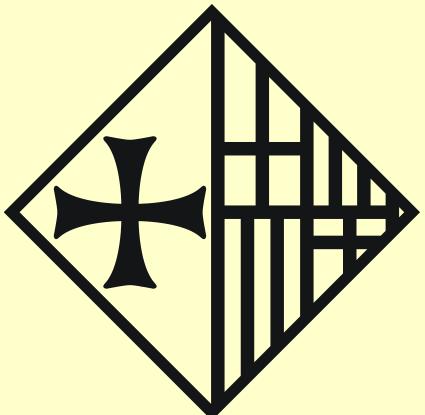


*prIME Oncology's 2015 Progress and
Controversies in Gynecologic Oncology
Conference, 16-17 January, 2015*

Pathologist's View on the Current Status of Borderline Tumors

Jaime Prat, M.D., Ph.D., F.R.C.Path.

Hospital de la Santa Creu i Sant Pau
Autonomous University of Barcelona, Spain



“There are no borderline tumors, only borderline pathologists”

Julian Smith, M.D.
Gynecologic Oncologist
M.D. Anderson Hospital
Houston, TX, USA (1975)

Ref. R.E.Scully. Discurs . Doctor Honoris Causa. Universitat Autonoma de Barcelona.
8 de novembre 2000

Ovarian Epithelial Tumors

WHO 1973 - 2014

Serous

Mucinous

Endometrioid

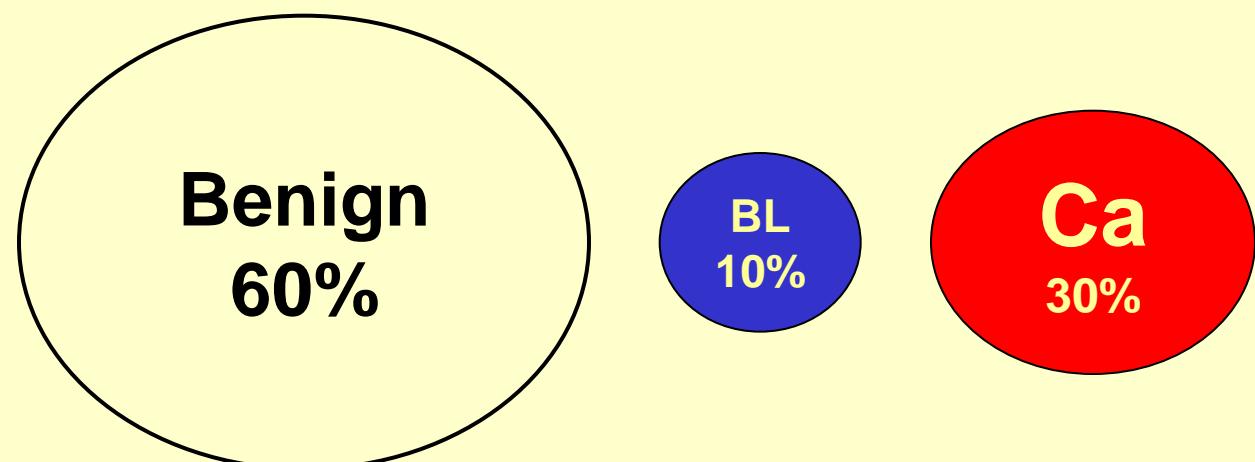
Clear cell

Transitional

Squamous

Mixed

Undifferentiated



Borderline Ovarian Tumors

- Epithelial hyperplasia
- Nuclear atypia
- Mitotic activity
- NO “destructive” stromal invasion

WHO 1973-2014

Serous Borderline Tumors

- The term “atypical proliferative” is redundant and misleading
- Although the word 'borderline' may suggest uncertainty, it accurately describes the ambiguous histologic and biologic features of these neoplasms

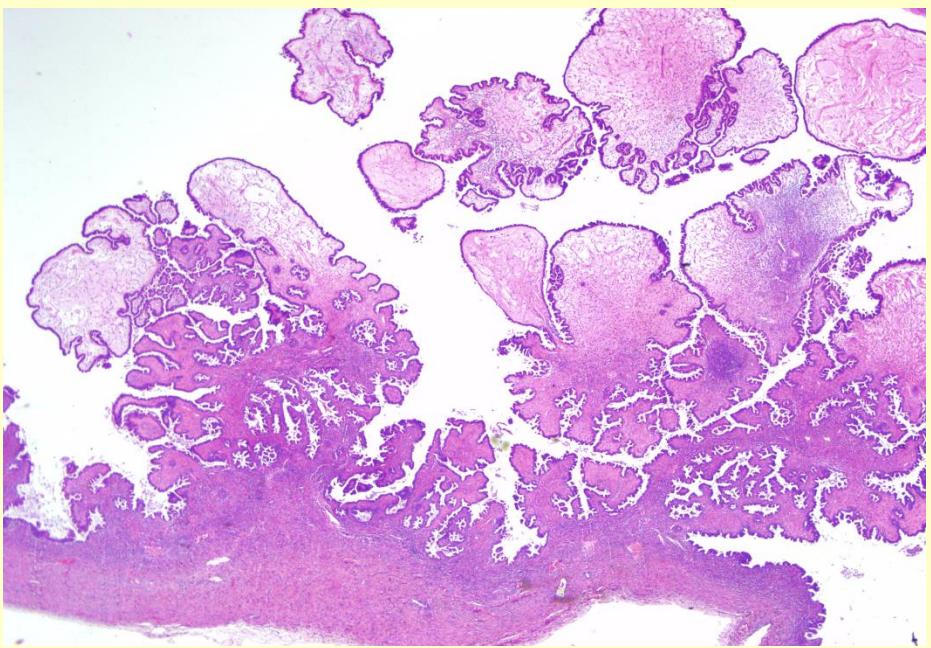
Serous Tumors of the Ovary

(30%-40% of all ovarian tumors)

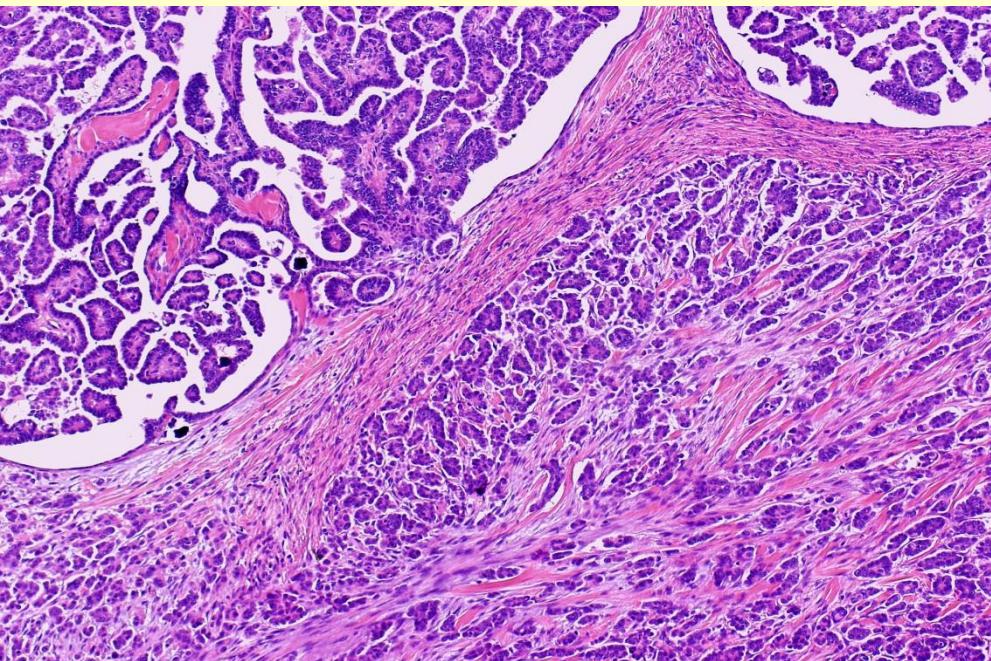
- Benign 70%
- Borderline 5%-10%
- Carcinomas 20%-25%

Serous Borderline Tumors

Frequency	25%-30% of Non-Bg
Age	30-50 yrs
Bilaterality	30%
Stage I	70%

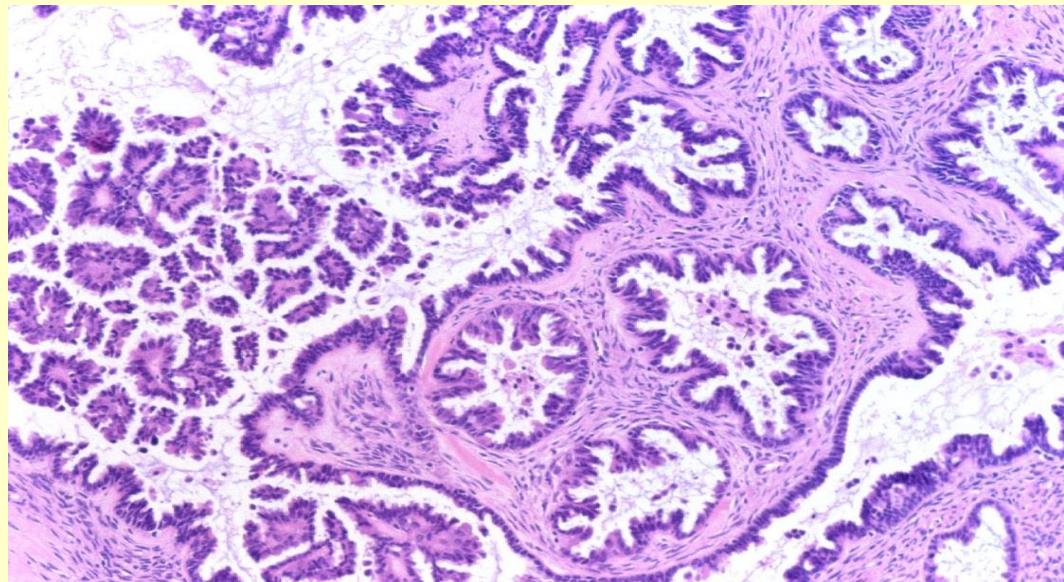
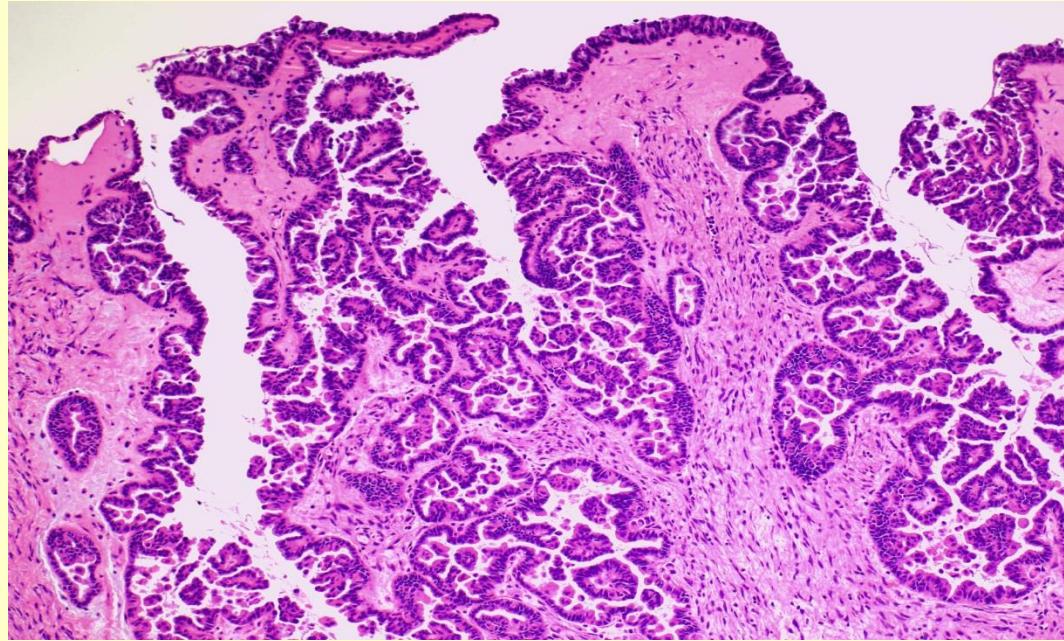
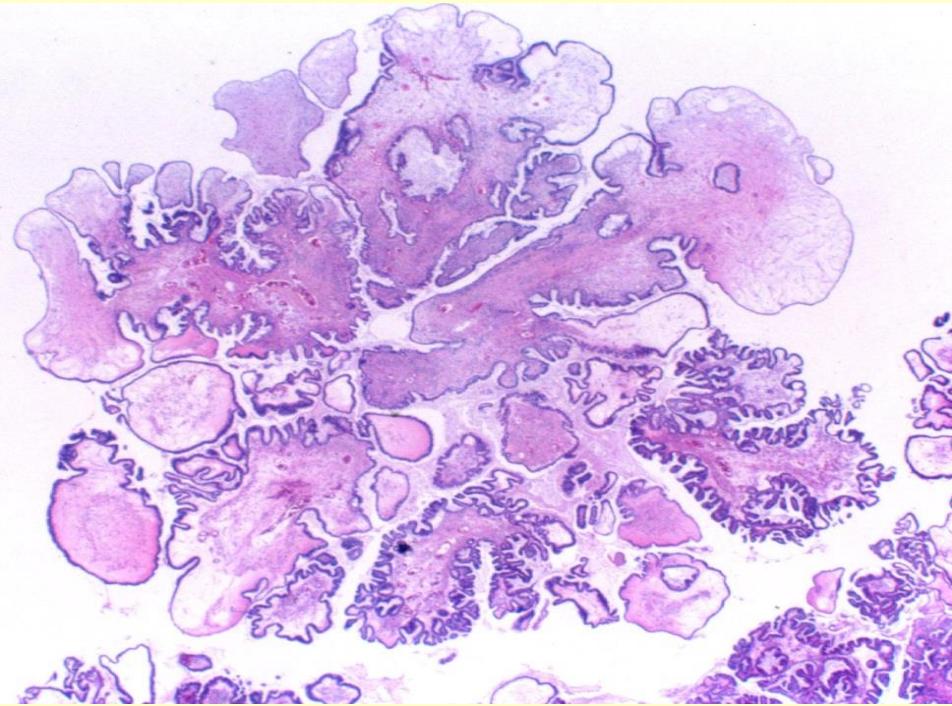


Serous Borderline Tumor (SBT)



SBT + Low-Grade Serous Carcinoma

Serous Borderline Tumor



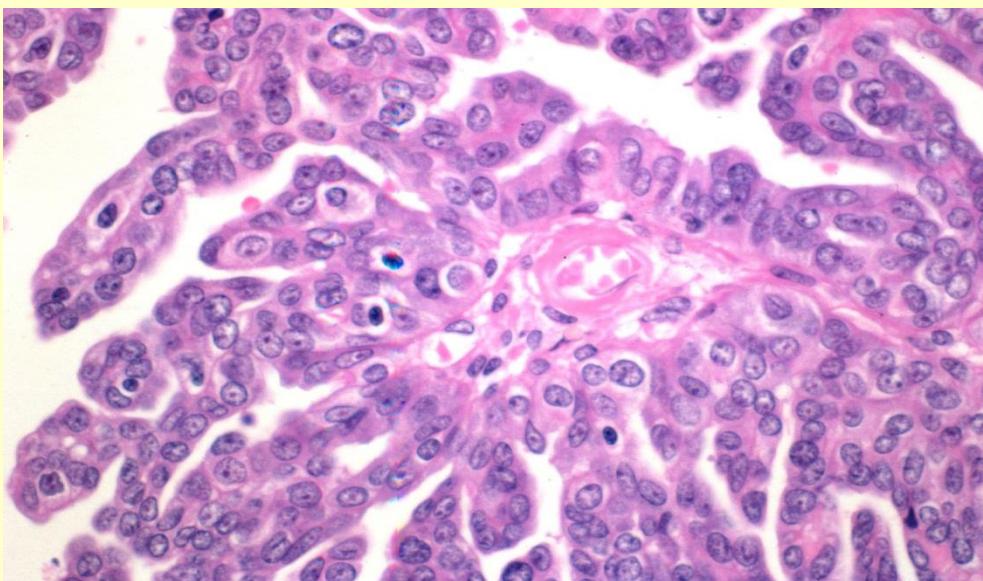
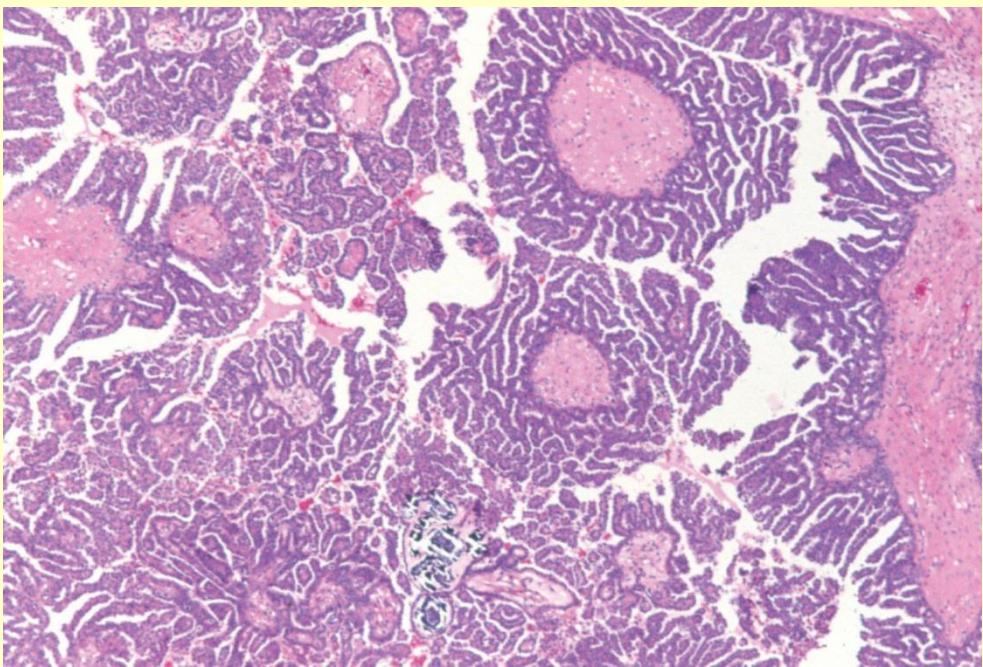
Diagnostic Features

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

Serous Borderline Tumors

(Micropapillary pattern)

- Nonspecific term (“flaw”)
- All SBT are micropapillary (descriptively)
- How many micropapillae? One? Two? 10? 100? 1000?...

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
2005	Longacre et al	Yes

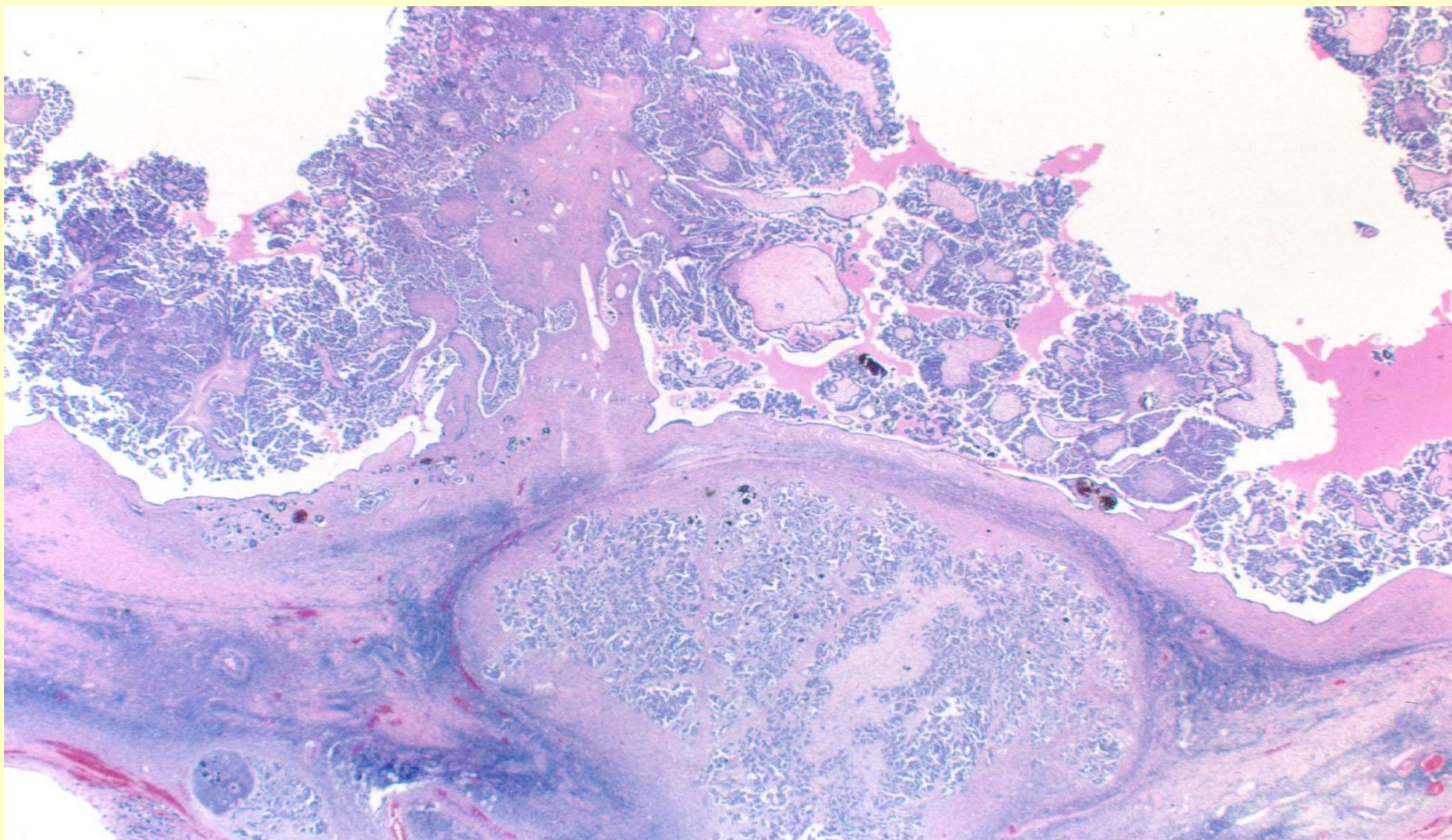
Overall survival similar to typical SBT

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)
	<i>(P = .0001)</i>	
 Noninvasive implants	20 (83)	12 (92)
Invasive implants	4 (17)	1 (8)

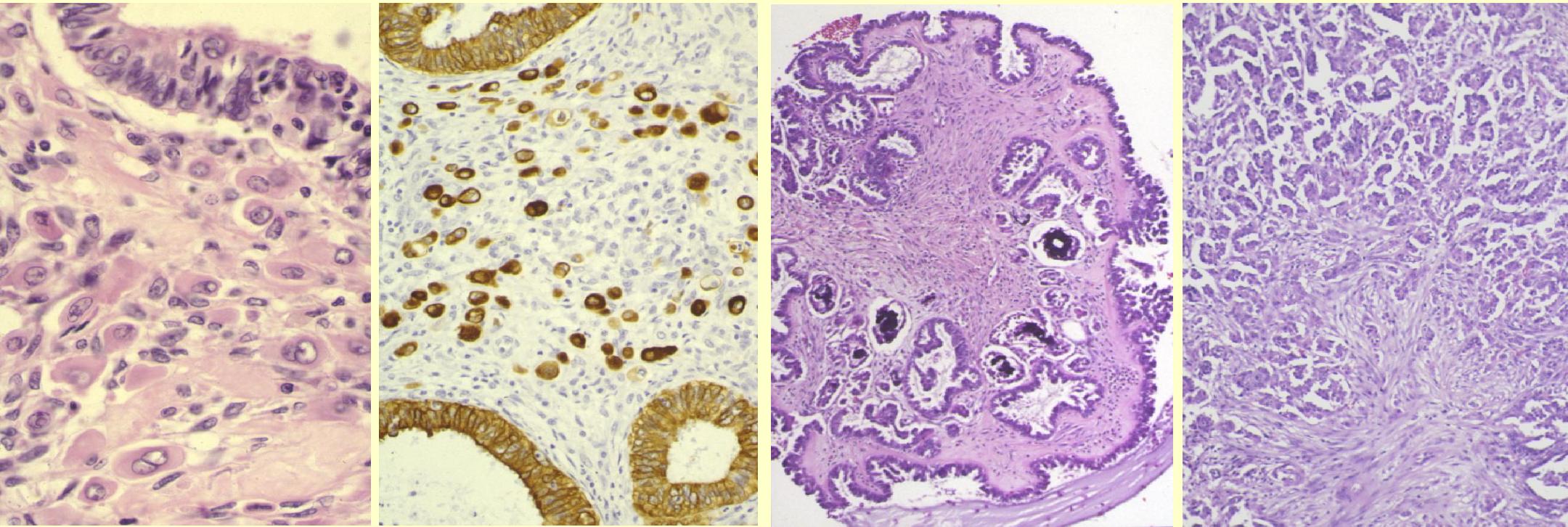
(a) Microinvasive + micropapillary (3 cases)

Prat J, de Nictolis M. *Am J Surg Pathol.* 2002;26(9):1111-1128.



Carcinoma (>3 mm) in SBT-MP

SBT With Microinvasion <10 mm²



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

SBT With Microinvasion

- Cells with abundant eosinophilic cytoplasm (EC) are 100% *BRAF*-mutated
- Loss of ER, PR, WT-1 expression
- Senescence markers: p16, p21, and low Ki-67 labeling index
- Apoptosis
- Blocking progression of SBT to LGSC
- Terminal differentiation
- Favorable outcome

Maniar KP, et al. *Am J Surg Pathol.* 2014;38(6):743-755.
Zeppernick F, et al. *Am J Surg Pathol.* 2014;38(12):1603-1611.

Serous Borderline Tumors

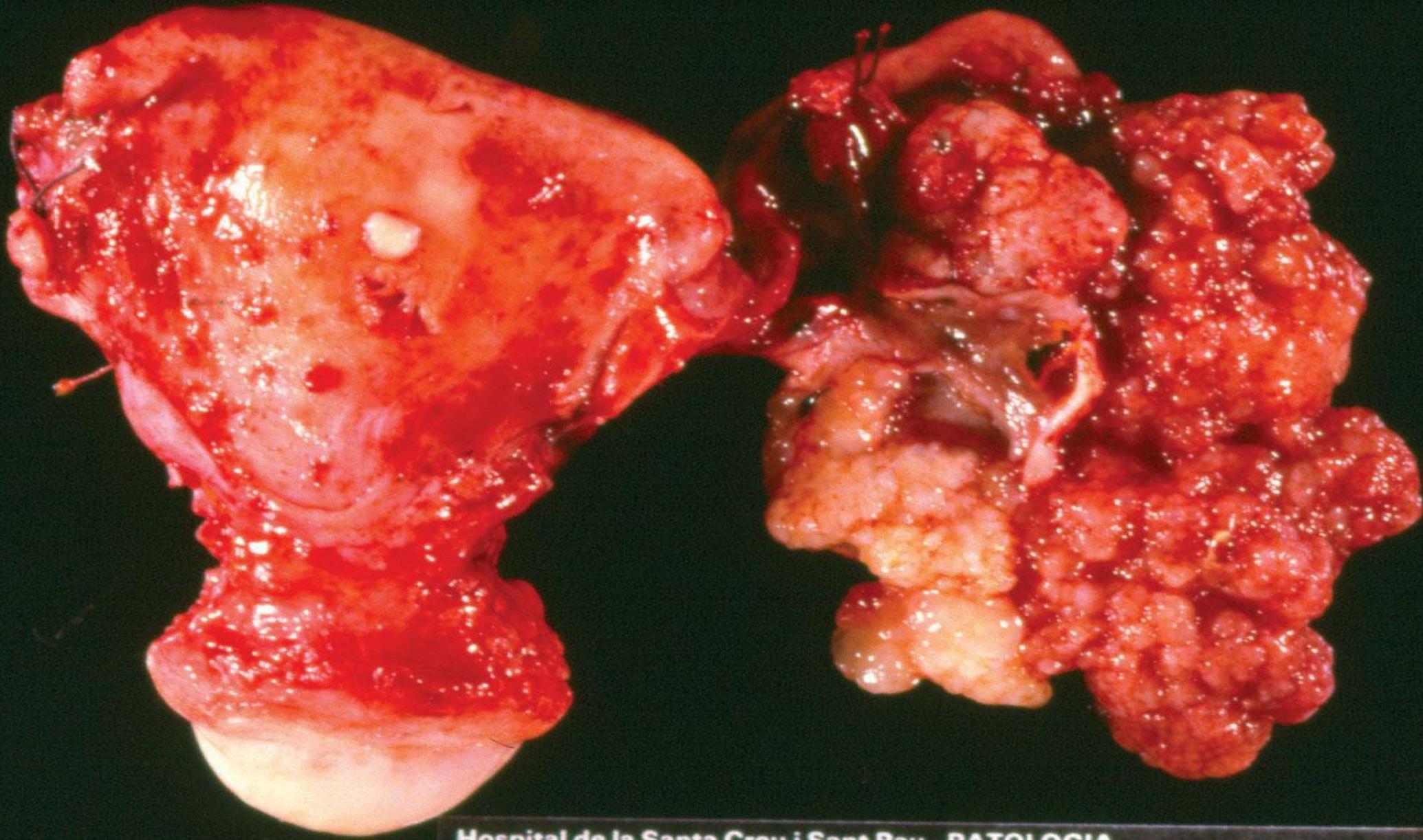
(Risk of progression)

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

Longacre TA, et al. *Am J Surg Pathol.* 2005;29(6):707-723.

Serous Borderline Tumors

Peritoneal Implants (30%)



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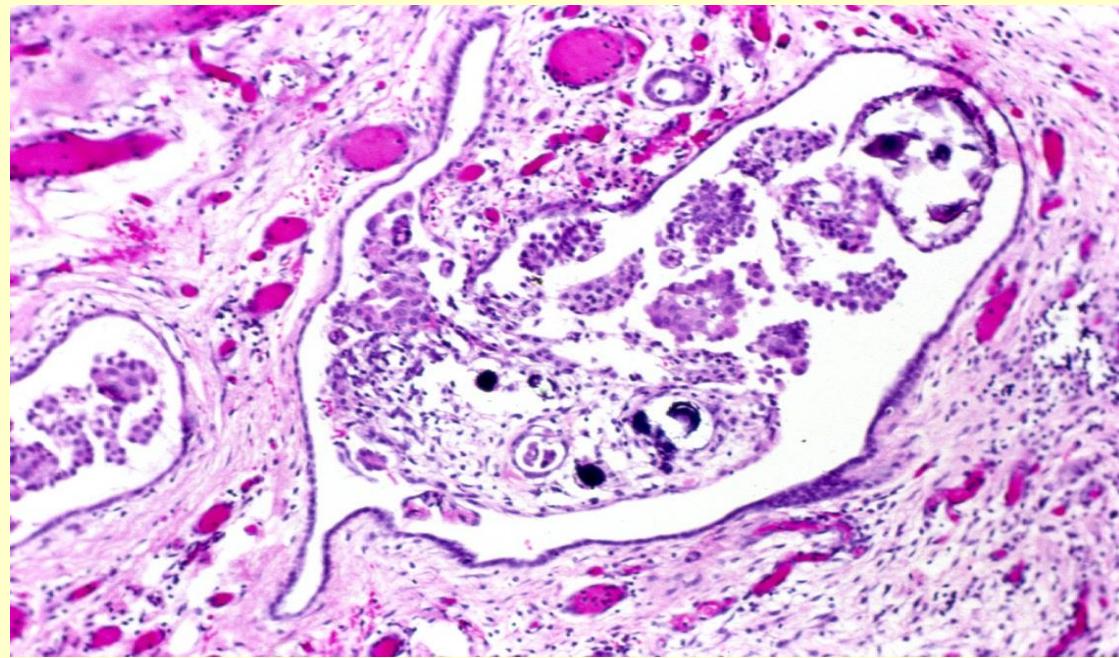
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0 1 2 3 4 5 6 7 8 9 10 11

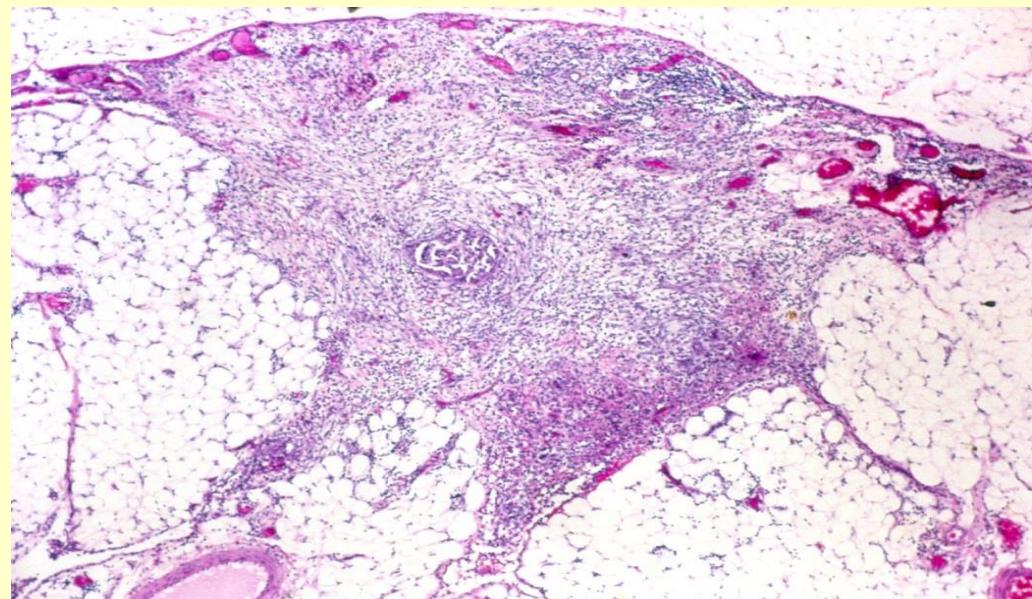
Peritoneal Implants (SBT)

- Noninvasive
 - Epithelial
 - Desmoplastic
- Invasive

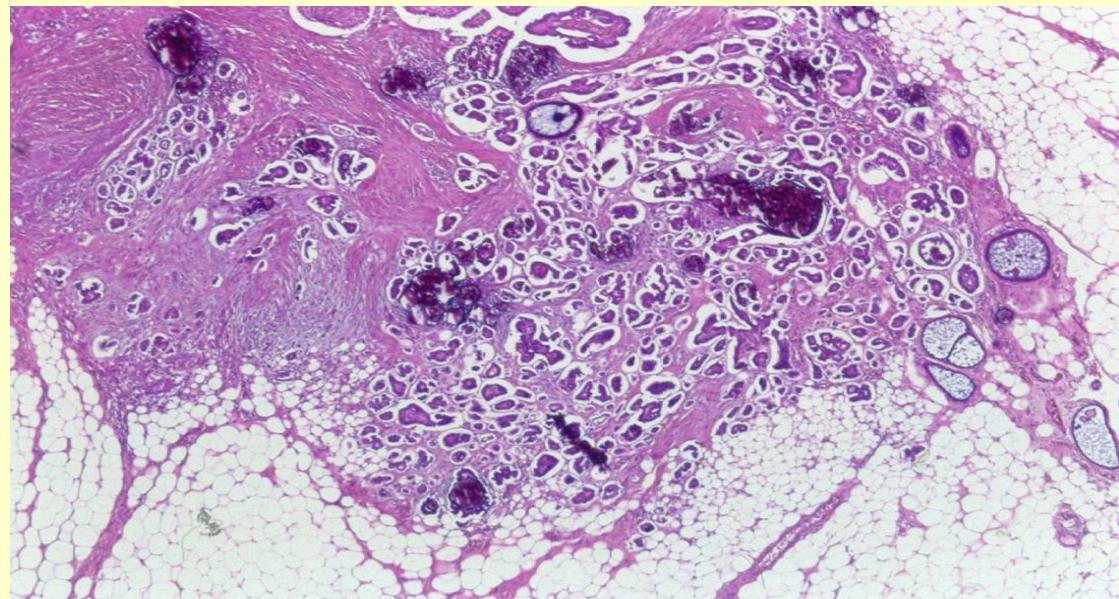
Bell DA, et al. *Cancer*. 1988;62(10):2212-2222.



Noninvasive epithelial implant



Noninvasive (desmoplastic) implant

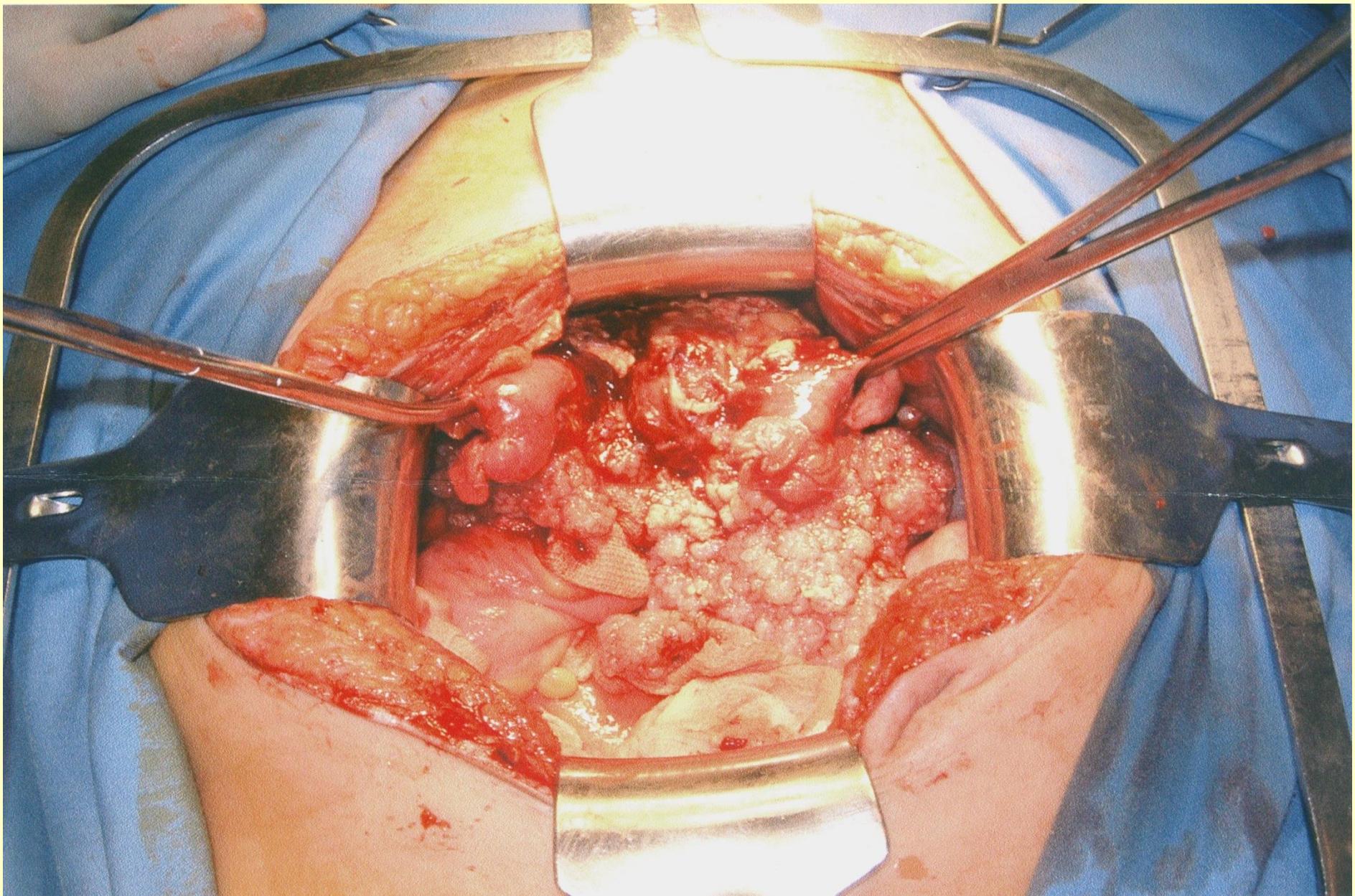


Invasive implant

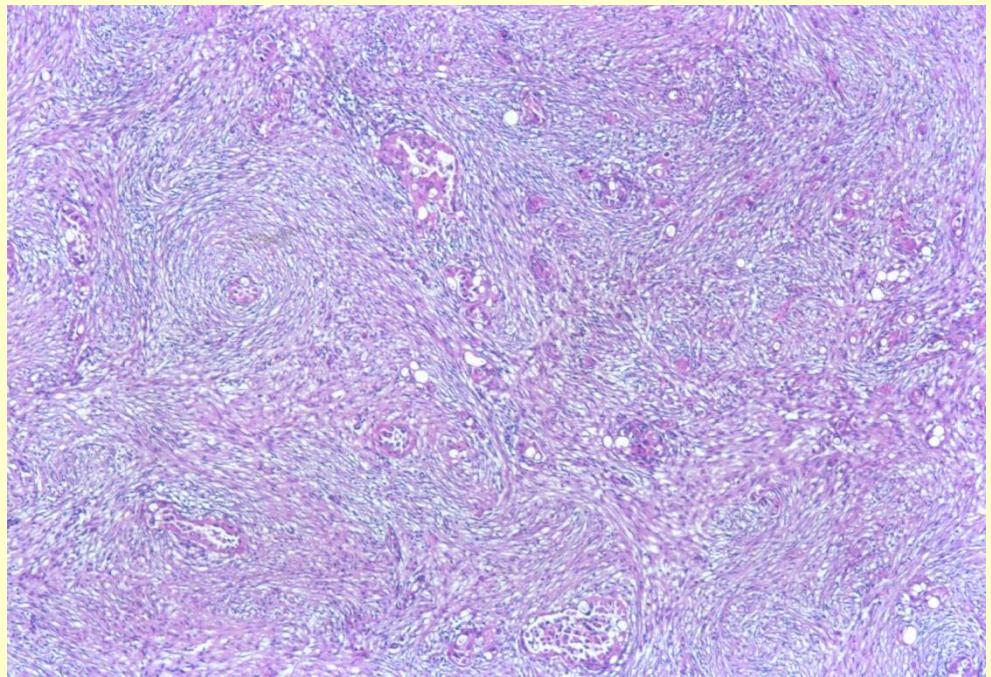
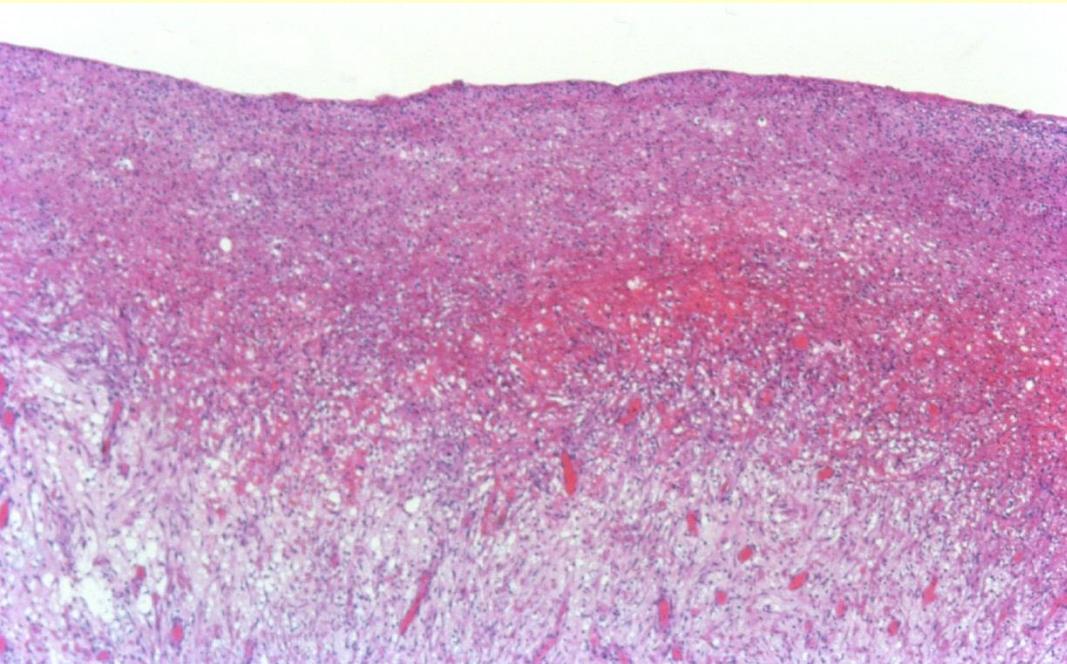
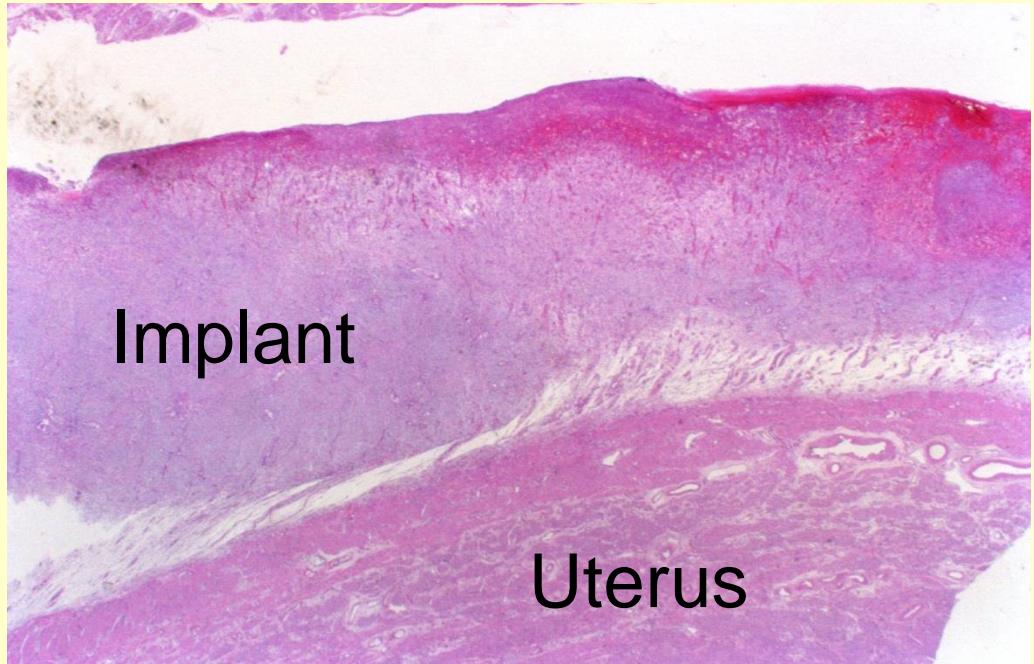
Serous Borderline Tumors

(Death from tumor 1984-2005)

	<u>Non-invasive implants</u>	<u>Invasive implants</u>
McCaughay et al	2/13	4/5
Bell DA et al	3/50	5/6
De Nictolis et al	0/10	4/9
Kennedy and Hart	1/25	0/1
Seidman and Kurman	1/51	2/3
Gershenson et al	6/73	6/39
Eichhorn et al	0/30	2/3
Bell KA et al	2/29	6/31
Prat and de Nictolis	0/34	3/6
Longacre et al	2/75	5/14
	<hr/>	<hr/>
	20/390 (5%)	37/117 (32%)



Serous borderline tumor with noninvasive implants

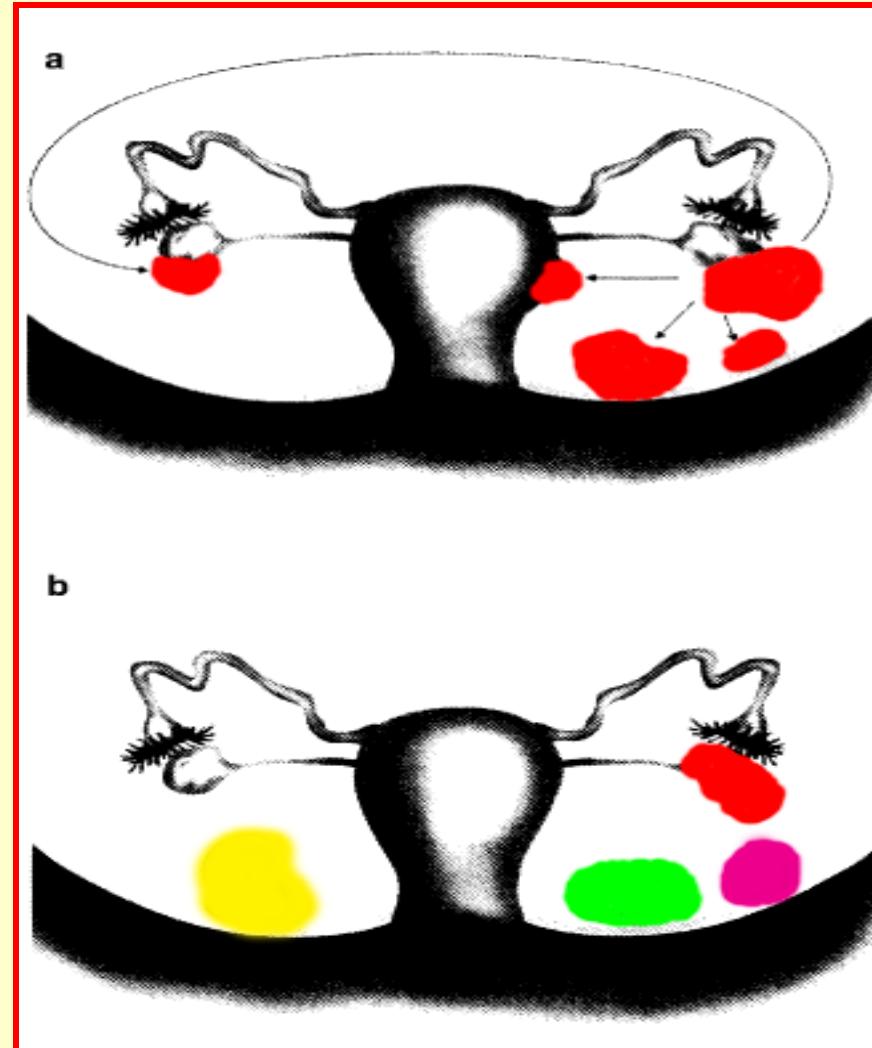


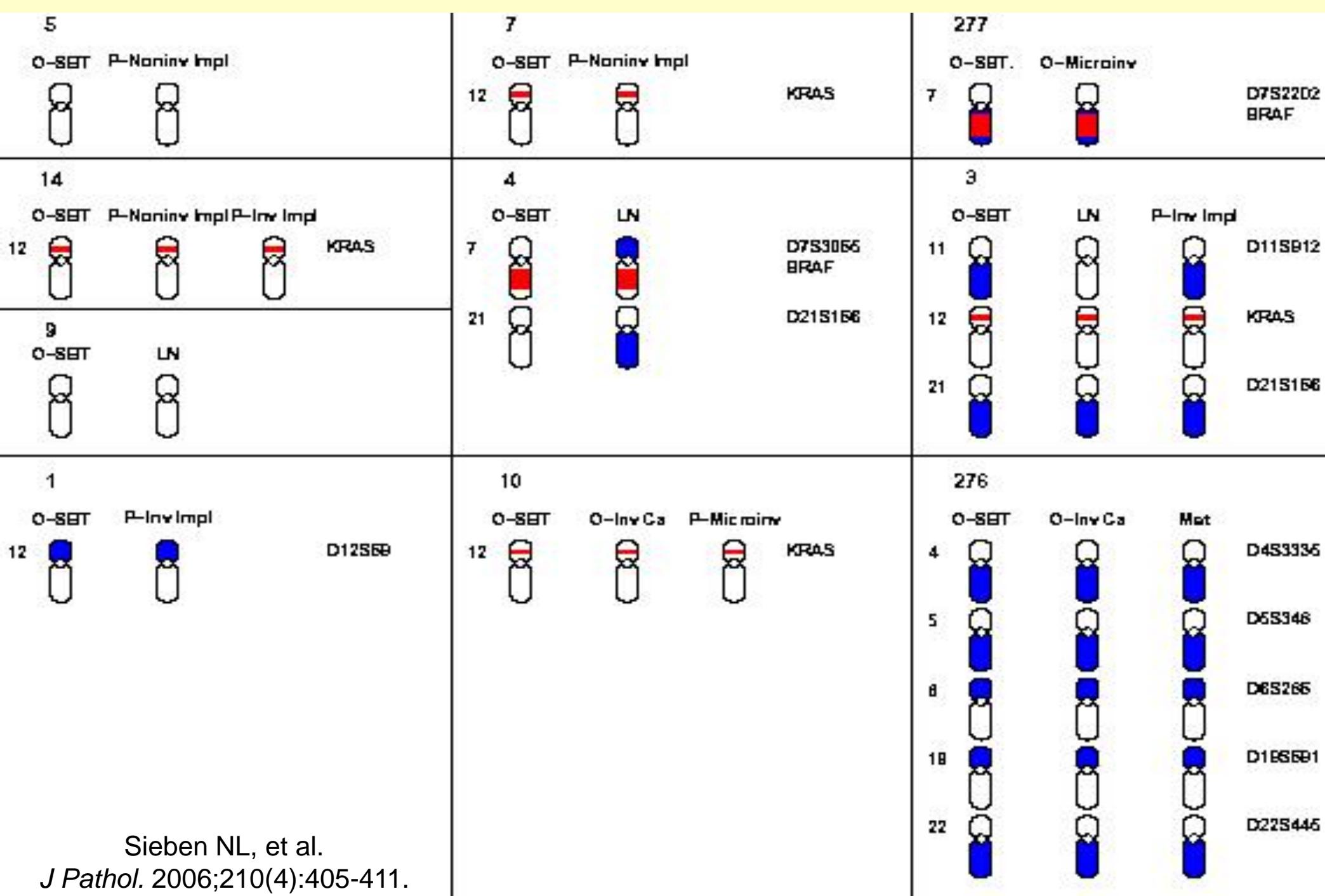
Noninvasive implant

- Zoning: necrosis, hemorrhage, and edema
- Abundant fibrous tissue with few tumor glands

Serous Borderline Tumors

Two hypotheses



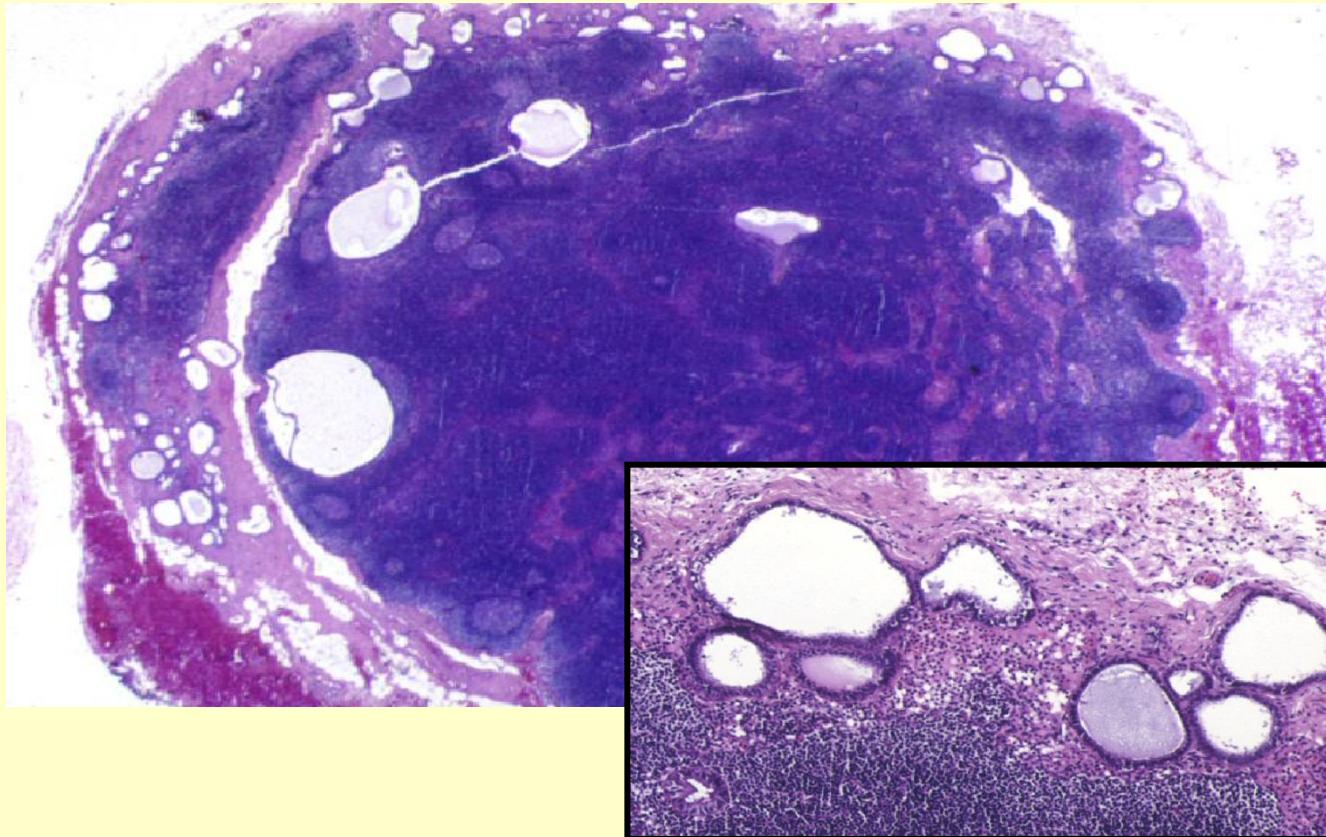


Serous Tumors

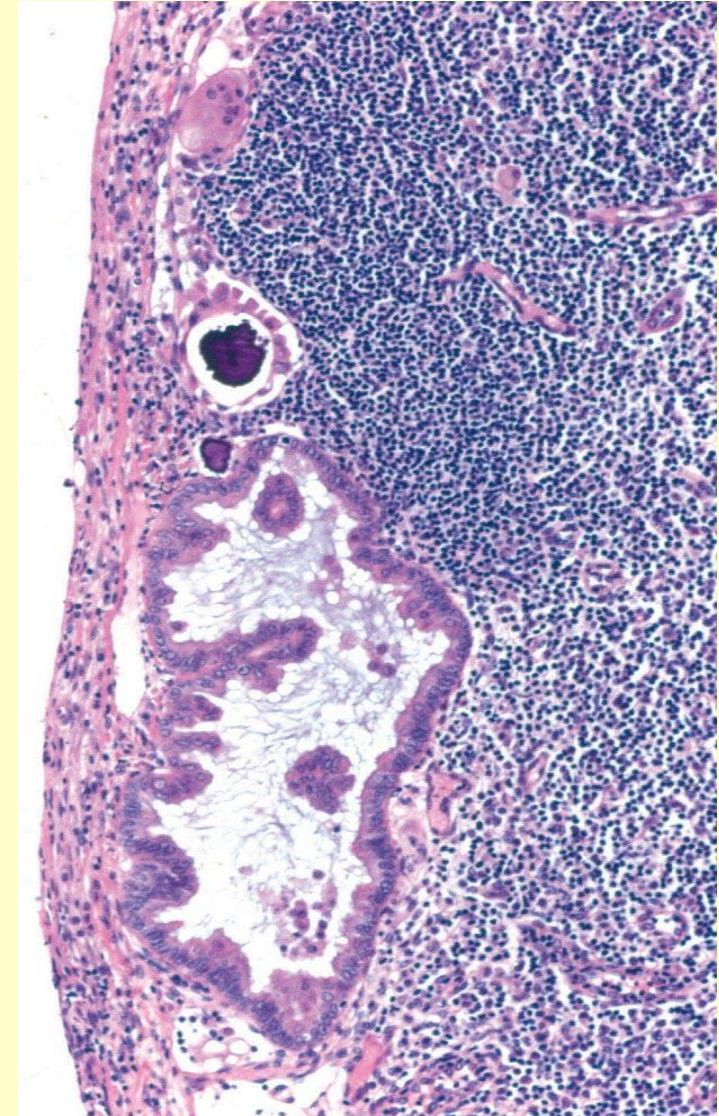
(10-yr Survival)

<u>Bord</u>	<u>Stage</u>	<u>Ca</u>
95%	1	54%
91%	1-4	23%
71%	2-4	20%

SBT in Lymph Nodes: 30%



LN: Mullerian cysts (endosalpingiosis)

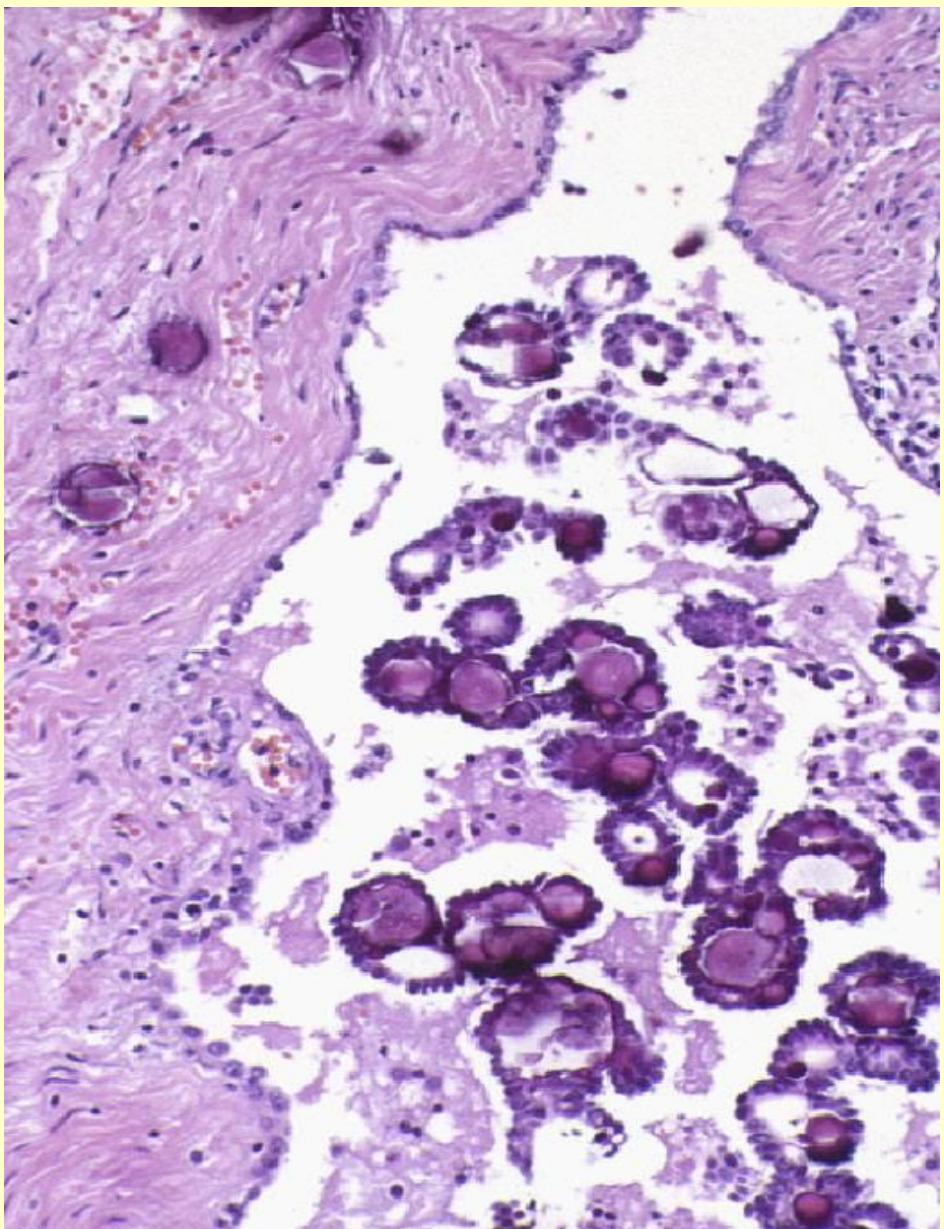
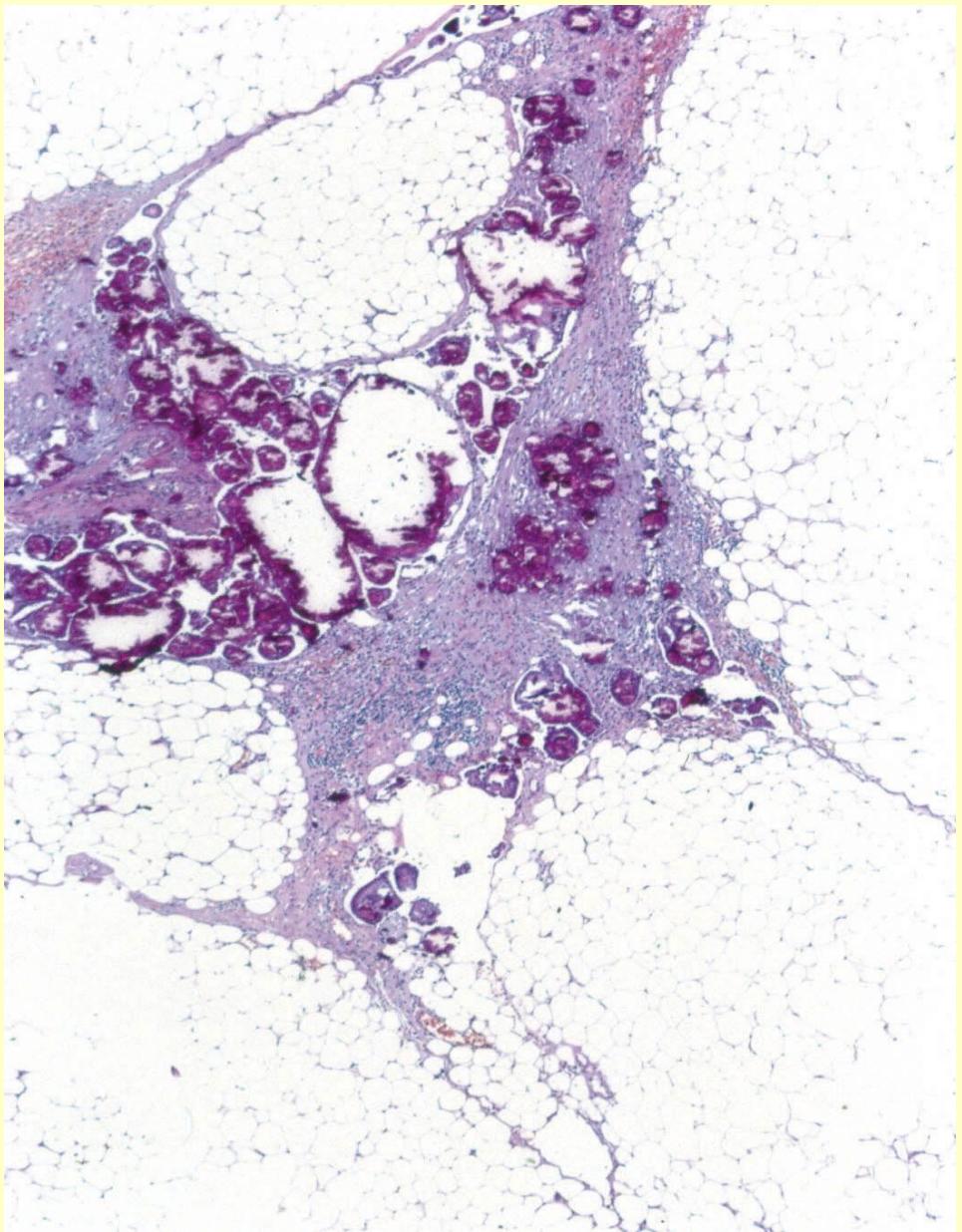


SBT in lymph node

SBT in Lymph Nodes

(30%)

- Gland inclusions (15%) → SBT
- SBT in lymph nodes
- Literature: No decreased survival
- SBT may originate in lymph nodes from endosalpingiosis



SBT of peritoneum without ovarian tumor

Serous Borderline Tumor

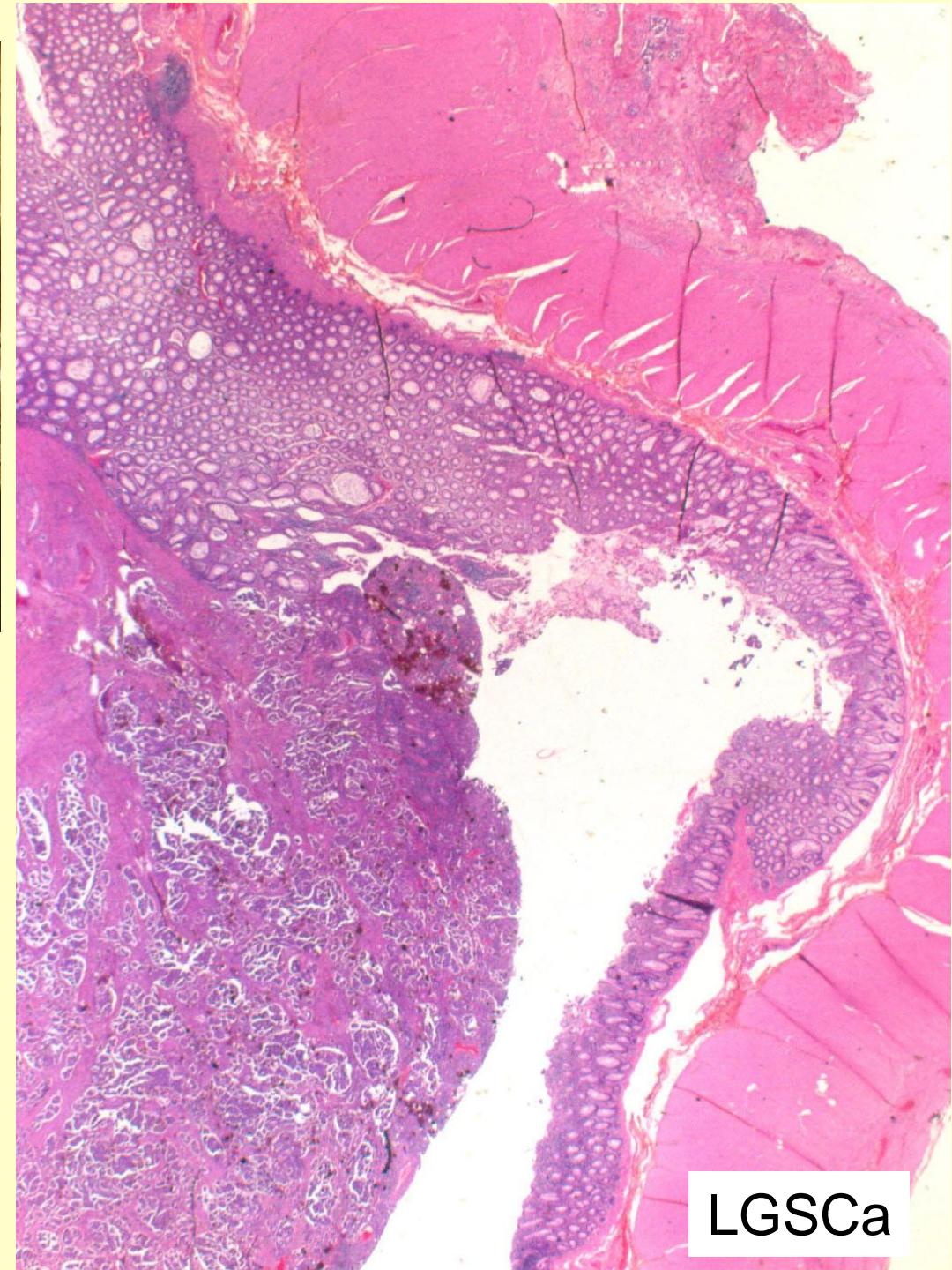
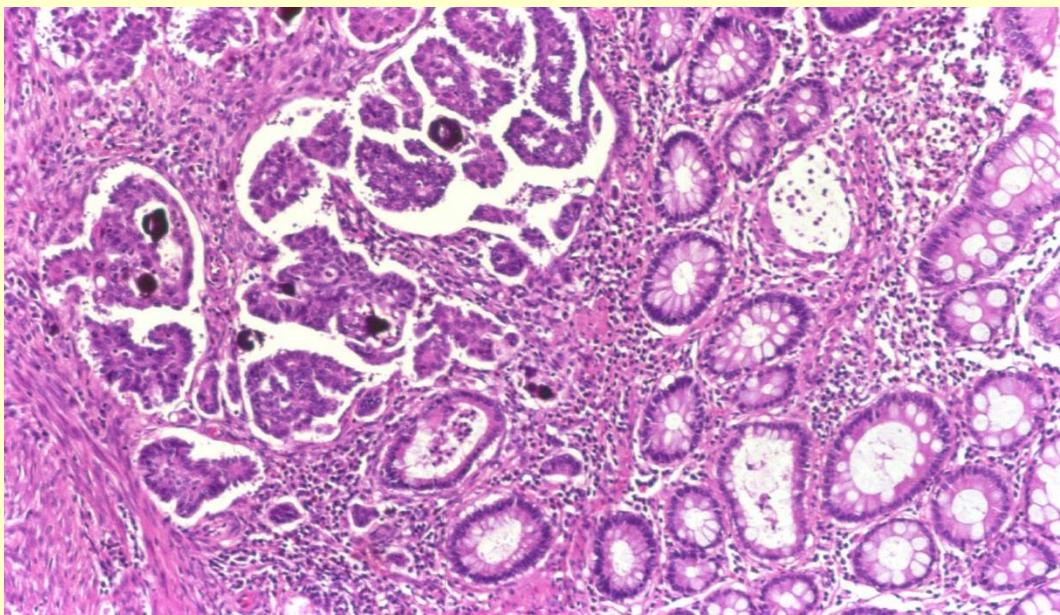


Carcinoma

- Rare
- Usually as low-grade carcinoma
- Limited sampling?
- Second primary?
- Stanford data: 6%-7% (late, with surface involvement)

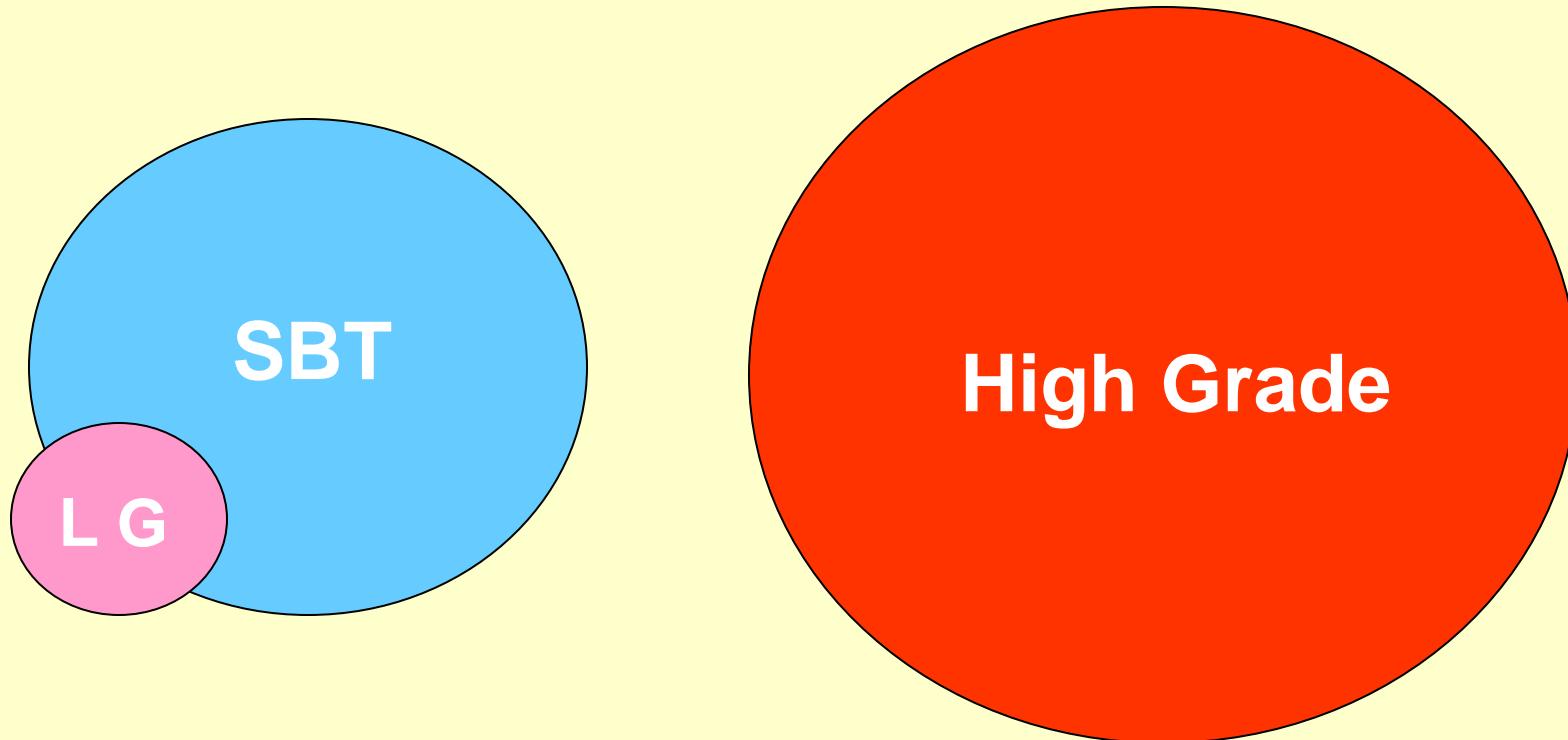


SBT + LGSCa



LGSCa

Ovarian Serous Tumors



Serous Tumors

(Pathogenesis - Dualistic model)

Bg → SBT → SBT-MP → LGSCa (Inv) Low-Gr Serous Ca

KRAS and *BRAF* mutations (70%)

High-Grade Serous Ca

p53 mutations, LOH 17q (80%)

BRCA inactivation (80%)

HER-2/neu amplification/overexpression

Singer G, et al. *Am J Pathol.* 2002;160(4):1223-1228.

Mutational Analysis

Tumor Subtype	<i>BRAF</i> Mutation	<i>KRAS</i> Mutation
Serous Borderline Tumor	20%-40%	40%
Low-grade SC	5%	20%-40%
High-grade SC	0%	0%-14%

Serous Borderline Tumors (SBTs)

(Summary)

- The vast majority of SBTs (are associated with good prognosis)
- Recurrence in contralateral ovary: 5%-10%
- Micropapillary pattern is a small risk factor. Prognosis is poor only with invasive implants
- Only SBT with invasive peritoneal implants may progress to low-grade serous carcinoma (rare – 6%-7% of SBTs)
- Non-invasive implants, common and benign (no treatment)
- Invasive implants, rare (12% of implants) and fatal (clonal)
- Invasive implants represent superficial and small foci of peritoneal low-grade serous carcinoma

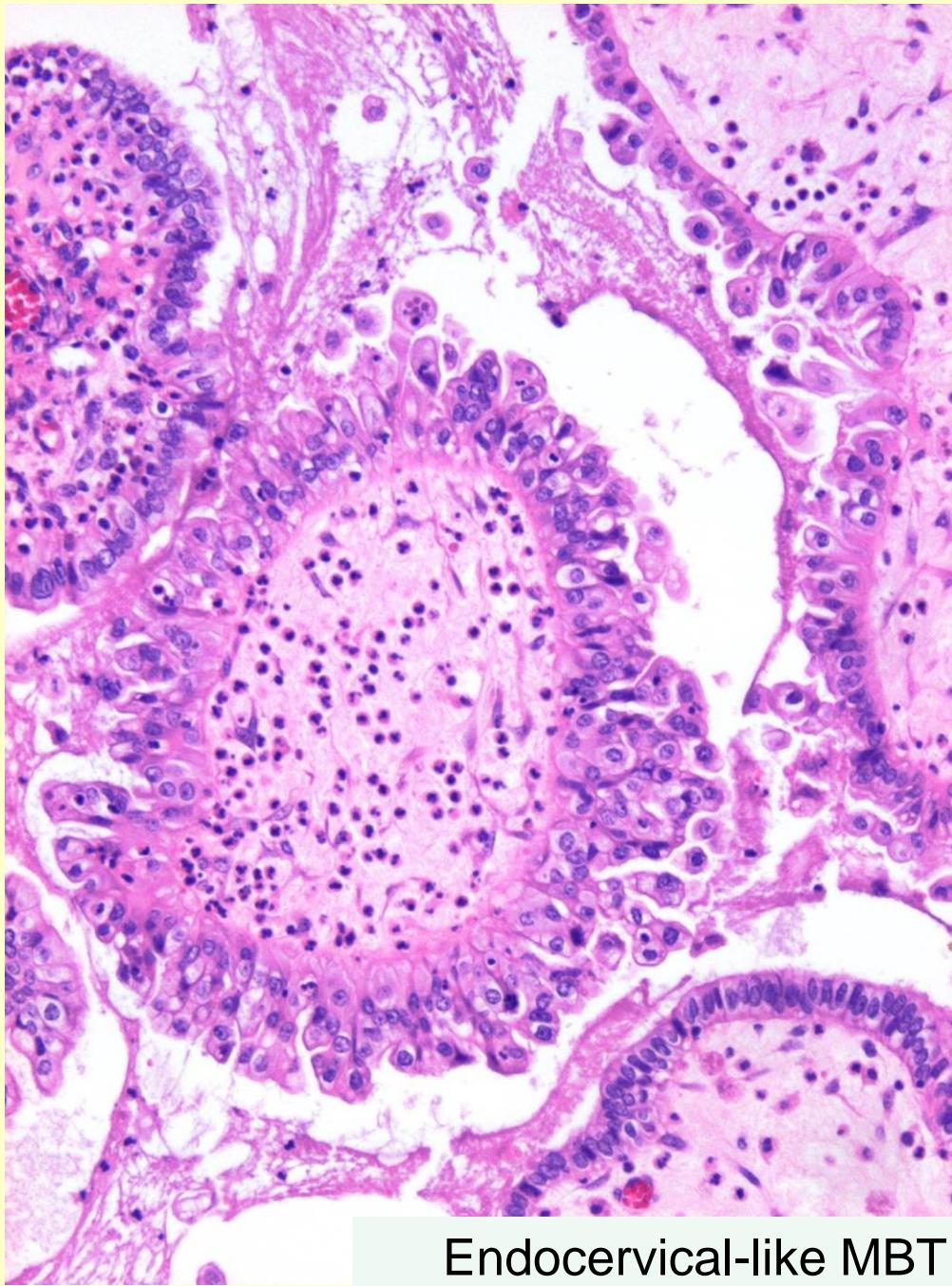
Mucinous Tumors of the Ovary

(10%-15% of all ovarian tumors)

- Benign 80%
- Borderline 17%
- Carcinomas 3%

Mucinous Borderline Tumors

- Intestinal type (IMBT) 85%
 - Endocervical-like (EMBT) 15%
- (Seromucinous type)

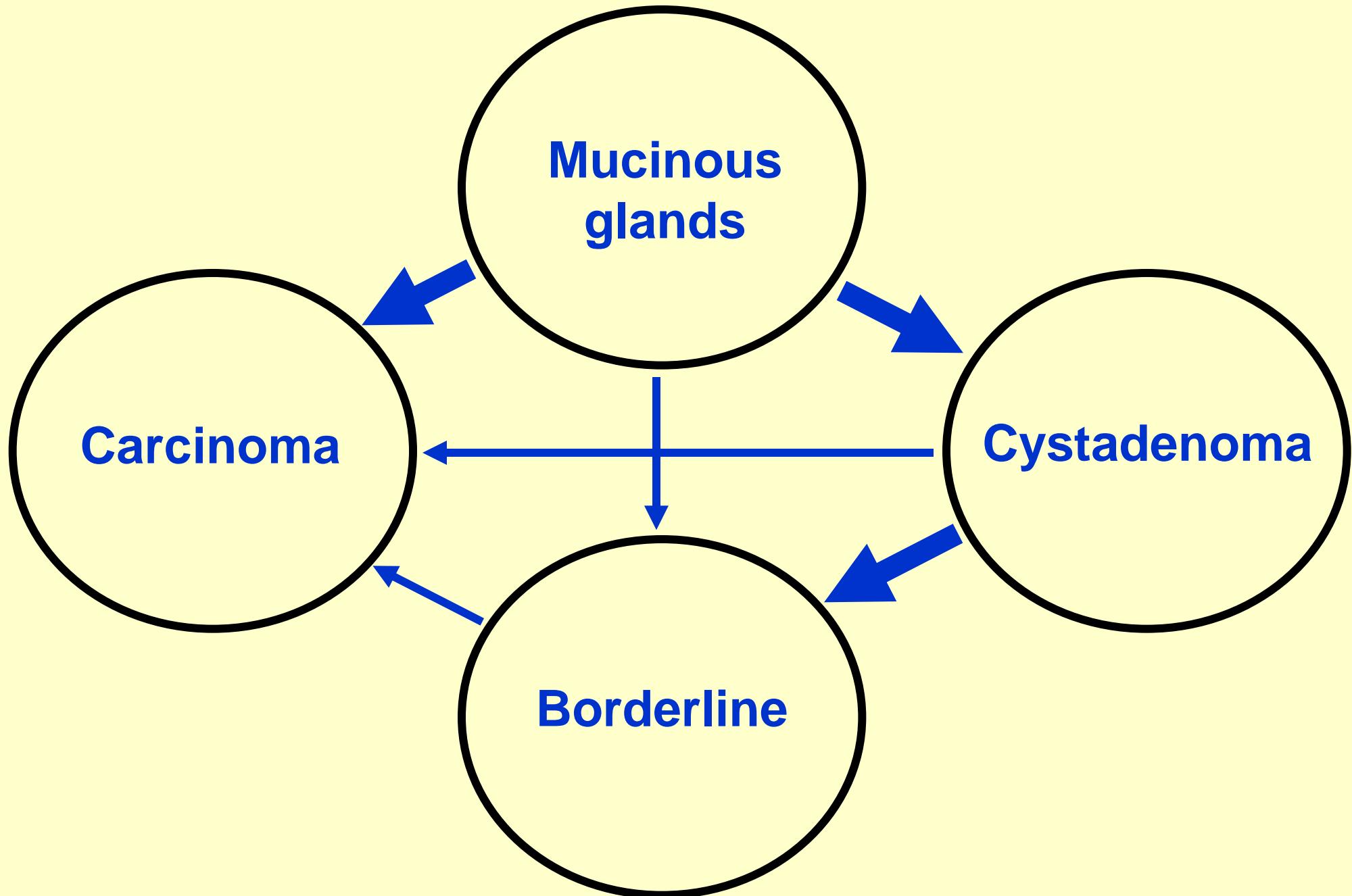


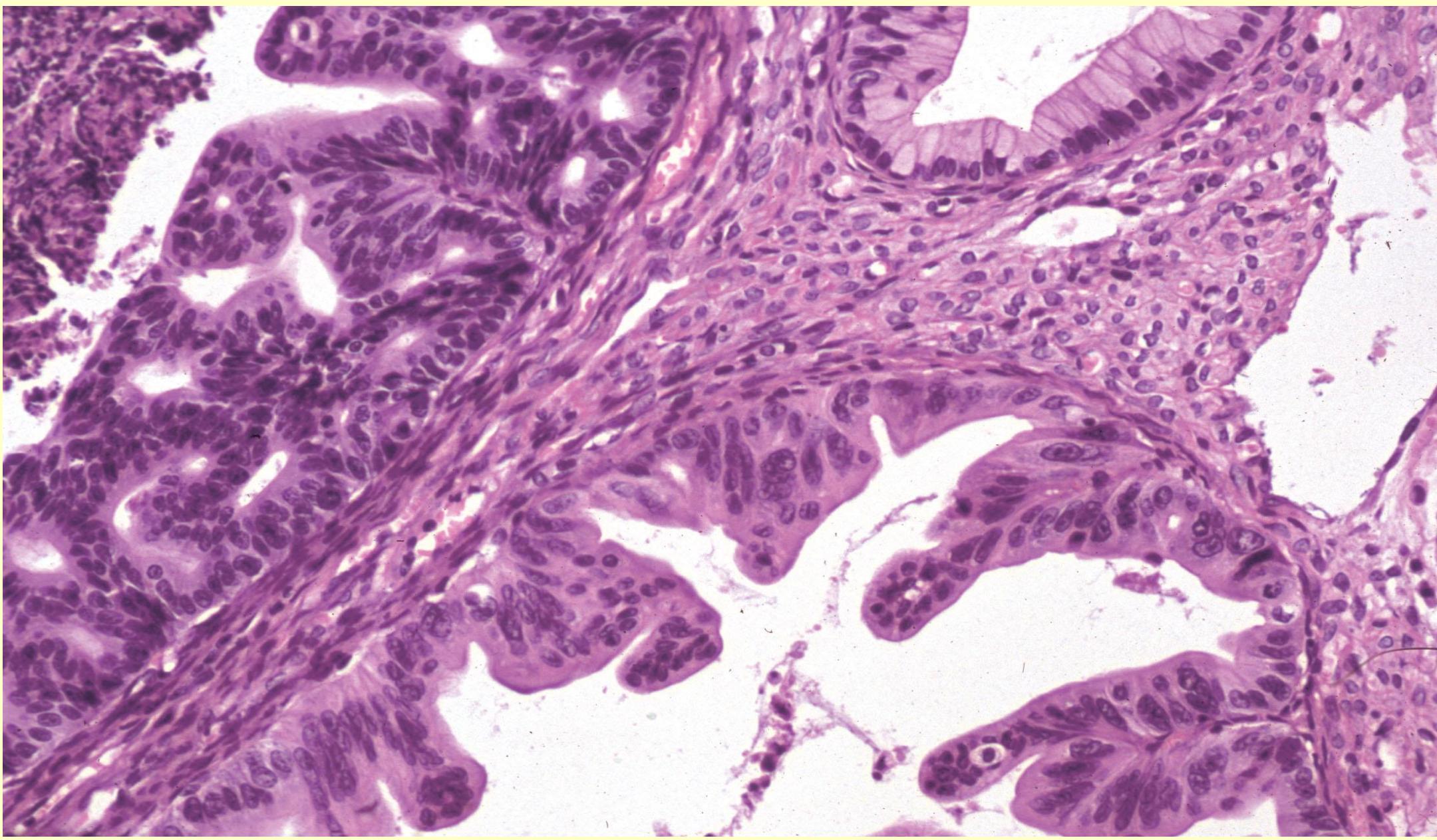
Endocervical-like MBT

Mucinous Borderline Tumors

(Intestinal type)

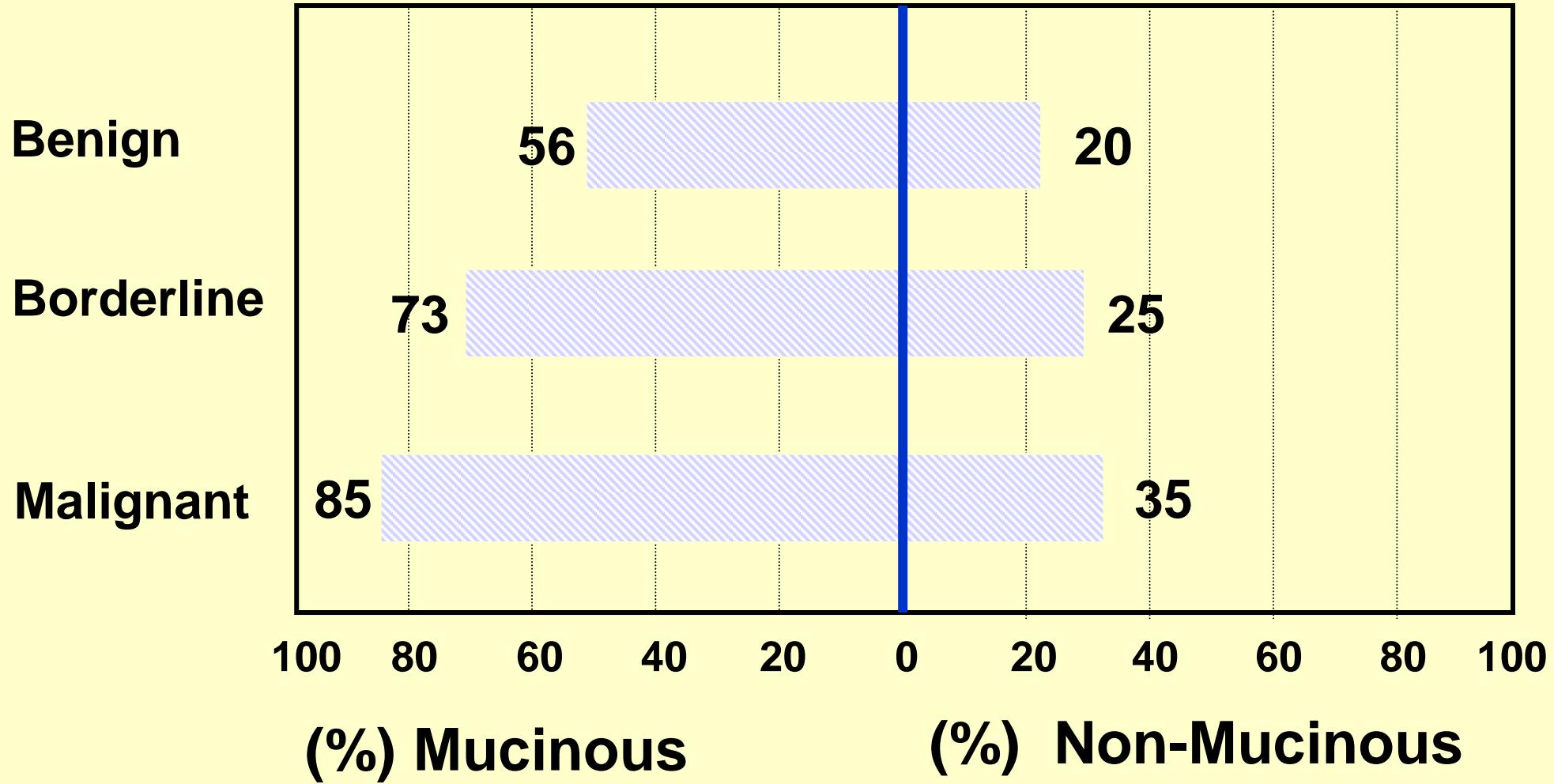
- Frequency 70% - 80% of Non-Bg
- Age 51 - 52 yrs
- Bilaterality <10%
- Stage I 80% - 90%



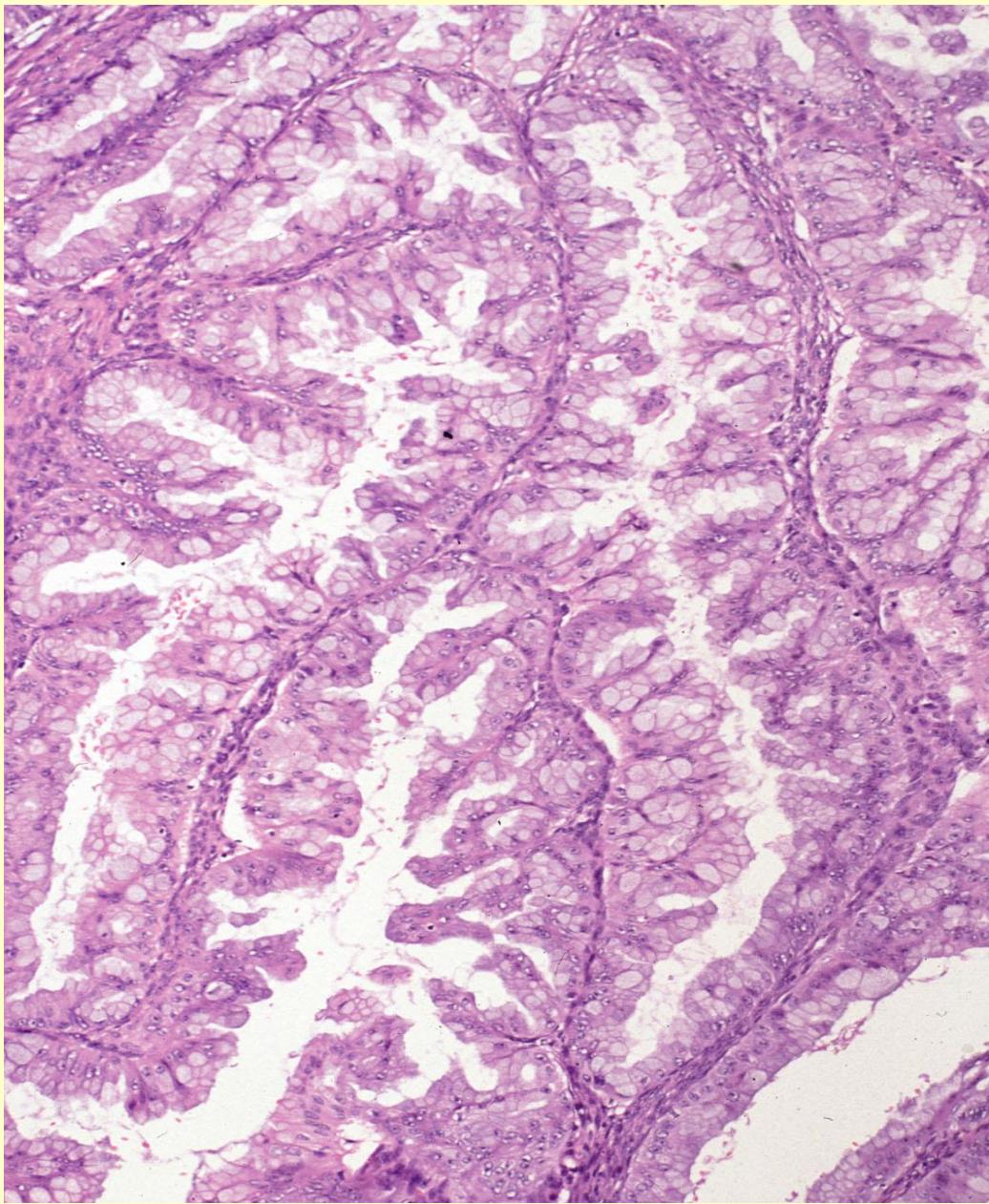


Epithelial Ovarian Tumors

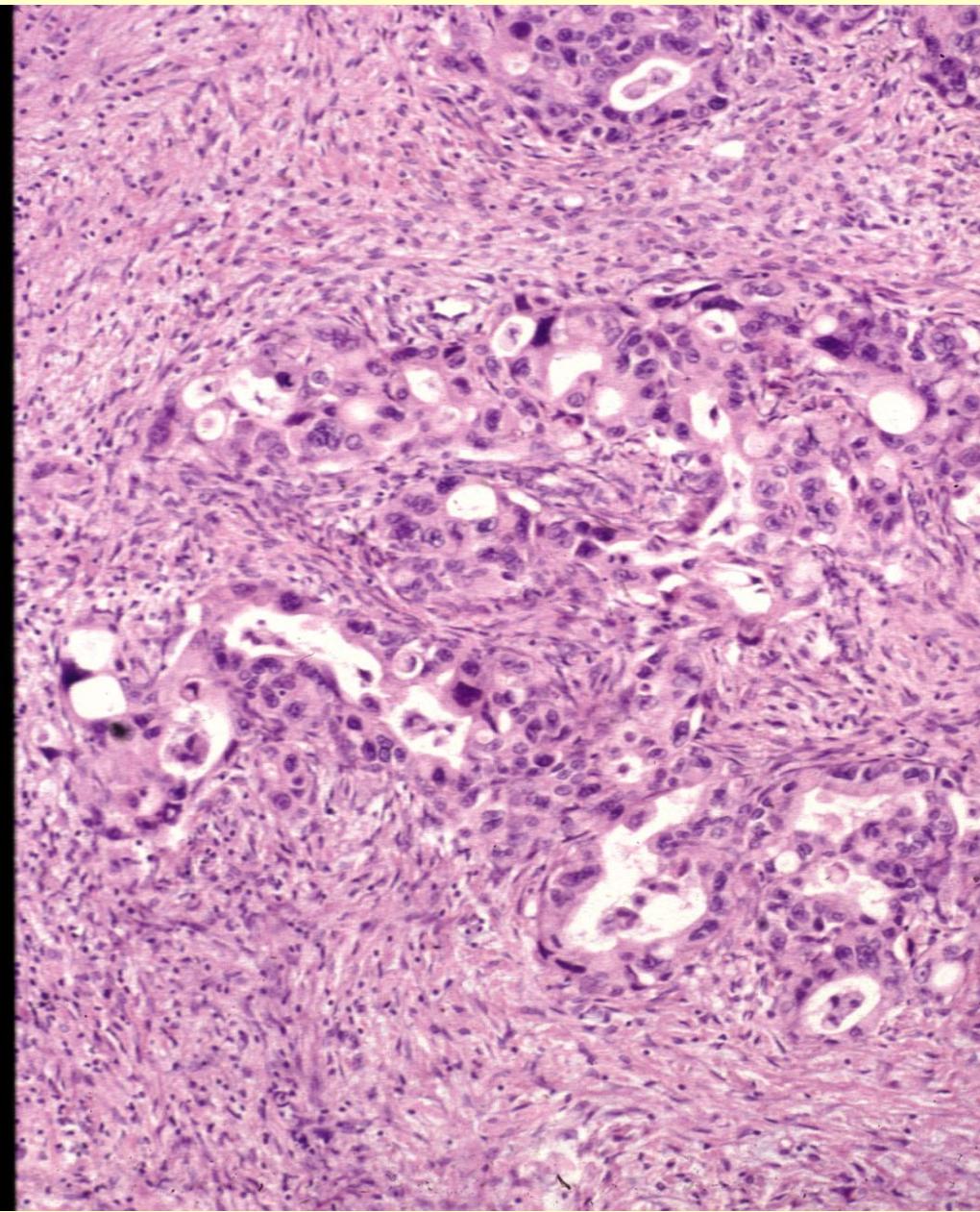
KRAS Mutations (12, 13)



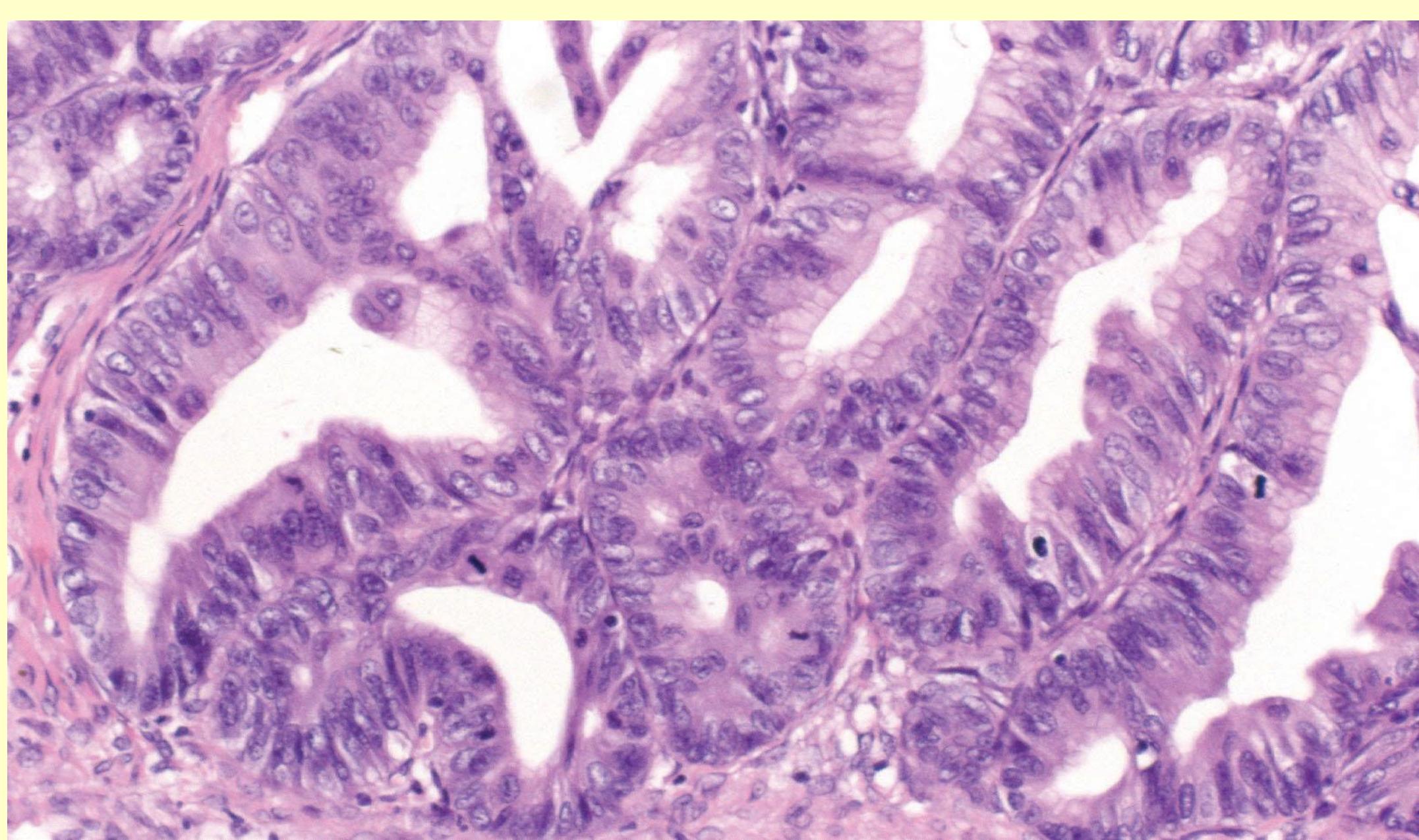
Cuatrecasas M, et al. Cancer. 1997;79(8):1581-1586.



Borderline



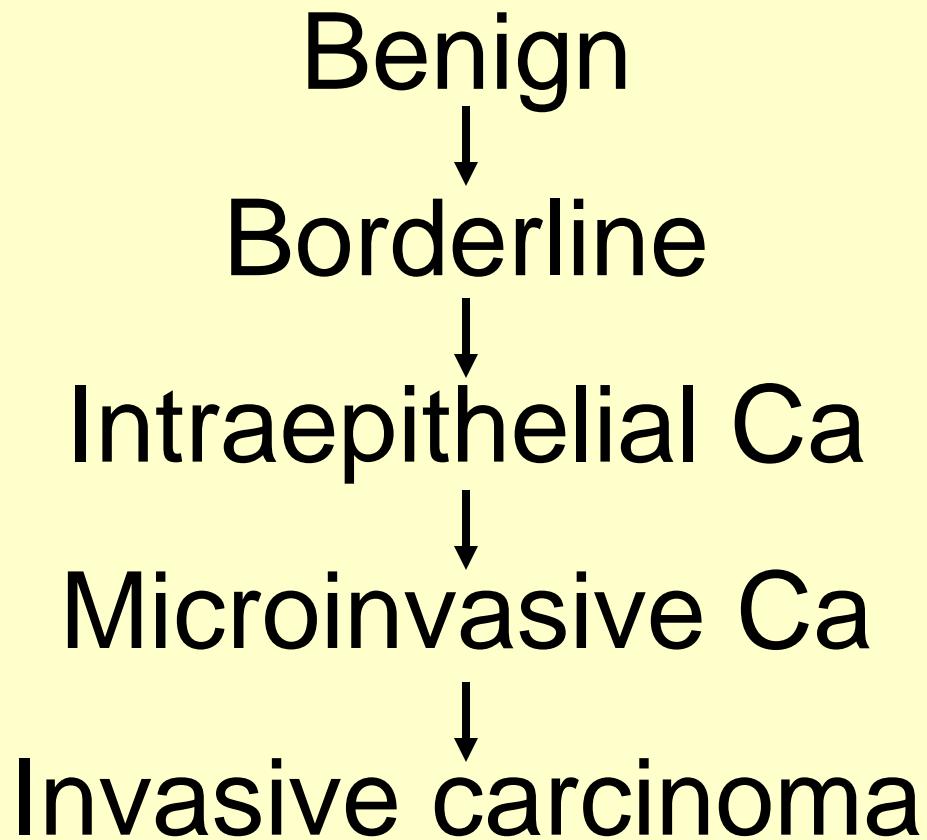
Carcinoma

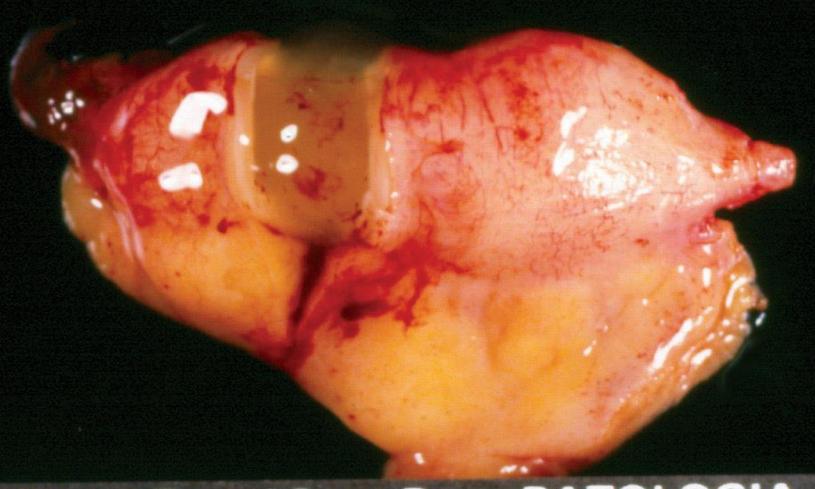


Borderline with intraepithelial carcinoma (BIECa)

Mucinous Tumors

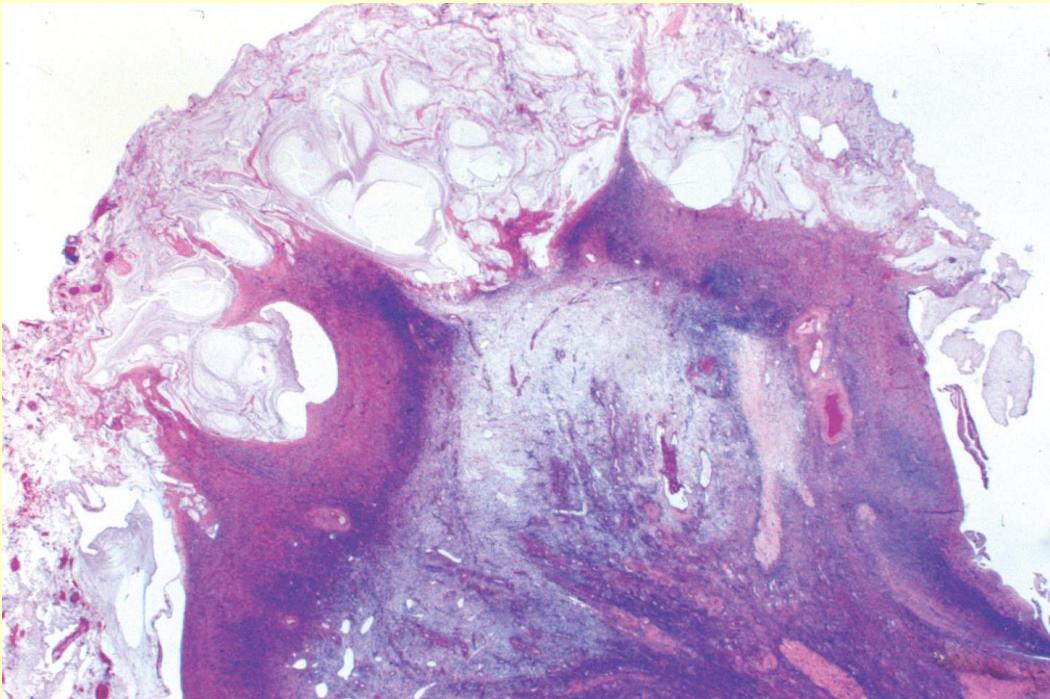
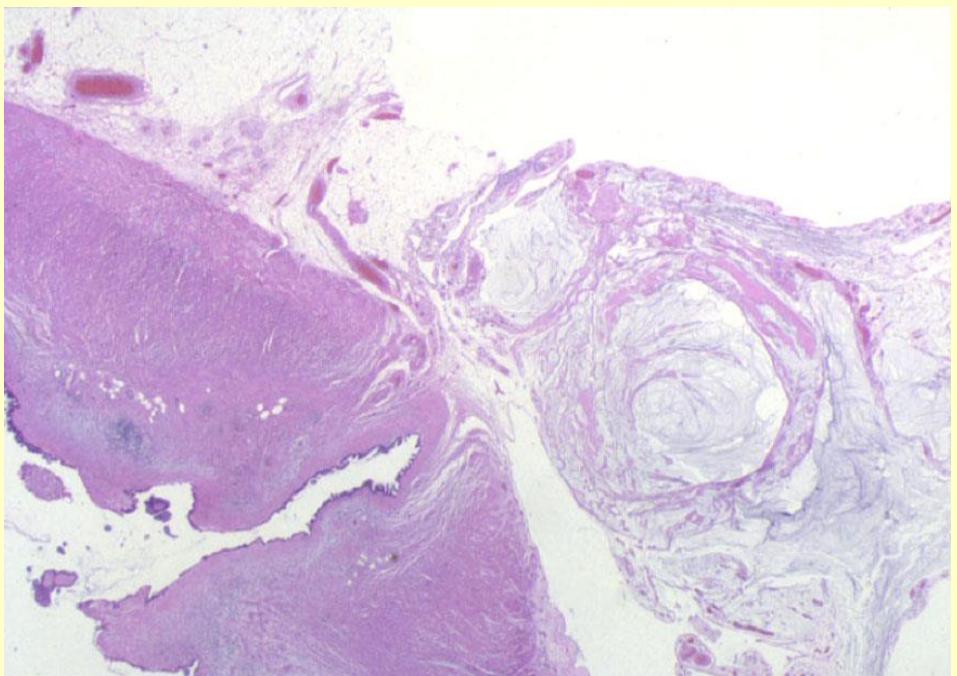
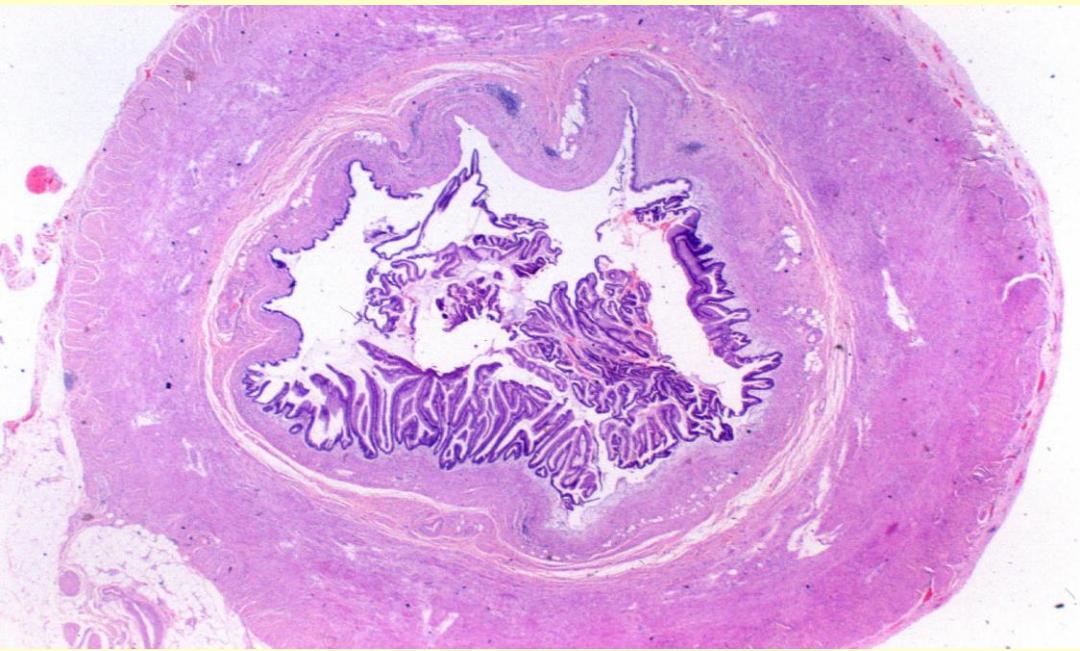
(Ovary)





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5 6 7 8



Mucinous Tumors

(Intestinal type)

5-yr survival

<u>Bord</u>	<u>Stage</u>	<u>Ca</u>
100%	1	83%
100%	2	55%
51%	3	21%
--	4	9%

Mucinous Borderline Tumors of the Ovary

1. 10%-15% of ovarian mucinous (intestinal) tumors.
2. Almost all stage Ia tumors with excellent prognosis.
3. Primary mucinous carcinomas are rare (3%) and almost always unilateral.
4. Mucinous carcinomas are heterogeneous (Bg + Bord + Ca), and extensive sampling is indicated.
5. After fertility-sparing surgery, mucinous borderline tumors may “recur” (independent primary tumor) as carcinomas in the contralateral ovary (Uzan et al. 2014; Trillsh et al. 2014).
6. Ovarian mucinous tumors with pseudomyxoma peritonei may resemble ovarian MBT, but are almost always of appendiceal or GI origin.
7. Endocervical-like MBT (seromucinous) are often bilateral and usually arise from endometriosis. Prognosis is highly favorable.

2015

Progress and Controversies in Gynecologic Oncology Conference

