Acadèmia de Ciències Mèdiques i de la Salut de Catalunya i de Balears
Societat Catalana d'Anatomia Patològica

"Tumores Ováricos Borderline": Un término ambíguo pero insustituible"

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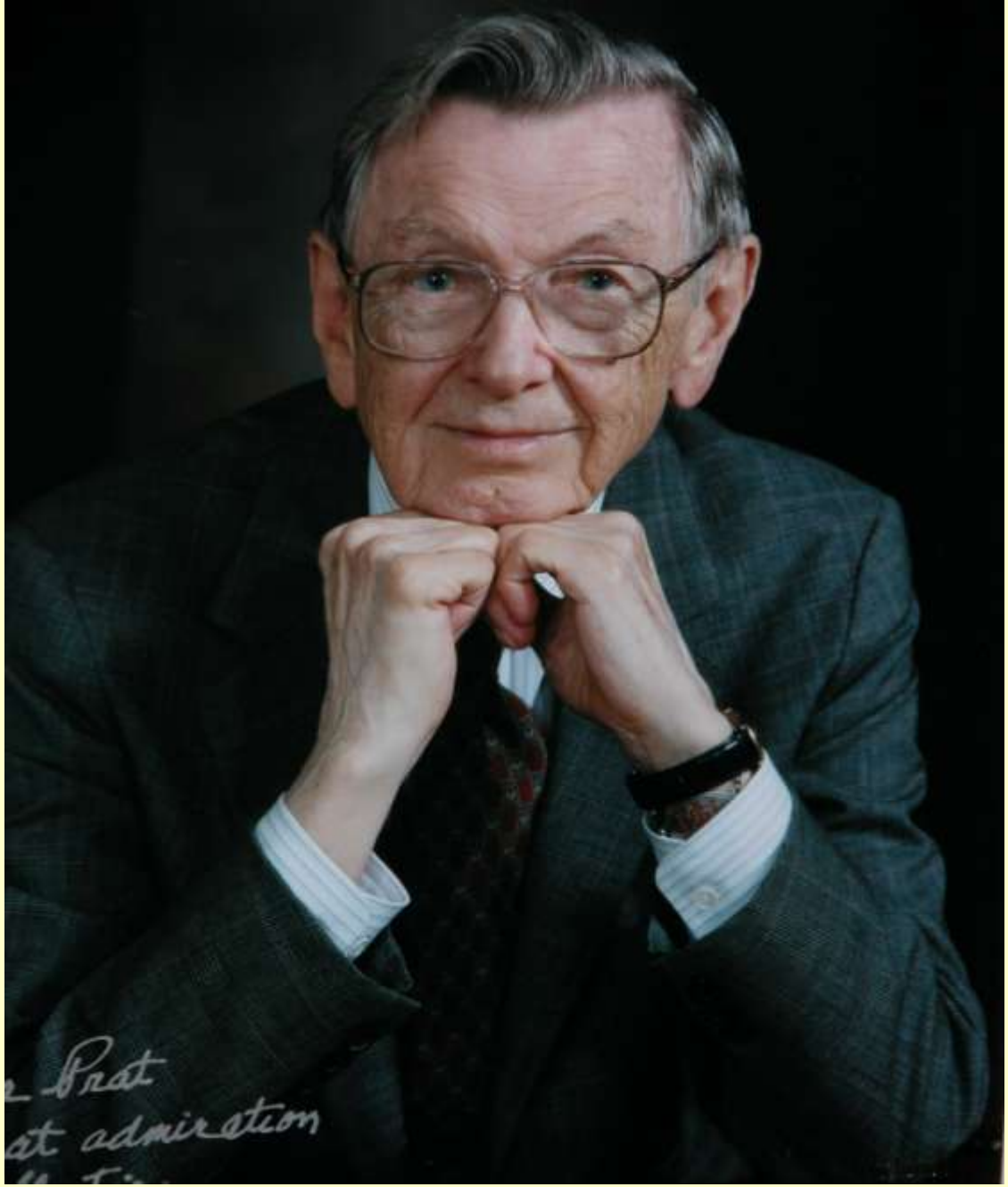
Hospital de la Santa Creu i Sant Pau
Unniversidad Autonoma de Barcelona

Universitat Autònoma de Barcelona

“There are no borderline tumors, only borderline pathologists”

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

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

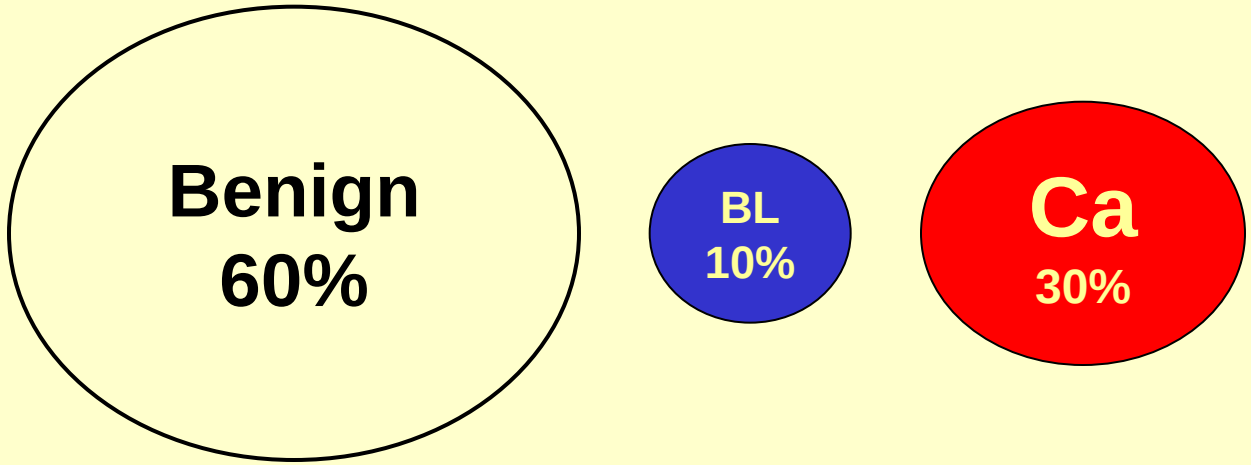


Robert E. Scully 1921-2012

Ovarian Epithelial Tumors

WHO 1999 and 2003

Serous
Mucinous
Endometrioid
Clear cell
Transitional
Squamous
Mixed
Undifferentiated



Serous Tumors of the Ovary

(30-40%)

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

Borderline Ovarian Tumors

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

WHO 1973-2013

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

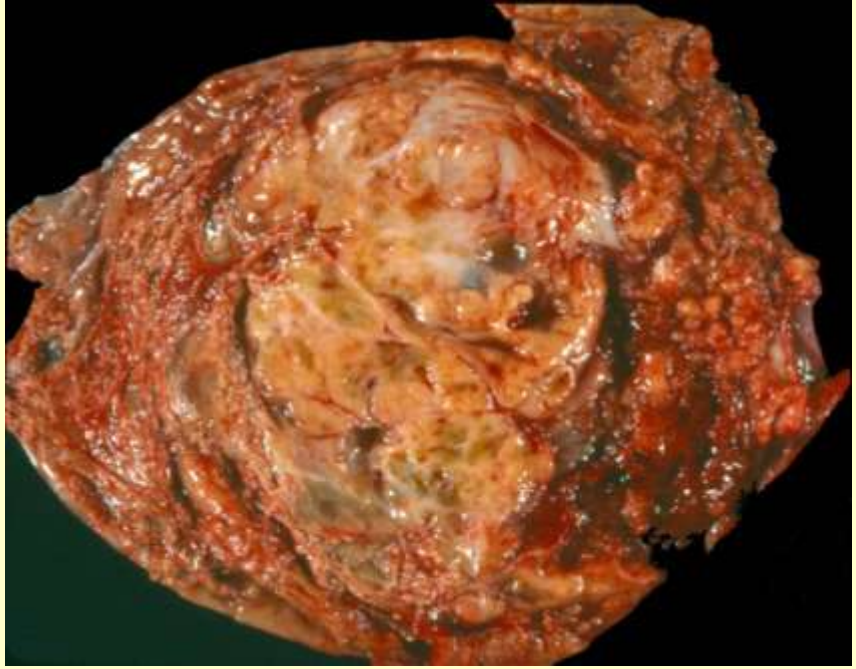
Kurman RJ, Carcangiu ML, Herrington CS, Young RH, eds.
WHO Classification of Tumours of Female Reproductive Organs.
4th edition. IARC: Lyon 2014.

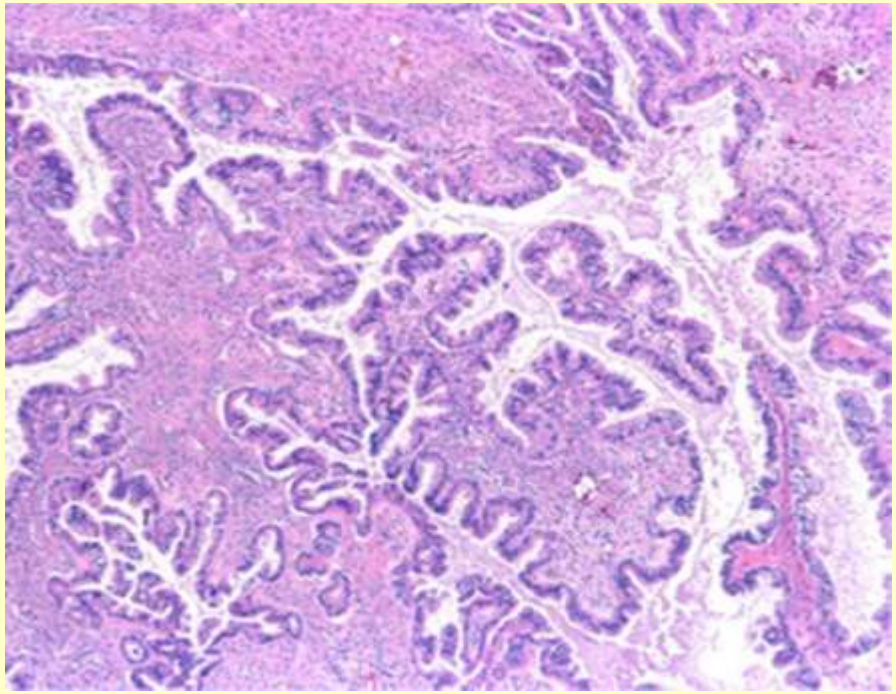
- “Serous borderline tumours/Atypical proliferative serous tumour”. Pag 18
- “Serous borderline tumour micropapillary variant / Non invasive low grade serous carcinoma”. Pag 20
- “A significant proportion of LGSCs have an associated component of serous borderline tumour/atypical proliferative serous tumour (SBT/APST)” Pag. 21
- “Seromucinous borderline tumour/ Atypical proliferative seromucinous tumour”. Pag. 38

Etc…

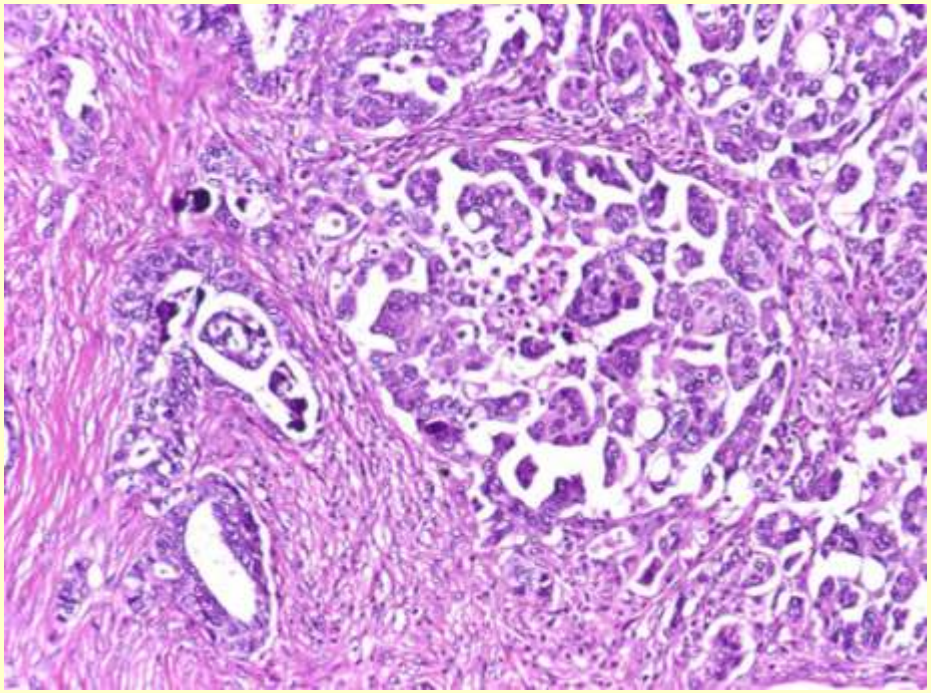
Serous Borderline Tumors

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



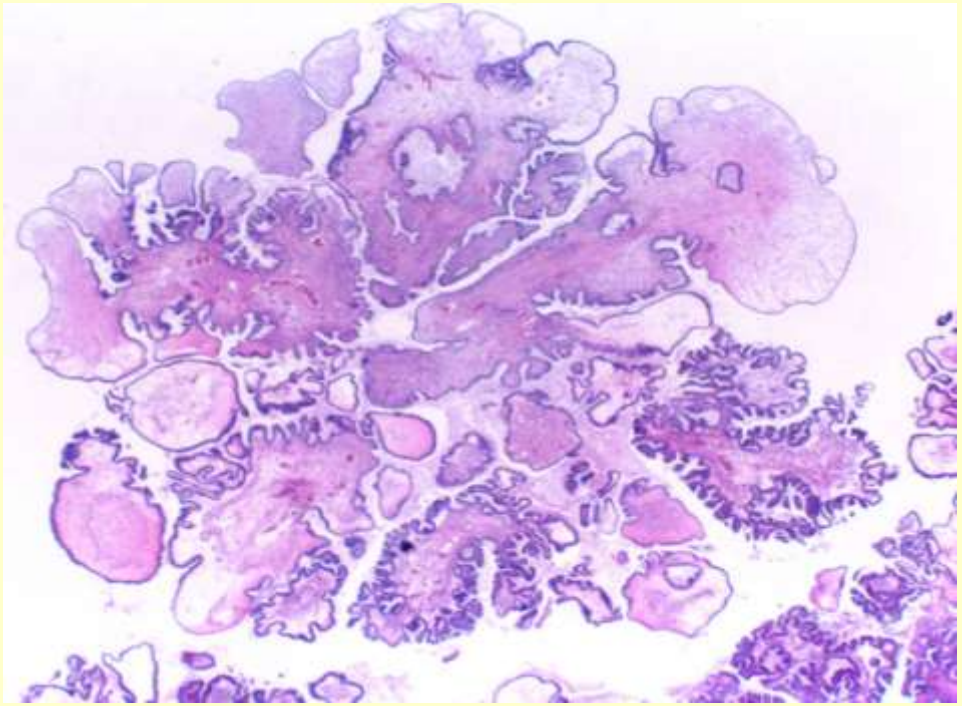


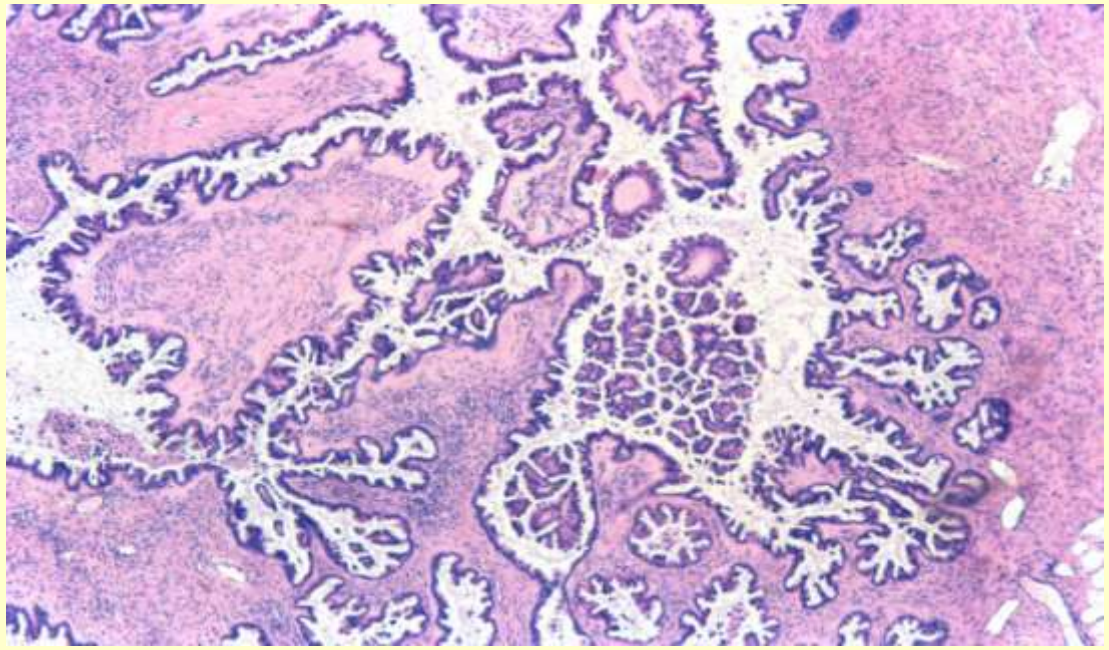
Serous Borderline Tumor

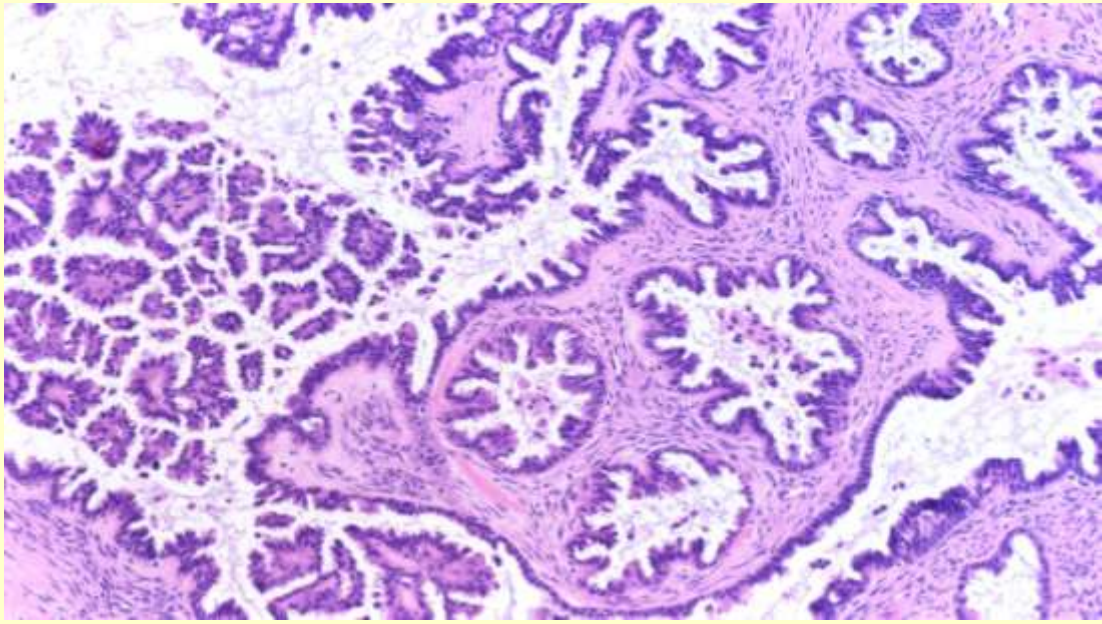


High-Grade Serous Carcinoma

Serous Borderline Tumor







Diagnostic Features

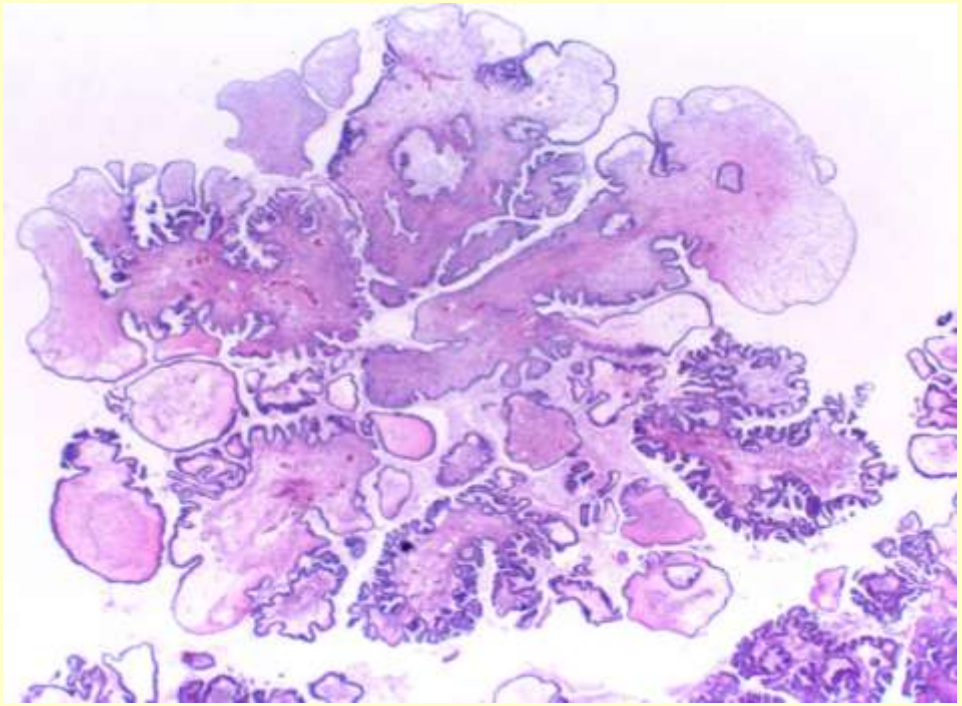
1. Branching papillae
2. Variable nuclear atypia
3. No stromal invasion

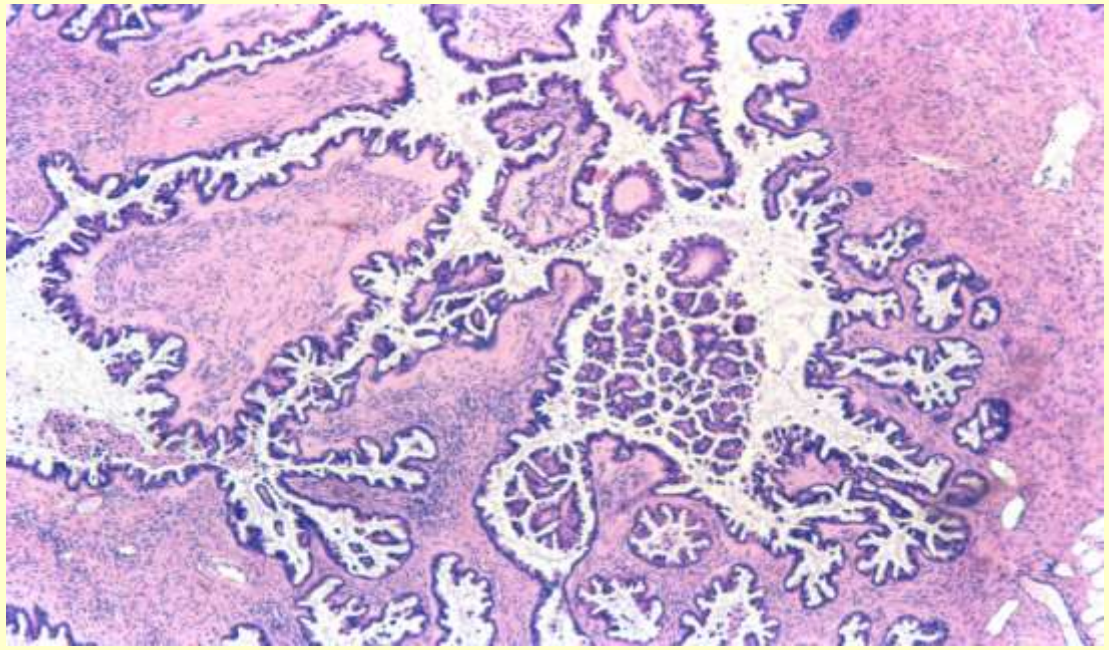
Serous Borderline Tumors

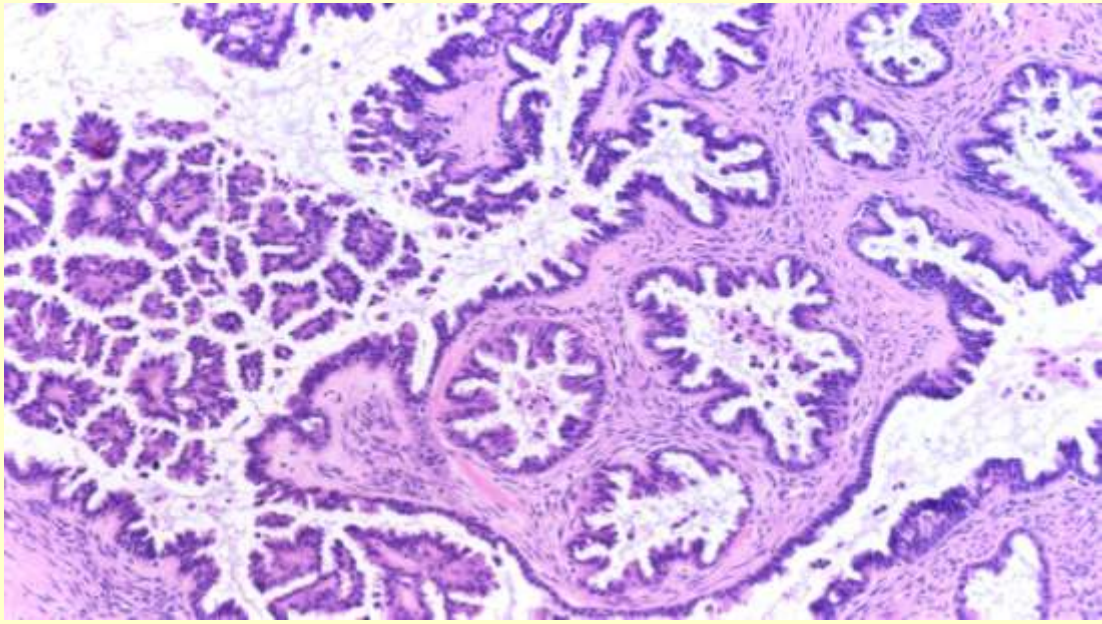
(Diagnostic Problems)

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

Serous Borderline Tumor







Diagnostic Features

1. Branching papillae
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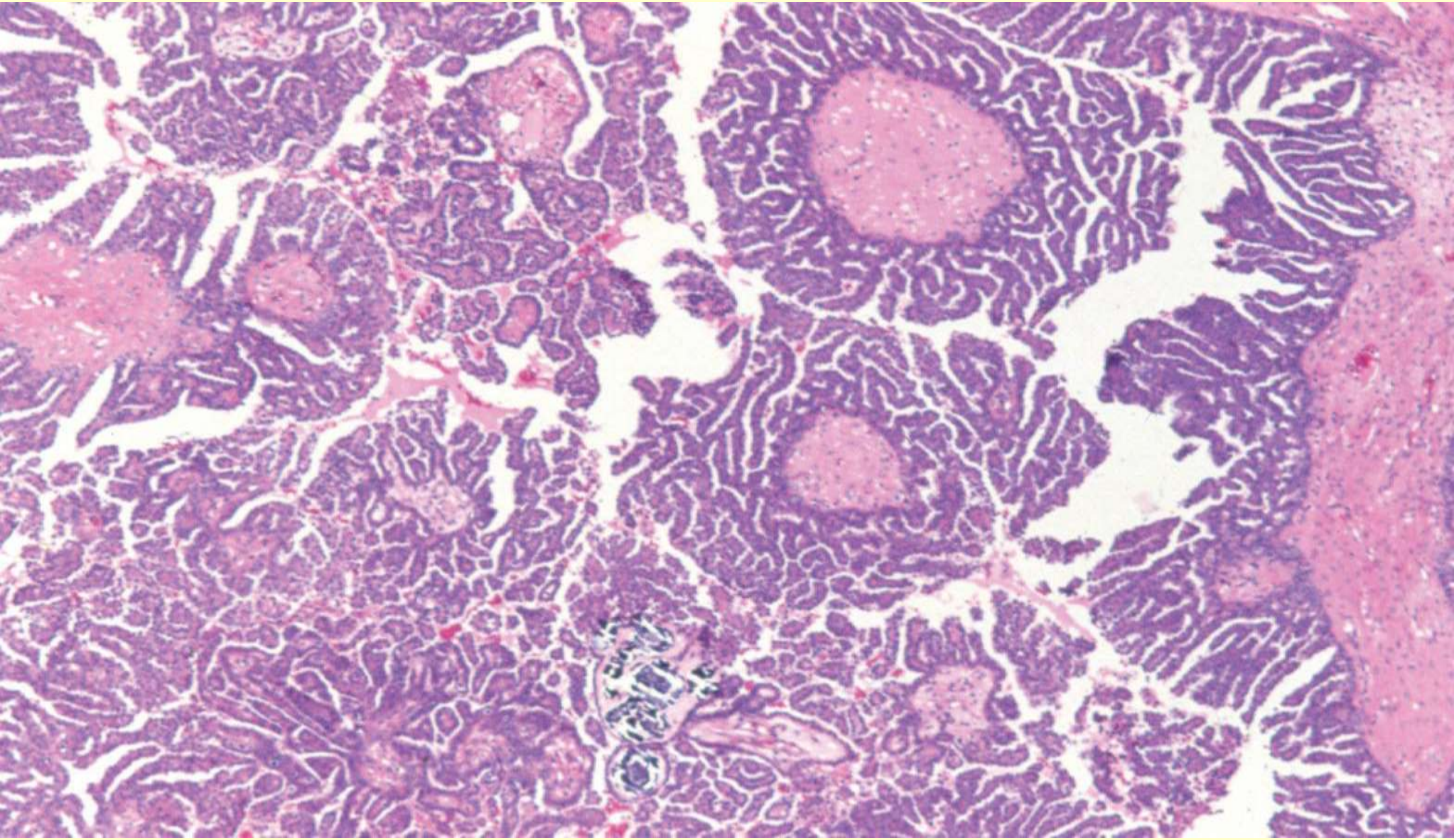
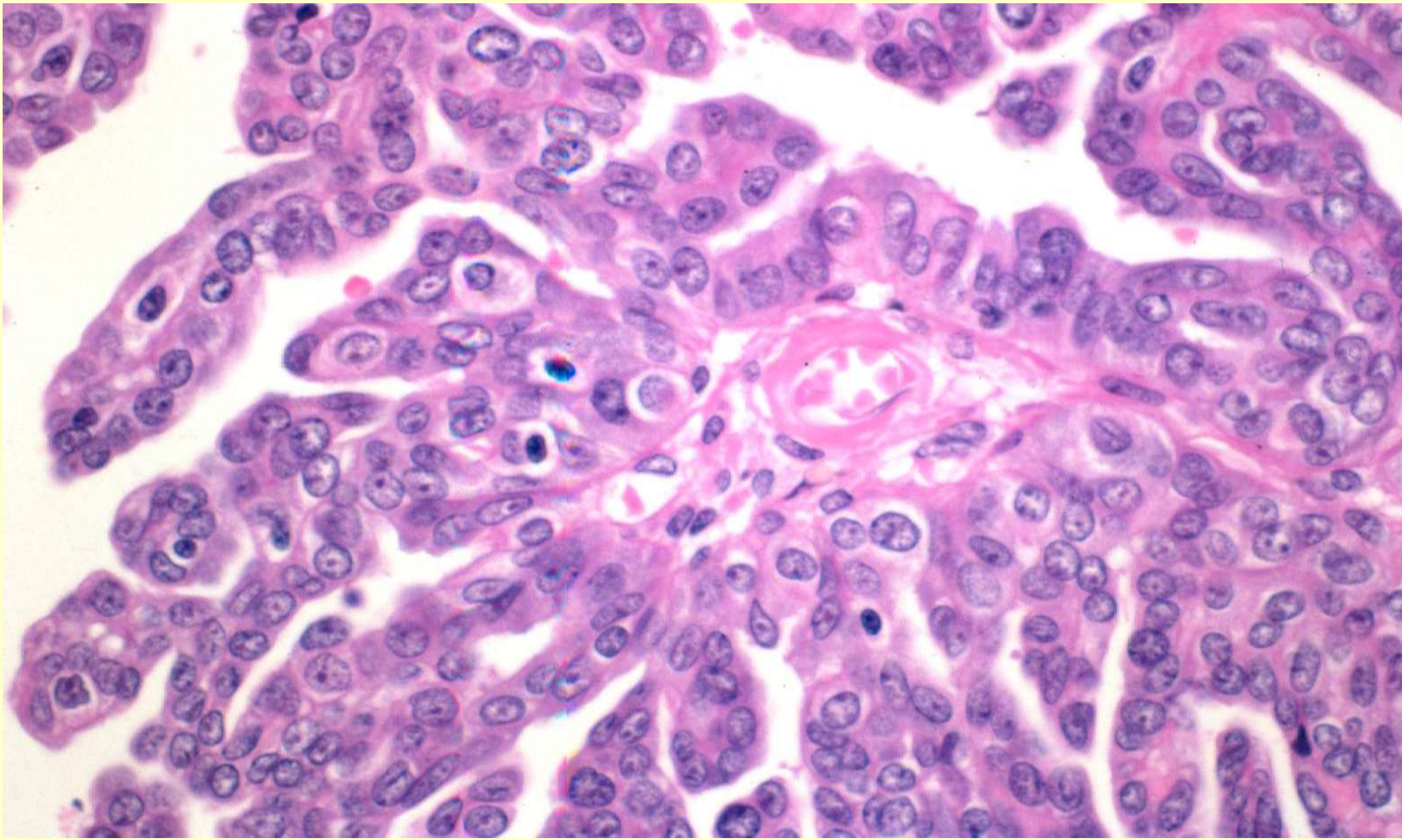


SBT - Micropapillary pattern



SBT - Micropapillary pattern

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)

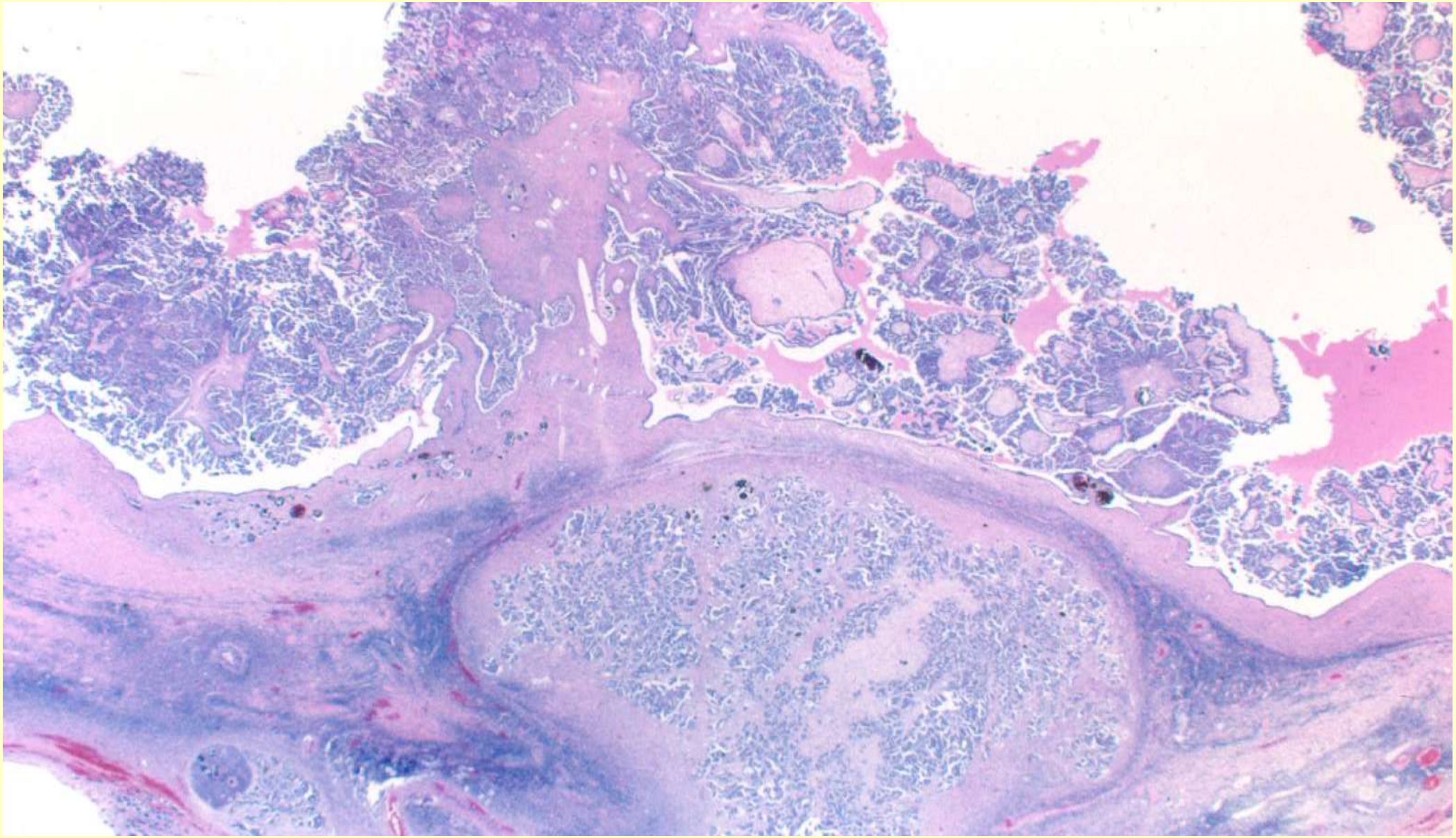
Prat J, de Nictolis M
Am J Surg Pathol 2002

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
2005	Longacre et al	Yes

Overall survival similar to typical SBT



Carcinoma (> 3 mm) in SBT-MP

Serous Borderline Tumors

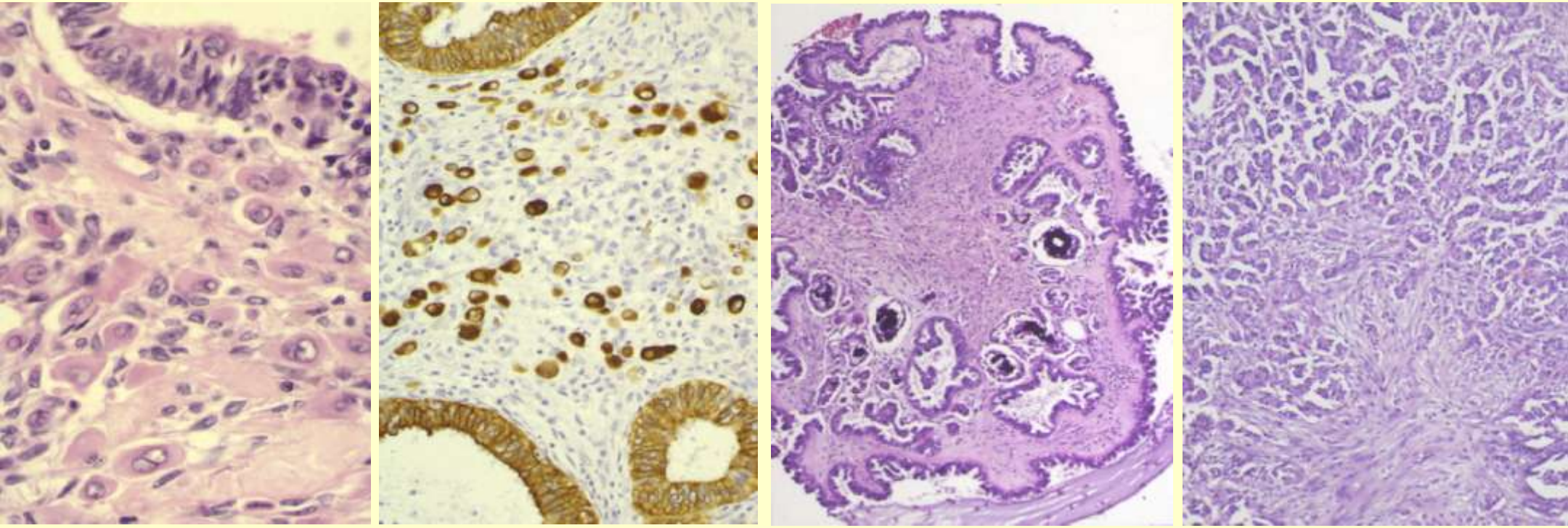
(Micropapillary pattern)

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

SBT with micropapillary pattern

- Micropapillarity is not a specific predictor of adverse prognosis
- A strong association of SBT with micropapillary pattern with invasive implants and poor outcome has been inconsistent
- Micropapillary pattern probably represents a small risk
- Almost all patients dying of recurrent tumor had invasive peritoneal implants which are the key feature associated with a poor prognosis

SBT with Microinvasion < 10 mm^2



Cumulative literature: Excellent prognosis

Stanford data: Risk factor for disease progression

Serous Borderline Tumors

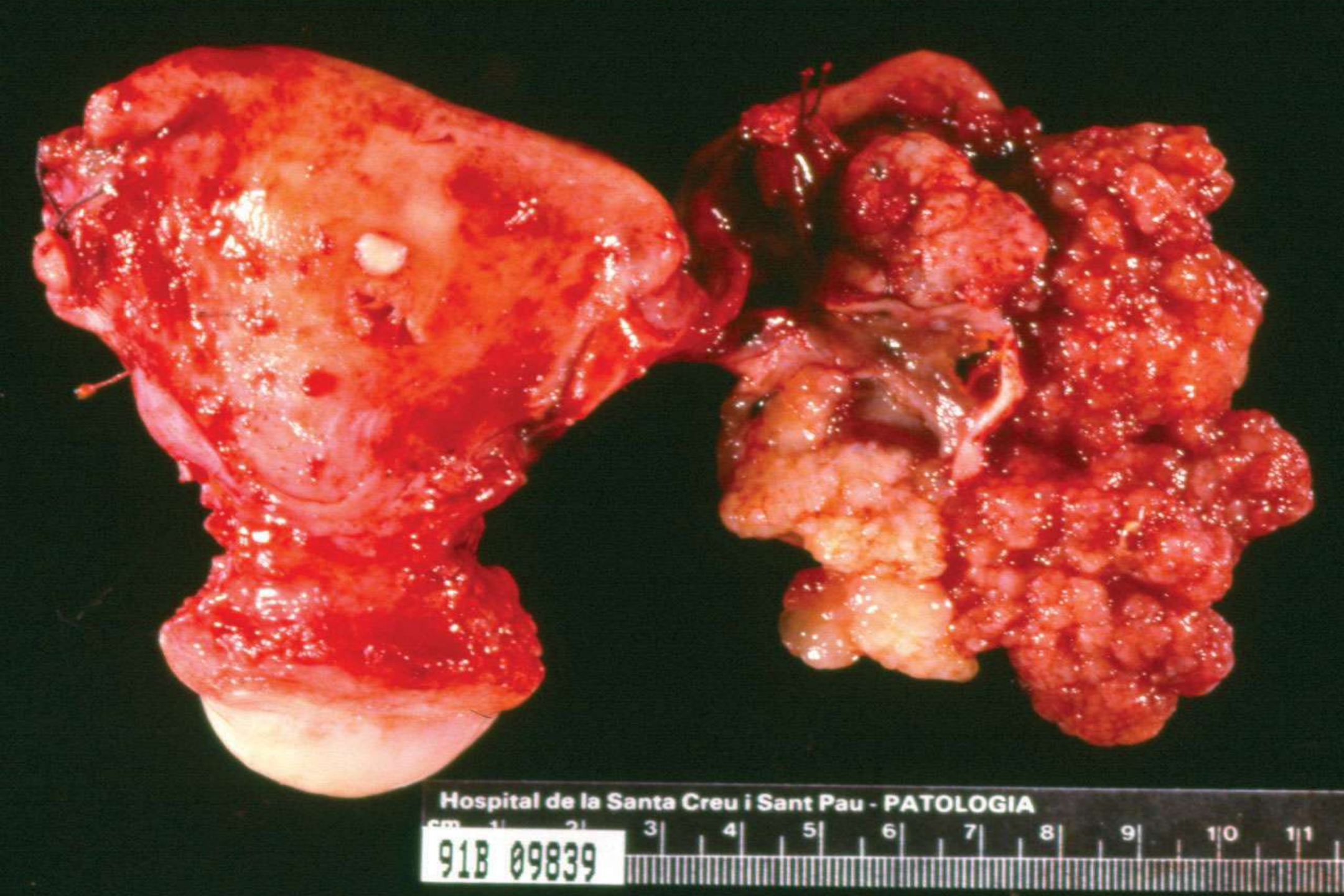
(Risk of progression)

- 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

Serous Borderline Tumors

Peritoneal Implants (30%)

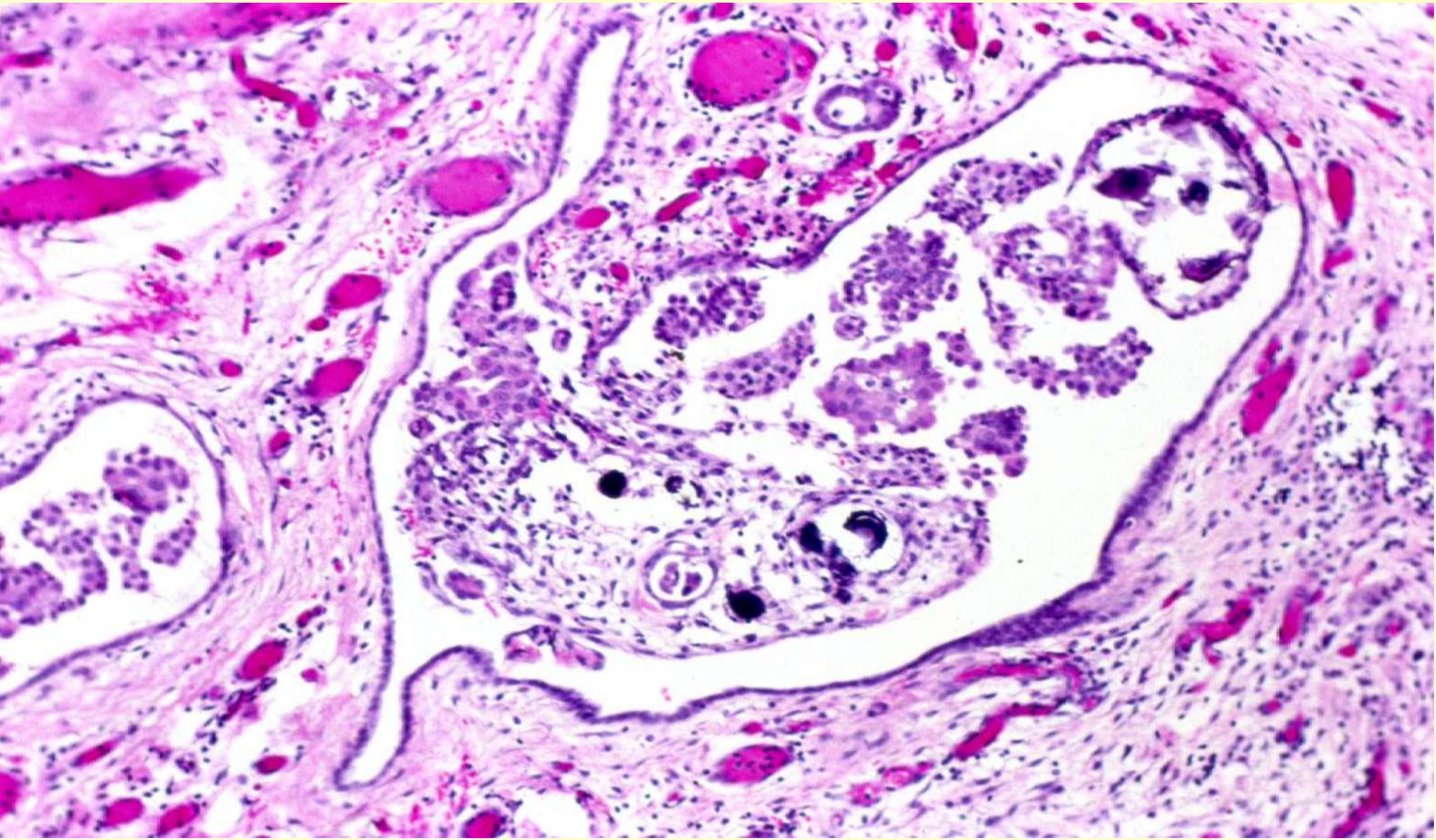

Hospital de la Santa Creu i Sant Pau - PATOLOGIA
91B 09839

Peritoneal Implants

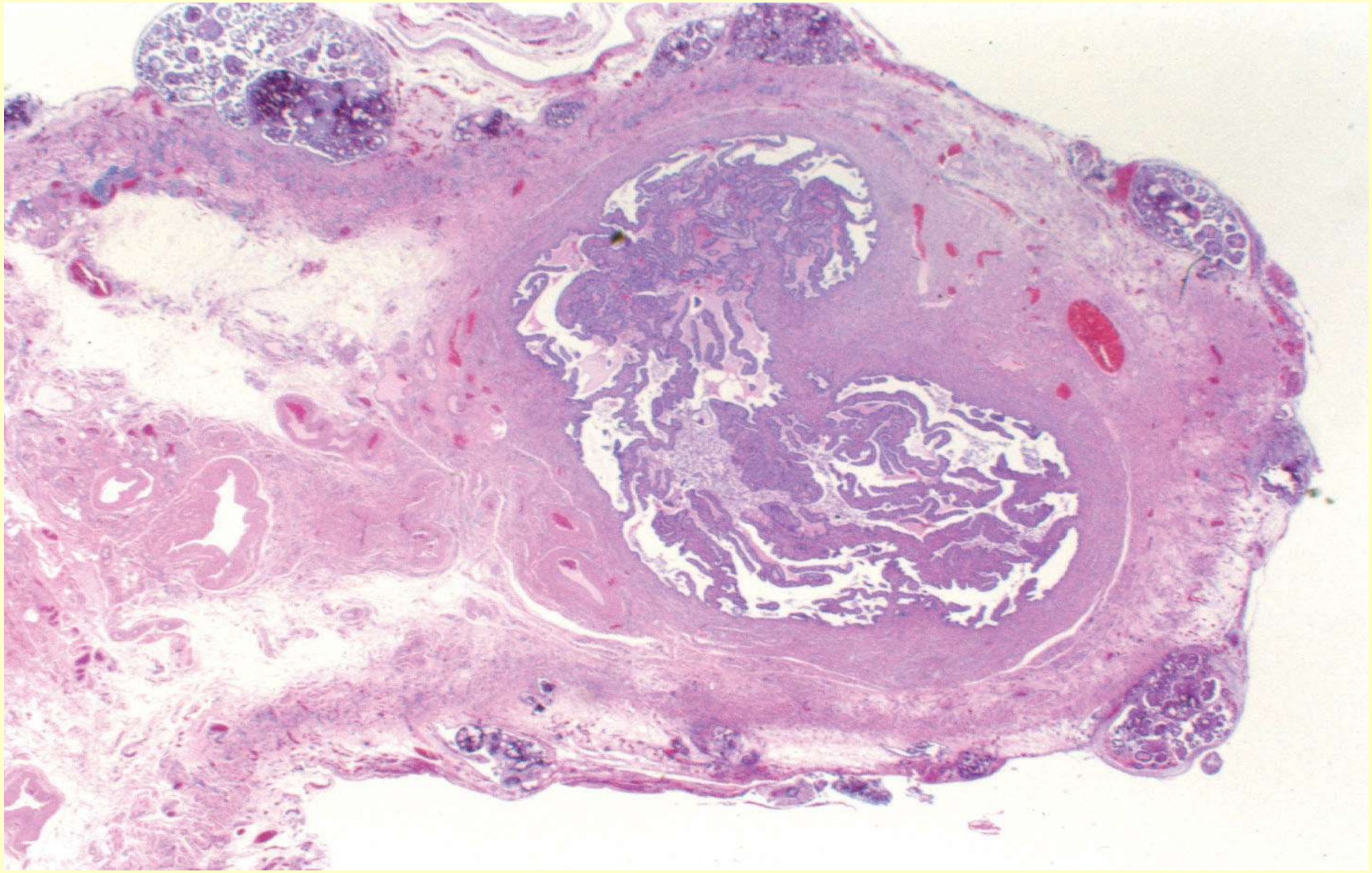
(SBT)

- Non-invasive
  - Epithelial
  - Desmoplastic
- Invasive

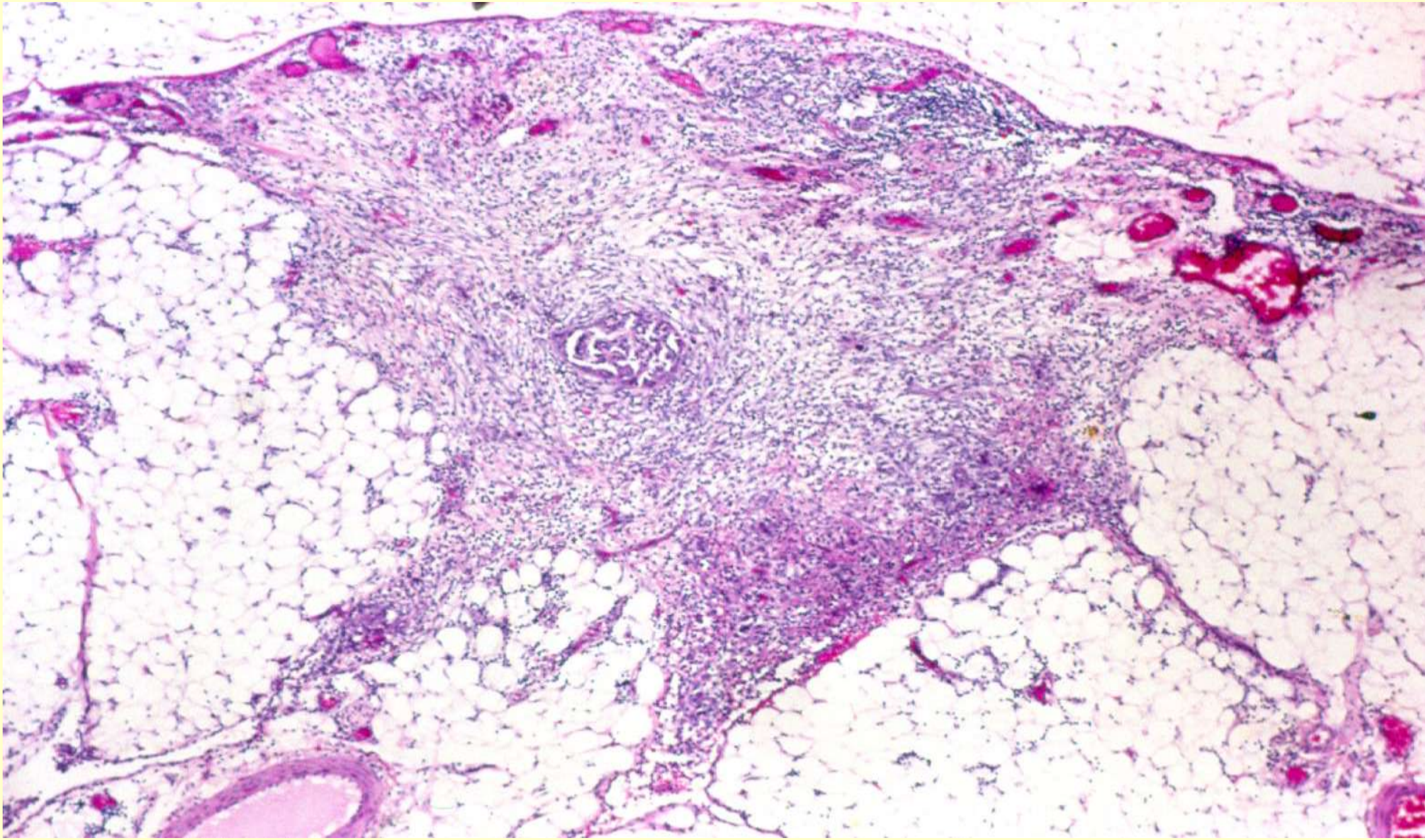
Bell DA, et al
Cancer 1988; 62:2212



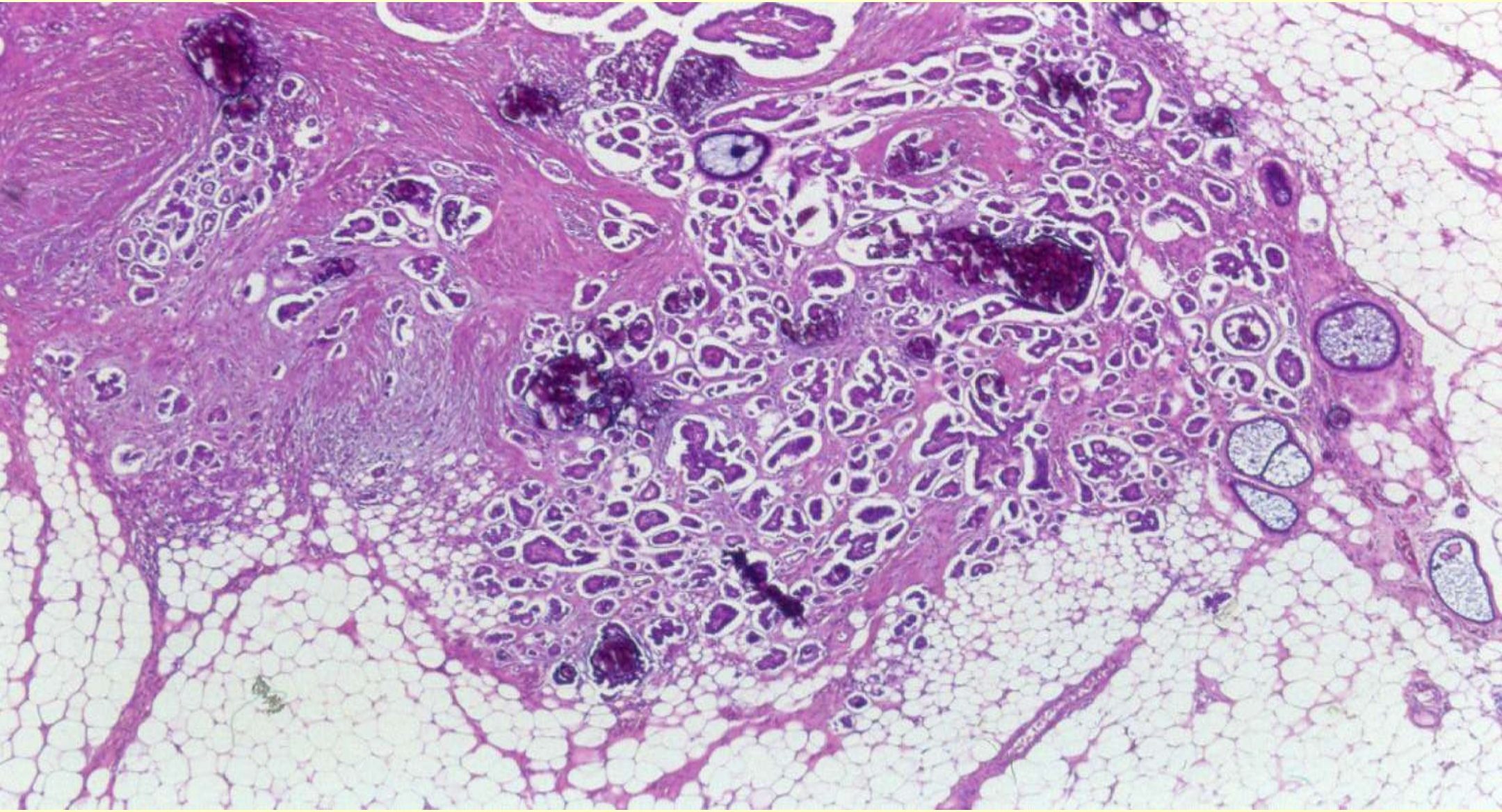
Noninvasive epithelial implant



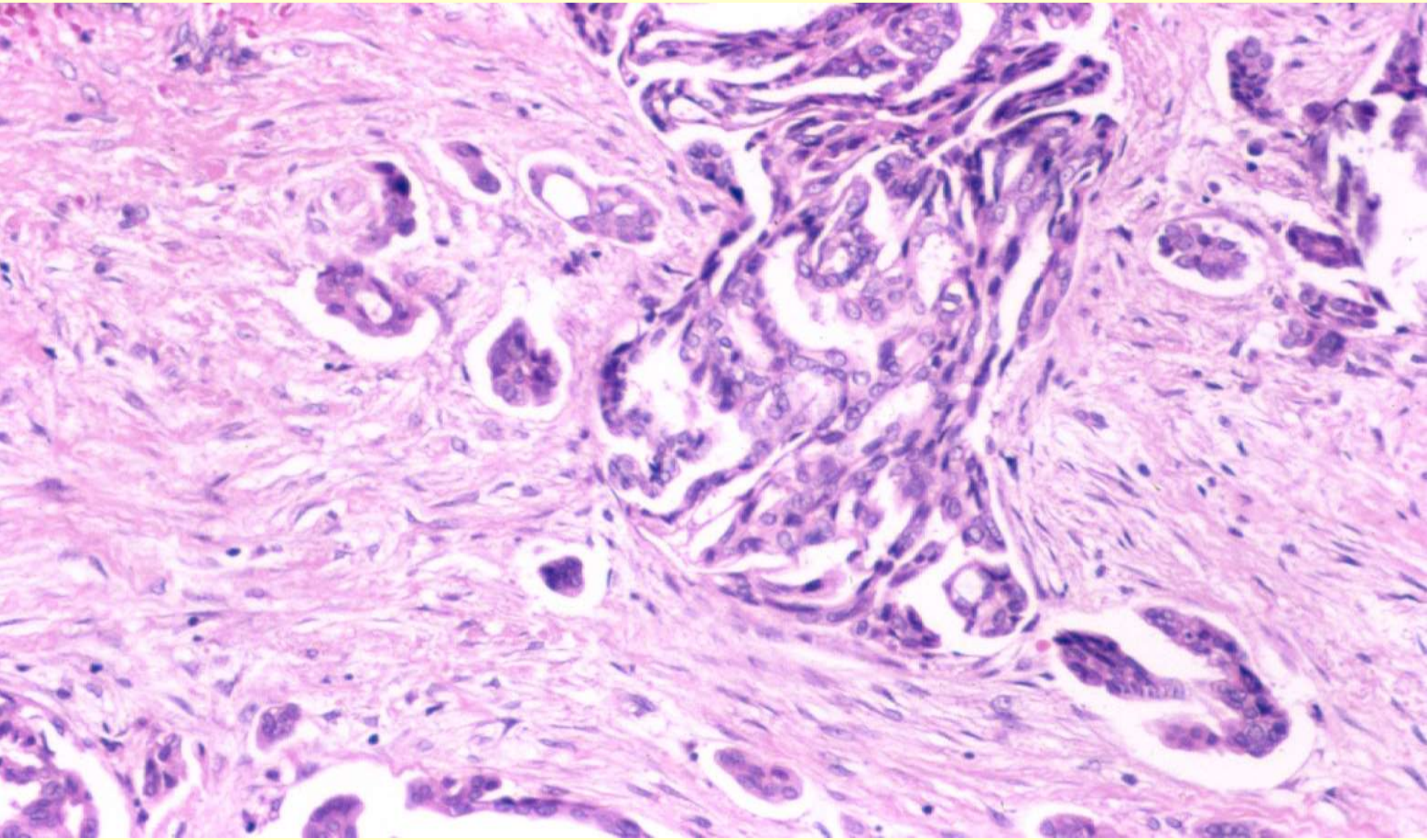
Noninvasive implants



Noninvasive (desmoplastic) implant



Invasive implant

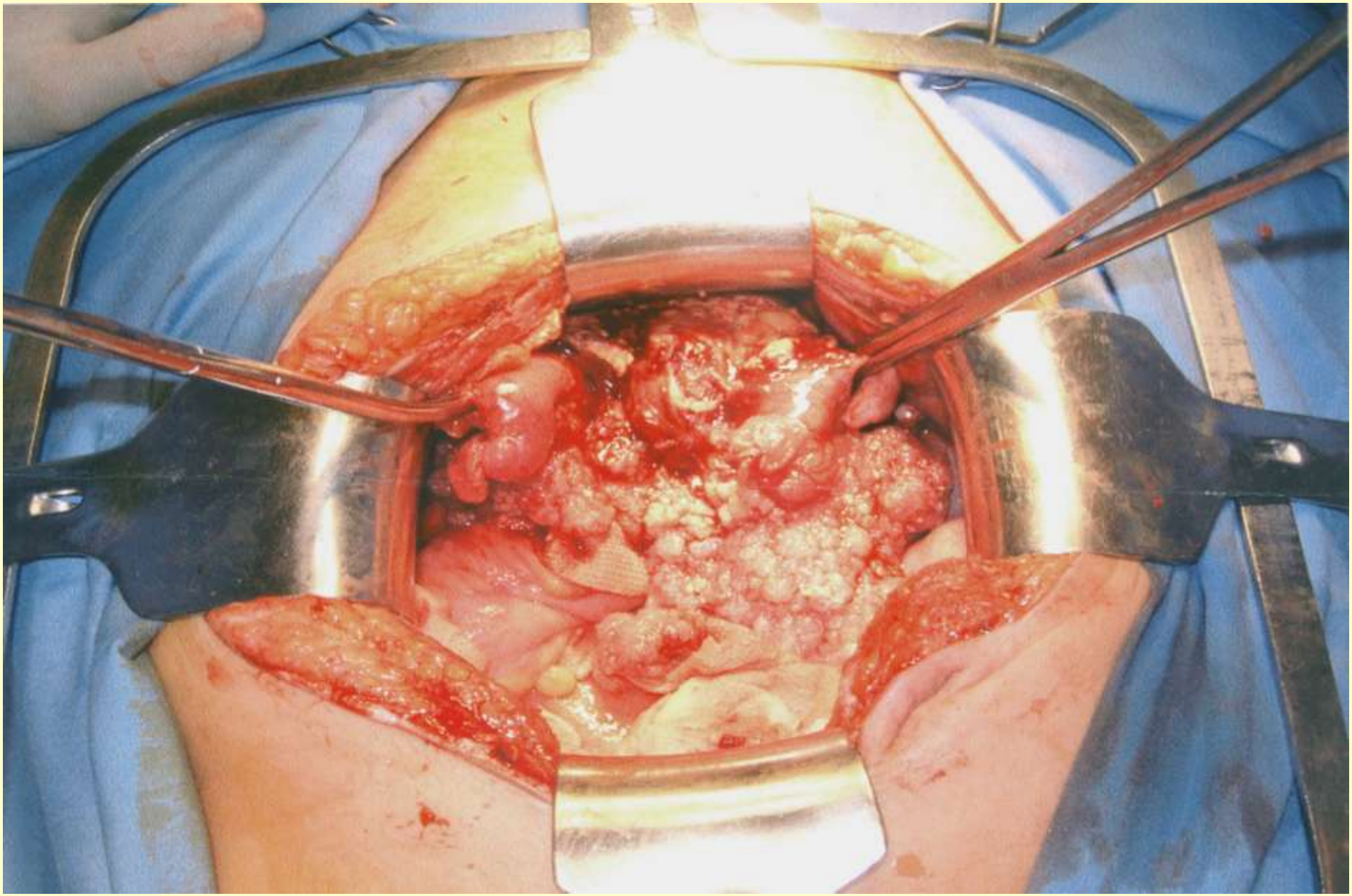


Invasive implant

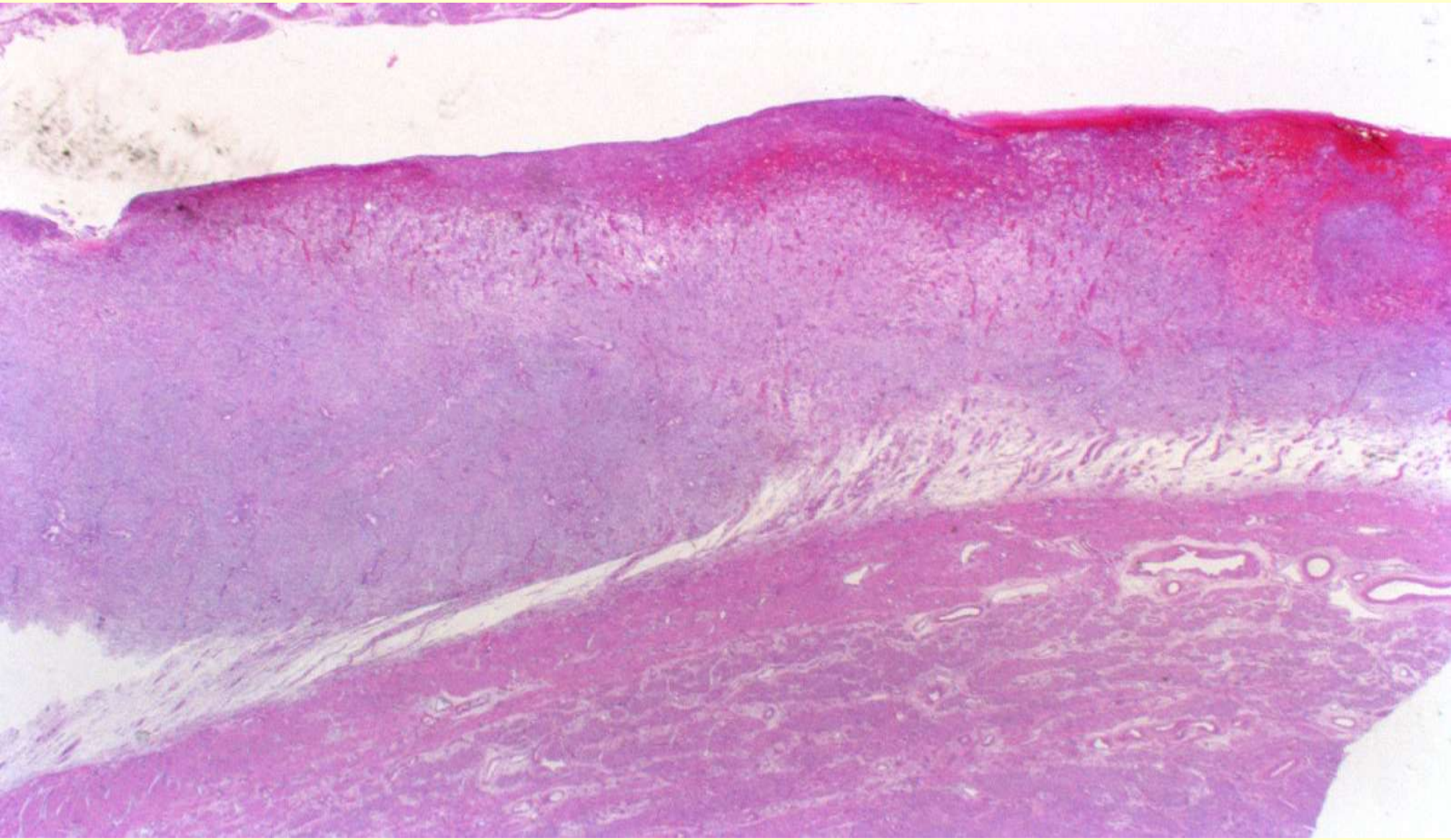
Serous Borderline Tumors

(Death from tumor 1984-2005)

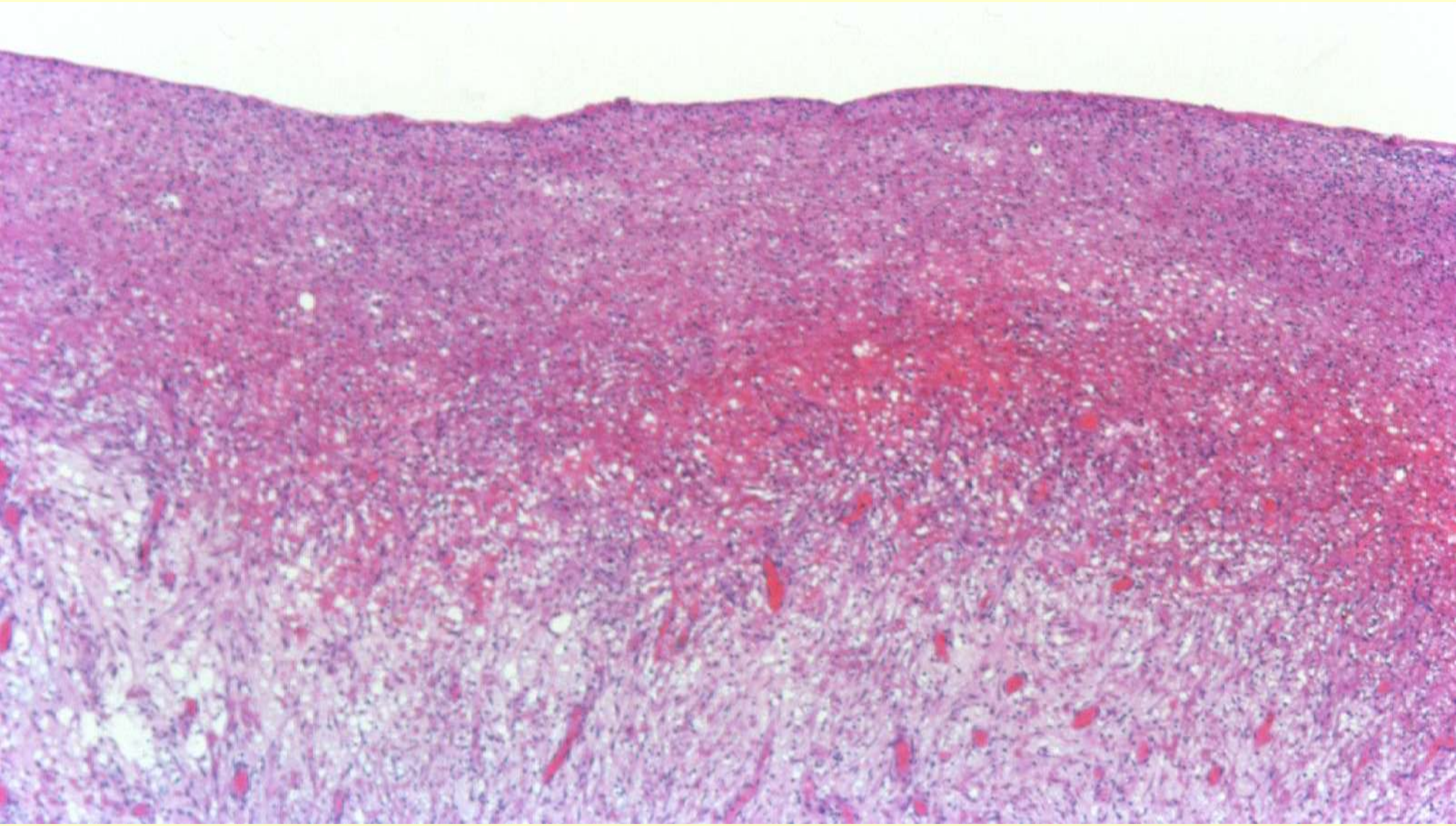
	Non-invasive implants	Invasive implants
McCaughey et al	2/13	4/5
Bell DA et al	3/50	5/6
De Nictolis et al	0/10	4/9
Kennedy and Hart	1/25	0/1
Seidman and Kurman	1/51	2/3
Gershenson et al	6/73	6/39
Eichhorn et al	0/30	2/3
Bell KA et al	2/29	6/31
Prat and de Nictolis	0/34	3/6
Longacre et al	2/75	5/14
	20/390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



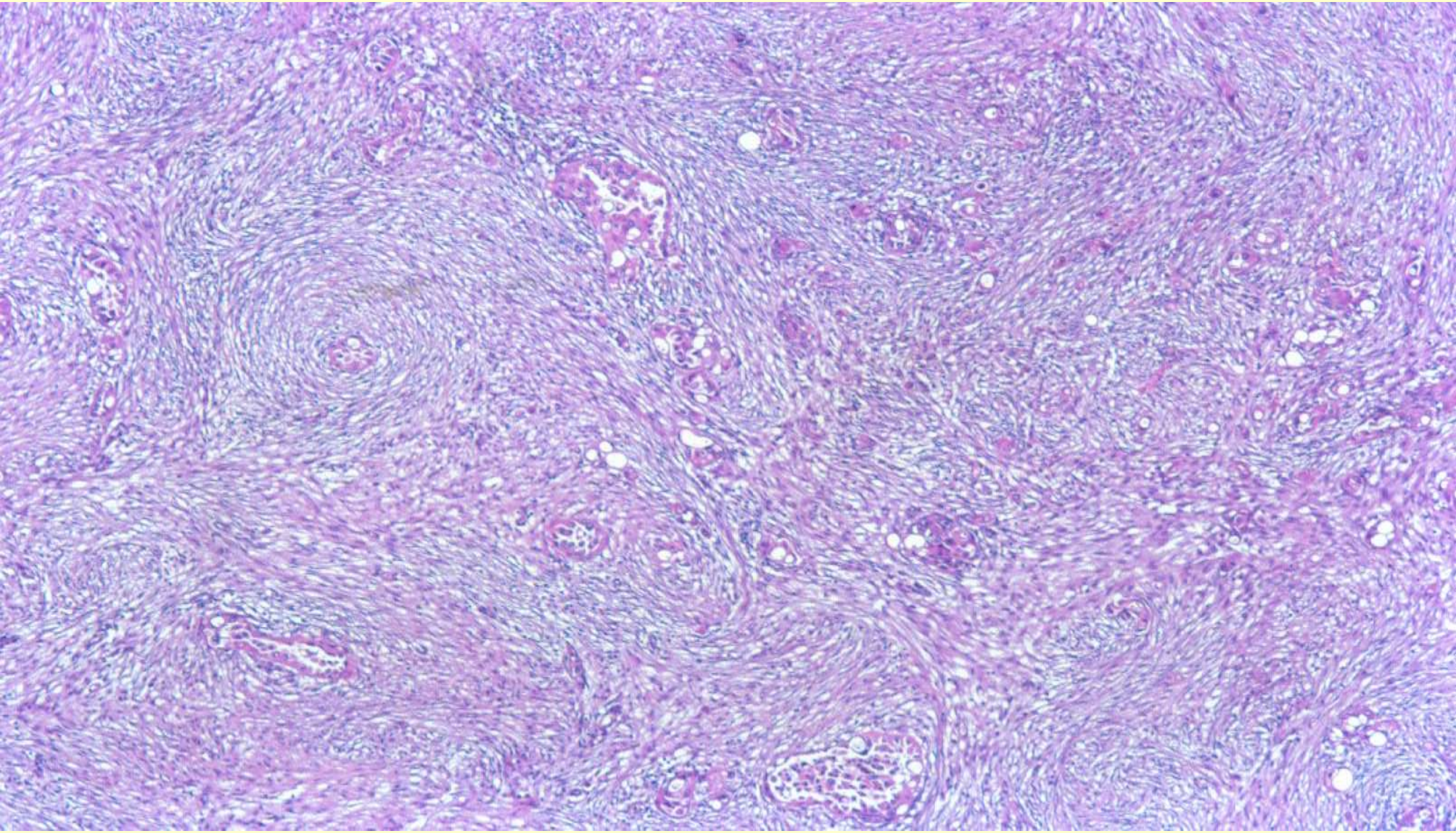
Serous borderline tumor with non-invasive implants



Non invasive implant (top) - uterine wall (bottom)



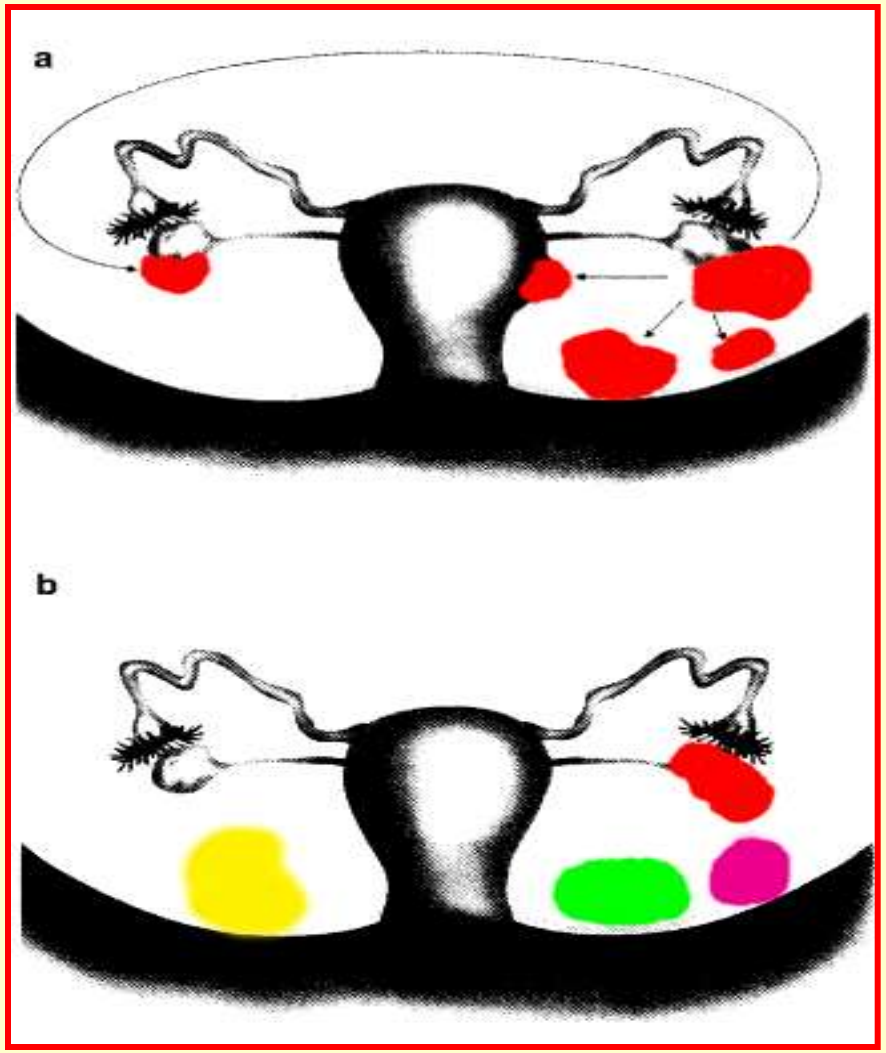
Non-invasive implant – Hemorrhage (red) and necrosis (dark)



Non-invasive implant - uterine serosa – Abundant fibrous tissue with few tumor glands

Serous Borderline Tumors

Two hypotheses

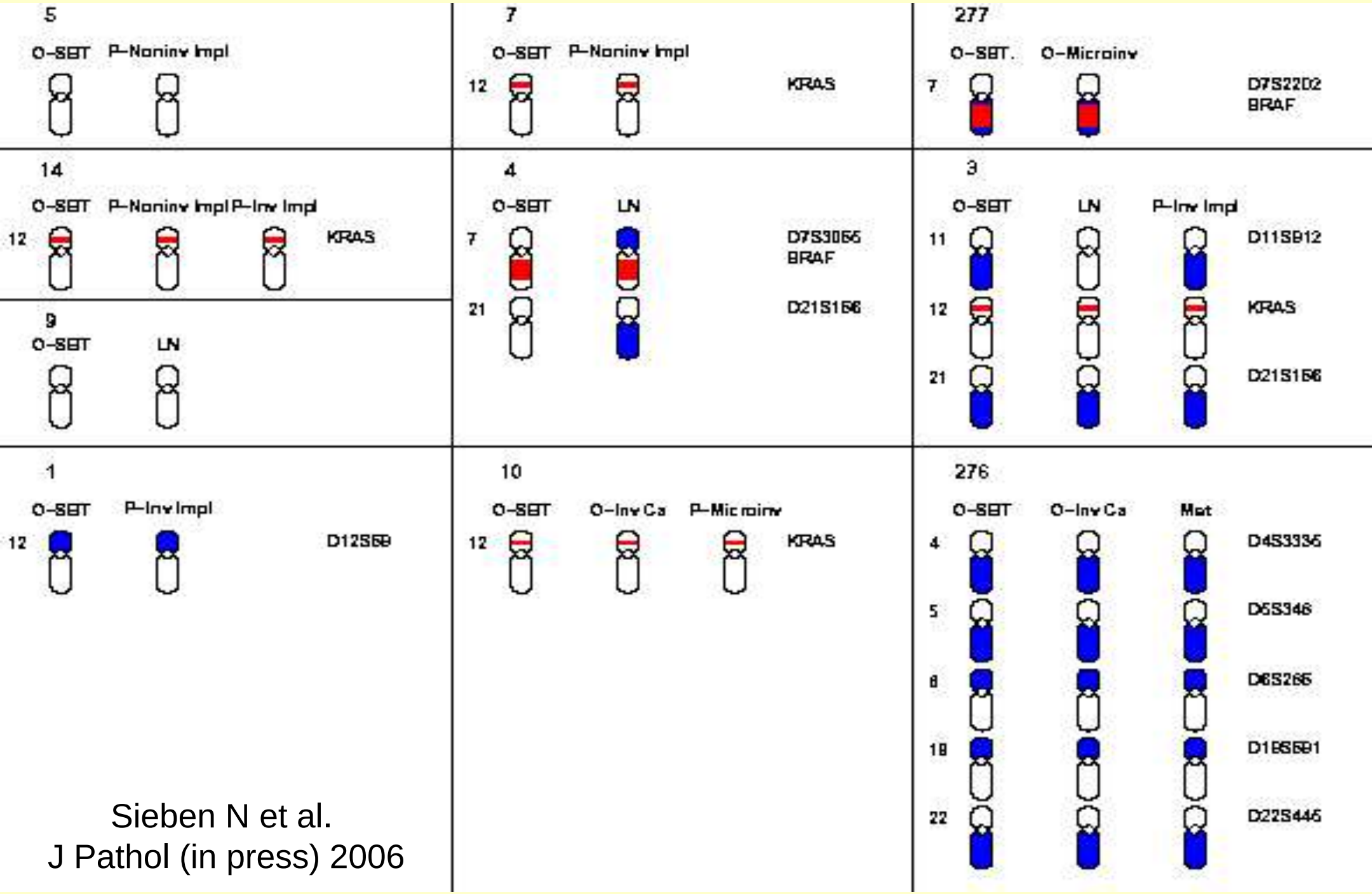


Serous Borderline Tumors

(Genome-wide allelotyping and B-RAF/K-RAS)

- 26 specimens from 10 patients
- 23 microsatellite markers
- Peritoneal implants (6 invasive, 4 noninvasive); lymph nodes (3)
- Concordance in 22 tumors of 8 informative patients

Sieben NLG et al
J Pathol (in press) 2006



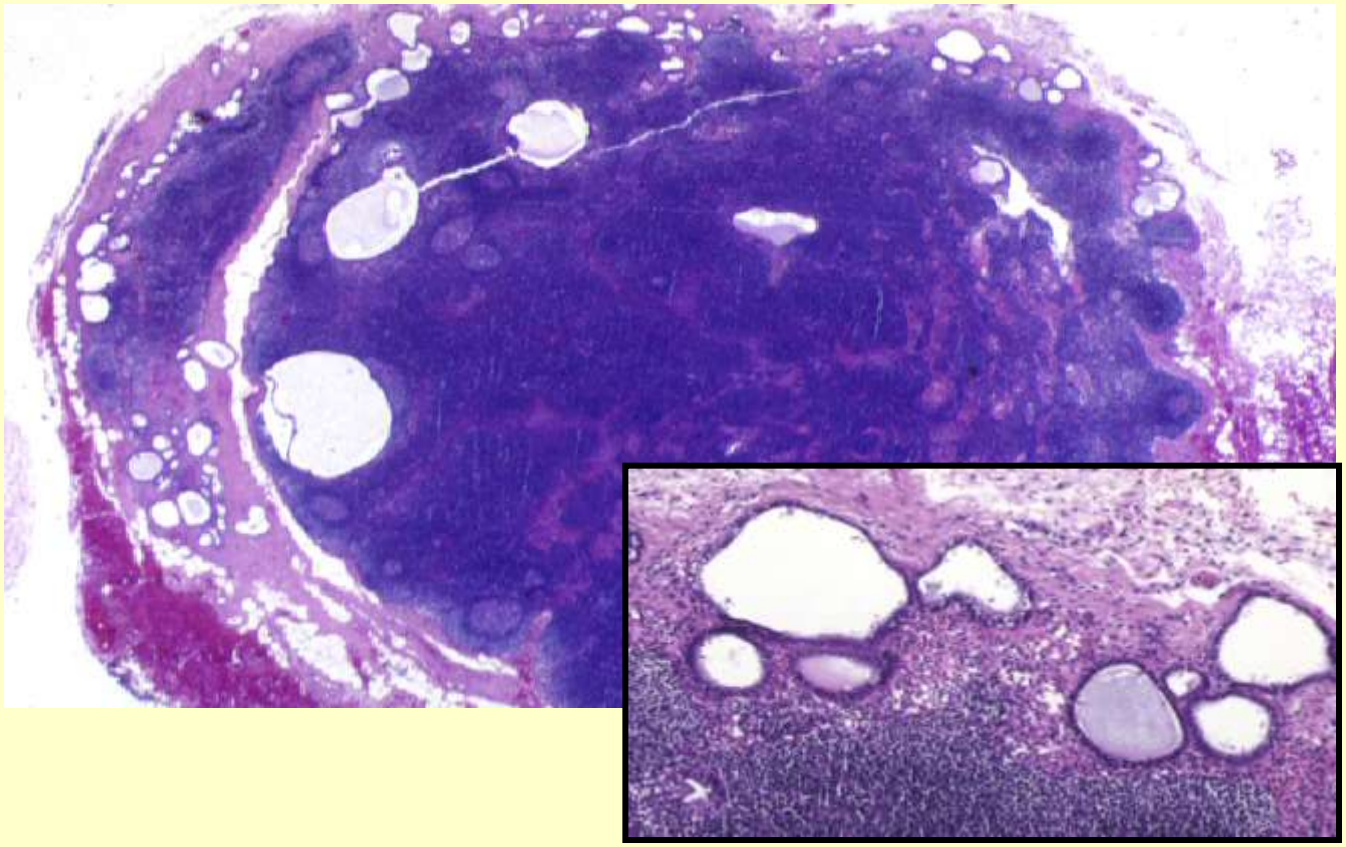
Sieben N et al.
J Pathol (in press) 2006

Serous Tumors

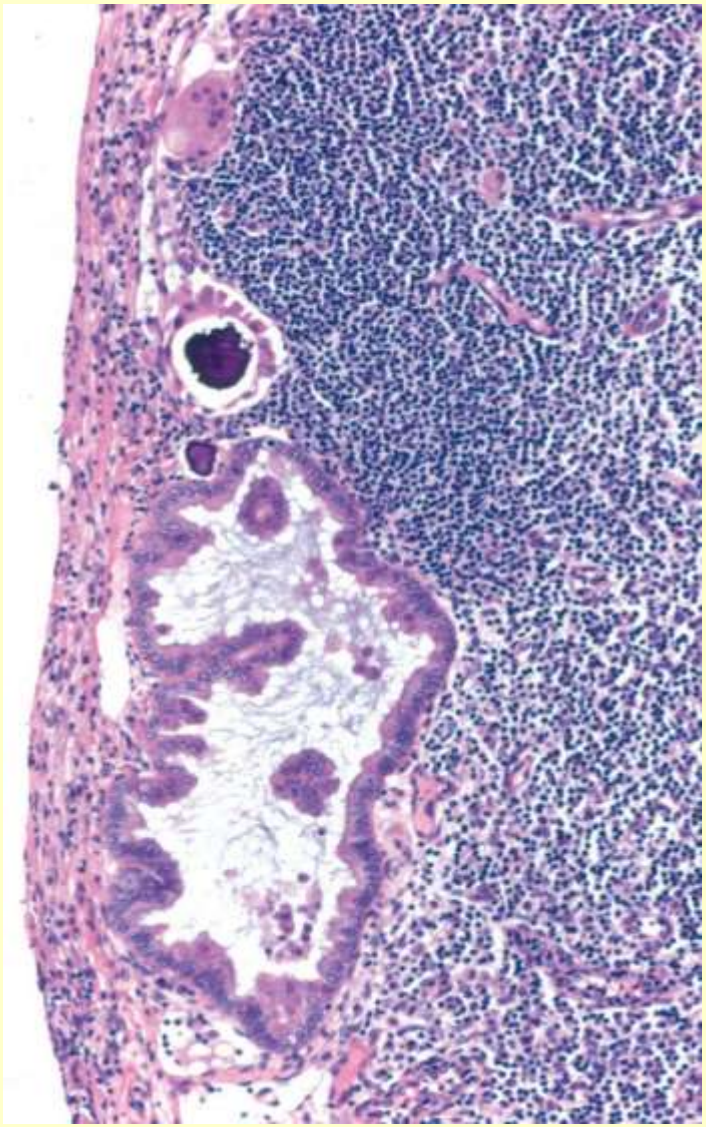
(10 yr Survival)

Bord	Stage	Ca
95%	1	54%
91%	1-4	23%
71%	2-4	20%

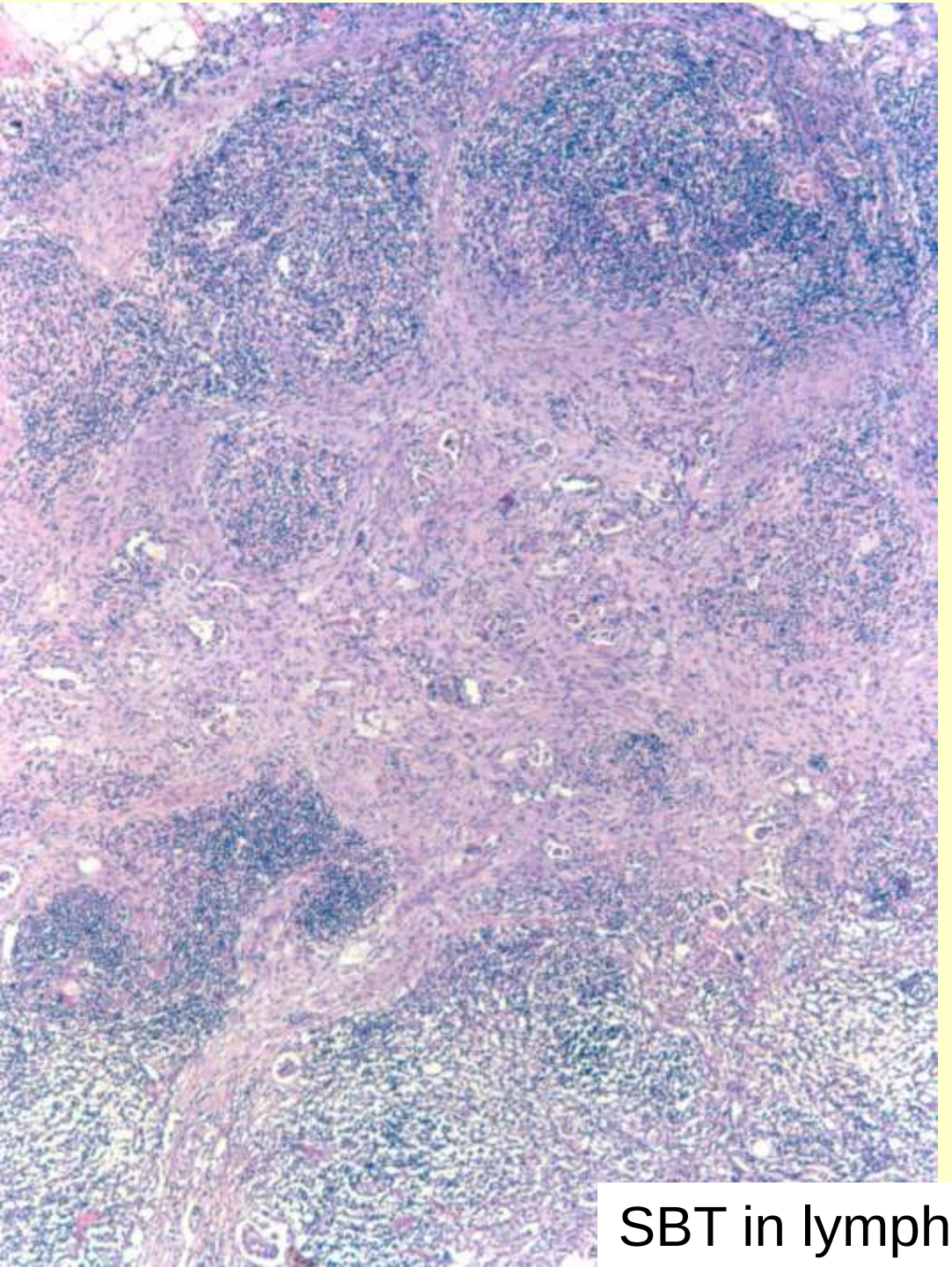
SBT in Lymph Nodes: 30%

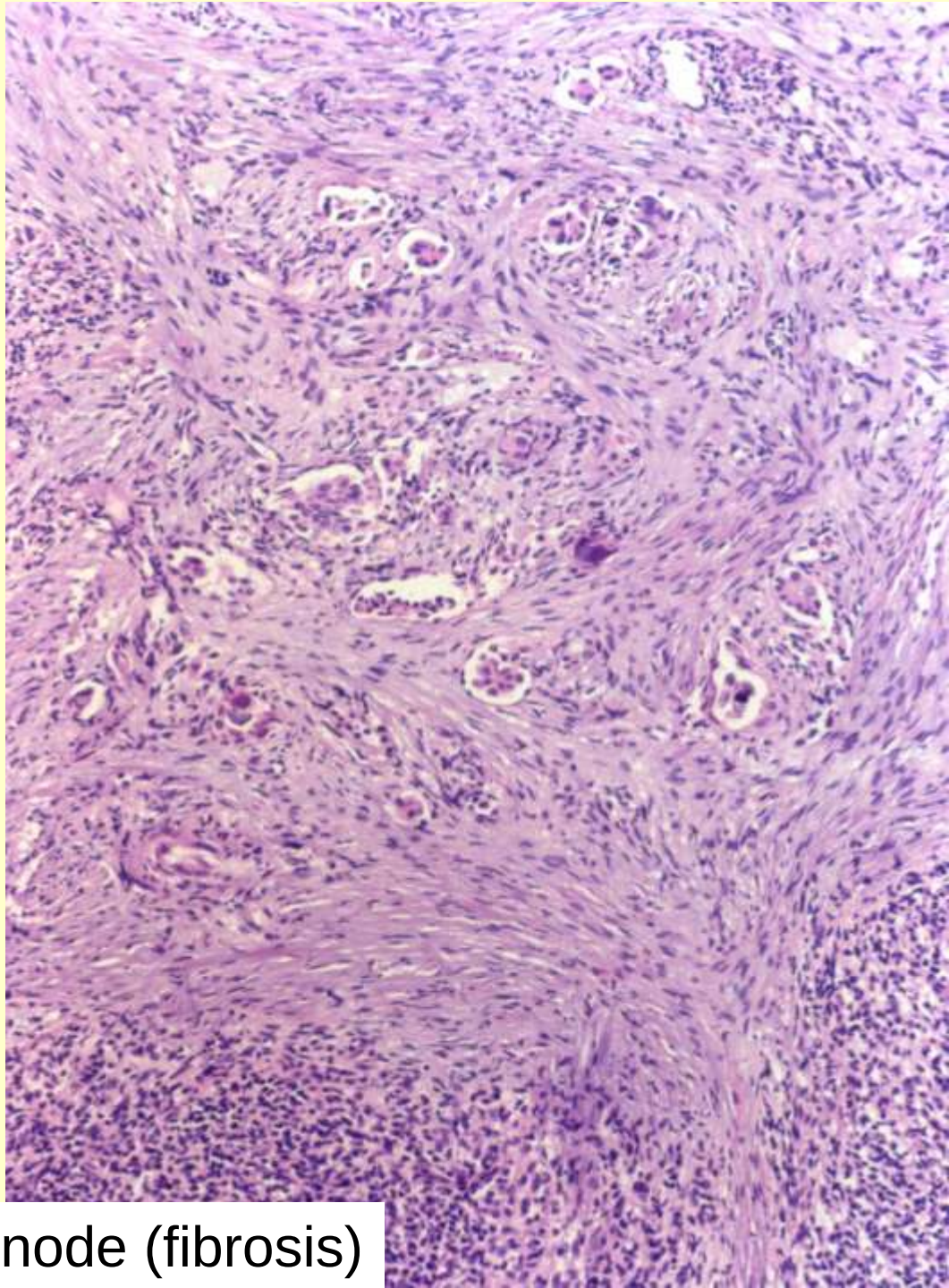


LN: Mullerian cysts (endosalpingiosis)



SBT in lymph node

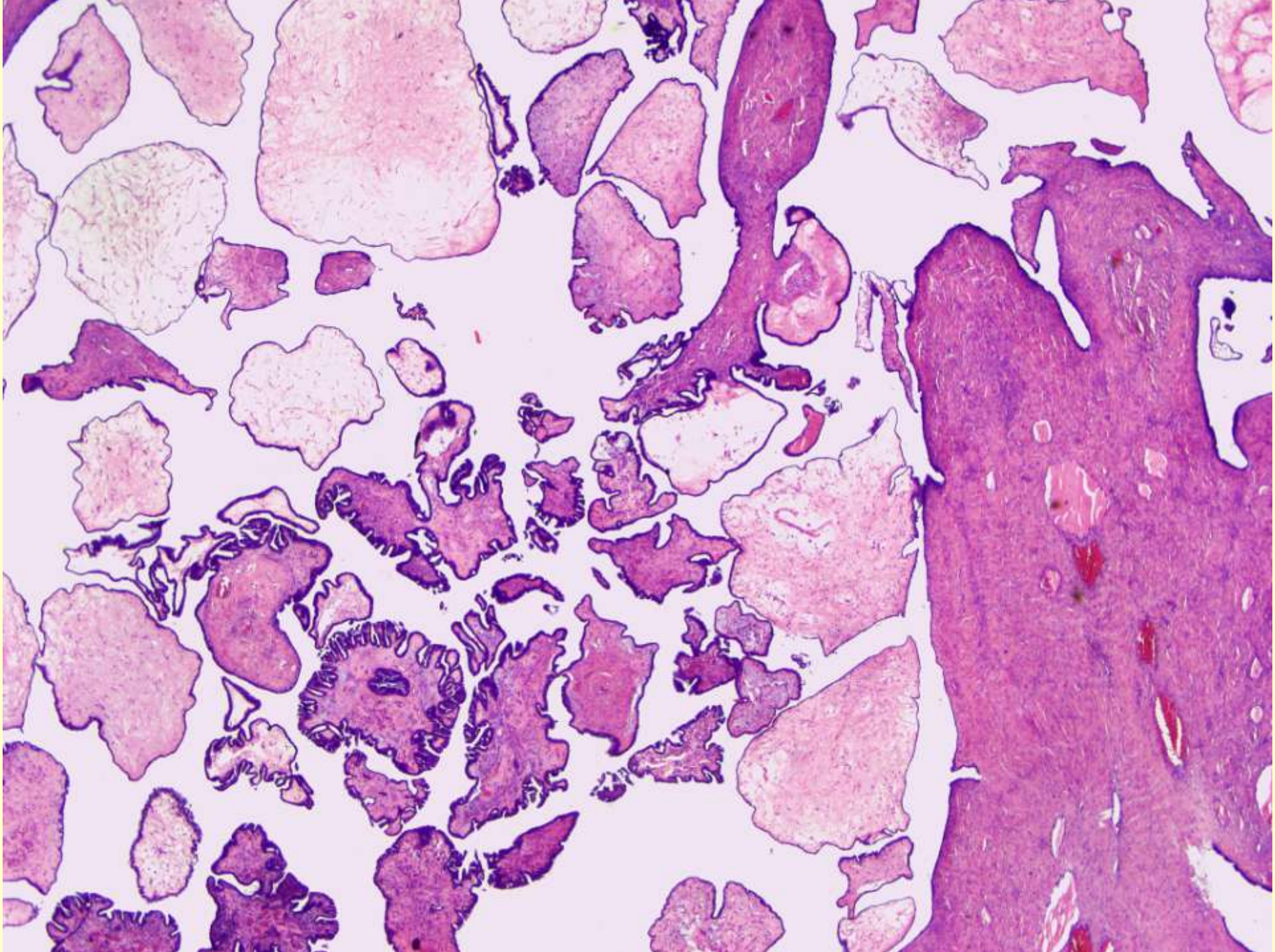


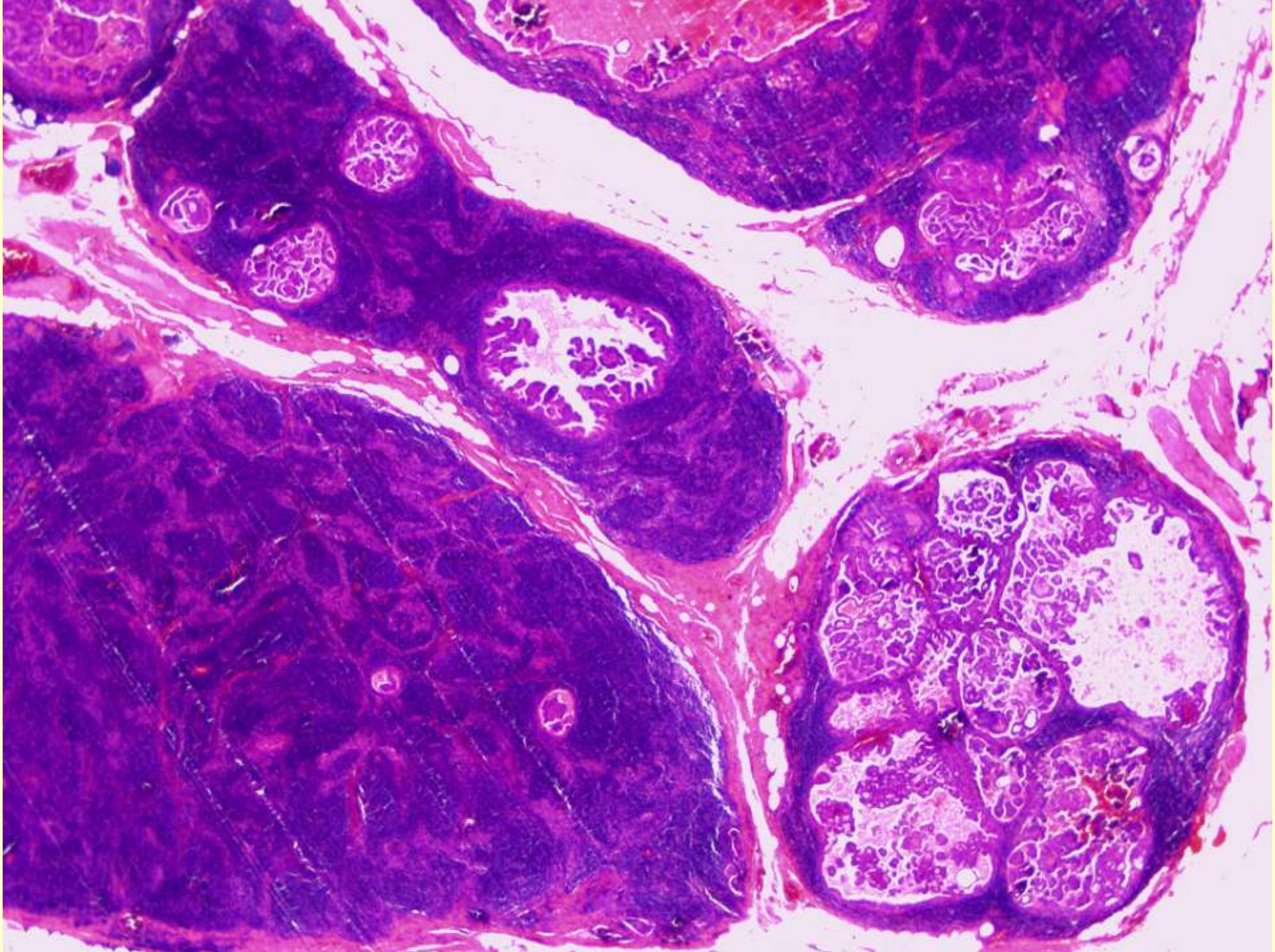


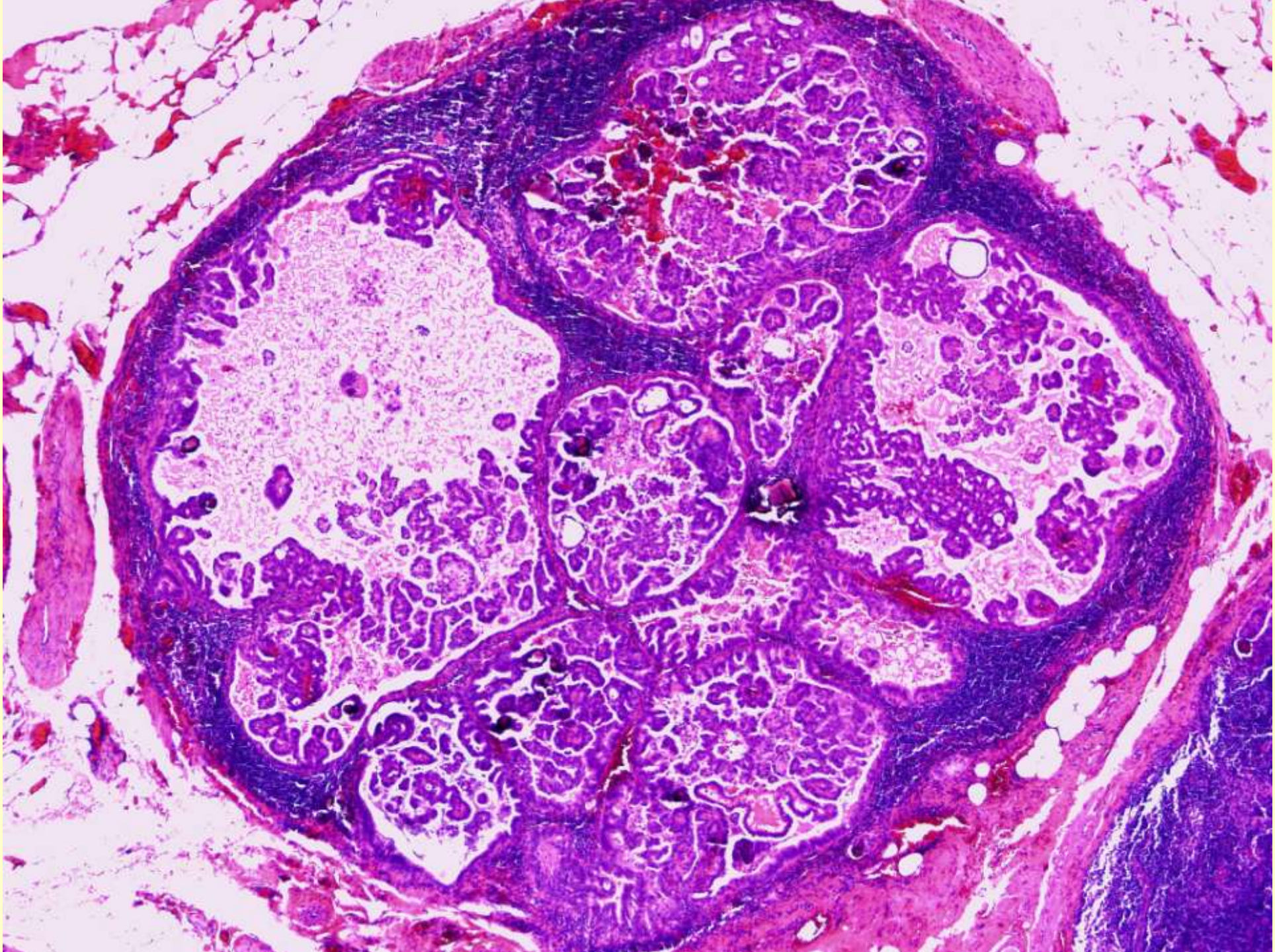
SBT in lymph node (fibrosis)

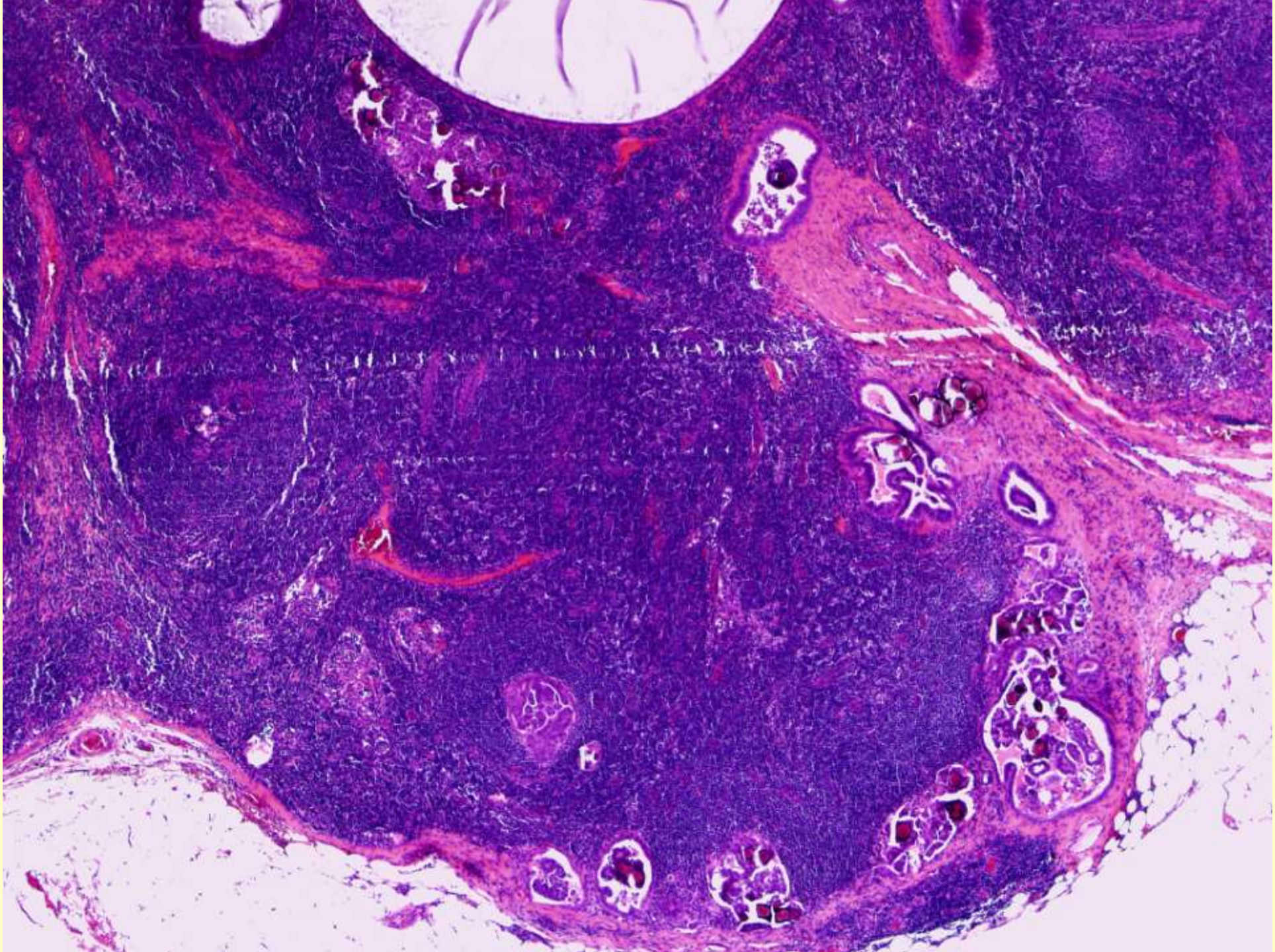
SBT in Lymph Nodes
(30%)

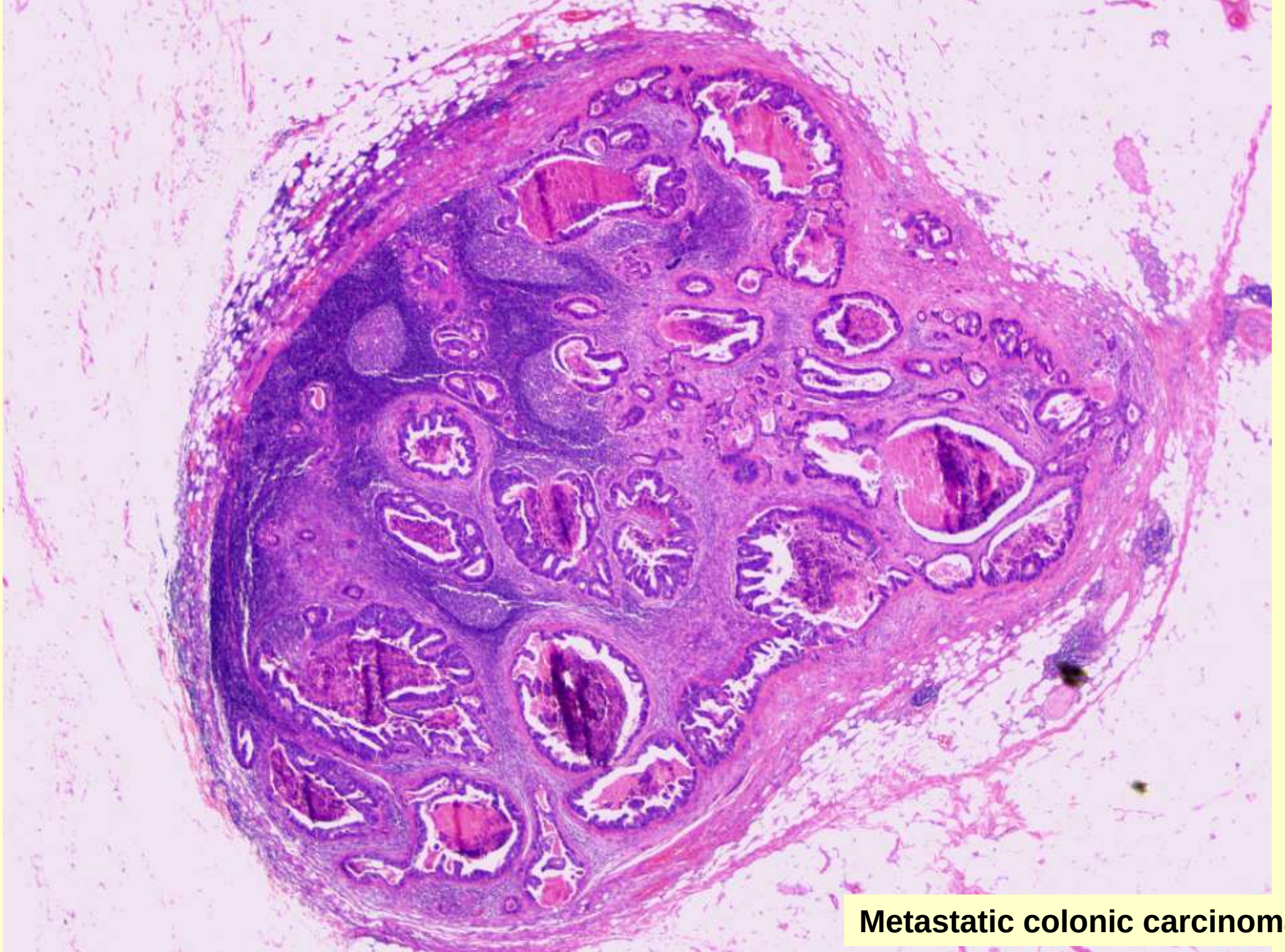
- Gland inclusions (15%) → SBT
- SBT in lymph nodes
- Literature: No decreased survival
- Stanford data: Aggregates (> 1 mm) equivalent to invasive implants (?)
- SBT may originate in lymph nodes from endosalpingiosis



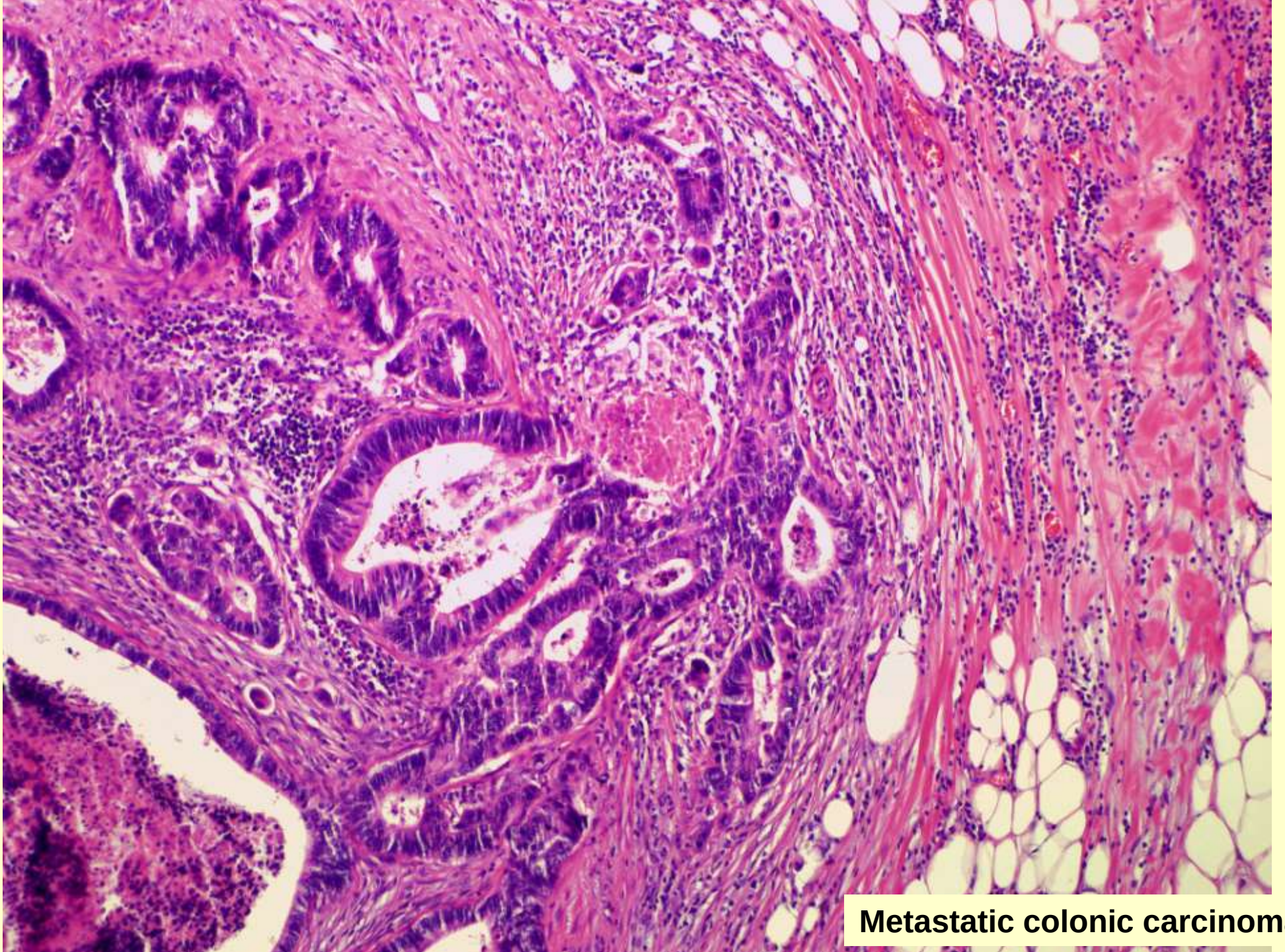








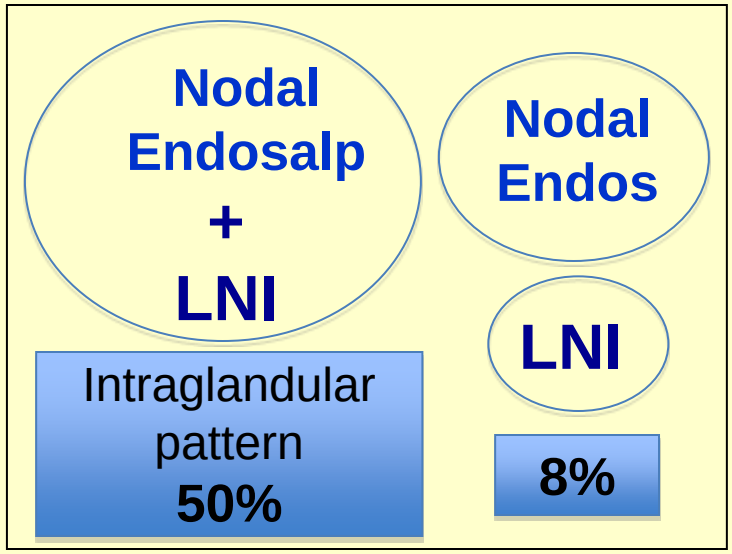
Metastatic colonic carcinoma

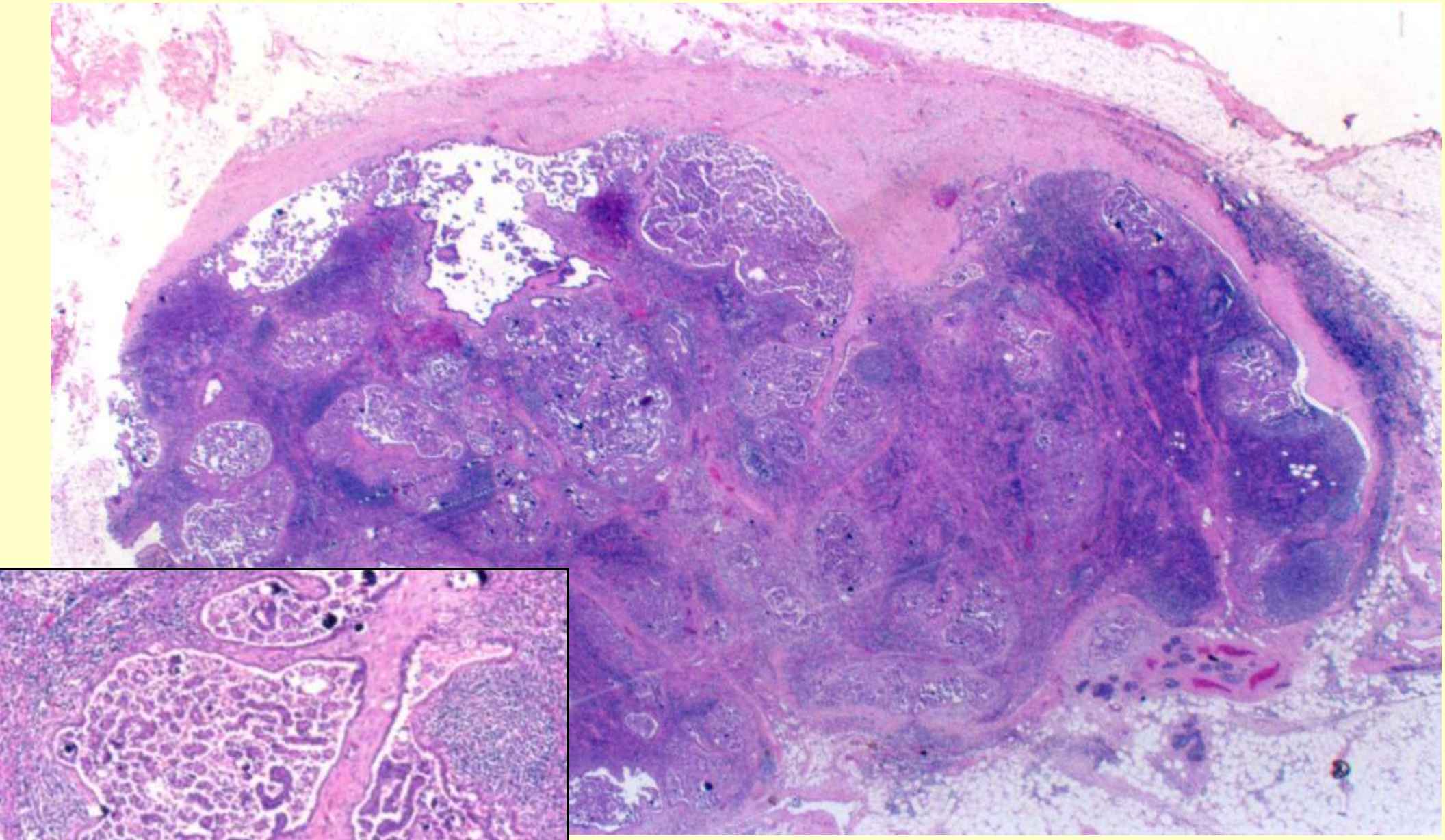

Metastatic colonic carcinoma

Nodal Endosalpingiosis in Ovarian Serous Borderline Tumors with Lymph Node Involvement

	Ovarian SBT	Cervical ADCa	Endometrial Endometrioid ADCa	SBT with LNInv	SBT without LNInv
N. Cases	30	30	30	36	36
Nodal Endosalp	**33 %**	0%	3%	**66%**	14%

Djordjevic et al
Am J Surg Pathol 2010





SBT in axillary lymph node (metastasis)

Serous Borderline Tumor

↓

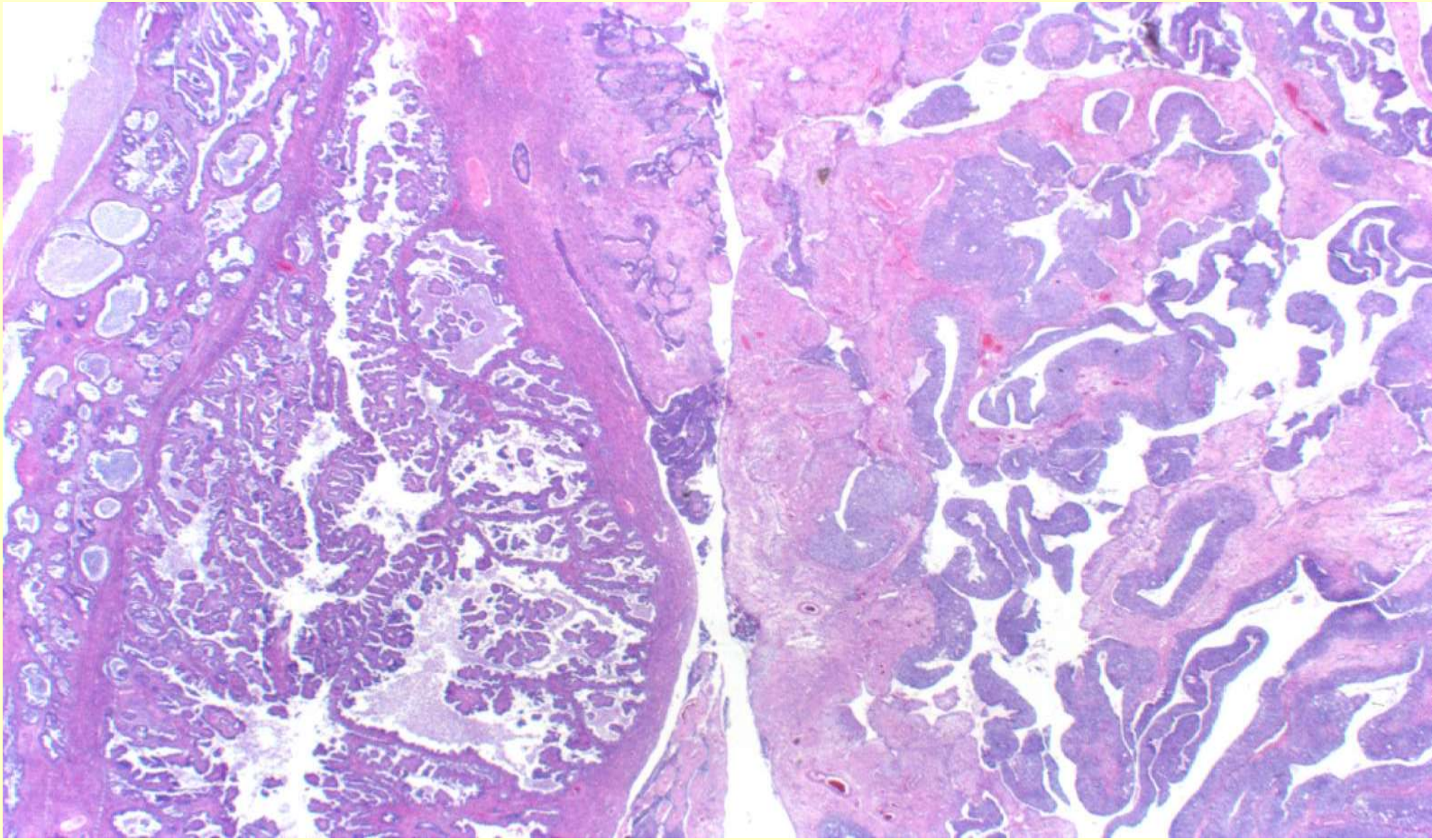
Carcinoma

Serous Borderline Tumor

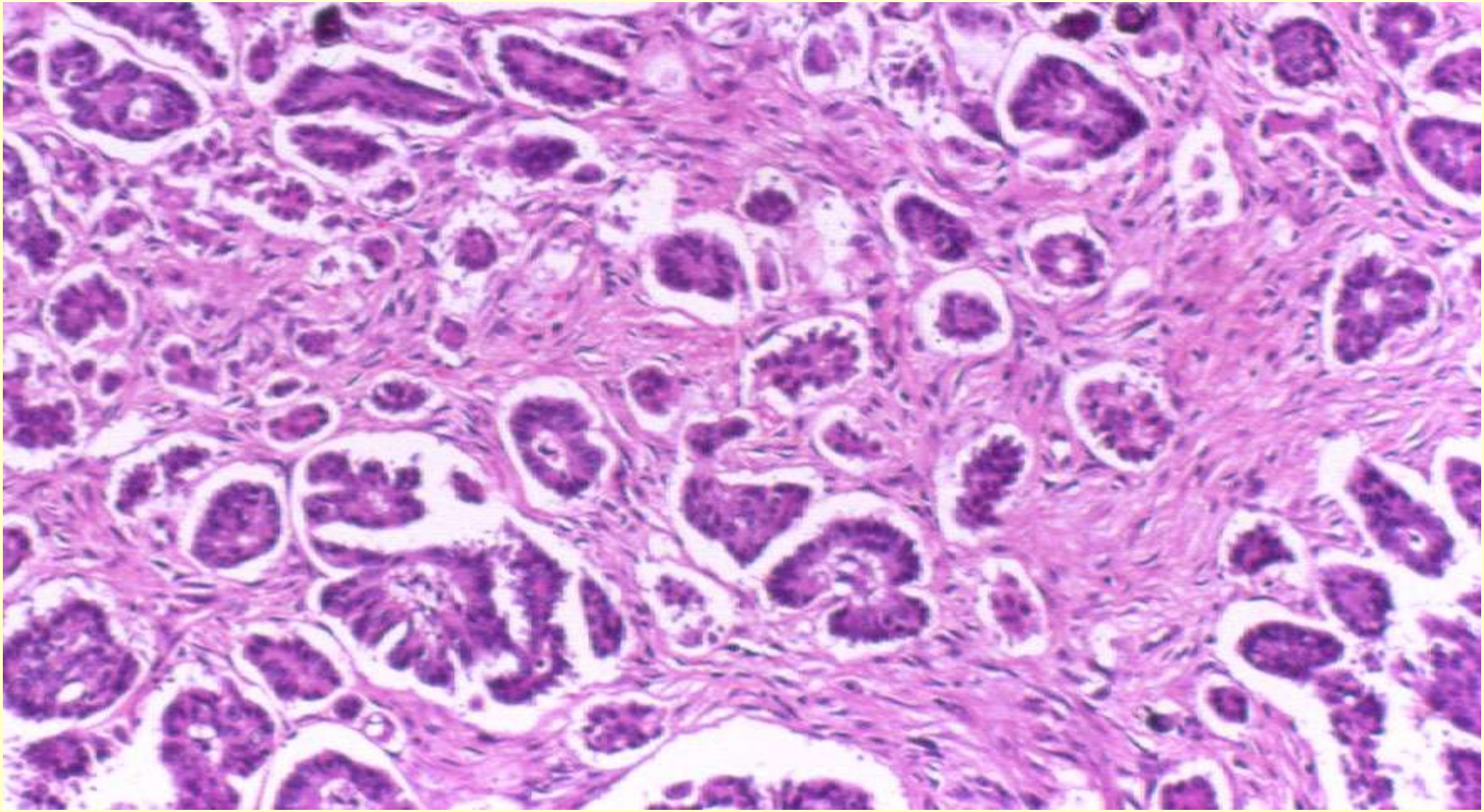
↓

Carcinoma

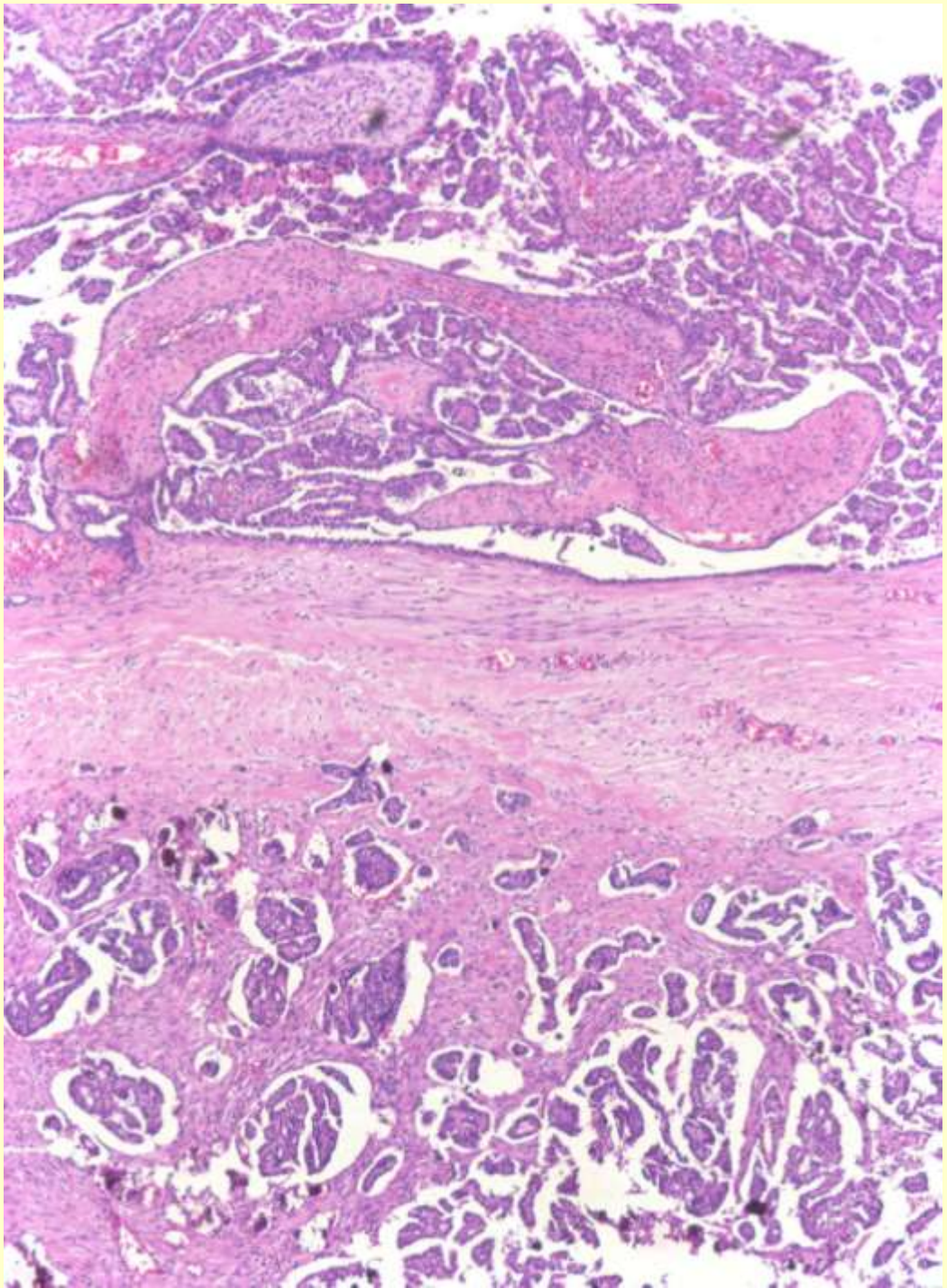
- Rare
- Usually as low grade carcinoma
- Limited sampling?
- Second primary?
- Stanford data: 6-7% (late, with surface involvement)



SBT 6th recurrence TCC



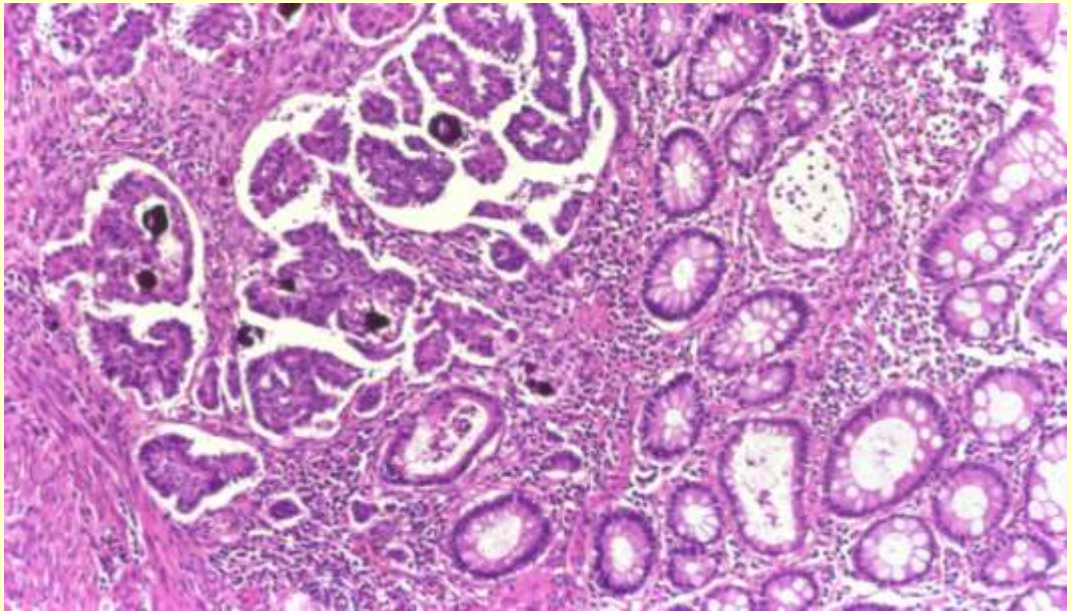
25 yr-old woman
Bx umbilicus – Low-grade serous carcinoma

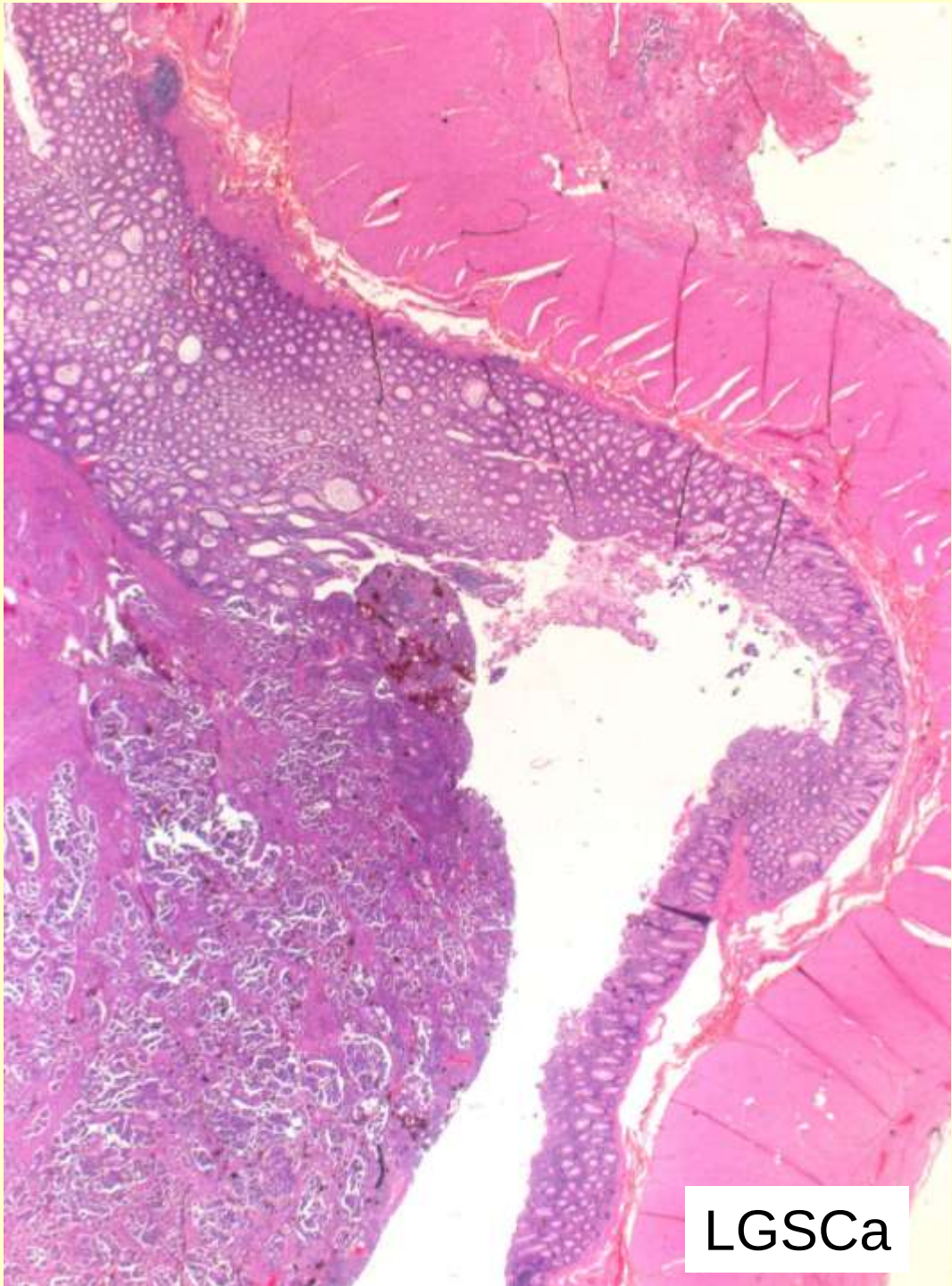


SBT

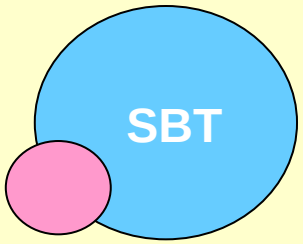
Invasive
LGSCa

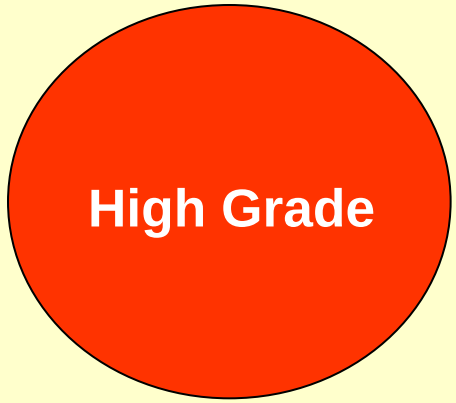
SBT + LGSCa

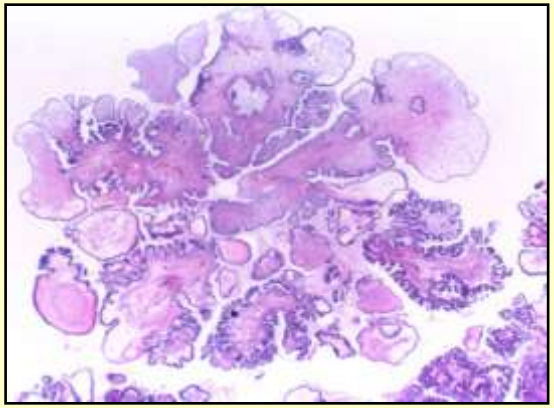




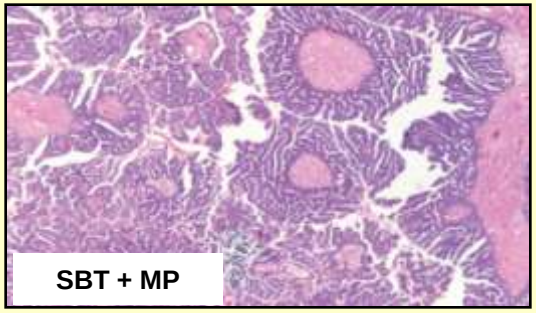
Serous Tumors : Borderline and Carcinomas

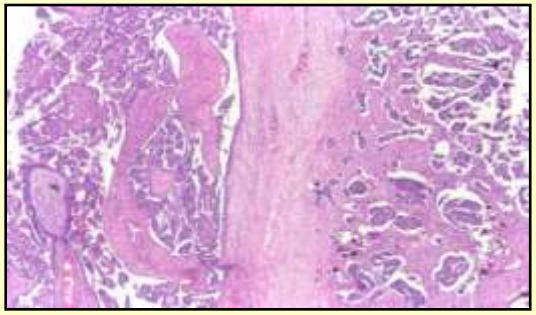




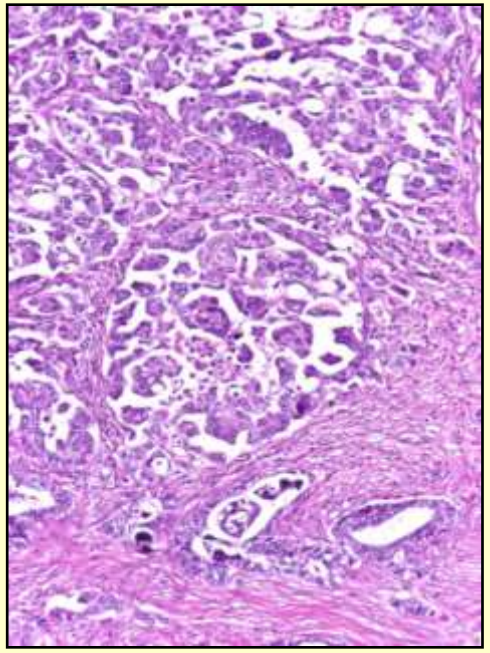


Serous Borderline Tumor (SBT)



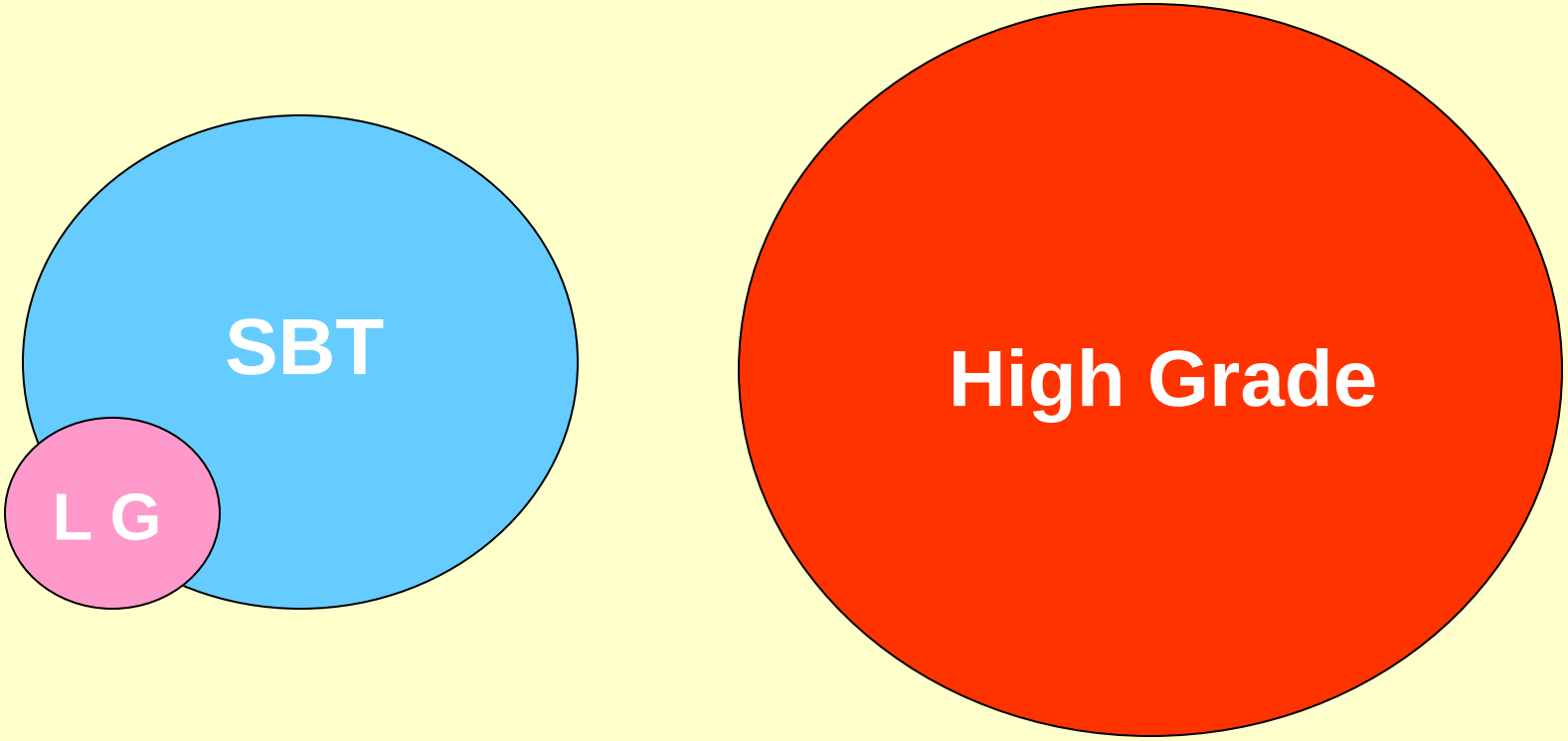


SBT + Low Grade Serous Carcinoma



High-Grade Serous Carcinoma

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 et al
Am J Pathol 2002

Serous Borderline Tumors (SBTs)

- The vast majority of SBTs are associated with good prognosis
- Only exophytic tumors with invasive peritoneal implants may progress to low-grade serous carcinoma (rare – 6-7% of SBTs)
- Low-grade serous carcinoma is rare (<5% of ovarian carcinomas) and totally different disease from high-grade serous carcinoma (70% of ovarian cancers)
- Micropapillary pattern is a small risk factor in SBT. Prognosis is poor only with invasive implants
- Association of SBT-micropapillary pattern with invasive implants is inconsistent
- 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

(Outline)

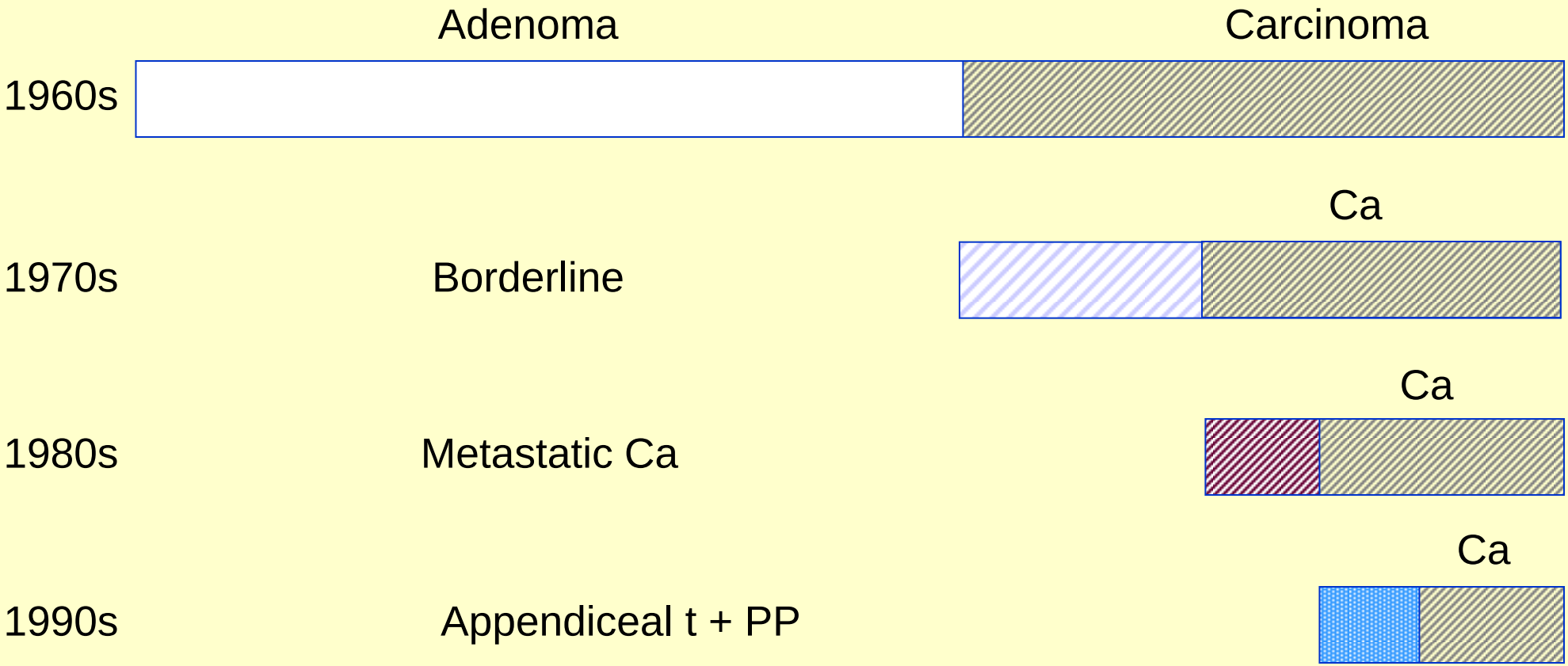
- Borderline: endocervical vs intestinal types
- Molecular genetics: *K-ras* and tumor progression
- Mucinous borderline vs carcinoma
- Stage I mucinous carcinoma: prognosis
- Primary vs metastatic mucinous carcinoma
- Mucinous tumors a/w pseudomyxoma peritonei

Mucinous Tumors of the Ovary

(10-15% of all ovarian tumors)

Mucinous Tumors of the Ovary

(From benign to malignant)



Mucinous Tumors of the Ovary

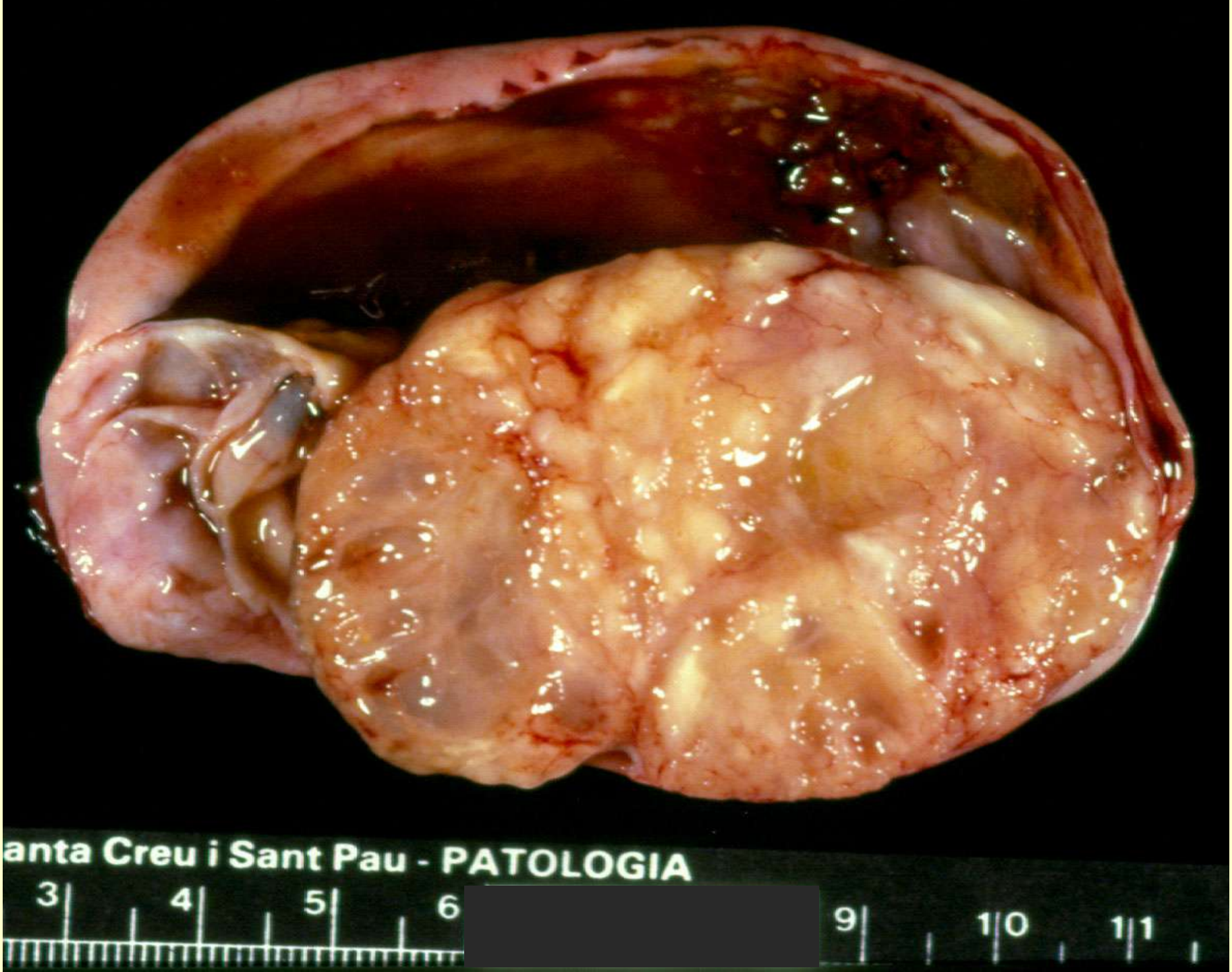
(10-15% of all ovarian tumors)

• Benign	75%	80%
• Borderline	10%	17%
• Carcinomas	15%	3%

Koonings, FIGO, 1988

Mucinous Borderline Tumors

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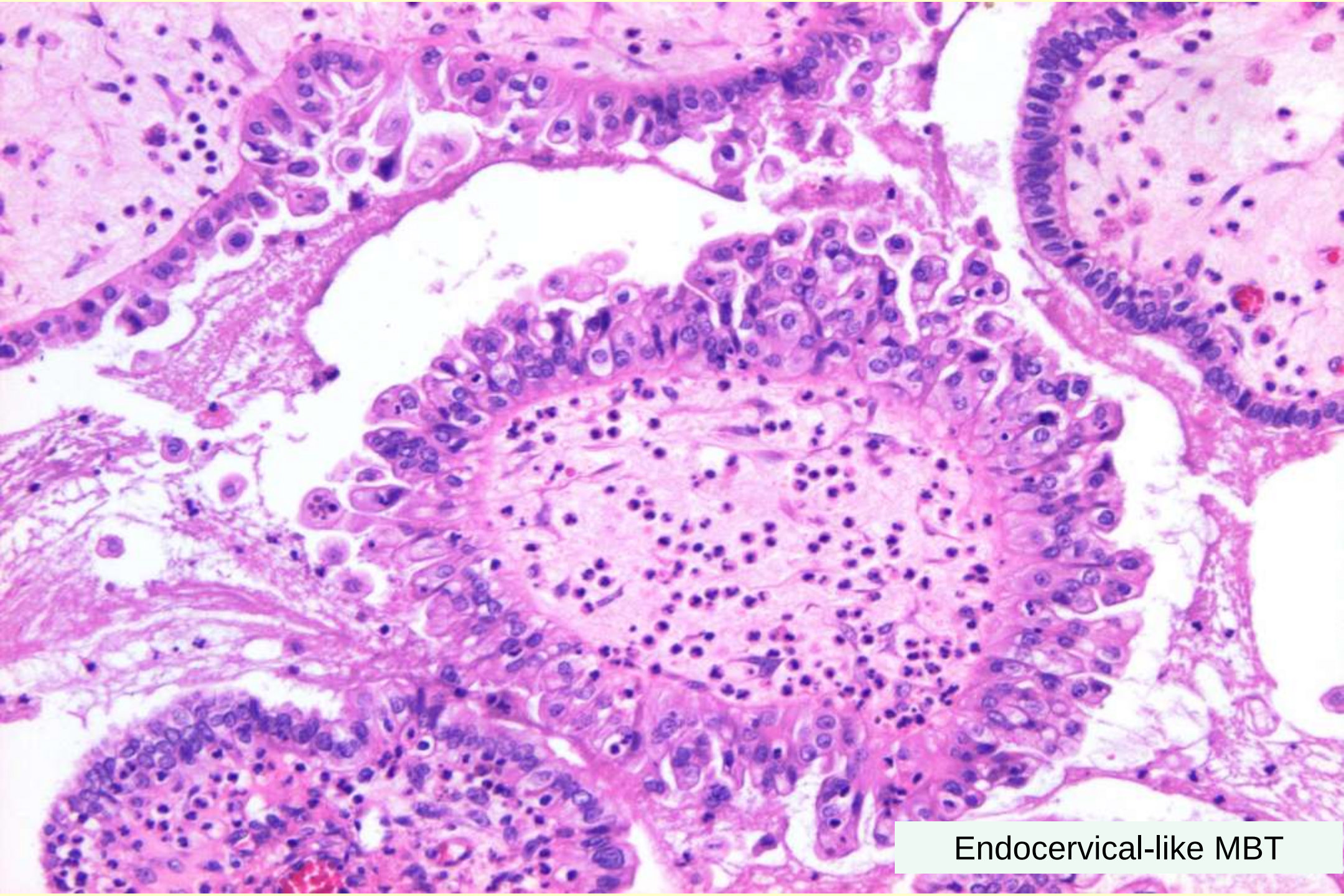
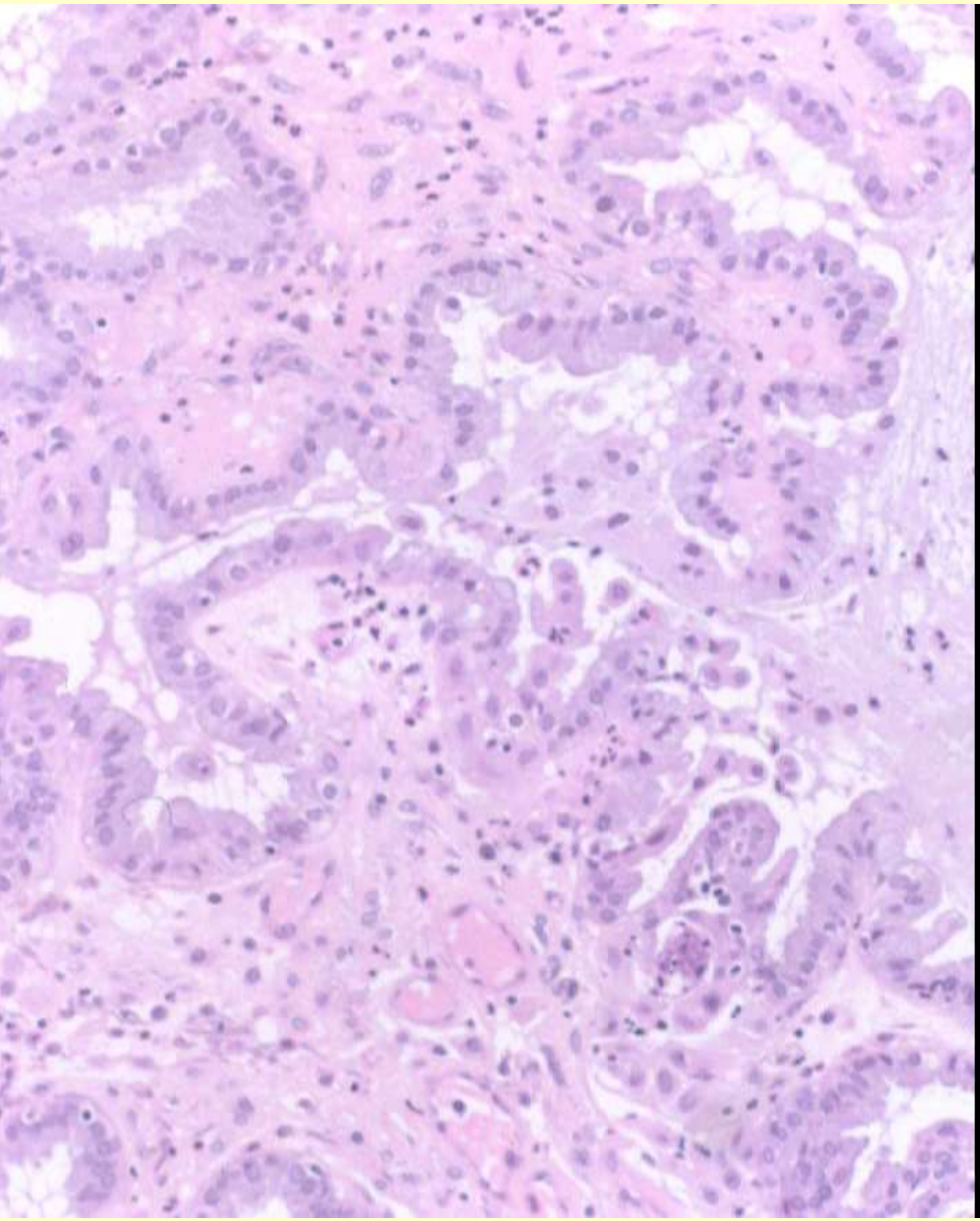
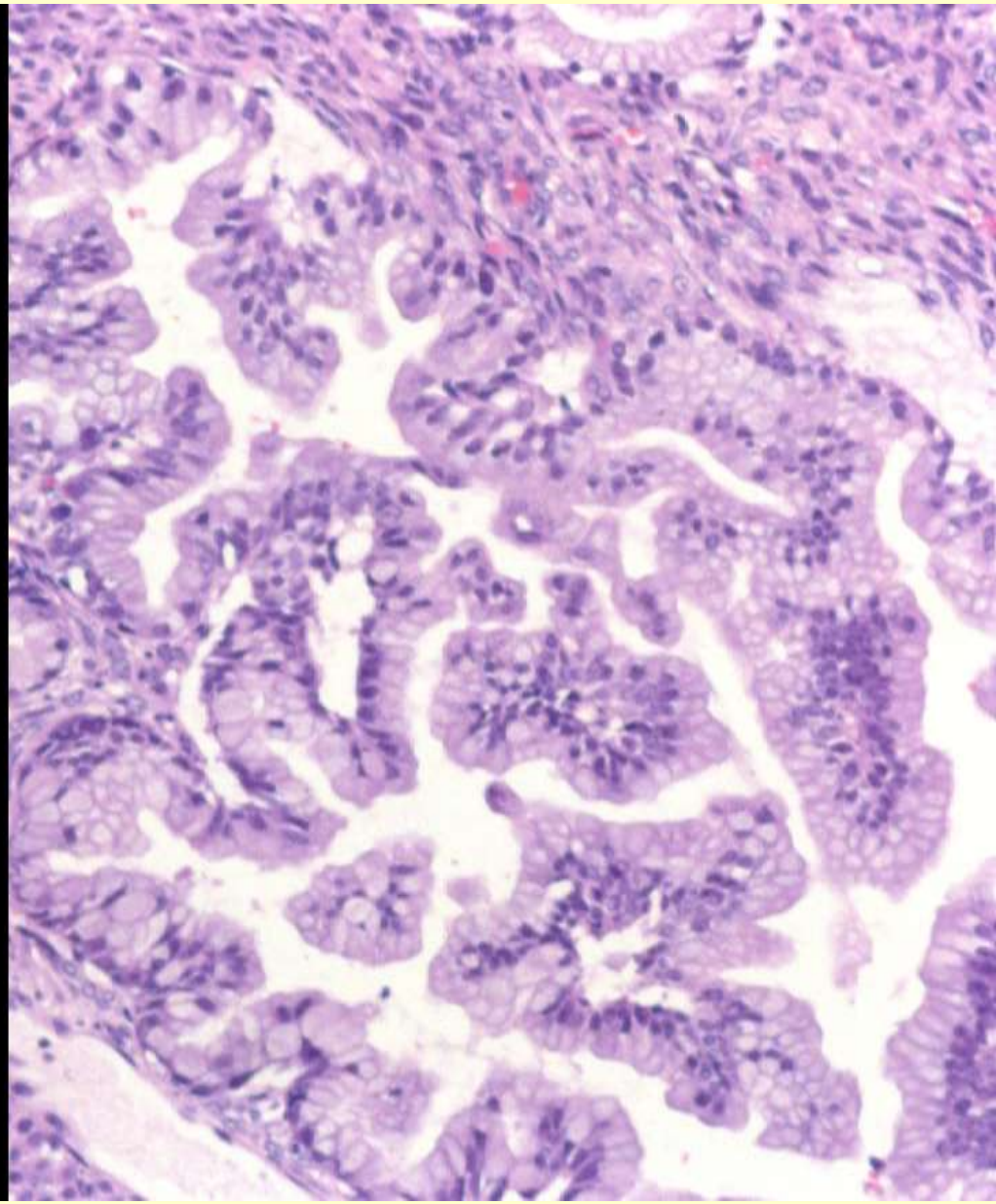

Endocervical-like MBT



Endocervical-like MBT

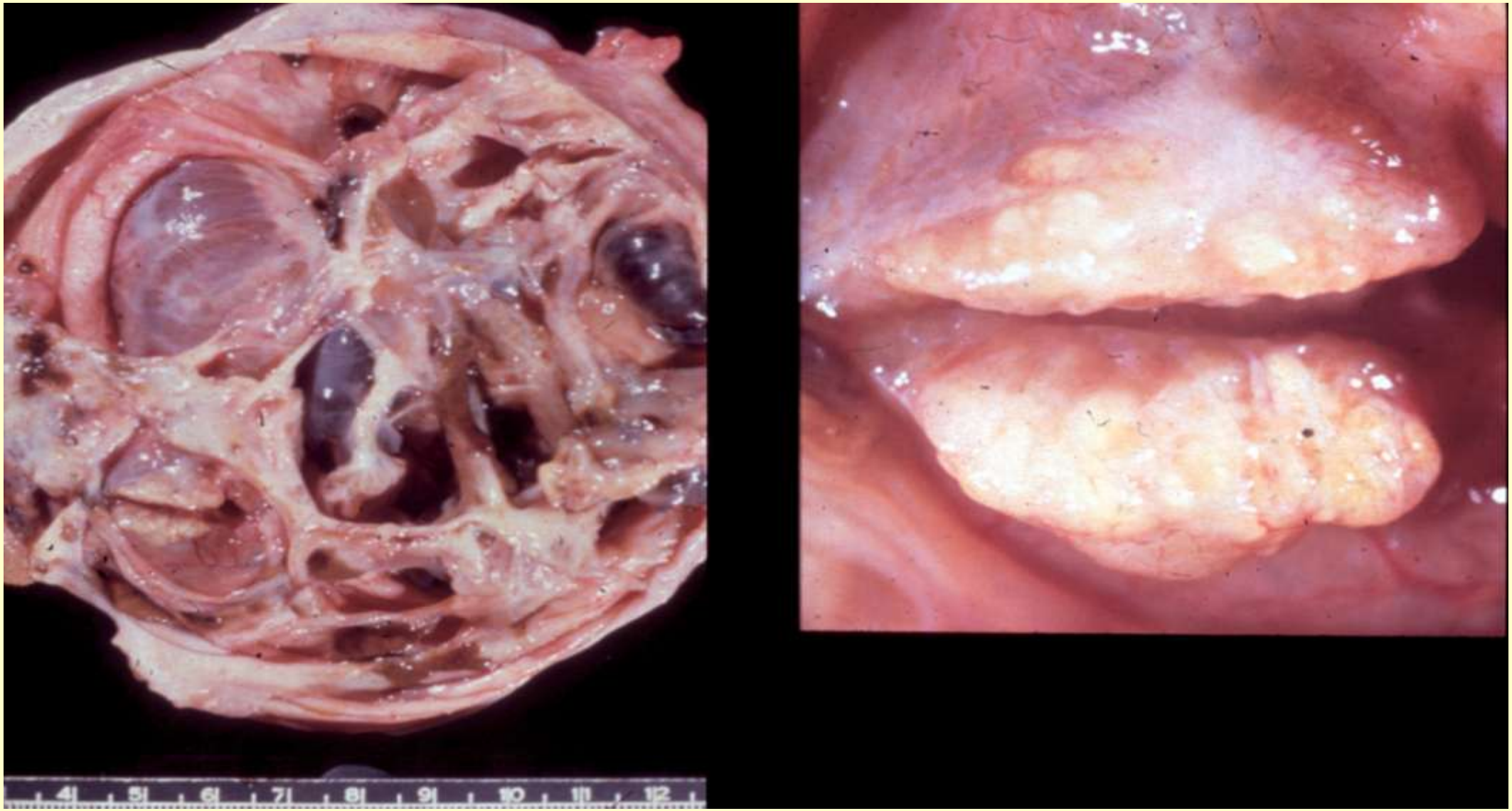


Intestinal MBT

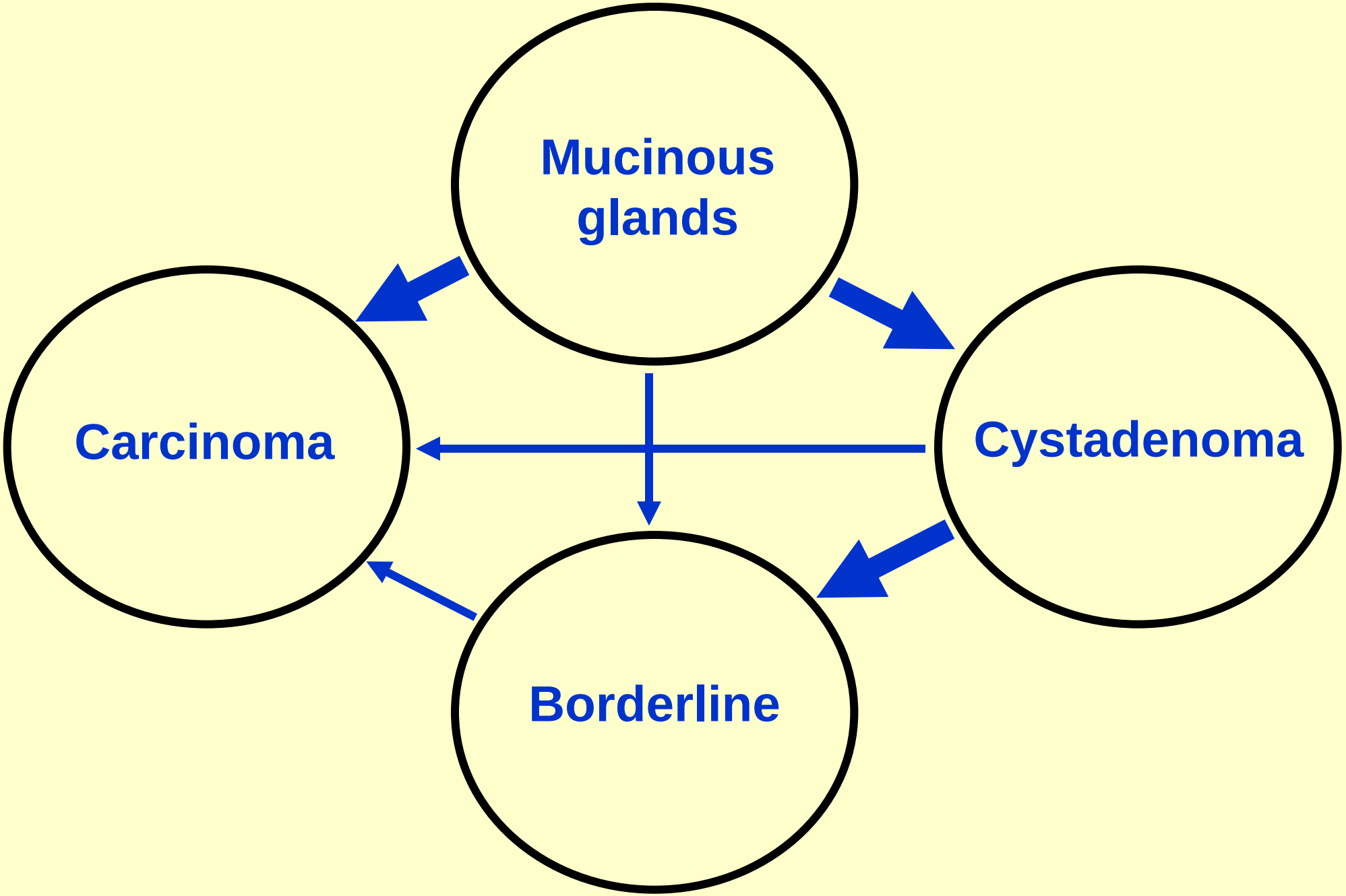
Mucinous Borderline Tumors
(Intestinal type)

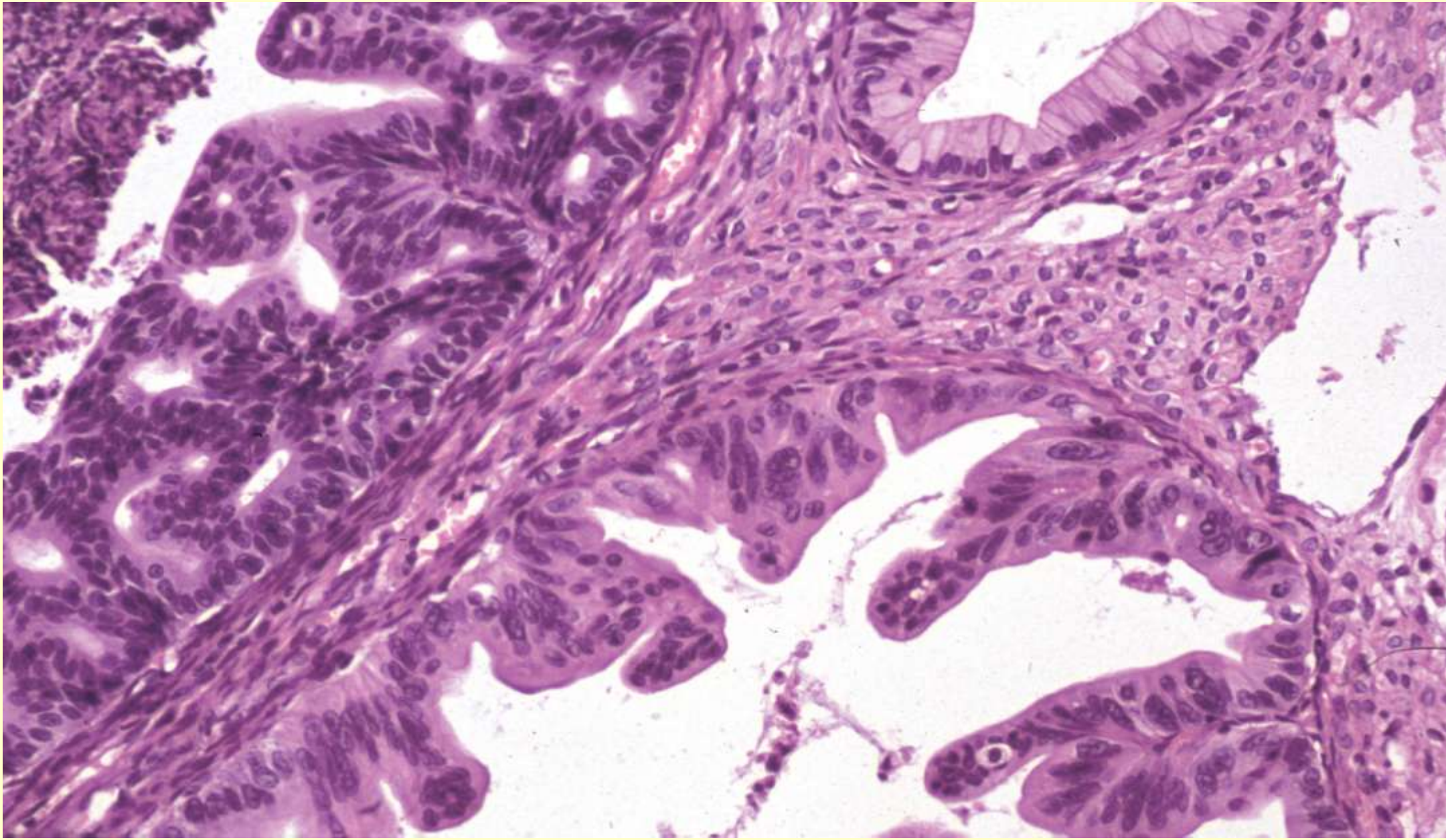
- Frequency 70 - 80% of Non-Bg
  - Age 51 - 52 yrs
    - Bilaterality < 10%
  - Stage I 80 - 90%

Mucinous intestinal borderline tumor



Mucinous intestinal borderline tumor + carcinoma


Mucinous glands
Carcinoma
Cystadenoma
Borderline



K-*ras* Mutations in Mucinous Ovarian Tumors

A Clinicopathologic and Molecular Study of 95 Cases

Miriam Cuatrecasas, M.D.
Alberto Villanueva, Ph.D.
Xavier Matias-Guiu, M.D.
Jaime Prat, M.D., F.R.C.Path.

Department of Pathology, Hospital de Sant Pau, Autonomous University of Barcelona, Barcelona, Spain.

Presented in part at the XVIIth National Congress of the Spanish Society of Pathology, Bar-

BACKGROUND. To assess the role of K-*ras* mutations in the pathogenesis of mucinous ovarian tumors, the authors looked for K-*ras* point mutations at codons 12 and 13 in 95 mucinous ovarian neoplasms. The results were subsequently correlated with the clinicopathologic data.

METHODS. Benign, borderline, and malignant mucinous ovarian tumors were identified microscopically. DNA was extracted from formalin fixed, paraffin embedded tissue, and target sequences were amplified in vitro by polymerase chain reaction. Mutations were detected by the presence of restriction fragment length polymorphisms artificially introduced by the use of mutant amplimers. In tumors containing areas that exhibited different histologic grade, precise microdissection of each of these areas was performed. The results were correlated with the clinical data and the morphologic features of the neoplasms.

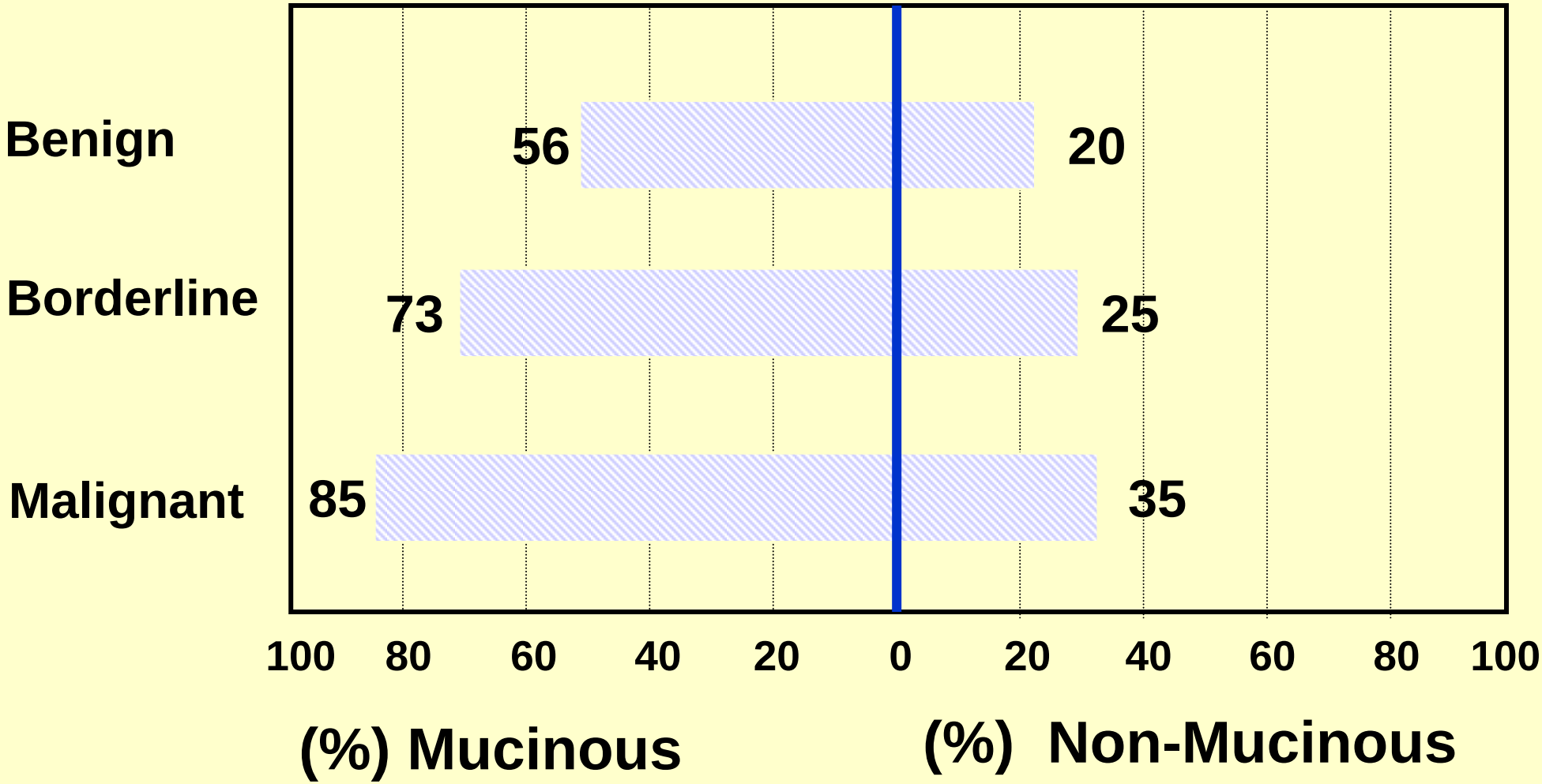
RESULTS. The overall frequency of codon 12/13 *ras* gene mutations was 68%. Codon 12 point mutations were present in 63% of the cases (55.7% of mucinous cystadenomas, 73% of borderline tumors, and 85% of carcinomas). Codon 13 mutations were detected in 11.5% of the tumors (five cystadenomas, three borderline tumors, and three carcinomas). Eight tumors (three benign, two borderline, and three malignant) exhibited mutations at codons 12 and 13. In 12 of the 15 tumors with 2 areas showing different histologic grade, identical point mutations were detected separately in both areas.

CONCLUSIONS. The results of this study confirm that K-*ras* mutations do occur in benign and particularly in malignant mucinous ovarian tumors. The authors' findings support the hypothesis that K-*ras* mutational activation is an early event in mucinous ovarian tumorigenesis. ***Cancer* 1997;79:1581–6.**

KEYWORDS: ovary, mucinous tumors, oncogenes, genes, c-K-*ras*.

Epithelial Ovarian Tumors

K-ras Mutations (12, 13)

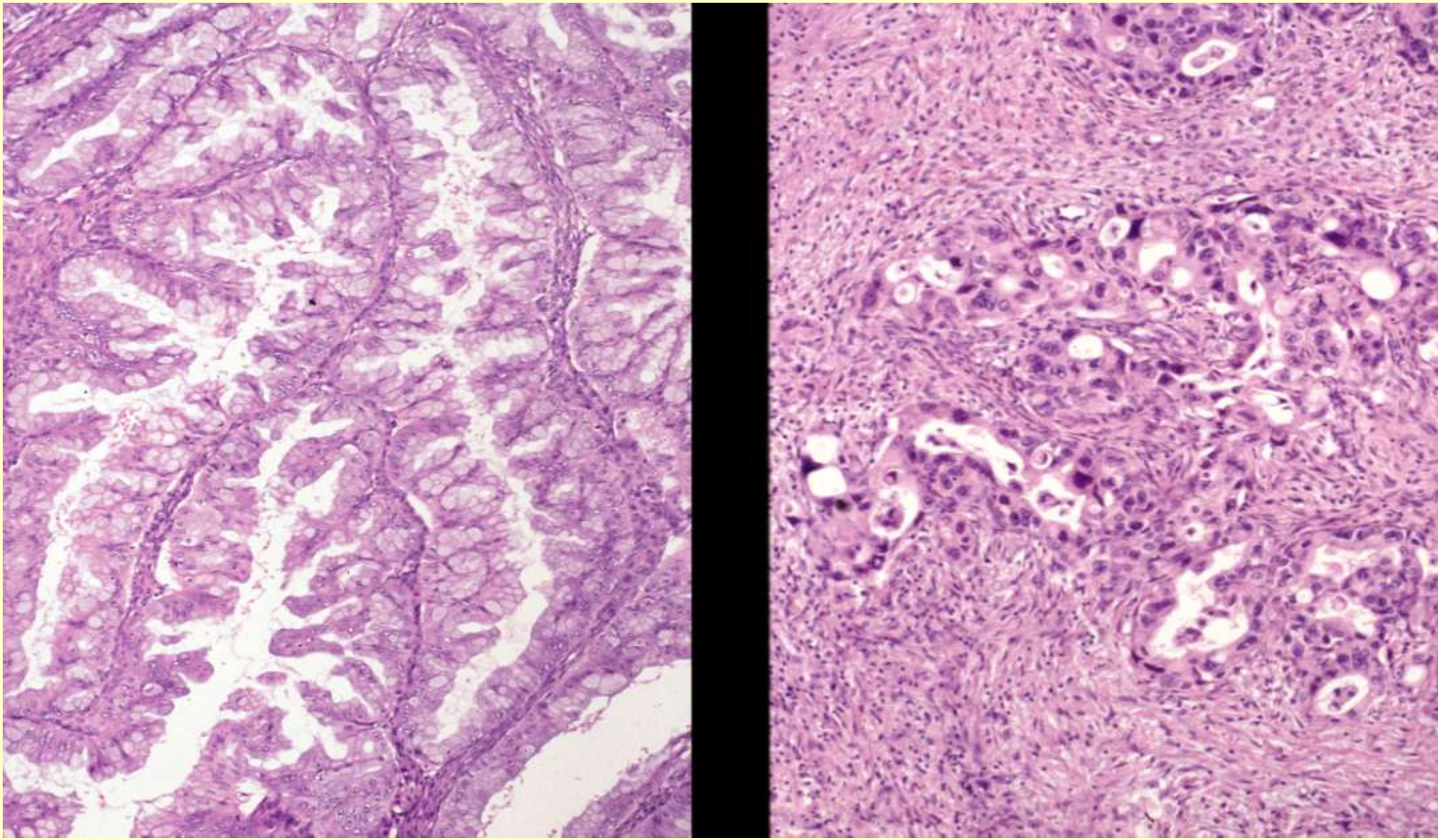


Cuatrecasas M, et al. Cancer 1997

Borderline

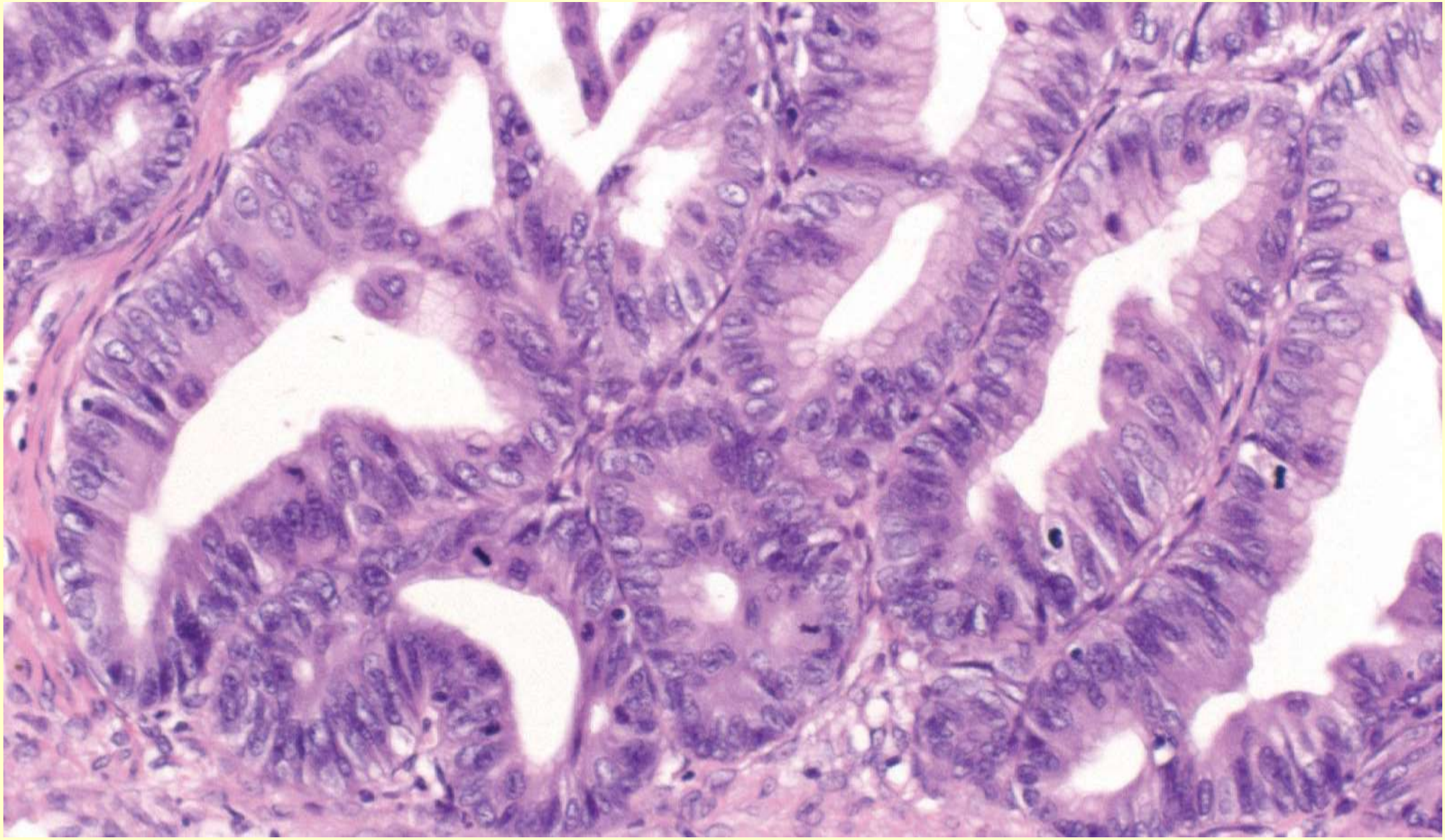
versus

Carcinoma

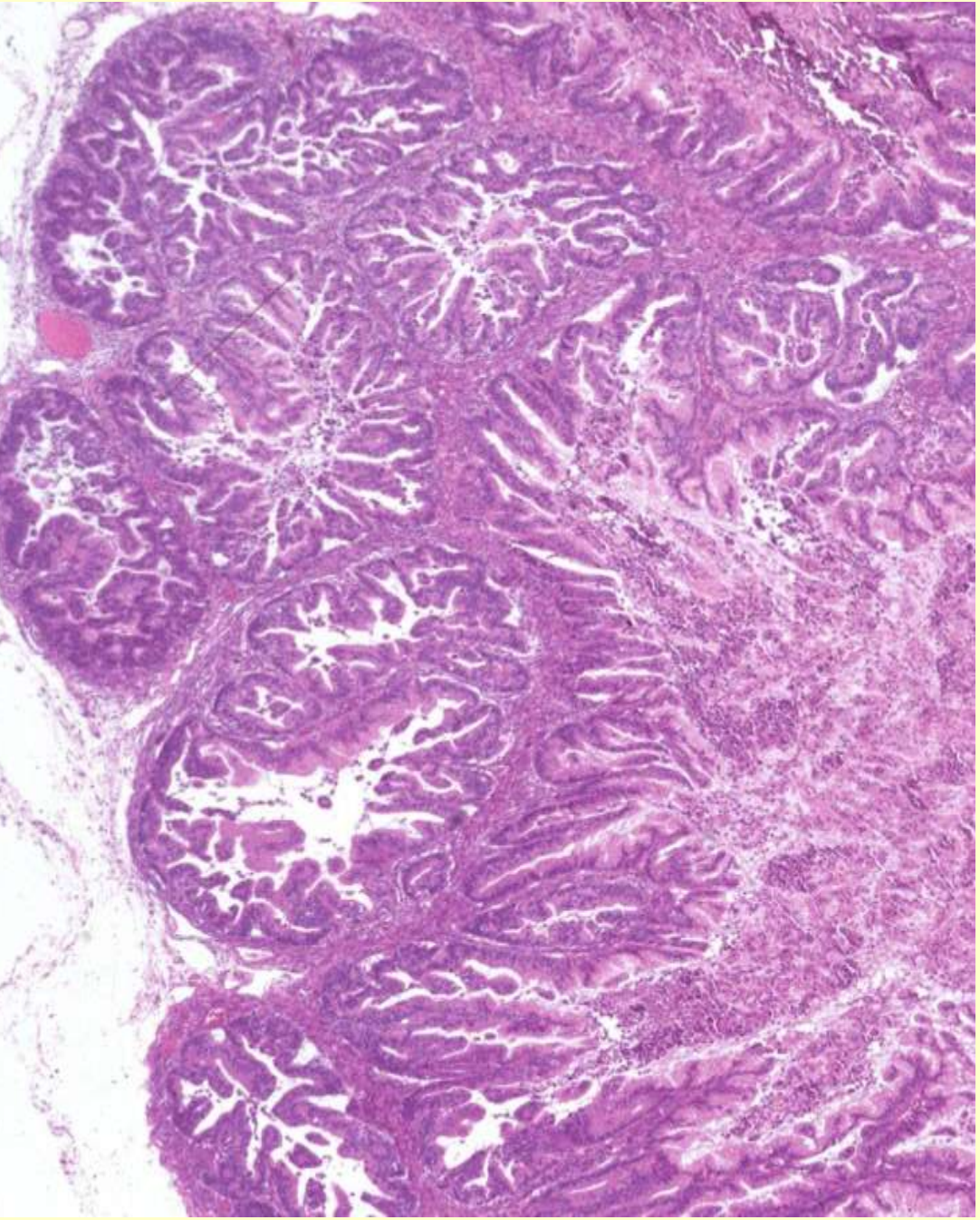


Borderline

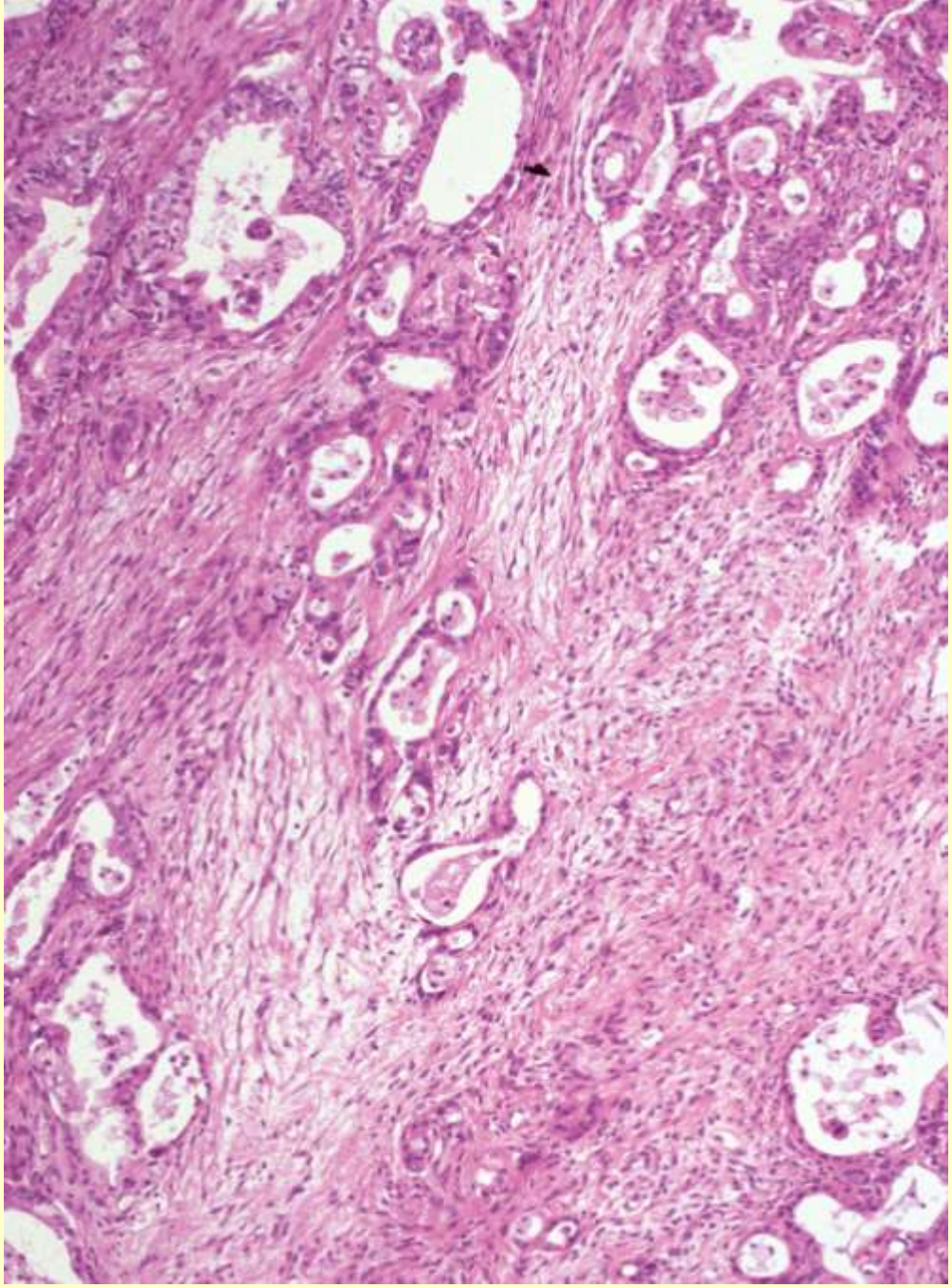
Carcinoma



Borderline with intraepithelial carcinoma (BIECa)



Expansile growth (non obvious invasion)



Infiltrative stromal invasion

Mucinous Carcinomas of the Ovary
(Stage I)

Favorable Px	Unfavorable Px	
Expansile	Infiltrative	(p = 0.002)
Nuclear G1-2	Nuclear G3	(p = 0.021)
Intact	Ruptured	

Rodríguez I, Prat J.
Am J Surg Pathol 2002

Mucinous Tumors

(Ovary)

Benign

↓

Borderline

↓

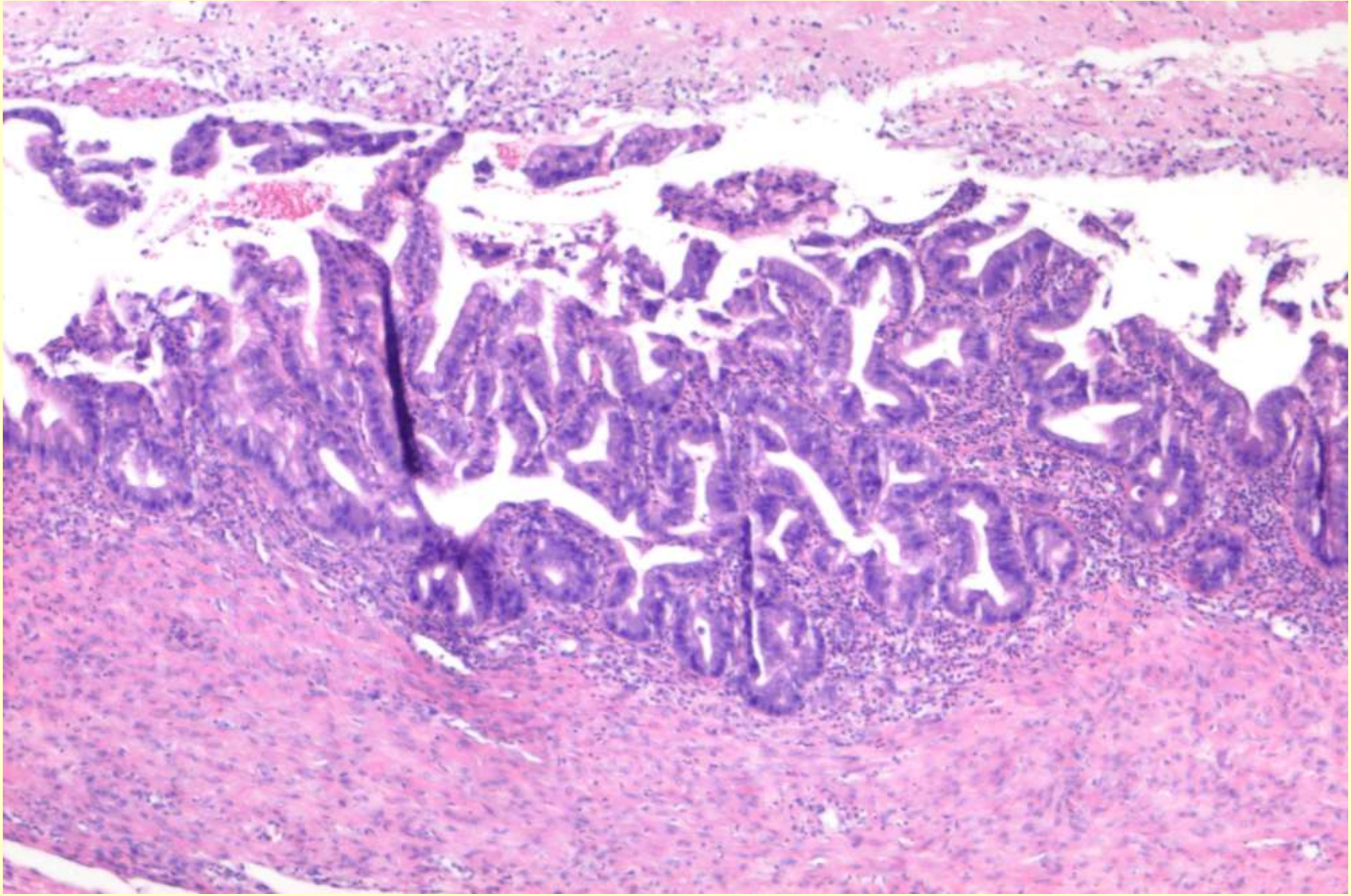
Intraepithelial Ca

↓

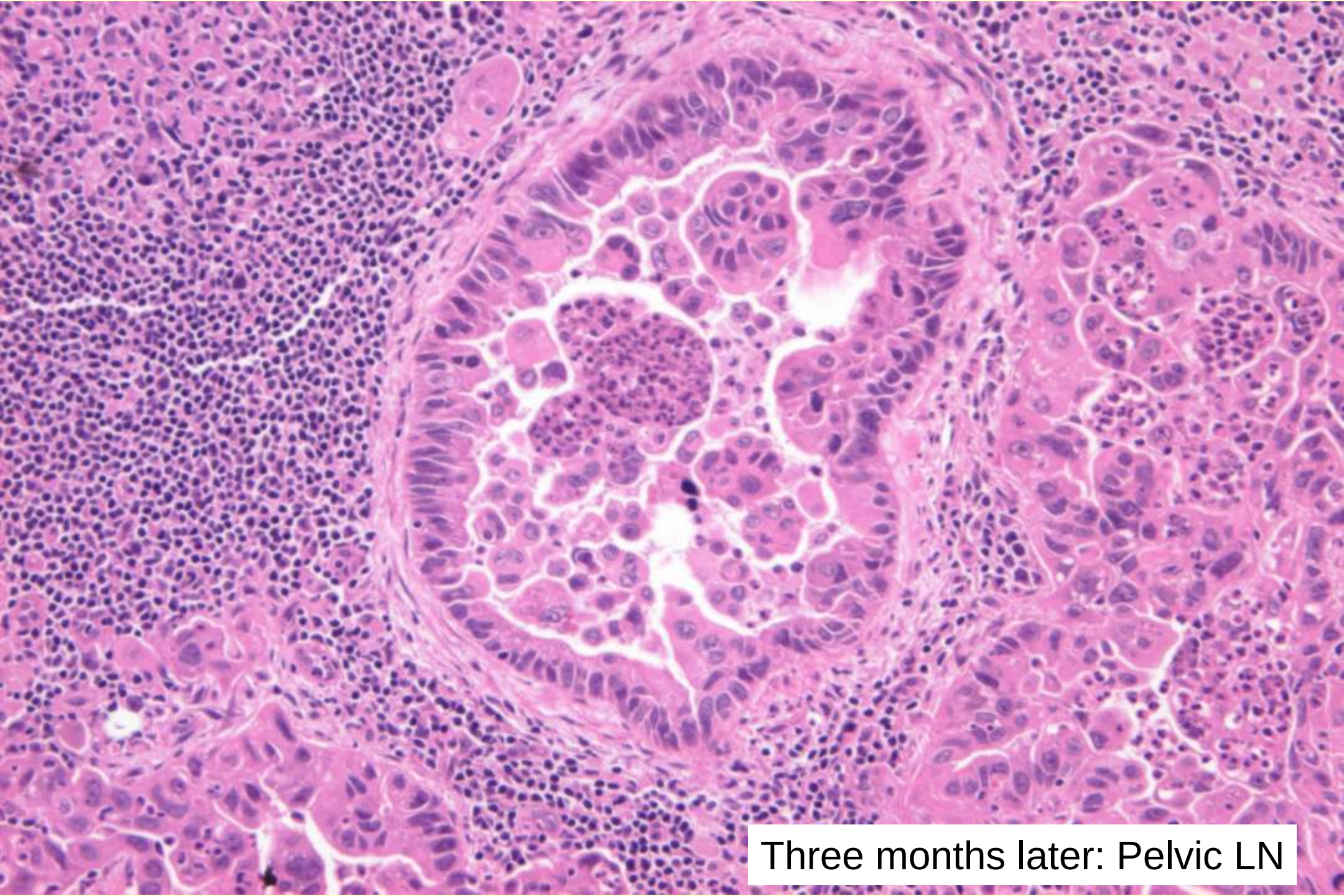
Microinvasive Ca

↓

Invasive carcinoma



17 yr-old female, cyst 32 cm, 111 sections, single focus: 4 mm


Three months later: Pelvic LN

Mucinous Carcinoma

(Metastatic)

- Large intestine
- Appendix
- Pancreas
- Biliary tract
- Stomach
- Endocervix

Mucinous Carcinoma

Metastatic

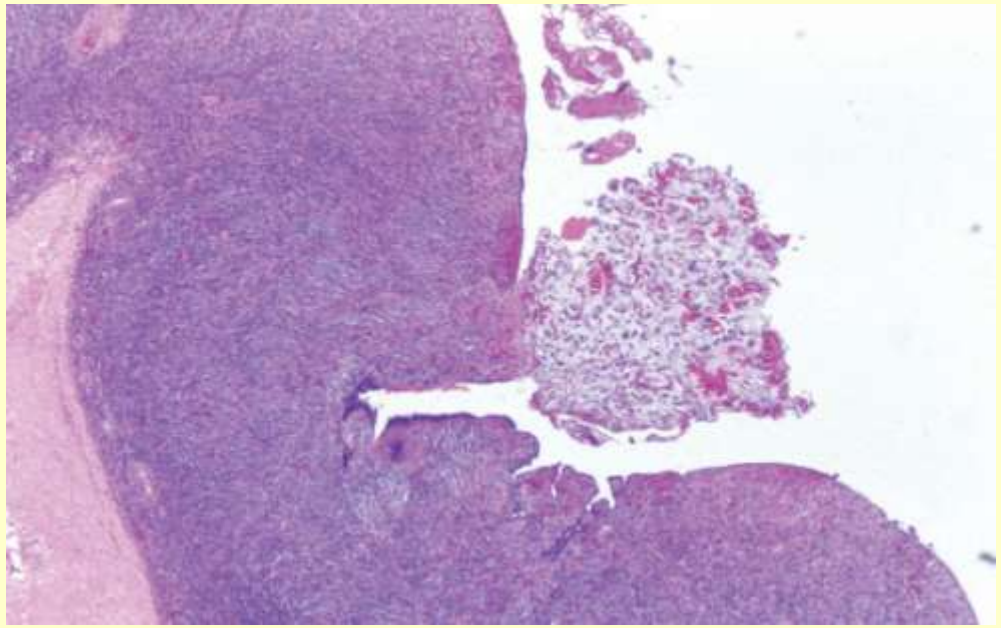
- Bilateral
  Unilateral
  < 10 cm

Primary

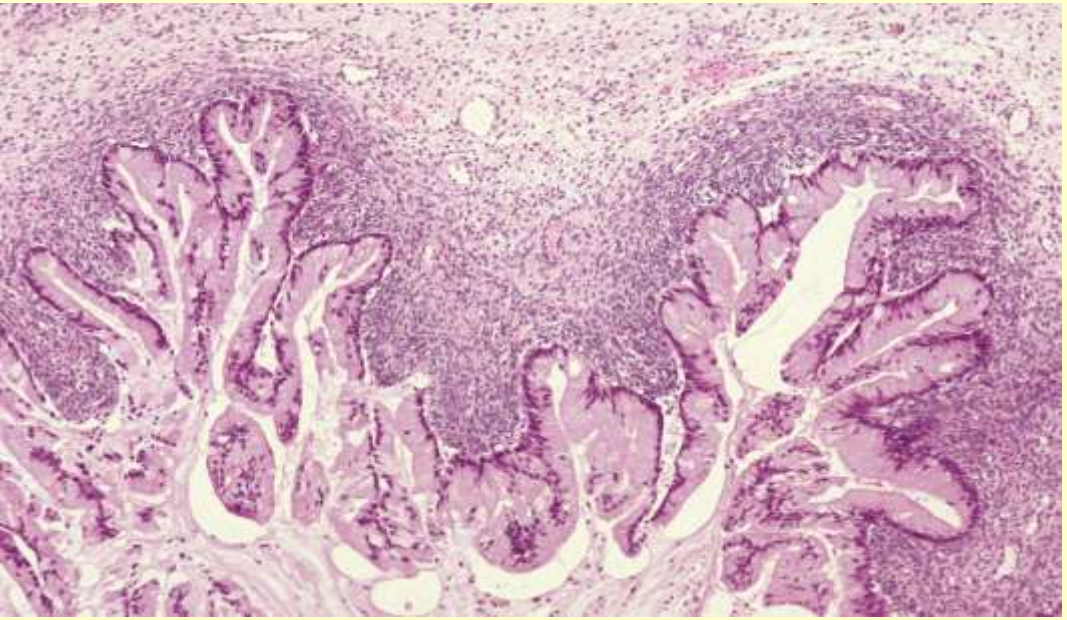
- Unilateral
  _ > 10 cm

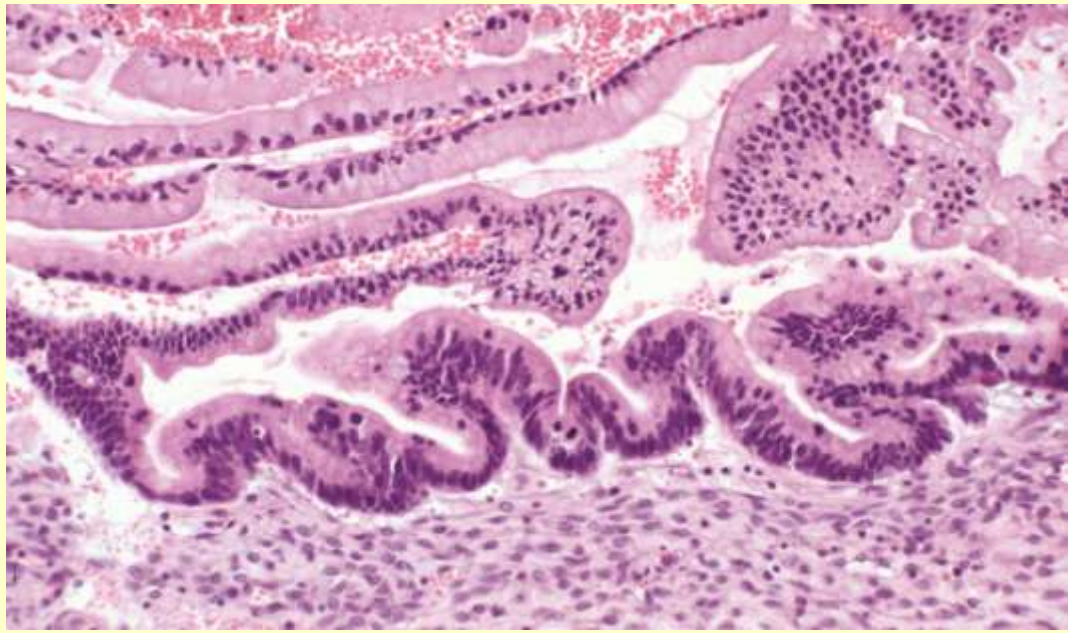
Seidman JD et al
Am J Surg Pathol 2003; 27:985

Metast Append Ca

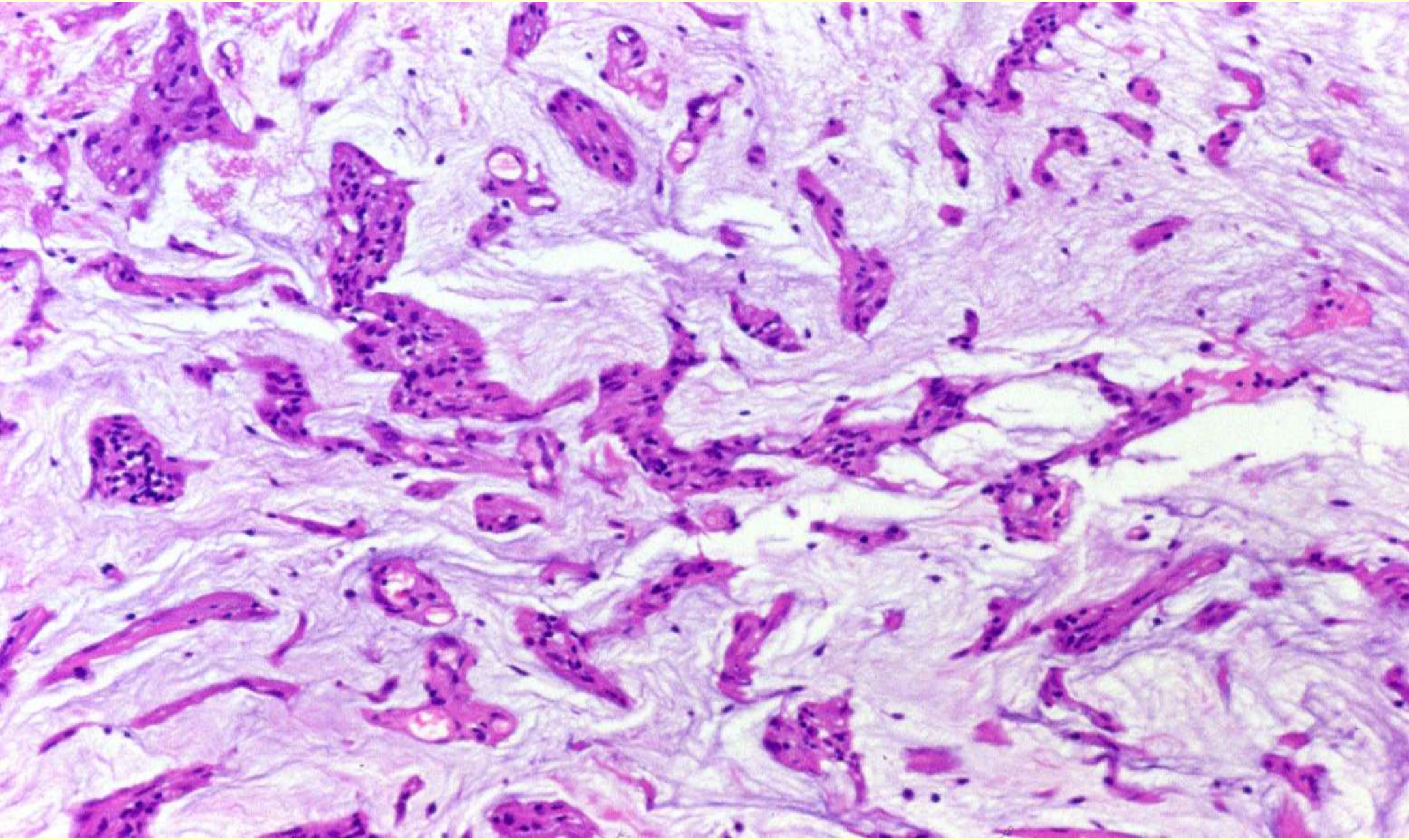


Metastatic colon ca

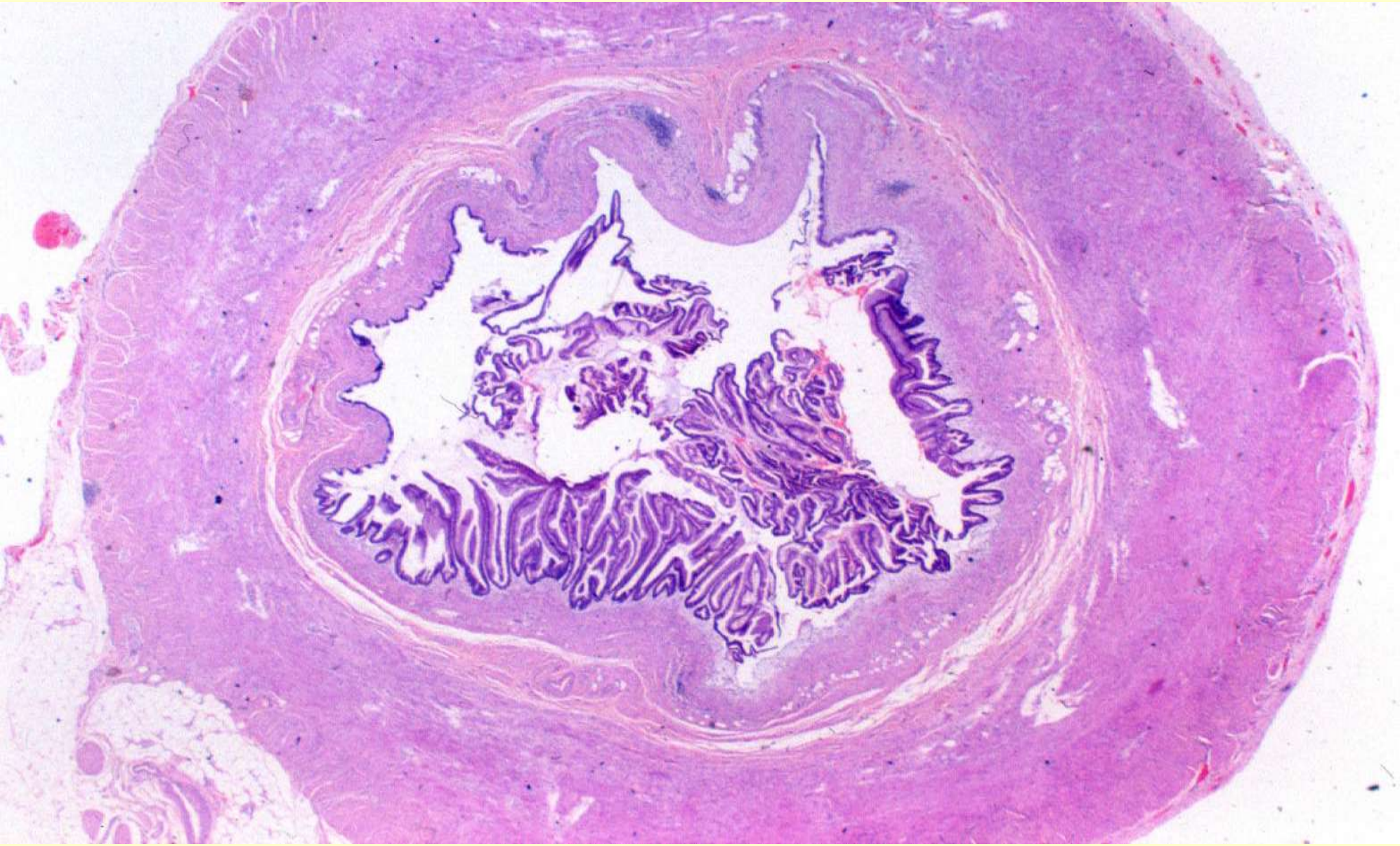




Metastatic adenocarcinoma of pancreas



Pseudomyxoma peritonei (no tumor cells)



Appendiceal mucinous tumor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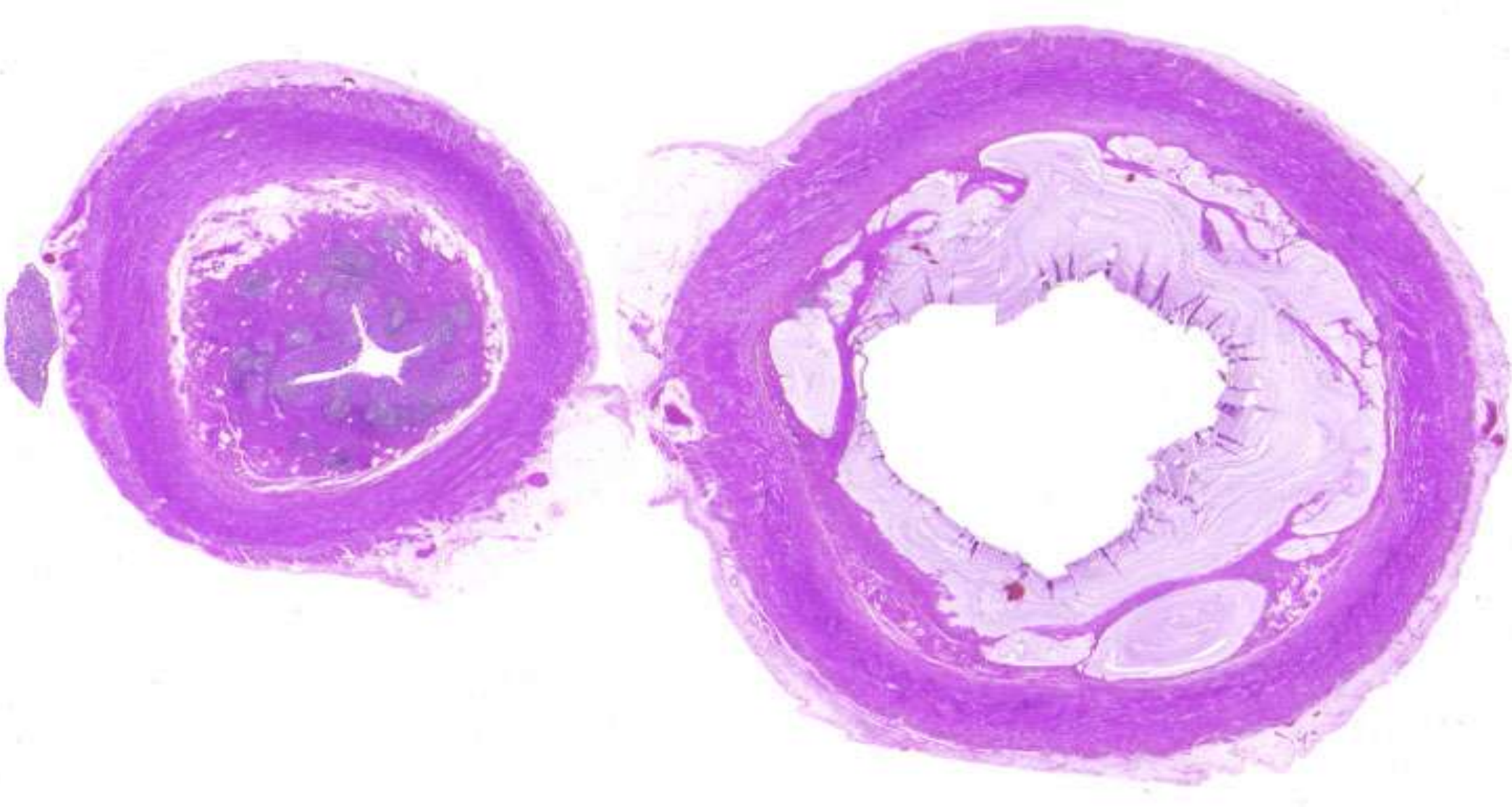
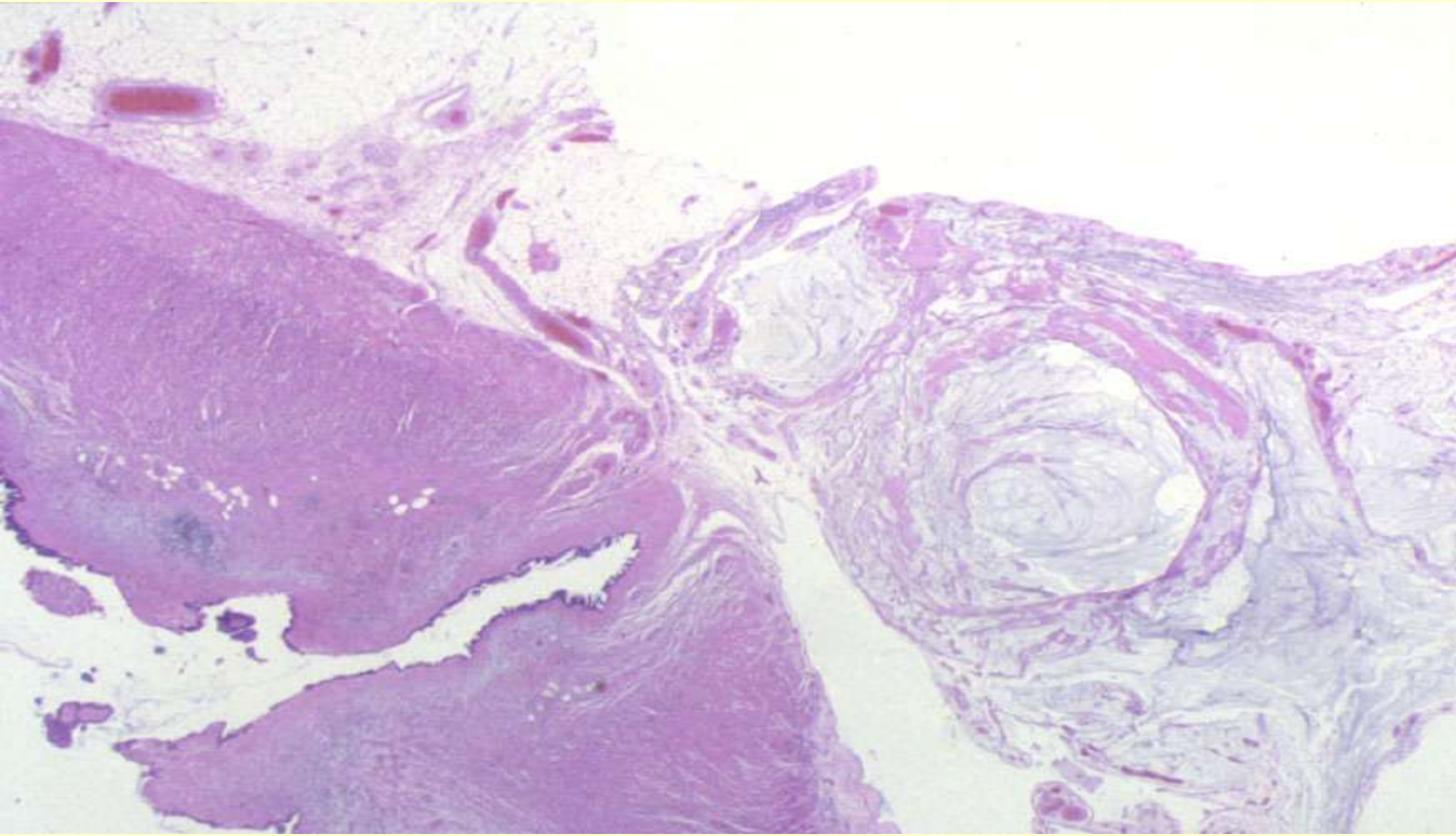
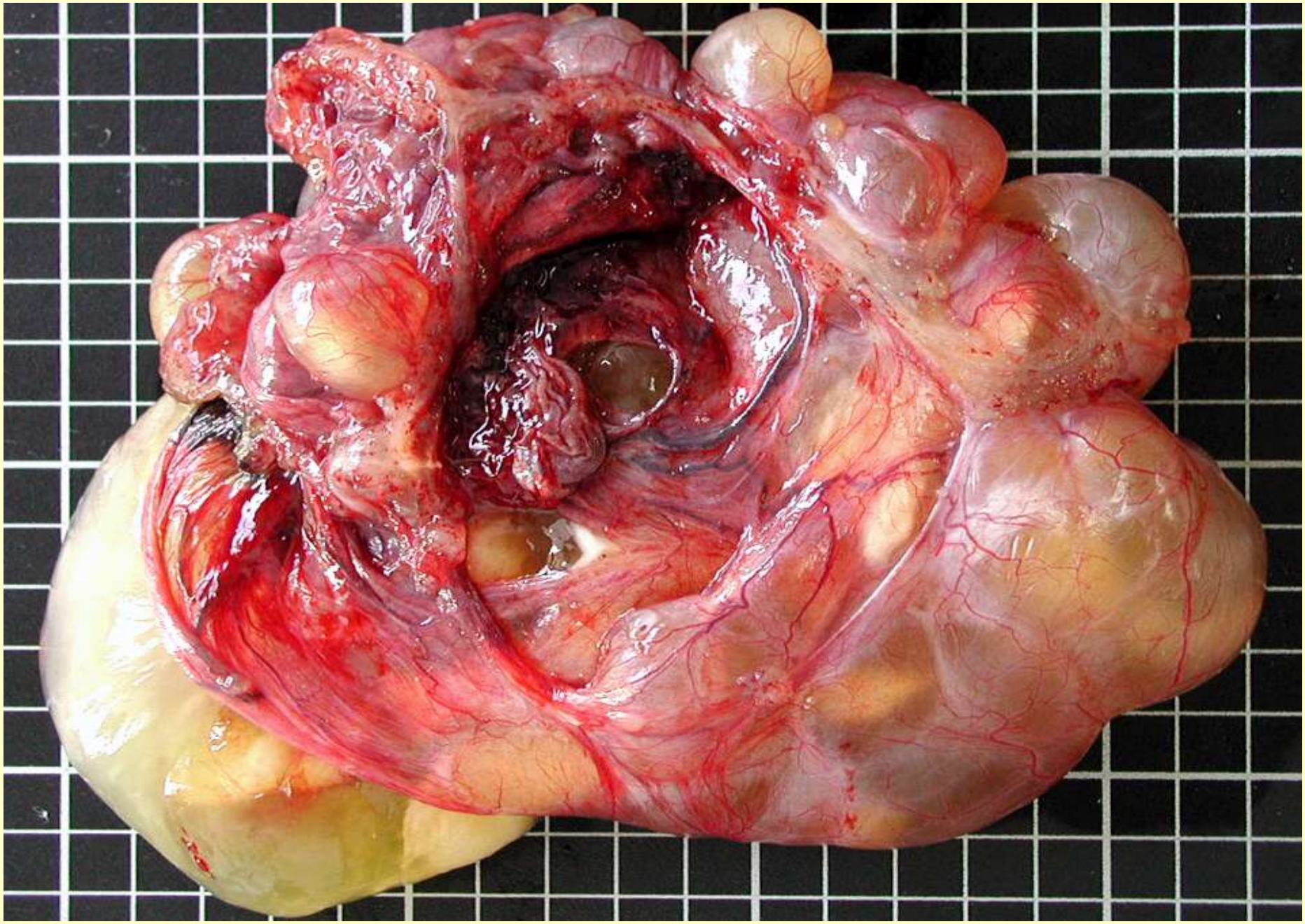
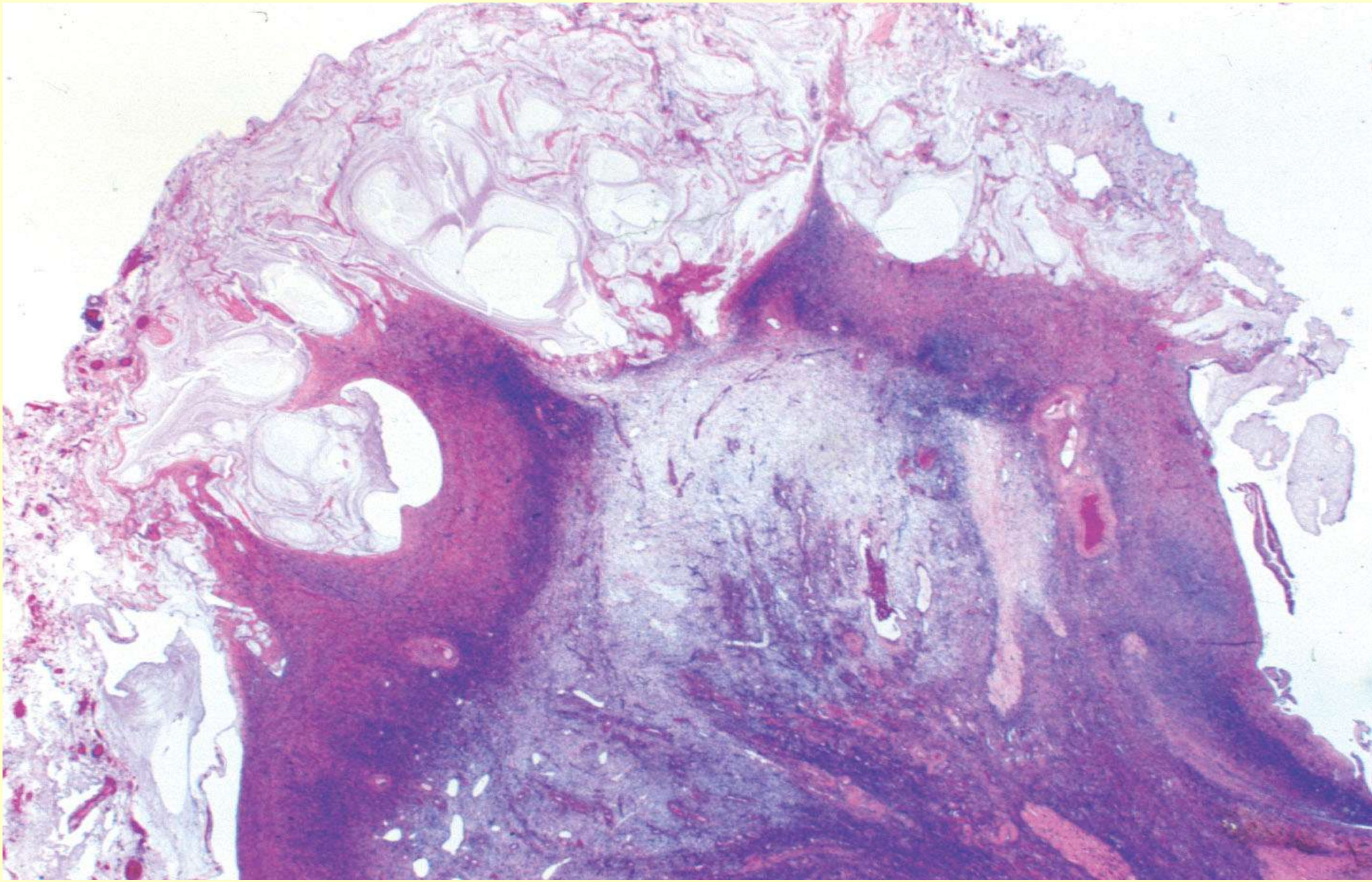


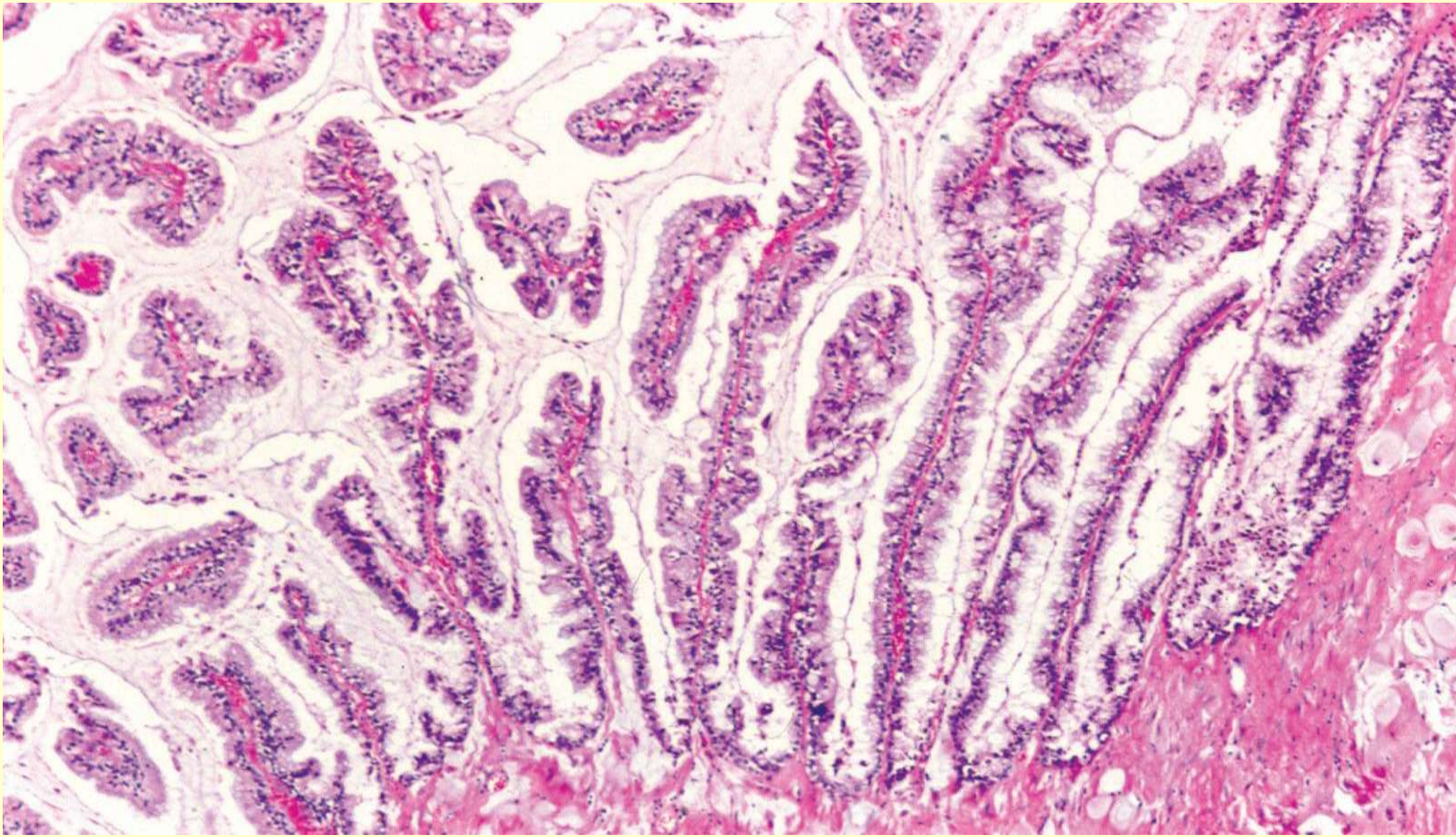


Low grade mucinous tumor

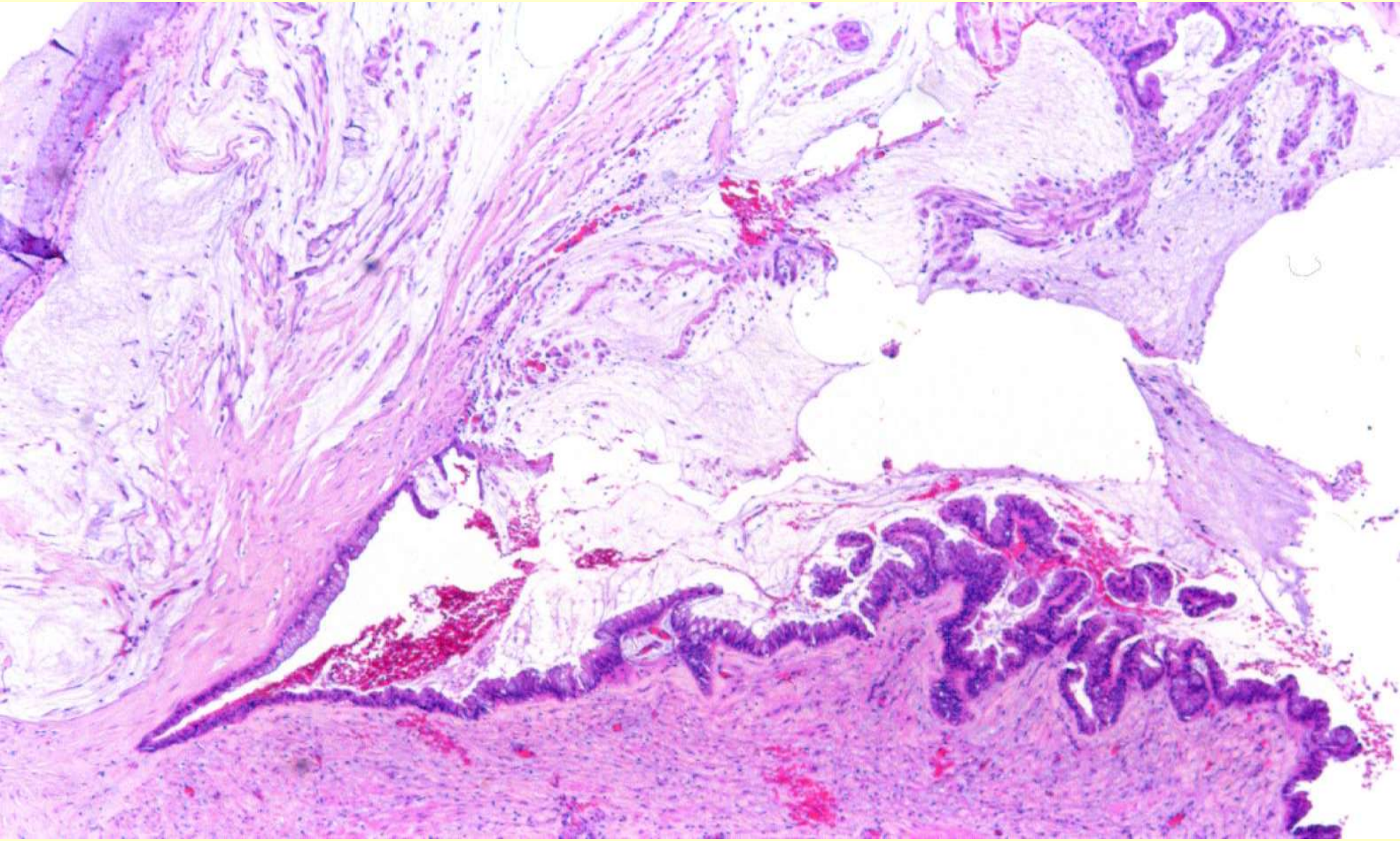


Secondary appendiceal mucinous ovarian tumor





Secondary appendiceal mucinous ovarian tumor



Pseudomyxoma ovarii

The American Journal of Surgical Pathology *20(6): 739–746, 1996*

Synchronous Mucinous Tumors of the Appendix and the Ovary Associated with Pseudomyxoma Peritonei

A Clinicopathologic Study of Six Cases with Comparative Analysis of c-Ki-*ras* Mutations

Miriam Cuatrecasas, M.D., Xavier Matias-Guiu, M.D., and Jaime Prat, M.D., F.R.C.Path

Cuatrecasas M et al.
Am J Surg Pathol 1996

Mucinous Tumors

(Intestinal type)

5 yr survival

Bord	Stage	Ca
92%	1	83%
100%	2	55%
51%	3	21%
--	4	9%

Mucinous Tumors of the Ovary

1. 10-15% of ovarian tumors.
2. Borderline tumors are usually stage Ia and have excellent prognosis.
3. Ovarian mucinous tumors with pseudomyxoma peritonei are almost always of appendiceal or GI origin.
4. Endocervical-like MBT are often bilateral and usually arise from endometriosis. Prognosis is favorable
5. Primary mucinous carcinomas are rare (3%) and almost always unilateral.
6. Metastatic mucinous carcinomas (GI) are far more common, are often bilateral, and usually <10 cm in size.
7. Primary ovarian mucinous carcinomas are heterogeneous (Bg, Bord, Mg) and extensive sampling is mandatory.
8. Stage I primary mucinous carcinomas: only infiltrative, nuclear grade 3, and ruptured tumors have an unfavorable prognosis.

Recent Publications

- Uzan C, Nikpayam M, Ribassin-Majed L et al. Influence of histological subtypes on the risk of an invasive recurrence in a large series of stage I borderline ovarian tumor including 191 conservative treatments. Ann Oncol May 2014.
- Trillsch F, Mahner S, Woelber L et al. Age-dependent differences in borderline ovarian tumours (BOT) regarding clinical characteristics and outcome: results from a subanalysis of the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) ROBOT Study. Ann Oncol May 2014.
- Prat J. The results of conservative (fertility-sparing) treatment in borderline ovarian tumors vary depending on age and histological type. Ann Oncol May 2014 (Editorial)

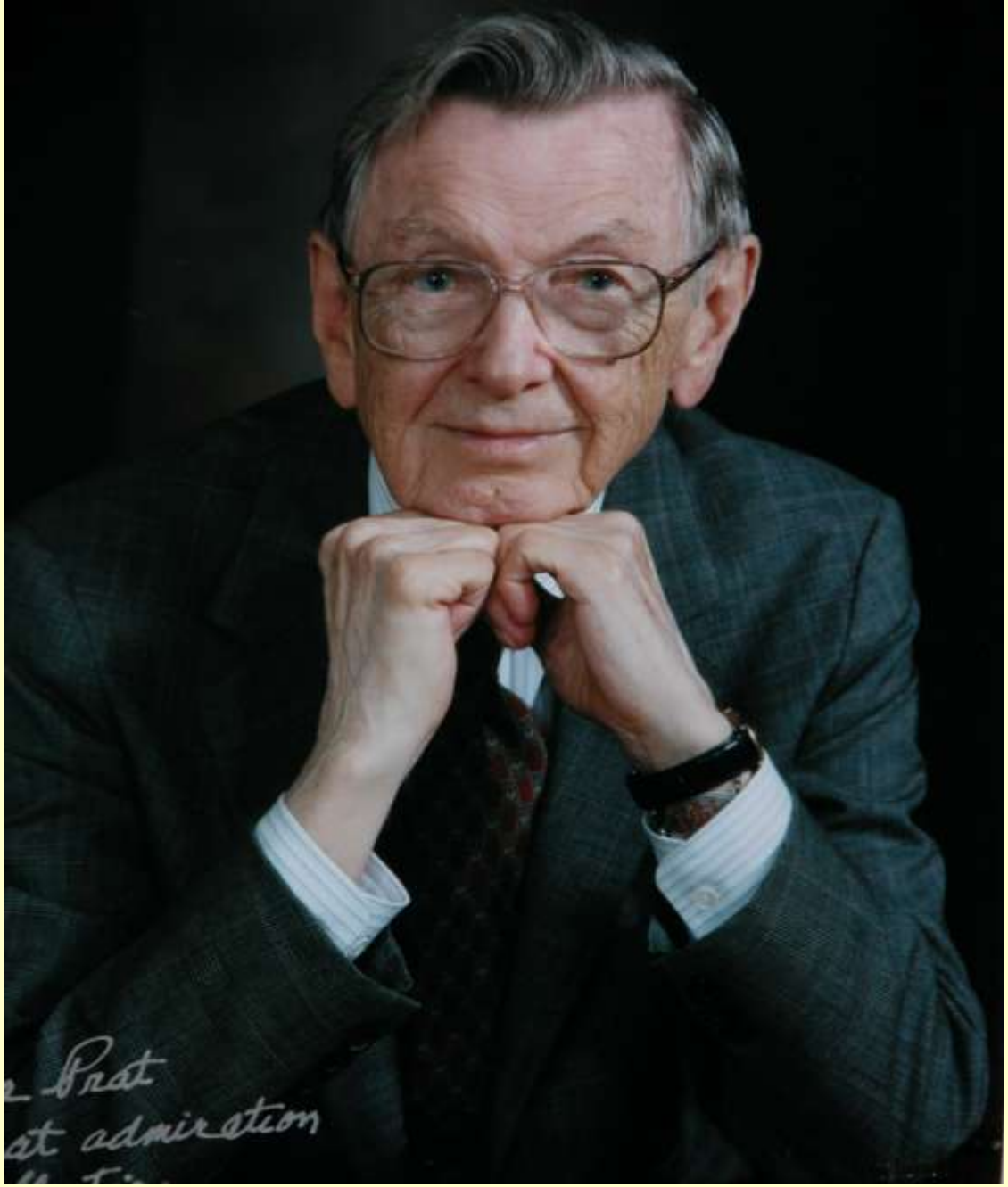
“Human mind like parachute; works best when open”

Charlie Chan
Fictional Cinema Detective
1930s, USA

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

Borderline Tumors of the Ovary

Jaime Prat



Robert E. Scully 1921-2012