Problems in the Evaluation of Surface Epithelial-Stromal Tumors of the Ovary: an Update

John H. Eichhorn
C. Blake Gilks

CASE 1A

A 27-year-old woman with primary infertility had a negative work-up, except for a right ovarian mass. A right salpingo-oophorectomy & omentectomy was performed, with bx of the contralateral ovary and peritoneal nodules. The right ovarian mass was 6 cm, cystic and solid, and had external surface exerences.

DIAGNOSIS

Serous cystic and surface borderline tumor, micropapillary type
FOLLOW-UP

Stage III tumor; only non-invasive implants.

Later procedures: 1. 16 mos, neg. pelviscopy; 2. in vitro fertilization; 3. Contralateral oophorectomy for residual tumor.

*Alive and free of disease at 15 years.*

CASE 1B

A 55-year-old woman presented with a right adnexal mass. An ultrasound study revealed a 20 cm complex mass with no evidence of ascites.

**DIAGNOSIS**

Serous cystic borderline tumor, micropapillary (cribriform) type
**“MICROPAPILLARY” SBTs**

<table>
<thead>
<tr>
<th>Cases</th>
<th>MP</th>
<th>CR</th>
<th>MP &amp; CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>11</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Age (y)

| Mean 38 | Mean 60 | 21, 36, 68 |

Bilateral

| 69 %    | 37 %    | 67 % |

MP, micropapillary; CR, cribriform


**DIAGNOSTIC CRITERIA**

1. Non-hierarchical branching of elongate “filiform” papillae with smooth contours from large papillae, cyst walls, or external surface

2. Cribriform pattern of cells lining these structures
DIAGNOSTIC CRITERIA

1. Non-hierarchical branching of elongate “filiform” papillae with smooth contours from large papillae, cyst walls, or external surface, and/or
2. Cribriform pattern of cells lining these structures
3. Confluent for at least 5 mm, on at least one slide
4. No more than moderate nuclear atypia
5. “Microinvasion” may be present

SEROUS BORDERLINE TUMORS: “MICROPAPILLARY” VS “TYPICAL”

Areas of agreement (10 studies; >250 cases):

- Average age: MSBT = TSBT
- Bilateral: More freq in MSBT (trend)
- Surface tumor: More freq in MSBT (trend)
- Extraovarian: More freq in MSBT (trend)
- Stage I prognosis: Excellent, both tumors
SEROUS BORDERLINE TUMORS: “MICROPAPILLARY” VS “TYPICAL”

Discordant observations:

Invasive implants: More, slightly more, same, fewer (1-2 studies each)
Recurrence rate: Higher, same (3-4 studies ea)
Mortality rate: Higher, same (3-4 studies ea)

IMPLICATIONS OF DIAGNOSIS

1. Sample primary tumor extensively
2. Designate borderline, micropapillary type
3. Examine extraovarian implants for invasion
4. Stage I cases have an excellent prognosis
5. Stage II and III cases without invasive implants have an excellent prognosis after surgery alone

SUMMARY

1. “Typical” & “micropapillary” serous borderline tumors (SBTs) often coexist.
2. 26% of SBTs were “micropapillary” in the one population-based study (Gilks 2003).
3. The data suggest that the somewhat poorer survival is more closely related to a higher frequency of invasive implants than to “micropapillarity” in the ovarian tumor.

Implants of Serous Borderline Tumors: A Tutorial

Invasive implants show destructive invasion, recognized by irregular, aggressive-appearing infiltration into underlying tissue with tumor replacing or destroying it, an appearance indistinguishable from low-grade invasive adenocarcinoma. To recognize invasion in omental biopsies there must be obliteration of omental tissue. The presence of small papillae or single tumor cells within abundant desmoplastic stroma is not interpreted as stromal invasion and such implants are considered noninvasive desmoplastic implants. Small superficial biopsy specimens of desmoplastic implants in which underlying tissue is absent are classified as noninvasive on the assumption that they have been easily stripped away from underlying tissue.
Table I-7. FIGO stage and outcome for patients with advanced stage serous borderline tumors

<table>
<thead>
<tr>
<th>Reference</th>
<th>Stage IIa</th>
<th>Stage IIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sutton et al., 1991 (59)</td>
<td>1/32</td>
<td>11/41</td>
</tr>
<tr>
<td>Leake et al., 1992 (30)</td>
<td>1/24</td>
<td>11/41</td>
</tr>
<tr>
<td>de Nictolis et al., 1992 (12)</td>
<td>0/5</td>
<td>4/14</td>
</tr>
<tr>
<td>Rainbow et al., 1993 (23)</td>
<td>3/13</td>
<td>5/13</td>
</tr>
<tr>
<td>Kennedy and Hart, 1996 (28)</td>
<td>0/9</td>
<td>1/17</td>
</tr>
<tr>
<td>Eichhorn et al., 1999 (13)</td>
<td>0/6</td>
<td>2/9</td>
</tr>
<tr>
<td>Prat and de Nictolis, 2002 (42)</td>
<td>1/11</td>
<td>2/28</td>
</tr>
<tr>
<td>Gilks et al., 2003 (14)</td>
<td>0/15</td>
<td>6/33</td>
</tr>
<tr>
<td>Longacre et al., 2005 (31)</td>
<td>5/45</td>
<td>6/67</td>
</tr>
<tr>
<td>Total</td>
<td>8/128 (6%)</td>
<td>38/254 (15%)</td>
</tr>
</tbody>
</table>

Figure I-1: Outcome of patients with advanced stage serous borderline tumors with (dotted line) and without invasive implants (solid line). This is a statistically significant difference (p=0.028)

![Graph showing outcome of patients](image)

Table I-8. Invasive versus noninvasive implants in patients with advanced stage serous borderline tumors

<table>
<thead>
<tr>
<th>Reference</th>
<th>Frequency of invasive implants</th>
<th>Noninvasive % patients alive</th>
<th>Invasive % patients alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell et al., (5)</td>
<td>11%</td>
<td>47/50 (94%)</td>
<td>1/6 (17%)</td>
</tr>
<tr>
<td>Eichhorn et al., (13)</td>
<td>8%</td>
<td>25/25 (100%)</td>
<td>1/3 (33%)</td>
</tr>
<tr>
<td>Prat and de Nictolis (42)</td>
<td>13%</td>
<td>24/24 (100%)</td>
<td>0/5 (0%)</td>
</tr>
<tr>
<td>Gilks et al. (14)</td>
<td>12%</td>
<td>39/42 (93%)</td>
<td>3/6 (50%)</td>
</tr>
<tr>
<td>Longacre et al. (31)</td>
<td>N.A.</td>
<td>80/85 (94%)</td>
<td>7/14 (50%)</td>
</tr>
</tbody>
</table>

Table I-8: Invasive versus noninvasive implants in patients with advanced stage serous borderline tumors

<table>
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</tr>
</tbody>
</table>

Infiltrative glands, solid nests and/or papillary structures are present. Other features that are often present include moderate or marked cytological atypia and conspicuous mitotic figures. A few investigators also consider the presence of a micropapillary architecture and small solid nests of cells surrounded by a space evidence of invasion, but a majority do not.
Assessment of invasiveness proved to be much more reproducible, whether according to the B&S criteria (kappa = .84) or the B&K criteria (kappa = .72) than assessment of individual histopathological variables.

Implant Case 1

- Uterine serosa (low, intermediate, and high power)
Implant Case 1 Dx:
  - noninvasive implant

Implant Case 2
  - Small bowel (low power and intermediate power)
Implant Case 2 Dx:
- invasive implant

Implant Case 3
- Pelvic sidewall (low, intermediate and high power)
Implant Case 3 Dx:
• noninvasive implant

Implant Case 4
• Serosal surface of uterus (low power, and intermediate power)

Implant Case 4 Dx:
• noninvasive implants

Implant Case 5
• Omentum (low and intermediate power)
Implant Case 5 Dx:
• invasive implants

Implant Case 6
• Uterine serosa (low and intermediate power)
Implant Case 6 Dx:
• noninvasive implants

Implant Case 7
• Serosal adhesions (low and intermediate power)

Implant Case 7 Dx:
• noninvasive implant

Implant Case 8
• Fallopian tube (low and intermediate power)
Implant Case 8 Dx:
• noninvasive implant

Implant Case 9
• Omentum (low and intermediate power)
Implant Case 9 Dx:
• noninvasive implant

Implant Case 10
• Omentum (low and high power)

Implant Case 10 Dx:
• invasive implant

Implant Case 11
• Omentum (low and intermediate power)
Implant Case 11 Dx:
• noninvasive implant

Implant Case 12
• Omentum (intermediate power)

Implant Case 12 Dx:
• invasive implant
Implant Case 13

- Serosa of bowel (low power)

Implant Case 14

- Omentum (low power)

Implant Case 13 Dx:

- noninvasive implant

Implant Case 14 Dx:

- noninvasive implant
Implant Case 15

- Vermiform appendix (low power)

Implant Case 15 Dx:

- noninvasive implant

Results of 7 pathologist’s assessment of implants (ISGP meeting, Atlanta, 2006)

- Complete agreement for 14 cases
- 6 of 7 pathologists in agreement for 1 case
- Split decision in last case (result of different criteria being applied by different groups)

Summary

- Stage and assessment of invasiveness of extraovarian implants are the most important prognostic indicators in patients with SBT
- The best validated criteria for diagnosis of invasive implants are reproducible and conservative (i.e. most patients will not have invasive implants)
CASE 2

A 48-year-old woman presented with bilateral adnexal masses. At laparotomy, these were seen to be smooth-surfaced, and no grossly suspicious lesions were noted on the peritoneal surfaces or omentum.
DIAGNOSIS

Serous cystic borderline tumor, with microinvasion

HISTOLOGICAL CRITERIA

1. Eosinophilic cell pattern (most reported cases)
   - Single cells or cell clusters with eosinophilic cytoplasm
   - Surrounding stroma usually normal, but may have clefts
   - Adjacent epithelium often has similar cells
   - True lymphatic invasion in up to 10%

2. Other patterns (infrequently reported)
   - Solid or arboriform masses, branching papillae, filiform papillae, stromal response, alone or in combination
QUANTITATIVE CRITERIA

None Katzenstein 1978, Tavassoli 1988
3 mm Bell 1990, & subsequent studies
10 sq mm Current AFIP fascicle
5 mm Some experts

MICROINVASION

10-15% of serous borderline tumors

Most reported cases Stage I
9-fold increase in pregnant patients
Of >100 with follow-up in 12 series (through '04), death in one Stage I case and two Stage III cases (one with invasive implants)

PROBLEMS WITH DATA INTERPRETATION

1. Insufficient follow-up; most cases Stage I
2. The different patterns of microinvasion are not itemized in most series
3. Different quantitative parameters are used
4. Not all studies comment on “micropapillarity” in the primary tumor, or the invasiveness of extra-ovarian implants

CONVENTIONAL WISDOM

Probably, patients with Stage I serous borderline tumors with the usual (eosinophilic cell) pattern of microinvasion have the same prognosis as those with Stage I tumors lacking microinvasion.

RECENT STANFORD DATA

28 patients with 5-43 year follow-up
14 Stage I and 14 Stage II-IV
Recurrence in 21%; tumor death in 29%
Microinvasion found to be adverse prognostic factor independent of stage and implant status in non-pregnant women

CAVEATS
Pregnant patients excluded
➢ Almost always Stage I
➢ Almost always usual pattern (single cells)
Includes uncommon patterns (“inverted macropapillae”) that others might call “microinvasive carcinoma”

UNRESOLVED ISSUES
1. Behavior and nomenclature of the less common patterns of intrastromal tumor (microinvasion versus microinvasive carcinoma)
2. Quantitative threshold
3. Importance of abundant separate foci

Case 3 History
A 58-year-old woman presented 9 years ago with vague abdominal discomfort and ascites. At laparotomy, she had bilateral ovarian surface tumors and small omental implants. Her tumor was debulked and she was given 6 cycles of carboplatin and Taxol, with clinical remission. An indolent rise in the CA125 level led to resection of peritoneal recurrences 5 years ago, then more chemotherapy. 4 years ago, a vaginal apex mass was found by imaging, and treated with Arimidex and tamoxifen, with marked decrease in its size. The recent detection of an enlarging mass in the right rectus sheath led to resection. Slide 3 is from this abdominal mass. The other tumors had the same appearance.
Case 3 Diagnosis

Low-grade (grade 1) serous adenocarcinoma

Table I-11: Universal grading system for ovarian carcinoma

<table>
<thead>
<tr>
<th>Score</th>
<th>Architecture</th>
<th>Cytologic atypia</th>
<th>MFs/10 HPF*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>glandular</td>
<td>slight</td>
<td>0-9</td>
</tr>
<tr>
<td>2</td>
<td>papillary</td>
<td>moderate</td>
<td>10-24</td>
</tr>
<tr>
<td>3</td>
<td>solid*</td>
<td>marked</td>
<td>≥25</td>
</tr>
</tbody>
</table>

* Mitotic figures are counted in the most active area, field area = 0.345 mm².

Total score 3-5 = grade 1, 6-7 = grade 2, and 8-9 = grade 3.

Survival of patients with stage III and IV epithelial ovarian carcinoma, based on tumor grade.
Assessment of Cytological Atypia

- Score 1: regular, uniform, no more than 2 fold variation in nuclear diameter
- Score 2: up to 4 fold variation in nuclear diameter, may be small nucleoli and/or some clumping of nuclear chromatin
- Score 3: marked variation in nuclear size (>4 fold), high N/C ratio, prominent nucleoli
Reproducibility of grading of ovarian carcinoma
- FIGO grading – kappa = 0.26
- Silverberg grading – kappa = 0.40

Genetic alterations in low grade serous carcinomas and serous borderline tumors
- Usually diploid (82.5% of advanced stage SBT – Yue et al. Int J Gynecol Pathol 2003)
- Fewer genetic abnormalities than serous carcinoma by CGH (Staabler et al. Hum Pathol 2002)

Response to chemotherapy
- 49 patients (36 with low grade serous carcinoma and 13 with serous borderline tumor)
- Complete response in 13%
- Partial response in 13%
- Crispens et al. Obstet Gynecol 2002
Summary

• Low grade serous carcinomas may arise de novo or by progression of serous borderline tumors
• Low grade serous carcinomas have a distinct natural history from usual high grade carcinoma

CASE 4

A 41-year-old woman had menometrorrhagia. Ultrasound examination showed a fibroid uterus. The serum CA125 level was 7 U/ml.

A 220 gm, 10.5 cm right ovarian mass was resected. The external surface was smooth, and the cut surface was solid, lobulated and tan-yellow with hemorrhage.
IMMUNOPROFILE

<table>
<thead>
<tr>
<th>Positive</th>
<th>Negative</th>
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</thead>
<tbody>
<tr>
<td>CK7</td>
<td>CK20, CEA, CA125,</td>
</tr>
<tr>
<td></td>
<td>WT1, calretinin,</td>
</tr>
<tr>
<td></td>
<td>alpha-inhibin</td>
</tr>
</tbody>
</table>

DIAGNOSIS

Transitional cell carcinoma
(malignant Brenner-like; fibroepithelial type)

TRANSITIONAL CELL TUMORS

“tumours composed of epithelial elements histologically resembling urothelium and its neoplasms” (WHO 2003)

- Brenner tumor
- Brenner tumor of borderline malignancy
- Malignant Brenner tumor
- Transitional cell carcinoma
BRENNER TUMORS

95%: 30 - 70 years of age

<table>
<thead>
<tr>
<th></th>
<th>Benign</th>
<th>Borderline</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>90%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Size (usual)</td>
<td>&lt;10 cm</td>
<td>&gt;10 cm</td>
<td>&gt;10 cm</td>
</tr>
<tr>
<td>Gross (usual)</td>
<td>solid</td>
<td>solid/cystic</td>
<td>solid/cystic</td>
</tr>
</tbody>
</table>

Unilateral 93% 100% 88%
Stage I 100% 100% 80%
**BRENNER TUMORS**

<table>
<thead>
<tr>
<th>Feature</th>
<th>WHO</th>
<th>Fascicle</th>
<th>Colgan/Roth</th>
<th>Trebeck</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign epithelium</td>
<td>Benign</td>
<td>Benign</td>
<td>Benign</td>
<td>Benign</td>
</tr>
<tr>
<td>No stromal invasion, w/ atypical epithelium</td>
<td>Grade 1</td>
<td>BL</td>
<td>BL</td>
<td>Prolif.</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>BL</td>
<td>BL w/ IC</td>
<td>Prolif.</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>BL</td>
<td>BL w/ IC</td>
<td>BL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BL = Borderline, IC = Intraepithelial carcinoma


**Malignant Brenner tumor**

<table>
<thead>
<tr>
<th>Transitional cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>(16 cases)</td>
</tr>
</tbody>
</table>

Stage II-IV 19% 31%

Stage I, deaths 15% 44%

**TRANSITIONAL CELL CARCINOMA**

Mean age in mid 50’s (broad range)

Silva 1990: TCC-pattern in 9% of 934 ov ca’s

1%: pure TCC
5%: predominantly TCC
3%: minor TCC component
TRANSITIONAL CELL CARCINOMA

Mean age in mid 50’s (broad range)
Silva 1990: TCC-pattern in 9% of 934 ov ca’s
  1%: pure TCC
  5%: predominantly TCC
  3%: minor TCC component
Bilateral: 1/2
Extraovarian spread: 2/3
5-year survival: 35%

Published criteria
Silva 1990: “thick papillary proliferations, a smooth luminal border, and projection into empty spaces”
Roth 1996: “papillary type” (as above) and “fibroepithelial type” (malignant urothelial-like nests in a fibrous stroma)

Transitional cell carcinoma of the ovary: a morphologic study of 100 cases with emphasis on differential diagnosis
John H. Eichhorn, MD,
Robert H. Young, MD

HISTOLOGICAL FEATURES

- Microspaces: 87%
- Large cystic spaces: 73%
- Large blunt papillae: 63%
- Slit-like fenestrations: 49%
- Bizarre giant cells: 35%
- Micropapillae: 18%
- Gland-like tubules: 17%
- Squamous elements: 13%
- Psammoma bodies: 4%
TRANSITIONAL CELL CARCINOMA
Immunohistochemical features*

<table>
<thead>
<tr>
<th></th>
<th>Ovarian TCC</th>
<th>Bladder TCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokeratin 7</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cytokeratin 20</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Thrombomodulin</td>
<td>- (usu.)</td>
<td>+ (usu.)</td>
</tr>
<tr>
<td>Uroplakin III</td>
<td>-</td>
<td>often +</td>
</tr>
<tr>
<td>Vimentin</td>
<td>often +</td>
<td>-</td>
</tr>
<tr>
<td>CA-125</td>
<td>often +</td>
<td>-</td>
</tr>
<tr>
<td>WT1</td>
<td>+ (usu.)</td>
<td>-</td>
</tr>
</tbody>
</table>

*Soslow 1996; Ordóñez 2000; Riedel 2001; Logani 2003

TRANSITIONAL CELL CARCINOMA
Behavior

Four studies, three from M.D. Anderson (1989, 1990, 1993), reported that patients with advanced Stage TCC-predominant tumors had a better chemotherapy response and survival than those with other tumor types.

Two other studies (Hollingsworth 1993; Costa 1998), with nearly as many cases, did not confirm this finding.

---

300 Stage III ovarian carcinomas treated with Taxol-carboplatin

Courtesy Prof. Dr. med. F. Kommoss, Germany
*Gynecol Oncol 2005;97:195-99*

TRANSITIONAL CELL CARCINOMA
Differential Diagnosis

Borderline and malignant Brenner tumor
Adult granulosa cell tumor
Serous adenocarcinoma
Endometrioid adenocarcinoma
Undifferentiated carcinoma
Metastatic transitional cell carcinoma

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Case 5 History

A 61-year-old woman complained of increased abdominal girth. Physical examination and imaging showed a 20 cm right adnexal mass with ascites and extensive omental disease. Cytological examination of the ascitic fluid revealed high-grade malignant epithelial cells, consistent with ovarian carcinoma. She then received 3 cycles of platinum/taxane chemotherapy, during which the serum CA125 levels dropped from 600 to 51 U/ml and the ascites resolved. She underwent hysterectomy, bilateral salpingo-oophorectomy and omentectomy. At operation, the omentum was abnormal, with firm white areas. No adenal masses were identified. *Slide 5 is from the right ovary.*
Case 5 Diagnosis

Carcinoma of ovary, post chemotherapy

Current data suggests that:

- Neoadjuvant chemotherapy is an appropriate treatment strategy for patients with tumors that cannot be optimally debulked
- Neoadjuvant therapy with interval debulking has the potential to be superior to primary cytoreductive surgery for routine use
Overall Survival post-neoadjuvant chemotherapy
Disease-Free Survival Post-Neoadjuvant Chemotherapy

CA125 High vs CA125 Low

Mitotic Index High vs. Low

Residual vs No Macroscopic Residual Disease

Summary

- Pre-surgical treatment of patients with ovarian cancer dramatically changes both the gross appearance/tumor distribution, and the histological appearance (cell type and grade)
Table IV-1. WHO classification of mucinous tumors

<table>
<thead>
<tr>
<th>Category</th>
<th>Subcategories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>Adenocarcinofibroma (malignant adenofibroma)</td>
</tr>
<tr>
<td>Borderline</td>
<td>Intestinal Type</td>
</tr>
<tr>
<td></td>
<td>Endocervical-like</td>
</tr>
<tr>
<td>Benign</td>
<td>Cystadenoma</td>
</tr>
<tr>
<td></td>
<td>Adenofibroma</td>
</tr>
<tr>
<td></td>
<td>Mucinous cystic tumor with mural nodules</td>
</tr>
<tr>
<td></td>
<td>Mucinous cystic tumor with pseudomyxoma peritonei</td>
</tr>
</tbody>
</table>

Case 6 History
A 19-year-old woman complained of increased abdominal girth. She was found to have a 20 cm left ovarian tumor (slide 6A). A left salpingo-oophorectomy was done, with peritoneal and omental biopsies. 15 months later she developed a pelvic mass (slide 6B); at the time of its removal, peritoneal implants were also biopsied.
Case 6 Diagnosis
Mucinous borderline tumor of intestinal type with intraepithelial carcinoma, with early recurrence and progression to adenocarcinoma.

- Mucinous tumors accounted for 39% of borderline tumors
- Mucinous tumors accounted for 7.7% of carcinomas and only 4.1% of advanced stage carcinomas

Benign vs Borderline
- Stratification
- Atypia
- Mitoses
- No Invasion!
Borderline vs Carcinoma

- Destructive stromal invasion
Hart and Norris, 1973

- If the atypical epithelium lining the cysts was greater than four cells thick –
  Dx: carcinoma

New entities at the interface between borderline and carcinoma

- Mucinous borderline tumor
- Mucinous borderline tumor with intraepithelial carcinoma
- Mucinous carcinoma with expansile invasion
- Mucinous carcinoma
Table IV-2. Behaviour, terminology, sampling and follow-up data in Stage 1 mucinous borderline tumors with intraepithelial carcinoma

<table>
<thead>
<tr>
<th>Reference</th>
<th>Deaths/No. of cases*</th>
<th>Terminology</th>
<th>Sampling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hart and Norris, 1973</td>
<td>3/12</td>
<td>Description only</td>
<td>Minimal data</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2/3 deaths inadequately sampled</td>
</tr>
<tr>
<td>Chaitin et al., 1985</td>
<td>5/16</td>
<td>Mucinous carcinoma with no stromal invasion</td>
<td>No details</td>
</tr>
<tr>
<td>Sumithran et al., 1988</td>
<td>3/12</td>
<td>Grade 4 Borderline tumor</td>
<td>Avg. 13 blocks/case.</td>
</tr>
<tr>
<td>Watkin et al., 1992</td>
<td>1/15</td>
<td>Non-invasive mucinous carcinoma</td>
<td>Avg. 8.9 sections/case</td>
</tr>
<tr>
<td>DeNictolis et al., 1994</td>
<td>0/15</td>
<td>Well differentiated mucinous carcinoma (no cases with destructive stromal invasion)</td>
<td>Avg. 12 slides/case/ inadequate sampling excluded</td>
</tr>
<tr>
<td>Guerrieri et al., 1994</td>
<td>1/18</td>
<td>Non-invasive mucinous carcinoma</td>
<td>Optimal 1/21; adequate 10/21; inadequate 10/21; death: inadequate sampling</td>
</tr>
<tr>
<td>Siriaunkgul et al., 1995</td>
<td>0/12</td>
<td>Grade 3 Borderline tumor</td>
<td>Avg. 10 slides/case</td>
</tr>
<tr>
<td>Kikkawa et al., 1996</td>
<td>0/13</td>
<td>Mucinous carcinoma without stromal invasion</td>
<td>Avg. 20 slides/case</td>
</tr>
<tr>
<td>Hoerl and Hart, 1998</td>
<td>0/16 (?15)</td>
<td>Intra-glandular carcinoma (non-invasive carcinoma)</td>
<td>6 cases inadequate sampling 10 cases 1 section/2cm</td>
</tr>
<tr>
<td>Riopel et al., 1999</td>
<td>0/11 IE ca</td>
<td>Intra-epitelial carcinoma</td>
<td>Excluded inadequate sampling</td>
</tr>
<tr>
<td>Nomura et al., 2000</td>
<td>0/18</td>
<td>Mucinous carcinoma with no destructive stromal invasion</td>
<td>All cases 1 section/2cm or less</td>
</tr>
<tr>
<td>Lee and Scully, 2000</td>
<td>2/69</td>
<td>Intra-epithelial carcinoma</td>
<td>Avg. 0.6 sections/cm hospital cases, Avg. 0.4 section/cm</td>
</tr>
<tr>
<td>Rodriguez and Prat, 2002</td>
<td>0/8</td>
<td>Intra-epithelial carcinoma</td>
<td>Avg. 1.2 sections/2cm for whole. Each series of pts avg.0.6/cm</td>
</tr>
</tbody>
</table>

Reported outcomes for patients with mucinous borderline tumors with intraepithelial carcinoma

- 13 studies
- 15 deaths/234 patients (6.4%)
- Only 3 or 4 deaths in patients with adequately sampled tumors
Mucinous carcinoma with expansile invasion

- Def’n – “complex, often labyrinthine arrangement of glands, cysts or papillae lined by malignant epithelium with minimal or no intervening stroma”
Mucinous carcinoma with expansile invasion

- Three studies within the past 6 years
- Some of these tumors were called borderline tumor with intraepithelial carcinoma in the past
- 23 patients reported, all alive and well

Table IV-3: Outcome of patients with mucinous borderline tumors, intestinal type, with microinvasion

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>alive without recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guerrieri et al.</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Siriaunkgul et al.</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Hoerl and Hart</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Vojtesek et al.</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Lee and Kelly</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Khunamornpong et al.</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Chen et al.</td>
<td>4</td>
<td>2 dead of disease</td>
</tr>
</tbody>
</table>

Conclusions

- Mucinous borderline tumors – almost invariably benign (some experts believe that these tumors should be renamed “mucinous cystadenomas with atypia” to indicate their benignity)
- Mucinous borderline tumors with intraepithelial carcinoma, mucinous carcinomas with only expansile invasion, or mucinous borderline tumors with microinvasion – only rare adverse outcomes
Case 7 History

43-year-old woman complained of left lower quadrant pain and was found to have a complex left ovarian mass. At laparotomy no other abnormalities were noted. On gross examination, the mass was 6 cm, cystic and solid, and had a smooth surface. Slide 7 is from this mass.
Case 7 Diagnosis

Mucinous borderline tumor, intestinal type, and trabecular carcinoid tumor

Summary

• An unknown percentage of ovarian mucinous tumors are associated with teratomatous components and have an intestinal phenotype and growth pattern
Case 8 History

A 52-year-old woman complained of abdominal discomfort, and was found to have a 23 cm left ovarian mass. She underwent hysterectomy and bilateral salpingo-oophorectomy. Slide 8A is from the left ovarian mass and slide 8B from the cervix.
Case 8 Diagnosis

Adenocarcinoma of the cervix with metastasis to ovary

Topics to be discussed

• Synchronous ovarian and cervical tumors
• Primary vs metastatic mucinous tumors of ovary

Table IV-4: Proposed criteria for distinction between primary ovarian tumor and secondary involvement of the ovary in patients with synchronous mucinous carcinomas of cervix and ovary (Modified from Young and Scully, ref 49)

<table>
<thead>
<tr>
<th>Characteristics of ovarian metastases of cervical adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cervical primary may be occult and only superficially invasive</td>
</tr>
<tr>
<td>• The cells in the ovarian tumor are diffusely atypical and often of indeterminate endometrioid/mucinous type</td>
</tr>
<tr>
<td>• Numerous apoptotic bodies and mitotic figures (typically apically located) are present</td>
</tr>
<tr>
<td>• HPV testing and p16 +ve, ER and PR -ve</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary vs Metastatic</th>
<th>Primary</th>
<th>Metastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval between tumors</td>
<td>long</td>
<td>short</td>
</tr>
<tr>
<td>Disease free follow-up after removal of tumors</td>
<td>long</td>
<td>short</td>
</tr>
<tr>
<td>Laterality of ovarian tumors</td>
<td>unilateral</td>
<td>bilateral</td>
</tr>
<tr>
<td>Histology of ovarian and cervical tumors</td>
<td>dissimilar</td>
<td>similar</td>
</tr>
<tr>
<td>Involvement of vascular spaces</td>
<td>superficial</td>
<td>deep</td>
</tr>
<tr>
<td>Lymphovascular invasion in either tumor</td>
<td>uncommon</td>
<td>common</td>
</tr>
</tbody>
</table>
Table IV-5: Summary of reported immunostaining profiles of mucinous ovarian tumors and metastatic colonic adenocarcinoma (modified from Chou et al, ref 3)

<table>
<thead>
<tr>
<th></th>
<th>CK7</th>
<th>CK20</th>
<th>CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>80-100%</td>
<td>40-100%</td>
<td>67-100%</td>
</tr>
<tr>
<td>Metastatic colorectal adenocarcinoma</td>
<td>0-29%</td>
<td>87-100%</td>
<td>98-100%</td>
</tr>
</tbody>
</table>

Table IV-6: Differential diagnosis of primary vs metastatic mucinous carcinoma of ovary (Modified from Lee and Young, ref 21)

<table>
<thead>
<tr>
<th></th>
<th>Primary %</th>
<th>Metastatic %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral</td>
<td>0</td>
<td>75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Surface involvement (microscopic)</td>
<td>0</td>
<td>79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nodular growth</td>
<td>0</td>
<td>42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infiltrative invasion pattern</td>
<td>16</td>
<td>91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Small glands/tubules</td>
<td>12</td>
<td>94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Single cells</td>
<td>8</td>
<td>42</td>
<td>0.005</td>
</tr>
<tr>
<td>Signet ring cells</td>
<td>0</td>
<td>27</td>
<td>0.032</td>
</tr>
<tr>
<td>Size greater than 10cm</td>
<td>88</td>
<td>48</td>
<td>0.007</td>
</tr>
<tr>
<td>Borderline appearing areas</td>
<td>76</td>
<td>36</td>
<td>0.008</td>
</tr>
<tr>
<td>Expansile invasion pattern</td>
<td>88</td>
<td>18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Microscopic cysts</td>
<td>84</td>
<td>40</td>
<td>0.002</td>
</tr>
<tr>
<td>Complex papillae</td>
<td>60</td>
<td>8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Necrotic luminal debris</td>
<td>44</td>
<td>14</td>
<td>0.019</td>
</tr>
</tbody>
</table>

A simple algorithm for intraoperative classification of atypical mucinous tumors (ref. 39)

- If bilateral – metastatic
- If unilateral and < 10 cm – metastatic
- If unilateral and > 10 cm - primary

Summary

- There is no single completely sensitive and specific criterion for recognition of metastatic carcinoma to the ovary
- Whenever mucinous adenocarcinoma is encountered in the ovary consideration should be given to the possibility of metastasis

ENDOMETRIOID TUMORS

"...resemble the various types of endometrial tumors (epithelial and/or stromal) of the uterine corpus." (WHO 2003)

Benign
Borderline
Malignant
  - Adenocarcinoma & adenocarcinofibroma
  - Malignant mixed mesodermal tumor
  - Adenosarcoma
  - Stromal sarcoma & undifferentiated sarcoma
CASE 9

A 73-year-old woman experienced post-menopausal bleeding, and was found to have a 7 cm complex left ovarian mass. An endometrial biopsy showed atrophic endometrium. Hysterectomy and bilateral salpingo-oophorectomy was performed.

DIAGNOSIS

Endometrioid adenofibroma of borderline malignancy
ENDOMETRIOID BORDERLINE TUMORS

WHO 2003: “tumours composed of atypical or histologically malignant endometrioid type glands or cysts often set in a dense fibrous stroma with an absence of stromal invasion”

Over 190 cases reported; but differing criteria and terminology used in the major series

EARLY SERIES

<table>
<thead>
<tr>
<th>1st author, yr</th>
<th>#</th>
<th>Terminology</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell DA '85</td>
<td>7</td>
<td>Atypical AF</td>
<td>Endometrioid hyperplasia</td>
</tr>
<tr>
<td>Snyder RR '88</td>
<td>7</td>
<td>Proliferative</td>
<td>Papillary/cribriform pattern uninterrupted by stroma for ≤5mm, mild to mod. atypia</td>
</tr>
<tr>
<td>Snyder RR '88</td>
<td>34</td>
<td>LMP</td>
<td>Same, but &gt;5mm, marked atypia, both</td>
</tr>
</tbody>
</table>

RECENT SERIES

<table>
<thead>
<tr>
<th>1st author, yr</th>
<th>#</th>
<th>Terminology</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell KA, 2000</td>
<td>33</td>
<td>AP (+/- IEC)</td>
<td>More complex, closely packed than benign tumors IEC: severe nuclear atypia</td>
</tr>
<tr>
<td>Roth LM, 2003</td>
<td>30</td>
<td>LMP (+/- IEC)</td>
<td>Same as above, but Microinvasion: &lt; 10 sq mm</td>
</tr>
</tbody>
</table>

KEY: AF, adenofibroma; LMP, low malignant potential
ENDOMETRIOID BORDERLINE VS GRADE 1 ADENOCARCINOMA

No “atypical”, “borderline”, “proliferative”, “atypical proliferative” or “low malignant potential” tumor (with/without intraepithelial carcinoma or microinvasion) has recurred.

With rare exceptions, all Stage I and unilateral.

Grade 1 endometrioid adenocarcinoma:
Recurrence in 14% (Bell KA 2000) and 20% (Roth LM 2003) of cases.

Features helpful in assigning tumors to the endometrioid category

- Tumor heterogeneity
- Squamous differentiation
- Adenofibromatous component
- Endometriosis
ENDOMETRIOID ADENOCARCINOMA
Uncommon variants and patterns

Mucin-rich         Secretory
Spindled           Basaloid
Oxyphilic          Ciliated-cell

Resembling sex cord-stromal tumors:
Sertoli or Sertoli-Leydig cell tumor
Adult granulosa cell tumor
A 69-year-old woman had lower abdominal fullness, and a mobile, non-tender right pelvic mass. A right ovarian tumor was resected, with the uterus and contralateral adnexa. The cut surface of the 13.5 cm mass was solid and multinodular, with small cysts, variegated, pinkish to yellow.
**IMMUNOPROFILE**

**Positive**
- CK7, EMA, ER, PR,
- WT1 (focal)

**Negative**
- vimentin, CA125, calretinin,
- alpha-inhibin

**DIAGNOSIS**

Endometrioid adenocarcinoma resembling ovarian sex cord-stromal tumor (with luteinized stromal cells)
ENDOMETRIOID ADENOCARCINOMA
Features causing confusion with sex cord-stromal tumors

- Sertoli/Sertoli-Leydig cell
- Hollow/solid tubules
- Thin cords/trabeculae
- Stromal lutein cells

ENDOMETRIOID ADENOCARCINOMA
Features causing confusion with sex cord-stromal tumors

- Sertoli/Sertoli-Leydig cell
- Adult granulosa cell
- Hollow/solid tubules
- Discrete nests
- Thin cords/trabeculae
- Diffuse sheets
- Stromal lutein cells
- Small cavities

Features favoring endometrioid carcinoma over sex cord-stromal tumor

- Older age (vs Sertoli/Sertoli-Leydig cell)
- Extra-ovarian spread
- Bilaterality
- Typical endometrioid adenocarcinoma
- Mucin secretion
- Squamous differentiation
- Lack of nuclear grooves (vs AGCT)
- Immunostains: + EMA; - inhibin

CASE 11

A 37-year-old woman was having surgery for fibroids, and a 10 cm left ovarian mass was found. The uterus had leiomyomas and the contralateral adnexa was unremarkable.
Case 11 - 4x

Case 11 - 10x

IMMUNOPROFILE

<table>
<thead>
<tr>
<th>SCL elements</th>
<th>Non-SCL stroma</th>
</tr>
</thead>
<tbody>
<tr>
<td>+:</td>
<td>WT1, calretinin</td>
</tr>
<tr>
<td>-:</td>
<td>CD10, PR</td>
</tr>
<tr>
<td>Both -:</td>
<td>CK7, CK20, EMA, CA125, ER, alpha-inhibin</td>
</tr>
</tbody>
</table>

DIAGNOSIS

Mesodermal adenosarcoma, with sex cord-like elements
ADENOSARCOMA

30 - 84 (mean 54) years of age
Unilateral
5.5 - 50 (mean 14) cm; solid with small cysts
Rupture in 2/3
Endometriosis in < 10%


ADENOSARCOMA
Diagnostic criteria

1. Conspicuous non-invasive Müllerian-type glands within a predominant stromal component, either homologous or heterologous.
2. Periglandular cuffs of cellular stroma, intraglandular protrusions of cellular stroma, or both.

ADENOSARCOMA
Additional features

1. Sarcomatous overgrowth (30% of cases).
2. Sex cord-like elements (15% of cases).
3. Heterologous elements (12.5% of cases).

ADENOSARCOMA
Diagnostic criteria

1. Conspicuous non-invasive Müllerian-type glands within a predominant stromal component, either homologous or heterologous.
2. Periglandular cuffs of cellular stroma, intraglandular protrusions of cellular stroma, or both.
3. Usually at least mild stromal atypia.
4. Stromal mitotic count variable, but may be low.
ADENOSARCOMA

Behavior

Extraovarian spread: 40%
Recurrence in 2/3, at 0.4 - 6.6 (mean 2.6 ) yr
Recurrent tumors:
  Adenosarcoma (with/without SO)
  Pure sarcoma (low or high grade)
5-,10-,15-year survival: 64%, 46%, 30%

ADENOSARCOMA

Possible prognostic factors

Young age (<53 years)
Tumor rupture
High grade
High grade sarcomatous overgrowth

CASE 12

A 55-year-old woman presented with a unilateral 16 cm ovarian mass. On gross examination, the cut surface was mostly solid, partly yellow and partly grey, with a few small cysts. The tumor appeared to invade the myometrium, and there were implants on the omentum.
Case 12 - 10x

Case 12 - 20x

IMMUNOPROFILE

<table>
<thead>
<tr>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK7, CD10 (focal)</td>
<td>CK20, vimentin, inhibin, AFP, RCC, CA125, WT1, ER</td>
</tr>
</tbody>
</table>

DIAGNOSIS

Clear cell adenocarcinoma, predominantly oxyphilic

CLEAR CELL CARCINOMA

6% epithelial-stromal cancers
97%: 30-70 years of age

Quite distinctive features to experienced pathologists; correct diagnosis may be increasingly important in assigning patients to treatment protocols

Microscopic features of clear cell carcinoma

Patterns
- Tubulocystic
- Papillary
- Diffuse (less common)
- Trabecular (rare)
- Reticular (rare)
Microscopic features of clear cell carcinoma

Cell types
- Clear
- Hobnail
- Flat/cuboidal
- Oxyphilic (seldom)
- Signet ring (rare)

Other features
- Hyaline globules
- Intracystic mucin
- Colloid-like material
- Psammoma bodies (seldom)

HELPFUL DIAGNOSTIC CLUES
1. Endometriosis
2. Adenofibromatous component
3. Dense hyaline accumulations

Clear cell carcinoma: ovarian versus renal

<table>
<thead>
<tr>
<th></th>
<th>Ovarian</th>
<th>Renal</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK7</td>
<td>+</td>
<td>- (usually)</td>
</tr>
<tr>
<td>CK20</td>
<td>-</td>
<td>- (usually)</td>
</tr>
<tr>
<td>RCC</td>
<td>- (usually)</td>
<td>+</td>
</tr>
<tr>
<td>CD10</td>
<td>- (usually)</td>
<td>+</td>
</tr>
<tr>
<td>CA125</td>
<td>+ (71%)</td>
<td>-</td>
</tr>
</tbody>
</table>
BEHAVIOR

5 year survival rates worse than for other types (I-69%, II-55%, III-14%, IV-4%) (Scully ‘98)

Chemoresistance-related protein MDR-1 more frequent in clear cell carcinoma than in other types (Ikeda et al 2003)

In a recent report of Stage I, II sporadic ovarian cancer, clear cell histology did not confer a worse outcome (Leitao et al 2004)