AJCC 8th & CAP for Upper and Lower GI Tract

Maria Westerhoff

University of Michigan

We will cover…

- Appendix
- Colon
- Ampulla of Vater
- Anus
- Small intestine
- Esophagus
- Stomach

…in thirty minutes

We will cover…

- Appendix
- Colon
- ~~Ampulla of Vater~~ → ***Won-Tak Choi cover***
- ~~Anus~~ ***Not much change (N sub)***
- ~~Small intestine~~ ***Not much change (T1a,N #)***
- Esophagus
- Stomach

…in thirty minutes

AJCC 7th – Appendix chapter

- Goblet cell carcinoid
- Well-differentiated NET
- Adenocarcinoma
- HG NET

NEW

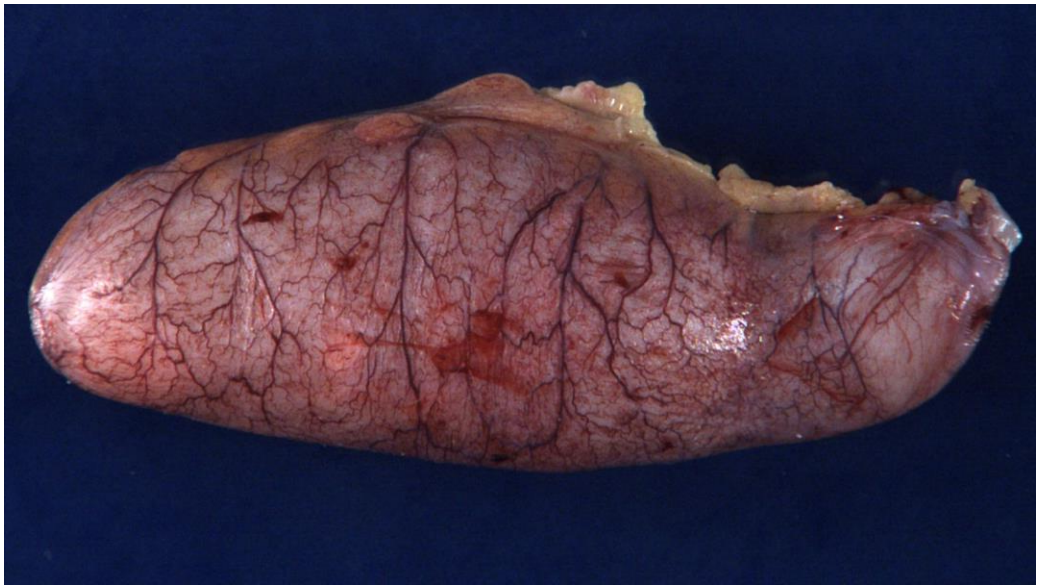
AJCC 8th – Appendix chapter

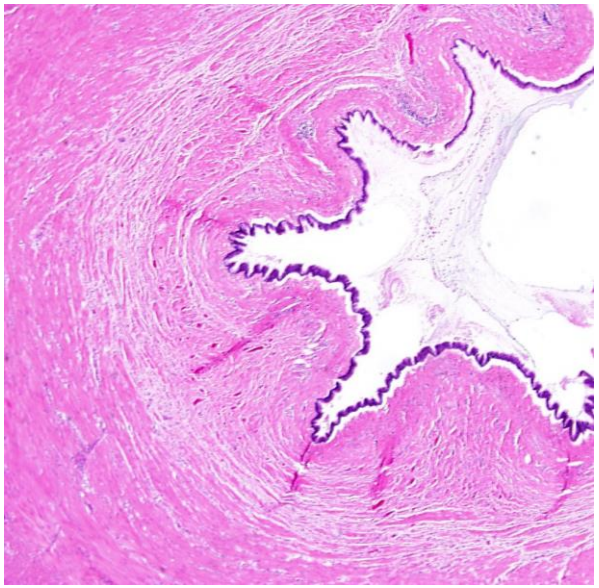
- Goblet cell carcinoid
- ~~Well-differentiated NET~~
- Adenocarcinoma
- HG NET

→ Own separate chapter

+ Low grade appendiceal mucinous neoplasm

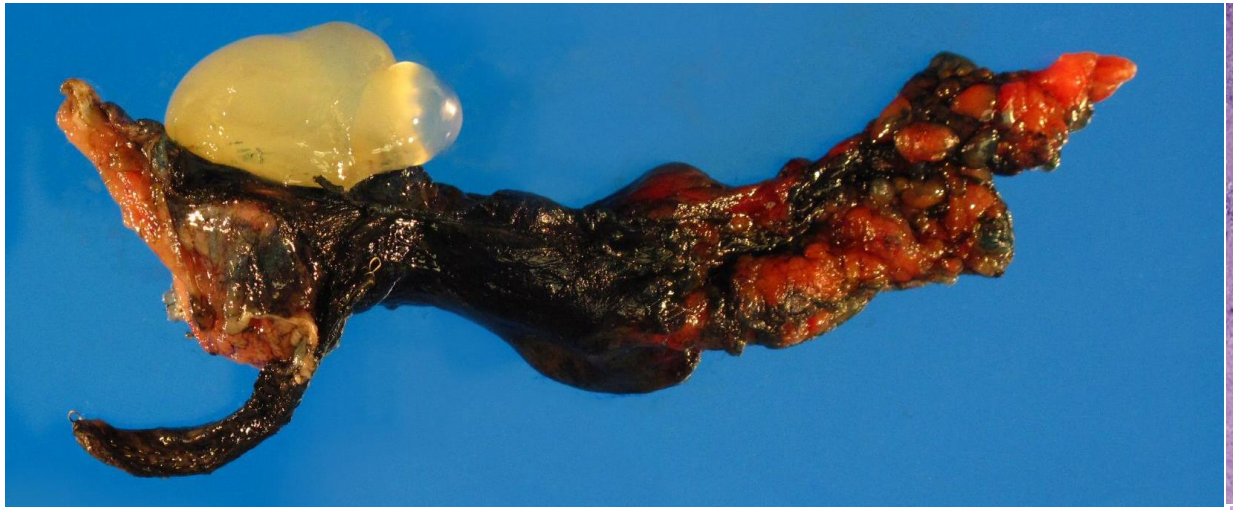
How I used to understand Appendiceal Mucinous Tumors

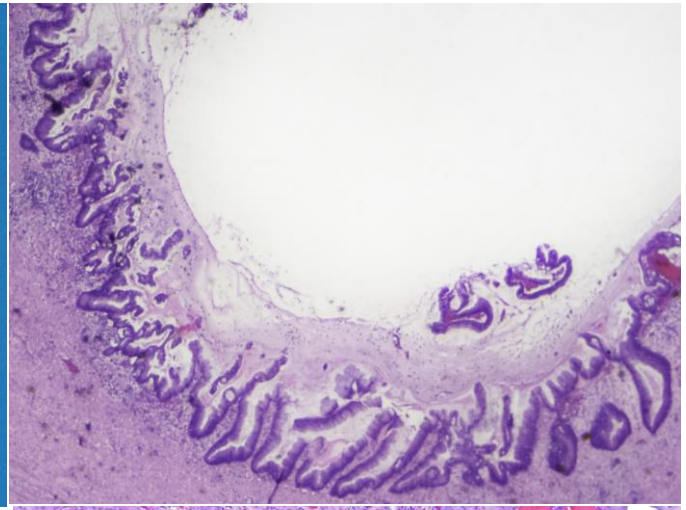


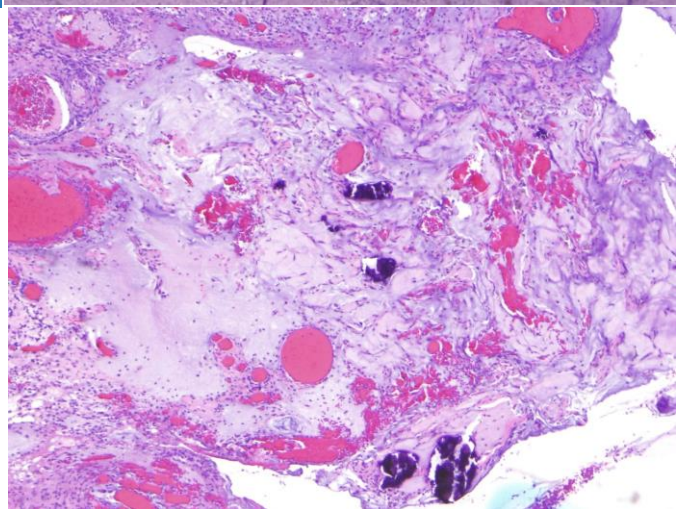


“Mucinous cystadenoma”

How I used to understand Appendiceal Mucinous Tumors



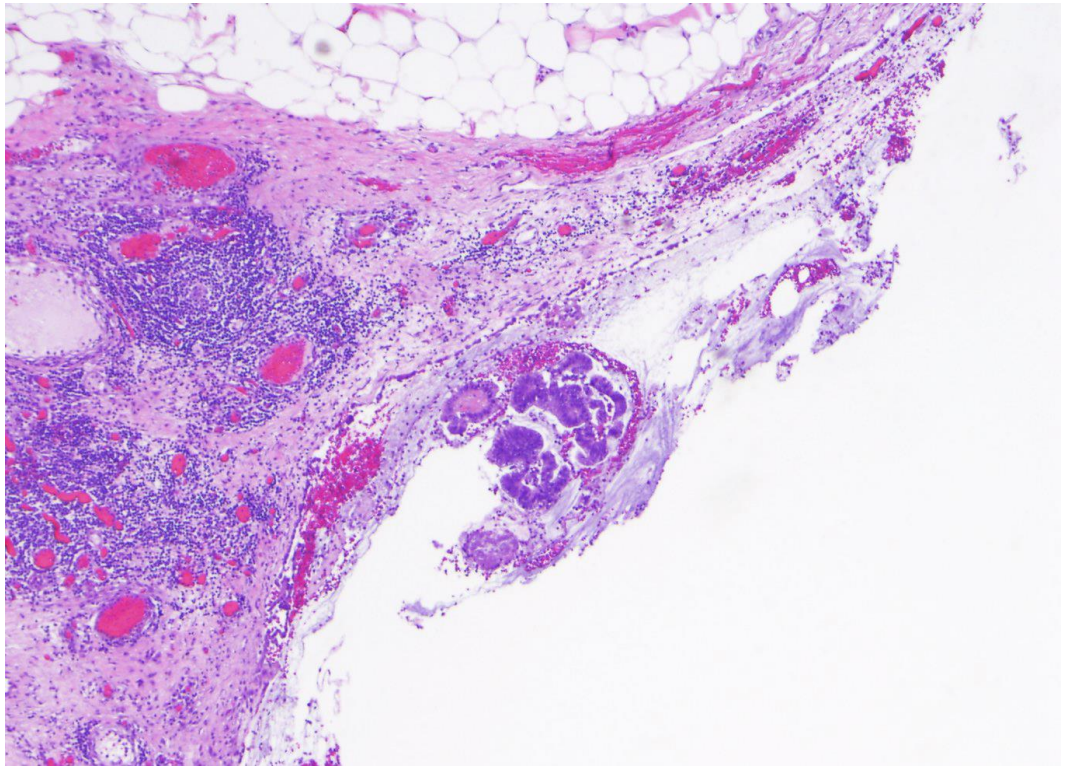




“LAMN – low risk”

3% risk of peritoneal recurrence

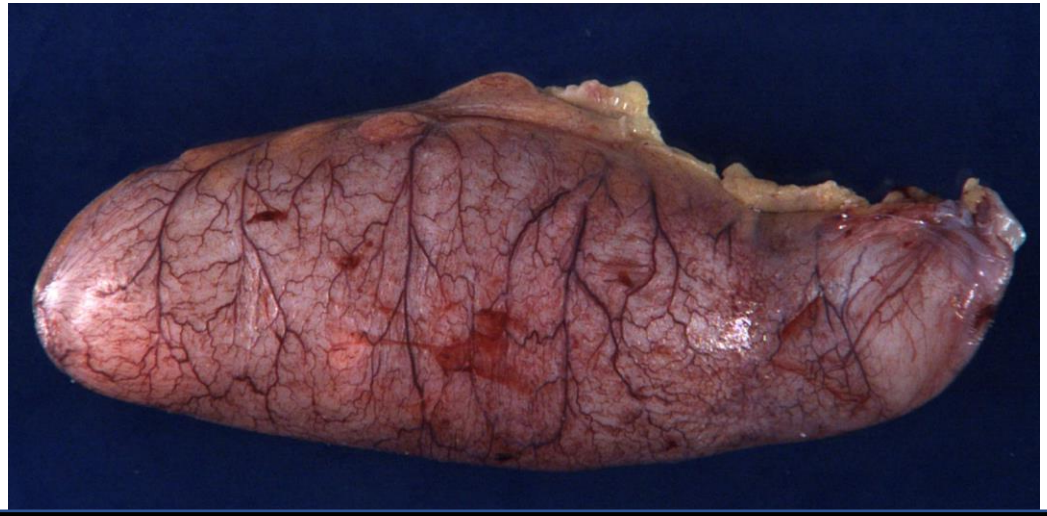
How I used to understand Appendiceal Mucinous Tumors

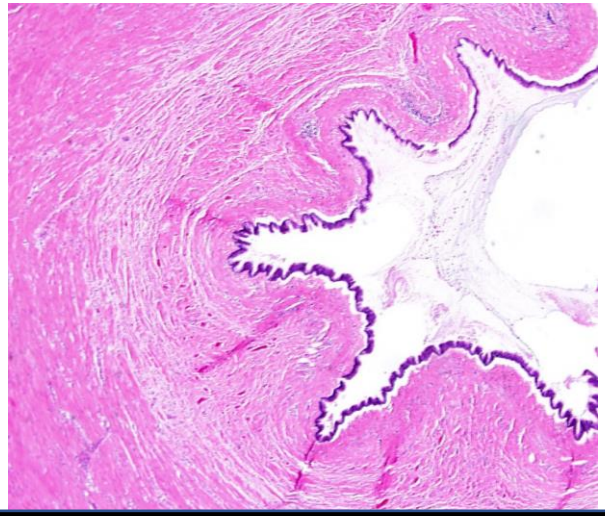


Cellular Mucin on Appendiceal Serosa

"LAMN – high risk" 36% risk of peritoneal recurrence

AJCC 8th





"By definition, LAMNs are associated with <u>obliteration of the muscularis mucosae</u>"

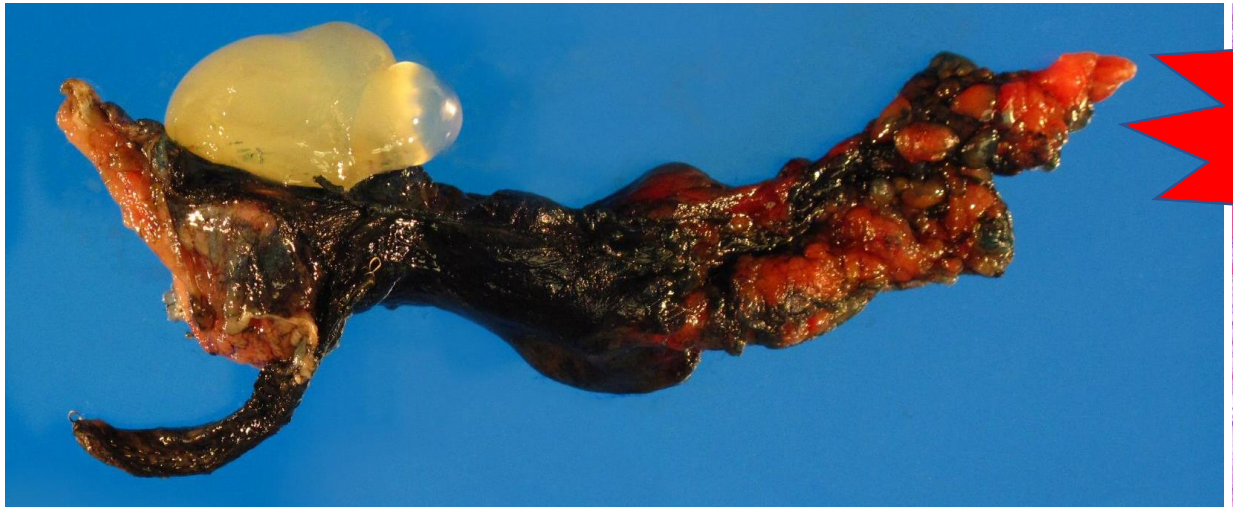
~~**"Mucinous cystadenoma"**~~ ➡ **LAMN**

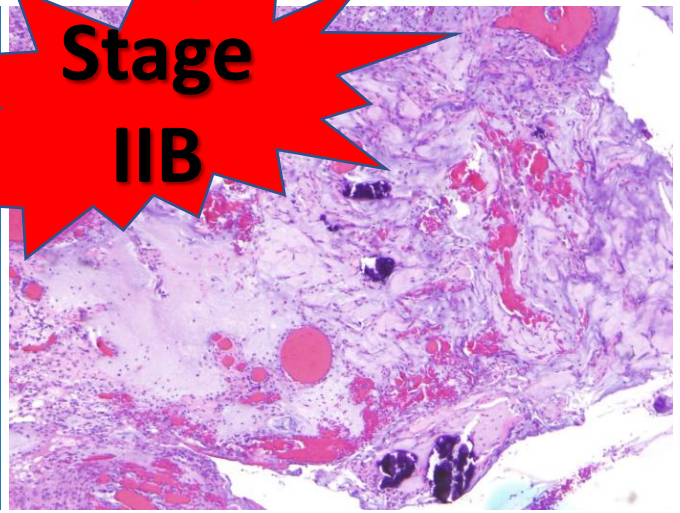
- Tis (LAMN): “confined by muscularis propria.”
- T1 or T2 not applicable to LAMN

Stage 0

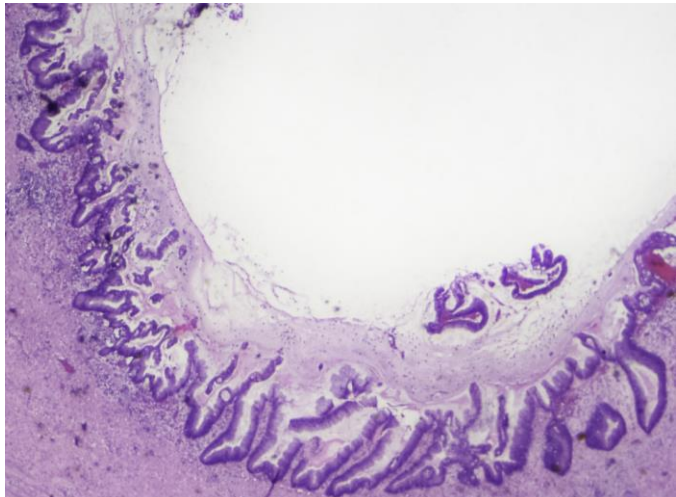
”Acellular mucin or mucinous epithelium that extends into subserosa or serosa should be classified as T3 or T4a respectively.”

AJCC 8th for: Acellular Mucin on Appendix Serosa or Mesoappendix



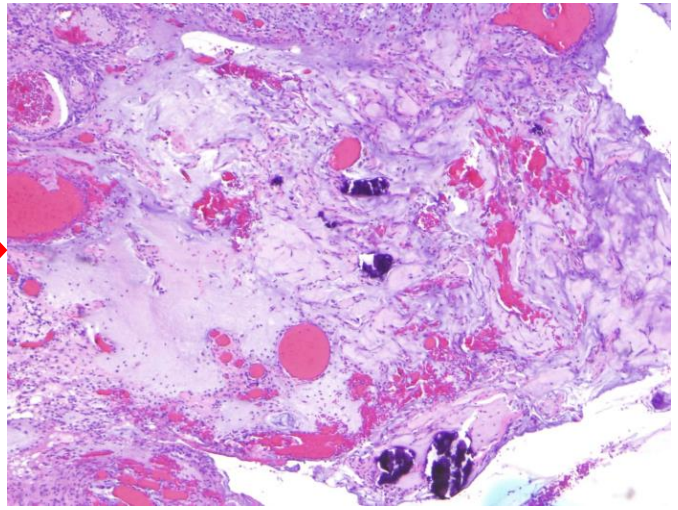


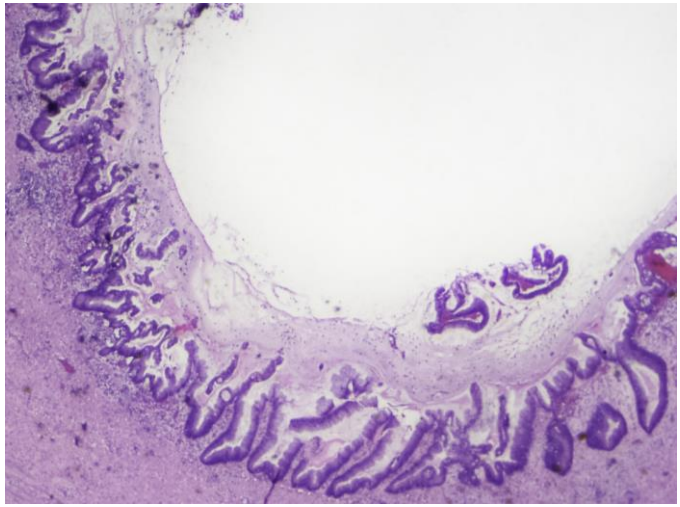
Tis → T4a



AJCC 8th

If acellular mucin <u>elsewhere</u> in peritoneum



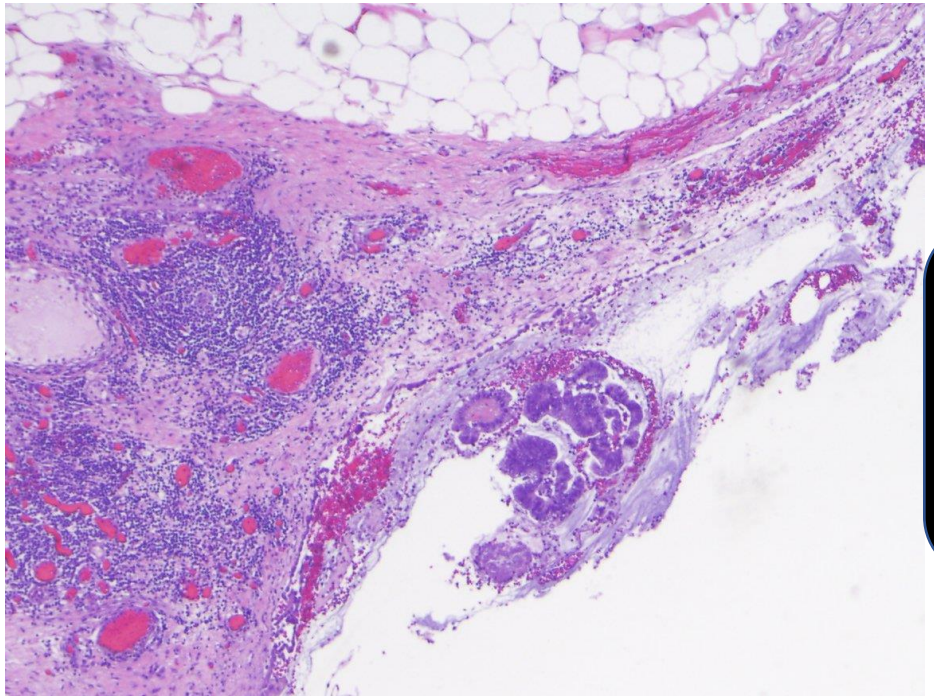


T4a

M1a

Stage IVa

…and if Cellular Mucin on Appendiceal Serosa?



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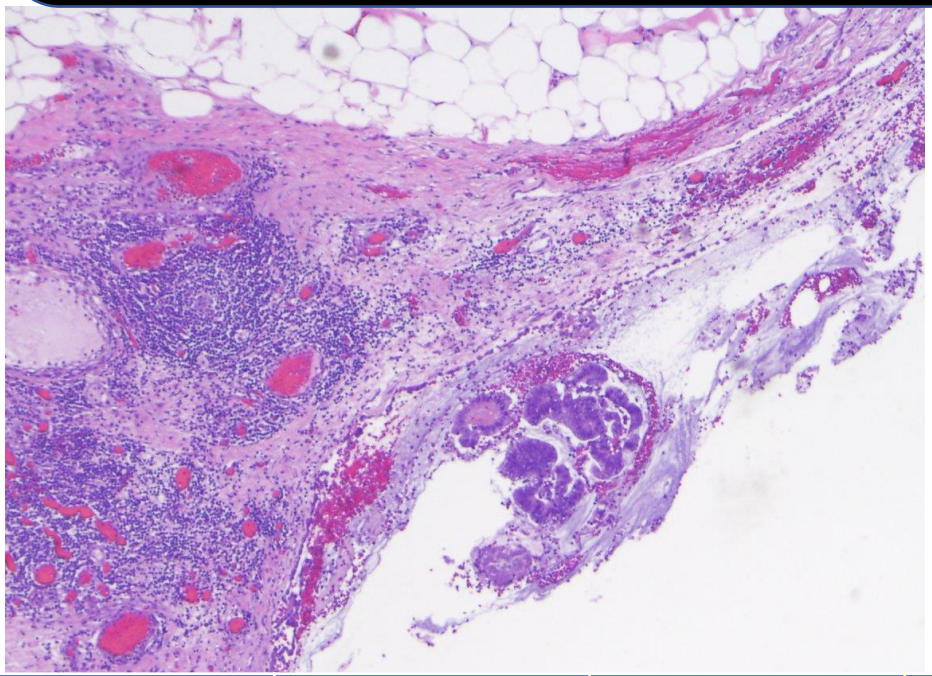
T4a T4b

“LAMN – high risk” 36% risk of peritoneal recurrence

If cellular mucin elsewhere in peritoneum



T4a
M1b
Stage IVa

Ext of Dx	Perit mucin	n	# f/u	Med f/u	Recurred
RLQ	Acellular	28	12	41 mo	1
Outside RLQ	acellular	4	2	185 mo	0
RLQ	cellular	4	4	85 mo	2
Outside RLQ	cellular	38	23	51 mo	18

Am J Surg Pathol. 2009 Feb;33(2):248-55

LAMN	Tis	T4a
Obliterates MM Intact M Propria	X	
Acellular mucin on APP Serosa or mesoapp		X
Cellular mucin on APP Serosa or mesoapp		X

LAMN	Tis	T4a	T4a M1a	T4a M1b
Obliterates MM Intact M Propria	X			
Acellular mucin on APP Serosa or mesoapp		X		
Cellular mucin on APP Serosa or mesoapp		X		
Intraperitoneal acellular mucin			X	
Intraperitoneal cellular mucin				X

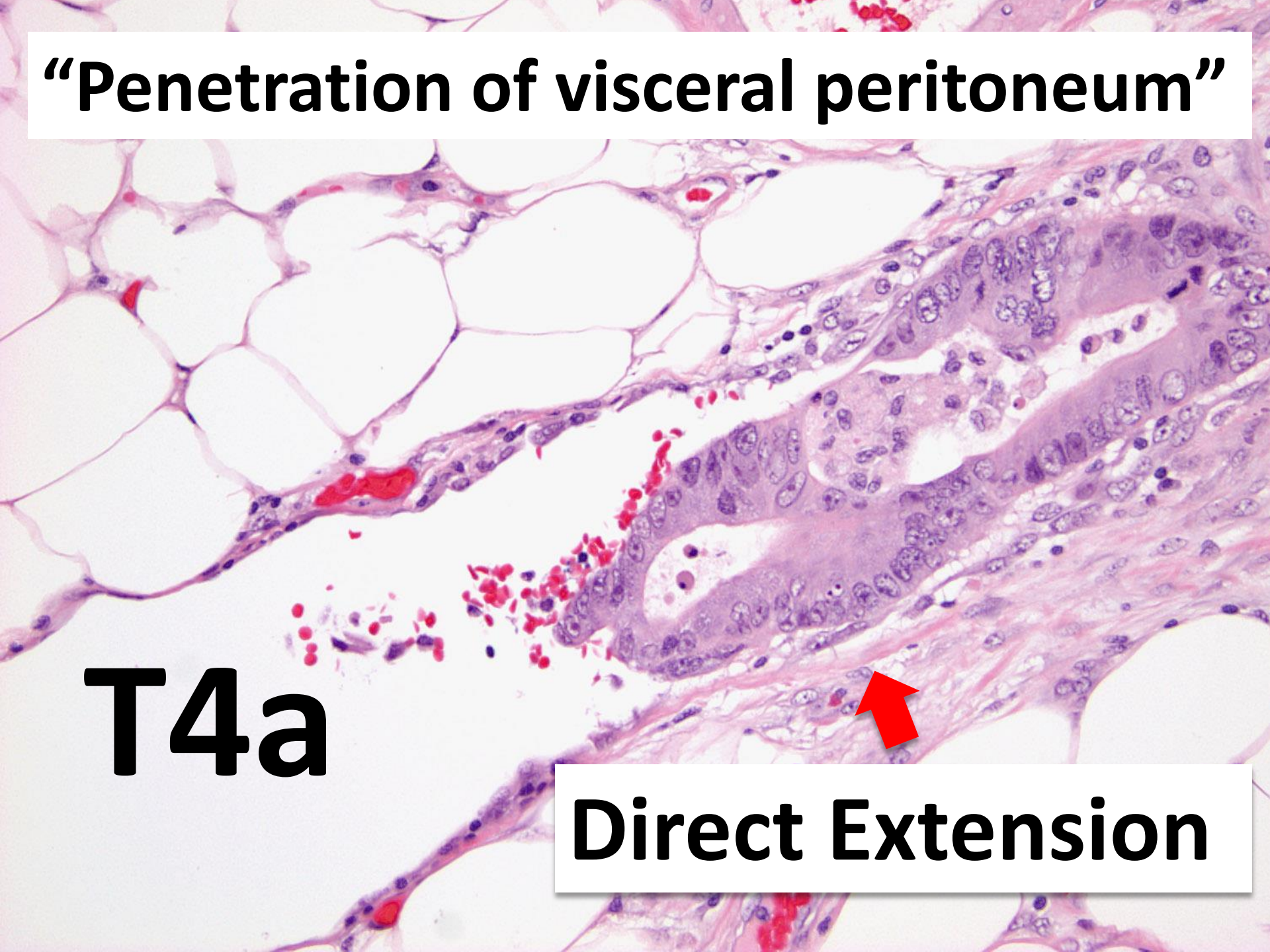
Until we know better…

- **Submit entire appendix**
- **Report on margin**

Arch Pathol Lab Med. 2015;139:518–521.

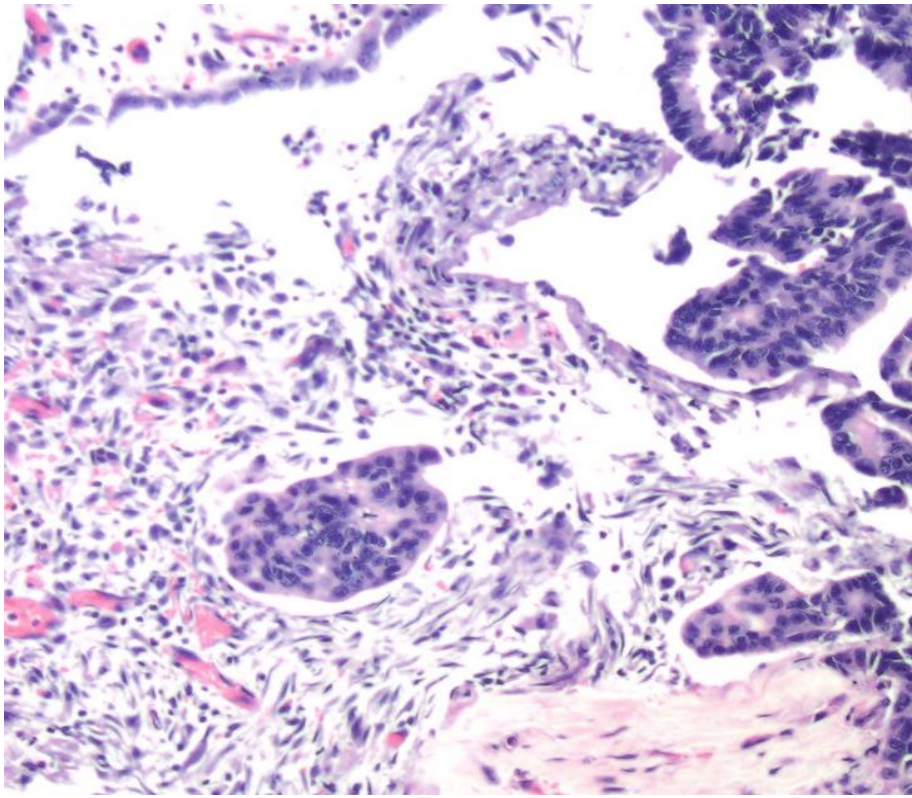
COLON

- T3 vs T4a
- LN-Size of Cancer


“Penetration of visceral peritoneum”
T4a
Direct Extension

Colon T4a Now Includes

- Gross perforation of bowel through tumor
- Invasion of tumor through areas of inflammation to serosa ?



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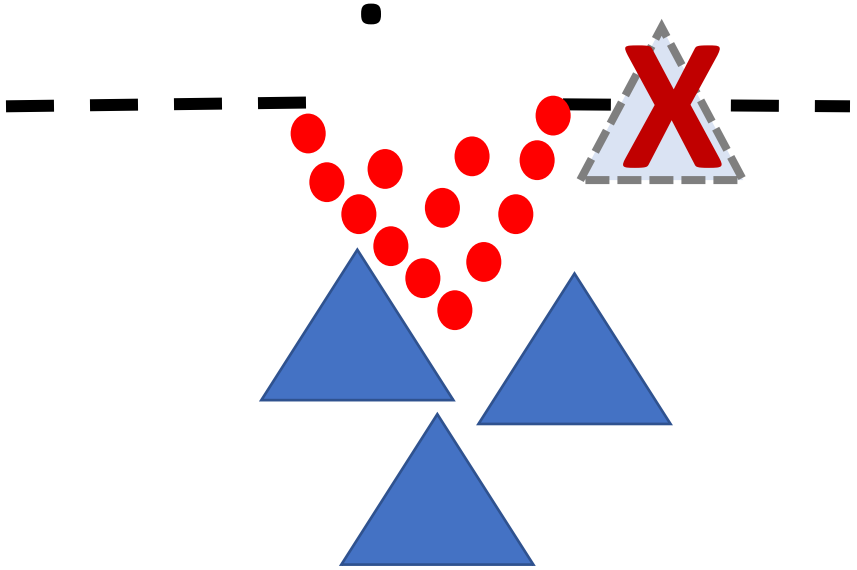

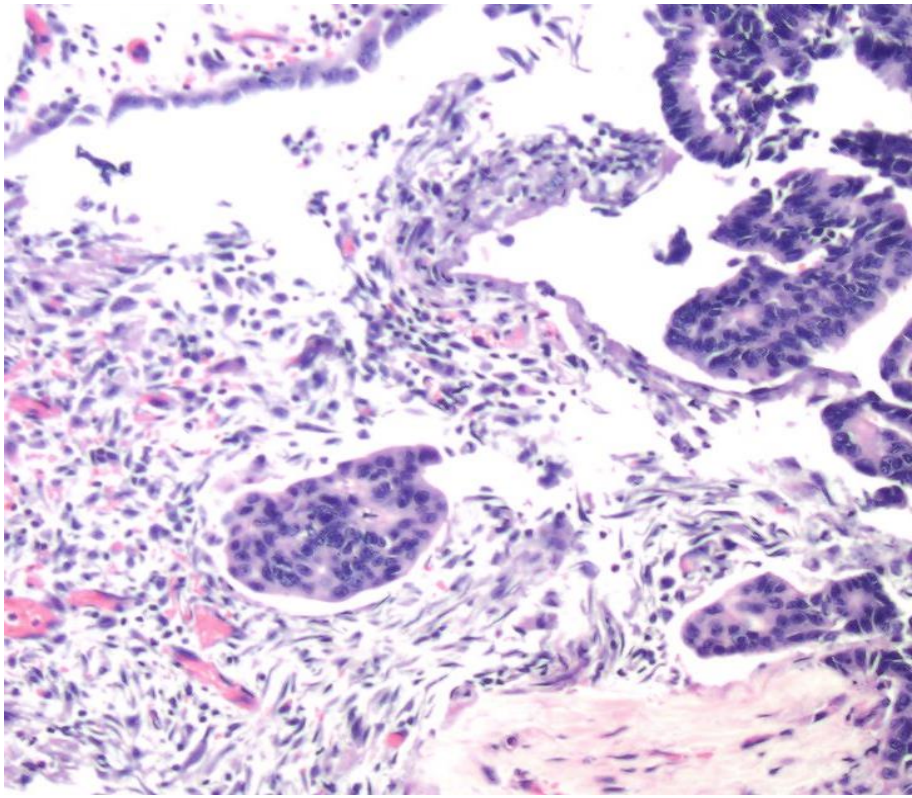

Colon T4a Now Includes

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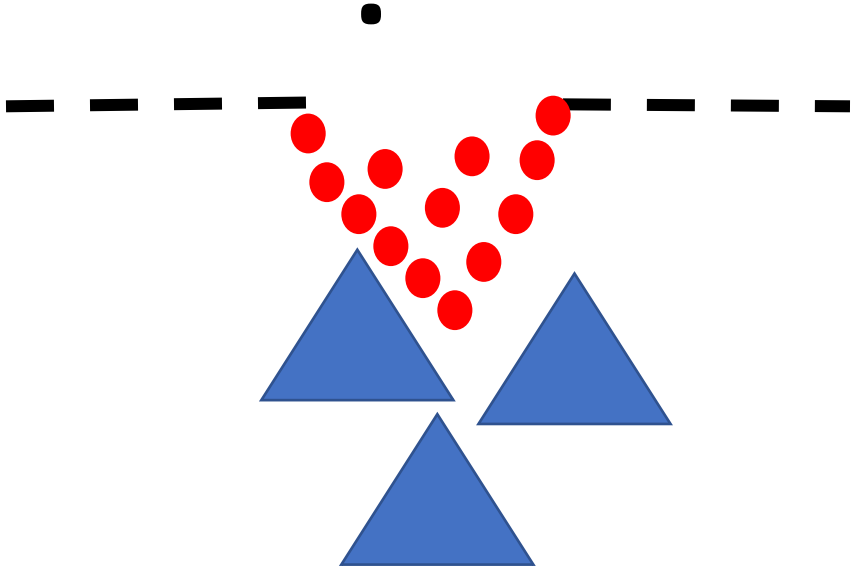
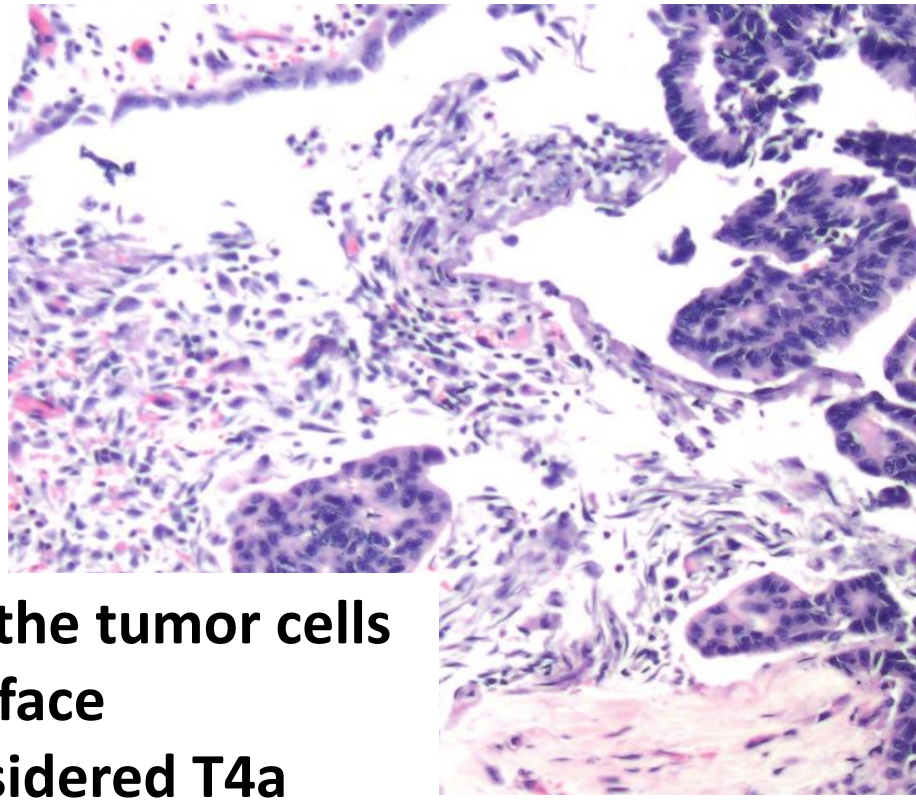




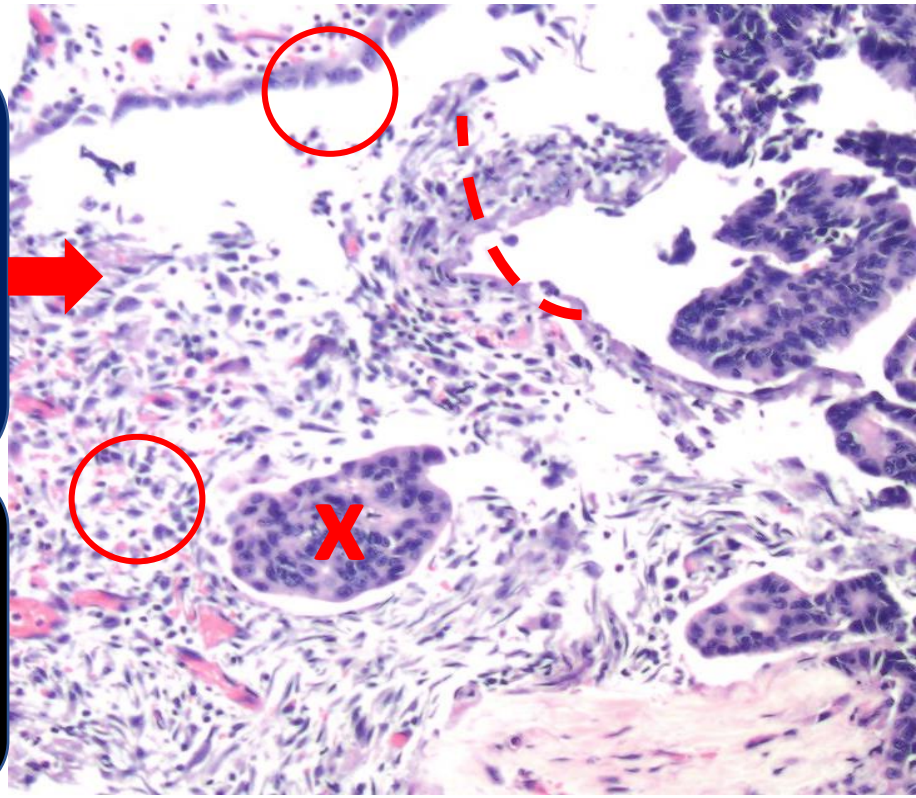
”Tumors with perforation in which the tumor cells are continuous with the serosal surface through inflammation also are considered T4a

Colon T4a Now Includes

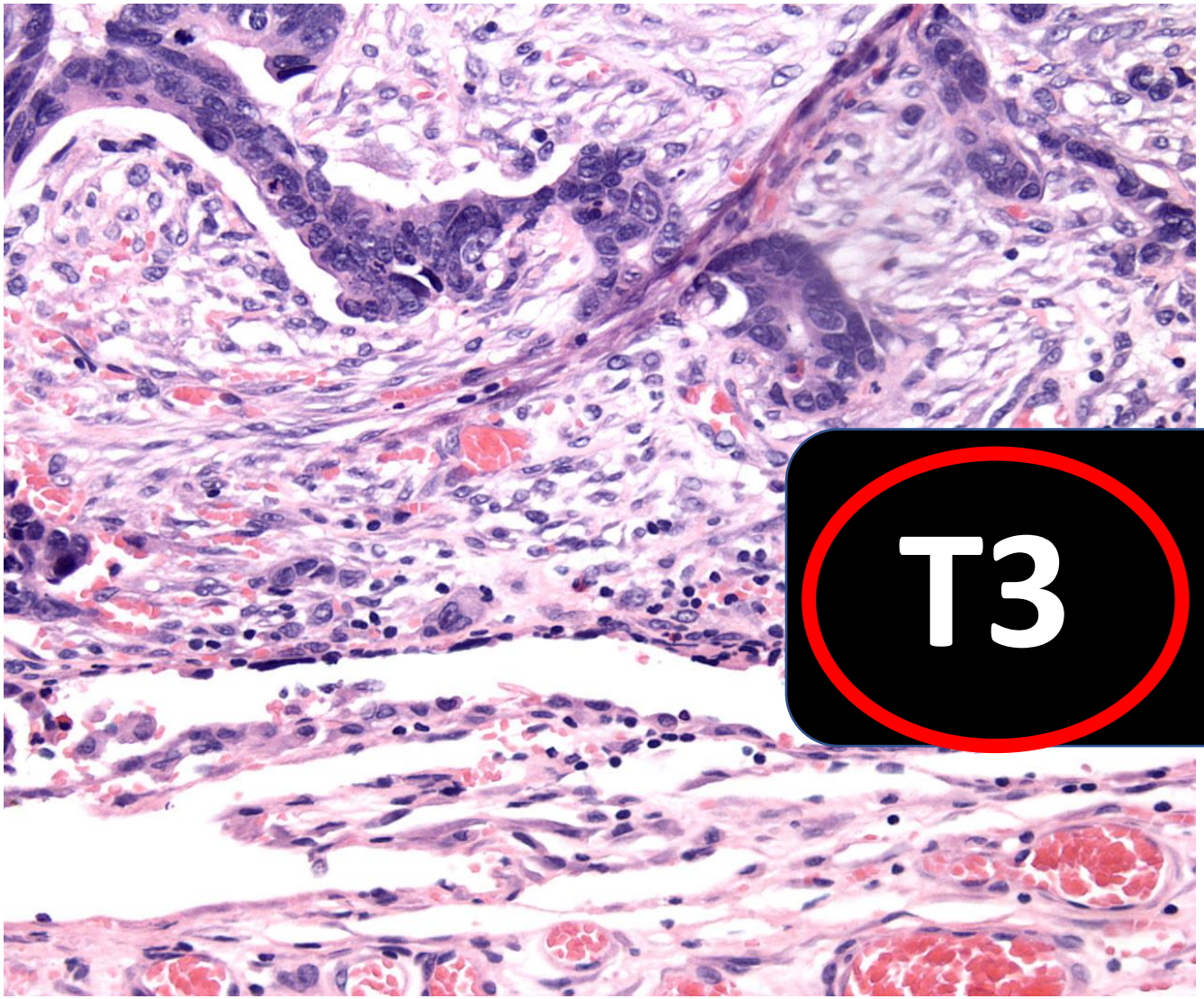
- Gross perforation of bowel through tumor
- Invasion of tumor through areas of inflammation to serosa

CAP

- **Free tumor cells on serosa with underlying erosion of mesothelium, mesothelial hyperplasia +/- inflammatory reaction**
- **Perforation in which tumor cells continuous with serosa through inflammation**



Does that mean tumor close to surface + serosal reaction?



?

T3

T4a

What T4a is NOT

Per AJCC & CAP: Tumors that are close to serosal surface with serosal reaction = T3

"Multiple level sections and/or additional section of the tumor should be examined in these cases"

"T3" with + Serosal Cytology

19% of T3 tumors had + cyto if:

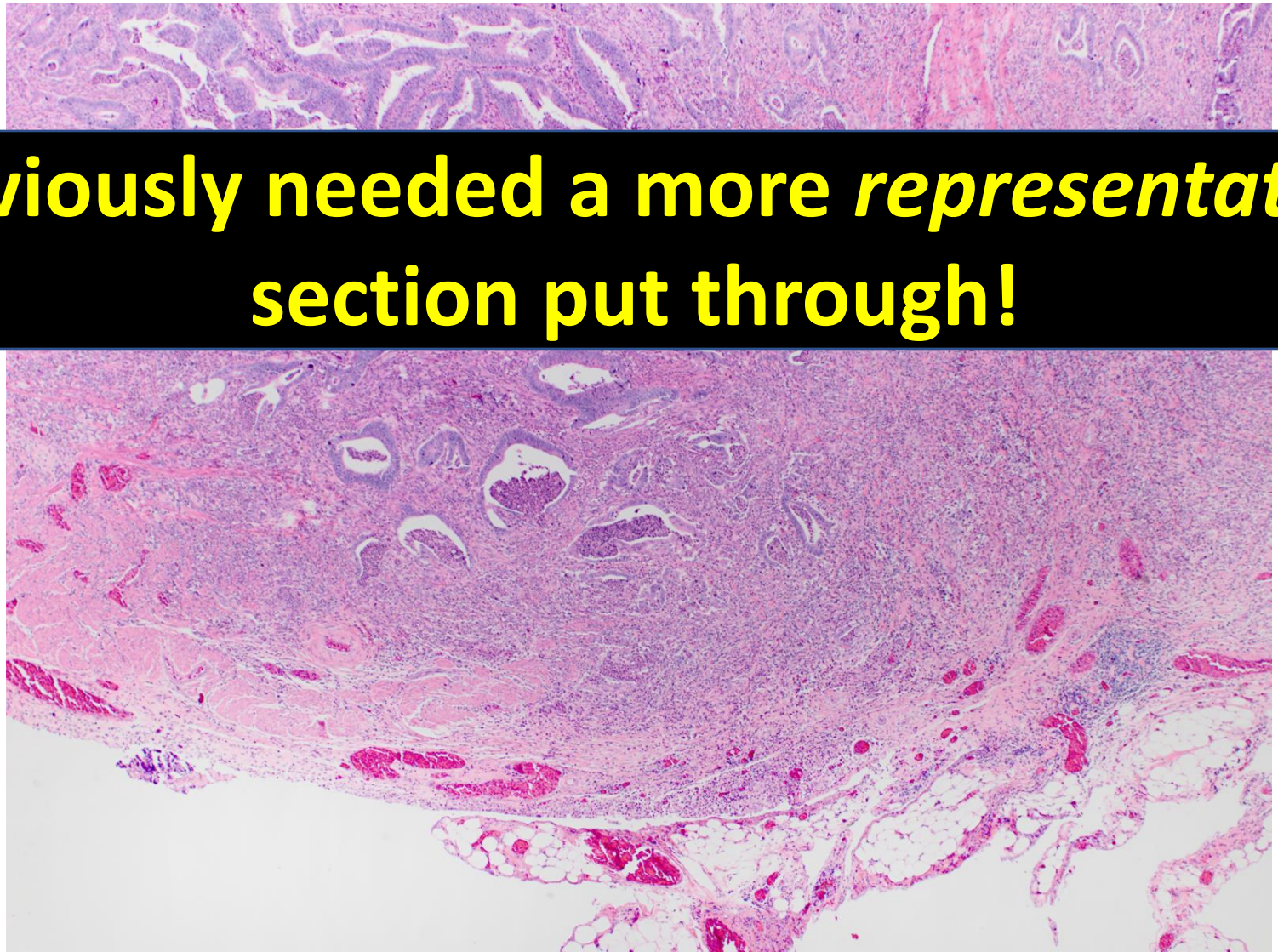
- CA <1mm from serosa
- fibroinflammatory rxn
- vascular proliferation
- hemorrhage or fibrin deposition
- reactive mesothelial cells

} **SEROSAL RXN**

46% of T3 <1 mm had + cyto comparable to 55% of T4

Am J Surg Pathol. 2013;37(8):1252-1258

+ Serosal Cytology



Obviously needed a more *representative* section put through!

Bottom Line

T4a

Direct tumor extension to serosa

T3

Tumors <1 mm from serosa is T3

- **AJCC & CAP → additional tissue blocks of tumor & examine multiple level sections to look for serosal involvement**

Colon – Lymph Nodes

"Suboptimal node count may lead to further dialogue between surgeon

Lymph Node Evaluation

- **The AJCC and College of American Pathologists recommend examination of a minimum of 12 lymph nodes to accurately stage colon cancers.[8,9,19] The literature lacks consensus as to what is the minimal number of lymph nodes to accurately identify stage II cancer. The minimal number of nodes has been reported as >7, >9, >13, >20, and >30.[20-28] The number of lymph nodes retrieved can vary with age of the patient, gender, tumor grade, and tumor site.[21] For stage II (pN0) colon cancer, if fewer than 12 lymph nodes are initially identified, it is recommended that the pathologist go back to the specimen and resubmit more tissue of potential lymph nodes. If 12 lymph nodes are still not identified, a comment in the report should indicate that an extensive search for lymph nodes was undertaken. The pathologist should attempt to retrieve as many lymph nodes as possible. It has been shown that the number of negative lymph nodes is an independent prognostic factor for patients with stage IIIB and IIIC colon cancer.[29]**

(e.g. fat clearance techniques) of the node bearing specimen to assure that a maximum node assessment is reached"

Per NCCN
Adverse Prognostic Factors

- **<12 LN**
- **Lymph/vasc invasion**
- **Poor diff histology (unless its MSI)**
- **PNI**
- **Margin status**

Positive lymph nodes

AJCC

N: tumor in LN ≥0.2mm

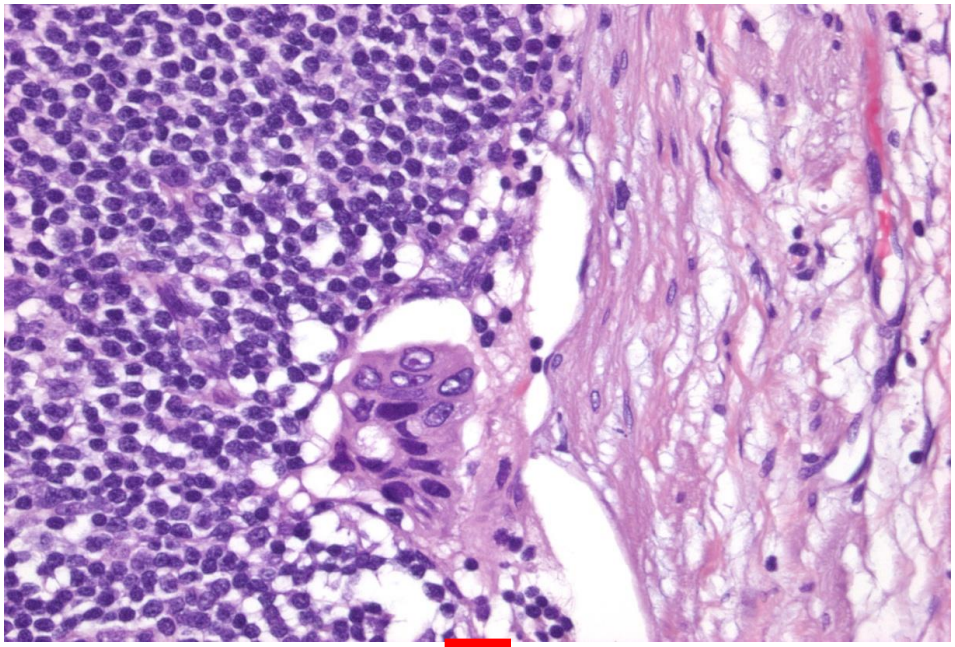
Do not match

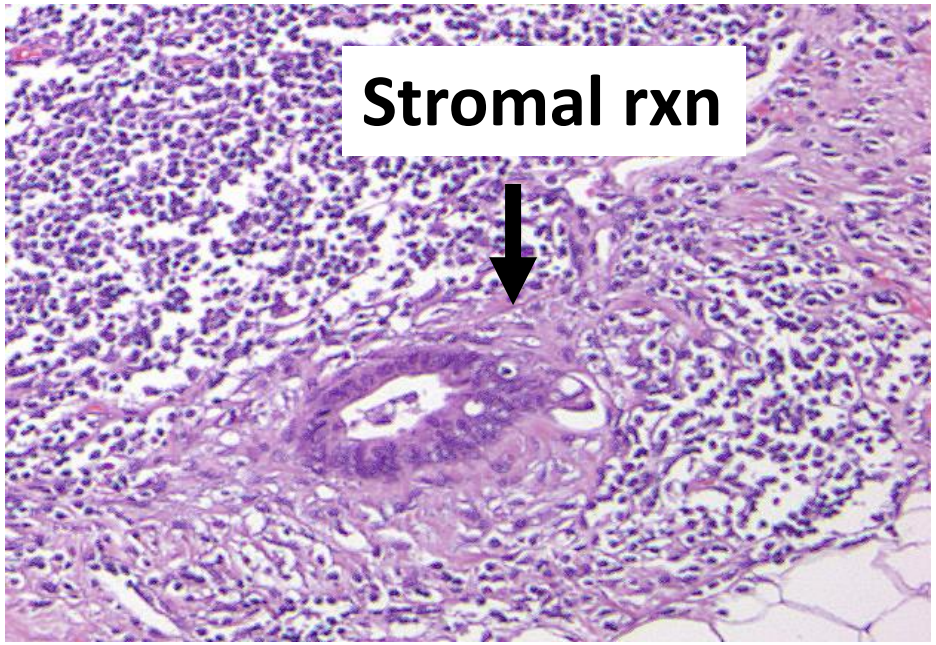
- **If <0.2 = <u>N0i+</u>**
- **ITCs = single tumor cells or small clusters of cells ≤0.2 mm without stromal response**

CAP

- **Single tumor cells or small clusters of cells ≤ 0.2 mm= <u>N0</u>**
- **Either single focus in single node, multiple foci within single or multiple nodes**

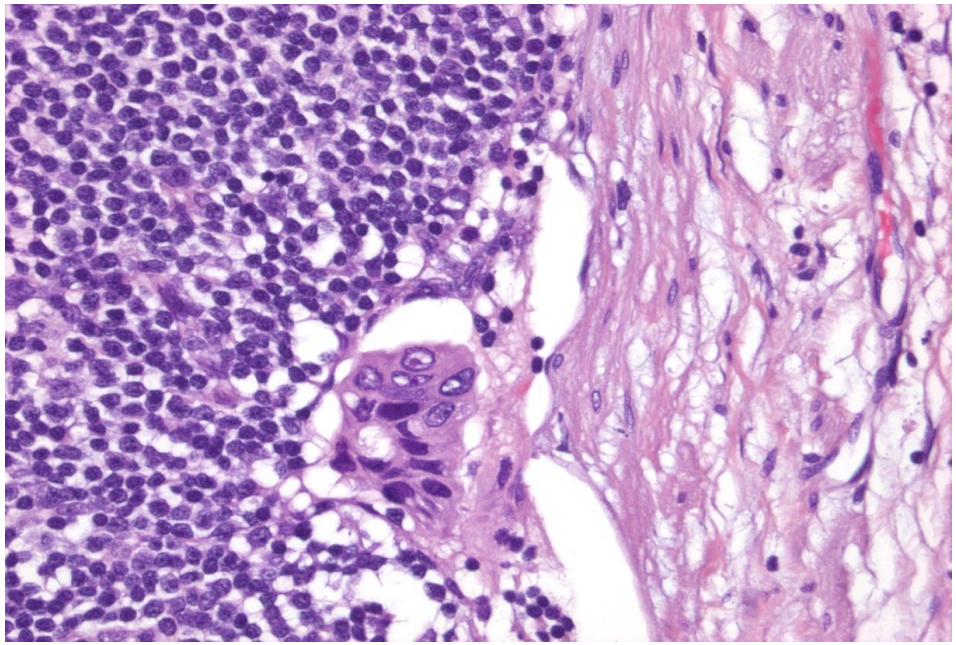
Tiny Focus

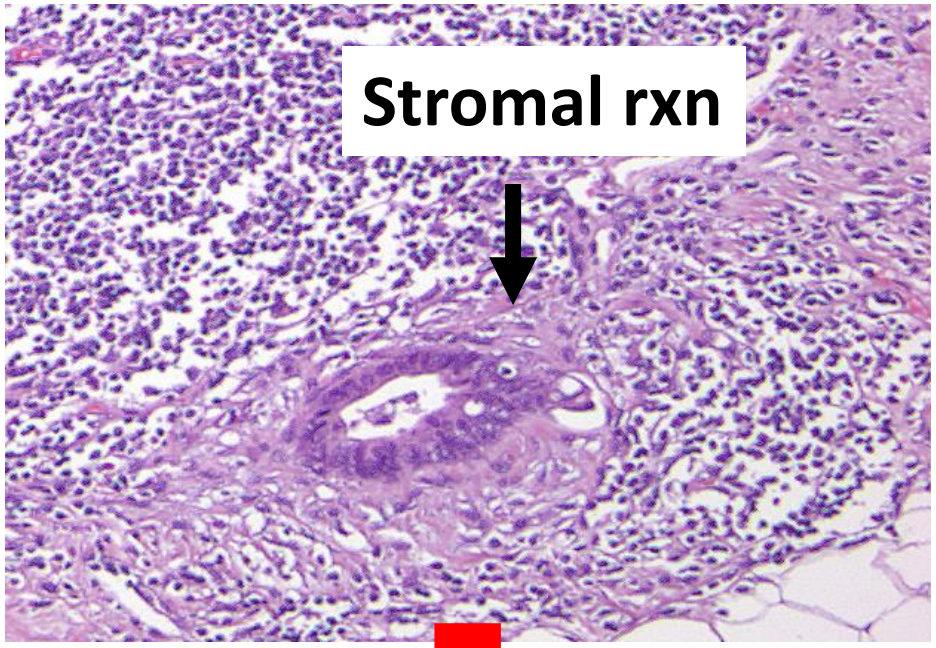




N0(i+)

Tiny Focus



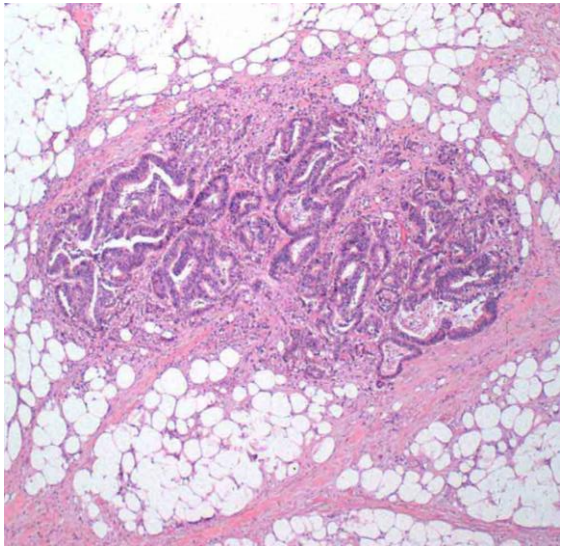


ITCs = Single tumor cells or small clusters of cells ≤0.2 mm *without stromal response*

N1 **N0(i+)**

Tumor Deposits

Discrete nodule of cancer in pericolic/perirectal fat or mesentery without identifiable lymph node tissue or vascular structure



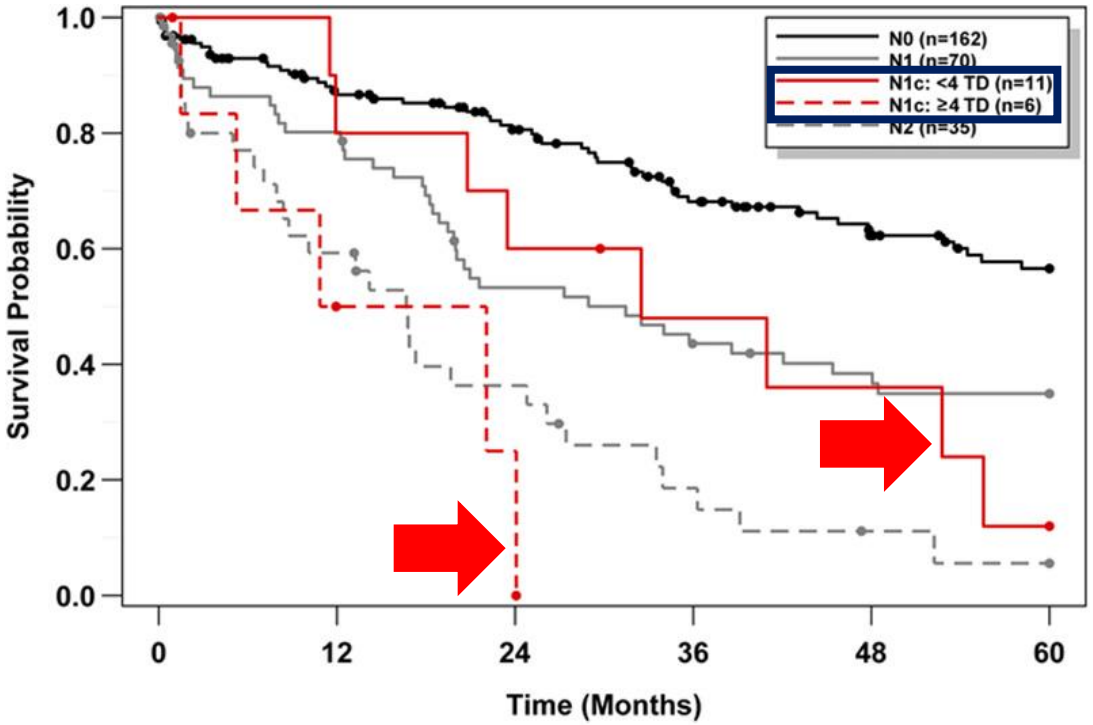
- No size rule (AJCC 5th)
- No contour rule (AJCC 6th)

Adverse prognostic factor; adjuvant therapy warranted in cases that are N1c regardless of T (bumps pt to stage III)

AJCC: Specify # of Tumor Deposits

- **AJCC: # of tumor deposits should be recorded as 1-4 vs. 5 and up *(typo?)***

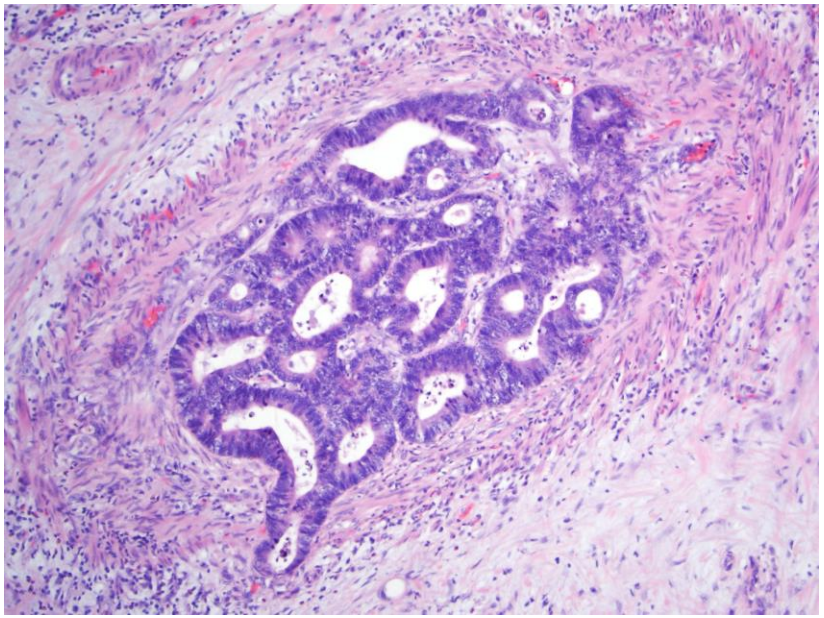
- **CAP just says record # of TD**



Am J Surg Pathol. 2015 Jan;39(1):109-15

AJCC: Large vessel invasion

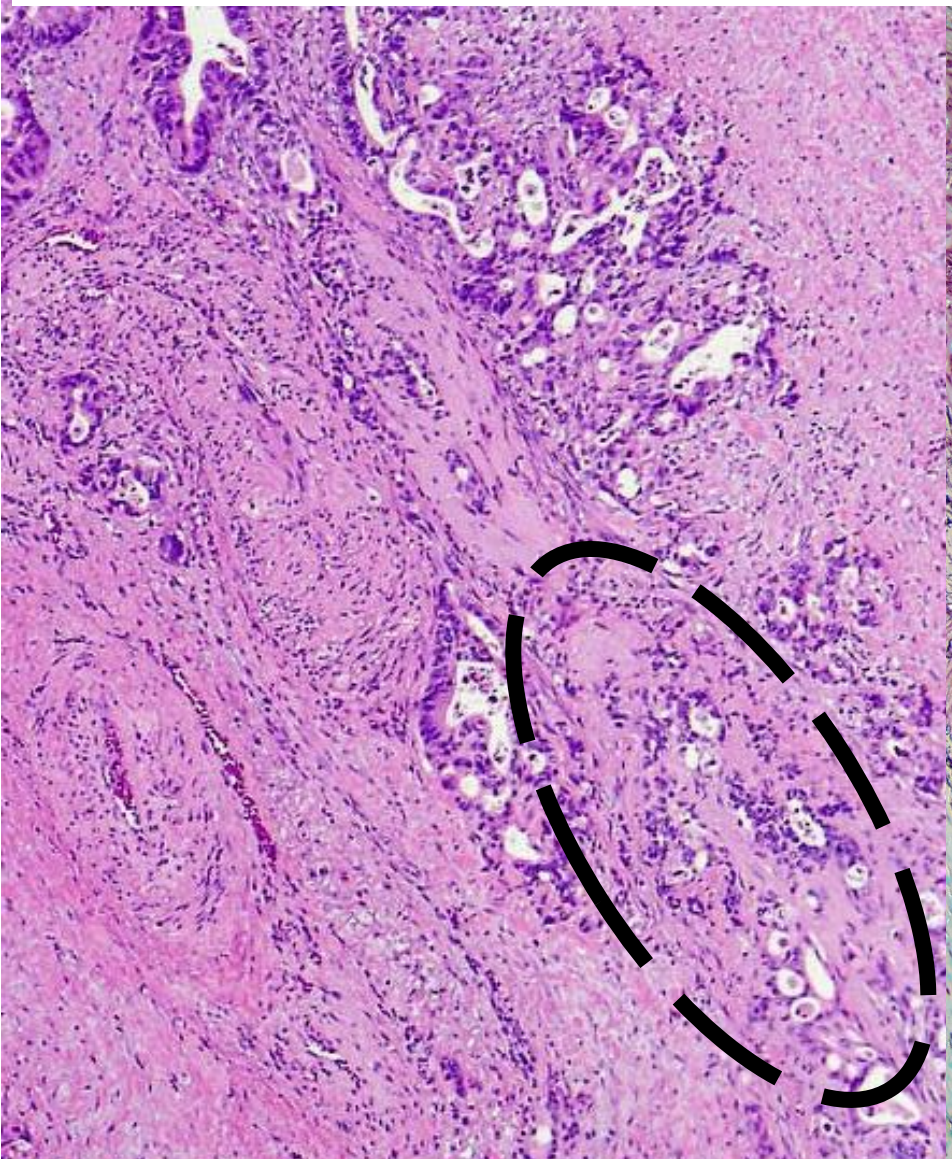
- **Tumor involving endothelium lined spaces that have elastic lamina +/-smooth muscle layer**

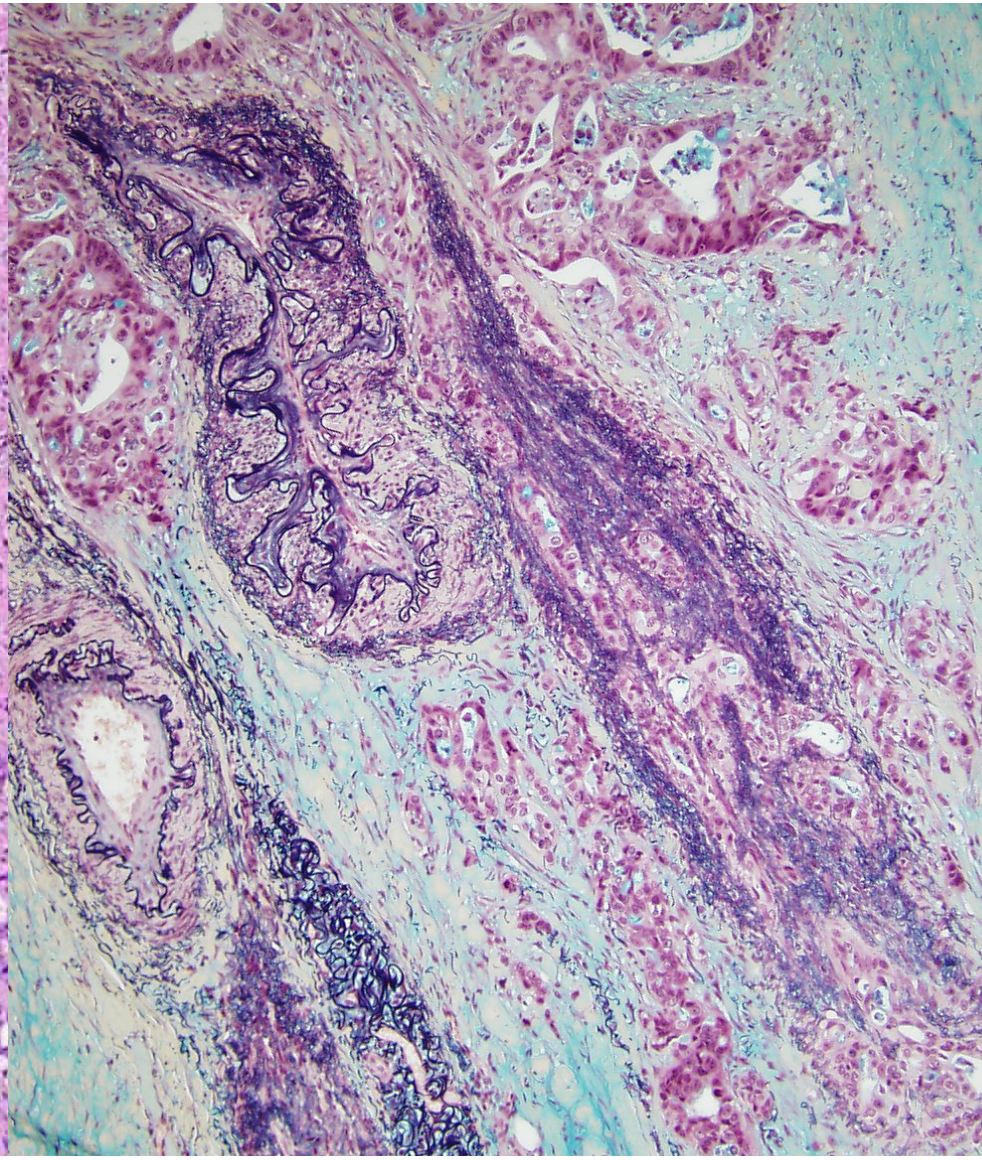


- **Extramural venous invasion: independent adverse prognostic factor & risk factor for liver mets**
  - In UK, venous invasion should be detected in at least 30% of CRC resections

Optional on CAP

Having Venous Invasion associated with ↓ 5 year survival





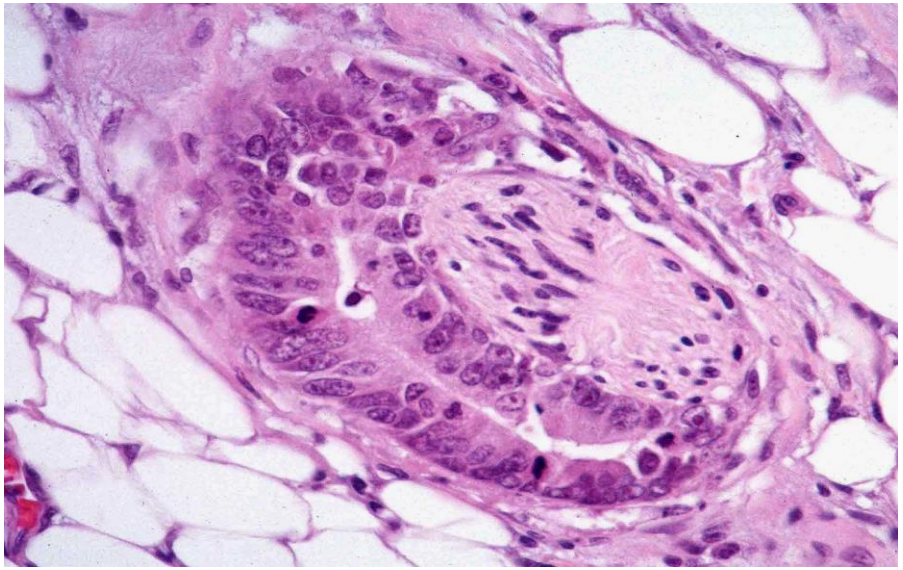
Venous invasion particularly important in stage II CRC: it may prompt oncologists to consider adjuvant chemotherapy

Tumor Budding?

- **Not required**

Mod Pathol. 2017 Sep;30(9):1299-1311.

Perineural



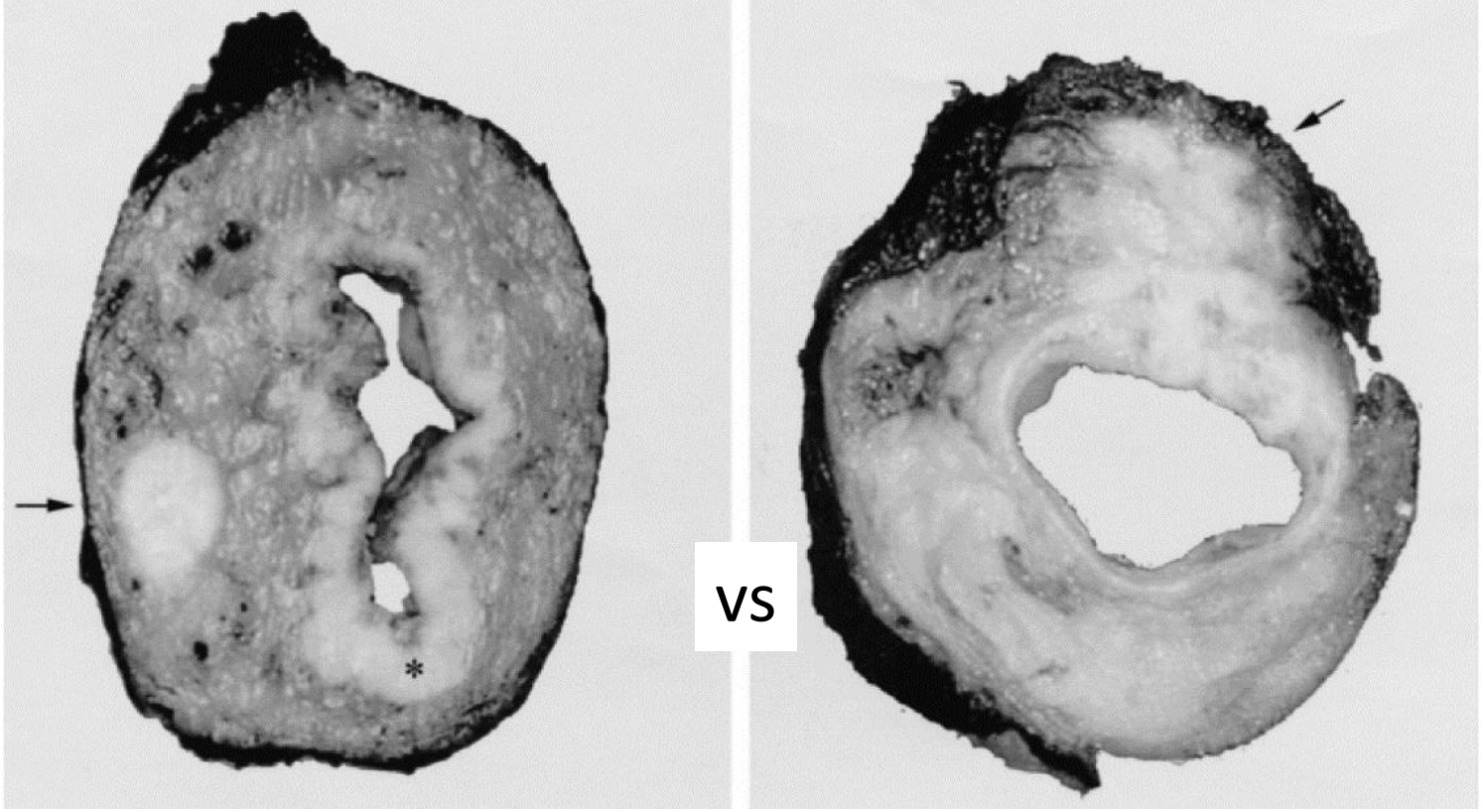
- **Should be reported but doesn't affect stage**

Margins: No change

- **If ≤1 mm = positive radial margin**

	CA ≤ 1mm from Margin	CA > 1mm from Margin
Local Control (no recurrence)	34%	92%

- **Positive margin doubles risk of death from disease**



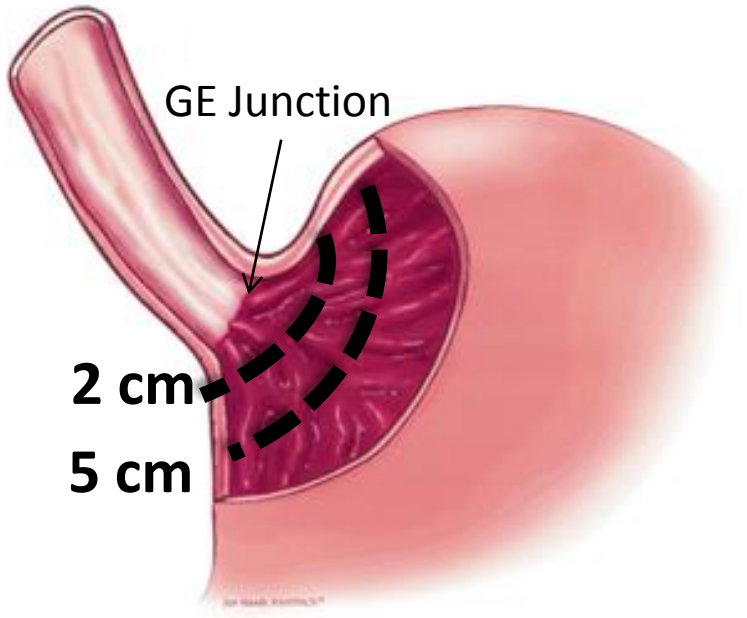
- **Positive lymph node or intravascular tumor within 1 mm of radial margin**
- What do you do?

No Guideline

Am J Surg Pathol. 2002 Mar;26(3):350-7.

ESOPHAGUS
(and Stomach Briefly)

LOCATION COUNTS

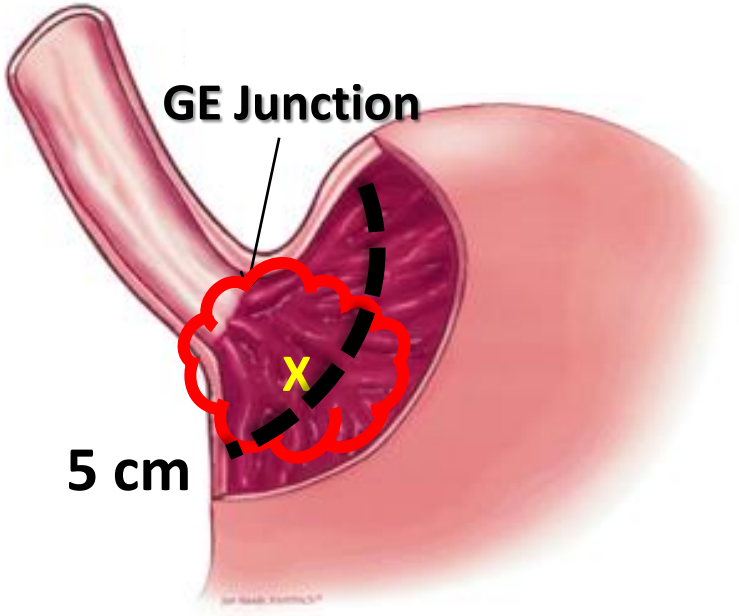


AJCC 7th – prox 5 cm

AJCC 8th – prox 2 cm

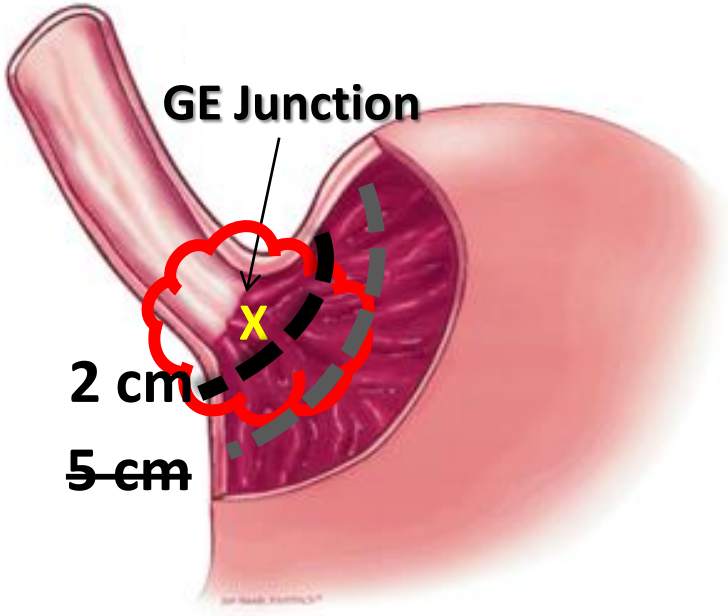
Gastroenterology 1999;117:218-28

AJCC 7th – CA Epicenter w/in prox 5 cm of Stomach, involving GEJ



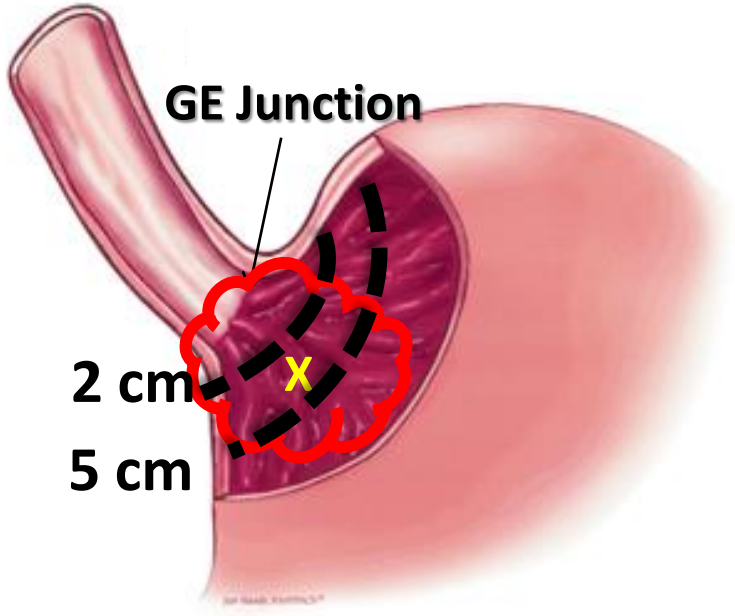
= ESOPHAGUS STAGING

AJCC 8th – CA Epicenter w/in prox 2 cm of Stomach, involving GEJ



= ESOPHAGUS STAGING

AJCC 8th – Epicenter >2 cm distal of GEJ *even involving GEJ* = STOMACH



7th

~~ESOPHAGUS~~

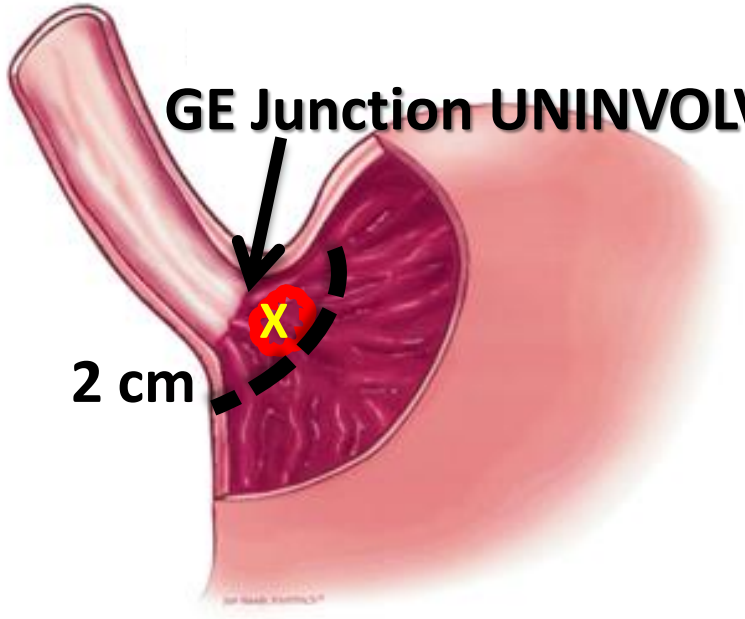
=

STOMACH

STAGING

AJCC 8th – w/in prox 2 cm of GEJ

NOT *involving GEJ* = STOMACH



~~**ESOPHAGUS**~~

= STOMACH

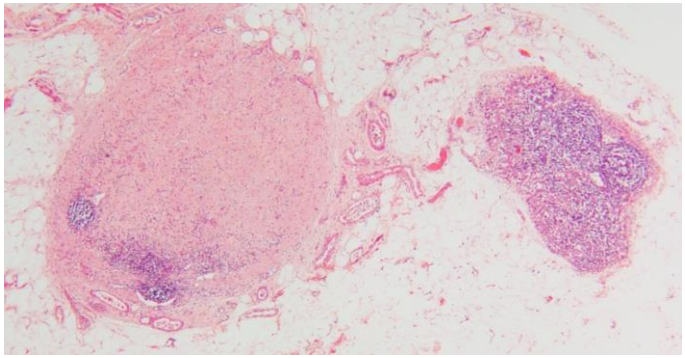
STAGING

Esophagus T category
Not much change

- **T1**
  - T1a: invades LP or MM (<2% risk of LN met)
  - T1b: invades SM (up to 20% risk of lymph node met)
- **T2** invades MP
- **T3** adventia (remember there is no serosa)
- **T4** (a & b) adjacent structures

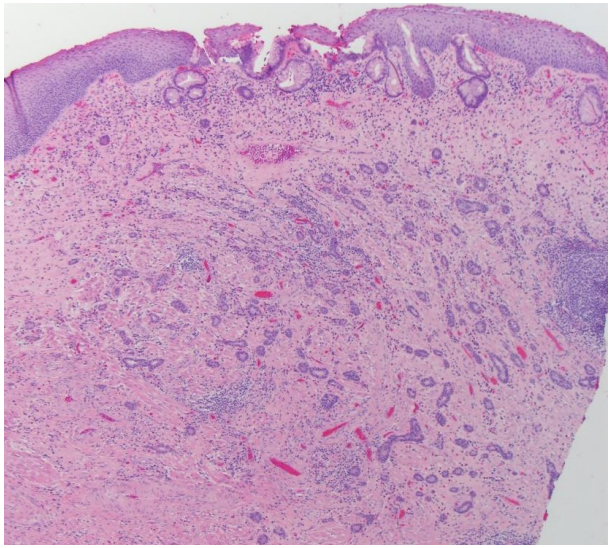
Most CA Esophagectomies have been treated

- **Assess entire tumor bed for residual cancer**
  (Don't just do one section and report complete response)
- **Surgeons may ask you for ~15 LN** (NCCN criteria),
  Even post-treatment: # depends on method of surgery
- **Treated LN with no cancer**
  not considered positive



Most CA Esophagectomies have been treated

- **Q: Do I have to grade cancers s/p neoadjuvant therapy?**

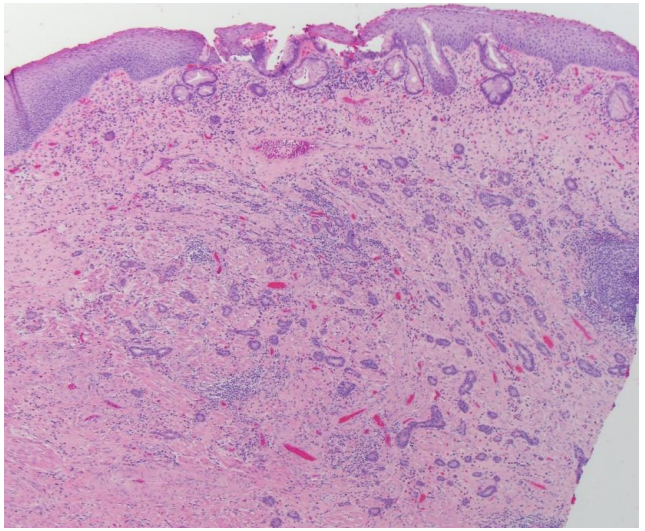


A: AJCC-wise… No

While Eso & Stom Stage groups do include Grade, <u>Separate Stage group for s/p RX does NOT INCLUDE GRADE</u>

Most CA Esophagectomies have been treated

- **Q: Do I have to grade cancers s/p neoadjuvant therapy?**



A: For CAP acc purposes…Yes (no exceptions made post-Rx)

Most CA Esophagectomies have been treated

- **TUMOR REGRESSION GRADING**
- **AJCC mentions Mandard**

AJCC: Mandard system – 5 tier

Concordance rate 50.9% (3 pathologists)

TRG1	Complete regression (fibrosis & no detectable CA cells)
TRG2	Fibrosis with scattered CA cells
TRG3	Fibrosis & CA cells with preponderance of fibrosis
TRG4	Fibrosis & CA cells with preponderance of CA cells
TRG5	CA without changes of regression

Am J Surg Pathol 2014;38:1551–1556

CAP Tumor Regression Grading

- **Optional (besides present/absent)**
- **Suggests modified Ryan scheme**

Rectal CA

Modified Ryan Scheme for Tumor Regression Score[11]

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

Sizable pools of acellular mucin may be present after chemoradiation but should not be interpreted as representing residual tumor.

This protocol does not preclude the use of other systems for assessment of tumor response.[12-14]

Histopathology. 2005;47(2):141-146.

CONCLUSIONS

- Appendix
- Colon
- Ampulla of Vater
- Anus
- Small intestine
- Esophagus
- Stomach

Main Changes Here

CONCLUSIONS

- **Appendix – LAMN**
- Colon
- Ampulla of Vater
- Anus
- Small intestine
- Esophagus
- Stomach

CONCLUSIONS

- **Appendix – LAMN**
- **Colon- T3 vs T4; LN met size**
- Ampulla of Vater
- Anus
- Small intestine
- Esophagus
- Stomach

CONCLUSIONS

- **Appendix – LAMN**
- **Colon- T3 vs T4; LN met size**
- Ampulla of Vater
- Anus
- Small intestine
- **Esophagus**
- **Stomach**

→ **LOCATION**

For More GI Cancer Staging this USCAP

- **Wendy Frankel: Colon Cancer Grossing**
  - Arthur Purdy Stout Session Sunday AM

- **Rupert Langner: Tumor Regression Grading in Esophageal Cancer**
  - GIPS Sunday PM

Special Thanks:

Laura Lamps

Henry Appelman

Karen Choi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Happy Birthday Laurel!


STANFORD
UNIVERSITY

AMPULLARY

- **Subtyping**
- **T Category Changes**

AJCC vs. CAP

Pancreatobiliary vs. Intestinal Subtypes Ampullary AdenoCA

AJCC vague about subtyping

CAP has subtypes listed (no longer optional)

- **"Controversial," "not conclusive"**
- **Prospective randomized study shows no diff in adj Rx effect**
  - Large indeterminate group (56%)

JAMA 2012;308 (2):147-156

CAP

No longer Optional to Subtype

Previous

+ = optional

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

___ Adenocarcinoma
+ ___ Adenocarcinoma, pancreaticobiliary type
+ ___ Adenocarcinoma, invasive intestinal type
___ ~~Medullary carcinoma~~
___ Invasive papillary adenocarcinoma
___ Mucinous adenocarcinoma
___ Clear cell adenocarcinoma
___ Signet-ring cell carcinoma
___ Adenosquamous carcinoma
___ Squamous cell carcinoma
___ Hepatoid adenocarcinoma
___ High-grade neuroendocrine carcinoma
___ Large cell neuroendocrine carcinoma
___ Small cell neuroendocrine carcinoma
___ Undifferentiated carcinoma
___ Undifferentiated carcinoma with osteoclast giant cells
___ Mixed adenoneuroendocrine carcinoma
___ Other (specify): _____
___ Carcinoma, not otherwise specified

Current

Histologic Type (Note C)

___ ~~Adenocarcinoma~~
___ Adenocarcinoma, pancreaticobiliary type
___ Adenocarcinoma, intestinal type
___ ~~Medullary carcinoma~~
___ Invasive papillary adenocarcinoma
___ Mucinous adenocarcinoma
___ Clear cell adenocarcinoma
___ Signet-ring cell carcinoma
___ Adenosquamous carcinoma
___ Squamous cell carcinoma
___ Hepatoid adenocarcinoma
___ Large cell neuroendocrine carcinoma
___ Small cell neuroendocrine carcinoma
___ Neuroendocrine carcinoma (poorly differentiated)[#]
___ Undifferentiated carcinoma
___ Undifferentiated carcinoma with osteoclast giant cells
___ Mixed adenoneuroendocrine carcinoma
___ Other histologic type not listed (specify): _____
___ Carcinoma, not otherwise specified

CAP

"This panel able to classify 92% of cases"

Ampullary CA Subtype	CK20	CDX2	MUC2	MUC1
Intestinal	+			-
		+		-
			+	-
	+	+	+	+/-
Pancreato-biliary	-	-	+/-	+

Am J Surg Pathol. 2014;38:1371–1379

CAP

"This panel able to classify 92% of cases"

Ampullary CA Subtype	CK20	CDX2	MUC2	MUC1
Intestinal	+			-
		+		-
			+	-
	+	+	+	+/-
Pancreato-biliary	-	-	+/-	+

Am J Surg Pathol. 2014;38:1371–1379

CAP

"This panel able to classify 92% of cases"

Ampullary CA Subtype	CK20	CDX2	MUC2	MUC1
Intestinal	+			-
		+		-
			+	-
	+	+	+	+/-
Pancreato-biliary	-	-	+/-	+

Am J Surg Pathol. 2014;38:1371–1379

No prognostic significance (overall survival)

Large ambiguous category (40%)

Ampullary CA Subtype	CK20	CDX2	MUC2	MUC1
Intestinal	+			-
		+		-
			+	-
	+	+	+	+/-
Pancreato-biliary	-	-	+/-	+

Mod Pathol. 2016;29:1575–1585.
AJSP 2017 Jul;41(7):865-876.

CAP: Two-Tier Approach

1 **PB Histology** + **MUC1 +** + **CDX2 –** = **Pancreato-biliary type**

2 **Everything else = Intestinal type**

Ampullary T category Subdivided

	PREVIOUS
T1	Limited to Ampulla of Vater or Sphincter of Oddi
T2	Invades Duodenal wall
T3	Invades Pancreas
T4	Invades peripancreatic tissue or adj organs/structures

T1a – Limited to AmpVater or Sph Oddi

T1b – Invades beyond AmpVater or Sph Oddi +/- Duod Submucosa

Ampullary T category Subdivided

	PREVIOUS
T1	Limited to Ampulla of Vater or Sphincter of Oddi
T2	Invades Duodenal ~~wall~~ **MP**
T3	Invades Pancreas
T4	Invades peripancreatic tissue or adj organs/structures

T1a – Limited to AmpVater or Sph Oddi

T1b – Invades beyond AmpVater or Sph Oddi +/- <u>Duod Submucosa</u>

Ampullary T category Subdivided

	PREVIOUS
T1	Limited to Ampulla of Vater or Sphincter of Oddi
T2	Invades Duodenal wall
T3	Invades Pancreas
T4	~~Invades peripancreatic tissue or adj organs/structures~~

T3a – Invades Pancreas up to 0.5 cm

T3b – Invades >0.5 cm into pancreas or peripancreatic soft tissue or duod serosa or periduodenal tissue

Ampullary T category Subdivided

	PREVIOUS
T1	Limited to Ampulla of Vater or Sphincter of Oddi
T2	Invades Duodenal wall
T3	Invades Pancreas
~~T4~~	~~Invades peripancreatic tissue or adj organs/structures~~
T4	**Involves celiac axis, SMA, +/- common hepatic artery irresp of size**

T3a – Invades Pancreas up to 0.5 cm

T3b – Invades >0.5 cm into pancreas or peripancreatic soft tissue or duod serosa or periduodenal tissue

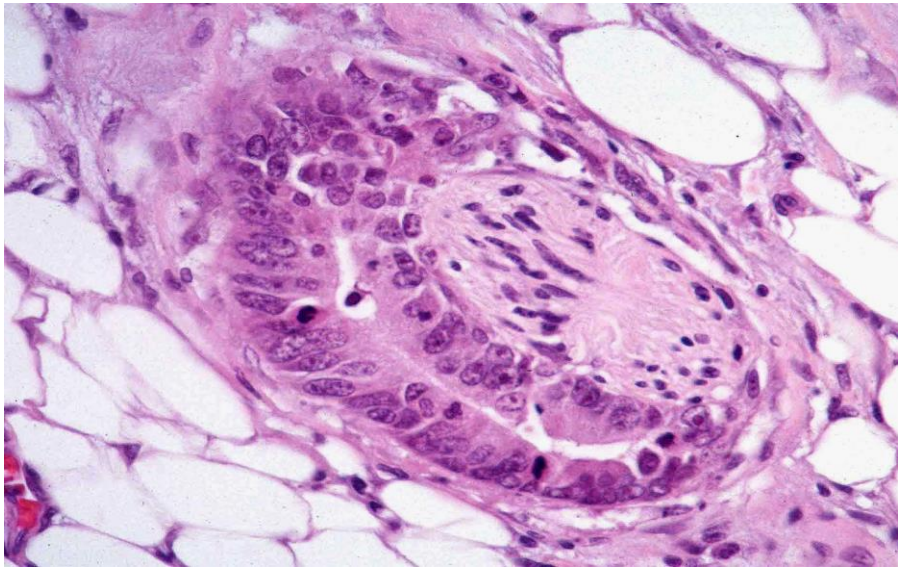
Grading: Back to Well, Mod, Poor

- **AJCC 7th:**
  - **Low (well, moderate)**
  - **High (poorly diff, undiff)**

- **AJCC 8th: back to:**
  - G1 – well
  - G2 – moderate
  - G3 – poor
  - G4 - undifferentiated

Not part of Staging (as it is in Appendix)

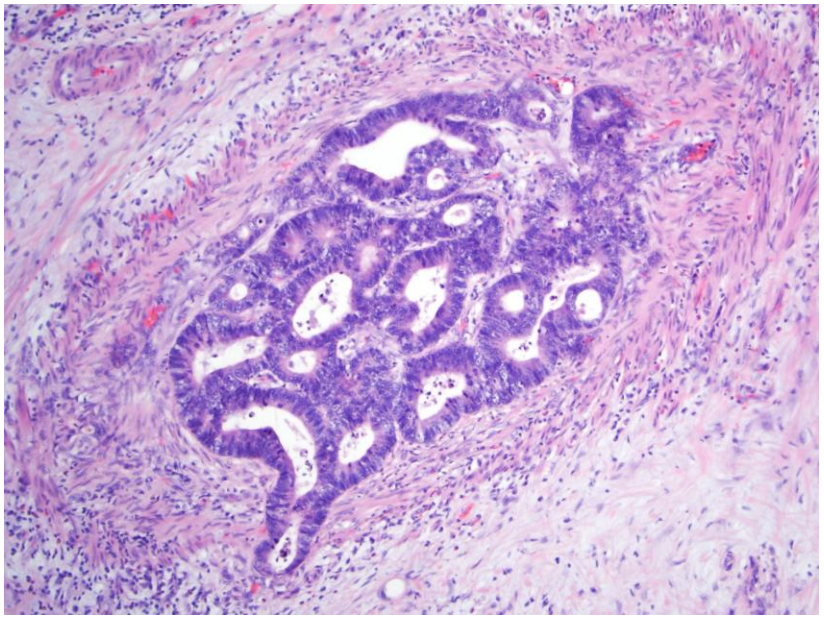
Perineural



- **Should be reported but doesn't affect stage**

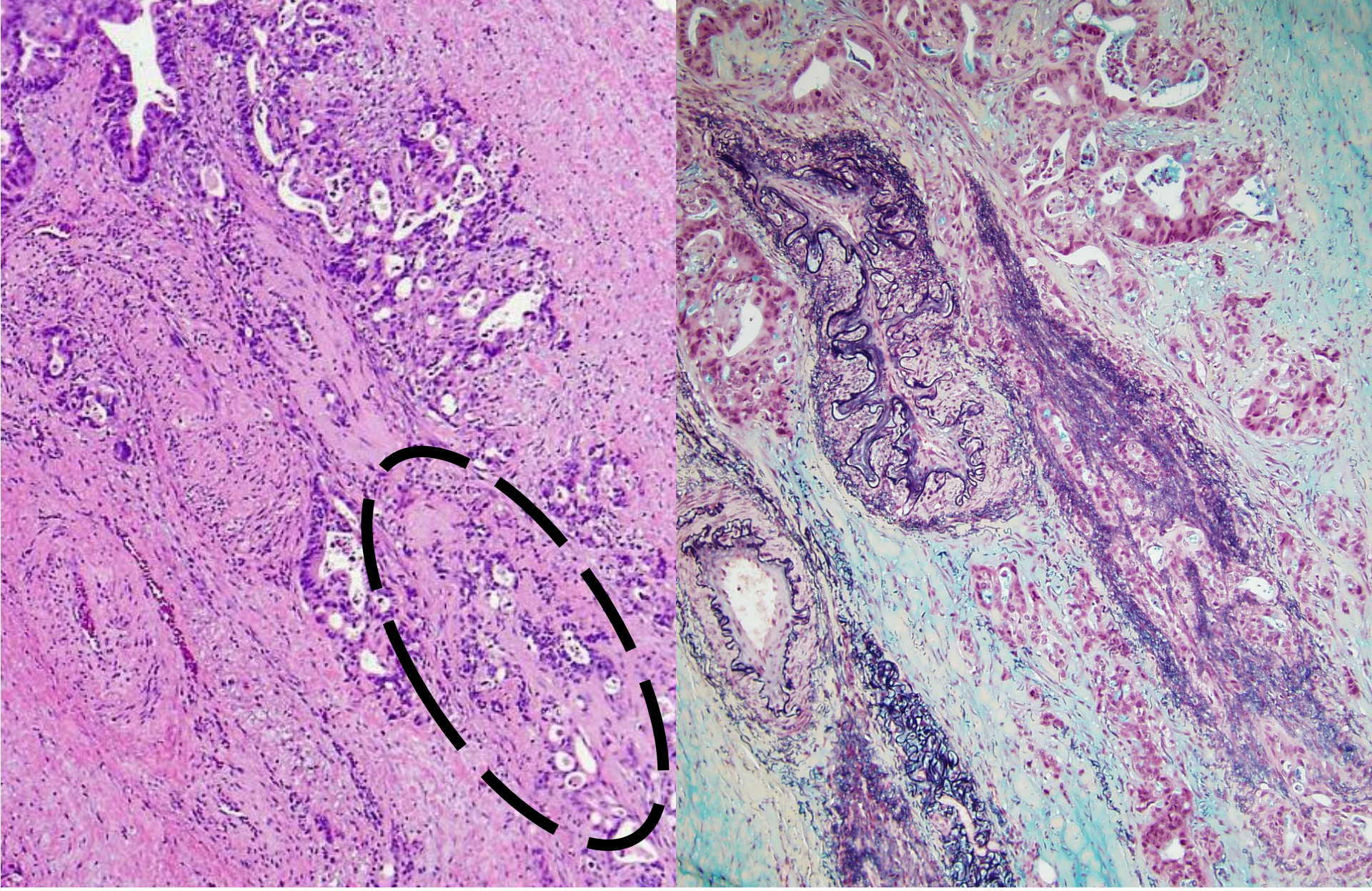
AJCC: Large vessel invasion

- **Tumor involving endothelium lined spaces that have elastic lamina +/-smooth muscle layer**



- **Extramural venous invasion: independent adverse prognostic factor & risk factor for liver mets**
  - In UK, venous invasion should be detected in at least 30% of CRC resections

Optional on CAP



Venous invasion particularly important in stage II CRC: it may prompt oncologists to consider adjuvant chemotherapy

Tumor Budding?

- **Not required**

My cheatsheet:

- **Scan for hot spot**
- **Count tumor buds (cluster of cells 4 or less) at 20x**
- **If your eyepiece says 22, divide # of tumor buds by 1.21**

Report # of buds and what it is by consensus 3 tiered system

Low: 0-4
Interm: 5-9
High: ≥10

Tell clinician:

- **Cancer in polyps:**
  -low is ok,
  -interm/high predicts LN mets
- **Stage 2 colon CA (invades past MP): it is adverse prognosticator (survival); may be important in chemo decisions**
  - Low/ interm ok,
  - high = bad prog

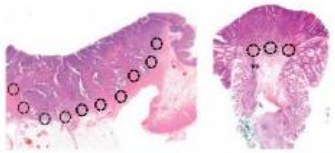
Mod Pathol. 2017 Sep;30(9):1299-1311.

1 **Define the field (specimen) area for the 20x objective lens of your microscope based on the eyepiece field number (FN) diameter**

Objective magnification: 20		
Eyepiece FN Diameter (mm)	Specimen Area (mm2)	Normalization Factor
18	0.636	0.810
19	0.709	0.903
20	0.785	1.000
21	0.866	1.103
22	0.950	1.210
23	1.039	1.323
24	1.131	1.440
25	1.227	1.563
26	1.327	1.690

2 **Select the H&E slide with greatest degree of budding at the invasive front**

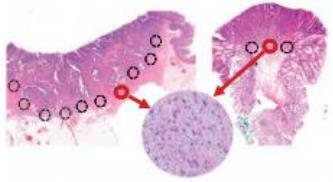
3 **Scan 10 individual fields at medium power (10x objective) to identify the "hotspot" at the invasive front**



For surgical resection specimens, scan 10 fields

For pT1 endoscopic resections (usually <10 fields available), scan all

4 **Count tumor buds in the selected "hotspot" (20x objective)**



Selected hotspot indicated in red

5 **Divide the bud count by the normalization factor (figure 2) to determine the tumor bud count per 0.785mm²**

Select the budding [Bd] category based on bud count and indicate the absolute count per 0.785mm² (see reporting example)

$$\text{Tumor bud count per 0.785 mm}^2 = \frac{\text{Bud count (20x objective)}}{\text{Normalization factor*}}$$

Bd1 (low):	0-4 buds	per 0.785 mm²
Bd2 (intermediate):	5-9 buds	
Bd3 (high):	≥10 buds	

Reporting example:
Tumor budding: Bd3 (high), count 14 (per 0.785 mm²)

Mod Pathol. 2017 Sep;30(9):1299-1311.

Pathologic Eval: Impact on Overall Survival

- Both post-therapy pathologic **stage** & **extent of residual CA**→independent predictors of overall survival (p = 0.02; p=0.04)

N = 235	**Overall Survival rate p = 0.003**	
	2 years	5 years
No residual carcinoma on pathology exam (30%)	78%	65%
Residual carcinoma	55%	29%

Cancer 2005;103:1347–55.

Stage 4A

- Any t with any N and M1a: intraperitoneal acellular mucin without identifiagle tumor cells
  - This has very low rate of recurrence, prolonged time even >10 years, may not need HIPEC
- Any T with any N, M1b, G1 (intraperitoneal met only including peritoneal mucinous deposits containing tumor cells
- AJCC considers "**serosal involvement of the appendix by acellular mucin may demonstrate excellent outcome with only localized surgical resection." but lumps acellular and cellular together as T4a**

8th vs 7th

- 4 pages on prognostic factors

- D
- CEA
- Tumor regression score
- CRM
- **LVI**
- PNI
- MSI
- KRAS, NRAS
- BRAF

- Prognostic Factors (site specific factors) recommended for collection: a list

- CEA
- TD
- CRM
- PN
- MSI
- Tumor regression grade
- KRAS

msi

- High levels of MSI (MSI-H) occur in ~15% colorectal carcinomas, associated with right sided colon cancers with good prog
- Hallmark of Lynch
- Sporadic usually but may occur in pts with germline DNA MMR gene mutation (Lynch)
- MSI H good prognostic factor and also predicts poor response to 5-FU chemo
- However, oxaliplatin addition in FOLFOX regimens negates adve??rse effects of MSI-H
- BRAF mutation + MSIH (there is an association) have significantly worse prognosis in Stage III and IV colon cancers (node mets or dist mets resp)

- MSI-H good
- MSI-H + BRAF not as good
- Still better than MSS without BRAF
- Which is better than MSS with BRAF

- Use FDA approved assay or standard genotyping/next-gen sequencing for BRAF
- Not IHC for BRAF

CAP

- Used to have a “features suggestive of Microscatellite instability” section (tumo infiltrating lymphocytes, Crohn like lymphocytic reaction, mucinous/signet ring, medullary)

- But now there is universal MSI testing recommended for <70 years