The Case for Chemoradiation treatment of patients with bladder cancer, especially in the Elderly:

UROLOGY GRAND ROUNDS
UNIV. BRITISH COLUMBIA
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Massachusetts General Hospital

2004-2008 National Cancer Data Base of MIBC patients in the U.S.

Age at Diagnosis (median 72 years)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;61 years</td>
<td>5,527</td>
<td>21%</td>
</tr>
<tr>
<td>61 – 70 years</td>
<td>6,974</td>
<td>25%</td>
</tr>
<tr>
<td>71 – 80 years</td>
<td>8,498</td>
<td>30%</td>
</tr>
<tr>
<td>80+ years</td>
<td>7,692</td>
<td>24%</td>
</tr>
</tbody>
</table>

P H Gray et al. European Urology, 2013
2004-2008 National Cancer Data Base of MIBC patients in the U.S.

What are the Patterns of Treatment for MIBC patients in the U.S. in the Elderly?
Based on U.S. National Registry Data
35% of all newly diagnosed MIBC patients are not receiving curative therapy. This rate increases to over 60% for patients over 80 years old.

2004-2008 National Cancer Data Base of MIBC patients in the U.S.
Gray et al., European Urology 2012

National Cancer Data Base for MIBC 2004-2008

Use of Aggressive Therapy for Muscle-Invasive Bladder Cancer

- Community Center
- Community Comprehensive Center
- Teaching Hospital
- NCI Designated Cancer Center

Gray et al., European Urology 2012

National Cancer Data Base for MIBC 2004-2008

Odds of Receiving Aggressive Therapy for MIBC

- White
- Hispanic
- Black
- Other
- Private
- Uninsured
- Medicaid
- Young Medicare
- Older Medicare

Gray et al., European Urology 2012
So we have an unmet need to improve the low rates of using potential curative therapy for elderly patients with MIBC

How effective and safe is bladder preservation by chemoradiation in elderly patients?

Level 1 Evidence that Chemoradiation is better than RT alone in tumor eradication in MIBC: EVIDENCE FROM TWO PHASE 3 TRIALS

1. **NCI – Canada:** Phase III trial with Cisplatin with RT vs. RT alone. 99 patients; pelvic control in 68% vs 47%; p = 0.03.

2. **United Kingdom:** BC 2001 Phase III with 5-FU + Mitomycin C and RT vs RT alone. 360 patients; bladder & pelvic control in 67% vs 54%; p = 0.02, without significant differences in toxicities.
How well does bladder preservation by chemoradiation work in the elderly patients --- using Cisplatin as the main radiosensitizing drug?

Long-term MGH Experience 1986-2002
Clinical stages T2-T4a

Disease-specific survival

80% of those alive at 5 years still have native bladder

95% CI  Survivor function

Number at risk

Follow-up time (years)

0 2.5 5 7.5 10 12.5 15

348 213 149 101 67 44 24

64% 59% 57%
MGH Patients > 75 years old have similar DSS


Pooled RTOG MIBC studies – Disease-specific Survival for Age < 75 vs. Age ≥ 75 (total N=468)

The acceptance of chemoRT using Cisplatin in patients with good renal function should not be limited by concerns of reduced disease specific survival, even in the elderly

How does bladder preservation by chemoradiation work in the elderly patients ---using radiosensitizing drugs other than Cisplatin?
Phase III randomized trial in muscle invasive bladder cancer --BC2001

- 360 patients 2001 – 2008
- Median age of 72 years
- Median follow-up 70 months

James et al, NEJM, April 2012

BC2001 trial design

Patients with muscle invasive bladder cancer

RANDOMISE

Radiotherapy alone

Radiotherapy with 5-FU & Mitomycin C
Age at diagnosis

U. K. Chemotherapy regimen for MIBC

MMC 12mg/m2
5FU 500mg/m2/d
RT 55 Gy/20 f or 64 Gy/32 f

Weeks 0 1 2 3 4 5 6 7
6 month toxicity outcomes

n= 291, 145 RT only, 146 chemo-radiotherapy

ND James, SUO presentation, Dec. 2008

Invasive loco-regional disease free survival with and without concurrent chemotherapy

HR = 0.53 (95% CI: 0.33, 0.84); p=0.007

Advantage of chemoradiation of XRT & 5-FU & MMC

• Clinically well tolerated in elderly U.K. patients, even in those with low-moderate renal function
• Proven to be better than XRT alone
• Low and reduced need for salvage cystectomy (11%)
• 48% overall survival at 5 years

Misconceptions about chemo-radiation in bladder cancer

The saved bladder functions poorly
MGH Quality of Life Study
221 patients
Median f/u 6.3 years
Urodynamics study, QOL questionnaire

• 78% have compliant bladders with normal capacity and flow parameters
• 85% have no urgency or occasional urgency
• 50% of men have normal erectile function

Zietman, Talcott, Krane et al J Urol 2003

RTOG Results of Late Pelvic Toxicity
157 patients with bladder preservation who have survived 2 to 10 years (median follow-up is 5.2 years)

• 21.7% Grade 1
• 10.2% Grade 2
• 7.0% Grade 3 (only 1 of 12 has persisted)
  – 5.7% GU
  – 1.9% GI

Late Pelvic Toxicity after bladder-sparing Therapy on 4 RTOG protocols: The effect of age in 157 patients

The acceptance of chemoRT used in modern bladder-sparing therapy should not be limited by concerns of high rates of late pelvic toxicity, even in the elderly

Misconceptions about chemo-radiation in bladder cancer

The urologist is excluded

For patients with MIBC

1. TURBT

2. XRT (40Gy) + Concomitant Chemotherapy

3. Cystoscopic response evaluation

   - CR
     - Consolidation Chemo-radiation (64Gy)
   - Non-CR
     - Radical cystectomy

4. Frequent cystoscopy, with RC for recurrence
The importance of a maximal TURBT

Long-term MGH Experience 1986-2006
The value of a visibly complete TURBT

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>TURBT complete</th>
<th>TURBT not complete</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>343</td>
<td>227</td>
<td>116</td>
<td></td>
</tr>
<tr>
<td>5 year outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Survival</td>
<td>52%</td>
<td>57%</td>
<td>43%</td>
<td>0.003</td>
</tr>
<tr>
<td>DSS</td>
<td>64%</td>
<td>68%</td>
<td>56%</td>
<td>0.03</td>
</tr>
<tr>
<td>% undergoing cystectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>29%</td>
<td>22%</td>
<td>42%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Immediate (non-CR)</td>
<td>17%</td>
<td>11%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>Salvage</td>
<td>12%</td>
<td>11%</td>
<td>13%</td>
<td></td>
</tr>
</tbody>
</table>

* Univariate analysis; European Urology, 2012
The importance of salvage cystectomy

Update of MGH Series 1986-2002
The 102 patients requiring a cystectomy

Disease-specific survival

Log-rank test: $p = 0.09$

Number at risk
Immediate
Delayed
60 48 30 23 11 7
42 38 26 21 13 8

Immediate cystectomy
Delayed cystectomy
Modern Bladder Preserving Approaches

The importance of life-long bladder surveillance

• Over 70% of all patients do not require a cystectomy for tumor recurrence and of these 75% are cured.

• The cure rates following salvage cystectomy are 45%.

Morbidity of salvage radical cystectomy at the MGH

<table>
<thead>
<tr>
<th>Grade</th>
<th>Total</th>
<th>&lt;30 days</th>
<th>MGH &lt;90 days</th>
<th>MSKCC Prim. Cyst-x</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72 39%</td>
<td>53 48%</td>
<td>58 45% 26%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>55 30%</td>
<td>42 38%</td>
<td>48 38% 62%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>32 28%</td>
<td>11 10%</td>
<td>18 14% 11%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3 2%</td>
<td>2 2%</td>
<td>2 2% 0%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1 1%</td>
<td>2 2%</td>
<td>2 2% 2%</td>
<td></td>
</tr>
</tbody>
</table>

Problems with chemo-radiation in bladder cancer

• Life-long bladder surveillance is required

• The risks of salvage cystectomy may be increased, and

• Neobladder conduits may be used less frequently

Contra-indications to chemo-radiation for bladder preservation

• Ulcerative colitis
• Prior pelvic radiation therapy
• A tumor that can not undergo a de-bulking TURBT, such as one in a diverticulum
• Pre-existing poor bladder capacity
The truth about chemo-radiation for MIBC patients

- It is used selectively
- Its use is approved by the NCCN and EAU guidelines
- More than 2/3 of bladders are spared
- The retained bladder functions well
- Patients want it and seek it

“Bladder preservation with chemoradiation is suitable for those who meet the specific requirements”
RTOG PROTOCOL 07-12 (Randomized Phase II)

**MIBC**
Stage T2 – T4a, No Hydronephrosis
Candidate for cystectomy, if necessary

**TURBT**

randomization

- **RTOG:** bid RT
  - 5FU
  - Cisplatin

- **Michigan:** qd RT
  - Gemcitabine

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**Protocol Update for Task Force Feb 16, 2013**

For MIBC patients, especially the elderly

**TITLE:**
A Phase II study of Tri-Modality Therapy for selective bladder preservation in MIBC patients with evaluations of biomarkers for predicting response to treatment
Co-Chairs of this protocol to be open in all CTEP GU groups and prepared by the RTOG (NRG)

Urology: M. Schoenberg, A. Kibel
Med. Oncology: M. Milowsky, D. Quinn
Rad. Oncology: M. Hagan, J. Efstathiou
Pathology: A. Magliocco, H. Al-Ahmedie
Translational Research: D. Theodorescu, F. Feng
Geriatric Oncology: A. Hurria, M. Galsky
Quality of Life: R. Chen
RTOG Statisticians: K. Winter, D. Hunt
Consultants: B. Mann, J. Simko

Recent developments in the therapeutic landscape in MIBC relevant to ChemoRT with selective bladder preservation

• Many elderly MIBC patients not receiving RC
• 5-FU + MMC-based ChemoRT effective in older patients
• Two recent reports identifying MRE11 expression predictive for success with RT and ChemoRT but not Cystectomy
• Bladder cancer Task Force interest in promoting clinical trials to evaluate translational science innovations
MRE 11 protein Predictive of Cancer Specific Survival Following XRT but not Cystectomy for MIBC

Radiation cohort

Cystectomy cohort

P < .001

P = .48


MRE 11 protein Predictive of Cancer Specific Survival with ChemoRT but not with Cystectomy

J.R. Laurberg et al BJU Int., 2012
Translational Science Project #199
Evaluation of MRE 11 in Patients on completed RTOG ChemoRT Protocols

**Specific Aim:**
To correlate the level of tumor MRE 11 staining with treatment responses including CR, DSS, and local bladder recurrence

**Goal:**
To determine a numerical threshold or cut point for MRE 11 staining that predicts for an increase in the CR rate and in the DSS

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**SCHEMA OF THE CHEMORADIATION (CRT) PROTOCOL**

Maximal TURBT with tumor specimen biomarker analysis

Concurrent 5-FU & Mitomycin C with XRT to 40Gy

- **Biopsy Negative**
  - Complete CRT to 65Gy
  - Long-term Cystoscopic Surveillance

- **Biopsy Positive**
  - Cystoscopic Biopsy of Tumor Site
  - Cystectomy Candidate?
    - **Yes**
      - Radical Cystectomy
    - **No**
      - Complete CRT to 65Gy with Gemcitabine
      - Long-term Cystoscopic Surveillance
**NCI Bladder Task Force Protocol**

*The Objectives* from prospective trial data:

1. To determine the CR rate following induction chemoradiation with 5-FU + MMC
2. To correlate a tumor MRE 11 expression cut point with improved CR rate.
3. Exploratory evaluations for other new biomarkers using IHC, RNA-based expression profiles, RNA-based COXEN analysis and SNPs from serum.
4. To evaluate the disease specific survival and the tolerance by QoL of this CRT regimen, especially in the elderly patients.

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**The Case for ChemoRT in the Elderly**

So we now have a therapy better than RT alone that:

- Saves lives
- Spares >70% of patients from major surgery
- Has been tested in the elderly
- Has relatively little toxicity

**Summing up message**

…..Now chemoRT can be recommended as one of the better & safest curative therapies for elderly patients.
The use of TURBT & ChemoRT
In patients with T1 tumors recurrent Following BCG therapy

RTOG # 0926
CHEMO-RADIATION PROTOCOL FOR initially T1 TUMORS, but only for BCG FAILURE
“Chemo-Radiation as conservative Salvage Therapy”

Protocol Co-Chairs:
D. M. Dahl, Urology and W.U. Shipley, Radiation Oncology
D.M. Michaelson, Medical Oncology
RTOG Protocol 0926 for patients with Initially T1 tumors that have recurred despite BCG therapy

In this group of patients both undertreatment and overtreatment are controversial and critical issues

HIGH-RISK T1 BLADDER TUMORS THAT RECUR FOLLOWING BCG THERAPY

• Standard treatment is radical cystectomy

• 75% to 80% disease specific survival at 10 years are reported
SECOND LINE INTRAVESICAL BIOLOGICAL OR CHEMOTHERAPY FOLLOWING BCG FAILURE WITH T1 BLADDER TUMOR

• BCG plus interferon
• Intravesical chemotherapy
  – Mitomycin C
  – Gemcitabine (19% RFS at 2 years)
  – Docetaxel
  – Apaziquone (Eoquin or E09)
  -Valrubicin (8% durable response for 21 months)

Results are generally poor—less than 1 year cancer free

LONG-TERM RESULTS of ChemoRT for cT2 RECURRENCE FOLLOWING BCG FAILURE

MGH – 18 NMIBC bladder cancer patients who later failed BCG and presented to us with cT2 disease.

We treated these 18 patients on our bladder preserving protocols using TURBT and ChemoRT:
* Median follow-up after ChemoRT was 7 years

*Only 1 has required a cystectomy.

*At 7 years, 10 are free of any bladder recurrence (59%)

* 7-yr DSS 70%

* 54% of patients at 7 years were alive with intact bladders and free of recurrence
RTOG # 0926

CHEMO-RADIATION PROTOCOL FOR initially T1 TUMORS, but only for BCG FAILURE

“Chemo-Radiation as conservative Salvage Therapy”

RTOG # 0926

ChemoRT for initially T1 TUMORS, but only in those who have FAILED BCG Therapy

The goal of the protocol is to prospectively evaluate the cure rate of TURBT surgery plus ChemoRT while preserving the patient’s bladder.
Initially T1 BLADDER TUMORS THAT RECUR FOLLOWING BCG THERAPY

- The main eligibility criteria:

The participating urologist judges that the standard next therapy, based on present urologic guidelines for the patient, is radical cystectomy.

Diagram:

- **TURBT**
  - XRT (61.2Gy) + Concomitant Chemotherapy
  - Cystoscopic response evaluation
    - CR
    - Non-CR
      - Frequent cystoscopy, with RC for recurrence
      - Radical cystectomy

RTOG 0926
SCHEMA:

PROTOCOL FOR initially T1 TUMORS, but only FOLLOWING BCG FAILURE

Maximal concurrent
TURBT for re-staging Radiation* and
— Chemotherapy **

*Total dose of 6120 cGy in
34 daily fractions.

** Cisplatin 3 days/week, or
5-FU & Mito C per BC2001

Cystoscopic Surveillance with Prompt Cystectomy for Recurrence

PROTOCOL FOR HIGH-RISK T1 TUMORS
FOLLOWING BCG FAILURE

PRIMARY OBJECTIVE

To evaluate the rate of both freedom from
cystectomy and freedom from the
development of local or distant disease
progression at 3-5 years.
RTOG # 0926

Projected Success rate from TURBT & ChemoRT:

10 year survival from bladder cancer  70- 80%

Likelihood of requiring a cystectomy  < 20%

Chance of having poor bladder function  5%