The International Academy of Pathology, Hong Kong Division

Colorectal Cancer Staging and Prognostic Factors: Where are we going with AJCC TNM Version 9?

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October 28, 2023

Topics

Current status of TNM for colorectal cancer

- How can we do better?
- What are potential consequences of changing?

Prognostic features

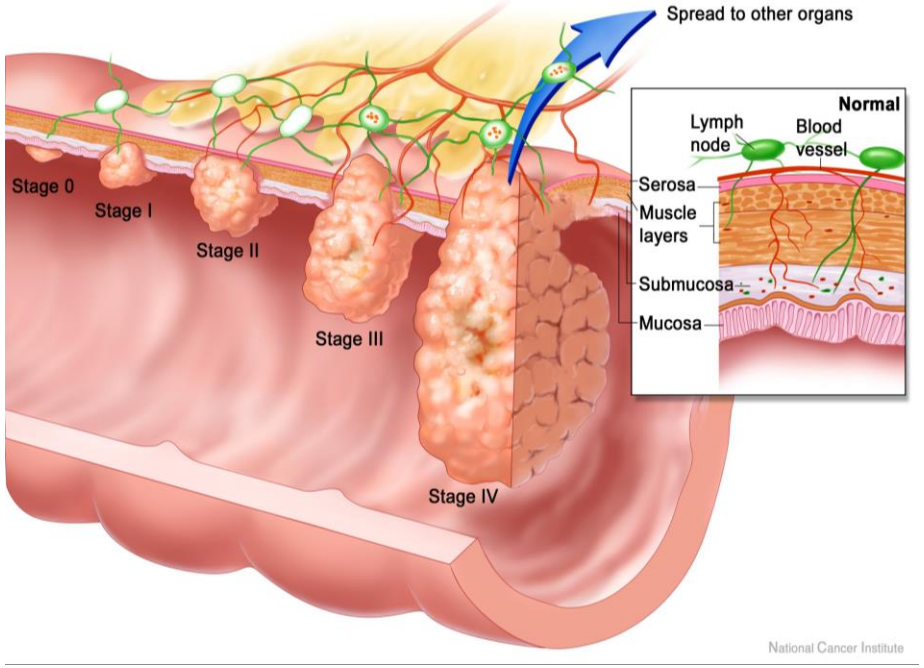
- What are the most important?
- Will they be incorporated into risk assessment (staging)?

Topics: Problematic Issues in Colorectal Cancer Staging

- **Localized peritoneal involvement (pT4a)**
- **Tumor deposits**
- **Small and large vessel invasion**
- **Will AJCC incorporate molecular features?**
- **Stage groupings for colorectal cancer are not hierarchical- how can we improve them?**

History of Colorectal Cancer Staging

- Originally published by C. E. Dukes, a surgeon, in 1932
  - Rectal cancer only
  - Did not include metastasis (Stage IV)
- Adapted by Kirklin in 1949 and later by Astler and Coller in 1953 for colon and rectum.
- Revised by Turnbull in 1967 to include stage for unresectable tumors and distant metastases.
- AJCC TNM manual, 1st edition, 1977



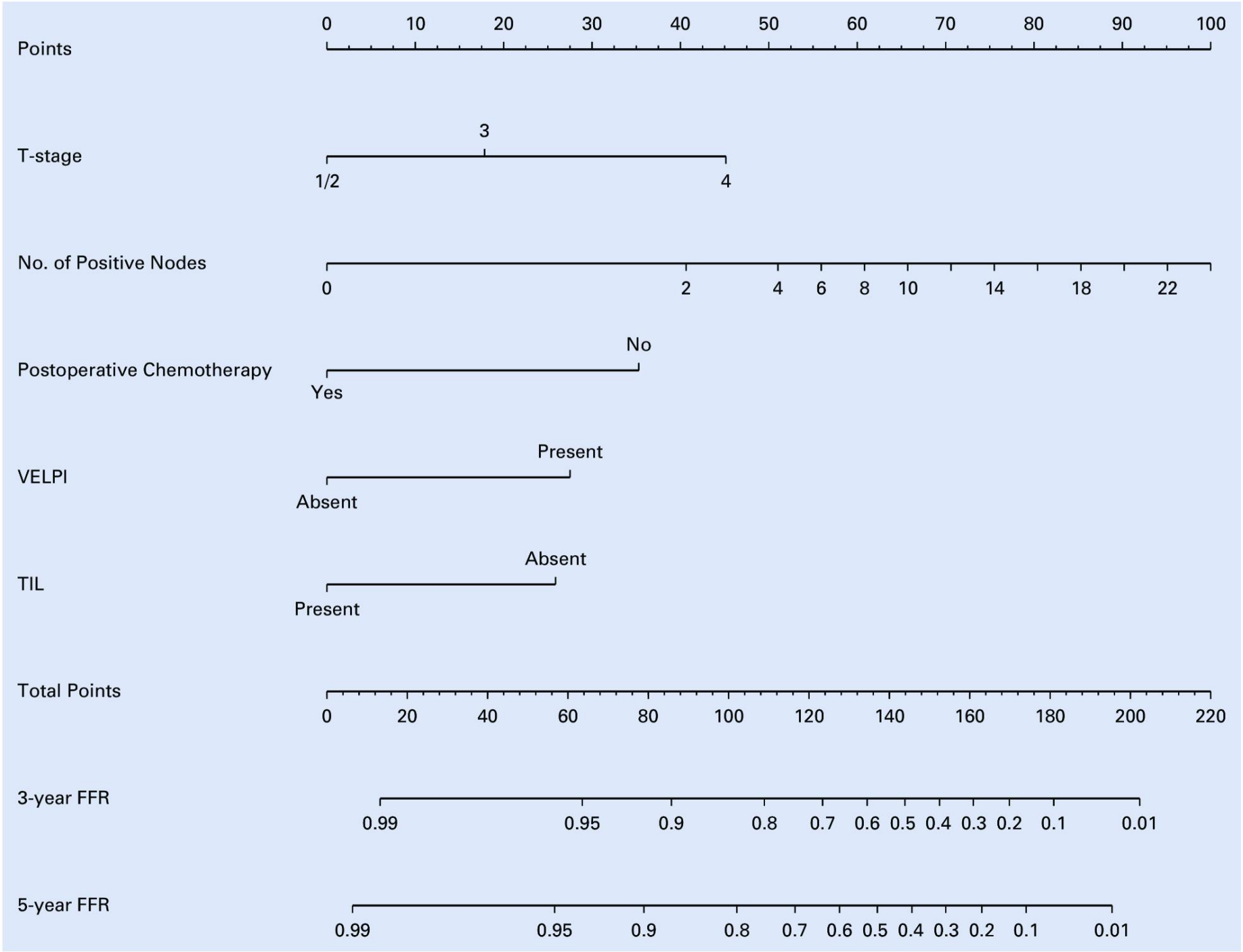
Clinical versus Pathological Staging

Clinical stage classification uses clinical exam and imaging studies done before initiation of treatment. It may be assigned based on whatever information is available, including results from biopsies.

Pathological stage classification is based on examination of the resected specimen.

The Role of Pathological Staging

- Pathological examination of resected colorectal cancer will continue to be the cornerstone of patient care, clinical trial enrollment, and tumor registry data collection for cancer control
- Development of prognostic tools that incorporate non-TNM data will make reporting of additional prognostic factors even more important
- Histologic findings and molecular testing will be complementary, not mutually exclusive
- Reporting requirements will become more complex, necessitating use of standardized structured reports



Third generation clinical risk calculator from MSKCC, for MSS or untested CRC

Weiser MR, et al. J Clin Oncol 2021; 39(8):911-9.

JOURNAL OF CLINICAL ONCOLOGY

Controversies and Pitfalls in Pathological Assessment of Cancer Resection Specimens

- **Subjective**
- **Need for standardized examination protocols**
- **Need for standardized reporting (current terminology has caused confusion)**
- **Should be evidence-based**
- **Data are often limited**
- **Gap between recommendations and reality**

Colorectal Cancer: Morphologic Prognostic Factors

- **Pathological Stage (TNM): Continues to be strongest predictor of survival**
  - **T category is more important than N category, for low number of positive lymph nodes**
- **Tumor Type**
  - **Special subtypes (signet ring cell, neuroendocrine carcinoma, mucinous, medullary, micropapillary types)**
  - **Grade**
- **Resection margin status**

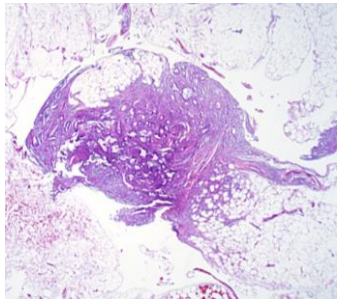
High Risk Features for Stage II CRC

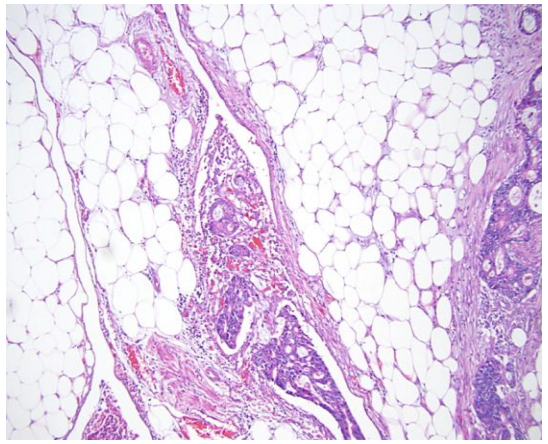
National Comprehensive Cancer Network 2023 (USA)

- **Less than 12 lymph nodes retrieved**
- **High tumor grade**
- **Lymphovascular invasion**
- **Perineural invasion**
- **Positive, close, or indeterminate margins**
- **Obstructing tumor or localized perforation**
- **High level of tumor budding**
- **T4 disease**

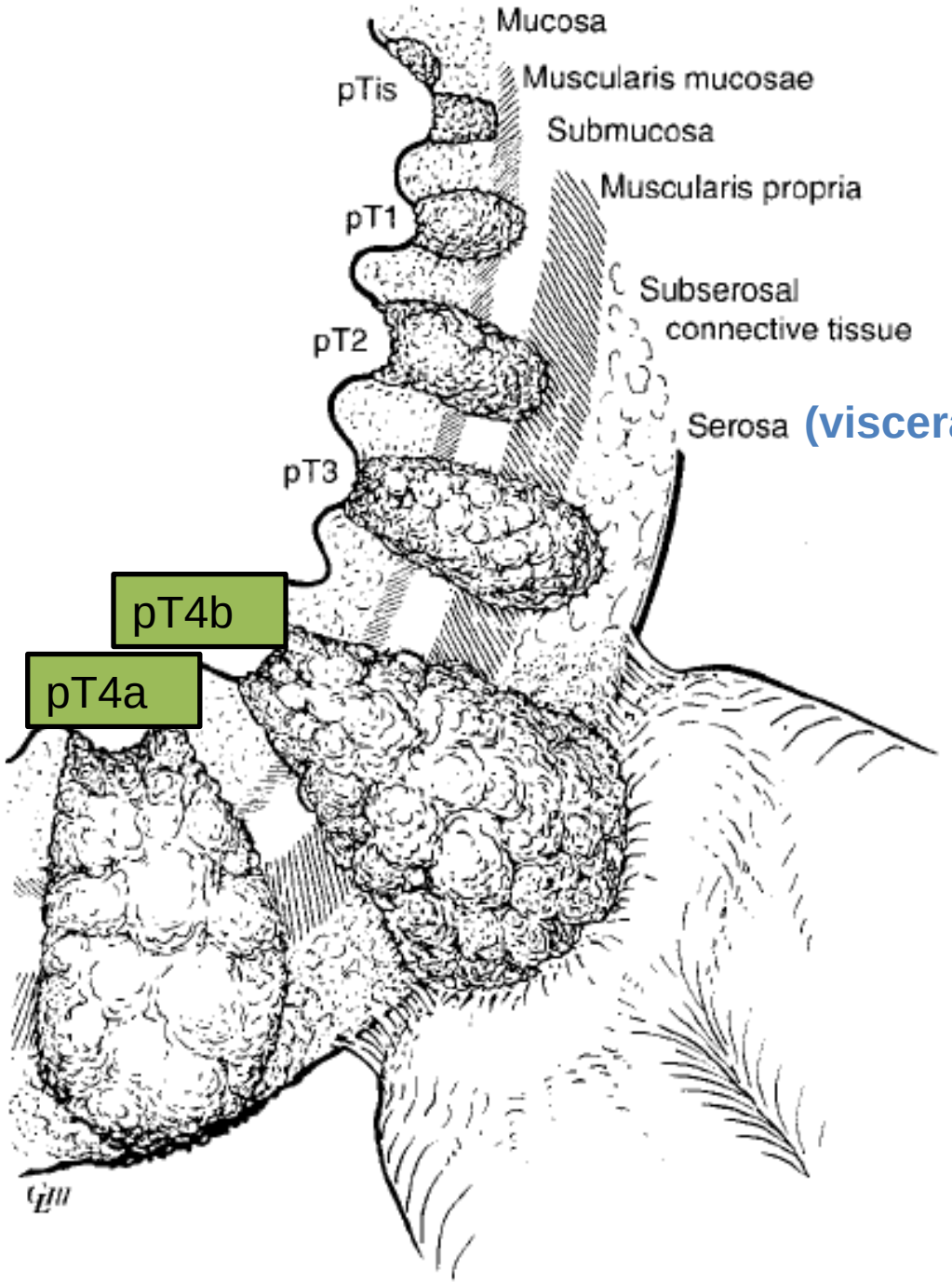
Persistent Challenges in CRC Staging

- **Survival curves are not hierarchical**
- **The importance of T category; underreporting of localized peritoneal involvement (pT4a)**
- **Discontinuous spread of tumor vs. completely replaced lymph nodes (tumor deposits); is there a better approach than N1c?**
- **Incorporation of molecular and other non-anatomic features**





T categories



Pericolic fat

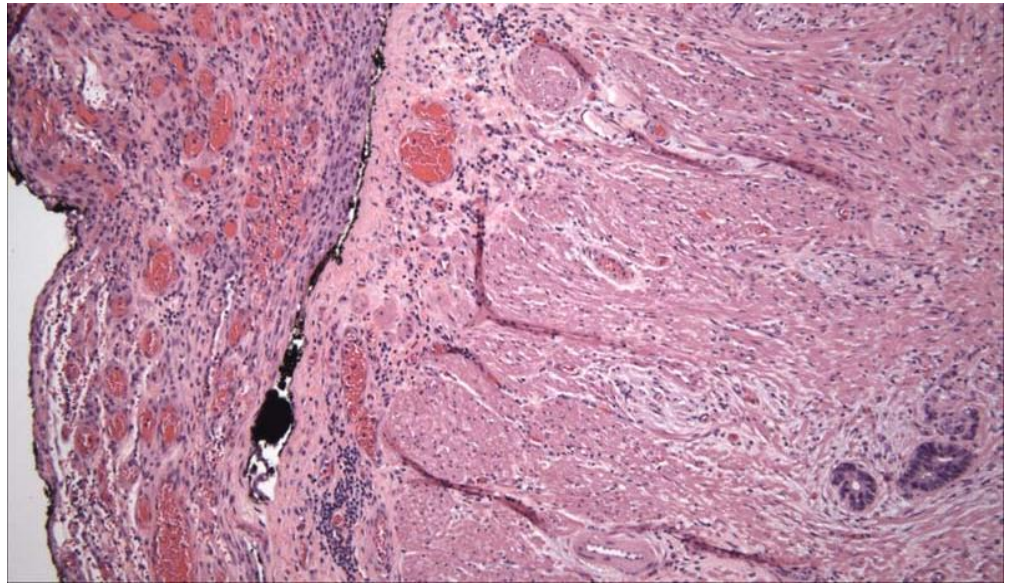
(visceral peritoneum)

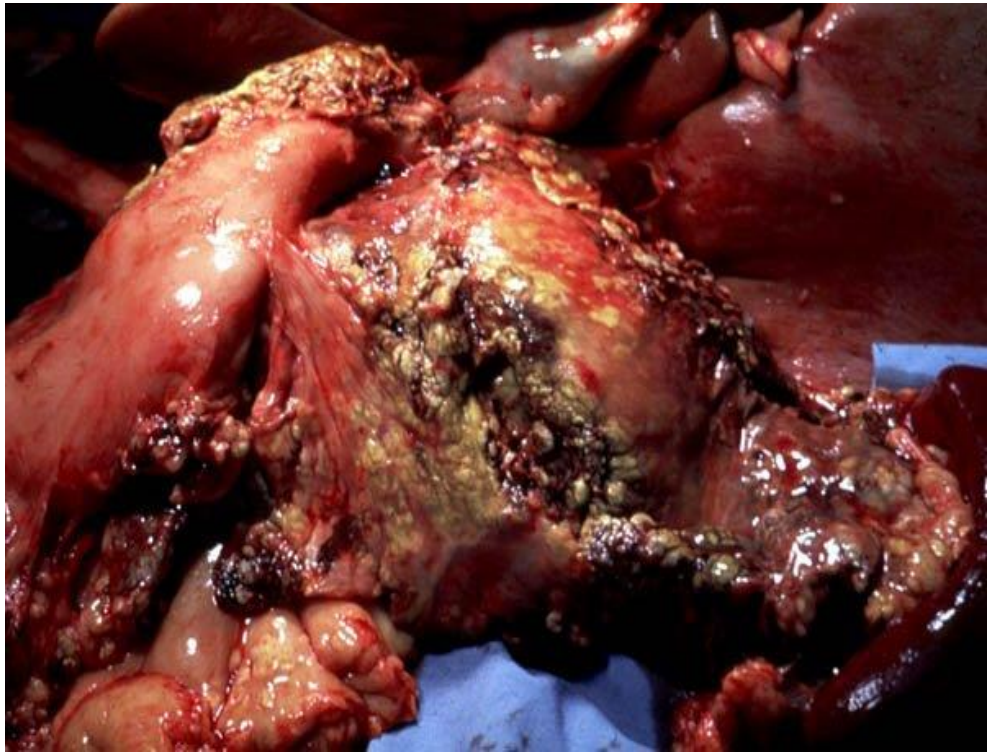
Subdivisions of pT: Can additional prognostic information be gained?

- **pT4 Subdivision into**
  - **pT4a: perforation of visceral peritoneum (serosa)**
  - **pT4b: invasion of adjacent organs**
- **Serosal involvement may be underdiagnosed by pathologists (may be present in up to 20% of cases)**
- **Can assessment of elastic lamina of peritoneum help with classification?**

pT4: Localized Peritoneal Involvement or Invasion of Adjacent Organs

- **Includes macroscopic perforation through tumor (assigned pT4a)**
- **Only ~ 34% of cT4 tumors are pT4 (fibrovascular adhesions)**

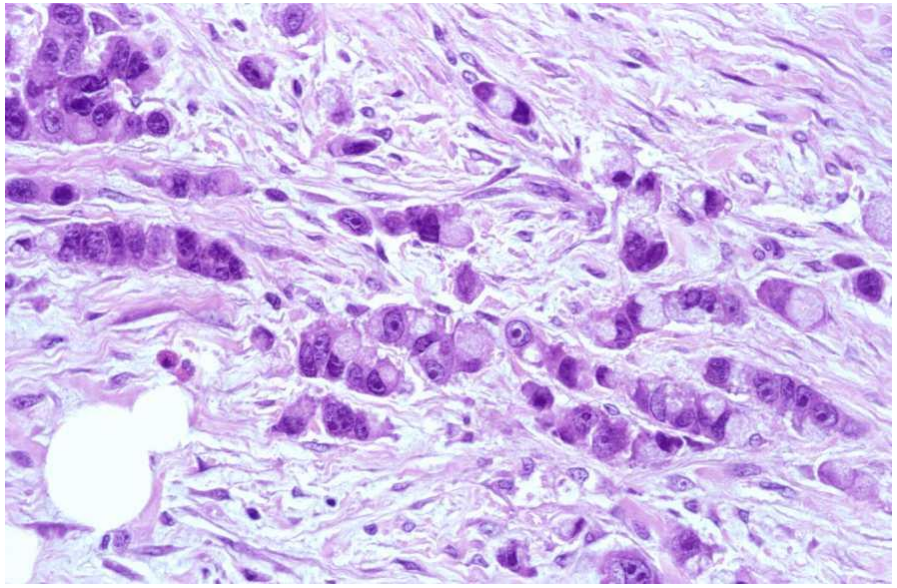


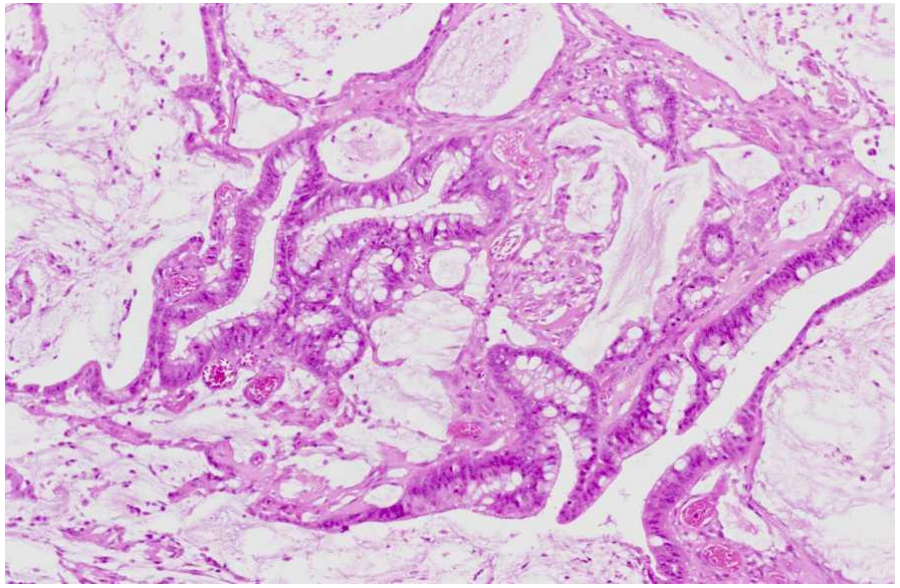


www.pathguy.com/~lulo/lulo0012.jpg

Peritoneal Involvement by Colorectal Cancer

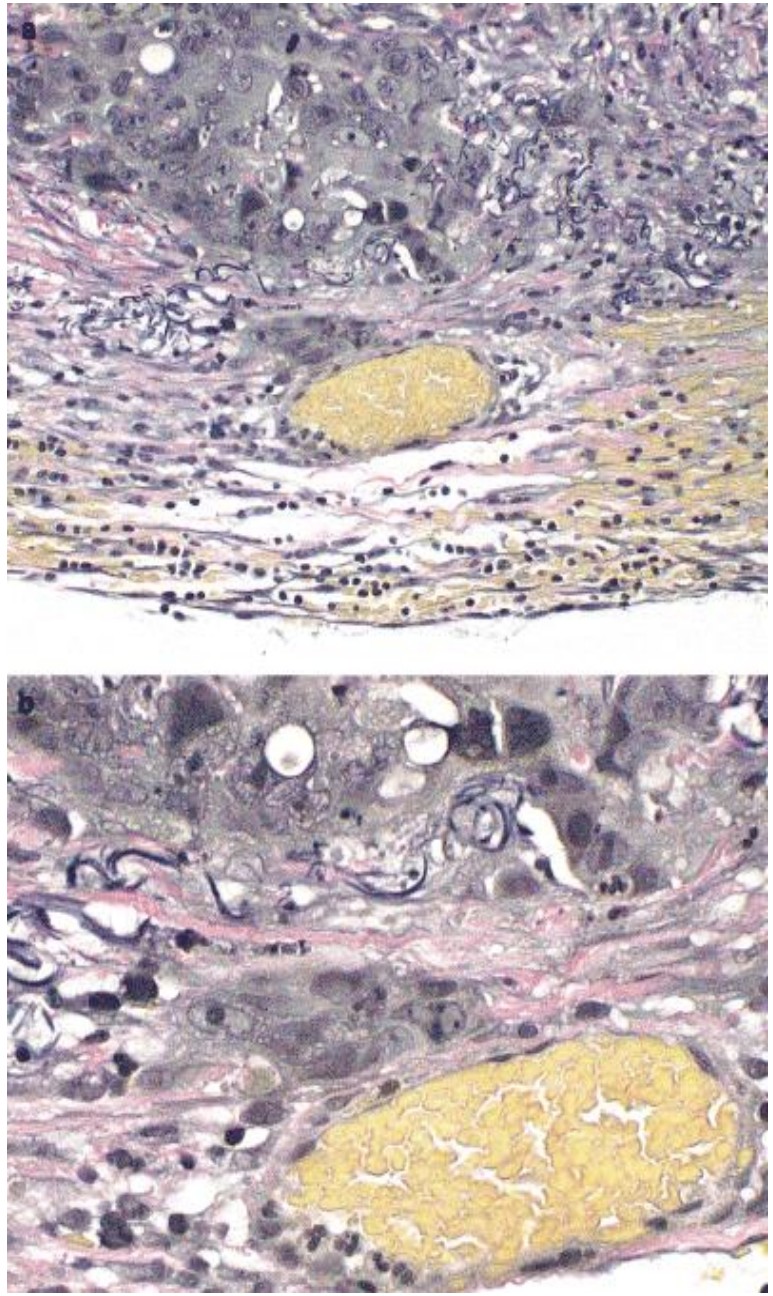
- **About 20% with a T4 cancer will develop peritoneal carcinomatosis**
- **Mucinous and signet ring cell carcinomas are more likely to involve peritoneum**





Local Peritoneal Involvement (pT4a)

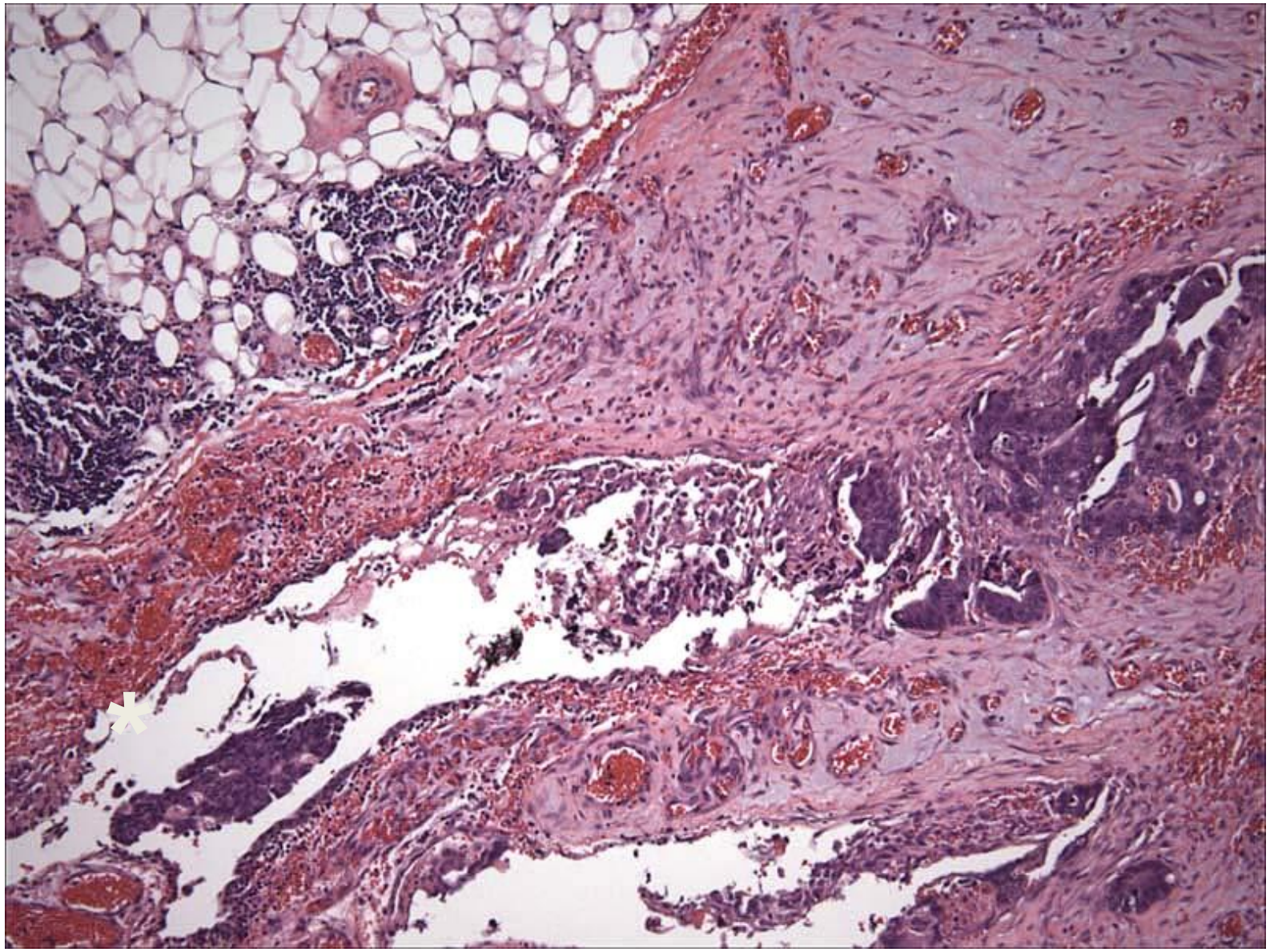
- **Associated with palliative surgery, high tumor grade, lymph node involvement, and infiltrative border**
- **Independent prognostic factor; predicts intraperitoneal recurrence**
- **Use of elastin stain when peritoneum is denuded has been proposed**



Shepherd et al. Gastroenterology 1997; 112:1096

Steward et al. Histopathology 2006;49:435-7

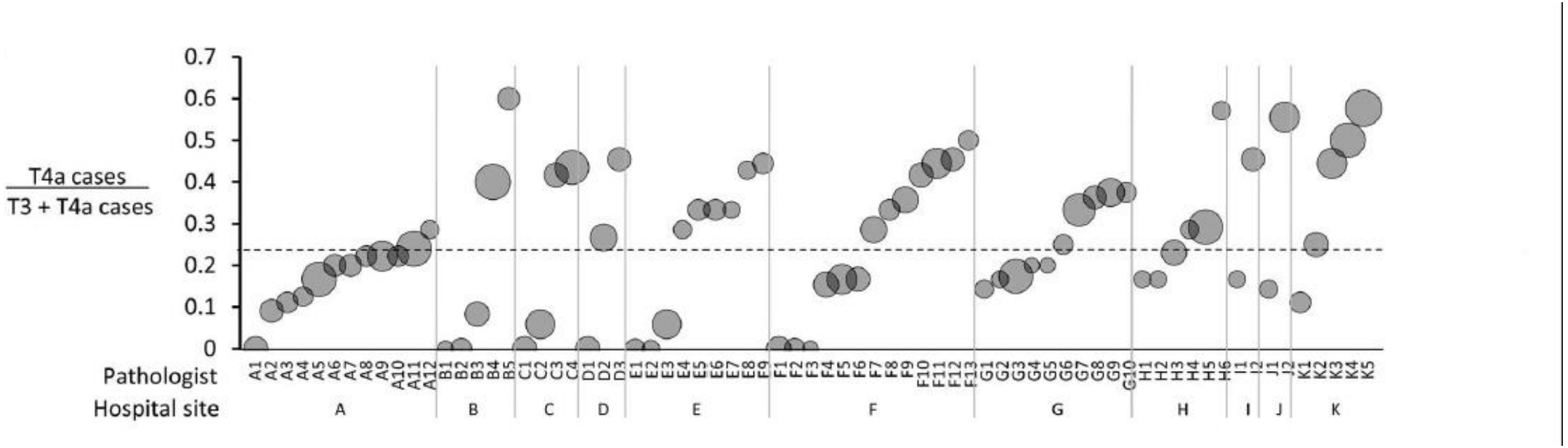
Local Peritoneal Involvement



Proposed Criteria for Local Peritoneal Involvement

- **Tumor present at the serosal surface with inflammatory reaction, mesothelial hyperplasia, and/or erosion/ulceration**
- **Free tumor cells on the serosal surface with underlying ulceration of the visceral peritoneum**
- **A mesothelial inflammatory and/or hyperplastic reaction with tumor close to, but not at, the serosal surface (controversial)**

Interpretation of pT4a by Pathologists is Inconsistent

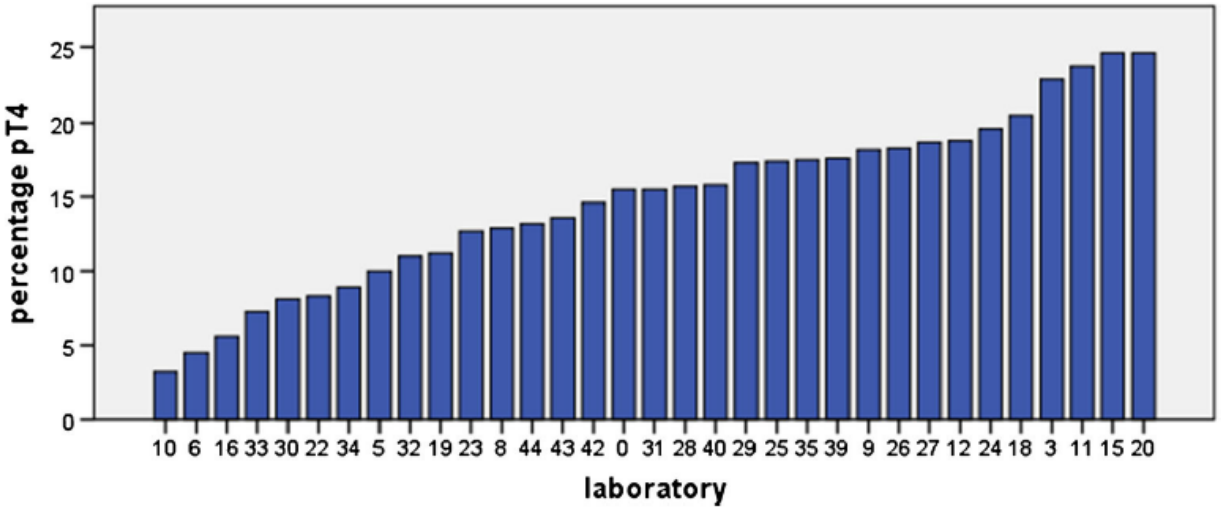


- Only ~ 50% of pathologists use CAP guideline that tumor communicating with serosa through inflammation is pT4a
- ~50% would comment for tumor <1 mm from the serosa
- K statistic was 0.54 with combined pre- and post-test (moderate)

Naso JR et al. Archives Pathol Lab Medicine 2021; 145:343-51

Is the pT4a Definition Ambiguous?

Proportion of pT4a diagnosis per laboratory for pT3 or pT4aN0M0 colorectal carcinomas

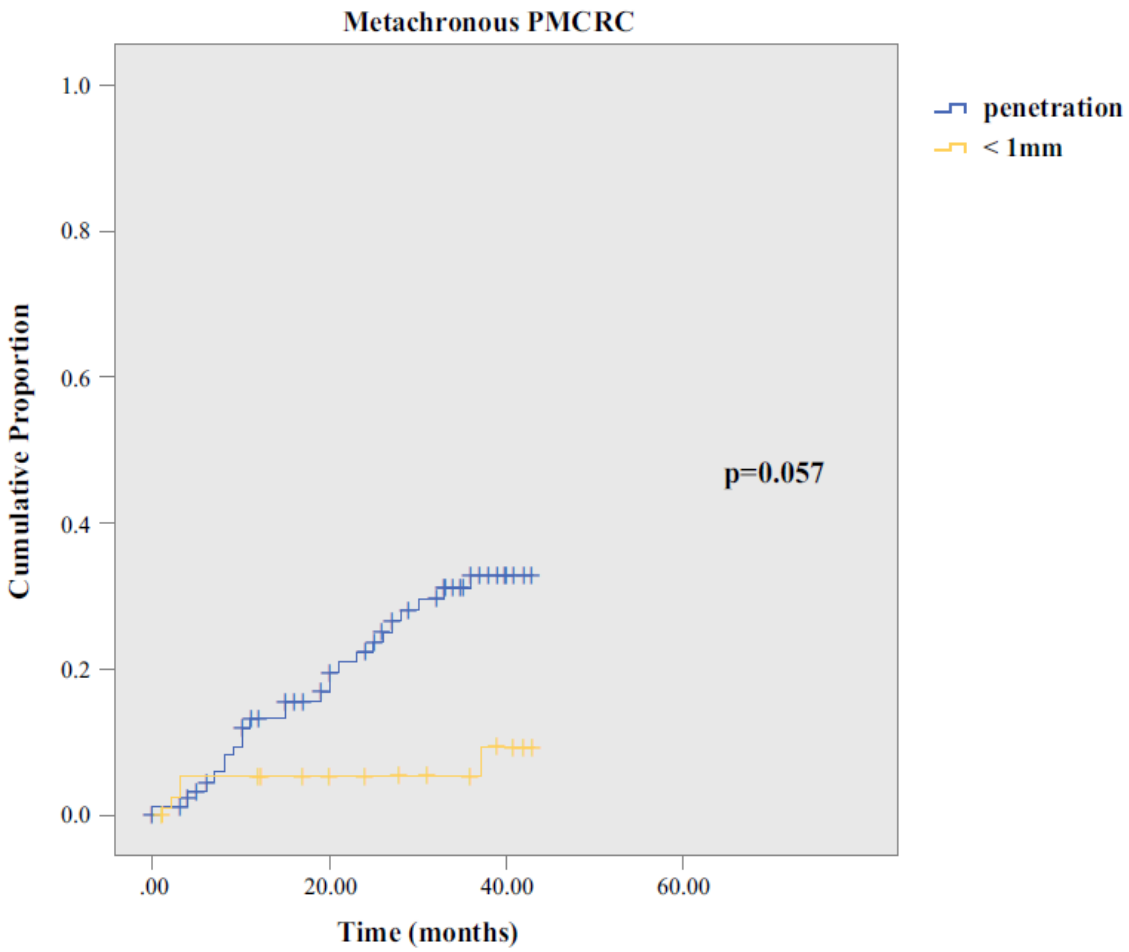


Issues in pT3 vs pT4a

- Anatomical reference point
- Tumor cells on or near serosa?
- Reactive changes necessary?
- Tissue artifacts/defects
- Sampling
- κ statistic varied from 0.48 to 0.52 for interobserver agreement

Klaver CEL, et al. Virchow Arch 2020;476:219-30

True Peritoneal Involvement has a Worse Outcome



	months	0	12	24	36	48	60
patients at risk	*penetration*	91	70	57	39	20	8
	< 1 mm	39	35	28	25	11	0

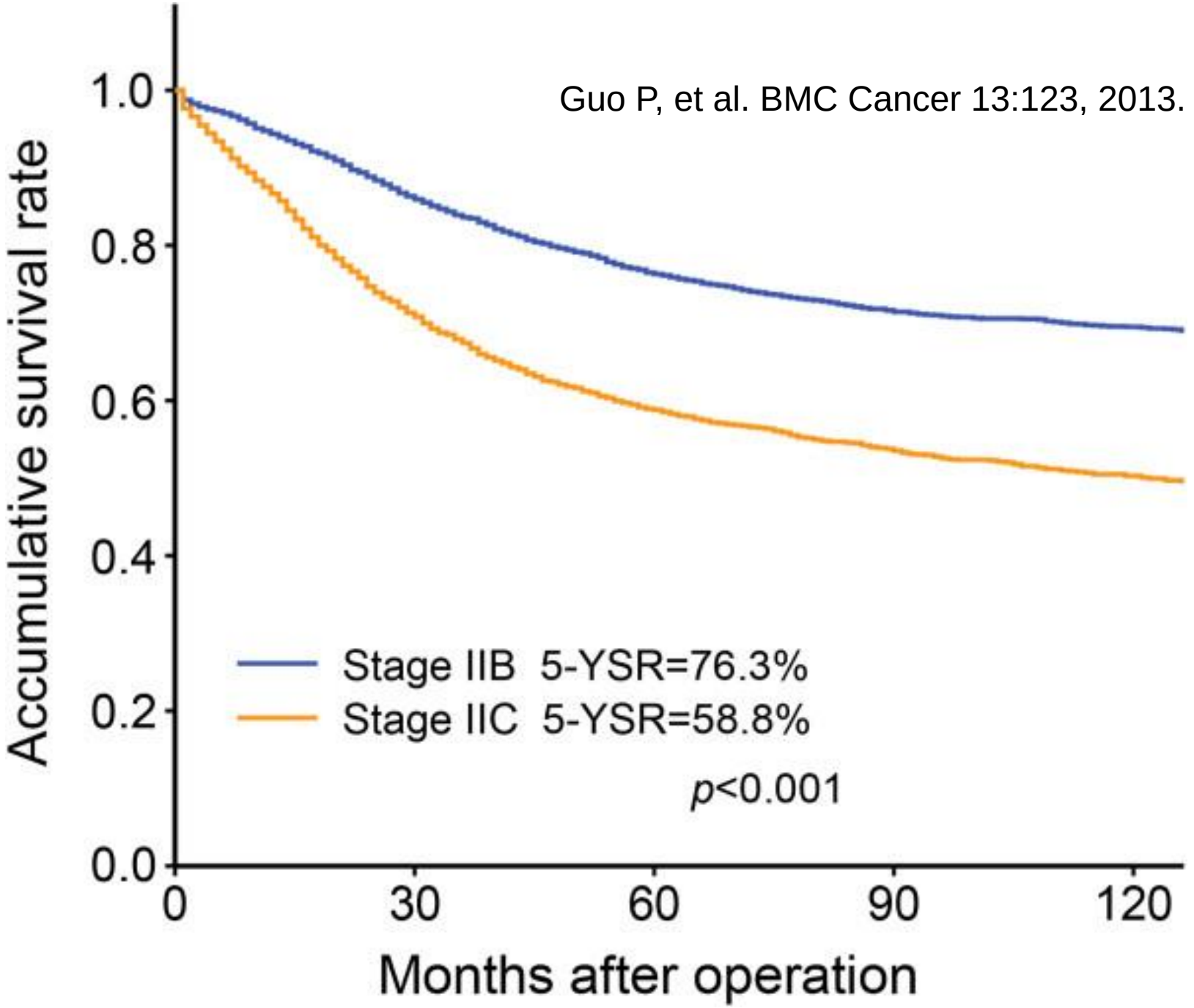
Single institutional study, consistent pathology review

159 cases

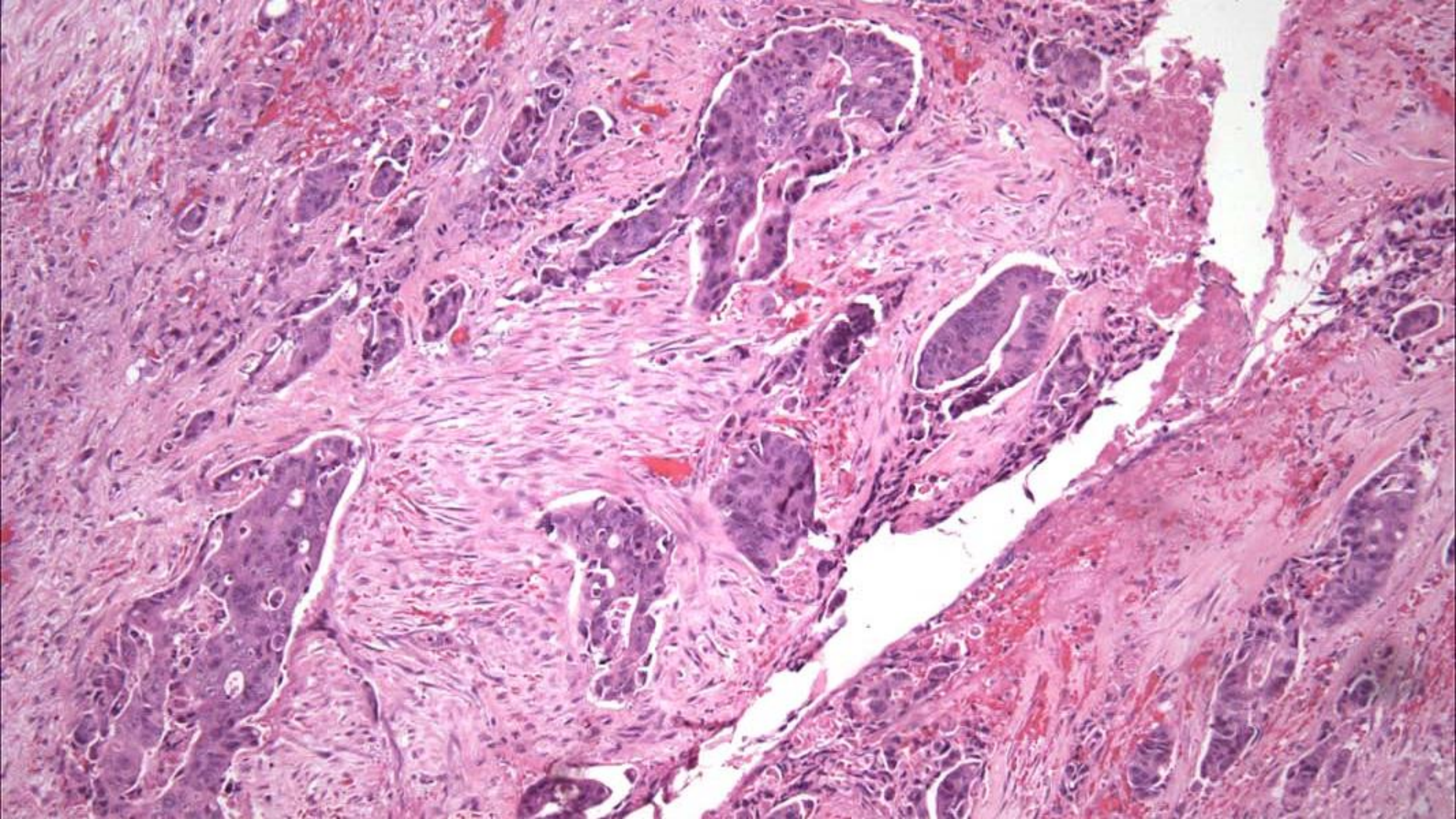
- **43 <1 mm from peritoneum**
- **113 true peritoneal penetration**

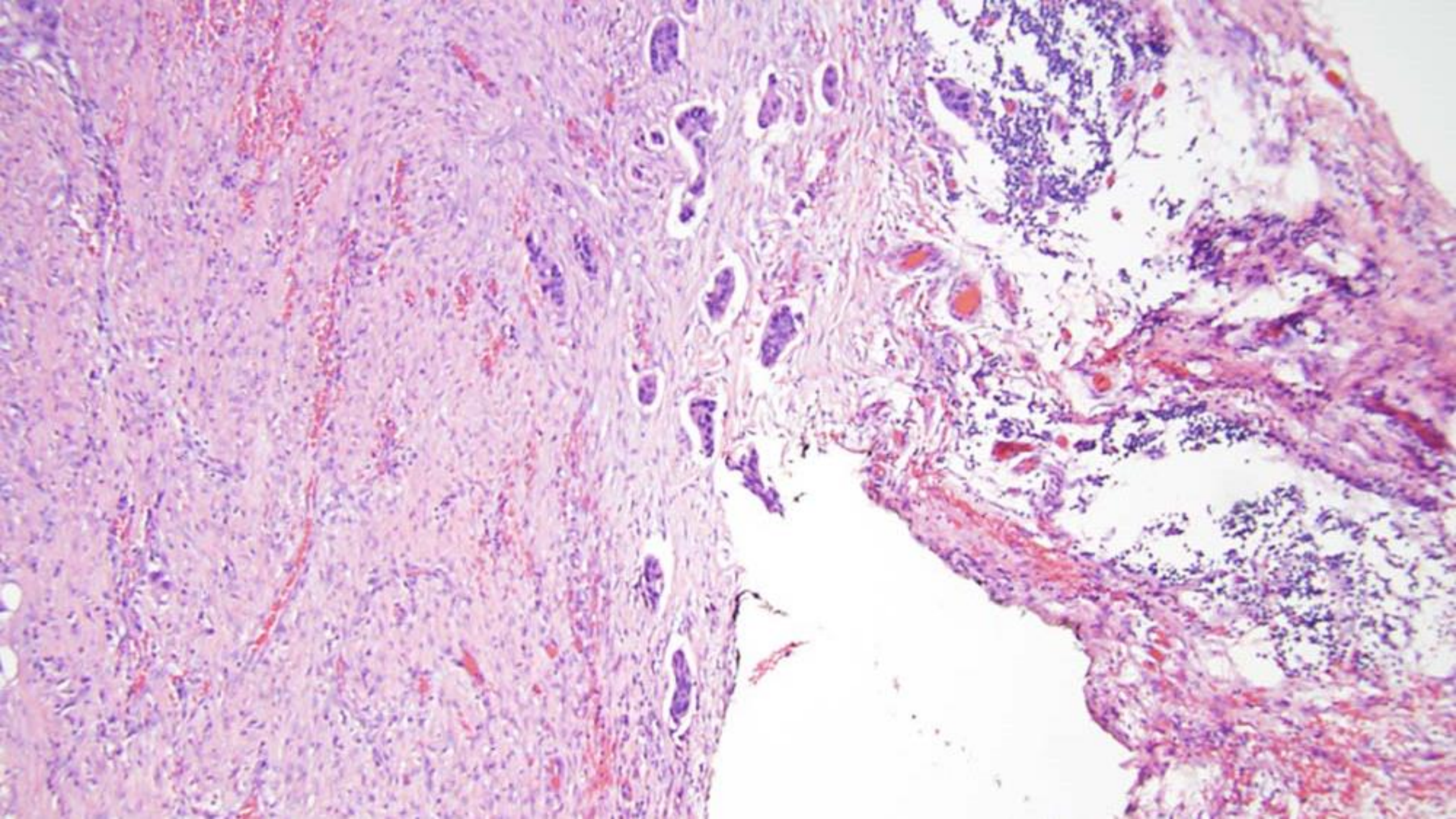
Klaver CEL, et al. Ann Surg Oncol 2018; 25:212-20.

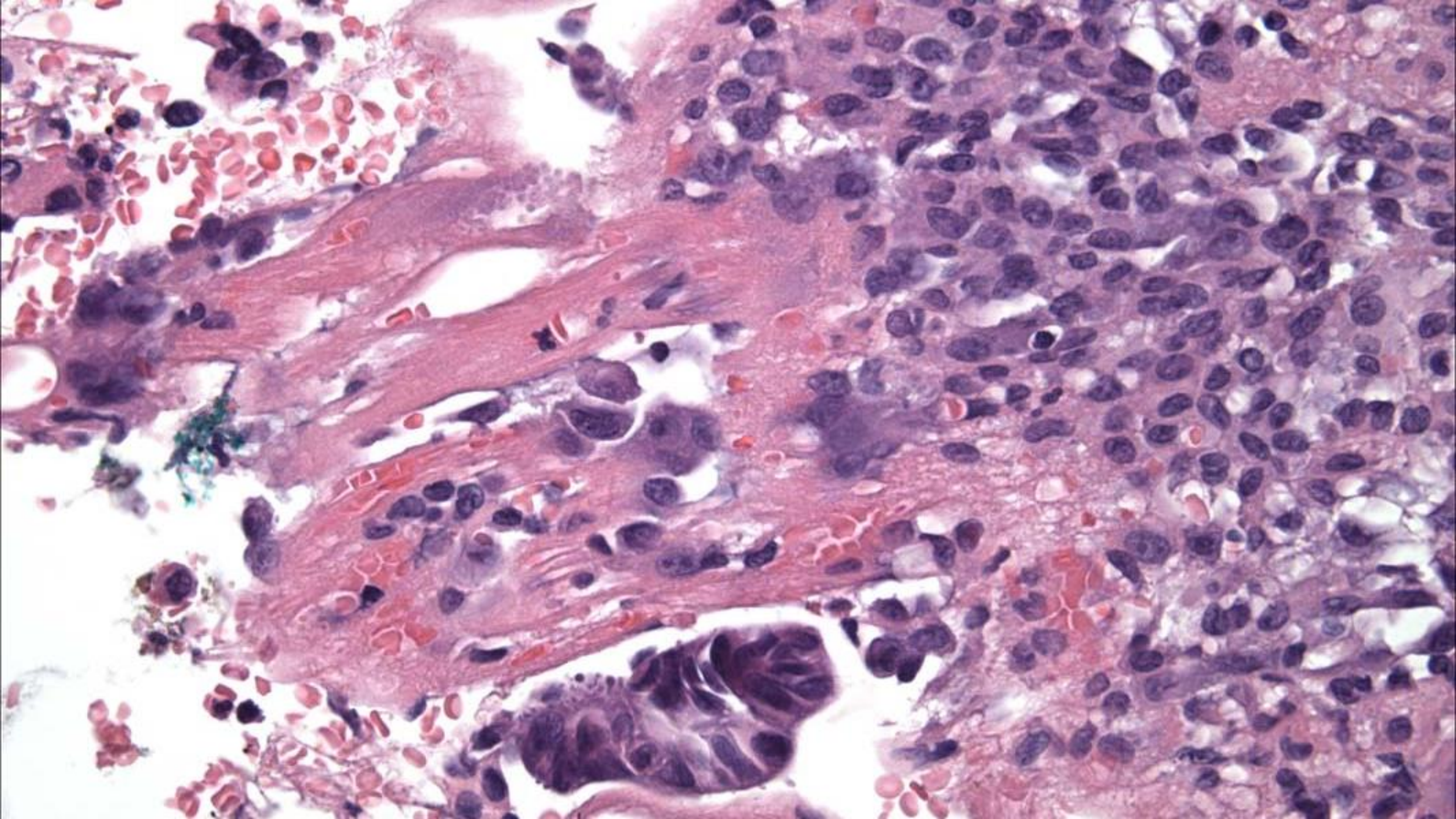
Guo P, et al. BMC Cancer 13:123, 2013.



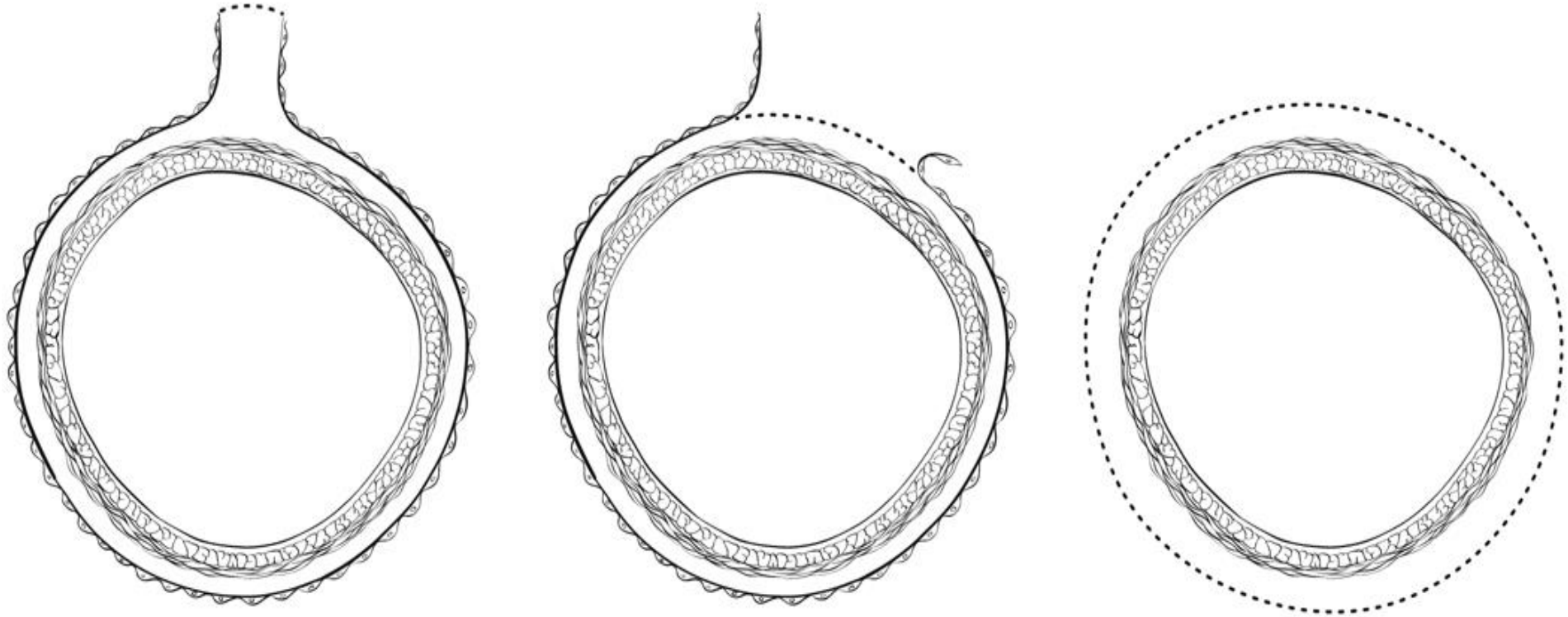
IIB=T4aN0
IIC=T4bN0

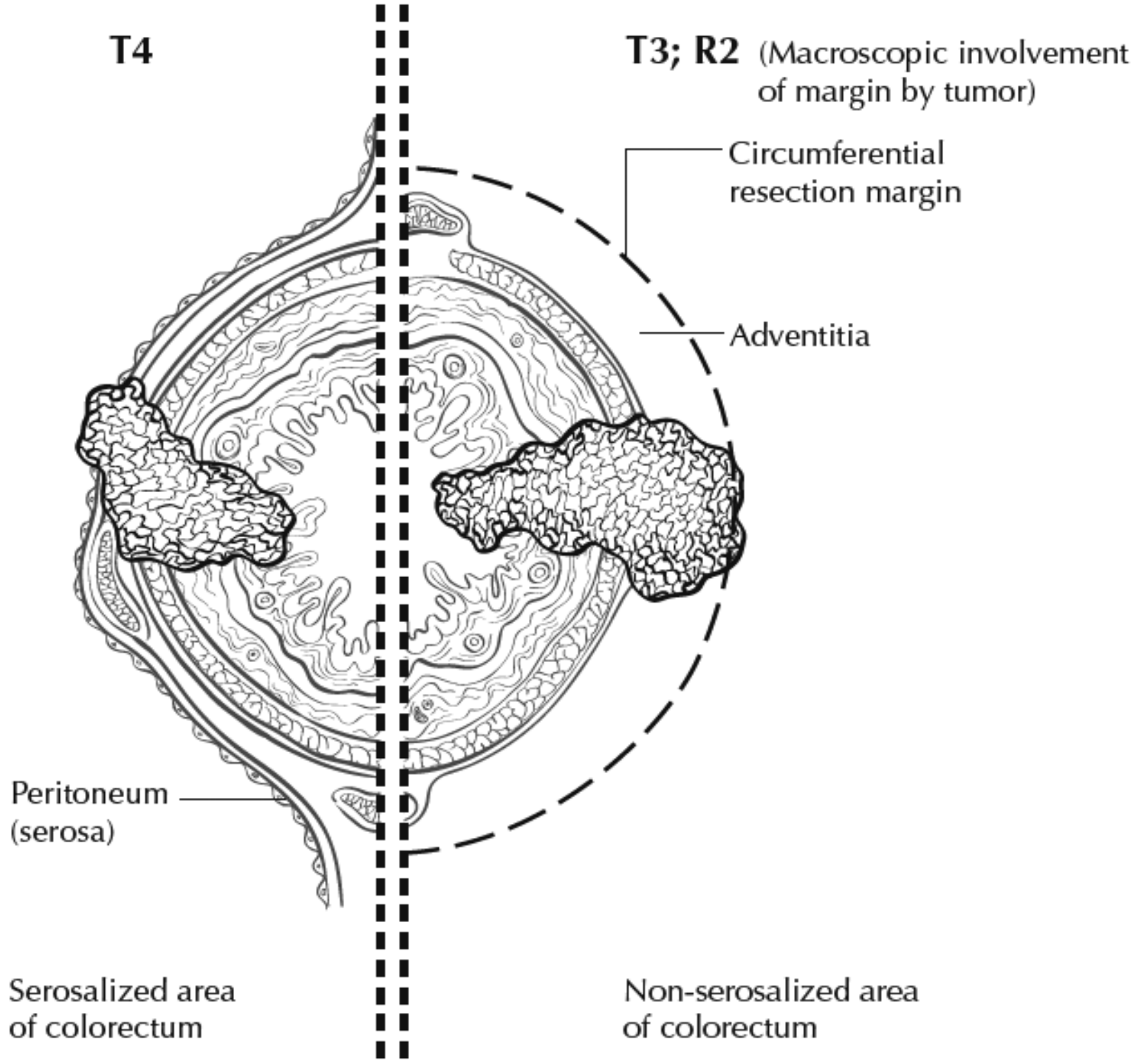






Circumferential/Radial/Mesenteric Margin: pT4a versus R1




T4
T3; R2 (Macroscopic involvement of margin by tumor)
Circumferential resection margin
Adventitia
Peritoneum (serosa)
Serosalized area of colorectum
Non-serosalized area of colorectum

Retroperitoneal Margin: the Cinderella Surgical Margin?

- **Few studies focus on this margin in non-rectal cancers**
- **Associated with advanced tumor stage and extramural spread**
- **Reported positive in 7- 8.4% of right-sided colon tumor cases**
- **Similar percentage (10%) of right-sided tumors recur locally**

Bateman AC, et al. J Clin Pathol 58:426-8, 2005

Scott N, et al. Colorectal Disease 10:289-93, 2008

Tips for Pathologists for Assessment of Local Peritoneal Involvement

- **Usually found in deep crevices adjacent to lobulated fat, not on flat surface**
- **Free-floating tumor cells may be confused with contamination from sectioning**
- **Adequate number of sections (at least 2 from areas of deepest tumor penetration) are needed**
- **Elastin stain is not recommended**

Improvements to Assessment of pT4a?

- **Current recommendation from AJCC is that tumor cells must be present on the surface for pT4a (tumor <1 mm is still pT3)**
  - **Available data, though limited, suggest that intermediate cases have behavior intermediate between true T3 and true T4a**
- **This definition will likely be retained for Version 9**
- **Explanatory text revision to offer clear guidance to pathologists**

Subdivisions of pT3:

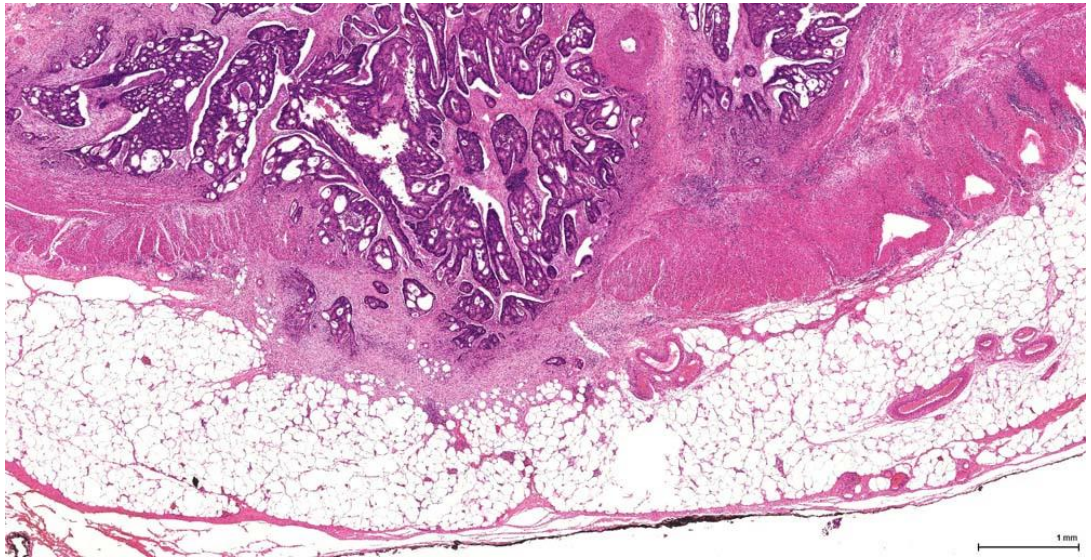
Can additional prognostic information be gained?

- **pT3 subdivision varies with study**
- **UICC:**
  - **pT3a (minimal invasion): <1 mm beyond MP**
  - **pT3b (moderate invasion): 1-5 mm**
  - **pT3c (extensive invasion): >5 to 15 mm**
  - **pT3d (extensive invasion): >15 mm**
- **Often collapsed into fewer categories**
  - **Binary division based on 5 mm cutoff**
- **Becoming more widely reported by radiologists for rectal MRI**
  - **Emerging evidence shows that measurement is accurate (Mercury trial)**

pT3 Subdivision: Data for Rectal Cancers

- **853 patients with pT3 rectal cancers**
- **pT3a=up to 5 mm; pT3b= more than 5 mm**
- **Cancer-related 5 year survival: no difference between pT3a and pT2; pT3b and pT4**
- **pT3b tumors were more likely to show lymph node metastases, vascular invasion, and high grade histology**

Merkel et al. Int J Colorectal Dis 2001; 16:298



AJCC Position on pT3 subdivisions

- **pT3 will not be subdivided for Version 9**
- **Reporting is recommended for rectal cancers as part of MRI report**
- **US NCCN guidelines do not incorporate it into treatment algorithm, although European guidelines do (ESMO)**
- **Would add complexity to TNM system**
- **Not all factors influencing prognosis or treatment can be incorporated into staging**
- **May eventually be incorporated into risk calculators**

Tumor Deposits

- **Discrete tumor deposits in pericolonic/perirectal fat**
  - **Discontinuous with bulk of tumor**
  - **In lymphatic drainage**
  - **May be similar to “melanoma in transit”**
- **No evidence of residual lymph nodal tissue, by definition**

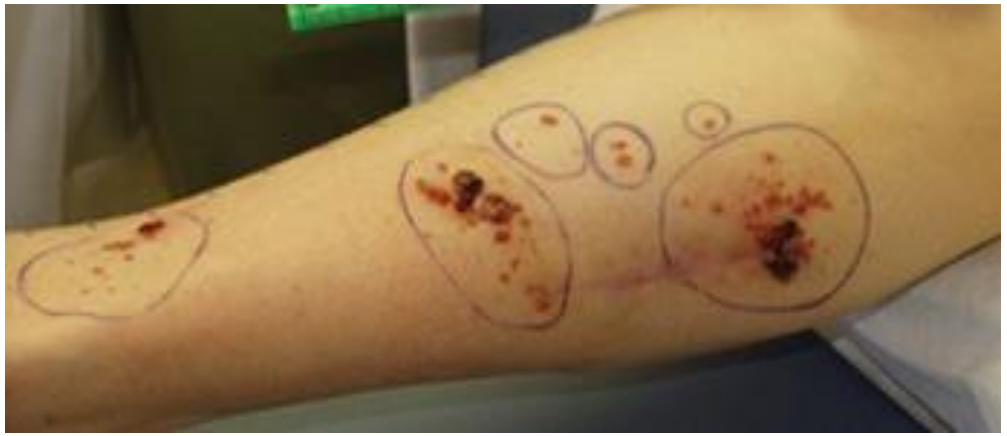
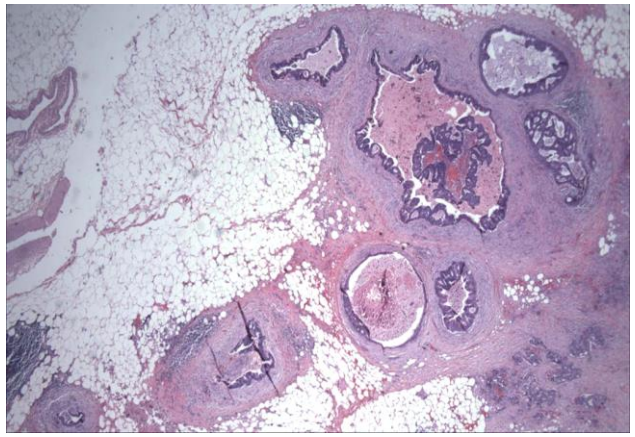
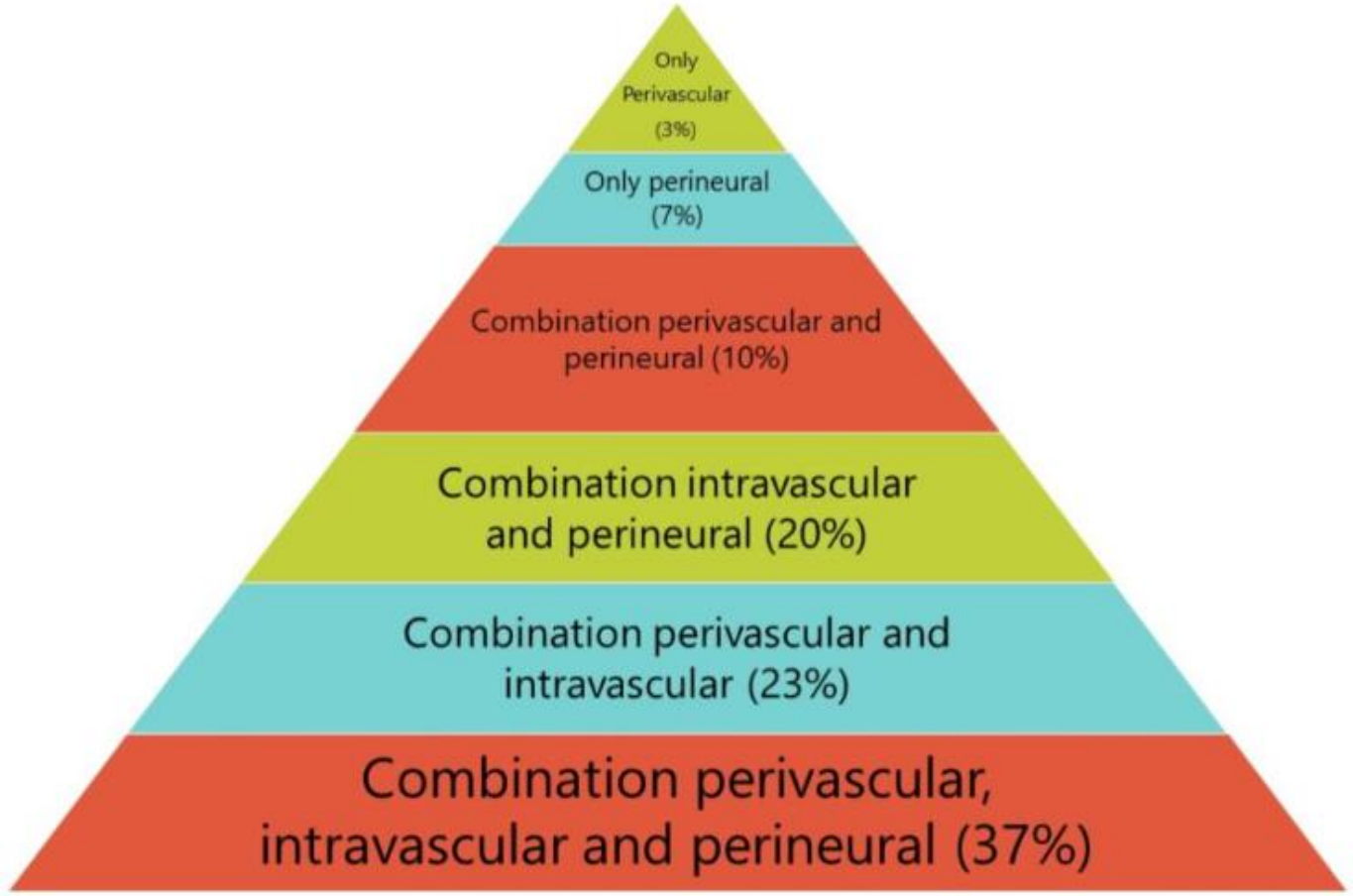
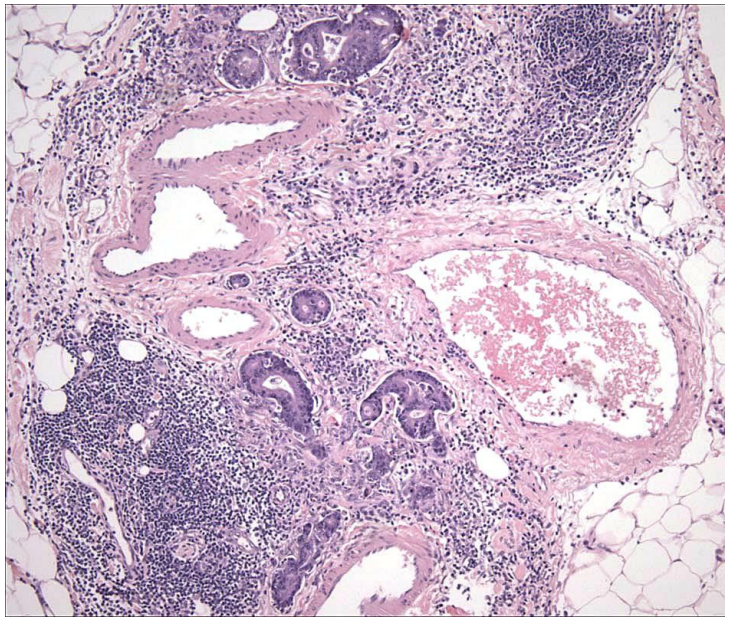


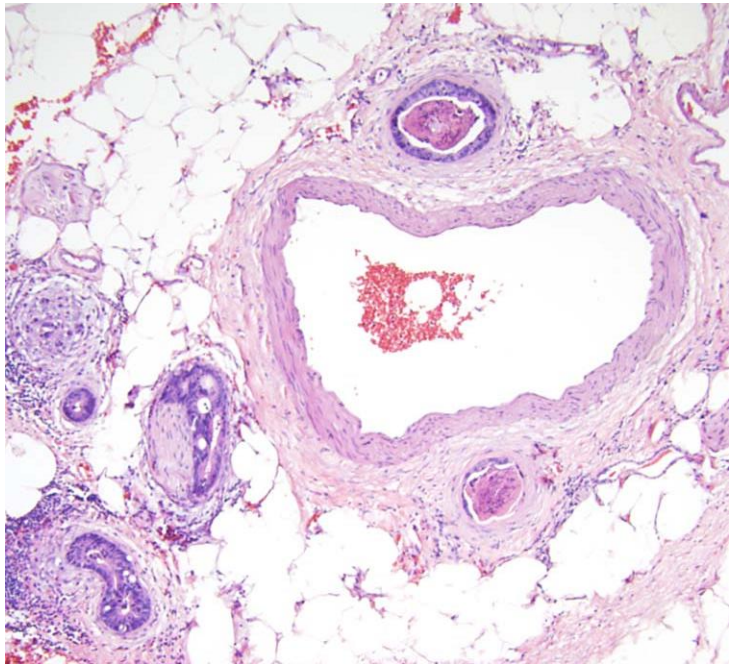
Image courtesy of MDConsult



The Histologic Origin of Tumor Deposits







How to handle tumor deposits?

Scenario: Tumor invades into muscularis propria (pT2) but there is a discontinuous nodule of tumor in the pericolic fat >1 cm from the leading edge. There are no positive lymph nodes.

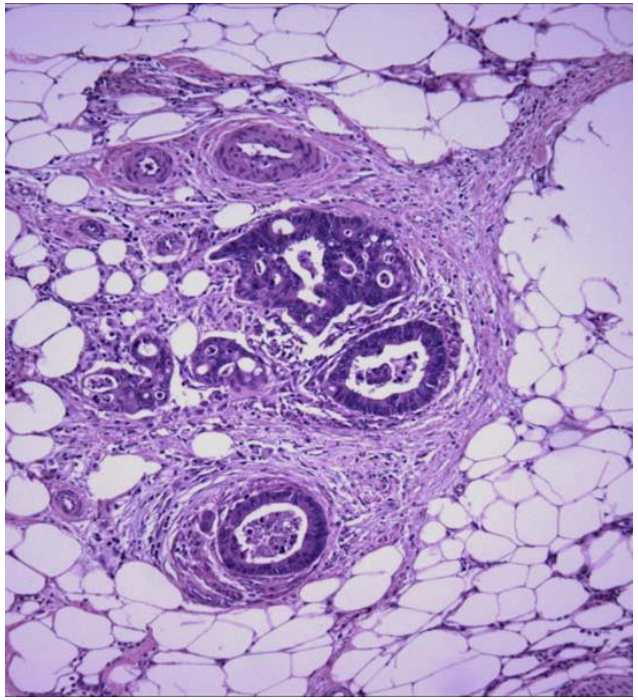
Possible stage (prior to AJCC TNM 7th edition):

- **pT2 with vascular invasion, pN0 (stage 1)**
- **pT3, pN0 (stage 2A)**
- **pT2, pN1 (stage 3A) [favored by medical oncologists]**

- **Currently would be staged as pT2pN1c (stage 3A)**

What is a Tumor Deposit?

- **Some characteristics of TD:**
  - **Irregular outline**
  - **Not associated with organized lymphoid tissue**
  - **Not surrounded by thick bundles of parallel collagen fibers**
  - **Sometimes near arteries**
- **Characteristics of replaced lymph nodes:**
  - **Rounded deposits with organized lymphoid tissue**
  - **Thick collagen capsules**
  - **Necrosis more likely**
- **Discretion of the pathologist to make the final decision**



When to Utilize N1c

- **Tumor deposits have been identified according to the criteria**

  <u>and</u>

- **There is no involvement of regional nodes**
- **Applicable with any pT category**

Other proposals:

-Include TDs in M category (Al Sahaf, 2011)

-Treat all TDs as lymph node metastases, regardless of contour (Ueno, 2012)

-Separate into nodal and non-nodal deposits (Brouwer, 2021)

Al Sahaf O, Myers E, Jawad M, Browne TJ, Winter DC, Redmond HP. The prognostic significance of extramural deposits and extracapsular lymph node invasion in colon cancer. *Dis Colon Rectum*. 2011;54(8):982-988. doi:10.1097/DCR.0b013e31821c4944

Ueno H, Mochizuki H, Shirouzu K, Kusumi T, Yamada K, Ikegami M, Kawachi H, et al. Multicenter study for optimal categorization of extramural tumor deposits for colorectal cancer staging. *Ann Surg*. 2012;255(4):739-746. doi:10.1097/SLA.0b013e31824b4839

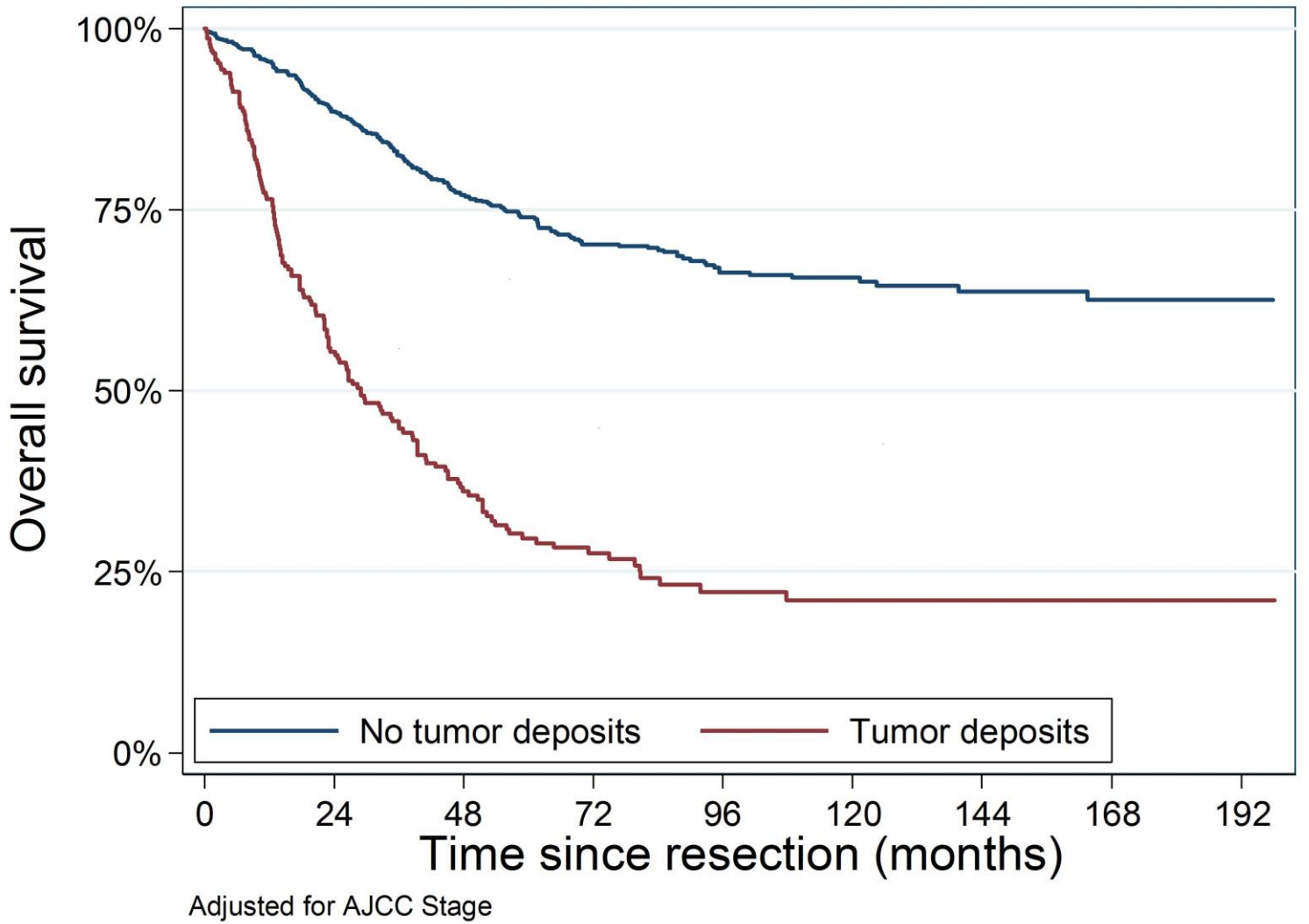
Brouwer NPM, Lord AC, Terlizzo M, Bateman AC, West NP, Goldin R, Martinez A, et al. Interobserver variation in the classification of tumor deposits in rectal cancer-is the use of histopathological characteristics the way to go?. *Virchows Arch*. 2021;479(6):1111-1118. doi:10.1007/s00428-021-03197-0

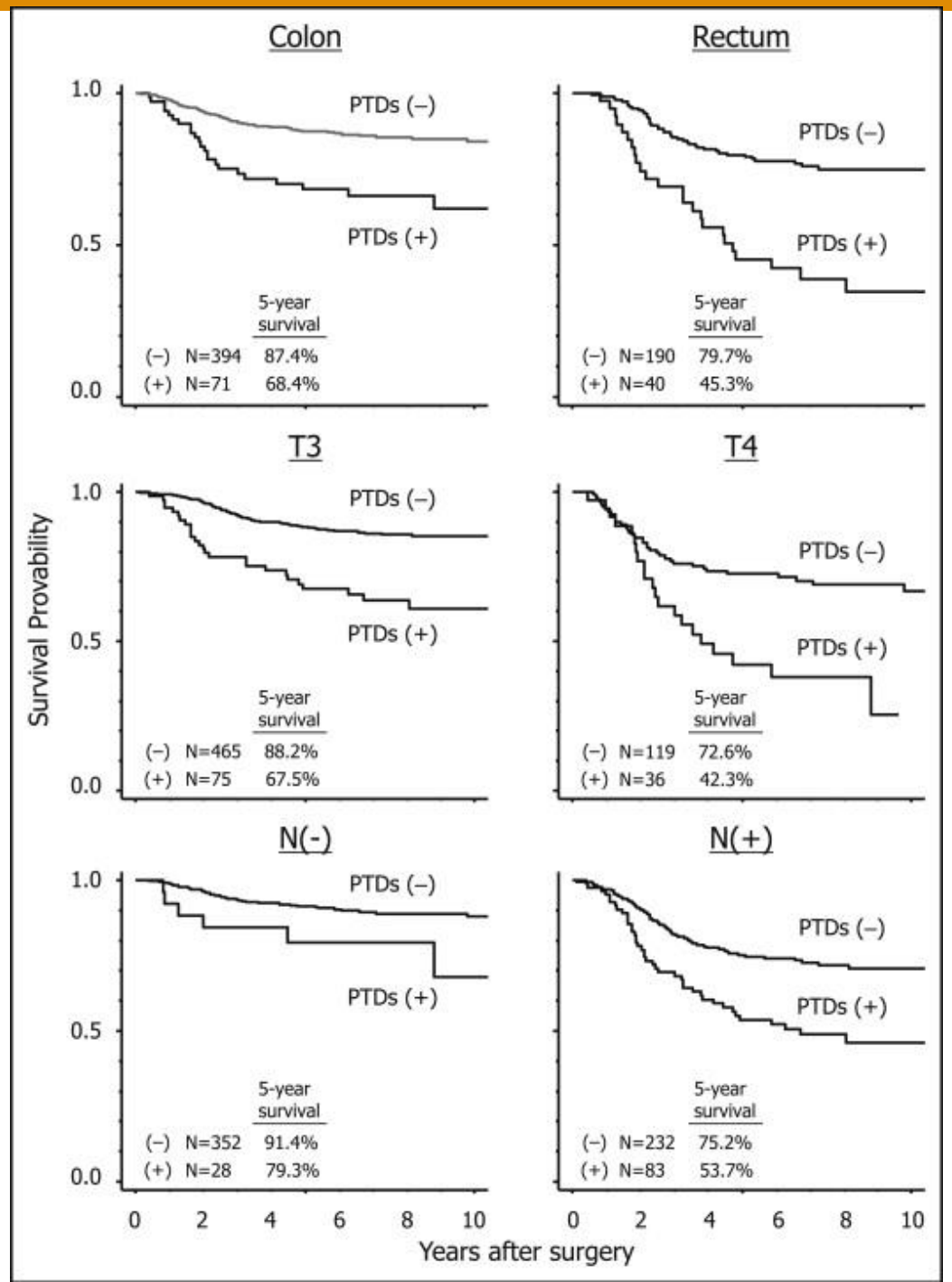
Tumor Deposit Incidence and Impact

- **Roughly 10-30% of CRC have tumor deposits, depending on cohort**
- **A small percentage (2-3%) of colonic and rectal cancers have TDs but negative lymph nodes**
- **TDs often seen in CRC with poor prognostic factors (vascular invasion, perineural invasion, positive lymph nodes)**
- **Presence impacts survival (hazard ratio 1.77- 4.0 (mostly ~2); independent on multivariate analysis)**

Vanderbilt Cohort: 1081 cases

- 252/1081 cases (23.3%) with TDs
- 52 classified as N1c (5%)
- 80% of cases with TDs had overtly positive lymph nodes
- Hazard ratio 3.97; when adjusted for stage, 1.72





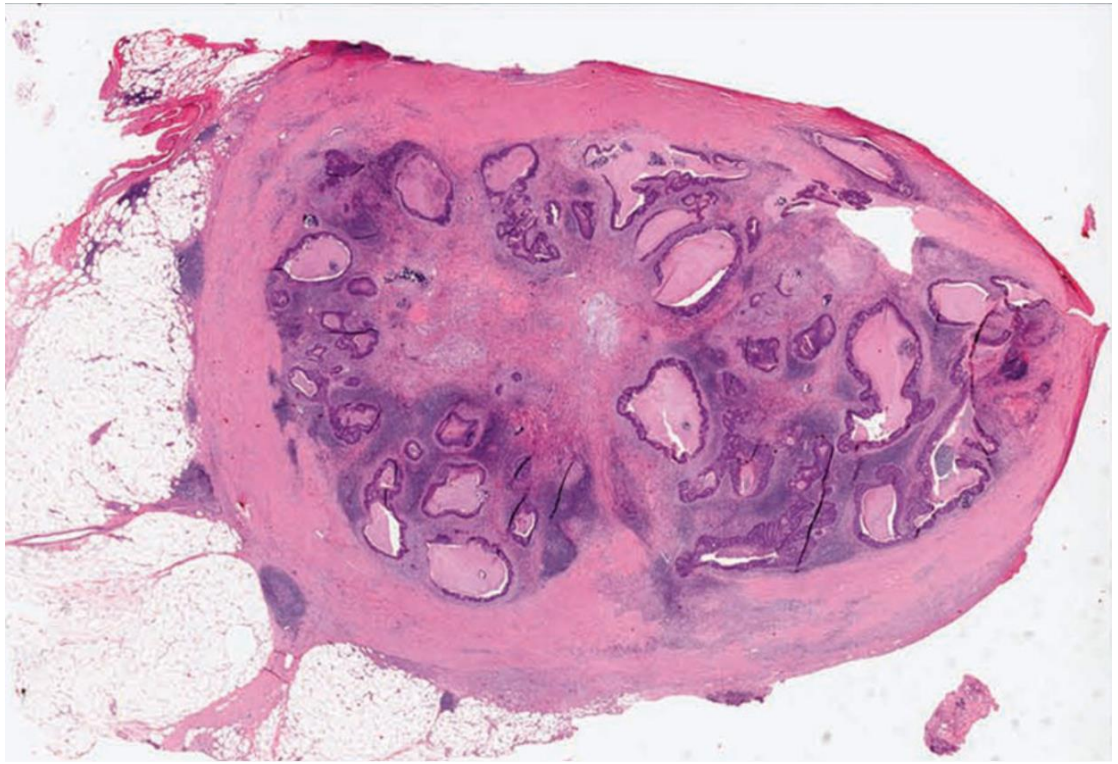
Impact of TDs on disease-specific survival according to tumor location, T category, and N category

Tumor deposits were associated with positive lymph nodes and serosal involvement on multivariate analysis

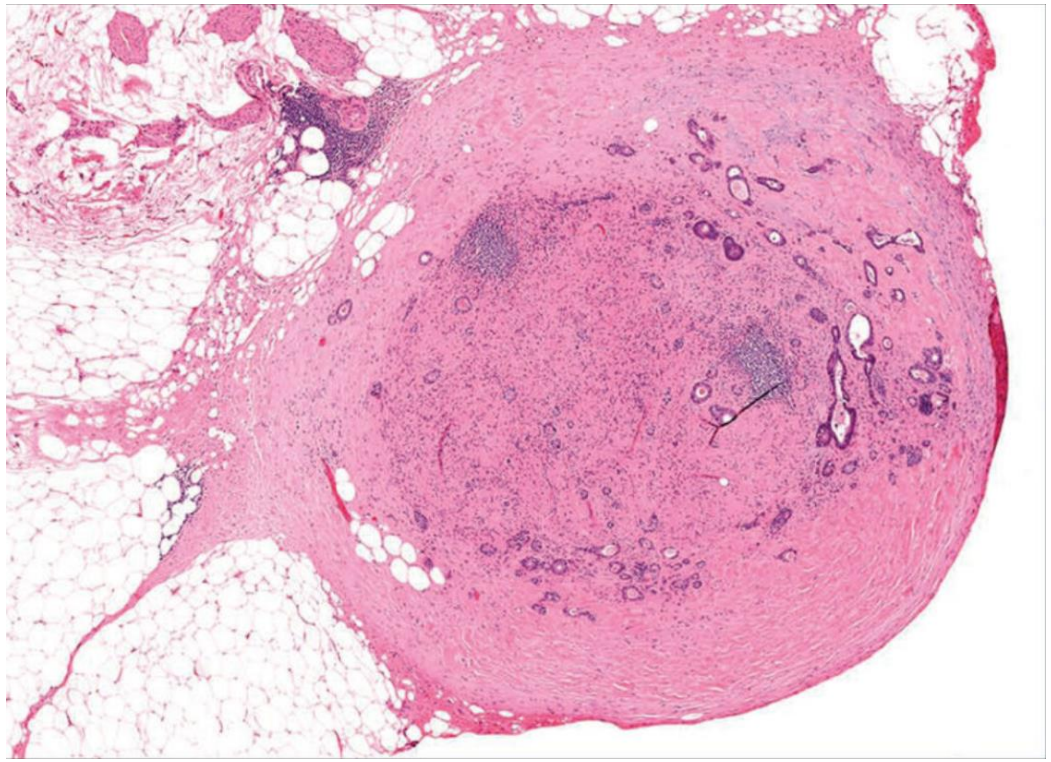
Ueno, H, et al. The American Journal of Surgery, Volume 207, Issue 1, 2014, 70 - 77

Expert (Dis)agreement in Diagnosing TDs

Diagnostic criteria most often utilized: round shape, thick capsule, peripheral lymphoid follicles, peripheral rim of lymphocytes, size greater than 3 mm



6 of 7 called this a LN

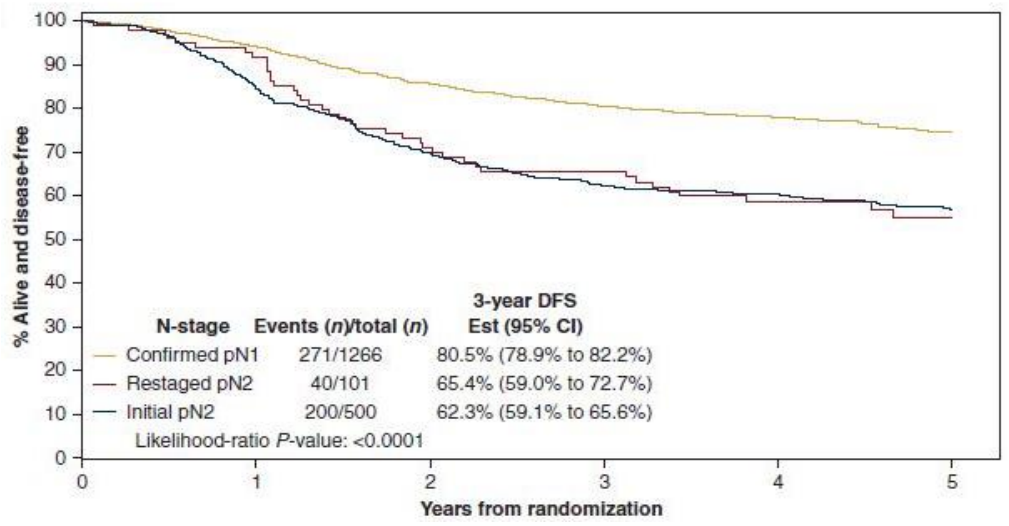


4 of 7 called this a LN

Rock JB, Washington MK, Adsay NV, Greenson JK, Montgomery EA, Robert ME, Yantiss RK, et al. Debating deposits: an interobserver variability study of lymph nodes and pericolonic tumor deposits in colonic adenocarcinoma. *Arch Pathol Lab Med*. 2014;138(5):636-642. doi:10.5858/arpa.2013-0166-OA

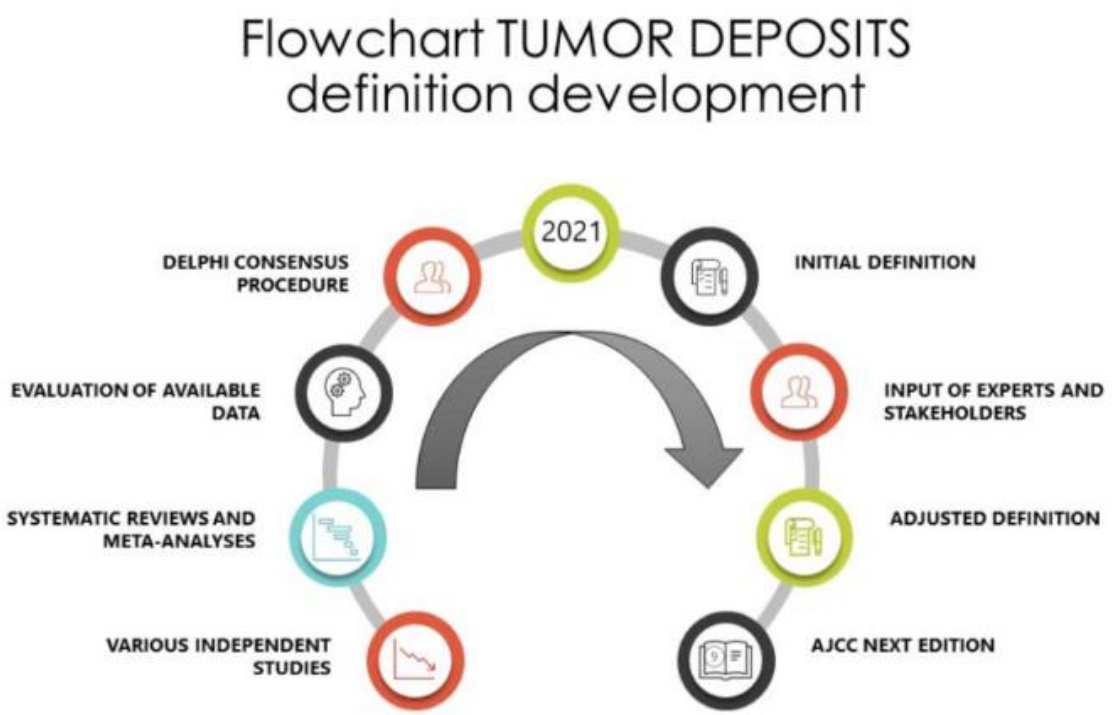
Is there a better way to handle TDs?

- **TDs have an adverse impact in node-positive cases**
- **TDs may be worse than positive LNs**
- **Data from 2 prospective Phase 3 trials suggest adding TDs to LNs for final pN category (PMID 34293461 and PMID 32167864)**



Cohen R, Shi Q, Meyers J, Jin Z, Svrcek M, Fuchs C, Couture F, et al. Combining tumor deposits with the number of lymph node metastases to improve the prognostic accuracy in stage III colon cancer: a post hoc analysis of the CALGB/SWOG 80702 phase III study (Alliance)☆. *Ann Oncol*. 2021;32(10):1267-1275. doi:10.1016/j.annonc.2021.07.009

AJCC Tumor Deposit Working Group



- **Recommending including all types of mesenteric tumor nodules as TDs, regardless of origin**
- **Proposing adding TDs to positive LNs for final lymph node count (analysis ongoing)**

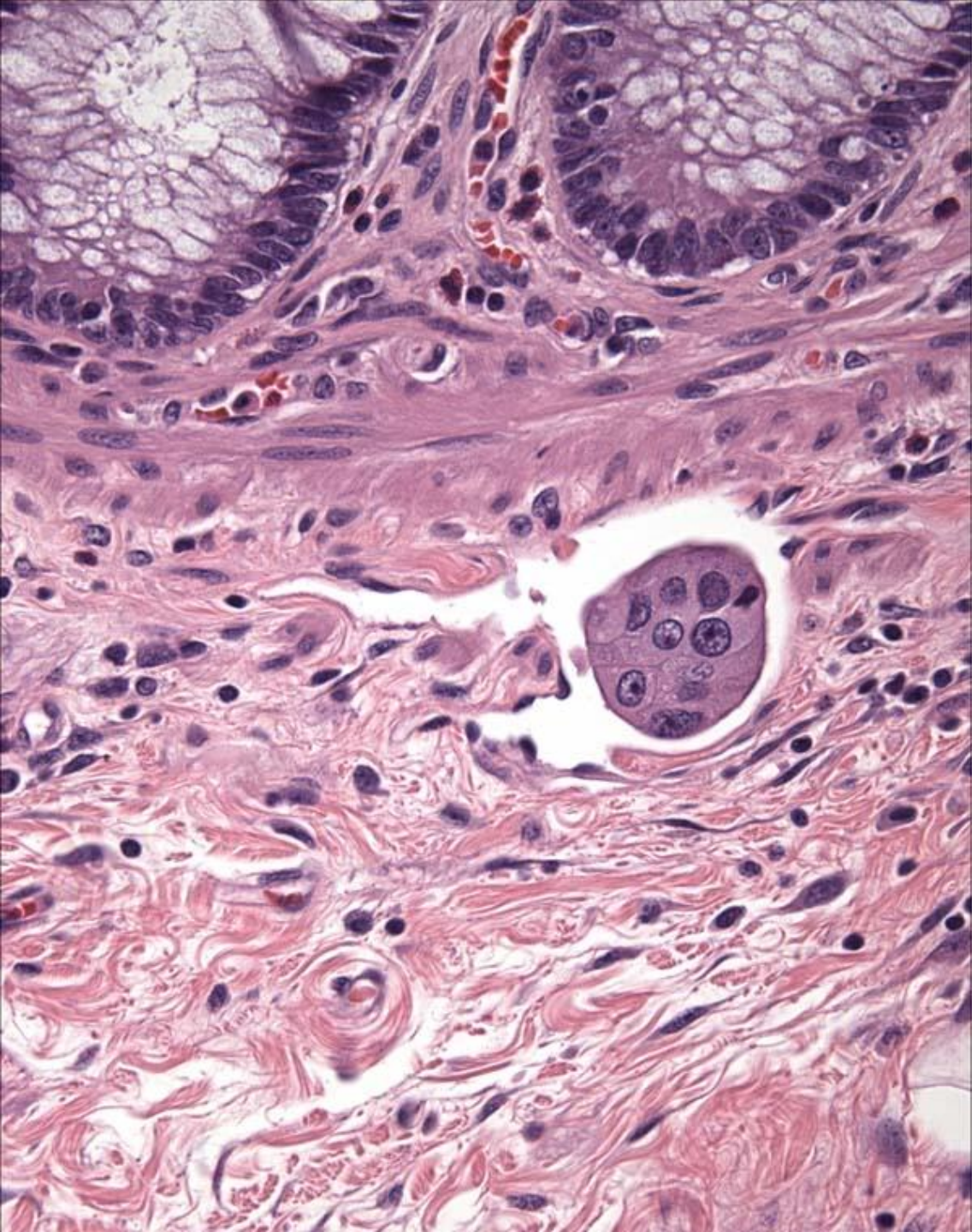
A Practical Approach for Pathologists for Now

- **Use your best judgment. Even the "experts" disagree.**
- **Does it affect the overall N category or stage grouping?**
- **Patients with positive LNs are more likely to receive adjuvant therapy than patients with only TDs, depending on local oncology practices**

Wong-Chong N, Motl J, Hwang G, Nassif Jr. GJ, Albert MR, Monson JRT, Lee L, et al. Impact of Tumor Deposits on Oncologic Outcomes in Stage III Colon Cancer. *Dis Colon Rectum*. 2018;61(9):1043-1052. doi:10.1097/DCR.0000000000001152

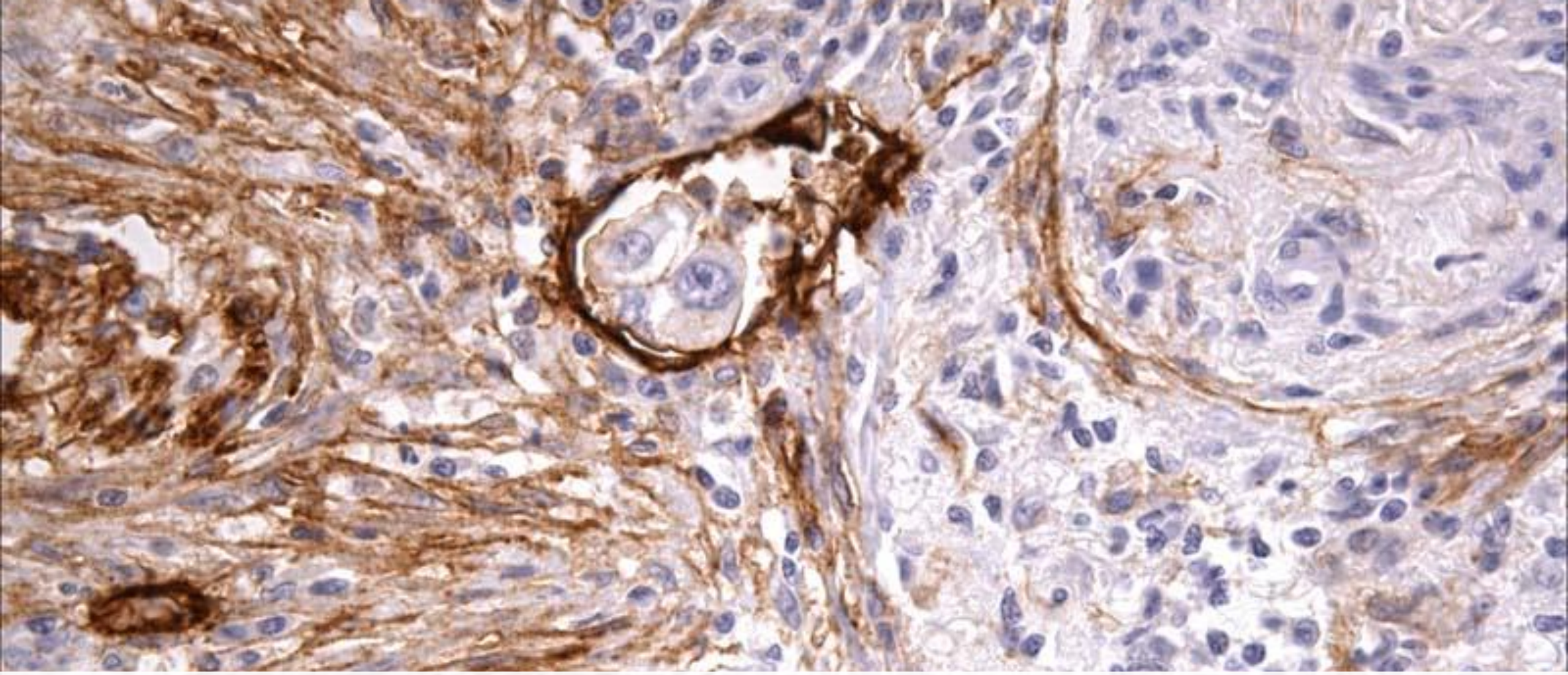
Stage-Independent Prognostic Factors: Small and Large Vessel (Venous) Invasion

- **Repeatedly demonstrated to be significant by multivariate analysis**
- **Some studies have shown venous invasion to be more important, some lymphatic**
- **Problems in interpretation:**
  - **Inter-observer variability**
  - **Special stains may not improve agreement**
  - **Minimal criteria not established**



Small Vessel (Lymphatic) Invasion

- Tumor present in endothelial-lined channel
- No smooth muscle in vessel wall
- No red cells in lumen



D2-40

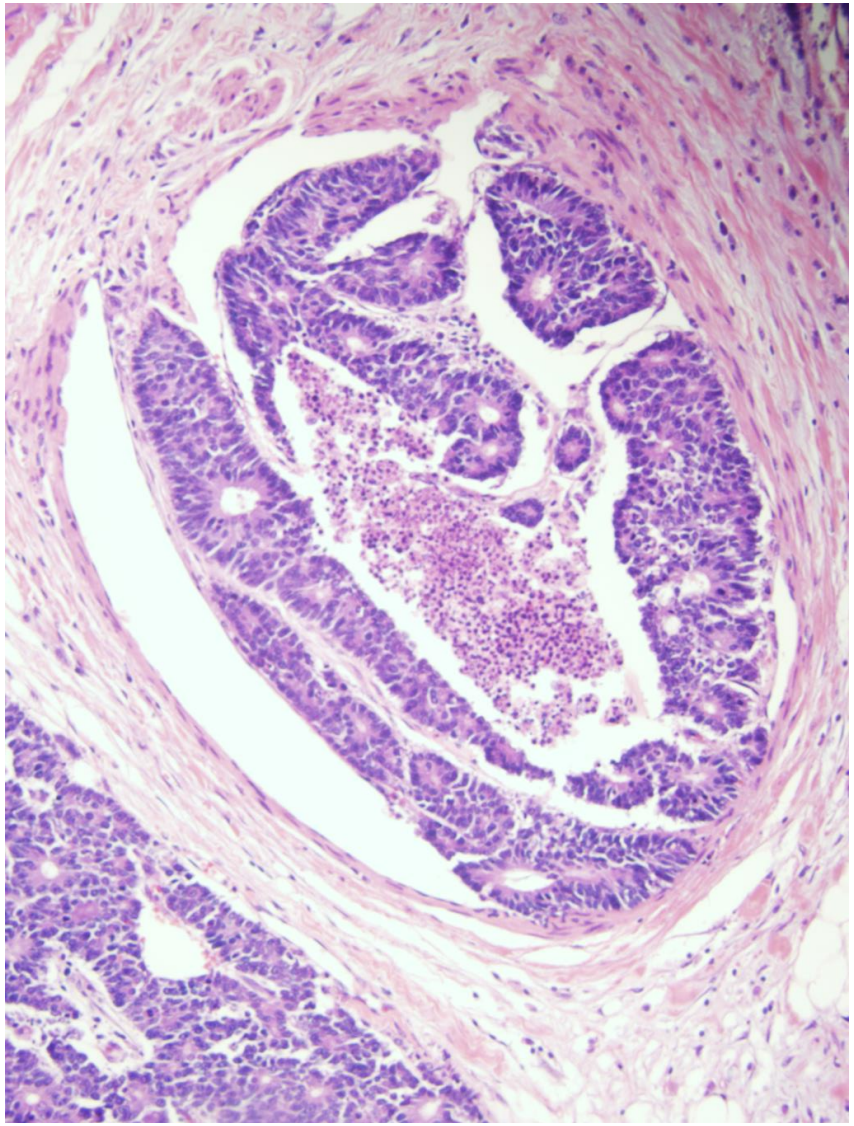
Extramural Venous Invasion: Definition

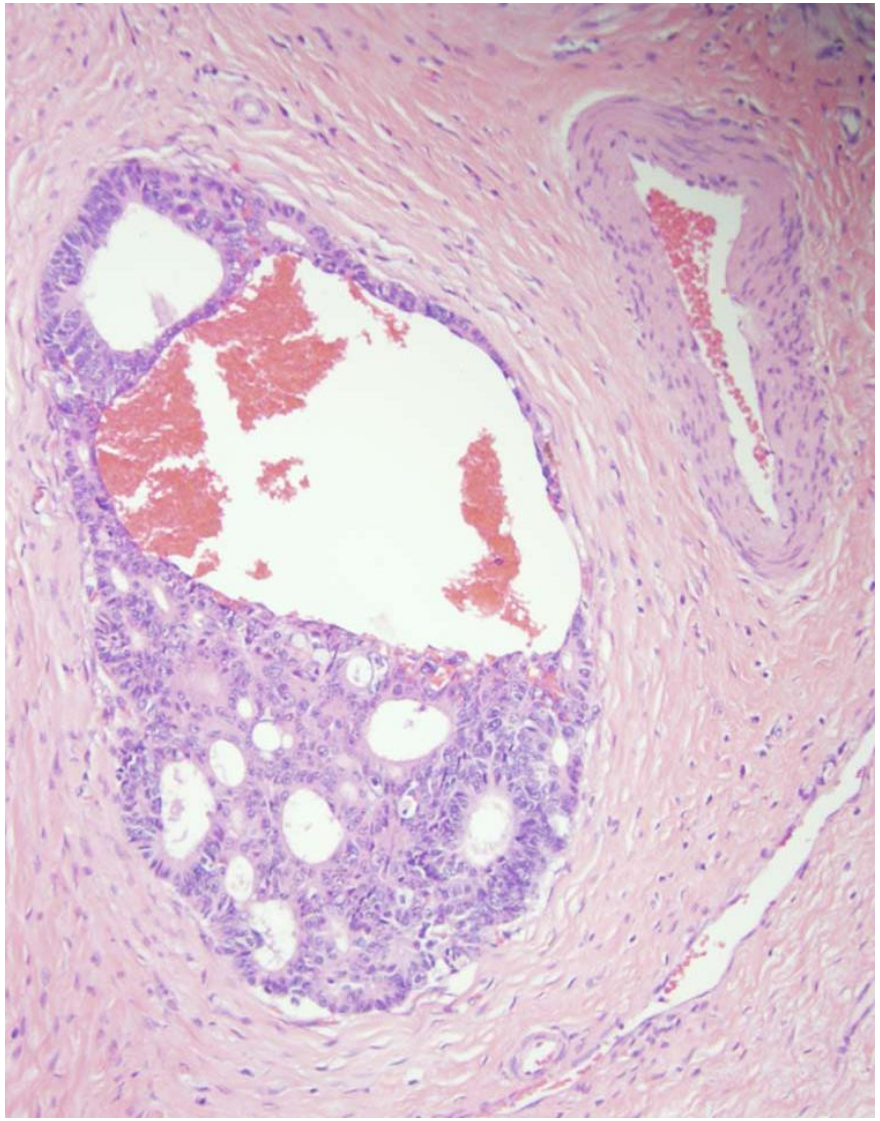
- **Tumor within an endothelial lined space:**
  - **Containing red cells**
  - **Or, surrounded by muscle**
- **Or, rounded or elongated tumor profiles surrounded by elastin staining and adjacent to arteries, even if endothelium is not seen**
  - In the absence of surrounding elastic staining, such tumor foci should not be regarded as positive for venous invasion.

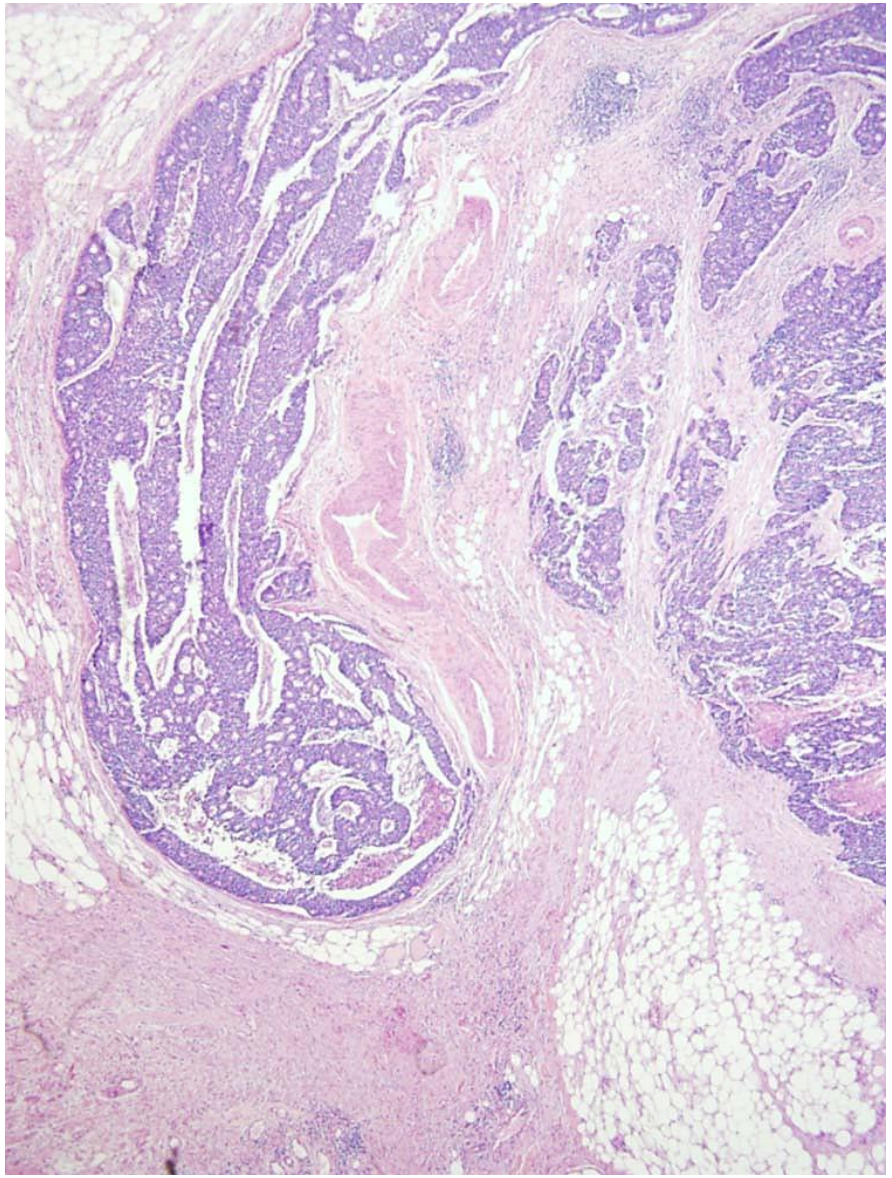
(from RCPath Colorectal Cancer Dataset)

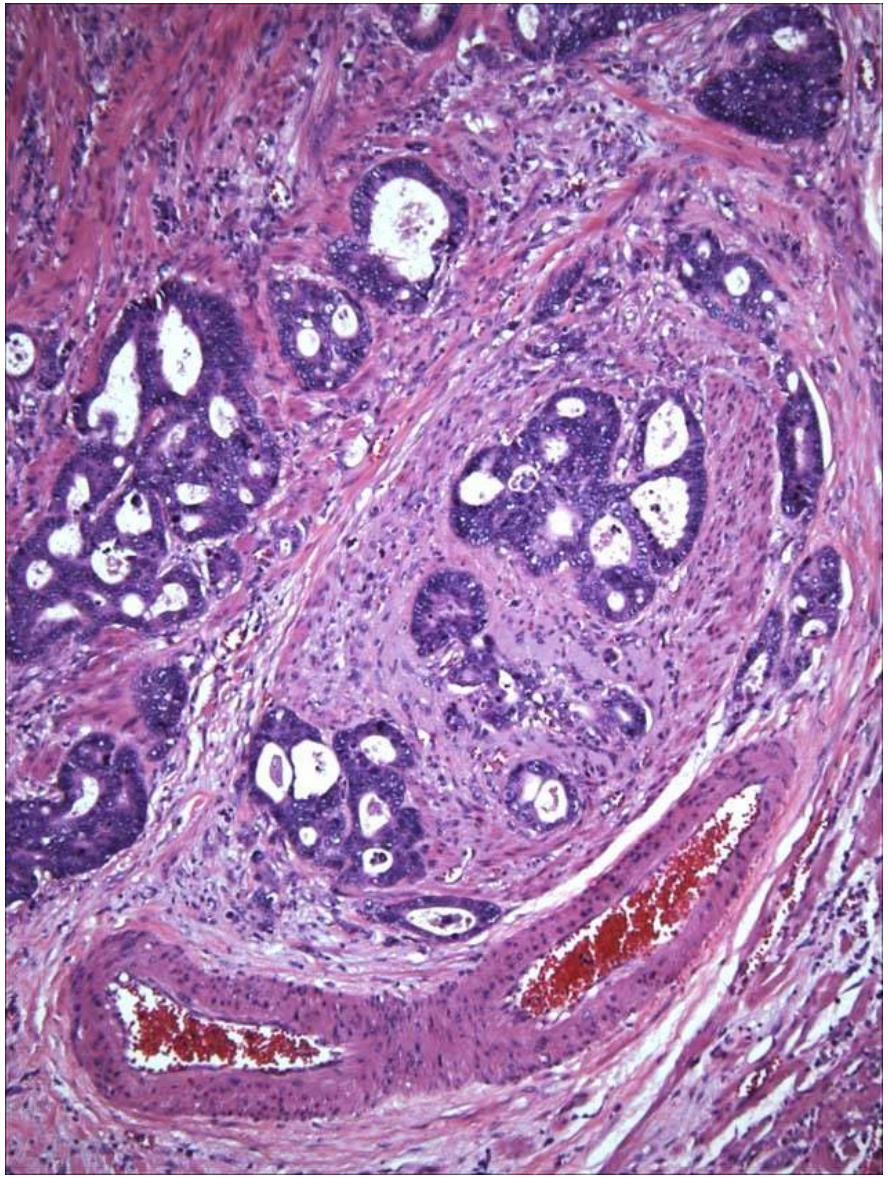
http://www.rcpath.org/publications-media/publications/datasets/colorectal-cancer

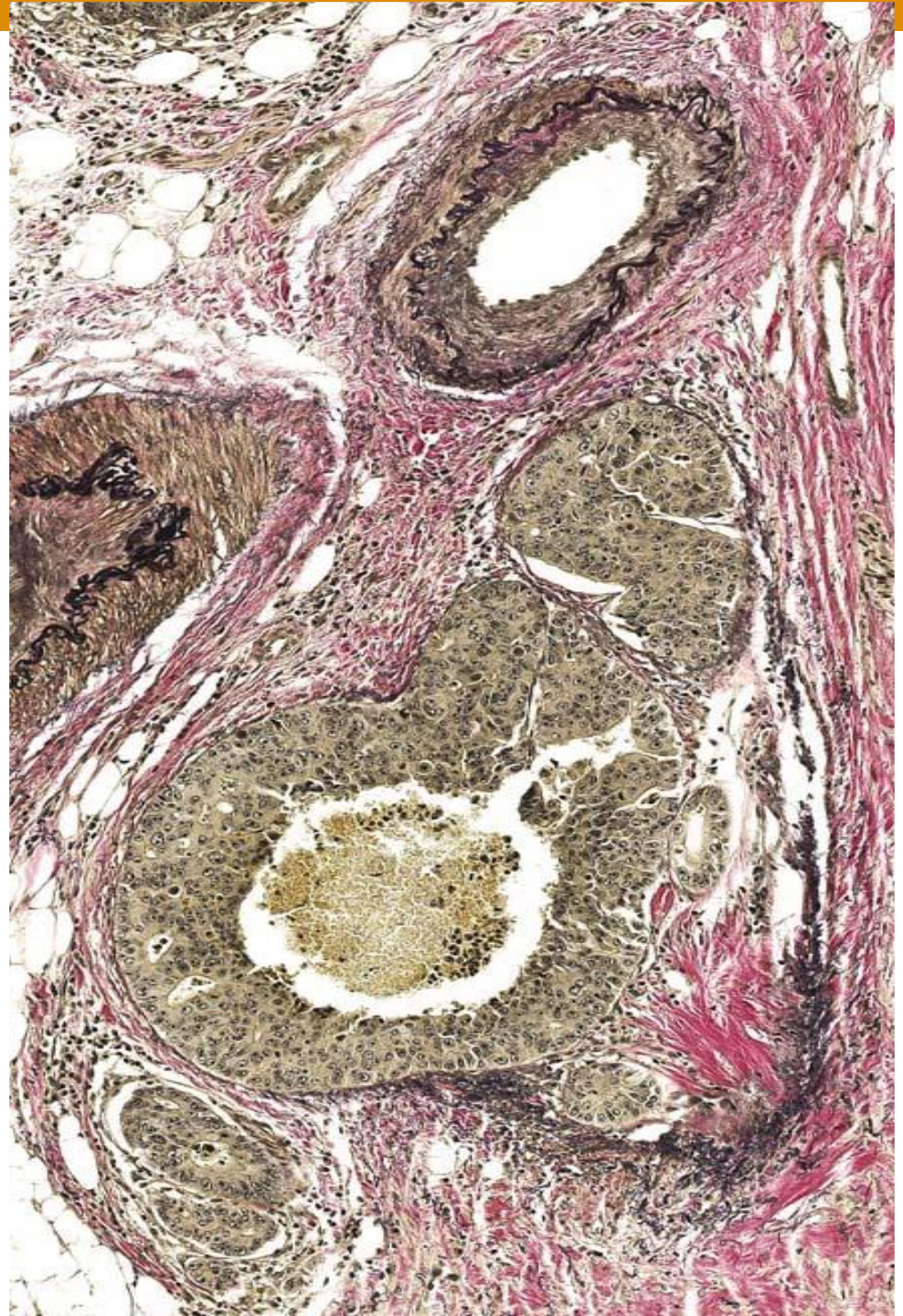
Venous Invasion

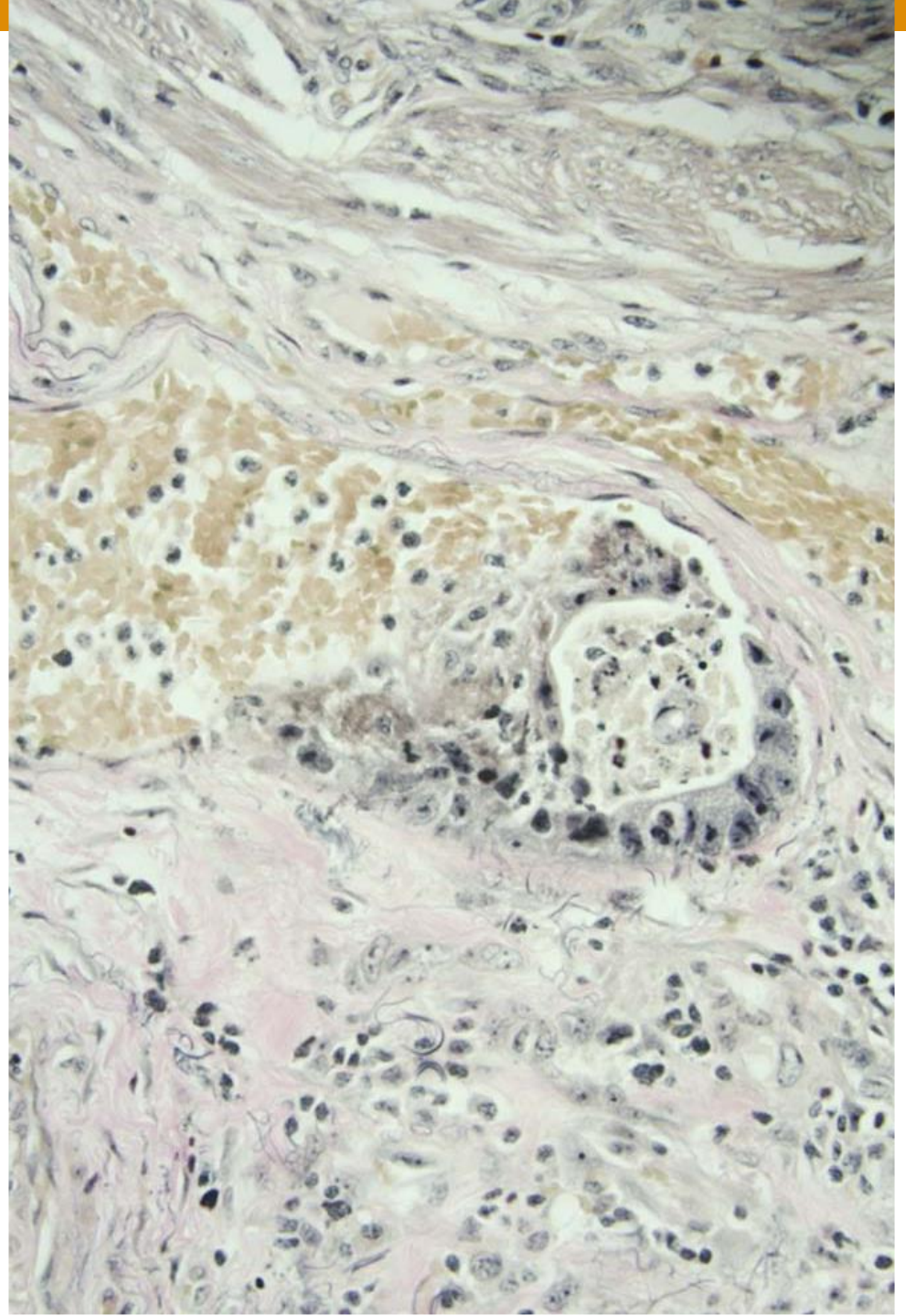




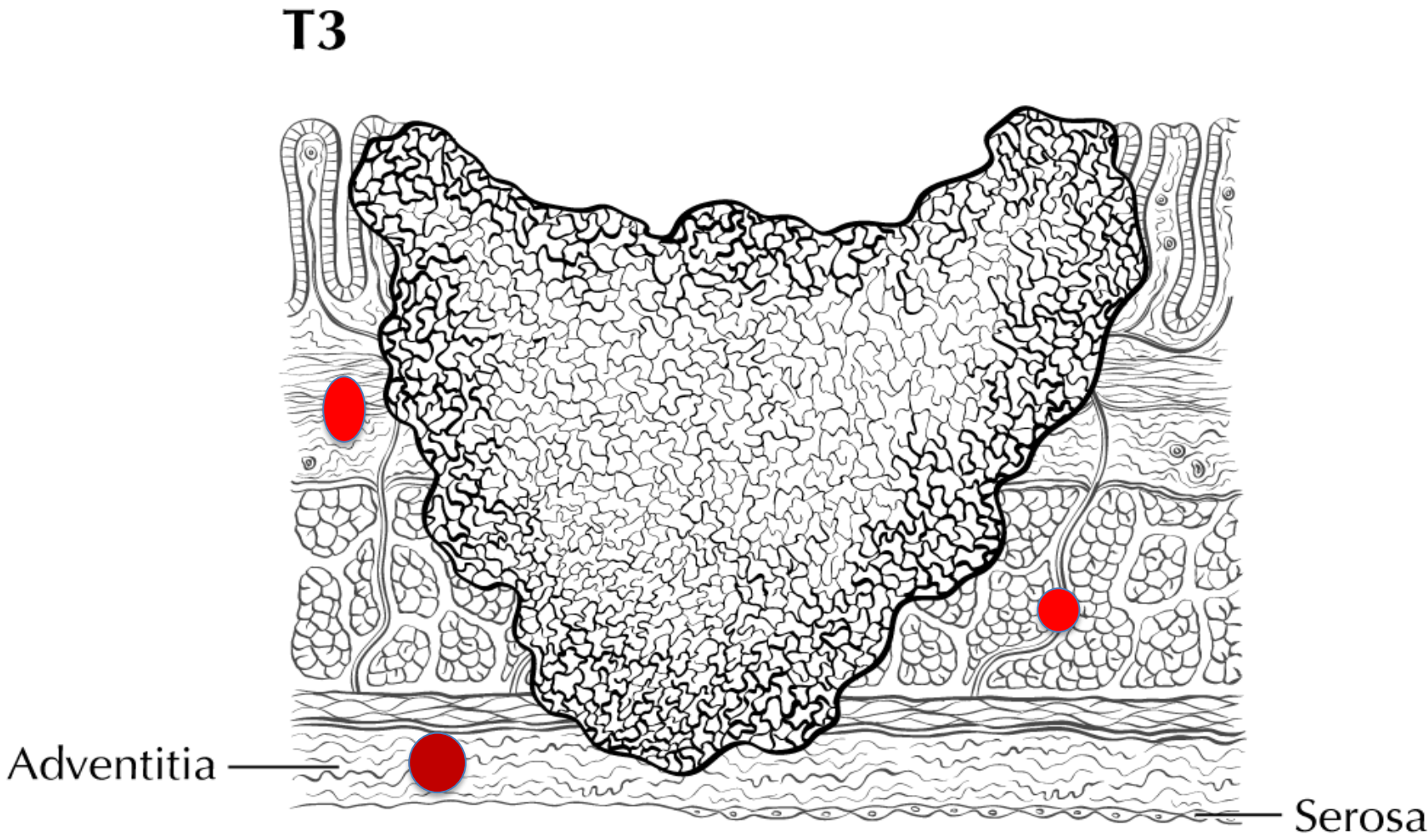








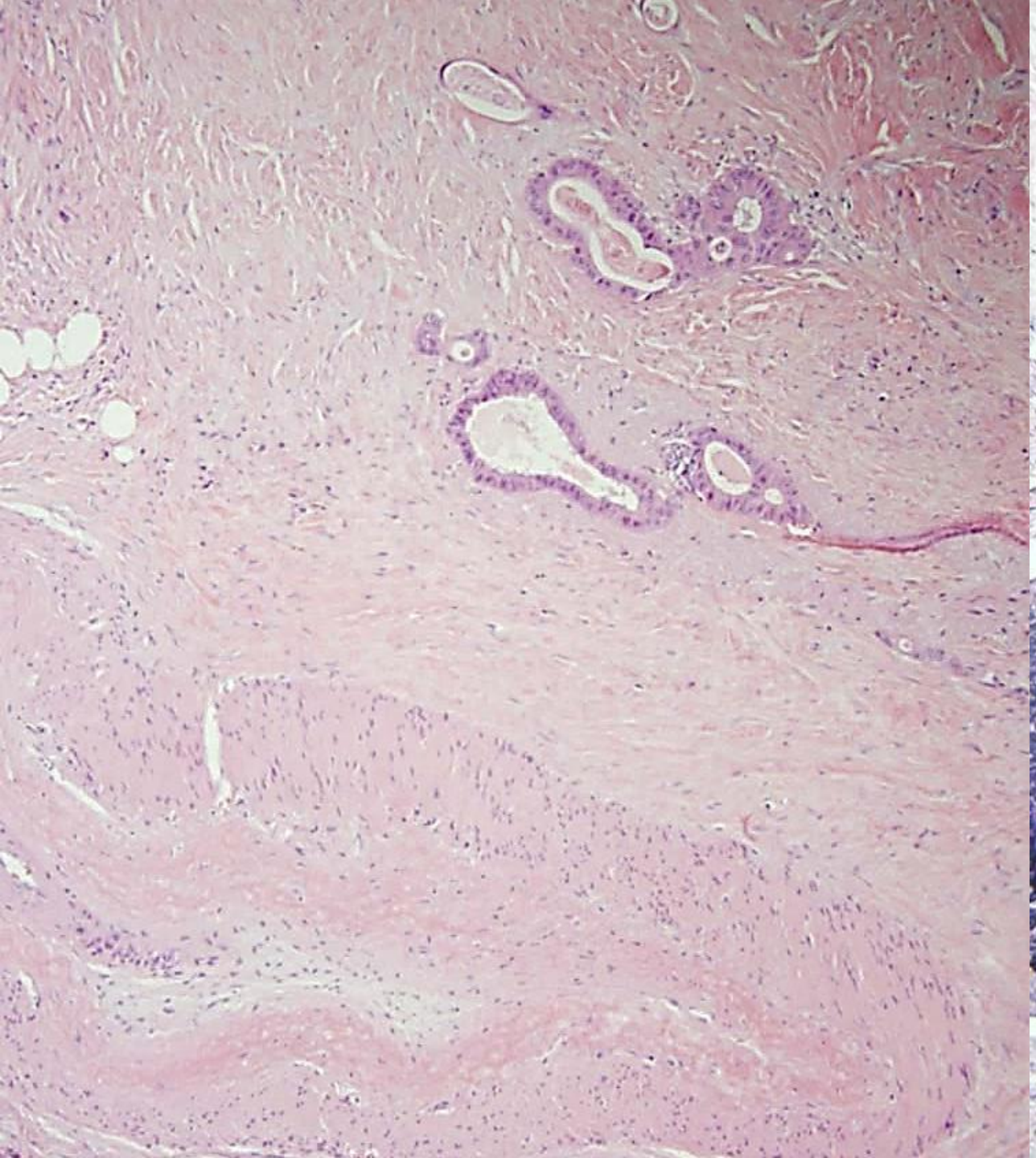
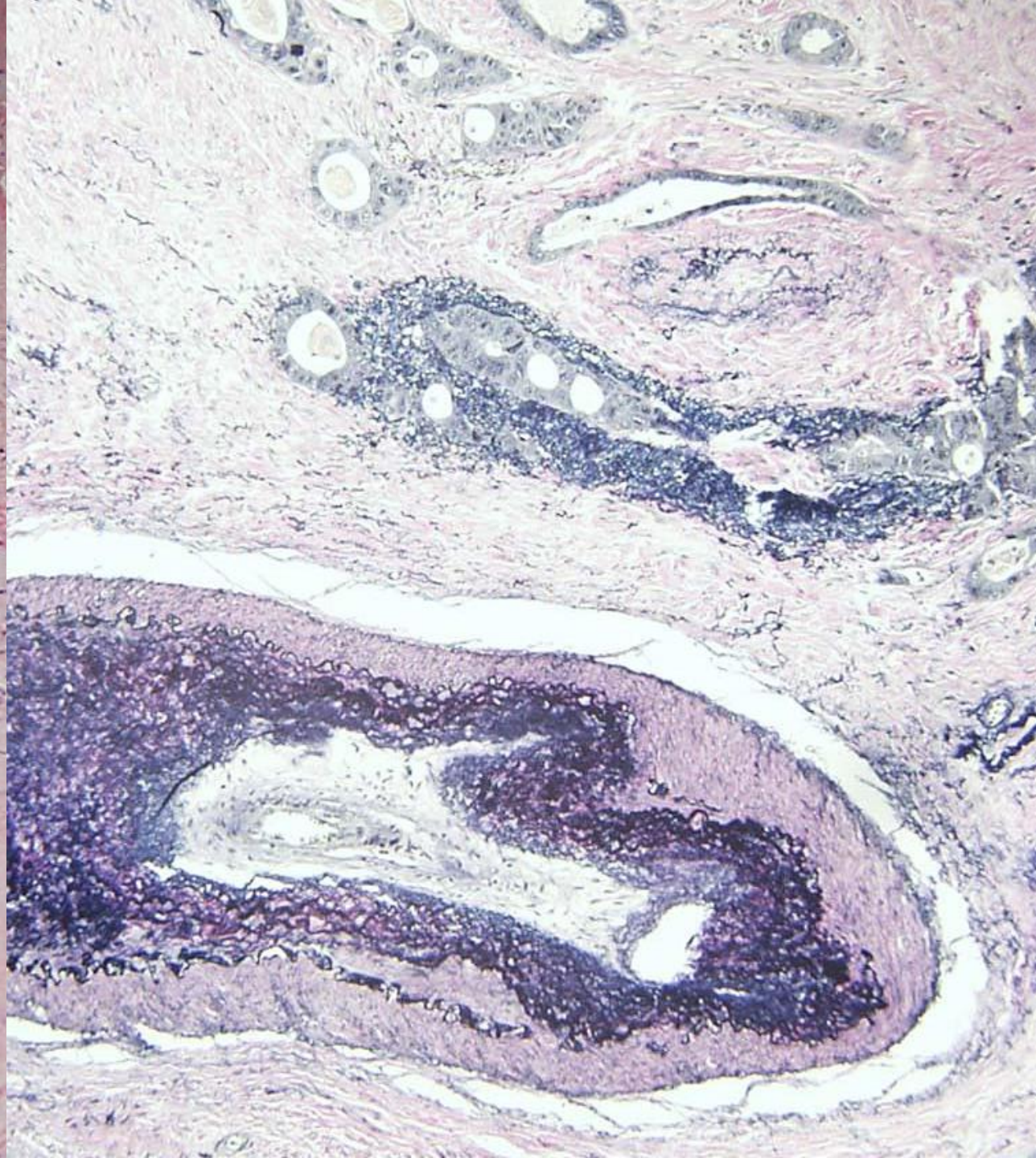
Intramural vs Extramural Venous Invasion

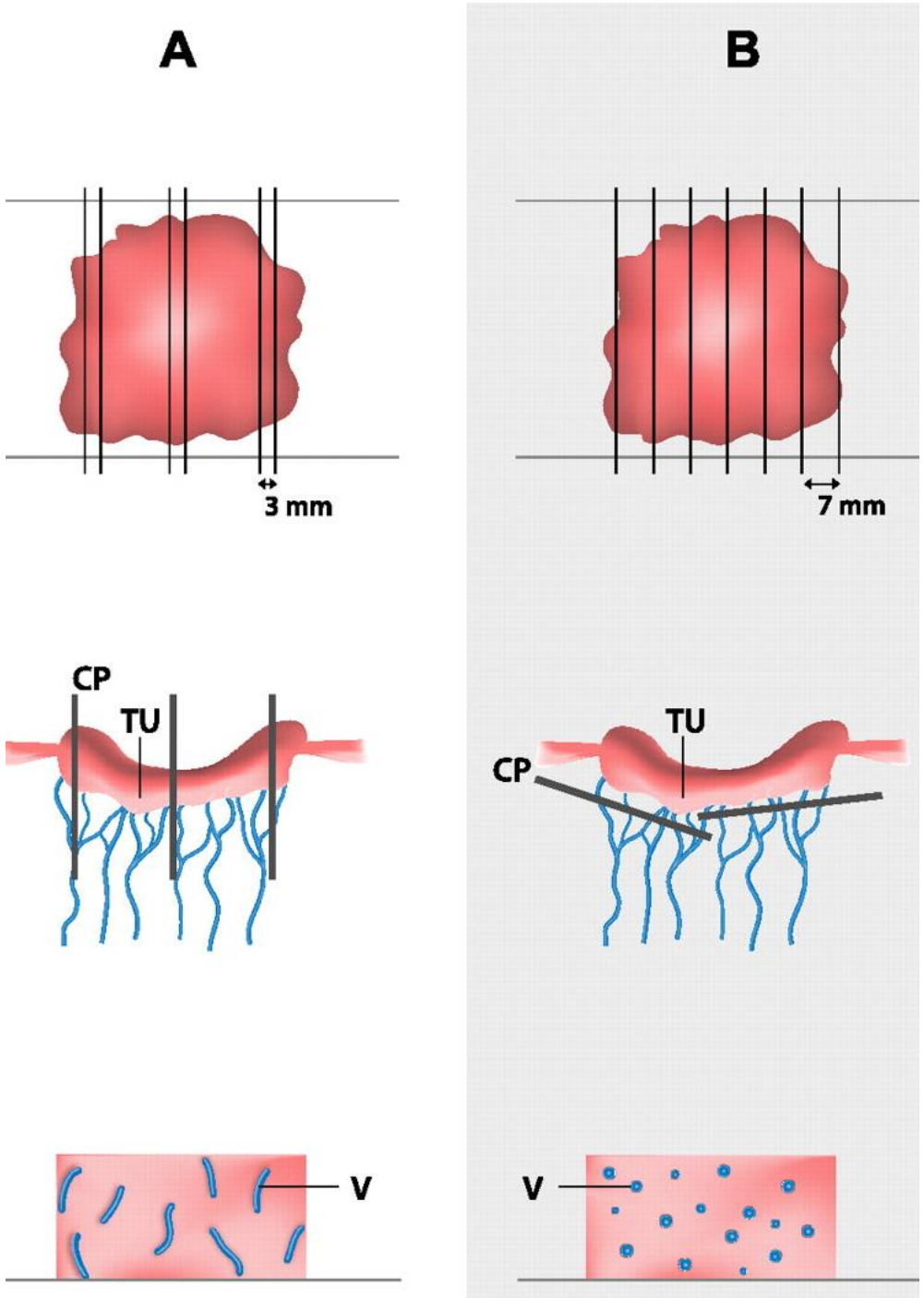


Compton, C.C., Byrd, D.R., et al., Editors. AJCC Cancer Staging Atlas, 2nd Edition. New York: Springer, 2012. ©American Joint Committee on Cancer

Venous Invasion is Common

- **UK is reporting 40% at some centers, minimal audit standard is at least 30% of all CRC resections (rarely achieved)**
- **Detection rate is improved 3-fold with elastin stain**
- **Missed because of obliterated vein wall**
- **Veins can be altered by radiation**



Comparison of the conventional (A) and tangential (B) method of dissection.

Klaus Dirschmid et al. J Clin Pathol 2012;65:619-623

JCP

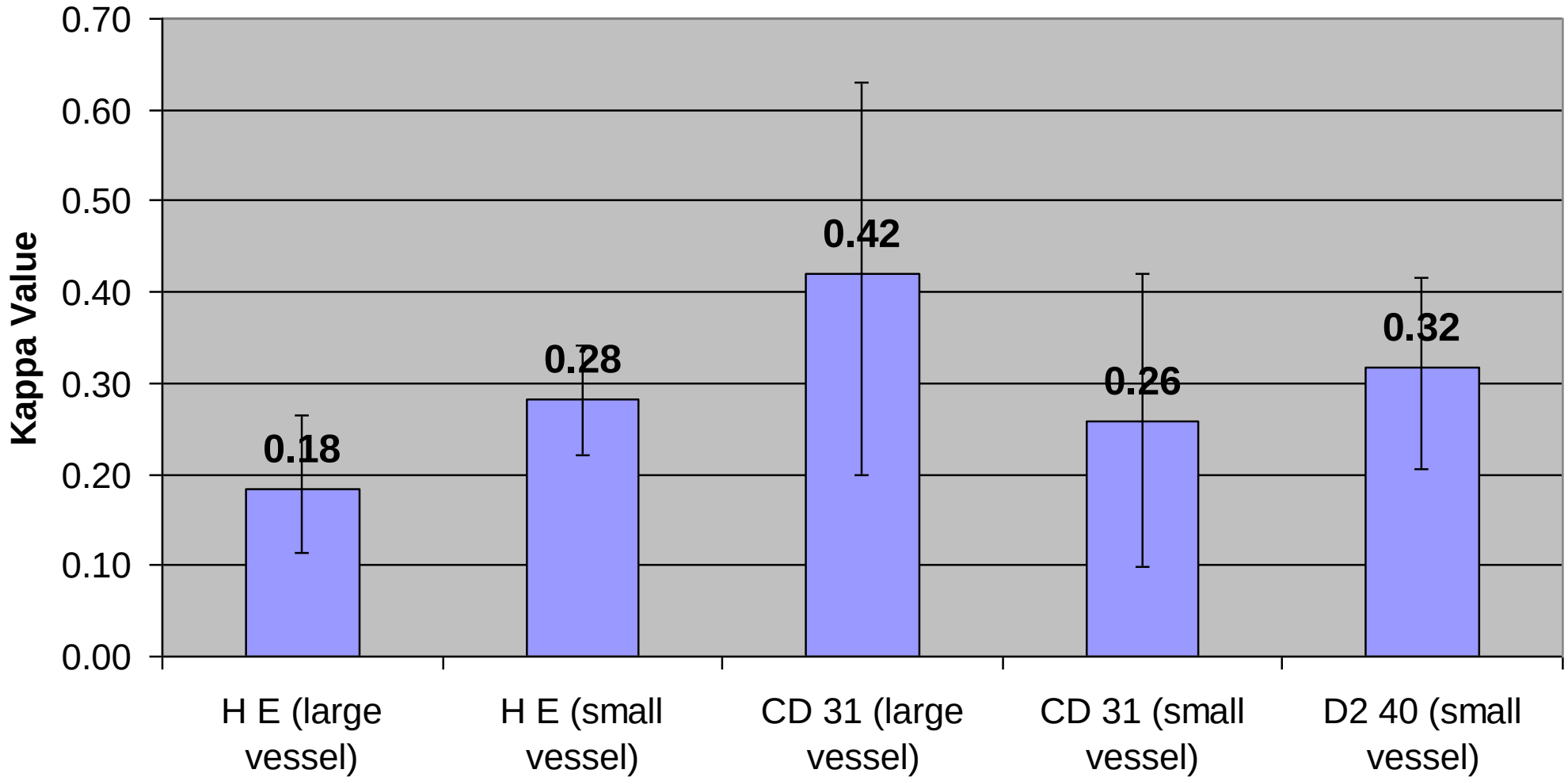
Interobserver Variability in LVI

- **Looked at 50 Stage II CRCs**
  - **H&E slide from each case assessed by 6 GI pathologists**
  - **Overall agreement was fair (75%) for small vessel invasion (pairwise kappa ranged from 0.1 to 0.6)**
  - **Agreement for small vessel LVI was not improved with special stains but large vessel assessment was**

- **Another study showed improvement in κ from 0.23 to 0.41 with use of Movat stain (6 GI and 6 general pathologists)**

Harris E et al. AJSP 32(12):1816-21, 2008
Kirsch R et al. AJSP 37(2):200-10, 2013

Interobserver Average Kappa Values for Lymphovascular Invasion in Colorectal Carcinoma

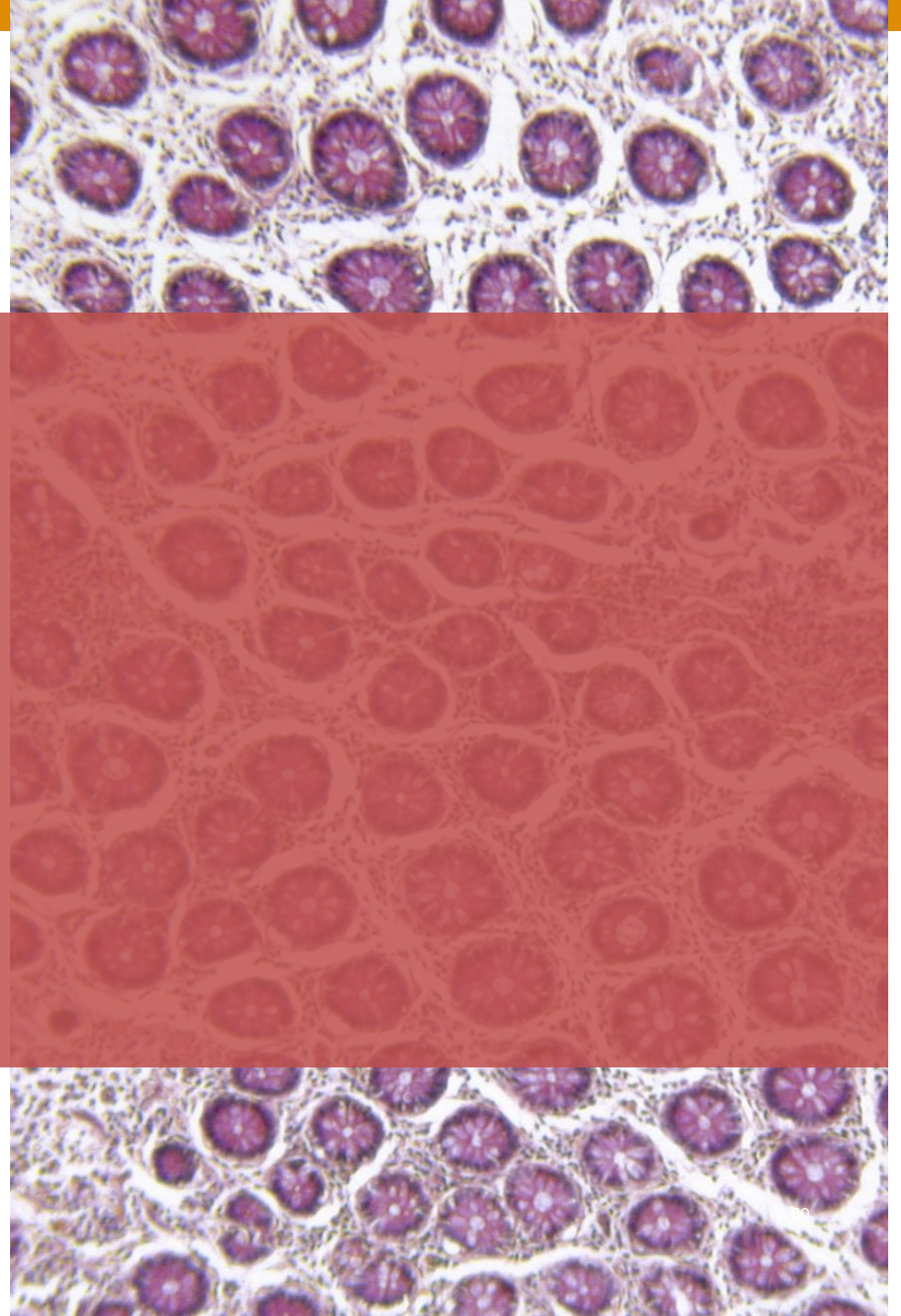


Practical Approach to Detection

- **Take a minimum of 4 or 5 tumor blocks**
- **Target areas of linear spiculation at the leading edge of the tumor**
- **For rectal cancers, MRI findings may be available**
- **Look for orphan artery/arteriole sign**
- **Perform elastin or Movat stains as needed, especially for Stage II cancers**

Should Molecular Features be Incorporated into Staging?

- Microsatellite Instability Testing
- Molecular Testing: *KRAS* and Beyond
- PDL1 testing
- HER2 testing



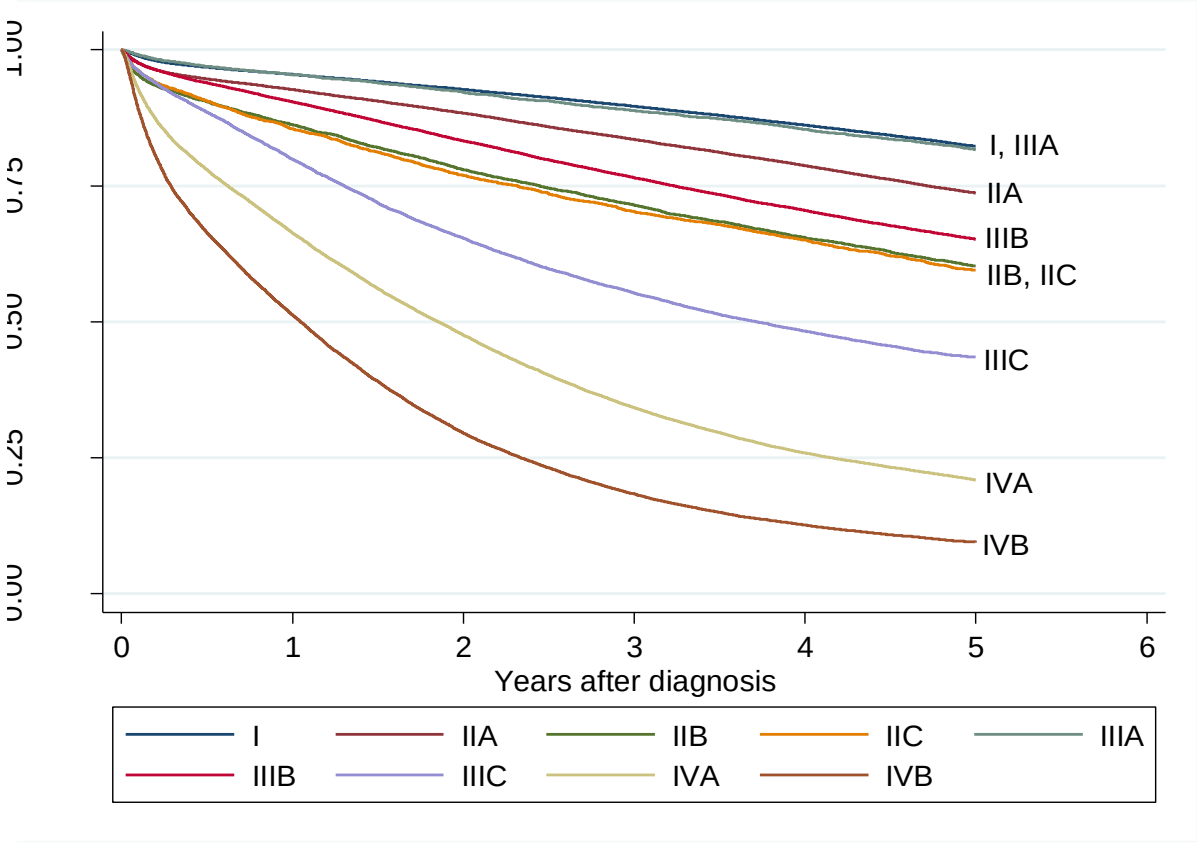
How Can Non-Anatomic Factors (Including Molecular Features) be Incorporated into TNM? Should they be?

- **Pros:**
  - **Some, such as MSI status, are strong prognostic factors**
  - **Some (MSI status) are routinely assessed in US and incorporated into guidelines**
  - **Cancer registries can capture the data**
- **Cons:**
  - **Not applicable globally, may not align with UICC's goals**
  - **Adds complexity to staging system**
  - **Not all prognostic factors can be included in TNM**

AJCC 9th Version- Colorectal Cancer

- **Expert panel has recommended against including molecular features in TNM at this time to avoid adding complexity**
- **May be incorporated into risk calculators, such as the MSKCC on-line resource**
- **No need for separate staging systems at this time for MSI-H and MSS cancers, but consider including separate survival curves in the 9th version**

Colon – Survival by Summary Stage Group (AJCC 8th edition) is not hierarchical

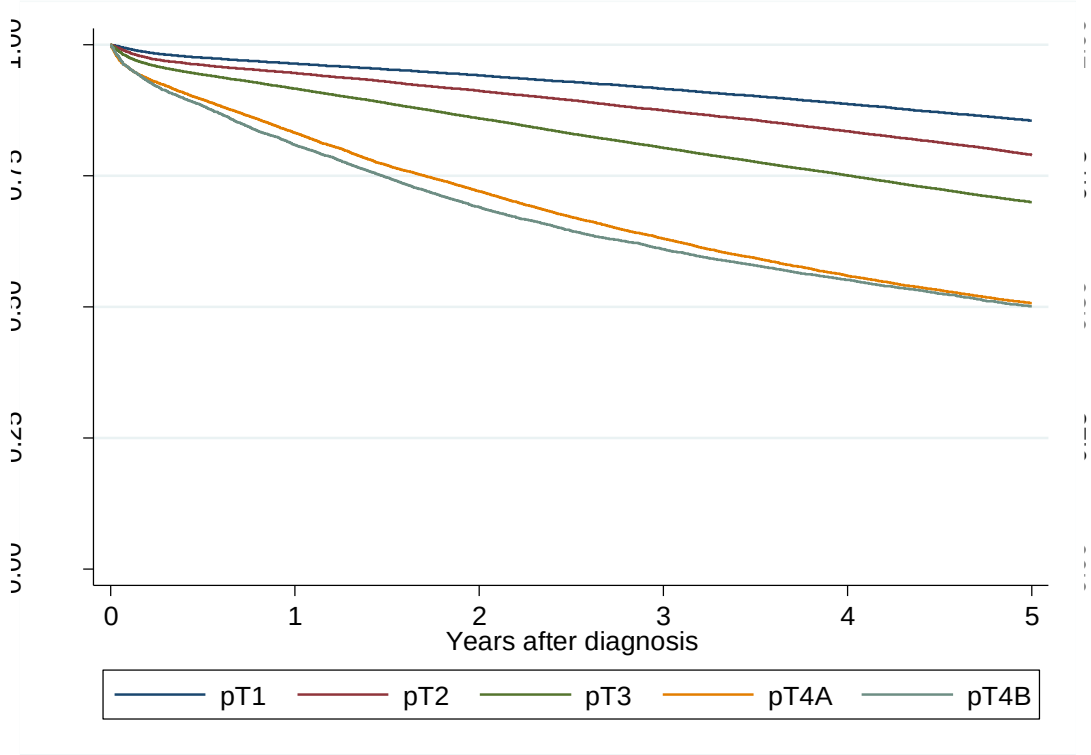


Current CRC cancer staging is not hierarchical for non-metastatic cases.

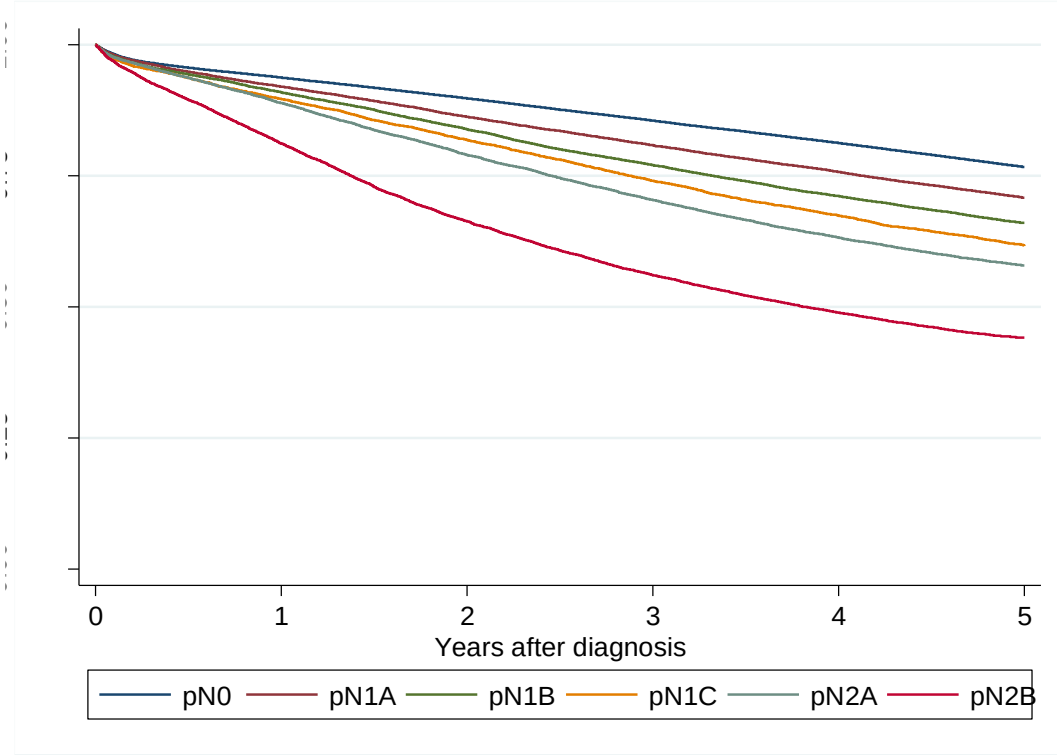
1. What are the relative contributions of T, N, and M category to survival/prognosis?
2. How should the staging system incorporate these contributions to optimize hierarchy in staging?
3. How can we synergistically utilize statistical models and the clinical perspective to optimize staging?

Colon – Survival by T or N Category, M0 cohort

Survival by pT

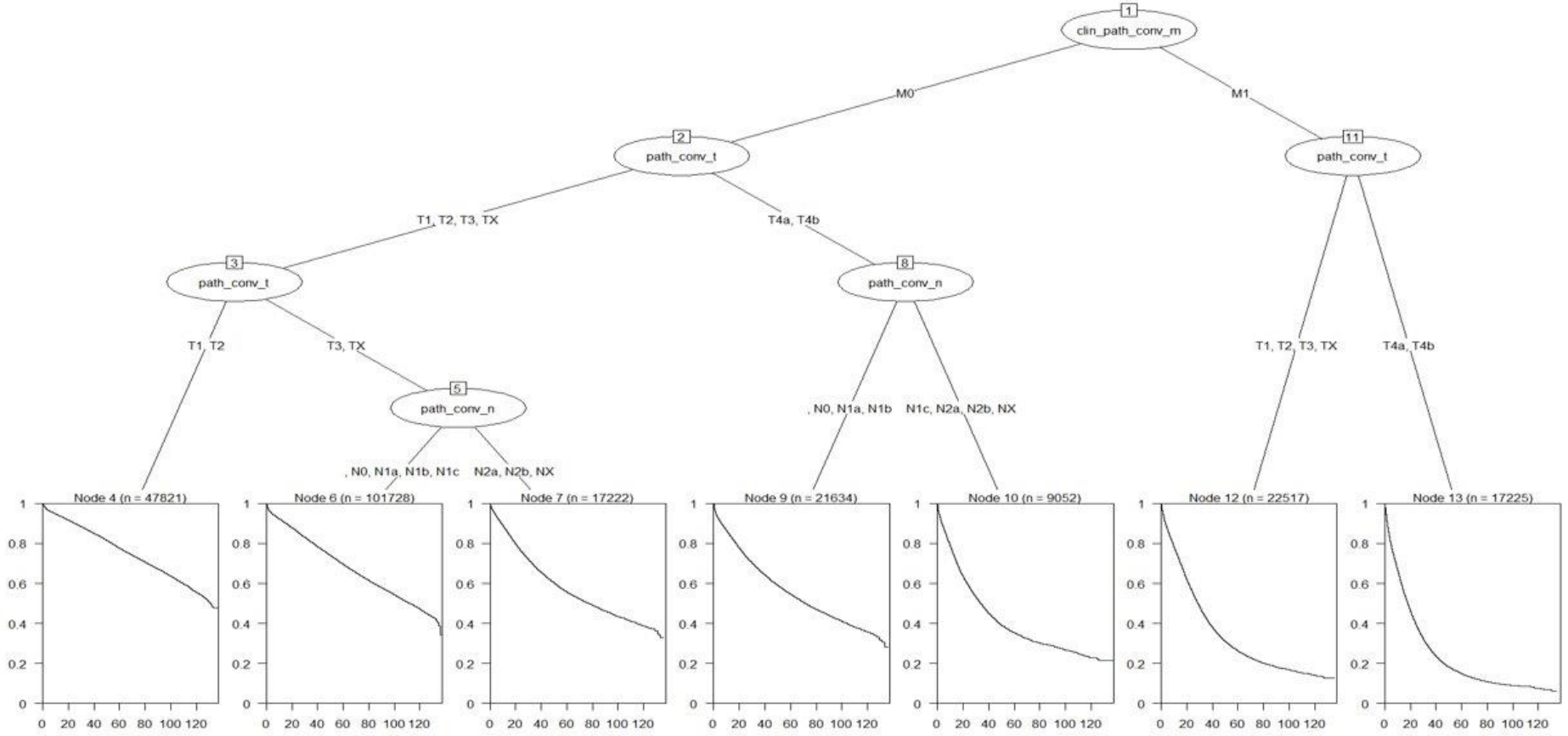


Survival by pN



Both High T and High N have disproportionately higher impact on survival and the interaction of T and N is important for determining survival prognosis

Colon –Machine Learning Approach



T1-2
N any
M0

T3, Tx
N0-1c
M0

T3, Tx
N2a-2b,
Nx
M0

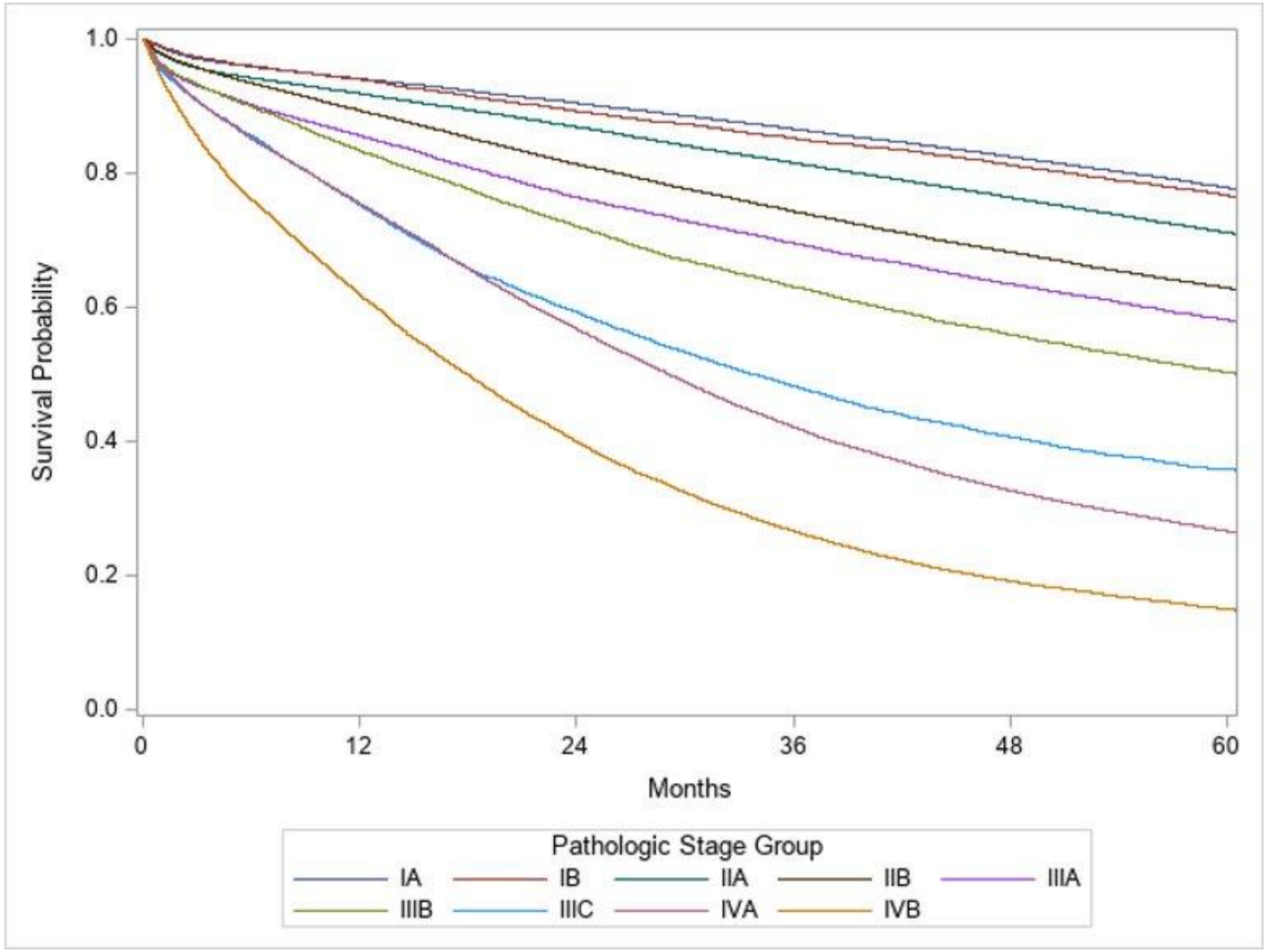
T4a, T4b
N0-1b
M0

T4a, T4b
N1c-2b, Nx
M0

T1-3, Tx
N any
M1

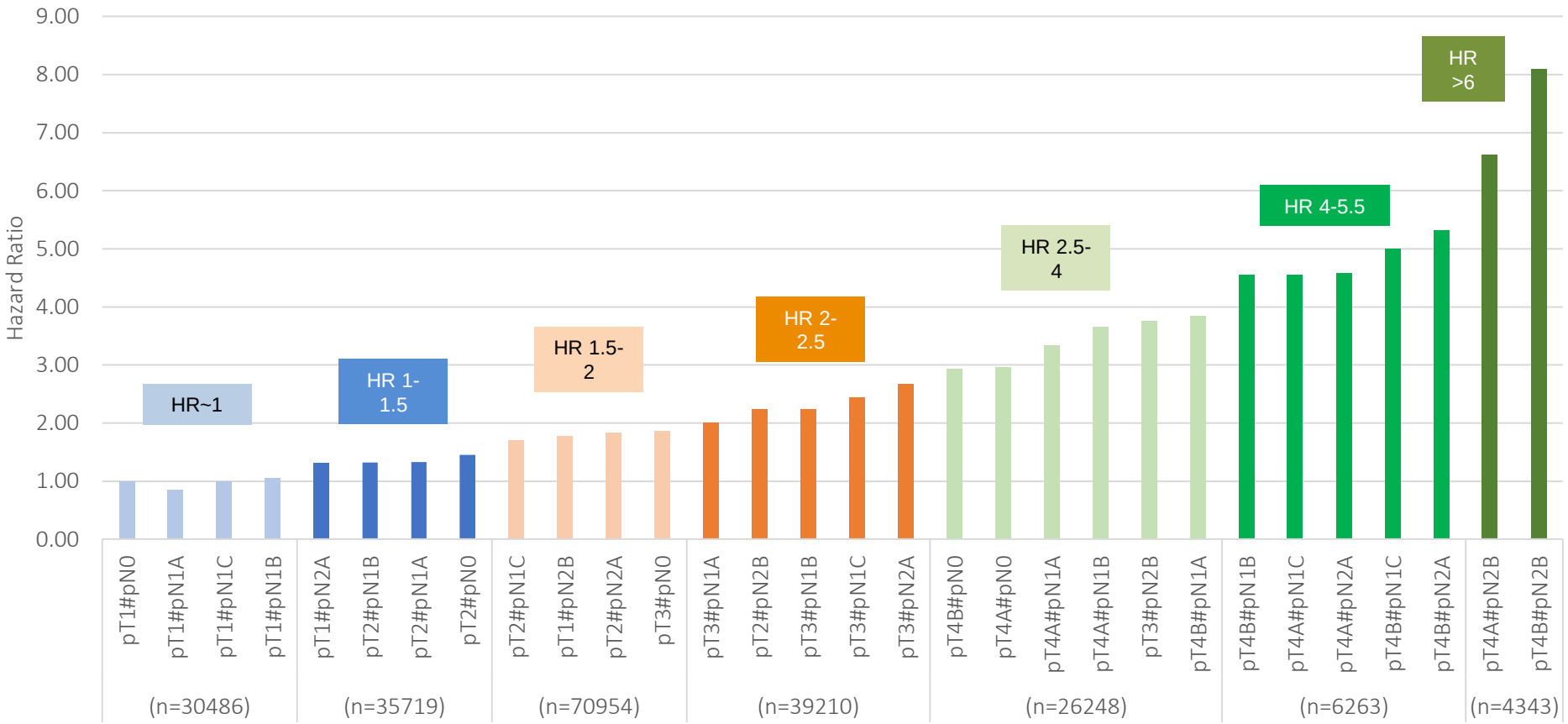
T4a, T4b
N any
M1

Colon – Clinically Optimized Machine Learning Model (9 groups)

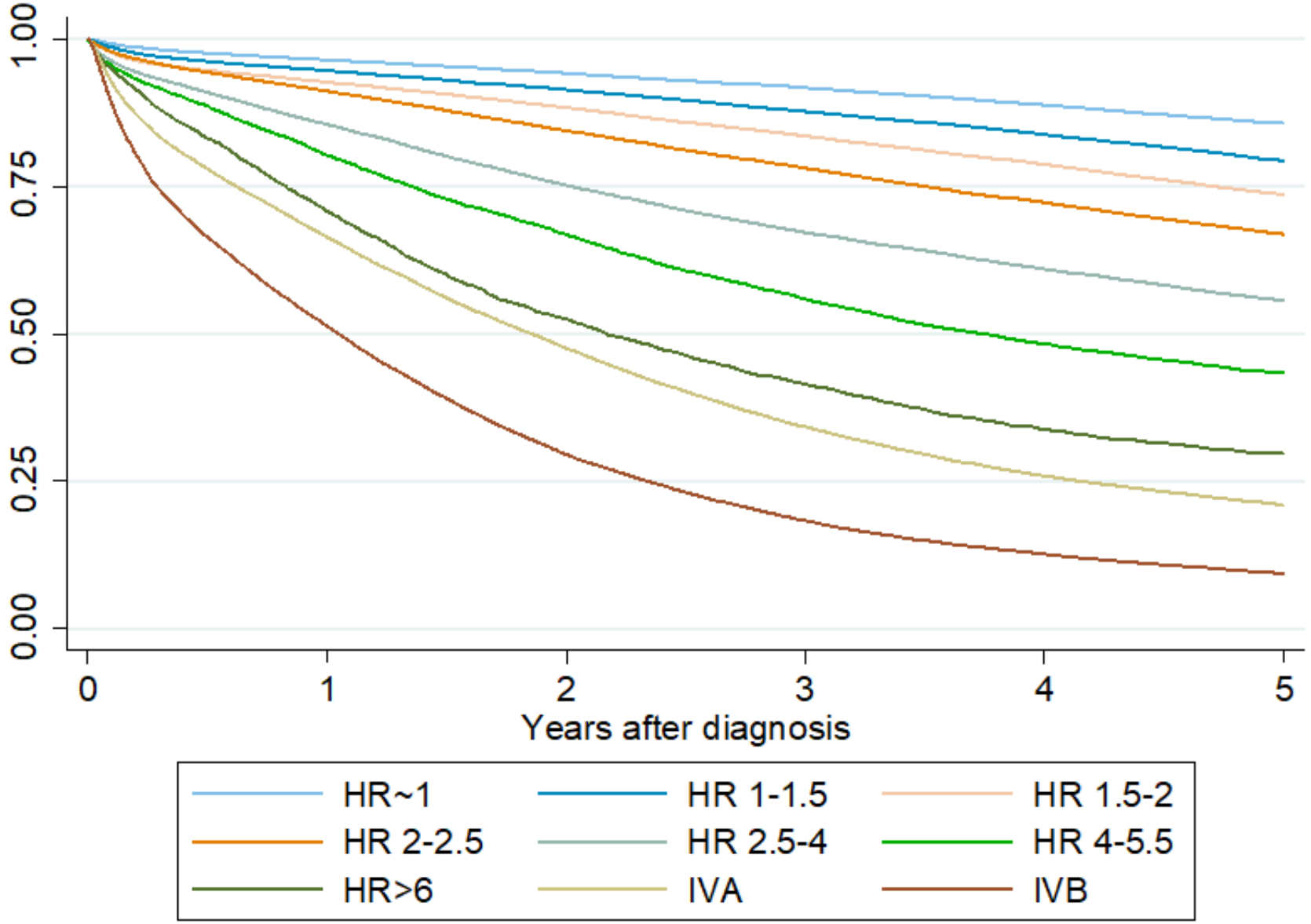


Stage	T	N	M
IA	T1-2	N0	M0
IB	T1-2	N1a-2b	M0
IIA	T3	N0	M0
IIB	T3	N1a-1b	M0
IIC	T3	N1c-2a	M0
IIIA	T4a, T4b	N0-1b	M0
IIIB	T4a, T4b	N1c-N2b	M0
IVA	T1-3	N any	M1
IVB	T4a, T4b	N any	M1

COLON, HR stratified TNM0 Hierarchical Survival Groups

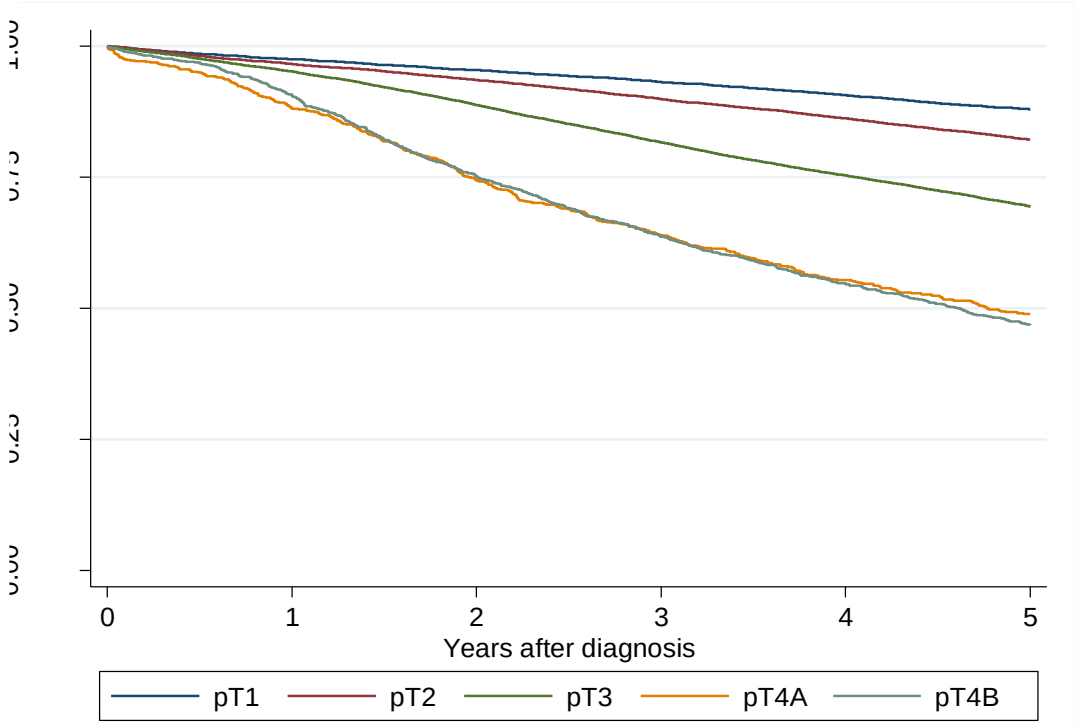


Hierarchical HR stratified Groupings for Colon

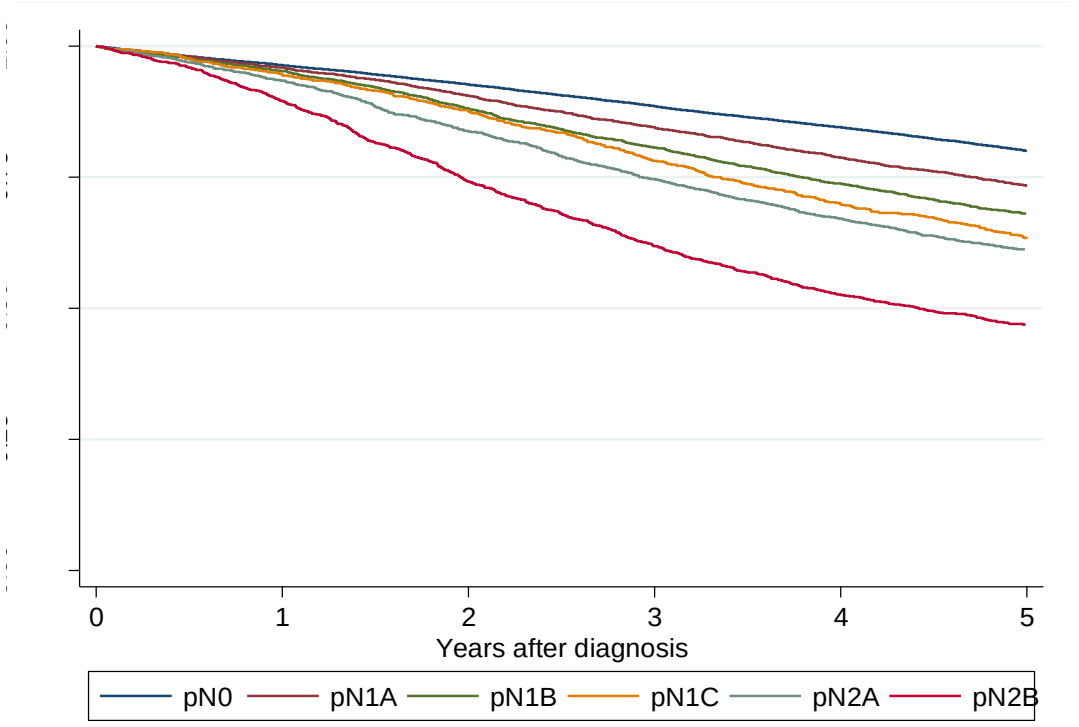


Rectum – Survival by pT and pN Category, M0 only

KM survival by pT category for rectum

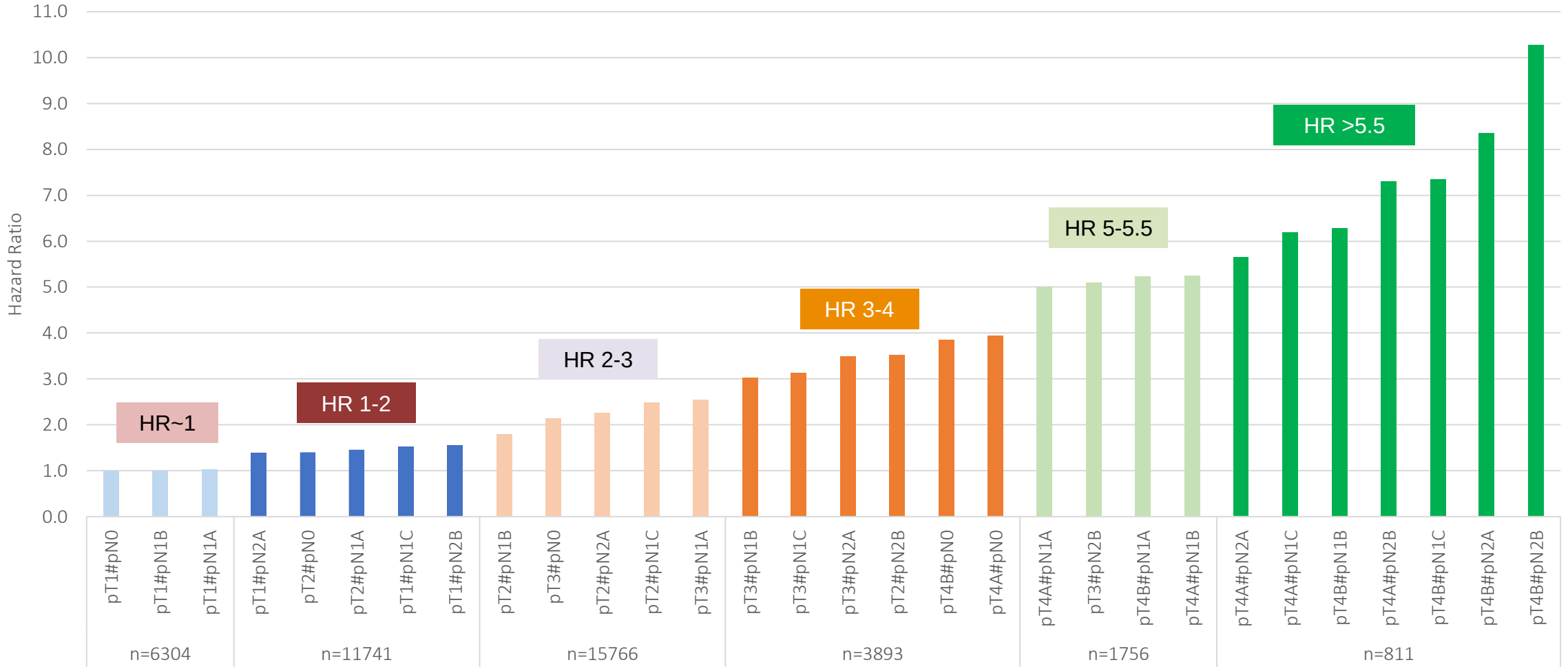


KM survival by pN category for rectum

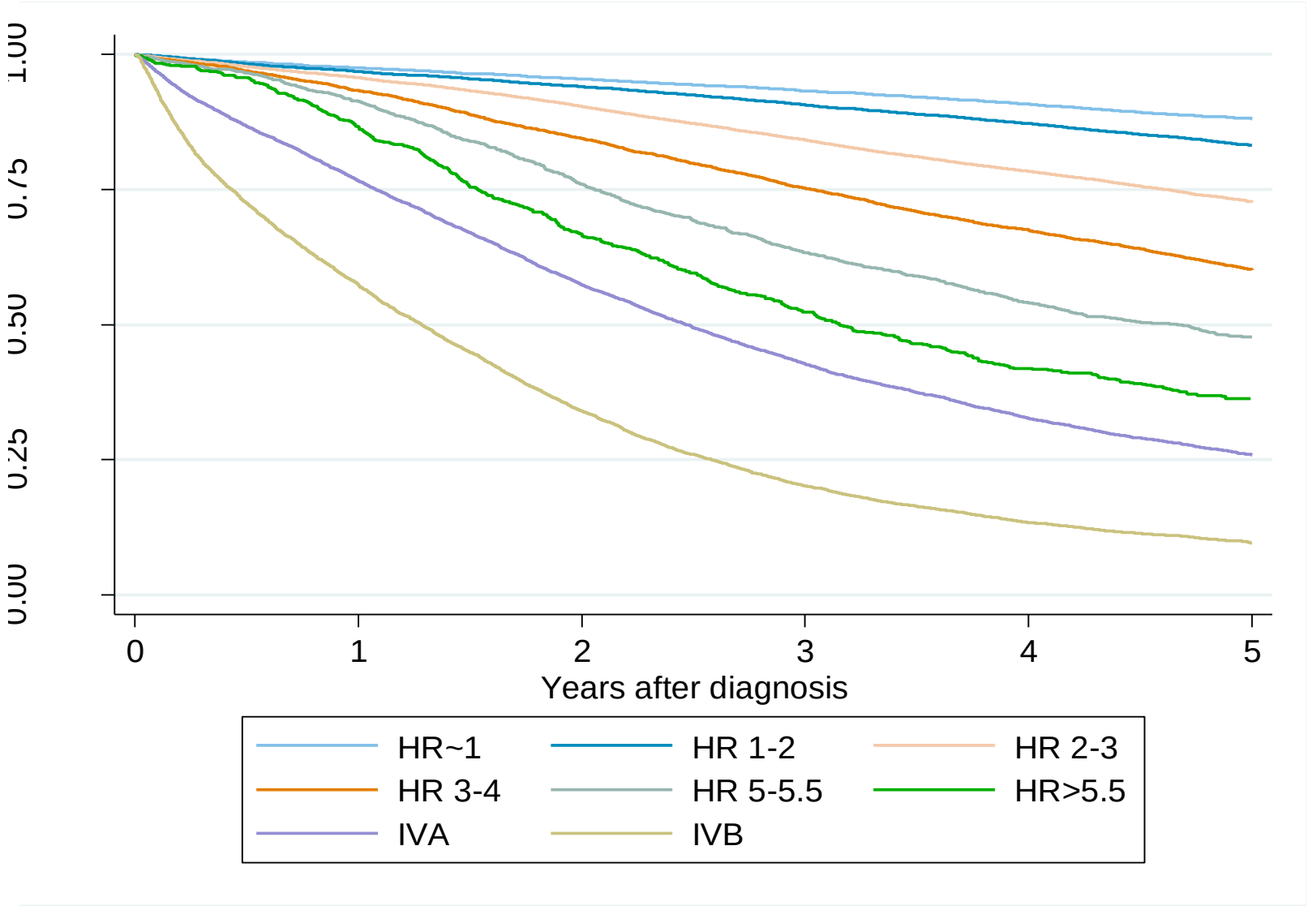


As for colon, both High T and High N have disproportionately higher impact on survival and the interaction of T and N is important for determining survival prognosis

RECTUM, HR stratified TNM0 Hierarchical Survival Groups



Hierarchical HR stratified Groupings for Rectum



Next Steps for AJCC for Colorectal Cancer Staging

- **Further analyses to determine optimal stage groupings**
  - **New stage groupings must account for power of T category over N category**
- **Open comment period to assess impact of radical change on stage groupings (i.e., stage III is no longer defined by positive LNs)**
- **Further analysis of how to handle tumor deposits**
  - **Should tumor deposits and positive lymph nodes be additive for N category?**
- **Clarifications regarding definition of localized peritoneal involvement**
- **No plans to include additional non-anatomic factors for Version 9**

Take Home Points for the Pathologist

- **Tumor deposit classification may not be entirely reproducible, but since TDs are (somewhat) equivalent to + LNs for staging, there should be little impact on patient care**
- **Look carefully for local peritoneal involvement.**
  - **Elastin stain is probably not warranted.**
- **Document extramural venous invasion, using elastin stains when indicated**
- **Changes to stage groupings are needed for colorectal cancer, and analysis is on-going**

Data Collection Tools for Standardized Reporting

- **College of American Pathologists**
  http://www.cap.org/

- **Royal College of Pathologists**

http://www.rcpath.org/index.asp?PageID=1153

- **International Collaboration on Cancer Reporting**

https://www.iccr-cancer.org/


Questions?