Current Concepts in Lymphadenectomy

Trushar Patel M.D.
USF Health
• Lymphatic system Functions
  – Immune Defense/Disease Resistance
  – Transport Fluid back to bloodstream

• Water/Blood Cells/Proteins
• Bacteria/Viruses/Cell debris
• Cancer Cells
Physiology

• One way system toward the heart
• No Pump
  – Milking action of skeletal muscle
  – Contraction of smooth muscle in vessel walls
• Defense in Cells within lymph nodes
  – Macrophages: engulf and destroy foreign substances
  – Lymphocytes: provide immune response to the antigens
Why Do Lymphadenectomy?

**Therapeutic**
- Tumors tend to metastasize from organs primary lymph nodes to regional lymph nodes
- Cure patients with limited metastatic disease

**Diagnostic**
- Identify patients with metastatic disease to allow for potential further treatment
Will Rogers Phenomenon

- “When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states.”

- Stage Migration
  - Improved detection of illness leads to the movement of people from the set of healthy people to the set of unhealthy people.
  - When more lymph nodes are removed at surgery and identified by the pathologist, the probability of finding lymph node metastases increases and up staging from N0 to N1 increases.
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<th>Renal Cell Carcinoma</th>
<th>Bladder Cancer</th>
<th>Prostate Cancer</th>
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<td>Benefit of</td>
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Renal Cell Carcinoma
Is Lymphadenectomy beneficial?

- Clinically node negative disease
- Clinically node positive disease
Renal Cell Carcinoma

- Lymph node status is a strong prognostic indicator in patients with kidney cancer

- Incidence of lymph node metastases in RCC ranges from 13% - 32%
  - 3-10% will have isolated lymph node metastasis

- Regional lymphadenectomy proposed as method of improving surgical results

Lymphatic Mapping

- RCC historically associated with predominately hematogenous route of metastasis
  - Isolated lymph node mets rare
  - High risk of micrometastatic disease

- Primates:
  - Renal lymphatics can directly drain into the vena cava and renal vein
Clinically Node Negative Disease

Radical Nephrectomy with and without Lymph-Node Dissection: Final Results of European Organization for Research and Treatment of Cancer (EORTC) Randomized Phase 3 Trial 30881

Jan H.M. Blom, Hein van Poppel, Jean M. Maréchal, Didier Jacqmin, Fritz H. Schröder, Linda de Prijck, Richard Sylvester, for the EORTC Genitourinary Tract Cancer Group

- 732 patients with RCC selected for randomization
  - 362 complete radical nephrectomy + lymph node dissection (RN+LND)
  - 370 radical nephrectomy alone (RN)

- LND extended from the crus of the diaphragm inferiorly to the bifurcation of the aorta or vena cava

Eur Urol 2009
• 272 patients died:
  – 135/389 in RN; 67 from renal cancer
  – 137/383 in RN +LND; 68 from renal cancer

  • \( p = 0.87 \)
### Progression-free survival

**Overall log-rank test:** $p = 0.844$

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<thead>
<tr>
<th>LN Dis</th>
<th>No. of patients at risk</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
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<td>No</td>
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<td>124</td>
<td>49</td>
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<tr>
<td>Yes</td>
<td>159 383</td>
<td>308</td>
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<td>220</td>
<td>186</td>
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<td>52</td>
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<tr>
<th>Event</th>
<th>Without lymph-node dissection (n = 389)</th>
<th>With complete lymph-node dissection (n = 383)</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
<th>p value</th>
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<td>Death</td>
<td>135 (35%)</td>
<td>137 (36%)</td>
<td>1.02</td>
<td>0.80–1.29</td>
<td>0.87</td>
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<td>Local regional progression</td>
<td>34 (9%)</td>
<td>26 (7%)</td>
<td>0.77</td>
<td>0.46–1.28</td>
<td>0.31</td>
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<td>Distant progression</td>
<td>58 (15%)</td>
<td>60 (16%)</td>
<td>1.05</td>
<td>0.73–1.50</td>
<td>0.81</td>
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<td>Local or distant progression</td>
<td>93 (24%)</td>
<td>87 (23%)</td>
<td>0.95</td>
<td>0.71–1.27</td>
<td>0.70</td>
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<td>Progression or death</td>
<td>156 (40%)</td>
<td>159 (42%)</td>
<td>1.02</td>
<td>0.82–1.28</td>
<td>0.84</td>
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<td>Second primary</td>
<td>45 (12%)</td>
<td>36 (9%)</td>
<td>0.79</td>
<td>0.51–1.22</td>
<td>0.28</td>
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Clinical Node Negative Disease

- In node-negative disease, lymph node dissection has no apparent therapeutic advantage.

- Only 4% of patients who underwent lymphadenectomy had positive nodes and, therefore, the trial was likely underpowered to detect a therapeutic benefit of node dissection.
Clinically Node Positive Disease

RENAL CELL CARCINOMA WITH RETROPERITONEAL LYMPH NODES: ROLE OF LYMPH NODE DISSECTION

ALLAN J. PANTUCK, AMNON ZISMAN, FREDRICK DOREY, DEBBY H. CHAO, KEN-RYU HAN,
JONATHAN SAID, BARBARA J. GITLITZ, ROBERT A. FIGLIN AND ARIE S. BELLEDEGRUN

- 900 patients underwent nephrectomy for unilateral RCC

- Patients divided into 4 pathological groups:
  - 535 with no regional LNs or metastatic disease (N0M0)
  - 43 with regional LNs only (N+M0)
  - 236 with distant metastatic disease only (N0M1)
  - 86 with regional LNs and distant metastatic disease (N+M1)

J Urol 2003
• Median time to death: 16 months
Renal Cell Carcinoma with Isolated Lymph Node Involvement: Long-term Natural History and Predictors of Oncologic Outcomes Following Surgical Resection

Boris Gershman, Daniel M. Moreira, R. Houston Thompson, Stephen A. Boorjian, Christine M. Lohse, Brian A. Costello, John C. Cheville, Bradley C. Leibovich

Natural History of N+M0 Disease following Lymphadenectomy

5 and 10 year
MFS: 16%-15%
CSS: 26%-21%
OS: 25%-15%

Long Term Survival:
- Lower pT stage
- Lower grade
- Lower incidence of sarcomatoid differentiation and tumor necrosis

Eur Urol, 2017
Lymphadenectomy
Cytoreductive Nephrectomy

- Retrospective analysis have shown **worse outcomes** in patients undergoing LND
- # of nodes taken has shown no effect on survival

Lymphadenectomy in Renal Cell Carcinoma

• In clinically node negative patients, lymphadenectomy does not appear to improve survival

• Lymphadenectomy may have some benefit for select patients with RCC
  – N+M0 (Possible Therapeutic Role)
  – M1 (Prognostic rather than therapeutic role)

• Template of dissection nor number of nodes to remove has not been evaluated in a prospective manner
Bladder Cancer
Extent of Lymphadenectomy
Bladder Cancer

• 76,960 New Cases (2016)

• Muscle invasive bladder accounts for 20-25% of all urothelial tumors

• ~25% of patients treated with RC/LND have pathologic positive lymph node metastasis

seer.cancer.gov/statfacts 2016
Disease-specific survival by stage

Fig. 2 – Disease-specific survival rates according to the tumor stage of the cystectomy specimen.

pN0-3 survival

Fig. 11 – Disease-specific survival according to the lymph node status.

Extent of Dissection

• **Limited dissection:** external iliac, internal iliac, and obturator nodes

• **Extended dissection:** limited template extending to the aortic bifurcation to include the hypogastrics, common iliac, and presacral lymph nodes

• **Super Extended:** Carry dissection to IMA
Extent of Dissection

Fig. 1. Cumulative percent of patients with lymph node metastases versus total number of lymph nodes examined.
1260 patients with clinically non metastatic disease (underwent cystectomy and were found to have lymph node mets)
Lymphadenectomy – Lymph Node Metastasis

Risk of Death

Wright et al. Cancer 2008
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<tr>
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<th># of Nodes Removed</th>
<th>Node Positive %</th>
<th>5 year RFS pT2T3N0</th>
<th>5 year OS pT2T3N0</th>
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<td></td>
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Hugen et al.  World J Urol, 2015
## Extent of LND

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Hugen et al.  World J Urol, 2015
Lymph Node Count Variability

- Surgical technique

- Variability in pathologic practices
  - Single Surgeon (Same technique/template - @ two separate institutions)
    - 72 vs 40 node count (p <0.001)
    - Virtually identical Lymph node metastasis (23% vs 24%)

- En Bloc vs Separate Packets

Lymph Node Count Variability

En Bloc Vs Separate Packets

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### Lymph Node Count Variability

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**Fig. 1** Overall survival.

**Fig. 2** Recurrence-free survival.
Future Trials

• NCT01215071
  German multi-institutional randomized controlled trial comparing limited to extended LAD at the time of radical cystectomy
  • **Limited:** Internal/External Iliac Nodes and Obturator Nodes
  • **Extended:** Limited Template including nodes caudal to the inferior mesenteric artery including the paracaval, interaortocaval, paraaortic, and common iliac

• NCT01224665 (SWOG S1011)
  Multi-institutional randomized controlled trial comparing standard to extended LAD in patients undergoing open radical cystectomy
  • **Standard:** Nodes caudal to the bifurcation of the common iliac artery comprising the external and internal iliac nodes, the obturator nodes, and perivesical nodes
  • **Extended:** Standard template including common iliac, presacral, and presciatic nodes
Extent of Lymphadenectomy in Bladder Cancer

- Retrospective data demonstrates benefit of more extensive LND (But there may be a limit to this benefit)

Future:

- Randomized Trials – Extent of Dissection
- Improving Preoperative Imaging – Move from template based dissection to Anatomic defined boundaries
Prostate Cancer
Salvage Lymphadenectomy
Salvage LND

- Node only recurrence – harbinger of metastatic disease/cancer specific mortality
  - Cancer specific survival: 25-50%  (Heidenreich et al. Eur Urol, 2013)

Salvage Lymphadenectomy

- Secondary nodal removal for node only recurrence or BCR following primary therapy
Salvage LND

• No specific guidelines addressing treatment in these specific patients as they are deemed to be metastatic
  – Traditional management with ADT

Goals of Salvage LND

• Cure limited regional nodal recurrences
• Delay risk of progression
Screening for Nodal Recurrence

• Conventional CT and Bone scan have very low sensitivity at low PSA levels for recurrence

• Optimal results with salvage therapies better when done early (low PSA level)

• Choline PET CT
• 68Ga-PSMA PET CT
Screening For Nodal Recurrence

Choline PET CT

- EAU Guidelines recommend Choline PET to detect nodal recurrences after local treatment

- Detection of nodal recurrences:
  - Sensitivity: 40-60%
  - Specificity: 90-100%

- PSA cutoff and PSA kinetics predictive of + findings
  - PSA 1.05 ng/ml
  - 6 month PSA doubling time

- Salvage LND in setting of + Choline PET CT = Underestimate the real extent of nodal invasion

Lead Time Bias

- Nodal Recurrence Detected through better imaging
- Recurrence Detected through symptoms

Initial Cancer Tx

Age 67

Lead Time

Perceived Survival Time

Age 72

Perceived Survival Time

Age 75

5 Year Survival 100%

5 Year Survival 0%
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<td>Tilki et al. 2015</td>
<td>58</td>
<td>[18F]Choline PET</td>
<td>18.6</td>
<td>67%</td>
<td>38.50% 0%</td>
<td>68.90% 35.90%</td>
<td>71% @ 5 years</td>
</tr>
<tr>
<td>Suardi et al. 2015</td>
<td>59</td>
<td>[11C]Choline PET</td>
<td>11.7</td>
<td>66.10%</td>
<td>58.8% @ 3 years</td>
<td>64.2% @ 3 years</td>
<td>89.1% @ 5 Years</td>
</tr>
<tr>
<td>Porres et al. 2017</td>
<td>87</td>
<td>[18F]Choline PET/[68Ga] PSMA PET</td>
<td>38.80%</td>
<td>69.3% @ 3 years</td>
<td>75% @ 3 years</td>
<td>96.3% @ 3 years</td>
<td></td>
</tr>
</tbody>
</table>
## Salvage LND

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Imaging Modality/PPV</th>
<th># of Node (Mean)</th>
<th>Adjuvant Tx</th>
<th>BCR-Free Survival</th>
<th>Clinical Recurrence Free Survival</th>
<th>Cancer Specific Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rigatti et al. 2011</td>
<td>72</td>
<td>[11C]Choline PET</td>
<td>30.6</td>
<td>65%</td>
<td>55%</td>
<td>10%</td>
<td>74%</td>
</tr>
<tr>
<td>Jilg et al. 2012</td>
<td>47</td>
<td>[11C/18F]Choline PET</td>
<td>23.3</td>
<td>29%</td>
<td>71.80%</td>
<td>8.70%</td>
<td>76.60%</td>
</tr>
<tr>
<td>Karnes et al. 2015</td>
<td>52</td>
<td>[11C]Choline PET</td>
<td>21.5</td>
<td>82.70%</td>
<td>57.7% at 20 months</td>
<td>75% @ 20 months</td>
<td>96.2% @ 20 months</td>
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</tbody>
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Salvage LND

Prognostic Factors

- PSA < 4 ng/ml
- Complete PSA response following salvage LND
- Absence of retroperitoneal LND
- # of positive nodes

Lack of standardization in patients, technique of LND, and use of ADT affect applicability
Future Trials

• NCT02274779
  – Phase II Trial: non castrate PCa patients with only pelvic nodal recurrence receiving stereotactic body RT with 6 month ADT

• NCT01558427
  – Phase II Trial: surveillance vs metastasis directed therapy for oligometastatic PCa recurrence
Conclusions:

- Short term oncologic outcomes
- No comparative or randomized controlled trial has been published to support salvage LND
- Role of ADT with salvage LND is unknown
- Ultimate role may be to delay systemic treatment
- Improvement in imaging = Lymph node + recurrences
Conclusions

Surgical Humility
Thank You