Endometrial cancer stage I

• Nicoletta Colombo
• Thomas Hogberg
Disclosure slide

• No relevant disclosures
Clinical case

- A 72 year-old woman with postmenopausal bleeding
- Weight: 95 Kg; Height: 160 cm; BMI: 37
- Endometrial biopsy: FIGO stage 3 endometroid endometrial carcinoma
- MRI: reveals a uterine mass of 3.5 cm with a focal myometrial invasion of more than 50%.
- CT scan: no distant metastases
Which type of access do you prefer in this case?

1. Abdominal
2. Vaginal
3. Laparoscopic (eventually combined with vaginal)
4. Robot assisted
5. Other
6. No surgery
Discussion on type of access

• Nicoletta Colombo
Surgical Scenario in Gyn Oncology
Which type of access do you prefer in this case?

Vaginal

• Does not allow abdominal exploration, peritoneal washings and lymph node dissection
• Often the BSO is challenging

Therefore not the preferred mode

Surgical Scenario in Gyn Oncology

Laparoscopic Surgery

- Expanded applications
- Faster learning curve
- Easy transition from Open Surgery Experience to Robotic-Assisted Laparoscopy Surgery

Robotic Surgery
“Minimally invasive surgery is the optimal treatment in the management of Endometrial Cancer”
Recurrence and Survival After Random Assignment to Laparoscopy Versus Laparotomy for Comprehensive Surgical Staging of Uterine Cancer: Gynecologic Oncology Group LAP2 Study

Joan L. Walker, Marion R. Piedmonte, Nick M. Spirito, Scott M. Eisenkop, John B. Schlaerth, Robert S. Mannel, Richard Barakat, Michael L. Pearl, and Sudarshan K. Sharma
Early Endometrial Cancer Surgical Treatment

Minimally Invasive Surgery

Traditional Laparoscopy

Laparoscopy Robotically Assisted
Surgical robotics is defined as a **computer interface** between the surgeon and the patient.

Computer-assisted surgery **can enhance** human visualization, strength, precision and degrees of motion in performing surgical tasks.
What does robotic surgery offer?

- Surgeon controls the robotic arms remotely
- 3-D image through stereoscopic viewer (high definition option)
- Seven degrees of movement mimic human wrist movement (eliminate fulcrum effect)
- Tremor filtration & motion scaling
What does robotic surgery offer?

• Intuitive motion
• Emulate “open” surgery
• Fast learning curve
• Ergonomic position for surgeon
Robotic vs Laparoscopic Hysterectomy & Staging: Endometrial Cancer

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>BMI (Kg/m²)</td>
<td>33 vs 29</td>
<td>33 vs 32</td>
<td>34 vs 29*</td>
</tr>
<tr>
<td>OP time (min)</td>
<td>191 vs 213*</td>
<td>184 vs 171</td>
<td>242 vs 287*</td>
</tr>
<tr>
<td>EBL (mL)</td>
<td>75 vs 146*</td>
<td>166 vs 253</td>
<td>100 vs 250*</td>
</tr>
<tr>
<td>LOS (day)</td>
<td>1.0 vs 1.2</td>
<td>2.0 vs 2.3</td>
<td>1 vs 2*</td>
</tr>
<tr>
<td>Nodes (n)</td>
<td>33 vs 23*</td>
<td>17 vs 17</td>
<td>21 vs 22</td>
</tr>
<tr>
<td>Conversion (%)</td>
<td>2.9 vs 4.9</td>
<td>NA</td>
<td>12 vs 26*</td>
</tr>
<tr>
<td>Complication (%)</td>
<td>5.8 vs 13.6</td>
<td>7.5 vs 20*</td>
<td>13 vs 14</td>
</tr>
</tbody>
</table>

* p< .01 (mean values)
Obese patient
Comprehensive Surgical Staging for Endometrial Cancer in Obese Patients: **Comparing Robotics and Laparotomy**

<table>
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<tr>
<th></th>
<th>TRH</th>
<th>TAH</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>58</td>
<td>65</td>
<td>.003</td>
</tr>
<tr>
<td>BMI (Kg/m2)</td>
<td>39.6</td>
<td>39.9</td>
<td>Matched</td>
</tr>
<tr>
<td>OR time (min)</td>
<td>228</td>
<td>143</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>EBL (mL)</td>
<td>109</td>
<td>394</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Transfusion Rate</td>
<td>2%</td>
<td>9%</td>
<td>.046</td>
</tr>
<tr>
<td>Hospital Stay (day)</td>
<td>1</td>
<td>3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total Nodes</td>
<td>24.7</td>
<td>23.9</td>
<td>NS</td>
</tr>
<tr>
<td>Pelvic Nodes</td>
<td>18.5</td>
<td>18.7</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic Nodes</td>
<td>8.5</td>
<td>7.2</td>
<td>NS</td>
</tr>
<tr>
<td>Complication</td>
<td>11%</td>
<td>27%</td>
<td>.0</td>
</tr>
</tbody>
</table>
Comprehensive Surgical Staging for Endometrial Cancer in Obese Patients: Comparing Robotics and Laparotomy
What is the **optimal minimally invasive** surgical procedure for endometrial cancer staging in the obese and morbidly obese woman?


<table>
<thead>
<tr>
<th></th>
<th>TRH</th>
<th>TLH</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>49</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td><strong>BMI (Kg/m2)</strong></td>
<td>37.5</td>
<td>35</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Distribution BMI</strong></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>35-39.9</td>
<td>41%</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>≥ 40</td>
<td>26%</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td><strong>OR time (min)</strong></td>
<td>189</td>
<td>215</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>EBL (mL)</strong></td>
<td>50</td>
<td>150</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Hospital Stay (day)</strong></td>
<td>1.0</td>
<td>1.2</td>
<td>0.011</td>
</tr>
<tr>
<td><strong>Total Nodes</strong></td>
<td>33.7</td>
<td>21.7</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Complication</strong></td>
<td>6</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Conversion</strong></td>
<td>1</td>
<td>3</td>
<td>NS</td>
</tr>
</tbody>
</table>
• In a world where we all drive a Ford Taurus...
• One day, a neighbor buys a Ferrari
  – It goes faster, it’s sexier, it’s smaller
• Do I need a randomized study to show it is faster on left handed turns, on right handed turns, the acceleration is faster, the leather is softer ...
Has the issue of minimally invasive surgery in endometrial cancer been settled?

A. I need more data before I will integrate MIS into routine practice
B. I think comparative trials between Robotic and Laparoscopic and/or Open surgery are still needed
C. The dust has settled, a new moon has risen- MIS is here to stay- move on already!
D. There is no data set that will make me incorporate MIS- ever!
In this obese patient I would prefer the robot-assisted access because:

- Endoscopy results in the same survival
- Less complications, shorter hospital stay and better QOL with endoscopy
- Robot-assisted surgery is easier to perform than laparoscopy in obese patients. One of the advantages is that it is possible to operate at lower pressure (5-7 mmHg) than with traditional endoscopy, due to the improved dexterity.
Which type of surgery do you recommend in this case?

1. Total abdominal hysterectomy bilateral salpingo-oophorectomy (TAH-BSO)
2. TAH-BSO + pelvic lymphadenectomy
3. TAH-BSO + pelvic and peri-aortic lymphadenectomy
Discussion on the role of lymphadenectomy

• Nicoletta Colombo
Religion vs Science

Why do we perform lymphadenectomy?

• Identify disease spread
  – Prognosis
  – Target postoperative treatment and potentially reduce the number of pts requiring postoperative treatment
• Therapeutic and debulking effect (node +)

Who should undergo lymphadenectomy?

• Selective
• All
• None
Lymphatic Dissemination in Endometrial Cancer

4-15%

- Negative Lymph Nodes
- Positive Lymph Nodes
Fraction of patients in each substage and percentage of node metastases

Chi et al., IJGC, 2008, 18:269-273
Creasman et al., Cancer, 1987, 60:2035-41
Preliminary Findings* on Patients from the Prospective Study (n=494)

Pelvic Lymph Node Invasion

- **Endometrioid G1-2**
  - Myo≤50%
  - TD ≤ 2 cm

  - 30% of pts

- 70% of pts

- **Mayo Clinic 2010**
  - 3%
  - 15%
  - 7%

- **Myo>50%**
  - G1
    - 14%
  - G2
    - 7%
    - 28%
  - G3
    - 15%
    - 53%
Preliminary Findings* on Patients from the Prospective Study (n=463)
Paraortic Lymph Node Invasion

<table>
<thead>
<tr>
<th>Endometrioid</th>
<th>Myo≤50%</th>
<th>Myo&gt;50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1-2</td>
<td>G1</td>
<td>11%</td>
</tr>
<tr>
<td>Myo≤50%</td>
<td>G2</td>
<td>6%</td>
</tr>
<tr>
<td>TD ≤ 2 cm</td>
<td>G3</td>
<td>10%</td>
</tr>
<tr>
<td>30% of pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70% of pts</td>
<td></td>
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</tr>
</tbody>
</table>

Mayo Clinic 2010

www.esmo2012.org
Our patient....

Has a 30-50% probability of having positive pelvic node
Has a 40% probability of having positive para-aortic nodes
Meta-analysis indicated:

- no significant difference in overall and recurrence-free survival between women who received lymphadenectomy and those who received no lymphadenectomy (pooled HR = 1.07, 95% CI: 0.81 to 1.43 and HR = 1.23, 95% CI: 0.96 to 1.58 for overall and recurrence-free survival respectively).

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Lymphadenectomy N</th>
<th>No lymphadenectomy N</th>
<th>log [Hazard Ratio] (SE)</th>
<th>Hazard Ratio IV</th>
<th>Weight</th>
<th>Hazard Ratio IV</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kitchener 2009</td>
<td>670</td>
<td>667</td>
<td>0.04 (0.17)</td>
<td></td>
<td></td>
<td>73.1 %</td>
<td>1.04 [0.75, 1.45 ]</td>
</tr>
<tr>
<td>Panici 2008</td>
<td>264</td>
<td>250</td>
<td>0.15 (0.28)</td>
<td></td>
<td></td>
<td>26.9 %</td>
<td>1.16 [0.67, 2.01 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.07 [0.81, 1.43]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.0; Chi² = 0.11, df = 1 (P = 0.74); I² = 0.0%

Test for overall effect: Z = 0.48 (P = 0.63)
Systematic Pelvic Lymphadenectomy vs No Lymphadenectomy in Early-Stage Endometrial Carcinoma: Randomized Clinical Trial

The writing committee on behalf of the ASTEC study group

Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRCASTEC trial): a randomised study
Low Risk Populations Included in the 2 Prospective Endometrial Cancer Studies

- Overall 13% of positive lymph nodes
- IA-IB G1 (45% of all cases)
- Overall 9% positive lymph nodes
Limited Extent of Lymphadenectomy in the 2 Prospective Endometrial Cancer Studies

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

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

Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC/ASTEC trial): a randomised study

- “Iliac and obturator nodes”
- Median Number of Nodes = 12
- 35% less than 10 nodes
- Paraaortic LND at the discretion of the physician
Results of including all different risk patients...
ASTEC/Italian Trials
Unanswered questions

• **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
Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis

Yukihiro Toda, Hidenori Kato, Masanori Kanouchi, Hidenichi Watarji, Mahito Takeda, Noriaki Sakuragi

Retrospective

P+PA

Intermediate/High Risk

Pelvic Only

Significant Improvement

RFS

DRS

OS

Disease-Related Survival

* At least one variable

The Lancet 2010

www.esmo2012.org
Question

• My interpretation of ASTEC + Benedetti LND studies is:

A. Well conducted RCT ➔ consistent information ➔ Very limited role for routine LND today

B. Interesting data ➔ but not convincing due to design flaws

C. The overwhelming evidence outside of these 2 studies favors routine LND
Conclusions

• Low Risk patients do NOT need LND

• High Risk patients (G3, DMI, non endometrioid histo) may benefit from PPALND

• Assess prognosis

• Determine adjuvant treatment

• Potentially reduce patients who need adjuvant treatment (morbidity)
Clinical case

• She is treated with robot assisted total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO), including pelvic and peri-aortic lymph node resection and pelvic washings.

• Pathology confirms a grade 3 tumor with invasion of the deep 1/3 of the uterine wall (within 2mm of serosa)

• Lymphonodes are negative
What to do next?

- Nothing
- Pelvic radiotherapy
- Pelvic+para-aortic radiotherapy
- Chemotherapy
- Concomitant Chemo-radiotherapy
- Chemotherapy followed by radiotherapy
In case lymphanectomy was not performed

What to do next?

• Nothing
• Pelvic radiotherapy
• Pelvic+para-aortic radiotherapy
• Chemotherapy
• Concomitant Chemo-radiotherapy
• Chemotherapy followed by radiotherapy
Discussion

• Thomas Hogberg
Question

A 72 yo with Stage IC, gr 3

- Presents for consultation
- 0/27 PPALN, cytology (-)

The real question today is?

A. What ???- she needs radiation!
B. We need better models to predict risk of recurrence
C. The question is cuff vs pelvic XRT
D. Would this patient benefit from chemotherapy?
Clinical case

• She is treated with pelvic radiotherapy and 18 months later returns for follow-up with complaints of persistent non-productive cough.
• Chest x-ray reveals small bilateral pulmonary nodules (largest 1.8cm).
• Fine needle aspiration under CT guidance confirms grade 2 adenocarcinoma.
• CT scan of abdomen and pelvis shows no other evidence of recurrent disease.
What would you recommend now?

1. Megestrol acetate (Megace)
2. Megestrol acetate alternating with tamoxifen
3. An aromatase inhibitor
4. Doxorubicin + cisplatin
5. Doxorubicin + cisplatin + paclitaxel (Taxol)
6. Carboplatin + paclitaxel
Discussion

• Thomas Hogberg