Prognostic factors in endometrial adenocarcinoma: FIGO staging and the CAP template

Richard J. Zaino, MD
Hershey Medical Center
Penn State University
Hershey, PA
rzaino@psu.edu

Objectives
1) Examine the changes and utility of the 2008 FIGO staging scheme for endometrial cancer
2) Examine the application of and significance of the CAP template for endometrial cancer
3) Review the biology of the major types of endometrial adenocarcinoma
4) Examine prognostic factors in endometrial carcinoma

Disclosure
Consultant for Becker (NSF International) for cervical cancer screening

Surgical Staging of Corpus Cancer (FIGO, 1988)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA G123</td>
<td>tumor limited to endometrium</td>
</tr>
<tr>
<td>IB G123</td>
<td>invasion to inner half of myometrium</td>
</tr>
<tr>
<td>IC G123</td>
<td>invasion to outer half of myometrium</td>
</tr>
<tr>
<td>IIA</td>
<td>endocervical gland involvement</td>
</tr>
<tr>
<td>IIB</td>
<td>cervical stromal invasion</td>
</tr>
<tr>
<td>IIIA</td>
<td>tumor invades serosa, adnexa, or + peritoneal cyto</td>
</tr>
<tr>
<td>IIIB</td>
<td>vaginal metastases</td>
</tr>
<tr>
<td>IIIC</td>
<td>pelvic or para-aortic lymph node metastases</td>
</tr>
<tr>
<td>IVA</td>
<td>tumor invades bladder or bowel mucosa</td>
</tr>
<tr>
<td>IVB</td>
<td>distant, intraabdominal or inguinal node metastases</td>
</tr>
</tbody>
</table>
Surgical Staging of Corpus Cancer (FIGO, 2008)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>G123 tumor to endometrium/inner half of myometrium</td>
</tr>
<tr>
<td>IB</td>
<td>G123 invasion to outer half of myometrium</td>
</tr>
<tr>
<td>II</td>
<td>endocervical cervical stromal invasion</td>
</tr>
<tr>
<td>IIIA</td>
<td>tumor invades serosa, adnexa</td>
</tr>
<tr>
<td>IIIB</td>
<td>vaginal metastases or parametrial extension</td>
</tr>
<tr>
<td>IIIC1</td>
<td>pelvic lymph node metastases</td>
</tr>
<tr>
<td>IIIC2</td>
<td>para-aortic lymph node metastases</td>
</tr>
<tr>
<td>IVA</td>
<td>tumor invades bladder or bowel mucosa</td>
</tr>
<tr>
<td>IVB</td>
<td>distant, intraabdominal or inguinal node metastases</td>
</tr>
</tbody>
</table>

Tumor Size
Greatest dimension: ___ cm
*Additional dimensions: ___ x ___ cm
___ Cannot be determined (see Comment)

Histologic Type
  ___ Endometrioid adenocarcinoma, not otherwise characterized
  ___ Endometrioid adenocarcinoma, variant (specify):
  ___ Mucinous adenocarcinoma
  ___ Serous adenocarcinoma
  ___ Clear cell adenocarcinoma
  ___ Mixed carcinoma (specify types and percentages):
  ___ Squamous cell carcinoma
  ___ Transitional cell carcinoma
  ___ Small cell carcinoma
  ___ Undifferentiated carcinoma
  ___ Carcinosarcoma (malignant müllerian mixed tumor)
  ___ Other (specify):

CAP approved
(so it must be good for us*)

Protocol for the Examination of Specimens from Patients with Carcinoma of the Endometrium

Based on AJCC/UICC TNM, 7th edition and FIGO 2008 Annual Report

Protocol web posting date: June, 2012
Surgical Pathology Cancer Case Summary (Checklist)

*as a current member of the CAP committee on gyn tumor synoptic reports, these comments do not reflect the opinions of the CAP
Significance of maximum size of endometrial adenocarcinoma

Relative few studies addressing size, but prognostically significant.

Mariani et al, 2001 and 2002

size > 2cm is a predictor of lymphatic failure and distant failure by univariate analysis but not by multivariate analysis.

Pathologic classification of endometrial adenocarcinomas

<table>
<thead>
<tr>
<th>1980</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>adenocarcinoma</td>
<td>endometrioid</td>
</tr>
<tr>
<td>adenoacanthoma</td>
<td>endometrioid w squamous diff</td>
</tr>
<tr>
<td>adenosquamous</td>
<td>villoglandular</td>
</tr>
<tr>
<td>clear cell</td>
<td>secretory</td>
</tr>
<tr>
<td></td>
<td>mucinous</td>
</tr>
<tr>
<td></td>
<td>serous (UPSC)</td>
</tr>
<tr>
<td></td>
<td>clear cell</td>
</tr>
<tr>
<td></td>
<td>undifferentiated</td>
</tr>
<tr>
<td></td>
<td>dedifferentiated</td>
</tr>
<tr>
<td></td>
<td>mixed</td>
</tr>
</tbody>
</table>

Tumor Size

Greatest dimension: ___ cm

* Additional dimensions: ___ x ___ cm

__ Cannot be determined (see Comment)

Histologic Type

___ Endometrioid adenocarcinoma, not otherwise characterized
___ Endometrioid adenocarcinoma, variant (specify):  
___ Mucinous adenocarcinoma
___ Serous adenocarcinoma
___ Clear cell adenocarcinoma
___ Mixed carcinoma (specify types and percentages):  
___ Squamous cell carcinoma
___ Transitional cell carcinoma
___ Small cell carcinoma
___ Undifferentiated carcinoma
___ Carcinosarcoma (malignant müllerian mixed tumor)
___ Other (specify):

uterine papillary serous carcinoma
### Survival in endometrial adenocarcinoma (all stages)

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>5 yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrioid</td>
<td>80 - 90%</td>
</tr>
<tr>
<td>UPSC</td>
<td>10 - 30%</td>
</tr>
</tbody>
</table>

### UPSC - patterns of spread

<table>
<thead>
<tr>
<th>Author</th>
<th>sites of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcangiu</td>
<td>intrabdominal/small bowel</td>
</tr>
<tr>
<td>Mallipeddi</td>
<td>ovaries, bowel, omentum, cyto</td>
</tr>
<tr>
<td>Lee</td>
<td>ovaries, nodes, peritoneum</td>
</tr>
<tr>
<td>Gitsch</td>
<td>cyto, nodes, omentum, liver, dia</td>
</tr>
<tr>
<td>Carcangiu</td>
<td>adnexa, peritoneum, omentum, nodes</td>
</tr>
<tr>
<td>Cirisano</td>
<td>nodes, ovaries, peritoneum, omentum</td>
</tr>
<tr>
<td>Wheeler</td>
<td>ovary, omentum, bowel</td>
</tr>
<tr>
<td>Goff</td>
<td>ovary, nodes, omentum, peritoneum</td>
</tr>
<tr>
<td>Sherman</td>
<td>nodes, cyto, ovary, omentum</td>
</tr>
<tr>
<td>Geisler</td>
<td>omentum, cyto, peritoneum, nodes</td>
</tr>
<tr>
<td>Cell type</td>
<td>ER/PR</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>+++^</td>
</tr>
<tr>
<td>Villoglandular</td>
<td>+++</td>
</tr>
<tr>
<td>Serous</td>
<td>-/+**</td>
</tr>
</tbody>
</table>

^ in high grade
* +++ reflects with >80% positive or completely neg, if mutation not recognized by Ab
** often focal and weak
Issues with clear cell carcinoma of the endometrium

Non homogeneous
  solid, papillary, tubulocystic
Clear cell often present in squamous or secretory variants
Clear cell carcinoma may coexist/blend with serous carcinoma
ER/PR, p53 expression variable

Clear cell carcinoma of ovary*

DeLair et al, 2011
Short papillae, no branching, little stratification
Often clear, cuboidal cytoplasm
Nuclear pleomorphism
Prominent nucleoli
Mitotic figures uncommon
ER, WT1, p53 usually negative

*unfortunately, this does not apply to endometrium

Clear cell adenocarcinoma
? Precursor to clear cell carcinoma
Undifferentiated and dedifferentiated carcinoma
Silva et al, Soslow et al

No gland formation (or bi-phasic with glands in differentiated areas only)
Often appear discohesive
Usually keratin negative
Usually ER/PR negative
Very aggressive behavior
Histologic Grade (if applicable)

(FIGO grading system applies to endometrioid and mucinous carcinomas only)

___ G1: 5% or less nonsquamous solid growth
___ G2: 6% to 50% nonsquamous solid growth
___ G3: More than 50% nonsquamous solid growth
Stage I adenocarcinoma of the endometrium  
(FIGO results, 2003)

<table>
<thead>
<tr>
<th>FIGO Grade</th>
<th>5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>92%</td>
</tr>
<tr>
<td>2</td>
<td>88%</td>
</tr>
<tr>
<td>3</td>
<td>75%</td>
</tr>
</tbody>
</table>

Grading endometrial adenocarcinoma  
Two grades versus three

FIGO - 3 grades, architecture +/- nuclear  
GOG - 3 grades, architecture  
Hachisuga - 3 grades, nuclear (quantitative)  
Taylor et al - 2 grades, architecture (10% solid)  
Scholten - 2 grades, architecture (50% solid)  
Lax - 2 grades, architecture (solid, pattern, necrosis)  
Alkushi - 2 grades, architecture and nuclear

Each prognosticates well

Reproducibility of grading

<table>
<thead>
<tr>
<th>Inter-observer kappa</th>
<th>2 grade</th>
<th>3 grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkushi (arch+nuclear)</td>
<td>0.76</td>
<td>0.61</td>
</tr>
<tr>
<td>Nielsen (arch)</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Nielsen (nuclear)</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Zaino (arch)</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>Zaino (nuclear)</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>Taylor (arch)</td>
<td>0.97</td>
<td>0.52</td>
</tr>
<tr>
<td>Lax (arch)</td>
<td>0.65</td>
<td>0.55</td>
</tr>
<tr>
<td>Scholten (arch, using Lax)</td>
<td>0.39</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Lymphatic invasion

Lymph-vascular invasion  
___ not identified  
___ present  
___ indeterminate

Prognostically important in almost every study

1) Use of immuno  
2) Where to look
lymphatic invasion

vascular pseudo-invasion
FIGO 1988 Stage I Corpus Cancer

1) Is the distinction of non-invasive from inner half invasion reliable?

2) Should invasion be assessed in thirds or halves of myometrial thickness?
Superficial myometrial invasion

Stage 1 Corpus Cancer
significance of invasion

Stage 5 year survival rates (FIGO, 2003)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival Rate</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>92%</td>
<td>inability to distinguish inter-</td>
</tr>
<tr>
<td>IB</td>
<td>91%</td>
<td>digitations from myo invasion</td>
</tr>
<tr>
<td>IC</td>
<td>81%</td>
<td>outer half invasion highly significant</td>
</tr>
</tbody>
</table>

Primary Tumor (pT)

- pTX [-]: Primary tumor cannot be assessed
- pT0 [-]: No evidence of primary tumor
- pT1a [IA]: Tumor limited to endometrium or invades less than one-half of the myometrium
- pT1b [IB]: Tumor invades greater than or equal to one-half of the myometrium
- pT2 [II]: Tumor invades stromal connective tissue of the cervix, but does not extend beyond uterus
- pT3a [IIIA]: Tumor involves serosa and/or adnexa (direct extension or metastasis)
- pT3b [IIIB]: Vaginal involvement (direct extension or metastasis) or parametrial involvement
- pT4 [IVA]: Tumor invades bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4)

FIGO 2008

Myometrial invasion or tumor in adenomyosis

1) Multiple studies (Hall, Jacques, Mittal) have demonstrated excellent prognosis when carcinoma is confined to foci of adenomyosis (superficial or deep)
2) Tumor confined to adenomyosis does not increase the FIGO stage
3) What are the criteria for identification of tumor in adenomyosis?
Recognition of tumor in adenomyosis
(Jacques and Lawrence, 1990)

Presence of endometrial stroma adjacent to neoplastic glands in the myometrium
Presence of adjacent benign glands
Bulging expansion of endometrial-myometrial junction or smoothly rounded contour of entirely intramyometrial foci
Absence of peritumoral desmoplasia

Recognition of tumor in adenomyosis - CD10

The presence of CD10 staining of small cells adjacent to tumor is a sensitive but not specific indicator of endometrial stromal differentiation
More than 50% of myoinvasive endometrial adenocarcinomas have CD10 positive staining at least focally around the tumor
Difficulties in assessing the depth of myometrial invasion in endometrial carcinoma

Ali, Black and Soslow, (IJGP, 2007)

Depth of invasion - disagreement in 29% of cases

Sources of disagreement:
- irregular endo-myometrial interface
- exophytic tumor
- smooth muscle metaplasia
- tumor in adenomyosis

Most frequently - pathologists overestimate invasion

---

Primary Tumor (pT)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>pTX [-]:</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>pT0 [-]:</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>pT1a [IA]:</td>
<td>Tumor limited to endometrium or invades less than one-half of the myometrium</td>
</tr>
<tr>
<td>pT1b [IB]:</td>
<td>Tumor invades greater than or equal to one-half of the myometrium</td>
</tr>
<tr>
<td>pT2 [II]:</td>
<td>Tumor invades stromal connective tissue of the cervix, but does not extend beyond uterus</td>
</tr>
<tr>
<td>pT3a [IIIA]:</td>
<td>Tumor involves serosa and/or adnexa (direct extension or metastasis)</td>
</tr>
<tr>
<td>pT3b [IIIB]:</td>
<td>Vaginal involvement (direct extension or metastasis) or parametrial involvement</td>
</tr>
<tr>
<td>pT4 [IVA]:</td>
<td>Tumor invades bladder mucosa and/or bowel mucosa (bullos edema is not sufficient to classify a tumor as T4)</td>
</tr>
</tbody>
</table>

FIGO 2008

Stage IA G123: tumor limited to endometrium
Stage IB G123: invasion to inner half of myometrium
Stage IC G123: invasion to outer half of myometrium
Stage IIA: endocervical gland involvement
Stage IIB: cervical stromal invasion
Stage IIIA: tumor invades serosa, adnexa, or + peritoneal cytosis
Stage IIIB: vaginal metastases
Stage IIIC: pelvic or para-aortic lymph node metastases
Stage IVA: tumor invades bladder or bowel mucosa
Stage IVB: distant, intraabdominal or inguinal node metastases

FIGO 1988
Primary Tumor (pT)

- pT1a [IA]: Tumor limited to endometrium or invades less than one-half of the myometrium
- pT1b [IB]: Tumor invades greater than or equal to one-half of the myometrium
- pT2 [II]: Tumor invades stromal connective tissue of the cervix, but does not extend beyond uterus
- pT3a [IIIA]: Tumor involves serosa and/or adnexa (direct extension or metastasis)
- pT3b [IIIB]: Vaginal involvement (direct extension or metastasis) or parametrial involvement
- pT4 [IVA]: Tumor invades bladder mucosa and/or bowel mucosa (bullos edema is not sufficient to classify a tumor as T4)

Stage II Corpus Cancer

Significance of true surgical pathologic staging: a GOG study
(Creasman et al, 1999)

148/1180 with clinical stage II (+ECC)
66/148 with disease in the cervix
31/66 with extraterine disease
35 (24%) with surgical stage II

Recurrence rates at 5 years:
- IIA - 18%
- IIB - 21%

Stage II Corpus Cancer

5 year survival - 75%, lower than Stage I (FIGO results, 2003)

More often associated with higher grade, deep myometrial invasion, and lymphatic invasion than Stage I

Stage II is not a significant prognosticator by multivariate analysis

1988 Stage II Corpus Cancer

IIA endocervical gland involvement
IIB cervical stromal invasion

Definitions applied in various publications:
IIA - surface epithelium only (Jordan)
IIA - gland involvement only (Fanning, Eltabbakh, Prat)
IIA - confined to endocervical epithelium (mucosa) (Clement and Young)

but endocervix lacks a mucosa
diagnostic reproducibility is low
how does it involve glands only?
Cervical Involvement in Corpus Cancer
(Zaino et al, Gyn Oncol, 2012)

Reproducibility and Prognostic Significance
for reproducibility
46 cases
6 pathologists (5 institutions) assessed patterns of stromal vs gland involvement

for outcome (recurrence free survival)
200 cases and 200 matched stage I controls
Reproducibility study

Patterns of cervical involvement | Kappa
---|---
gland involvement | 0.15
stromal invasion | 0.28
vascular invasion only | 0.09
contiguous spread | 0.29
 discontinuous spread | 0.49

Kappa of 0-0.2 (slight), 0.2-0.4 (fair), 0.4-0.6 (moderate), 0.6-0.8 (substantial), 0.8-1.0 (almost perfect)

Results

Patterns of cervical involvement

<table>
<thead>
<tr>
<th>Patterns of cervical involvement</th>
<th>range of pathologists</th>
<th>ID of feature</th>
</tr>
</thead>
</table>
gland involvement | 63-91% | 
stromal invasion* | 30-78% | 
vascular invasion only | 0-9% | 
contiguous spread | 56-80% | 
discontinuous spread | 13-37% | 

*Definition of stage II (FIGO 2009)

Stage II Corpus Cancer

(Zaino et al, 2012)

Reproducibility

Reproducibility of distinction of gland involvement from stromal invasion is poor

Kappa = 0.28

Prognostic Significance

Cervical involvement is not a significant prognosticator by univariate or multivariate analysis

Conclusions for cervical spread

1) Experienced pathologists do not reliably distinguish endocervical stromal invasion from gland involvement

2) Clear criteria of stromal invasion are needed if endocervical stromal invasion remains the defining feature of FIGO stage II

3) Endocervical stromal invasion is associated with deep myoinvasion and high grade, but is not an independent predictor of prognosis by multivariate analysis in a large cohort
Primary Tumor (pT)
___ pT1a [IA]: Tumor limited to endometrium or invades less than one-half of the myometrium
___ pT1b [IB]: Tumor invades greater than or equal to one-half of the myometrium
___ pT2 [II]: Tumor invades stromal connective tissue of the cervix, but does not extend beyond uterus
___ pT3a [IIIA]: Tumor involves serosa and/or adnexa (direct extension or metastasis)
___ pT3b [IIIB]: Vaginal involvement (direct extension or metastasis) or parametrial
___ pT4 [IVA]: Tumor invades bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4)

Stage III Corpus Cancer:
Are all forms of Stage IIIA disease equivalent?

Positive peritoneal cytology
Tumor involves uterine serosa or adnexa (Direct extension or metastasis)

Stage IIIA Corpus Cancer + adnexal involvement
(Connell et al, 1999)

5 year DFS - 37% overall
Often associated with higher grade, lymphatic invasion, other extrauterine disease

5 year DFS - 71% without other extrauterine spread
Stage IIIA Corpus Cancer + serosal involvement (SI)
(Ashman et al, 2001)

5 year DFS - 29%
5 year DFS - 20%, SI + other extraterine sites
5 year DFS - 42%, SI only

Stage IIIB - parametrical involvement or vaginal metastases

Very rare, (less than 1% of corpus cancer and about 2% of stage III pts)
Vaginal mets often associated with nodal or distant metastases
Prognosis poor - 5 year survival about 25%

FIGO 2008

Stage IIIC1 and IIIC2
Regional Lymph Nodes (pN)

___ pN1 [IIIC1]: Regional lymph node metastasis to pelvic lymph nodes
___ pN2 [IIIC2]: Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes

Pelvic lymph nodes:
  Number examined: ___
  Number involved: ___

Para-aortic lymph nodes:
  Number examined: ___
  Number involved: ___
Stage III Corpus Cancer

Stage III C - pelvic/paraortic nodal mets

(Mariani et al, 2002)
Stage IIIC often are also Stage IIIA/IIIB
5 year DFS - 33% Stage IIIC with IIIA/B mostly extranodal failures
5 year DFS - 68% Stage IIIC without IIIA/B mostly nodal failures

Stage III Corpus Cancer

Stage III C - pelvic/paraortic nodal mets
5 year DFS - about 65-80% + pelvic node
5 year DFS - about 30% + paraaortic node

Significant survival differences between microscopic and grossly positive nodes, resected vs non-resected disease, radiated vs non-irradiated nodal beds, and capsular invasion and desmoplasia

Nodes with isolated tumor cells

Very few studies
Use of sentinel node examination currently undefined
Immunohistochemistry discloses isolated histiocyte-like cells (esp. with MELF)
Significance uncertain
Staging rule is undefined
Tentative staging conclusions

Stage IA can reliably be distinguished from Stage IB pathologically
Stage II is poorly defined pathologically and may not be prognostically significant
Stage III disease is heterogeneous
Stage IIIA alone is heterogeneous
  + adnexal spread diminishes survival (70%)
  + uterine serosa carries a worse prognosis (30%)

Stage IIIB (parametrium/vaginal mets) is rare, with a poor prognosis (25%)
Stage IIIC (good to have split)
  IIIC1 + pelvic nodes significant (70%)
  IIIC2 + paraaortic nodes significantly worse (30%)
  (Stage IIIC limited to nodes usually fails in nodal area)

Surgical Staging of Corpus Cancer (FIGO, 2008)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA G123</td>
<td>tumor to endometrium/inner half of myometrium</td>
</tr>
<tr>
<td>IB G123</td>
<td>invasion to outer half of myometrium</td>
</tr>
<tr>
<td>II</td>
<td>endocervical cervical stromal invasion</td>
</tr>
<tr>
<td>IIIA</td>
<td>tumor invades serosa, adnexa</td>
</tr>
<tr>
<td>IIIB</td>
<td>vaginal metastases or parametrial extension</td>
</tr>
<tr>
<td>IIIC1</td>
<td>pelvic lymph node metastases</td>
</tr>
<tr>
<td>IIIC2</td>
<td>para-aortic lymph node metastases</td>
</tr>
<tr>
<td>IVA</td>
<td>tumor invades bladder or bowel mucosa</td>
</tr>
<tr>
<td>IVB</td>
<td>distant, intraabdominal oringuinal node metastases</td>
</tr>
</tbody>
</table>

The future?

1) Pathologists need to be outspoken in the identification of characteristics that relate to prognosis and response to therapy.

2) Future refinements are needed in identification of cell types.

3) Pathologists need to identify features that can help guide individualized treatment for endometrial carcinoma
Objectives

1) Examine the changes and utility of the 2008 FIGO staging scheme for endometrial cancer
2) Examine the application of and significance of the CAP template for endometrial cancer
3) Review the biology of the major types of endometrial adenocarcinoma
4) Examine prognostic factors in endometrial carcinoma