The role of Debulking Surgery in advanced-stage Endometrioid Endometrial Cancer

Kunter Yüce M.D
Hacettepe University Medical Faculty
Prof and Head of Gynecologic Oncology
Endometrial Cancer

most common gynecologic malignancy in western country

75 % early stage

13-15 % Stage III
3-5 % Stage IV

## Endometrial Cancer 5 year survival

<table>
<thead>
<tr>
<th>Stage</th>
<th>5 year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIa</td>
<td>60</td>
</tr>
<tr>
<td>IIIb</td>
<td>41</td>
</tr>
<tr>
<td>IIIc</td>
<td>32</td>
</tr>
<tr>
<td>IVa</td>
<td>20</td>
</tr>
<tr>
<td>IVb</td>
<td>5</td>
</tr>
</tbody>
</table>

**Advanced stage** ⇒ **50 % of all uterine cancer-related death**

Pecorelli S, J Epidemiol Biostat, 1998  
Lambrou NC et al, Gynecol Oncol 2004  
Barlin JN et al Gynecol Oncol 2010;118;14
An effective treatment regimen has not been established for women with recurrent disease, and the majority of advanced-stage cancer patients will recur
Two types of endometrial cancer different in molecular pattern, therapeutic strategy, prognosis

Type I  low grade endometrioid
unopposed estrogen, often arise out of endometrial hyperplasia
mutations in the PTEN gene, K-ras and microsatellite instability inception

Type II  grade 3 endometrioid, serous, clear
not estrogen-related, postmenopausal, poor prognosis, mutations in p53 and HER2/NEU
Preoperative characterization of the disease type is an essential step for a right diagnosis and treatment
All patients should undergo surgical staging except who are inoperable, according to FIGO recommendation.

Medical comorbidities (obesity, diabetes, cardiovascular disease, pulmonary disease) complete resection is unlikely and can be extremely morbid (extent to the vagina, bladder, bowel/rectum, or parametrium).
SURGICAL INTERVENTION

Vertical midline incision
Peritoneal washing cytology
Exploration
Ekstrafacial total hysterectomy
Bilateral salpingo-oophorectomy

if indicated:
Infracolic omentectomy
Pelvic-paraortic lymphadenectomy
Debulking of intra-abdominal disease
FIGO Staging for Endometrial Cancer 2009

Stage I Tumor is confined to the uterine corpus but not the uterine serosa
IA No or <50% myometrial invasion
IB Myometrial invasion >50%

Stage II Tumor invades cervical stroma but does not extend beyond the uterus
(endocervical glandular involvement only should be considered as stage I and no longer stage II)
FIGO Staging for Endometrial Cancer 2009

Stage III

Tumor involves the uterine serosa, adnexae, vagina, or retroperitoneal lymph nodes

IIIA Involvement of the uterine serosa, involvement of the adnexae

IIIB Vaginal and/or parametrial involvement

IIIC Involvement of the retroperitoneal lymph nodes

IIIC1 Positive pelvic nodes

IIIC2 Positive para-aortic lymph nodes with or without positive pelvic lymph nodes

Stage IV

Tumor involves the rectal or bladder mucosa and/or distant organs

IVA Involvement of the mucosa of the rectum or bladder

IVB Intra-abdominal or extra-abdominal metastases (including inguinal lymph nodes)
Advanced Stage End Ca
Strategy Options

Hormonal therapy with progestational agents

Thigpen JT et al  GOG J Clin Oncol 1999;17:1736
Lentz SS et al GOG J Clin Oncol 1996;14:357
Whitney CW et al GOG Gynecol Oncol 2004;92:4

Radiation

Pliskow S et al Gynecol Oncol 1990;38:210
Keys HM et al GOG Gynecol Oncol 2004;92:744
Sutton G et al GOG Gynecol Oncol 2005;97:755

Chemotherapy

Randall ME et al GOG J Gynecol Oncol 2006;24:36
Optimal management in women with advanced-stage endometrial cancer is not well defined,

several retrospective studies have investigated the role of surgical cytoreduction in this setting
Cytoreductive surgery in advanced ovarian cancer is well accepted as a standard of care. An inverse relationship between postoperative residual tumor size and overall patient survival is recognized.

Munnell EW Am J Obstet Gynecol 1968
Griffiths CT Natl Cancer Inst Monogr 1975
Bristow RE J Clin Oncol 2002;20:1248
improvement of perfusion and drug delivery
decrease in advanced metabolic events to improve performance status
reduction of viable tumor cells with potential for somatic mutations that can cause drug resistance
increase immun response

Munkarah A et al Gynecol Oncol 2001;81:237
are all benefits also true for endometrial cancer?
Advanced Stage Strategy Options

Surgical debulking
Neo-adjuvant chemotherapy and interval debulking
First study in literature

Greer BE, Hamberger AD  Gynecol Oncol 1983;16:365

intraperitoneal metastatic adenocarcinoma of the endometrium (n=31)

Surgery + whole-abdomen RT

5 year survival:

≤2 cm residue (n=27):  80 %

>2 cm residue (n= 4):  0 %
Stage III = 66   Stage IV = 19
endometrioid = 83,    adenosquamous = 2
Pelvic RT = 28, vaginal BT = 7, WART = 10
ChT = 23, ChT ± hormonal T] = 18

<table>
<thead>
<tr>
<th>Surgical procedure</th>
<th>Suboptimal group n (%)</th>
<th>Optimal group n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAH ± BSO(^a)</td>
<td>2 (12.5)</td>
<td>6 (8.7)</td>
</tr>
<tr>
<td>TAH ± BSO(^b)</td>
<td>14 (87.5)</td>
<td>63 (91.3)</td>
</tr>
<tr>
<td>Lymphadenectomy</td>
<td>8 (50.0)</td>
<td>56 (81.2)</td>
</tr>
<tr>
<td>Bowel resection</td>
<td>4 (25.0)</td>
<td>10 (14.5)</td>
</tr>
<tr>
<td>Debunking</td>
<td>7 (43.8)</td>
<td>15 (21.7)</td>
</tr>
<tr>
<td>Omentectomy</td>
<td>10 (62.5)</td>
<td>18 (26.0)</td>
</tr>
</tbody>
</table>

Lambrou NC Gynecol Oncol 2004;93:653
Advanced Stage End Ca Cytoreductive Surgery Miami

**Optimal**
- Stage IIIa b: 27/27 (100 %)
- Stage IIIc: 33/39 (85 %)
- Stage IV: 9/19 (47 %)

**Suboptimal**
- Stage IIIc: 6/39 (% 15)
- Stage IV: 10/19 (% 53)

*Lambrou NC Gynecol Oncol 2004;93:653*
Stage IIIc-IV endometrial cancer (n=58)

optimal cytoreduction:

\[ \leq 2 \text{ cm residue} \]

72 % optimal cytoreduction

Stage IIIc: 33/39 (85 %)

Stage IV: 9/19 (47 %)

Lambrou NC et al, Gynecol Oncol 2004;93:653
Advanced Stage End Ca
Cytoreductive Surgery Miami

Stage IIIC & IV  Median survival:
Optimal cytored:  17.8 months
Suboptimal cytored:  6.7 months
p=0.001

Lambrou NC Gynecol Oncol 2004;93:653
Morbidity of cytoreductive surgery in optimal vs suboptimal groups

**Intraoperative complications** same
(blood loss is greater in suboptimal group)

**Minor postoperative complications** same
(febrile episodes, urinary tract infection, surgical site infection, simple pneumonia, ileus)

**Major postoperative complications** greater in suboptimal group
(severe cardiopulmonary compromise, pulmonary embolus, dehiscence, sepsis, bowel obs, re-L/T)

*Lambrou NC et al, Gynecol Oncol 2004;2004:93:653*
Debulking surgery

- **Maximal debulking (R0)**
  - No gross residual tumor

- **Optimal debulking (R1)**
  - $\leq 1\text{cm}$ residual tumor

- **Suboptimal debulking (R2)**
  - $> 1\text{ cm}$ residual tumor
Does debulking of enlarged positive lymph nodes improve survival

One of the most important prognostic factors for endometrial carcinoma is the presence of extrauterine disease (particularly pelvic and paraaortic lymph node metastases)

According to FIGO
the status of both pelvic and paraaortic lymph nodes should be assessed intraoperatively in all patients

Somashekhar SP et al  Best Pract Research Clin Obstet Gynecol 2015:29;870
Abu-Rustum JD et al Gynecol Oncol 2009;115:235
Does debulking of enlarged positive lymph nodes improve survival

LND an important aspect of the management of EC

Complete pelvic and paraaortic node dissection be performed rather than selective nodal sampling

in patients with Stage IIIC-IV

5-year survival extensive nodal resection

72 % for 20 nodes vs

53 % for two to five nodes

Chan JK et al Cancer 2006;107;1823
Does debulking of enlarged positive lymph nodes improve survival

Stage IIIC Endometrial Cancer  pelvic and paraaortic LND

5-year disease-specific survival rate

63%  in patients with microscopic metastatic disease

50%  in patients with complete resection of grossly positive lymph node

43%  in patients with residual macroscopic disease

Havrilesky JM et L  Gynecol Oncol 2005;99:689
Stage IIIc endometrial cancer (n=41)

5-year disease-specific survival

Complete resection of macroscopic lymph nodes: 37.5 months

Gross residual nodal disease: 8.8 months

p=0.006

Bristow RE et al, Int J Gynecol Cancer 2003
Stage IIIC End Ca

Paraaortic metastases more important than pelvic metastases

No of metastatic lymph node correlates with OS

Watari, Gynecol Oncol 2005
Prognosis in patients with PA LND and without PA LND

<table>
<thead>
<tr>
<th></th>
<th>PA LND (-)</th>
<th>PA LND (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>36 %</td>
<td>72 %</td>
</tr>
<tr>
<td>OS</td>
<td>42 %</td>
<td>76 %</td>
</tr>
</tbody>
</table>

no lymph node recurrence in patients with PA LND

Paraaortic lymph adenectomy therapeutic !!

Mariani A, Gynecol Oncol, 2000
STAGE IIIC

• Lymphatic metastases is prognostic and the number of metastatic lymph node is important

• Paraaortic metastases means worse prognosis than pelvic node metastases

• If lymphatic metastases is with the other abdominal metastases, prognosis is worse

• Lymphadenectomy is also a diagnostic procedure for determining adjuvant therapy

• Lymphadenectomy is also therapeutic (cytoreduction)
Stage IV endometrial cancer (n=47)  
Massachusetts 1976-1991

left no bulky disease  29 patients
no surgery  18 patients
(diffuse peritoneal carcinomatosis; lung metastases; bladder invasion; involvement of pelvic side wall; distant bone metastases; liver metastases)

Median survi:
Complete cytoreduction  19 months
No complete cytoreduction  8 months

p=0.0001

Only successful cytoreduction is significant prognostic variable
Extraabdominal metastases are not prognostic

Goff BA et al, Gynecol Oncol 1994;52:237
Surgical Cytoreduction in Stage IV endometrial carcinoma

Memorial Sloan-Kettering NY 1977-1995

55 patients

Group 1 (44%  n:24)  optimal cytoreduc <2cm
Group 2 (38%  n:21)  suboptimal cytoreduc >2 cm
Group 3 (18%  n:10)  unresectable carcinomatosis

Median survival

31 months; 12 months; 8 months

Only the extent of surgical cytoreduction has prognostic significance on survival

$p<0.01$

Chi DS et al  Gynecol Oncol 1997;67:56
Surgical Cytoreduction in Stage IV endometrial carcinoma

65 patients with Stage IVB endometrial cancer
John Hopkins USA 1990-1998 retrospective
Endometrioid histology 34%

Optimal resection 55.4 %
median survival 34 months

Suboptimal resection (>1 cm)
median survival 11 months

Bristow R et al Gynecol Oncol 2000;78;85
Surgical Cytoreduction in Stage IV endometrial carcinoma

Among those optimally resected, patients with only microscopic residual disease survived longer than patients with optimal but macroscopic tumor residual.

Maximal cytoreduction at the time of primary surgery should be the goal in advanced uterine carcinoma.

Bristow R et al  Gynecol Oncol 2000;78;85
The influence of cytoreductive surgery on survival and morbidity in stage IVB endometrial cancer

A. AYHAN*, C. TASKIRAN*, C. CELIK*, K. YUCE* & T. KUCUKALI
Departments of *Obstetrics and Gynecology and †Pathology, Hacettepe University Hospitals, Ankara, Turkey

Stage IVb endometrial cancer
1977-1998 n=37  Endometrioid= 78%

optimal cytoreduction (≤1 cm residue):
22 patients 60%

suboptimal cytoreduction
15 patients 40%

Adjuvant treatment:
38% (14) KT + RT
27% (10) KT
27% (10) RT
3 patients did not want adjuvant therapy
Stage IV, n=37

Optimal cytoreduction (residue ≤1cm) (n=22 % 60)

Suboptimal cytoreduction (residue>1cm) (n=15)

Endometrioid= 78%

No residual tumor n=12

25 months

10 months

48 months
Median survival:

Overall: 15 months

Optimal cytored (n:22): 25 months
Suboptimal cytored (n:15): 10 months

p=0.001

Optimal cytoreduction group:

➢ No gross residue (n:12) 48 months
➢ < 1 cm gross residue (n:10) 13 months

p=0.001

Ayhan A et al  Int J Gynecol Cancer 2002;12:448-453
<table>
<thead>
<tr>
<th>Location</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvis</td>
<td>30</td>
<td>81</td>
</tr>
<tr>
<td>Peritoneal surfaces</td>
<td>26</td>
<td>70</td>
</tr>
<tr>
<td>Omentum</td>
<td>18</td>
<td>48</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>19</td>
<td>51</td>
</tr>
<tr>
<td>Liver/spleen/diaphragma</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>Large bowel</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>Small bowel</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>Bladder</td>
<td>1</td>
<td>2.7</td>
</tr>
<tr>
<td><em>Extraabdominal</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>2</td>
<td>5.4</td>
</tr>
<tr>
<td>Brain</td>
<td>1</td>
<td>2.7</td>
</tr>
<tr>
<td>Bone</td>
<td>1</td>
<td>2.7</td>
</tr>
<tr>
<td>Supraclavicular lymph node</td>
<td>1</td>
<td>2.7</td>
</tr>
<tr>
<td>Inguinal lymph node</td>
<td>1</td>
<td>2.7</td>
</tr>
</tbody>
</table>
Adjuvant therapy median survi:

RT + cisplatin: 54 months
RT: 15 months
KT: 13 months
p=0.0003

Ayhan A et al  Int J Gynecol Cancer 2002;12:448-453
Morbidity: 40.5%
Mild: 16%
Severe: 24%
Mortality: 2.7%

<table>
<thead>
<tr>
<th>Classification</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary infection</td>
<td>2</td>
<td>(5.4)</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>1</td>
<td>(2.7)</td>
</tr>
<tr>
<td>Lymphocyst</td>
<td>3</td>
<td>(8.1)</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>1</td>
<td>(2.7)</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>1</td>
<td>(2.7)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1</td>
<td>(2.7)</td>
</tr>
<tr>
<td>Bladder injury</td>
<td>1</td>
<td>(2.7)</td>
</tr>
<tr>
<td>Bowel obstruction</td>
<td>2</td>
<td>(5.4)</td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>2</td>
<td>(5.4)</td>
</tr>
<tr>
<td>Relaparotomy because of hemorrhage</td>
<td>1</td>
<td>(2.7)</td>
</tr>
</tbody>
</table>

Ayhan A et al  Int J Gynecol Cancer 2002;12:448-453
Prognostic factors

Univariate analysis ⇒ extraabdominal met., suboptimal cytoreduction, PPALN involvement, cervical involvement

Multivariate analysis ⇒ optimal cytoreduction - residue cisplatin + RT extraabdominal metastases

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

14 studies 1997-2009 672 patients Retrospective

Optimal cytoreduction:

< 2 cm 20.8% < 1 cm 55.8%;
no gross evidence 23.3%

optimal surgical cytoreduction 52% - 75%
complete surgical cytoreduction 18% - 75%
adjuvant therapies ??

Barlin JN Gynecol Oncol 2010;118:14
Cytoreductive surgery for advanced or recurrent endometrial cancer: A meta-analysis 2010

Despite limitations

Optimal cytoreduction achievable 52-75 %
Complete cytoreduction possible 18-75 %

Complete cytoreduction associated with a statistically significant improvement in median overall survival time

each 10% increase in cytoreduction to no gross evidence of disease was associated with a 9.3-month increase in survival

Barlin JN  Gynecol Oncol  2010;118:14
Surgical cytoreduction in stage IV endometrioid endometrial carcinoma

Memorial Sloan-Kettering  NY  1977-2003  58 patients  stage IV endometrioid

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>OS  (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No gross residual</td>
<td>15.5%</td>
<td>40.3 mo</td>
</tr>
<tr>
<td>residual disease &lt; 1 cm</td>
<td>19.0%</td>
<td>11 mo</td>
</tr>
<tr>
<td>residual disease &gt; 1 cm</td>
<td>55.1%</td>
<td>11 mo</td>
</tr>
<tr>
<td>no cytoreduction</td>
<td>10.3%</td>
<td>2.2 mo</td>
</tr>
</tbody>
</table>

Conc: Surgical cytoreduction to no gross residual disease in a highly select group of patients is associated with improved survival

Shih KK et al  Gynecol Oncol  2011;122:608
Survival impact of cytoreduction to microscopic disease
Brooklyn NY USA 2015

168 patients FIGO 2009 Stage III-IV 1984-2009

adenocarcinoma 60
MMMT 54
Serous/clear cell 54
Stage III 97 (58%)
Stage IV 71 (42%)

TAH+BSO 150 (7 radical); P PA LND 114; Omentectomy 98
bowel resection 20; splenectomy 1; liver resection 1;
diaphragmatic resection 1

Complete surgery R0 105 (63%)

suboptimal debulked:
in pelvis 61%, mid-abdomen 35%, upper abdomen 35%

95 patients (57%) postop chemotherapy 39 patients (23%) also RT
34 patients radiation therapy alone; 32 patients no adjuvant

Overall survival of patients with Stage III-IV uterine cancer by residual disease status

Product-Limit Survival Estimates

Survival Probability

Survival Months

Debulking

Gross residual

No gross residual

25 months

13 months

Overall survival of patients with Stage III-IV uterine cancer by residual disease status (various histologies)

a. Type I endometrial

There is no significant interaction between histologic subtype and feasibility of complete cytoreduction.

b. Type II endometrial

c. CS

OS of patients that underwent surgery before and after year 2000
The rate of optimal cytoreduction  53% before 2000    69% after 2000

Comment

• Optimal debulking is associated with improved survival in uterine cancer

• The survival benefit is uniform among histologic types

• There is no interaction between histologic type and feasibility of optimal debulking

Unresectable disease because of patient factors or extent of disease often beneficial to perform a palliative hysterectomy.

Unresected uterine tumor outgrows its blood supply and become necrotic:
- foul odor
- bothersome drainage
- erode into vasculature:
  - bleeding-hemorrhage
- painful

_Vitale SG  Updates Surg  2016;68:149_
Neo-adjuvant chemotherapy for advanced stage endometrial carcinoma:

Resnik E et al  Neoadjuvant chemotherapy in uterine papillary serous carcinoma Gynecol Oncol 1996;62:123

Vandenput I et al  BrJ Cancer  2009;101:244

30 stage IVb End Ca   diagnostic laparoscopy
3-4 cycles platinum-based NAC
followed by debulking surgery
complete or partial response to NAC   74 %
14.3 % remained inoperable,
in 92 % of operated patients, max cytoreduction achieved
OS, PFS, postop complications rate improved
Conc: NAC resulted in a higher probability for complete surgical resection with less postop morbidity
Neo-adjuvant chemotherapy for advanced stage endometrial carcinoma:

retrospective multi-institutional study in Japan

426 stage IV EC patients
279 primary surgery
59 NAC followed by surgery and postop adjuvant initial complete or partial response 68 %

compared to the primary surgery group
debulking to no visible lesion or lesions < 1 cm, in more patients 57 vs 45 %, but not statistically significant

median OS similar

Conc:NAC may be a useful treatment option for highly selected patients

Eto T et al  Gynecol Oncol 2013;131:574
Neo-adjuvant chemotherapy for advanced stage endometrial carcinoma:

Primary surgery 34 pts  NAC 10 pts

90 % partial or complete response to chemotherapy

all patients underwent debulking to no visible disease or lesions < 1 cm

10 % minor complication

lower blood loss

not statistically significant

shorter operation time and hospital stay

median PFS and OS same

Neo-adjuvant chemotherapy for advanced stage endometrial carcinoma: a glimmer of hope in select patients: A review

Treatment of advanced stage endometrial carcinoma aggressive cytoreduction followed by adjuvant chemotherapy or chemotherapy alone

The prognosis of patients that cannot undergo surgery is extremely poor

Preoperative reduction of tumor burden by chemotherapy facilitate surgery in patients previously considered to have an unresectable disease, identify patients with chemosensitive tumors that are more likely to benefit from surgery, enable a less aggressive surgery thus reducing morbidity

Rabinovich A Arch Gynecol Obstet 2016;293:47
Neoadjuvant chemotherapy and interval debulking

The data in support of neoadjuvant chemotherapy and interval debulking in endometrial cancer lag behind those in ovarian cancer.

Data have shown that chemotherapy is effective in advanced endometrial cancer, although not nearly so effective as it is in ovarian cancer.

Identifying patients responsive to chemotherapy could assist in triaging which patients might benefit from extensive cytoreduction.

Randall ME et al. J Clin Oncol 2006;24:36
Landrum LM et al. Gynecol Oncol 2009;112:337
Advanced Stage End Ca Cytoreductive Surgery

Surgical cytoreduction is an independent prognostic factor for progression free survival (PFS) and overall survival (OS)

Shih KK et al. Gynecol Oncol. 2011;122:608
Goff BA et al. Gynecol Oncol. 1994;52:237
Lambrou NC et al. Gynecol Oncol. 2004;93:653

improved performance status
decreased tumor burden
improved vascular perfusion and drug delivery
decreased tumor volume that would have had mutation potential for drug resistance (Goldie-Coldman model)

Advanced Stage End Ca
Cytoreductive Surgery

Surgery should only be considered for patients with bulky FIGO stage IIIA-IV if successful cytoreduction with no macroscopic residual disease is anticipated.


A meta-analysis of retrospective data showed that no residual disease was associated with an improvement in median OS. However, there was no significant difference in survival for patients with 0-2 cm residual disease.

Barlin JN. A meta-analysis. Gynecol Oncol 2010;118:14
Survival impact of cytoreduction to microscopic disease

Brooklyn NY USA

Complete gross cytoreduction often requires extensive surgical procedures that may lead to perioperative complications with negative impact on life expectancy and quality of life

Alagkiozidis I Int J Surg 2015;14:61
benefit of cytoreduction

Due to tumor biology
Due to surgical effort

??
Tumor biology

Survival is better in patients who have microscopic disease before the operation than in patients who are operated on and debulked to microscopic disease

Greer BE, Hamberger AD Gynecol Oncol 1983
Thank you for everything