Kidney Cancer Management: The Role of Lymph Node Dissection

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Lymph Node Invasion (LNI) in Kidney Cancer:

• LNI is universally considered a poor prognostic sign in any form of malignancy
• Independent predictor of Progression and DSS
• LND is common surgical procedure
  – Staging and therapeutic benefits in specified clinical scenarios
• In RCC, isolated LNI is rare
  – Predominant Hematogenous Metastases
  – 26% of patients with M1 have LNI
  – Enlarged LN common (19-23%) of which 10% have LNI
  – Autopsy and surgical studies: 2-6% LNI
  – Associated median time to progression 12 – 14 mos
  – 5-year Disease Specific Survival: 20%

Pantuck (Cancer 2003)
Blute (J Urol 2004)
Crisen (E Urol 2011)
Russell ( J Urol 2014)
Controversy: Defining the Role of LND in RCC

• LND is effective in other malignancies
• Long term survival has been seen in RCC patients with LNI following LND

• Problems:
  – LND templates are large for RCC = major surgery
  – Patient Selection – Who could benefit?
  – Undefined Biological Basis
  – Relevance in the targeted therapy TKI Era - uncertain
    • Adjuvant trial eligibility
    • Tissue for genomic studies
Routine LND in patients with RCC

Unwarranted

- 1087 patients
  - 535 (59%) N0M0
  - 43 (4%) N1M0
  - 236 (26%) N0M1
  - 86 (8%) N+M1
- LNI: Stage (T3, T4), Grade, Younger Age, Right side, Sarcomatoid, Poor ECOG
- Patients with N1M0 fared similarly to N0M1
- 27% of M1 patients had LNI and had worst survival
- M1 patients proceeding to IFN did better with LND
- Concl: Routine LND not indicated in cN0 cases, LND appears beneficial in Selected cases (cytoreduction)
- Limitations: Case selection, No standard template
The Role of Routine LND

- 732 patients with clinical M0 RCC
  - Majority w T2/T3 disease
  - LND: Hilum to Ao/Vc bifurcation
  - Ipsilateral Dissection
  - Overall 4% LN+ Rate
  - No survival difference

Concl: No benefit to routine LND
- Limitations: Imaging exclusion, No LN yield data provided, Limited LND performed in control group, Local/Regional Progression rates similar (7-9%)
Case Selection in LND

- 2028 Surgical Patients, pM0
  - 89 had pN1/2; 68 were clear cell
  - 4.4% rate of LNI
  - Pap (5.9%), Clear Cell (4.1%), Chrom (2%)
  - Features associated with LNI incl
    • Grade, Stage, Sarcomatoid, > 10 cm, Necrosis
  - Case selection: 2 or more points, standardized template

Limitations: Selection, pNx included, non-standard templates, excluded other subtypes
Results in High-Risk Patients

Anatomic Patterns of LNI

- 169 patients with 2 or more risk factors
  - 64 (38%) with LNI
  - Extended LND
  - Primary landing zones evaluated
  - Right to Left Pattern
  - Hilar node basins not always primary site

Concl: Validation of selection criteria for high risk, Extended Templates

Limitations: Variable Templates, Surgical Series, Survival data
Dissection Extent and Survival Outcomes

- SEER database
- 9586 Surgical M0 RCC Patients
- Controlled for confounders
- 13% LNI
  - Age
  - Grade
  - Papillary Histology

Improved DSS in patients with increasing node yield (> 5 and > 15)

Limitations: Absent Data and Mishandling
Meta-Analysis

• Review of contemporary literature
• Several sources of significant bias in existing studies
• However: Evidence of trend toward improvement in CSS in cT3 disease
Lymph Node Dissection in Renal Cell Carcinoma

Umberto Capitanio, Frank Becker, Michael L. Blute, Peter Mulders, Jean-Jacques Patard, Paul Russo, Urs E. Studer, Hein Van Poppel

<table>
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<tr>
<th>Author</th>
<th>Study design</th>
<th>Cases with RCC, no.</th>
<th>Hilar, %</th>
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<td>56.2</td>
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RCC = renal cell carcinoma; NA = not applicable.
* Right kidney.
* Left kidney.

Clinical staging

- Clinically T1–T2 negative nodes
- Clinically T3–T4 negative nodes
- Clinically positive nodes
- Metastatic patients: candidates to cytoreduction

LND should be considered for staging purposes only (level of evidence 1 [3])

Evidence of additional unfavorable characteristics at surgery

Extended LND (level of evidence 2 [6,31,35–37])

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Extended LND (level of evidence 2 [6,31,35–37])

Extended LND (level of evidence 2 [6,12,31,35–37,39])
Additional Consideration: Histologies at High Risk for LNI

- 62 yo man with growing neck mass
- CT: Left renal mass and enlarged nodes
• Papillary Type 2 HLRCC

Hereditary Leiomyomatosis and RCC Syndrome

Germline Mutation in Fumarate Hydratase

Phenotype: Degenerating uterine leiomyomas, skin leiomyomas and aggressive kidney cancers

Long term survivors with aggressive LND
12 mos after Partial Nephrectomy
Refused Other Therapy

NE Power (BJUI 2011)
<table>
<thead>
<tr>
<th>Patients</th>
<th>19</th>
<th>11 Women</th>
<th>8 Men</th>
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<tr>
<td>Median Age</td>
<td>39 years</td>
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<td>Median Follow-up</td>
<td>34 months</td>
<td>6-141 months</td>
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<td>Median Tumor Size</td>
<td>7.8 cm</td>
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<td>T1 tumors with +LN</td>
<td>4 / 7</td>
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<td>Overall +LN</td>
<td>9 / 19</td>
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LNI and the tumor microenvironment
Summary

Current Status

- Routine use of LND does not demonstrate therapeutic benefit in patients with low stage disease or non-suspicious nodes. (Level 1)
- LND as a staging procedure has utility for trial eligibility and tailoring post-surgical follow-up
- Unanswered: The role of extended LND in higher-risk patients (pT3+, High Grade, specific histologies) - though trend has been identified
- Standardization of LND nomenclature is key to registry studies.
- Accumulating data suggest trophic features in lymphatic priming and development of LNI tumor microenvironment selecting for resistant cell populations. Combination therapies with surgery?