

Kate O’Hanlan, M. D.
Gynecologic Oncology, Surgery and Endoscopy
4370 Alpine Road
Portola Valley, CA 94028-7927

Phone: (650)-851-6669

FAX: (650)-851-9747

OVARIAN CARCINOMAS

2% of all women develop ovarian cancer. 18,000 new cases of ovarian carcinoma yearly (23% of all GYN cancers); 11,400 deaths yearly due to ovarian carcinoma (47% of GYN cancer deaths).

Embryological origins:

4th Week: GERM CELLS migrate to the genital ridge, where they induce a proliferation of the underlying NONSPECIFIC MESENCHYME into SPECIALIZED GONADAL STROMA within the covering invested by COELOMIC EPITHELIUM. These are the cancer cell lines:

I. Coelomic Epithelium

- A. Serous tumor
- B. Mucinous tumor
- C. Endometrioid tumor
- D. Mesonephric (clear cell) tumor
- E. Brenner tumor
- F. Undifferentiated carcinoma
- G. Carcinosarcoma, mixed mesodermal tumor

II. Germ Cell Tumors

- A. Teratoma
 - 1. Mature teratoma
 - a. Solid adult teratoma
 - b. Dermoid cyst
 - c. Struma ovarii
 - d. Malignant Neoplasm’s arising from mature cystic teratoma
 - 2. Immature teratoma
- B. Dysgerminoma
- C. Embryonal carcinoma
- D. Endodermal sinus tumor
- E. Choriocarcinoma
- F. Gonadoblastoma

III. Specialized Gonadal Stroma

- A. Granulosa-theca tumors
 - 1. Granulosa tumor
 - 2. Thecoma
- B. Sertoli-Leydig tumors
 - 1. Arrhenoblastoma
 - 2. Sertoli tumor
- C. Gynandroblastoma
- D. Lipid-cell tumors

IV. Nonspecific Mesenchyme

- A. Fibroma, hemangioma, leiomyoma, lipoma
- B. Lymphoma
- C. Sarcoma

V. Neoplasms Metastatic to the Ovary

- A. GI tract (Krukenberg)
- B. Breast
- C. Endometrium
- D. Lymphoma

BORDERLINE TUMORS OF OVARY

Not benign because there is cytologic and architectural atypia e.g. nuclear hyperchromasia, enlargement and pleomorphism, prominent nucleoli and increased mitotic activity. Can see necrosis, inflammation and psammoma bodies, frequent tufting, stratification and complex papillary architecture. Can recur.

Not malignant because there is no stromal invasion in the ovaries, despite severe atypia and frequent mitosis. Can be seen in ovaries with benign and malignant elements.

Risk factors: Pregnancy reduces-OR.54 with 2 children and ,37 with 4 children. Use of Oral contraceptive pills for >5 years reduces risk by 25% and for 10 years by 50%. Breast-feeding also reduces risk. Age and obesity both increase risk.

Work-up: Sonogram - unparalleled detail of pelvic anatomy by sonogram. If complex cysts are seen with intracystic papillation, mural nodules, some septa, concern of ovary cancer increases. Get Ca125 and CEA.

Serous Epithelial Carcinoma, LMP, comprise 50%

- a. stratification of epithelial lining of papillae to 4mm or less cell layers
- b. papillary projections, tufts from epithelial linings of papillae, individual cells
- d. Intra-epithelial carcinoma: cribriform area > 4mm. If >4mm treat as invasive.

Mucinous Epithelial Carcinoma, LMP, comprise 30%

- a. papillary structure + solid thickening 25-50%
- b. epithelial stratification of 2-3 layers
- c. rarely bilateral (5%). Think invasive carcinoma if bilateral.

Can see pseudomyxoma ovarii Do appendectomy and run bowel for all mucinous pathology. Can see intraepithelial carcinoma if >4 layers of thick confluence or thick stratification. Borderline are typical to mild atypical or intraepithelial carcinoma, or intraglandular mucinous carcinoma, or cribriform less than 10 mm². Usually unilateral, but bilateral can be primary or metastatic. 98% survive stage I but only 35% survive higher stages especially when metastatic deposits are invasive--treat these as malignant and invasive. Rupture does not increase recurrence. Higher stage--think appendix and pseudomyxoma peritonei. See filiform papillae (little storma).or sever nuclear atypia with marked nuclear stratification >4 cells height. Many goblet cells and AMF's. Gland mucus can rupture into stroma with histiocytic response.

Endometrioid Epithelial Carcinoma, LMP, very rare

can see atypical endometrioid hyperplasia in glands with stroma endometriosis seen adjacent, or elsewhere in pelvis often seen with unopposed estrogen or obesity.

Implants - **20% metastatic to abdominal surfaces. Resect these implants, not peel off, to see if invasive.**

Therapy For Borderline Ovarian Tumors

Stage IA: Fertility desired: LMP or grade 1 and appears Stage IA, do USO, only and get frozen section. Do washings, nodes, omentectomy, appendectomy, and biopsy contralateral ovary if pathologist cannot rule out grade 1 invasive cancer.

May need to return for TAH-BSO if biopsies show Grade 2 or Stage II or higher.

Fertility not desired- TAH-BSO and frozen section for possible staging. Chemotherapy is not helpful. .5% recurrence.

Stage II-IV: TAH-BSO, Debulking, Staging: omentectomy, appendectomy, nodes. Resect all mets to make sure they are not invasive, which would indicate chemotherapy.

No residual—observe and reassure.

Bulky residual--observe. Small possibility of transition into invasive over time, so try to resect all.

Recurrence: Debulking laparotomy. Pathology to see if recurrence is higher grade and to improve disease-free interval. If still LMP then follow. If invasive then chemotherapy with Tax and CBDCA.

Prognosis

Of 168 cases of Stage I serous LMP tumors from the series above there were two recurrences, both in the preserved ovary. Many of higher stages whose tumors persist were still clinically well, without progression or symptoms.

Of 234 mucinous LMP tumors in Stage I, 9 recurred and all died of disease.

Approximately 40% of Stage III mucinous LMP tumors die (pseudomyxoma peritonei occurs from ruptured appendix). Remove appendix and all peritoneal lesions.

If metastases are not invasive:

Stage	survival	survival
I	98	99
II	95]
III	56] 92
III	40]

When mets are invasive:

Stage	survival	survival
I	98	99
II	95	
III	56	
III	40	

MALIGNANT EPITHELIAL OVARIAN NEOPLASMS

Risk:	<2% lifetime risk, but usually ages 50 - 60 years
Factors:	Obesity. Age. Industrial countries. O.C.'s: .6 relative risk No virus implicated. Low parity. Delayed childbirth.
Symptoms:	None. Bloating, dyspepsia, constipation, tenesmus, pressure symptoms - 25% see LMD for above, must be "observed"
Signs:	Increased abdominal girth, ascites, mass, postmenopausal palpable ovary, obstruction of GI tract
Staging:	Surgical. Determines type of therapy.

FIGO Staging for Primary Carcinoma of the Ovary (1985)

Stage I Growth limited to the ovaries.

Stage Ia	Growth limited to one ovary; no ascites. No tumor on the external surface; capsule intact.
Stage Ib	Growth limited to both ovaries: no ascites. No tumor on the external surfaces; capsules intact.
Stage Ic	Tumor either stage Ia or Ib but with tumor on surface of one or both ovaries, or with capsule ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.

Stage II Growth involving one or both ovaries with pelvic extension.

Stage IIa	Extension and/or metastases to the uterus and/or tubes.
Stage IIb	Extension to other pelvic tissues.
Stage IIc	Tumor either stage IIa or IIb. but with tumor on surface of one or both ovaries: or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.

Stage III Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis equals stage III. Tumor is limited to the true pelvis but with histologically proven malignant extension to small bowel or omentum.

Stage IIIa	Tumor grossly limited to true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces.
Stage IIIb	Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces none exceeding 2 cm in diameter. Nodes are negative.
Stage IIIc	Abdominal implants greater than 2 cm in diameter and/or positive retroperitoneal or inguinal nodes.

Stage IV Growth involving one or both ovaries, with distant metastases. If pleural effusion is present, there must be positive cytology. Parenchymal liver metastases equal stage IV.

Stage of Carcinomas of the Ovary by Histologic Subtype: Percentage in Each Stage

Stage	Mucinous (N= 123)	Endometrioid (N= 205)	Clear Cell (N= 63)	Serous (N= 283)	Undiff. (N= 155)	All (N= 829)
I	19.1	50.8	47.6	35.2	57.1	26.5
II	23.0	28.7	24.5	25.5	25.4	29.2
III	43.1	13.9	21.2	27.6	7.9	26.5
IV	14.8	6.5	6.7	11.7	9.5	17.7

Aure et al, 1971.

Mechanism of spread:

1. Intra abdominal currents allow cytologic seeding to follow flow clockwise from the pelvis and surfaces of small bowel, liver, and omentum to the right gutter to right hemidiaphragm through Bochdalek's foramina.
2. Lymphatic: both pelvic and Aortic nodes to mediastinum to supraclavicular to lung.
4. Hematogenous: rare.

SURGICAL MANAGEMENT AND STAGING:

Two goals: know physical extent of spread and remove every visible tumor.

Vertical incision

Opening cytology: 20% of Stage I/II Positive.

Inspect every surface. Palpate every surface. Biopsy every suspicious lesion.

30% are upstaged at re-exploration because of spread to aortic nodes, pelvic nodes, cul-de-sac, diaphragm, or omentum.

Run large and small bowel. Do appendectomy.

Omentectomy: 25% of Stage I and II are found to be positive.

Pelvic and aortic nodes--45% occult positives. 3-6% of Stages I/II are positive.

Debulk all tumor. >95% of patients can be meticulously debulked to zero by Gynecologic Oncologist when previous surgeon referred as non-debulkable.

Hysterectomy is standard. If cannot reduce bulk safely then relieve impending problems: i.e., remove large masses, relieve bowel obstructions, and avoid future bowel obstructions.

Chemotherapy for invasive epithelial carcinoma of the ovary: Usually Carboplatin with Taxol for 6 courses. Follow CA-125 and do clinical exam to r/o progression on chemo.

Second Look is not standard now.

The procedure requires a methodical, meticulous exploration of the abdomen and pelvis, with four-quadrant peritoneal cytology specimens, biopsy of all lesions, all sites where residual left (must *study* original surgical report), resection of all adhesions, removal of omental pedicles, resection of ovarian pedicles with peritoneum. Resection or biopsy of cul-de-sac peritoneum, bowel adhesions, and peritoneal patches from paracolic gutters. Selective dissection of pelvic and aortic lymph nodes if not done previously.

Appendectomy, if not already done. Resection of all residual carcinoma.

Four types:

1. Interval Primary debulking: Given after two or three courses of chemotherapy to facilitate debulking of patients with a large tumor bulk who could not or were not debulked initially.
2. Interval Progression debulking: Debulking of patients who progress (new mass grows) during initial platinum containing chemotherapy regimens. Rarely appropriate or indicated as prognosis very poor.
3. Classic Second look: Procedure does not prolong life and has no indication currently. Useful in protocols to assess disease status. Also useful if patient did not have all indicated procedures prior to initiating chemotherapy. Goal is to determine if patient appears to be disease-free in order to stop therapy. Eligible patients must have no evidence of tumor by CT, sono, or MRI, and a negative CA-125.
4. Recurrence resection of post-chemo recurrent mass: Can debulk again if recur more than six months since completion of chemo and tumor initially responsive to chemo. Not appropriate if none of the available chemotherapeutic regimens are effective for ovarian tumors, or if recurrence occurs in less than six months after completion of chemotherapy because prognosis poor. Don't operate unless there is reasonable chemo plan available, but do relieve obstructions, palliate pain.

Therapy for recurrent tumor: If patient was originally sensitive to carboplatin and taxane given many years ago, can give this again. Intraperitoneal chemotherapy may hold promise for the future; studies underway now.

METASTATIC DISEASE TO OVARY

Possible with all ages 29-89, especially bilateral, cystic ovaries. Get good history, while ruling out metastatic disease carefully. Always rule out metastatic disease if high stage mucinous with colonoscopy and esophagogastroduodenoscopy. Do very thorough exploratory laparotomy. Possibilities include:

Colon

Gastric

Breast

Pancreas

Appendix

Pseudomyxomatous Peritonei Carcinoma

Clinical condition of gelatinous mucin filling peritoneal cavity mucinous implants and fibrous adhesion. Associated with appendix, ovary, intestine, bile duct and pancreas.

Histogenesis: peritoneal metaplasia. Now believed a form of metastatic sites of peritoneal fluid accumulates in right hemidiaphragm and in pelvis.

Clinical symptoms: distension, age mid 50, acute appendix, anorexia, and early satiety from gastric compression.

Micro: see much mucin without mucin cells or with a scanty epithelium showing low-grade atypia = low grade adenomucinosis. Or see mucin with abundant epithelium showing high-grade atypical peritoneal mucinous carcinomatosis. Usually see inflammatory reaction with lymphocytes. If see clusters of signet ring then think adencarcinoma.

Pseudomyxoma ovarii-condition limited to ovary

Pseudomyxoma peritonei usually with appendiceal adenomas, possibly with high-grade dysplasia (ACIS) or low-grade adenocarcinoma or high-grade carcinoma. Very rare because high grade grow so fast causing mortality.

Appendix is usually the origin of PMP. Whatever we see in the ovary is secondary involvement, synchronous tumors. Bilateral ovarian tumors are usually met of PMP and have predominant surface involvement. Can see separate tumor if ovarian tumor is large, if there is benign mucinous element.