Optimizing Quality and Outcomes with Radical Cystectomy

Seth P. Lerner, MD, FACS
Professor of Urology, Beth and Dave Swalm Chair in Urologic Oncology, Scott Department of Urology, Baylor College of Medicine; Houston, TX

Objectives:

- Review surgical and other quality metrics in order to optimize outcomes of radical cystectomy
- Discuss the evidence regarding the extent of lymphadenectomy and identification of lymph node metastases and the impact on locoregional cancer control and outcome
- Recognize Level I evidence and guideline recommendations for integration of peri-operative chemotherapy and identify barriers to implementation
Optimizing Quality and Outcomes Associated with Radical Cystectomy

Seth P. Lerner, MD, FACS
Professor of Urology
Beth and Dave Swalm Chair in Urologic Oncology
Scott Department of Urology
Baylor College of Medicine
Houston, Texas

Intermountain Healthcare

6th Annual Excellence in Urology Seminar
February 5-8, 2014
Disclosures

- Laboratory research
  - Celgene, Cephalon

- Clinical trials
  - NCI, Endo, FKD, Imalux, Tengion

- Advisory Board
  - Imalux, Photocure, Taris, Tengion

- Consultant
  - BioCancell, Dendreon, Physion, Theracoat, Vaxiion
Objectives

• Review surgical and other quality metrics in order to optimize outcomes of radical cystectomy
• Understand the evidence regarding the extent of lymphadenectomy and identification of lymph node metastases and the impact on locoregional cancer control and outcome
• Level I evidence and guideline recommendations for integration of peri-operative chemotherapy and identify barriers to implementation
Natural History

- 15-20% of patients with Ta, T1 or Tis cancer progress to muscle invasion
- 80% of patients with muscle invasive cancer present de novo
- Distant metastases most common cause of treatment failure
  - Present at the time of cystectomy
  - Occurs in 40-50% within 2 years without additional therapy
Natural History

• These data dictate a carefully planned treatment program that goes beyond the ablation of the primary tumor and regional lymph node metastases

• **Muscle invasive urothelial bladder cancer is a systemic disease**
Treatment Goals

• Sterilize the regional tumor
  – Radical cystectomy and pelvic lymphadenectomy
  – Bladder sparing treatments

• Control occult regional and distant metastases
  – Neo-adjuvant and adjuvant chemotherapy

• Preserve functional voiding per urethra or by a continent catheterizable stoma

• Minimize treatment related morbidity
It all Starts with a High Quality TURBT

- TURBT and bimanual exam under anesthesia
  - Establish histology
    - Lymphatic/vascular invasion – risk factor for metastases
  - Depth of penetration
  - *Complete resection not necessary when cystectomy anticipated*
  - Directed biopsies to detect CIS
  - Urethra
    - TUR biopsies prostatic urethra
    - Bladder neck biopsies (women)
Organ-Confined Cancer - Understaging

• Netherlands Comprehensive Cancer Center Region (Urol Oncol 30:247, 2012)
  – 738 patients; 142 organ-confined
  – Bimanual exam accurate in 58%
  – Understaging 37%
  – Overstaging 11%

• International consortium (BJU Int 107:898-904, 2011)
  – 3166 patients – 43% upstaged to non-organ confined
Higher risk of relapse:

- 3-D mass on EUA
- Prostatic stroma, vaginal wall involvement (T4a)
- LVI - increased risk of occult nodal involvement
- Hydronephrosis - Increased risk of extra-vesical extension
- Micropapillary tumor
- Small cell neuroendocrine tumor

Use of these criteria:

80% likelihood of upstaging to ≥pT3b or N+ with initial surgery (Millikan et al. JCO 2001)
Risk Factors for Extravesical and Occult Metastatic Disease

Early Post-operative Complications

- MSKCC 1,145 patients
- 1995-2005
- 64% ≥ 1 complication
  - 83% grade 2-5 (modified Clavien)
    - 57% within 90 days of surgery
  - 26% re-admission
- Post operative morbidity may limit up to 30% of patients from undergoing adjuvant chemotherapy

Strategies to Reduce Peri-operative Morbidity

- Optimize performance status and nutritional status
- No mechanical bowel prep
- Level I evidence supporting peripheral μ-opioid receptor blockade
- Strict management of intraoperative fluids and hemodynamics
The protocol focuses on avoiding bowel preparation and nasogastric tubes, early feeding, non-narcotic pain management, and the use of a peripheral μ-opioid antagonist.

40 prospective patients compared to 480 patients in STAR trial

<table>
<thead>
<tr>
<th></th>
<th>ERAS</th>
<th>STAR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median LOS</td>
<td>4 (3-16)</td>
<td>8 (0-70)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>30d comp rate</td>
<td>25 (62.5%)</td>
<td>271 (56%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Re-admit rate</td>
<td>9 (22.5%)</td>
<td>107 (22.1%)</td>
<td>0.9</td>
</tr>
</tbody>
</table>
### Fluid Restriction and α-Agonists

- **Randomized trial**  \( n=167 \)

<table>
<thead>
<tr>
<th>Low volume (n=83)</th>
<th>Control (n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine 2 ug/kg/hr</td>
<td>Ringers 6ml/kg bolus</td>
</tr>
<tr>
<td>Titrate Nepi up to 8ug/kg/hr</td>
<td></td>
</tr>
<tr>
<td>MAP 60-100mmHg</td>
<td></td>
</tr>
<tr>
<td>Ringers 1ml/kg/hr during RC</td>
<td>Ringers 6ml/kg/hr</td>
</tr>
<tr>
<td>3ml/kg/hr after bladder out</td>
<td></td>
</tr>
<tr>
<td>Replace ( \geq 500 )cc EBL 1:1 with Ringers</td>
<td>Same</td>
</tr>
<tr>
<td>Transfuse if Hgb &lt; 8mg/dl</td>
<td>same</td>
</tr>
<tr>
<td>If MAP &lt; 60: Nepi 10ug bolus</td>
<td>Bolus 250cc Ringers up to 2x</td>
</tr>
<tr>
<td>Bolus 250cc Ringers prn</td>
<td>Nepi 10ug bolus for rescue</td>
</tr>
</tbody>
</table>

EBL and Blood Transfusions

- Significant reductions in ileus, CV complications
- EBL 800cc (300-1800) vs 1200 (400-3000)
  - Intra-operative blood tx 8% vs 31%

Relationship of Blood Transfusions and Oncologic Outcomes in RC

Receipt of Blood Tx
RFS 1.20 [95% CI: 1.01–1.42] p = 0.04
Ca-Spec Survival 1.31 [95% CI: 1.10–1.57] p = 0.003
OS 1.27 [95% CI: 1.12–1.45] p = 0.0002

Relationship of Blood Transfusions and Oncologic Outcomes in RC

323/777 (41.9%) of patients transfused

<table>
<thead>
<tr>
<th></th>
<th>RARC</th>
<th>Open</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parekh (n=40)</td>
<td>400 ml</td>
<td>800 ml</td>
</tr>
<tr>
<td></td>
<td>IQR 300-762.5</td>
<td>IQR 400-1,100</td>
</tr>
<tr>
<td>Transfusion</td>
<td>40%</td>
<td>50%</td>
</tr>
<tr>
<td>Pruthi (n=41)</td>
<td>258 (mean)</td>
<td>575</td>
</tr>
<tr>
<td>Transfusion</td>
<td>0.5</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Radical Cystectomy Quality Metrics

• 90-day mortality 2.8-3.9%
• 90-day hospital readmission rate
  – 25%
• Quality influenced by several metrics:
  – Hospital size and volume of cystectomies
  – Surgeon experience
  – Patient socioeconomic status
What is the evidence regarding the extent of lymphadenectomy and identification of lymph node metastases and how does this impact on locoregional cancer control and outcome?
What is Known About LN Metastasis?

• Increasing incidence associated with increased pT stage
• Anatomy and location of LN mets known
• Bilateral – cross over common
• App 50% of patients with N+ disease are N2 or N3
Positive Lymph Node Distribution in 84 patients

- Aortic bifurcation nodes: 23%
- Common iliac nodes – Rt: 24%
- Common iliac nodes – Lt: 29%
- Presacral nodes: 17%
- Pelvic nodes – Rt: 57%
- Pelvic nodes – Lt: 55%
- Perivesical nodes: 20%

Metrics for LN Mets and Outcome

• Quality of the LND and loco-regional control
• Accuracy of N stage
• Is there a survival benefit to extent of LND?
LND and Local Control

SWOG

- ≤pT2 (N=183) 5 yr LF 8%
- ≥pT3 & (-)Marg & ≥10 nodes removed (N=32) 20%
- ≥pT3 with (+)Marg or <10 nodes removed (N=46) 41%

PENN

- ≤pT2 (N=232) 5 yr LF 8%
- ≥pT3 & (-)Marg & ≥10 nodes removed (N=115) 19%
- ≥pT3 with (+)Marg or <10 nodes removed (N=89) 41%

Christodoulou, et al Cancer epub 1/3/2014
Rationale for Extended Pelvic and Iliac LND

• Standard LND includes external/internal iliac and obturator lymph nodes
  – Identifies ≥95% of N1; skip metastases rare

• Extended LND includes pre-sacral, Cl and distal aorta/IVC nodes
  – increases node yield by 34-40%
  – 36-43% of P3,P4N+ have node metastasis above Cl bifurcation
The Number of Nodes Removed and Sensitivity for N+

25 nodes detected 75% N+

40 nodes detected 90% N+

• **Pancreatic Head Cancer** (Surgery 138:618, 2005)
  – Early closure after interim analysis showed increased morbidity and decreased survival with extended LND

• **Esophageal Cancer** (Ann Surg 246:992, 2007)
  – Extended transthoracic resection compared with limited transhiatal resection - No survival benefit

• **Gastric Cancer** (NEJM 359:453, 2008)
  – No difference in RFS and OS
  – Non-significant increase in morbidity w/extended LND
P53 trial  Extent of Lymph Node Dissection

LND initiated at the aortic bifurcation ≥ 15 nodes or post-op CT

<table>
<thead>
<tr>
<th></th>
<th>Canada</th>
<th>Europe</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>22</td>
<td>8</td>
<td>194</td>
</tr>
<tr>
<td>Extended</td>
<td>0</td>
<td>19</td>
<td>186</td>
</tr>
</tbody>
</table>
LEA - Conventional vs extended pelvic lymph node dissection in bladder cancer patients undergoing radical cystectomy

Jürgen E. Gschwend, Munich, Germany
Schema – SWOG 1011

T2, T3, T4a Radical Cystectomy (Neoadjuvant Ctx allowed)

Standard PLND
External/internal iliac, obturator nodes

Extended LND
Standard + Cl, pre sacral, distal IVC and aorta (optional)

N+ Adjuvant Chemotherapy

Sample size 564 patients
Powered to detect 10% improvement in 3 yr DFS from 55-65%

Leading cancer research. Together.
Objectives

- **Primary objective**
  - To compare disease-free survival (DFS) in patients undergoing radical cystectomy for muscle-invasive urothelial carcinoma of the bladder (UCB) treated with radical cystectomy and extended pelvic lymph node dissection (PLND) compared to radical cystectomy and standard pelvic lymphadenectomy.

- **Accrual 286 through 12/31/2013**
What are level I evidence and guideline recommendations for integration of peri-operative chemotherapy and understand the barriers to implementation?
SWOG 8710: Overall Survival by Treatment Arm

<table>
<thead>
<tr>
<th>ARM</th>
<th>No. Pts.</th>
<th>No. Pts. Dead</th>
<th>Median Survival</th>
<th>%5 Yr Survival</th>
<th>p Value (log-rank, 1-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 154 96</td>
<td>43.2 mos</td>
<td>42.1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVAC 153 90</td>
<td>74.7 mos</td>
<td>57.2%</td>
<td></td>
<td></td>
<td>0.044</td>
</tr>
</tbody>
</table>

Overall Survival by Treatment Arm
International Trial of Neoadjuvant Chemotherapy + RC or XRT

Kaplan-Meier curves for (A) overall survival, (B) metastasis-free survival, (C) locoregional disease-free survival, and (D) disease-free survival.

JCO 29:2171, 2011
## Neoadjuvant Chemotherapy Improves pCR (P0) rate

<table>
<thead>
<tr>
<th>Study</th>
<th>CTx + cyst</th>
<th>cyst alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC/International (CMV)</td>
<td>32.5%</td>
<td>12.3%</td>
</tr>
<tr>
<td>SWOG (MVAC)</td>
<td>38%</td>
<td>15%</td>
</tr>
<tr>
<td>Nordic II (MTX/Cisplatin)</td>
<td>26.4%</td>
<td>11.5%</td>
</tr>
<tr>
<td>MSKCC (GC)</td>
<td>26%</td>
<td>NA</td>
</tr>
<tr>
<td>MSKCC (M-VAC)</td>
<td>28%</td>
<td>NA</td>
</tr>
<tr>
<td>Columbia (MVAC)</td>
<td>31%</td>
<td>NA</td>
</tr>
<tr>
<td>Columbia (GC)</td>
<td>25%</td>
<td>NA</td>
</tr>
<tr>
<td>CCF (GC)</td>
<td>7%</td>
<td>NA</td>
</tr>
<tr>
<td>International consortium</td>
<td>NA</td>
<td>5.1%</td>
</tr>
</tbody>
</table>
Correlation of Pathologic Complete Response with Survival After Neoadjuvant Chemotherapy in Bladder Cancer Treated with Cystectomy: A Meta-analysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>pCR Events</th>
<th>Total</th>
<th>no pCR Events</th>
<th>Total</th>
<th>pCR Total</th>
<th>Risk Ratio M-H, Fixed, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dreicer 1993</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>9</td>
<td>Not estimable</td>
<td>1993</td>
</tr>
<tr>
<td>Herr 1994</td>
<td>2</td>
<td>12</td>
<td>7</td>
<td>14</td>
<td>3.7%</td>
<td>0.33 [0.08–1.31] 1994</td>
</tr>
<tr>
<td>Hatcher 1994</td>
<td>0</td>
<td>15</td>
<td>10</td>
<td>17</td>
<td>5.6%</td>
<td>0.05 [0.00–0.84] 1994</td>
</tr>
<tr>
<td>Sagaster 1996</td>
<td>3</td>
<td>17</td>
<td>15</td>
<td>37</td>
<td>5.4%</td>
<td>0.44 [0.15–1.31] 1996</td>
</tr>
<tr>
<td>Scattoni 1996</td>
<td>1</td>
<td>6</td>
<td>25</td>
<td>61</td>
<td>2.5%</td>
<td>0.41 [0.07–2.50] 1996</td>
</tr>
<tr>
<td>Sternberg 1999</td>
<td>2</td>
<td>13</td>
<td>15</td>
<td>31</td>
<td>5.0%</td>
<td>0.32 [0.08–1.20] 1999</td>
</tr>
<tr>
<td>Matsui 2005</td>
<td>3</td>
<td>21</td>
<td>36</td>
<td>98</td>
<td>7.2%</td>
<td>0.39 [0.13–1.14] 2005</td>
</tr>
<tr>
<td>Sonpavde 2009</td>
<td>23</td>
<td>46</td>
<td>52</td>
<td>69</td>
<td>23.7%</td>
<td>0.66 [0.48–0.91] 2009</td>
</tr>
<tr>
<td>Ghadjar 2010</td>
<td>3</td>
<td>9</td>
<td>13</td>
<td>21</td>
<td>4.4%</td>
<td>0.54 [0.20–1.44] 2010</td>
</tr>
<tr>
<td>Kaneko 2011</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>12</td>
<td>Not estimable</td>
<td>2011</td>
</tr>
<tr>
<td>Rosenblatt 2012</td>
<td>6</td>
<td>51</td>
<td>84</td>
<td>174</td>
<td>21.7%</td>
<td>0.24 [0.11–0.52] 2012</td>
</tr>
<tr>
<td>Meijer 2013</td>
<td>15</td>
<td>33</td>
<td>62</td>
<td>79</td>
<td>20.8%</td>
<td>0.58 [0.39–0.86] 2013</td>
</tr>
</tbody>
</table>

Total (95% CI) 239 622 100.0% 0.45 [0.36–0.56]

Fig. 2 Forest plot of pooled relative risk for overall survival from eligible studies reporting outcome associated with achieving a pathologic complete response (pCR). Horizontal lines represent 95% confidence intervals (CIs). The area of each square represents...
Patients with early stage muscle invasive disease (cT2) also benefit from neoadjuvant MVAC chemotherapy.

Median survival:
cT2: 105 vs. 75 mos

cT3-T4a: 65 vs. 24 mos

Surgical margins status and number of nodes removed were independently associated with local pelvic recurrence.

Neo-adjuvant Chemotherapy Meta Analysis
5% Survival Advantage

- Individual patient data from 6 randomized trials
- 9% survival benefit with platinum based combination chemotherapy

• Neoadjuvant chemotherapy with cis-platin based multi-agent regimen standard of care

• M-VAC/CMV only regimens tested in Phase III trials

• Common use of GC based on patients with metastatic disease and has not been evaluated in Phase III neoadjuvant trials

• Neoadjuvant chemotherapy is not recommended in patients with PS > 2 and impaired renal function
“Houston, We Have a Problem”

Apollo 13 flight to the moon reporting a problem
April 14, 1970
Neoadjuvant Chemotherapy
Low Utilization

• National Cancer Database
• 7161 patients with Stage III bladder cancer
  – Peri-operative chemotherapy 11.6%
  – Adjuvant 10.4%
  – Neoadjuvant 1.2%
• Utilization improved from 11.3% in 1998 to 16.8% in 2003 (after publication of SWOG 8710)

Barriers to Utilization

- Patient anxiety and preference for initial surgery
- Urologist failure to refer
  - Is the magnitude of the benefit enough to justify treating all patients with muscle invasive cancer with systemic chemotherapy?
- Lack of time/support to accrue to trials
- Lack of exciting agents
- Inadequate renal function for cisplatin based therapy

Rosenberg, J NCI Translational Sci Workshop
Contemporary Neoadjuvant Chemotherapy Utilization

- SWOG1011
- 271 randomized patients
- Neoadjuvant chemotherapy 140 (52%)
  - 117 (84%)
  - 11 (8%)
  - 12 (9%)
- BCAN QCI
- 9 academic institutions
- One year prospective
- 395 pts with T2-4N0M0
- 56% peri-op ctx
- 47% neoadjuvant cisplatin-based
- 9% adjuvant cisplatin-based
- 3.4 fold increase compared to baseline data
I Will Give Adjuvant Chemotherapy Instead

Is there High Level Evidence Supporting the use of Chemotherapy post-Cystectomy?

NO
Adjuvant Chemotherapy Meta Analysis (HR 0.75)
9% (95% CI 1-16%) Overall Survival Advantage at 3 Years

- Individual patient data (n=491) from 6 randomized trials
- 11% survival benefit at 3 years with platinum based combination chemotherapy

Adjuvant Chemotherapy for Invasive Bladder Cancer: A 2013 Updated Systematic Review and Meta-Analysis of Randomized Trials

Fig. 2  Pooled hazard ratios across all nine studies by chemotherapy type. CI = confidence interval; ES = effect size.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin-based combinations:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bono</td>
<td>0.65 (0.34–1.25)</td>
<td>9.83</td>
</tr>
<tr>
<td>Freiha</td>
<td>0.74 (0.36–1.53)</td>
<td>8.61</td>
</tr>
<tr>
<td>Otto</td>
<td>0.82 (0.48–1.39)</td>
<td>12.37</td>
</tr>
<tr>
<td>Skinner</td>
<td>0.75 (0.48–1.18)</td>
<td>14.22</td>
</tr>
<tr>
<td>Lehmann</td>
<td>0.57 (0.31–1.05)</td>
<td>10.57</td>
</tr>
<tr>
<td>Stadler</td>
<td>1.11 (0.45–2.73)</td>
<td>6.35</td>
</tr>
<tr>
<td>Subtotal (I² = 0.0%, p = 0.880)</td>
<td>0.74 (0.58–0.94)</td>
<td>61.95</td>
</tr>
<tr>
<td>Single agent cisplatin:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studer</td>
<td>1.02 (0.57–1.83)</td>
<td>11.09</td>
</tr>
<tr>
<td>Subtotal (I² = .%, p = .)</td>
<td>1.02 (0.57–1.83)</td>
<td>11.09</td>
</tr>
<tr>
<td>Gemcitabine–cisplatin combinations:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spanish</td>
<td>0.38 (0.22–0.65)</td>
<td>12.13</td>
</tr>
<tr>
<td>Subtotal (I² = 91.8%, p = 0.000)</td>
<td>0.71 (0.21–2.35)</td>
<td>26.96</td>
</tr>
<tr>
<td>Overall (I² = 46.5%, p = 0.060)</td>
<td>0.77 (0.59–1.00)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random-effects analysis.

This disease-free survival benefit was more apparent among those with positive nodal involvement (p = 0.010)
Summary

• High quality TURBT and recognition of high risk features will optimize clinical stage determination

• Radical cystectomy and bilateral PLND optimize accurate N stage determination and loco-regional cancer control

• Integration of peri-operative cisplatin based chemotherapy improve RFS and overall survival