OVARIAN AND FALLOPIAN TUBE CARCINOMA

J Morgan
5/6/15
Totally ignoring borderline tumors (LMPs) today

Focus on Epithelial tumors

Flying overview
Epithelial
Germ Cell
Sex Cord/Stromal
Secondary
# Histologic types

<table>
<thead>
<tr>
<th>Epithelial Cancers (&gt;90%)</th>
<th>Malignant germ cell tumors (3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High-grade serous carcinoma (HGSC-70%)</td>
<td>• Dysgerminomas</td>
</tr>
<tr>
<td>• Endometrioid carcinoma (EC 10%)</td>
<td>• Yolk sac tumors</td>
</tr>
<tr>
<td>• Clear-cell carcinoma (CCC 10%)</td>
<td>• Immature teratomas</td>
</tr>
<tr>
<td>• Mucinous carcinoma (MC 3%)</td>
<td>Potential malignant sex cord-stromal tumors (1%-2%)</td>
</tr>
<tr>
<td>• Low-grade serous carcinoma (LGSC &lt;5%)</td>
<td>• Granulosa cell tumors</td>
</tr>
<tr>
<td>• Undifferentiated (1%)</td>
<td></td>
</tr>
</tbody>
</table>
FALLOPIAN TUBE CARCINOMA

- Adenocarcinoma
  - Serous

Increased incidence among BRCA carriers
PRESENTATION OF OVARIAN CANCER

- Highly variable
- Non specific
- No effective screening or early detection
- Symptom review index of limited utility in detecting early stage disease
EARLY DISEASE SYMPTOMS

- Pelvic pain
- Pelvic Mass
- None
FALLOPIAN TUBE CARCINOMA PRESENTATION- TRIAD

- Pelvic mass
- Pelvic pain
- Hydrops tubae profluens
Abdominal pain
Abdominal distension
Bloating
Early satiety
N/V
Reflux
Change in bladder or bowel function
Dyspnea

METASTATIC DISEASE PRESENTATION
Intra peritoneal
- Trans coelomic
- One cell away from entire peritoneal cavity
- Tumor ileus- functional

Lymphatic
- Pelvic and/or periaortic

Hematogenous

**SPREAD PATTERNS**
STAGING

- Anatomic
  - FIGO 2014

- Cell type
  - Epithelial
  - Germ cell
  - Sex cord Stromal

- Tissue Origin
  - Ovary
  - Fallopian tube
  - Peritoneum
<table>
<thead>
<tr>
<th>FIGO Staging System for Ovarian Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
</tr>
<tr>
<td>Stage I</td>
</tr>
<tr>
<td>IA  Growth limited to one ovary; no</td>
</tr>
<tr>
<td>IB  Growth limited to both ovaries; no</td>
</tr>
<tr>
<td>IC  Tumor either stage Ia or stage Ib</td>
</tr>
<tr>
<td>or stage Ib but with tumor on the</td>
</tr>
<tr>
<td>surface of one or both ovaries;</td>
</tr>
<tr>
<td>or with capsule(s) ruptured; or</td>
</tr>
<tr>
<td>with ascites present containing</td>
</tr>
<tr>
<td>malignant cells or with positive</td>
</tr>
<tr>
<td>peritoneal washings.</td>
</tr>
<tr>
<td>Stage II</td>
</tr>
<tr>
<td>IIA Extension and/or metastases to</td>
</tr>
<tr>
<td>IIB Extension to other pelvic tissues.</td>
</tr>
<tr>
<td>IIC Tumor either stage Ila or Ib but</td>
</tr>
<tr>
<td>with tumor on the surface of one</td>
</tr>
<tr>
<td>or both ovaries; or with capsule(s)</td>
</tr>
<tr>
<td>ruptured; or with ascites present</td>
</tr>
<tr>
<td>containing malignant cells or with</td>
</tr>
<tr>
<td>positive peritoneal washings.</td>
</tr>
<tr>
<td>Stage III</td>
</tr>
<tr>
<td>IIIA Tumor involving one or both</td>
</tr>
<tr>
<td>ovaries with peritoneal implants</td>
</tr>
<tr>
<td>outside the pelvis and/or positive</td>
</tr>
<tr>
<td>retroperitoneal or inguinal nodes;</td>
</tr>
<tr>
<td>surface liver metastases equals</td>
</tr>
<tr>
<td>stage III; tumor is limited to</td>
</tr>
<tr>
<td>the true pelvis but with</td>
</tr>
<tr>
<td>histologically verified malignant</td>
</tr>
<tr>
<td>extension to small bowel/large</td>
</tr>
<tr>
<td>bowel or omentum.</td>
</tr>
<tr>
<td>IIIB Tumor grossly limited to the</td>
</tr>
<tr>
<td>true pelvis with negative nodes</td>
</tr>
<tr>
<td>but with histologically confirmed</td>
</tr>
<tr>
<td>microscopic seeding of abdominal</td>
</tr>
<tr>
<td>peritoneal surfaces.</td>
</tr>
<tr>
<td>IIIC Tumor of one or both ovaries;</td>
</tr>
<tr>
<td>histologically confirmed implants</td>
</tr>
<tr>
<td>of abdominal peritoneal surfaces,</td>
</tr>
<tr>
<td>none exceeding 2 cm in diameter;</td>
</tr>
<tr>
<td>nodes negative.</td>
</tr>
<tr>
<td>IIIC Abdominal implants greater than</td>
</tr>
<tr>
<td>Stage IV</td>
</tr>
<tr>
<td>Growth involving one or both ovaries</td>
</tr>
<tr>
<td>with distant metastases; if pleural</td>
</tr>
<tr>
<td>effusion is present, there must be</td>
</tr>
<tr>
<td>positive cytologic test results to</td>
</tr>
</tbody>
</table>

# Stage I Changes

## Stage I (FIGO, 1988)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Growth limited to one ovary; no tumour on the external surface, capsule intact, no ascites</td>
</tr>
<tr>
<td>IB</td>
<td>Growth limited to both ovaries; no tumour on the external surface, capsule intact, no ascites</td>
</tr>
<tr>
<td>IC</td>
<td>Tumour with IA or IB but with tumour on the external surface, capsule ruptured; ascites containing malignant cells or positive peritoneal washing</td>
</tr>
</tbody>
</table>

* It is important to know

(i) If the capsule was ruptured intraoperatively or before surgery

(ii) Whether malignant cells were present in the ascitic fluid or in peritoneal washing

## Stage I (FIGO 2014)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1a N0 M0  Growth limited to one ovary; no tumour on the external surface, capsule intact, no ascites</td>
</tr>
<tr>
<td>IB</td>
<td>T1b N0 M0  Growth limited to both ovaries; no tumour on the external surface, capsule intact, no ascites</td>
</tr>
<tr>
<td>IC</td>
<td>T1c N0 M0  Tumor limited to one or both ovaries</td>
</tr>
</tbody>
</table>

| IC1   | Surgical spill |
| IC2   | Capsule rupture before surgery or tumor on ovarian surface |
| IC3   | Malignant cells in the ascites or peritoneal washings |
### Stage II (FIGO, 1988)

<table>
<thead>
<tr>
<th>Stage II</th>
<th>Growth involving one or both ovaries with pelvic extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA</td>
<td>Extension and/or metastasis to tubes and/or uterus</td>
</tr>
<tr>
<td>IIB</td>
<td>Extension to other pelvic tissues</td>
</tr>
<tr>
<td>IIC</td>
<td>Tumour with IIA or IIB but with tumour on the external surface, capsule ruptured; ascites containing malignant cells or positive peritoneal washing</td>
</tr>
</tbody>
</table>

### Stage II (FIGO 2014)

<table>
<thead>
<tr>
<th>Stage II</th>
<th>Tumor involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA</td>
<td>T2A N0 M0 Extension and/or implant on uterus and/or Fallopian tubes</td>
</tr>
<tr>
<td>IIB</td>
<td>T2B N0 M0 Extension to other pelvic intraperitoneal tissues</td>
</tr>
<tr>
<td>IIC</td>
<td></td>
</tr>
</tbody>
</table>
**Stage III (FIGO, 1988)**

<table>
<thead>
<tr>
<th>Stage III</th>
<th>Growth involving one/both ovaries with peritoneal implants outside the pelvis and/or retroperitoneal and/or inguinal lymph nodes. Superficial liver metastasis equals stage III. Tumour limited to true pelvis but histologically proven malignant extension to small bowel and omentum.</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIA</td>
<td>Tumour grossly limited to true pelvis with negative nodes. But histologically confirmed microscopic seeding of abdominal peritoneal surface.</td>
</tr>
<tr>
<td>IIIB</td>
<td>Tumour of one or both ovaries. With histologically confirmed implants on abdominal peritoneal surface, none more than 2 cm in diameter, node negative.</td>
</tr>
<tr>
<td>IIIC</td>
<td>Abdominal implants more than 2 cm diameter. And/or retroperitoneal or inguinal lymph nodes or both.</td>
</tr>
</tbody>
</table>

**Stage III**

<table>
<thead>
<tr>
<th>IIIA</th>
<th>Tumor involves 1 or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIA1</td>
<td>T1/2 N1 M0 Positive retroperitoneal lymph nodes and/or microscopic metastasis beyond the pelvis                                                                roteperitoneal lymph nodes only (cytologically or histologically proven):</td>
</tr>
<tr>
<td>IIIA1 (i)</td>
<td>Metastasis up to 10 mm in greatest dimension</td>
</tr>
<tr>
<td>IIIA1 (ii)</td>
<td>Metastasis more than 10 mm in greatest dimension.</td>
</tr>
<tr>
<td>IIIA2</td>
<td>T3A N0/1 M0 Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes.</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3B N0/1 M0 Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes.</td>
</tr>
<tr>
<td>IIIC</td>
<td>T3C N0/1 M0 IIIC: Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ).</td>
</tr>
</tbody>
</table>
Conclusion- Patients with stage IIIC epithelial ovarian cancer due to positive nodes only had a more favorable prognosis compared to other stage IIIC patients. Therefore, reevaluation of the current FIGO staging system for stage IIIC epithelial ovarian cancer is required.
<table>
<thead>
<tr>
<th>Stage IV (FIGO, 1988)</th>
<th>Stage IV (FIGO, 2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth involving one/both ovaries with distant metastasis</td>
<td>Distant metastasis excluding peritoneal metastases</td>
</tr>
<tr>
<td>If pleural effusion is present, there must be a cytologic result</td>
<td>I VA</td>
</tr>
<tr>
<td>Parenchymal liver metastasis equals to stage IV</td>
<td>IVB</td>
</tr>
</tbody>
</table>
EPITHELIAL CARCINOMA

- Ovarian
- Fallopian tube
- Primary peritoneal
Specifically related to serous adenocarcinoma
Tubal intraepithelial carcinoma (TIC)

Overall, 71% and 48% of "ovarian" serous carcinomas had endosalpinx involvement or TIC. TIC coexists with all forms of pelvic serous carcinoma and is a plausible origin for many of these tumors.
INHERITED SYNDROMES

- BRCA 1 & 2
- Lynch
- Other

- Most is sporadic or unknown
- Tumor suppressor gene
- Repair damaged DNA
- Repair double stranded DNA breaks
- Destroy cells with irreparable DNA damage

- Increased risk of ovarian, FT, primary peritoneal, prostate, pancreatic and melanoma

BRCA
► 17q2
► 40-55% risk of ovarian cancer

BRCA 1
13q12

20-25% risk of ovarian carcinoma

BRCA 2
HNPCC
Autosomal dominant
Impaired DNA mismatch repair
- MSH2, MLH1, PMS
Linked to colon, endometrial, ovarian, stomach, intestine, hepatobiliary, urinary tract, brain and skin malignancies
Lynch I - Colon cancer
Lynch II - GI and GU/reproductive carcinomas
10-15% risk of ovarian carcinoma

LYNCH
Amsterdam Criteria:
- Three or more family members with a confirmed diagnosis of colorectal cancer, one of whom is a first degree (parent, child, sibling) relative of the other two
- Two successive affected generations
- One or more colon cancers diagnosed under age 50 years
- (FAP) has been excluded

Amsterdam Criteria II:
- Three or more family members with HNPCC-related cancers, one of whom is a first degree relative of the other two
- Two successive affected generations
- One or more of the HNPCC-related cancers diagnosed under age 50 years
- (FAP) has been excluded

Will miss 30% of Lynch carriers
- Microsatellite instability profiling (MSI)
- IHC- DNA mismatch repair gene expression
- Both together more effective
OTHER GENETIC SYNDROMES

- Hereditary ovarian cancer
- Hereditary breast/ovarian cancer
- Unknown genes
- Multipanel testing
  - VUS
- Constantly evolving area
- *Genetic counselling
SCREENING FOR GENETIC HIGH RISK PATIENTS

- Accurate family history
- Test affected family members
- Focused genetic testing of relatives
- Genetic counselling

- No effective screening guidelines
- Consider 6-12 monthly exam, pelvic U/S and Ca125 level
RISK REDUCTION FOR HIGH RISK PATIENTS

- OCP if fertility desired
  - 5 year use - 50% risk reduction

- Risk reducing surgery once fertility no longer desired
  - Ideally 10 yrs prior to age of affected relative
  - Salpingectomy vs salpingo-ophorectomy
NON GENETIC RISK FACTORS

- Low parity
- Infertility
- Incessant ovulation
- Obesity
- Estrogen alone replacement
- Western countries
- Endometriosis
EPITHELIAL TUMORS
- Most common epithelial carcinoma
- “Typical” ovarian cancer presentation
- High grade
- Linked to BCRA mutation

SEROUS
- Large tumors
- Gyn vs intestinal differentiation
- Difficult frozen section interpretation
- Lynch syndrome
- Pseudomyxoma?? Appendiceal origin

MUCINOUS
- Associated with endometriosis
- Poorly differentiated
- More aggressive
- Increased risk of DVT/PE
Often associated with endometriosis
Synchronous primary tumors
Well differentiated
Early stage more often
- Urothelial cell tumor
- May or may not be related to brenner tumor
- Aggressive
- Indolent, but poorly responsive serous carcinoma
EVALUATION

- Exam
  - Mass
    - Fixed vs mobile
  - Fluid wave
  - Pain
  - Umbilical nodule
- History
  - Pain
  - Duration of symptoms
  - GI and GU symptoms
  - Family Hx
- Lab
- Imaging
Ca125
Ca19-9
CEA
OVA-1
HE-4
AFP
HCG
LDH
INHIBIN
IMAGING

- Pelvic U/S
- CT
- MRI
- Chest
### Table 3
**Society of Gynecologic Oncologists Guidelines for Referral to a Gynecologic Oncologist**

- Evidence of advanced disease: pelvic mass with omental caking, presence of effusion or ascites
- Diagnosis of a clinically suspicious pelvic mass (large [≥ 10 cm] complex, fixed, nodular, bilateral)
- Premenarchal girls requiring surgical treatment for a pelvic mass
- Postmenopausal women with suspicious ovarian masses or elevated tumor markers
- Perimenopausal women with ovarian masses, particularly when associated with elevated CA-125
- Young patients with a pelvic mass and elevated tumor markers (CA-125, alpha-fetoprotein [AFP], human chorionic gonadotropin [hCG])
- Suspicious findings present on imaging studies
- Presence of complex masses with solid components or excrescences, or otherwise suspicious for cancer
- Suspicious pelvic masses found in women with a significant family or personal history of ovarian, breast, or other cancers (one or more first-degree relatives)
Clinical suspicion and imaging alone not sufficient
Cytology - ascites or pleural fluid
CT Guided biopsy of mass/omentum
Surgically resected tissue
- Useful if drainage of pleural fluid or ascites required for symptom relief
- Potentially avoid abdominal surgery initially
- Avoid “Peek and Shreik”
CT GUIDED BIOPSY

- Useful if patient a poor surgical candidate currently but potentially could benefit from chemotherapy
  - Recent DVT/PE
  - Poor nutritional status
  - Other significant comorbidities
- Not if planning primary surgery
SURGICAL RESECTION

- Goal to removal all tumor - cytoreduction
- Remove contained tumor intact
- Evaluate for and report visible tumor
- Obtain samples to assess for disease spread - staging
- Correct any physical compromise to GI or GU systems
- Remove mass intact
- If need to rupture, do in contained manner - endobag
- Document if rupture or spillage

**ISOLATED PELVIC MASS**
STAGING

- Peritoneal washings
- Exploration and documentation of tumor size and location
- Removal of FT and ovaries, uterus
- Peritoneal biopsies, lesions or random if no lesions
- Omentectomy
- Pelvic and periaortic lymph node dissection
- Biopsy or cytology of diaphragm surface
- *Fertility preservation options*
STAGING
Optimal vs Optimal-ish

- Incremental benefit related to burden of disease remaining post surgery (<2cm, <1cm, <1mm)
- <2cm previously considered optimal
- Now “no visible disease” goal
- Reflects both tumor biology and aggressiveness of surgery

“Big whack”
CYTOREDUCTION SURVIVAL BENEFIT
- Removing large necrotic masses promotes drug delivery to smaller tumors with good blood supply
- Removing resistant clones decreases the likelihood of early onset drug resistance
- Tiny implants have a higher growth fraction that should be more chemosensitive
- Removing cancer in specific locations, such as tumors causing a bowel obstruction, improves the patient’s nutritional and immunologic status
AGGRESSIVE CYTOREDUCTION

DOWNSIDES

- Surgical morbidity and mortality
- Delay initial chemotherapy
- Achieving optimal status may reflect favourable tumor biology
CT imaging
- Diffuse peritoneal thickening
- Large volume ascites
- 50% reduction in optimal cytoreduction

Diagnostic laparoscopy
- In clinical trial protocol setting
CT imaging within 30 days of optimal cytoreductive surgery, <1cm residual per surgeon report

Over 20% of patients had measurable disease > 2cm

Rapid disease growth vs unrecognised disease vs wishful thinking/overt lying
- Poor surgical candidate
- Extensive, unresectable, or extraperitoneal disease
- Non inferior to primary surgery
- Interval cytoreductive surgery

**NEOADJUVANT CHEMOTHERAPY**
PRIMARY THERAPY
- IV therapy
- Carboplatin and Paclitaxel IV q 21 days
- Acceptably tolerated
- Acceptable schedule

HAPPY MEAL
- Carboplatin q 21 days or weekly
- Paclitaxel weekly

- Decreased toxicity
- Improved PFS
IV/IP (INTRAPERITONEAL) THERAPY

- Day 1-IV Paclitaxel
- Day 2- IP Cisplatin
- Day 8 IP Paclitaxel

- 16month improved survival
- Increased toxicity
  - Nausea, vomiting
  - Dehydration
  - Electrolyte abnormality
  - Renal impairment
  - Port complications
POST INITIAL THERAPY

- Complete response
  - Observation
  - Maintainence chemotherapy

- Refractory or Resistant disease
  - Second line therapy
- 3 monthly for 2 yrs, then 6 monthly for 3 yrs, then annually

- Symptom review
- Physical and pelvic exam
- Ca125 level
- CT or PET imaging as indicated
- Genetic testing
- Elevated ca125 only
- No clinical or imaging evidence of disease
- Await above vs clinical trial
- Treating at this time has no effect on overall survival, but does result in more chemotherapy administration
**Clinical trial**

Olaparib

## RECURRENT DISEASE THERAPY

### Ovarian Cancer

#### Acceptable Recurrence Therapies

<table>
<thead>
<tr>
<th>Agents</th>
<th>Cytotoxic Therapy</th>
<th>Hormonal Therapy</th>
<th>Targeted Therapy</th>
<th>Radiation Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred Agents</td>
<td>Combination if platinum sensitive&lt;br&gt;Carboplatin/paclitaxel (category 1)&lt;sup&gt;2&lt;/sup&gt;&lt;br&gt;Carboplatin/docetaxel&lt;sup&gt;1&lt;/sup&gt;&lt;br&gt;Carboplatin/gemcitabine&lt;sup&gt;2&lt;/sup&gt;&lt;br&gt;Cisplatin/gemcitabine&lt;sup&gt;4&lt;/sup&gt;&lt;br&gt;Singl-agent if platinum sensitive&lt;br&gt;Carboplatin&lt;br&gt;Cisplatin&lt;br&gt;Singl-agent non-platinum based if platinum resistant&lt;br&gt;Docetaxel&lt;br&gt;Etoposide, oral&lt;br&gt;Gemcitabine&lt;br&gt;Liposomal doxorubicin&lt;br&gt;Paclitaxel, weekly&lt;br&gt;Pemetrexed&lt;br&gt;Topotecan</td>
<td></td>
<td>Bevacizumab&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Other Potentially Active Agents</td>
<td>Alitretinine&lt;br&gt;Capecebrine&lt;br&gt;Cyclophosphamide&lt;br&gt;Inoxafamide&lt;br&gt;Irinotecan&lt;br&gt;Melfalan&lt;br&gt;Oxaliplatin&lt;br&gt;Paclitaxel&lt;br&gt;Vinorelbine</td>
<td>Anastrozole&lt;br&gt;Letrozole&lt;br&gt;Leuprolide&lt;br&gt;Megestrol acetate&lt;br&gt;Tamoxifen</td>
<td>Palliative localized radiation therapy</td>
<td></td>
</tr>
</tbody>
</table>
- Long disease free interval
- Isolated resectable disease

- Unable to recruit to randomized study of secondary cytoreduction vs chemotherapy

- Typically followed by chemotherapy
DRUGS- CARBOPLATIN

- Alkalating agent

- Toxicity- Myelosuppresion, N/V, renal impairment, low Mg
DRUGS- PACLITAXEL

- Microtubal stabilization
- Toxicity - myelosuppression, alopecia, hypersensitivity, neuropathy
- Docetaxel
  - Less hypersensitivity and neuropathy, more rash
- Nab-paclitaxel
  - Less hypersensitivity

DRUGS- OTHER TAXANES
- Inhibits nucleic acid synthesis
- Toxicity - rash, PPE, cardiotoxicity, myelosuppression
- Binds to topoisomerase, stabilising ss DNA breaks

- Toxicity: myelosuppression, alopecia, N, V, diarrhea
Blocks DNA synthesis

Toxicity - myelosuppression, N/V, radiation recall, hypersensitivity
DRUGS- ETOPOSIDE

- Causes ss and ds DNA breaks thru topoisomerase II, microtubule stabilizer
- Toxicity- anaphylaxis, N/V, myelosupression
- VEGF inhibitor
- Impairs new vessel development

- Toxicity: fatigue, HTN, proteinuria, GI perforation, poor wound healing
DRUGS- OLAPARIB

- Newest FDA approval
- PARP inhibitor
- Third line in BRCA carriers only
- Toxicity- minimal, fatigue, nausea, anorexia, low plts