Bladder Sparing Protocols for Urothelial Cancer: Indications & Contraindications

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Disclosures

• Disclosures: Advisory Panel Member and Investigator for Altor Bioscience Corporation (Active)

• No conflicts of interest pertaining to this CME activity
Objectives

1. Describe bladder preservation strategies
2. Identify clinical and pathologic characteristics associated with favorable oncologic outcomes when applying bladder preservation strategies for urothelial cancer
3. Describe outcomes of salvage cystectomy when bladder preservation fails
Index Patient

• For purposes of this lecture – will assume that our index patient has no significant comorbidities that preclude any or all management options for invasive bladder urothelial cancer unless stated otherwise.
• This lecture does not address tumor in a diverticulum, urachal adenocarcinomas, variant histologies
Bladder Preservation and Guidelines
Bladder Preservation

Advantages and Disadvantages

✓ Reduction in morbidity
✓ In-hospital complication rates following RC as high as 67% (13% Clavien grade 3 to 5)

• **Lifelong** endoscopic surveillance
  • Most RC patients that recur do so within 2-3 years
  • Risk for delayed *local* recurrences
• 1/3\(^{rd}\) of patients progress to salvage RC
Bladder Preservation Strategies

1. Radical TUR (+/- Intravesical therapy)
2. Radiation alone
3. Combination chemotherapy & radiation
4. Chemotherapy (or systemic therapy alone)
5. Partial cystectomy and BPLND
Optimal Selection Criteria for Bladder Preservation

• Fit T2 patient who desires bladder preservation:
  – Conventional urothelial histology
  – Minimally invasive T2 disease (i.e. cT2A)
  – Complete tumor resection at TUR
  – Absence of tumor associated hydronephrosis
  – Adequate bladder capacity
  – Absence of multifocal disease or CIS

• Unfit patients
  – Adequate bladder function
  – Absence of extensive CIS

AUA/SUO Guidelines for Muscle Invasive Bladder Cancer
NCCN Guidelines

CLINICAL STAGING:
- cT2 (Abdominal/pelvic CT or MRI)

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

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

Follow-up (BL-7):
- Observation or completion of RT up to 66 Gy and consider adjuvant chemotherapy (category 2B)

Tumor:
- No tumor
- Resectable or completion of RT with alternative radiosensitizing chemotherapy and/or alternative chemotherapy
- Unresectable or not a surgical candidate

See BL-6 (follow treatment as for T4b with positive nodes)

See Principles of Surgical Management (BL-A).
See Principles of Chemotherapy Management (BL-G).
See Principles of Radiation Management of Invasive Disease (BL-H).

The modifier "c" refers to clinical staging based on bimanual examination under anesthesia and endoscopic surgery (biopsy or transurethral resection) and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.

See Follow-Up After Cystectomy (BL-E).
NCCN Guidelines
## European Guidelines

**Table 6 – Recommendations for bladder-sparing treatments for muscle-invasive bladder cancer**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bladder-sparing treatments for localised MIBC</strong></td>
<td></td>
</tr>
<tr>
<td>Do not offer transurethral resection of bladder tumour alone as a curative treatment option because most patients will not benefit. *</td>
<td>B</td>
</tr>
<tr>
<td>Do not offer radiotherapy alone as primary therapy for localised bladder cancer.</td>
<td>B</td>
</tr>
<tr>
<td>Do not offer chemotherapy alone as primary therapy for localised bladder cancer.</td>
<td>A</td>
</tr>
<tr>
<td><strong>Multimodality treatment in MIBC</strong></td>
<td></td>
</tr>
<tr>
<td>Offer surgical intervention or multimodality treatments as primary curative therapeutic approaches because they are more effective than radiation therapy 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>

GR = grade of recommendation; MIBC = muscle-invasive bladder cancer.

* Level of evidence 2a.

Radical TUR Alone
TUR Alone for T2 Bladder Cancer

• Prospective, phase II nonrandomized study (133 patients)
• Radical TURB & restaging (or concurrent) negative biopsies
  – 3 or more biopsies of healthy appearing muscle fibers
  – cold cup biopsies of perivesical fat in areas when structure visible
• Excluded patients:
  – Macroscopically residual tumor after TUR
  – Hydronephrosis
  – Lymph node involvement
  – distant metastases
  – Sessile morphology and tumor size > than 3 cm (risks for under staging determined following interim analysis)
• Did not exclude CIS (24%) or multifocality (15%)

TUR Alone for T2 Bladder Cancer

• Surveillance
  – First 2 endoscopic evaluations at 3 and 6 months; wide TUR of the scar tissue was performed
  – Q3 months for 2 years, then Q6 months for 3 more years and annually thereafter
  – At each evaluation cystoscopy, urinary cytology, random bladder mucosa biopsies and bimanual examination were done

• 15-yr minimum follow-up:
  – 30% had recurrent NMIBC and went on to intravesical therapy
  – 30% (n=40) progressed (27 died of BCa)
TUR Alone for ≥T2 Bladder Cancer

Table 4. Survival and bladder preservation

<table>
<thead>
<tr>
<th></th>
<th>5 Yrs</th>
<th>10 Yrs</th>
<th>15 Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (%)</td>
<td>73.7</td>
<td>39.8</td>
<td>24.8</td>
</tr>
<tr>
<td>Ca specific (%)</td>
<td>81.9</td>
<td>79.5</td>
<td>76.7</td>
</tr>
<tr>
<td>Progression-free with bladder preserved (%)</td>
<td>75.5</td>
<td>64.9</td>
<td>57.8</td>
</tr>
<tr>
<td>Local progression-free with bladder preserved (%)</td>
<td>81.8</td>
<td>70.2</td>
<td>61.9</td>
</tr>
</tbody>
</table>

- No factors predicted for progression or cancer specific survival
- Only age was predictive for overall survival

TUR Alone for ≥T2 Bladder Cancer

<table>
<thead>
<tr>
<th></th>
<th>No. Pts (%)</th>
<th>Median Mos Followup</th>
<th>Mean Mos Followup (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>40 (30)</td>
<td>21</td>
<td>43.9 (3–247)</td>
</tr>
<tr>
<td>Progression</td>
<td>40 (30)</td>
<td>26</td>
<td>31.5 (3–135)</td>
</tr>
<tr>
<td>T≥2M0</td>
<td>30 (22.5)</td>
<td>29</td>
<td>35.4 (3–135)</td>
</tr>
<tr>
<td>T≥2M1</td>
<td>3 (2.2)</td>
<td>12</td>
<td>17.0 (3–36)</td>
</tr>
<tr>
<td>T0M1</td>
<td>7 (5.2)</td>
<td>21</td>
<td>21.3 (11–30)</td>
</tr>
<tr>
<td>Lost to followup</td>
<td>9 (6.7)</td>
<td>159</td>
<td>170.6 (120–238)</td>
</tr>
<tr>
<td>Died of tumor</td>
<td>27 (20.3)</td>
<td>34</td>
<td>39.7 (11–183)</td>
</tr>
<tr>
<td>Alive free of tumor</td>
<td>14 (10.7)</td>
<td>220</td>
<td>223.6 (192–264)</td>
</tr>
<tr>
<td>Died free of tumor</td>
<td>83 (62.4)</td>
<td>99</td>
<td>110.6 (44–305)</td>
</tr>
</tbody>
</table>

Radiation Alone vs. Multimodality Therapy (Radical TUR + Chemo + Radiation)
External Radiation Alone

• XRT (+/- Intensity Modulation)
  – <5% rate of major late bladder or bowel morbidity in tumor free patients
  – XRT can be an alternative treatment in patients unfit for or unwilling to undergo radical cystectomy or multimodality treatment
  – Inferior to combination therapy

Trimodality Therapy (TMT)

• Superior to RT alone
  – 2-year locoregional DFS 0.68 [CI 0.48–0.96] p=0.03
• Combination of TUR and RT for local control
• Radio sensitizers to potentiate RT
  – Cisplatin-based
  – Mitomycin-C plus 5-fluorouracil
  – Low-dose gemcitabine
• No RCT comparing surgery vs. TMT

Trimodality Therapy (TMT)

• TMT results:
  – > 70% achieve CR and retain bladder
  – 5-yr CSS rates 50% to 82%
  – 5-yr OS rates 36% to 74%
  – Salvage cystectomy rates are 25–30%
  – Neoadjuvant or adjuvant chemo does not improve outcome

• Quality of life studies
  – good function of native bladder
  – mild long-term toxic effects

Trimodality Therapy
Massachusetts General Hospital

- 475 patients with cT2–T4a MIBC (1986 - 2013)
- 5 & 10-yr DSS rates = 66% and 59%
- 5 & 10-yr OS rates = 57% and 39%
- Risk of salvage cystectomy at 5 yrs = 29%

Trimodality Therapy (MGH)

  - Rates of CR improved from 66% to 88%
  - 5-yr DSS improved from 60% to 84%
  - 5-yr salvage RC rate decreased from 42% to 16%

- Multivariate - significant predictors of OS/DSS:
  - T2 disease vs. T3/T4a [HR 0.57 and HR 0.51]
  - CR to chemoradiation [HR 0.61 and HR 0.49]
  - Presence of CIS [HR 1.56 and HR 1.50]

- Salvage RC, and timing (immediate vs. delayed) not associated with survival
Trimodality Therapy (MGH)

• Six treatment-related deaths:
  – 5 heme / infectious following neoadj. chemo
  – 1 cardiopulmonary arrest after salvage RC

• One RC for radiation cystitis
Fig. 2 – (A) Improvements in overall survival, (B) disease-specific survival over three treatment eras.
Trimodality Therapy (MGH)

Fig. 2 – (C) bladder-intact disease-specific survival over three treatment eras.
Trimodality Therapy (MGH)

Fig. 2 – (D) Reduction in crude rate of salvage cystectomy over 3 treatment eras.
MRE11

- Predictive marker for outcome following XRT
- DNA double-strand breaks (DSB) - most lethal form of ionizing radiation induced DNA damage
- Damage detected by the MRE11-RAD50-NBS1 (MRN) complex, resulting in rapid recruitment of signaling and repair proteins
- Failure to repair such breaks results in tumor cell death
- Contrary to initial hypotheses, low tumor MRE11 protein expression was an independent factor associated with worse CSS following XRT for bladder cancer

Systemic Chemotherapy Alone
Systemic Chemotherapy Alone

- 109 patients with ≥ T2 bladder cancer treated with platinum-based neoadjuvant chemotherapy
- Post treatment cystoscopy with biopsies/TUR + cross-sectional imaging

Systemic Chemotherapy Alone

- 129 patients received neoadjuvant chemotherapy
- 20 patients were <T2
- 109 patients were stage ≥T2
- 77 patients were >cT0 on first cystoscopic biopsy
- 32 patients were cT0 on first cystoscopic biopsy
- 7 patients underwent immediate cystectomy
- 7 patients underwent delayed cystectomy
- 25 patients refused immediate cystectomy
- 18 patients retained their bladders
- 6 patients received BCG therapy
- 12 patients followed up with cystoscopic surveillance
Systemic Chemotherapy Alone

- 32 patients (29.4%) were cT0
  - 7 patients immediate radical cystectomy
    - Caution: 3/7 with residual tumor found at RC
  - 25 patients elected bladder preservation
    - 7 (28%) underwent delayed RC
    - 18 (72%) retained the bladder
      - 6 (24%) who were managed conservatively for nonmuscle invasive relapses
      - 12 (48%) with no recurrence
  - 5-year CSS 88%

## Systemic Chemotherapy Alone

<table>
<thead>
<tr>
<th></th>
<th>Immediate Cystectomy</th>
<th>Delayed Cystectomy</th>
<th>Bladder Preservation + Recurrence</th>
<th>Bladder Preservation, No Recurrence Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>PreNC clinical stage (No. pts)</td>
<td>cT2 (7)</td>
<td>cT3 (1), cT2 (6)</td>
<td>cT2 (6)</td>
<td>cT3 (1), cT2 (11)</td>
</tr>
<tr>
<td>Median days MIBC diagnosis-NC (range)</td>
<td>55 (5—95)</td>
<td>48 (0—70)</td>
<td>21 (3—121)</td>
<td>53 (11—118)</td>
</tr>
<tr>
<td>No. death/total No.</td>
<td>4/7</td>
<td>3/7</td>
<td>1/6</td>
<td>2/18</td>
</tr>
<tr>
<td>No. Ca related death/total No.</td>
<td>2/4</td>
<td>2/3</td>
<td>0/1</td>
<td>0/2</td>
</tr>
</tbody>
</table>
Partial Cystectomy
Partial Cystectomy

• 1970s: PC with “Bad Rap”
  – 5-year OS rates found to be as low as 24%
  – local recurrence 40% to 78%
  – Inability to address metachronous tumors in remaining urothelium

• 2000s: PC “resurgence”
  – More rigorous patient selection
    • Solitary tumors in areas amenable to resection
    • No evidence of CIS
    • Patients who cannot tolerate radical surgery
  – 2.8% of “cystectomies” for treatment of MIBC
  – 3.3% (20 of 615 “cystectomies”) in my practice

Partial Cystectomy
Contemporary Outcomes

- 5-year RFS 39% to 67%.
- Matched cohort series: 86 PC and 167 RC pts
  - 10-year MFS (61% vs. 66%; P = 0.63)
  - 10 year CSS (58% vs. 63%; P = 0.67)
  - Intravesical recurrence rates ~ 38%
  - Salvage cystectomy rate 19%

Partial Cystectomy

Complications

- Nationwide Inpatient Sample Study
- > 10,000 patients underwent PC
  - ~16% complication rate
  - 1.8% death rate
  - PC patients significantly older vs. RC patients (mean age = 74.1 vs. 70.4; P < 0.001).
Predictors of Poor Outcome Following Partial Cystectomy

• Prior history of urothelial carcinoma
• Lymphovascular invasion
• Need for ureteral reimplantation
• Tumor size > 5 cm
• Tumor multifocality effect is less clear (synchronous or metachronous)
Recurrence Following Robotic Partial
Salvage Cystectomy
Salvage Cystectomy Following Partial Cystectomy

- Median time from PC to RC ~ 1.6 years.
- ≤ T2N0 (organ confined) 61.2%
- ≥ T3N0 (extravesical tumor) 19.4%
- TanyN+ 19.4%

Salvage Cystectomy Following Partial Cystectomy

• Survival characteristics:
  – 5-year RFS 56%
  – 5-year OS 41%
  • For ≤ T2N0, no difference in OS vs. stage-matched patients undergoing primary RC
  • For ≥ T3 or N+, worse 5-year survival vs. stage-matched patients undergoing primary RC (22% vs. 36%; P = 0.027).
Conclusions

- Patient selection is key
  - Attention to appropriate clinical & pathologic criteria
  - Aim for definitive management
- Patient counseling critical
  - Surveillance strategies (differ from RC)
  - Side effects (balance vs. RC)
- Salvage cystectomy offers good outcomes
  - Better for organ confined tumors
  - Might affect choice of diversion
References

References


• Lyons MB and Smith AD. Surgical bladder-preserving techniques in the management of muscle-invasive bladder cancer. Urol Oncol 34 (2016);262–270.