Challenges in Colon Cancer Reporting

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Conflicts of Interest

- I have done consulting work for
  - Astellas Pharma Inc
  - Bristol Myers Squibb
  - GlaxoSmithKline
  - Vertex Pharmaceuticals

- No information related to these activities will be discussed in this talk

Outline

1. Case 1 – challenges in T-category staging (no neoadjuvant tx)
2. Case 2 – challenges in T-category staging (neoadjuvant tx)
3. Case 3 – challenges in N-category staging
4. Additional challenges in N-category staging
5. Other challenges in synoptic reporting

AJCC 8th Edition Staging for Colon Cancer

- pTis: Carcinoma in situ
- pT1: Invasion of submucosa
- pT2: Invasion of muscularis propria
- pT3: Invasion of pericolorectal tissue (including subserosa)
- pT4a: Invasion of visceral peritoneum
- pT4b: Direct invasion into/adherence to other structures

AJCC 8th Edition Staging for Colon Cancer

- pN0: 0 nodes involved
- pN1a: 1 node involved (tumor measuring ≥0.2 mm)
- pN1b: 2-3 nodes involved
- pN1c: Tumor deposits and no nodes involved
- pN2a: 4-6 nodes involved
- pN2b: >6 nodes involved

AJCC 8th Edition Staging for Colon Cancer

- pM0: No distant metastasis (not a pathologist determination)
- pM1a: Metastasis to 1 distant site/organ, no peritoneal mets
- pM1b: Metastasis to >1 distant site/organ, no peritoneal mets
- pM1c: Peritoneal mets, +/- distant mets

Why Does Staging Matter?

- Stage I (pT2N0 or better) – probably no adjuvant therapy
- Stage IIB-IVC (pT4aN0 or worse) – probably adjuvant therapy
- Stage IIA (pT3N0) – the area of uncertainty
  - Any adverse risk factors? LVI, PNI, high-grade, tumor budding, perforation, etc.

Case 1

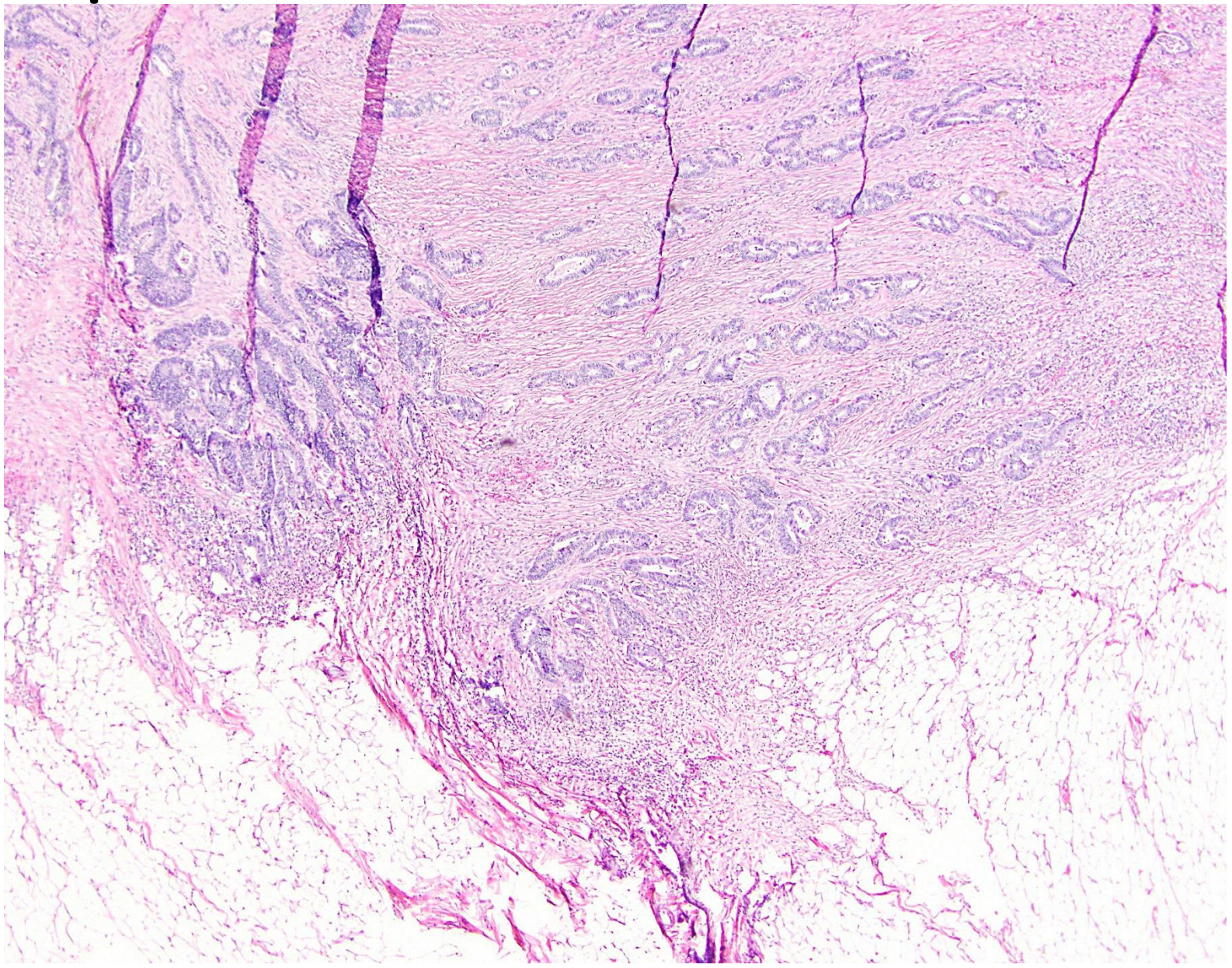
- An untreated colorectal carcinoma extends to within 1 mm of the serosal surface. There is inflammation and fibrosis between the tumor and the serosal surface.

- Should this be staged as pT3 or pT4a?

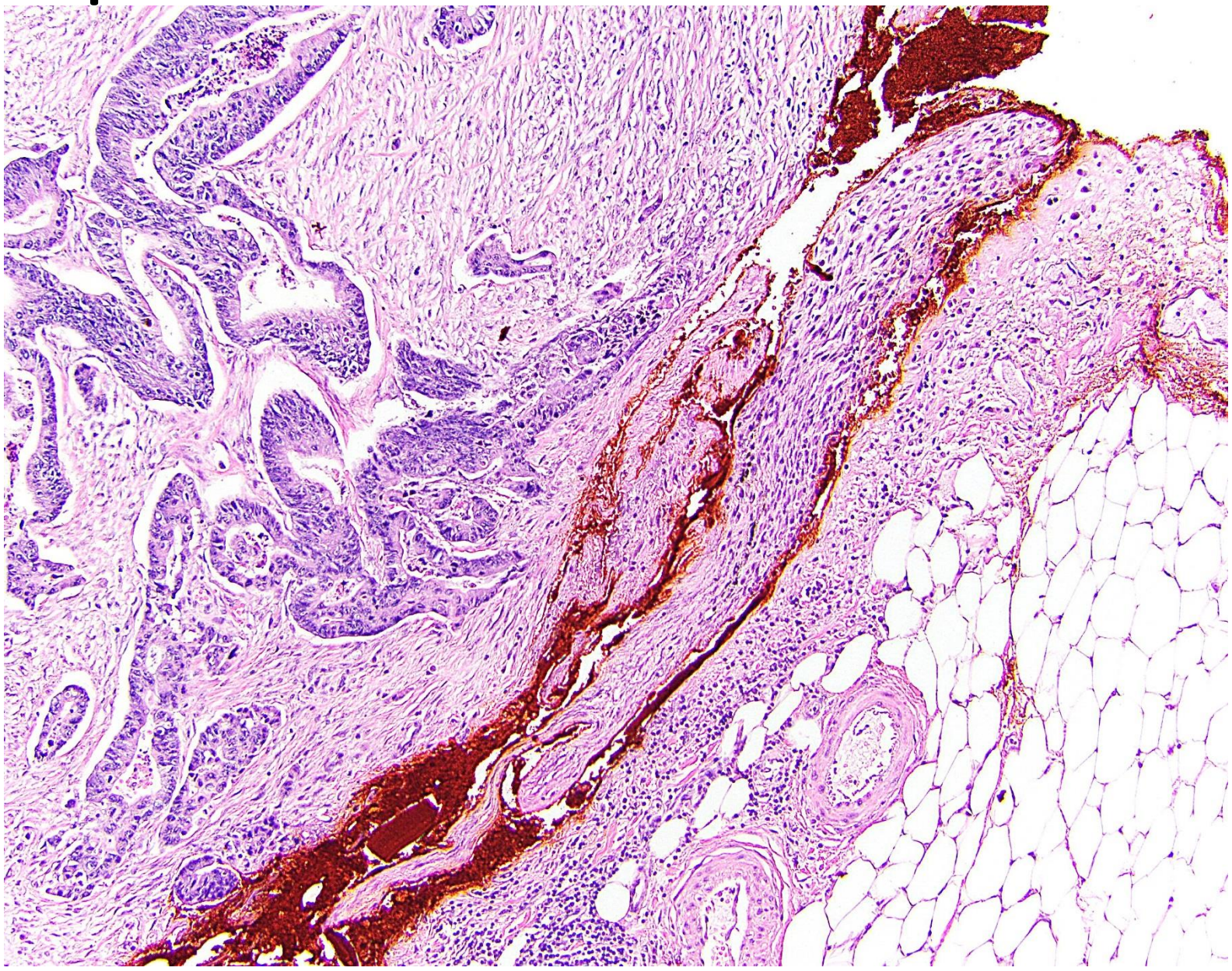
pT3 and pT4 – so close, yet so far

- CRC may extend to within 1 mm of serosal surface, sometimes with accompanying inflammatory reaction
- Unclear whether this should be considered serosal disease or not
  - Several studies have indicated no
- Panarelli et al: 11% of such cases developed peritoneal carcinomatosis
  - Compared to 3% of clear pT3 and 18% of clear pT4a

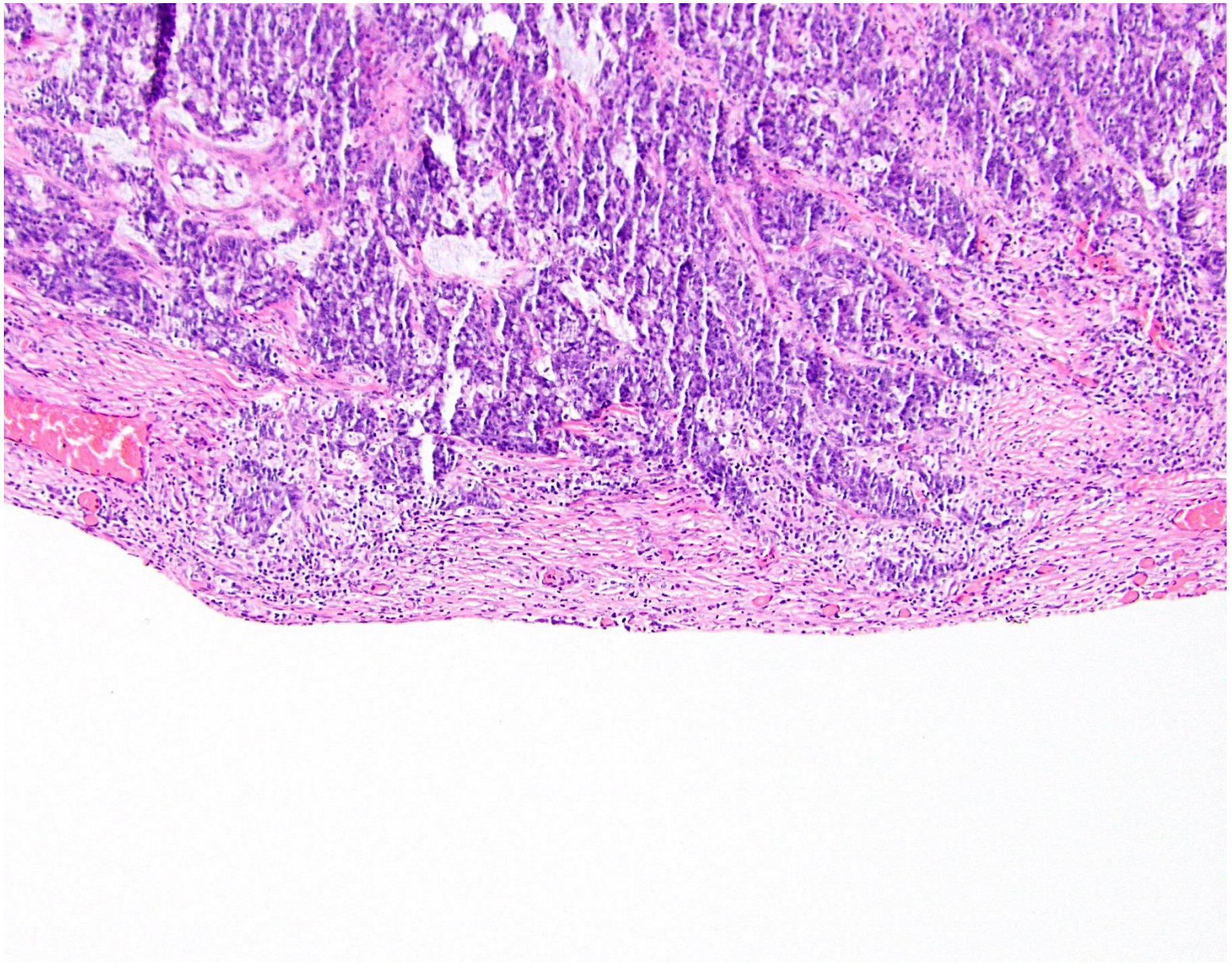
Obvious pT3



Obvious pT4



Now What?



Options for Evaluating Equivocal T3/T4 Disease

- Additional levels or additional gross sections
  - CAP recommendation
- Elastic stain
  - Highlights peritoneal elastic lamina – but does breach prove pT4a?
- Touch prep of serosal surface
  - Panarelli et al: 46% of CRC with tumor < 1mm from serosa had tumor cells on touch prep
- Just call it pT4!

Survey

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ARTICLE

Challenges with colorectal cancer staging: results of an international study

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Survey

- H&E section from surgical resection of untreated colon cancer shows viable tumor that is >1 mm from the serosal surface but is continuous with the peritoneal surface through inflammation. How will you stage this tumor?
- pT3: 49%
- pT4: 51%

Case 2

- A treated rectal carcinoma is resected, and there is residual tumor consisting of strips of malignant epithelium floating in large mucin pools. The deepest pool extends into the muscularis propria, but the malignant epithelial cells float in the upper part of the mucin pool, in the region of the submucosa.

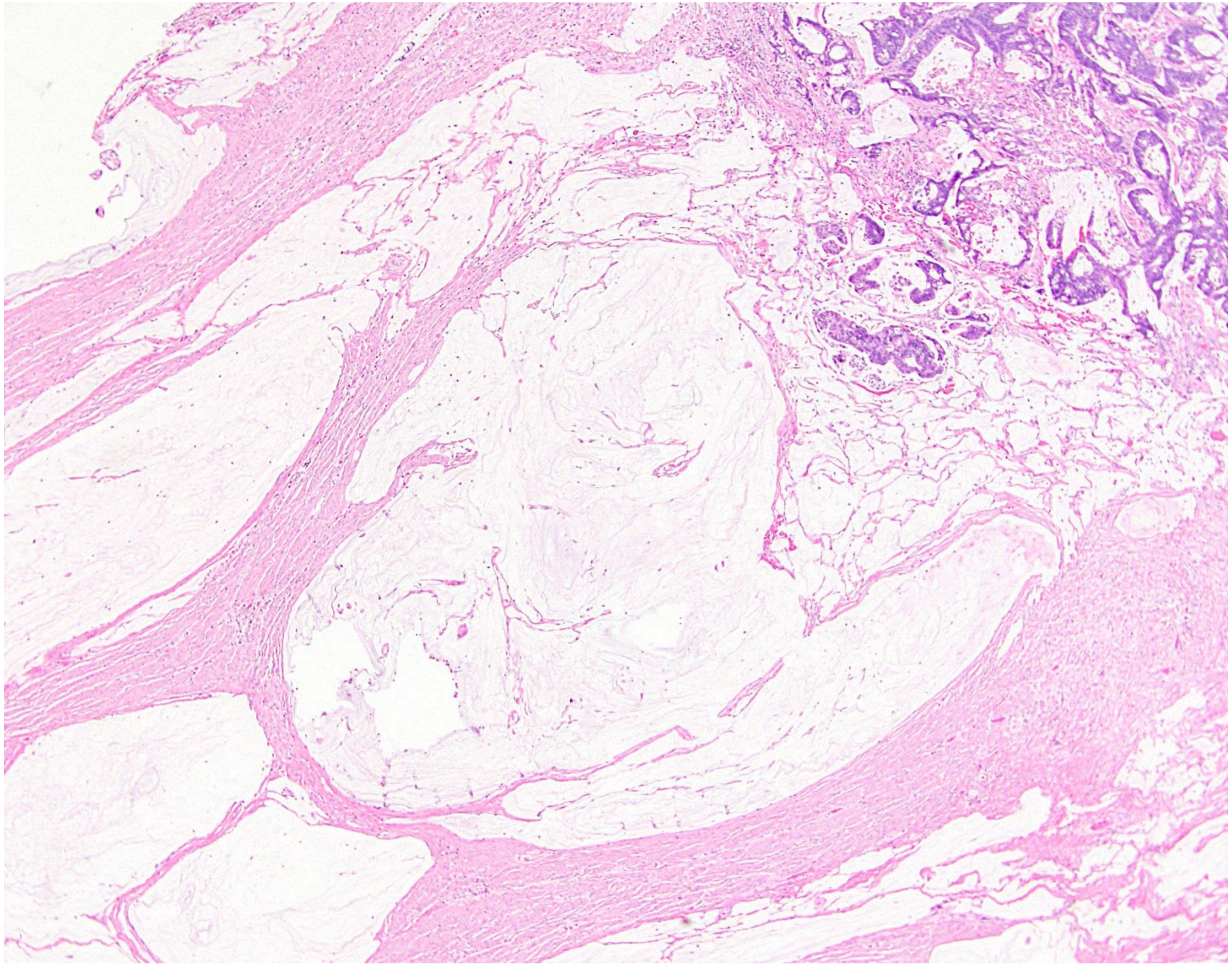
- Should this be staged as ypT1 or ypT2?

Neoadjuvant Therapy in Rectal Carcinoma

- Advanced rectal cancer typically undergoes neoadjuvant therapy prior to resection
- In cases with moderate response, some of the tumor dies off, leaving acellular or paucicellular mucin in its place

- Should staging report where the tumor is? Where the tumor was? Where the tumor could be?

How Low Can You Go?



Survey

- A neoadjuvant-treated rectal cancer consists of large mucin pools that dissect into muscle wall. Viable tumor cells (floating in mucin pools, marked by arrow) are only found in the submucosa, but the same mucin pools extends into the muscularis propria where they contain no epithelium. How would you stage this?
- ypT1: 65%
- ypT2: 35%

Case 3

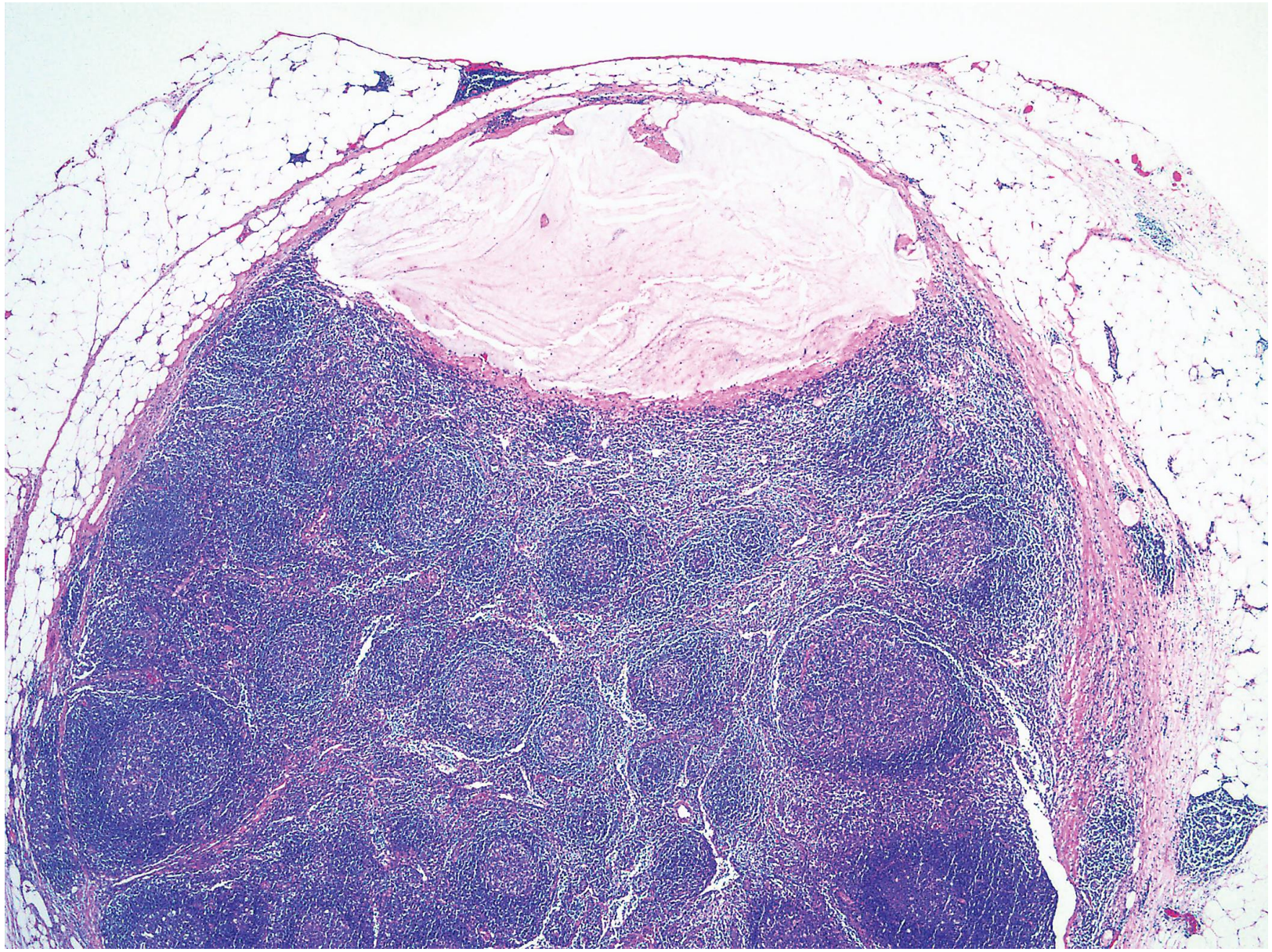
- An untreated colorectal carcinoma is resected, and none of the nodes show malignant epithelium. However, two nodes show acellular mucin, with no cells seen on levels or immunohistochemical stains.

- Should this be staged as pN0 or pN1b?

Acellular Mucin, Sans Neoadjuvant Therapy

- “Treated lymph nodes” with acellular mucin are not uncommon in rectal cancer following neoadjuvant therapy
- Rarely, they can be seen in the absence of presurgical treatment
  - CAP and AJCC: no recommendation
  - UICC: positive for carcinoma

No Neoadjuvant Therapy

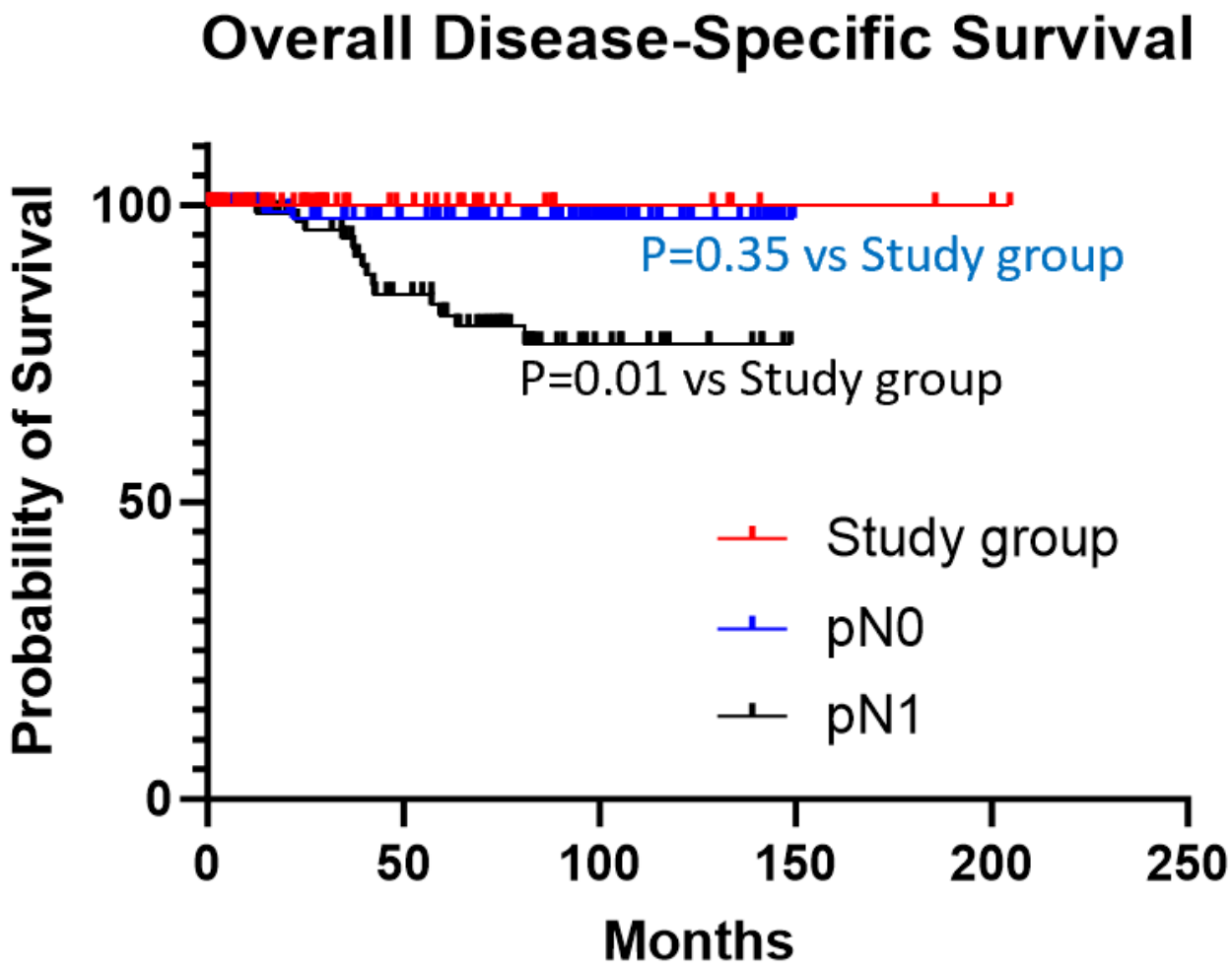


Survey

- Left hemicolectomy of an untreated colonic carcinoma … 2 of 35 lymph nodes show acellular mucin with no viable tumor cells (despite multiple deeper levels). How would you stage this?
- pN0: 67%
- pN1b: 33%

Acellular Mucin, Sans Neoadjuvant Therapy

- Recent publications indicate this is almost exclusively seen in MMR-deficient CRC and does not indicate poor prognosis
  - Therefore, behaves like pN0



Additional Challenges in N-Category Staging

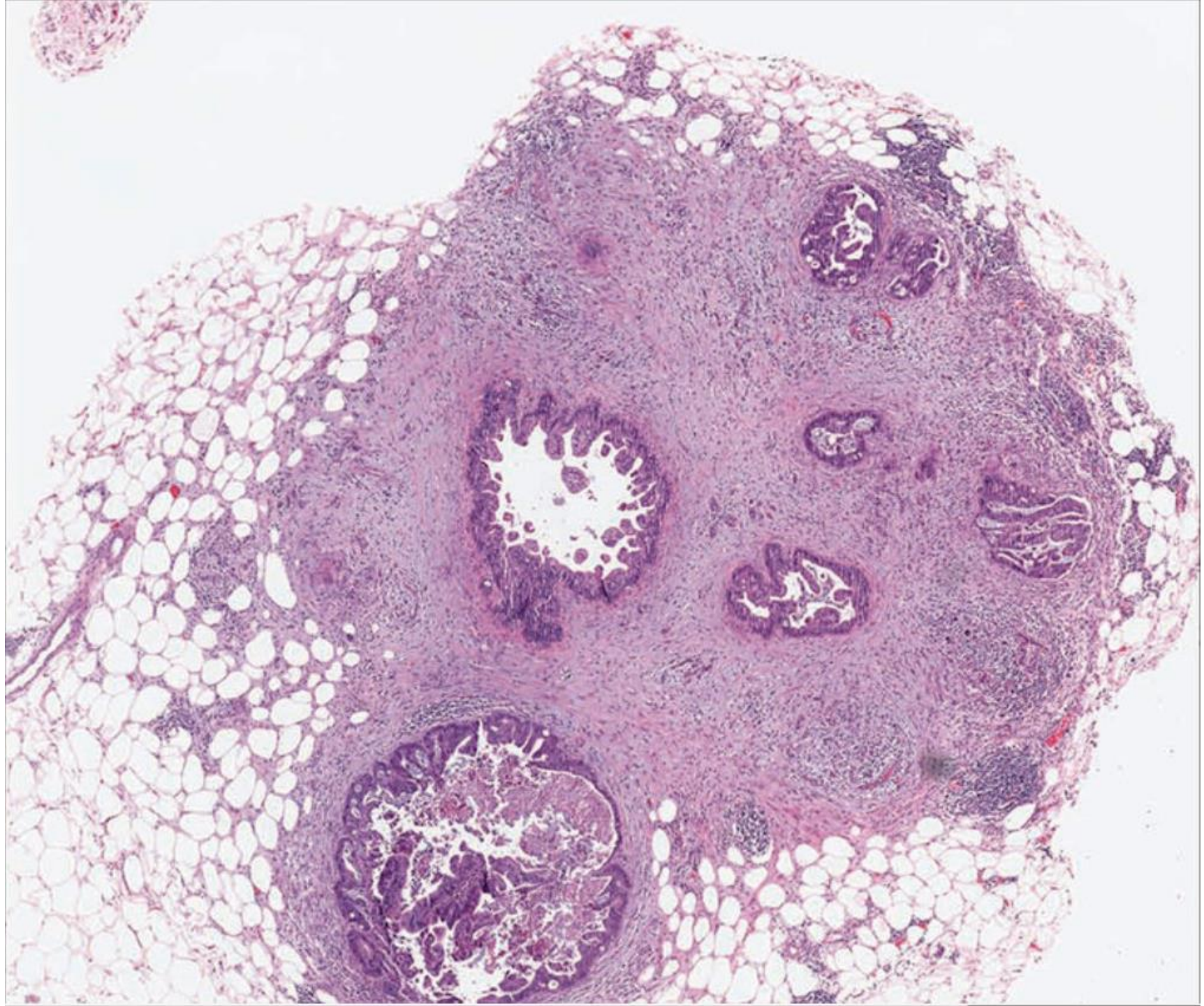
- Sufficient number of lymph nodes
- Tumor deposits
- Isolated tumor cells

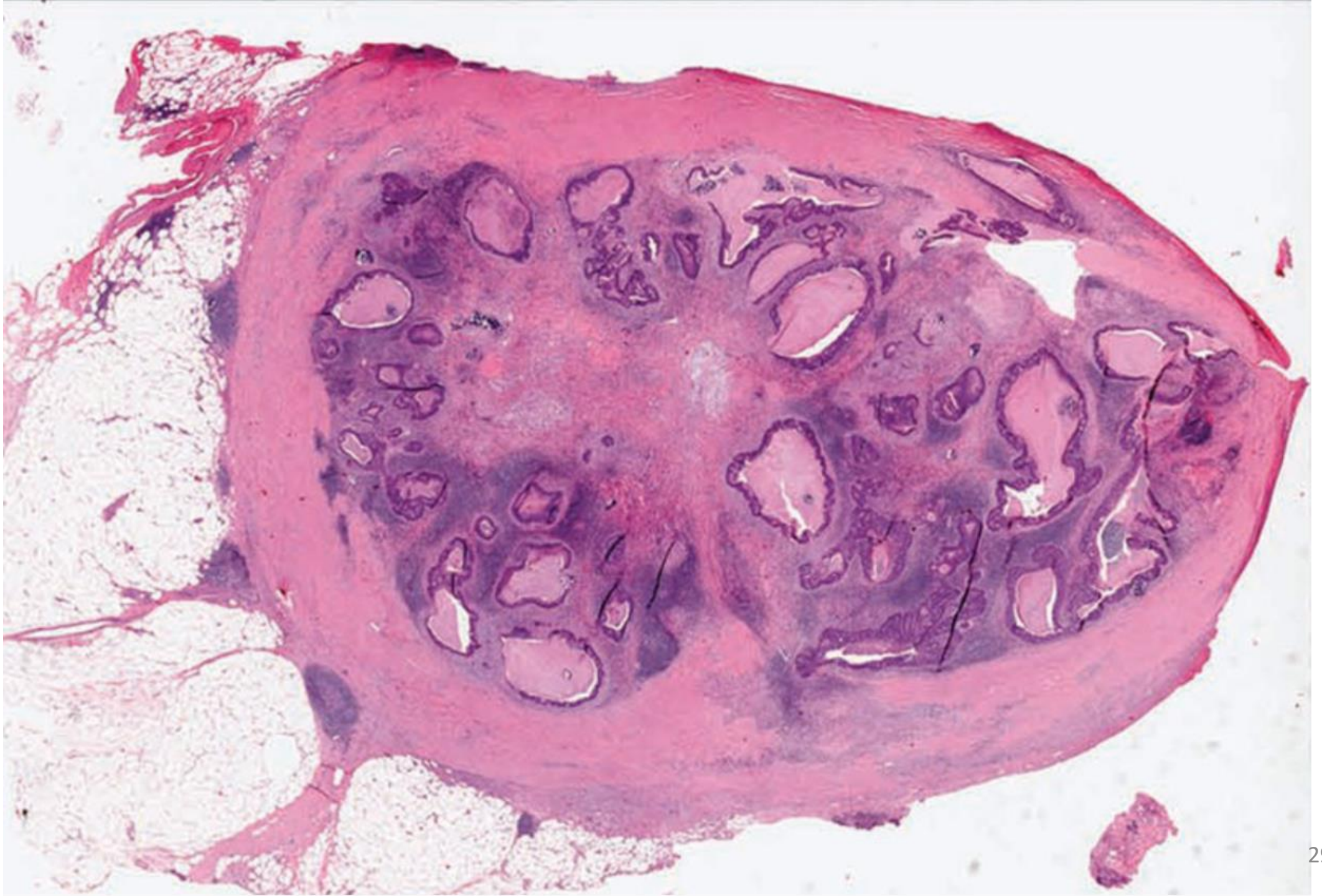
More Lymph Nodes, Please

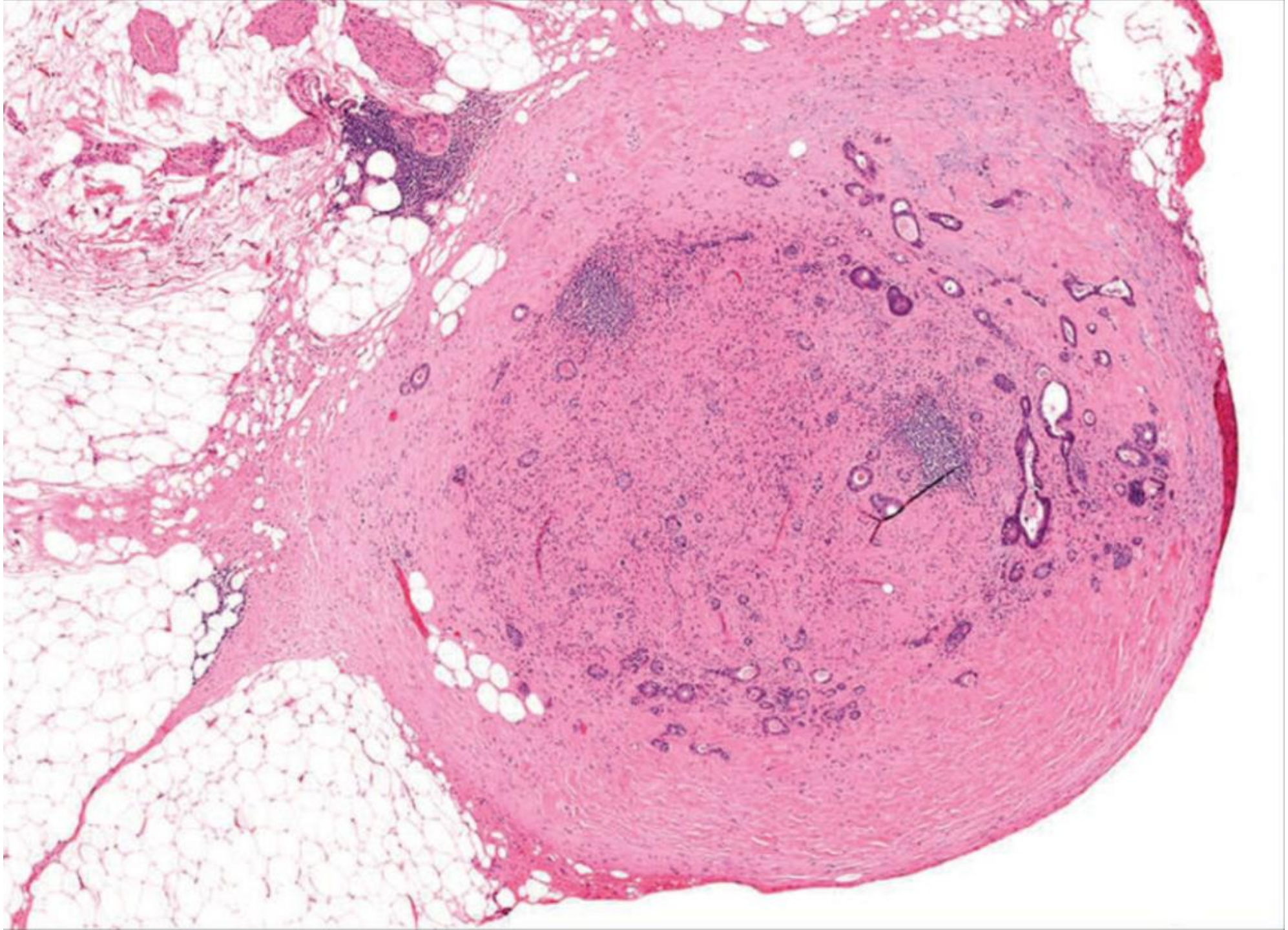
- General minimum consensus standard is 12 nodes
  - AJCC, ACS, NQF, etc.
  - Various studies have suggested from 7 to 17 nodes
- Small nodes can be easily missed grossly but still contain metastasis
- Some studies have indicated poor survival in patients with fewer reported nodes
  - Are we missing metastases?
  - Or do these patients have decreased immune response?
- Oncologist may not trust the accuracy if < 12 LNs reported – chemo?
- Options: clearing solutions, tossing in fat, apologetic comment

Tumor Deposits … What, Where, Why

- Discrete, discontinuous focus of carcinoma separate from the primary mass, located in the subserosa, mesentery, or nonperitonealized pericolic or perirectal/mesorectal tissue
- Does not represent lymph node involvement, lymphovascular invasion, perineural invasion, or direct tumor spread
- Landau et al, study of 150 stage 3 CRC:
  - Patients with TDs have worse disease-specific survival than patients with 0-3 positive LNs ($P<0.001$ for 0; $P=0.02$ for 1-3)
  - Patients with TDs have a 2.2-fold risk of disease recurrence ($P=0.02$)

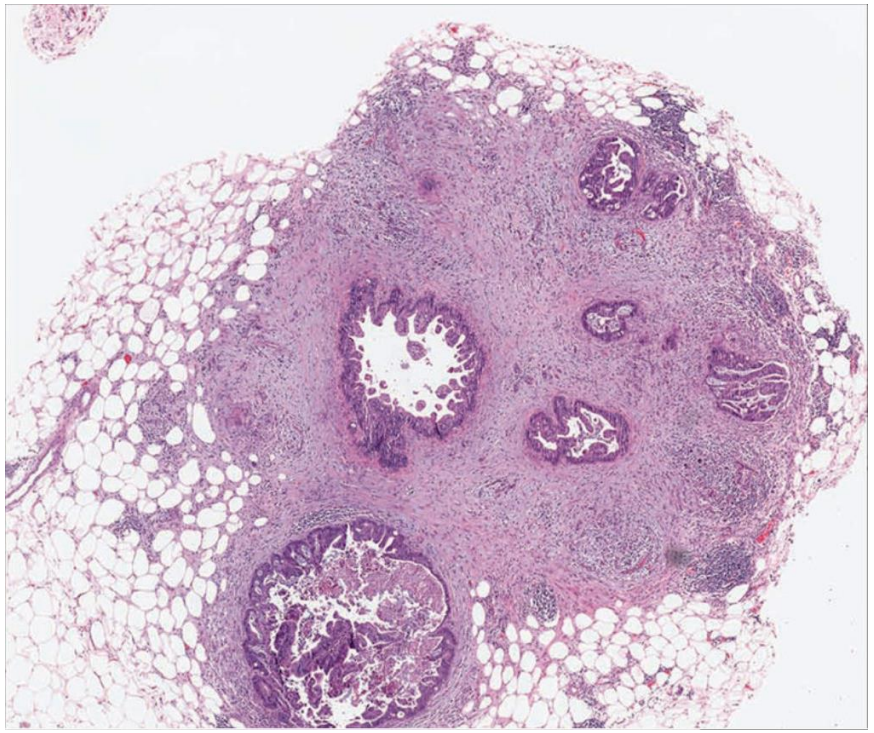






Expert (Dis)agreement in Diagnosing TDs

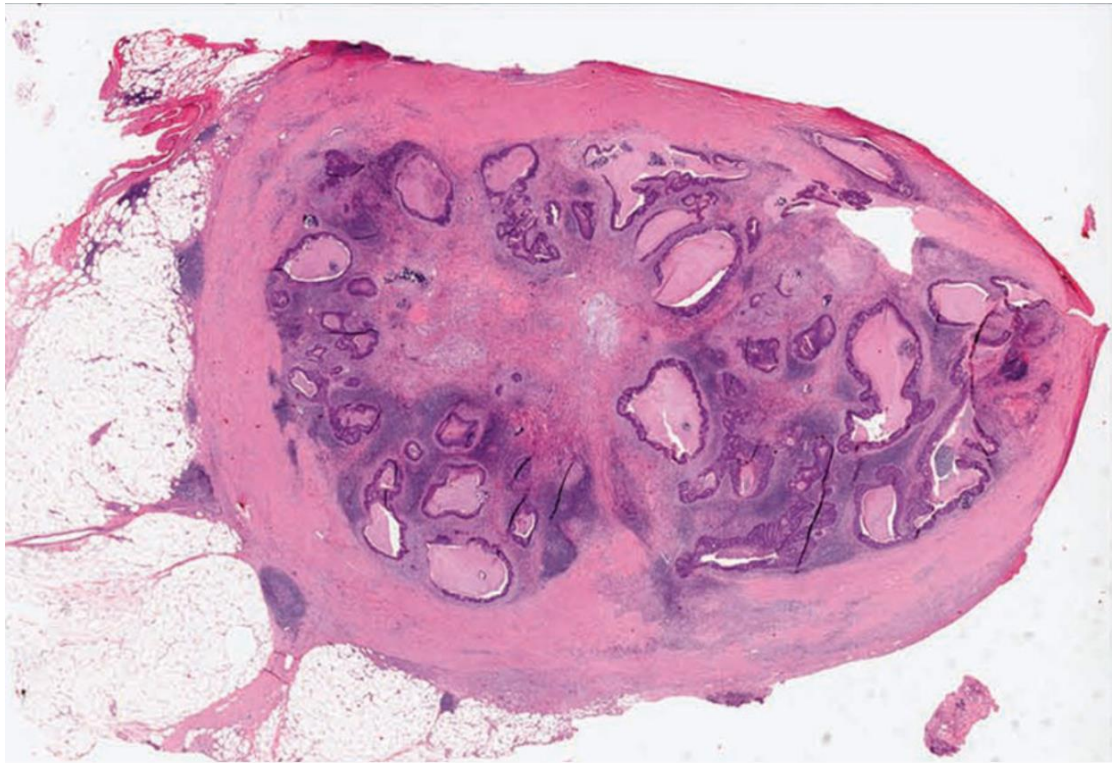
- Rock et al: 25 tumor foci were circulated among 7 gastrointestinal pathologists
- Complete agreement was found for 11: 5 LNs and 6 TDs



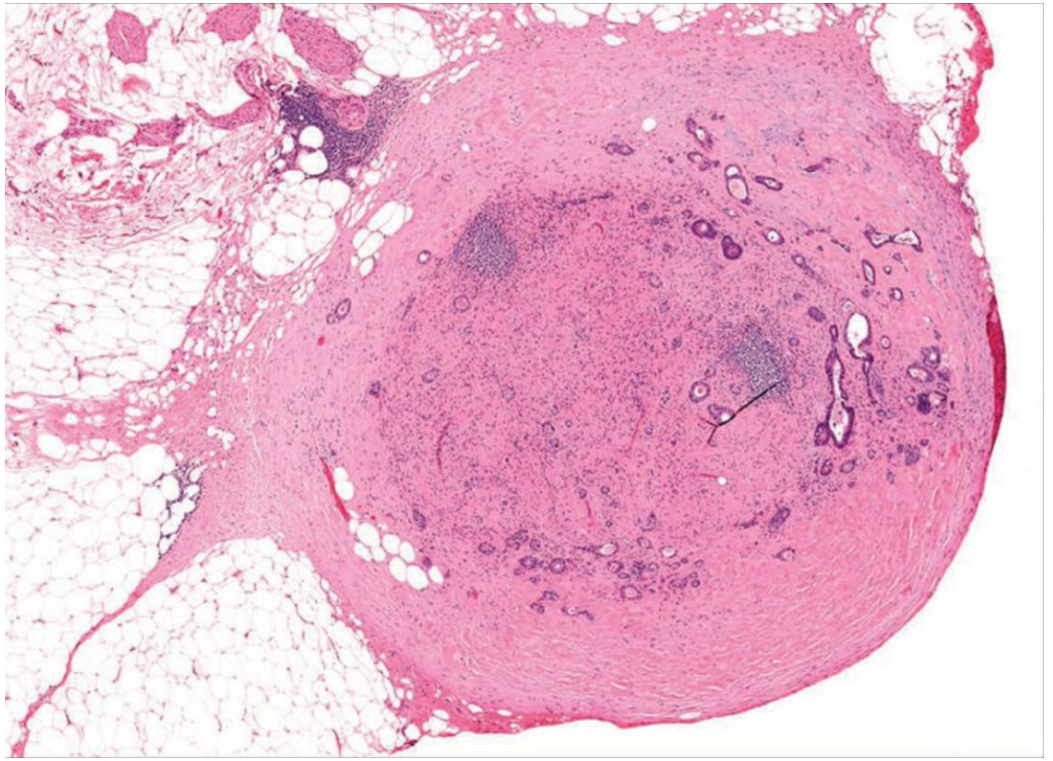
7 of 7 called this a TD

Expert (Dis)agreement in Diagnosing TDs

- Diagnostic criteria most often utilized: round shape, thick capsule, peripheral lymphoid follicles, peripheral rim of lymphocytes, > 3mm

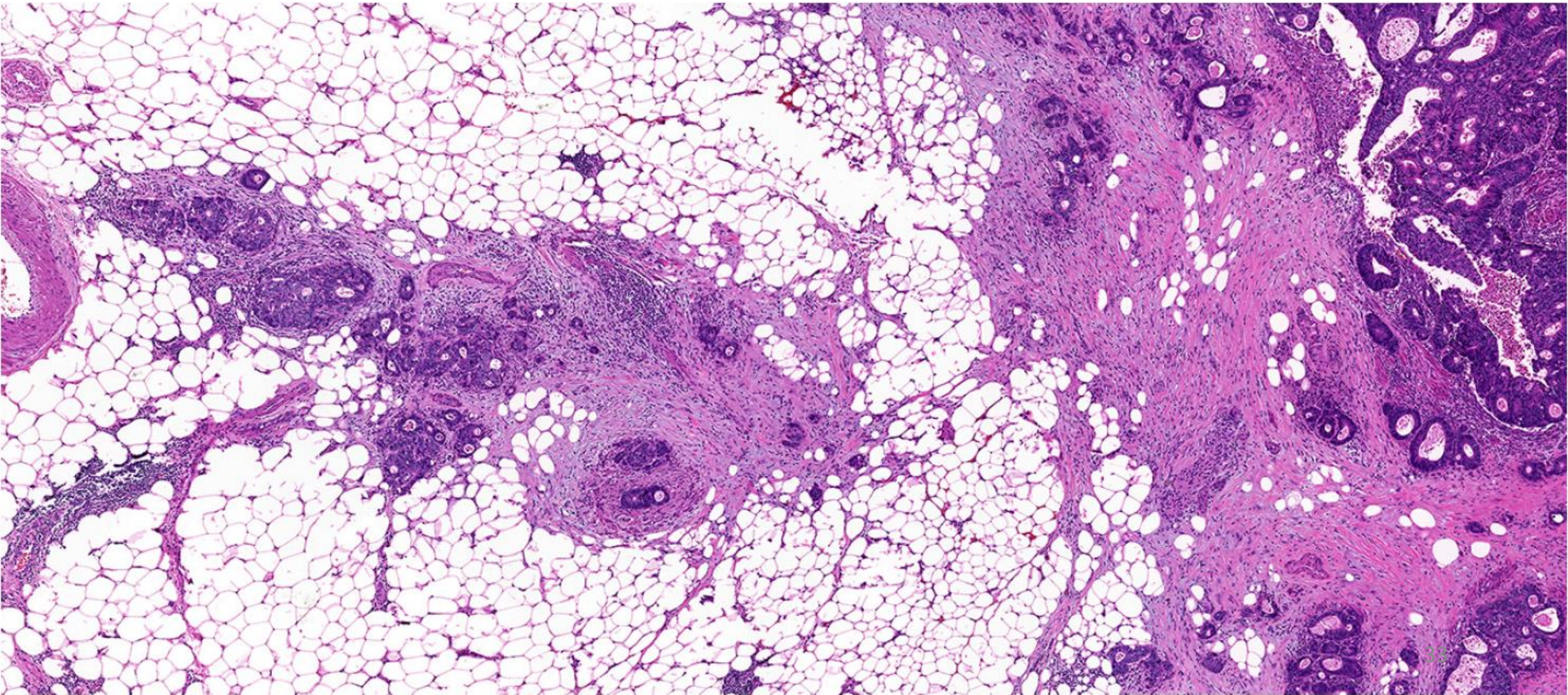


6 of 7 called this a LN



4 of 7 called this a LN

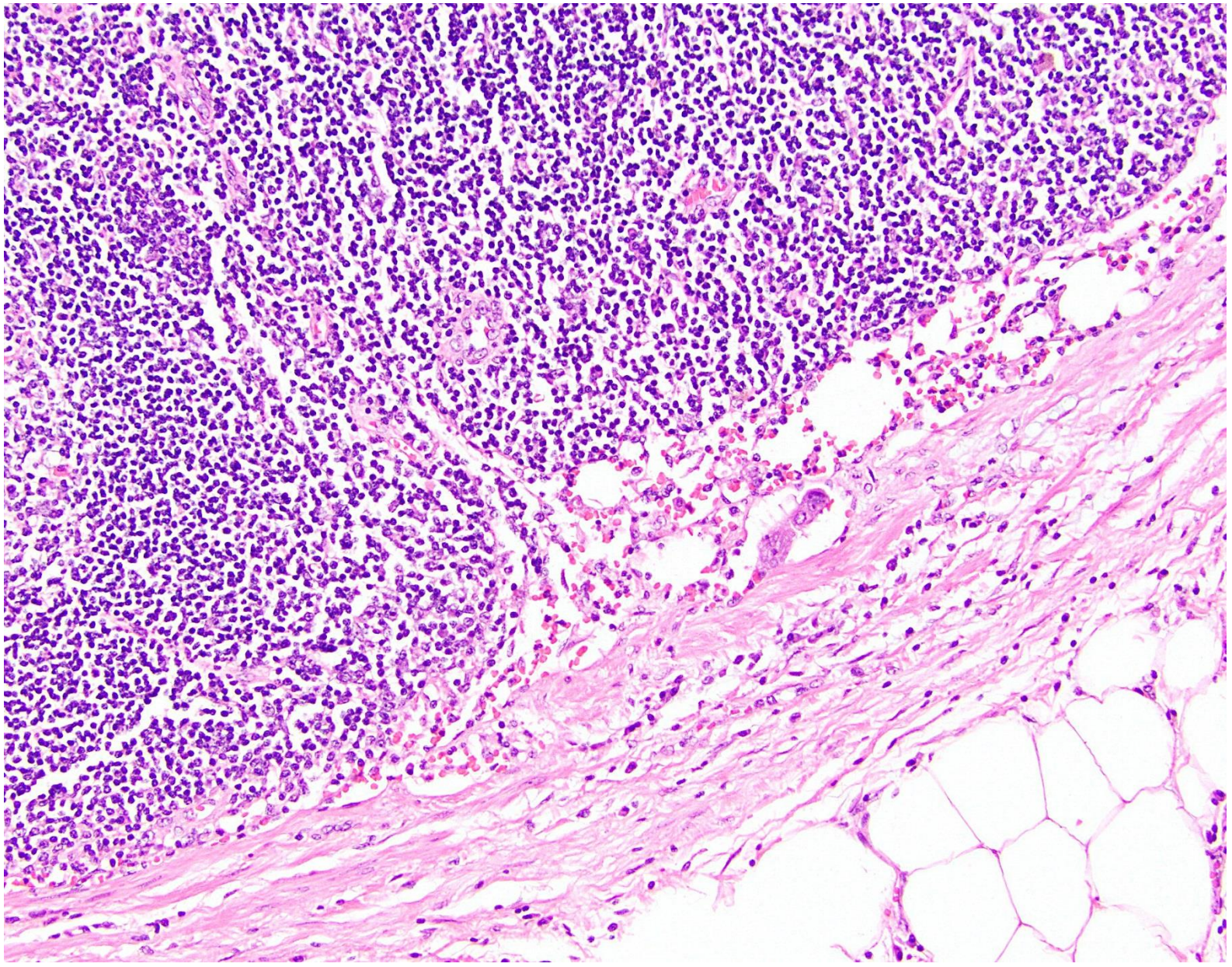
No Distance Cutoff (But 2 mm Seems OK)



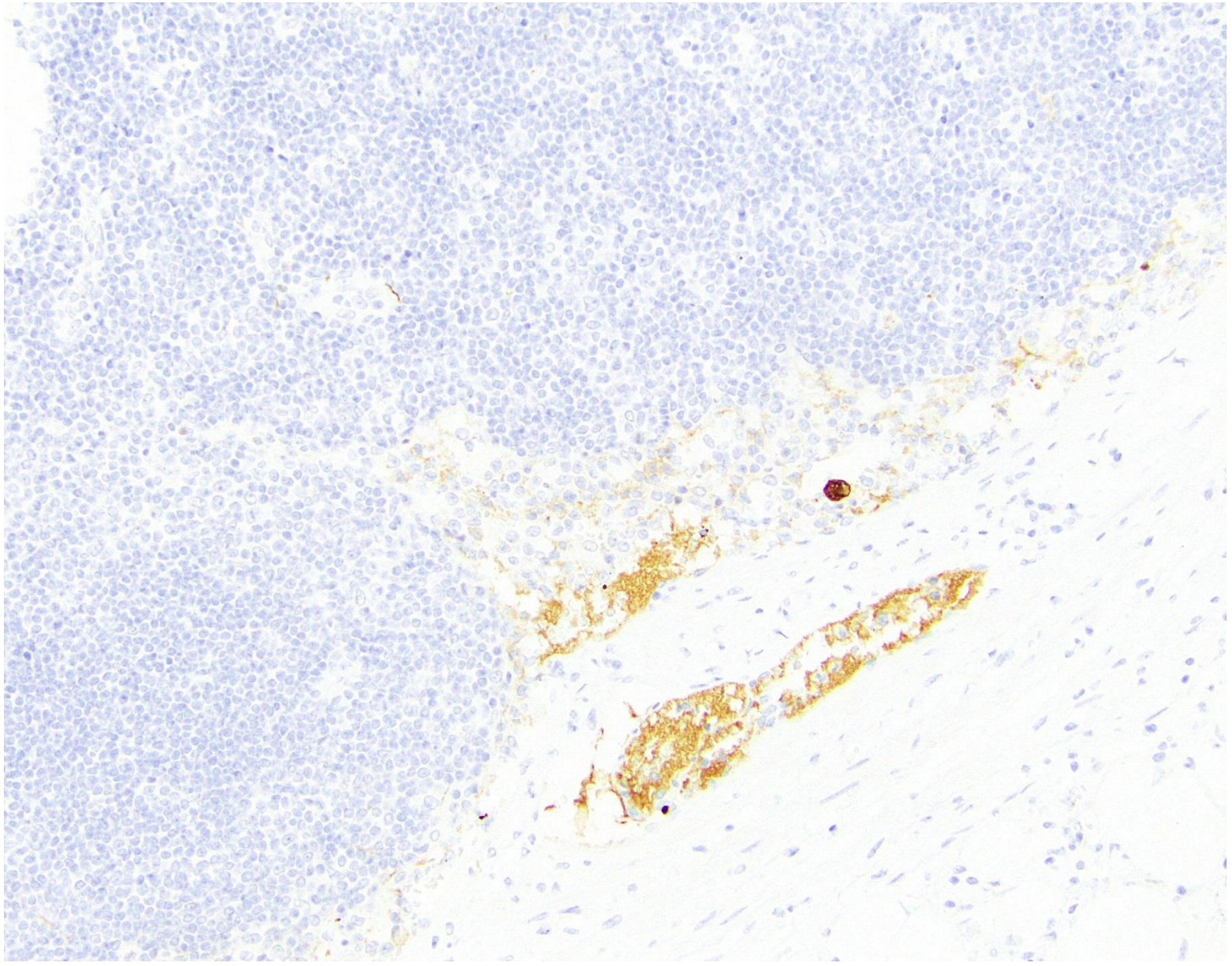
Isolated Tumor Cells

- AJCC: single tumor cells or small clusters of tumor cells in lymph nodes, less than 0.2 mm
- pN0(i+)
- May be occult (visible on keratin IHC but not on H&E)
- Significance is unclear, and published studies have disagreed
  - Different size cutoffs, definitions, and terminology
  - May be more important in pT3 and pT4 cases

Blink and You'll Miss Them



Keratin IHC to Confirm



Survey

- Left hemicolectomy of an untreated colonic carcinoma … one of 40 lymph nodes show tumor cells measuring <0.2 mm. How do you stage this?
- Negative lymph node: 5%
- Negative lymph node (with isolated tumor cells): 47%
- Positive lymph node: 48%

Other Challenges in Synoptic Reporting

- Tumor grading
- Tumor budding
- LVI

Tumor Grading

- AJCC 8th edition: four-tier grading system
  - G1, well differentiated (>95% gland formation)
  - G2, moderately differentiated (50-95% gland formation)
  - G3, poorly differentiated (<50% gland formation)
  - G4, undifferentiated (no gland formation)
- WHO 2019: low-grade (formerly WD and MD) or high-grade (formerly PD), based on gland formation in the least differentiated component, ignoring invasive front
- Some colorectal carcinoma subtypes have an “intrinsic grade”
  - SRC and micropapillary effectively high-grade, for instance
  - Medullary looks high-grade but behaves low-grade

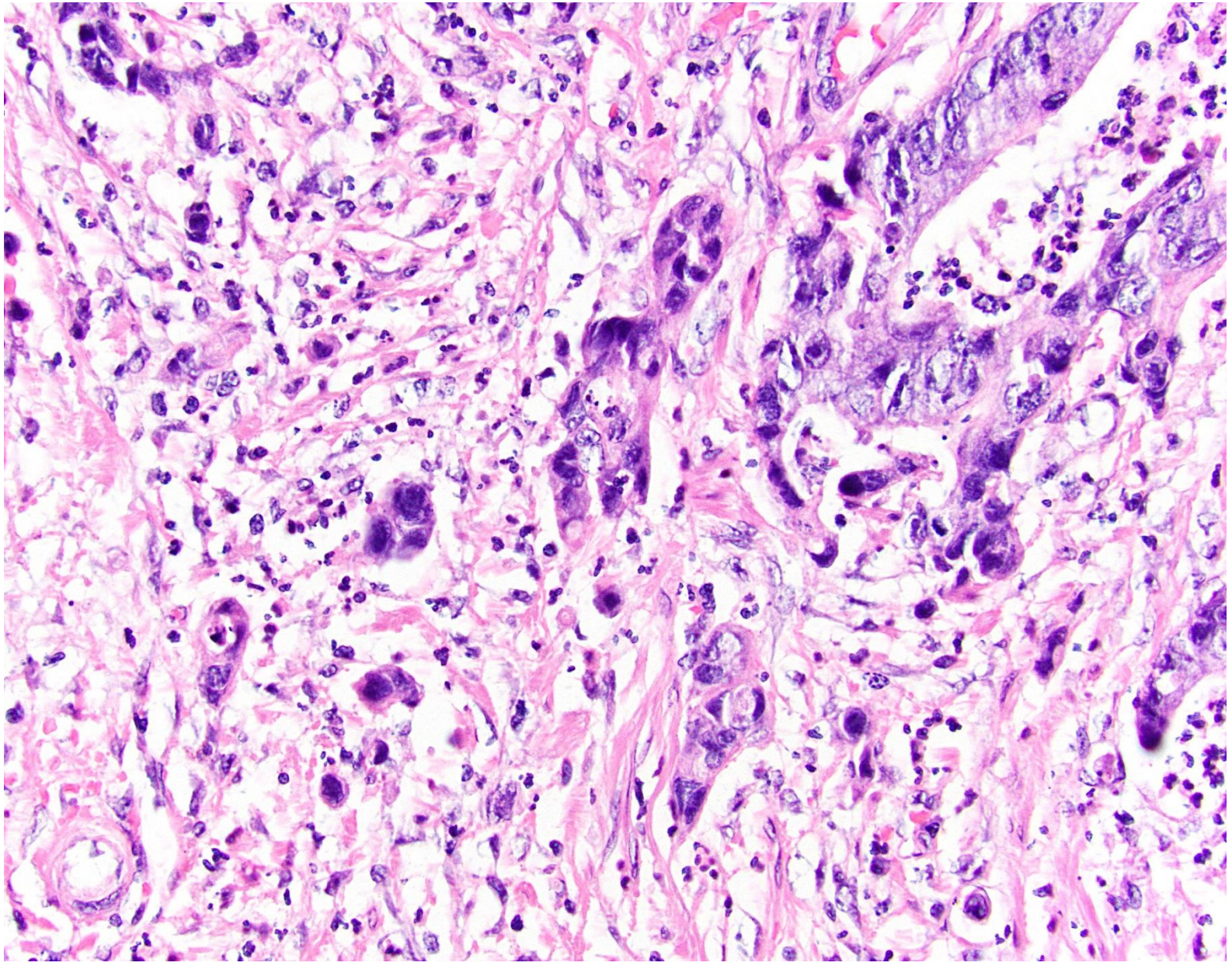
Tumor Budding

- Small clusters of cells at invasive edge of malignancy
- Recognized for decades as potentially prognostically significant
- May also indicate epithelial-mesenchymal transition

- Independent predictor of lymph node metastasis in pT1 CRC
- Independent predictor of survival in stage II CRC

- ITBCC codified criteria in 2016
  - A single tumor cell or a cell cluster of up to 4 tumor cells

What Counts as a Bud?



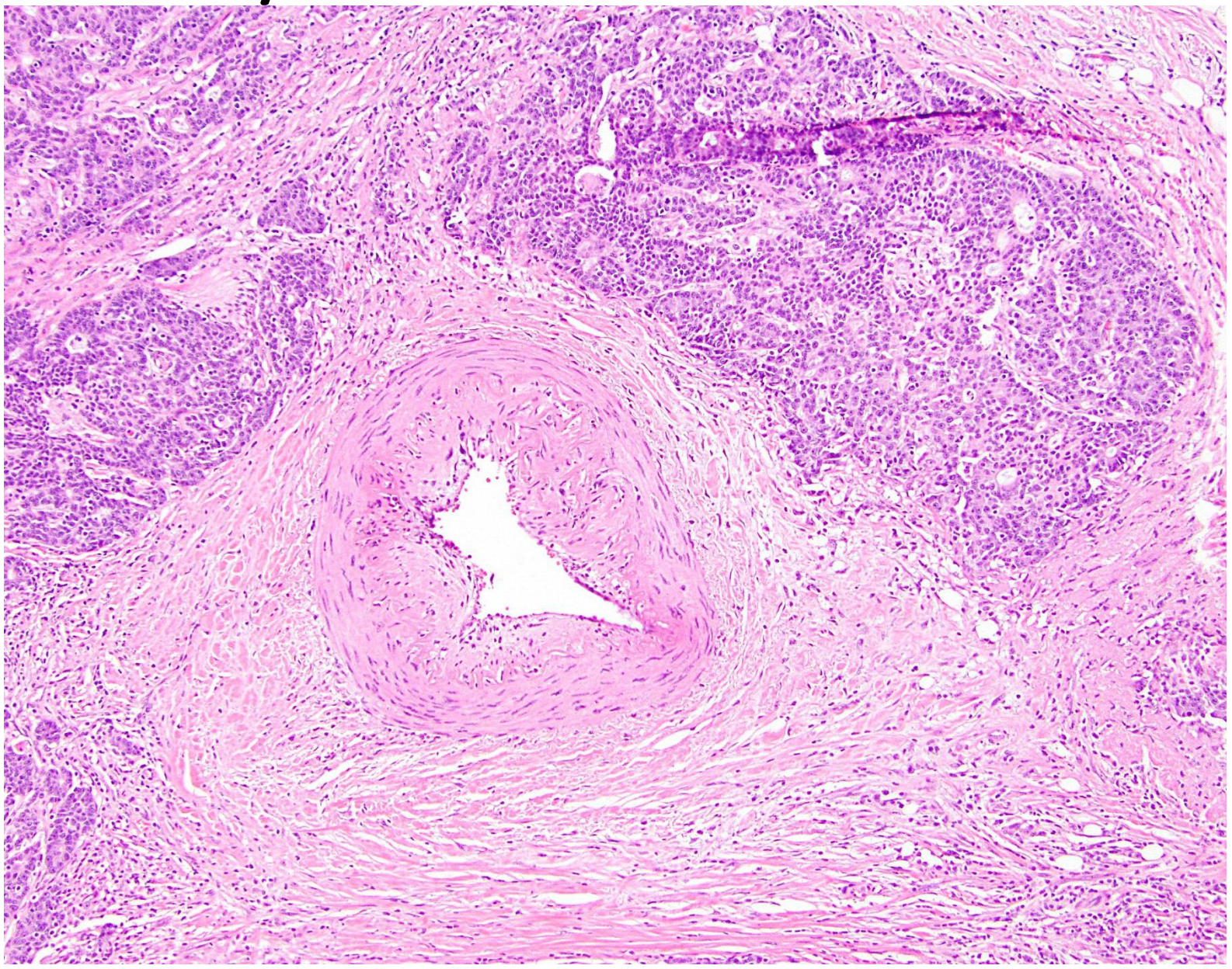
How To Count Tumor Buds

1. Pick H&E (not IHC) slide with greatest tumor budding
2. Scan at 10x to find hottest spot (10 fields recommended)
3. Count tumor buds in hotspot at 20x
4. Correct for count using normalization factor (PMID 28548122)
5. Report as:
   - Bd1 (0-4 buds per 0.785 mm^2)
   - Bd2 (5-9 buds per 0.785 mm^2)
   - Bd3 ($\geq$10 buds per 0.785 mm^2)

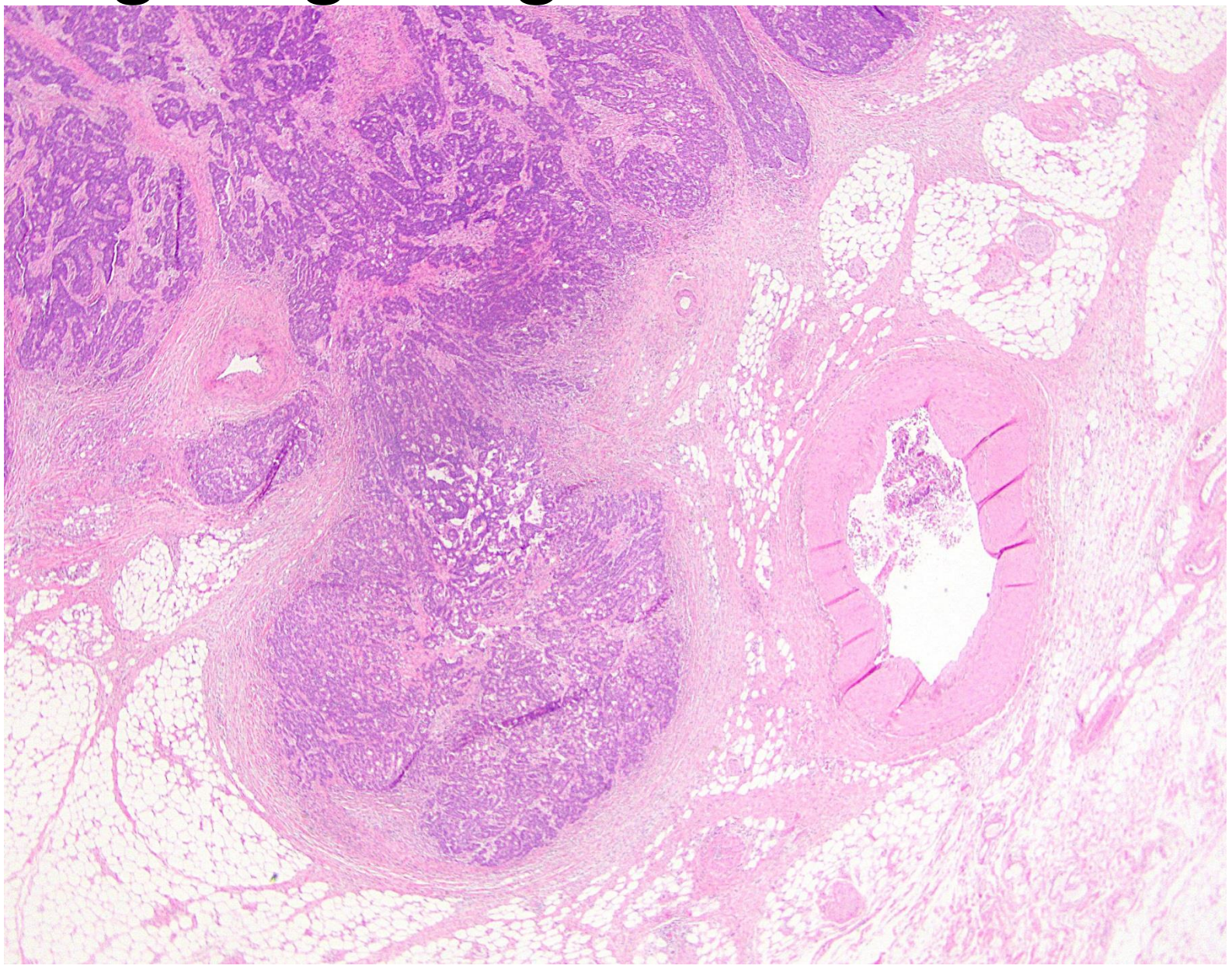
The Many Flavors of LVI

- Small vessel invasion: tumor involving thin-walled structures lined by endothelium, without an identifiable smooth muscle layer or elastic lamina
  - Lymphatics, capillaries, postcapillary venules
- Venous (large vessel) invasion: tumor involving endothelium-lined spaces with an identifiable smooth muscle layer or elastic lamina
  - Various methods can help improve detection
- Some studies have conflated these, but significance may differ
  - Large vessel definitely an adverse indicator; small vessel probably also
  - Extramural likely worse than intramural, for both

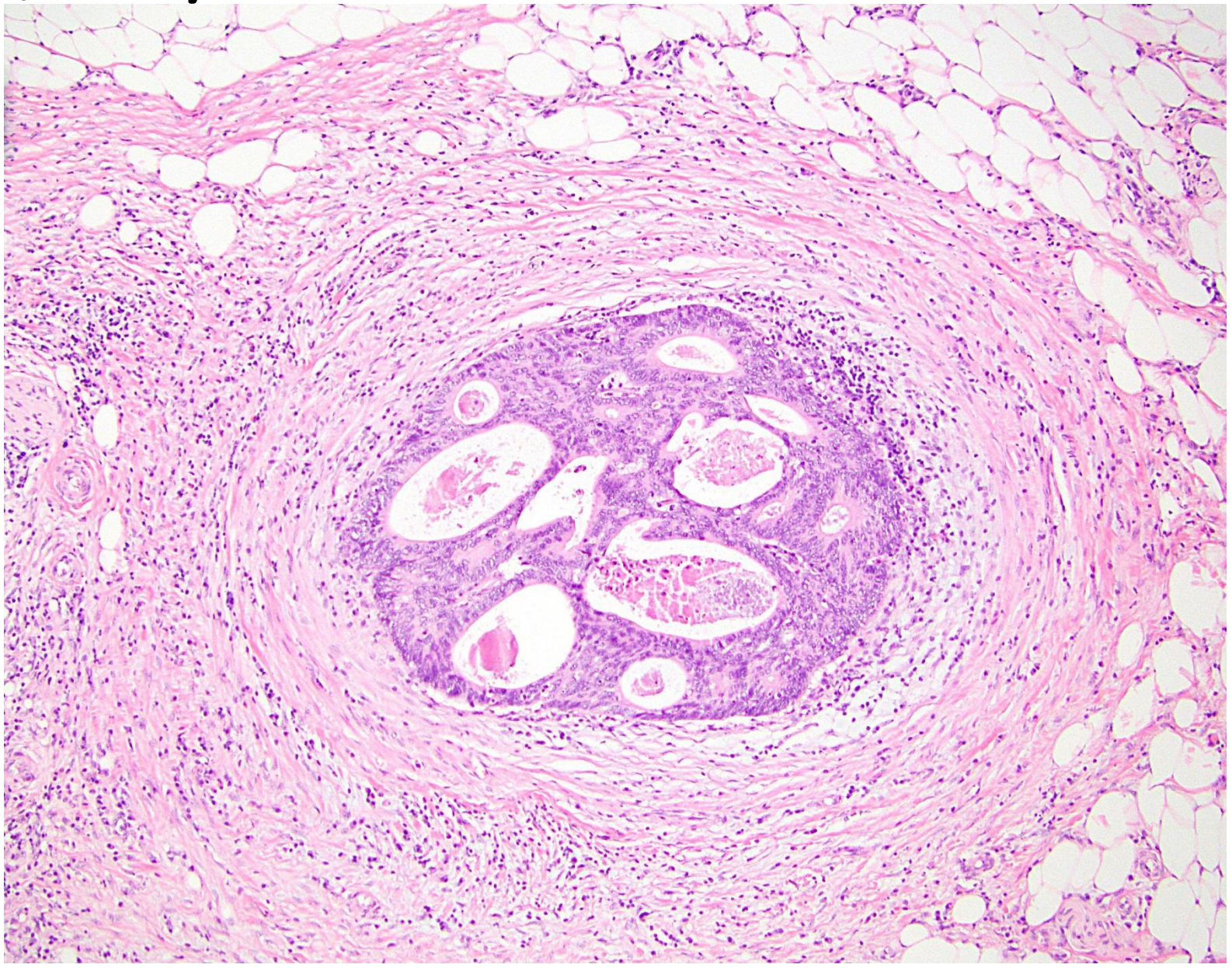
Orphan Artery



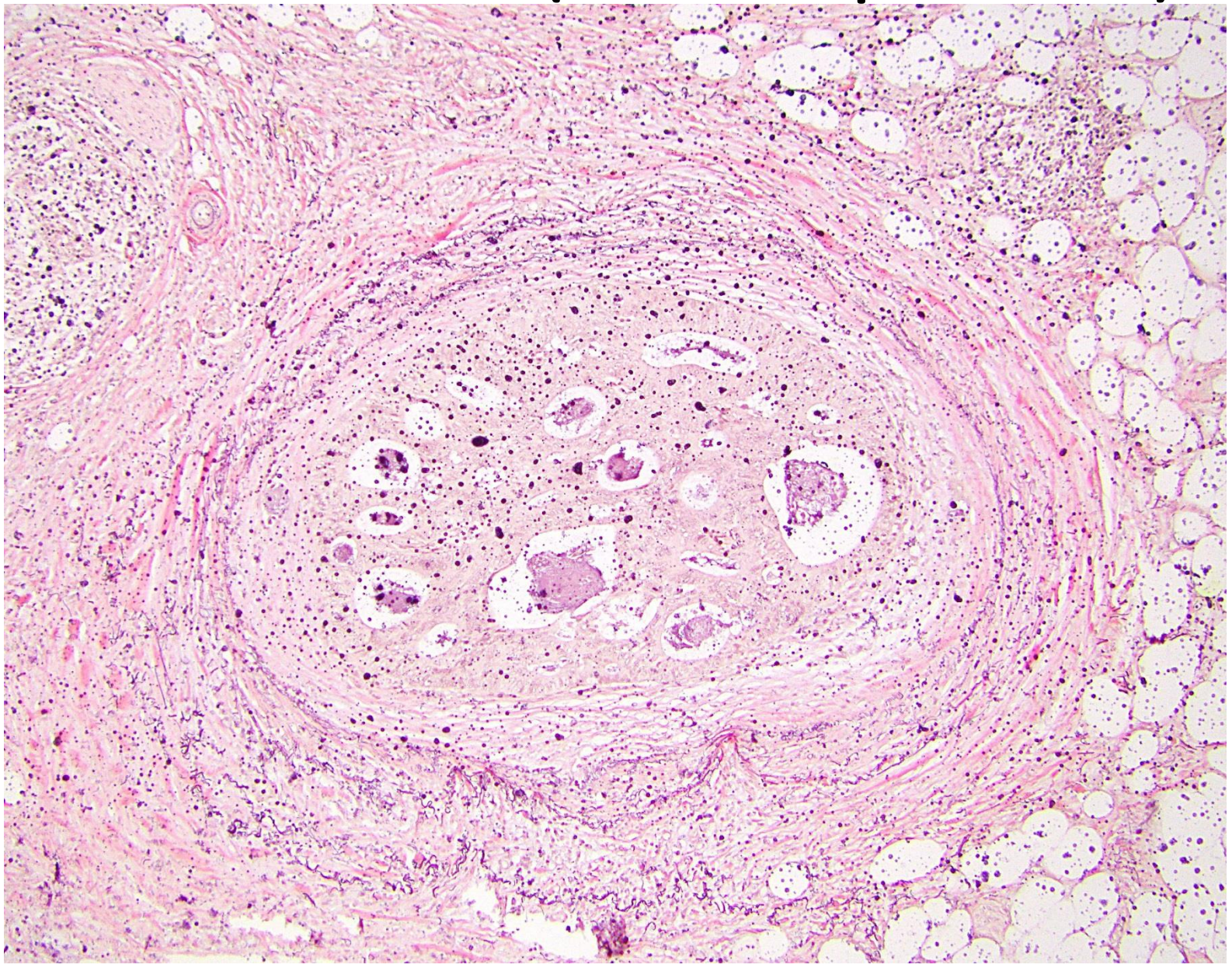
Protruding Tongue Sign



Maybe, Maybe Not



Elastin to the Rescue (Order Up Front?)



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Questions?