Transperitoneal Infrarenal Lymphadenectomy

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Conflicts of Interest

• I have no conflicts of interest relevant to this talk
• Other relationships
  - Alexion - consulting
  - Merck - consulting/research
  - Novocure - consulting
  - Biodesix - consulting
  - Genentech - consulting/speaker’s bureau
  - Clovis - consulting
  - Janssen - consulting
Objectives

• Review the data on use of Para-aortic lymphadenectomy
• Review surgical techniques

ACOG Statement on Endometrial Cancer

ACOG Practice Bulletin
Clinical Management Guidelines for Obstetrician-Gynecologists
Number 65, August 2005

Management of Endometrial Cancer

Endometrial carcinoma is the most common gynecologic malignancy that will be encountered by almost every gynecologist. A thorough understanding of the epidemiology, pathophysiology, and management strategies allows the obstetrician-gynecologist to identify women at increased risk, to counsel women toward risk reduction, and to facilitate early diagnosis of this cancer. The purpose of this document is to review the risks and benefits of current treatment options to optimize outcomes for women with endometrial cancer.
Pelvic Lymphadenectomy

Two large prospective randomized trials of pelvic lymphadenectomy have failed to show a difference in outcome.

ASTEC
- Randomization to pelvic radiation based on pathologic risk factors and not pelvic lymph node status
- Only 27 patients with positive lymph nodes in the lymphadenectomy group
- Only half of the patients with positive node received pelvic radiation

Italian Trial
- Postoperative treatment was not standardized and more patients without lymphadenectomy got radiation ($P=0.07$)

GOG 33 compared to ASTEC/EN.5
Rates of Lymphatic Involvement

- Pelvic Nodes: GOG 33: 9.0%, ASTEC: 5.0%
- Para-aortic Nodes: GOG 33: 5.5%, ASTEC: 0.4%

Very few PAN done!

Are Lymph Node Counts Important?

- ASTEC
- Lap-2

Chan JK, Cancer 109(12):2545, 2007
**ASTEC/EN.5 Trial**

Cancer Clinically confined to the Uterus

Randomize

- Hysterectomy BSO
- Hysterectomy BSO + PN ± PAN

5% had nodes

Randomize IA/B Gr3 or IC Gr-any or advanced disease*

*Randomization WITHOUT regard to nodal status!

92% had nodes

median = 12

Brachytherapy was allowed and NOT standardized

90% Power - 10% difference in O.S. (80% --> 90%)

n = 1400

Kitchener H, Lancet 373:125, 2009

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**ASTEC/EN.5 Trial Positive Nodes**

1,408 patients

<table>
<thead>
<tr>
<th>Standard</th>
<th>Lymphadenectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 5 (27%)</td>
<td>n = 27 (5%)</td>
</tr>
<tr>
<td>n = 3 (60%)</td>
<td>n = 13 (48%)</td>
</tr>
<tr>
<td>n = 2 (40%)</td>
<td>n = 14 (52%)</td>
</tr>
</tbody>
</table>

Randomize IA/B Gr3 or IC Gr-any or advanced disease*

*Randomization WITHOUT regard to nodal status!

Kitchener H, Lancet 373:125, 2009
**Italian Lymphadenectomy Trial**

Clinical stage I Endometrial Cancer

Randomize

Staging not required

Endpoint - PFS/OS

Powered for decrease in survival by %

<table>
<thead>
<tr>
<th>No Lymphadenectomy</th>
<th>Pelvic Lymphadenectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 250</td>
<td>n = 264</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>+ Nodes</th>
<th>PFS</th>
<th>OS</th>
<th>RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Nodes</td>
<td>3.2%</td>
<td>82%</td>
<td>90%</td>
</tr>
<tr>
<td>PN</td>
<td>13.3%</td>
<td>81%</td>
<td>86%</td>
</tr>
<tr>
<td>( p ) value</td>
<td>&lt;0.001</td>
<td>0.68</td>
<td>0.5</td>
</tr>
</tbody>
</table>


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"this model shows that the ASTEC trial would not have shown a difference in outcome from lymphadenectomy due to the trial design alone, even if a difference had existed. In addition to being underpowered, the design of the ASTEC trial negated any possible advantage to lymph node detection by not giving adjuvant therapy to those patients with positive nodes. This model predicts that even if the lymphadenectomy by itself had been 100% successful in eradicating disease, no detectable difference between the two arms would have been seen."

Naumann RW, Gynecol Oncol 126:5, 2012
Compared patients from two institutions
- 325 patients with PN
- 346 patients with PN + PAN

Survival was longer for PN + PAN (HR 0.53, 95% CI 0.38–0.76; p=0.0005)

Survival better in 407 patients at intermediate or high risk (p=0.0009), but overall survival was not related to lymphadenectomy type in low-risk patients

Multivariate analysis of prognostic factors showed that in patients with intermediate or high risk of recurrence, PN + PAN reduced the risk of death compared with pelvic lymphadenectomy (0.44, 0.30–0.64; p<0.0001)
Low risk = > 1/2 invasion, grade 1-2, no LVSI

What do we need to know for node dissection?

• What is the risk of nodal metastasis?
• What is the morbidity of nodal dissection?
Risk of Lymph Node Metastasis
Data from GOG 33

<table>
<thead>
<tr>
<th>Location</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endo Only</td>
<td>Low Risk</td>
<td></td>
<td>High Risk</td>
</tr>
<tr>
<td></td>
<td>4% PN</td>
<td>2% PAN</td>
<td>16% PN</td>
</tr>
<tr>
<td>Inner ⅓</td>
<td></td>
<td></td>
<td>10% PAN</td>
</tr>
<tr>
<td>Middle ⅓</td>
<td>56% of pt / ~25% (+) nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outer ⅓</td>
<td>46% of pt / ~75% (+) nodes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Creasman WT. Cancer 60:2035, 1987

High Risk Factors for Lymphatic Spread - Mayo Clinic

- Deep myometrial invasion (Outer 1/2)
- High grade tumors
- LVSI
- Tumors > 2 cm in size
- Any spread outside the uterus
- Type II tumors

Mariani A, Gynecol Oncol 109:11, 2009

Risk of nodal disease 22% - no nodal recurrences in absence of these factors
Mayo Clinic Algorithm

• Overall 22% positive
• If pelvic nodes are positive the para-aortic nodes will be positive in $\frac{2}{3}$ of cases
• $\frac{3}{4}$ of positive para-aortics were positive above the IMA
  – 60% were negative below the IMA

Indications: Grade 3, Outer $\frac{1}{2}$ invasion, > 2 cm tumor

Mariani A, Gynecol Oncol 109:11, 2008

Technique
Considerations for Choosing a Surgical Method

- Technical feasibility
- Adequacy of procedure
- Complication rates
- Conversion rates
- Cosmesis

Is Transperitoneal Para-aortic Lymphadenectomy Technically Feasible?
• GOG Protocol in cervical cancer
  – Laparoscopic lymphadenectomy prior to open radical hysterectomy
  – 40 patients evaluable
  – Excluded BMI > 35
• Node Counts
  – Pelvic - 31.1
  – Para-aortic - 12.1 (did not require above IMA)

Schlaerth JB, Gynecol Oncol 85(1):81, 2002

Lap-2

• Randomized clinical trial demonstrating
  – Decreased short term morbidity
  – Improved quality of life
  – No difference in overall recurrence rate or survival
• Compared LAPAROSCOPY to OPEN
  – No data comparing outcomes for robotics
  – Surgery feasible in 74% of all patients
  – Laparoscopy 74 minutes longer
### Lap-2

<table>
<thead>
<tr>
<th></th>
<th># nodes</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic Nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laparoscopy</td>
<td>17</td>
<td>98%</td>
</tr>
<tr>
<td>Open</td>
<td>18</td>
<td>99%</td>
</tr>
<tr>
<td>Para-aortic Nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laparoscopy</td>
<td>7</td>
<td>97%</td>
</tr>
<tr>
<td>Open</td>
<td>7</td>
<td>94%</td>
</tr>
</tbody>
</table>

### Comparison of Trans-peritoneal to Bilateral and Left Retro-peritoneal Techniques

<table>
<thead>
<tr>
<th></th>
<th>Convert</th>
<th># nodes</th>
<th>R nodes</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trans-peritoneal</td>
<td>22%</td>
<td>19</td>
<td>7</td>
<td>160 min</td>
</tr>
<tr>
<td>Bilateral Retro-peritoneal</td>
<td>21%</td>
<td>16</td>
<td>7.7</td>
<td>153 min</td>
</tr>
<tr>
<td>L Retro-peritoneal</td>
<td>14%</td>
<td>15</td>
<td>2.4</td>
<td>119 min</td>
</tr>
</tbody>
</table>

Dargent D. Gynecol Oncol 77:87, 2000
Are conversion rates higher than robotics?
Success Rate by BMI

- 65% Success at BMI of 35
- 74% success rate

Converted to Laparotomy

- Randomization
  - 920 patients randomized to laparotomy
  - 1696 patients randomized to laparoscopy
- Laparoscopy outcomes
  - 408 of 1696 (24%) patients converted to laparotomy due to complications
    - 231 (13.6%) Poor Exposure
    - 73 (4.3%) Technical difficulty
    - 9 (0.6%) Equipment Failure
    - 47 (2.8%) Bleeding
    - 48 (2.8%) Other
### Reasons for Conversion

<table>
<thead>
<tr>
<th>Reason</th>
<th>Robotic</th>
<th>Laparoscopic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor Exposure</td>
<td>105</td>
<td>76</td>
</tr>
<tr>
<td>Bleeding</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Technical Difficulty</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>12.4%</td>
<td>26.3%</td>
</tr>
</tbody>
</table>

**Adapted from:** Naumann RW. "Laparoscopic Management of Gynecologic Malignancies" in Minimal Access Cancer Management, 2nd ed. F Greene and RT Heniford (Eds.), Springer and company – in press.

### Endometrial Cancer Conversion Rates with Laparoscopy

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
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<tbody>
<tr>
<td>Hildebaugh 1997</td>
<td>24</td>
<td>9%</td>
</tr>
<tr>
<td>Gemignani 1999</td>
<td>69</td>
<td>4%</td>
</tr>
<tr>
<td>Eltabbakh 2001</td>
<td>100</td>
<td>6%</td>
</tr>
<tr>
<td>Serbou 2004</td>
<td>73</td>
<td>39%</td>
</tr>
<tr>
<td>Holub 2002</td>
<td>96</td>
<td>4%</td>
</tr>
<tr>
<td>Langebeekke 2002</td>
<td>27</td>
<td>7%</td>
</tr>
<tr>
<td>Murosobu 2002</td>
<td>173</td>
<td>5%</td>
</tr>
<tr>
<td>Knoppalu 2004</td>
<td>40</td>
<td>3%</td>
</tr>
<tr>
<td>Obermair 2004</td>
<td>226</td>
<td>5%</td>
</tr>
<tr>
<td>Twiz 2005</td>
<td>61</td>
<td>8%</td>
</tr>
<tr>
<td>Wang 2005</td>
<td>20</td>
<td>5%</td>
</tr>
<tr>
<td>Cio 2007</td>
<td>165</td>
<td>5%</td>
</tr>
<tr>
<td>Kalopissas 2007</td>
<td>69</td>
<td>6%</td>
</tr>
<tr>
<td>Nezhut</td>
<td>127</td>
<td>13%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>127</td>
<td>7%</td>
</tr>
</tbody>
</table>
### Endometrial Cancer Conversion Rates with Robotics

<table>
<thead>
<tr>
<th>Series</th>
<th>n</th>
<th>Convert</th>
<th>% Staged</th>
<th>BMI</th>
<th># PAN</th>
<th>Above IMA?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denardis 2008</td>
<td>56</td>
<td>5.4%</td>
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<td>28</td>
<td>6.5</td>
<td>N.S.</td>
</tr>
<tr>
<td>Seamon 2008</td>
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<td>34</td>
<td>9</td>
<td>NO</td>
</tr>
<tr>
<td>Boggess 2008</td>
<td>103</td>
<td>3%</td>
<td>100%</td>
<td>33</td>
<td>12</td>
<td>NO</td>
</tr>
<tr>
<td>Lowe 2009</td>
<td>405</td>
<td>6.7%</td>
<td>72%</td>
<td>32</td>
<td>2.8</td>
<td>N.S.</td>
</tr>
<tr>
<td>Peiretti 2009</td>
<td>80</td>
<td>3.7%</td>
<td>4%</td>
<td>25</td>
<td>-</td>
<td>NO</td>
</tr>
<tr>
<td>TOTAL</td>
<td>749</td>
<td>7%</td>
<td>68%</td>
<td>5.5</td>
<td>NONE</td>
<td></td>
</tr>
</tbody>
</table>

Same as Laparoscopy?

### Endometrial Cancer Lymphadenectomy with Robotics

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<th>n</th>
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<th>BMI</th>
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<td></td>
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</table>

Isn’t this lower than Lap-2?

Very Low
Surgical Approach

Laparoscopic Incisions for Radical Hysterectomy

- Grasper
- Scissors/Bipolar
- 10 mm - 0° Scope
- Optional Grasper

Scissors/Bipolar

Grasper

Optional Grasper

10 mm - 0° Scope
Cosmetic?

True Minimally Invasive Surgery!

Laparoscopic Para-Aortic Node Dissection
PAN from Left

Carolinias Medical Center

MIGS

PAN Dissection from Right

Carolinias Medical Center

MIGS
Removing the Left Gonadal Vessels

Caution!!
PAN with Barbed Suture

PAN in Obese Patient
PAN taking the IMA

Radical PAN

HAND ASSISTED
RADICAL EXPOSURE OF PARA-AORTIC AREA
Thank you!