Surgical Treatment of Endometrial Cancer

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Endometrial Cancer (EC)

- The most common gynecologic malignancy
- The 4th most common woman’s cancer (breast, lung, colorectal)
- 49,560 new cases → 8190 death (USA, 2013)
- Mostly early stage (75%)
- Adenocancer (85%), USC (5-10%), Clear cell (5%)
Types of EC

Type 1 (80%)
- Estrogen dependent
- Endometroid adenocancer
- 63 y
- 70% stage I
- 5 y. surv. ≈ 83%

Type 2
- Estrogen unrelated
- Non-endometrioid cancer
- 67 y
- 50% advanced stage
- 5 y. surv. ≈ 53% USC
- 57% CC
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I*</td>
<td>Tumor confined to the corpus uteri</td>
</tr>
<tr>
<td>IA*</td>
<td>No or less than half myometrial invasion</td>
</tr>
<tr>
<td>IB*</td>
<td>Invasion equal to or more than half of the myometrium</td>
</tr>
<tr>
<td>II*</td>
<td>Tumor invades cervical stroma, but does not extend beyond the uterus**</td>
</tr>
<tr>
<td>III*</td>
<td>Local and/or regional spread of the tumor</td>
</tr>
<tr>
<td>IIIA*</td>
<td>Tumor invades the serosa of the corpus uteri and/or adnexae#</td>
</tr>
<tr>
<td>IIIB*</td>
<td>Vaginal and/or parametrial involvement#</td>
</tr>
<tr>
<td>IIIC*</td>
<td>Metastases to pelvic and/or para-aortic lymph nodes#</td>
</tr>
<tr>
<td>IIIC1*</td>
<td>Positive pelvic nodes</td>
</tr>
<tr>
<td>IIIC2*</td>
<td>Positive para-aortic lymph nodes with or without positive pelvic lymph nodes</td>
</tr>
<tr>
<td>IV*</td>
<td>Tumor invades bladder and/or bowel mucosa, and/or distant metastases</td>
</tr>
<tr>
<td>IVA*</td>
<td>Tumor invasion of bladder and/or bowel mucosa</td>
</tr>
<tr>
<td>IVB*</td>
<td>Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes</td>
</tr>
</tbody>
</table>

*Either G1, G2, or G3.

**Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.

#Positive cytology has to be reported separately without changing the stage.
Mortality

- Advanced stage disease (50% of all deaths)
- High risk histology
- Not comprehensive surgical staging?
- Poor performance
Prognostic Factors

**Uterine**
- MI
- LVSI
- Cervical involvement

**Extrauterine**
- Adnexial involvement
- Intraperitoneal dissemination
- Peritoneal cytology ??
- Lymph node met.

**Tumoral**
- Histologic types
- Grade
- Tumor diameter
- Molecular
  - DNA ploidi
  - E, P receptors
  - P53, PTEN etc.
<table>
<thead>
<tr>
<th>Risk</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Confined to uterus; MI (-) or ≤1/2</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Confined to uterus MI &gt;1/2, occult cx involvement</td>
</tr>
<tr>
<td></td>
<td>One of poor prognostic factors (PPF) MI &gt;1/3, G2-3, LVSI (+)</td>
</tr>
<tr>
<td>High-intermediate</td>
<td>50-69 Y; three of PPF</td>
</tr>
<tr>
<td></td>
<td>≥70 Y; two of PPF</td>
</tr>
<tr>
<td>High</td>
<td>Stage II-IV, PSC or clear cell</td>
</tr>
</tbody>
</table>
Endometrium CA: Lymphatic Drainage and Metastasis

- Primary => Pelvic lymph nodes
- Pelvic lymph node (-) => isolated paraaortic LN involvement 2%

- Pelvik LN (+)
- Advanced stage
- MI >50%
- G3, High risk histology

Aortic LN met. risk

Onda. Br J Cancer 1977
Chen Gynecol Oncol 1985
Creasman. Cancer 1987
Treatment

Surgery
- Staging
- Debulking

Adjuvant Radiotx.
- Before
- After

Chemotx.
- Hormonal
- Cytotoxic
Surgical Treatment

Comprehensive Surgical staging

High risk factors

Adjuvant treatment

Recurrence (local, dist.)
Early Stage EC

Surgical Staging

- Peritoneal cytology
- Exploration
- Open Surgery or MIS
- TAH + BSO
- PPALND
Topics of debate in surgical treatment of early stage EC

- LND to all patients?
- Type of LND; sampling vs systematic?
- Only pelvic vs PABPLND?
- LND; therapeutic or diagnostic?
- MIS vs Laparotomy?
- Sentinel Lymph Node Concept?
Topics of debate in surgical treatment of early stage EC

• LND to all patients?
  • Type of LND; sampling vs systematic?
  • Only pelvic vs PABPLND?
  • LND; therapeutic or diagnostic?
  • MIS vs Laparotomy?
  • Sentinel Lymph Node Concept?
LN Met. in EC

- # 422
- LND (-) (27%)
  - Endometrioid (G1 ve G2), MI ≤1/2, PTD* ≤ 2cm
  - Endometrioid and MI( -)(Grade ve PTD independendly)
- LN #: pelvik 36.5 ± 13.4, PA 17.4 ± 8.1
- LN Met (High risk group)
  - Endometrioid 16%, nonedometrioid 40%
  - İzole pelvik 33%, izole PA 16%, pelvik+PA 51%

*PTD: Primer tümör çapı

• Mariani A, Gynecol Oncol 2008
No LND

Endometrioid (G1 ve G2), MI ≤1/2, PTD* ≤ 2cm

Endometrioid and MI(-) (independently from Grade ve PTD )
If there is one of them:
Extrauterine disease
Grade 3
Non endometrioid
MI>50%
Adnexiel met.

Yes

BPPALND (non-endometrioid omentectomy, appendectomy, peritoneal biopsy)

No

One of them
Tumor ≥ 2 cm and MI< 50%
Cervical involv.

Yes

BPLND (frozen pelvic LN (+) PALND)

No

Operation stop

(cervical involv.; RH)
If \( \varnothing \leq 2 \text{ cm} \), stop.

If \( \varnothing > 2 \text{ cm} \), perform Pelvic LND.*

- **Myo\leq50\%**
- **Myo>50\%**

**G1**

**G2**

**G3**

* PA LND, only if Pelvic Nodes Positive at FS.

Mayo 2010
Frozen-Section (FS) and Final Pathology

- Grade: %35
- MI: %28
- Cervical involvement: %13
- LVSI: %32
- Staging with intraoperative FS: 6.6 – 13% suboptimal

Kumar S, Cancer.(2011)
Radiologic Examination

USG, CT, MRI

Sensitivity 29-90%

PET

Sensitivity 60%

• Horowitz NS, Gynecol Oncol, 2004; Kinkel K, Radiology, 1999; Rockall AG, J Clin Oncol, 2005
Summary

LND to all patients

- Because of diagnostic inaccuracy of FS, all patients with early stage EC should undergo comprehensive surgical staging.
Topics of debate in surgical treatment of early stage EC

• LND to all patients?
• Type of LND; sampling vs systematic?
• Only pelvic vs PABPLND?
• LND; therapeutic or diagnostic
• MIS vs Laparotomy
Type of LND

- **Sampling**
  - Only 10% of LN : palpable
  - 37% of LN met. <2 mm
  - Sufficient LN # ?
  - 62% of PLN and 17% PALN mets. are missed out

- **Systematic**
  - LN mets. and micromets. are taken out
Therapeutic effect of LN counts

A: Low risk
B: Intermediate
C: High risk

Chan JK. Cancer 2006 (SEER Data)
Topics of debate in surgical treatment of early stage EC

- LND to all patients?
- Type of LND; sampling vs systematic?
- Only pelvic vs PAPLND?
- LND; therapeutic or diagnostic
- MIS vs Laparotomy
Only Pelvic or Pelvic+Paraortic
What is the incidence of isolated paraaortic nodal metastasis in patients with negative pelvic nodes

• 2-3%
- Sol ovarian ven
- IMA
Topics of debate in surgical treatment of early stage EC

- LND to all patients?
- Type of LND; sampling vs systematic?
- Only pelvic vs PABPLND?
- LND; therapeutic or diagnostic?
- MIS vs Laparotomy?
- Sentinel Lymph Node Concept?
### Low risk Group
LND and Survival

<table>
<thead>
<tr>
<th>Study</th>
<th>HR</th>
<th>95% CI</th>
<th>Weight (%)</th>
<th>HR with 95% CI (fixed effect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al. (10)</td>
<td>1.10</td>
<td>0.81–1.49</td>
<td>79.1</td>
<td></td>
</tr>
<tr>
<td>Cragun et al. (11)</td>
<td>1.08</td>
<td>0.40–2.95</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>Kitchener et al. (6)</td>
<td>1.40</td>
<td>0.68–2.91</td>
<td>13.7</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1.14</td>
<td>0.87–1.49</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $X^2=0.36$, df=2 ($P=0.84$); $I^2=0$

Test for overall effect: $Z=0.94$ ($P=0.35$)

---

Kim HS, Jpn J Clin Oncol 2012
Intermediate, High Risk Group; LAND and Survival

<table>
<thead>
<tr>
<th>Study</th>
<th>HR</th>
<th>95% CI</th>
<th>Weight (%)</th>
<th>HR with 95% CI (fixed effect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al. (10)</td>
<td>0.76</td>
<td>0.68–0.85</td>
<td>62.1</td>
<td></td>
</tr>
<tr>
<td>Cragun et al. (11)</td>
<td>0.55</td>
<td>0.31–0.99</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Jeong et al. (12)</td>
<td>0.46</td>
<td>0.19–1.09</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Kitchener et al. (6)</td>
<td>0.95</td>
<td>0.61–1.47</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(early-stage high-risk)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kitchener et al. (6)</td>
<td>1.27</td>
<td>0.83–2.00</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(advanced-stage high-risk)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>0.77</td>
<td>0.70–0.86</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $X^2=7.96, \text{df}=4 (P=0.09); I^2=47\%$

Test for overall effect: $Z=4.78 (P<0.000001)$
### SEPAL Study (Survival Effect of Para-Aortic Lymphadenectomy in endometrial cancer)

**Table 4: Overall, disease-specific, and recurrence-free survival of patients with endometrial carcinoma according to type of lymphadenectomy and risk of recurrence**

<table>
<thead>
<tr>
<th></th>
<th>Low risk</th>
<th>Intermediate or high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pelvic lymphadenectomy (n=131)</td>
<td>Pelvic and para-aortic lymphadenectomy (n=133)</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died</td>
<td>13 (10%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>3 years</td>
<td>98.4%</td>
<td>97.0%</td>
</tr>
<tr>
<td>5 years</td>
<td>94.2%</td>
<td>96.2%</td>
</tr>
<tr>
<td>8 years</td>
<td>93.1%</td>
<td>96.2%</td>
</tr>
<tr>
<td><strong>Disease-specific survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died</td>
<td>5 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>3 years</td>
<td>99.2%</td>
<td>99.2%</td>
</tr>
<tr>
<td>5 years</td>
<td>96.7%</td>
<td>99.2%</td>
</tr>
<tr>
<td>8 years</td>
<td>95.5%</td>
<td>99.2%</td>
</tr>
<tr>
<td><strong>Recurrence-free survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsed or died</td>
<td>14 (11%)</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>3 years</td>
<td>96.9%</td>
<td>97.0%</td>
</tr>
<tr>
<td>5 years</td>
<td>92.7%</td>
<td>95.3%</td>
</tr>
<tr>
<td>8 years</td>
<td>92.7%</td>
<td>94.4%</td>
</tr>
</tbody>
</table>

Data are number of patients (%) or percentage survival. Numbers of patients were recorded at least 5 years after treatment completion. Percentage survival at 3 years, 5 years, and 8 years was estimated by Kaplan-Meier analysis (figure 2).

Figure 2: Cox regression analysis of overall survival with pelvic and para-aortic lymphadenectomy compared with pelvic lymphadenectomy alone according to risk of recurrence. Data not available.

Todo Y, Lancet, 2010
Recurrence; LN (+) > LN (-): 6X

Morrow CP, Gynecol Oncol 1991
LND - Survival

LND, no effect on survival in low risk group

LND, positive effect on survival in intermediate and high risk group

Kim HS, Jpn J Clin Oncol 2012 (Metaanalysis)
Lymphadenectomy-Summary

Correct question
- Whom
- When

Wrong question
- Yes
- No
Surgical Treatment in Stage II

- Cervical adenocarcinoma should be excluded
Clinical Stage II EC

**TREATMENT**

- Extrrafascial hysterectomy + Staging + Rtx

- Radical Hysterectomy + Staging + Adj. Rtx (if indicated)
## Stage II; Radical Hys. vs Simple Hys.

<table>
<thead>
<tr>
<th></th>
<th>Simple Hys.</th>
<th>Radical Hys.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No of patients</strong></td>
<td>315</td>
<td>127</td>
</tr>
<tr>
<td><strong>LA (%)</strong></td>
<td>233 (74)</td>
<td>126 (99.2)</td>
</tr>
<tr>
<td><strong>Adj RT (%)</strong></td>
<td>220/258 (85)</td>
<td>43/119 (36)</td>
</tr>
<tr>
<td><strong>Rec(%)</strong></td>
<td>57 (18)</td>
<td>10 (7.8)</td>
</tr>
<tr>
<td><strong>Local rec.(%)</strong></td>
<td>27 (8.5)</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td><strong>Distant rec.(%)</strong></td>
<td>34 (11)</td>
<td>7 (5.5)</td>
</tr>
<tr>
<td><strong>Death (%)</strong></td>
<td>16/136 (12)</td>
<td>2/59 (3.4)</td>
</tr>
</tbody>
</table>

- Eltabbakh GH, Gynecol Oncol 1999; Calvin DP, Am J Clin Oncol 1999; Feltmate CM, Gynecol Oncol 1999;
- Mariani A, Gynecol Oncol 2001; Sartori E, Int J Gynecol Cancer 2001; Ayhan A, Gynecol Oncol 2004
Advanced Stage EC
Advanced stage & Treatment

Cytoreductive Surgery
Advanced Stage Surgery

- Exp.
- TAH + BSO
- Lmp.
- Debulk.
- Oment.

- Eradication of ALL Macroscopic tumors
TABLE 2. The effect of surgical cytoreduction in endometrial cancer

<table>
<thead>
<tr>
<th>Authors (reference)</th>
<th>Year</th>
<th>N</th>
<th>FIGO stage</th>
<th>Definition of surgical cytoreduction</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aalders et al(^{17})</td>
<td>1984</td>
<td>108</td>
<td>III(^{*})</td>
<td>Surgical resection of all macroscopic tumor</td>
<td>5-year survival(^{†}): 41% vs 11%</td>
</tr>
<tr>
<td>Greven et al(^{18})</td>
<td>1989</td>
<td>52</td>
<td>III(^{*})</td>
<td>Surgical resection not further specified</td>
<td>5-year survival(^{†}): 48% vs 36%</td>
</tr>
<tr>
<td>Goff et al(^{19})</td>
<td>1994</td>
<td>47</td>
<td>IV</td>
<td>Leaving no bulky disease; tumor residuum not stated</td>
<td>Median survival(^{†}): 18 vs 8 months(^{‡})</td>
</tr>
<tr>
<td>Chi et al(^{20})</td>
<td>1997</td>
<td>55</td>
<td>IV</td>
<td>Optimal cytoreduction defined as largest tumor nodule ≤ 2 cm residual disease</td>
<td>Median survival: 31 months vs 12 months(^{‡})</td>
</tr>
<tr>
<td>Bristow et al(^{21})</td>
<td>2000</td>
<td>65</td>
<td>IVB</td>
<td>Optimal cytoreduction defined as largest residual tumor ≤ 1 cm</td>
<td>Median survival(^{§}): 34 months vs 11 months(^{‡})</td>
</tr>
<tr>
<td>Ayhan et al(^{22})</td>
<td>2002</td>
<td>37</td>
<td>IVB</td>
<td>Optimal cytoreduction defined as largest residual tumor ≤ 1 cm</td>
<td>Median survival(^{§}): 25 months vs 10 months(^{‡})</td>
</tr>
<tr>
<td>Van Wijk et al(^{23})</td>
<td>2006</td>
<td>67</td>
<td>III or IV</td>
<td>Optimal cytoreduction defined as macroscopic removal of all tumor</td>
<td>5-year survival(^{§}): 66% vs 41%</td>
</tr>
</tbody>
</table>

\(^{*}\)Clinical stage.
\(^{†}\)Cytoreduction versus no cytoreduction.
\(^{‡}\)Statistically significant.
\(^{§}\)Optimal cytoreduction versus not optimal cytoreduction.
Advanced Stage EC

MORBIDITY $\Rightarrow$ %16 - 24

Lambrou, Oncol, 2004 Gynecol
Ayhan, Int J Gynecol Cancer, 2002
Topics of debate in surgical treatment of early stage EC

• LND to all patients?
• Type of LND; sampling vs systematic?
• Only pelvic vs PABPLND?
• LND; therapeutic or diagnostic?
• MIS vs Laparotomy?
• Sentinel Lymph Node Concept?
Role of MIS in Endometrial Carcinoma

- Application
- Complications
- QOL
- Oncogic outcome and safety
Laparoscopy
Early stage endometrial cancer

MIS

Evaluation of peritoneal cavity
Peritoneal cytology

- LAVH or LH
- Prognostic factors
- Laparoscopic lymphadenectomy

- MI > %50
- G3
- Cervical involvement
- Adnexal involvement

IP disease
- L/T
Laparoscopy is associated with similar or lower complication rates compared to laparotomy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Laparoscopy</th>
<th>Laparotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scribner et al. (1999) [9]</td>
<td>10.5</td>
<td>17.6</td>
</tr>
<tr>
<td>Eltabbakh et al. (2000) [10]</td>
<td>7.5</td>
<td>10.0</td>
</tr>
<tr>
<td>Langebrekke et al. (2002) [12]</td>
<td>3.7</td>
<td>4.1</td>
</tr>
<tr>
<td>Holub et al. (1998) [6]</td>
<td>15.2</td>
<td>20.4</td>
</tr>
<tr>
<td>Litta et al. (2003) [14]</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Kuoppala et al. (2004) [16*]</td>
<td>17.5</td>
<td>32.5</td>
</tr>
</tbody>
</table>
### Laparotomy vs Laparoscopy

<table>
<thead>
<tr>
<th>Author</th>
<th>Recurrence (%)</th>
<th>DFS(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LPT</td>
<td>LS</td>
</tr>
<tr>
<td>Eltabbakh GH</td>
<td>10.5</td>
<td>7</td>
</tr>
<tr>
<td>Holub Z</td>
<td>6.8</td>
<td>6.2</td>
</tr>
<tr>
<td>Langebrekke A</td>
<td>4.1</td>
<td>0</td>
</tr>
<tr>
<td>Kuoppala T</td>
<td>2</td>
<td>2.5</td>
</tr>
</tbody>
</table>

- Recurrence and DFS are similar between laparoscopy and laparotomy group

Magrina JF, Curr Opin Obstet Gynecol, 2005
Quality of Life

Zullo F, Am J Obstet Gynecol 2005
Robotic Surgery
• 415 EC
  – 183 robotic (97% pelvic, 73% paraaortic LND)
  – 232 laparoskopic (%94% pelvic, %63 paraaortic LND)
Survival analysis of robotic versus traditional laparoscopic surgical staging for endometrial cancer

Joel Cardenas-Goicoechea, MD; Amanda Shepherd, MD; Mazdak Momeni, MD; John Mandeli, PhD; Linus Chuang, MD; Herbert Gretz, MD; David Fishman, MD; Jamal Rahaman, MD; Thomas Randall, MD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Robotic (n = 193)</th>
<th>Laparoscopy (n = 232)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (range)</td>
<td>62 (30–86)</td>
<td>61 (27–86)</td>
<td>.56</td>
</tr>
<tr>
<td>BMI, kg/m² (range)</td>
<td>29.2 (17–55)</td>
<td>29.3 (17–58)</td>
<td>.20</td>
</tr>
<tr>
<td>Comorbid condition, n (%)</td>
<td>118 (65)</td>
<td>145 (63)</td>
<td>.68</td>
</tr>
<tr>
<td>HTN, n (%)</td>
<td>89 (49)</td>
<td>129 (52)</td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>29 (16)</td>
<td>37 (16)</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>13 (7)</td>
<td>17 (7)</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>61 (33)</td>
<td>62 (27)</td>
<td></td>
</tr>
<tr>
<td>Conversion, n (%)</td>
<td>5 (2.7)</td>
<td>12 (5.2)</td>
<td>.21</td>
</tr>
<tr>
<td>Surgical stage, n (%)</td>
<td></td>
<td></td>
<td>.25</td>
</tr>
<tr>
<td>I</td>
<td>153 (84)</td>
<td>197 (85)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>4 (2)</td>
<td>12 (5)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>23 (13)</td>
<td>21 (9)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>3 (1.6)</td>
<td>2 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Grade, n (%)</td>
<td></td>
<td></td>
<td>.15</td>
</tr>
<tr>
<td>1</td>
<td>79 (43)</td>
<td>113 (49)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>52 (28)</td>
<td>72 (31)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>52 (28)</td>
<td>47 (20)</td>
<td></td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td></td>
<td></td>
<td>.71</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>146 (80)</td>
<td>196 (84)</td>
<td></td>
</tr>
<tr>
<td>Serous</td>
<td>14 (8)</td>
<td>14 (6)</td>
<td></td>
</tr>
<tr>
<td>Clear-cell</td>
<td>4 (2)</td>
<td>3 (1)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>12 (7)</td>
<td>10 (4)</td>
<td></td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>7 (3.6)</td>
<td>13 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>0</td>
<td>1 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Median node counts</td>
<td></td>
<td></td>
<td>&gt; .05</td>
</tr>
<tr>
<td>Pelvic (range)</td>
<td>13 (2–50)</td>
<td>15 (1–52)</td>
<td></td>
</tr>
<tr>
<td>Paraortic (range)</td>
<td>8 (1–27)</td>
<td>7 (1–29)</td>
<td></td>
</tr>
<tr>
<td>Total (range)</td>
<td>19 (2–61)</td>
<td>20 (2–60)</td>
<td></td>
</tr>
<tr>
<td>Adjuvant therapy, n (%)</td>
<td></td>
<td></td>
<td>.11</td>
</tr>
<tr>
<td>No treatment</td>
<td>108 (59)</td>
<td>156 (67)</td>
<td></td>
</tr>
<tr>
<td>Radiation only</td>
<td>24 (13)</td>
<td>34 (15)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy only</td>
<td>19 (10)</td>
<td>19 (8)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy + radiation</td>
<td>32 (17)</td>
<td>22 (9)</td>
<td></td>
</tr>
<tr>
<td>Refused</td>
<td>0</td>
<td>1 (0.4)</td>
<td></td>
</tr>
</tbody>
</table>
Recurrence and over-all survival are similar in both group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Robotic, n = 183</th>
<th>Laparoscopy, n = 232</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence, n (%)</td>
<td>27 (14.8)</td>
<td>28 (12.1)</td>
<td>.42</td>
</tr>
<tr>
<td>Isolated vaginal cuff, n (%)</td>
<td>1 (0.5)</td>
<td>5 (2.2)</td>
<td>.17</td>
</tr>
<tr>
<td>Pelvis, n (%)</td>
<td>7 (3.8)</td>
<td>10 (4.3)</td>
<td>.80</td>
</tr>
<tr>
<td>Abdomen ± pelvis, n (%)</td>
<td>15 (8.2)</td>
<td>11 (4.7)</td>
<td>.15</td>
</tr>
<tr>
<td>Distant ± pelvis ± abdomen, n (%)</td>
<td>9 (4.9)</td>
<td>9 (3.9)</td>
<td>.61</td>
</tr>
<tr>
<td>Time for surgery to first recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, mo (range)</td>
<td>19 (2–50)</td>
<td>11.25 (2–70)</td>
<td>.36</td>
</tr>
</tbody>
</table>

MIS in EC
SUMMARY

• If performed experienced surgeon
  – Similar oncologic outcome with laparotomy
  – Short hospital stay
  – Better QOL
  – Early adjuvant treatment
  – Preferable in morbid obese patients
Topics of debate in surgical treatment of early stage EC

- LND to all patients?
- Type of LND; sampling vs systematic?
- Only pelvic vs PABPLND?
- LND; therapeutic or diagnostic?
- MIS vs Laparotomy?

- Sentinel Lymph Node Concept?
Why SLN mapping?

- Avoid excessive lymphadenectomy and reduce operative time and morbidity
- Proper tailoring of the extent of lymphadenectomy
- Increase the detection rate of positive node (IHC, ultrasectioning)
• Current Practice
• “LESS IS MORE”

• Sentinel Node Mapping
• Lymphadenectomy
Uterine SLN
Complex Lymphatic Drainage
Debate

Cervical vs. Fundal Injections vs. Hysteroscopic
Blue Dye Cervical Injection Under Anesthesia
Isosulfan Blue 1% (50mg/5ml)
2cc at 3 O’clock & 2cc at 9 O’clock

Sold as a sterile powder
Dilute with sterile water to 2.5 mg/mL before injection
Improving SLN detection rates
How many cases are needed?

- After the first 30 cases
  - Rate of successful mapping increased from 77% to 94% (P=0.03)

• Khoury-Collado F, et al. Gynecol Oncol 2009
MSKCC Results

Number of cases: 266

SLN Detection rate: 84%

• Khoury-Collado F, et al. Gynecol Oncol 2011
# SLN Mapping for EC

## Table 1. Sentinel node mapping for endometrial cancer

<table>
<thead>
<tr>
<th>Author [reference]</th>
<th>No. of patients</th>
<th>Substance</th>
<th>Injection site</th>
<th>Detection rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burke et al. [44]</td>
<td>15</td>
<td>B</td>
<td>S</td>
<td>67</td>
</tr>
<tr>
<td>Echt et al. [47]</td>
<td>8</td>
<td>B</td>
<td>S</td>
<td>0</td>
</tr>
<tr>
<td>Holub et al. [48]</td>
<td>25</td>
<td>B</td>
<td>C, S</td>
<td>84</td>
</tr>
<tr>
<td>Gien et al. [49]</td>
<td>9</td>
<td>B</td>
<td>S</td>
<td>56</td>
</tr>
<tr>
<td>Li et al. [50]</td>
<td>20</td>
<td>B</td>
<td>S</td>
<td>75</td>
</tr>
<tr>
<td>Frumovitz et al. [51]</td>
<td>18</td>
<td>R, B</td>
<td>S</td>
<td>45</td>
</tr>
<tr>
<td>Altgassen et al. [52]</td>
<td>23</td>
<td>B</td>
<td>S</td>
<td>92</td>
</tr>
<tr>
<td>Lopes et al. [53]</td>
<td>40</td>
<td>B</td>
<td>S</td>
<td>78</td>
</tr>
<tr>
<td>Robova et al. [54]</td>
<td>67</td>
<td>R, B</td>
<td>S</td>
<td>73</td>
</tr>
<tr>
<td>24</td>
<td>R</td>
<td>H</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Niikura et al. [55]</td>
<td>28</td>
<td>R</td>
<td>H</td>
<td>82</td>
</tr>
<tr>
<td>Fersis et al. [56]</td>
<td>10</td>
<td>R</td>
<td>H</td>
<td>50</td>
</tr>
<tr>
<td>Maccauro et al. [57]</td>
<td>26</td>
<td>R, B</td>
<td>H</td>
<td>100</td>
</tr>
<tr>
<td>Delaloye et al. [58]</td>
<td>60</td>
<td>R, B</td>
<td>H</td>
<td>82</td>
</tr>
<tr>
<td>Solima et al. [59]</td>
<td>80</td>
<td>R</td>
<td>H</td>
<td>95</td>
</tr>
<tr>
<td>Perrone et al. [60]</td>
<td>17</td>
<td>R</td>
<td>H</td>
<td>65</td>
</tr>
<tr>
<td>Bats et al. [61]</td>
<td>43</td>
<td>R, B</td>
<td>C</td>
<td>70</td>
</tr>
<tr>
<td>Delpech et al. [62]</td>
<td>23</td>
<td>R, B</td>
<td>C</td>
<td>83</td>
</tr>
<tr>
<td>Mais et al. [63]</td>
<td>34</td>
<td>B</td>
<td>C</td>
<td>62</td>
</tr>
<tr>
<td>Ballester et al. [64]</td>
<td>133</td>
<td>R, B</td>
<td>C</td>
<td>89</td>
</tr>
<tr>
<td>Barlin et al. [46]</td>
<td>498</td>
<td>B (75 patients also with R)</td>
<td>C</td>
<td>81</td>
</tr>
<tr>
<td>Gargiulo et al. [65]</td>
<td>11</td>
<td>R, B</td>
<td>C</td>
<td>100</td>
</tr>
<tr>
<td>Pelosi et al. [66]</td>
<td>16</td>
<td>R, B</td>
<td>C</td>
<td>94</td>
</tr>
<tr>
<td>Lelievre et al. [67]</td>
<td>12</td>
<td>R, B</td>
<td>C</td>
<td>91</td>
</tr>
</tbody>
</table>

- B, blue dye; S, subserosal; C, cervical; R, radioactive; H, hysteroscopic.
Sentinel Lymph Node in Endometrial Cancer: A Review

Cyril Touboul - Enrica Bentivegna - Catherine Uzan - Sebastien Gouy - Patricia Pautier - Catherine Lhomme - Pierre Davillard - Christine Haie-Meder - Philippe Morice

Published online: 5 November 2013

Review of a total of 899 patients with cervical injection
for detection of SLN in endometrial cancer
Radiocolloid + dye in 854 patients

96 pttn (10.7%) node positive  11 pttn (10.2%) false negative
Pelvic detection rate 82.9%  Paraaortic detection rate 6.5%
Mean number of nodes detected 2.4
Fig. 1. Surgical algorithm for endometrial cancer. LND, lymph node dissection (From Barlin JN, et al. Gynecol Oncol 2012;125:531-5, with permission from Elsevier) [46].
Sentinel node mapping (Algorithm)

- After applying the algorithm, the false negative rate for detecting nodal metastasis dropped from 15% to 2%

Barlin et al. Gynecol Oncol 2012;125:531-5
# Recurrence

<table>
<thead>
<tr>
<th>Stage</th>
<th>(%)</th>
<th>Site</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>15</td>
<td>Distant</td>
<td>65</td>
</tr>
<tr>
<td>Stage II-IV</td>
<td>25-45</td>
<td>Vagina</td>
<td>6</td>
</tr>
<tr>
<td>Overall</td>
<td>15</td>
<td>Pelvic</td>
<td>15</td>
</tr>
</tbody>
</table>

Aalders, Gynecol Oncol, 1983
Recurrent EC-Treatment

- Patient’s performance
- Primary treatment
- Site of recurrence

**Surgery**

- XRT
- HORMONAL THERAPY
- CHEMOTHERAPY AND TARGETED THERAPY
Isolated Lymphatic Recurrence
Isolated intestinal recurrence
Pelvic Exenteration
(Pelvic recurrence)

- Endometrial cancer?
- Total exenteration is better than standard debulking surgery plus XRT has not shown
  5Y OS; %30-56
- Major surgical complication; 60-80%
  Fistula, abcess, septisemia

Barakat RR, Gynecol Oncol, 1996; 1999; Morris M, Gynecol Oncol, 1996;
Peritoneal Carcinomatosis

- Peritoneal Carcinomatosis
  Cytoreductive surgery

  Chemo. or Hormonal Therapy (G1)
Surgical Treatment of EC
Summary

• In early stage EC, comprehensive surgical staging except low risk group
• In advanced EC: Cytoreductive surgery
• MIS has similar oncologic outcome, less complications, better QOL vs open surgery
• MIS or vaginal Hys. is preferable in obese patients with EC because of morbidity
• Sentinel LN mapping is applicable but not standard yet.
Thanks!
Pelvic Lymphadenectomy
Paraaortic Lymphadenectomy
<table>
<thead>
<tr>
<th>Stage</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>73</td>
</tr>
<tr>
<td>II</td>
<td>11</td>
</tr>
<tr>
<td>III</td>
<td>13</td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
</tr>
</tbody>
</table>

Levine DA. Cancer J 2002; 8:31-40
Cytoreduction in Stage IV EC

Conclusions

All studies are retrospective

Relatively small number of patients

Residual tumor is prognostic for outcome

Neoadj Ctx ?
Postoperative standard Treatment?
MIS vs LPT Primary Results

- Recurrence-free Survival (RFS)
- Overall Survival (OS)

• MIS: Minimal invaziv cerrahi, LPT: Konvansiyonel cerrahi
The use of SLN techiques in cervical and endometrial cancer

Avoid excessive lymphadenectomy / reduce operative time and morbidity

Proper tailoring of the extent of lymphadenectomy

Increase the detection rate of positive node (ultrasectioning, IHC)

Identify nodes outside normal retrieval areas

Learning the anatomy of the lymphatic system
Controversies in endometrial cancer

Principles for risk groups not consistent

Survival benefit from lymphadenectomy?

Appropriate extent of lymphadenectomy?

Diagnostic or therapeutic lymphadenectomy?

Principles for adjuvant/ oncological treatment not consistent

Effective treatment in case of paraaortic/ disseminated spread?

The morbidly obese/ comorbid patient dilemma
Basic data endometrial Cancer

Endometrial cancer

5 year Disease free survival
87% node negative patients
71% pos pelvic nodes
36% pos paraaortic node*

We need to know nodal status
To give the right treatment
To evaluate treatments
To schedule follow up
Intervals and how to check

* Morrow CP et al, GOG study Gynecol Oncol 1991
Nodal involvement in EC

High Risk EC (appr 70%*)

>2cm or >50%M1 or Grade III, non endometrioid hist (*Mayo criteria*)

20% node positive (17% p+-pa, 3% skip pa)

Low Risk EC (appr 30%)

None of above

Appr 5% node positive

89% of 514 (457pts) high risk patents were staged

Mean number of pelvic nodes
36 (+ -14)
Mean number of paraaortic nodes
18 (+ -9)

* Kumar, Podratz; Mariani et al. Gynecol Oncol 2013
Isolated positive paraaortic nodes 3% of high risk patients (negative pelvic nodes)

Positive pelvic AND paraaortic nodes 9%

Positive pelvic nodes* 17%

* Includes patients with positive paraaortic nodes

Positive pelvic nodes means an appr 50% risk of positive paraaortic node

85% of node positive patients have positive pelvic nodes
Positive paraaortic nodes include the supravesesenteric area in 88% of cases.

35% paraaortic positive nodes are ONLY in the supravesenteric area.

Tumor spread high paraaortic nodes via the IP ligament or by further presacral spread.

Tumor spread to low paraaortic nodes via presacral lymphatics or further spread from lateral pelvic lymphatics.

A paraaortic LND should involve the supravesenteric area.

Problematic to define paraaortic SLN's.

Positive pelvic nodes means an appr 50% risk of positive paraaortic node.
Injection technique

Use a 1 mL syringe with thin long needle
"the hydraul principle"
Pressure = N/sqm = 1 Pascal
The force to press the syringe piston will be multiplied by the difference between syringe needle area and piston area

Injection technique
Chapel Hill (Rossi*)
0.5mg 1cm into the cervical stroma 3 and 9 clockwize

Florida (Holloway**) 
0.6mg "each cervical quadrant" depth not stated

Lund:
Slowly submucosally (cervical ca)
at 2-4-8-10 clockwize at cervix (total 1.25 mg/side)

Slowly submucosally + 2cm into stroma (endom ca)

Optimal dose
0.65-1.25 mg per side
(0.25-0.5 mL)

*Rossi et al. Robotically assisted fluorescence-guided Lymph node mapping with ICG for gynecologic Malignancies: feasibility study. Gynecol Oncol (124);78-82

**Holloway R et al. Detection of sentinel lymph nodes in Patients with endometrial cancer undergoing robotic-assisted Staging...... Gynecol Oncol 2012(126); 25-9
There are only two ways routes for lymphatic spread from the uterus

Paraortic skip met's are rare

85% of node positive patients have positive pelvic nodes

Pelvic nodes are well defined by a cervical injection of SLN tracer

Do we need a technique that detects paraaortic SLN's separately?
NCCN Guideline

- **Operable**
  - Disease limited to the uterus (endometrioid histologies)
    - Total hysterectomy and bilateral salpingo-oophorectomy (TH/BSO)
      - Cytology
      - Pelvic and para-aortic lymph node dissection
  - Medically inoperable
    - Tumor-directed RT
      - or Consider hormone therapy in select patients

---

a: Disease limited to the uterus (endometrioid histologies)
b: Tumor-directed RT
c, d: Consider hormone therapy in select patients
e: Total hysterectomy and bilateral salpingo-oophorectomy (TH/BSO)
f: Cytology

---

h, i: Pelvic and para-aortic lymph node dissection
Follow-up and Recurrence

<table>
<thead>
<tr>
<th>SURVEILLANCE</th>
<th>CLINICAL PRESENTATION</th>
<th>THERAPY FOR RELAPSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical exam every 3-6 mo for 2 y, then 6 mo or annually</td>
<td>Local/regional recurrence</td>
<td>See Therapy For Relapse</td>
</tr>
<tr>
<td>Vaginal cytology (category 3)</td>
<td>Negative distant metastases on radiologic imaging</td>
<td></td>
</tr>
<tr>
<td>Patient education regarding symptoms</td>
<td>Isolated metastases</td>
<td>Consider resection ± RT</td>
</tr>
<tr>
<td>CA-125 (optional)</td>
<td>Unresectable or further recurrence</td>
<td></td>
</tr>
<tr>
<td>Chest x-ray annually (category 2B)</td>
<td>Treat as disseminated metastases (See below)</td>
<td></td>
</tr>
<tr>
<td>CT/MRI as clinically indicated</td>
<td>Disseminated metastases</td>
<td>Low grade or Asymptomatic</td>
</tr>
<tr>
<td>Consider genetic counseling/testing for young patients (&lt; 55y) with a significant family history and/or selected pathologic risk features</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Low grade or Asymptomatic
  - Hormone therapy
    - If progression, chemotherapy
      - If progression, Best supportive care (See NCCN Palliative Care Guidelines) or Clinical trial
- Symptomatic or Grade 2, 3 or Large volume
  - Chemotherapy ± palliative RT
LND; Sampling vs Systematic

- # 11.443
- Stage I 78.7%, Stage II 10.3%, stage III 11.0%
- Grade 1 31.5%, grade 2 40.6%, grade 3 24.3%
- Detection of one positive LN involvement %45

- Low risk group (Stage IA, all G; stage IB G1,2) 5Y DFS; no advantage
- Intermediate and high risk group; 5 Y DFS
  - LN #1: 75.3%
  - LN #6-10: 84.1%
  - LN #>20: 86.8% (p<0.001)

• Chan JK, Cancer, 2007
Local Recurrence

Local recurrence, usually at vaginal cuff

Confirmation by radiologic exam (PET-CT, MRI)

- **lokal recur.in RT-naive site:**
  - $< 3\text{cm} - \text{EBPRT} /+, - \text{Brachitherapy}$
  - $> 3\text{cm} - \text{Debulking} /+, - \text{IORT}$
  - Neoadjuvan KT + Debulking or RT

- **Local recur. in previously RT:** Exenteration, Debulking + IORT