MUSCLE INVASIVE BLADDER CANCER: BLADDER CONSERVATION PROTOCOLS
OVERVIEW

INTRODUCTION

MANAGEMENT OF MUSCLE INVASIVE BLADDER CANCER

BLADDER CONSERVATION PROTOCOLS

QUALITY OF LIFE ASSESSMENT

RADIATION THERAPY TECHNIQUE

CONCLUSIONS
INTRODUCTION
What is Muscle Invasive Bladder Cancer?

**T Staging for Bladder tumors**
- **Tx** - Primary tumour cannot be assessed
- **T0** - No evidence of primary tumour
- **Ta** - Non-invasive papillary carcinoma
- **Tis** - Carcinoma in situ: ‘flat tumour’
- **T1** - Tumour invades subepithelial connective tissue
- **T2** - Tumour invades muscle
  - **T2a** - Tumour invades superficial muscle (inner half)
  - **T2b** - Tumour invades deep muscle (outer half)
- **T3** - Tumour invades perivesical tissue:
  - **T3a** - microscopically
  - **T3b** - macroscopically (extravesical mass)
- **T4** - Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
  - **T4a** - Tumour invades prostate stroma, seminal vesicles, uterus, or vagina
  - **T4b** - Tumour invades pelvic wall or abdominal wall
Extent of Primary Bladder Cancer
AJCC - 2010
N0 - No regional lymph node metastasis
N1 - Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2 - Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3 - Metastasis in a common iliac lymph node(s)
## Correlation of pathological T stage with LN metastases

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
<td>191</td>
<td>686</td>
<td>1054</td>
<td>507</td>
<td>290</td>
<td>176</td>
<td>418</td>
<td>788</td>
<td>2720</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% of LN metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT0, pTis, and pT1</td>
</tr>
<tr>
<td>pT2a</td>
</tr>
<tr>
<td>T2b</td>
</tr>
<tr>
<td>pT3</td>
</tr>
<tr>
<td>pT4</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Reference: Lymphadenectomy in management of Invasive Bladder Cancer; Ramy F. Youssef and Ganesh V. Raj; International Journal of Surgical Oncology; Volume 2011
### STAGE GROUPING FOR BLADDER TUMORS

<table>
<thead>
<tr>
<th>Stage Grouping (N)</th>
<th>T1</th>
<th>T2a</th>
<th>T2b</th>
<th>T3a</th>
<th>T3b</th>
<th>T4a</th>
<th>T4b</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>I</td>
<td>II</td>
<td>II</td>
<td>III</td>
<td>III</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>N1</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>N2</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>N3</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>M1</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>Stage</td>
<td>Relative 5 year survival rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>--------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>88%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>63%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>46%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>15%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MANAGEMENT OF MUSCLE INVASIVE BLADDER CANCER
Staging workup

Cystoscopy

Transurethral Resection of Bladder Tumor (TURBT) – For pathological diagnosis

Imaging:
- Ultrasound Abdomen/Pelvis
- CT scan
- MRI

Bone scan
Goals of Treatment

- Cure patient
- Optimize survival
- Prevention of Pelvic failure and Distant metastasis
- Functional Urinary reservoir and High Quality Of Life (QoL)
MUSCLE INVASIVE BLADDER CANCER

RADICAL CYSTECTOMY WITH RECONSTRUCTION

BLADDER CONSERVATION PROTOCOLS

RELAPSE OR PROGRESSION
Surgery

- Treatment of choice
- Radical cystectomy with pelvic lymphadenectomy is considered the standard of care.
  - Includes perivesicular fat and urethra
  - In women, the anterior wall of the vagina, the ovary and the uterus are also taken
  - In men, the prostate and seminal vesicles are taken
- Bladder reconstruction: Neo Bladder or Ileal Conduit
NCCN Guidelines Version 1.2014
Bladder Cancer

CLINICAL STAGING

Radical cystectomy\(^b\) and strongly consider neoadjuvant cisplatin-based combination chemotherapy (category 1)
or
Segmental (partial) cystectomy\(^b\) (highly selected patients with solitary lesion in a suitable location: no Tis) and consider neoadjuvant cisplatin-based combination chemotherapy\(^m\)
or
Bladder preservation\(^b\) following maximal TURBT with concurrent chemotherapy\(^m\) + RT\(^m\) (category 2B)
or
For patients with extensive comorbid disease or poor performance status: TURBT alone\(^b\) or RT + chemotherapy\(^m, n\) or Chemotherapy alone\(^m\)

Reassess tumor status 3 weeks after 40-45 Gy or 2-3 months after full dose (60-65 Gy)

ADJUVANT TREATMENT

Consider adjuvant chemotherapy\(^m\) (category 2B) based on pathologic risk (pT3-4 or positive nodes) if no neoadjuvant treatment given
Consider adjuvant RT\(^m\) (category 2B) or chemotherapy\(^m, n\) (category 2B) based on pathologic risk (pT3-4, positive nodes, positive margin, or high-grade) if no neoadjuvant treatment given

Observation or Completion of RT\(^m\) up to 66 Gy
Cystectomy\(^b, f\) (preferred)

Reassess tumor status 2-3 months after treatment

No tumor

Observation

No tumor

Tumor

Resectable

Cystectomy\(^b, f\) (preferred)

Consider completion of RT with alternative radiosensitizing chemotherapy\(^m, n\) and/or Alternative chemotherapy\(^m\)

Unresectable or not a surgical candidate

See BL-6 (follow treatment as for T4b with positive nodes)
BLADDER CONSERVATION PROTOCOLS
Methods of Conservation

Conservative Surgery
  ◦ Partial Cystectomy
  ◦ Trans Urethral Resection of Bladder Tumor (TURBT) alone

Radical External Beam Radiation Therapy

Interstitial Brachytherapy

Combined modality treatment
  ◦ Chemotherapy and Local Therapy
  ◦ Trimodality Therapy
No trials have till date directly compared Cystectomy and Bladder-preservation
Bladder Conservation approach

2 main concerns about bladder preservation compared with radical cystectomy:

◦ **Toxicity of radiation therapy** on bladder function

◦ **Field cancerization effect**:
  ◦ 30-50% of patients experience a local recurrence (~50% invasive and ~50% superficial), either in the area of tumor or in a different part of bladder
  ◦ If bladder preservation is selected, **close surveillance is critical**
Partial Cystectomy

6% to 19% of patients with primary, muscle-invading bladder cancer are potential candidates.

Local recurrence rates: 38% to 78%.

Half of the recurrences appear in the first year and two thirds by 2 years.
Partial Cystectomy

Careful patient selection
- Solitary lesion
- Located in a region of the bladder that allows for complete excision with a 2-cm tumor-free margin (Bladder dome)
Partial Cystectomy

Contraindications:

- Association with *carcinoma in situ* in other sites of the bladder
- Prostatic urethral involvement
- Prior recurrent bladder or upper tract tumors
- Bladder neck or trigone tumors (Ureteral reimplantation would be required to achieve an adequate margin)
Transurethral Resection of Bladder Tumor (TURBT) alone

Clinical complete response rates (assessed cystoscopically with repeat biopsy 3 weeks after initial TURBT) for T2 and T3 cancers: 10% to 20%

5 year Overall Survival - 27%

TURBT alone is not sufficient as monotherapy in muscle-invading bladder cancer
Radical External Beam Radiation Therapy

Historically, External Beam Radiation therapy was used as monotherapy for muscle invasive bladder cancer which were medically inoperable

5-year local control rate
- 31% to 50% for the entire patient population
- 49% to 79% for the subgroup of patients with a complete response
### External Beam Irradiation Alone for Muscle-Invasive Bladder Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. Patients</th>
<th>T2</th>
<th>T3 (T3a/T3b)</th>
<th>T4</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duncan</td>
<td>1986</td>
<td>963</td>
<td>40</td>
<td>26</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>Blandy</td>
<td>1988</td>
<td>614</td>
<td>27</td>
<td>38</td>
<td>9</td>
<td>—</td>
</tr>
<tr>
<td>Jenkins</td>
<td>1988</td>
<td>182</td>
<td>46</td>
<td>35</td>
<td></td>
<td>40</td>
</tr>
<tr>
<td>Gospodarowicz</td>
<td>1991</td>
<td>355</td>
<td>50</td>
<td>(38/28)</td>
<td></td>
<td>46</td>
</tr>
<tr>
<td>Johnson</td>
<td>1991</td>
<td>319</td>
<td>31</td>
<td>16</td>
<td>6</td>
<td>28</td>
</tr>
<tr>
<td>Davidson</td>
<td>1990</td>
<td>709</td>
<td>49</td>
<td>28</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Greven</td>
<td>1990</td>
<td>116</td>
<td>59</td>
<td>10</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Smaaland</td>
<td>1991</td>
<td>146</td>
<td>26</td>
<td>10†</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Fossa</td>
<td>1993</td>
<td>308</td>
<td>38‡</td>
<td>14§</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>Pollack</td>
<td>1994</td>
<td>135</td>
<td>42</td>
<td>20</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>Moonen</td>
<td>1998</td>
<td>379</td>
<td>25</td>
<td>17</td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>Borgaonkar</td>
<td>2002</td>
<td>163</td>
<td>48</td>
<td>26</td>
<td></td>
<td>45</td>
</tr>
</tbody>
</table>
Radical External Beam Radiation Therapy

Factors having significant favourable effect on local control with Radiotherapy:

- Early clinical stage (T2 and T3a)
- Absence of ureteral obstruction
- Complete response
- Visibly complete TURBT
- Absence of coexisting carcinoma in situ
- Small tumor size (<5 cm maximum diameter)
- Solitary tumors
- Tumor configuration (Papillary / Sessile)
- Haemoglobin level (>10 mg/dL)
Interstitial Brachytherapy

It has been combined with EBRT to provide a radiation boost to the primary tumor

Appropriate candidates for brachytherapy:

- Solitary TCC with a diameter of less than 5 cm
- Stage T1 disease (with high grade) to T3a disease (muscle invasion but no extension through the wall)
### Treatment Outcome for Brachytherapy in Combination with External Beam Irradiation

<table>
<thead>
<tr>
<th>Study*</th>
<th>Local Control (5-yr)</th>
<th>Overall Survival (5-yr)</th>
<th>Disease-Specific Survival (5-yr)</th>
<th>Survival with Preserved Bladder (5-yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moonen&lt;sup&gt;181&lt;/sup&gt;</td>
<td>84%</td>
<td>86%</td>
<td>—</td>
<td>90%</td>
</tr>
<tr>
<td>Wijnmaalen I&lt;sup&gt;182&lt;/sup&gt;</td>
<td>88%</td>
<td>48%</td>
<td>69%</td>
<td>—</td>
</tr>
<tr>
<td>Van der Steen&lt;sup&gt;121&lt;/sup&gt;</td>
<td>70%</td>
<td>—</td>
<td>T1 80% T2 60%</td>
<td>—</td>
</tr>
<tr>
<td>Mazeron&lt;sup&gt;184&lt;/sup&gt;</td>
<td>77%</td>
<td>72%</td>
<td>73%</td>
<td>95%</td>
</tr>
<tr>
<td>Rozan&lt;sup&gt;185&lt;/sup&gt;</td>
<td>—</td>
<td>67%</td>
<td>83%</td>
<td>96.1%</td>
</tr>
<tr>
<td>Pernot&lt;sup&gt;196&lt;/sup&gt;</td>
<td>73%</td>
<td>71%</td>
<td>77%</td>
<td>—</td>
</tr>
<tr>
<td>Pos&lt;sup&gt;187&lt;/sup&gt;</td>
<td>73%</td>
<td>62%</td>
<td>73%</td>
<td>90%</td>
</tr>
</tbody>
</table>
Interstitial Brachytherapy

Five-year local control rates for selected patients treated with brachytherapy in combination with EBRT appear to be excellent
  ◦ 70% and 90%

High rates of bladder preservation

Acute toxicity:
  ◦ Fistula formation with wound leakage
Chemotherapy and Local Therapy

**Chemotherapy and Conservative Surgery**
- Chemotherapy has been used in combination with TURBT in highly selected population
- 5-year local control rates of up to 48%
- Complete response rates after chemotherapy and TURBT range from 45% to 54%
- Studies have shown that addition on MVAC to TURBT gives local control advantage over either alone
Chemotherapy and Conservative Surgery

- In a highly selected patient population, chemotherapy followed by partial cystectomy in conjunction with pelvic lymphadenectomy has been used in an attempt to spare the bladder.

- 5-year survival rate is high ~ 50%

- Bladder preservation is possible in less than half of these patients.
Chemotherapy and Conservative Surgery

Criteria to be considered for such treatment:
- Complete or major response to chemotherapy
- Solitary lesion in the dome or the anterior wall of the bladder
- No history of prior invasive bladder cancer
- No CIS
- Good bladder capacity
Chemotherapy and Radical Local Therapy

- **Neoadjuvant chemotherapy** prior to definitive local therapy
  - Advantage:
    - To assess the response of the primary lesion
    - For tumor down staging
  - Neoadjuvant chemotherapy seems to improve survival rates only marginally
  - There is significant impact in terms of tumor down staging
  - Complete clinical response - as evaluated by repeat cystoscopy and biopsy after chemotherapy, ranges from 25% to 57%
Neoadjuvant Chemotherapy

- Response to Neoadjuvant therapy certainly seems to predict survival

- 5 year Survival rates
  - 62% to 75% among responders
  - 20% to 26% among non responders
Randomized Phase III Trials of Neoadjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Neoadjuvant Arm</th>
<th>Standard Arm</th>
<th>No. Patients</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cisplatin Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia/UK(^{205})</td>
<td>DDP/RT</td>
<td>RT</td>
<td>255</td>
<td>No difference</td>
</tr>
<tr>
<td>Canada/NC(^{215})</td>
<td>DDP/RT or preoperative RT + cystectomy</td>
<td>RT or preoperative RT + cystectomy</td>
<td>99</td>
<td>No difference</td>
</tr>
<tr>
<td>Spain (CUETO)(^{207})</td>
<td>DDP/cystectomy</td>
<td>Cystectomy</td>
<td>122</td>
<td>No difference</td>
</tr>
<tr>
<td><strong>Combination Chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC/MRC(^{210})</td>
<td>MCV/RT or cystectomy</td>
<td>RT or cystectomy</td>
<td>976</td>
<td>5.5% difference in favor of MCV</td>
</tr>
<tr>
<td>RTOG(^{209})</td>
<td>MCV/RT + C</td>
<td>RT + C</td>
<td>126</td>
<td>No benefit</td>
</tr>
<tr>
<td>SWOG Intergroup(^{216})</td>
<td>MVAC/cystectomy</td>
<td>Cystectomy</td>
<td>317</td>
<td>Benefit with MVAC</td>
</tr>
<tr>
<td>Italy (GUONE)(^{214})</td>
<td>MVAC/cystectomy</td>
<td>Cystectomy</td>
<td>206</td>
<td>No difference</td>
</tr>
<tr>
<td>Italy (GISTV)(^{208})</td>
<td>MVEC/cystectomy</td>
<td>Cystectomy</td>
<td>171</td>
<td>No difference</td>
</tr>
<tr>
<td>Genoa(^{211})</td>
<td>DDP/5-FU/RT/cystectomy</td>
<td>Cystectomy</td>
<td>104</td>
<td>No difference</td>
</tr>
<tr>
<td>Nordic 1(^{206})</td>
<td>ADM/DDP/RT/cystectomy</td>
<td>RT/cystectomy</td>
<td>325</td>
<td>No difference, 15% benefit with ADM + DDP in T3-T4a</td>
</tr>
<tr>
<td>Nordic 2(^{212})</td>
<td>MTX/DDP/cystectomy</td>
<td>Cystectomy</td>
<td>317</td>
<td>No difference</td>
</tr>
<tr>
<td>Abol-Enein(^{213})</td>
<td>CarboplatinMV/cystectomy</td>
<td>Cystectomy</td>
<td>194</td>
<td>Benefit with carboplatinMV</td>
</tr>
</tbody>
</table>
Absolute Survival benefit of 6.5% for Neoadjuvant chemotherapy
Neoadjuvant Chemotherapy

There have been two large randomized Neoadjuvant chemotherapy studies in muscle-invasive bladder cancer – SWOG Intergroup study and MRC/EORTC study
  ◦ Both showing significant survival advantage

However, Neoadjuvant chemotherapy is still not considered as standard of care for Muscle Invasive Bladder cancer – Unlike other malignancies
Neoadjuvant Chemotherapy

Reasons:

- Selection of patients in the trial setting is different from the patients seen in clinical setting
- Most are old with impaired renal functioning
- Also, regimes require in-patient treatment with hydration – Affects Quality of Life
Trimodality Therapy

- Combination of Limited Resection, Chemotherapy, and Irradiation in Bladder Preservation
- Best results till date in bladder preservation when the 3 modalities are combined together
- Based on both single institutional data and large randomised control trials
PIONEERING SINGLE INSTITUTION STUDIES OF TRIMODALITY TREATMENT

**MGH**
- TURBT
- RT + CHT (Induction)
- Restaging cystoscopy
  - Complete Response
  - Incomplete Response
  - RT + CHT (Consolidation)
  - Cystectomy
- Restaging cystoscopy
  - NED
  - FU
  - Recurrence
  - Cystectomy

**ERLANGEN**
- TURBT
- RT + CHT (Whole treatment)
- Restaging cystoscopy
  - Complete Response
  - Incomplete Response
- FU
  - NED
  - FU
  - Recurrence
  - Cystectomy
  - Cystectomy
<table>
<thead>
<tr>
<th>Investigators</th>
<th>Stage</th>
<th>Treatment</th>
<th>No. of Patients</th>
<th>Survival With Intact Bladder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shipley et al</td>
<td>T2-T4a</td>
<td>TURBT + chemotherapy + radiation therapy</td>
<td>190</td>
<td>45% (10-yr DSS with intact bladder)</td>
</tr>
<tr>
<td>Rödel et al</td>
<td>T1-T4</td>
<td>TURBT + chemotherapy + radiation therapy</td>
<td>415</td>
<td>42% (5-yr OS with intact bladder)</td>
</tr>
<tr>
<td>Housset et al</td>
<td>T2-T4</td>
<td>TURBT + chemotherapy + radiation therapy</td>
<td>54</td>
<td>Not reported (62% 3-yr DSS)</td>
</tr>
<tr>
<td>Sternberg et al</td>
<td>T2-T4</td>
<td>Neoadjuvant M-VAC + TURBT</td>
<td>104</td>
<td>44% (5-yr OS, with intact bladder)</td>
</tr>
<tr>
<td>Herr</td>
<td>T2</td>
<td>TURBT alone</td>
<td>99</td>
<td>57% (10-yr with intact bladder; includes only patients selected for bladder sparing)</td>
</tr>
</tbody>
</table>

TURBT = transurethral resection of the bladder tumor
M-VAC = methotrexate, vinblastine, doxorubicin, and cisplatin
DSS = disease-specific survival
OS = overall survival
<table>
<thead>
<tr>
<th>RTOG Study</th>
<th>Radiation Therapy</th>
<th>Radiosensitizing Chemotherapy</th>
<th>No. of Patients</th>
<th>5-Year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>85-12³</td>
<td>Daily (64.8 Gy)</td>
<td>Cisplatin</td>
<td>42</td>
<td>52</td>
</tr>
<tr>
<td>88-02³</td>
<td>Daily (64.8 Gy)</td>
<td>Cisplatin</td>
<td>91</td>
<td>62</td>
</tr>
<tr>
<td>89-03³</td>
<td>Daily (64.8 Gy)</td>
<td>Cisplatin</td>
<td>123</td>
<td>49</td>
</tr>
<tr>
<td>95-06⁷</td>
<td>Hypofractionated</td>
<td>Cisplatin and 5-fluorouracil</td>
<td>34</td>
<td>N/A</td>
</tr>
<tr>
<td>97-06³</td>
<td>Hyperfractionated</td>
<td>Cisplatin</td>
<td>52</td>
<td>N/A</td>
</tr>
<tr>
<td>99-06</td>
<td>Hyperfractionated</td>
<td>Cisplatin and paclitaxel</td>
<td>84</td>
<td>N/A</td>
</tr>
<tr>
<td>Trial</td>
<td>Induction RT</td>
<td>Induction chemo</td>
<td>Planned break</td>
<td>Consolidative RT</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------</td>
<td>-----------------------</td>
<td>---------------</td>
<td>------------------</td>
</tr>
<tr>
<td>RTOG 99-06</td>
<td>40.3/26</td>
<td>cisplatin/taxol</td>
<td>3 weeks</td>
<td>24/16</td>
</tr>
<tr>
<td>RTOG 97-06</td>
<td>40.8/24</td>
<td>cisplatin</td>
<td>3 weeks</td>
<td>24/16</td>
</tr>
<tr>
<td>RTOG 95-06</td>
<td>24/8</td>
<td>cisplatin/5-FU</td>
<td>3-4 weeks</td>
<td>20/8</td>
</tr>
<tr>
<td>RTOG 89-03</td>
<td>39.6/22</td>
<td>±MCV x2 alone, then cisplatin</td>
<td>4 weeks</td>
<td>25.2/14</td>
</tr>
<tr>
<td>RTOG 88-02</td>
<td>39.6/22</td>
<td>MCV x2 alone, then cisplatin</td>
<td>2 weeks</td>
<td>25.2/14</td>
</tr>
<tr>
<td>RTOG 85-12</td>
<td>40/20</td>
<td>cisplatin</td>
<td>2 weeks</td>
<td>24/12</td>
</tr>
<tr>
<td>Harvard; 1993</td>
<td>39.6/22</td>
<td>MCV x2 alone, then cisplatin</td>
<td>2 weeks?</td>
<td>25.2/14</td>
</tr>
<tr>
<td>Paris; 1993</td>
<td>24/8</td>
<td>cisplatin/5-FU</td>
<td>6 weeks</td>
<td>20/8</td>
</tr>
</tbody>
</table>
# Survival Data of Radical Cystectomy and Selective Bladder Preservation

<table>
<thead>
<tr>
<th>Series</th>
<th>Year</th>
<th>Category</th>
<th>No. Patients</th>
<th>5-yr</th>
<th>10-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USC</td>
<td>2001</td>
<td>pT2-pT4a</td>
<td>633</td>
<td>48%</td>
<td>32%</td>
</tr>
<tr>
<td>MSKCC</td>
<td>2001</td>
<td>pT2-pT4a</td>
<td>181</td>
<td>36%</td>
<td>27%</td>
</tr>
<tr>
<td>SWOG/ECOG/CALGB</td>
<td>2002</td>
<td>cT2-cT4a</td>
<td>317</td>
<td>49%</td>
<td>34%</td>
</tr>
<tr>
<td>Selective Bladder Preservation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University of Erlangen</td>
<td>2002</td>
<td>cT2-cT4a</td>
<td>326</td>
<td>45%</td>
<td>29%</td>
</tr>
<tr>
<td>MGH</td>
<td>2009</td>
<td>cT2-cT4a</td>
<td>348</td>
<td>52%</td>
<td>35%</td>
</tr>
<tr>
<td>RTOG</td>
<td>1998</td>
<td>cT2-cT4a</td>
<td>123</td>
<td>49%</td>
<td></td>
</tr>
</tbody>
</table>
KAPLAN – MEIER GRAPH OF SURVIVAL IN MUSCLE INVASIVE BLADDER CANCER

Also included Non Muscle Invasive Bladder Tumors

Radical Cystectomy alone
KAPLAN - MEIER GRAPH SHOWING IMPROVED LOCOREGIONAL DISEASE FREE SURIVAL WITH ADDITION OF CONCURRENT CHEMOTHERAPY IN MUSCLE INVASIVE BLADDER CANCER: BC2001 TRIAL
Trimodality Treatment

Ideal candidates for Bladder preservation with Trimodality treatment:

- Solitary T2 or early T3 tumors < 6 cm
- No tumor-associated hydronephrosis
- Tumors allowing a visibly complete TURBT
- Invasive tumors not associated with extensive carcinoma in situ
- Adequate renal function to allow cisplatin concurrent with radiation
- TCC histology
- Willing for being on close surveillance
- Willing for cystectomy in case of progression or relapse
Bladder Preservation

Success rate of bladder preservation:
- TURBT alone - 20% free of invasive bladder recurrence
- Radiation Therapy alone - 41%
- Chemotherapy alone - 19%

Complete response rate:
- Radiation Therapy alone - 45%
- Chemotherapy alone - 27%
- TURBT + chemotherapy - 51%
- TURBT + chemo irradiation - 70-80%
Those involved in the management of muscle invasive bladder cancer should “take a leaf from the book” on sarcoma and breast cancer management, where multidisciplinary collaborative approach with knowledge and respect for the benefits and shortcomings of individual treatment modalities has led to a **standard of organ preservation**.
QUALITY OF LIFE ASSESSMENT
221 patients, T2-4Nx-0M0 bladder cancer, Treated on protocols 1986-2000, median follow up: 6.3 years 
Urodynamic study, QOL questionnaire

- 78% have compliant bladders with normal capacity and flow parameters
- 85% have no urgency or occasional urgency
- 25% have occasional to moderate bowel control symptoms
- 50% of men have normal erectile function
157 patients with Bladder Preservation who survived 2 to 13 years (Median follow-up - 5.2 years)

- 22% - Grade 1
- 10% - Grade 2
- 7% - Grade 3 (5.7% GU, 1.9% GI)
- 0% - Grade 4
- 0% - Grade 5
Conclusions: Concurrent chemoradiation therapy allowed bladder preservation with tumor control for 67% patients at 8 years. Quality of life and quality of bladder function were satisfactory for 67% of patients.

This prospective evaluation supports the published retrospective data suggesting good QoL for those invasive bladder cancer patients managed by bladder preservation after TUR and concurrent chemoradiotherapy. The most frequently reported sequela was an increase in moderate urinary frequency.
Patient quality of life evaluation according to the QLQ-C30 scale
QoL Assessment: Radical Cystectomy versus Organ Preservation Therapy

2 comparative cross sectional studies available:

**Trento, Italy 1996:**

Retrospective study

59 patients, treated conservatively (49%) or with cystectomy (51%), who returned questionnaire (~65% rate in both)

Quality of life is better after conservative therapy than after cystectomy

QoL Assessment : Radical Cystectomy versus Organ Preservation Therapy

Karolinska, Sweden 2002:

58 patients treated with radical RT before 1995 (63-68 Gy split course)

Compared with 251 patients with radical cystectomy and 310 general population patients

- Three quarters of long-terms survivors after radical RT had functioning urinary bladder with little or no distress from urinary tract.
- Prevalence of sexual dysfunction was lower than after surgery, with comparable GI dysfunction

Quality of Life after Bladder conservation Approach

<table>
<thead>
<tr>
<th>ADVANTAGE OF COMBINED MODALITY TREATMENT</th>
<th>EQUIVALENCE TO SURGERY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological adjustment</td>
<td>Social functioning</td>
</tr>
<tr>
<td>Physical well-being</td>
<td>Bowel function</td>
</tr>
<tr>
<td>Sexual function</td>
<td></td>
</tr>
<tr>
<td>Urinary function</td>
<td></td>
</tr>
</tbody>
</table>
RADIATION THERAPY
TECHNIQUE
Modalities of External Beam Radiation Therapy

2D Conventional

3D Conformal Radiation therapy

Intensity Modulated Radiation Therapy (IMRT)
Patient Position and Immobilization

- The patient should be planned and treated in the same position
  - Supine with arms on their chest
  - Knee and ankle immobilization should be used to ensure patient positioning is reproducible.
- The rectum should be empty of flatus and faeces.
- Patients should be asked to empty the bladder 15 minutes prior to scan.
- While breathing normally, the patient should have a CT scan performed with 3 to 5-mm slice spacing.
- Neither intravenous nor oral contrast is beneficial.
Radiation Therapy Volumes

**Gross tumor volume** - Should integrate information from the staging CT or MRI as well as the TURBT.

- The use of fiducial markers or contrast medium such as lipiodol at the time of TURBT has been explored - May help identify tumor for image-guided adaptive radiotherapy.

- There are few data on the optimal radiotherapy volume.

**Planning target volume** : The whole bladder with a 1.5-cm margin plus extravesical extent of tumor with a 2-cm margin.
Radiation Therapy Volumes

No data to support the routine irradiation of radiologically negative lymph nodes

Nodal relapse rate in the BC2001 trial
- 3% in the chemo radiotherapy arm
- 6% in radiotherapy only arm
Radiation Therapy Volumes

All planning and treatment should be carried out with the bladder empty
- To minimize the risk of geographic miss
- To keep the treated volumes as small as possible

Patients with significant residual volumes post voiding should be considered for planning and treatment with a catheter *in situ*
Radiation Therapy Doses

Optimal radiotherapy schedule is yet to be established

Most commonly used schedule: **SPLIT SCHEDULE**
- 40-45 Gy in 1.8-2 Gy/fraction – Initially
- If good response – To go to radical dose of 64-66 Gy

Hypofractionation (55 Gy in 20 fractions) – Practiced in some centres in UK
Hyperfractionation (Twice daily RT) – Also tried and used in trials
CONCLUSIONS
Conclusions

- Combined modality therapy achieves a complete response and preserves the native bladder in ~70% of patients, while offering long-term survival rates comparable to contemporary radical cystectomy series.

- QoL studies have demonstrated that the retained native bladder functions well and long-term toxicity of chemo irradiation to pelvic organs is relatively low.

- These results support the acceptance of modern bladder-sparing Trimodality therapy for selected patients as a proven alternative to cystectomy.
Conclusions

• The optimal regimen of combined chemo irradiation, as well as the addition of rational molecular targeted therapy and personalized treatment selection, continues to be investigated.

• The contribution of selective bladder sparing therapy to the quality of life of patients represents a unique opportunity for urologic surgeons, radiation oncologists, and medical oncologists to work hand in hand in a truly multidisciplinary effort.