

GRADING

Az emlő invazív és in situ carcinomái

Kulka Janina
Semmelweis Egyetem II. sz. Pathologiai Intézet

Invazív carcinoma

- Scarff-Bloom-Richardson grade
- Elston és Ellis által módosított Scarff-Bloom-Richardson grade
- **Nottingham grade**

Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up

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1. Hansemann D von. Ueber assymetrische Zelltheilung in Epithelkrebsen und deren biologische Bedeutung. *Virchows Arch. Pathol. Anat.* 1890; 119; 299-326.
2. Broders AC. Squamous-cell epithelioma of the lip. *JAMA* 1920; 74; 656-664.
3. Broders AC. Squamous-cell epithelioma of the skin. *Ann. Surg.* 1921; 73; 141-160.
4. Greenhough RB. Varying degrees of malignancy in cancer of the breast. *J. Cancer Res.* 1925; 9; 452-463.
5. Elston CW. Grading of invasive carcinoma of the breast. In: Page DL, Anderson TJ, eds. *Diagnostic Histopathology of the Breast*. Edinburgh: Churchill Livingstone, 1987; 300-311.
6. Patey DH, Scarff RW. The position of histology in the prognosis of carcinoma of the breast. *Lancet* 1928; i; 801-804.
7. Bloom HJG. Prognosis in carcinoma of the breast. *Br. J. Cancer* 1950; 4; 259-288.
8. Bloom HJG. Further studies on prognosis of breast carcinoma. *Br. J. Cancer* 1950; 4; 347-367.
9. Bloom HJG, Richardson WW. Histological grading and prognosis in breast cancer. *Br. J. Cancer* 1957; 11; 359-377.

Scarff-Bloom-Richardson (SBR)

radiológus

sebész

- 1957
- Tubulusképzés
- Mag polimorfizmus
- Mitózisok
- Scoring rendszer:
enyhe – közepes – súlyos szubjektív megítélést
számok helyettesítik 1-3-ig
- 1971-ben, 20 éves betegkövetési adatok alapján
megerősítették a grade prognosztikus értékét

Nottingham grade

- Szemikvantitatív értékelés
- A SBR grade módosítása először a mitózisok számolása terén
- Az Elston-Scarff-Bloom-Richardson grade meghatározás módszerének további pontosítása a Nottingham grade

A Nottingham grade elemei

- **TUBULUSKÉPZÉS**

- >75% score1
- 10-75% score2
- <10% score3

- **MAGPOLYMORPHISMUS**

- Kis, egyforma magok score1
- Nagyság és változatosság tekintetében közepes magok score2
- Kifejezett változatosság a magok morfológiájában score3

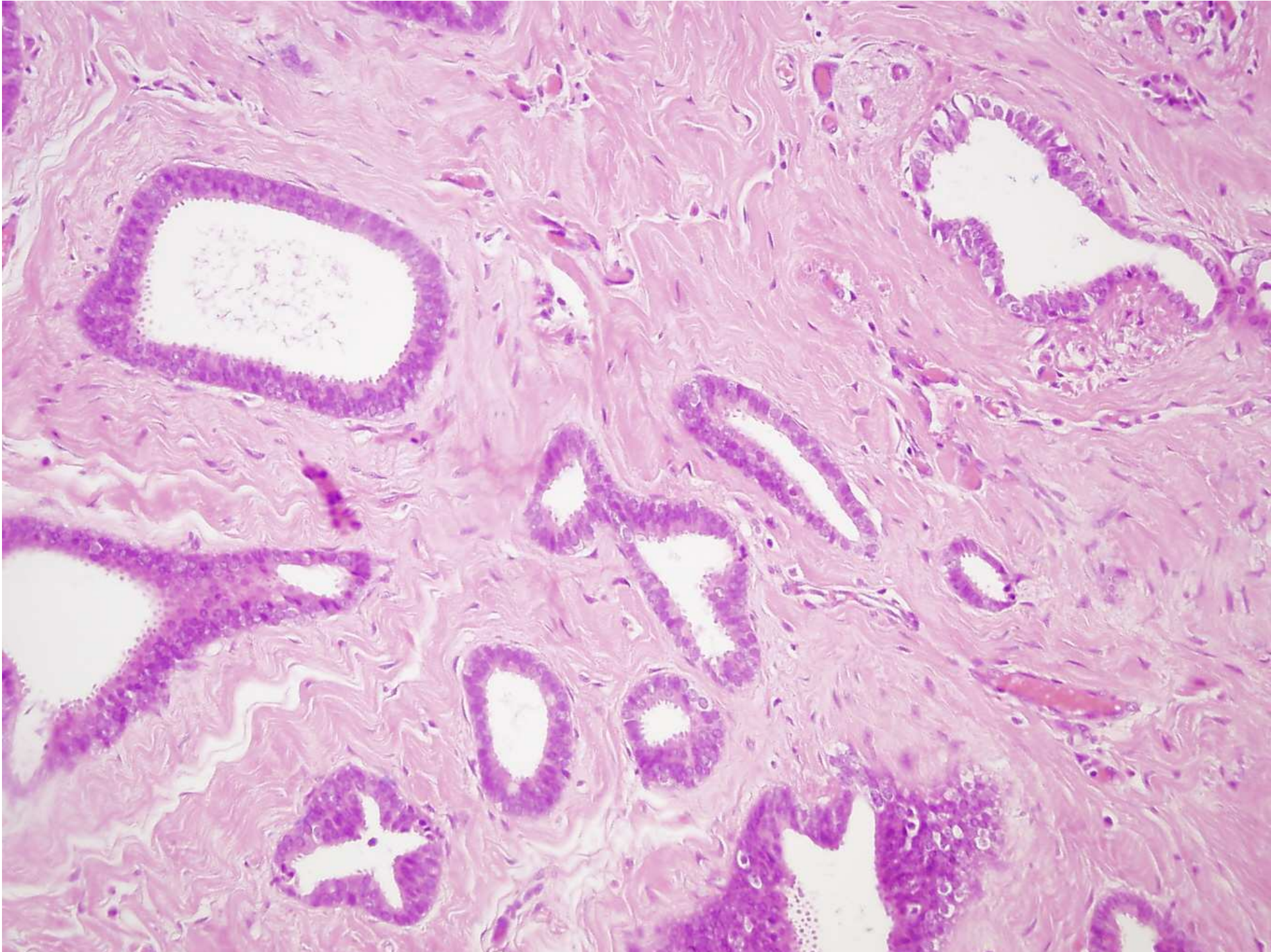
- **MITÓZISOK**

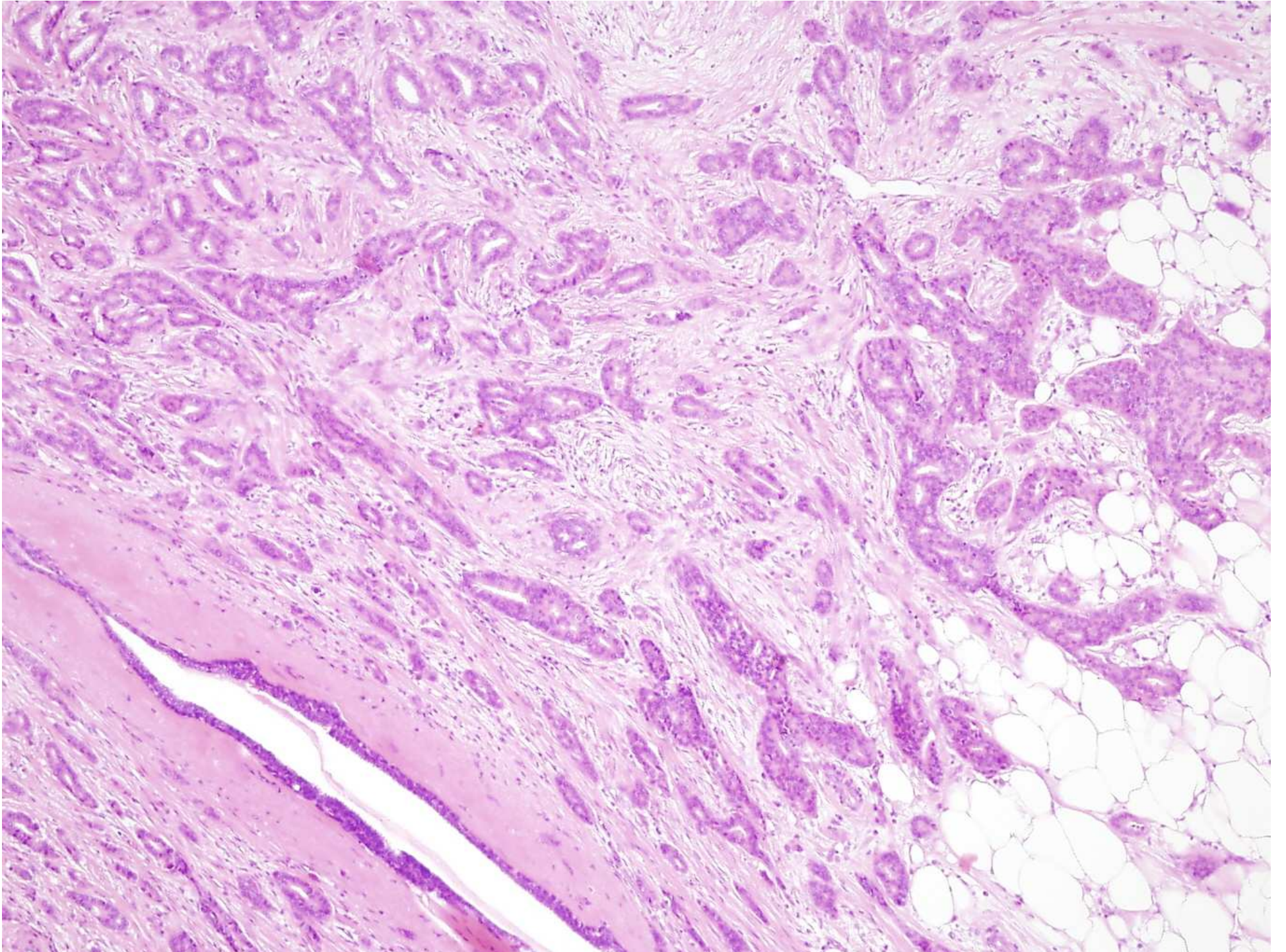
- A mikroszkóp 40x látóteréhez kalibrált skálán megadva score1-3

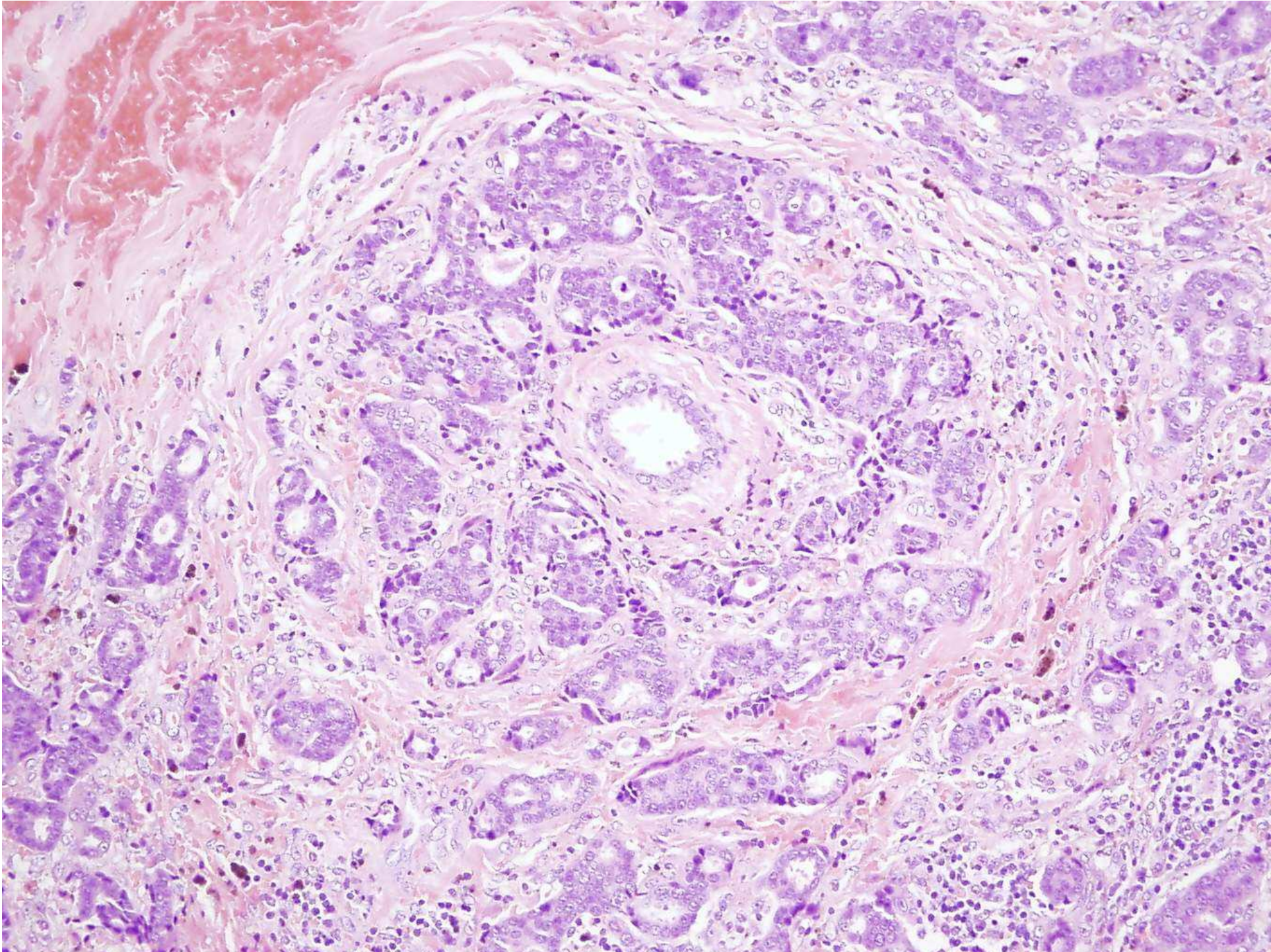
- GRADE 1 score 3-5
- GRADE 2 score 6-7
- GRADE 3 score 8-9

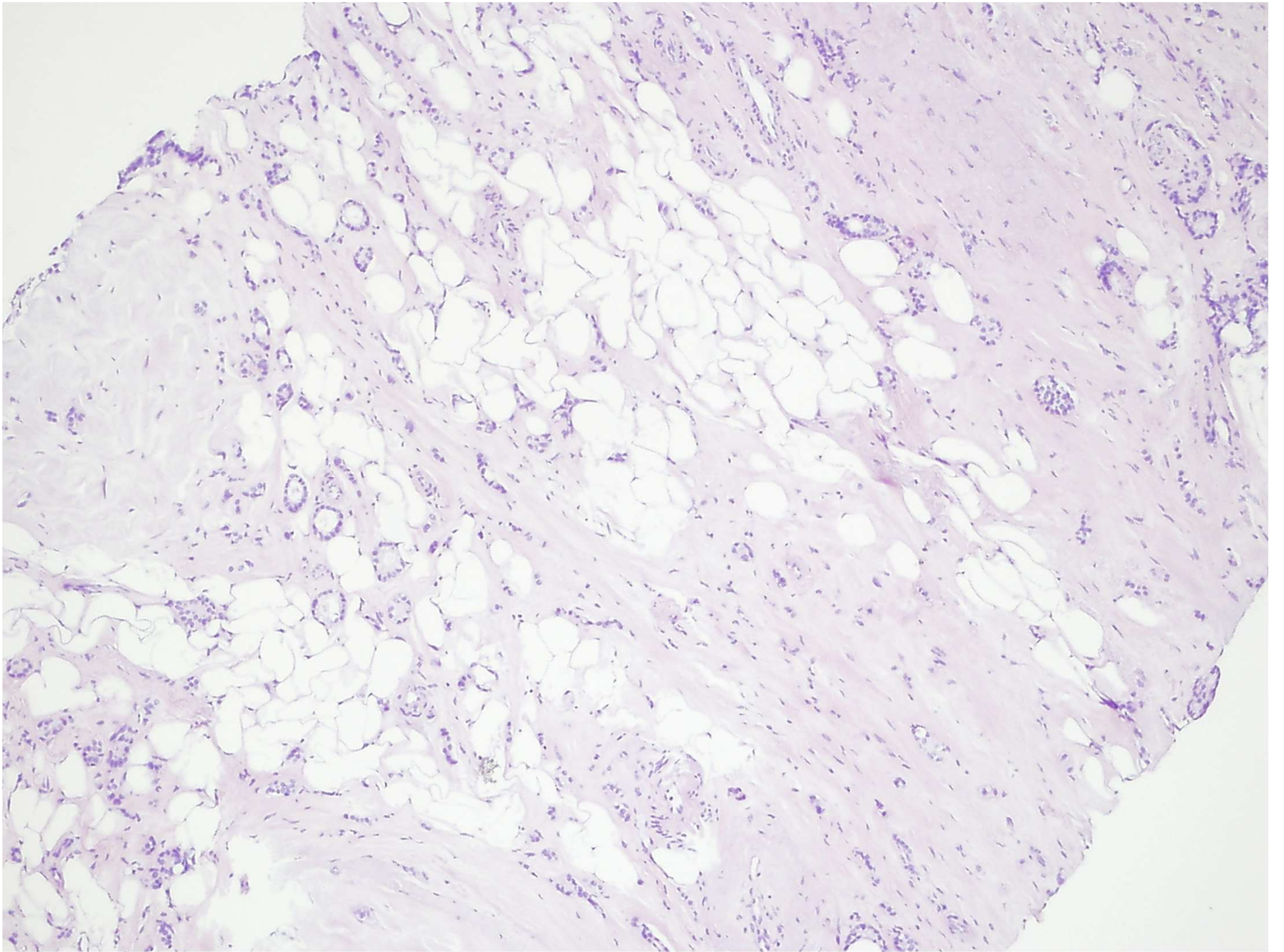
Tubulusképzés

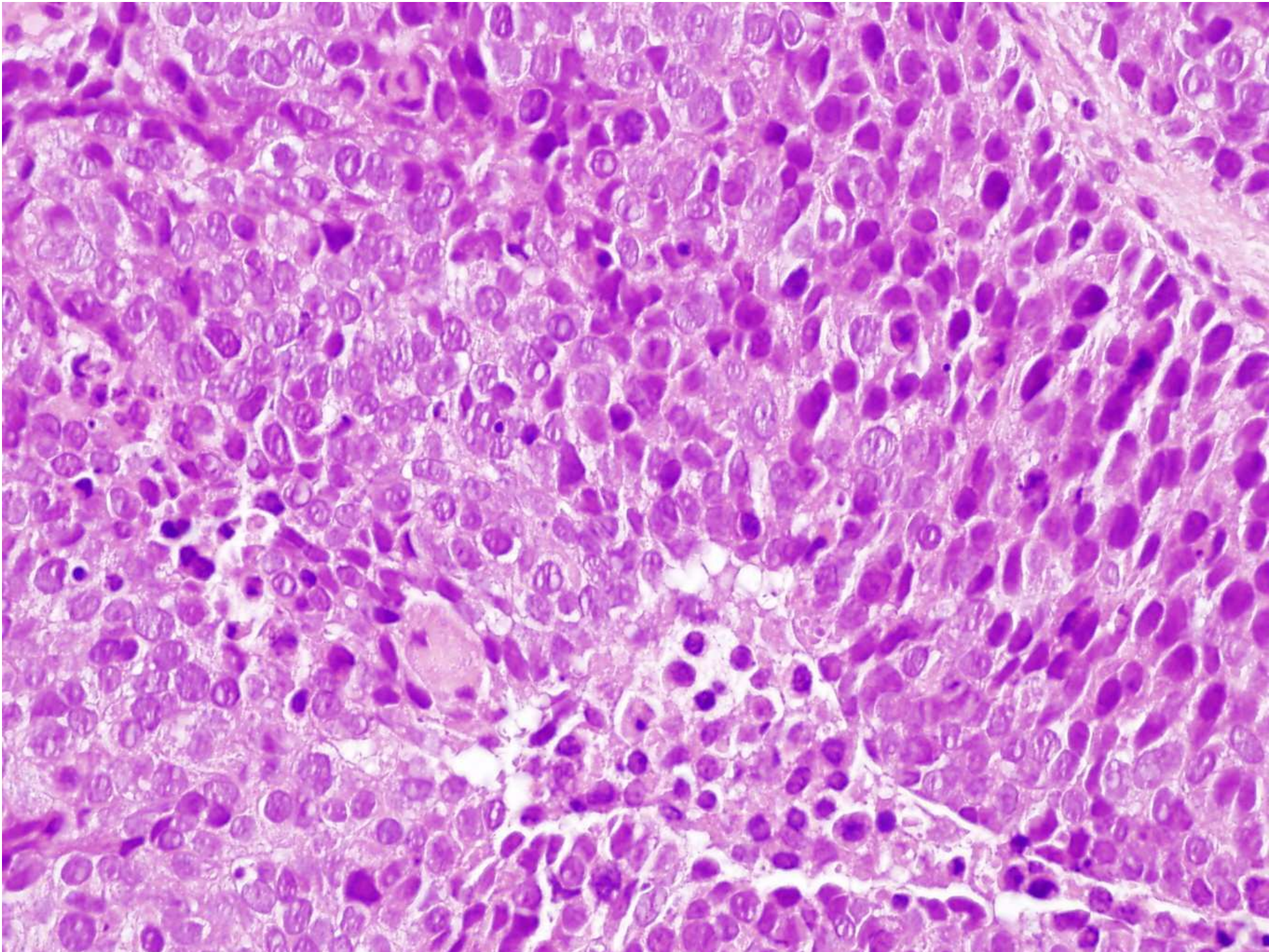
- „Tubulus”-ként csak a teljesen jól látható lumennel rendelkező struktúrákat értékeljük
- Optimális fixálás szükséges
- A tumor rendelkezésre álló minden területét vizsgáljuk

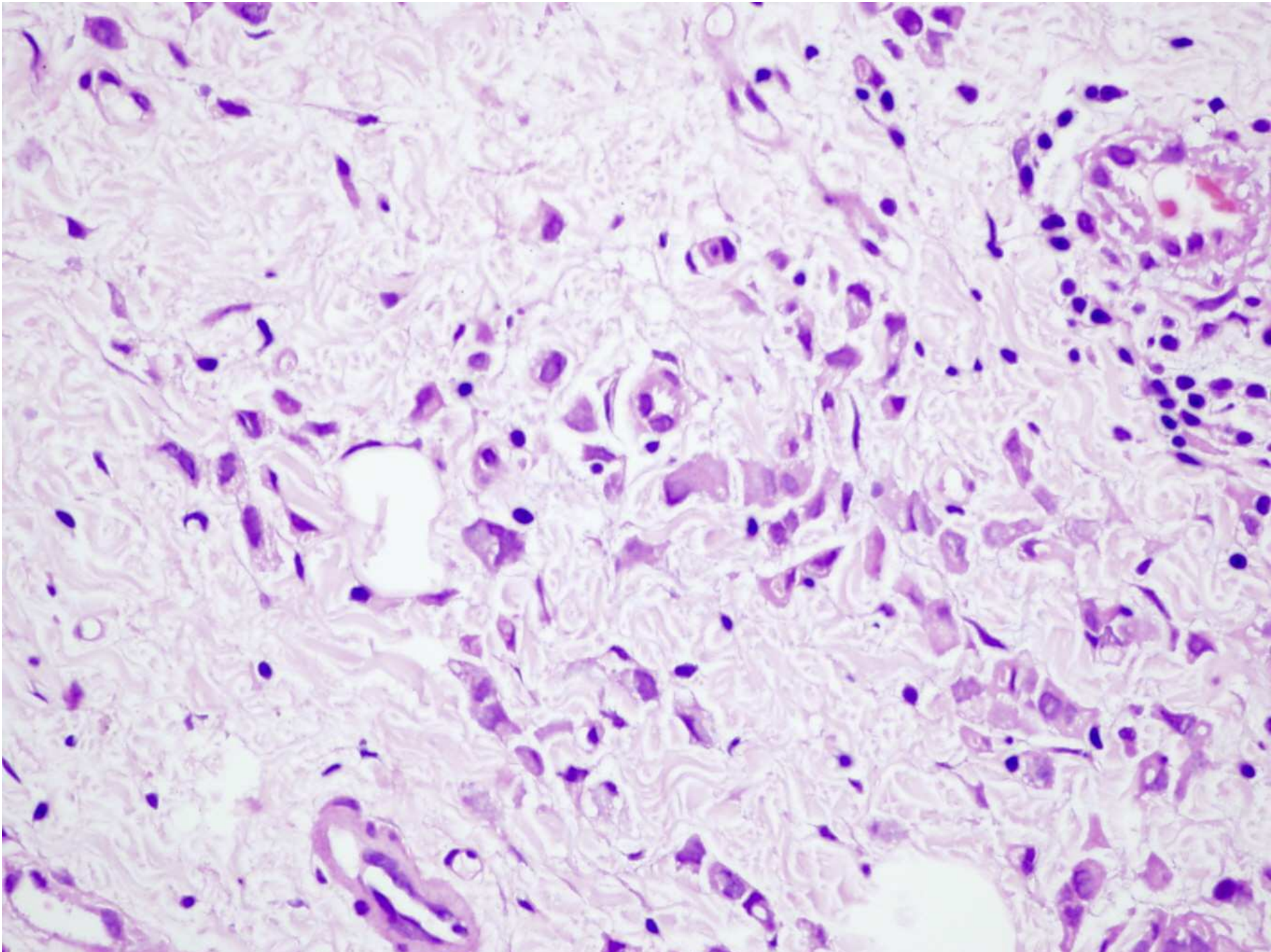


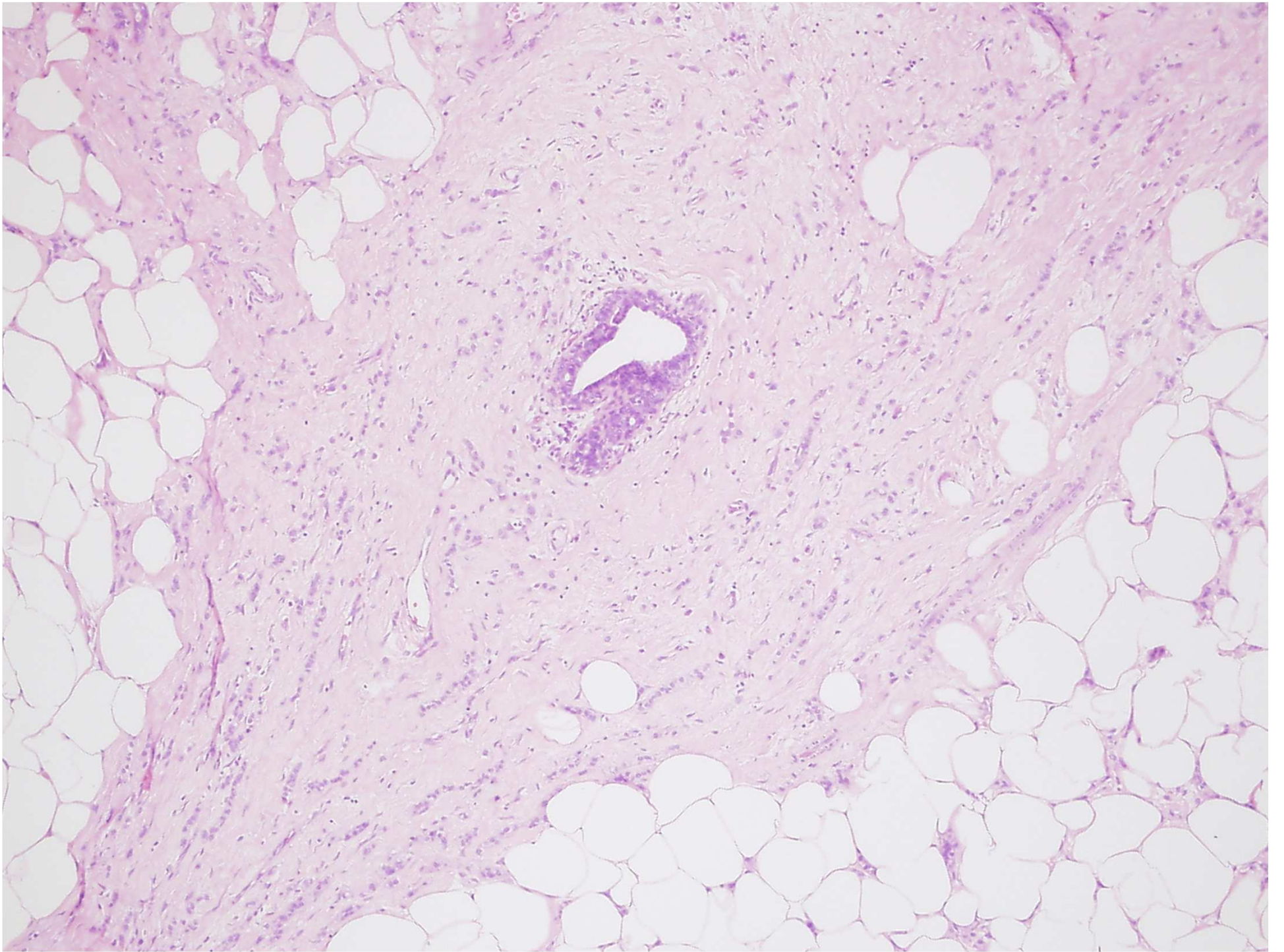






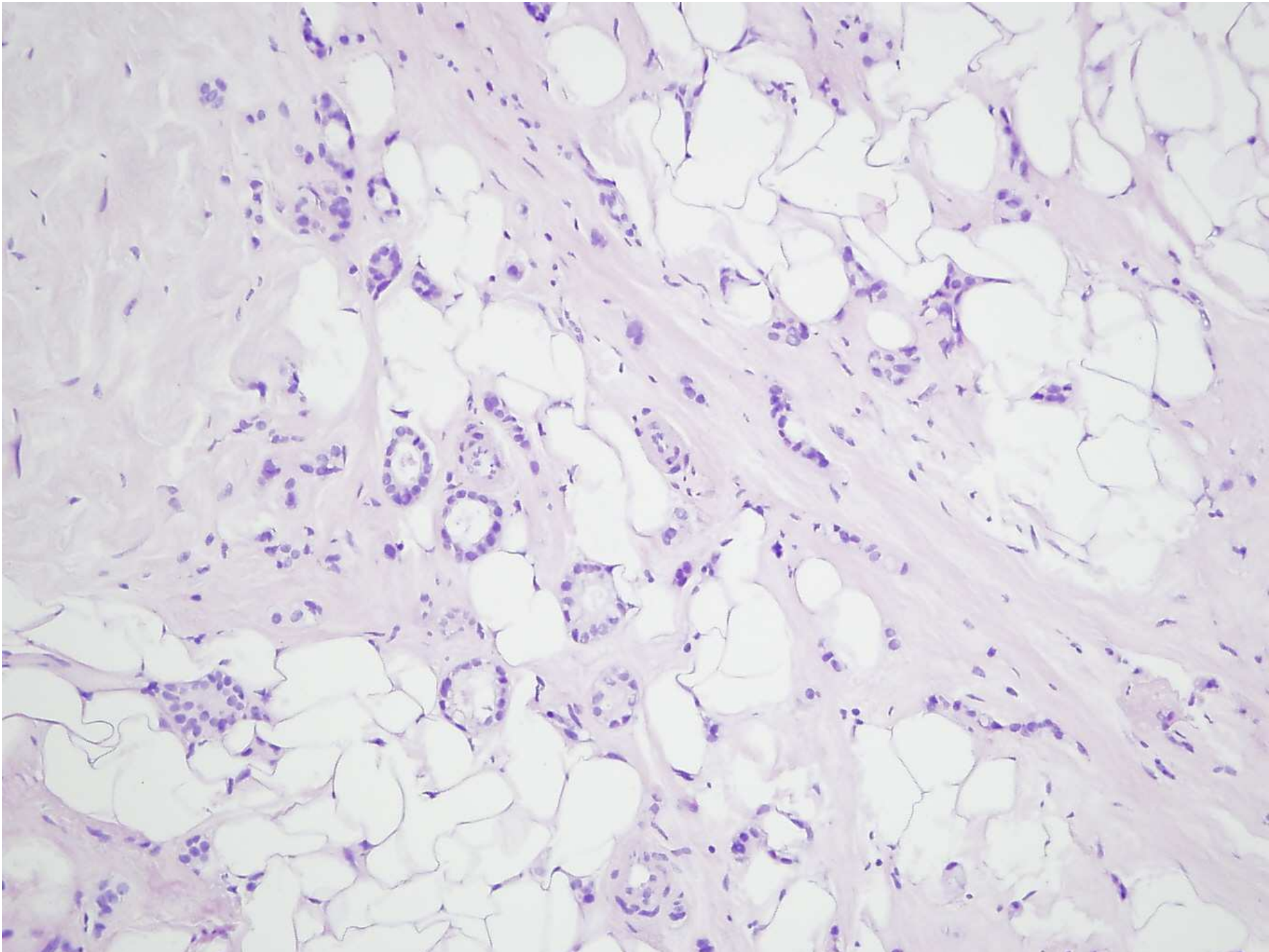


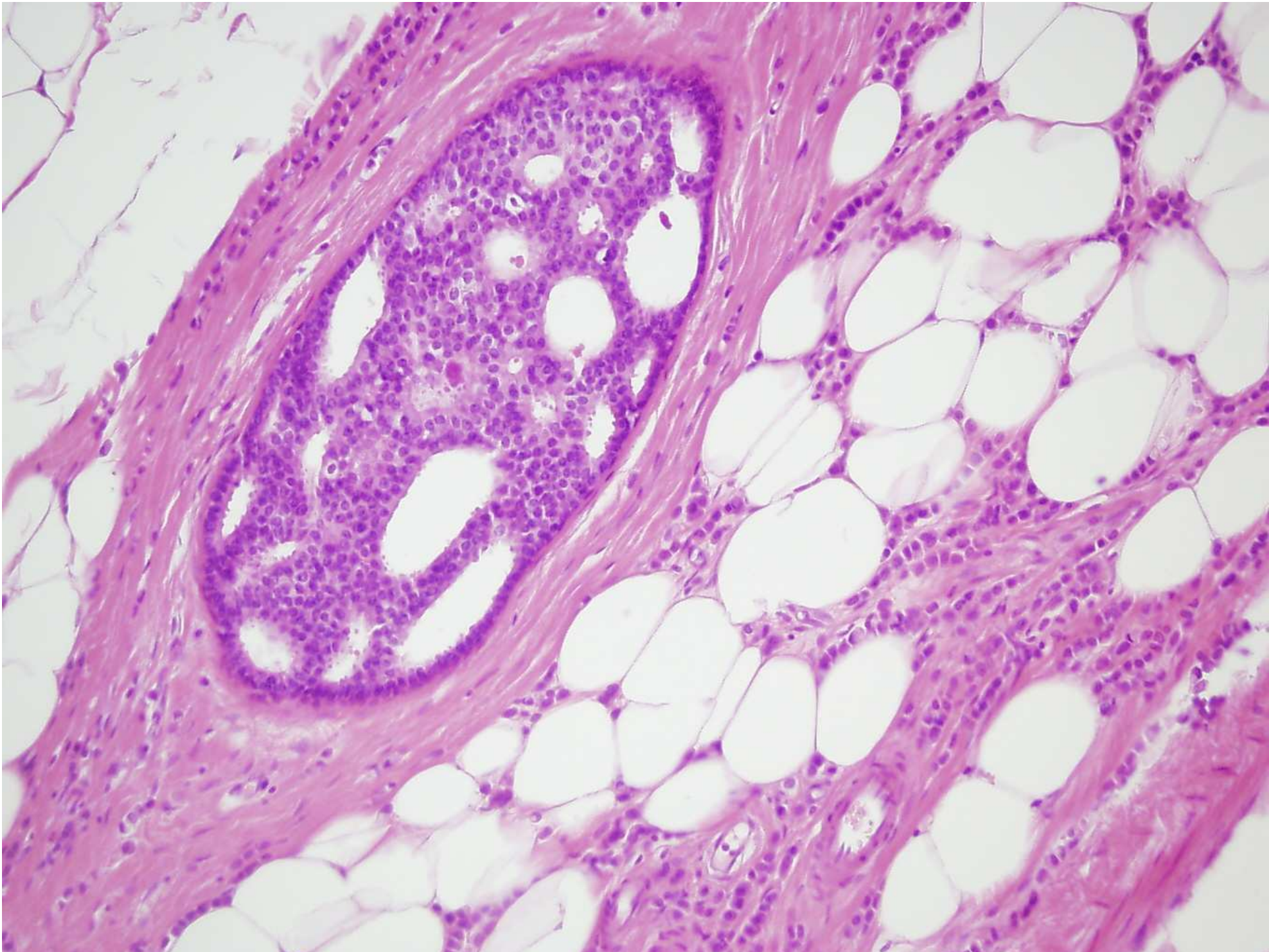


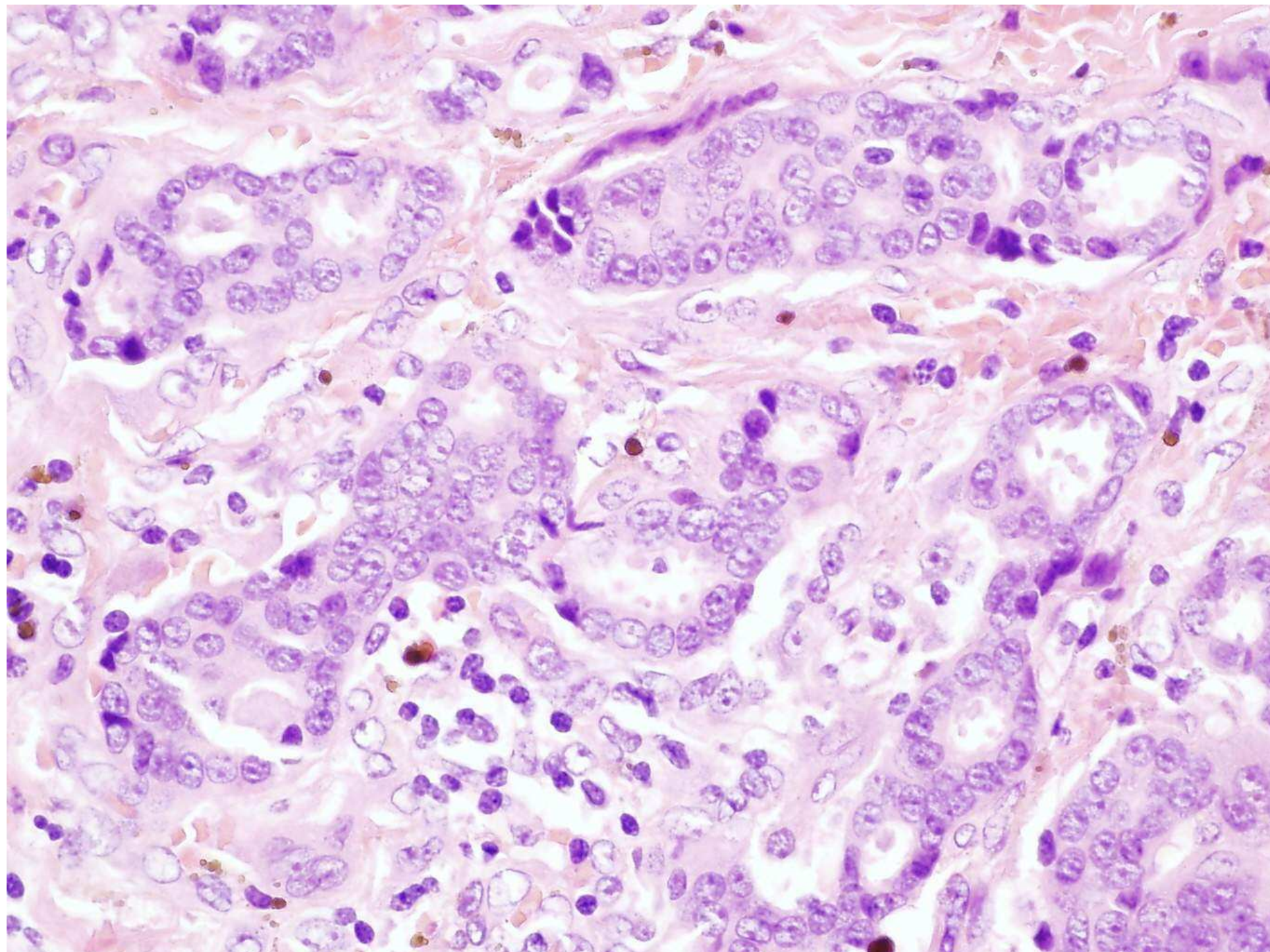


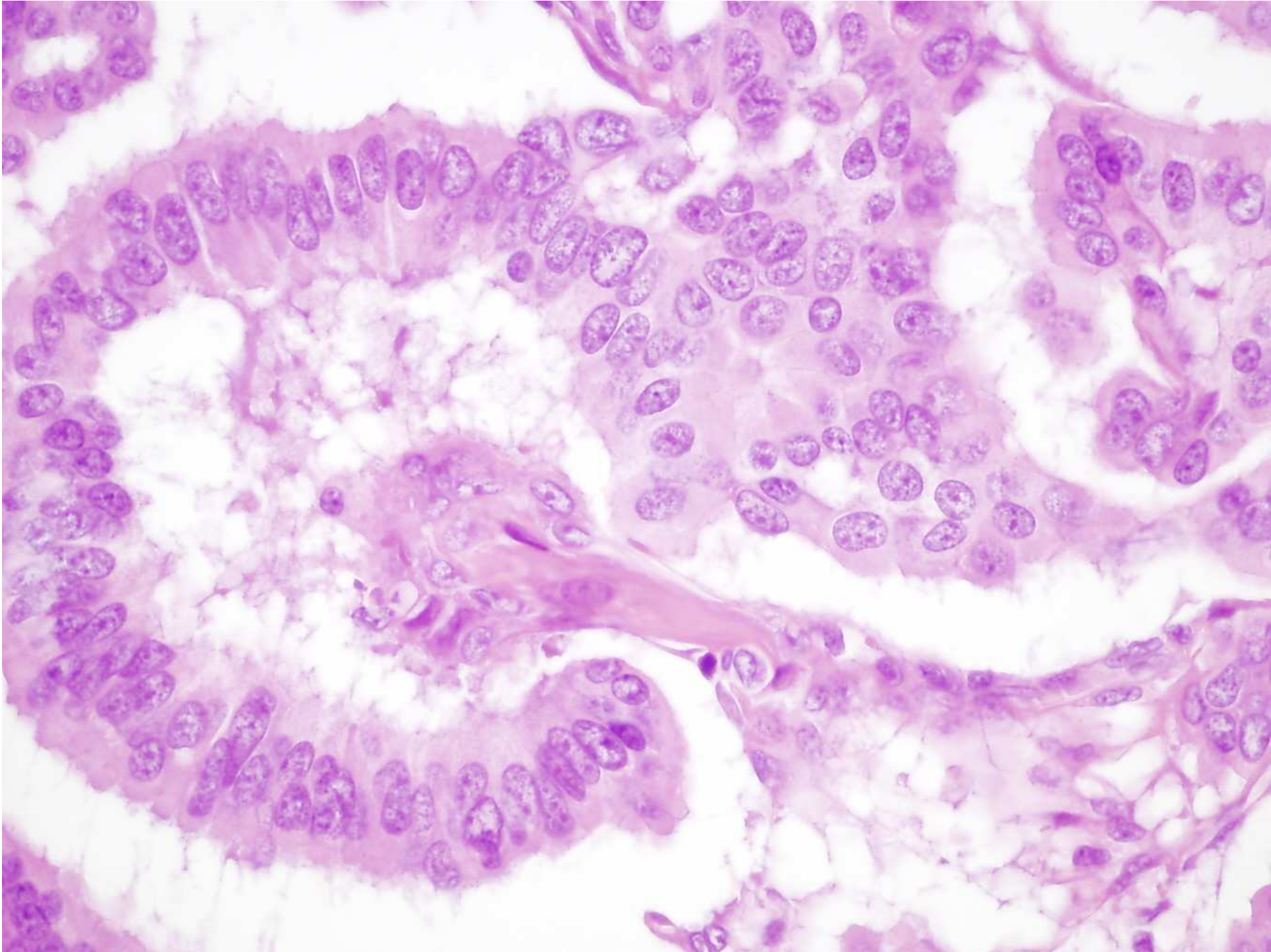
Nuclearis grade

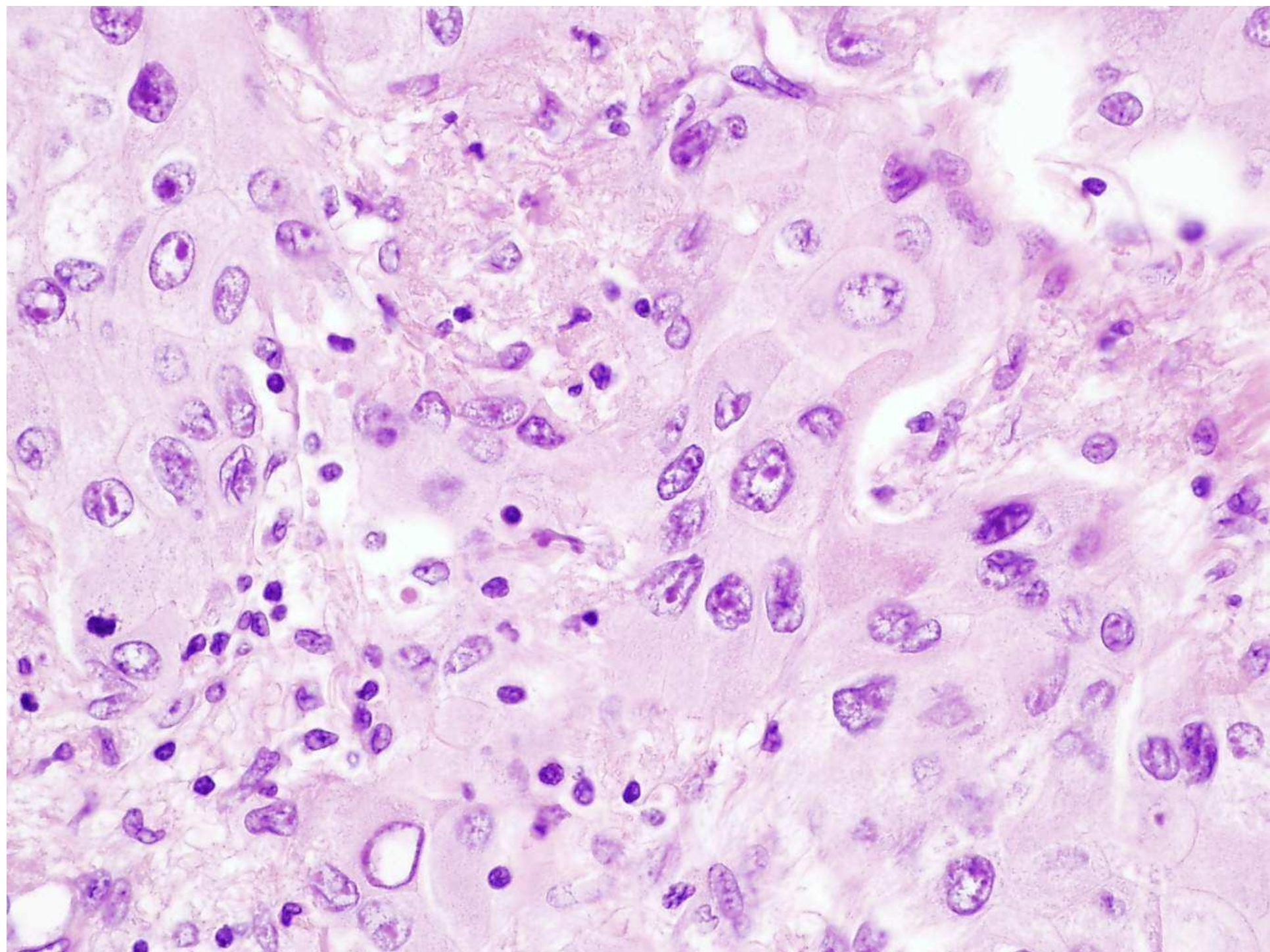
- Referencia: a normál hámban látható sejtmagok vagy ezek hiányában a lymphocyták nagysága
- Nuclearis grade 1: kis magok, szabályos magkontúr, egyenletes chromatin eloszlás
- Nuclearis grade 2: a hámsejtek magjánál nagyobb, vesicularis magok, közepes alak-és nagyságbeli változatossággal gyakran egy látható nucleolusszal
- Nuclearis grade 3: nagy, bizarr, kifejezett alak-és nagyságbeli eltéréseket mutató, vesicularis magok, gyakran több nucleolus

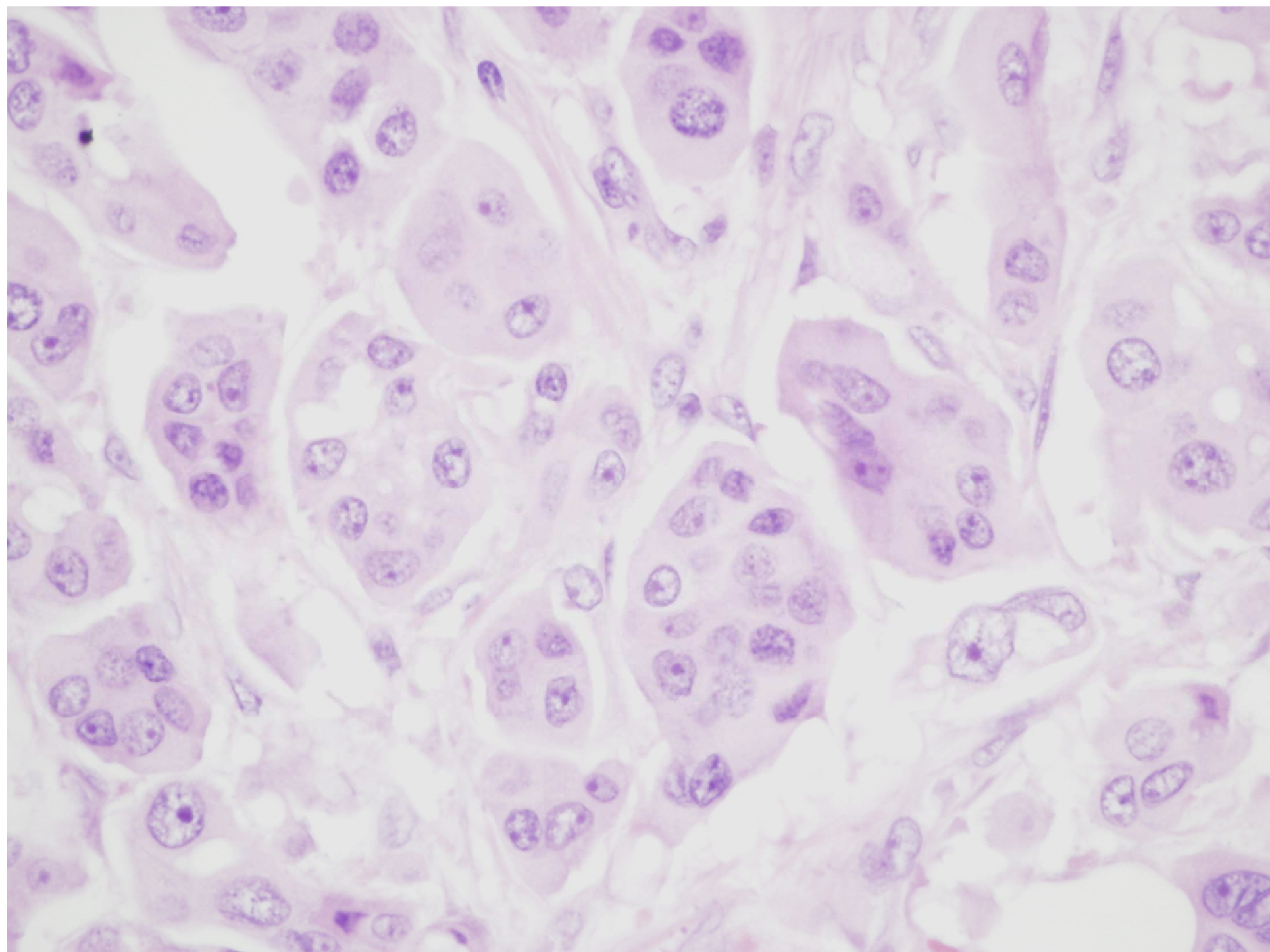


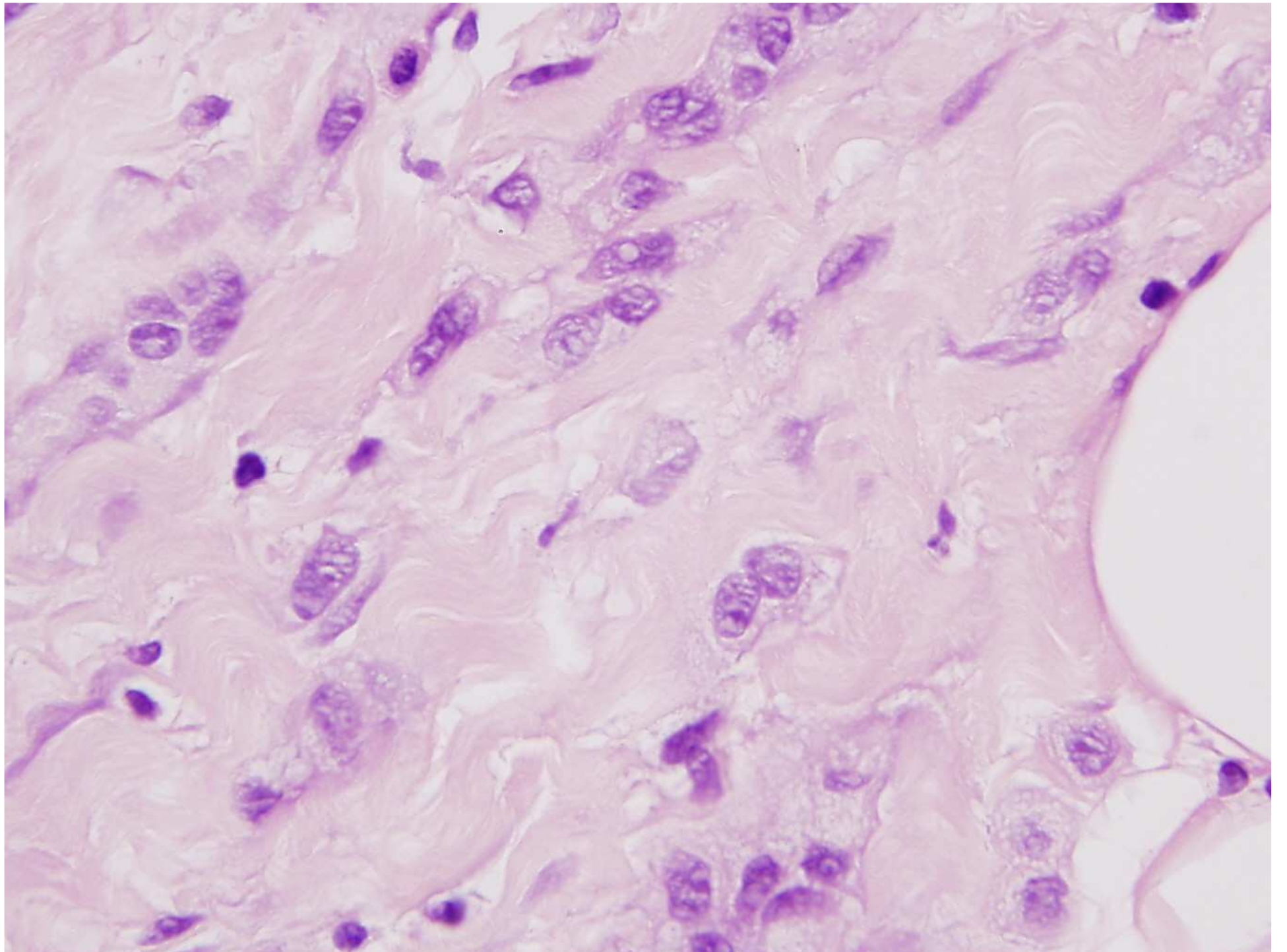






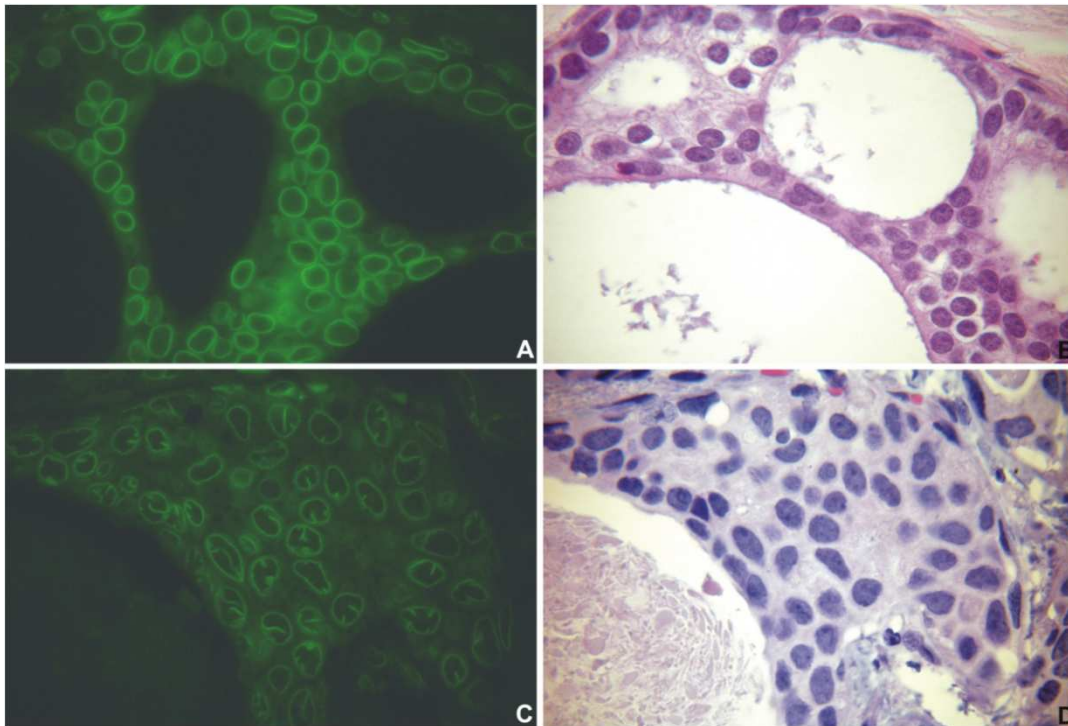






Alternatívák

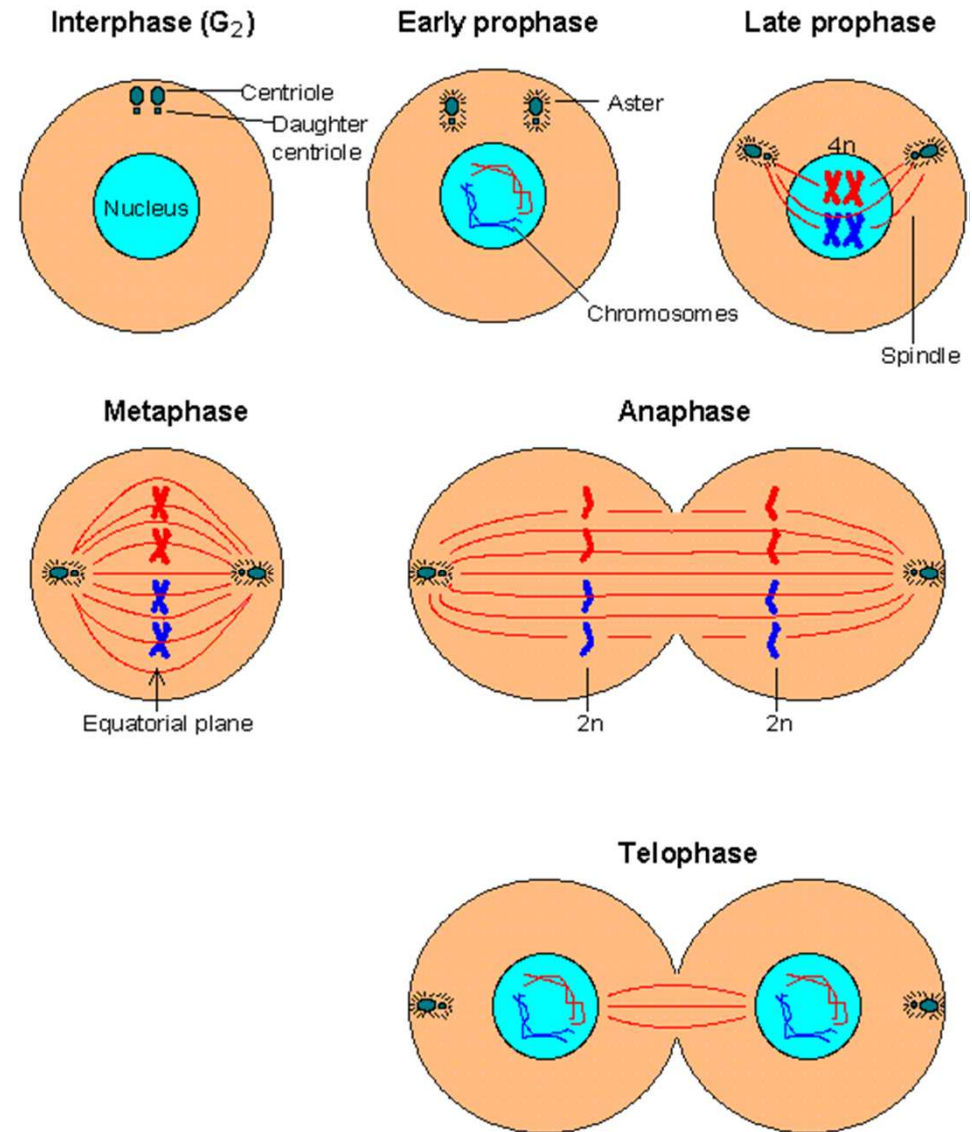
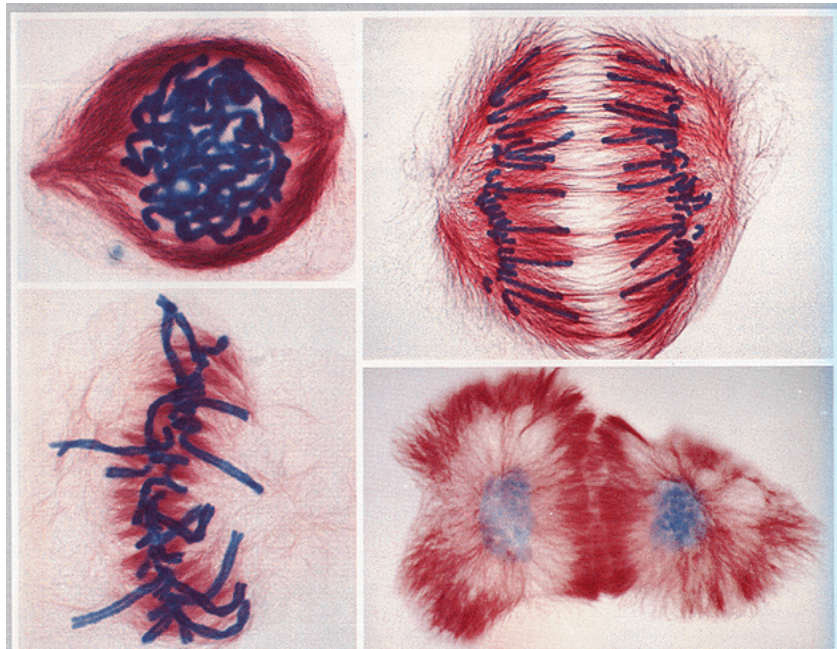
- Morfometria
- „Nuclear envelope” (Bussolati G)



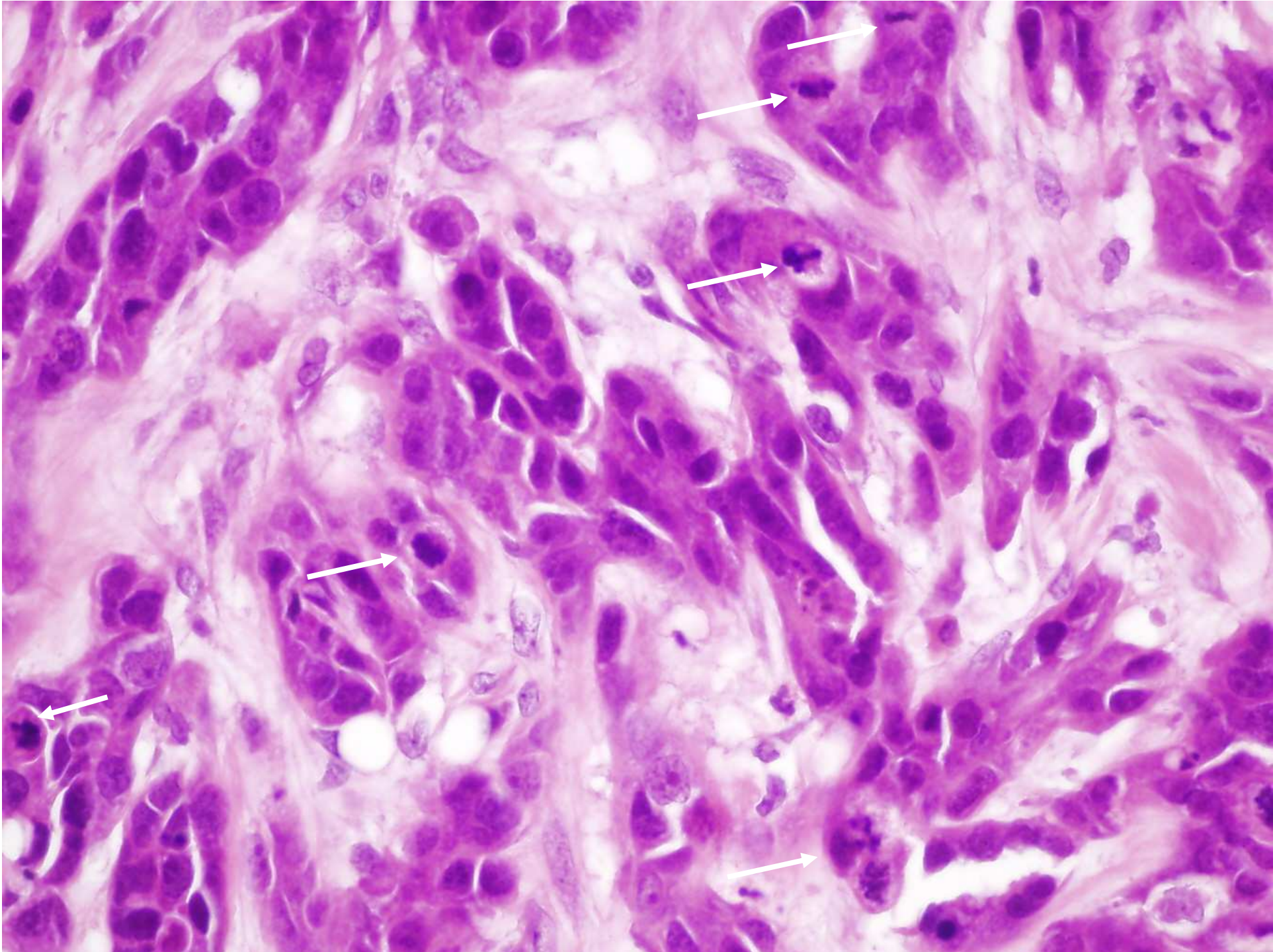
Lamin B
Emerin

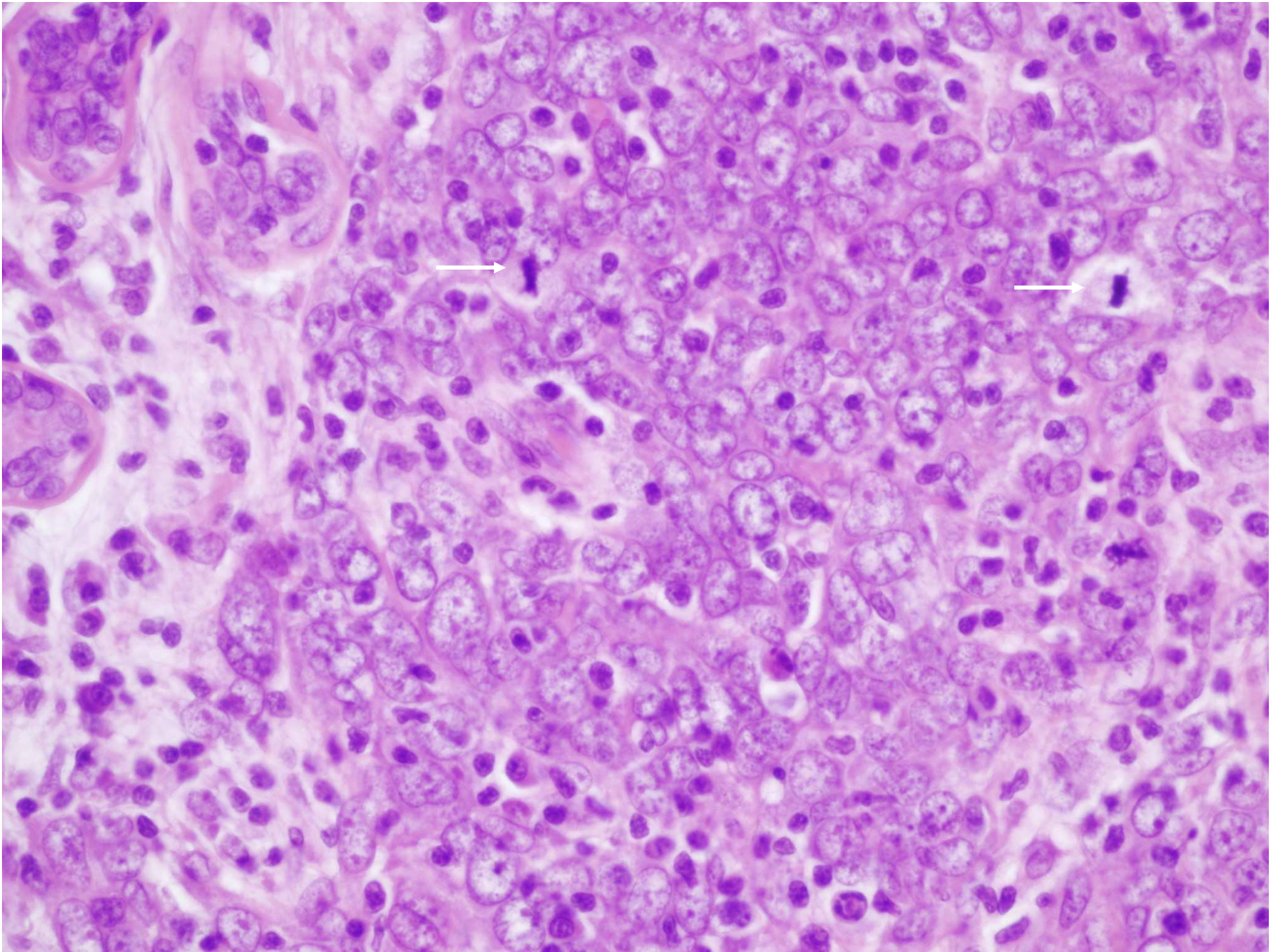
Mitózis számolás

- profázis,
- metafázis,
- anafázis,
- telofázis



- A tumor
 - széli területén
 - a legaktívabban osztódó gócban
 - 10 nagy nagyítású (x400) látótérben
 - szükség lehet többször 10 nn látóteret leszámolni



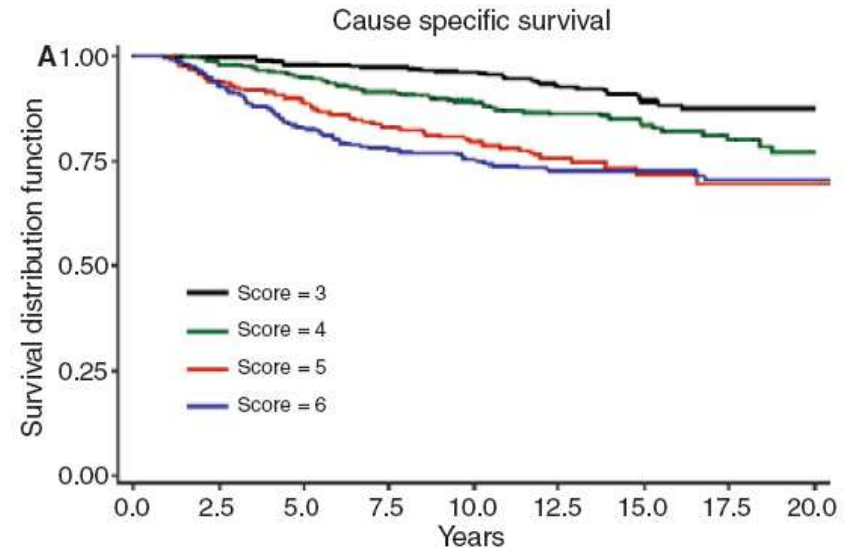


Heterogenitás

- Bizonyos esetekben nehézségeket okoz
- Az összes tumort tartalmazó metszet átnézése után adjuk meg a tumor grade-jét
- Heterogén magmorfológia esetén:
 - Ha a magasabb nuclearis grade a tumorsejtek legalább negyedrészében látható

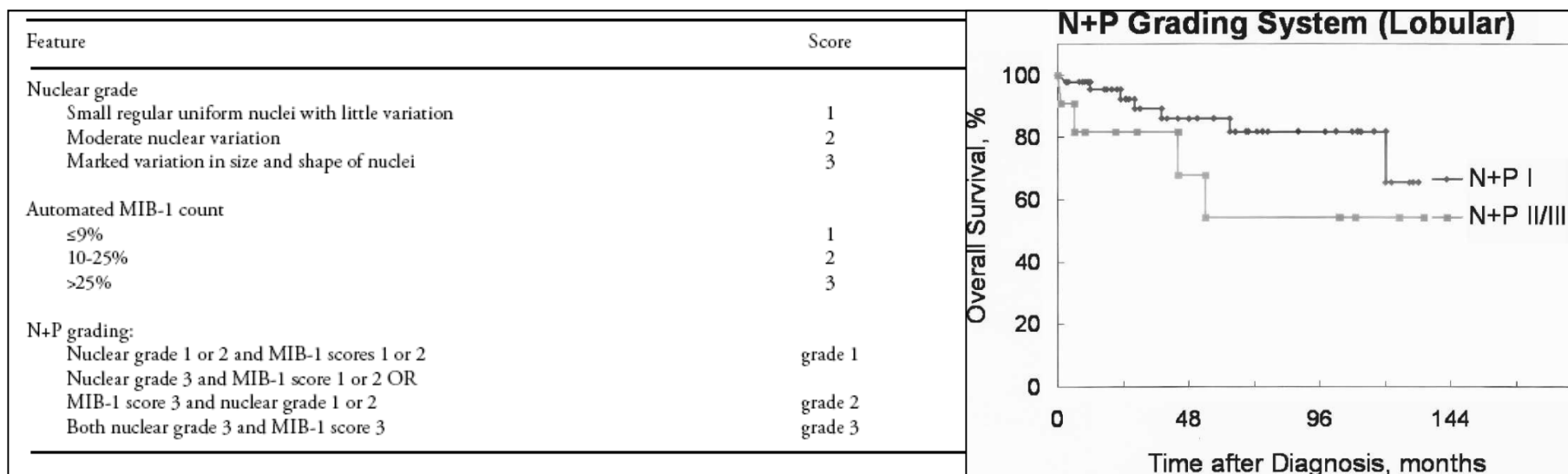
Újabb ötletek

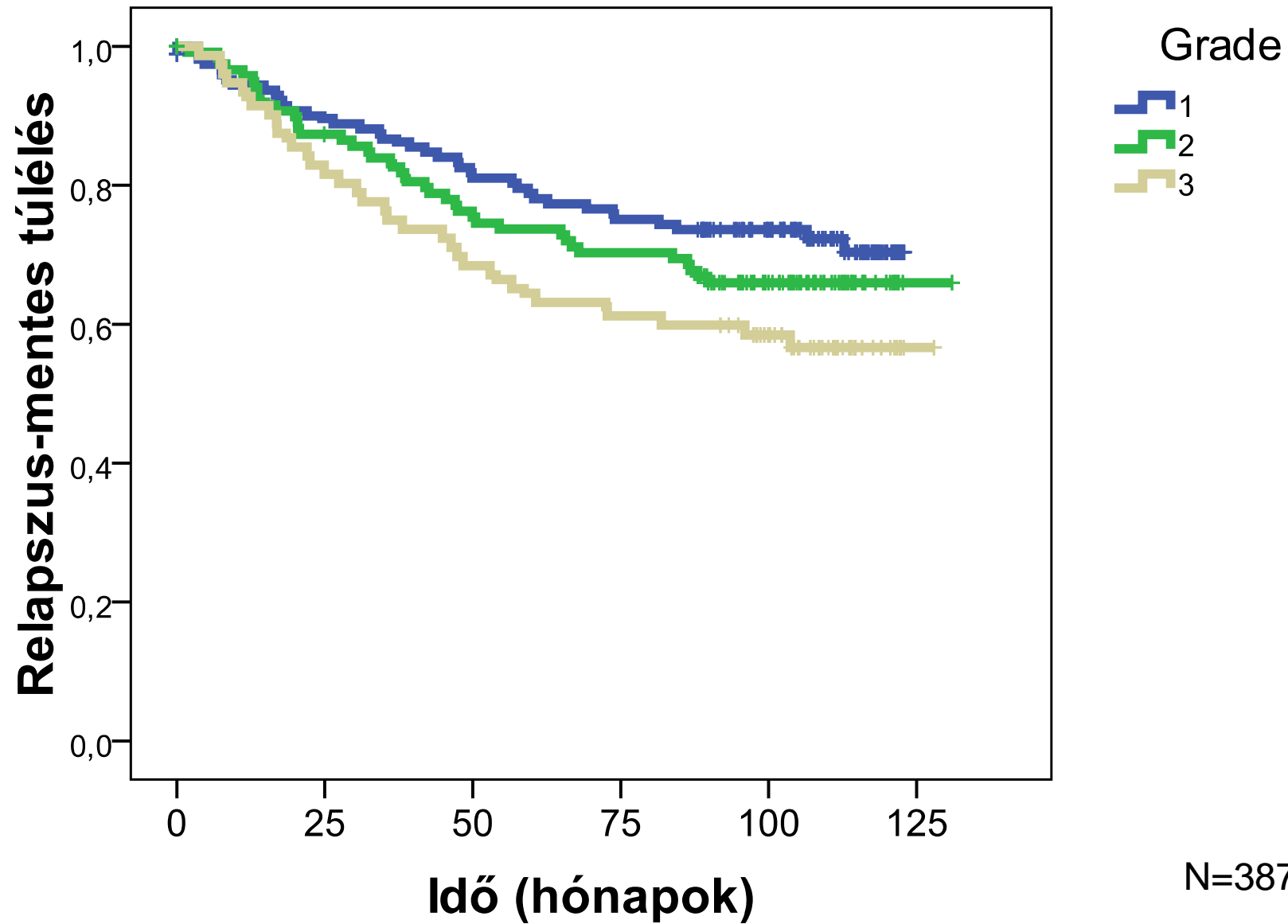
- Histopathology
2009;54:724-731 Thomas
JSJ: Egyszerűsített
bináris scoring rendszer
(SBS) alkalmazásával a
G2 tumorok kettéválnak,
négy csoport alakul ki:
Score 3, 4, 5, 6



	Score 1	Score 2
Tubulusképzés	>10%	<10%
Mag polymorphismus	Nem polymorph	Polymorph
Mitózisok	<7/10 hpf	>7/10 hpf

A Newly Proposed Semi-Automated Method of Grading Invasive Lobular Carcinoma: A Unifying Concept and Correlation with Prognostic Markers and Patient Survival





In situ carcinoma

- DCIS

- Speciálisan képzett emlőpatológusok között nagyobb az egyetértés
- Számos rendszer
- Magmorfológia + mitózisok + necrosis
- Általában a Van Nuys grade rendszert tartják a legjobban reprodukálhatónak
- Consensus Conference
CANCER, 1997 / Volume 80 / Number 9

TABLE 11.1 Consensus Committee
Recommendation for Nuclear
Grading of Intraductal Carcinoma*

Low Nuclear Grade (NG1)

- Monomorphic (monotonous) appearance
- Size of duct epithelial nuclei or 1.5–2.0 normal red blood cell
- Chromatin diffuse, finely dispersed
- “Occasional nucleoli and mitoses”
- Cells usually polarized

High Nuclear Grade (NG3)

- “Markedly pleomorphic”
- Size usually more than 2.5 duct epithelial nuclei
- Chromatin vesicular with irregular distribution
- “Prominent, often multiple nucleoli”
- “Mitoses may be conspicuous”

Intermediate Nuclear Grade (NG2)

- “Nuclei that are neither NG1 nor NG3”
-

*Based on The Consensus Conference Committee. Consensus Conference on the classification of ductal carcinoma in situ. *Cancer* 1997;80:1798–1802.

TABLE 11.2 Consensus Committee
Recommendation for Reporting
Necrosis in Intraductal Carcinoma*

Comedonecrosis

- “Central zone necrosis within a duct, usually exhibiting a linear pattern within ducts if sectioned longitudinally”

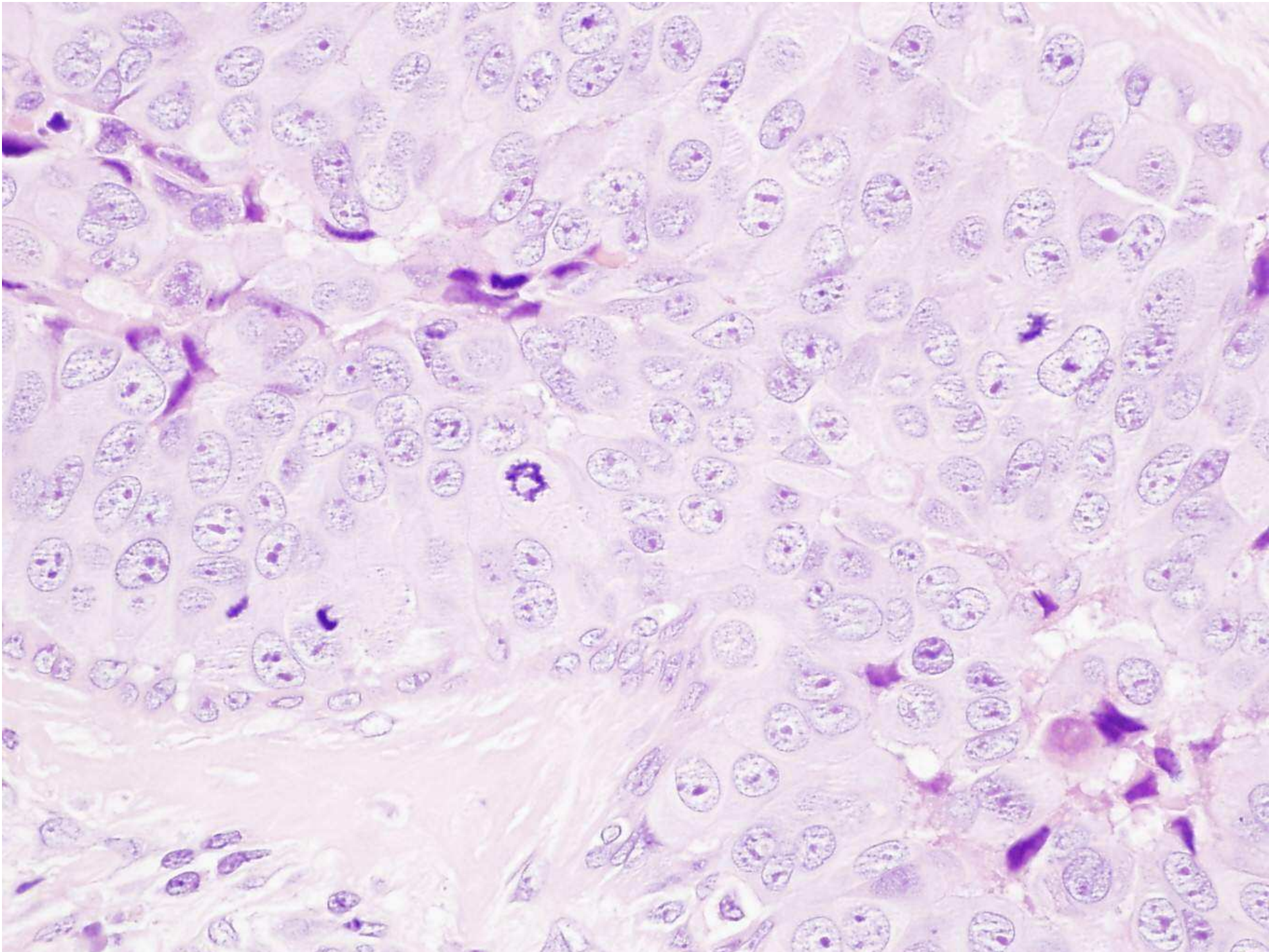
Punctate

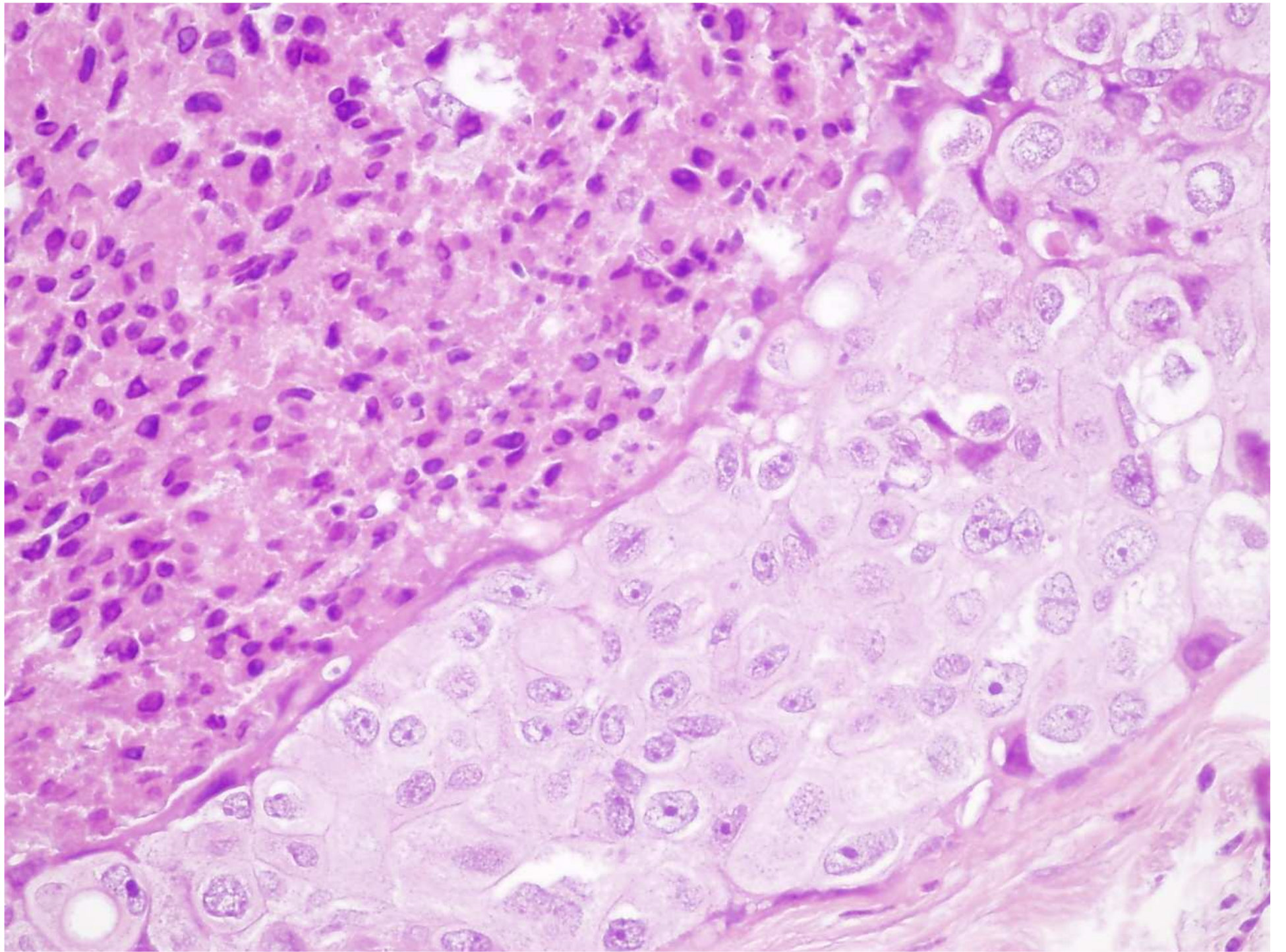
- “Non-zonal type necrosis (foci of necrosis that do not exhibit a linear pattern if longitudinally sectioned)”
-

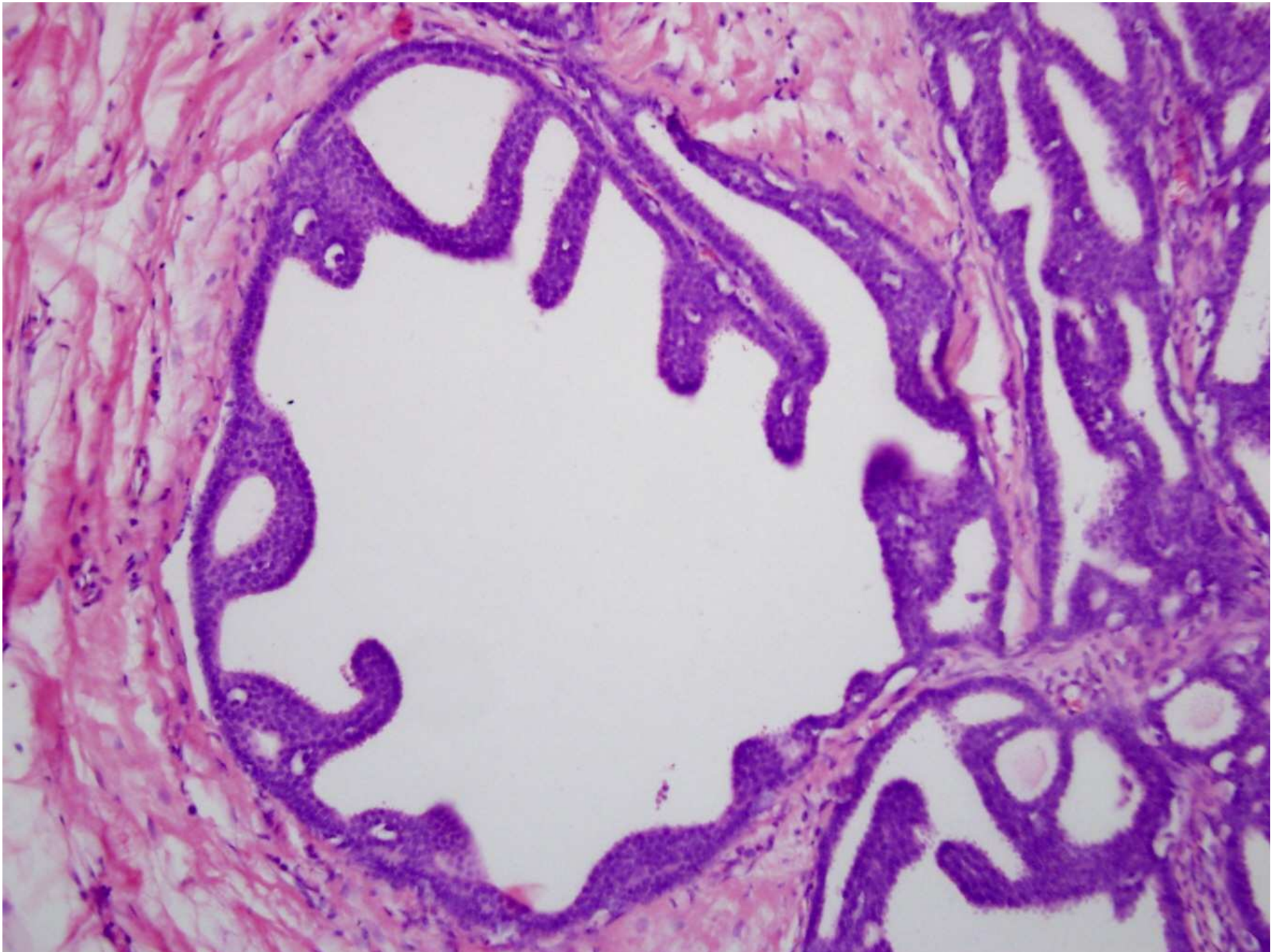
*Based on The Consensus Conference Committee. Consensus Conference on the classification of ductal carcinoma in situ. *Cancer* 1997;80:1798–1802.

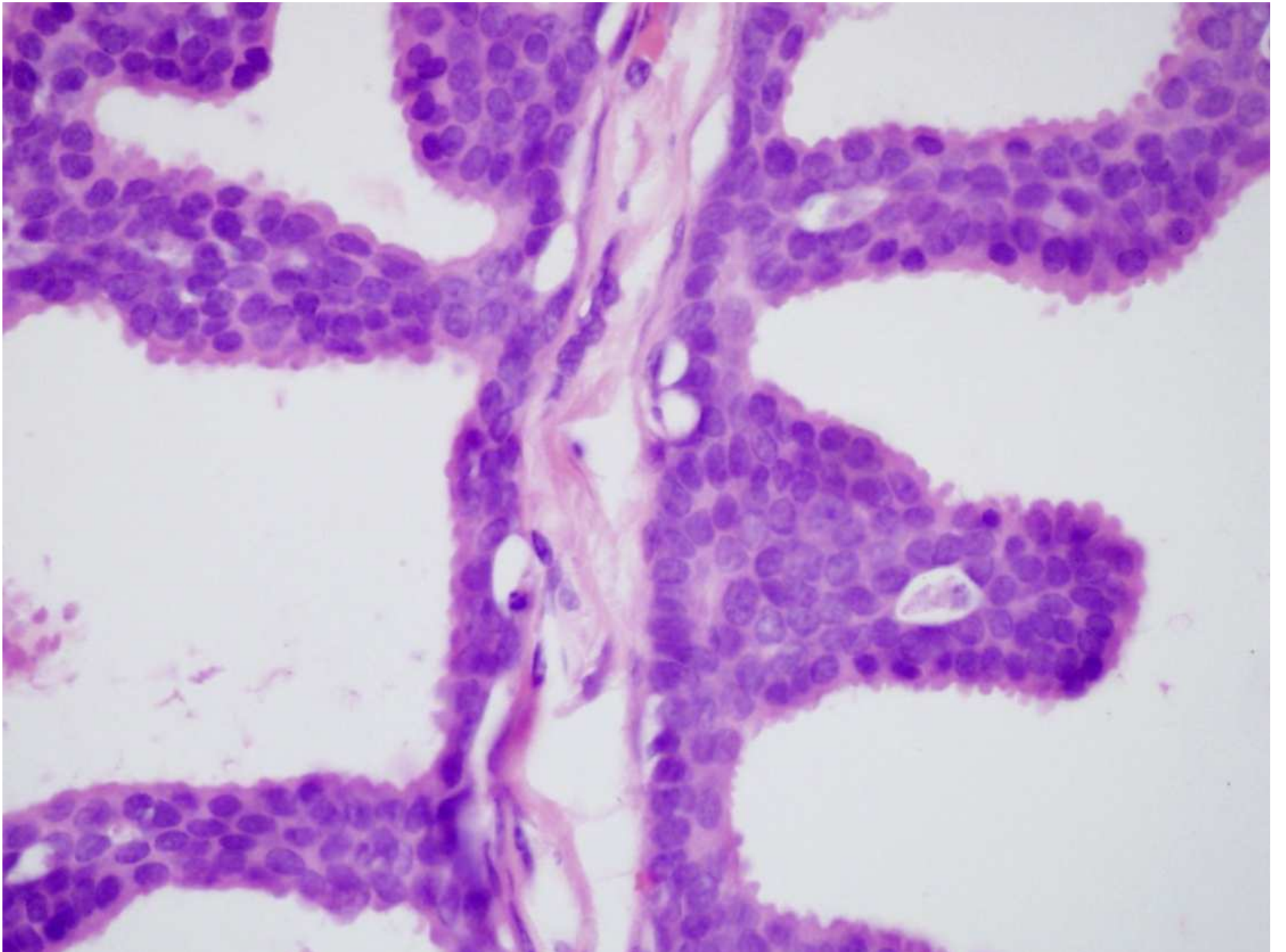
C. Cell polarization

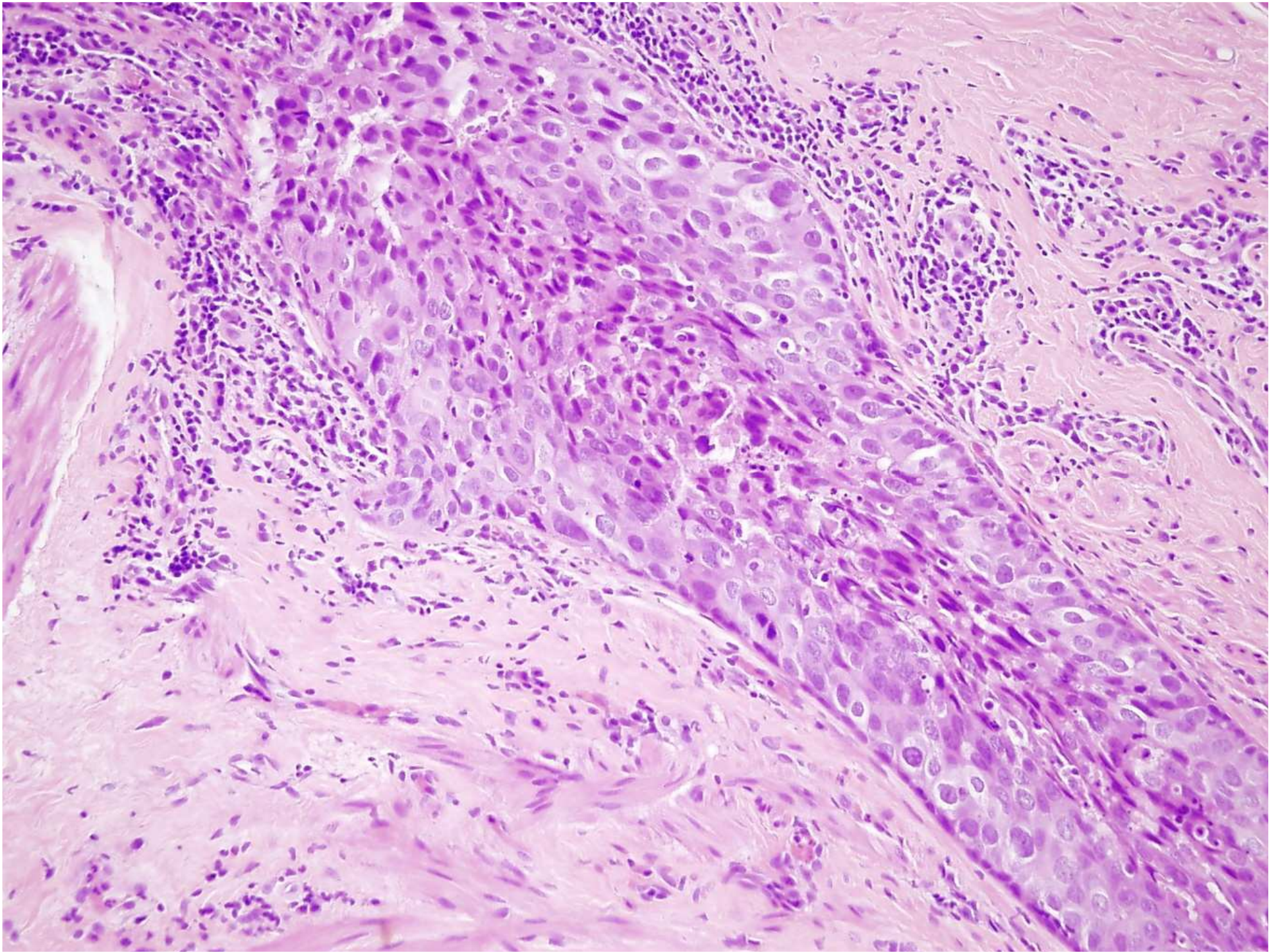
Polarization reflects the radial orientation of the apical portion of tumor cells towards intercellular (lumen-like) spaces, either larger lumina or minute “microacinar” spaces which produce a rosette-like appearance. Such polarization is characteristic of lower grade DCIS with cribriform and solid architecture, but can also be recognized in epithelial protuberances, bridges, arcades and micropapillae of DCIS of lower grades with micropapillary architecture.

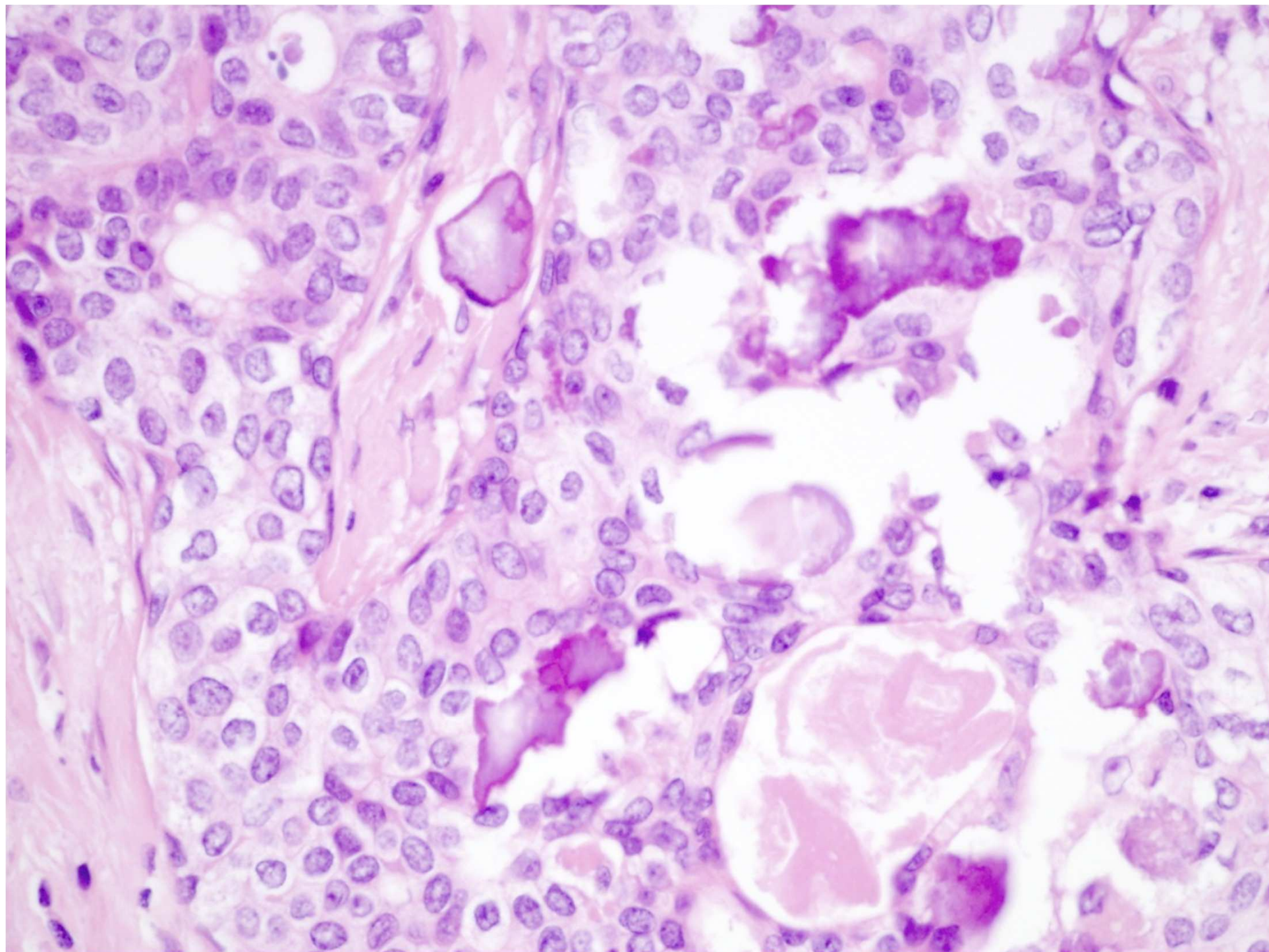


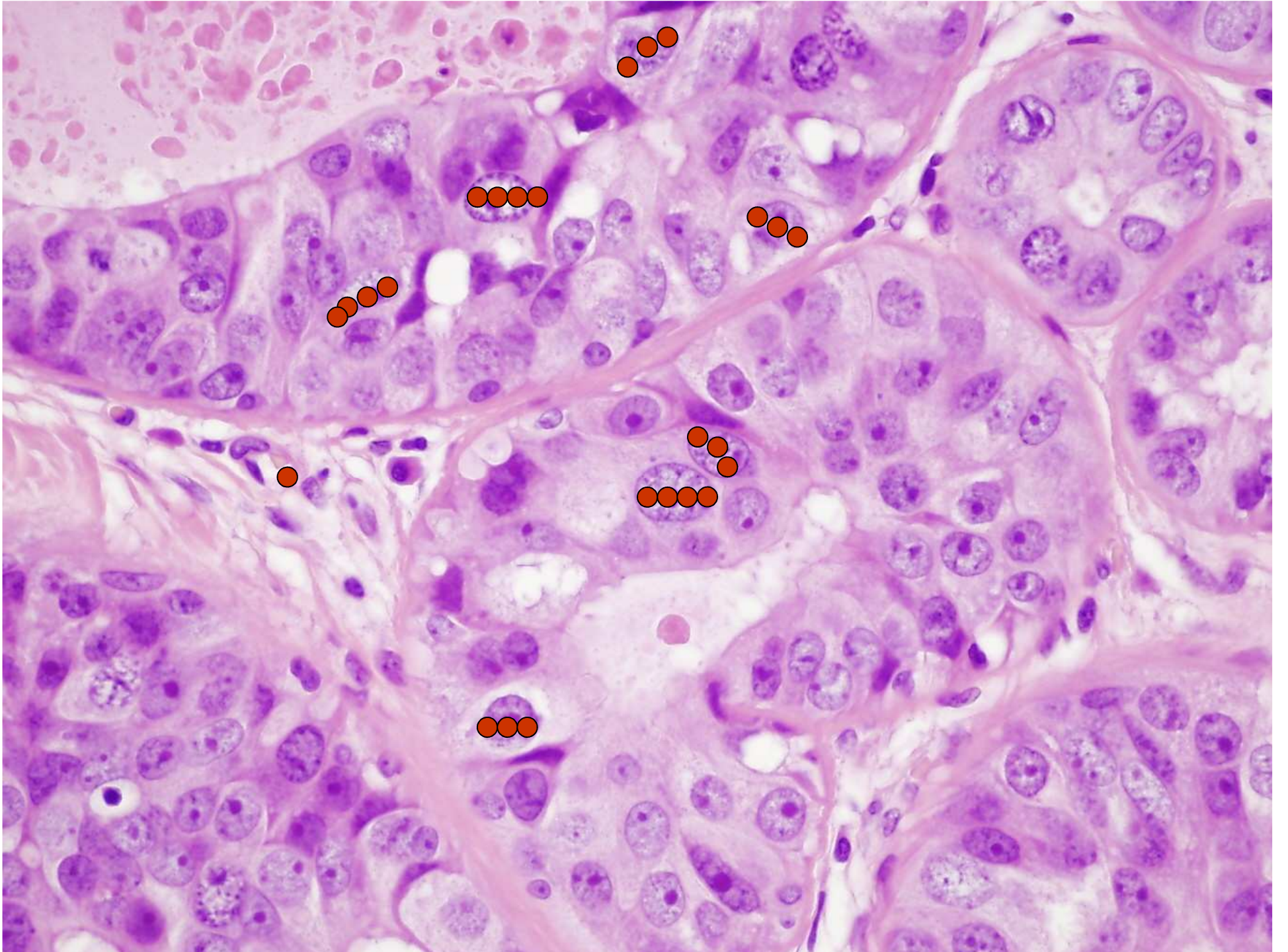


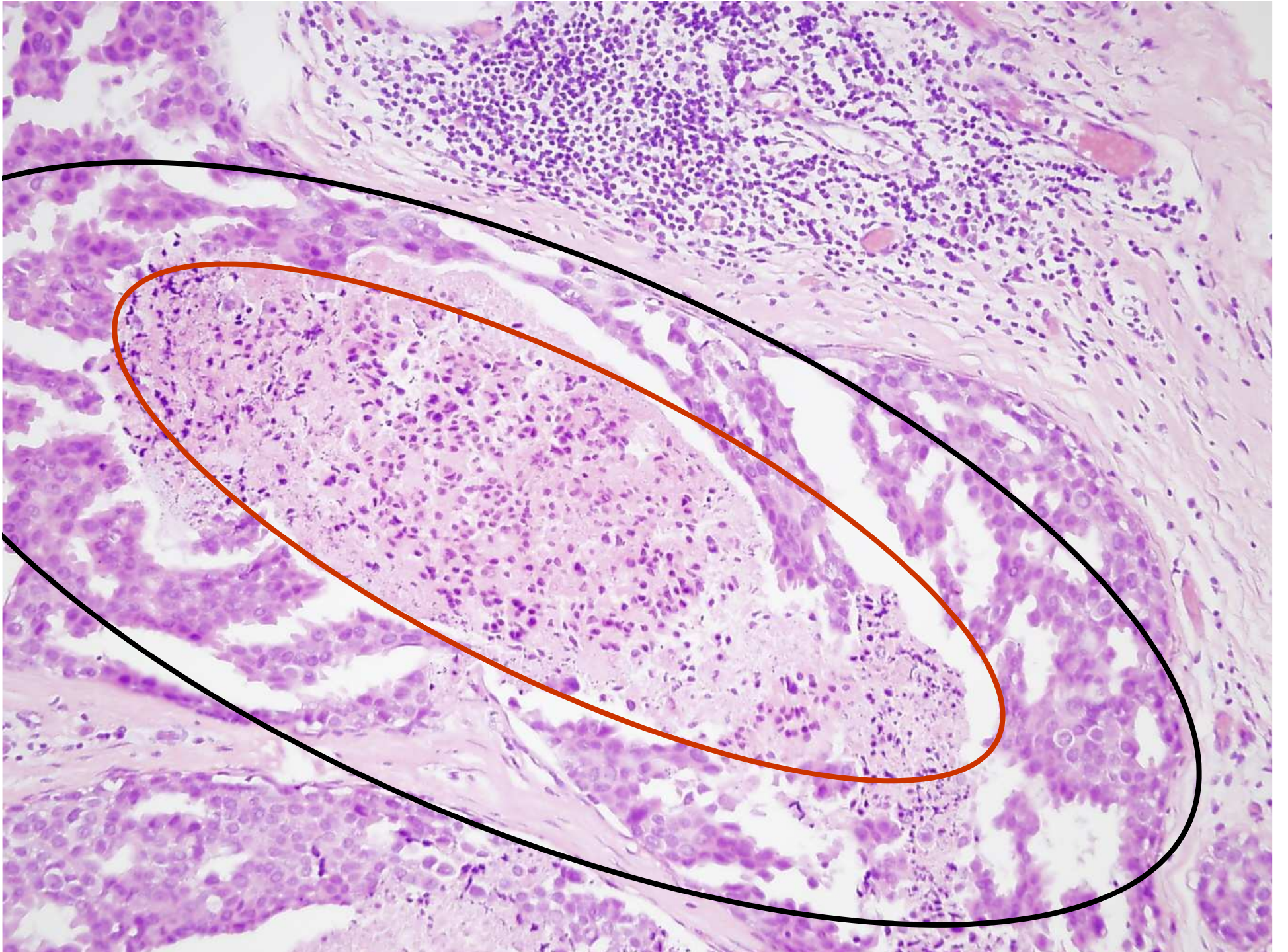


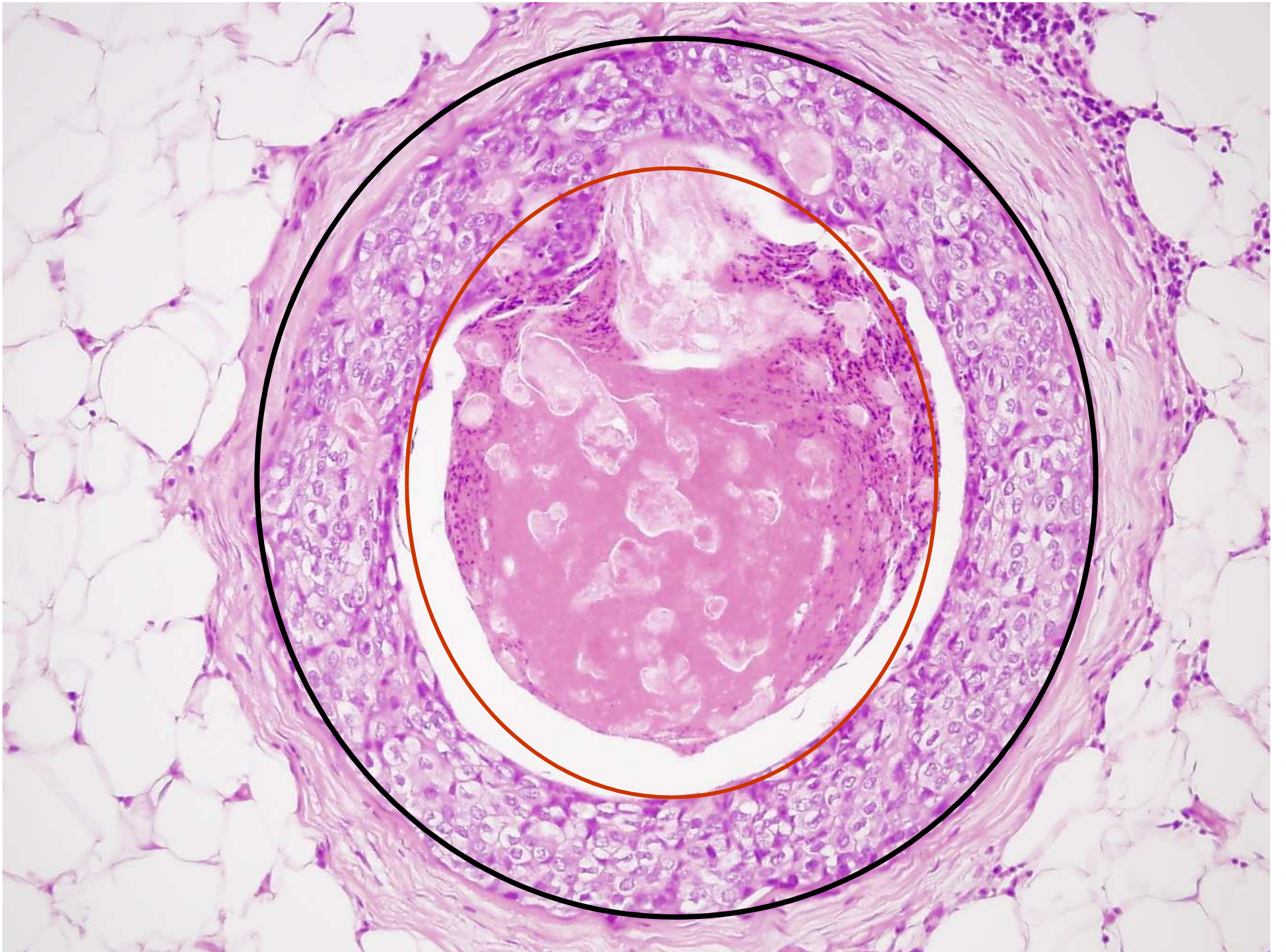


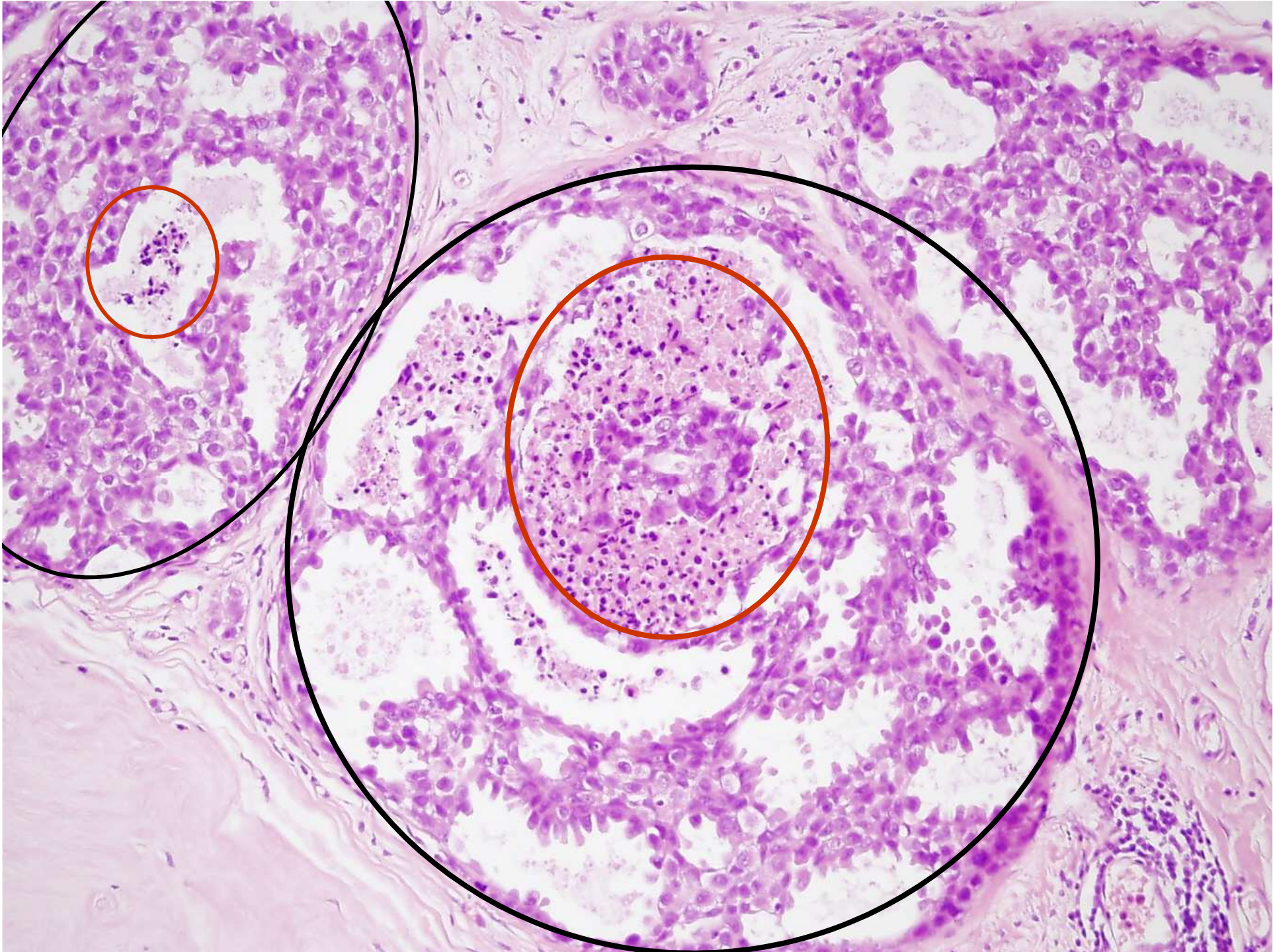














Nem necrosis!!!!

This histological image shows a cross-section of a breast duct. The duct is filled with a dense population of cells, many of which are arranged in a solid pattern. The central portion of the duct contains a large area of necrosis, which is a pale, amorphous mass of dead tissue. The surrounding stroma is composed of fibrous connective tissue and adipose tissue, which is visible as large, clear spaces. The overall appearance is characteristic of a ductal carcinoma in situ (DCIS) with central necrosis.

Van Nuys Grade

- Non-high grade, necrosis nincs 1
- Non-high grade, necrosis van 2
- High grade 3

Van Nuys prognosztikai index

Score	grade	méret	szélek	kor
1	1	$\leq 15\text{mm}$	$\geq 1\text{cm}$	>60
2	2	$>15 \leq 40\text{mm}$	$>1\text{mm} < 1\text{cm}$	40-60
3	3	$>40\text{mm}$	$\leq 1\text{mm}$	<40

Table 1. Summary of DCIS classification systems

Classification (feature(s) assessed)	Grade		
	High	Intermediate	Low
Lagios ^{2,14} (nuclear grade, mitoses, necrosis)	<i>High grade.</i> Large nuclei (two red blood cells in diameter) with vesicular chromatin, one or more nucleoli and a high mitotic index (2+ mitoses/10 hpf). Extensive linear coagulative necrosis of comedo type is present.	<i>Intermediate grade.</i> Intermediate nuclei (1–2 red blood cells in diameter) with coarse chromatin, infrequent nucleoli and an intermediate mitotic index (1–2 mitoses/10 hpf). Punctate necrosis may be present.	<i>Low grade.</i> Small nuclei (1–1.5 red blood cells in diameter) with diffuse chromatin, inapparent nucleoli and a low mitotic index (< 1 mitoses/10 hpf). Necrosis absent.
Tavassoli ²¹ (cytological atypia, necrosis)	<i>High grade.</i> DCIS showing cytological atypia and necrosis. Includes all comedo carcinomas and signet ring cell variants of intraductal carcinoma and many intraductal apocrine carcinomas.	<i>Moderate grade.</i> This category contains three groups. (1) DCIS lacking cellular atypia and forming solid, cribriform or micropapillary patterns with central necrosis. (2) Cribriform, micropapillary or solid patterns with cytologic atypia but no necrosis. (3) DCIS variants showing an admixture of two uniform cell types ± necrosis.	<i>Low grade.</i> Cribriform and micropapillary patterns. Uniform population of cells lacking necrosis or atypia.
European Pathologists Working Group ²² (differentiation = nuclear grade & cell polarization)	<i>Poorly differentiated.</i> Nuclei very pleomorphic with irregular outlines and spacing. Chromatin coarse and clumped with prominent nucleoli. Mitoses often seen. Cell polarization absent or minimal. Central necrosis and individual cell necrosis usually present, often associated with amorphous calcification.	<i>Intermediately differentiated.</i> Nuclei mildly or moderately pleomorphic with some variation in size, outline and spacing. Chromatin fine to coarse and nucleoli evident. Occasional mitoses. Cell polarization seen. Central necrosis variable. Individual cell necrosis may be present. Calcifications amorphous or laminated.	<i>Well differentiated.</i> Evenly spaced monomorphic nuclei of uniform size and regular outline. Chromatin uniform and fine, nucleoli insignificant and mitoses rare. Polarization of cells marked. Necrosis absent or minimal. Calcifications usually laminated and rarely amorphous.
European Breast Screening Groups ^{11,23} (nuclear grade)	<i>High nuclear grade.</i> Pleomorphic cells with irregularly spaced and usually large nuclei exhibiting marked variation in size, irregular nuclear contour, coarse chromatin and prominent nucleoli. Mitoses frequent and abnormal forms may be seen. Growth patterns variable but often solid or comedo. Cell polarization rare.	<i>Intermediate nuclear grade.</i> Mild to moderate nuclear pleomorphism, less than that in high-grade DCIS but without the monotony of the low-grade type. Nucleo-cytoplasmic ratio often high. One or two nucleoli may be identified. Growth pattern usually solid, cribriform or micropapillary. Some degree of cell polarization.	<i>Low nuclear grade.</i> Monomorphic, evenly spaced cells with roughly spherical centrally placed nuclei and inconspicuous nucleoli. Mitoses few. Individual cell necrosis rare. Architecture often micropapillary and cribriform with polarized cells.
Nottingham ¹² (necrosis and morphology)	<i>Pure comedo.</i> Central lumina containing necrotic debris surrounded by large pleomorphic viable cells in solid masses.	<i>DCIS with necrosis (non-pure comedo).</i> Necrotic neoplastic cells within duct lumina but lacking a pure comedo pattern and often showing a cribriform or micropapillary architecture.	<i>DCIS without necrosis.</i> No necrosis or necrosis limited to a few necrotic or desquamated cells within intraductal lumina. Includes majority of classical cribriform, papillary and micropapillary subtypes.
Van Nuys ²⁴ (nuclear grade, necrosis)	<i>High grade.</i> Nuclei greater than two red blood cells in diameter, with vesicular chromatin and one or more nucleoli. Comedo necrosis (DCIS with central lumina containing necrotic debris surrounded by large pleomorphic cells or necrotic neoplastic cells within ducts with other architectural patterns, e.g. cribriform or micropapillary) usually present but not essential.	<i>Non-high grade with necrosis.</i> Low grade nuclei (1–1.5 red blood cells in diameter with diffuse chromatin and inapparent nucleoli) or intermediate grade nuclei (1–2 red blood cells in diameter with coarse chromatin and infrequent nucleoli) and comedo type necrosis. No minimum requirement for comedo necrosis but individual necrotic cells not scored.	<i>Non-high grade without necrosis.</i> Low or intermediate grade nuclei and no comedo necrosis.
Ottesen <i>et al.</i> ¹⁷ (size, circumscription, stromal fibrosis)	<i>Tumour forming.</i> DCIS macroscopically larger than 5 mm with closely related <i>in situ</i> formations and the surrounding stroma showing confluent fibrosis.	<i>Diffuse.</i> DCIS macroscopically and microscopically ill delimited, larger than 5 mm and exhibiting segmental-like extensions. Stromal fibrosis varies from little to moderate.	<i>Microfocal.</i> DCIS measuring 5 mm or less in diameter. Localized to one or a few lobules or ducts.

- LCIS

- Nem általánosan terjedt el a LCIS esetekben a grade megadása
- Fel kell azonban ismerni a high grade LCIS eseteket, amelyek radiológiai és szöveti képe nagyon hasonlíthat DCIS-re

Clinical Importance of Histologic Grading of Lobular Carcinoma In Situ in Breast Core Needle Biopsy Specimens

Current Issues and Controversies

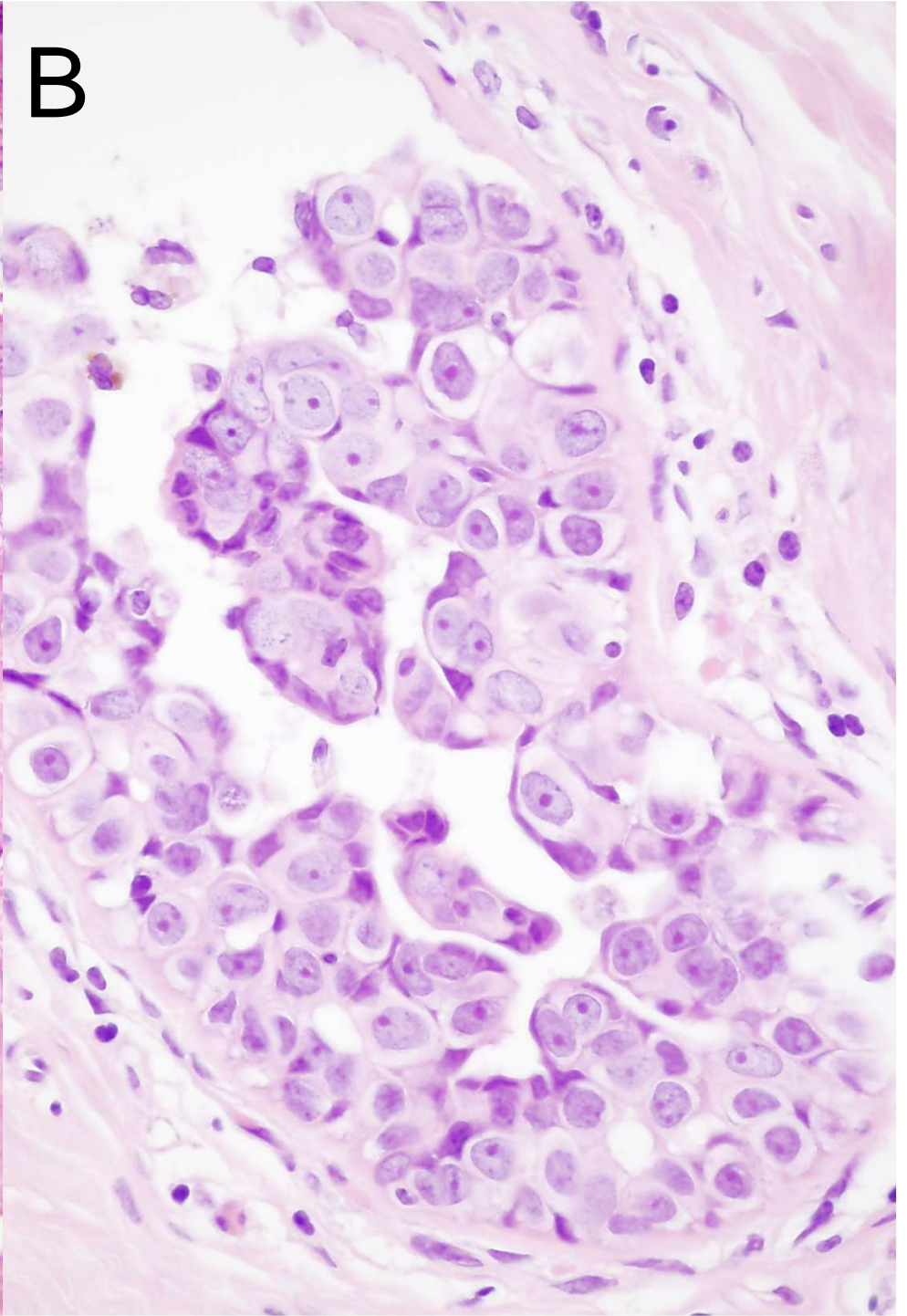
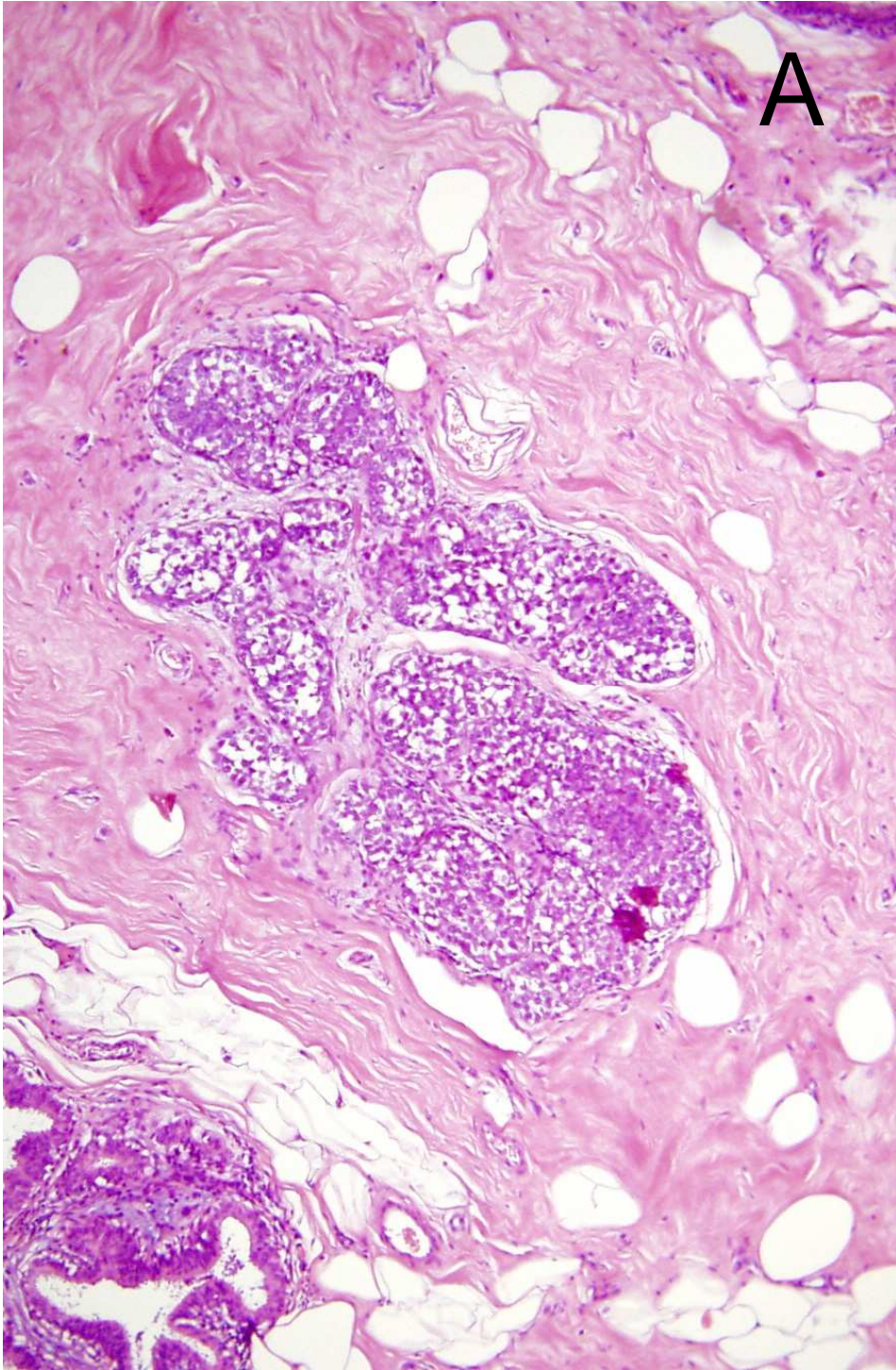
Faye Gao, MD, PhD, Gloria Carter, MD, George Tseng, ScD, and Mamatha Chivukula, MD

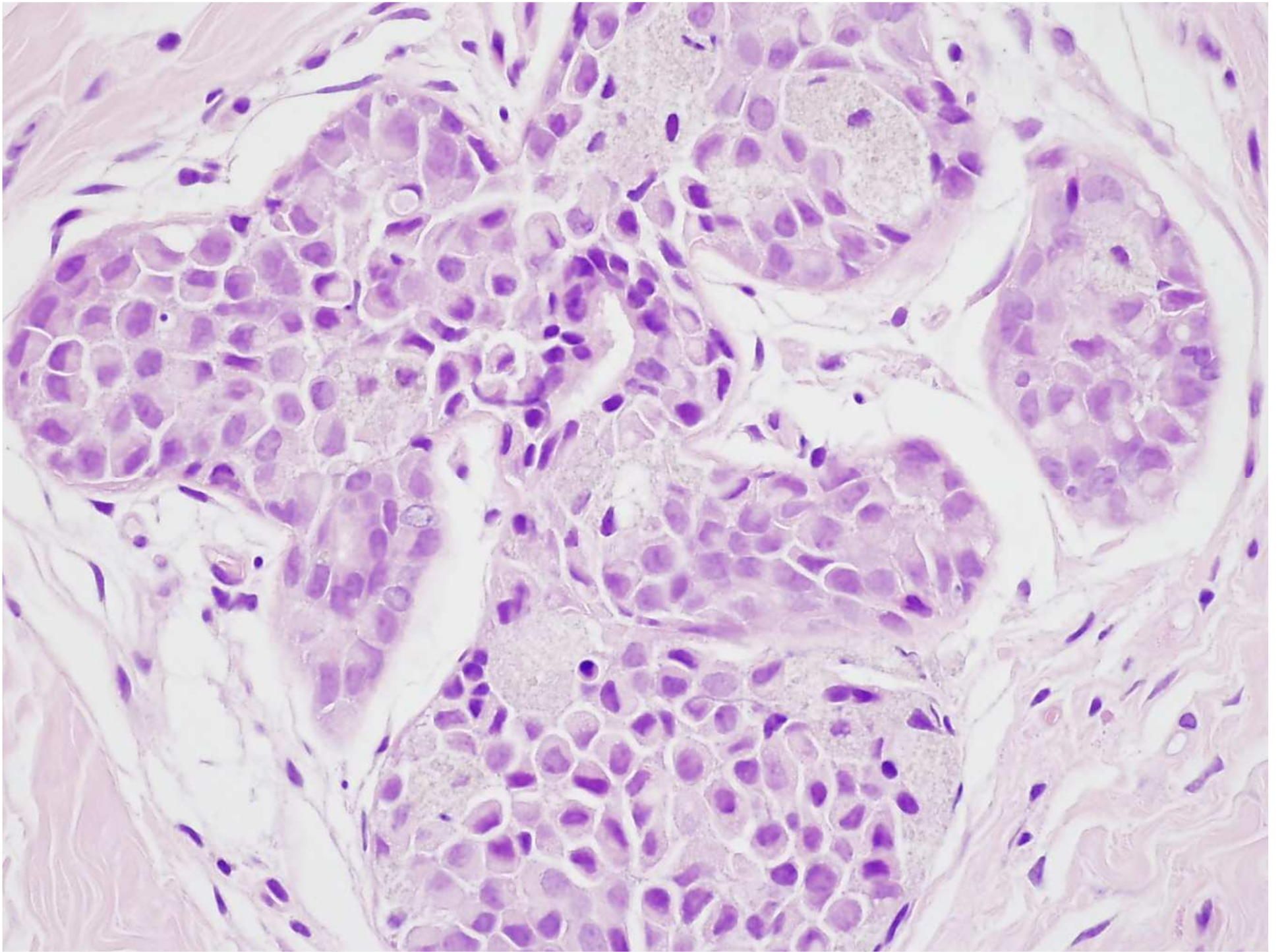
A típusú sejtek: kis, egyforma, kerek, keskeny cytoplazmájú, hyperkróm magvú diszkohezív sejtek

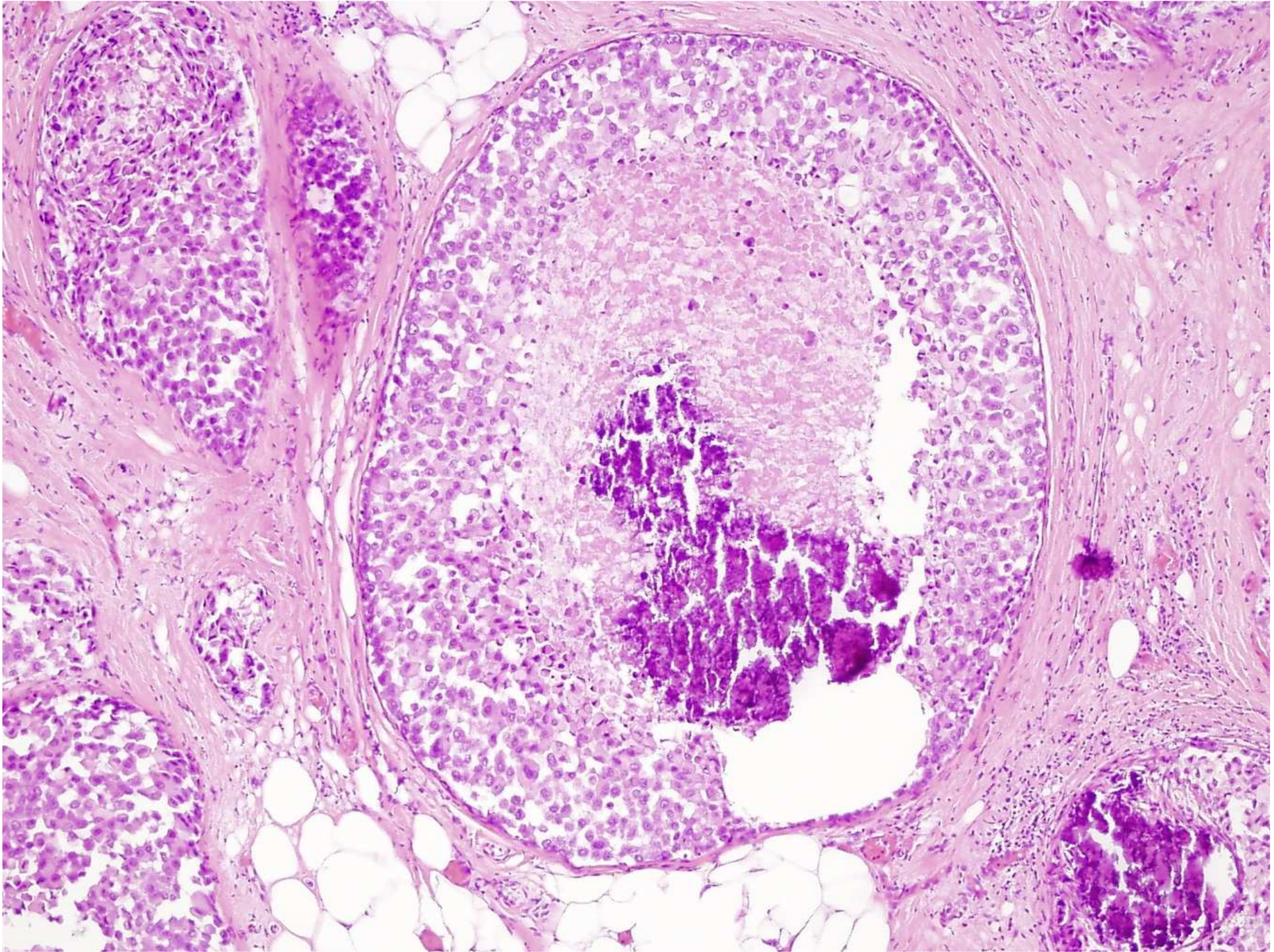
B típusú sejtek: közepesen polimorf, szélesebb-világos festődésű cytoplazmával és rögös kromatinállományú, jól látható nucleoluszt tartalmazó maggal rendelkező diszkohezív sejtek

Pleomorf LCIS nagy, pleomorf, diszkohezív sejtek, grade 3 magokkal, széles eozinofil cytoplazmával. Comedo nekrosis gyakori

- LCIS grade 1: predomínánsan A típusú sejtek alkotják
- LCIS grade 2: >10-90% B típusú sejtek alkotják
- LCIS grade 3: pleomorf LCIS







Köszönöm a figyelmet

