Bladder Sparing Treatment of Muscle Invasive Bladder Cancer

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High-Risk Invasive and Muscle-Invasive BCa

Radical cystectomy + bilateral pelvic lymph node dissection +/- neo-adjuvant chemotherapy

= gold standard

Rationale:
1) best local disease control and long-term survival
2) decreasing morbidity and mortality
3) allows for accurate pathologic staging
Long term results:
Radical Cystectomy alone

<table>
<thead>
<tr>
<th>Reference</th>
<th>N=</th>
<th>Stage</th>
<th>10Y LC</th>
<th>10Y DM</th>
<th>5Y</th>
<th>10Y OS</th>
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<tbody>
<tr>
<td>Stein et al (USC) 2001</td>
<td>1,054</td>
<td>≤T2b,N0</td>
<td>93%</td>
<td>13%</td>
<td>78%</td>
<td>56%</td>
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<td>T3-T4, N0</td>
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<td>N+</td>
<td>87%</td>
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<td>(24%)</td>
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<tr>
<td>Shariat et al (UTSW) 2006</td>
<td>978</td>
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<td>17%</td>
<td>71%</td>
<td>58%</td>
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<td>T3-T4,N0</td>
<td>89%</td>
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<td>N+</td>
<td>87%</td>
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<td>(24%)</td>
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<td>Hautmann et al (Ulm) 2007</td>
<td>788</td>
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<td>(63%)</td>
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<td>45%</td>
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<td>T3-T4,N0</td>
<td>84%</td>
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<td>(18%)</td>
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</table>
## Bladder Sparing?

<table>
<thead>
<tr>
<th>Recommendations for bladder-sparing treatments for localised disease</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not offer transurethral resection of bladder tumour alone as a curative treatment option. Most patients will not benefit.</td>
<td></td>
</tr>
<tr>
<td>Do not offer pre-operative radiotherapy to improve survival.</td>
<td>A</td>
</tr>
<tr>
<td>Do not offer radiotherapy alone as primary therapy for localised bladder cancer.</td>
<td>B</td>
</tr>
<tr>
<td>Offer pre-operative radiotherapy for operable MIBC since it can result in tumour downstaging after 4-6 weeks.</td>
<td>C</td>
</tr>
<tr>
<td>Do not offer chemotherapy alone as primary therapy for localised bladder cancer.</td>
<td>A</td>
</tr>
<tr>
<td>Offer surgical intervention or multimodality treatments as primary curative therapeutic approaches since they are more effective than radiotherapy alone.</td>
<td>B</td>
</tr>
<tr>
<td>Offer multimodality treatment as an alternative in selected, well-informed and compliant patients, especially for whom cystectomy is not an option.</td>
<td>B</td>
</tr>
</tbody>
</table>
Bladder Sparing

• For Who?
  • Elderly patients?
  • Unique tumor
  • IntraDiverticula tumor

• Which Approach?
  • Radical TransUrethral Bladder Resection
  • Partial cystectomy + BPLND
  • Radiation therapy alone?
  • TUR + radiation therapy + chemotherapy

• For which oncological outcomes?
1/3 patient had disease recurrence/progression
45% patients required salvage RC
Radical Trans Urethral Resection

- Not in dome or high posterior wall
- Size $\leq 3$cm
- No CIS and unifocal
- T2 (no palpable mass)
- Re-resect at 3 months to assure complete removal

Disadvantages
- No pathologic node staging
- Lifelong surveillance - up to 45% require cystectomy
**Partial Cystectomy and pelvic LND**

- Strict inclusion criteria
  - Primary tumor, no CIS, and unifocal
  - Location suitable for bladder preservation – dome
  - Bladder tumor in a diverticulum

- + bilateral pelvic lymphadenectomy

- High relapse rate despite strict inclusion criteria

- Possible use: patients with CR (or PR) to neo-adjuvant chemotherapy

- Preferred for patients with urachal adenocarcinoma – resect posterior rectus sheath, urachus, and bladder dome en bloc
Partial Cystectomy and pelvic LND

IntraDiverticula Cancer / Partial Cystectomy

• 60% pT3a
• 33% R1
• 50% disease free survival

± Lymph node dissection
  = 3% pN1

± Radiation – chemo therapies

Golijanin, J Urol. 2003
Tamas, Arch Pathol Lab Med. 2009
Montague DK et al. J Urol. 1976
Aubert, J Urol (Paris). 1982
Dondalski, AJR, Am J Roentgenol. 1993
Rozet, Prog Urol. 1997
Radiation therapy alone

Radiation therapy as single modality:
inferior local and distant control rates
5-yrs disease-specific survival : 22-32%

Duncan et al., 1986, Gospad et al., 1989, Pollack et al., 1994

Stein et al: 1054 cystectomy patients
5- and 10-YS 60% and 43%

Rödel et al: 415 RT patients
5- and 10-YS 51% and 31%
Organ preservation has been successful in other sites (breast, head/neck, anal) but only in the setting of comparable outcomes.

Single modality therapy → unacceptable results

**Local control**

- TURBT alone: 20-40%
- RT alone: 20-30%
- Chemo alone: 10-30%

Chemotherapy + radiation therapy = synergistic
Radical cystectomy vs Multimodality bladder preservation therapy

Primary goal: cure the patient
Secondary goal: preserve QOL
TURB + Radiation therapy + Chemotherapy

Exclusion criteria

- **Multifocal disease**
  - Large treatment volumes
- **Poor bladder function**
  - No benefit of sparing
- **Abnormal renal function/hydronephrosis**
  - Optimal chemotherapy critical
- **Previous radiation therapy to pelvis**
  - Dose limitations
  - High risk of late complications i.e. small bowel obstruction
TURB + Radiation therapy + Chemotherapy

35% of failures at 6 wks (21% invasive and 14% non-muscle inv)
20% salvage cystectomy for incomplete response or recurrence

**Cancer-specific survival**

- 5Y 50% for Complete Response
- 21% for No Response

Most important predictors of CR and survival

- Early stage
- Complete TUR prior to chemoRT
<table>
<thead>
<tr>
<th>RTOG</th>
<th>N=</th>
<th>Treatment regimen</th>
<th>CR</th>
<th>5yr LC</th>
<th>5yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>85-12</td>
<td>42</td>
<td>TURBT→RT +cisplatin</td>
<td>66%</td>
<td>39%</td>
<td>52%</td>
</tr>
<tr>
<td>88-02</td>
<td>91</td>
<td>TURBT→MCV x 2→RT +cisplatin</td>
<td>75%</td>
<td>57%</td>
<td>51%</td>
</tr>
<tr>
<td>89-03</td>
<td>123</td>
<td>1) TURBT→MCV x 2→RT+cisplatin  2) TURBT→RT+cisplatin</td>
<td>61%</td>
<td>39%</td>
<td>48%</td>
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<td></td>
<td>55%</td>
<td>45%</td>
<td>49%</td>
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</tbody>
</table>
| 95-06  | 34 | TURBT→alt frac RT + 5FU/cisplatin (Housett regimen)  
-21% G3/4 hem tox (no death)  
-no pt required RC for toxicity | 67% | 55%    | 83% at 3y |
| 97-06  | 52 | TURBT→alt frac RT +cisplatin →MCV x 3                        | 74% | 80% at 2y | 61% at 3y |
| 99-06  | 81 | TURBT→alt frac RT +cisplatin /taxol  
→cisplatin/gemcitabine x 4 | 87% | 82% at 2y | 79% at 2y |
• 190 patients T2-T4a bladder cancer

Medial f/u 6.7y

40% local recurrence

• 26% non-invasive → 56% conservatively salvaged

• 18% invasive

10 y DSS for all patients: 59%

10y DSS with intact bladder: 45%

Shipley et al Urol 2002
**Acute morbidity : 23 - 80%**

Genitourinary:
- irritative urinary symptoms: dysuria, frequency, urgency
- incontinence, hematuria rare

Gastrointestinal:
- Bowel frequency, urgency, bloating

Fatigue

**Late morbidity**
- salvage cystectomy for poor function quite rare by urodynamics, 75% have normal function
- Sexual function satisfactory
  - 71% in women and 50% in men

**Zietman J Urol 70:1772,2003**
**TURB + Radiation therapy + Chemotherapy**

Combined patients from 4 RTOG trials surviving with bladder preserved at least 2 years from enrollment
Followed q3 ms for first 2 yrs, then q6 ms for 3 years
Toxicity data collected prospectively
Median f/u 5.4 years
Median age 65 years

**Results**

- **7%** grade 3 pelvic toxicity: 5.7% GU + 1.9% GI
- **10%** grade 2 pelvic toxicity: 9.6% GU + 1.9% GI
- **22%** grade 1 pelvic toxicity

Late Pelvic Toxicity After Bladder-Sparing Therapy in Patients With Invasive Bladder Cancer: RTOG 89-03, 95-06, 97-06, 99-06

JCO 27, 2009
TURB + Radiation therapy + Chemotherapy

- Limited conclusions due to small studies, limited follow-up, variety of protocols
- Local recurrence rate 35-40%
- 5-year survival with bladder ~40%
- However, toxicities appear well-tolerated

Younger age (<65 yrs)
Lower T stage (cT1-2)
Unifocal
Node negative (preop imaging insufficient)
Normal renal function (less than 60% of pts)
No hydronephrosis
Normal hemoglobin
Complete TURBT

20% of Eligible Patients
Lotan, Shariat et al., J Urol 2008
Conclusions

Radical cystectomy ± chemotherapy
  Remains the gold standard

Bladder preserving therapies is an option for very select patients
  Survival outcomes seems inferior to radical cystectomy

→ Need to identify best therapy for individual patient based on biologic predictors, health status, and preferences