

BRITISH DIVISION OF THE INTERNATIONAL ACADEMY OF PATHOLOGY



SYMPOSIUM ON UPPER GI and PANCREATOBILIARY

2-3 December 2016: Royal Institute of British Architects, London

**Reporting pancreatic cancer resections
after neoadjuvant therapy**

C Verbeke



UiO : Universitetet i Oslo

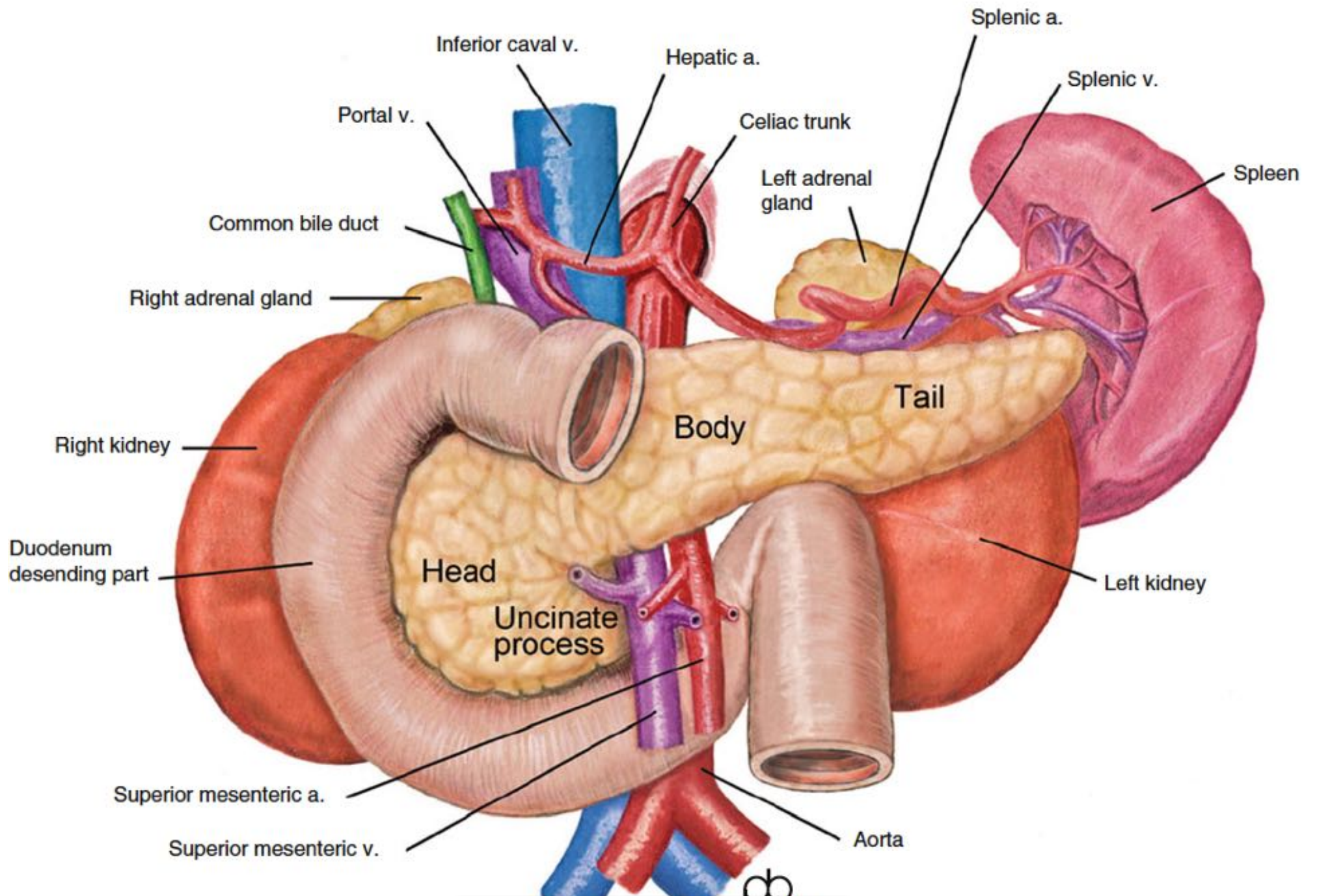


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Indications for neoadjuvant therapy (NAT)

- **Borderline resectable**
= limited involvement of veins (SMV, PV) and/or arteries (HA, SMA)
- **Locally advanced**
= beyond resectable
- **Primary resectable**
→ clinical trials:
 - disease is already systemic ("occult metastasis")
 - proportion of patients cannot be treated adjuvantly



Neoadjuvant therapy (NAT)

- **Chemotherapy**
 - Gemcitabine
 - FOLFIRINOX
 - Folinic acid
 - 5-FU
 - Irinotecan
 - Oxaliplatin
- **(Chemoradiotherapy)**

Surgical procedures following NAT

- **Standard resection:**
 - Whipple's/pylorus-preserving pancreatectomy
 - Distal pancreatectomy
 - Total pancreatectomy

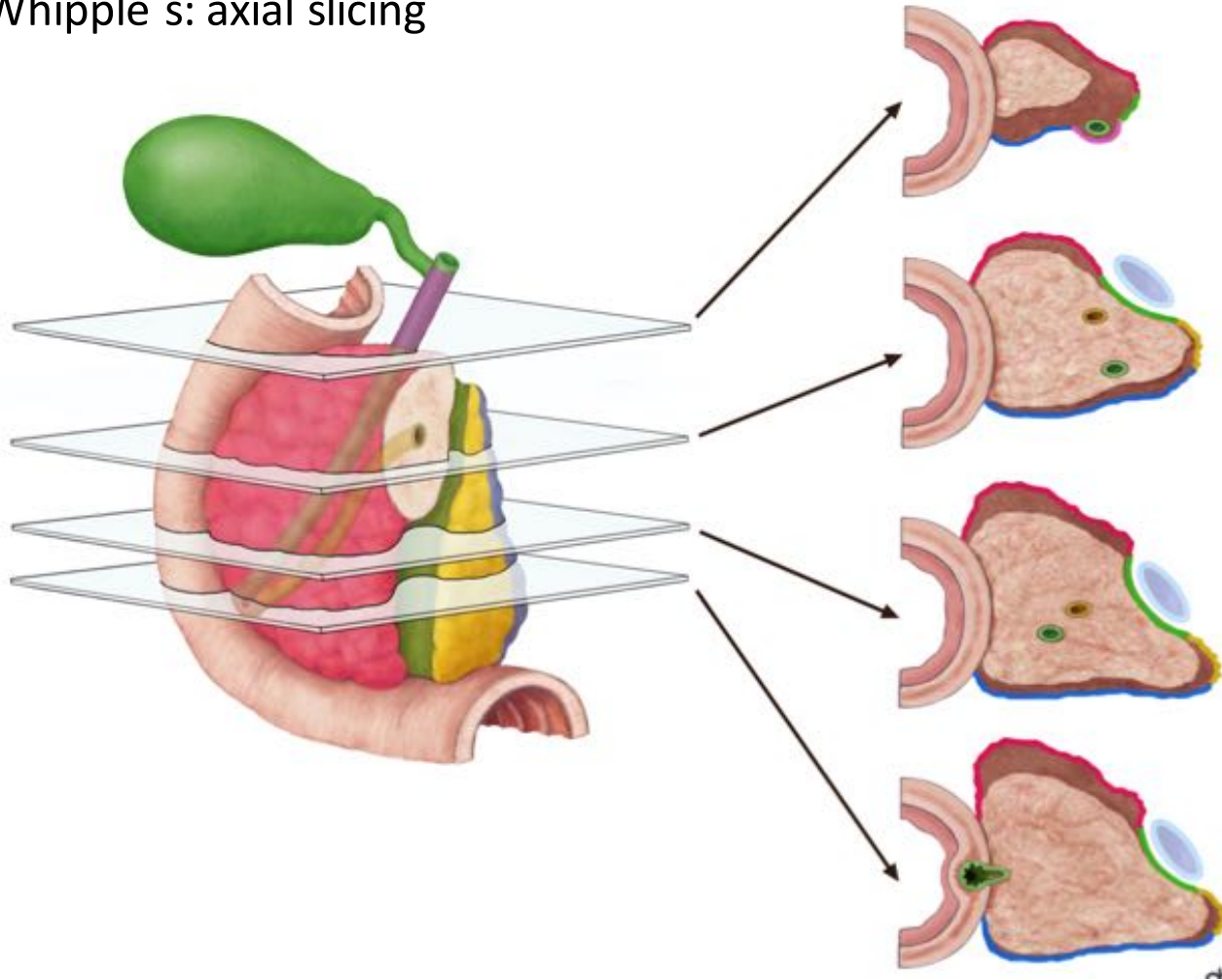
- **Extended resection: standard +**
 - Blood vessels:
 - superior mesenteric vein (SMV) / portal vein (PV)
 - hepatic artery
 - superior mesenteric artery (SMA)
 - Small bowel, colon
 - Stomach
 - Adrenal, kidney

Macroscopic examination

- **Dissection**
- **Examination**
- **Sampling**

Specimen dissection

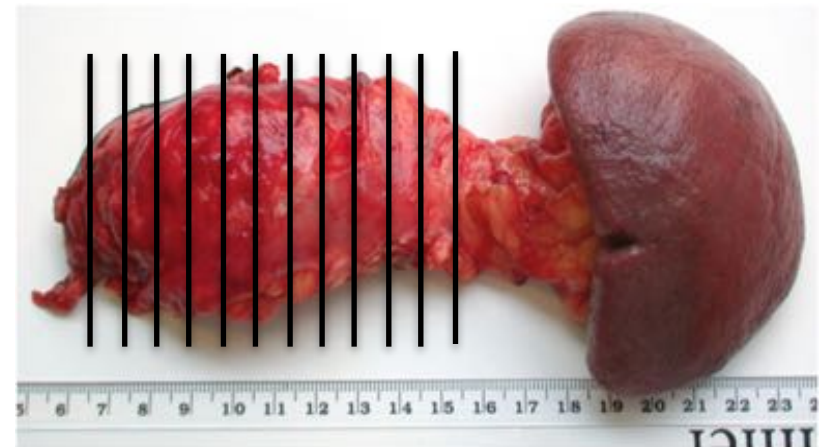
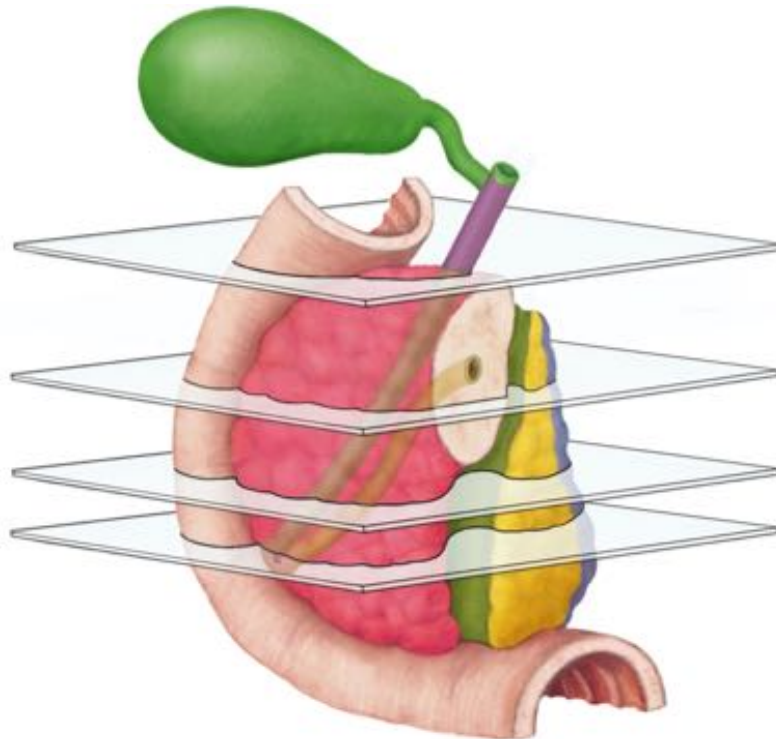
- Standard specimens:
 - Whipple's: axial slicing



Specimen dissection

- **Standard specimens:**

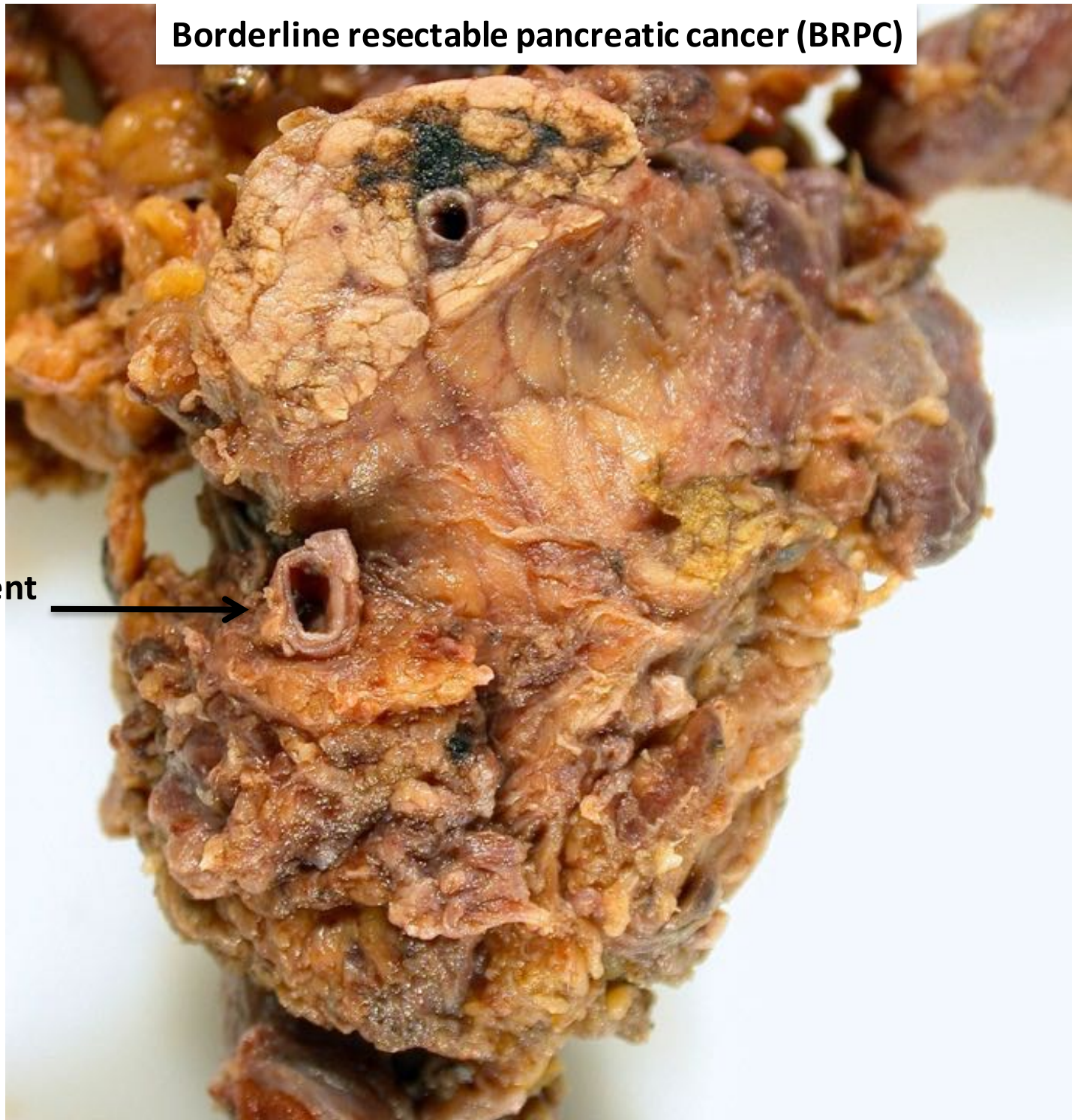
- Whipple's: axial slicing
- Distal pancreatectomy: sagittal slicing
- Total pancreatectomy: combined axial + sagittal slicing



Specimen dissection

- **Standard specimens:**
 - Whipple's: axial slicing
 - Distal pancreatectomy: sagittal slicing
 - Total pancreatectomy: combined axial + sagittal slicing
- **Extended resection specimens:**
 - Display relationship between tumour and additionally resected structures

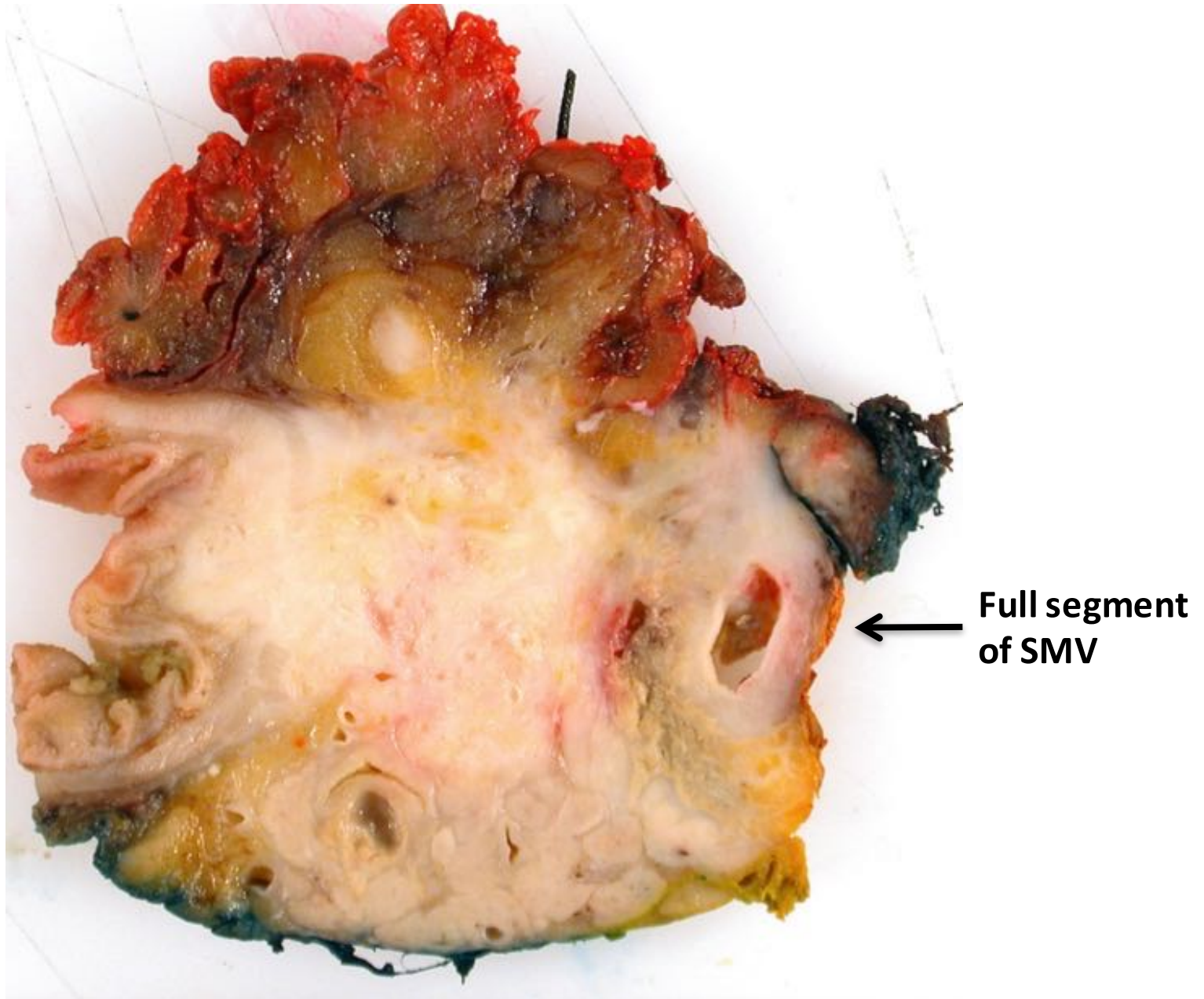
Borderline resectable pancreatic cancer (BRPC)



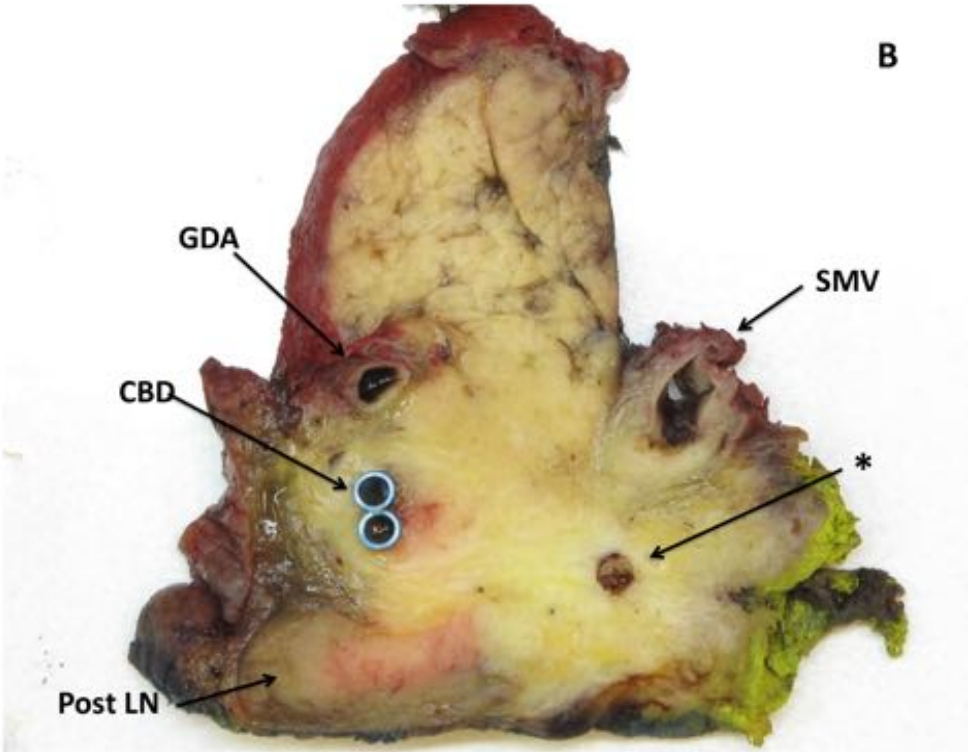
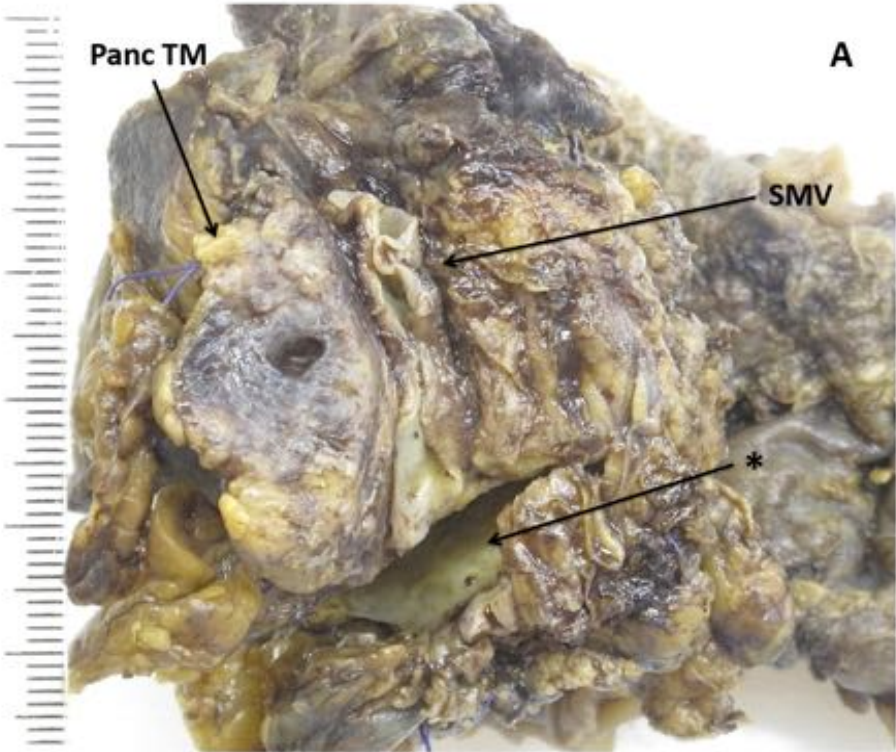
**Full segment
of SMV**

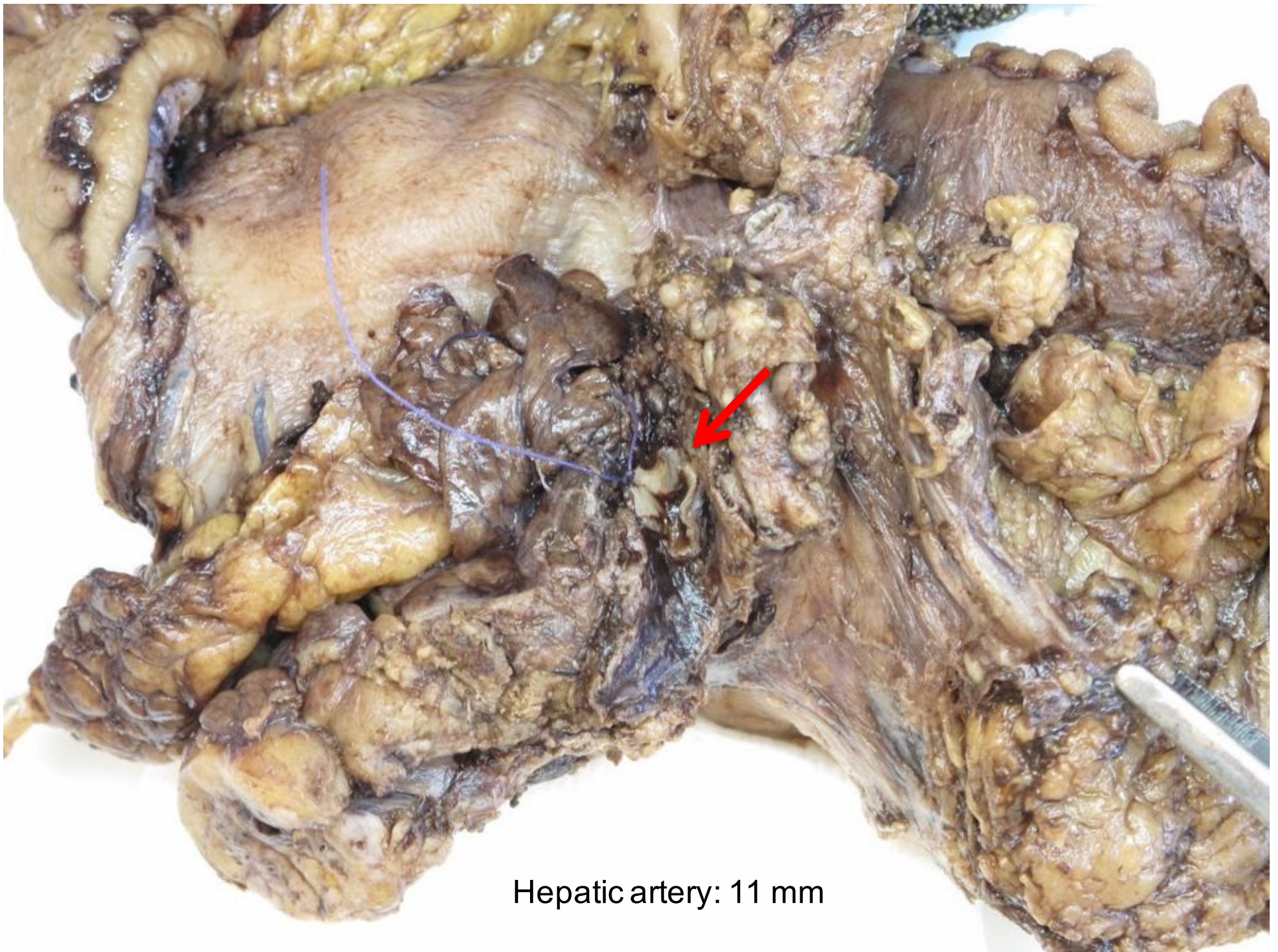


Borderline resectable pancreatic cancer (BRPC)



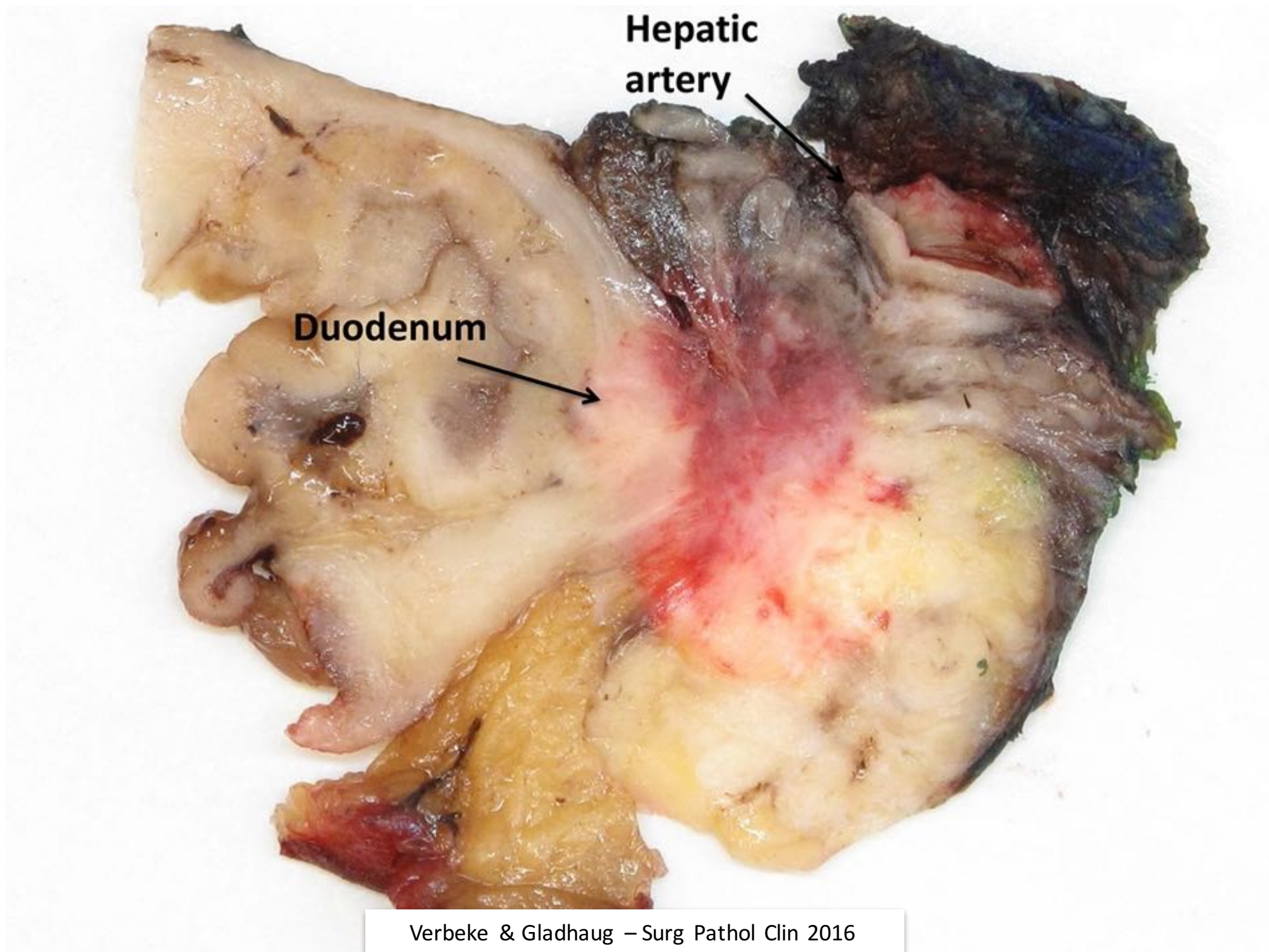
Primary resectable pancreatic cancer (PRPC)

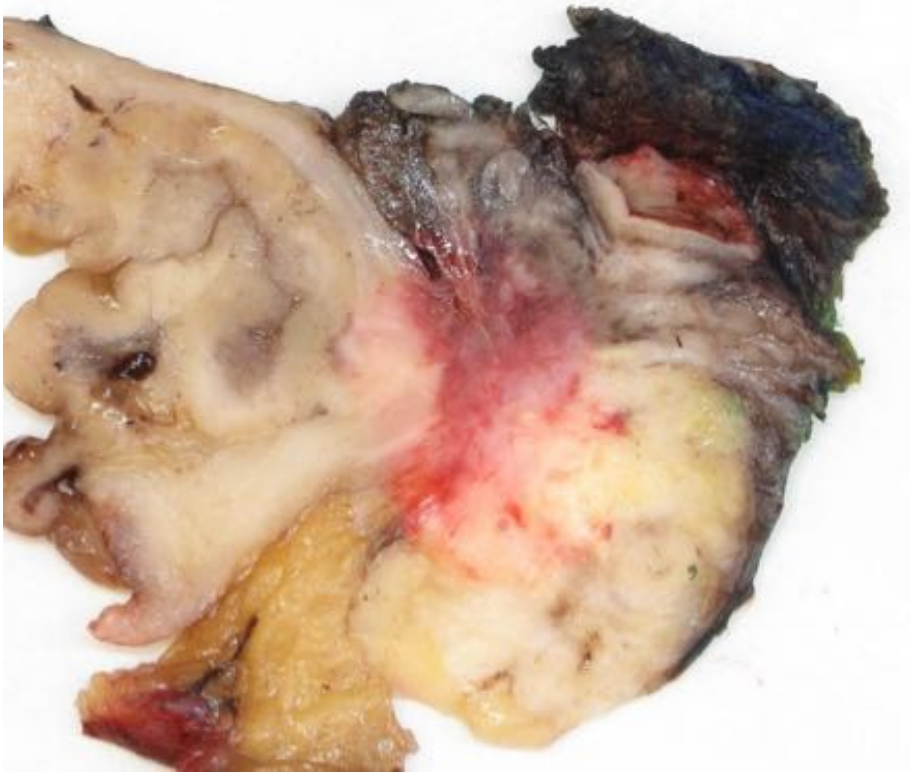




Hepatic artery: 11 mm



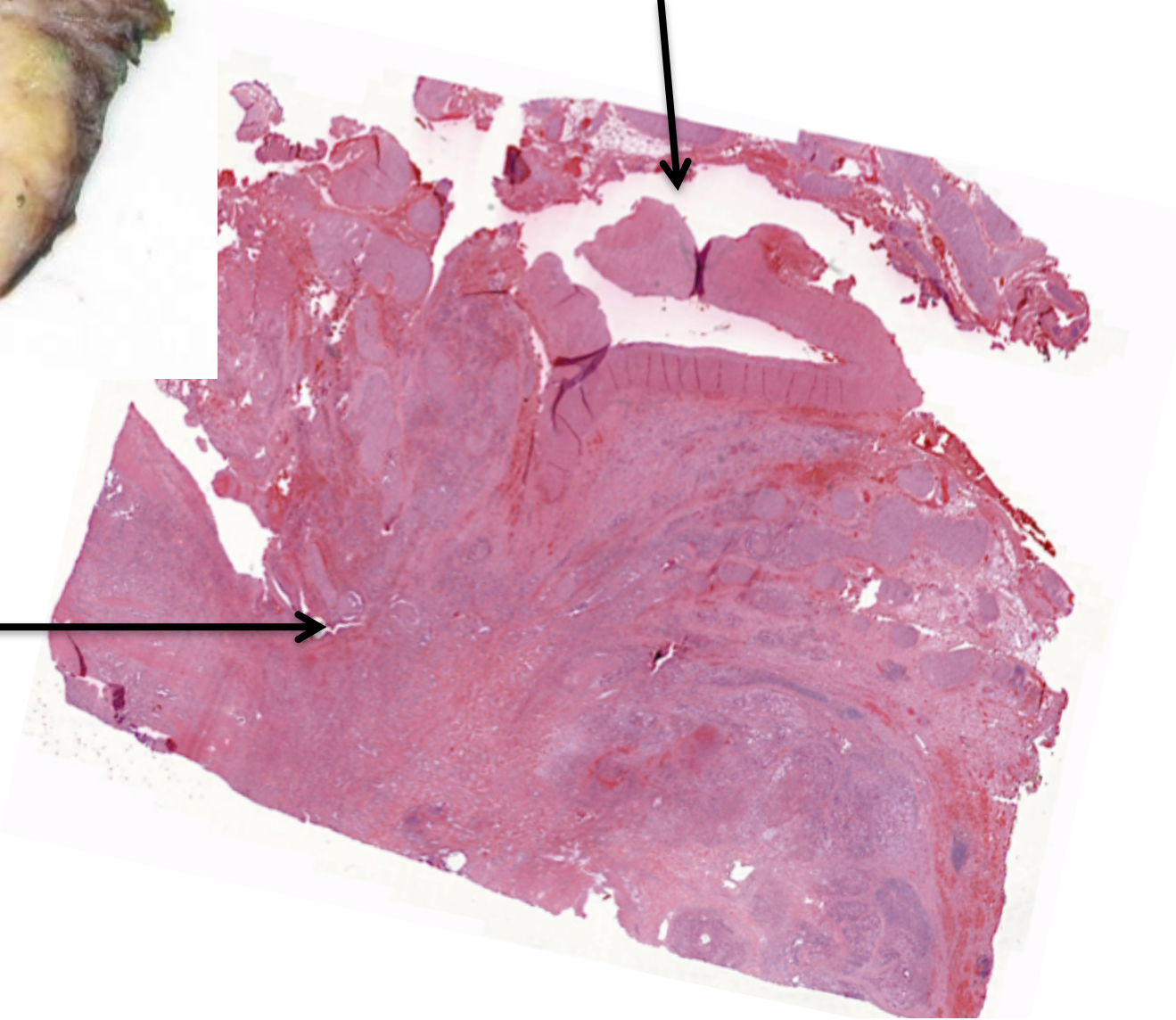
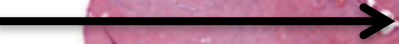


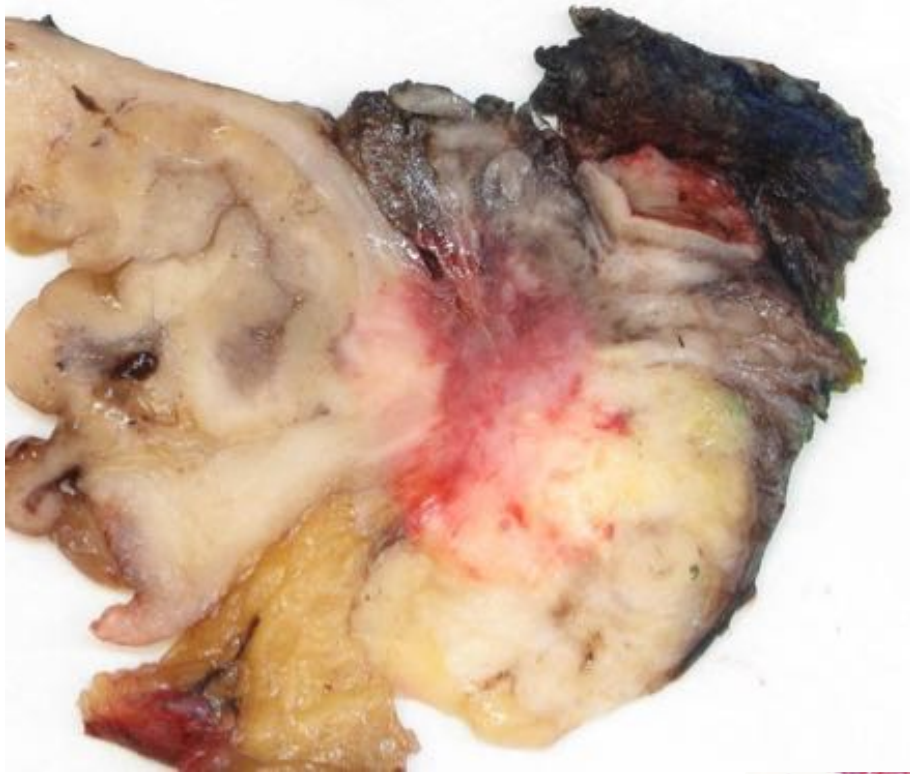


Hepatic artery

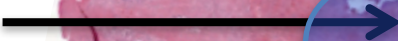


Duodenum

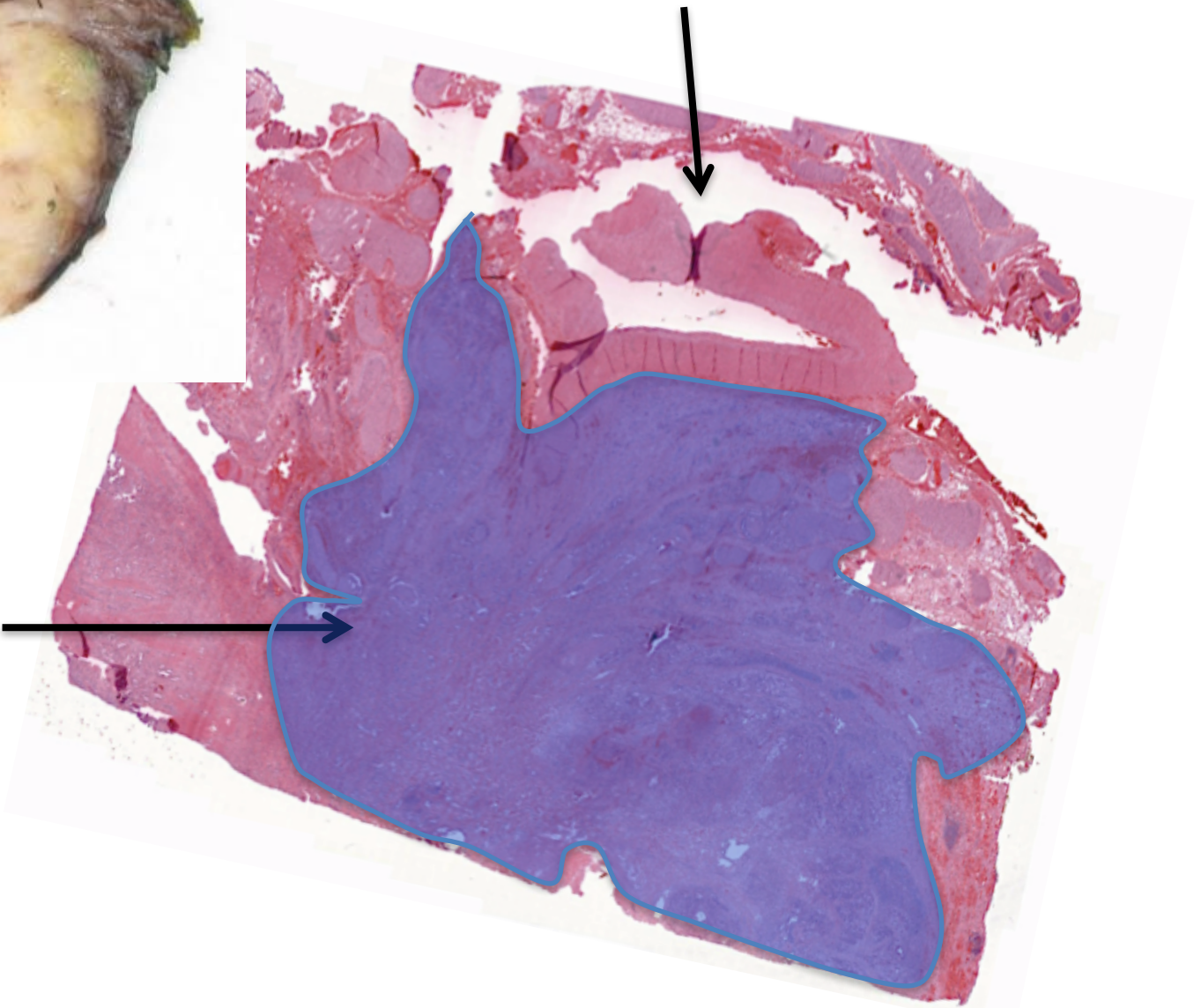


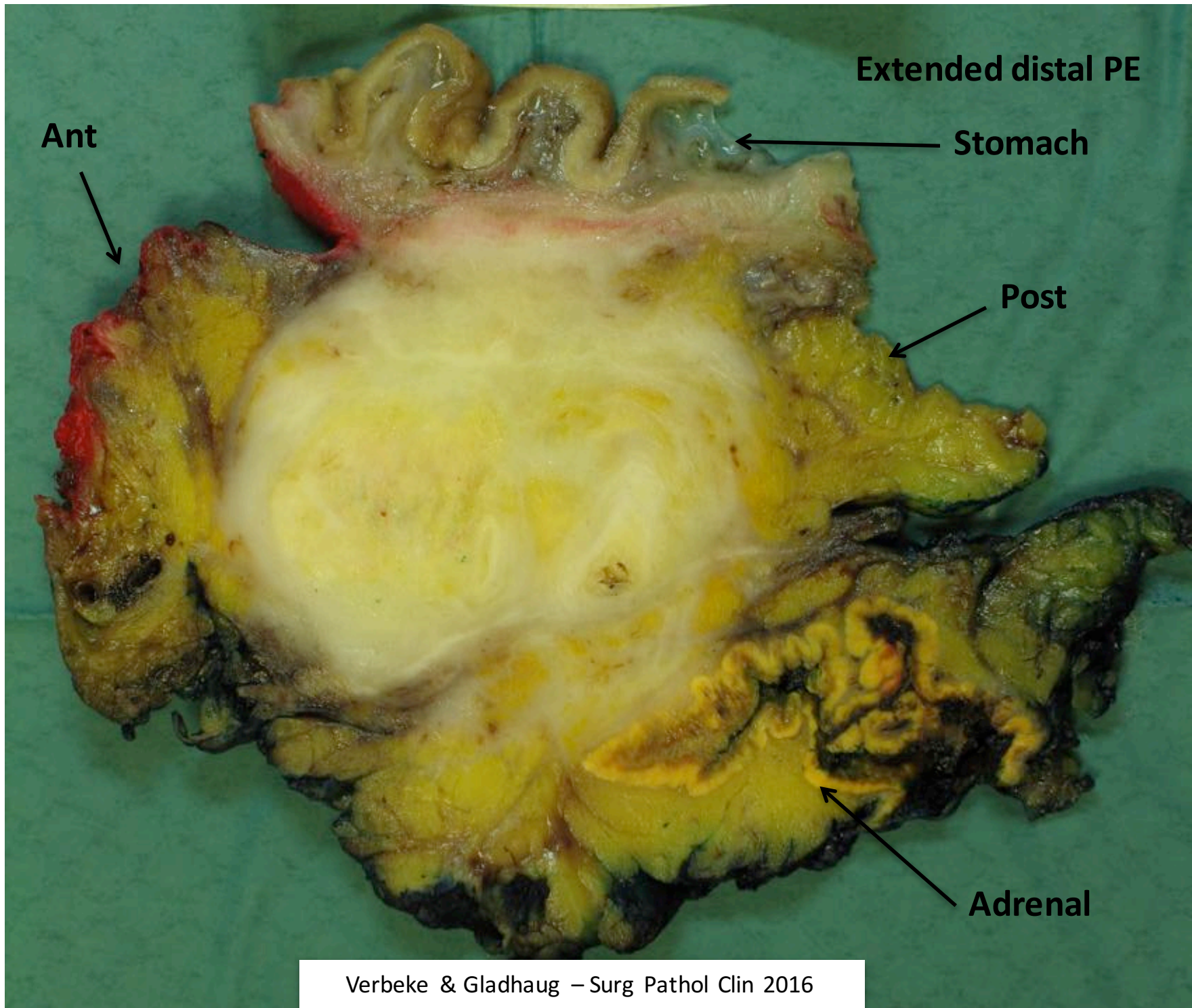


Duodenum



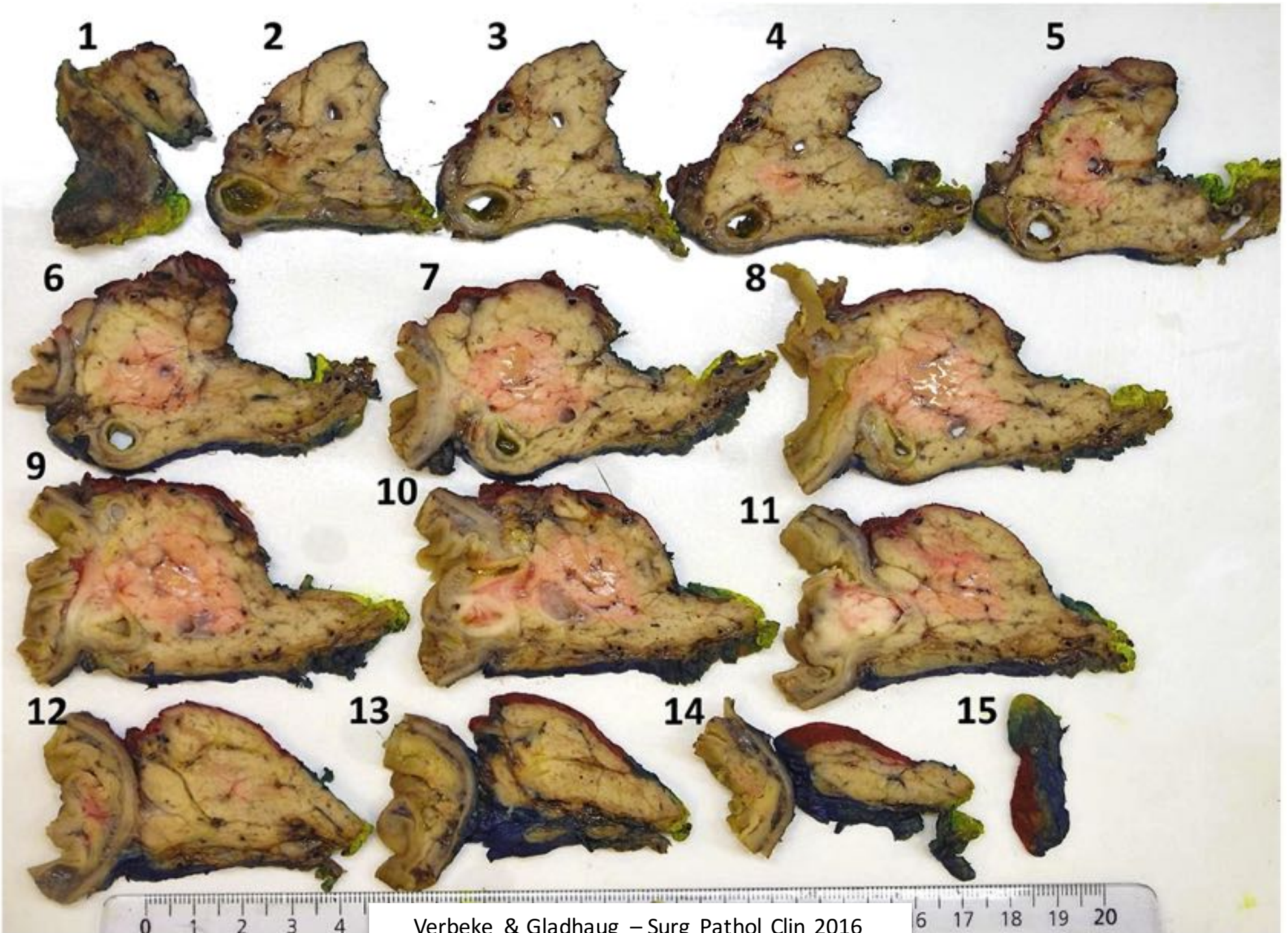
Hepatic artery





Macroscopic inspection

- Complex specimens
- Distorted anatomy



Whipple's after NAT



Macroscopic examination

- Complex specimens
- Distorted anatomy
- Blurred tumour outlines

Pancreatic cancer (after NAT)



Sampling

- Extensive – (sub-)total
- "New", relevant margins of and around additionally resected structures

Microscopic examination

- **Treatment-induced changes**
- **Staging**
- **Tumour regression grading**
- **Margin status**

Treatment-induced changes of the tumour

- Necrosis: rare
- Reduction of tumour cell mass
- Change in tumour morphology

Common histological features

Cytoplasmic eosinophilia

- ▶ Hyperchromasia
- ▶ Pyknosis
- ▶ Bizarre nuclei

Clear cell change

- ▶ Wrinkled nuclei
- ▶ Voluminous clear cytoplasm
- ▶ 'Lipoblast-like' cells
- ▶ 'Signet ring-like' cells

Tumours accompanied by

- ▶ Mucin pools
- ▶ Foamy macrophages
- ▶ Foreign body-type giant cells

Uncommon histological features

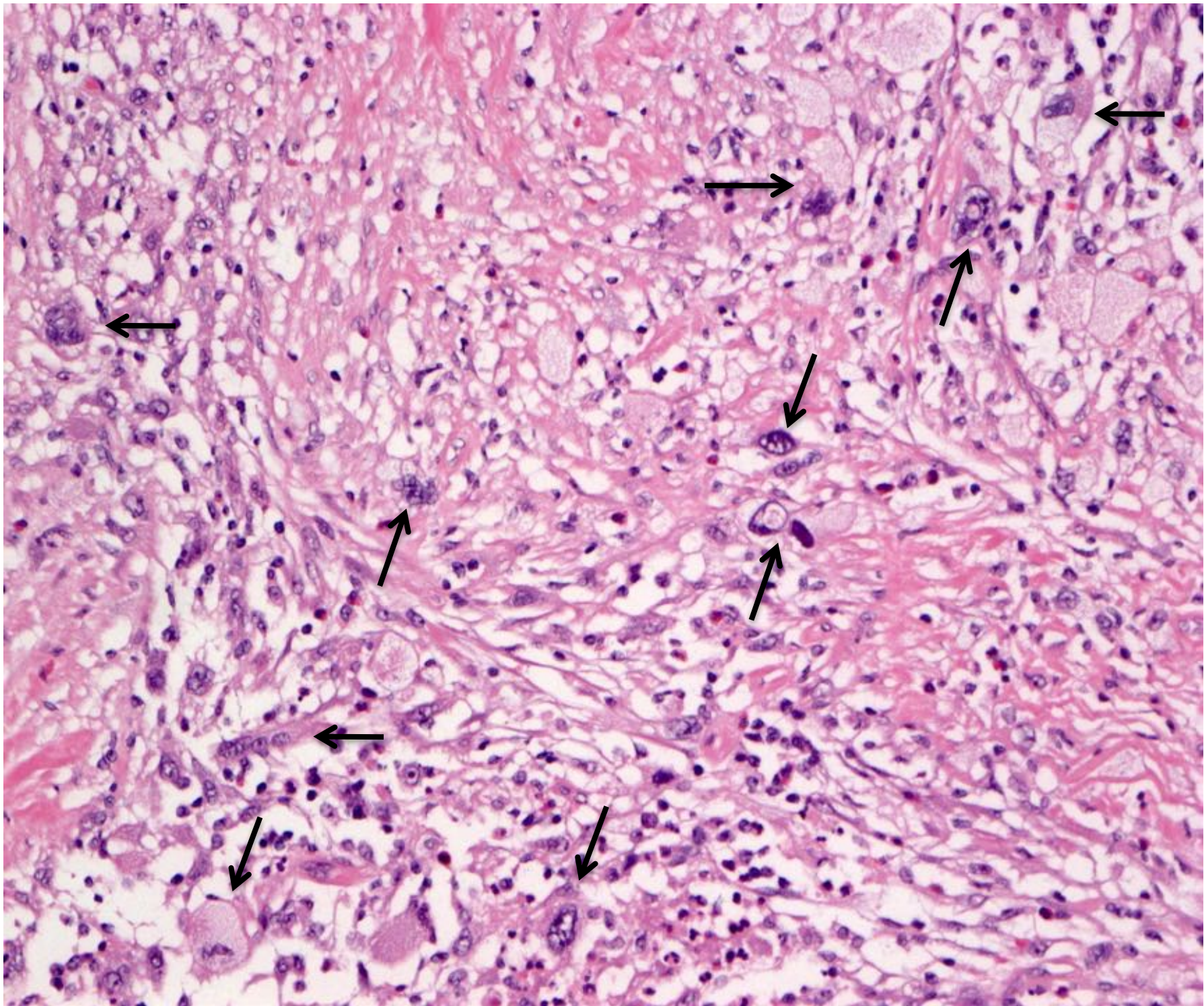
Oncocytic/'oncocyte-like' change

- ▶ Polygonal cells
- ▶ Eosinophilic, granular cytoplasm
- ▶ Round hyperchromatic nuclei
- ▶ Cherry red, prominent nuclei

Rhabdoid change

- ▶ Globular, hyaline intracytoplasmic inclusion
- ▶ Highlighted by cytokeratin staining
- ▶ Also known as 'cytokeratin aggresomes'

Squamous metaplasia/differentiation



Treatment-induced changes of the tumour

- Necrosis: rare
- Reduction of tumour cell mass
- Change in tumour morphology → No grading of tumour differentiation
- Stroma:
 - fibromyxoid
 - dense, keloid-like
 - cellular, nodular fasciitis-like

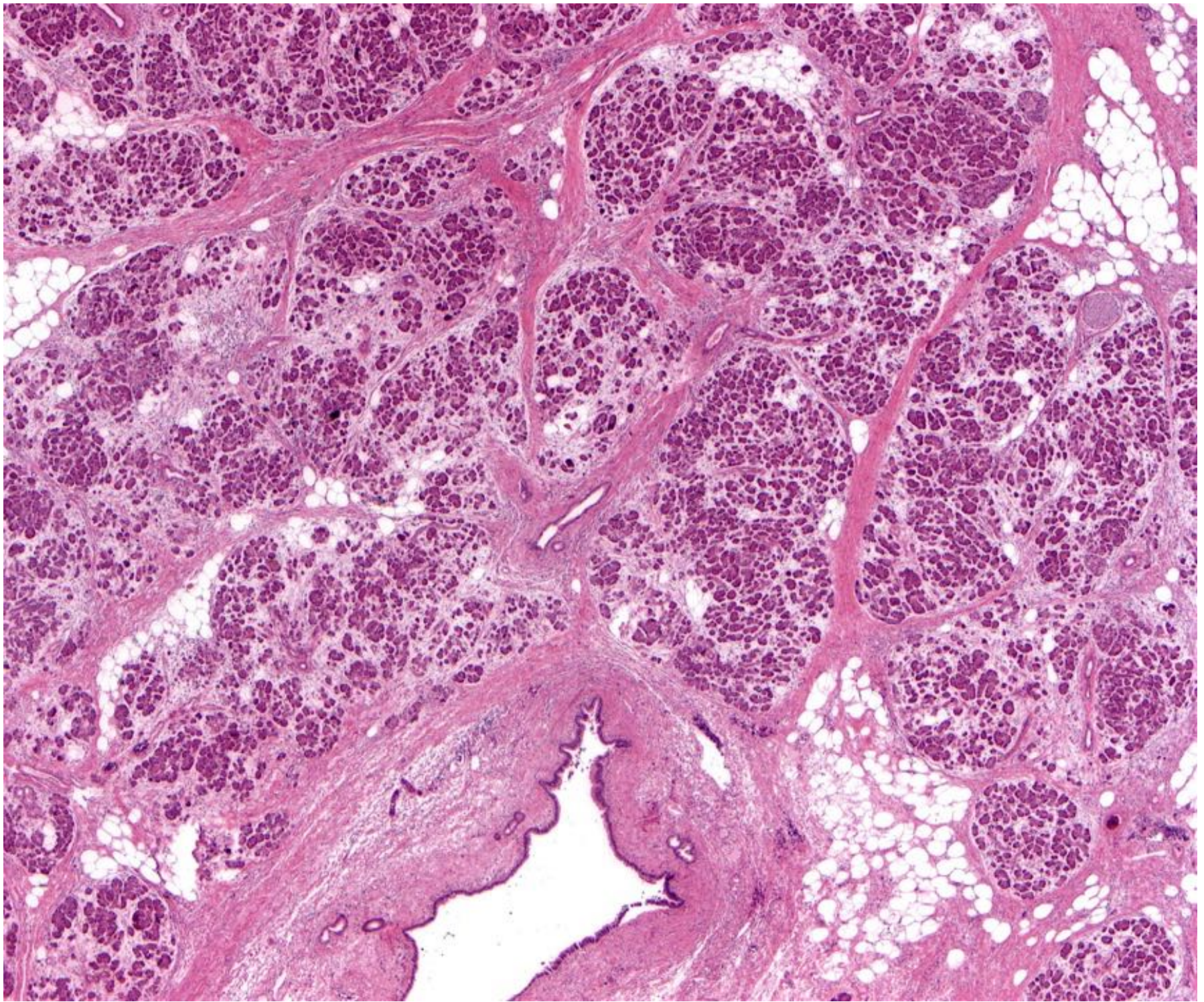
Treatment-induced changes of the tumour

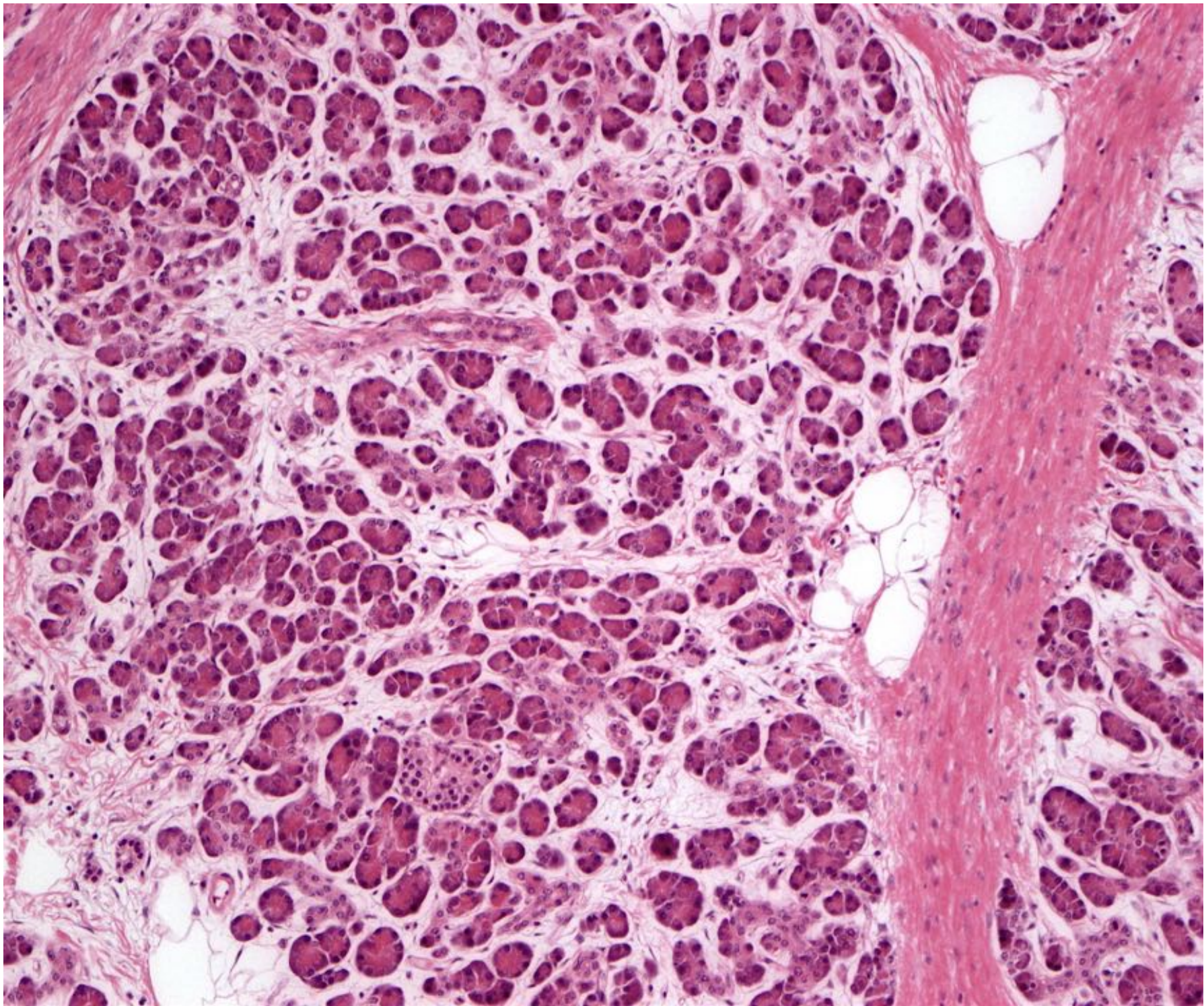
- Necrosis: rare
- Reduction of tumour cell mass
- Change in tumour morphology
- Stroma:
 - fibromyxoid
 - dense, keloid-like
 - cellular, nodular fasciitis-like
- Tumour-associated changes:
 - mucin pools
 - foamy macrophages
 - inflammation?

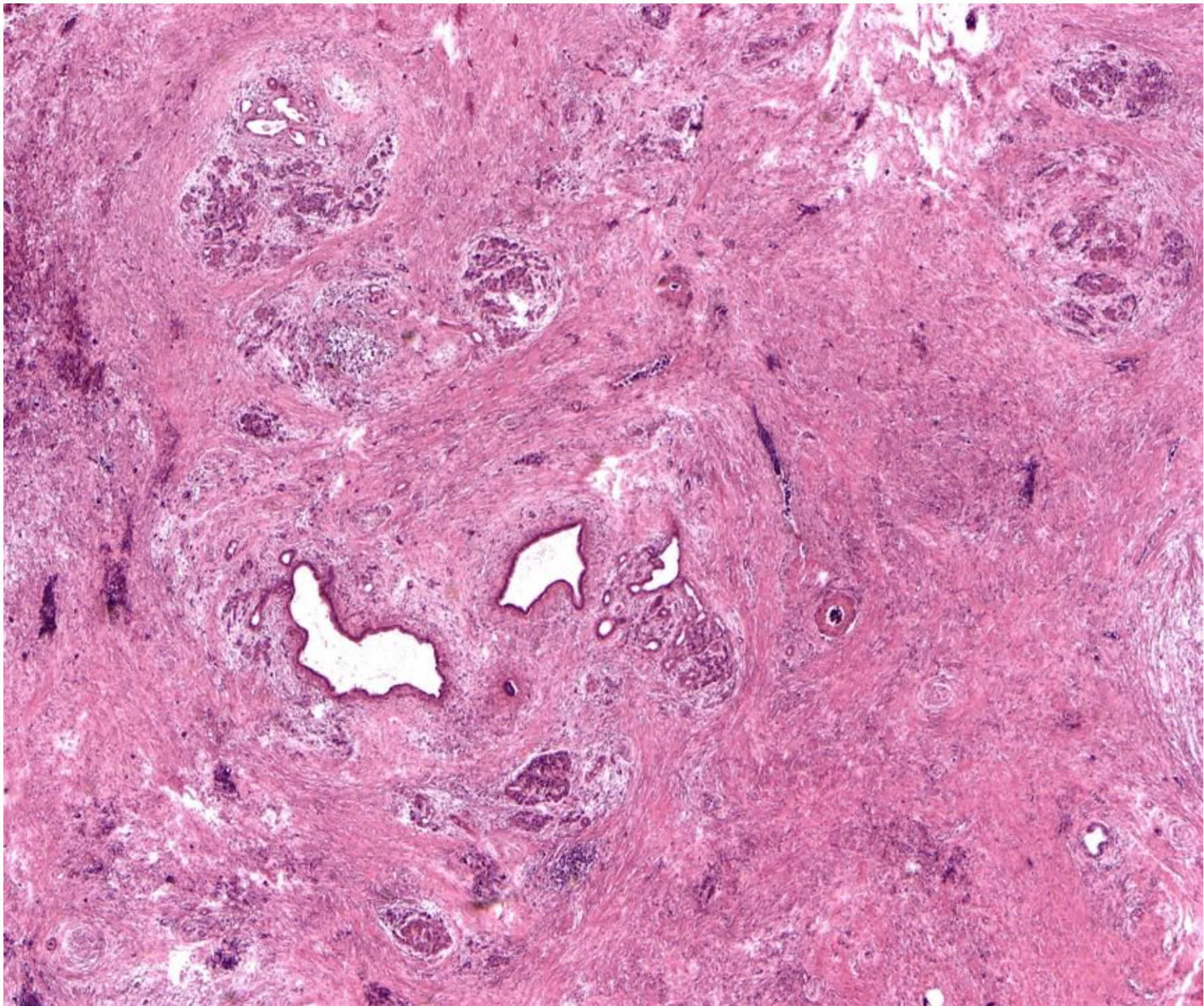
→ No grading of tumour differentiation

Treatment-induced changes in non-neoplastic tissues

- Blood vessels:
 - myxohyaline intimal proliferation
 - elastosis/elastic degeneration
- Nerve bundles: hypertrophy
- Acinar parenchyma: atrophy

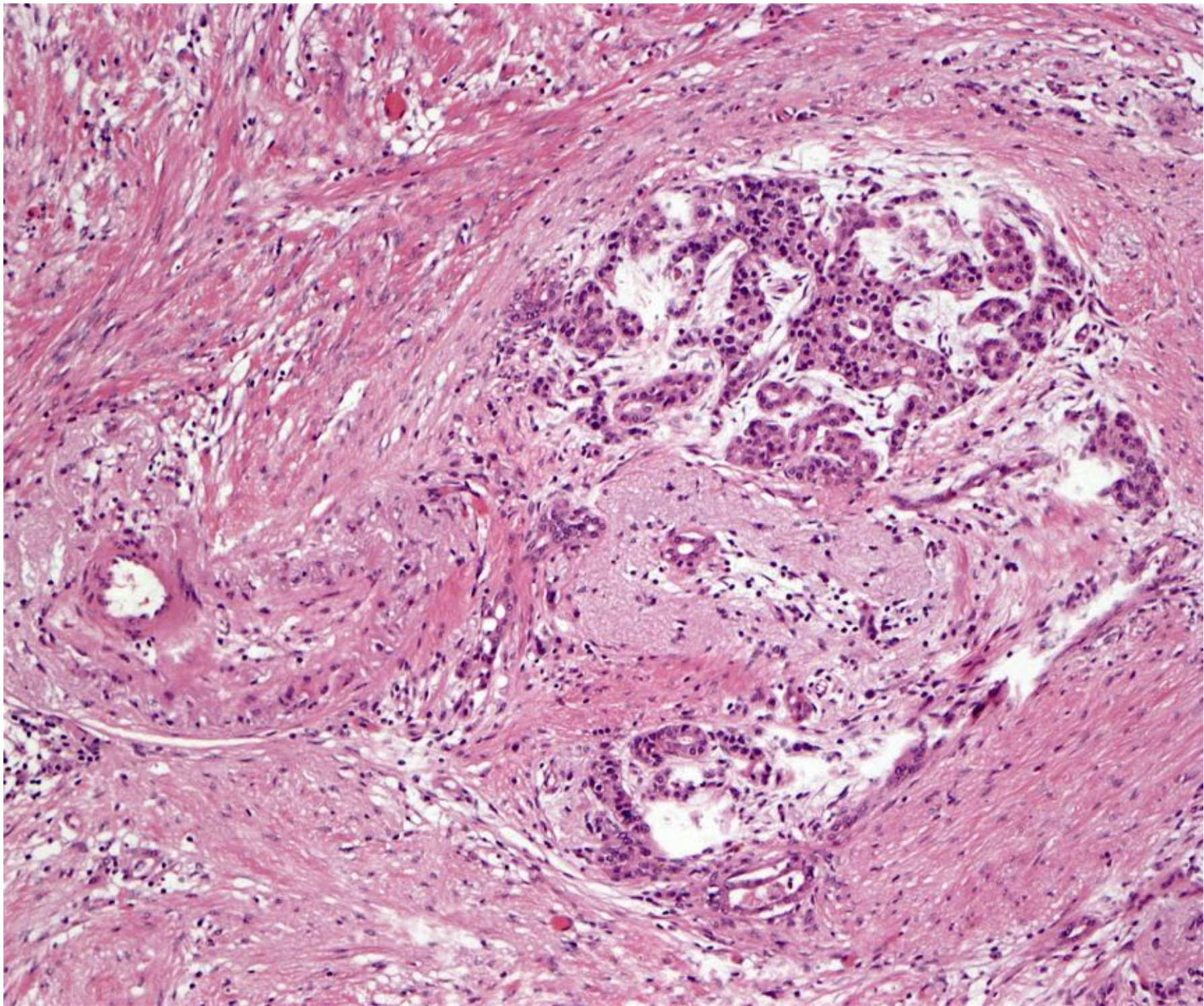


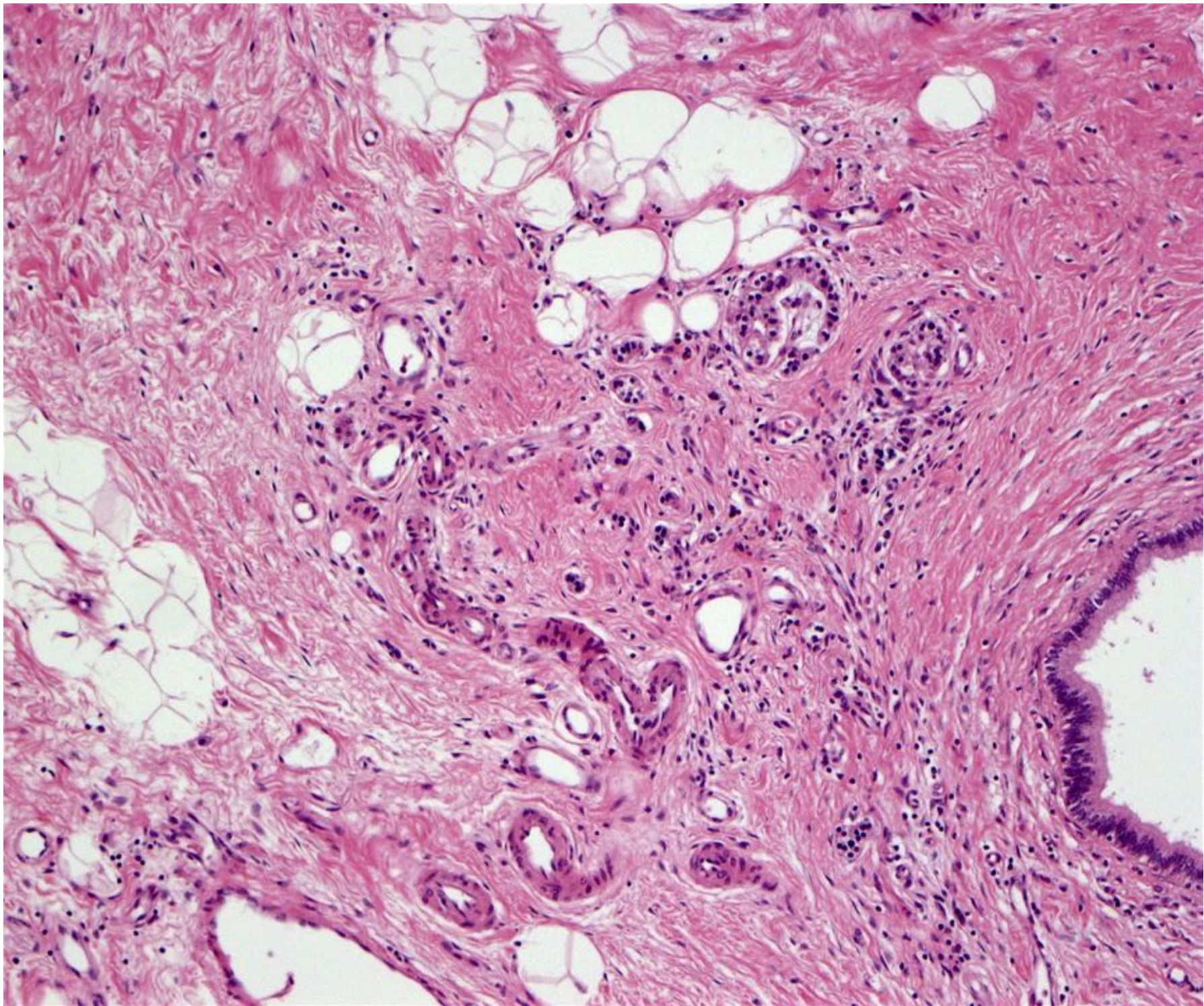


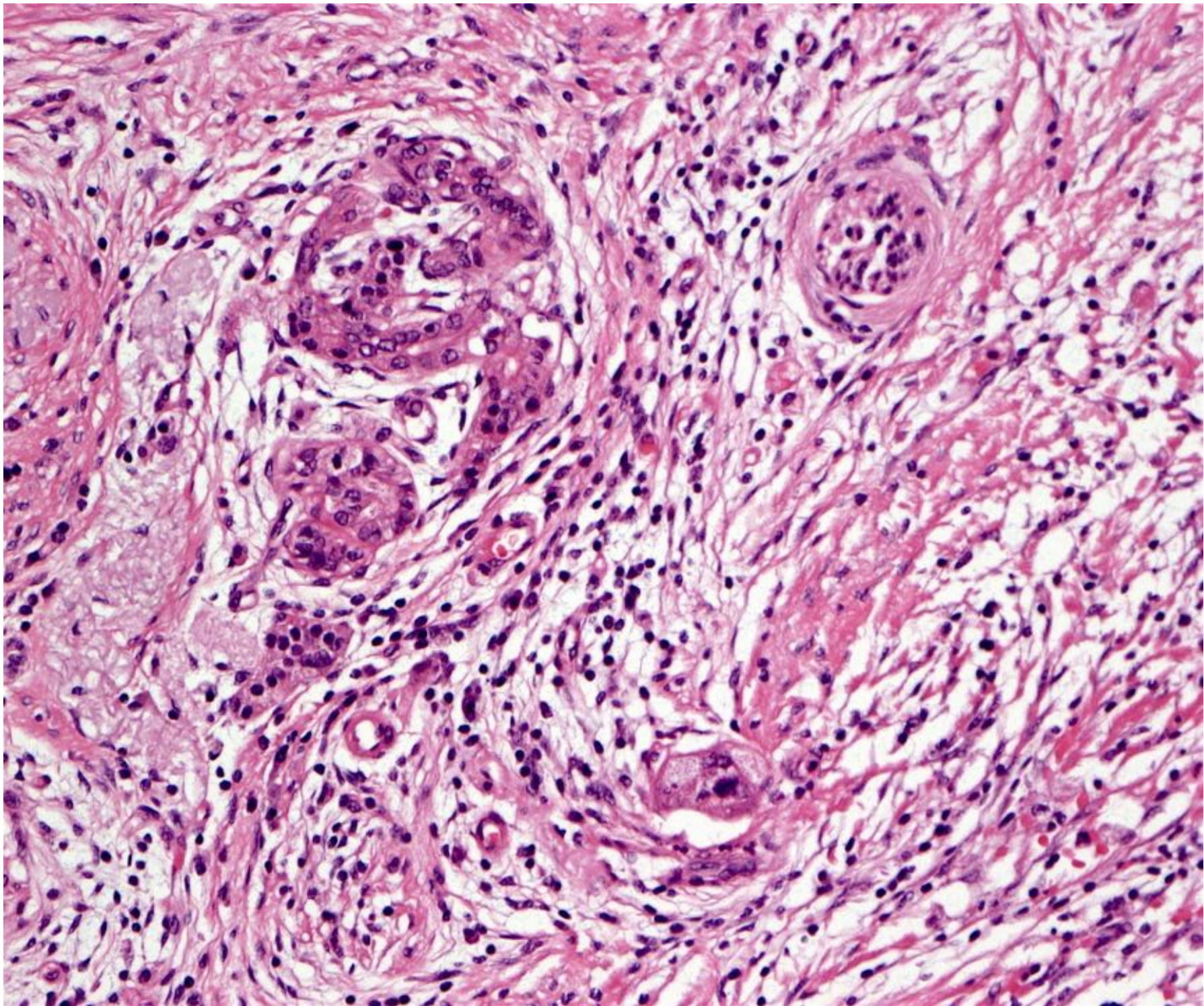


Treatment-induced changes in non-neoplastic tissues

- Blood vessels:
 - myxohyaline intimal proliferation
 - elastosis/elastic degeneration
- Nerve bundles: hypertrophy
- Acinar parenchyma: atrophy
- Pancreatic islets:
 - scattered, "single file"
 - hypertrophic
 - occasionally "intraneural" location

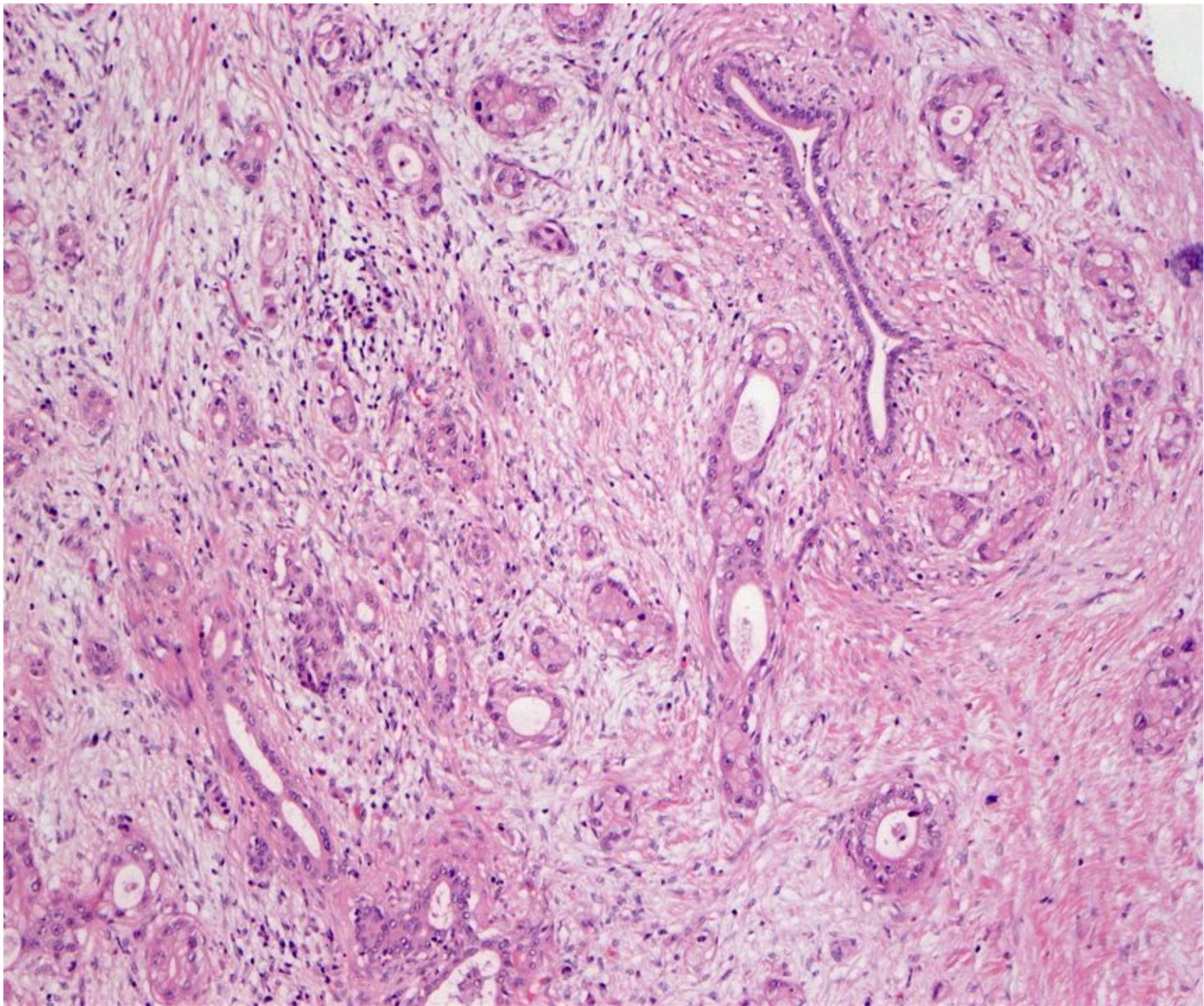


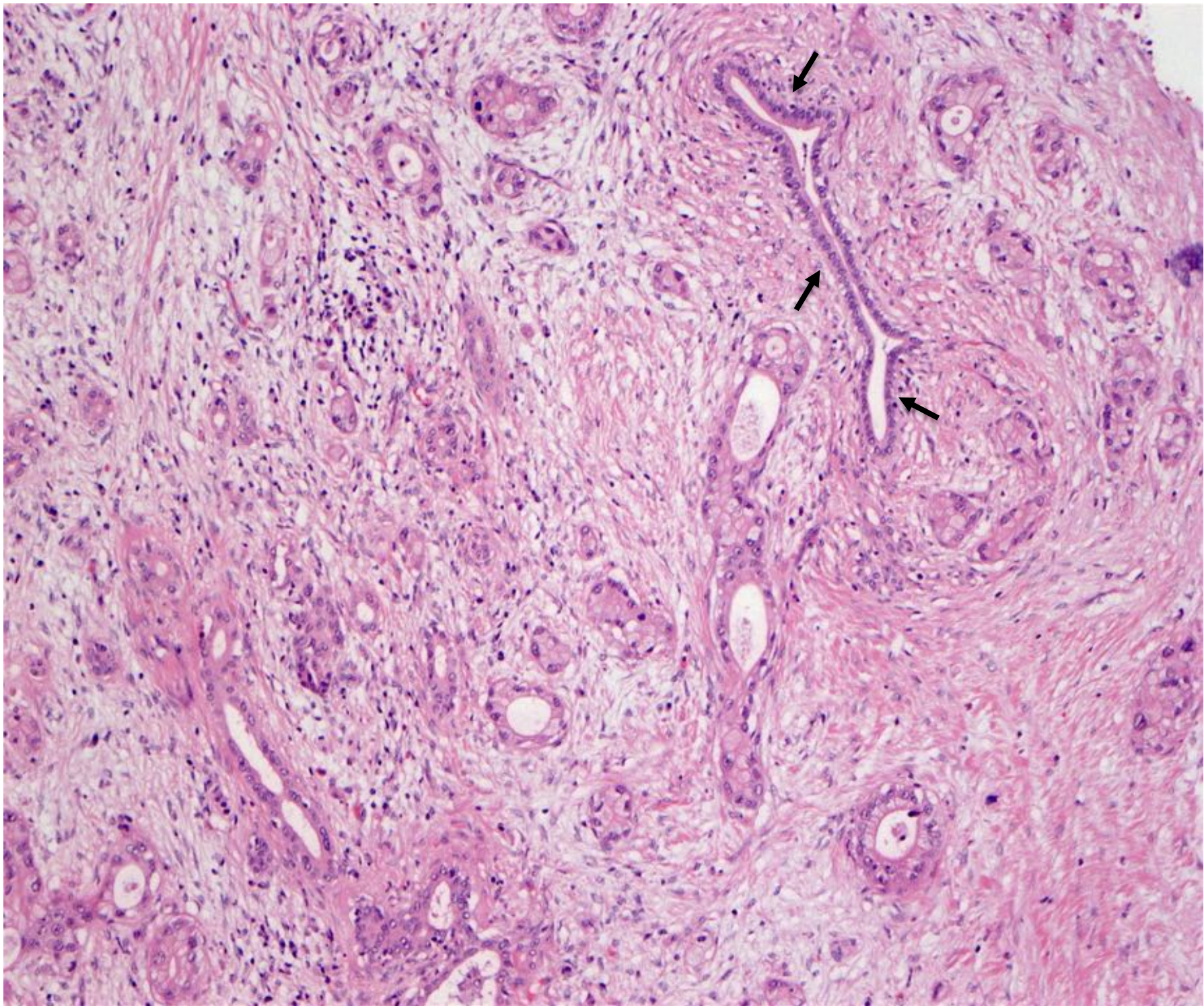


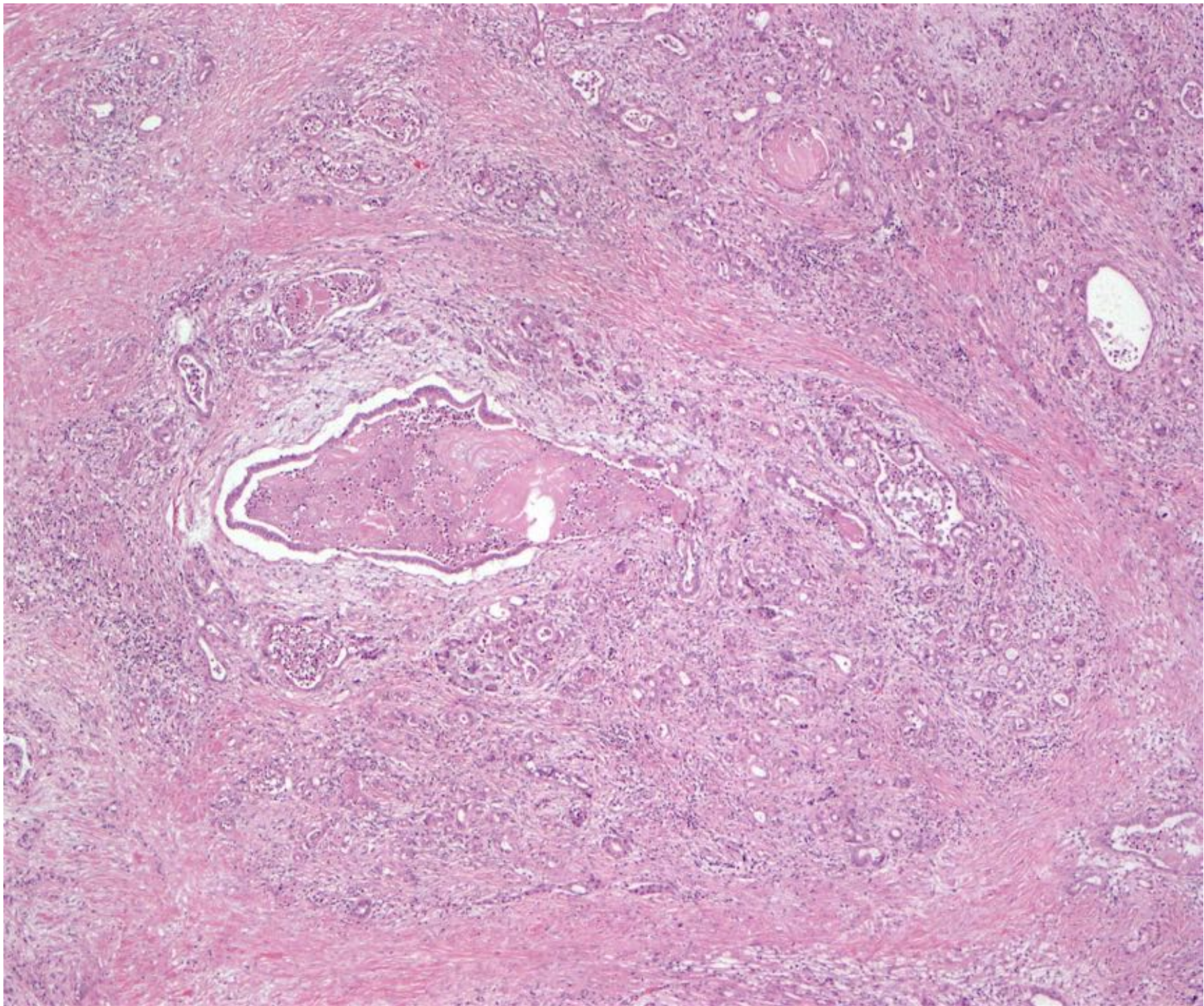


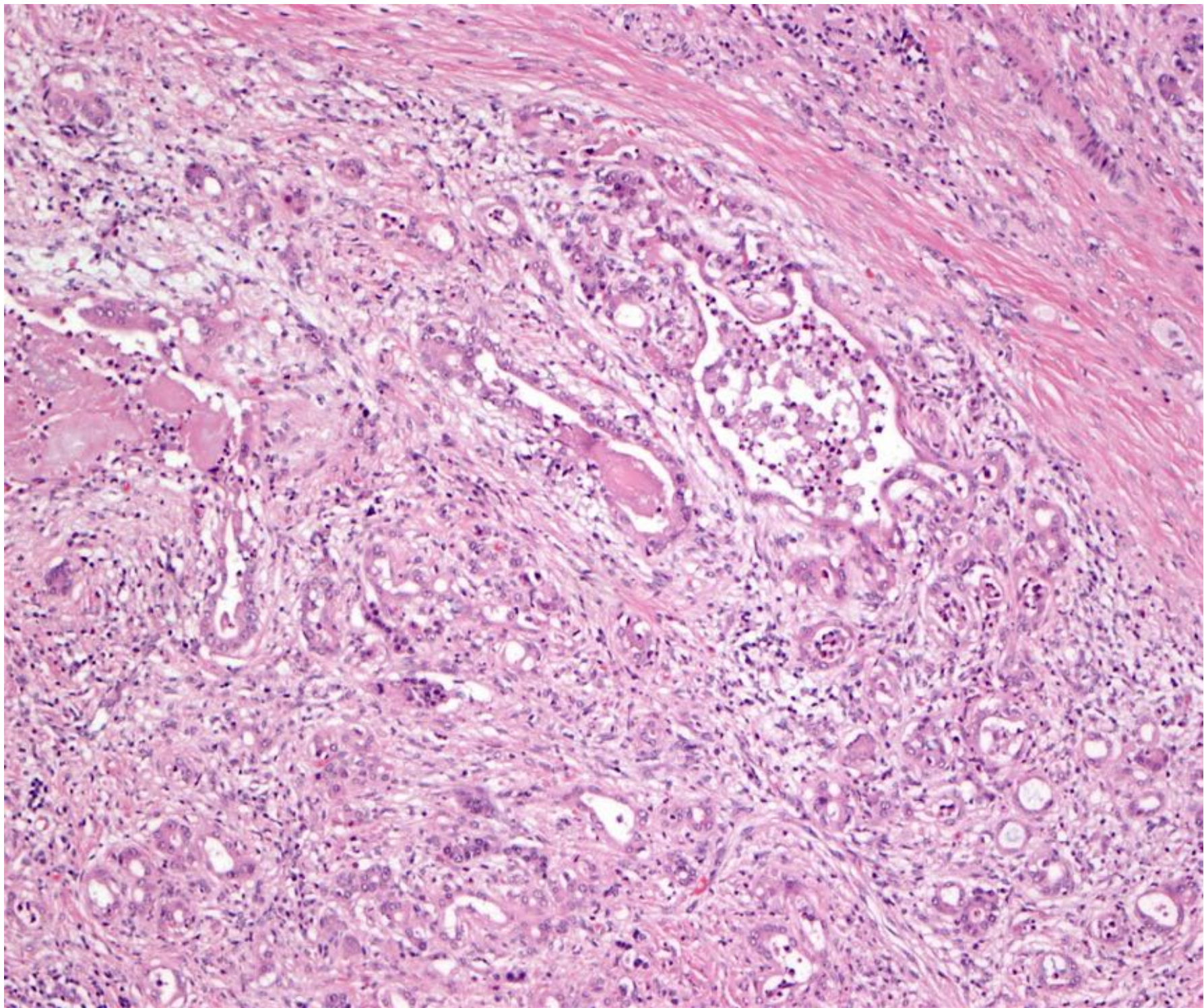
Treatment-induced changes in non-neoplastic tissues

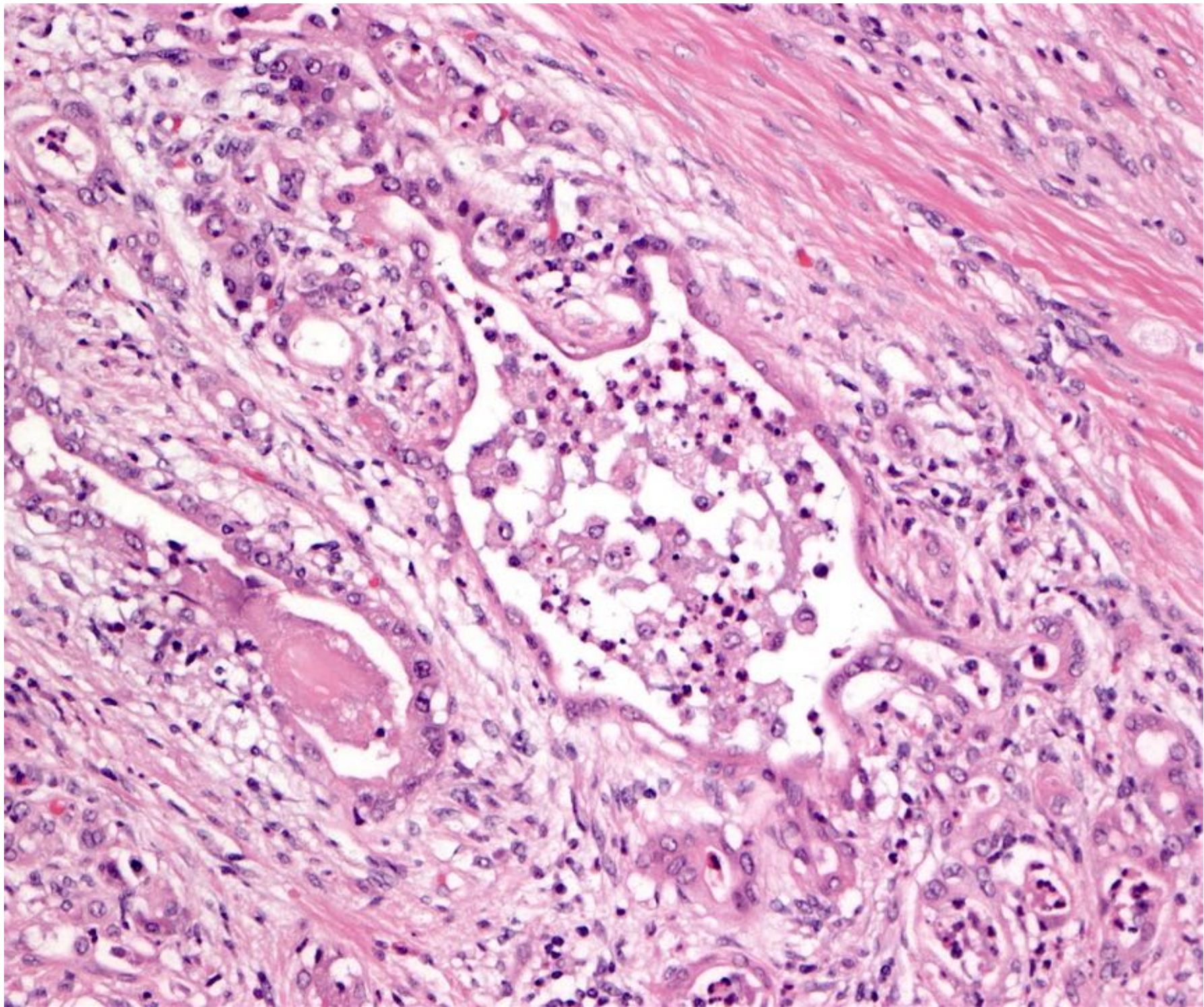
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- Nerve bundles: hypertrophy
- Acinar parenchyma: atrophy
- Pancreatic islets:
 - scattered, "single file"
 - hypertrophic
 - occasionally "intraneural" location
- Pancreatic ducts:
 - irregular shape, cytological atypia (mild)
 - eosinophilic cytoplasm

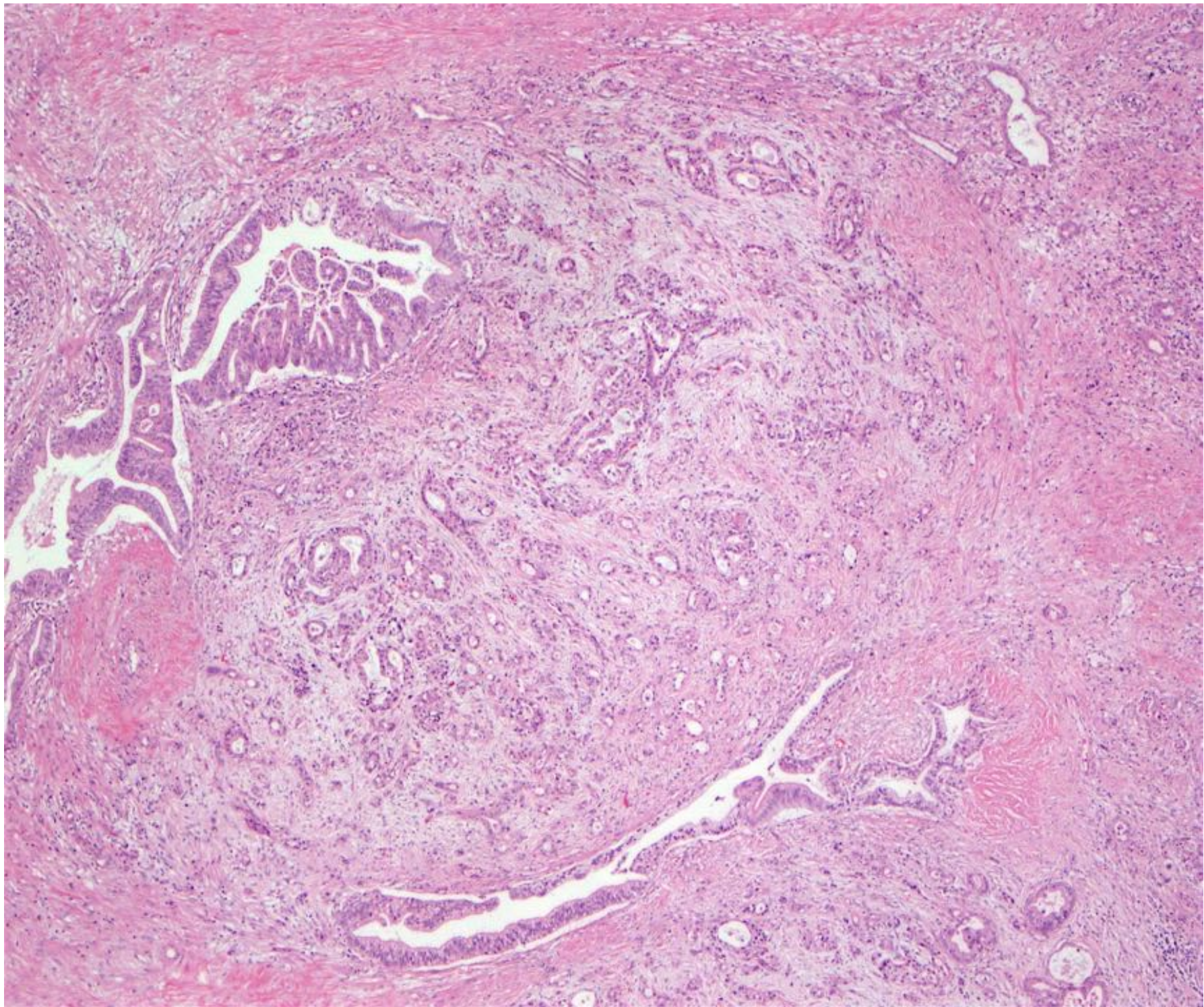


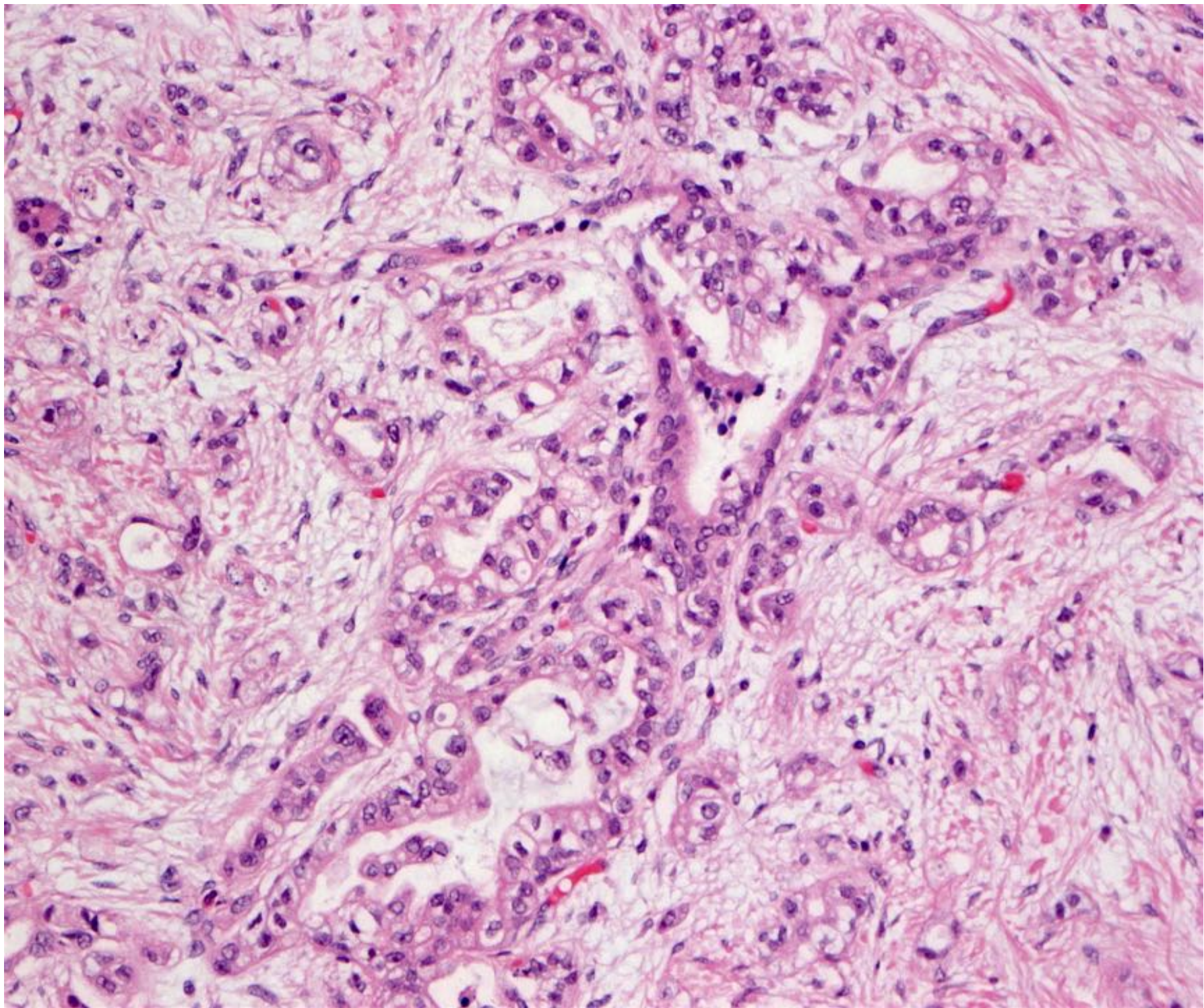


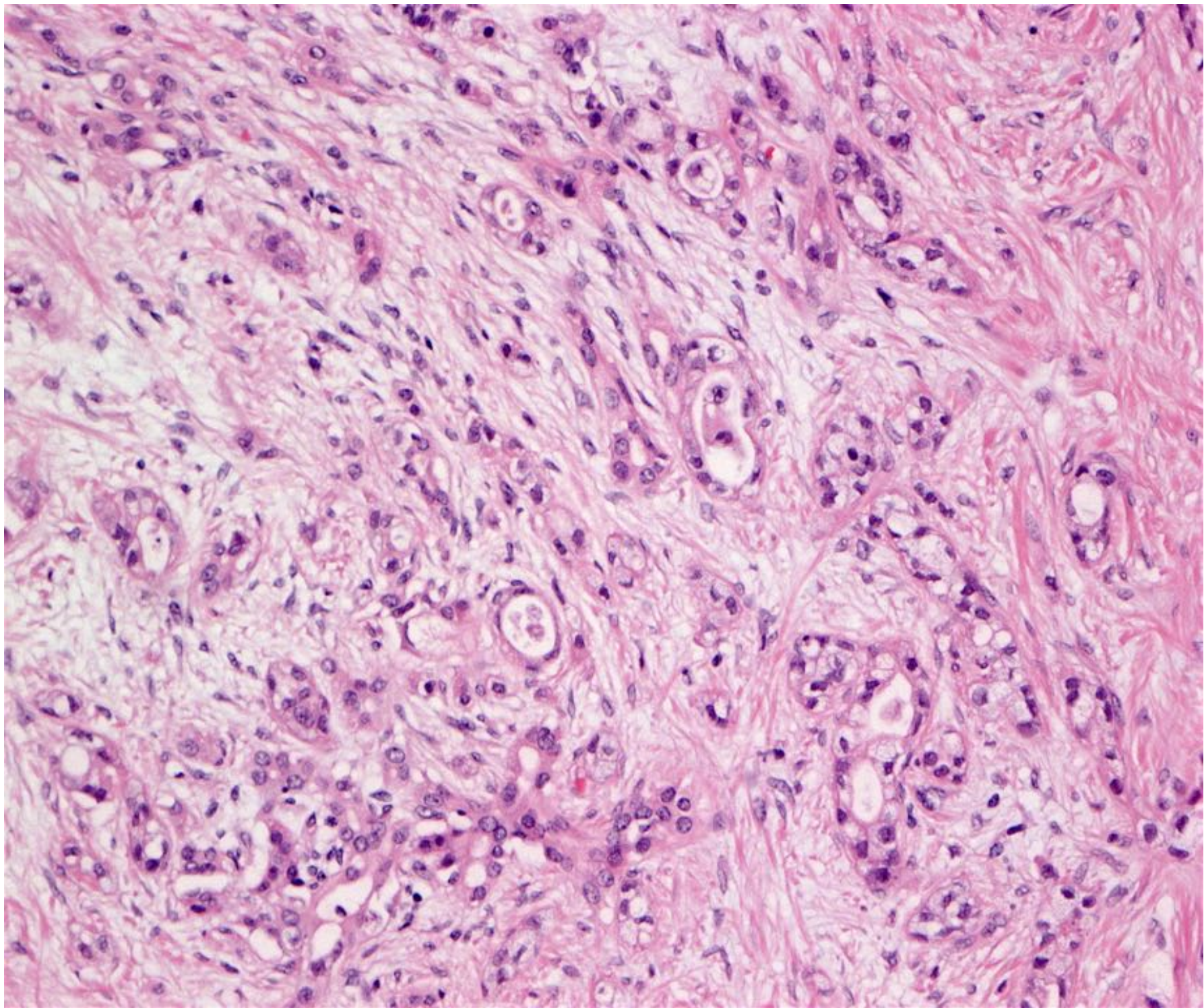


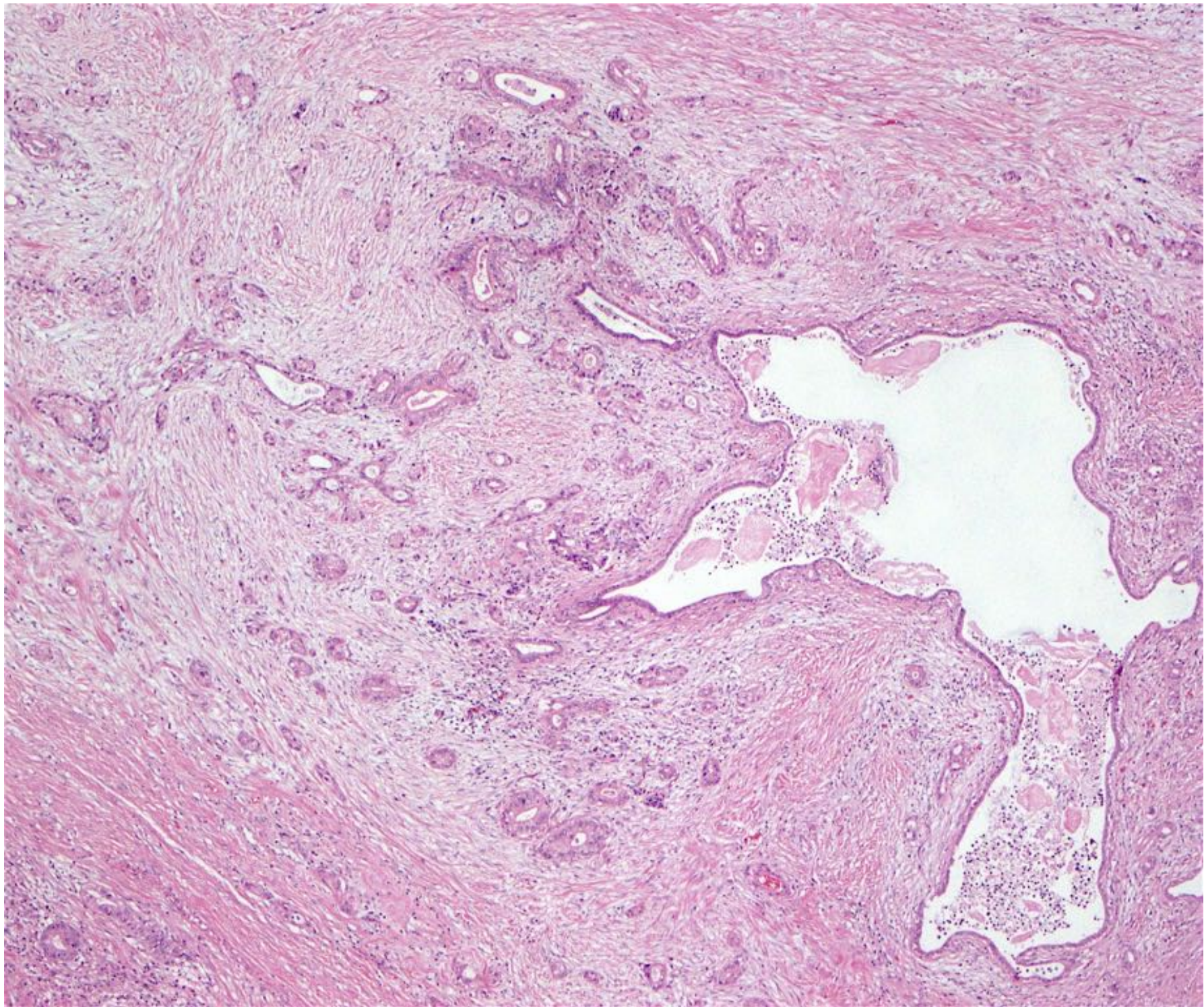


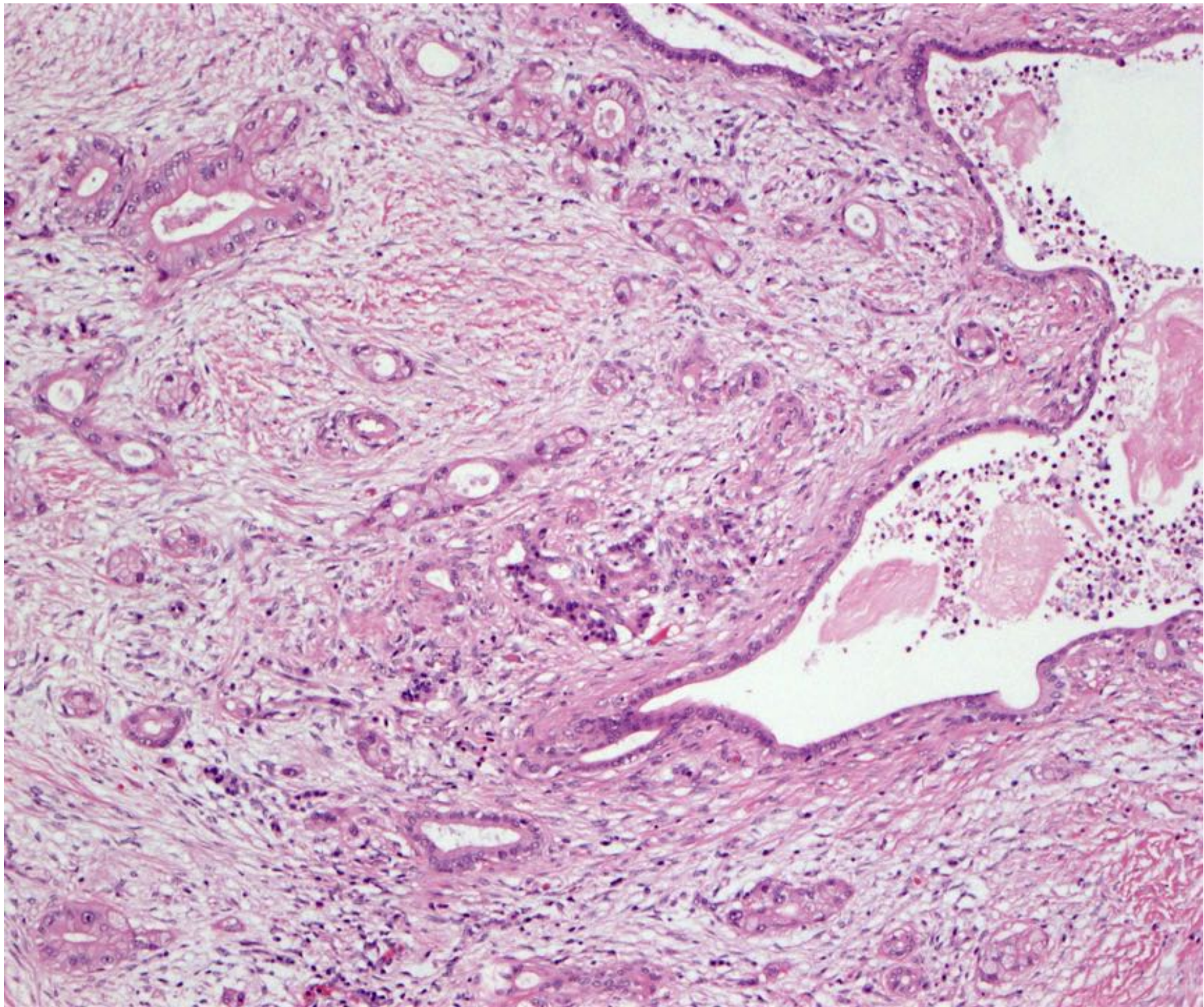


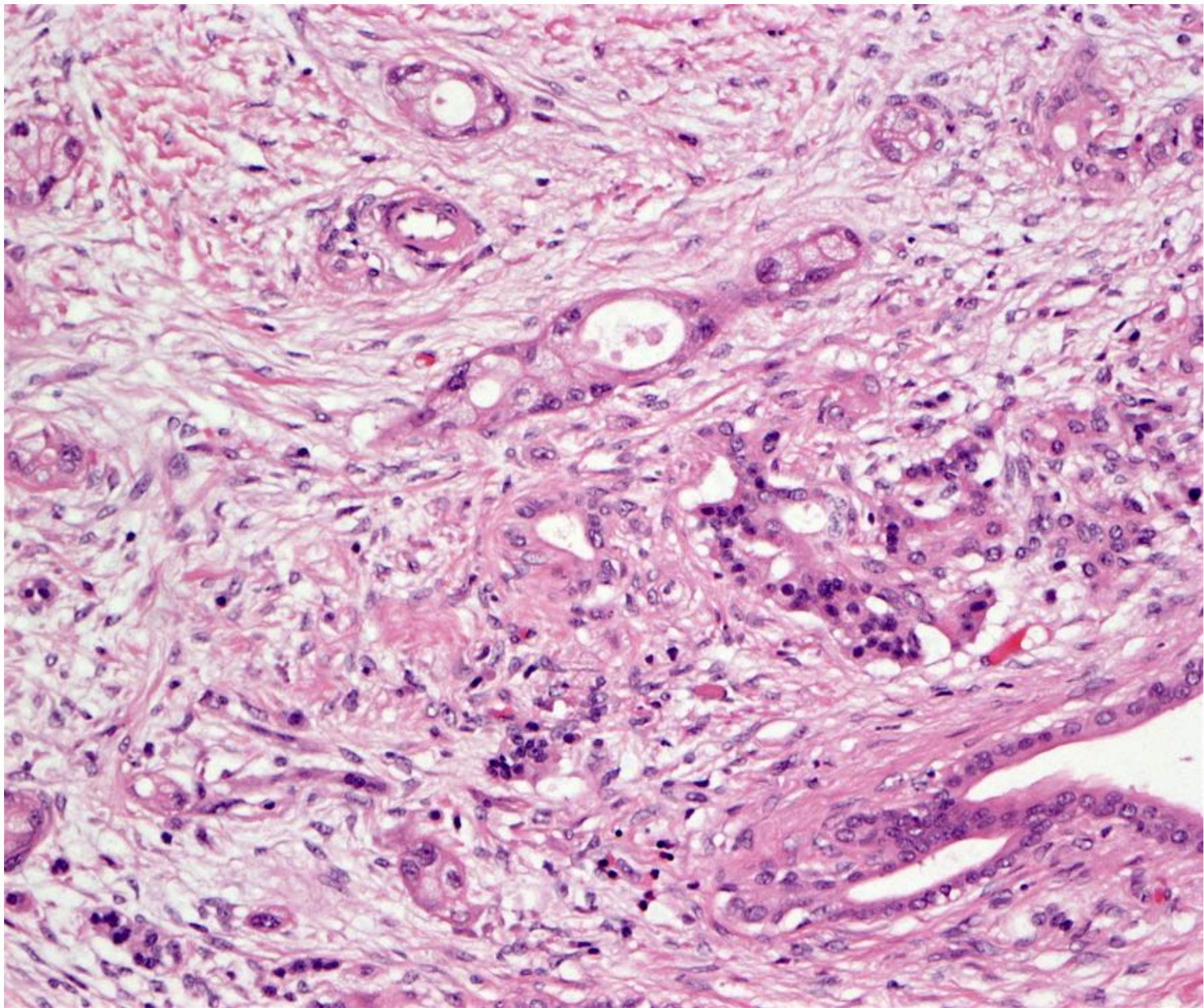






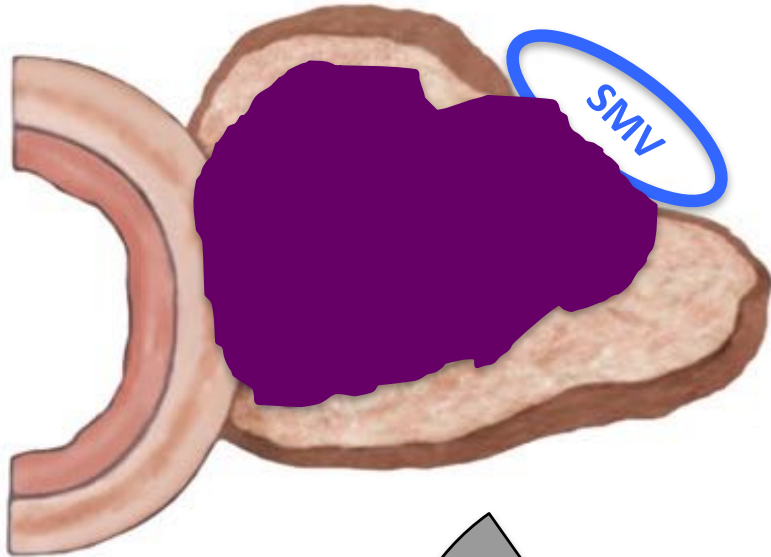






Tumour staging (yp-)

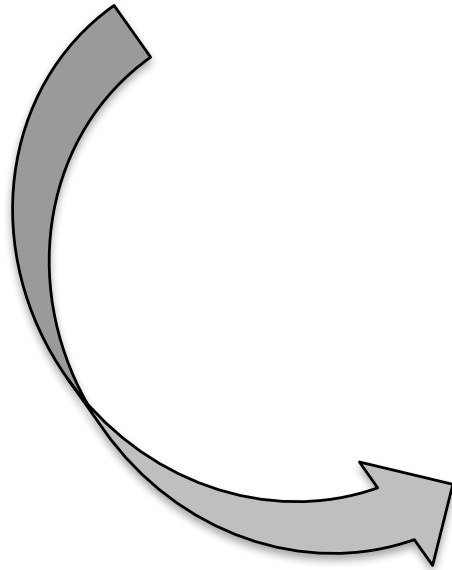
- T:
 - evaluated as usual



Before neoadjuvant therapy:

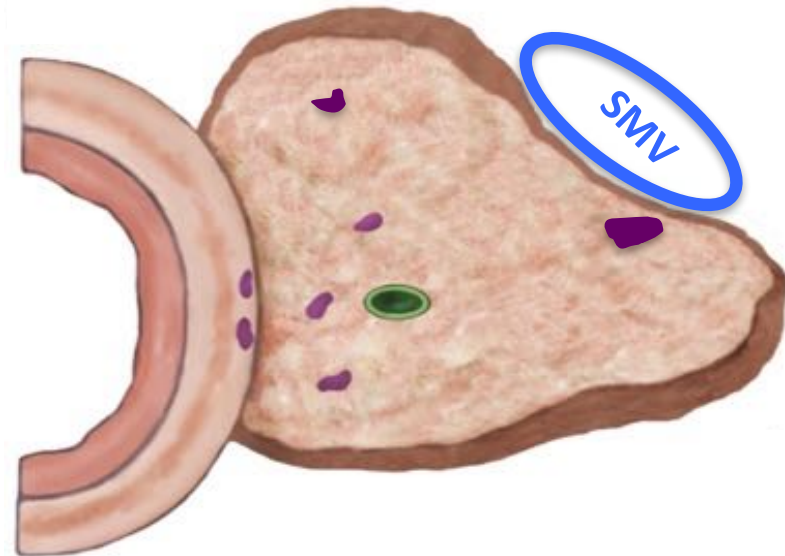
- 45 x 38 mm
- pT3

Neoadjuvant
treatment



After neoadjuvant therapy:

- 42 x 36 mm
- ypT3 → **debulking**



Tumour staging (yp-)

- T:
 - evaluated as usual
 - most still ypT3
- N:
 - staging as usual
 - often lower lymph node yield

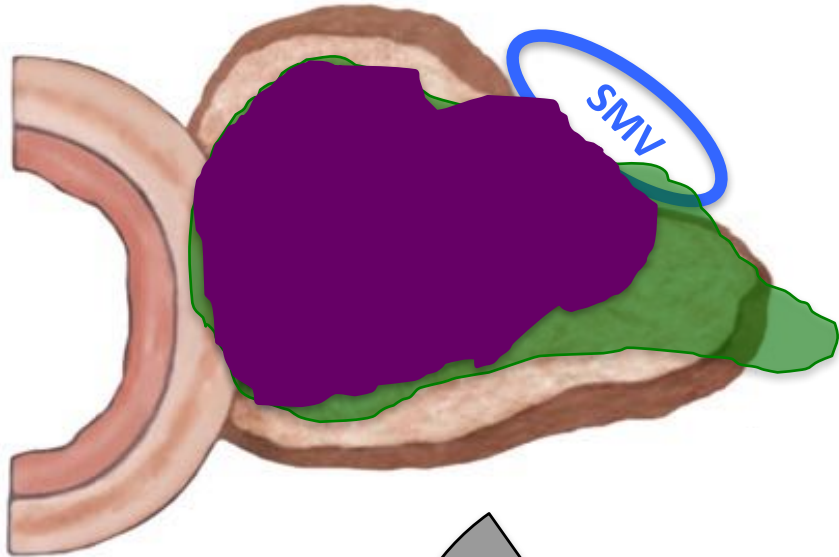
Tumour regression grading

- **Important:** evaluation of effect of treatment
- **Confusing:** various grading systems

Tumour regression grading systems for PDAC

	Ishikawa et al. [28]	Evans et al. [29]	White et al. [30]
Criterion	Proportion severely damaged cancer cells	Percentage tumour cell destruction/ viable cancer cells	Percentage viable cancer cells
Grade	I = <1/3 II = 1/3-2/3 III > 2/3	I = 0-9% tumour cell destruction IIa = 10-50% tumour cell destruction IIb = 51-90% tumour cell destruction III = <10% viable cancer cells IV = 0% viable cancer cells	Large = >90% Moderate = 10-90% Small = 0 to <10%

Comparison of residual with original tumour volume



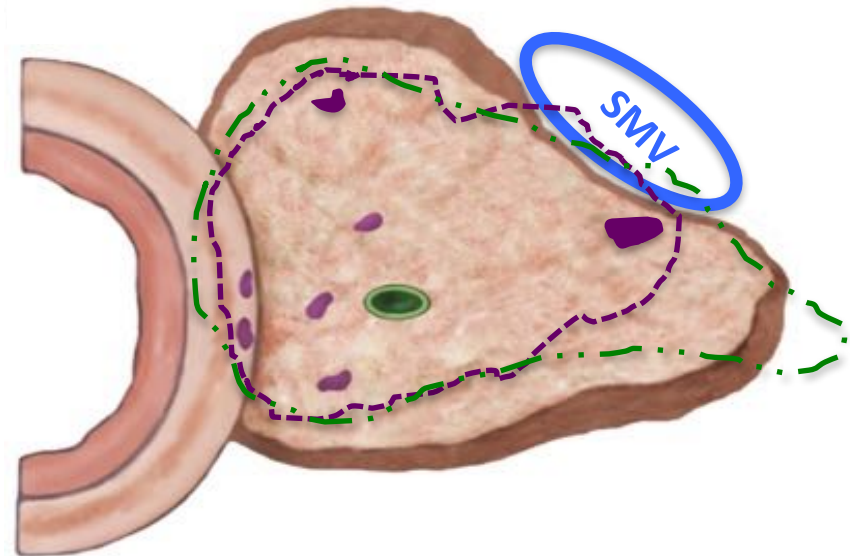
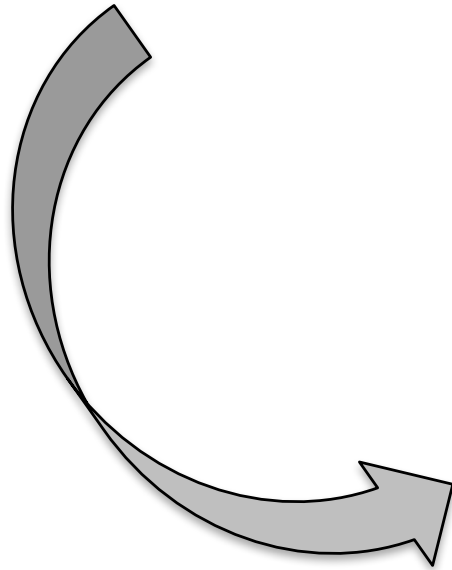
Before neoadjuvant therapy:

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Neoadjuvant
treatment



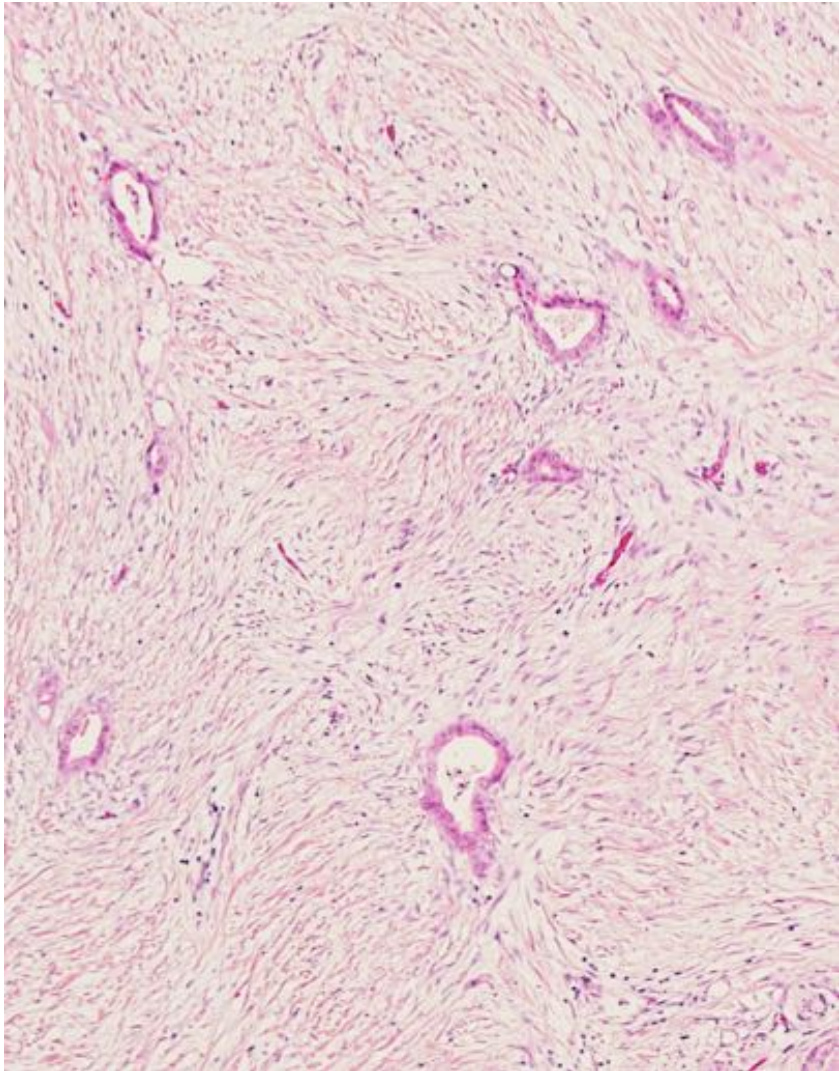
Tumour regression grading systems for PDAC

CAP [31]	
Criterion	Extent residual cancer
Grade	0 = Complete response: no residual cancer cells I = Marked response: minimal residual cancer cells (single/ small groups of cancer cells) II = Moderate response: cancer cells outgrown by fibrosis III = Poor/no response: extensive residual cancer

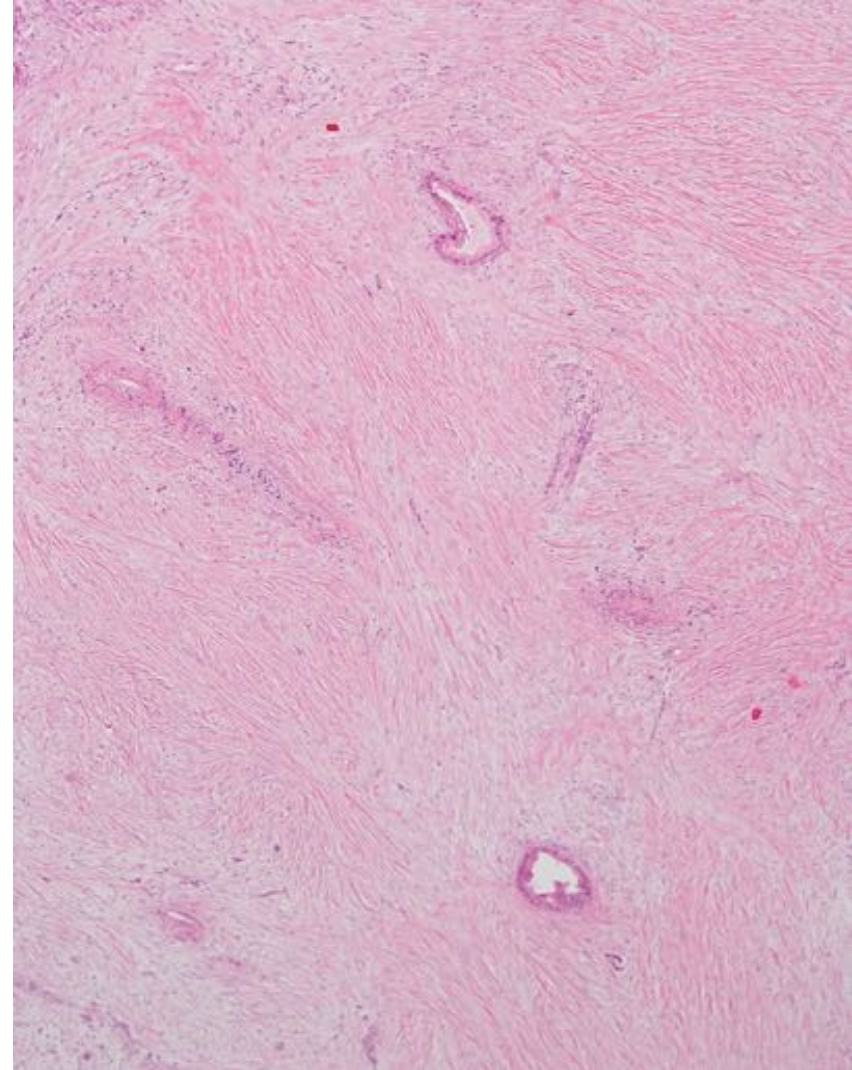
Abbreviation: CAP – College of American Pathologists.

Comparison of residual tumour volume with (treatment-induced) fibrosis

After neoadjuvant therapy



No neoadjuvant therapy



Tumour regression grading

- **Important:** evaluation of effect of treatment
- **Confusing:** various grading systems
- **Difficult:** inhomogeneous tumour regression

Tumour regression grading

- **Important:** evaluation of effect of treatment
- **Confusing:** various grading systems
- **Difficult:** inhomogeneous tumour regression
 - Importance of extensive sampling

TRG system – Chatterjee et al. Cancer 2012

Grade	Residual cancer
0	None
1	Minimal (single cells or small groups; < 5%)
2	> 5%



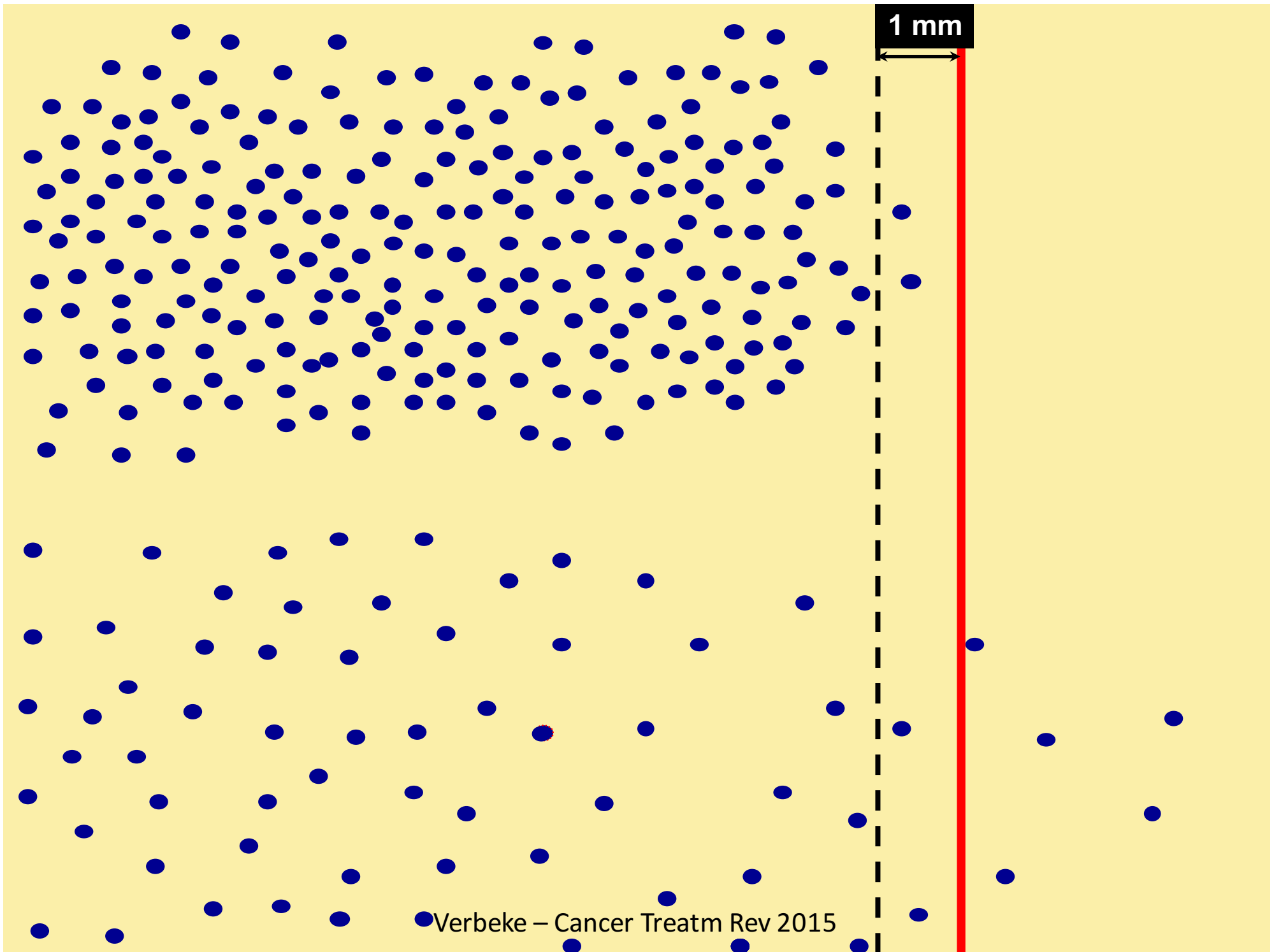
Encompasses CAP grade 2 and 3

Lee et al. AJSP 2016:

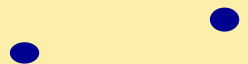
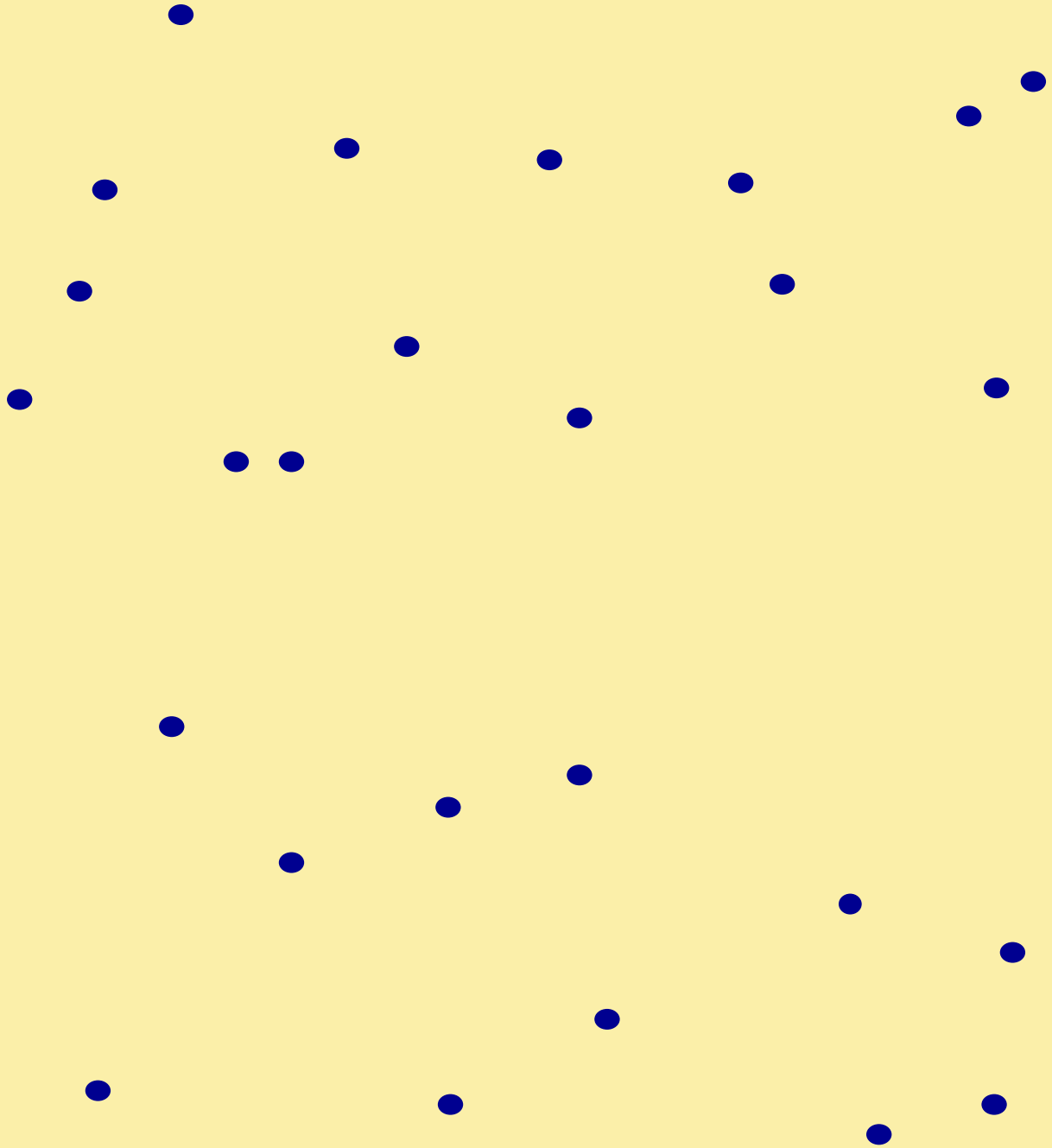
- Significant difference in OS and DFS between Chatterjee grade 0-1 and grade 2
- No difference in OS or DFS between CAP grade 2 and 3
- Too few patients with grade 0 (1.8%) to evaluate possible difference in survival between grade 0 and grade 1

Margin status following NAT

- R1 rate: often used as outcome measure for effect of neoadjuvant treatment
- Detection rate of R1 depends on extent of sampling
- Definition of R1 based on 1 mm clearance does not apply
 - \rightarrow clearance > 1 mm \neq R0



1 mm



Conclusions

- Tumour regression is often inhomogeneous throughout a tumour
- Tumour regression grading is often difficult
- Complete response is extremely rare
- Tumour regression does usually not lead to down-staging
- Extensive, (sub-)total sampling is key to correct evaluation of tumour size, stage and grade of tumour regression.