Critical analysis of bladder sparing trimodal therapy in muscle-invasive bladder cancer

Andrei Fodor, Italy
<table>
<thead>
<tr>
<th>PRIMARY TREATMENT</th>
<th>ADJUVANT TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radical cystectomy and strongly consider neoadjuvant cisplatin-based combination chemotherapy (category 1) or Segmental (partial) cystectomy (highly selected patients with solitary lesion in a suitable location; no T3a) and consider neoadjuvant cisplatin-based combination chemotherapy.</td>
<td>Consider adjuvant chemotherapy (category 2B) based on pathologic risk (pT3-4 or positive nodes) if no neoadjuvant treatment given. Consider adjuvant RT (category 2B) or chemotherapy (category 2B) based on pathologic risk (pT3-4 or positive nodes, or high-grade) if no neoadjuvant treatment given.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLINICAL STAGING</th>
<th>ADJUVANT TREATMENT</th>
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<tbody>
<tr>
<td>Muscle invasive and selected metastatic disease treated with curative intent</td>
<td>Bladder preservation following maximal TURBT with concurrent chemotherapy (category 2B).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-Up</th>
<th>RECURRENT OR PERSISTENT DISEASE</th>
<th>TREATMENT OF RECURRENT OR PERSISTENT DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>Local recurrence or persistent disease: Preserved bladder</td>
<td>Cystectomy and/or chemotherapy if no surgical candidate or RT (if no prior RT).</td>
</tr>
<tr>
<td></td>
<td>Urothelial, liver function tests, creatinine, electrolytes every 8-12 mo.</td>
<td>Chemotherapy.</td>
</tr>
<tr>
<td></td>
<td>Imaging of chest, upper tracts, abdomen, and pelvis for recurrence every 5-6 mo for 2 yr then as clinically indicated.</td>
<td>Cystectomy (category 1).</td>
</tr>
<tr>
<td></td>
<td>If bladder preservation, cystoscopy and urino-urology 2 selected mapping biopsy every 3-4 mo for 2 yr then increasing intervals as appropriate.</td>
<td>Cystectomy (category 1).</td>
</tr>
<tr>
<td></td>
<td>Metastatic or local recurrence (postcystectomy)</td>
<td>Chemotherapy and/or RT.</td>
</tr>
</tbody>
</table>

\[\text{Note: All recommendations are category 2B unless otherwise indicated.}

\text{Clinical Trials: NCCN believes that the best-managed of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.} \]
**BLADDER CANCER**

**EDITORS**
Mark Soloway - Saad Khoury

2nd International Consultation on Bladder Cancer - Vienna 2012

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<td>3. Radiation-Based Bladder-Preserving Strategies</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
</tr>
</tbody>
</table>

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**Figure 3:** Current Schema for Trinodality Treatment of Muscle-Invasive Bladder Cancer With Selective Bladder Preservation.

**Figure 4:** Long-term Disease-specific Survival with Selective Bladder Preservation from the Massachusetts General Hospital Experience (29).
Trimodal Therapy results

- Adequate local control cannot be achieved with TURBT, chemotherapy or radiotherapy, when used alone

- It is generally recognised that **TURBT alone provides inadequate cancer control** and high rate of bladder cancer recurrence *(Herr HV et al, JCO 2001; Leibovici D et al, Urology 2007; Solsona E et al J Urol 2010)*

- Randomized trial of **RT vs chemo-RT** in bladder cancer demonstrated an **improved control rate with concurrent CDDP** *(Coppin CM et al, JCO 1996)*. Results confirmed also by BC2001 trial for RT vs RT + concurrent MMC+ 5 FU *(James ND et al, N Engl J Med 2012)*. Erlangen study showed a RR of 61% for RT alone and 82% for RT+ CDDP, and a significant improvement in OS *(Rodel C et al, JCO 2002)* → **Level of Evidence 1b**
## Trimodal Therapy results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>%CR</th>
<th>OS5</th>
<th>% requiring cystectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>TURBT+ M-VAC</td>
<td>33-54%</td>
<td>58%</td>
<td>66%</td>
</tr>
<tr>
<td>TURBT+ RT+ CT</td>
<td>64-87%</td>
<td>45-62%</td>
<td>29-35%</td>
</tr>
</tbody>
</table>

Cystectomy rate was increased by 88-125% without radiation!- *(Sternberg CN et al, Cancer 2003)*
«Old» evidence

<table>
<thead>
<tr>
<th>Series</th>
<th>No. of Patients</th>
<th>Clinical Stage</th>
<th>Neoadjuvant Treatment</th>
<th>Concurrent Treatment</th>
<th>Complete Response pCR (%)</th>
<th>Consolidation CRT-Regimen for Complete Responders (± adjuvant chemotherapy)</th>
<th>5-Year Overall Survival (%)</th>
<th>5-Year OS With Bladder (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGH 1986-1993⁸</td>
<td>106</td>
<td>T2-4a</td>
<td>TURBT, 2 cycles MCV</td>
<td>39.6 Gy in 1.8 Gy plus cisplatin</td>
<td>66</td>
<td>25.2 Gy in 1.8 Gy plus cisplatin</td>
<td>52</td>
<td>43</td>
</tr>
<tr>
<td>RTOG 85-12 1986-1988⁸</td>
<td>42</td>
<td>T2-4a</td>
<td>TURBT</td>
<td>40 Gy in 2 Gy plus cisplatin</td>
<td>66</td>
<td>24 Gy in 2 Gy plus cisplatin</td>
<td>52</td>
<td>42</td>
</tr>
<tr>
<td>RTOG 88-02 1988-1990⁷</td>
<td>91</td>
<td>T2-4a</td>
<td>TURBT, 2 cycles MCV</td>
<td>39.6 Gy in 1.8 Gy plus cisplatin</td>
<td>75</td>
<td>25.2 Gy in 1.8 Gy plus cisplatin</td>
<td>62 (4 years)</td>
<td>44 (4 years)</td>
</tr>
<tr>
<td>RTOG 89-03 1990-1993⁸</td>
<td>123</td>
<td>T2-4a</td>
<td>TURBT, 2 cycles MCV, v no chemotherapy</td>
<td>39.6 Gy in 1.8 Gy plus cisplatin</td>
<td>61 v 55</td>
<td>25.2 Gy in 1.8 Gy plus cisplatin</td>
<td>49 v 48</td>
<td>36 v 40</td>
</tr>
<tr>
<td>MGH 1993-1994⁹</td>
<td>18</td>
<td>T2-4a</td>
<td>TURBT</td>
<td>42.5 Gy in 1.25 und 1.5 Gy bid plus FU und cisplatin</td>
<td>78</td>
<td>22.5 Gy in 1.25 and 1.5 Gy bid plus FU and cisplatin, 3 cycles adjuvant MCV</td>
<td>83 (3 years)</td>
<td>78 (3 years)</td>
</tr>
<tr>
<td>RTOG 95-06 1995-1997¹⁰</td>
<td>34</td>
<td>T2-4a</td>
<td>TURBT</td>
<td>24 Gy in 3 Gy bid plus 5-FU and cisplatin</td>
<td>67</td>
<td>20 Gy in 2.5 Gy bid plus FU and cisplatin</td>
<td>83 (3 years)</td>
<td>66 (3 years)</td>
</tr>
<tr>
<td>RTOG 97-06 1997-1999¹¹</td>
<td>47</td>
<td>T2-4a</td>
<td>TURBT</td>
<td>40.8 Gy in 1.8 und 1.6 Gy bid plus cisplatin</td>
<td>74</td>
<td>24 Gy in 1.5 Gy bid plus cisplatin, 3 cycles adjuvant MCV</td>
<td>61 (3 years)</td>
<td>48 (3 years)</td>
</tr>
</tbody>
</table>

Abbreviations: MGH, Massachusetts General Hospital; RTOG, Radiation Therapy Oncology Group; TURBT, transurethral resection of bladder tumor; MCV, methotrexate, cisplatin, vinblastine; FU, fluorouracil; pCR, pathologic complete response; OS, overall survival.

Rodel C et al, JCO 2006
**«Old» evidence**

**RTOG 85-12**: phase II (first trial to use the classic RTOG approach) - *(Tester W et al, IJROBP 1993)*
- 42 pts T2-T4N0-2
- WPRT 40 Gy (2 Gy/fr) + 2c CDDP → restage after 2 wks: cystoscopy, biopsy, clinical exam under anesthesia, CT: → CR: RT boost 24 Gy (2 Gy/fr) + 3°c CDDP
  → no CR = cystectomy
- Results: CR = 67%; OS5 = 52%; All pts LC = 42%; Invasive only LC = 50%, LF5 = 25%

**RTOG 88-02**: phase II - *(Tester W et al, JCO 1996)*
- 91 pts T2-T4N0-2
- Neoadjuvant MCV (Methotrexate, Cisplatin, Vinblastine) → then RT + CDDP same as RTOG 85-12
- Results: CR = 75%; OS5 = 62%.
«Old» evidence

RTOG 89-03: phase III- *(Shipley WU et al, JCO 1998)*
- 123 pts T2-T4aNx- maximal TURBT
- Randomized: - Neoadjuvant MCV x 2c then WPRT 39.6 Gy (1.8 Gy/fr)+ 2c CDDP *vs* WPRT+ CDDP only
- Restage after 4 wks: cystoscopy, biopsy, clinical exam under anesthesia, cytology
  → CR: RT boost 25.2 Gy (1.8 Gy/fr)+ 3°c CDDP
- Stopped early (projected 174 pts) due to MCV toxicity *(14% died)*. No significant change in CR, OS, DMFS

RTOG 95-06: phase II- *(Kaufman DS et al, Oncologist 2000)*- accelerated hypofractionated RT
- 34 pts T2-T4aNx
- TURBT→WPRT 3 Gy twice daily to 24 Gy+ concurrent 5-FU+ CDDP
- Restage after 4 wks: → CR: 2.5 Gy twice daily to 20 Gy+ concurrent 5-FU+ CDDP
  → No CR= cystectomy
- Results: CR= 67%, OS3= 83%, 66% of whom with intact bladder; G3/4= 20%, LR= 45%
«Old» evidence

RTOG 97-06: (Hagan MP et al, IJROBP 2003) - accelerated standard fractionation RT

- 52 pts T2-T4aN0
- TURBT \(\rightarrow\) within 6 wks twice daily RT: WPRT 21.6 Gy/13 fr (1.8 Gy/fr) a.m.+ bladder boost to 40.8 Gy/13 days (1.6 Gy/fr) p.m.+ concurrent CDDP
- Restage at 4 wks: biopsy+ cytology: \(\rightarrow\) CR: twice daily RT in 8 days: WPRT to 45.6 Gy and bladder to 64.8 Gy + CDDP + 3 cycles MCV
  \(\rightarrow\) No CR= cystectomy+ 3 cycles MCV
- Results: CR = 74%; OS3 = 61%, with intact bladder 48%; G3/4 RT+CT = 11%; only 40% pts received 3c MCV and G3= 41%, G4= 36%; total G3 and 4 adj CT = 77%! ; LR3= 27%, DM= 29%.

MGH: phase II- III (Shipley WU et al, Urology 2002)

- 190 pts T2-T4aNx treated: WPRT 40Gy+ 2c CDDP \(\rightarrow\) restage: CR \(\rightarrow\) RT boost 24-25 Gy + 3°c CDDP/No CR- Cystectomy
- Additional multidrug chemotherapy neoadjuvant/adjuvant
- Results: OS5= 54%(T2 62%; T3-4a 47%); DSS5= 63% (T2 74%, T3-4a 53%); DSS5 with intact bladder= 46% (T2 57%; T3-4a 35%). Only 35% needed cystectomy, including salvage for recurrence.
Table 2: Survival Outcomes by Patient and Tumor Characteristics

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>n</th>
<th>5 yr. Survival (%)</th>
<th>10 yr. Survival (%)</th>
<th>P Value</th>
<th>Disease-Specific Survival (%)</th>
<th>5 yr.</th>
<th>10 yr.</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>190</td>
<td>54 ± 7.5*</td>
<td>36 ± 8.3*</td>
<td></td>
<td>63 ± 7.5*</td>
<td>59 ± 8.0*</td>
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<td>NS</td>
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<tr>
<td>Age at entry (yr)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;75</td>
<td>155</td>
<td>55</td>
<td>40</td>
<td>0.04</td>
<td>65</td>
<td>60</td>
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<td>&gt;75</td>
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<td>51</td>
<td>22</td>
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<td>Sex</td>
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</tr>
<tr>
<td>Female</td>
<td>47</td>
<td>59</td>
<td>40</td>
<td>0.67</td>
<td>60</td>
<td>52</td>
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<tr>
<td>Male</td>
<td>143</td>
<td>52</td>
<td>34</td>
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<td>64</td>
<td>62</td>
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<td>Clinical stage</td>
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</tr>
<tr>
<td>T2</td>
<td>90</td>
<td>62</td>
<td>41</td>
<td>0.02</td>
<td>74</td>
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<td>T3-T4a</td>
<td>100</td>
<td>47</td>
<td>31</td>
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<td>53</td>
<td>52</td>
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<td>Hydronephrosis</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>163</td>
<td>55</td>
<td>37</td>
<td>0.15</td>
<td>64</td>
<td>61</td>
<td></td>
<td>0.09</td>
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<tr>
<td>Yes</td>
<td>27</td>
<td>48</td>
<td>29</td>
<td></td>
<td>53</td>
<td>49</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*95% confidence interval.

Table 3: Treatment Outcomes by Extent of TURBT

<table>
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<tr>
<th>Outcomes</th>
<th>All Patients</th>
<th>TURBT Visibly Complete</th>
<th>TURBT not Visibly Complete</th>
<th>Univariate P Value</th>
<th>Multivariate P Value**</th>
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</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>179</td>
<td>109</td>
<td>70</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>At 5 years</td>
<td>55%</td>
<td>59%</td>
<td>49%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 10 years</td>
<td>35%</td>
<td>38%</td>
<td>31%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease-specific survival (DSS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 5 years</td>
<td>64%</td>
<td>69%</td>
<td>58%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 10 years</td>
<td>60%</td>
<td>64%</td>
<td>54%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSS with bladder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 5 years</td>
<td>44%</td>
<td>51%</td>
<td>35%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 10 years</td>
<td>42%</td>
<td>47%</td>
<td>33%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Undergoing cystectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>37%</td>
<td>29%</td>
<td>50%</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Immediate (non-CR)</td>
<td>23%</td>
<td>16%</td>
<td>33%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salvage</td>
<td>14%</td>
<td>13%</td>
<td>17%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Includes only patients with TURBT status known.
**Includes T stage (T2 versus T3-T4a), grade, and gender.
«Old» evidence reproducibility

Erlangen: T2-T4Nx- (Rodel C et al, JCO 2002)

- 415 pts (89 pts T1 high risk, 326 pts T2-T4), 289 pts TMT
- WPRT to a median dose of 45 Gy (40-59.4 Gy), bladder boost to a median dose of 54 Gy (45-69.4 Gy)+ concurrent CDDP/CBDCA +/- 5FU
- Results: CR= 72%; LC10 in CR= 64%; DM10= 35%; salvage cystectomy for LR\( \rightarrow \) DSS10 = 45%; Toxicity: bladder.

Cluj (IOCN): T2-T4aNx

- 49 pts: TURBT \( \rightarrow \) WPRT 40-50 Gy (2Gy/fr)+ 2c CDDP
- Restage: CR: Bladder boost 20 Gy (2 Gy/fr)+ CDDP
  - No CR= cystectomy
- Results: OS3= 54%, with intact bladder 38%; LC with intact bladder= 53%; acute G3&4: 6% GI, 18% GU, late G3&4: GI= 2%, GU=8%
QoL after Radiotherapy

**MGH study** on 221 pts: urodynamics, QoL questionnaire:-(Zietmann AL et al, J Urol 2003)
- 78% had compliant bladders with normal capacity and flow parameters
- 85% had no urgency or only occasional urgency
- 25% had occasional to moderate bowel control symptoms
- 50% of men had normal erectile function

**Comparative cross-sectional study** – (Henningsohn L et al, Radiother Oncol 2002)
- Urinary function: 74% of RT pts had little or no urinary symptom distress
- Bowel function: 32% of RT pts and 24% of cystectomy pts presented moderate or much distress (statisticaly not significant) vs 9% in control groups (significant vs both)
- Sexual function: 38% intercourse in the previous month in RT arm vs 13% in cystectomy arm
348 pts cT2-T4a (1986-2006)
102 pts = 29% underwent radical cystectomies (60 pts for less than CR and 42 pts for recurrent invasive tumors)

Results: CR= 72% (78% for T2)
- DSS5= 64%, DSS10= 59%, DSS15= 57% (T2=74%, 67%, 63% vs T3-4: 53%, 49%, 49%)  
- OS5= 52%, OS10= 35%, OS15=22% (T2= 61%, 43%, 28% vs T3-4= 41%, 27%,16%)
- LR 10 non invasive= 29%, invasive= 16%, pelvic= 11%, distant= 32%
- Salvage cystectomy in 22% of pts with complete TURBT vs 42% with incomplete TURBT

- Bladder preserved in >70% pts
- Multivariate analysis: T stage and CR→ OS and DSS. Neoadjuvant CT- no effect
RTOG 99-06: phase I-II trial on 80 pts (Kaufman DS et al, Urology 2009), accelerated hyperfractionated RT
- TURBT → induction therapy in 13 days with concomitant boost: 1.6 Gy to the pelvis in the morning followed by 1.5 Gy to the bladder for the first five sessions (7.5 Gy), then to the tumor for eight sessions (12 Gy) in the afternoon for a total dose of 20.8 Gy to the pelvis, 28.3 Gy to whole bladder and 40.3 Gy to the tumor.
- Weekly CDDP and paclitaxel were included as radiation sensitizers.
- CR pts- consolidation CRT: 1.5 Gy pelvic RT twice daily to 24 Gy for a total dose of 44.8 Gy to the pelvic lymph nodes and 64.3 Gy to the tumor
- Adjuvant chemotherapy: 4 cycles Gemcitabine+ Cisplatin

CR= 81%, 36/80 pts died, 22 of bladder cancer → actuarial OS5= 56%, DSS5= 71%
Chemo- RT G3&4 acute toxicity= 26% (25% GI)
Adjuvant CT toxicity: G3= 46%, G4= 26%; 1 fatal hemorrhagic stroke
Late toxicity: G3 bladder 3/53 pts with fup > 2 year
«New» evidence

- 360 pts with median f-up of 69.9 mts
- Compared RT alone vs RT + concurrent MMC + 5 FU
- Pts were also randomly assigned to undergo whole bladder or modified -volume RT (the volume of bladder receiving full-dose RT was reduced) in a partial 2 by 2 factorial design

**Results:**
- LDFS 2y = 67% in CRT arm vs 54% in RT arm
- OS 5y = 48% in CRT arm vs 35% in the RT arm
- Acute G3&4 = 36% vs 27.5%, p = 0.07
- Late G3&4 = 8.3% vs 15.7%, p = 0.07

**RTOG 05-24**: phase I-II trial *(Michaelson MD et al, JCO 2014, ASCO abstract)*
- 68 pts: 21 pts Her2neu ≥2+ received concurrent weekly paclitaxel and weekly trastuzumab vs 47 pts Her2neu< 2+ with paclitaxel only. *Both groups received RT to 64.8 Gy/ 36 fr*
- G3 toxicity: 33% arm I vs 30% arm II, mostly marrow supression, diarrhea and hyponatriemia.
- Three pts died: colonic perforation, pneumonia, sudden death. RT completion rates: 72 vs 85%, CT completion rates: 52 vs 51%.
«New» evidence

RTOG Genitourinary Translational Research Group:
- Her2 expression was significantly associated with reduced tumor response
- EGFR expression intriguingly predicted improved overall and disease-free survival

(Chakravarti A et al, IJROBP 2005)

RTOG 05-24 trial was activated, using chemoradiotherapy with paclitaxel and trastuzumab for Her 2-neu overexpressing tumors (≥2+) whereas pts < 2+ will receive radiotherapy with weekly paclitaxel.

( Rodel C et al, JCO 2006)
Toxicity: analysis on 157 pts treated with combined modality treatment of 285 pts enrolled on RTOG 8903, 9506, 9706 and 9906 prospective trials- \textit{(Efstathiou et al, JCO 2009)}

Median follow up: 5.4 yrs (2-13.2 yrs)

G1= 22\%, G2= 10\%, G3= 7\% \textit{(5.7\% GU, 1.9\% GI)} ; G4&5= 0

G3 GU toxicity persisted in only 1 of 9 pts.

QoL: \textit{(Weiss C et al, JCO 2006)}- T1 pts(!) treated with trimodal therapy:

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
& Delighted & Pleased & Mostly Satisfied & About Equally Satisfied and Dissatisfied & Mostly Dissatisfied & Unhappy & Terrible \\
\hline
16.9\% & 53.5\% & 15.5\% & 12.7\% & 0\% & 1.4\% & 0\% & 0\% \\
\hline
\end{tabular}
\caption{Quality of Life Due to Urinary Symptoms}
\end{table}

\textit{NOTE.} Seventy-one of 72 patients alive with their native bladder completed the question: "If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?"
Evidence conclusion

<table>
<thead>
<tr>
<th>Treatment/comparison</th>
<th>Evidence</th>
<th>Level of evidence</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemoradiotherapy vs RT alone</td>
<td>Two RCTs report significant improvement in bladder tumor eradication.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Chemoradiotherapy preserves good bladder</td>
<td>Three QOL studies and RTOG protocols report good tolerance.</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>function</td>
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<tr>
<td>Complete TURBT with chemoradiotherapy</td>
<td>Three reports (one phase 3, two phase 2) show benefit.</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>Trimodality therapy vs immediate cystectomy</td>
<td>Comparison of three contemporary series of each treatment report similar 5- and 10-yr survival.</td>
<td>3</td>
<td>C</td>
</tr>
</tbody>
</table>

RT = radiation therapy; RCT = randomized controlled trial; QOL = quality of life; RTOG = Radiation Therapy Oncology Group; TURBT = transurethral resection of bladder tumor.

Gakis G et al, Eur Urol 2013
Controversies

1) **Comparison with radical cystectomy**: no randomized controlled trials!

Cystectomy series OS5 = 62-68% in centers of excellence *(Madersbacher S et al, JCO 2003)* vs
48-60% for trimodal therapy *(Kotwal S et al, IJROBP 2008; Mitin T et al Lancet Oncol 2013)*.

In the update of Medical Research Council neoadjuvant trial BA06 30894, which randomised pts
to neoadj CT or not followed by cystectomy, RT alone or RT+cystectomy the *OS rate of pts in the
cystectomy arm was higher than in the RT arm* *(Griffiths G et al, JCO 2011)*. But the
randomisation was for neoadjuvant CT and there was a *selection bias* in subsequent local
therapy choice.

*Different inclusion criteria* in cystectomy and chemo-RT, *clinical* (TURBT in RT-CT) vs *pathologic*
(cystectomy) *staging* also *limit the validity* of any comparison.

2) **Range of results**: study pooling various protocols *(Efstathiou JA et al, Eur Urol 2012)*:

   CSS 5= 60-65%; Range 50-82%
   OSS 5= 50%; Range 36-74%

Cause: differences in: inclusion period, patient selection, accuracy of staging, duration of follow-
up, chemotherapy and radiation regimens, use of neoadjuvant/adjuvant chemotherapy.
3) **TMT strategy:** maximal TURBT $\rightarrow$ RT+CT, *but* includes salvage cystectomy for pts without CR or with LR $\rightarrow$ more an *attempt* at bladder preservation than *definitive* bladder preservation – *(Ploussard G et al, Eur Urol 2014).* Early salvage cystectomy prevents a loss in survival!

4) **Split vs Continuous RT:** *Induction* therapy consists of radiation to a dose of 40 Gy. *Consolidation* is continued to a full dose of approximately 65 Gy after the restaging in *split course* trials *or the restage is deferred until* up to 1-3 months after the end of TMT in continuous course.

A *split course* is of some *radiobiologic concern* since tumor cell proliferation may occur during interruption $\rightarrow$ a retrospective analysis *(Wittlinger M et al, Radiother Oncol 2009)* suggests that tumor clonogenic *repopulation* in bladder cancer *accelerates* after a lag period of 5-6 wks after the start of treatment $\rightarrow$ dose increment of 0.36 Gy/day is required to compensate the repopulation!
Controversies

5) **Early vs late response evaluation:** *(Rodel C et al, JCO 2006)*
- The early-response evaluation selects non-responders as early as possible because the curative potential of cystectomy might decrease if delayed.
- The late-response evaluation may theoretically increase the chance of bladder preservation, because some slow-responders may maintain the bladder with late-response evaluation.

What would be the best approach?

6) **Radiation therapy fractionation regimens: Which is best?**
- RTOG 95-06 used *accelerated hypofractionation* (3 Gy bid first phase, 2.5 Gy bid second phase),
- RTOG 97-06 used *accelerated radiotherapy*, but *normal fractionation* (1.6-1.8 Gy),
- RTOG 85-12, 88-02 and 89-03 used *standard fractionation* (1.8-2 Gy, 1 fr/ day)
- MGH 1993-1994 used *accelerated hypefractionation* (1.25-1.5 Gy bid)

*Stuschke M et al, IJROBP 1997*, in a meta analysis based on pooled data of two old studies observed a significant improvement in local control and overall survival with hyperfractionated treatment and higher total dose. *Horwich A et al, Radiother Oncol 2005*, in a randomized trial suggested equivalent efficacy for twice daily vs once-daily treatments.

LoE → we have to await the results of RTOG 07-12 protocol to evaluate twice daily vs once daily regimens.
7) **What total dose?**
Generally 64-65 Gy but a meta-analysis of 15 radiation series with different fractionation schedules and total dose *Pos FJ et al, IJROBP 2006* found evidence for an **overall dose-response relationship** with an increase in local control by a factor of 1.44 to 1.47 for an increment in dose of 10 Gy → *indicates that a dose escalation could significantly improve local control.*

8) **Inclusion of pelvic lymph-nodes:** lymphadenectomy and number of nodes removed have proven to be independent predictors of survival after cystectomy *(Svatek R et al, Curr Urol Rep 2012)*
Generally in *induction phase RT is performed on pelvis* but *Tunio MA et al, IJROBP 2012,* on a randomised trial including 230 pts targeted only the bladder with 2 cm margins without affecting survival! The BC2001 trial *(James ND et al, N Engl J Med 2012)* comparing RT with or without CT (MMC+ 5 FU) targeted the bladder + 1.5 cm (2 cm around visible tumor)- *only 5% nodal recurrence!*
9) **Whole-bladder or partial bladder volume?** – BC 2001 trial also randomly assigned pts to undergo either whole-bladder or reduced bladder volume RT *(Huddart RA et al, IJROBP 2013)* - failed to demonstrate any side effect benefit from reducing the volume - the non-inferiority of locoregional control could not be concluded formally!

10) **Concurrent chemotherapy regimens:**

Analysis of 17 trials or retrospective studies - Cisplatin is the most active single agent, improves local control, no impact on OS *(Ploussard G et al, Eur Urol 2014; Sternberg C et al, Eur Urol 2013)*. **Different schedules = similar response rate.** Intensification - no definitive benefit. **Intra-arterial** - higher toxicity.

11) New technologies? Daily CT set-up has been shown to be superior to traditional EPID portals and to decrease treatment related toxicity (Foroudi F et al, Clin Oncol 2012)

= conserve the small bowel for future urinary diversions, if necessary!

Proton beam - only preliminary reports (Hata M et al, IJROBP 2006)

(Rodel C et al JCO 2006)
Controversies

12) **Role of Neoadjuvant chemotherapy:** evident role before cystectomy (Yafi FA et al, BJU Int 2011; Bekelman JE et al, Value Health 2013, Sternberg C et al, Eur Urol 2013) with a 5% improvement in OS 5 in a meta-analysis (Smith ZL et al BJU Int 2013). But:

a) BA06 30894 suggests a greater impact in LRFS before cystectomy (a significant 26% RR) than before RT (a non significant 9% RR) - (Griffiths G et al, JCO 2011)

b) limited completion rates because of high toxicity rates (77% G3&4 in RTOG 89-03, stopped early, with no significant difference in CR, DMFS, OS)

MGH did not find neoadjuvant chemotherapy to be a predictor of better survival (Efstathiou JA et al, Eur Urol 2012)


13) **Role of Adjuvant chemotherapy:**

Lower completion than for neoadjuvant treatment (45-70%) (Hagan MP et al, IJOBP 2003; Kaufman DS et al, Urology 2009) with high G3&4 toxicity.

But no survival outcomes from phase III trials evaluating adjuvant chemotherapy following trimodal therapy have yet been published (Ploussard G et al, Eur Urol 2014).
14) **Bladder preservation assessed** in different cohorts of inoperable pts: Medically inoperable patients vs surgically unresectable disease - in SWOG 9312 trial pts classified in the two categories→ medical comorbidities contraindicating general anesthesia or surgery were associated with poorer OS (Hussain MH et al, J Urol 2001); result confirmed by the GETUG 97-015 QoL assessment by Lagrange JL et al, IJROBP 2011.

15) **Real response rate?** Overall mean response rate 73% (Ploussard G et al, Eur Urol 2014). Defined by: absence of visible tumor+ absence of persistent pathologically proven bladder tumor on biopsy+ absence of tumor cells in the urine cytology→ **significantly better (by one third) survival rate than no CR. But:**
- Housset et al, JCO 1993 observed that only 45% of CR pts treated with cystectomy and without TMT completion were pT0 disease!!!
- Donat SM et al, J Urol 1996- MSKCC experience: 30% of pts following chemotherapy alone have residual disease after cystectomy that was not detected by preoperative TURBT.

Probably today we perform better, but what is the real response rate?- Downstaging rate between TURBT and cystectomy series ranging from 17-30% and presumed cT2 tumors treated by chemo-RT may persist as pT0/pT1 after TURBT (Svatek RS et al, BJU Int 2011; Yafi Fa et al, BJU Int 2011; Culp SH et al, J Urol 2014)
16) Predictors of response: identify the subgroup of bladder cancer pts that would not respond with lower CSS 5 = 20-40% (Efstathiou JA et al, Eur Urol 2012):

a) Carcinoma in situ (not in multivariable analysis…),

b) incomplete resection (20% loss in CR)- re-TURBT?,

c) locally advanced disease (T4),

d) urethral obstruction, hydronephrosis (occur in 10-35% of pts),

e) multiplicity (yes/no?),

f) Pathologic: clinical stage, high tumor grade, lymph node involvement, L-VI

à Limited number of pts meet the criteria! - 10-15% of medically operable pts (Smith ZL et al, BJU Int 2013) but- limited level of evidence and trimodal therapy is used as an alternative in non ideal candidates for cystectomy…
Controversies

17) **Follow-up**: requires: voided urine cytology, cystoscopy, CT/MR and prompt salvage cystectomy, risk adapted surveillance for distant metastasis and the upper tract.

Some authors suggest systematic tumor-site rebiopsy, bi-manual examination under general anesthesia with additional biopsies if negative cystoscopy but tumor growth underneath the TUR scar- no strong Level of evidence.

*How long?*

Risk of late metastatic or muscle –invasive bladder failure decrease in time and a flattening of CSS curve beyond the first 5 years after trimodal treatment, similar to cystectomy results, was observed in some trials *(Efstathiou JA et al, Eur Urol 2012)*

Other series report late recurrences beyond the first 5 years *(Herr HW et al, Br j Urol 1997; Zietman AL et al, Urology 2001; Weiss C et al, IJROBP 2008)*

*Lifelong cystoscopy follow up recommended!!!* *(Ploussard G et al, Eur Urol 2014)*

Costs and quality of life of follow-up?

18) **Late toxicity and QoL**: many toxicities were physician reported rather than patient reported. *Was late toxicity underestimated?* QoL studies are small with interpretation biases→LoE 2°

Many bladder cancer pts have *significant lower urinary tract symptoms* from *benign prostatic obstruction*- The symptoms worsen after irradiation? *(Ploussard G et al, Eur Urol 2014)*
Conclusions

1) Trimodal therapy is the primary bladder preservation strategy

2) Ideal candidates for bladder preservation should:

   a) have adequate renal function (allow Cisplatin based chemotherapy)
   b) have adequate bladder capacity and function
   c) be motivated, without history of pelvic radiation, accepting an ileal neobladder upon recurrence
   d) have organ confined tumor (cT2), small tumor size, absence of palpable mass
   e) have undergone a TUR of all visible tumor
   f) have no hydronephrosis
   g) have no extensive CIS
   h) have no multifocal disease
   i) have negative Her2-neu and positive EGFR
San Raffaele Scientific Institute

Thank you!