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S1882 Applying the New AJCC Staging System to Daily Diagnostic Practice: Gastrointestinal Pathology

Amitabh Srivastava, MBBS, FCAP
Hanlin L. Wang, MD, PhD

Agenda

Applying the New AJCC Staging System to Daily Diagnostic Practice: Gastrointestinal Pathology
Opening/Introductions - Maria Westerhoff, MD
Esophagus and stomach - Amitabh Srivastava, MBBS, FCAP
Small intestinal carcinomas and NE tumors - Hanlin L. Wang, MD, PhD
Colon and anus - Amitabh Srivastava, MBBS, FCAP
Appendix - Hanlin L. Wang, MD, PhD
Summary and Closing – All faculty

Objectives

- **Identify new staging parameters in gastrointestinal tumors**
- **Recognize strengths and weaknesses of the evidence behind the changes in staging parameters**
- **Accurately diagnose pathological aspects of gastrointestinal tumors that may impact clinical management, such as proper grossing, margin assessment, and other staging components**
- **Identify the latest clinical treatments of GI tumors**

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S1882 Applying the New AJCC Staging System to Daily Diagnostic Practice: Gastrointestinal Pathology

Amitabh Srivastava, MD, Associate Professor of Pathology, Harvard Medical School, Associate Director, Surgical Pathology, Director, Surgical Pathology Fellowship Program, Brigham and Women's Hospital

Objectives

- **Familiarize with changes in AJCC 8th edition**
- **Understand the rationale behind the changes**
- **Discuss potentially confusing issues in the new system that may affect our practice**

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Esophagus

CAP/AJCC 8th Edition Esophagus Protocol

For accreditation purposes, this protocol should be used for the following procedures and tumor types:

Procedure:

- Surgical Resection - Includes specimens designated esophagectomy and esophagogastrectomy

Tumor Type:

- Epithelial tumors of the esophagus - Includes all carcinomas and well-differentiated neuroendocrine tumors
- Epithelial tumors of the esophagogastric junction - Includes tumors involving the esophagogastric junction with center no more than 2 cm into the proximal stomach

This protocol is NOT required for accreditation purposes for the following:

Procedure:

- Biopsy
- Excisional biopsy (includes endoscopic resection and polypectomy)
- Primary resection specimen with no residual cancer (eg, following neoadjuvant therapy)
- Recurrent tumor
- Cytologic specimens

CAP/AJCC 8th Edition Esophagus Protocol

This protocol applies to:

1) All carcinomas arising in the esophagus
2) Carcinomas involving the esophagogastric junction (EGJ), with tumor midpoint ≤2 cm into the proximal stomach/cardia
3) Well-differentiated neuroendocrine tumors, WHO grade 1, 2 and grade 3 (stage grouping for prognosis is not used)#

Esophageal well-differentiated neuroendocrine tumors are so rare, a separate staging system is not warranted.

CAP/AJCC 8th Edition Esophagus Protocol

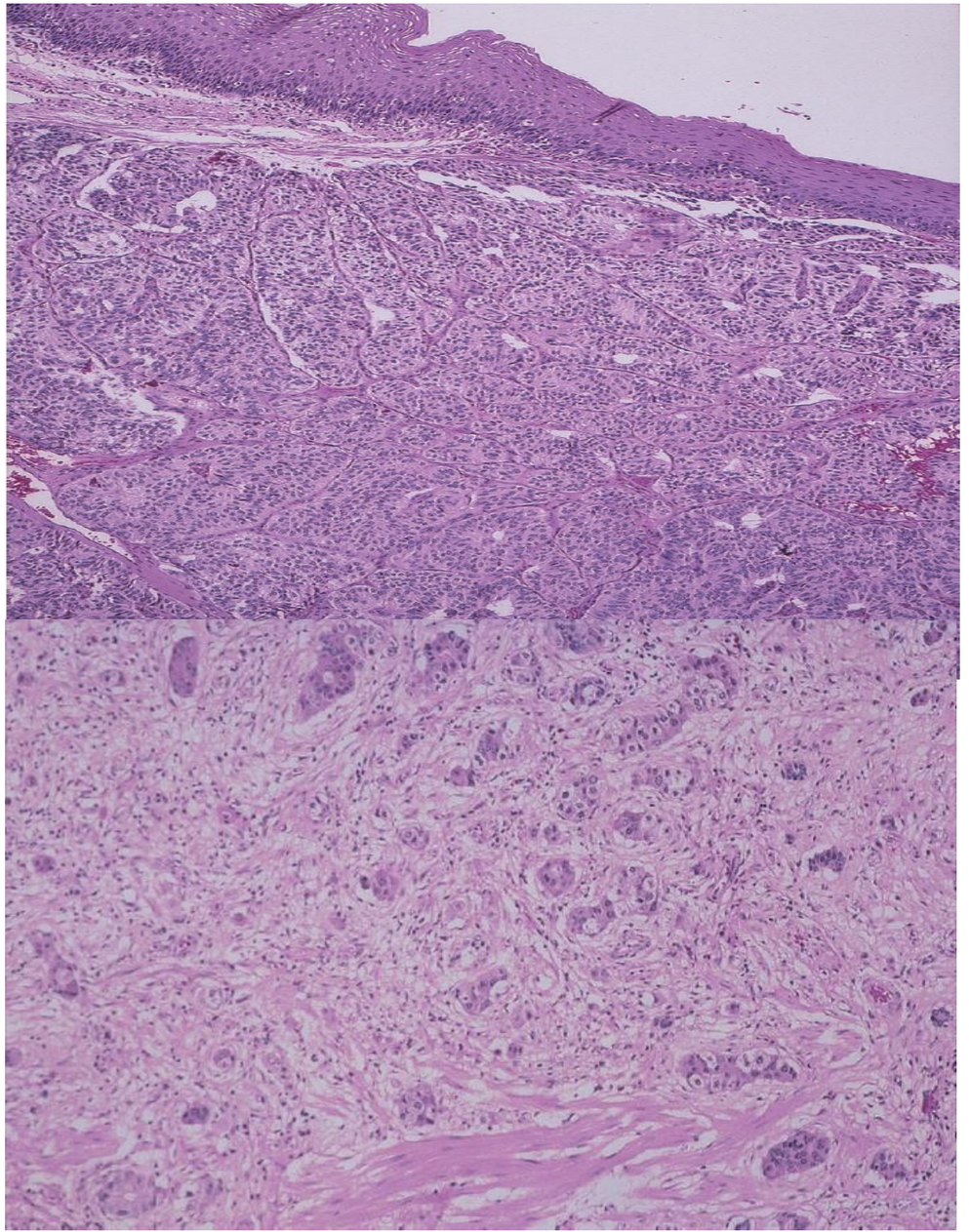
The following tumor types should NOT be reported using this protocol

Tumor Type:

- Tumor involving the esophagogastric junction (EGJ) with the tumor midpoint more than 2 cm into the proximal stomach (consider the Stomach Carcinoma protocol, see notes in relationship to EGJ)
- Tumor midpoint is less than 2 cm into the proximal stomach, but the tumor does not involve the EGJ (consider the Stomach Carcinoma protocol)
- Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocol)
- Gastrointestinal stromal tumor (GIST) (consider the GIST protocol)
- Non-GIST sarcoma (consider the Soft Tissue protocol)

Carcinoid Tumor of the Esophagus

- Primary esophageal WDNET are extremely rare
- Present as:
  - Single polypoid tumor
  - In association with adenocarcinoma in BE
- Uncertain outcomes
- Small localized tumors treated endoscopically
- Large or node positive tumors with resection and chemotherapy



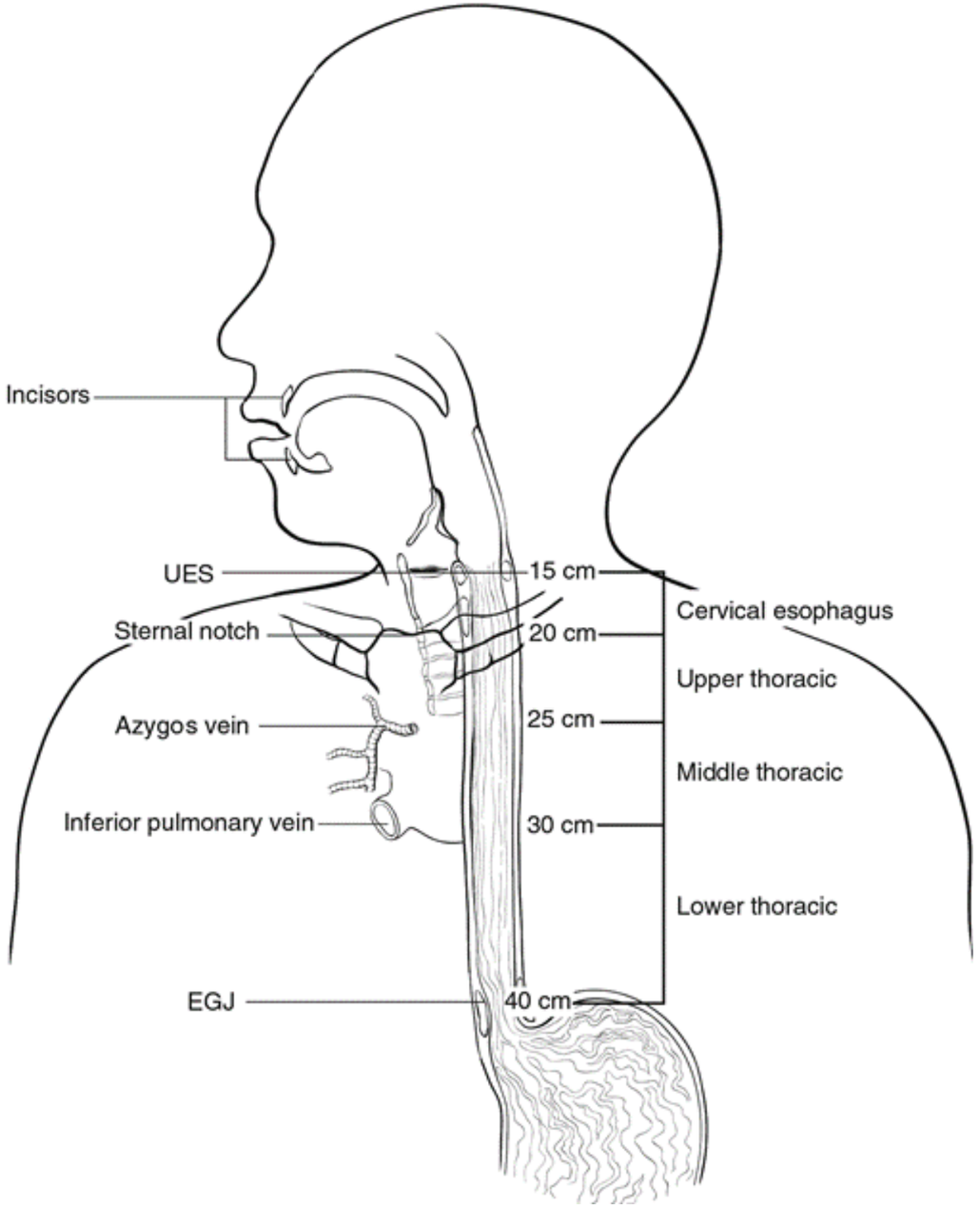
Hoang MP et al, Am J Surg Pathol 2002, 26: 517-522

CAP Esophagus Protocol Summary of Changes

The following data elements have been modified:

- Relationship of Tumor to Esophagogastric Junction
- Histologic Type
- Histologic Grade
- Microscopic Tumor Extension
- Pathologic Stage Classification (pTNM, AJCC 8th Edition)

Tumor location defined by epicenter of lesion



Tumor Location

WHO:

- Entirely above EGJ: Esophagus
- Entirely below EGJ: Stomach
- Crossing the EGJ: EGJ

Siewart:

- Type I: Esophageal carcinoma, with or without involvement of EGJ
- Type II: Gastric cardia carcinoma
- Type III: Subcardial gastric carcinoma with EGJ/distal esophagus involvement

AJCC 8th ed:

- Esophagus: Tumors with midpoint within proximal 2 cm of cardia/proximal stomach
- Stomach: Epicenter >2cm from EGJ, even if EJG is involved.

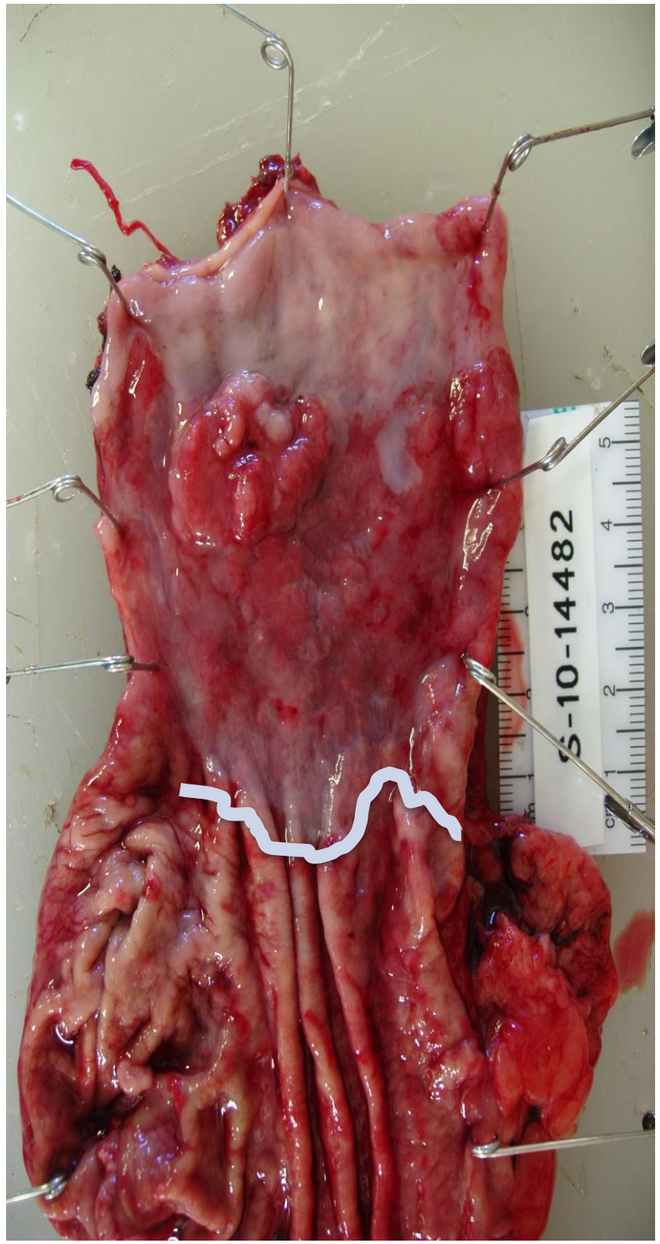
Relationship of Tumor to EGJ

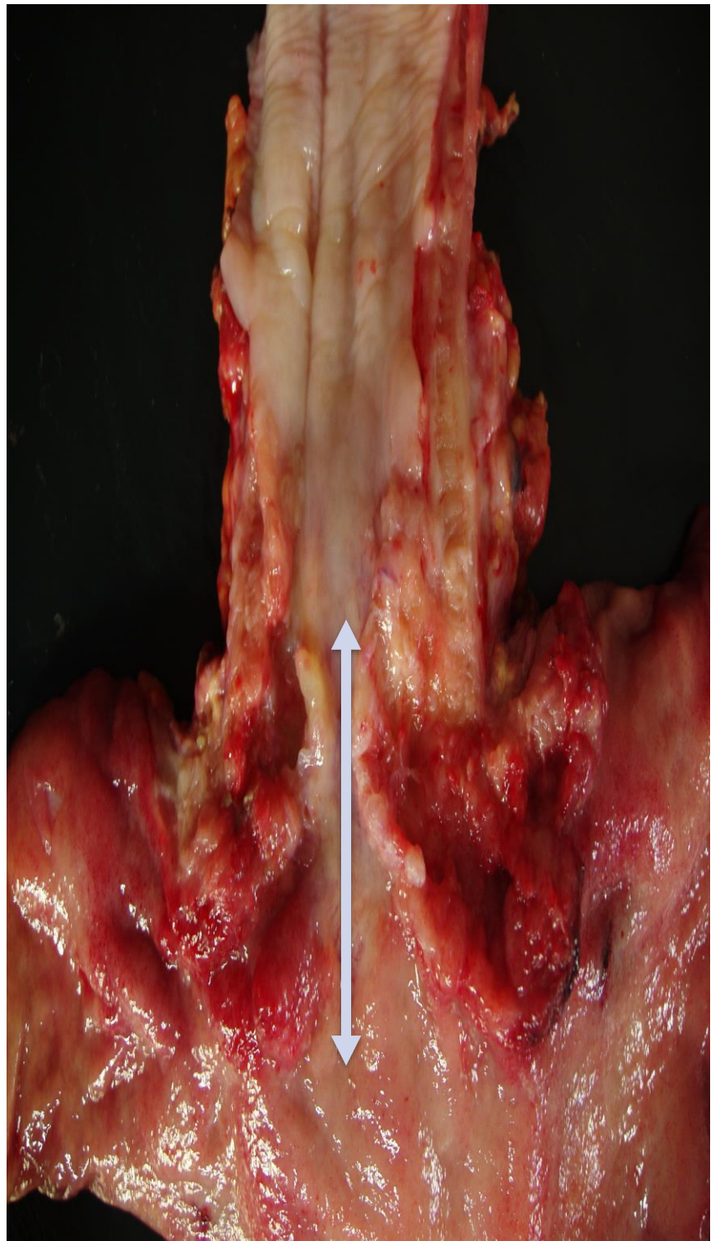
EGJ: Junction of the tubular esophagus and the stomach

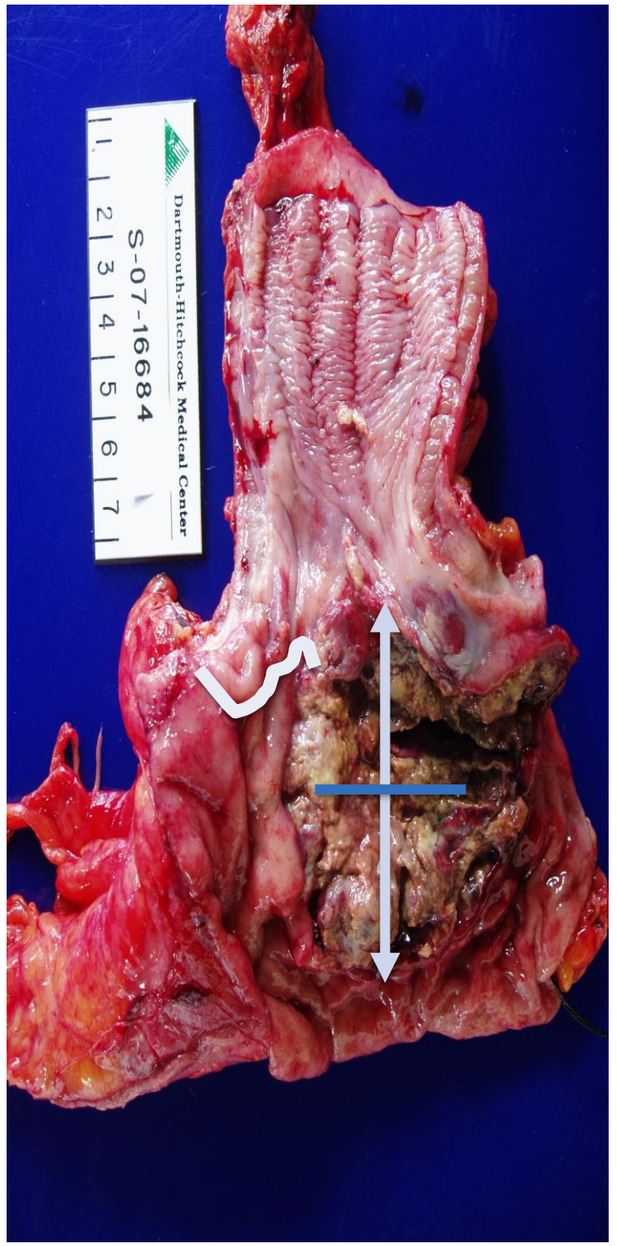
Macroscopic examination of esophagogastrectomy specimens:

- Maximum longitudinal dimensions of tumor mass
- Distance of tumor midpoint from EGJ
- Relative proportions of tumor mass in esophagus and stomach

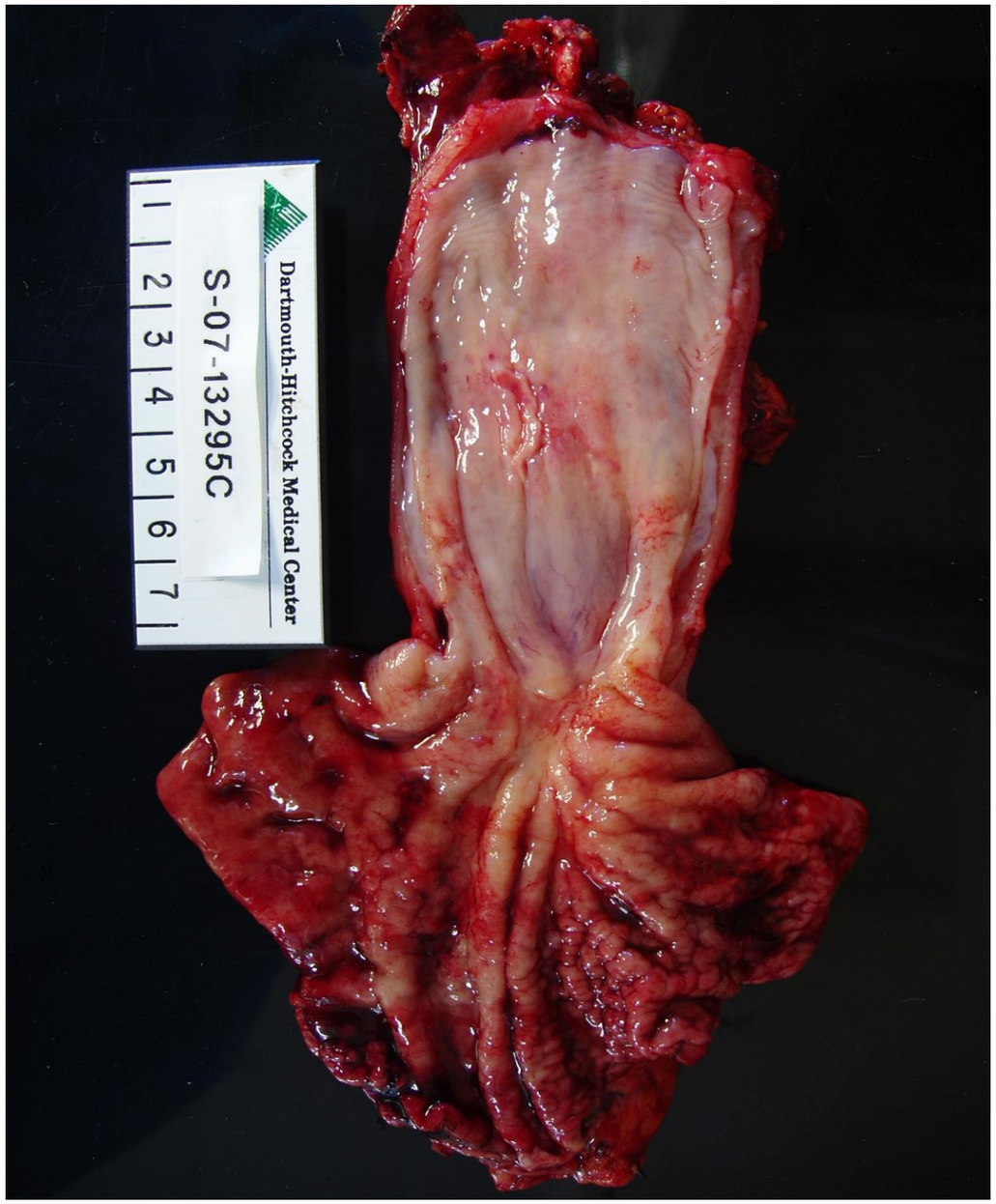
Tumor location defined by epicenter of lesion







Tumor location defined by epicenter of lesion



- Epicenter may not be easily determined in post-neoadjuvant resections with complete/near complete response
- Use epicenter of residual scar/pre-resection endoscopy report

Histologic Type

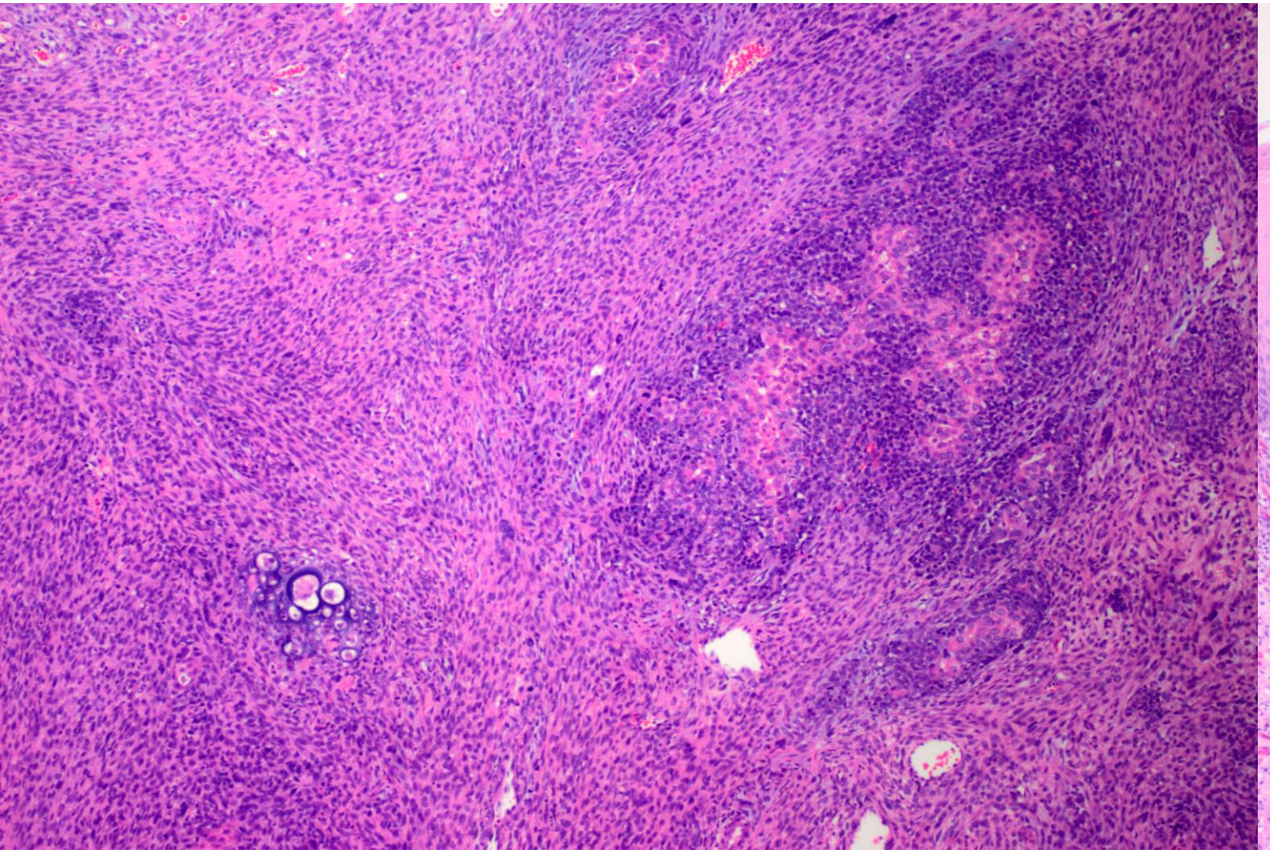
WHO Classification of Carcinoma of the Esophagus

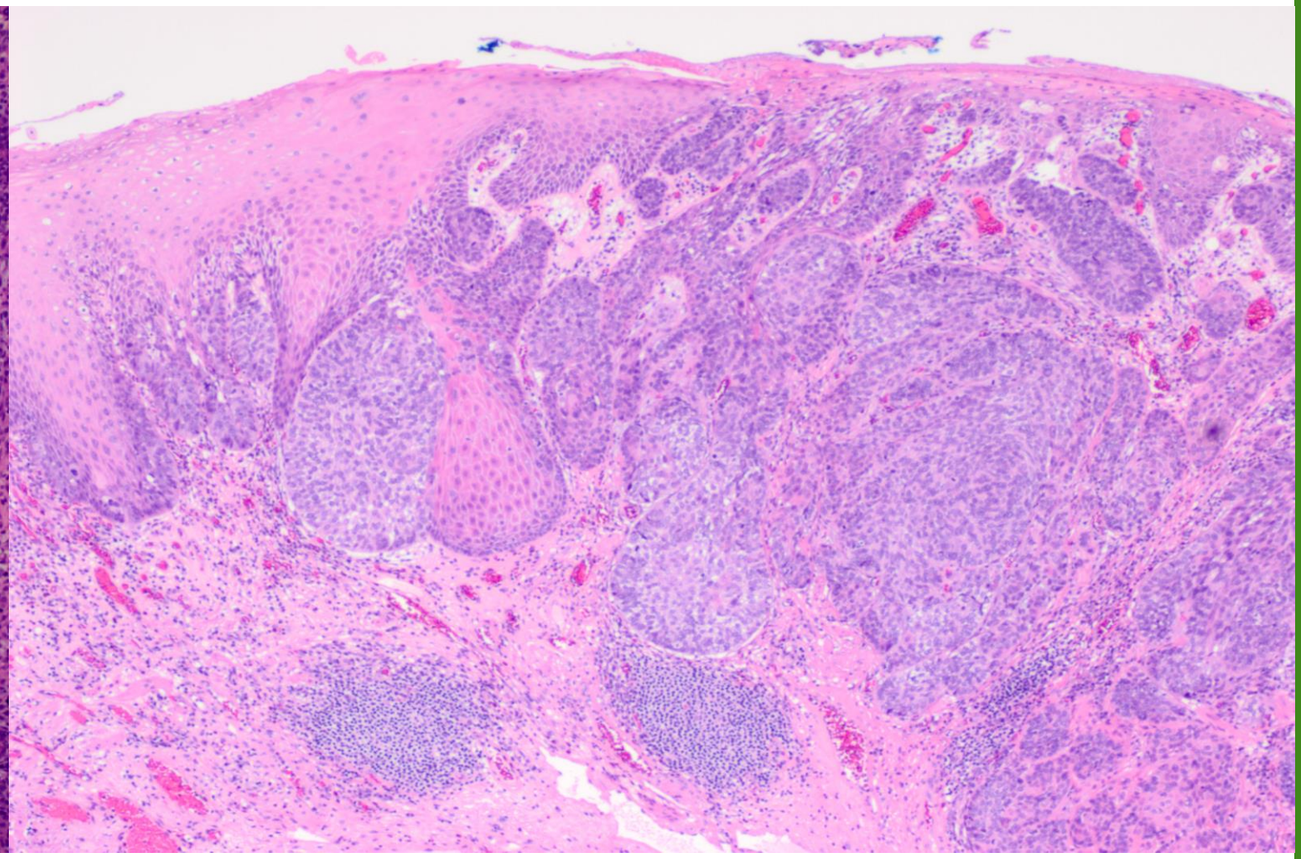
7th Edition
Squamous cell carcinoma
Verrucous (squamous) carcinoma
Spindle cell (squamous) carcinoma
Adenocarcinoma
Adenosquamous carcinoma
Mucoepidermoid carcinoma#
Adenoid cystic carcinoma#
High-grade neuroendocrine carcinoma Large cell neuroendocrine carcinoma# Small cell neuroendocrine carcinoma#
Undifferentiated carcinoma#
Others
#These types are not generally graded

8th Edition
Squamous# Squamous cell carcinoma Basaloid squamous cell carcinoma Adenosquamous carcinoma Verrucous (squamous) carcinoma Spindle cell (squamous) carcinoma Undifferentiated carcinoma with squamous component Undifferentiated carcinoma
Adenocarcinoma## Adenocarcinoma Mucoepidermoid carcinoma Adenoid cystic carcinoma Mixed adenoneuroendocrine carcinoma Undifferentiated carcinoma with glandular component
Other histologies### Well-differentiated neuroendocrine tumor WHO grade 1 WHO grade 2 WHO grade 3 High-grade neuroendocrine carcinoma Large cell neuroendocrine carcinoma Small cell neuroendocrine carcinoma Neuroendocrine carcinoma, large cell or small cell cannot be determined

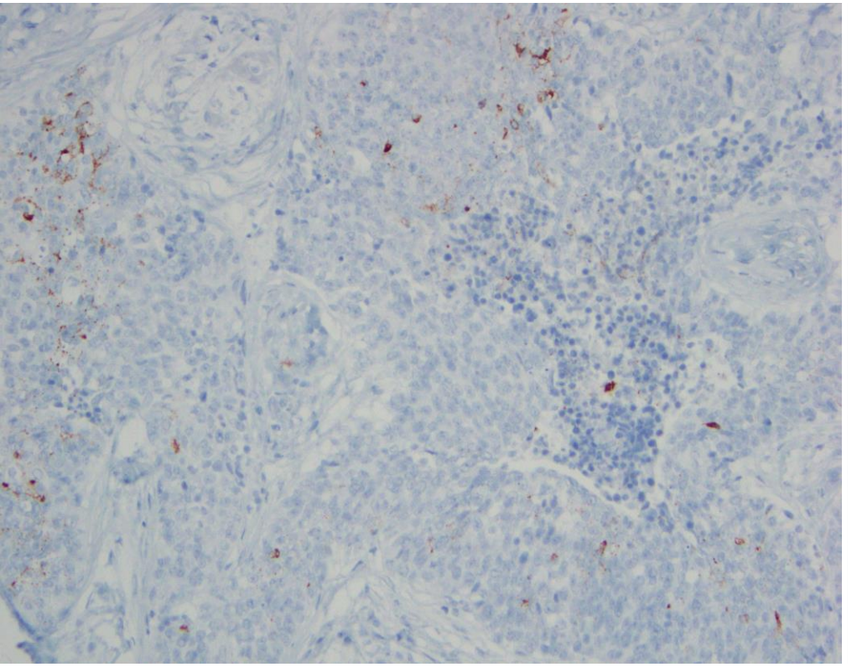
Use squamous cell carcinoma grouping system. ## Use adenocarcinoma grouping system. ### No stage grouping for these tumors.

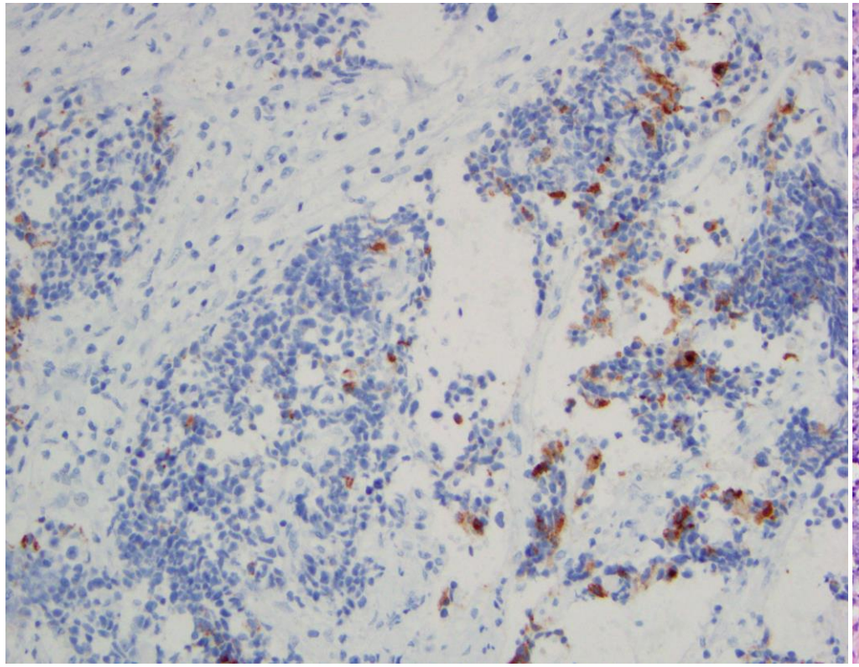
Esophageal Carcinosarcoma (Polypoid Carcinoma): Variant of Squamous cell carcinoma



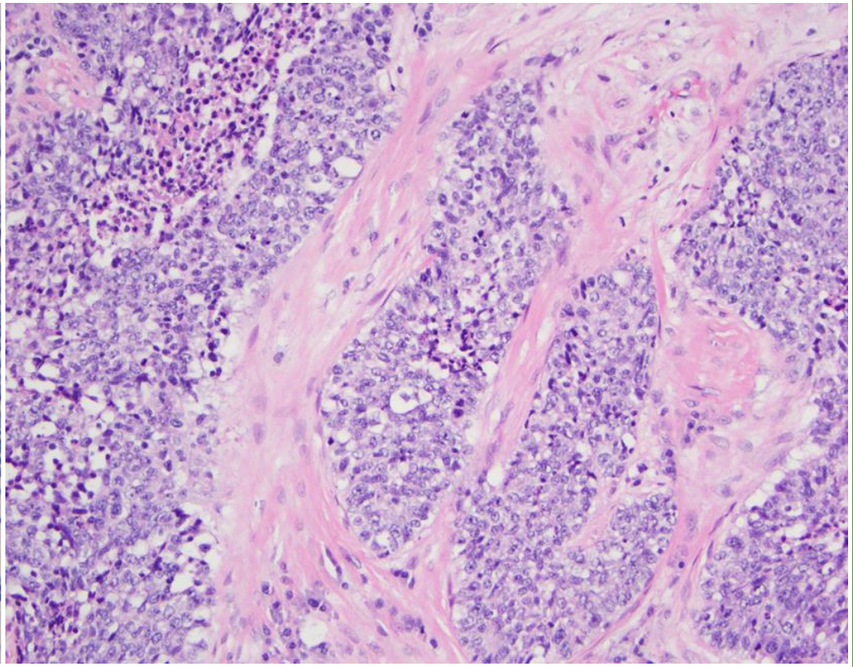


Undifferentiated (Adeno)Carcinoma



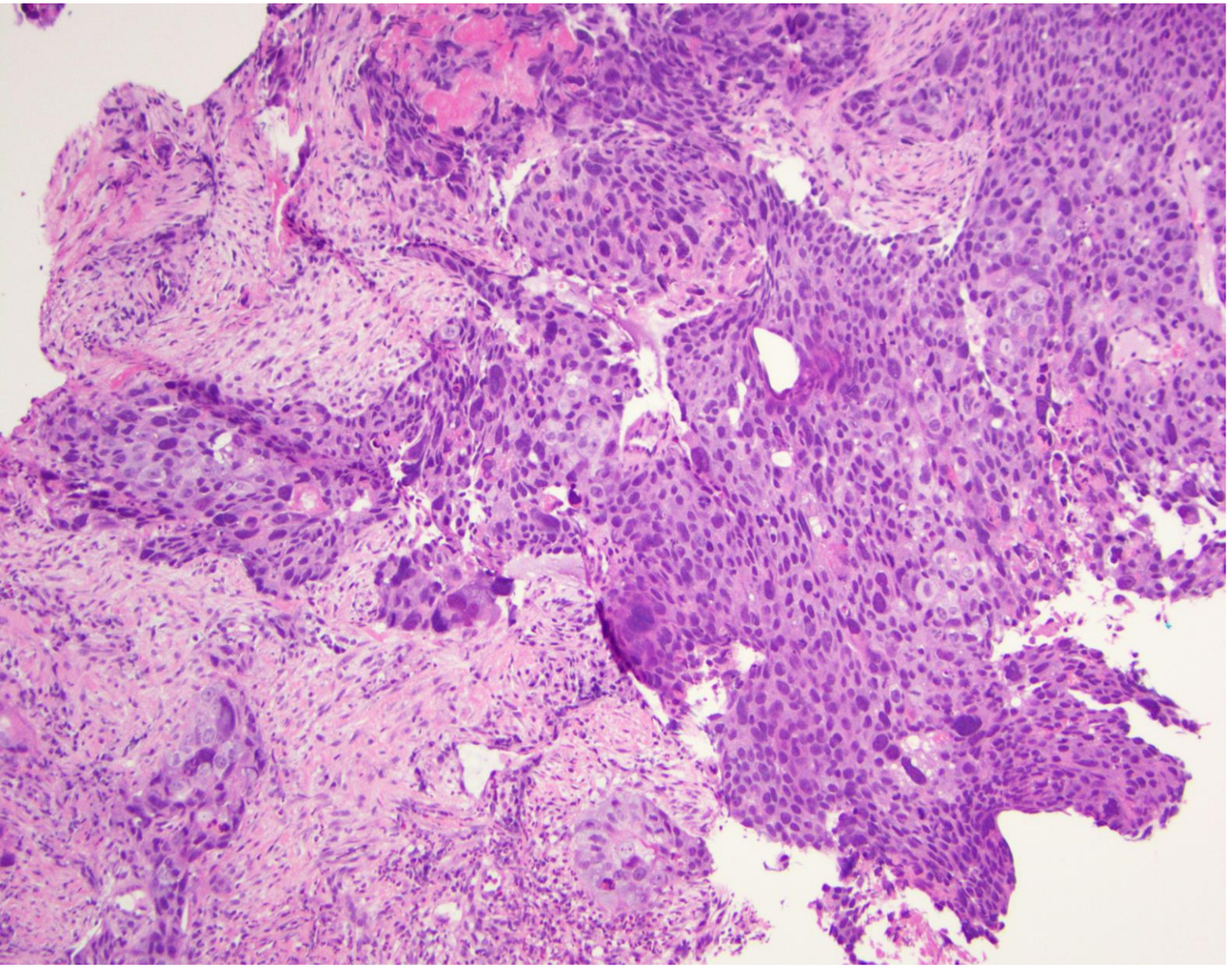


synaptophysin

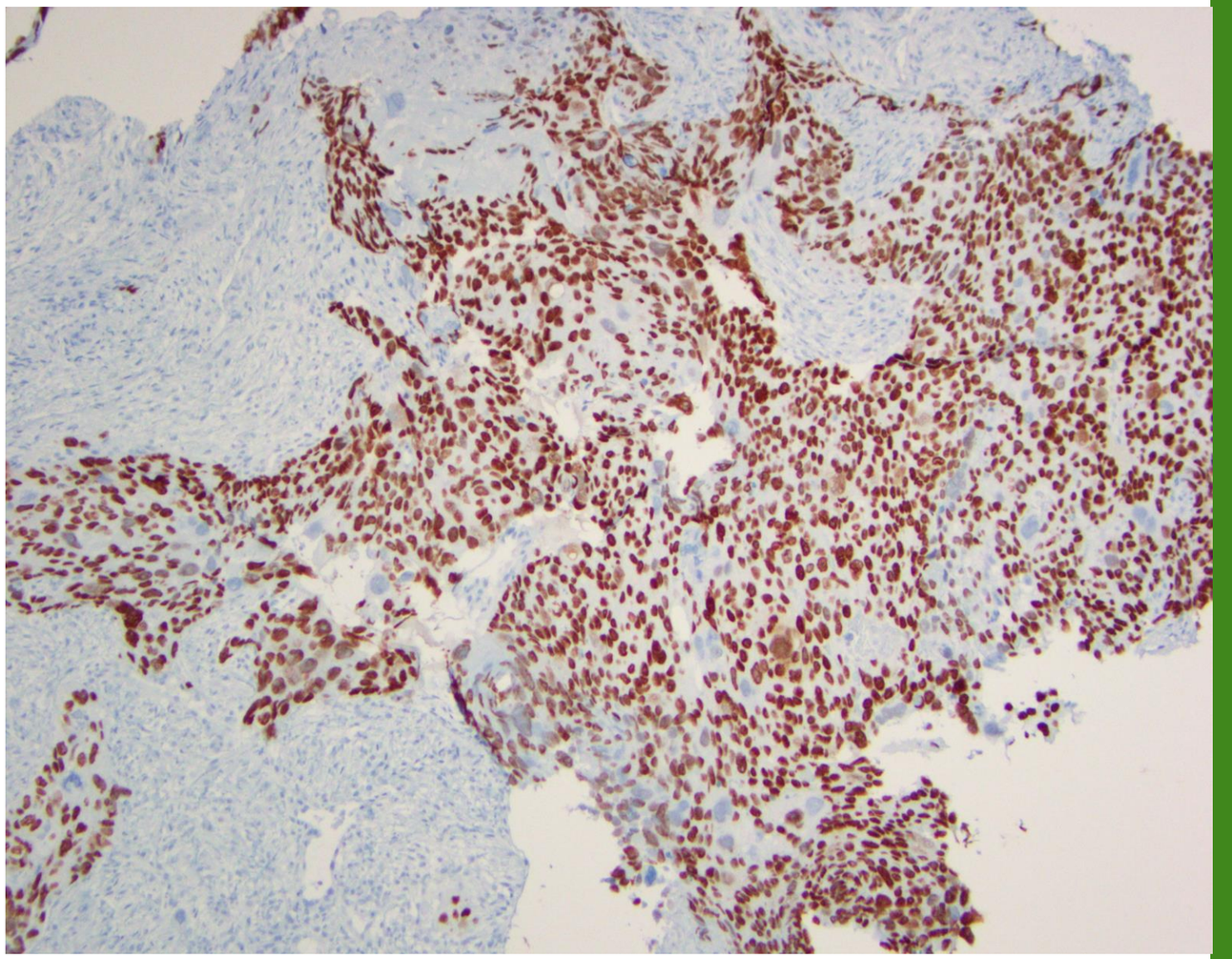


MUC5

‘Undifferentiated’ Carcinoma



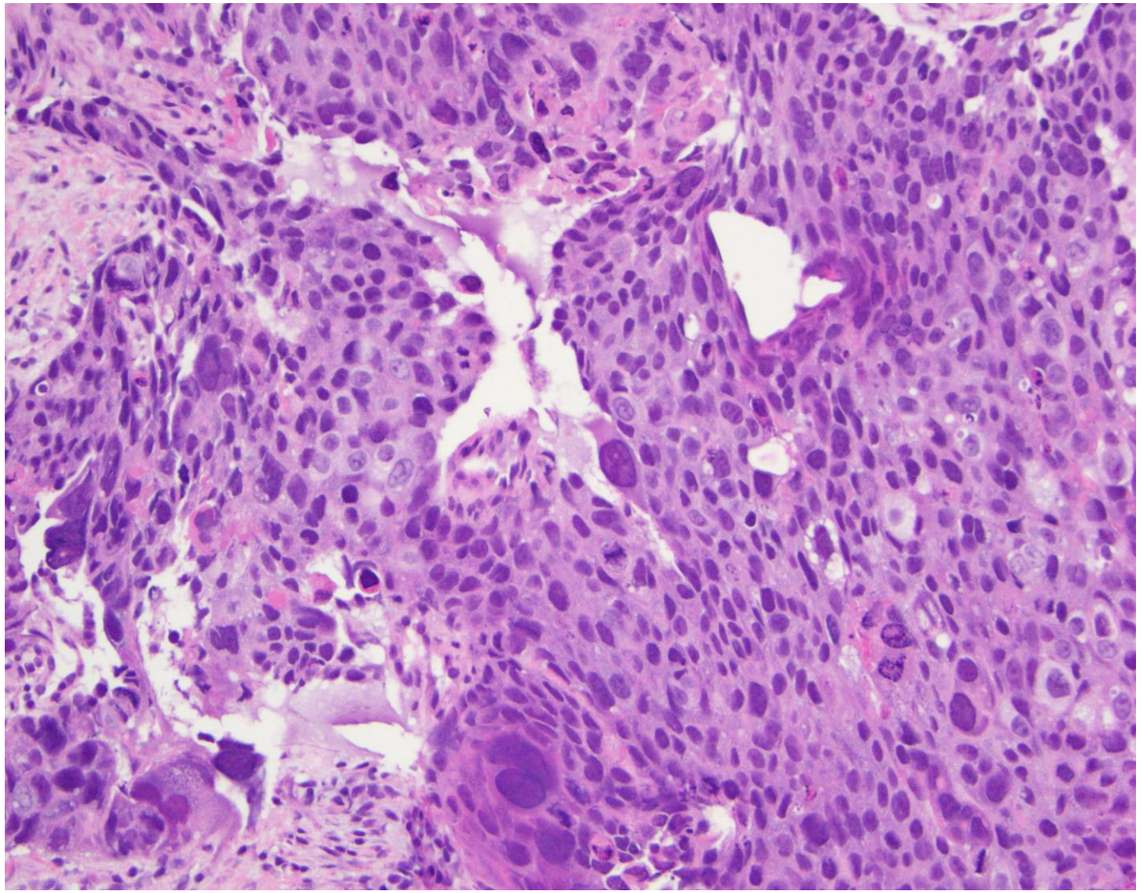
2/3 are SALL4 positive

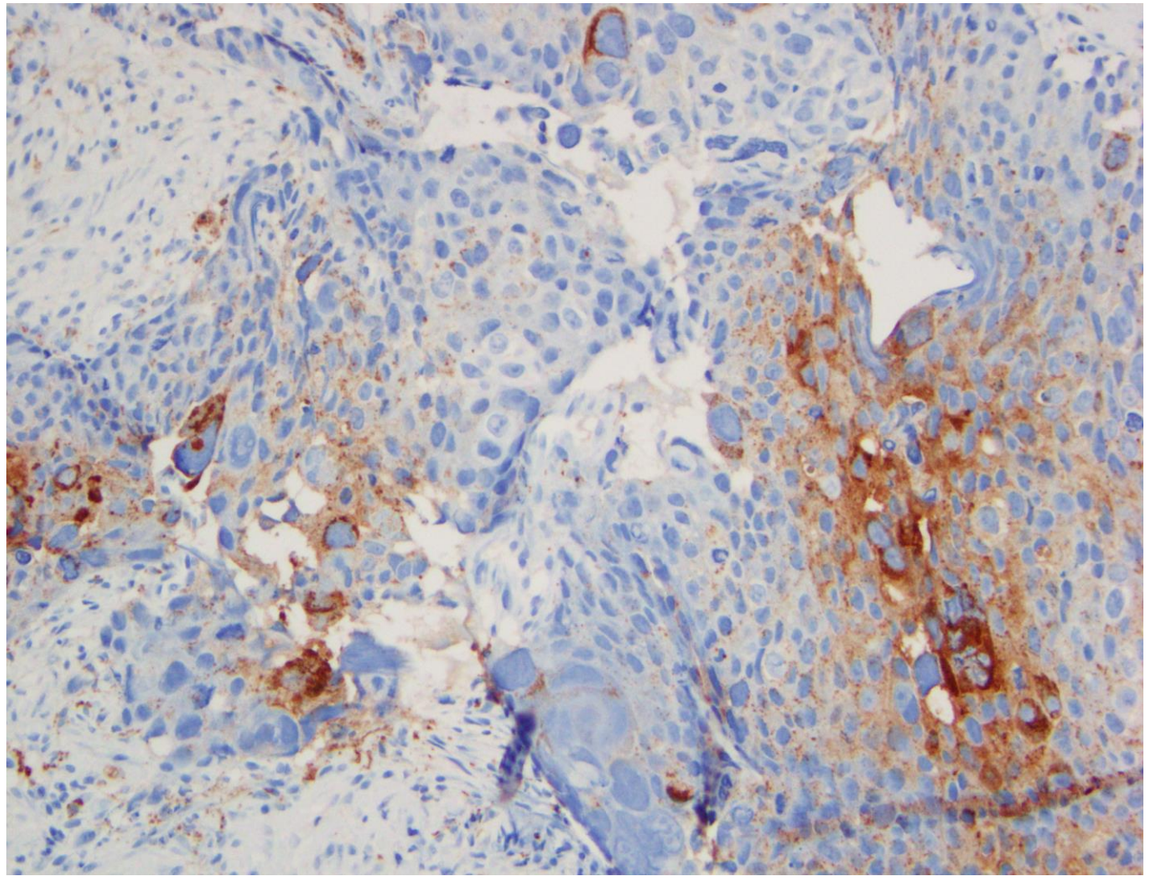


SALL4

Singhi A et al. Hum_Pathol 2015, 46(3):366-75

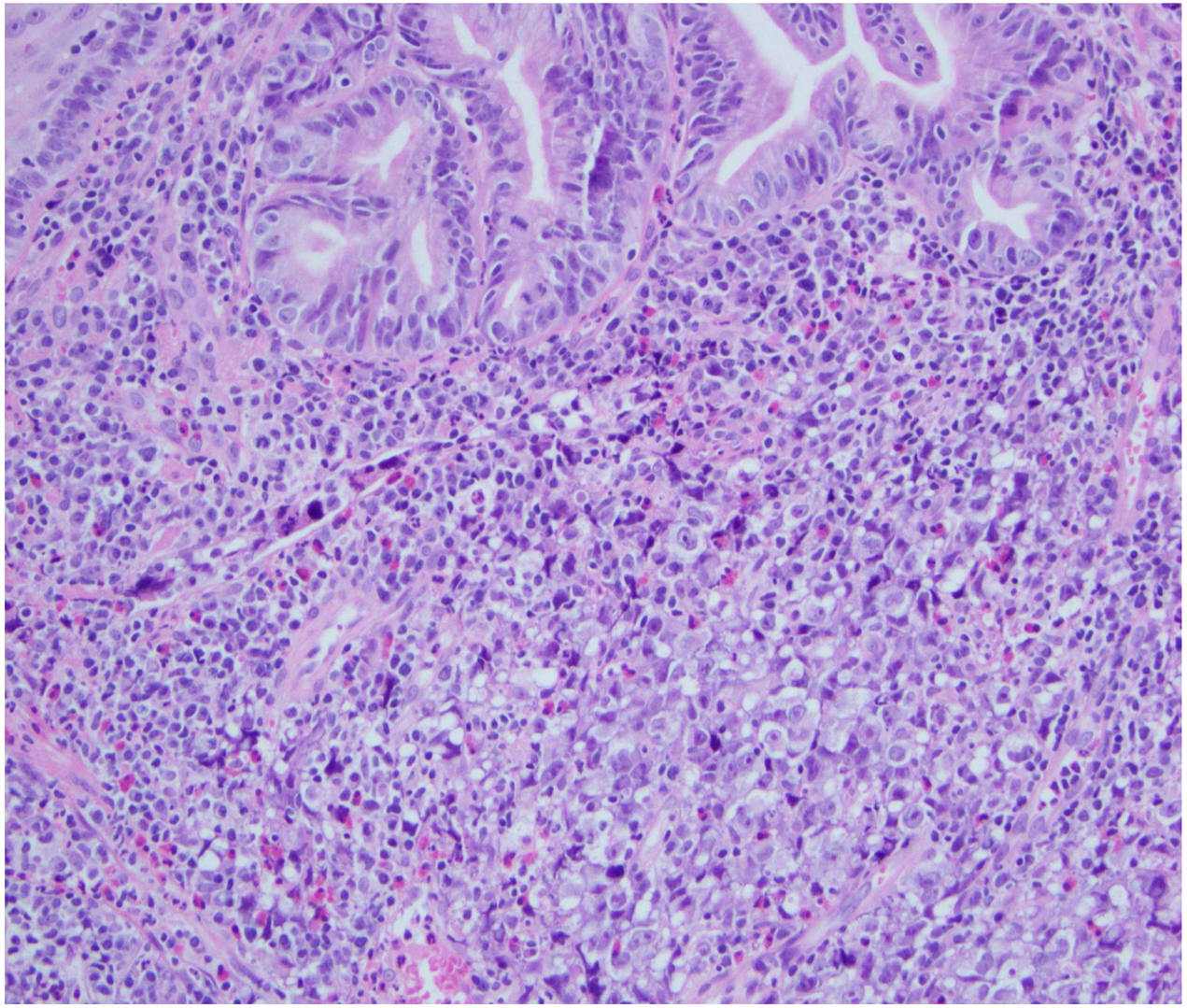
‘Undifferentiated’ Carcinoma (with syncytiotrophoblastic giant cells)

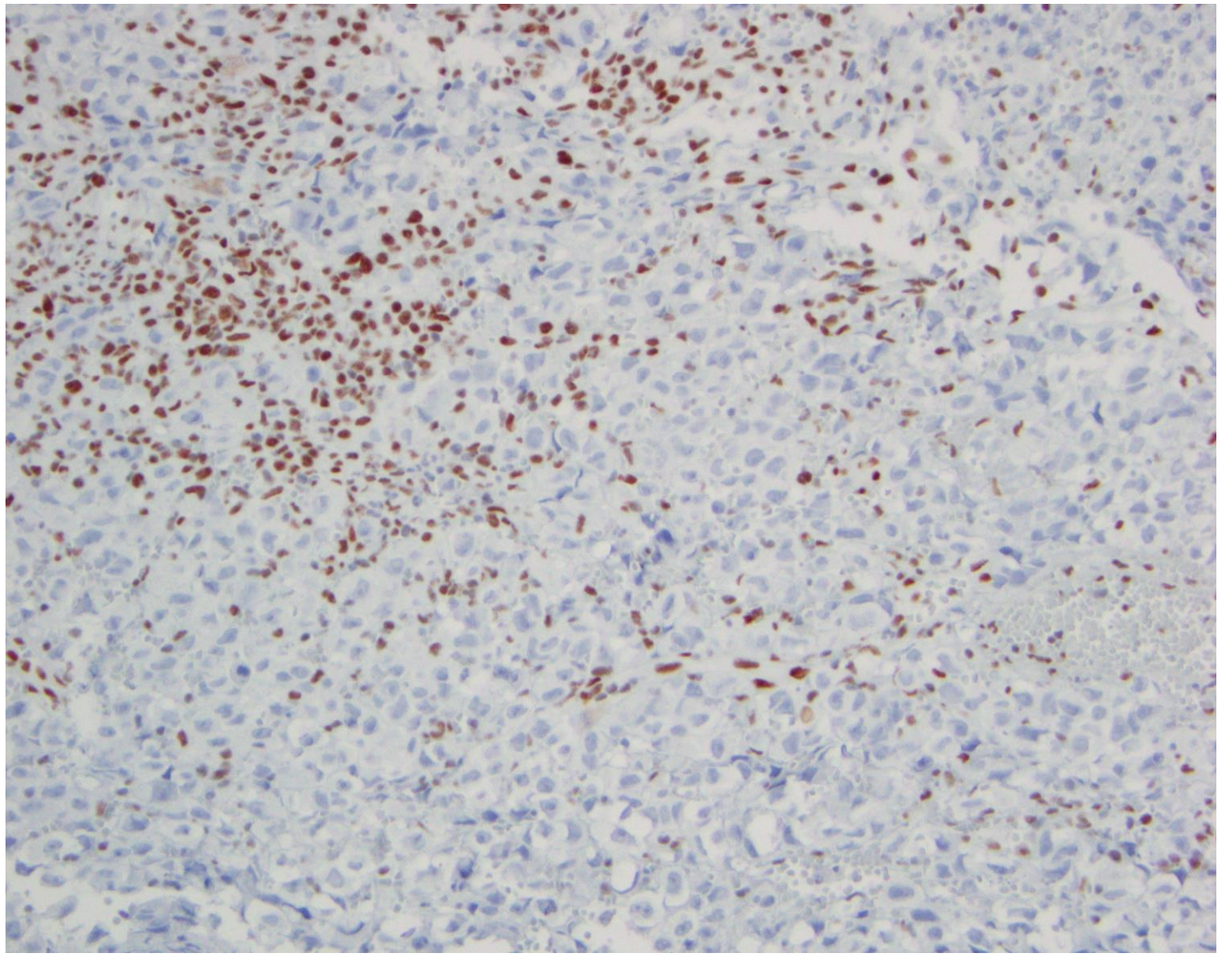




Beta-HCG

Undifferentiated Carcinoma (SMARCA4 Deficient)





SMARCA4

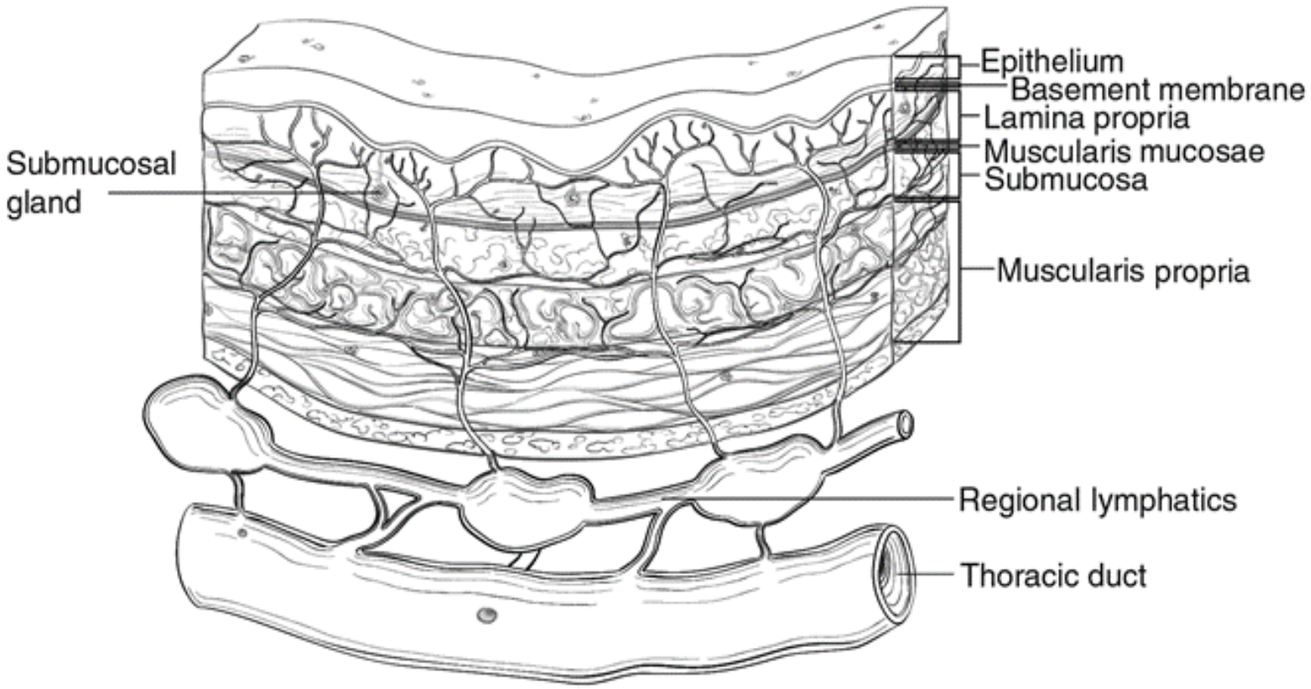
Histologic Grade

7th Edition		8th Edition	
Squamous Cell Carcinomas			
Grade X	Grade cannot be assessed	Grade X	Grade cannot be assessed
Grade 1	Well differentiated	Grade 1	Well differentiated
Grade 2	Moderately differentiated	Grade 2	Moderately differentiated
Grade 3	Poorly differentiated	Grade 3	Poorly differentiated, undifferentiated, undifferentiated with squamous component

Histologic Grade

7th Edition		8th Edition	
Adenocarcinoma			
Grade X	Grade cannot be assessed	GX	Cannot be assessed
Grade 1	Well differentiated (greater than 95% of tumor composed of glands)	G1	Well differentiated
Grade 2	Moderately differentiated (50% to 95% of tumor composed of glands)	G2	Moderately differentiated
Grade 3	Poorly differentiated (49% or less of tumor composed of glands)	G3	Poorly differentiated, undifferentiated

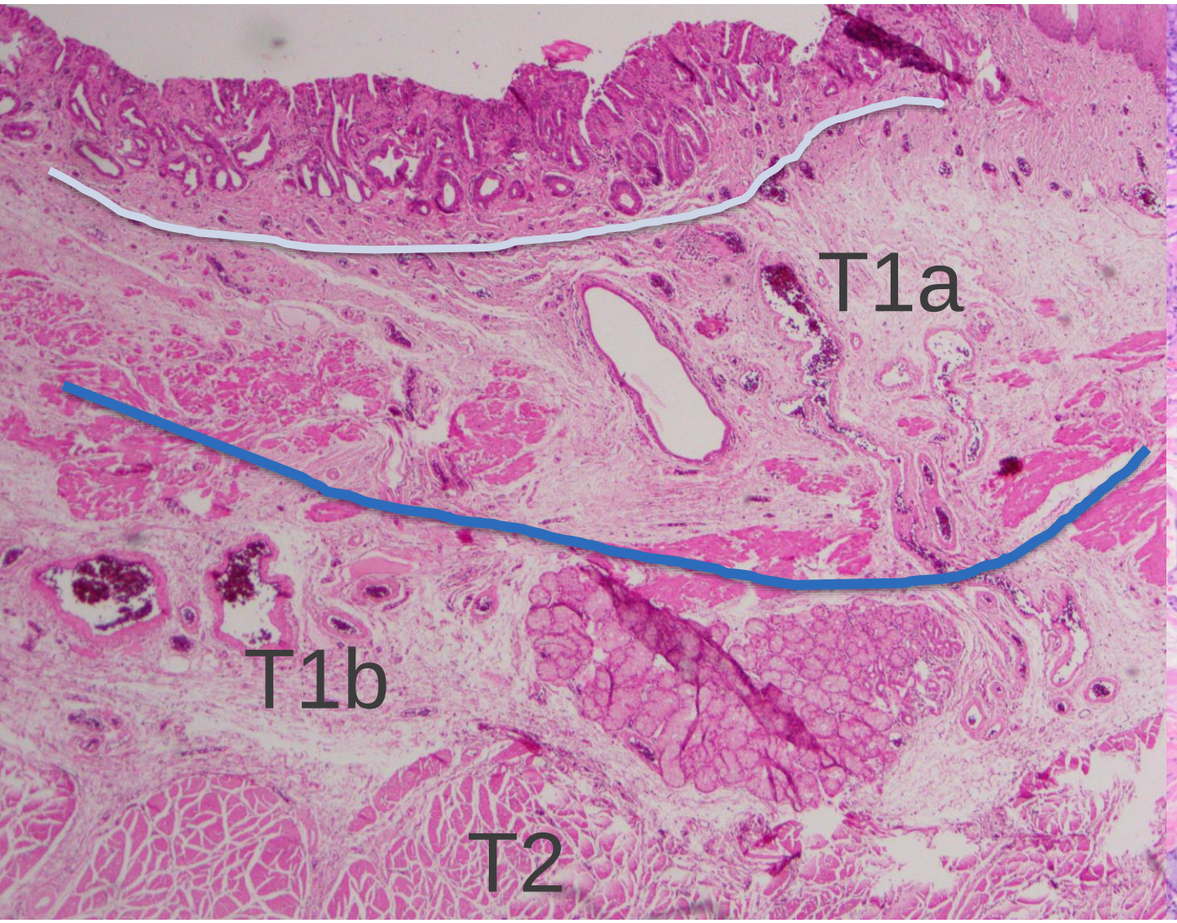
Microscopic tumor extension

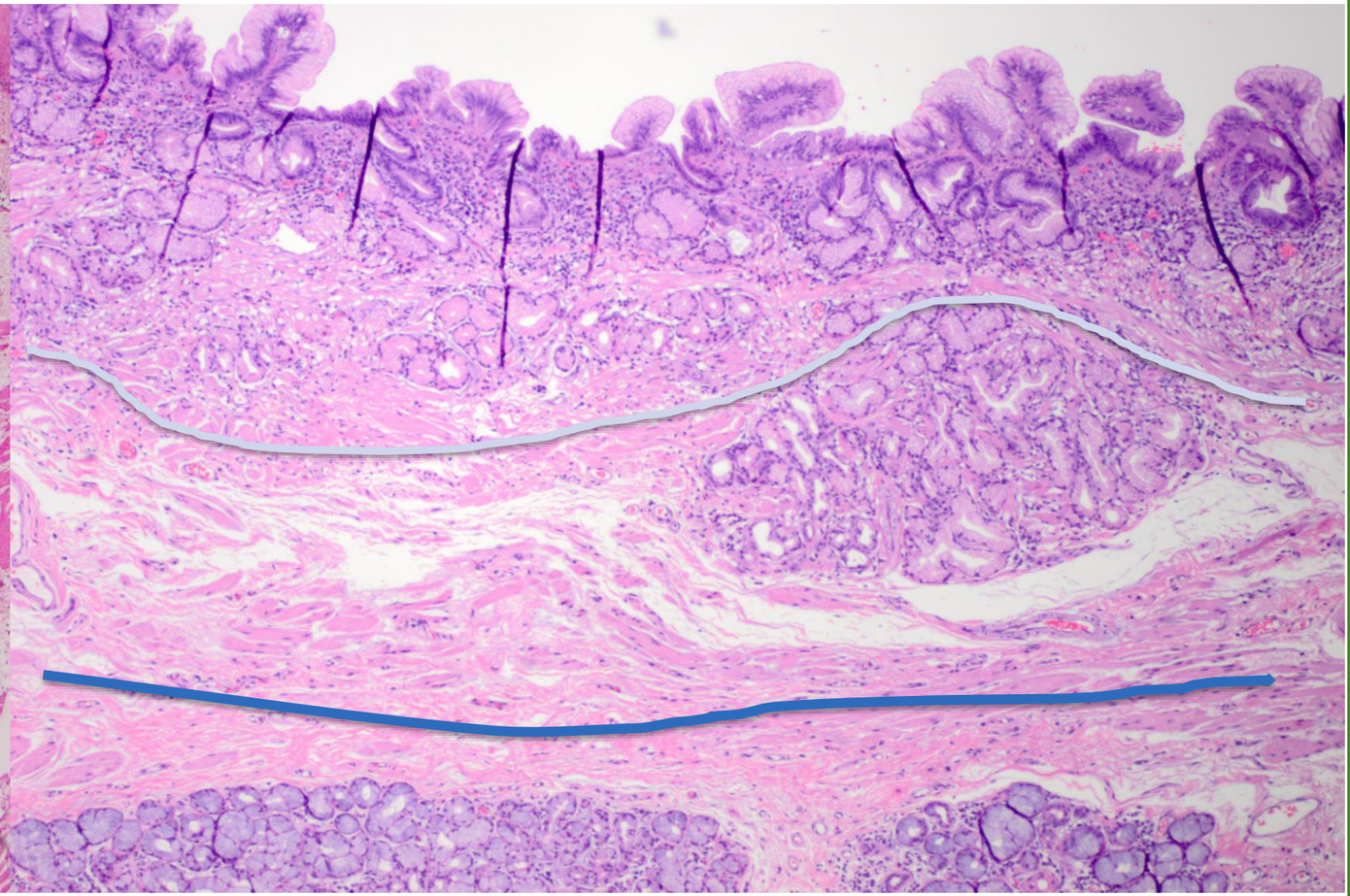


- Lymphatics concentrated in submucosa
- Submucosal lymphatic plexus organized in longitudinal plane
- Skip lesions may be present
- Multiple discrete lesions: measure from top of highest to bottom of lowest and use suffix “m”
- Tumor length may be strong predictor for presence or absence of nodal disease in early to intermediate stage esophageal cancer

Microscopic tumor extension

Duplicated muscularis mucosa in Barrett's esophagus

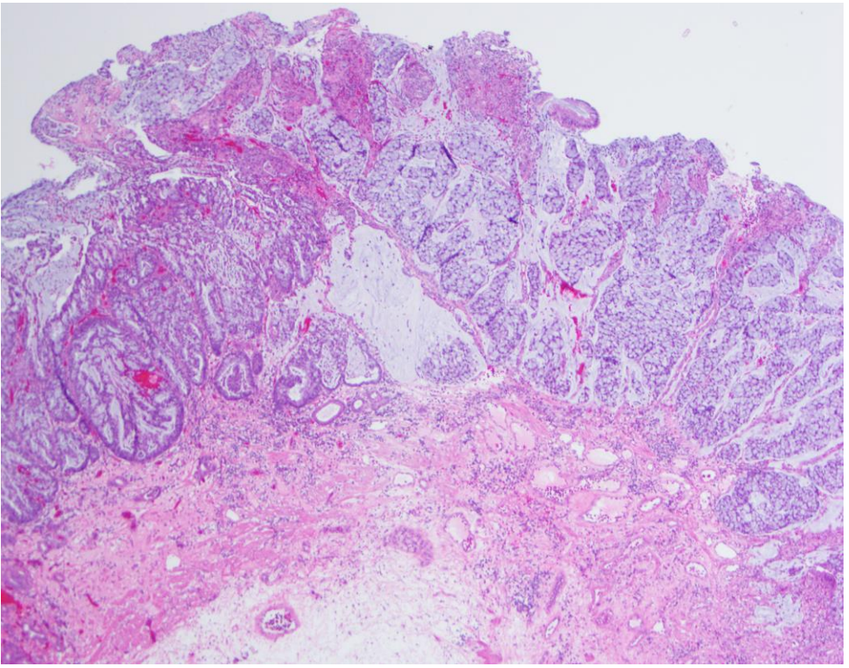




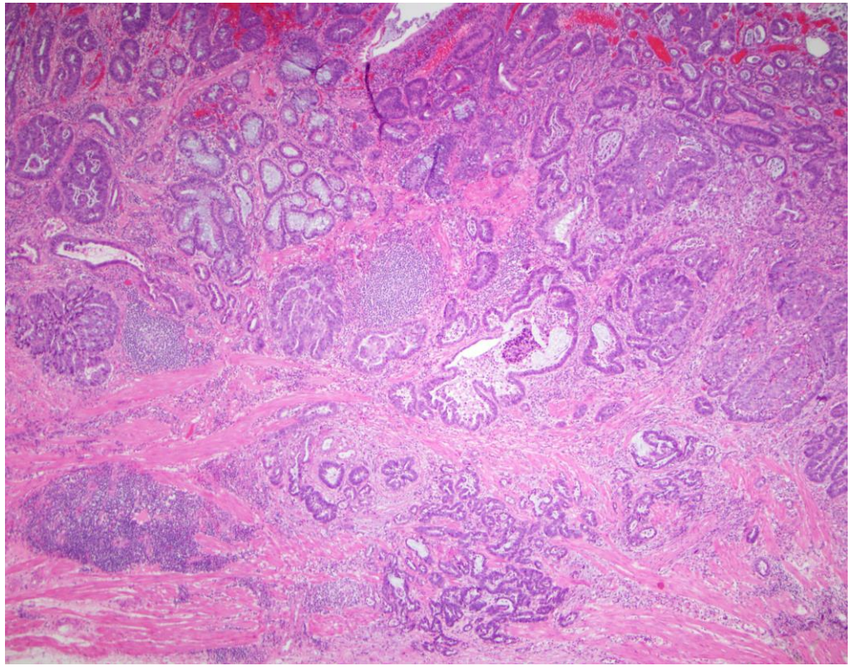
Second layer thick; can be mistaken for muscularis propria

Microscopic tumor extension

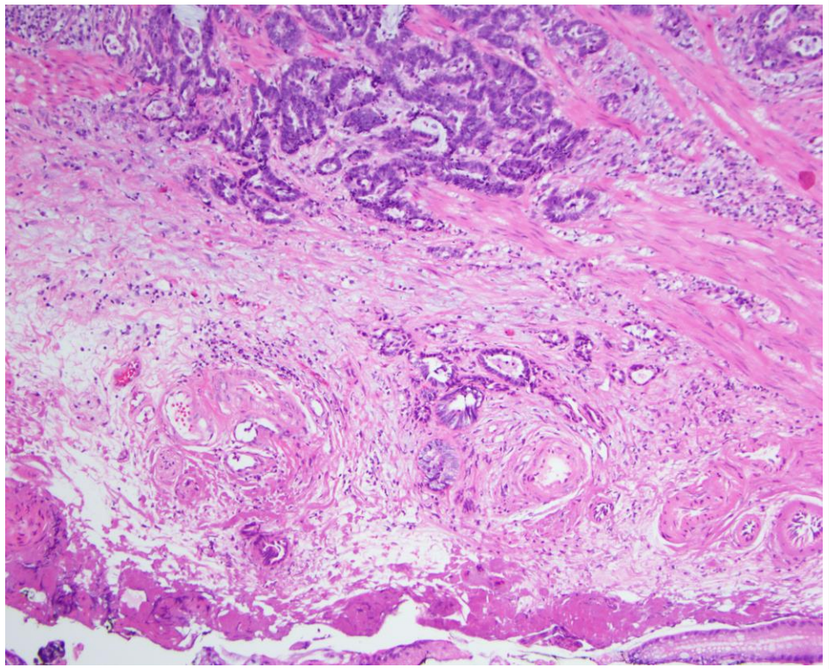
Duplicated muscularis mucosa in Barrett’s esophagus



T1a



T1a

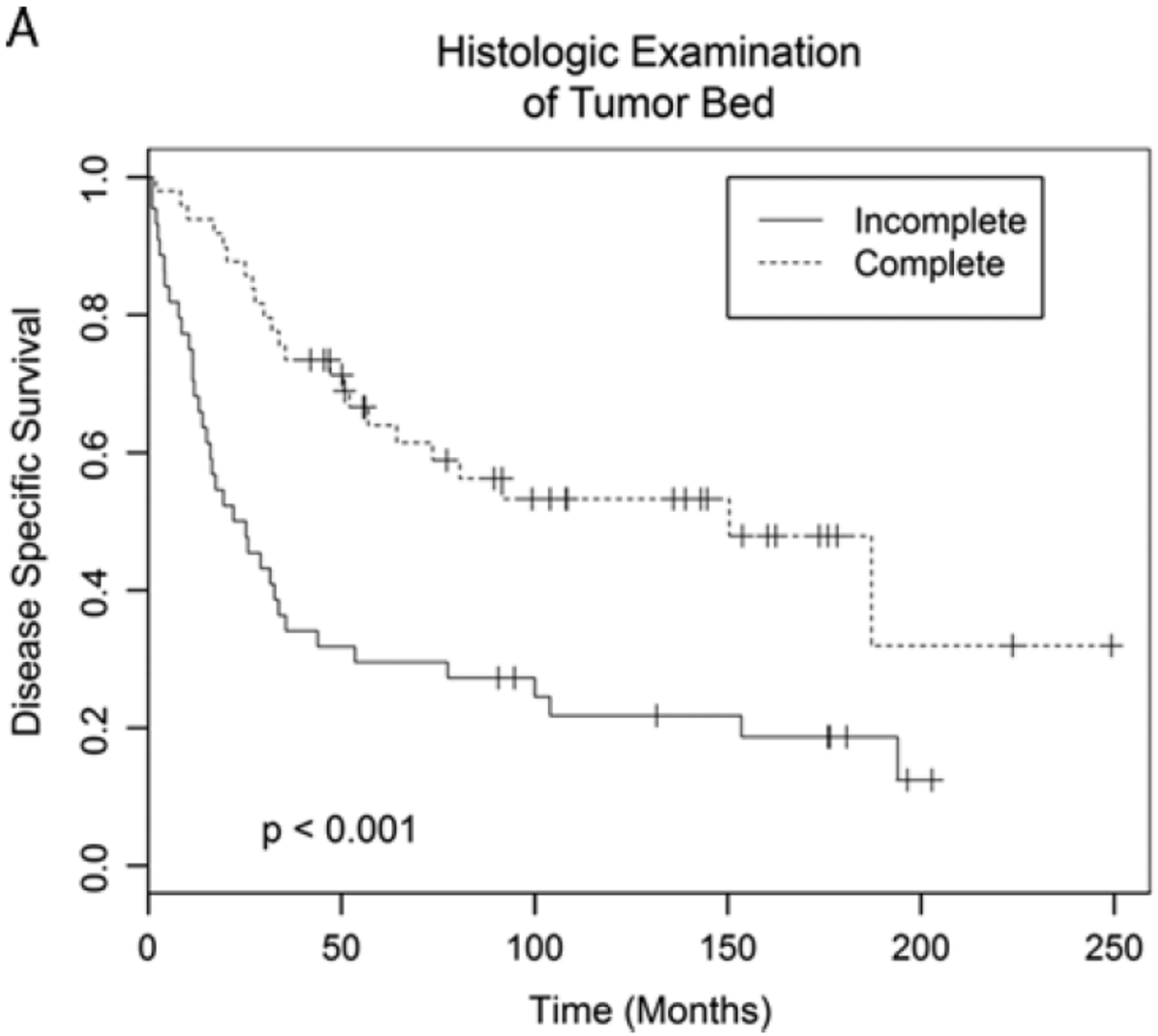


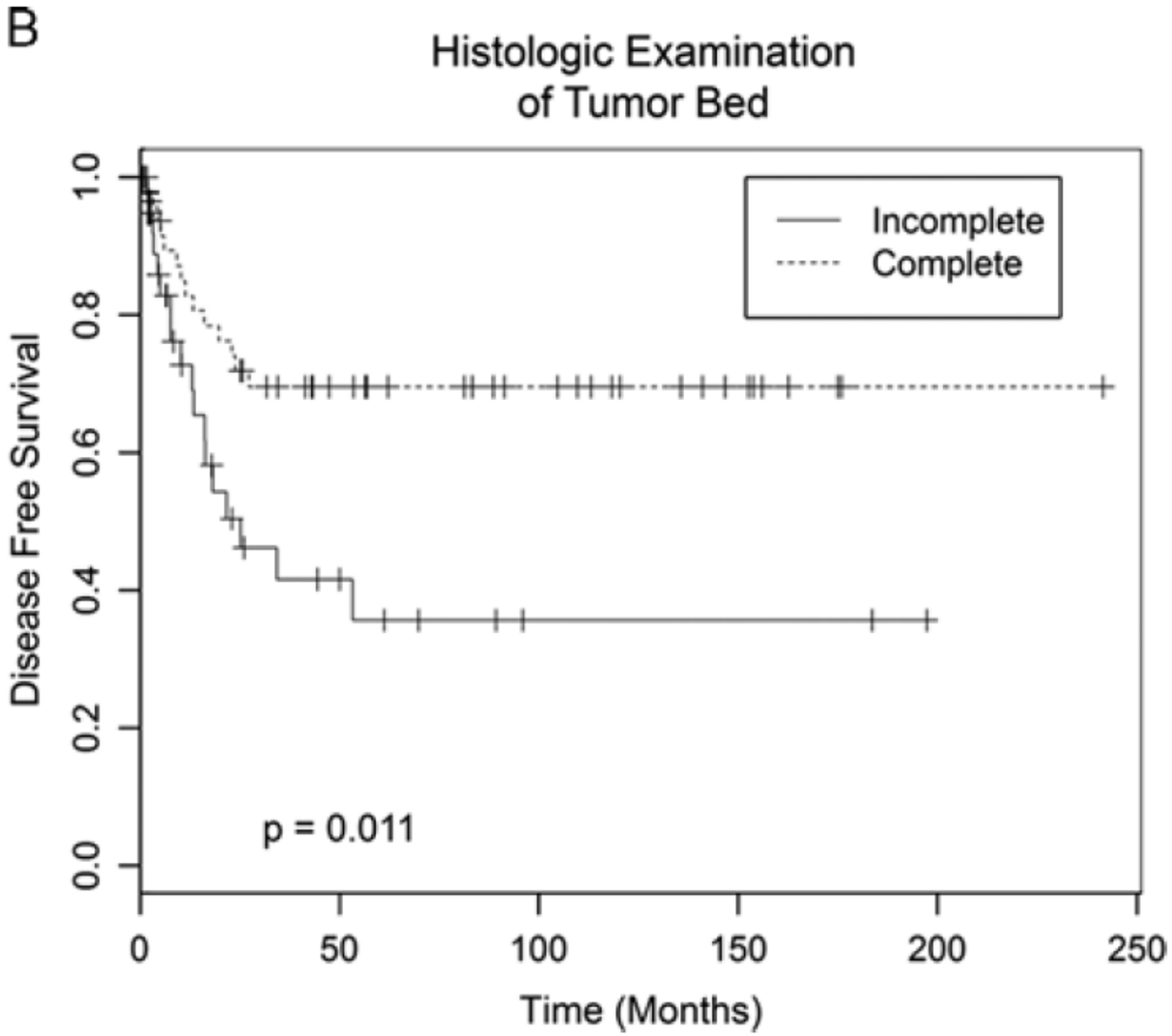
T1b

Post-treatment resections

Description	Tumor Regression Score
Adenocarcinoma	
No Viable cancer cells (complete response)	0
Single cells or rare small groups of cancer cells (near complete response)	1
Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response)	2
Extensive residual cancer with no evident tumor regression (poor or no response)	3

Post-treatment resections: Entirely submit tumor bed before reporting pCR





Agoston A et al. Am J Surg Pathol 2015;39:1085–1092

Primary Tumor (pT)

7th Edition	8th Edition
pTX: Cannot be assessed	pTX: Primary tumor cannot be assessed
pT0: No evidence of primary tumor	pT0: No evidence of primary tumor
pTis: High-grade dysplasia	pTis: Carcinoma in situ, intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
pT1: Tumor invades lamina propria, muscularis mucosae, or submucosa	pT1: Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
pT1a: Tumor invades lamina propria or muscularis mucosae	pT1a: Tumor invades the lamina propria or muscularis mucosae
pT1b: Tumor invades submucosa	pT1b: Tumor invades the submucosa
pT2: Tumor invades muscularis propria	pT2: Tumor invades the muscularis propria
pT3: Tumor invades adventitia	pT3: Tumor invades adventitia
pT4: Tumor invades adjacent structures (specify):_____	pT4: Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure
pT4a: Resectable tumor invading pleura, pericardium, or diaphragm	pT4a: Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
pT4b: Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, traches, etc.	pT4b: Tumor invades other adjacent structures such as aorta, vertebral body, or airway

Prognostic/Stage Groupings for Post-treatment resections

Prognostic implication for ypTNM differs from those of equivalent pTNM

Stage grouping: ypTNM (applies to both squamous and adenocarcinomas)

Stage	T	N	M
Stage I	T0-2	N0	M0
Stage II	T3	N0	M0
Stage IIIA	T0-2	N1	M0
Stage IIIB	T3	N1	M0
	T0-3	N2	M0
	T4a	N0	M0
Stage IVA	T4a	N1-2, NX	M0
	T4b	N0-2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

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Stomach

Stomach 2017 version 8th ed.

For accreditation purposes, this protocol should be used for the following procedures AND tumor types:

Procedure:

- Resection - Includes partial or complete gastrectomy

Tumor Type:

- Carcinomas:
  - Involving EGJ with tumor midpoint >2 cm into the proximal stomach
  - Involving cardia/proximal stomach without involvement of the EGJ (even if tumor midpoint is ≤2 cm into the proximal stomach)

Stomach 2017 version 8th ed.

The following data elements were modified:

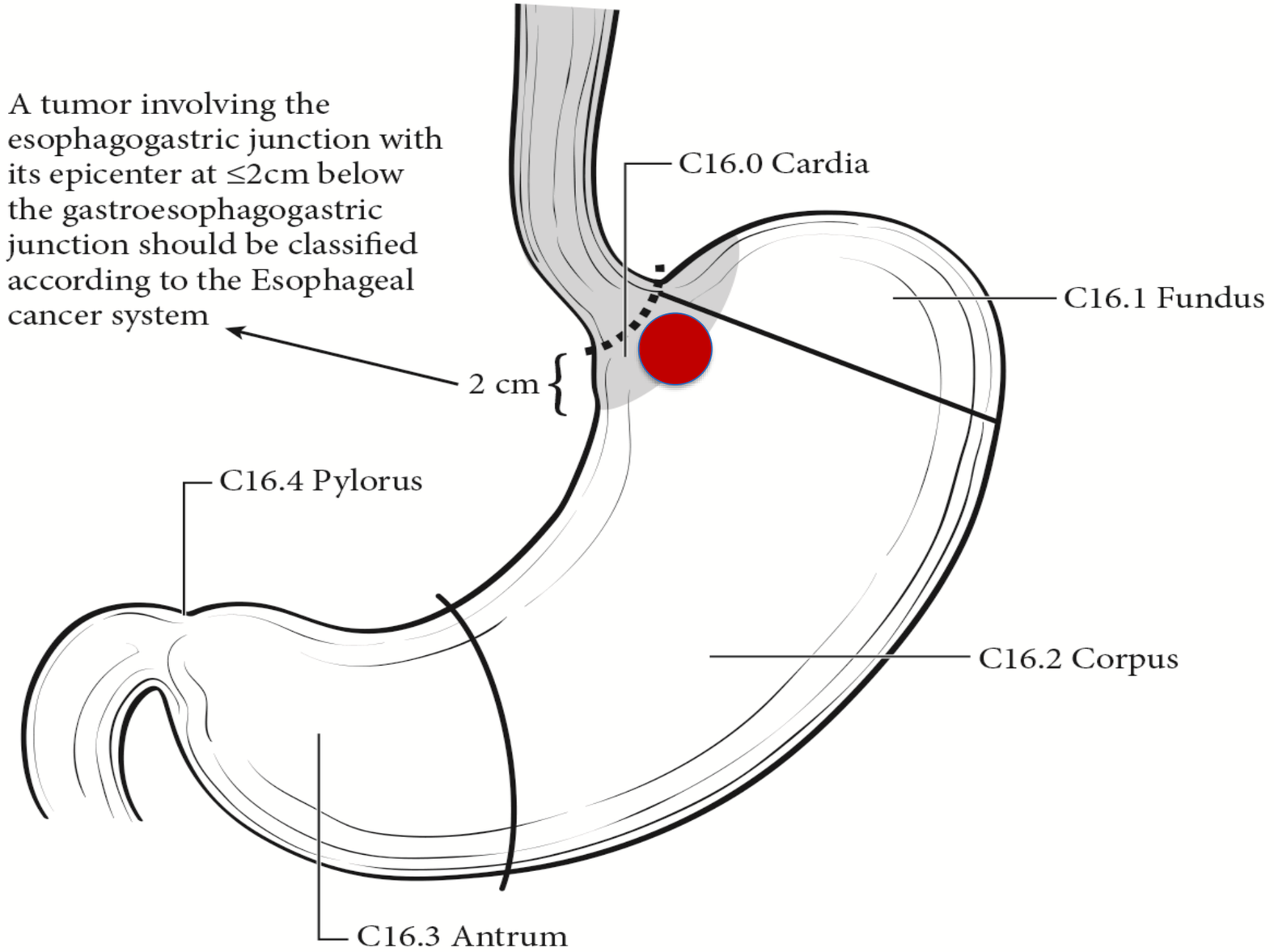
Pathologic Stage Classification (pTNM)

Tumor Site

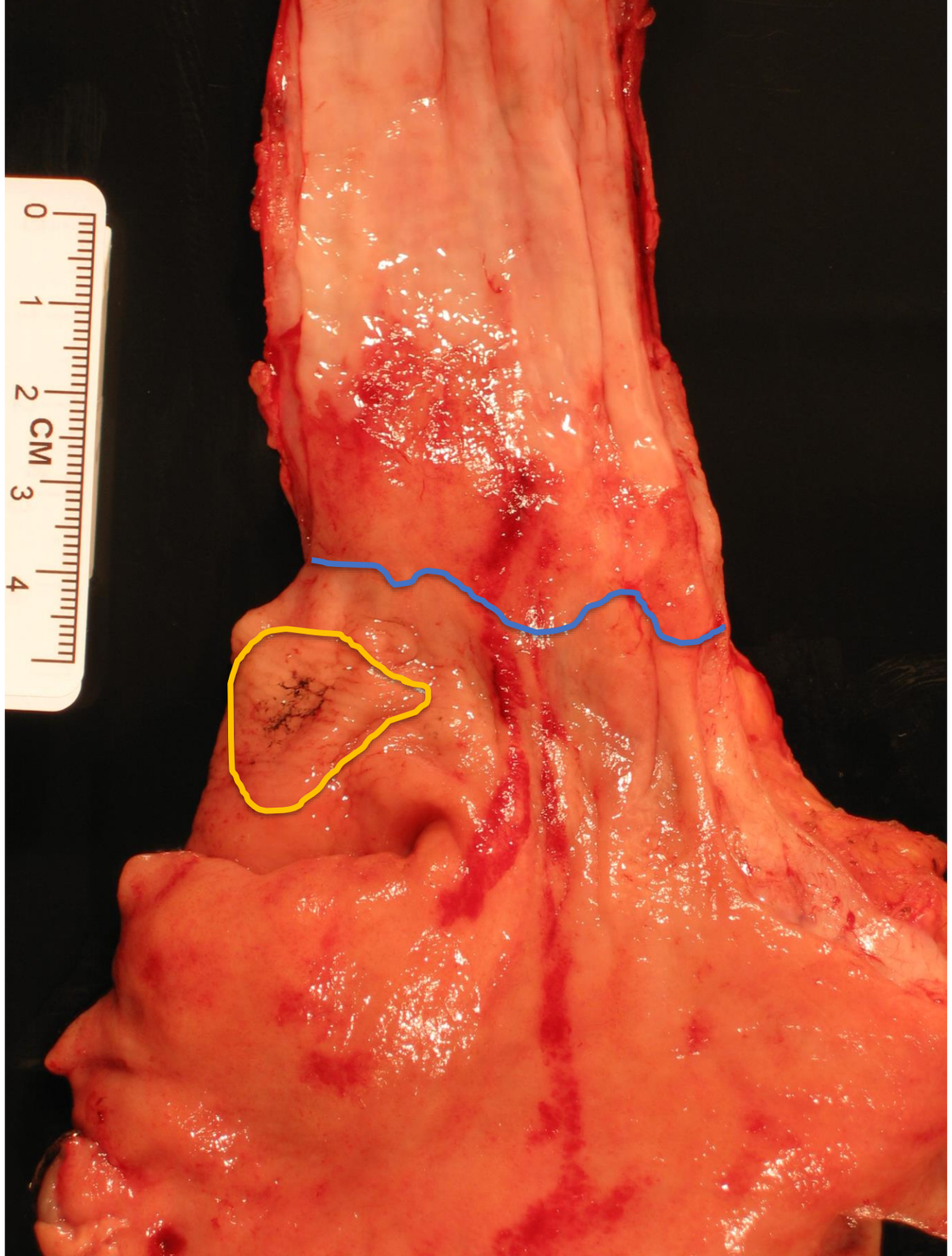
Histologic Type

Microscopic Tumor Extension

Treatment Effect



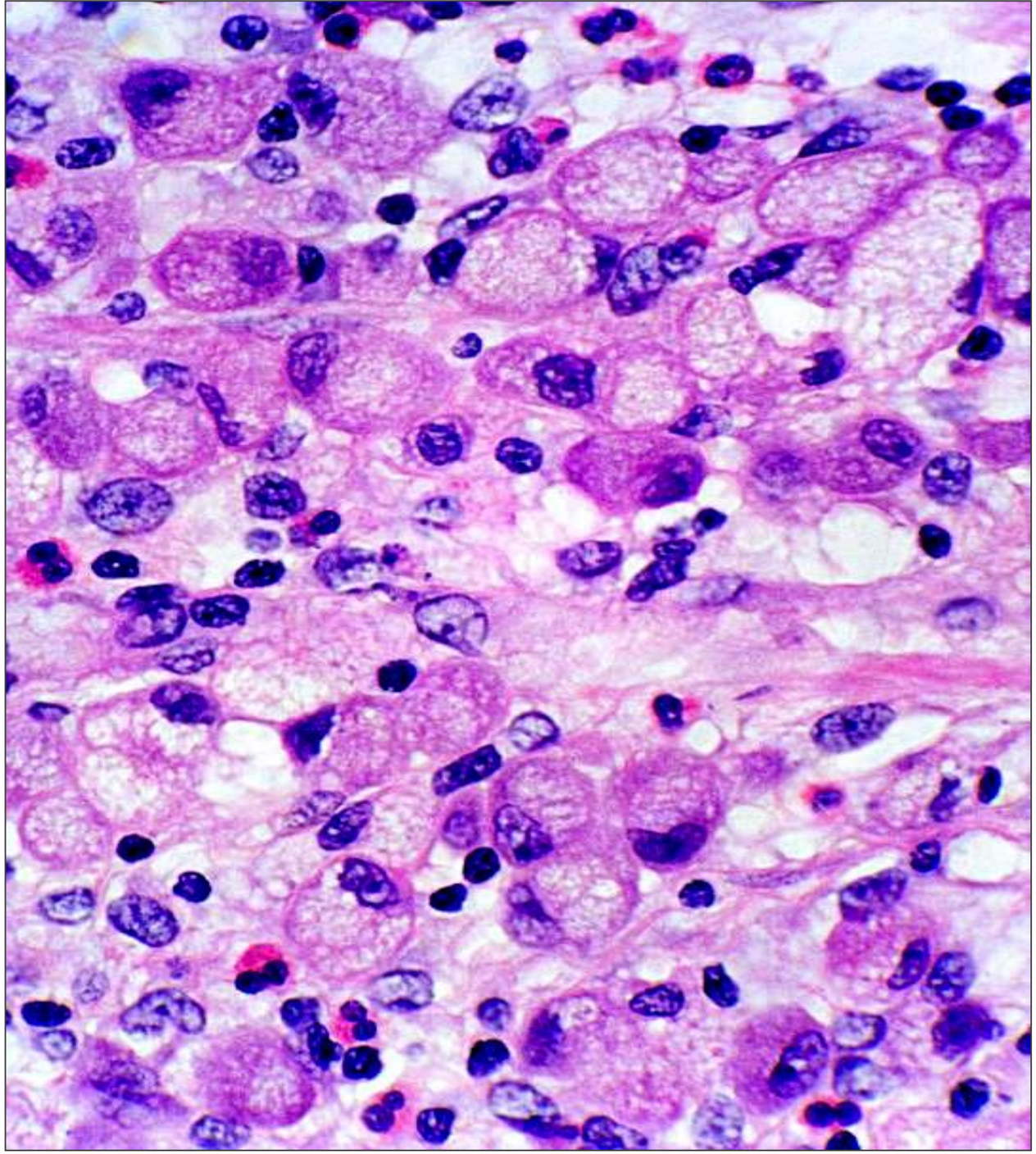
Tumors involving the EGJ with epicenter >2 cm into the proximal stomach and any tumors in the stomach, including cardia cancers, without involvement of the EGJ should use the CAP protocol for the stomach.

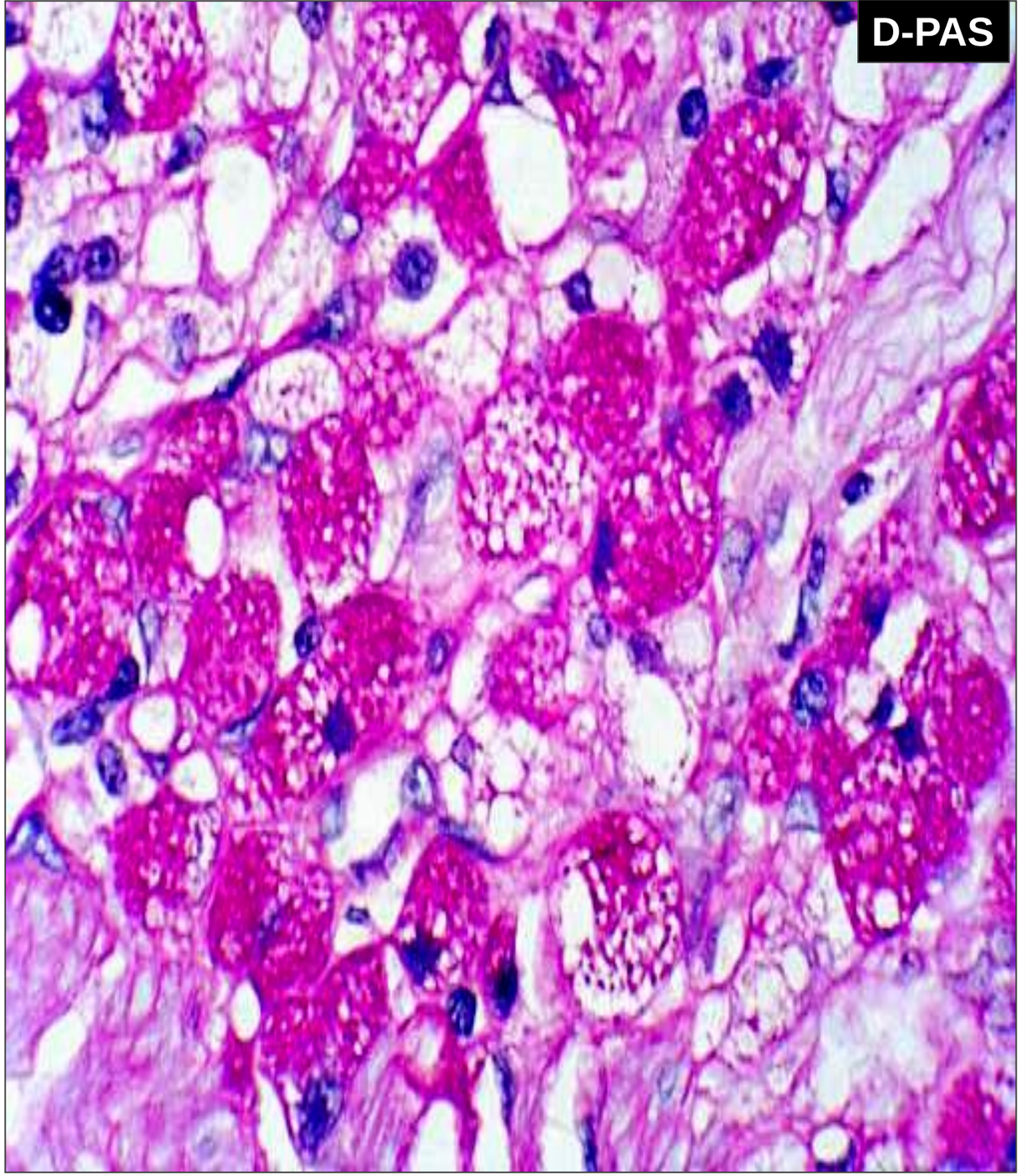

0
1
2 CM
3
4

Histologic Type

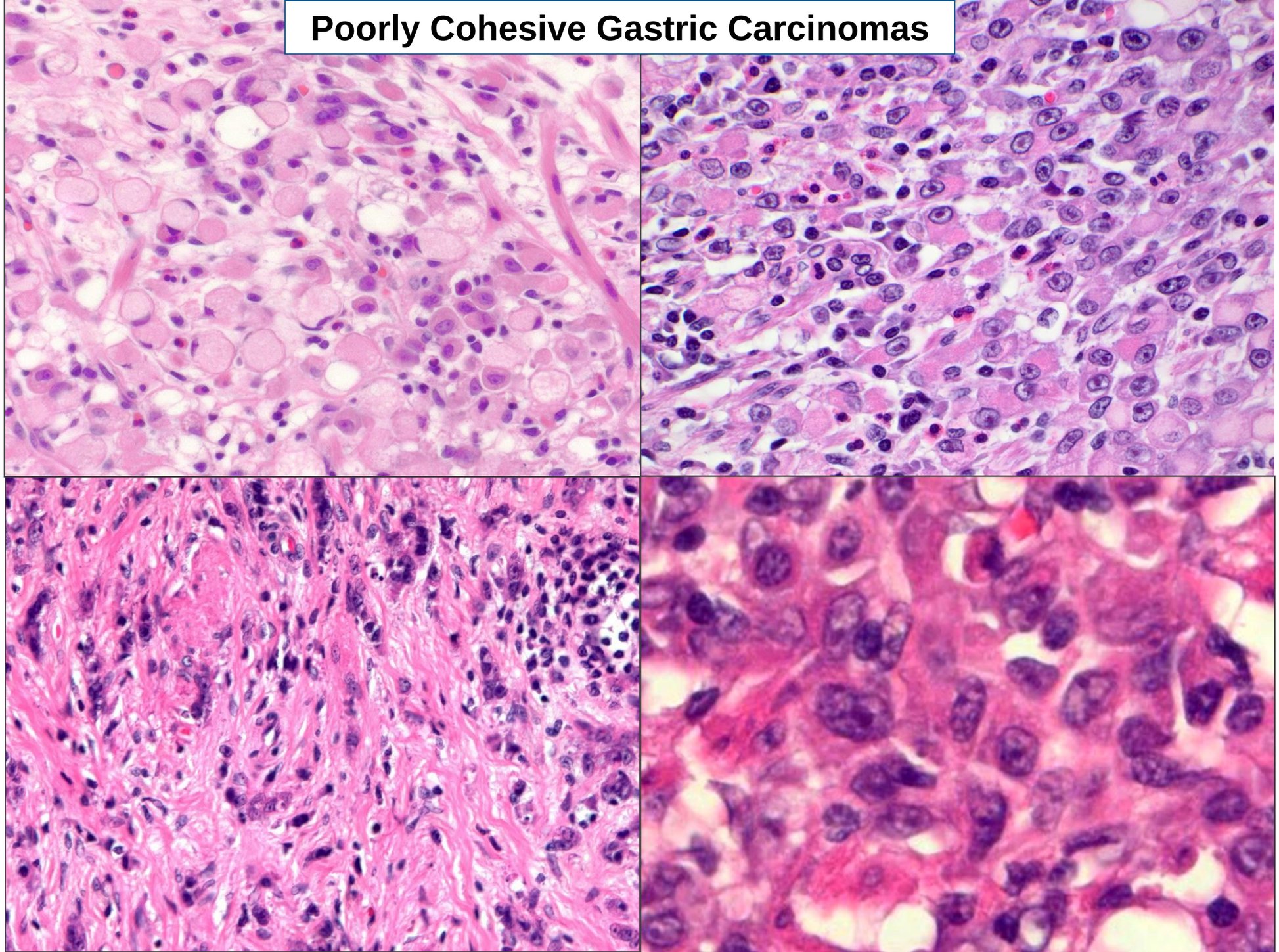
7th Edition	8th Edition
Classification of Carcinoma of the Stomach	
Adenocarcinoma Lauren classification of adenocarcinoma: Intestinal type Diffuse type (signet-ring carcinoma if >50% signet-ring cells) Mixed (approximately equal amounts of intestinal and diffuse) + Alternative optional classification (based on WHO classification): +Tubular (intestinal) adenocarcinoma +Poorly cohesive carcinoma (including mixed adenocarcinoma with >50% signet- ring cell features) +Diffuse carcinoma (noncohesive carcinoma, >80% diffuse/signet-ring cells) +Mucinous adenocarcinoma (>50% mucinous) +Papillary adenocarcinoma	Adenocarcinoma Lauren classification of adenocarcinoma: Intestinal type Diffuse type (includes signet-ring carcinoma, classified as >50% signet-ring cells) Mixed (approximately equal amounts of intestinal and diffuse) + Alternative optional classification (based on WHO classification): + Tubular (intestinal) adenocarcinoma + Poorly cohesive carcinoma (including signet-ring cell carcinoma and other variants) + Mucinous adenocarcinoma (>50% mucinous) + Papillary adenocarcinoma + Mixed carcinoma (mixture of discrete glandular (tubular/papillary) and signet-ring/poorly cohesive cellular histological components)
Hepatoid adenocarcinoma	Hepatoid adenocarcinoma
Carcinoma with lymphoid stroma (medullary carcinoma)	Carcinoma with lymphoid stroma (medullary carcinoma)
High-grade neuroendocrine carcinoma Large cell neuroendocrine carcinoma Small cell neuroendocrine carcinoma	Large cell neuroendocrine carcinoma Small cell neuroendocrine carcinoma Neuroendocrine carcinoma (poorly differentiated)#
Mixed adenoneuroendocrine carcinoma	Mixed adenoneuroendocrine carcinoma
Squamous cell carcinoma	Squamous cell carcinoma
Adenosquamous carcinoma	Adenosquamous carcinoma
Undifferentiated carcinoma	Undifferentiated carcinoma
Other (specify): __	Other histologic type not listed (specify): _____

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
# Note: Select this option only if large cell or small cell cannot be determined.




D-PAS

Poorly Cohesive Gastric Carcinomas



Tumor Extension

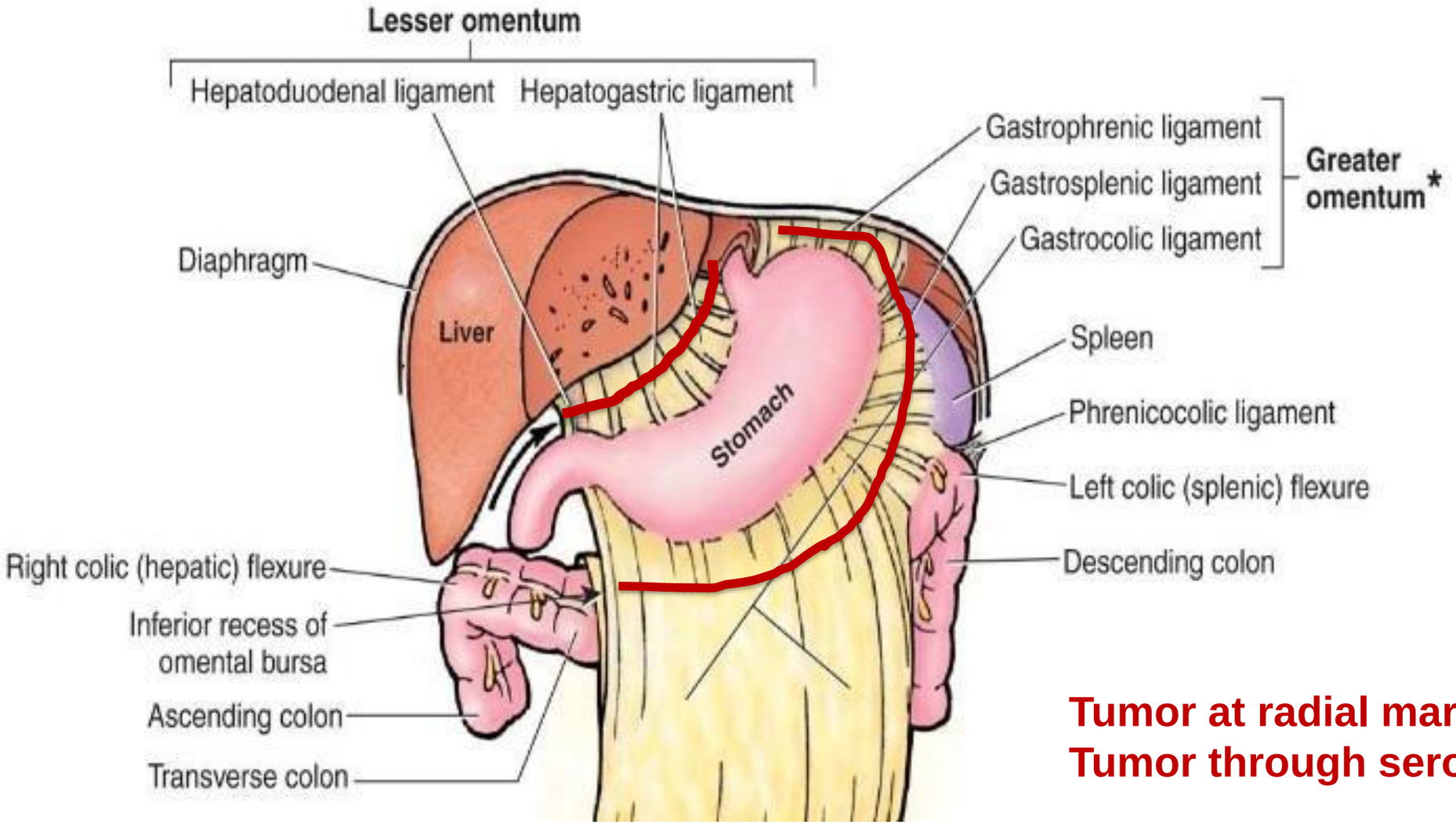
7th Edition	8th Edition
pTX: Cannot be assessed	pTX: Primary tumor cannot be assessed
pT0: No evidence of primary tumor	pT0: No evidence of primary tumor
pTis: Carcinoma *in situ*/high-grade glandular dysplasia	pTis: Carcinoma *in situ:* intraepithelial tumor without invasion of the lamina propria, high-grade dysplasia
pT1: Tumor invades lamina propria, muscularis mucosae, or submucosa	pT1: Tumor invades the lamina propria, muscularis mucosae, or submucosa
pT1a: Tumor invades lamina propria or muscularis mucosae	pT1a: Tumor invades the lamina propria or muscularis mucosae
pT1b: Tumor invades submucosa	pT1b: Tumor invades the submucosa
pT2: Tumor invades muscularis propria	pT2: Tumor invades the muscularis propria[#]
pT3: Tumor invades subserosal connective tissue, without involvement of visceral peritoneum or adjacent structures	pT3: Tumor penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures[##, ###]
pT4: Tumor invades serosa (visceral peritoneum) or adjacent structures	pT4: Tumor invades the serosa (visceral peritoneum) or adjacent structures[##, ###]
pT4a: Tumor invades serosa (visceral peritoneum)	pT4a: Tumor invades the serosa (visceral peritoneum)
pT4b: Tumor invades adjacent structures	pT4b: Tumor invades adjacent structures/organs

[#] A tumor may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case, the tumor is classified as T3. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified as T4.

[##] The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.

[###] Intramural extension to the duodenum or esophagus is not considered invasion of an adjacent structure, but is classified using the depth of the greatest invasion in any of these sites.

Gastric Carcinoma: Tumor Extension



Tumor at radial margin: pT3
Tumor through serosa: pT4a

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Tumor Grade

7th Edition	8th Edition	
Histologic Grade (Note D)		
Not applicable		
GX: Cannot be assessed	Grade X	Cannot be assessed
G1: Well differentiated	Grade 1	Well differentiated (greater than 95% of tumor composed of glands)
G2: Moderately differentiated	Grade 2	Moderately differentiated (50% to 95% of tumor composed of glands)
G3: Poorly differentiated	Grade 3	Poorly differentiated (49% or less of tumor composed of glands)
G4: Undifferentiated		
Other (specify):_____		

Regional Nodes

No change in pN classification

7th Edition	8th Edition
pNX: Cannot be assessed	pNX: Regional lymph node(s) cannot be assessed
pN0: No regional lymph node metastasis	pN0: No regional lymph node metastasis
pN1: Metastasis in 1 to 2 perigastric lymph nodes	pN1: Metastasis in one or two regional lymph nodes
pN2: Metastasis in 3 to 6 perigastric lymph nodes	pN2: Metastasis in three to six regional lymph nodes
pN3: Metastasis in 7 or more perigastric lymph nodes	pN3: Metastasis in seven or more regional lymph nodes
pN3a: Metastasis in 7 to 15 perigastric lymph nodes	pN3a: Metastasis in seven to 15 regional lymph nodes
pN3b: Metastasis in 16 or more perigastric lymph nodes	pN3b: Metastasis in 16 or more regional lymph nodes

Tumor Regression Grade

7th Edition		8th Edition	
Description	**Tumor Regression Grade**	**Description**	**Tumor Regression Score**
No viable cancer cells	0 (Complete response)	No viable cancer cells (complete response)	0
Single cells or small groups of cancer cells	1 (Moderate response)	Single cells or rare small groups of cancer cells (near complete response)	1
Residual cancer outgrown by fibrosis	2 (Minimal response)	Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response)	2
Minimal or no tumor kill; extensive residual cancer	3 (Poor response)	Extensive residual cancer with no evident tumor regression (poor or no response)	3

Stage groupings for ypTNM

Stage	T	N	M
Stage I	T1-2	N0	M0
	T1	N1	M0
Stage II	T1	N2-3	M0
	T2	N1-2	M0
	T3	N0-1	M0
	T4a	N0	M0
Stage III	T2	N3	M0
	T3	N2-3	M0
	T4a	N1-3	M0
	T4b	Any N	M0
Stage IV	Any T	Any N	M1

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Applying the New AJCC Staging System to Daily Diagnostic Practice: Gastrointestinal Pathology

QUESTIONS?

Amitabh Srivastava, MD, Associate Professor of Pathology, Harvard Medical School, Associate Director, Surgical Pathology, Director, Surgical Pathology Fellowship Program, Brigham and Women's Hospital

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Applying the New AJCC Staging System to Daily Diagnostic Practice: Gastrointestinal Pathology

Carcinomas of the Small Intestine

Neuroendocrine Tumors of the Gastrointestinal Tract

Hanlin Wang, MD, PhD
University of California Los Angeles

Objectives

- Familiarize with changes in the new AJCC Staging Manual
- Understand the rationale behind the changes
- Discuss potentially confusing issues in the new system that may affect our practice

Staging System for Carcinomas of the Small Intestine

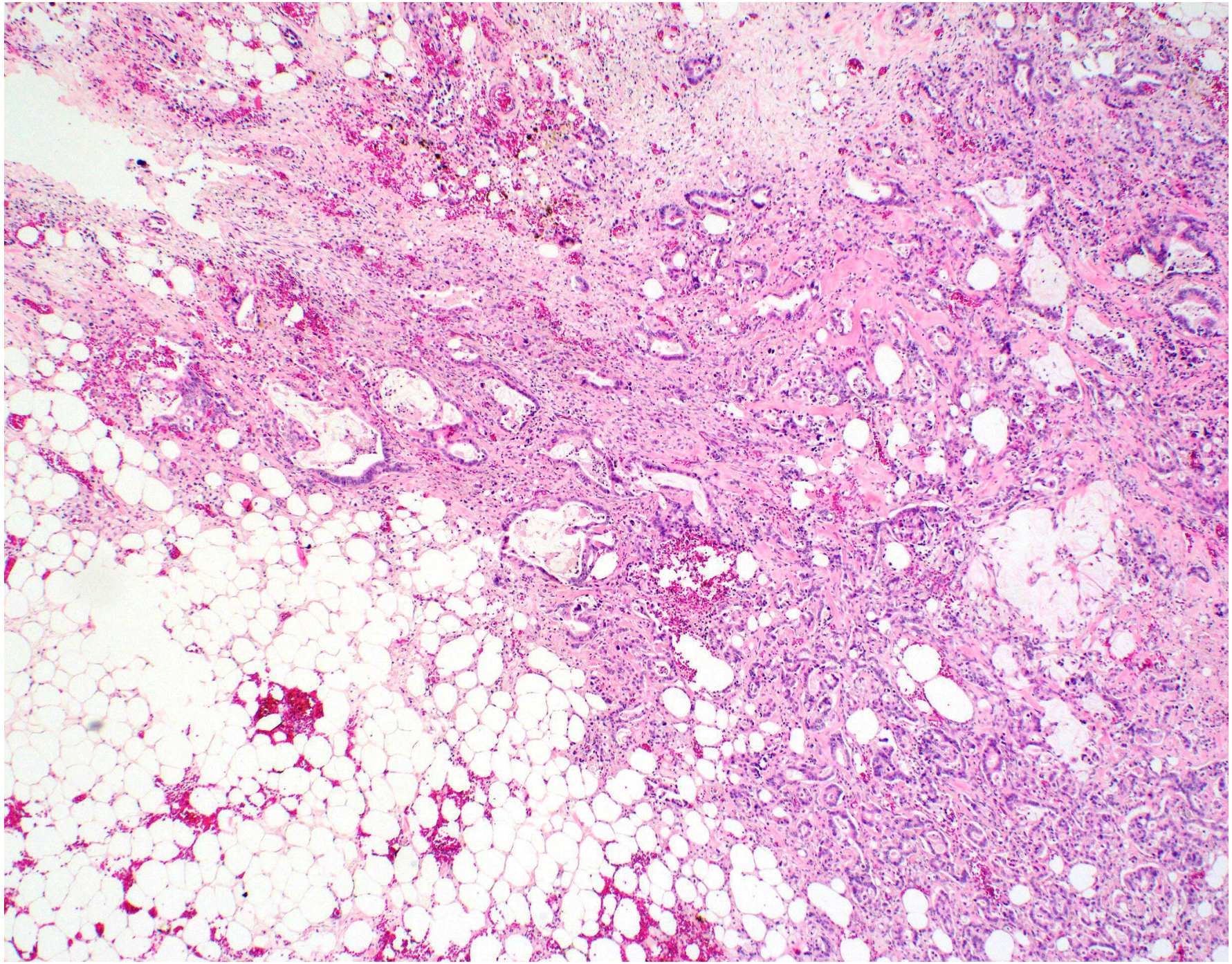
- Designed for carcinomas of the nonampullary duodenum, jejunum and ileum
- The following tumor types should not be staged using this system
  - Carcinomas of the ampulla
  - Well differentiated neuroendocrine tumor

Comparison between 8th and 7th Editions: T Category

	8th Edition	7th Edition
Tis	High-grade dysplasia/carcinoma in situ	Carcinoma in situ
T1	Tumor invades the lamina propria or submucosa	Tumor invades the lamina propria or submucosa
T1a	Tumor invades the lamina propria	Tumor invades the lamina propria
T1b	Tumor invades the submucosa	Tumor invades the submucosa
T2	Tumor invades the muscularis propria	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into the subserosa, or extends into nonperitonealized perimuscular tissue (mesentery or retroperitoneum) without serosal penetration	Tumor invades through the muscularis propria into the subserosa or into the nonperitonealized perimuscular tissue (mesentery or retroperitoneum) with extension 2 cm or less
T4	Tumor perforates the visceral peritoneum or directly invades other organs or structures (e.g., other loops of small intestine, mesentery of adjacent loops of bowel, and abdominal wall by way of serosa; for duodenum only, invasion of pancreas or bile duct)	Tumor perforates the visceral peritoneum or directly invades other organs or structures (including other loops of small intestine, mesentery, or retroperitoneum more than 2 cm, and abdominal wall by way of serosa; for duodenum only, invasion of pancreas or bile duct)

Changes in T Category

- For T3 and T4, the description of extent of penetration into the mesentery or peritoneum (≤2 cm or >2 cm) was removed
- Rationale
  - Not reliably reported in pathology assessment
  - Not a valid prognostic factor



Small bowel adenocarcinoma extending into the mesentery

7th edition: need to know the distance (2 cm?)

8th edition: no need to know the distance

Comparison between Systems for Carcinomas of the Small Intestine and Stomach: T Category

	Small Intestinal	Stomach
Tis	High-grade dysplasia/carcinoma in situ	High-grade dysplasia/carcinoma in situ
T1	Tumor invades the lamina propria (T1a) or submucosa (T1b)	Tumor invades the lamina propria (T1a) or submucosa (T1b)
T2	Tumor invades the muscularis propria	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into the subserosa, or extends into nonperitonealized perimuscular tissue (mesentery or retroperitoneum) without serosal penetration	Tumor penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures
T4	Tumor perforates the visceral peritoneum or directly invades other organs or structures (e.g., other loops of small intestine, mesentery of adjacent loops of bowel, and abdominal wall by way of serosa; for duodenum only, invasion of pancreas or bile duct)	Tumor invades the visceral peritoneum (T4a) or adjacent structures/organs (T4b)

Comparison between Systems for Carcinomas of the Small and Large Intestines: T Category

	Small Intestinal	Colorectal
Tis	High-grade dysplasia/carcinoma in situ	Carcinoma in situ, intramucosal carcinoma (involvement of lamina propria with no extension through the muscularis mucosae)
T1	Tumor invades the lamina propria (T1a) or submucosa (T1b)	Tumor invades the submucosa (through the muscularis mucosae but not into the muscularis propria
T2	Tumor invades the muscularis propria	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into the subserosa, or extends into nonperitonealized perimuscular tissue (mesentery or retroperitoneum) without serosal penetration	Tumor invades through the muscularis propria into pericolorectal tissues
T4	Tumor perforates the visceral peritoneum or directly invades other organs or structures (e.g., other loops of small intestine, mesentery of adjacent loops of bowel, and abdominal wall by way of serosa; for duodenum only, invasion of pancreas or bile duct)	Tumor invades the visceral peritoneum (T4a) or invades or adheres to adjacent organs or structures (T4b)

Comparison between 8th and 7th Editions: N Category

N Category	8th Edition	7th Edition
NX	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	Metastasis in 1 or 2 regional lymph nodes	Metastasis in 1-3 regional lymph nodes
N2	Metastasis in 3 or more regional lymph nodes	Metastasis in 4 or more regional lymph nodes

Rationale for the change

- **To harmonize N1 staging with the rest of the upper GI tumors**
- **To provide improved stage-specific discrimination based on a new National Cancer Data Base query**
  - **3,141 patients with nonampullary duodenal adenocarcinoma**
  - **3,807 patients with nonduodenal small intestinal adenocarcinoma**

Comparison among Systems for Carcinomas of the Small Intestine, Esophagus/GE Junction, Stomach and Colorectum: N Category

T Category	Small Intestinal	Esophagus/GEJ	Stomach	Colorectal
N1	1-2	1-2	1-2	1-3
N1a				1
N1b				2-3
N1c				Tumor deposit(s)
N2	3 or more	3-6	3-6	4 or more
N2a				4-6
N2b				7 or more
N3	N/A	7 or more	7 or more	N/A
N3a			7-15	
N3b			16 or more	

Minimum Number of Lymph nodes for Optimal Nodal Staging of Small Intestinal Carcinoma

- **Not well defined**
- **At least 8**

  Overman MJ, et al. Cancer 2010; 116: 5374-82

- **At least 5 for nonampullary duodenal adenocarcinoma**
- **At least 9 for jejunoileal adenocarcinoma**

  Tran TB, et al. Surgery 2015; 158:486-93

- **At least 9**

  Wilhelm A, et al. J Gastrointest Surg 2016; 20:401-10

Staging Systems for Neuroendocrine Tumors of the Gastrointestinal Tract

- Designed for well differentiated neuroendocrine tumors (G1, G2, and rarely well differentiated G3)
- Site-specific staging systems
- The following tumor types should not be staged using these systems
  - Poorly differentiated neuroendocrine carcinoma (small cell and large cell neuroendocrine carcinomas)
  - Mixed adenoneuroendocrine carcinoma
  - Goblet cell carcinoid

Site-specific Staging Systems for Neuroendocrine Tumors of the Gastrointestinal Tract: T Category

	Stomach, jejunum and ileum	Duodenum and ampulla	Appendix	Colorectum
T1	Invades the lamina propria or submucosa; and ≤1 cm	Invades the mucosa or submucosa (duodenum); confined within the sphincter of Oddi (ampulla); and ≤1 cm	≤2 cm	Invades the lamina propria or submucosa; and ≤2 cm T1a: <1 cm T1b: 1-2 cm
T2	Invades the muscularis propria; or >1 cm	Invades the muscularis propria (duodenum); invades through sphincter into duodenal submucosa or muscularis propria (ampulla); or >1 cm	>2 cm but ≤4 cm	Invades the muscularis propria; or >2 cm with invasion of the lamina propria or submucosa
T3	Invades through the muscularis propria into subserosal tissue without penetration of overlying serosa	Invades the pancreas or peripancreatic adipose tissue	>4 cm; or with subserosal invasion or involvement of the mesoappendix	Invades through the muscularis propria into subserosal tissue without penetration of overlying serosa
T4	Invades visceral peritoneum (serosa) or other organs or adjacent structures	Invades the visceral peritoneum (serosa) or other organs	Perforates the peritoneum or directly invades other adjacent organs or structures (excluding direct mural extension to adjacent subserosa of adjacent bowel), eg, abdominal wall and skeletal muscle	Invades visceral peritoneum (serosa) or other organs or other adjacent structures

Site-specific Staging Systems for Neuroendocrine Tumors of the Gastrointestinal Tract: N Category

	Stomach, duodenum/ampulla, appendix, and colorectum	Jejunum and ileum
NX	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	Regional lymph node metastasis	Regional lymph node metastasis <12 nodes
N2		Large mesenteric masses (>2 cm) and/or extensive nodal deposits (≥12), especially those that encase the superior mesenteric vessels

Changes in 8th Edition

	Changes	Rationale
Stomach	The Tis category, defined as “carcinoma in situ/dysplasia (<0.5 mm), confined to mucosa” is eliminated	
Small intestine and ampulla	Tumors of the duodenum and ampulla are separated from those of the jejunum and ileum into two independent groups A N2 category is created for tumors of the jejunum and ileum	Different underlying tumor biology and prognosis Potential adverse effect of large mesenteric masses (>2 cm) or encasement of the mesenteric vessels on survival It does not affect stage groups
Appendix	Subdivision of T1 into T1a and T1b is eliminated “Tumor with extension to the cecum” is eliminated from T2 category “Tumor with extension from the ileum” is eliminated from T3 category “Tumor perforates the peritoneum” is added to the T4 category	
Colorectum	No change	

Prognostic Stage Groups

7th Edition			
Stage 0	Tis*	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T4	N0	M0
Stage IIIB	Any T	N1	M0
Stage IV	Any T	Any N	M1

* This applies only to stomach

8th Edition (colorectum)			
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T4	N0	M0
Stage IIIB	Any T	N1	M0
Stage IV	Any T	Any N	M1

8th Edition (non-colorectum)			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage II	T3	N0	M0
Stage III	T4	N0	M0
Stage III	Any T	N1,N2	M0
Stage IV	Any T	Any N	M1

Grading Neuroendocrine Tumors of the Gastrointestinal Tract

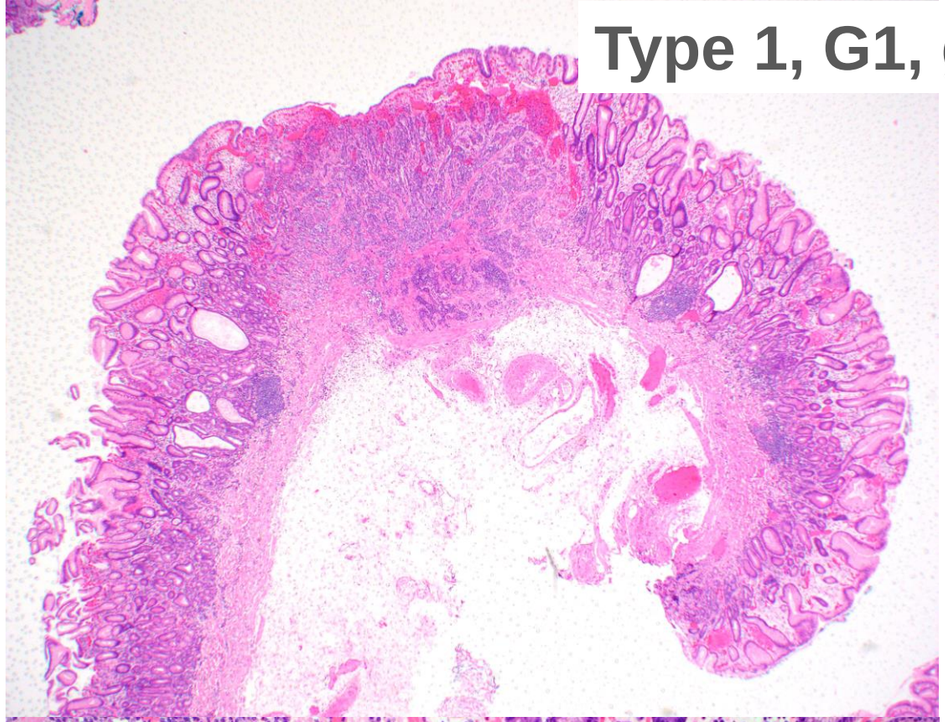
Grade	Mitotic count (per 10 HPF or 2 mm^2)	Ki-67 index (%)
WD NET, G1	<2	<3
WD NET, G2	2-20	3-20
WD NET, G3	>20	>20

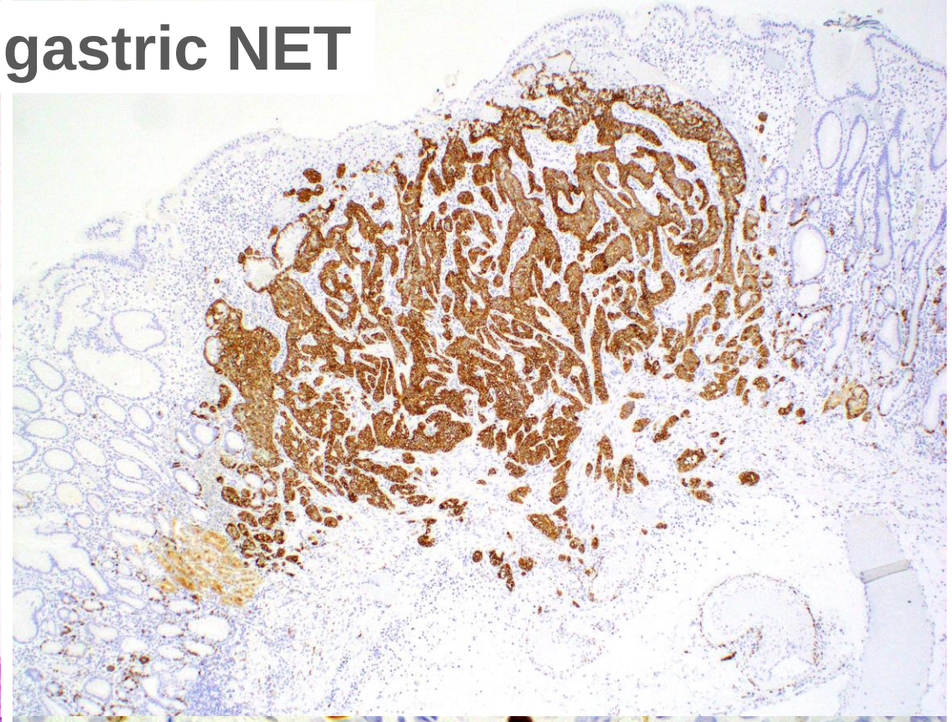
Recommendation

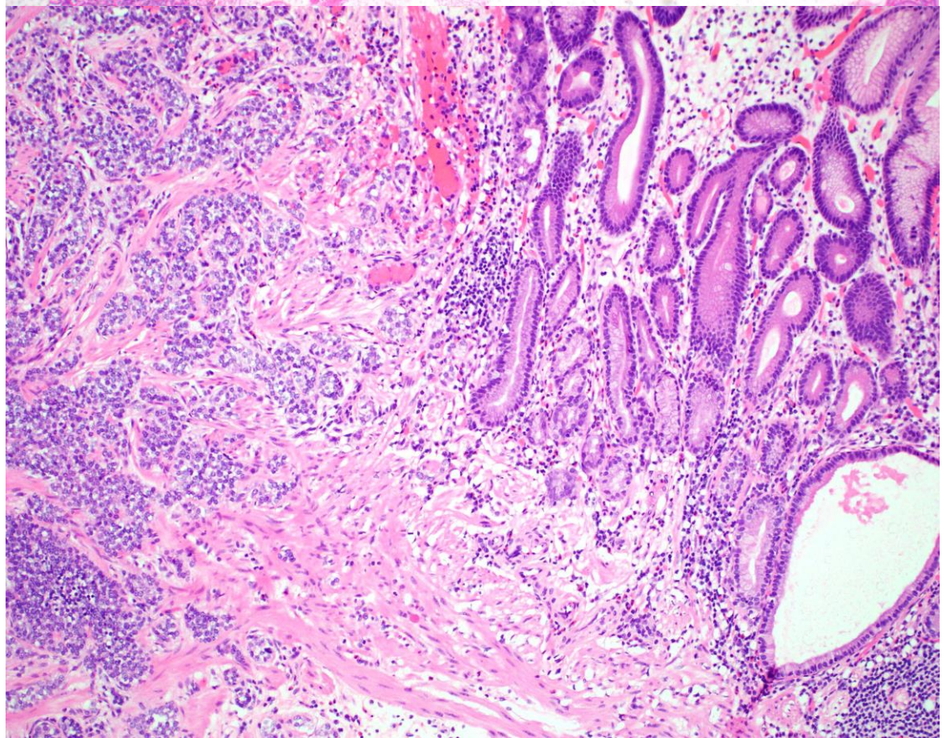
Mitotic count: at least 10 mm^2 or at least 50 high power fields (40x) should be assessed in most mitotically active areas

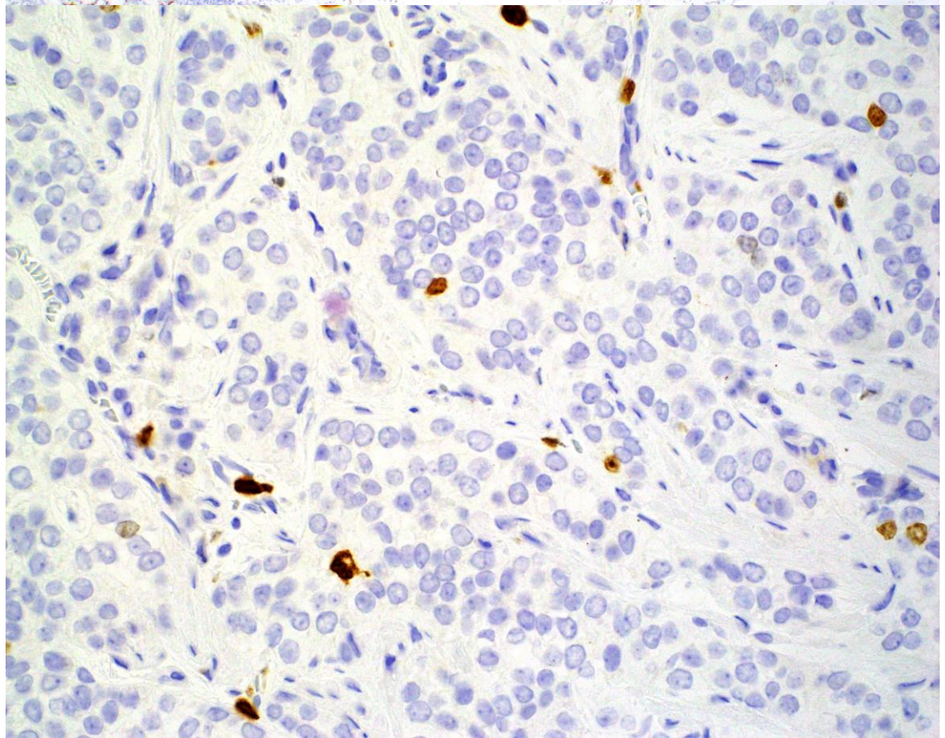
Ki-67: a minimum of 500 tumor cells should be counted in areas of highest nuclear labeling (hot spot) by either eyeballing or manual count on a print of camera-captured image of the hot spot

Type 1, G1, gastric NET

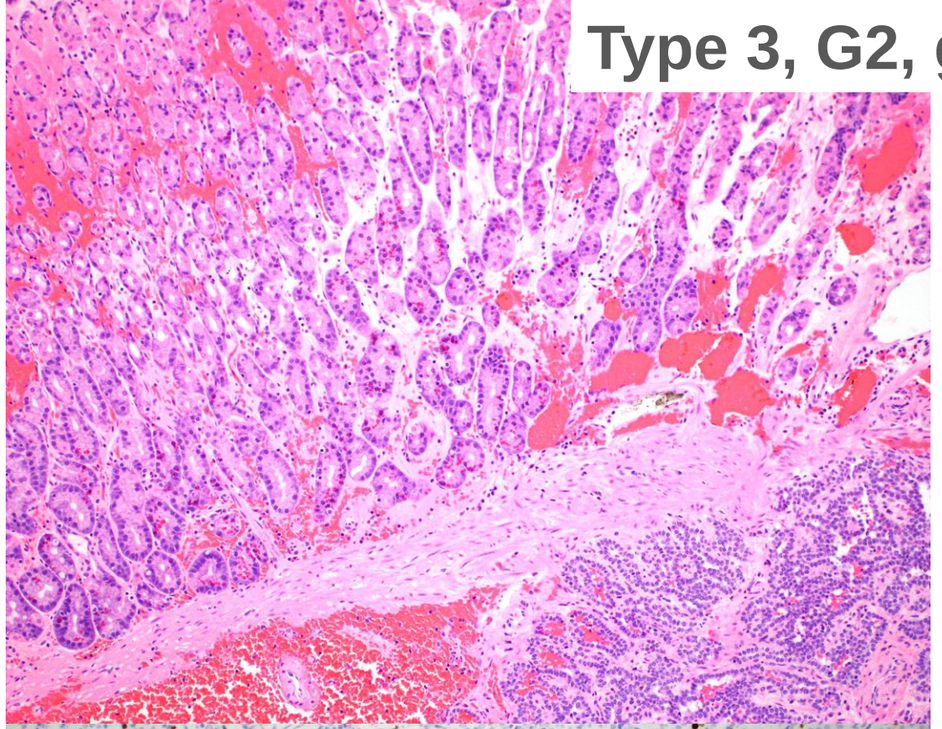


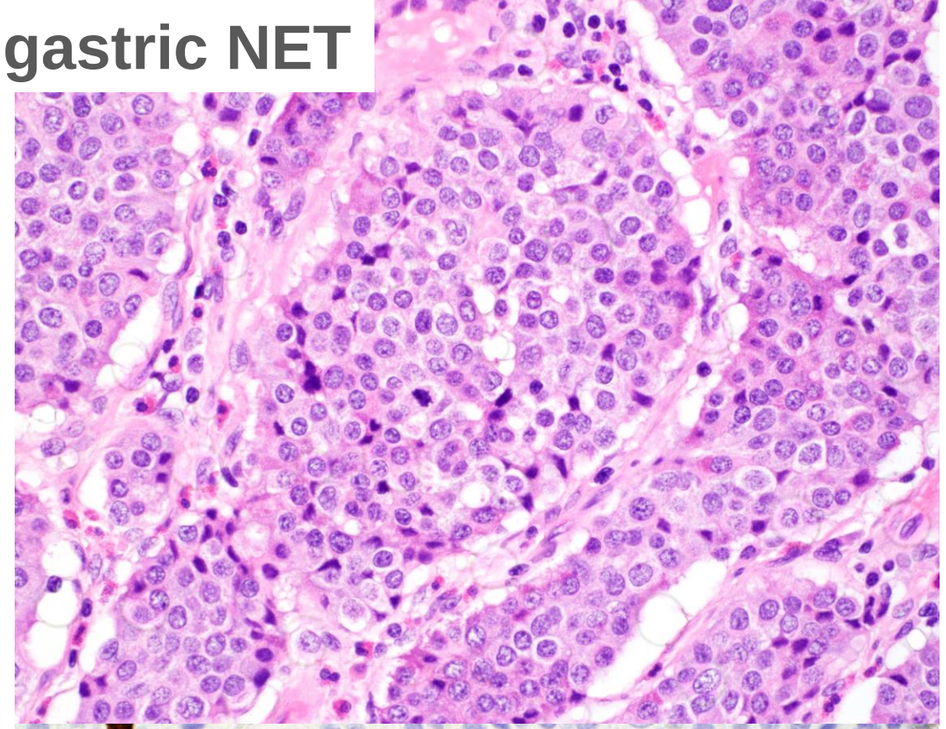


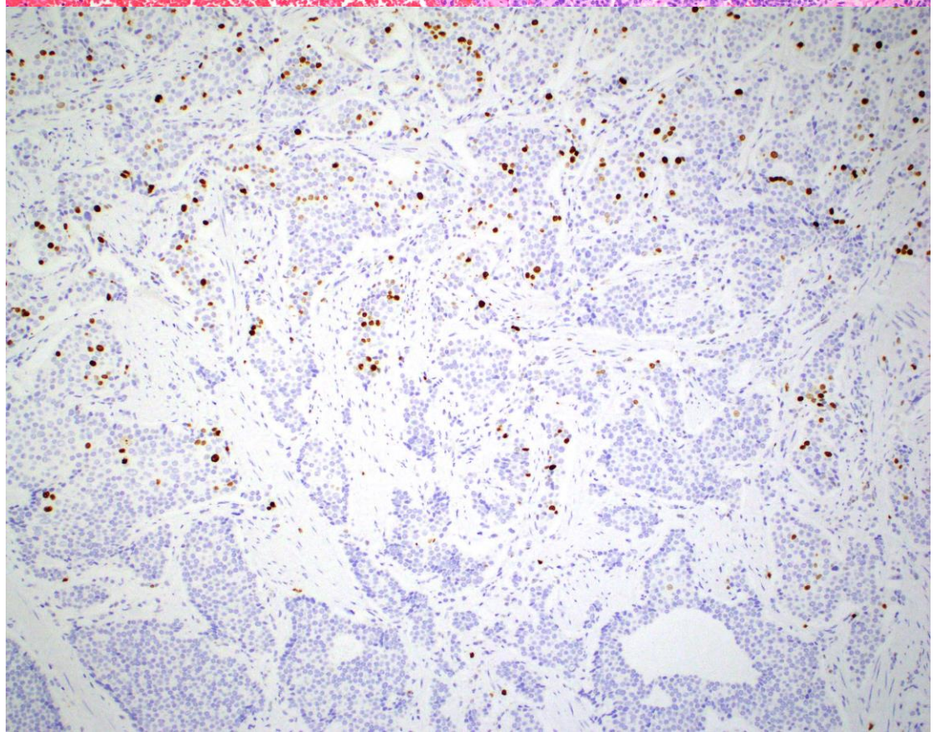


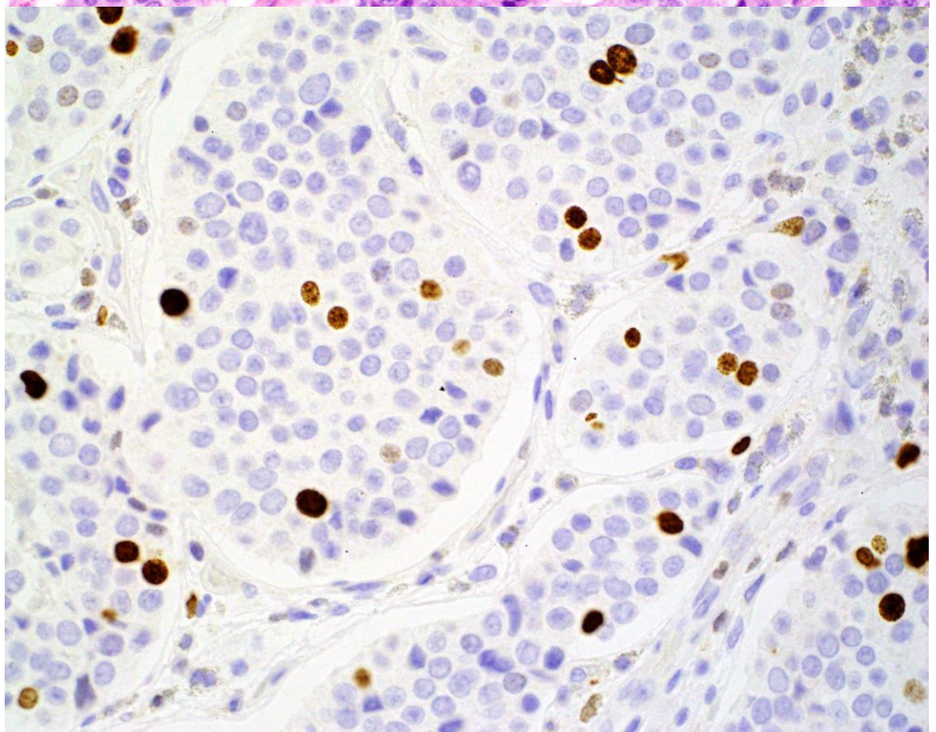


Type 3, G2, gastric NET









Summary

- It is easier now for pathologists to provide more accurate staging information with changed definition of T3 and T4 for carcinoma of the small intestine
- Site-specific staging systems for neuroendocrine tumors of the gastrointestinal tract, in addition to established grading schema, may potentially better predict prognosis

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Colon and Rectum

CAP Colon and Rectum Protocol Summary of Changes

COLON	RECTUM
The following data elements were modified:	**The following data elements were modified:**
Histologic Type	Histologic Type
Histologic Grade	Histologic Grade
Type of Polyp in Which Invasive Carcinoma Arose	Tumor Extension
	Margins
	Pathologic Stage Classification (pTNM, AJCC 8th Edition)
	Type of Polyp in Which Invasive Carcinoma Arose
Additional Pathological Findings	Additional Pathologic Findings
Tumor budding	Peritumoral tumor budding
The following data element was removed: Histologic Features Suggestive of Microsatellite Instability	

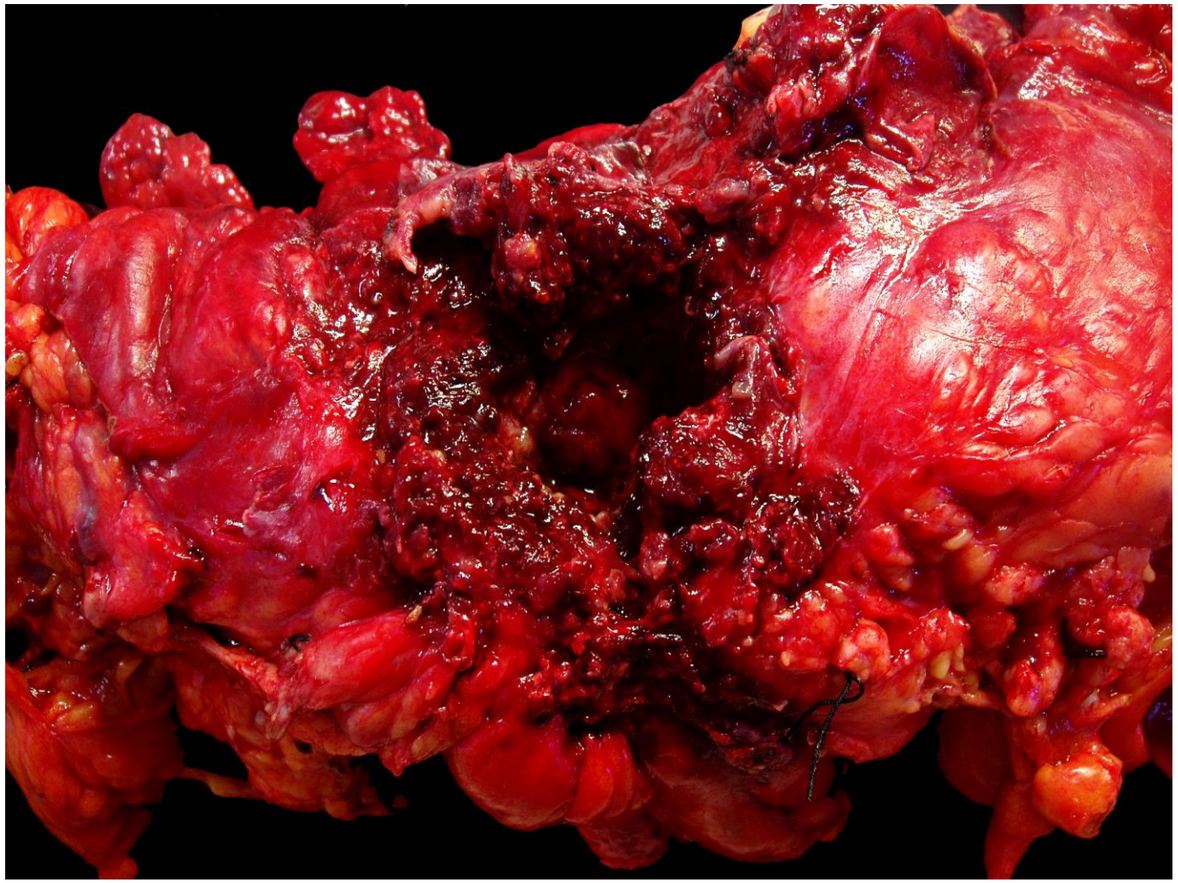
CAP Colon and Rectum Protocol Summary of Changes

Change	Details of Change	Level of Evidence
Definition of Distant Metastasis (M)	Introduced M1c, which details peritoneal carcinomatosis as a poor prognostic factor	I
Definition of Regional Lymph Node (N)	Clarified the definition of tumor deposits	II
Additional Factors Recommended for Clinical Care	Lymphovascular invasion: reintroduced the L and V elements to better identify lymphatic and vessel invasion	I
Additional Factors Recommended for Clinical Care	Microsatellite instability (MSI): clarified the importance of MSI as a prognostic and predictive factor	I
Additional Factors Recommended for Clinical Care	Identified *KRAS*, *NRAS*, and *BRAF* mutations as critical prognostic factors that are also predictive	I and II

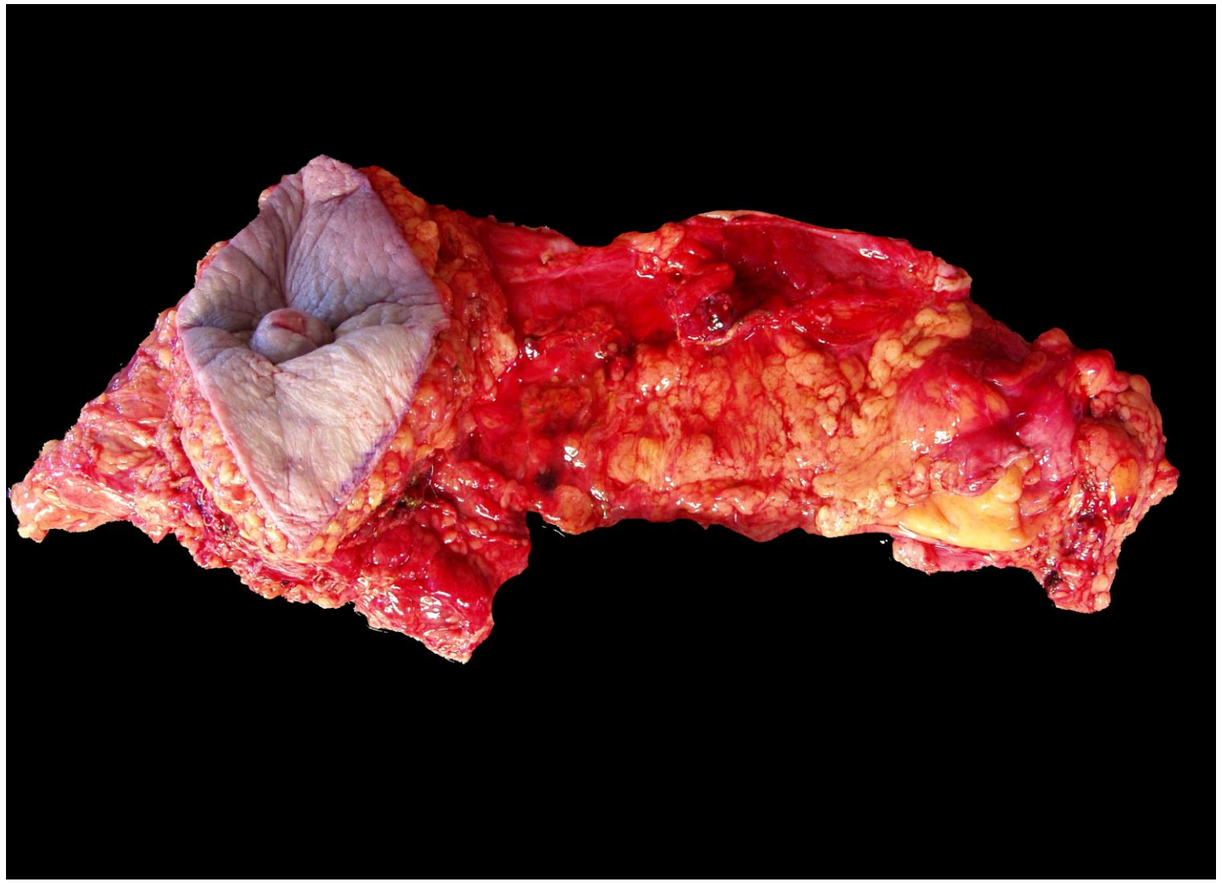
pT Stage

7th Edition	8th Edition
Primary Tumor (pT)	
pTX: Cannot be assessed	pTX: Primary tumor cannot be assessed
pT0: No evidence of primary tumor	pT0: No evidence of primary tumor
pTis: Carcinoma *in situ,* intraepithelial (no invasion of lamina propria), invasion of lamina propria/muscularis mucosae	pTis: Carcinoma in situ, intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
pT1: Tumor invades submucosa	pT1: Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
pT2: Tumor invades muscularis propria	pT2: Tumor invades the muscularis propria
pT3: Tumor invades invades through the muscularis propria into pericolorectal tissues	pT3: Tumor invades through the muscularis propria into pericolorectal tissues
pT4a: Tumor invades penetrates the visceral peritoneum	pT4a: Tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
pT4b: Tumor directly invades or is adherent to other organs or structures	pT4b: Tumor directly invades or adheres to adjacent organs or structures

pT Stage

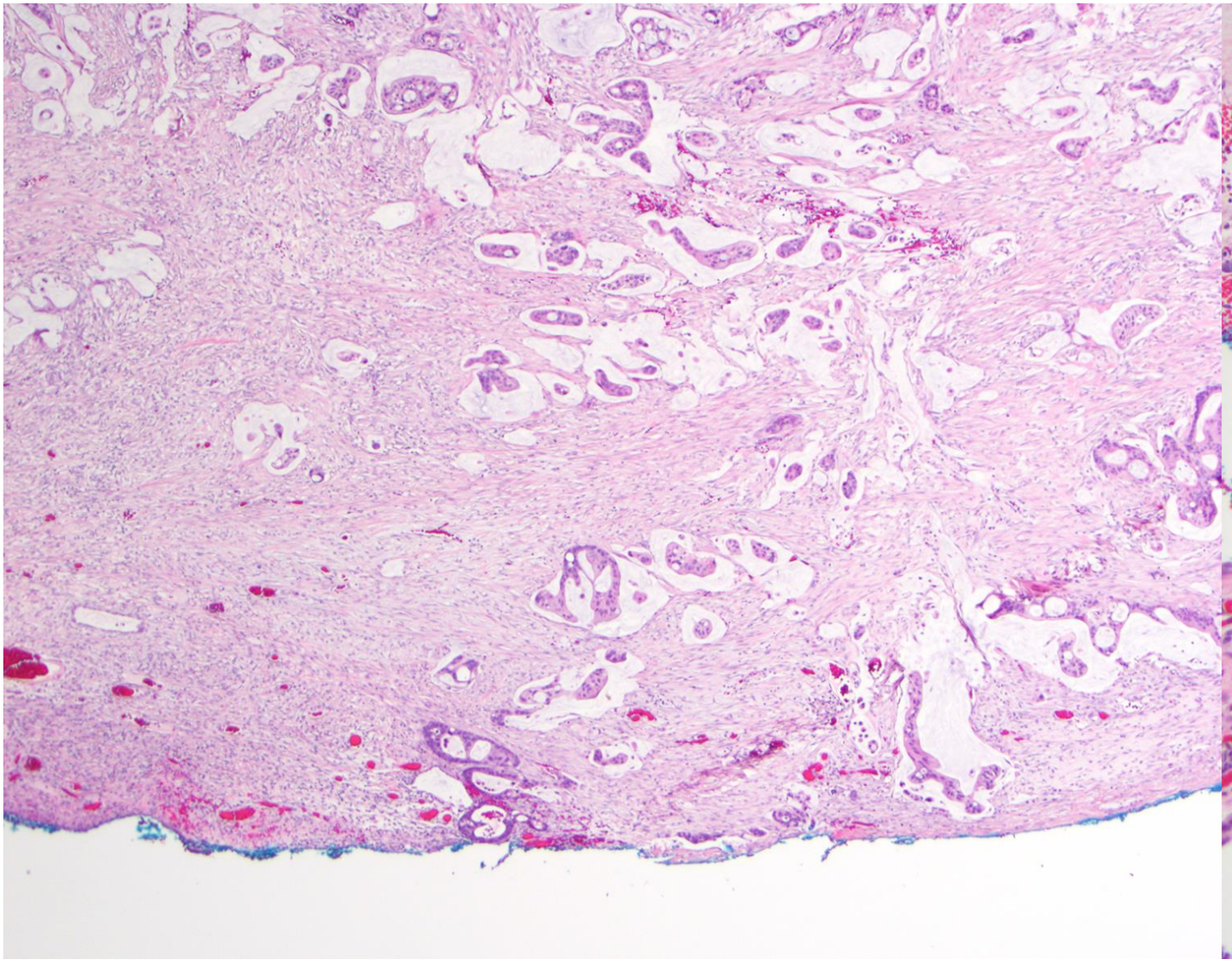


pT4a

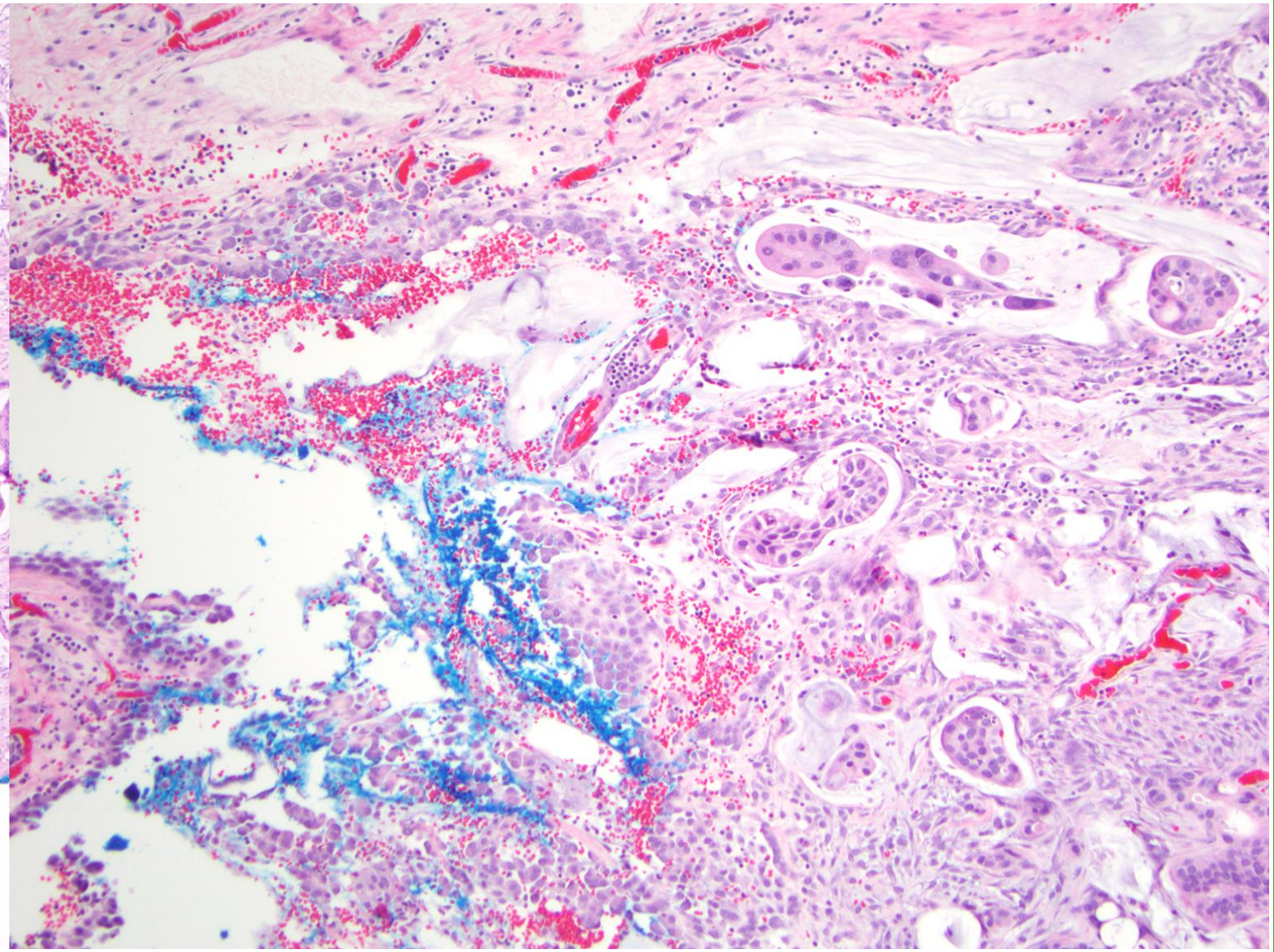


pT4b

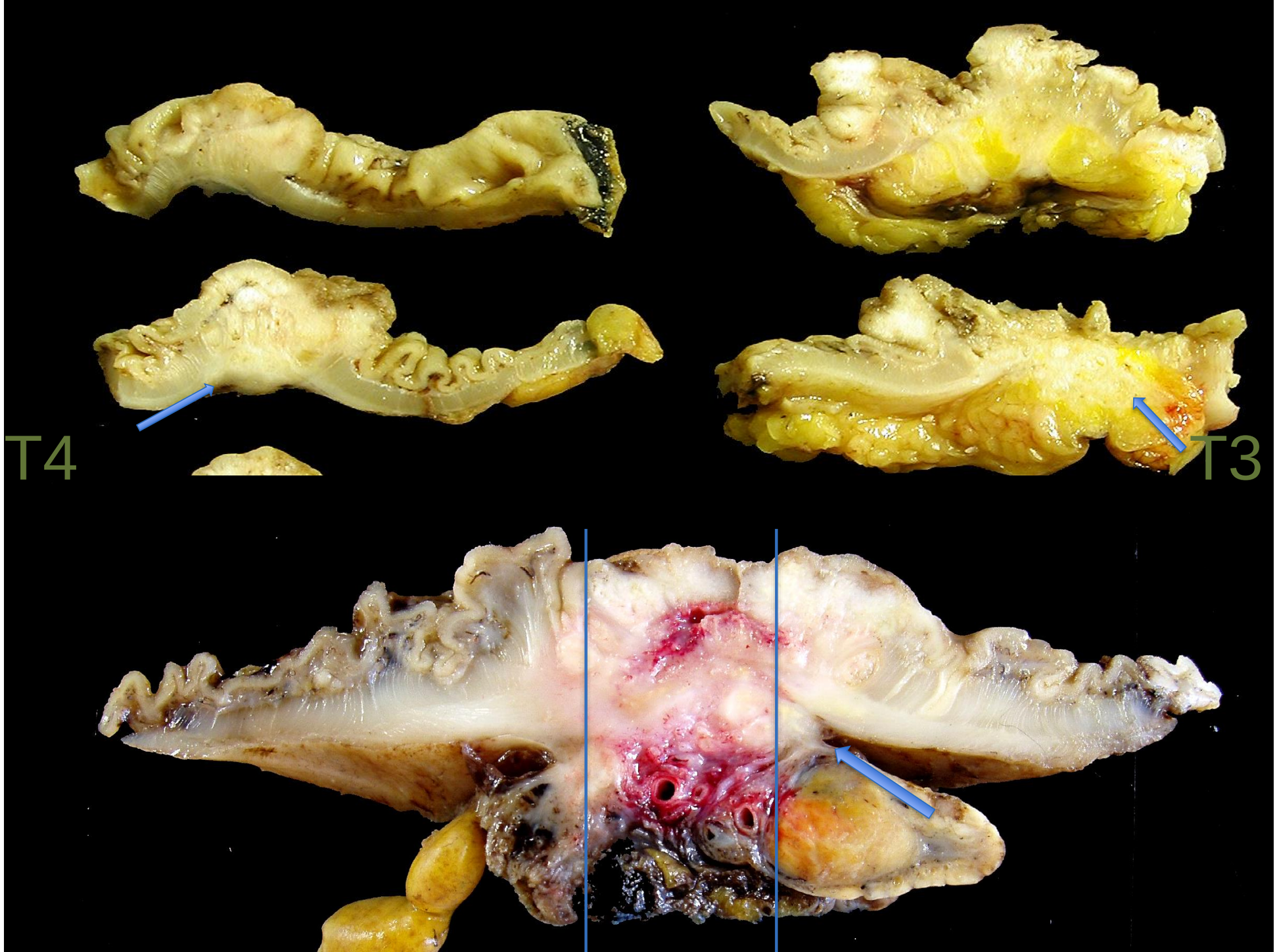
pT4a

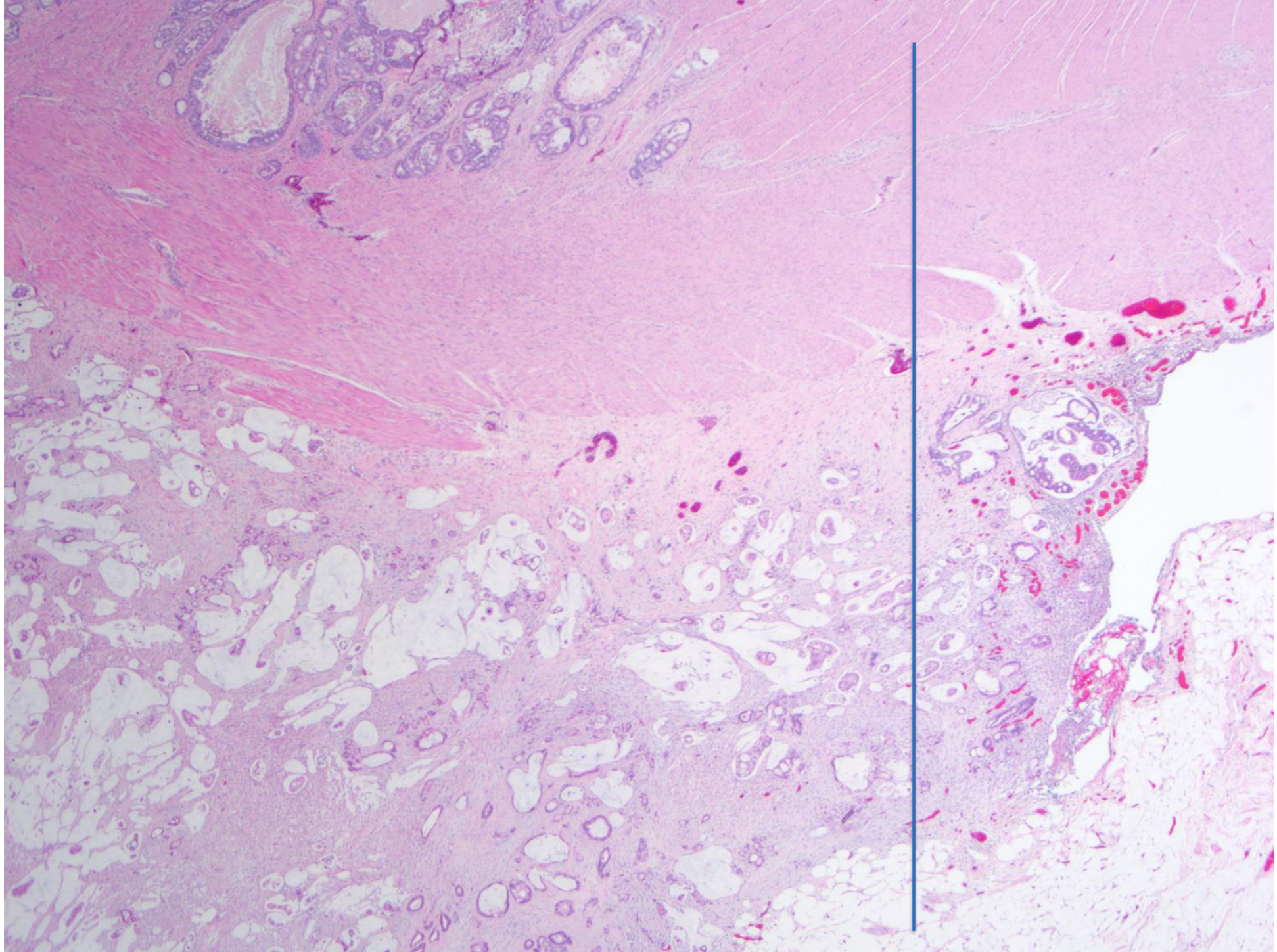


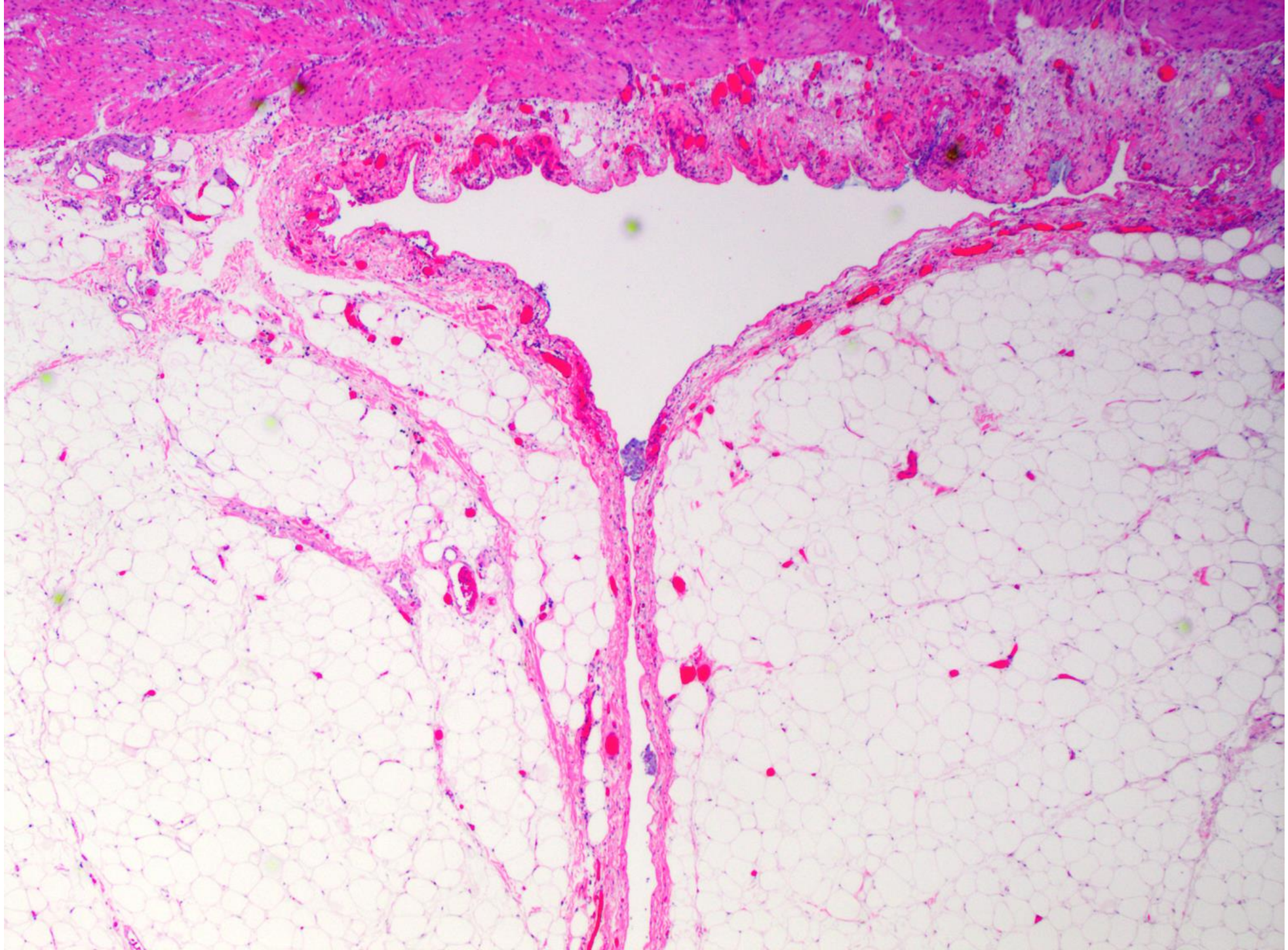
Tumor invades through the visceral peritoneum

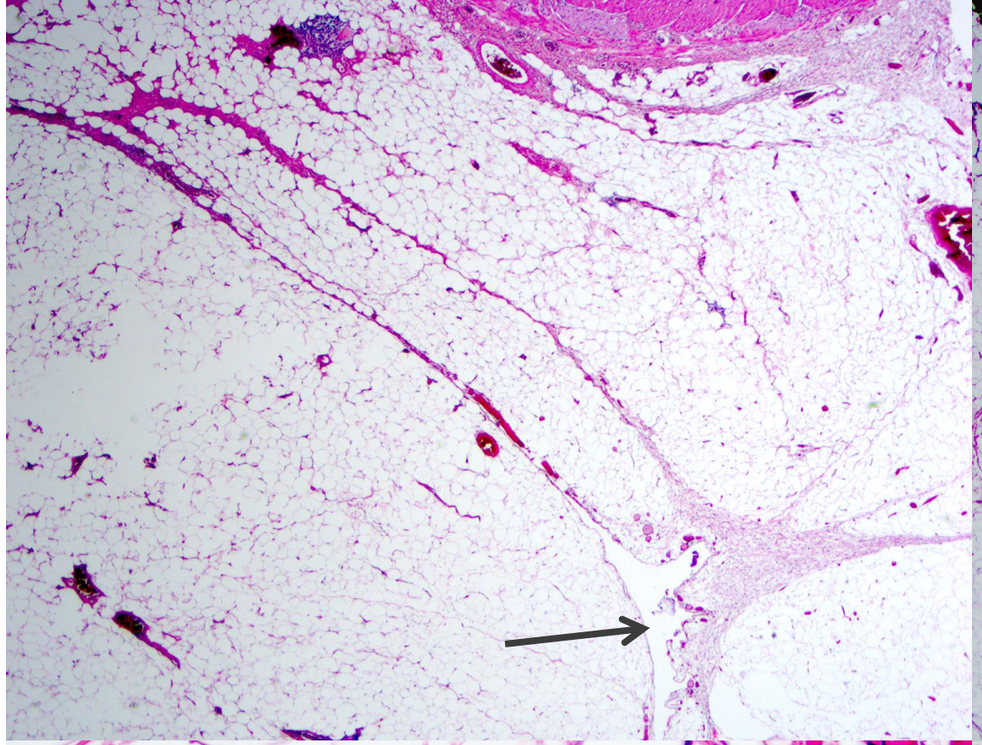


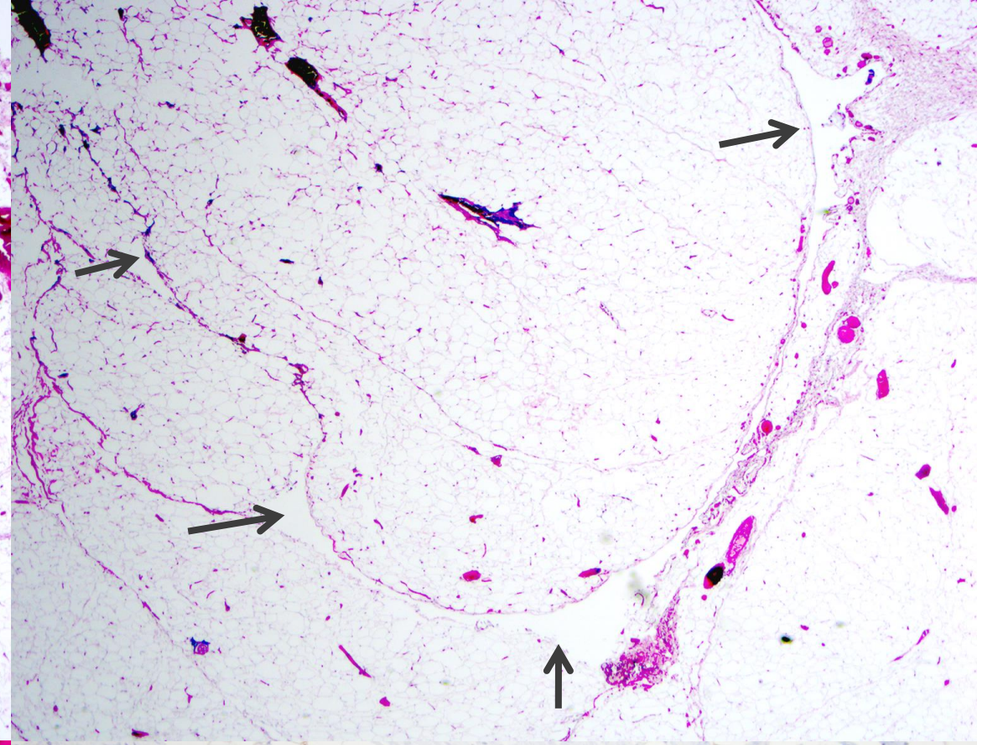
Continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum

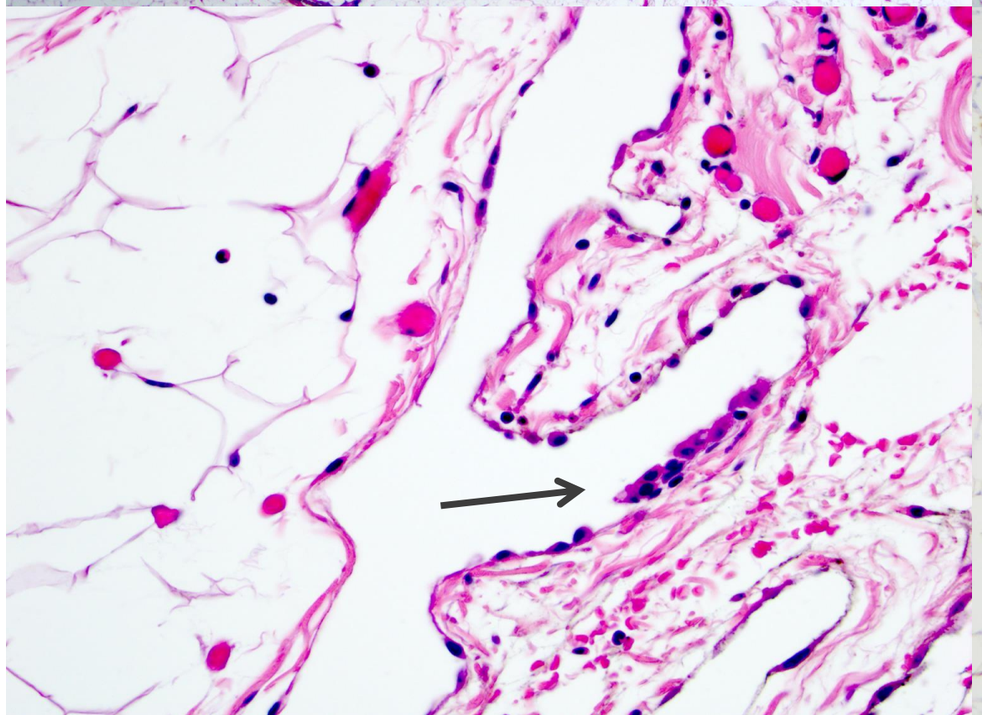

T4
T3

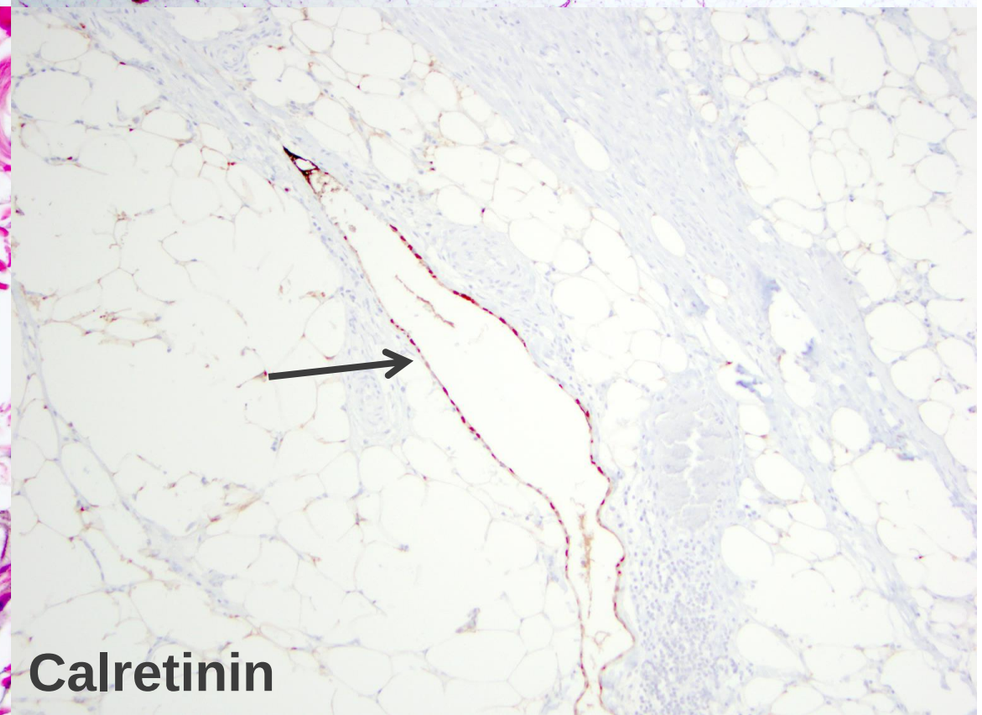




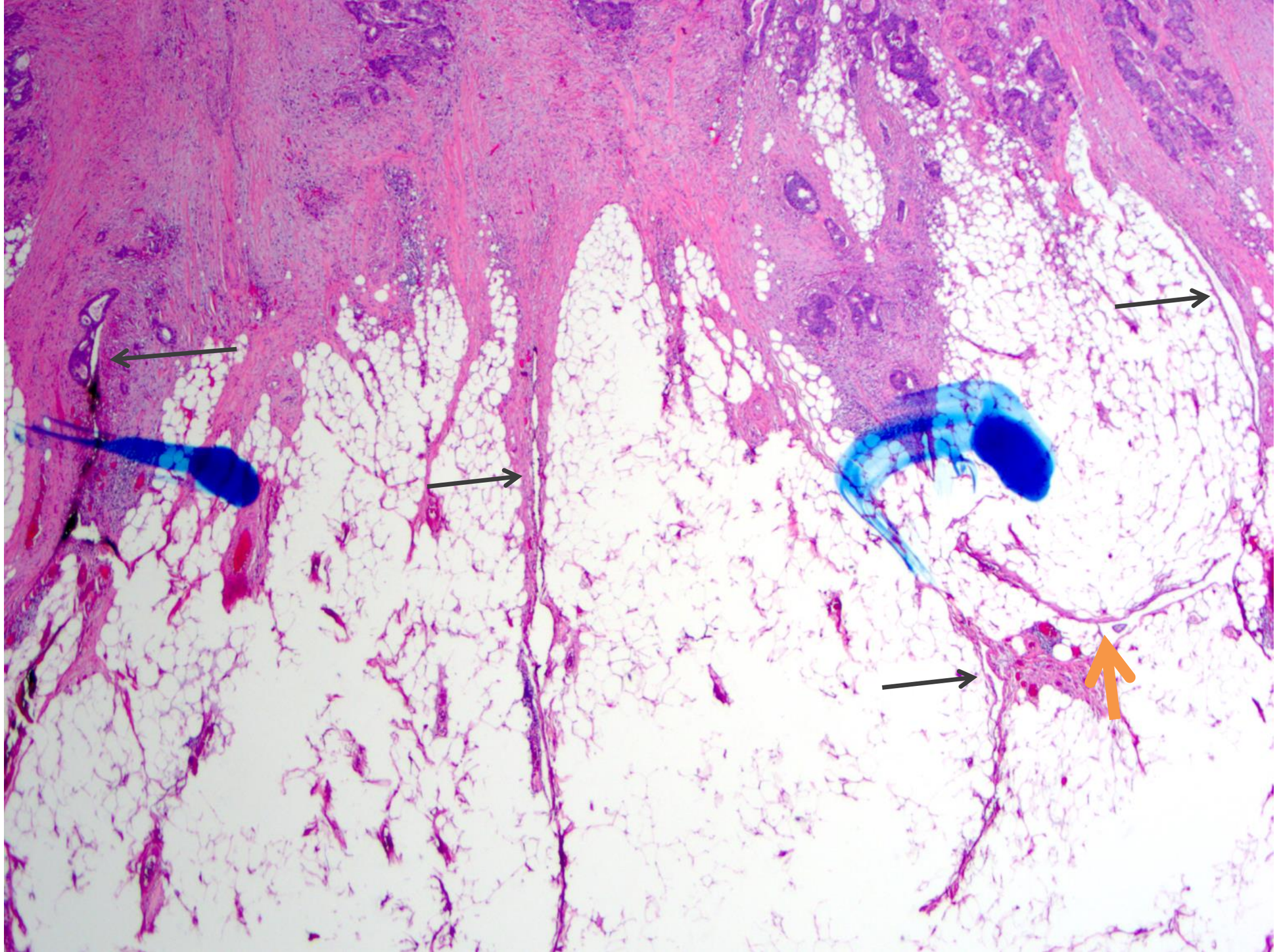


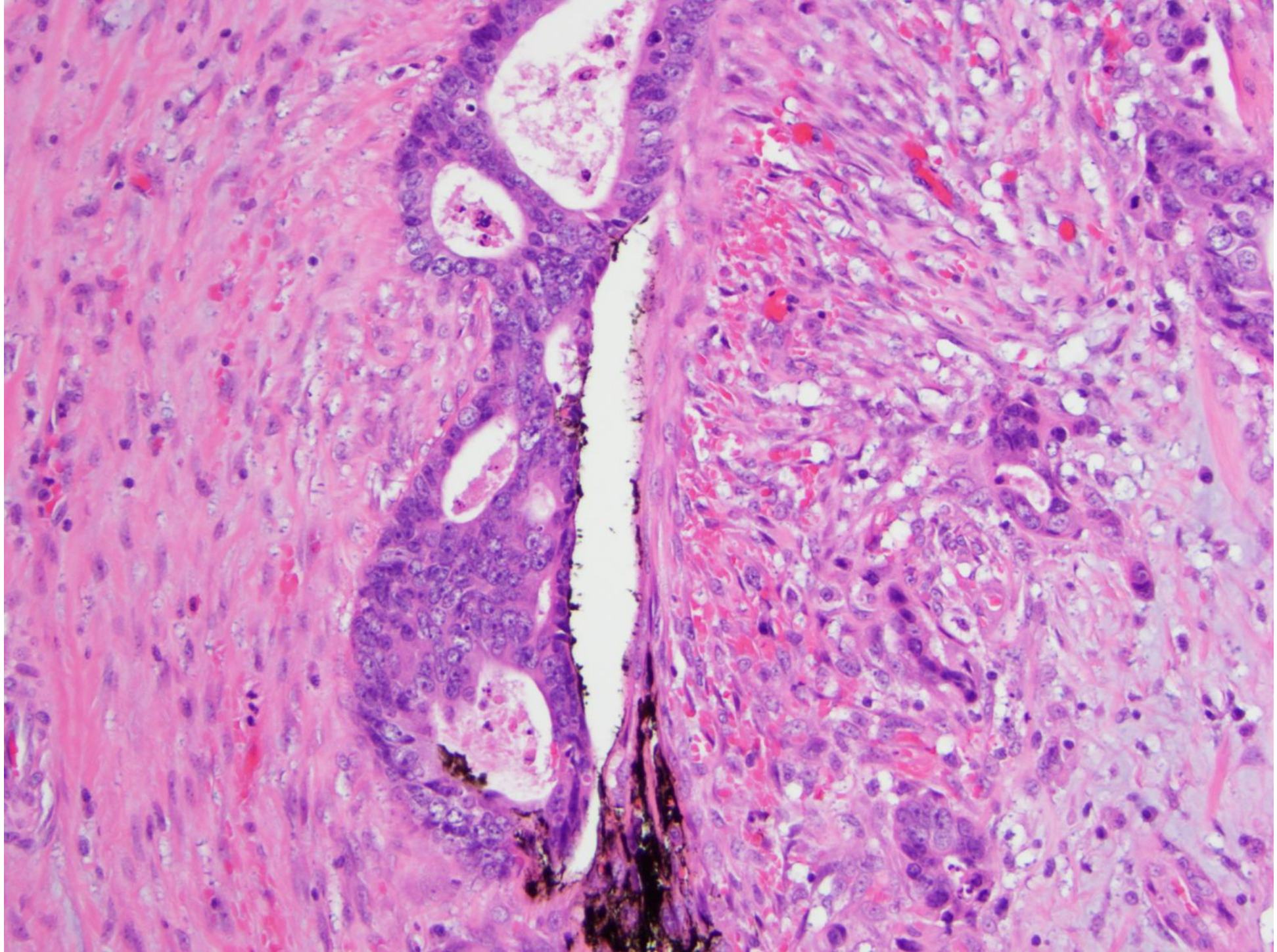


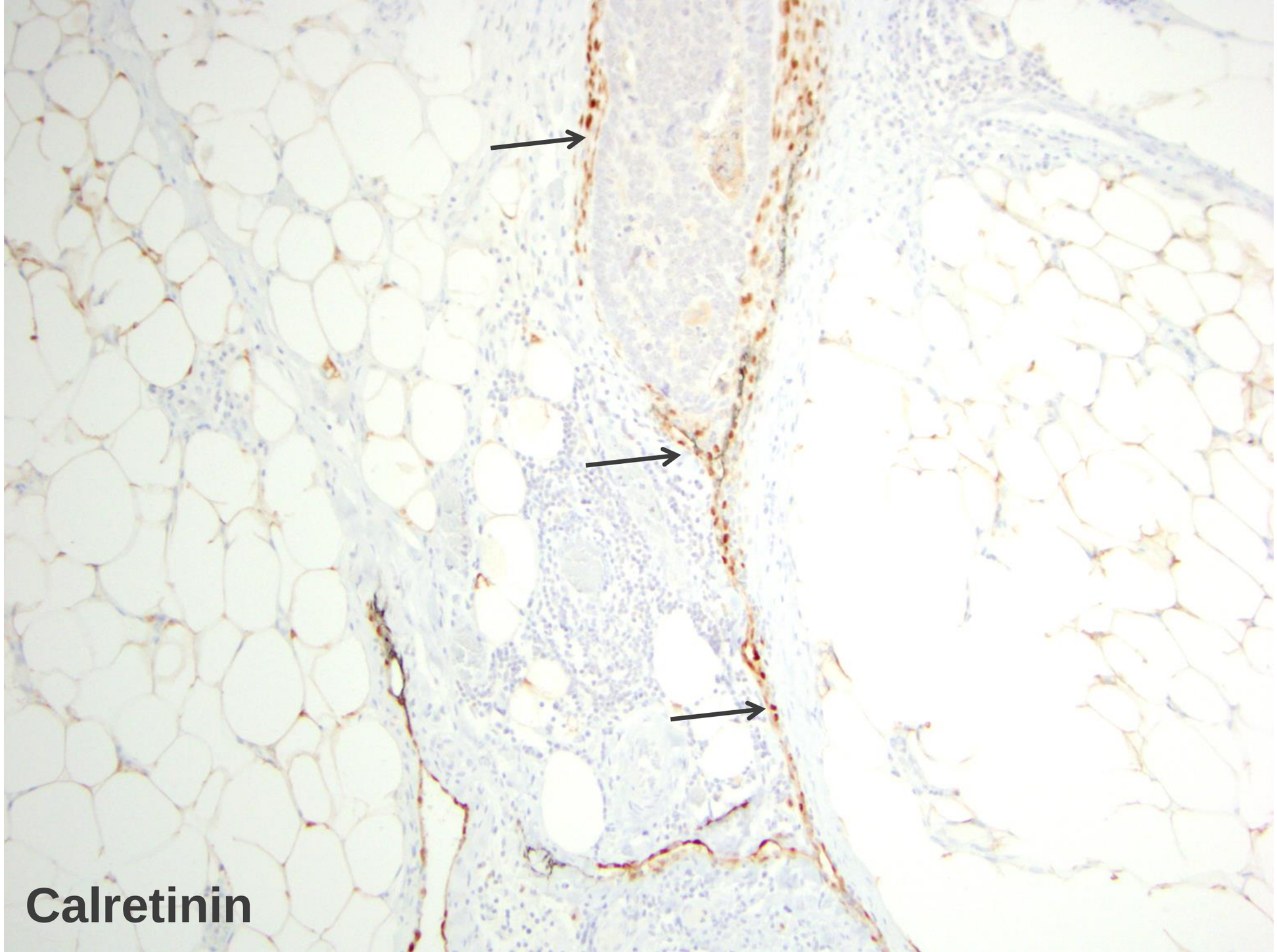




Calretinin

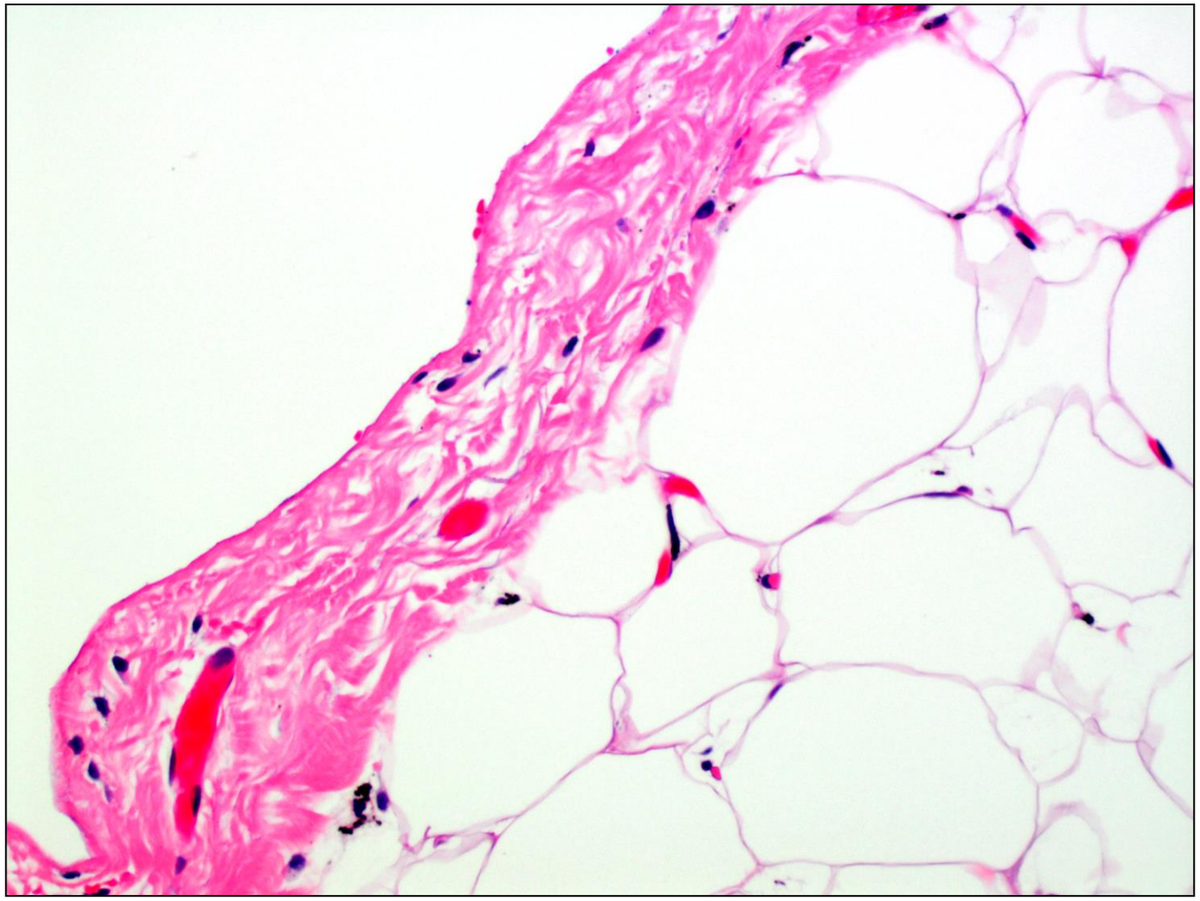


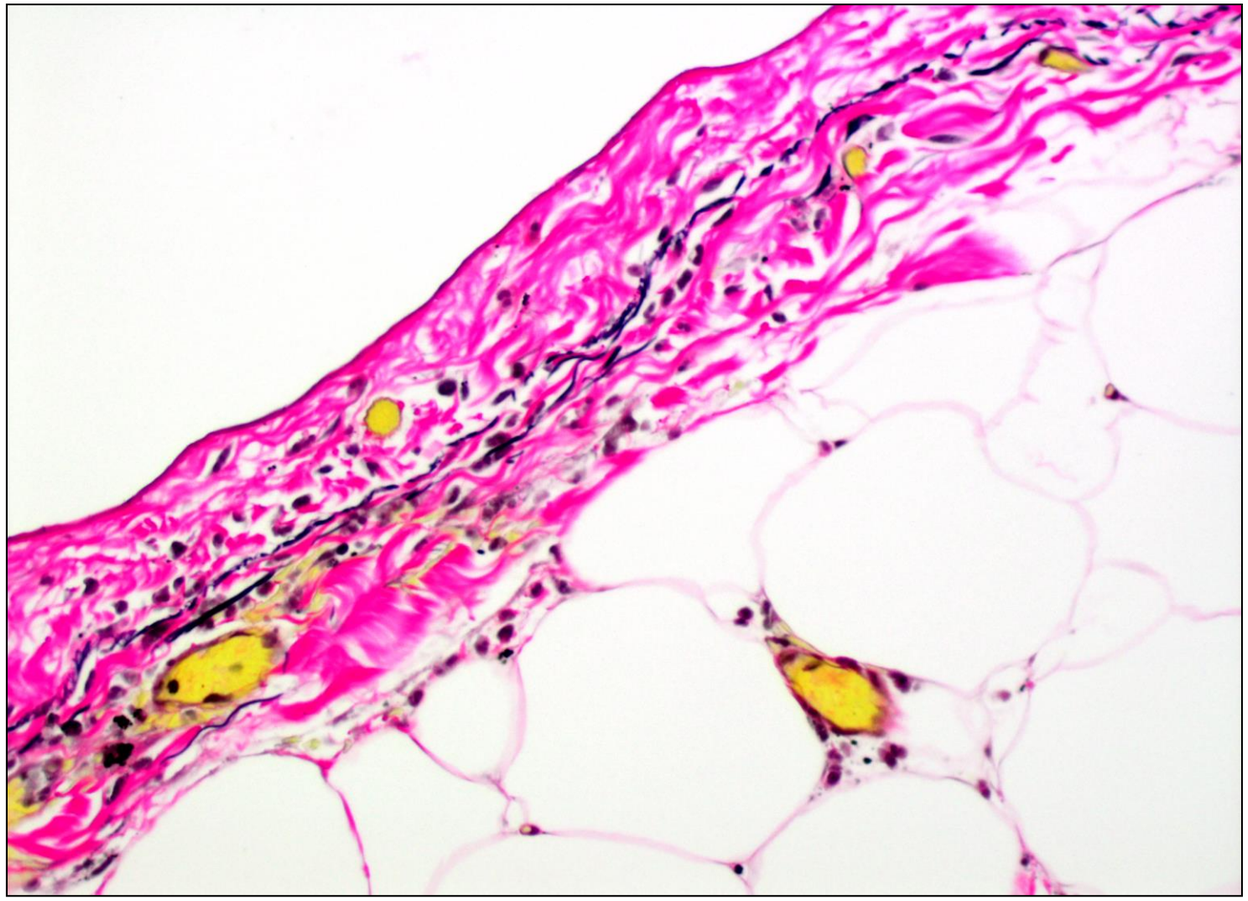




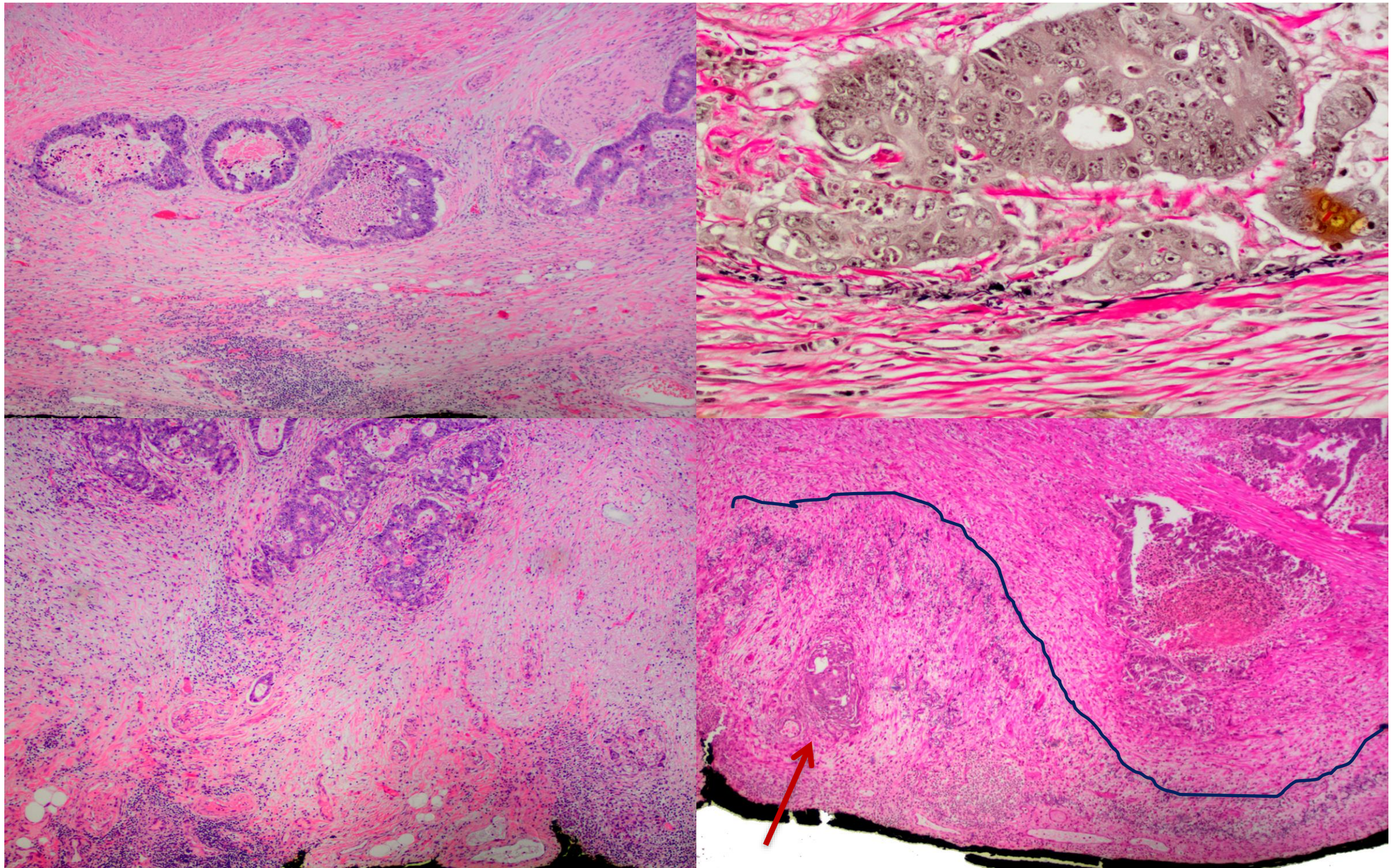
Calretinin

Elastic Lamina Invasion





Elastic Lamina Invasion

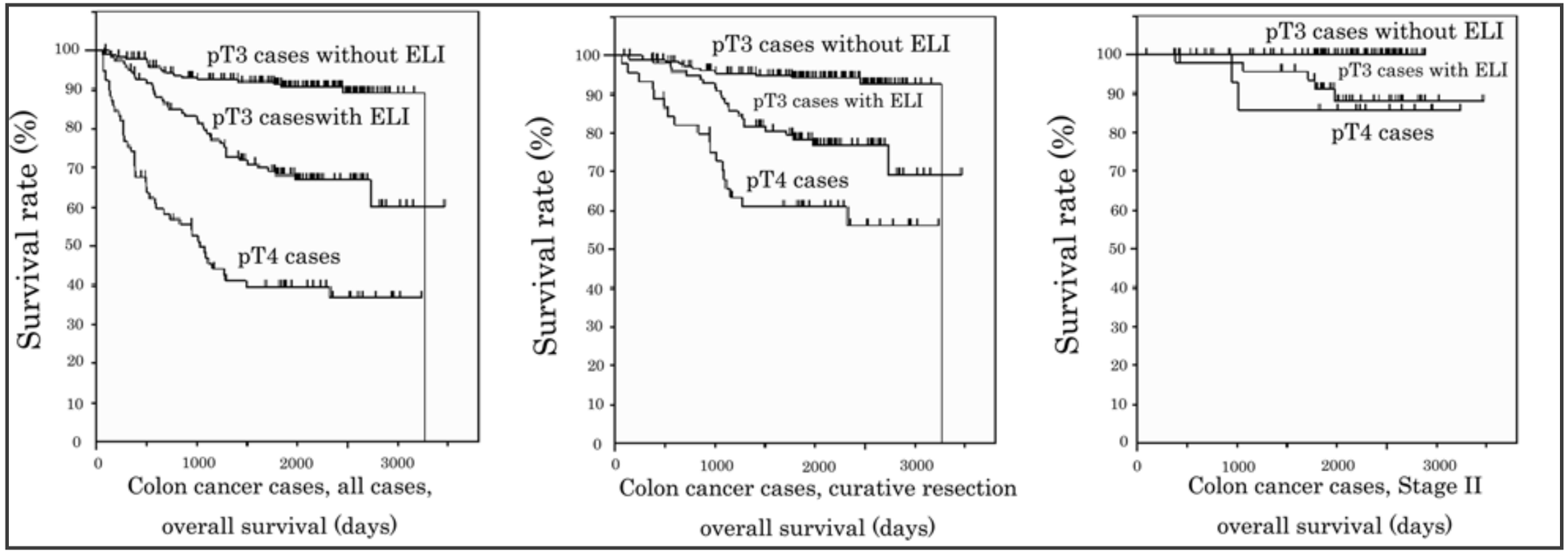


Peritoneal Elastic Laminal Invasion in Colorectal Cancer. The Diagnostic Utility and Clinicopathologic relationship

Feature	Positive ELI	Negative ELI	p
N	248	316	-
Stage			
II	71	160	<0.001
III	90	109	
IV	87	47	
pT stage			
T3	149	306	<0.001
T4a	99	10	
LPI			
Group1	7	152	<0.001
Group 2	142	154	
Group 3	65	4	
Group 4	34	6	
Budding Grade			
Grade 1	128	232	<0.001
Grade 2	64	60	
Grade 3	56	24	

Kojima M et al. Am J Surg Pathol 2010; 34:1351-1360

Peritoneal Elastic Laminal Invasion in Colorectal Cancer. The Diagnostic Utility and Clinicopathologic relationship



p<0.001
(all comparisons)

p<0.001
(all comparisons)

p<0.001
(pT3 with vs. without ELI
pT3 without ELI vs. T4)
pT3 with ELI vs. pT4 (p=0.724)

Kojima M et al. Am J Surg Pathol 2010; 34:1351-1360

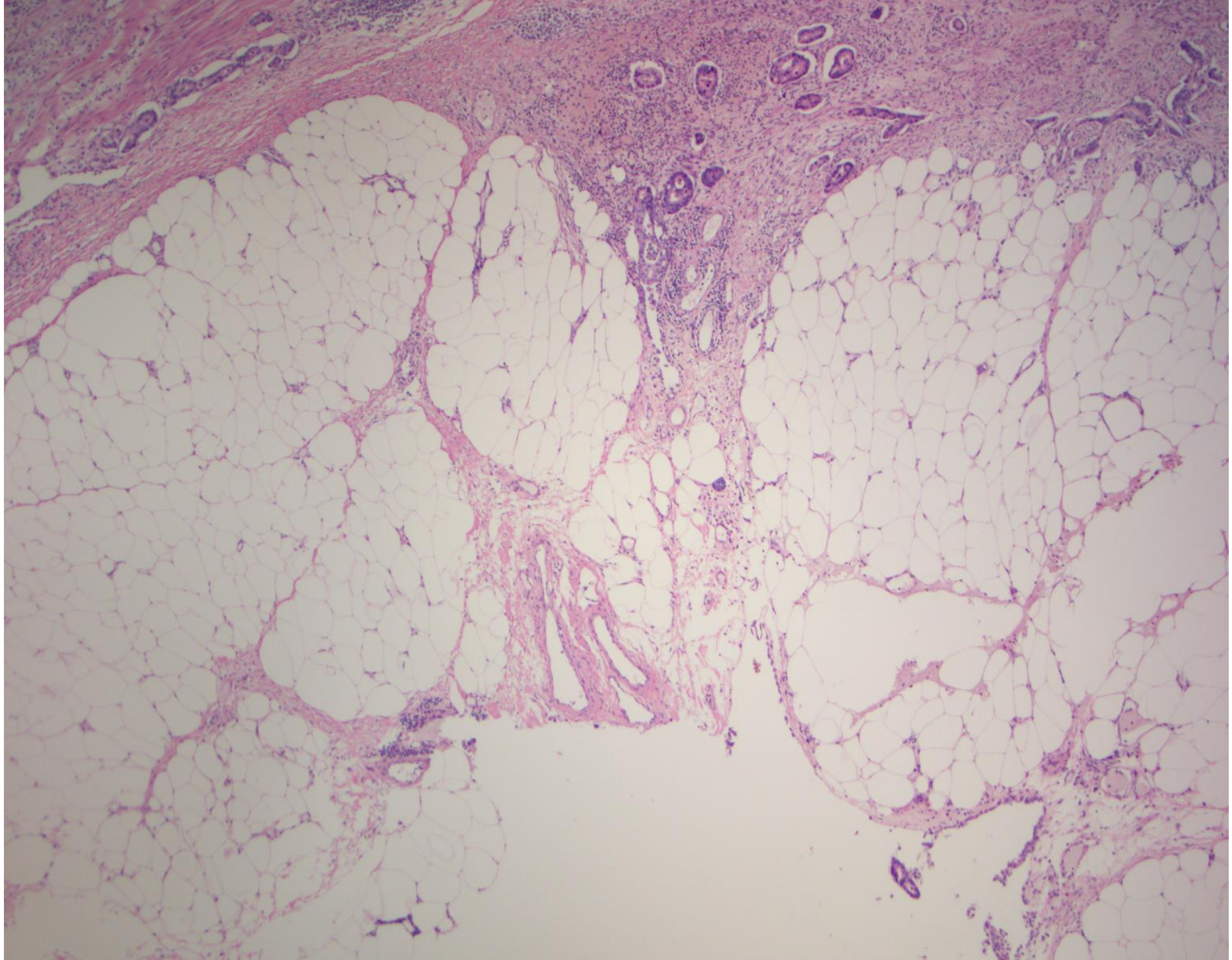
Elastic Lamina Invasion

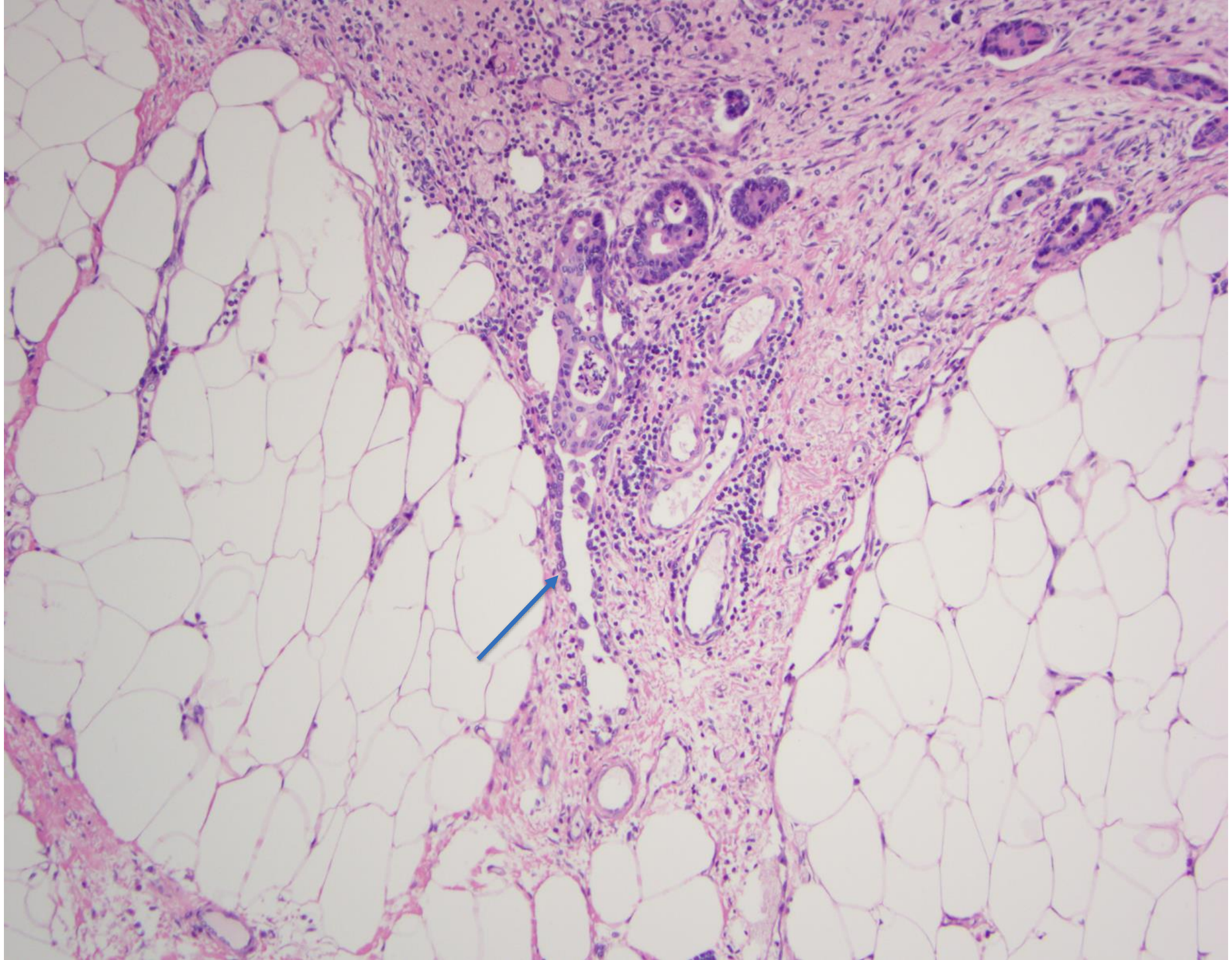
Study, year	# Patients and stage	Elastin stain	# of Slides stained	% Non-evaluable	Elastin stain results	Outcome[a]
Grin, 2013[14]	217 (186 T3 and 31 T4)	Elastic trichrome or Movat pentachrome	1.5 (mean)	18% (only 28% of cases strong continuous)	65% EL−; 17% EL+	DFS not sig worse El+ vs El−; T4 DFS sig worse vs T3
Liang, 2013[13]	244 T3	Elastic von Gieson	1	59%	17% EL−; 25% EL+	DFS and OS sig worse EL+ *vs* El−
Kojima, 2010[15]	564 (455 T3 and 109 T4a)	Elastica	4.6 (mean)	1.8% (10 cases T4a)	56% EL−; 44% EL+	OS sig worse EL+ *vs* EL−; T3 EL+ no diff *vs* T4a
Shinto, 2004[16]	325 T3 (39 T2 and 113 T4 for outcome analysis)	Victoria-blue H&E or Elastic von Gieson	Not stated	'almost all cases could be judged'	47% EL− (shallow); 53% EL+ (deep)	RR/OS sig worse EL+ *vs* EL−; T3 EL+ no diff *vs* selected T4 (without metastasis)

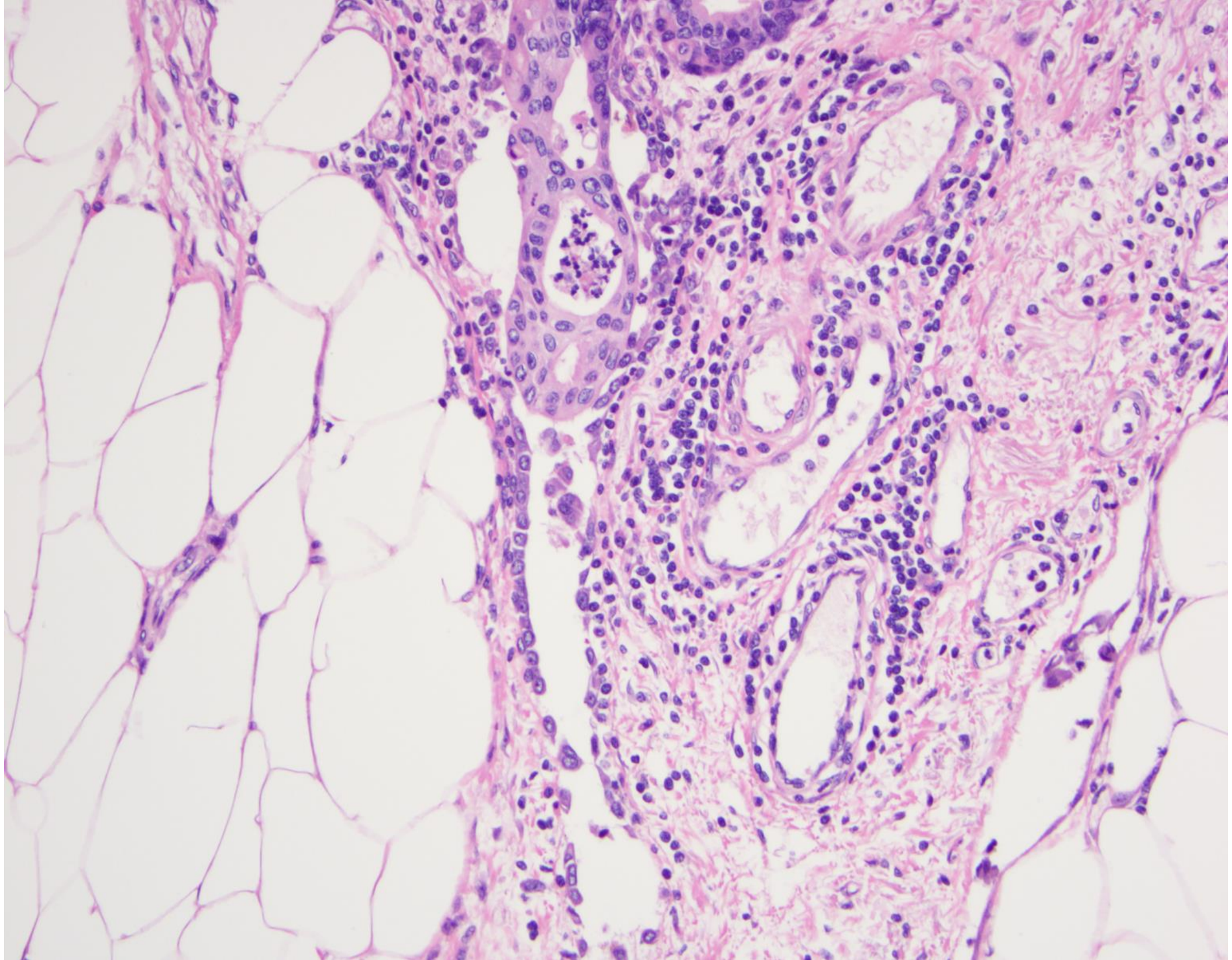
Abbreviations: DFS, disease-free survival; diff, difference; EL, elastic lamina invasion; OS, overall survival; RR: recurrence rate; sig, significantly.

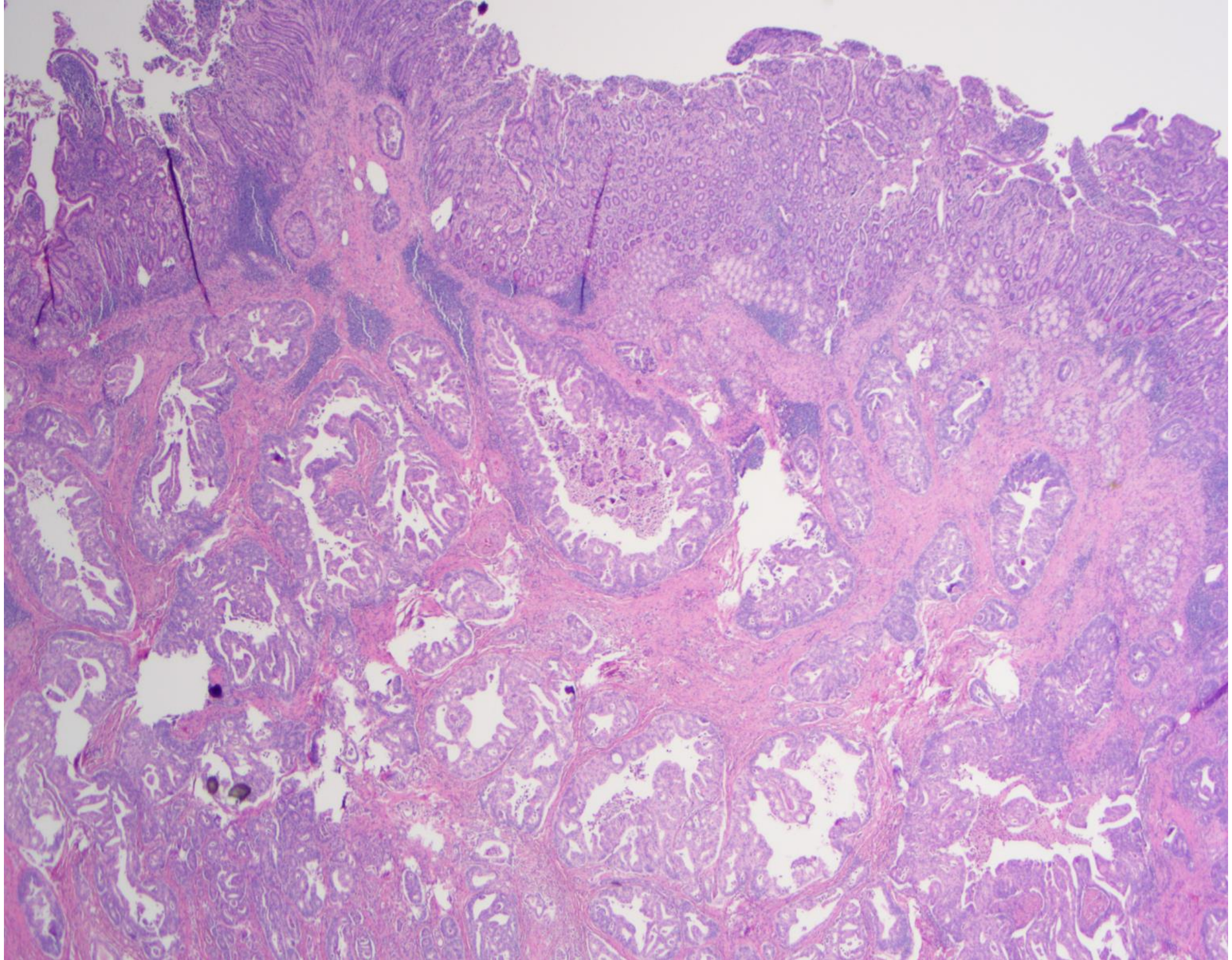
[a] In Kojima 2010, results significant only in colon not in rectum.

* Frankel et al, Modern Pathology 2105



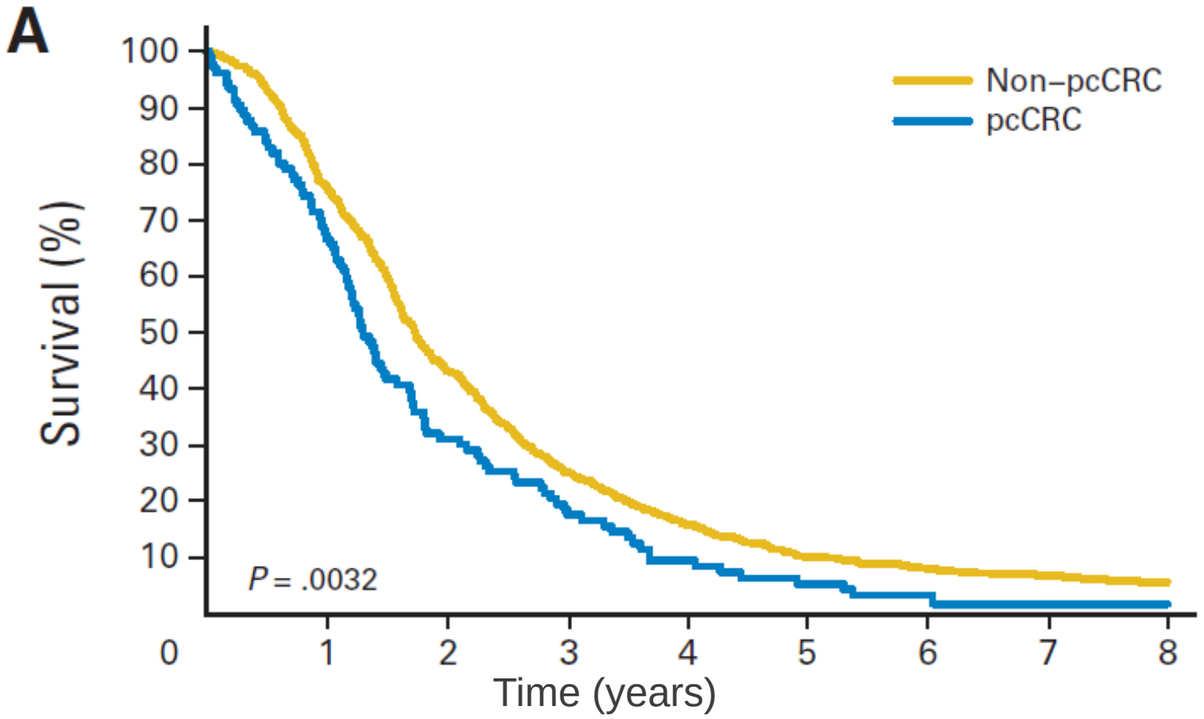


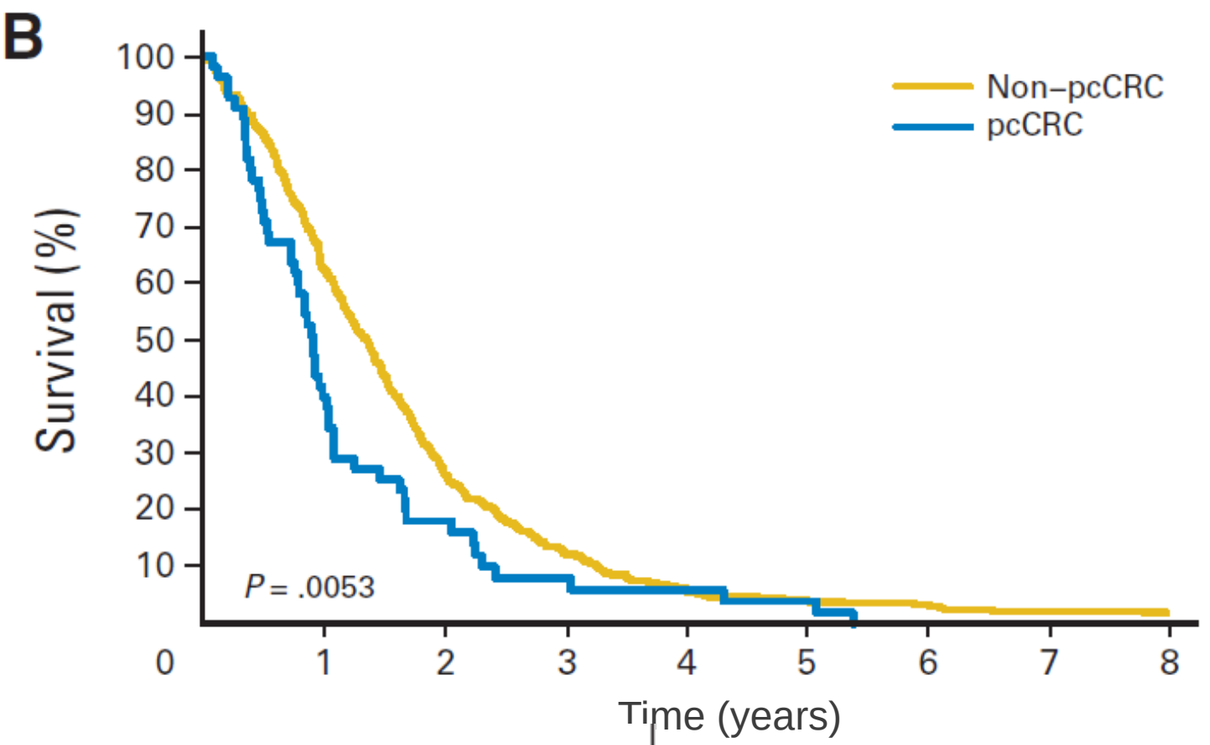


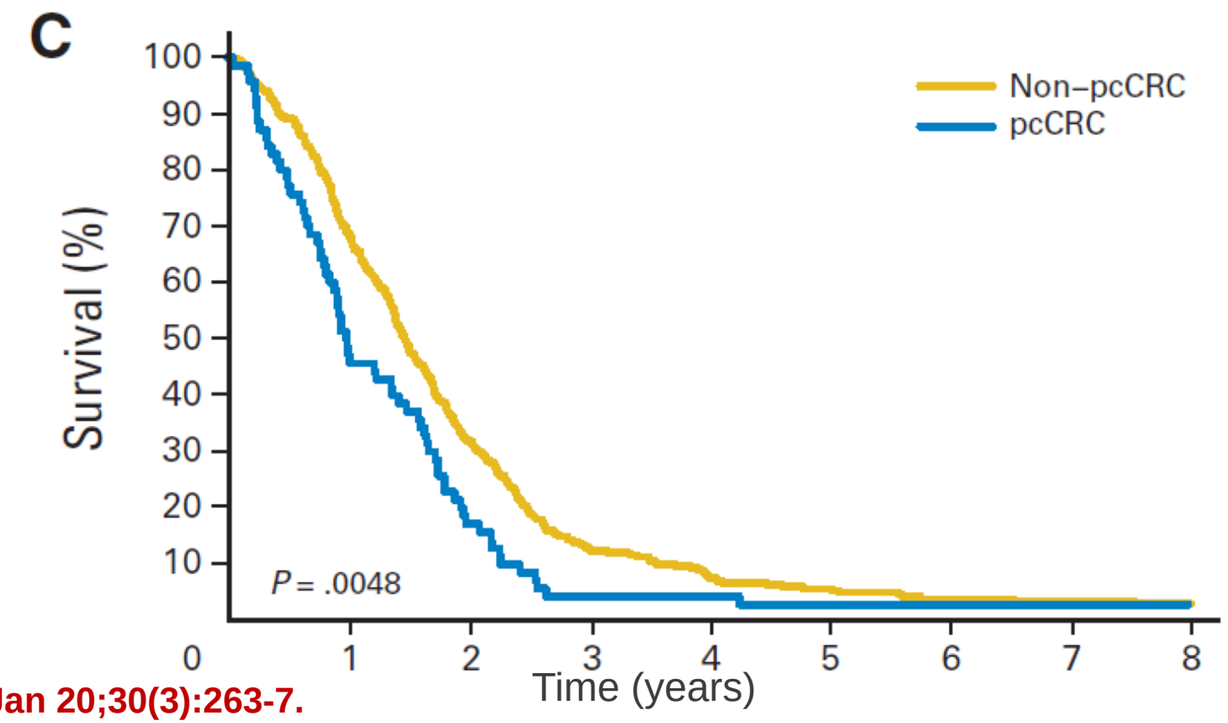


pM Stage

7th Edition		8th Edition	
Distance Metastasis (pM)			
pM1:	Distant metastasis	pM1:	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
pM1a:	Metastasis to single organ or site (eg liver, lung, ovary, nonregional lymph node)	pM1a:	Metastasis to one site or organ is identified without peritoneal metastasis
pM1b:	Metastasis to more than 1 organ/site or to the peritoneum	pM1b:	Metastasis to two or more sites or organs is identified without peritoneal metastasis
		pM1c:	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases







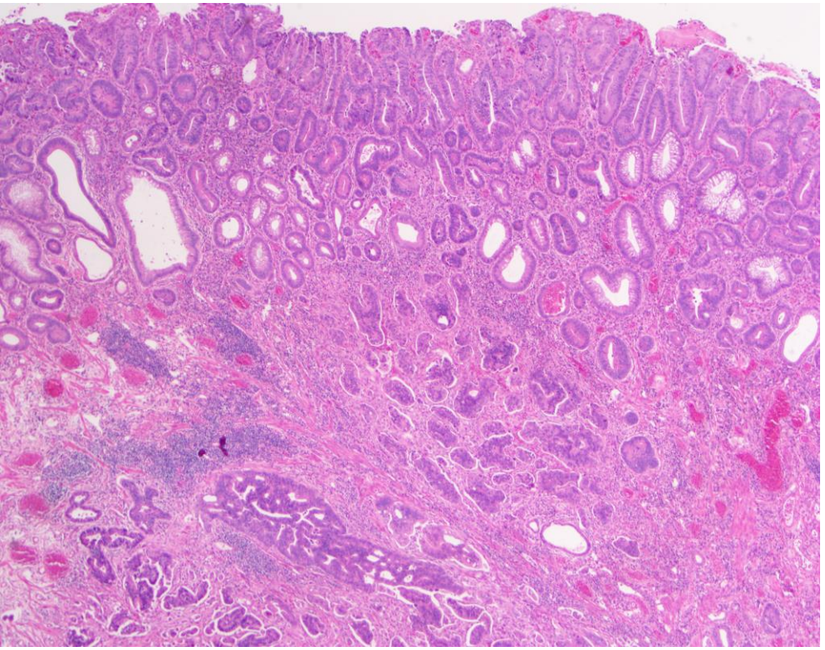
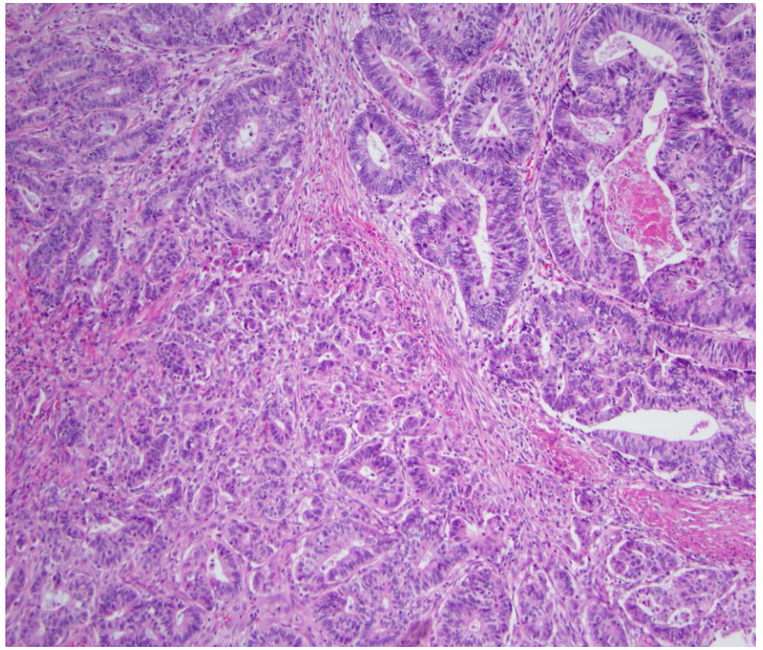
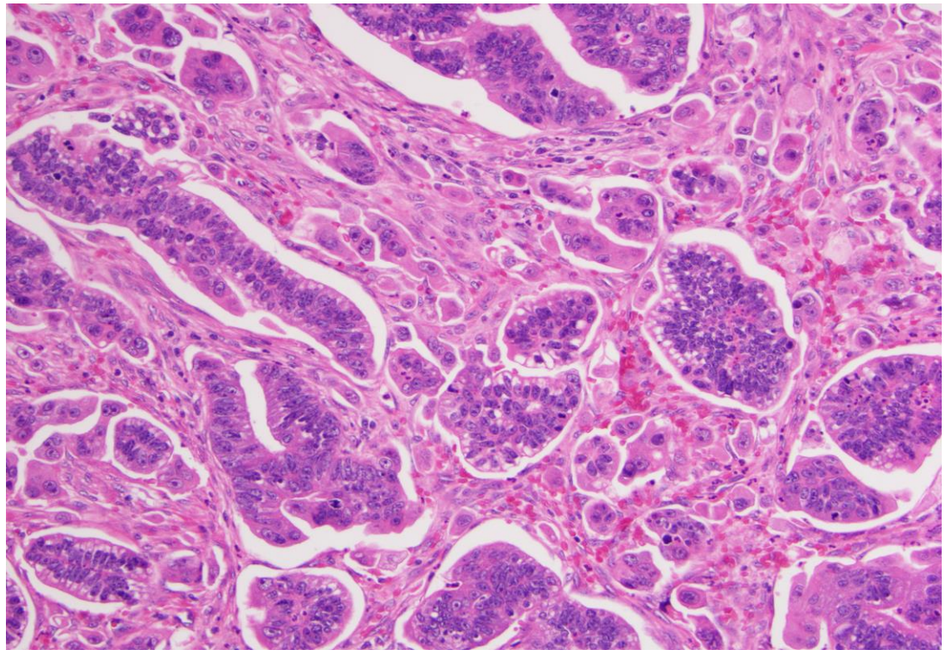
Franko J. et al. J Clin Oncol. 2012 Jan 20;30(3):263-7.

Histologic Type

WHO Classification of Carcinoma of the Esophagus

7th Edition	8th Edition
Adenocarcinoma	Adenocarcinoma
Mucinous (colloid) adenocarcinoma (greater than 50% mucinous)	Mucinous (colloid) adenocarcinoma (greater than 50% mucin)
Signet-ring cell carcinoma (greater than 50% signet-ring cells)#	Signet-ring cell carcinoma (greater than 50% signet-ring cells)
Squamous cell carcinoma	Medullary carcinoma
Adenosquamous carcinoma	Micropapillary adenocarcinoma
Medullary carcinoma	Serrated adenocarcinoma
Cribriform comedo-type, micropapillary and serrated adenocarcinomas as well as spindle cell carcinoma	Squamous cell carcinoma
Neuroendocrine carcinoma Large cell neuroendocrine carcinoma Small cell neuroendocrine carcinoma	Adenosquamous carcinoma
Mixed adenoneuroendocrine carcinoma	Spindle cell carcinoma
Undifferentiated carcinoma#	Poorly differentiated neuroendocrine carcinoma
	Large cell neuroendocrine carcinoma
	Small cell neuroendocrine carcinoma
	Mixed adenoneuroendocrine carcinoma
	Undifferentiated carcinoma
#These types are not generally graded.	

Micropapillary CA

- Usually a minor component
- Clear space around solid clusters
- Inverted brush border

Micropapillary CA

Table 3 Distribution micropapillary component *vs* metastasis

% MC	*Nodal metastasis (%)* P-*value*	*Distant metastasis (%)* P-*value*
	$\mathbf{8.49 \times 10^{-9}}$	**0.0479**
$<5\%$ $(n=319)$	127 (40)	25 (8)
≥ 5–10% $(n=43)$	32 (74)	7 (16)
>10–30% $(n=14)$	13 (93)	2 (14)
>30 $(n=3)$	3 (100)	1 (33)

Verdú et al. Modern Pathology (2011) 24,729-738

Table 2 Nodal metastasis of colorectal carcinomas with different percentages of MPC

Colorectal carcinoma	*Nodal metastasis*	
	No. of cases	*%*
No MP $(n=144)$	61	42.4
$\leq 10\%$ MP $(n=25)$	16	64.0
$>10\%$ MP $(n=9)$	9	100*

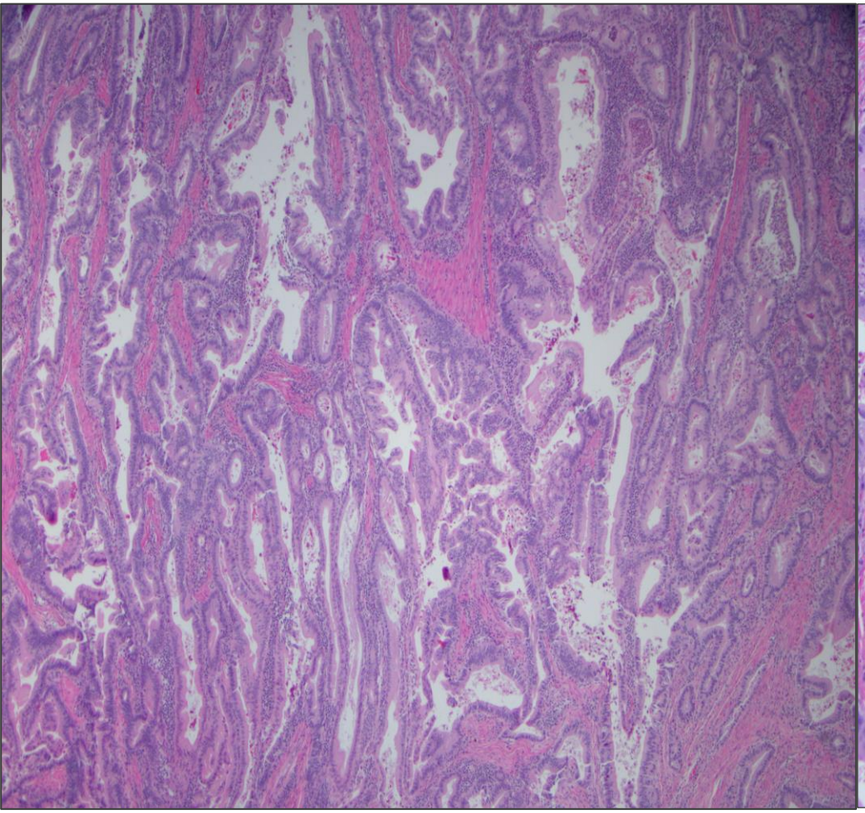
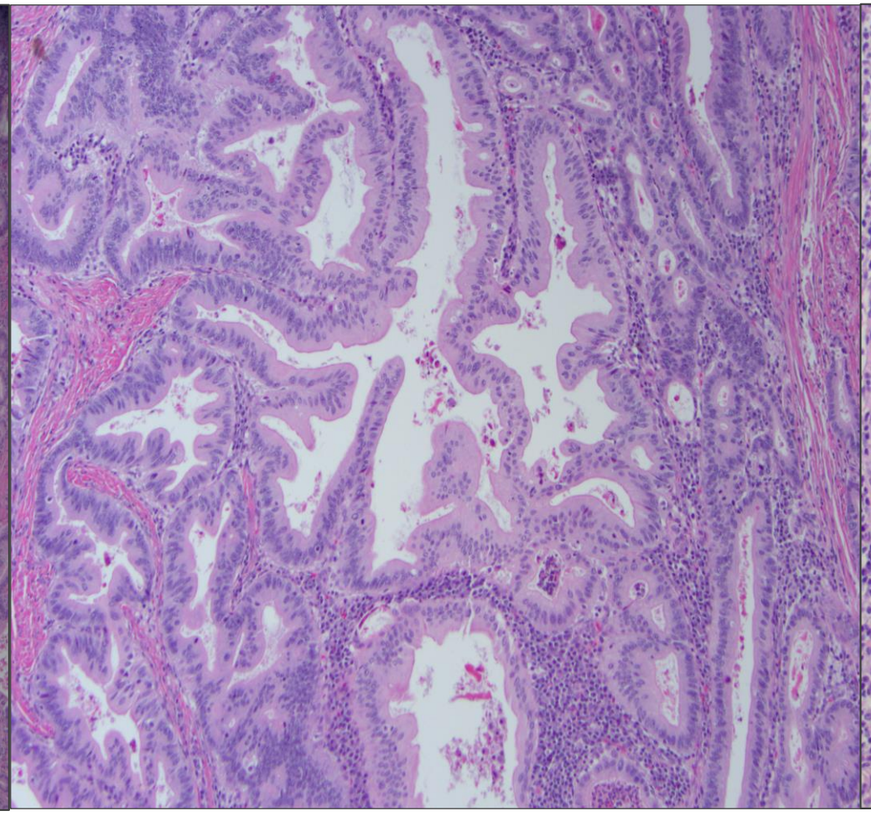
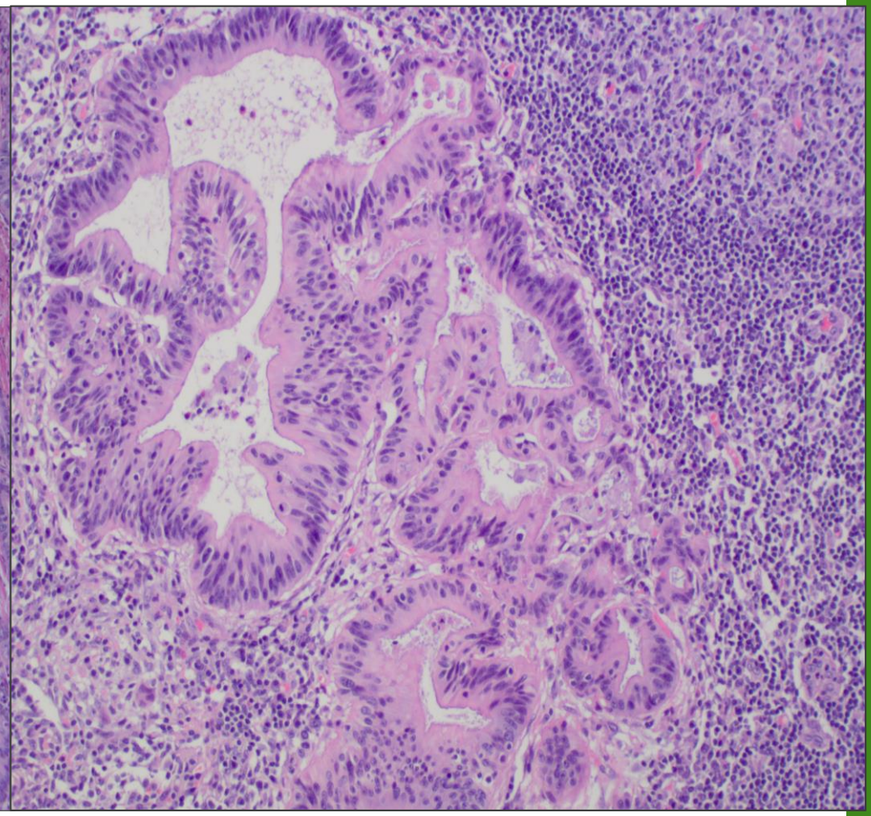
*$P=0.073$ when comparing with colorectal carcinomas with $\leq 10\%$ MPC and $>10\%$ MPC.

Table 3 Regression analysis of clinicopathologic factors for prediction of lymph node metastasis

	Hazard ratio	*95% CI*	P *value*
Age	0.99	0.962–1.018	0.486
Gender	0.538	0.252–1.151	0.145
Tumor location	1.496	0.821–2.728	0.202
Tumor grade	1.042	0.484–2.242	0.675
T stage	2.274	1.302–3.971	0.001
Tumor with MP component	4.343	1.479–12.754	0.004
Lymphovascular invasion	7.33	2.622–20.481	<0.001

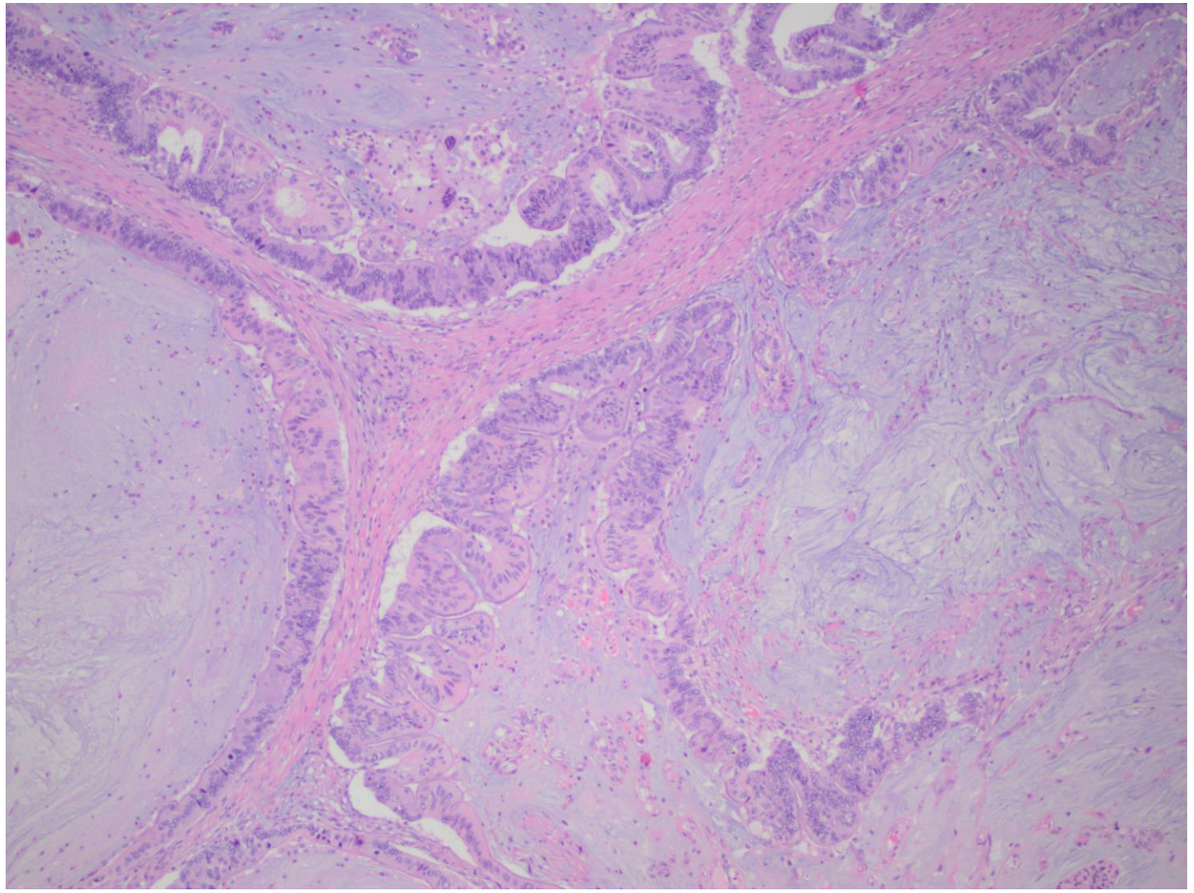
Haupt B. et al. Modern Pathology (2007) 20,729-738

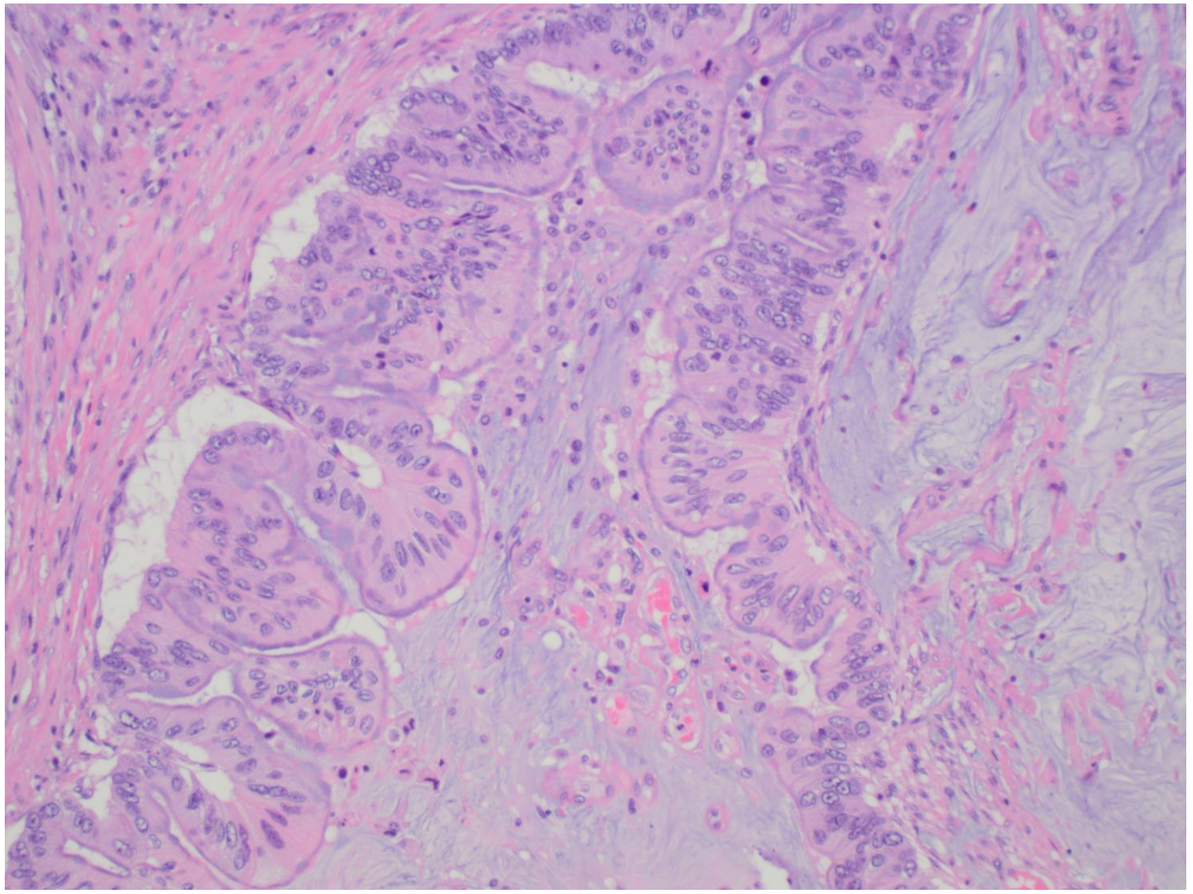
Serrated Adenocarcinoma

Resemble Traditional serrated adenomas
May retain serrated architecture in metastasis

Serrated Adenocarcinoma

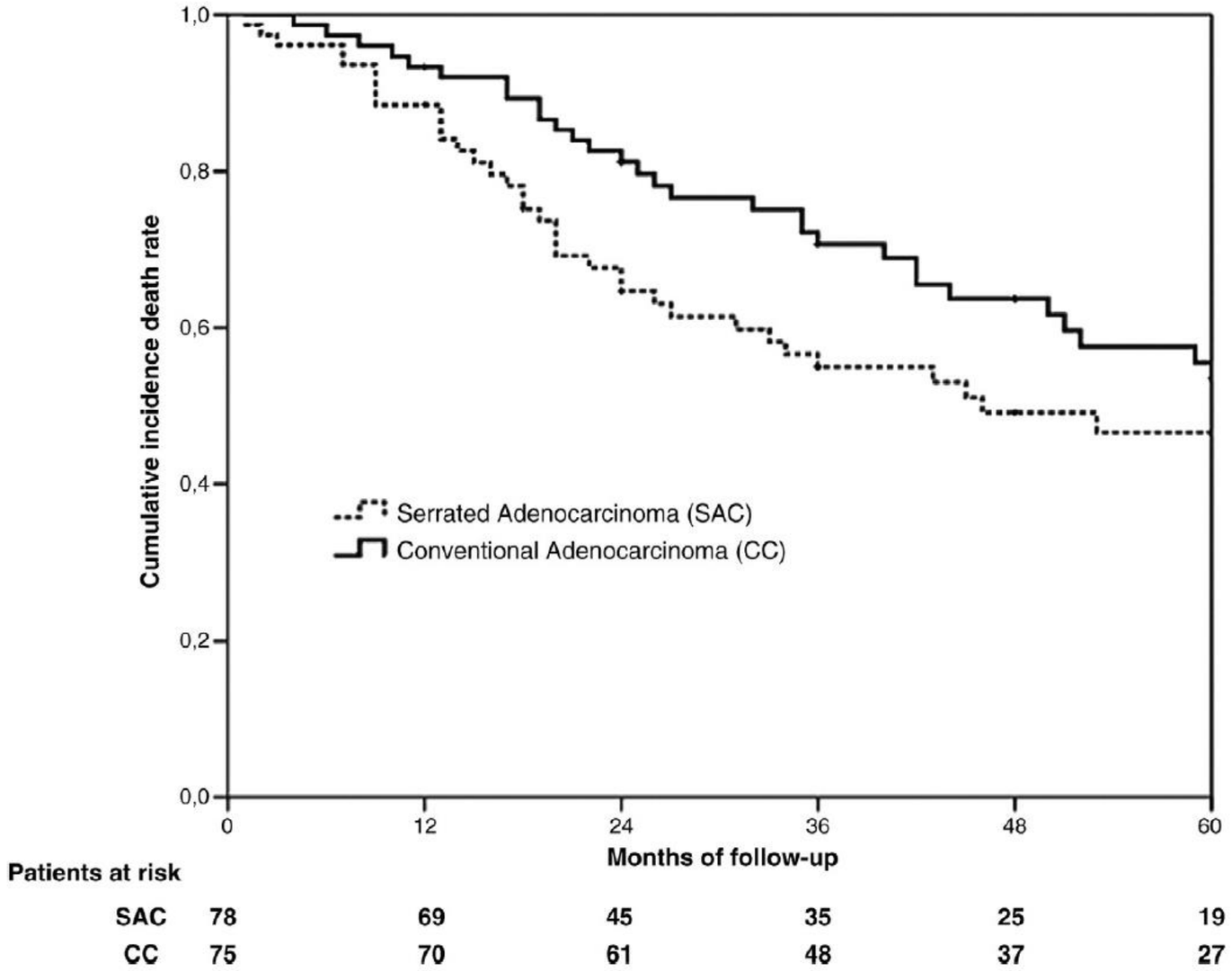




May overlap with mucinous adenocarcinomas

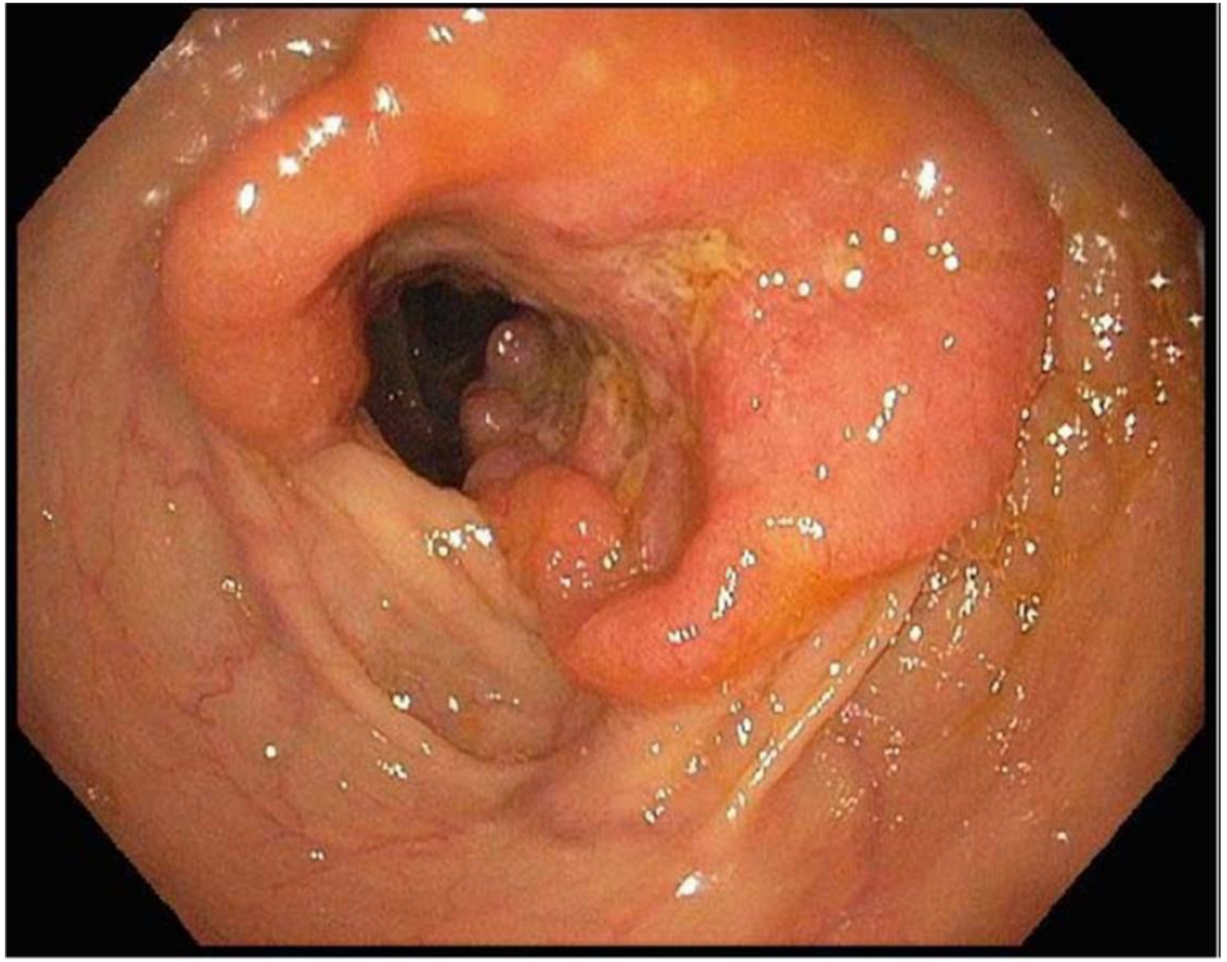
Serrated Adenocarcinoma

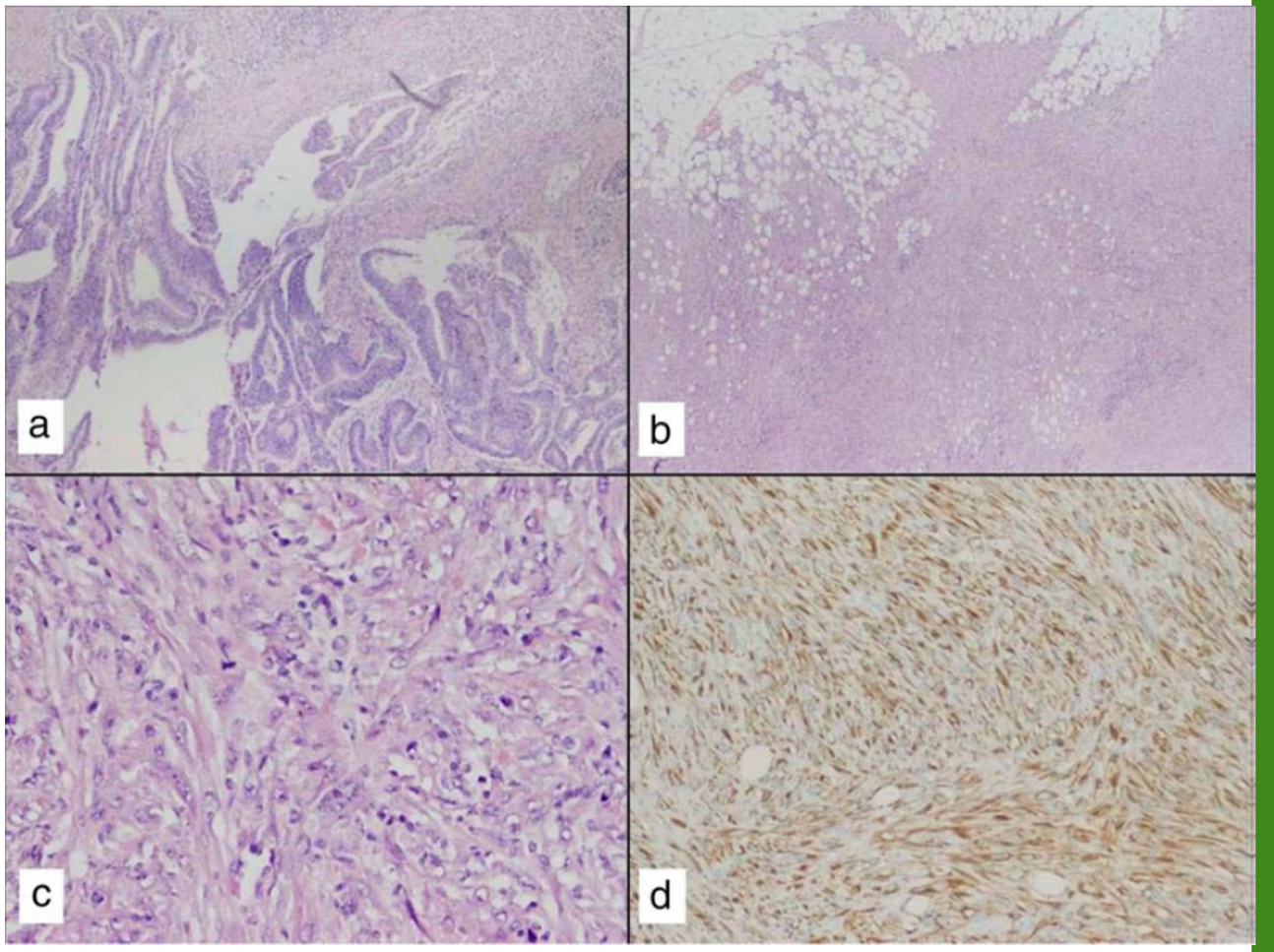
- **Associated with poor prognosis in some studies**
- **May be related to KRAS mutant status**



García-Solano J, et al.Hum Pathol. 2010 Oct;41(10):1359-68

Spindle cell Carcinoma





De Luca-Johnson et al, J Gastroenterol Hepatol. 2016 Jan;31(1):7

Histologic Grade

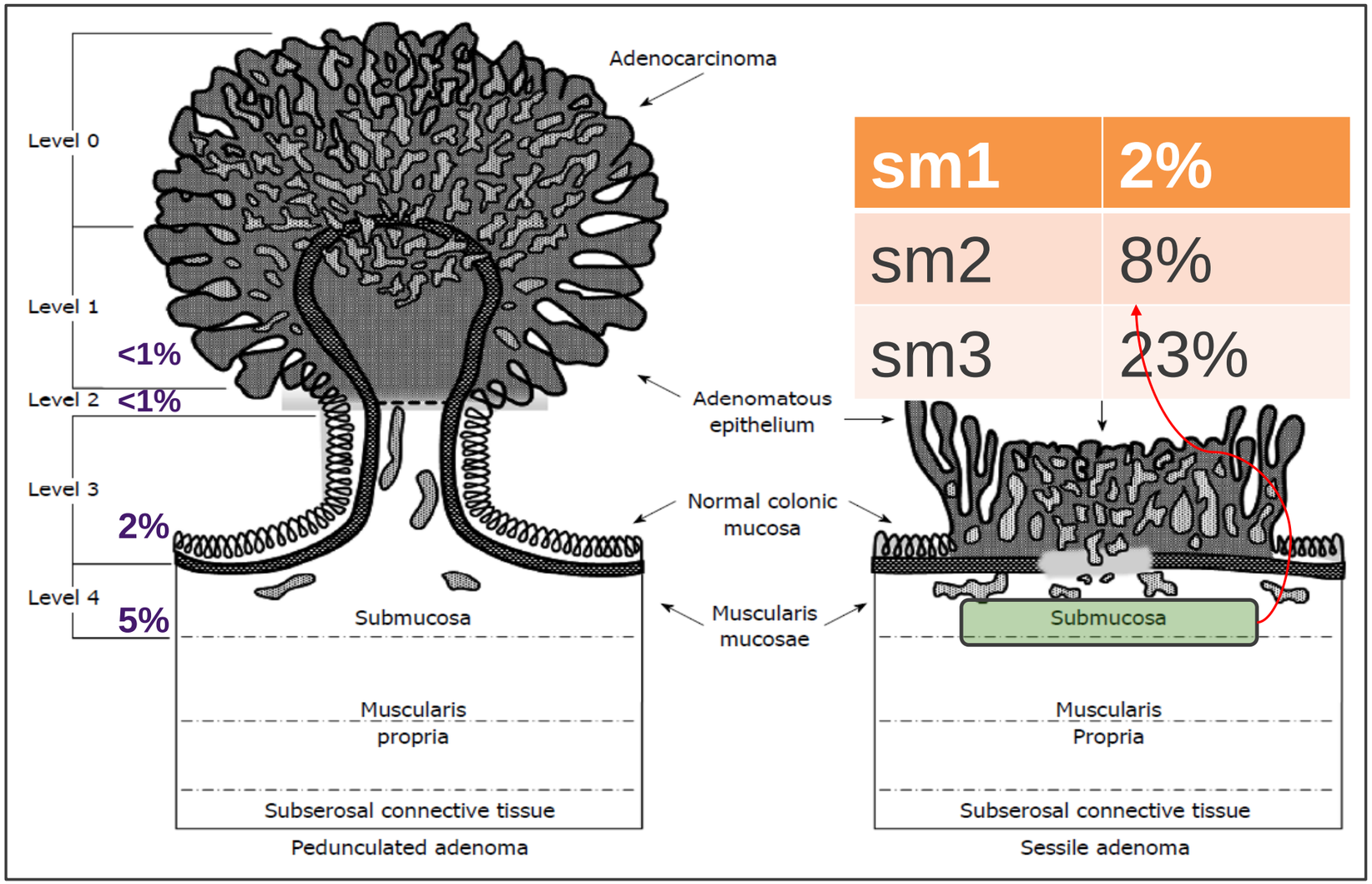
7th Edition		8th Edition	
Grade 1	Well differentiated	Grade 1	Well differentiated (>95% gland formation)
Grade 2	Moderately differentiated	Grade 2	Moderately differentiated (50-95% gland formation)
Grade 3	Poorly differentiated	Grade 3	Poorly differentiated (<50% gland formation)
Grade 4	Undifferentiated	Grade 4	Undifferentiated (no gland formation or mucin; no squamous or neuroendocrine differentiation)

Low grade: Greater than or equal to 50% gland formation
High grade: Less than 50% gland formation

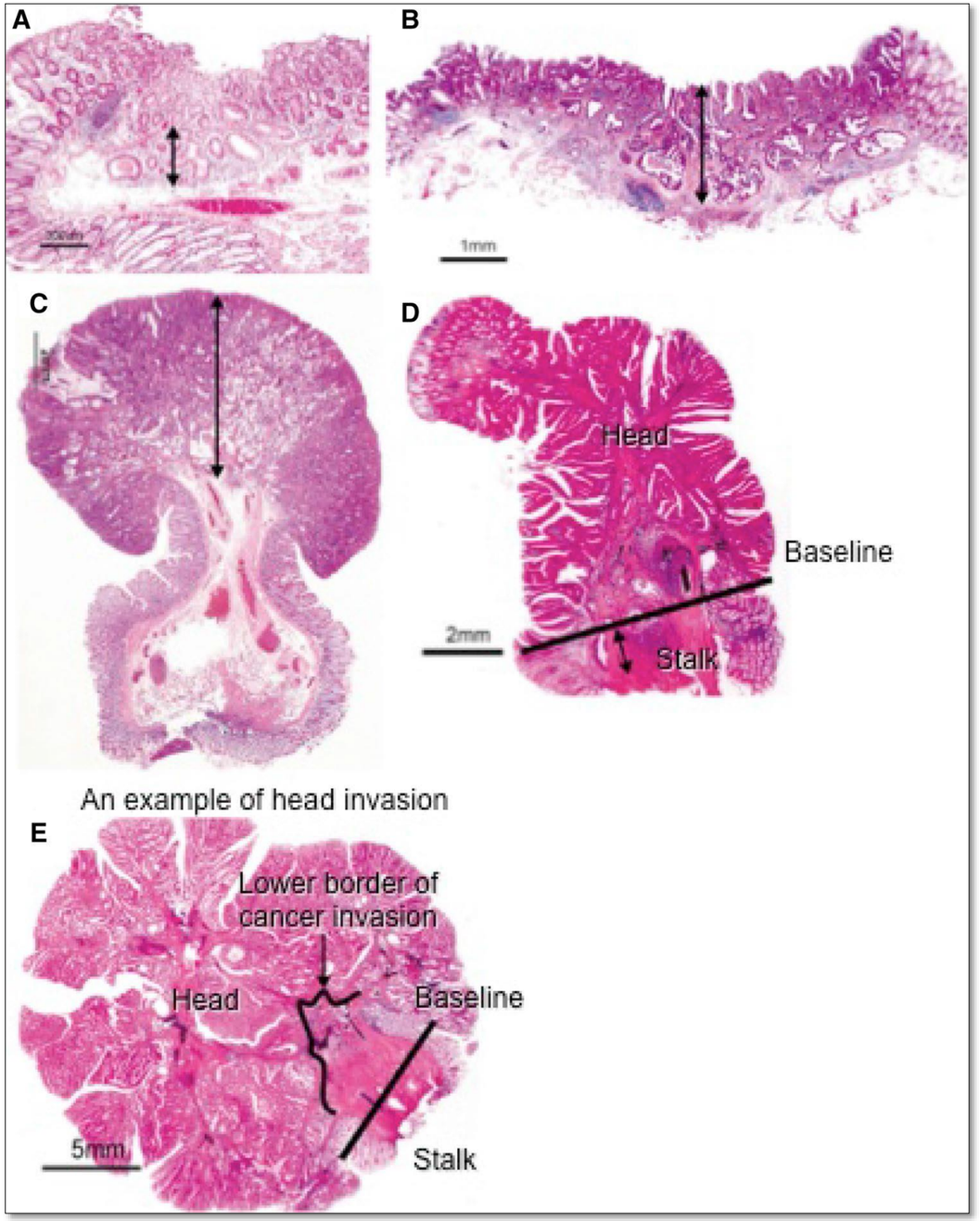
Carcinoma in Adenoma

7th Edition	8th Edition
Histologic grade	Histologic grade
Status of the resection margin	Status of the resection margin
Lymphatic/venous vessel involvement	Lymphatic/venous vessel involvement
Additional histologic factors: • Tumor budding • Depth/area of submucosal masses - Kikuchi level (sm 1-3) - Haggitt levels (head, neck, stalk, beyond stalk) • Measurement: >1mm from muscularis mucosa or from surface is adverse prognostic factor	

Depth of invasion in pedunculated and sessile malignant polyps (Haggitt & Kikuchi levels)



sm1	**2%**
sm2	8%
sm3	23%



Int J Clin Oncol. 2015; 20(2): 207–239.

Indications for Colectomy in Malignant Polyps

- **Poorly differentiated carcinoma**
- **Distance of invasive tumor from margin (1 mm or less = positive margin)**
- **Lymphovascular invasion**
- **Not universally reported features:**
  - **Tumor budding (high= ≥5 buds in 200x field)**
  - **Haggitt level in pedunculated polyps (level 4)**
  - **Kikuchi level in sessile polyps (Sm 2/3)**

Clinicopathologic Risk Factors and Risk of Recurrence in Malignant Polyps

	ER only			ER + SURG		
	Recurrence			Recurrence		
Factors	No	Yes	HR[a] (95% CI)	No	Yes	HR[a] (95% CI)
Location						
Right colon	53	2	0.2 (0.4–1)	42	0	N/A
Left colon	90	6	0.3 (0.1–1.2)	138	3	0.2 (0.4–1.4)
Rectum	27	6	Reference	20	2	Reference
Configuration						
Pedunculated	53	1	Reference	58	1	Reference
Sessile	64	7	6.2 (0.8–50.2)	99	3	1.7 (0.2–16.8)
Flat elevated	44	5	6.5 (0.8–55.8)	26	0	N/A
Depressed	9	1	7.2 (0.5–116.1)	17	1	3.0 (0.2–48.2)
Resection method						
En bloc	145	7	Reference	155	5	Reference
Piecemeal	25	7	5.3 (1.9–15.2)	45	0	N/A
Vertical margin						
–	161	7	Reference	167	3	Reference
+	9	7	16 (5.5–46.6)	33	2	3.3 (0.5–19.6)
Submucosal invasion						
Superficial	94	3	Reference	34	0	Reference
Deep	76	11	4.3 (1.2–15.3)	166	5	N/A
Lymphatic invasion						
–	167	12	Reference	183	4	Reference
+	3	2	7.3 (1.6–33.2)	16	1	2.2 (0.2–20)
Venous invasion						
–	166	12	Reference	181	4	Reference
+	4	2	6.1 (1.3–27.8)	19	1	2.5 (0.3–22)
Histologic type						
well, mod	164	11	Reference	179	3	Reference
por, sig, muc	6	3	5.7 (1.6–20.6)	21	2	5.3 (0.9–31.5)
Tumor budding						
Low grade	161	12	Reference	185	4	Reference
High grade	9	2	3.8 (0.9–17.3)	15	1	3 (0.3–26.6)
Surgical indication (JSCCR, 2010)						
No	87	1	Reference	25	0	Reference
Yes	83	13	12.9 (1.7–98.5)	175	5	N/A
Total	170	14		200	5	

>1000mm is deep submucosal invasion
≥5 buds in 200x is high grade tumor budding

Clin Gastroenterol Hepatol. 2014 Feb;12(2):292-302.e3.

Tumor Budding

- **Not required element**
- **Recommended for cancer in polyps and Stage I/II tumors**
- **Perform on H&E sections**
- **Select hotspot**
- **Total number in 0.785mm^2 (20X)**
- **Report total number and score**
  - **Low (0-4)**
  - **Intermediate (5-9)**
  - **High (≥10)**

Appendiceal Mucinous Neoplasms

Without infiltrative invasion

- Low-grade appendiceal mucinous neoplasm (LAMN)
- High-grade appendiceal mucinous neoplasm (HAMN)

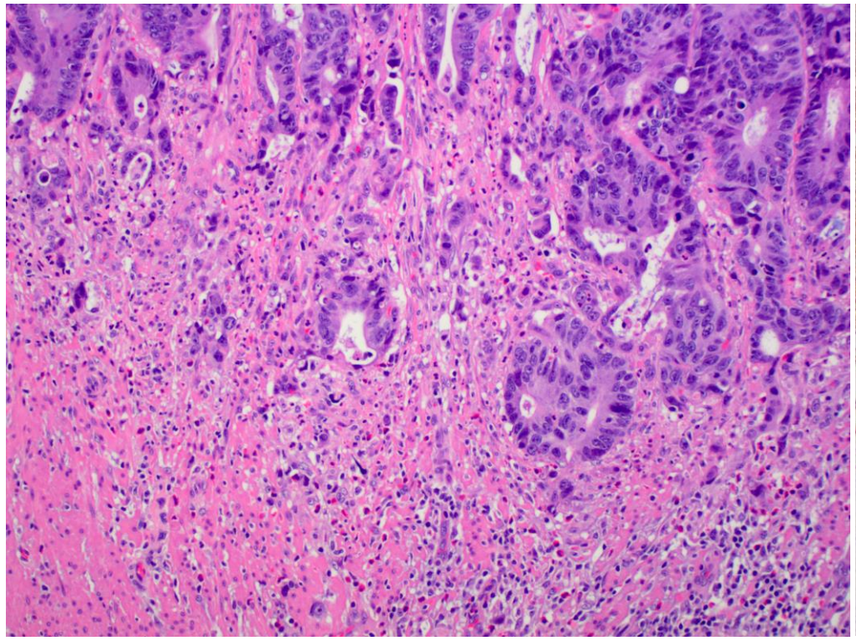
With infiltrative invasion

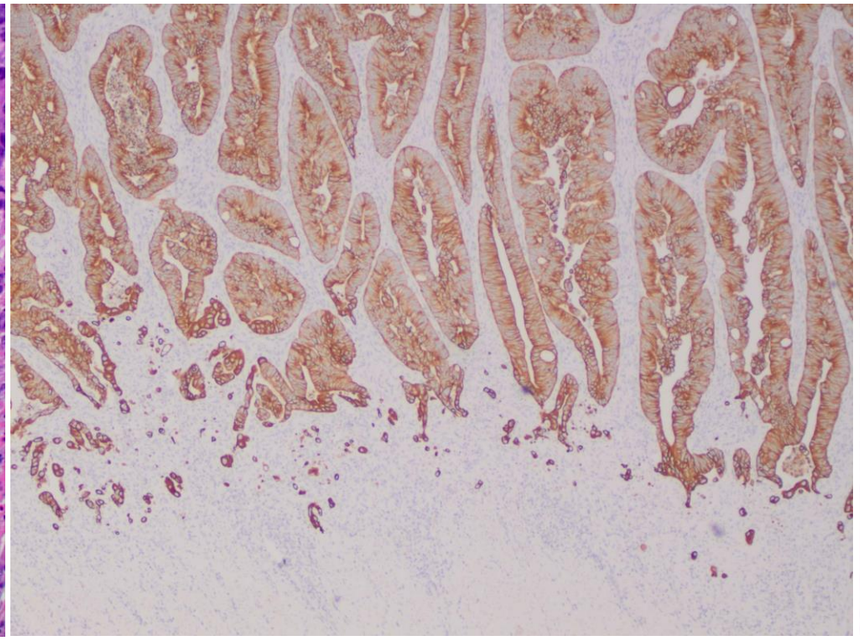
- Mucinous adenocarcinoma
- Mucinous adenocarcinoma with signet-ring cells (≤50%)
- Signet-ring cell carcinoma (>50%)

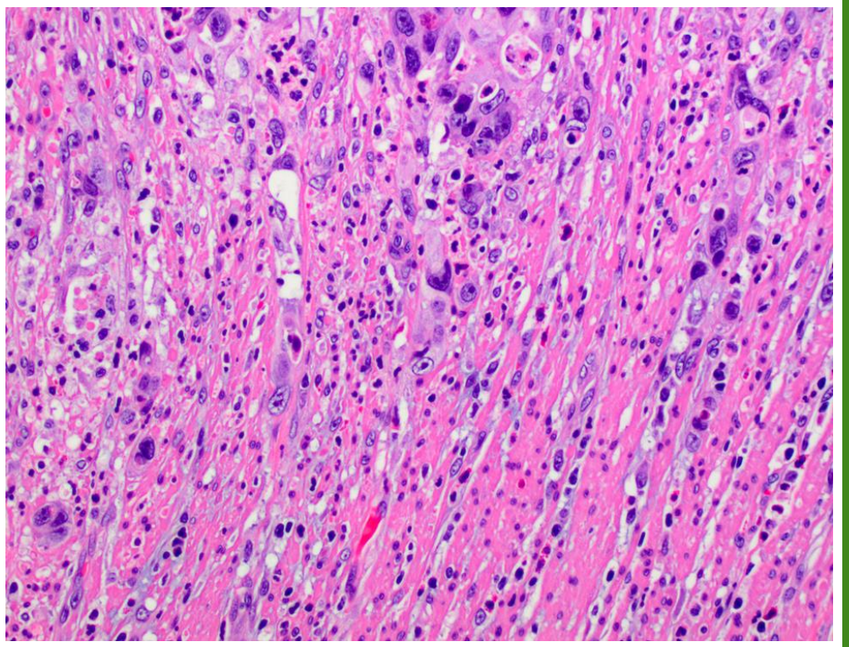
Carr NJ, et al. Am J Surg Pathol 2016; 40:14-26

Tumor Budding

Single cells or small clusters (<5) at invasive front







Tumor Budding

Predictors of Lymph Node Metastasis in T1 CRC*

All Studies

Study	Year	Definition	Positive	Negative	Univariate analysis
			Events (Total)	Events (Total)	OR (95%CI)
Kaneko	2007	Ueno	15(29)	24(239)	9.6(1.67-55.27)
Kawaura	2007	Ueno	8(20)	15(102)	3.9(0.77-19.43)
Suzuki	2009	Ueno	6(18)	3(106)	17.2(0.45-653.60)
Wada	2013	Ueno	3(12)	5(108)	6.9(0.28-168.65)
Subtotal			32(79)	47(555)	7.45 (4.27 – 13.02)

Heterogeneity: Chi = 0.95, df = 4 (P = 0.92), I2 = 0%
Test for over all effect: Z=-0.026 (P = 0.01)

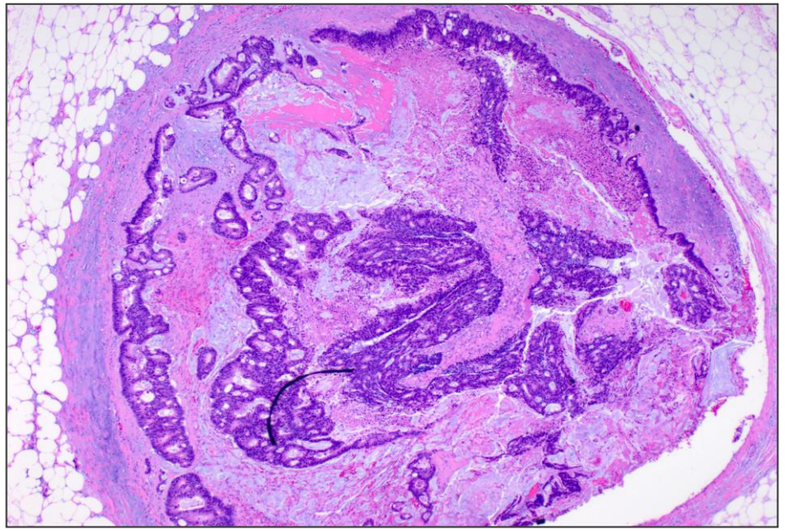
***Wada et al, J Gastroenterol 2015 (Meta-analysis 369 studies; LVI indentified by anti podoplanin)**

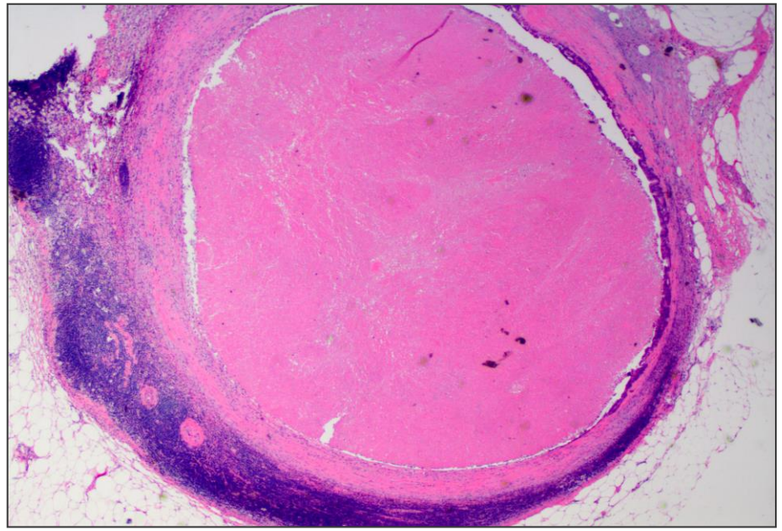
Tumor Deposits

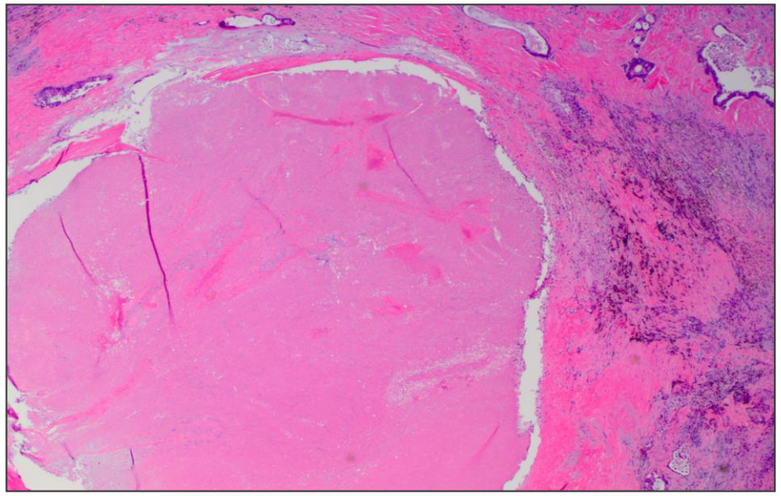
7th Edition	8th Edition
Discrete tumor deposits in pericolic or perirectal fat away from the leading edge of the tumor and showing no evidence of residual lymph node tissue, but within the lymphatic drainage of the primary carcinoma, are considered tumor deposits or satellite nodules and are not counted as lymph nodes replaced by tumor. Most examples are due to venous invasion and, less commonly, small vessel or perineural invasion.	A tumor focus in the pericolic/perirectal fat or in adjacent mesentery (mesocolic or rectal fat) within the lymph drainage area of the primary tumor, but without identifiable lymph node tissue or vascular structure. If the vessel wall or its remnant is identified (H&E, elastic, or any other stain), it should be classified as vascular (venous) invasion, and not as tumor deposit. Similarly, a tumor focus is present in or around a large nerve, should be classified as perineural invasion and not as tumor deposit. Size and shape of the tumor focus are not relevant for classification as a tumor deposit.
If accompanied by positive lymph nodes, do not use N1c	
Use N1c with caution in post-neoadjuvant therapy resections.	

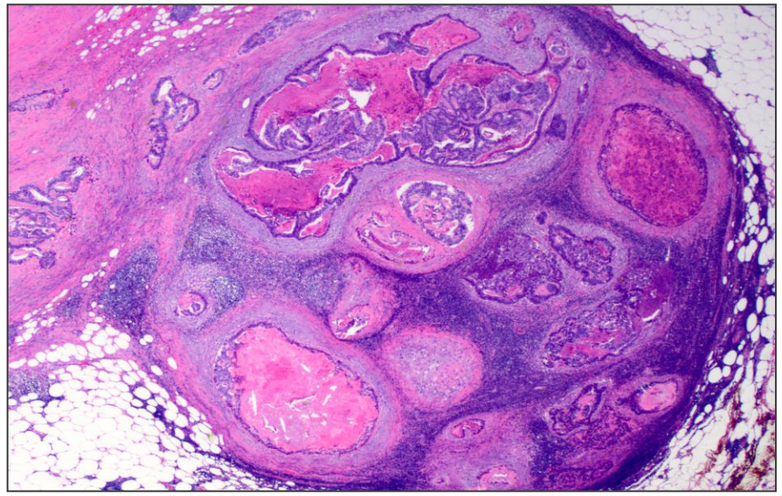
Tumor Deposits

Limitations of the Shape Criterion





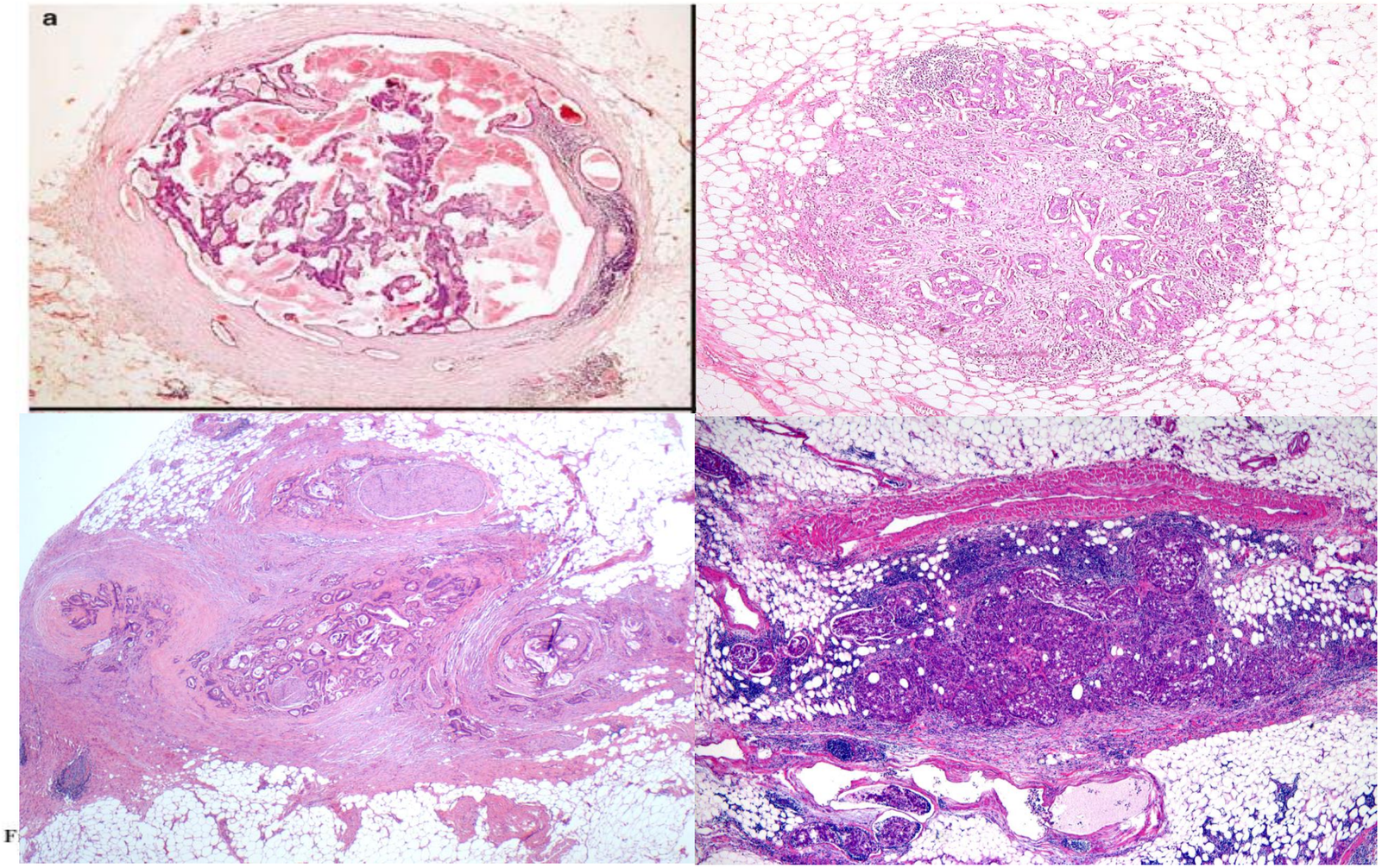




Venous Invasion

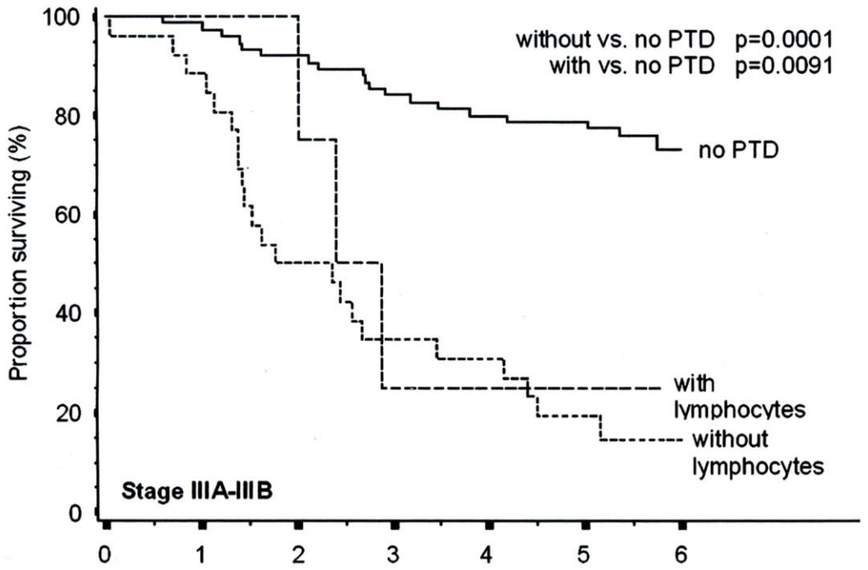
Nodal Invasion

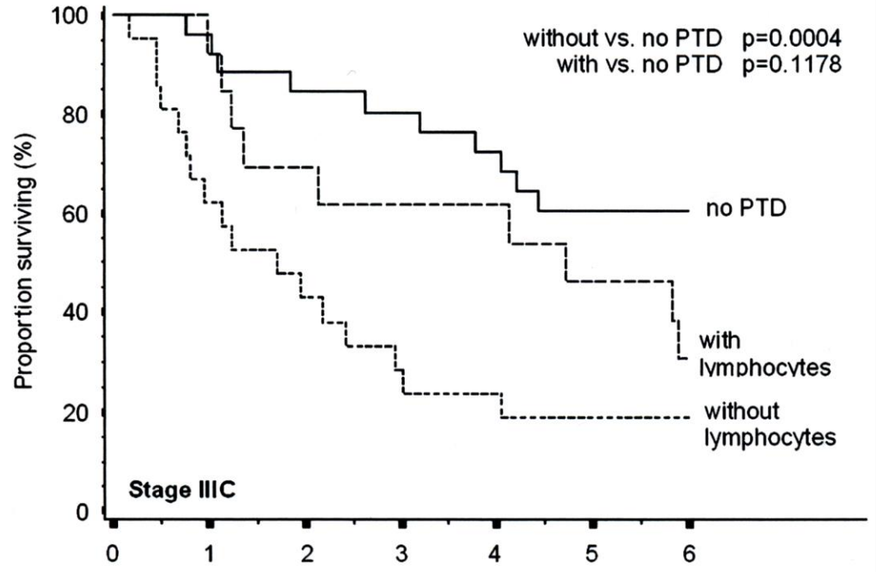
Pathological assessment of pericolonic tumor deposits in advanced colonic carcinoma: relevance to prognosis and tumor staging



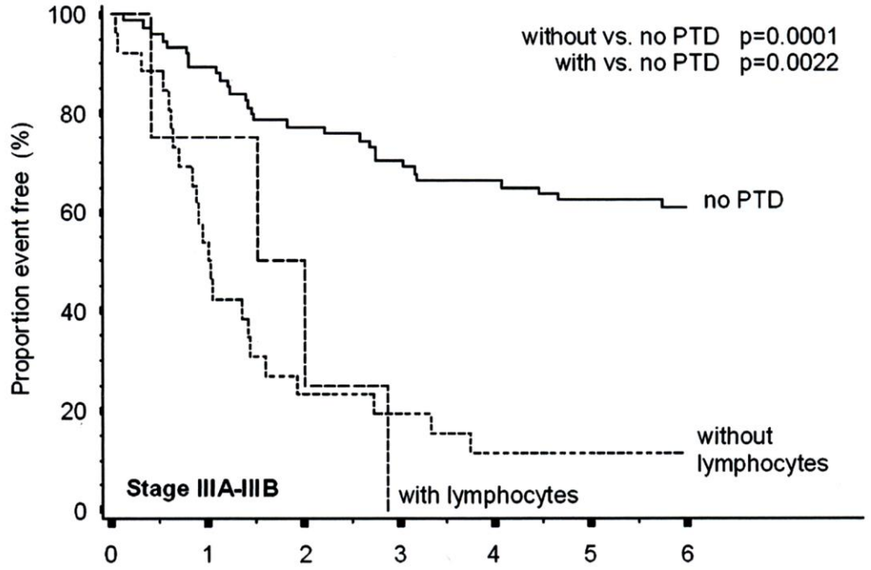
Puppa, et al Modern Pathology (2007) 1-13

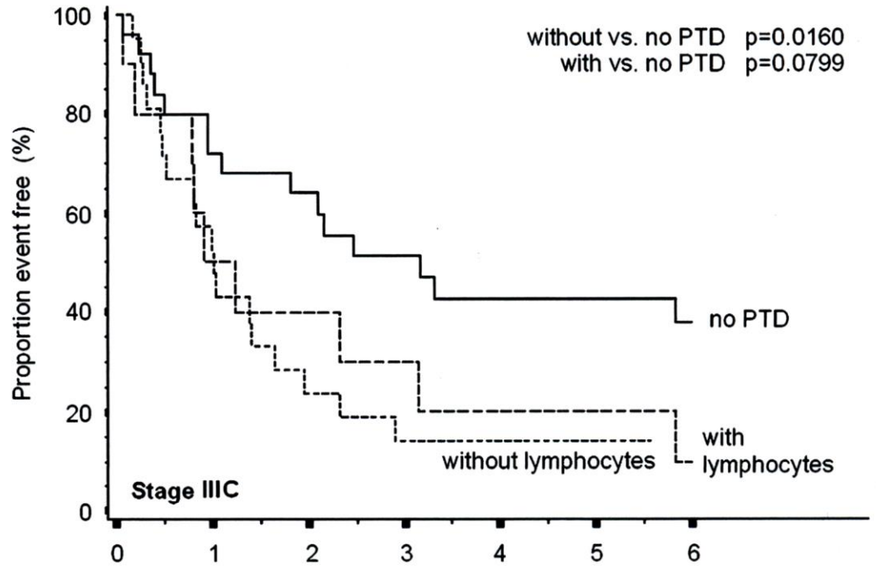
Overall survival





Disease free survival





Puppa G. Modern Pathol 2007;20

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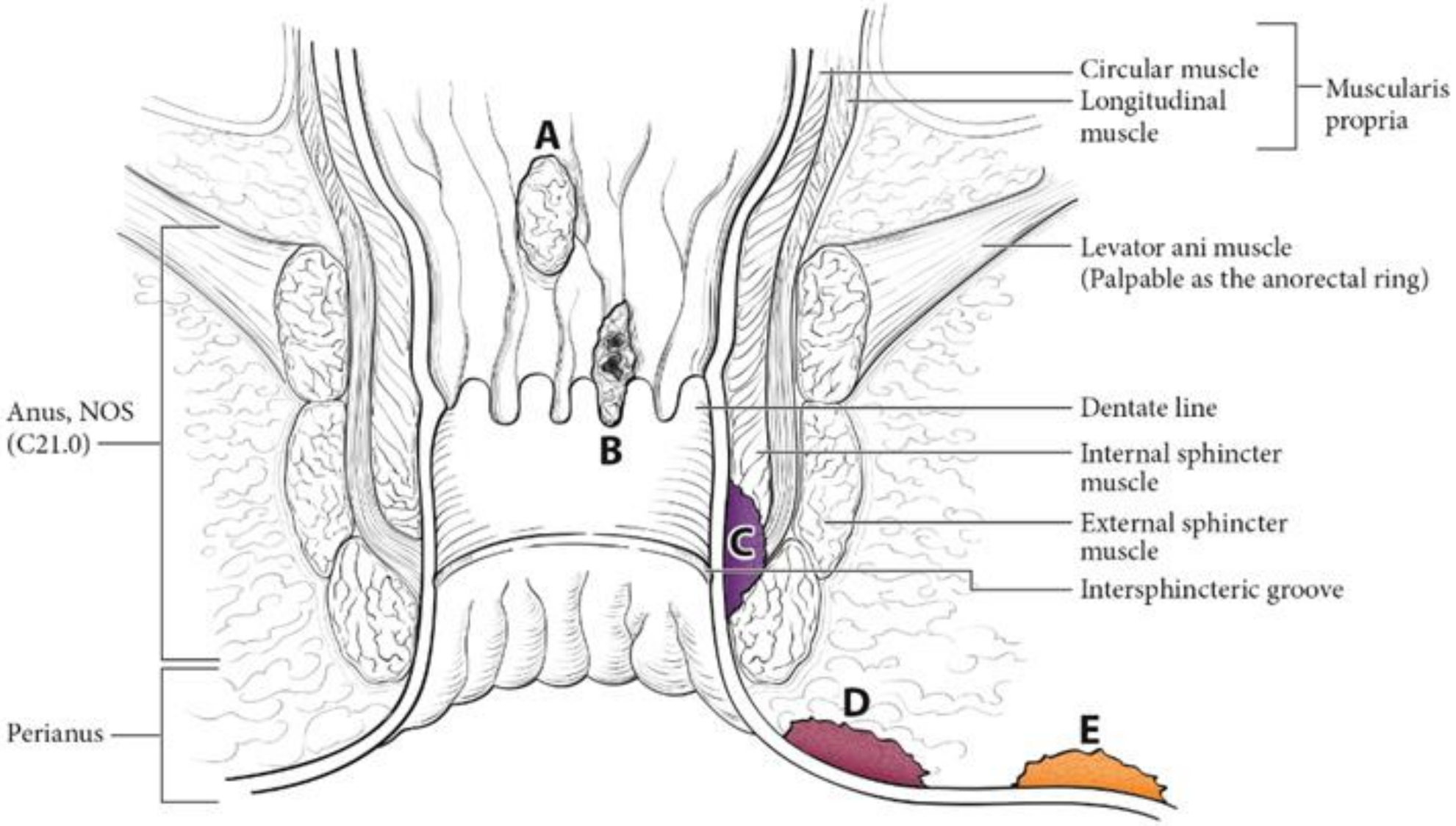
Anal Canal

Amitabh Srivastava, MD

Tumor Site

7th Edition	8th Edition
Anal canal	Anal canal
Anorectal junction	Perianal region
Anus, not otherwise specified	Anus, not otherwise specified
Unknown	Unknown
Other (specify): _____	Other (specify): _____

Tumor Site

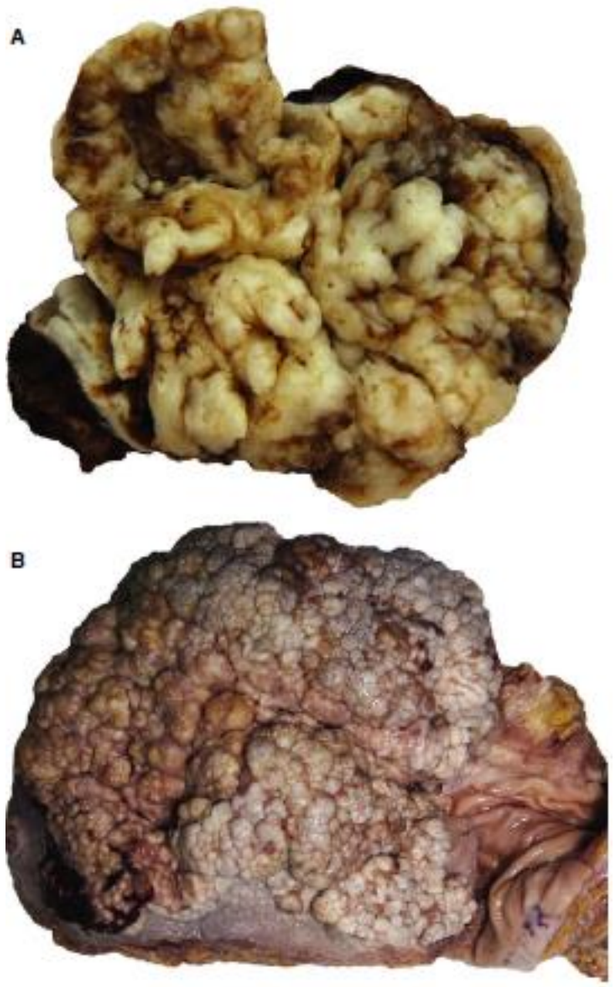

Circular muscle
Longitudinal muscle
Muscularis propria
A
Levator ani muscle
(Palpable as the anorectal ring)
Anus, NOS
(C21.0)
B
Dentate line
Internal sphincter muscle
C
External sphincter muscle
Intersphincteric groove
Perianus
D
E

Histologic Type

7th Edition	8th Edition
Squamous cell carcinoma	Squamous cell carcinoma
	Verrucous carcinoma
	Basal cell carcinoma
Adenocarcinoma	Adenocarcinoma
Mucinous adenocarcinoma	Mucinous adenocarcinoma
High-grade neuroendocrine carcinoma Large cell neuroendocrine carcinoma Small cell neuroendocrine carcinoma	Large cell neuroendocrine carcinoma Small cell neuroendocrine carcinoma Neuroendocrine carcinoma (poorly differentiated)#
Undifferentiated carcinoma	
Paget disease	
Other (specify):_____	Mixed adenoneuroendocrine carcinoma
	Undifferentiated carcinoma
	Paget disease
	Carcinoma, type cannot be determined
	Other histologic type not listed (specify):_____

Note: Select this option only if large cell or small cell cannot be determined

Verrucous carcinoma



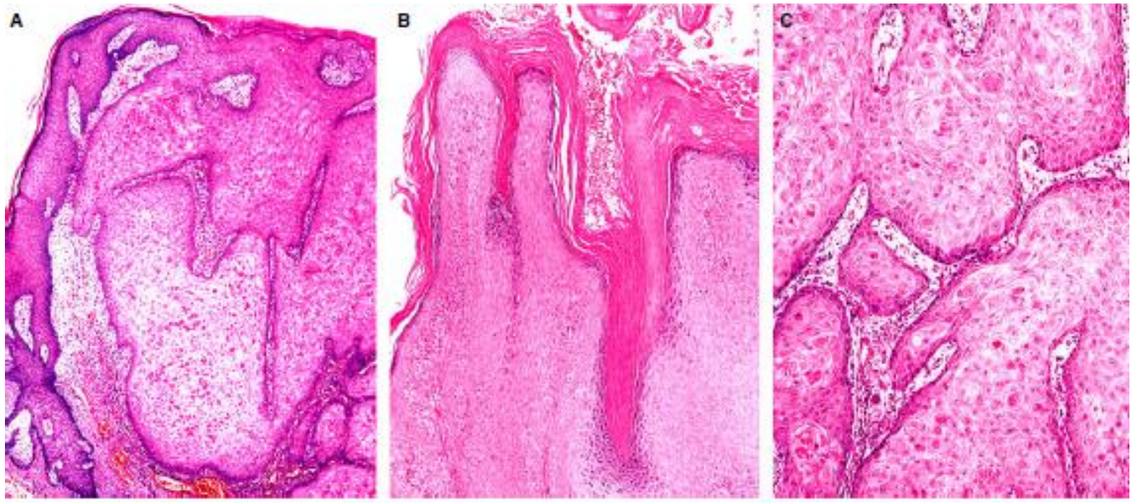
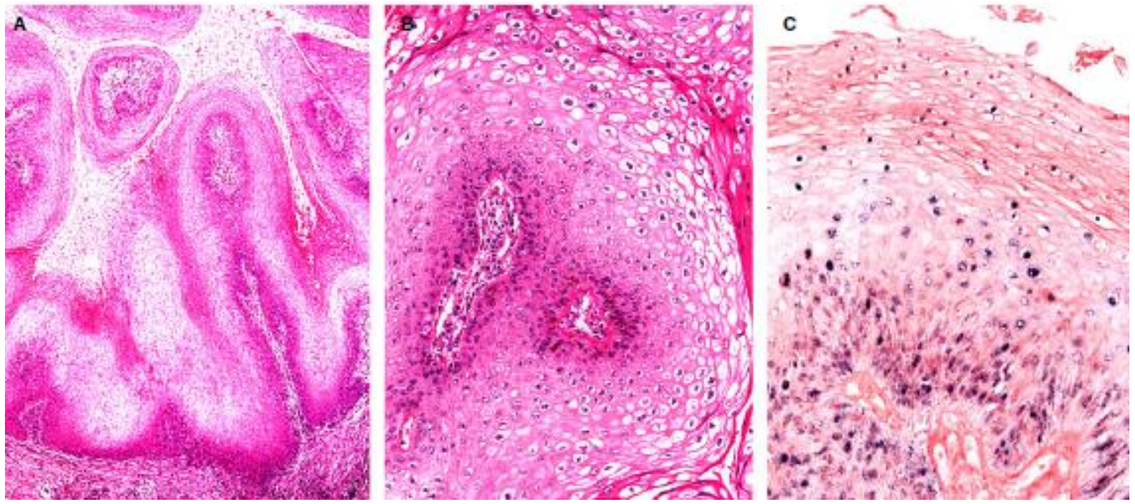
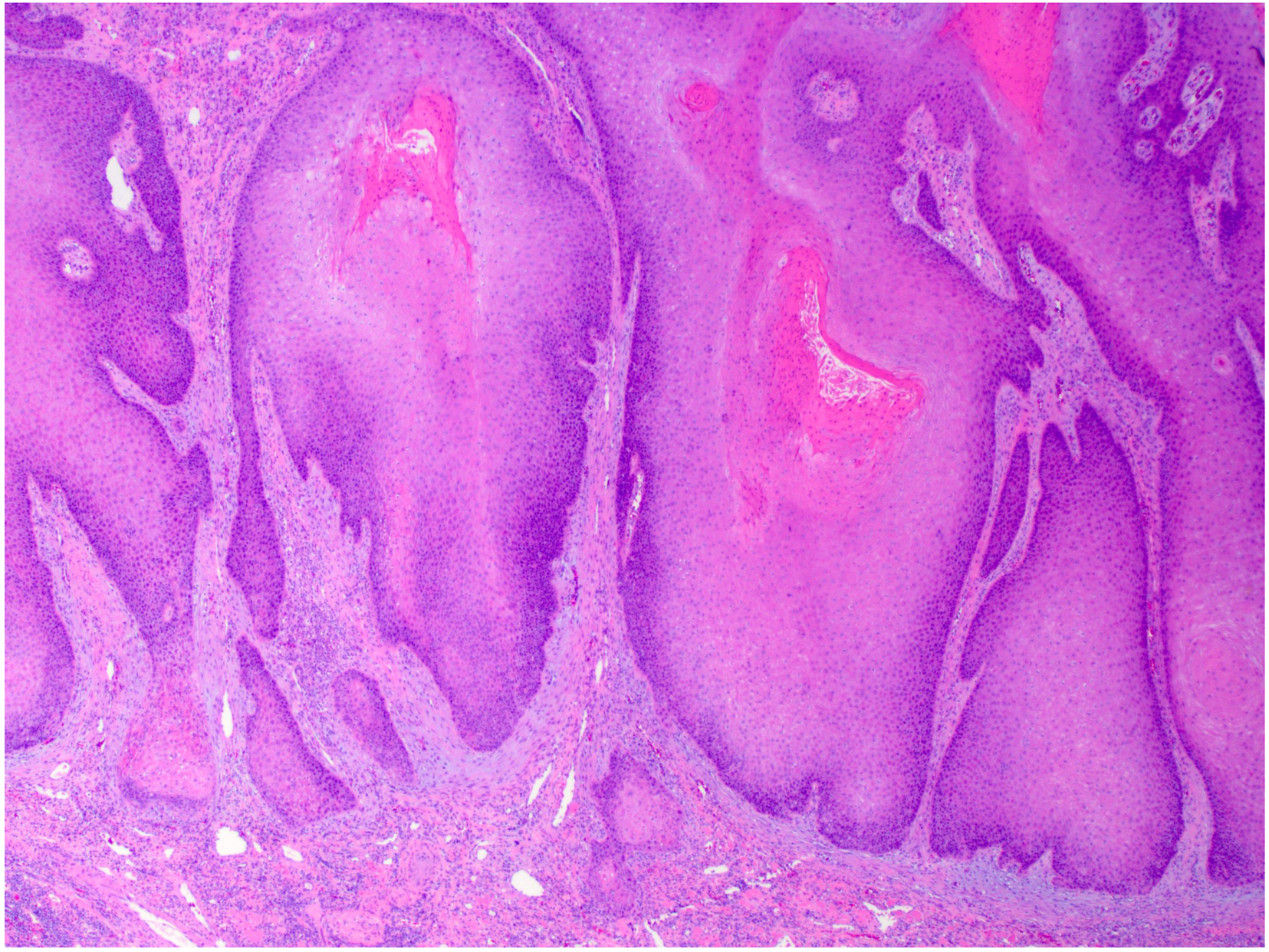


Figure 2. Verrucous carcinoma. A, Transition from the normal squamous epithelium to verrucous carcinoma. B, Elongated projections wit narked surface keratosis (church spire keratosis). C, The invasive part of the tumour is composed of thick islands of well-differentiated squ nous epithelium with no atypia.

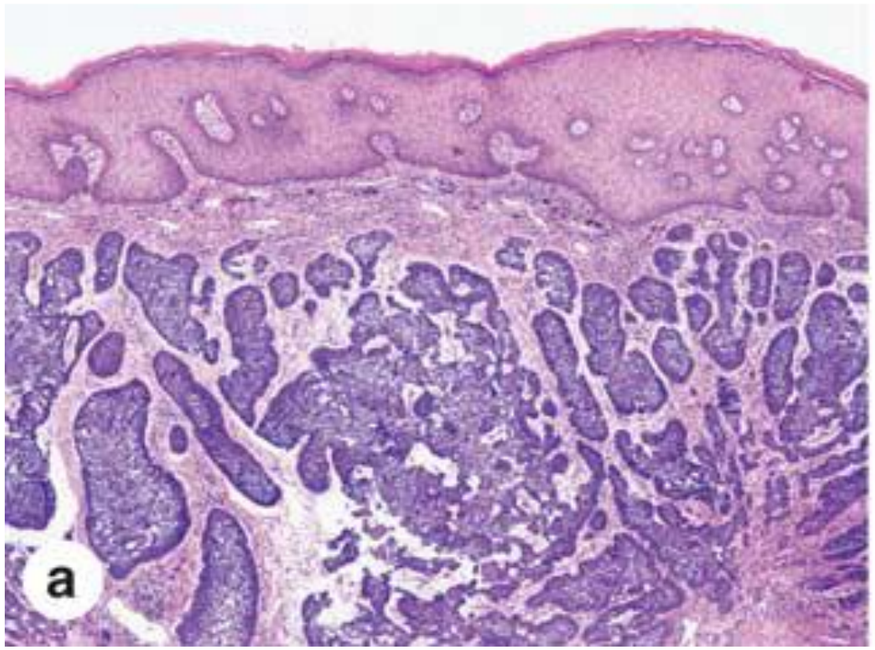


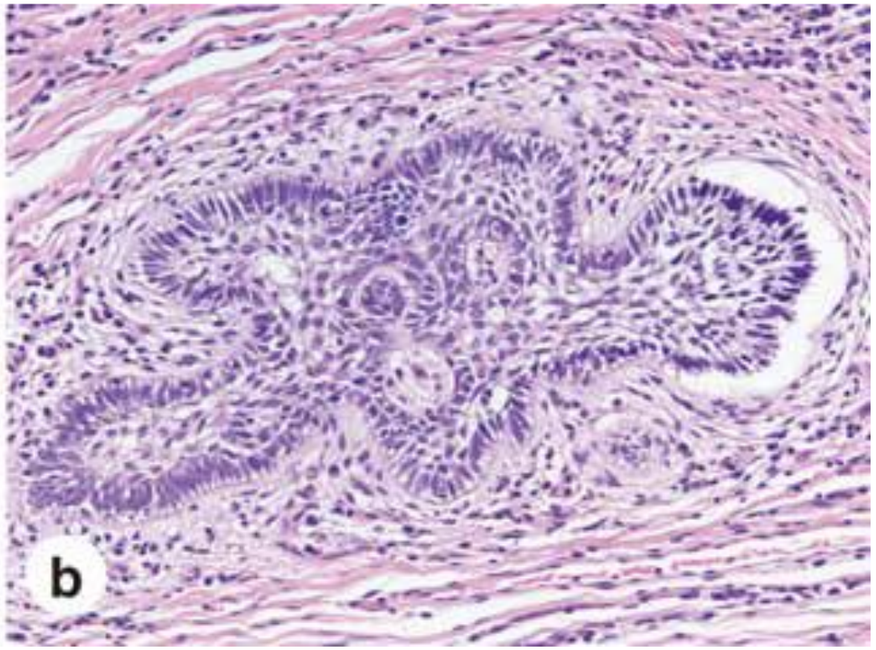
Zidar, et al. Histopathology 2017, 70, 938-945

Anal Verrucous carcinoma



Basal cell carcinoma





Perianal location
Nodular subtype most common
Retraction artifact common
No atypical mitoses
No in-situ squamous neoplasia
Lack of diffuse CDKN2A and Sox2 expression

Patil DT, et al Modern pathology (2013) 26, 1382-1389

Local Excision: Margins

7th Edition	8th Edition
Margins (select all that apply)	Deep Margin
Cannot be assessed	Cannot be assessed
Margins uninvolved by invasive carcinoma	Uninvolved by invasive carcinoma
Distance of invasive carcinoma from closest margin:_ mm or_____cm	Distance of invasive carcinoma from closest margin (millimeters *or* centimeters): ___ mm *or* ___ cm
Specify margin (if possible): _____	Involved by invasive carcinoma
Carcinoma in situ (high-grade squamous intraepithelial lesion) absent	Mucosal Margin
Carcinoma in situ (high-grade squamous intraepithelial lesion) present	Cannot be assessed
Margin(s) involved by invasive carcinoma	Uninvolved by invasive carcinoma, or precursor
Specify margin (if possible): _____	Uninvolved by invasive carcinoma but involved by precursor
Not applicable (specify reason): __	Involved by invasive carcinoma but not by precursor
	Involved by invasive carcinoma AND precursor
	Involved by: Intramucosal adenocarcinoma + Specify location (eg, o'clock position), if possible: _____ High-grade dysplasia + Specify location (eg, o'clock position), if possible: _____ Adenoma + Specify location (eg, o'clock position), if possible: _____

pN Stage

7th Edition	8th Edition
Regional Lymph Nodes (pN)	
pNX: Cannot be assessed	pNX: Regional lymph nodes cannot be assessed
pN0: No regional lymph node metastasis	pN0: No regional lymph node metastasis
pN1: Metastasis in perirectal lymph nodes	pN1: Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes
pN2: Metastasis in unilateral internal iliac and/or inguinal lymph node(s)	pN1a: Metastasis in inguinal, mesorectal, or internal iliac lymph nodes
pN3: Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes	pN1b: Metastasis in external iliac lymph nodes
	pN1c: Metastasis in external iliac with any N1a nodes

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S1882 Applying the New AJCC Staging System to Daily Diagnostic Practice: Gastrointestinal Pathology

QUESTIONS?

Amitabh Srivastava, MD, Associate Professor of Pathology, Harvard Medical School, Associate Director, Surgical Pathology, Director, Surgical Pathology Fellowship Program, Brigham and Women's Hospital

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Applying the New AJCC Staging System to Daily Diagnostic Practice: Gastrointestinal Pathology (Appendiceal Carcinomas)

Hanlin Wang, MD, PhD
University of California Los Angeles

Objectives

- Familiarize with changes in the new AJCC Staging Manual
- Understand the rationale behind the changes
- Discuss potentially confusing issues in the new system that may affect our practice

Staging System for Appendiceal Carcinomas

- Designed for carcinomas of the appendix, including poorly differentiated neuroendocrine carcinoma, goblet cell carcinoid, low-grade and high-grade appendiceal mucinous neoplasms
- Well differentiated neuroendocrine tumor should not be staged using this system

Comparison between 8th and 7th Editions: T Category

	8th Edition	7th Edition
Tis	Carcinoma in situ (intramucosal carcinoma; invasion of the lamina propria or extension into but through the muscularis mucosae)	Carcinoma in situ: intraepithelial or invasion of the lamina propria
T1	Tumor invades the submucosa	Tumor invades the submucosa
T2	Tumor invades the muscularis propria	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into the subserosa or the mesoappendix	Tumor invades through the muscularis propria into the subserosa or the mesoappendix
T4	Tumor invades the visceral peritoneum, including the acellular mucin or mucinous epithelium involving the serosa of the appendix or mesoappendix, and/or directly invades adjacent organs or structures	Tumor penetrates the visceral peritoneum, including mucinous peritoneal tumor within the right lower quadrant and/or directly invades other organs or structures
T4a	Tumor invades through the visceral peritoneum, including the acellular mucin or mucinous epithelium involving the serosa of the appendix or mesoappendix	Tumor penetrates the visceral peritoneum, including mucinous peritoneal tumor within the right lower quadrant
T4b	Tumor directly invades or adheres to adjacent organs or structures	Tumor directly invades other organs or structures

Unique T Definition for LAMN: 8th Edition

	LAMN	Invasive Carcinoma
Tis	Confined by the muscularis propria. Acellular mucin or mucinous epithelium may invade into the muscularis propria	Carcinoma in situ (intramucosal carcinoma; invasion of the lamina propria or extension into but through the muscularis mucosae)
T1	N/A	Tumor invades the submucosa
T2	N/A	Tumor invades the muscularis propria
T3	Acellular mucin or mucinous epithelium extends into the subserosa or mesoappendix	Tumor invades through the muscularis propria into the subserosa or mesoappendix
T4	Acellular mucin or mucinous epithelium involves the serosa (visceral peritoneum) of the appendix or mesoappendix, and/or directly involves adjacent organs or structures	Tumor invades the visceral peritoneum, including the acellular mucin or mucinous epithelium involving the serosa of the appendix or mesoappendix, and/or directly invades adjacent organs or structures
T4a	Acellular mucin or mucinous epithelium involves the serosa (visceral peritoneum) of the appendix or mesoappendix	Tumor invades the visceral peritoneum, including the acellular mucin or mucinous epithelium involving the serosa of the appendix or mesoappendix
T4b	Acellular mucin or mucinous epithelium directly invades or adheres to adjacent organs or structures	Tumor directly invades or adheres to adjacent organs or structures

LAMN, low-grade appendiceal mucinous neoplasm

Changes in T Category

- A unique Tis category was created for LAMN, which previously was recorded as TX or unstaged
  - For LAMNs confined to the appendix, the depth of appendiceal wall involvement is not a significant risk factor for recurrence
- T4 was redefined ("right lower quadrant" was deleted)
  - "Mucinous appendiceal carcinoma with peritoneal involvement limited to the right lower quadrant is much less aggressive than tumor that has gone beyond the RLQ, justifying a T4 designation rather than M1" (7th edition)

WHO Classification of Epithelial Tumors of the Appendix (2010)

Premalignant

Adenoma

- Tubular, villous, tubulovillous

Dysplasia

- Low-grade, high-grade

Serrated lesions

- Hyperplastic, SSA/P, TSA

Carcinoma

Adenocarcinoma

- Mucinous
- Low-grade appendiceal mucinous neoplasm
- Signet-ring cell carcinoma

Undifferentiated carcinoma

Neuroendocrine neoplasms

TABLE 1. Classification of Noncarcinoid Epithelial Neoplasia of the Appendix

Lesion	Terminology
Adenoma resembling traditional colorectal type, confined to mucosa, muscularis mucosae intact	Tubular, tubulovillous or villous adenoma, low-grade or high-grade dysplasia
Tumor with serrated features, confined to mucosa, muscularis mucosae intact	Serrated polyp with or without dysplasia (low grade or high grade)
Mucinous neoplasm with low-grade cytologic atypia and any of: Loss of muscularis mucosae Fibrosis of submucosa "Pushing invasion" (expansile or diverticulum-like growth) Dissection of acellular mucin in wall Undulating or flattened epithelial growth Rupture of appendix Mucin and/or cells outside appendix	Low grade appendiceal mucinous neoplasm
Mucinous neoplasm with the architectural features of LAMN and no infiltrative invasion, but with high-grade cytologic atypia	High grade appendiceal mucinous neoplasm
Mucinous neoplasm with infiltrative invasion*	Mucinous adenocarcinoma—well, moderately, or poorly differentiated
Neoplasm with signet ring cells (≤50% of cells)	Poorly differentiated (mucinous) adenocarcinoma with signet ring cells
Neoplasm with signet ring cells (> 50% of cells)	(Mucinous) signet ring cell carcinoma
Nonmucinous adenocarcinoma resembling traditional colorectal type	Adenocarcinoma—well, moderately, or poorly differentiated

*Features of infiltrative invasion include tumor budding (discohesive single cells or clusters of up to 5 cells) and/or small, irregular glands, typically within a desmoplastic stroma characterized by a proteoglycan-rich extracellular matrix with activated fibroblasts/myofibroblasts with vesicular nuclei.

Carr NJ, et al. Am J Surg Pathol 2016; 40:14-26

Appendiceal Mucinous Neoplasms

Without infiltrative invasion

- Low-grade appendiceal mucinous neoplasm (LAMN)
- High-grade appendiceal mucinous neoplasm (HAMN)

With infiltrative invasion

- Mucinous adenocarcinoma
- Mucinous adenocarcinoma with signet-ring cells (≤50%)
- Signet-ring cell carcinoma (>50%)

Carr NJ, et al. Am J Surg Pathol 2016; 40:14-26

CAP Cancer Protocols

2013

Histologic Type (Note C)

___ Adenocarcinoma
___ Mucinous (colloid) adenocarcinoma (greater than 50% mucinous)
___ Signet-ring cell carcinoma (greater than 50% signet-ring cells)
___ High-grade neuroendocrine carcinoma
    ___ Large cell neuroendocrine carcinoma
    ___ Small cell neuroendocrine carcinoma
___ Undifferentiated carcinoma
___ Typical goblet cell carcinoid
___ Adenocarcinoma ex goblet cell carcinoid
___ Other (specify): _____
___ Carcinoma, type cannot be determined (see Comment)

2016

Histologic Type (select all that apply) (Note C)

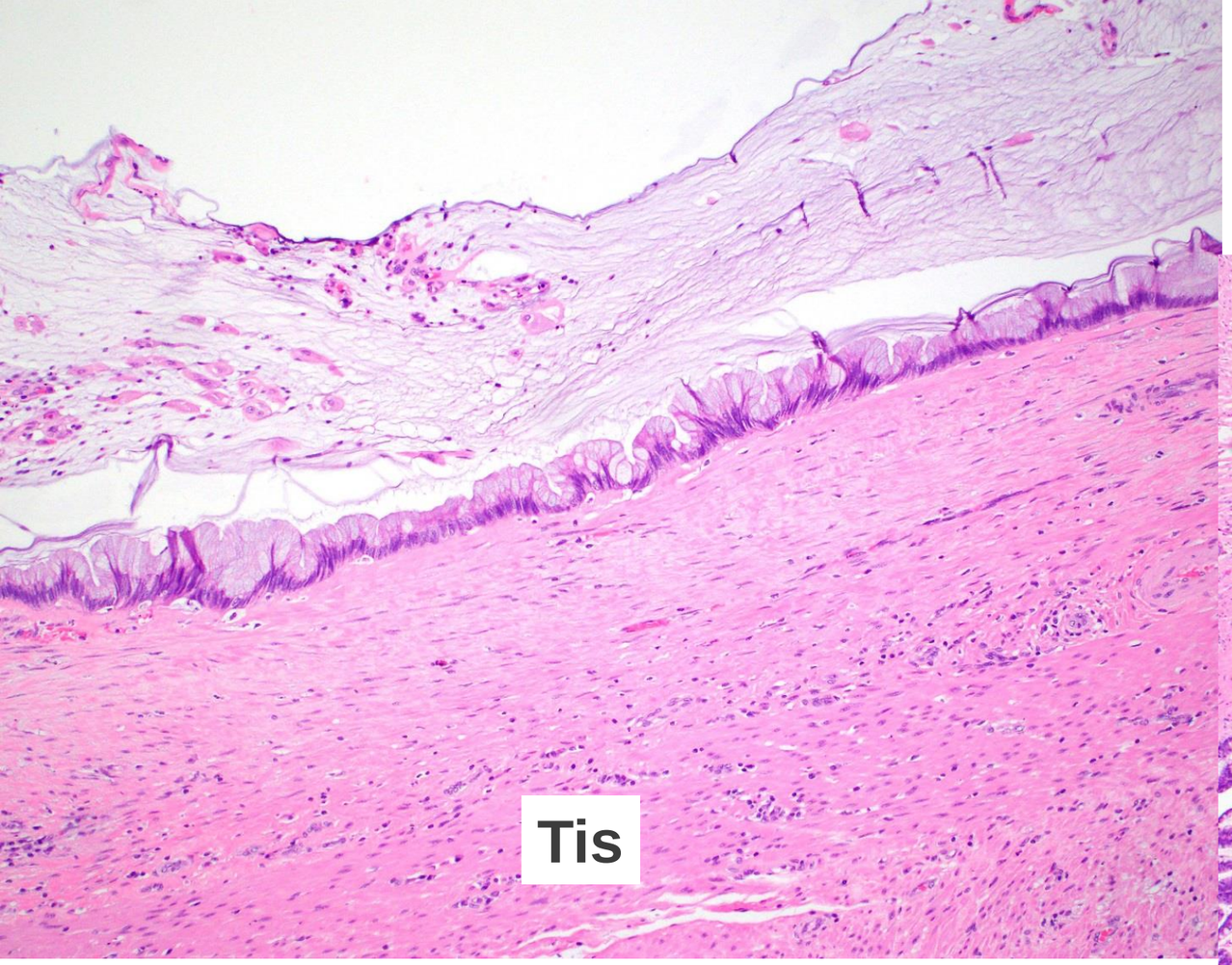
___ Adenocarcinoma
___ Mucinous adenocarcinoma
___ Low-grade appendiceal mucinous neoplasm
___ High-grade appendiceal mucinous neoplasm
___ Signet-ring cell carcinoma
___ Goblet cell carcinoid
___ Mixed adenoneuroendocrine carcinoma (mixed goblet cell carcinoid-adenocarcinoma or adenocarcinoma ex goblet cell carcinoid)
___ High-grade neuroendocrine carcinoma
    ___ Large cell neuroendocrine carcinoma
    ___ Small cell neuroendocrine carcinoma
___ Undifferentiated carcinoma
___ Other (specify): _____
___ Carcinoma, type cannot be determined (explain): _____

2017

Histologic Type (Note C)

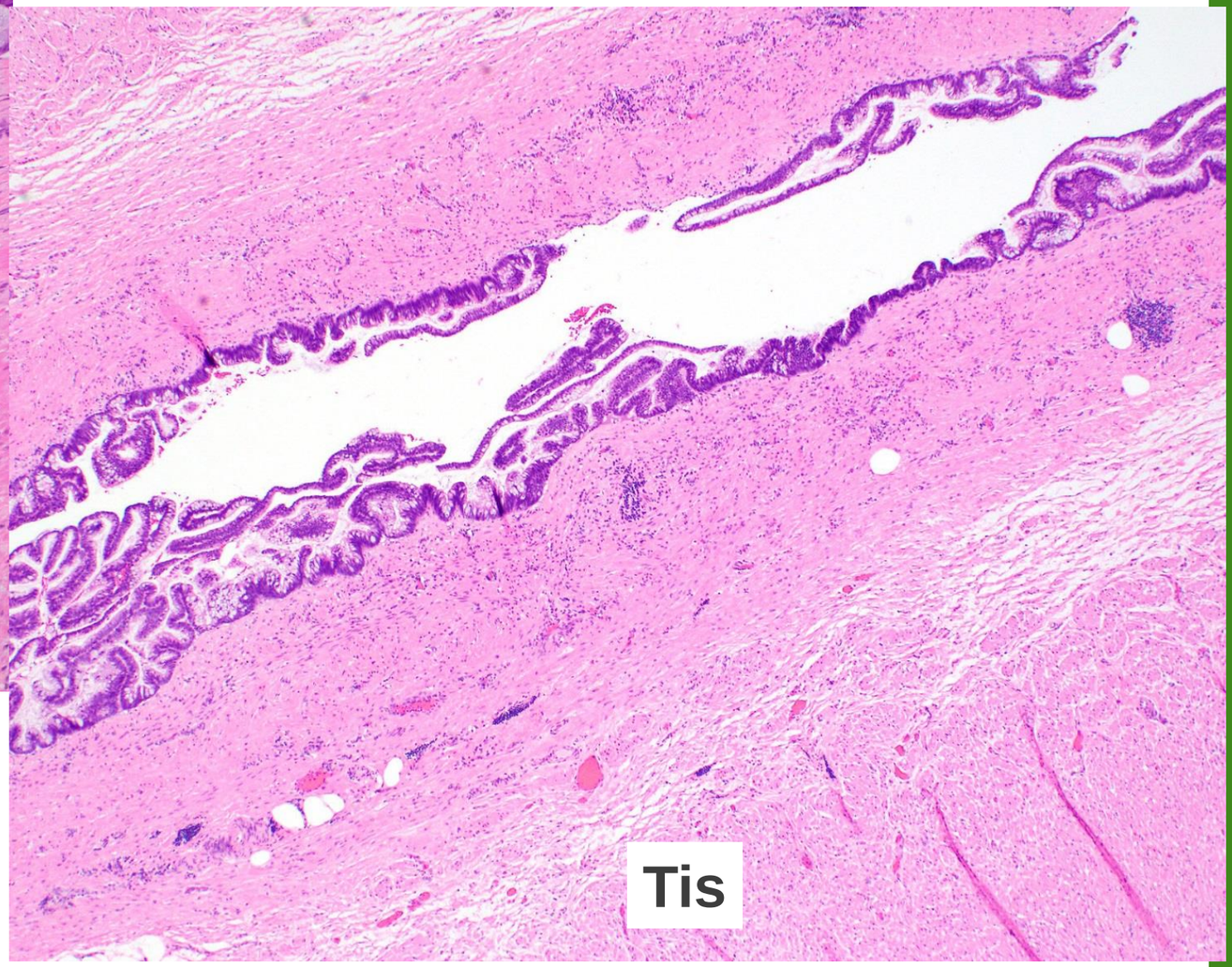
___ Adenocarcinoma
___ Mucinous adenocarcinoma
___ Low-grade appendiceal mucinous neoplasm
___ High-grade appendiceal mucinous neoplasm
___ Signet-ring cell carcinoma
___ Goblet cell carcinoid
___ Mixed goblet cell carcinoid-adenocarcinoma (adenocarcinoma ex goblet cell carcinoid)
___ Large cell neuroendocrine carcinoma
___ Small cell neuroendocrine carcinoma
___ Neuroendocrine carcinoma (poorly differentiated)[#]
___ Mixed adenoneuroendocrine carcinoma
___ Medullary carcinoma
___ Adenosquamous carcinoma
___ Undifferentiated carcinoma
___ Other histologic type not listed (specify): _____
___ Carcinoma, type cannot be determined (explain): _____

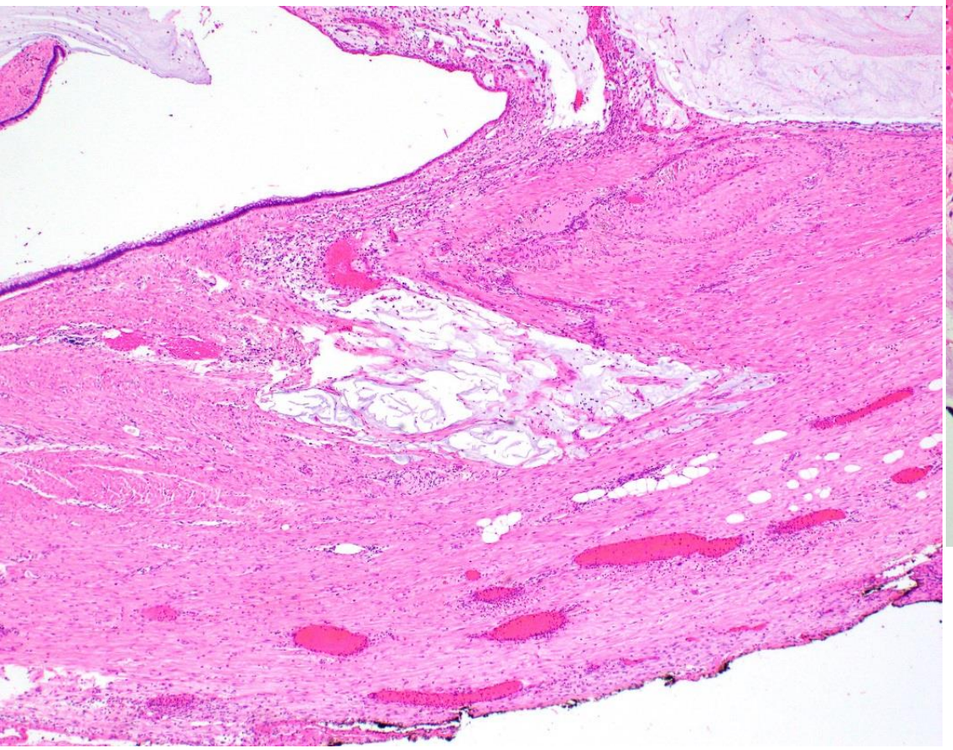
[#] *Note: Select this option only if large cell or small cell cannot be determined.*



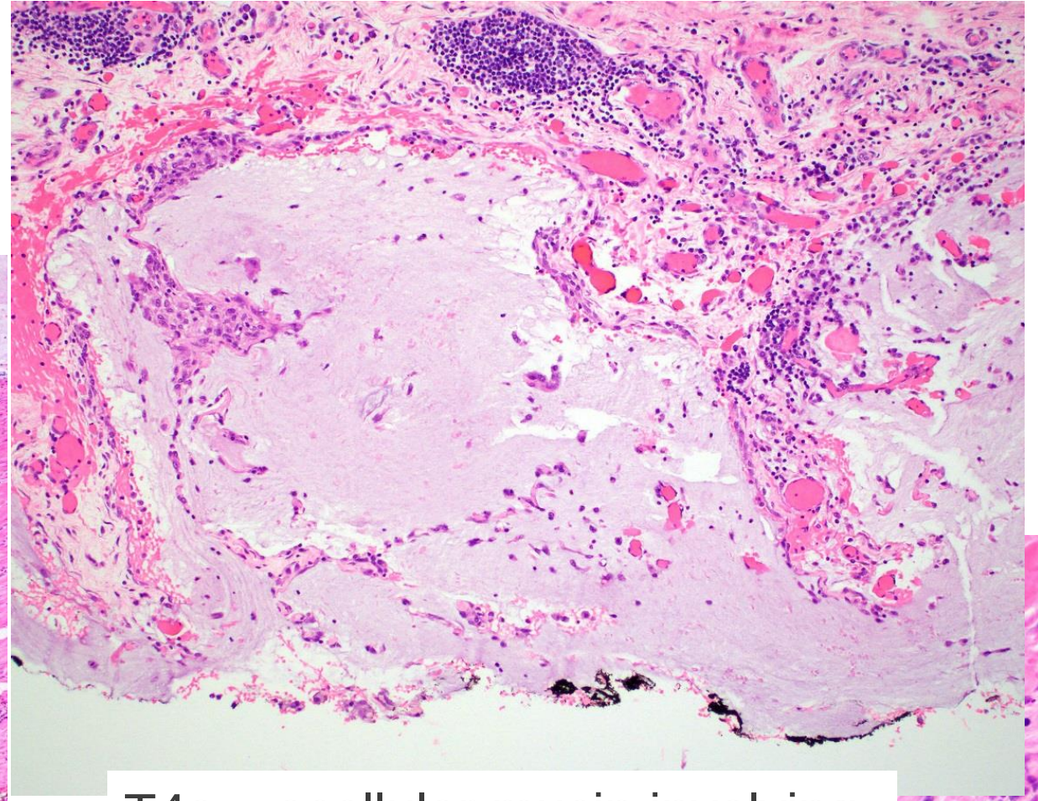
Loss of lamina propria
Loss of muscularis mucosae
Submucosal fibrosis

Flattened or undulated epithelium

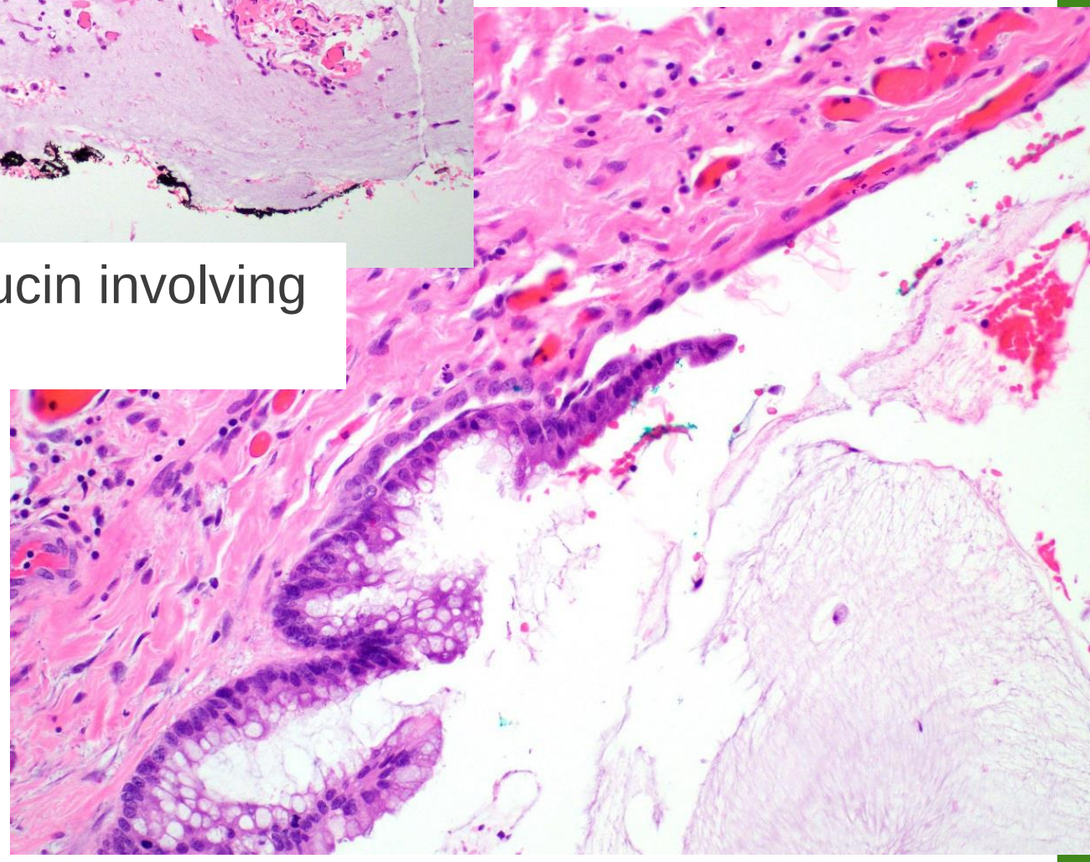




Tis – acellular mucin invading into the muscularis propria



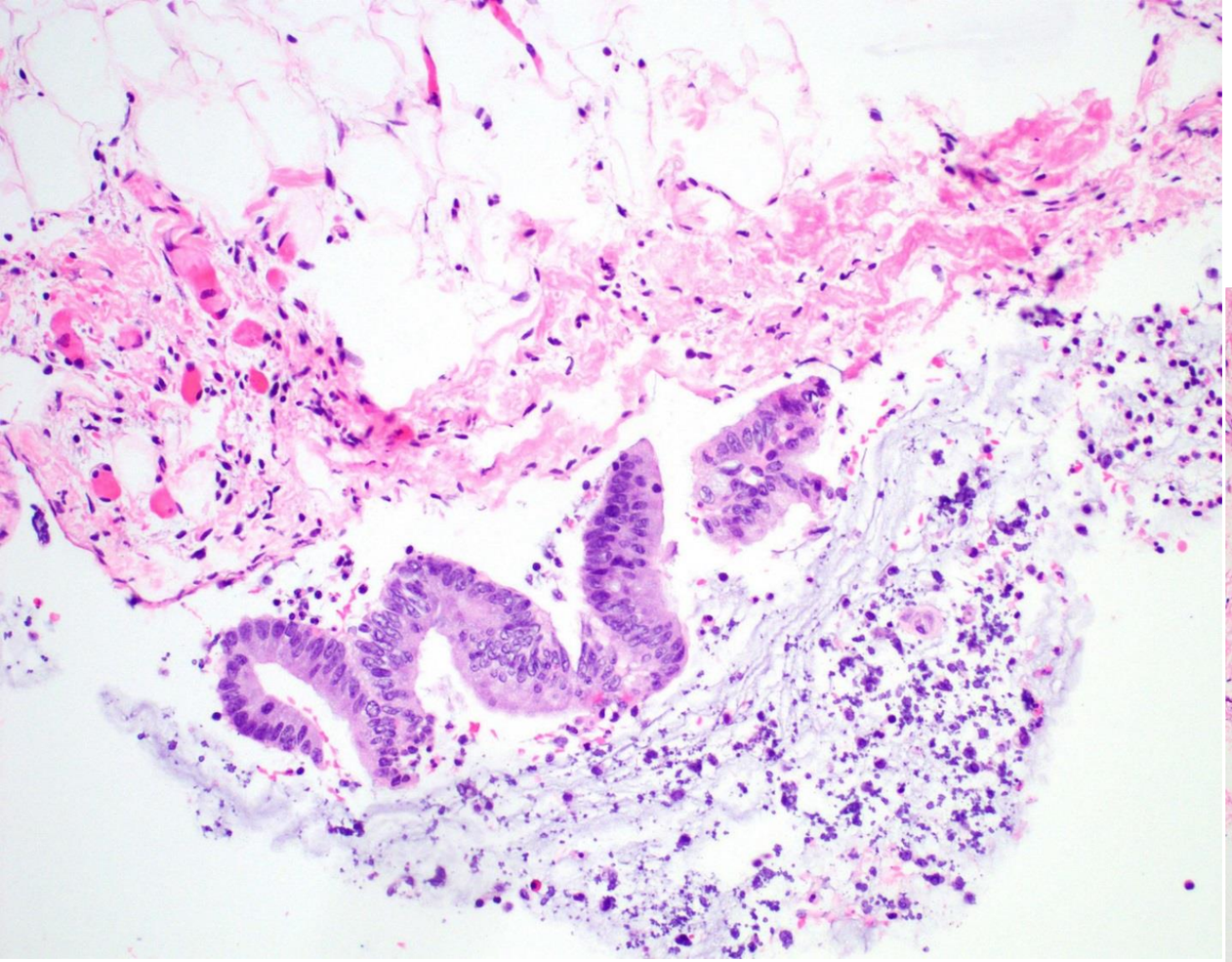
T4a – acellular mucin involving serosal surface



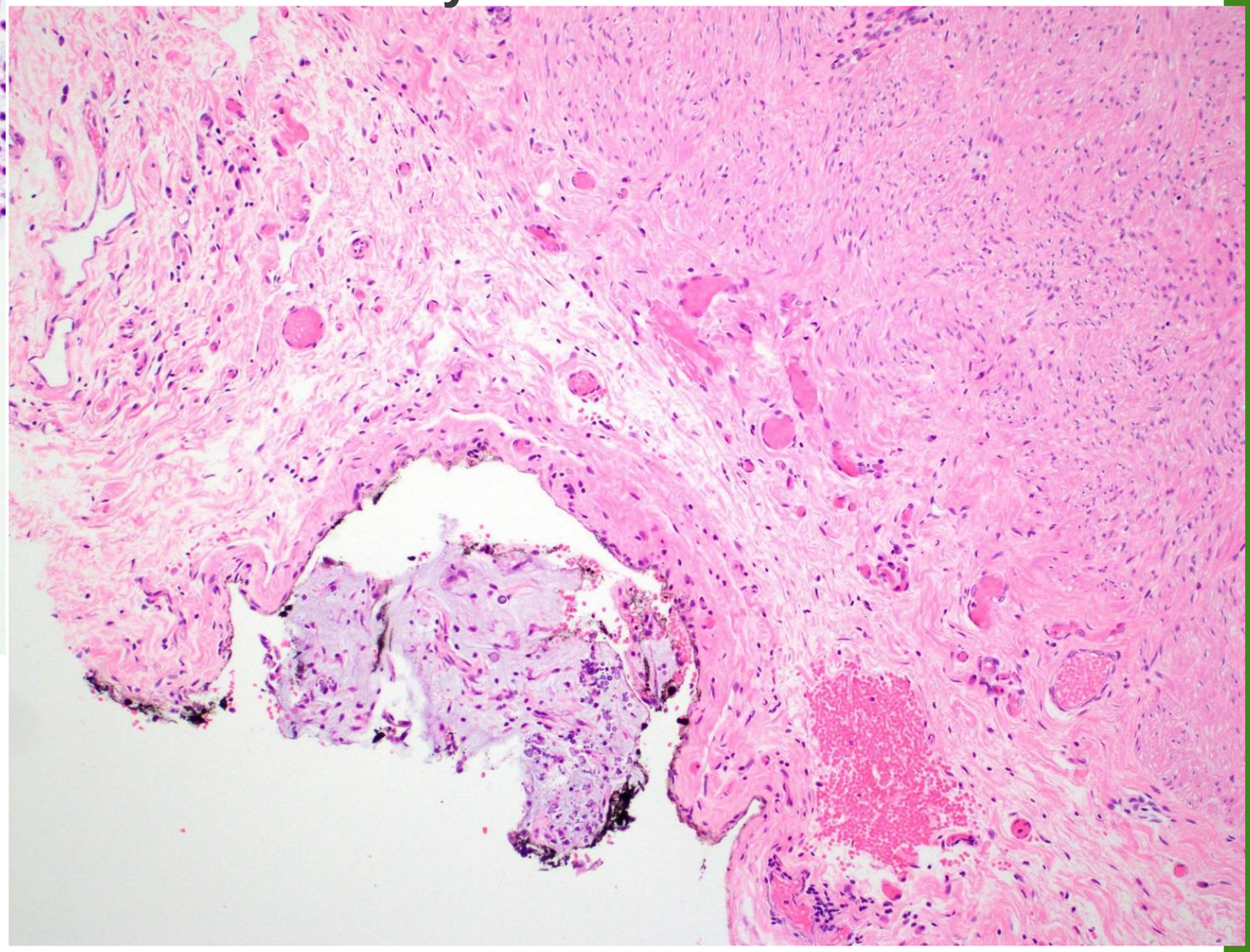
T4a – mucinous epithelium involving serosal surface

Staging LAMN (AJCC 8th edition)

- The entire appendix needs to be submitted for histologic examination
- Acellular mucin may be artifactually present on the serosal surface due to “carry-over” during specimen handling, which may falsely overstage the tumor
- Staging acellular mucin similarly to cellular mucin remains controversial
  - Low risk of peritoneal recurrence (~3%) due to acellular mucin
  - Higher risk of peritoneal recurrence (~36%) due to cellular mucin

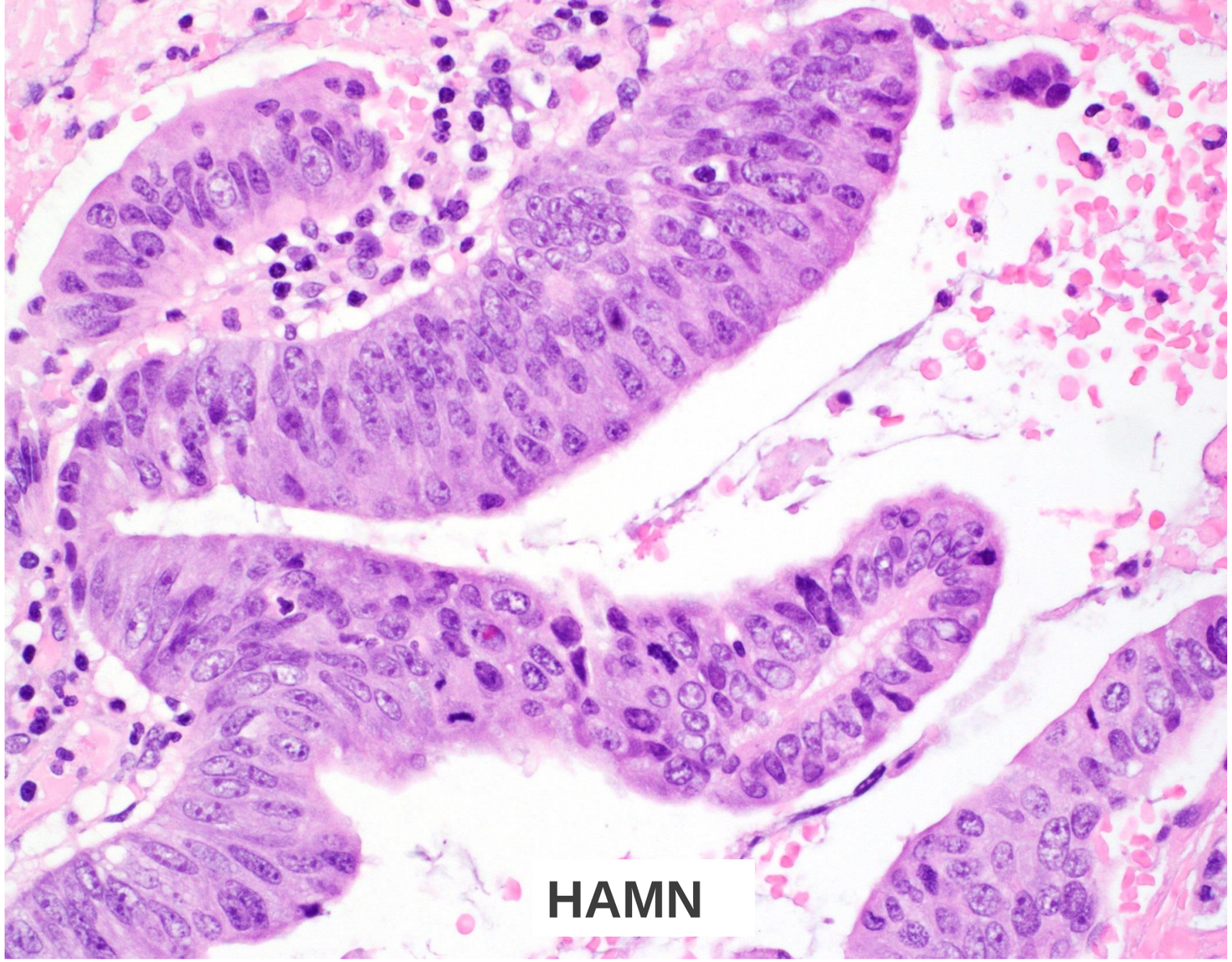


“Carry-over” artifact



<u>True serosal surface involvement</u>

- Mucin dissection of submesothelial stroma
- Inflammatory response
- Mesothelial hyperplasia
- Neovascularization



Staging system for invasive adenocarcinoma should be used for HAMN because of its higher risk of recurrence

Comparison between 8th and 7th Editions: N Category

	8th Edition	7th Edition
NX	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastasis	No regional lymph nodes metastasis
N1	Metastasis in 1-3 regional lymph nodes, or any number of tumor deposits is present and all identifiable lymph nodes are negative	Metastasis in 1-3 regional lymph nodes
N1a	Metastasis in 1 regional lymph node	N/A
N1b	Metastasis in 2-3 regional lymph nodes	N/A
N1c	No positive regional lymph nodes, but there are tumor deposits in the subserosa or mesentery	N/A
N2	Metastasis in 4 or more regional lymph nodes	Metastasis in 4 or more regional lymph nodes

* Positive lymph node: tumor in lymph node measuring ≥0.2 mm
** 12 or more lymph nodes should be examined for a right hemicolectomy specimen
*** As a general rule, the presence of acellular mucin within lymph nodes or tumor deposits is not considered involvement and is categorized as pN0

Comparison between 8th and 7th Editions: M Category

	8th Edition	7th Edition
M0	No distant metastasis	No distant metastasis
M1	Distant metastasis	Distant metastasis
M1a	Intraperitoneal acellular mucin, without identifiable tumor cells in the disseminated peritoneal mucinous deposits*	Intraperitoneal metastasis beyond the right lower quadrant, including pseudomyxoma peritonei
M1b	Intraperitoneal metastasis only, including peritoneal mucinous deposits containing tumor cells	Nonperitoneal metastasis
M1c	Metastasis to sites other than peritoneum	

* For specimens containing acellular mucin without identifiable tumor cells, efforts should be made to obtain additional tissue for thorough histologic examination to evaluate for cellularity

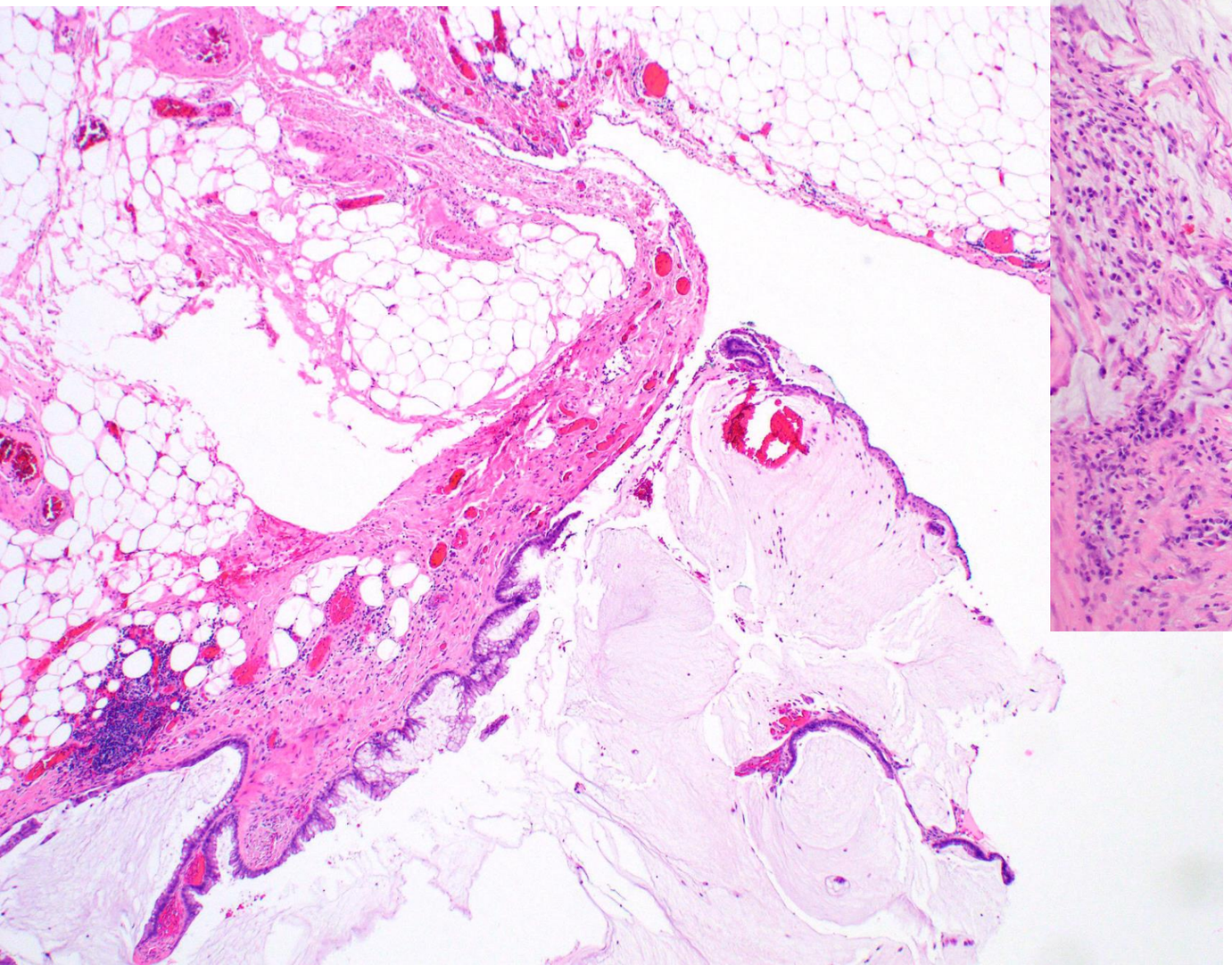
Changes in N and M Categories

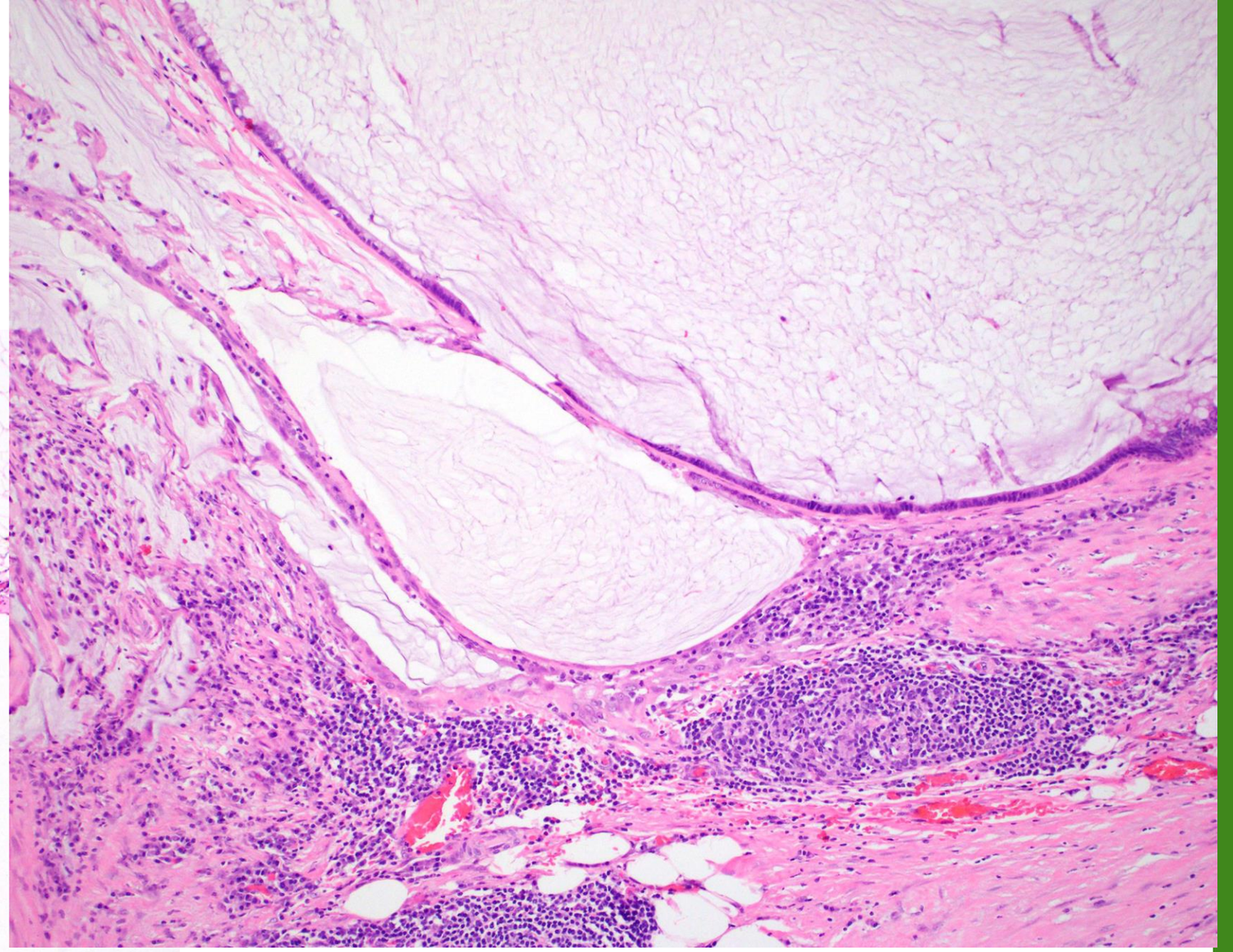
- Essentially adopted the N definition for CRC, but no further substratifying N2 into N2a and N2b
  - Acellular mucin was used for T and M classifications, but not for N
- Acellular mucin or mucinous tumor cells involving the peritoneum limited to the right lower quadrant, previously T4a, was reclassified into M1a or M1b
  - “Pseudomyxoma peritonei” was considered a clinical syndrome, and the term was removed from the M1a definition

Grading Mucinous Adenocarcinoma

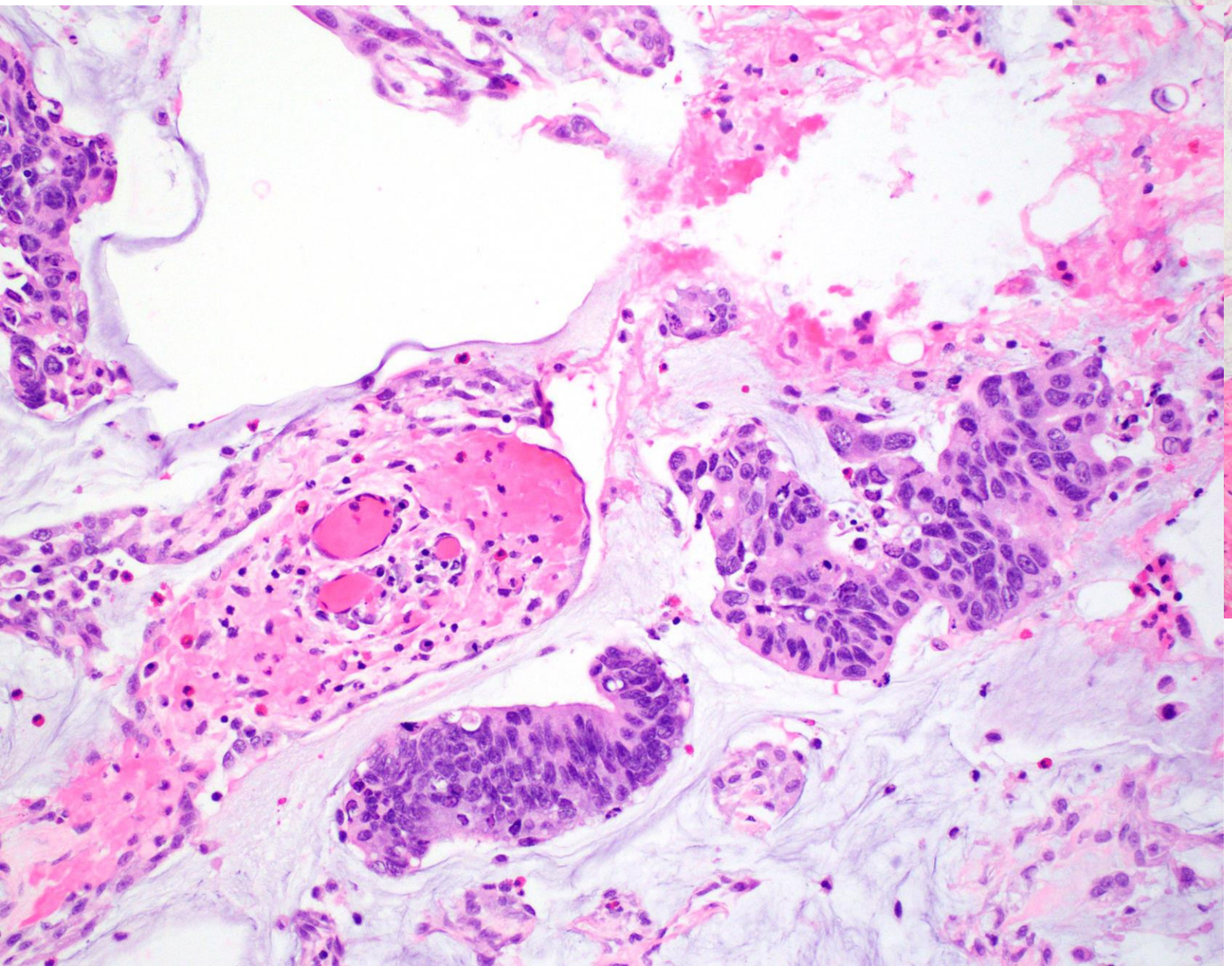
Differentiation	Histology
Well differentiated (G1) (=LAMN)	Low-grade cytologic atypia No signet-ring cells Lack of typical features of invasion If the peritoneum is involved Acellular mucin or low cellularity (<20%) Lack of infiltrative invasion of the peritoneum or other organs Absence of lymphovascular and perineural invasion
Moderately differentiated (G2)	Mixed low- and high-grade cytologic atypia or diffuse high-grade No signet-ring cell component Most cases show features of invasion (at least focally), but rare cases may lack invasion (HAMN) If the peritoneum is involved Often high cellularity (>20%) Infiltrative invasion into the peritoneum or other organs may be seen Lymphovascular and perineural invasion may be present
Poorly differentiated (G3)	High-grade cytologic atypia Usually have signet-ring cell component If the peritoneum is involved Often high cellularity (>20%) Infiltrative invasion into the peritoneum or other organs may be seen Lymphovascular and perineural invasion may be present

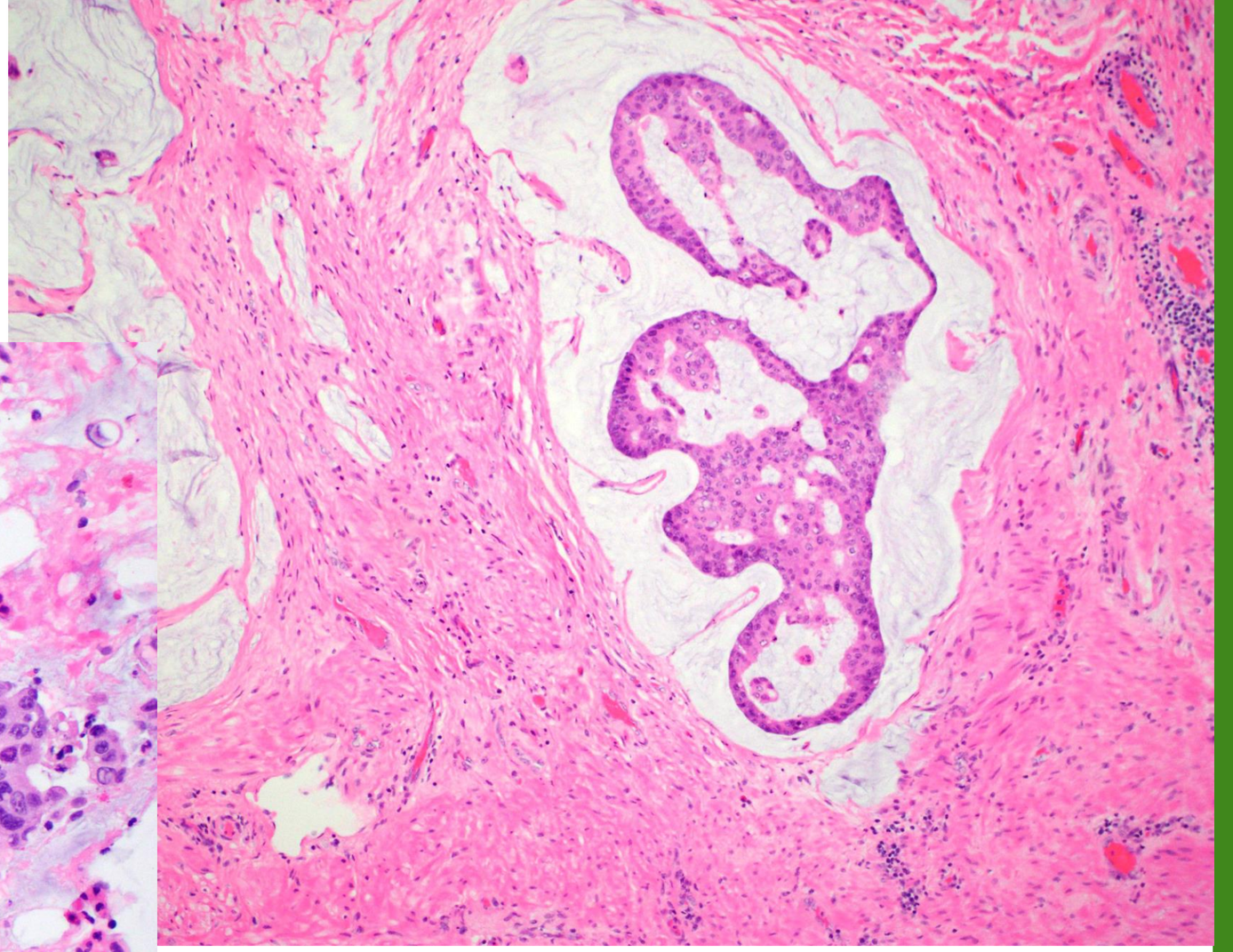
Well differentiated



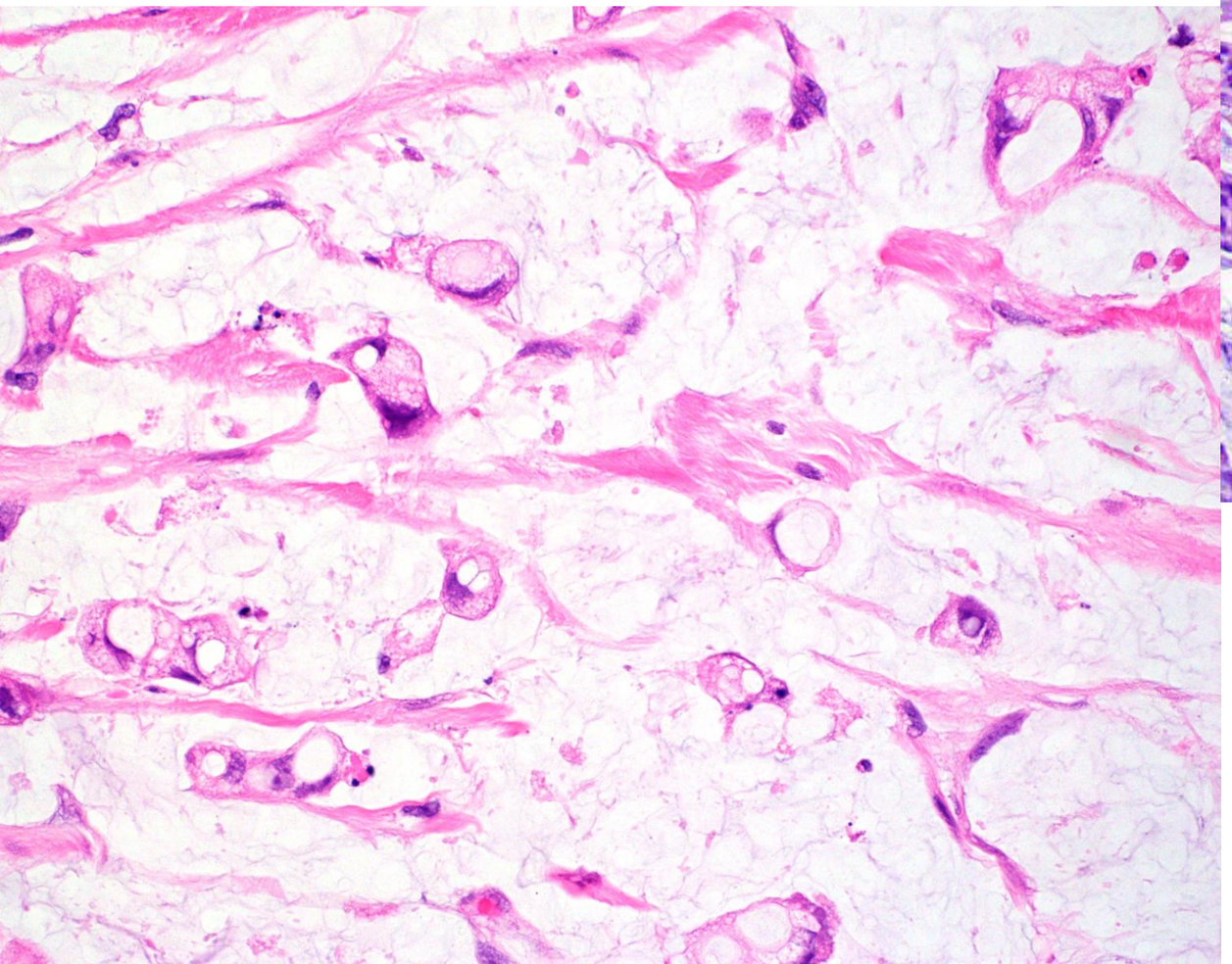


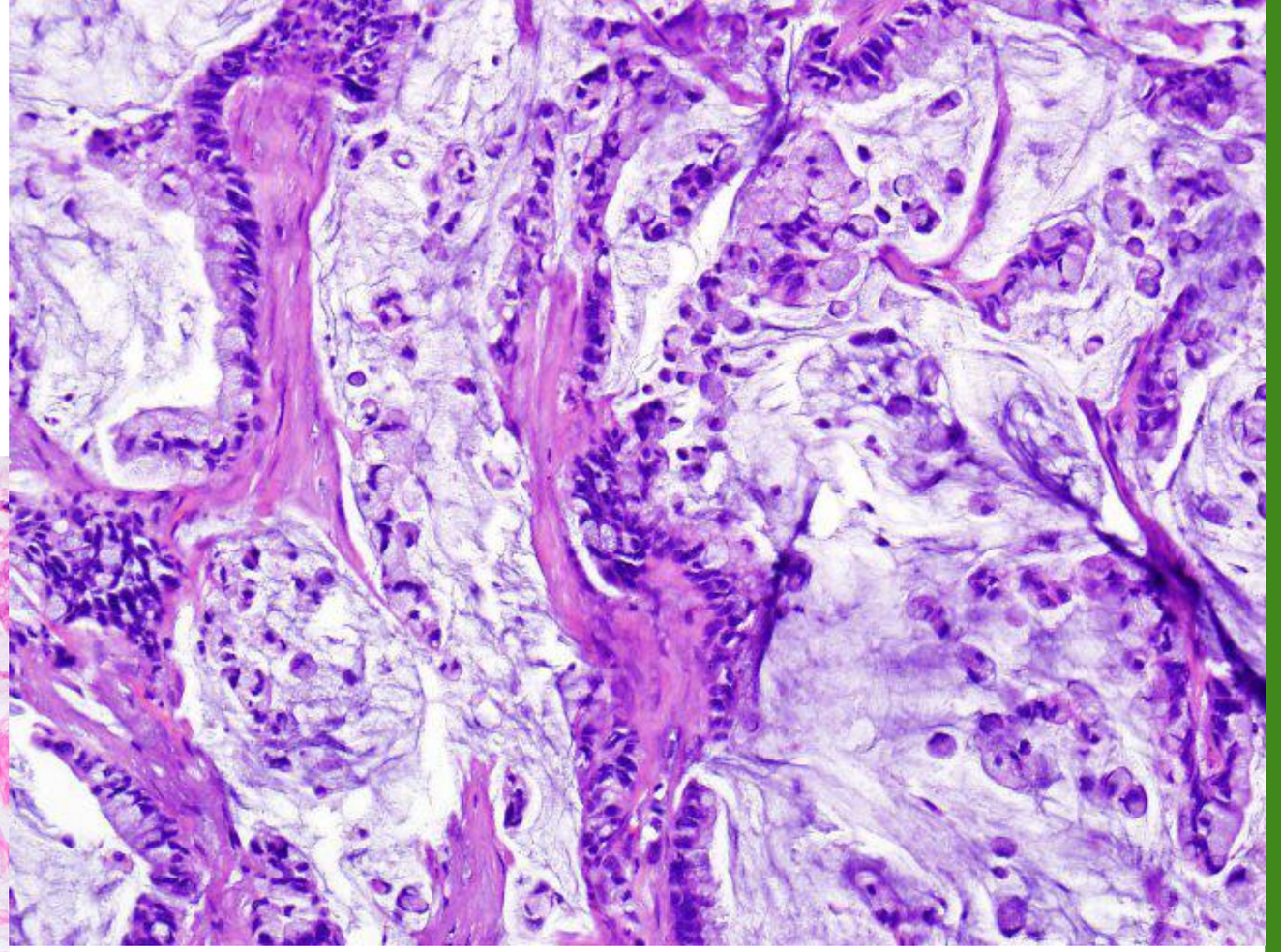
Moderately differentiated



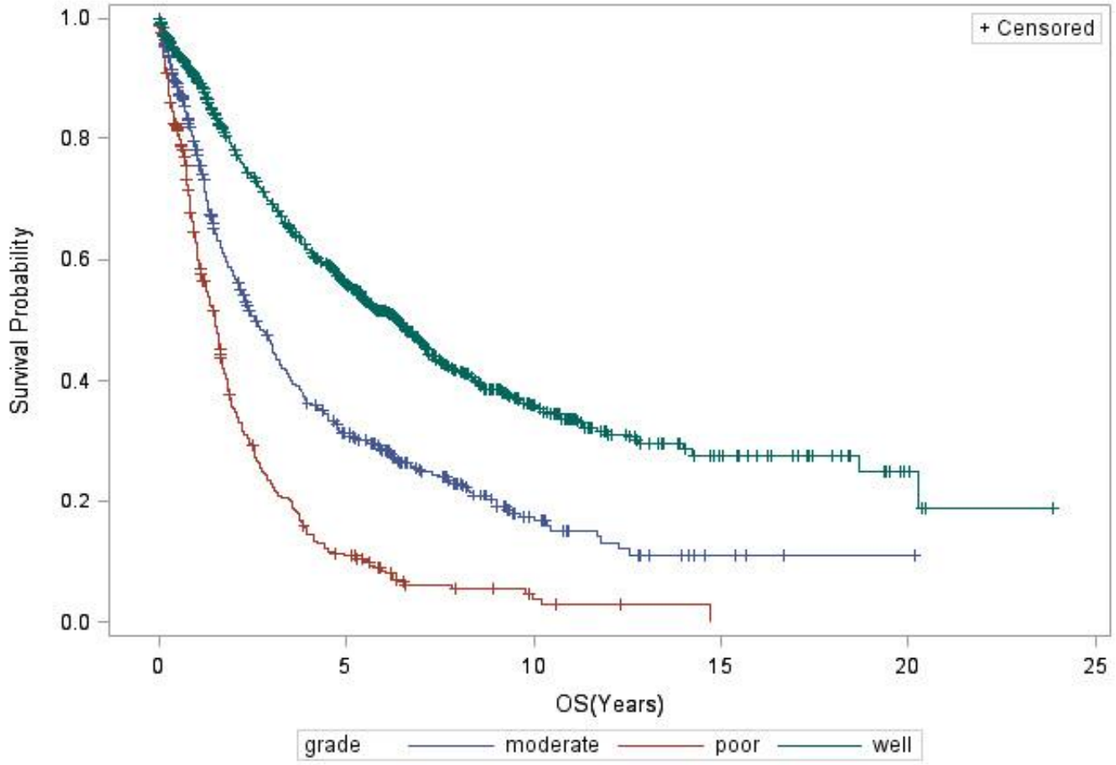


Poorly differentiated





Overall Survival of Stage IV Appendiceal Mucinous neoplasms Stratified by Histologic Grade Based on National Cancer Database (n=5971)



5-year overall survival

Well – 56.7%
Moderate – 31.5%
Poor – 11.3%

Asare EA, et al. Cancer 2016; 122:213-21

Stratification of Stage IV by Histologic Grade: 8th Edition

Stage	T	N	M	Grade
IVA	Any T	N0	M1a	
IVA	Any T	Any N	M1b	G1
IVB	Any T	Any N	M1b	G2, G3, or GX
IVC	Any T	Any N	M1c	Any G

Summary

- A unique Tis category was created for LAMN
- Acellular mucin was included for T and M staging for appendiceal mucinous neoplasms, although it bears a much better prognosis than cellular mucin
- A 3-tier grading system was recommended for appendiceal mucinous neoplasms, which was integrated in the substratification of stage IV
- Confusion may be present for staging HAMN, but this is a rare condition

Thanks for Attending!

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