XX Congreso Chileno de Anatomia Patologica

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Carcinomas de Ovario: al menos 5 enfermedades diferentes

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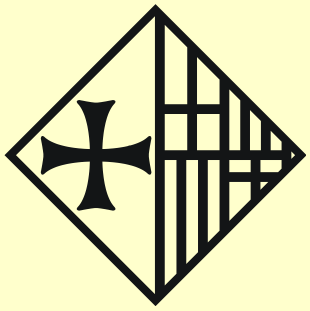
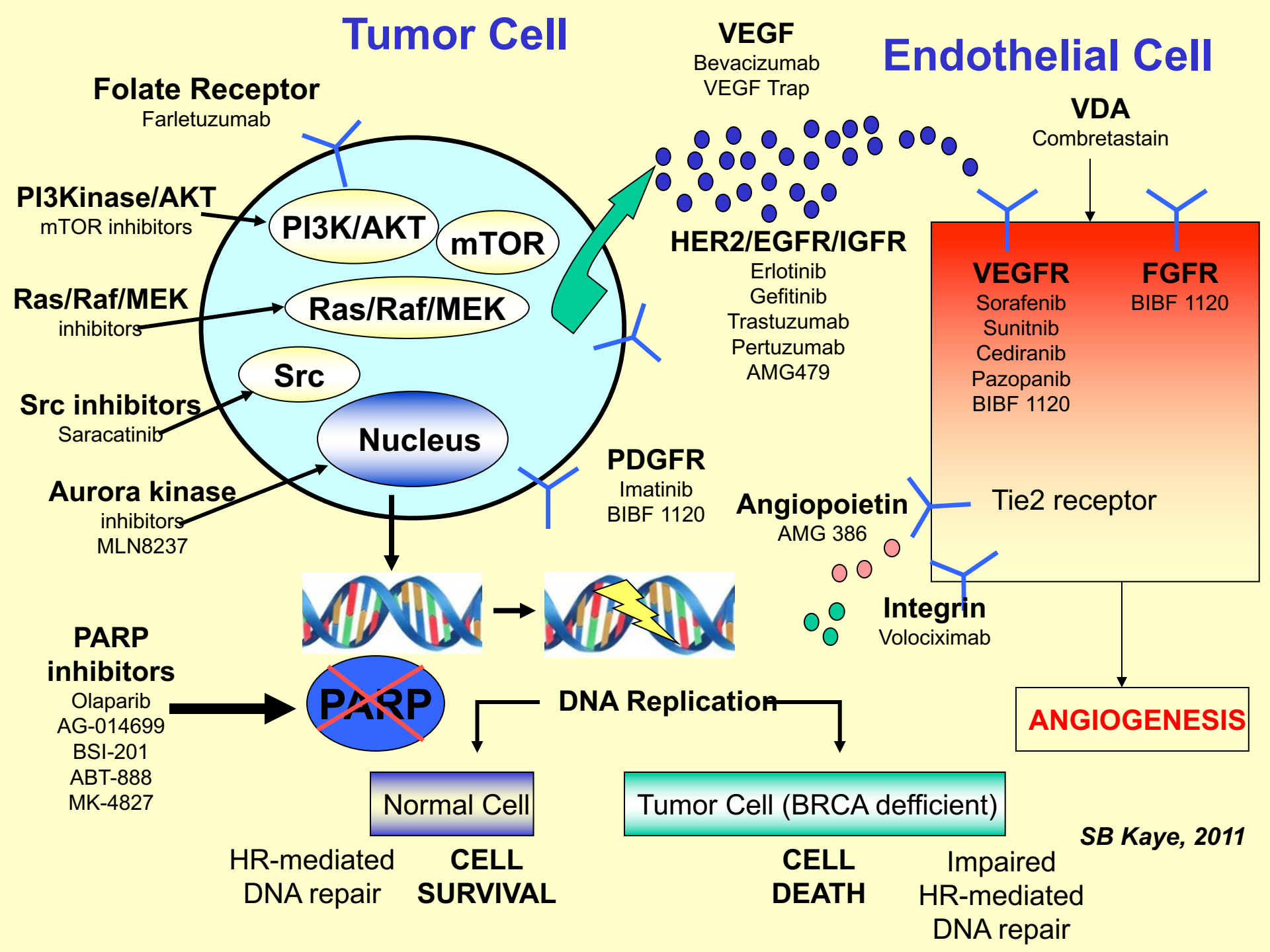
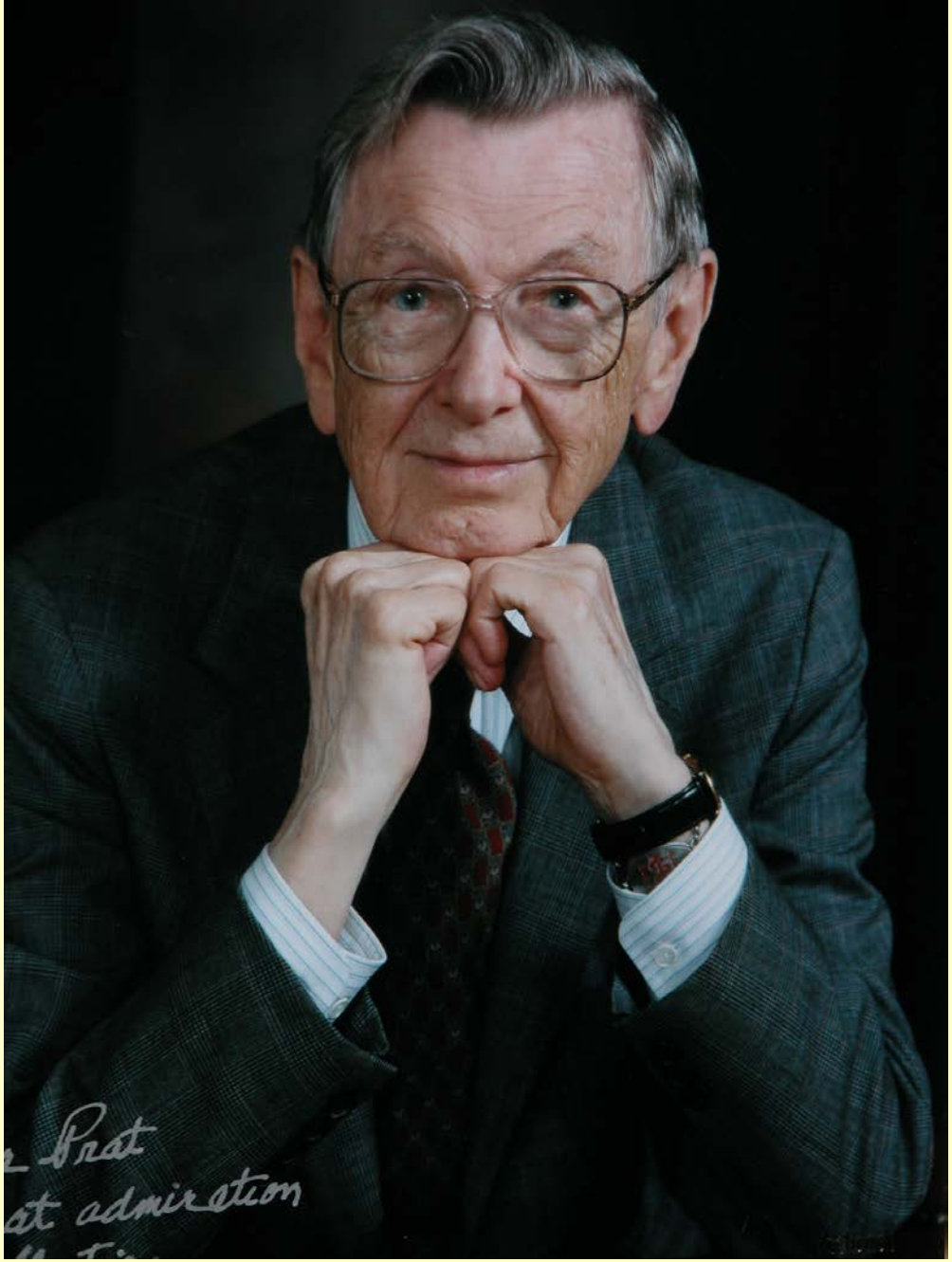


Cancer de Ovario
The Clinical Problem

- **250,000 women diagnosed yearly worldwide**
- **75%** patients present with advanced stage disease
- **80%** respond to chemotherapy
- Vast majority of patients relapse and eventually develop drug resistant disease
- Overall survival over last 30 years: minimal increase
- 160,000 deaths yearly (2010)
- Highest mortality rate for gynecologic cancers in the world
- All ovarian cancers treated with surgery/chemotherapy


Tumor Cell
Endothelial Cell
Folate Receptor
Farletuzumab
VEGF
Bevacizumab
VEGF Trap
VDA
Combretastain
PI3Kinase/AKT
mTOR inhibitors
PI3K/AKT
mTOR
Ras/Raf/MEK
inhibitors
Ras/Raf/MEK
Src
Src inhibitors
Saracatinib
Nucleus
Aurora kinase
inhibitors
MLN8237
HER2/EGFR/IGFR
Erlotinib
Gefitinib
Trastuzumab
Pertuzumab
AMG479
VEGFR
Sorafenib
Sunitnib
Cediranib
Pazopanib
BIBF 1120
FGFR
BIBF 1120
PDGFR
Imatinib
BIBF 1120
Angiopoietin
AMG 386
Tie2 receptor
Integrin
Volociximab
PARP inhibitors
Olaparib
AG-014699
BSI-201
ABT-888
MK-4827
PARP
DNA Replication
ANGIOGENESIS
Normal Cell
Tumor Cell (BRCA defficient)
HR-mediated DNA repair
CELL SURVIVAL
CELL DEATH
Impaired HR-mediated DNA repair
SB Kaye, 2011

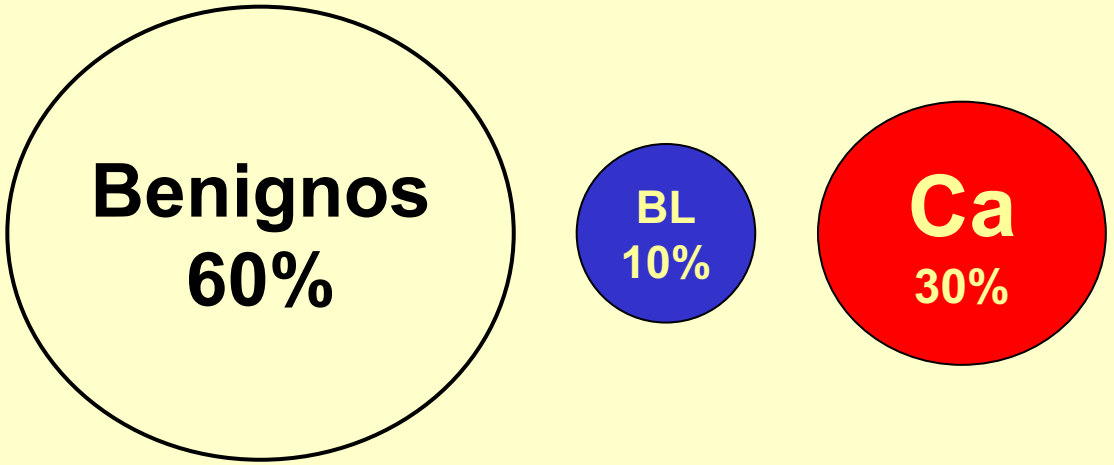


Robert E. Scully 1921-2012

Tumores Ováricos Epiteliales

OMS 1973-2014

Serosos
Mucinosos
Endometrioides
Células claras
Transicionales
Escamosos
Mixtos
Indiferenciados



Histopatología
Inmunohistoquímica
Genética molecular

Han identificado varias (5) enfermedades distintas cuya genesis pone en duda conceptos tradicionales sobre el cáncer de ovario

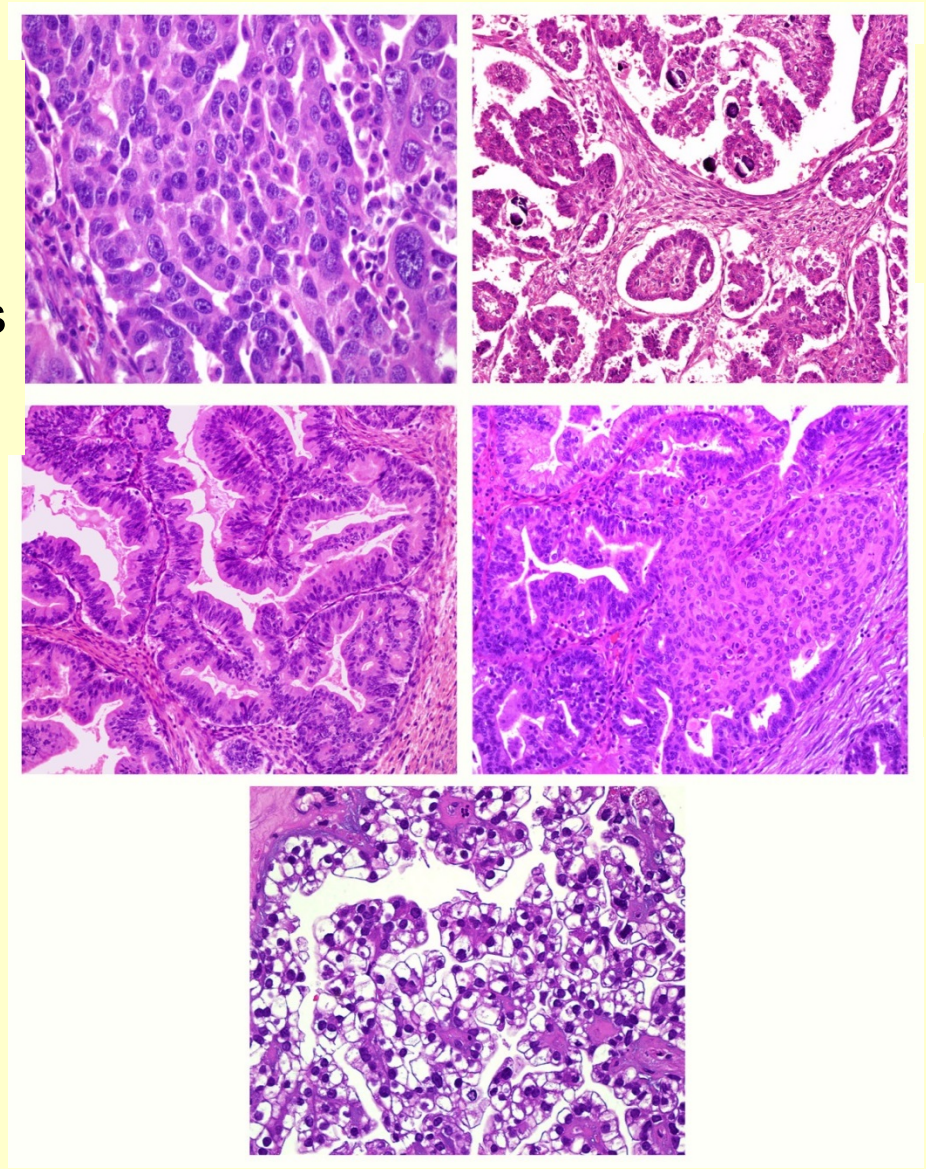
- **HG-Serous**

  Genomic chaos

  P53, *BRCA*

- **Mucinous**

  Abnormal *RAS*
  ERBB2



- **LG-Serous**

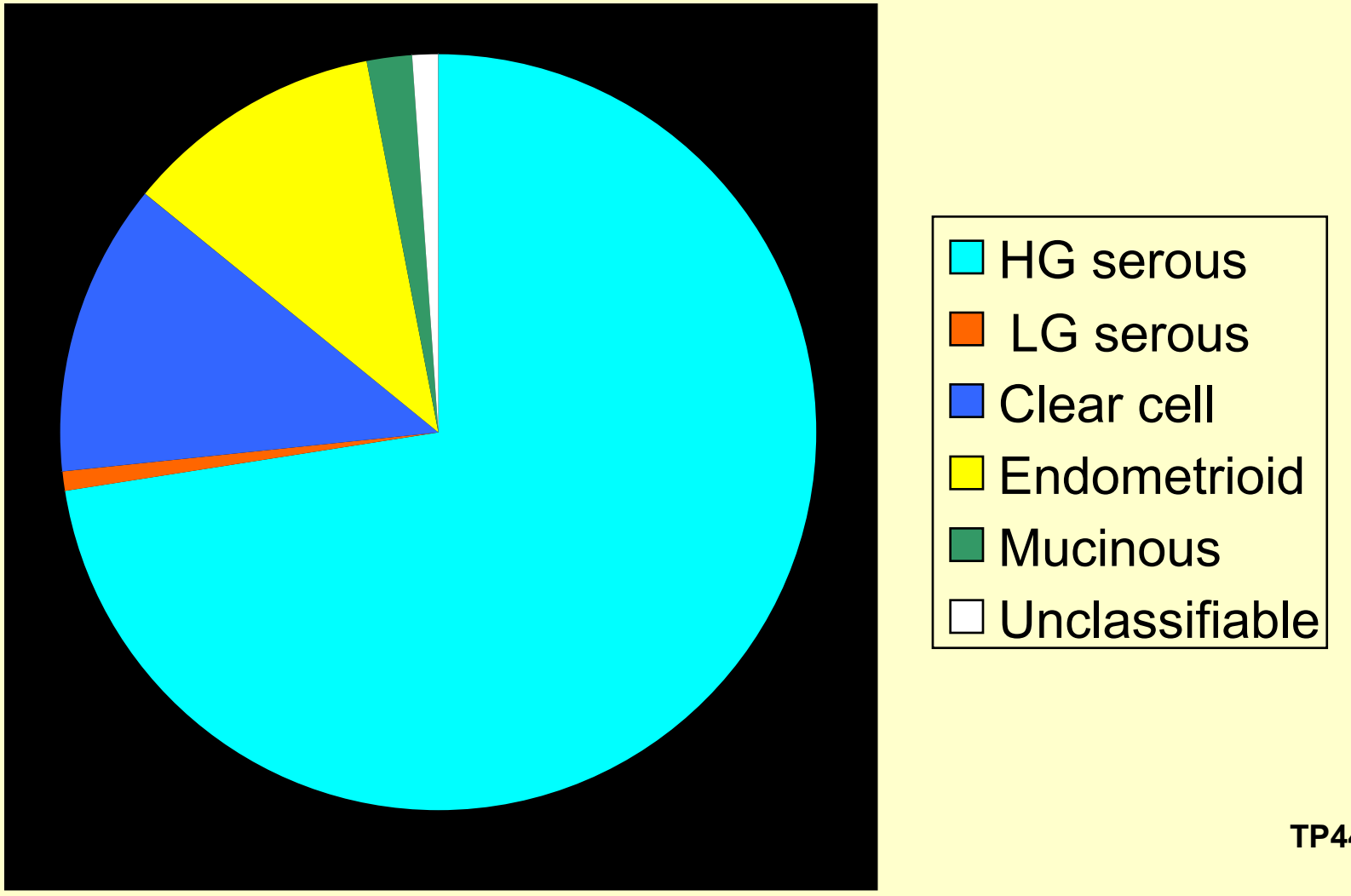
  MAPK pathway
  (*KRAS*, *BRAF*)

- **Endometrioid**

  Abnormal
  PTEN,PI3K,AKT
  signaling

- **Clear cell** – A disease of
  ARID1A

Nueva Clasificación: Frecuencia



TP44

Estos tipos se distinguen entre sí en cuanto a:

1. Factores de riesgo y lesiones precursoras
2. Modos de diseminación
3. Alteraciones geneticas
4. Respuesta a la quimioterapia
5. Pronóstico

Obviamente, son enfermedades distintas

Carcinoma Seroso
(de Alto Grado)

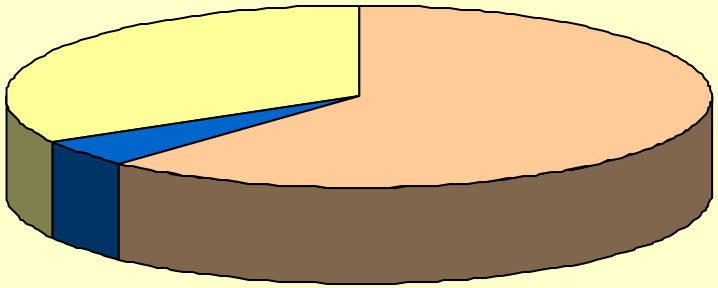
Donde y cómo se origina el CSAG?

- Mesotelio de la superficie ovárica (quistes corticales de inclusión) → Metaplasia (mulleriana) tubárica → Carcinoma
- Implantación de epitelio tubárico en el ovario (endosalpingiosis) → Carcinoma
- Transformación maligna del epitelio tubárico → carcinoma seroso intraepitelial de la trompa (STIC) → diseminación

HEREDITARY SUSCEPTIBILITY TO OVARIAN CANCER

BRCA2 (30%)

Lifetime risk 15-30%

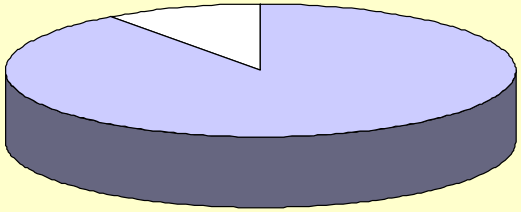


BRCA1 (65%)

Lifetime risk 30-60%

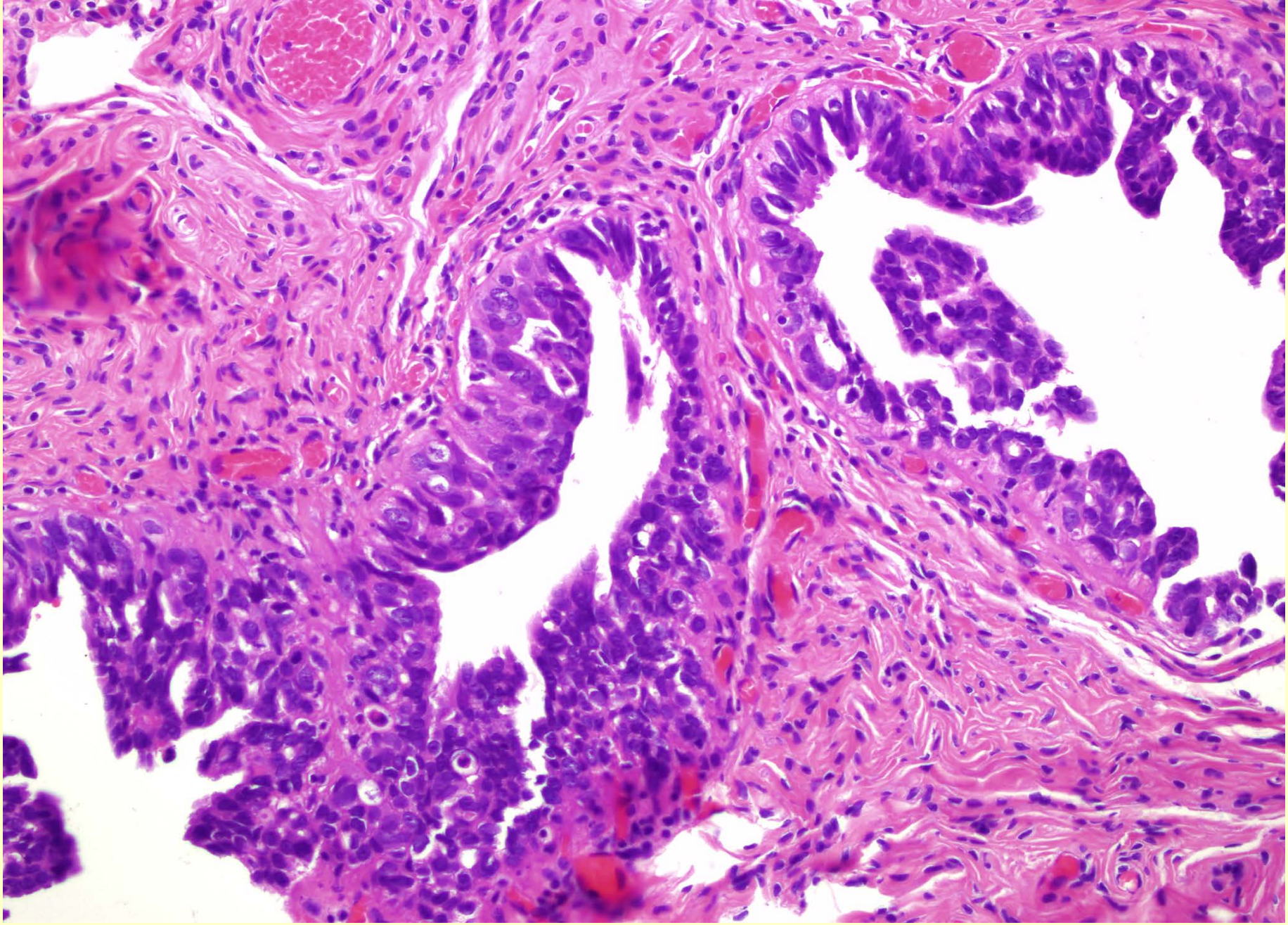
HNPCC (7%)

Hereditary (10%)



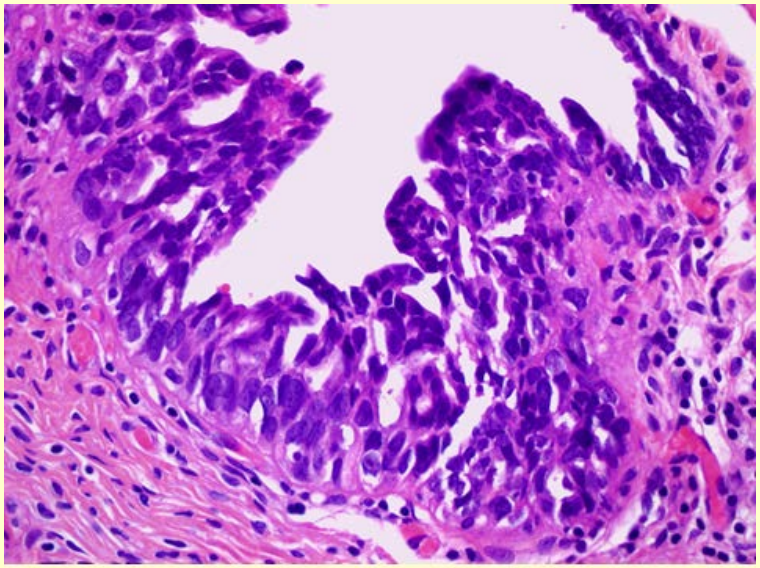
Sporadic (90%)

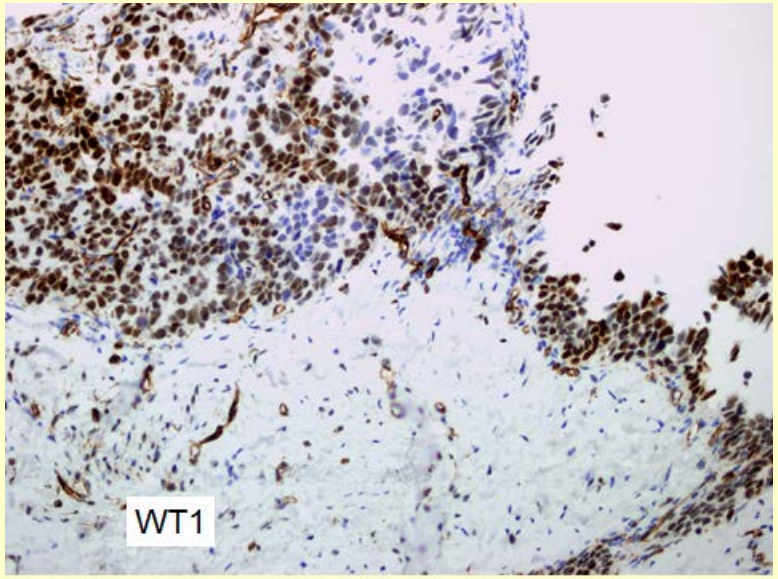
Rebbeck TR, Lynch HT, et al. NEJM 2002

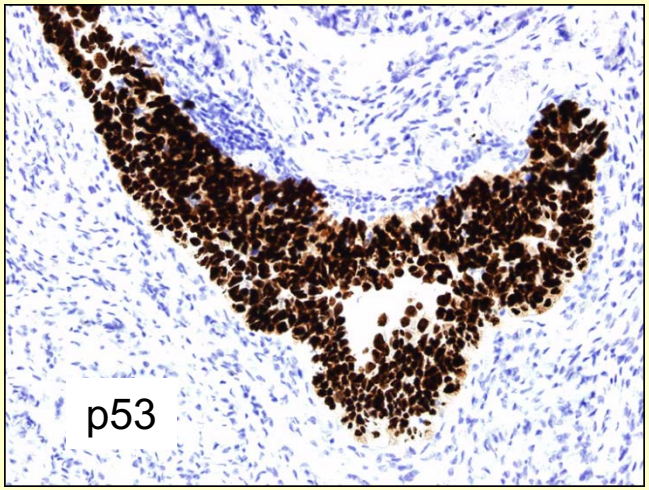


Fallopian Tube Fimbria (STIC)

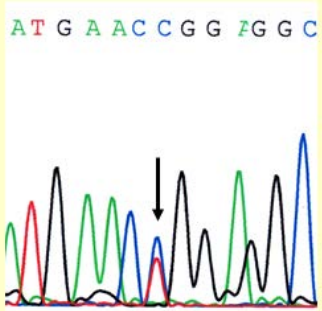
Serous “Intraepithelial” Carcinoma STIC

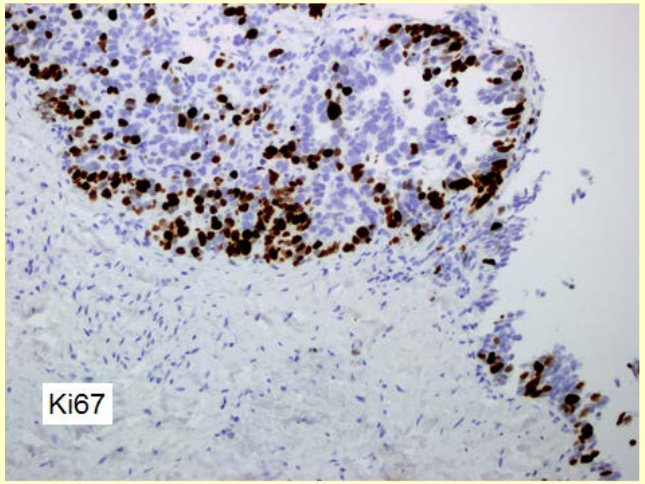




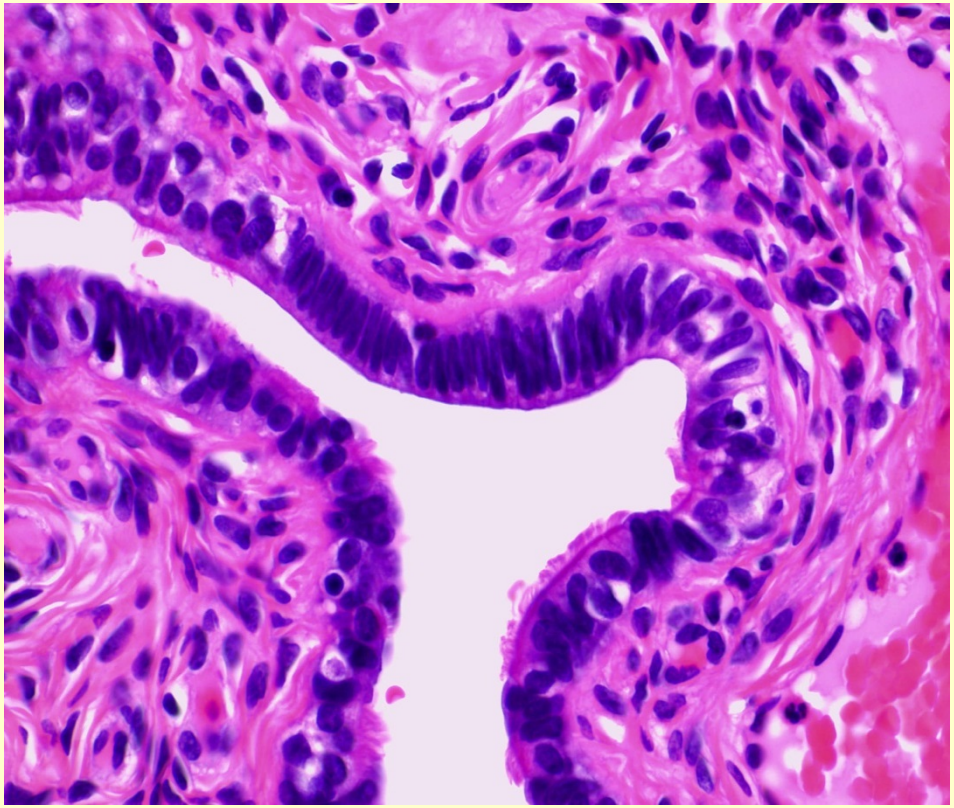


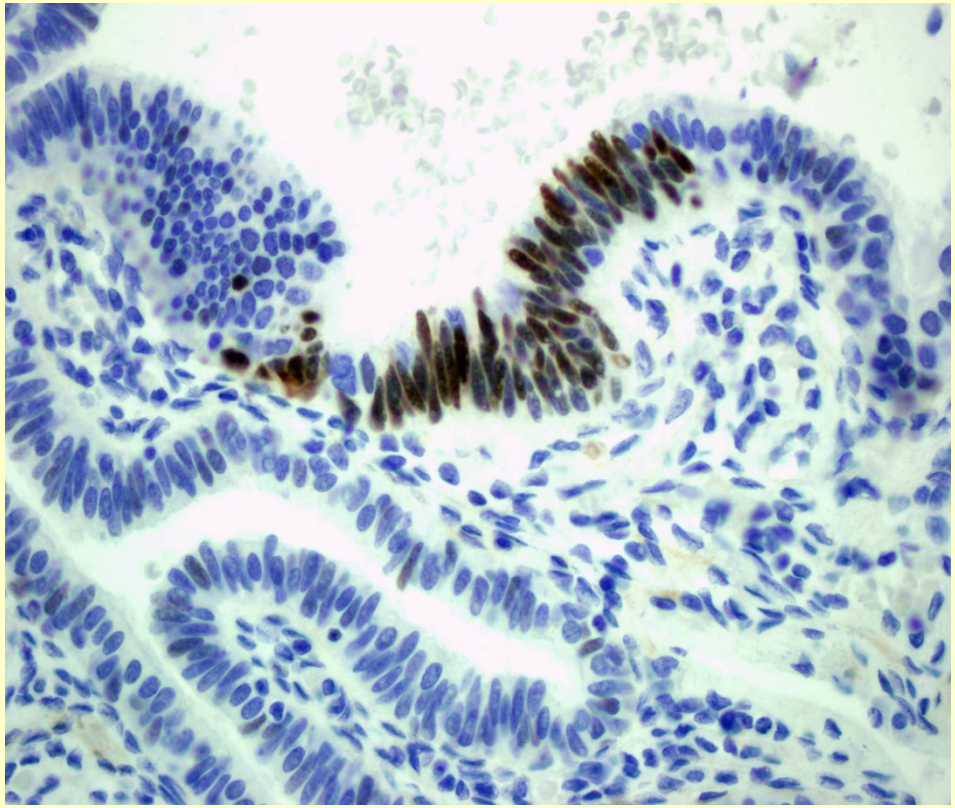
P53
R248W
(Exon 7)





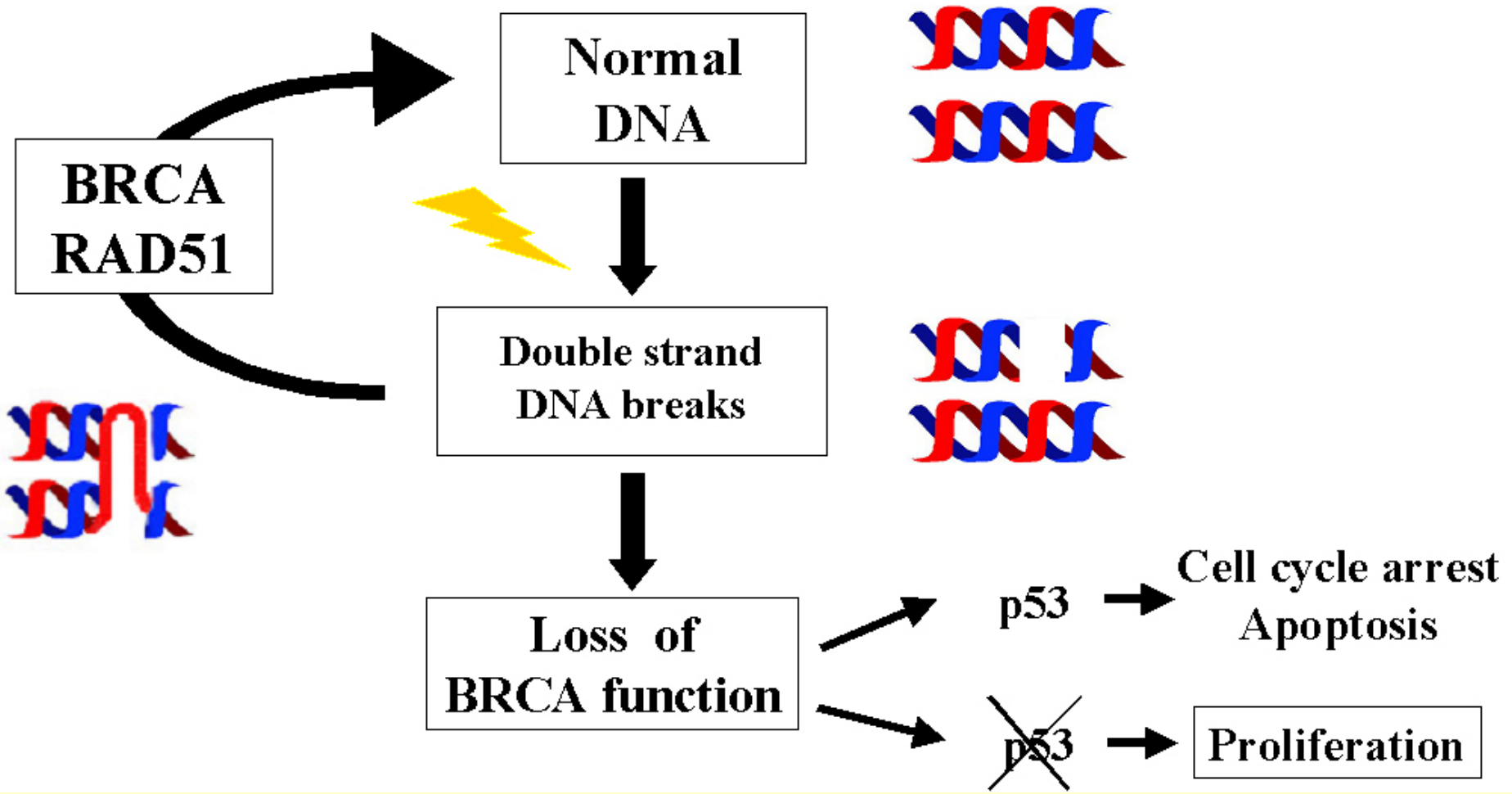
Menos que “STIC”?





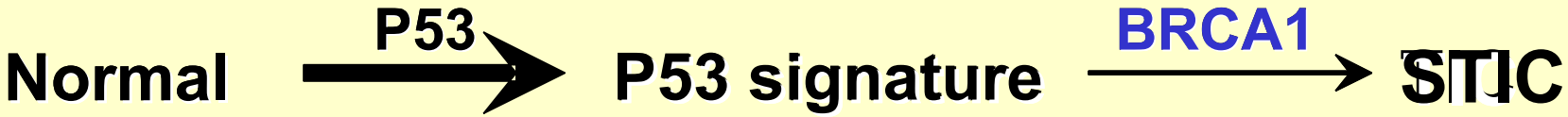
P53 Signature

BRCA function



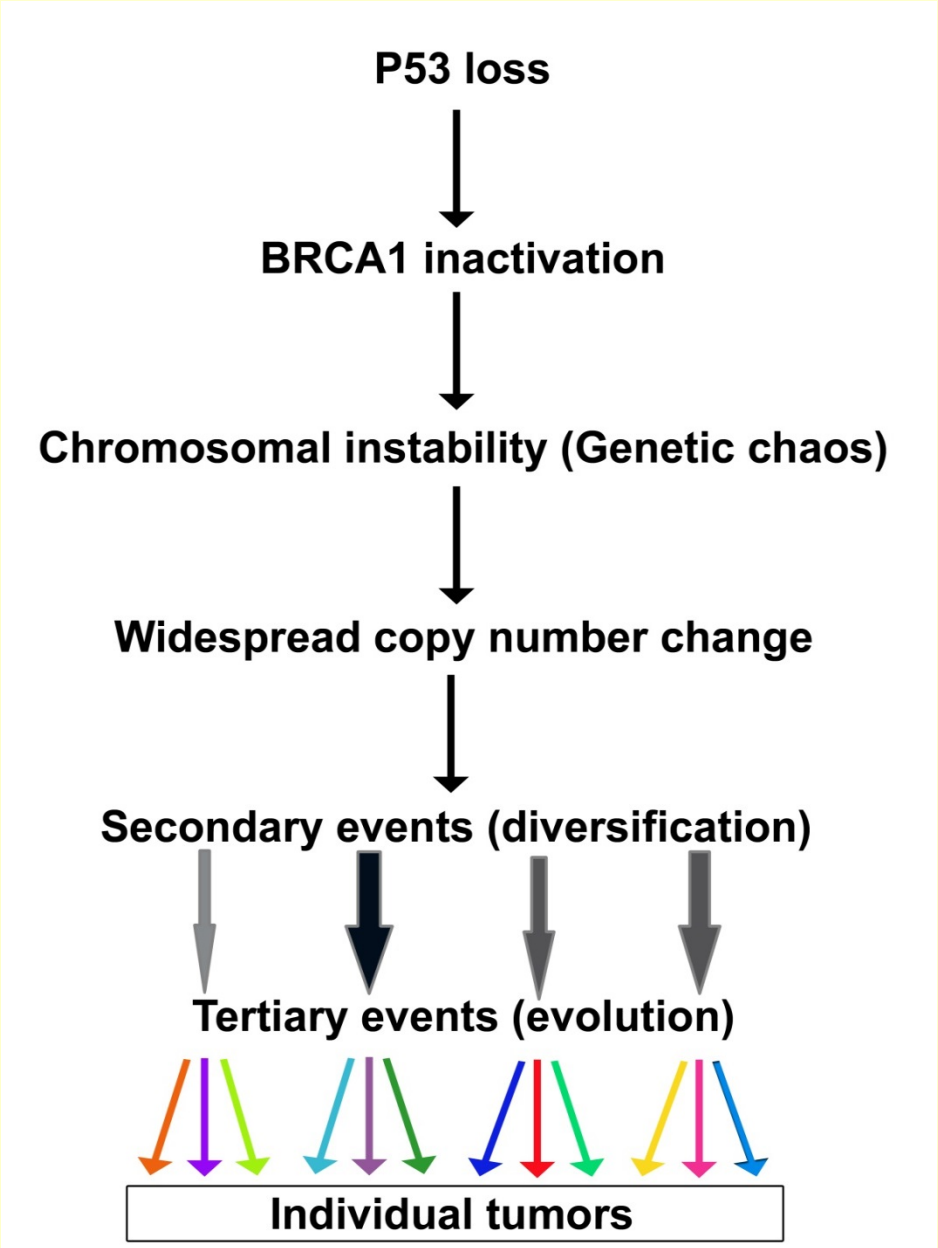
BRCA Promotes P53 Signature to STIC

Hereditary: BRCA1 mutation constitutive

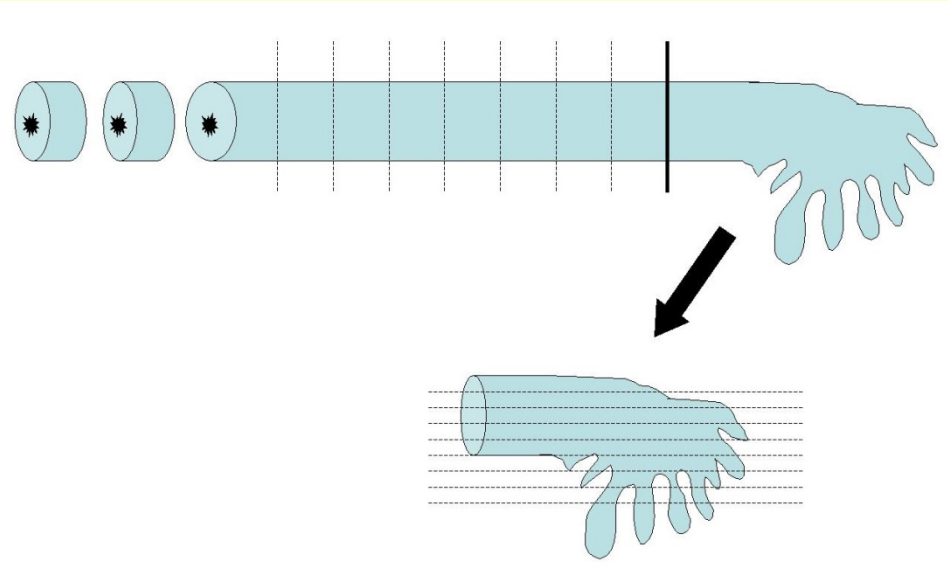


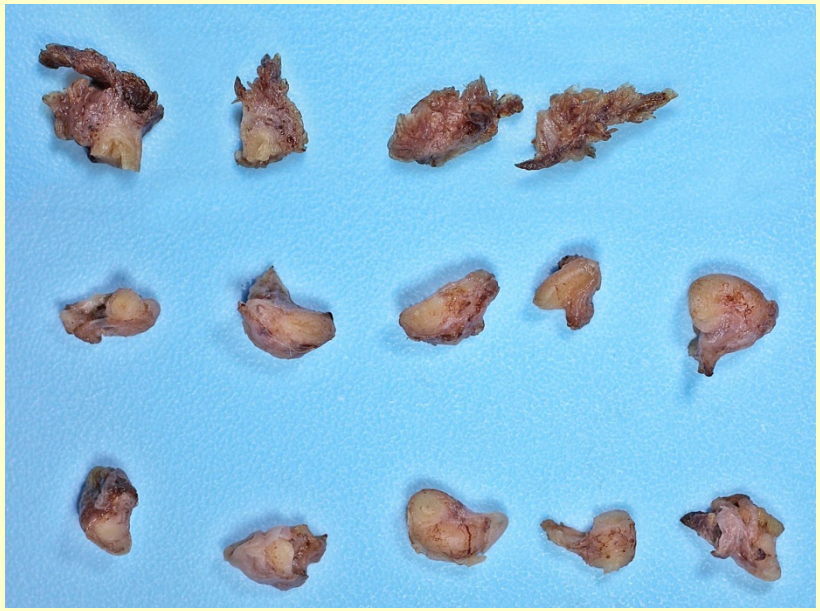
Sporadic: BRCA1 methylation/mutation new event

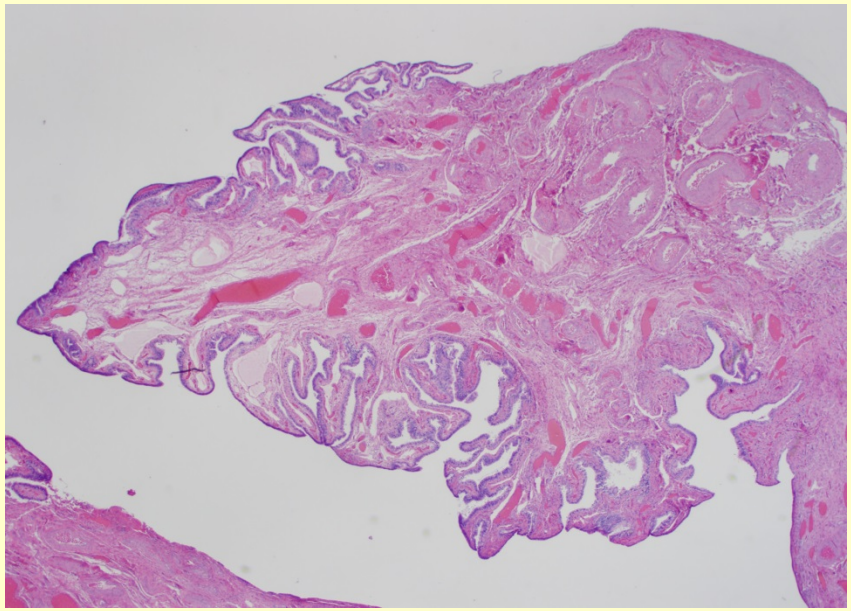
HGSC – Pathogenetic Model



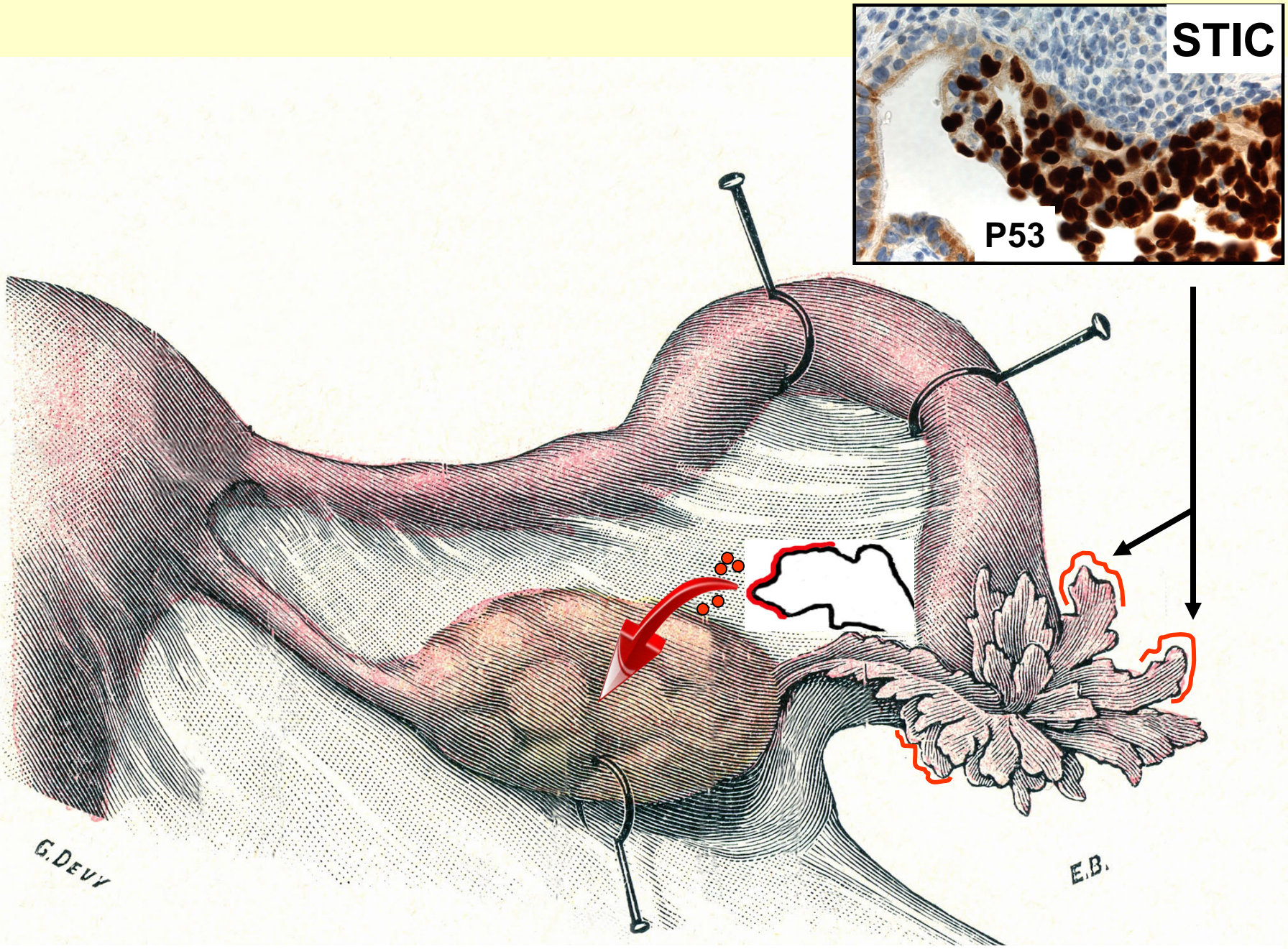
DDL Bowtell Nature Rev Cancer 2010



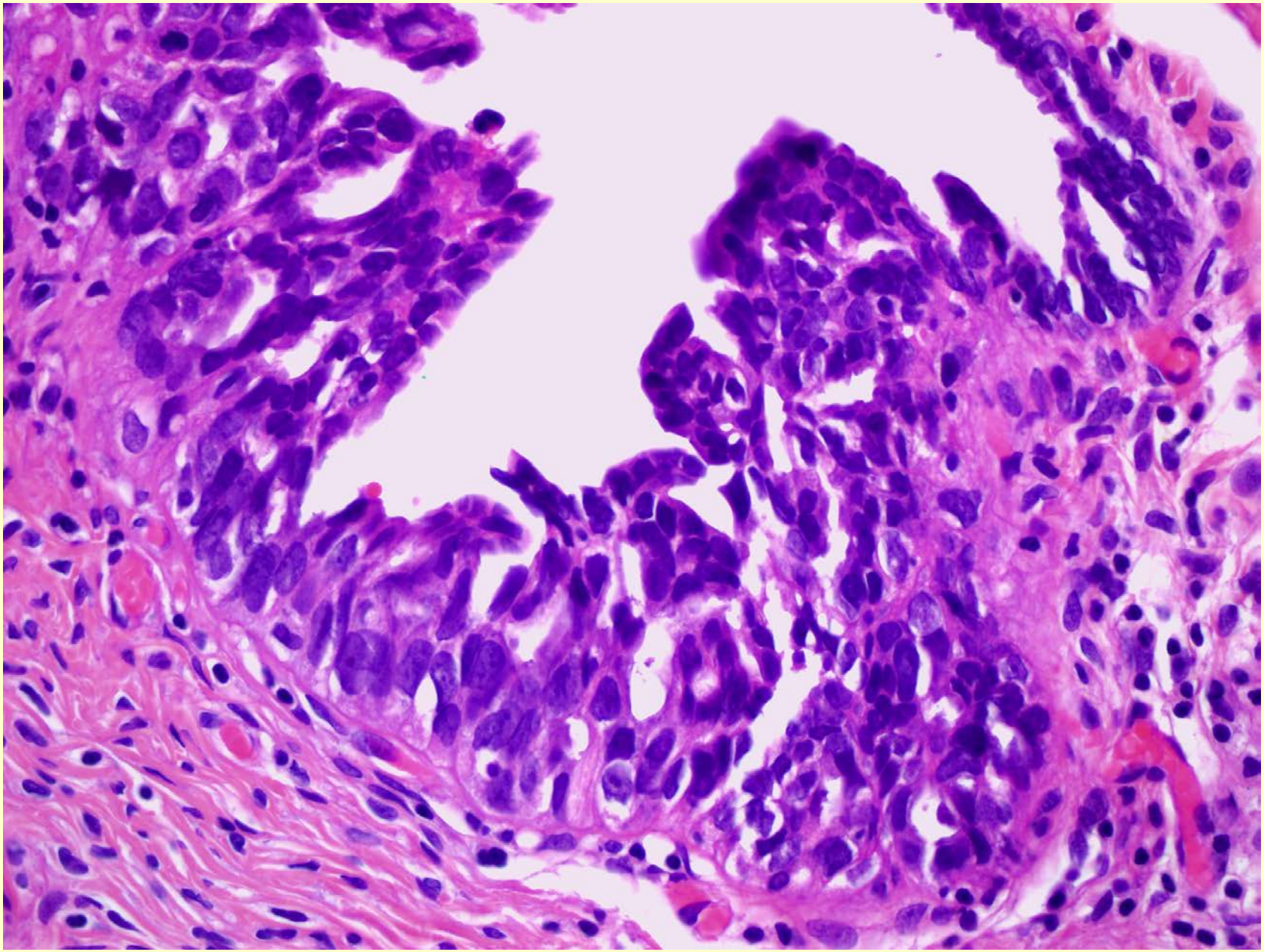




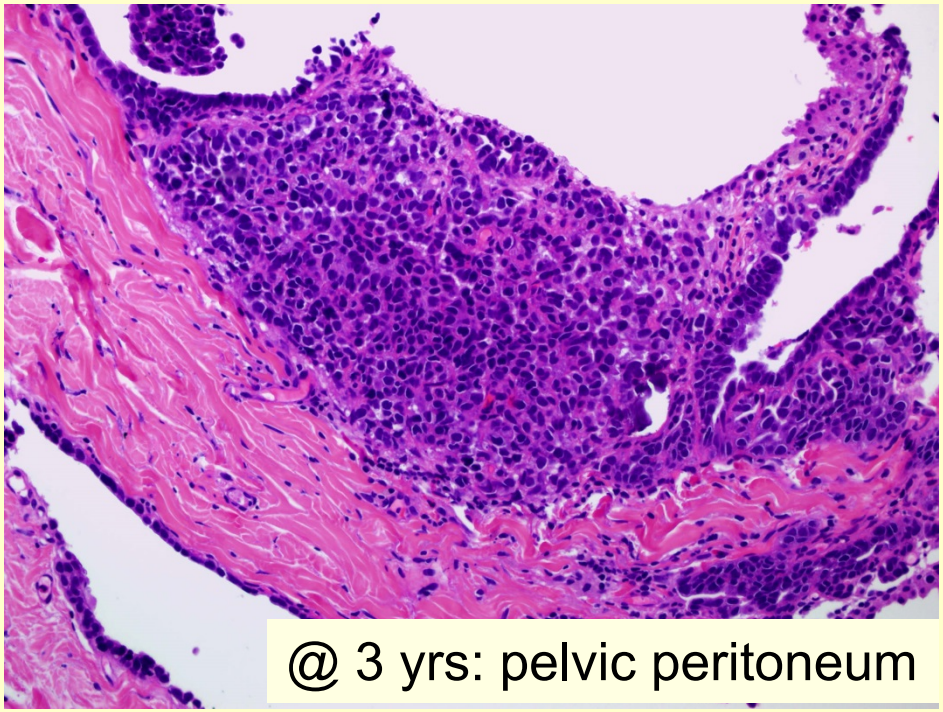
Sectioning and extensively examining the fimbriated end (SEE-FIM Protocol)

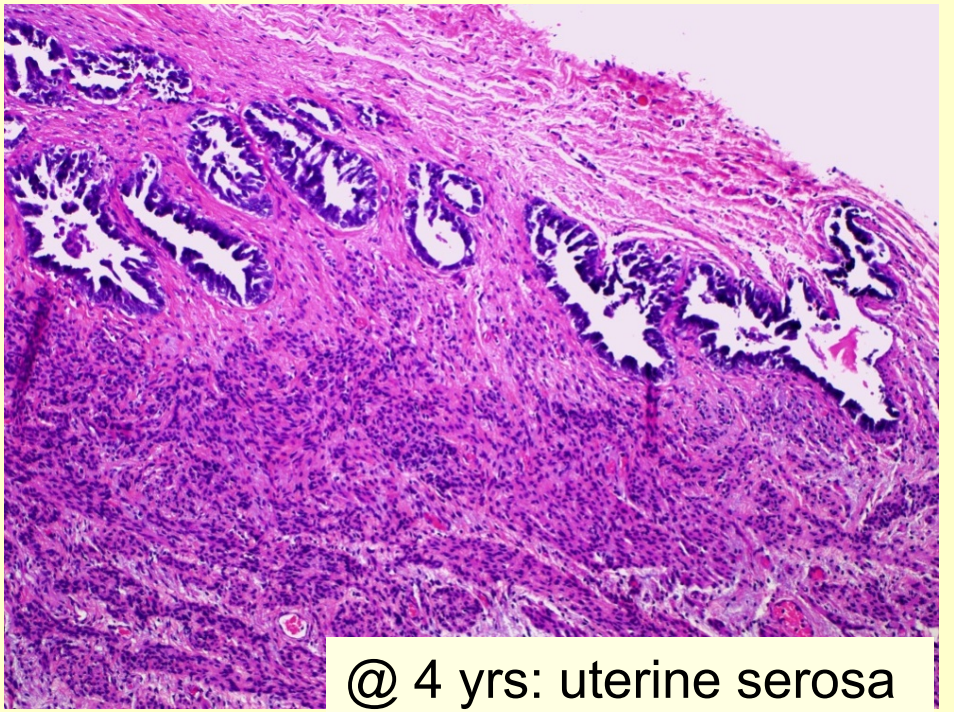


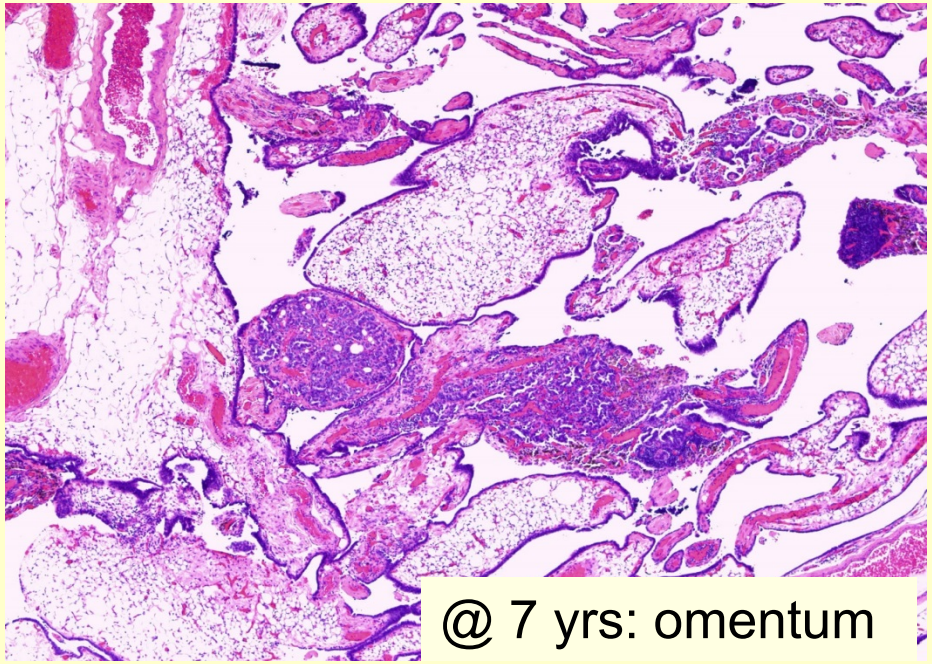
High Grade Serous Carcinoma

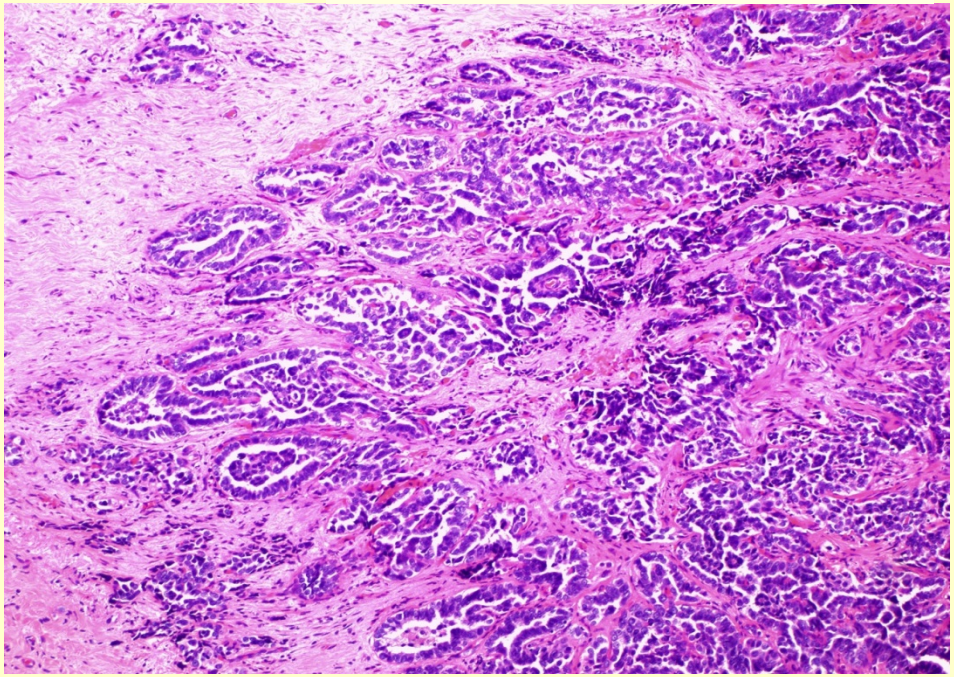


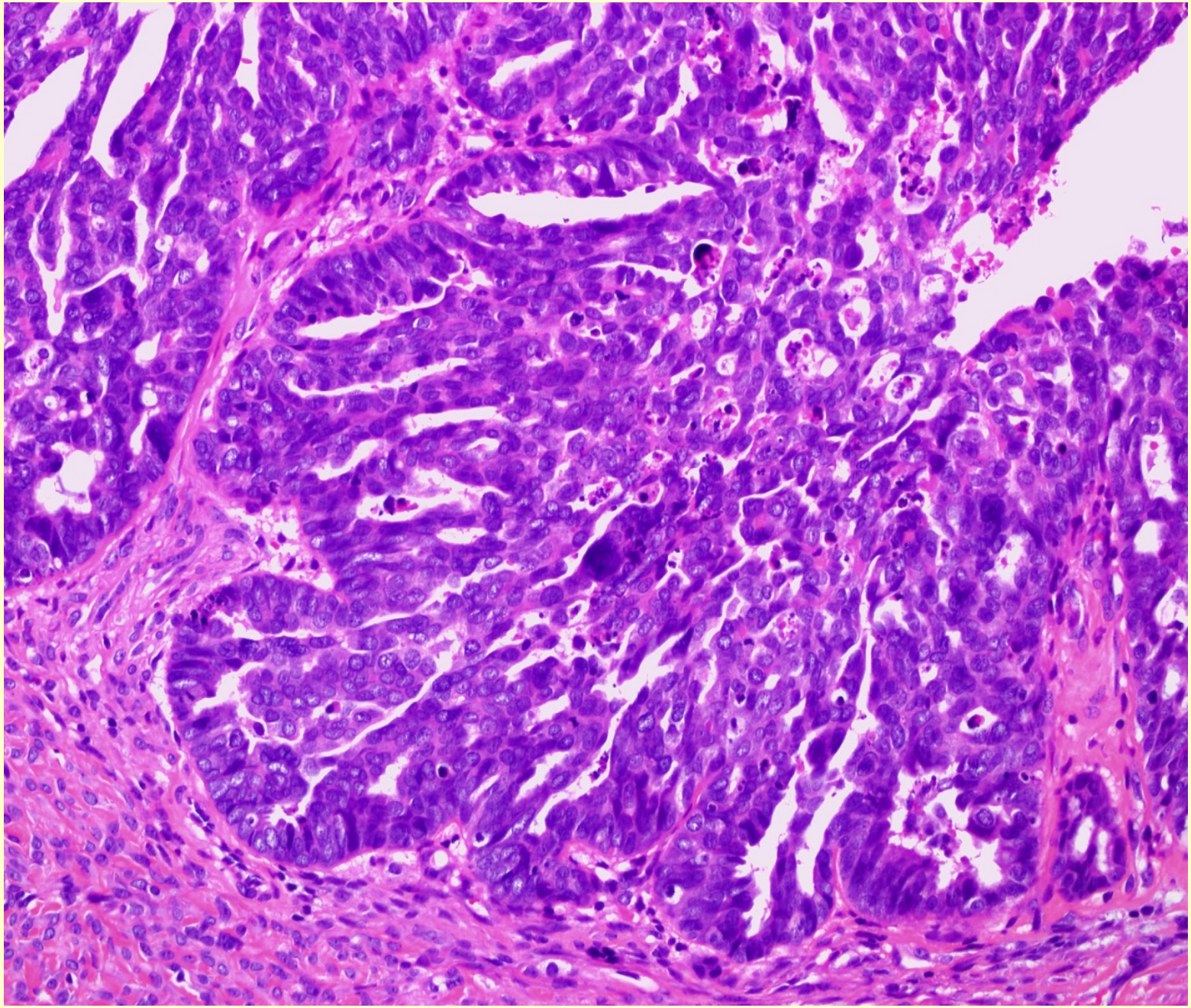
SOB profiláctica (RRSO) 10 a. después del Dx de Ca de Mama


@ 3 yrs: pelvic peritoneum

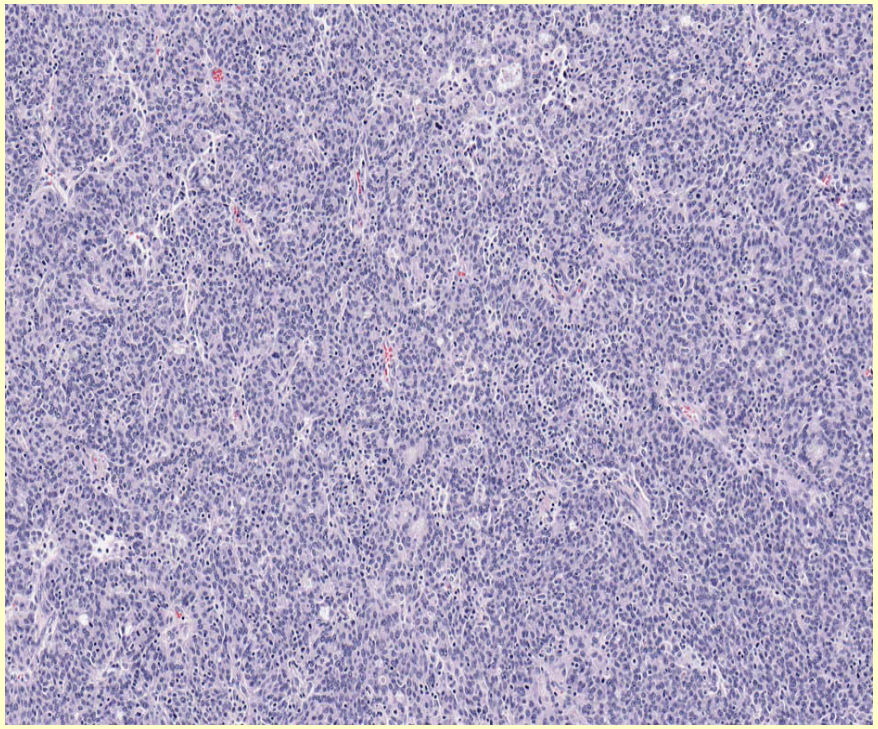

@ 4 yrs: uterine serosa

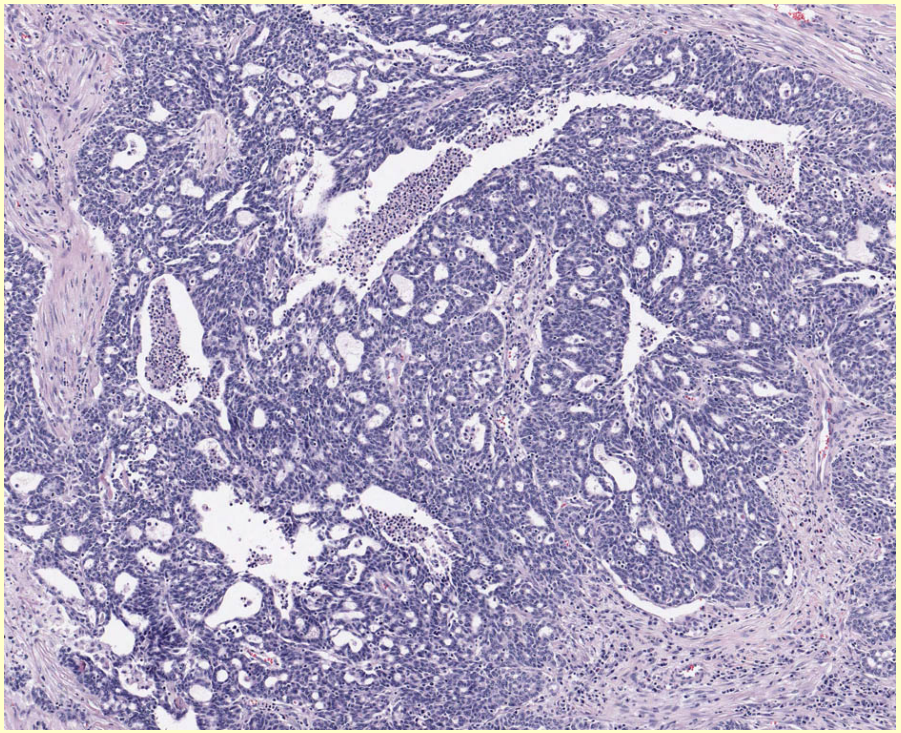

@ 7 yrs: omentum

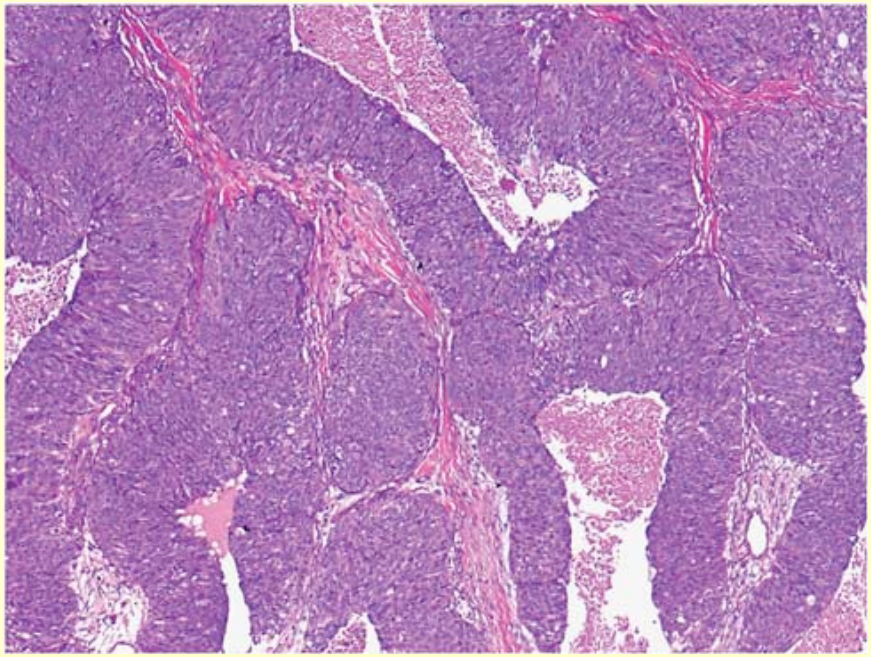




Carcinoma seroso de alto grado (CSAG)







BRCA+ HGSC ("SET")

- Solid
- Pseudoendometrioid
- Transitional

Soslow RA et al, Mod Pathol 2012

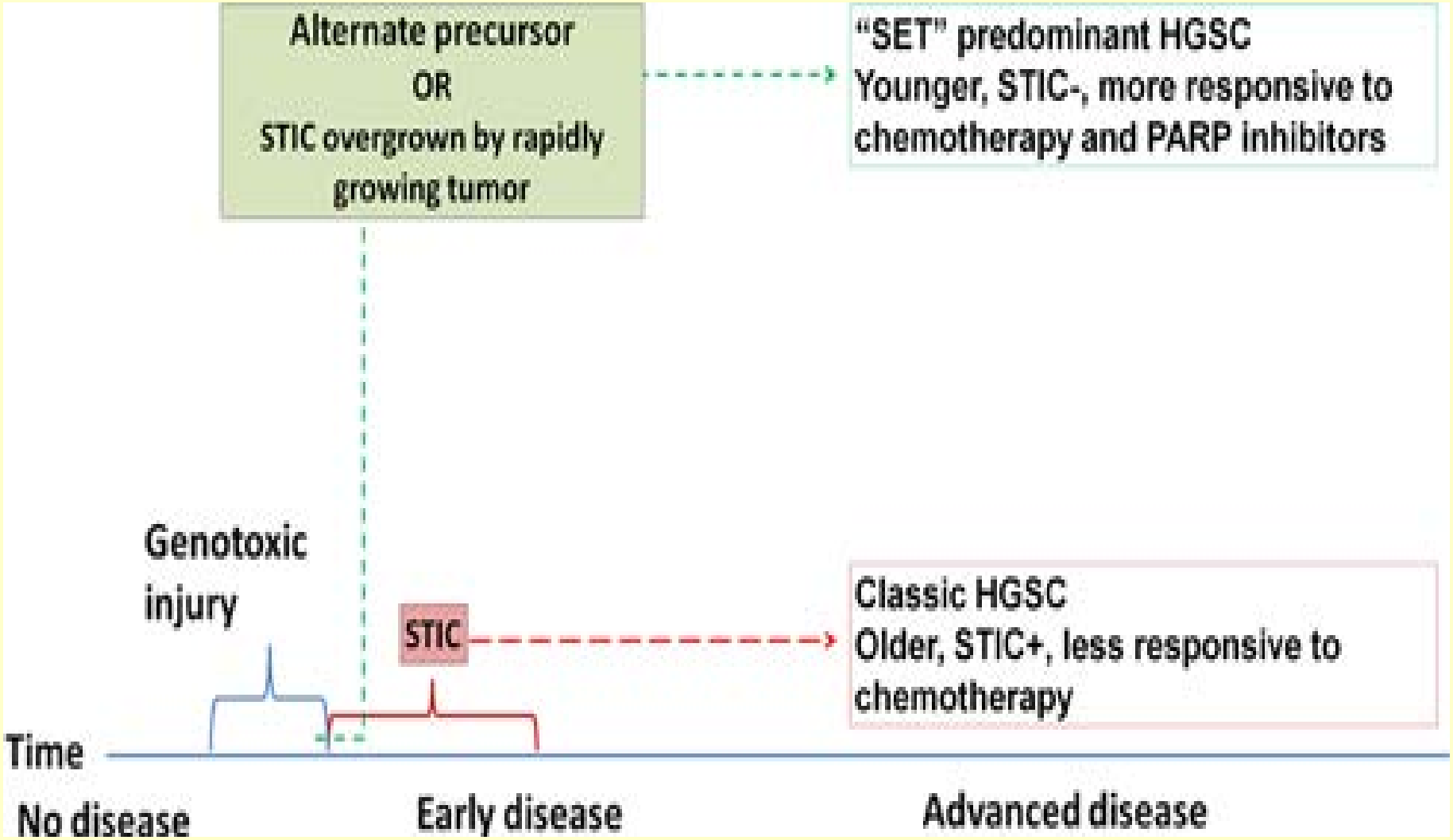
Carcinoma Seroso Tubárico Intraepitelial (STIC)

- Asintomáticas *BRCA*+ RRSO – **4%** STIC
- Asintomáticas *BRCA*+ RRSO – **CSAG temprano** (**raro**) – **80%** STIC

- CSAG Avanzado: *BRCA*+ (31% STIC); *BRCA*- Clásico (83%) vs SET (sólido,end,trans - 22%)???

- SET (*BRCA*+): muy proliferativo – (23%) borra el STIC?
- Clásico (advanced): secundario, invasión pagetoide

Crum C. et al 2012

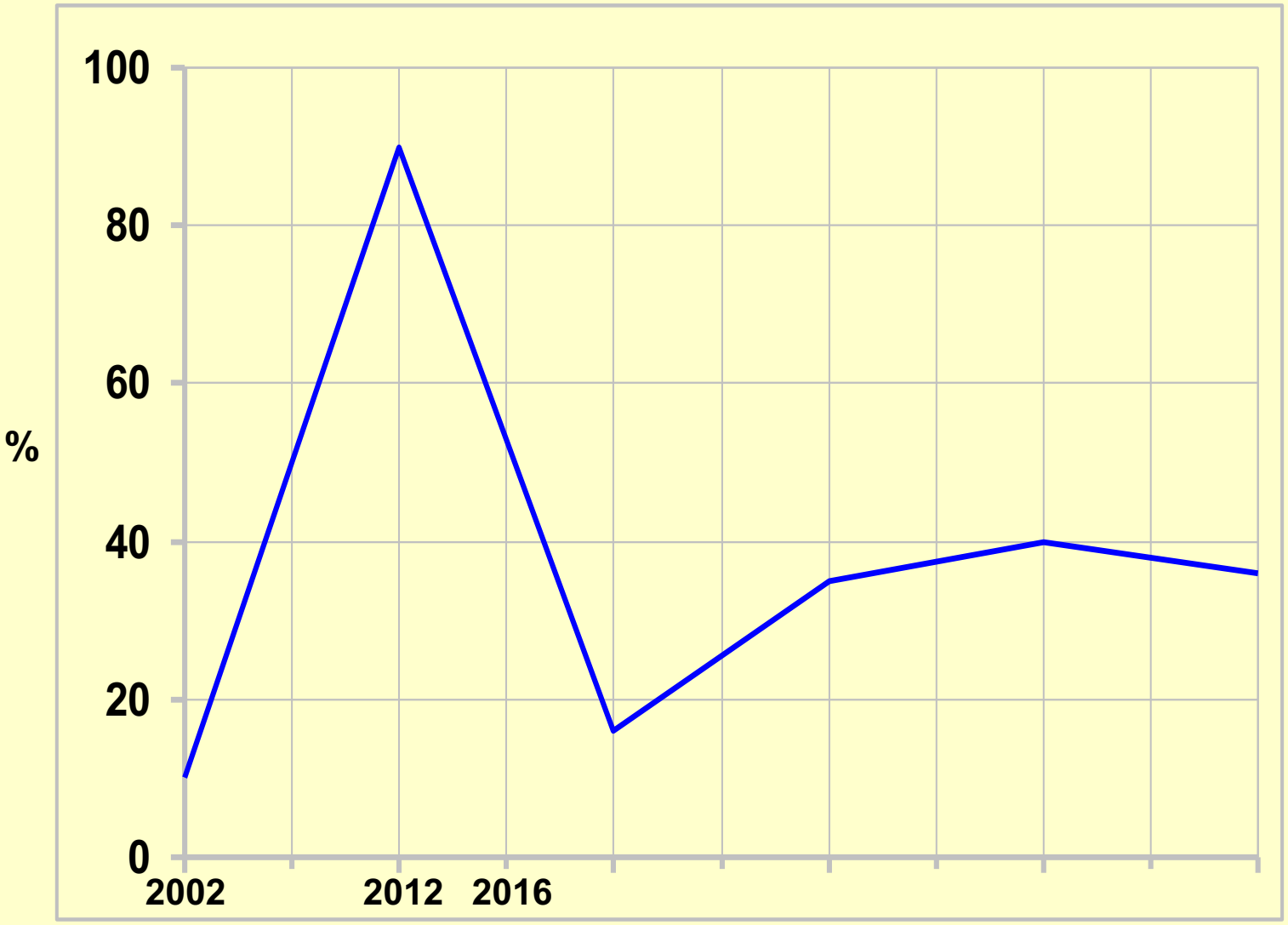


Dual model of HGSC pathogenesis according to age, outcome, precursor lesion and tumor evolution: classic pathway (STIC) and SET pathway

Howitt BE, AJSP 2015

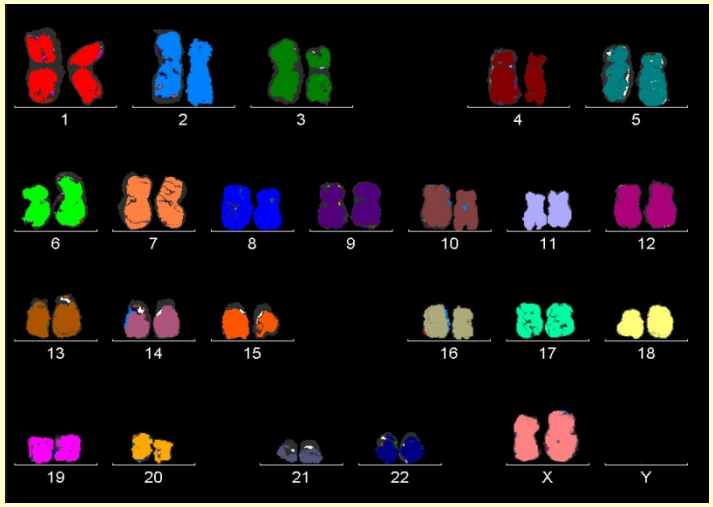
Cáncer de ovario (CSAG)

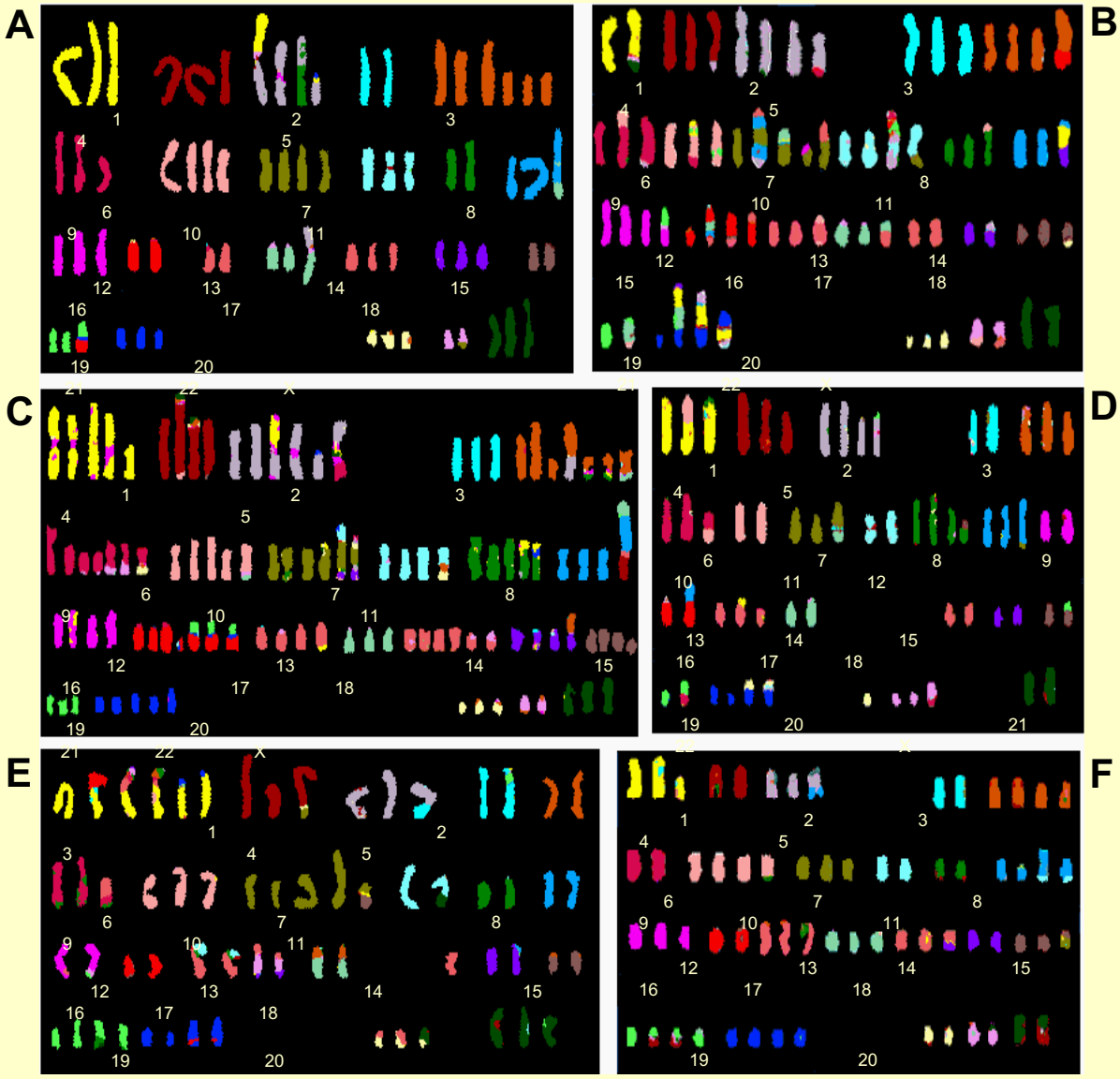
- Son todos los CSAG de origen tubárico?
- Sólo algunos CSAG?
- Sólo los CSAG *BRCA*+ ?
- Deben quitarse las trompas en todas las cirugías pélvicas por enfermedades benignas?

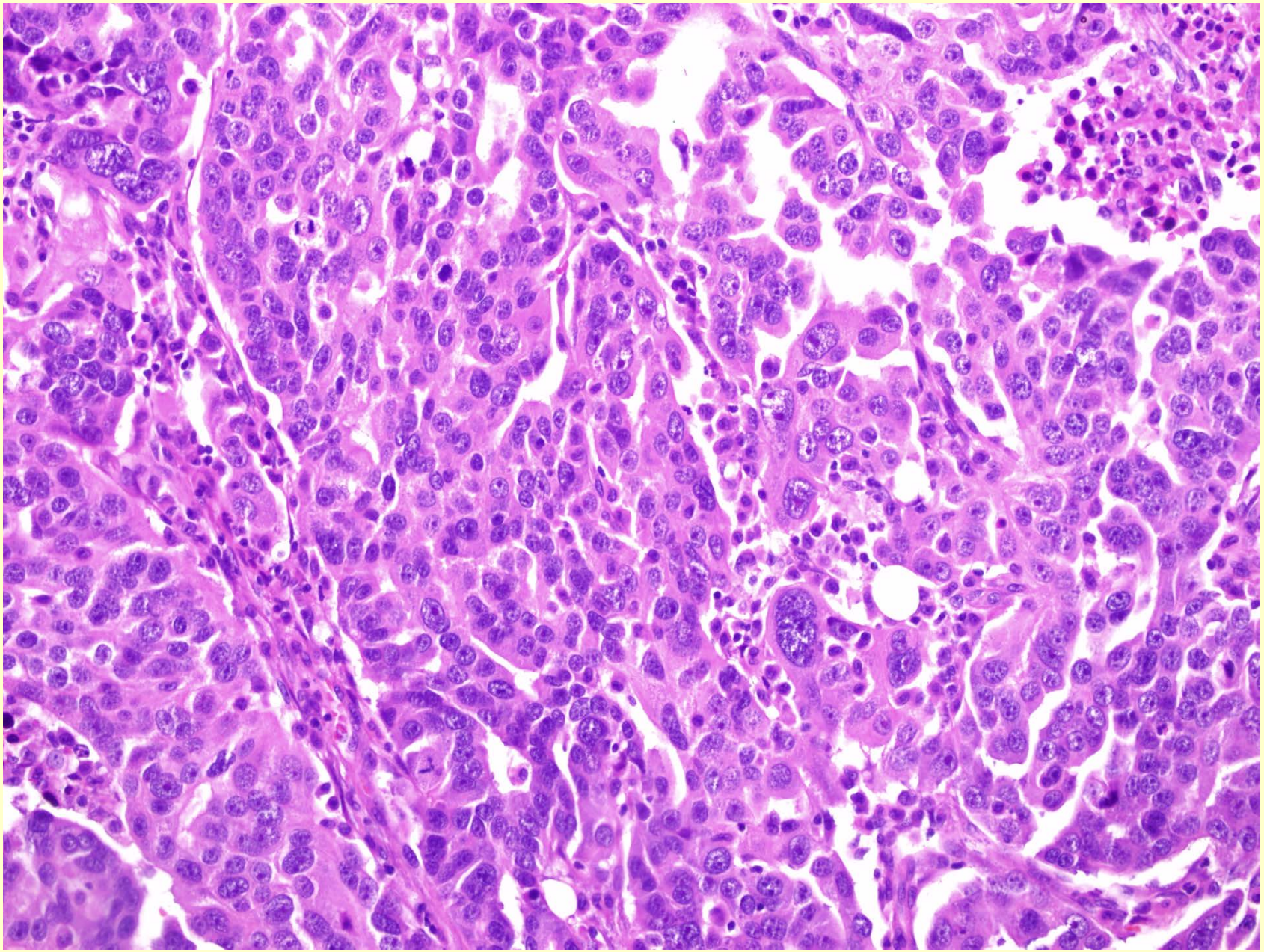


Origen tubárico de los carcinomas serosos de alto grado (opinión personal)

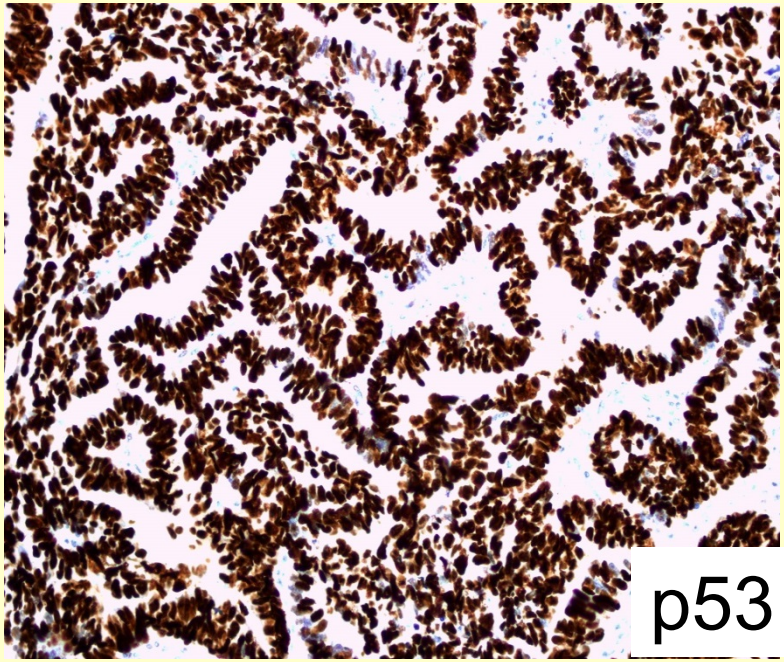
Seis (6) CSAG con inestabilidad cromosómica

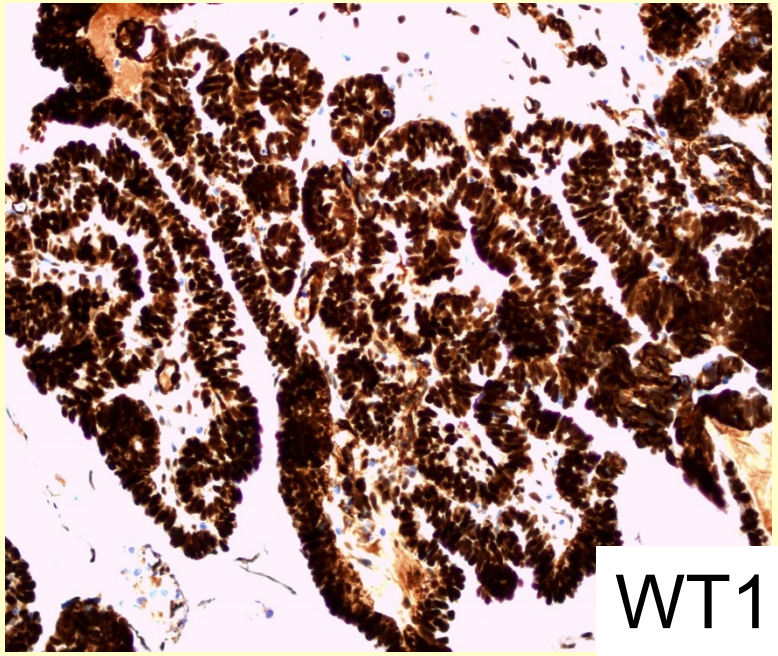


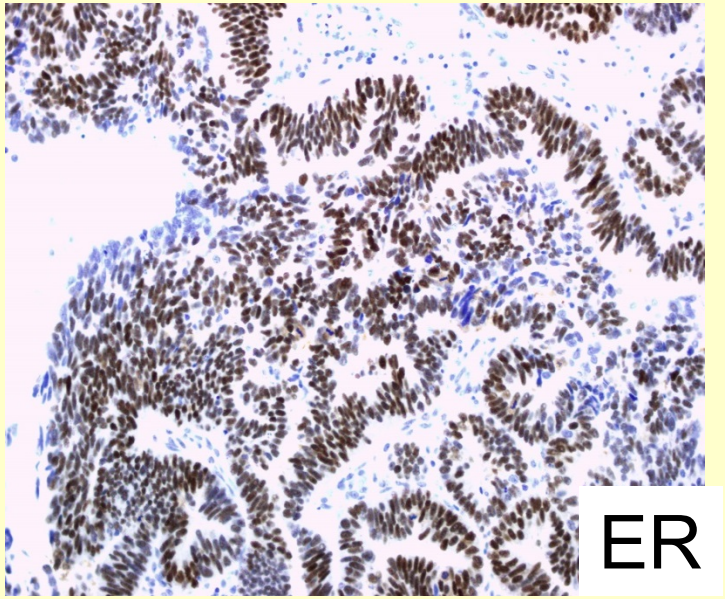




Carcinoma seroso de alto grado (grado 3)

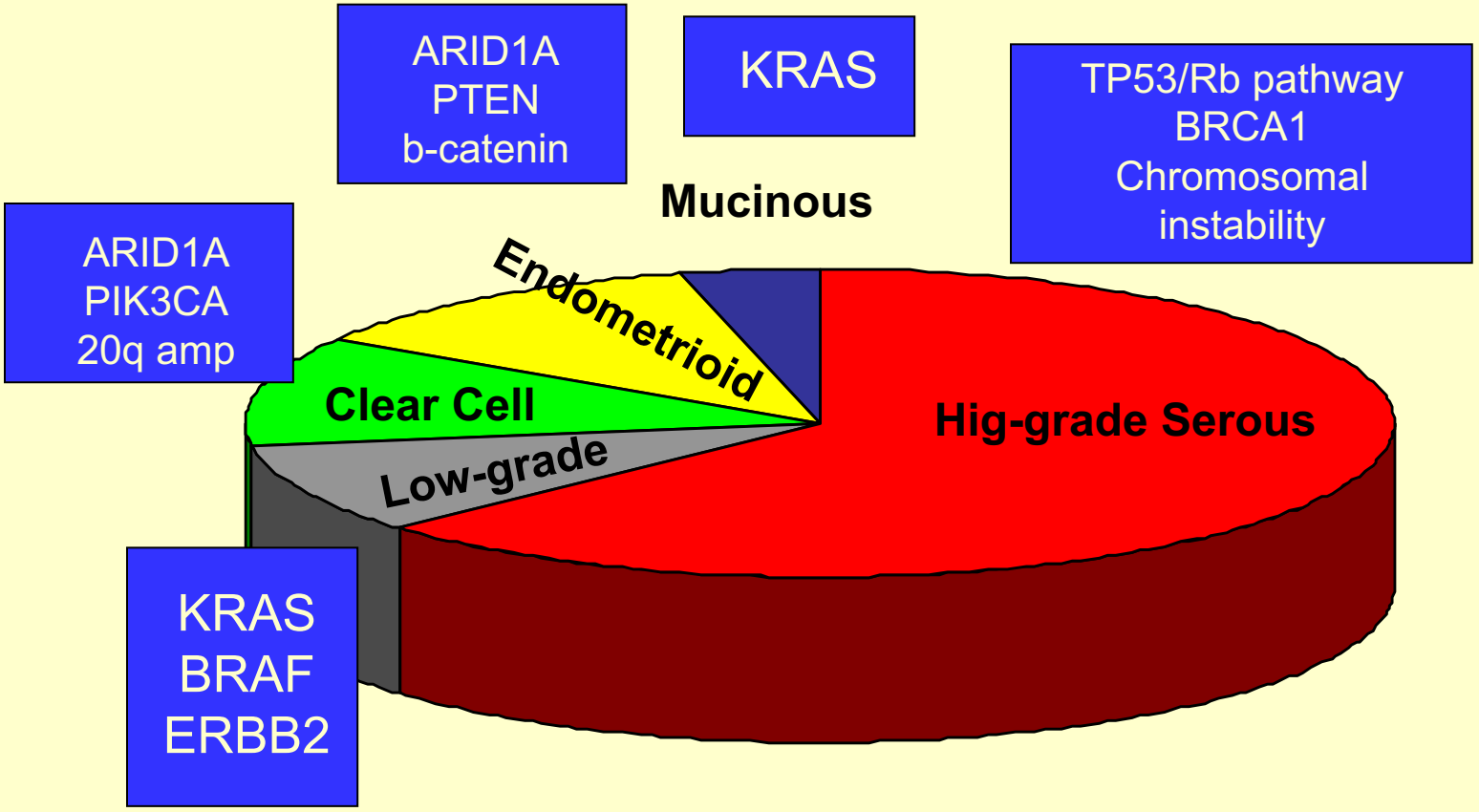

p53

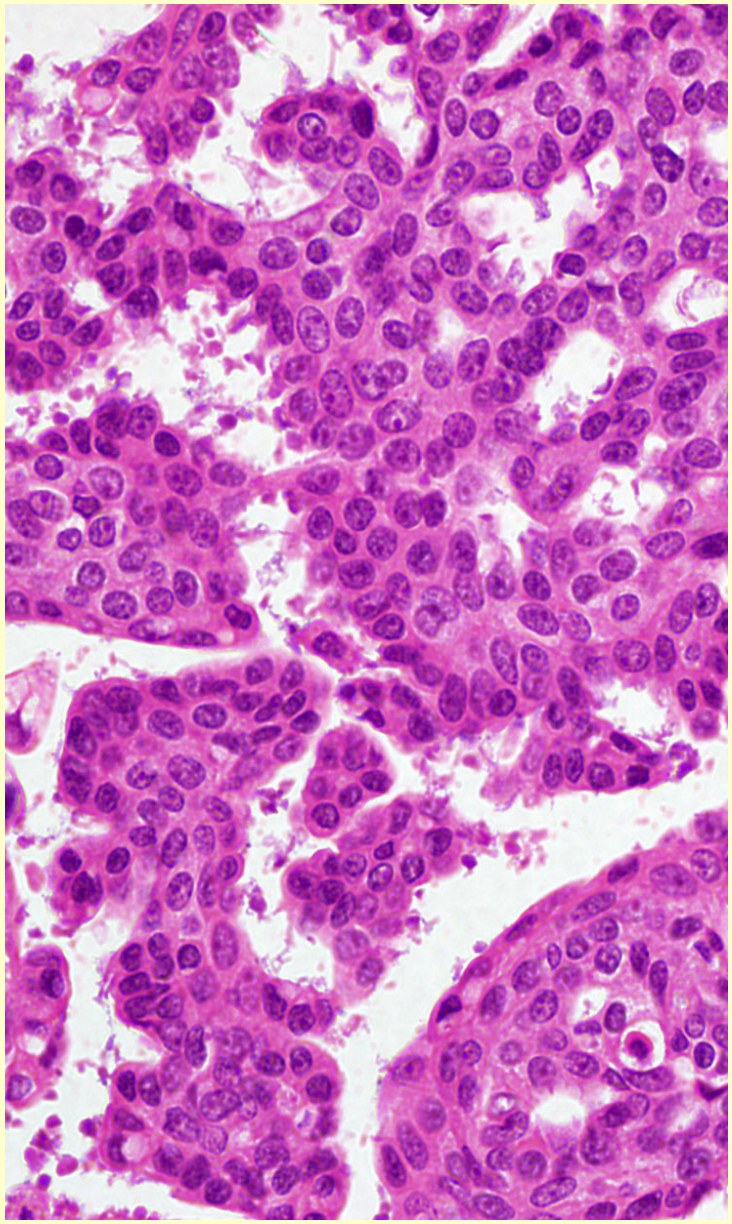

WT1


ER

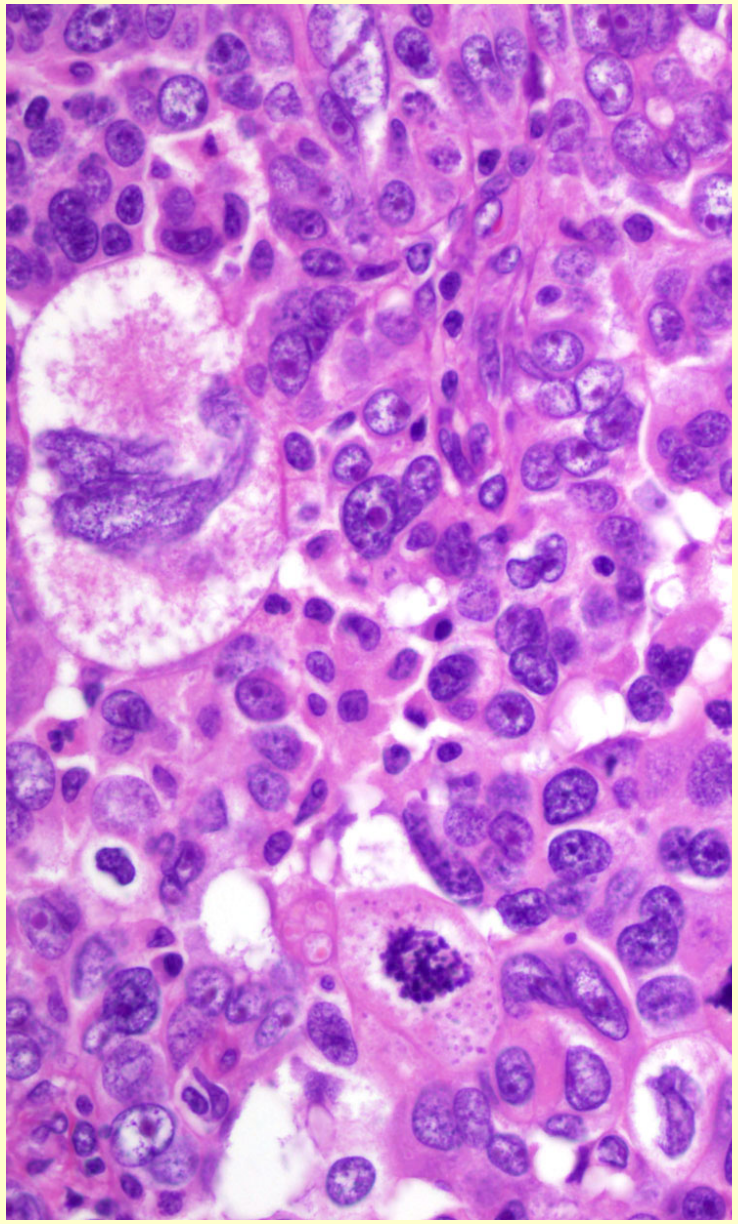
High-grade Serous Carcinomas Immunoprofile

CAM 5.2 and CK7 (100%), BER-EP (95%), B72.3 (73%)	Positive (C)
CA-125 (91%)	
CK20 (66%), Vimentin (55%), CEA (81%), S-100 (70%)	Negative
EMA (100%)	Positive (M)
WT1 (90%), **ER** (95%), **p53**, **PAX 8** (most cases)	Positive (N)
p16 (most cases)	Positive (C&N)
PR (75%)	
Calretinin (75%)	Negative
TTF-1 (75%)	Negative
CD99	Positive (M)


ARID1A
PTEN
b-catenin
KRAS
TP53/Rb pathway
BRCA1
Chromosomal
instability
Mucinous
ARID1A
PIK3CA
20q amp
Endometrioid
Clear Cell
Low-grade
Hig-grade Serous
KRAS
BRAF
ERBB2



Bajo grado



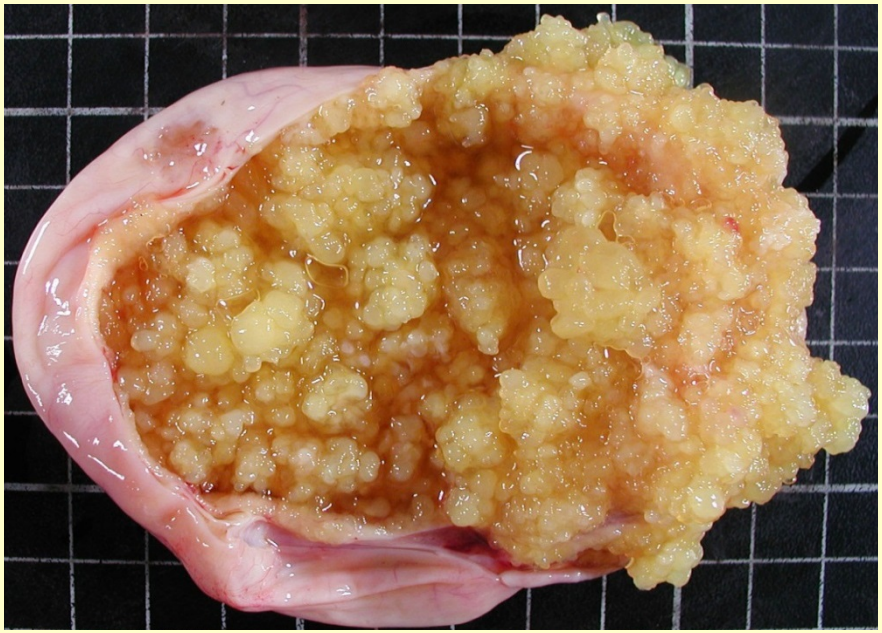
Alto grado

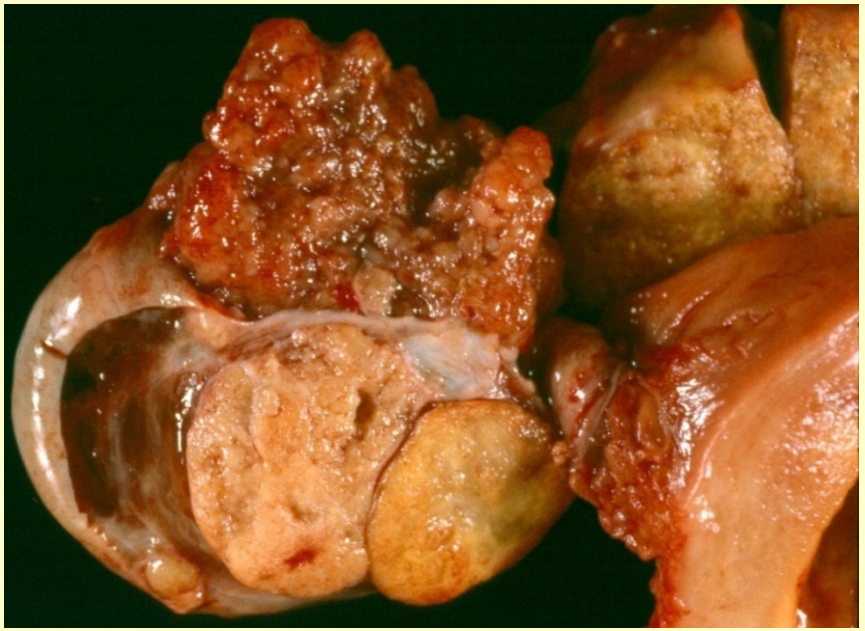
Carcinoma Seroso de Bajo Grado

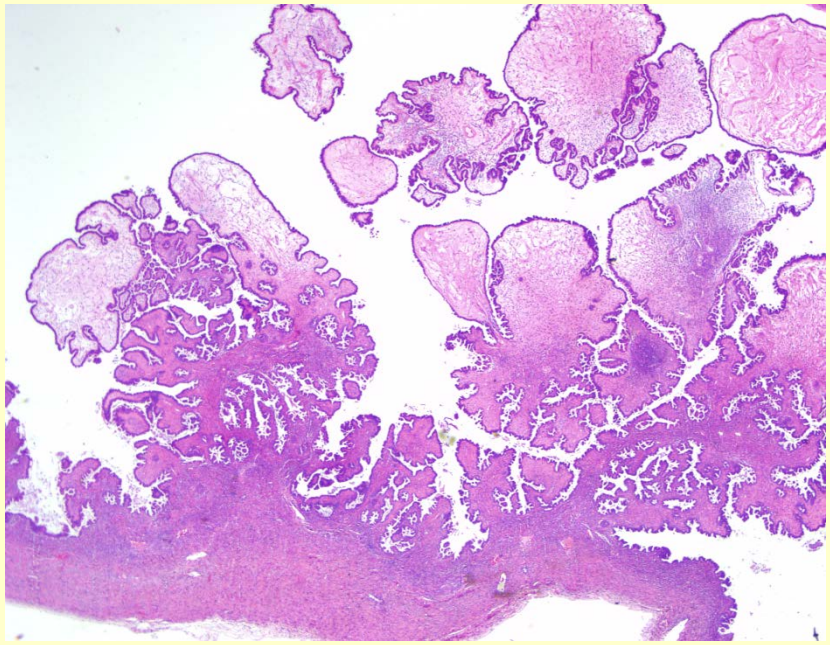
(<5% de los carcinomas ovaricos)

- Progresión of TSB (6-7%)
- Relativa quimiorresistencia
- Supervivencia media global = 7 yr

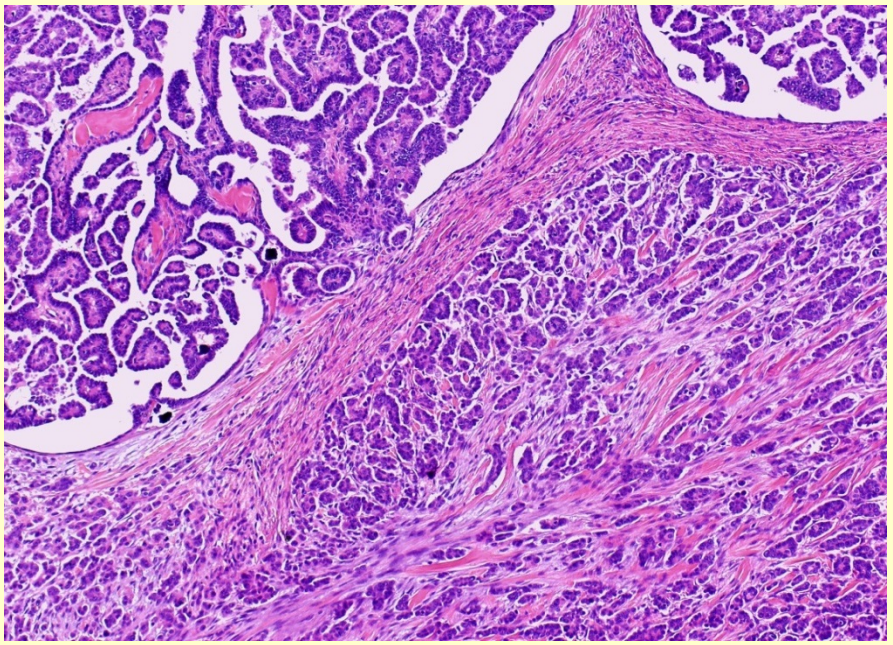
Gershenson et al,
Obtet Gynecol 2006





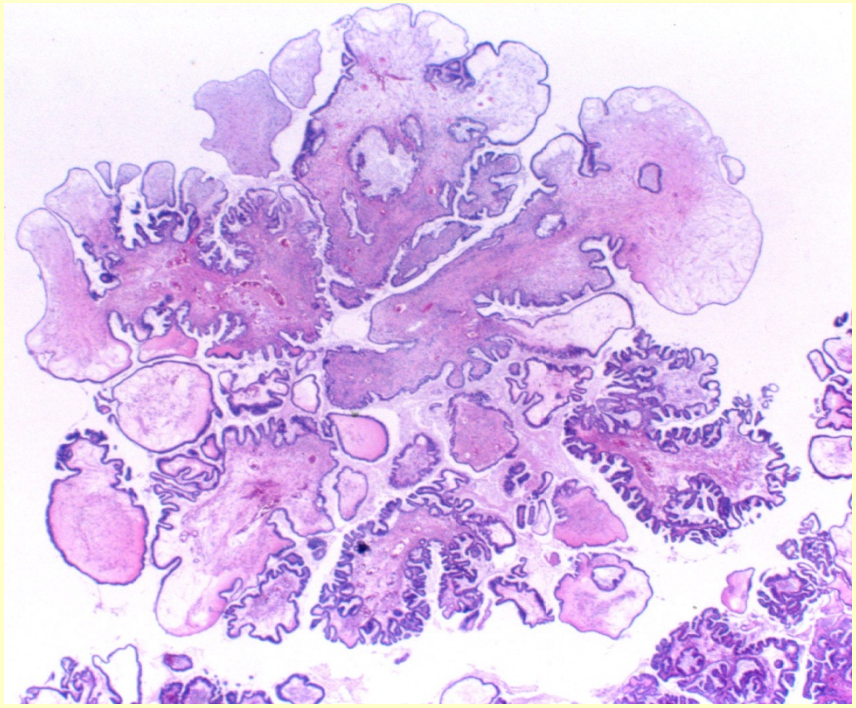


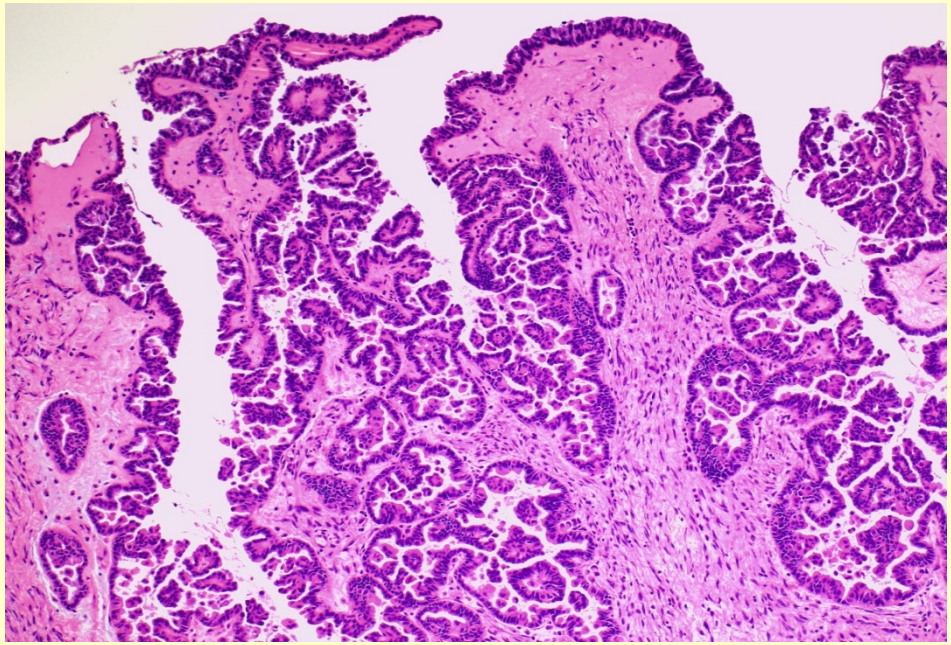
Tumor Seroso Borderline

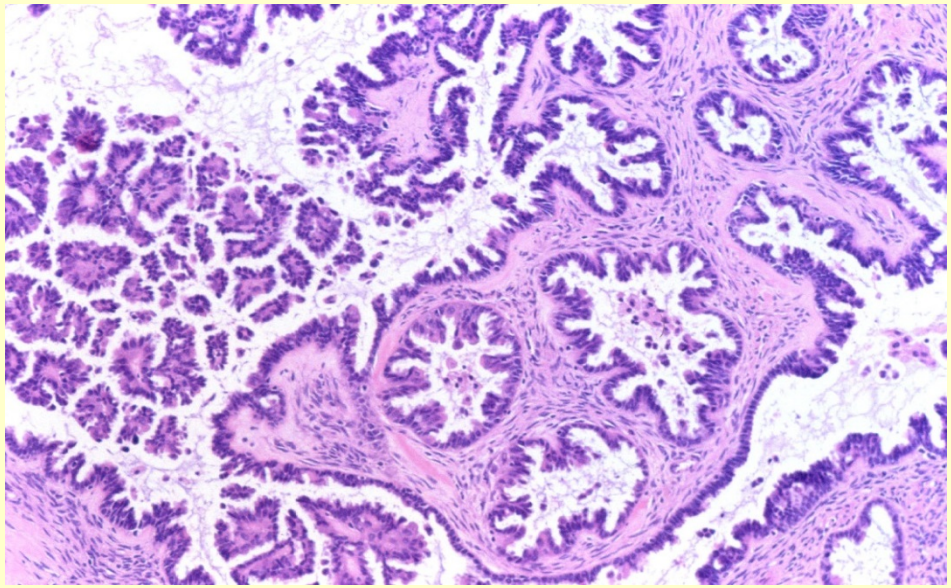


TSB + Carcinoma Seroso de Bajo Grado

Serous Borderline Tumor







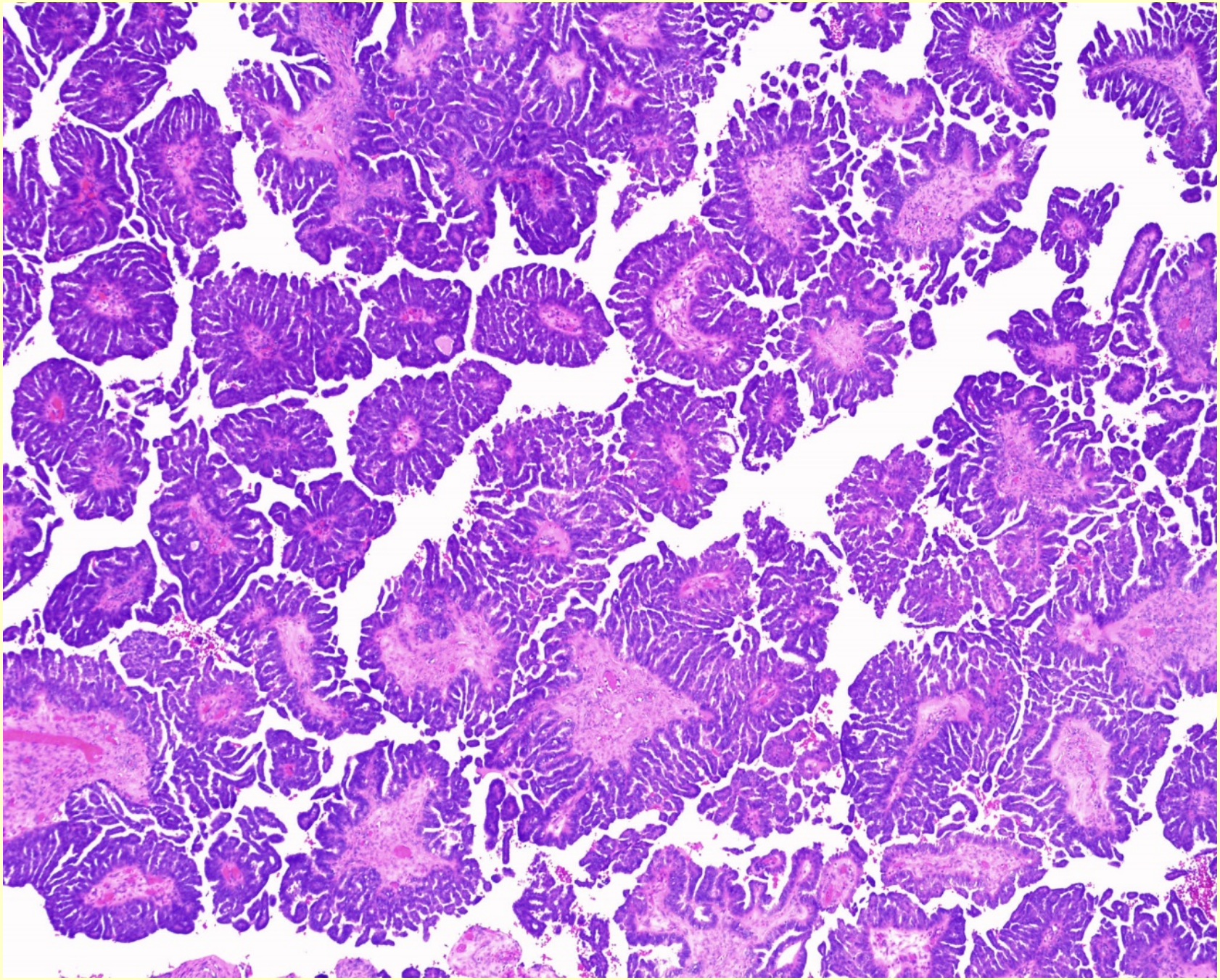
Diagnostic Features

1. Branching papillae
2. Variable nuclear atypia
3. No stromal invasion

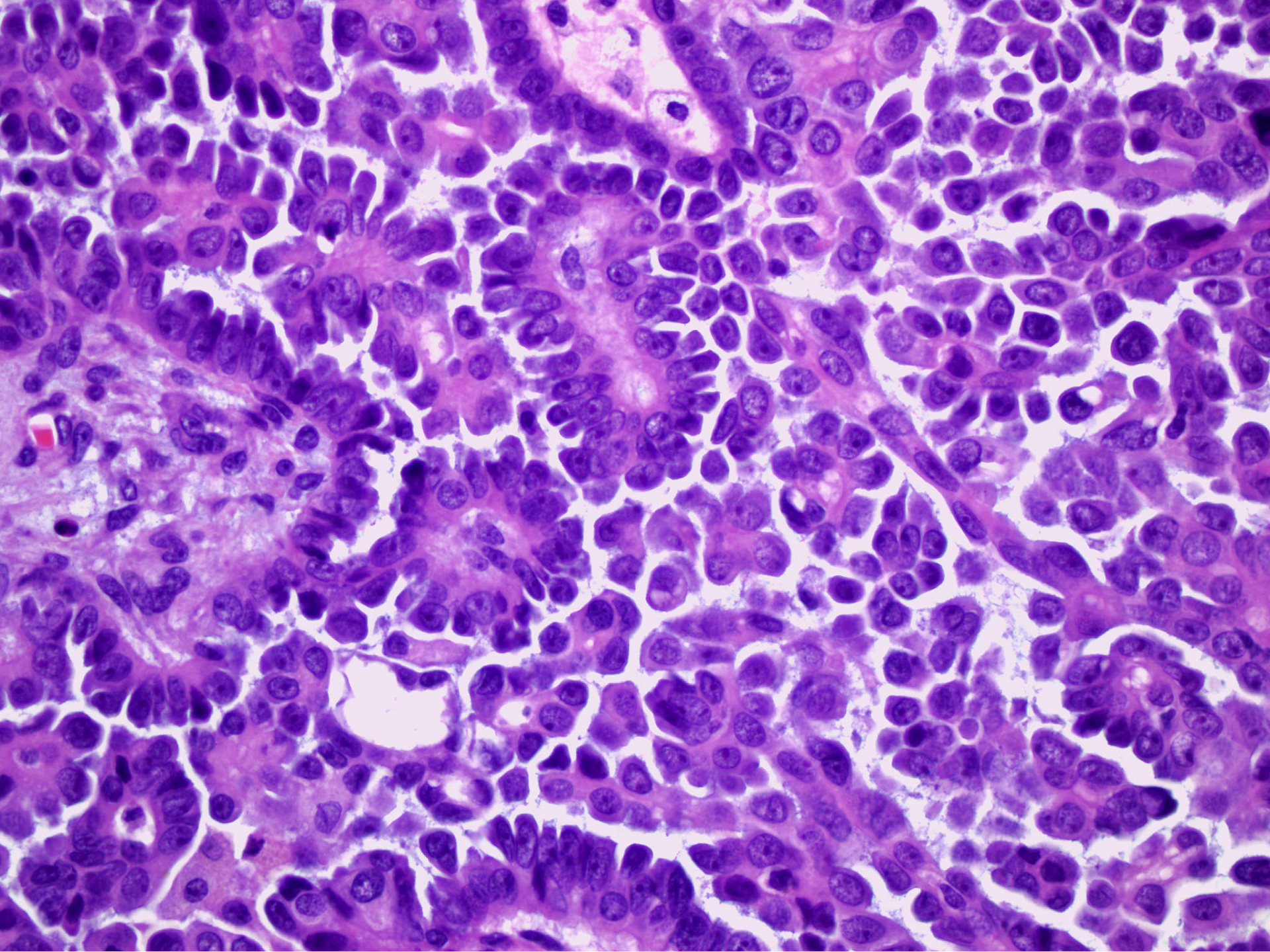
Serous Borderline Tumors

(Diagnostic Problems)

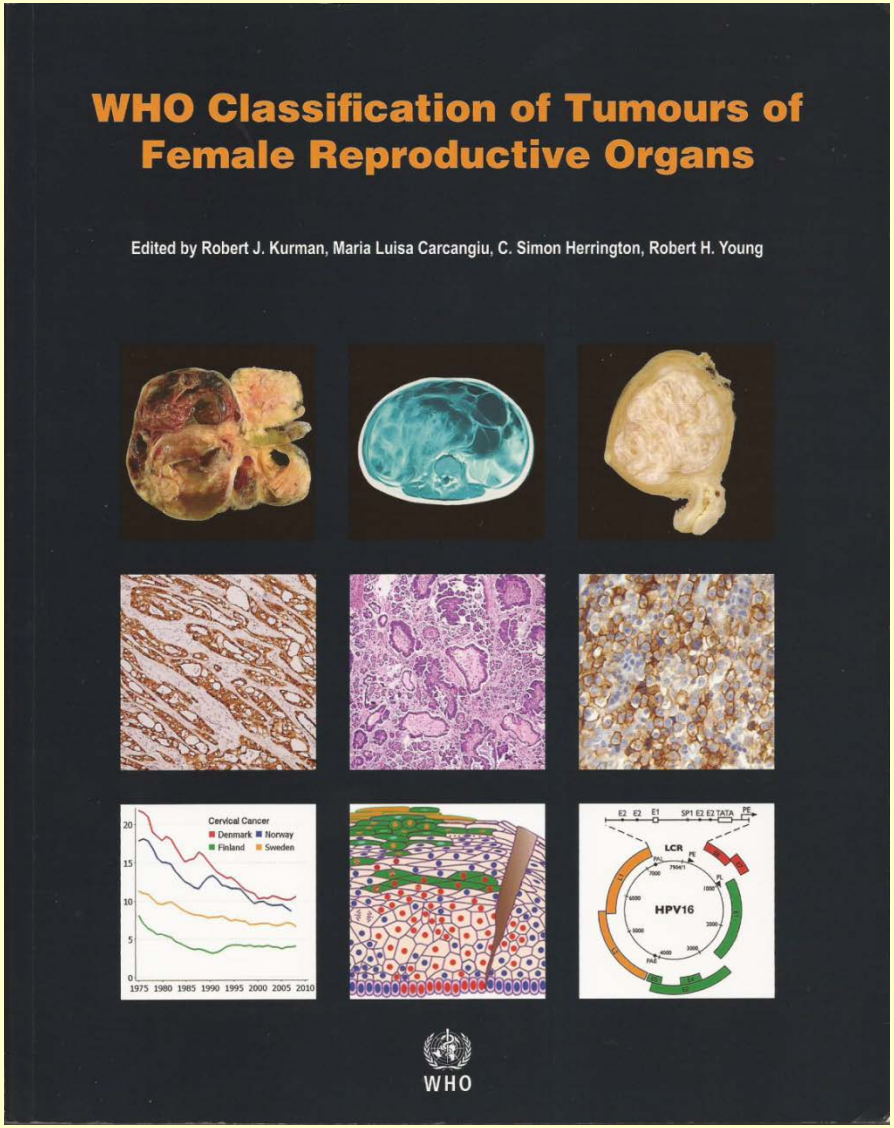
- Micropapillary pattern
- Microinvasion
- Peritoneal implants
- SBT in lymph nodes
- SBT of the peritoneum



SBT - Micropapillary pattern



2014 WHO Classification of Tumours of Female Reproductive Organs



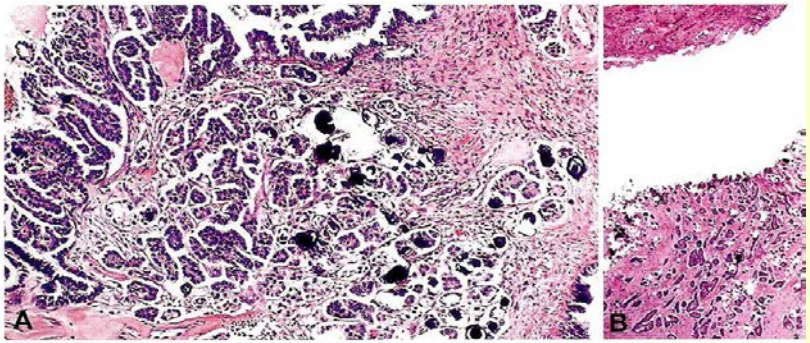


Fig. 1.09 Serous borderline tumour/atypical proliferative serous tumour (SBT/APST) with focus of low-grade serous carci most of the field measures < 5 mm and represents low-grade serous carcinoma. **B** Low-grade serous carcinoma in para ovarian low-grade serous carcinoma. Although occasionally associated with a serous borderline tumour/atypical proliferati associated with serous borderline tumour, micropapillary variant/non-invasive low-grade serous carcinoma.

{1770}. Lymph node involvement as described above has no adverse effect on outcome. In summary, deaths from SBT/APSTs are due to progression to LGSC which occurs in about 5% {1117} of cases and non-cancer causes (i.e. bowel obstruction or complications from treatment).

Serous borderline tumour - micropapillary variant / Non-invasive low-grade serous carcinoma

Definition

A non-invasive tumour displaying a non-hierarchical branching architecture featuring micropapillary and/or cribriform patterns composed of rounded cells with scant cytoplasm and moderate nuclear atypia.

ICD-O code 8460/2

non-hierarchical branching architecture in which a myriad of fine, micropapillae, usually five times taller than they are wide, emanate directly from large, often fibrotic papillae. The micropapillae have scant or no stromal cores and in contrast to serous borderline tumour/atypical proliferative serous tumour (SBT/APST), which contain columnar cells that are frequently ciliated, the cells in these tumours are cuboidal to polygonal with a high nuclear to cytoplasmic ratio and small, uniform, more atypical nuclei. Small but prominent (often cherry-red) nucleoli are seen and cilia are conspicuously absent.

The mitotic index is low but typically higher than in SBT/APST. Some tumours display a cribriform pattern on the surfaces of the papillae and occasional tumours are purely cribiform and/or show a slit-like glandular pattern without micropapillae. The micropapillary/cribriform features may coexist with usual SBT/APST. A diagnosis of non-invasive LGSC requires at least one confluent area of micropapillarity measuring 5 mm in one dimension and

WHO Classification of Tumours of Female Reproductive Organs

Consensus and Editorial meeting, IARC, Lyon, 13–15 June 2013

Serous Borderline Tumors

	Typical n=102 (%)	Micropapillary n=18 [a] (%)
Mean age	**45**	**37**
Bilateral	**22/96** (23)	**12** (67)
Exophytic growth	**27/92** (29)	**7/16** (44)
Stage		
I	**78** (76)	**5** (28)
II+	**24** (24)	**13** (72)
		(p = 0.0001)
Noninvasive implants	**20** (83)	**12** (92)
Invasive implants	**4** (17)	**1** (8)

(a) Microinvasive + micropapillary (3 cases)

Prat J, de Nictolis M
Am J Surg Pathol 2002

SBT - Micropapillary

(More invasive implants?)

1999	Eichhorn et al	Possible
2002	Slomovitz et al	No
2002	Deavers et al	Yes (17% vs 6%)
2002	Prat & De Nictolis	No
2003	Gilks et al	No (Yes?)
2005	Longacre et al	Yes

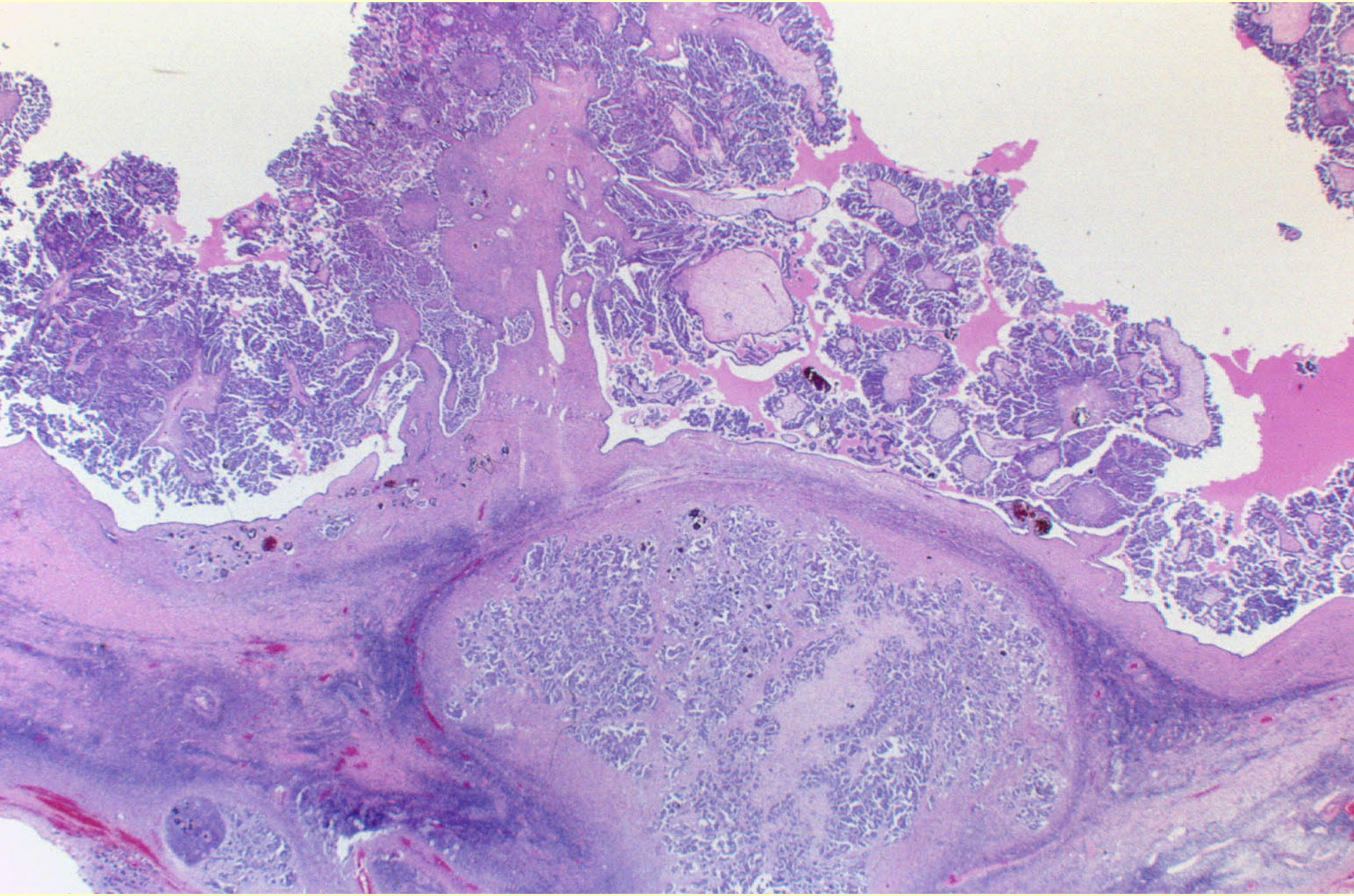
Overall survival similar to typical SBT

Serous Borderline Tumors

(Risk of progression)

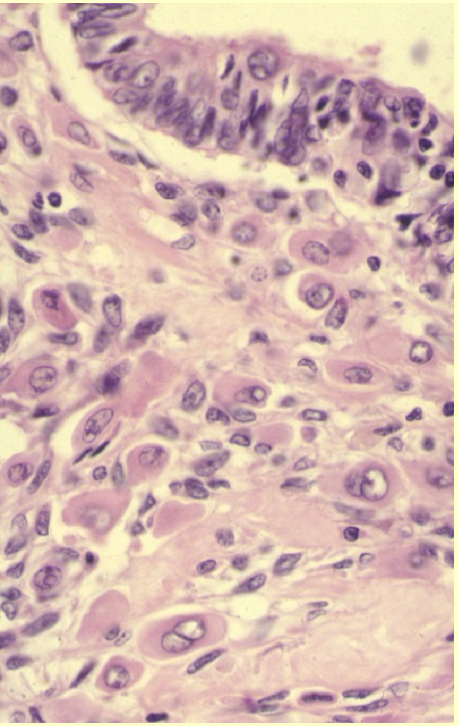
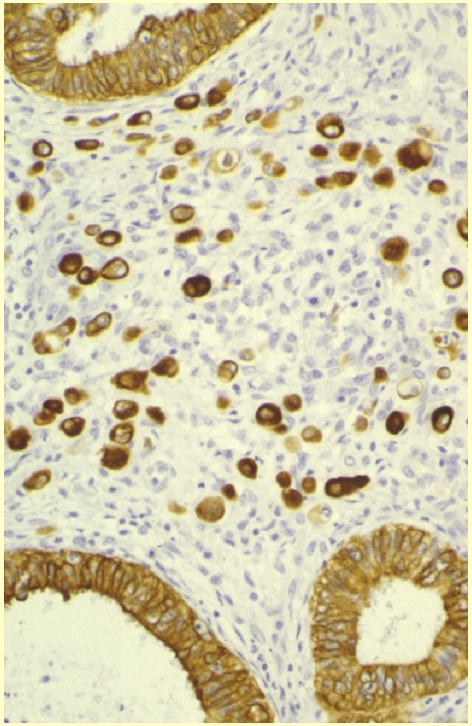
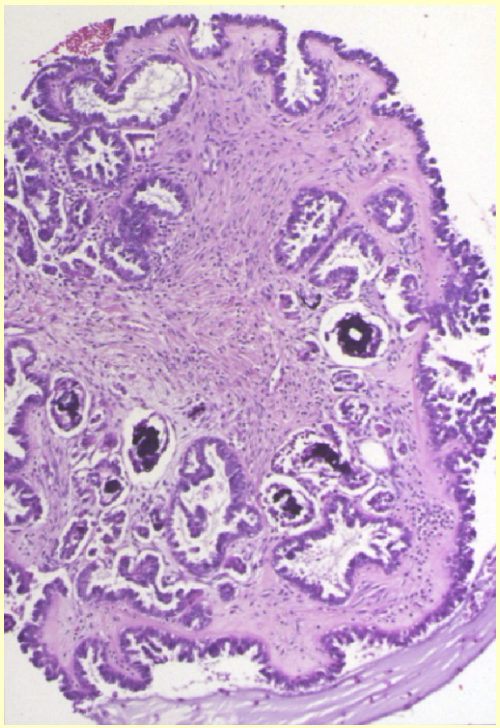
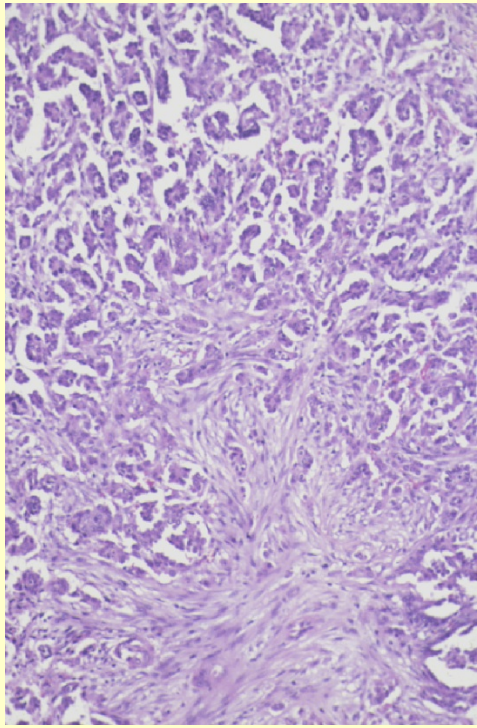
- Stage
- Florid epithelial proliferation
  (MP-cribriform pattern)
- Microinvasion (?)
- Type of peritoneal implants
- Other factors yet unidentified

TA Longacre et al
Am J Surg Pathol 2005



Carcinoma (> 3 mm) in SBT-MP

SBT with Microinvasion < 10 mm^2

Cumulative literature: Excellent prognosis
Stanford data: Risk factor for disease progression

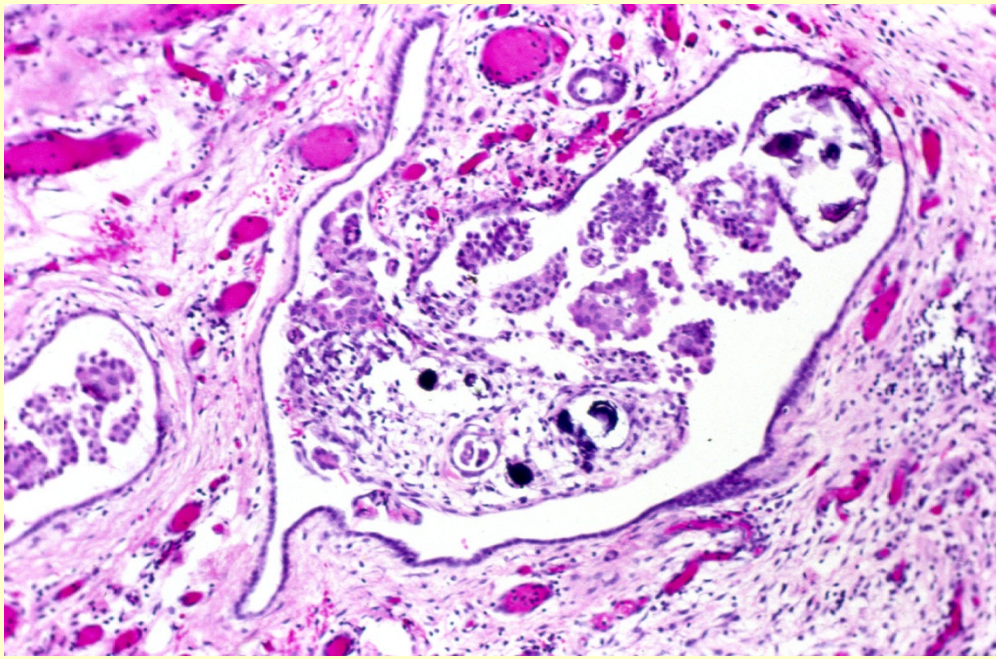
Serous Borderline Tumors

Peritoneal Implants (30%)

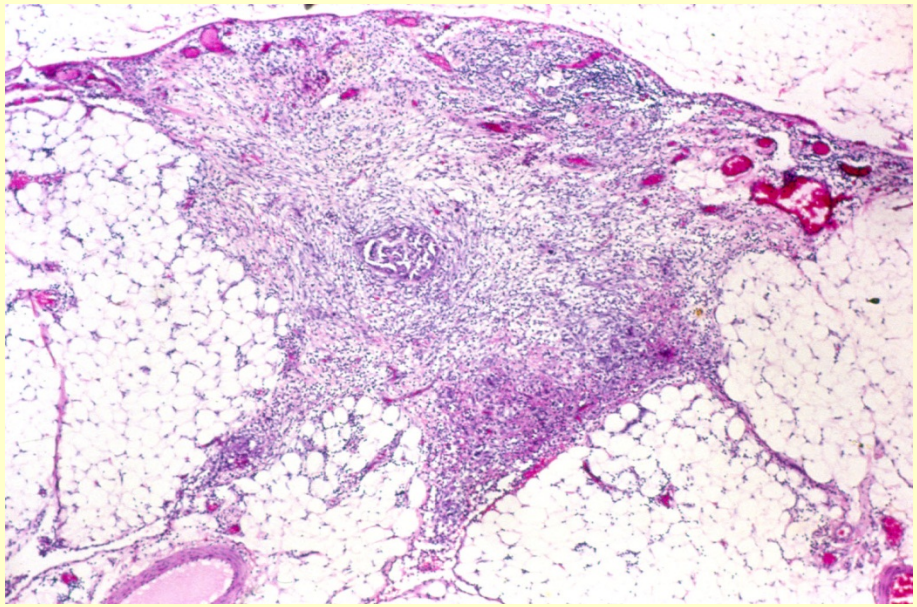
Peritoneal Implants (SBT)

- Non-invasive
  - Epithelial
  - Desmoplastic
- Invasive

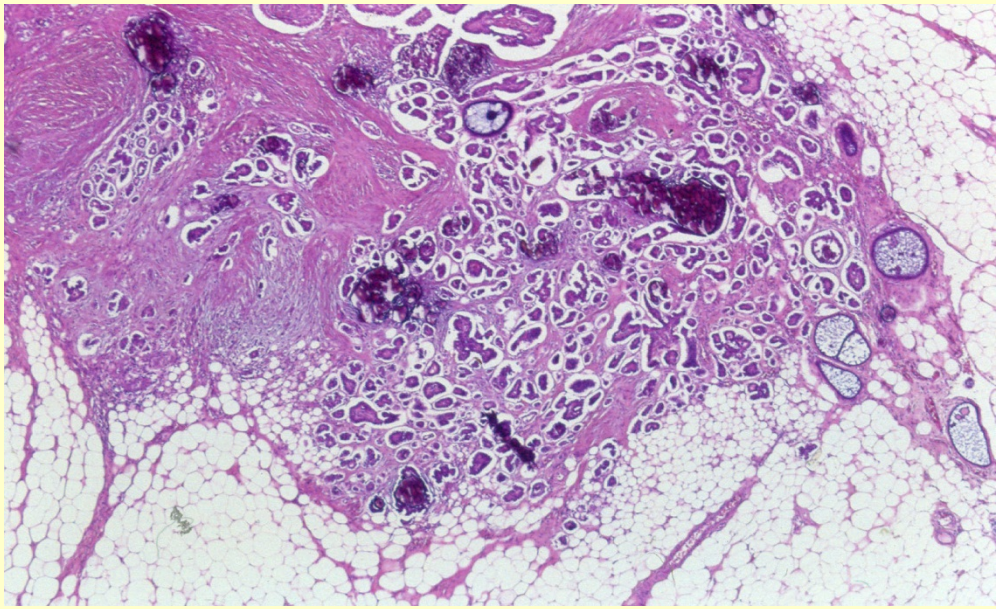
Bell DA, et al
Cancer 1988; 62:2212



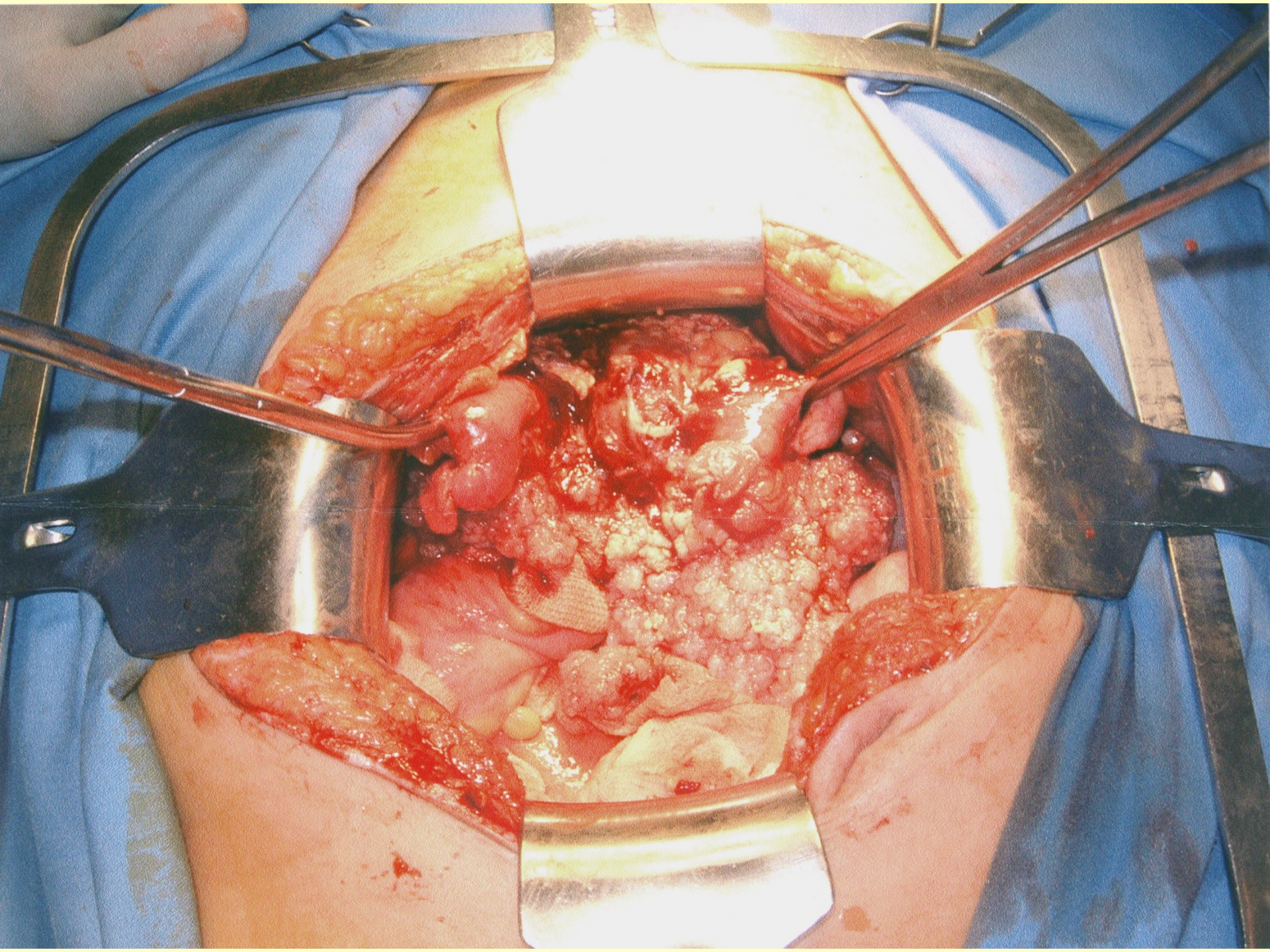
Noninvasive epithelial implant

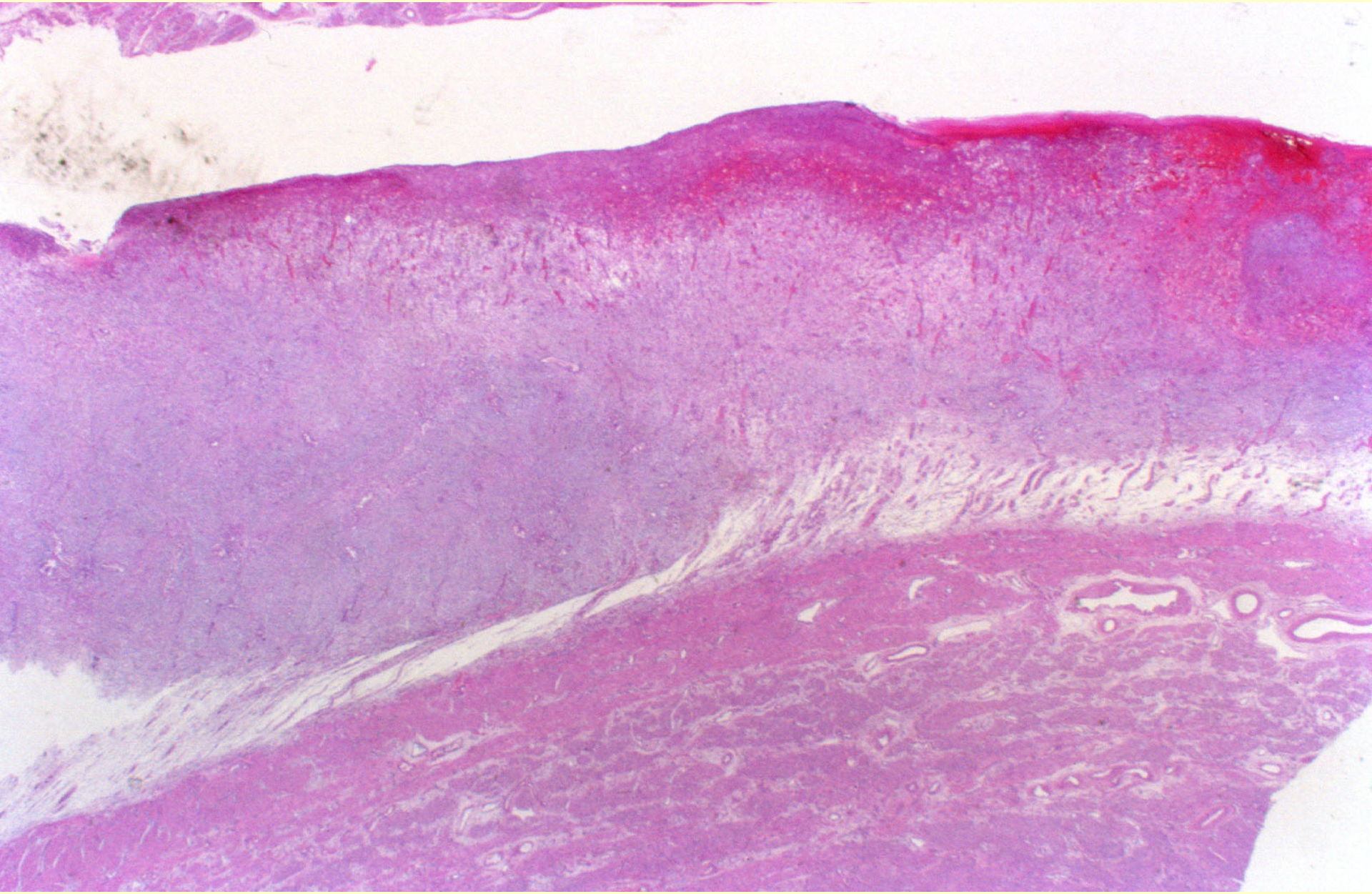


Noninvasive (desmoplastic) implant

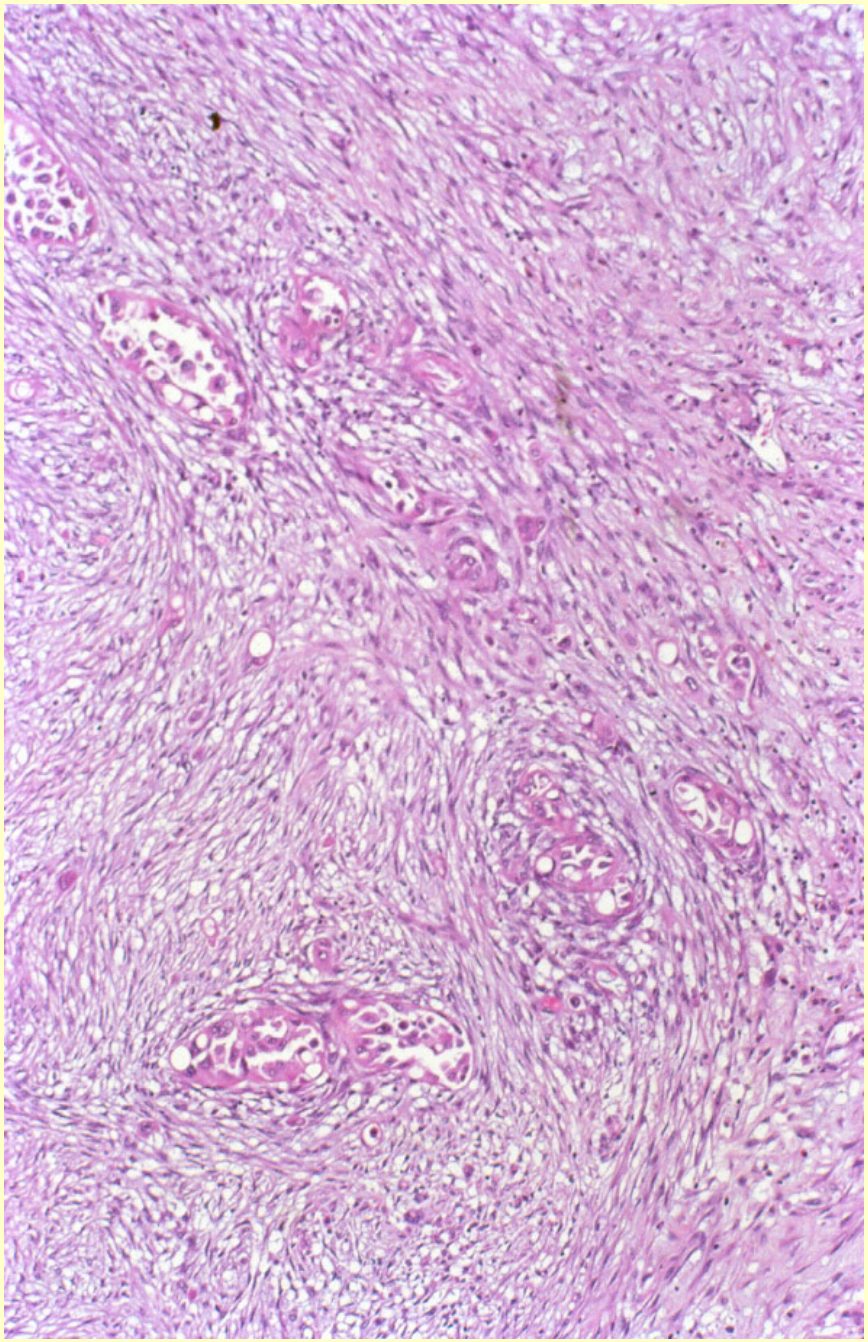


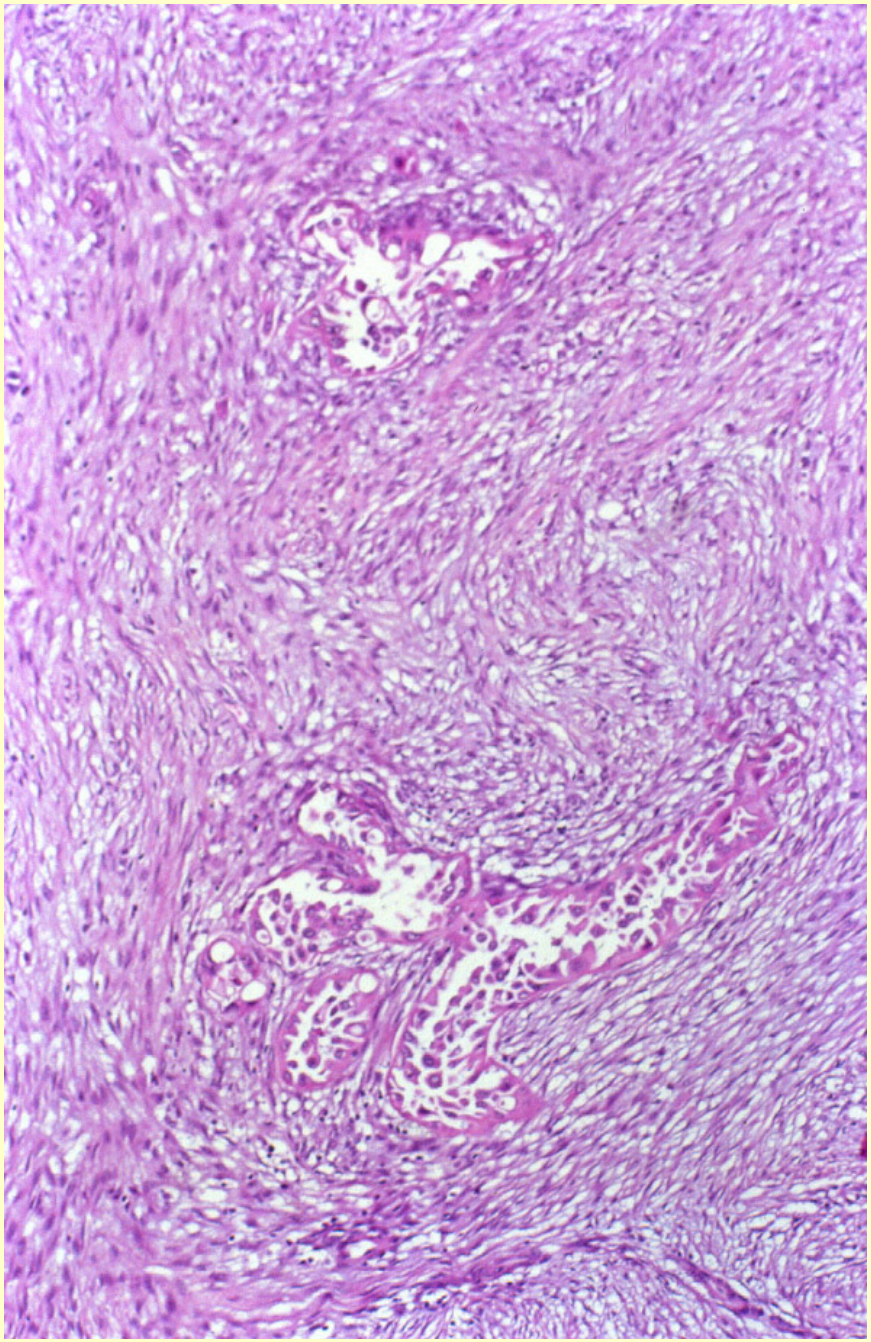
Invasive implant





Tumor - uterine serosa





Tumor - uterine serosa