Management of Adnexal Masses

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MASSACHUSETTS GENERAL HOSPITAL
VINCENT OBSTETRICS & GYNECOLOGY

HARVARD MEDICAL SCHOOL

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No disclosures

Practice locations:

- **MGH Cancer Center – Boston**
- **Mass General / North Shore Cancer Center – Danvers**
- **Elliot Hospital in Manchester, NH**

Agenda

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1. Background

2. Diagnostic Evaluation

3. Management

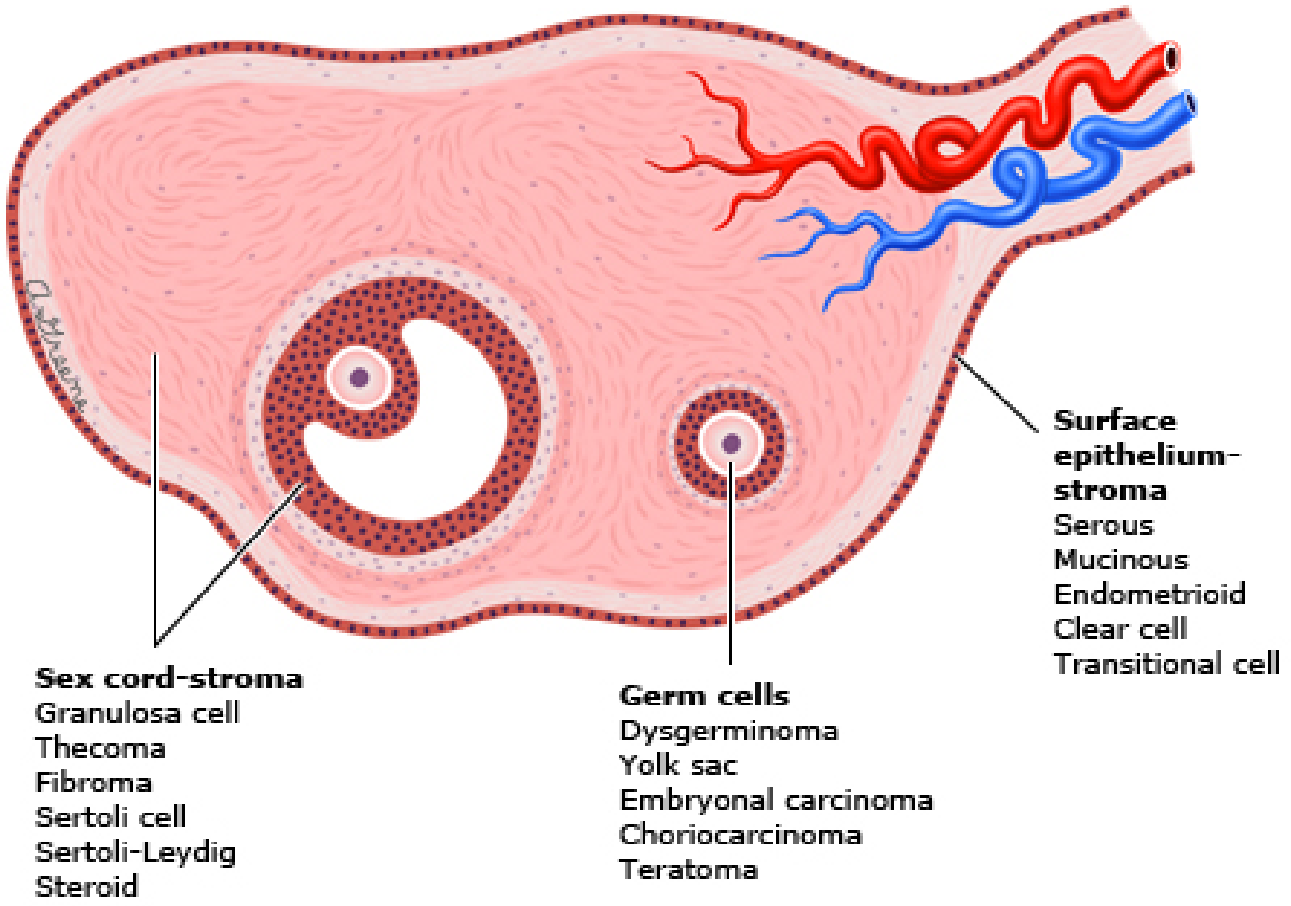
- Assessing need for urgent intervention
- Determining risk of malignancy
- Considering fertility and hormonal preservation

4. Special considerations

- Adolescent patients
- Pregnant patients
- Patients with hereditary ovarian cancer syndrome

Background

- The ovary is a complex and dynamic organ, essential for steroidogenesis and human reproduction
- Composed of 3 types of ovarian tissue, each with potential to develop a pathologic (benign or malignant) process
- Fallopian tube: fimbriated end is histologically similar to the epithelium of the ovary; has been increasingly implicated as the progenitor of many serous adenocarcinomas
- Ovarian masses are relatively common; identified in up to 35% of premenopausal patients and up to 17% of postmenopausal patients



Assessing Need for Urgent Surgery

- Adnexal masses may necessitate emergent surgery:
  - Ovarian torsion
  - Ruptured ectopic pregnancy
  - Bowel obstruction due to a malignant lesion
  - Tubo-ovarian abscess
- Evaluate the following patients for prompt surgical intervention:
  - Hemodynamic instability
  - Peritonitis
  - Evidence of bowel or urinary obstruction
- Patients of reproductive age must immediately be tested for hCG to rule out ectopic pregnancy

Determining Risk of Malignancy

- History: critical
  - Age: older age is greatest risk factor for ovarian and tubal cancer
    - Median age at ovarian cancer diagnosis is 63 years
    - 70% of patients are 55 or older
  - Family history: very important
    - For a 35 year old patient with 1 affected family member, lifetime risk of ovarian cancer increases from 1.6% to 5%
    - With a BRCA1 mutation, the risk is 41-46% by age 70
    - With a BRCA2 mutation, the risk is 10-27% by age 70
    - With Lynch syndrome, the risk is 5-10% by age 70
    - Other risk factors: nulliparity, early menarche, late menopause, white race, primary infertility, and endometriosis

Determining Risk of Malignancy

- Physical examination: important but limited
  - Low sensitivity for detecting masses and worsens with increasing BMI
  - Can inform surgical planning
- Imaging:
  - Pelvic US is the most important imaging tool and should be the initial radiologic test
  - MRI has sensitivity of 81% and specificity of 98% for categorizing as malignant a lesion thought to be indeterminate by US. May help to distinguish origin of pelvic mass when US is indeterminate (ie ovarian vs uterine)
  - CT is the test of choice for clinical staging and recurrence, but poor in assessment of the adnexal mass
    - Recommended if US or MRI is suggestive of malignancy to identify metastatic disease
    - Helpful if concern for bowel involvement or suspicion of non-GYN origin of malignancy (ie GI, pancreatic)

Laboratory Testing

- hCG in reproductive age patients: ectopic pregnancy; gestational trophoblastic neoplasa; pregnancy concurrent with an adnexal mass
- CBC: guide clinical management when infection (ie tubo-ovarian abscess) or bleeding is suspected
- Serum tumor markers:
  - CA-125: most extensively studied and commonly used
    - Elevated in 80% of patients with epithelial ovarian or tubal cnacers
    - Most reliable in post-menopausal patients
    - Less reliable in early stage disease, premenopausal patients, and in non-epithelial ovarian cancer
  - HE4: another markers approved for determining the likelihood that a mass is cancerous

Laboratory Testing

- Additional serum markers:
  - CEA: may be elevated in mucinous cancer associated with the GI tract or the ovary
    - CA-125 to CEA ratio of >25 is indicative of a primary ovarian malignancy
  - CA 19-9: mucin protein which may be elevated in gastric, pancreatic, and gallbladder cancers, as well as in cholangiocarcinoma
  - In patients <40 years old, additional tumor markers may help to identify a non-epithelial malignancy
    - hCG (choriocarcinoma, embryonal cell carcinoma)
    - AFP (yolk sac tumors, mixed germ cell tumors)
    - LFH (dysgerminoma)
    - Inhibin B (granulosa cell tumor)

Risk of Malignancy Tools and Calculators

- Ultrasound evaluation:
  - International Ovarian Tumor Analysis (IOTA) simple rules: 93% sensitivity and 81% specificity for predicting a malignant process

IOTA Simple Rules (2010)
Benign features
Unilocular cyst (any size)
No solid components, or solid components <7mm in diameter
Presence of acoustic shadowing
Smooth multilocular cyst <10cm in diameter
No blood flow
Malignant features
Irregular solid tumor
Ascites
≥ Papillary structures
Irregular solid multilocular tumor, with largest diameter >10cm
Very strong color Doppler flow

Risk of Malignancy Tools and Calculators

- American College of Radiologists Ovarian-Adnexal Reporting and Data System (O-RADS) for Classification of Adnexal Lesions
  - Emerging system, published in 2020
  - Validation study of 1054 adnexal masses, 300 of 304 malignant masses were categorized as O-RADS 4 or 5 -> 98.7% sensitivity and 83.2% specificity for detection of cancer

Category	Description (Risk of Cancer)	Follow Up Recommendations
O-RADS 1	Normal ovary (no risk of cancer)	
O-RADS 2	Almost certainly benign lesion (<1% chance of cancer)	Observation / repeat imaging
O-RADS 3	Low-risk lesion (1 to <10% chance of cancer)	Referral to a specialist
O-RADS 4	Intermediate-risk lesion (10 to 50% chance of cancer)	Referral to a GYN Oncologist
O-RADS 5	High-risk lesion (>50% chance of cancer)	Referral to a GYN Oncologist

Risk of Malignancy Tools and Calculators

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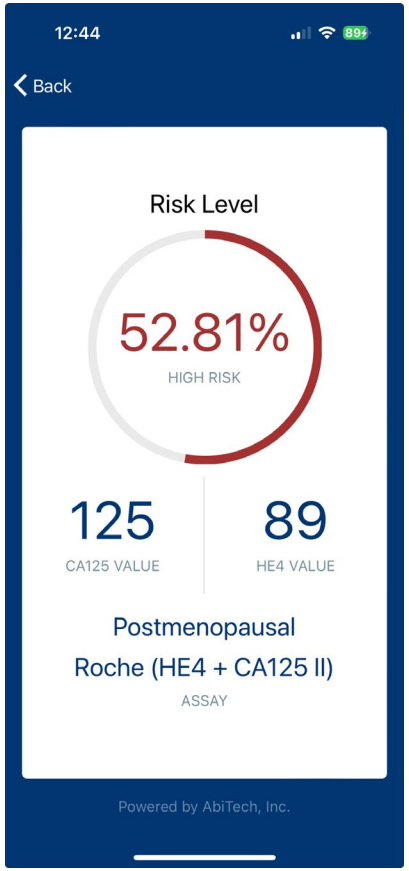
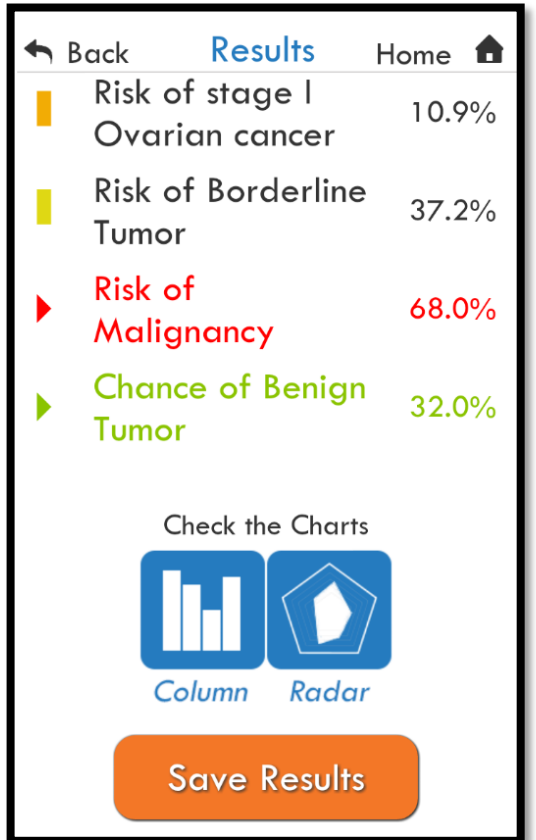
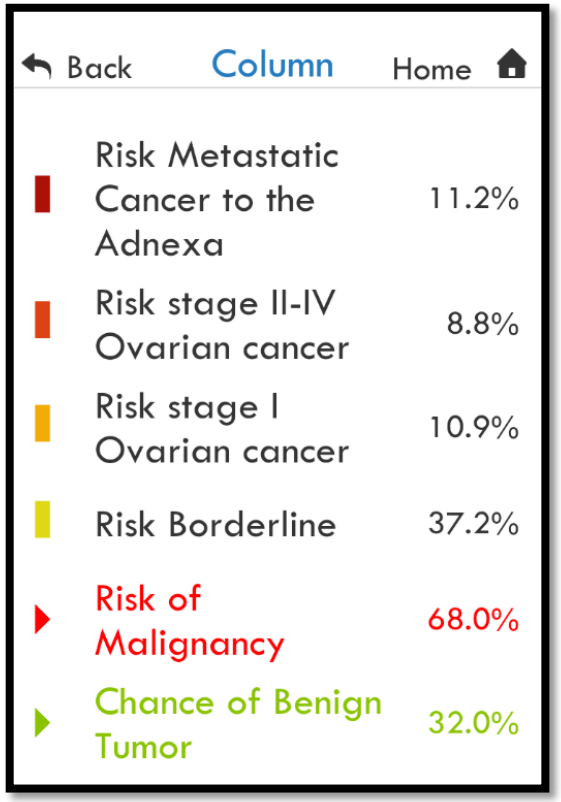
ROMA App: Combines CA-125 level, HE4 level and menopausal status to produce a risk of malignancy percentage; FREE



ADNEX Model: Combines age, CA-125 level, type of center (oncology vs other), max lesion diameter, proportion of solid tissue, # cyst locules, # papillary projections, acoustic shadows, ascites. Currently unavailable.





Commercially Available Multivariate Index Assays

- **OVA1 (Aspira Women's Health Inc)**
  - Serum multivariate index assay; integrates the concentrate of 5 serum proteins: apolipoprotein A-1 (APO-A1), transthyretin (TRF), beta2-microglobulin, transferrin, and CA125-II
  - These inputs are combined by a proprietary support vector machine learning algorithm to generate a unitless score ranging from 1.0 to 10.0.
- **Overa: second-generation index assay, developed to improve the specificity of OVA1**
  - Serum concentrations of APO-A1, TRF, CA125, HE4 and FSH

Putting it all together

OXFORD

JNCI J Natl Cancer Inst (2015) 107(1): dju322

doi:10.1093/jnci/dju322
First published online December 16, 2014
Article

- Microsimulation model to compare 5 referral strategies
  - ACOG guidelines
  - Multivariate Index Assay (MIA) – OVA1
  - ROMA
  - CA-125 alone
  - Referral of all women (“Refer All”)

ARTICLE

Costs, Effectiveness, and Workload Impact of Management Strategies for Women With an Adnexal Mass

Laura J. Havrilesky, Michaela Dinan, Gregory P. Sfakianos, Lesley H. Curtis, Jason C. Barnett, Toon Van Gorp, Evan R. Myers

- Medical costs estimated using Medicare reimbursements; travel costs estimated using SEER-Medicare and State Inpatient Databases
- Refer All was cost-effective compared with less expensive strategies in both pre-menopausal (ICER $9423/year of life saved) and premenopausal (ICER $10 644/YLS) but would result in an additional 73 cases/year/subspecialist
- MIA more expensive and less effective than Refer All
- Authors’ conclusion: If “refer all” is not a viable option, CA125 is an optimal strategy

Special Considerations: Adolescent Patients

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- Usually are benign and can be managed expectantly
- Malignancy is rare: 3 cases per 100,000 children per year
- Less likely to be found incidentally: generally present with pain, menstrual disorders, or precocious puberty
- Imaging and tumor markers remain most important tools for determining risk of malignancy
- Goal in surgical management of adnexal torsion is ovarian preservation
- Pediatric patients with a germ cell malignancy limited to one ovary may undergo fertility-sparing treatment

Special Considerations: Pregnant Patients

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- Usually diagnosed incidentally on routine obstetrical ultrasound
- Most common mass diagnosed in pregnancy: dermoid cyst
- Ovarian cancer may be diagnosed during pregnancy at an earlier stage due to frequency of imaging; ovarian malignancy diagnosed in pregnancy is more likely to be non-epithelial than in the general ovarian cancer population
- Tumor markers including CA-125 and hCG are elevated during normal pregnancy
- Inhibin B, AMH and LDH are not affected by pregnancy
- MRI without gadolinium can be helpful to determine the characteristic of an adnexal mass
- Surgical management of a concerning mass can typically be accomplished laparoscopically in the 2nd trimester

Special Considerations: Patients with Hereditary Ovarian Cancer Syndrome

- When performing risk-reducing salpingectomy or salpingo-oophorectomy in patients with hereditary ovarian cancer syndrome, special steps must be taken:
  - Collection of pelvic washings
  - Complete resection of the fallopian tubes
  - Pathologic examination according to the SEE-FIM (sectioning and extensively examining the fimbriated end) protocol

Table 1. Genetic Mutations Associated With Hereditary Breast and Ovarian Cancer Syndrome

Gene	Breast Cancer Risk	Ovarian Cancer Risk*	Other Cancer Risk
ATM	Increased	No increased risk	Insufficient evidence
BRCA1	Increased	Increased	Prostate
BRCA2	Increased	Increased	Melanoma, pancreas, prostate
BRIP1	No increased risk	Increased	Insufficient evidence
CDH1	Increased	No increased risk	Stomach
CHEK2	Increased	No increased risk	Colon
Lynch Syndrome Genes: *MSH2, MLH1, MSH6, PMS2, and EPCAM*	Insufficient evidence	Increased	Colon, uterine, renal pelvis, small bowel, and others
PALB2	Increased	No increased risk	Unknown
PTEN	Increased	No increased risk	Cowden Syndrome
RAD51C	No increased risk	Increased	Unknown
RAD51D	No increased risk	Increased	Unknown
STK11	Increased risk	Increased risk of sex cord stromal tumors	Peutz–Jehger Syndrome
TP53	Increased	No increased risk	Li–Fraumeni Syndrome

*Includes fallopian tube cancer and primary peritoneal cancer.

Data from National Comprehensive Cancer Network. Genetic/familial high risk assessment: breast and ovarian. Version 2.2017. NCCN Clinical Practice Guidelines in Oncology. Fort Washington (PA): NCCN; 2016. Available at: https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf.

Summary

- Adnexal masses may present with clinical scenarios which require immediate surgical management

- Patients with masses suspicious for malignancy, based on age, menopausal status, imaging characteristics, tumor markers, and / or family history, should be referred to a gynecologic oncologist for management

- Adnexal masses in special populations – including pediatric patients, pregnant patients, and patients at high risk of epithelial ovarian and fallopian tube cancer – require a different decision model for management and may require a lower threshold for referral to a specialist and decision for surgical management

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