Overall cure rate – *not improved*

**STAGING** and
**HIGH-RISK IDENTIFICATION**

Failure of secondary prevention strategies

**TREATMENT** of
**HIGH-RISK** and
**ADVANCED**
Endometrial Cancer – Surgical Issues

- Surgical Approach
- Ovarian Preservation
- Lymphadenectomy
- Surgery in Advanced Disease
- Conservative Surgery

?
# FIGO Stage Classification

<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 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>

**Extrauterine disease spread:** 10-15%

FIGO, 2009
Pts with extraut. disease spread:
>50% of all deaths

Stage IV ip
5y OS: <40%

5y OS: 10-20%
Advanced + Rec. EC - Role of Cytoreductive Surgery

Metanalysis 1997-09, 14 studies (N=672)
Advanced N=515  Recurrent N=157

R0: each 10% increase improving OS by 9.3m
P=0.04

<table>
<thead>
<tr>
<th>Change in median overall survival time (months)</th>
<th>Increase</th>
<th>95 CI or CL</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>−1.54</td>
<td>−7.33, 4.25</td>
<td>0.57</td>
</tr>
<tr>
<td>Primary vs. recurrent</td>
<td>−7.60</td>
<td>−46.28, 31.07</td>
<td>0.67</td>
</tr>
<tr>
<td>UPSC</td>
<td>−1.8</td>
<td>−5.6, 2.0</td>
<td>0.32</td>
</tr>
<tr>
<td>Clear cell</td>
<td>−1.7</td>
<td>−8.8, 5.4</td>
<td>0.61</td>
</tr>
<tr>
<td>Grade 3</td>
<td>−3.4</td>
<td>−9.5, 2.6</td>
<td>0.23</td>
</tr>
<tr>
<td>Stage 4</td>
<td>−3.2</td>
<td>−8.0, 1.6</td>
<td>0.16</td>
</tr>
<tr>
<td>Percent optimal</td>
<td>16.01</td>
<td>−0.7, 32.7</td>
<td>0.05</td>
</tr>
<tr>
<td>Percent complete</td>
<td>9.3</td>
<td>0.1, 18.5</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Barlin, 2010
Cytoreductive surgery for advanced or recurrent endometrial cancer: A meta-analysis

• 14 retrospective cohorts, 672 patients
• Huge Heterogeneity
  – definition of “optimal”: ≤ 2 cm (3 studies) vs ≤ 1 cm (7 studies) vs no-gross residual (4 studies)
  – R=0 achieved in the range of 18-75% of cases
  – primary surgery (10 studies, 515 pts) vs for recurrent disease (4 studies; 157 pts)
  – Histology in primary surgery: 5 studies only UPSC and 5 studies included all histologies
  – Only data of adjuvant therapy in 12 studies
• OS associated with complete surgical cytoreduction (each 10% increase improving survival by 9.3 months, p=0.04)

Joyce N. Barlin, IshaPuri, Robert E. Bristow. Gynecol Oncol 2010
Surg. Stage IVB EC (excl. liver/extra-abd. mets) vs OC (by age/RD) (1:2) Case Control Study

**OS**: Optimally debulked EC vs OC
Stage IVB EC – *Retrospective Study (Japan)*

![Graph showing survival probability over time for different treatments: Primary surgery, Primary chemotherapy, Palliative care. Key points marked at 1m, 12m, and 21m.](image)

*Eto, 2013*
## Stage IVB EC – Retrospective Study (Japan)

### Patient/disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Primary Surgery %</th>
<th>Primary Chemotherapy %</th>
<th>Palliative Care %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age</td>
<td>59 (30-89)</td>
<td>58 (30-83)</td>
<td>73 (53-84)</td>
<td></td>
</tr>
<tr>
<td>ECOG PS: 0-1</td>
<td>91</td>
<td>77</td>
<td>32</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8</td>
<td>18</td>
<td>18</td>
<td>0.003</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19</td>
<td>28</td>
<td>45</td>
<td>0.04</td>
</tr>
<tr>
<td>Extra-abd. mets</td>
<td>38</td>
<td>82</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>&gt;2 regions</td>
<td>9</td>
<td>43</td>
<td>54</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Eto, 2013
**Recommendation 6.4**
Complete macroscopic cytoreduction and comprehensive staging is recommended in advanced endometrial cancer

Level of evidence: IV  Strength of recommendation: A
The management of patients with EC is probably the least uniform when compared to that for patients with other gynecological malignancies.
Questionnaire to Italian NHS 283 Institutions with >20 surgical op. for gynecol. cancer/y

92% believe appropriate a surgical cytoreductive intent in advanced disease
Questionnaire to Italian NHS 283 Institutions with >20 surgical op. for gynecol. cancer/y

Declared proportion of pts undergoing surgery with cytored. intent: 5-50%
a. Type I endometrial

Surgical cytoreduction & Histology: p=0.39

21 vs 36m

Test of homogeneity
OS differences by Histo
p=0.007

b. Type II endometrial

c. CS

12 vs 22m

9 vs 21m

Alagkiozidis, 2015
4 TGCA SUBGROUPS

(a) Mutations per Mb:
- POLE (ultramutated)
- MSI (hypermutated)
- Copy-number low (endometrioid)
- Copy-number high (serous-like)

(b) Substitution frequency (%):
- POLE
- MSI/MLH1
- CN cluster

(c) PTEN
- TP53
- Histology (Tumour grade)

(d) Mutations (per tumour):
- POLE mutations
- MSI
- DNA methylation
- CN cluster
- Mutations
- Histology
- Tumour grade

Legend:
- CA, CG, CT, TA, TC, TG
- V411L, P286R, Other
- MSI high, MSI low, MS stable, NA
- MLH1 silent
- 1, 2, 3, 4
- Nonsense, Missense, Frameshift
- Serous, Mixed, Endometrioid
- 3, 2, 1

Log-rank P = 0.02
Limitation of current evidence for upfront surgery

- Bias related to the retrospective nature of the data.
- Lack of good evidence regarding the impact of histological subtype (type I vs Type II) and endometrioid molecular subtypes in the potential resectability and the outcome after complete resection.
- Impact of adjuvant chemo/radiation therapy.
- The rate of upfront complete cytoreduction is surgeon dependent.
Advanced EC  Cytoreductive Surgery

Survival Benefit

Feasibility
Pt Selection
NACT
Advanced EC – Study on Cytoreductive Surgery

• Retrospective (2005-2015)
• Multicenter, oncol. ref. centres (ORC)
• Eligible: Clin./intraop. FIGO Stage IIIA-B, IIIC bulky, IV i.p.
• Objectives:
  i) to assess the therapeutic strategy adopted in ORC
  ii) to evaluate feasibility & compl. of cytoreductive surgery (CRS)
  iii) to evaluate survival predicting factors
  iv) to identify predictors of complete surgical cytoreduction (*)
  v) to evaluate the role of NACT

(*) Planned analysis of TGCA subgroups
Advanced EC – Study on Cytoreductive Surgery

1. **Data Set – Items**

1. ID Code (initials)
2. Date of birth
3. BMI
4. DIAGNOSIS (date of treatment start)
5. COMORBIDITY (list)
6. PS (ECOG)
7. SERUM MARKERS - CA125 Pre-treatment
8. SERUM MARKERS - CA19-9 Pre-treatment
9. SERUM MARKERS - HE4 Pre-treatment
10. IMAGING - MR scan (no:0; yes:1) (if possible, include report)
11. IMAGING - CT scan (no:0; yes:1) (if possible, include report)
12. IMAGING - PET scan (no:0; yes:1) (if possible, include report)
13. ASCITES (no:0; estimate <500cc:1; estimate >500cc:2)
14. PATHOLOGY – Histotype
15. PATHOLOGY – Grade FIGO
16. CLINICAL STAGE - FIGO (IIIAbulky:1; IIIB:2; IIIICbulky:3; IIIC2bulky:4; IVA:5; IVB intra-abdominal:6)
17. CLINICAL STAGE – Abdominal quadrants (cm max diameter); pelvic retroperitoneum; aortic retroperitoneum.
Advanced EC – Study on Cytoreductive Surgery

DATA SET – ITEMS

2. Treatment Characteristics

18. PRIMARY TREATMENT (surgery:1; chemotherapy:2; radiotherapy:3; concurrent RT-CT:4)
19. PRIMARY TREATMENT - Reasons for treatment choice (report)
20. CT (primary treatment) (no:0; yes:1)
21. CT – Setting (NACT:1; exclusive CT:2; concurrent CT-RT:3; sequential CT-RT:4); Regime (report); Cycles (no.)
22. CT - Clinical response (RECIST) (if exclusive CT or NACT) (CR:1; PR:2; SD:3; PD:4)
23. SURGERY (primary treatment) (no:0; yes:1)
24. SURGERY – Setting (upfront:1; after NACT:2; after RT:3); Date (dd/mm/yy); Disease sites at definitive pathology
25. SURGERY – Procedures; Post-surgical residual disease (no:0; yes:1)
26. SURGERY – Duration (min); Estimated blood loss (cc); no. blood units
27. SURGERY – Perioperative complications (within 30d from surgery); H postoperative stay (days)
28. POST-SURGICAL THERAPY (no:0; yes:1)
29. POST-SURGICAL THERAPY – If yes (CT:1; RT:2; concurrent CT-RT:3; sequential CT-RT:4)
30. POST-SURGICAL THERAPY – if yes, date of start (dd/mm/yy); date of end (dd/mm/yy)
31. POST-SURGICAL THERAPY – if CT, specify regimen (report); cycles (no.)
32. POST-SURGICAL THERAPY – if RT, details to be included (report)
33. POST-SURGICAL THERAPY – if postop. RD present, specify response (RECIST) (CR:1; PR:2; SD:3; PD:4)
34. RADIOTHERAPY (primary treatment) (no:0; yes:1)
35. RADIOTHERAPY - Setting (upfront:1; concurrent with CT:2; sequential after CT:3)
36. RADIOTHERAPY - if yes, details to be included (report)
3. **Outcomes**

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>37.</td>
<td>RECURRENCE/PROGRESSION (no:0; yes:1); Date (dd/mm/yy); Site</td>
</tr>
<tr>
<td>38.</td>
<td>RECURRENCE/PROGRESSION – Secondary Treatment (no:0; surgery:1; CT:2; RT:3; CT-RT:4)</td>
</tr>
<tr>
<td>39.</td>
<td>SECONDARY TREATMENT – if yes, date of start (dd/mm/yy); end date (dd/mm/yy)</td>
</tr>
<tr>
<td>40.</td>
<td>SECONDARY TREATMENT – if CT, specify regimen (report); cycles (no.)</td>
</tr>
<tr>
<td>41.</td>
<td>SECONDARY TREATMENT – If RT, details to be included (report)</td>
</tr>
<tr>
<td>42.</td>
<td>SECONDARY TREATMENT – Response (RECIST) (CR:1; PR:2; SD:3; PD:4)</td>
</tr>
<tr>
<td>43.</td>
<td>2nd RECURRENCE/PROGRESSION (no:0; yes:1)</td>
</tr>
<tr>
<td>44.</td>
<td>2nd RECURRENCE/PROGRESSION – Date (dd/mm/yy); Site</td>
</tr>
<tr>
<td>45.</td>
<td>2nd RECURRENCE/PROGRESSION – Tertiary Treatment (no:0; surgery:1; CT:2; RT:3; CT-RT:4)</td>
</tr>
<tr>
<td>46.</td>
<td>TERTIARY TREATMENT – if yes, date of start (dd/mm/yy); end date (dd/mm/yy)</td>
</tr>
<tr>
<td>47.</td>
<td>TERTIARY TREATMENT – if CT, specify regimen (report); cycles (no.)</td>
</tr>
<tr>
<td>48.</td>
<td>TERTIARY TREATMENT – If RT, details to be included (report)</td>
</tr>
<tr>
<td>49.</td>
<td>TERTIARY TREATMENT – Response (RECIST) (CR:1; PR:2; SD:3; PD:4)</td>
</tr>
<tr>
<td>50.</td>
<td>LAST DATE FOLLOW-UP (dd/mm/yy)</td>
</tr>
<tr>
<td>51.</td>
<td>SURVIVAL (alive:1; dead for disease:2; dead for other cause:3)</td>
</tr>
<tr>
<td>52.</td>
<td>DISEASE STATUS AT LAST FOLLOW-UP (NED:1; ED:2)</td>
</tr>
</tbody>
</table>
Each participating center will be provided with a study database

Centralised analysis c/o NCI - Naples Data Center
Advanced EC – Study on Cytoreductive Surgery

- Ist. Naz. Tumori di Napoli
- H San Raffaele, Milano
- Centro Rif. Oncologico, Aviano
- University, Bologna
- University, Bari
- University, Varese
- H Civili, Bergamo
- H Reggio Emilia
Advanced EC – Study on Cytoreductive Surgery

• Expanding the study to other Groups

• Evaluation of the “geographic” pattern of the decision-making process

• If successful CRS is confirmed as the most potent prognosticator after appropriate analysis:
  - Definition of a score predicting R0-1 (including biomolecular grouping)

• Potential subsequent prospective phase to validate