Breast cancer, primary peritoneal malignant mixed mullerian tumor and fallopian tube carcinoma: incidental concomitant malignancies or evidence for a new genetic cancer predisposition syndrome?

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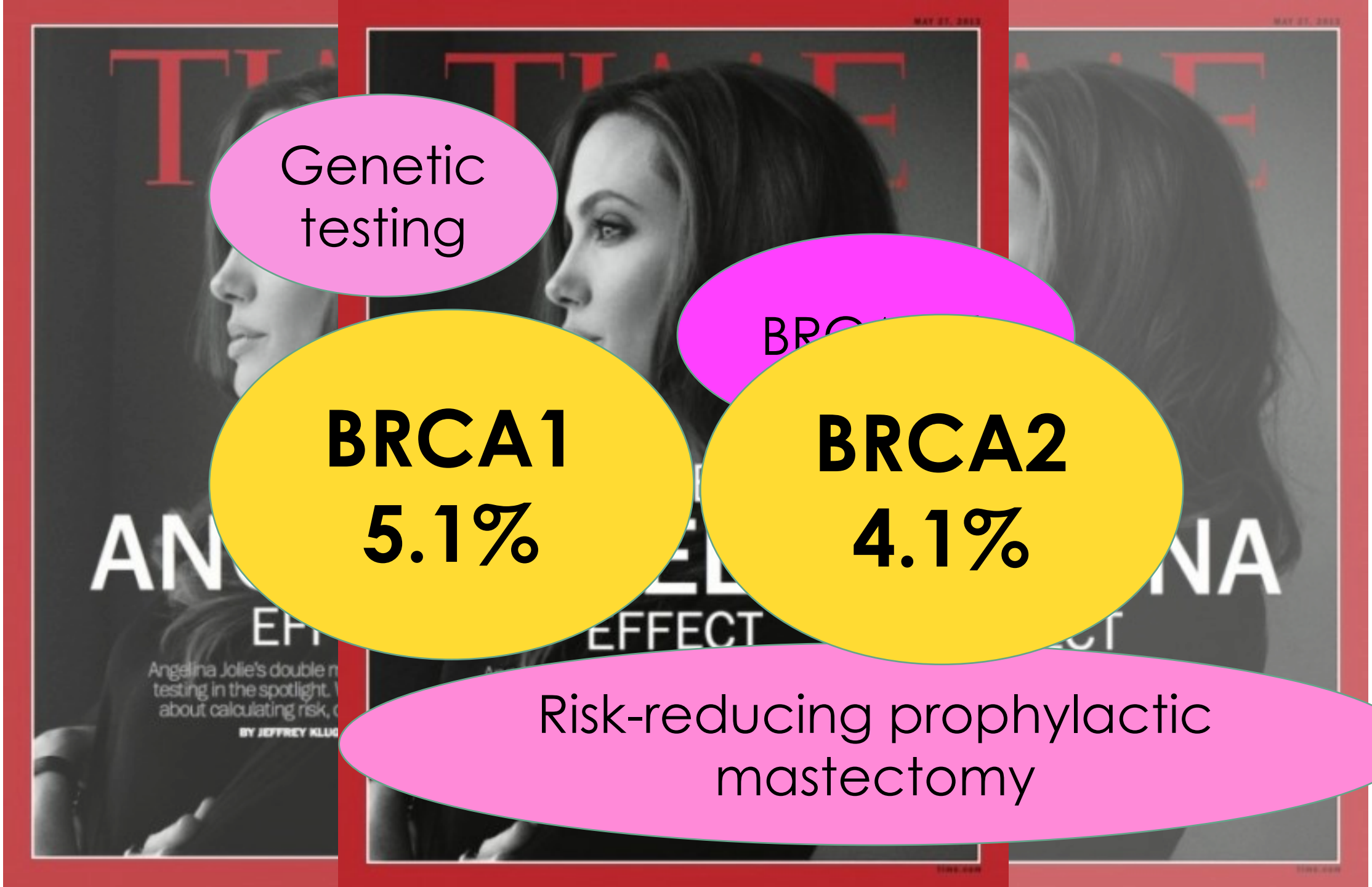
RONALD AUGUSTINE CAMPOS, MD, FPOGS, FSGOP, FPSCPC


Genetic testing
BRCA1
5.1%
BRCA2
4.1%
Risk-reducing prophylactic mastectomy

Known genetic cancer predisposition syndromes linked with gynecologic malignancies

Hereditary breast and ovarian cancer syndrome (BRCA1 and BRCA2 mutations)

Lynch syndrome

Peutz-Jeghers syndrome

Cowden syndrome

Case	Year of Report	Authors	Age	Site
1	1955	Ober and Black	74	Pelvic peritoneum
2	1967	Ferrie and Ross	47	Abdominal retroperitoneum
3	1977	Weiss-Carrington et al.	77	Cecal peritoneum
4	1982	Marchevsky et al.	40	Cul-de-sac periton
5	1983	Herman and Tessler	72	Abdominal posterior peritoneum
6	1984	Hasiuk et al.	77	Abdominal posterior peritoneum
7			67	Rec eritoneum
8			58	Pel ritoneum
9			52	m
10			51	m
11			76	Asc g colon per um
12	1989	Ohno et al.	66	Descending sigmoid colon peritoneum
13	1990	Fenoglio-Preiser et al.	?	Cecal peritoneum
14	1991	Solis et al.	54	Cul-de-sac peritoneum
15	1991	Garde et al.	65	Diaphragm peri
16	1993	Nimaroff et al.	82	Sigmoid colon p
17	1994	Garamvoelgyi et al.	59	Pelvic peritoneu
18	1994	Garamvoelgyi et al.	64	Pelvic peritoneu sac
19	1994	Garamvoelgyi et al.	84	Uterine subserosa
20	1994	Choong et al.	63	Serosa of sigmoid colon
21	1995	Mira et al.	62	Pelvic peritoneum
		l.	83	Cecal peritoneum
		al.	46	Abdominal peritoneum
		al.	57	Cul-de-sac peritoneum
		al.		nd
26	1997	Rose et al.		
27	2001	Shintaku and	51	Retroperitoneum lateral pelvic wall
				Pelvic peritoneum
				Omentum, pelvic peritoneum
				Pelvic peritoneum
	2002			Omentum
31	2002	Wei et al.		
32	2005	Ma-Lee Ko e		
33	2005	Shaco-Levy I		
34	2009	Hussein MR e		
		MR et	76	Pelvic peritoneum
			46	Pelvic peritoneum
		al.		Pelvic peritoneum
		al.	50	Rectal peritoneum
39	2016	Chir R.	57	Abdominal posterior peritoneum

ovarian tumors

endometrial cancer

Primary peritoneal MMMTs

cervical adenocarcinoma

colonic carcinomas

peritoneal serous carcinoma

Case

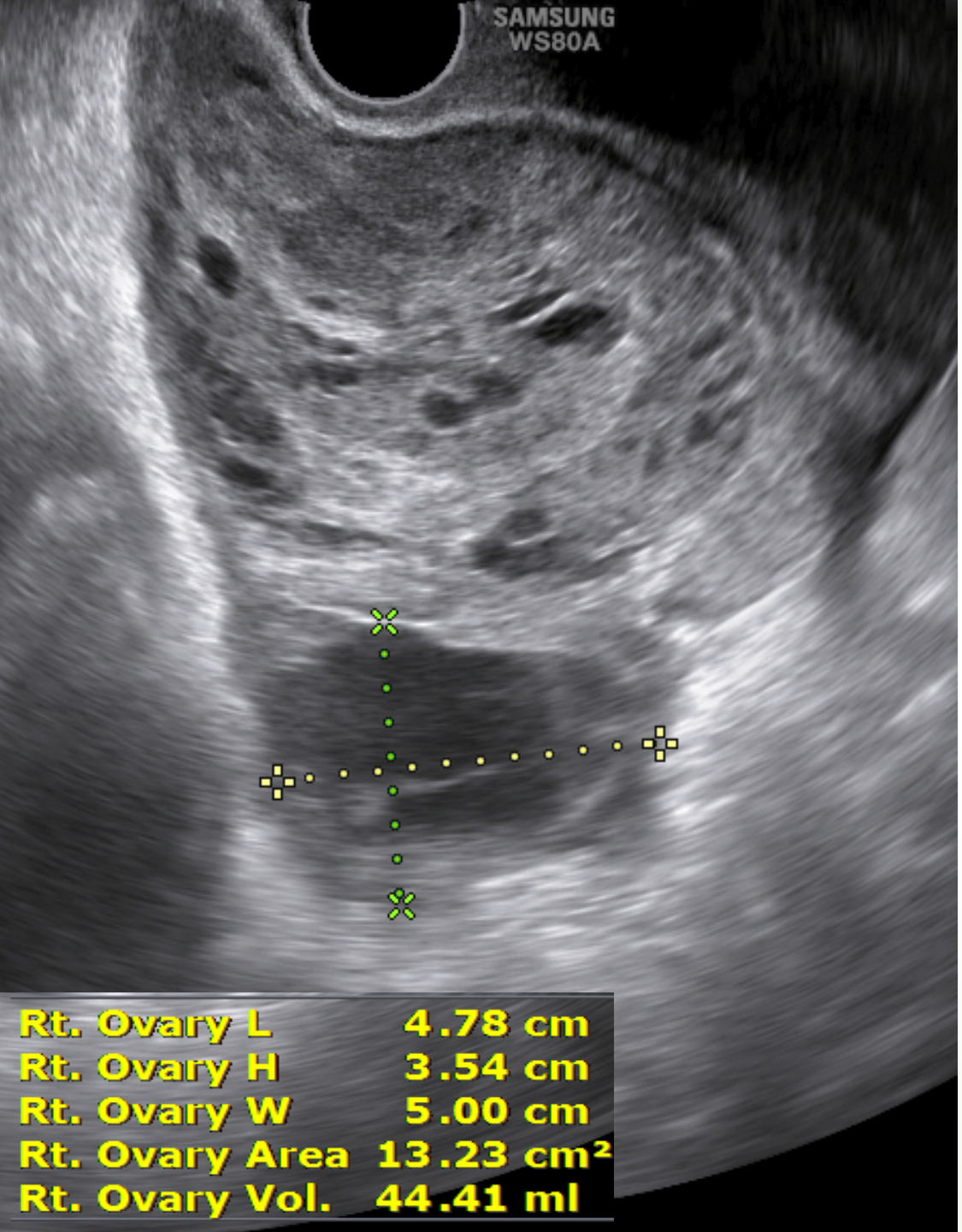
74 year old

G4P4 (4-0-0-4)

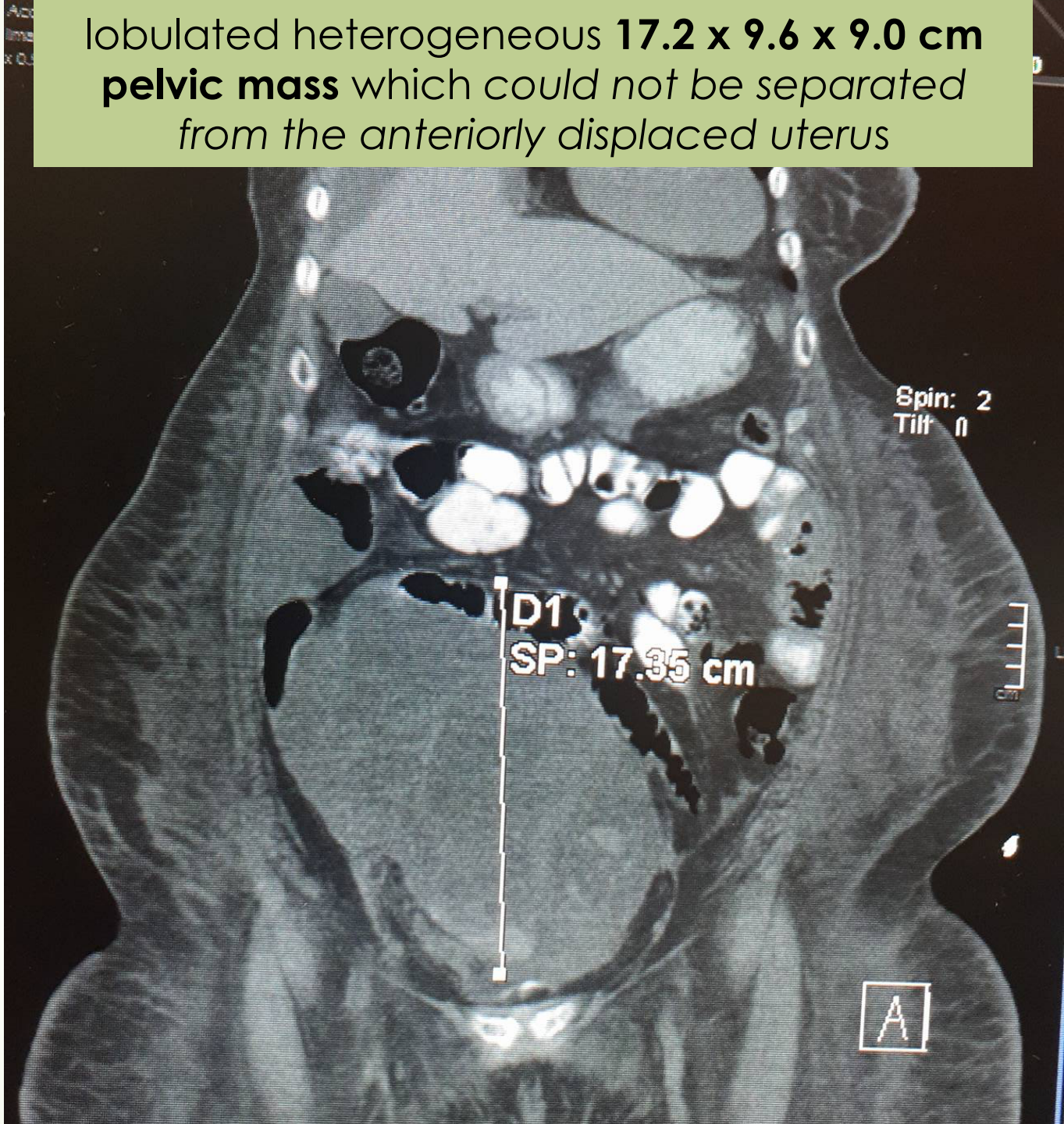
CC: hypogastric pain

Known case of breast cancer, s/p MRM, right, maintained on Anastrozole

Strong family history of malignancy (breast, cervical, RCC)



lobulated heterogeneous **17.2 x 9.6 x 9.0 cm** **pelvic mass** which *could not be separated from the anteriorly displaced uterus*



CA-125
868.1 U/ml

Postmenopausal
ROMA
97.85%

HE4 802.7
pmol/l

CA 15-3 36.9 U/ml
normal range 0.0-31.3 U/ml

Preoperative diagnosis

G4P4 (4-0-0-4) Ovarian new growth, right, probably malignant;
Breast Cancer Stage I, s/p radical mastectomy, right (2016)

Procedure

Radical dissection of adnexal mass with frozen section,

Tumor debulking,

Extrafascial hysterectomy with bilateral salpingooophorectomy,

Anterior and posterior peritonectomy,

Peritoneal fluid cytology,

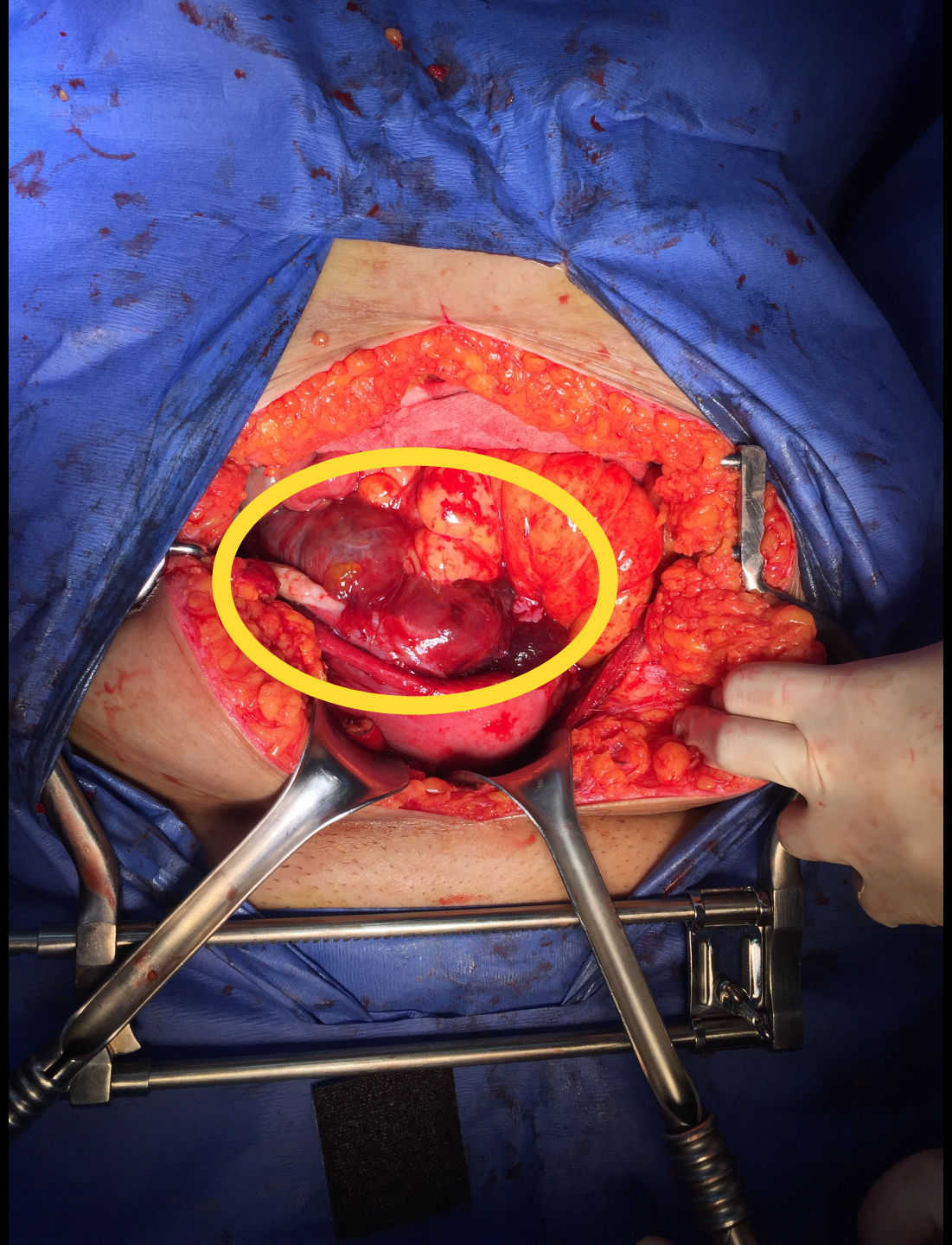
Infracolic omentectomy

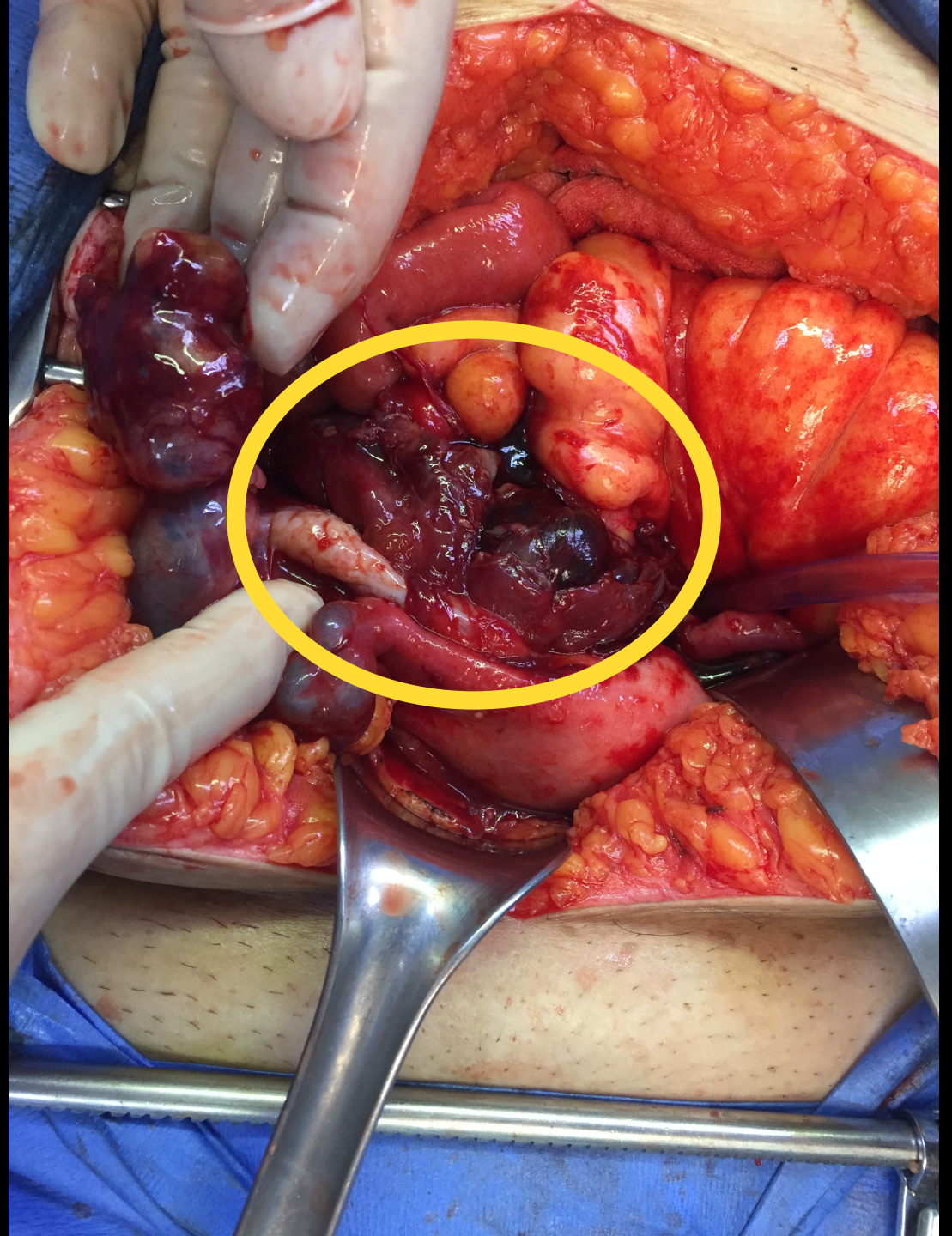
Enterolysis

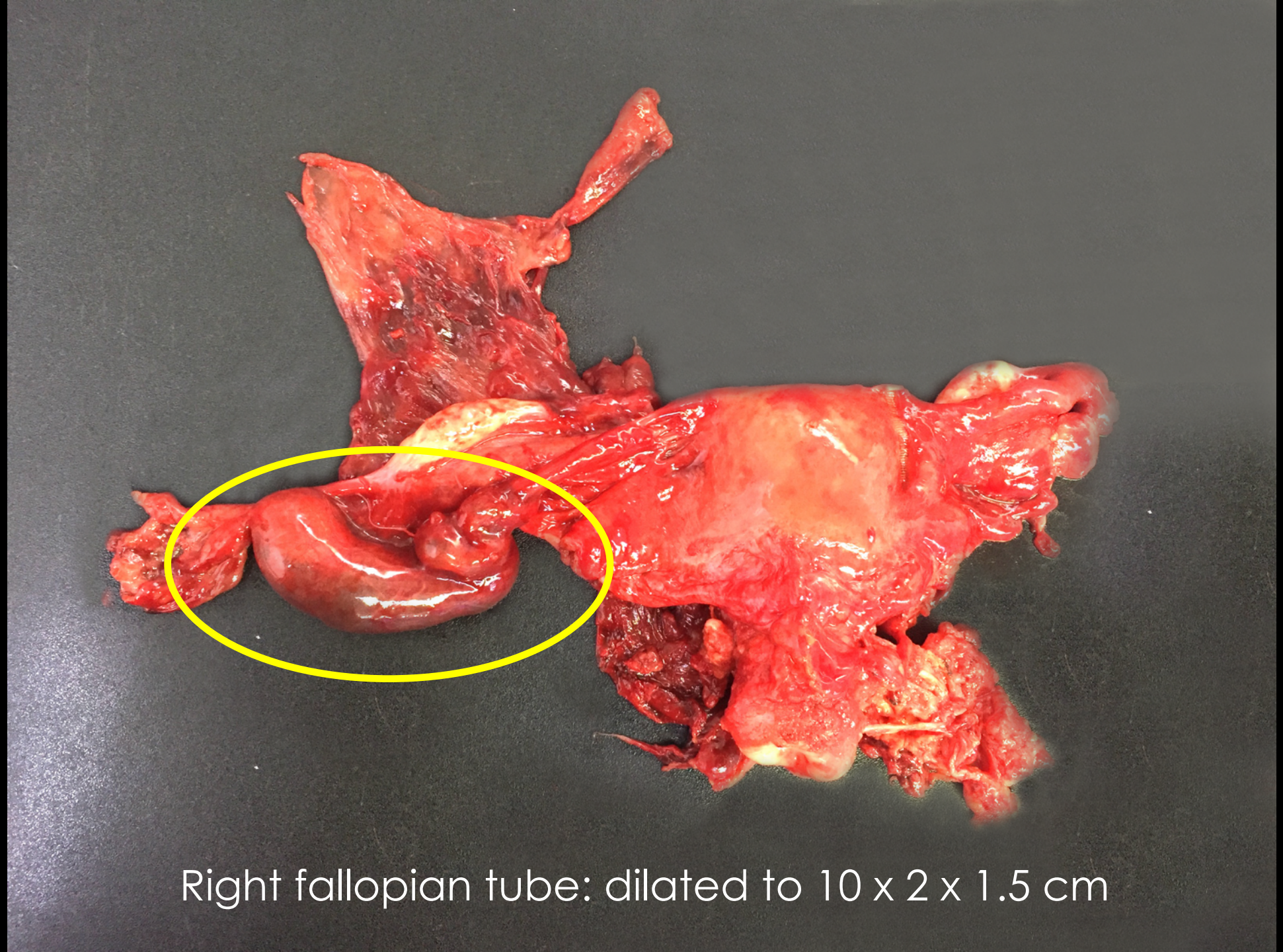
Cystoretrograde pyelography, bilateral,

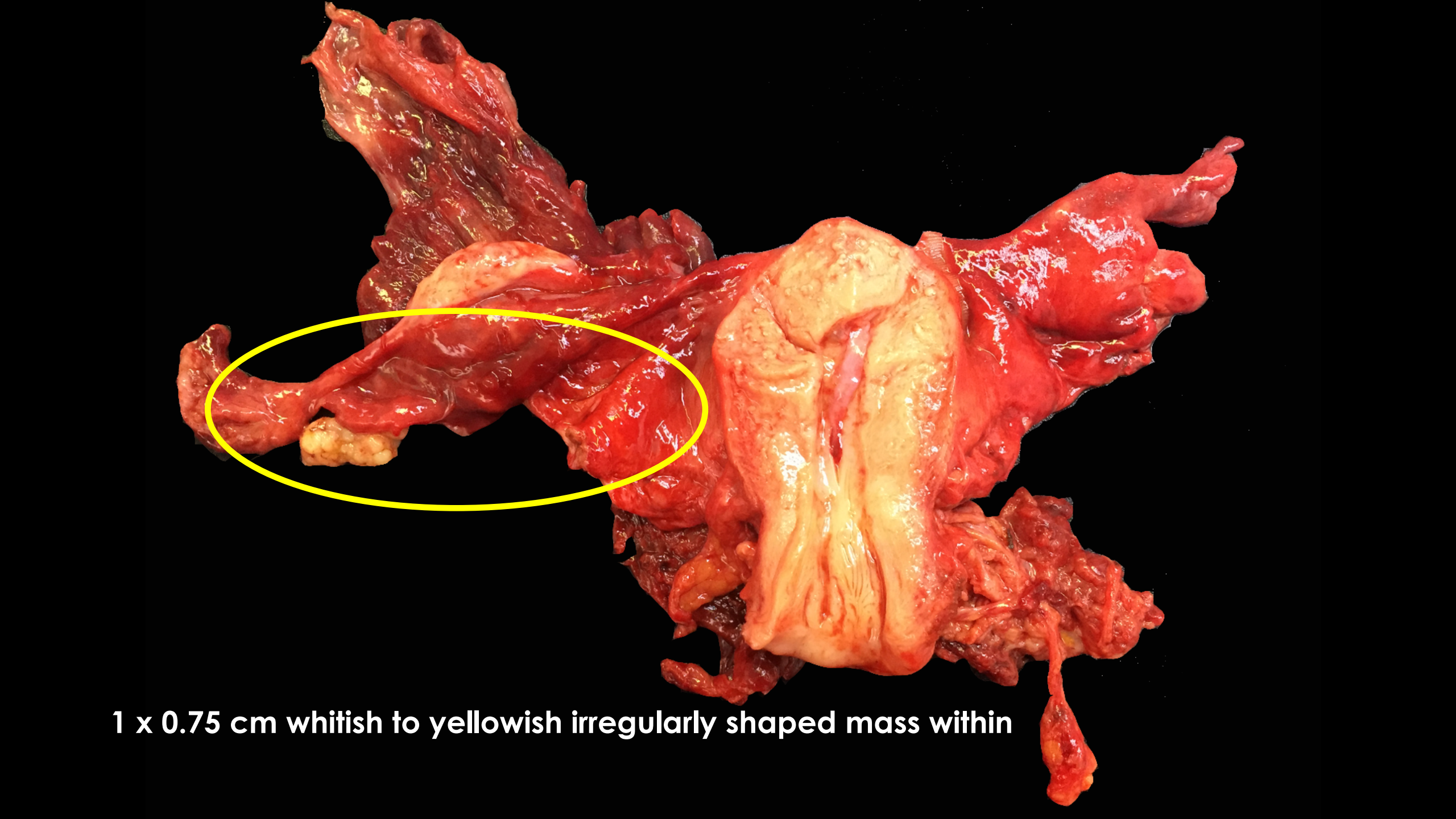
DJ stent insertion, bilateral

under combined general and epidural anesthesia






Right fallopian tube: dilated to 10 x 2 x 1.5 cm



1 x 0.75 cm whitish to yellowish irregularly shaped mass within

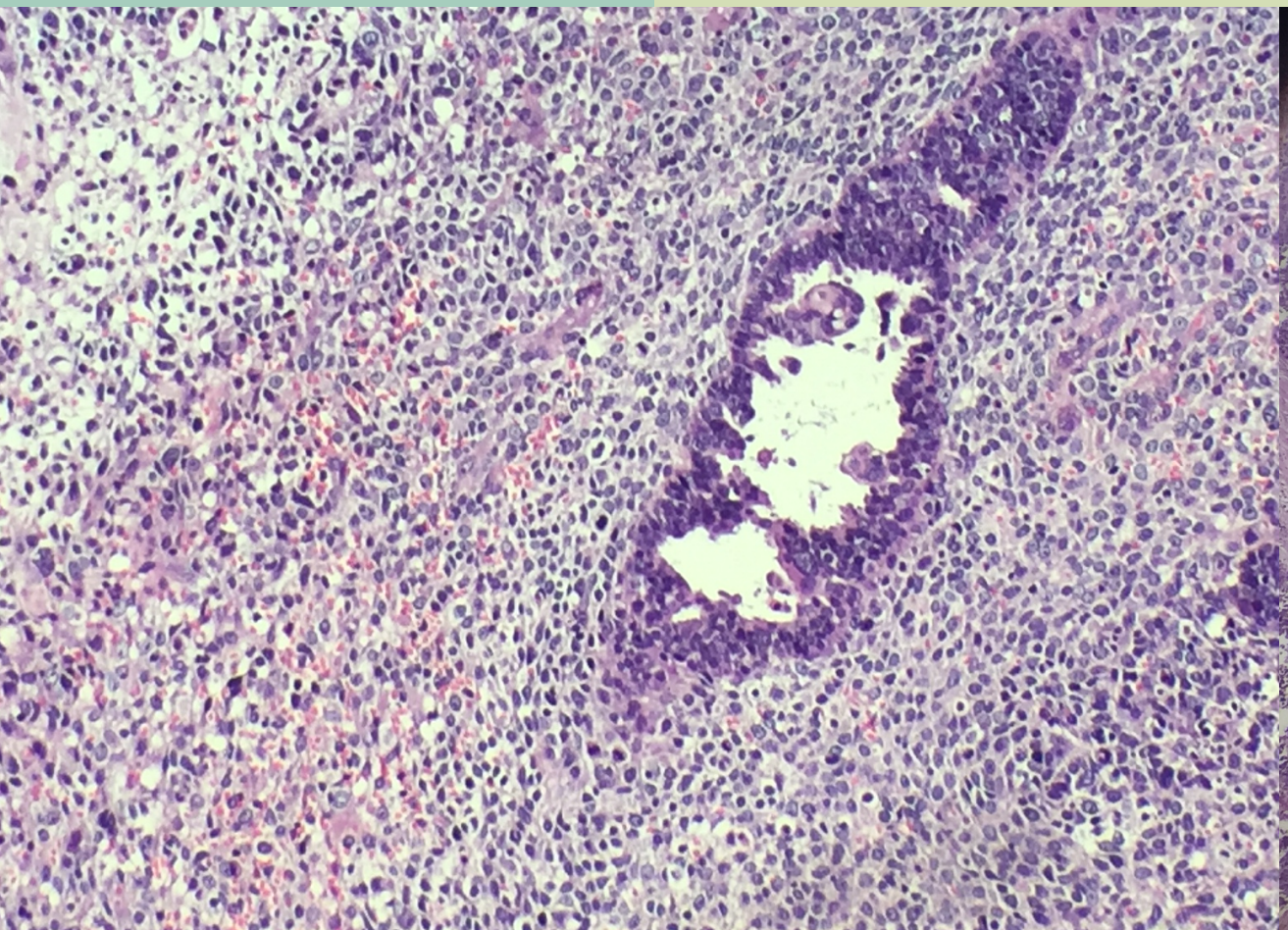
Pelvic mass:

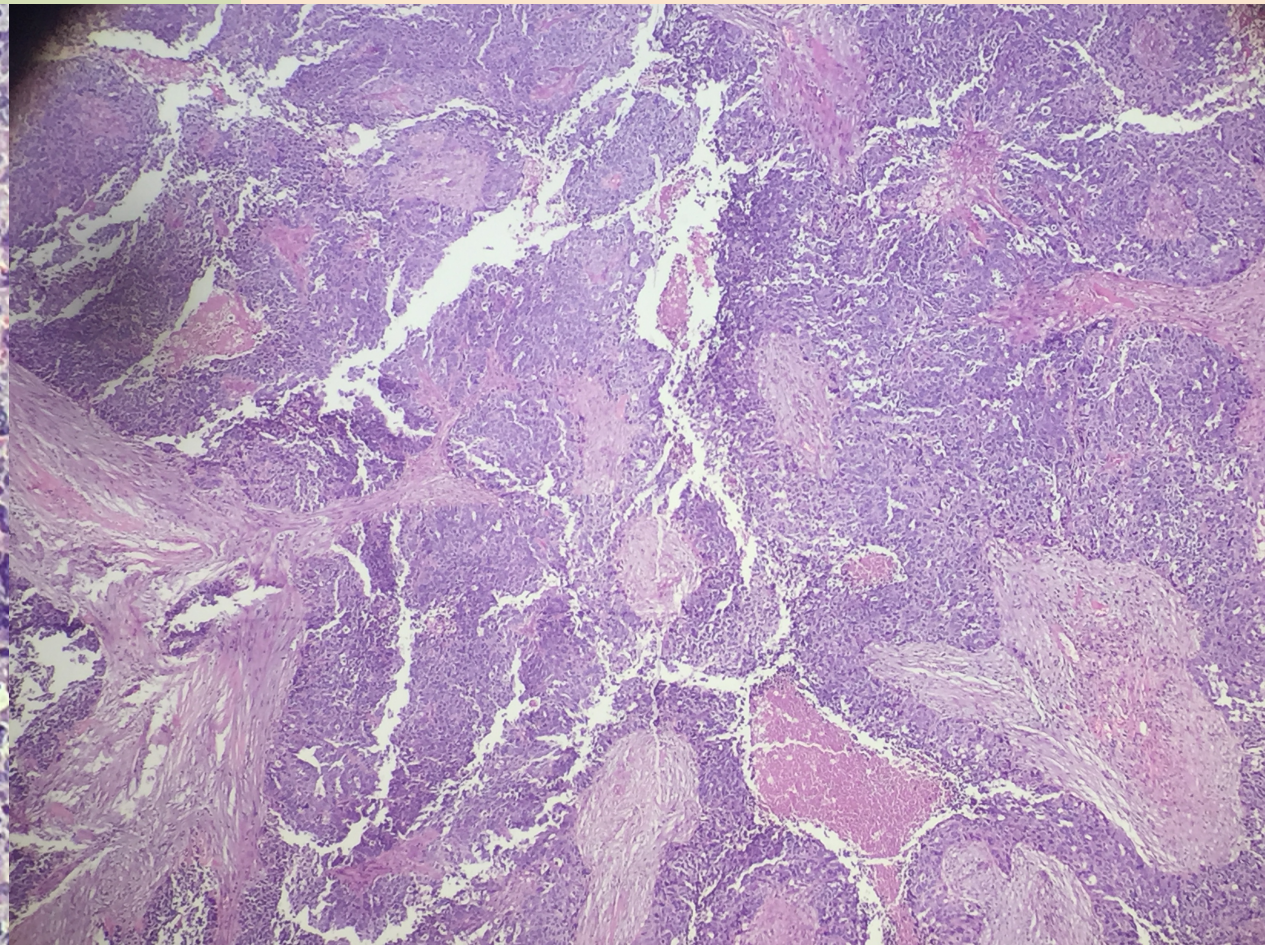
Malignant mixed mullerian tumor

Right fallopian tube:

High grade serous carcinoma, right fallopian tube, with intra-epithelial neoplasia.

Negative for tumor:
right and left ovaries, left fallopian tube, cervix, broad ligament margins, right parametrial margin, omentum, peritoneal fluid cell block





G4P4 (4-0-0-4)
Peritoneal malignant mixed mullerian tumor
High grade serous carcinoma, fallopian tube, stage IIA
Breast cancer stage I, s/p radical mastectomy, right (2016)

Chemotherapy with Carboplatin and Paclitaxel

One patient

3 tumors

*strong family history of cancer

Breast cancer

Fallopian tube carcinoma

Peritoneal malignant mixed mullerian tumor

Case	Year of Report	Authors	Age	Site
1	1955	Ober and Black	74	Pelvic peritoneum
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6	1984	Hasiuk et al.		peritoneum
7	1986	Chumas et al.	67	Rectal peritoneum
8				
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13				
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22	1995	Mira et al.	83	Cecal peritoneum
			46	Abdominal peritoneum
			57	Cul-de-sac peritoneum
			71	Peritoneum of liver and other surfaces
			67	Omentum and peritoneum
27	2001	Shintaku and Matsumoto	51	Retroperitoneum lateral pelvic wall
35	2009	Naniwadekar MR et al.	76	Pelvic peritoneum
36	2009	Uña E et al.	46	Pelvic peritoneum
37	2010	Kurshumliu F et al.		Pelvic peritoneum
38	2011	Huang CC et al.	50	Rectal peritoneum
39	2016	Chir R.	57	Abdominal posterior peritoneum

✓postmenopausal women
✓abdominal pain
✓poor prognosis

✓associated with synchronous/metachronous malignancies
✓Tamoxifen, RT

✗ Breast cancer
✗ Fallopian tube carcinoma
✗ Anastrozole

Three tumors, one gene

Primary Peritoneal

HGSC of the

HGSC of the fallopian tube

Primary peritoneal MMMT

metastasized to the peritoneum

Sarcomatous metaplasia

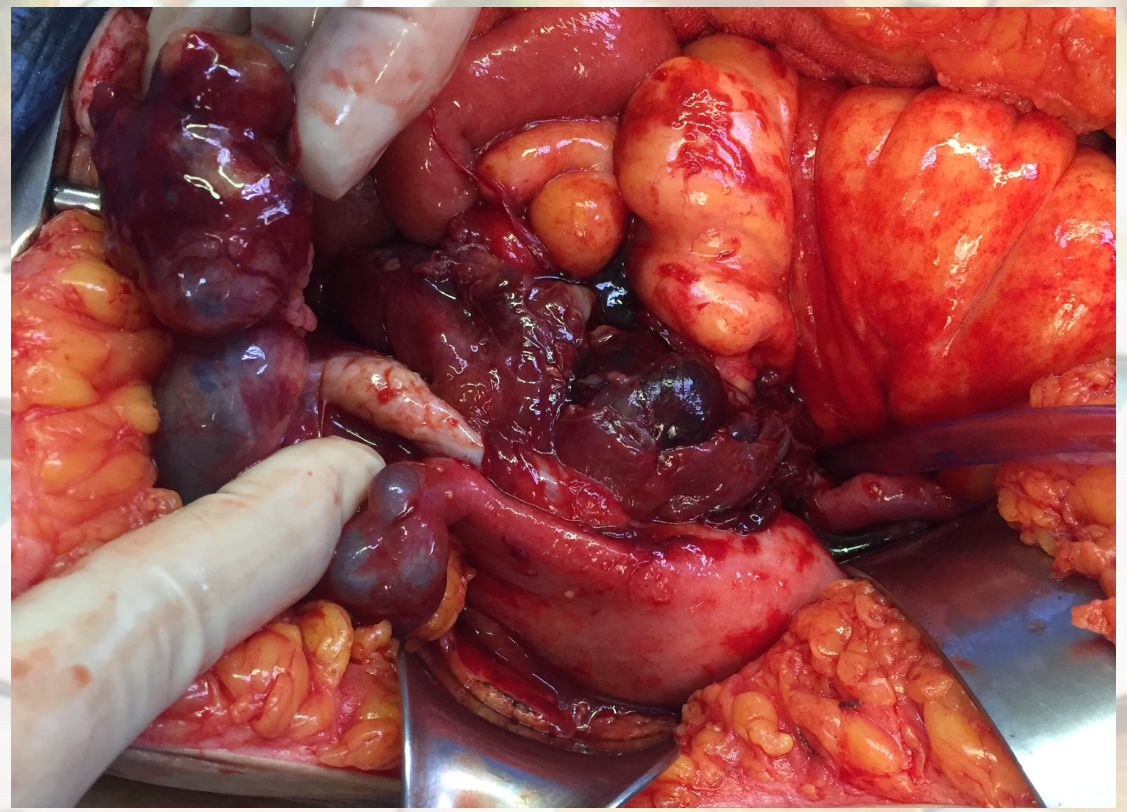
Carcinomatous component metastasized to the fallopian tube

SCENARIO 1

SCENARIO 3?

SCENARIO 2

SCENARIO 3?



- **Coincidence?**
- **New genetic cancer predisposition syndrome?**

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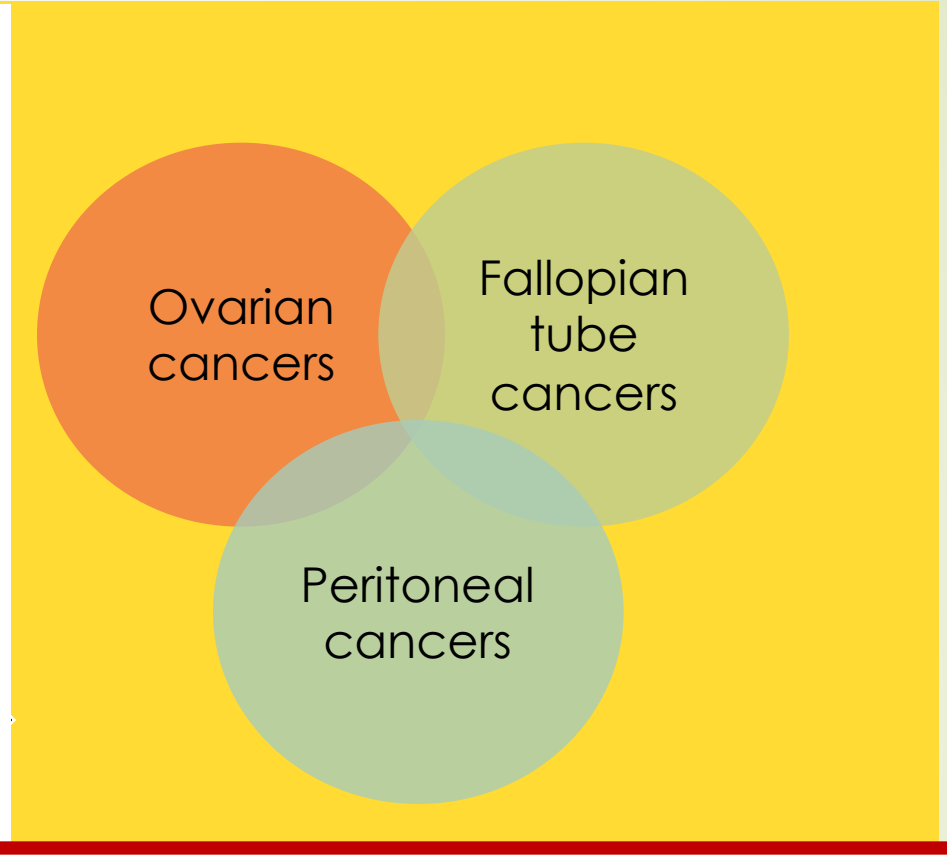
Lancet Oncol. 2008 December ; 9(12): 1191–1197. doi:10.1016/S1470-2045(08)70308-5.

THE CELL OF ORIGIN OF OVARIAN EPITHELIAL TUMORS

Louis Dubeau, MD, PhD
Professor of Pathology, Keck School of Medicine of USC, USC/Norris Comprehensive Cancer Center, University of Southern California, 1441 Eastlake Avenue, Los Angeles, CA 90033

Abstract

Although ovarian epithelial tumors are widely believed to arise in the coelomic epithelium that covers the ovarian surface, it was also suggested that they could instead arise from tissues that are embryologically derived fr… epidemiological and molecu… histopathological observati… predisposition. Morphologi… epithelial tumors that must … reviewed, followed by com… these characteristics. An arg… carcinomas, and primary pe… regarded as a single disease… as of primary ovarian origin… account for an equally signi… components of the secondar…



reviewed, followed by comments about the ability of these two hypotheses to account for each of these characteristics. An argument is made that primary ovarian epithelial tumors fallopian tube carcinomas, and primary peritoneal carcinomas are all mullerian in nature and could therefore be regarded as a single disease entity. Although a significant proportion of cancers presently regarded as of primary ovarian origin arise in the fimbriated end of the fallopian tube, this site cannot account for an equally significant proportion of these tumors, which are most likely derived from components of the secondary mullerian system.

Breast cancer and MMMT

Gynecol Oncol. 2003 Nov;91(2):426-8.

Malignant mixed mullerian tumor of the ovary and bilateral breast cancer: an argument for BRCA3, or a coincidental cluster of unconnected cancers?

Burns BA[1], Geisler JP, Hatterman-Zogg MA, De Young B, Buller RE.

Abstract

OBJECTIVES: Malignant mixed mullerian tumors (MMMTs) of the ovary are a rare, aggressive subtype of ovarian cancer without a clear relationship to familial breast-ovarian cancer syndromes.

CASE: We present the case of a woman with bilateral breast cancers who subsequently developed a stage IIIc MMMT of the ovary. The patient had a first-degree female relative with breast and ovarian cancer (not MMMT), as well as second- and third-degree female relatives each with bilateral breast cancers. BRCA1 and BRCA2 sequencing of germline DNA revealed no evidence of a heritable mutation.

CONCLUSIONS: Ovarian MMMTs may be a hallmark of breast/ovarian cancer secondary to genetic risk independent of classic BRCA1/2 pathways.

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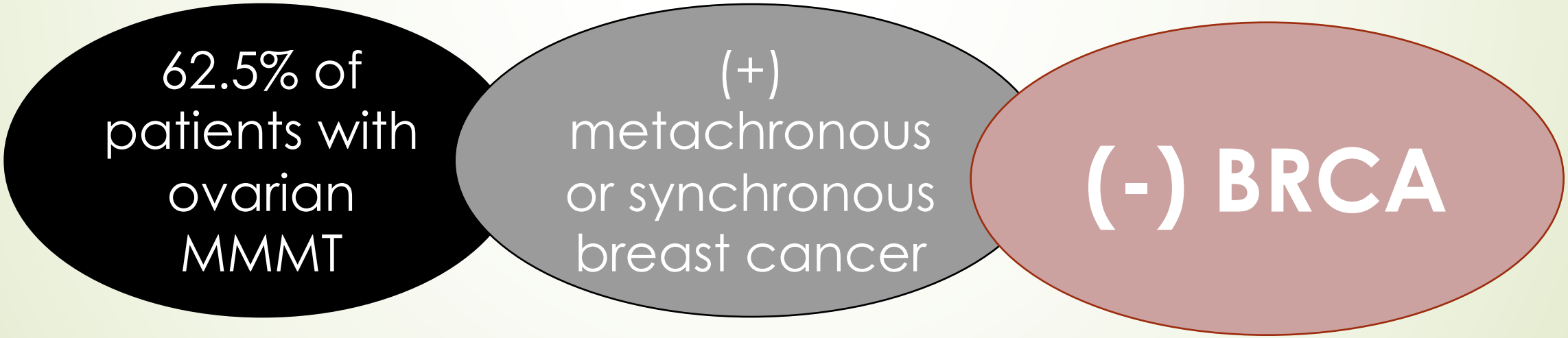
OF CLINICAL ONCOLOGY

Breast Cancer is Common in Women With Ovarian Malignant Mixed Mullerian Tumors

Whynott, Rachel, M., MD; Manahan, Kelly, J., MD; Geisler, John, P., MD

American Journal of Clinical Oncology: March 2018 - Volume 41 - Issue 3 - p 286–288
doi: 10.1097/COC.0000000000000266
Original Articles: Gynecologic




74
malig ancy

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- Dr. Jericho Thaddeus Luna and Dr. Ana Dy Echo
- Dr. Maria Rosario Castillo-Cheng
- Dr. Eileen Grace Tancinco

Primary Peritoneal Malignant Mixed Mullerian Tumor

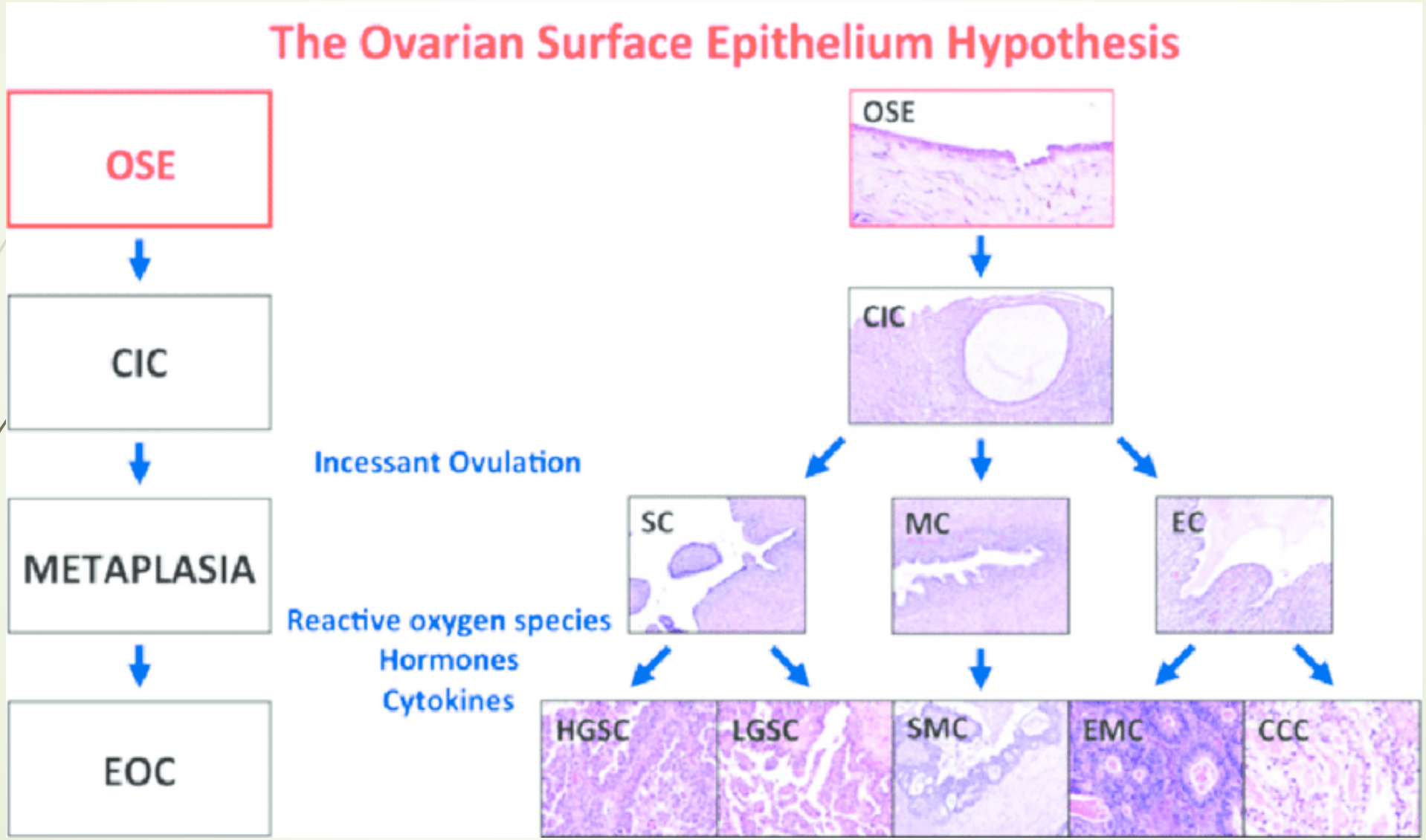
High Grade Serous Carcinoma (HGSC) of the Fallopian Tube

- Both rare gynecologic malignancies

- Since 1955, only 40 reported cases
  - In our institution, only 5 MMMTs in the last 4 years, none of which were peritoneal
  - First primary peritoneal MMMT in Philippine literatiure
- "carcinosarcoma"
- from the endometrium, endocervix, fallopian tube or the peritoneum

- Incidence: 0.1-1.8% of all gynecologic malignancies
  - In the Philippines: only 4 reported cases
  - In our institution: only 7 documented cases since 2006
- has taken center stage in the paradigm shift in the tumorigenesis of ovarian cancer

Traditional ovarian carcinogenesis: *a story of metaplasia*



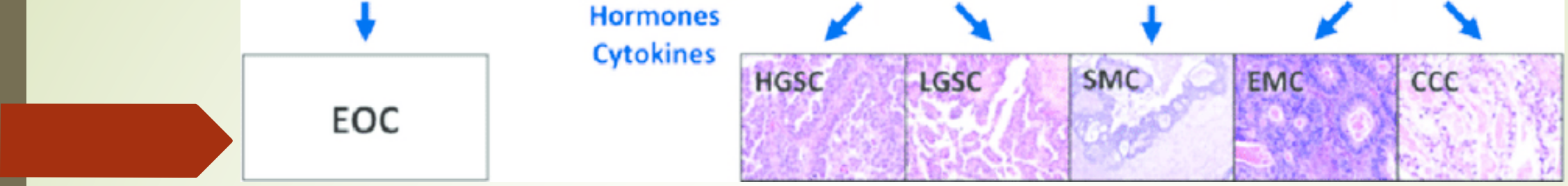
Accepting the theory of multifocal tumorigenesis from tissue of the same embryologic origin opens a window of speculation …

One patient

3 tumors

***strong family history of cancer**

- **Breast cancer**
- **Fallopian tube carcinoma**
- **Peritoneal malignant mixed mullerian tumor**



serous

fallopian tube

endometrioid

endometrium

clear cell

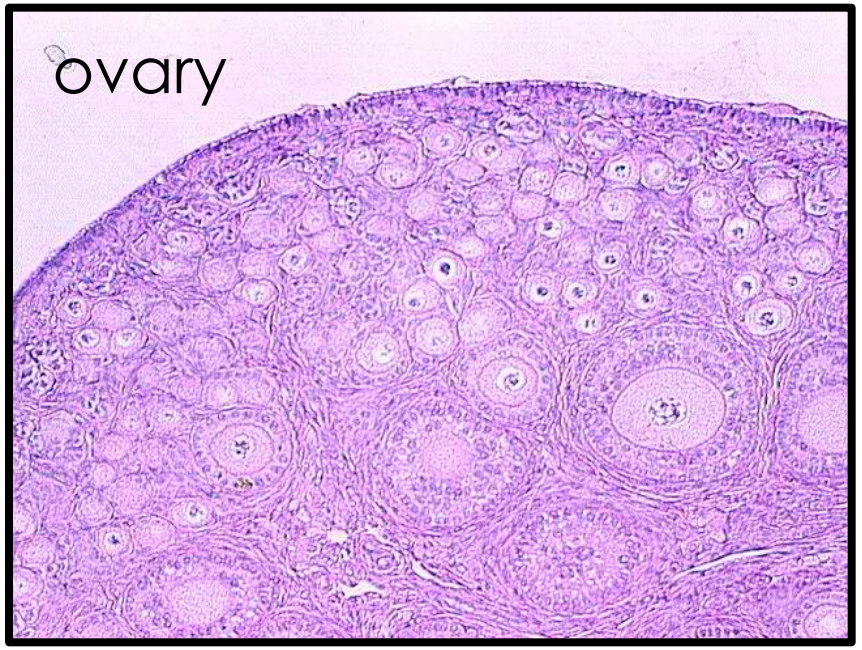
GI tract

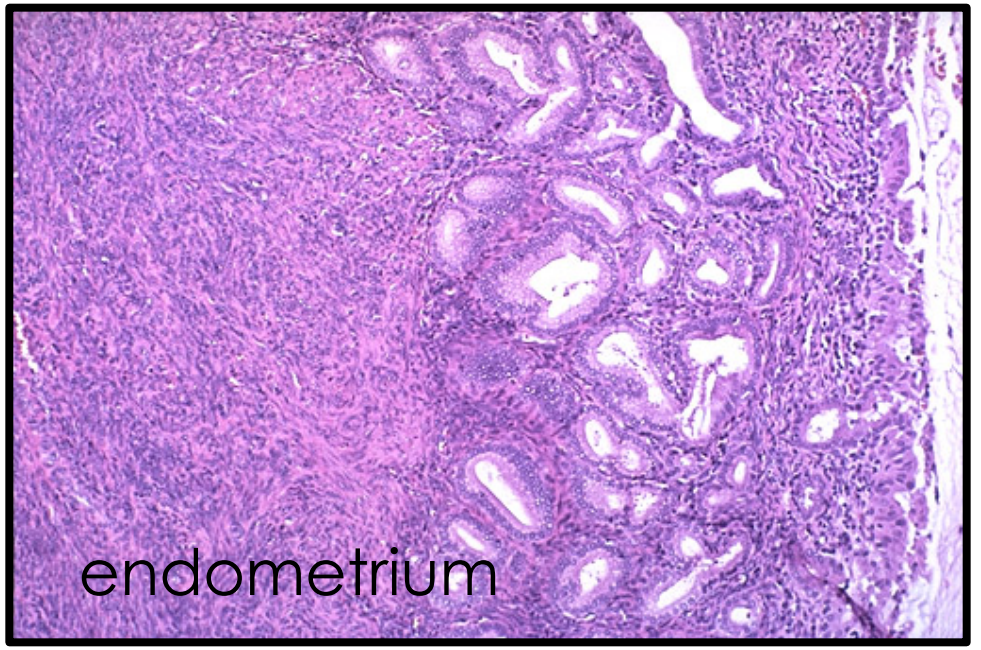
mucinous

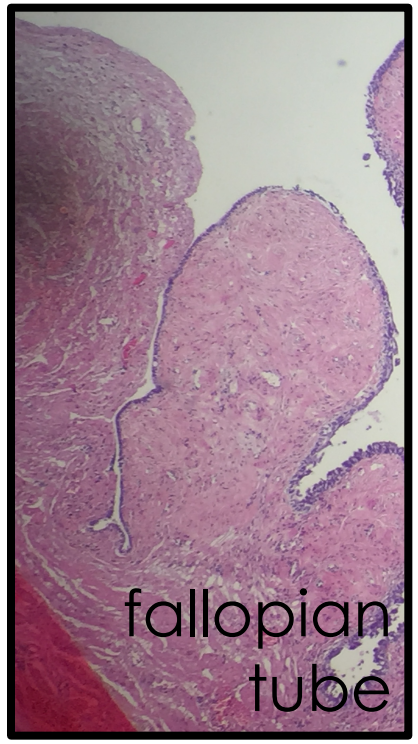
endocervix

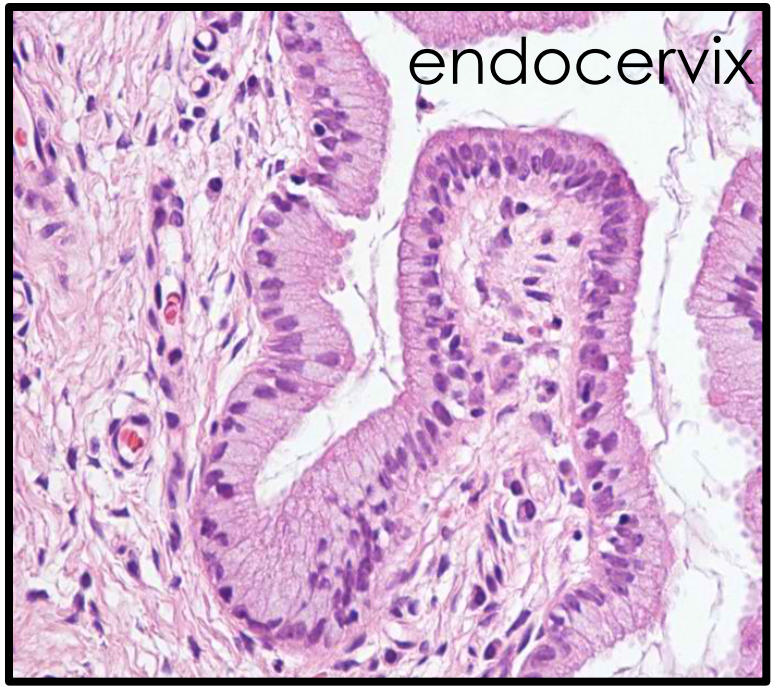
transitional cell tumors

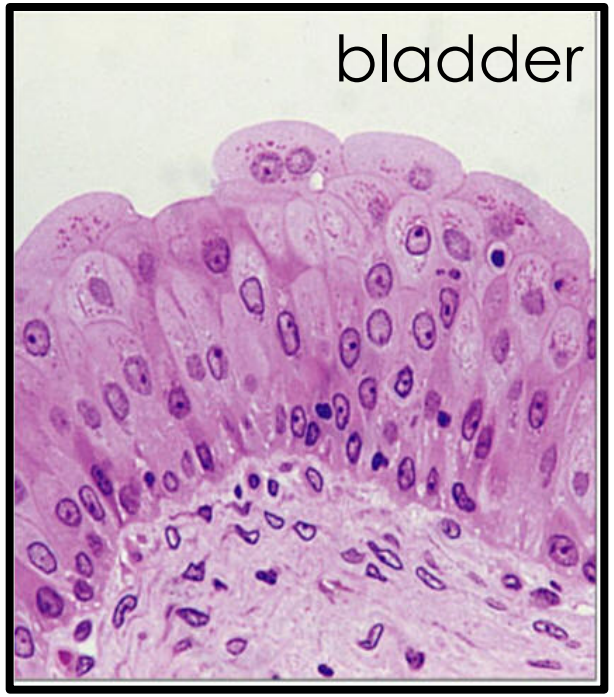
Urinary bladder

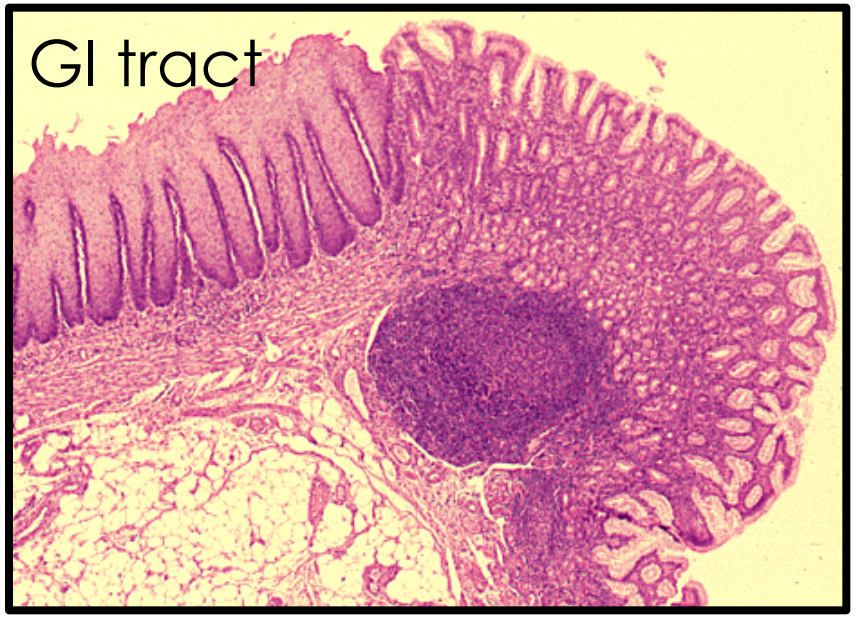

ovary

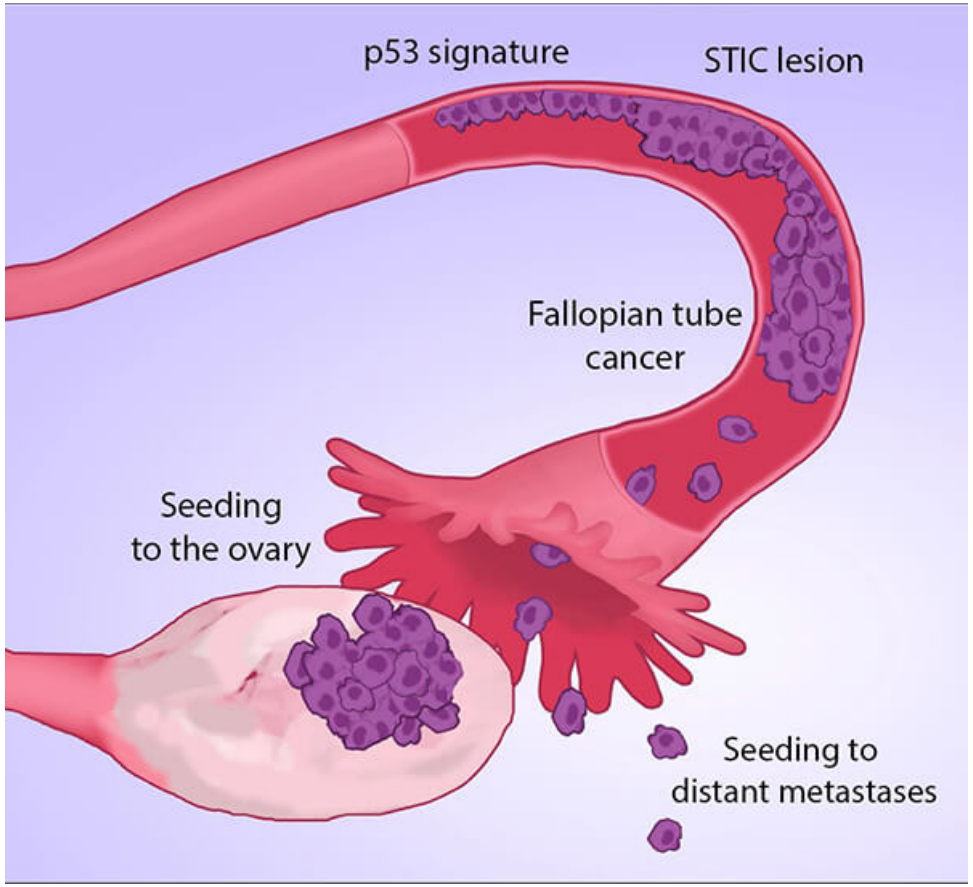

endometrium

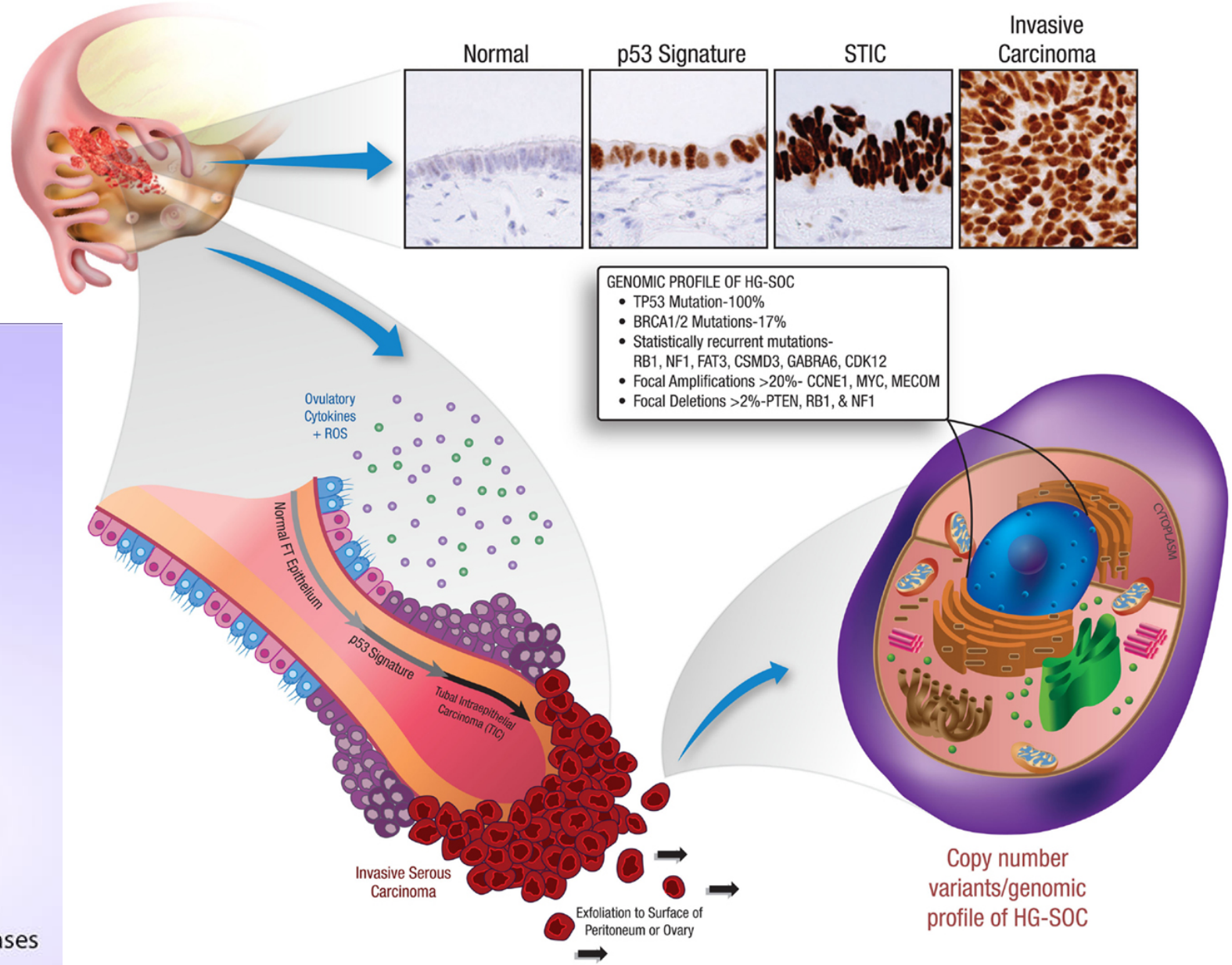

fallopian
tube


endocervix


bladder


GI tract


p53 signature
STIC lesion
Fallopian tube cancer
Seeding to the ovary
Seeding to distant metastases


Normal
p53 Signature
STIC
Invasive Carcinoma
GENOMIC PROFILE OF HG-SOC
• TP53 Mutation-100%
• BRCA1/2 Mutations-17%
• Statistically recurrent mutations- RB1, NF1, FAT3, CSMD3, GABRA6, CDK12
• Focal Amplifications >20%- CCNE1, MYC, MECOM
• Focal Deletions >2%-PTEN, RB1, & NF1
Ovulatory Cytokines + ROS
Normal FT Epithelium
p53 Signature
Tubal Intraepithelial Carcinoma (TIC)
Invasive Serous Carcinoma
Exfoliation to Surface of Peritoneum or Ovary
CYTOPLASM
Copy number variants/genomic profile of HG-SOC

Classification of Ovarian Cancer based on Molecular Genetic Features
Kurman RJ et al.

Type I Ovarian Tumors
Low grade serous carcinoma
Low grade endometrioid
Clear cell
Mucinous
Transitional (Brenner) carcinoma

Type II Ovarian Tumors
High grade serous carcinoma
Undifferentiated carcinoma
Malignant mixed mesodermal tumors

Lack TP53 mutations

indolent in behavior
usually confined to the ovary upon presentation

With TP53 mutations

more aggressive
present in advanced stages

Hereditary syndromes:

On BRCA and Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)

BRCA 1

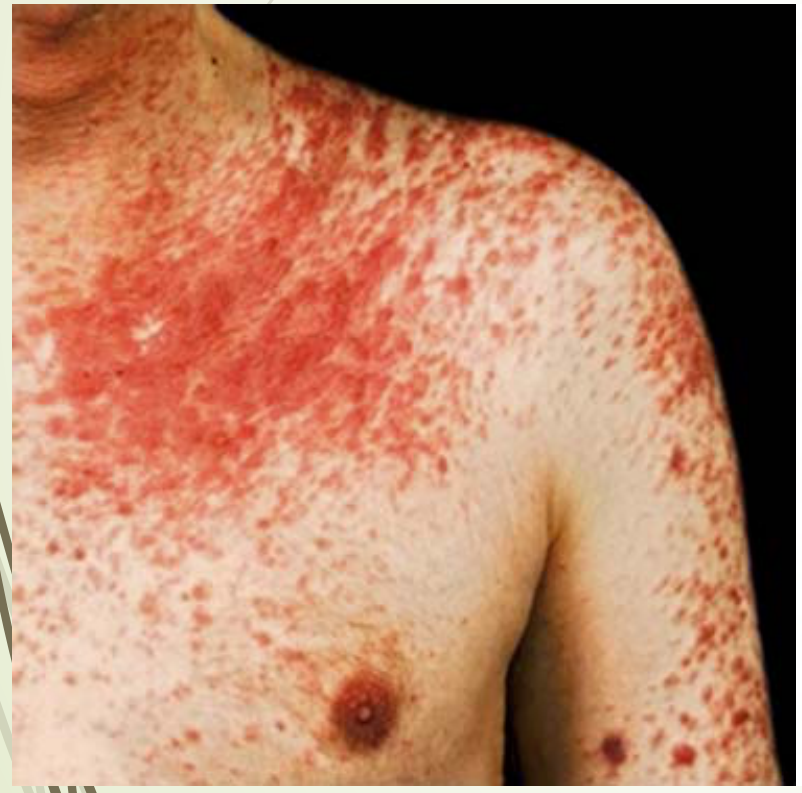
- Ovarian cancer risk 40-50% higher

BRCA 2

- Ovarian cancer risk 10-20% higher

Other associations: fallopian tube, peritoneal, prostate, colon andpancreatic cancer

Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)



Major criteria (high likelihood of HLRCC)

- Multiple cutaneous leiomyomata with at least one biopsy proven/ histologically confirmed

Minor criteria (suspicious for HLRCC)

- Solitary cutaneous leiomyoma and family history of HLRCC
- Early onset renal tumors of type 2 papillary histology
- Multiple early onset (<40 years) symptomatic uterine fibroids

Definitive diagnosis

- Positive germline *FH*-mutation test