th>
<th>Cystectomy (High MRE11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>134</td>
<td>35</td>
</tr>
<tr>
<td>25</td>
<td>88</td>
<td>25</td>
</tr>
<tr>
<td>50</td>
<td>54</td>
<td>16</td>
</tr>
<tr>
<td>75</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>100</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>125</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

HR = 0.60 (95% CI: 0.39–0.93)

Low MRE11 Patients \( P < 0.13 \)

Log-rank \( P = 0.13 \)

<table>
<thead>
<tr>
<th>Survival from treatment (mo)</th>
<th>Cystectomy (Low MRE11)</th>
<th>RT (Low MRE11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>44</td>
<td>15</td>
</tr>
<tr>
<td>25</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>50</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>75</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>100</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>125</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
One hypothesis is that low levels of MRE 11 protein result in aberrant cell cycle arrest and paradoxically result in less apoptosis following radiation.

Hypothesis needs to be tested in subsequent studies, but the implications are provocative.
PROGNOSTIC FACTORS

- **Tumor factors:**
  - Depth of invasion: 5YOS decreases with increasing depth of invasion: 60% for pT2, 50% for pT3a, and 20% for pT3b
  - Nodal disease
    - 5YOS is low with positive nodal disease: 5 – 20%
  - Tumor > 5 cm, – Hydronephrosis from ureteral obstruction
  - Associated CIS
  - Grade (1-2 vs. 3-4)
  - Morphology (papillary/mixed vs. Solid)
  - LVI
  - Accumulation of p53 in nucleus of TCC.
  - Immunohistochemical analysis of microvessel density
  - Multifocality
PROGNOSTIC FACTORS

- **Treatment factors:**
  - Gross residual disease after TURBT

- **Patient factors:**
  - Low hemoglobin
  - KPS <80%
What’s Next: RTOG OPEN TRIALS?

09-26  A Phase II Protocol For Patients With Stage T1 Bladder Cancer To Evaluate Selective Bladder Preserving Treatment By Radiation Therapy Concurrent With Cisplatin Chemotherapy Following a Thorough Transurethral Surgical Re-Staging

07-12  A Phase II Randomized Study For Patients With Muscle-Invasive Bladder Cancer Evaluating Transurethral Surgery And Concomitant Chemoradiation By Either BID Irradiation Plus 5-Fluorouracil And Cisplatin Or QD Irradiation Plus Gemcitabine Followed By Selective Bladder Preservation And Gemcitabine/Cisplatin Adjuvant Chemotherapy

05-24  A Phase I/II Trial Of A Combination Of Paclitaxel And Trastuzumab With Daily Irradiation Or Paclitaxel Alone With Daily Irradiation Following Transurethral Surgery For Non-Cystectomy Candidates With Muscle-Invasive Bladder Cancer
CONCLUSIONS

- Superficial bladder cancer accounts for the majority of patients at presentation.
  - Difficult to eradicate by local treatment.
- Mainstay of treatment after TURBT is via the intravesical route.
- For muscularis-propria invading lesions, there have been improvements in surgical technique improving QOL.
- Evidence for combined modality approaches is equivocal but such approaches are thought to be important for optimal treatment.
  - Evidence for benefit of bladder sparing with neoadjuvant approaches are stronger than for adjuvant approaches.
- ChemoRT appears to offer superior local control than RT alone.
No definitive evidence for or against bladder preservation techniques
► Ideal for patients medically unfit for cystectomy
► Complete TURB
► Clinical T2
► CR following chemoRT.
THANK YOU