

OVARIAN CANCER

FLAME LECTURE: 232

BURNS / DELGADO 8.12.19

LEARNING OBJECTIVES

- ▶ Describe the symptoms and physical findings associated with ovarian cancer
- ▶ List the risk factors for ovarian cancer
- ▶ Describe the histologic categories of ovarian cancer
- ▶ Prerequisites:
 - ▶ NONE
- ▶ See also – for closely related topics
 - ▶ FLAME LECTURE 230 – Premenopausal Adnexal Mass
 - ▶ FLAME LECTURE 231 – Postmenopausal Adnexal Mass

INTRODUCTION

- ▶ 2nd most common gynecologic cancer
 - ▶ 22,000 new cases each year in US
- ▶ However, it is the #1 cause of GYN cancer death in US
 - ▶ 14,000 related deaths in the US per year
- ▶ No consensus regarding standard screening modalities
 - ▶ US continues to not prove beneficial for screening all women
- ▶ Differential dx of adnexal masses is vast
 - ▶ Ovarian cysts, tubo-ovarian abscesses (TOA), endometriomas, benign tumors, malignant tumors, metastases

RISK FACTORS

- ▶ Age
 - ▶ Most important independent risk factor
 - ▶ Between 2009-2013, median age at ovarian cancer diagnosis was 63 y/o
- ▶ Family history of breast or ovarian cancer
 - ▶ BRCA 1 mutation: 41–46% risk by 70 y/o
 - ▶ BRCA 2 mutation: 10–27% risk by 70 y/o
 - ▶ Lynch syndrome: 5-10% by 70 y/o
- ▶ Early menarche / Late menopause / Nulliparity / Infertility / Never using hormonal contraception / Never breastfeeding
 - ▶ All things that increase the number of cycles patients have experienced
- ▶ White race
- ▶ Endometriosis

CLINICAL PRESENTATION

- ▶ Most cancers are discovered incidentally on pelvic exam or imaging
- ▶ Unfortunately, early ovarian cancer is largely asymptomatic and symptoms typically begin with late-stage disease
 - ▶ Abdominal pain
 - ▶ Pelvic pain
 - ▶ Bloating / Distension / Bowel obstruction
 - ▶ Urinary symptoms (urgency or frequency)
 - ▶ Early satiety
 - ▶ Shortness of breath (due to pleural effusion from distant metastasis)
- ▶ Occasionally the diagnosis is made following a new diagnosis of DVT/PE

WORK-UP

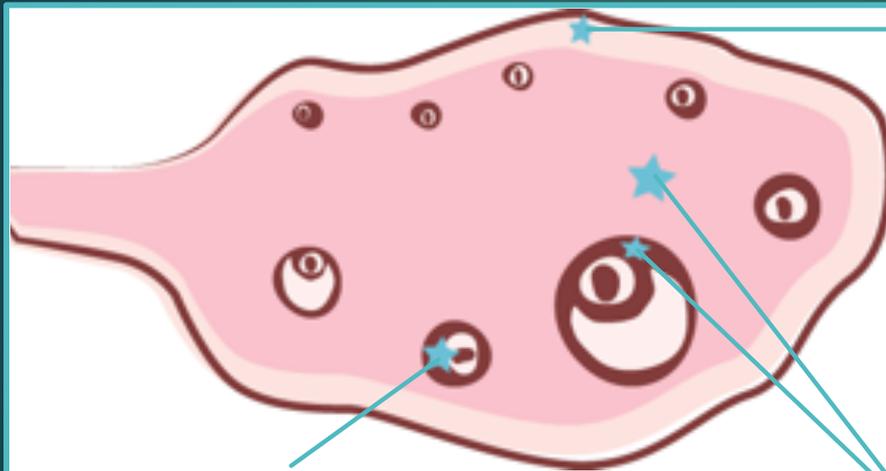
- ▶ See [FLAME 230 & 231](#) for initial evaluation following discovery of pre-menopausal and post-menopausal adnexal masses in greater detail
- ▶ Physical exam including pelvic exam
 - ▶ Evaluate for presence of a mass or fluid wave (ascites)
- ▶ TVUS (transvaginal ultrasound)
 - ▶ Evaluate size of mass and complexity (i.e. simple cyst vs. complex cyst w/ septations, loculations, solid components/nodules) and color flow doppler evaluation
- ▶ Tumor Markers / Biomarkers
 - ▶ CA-125 is a cell-surface glycoprotein antigen expressed on coelomic tissues (peritoneum, ovaries, fallopian tubes, etc)
 - ▶ Inhibin, LDH, AFP, HCG may also be considered if concern for non-epithelial CA
 - ▶ MRI or CT may help with surgical planning and evaluation for metastasis
- ▶ There are risk-stratifying algorithms combining tumor markers to also help (next slide)

RISK STRATIFYING ALGORITHMS

- ▶ HE4 (Human epididymis protein-4) immunoassay:
 - ▶ Is overexpressed in 93% of serous, 100% of endometrioid, and 50% of clear cell tumors, but not in mucinous ovarian carcinomas
 - ▶ Is elevated in >50% of patients who did not have elevated CA125 levels
- ▶ ROMA (Risk of Malignancy Index):
 - ▶ Combines CA 125, HE4, and patient's postmenopausal status to generate a score evaluating risk of malignancy
- ▶ OVA 1:
 - ▶ Combines CA125, transthyretin (prealbumin), apolipoprotein A1, beta2 microglobulin, and transferrin levels and postmenopausal status to generate a score evaluating risk of malignancy

Uses of Algorithm	CA125	HE4	OVA1
Screening	No	No	No
Discrimination of benign vs. malignant masses	Yes	Yes	Yes
Monitoring Treatment	Yes	Yes	No
Detection of Recurrence	Yes	Yes	No

CANCERS ARISE FROM DIFFERENT CELL-TYPES



Epithelial Tumor (95%)

- Serous type
- Mucinous type
- Clear cell type
- Endometrioid type
- Brenner tumor
- Undifferentiated

Germ Cell Tumor (<5%)

- Immature Teratoma
- Dysgerminoma
- Endodermal sinus tumor
- Choriocarcinoma
- Embryonal carcinoma

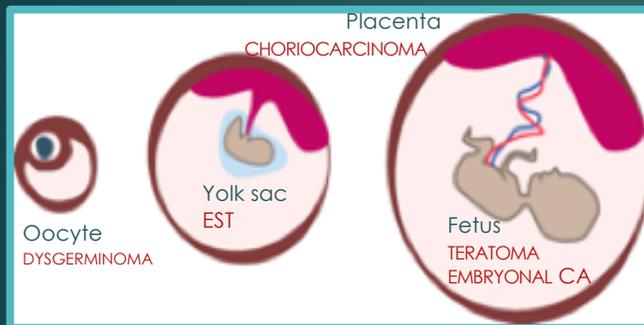
Sex Cord Stromal Tumor (<5%)

- Granulosa-theca cell tumor
- Sertoli-Leydig cell tumor

EPITHELIAL OVARIAN CANCERS

- ▶ Usually large, cystic, and 65% are bilateral
- ▶ Serous adenocarcinoma is the most common, and associated with BRCA 1/2
- ▶ Clear cell adenocarcinoma is associated with DES exposure and endometriosis
- ▶ Endometrioid adenocarcinoma is associated with Lynch syndrome
- ▶ Initial treatment Overview:
 - ▶ Primary cytoreductive surgery means starting with surgical debulking (loosely defined as removing the uterus, ovaries, and omentum + all traces of cancer no matter what organ it is growing on, unless you can't), and followed by chemotherapy with carboplatin/paclitaxel
 - ▶ Occasional the chemotherapy is administered IV and IP (Intraperitoneal)
 - ▶ Neoadjuvant chemotherapy means starting with chemotherapy first to help shrink tumor bulk with hopes patient is a candidate for debulking surgery after
- ▶ Prognosis: poor – 20% survival with frequent recurrence

GERM CELL TUMORS



TYPES

- ▶ Dysgerminoma (50% of GCTs): secrete **LDH**
 - ▶ Particularly sensitive to radiation
 - ▶ Choriocarcinoma: secrete **β -hCG**
 - ▶ Histology: contain *schiller-duval bodies*
 - ▶ Endodermal Sinus Tumor (20% of GCTs): secrete **AFP**
 - ▶ Teratoma
 - ▶ Mature: benign, also called dermoid cyst
 - ▶ Contain mature adult tissue like skin, teeth, sebaceous material (making it cystic)
 - ▶ Struma ovarii: teratoma with functional thyroid tissue resulting in hyperthyroidism
 - ▶ Often must do cystectomy to differentiate between mature and immature
 - ▶ Immature (20% of GCTs): malignant
 - ▶ Undifferentiated embryonal carcinoma: secretes **AFP & β -hCG**
- ▶ Grow rapidly, unilateral
 - ▶ Treatment:
 - ▶ Unilateral oophorectomy (or bilateral if done with child-bearing)
 - ▶ Omentectomy + Lymph node dissection
 - ▶ Chemo: BEP (bleomycin, etoposide, cisplatin)
 - ▶ Prognosis: good! 85% survival

SEX CORD STROMAL TUMORS

- ▶ Granulosa-Theca Cell Tumor
 - ▶ Functional: secretes **Estrogen + Inhibin A/B**
 - ▶ Inhibin A/B are good tumor markers to evaluate for this cancer and monitor for recurrence
 - ▶ Increased estrogen → **endometrial hyperplasia** (or precocious puberty in children) due to unopposed action
 - ▶ Thus, consider EMB to check for hyperplasia/carcinoma
 - ▶ Histology: evaluate for *Call-Exner bodies* (coffee bean nuclei)
- ▶ Sertoli-Leydig Cell Tumor
 - ▶ Most commonly premenopausal
 - ▶ Functional: secrete **Androgens** → symptoms of hirsutism/virilization
- ▶ Fibroma (benign)
 - ▶ Nonfunctional
 - ▶ Commonly presents with Meigs Syndrome (fibroma + ascites + right hydrothorax)
- ▶ They are all low-grade, unilateral, rarely recurring tumors
- ▶ Treatment: unilateral salpingo-oophorectomy (bilateral in postmenopausal women)
 - ▶ No chemotherapy or omentectomy usually needed
 - ▶ Prognosis: good! 70-90% survival!

STAGING OF OVARIAN CANCER

GENERAL PRINCIPLES

- ▶ TNM staging uses 3 factors to stage (or classify):
 - ▶ The extent (size) of the tumor (T): Has the cancer spread outside the ovary/fallopian tube? Has the cancer reached nearby pelvic organs like the uterus or bladder?
 - ▶ The spread to nearby lymph nodes (N): Has the cancer spread to the lymph nodes in the pelvis or around the aorta (aka pelvic and para-aortic LNs)?
 - ▶ The spread (metastasis) to distant sites (M): Has the cancer spread to distant organs or to fluid around the lungs (malignant pleural effusion)?
- ▶ Ovarian cancers can also be graded:
 - ▶ Grade 1 (well-differentiated) cancers have cells that closely resemble normal cells and are less likely to spread or recur
 - ▶ Grade 2 (moderately-differentiated) and Grade 3 (poorly-differentiated) show increasing abnormality of appearance compared to normal cells and are increasingly more likely to spread and recur
- ▶ The next few slides include the TNM and FIGO staging criteria (last updated 2014), which are presented for your reference
 - ▶ Note, these are not something that medical students are expected to know for SHELF exams, however, are useful for referring to during a Gyn Onc rotation

STAGING OF OVARIAN CA

STAGE 1

- ▶ Stage IA (T1A-N0-M0): Only 1 ovary (or tube) is affected by the CA, and the tumor is confined to the inside of the affected ovary/tube. No cancer is detected on the surface and there are no malignant cells detected in the washing fluid from the abdomen and pelvis
- ▶ Stage IB (T1B-N0-M0): Both ovaries (or tubes) are affected by the cancer but no cancer is detected in either the surface of the ovaries/tubes or in washings
- ▶ Stage IC (T1C-N0-M0): Cancer is limited to one or both ovaries or fallopian tubes, with any of the following:
 - ▶ Stage IC1: (T1C1-N0-M0): The ovary tissue surrounding the tumor (capsule) is no longer intact as it was ruptured during the surgery
 - ▶ Stage IC2: (T1C2-N0-M0): The ovary capsule ruptured before surgery OR there is evidence of cancer on the outer surface of at least one of the ovaries/tubes
 - ▶ Stage IC3: (T1C3-N0-M0): Cancerous cells are detected in washings

STAGING OF OVARIAN CA

STAGE 2-4

- ▶ Stage IIA (T2A-N0-M0): Cancer has spread into the uterus or tubes
- ▶ Stage IIB (T2B-N0-M0): Cancer is affecting bladder or rectum
- ▶ Stage IIIA (T1/2-N1-M0 or T3A-N0/N1-M0): Cancer is in one or both ovaries/tubes. During surgery no gross evidence of cancer, but microscopic disease is detected in the peritoneal lining or omentum. It also may involve nearby lymph nodes.
- ▶ Stage IIIB (T3B-N0/N1-M0): Tumors <2cm in diameter are visible outside the pelvis within the abdomen. It also may involve nearby lymph nodes.
- ▶ Stage IIIC (T3C-N0/N1-M0): Tumors more than 2cm in diameter are detected outside the pelvis within the abdomen and may be on the outside of the liver or spleen
- ▶ Stage IVA (any T-any N-M1A): Malignant pleural effusion present
- ▶ Stage IVB (any T-any N-M1B): Malignant spread to distant lymph nodes or all other organs

IMPORTANT LINKS & REFERENCES

- ▶ [ACOG Practice Bulletin 83](#), 2007, Management of Adnexal Masses
- ▶ ACOG Practice Bulletin 182, 2017, BRCA
- ▶ Callahan & Caughey *Blueprints: Obstetrics & Gynecology* 6th ed. 2013
- ▶ Wentzensen 2016, Ovarian Cancer Risk Factors
- ▶ Herzog 2013, Ovarian cancer clinical trial endpoints: SGO white paper
- ▶ Montagnana 2014. ROMA score.
- ▶ <https://www.aacc.org/publications/cln/articles/2013/march/ovarian-cancer>
- ▶ https://www.sgo.org/wp-content/uploads/2012/09/FIGO-Ovarian-Cancer-Staging_1.10.14.pdf