

2018 Park City AP Update

Staging updates in AJCC 8th ed Colorectal and selected GI sites

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Outline

- **Updates in Colorectal cancer**

 - Definition of T4a

 - Tumor deposits

 - Isolated tumor cells

 - Adenocarcinoma arising in a polyp

- **Selected other updates**

 - Liver, pancreas, gallbladder, ampulla

Definition of pT4

AJCC 8th edition

T category	Definition
pT4a	Tumor invades through the visceral peritoneum
pT4b	Tumor directly invades other organs or structures

Criteria for serosal involvement

- Tumor directly extends to involve serosal surface
- Tumor continuous with serosal surface through perforation (inflammatory reaction)

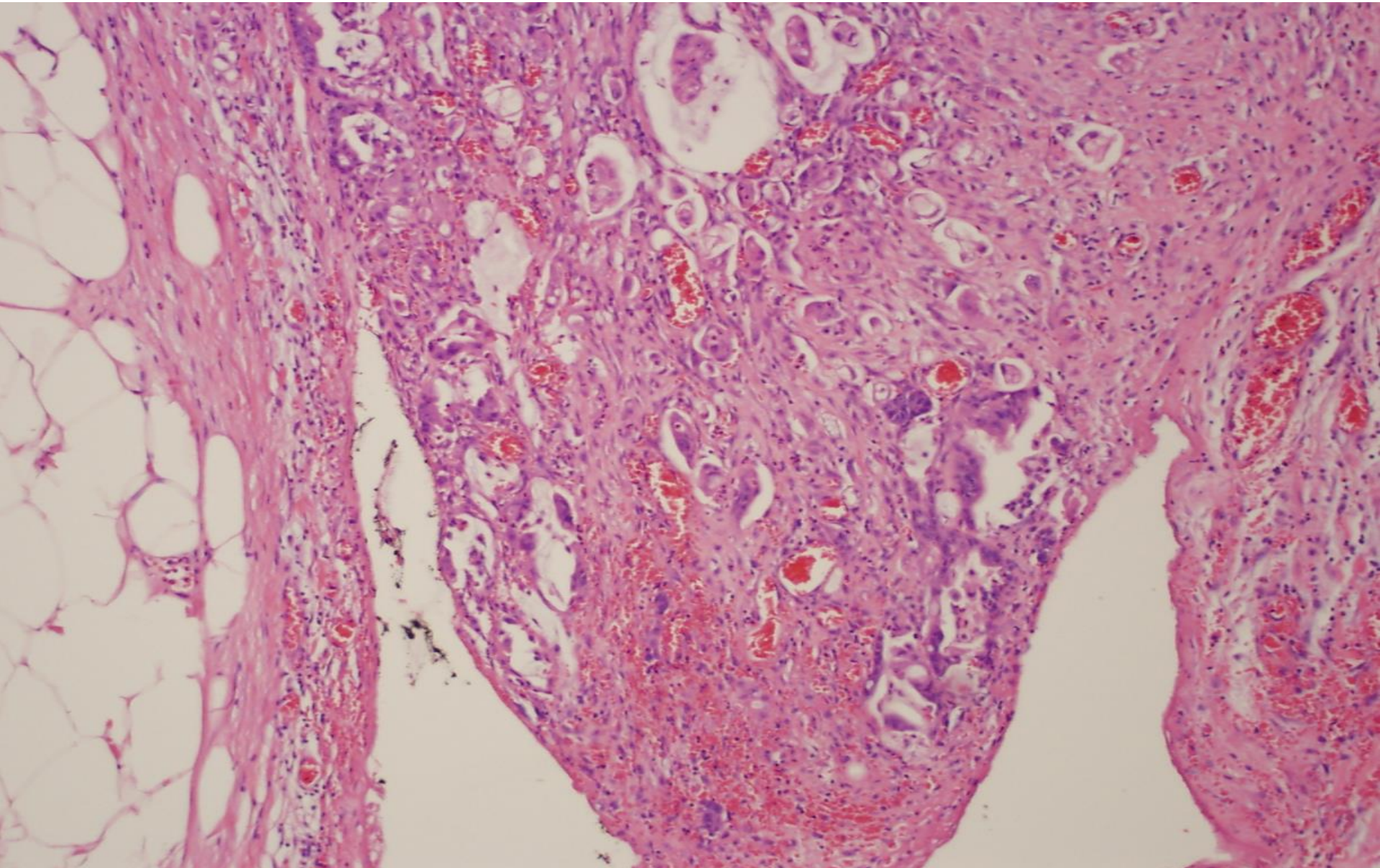
Shepherd, Gastroenterol 1997

Peterson, Gut 2002

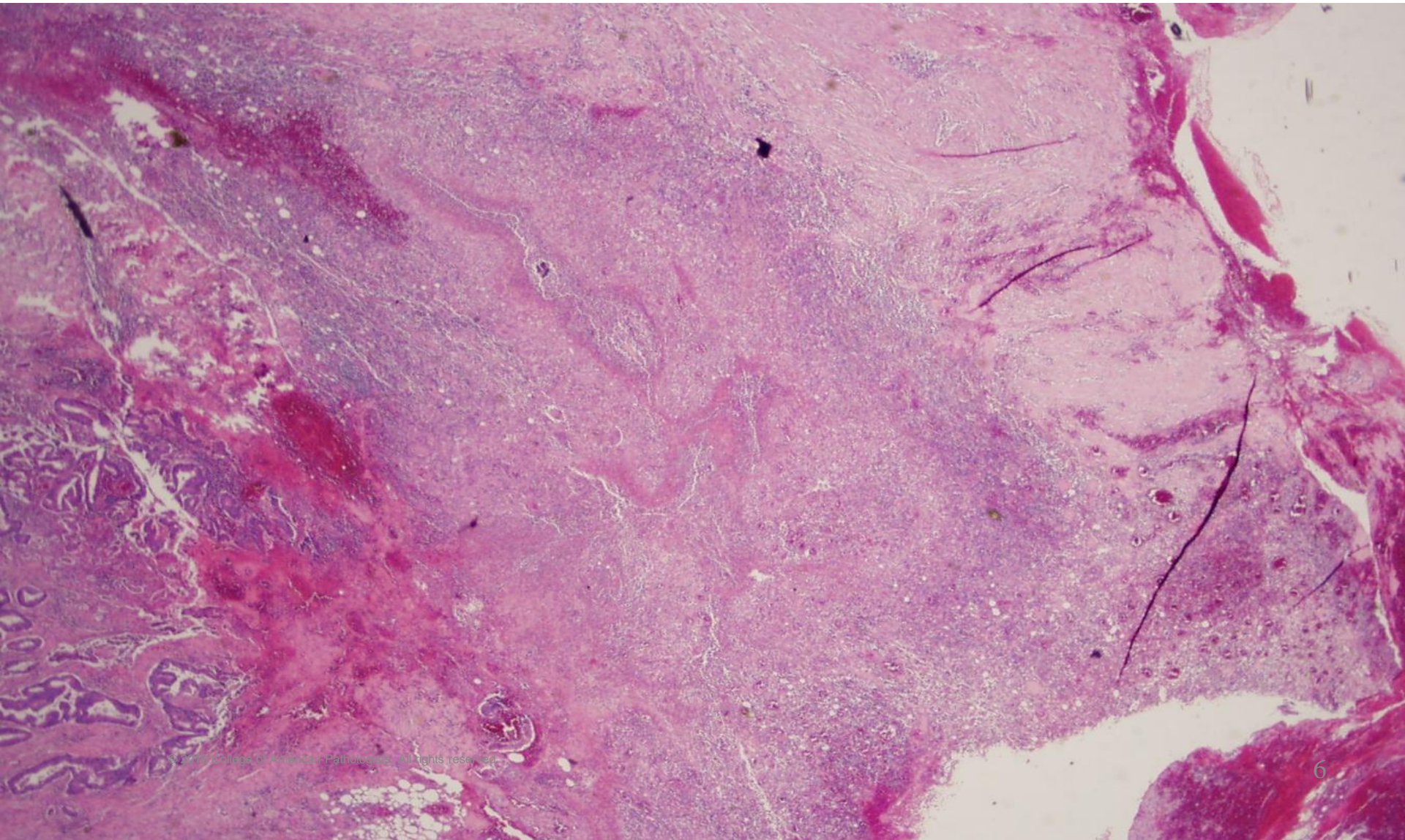
Ludeman, Histopathol 2005

Stewart, Histopathol 2006

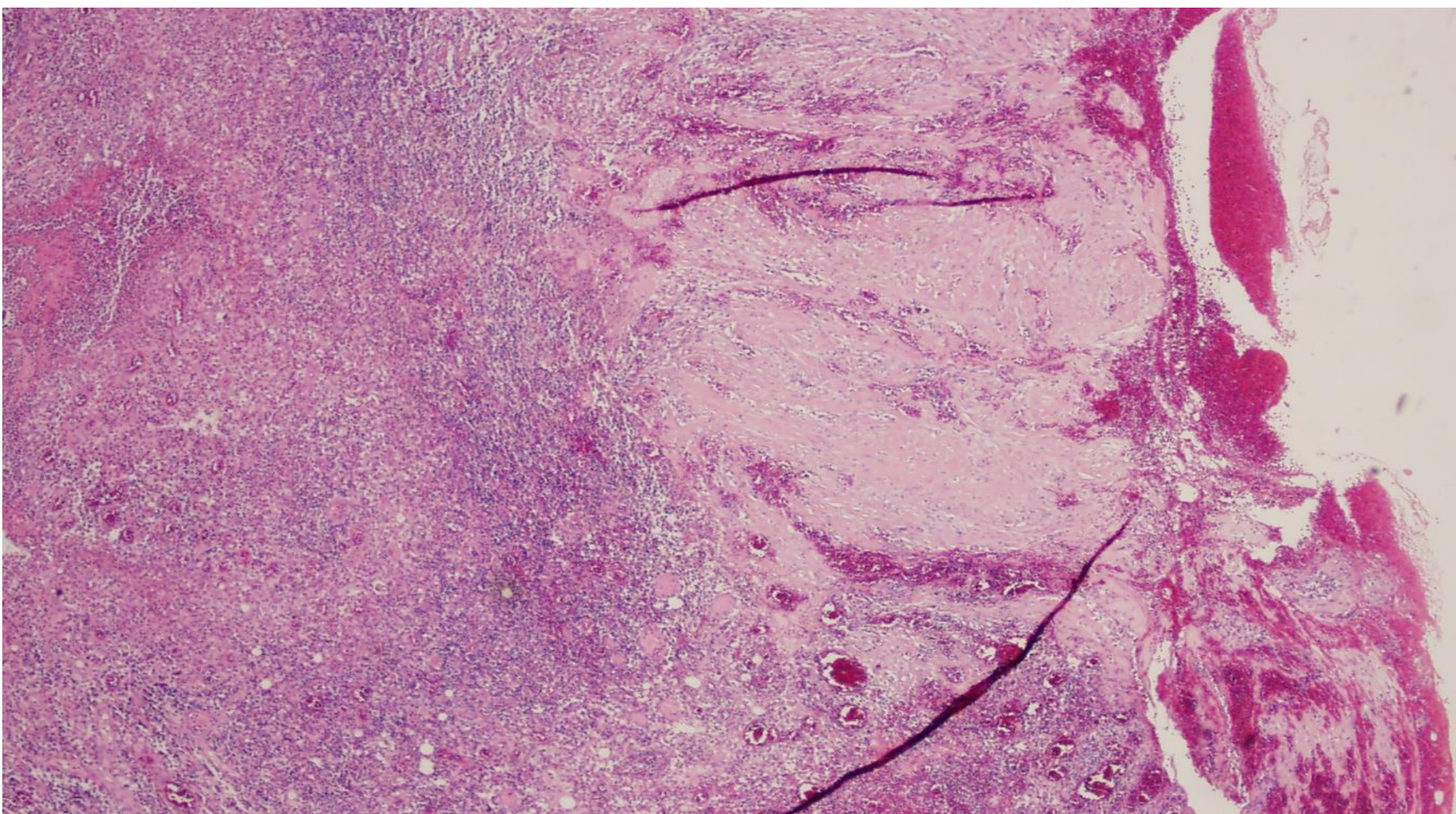
Tumor directly extends to serosal surface



Colonic adenocarcinoma with perforation



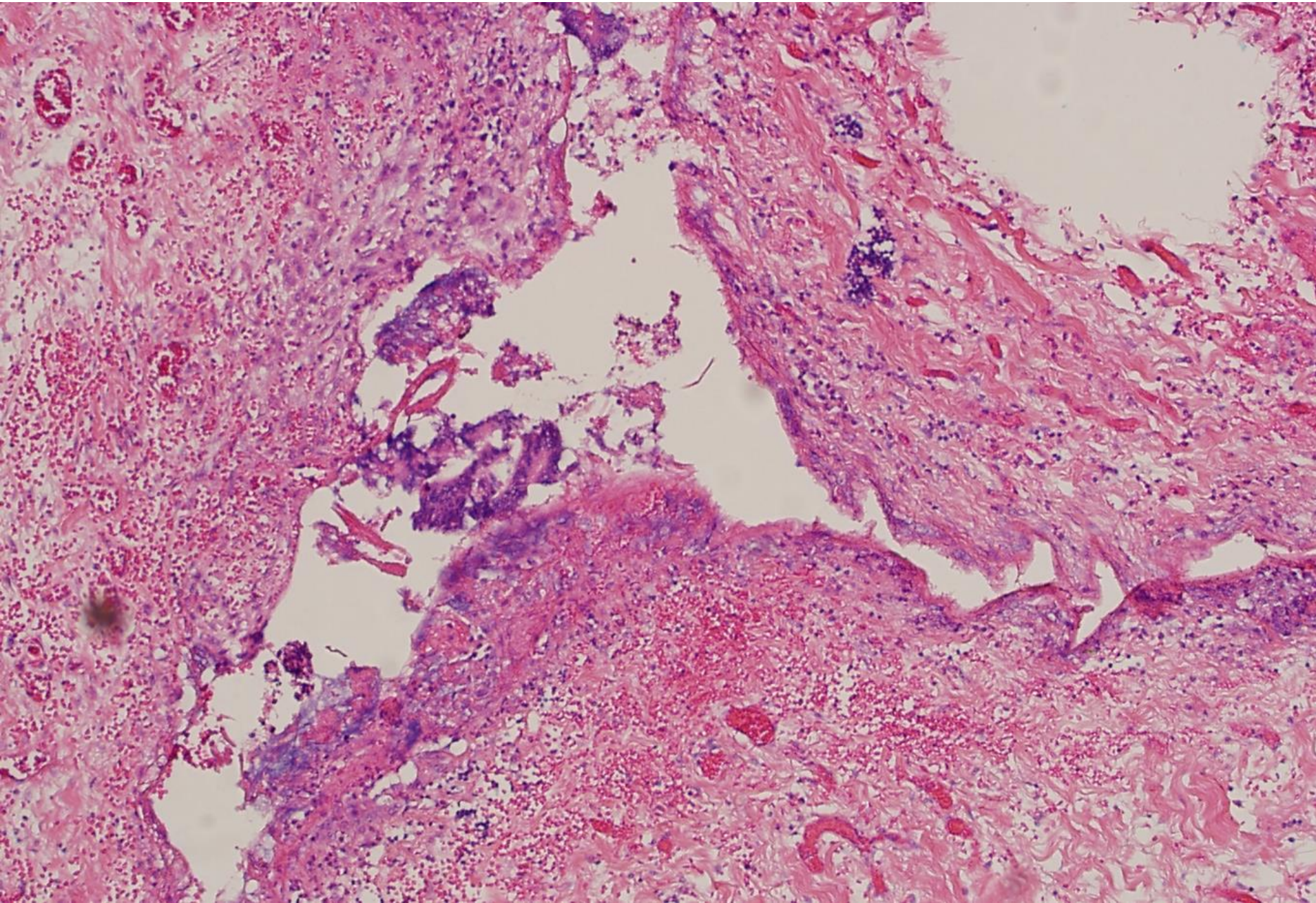
**Perforation: tumor continuous with serosal surface
through inflammatory reaction**



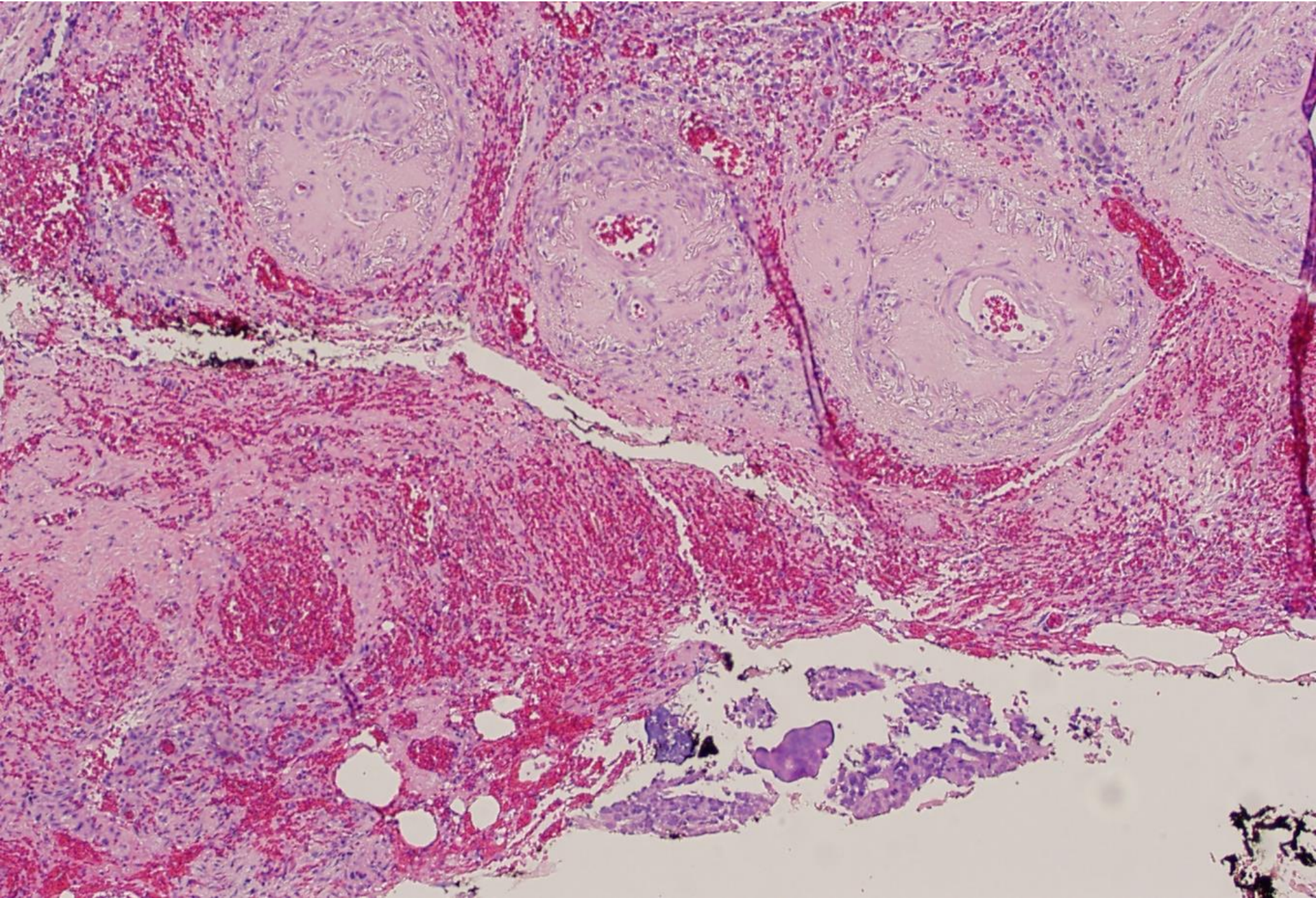
T4a: challenges

- **Free floating tumor cells**
- **Tumor within 1 mm of serosal surface**
- **Acellular mucin on serosal surface**
- **Elastic stain**

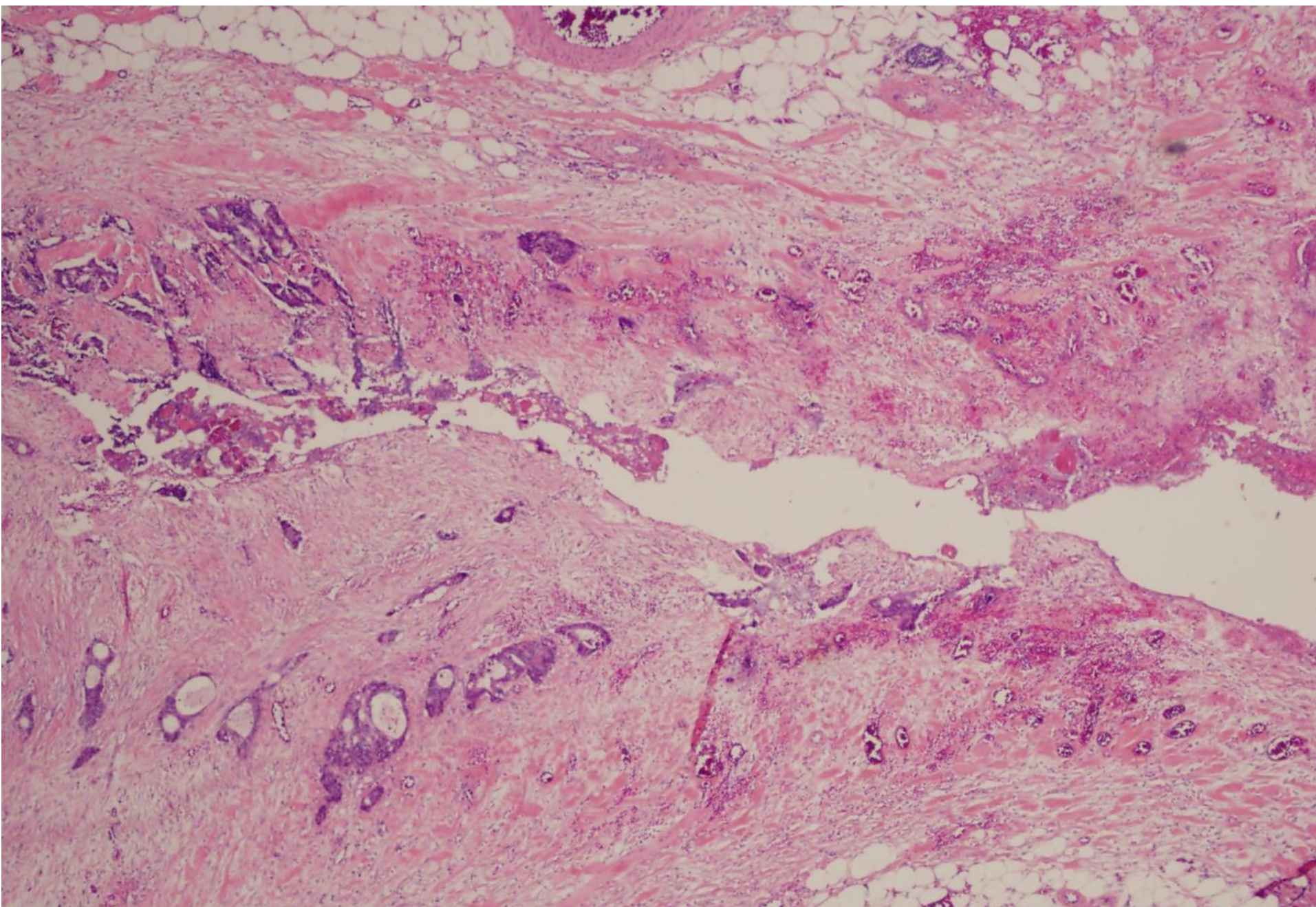
Free floating tumor cells in clefts and mesothelial 'ulceration'



Disrupted serosal surface with free floating tumor cells



Additional sections: obvious pT4a



Tumor ≤ 1 mm with reaction

Study	Results
Panarelli, AJSP 2014	Positive cytology from serosal surface of specimens: 46% pT3 ≤ 1 mm from serosal surface 55% of pT4a Peritoneal recurrence: 11% in pT3 ≤ 1 mm 18% in pT4a
-Shepherd, Gastroenterology 1997 -Lennon, AJCP 2003 -Douard, AJCP 2004	Peritoneal/pelvic recurrence only with Direct invasion of serosal surface Free floating tumor cells

Not T4a (AJCC 8th)

- **Tumor close to serosal surface with serosal reaction**
- **Acellular mucin**

Deeper levels, additional sections

Elastic stain

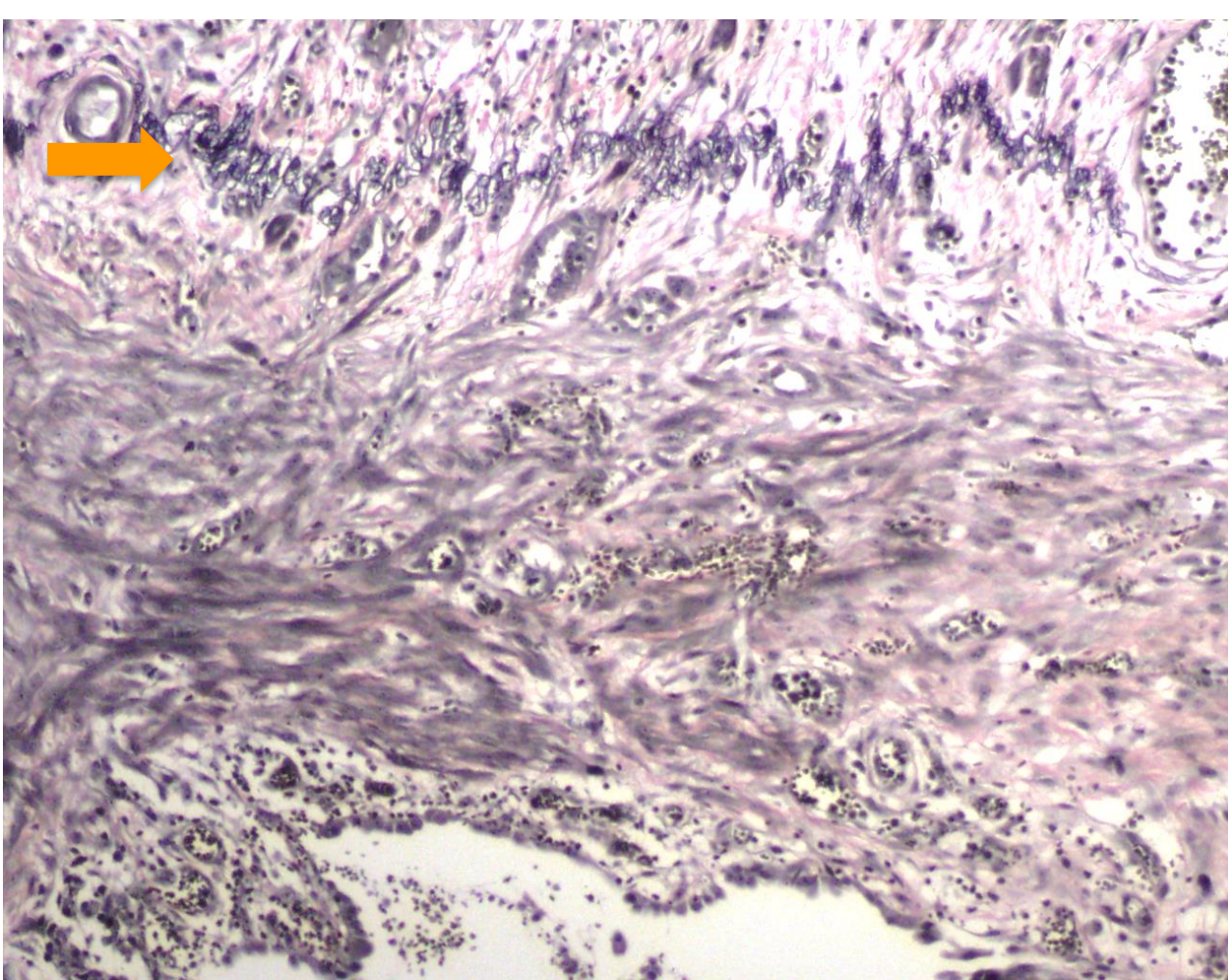
- **Submesothelial elastic lamina**
- **Involvement associated with poor prognosis in some studies**

Shinto, Dis Col Rectum 2004

Kojima, AJSP 2010

Grin, Hum Pathol 2013

Elastic stain



Difficult to interpret

- **Elastic lamina discontinuous**
- **Retracted by desmoplasia**
- **Variable distance from mesothelium**

pT4a: clinical significance

- **Prognosis**
- **Peritoneal recurrence**
- **Choice of therapy**

NCCN guidelines: High risk feature in stage II

Likely adjuvant chemotherapy

Possible local radiation or intra-peritoneal chemo in the future

ASCO GI meeting 2017

Home » Meeting Library » Virtual Meeting » 2017 Gastrointestinal Cancers Symposium

Breakout Session: Pro/Con-Hyperthermic Intraperitoneal Chemotherapy for Metastatic Colorectal Cancer

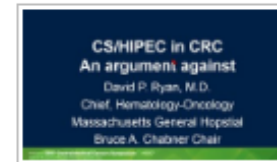
General Session

Cancers of the Colon, Rectum, and Anus Track
2017 Gastrointestinal Cancers Symposium



Pro
Hans J. Schlitt, MD
Speaker

[Watch Video](#)



Con
David P. Ryan, MD
Speaker

[Watch Video](#)

- Some but not all studies: advocated HIPEC
- No clear guidelines

Baratti, Ann Surg Oncol 2016
Elias, J Clin Oncol 2009

Outline

- **Updates in Colorectal cancer**

Definition of T4a

Tumor deposits

Isolated tumor cells

Tumor deposits: AJCC 7th Edition

- Discrete foci of tumor in pericolic fat**
- No evidence of residual lymph node tissue**
- N1c in the absence of nodal involvement**

Tumor Deposits

Reasons for discrepancy

- **Minimum distance from invasive front**
- **Minimum size**
- **Venous invasion/perineural invasion or tumor deposit**
- **Tumor deposit after neoadjuvant therapy**

Challenges in Interpretation

Distance from Invasive Front	Study
>2 mm	Ueno, Am J Surg 2014
>5 mm	Nagoyoshi, Dis Colon Rectum 2014
>10 mm	Gopal, Mod Pathol 2014

Study	Size of Tumor Deposit
Nagtegaal, J Clin Oncol 2011	<3 mm
Nagayoshi, Dis Col Rectum 2014 Lin, Oncol Targets 2015	Only if grossly identified
Other studies	Criteria not specified

AJCC definition

- No minimum distance
- No minimum size

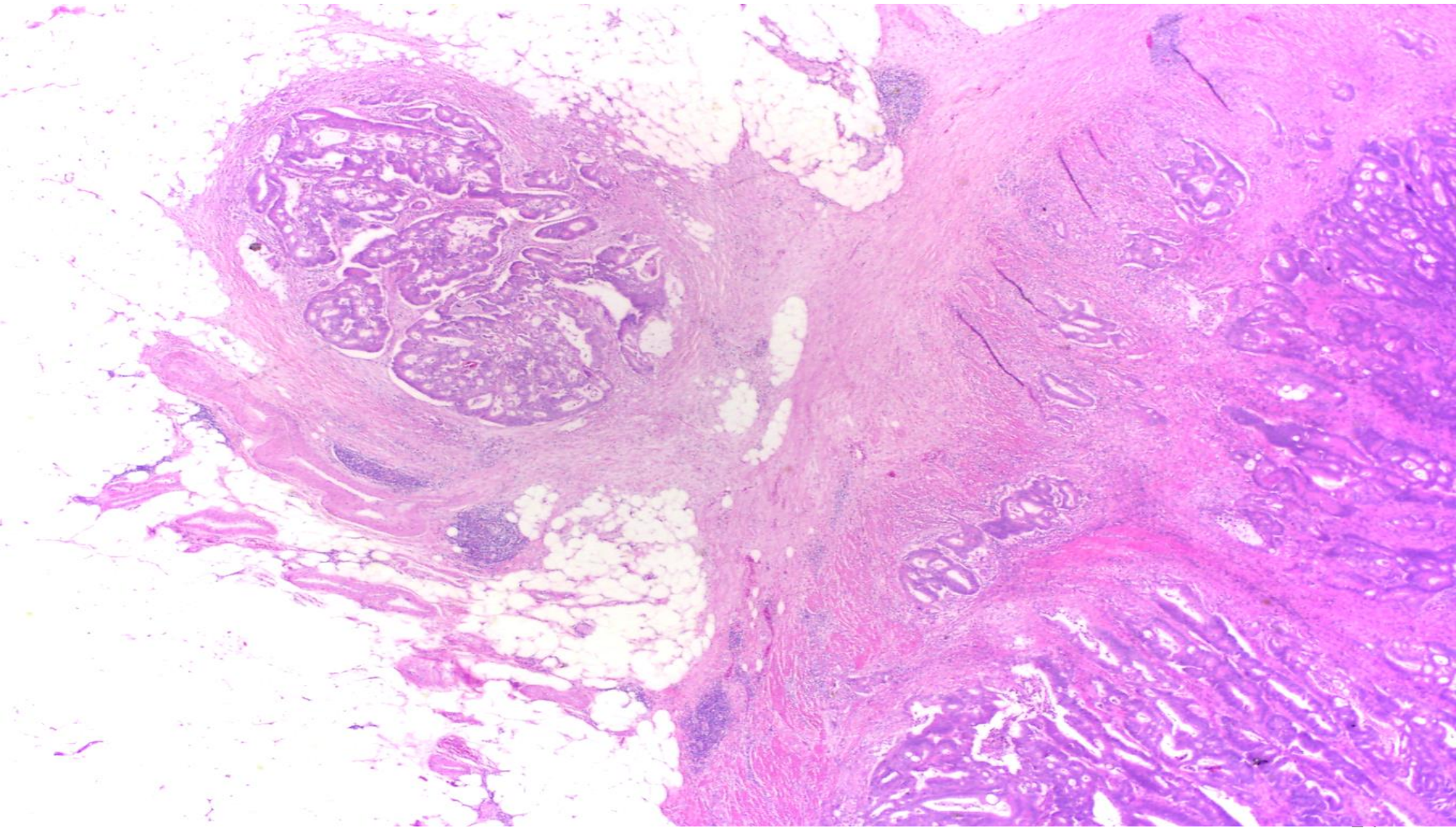
Venous invasion or tumor deposit

	VI with extravascular spread	VI confined to vessel wall
Goldstein (2000)	Tumor deposit	
Lin (2015) Nagoyoshi (2014) Ueno (2011)	Tumor Deposit	Vascular invasion

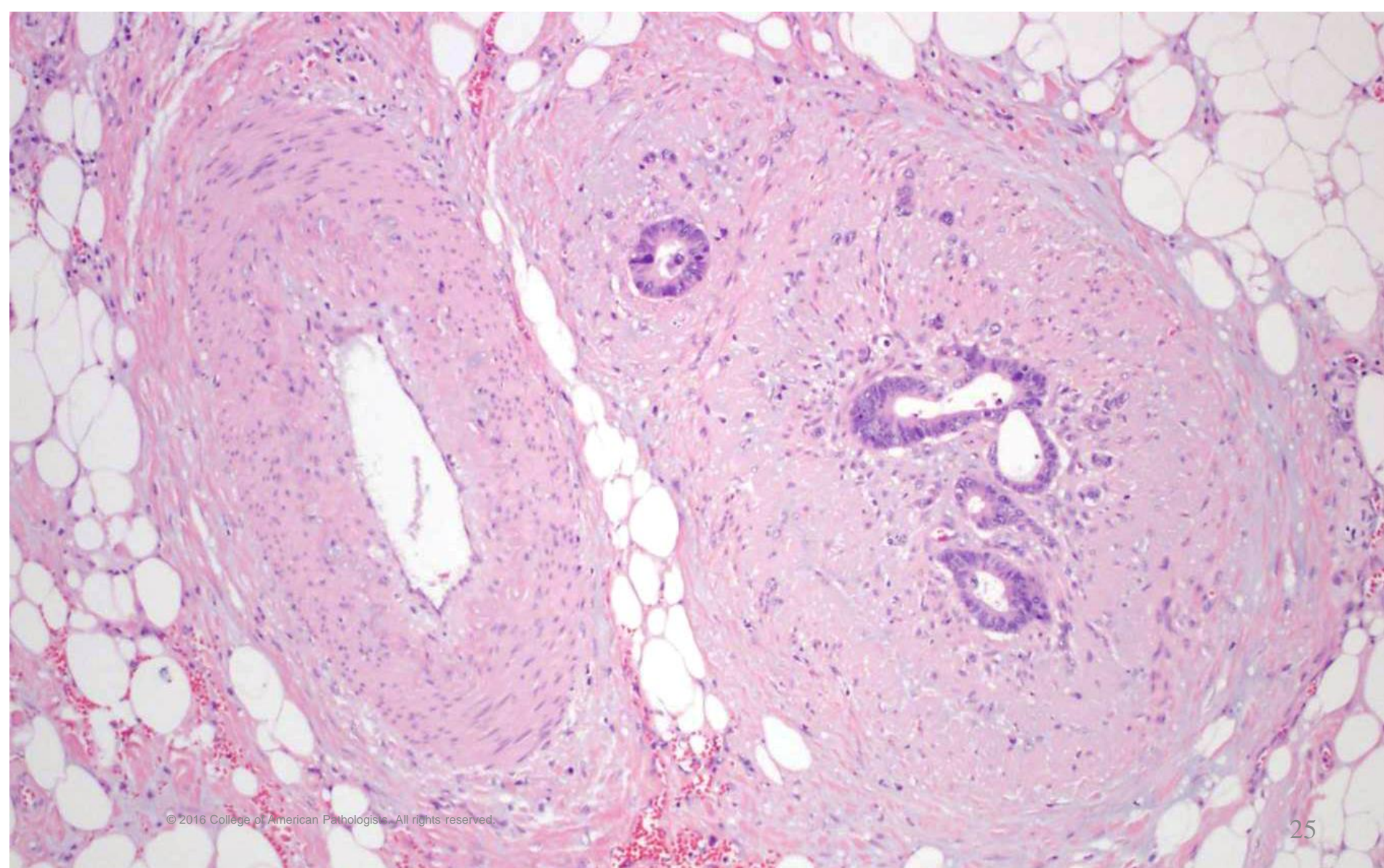
Tumor deposits: AJCC 8th Edition

- Tumor focus in the pericolic/perirectal fat or in adjacent mesentery within the lymph drainage area of the primary tumor, but without identifiable lymph node or vascular structure
- Vessel wall or its remnant (H&E, elastic, or any other stain): vascular (venous) invasion
- Tumor focus in or around a large nerve: PNI

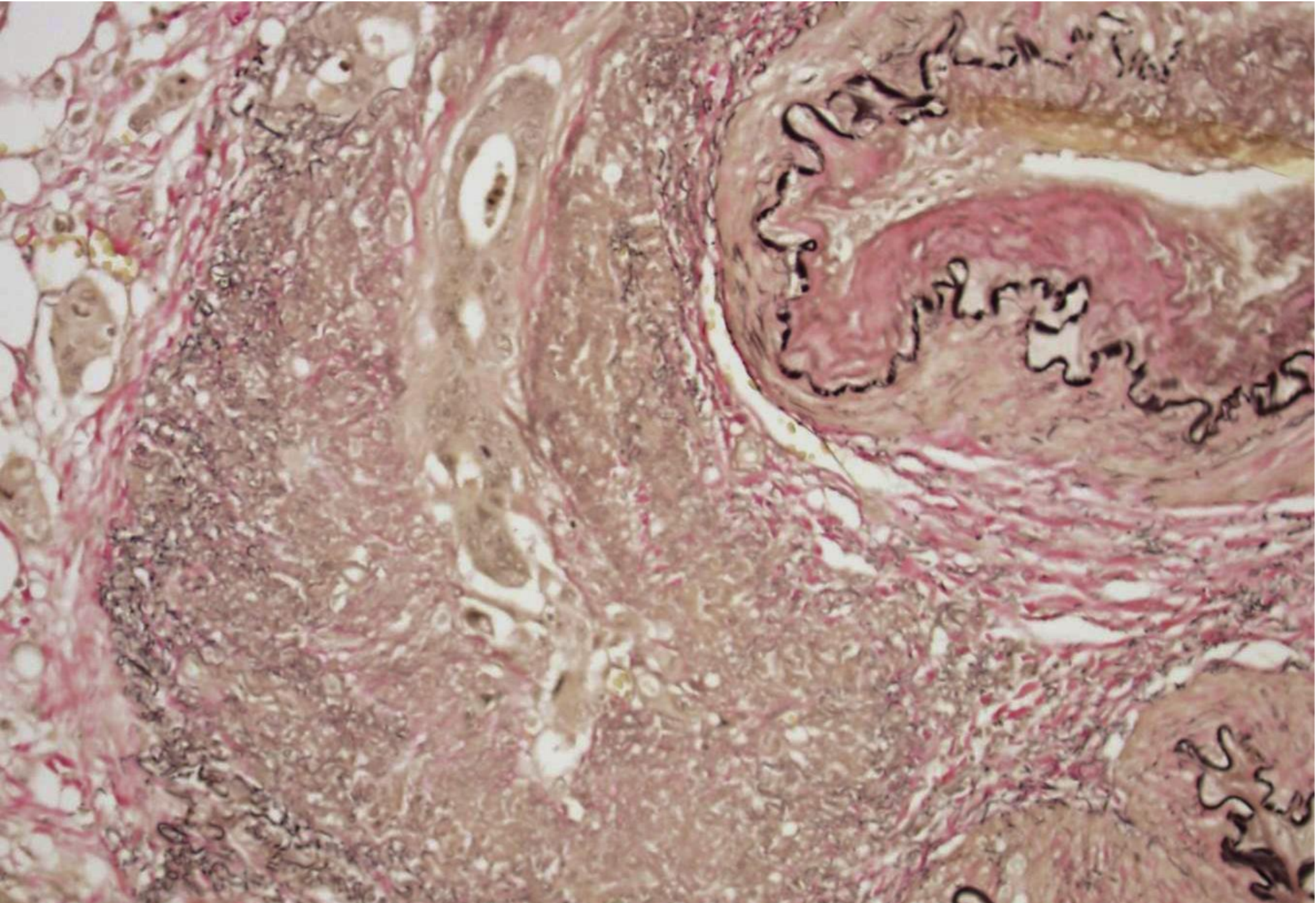
'Protruding Tongue' sign



'Orphan Artery' sign

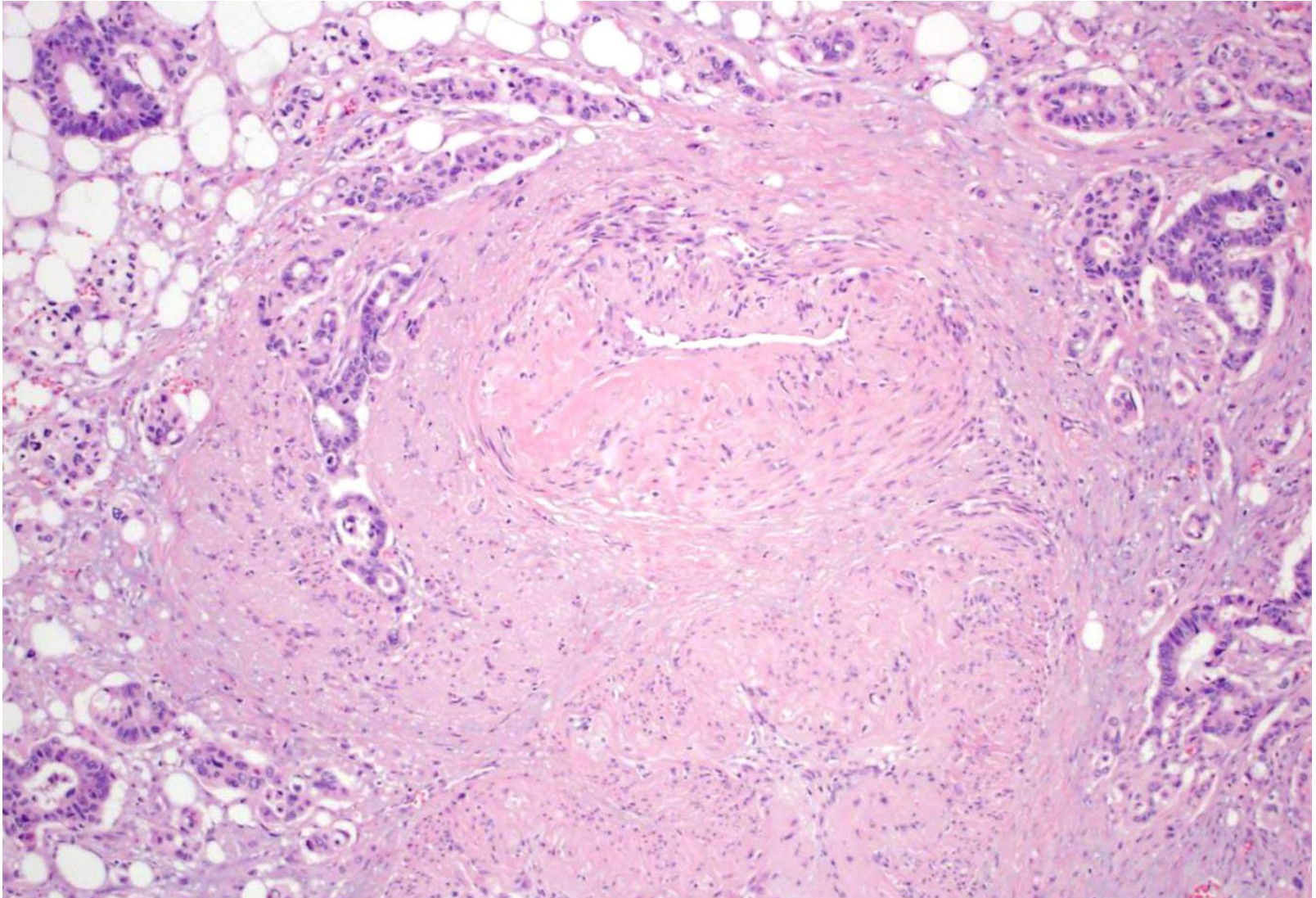


Elastic stain: venous invasion



T3 tumor, negative lymph nodes

T3N1c: stage III or T3N0 with VI: Stage II



CRC: Extramural venous invasion

- **Independent predictor of poor outcome**
- **NCCN: High risk feature in stage II disease**
- **Likely to receive chemotherapy**

Recommendations:

- **Record separately from small vessel invasion**
- **Consider elastic stain**

Challenges in Interpretation

- Minimum distance from invasive front
- Minimum size
- Replaced lymph node or tumor deposit
- Venous invasion/perineural invasion or tumor deposit
- **Tumor deposit after neoadjuvant therapy**

Tumor deposit after therapy

- **Residual primary tumor can be mistakenly classified as N1c**
- **Proximity to areas of fibrosis or acellular mucin favors residual primary tumor**
- **Elastic stain: venous invasion**

N1c in practice

Lymph node	Thick capsule Subcapsular sinus Rim of lymphocytes
Venous invasion	Accompanying artery Elastic stain
Perineural invasion	Large nerves
Tumor deposit	No remnant lymph node, large nerve or vein

Do not add tumor deposits and lymph nodes for

- **N category**
- **Assessing adequacy of LN dissection**

Isolated tumor cells

Size of nodal metastasis	AJCC 7 th edition
0.2 to 2 mm	Micrometastasis pN1mi
Less than 0.2 mm	Isolated tumor cells (ITC) pN0 (i+) pN0 (mol+)

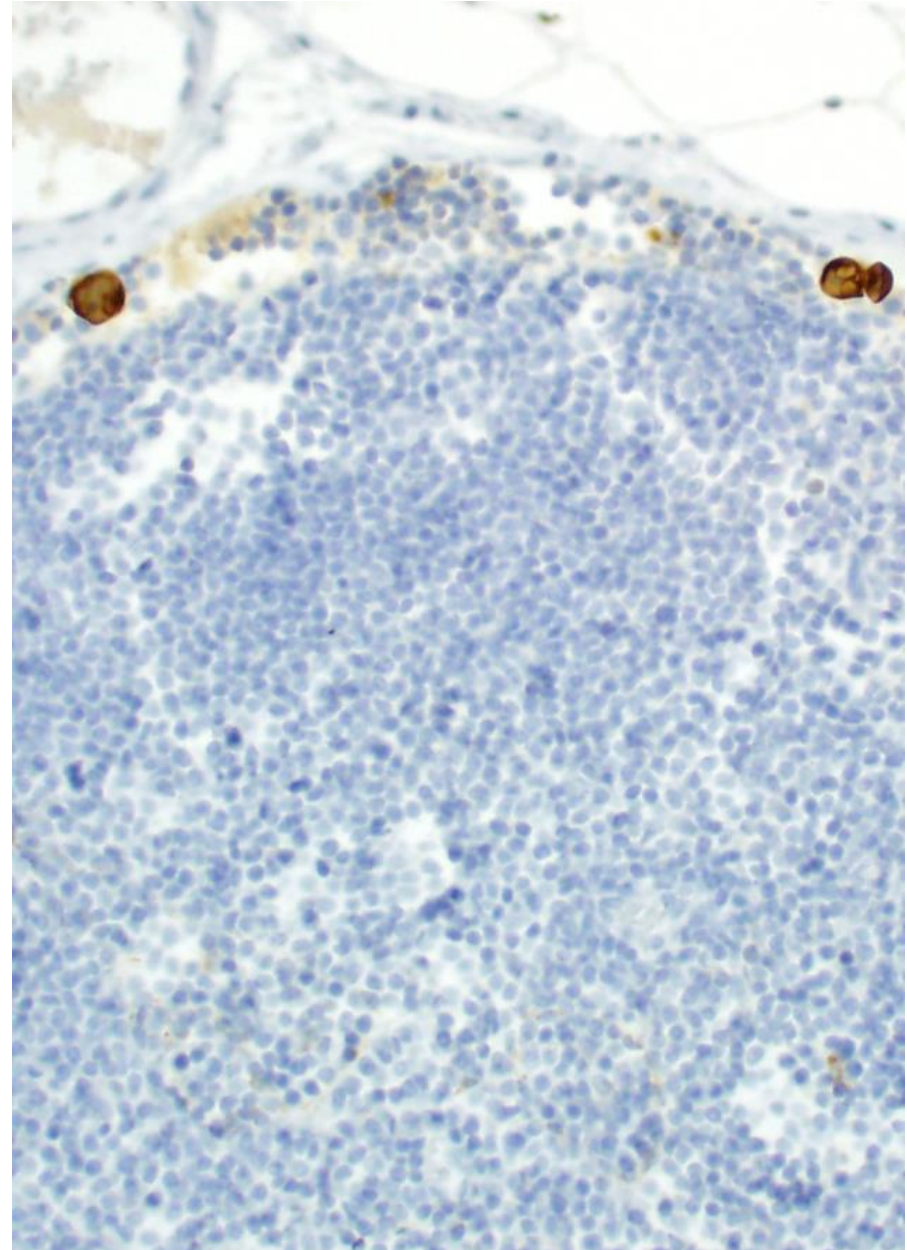
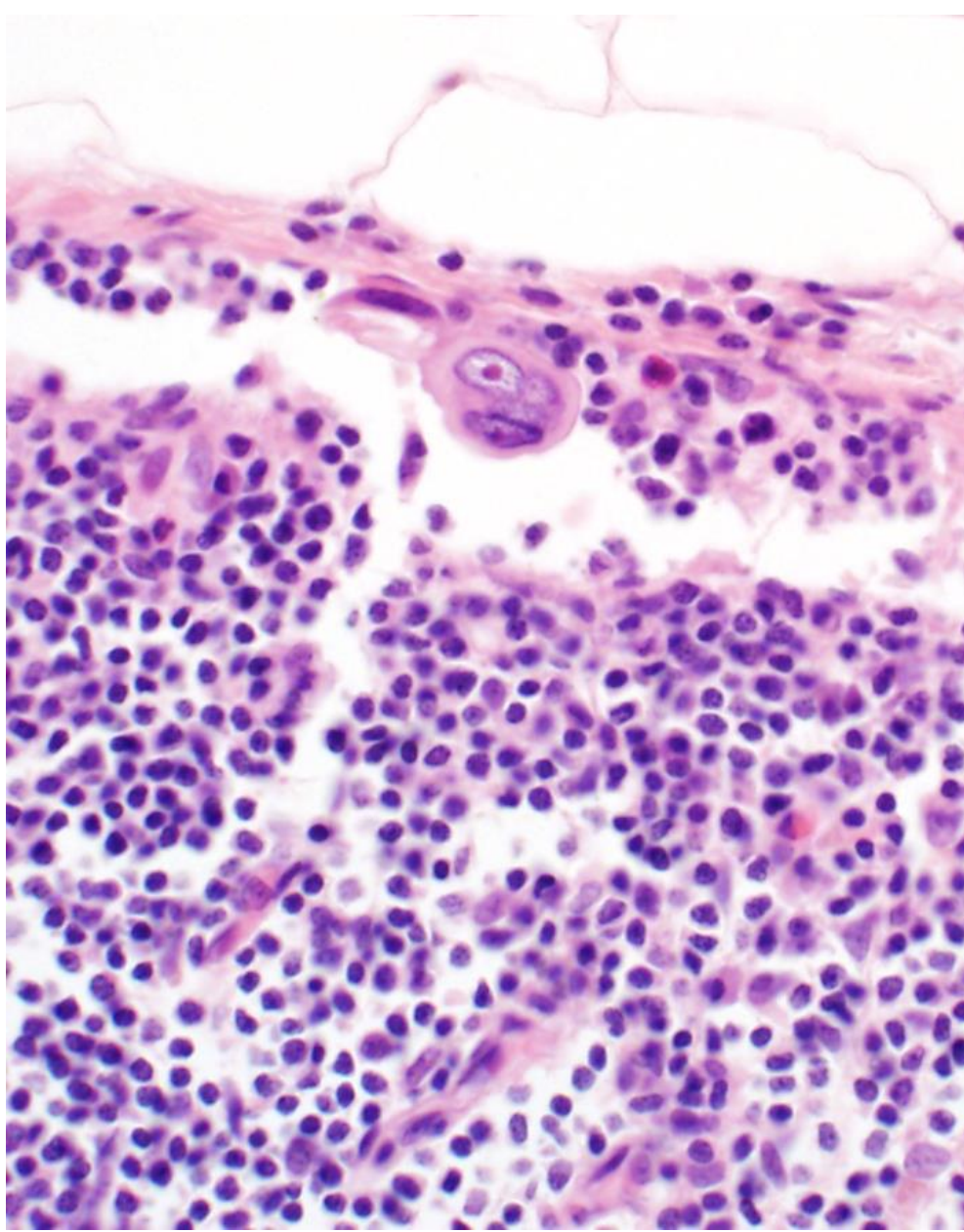
Isolated tumor cells, micrometastasis

Study	Design	Conclusion
Sloothak, Eur J Surg Oncol 2014	Meta-analysis 5 studies	-Increased recurrence with micrometastasis -No increased risk with ITC
Rahbari, JCO 2012	Meta-analysis 39 studies	-Increased recurrence with micrometastasis -Insufficient data for ITC
Mescoli, JCO 2012	Keratin in N0, n=312	-Higher relapse with ITC (14% vs. 5%)
Protic, J Am Coll Surg 2015	Keratin in N0, n=312 Prospective	-Higher relapse with ITC (17% vs. 3%) -T3 and T4 (not T1 and T2)
Greenon, Cancer 1994	Keratin in N0, n=50	-Higher relapse with ITC (43% vs. 3%)

AJCC 8th edition

Size of nodal metastasis	AJCC 8 th edition
0.2 to 2 mm	Use pN1 pN1mi not necessary
Less than 0.2 mm	Use N0 No definite recommendation for using N0(i+)

Isolated tumor cells



Adenocarcinoma in polyp

AJCC 8th edition: definitions clarified

- **Intramucosal adenocarcinoma (Tis)**

Not beyond muscularis mucosa

- **Invasive adenocarcinoma (T1 or beyond)**

Submucosa or beyond

Tis and T1 in practice

- **Clarify in report**

Intramucosal adenocarcinoma is Tis and has virtually no propensity for LN mets

- **T1 adenocarcinoma in polyp**

Include prognostic factors to enable decision about resection

Invasive adenocarcinoma (T1) in polyp

Indications for colectomy

Prognostic features

Grade: poor differentiation

Lymphovascular: present

Margin: ≤ 1 mm

Depth of submucosal invasion

Tumor budding

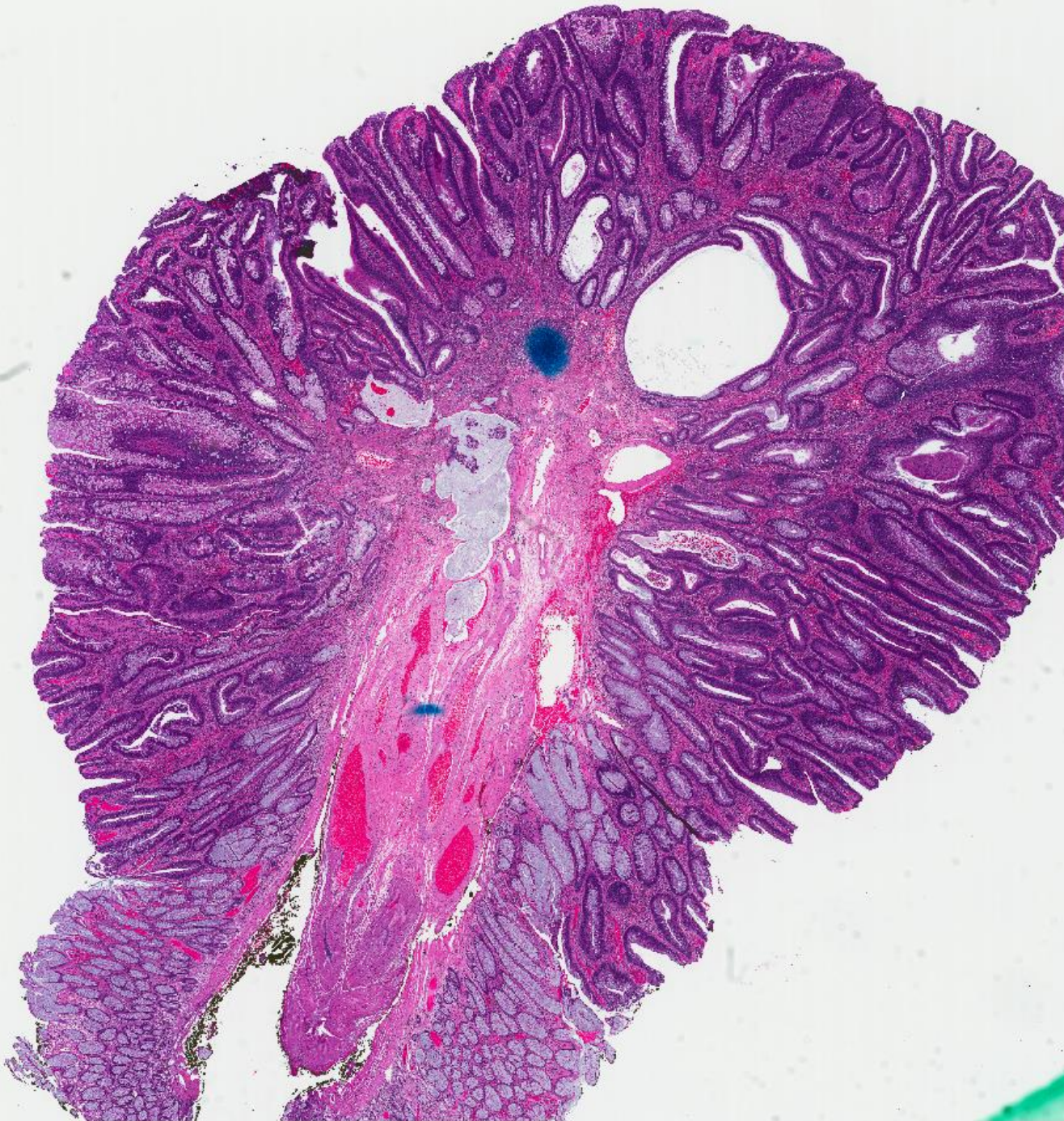
Pedunculated polyp: Haggitt levels

Level 1: Head

Level 2: Neck

Level 3: Stalk

Level 4: Beyond stalk

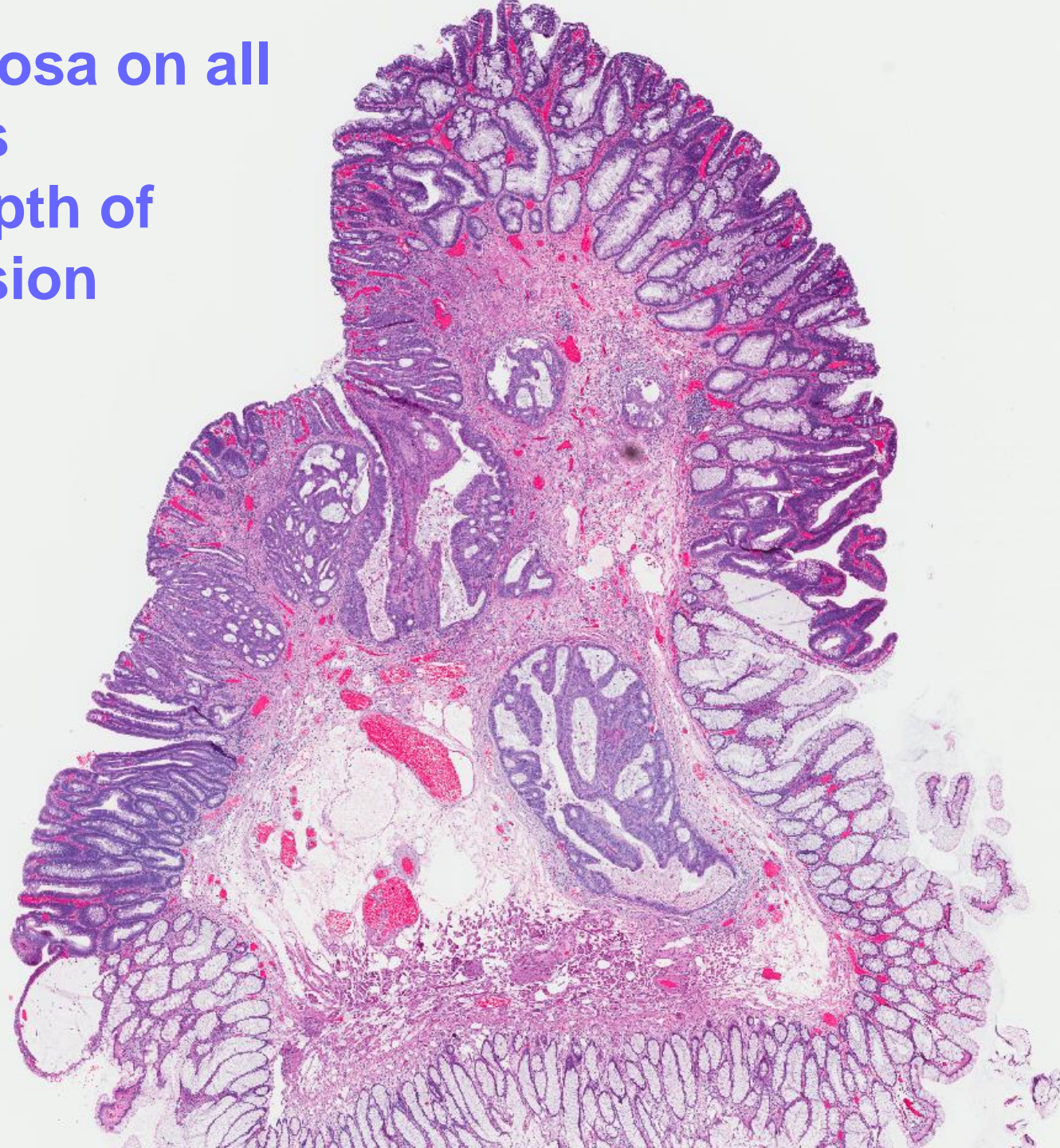


Kikuchi levels

SM1, SM2 and SM3

- Difficult to judge depth in absence of muscularis propria
- Measure depth from base of muscularis mucosa:
>1 mm is a high risk feature

-Mucosa on all
sides
-?Depth of
invasion



Invasive adenocarcinoma (T1) in polyp

Indications for colectomy

Prognostic features

Grade: poor differentiation

Lymphovascular: present

Margin: ≤ 1 mm

Depth of submucosal invasion

Tumor budding

Tumor budding

- Individual or small discrete cell clusters (<5 cells) at the invasive edge
- Independent adverse prognostic factor

Adjuvant therapy in stage II

Colectomy for malignant polyps

- Recommended:

UICC, ADASP, CAP, UK Royal College

Not included in NCCN

Steering Committee



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April 27–29, 2016

Kursaal Bern, www.kursaal-bern.ch

International Tumor Budding Consensus Conference ITBCC 2016



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Participants

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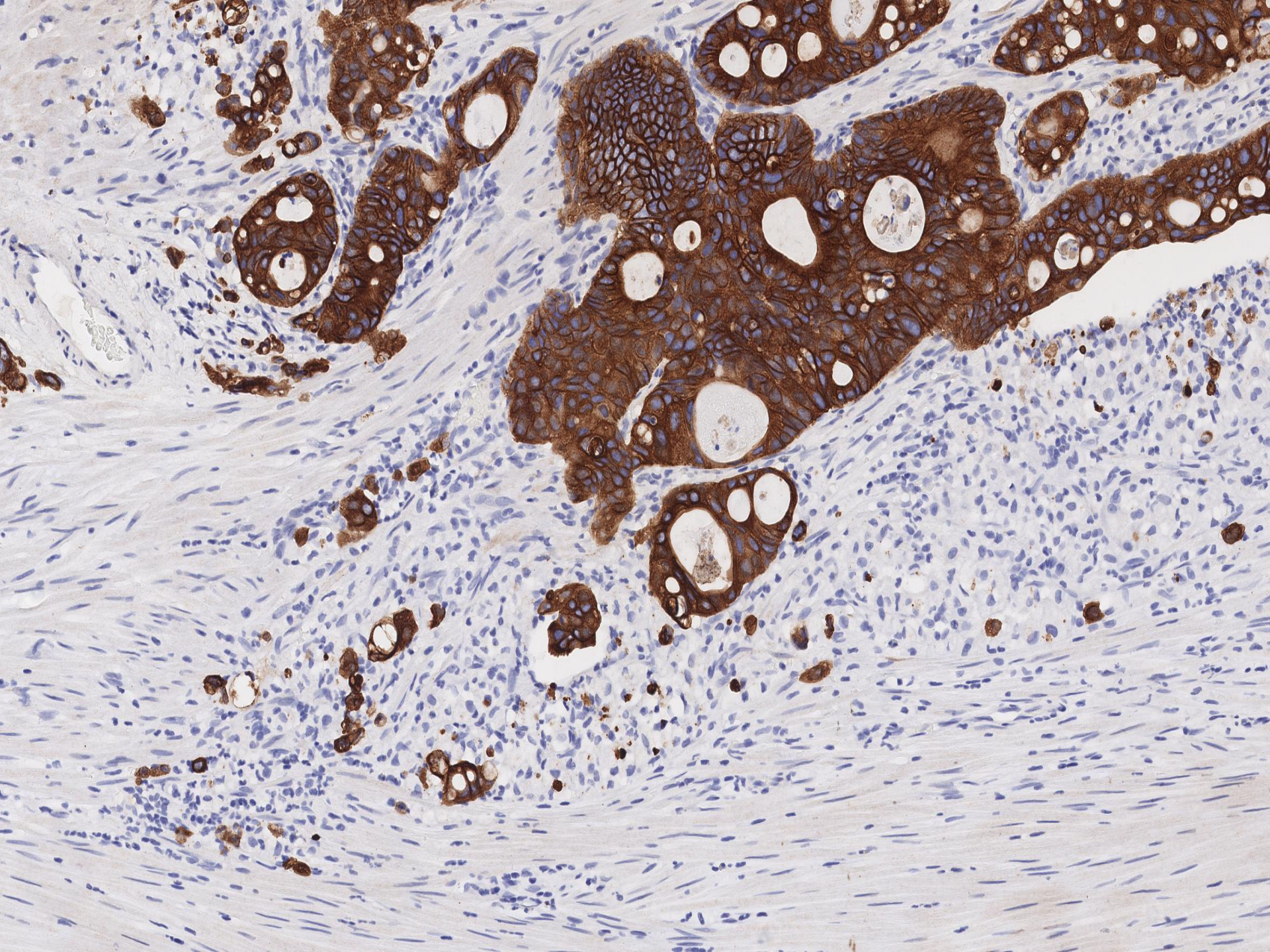
Consensus statements

Counting tumor buds

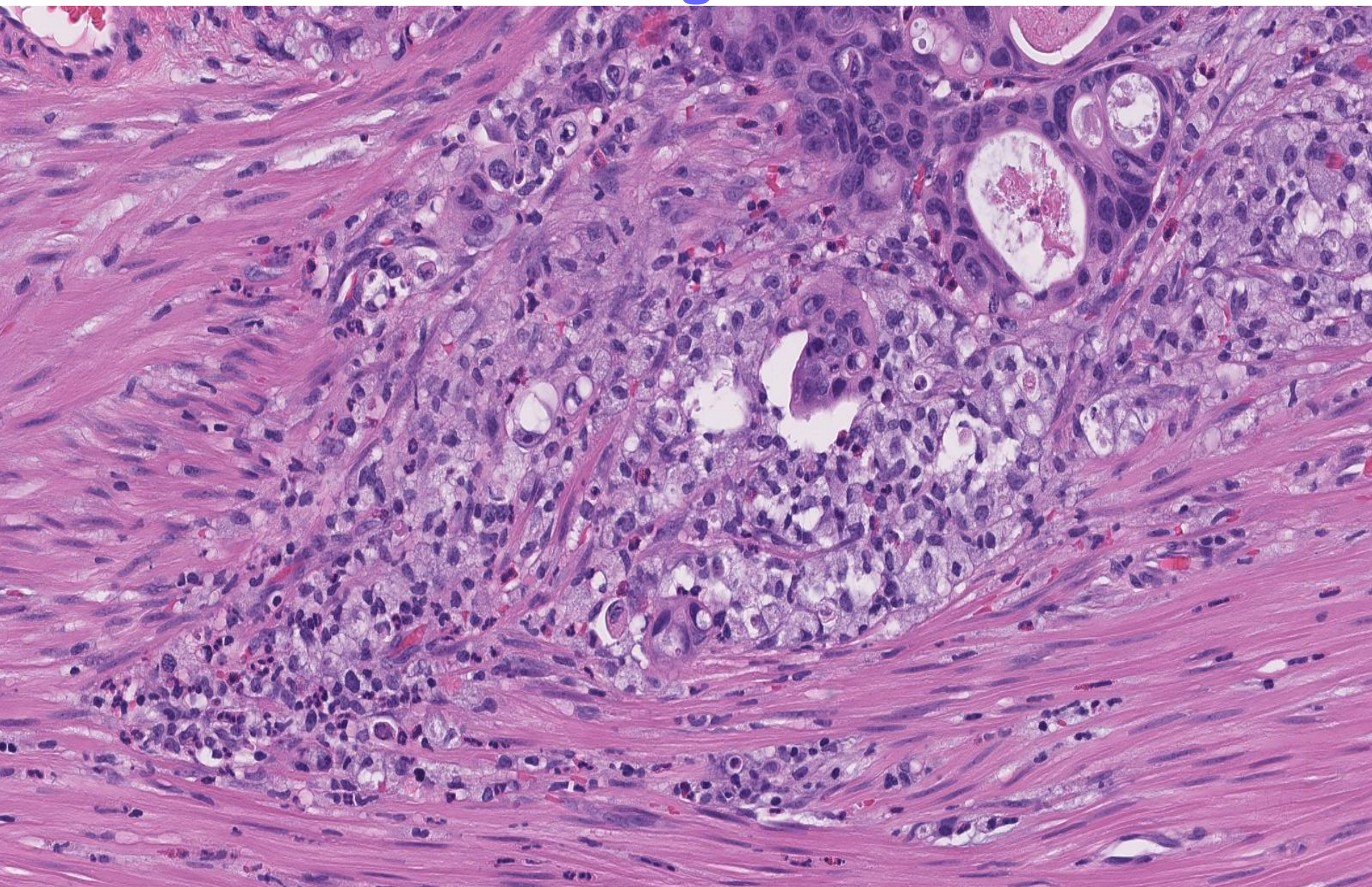
- **Tumor budding is counted on H&E**

Use of cytokeratin

- Most of the data is based on H&E stain
- Can increase tumor bud counts 3x
- Can use it in challenging cases (obscuring inflammation), but final count should be done on H&E



**Go back to H&E stain for
budding count**



Consensus statements

Counting tumor buds

- **The hot spot method (single field at the invasive front, size 0.785 mm²) is recommended**
 - Choose a 'hotspot'
 - Count in 20x field
 - Apply appropriate correction factor for your microscope

Conversion table

	Objective Magnification: 20x			
Eyepiece FN Diameter	Eyepiece FN Radius	Specimen FN radius	Specimen Area	Normalization Factor
(mm)	(mm)	(mm)	(mm ²)	
18	9.0	0.450	0.636	0.810
19	9.5	0.475	0.709	0.903
20	10.0	0.500	0.785	1.000
21	10.5	0.525	0.866	1.103
22	11.0	0.550	0.950	1.210
23	11.5	0.575	1.039	1.323
24	12.0	0.600	1.131	1.440
25	12.5	0.625	1.227	1.563
26	13.0	0.650	1.327	1.690

Consensus statements

Counting tumor buds

- A three-tier system should be used along with the budding count in order to facilitate risk stratification in CRC

Tumor budding score (0.785 mm²)

Low	0-4
Intermediate	5-9
High	≥ 10

Other changes: CAP protocol

Microsatellite instability

- Morphologic features omitted
- Universal testing recommended
- MMR immunohistochemistry or PCR

NCCN guidelines

EGAPP guidelines, Nat Genetics, 2009

Outline

- **Updates in Colorectal cancer**

 - Definition of T4a

 - Tumor deposits

 - Isolated tumor cells

- **Selected other updates**

 - Pancreas, gallbladder, ampulla

Ampulla: staging challenges

Location

- Intra-ampullary
- Peri-ampullary

Histologic subtype

- Pancreaticobiliary
- Intestinal

Ampulla: AJCC 8th edition

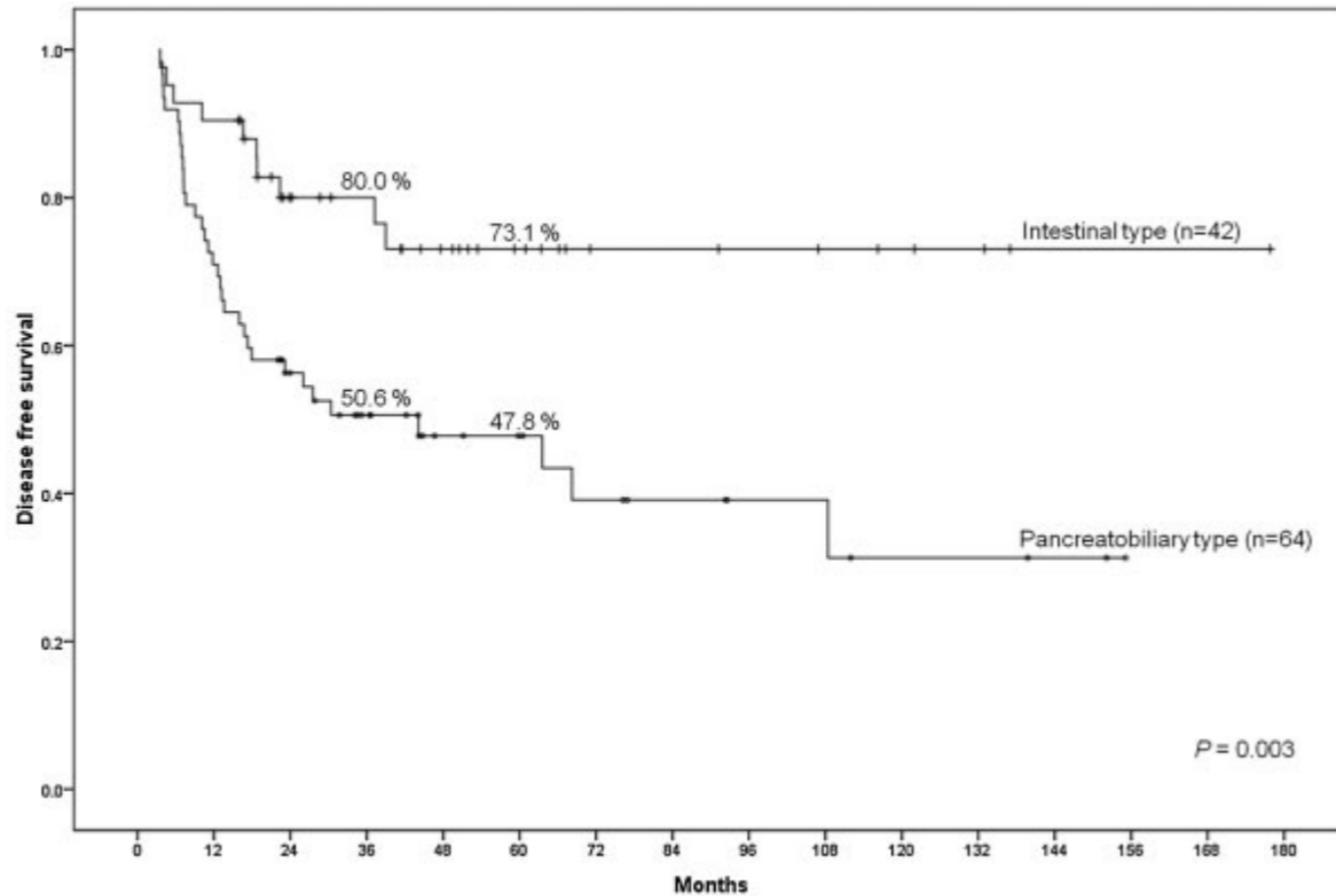
Change	Details
T1 subdivision	T1a: Limited to ampulla of Vater or sphincter of Oddi T1b: Invades beyond the sphincter of Oddi and/or into the duodenal submucosa
T2 redefined	Invasion into the muscularis propria of duodenum
T3 subdivision	T3a: Directly invades the pancreas (up to 0.5 cm) T3b: Extends more than 0.5 cm into the pancreas or extends into peripancreatic or periduodenal tissue or duodenal serosa

Ampulla

Change	Details
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, irrespective of size

Ampullary adenocarcinoma

Pancreaticobiliary vs intestinal



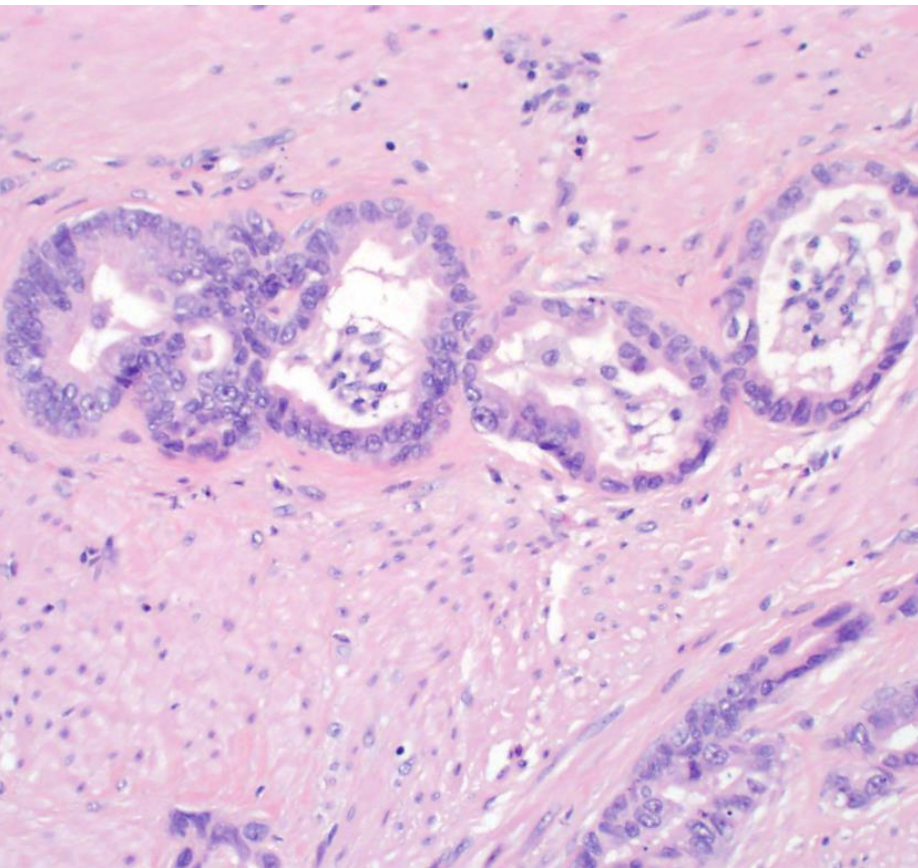
AJCC 8th edition: Ampulla

Recommendation

- Histologic subtypes should be characterized for patient care
- May help guide the use of adjuvant therapy
Gemcitabine-based (pancreaticobiliary) vs.
5-FU based (gastrointestinal)

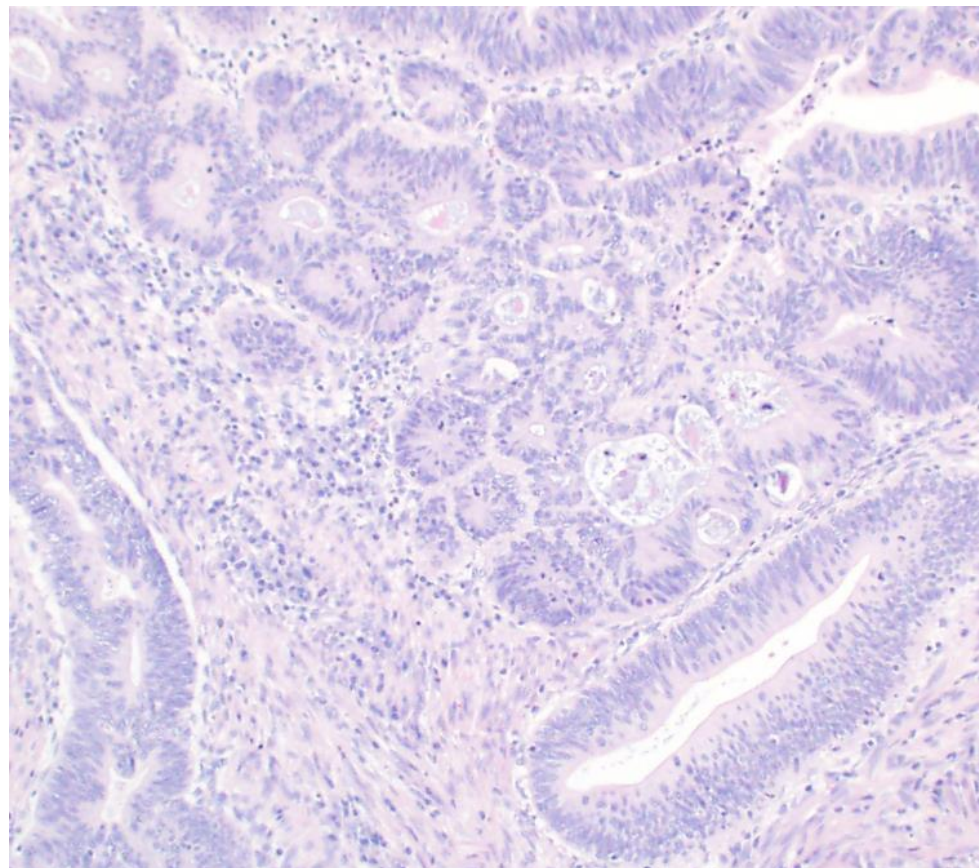
Pancreaticobiliary

- Rounded, cuboidal to low columnar
- No pseudostratification
- Marked variation in size shape
- Desmoplastic stroma



Intestinal

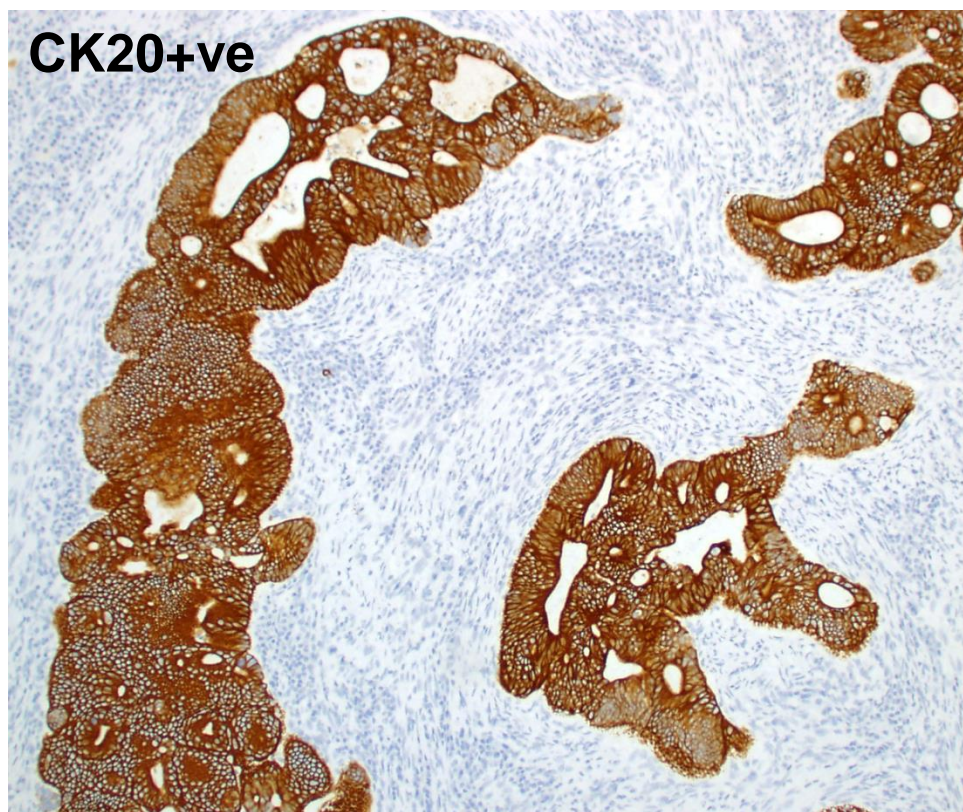
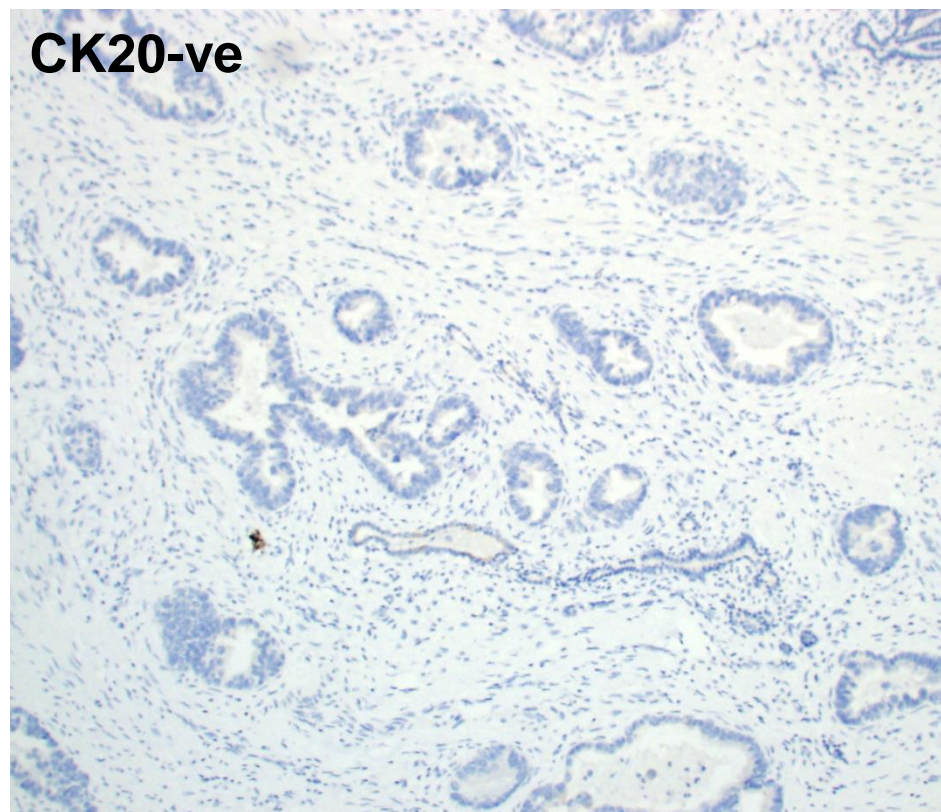
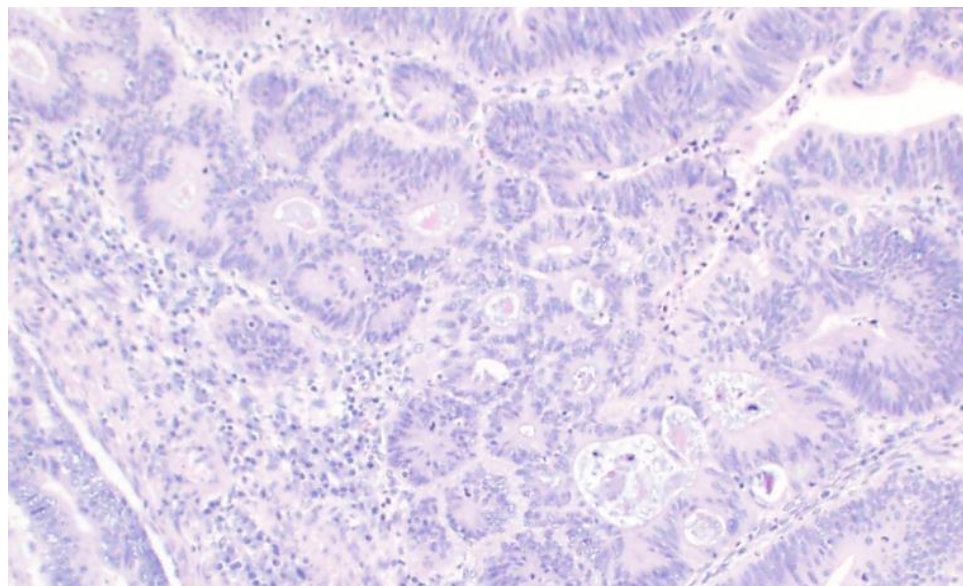
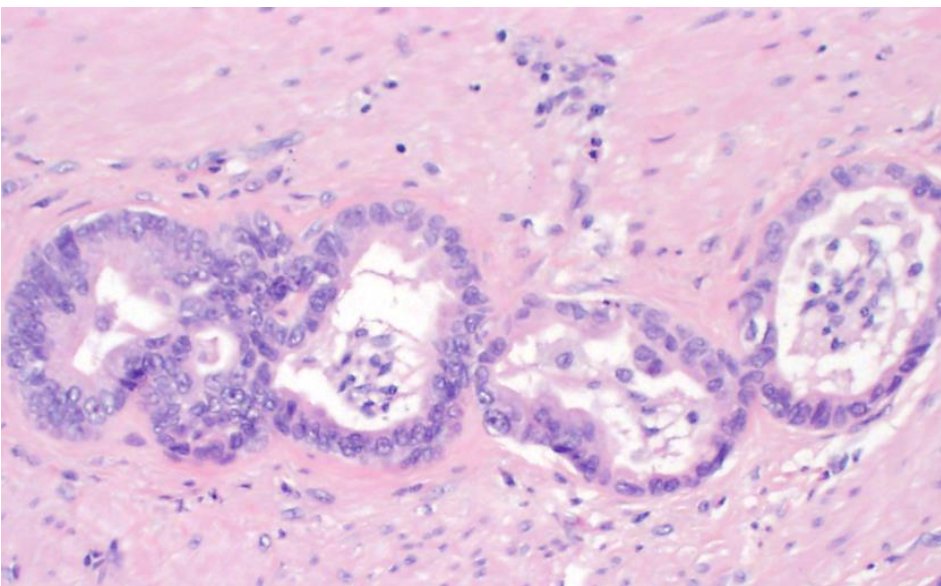
- Resemble colon cancer
- Cribriform architecture
- Tall, pseudostratified columnar
- 'Dirty necrosis'
- Extracellular mucin

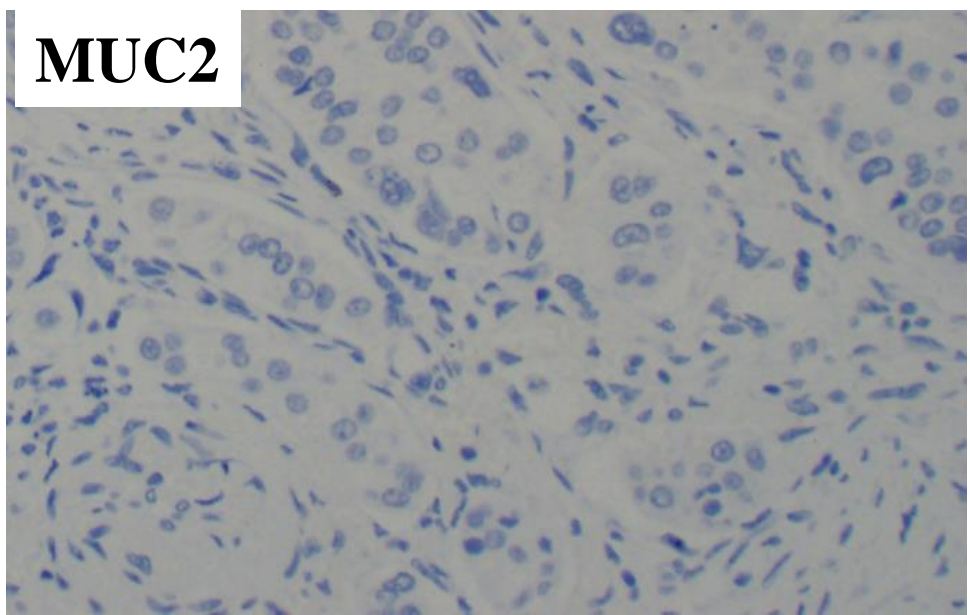
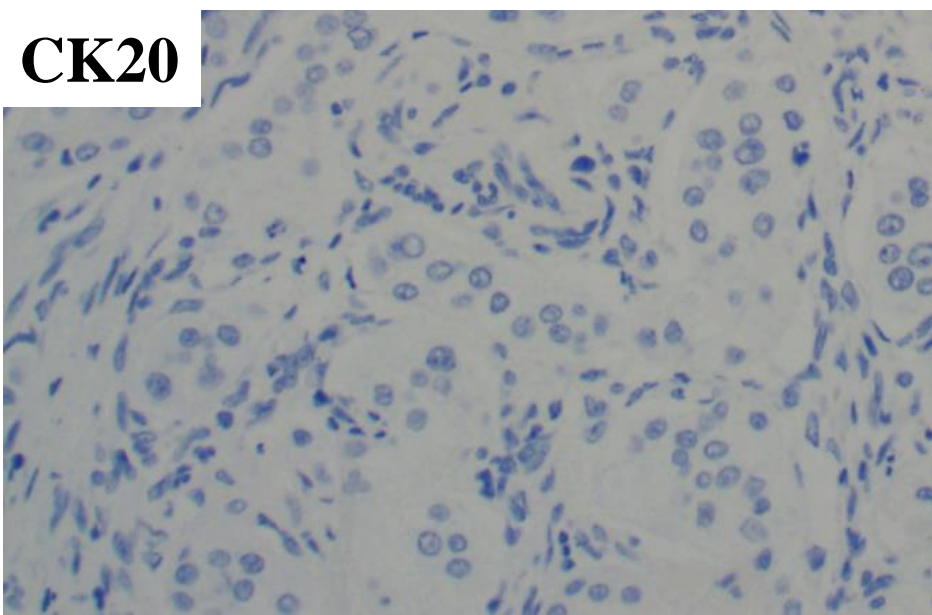
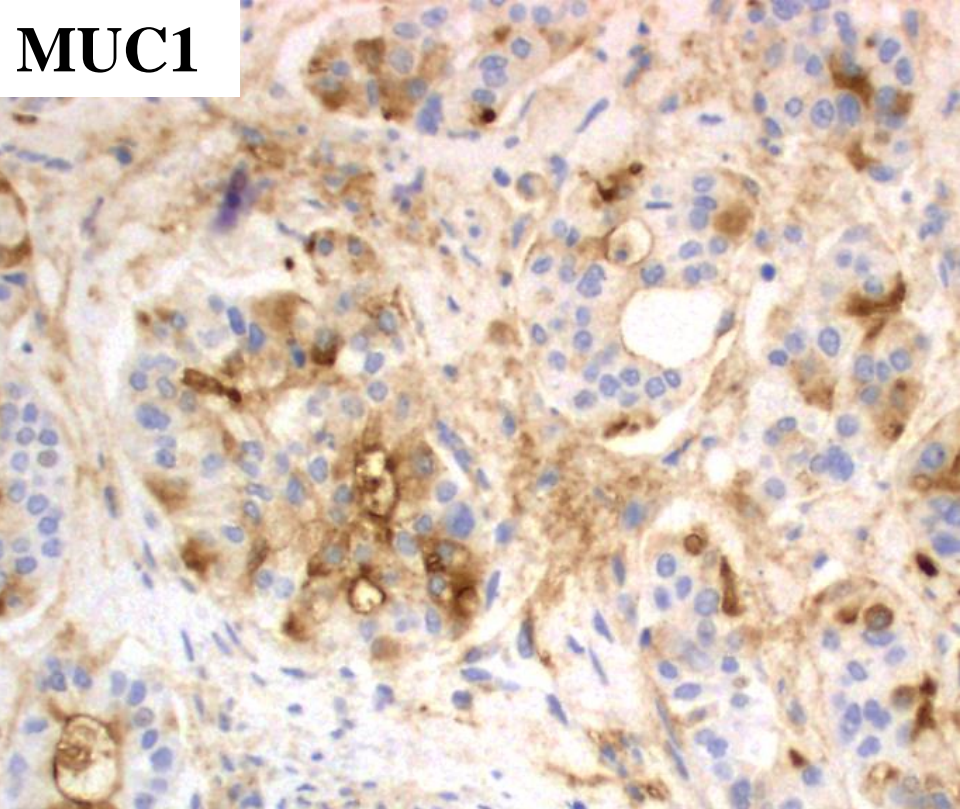
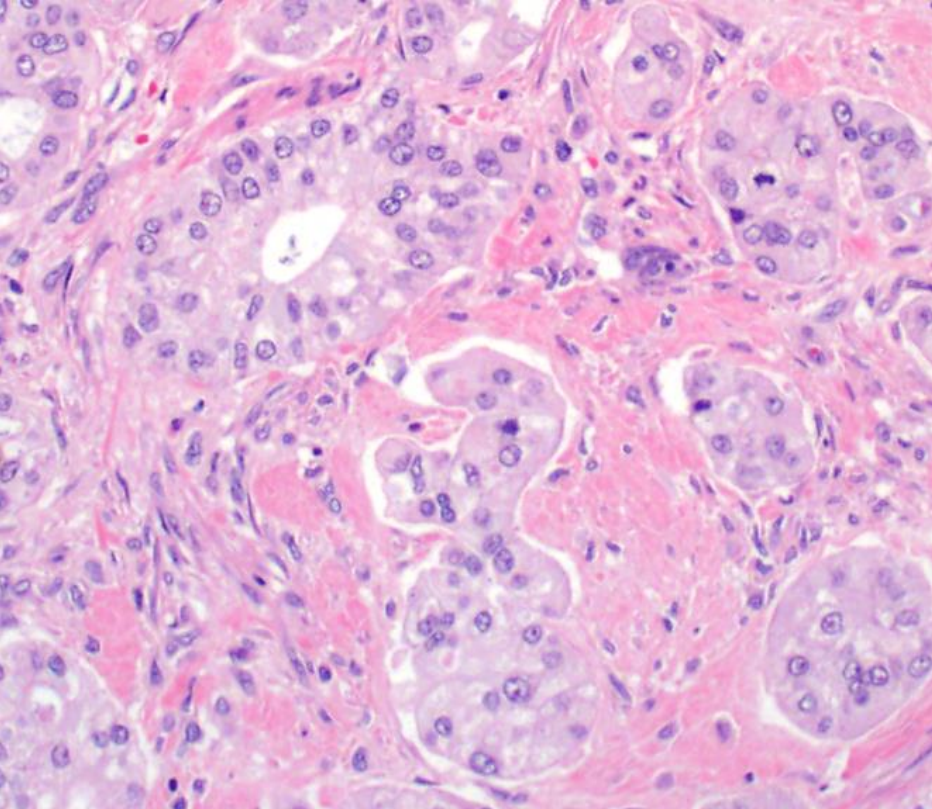


Ampullary adenocarcinoma

Immunohistochemistry

Study	Definition of subtype
Ang, AJSP 2014 CK20, CDX2, MUC1, MUC2 >25% staining considered +ve	INT: <ul style="list-style-type: none">• CK20+ or CDX2+ <u>or</u> MUC2+ and MUC1 negative, or• CK20+ CDX2+ <u>and</u> MUC2+ Irrespective of MUC1 PB: MUC1+, CDX2- MUC2- Irrespective of CK20





Ampullary adenocarcinoma

Immunohistochemistry

Study	Definition of subtype
Scheuneman, Br J Cancer 2015 MUC1: any CDX2: score >35	PB: PB histology, MUC1+, CDX2- INT: all others

Ampullary adenocarcinoma

Histologic typing: Problems

- **15-20% ambiguous even after immunohistochemistry**
- **Not independent predictor of outcome in some studies**
- **Biopsies may not be representative**

Reid, Mod Pathol 2016

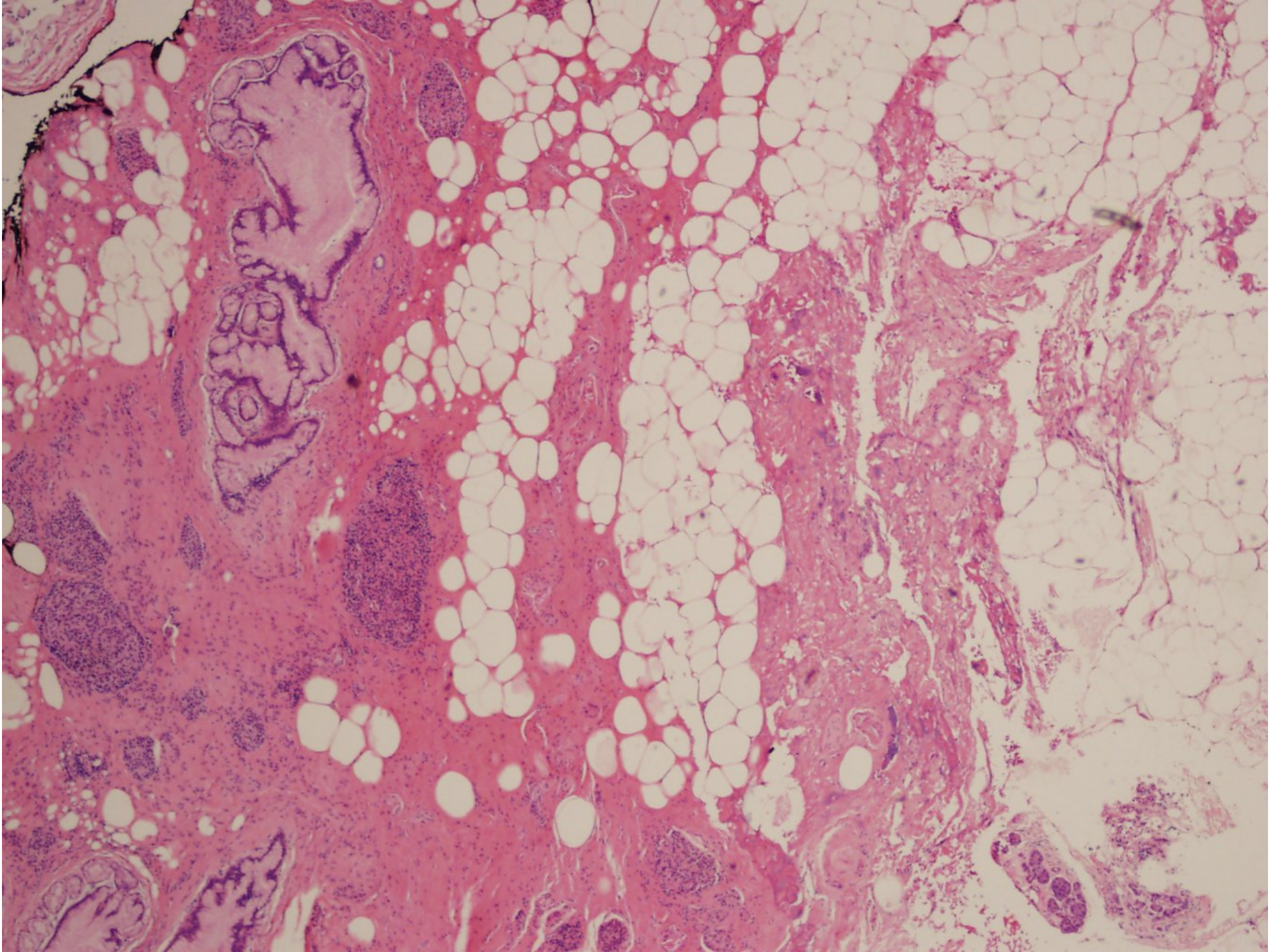
Perysinakis, Int J Surg Pathol 2017

Pancreas: staging updates

- **Changes in T category**
- **Changes in N category**
- **Definition of positive uncinate margin**

Pancreas: Problems in staging in AJCC 7th edition

T stage	Problem
T1 T2 T3	<ul style="list-style-type: none">-Uneven stage groupings-Lack of correlation with outcome
T3 criteria	<ul style="list-style-type: none">-Extrapancreatic involvement

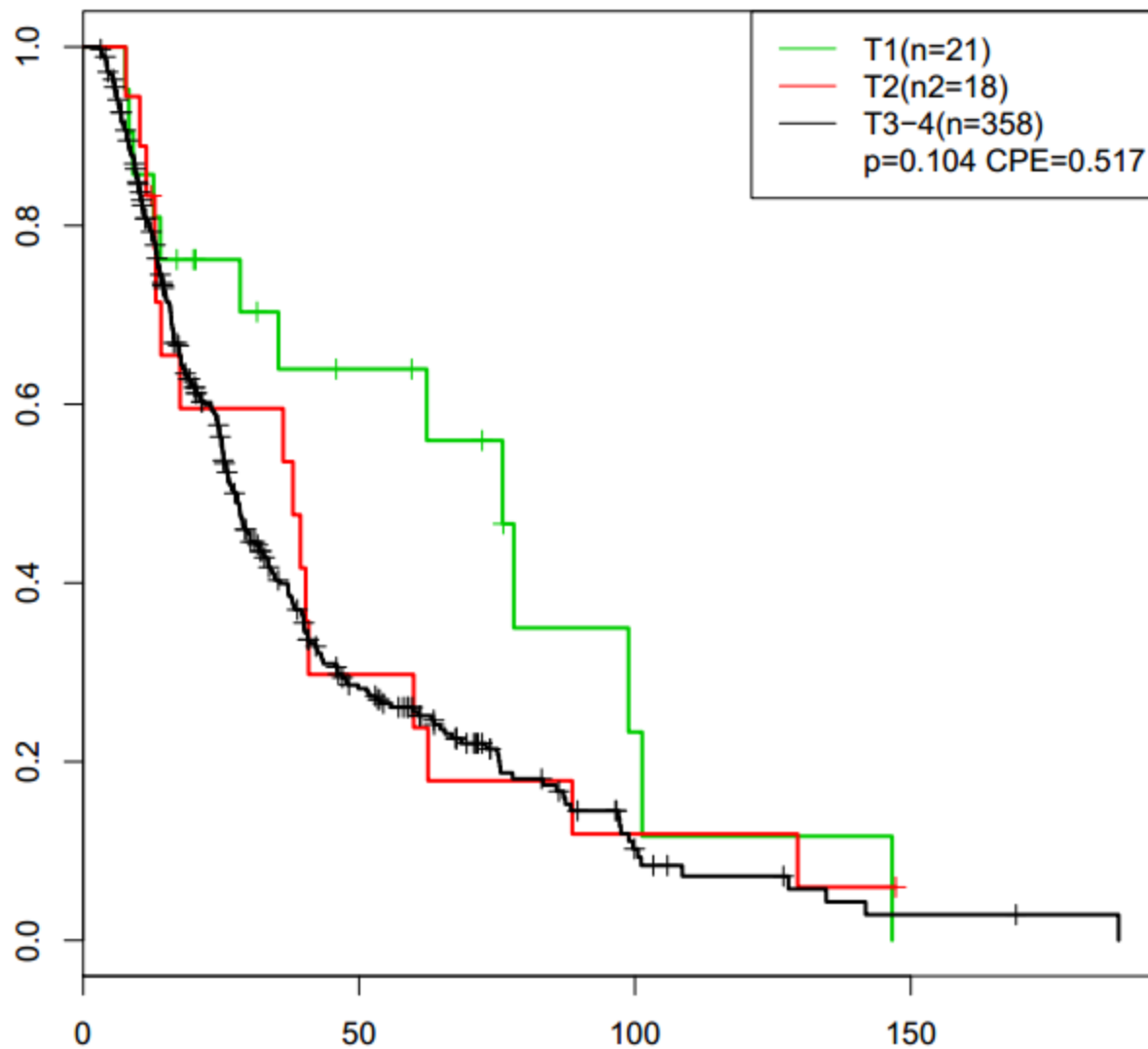


T1 vs. T2 vs. T3

uneven stage groupings

Study	T grouping
Ferrone, Surgery 2012 (n=499)	T1: 9% T2: 15% T3: 76%
Saka/Adsay, USCAP 2014 (n=250)	T1: 2% T2: 2% T3: 95%
Basturk/Allen/Klimstra, MSKCC, unpublished (n=397)	T1: 5% T2: 5% T3: 90%

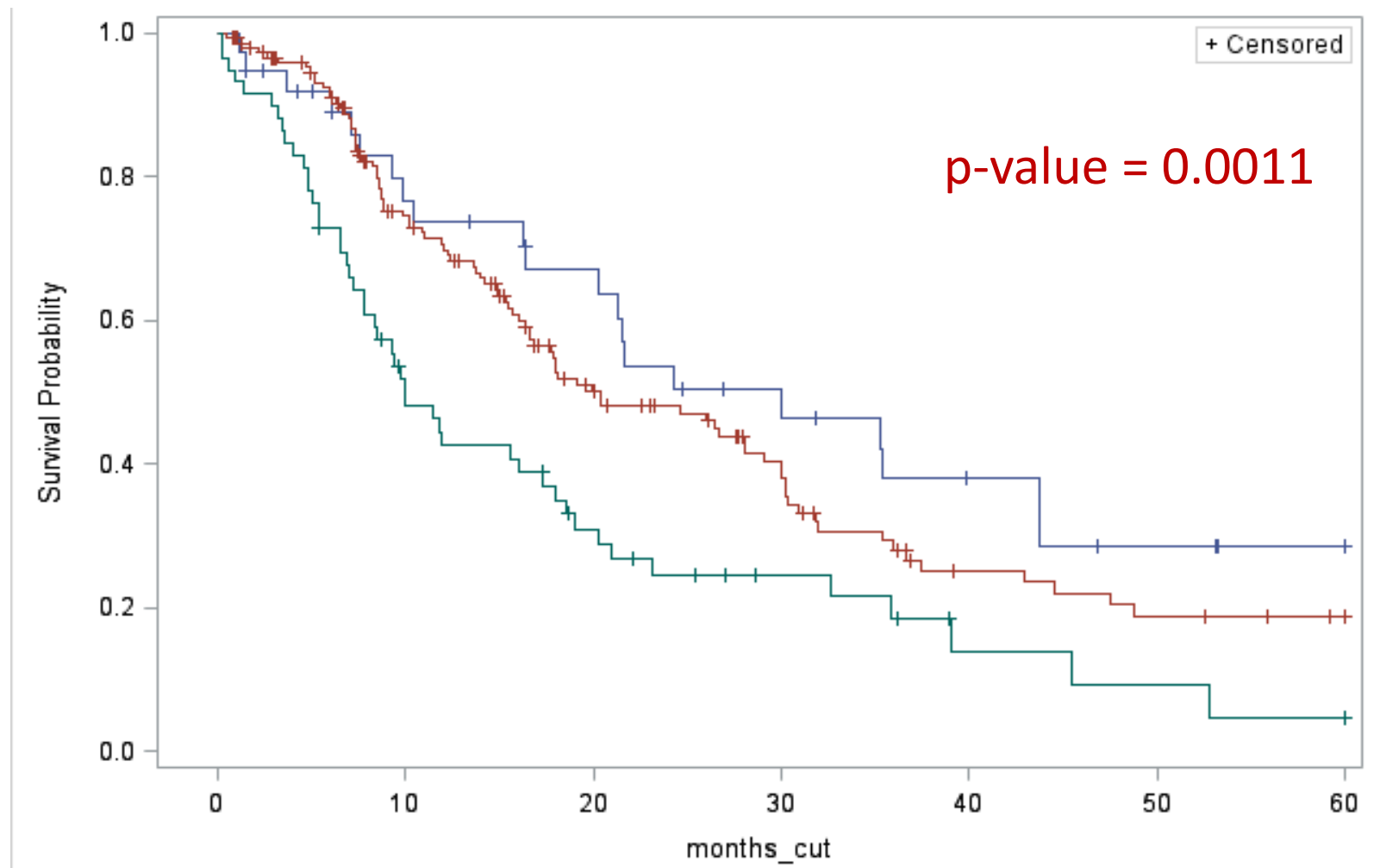
Allen, Ann Surg 2017



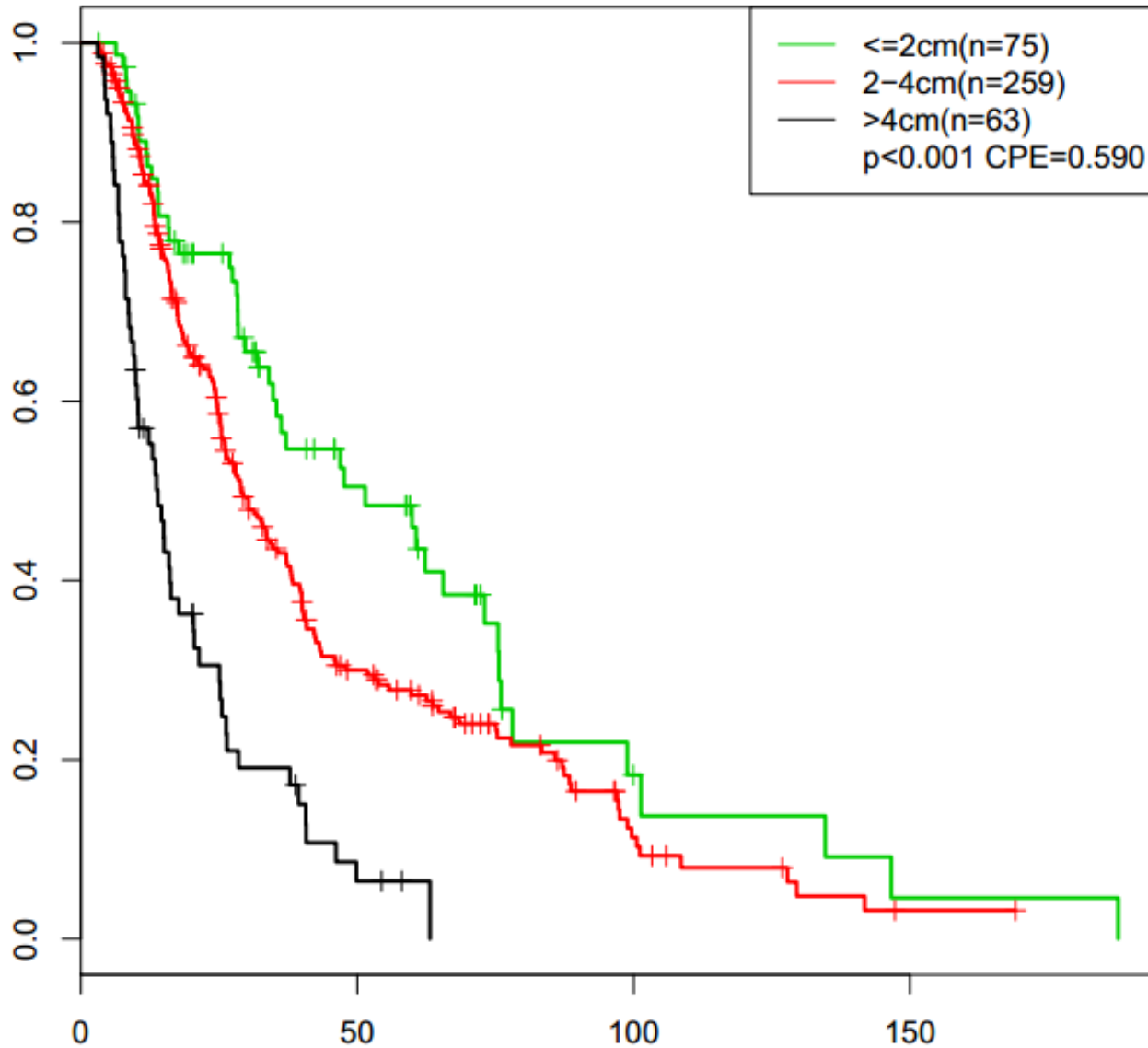
Pancreas staging: 8th edition

Change	Details
T1 subcategories	T1: Up to 2 cm T1a ≤ 0.5 cm T1b $>0.5 <1$ cm T1c 1-2 cm
T2 and T3 based on size	T2: >2 and <4 cm T3: >4 cm Extrapancreatic extension is no longer part of the definition

Saka, Ann Surg Oncol 2016



Allen, Ann Surg 2017



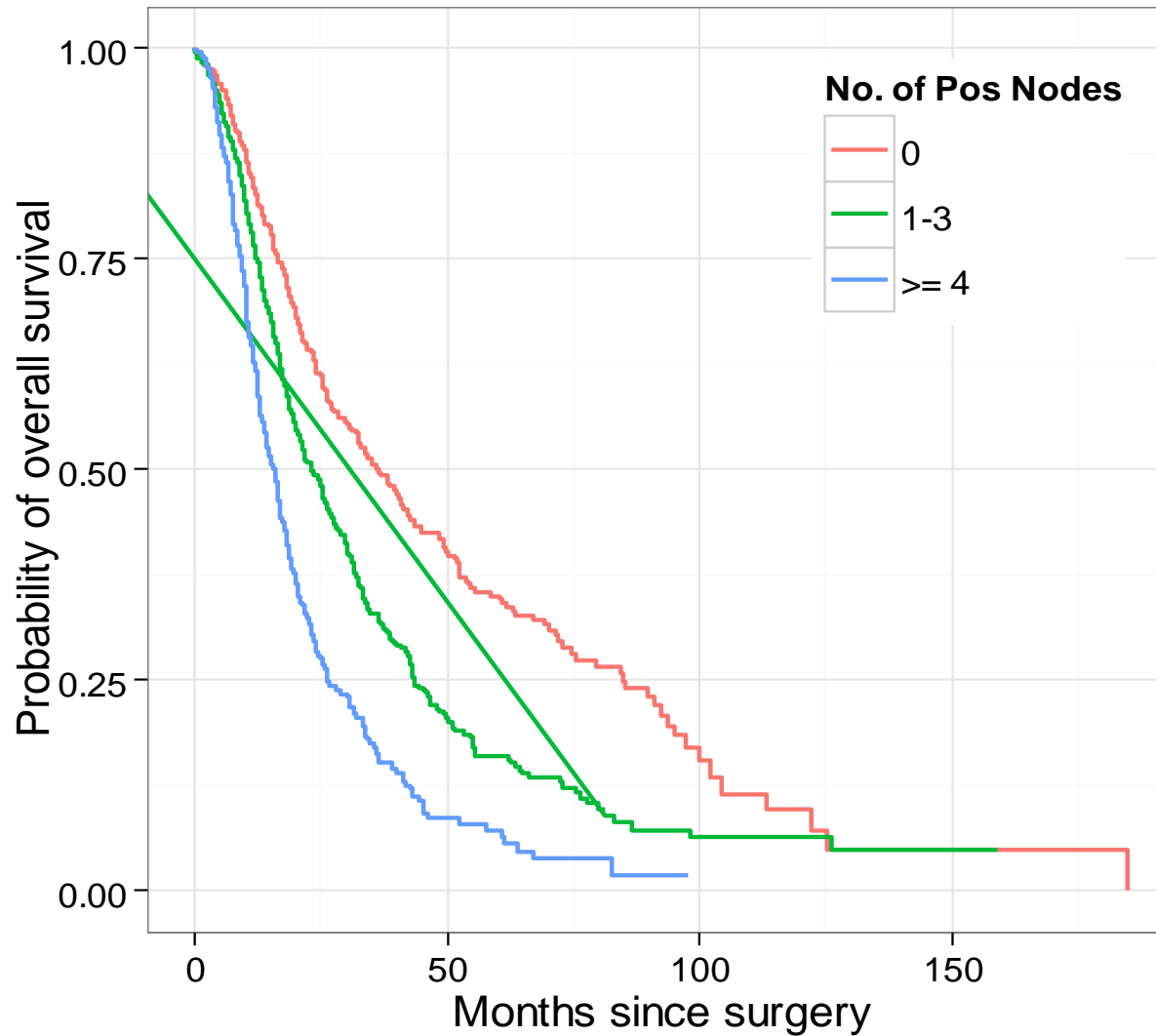
Pancreas staging: 8th edition

Change	Details
N categories	N1: Up to 3 lymph nodes N2: 4 or more lymph nodes

Saka, Ann Surg Oncol 2016

Allen, Ann Surg 2017

Allen, Ann Surg Oncol 2017



Definition of positive uncinate margin

Reference	Outcome
Campbell, Histopathol, 2009 (n=163)	Survival in tumor at margin same as tumor <1 mm
Chang, J Clin Pathol, 2009	Survival in tumor at margin same as tumor <1.5 mm
Van Den Broek, Eur J Oncol, 2009 (n=145)	Tumor <1 mm adverse prognostic factor

Definition of positive uncinate margin

Reference	Outcome: R0 and R1
Royal College UK	Negative: Tumor ≥ 1 mm from margin Positive: Tumor at or < 1 mm from margin
CAP protocol	Adopted the same definition

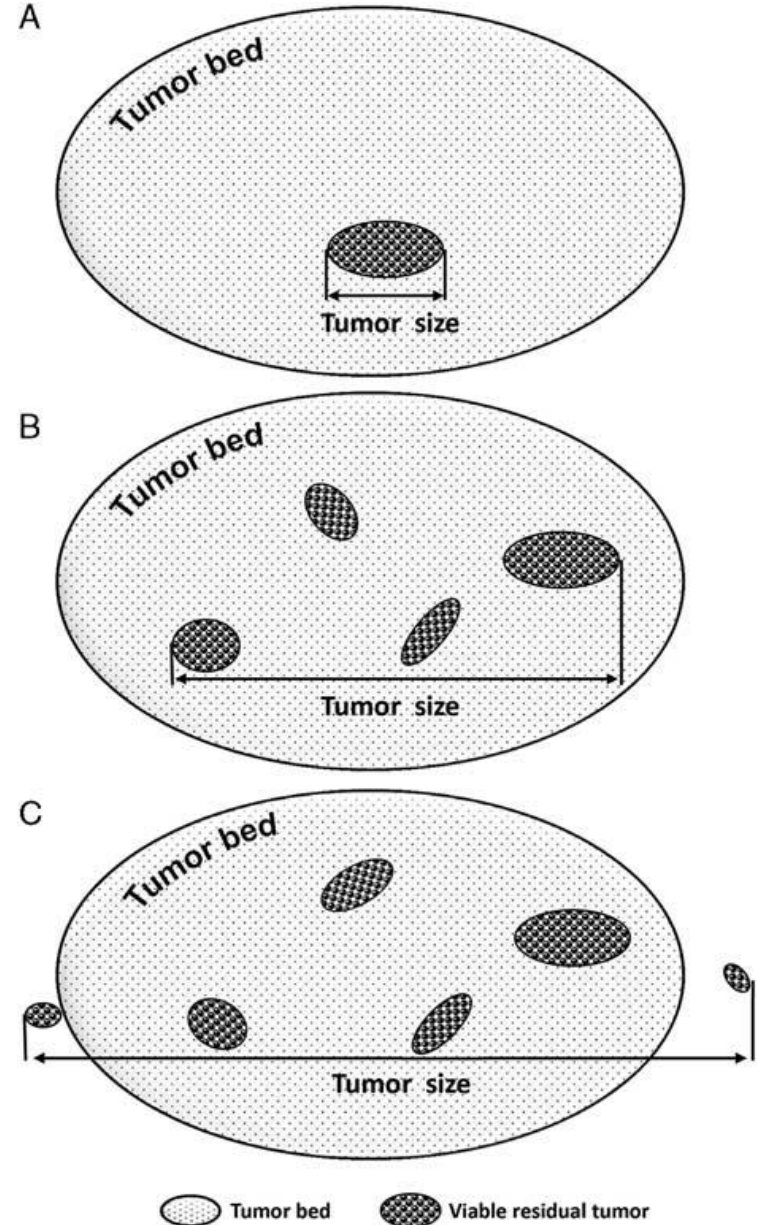
Modified Ryan scoring scheme (CAP)

Description	Tumor Regression Score
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

Size of tumor after neoadjuvant therapy

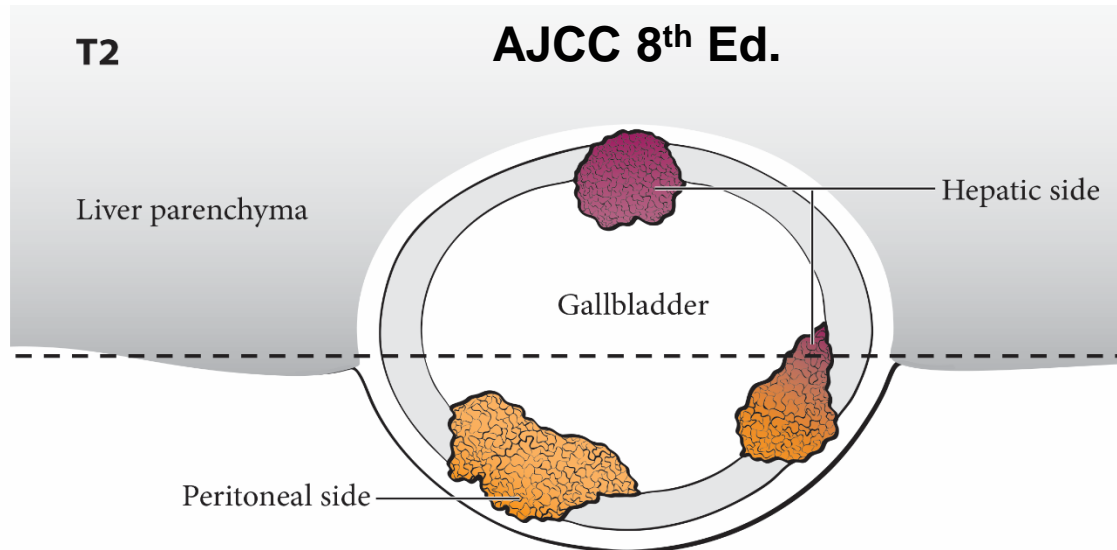
Submit the entire tumor bed

- Measure viable tumor foci and add them, or
- Measure extent across viable tumor foci are present including intervening non-tumor areas



Gallbladder

Change	Details
Subdivision of T2	T2a: Tumors on the peritoneal side T2b: Tumors on the hepatic side



Intrahepatic cholangiocarcinoma

AJCC 7th edition

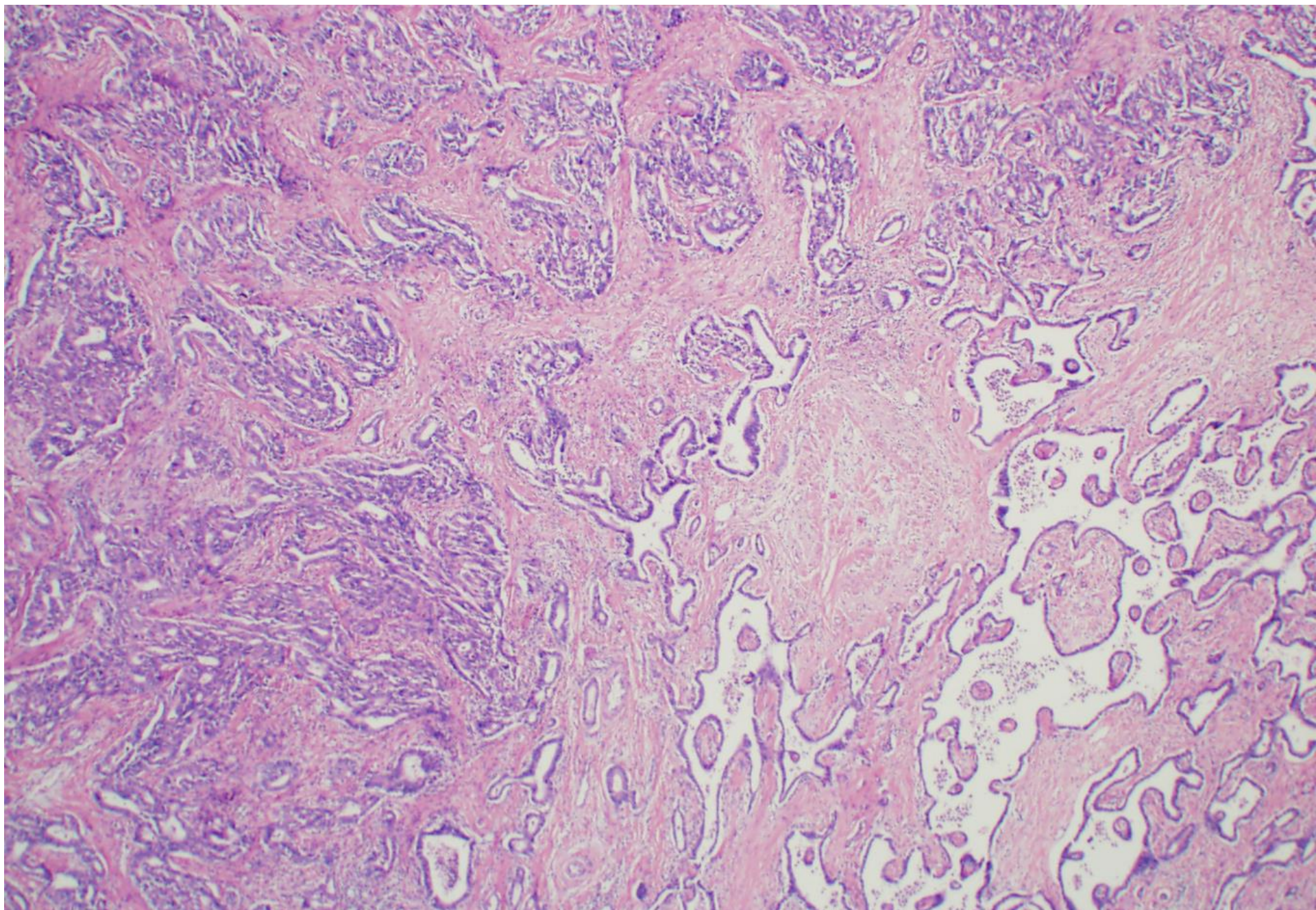
T category	Definition
T1	Solitary tumor without vascular invasion
T2	T2a: Solitary with vascular invasion T2b: Multiple tumors
T3	Involving visceral peritoneum or direct invasion into extrahepatic structures
T4	Tumor with periductal invasion

Periductal invasion

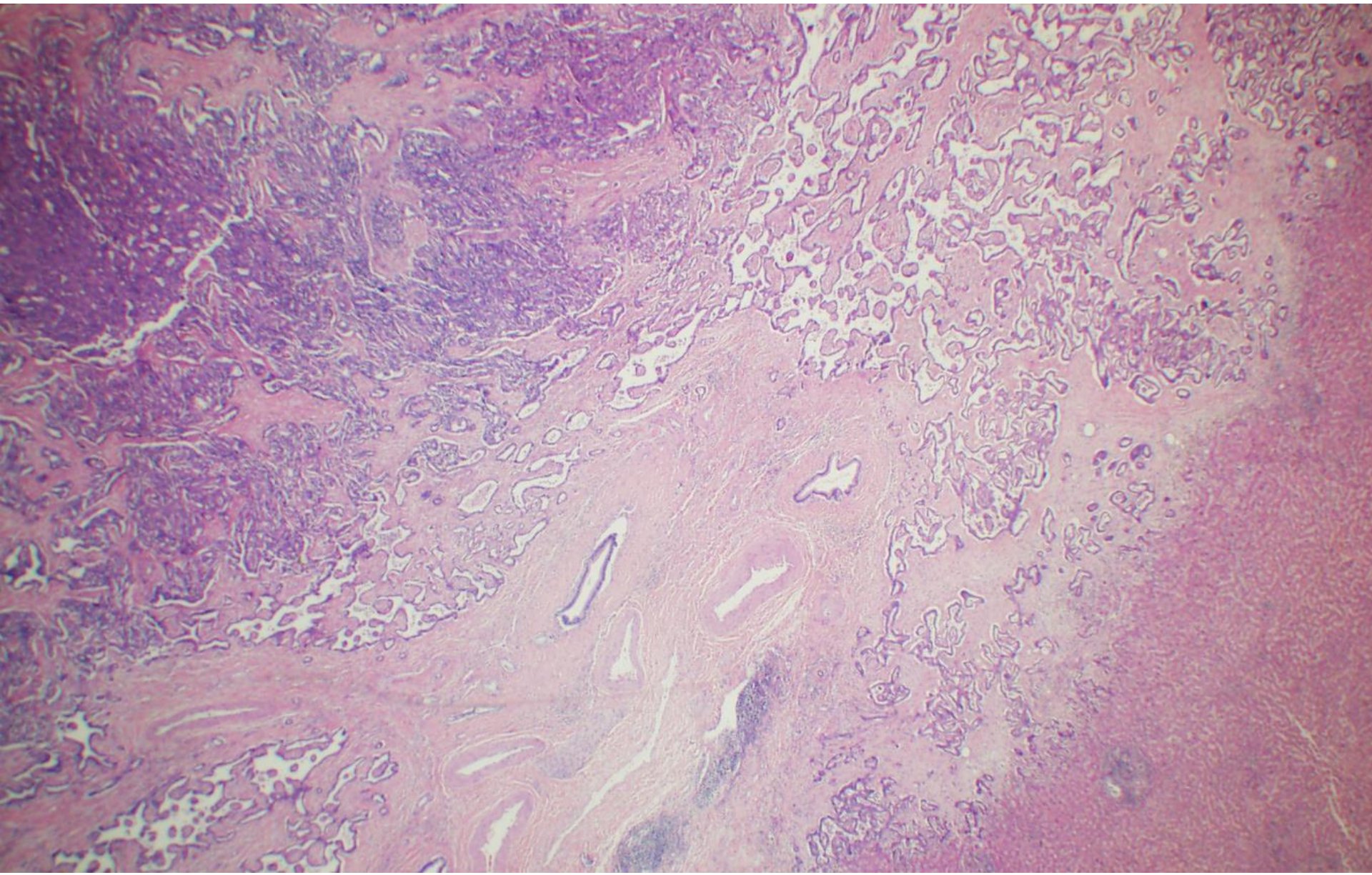
- **Intrahepatic CC, macroscopic types**
Mass forming, periductal, intraductal, mixed
- **Periductal: worse prognosis**
Extensive intraductal growth: T4
- **Problems**
How extensive is 'extensive'
Recent studies do not confirm worse outcome

Hirohashi, Hepatogastroenterol 2002
Uno, Surg Today, 2012

Intrahepatic cholangiocarcinoma, 3 cm, no VI



T1 or T4



Intrahepatic cholangiocarcinoma

AJCC 8th edition

T category	Definition
T1	T1a: Solitary tumor ≤ 5 cm without vascular invasion T1a: Solitary tumor > 5 cm without vascular invasion
T2	Solitary with intrahepatic vascular invasion or multiple tumors
T3	Involving visceral peritoneum
T4	Direct invasion into extrahepatic structures

Distal bile duct adenocarcinoma

AJCC 8th edition

T category	Definition
T1	Tumor invades the bile duct wall with a depth of less than 5 mm
T2	Tumor invades the bile duct wall with a depth of 5-12 mm
T3	Tumor invades the bile duct wall with a depth more than 12 mm
T4	Tumor involves celiac axis, superior mesenteric artery, and/or common hepatic artery

Depth is measured from the basement membrane of adjacent normal or dysplastic epithelium to the point of deepest tumor invasion

Perihilar bile duct adenocarcinoma

AJCC 8th edition

T category	Definition
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2	T2a: Tumor invades beyond the wall of the bile duct to surrounding adipose tissue T2b: Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades main portal vein or its branches bilaterally, or the common hepatic artery; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery

AJCC staging

The Future

Consensus Molecular Subtypes (CMS)

6 gene expression studies

CMS1 MSI/Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI-high CIMP-high	High copy number alteration	Low copy number alteration	High copy number alteration
Right	Left		High stage
<i>BRAF</i> mutation	<i>Wnt</i> activation	<i>KRAS</i> mutation	<i>TGFβ</i> activation
	<i>Myc</i> activation		EMT genes
Immune infiltration		Metabolic dysregulation	Angiogenesis Prominent stroma
Worse outcome after relapse			Worse outcome

TNM Staging in Colorectal Cancer: T Is for T Cell and M Is for Memory

- **Host immune response better prognostic indicator than TNM**
- **‘Immunoscore’: Quantify the immune infiltrate**

Galon, J Pathol 2014

TNM-I staging

Immunoscore

- CD3 and CD8
- Numbers in center and invasive front
- 5 categories: I-0 to I-4