Are There Still Indications for Lymphadenectomy in Endometrial Cancer?

A Mariani
Mayo Clinic – Rochester - MN
Endometrial Cancer
Lymphadenectomy

Yes or No?

Endometrial Cancer
Lymphadenectomy

X

Yes or No?
Endometrial Cancer
Surgical Staging
Appropriate Questions

1) Population at risk

2) Adequacy and Quality

3) Utilization of the Info provided by Staging for Postoperative Treatment

4) M&M and Costs

Can they answer our questions?
Low Risk Populations Included in the 2 Prospective Endometrial Cancer Studies

Systematic Pelvic Lymphadenectomy vs No Lymphadenectomy in Early Stage Endometrial Carcinoma Randomized Clinical Trial

- Overall 13% of positive lymph nodes
- IA-IB G1 (45% of all cases)
- Overall 9% positive lymph nodes
Selection of Patients who may Benefit Of Treatment

Radiotherapy

Chemotherapy

Lymphadenectomy (?)

EndoCa

Limited Extent of Lymphadenectomy in the 2 Prospective Endometrial Cancer Studies

- Pelvic LND: at least 20 nodes required
- Median Number of pelvic nodes = 26
- Paraaortic LND at the discretion of the physician (performed in 26%)

“IIlac and obturator nodes”
- Median Number of Nodes = 12
- 35% less than 10 nodes
- Paraortic LND at the discretion of the physician

Median LND at Mayo: 35 pelvic; 17 PA
Great merit of the 2 prospective trials

We still do not have an adequate answer on the role of lymphadenectomy in endometrial cancer

Inappropriately Interpreted Prospective data Not Better than Good Retrospective data

Is Any Change in our Practice Necessary After the ASTEC/Italian Trials?

• Pelvic Lymphadenectomy (or sampling), if performed in every patient (including low risk patients) does not improve survival

• However, no significant conclusion can be drawn regarding the role of complete surgical staging (i.e. systematic pelvic and paraaortic lymphadenectomy) in high risk endometrial cancer
Is Any Change in our Practice Necessary After the ASTEC/Italian Trials?

- Therefore, **no change in the previous practice** should be suggested in **high risk** endometrial cancer patients.

- But, how do we define “high risk”?

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Prospective Analysis
Mayo Clinic (2004-08)
Criteria for Staging Patients

<table>
<thead>
<tr>
<th>No SURGICAL STAGING*</th>
<th>SURGICAL STAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Endometrioid</td>
<td>• All the others</td>
</tr>
<tr>
<td>• Myometrial Invasion &lt; 50%</td>
<td></td>
</tr>
<tr>
<td>• Grade 1 or 2</td>
<td></td>
</tr>
<tr>
<td>• Tumor Diameter ≤ 2 cm</td>
<td></td>
</tr>
<tr>
<td>• No macroscopic evidence of extrauterine tumor</td>
<td></td>
</tr>
</tbody>
</table>

* When all the criteria are present.
Preliminary* Data of Prospective Study

• **793** patients with endometrial cancer had hysterectomy during **60 months** (2004-08)

* Need Pathology Review

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Need for Surgical Staging by Protocol Criteria

793 EndoCa Patients

- 240 (30%) No Need LND
  - 54 (23%) had LND
  - 186 (77%) No LND

- 553 (70%) Need LND
  - 495 (90%) had LND
  - 58 (10%) No LND
### Preliminary Findings on Patients from the Prospective Study (n=494)

#### Pelvic Lymph Node Invasion

<table>
<thead>
<tr>
<th>Endometrioid</th>
<th>M≤50%</th>
<th>M&gt;50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1-2 M≤50% TD ≤ 2 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30% of pts</td>
<td>3%/**</td>
<td>14%</td>
</tr>
<tr>
<td>70% of pts</td>
<td>7%</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td>15%</td>
<td>53%</td>
</tr>
</tbody>
</table>

*Still waiting for path review

**95% CI 1% to 7.5%

### Preliminary Findings on Patients from the Prospective Study (n=463)

#### Paraaortic Lymph Node Invasion

<table>
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<th>M≤50%</th>
<th>M&gt;50%</th>
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<td>G1-2 M≤50% TD ≤ 2 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30% of pts</td>
<td>0.9%/**</td>
<td>11%</td>
</tr>
<tr>
<td>70% of pts</td>
<td>6%</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td>41%</td>
</tr>
</tbody>
</table>

*Still waiting for path review

**95% CI 0.2% to 4.6%
% Positive Lymph Nodes
Identify a Population at Risk for LN Invasion
• 98 of 495 (20%) patients who had lymphadenectomy had positive nodes

Grade 3 or Myometrial inv > 50%*

26% Positive LNDs

* Excluding stage IV

Endometrial Cancer
Surgical Staging

1) Population at risk

2) Adequacy and Quality

3) Utilization of the Info provided by Staging for Postoperative Treatment

4) M&M and Costs
PATIENTS WITH POSITIVE LYMPH NODES
Sites of Lymph Node Invasion

PA = Paraaortic
P = Pelvic

Patterns of Lymphatic Spread

Tumor above IMA

77% of PA+ have tumor above IMA
60% skipping of nodes below IMA
Definition of Adequate Lymph Node Dissection
Quality Control

A Study on the Therapeutic Role of Lymphadenectomy

Needs to Include the Para-aortic Area

Needs to Extend the Dissection Above the IMA (Renal veins)

Survival of Intensively Staged Patients with Positive Lymph Nodes

Onda 1997
75% 5-yr survival
Positive PA LND

Mariani 2000
76% 5-yr RFS
0% 5-yr PA Rec

Fujimoto 2007
3% PA rec

Mariani 2006
0% 5-yr PA Rec

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<th>Onda 1997</th>
<th>Survival of Intensively Staged Patients with Positive Lymph Nodes</th>
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<td>75% 5-yr RFS</td>
<td>Positive PA LND</td>
</tr>
<tr>
<td>Mariani 2000</td>
<td>76% 5-yr RFS, 0% 5-yr PA Rec</td>
</tr>
<tr>
<td>Fujimoto 2007</td>
<td>3% PA rec</td>
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</tbody>
</table>

| Table 1: Survival of Intensively Staged Patients with Positive Lymph Nodes |
|-----------------|-----------------|-----------------|
| Onda 1997       | Survival of Intensively Staged Patients with Positive Lymph Nodes |
| 75% 5-yr RFS    | Positive PA LND                                           |
| Mariani 2000    | 76% 5-yr RFS, 0% 5-yr PA Rec                              |
| Fujimoto 2007   | 3% PA rec                                                 |
Endometrial Cancer
Surgical Staging

1) Population at risk

2) Adequacy and Quality

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Unstaged Endometrial Cancer at risk for LN invasion, but Treated with Pelvic RT

If No Lymphadenectomy:

Pelvic RT for high risk

Undertreatment 62% of patients with LN+ but with tumor in the PA

Overtreatment (?)

% with LN-
PORTEC
Endometrial Cancer IC AND Grade 3 Hysterectomy + EBRT

58% overall survival
31% distant mets

Mayo data (G3 AND M≥50%): 35-53%* Positive pelvic LNDs
26-41%* positive PA LNDs

* The second number includes stage IV patients

Mayo Clinic Approach to Endometrial Cancer
DISEASE-BASED THERAPY

Using the Info Provided by the Final Path Report in the Uterus and Staging Information

Mayo Clinic 2004-2009
Endometrial Cancer Predictors of Recurrence

Risk Factors

Vaginal Spread
- Histologic Grade 3, LVI

Hematogenous Dissemination
- Myometrial Invasion >50% (≥ 66% at stage I)

Lymphatic Embolization
- LVI, Cervical Stromal Invasion, Lymph node mets

✓ Peritoneal Dissemination
  ✓ Stage IV
  ✓ Stage I-III -- CSI, PPC, LN mets, non-endometrioid (>2)
Disease-Based Therapy

At Risk For:
Hematogenous Rec
(Mb<50%; Mb<66% stage I)
Peritoneal Rec
(Stage 4 or PPC, type II, LN+, CSI >=2)

At Risk For:
Lymphatic Recurrence
(CSI, LN+)
Vaginal Recurrence
(G3, LVI)

Endometrial Cancer
Surgical Staging

1) Population at risk

2) Adequacy and Quality

3) Utilization of the Info provided by Staging for Postoperative Treatment

4) M&M and Costs
Toxicity of postoperative EBRT Increased after Surgical Staging

Table 1: Comparison of the outcome in terms of lymphedema in stage I and II melanoma patients.

<table>
<thead>
<tr>
<th>Trial</th>
<th>LND+ (n=182)</th>
<th>LND- (n=69)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphedema</td>
<td>14 (8%)</td>
<td>1 (1%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Infected / symptomatic lymphocele/hematoma/abscess</td>
<td>12 (7%)</td>
<td>1 (1%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Thromboembolic Complications</td>
<td>8 (4%)</td>
<td>1 (1%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Operative Time (minutes)</td>
<td>106.7 ± 62.5</td>
<td>199.1 ± 81.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Estimated Blood Loss (ml)</td>
<td>329 ± 242.3</td>
<td>429 ± 309.5</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Currently Studying lymphedema more in detail with questionnaires

Surgical Complications

**Toxicity of Chemotherapy**

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>LND+ Grade 3</th>
<th>LND+ Grade 4</th>
<th>LND+ Grade 5</th>
<th>LND- Grade 3</th>
<th>LND- Grade 4</th>
<th>LND- Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/nauseo</td>
<td>7.1 (66.6)</td>
<td>3.8 (57.1)</td>
<td>0 (0)</td>
<td>5.6 (40.0)</td>
<td>2.7 (55.6)</td>
<td>0 (66.7)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>0.7 (57.1)</td>
<td>4.3 (65.6)</td>
<td>0 (0)</td>
<td>4.0 (33.3)</td>
<td>1.9 (42.9)</td>
<td>0 (50)</td>
</tr>
<tr>
<td>Anemia/anaemia</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0 (0)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>WBC alopecia</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0 (0)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hematoma</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0 (0)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Thrombolytic complications</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0 (0)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
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Creutzberg 2004

Kuoppala 2008

Mayo Clinic 2004-2006 – Preliminary data

ASTEC 2009
Analysis of Mayo Clinic (1999-2008)
M&M and Costs is in Progress

Mariani, Dowdy

A Prospective Study on the Role of Surgical Staging

- Needs to analyze the impact of staging on M&M, Costs and QOL with appropriate utilization of staging information and targeted postoperative treatment
CONCLUSIONS

• Consensus on the role of surgical staging in endometrial cancer still not available

• ASTEC / Italian trials did not appropriately address the role of systematic surgical staging (pelvic + paraaortic LND) in high risk endometrial cancer

• Adequate data that indicate the need to abandon surgical staging in high risk patients are not available

CONCLUSIONS

• Need to combine our efforts to find an answer for the best individualized treatment of endometrial cancer

• International Consortium – Randomized Prospective Trial
Questions that Need to be Answered by a Randomized Prospective Trial

- Select those patients who might potentially benefit of staging
- Define the adequacy and quality of staging, including paraaortic LND
- Identify the role of postoperative treatment targeted at patients and areas found positive at staging
- Identify the best cost-effective treatment that carries less M&M, better QOL, and better prognosis

Staging → Targeted Postoperative Treatment

No Staging → More frequent Postoperative Treatment

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