Invasive Endocervical Adenocarcinoma
Invasive Endocervical Adenocarcinoma (IEAC)

- Invasive Cervical Squamous Cell Carcinoma
  a) Well-standardized parameter for the diagnosis and subsequent management
  b) No specific and clinically relevant pathologic criteria for assessment of IEAC
  c) Same definitions and staging have been applied to both squamous and glandular lesions:
    • They represent distinct tumor types
Invasive Endocervical Adenocarcinoma (IEAC)

• Part of the problema in better characterizing IEAC and determining an appropriate treatment:
  – Difficulty in accurately assessing depth of invasion (DOI)
  – Cervical tumors, particularly in their earlier phases:
    • Staged and treated based on their size and DOI

Int J Gynecol Obstet 2009;105:103-104
Invasive Endocervical Adenocarcinoma (IEAC)

- Carcinomas with > 3 mm invasion are at increased risk of presenting with positive lymph nodes
- Most of the cases, lymphadenectomy do not demonstrate metastases
- Conversely, superficial tumors can occasionally present with relatively advanced disease

Int J Gynecol Cancer 2011;21:1640-1645
Invasive Endocervical Adenocarcinoma

• Currently, the resection of lymph nodes (LN) in cases of EAC depends mainly on the depth of invasion (DOI)
• Lack of a uniform definition on Microinvasive Adenocarcinoma (MICA) and methodology for measuring the DOI make interpretation of the published data difficult
• The maximal DOI in studies of MICA varies from 1 to 5 mm
Invasive Endocervical Adenocarcinoma

• Defining what constitutes “deeply enough” (AIS vs Invasive) is often the problem
• Arbitrarily, extension to more than 1mm below adjacent gland generally qualifies
• IEAC stage IA1/1 A2: currently there is not consensus:
  For the optimal therapy for either stage

Gyn Oncol 2012; 125:285-286
Obstet Gynecol 2001;97:701-706
Invasive Endocervical Adenocarcinoma

- Lymph node dissection seems like the proper approach, but: It is not performed without risk of significant morbidity for patients
- The development of novel and more reproducible parameters that can better identify patients at risk for developing LN metastasis are necessary
Invasive Endocervical Adenocarcinoma (IEAC)

• There are well-established criteria for determination of invasion:
  – Presence of single cell
  – Malignant glands running through the cervical stroma
  – Malignant glands eliciting desmoplasia
  – LVI

• In cases of well-differentiated adenocarcinoma, these features are not as obvious

Int J Gynecol Pathol 2002;21:314-326
Invasive Endocervical Adenocarcinoma

• Early Invasive Adenocarcinoma:
• Main issues are:
  – Differentiation of adenocarcinoma in situ (AIS) from invasive glands and establishing the point of origin of invasion
• Most cases:
  – DOI is measured from the Surface rather than from the point of origin in AIS

Diagnostic Pathology 2010;16:455-467
Invasive Endocervical Adenocarcinoma

• Östor:
  – In doubtful cases:
    • “The entire tumor thickness should be measured rather than DOI”

Int J Gynecol Pathol 2000;19:29-38
Microinvasive Adenocarcinoma of the Cervix

- Complicated issue by the presence of multiple definitions:
  - SGO:
    - Lesion with stroma invasion ≤ 3 mm
    - Absence of lymphatic or blood vessel invasion

Diagnostic Pathology 2010;16:455-467
Microinvasive Adenocarcinoma of the Cervix

- FIGO divides stage IA cervical tumors into:
  - Stage IA1:
    - Stromal invasion, \( \leq 3 \text{ mm in depth} \)
    - \(< 7\text{mm in lateral extensión}\)
  - Stage IA2:
    - Stromal invasion \( > 3 \text{ mm but not } >5 \text{ mm in depth and not } >7\text{mm in width} \)

Int J Gynecol Pathol 2002;21:314-326
Invasive Endocervical Adenocarcinoma

• Even slight variation in reported DOI have important clinical implications
  – Stage IA1 are treated with hysterectomy or cervical conization alone
  – Stage IA2 and larger:
    – Radical hysterectomy and lymph node dissection
• In most cases lymph nodes are negative

Gynecol Oncol 2006;103:960-965
Invasive Endocervical Adenocarcinoma

Poynor et al:
33 patients conization/
Hysterectomy + LN dissection

21 DOI: ≤ 3 mm
None LN mets

12, DOI: 3-5 mm
1 had LVI
None mets

Gynecol Oncol 2006;103:960-965
Invasive Endocervical Adenocarcinoma

- Literature review:
  a) SIA1 patients:
     • 0.8%, LN metastases
  c) SIA2:
     • 1.7%, LN metastases

Gynecol Oncol 2006;103:960-965
Invasive Endocervical Adenocarcinoma (IEAC)

- Lymph node (LN) involvement is an important prognostic factor in IEAC and is associated with a need for adjuvant therapy.
- The standard of care for early stage (IA2, IB1 and IIA) tumors:
  - Radical hysterectomy with bilateral pelvic lymph node dissection (PLND)

Obstet Gynecol 2010; 116:1150-1157
Invasive Endocervical Adenocarcinoma (IEAC)

• >95% of LNs resected in IEAC are negative
• PLND has associated morbidity
• The role of PLND in the management of IEAC remains controversial.

Int J Gynecol Cancer 2011;21:1640-1645
Invasive Endocervical Adenocarcinoma and Pelvic Lymph Node Dissection

• Despite a variety of histopathologic markers that are correlated to LN metastases:
  – There are no guidelines to suggest which patients with early disease may safely avoid lymphadenectomy.
Invasive Endocervical Adenocarcinoma: Proposal for a New Pattern-based Classification System with Significant Clinical Implications

• Main goal:
  – To evaluate how the pattern of invasion, independently of the DOI or horizontal extension, predicts risk of lymph node metastasis and patient survival
Invasive Endocervical Adenocarcinoma: New Pattern-based Classification System

- Selection Criteria:
  1. Diagnosis of IEAC
  2. Treatment by cone/LEEP or hysterectomy
  3. Negative surgical margins
  4. Lymphadenectomy with > 1 LN available for evaluation.

Int J Gynecol Pathol 2013;32:592-601
Invasive Endocervical Adenocarcinoma: New Pattern-based Classification System

- 352 women
- 20 to 83 years old (mean: 45 yrs)
- Total number of resected lymph nodes:
  - 6,506
  - 78 were positive
- Recurrences: 39 patients (11.4%)
- 16 DOD (4.6%)
Invasive Endocervical Adenocarcinoma

Standard Method

Stage I
- IA1 7.5%
- IA2 7.5%
- IB 85%
- 88.3%

DOI
0.2 to 27 mm
(m:6.7mm)

Stage II to IV
- 11.7%
<table>
<thead>
<tr>
<th>Pattern</th>
<th>Silva system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pattern A</td>
<td>- Well-demarcated glands with rounded contours, frequently forming groups</td>
</tr>
<tr>
<td></td>
<td>- No single cells or desmoplastic stromal reaction</td>
</tr>
<tr>
<td></td>
<td>- Irrelevant relationship to large cervical vessels or depth of the tumor</td>
</tr>
<tr>
<td></td>
<td>- Complex intraglandular growth allowed (i.e. cribiform, papillae)</td>
</tr>
<tr>
<td></td>
<td>- No lymphovascular invasion</td>
</tr>
<tr>
<td></td>
<td>- Well or moderate differentiation</td>
</tr>
<tr>
<td>Pattern B</td>
<td>- Early destructive stromal invasion arising from well-demarcated glands</td>
</tr>
<tr>
<td></td>
<td>(pattern A-like glands)</td>
</tr>
<tr>
<td></td>
<td>- +/- Lymphovascular invasion</td>
</tr>
<tr>
<td>Pattern C</td>
<td>- Diffuse destructive invasion</td>
</tr>
</tbody>
</table>
Pattern A
Pattern A
Pattern A
Invasive Endocervical Adenocarcinoma: New Classification System (Silva System)

- Pattern of invasion rather than DOI
- Tumors with Pattern A
  - Do not metastasize
  - 100% long-term survival
  - 20.7% cases, fall in this category
  - At least, 1/5 could potentially spared from LN resection and risk of associated complications
Invasive Endocervical Adenocarcinoma: Silva System

- Distinction between adenocarcinoma in situ and invasive adenocarcinoma become inconsequential
- Some IEAC pattern A might resemble adenocarcinoma in situ
  - Mean DOI: 3.8mm
  - 27% >5mm
  - 1 case >10 mm
- Lesions pattern A
  - Deep in situ lesions?
  - Or invasive neoplasias with a growth pattern without metastatic potential
Pattern B
Pattern B
Pattern B
Invasive Endocervical Adenocarcinoma: Silva System

• Pattern B cases:
  – Early stroma invasion
  – Positive LN 4.4%
• The value of performing sentinel LN instead of complete lymphadenectomy should be explored
• Key finding in predicting risk:
  – LVI?
Pattern C
Invasive Endocervical Adenocarcinoma
“Mixed pattern” of invasion

• To correctly classify a tumor as having a pattern A of invasion:
  – Evaluation of entire lesion
• Tumor must always be classified:
  – Highest identified pattern
• Cone/LEEP with negative margins is required
Invasive Endocervical Adenocarcinoma

- Examination of biopsies to exclude Pattern A
- Assess for:
  - Desmoplastic reaction
  - Isolated invasive cells
  - LVI
  - High nuclear grade
  - Solid/papillary areas
- Patient will benefit from hysterectomy + LND or sentinel LN
Invasive Endocervical Adenocarcinoma (IEAC)

Conclusion:
• Classifying IEAC by patterns of invasion rather than DOI:
  – Identifies 20.7% of patient who do not require LND
  – Excellent prognosis (Pattern A)

Int J Gynecol Pathol 2013;32:592-601
A Novel Classification System for Patients with IEAC.

- An study of 411 cases. Alvarado-Cabrero I, et al.
  - Analysis of additional cases following our initial study.
  - Goals:
    - To determine if the presence of LVI, tumor size, grade of differentiation, DOI and the new system provide prognostic information

Mod Pathol 2013;26:265A
A Novel Classification System for Patients with IEAC.

- 411 cases from 14 international institutions
- Age: 20 to 86 years

<table>
<thead>
<tr>
<th>Patterns of Growth</th>
<th>LN Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>20%</td>
</tr>
<tr>
<td>B</td>
<td>25%</td>
</tr>
<tr>
<td>C</td>
<td>55%</td>
</tr>
</tbody>
</table>

All LVI

Mod Pathol 2013;26:265A
### Pattern A

<table>
<thead>
<tr>
<th>DOI (mm)</th>
<th>No. of cases</th>
<th>LVI</th>
<th>Stage</th>
<th>LN mets</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>4 (5%)</td>
<td>0</td>
<td>IA1</td>
<td>0</td>
</tr>
<tr>
<td>1-3</td>
<td>37 (45%)</td>
<td>0</td>
<td>IA1</td>
<td>0</td>
</tr>
<tr>
<td>3.1-5</td>
<td>20 (24%)</td>
<td>0</td>
<td>IA2</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>21 (26%)</td>
<td>0</td>
<td>IB</td>
<td>0</td>
</tr>
</tbody>
</table>
Pattern B

- Patients with LN metastasis 8/102 (7.8%)

<table>
<thead>
<tr>
<th>DOI (mm)</th>
<th>No. of cases</th>
<th>LVI</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>2</td>
<td>yes</td>
<td>IA1</td>
</tr>
<tr>
<td>1-3</td>
<td>2</td>
<td>yes</td>
<td>IB1</td>
</tr>
<tr>
<td>3.1-5</td>
<td>1</td>
<td>yes</td>
<td>IA2</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>3</td>
<td>yes</td>
<td>2IB1/1 IIA</td>
</tr>
</tbody>
</table>
## Pattern B

<table>
<thead>
<tr>
<th>DOI (mm)</th>
<th>No. Of patients</th>
<th>All patients</th>
<th>LN metastasis (%)</th>
<th>Recurrences (%)</th>
<th>DOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>24 (23.5%)</td>
<td>2 (1.9%)</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>14 (13.7%)</td>
<td>2 (1.9%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3.1-5</td>
<td>1 (0.9%)</td>
<td>1 (0.9%)</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>&gt; 5</td>
<td>3 (2.9%)</td>
<td>3 (2.9%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Comparison of histologic features encountered in patterns A, B and C

<table>
<thead>
<tr>
<th>Pattern</th>
<th>No. Of Patients</th>
<th>DOI (mean in mm)</th>
<th>Patients with LN + (Tumor size (≤10mm))</th>
<th>Recurrences</th>
<th>DOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>82 (20%)</td>
<td>5.3</td>
<td>0 (%)</td>
<td>34 (42%)</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>102 (25%)</td>
<td>5.3</td>
<td>8 (7.8%)</td>
<td>25 (26%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>C</td>
<td>227 (55%)</td>
<td>10mm</td>
<td>58 (26%)</td>
<td>6 (11%)</td>
<td>43 (19%)</td>
</tr>
</tbody>
</table>
A Novel Classification System for Patients with IEAC. An study of 411 cases

• Analysis of additional cases following our initial study:
  – Validates our observation of the clinical utility of the pattern based classification

• There were no LN metastasis in cases with a growth pattern A

• “All pattern B and C cases with LN metastasis had LVI”
Given the relative low risk for metastasis in pattern B tumors (5.5):

- The value of performing sentinel LN should be further explored
- Preliminary data suggests that a key finding in this group might be the presence of LVI
A Novel Classification System for Patients with IEAC. An study of 411 cases
Alvarado-Cabrero I et al

• If superficial invasion is found without obvious LVI:
  – Careful examination of the pathology is recommended
  – In our series of 102 cases with pattern B, only those with LVI had LN metastasis as well as 26% of pattern C cases
Thank you