Sentinel Lymph Node Mapping in Uterine Cancer: Paradigm Change

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University of Alabama at Birmingham
A disease whose management is in turmoil or natural evolution.
Corpus Cancer: Annual Incidence and Mortality

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>35,000</td>
<td>2,900</td>
</tr>
<tr>
<td>2012</td>
<td>47,130</td>
<td>8,010*</td>
</tr>
</tbody>
</table>

Why has the number of deaths gone up so dramatically?
Both pelvic and para-aortic nodes are at risk for metastatic disease

### Percentage of Pelvic/Aortic Node Metastasis by Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>% PV Node Met.</th>
<th>% PA Node Met.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>11</td>
</tr>
</tbody>
</table>

### Percentage of Pelvic/Aortic Node Metastasis by Myometrial Invasion

<table>
<thead>
<tr>
<th>Myometrial Invas.</th>
<th>% PV Node Met.</th>
<th>% PA Node Met.</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&lt; 1/3</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 2/3</td>
<td>31</td>
<td>18</td>
</tr>
</tbody>
</table>
## Endometrial Cancer: Lymphadenectomy

<table>
<thead>
<tr>
<th>G1, no myometrial invasion, no extrauterine disease</th>
<th>% Positive Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>G2 or G3, inner 1/3 invasion, no extrauterine disease</th>
<th>% Positive Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-9% Pelvic</td>
<td></td>
</tr>
<tr>
<td>4% Periaortic</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>G3, outer muscle, and/or extrauterine disease</th>
<th>% Positive Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-60% Pelvic</td>
<td></td>
</tr>
<tr>
<td>10-30% Para-Aortic</td>
<td></td>
</tr>
</tbody>
</table>

**Surgery upstages ~23% cases**  
GOG33 Creasman et al, Cancer 1987
What have we learned?

• Morbidity of node dissection was low
• Most patients did not need radiation therapy
• We are mediocre at predicting which patients needed post op therapy without staging
• Other prognostic features
  – LVSI
  – Depth of invasion
  – Aggressive histologic types
Stage everyone?

- Cannot reliably identify those with nodal metastases
  - Only 10% of nodes are palpable
  - Clinical assessment of risk factors is wrong 15% of the time
  - Up to 5% of low risk patients have positive nodes
- Lymphadenectomy may be therapeutic (?)
- Low morbidity
Endometrial Cancer: Surgical Staging

• **Conceptual rationale**
  – Defines extent of disease
  – Minimizes over/under treatment
  – Minimal increase in perioperative morbidity/mortality
  – Decreases overall Rx risks and costs
  – Allows comparison of therapeutic results
Effect of Nodal Sampling

Kilgore LC, Gynecol Oncol 56:23, 1995
Lymphadenectomy’s role...

Chan JK, Huh WK et al, Cancer 2006

• Assess potential therapeutic role of lymphadenectomy in women with EMCA

• Methods:
SEER 1988-2001
Inclusion: All stages, TAH + “LND” (≥ 1 LN)
Exclusion: UPSC, CCC, sarcoma...

• Results, N= 12333:
LN count (x): 7-12
“Trend” ↓ counts = ↑ adjuvant RT

5-yr Cause Specific Survival

<table>
<thead>
<tr>
<th>LN count</th>
<th>1</th>
<th>2-5</th>
<th>6-10</th>
<th>11-20</th>
<th>&gt;20</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-Intermediate Risk</td>
<td>75%</td>
<td>82%</td>
<td>84%</td>
<td>85%</td>
<td>87%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>IIIC – IV</td>
<td>51%</td>
<td>53%</td>
<td>53%</td>
<td>60%</td>
<td>72%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Low risk</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>0.23</td>
</tr>
</tbody>
</table>

FIGURE 1. (A) Kaplan-Meier disease-specific survival by number of lymph nodes removed in low-risk patients (Stage I, all grades; Stage IB, Grades 1 and 2). (B) Kaplan-Meier disease-specific survival by number of lymph nodes removed in intermediate-risk patients (Stage IB, Grade 3; Stage IIC-IV, all grades). (C) Kaplan-Meier disease-specific survival by number of lymph nodes removed in patients with nodal disease (Stage IIIC-IV).
Lymph node Sampling vs Dissection

• Pelvic and Aortic node dissections ⇒ improved survival and fewer retroperitoneal recurrences
  • (Chuang et al, Gynecol Oncol 58:189, 1995)
  • (Mohan et al, Gynecol Oncol 70:165, 1998)
  • (Mariani et al, Gynecol Oncol 76:348, 2000)

• If nodes are negative - no XRT
  • (Gretz et al, Gynecol Oncol 61:409, 1996)
  • (Berclaz et al, Int J Gynecol Cancer 9:322, 1999)
  • (Straughn et al, Gynecol Oncol 84(2):194-200, 2002)

• Even for IC lesions: UAB, WU, FL, OSU
  • (Straughn et al, Gyn Onc, 2003)
The Lymph Node Conundrum

• Role and widespread use of systematic staging is ↑ debated
• Changes in staging models and therapeutic paradigms have not improved outcomes
• What patients need therapy and what therapy will they benefit from?
**Surgical staging**

*ASTEC, The Lancet 2008*

- **Objective:** Assess potential of pelvic lymphadenectomy to improve survival in women with EMCA

- **Method:** RCT, 85 centers, 4 countries
  
  Clinical stage I/II
  
  TAH+BSO+washings+Palpation PALNs
  
  vs.
  
  Standard + PV lymphadenectomy
  
  Primary outcome OS
  
  Power 90%, 5-yr OS 80% to 90% [HR 0.47] in PVLND group, p=0.05)
  
  I/II intermediate or high-risk randomized to RT ASTEC (independent of LNs)

- **Results:** N= 704 vs. 704, Median LN 2 vs. 12
  
  Median f/u 37 Mo: 88 vs. 103 deaths
  
  5-yr OS difference = 1% (-4 – 6)
  
  Adjusted OS HR 1.04 (0.74-1.45; p=0.83)

  5-yr DFS difference = 6% (1 – 12)

  Adjusted DFS HR 1.25 (0.93-1.66; p=0.14)
Objective: Determine whether addition of PV lymphadenectomy to standard TAH+BSO improves OS and DFS.

Method: RCT, multi-institutional, Italy, 1996-2006
Clinical stage I
TAH+BSO +/- PV Lymphadenectomy
Primary outcome OS
Power 80%, 5-yr OS 80% to 88% [HR 0.52] in PVLND group, p=0.05
Adjuvant chemo +/- EBRT/EFRT/VB in those deemed high risk based on results

Results: N= 250 vs. 264, Median LN 30 vs. 0
More complications in LND group (p<0.001)
Median f/u 49 Mo
5-yr OS difference = 4.1% (NS)
OS HR 1.20 (0.70-2.07; p=0.50)
5-yr DFS difference = 0.7% (NS)
DFS HR 1.10 (0.70-1.71; p=0.68)
Endometrial Cancer
Surgical Management*

- Hysterectomy, BSO, Peritoneal Cytology, Pelvic/Para-aortic lymphadenectomy (up to renal vessels)
  - Omit lymphadenectomy if Grade 1 or 2, endometrioid, MI < 50%, and PTD < 2 cm
  - Omit lymphadenectomy if non-invasive endometrioid regardless of PTD or grade
  - Separately submit nodes above & below IMA
  - If non-endometrioid, add complete omentectomy, appendectomy, peritoneal biopsies, cytoreduction

Surgical staging - ‘Mayo Data’

Paraortic Node Metastases
Skipping Common Iliac Nodes

71%
Surgical staging - ‘Mayo Data’

Paraortic Node Metastases
Metastasis above IMA

77%
IMA
Surgical staging - ‘Mayo Data’

Endometrial Cancer

Surgical Staging*

- Lymphadenectomy up to IMA only
  - 38-46% PA node Positive cases missed
  - 62% cases node positive below IMA are node positive above IMA

Low Risk Endometrial Cancer: The Denouement?

Risk factors that mitigate the role of paraaortic lymphadenectomy in uterine endometrioid cancer

S. Kumar a, A. Mariani a, J.N. Bakkum-Gamez a, A.L. Weaver b, M.E. McGree b, G.L. Keeney c, W.A. Cliby a, K.C. Podratz a, S.C. Dowdy a,⁎

a Division of Gynecologic Surgery, Mayo Clinic, Rochester, MN, USA
b Division of Biomedical Statistics And Informatics, Mayo Clinic, Rochester, MN, USA
c Department of Anatomic Pathology, Mayo Clinic, Rochester, MN

HIGHLIGHTS

• Positive pelvic nodes, lymphovascular space invasion and myometrial invasion >50% are key factors to direct paraaortic lymphadenectomy.
• Omitting paraaortic lymphadenectomy for any grade endometrioid tumor with ≤50% myometrial invasion only missed 1.1% paraaortic node metastasis or recurrence.
• Using these criteria, para-aortic lymphadenectomy may be omitted in 77% of patients with endometrioid endometrial cancer.
The Sentinel Lymph Node Concept

- The first lymph node to which cancer is likely to spread from the primary tumor.
- These nodes can be identified and excised for histological analysis.
Why Should Sentinel Nodes be Considered in Endometrial Cancer?

- Standard of care in early stage breast cancer
  - ? Standard of care in vulvar cancer
- These nodes can be identified and excised for histological analysis (NPV: 91-96%, Sens: 89-92%)
- Minimize complications related to full lymphadenectomy including lymphedema, vascular/nerve injuries
- More than 90% of the removed lymph nodes are free of metastatic disease.
- Feasibility of a ‘full’ nodal dissection in Class III Obese Women
Prospective, cohort multicenter study

- 385 patients enrolled (clinical Stage I endometrial cancer)
- 340 with sentinel lymph node mapping + complete pelvic LND (196 with PA LND)
- 12% with positive nodes (36/41 w/ one mapped SN)
- Nodal mets identified in 35/36 of patients (97% with sens: 97%, PPV: 99.6%)
Today Sentinel Lymph Node is Common Ground

Is the “Gold Standard” Renal LND achievable?
Is it attainable in our patients & within our capabilities and practices worldwide?
971 Endometrioid with complete path data
65/971 = 6.7% positive nodes

In the 65 node positive cases:
- 60% of node positive cases were G1-2
- 48% had < 50% myoinvasion
- 23% had tumor size < 2cm

What is the Adequacy of Lymphadenectomy for Staging?

• Should be if we remove 20, 30, or 40 (-) LN

• Adequacy for staging is to find metastatic disease: a (+) node

• This depends on what we do in the operating room and on how the pathologists examine the nodes

• “if you want 10 lymph nodes I’ll give you 10 lymph nodes…” - Dr. R.J. Zaino

The Real Truth about Lymph Node Counts
Isolated (+) PAN with (-) Pelvic Nodes

<table>
<thead>
<tr>
<th>Myometrial invasion</th>
<th>Positive aortic nodes in %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
</tr>
<tr>
<td>1988 FIGO</td>
<td></td>
</tr>
<tr>
<td>None (IA)</td>
<td>0.60</td>
</tr>
<tr>
<td>&lt; 50% (IB)</td>
<td>0.62</td>
</tr>
<tr>
<td>&gt; 50% (IC)</td>
<td>1.56</td>
</tr>
</tbody>
</table>

Boronow RC. Gynecol Oncol. 2008
Mariani et al *Gynecol Oncol* (2004): “Notably, only 2% of patients with negative pelvic nodes had PA mets” (2 cases in 612 series)
Mariani et al Gynecol Oncol (2004): “Notably, only 2% of patients with negative pelvic nodes had PA mets” (2 cases in 612 series)

Based on LAP2

Table 5. Pelvic and Periaortic Nodal Metastasis Risk in High-Risk Patients

<table>
<thead>
<tr>
<th>Periaortic Lymph Nodes Positive</th>
<th>No (n=551)</th>
<th>Yes (n=31)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic lymph nodes positive</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No (n=532)</td>
<td>97.7 (520)</td>
<td>2.3 (12)</td>
<td></td>
</tr>
<tr>
<td>Yes (n=50)</td>
<td>62 (31)</td>
<td>38 (19)</td>
<td></td>
</tr>
</tbody>
</table>

2.3%
RARE
Isolated paraaortic metastasis with **negative** pelvic nodes

Rationale for Cervical Injection
Triple lymphatic origins of the uterus & cervix

Arise from 3 capillary networks
– Mucosa
– Muscularis
– Serosa

Cervical Injection Under Anesthesia
22GA Spinal Needle 2cc at 3 & 2cc at 9 O’clock

1981 FDA

1891 Not FDA

WWII
1959 FDA approved for liver & cardiac
Cervical Injection Sites
Location of SLN in Endometrial Cancer

They are NOT “all over the place”

90% are found here

Abu-Rustum NR, et al Gynecol Oncol 2009
Most Common Pattern of Drainage
Less Common Pattern of Drainage
SLN Improves the Detection of Metastasis

Positive Nodes

24/801 (3%) SLN

30/2698 (1%) non-SLN

3X

Using a cervical injection, metastatic cells are 3X more likely detected in the sentinel vs. the non-SLN

Are we diagnosing less stage IIIC?
Between 2008 -2010 (507 MIS cases)

Median number of lymph nodes

- 2008 (20)
- 2009 (10)
- 2010 (7) (P<0.001)

Stage IIIC Cases

- 2008 (10/143; 7%)
- 2009 (15/166; 7.9%)
- 2010 (13/164; 7.5%)

Leitao MM, et al. (MSKCC) Gynecol Oncol 2013
Surgical Algorithm for Endometrial Cancer
(Surgical staging for all cases, pro MIS)

Peritoneal & serosal evaluation & washings

Retroperitoneal evaluation

Remove SLN

Any suspicious nodes must be removed regardless of mapping

If there is no mapping on a hemi-pelvis, a side-specific LND is performed

Paraaortic LND at attending discretion

Barlin JN, et al. Gynecol Oncol 2012
PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

Figure 1: Common cervical injection sites for mapping uterine cancer†

Figure 2: Most common location of SLNs (blue, arrow) following a cervical injection†

Figure 3: Less common location of SLNs (green, arrow) usually seen when lymphatic trunks are not crossing over the umbilical ligament but following the mesoureter cephalad to common iliac and presacral region†
PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

Figure 4: The SLN algorithm for surgical staging of endometrial cancer

1. Peritoneal & serosal evaluation & washings

2. Retroperitoneal evaluation
   - Excision of all mapped SLN with ultrastaging
   - Any suspicious nodes must be removed regardless of mapping

3. If there is no mapping on a hemi-pelvis, a side-specific LND is performed
   - Para-aortic LND—done at attending discretion
Issues and Concerns that should be Addressed and Discussed (I)

• Do we need a confirmatory study to assess the safety of replacing lymphadenectomy with sentinel nodes (like GOG 174)?
  – Assessment of false negative predictive value (1-NPV)
  – Does it require a para-aortic dissection?
  – ICG vs Lymphazurin vs Methylene Blue?
  – What if sentinel nodes are in the NCCN Guidelines (Category 2A-3)

• Need a well-defined clinical protocol for non-detectable sentinel nodes, enlarged nodes, and when to a para-aortic dissection
Issues and Concerns that should be Addressed and Discussed (II)

• Address the expectations and algorithm for ultra-staging
  – Will the information be used to define prognosis and treatment?
• Apply to just higher risk patients or alternatively, just CAH?
• Impact of fellow training
• Billing
Questions?