Fallopian Tube Cancer:

Hereditary Risks / BRCA, Prophylactic Surgery & Pathology

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Tubal Ligation

Tubal Pregnancy

Gabriele Falloppio
1561

Max Broedel
1895
Early Tubal Carcinoma in BRCA mutation carriers

Outline of Talk

- Hereditary Ovarian Cancer (BRCA)
  - Preventive Surgery (RRSO)
- Pathologic Evaluation of RRSO Specimens
  - Specimen Processing
  - Diagnostic Criteria for Early Cancer
  - Mimics of Early Cancer
- Implications for Origin of GYN Serous Cancer

Leading Cancer Deaths in Women 2000-2004

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Incidence 2004</th>
<th>5 yr Survival 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>334,646</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>207,353</td>
<td>90.3%</td>
</tr>
<tr>
<td>Colon</td>
<td>140,153</td>
<td>44.7%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>77,529</td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>72,529</td>
<td></td>
</tr>
</tbody>
</table>

Breast Cancer 2004: ~210,000
Ovarian Cancer 2004: ~25,000

Incidence 2004

Mortality Change 1950 vs 2004

National Cancer Institute
SEER Cancer Statistics Review 1975-2004
**Stage at Diagnosis**

<table>
<thead>
<tr>
<th>Stage at Diagnosis</th>
<th>Breast Cancer</th>
<th>Ovarian Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA-IB</td>
<td>Stage I &amp; II</td>
<td>Stage I &amp; II</td>
</tr>
<tr>
<td>Stage IIA-IIB</td>
<td>Stage III</td>
<td>Stage IIIA-C</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>Stage IV</td>
<td>Stage IV</td>
</tr>
</tbody>
</table>

**Genetics of Ovarian Cancer**

- **Lifetime Risk For Ovary CA**
  - Sporadic: 1.6%
  - Family history: 5 – 7%
  - BRCA 1: 45 – 65%
  - BRCA 2: 15 – 30%
  - HNPCC (Lynch syndrome): ~15%

**Hereditary Breast Ovarian Cancer Syndrome**

- **Breast Cancer Risk**
- **Ovarian Cancer Risk**

- Type: Serous
- Grade: High
- Behavior: Aggressive

*From WHO 2003 Tumors of the Breast and Female Genital Organs*
GYN Organs at Risk in BRCA Syndrome

- Ovary
- Fallopian Tube
  16% of Tubal Cancer patients are BRCA+
- Peritoneum

Shared Embryologic Relation:
Epithelium of Ovary/Tube/Peritoneum

Undifferentiated gonad, day 38

Mullerian System

“Secondary” Mullerian System

References:
Aziz, Gyn Onc 2001
Levine, Gyn Onc 2002
Schubert, Am J Hum Genet 1997
Zweemer, Gyn Oncol 2000
Friedman, Am J Hum Genet 1995
Tonin, Hum Genet 1995

from AFIP Ovary Fascicle, 3rd ed, 1998
Risk Reduction Salpingo-Oophorectomy
A Coordinated Surgical / Pathologic Procedure

- Peritoneal washings
- Exploration
- Bilateral salpingo-oophorectomy
- Random peritoneal biopsies
- Random omental biopsies

Pathology
- Detailed evaluation of entire specimen

Efficacy of RRSO for BRCA carriers

- 80% reduction in GYN cancer
- 50% reduction in breast cancer


Who should undergo RRSO?

- BRCA1 or BRCA2 mutation carriers
- Ideally between ages 35 to 40

Finch A et al, JAMA 2006; 296: 185
After RRSO, Risk Remains for Peritoneal Carcinoma

Close follow up is critical

Two Benefits of RRSO

1. Risk reduction for GYN and Breast cancer
2. Detection of occult early carcinoma at time of RRSO

Carcinoma in RRSO Specimens

- Risk: ~ 2 - 17%
- Sites: Most common = fimbria of the tube, Less common = surface of ovary
- Size: ~ few millimeters
- Stage: Mostly non-invasive
- Clinical significance: ? (spread / deaths reported)

Early Ovarian Cancer is Uncommon

SEER 1992-1997
Cancer; 2003; 97: 2648
Early De Novo Ovarian Carcinoma
A Study of Fourteen Cases
Debra A. Bell, M.D., and Robert E. Scully, M.D.
Cancer, 1994

- Normal gross appearance of ovaries
- Cytologically malignant epithelium of ovary surface or cortex
- Absence of
  - benign epithelial ovarian tumor
  - peritoneal tumor
  - endometriosis

Ovarian Surface Epithelium

Mostly serous carcinoma
Average 3.5 mm size
All surface / superficial

Behavior of Early Ovarian Cancer

<table>
<thead>
<tr>
<th>“Early Ovarian Cancer”</th>
<th>14 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritoneal Carcinomatosis</td>
<td>5 cases</td>
</tr>
<tr>
<td>Died of disease</td>
<td>4 cases</td>
</tr>
</tbody>
</table>

The patients received chemotherapy (Chemo) and the follow-up period was from 0 to 15 years.

Behavior of Early Tubal Carcinoma

If fimbria involved, worse prognosis even if non-invasive

Alvarado-Cabrero et al Gyn Onc 1998; 72: 387

Bockman III, Cancer 2000; 89: 2076
Early Tubal / Ovarian Cancer Detection

Malignant Potential Exists Despite:
- Occult Presentation
- Microscopic Size
- Lack of Invasion

Goal is to Detect Tumors of the Fimbria

Management of Early Tubal Cancer in RRSO

A Work in Progress

Stage 1: No adjuvant treatment
Careful clinical surveillance
Serial CA125
? Hormonal prophylaxis

> Stage 1: Treat like ovarian cancer

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Diagnostic Criteria of Early Tubal Cancer
Tubal Intraepithelial Carcinoma

Synonyms
- Early tubal carcinoma
- Tubal intraepithelial carcinoma
- Tubal carcinoma in situ
- Adenocarcinoma in situ
- Dysplasia

Diagnostic Criteria
- Same as for minimal serous carcinoma of endometrium
- Criteria apply to:
  - Tube
  - Ovary
  - Peritoneum

Diagnostic Criteria: Tubal Intraepithelial Carcinoma
- Nuclear atypia
  - Enlargement
  - Pleomorphism
  - Hyperchromasia
  - Macronucleoli
- Mitoses
  - Crowding
  - Piling/tufting/budding
  - Stratification
  - Invasion

Normal p53 signature TIC Serous Ca

Genotoxic damage (DNA strand breakage, Cell cycle arrest, PS1 mutation) Additional genetic disturbances (Cell cycle activation, Proliferation, Early malignant phenotype) Tumor expansion (Exfoliation, Peritoneal/ovarian seeding, Metastasis) Enlargement, Pleomorphism, Hyperchromasia, Macronucleoli Crowding, Piling/tufting/budding, Stratification, Invasion

**Diagnostic Criteria: Tubal Intraepithelial Carcinoma**

- **Nuclear atypia**
  - Enlargement
  - Pleomorphism
  - Hyperchromasia
  - Macronucleoli

- **Mitoses**
  - Crowding
  - Piling/tufting/budding
  - Stratification
  - Invasion

- **Altered cell pattern**
  - Crowding
  - Piling/tufting/budding
  - Stratification
  - Invasion

- **Invasion is not required**

- **Helpful findings:**
  - Loss of cilia
  - p53 positive

**Tubal Intraepithelial Carcinoma**

Invasive Serous Carcinoma of Tube

Early Ovarian Carcinoma

Invasive Serous Carcinoma of Tube

p53

Early Ovarian Carcinoma
### Cancer in RRSO is Small

<table>
<thead>
<tr>
<th></th>
<th>Average</th>
<th>Range</th>
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<tbody>
<tr>
<td>Tubal Cancer</td>
<td>3.7 mm</td>
<td>1 – 11 mm</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>9 mm</td>
<td>3 – 13 mm</td>
</tr>
</tbody>
</table>

*data from UCSF series of RRSO in BRCA carriers*

### TIC is Small

- Maximize visualization of Ovarian surface Tubal fimbriae
- Thin tissue slices
- Completely embed all tissue

Detecting Cancer in RRSO Requires Special Processing
Fresh Dissection is Problematic: Tissue Curls, Twists, Folds

![Image of dissected tissues showing curls, twists, and folds]

RRSO Grossing Protocol

- Fix tissue first, ink margin
- Submit all tissue
- Slice at 2-3 mm intervals
- Tube: Cross section
- Fimbria: Amputate from tube
- Longitudinal section
- Ovary: Perpendicular to long axis
- Peritoneum: Submit all, & omentum

Thin Slicing yields 10-15 blocks per Side

![Image of sliced tissues showing thin sections]
Ovary                         Fimbriae                            Isthmus

Slice thickness affects chance of detection

US Nickel is 1.95 mm Thick

TIC is Small

US Nickel is 1.95 mm Thick

Slice thickness affects chance of detection

5 millimeter

2 millimeter

2 millimeter

5/30/2009
Are Multistep Level Sections Helpful?

**UCSF Study:**

RRSO from 95 BRCA patients

3 deep levels on all fimbriae blocks

no new cancer found on any level

**Levels are not needed if tissue slice is thin**

Recommended Slide Processing:

**Fimbrial blocks**

1 H&E stain

3 unstained reserved for immunos (p53, MIB-1) from same ribbon

**Isthmus, ovary blocks**

1 H&E stain

Intraoperative RRSO Evaluation

**Rationale for diagnosis cancer intraoperatively:**

- Immediate surgical staging can be done
- Eliminate “second” surgery

**Diagnostic options:**

- Gross external evaluation
- Slice then gross evaluation
- Slice then frozen section

Correlation of Gross & Microscopic Features in RRSO

<table>
<thead>
<tr>
<th>Gross</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian Cyst</td>
<td>0 / 61</td>
</tr>
<tr>
<td>Tubal Cyst</td>
<td>0 / 45</td>
</tr>
<tr>
<td>Tubal Nodule</td>
<td>1 / 8</td>
</tr>
<tr>
<td>Ovarian Nodule</td>
<td>2 / 20</td>
</tr>
</tbody>
</table>

**No gross lesion in 7 / 10 cases of cancer**

from UCSF data in Mackey,A et al. USCAP 2009 poster
Advice for Intraoperative RRSO Evaluation

Currently under study....

Unless a >0.5 cm nodule is visible, detection of cancer is best done by first fixing, then slicing

Pre-operative discussion with surgeon may help

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Normal Fimbrial Mucosa

Normal Tubal Serosa

Normal Ovarian Surface

Normal Peritoneal Surface
Mimics of Tubal Intraepithelial Carcinoma

- Tangential sectioning
- Mucosal hyperplasia
- Pseudocarcinomatous hyperplasia
- Mucosal adenofibroma
- Transitional cell metaplasia

Scan Low Magnification for Hyperchromatic Clusters

Tangential Sectioning

Tangential Sectioning
Tangential Sectioning

"Benign" features
- Cilia / terminal bars
- Peg cells

Concurrent TIC and Tangential Sectioning

Mucosal Hyperplasia
Mucosal Hyperplasia

Mucosal Hyperplasia

Papillary Mucosal Hyperplasia

p53 Negative
MIB-1 not increased
Papillary Mucosal Hyperplasia

Mucosal Adenofibroma

Bossuyt V et al. *Int J Gynecol Pathol.* 2008;27:390

p53

Mucosal Adenofibroma

Mucosal Adenofibroma

Pseudocarcinomatous hyperplasia in tuberculous salpingitis

from Young RH. Pathology 2007; 39: 119

Transitional Cell Metaplasia

- Metaplastic focus resembling urinary bladder mucosa
- GYN sites involved
  - Common: Serosa of Tube (Walthard nest)
  - Uncommon: Cervix
  - Rare: Ovarian hilum
  - Never: Endometrium
  - Case reports: Fimbria of Tube

Transitional Cell Metaplasia of Tubal Serosa

“Walthard nests”
Transitional Cell Metaplasia of Cervix

Transitional Cell Metaplasia of the Fimbria

Nuclear Grooves

Transitional Cell Metaplasia of the Fimbria

Diagnosis?

Tubal Intraepithelial Carcinoma
How should p53 negative mild atypia be classified?

Normal Mucosa  →  Mucosal Hyperplasia  →  ?  →  TIC

Mimics of Early Ovarian / Peritoneal Carcinoma

- Mesothelial hyperplasia
- Well differentiated papillary mesothelioma
- Ovarian surface stromal papillary projections
- Reactive atypia in endometriosis/endosalpingiosis

Mesothelial Hyperplasia

Walthard Nest
Well Differentiated Papillary Mesothelioma

Ovarian Surface Stromal Papillary Proliferation

Metastatic Breast Cancer in RRSO

- Majority of RRSO patients already have breast cancer
- Distinction from primary ovarian cancer
- Distinction from benign ovarian lesions
Metastatic Breast Cancer in Ovary

- Papillary
- Solid
- Tubuloglandular

Metastatic Breast Cancer in RRSO

Majority of RRSO patients already have breast cancer

- Distinction from primary ovarian cancer
- Distinction from benign ovarian lesions

Immunohistochemistry

<table>
<thead>
<tr>
<th>Primary Ovarian Serous Carcinoma</th>
<th>Metastatic Breast Cancer to Ovary</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT-1, p53, CA125</td>
<td>Mammaglobin GCDFP-15</td>
</tr>
</tbody>
</table>

- WT1
- p53
- CA125

Mimics of Metastatic Breast Cancer in RRSO

- Tubuloglandular
- Foamy
- Infiltrative

Mimics of Metastatic Breast Cancer in RRSO

- **Pattern**: Tubuloglandular
- **Problem**: Ductal Carcinoma
- **Mimics**:
  - Granulosa cell tumor
  - SCTA T
  - Adenomatoid tumor
  - Brenner tumor
  - Rete ovarii hyperplasia
  - Endometriosis

---

Rete Ovarii Hyperplasia

Adenomatoid Tumor
Sex Cord Tumor with Annular Tubules (SCTAT)

Metastatic Breast Cancer

Mimics of Metastatic Breast Cancer in RRSO

Pattern: Infiltrative
Problem: Lobular Carcinoma
Mimics: Stromal Hyperthecosis, Atretic Follicle

Brenner Tumor

Metastatic Breast Cancer

Normal Ovary
Stromal Hyperthecosis
Stromal Hyperthecosis

Atretic Follicle

Mimics of Metastatic Breast Cancer in RRSO

Pattern: Foamy
Problem: Chemo-Treated Carcinoma
Mimics: Steroid cell nodule, Stromal hyperthecosis, Hilus cell rests, Adrenal rests, Brenner tumor

Hilus Cells
Perineural “invasion” by Hilus Cells

Hilus Cell Variations
Nodules, Proliferation, Multifocality

Hilus Cells
Calretinin / Inhibin
Keratin

Adrenal Cortical Rest
Neoadjuvant Treated Primary Breast Cancer  Metastasis to RRSO

Tips for RRSO Evaluation

- Obtain clinical history
  - ? History of breast cancer
  - ? History of chemotherapy / radiation
- Use immunohistochemistry when uncertain

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Implications of TIC on Classifying Origin of Pelvic Serous Carcinoma

- Does TIC imply that the tube is the primary origin?

Primary tubal serous carcinoma
Primary ovarian serous carcinoma
Primary peritoneal serous carcinoma

- Same
  - Morphology
  - Immunostaining
  - Molecular

Current GOG Consensus criteria
- Histology = serous carcinoma
- Ovaries = normal size or benign enlargement
- Tumor burden in peritoneum > ovaries
- Ovarian tumor nodules <0.5 cm
  or invade <0.5 cm from surface into cortex

Features favoring primary peritoneal origin

- ~half of primary ovarian cancers have TIC
- ~half of primary peritoneal cancers have TIC
- p53 mutations are concordant

Bloss JD et al. Gynecol Oncol 1993; 50: 347

Implications of TIC on Classifying Origin of Pelvic Serous Carcinoma

Possible options

<table>
<thead>
<tr>
<th>TIC in Fallopian Tube</th>
<th>Tumor in Ovary or Peritoneum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Secondary</td>
</tr>
<tr>
<td>Primary</td>
<td>Primary</td>
</tr>
<tr>
<td>Secondary</td>
<td>Primary</td>
</tr>
</tbody>
</table>

*All are plausible options but currently no way to confirm in a given case
*Use GOG criteria in meantime

UCSF Hereditary GYN Cancer Program

<table>
<thead>
<tr>
<th>Gyn Onc Surgery</th>
<th>Gyn Genetic Counseling</th>
<th>Gyn Pathology &amp; Molecular Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bethan Powell</td>
<td>Beth Crawford</td>
<td>Charles Zaloudek</td>
</tr>
<tr>
<td>Lee-may Chen</td>
<td>Jane McClellan</td>
<td>JP Grenert</td>
</tr>
<tr>
<td></td>
<td>Aimee Blanco</td>
<td>Joe Rabban</td>
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