Uterine Cancer:
Grading, Staging, Lynch Syndrome

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Pathology Department

Outline of Talk

Sub-typing Endometrial Carcinoma

- Grading
- Staging
- Lynch syndrome screening

Grading Endometrial Carcinoma

- FIGO grading system
  - GOG modifications
  - Unresolved / controversial issues
- Pitfalls of over-grading
- Pitfalls of under-grading

FIGO Grading of Endometrial Carcinoma

- Serous, clear cell, carcinosarcoma:
  - grade 3
- Endometrioid:
  - <5% solid: grade 1
  - 5-50% solid: grade 2
  - >50% solid: grade 3

upgrade to grade 3 if there is
"notable nuclear atypia inappropriate for architecture"
FIGO Grading of Endometrial Carcinoma

- Serous, clear cell, carcinosarcoma:
  grade 3

- Endometrioid:
  - <5% solid: grade 1
  - 5-50% solid: grade 2
  - >50% solid: grade 3

**GOG Modification:** increase 1 grade if >50% nuclei show nuclear atypia:
- Large, pleomorphic nuclei
- Coarse chromatin
- Large irregular nucleoli

**Modification for mixed type:** assign as grade 3 if >10% is serous, clear cell, or undifferentiated

Severe nuclear atypia: increase 1 grade higher if seen in >50% tumor cells

Squamous differentiation:
- Not solid growth
- True solid growth

Pitfalls of under-grading

<table>
<thead>
<tr>
<th>Correct Grade</th>
<th>Pitfalls of under-grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Mixed type with &lt;50% serous, clear cell, or carcinosarcoma</td>
</tr>
<tr>
<td>3</td>
<td>Undifferentiated or dedifferentiated carcinoma</td>
</tr>
<tr>
<td>3</td>
<td>Pseudo-glandular serous carcinoma</td>
</tr>
</tbody>
</table>

Pitfalls of over-grading

<table>
<thead>
<tr>
<th>Architectural grade only</th>
<th>Architectural grade of glandular component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear atypia in &lt;50% of pure endometrioid adenocarcinoma</td>
<td>Grading spindled, corded, squamous elements as solid</td>
</tr>
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Staging Endometrial Carcinoma

- FIGO staging system
  - 2009 Modifications
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- Problematic patterns:
  - Myometrial invasion
  - Lymphatic invasion
  - Cervical invasion
  - Adnexal, peritoneal spread

FIGO Staging of Endometrial Carcinoma

2009 FIGO Staging Modifications

<table>
<thead>
<tr>
<th>Change</th>
<th>Less to worry about:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eliminated pT1a versus pT1b</td>
<td>“superficial” myometrial invasion</td>
</tr>
<tr>
<td>Eliminated pT2a</td>
<td>endocervical mucosal growth</td>
</tr>
<tr>
<td>Eliminated peritoneal cytology</td>
<td>pelvic washings</td>
</tr>
<tr>
<td>Subdivided N1 versus N2</td>
<td>a bit of extra work (not too bad)</td>
</tr>
</tbody>
</table>
FIGO Staging of Endometrial Carcinoma

<table>
<thead>
<tr>
<th>AJCC</th>
<th>FIGO</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT1a</td>
<td>IA</td>
<td>Confined to endometrium or invades less than half of myometrium</td>
</tr>
<tr>
<td>pT1b</td>
<td>IB</td>
<td>Outer half of myometrium</td>
</tr>
<tr>
<td>pT2</td>
<td>II</td>
<td>Stroma of cervix</td>
</tr>
<tr>
<td>pT3a</td>
<td>IIIA</td>
<td>Uterine serosa or adnexa</td>
</tr>
<tr>
<td>pT3b</td>
<td>IIIB</td>
<td>Vagina or parametrium</td>
</tr>
<tr>
<td>pT4</td>
<td>IVA</td>
<td>Bladder mucosa or bowel mucosa</td>
</tr>
<tr>
<td>pN1</td>
<td>IIIC1</td>
<td>Pelvic lymph node metastasis</td>
</tr>
<tr>
<td>pN2</td>
<td>IIIC2</td>
<td>Para-aortic lymph node metastasis</td>
</tr>
<tr>
<td>pM1</td>
<td>IVB</td>
<td>Distant metastasis including omentum, inguinal lymph nodes. Excludes pelvic sites/serosa.</td>
</tr>
</tbody>
</table>

Staging Endometrial Carcinoma

- FIGO staging system
  - 2009 Modifications
  - Unresolved / controversial issues
- Problematic patterns:
  - Myometrial invasion
    - Lymphatic invasion
    - Cervical invasion
    - Adnexal, peritoneal spread
  - Conventional
    - Jagged, irregular contours of tumor nests
    - Single tumor cells or clusters in myometrium
    - Lack of normal glands/stroma at the leading edge of tumor
    - Haphazard distribution of tumor nests in myometrium
    - Deep location of tumor nests, near large vessels
  - Desmoplastic stroma
    - Edematous / myxoid background
    - Reactive stromal cells
      - Stellate shape
      - Nuclear enlargement
      - Nucleoli
    - Inflammation

Myometrial Invasion Patterns

- Conventional invasion
- Problematic patterns
  - Pushing
  - MELF
  - Diffusely infiltrating (adenoma malignum-like)
  - Pseudo-glandular serous carcinoma
- Additional Problems
  - Recognizing endometrial stromal metaplasia
  - Evaluating invasion with irregular endomyometrial junction
  - Evaluating invasion with adenomyosis present
  - Measuring depth with exophytic component
Conventional pattern of myoinvasion.

- Desmoplastic stroma.

Problem in Evaluating Myoinvasion:

- Metaplasia of normal endometrial stroma:
  - Fibroblastic or myoid metaplasia
  - Normal process, unclear etiology; it is not atrophy
  - More common in deeper endometrium
  - May affect adenomyosis

- Creates a pitfall in assessing for myoinvasion:
  - Fibroblastic metaplasia:
    - Makes it look like endometrial stroma is absent
  - Myoid metaplasia:
    - Makes endometrial stroma look like myometrium
  - Leads to overdiagnosis of myoinvasion
Original Article
Difficulties in Assessing the Depth of Myometrial Invasion in Endometrial Carcinoma

Asya Ali, M.D., Devin Blask, M.D., and Robert A. Sedlow, M.D.
Fibroblastic metaplasia of normal endometrial stroma

CD10 Fibroblastic metaplasia of normal endometrial stroma

Fibroblastic metaplasia of normal adenomyosis stroma

Fibroblastic metaplasia of normal adenomyosis stroma
Fibroblastic metaplasia of normal adenomyosis stroma

Benign glands at interface No of tumor / myometrium Fibrous / myoid metaplasia No of endometrial stroma Loss of endometrial stroma Yes Desmoplastic stroma Yes

Assessing stroma next to cancer near myometrium

<table>
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<th>Myoinvasion</th>
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<td>Benign glands at interface of tumor / myometrium</td>
</tr>
<tr>
<td>Fibrous / myoid metaplasia of endometrial stroma</td>
</tr>
<tr>
<td>Loss of endometrial stroma</td>
</tr>
<tr>
<td>Desmoplastic stroma</td>
</tr>
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Benign glands at leading edge of cancer: No myoinvasion
Benign glands at leading edge of cancer: No myoinvasion

Undulating endomyometrial junction and metaplasia: no myoinvasion

Metaplastic endometrial stroma: no myoinvasion
Highly suspicious for myoinvasion

Undulating endomyometrial junction with cancer: ? myoinvasion

Myometrial Invasion Patterns

- MELF = Microcystic, Elongated, Fragmented Pattern
  - Seen in grade 1 endometrioid adenocarcinomas
  - Leading edge of tumor attenuates, pinches off
    - Glands resemble microcysts or lymphatics
    - Thin, eosinophilic cytoplasm
  - Acute inflammation in epithelium and lumen
  - Desmoplastic stroma

Pitfalls:
- Under-recognized: foci are small, easy to miss
- Mimics LVI
- Mimics adenomyosis

Beginning of MELF pattern of myoinvasion
MELF pattern of myoinvasion: mimics LVI

Myometrial Invasion Patterns

- Diffusely infiltrating / “adenoma malignum-like” pattern
  - Scattered simple glands, nests
  - No jagged contours
  - No desmoplastic stroma

Pitfalls:
- Mimics stroma poor adenomyosis
- Mimics adenoma malignum of cervix
Diffusely infiltrating, adenoma malignum-like myoinvasion
Myometrial Invasion Patterns

Cancer in adenomyosis: *is there myoinvasion?*

- Use “conventional invasion” criteria
  - Jagged contours
  - Loss of stroma / metaplastic stroma of adenomyosis
  - “Expansile” growth compared to adjacent adenomyosis

Can CD10 be used to look for loss of endometrial stroma? No.

- False positive CD10: Myoinvasive cancer can have CD10 positive stroma
- False negative CD10: Metaplastic endometrial stroma may lose CD10

Myometrial Invasion Patterns

Problem: Measuring depth of invasion of cancer from adenomyosis

- No rules exist
- Based on outcome studies, proposed convention is to measure from deepest point of adenomyosis not from endomyometrial junction

Staging Endometrial Carcinoma

- FIGO staging system
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- Problematic patterns:
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      - Adnexal, peritoneal spread
Lymphovascular Invasion Patterns

**Problems**
- "Artifactual" LVI due to mechanical displacement
  - Due to friable, fragmented tumor
  - Due to surgical technique (uterine manipulator)
- Mimics of LVI
  - MELF
  - Intravenous leiomyomatosis
  - Intravascular menses / adenomyosis / endometriosis

Artifactual LVI Due to Mechanical Displacement

**Causes of Fragmentation**
- Exophytic, papillary tumor
- Poorly-fixed tumor
- Mechanical trauma by hysterectomy using uterine manipulator

**Causes of Displacement**
- "Knife" displacement during specimen dissection
- Increased intra-uterine pressure by uterine manipulator

Uterine manipulator for laparoscopic hysterectomy

- Mechanical fragmentation of tumor
- Increased intrauterine pressure displaces tumor into lymphatics, into fallopian tubes
Fragmented tumor due to uterine manipulator

Uterine manipulator for laparoscopic hysterectomy

Compared to hysterectomy without uterine manipulator:

- Much higher incidence of:
  - Fragmented tumor
  - LVI (up to 20%-50% of cases)
  - Floating tumor in fallopian tube lumens (up to 20% cases)
  - Positive peritoneal cytology (conflicting data)
- Same incidence of:
  - Lymph node metastases

Proposed Criteria to Define LVI

<table>
<thead>
<tr>
<th></th>
<th>“True” LVI</th>
<th>“Artifactual” LVI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohesive tumor clusters</td>
<td>Yes</td>
<td>No, disaggregated</td>
</tr>
<tr>
<td>Altered tumor cell cytology</td>
<td>Yes</td>
<td>No, resembles main tumor</td>
</tr>
<tr>
<td>Admixed inflammatory cells</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Present in deeper lymphatics</td>
<td>Yes</td>
<td>No, superficial only</td>
</tr>
<tr>
<td>Near larger vessels</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Nearby lymphoid aggregates</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Nearby retraction artifact</td>
<td>No</td>
<td>Yes</td>
</tr>
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Folkins, Med Pathol 2010

True LVI: Contour molding; cytologic change of tumor
True LVI: Perivascular lymphoid aggregates

True LVI: adjacent to deep thick walled vessels

Fragmented tumor due to uterine manipulator

Fragmented tumor due to uterine manipulator
Reporting Artifactual Displacement

If uterine manipulator was used and criteria suggest artifact

- Do not issue a definitive yes/no.
- Report in comment as:
  “floating tumor cells within lymphatic spaces, cannot exclude mechanical artifact”
- Do not upstage if floating tumor in fallopian tube lumens
- Communicate clearly with surgeon and in report.
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  - Cervical invasion
    - Adnexal, peritoneal spread

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**Cervical Invasion by Endometrial Cancer**

**Criteria**

- Stromal versus glandular involvement
- Endocervix versus lower uterine segment involvement

**Non-stage II tumor growth**

- Prolapsed endometrial cancer
- Exophytic endometrial cancer
- Cervical polyp involved by endometrial cancer

**Primary cervical lesions**

- Malignancies
- Benign lesions

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**Endocervical stroma versus Lower uterine segment**

**Anatomic boundary: there is none**

- Glands from both areas may co-mingle
- Stroma from both areas may co-mingle
- CD10 expressed in stroma at both sites
- Smooth muscle bundles can extend into endocervix

**Advised to keep strict criteria for designating cervical invasion**

- No endometrial glands / stroma
- Presence of endocervical glands
- Gross diagnosis is not sufficient

**Endometrioid adenocarcinoma in cervical stroma = stage II**
Endometrioid adenocarcinoma in cervical stroma = stage II

Prolapse of polypoid endometrial cancer (not in stroma): NOT stage II

Tumor in lower uterine segment (stage I) or endocervix (stage II) ?

Mimics of Cervical Invasion by Endometrial Cancer

Malignant mimics

- Primary endocervical adenocarcinoma
- Conventional or minimal deviation-type
- Mesonephric adenocarcinoma
- Adenoid basal carcinoma
Mimics of Cervical Invasion by Endometrial Cancer

Malignant mimics

- Primary endocervical adenocarcinoma
  - Conventional or minimal deviation-type
  - Mesonephric adenocarcinoma
- Adenoid basal carcinoma

Benign mimics

- Mesonephric hyperplasia
- Diffuse / lobular endocervical glandular hyperplasia
- Deep endocervical glands; tunnel clusters
- Cervical endometriosis
- Tubal / tubo-endometrioid metaplasia

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Problems with Stage IIIA: Spread to Ovaries / Tubes

- Is ovarian tumor a metastasis or synchronous primary ovarian cancer
  - Controversial issue; no gold standard way to resolve
    - If endometrioid histology, use AFIP consensus criteria
    - If serous histology, no clear guidelines
      - WT1 loss favors uterine origin
- Mechanical displacement to fallopian tubes
  - Do not upstage if free-floating fragments
- Benign mimics of metastasis
  - Keratin granulomas
  - Atypical endometriosis

Artifactual Displacement of Endometrial Tumor into Fallopian Tube

Do not increase stage
Artifactual Displacement of Endometrial Tumor into Fallopian Tube

Do not increase stage

Omental / Extra-pelvic abdominal Spread

- Stage pM1 , FIGO IVB
  - Unlike rules for primary ovarian cancer, which would be pT3, FIGO III

Outline of Talk

Sub-typing Endometrial Carcinoma
Grading
Staging
- Lynch syndrome screening

Epidemiology of Endometrial Cancer

~95% Sporadic
~5% Inherited
Most are Lynch Syndrome

Definition of Lynch Syndrome

Autosomal dominant cancer syndrome due to germline mutations in mismatch repair (MMR) genes

- Colorectal cancer
- Endometrial cancer
- Other:
  - Ovary
  - Renal pelvis/ureter
  - Stomach
  - Pancreas
  - Small bowel
  - Brain


Cancer Risk in Lynch Syndrome

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Lifetime Risk</th>
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<tr>
<td>Colon cancer</td>
<td>~70 %</td>
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<tr>
<td>Endometrial cancer</td>
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</tr>
<tr>
<td>Two primary cancers</td>
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</tr>
<tr>
<td>Three primary cancers</td>
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Lindor NM et al. JAMA 2006; 296:1507
Lynch HT Cancer 1977; 40: 1849

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50% of LS women will present first with endometrial cancer

Lindor NM et al. JAMA 2006; 296:1507
Lynch HT Cancer 1977; 40: 1849

Diagnosis of Endometrial Cancer

- Screening for LS-type Cancers
- Prophylaxis against LS-type Cancers
Screening Recommendations in Lynch Syndrome

- Colonoscopy q 1-2 yrs @ age 20
- Endometrial biopsy q 1 yr @ age 30
- Urinalysis with cytology q 1-2 yrs @ age 25-35

Lindor NM et al. JAMA 2006; 296: 1507

Prophylactic Options in Lynch Syndrome

- Not enough studies yet for definite recommendation
- Prophylactic hysterectomy / oophorectomy
  - Chen LM et al. Obstet & Gynecol 2007; 110: 18
- Oral contraceptives
  - Studies underway

Lindor NM et al. JAMA 2006; 296: 1507

Multidisciplinary System of Detecting Lynch Syndrome in Endometrial Cancer Patients

- GYN Oncology Surgeon
  - To obtain personal/family cancer history (Bethesda Guidelines data)
- Pathologist
  - To identify morphologic risk factors in the endometrial cancer
  - To order and interpret screening tests
- Genetic Counselor
  - To guide management based on screening results

Lindor NM et al. JAMA 2006; 296: 1507
How is Lynch Syndrome Diagnosed in Endometrial Cancer

Gold Standard Diagnosis

Germline mutation analysis of MMR Genes

Problems:
- Labor intensive; specialty lab
- Costly
- Not practical at a population level (only 5% incidence)

Alternate approach:

Germline test only the highest risk patients

- Who is at highest risk for LS?
  - Cancers with Microsatellite Instability (MSI)
  - Cancers with loss of MMR proteins by IHC

IHC MMR Protein Loss in Endometrial Cancer is not Pathognomonic For Lynch Syndrome

IHC Stain Result

- MLH1 protein loss
  - >90% due to gene methylation (not LS)
  - 1% due to gene mutation

- PMS2 protein loss

- MSH2 protein loss

- MSH6 protein loss
  - >99% due to gene mutation

Endometrial Cancer Microsatellite Instability is not Pathognomonic For Lynch Syndrome


| MSI Test Result | Instability (high) | >90% due to gene methylation (not LS)
|                 | Stable             | 1% due to gene mutation

~50% of MSH6 Lynch Syndrome tumors are MSI-Stable

Which LS-screening test is better?
The answer is still being studied...

- Neither is perfectly sensitive or specific
- Each have unique pros and cons
- Many centers perform both in the interim

Which Endometrial Cancer patients should get a LS-screening test?
The answer is still being studied...

At UCSF, any patient with 1 or more of these criteria:

1. Age ≤ 50
2. Bethesda Guidelines fulfilled
3. MMR-Tumor Morphology present

Any 1 or more:

- Tumor infiltrating lymphocytes
- Peritumoral lymphocytes
- Undifferentiated histology
- Lower uterine segment origin
- Concurrent ovarian cancer
Peritumoral inflammation in endometrial cancer

Tumor infiltrating lymphocytes in endometrial cancer

Lower uterine segment origin of Lynch syndrome endometrial cancer
Screening Endometrial Cancer Patients for Lynch Syndrome at UCSF

- No < 50
- No BG history
- No MMR tumor morphology

- Age < 50
- BG history
- MMR tumor morphology

- MMR IHC normal
  - no MSI-High

- MLH1 Loss

- MLH2/MSH6 loss
  - MSI-High

- MMR Germline Mutation Analysis

Not Lynch

Management of Endometrial Cancer Patients with Abnormal MMR/MSI (UCSF Protocol)

- Formal genetics counseling consultation
- Pedigree determined
- Blood sample obtained

- Germline mutation analysis of all 4 MMR genes

If no mutations:
- No further evaluation

If any mutations:
- Patient and family counseled
- Screening / prophylaxis

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