63RD ANNUAL HSCP SPRING SYMPOSIUM

CURRENT CONCEPTS IN GYNECOLOGIC PATHOLOGY

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Traditional Pathology

vs

New Techniques

Neuroblastomas and Neuroendocrine Carcinomas of the Nasal Cavity

A Proposed New Classification

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The histologic characteristics of 29 nasal tumors previously diagnosed as neuroblastomas, unclassified carcinomas, or unclassified malignant neoplasms were reviewed. Electron microscopy was performed in 17. Nine tumors were neuroblastomas; six of these were classical neuroblastomas while the other three exhibited olfactory differentiation in addition to the classical neuroblastoma component. Areas of ganglioneuroblastoma were found in the metastasis of one of the three olfactory neuroblastomas. Twenty tumors were classified as neuroendocrine carcinoma because all showed a neuroendocrine pattern with remarkably uniform cells growing from benign glandular epithelium; membrane bound granules were present in the cytoplasm of cells of the ten cases in this group examined by electron microscopy. The mean age of the patients with neuroblastomas was 20 years; survival in this group was 75% at five and seven years, respectively, and 67% at ten years. Recurrences, metastasis, and death occurred within 3 years of diagnosis. There was a low percentage (25%) of multiple recurrences. The metastases were located in cervical lymph nodes, brain and spine. The mean age of the patients with neuroendocrine carcinoma was 50 years. Survival was 100% at five years, 88% at seven years, and 77% at ten years. Recurrences and metastasis in 70% of the cases occurred later than the third year. Multiple recurrences were present in 54% of the cases. The metastases affected lymph nodes, brain and spine in all cases except in one in which lungs and femur were involved. In the latter case adenocarcinoma was also present in addition to the neuroendocrine carcinoma. Three patients died, all more than five years from the time of diagnosis. No correlation was found between staging and prognosis in either group, except for Stage I disease.

Cancer **50:2388–2405, 1982.**

1982–1983

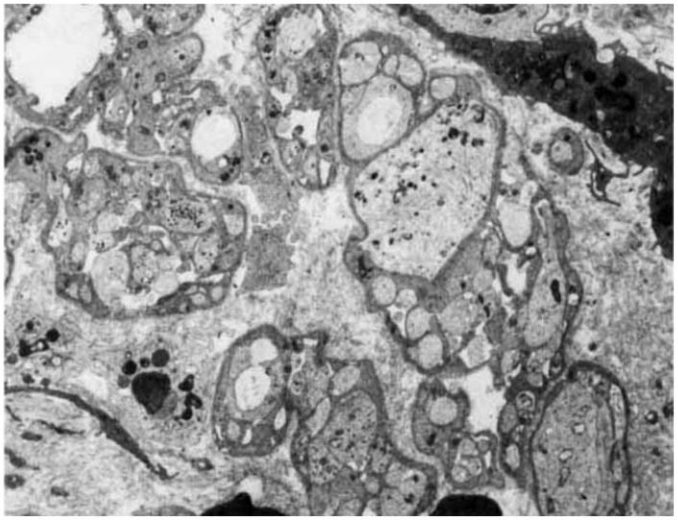


FIG. 3. Neuroblastoma without olfactory differentiation. Groups of cell processes surrounded by a thin ring of more dense cytoplasm bordered by external lamina (×3900).

cases, some variation was observed in the solid component. The mitoses were present in the solid areas as well as in the rosettes.

In one of the cases, areas of classical neuroblastoma were present in the solid part. Fifty to 70 mitosis per 10 HPF were seen. Grimelius and Fontana-Masson stains were negative. Ultrastructural examination of this case revealed both areas of classical neuroblastoma, with very sparse small granules, and olfactory rosettes. These reproduced the olfactory mucosa with the majority of cells having the microvilli at their luminal borders, but with some intercalated cells showing thin projections toward the lumen that ended in a round formation, the olfactory vesicle, projecting into the lumen (Fig. 5).

The second case of neuroblastoma with olfactory differentiation was a patient who presented with a tumor in the nose and sinuses and metastasis in the lymph nodes of the neck. A biopsy specimen from the nasal

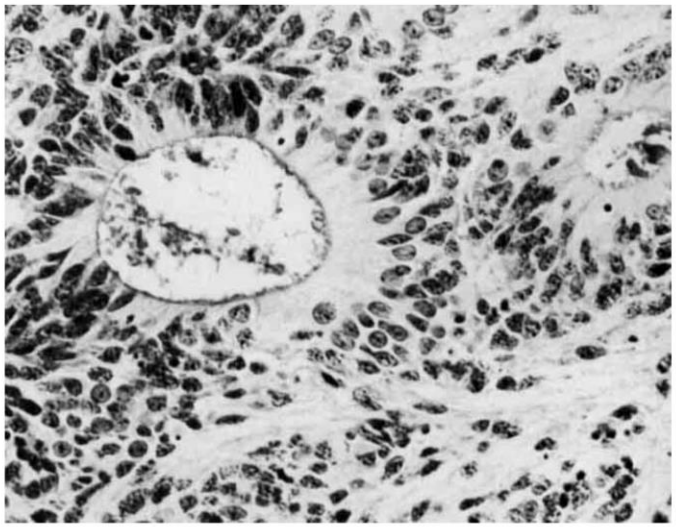


FIG. 4. Neuroblastoma with olfactory differentiation. Two olfactory rosettes containing granular debris. Tall columnal cells with basally located nuclei are forming the rosettes (×230).

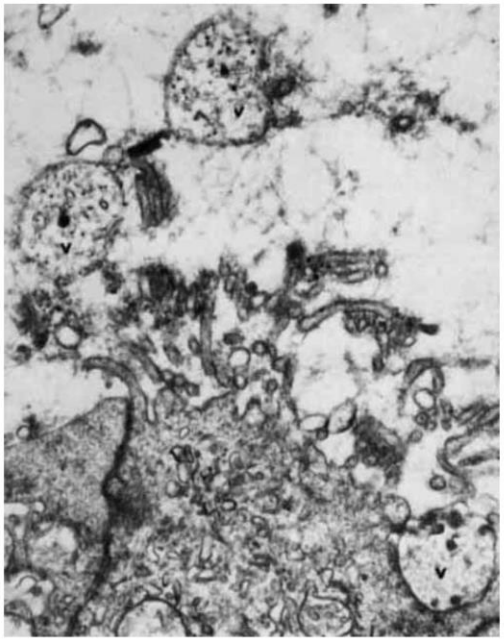


FIG. 5. Neuroblastoma with olfactory differentiation. Olfactory vesicles (V) intermingled with microvilli (original magnification ×23.750).

tumor showed olfactory rosettes and solid areas where fibrillar material was present between the cells. In the lymph node, there were definite areas of ganglioneuroblastoma (Fig. 6), in addition to the features of the nasal tumor. Fifteen to 20 mitosis per 10 HPF were present in this case. Electron microscopic studies showed areas of classical neuroblastoma as well as olfactory rosettes. However rosettes were sparse, and many were lined by flat epithelial cells in the metastasis, which was the source of the tissue for electron microscopy.

In the third case, the tumor consisted largely of olfactory rosettes with some solid areas between them. Definite fibrillary material was not seen by light microscopy. Thirty to 40 mitoses per 10 HPF were seen in this case. Grimelius and Fontana-Masson stains were negative. Ultrastructural examination showed few cell processes without membrane-bound granules in the solid areas and a budding type of projection in the apical border of the cells lining the rosettes (Fig. 7). This enlargement of the tip of the cells projections had the appearance of an early or immature olfactory vesicle.

Neuroendocrine Carcinoma

The term neuroendocrine carcinoma is used for malignant epithelial tumors showing a characteristic light microscopic pattern and cytologic features (see below); the cells contain membrane bound granules in the cytoplasm which can be demonstrated by argentaffin stains, argyrophil stains or electron microscopy. When biochemical products are demonstrated in the cytoplasm of the tumor cells, these are of endocrine effects.

By light microscopy the neuroendocrine carcinomas (found in 20 cases) exhibited well-demarcated groups of cells usually surrounded by connective tissue (Fig. 8); when the foci of tumor cells were large, groups of cells

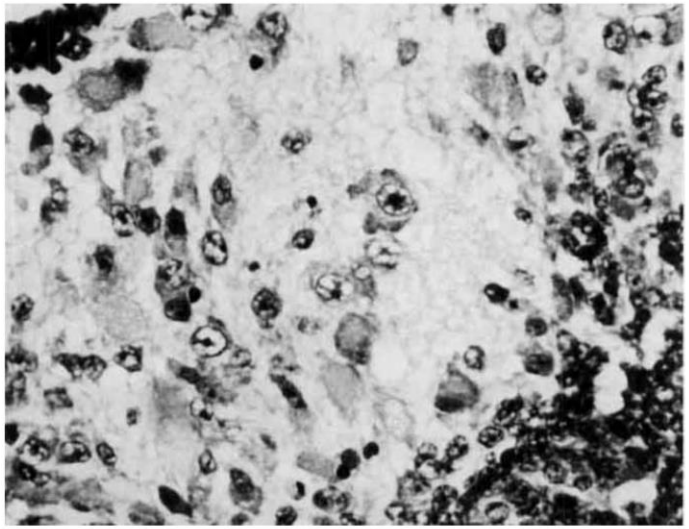
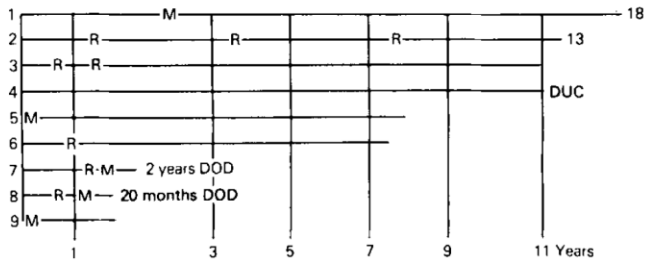


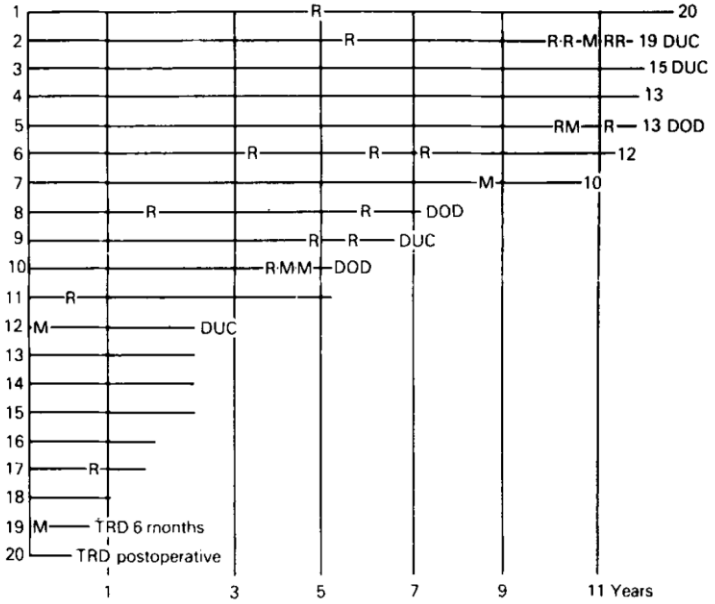
FIG. 6. Neuroblastoma with ganglioneuroblastic differentiation Ganglion cells admixed with fibrillar material (×230).

TABLE 4. Recurrences and Metastases in All Patients Studied

Neuroblastomas · Follow-up *



Neuroendocrine Carcinomas · Follow-up



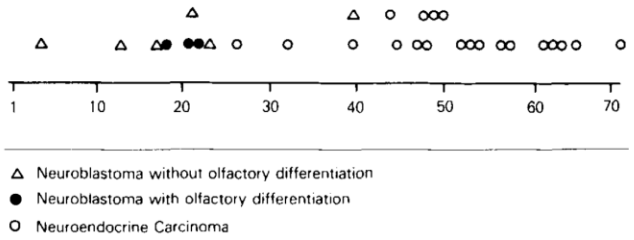
M: metastases; R: recurrence; DOD: died of disease; DUC: died of unrelated cause; TRD: tumor-related death.

* Cases 1, 7, and 9 are neuroblastomas with olfactory differentiation.

norrhea) was investigated in all patients. In the classic neuroblastoma group, information concerning sinusitis could not be obtained in one patient. Another patient was three years old with no history of sinusitis or allergies. Histories of repeated episodes of sinusitis was obtained from the remaining four patients with classical neuroblastoma. One of these patients had episodes of sinusitis for three years prior to discovery of the tumor, with documented hay fever, and allergies to dust and wool. Another patient had episodes of chronic sinusitis and asthma for at least ten years. The other two patients presented histories of sinusitis for 20 and 25 years, respectively. Only two of the patients with neuroendocrine carcinoma gave histories of chronic sinusitis.

Five of the patients with neuroblastoma presented with tumor in the right nostril and four with tumor in the left nostril. In the neuroendocrine carcinoma group, 12 tumors were located in the right nostril, six were in the left nostril, and two were bilateral. All the tumors were located primarily in the middle and upper portion of the nasal cavity. In the neuroblastoma group, the precise site of origin within the nasal cavity was very difficult to identify for all but one patient, whose tumor arose from the cribriform plate. The precise site of origin could not be ascertained for 14 of the neuroendocrine carcinomas. The site of origin was known for six neuroendocrine carcinomas: two arose from the middle turbinate, two involved the middle turbinate and maxillary

TABLE 1. Age Distribution of Nine Cases of Neuroblastoma and 20 Cases of Neuroendocrine Carcinoma



due to their tumor or survived for at least seven years. Fourteen of these 15 cases were staged retrospectively according to the information given by clinical examination, radiologic evaluation, and surgical exploration. This was compared with staging by examination of tissue obtained either by biopsy or surgical resection. We found that the evaluation of tumor extension based on clinical and radiologic examination was correct in six cases and incorrect in eight cases. However, of the eight patients in whom staging was incorrect, seven presented with the tumor before 1973, while three of the six patients with correct staging were first seen after 1975. The results of the staging done by biopsy specimens are in Table 3. No correlation was found between the staging system proposed by Kadish and colleagues and prognosis. However, all of the patients whose tumors were diagnosed as Stage I by examination of tissue are alive.

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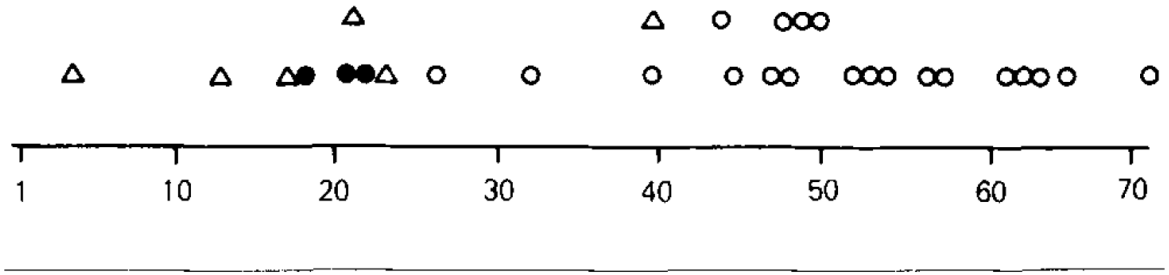


△ Neuroblastoma without olfactory differentiation

● Neuroblastoma with olfactory differentiation

O Neuroendocrine Carcinoma

Case History

52 year-old female

Pelvic mass, possible lymphoma

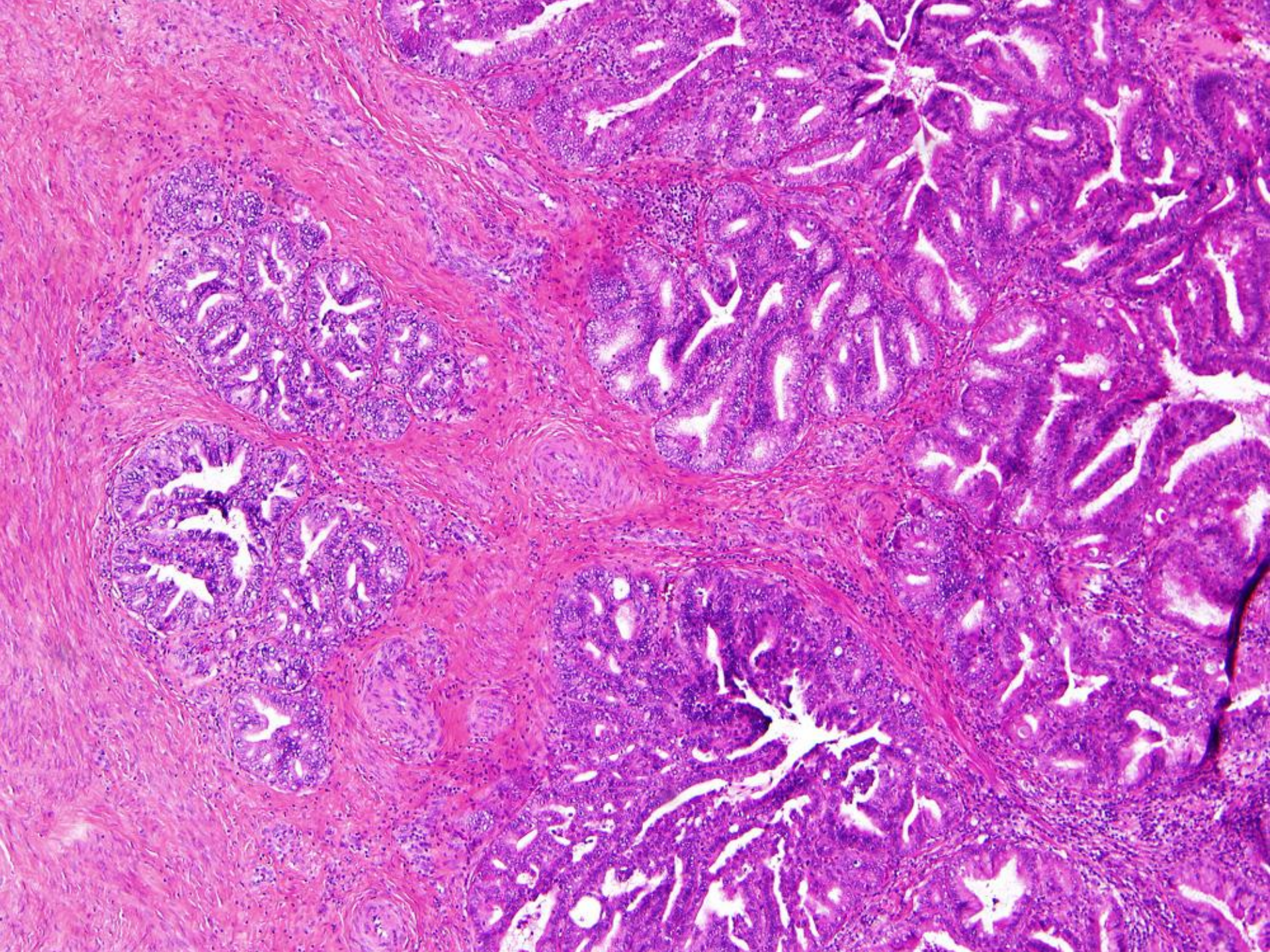
Medical history:

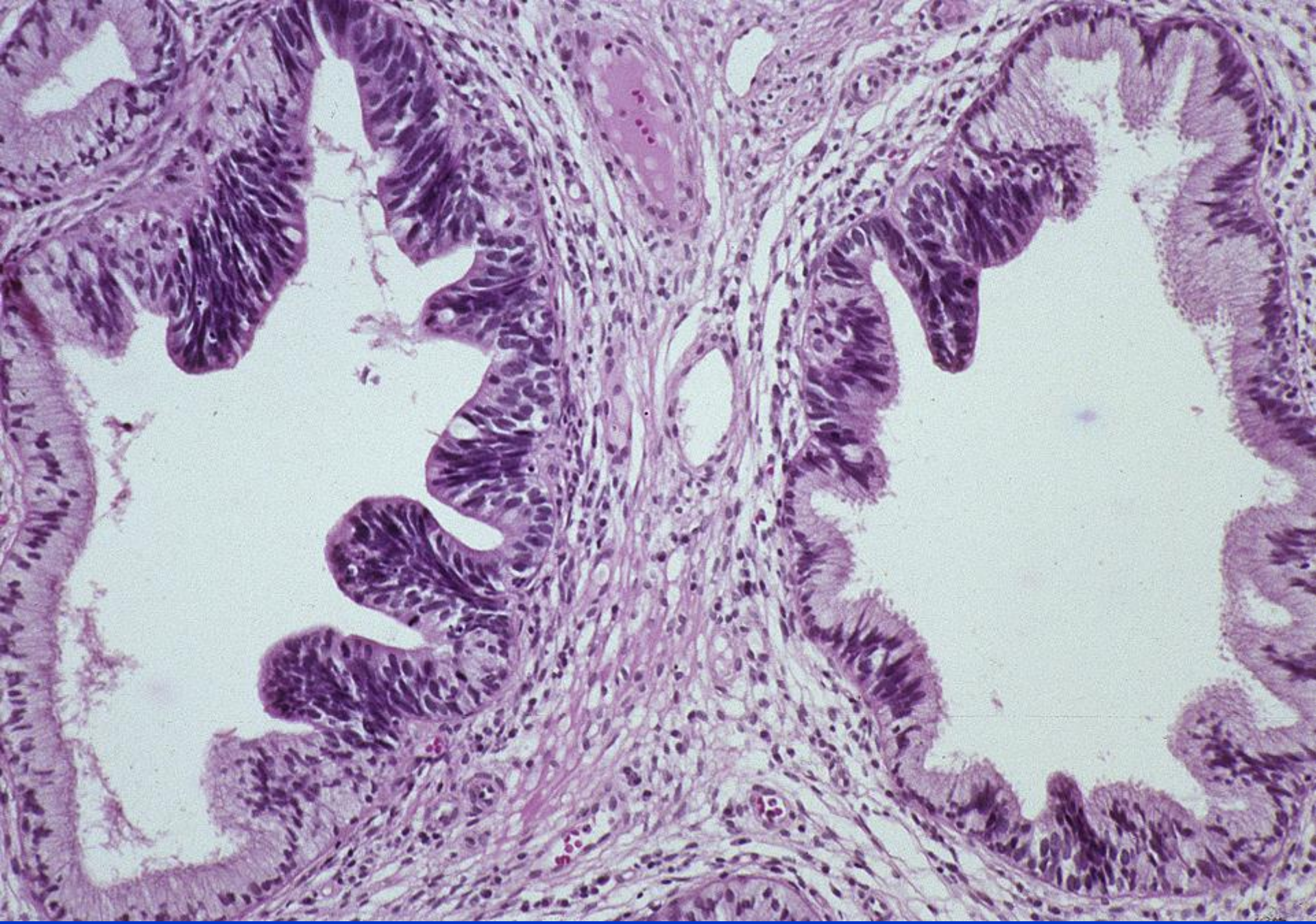
Adenocarcinoma of Cervix 10 years ago

MD Adenocarcinoma of cervix
Invasive, depth of invasion 8 mm

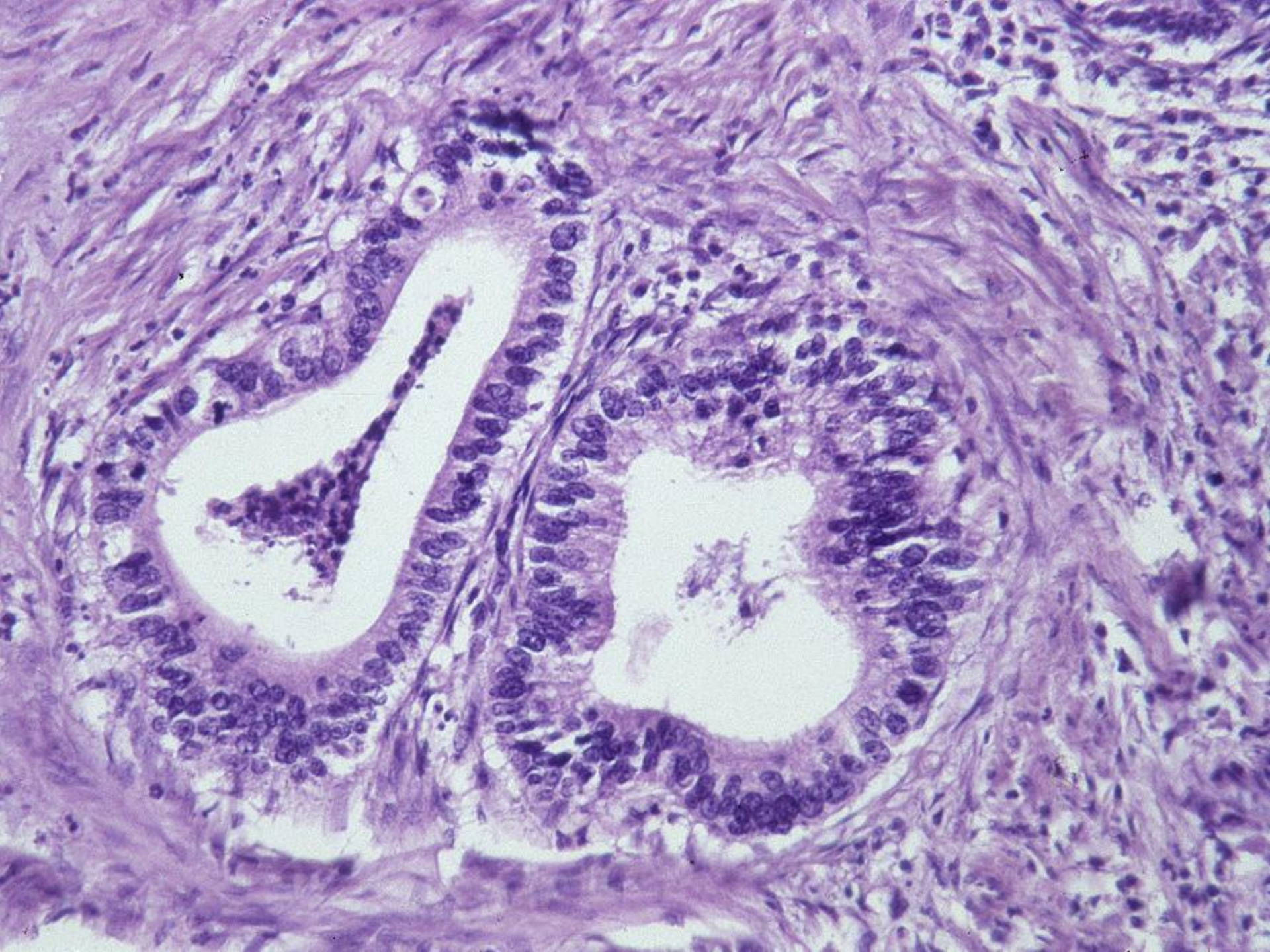
Treatment

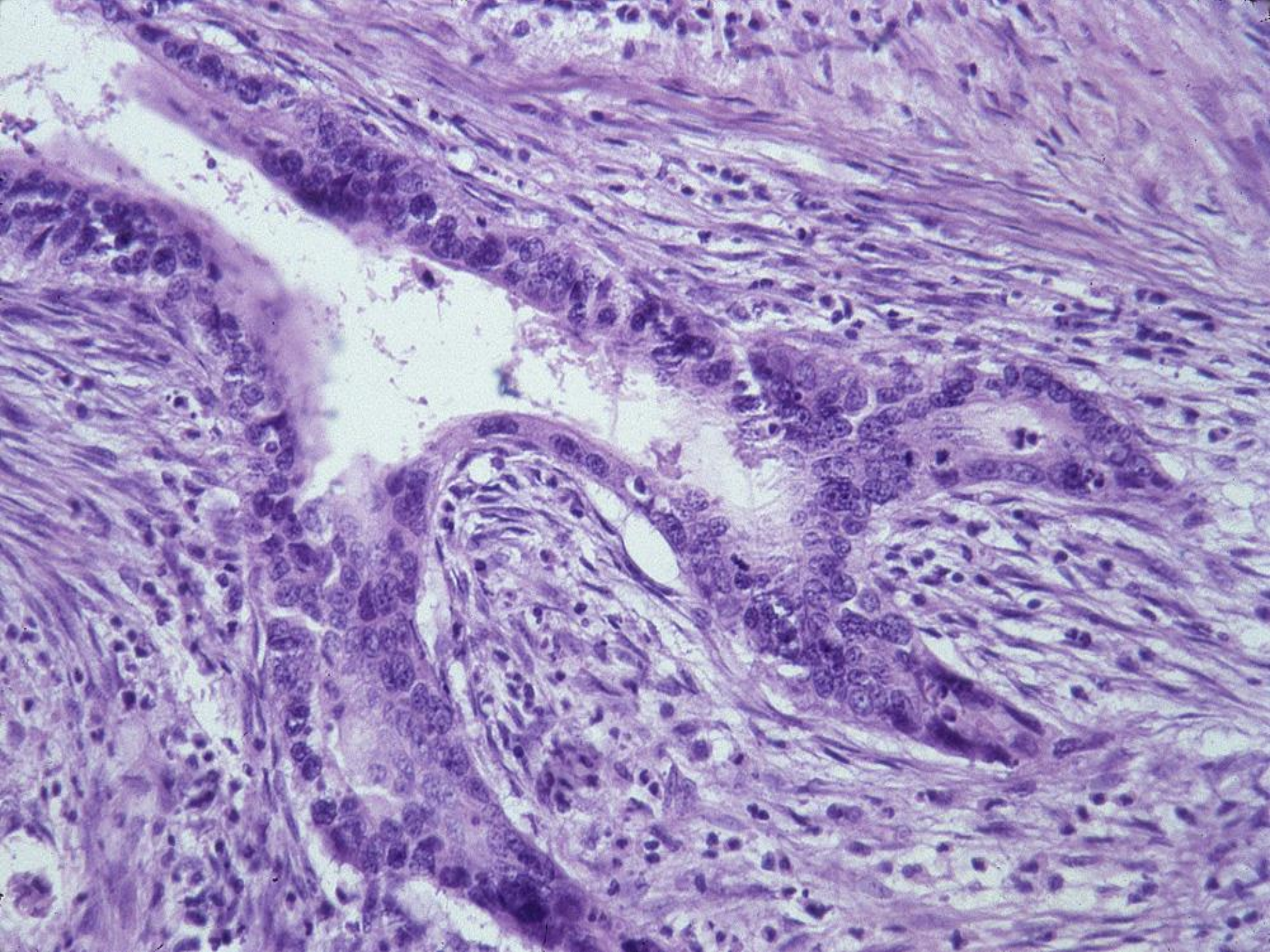
Radical hysterectomy
Bilateral lymphadenectomy (20 Neg LNs)
Pelvic radiotherapy





Adeno Ca In Situ





AdenoCa EndoCx

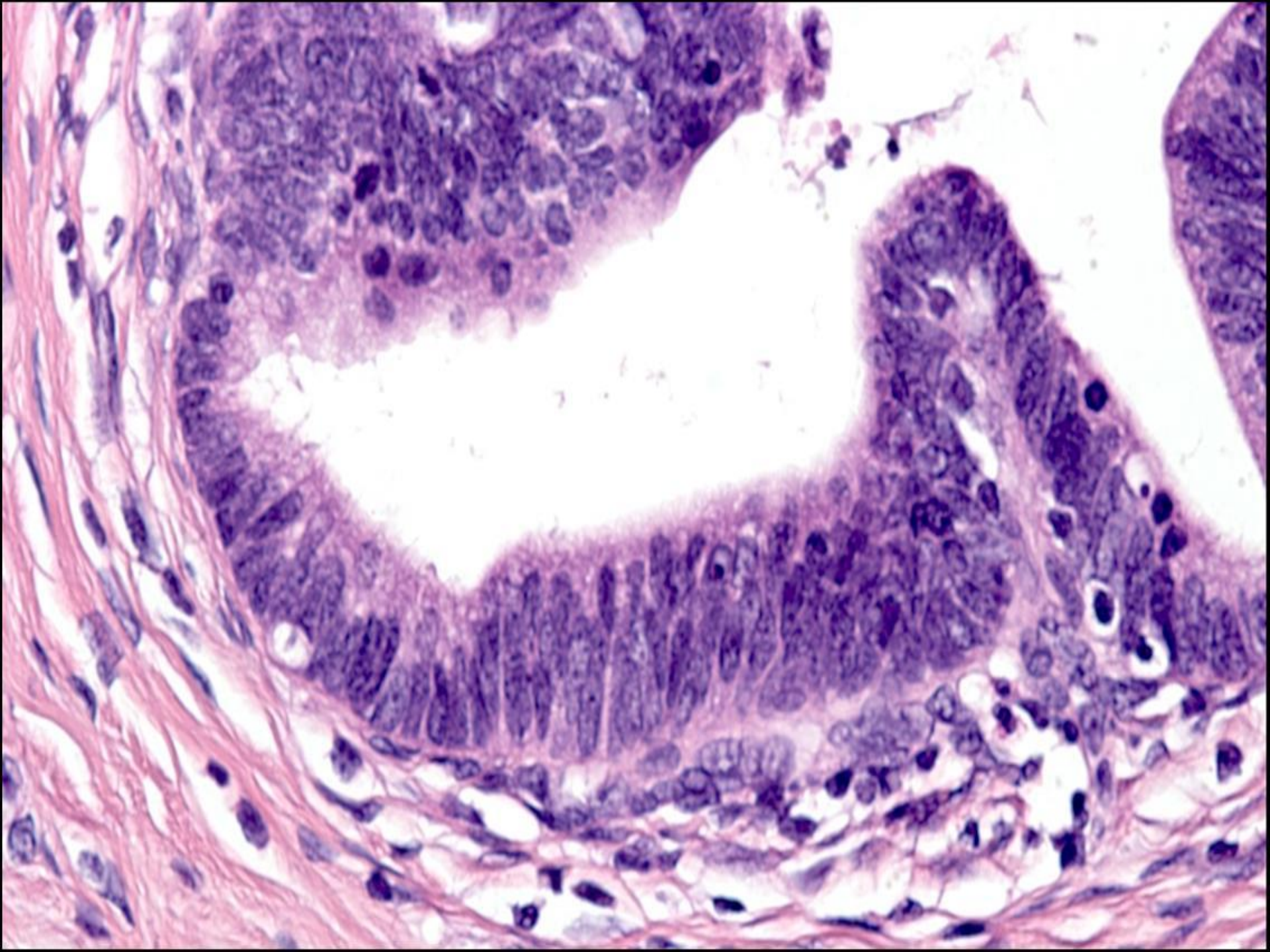
Invasion

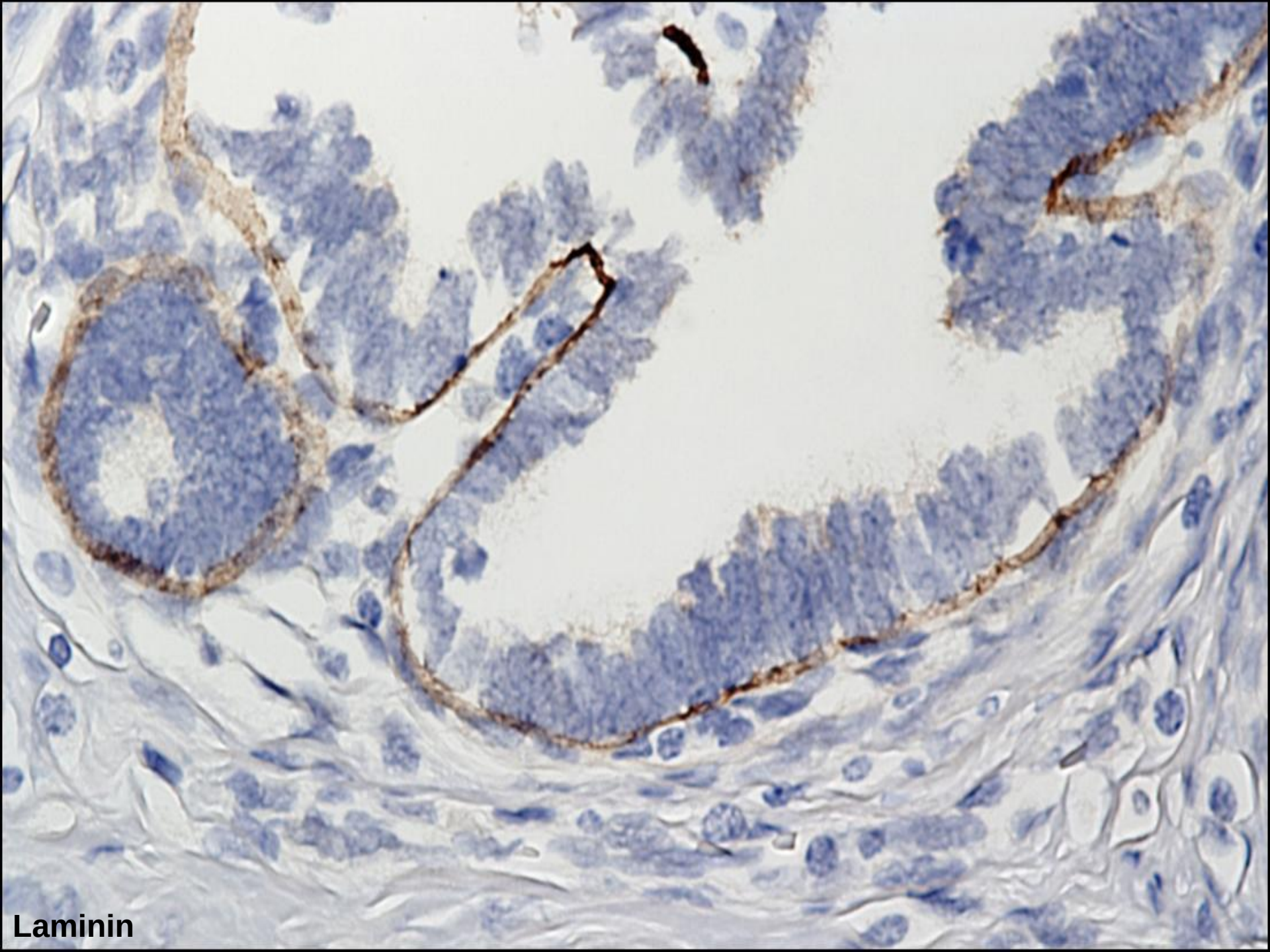
- Glands deeper than the normal for the pt
- Glands between large thick vessels
- Glands deeper than 5 mm
- Glands with epithelial proliferation

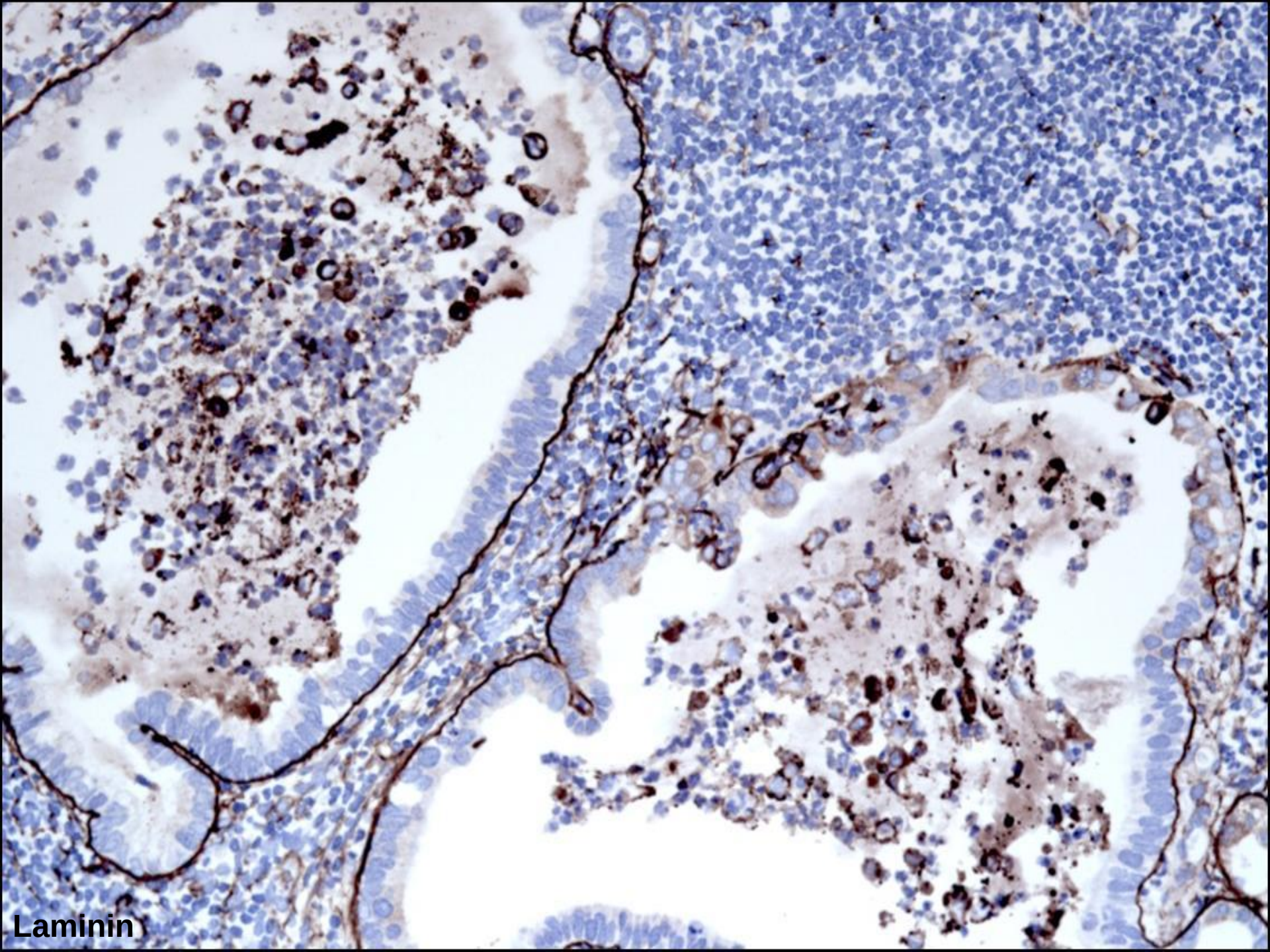
AdenoCa of the EndoCx

“Report your best possible measurement”

“Report tumor thickness rather than depth”




Laminin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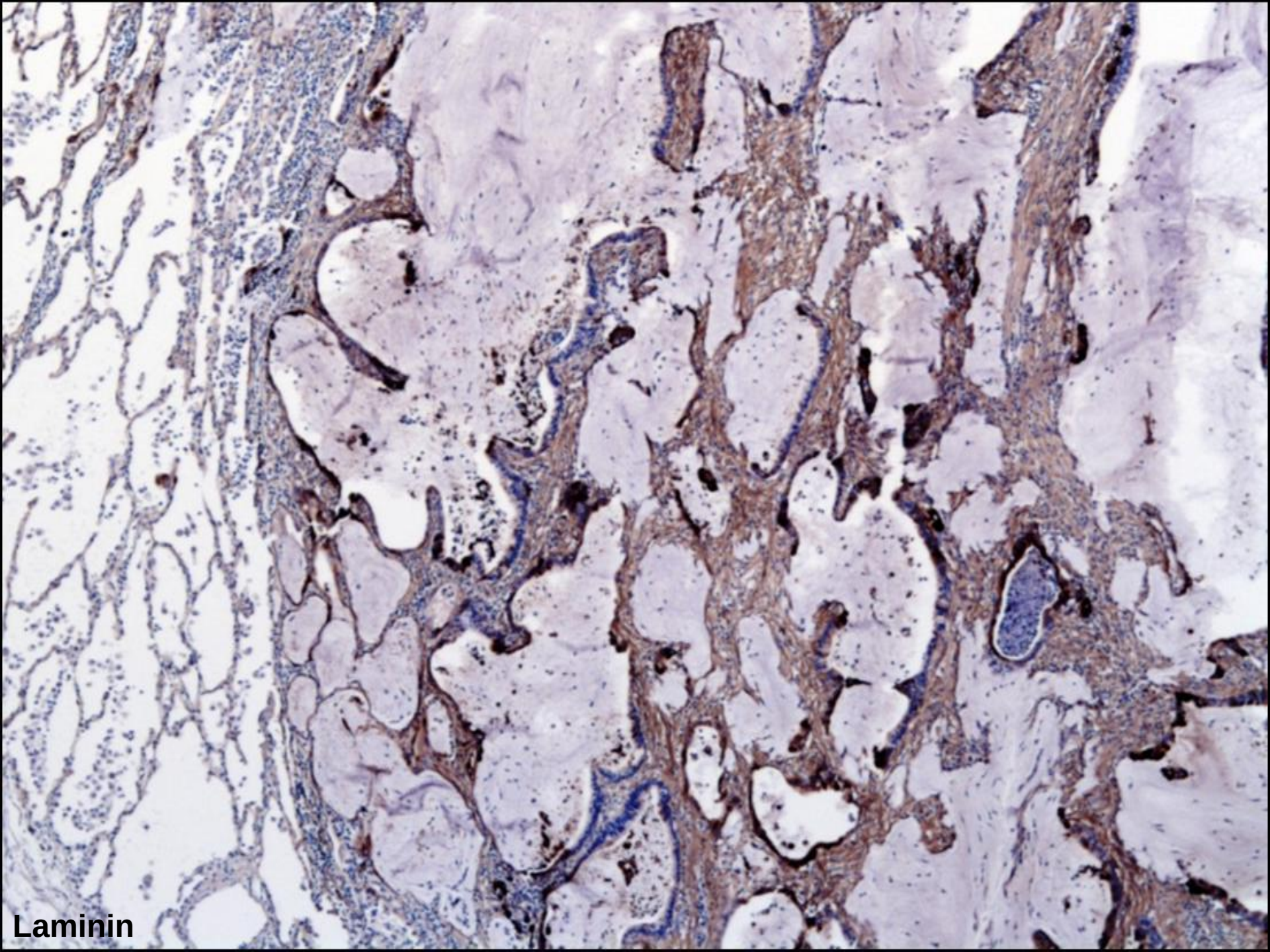

Laminin

The Wrong Start

Cas invading deeper than 1mm

Hysterectomy

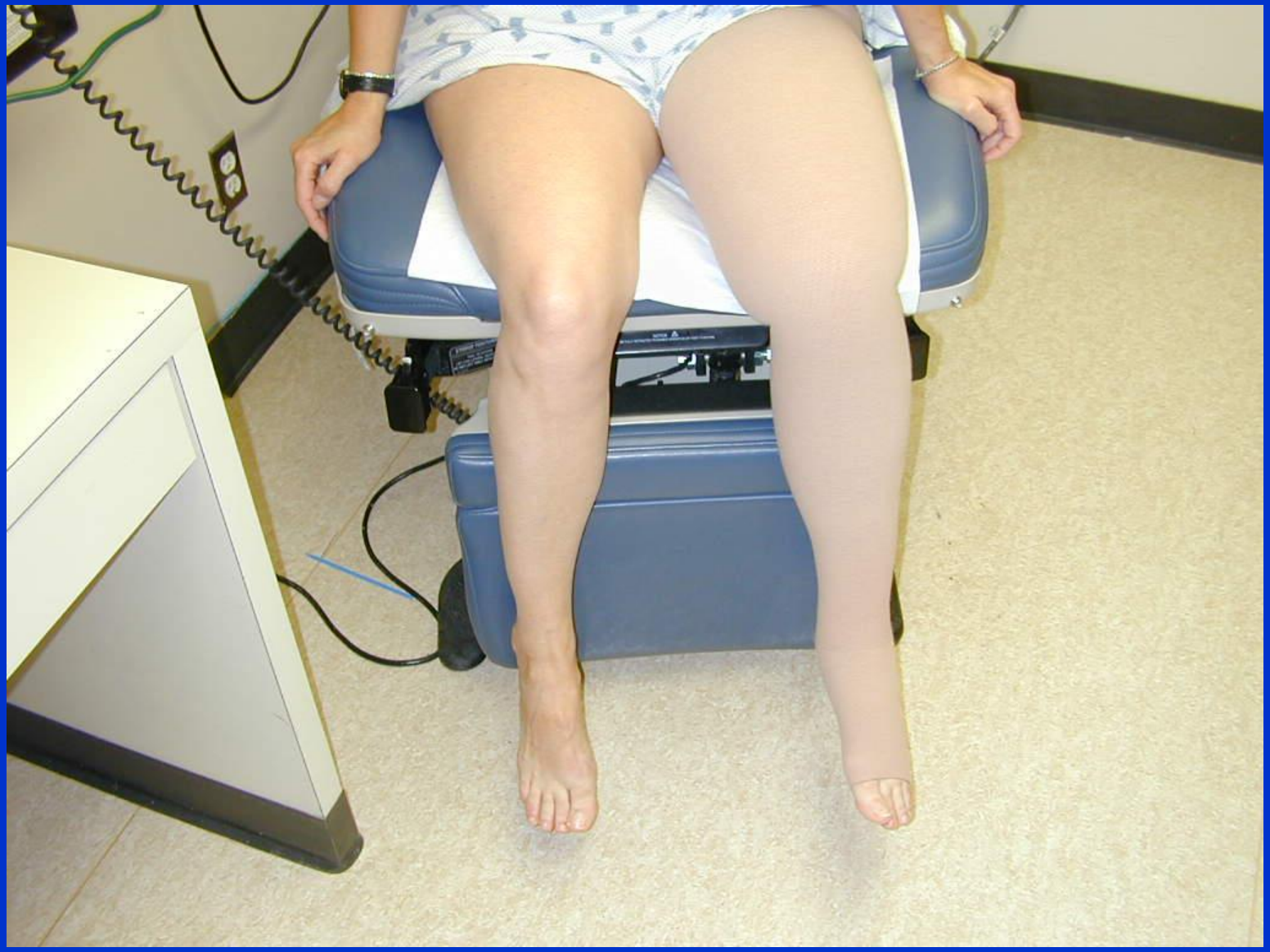
LN resection

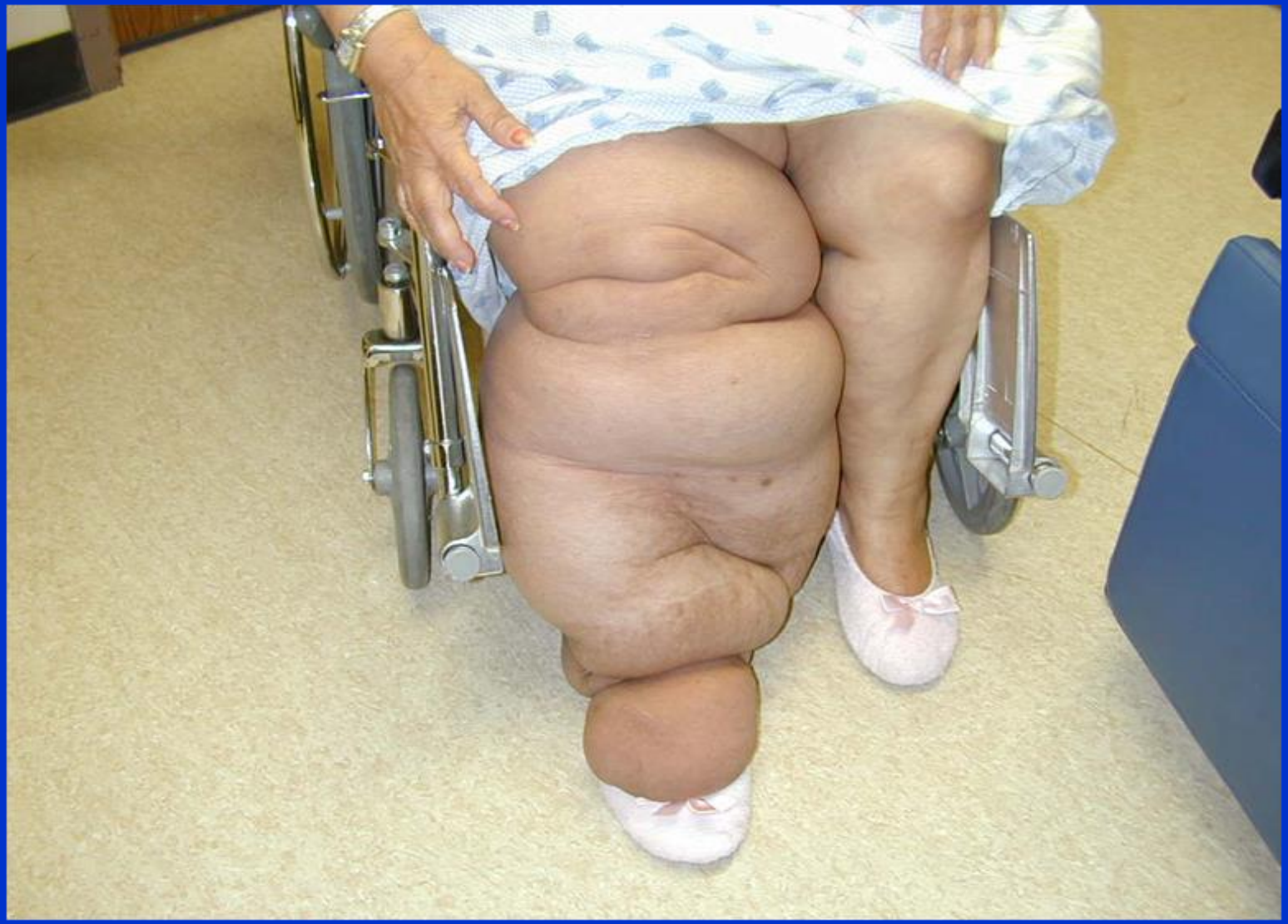
Endocervical Adenocarcinoma

Radical Surgery + LN resection

Complications found in 48% of the patients

1. Transient bladder or sexual dysfunction 70%
2. Lymphedema 25%
3. Neuropathy 5%





The Problem

The surgical treat of AdenoCa of Cx has been based on the depth of invasion knowing that it is not possible to do this accurately

AdenoCa of the Endocervix
The Disastrous End

86 pts
Total number of LNs resected – 1672

- LNs resected in 81 Pts
- LNs negative in 70 Pts (88%)
- Number of positive LNs – 11 (<1%)
- Average # of LNs/ Pt – 20
- Mean Pts' age 43 yo

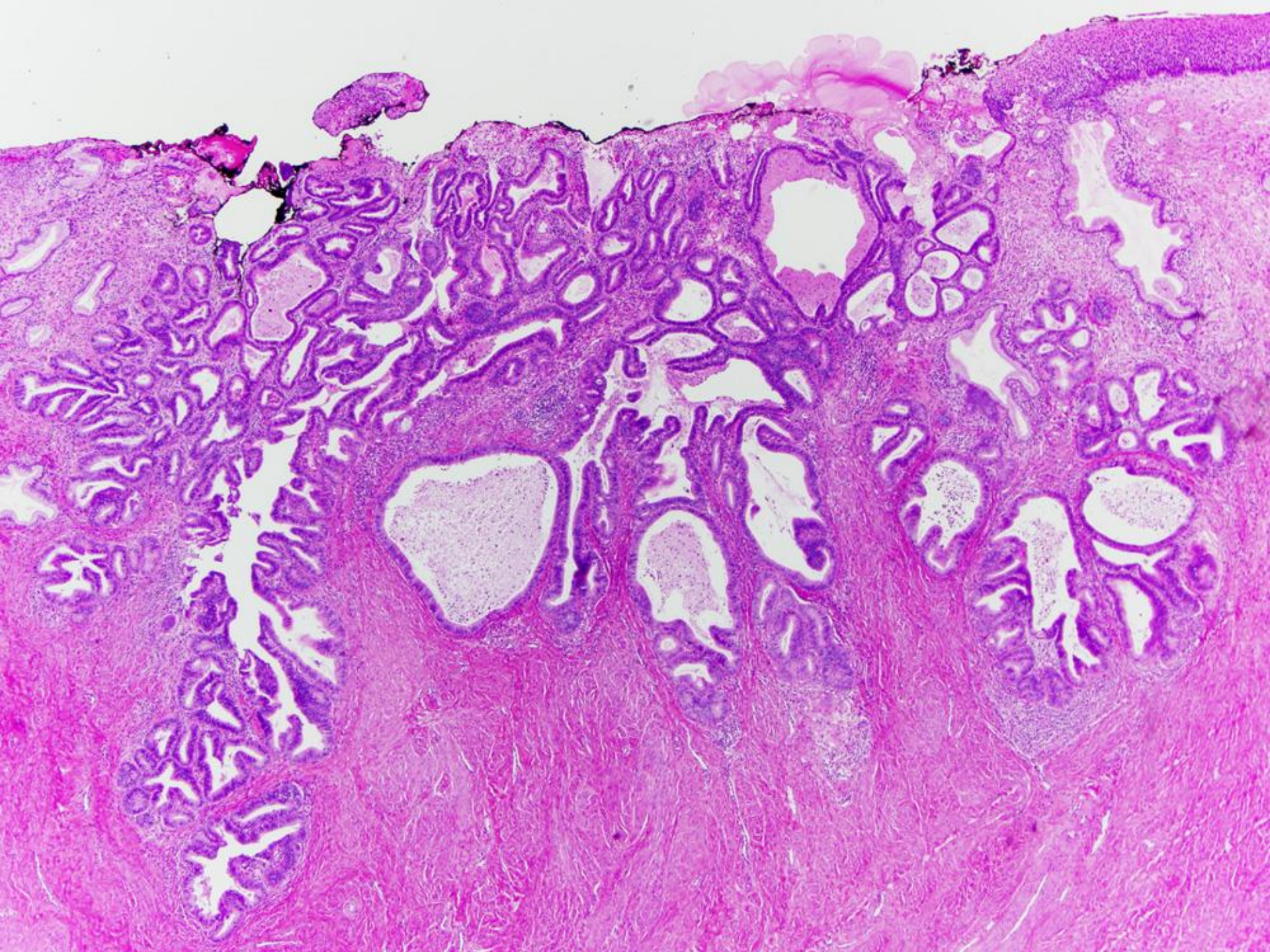
AdenoCa EndoCx

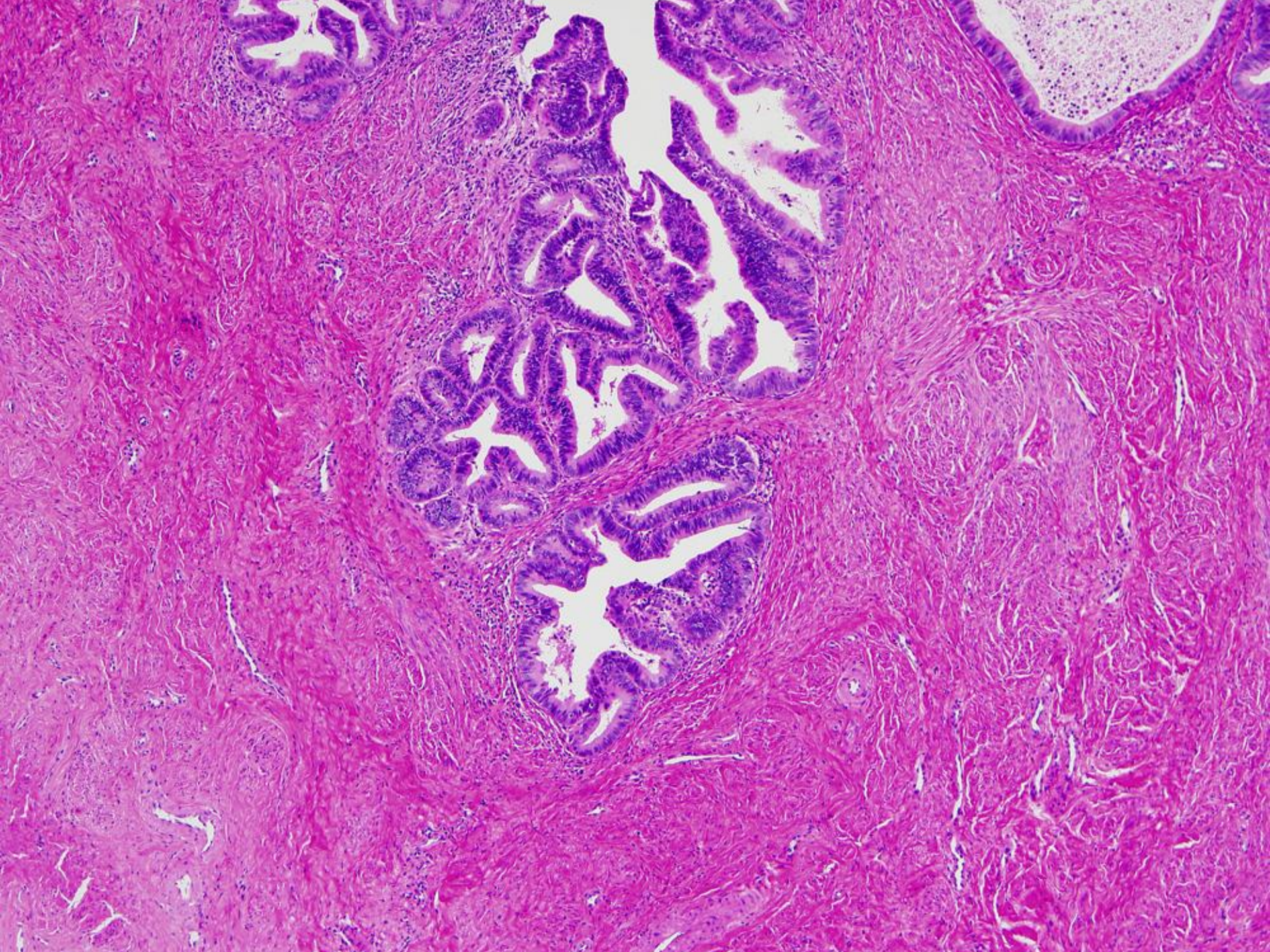
A possible solution

↓

Classical features of invasion

Patterns of invasion?





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Joanne KL Rutgers	Long Beach Memorial Hospital, LA
Andrea Diaz De Vivar	Texas Children's Center, Houston
Andres A Roma	Cleveland Clinic, Cleveland
Rouba Ali-Fehmi	Wayne State University, Detroit
Golnar Rasty	University of Toronto, Canada
Isabel Alvarado-Cabrero	Mexican Oncology Hospital, Mexico
Jose Chanona-Vilchis	Instituto Nacional de Cancerologia, Mexico
Sung R Hong	Korea University Anam Hospital, Korea
Norihiro Teramoto	Shikoku Cancer Center, Japan
Yoshiki Mikami	Kyoto University Hospital, Japan
Elvio G Silva	Cedars Sinai Medical Center, LA

Hypothesis

Endocervical adenocarcinoma categorized by morphologic ‘pattern of invasion’ rather than traditional ‘depth of invasion’ better predicts for lymph node metastasis

Design

- Larger multi-institutional study (12 institutions)
- Dx of Invasive Endocervical Adenocarcinoma (usual type only, no variants)
- Only resected cases (hyst/trach/cone) with lymph node sampling and/or recurrence

Design

- At least 20 months of follow up (up to 392m, mean 54m)
- Pathologic parameters assessed:
  - Depth of tumor
  - Tumor size
  - Lymphovascular invasion
  - Pattern of tumor invasion (new system)

New method

Pattern A

- Well-demarcated glands with rounded contours, frequently forming groups
- Glands may have complex intraglandular growth (cribriforming, papillae)
- No cell detachment or obvious desmoplastic stromal invasion
- Depth of tumor or relation to large vessels not relevant
- No lymphvascular space invasion

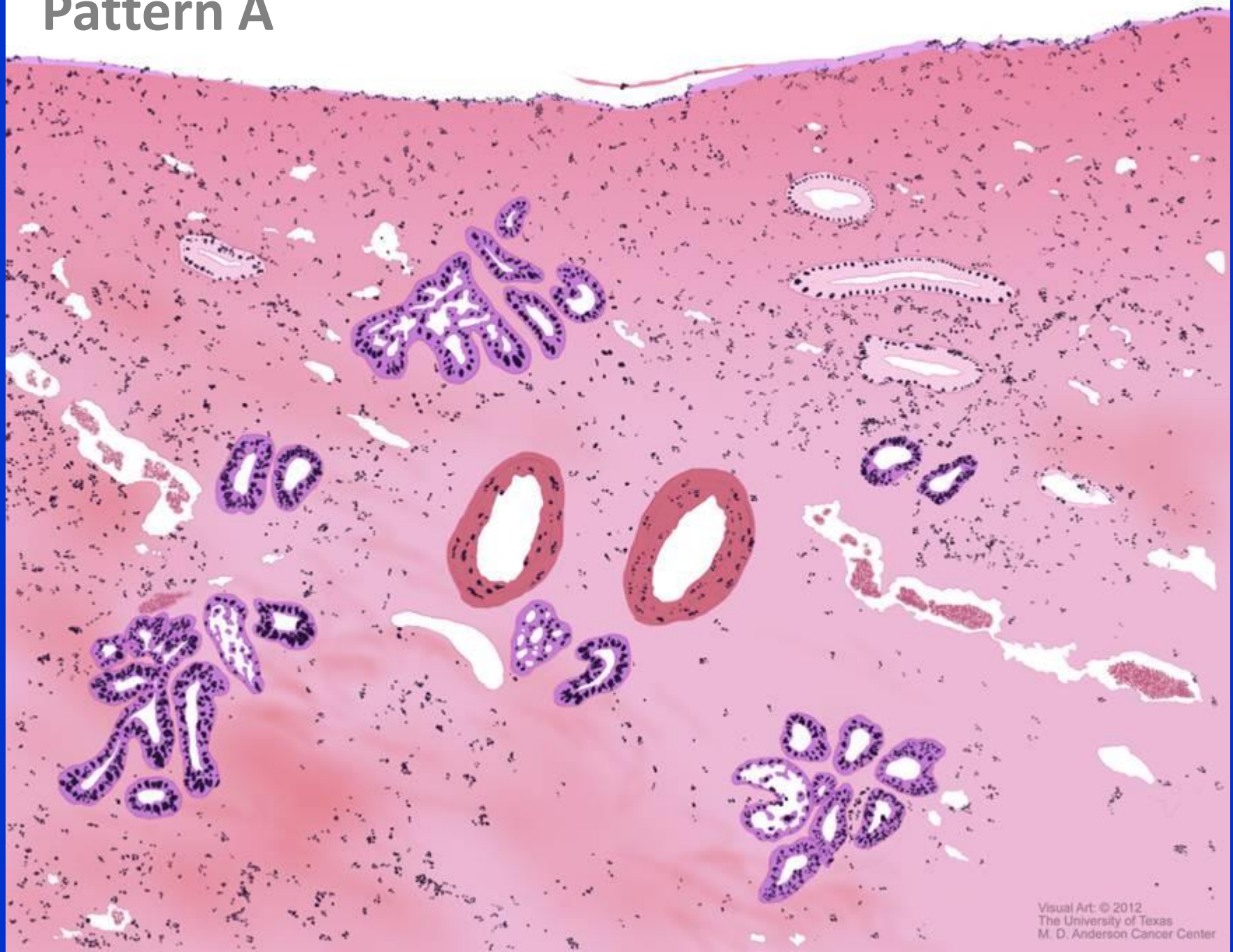
Pattern B

- Early stromal invasion arising from well-demarcated glands

Pattern C

- Diffuse destructive stromal invasion with desmoplasia
- Glands often angulated and with a canalicular pattern and open glands
- Poorly differentiated Cas.
- Only Ca. in a 4x

Pattern A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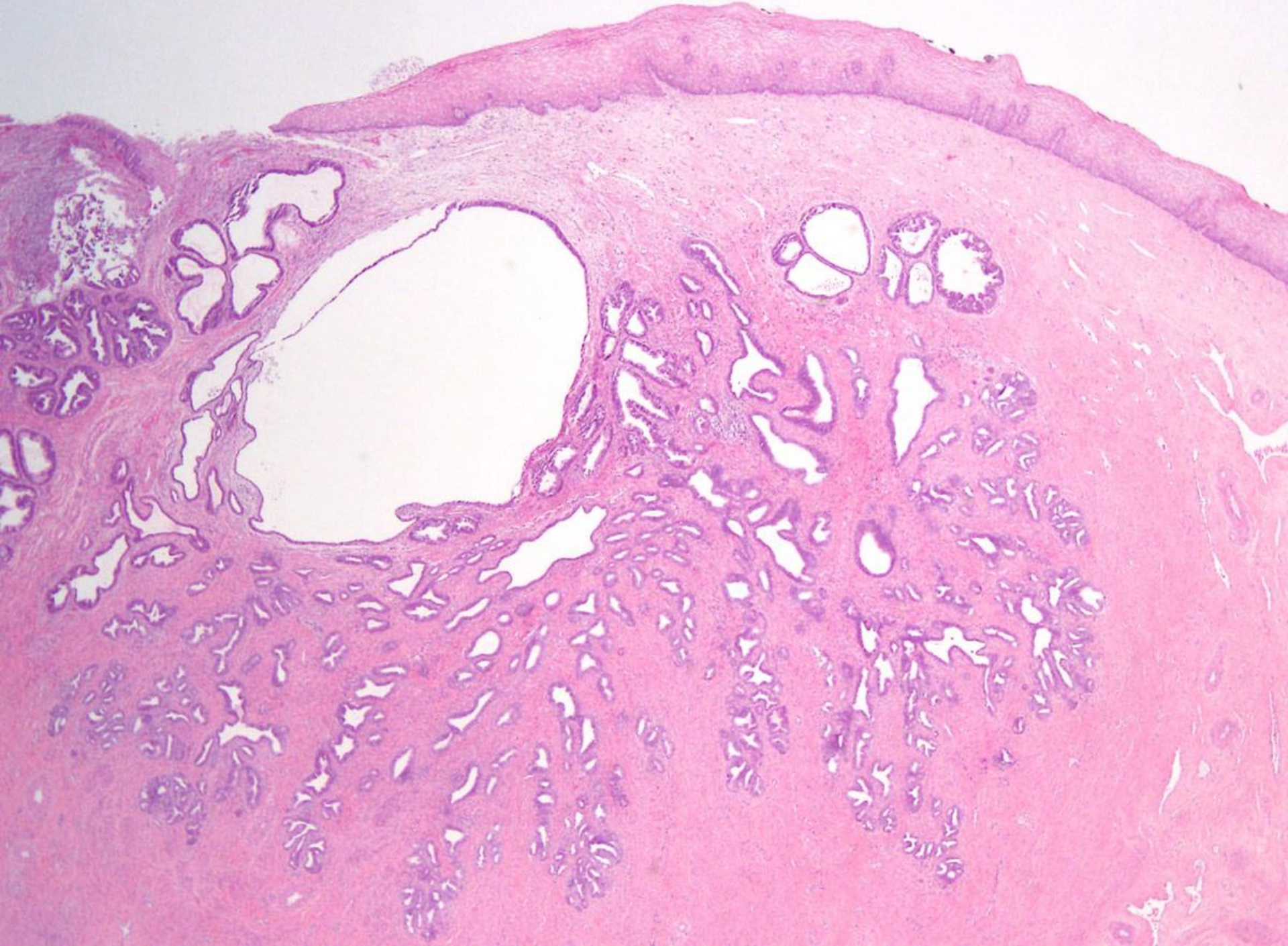

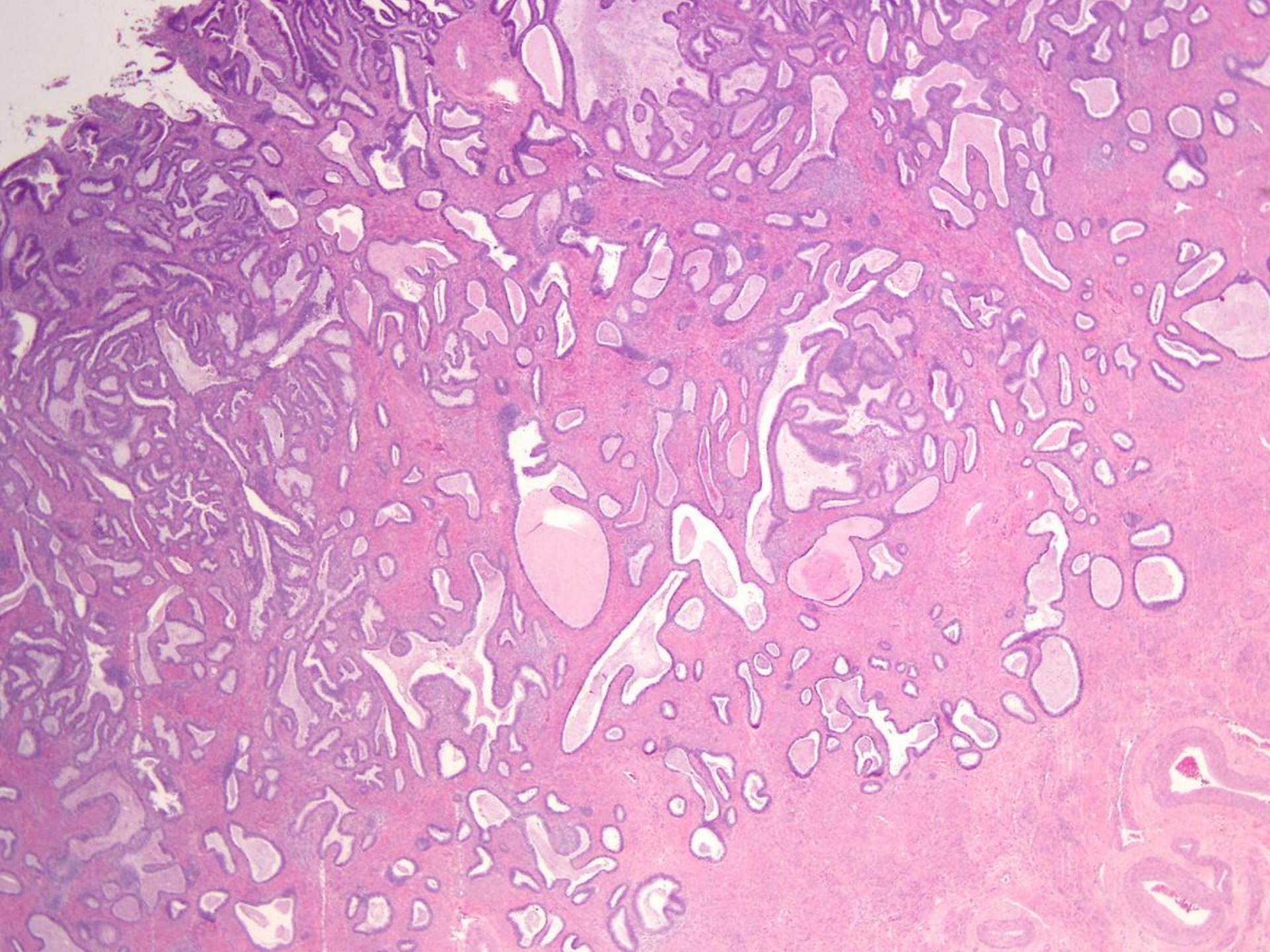

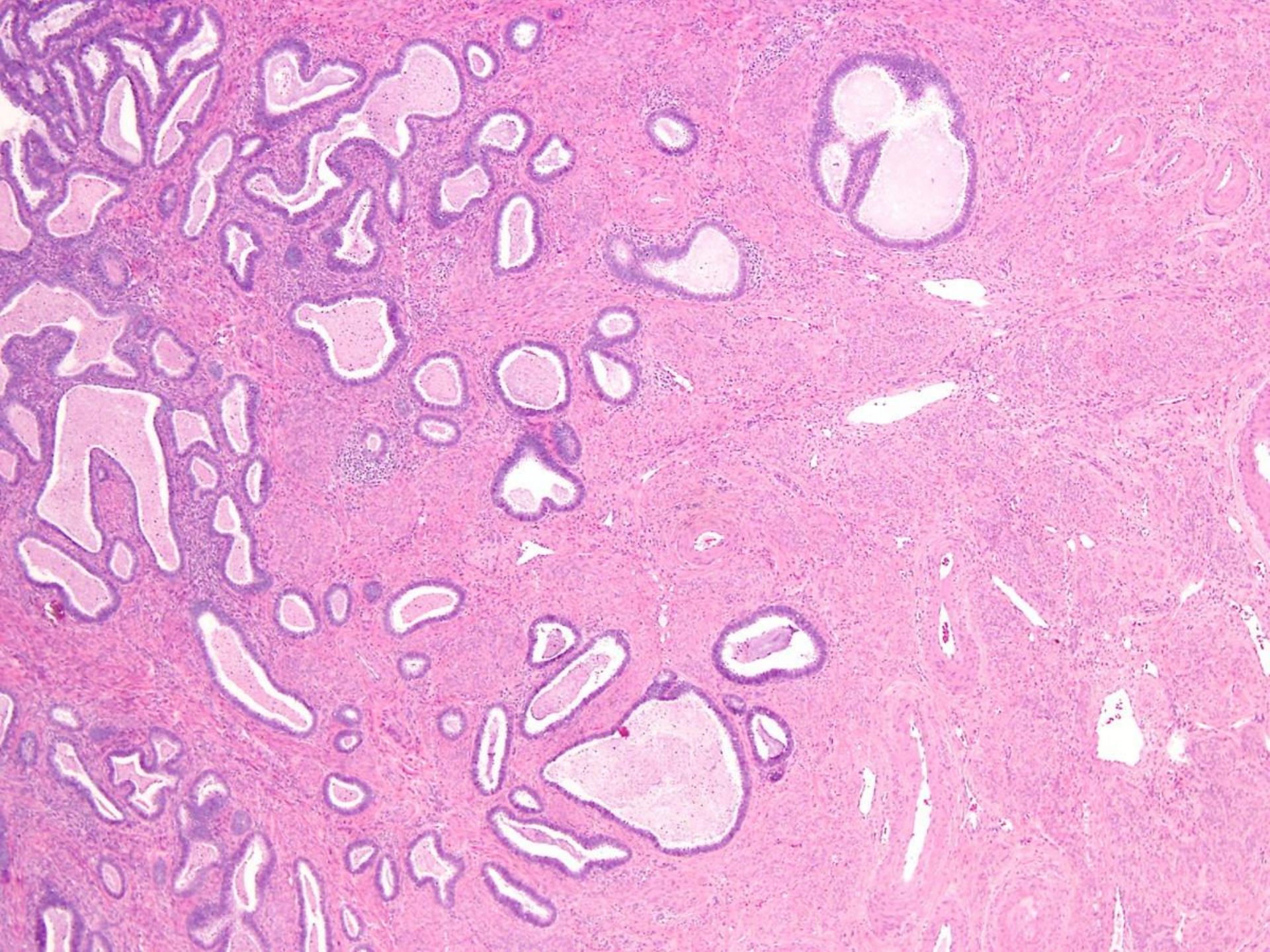

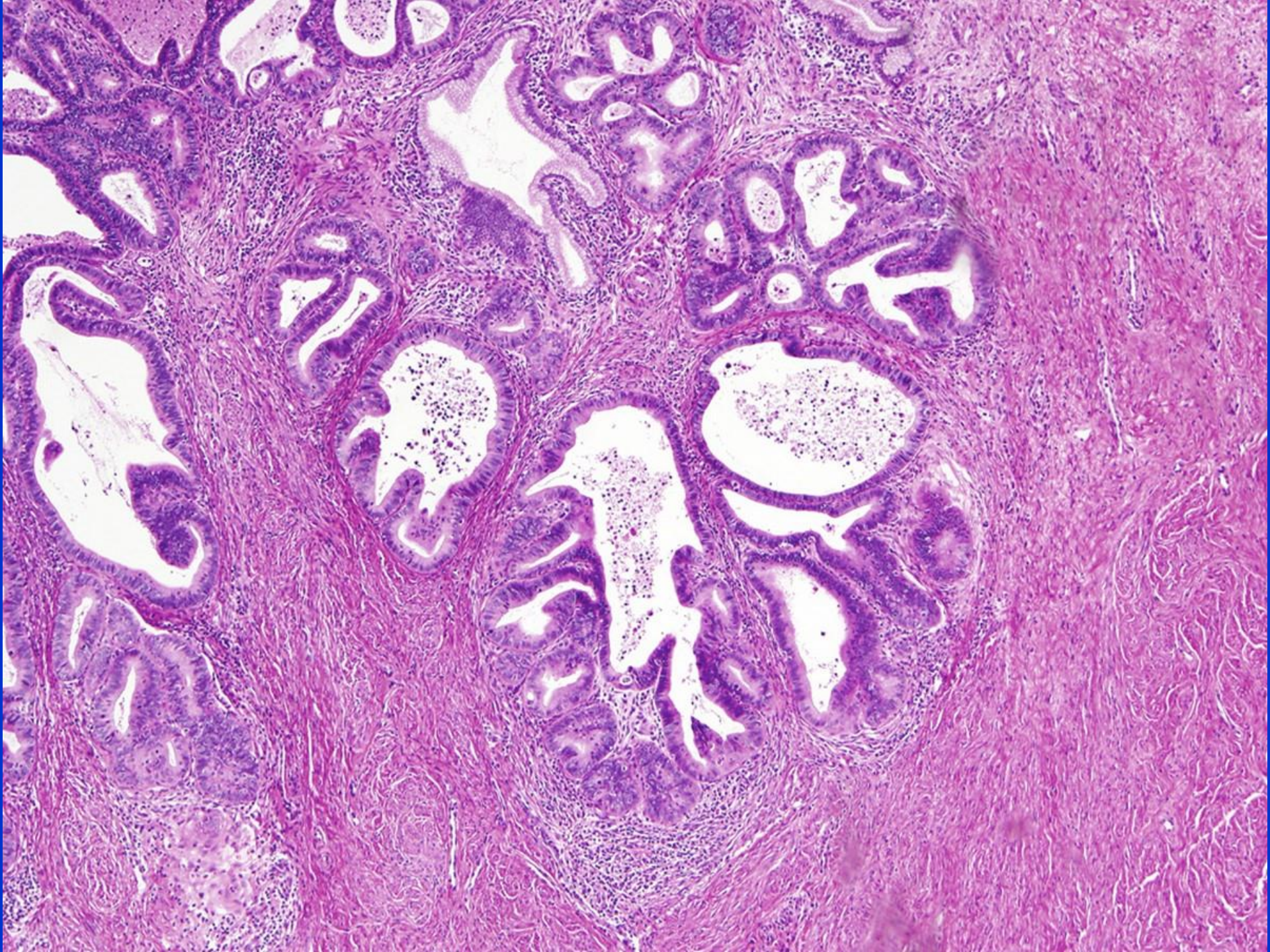

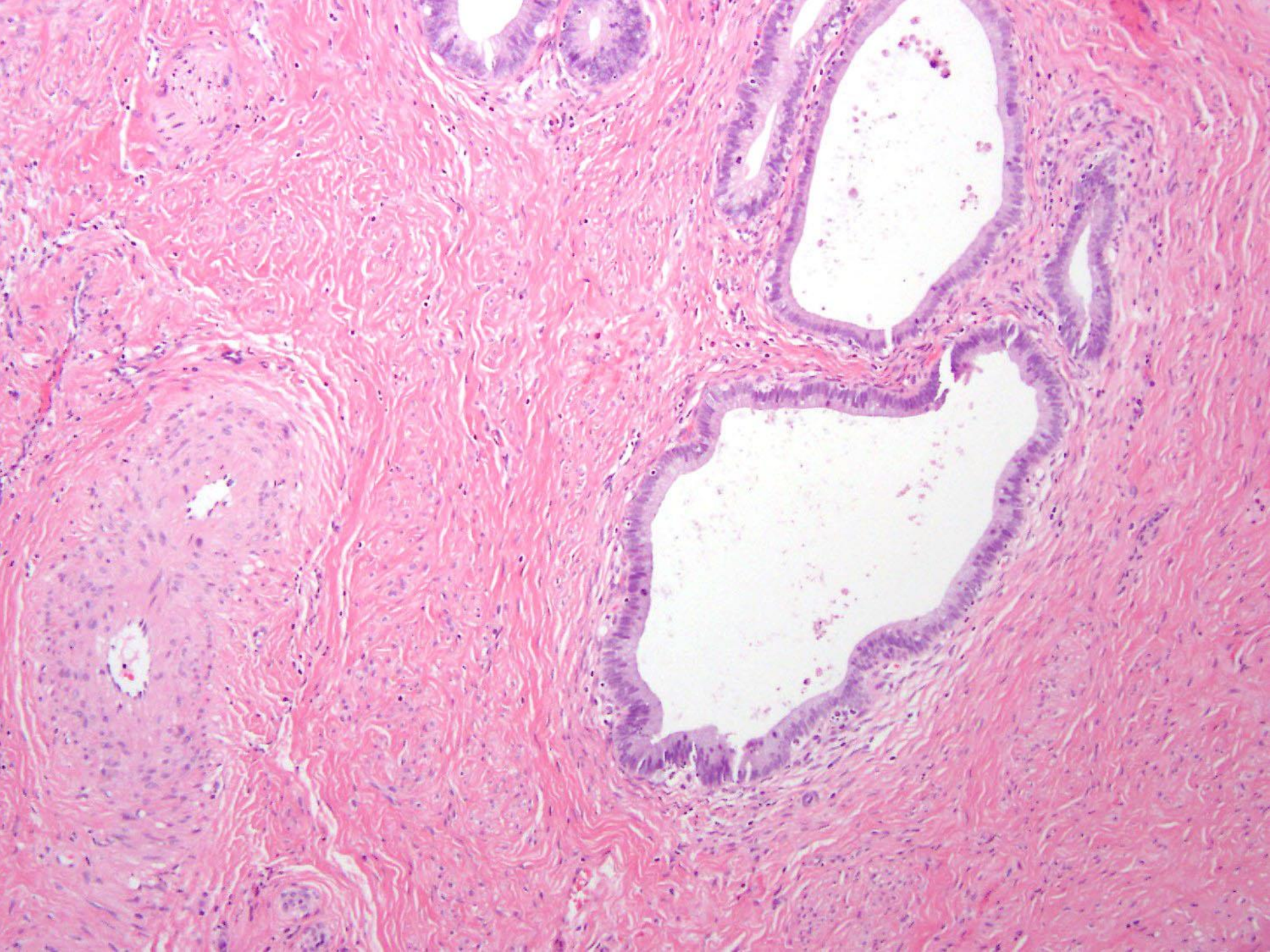

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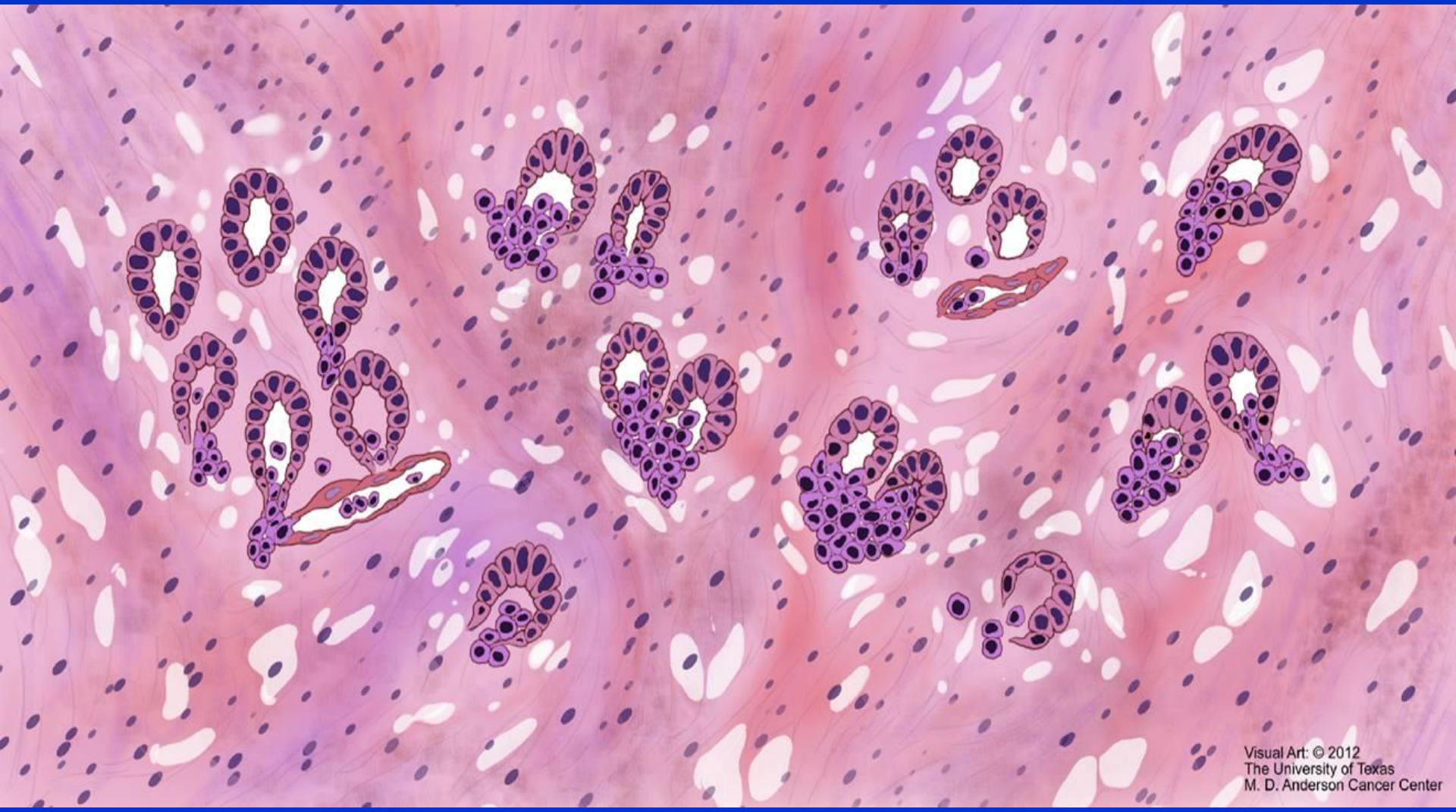
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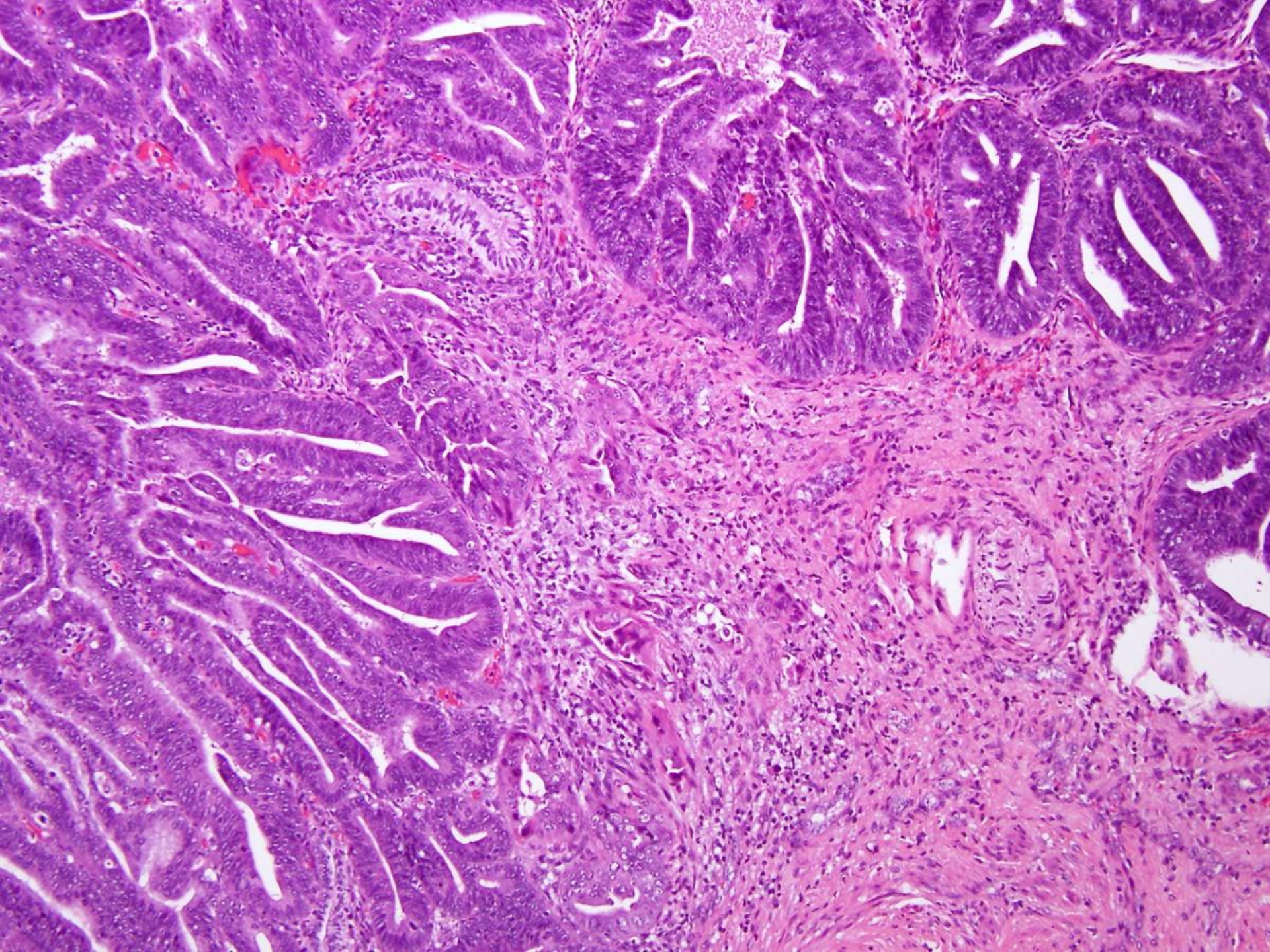

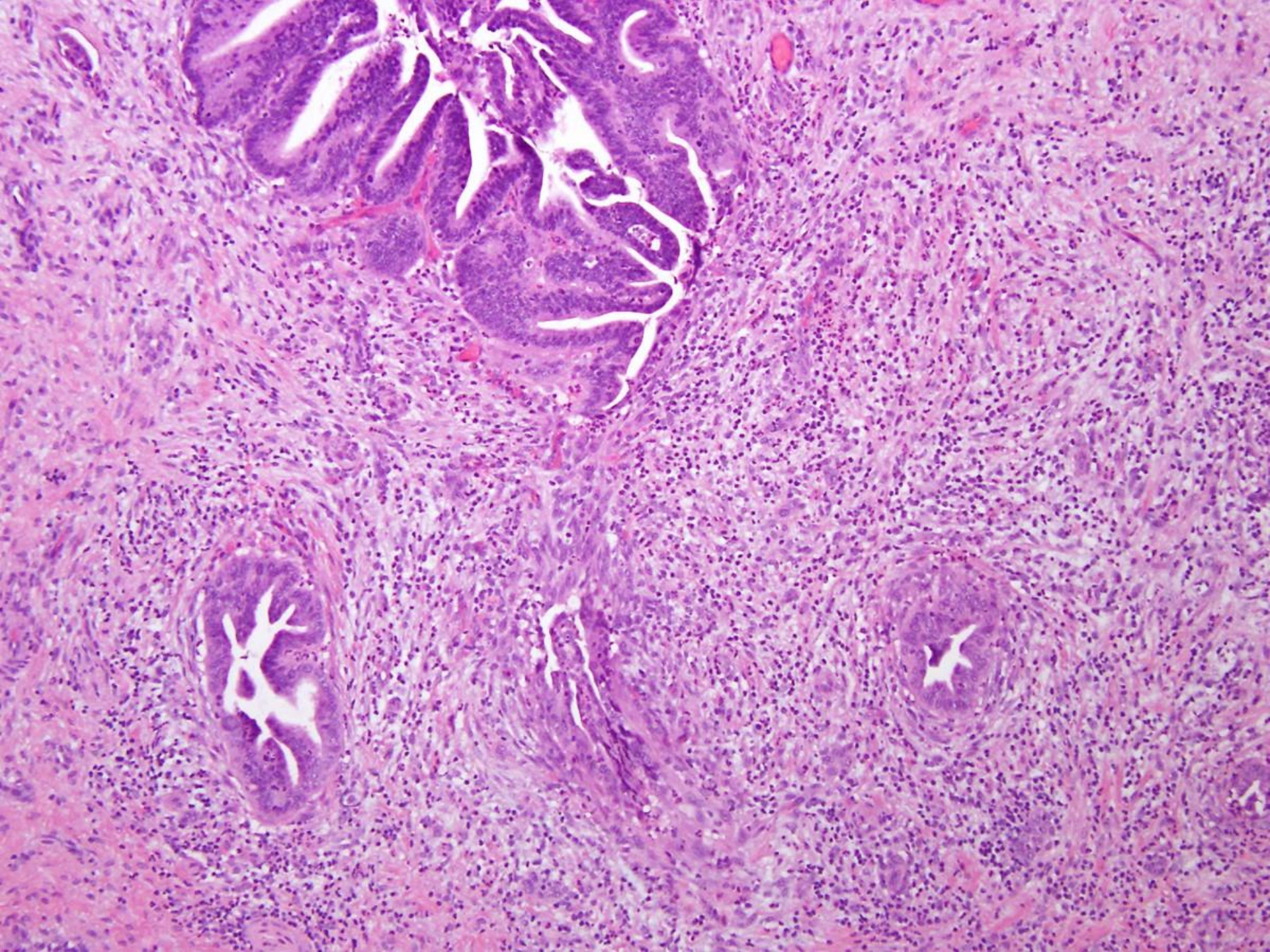

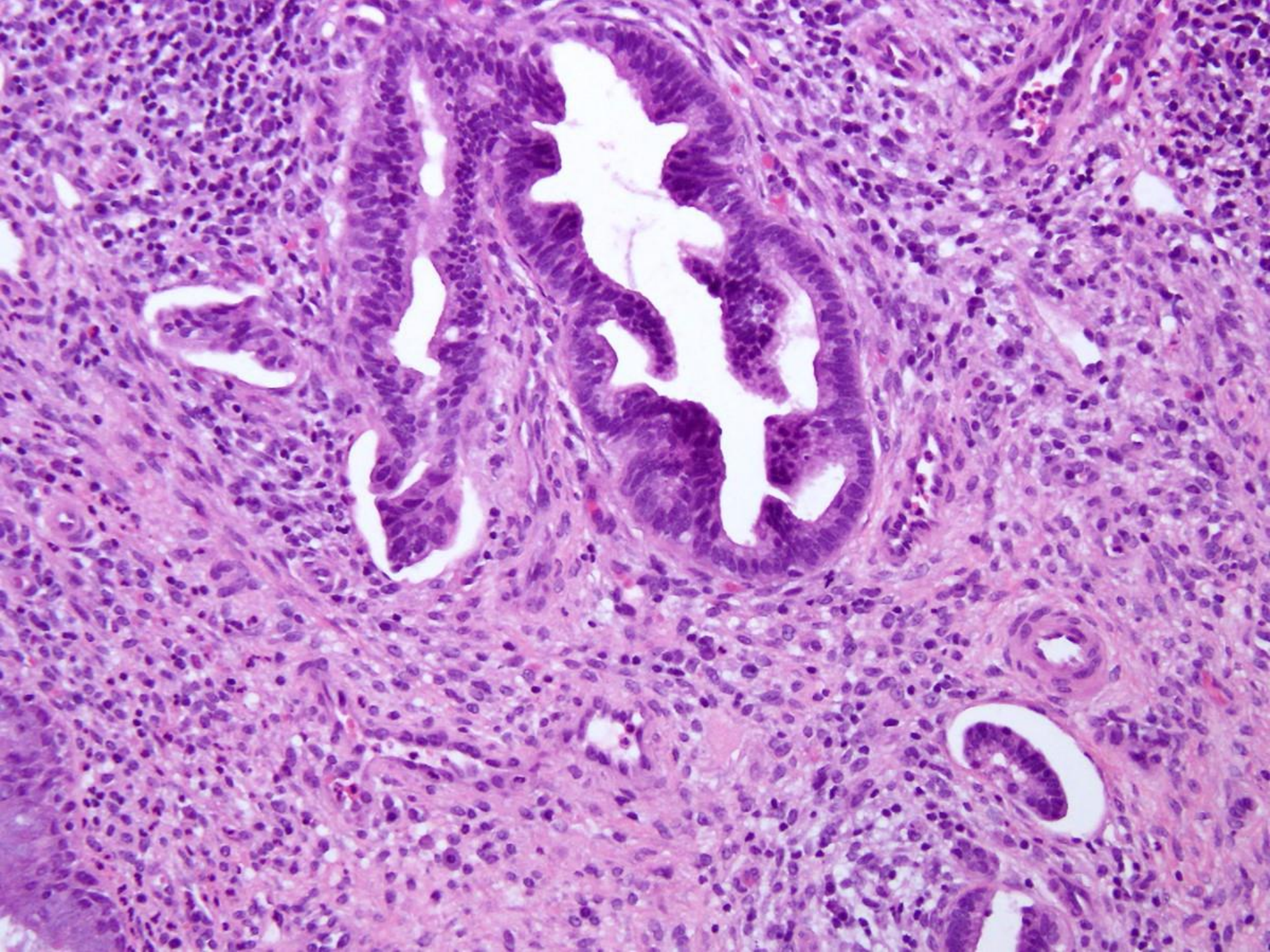

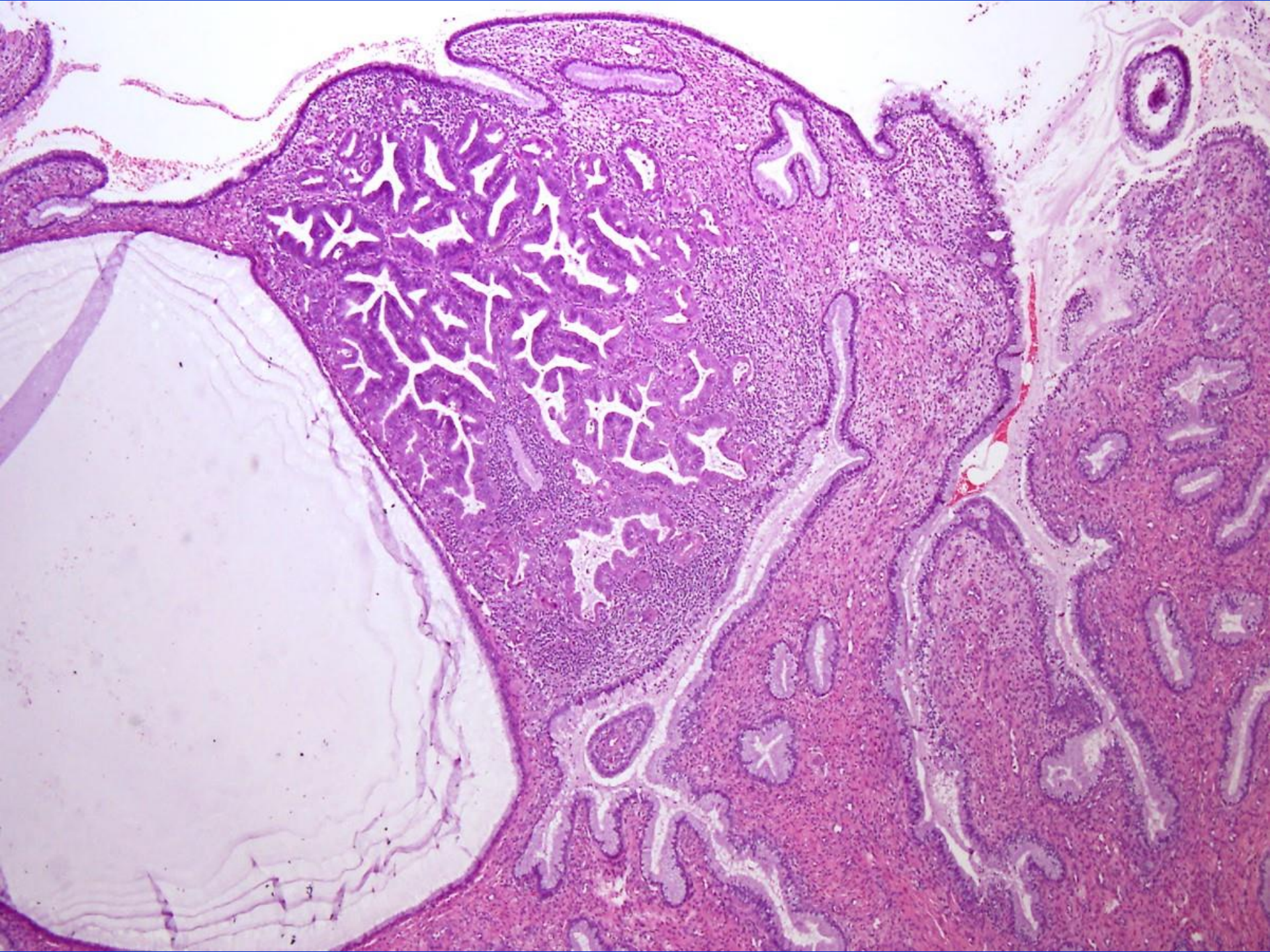

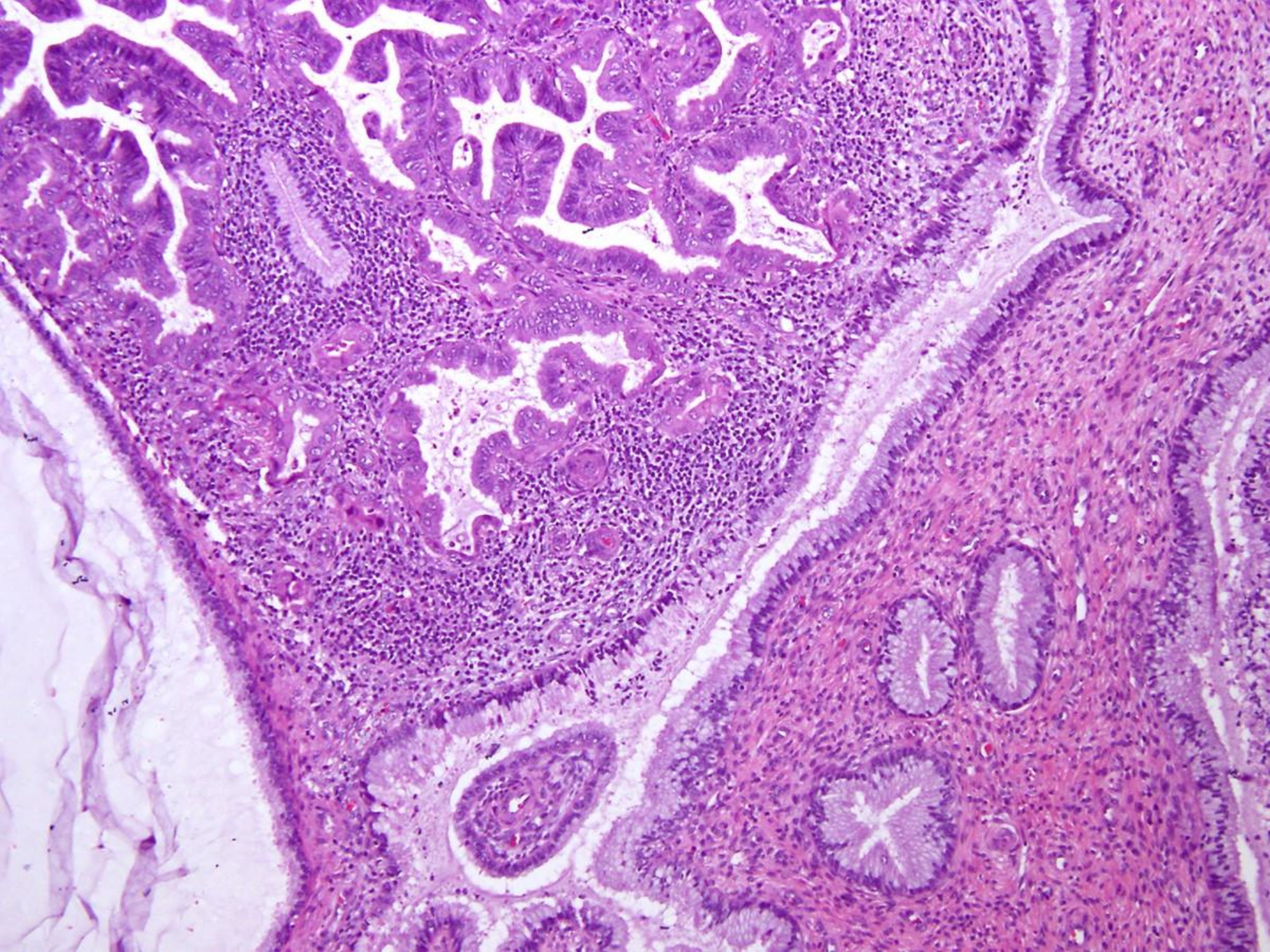

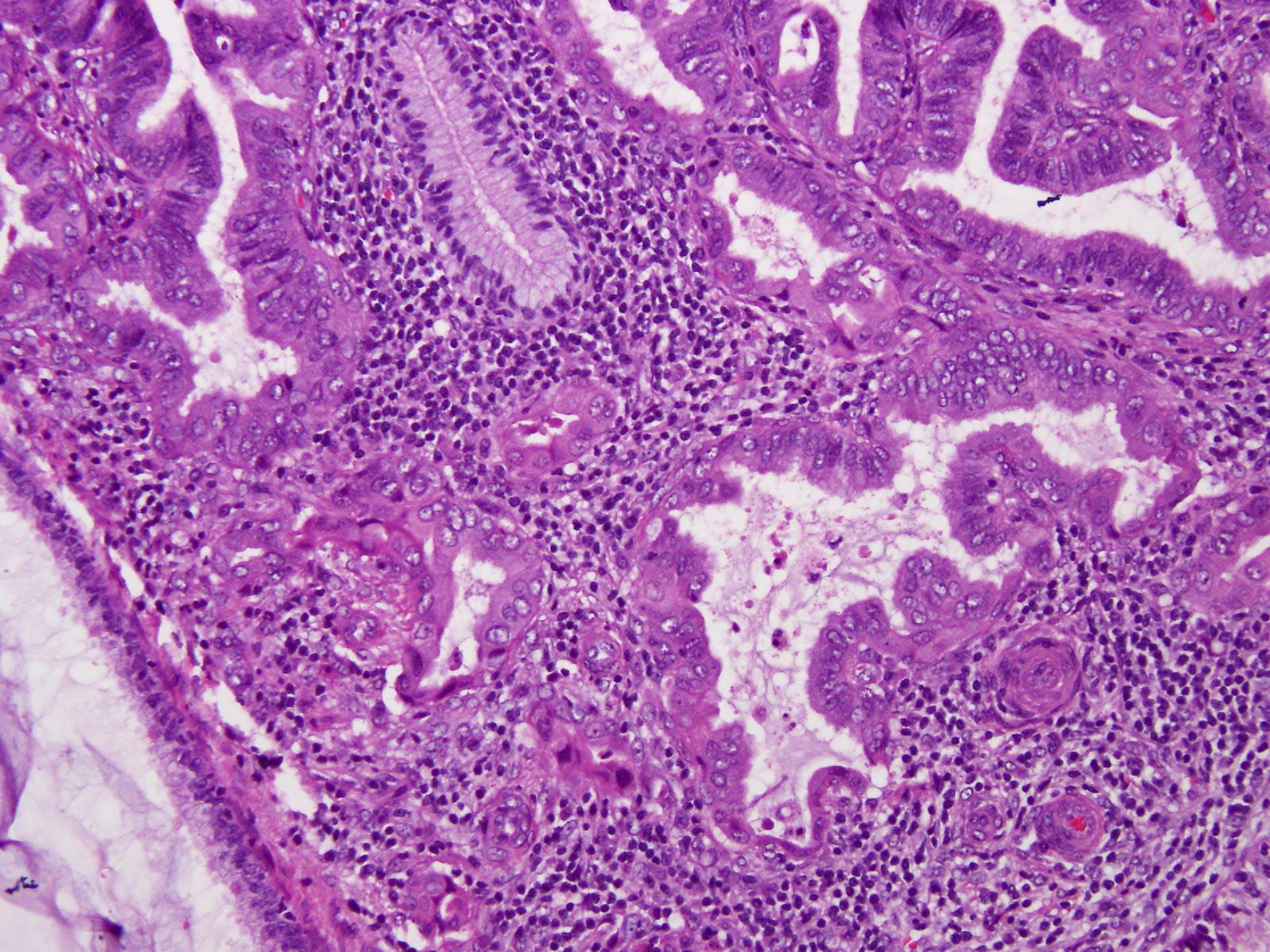

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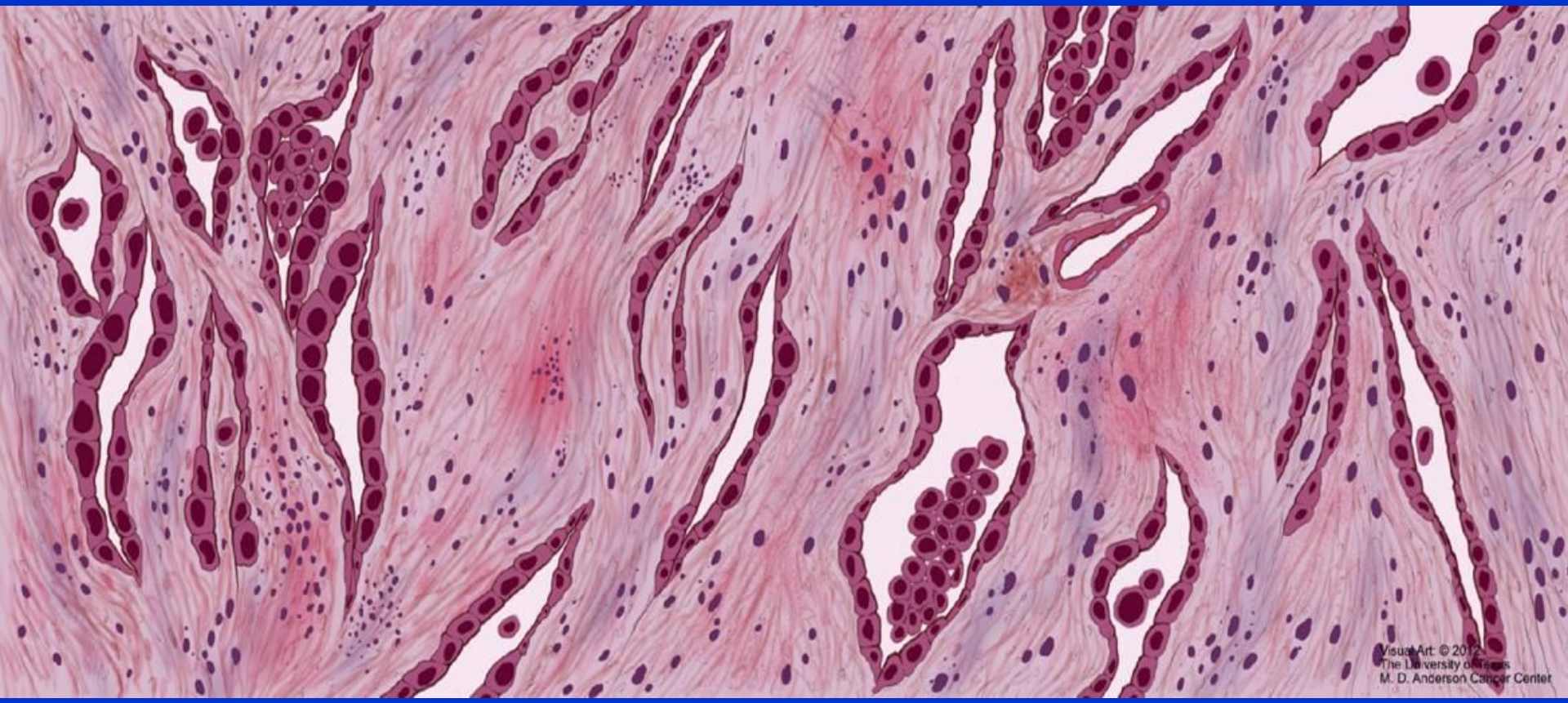
Pattern C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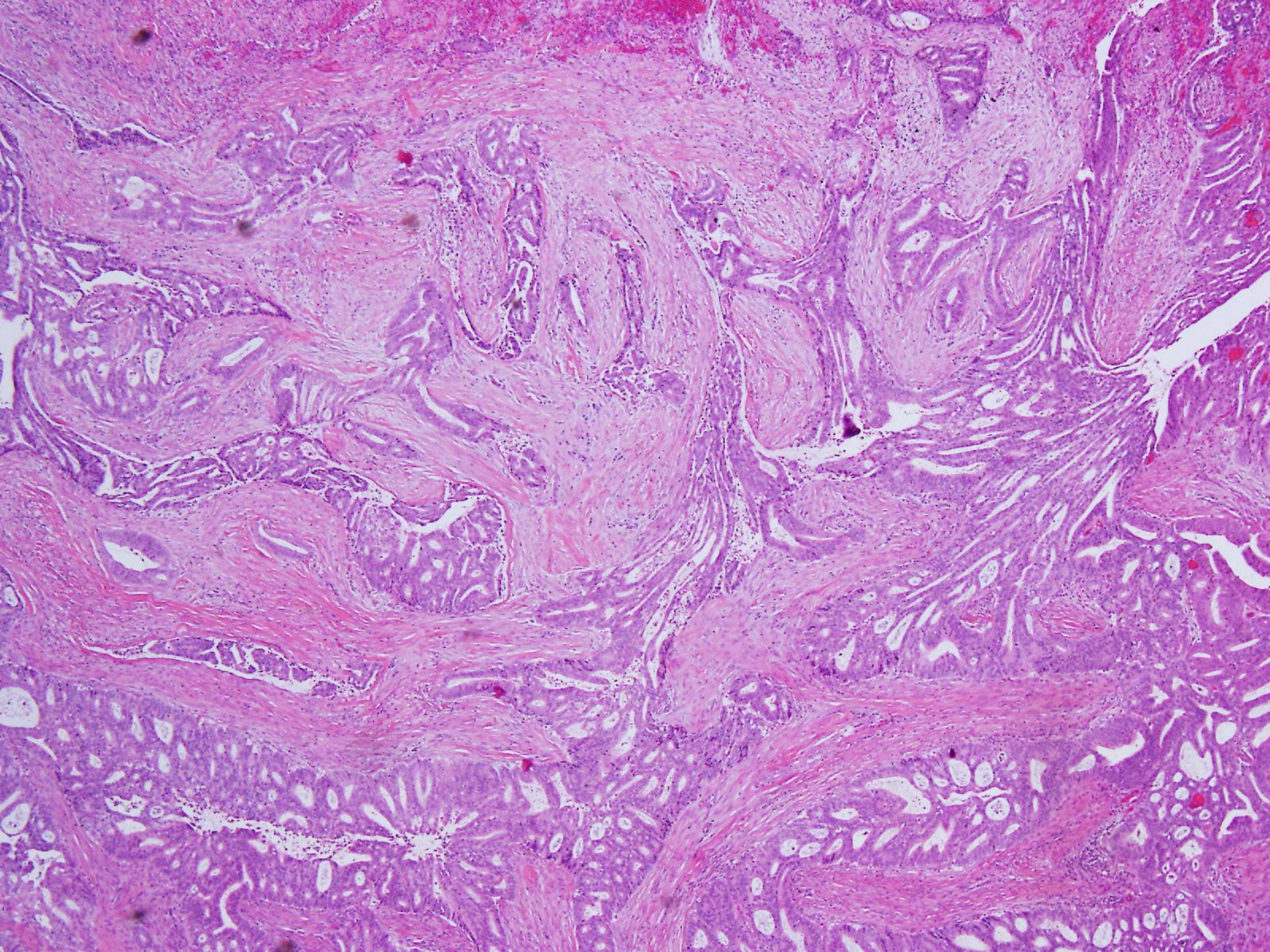
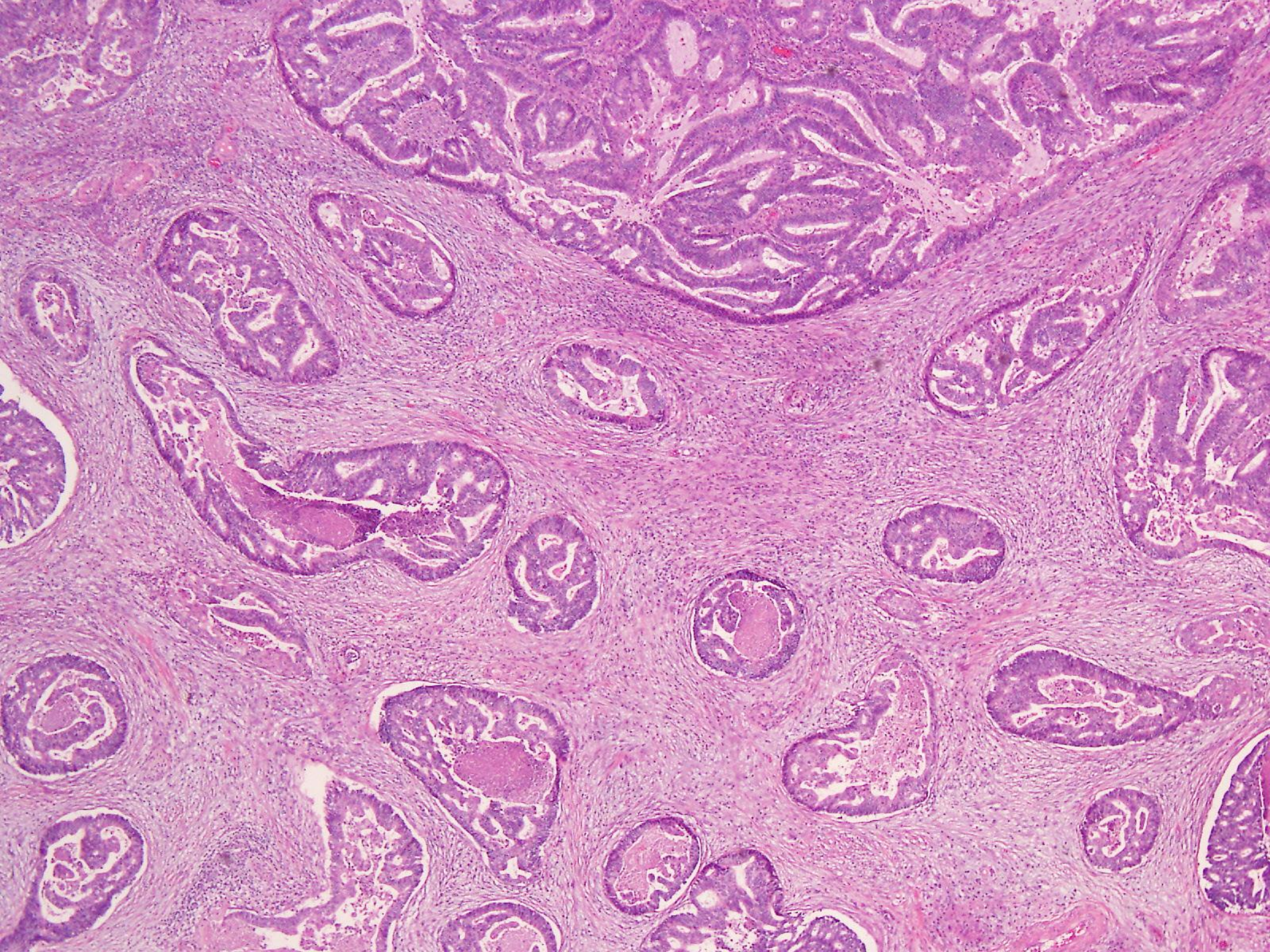
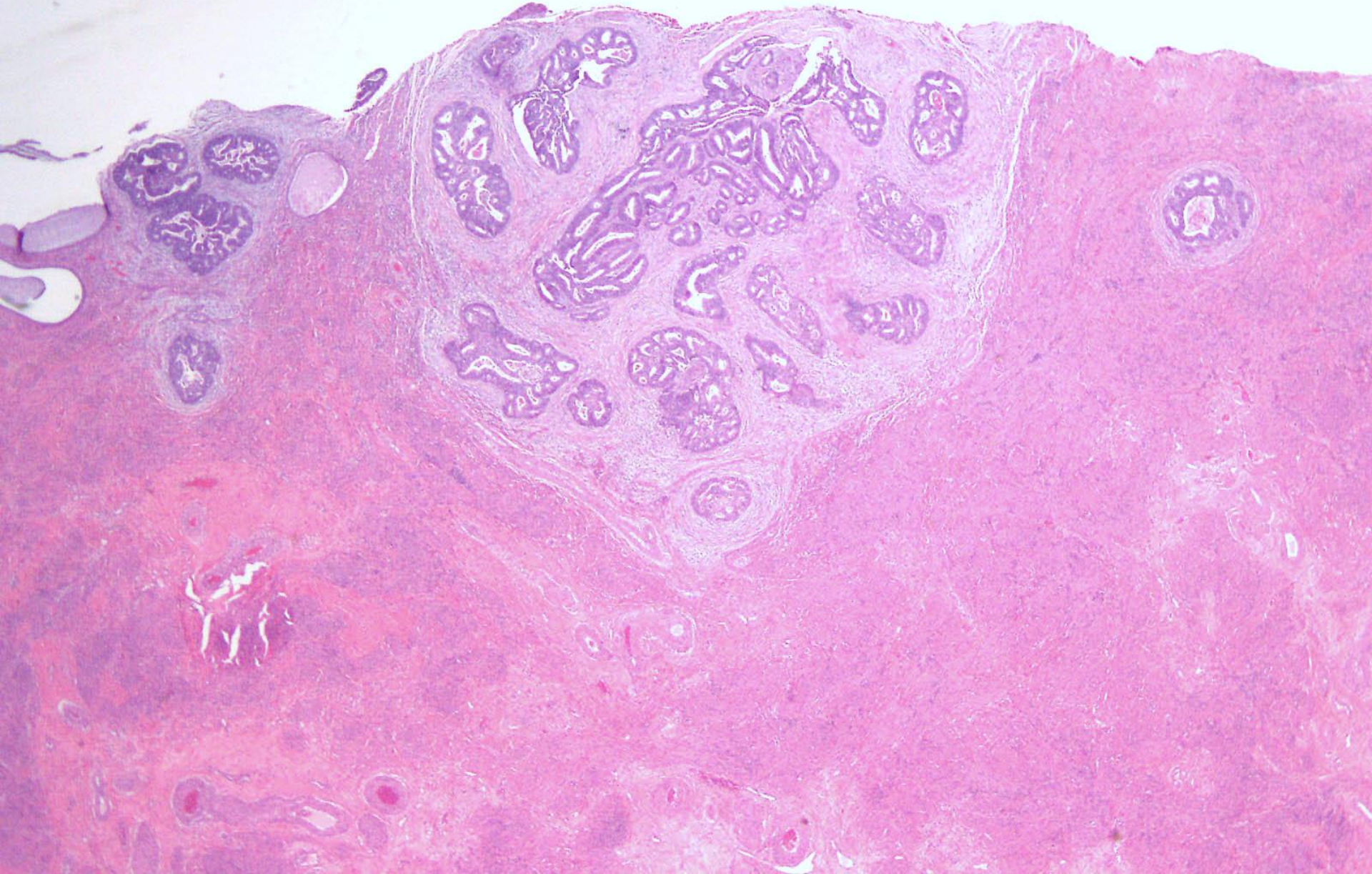






Results

	Patients	Pts with pos LN	Total LN	# Pos LN	Stage I	Stage II-IV

LN metastases

p<0.0001 comparing Pattern A to B/C
p=0.0153 comparing Pattern A to B
p<0.0001 comparing Pattern A to C

22% of patient – spared lymphadenectomy

IMPORTANT!!!

NOTE: Must be certain that entire tumor was evaluated histologically

Conclusions

- Classifying endocervical adenocarcinoma by ‘pattern of invasion’ rather than ‘depth of invasion’ would have identified 22% of patients who did not need LND (Pattern A)
- Pattern B rarely has lymph node mets
- Aggressive treatment for patients with pattern C
- Pattern-based classification is simple, reproducible and clinically significant
- Destructive stromal invasion and LVI more important than ‘depth of invasion’

Adeno Ca of Endocervix

Problems using the pattern system

A vs B

B vs C

A vs C

Comparison of Histologic Features between Patterns A and C

	Pattern A	Pattern C
Diffuse desmoplasia	No	Yes
Gland contour	Round	Angulated
Interspersed open glands	No	Yes
Cluster or groups of glands	Yes	No
Canalicular pattern**	No	Yes

*Open glands (incomplete glandular structures) describes a gland with a discontinuous contour showing a break opening to the stroma, often associated with loosened stroma and or inflammatory cells.

** Canalicular pattern means labyrinthine, interconnected glands

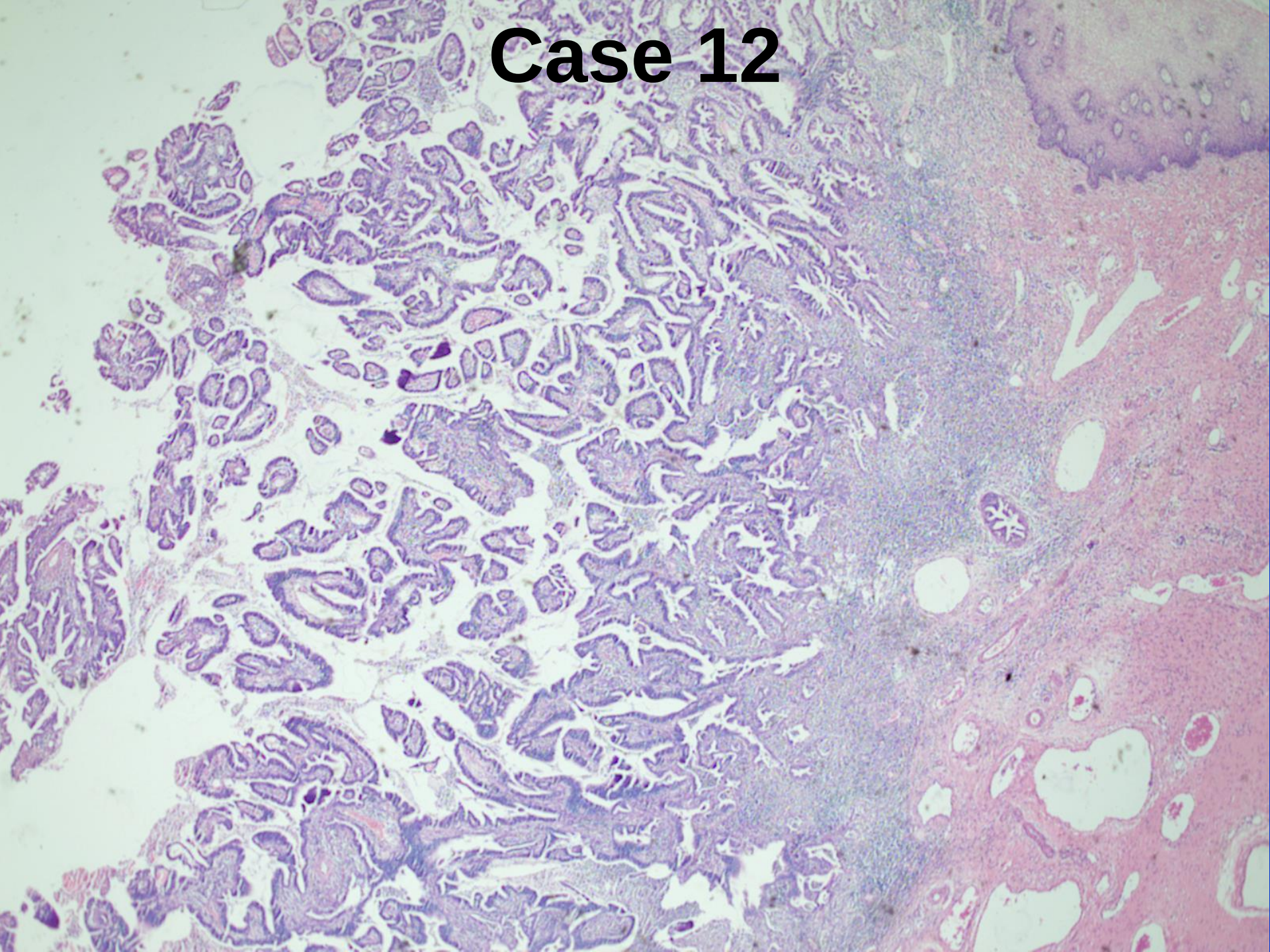
Endocervical AdenoCa
New Pattern System

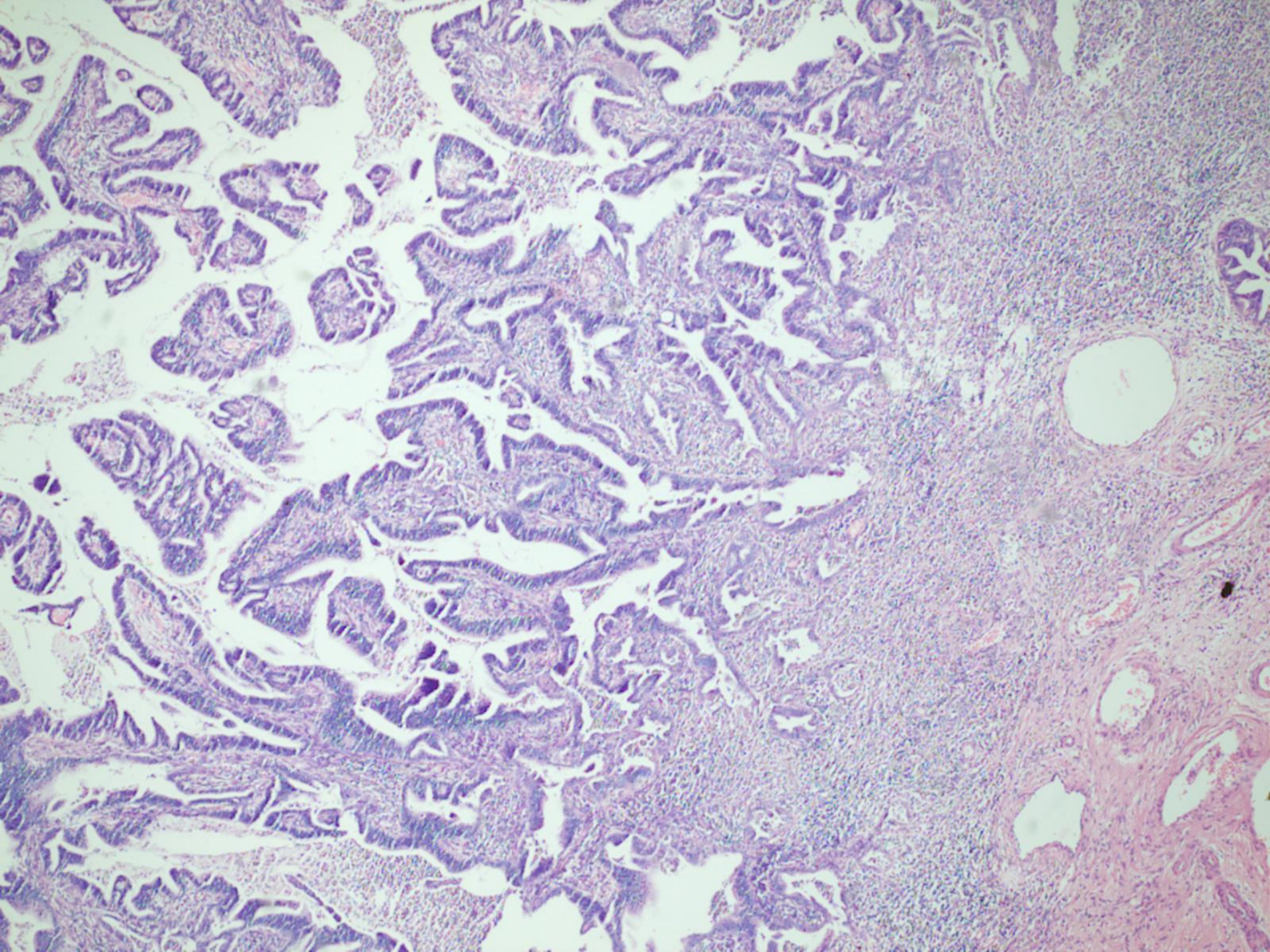
	130 Pts	+LNs
Pattern A	12%	0
Pattern B	17%	9%
Pattern C	71%	26%

Endocervical AdenoCa

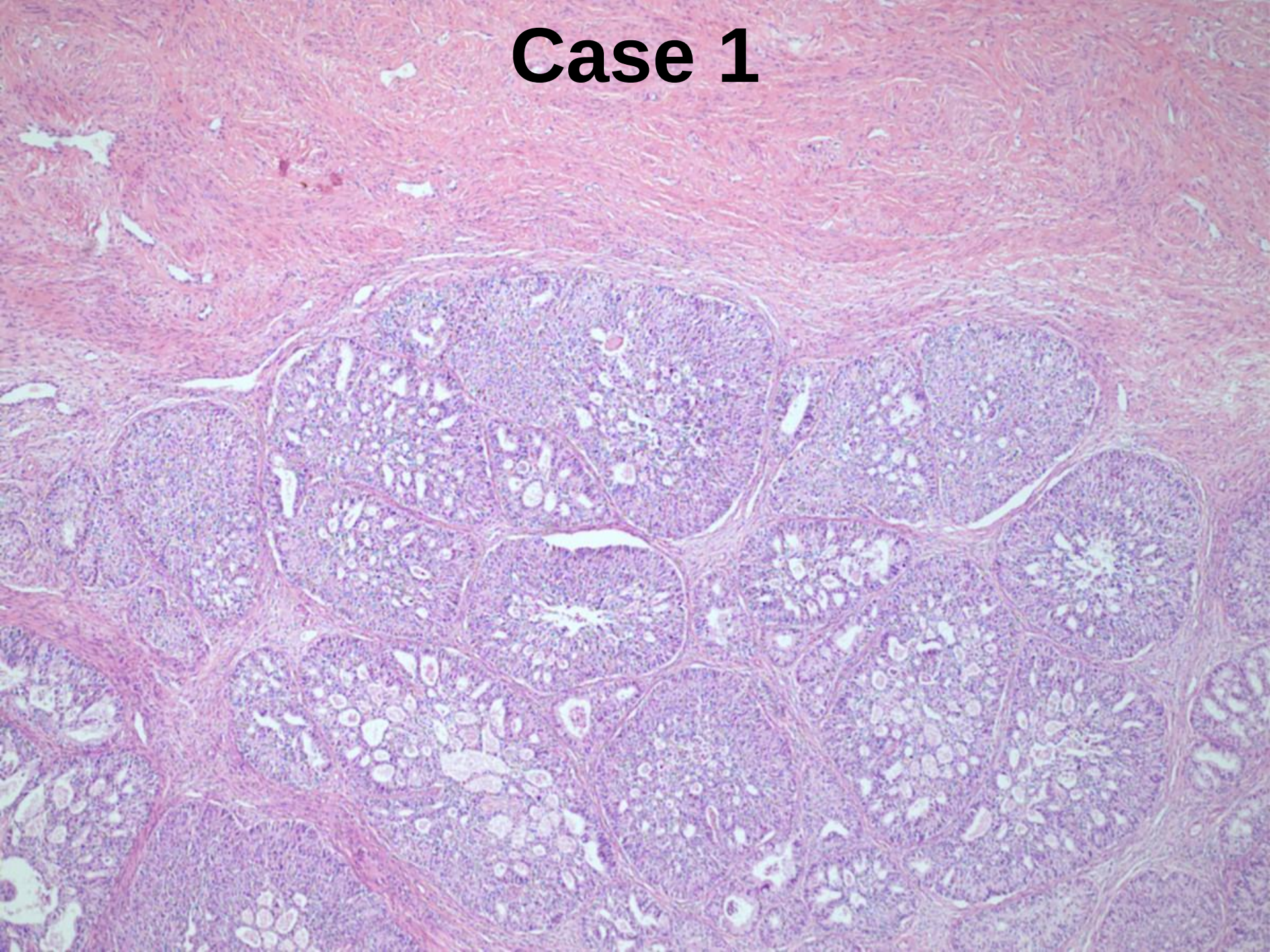
Pattern C

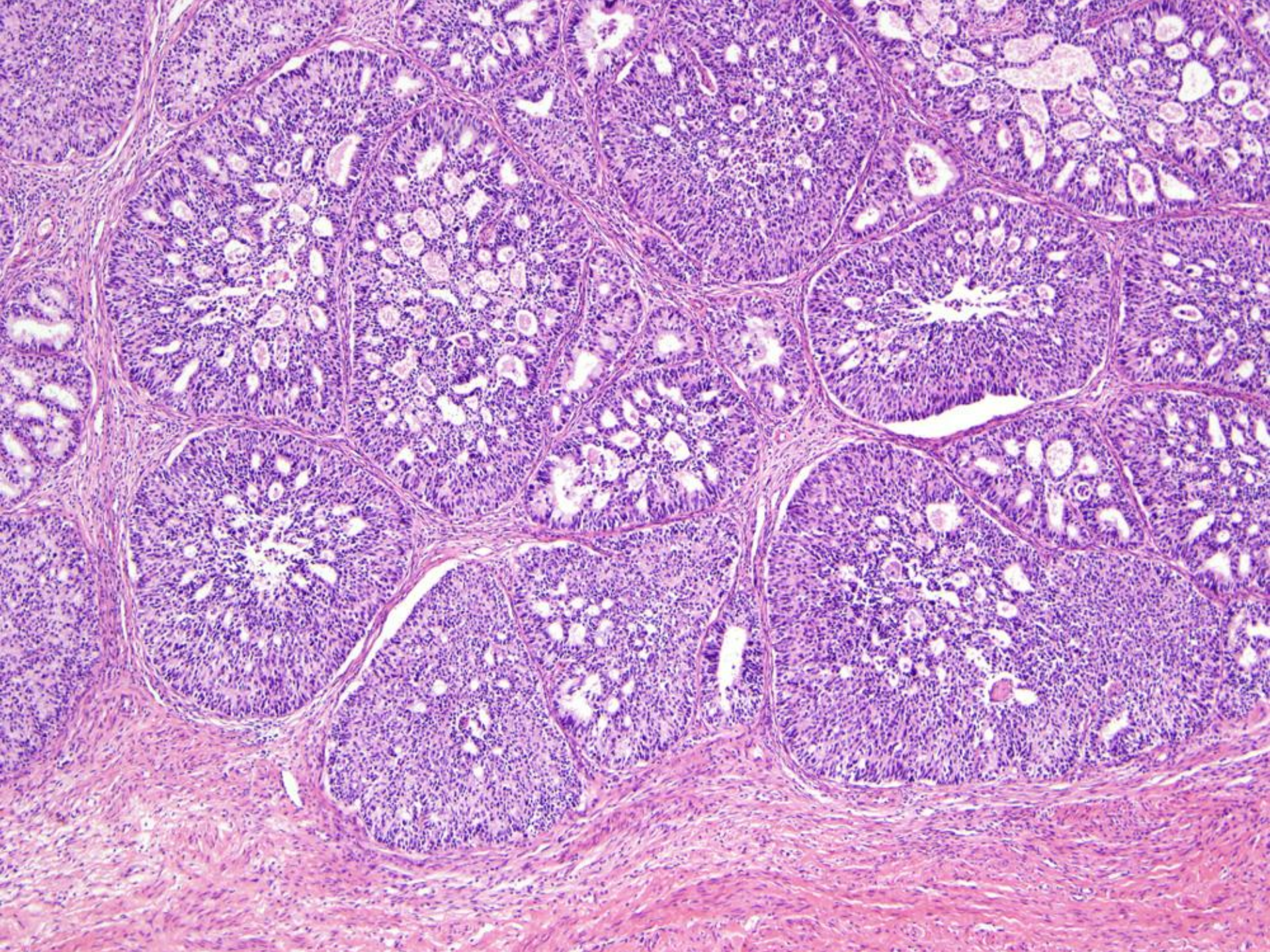
Case 12



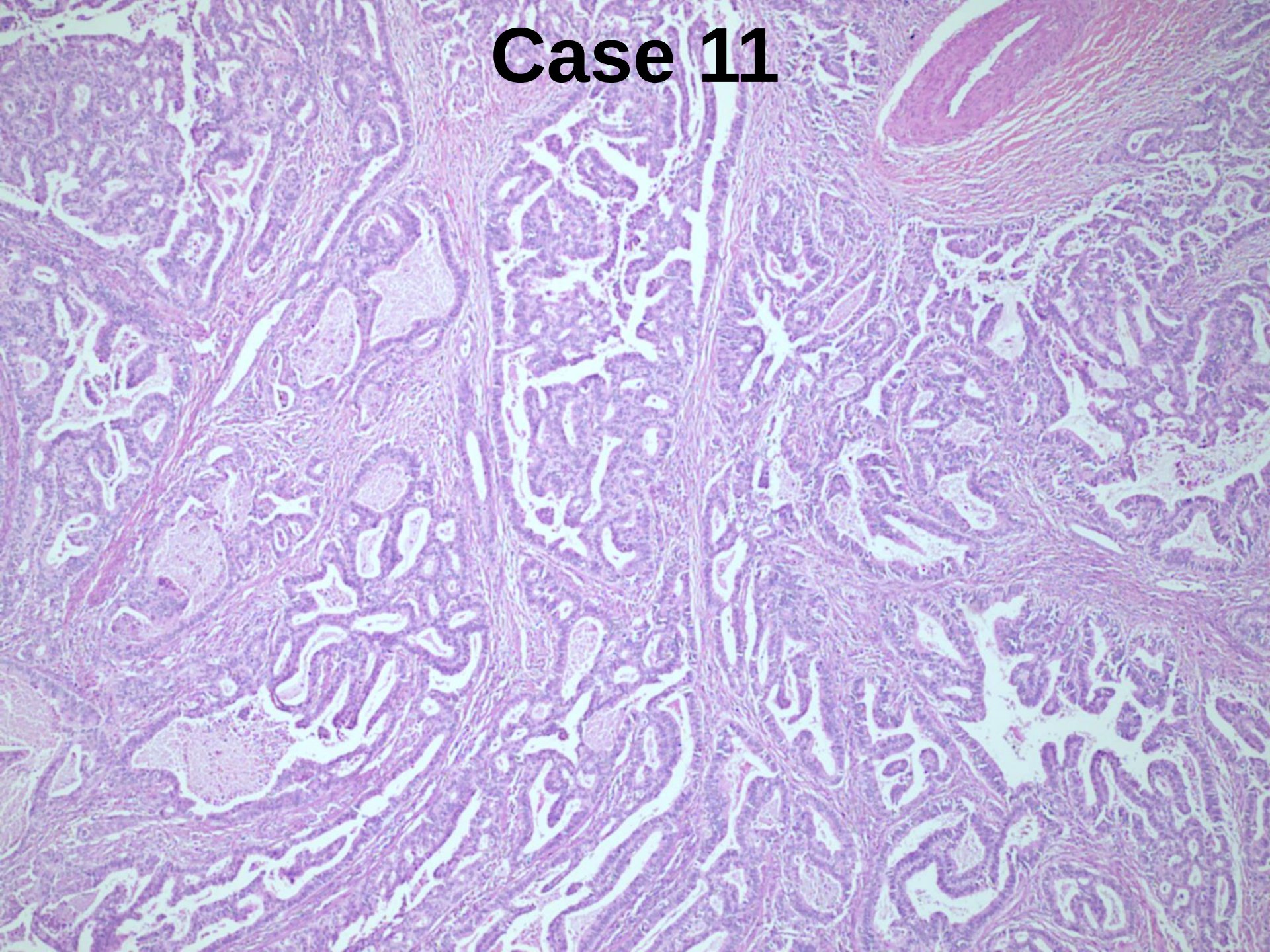


Case 1

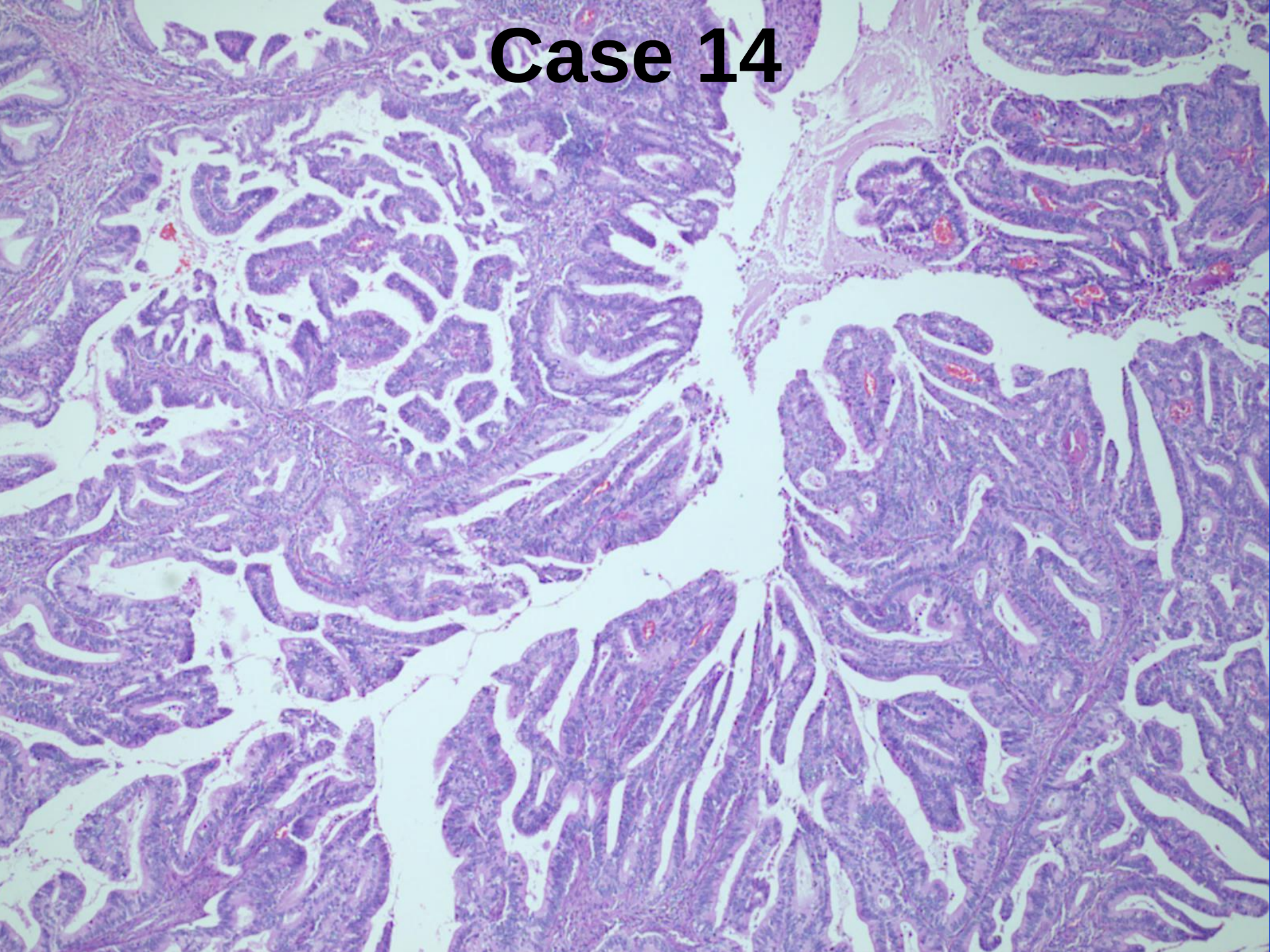




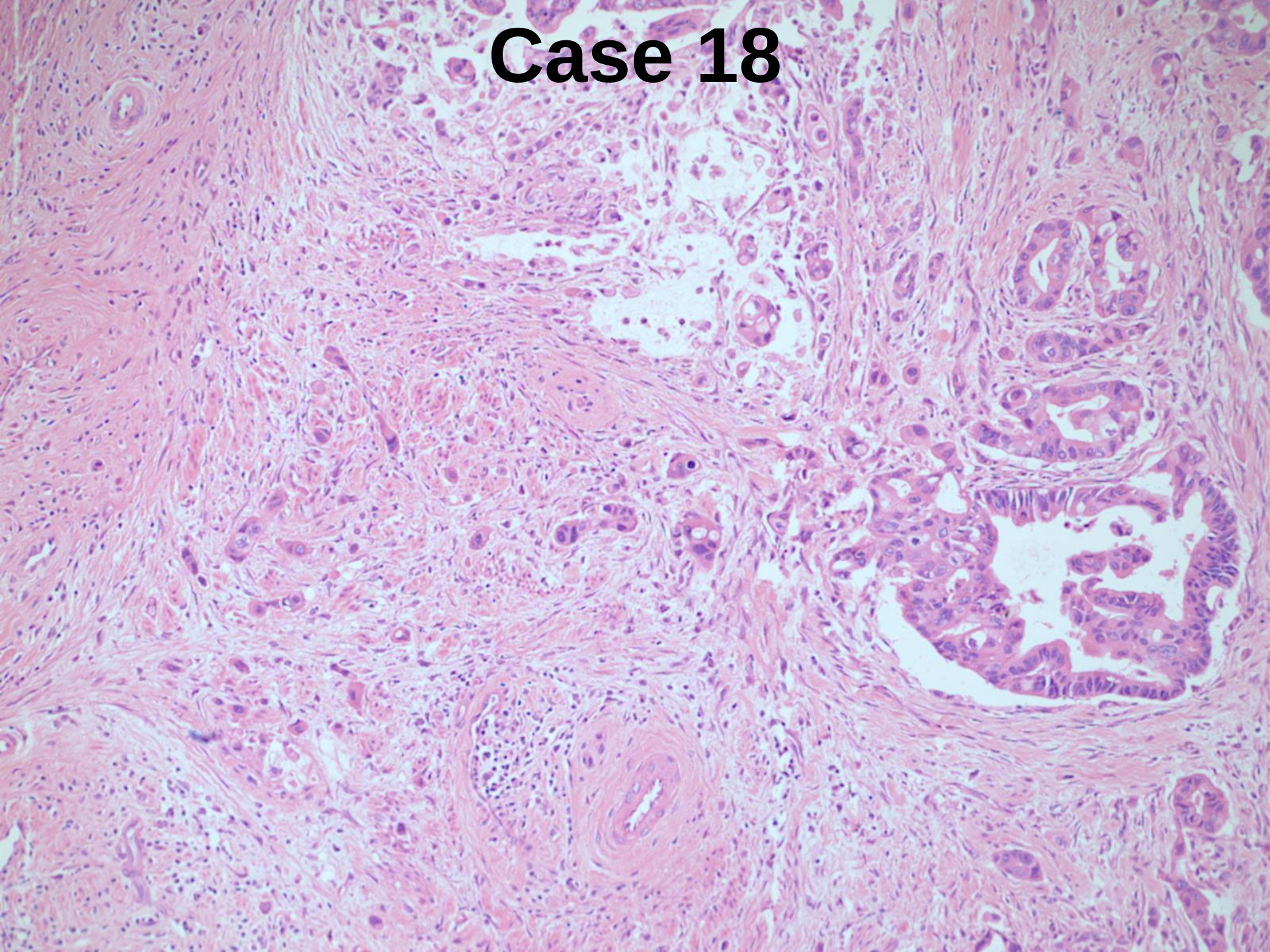
Case 11



Case 14



Case 18



Endocervical AdenoCa Pattern C

180 Pts – 47(26%) had LN mets

Linear destructive (>10x)
Band like lymphocytic infiltrate
Solid

No LN mets

Diffuse destructive
Confluent
Micropapillary

LN mets +

How not to Sign Out These Cases

Endocervical Adeno Ca invasive

Depth of invasion 4mm

Pattern A

How to Sign Out These Cases?

Pattern A

Endocervical AdenoCa without destructive stromal invasion (Pattern A)

Treat. Based on Tumor Pattern

Pattern A ------ Resect entire tumor

Pattern B ------ Resection + Sentinel LN

Pattern C ------ Measure the tumor

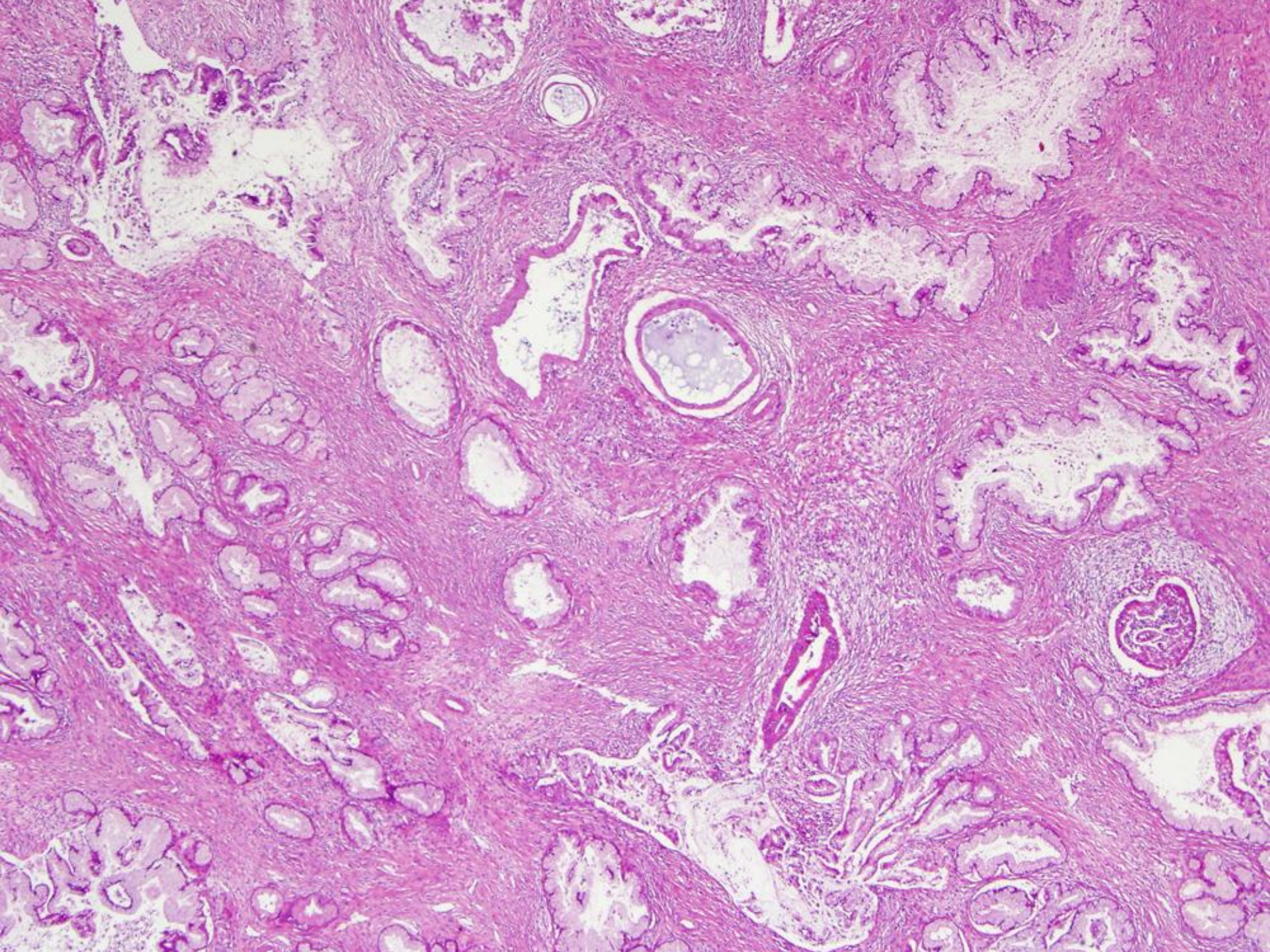
Cervix Cancer Staging

- Stage I A Depth < 3MM AP<7MM
- Stage I B Depth < 5 MM AP < 7 MM

Endocervix Adenocarcinomas Unrelated to HPV

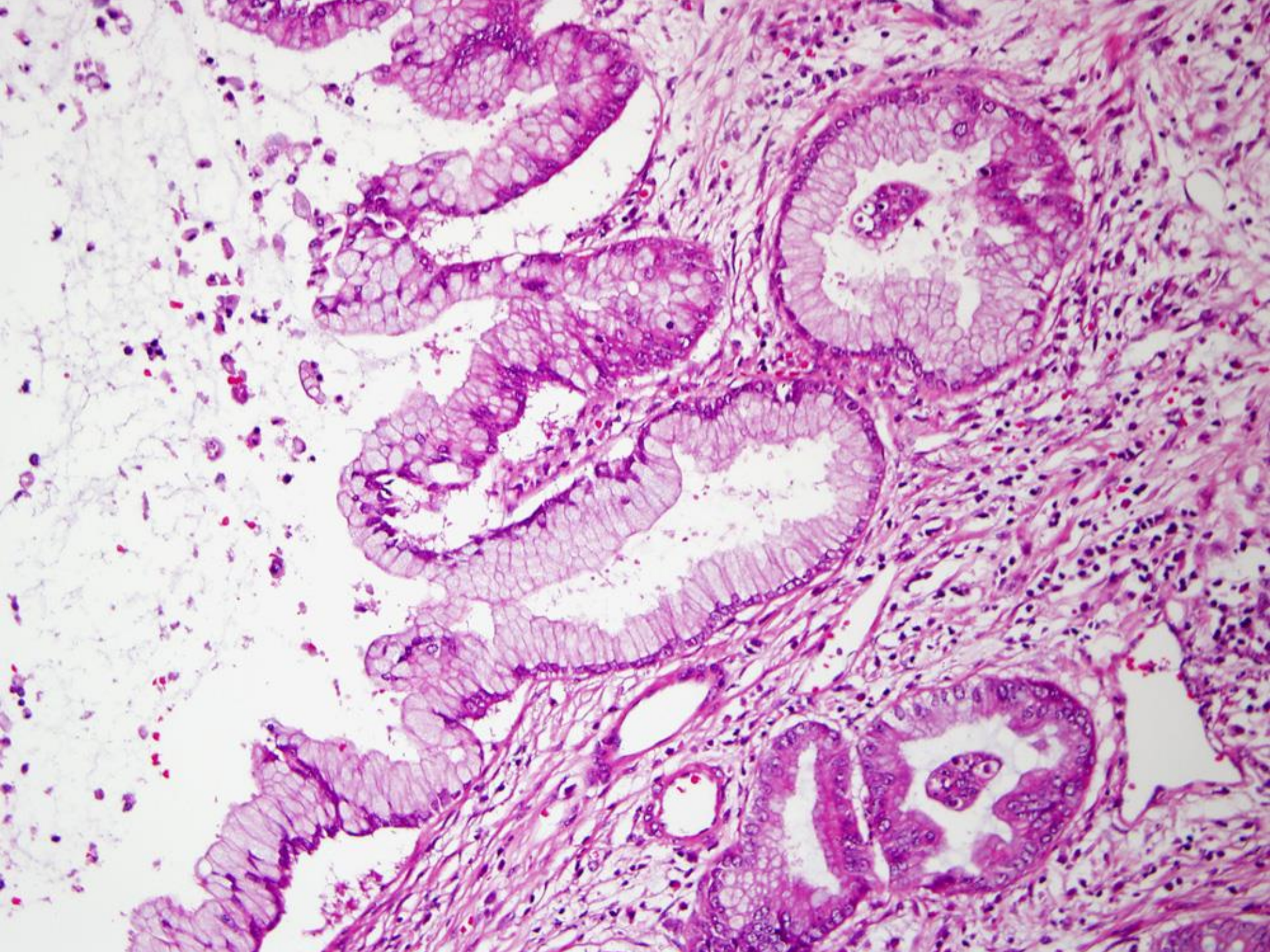
10% of adenocarcinomas

Endometrioid
Gastric type and MDA
Clear cell carcinoma
Serous carcinoma
Mesonephric adenocarcinoma



MDA

"an invasive adenocarcinoma with glands – lined mostly by benign-appearing epithelium but focally by malignant appearing epithelium"



MDA

1. Enlarged Cervix: the diagnosis of MDA start with the clinician

2. Large cervix but the biopsy is not very abnormal

3. Focally obvious adenocarcinoma

MDA

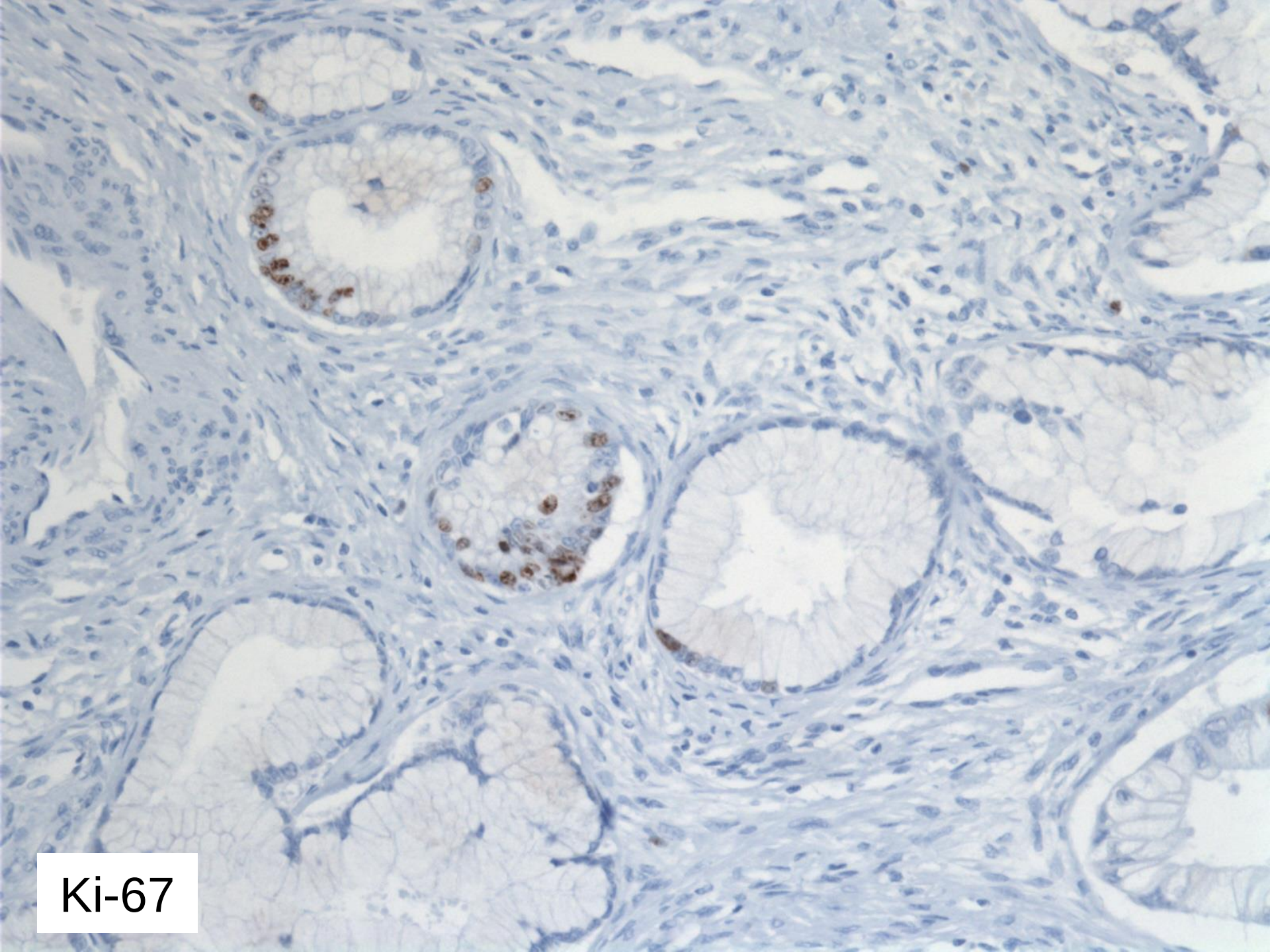
Main Problem: a small biopsy

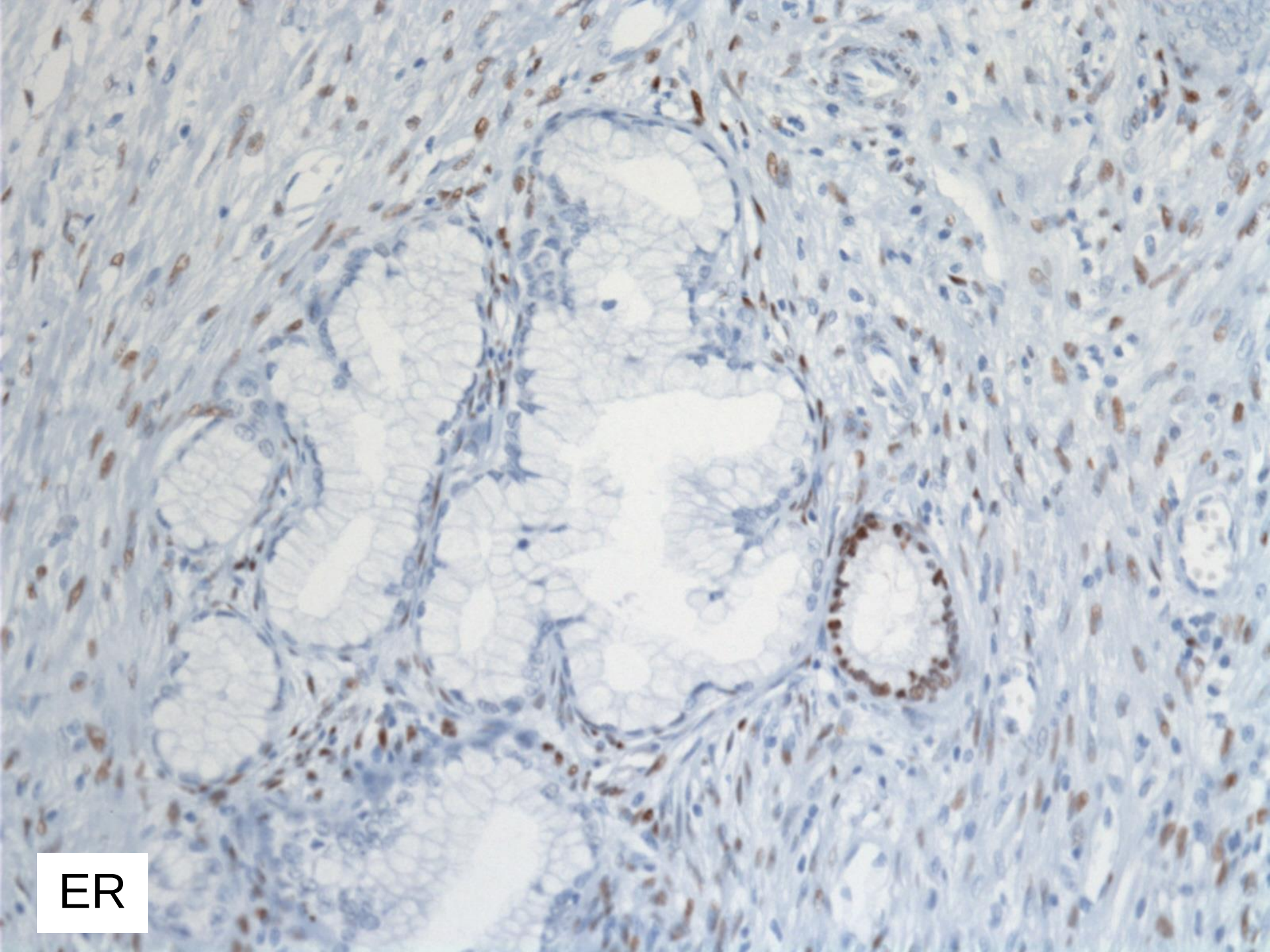
1. Too many glands
2. Glands are disorganized
3. Some do not have mucin and the nuclei are enlarged

IMMUNOS

MDA Immunohistochemistry

	Normal	Reactive	MDA
Ki-67	-	-	++
p53	WT	WT	Aberrant
ER	++++	++++	-


Ki-67

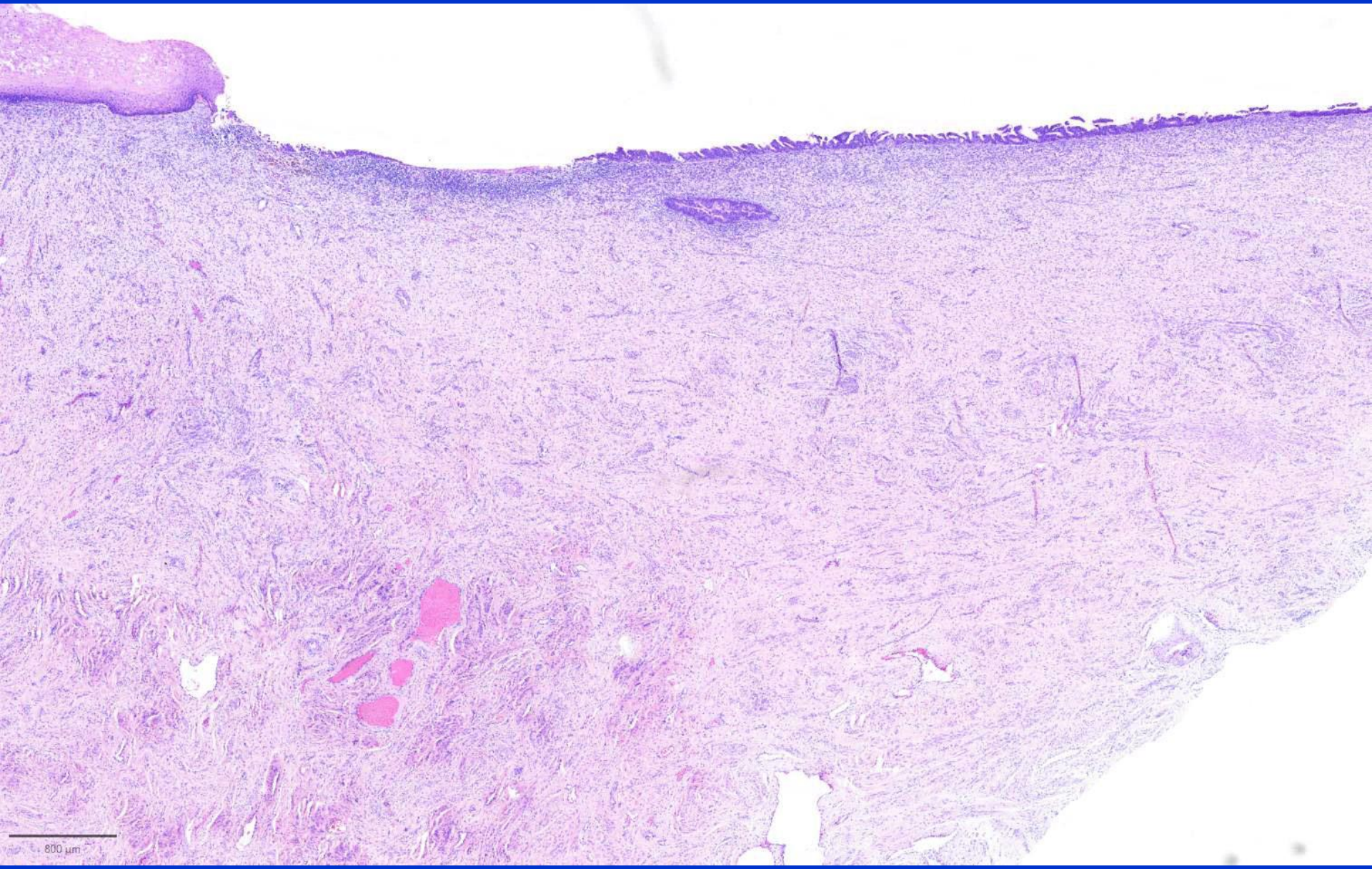

ER

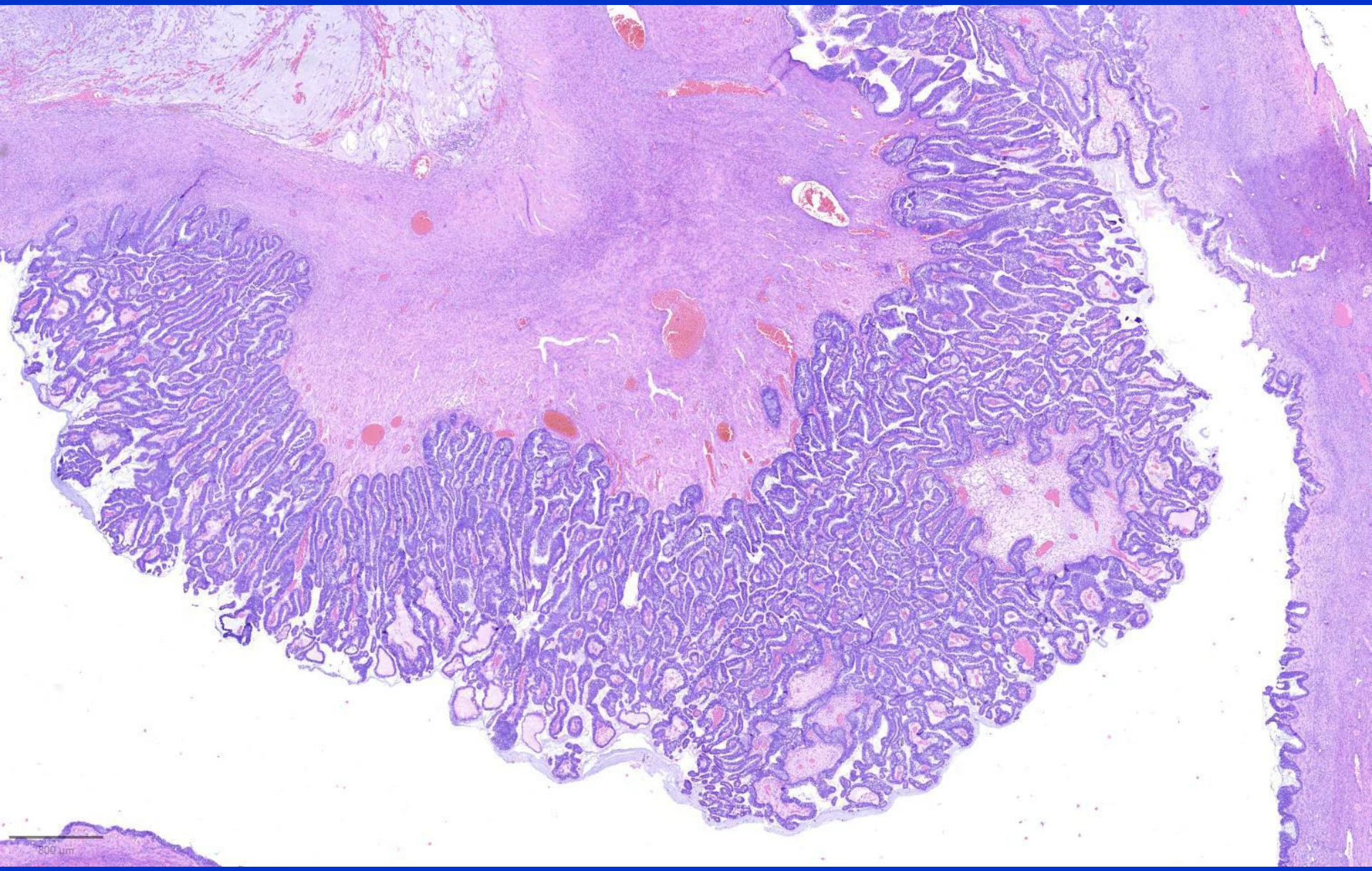
Adenocarcinoma of Cervix

When is the prognosis unrelated to the Pattern System?

Prognosis Unrelated to the Pattern System

- Superficial Ca ---------- Ovarian mets
- Micropapillary Ca
- After a recurrence in vagina


800 µm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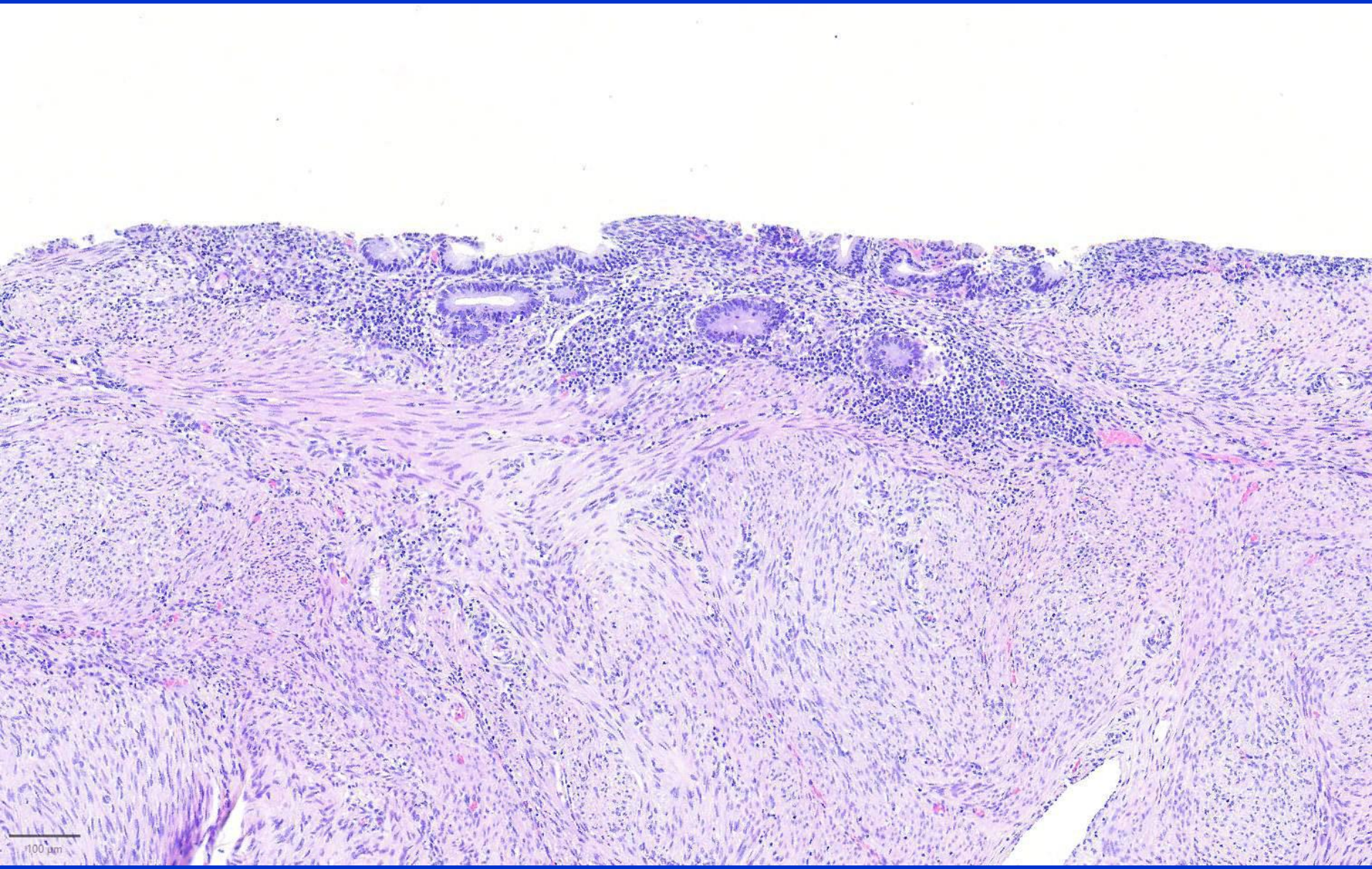
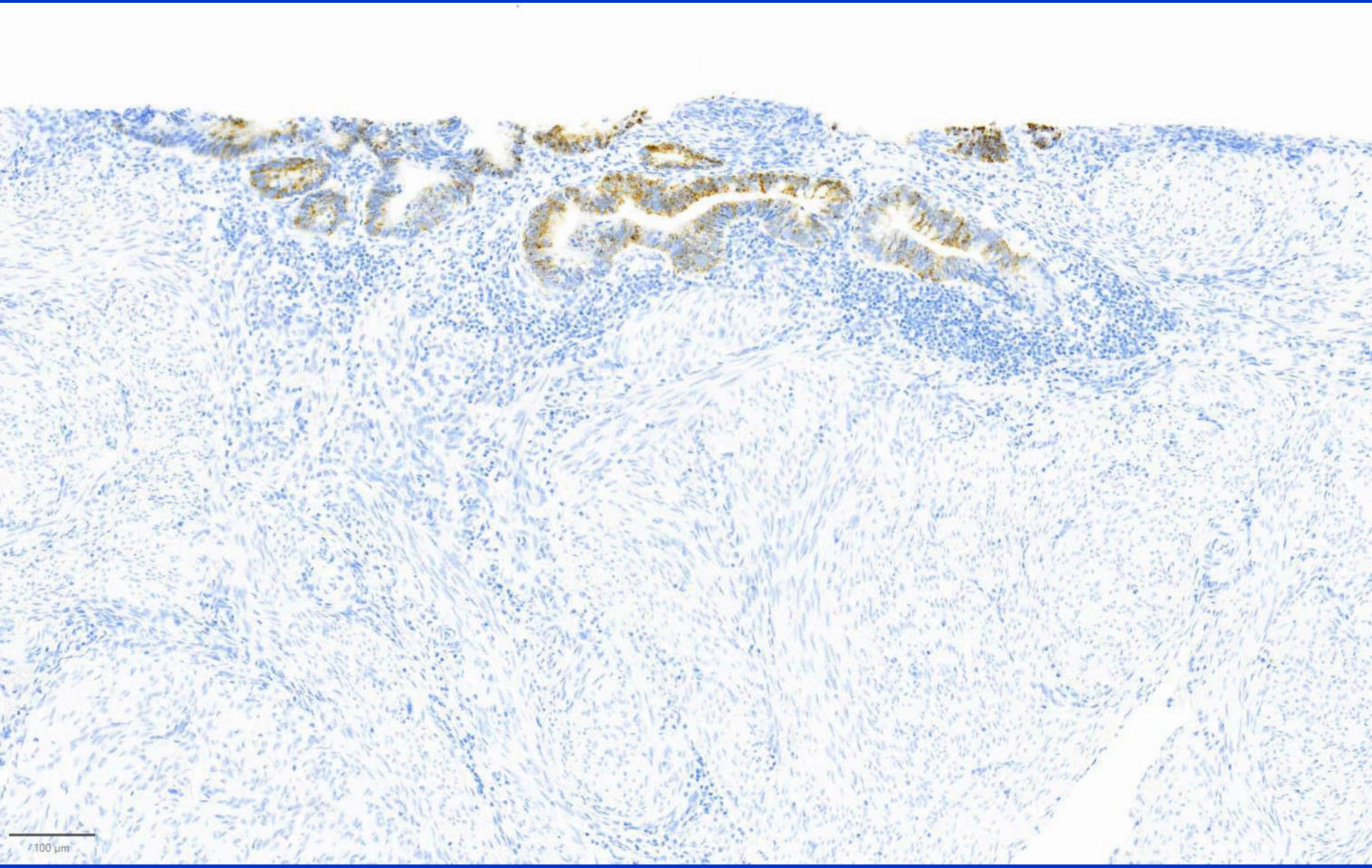

100 µm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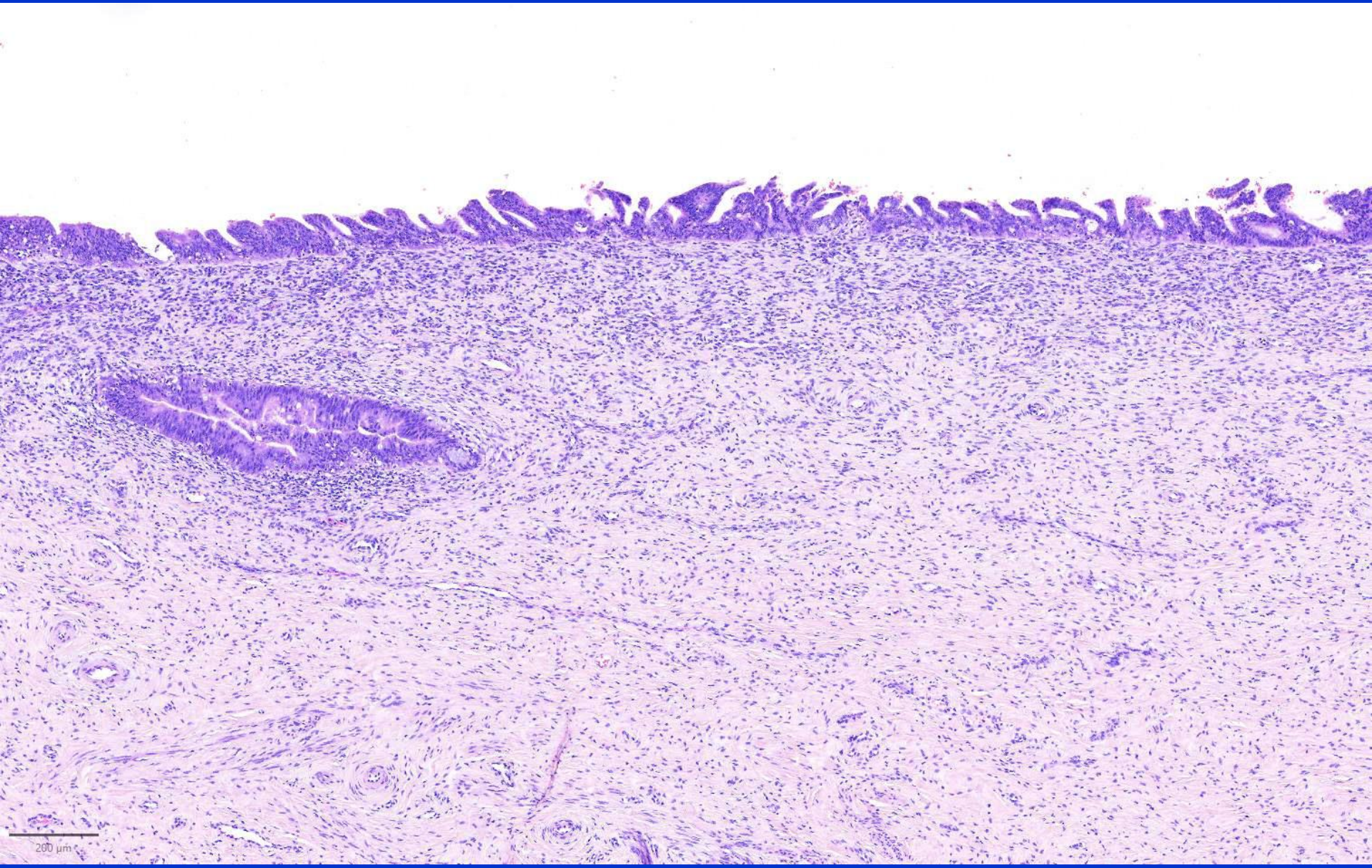
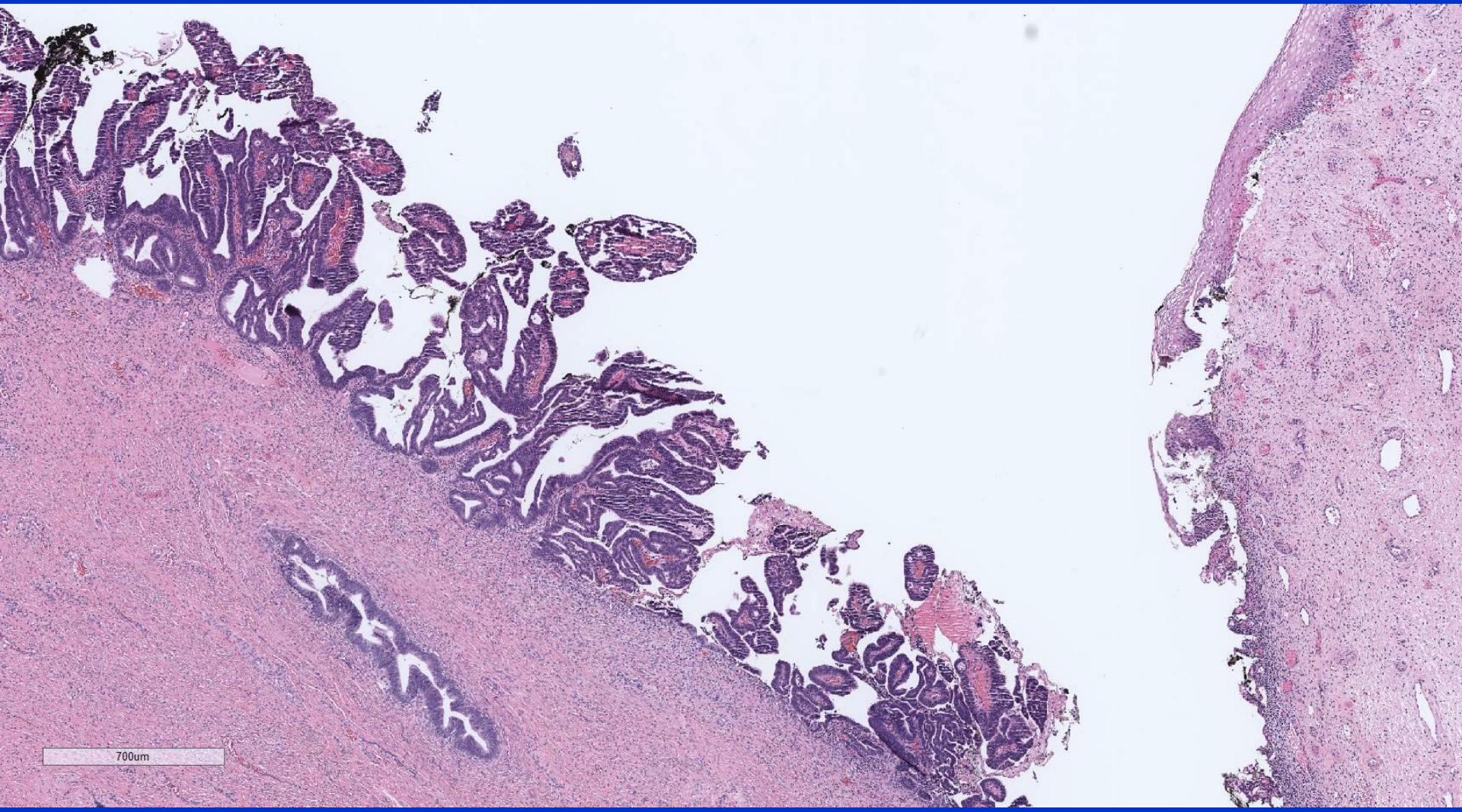
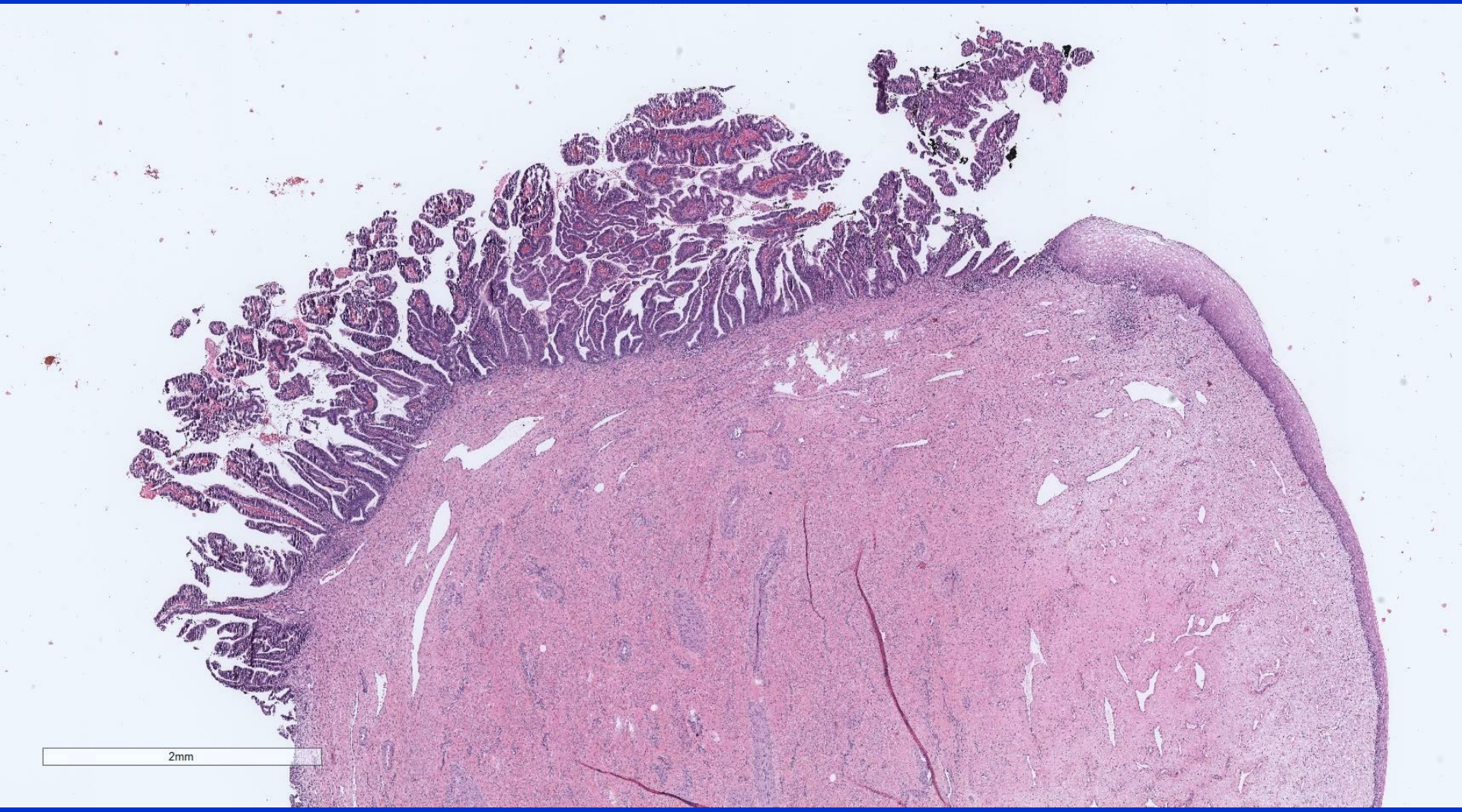
Prognosis Unrelated to the Pattern System

Micropapillary Ca


200 µm


700um


2mm

Prognosis Unrelated to the Pattern System

After a recurrence in vagina

- 35 year-old patient
- Trachelectomy for adenoca. Cx
- Pattern A
- 3 years after: Lung Mets

- 1 year after trachelectomy the carcinoma recurred in vagina

New Techniques
vs
Traditional Pathology

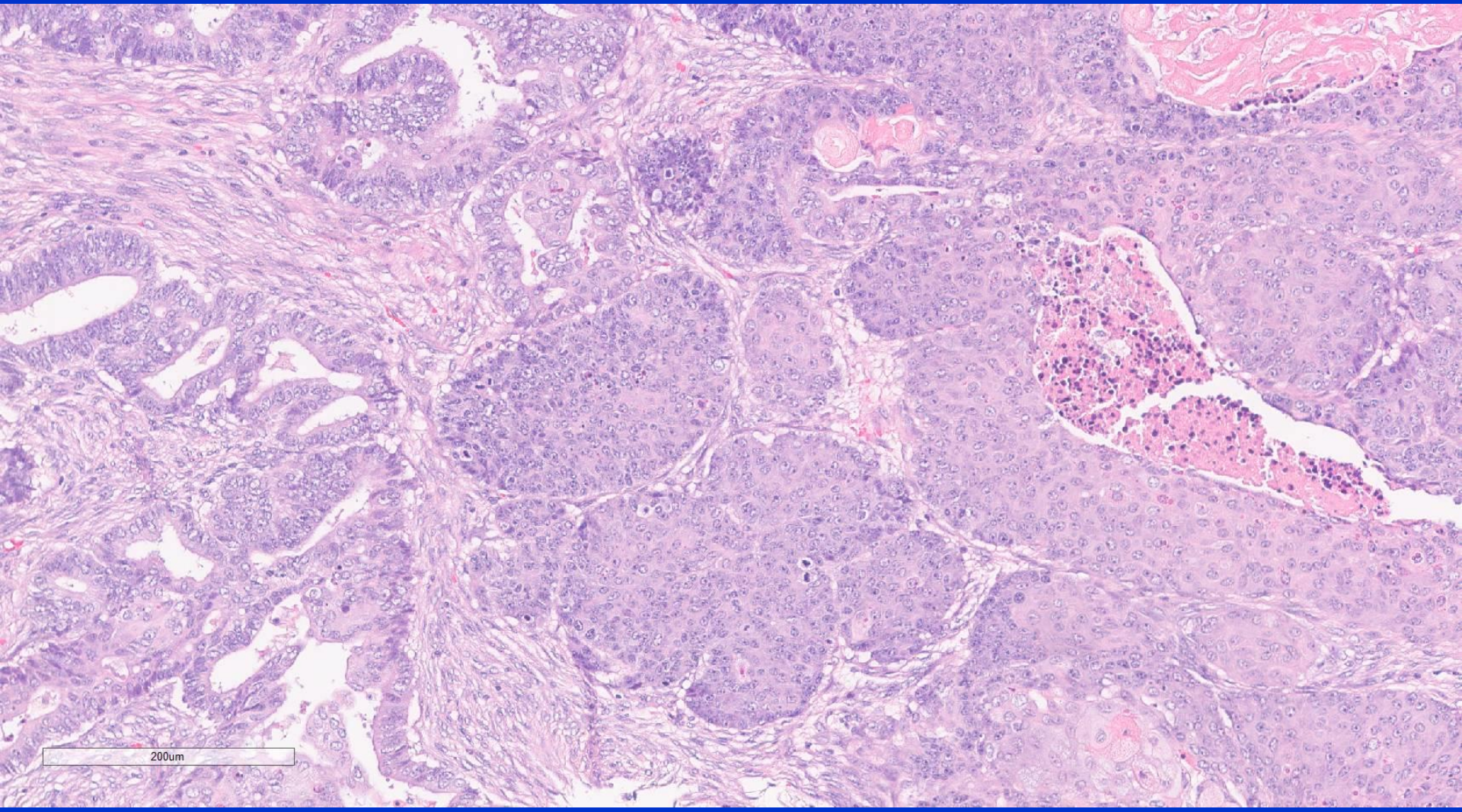
Eminence vs Evidence Based Medicine

Where is Common sense?

Case 1

- 38 years old female
- 2022 Right ovary:
  Endometrioid carcinoma G2

  Endometrium:
  Endometrioid carcinoma G1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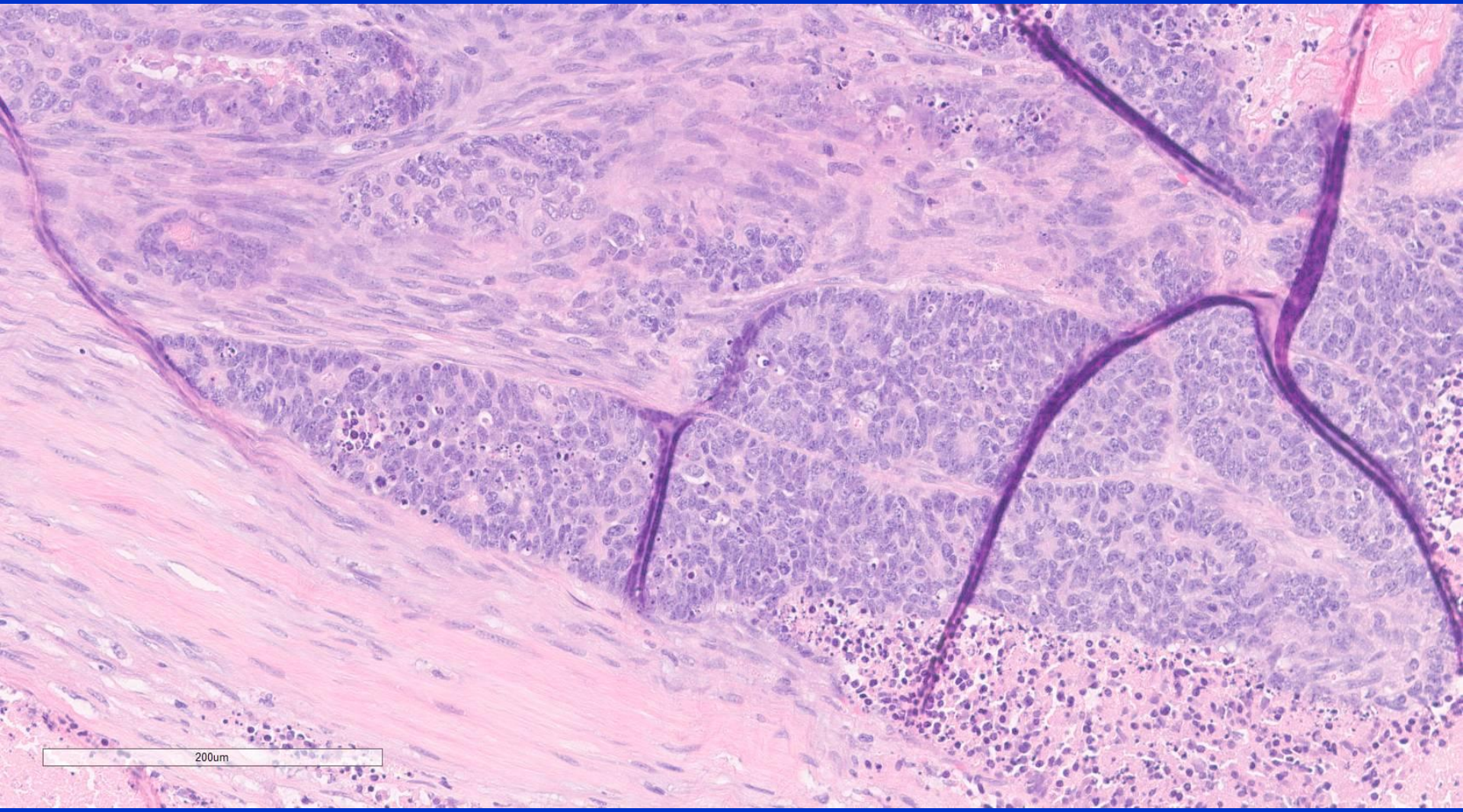
200um

Case 1

Focal small solid area in ovarian tumor

- Immunos
- CK7 +
- Pax 8 +
- BRG1 +
- INI-1 +
- P53 wild pattern

Case 1

- 2022 Diagnosis:
  - Low-grade endometrioid carcinoma
- 2023 Diagnosis:
  - Metastases in lung and brain

Solid Areas in Endometrioid Ca

Cords or glands are present:

Adenoca Grade 2 or 3

Patternless: Undifferentiated Ca

Endometrial Adeno Ca

	5 year survival
Grade 2	90%
Dedifferentiated	25%

International Journal of Gynecological Pathology
25:52–58, Lippincott Williams & Wilkins, Baltimore

Association of Low-Grade Endometrioid Carcinoma of the Uterus and Ovary With Undifferentiated Carcinoma: A New Type of Dedifferentiated Carcinoma?

Elvio G. Silva, M.D., Michael T. Deavers, M.D., Diane C. Bodurka, M.D., and Anais Malpica, M.D.

Summary: Low-grade endometrioid carcinomas, either of the endometrium or the ovaries, usually have an excellent prognosis. The association of this type of tumor with undifferentiated carcinoma is rare. In this study, we present the clinicopathologic features of 25 such cases. The age of the patients ranged from 30 to 82 years (median, 51 years). At presentation, the patients had either vaginal bleeding or pelvic pain. The endometrioid carcinoma involved the endometrium in 14 cases, the endometrium and 1 or both ovaries in 9 cases, and the ovaries in 2 cases. Undifferentiated carcinoma associated with low-grade endometrioid carcinoma was found at presentation in 19 grade 1 or 2 endometrioid carcinomas: 15 in the endometrium and 5 in the ovary. In one of these cases, undifferentiated carcinoma was found in the endometrium and the ovary. Undifferentiated carcinoma was found after resection of low-grade endometrioid carcinoma in six cases, involving the retroperitoneum, pelvis, vagina, or liver. The undifferentiated carcinoma was composed exclusively of diffuse sheets and solid nests of epithelial cells in l0 cases. Epithelial cells with isolated foci of keratinization were seen in nine cases and rhabdoid cells in a myxoid background in six cases. Twenty-four patients were treated with total abdominal hysterectomy and with bilateral salpingo-oophorectomy. Twenty-two patients received additional therapy as follows: chemotherapy (18), radiotherapy (4), and tamoxifen (1). Follow-up showed that 15 patients died of disease in 1 to 60 months (median, 6 months), and 5 patients are alive with progressive disease with a follow-up between 6 and 8 months; 1 patient is alive with no evidence of disease at 104 months. In four cases, the diagnosis was made recently, with short follow-ups of 3 and 4 months. Foci of undifferentiated carcinoma may be confused with solid endometrioid adenocarcinoma erroneously leading to the diagnosis of a grade 3 or a significantly less aggressive grade 2 endometrioid carcinoma. The recognition of undifferentiated carcinoma in an otherwise low-grade endometrioid adenocarcinoma is extremely important because it indicates aggressive behavior. In asynchronous cases, being aware of this association can explain the absence of a second primary. **Key Words:** Undifferentiated carcinoma—Dedifferentiated carcinoma—Endometrioid carcinoma.

The association of low-grade endometrioid carcinoma of the endometrium and ovary with undifferentiated carcinoma has received minimal attention in the literature. Pathology books and extensive reviews on carcinomas of the uterine corpus have only mentioned this association and have even suggested that it probably does not have clinical significance (1,2). In a previous study, we provided the criteria to diagnose undifferentiated carcinoma of the endometrium to separate it from grade 3 endometrioid adenocarcinoma; we determined its frequency and showed the aggressive behavior of this neoplasm in the endometrium, similar to that of serous carcinoma and worse than that of clear cell carcinoma (3). In this study, we review the association of low-grade endometrioid carcinoma with undifferentiated carcinoma. Lack of recognition of this association may prompt erroneous Federation of Gynecology and Obstetrics grading of endometrial and ovarian tumors of the endometrioid type (i.e., grade 1 or 2 endometrioid adenocarcinoma associated with an area of undifferentiated

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DOI: 10.1097/01.pgp.0000183048.22588.18

carcinoma may be erroneously designated as endometrioid adenocarcinoma, either grade 2 or 3, because the solid component can be misinterpreted as an area of solid endometrioid adenocarcinoma). In addition, based on the histologic changes seen in the recurrences of two cases, we suggest that the presence of undifferentiated carcinoma in this situation may be secondary to a process of dedifferentiation.

MATERIALS AND METHODS

Thirty-four cases of undifferentiated carcinoma associated with low-grade endometrioid adenocarcinoma were found during reviews of undifferentiated carcinoma of the endometrium (10 cases) and endometrioid adenocarcinoma (15 cases) and from personal consults (9 cases).

Endometrioid adenocarcinomas associated with solid areas of spindled cells were not included in this study. In 9 cases, the clinical information or pathology material was incomplete. The remaining 25 cases are the basis of this study.

Grades 1 and 2 endometrioid adenocarcinomas are neoplasms with 5% or less and 6 to 50% of solid areas, respectively. The cells in the solid areas are similar to the cells in the glandular areas, and they form well-demarcated groups and cords. In this study, we used the same definition of undifferentiated carcinoma that we used in a previous study on this subject: a malignant epithelial neoplasm arising in the endometrium or ovary characterized by a total absence of glandular differentiation and a patternless solid growth of tumor cells, with absence or minimal neuroendocrine differentiation (3).

Five to 57 hematoxylin and eosin–stained slides per case (mean, 17 slides/case) were reviewed. Immunoperoxidase studies using the avidin-biotin method were performed in 15 cases in which tissue blocks were available. The following markers were used: Pan Keratin cocktail, epithelial membrane antigen (EMA) (E29, 1:20; Dako, Carpinteria, CA), synaptophysin (Syn-88, 1:75; Biogenex, San Ramon, CA), and chromogranin A (1:4000; Chemicon, Temecula, CA). The Pan Keratin cocktail contains five different keratins including AE1/AE3 (1:500); Cam 5.2 (1:50, Becton Dickinson, San Jose, CA); cytokeratin MNF116 (1:50; Dako), and keratin 8 and 18 (1:25; Zymed, South San Francisco, CA).

Clinical information was obtained from the patients' charts. Institutional Review Board approval was obtained before the initiation of this study.

RESULTS

The clinicopathologic features of the cases are summarized in Table 1. The age of the patients ranged from 30 to 82 years (median, 51 years). Twenty-three patients presented because of vaginal bleeding and two because of pelvic pain. Twenty-three of the patients had endometrioid adenocarcinoma of the endometrium and nine of these patients also had an endometrioid adenocarcinoma of the ovary, which were considered independent primaries because of some histologic differences between both adenocarcinomas, lack of deep invasion of the myometrium, and lack of surface involvement of the ovarian surface. The stages of the cases with endometrial carcinoma was as follows: 14 stage I, 1 stage II, 6 stage III, and 4 stage IV. The stages of the ovarian carcinoma cases was as follows: 10 stage I, 1 stage II

The endometrioid
trium was FIGO gra
patients. The endom
was grade 1 in six p

Of the 14 patient
carcinoma of the en
trial invasion, 7 ha
one-half of the myo
of more than one-ha

Undifferentiated c
at presentation in 1
admixed with areas
FIGO grade 1 (3 c
(Fig. 1A and B). U
the ovary at present
with endometrioid a
grade 1 (two cases) a
In one patient, the u
both the ovary and
Table 2 shows th
carcinoma in the
adenocarcinoma. In
noma was found
adenocarcinomas in
trium in five cases
(Fig. 3A–D). The in
uterine or ovarian en
development of the
from 7 to 168 mon
entiated carcinoma involved the pelvis in three cases and the vagina, abdomen, retroperitoneum, and liver in one case each. In two of these six cases, the undifferentiated carcinoma developed after the low-grade endometrioid adenocarcinoma transformed into a high-grade endometrioid adenocarcinoma. In case 1, after 7 months, a grade 2 endometrioid adenocarcinoma recurred as a grade 3 adenocarcinoma, and after 6 months, an undifferentiated adenocarcinoma was found. In case 25, a grade 1

Grades 1 and 2 endometrioid adenocarcinomas are neoplasms with 5% or less and 6 to 50% of solid areas, respectively. The cells in the solid areas are similar to the cells in the glandular areas, and they form well-demarcated groups and cords. In this study, we used the same definition of undifferentiated carcinoma that we used in a previous study on this subject: a malignant epithelial neoplasm arising in the endometrium or ovary characterized by a total absence of glandular differentiation and a patternless solid growth of tumor cells, with absence or minimal neuroendocrine differentiation (3).

International Journal of Gynecological Pathology
35:410–418, Lippincott Williams & Wilkins, Baltimore

Original Article

Undifferentiated Carcinoma of the Endometrium: An Expanded Immunohistochemical Analysis Including PAX-8 and Basal-Like Carcinoma Surrogate Markers

Preetha Ramalingam, M.D., Ramya P. Masand, M.D., Elizabeth D. Euscher, M.D., and Anais Malpica, M.D.

Summary: Undifferentiated carcinoma of the endometrium (UCAe) is an aggressive, underrecognized high-grade carcinoma that can occur either in pure form or in conjunction with low-grade endometrioid adenocarcinoma (i.e. dedifferentiated carcinoma). The typical solid growth pattern of UCAe can create a diagnostic dilemma as it is frequently misinterpreted as the solid component of an endometrial carcinoma or as a sarcoma. In addition, the high nuclear:cytoplasmic ratio, high mitotic index, and geographic necrosis are reminiscent of basal-like carcinoma of breast (BLCB). This study was undertaken to determine the role of a selected group of immunomarkers in the distinction of UCAe from other endometrial carcinomas, and assess the expression of DNA mismatch repair proteins, and surrogate BLCB immunomarkers in this type of tumor. Cases of UCAe were stained with antibodies against keratin cocktail, CK8/18, PAX-8, and estrogen receptor: 35 cases; progesterone receptor and Her-2/neu: 33 cases; CD44, e-cadherin, p16, and p53: 32 cases; and CK5/6, EGFR, and c-Kit: 18 cases. In addition, mismatch repair protein markers MLH1, MSH2, MSH6, and PMS2 were performed in 34 cases. We found that PAX-8 expression was lost in most cases (83%). In addition, estrogen and progesterone receptors were negative in 83% and 82% of cases, respectively. Seventy-seven percent of cases were positive for keratin cocktail and keratin 8/18, whereas only 11% of cases were positive for keratin 5/6. p16 was diffusely positive in 34% of cases, whereas p53 was expressed in >75% of the tumor cells in 31% of cases. MLH1 and PMS2 were concurrently lost in 50% of cases, whereas MSH2 and MSH6 were lost in 1 case (3%). E-cadherin and CD44 were completely lost in 50% of cases, whereas Her-2/neu was negative in all cases. EGFR was negative in 67% of cases, whereas 22% of cases showed diffuse membranous staining for this marker. UCAe is a high-grade carcinoma of Müllerian origin which tends to be negative for PAX-8. The loss of this marker appears to be a more reliable discriminator than the loss of keratin expression in the differential diagnosis with endometrioid carcinoma or serous carcinoma. UCAe tends to be diffusely positive for p53, but patchy positive for p16. Although UCAe appears to share not only some histologic features with BLCB, but also some of its immunohistochemical features (loss of estrogen receptor, progesterone receptor, and Her-2/neu, a tendency to loose e-cadherin and to express CD44), UCAe appears not to be related to BLCB because it usually lacks the expression EGFR, CK5/6, and c-Kit. **Key Words:** Undifferentiated carcinoma—Endometrium—Carcinoma—PAX-8—Microsatellite instability—Hormone receptors—Immunohistochemistry—Basal-like carcinoma.

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The authors declare no conflict of interest.
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Endometrial Ca

Endometrioid G3	Undifferentiated
ER +	Could be neg
PAX8 +	Could be neg
Keratin Cocktail +	Could be neg
Keratin 8/18 +	Frequently +
EMA +	Frequently +

Experience

If you were wrong the first time

You will repeat the mistake

Increasing confidence

Eminence vs Evidence

Blind Authority

Driven by EGO

EGO Definitions

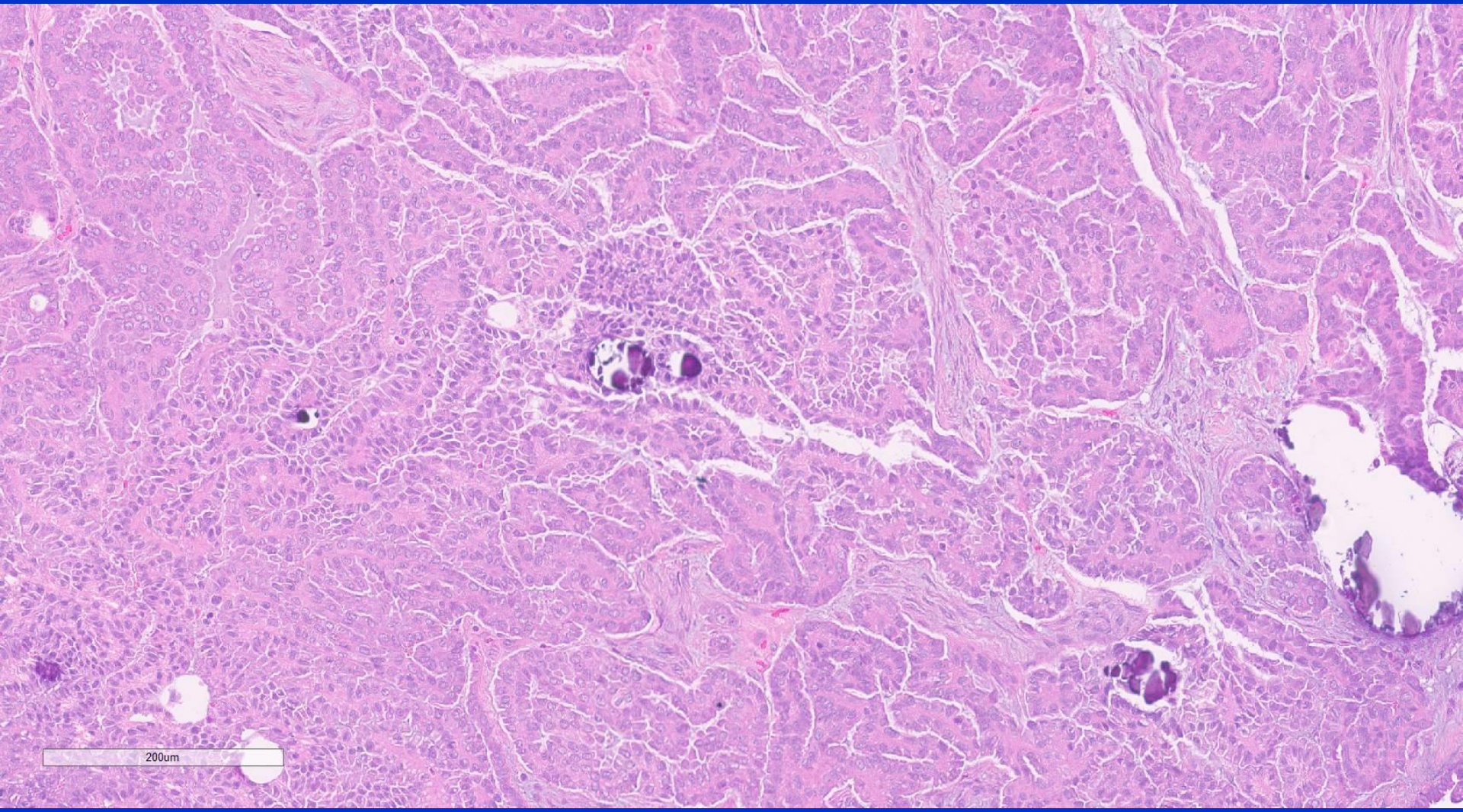
$$EGO = \frac{1}{Knowledge}$$

The small Argentinian we all have inside

Case 2

43 year-old female

Resection of a pelvic mass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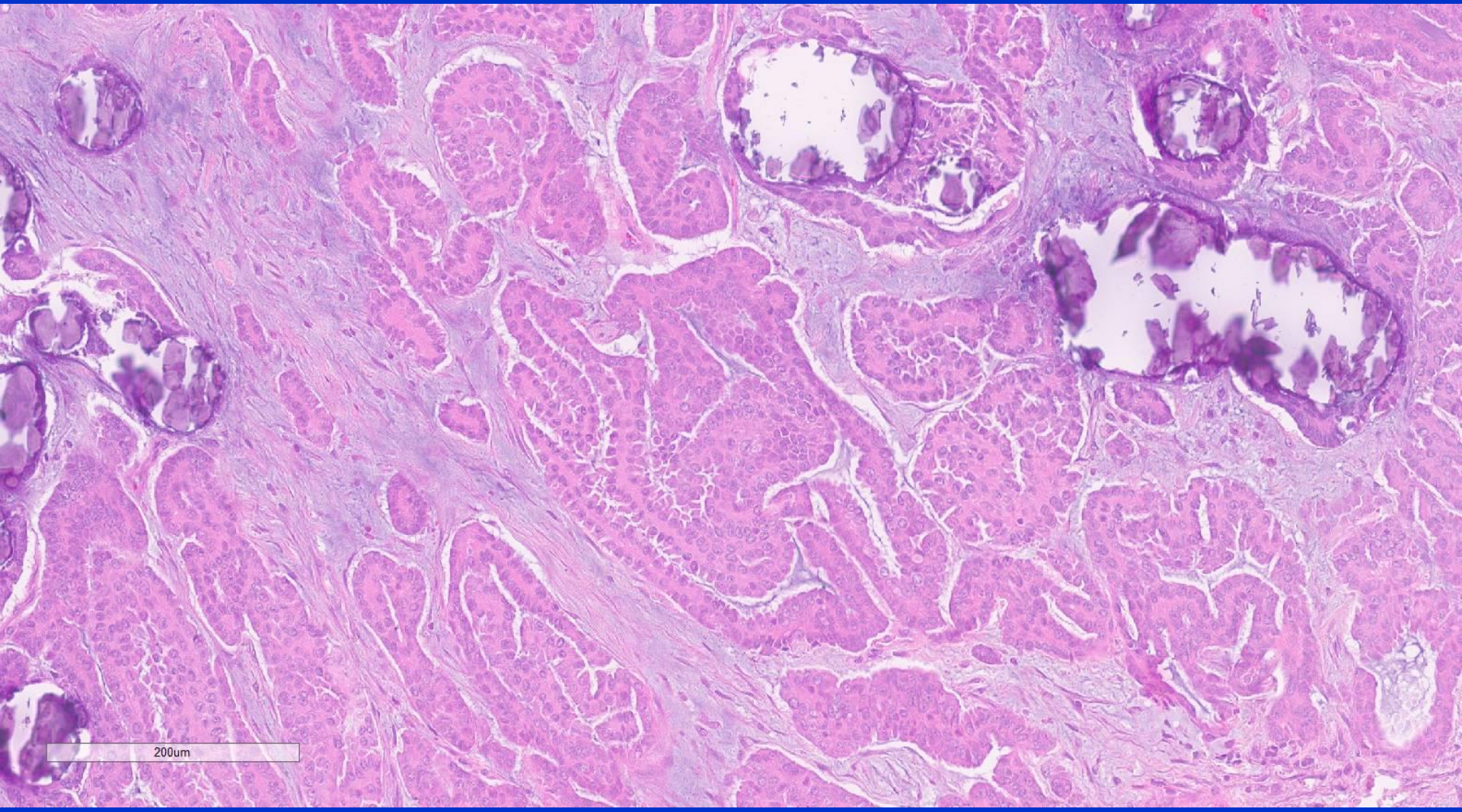
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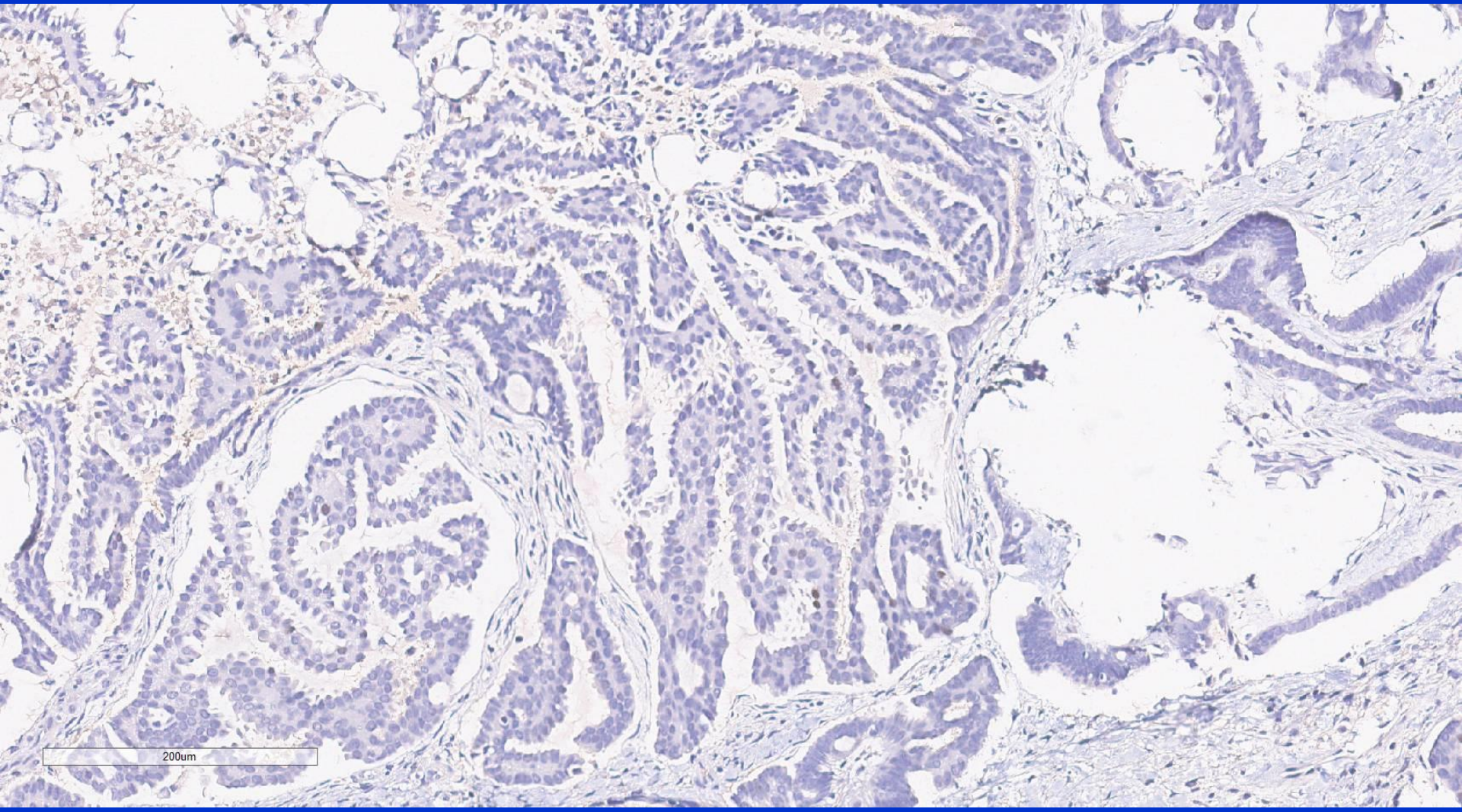
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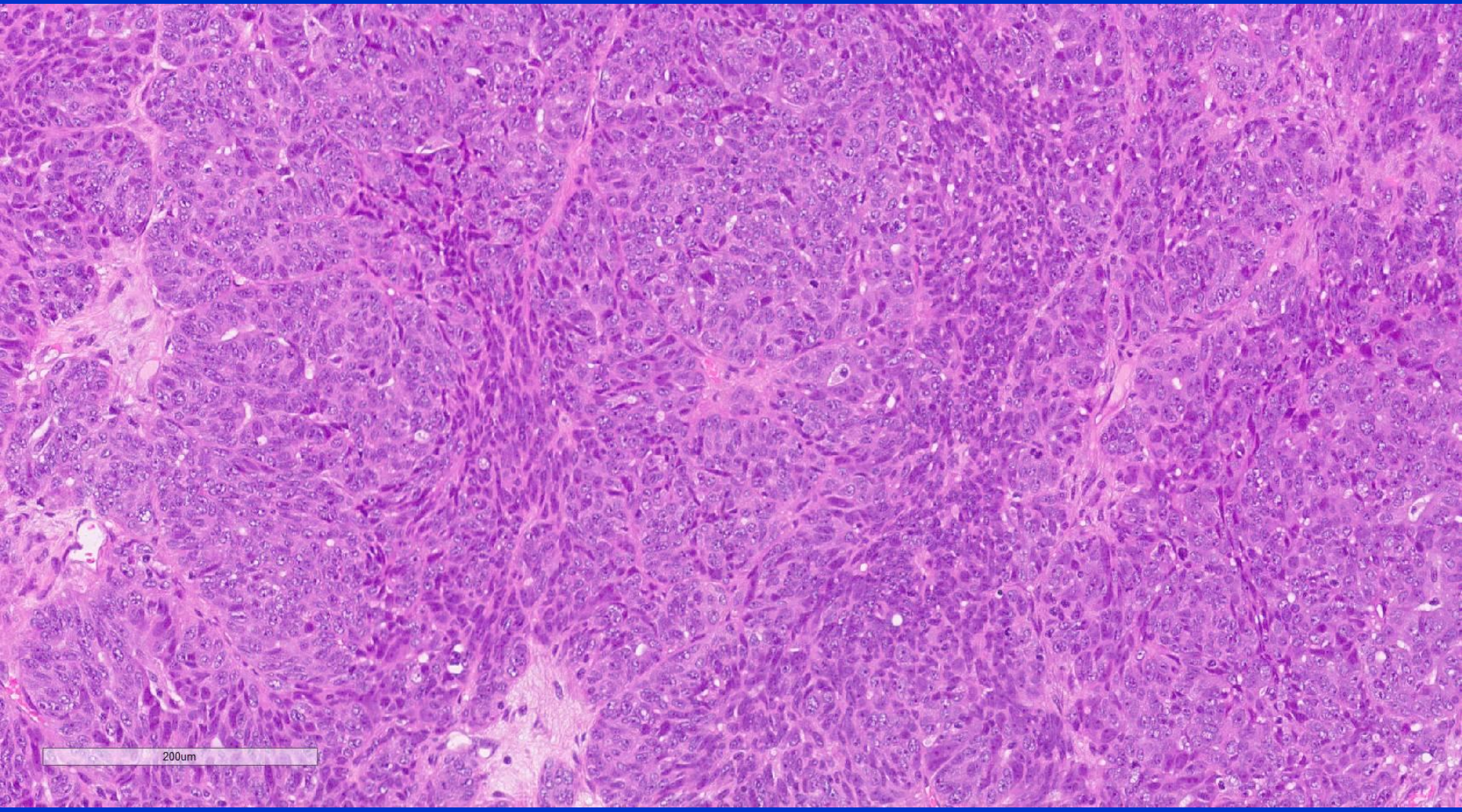
Case 3

57 year-old female

Cystic and solid ovarian mass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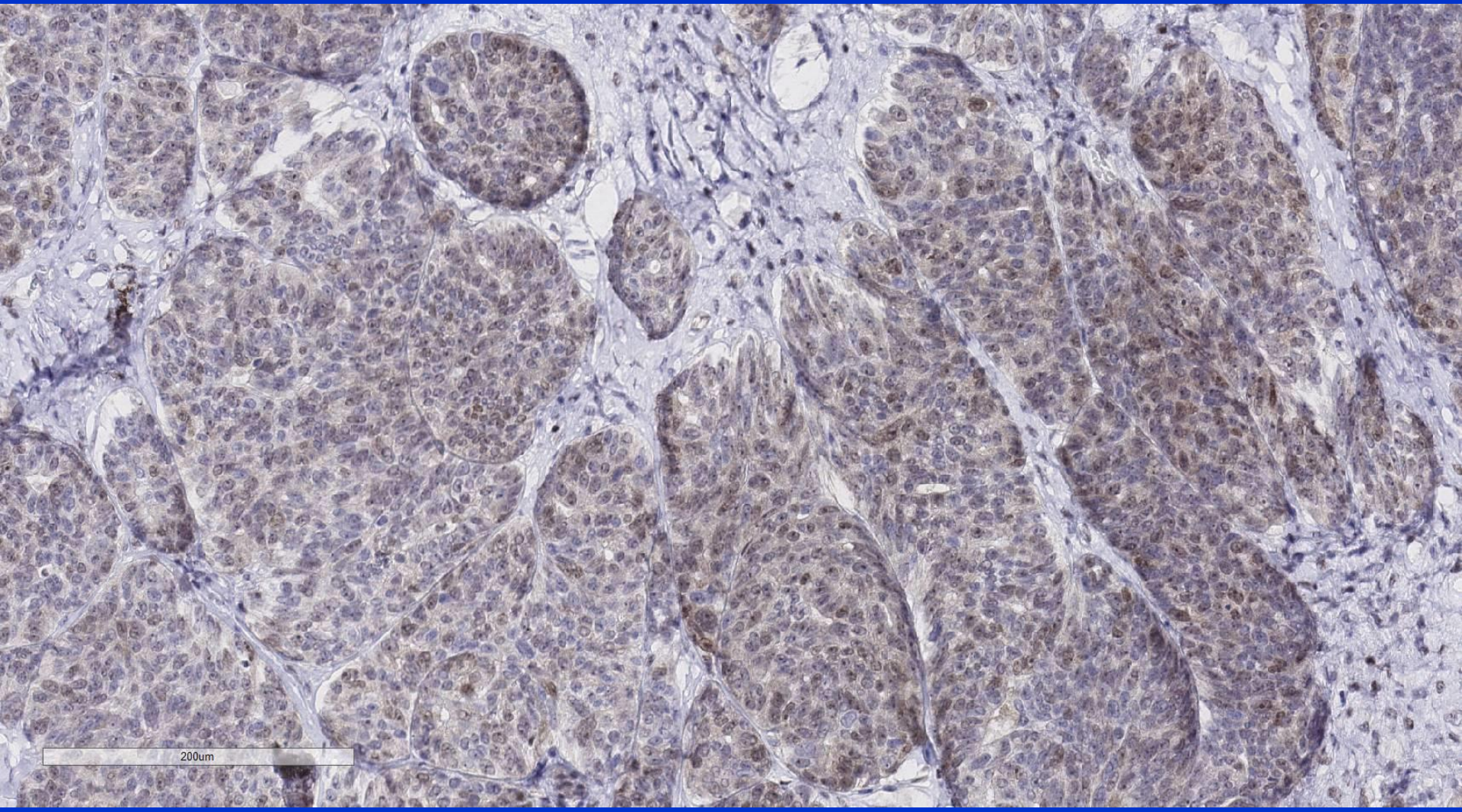
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High Grade Ovarian Serous Ca

p53 Immunohistochemistry

Overexpression -----	66%
Null ----------	25%
Cytoplasmic ----------	4%
Wild type ----------	5%

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Uterine papillary serous carcinoma

A highly malignant form of endometrial adenocarcinoma*

ABSTRACT A review of 256 cases of pathologic Stage I uterine adenocarcinoma treated at Stanford University Hospital revealed 26 cases of uterine papillary serous carcinoma (UPSC), a clinically aggressive and morphologically distinct variant of adenocarcinoma which closely resembles ovarian papillary serous carcinoma. These lesions are easily recognized by microscopic examination and typically feature a high degree of cytologic anaplasia and a papillary growth pattern. Invasion of the lymphatics has been a frequent finding. The relapse rate among patients with pathologic Stage I UPSC was 50% (13/26), five times the rate which would have been predicted by the incidence of UPSC. Patients with Stage I UPSC fared significantly worse than the group of nonpapillary grade II or grade III adenocarcinomas (p <0.0001). Forty percent of Stage I UPSC patients had deep myometrial invasion, as compard with 12% of those with all other histologic types of adenocarcinoma (p = 0.001). Women with UPSC deeply invading the myometrium tended to do worse than those with deeply invasive lesions of the more usual endometrioid type as reflected by relapse rates (after surgery alone) of 63% and 30%, respectively. Of seven Stage I corpus carcinoma patients whose initial site of failure was in the upper abdomen, six had UPSC. Thus, UPSC shares the tendency of its ovarian counterpart to spread over peritoneal surfaces. In addition to the original study group of 26 Stage I patients, 34 patients with more advanced stages of UPSC were also reviewed. Of these, 26 have been followed and four survive. Eleven of these women presented or relapsed with abdominal carcinomatosis. UPSC is a clinically aggressive neoplasm which should be distinguished from other types of primary endometrial adenocarcinoma. In cases of invasive UPSC the mode of spread, similar to that of ovarian surface epithelial carcinomas, suggests the need for adjuvant upper abdominal and pelvic irradiation or effective chemotherapy.

Am J Surg Pathol 6: 93–108, 1982.

INTRODUCTION

It has long been known that endometrial carcinoma comprises a morphologically heterogeneous group. The different histologic patterns encountered include not only carcinomas composed of glands resembling endometrium (endometrioid carcinomas), but also differentiated epithelial neoplasms that more frequently arise in other components of what Lauchlan[18] has termed the extended müllerian system. This embryologically related organ system consists of the müllerian duct derivatives (upper vagina, cervix, uterine corpus, and fallopian tubes) and the ovarian surface mesothelium. Thus, primary uterine corpus carcinoma may have morphologic features identical to those of mucinous carcinoma of the ovary or endocervix, clear cell carcinomas of the vagina and ovary, or squamous carcinomas of the cervix. Mixtures of these "special variants," with or without typical "endometrioid" adenocarcinoma, are also encountered frequently in the endometrium.

Our interest in these "special variant" carcinomas of the uterine corpus was heightened by the results of a recently completed review of all Stage I endometrial carcinomas diagnosed at Stanford University Hospital during the period 1959–1975. This paper details the clinicopathologic features of a highly aggressive variant of uterine adenocarci-

* Presented at the International Academy of Pathology meetings in Chicago, Illinois, March 2, 1981.

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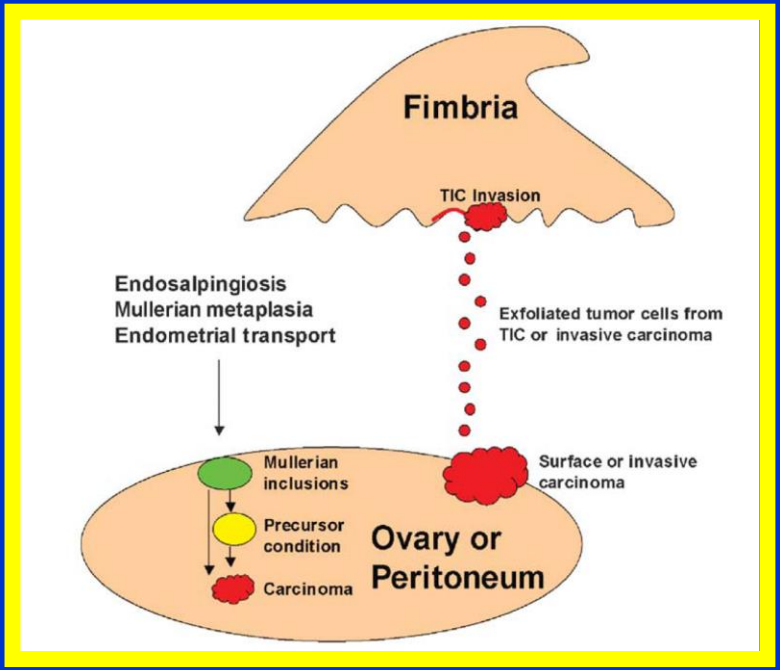
Origin of Pelvic Serous Tumors

Ovary

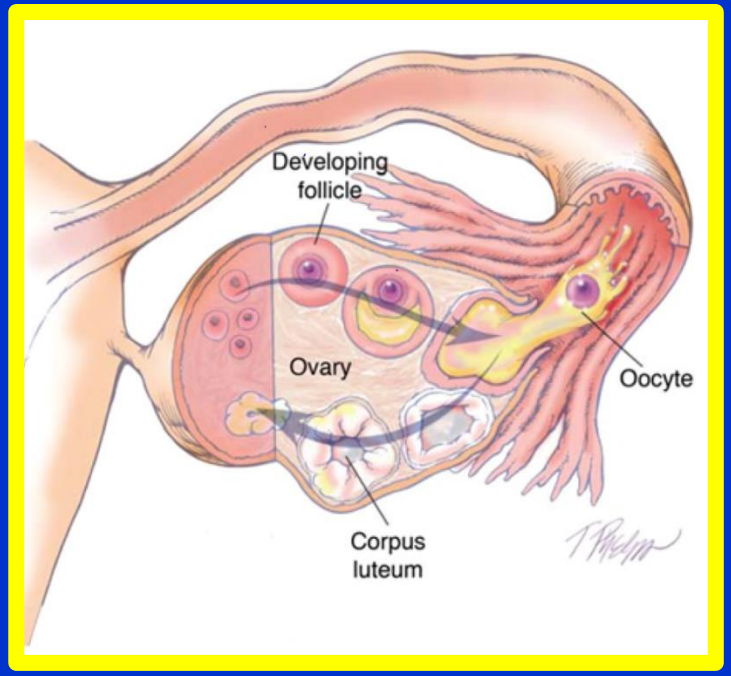
vs

Fallopian tube

2006



C. Crum



R. Kurman

Never Believe Theories

Based on Diagrams

Evidence for a Dualistic Model of High-grade Serous Carcinoma

BRCA Mutation Status, Histology, and Tubal Intraepithelial Carcinoma

Brooke E. Howitt, MD, Suchanan Hanamornroongruang, MD,† Douglas I. Lin, MD, PhD,* James E. Conner, MD, PhD,* Stephanie Schulte, MD, PhD,* Neil Horowitz, MD,‡§ Christopher P. Crum, MD,* and Emily E. Meserve, MD, MPH**

Abstract: Most early adnexal carcinomas detected in asymptomatic women with germline *BRCA* mutations (*BRCA*$^+$) present as serous tubal intraepithelial carcinomas (STIC). However, STICs are found in only ~40% of symptomatic high-grade serous carcinomas (HGSCs) and less frequently in pseudoendometrioid variants of HGSC. Consecutive cases of untreated HGSC from *BRCA*$^+$ and *BRCA*$^-$ women with detailed fallo- need for further study of HGSC precursors to determine their relevance to the prevention of this lethal malignancy.

Key Words: fallopian tube, neoplasia, serous carcinoma, BRCA, endometrioid, tubal intraepithelial carcinoma, risk-reduction salpingo-oophorectomy

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Serous Ca of the Ovary

IS NOT FROM THE FALLOPIAN TUBE

60% OF HGSCa do not have STIC

Dr. C. Crum

Fallopian Tube Origin

Clonality

Clonality

Started in the 70's with two goals

Neoplastic (monoclonal) vs non-neoplastic

Mets. vs independent lesions

Clonality

Neoplastic vs non-neoplastic

Endometriosis
Synovial chondromatosis
Pigmented nodular synovitis

Are monoclonal

Clonality

Metastasis vs Independent Neoplasms

Peritoneal leiomyomatosis is monoclonal

Discordant results in peritoneal HGSC

Results do not agree with the follow-up

Monoclonal Neoplasms

Papillary carcinoma of the thyroid

Multiple squamous carcinoma in H&N

WD Papillary carcinoma of the bladder

WD Papillary Carcinoma of the Bladder

Multiple tumors

No invasion of the muscle

Excellent prognosis

Cannot be metastatic

The cells forming the bladder mucosa come from a “patch” of cells that have similar genes

Monoclonality in Bladder WD Papillary Carcinoma

Since the tumor cells are all coming from a patch of cells, they all have the same clone

Monoclonality in the bladder supports

Independent Primaries

Monoclonality in GYN

Endometrium and Ovary

Ovary and Peritoneum

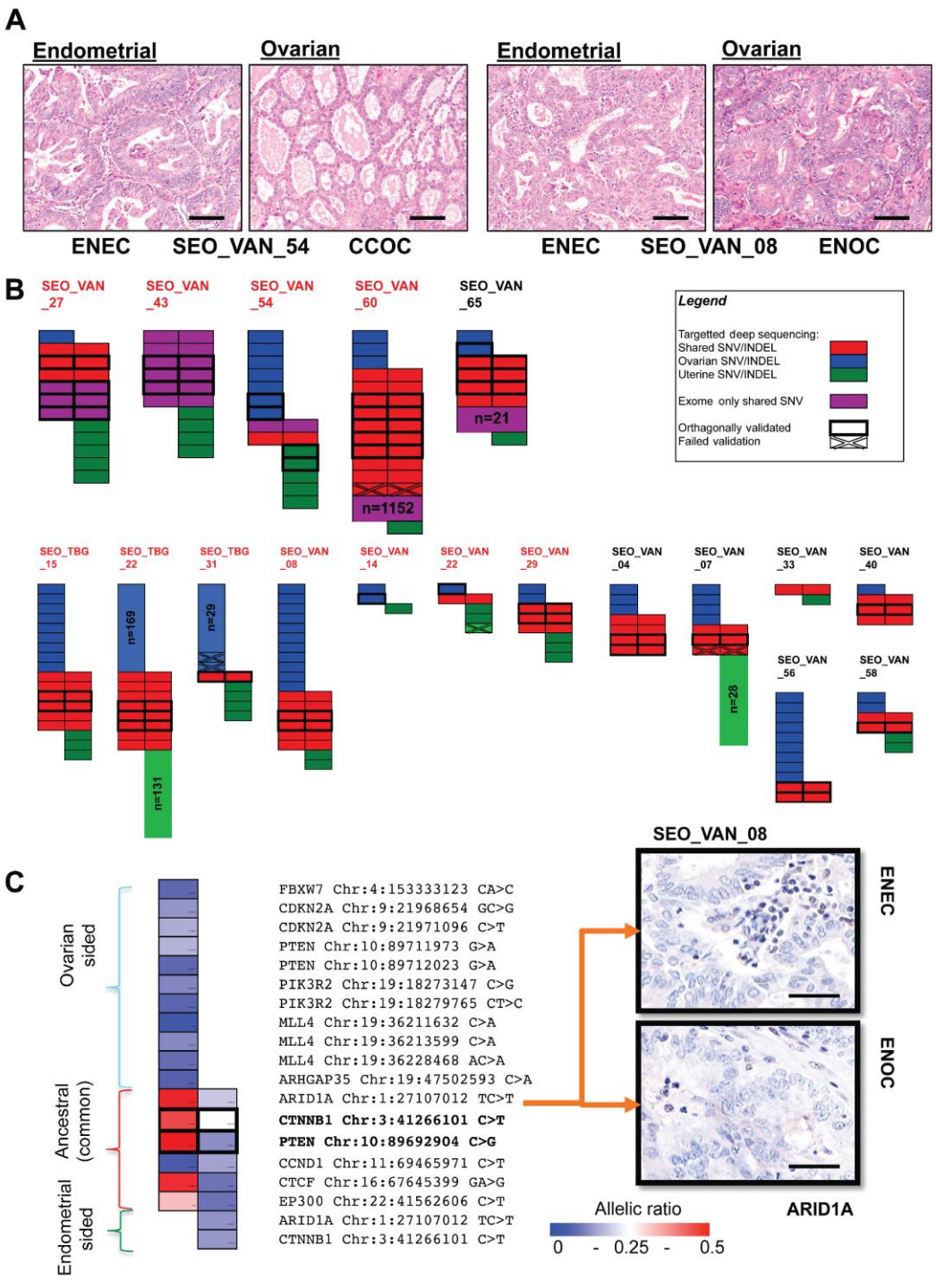
Are Monoclonal

Cas Ovary-Endometrium

Monoclonality = Metastasis

Same p53 mutation

New techniques are showing different genes


A
Endometrial
Ovarian
Endometrial
Ovarian
ENEC
SEO_VAN_54
CCOC
ENEC
SEO_VAN_08
ENOC
B
SEO_VAN _27
SEO_VAN _43
SEO_VAN _54
SEO_VAN _60
SEO_VAN _65
n=21
n=1152
Legend
Targetted deep sequencing:
Shared SNV/INDEL
Ovarian SNV/INDEL
Uterine SNV/INDEL
Exome only shared SNV
Orthagonally validated
Failed validation
SEO_TBG _15
SEO_TBG _22
SEO_TBG _31
SEO_VAN _08
SEO_VAN _14
SEO_VAN _22
SEO_VAN _29
SEO_VAN _04
SEO_VAN _07
SEO_VAN _33
SEO_VAN _40
SEO_VAN _56
SEO_VAN _58
n=169
n=131
n=29
n=28
C
Ovarian sided
Ancestral (common)
Endometrial sided
FBXW7 Chr:4:153333123 CA>C
CDKN2A Chr:9:21968654 GC>G
CDKN2A Chr:9:21971096 C>T
PTEN Chr:10:89711973 G>A
PTEN Chr:10:89712023 G>A
PIK3R2 Chr:19:18273147 C>G
PIK3R2 Chr:19:18279765 CT>C
MLL4 Chr:19:36211632 C>A
MLL4 Chr:19:36213599 C>A
MLL4 Chr:19:36228468 AC>A
ARHGAP35 Chr:19:47502593 C>A
ARID1A Chr:1:27107012 TC>T
CTNNB1 Chr:3:41266101 C>T
PTEN Chr:10:89692904 C>G
CCND1 Chr:11:69465971 C>T
CTCF Chr:16:67645399 GA>G
EP300 Chr:22:41562606 C>T
ARID1A Chr:1:27107012 TC>T
CTNNB1 Chr:3:41266101 C>T
SEO_VAN_08
ENEC
ENOC
Allelic ratio
0 - 0.25 - 0.5
ARID1A

Cas Endometrium - Ovary - Peritoneum

Endometrium and Ovary
Good prognosis

Ovary and peritoneum
Bad prognosis

All are monoclonal
The difference is in the microenvironment

Cas Ovary-Endometrium

Monoclonality = Metastasis

New techniques are showing different genes

Tumor progression

Molecular catastrophe

Ancestry

Microenvironment

Clonality

Endometriosis is a neoplasm

Leiomyomatosis is malignant

In bladder clonality = Independent Ts

In endometrium and ovary = Good Mets.

In ovary and peritoneum = Bad Mets.

Clonality is a Circus

It should be called Clownality

Thank You