Radiation therapy for bladder cancer

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Making Cancer History™
When to consider RT

• Muscle invasive – organ conservation
  – TURBT + CT +RT

• Locally-advanced
  – Definitive vs. Preop
  – IORT

• Poor performance status
• Palliative

• Try to avoid RT post-op
Radiotherapy for Bladder Cancer

Michael Milosevic, Mary Gospodarowicz, Anthony Zietman, Farhat Abbas, Karin Haustermans, Luc Moonen, Claus Rödel, Mark Schoenberg, and William Shipley

Muscle-invasive urothelial carcinoma

- Low-risk
  - T2
  - <5 cm in size
  - No CIS
  - No gross LN metastases
  - Transurethral resection
  - External-beam RT to primary bladder tumor and pelvic LN + concurrent cisplatin

- High-risk
  - T3-T4
  - >5 cm in size
  - Hydronephrosis
  - Pelvic LN metastases
  - Neoadjuvant combination platinum-based chemotherapy
  - Consolidative external-beam pelvic RT

Evaluation of response at 3 months + lifelong bladder surveillance
Location

• 25% multifocal
  – 40% lateral walls
  – 11% posterior
  – 3% anterior
  – 17% adjacent to ureteral orifice
  – 13% trigone, 9% dome, 7% neck

  – For RT, dome can be difficult b/c of proximity to bowel
2002 AJCC staging

- Ta  non-invasive papillary tumor
- Tis  In-situ ca (flat tumor, may extend)
- T1  Sub-epithelial connective tissue
- T2a  Inner half of muscle layer
- T2b  Outer half (deep muscle)
- T3a,b  Perivesical fat (micro, macro)
- T4a,b  Other adjacent structures
1992 AJCC path staging

- **T0**: No evidence
- **Tis**: CIS
- **Ta**: Non-invasive papillary
- **T1**: Invades submucosa/lamina prop
- **T2**: Superficial muscle
- **T3a**: Deep muscle
- **T3b**: Perivesical fat
- **T4**: Adjacent organs
1992 T-Stage (depth of invasion) and N+

- pT1 5%
- pT2 30%
- pT3a 31%
- pT3b 64%
- pT4 50%

- [J Urol 1982;127]
Muscle-invasive bladder ca

• Radical cystectomy
  – Most prevalent therapy in U.S.

• Trimodality therapy for bladder preservation
  – TURBT + CT-RT
  – Unifocal T2-early T3’s are best candidates
  – Recurrences may be superficial
Radical cystectomy

- Male: Bladder, prostate, SV, proximal vas deferens, 1-2 cm proximal urethra w/ margin
- Female: Anterior exenteration: bladder, urethra, uterus, fallopian tubes, ovaries, ant vaginal wall, and surrounding tissues en bloc
- Long term local control rates can be > 80%.
- 5 y Overall survival 40-60%
Radiation therapy alone suboptimal

• Long term local control rates < 35%

• 5 year overall survival ~20-40%
  – Patient selection may bias poor results?

• Potential prognostic factors
  – T-stage, T4 <10% 5y OS
  – T >5cm, Incomplete TURBT
  – Ureteral obstruction
  – Grade
  – Level of response
Bladder preservation—single modality

- TURBT  20% bladder w/ no recurrence
- RT alone  40%
- CTx alone  20%

- Non-surgical single modality therapies usually not curative
Multi-modality

• RT alone 45% complete response
• CTx alone 25-30%
• TURBT + CTx 50%
• TURBT + CTx-RT 70%-80%

– Tri-modality therapy
  • 50-60% 5y OS
  • 40-45% 5y survival w/ bladder preservation
    – w/ out RT ~50% 5y OS but <30% bladder preservation.
# Cystectomy vs. Bladder preservation

<table>
<thead>
<tr>
<th>Series (yr)</th>
<th>Stages</th>
<th>No.</th>
<th>5-yr (%)</th>
<th>10-yr (%)</th>
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<tbody>
<tr>
<td><strong>Cystectomy</strong></td>
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<tr>
<td>University of Southern California [21] (2001)</td>
<td>P2-P4a</td>
<td>633</td>
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<td><strong>Selective bladder preservation</strong></td>
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</table>

Urologic Oncol 25, 2007
MGH protocol
[NEJM 1993;329:1377-82]

Transurethral Resection

53 patients

Systemic Chemotherapy: 2 cycles of MCV

49 patients

Cisplatin, with 4000 cGy

46 patients

Urologic Evaluation

10

Incomplete response and suitability for surgery

Radical Cystectomy

8 completed therapy

36

Complete response or unsuitability for surgery

Consolidation with Cisplatin and 2480 cGy

34 completed therapy

Few week break
...split-course RT
MGH protocol

- 79% completed therapy
- Median FU 48 months
- 5y OS 48% for all patients
- Overall rate of being alive w/ tumor free bladder was 38%.
Prognostic factors

• If initial complete response, then 5y OS 63% vs. 27% for non-CR

• Hydronephrosis
  – Negative factor on univariate (p=0.03) and approached on MVA (p=0.07).
  – Negative factor for bladder preservation w/ out recurrence.
    • 23% bladder preservation w/ hydro vs. 70% w/ out
Role of neoadjuvant CTx
RTOG 89-03 [JCO 1998;16]

- Randomized 126 pts w/ T2-4aNxM0
- TURBT +/- MCV (Mtx, Cisplatin, Vinblastine) x 2
- 39.6 Gy w/ CDDP (100, days 1,22)
- Re-eval ⇒ if CR, then 25.2 Gy + CDDP.
- If not CR, then cystectomy.
Fig 1. Arm 1 of RTOG 89-03 for the treatment of invasive bladder cancer with combined TURBT, chemotherapy, and radiation therapy for attempted bladder preservation.

Fig 2. Arm 2 of RTOG 89-03 for the treatment of invasive bladder cancer with combined TURBT and concurrent chemotherapy and radiotherapy for attempted bladder preservation.
Table 2. Protocol Completion Rate

<table>
<thead>
<tr>
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<th>Arm 1 (MCV)</th>
<th>Arm 2 (no MCV)</th>
<th>Total</th>
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<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
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<td>Patients eligible</td>
<td>61</td>
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<td>62</td>
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<tr>
<td>Completed MCV</td>
<td>51</td>
<td>84</td>
<td>-</td>
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<tr>
<td>Completed induction</td>
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<tr>
<td>chemoradiation</td>
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<td>80</td>
<td>58</td>
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<tr>
<td>Completed protocol</td>
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<td></td>
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<tr>
<td>with no or minor deviation</td>
<td>41</td>
<td>67</td>
<td>50</td>
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Table 4. Results by Treatment Assignment, Status After TURBT, and Presence or Absence of Hydronephrosis

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>No.</th>
<th>Alive, %</th>
<th>cCR Rate, %</th>
<th>Total Pelvic Failure, %</th>
<th>Distant Failure, %*</th>
<th>Alive With Intact Bladder, %*</th>
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<tr>
<td>All eligible</td>
<td>123</td>
<td>50</td>
<td>59</td>
<td>12</td>
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<td>61</td>
<td>9.8</td>
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<td>No MCV</td>
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<td>50</td>
<td>55</td>
<td>14.5</td>
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<td>40</td>
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<tr>
<td>Status after TURBT</td>
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<tr>
<td>Visibly complete</td>
<td>88</td>
<td>55</td>
<td>65</td>
<td>13</td>
<td>34</td>
<td>43</td>
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<tr>
<td>Visibly incomplete</td>
<td>32</td>
<td>53</td>
<td>44</td>
<td>12</td>
<td>38</td>
<td>26†</td>
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<tr>
<td>Hydronephrosis</td>
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<td></td>
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<tr>
<td>Absent</td>
<td>99</td>
<td>54</td>
<td>64</td>
<td>11</td>
<td>35</td>
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<td>Present</td>
<td>24</td>
<td>33†</td>
<td>38‡</td>
<td>25</td>
<td>42</td>
<td>33</td>
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</tbody>
</table>

Abbreviation: cCR, clinical complete response, i.e., tumor site rebiopsy negative and cytology negative.

*Actuarial rate at 5 years.

†P = .06.

‡P = .02.
Fig 3. Overall survival rates for patients randomized to neoadjuvant MCV chemotherapy on arm 1 compared with those randomized to no MCV (arm 2).
# Long-term MGH experience

[Urology 2002]

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<thead>
<tr>
<th></th>
<th>5 year</th>
<th>10 year</th>
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<tbody>
<tr>
<td>Actuarial OS</td>
<td>54%</td>
<td>36%</td>
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<tr>
<td>DSS</td>
<td>63%</td>
<td>59%</td>
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<tr>
<td>DSS w/ bladder</td>
<td>T2 57%</td>
<td>T2 50%</td>
</tr>
<tr>
<td></td>
<td>T3-4 35%</td>
<td>T3-4 24%</td>
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</tbody>
</table>

Pelvic failure rate 8.4%

Not all relapses are muscle invasive!
Overall survival: T2 better than T3-4
Disease specific survival: T2 better than T3-4
Re-evaluation

- After ~40 Gy and 4 week break
- Examine under anesthesia
- Cystoscopy w/ tumor-site biopsy
- Urinary cytology

- If any of the above is positive, then cystectomy.
Erlangen protocol

- Higher RT dose (45-50Gy) prior to re-evaluation
- Concurrent CDDP +/- 5-FU
- Dose depends upon level of TURBT

  - 45-50 Gy to slightly larger pelvic field
  - Immediate boost to entire bladder
  - 54Gy for R0, 59.6Gy for R1/2
  - Re-evaluation after 4-6 weeks

- Theoretical advantages to either technique
- Overall results similar

J Clin Oncol 20, 2002
Fig. 1 Combined Modality Bladder Preservation Therapy

1. Transurethral Reseektion (R0, if possible)
2. Radiochemotherapy
3. Restaging-TURBT

- Muscle-invasive Residual Tumor
  - Salvage-Cystectomy
- Superficial Residual Tumor
  - TURBT + intravesical therapy
- Complete Remission
  - Follow-up

- Superficial Relapse
  - Muscle-invasive Relapse
Fig.2 Erlangen RCT-Regimen for Bladder Cancer

Radiotherapy:
28 x 1.8 Gy
5.4 - 9 Gy Boost

Chemotherapy:
Cisplatin 20 mg/m²/d
5-FU 600 mg/m²/d
RT technique

- Target is bladder w/ true pelvic LN’s
- 4 field with higher energy preferred
- Small pelvic field (40-50Gy)
- Boost field (64-70Gy)
- Bladder mapping, Examine under anesthesia
- Cystogram
- Rectal contrast

CT planning has largely replaced these
Specify location/origin of primary (at cysto or TURB)____________________________________

Visibly complete TURB? ________________________________ Yes __ No __

Palpable mass or indentation persists after TURB? ____________________________ Yes __ No __

Initial largest tumor (diameter): < 1 cm __ 1.1-2.9 cm __ 3.0-4.9 cm __ ≥ 5 cm __

Does tumor invade prostate or vagina? ________________________________ Yes __ No __

Is tumor fixed to pelvic/abdominal wall? ________________________________ Yes __ No __

PLEASE COMPLETE THE FOLLOWING TWO DIAGRAMS:

A. TUMOR LOCATION BEFORE TURB

B. POST-TURB: IF MACROSCOPIC TUMOR REMAINS AT END OF PROCEDURE, INDICATE ITS LOCATION. IF NOT, CHECK "NONE."

NONE □
Small pelvic fields

- Target is tumor, bladder, proximal urethra (male entire prostatic urethra) and first LN’s (nodes below bifurcation of int-ext iliacs)

- Superior
- Mid-SI (S2-S3 junction)
- Inferior
- Bottom obturator foramen
- Lateral
- 1.0 cm (1.5) on pelvic brim
- Block femoral heads
MGH/RTOG Pelvic fields
MGH/RTOG Boost fields
Empty vs. Full bladder

• Depends…

• Empty bladder allows for slightly smaller field but at potential cost of treating more small bowel

• Full bladder may be better for boost to spare some bladder mucosa
Location of tumor matters

- **Good**
  - Bladder neck
  - Lateral
  - Posterior
  - Anterior

- **Bad**
  - Dome
  - Anything near small bowel
3D CRT and IMRT boost
Proton bladder boost (AP and Lt lateral)

Int J Radiat Biol Phys 64, 2006
Bladder preservation

• **GOOD Candidates**
  – Unifocal w/ no CIS
  – < 5cm
  – Complete TURBT
  – Lower T (T2-3a)
  – No hydronephrosis
  – Complete response
  – 2 hour bladder
  – Will come for FU

• **“BAD” Candidates**
  – Multifocal or CIS
  – Incomplete TURBT
  – T3b-4
  – Hydronephrosis
  – Incomplete response

  – Tumors on dome are challenging
Bladder preservation relies on multi-disciplinary team

- Urologic surgeon
- Medical oncologist
- Radiation oncologist

- Combination therapy is better than one
MDACC bladder RT recommendations

• Complete TURBT

• Pelvic RT (40-45 Gy) w/ concurrent cisplatin (+/- 5FU)

• Boost tumor (64-66 Gy) w/ cisplatin
  • Avoid treating entire bladder to high dose
Clinically locally-advanced bladder cancer

Consider preoperative therapy (chemotherapy and radiation therapy)
Preop therapy

• Majority of randomized studies comparing preop RT and immediate cystectomy did not show OS advantage over RT followed by delayed salvage cystectomy.

• Except MDAH in big (clinical) T3
  – 50Gy + cyst vs. 60Gy + salvage cystectomy
  – 5y OS 46% vs. 22%
  – Potential selection bias

[Cancer 39:973,1977]
1983 AJCC cT3b: MDACC data

- Retrospective review [IJROBP 32:331,1995]
- 45-50 Gy ⇒ cystectomy (338) vs. cystectomy alone (232) for *clinical* T2-4.
  - 65-70% downstaged
  - ~45% had path CR
- No LC difference for *clinical* T2-3a
  - cT3a=residual induration on bimanual exam after TURBT.
## MDACC series - local control

<table>
<thead>
<tr>
<th>c-stage</th>
<th>PREOP</th>
<th>CYST</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>92%</td>
<td>93%</td>
<td>0.81</td>
</tr>
<tr>
<td>T3a</td>
<td>90%</td>
<td>91%</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>T3b</strong></td>
<td><strong>91%</strong></td>
<td><strong>72%</strong></td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>T4</td>
<td>3 pts</td>
<td>61%</td>
<td></td>
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* cT3b = residual mobile mass
MDACC series

• Benefit for preop RT seen in cT3b
  • cT3b = residual mobile mass

<table>
<thead>
<tr>
<th>a5y actuarial</th>
<th>PREOP</th>
<th>CYST</th>
<th>p-value</th>
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<tbody>
<tr>
<td>LC</td>
<td>91%</td>
<td>72%</td>
<td>0.003</td>
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<tr>
<td>Pelvic control</td>
<td>88</td>
<td>72</td>
<td>0.01</td>
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<tr>
<td>Freedom from DM</td>
<td>67</td>
<td>54</td>
<td>0.29</td>
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<td>Disease freedom</td>
<td>59</td>
<td>47</td>
<td>0.18</td>
</tr>
<tr>
<td>OS</td>
<td>52</td>
<td>40</td>
<td>0.19</td>
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</table>
Pelvic side wall involvement
After neoadjuvant CTx
Intra-operative radiation therapy (IORT)

- IORT is one large fraction “blast” (electrons or gamma rays)
  - Limited total dose compared to fractionated regimen

- ALWAYS give pre-op external beam first

- Unlikely to be effective on its own
Why IORT?

• Dose escalation
  – very high doses can be delivered
• Avoiding critical structures
• Targets area of concern
Fractionated Radiotherapy

Fractionated

Single Fraction

Dose (cGy)

0 2 4 6 8 10

0.01 0.1 1
2 Gy Equivalent of Single IORT Dose

$$D = D_0 \left( \frac{\alpha/\beta + d_0}{\alpha/\beta + d} \right)$$

$$D = \text{Dose}_{\text{IORT}} \left( \frac{\alpha/\beta + D_{\text{IORT}}}{\alpha/\beta + 2} \right)$$

2 Gy Equivalent Dose vs. IORT Dose (Gy)

- Late Side Effects
- Tumor Kill
Radiobiological Conclusions

Improved Therapeutic Ratio

Dose Escalation

Avoid Critical Structures

• Not adequate by itself
Intraoperative Electron Beam
MOBETRON®
“mobile”
electron accelerator
Kept in Shielded OR Suite
Intraoperative High Dose Rate Brachytherapy
Flexible IOHDR applicator - Radioactive Source Delivers $\gamma$-Rays
IOHDR APPLICATORS

Foam  Template  Silicon  Delrin

S. Nag
Post-op RT after CYST

• Studies have shown better LC and DFS (25% vs. 45%) w/ PORT

• Increased risk of small bowel obstruction
  (8% vs. 37%). [IJROBP 24:463]
  • Post-op…small bowel falls into field.

• Post-op RT may benefit squamous cell carcinoma
  – 5 year DFS  45-50% vs. 25%
  – 5 year LC  87-93% vs. 50%
  – 65-70% SCC (Egypt)  [IJROBP 23:511]
Future directions

- Altered fractionation (e.g. BID)
- Dose escalation
- Different chemotherapy in neoadjuvant or concurrent setting (taxanes and gemcitabine)
- MCV (mtx, cisplatin, vinblastine) is not well-tolerated

- RTOG trials have finished and awaiting followup
- No significant difference yet
<table>
<thead>
<tr>
<th>Series</th>
<th>Patients (n)</th>
<th>Median follow-up (mo)</th>
<th>Bladder recurrence (Total/invasive/initial CRs)</th>
<th>Regional nodal failure (%)</th>
<th>Distant metastasis (%)</th>
<th>Durable CRs* (%)</th>
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<td>Conventional RT (C)</td>
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<td>RTOG 85-12</td>
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<td>36</td>
<td>11/7/28</td>
<td>11</td>
<td>43</td>
<td>50</td>
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<td>RTOG 89-03 (Arm 2)</td>
<td>62</td>
<td>60</td>
<td>17/5/37</td>
<td>14.5</td>
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<td>Readjuvant MCV + RT (C)</td>
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<td>RTOG 88-02</td>
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<td>46</td>
<td>37/18/68</td>
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<td>60</td>
<td>24/6/35</td>
<td>9.8</td>
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<td>47</td>
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<td>MGH 1997 (13)</td>
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<td>53</td>
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<td>Paris (4)</td>
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<td>4/3/22</td>
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<tr>
<td>RTOG 95-06</td>
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<td>9/3/20</td>
<td>NR</td>
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<td>57</td>
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<td>Hyperfractionated RT/(C/5-FU) + adjuvant MCV</td>
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<td>MGH 1998 (18)</td>
<td>18</td>
<td>32</td>
<td>3/0/14</td>
<td>NR</td>
<td>22</td>
<td>78</td>
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<tr>
<td>RTOG 97-06 (present study)</td>
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<td>26</td>
<td>6/2/32</td>
<td>15</td>
<td>29</td>
<td>64</td>
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* Abbreviations: CR = complete response; RT = radiotherapy; C = cisplatin; RTOG = Radiation Therapy Oncology Group; MCV = methotrexate, cisplatin, vinblastine; MGH = Massachusetts General Hospital; 5-FU = 5-fluorouracil.

* Product of complete response rate and freedom from invasive recurrence.
Special situations

- Symptomatic pelvic recurrence after CYST
- Muscle-invading tumor w/ hydronephrosis
- Nodal mets
- S/P partial cystectomy w/ positive margin
- Palliation of bleeding
Thank you