Quality Indicators in Radical Cystectomy

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Disclosures

• Clinical trials
  – Endo, FKD, Viventia, NCI/SWOG – Roche/GNE, JBL

• Advisory Board
  – Ferring

• Consultant
  – Biocancell, UroGen, Vaxiion
Learning Objectives

• To understand pre-operative and pathologic outcome measures on long term cancer control

• To describe the stage specific association of lymph node metastasis and to determine the proper anatomic extent of lymphadenectomy

• To understand status of current Phase III clinical trials of extended vs. standard PLND

• To be able to incorporate peri-operative and intra-operative strategies and techniques to minimize post-operative morbidity
• 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)
Risk Factors for Extravesical and Occult Metastatic Disease

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

vonRundstedt, et al Bladder Cancer in press
- Meta-analysis confirms low incidence (5%) and HR 1.68 for overall survival (Hong, et al Oncotarget epdb 10/25/2016)
Nomograms Predicting Outcome

Table 3. Nomogram ROC-AUC analysis results

<table>
<thead>
<tr>
<th>Predicted Outcome</th>
<th>2 Yrs</th>
<th>5 Yrs</th>
<th>8 Yrs</th>
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<tbody>
<tr>
<td>Recurrence</td>
<td>0.776</td>
<td>0.809</td>
<td>0.794</td>
</tr>
<tr>
<td>Ca specific survival</td>
<td>0.822</td>
<td>0.840</td>
<td>0.849</td>
</tr>
<tr>
<td>Overall survival</td>
<td>0.812</td>
<td>0.820</td>
<td>0.825</td>
</tr>
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</table>

Disease-Specific Survival According to pN Stage at Cystectomy

According to pN Stage at Cystectomy:
- N0
- N1 single node ≤ 2cm
- N2 single node >2≤ 5cm; Mult nodes none >5cm
- N3 node > 5cm
- Common iliac or above
- M1
“New” Node Staging

- N1 – single node in true pelvis
- N2 – multiple nodes in true pelvis
- N3 – lymph node metastasis in common iliac nodes
- True pelvis includes external and internal iliac, obturator and presacral nodes
- >12 nodes for adequate staging
Positive Lymph Node Distribution in 84 patients

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

Anatomic Distribution of Lymph Node Drainage of the Bladder

Outcome in Node Positive Patients

- Number of lymph nodes removed
  - Important in both node negative and node positive patients
- Number of positive lymph nodes
- Percent of nodes involved with cancer
  - Lymph node density
- Pathologic stage of the primary tumor
- New TNM staging recommends > 12 nodes as minimum standard
The Number of Nodes Removed and Sensitivity for N+


40 nodes detected 90%
N+

25 nodes detected 75%
N+
No PLND associated with higher Ca-spec mortality only in organ-confined disease but overall mortality in all stages.

Overall mortality

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 presacral, CI and distal aorta/IVC nodes
  – increases node yield by 34-40%
  – 36-43% of P3,P4N+ have node metastasis above CI bifurcation
LND and Local Control

**SWOG**

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

**PENN**

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

RTOG 1324

• Randomized Phase II Trial of Postoperative Adjuvant IMRT Following Cystectomy for pT3/4N0-2 without neobladder, adjuvant or neoadjuvant chemo are permitted
Does a More Extensive LND Improve Survival?

- **SEER – 1988-1996** ¹
  - 1923 patients
  - Improved survival with high number of nodes especially Stage III and IV

- **SEER17 (1988-2003)** ²
  - 1260 pts node pos
  - More LN removed associated with lower mortality

1 Konety et al J Urol 169:946, 2003
Post-cystectomy survival by node status and number of nodes removed – SWOG 8710

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

Bilateral PLND including external and internal iliac nodes including fossa of Marcille distal to CI bifurcation and complete dissection of obturator fossa provides adequate pathologic N staging

Many consistent and concordant observations, although of low levels of evidence, document that the extent of LND may influence DFS independent of pT and pN stage
Take Home Message

• It is the anatomic extent and completeness of the lymphadenectomy that matters
• This is the most likely variable to affect the sensitivity for detection of node metastases and long-term survival
What is the Surgical Standard for Pelvic Lymphadenectomy and Radical Cystectomy?

Roth, et al Eur urol 57:205, 2010
Extent of LND and Survival
No Level I Evidence Supporting Extended LND

• 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 Targeted Therapy Trial Surgical Quality

- 33% had < 15 nodes
- Associated with extent of LND
- 53% standard vs. 20% extended

LEA – Conventional vs extended pelvic lymph node dissection in bladder cancer patients undergoing radical cystectomy

Jürgen E. Gschwend
LEA-CONSORT-Diagram
(CONsolidated Standards of Reporting Trials)

Assessed for Eligibility n=438

Randomised n = 433

Allocated to limited LA n=218

Drop-out n=30

ITT analysis n=188 (39f/149m, Ø68y)
Available Results n=178
Median removed LN n=19 (2-66)
Median positive LN n=2 (1-32)

Allocated to extended LA n=215

Drop-out n=41

ITT analysis n=174 (41f/133m, Ø67y)
Available Results n=170
Median removed LN n=31 (1-122)
Median positive LN n=3 (1-23)

Courtesy Jürgen Gschwend
Distribution of micromets in pN0 nodes (%) by RT-PCR

- Limited field LEA trial: 50/75 LN micrometastasis: 66.7%
- Extended field LEA trial: 25/75 LN micrometastasis: 33.3%

Courtesy Jürgen Gschwend
• Negative trial for primary endpoint
• Included T1
• Standard LND was limited – no dissection below obturator nerve
• No neoadjuvant chemotherapy
  – T2 possible benefit
Schema – SWOG S-1011

T2+LVI, T3,T4a Radical Cystectomy

Randomize

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

Standard PLND
External/internal iliac, obturator nodes

Extended LND
Standard + CI, pre sacral, distal IVC and aorta

N+ Adjuvant Chemotherapy

Leading cancer research. Together.
Accrual

- 24 centers have accrued patients SWOG (11) CALGB/Alliance (6) ECOG/ACRIN (3) NCIC (3) NCCTG (1)
  - 36 credentialed surgeons (35 have registered pts)

Accrual: 627 reg (620); 590 randomized (564)

As of November 6, 2016
High volume surgeons and high volume hospitals have better outcomes

Alvimopam reduces time to resolution of ileus

Volume restriction and alpha agonists reduce blood loss – transfusion rates associated with survival

MIS is not associated with a 20% improvement in 90 day morbidity

Quality of LN dissection associated with number of nodes identified and survival (?)
Contemporary Morbidity and Mortality

- 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*
- 90-day mortality ranges from 2.7-12.7%

How 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
A Randomized Trial of Robot-Assisted Laparoscopic Radical Cystectomy

Table 1. Outcomes after Radical Cystectomy in the Intention-to-Treat Analysis.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Robot-Assisted Surgery (N=60)</th>
<th>Open Surgery (N=58)</th>
<th>Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complication — no. of patients (%)</td>
<td>37 (62)</td>
<td>38 (66)</td>
<td>-4 (-21 to 13)</td>
<td>0.66</td>
</tr>
<tr>
<td>Grade 3-5</td>
<td>13 (22)</td>
<td>12 (21)</td>
<td>1 (-14 to 16)</td>
<td>0.90</td>
</tr>
<tr>
<td>Operating-room time — min</td>
<td>456±82</td>
<td>329±77</td>
<td>127 (98 to 156)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of stay in hospital — days</td>
<td>8±3</td>
<td>8±5</td>
<td>0 (-2 to 1)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

*Cost higher for RARC in both IC and neobladder diversion

“The confidence intervals argue against a large benefit of robotic techniques with respect to peri-operative morbidity...these results highlight the need for randomized trials to inform the benefits and risk of new surgical technologies before widespread implementation.”

RCT Open vs. Robotic Assisted Lap RC

- NCT 01157676 (PI – Parekh)
- Multicenter (n=15)
- Eligibility: T1-T4, N0-1, M0, or refractory CIS
- Primary endpoint
  - 2-year PFS – Estimate 70% in open RC arm
  - Non-inferiority margin ≤ 15% in experimental arm
  - 144 per arm; 80% power
- All extracorporeal diversion
- Accrual completed!
- NB: RARC associated with reduced EBL and blood transfusion rate\(^1,2\)

\(^1\) Parekh, et al J Urol 189:474, 2013
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

Fig. 1 – Recurrence-free survival following radical cystectomy (RC) for bladder cancer, stratified by receipt of perioperative blood transfusion (PBT).

Fig. 2 – Cancer-specific survival following radical cystectomy (RC) for bladder cancer, stratified by receipt of perioperative blood transfusion (PBT).

Anemia and Post-operative Mortality Risk

• AABB transfusion recommendations
  – Hgb <6 g/dL – Recommended except in exceptional circumstances
  – Hgb 6 to 7 g/dL – Generally likely to be indicated
  – Hgb 7 to 8 g/dL – Should be considered
  – Hgb 8 to 10 g/dL – Generally not indicated unless symptomatic, active bleeding, acute CS
  – Hgb >10 g/dL – Transfusion generally not indicated except in exceptional circumstances

Fluid Restriction and α-Agonists

- Randomized trial  n=167
  - Low volume (n=83)
    - Norepinephrine 2 ug/kg/hr
    - Titrate Nepi up to 8ug/kg/hr
  - Control (n=84)
    - Ringers 6ml/kg bolus

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

Transfuse if Hgb < 8mg/dl
If MAP < 60: Nepi 10ug bolus
Bolus 250cc Ringers prn

CSE – combined spinal epidural
Limit use of narcotic analgesics

Tony Kim – Chief of Anesthesia BSLMC