Endometrial Cancer: Who Needs Lymphadenectomy

A Mariani, SC Dowdy, MB Jones, WA Cliby, BS Gostout, TO Wilson, KC Podratz

An exigent need exists for a paradigm shift in the management of endometrial cancer. The continuing debate as to whether to perform lymphadenectomy (LND) versus radiotherapy (RT) exemplifies a modality-based approach to treatment rather than using a disease-based care pathway. The primary objectives for a revised paradigm should be to optimize outcomes through minimizing both overtreatment and undertreatment. Overtreatment can be minimized by identifying patients not requiring LND or RT and undertreatment minimized by identifying patients benefiting from one or both modalities. Disease-based therapy should be predicated on anticipated patterns of failure predicted by pathologic (and/or molecular) determinants. The merits of LND are diagnostic, prognostic, therapeutic and predictive of the requirement for adjuvant therapy. LND should be reserved for patients at risk for node metastasis. An absence of nodal involvement and a 5 year survival of 100% were observed in a cohort of 123 consecutive patients fulfilling the following criteria: Grade 1/2, endometrioid, ≤ 50% myometrial invasion and primary tumor diameter ≤ 2 cm. Accordingly, LND is not indicated in these low risk patients. This group accounted for 20% of the overall population and 29% of endometrioid patients. Node positivity in the remaining endometrioid population (71%) was 17%. Thus, for all other endometrioid as well as nonendometrioid patients we recommend a systematic LND up to the renal vessels. The independent risk factors dictating pelvic sidewall failure include cervical stromal invasion and lymph node metastasis (LNM); 5 year failure rates are <1 % in the absence of these factors and 26% when either or both were present (p<0.001) despite traditional modality based treatment. Pelvic sidewall failures at 5 years in patients with positive nodes approximated 10% in our cohort treated with combined systematic LND and adjuvant RT compared to >50% for patients treated with either LND or RT alone (p<0.01). Furthermore, in the presence of pelvic LNM, the greater majority of patients had either paraaortic LNM at the time of surgery or subsequently failed in the paraaortic area. Importantly, in a recently completed prospective assessment, the majority of patients with paraaortic node involvement had negative nodes below the inferior mesenteric artery (IMA) while the greater majority had documented positive nodes above the IMA. Hence, LND is a determinant for adjuvant therapy including the requirement for extended RT fields including the paraaortic area whenever LNM is detected in either the pelvic or paraaortic node bearing regions.

REFERENCES


Endometrial Cancer
Surgical Staging
Role of Lymphadenectomy

Karl Podratz MD PhD FACS
Endometrial Cancer

Surgical Staging

• Definitive Staging
  • TAH/BSO/Peritoneal cytology
  • Pelvic/Paraaortic LND*
  • Biopsy/Omentectomy
  • Cytoreduction (Rx)

*LND = Lymph node dissection
Endometrial Cancer
Role of Lymphadenectomy vs Radiotherapy

- Modality-based therapy*
  - Lymphadenectomy
  - Radiotherapy

*Traditions, physician preferences, suboptimal study designs, etc.
## Endometrial Cancer
### Annual Incidence Cases and Deaths

<table>
<thead>
<tr>
<th>Year</th>
<th>ACS Estimates*</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cases</td>
<td>Deaths</td>
</tr>
<tr>
<td>1987</td>
<td></td>
<td>35,000</td>
<td>2,900</td>
</tr>
<tr>
<td>2007</td>
<td></td>
<td>39,080**</td>
<td>7,400***</td>
</tr>
</tbody>
</table>

*Ca 1987; CA 2007
**11.7% increase; ***155% increase
Endometrial Cancer
Role of Radiotherapy and Lymphadenectomy

• Treatment paradigm shift
  • Minimize overtreatment
    – Identify pts not requiring LND and/or RT
  • Minimize undertreatment
    – Identify pts benefiting from LND and/or RT
• Maximize outcomes
Endometrioid Endometrial Cancer
Role of Radiotherapy and Lymphadenectomy

• Modality-based therapy
  • Radiotherapy vs. lymphadenectomy
  • Uterine histology

• Disease-based therapy
  • Based on patterns of failure
    » Predicted by pathologic determinants
  • Selective Lymphadenectomy
  • Selective Radiotherapy
  • Selective Chemotherapy
Endometrial Cancer

Selective Lymphadenectomy
(not sampling)

• Lymph Node Dissection (LND)
  • Low risk: Not indicated
  • All others: Systematic
Endometrial Cancer

Selective Lymphadenectomy

• Lymphadenectomy not indicated*
  • Low risk:
    » Endometrioid
    » G 1&2
    » MI ≤ 50%
    » PTD ≤ 2 cm

Endometrioid Endometrial Cancer
Low risk: G1/2, < 2 cm, < 50% MI

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pt (no.)</th>
<th>% 5 yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hysterectomy only</td>
<td>59</td>
<td>100</td>
</tr>
<tr>
<td>Hyst + LND* +/- or RT**</td>
<td>64</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>123</td>
<td></td>
</tr>
</tbody>
</table>

^3/113 recurred (vagina) without RT; all salvaged
*All nodes negative; **10 RT; 7 for PPC
Mariani et al. Am J Ob Gyn 2000
Endometrioid Endometrial Cancer

Low Risk: G 1/2, MI ≤ 50%, PTD ≤ 2 cm

- Lymphadenectomy not indicated
  - 20% Overall population*
  - 29% Endometrioid patients*

Endometrioid Endometrial Cancer

Selective Lymphadenectomy

- Lymphadenectomy not indicated
  - Low risk: G 1/2, MI ≤ 50%, PTD ≤ 2 cm

- Systematic Lymphadenectomy
  - All others (not low risk)
  - 17% positive nodes
### Endometrial Cancer Failures

#### Pelvic Lymphatic Failures

<table>
<thead>
<tr>
<th>Lymphatic Site</th>
<th>Failure rate % at 5 years</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic Sidewall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>&lt;1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High risk*</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>

**Low risk = absence of high risk factors**

**High risk = *CSI and/or LN mets**
## Endometrial Cancer Failures
### Lymphatic Failures

<table>
<thead>
<tr>
<th>Lymphatic Site(s)</th>
<th>Failure rate % at 5 years</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pelvic Sidewall</strong></td>
<td></td>
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<tr>
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</tr>
<tr>
<td>High risk*</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td><strong>Para-aortic area</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High risk**</td>
<td>33</td>
<td></td>
</tr>
</tbody>
</table>

*Low risk = absence of high risk factors

High risk = *CSI and/or LN mets; **LN mets only
Endometrial Cancer Failures
Paraaoortic Lymphatic Involvement

• 33% para-aortic failures with pelvic and/or para-aortic LN mets

• 47% para-aortic LN mets or para-aortic failures with pelvic LN mets*

*Mariani et al 2002 (Mayo series)
Endometrial Cancer Failures

Paraaortic Lymphatic Involvement

• 47% with positive pelvic LN either had para-aortic LN mets or para-aortic failures *

*Mariani et al 2002 (Mayo series)*
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

Endometrial Cancer
Quality Assessment LND

Number paraaortic nodes removed per surgeon during phase I

Mayo QI Project
Endometrial Cancer
Quality Assessment LND

Number paraaortic nodes removed per surgeon during phase II

Mayo QI Project
Endometrial Cancer

Surgical Management*

• Objectives of Prospective Rx Algorithm
  • Prevalence Pelvic LN mets according to histologic subtype
  • Prevalence Para-aortic LN mets with lymphatic dissemination
  • Para-aortic metastatic site frequency as function of IMA

Endometrial Cancer

Surgical Management*

• 422 patients
  • 112 (27%) LND not indicated
    » 90 (80%) no LND
    » 22 (20%) had LND (all neg)
  • 310 (73%) required LND
    » 29 (9%) no LND
    » 281 (91%) had LND

Endometrial Cancer

Surgical Management*

• 281 at-risk patients LND
  • 15 pelvic (P) LND only
  • 1 para-aortic (PA) LND only
  • Median # nodes harvested
    » Pelvis 35
    » Para-aorta 17

• 63 (22%) positive nodes

## Endometrial Cancer
### Surgical Staging

<table>
<thead>
<tr>
<th>Node Site</th>
<th># Pos</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>P+PA</td>
<td>29</td>
<td>46</td>
</tr>
<tr>
<td>P</td>
<td>24</td>
<td>38</td>
</tr>
</tbody>
</table>

- **PA**: 10 of 63 patients (16%) had positive nodes.
- **P+PA**: 29 of 63 patients (46%) had positive nodes.
- **P**: 24 of 63 patients (38%) had positive nodes.

*63/281 (22%) at-risk patients had positive nodes.
## Endometrial Cancer

### Surgical Staging

<table>
<thead>
<tr>
<th>Node Site</th>
<th># Pos</th>
<th>%</th>
<th>Node</th>
<th># Pos</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA</td>
<td>9</td>
<td>16</td>
<td>PA</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>P+PA</td>
<td>29</td>
<td>51</td>
<td>P</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>19</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*57/265 (22%) at-risk pts had both P+PA LND & + nodes

Mayo prospective accrual 1/2004 to 12/2006
Endometrial Cancer

Surgical Staging*

• 63 (22%) at-risk pts Pos Nodes
  • 84% + pelvic nodes
  • 67% + paraaortic nodes
  » 71% com Iliacs neg

Paraaortic Node Metastases

Skipping Common Iliac Nodes

71%
Endometrial Cancer

Surgical Staging*

- 63 (22%) at-risk pts Pos Nodes
  - 84% + pelvic nodes
  - 67% + paraaortic nodes
    » 71% com Iliacs neg
    » 60% neg below IMA

Endometrial Cancer

Surgical Staging*

• 63 (22%) at-risk pts Pos Nodes
  • 84% + pelvic nodes
  • 67% + paraaortic nodes
    » 71% com Iliacs neg
    » 60% neg below IMA
  » 77% + above IMA

Paraaortic Node Metastases

Metastasis above IMA

77%
INVASION OF THE GONADAL VESSELS or surrounding soft tissue

28%
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

Non-Endometrioid Endo Ca (NEEC)
Role of Surgical Staging

• Surgical Staging required
  • Managed as ovarian
• 422 EC pts Rx’ed surgically*
  • **82 (19%)** NEEC
    – 37% Macro extra-uterine disease
    – 21% Micro extra-uterine disease
      » 25% noninvasive
    – 40% Node metastasis

*Mayo prospective series: 1/04-12/06
Endometrioid Endometrial Cancer

Surgical Management*

- 340 (81%) patients
  - 112 (33%) LND not indicated
    » 90 (80%) no LND
    » 22 (20%) had LND (all neg)
  - 228 (67%) required LND
    » 19 (8%) no LND
    » 209 (92%) had LND

Endometrioid Endometrial Cancer

Surgical Management*

- 209 at-risk patients LND
  - 11 pelvic LND only
  - Median # nodes harvested
    » Pelvis 36
    » Para-aorta 17
  - 34 (16%) positive nodes
    » 10% population

Endometrioid Endometrial Cancer
Surgical Staging

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<tr>
<th>Node Site</th>
<th># Pos</th>
<th>%</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PA</td>
<td>6</td>
<td>19</td>
<td>PA 63%</td>
</tr>
<tr>
<td>P+PA</td>
<td>14</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>12</td>
<td>37</td>
<td>P 81%</td>
</tr>
</tbody>
</table>

*32/198 (16%) at-risk pts had both P+PA LND & + nodes
Mayo prospective accrual 1/2004 to 12/2006
Endometrioid Endometrial Cancer

Surgical Staging*

- 32 (16%) at-risk pts Pos Nodes
  - 81% + pelvic nodes
  - 63% + paraaortic nodes
    » 67% com Iliacs neg
    » 73% Ipsi neg below IMA
    » 69% pos above IMA

Endometrioid Endometrial Cancer
Role of Radiotherapy and Lymphadenectomy

• **Treatment paradigm shift**
  • **Minimize overtreatment**
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  - Selective Radiotherapy
  - Selective Chemotherapy
Endometrial Cancer
Surgical Staging
Role of Lymphadenectomy

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