

Critical Issues in the Surgical Pathology of Colorectal Cancer Specimens



Pathologic Analysis and Its Clinical Significance

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Colorectal Cancer



- ⌘ A quintessentially “surgical disease”
- ⌘ Resection performed in:
 - ☒ 92% of colon
 - ☒ 84% of rectal cancer cases
- ⌘ Goal is complete excision (cure) in almost all cases
- ⌘ The resection specimen: key source of data relevant to post-operative patient management and outcome

The Resection Specimen in Cancer-Directed Surgery



- ⌘ Pathological assessment of the resection specimen
 - ☒ Gold standard of local extent of disease (stage)
 - ☒ Stage-independent, tissue-based prognostic factors
 - ☒ Appropriateness of adjuvant therapy
 - ☒ Prediction of response to therapy?
 - ☒ Prognosis for patient
 - ☒ Quality control on surgery, radiology

The All-Powerful Stage

- ⌘ TNM staging system
 - ☒ College of American Pathologists
 - ☒ Royal College of Pathologists
 - ☒ National Cancer Institute: Common Data Elements
- ⌘ Developed by UICC (Europe) and AJCC (North America)
- ⌘ AJCC and UICC systems identical for 1st time in 2003

TNM Staging



- ⌘ Data-driven
- ⌘ Timely: regular updates
- ⌘ Rules of application and interpretation
- ⌘ Clinically important: Most powerful prognosticator for GI cancer - used routinely to make Rx decisions
- ⌘ Scientifically important: international standardization for clinical trials and correlative science

TNM Staging



⌘ Based on 3 parameters

☒ T= Local extent of primary tumor

☒ N= Regional lymph node metastasis

☒ M= Distant metastasis

⌘ Prognosis related to **stage grouping**, not individual parameters

Pathologic Stage



⌘ cTNM = clinical stage

☑ Based largely on imaging studies

⌘ pTNM = pathologic stage

☑ Based largely on resection specimens

⌘ pT, pN, or pM more accurate than cT, cN, or cM

⌘ Hybrid stage groupings common: pT; pN; cM

pTNM Staging



- ⌘ Prognostic power based on previously **untreated** tumor
- ⌘ Prognosis based on TNM does not apply to residual tumor in the specimen (following neoadjuvant treatment)
- ⌘ Prognosis is also modified by residual tumor in the patient (incomplete resection)

TNM Staging: General Rules

RESIDUAL TUMOR IN THE PATIENT

- ⌘ Tumor remaining in the patient after surgical resection
- ⌘ Described by R classification (prognostically important):
 - RX Presence of residual tumor cannot be assessed
 - R0 No residual tumor
 - R1 Microscopic residual tumor
 - R2 Macroscopic residual tumor
- ⌘ Pathologically corresponds to **positive resection margin**

TNM Staging: General Rules



RESIDUAL TUMOR IN THE SPECIMEN

- ⌘ Tumor remaining in the surgical resection specimen following neoadjuvant therapy (chemo or radiation)
- ⌘ ypTNM notation
- ⌘ NOT rpTNM
 - ⊠ r = recurrent tumor
 - ⊠ r = following documented disease-free interval

What's New in TNM? Changes to the 6th Edition of the TNM Staging Manual

⌘ Colon

- ☒ Boundary with anal canal better defined
- ☒ Appendix eliminated as a colorectal site
- ☒ Extramural tumor nodules = nodal metastasis
- ☒ Stage II (node-) subdivided by T3 or T4
- ☒ Stage III (node+) subdivided by T1/2, T3/4, N1/2

Colorectal Cancer: The Basics

⌘ Validated tissue-based prognostic factors

- ⊞ Pathologic stage

- ⊞ Resection margin status

- ⊞ Vessel invasion

 - ⊞ Small vessel (lymphovascular) invasion

 - ⊞ Large vessel (extramural venous) invasion

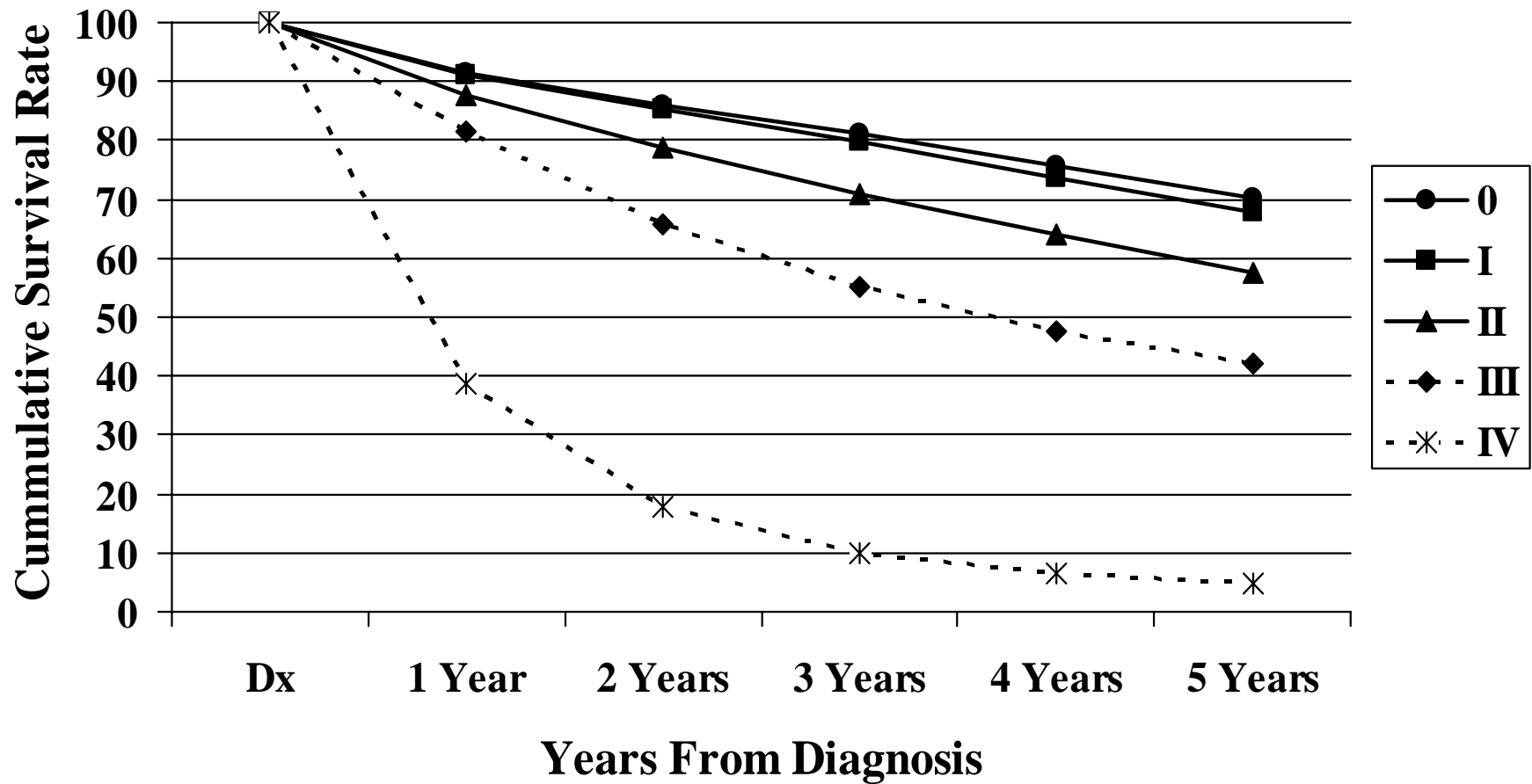
- ⊞ Tumor grade

Colorectal Cancer: The Not So Basics



- ⌘ Well documented, but not-yet-validated prognostic factors
 - ☑ High-grade histologic types
 - ☑ Perineural invasion
 - ☑ Tumor border configuration
 - ☑ Host lymphoid response to tumor
 - ☑ Microsatellite stability (DNA repair gene) status
 - ☒ Medullary carcinoma
 - ☑ Loss of heterozygosity at 18q

TNM Stage-Stratified 5-Yr Survival Rates: 116,847 Colon Cancers Diagnosed 1994-1995



Data from the National Cancer Data Base, ACoS

Colon Cancer Update 2003

- ⌘ Outcomes research showing differences in survival of stage II and stage III patients based on T category

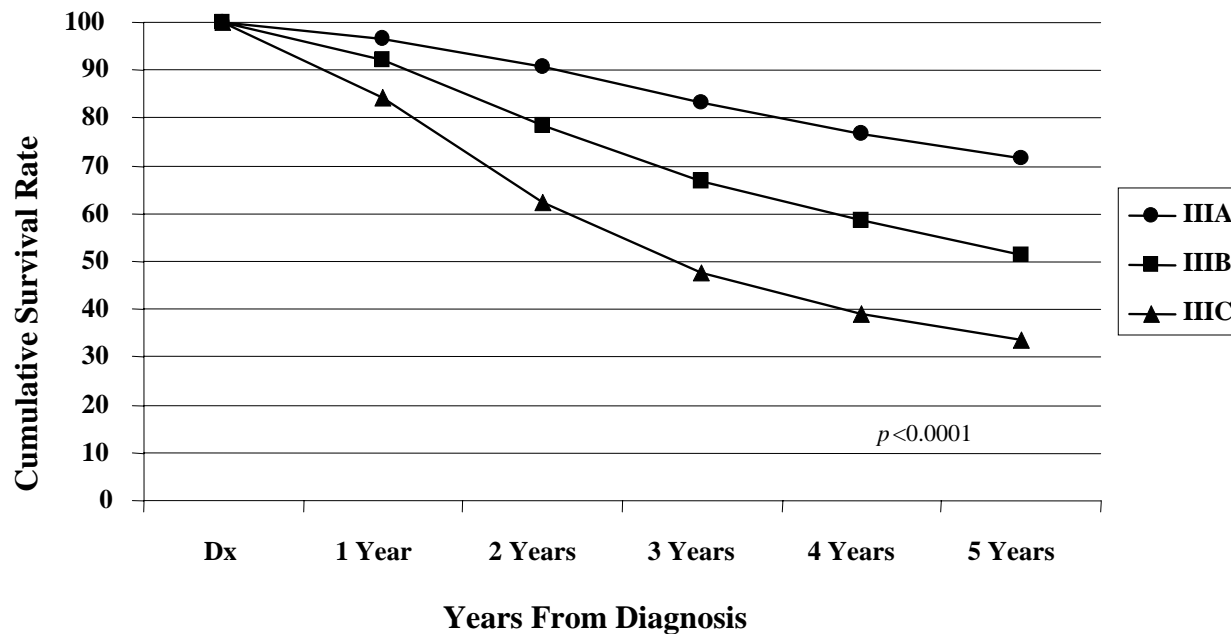


Figure 2

TNM Stage Groupings: 6th Edition

TNM Stage Groupings				Astler-Coller	Dukes
Stage 0	Tis	N0	M0	N/A	N/A
Stage I	T1	N0	M0	Stage A	A
	T2	N0	M0	Stage B1	A
Stage IIA	T3	N0	M0	Stage B2	B
Stage IIB	T4	N0	M0	Stage B3	B
Stage IIIA	T1-T2	N1	M0	Stage C1	C
Stage IIIB	T3-T4	N1	M0	Stage C2; C3	C
Stage IIIC	Any T	N2	M0	Stage C1;C2;C3	C
Stage IV	Any T	Any N	M1	Stage D	N/A

Pathologic Staging (pTNM): pT Issues



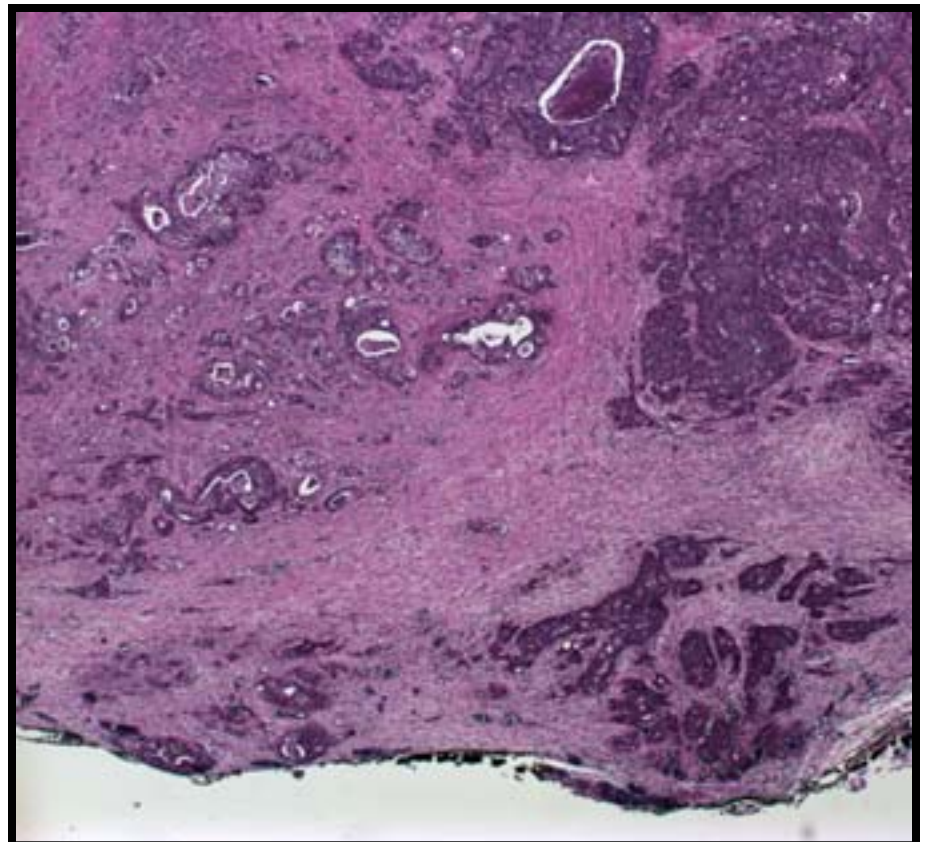
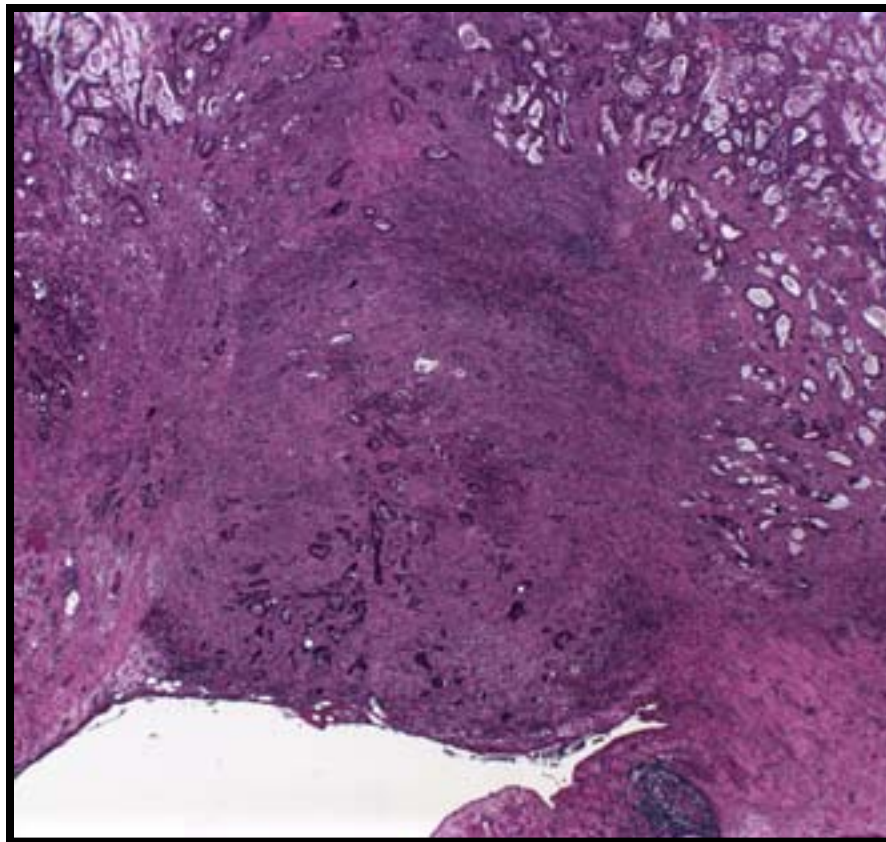
T = Primary Tumor

- Tis Carcinoma *in situ* (intraepithelial or intramucosal)
- T1 Invades submucosa
- T2 Invades muscularis propria
- T3 Invades through muscularis propria into subserosa or nonperitonealized extramural tissues
- T4 Directly invades other organs or structures (T4a) or “perforates” visceral peritoneum (T4b)

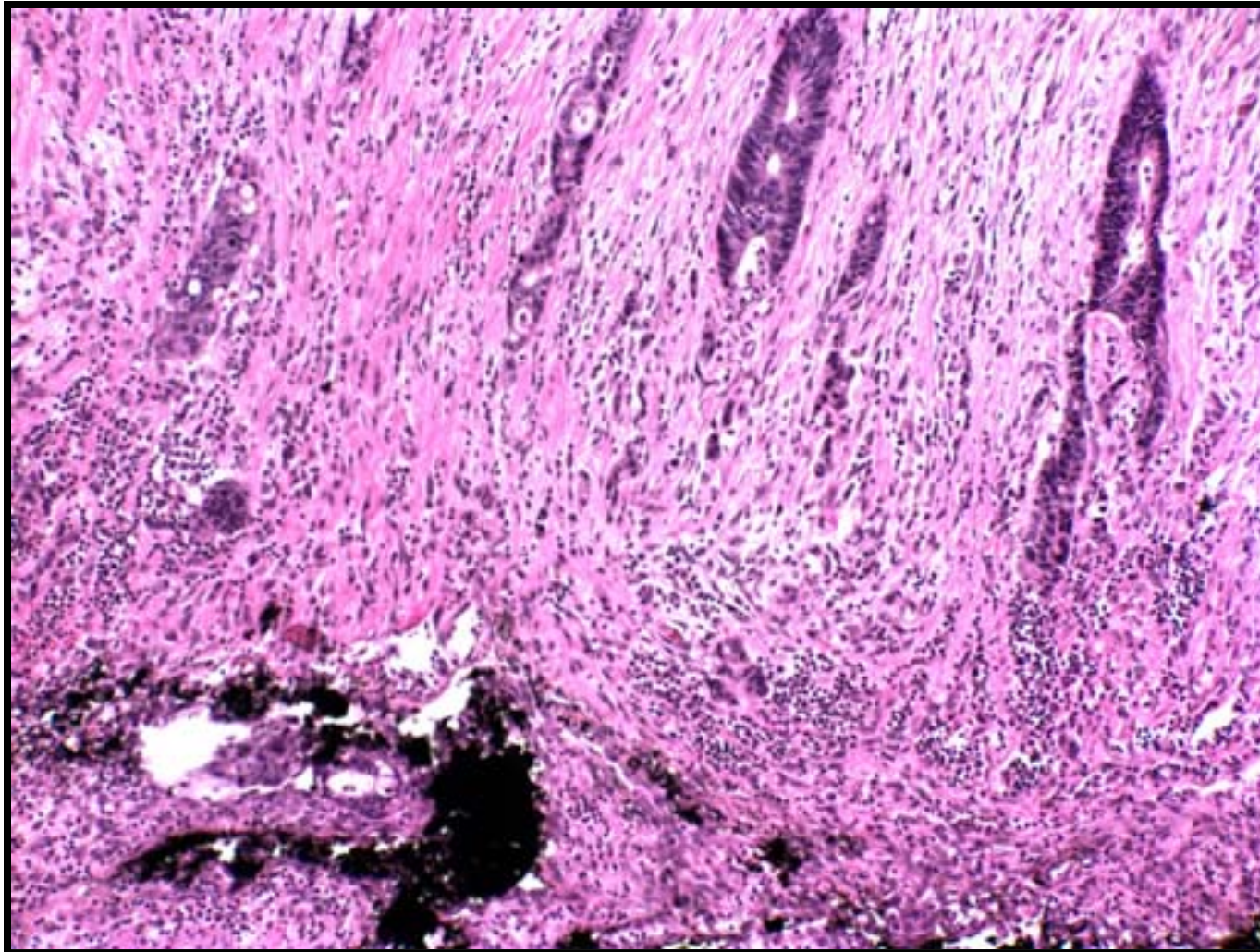
pT4: Serosal Involvement

- ⌘ 3 types of serosal involvement (Shepherd et al, Gastroenterol 1997):
 - ☒ tumor close to, but not at, the serosal surface with mesothelial inflammatory and/or hyperplastic reaction
 - ☒ tumor at the serosal surface with inflammatory reaction, mesothelial hyperplasia, and/or erosion
 - ☒ free tumor cells on the serosal surface with underlying ulceration
- ⌘ All 3 types: decreased survival, especially latter 2
- ⌘ Tumor well clear of serosa - no independent adverse effect

pT4: Serosal Involvement



pT4: Serosal Involvement



pT4: Serosal Involvement



Underestimating serosal involvement:

26% of cancers judged as T3 by histopathology
have tumor cells on serosal cytologic touch preps

— Zeng et al, Cancer 1992

Pathologic Staging (pN) Issues

N = Regional Lymph Nodes

N0 No regional lymph node metastasis

N1 Metastasis in 1 to 3 lymph nodes

N2 Metastasis in 4 or more lymph nodes


M= Distant Metastasis

M0 No distant metastasis

M1 Distant metastasis *

* Includes metastasis in non-regional lymph nodes and/or positive peritoneal cytology

pN Issues: What Counts as a Lymph Node?



⌘ Extramural nodules w/o evidence of residual nodal tissue

☒ Round nodules: each classified as a replaced node

☒ Goldstein NS, Turner JR. Cancer 2000; 88:2228-38

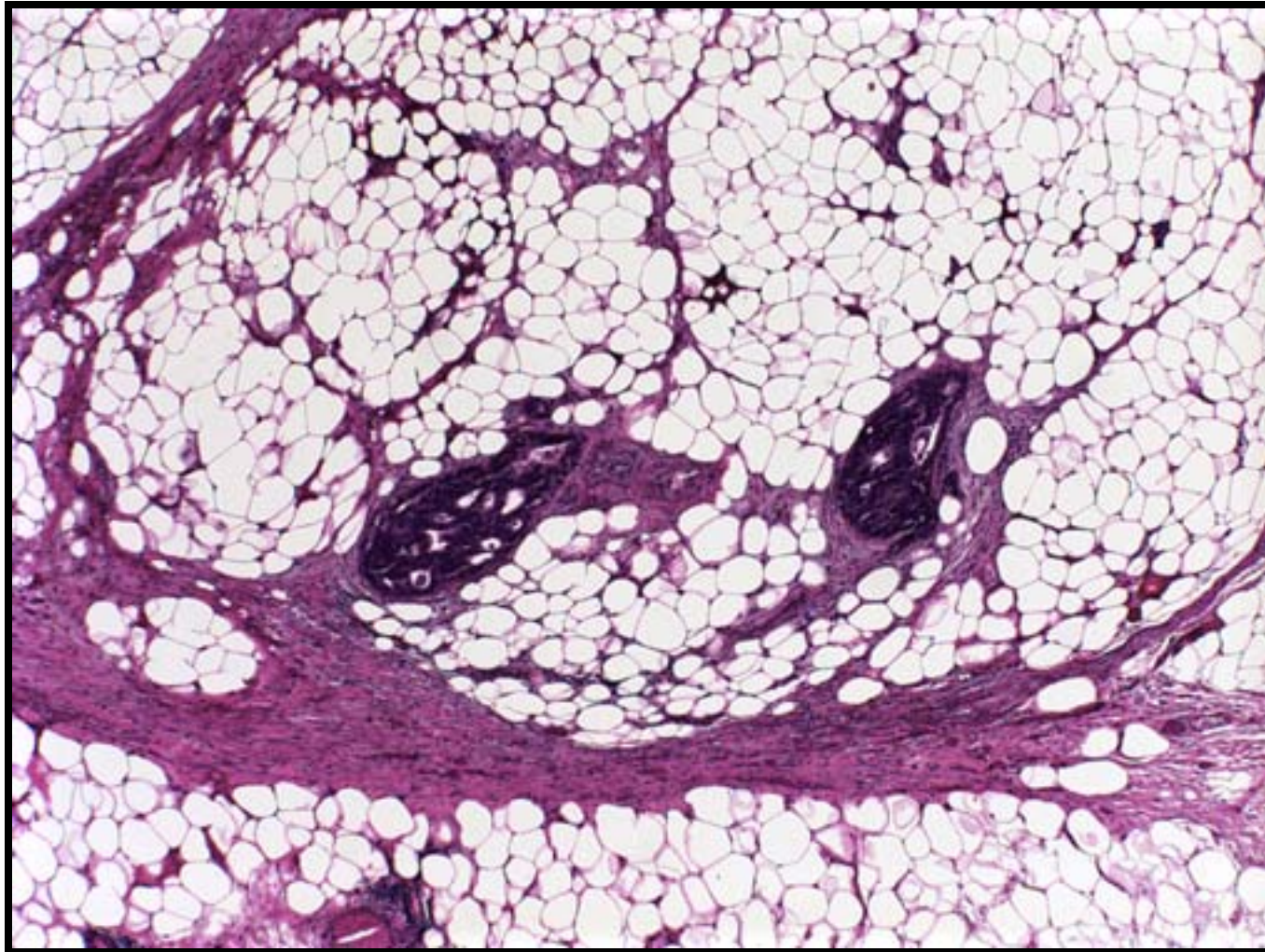
☒ Harrison JC, et al. Hum Pathol 1994; 25: 498-505

☒ Harrison JC, et al. Hum Pathol 1995; 26: 31-38

☒ 3-mm rule abolished

☒ Irregular nodules are classified as discontinuous extension of tumor and classified in the T category

pN Issues: What Counts as a Lymph Node?



pN Issues: The Magic Number

⌘ pN0 **not** accurately predicted by **<12-18** lymph nodes

- ☒ Blenkinsopp WK, et al. J Clin Pathol 1981; 34:509-13
- ☒ Scott KWM, Grace RH. Br J Surg 1989; 76:1165-7
- ☒ Goldstein N, et al. Am J Clin Pathol 1996; 106:209-16
- ☒ Ratto C, et al. Dis Colon Rectum 1999; 42:143-58
- ☒ Burdy G, et al. Dis Colon Rectum 2001; 44:1682-8
- ☒ Tepper JE, et al. J Clin Oncol 2001; 19:157-63
- ☒ Cianchi F, et al. World J Surg 2002; 26:384-9
- ☒ Goldstein N. Am J Surg Pathol 2002; 26:179-189
- ☒ Wong JH, et al. Dis Colon Rectum 2002; 45:1341-8
- ☒ LeVoyer TE, et al. J Clin Oncol 2003; 21: 2912-9
- ☒ Swanson RS, et al. Ann Surg Oncol 2003; 10:65-71
- ☒ Joseph NE, et al. Ann Surg Oncol 2003; 10:213-8
- ☒ Law CHL, et al. J Surg Oncol 2003; 84: 120-6

pN Issues: The Magic Number



- ⌘ There is no minimum number
- ⌘ The number of lymph nodes harvested is itself a stage-independent prognostic factor

- Le Voyer TE, et al. J Clin Oncol 2003; 2:2912-9

pN Issues: The Magic Number

⌘ The efficacy of gross identification of lymph nodes is low but the penalty is high

☒ Average # found on diligent search: 21

☒ Average # seen on microscopic exam of extramural fat: 69

☒ 83% of additional nodes were ≤ 2.0 mm

☒ 75% of all positive nodes were < 2.0 mm in size

- Brown HG, et al. Modern Pathology 2004; 17:402-6

pN Issues: The Magic Number

⌘ Number of nodes recovered determined by:

☒ Patient anatomic variation and/or age

☒ Pathologic examination

☒ Less than diligent

☒ Not informed by data/guidelines

- <25% of Canadian pathologists knew that a minimum of 12 lymph nodes are necessary for accurate assignment of pN0

– Wright FC, et al. Am J Clin Pathol 2004; 121:663-70

☒ No use of fat clearing (visual enhancement techniques) - proven effective but controversial as standard practice

pN Issues: The Magic Number



- ☒ Surgeon not experienced in colorectal surgery
 - ☒ Non-colorectal surgeons have lower survival and higher local recurrence rates
 - Dorrance HR, et al. Dis Colon Rectum 2000; 43:492-8
 - Abulafi AM et al. Br J Surg 1994; 81:7-19
- ☒ Colorectal surgeon not trained in TME
 - ☒ Untrained in TME, local recurrence 25-45%
 - ☒ Trained in TME, local recurrence <7%

pN Issues: The Magic Number

- ☒ Surgical technique (NCI *Guidelines 2000 for Colon and Rectal Surgery*)
 - ☒ Mesentery trimmed too close to wall
 - ☒ Inadequate TME technique ⇒ incomplete removal of regional nodes
 - Number of nodes in a TME specimen can be used to predict the effectiveness of a TME
- Pocard M, et al. *Dis Colon Rectum* 1998; 41:839-45
- ☒ <10 cm normal colon resected on either side of the tumor
 - ☒ Feeding artery not ligated at its origin
 - ☒ Lymph nodes not removed en bloc
 - ☒ Lack of “no-touch” isolation technique
 - ☒ Adherent/infiltrated organs separated from the tumor

Where are the Nodes?



⌘ Rectal cancer

- ☑ Most mesorectal lymph nodes are located in the posterior upper two-thirds of the mesorectum (Galandiuk et al. 2005)

HOWEVER

- ☑ Laterally: +nodes may abut the mesorectal fascia
- ☑ Distally: 25-52% of tumors have distal +nodes (Scott et al, 1995; Reynolds et al, 1996)

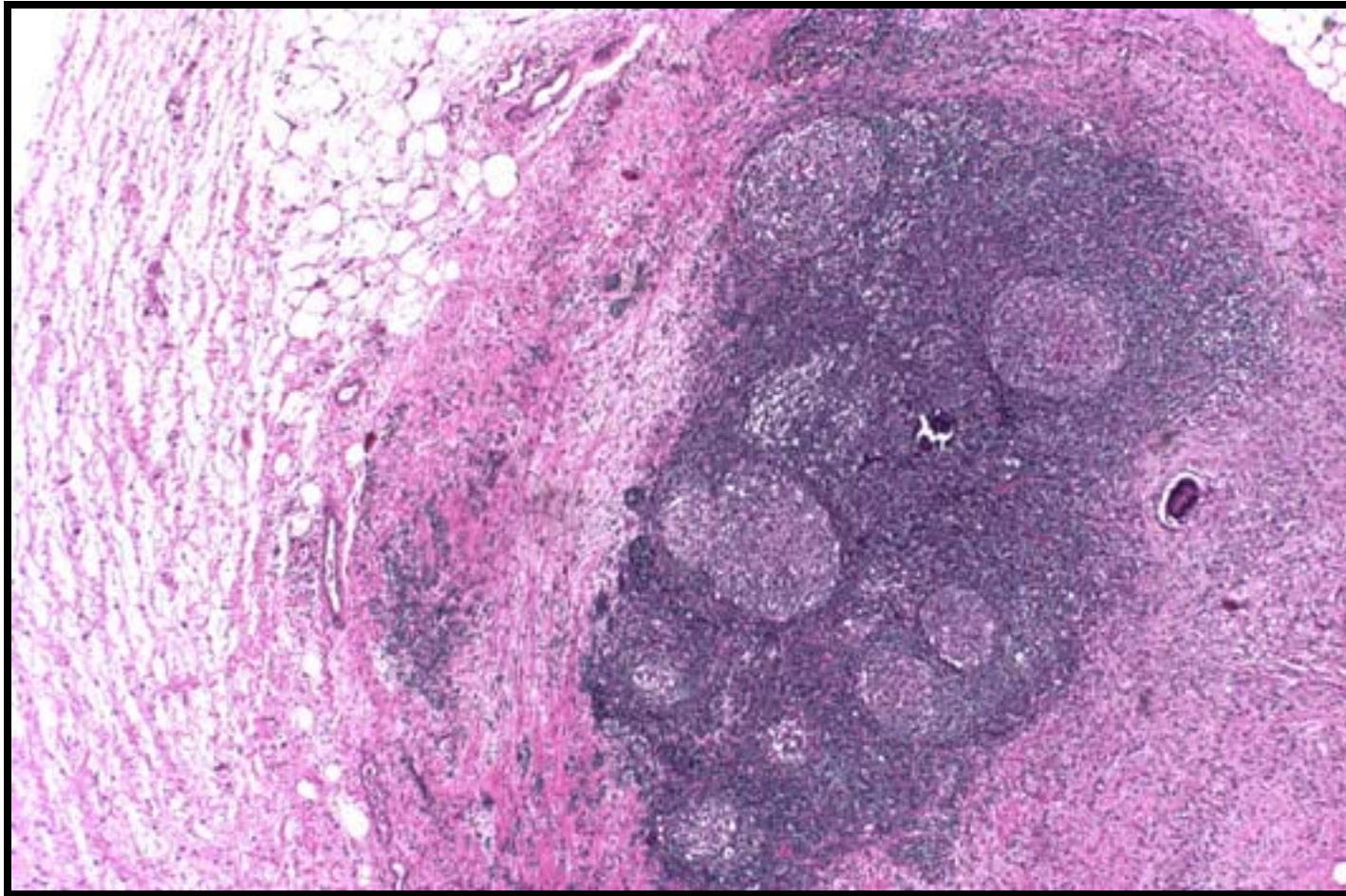
pN Issues: What Counts as a Metastasis?

⌘ Isolated Tumor Cells (Micrometastasis)

- ☒ Single tumor cells or minute clusters of tumor cells
- ☒ Seen on H&E or IHC: measure ≤ 0.2 mm in diameter
- ☒ Detected only by special studies
- ☒ Classified as **pN0**(i+) or (mol+) / pM0 (i+) or (mol+)

⌘ To date, no definitive data to show that micrometastasis discriminates between high- and low-risk in node-negative disease (routine histology)

pN Issues: What Counts as a Metastasis?



Margin Issues: Transverse Margins



- ⌘ Transverse margins: To sample or not to sample?
 - ☒ Anastomotic recurrence rare if ≥ 5 cm
 - ☒ Royal College of Pathologists (UK) guidelines:
 - No histology required for margins >3 cm
 - ☒ Distal margin of 2 cm proven adequate for LAR
 - 1 cm often adequate for T1 and T2 tumors

Margin Issues: CRM



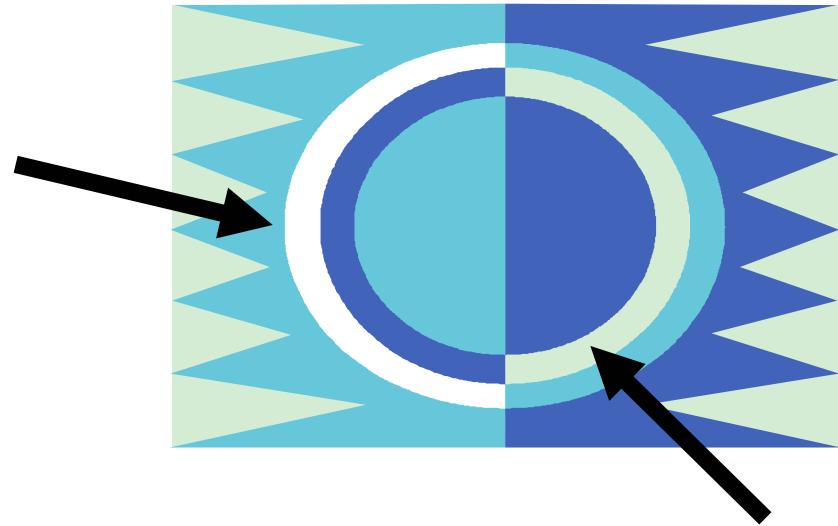
- ⌘ Circumferential (radial) resection margin (CRM)
 - ☒ Soft tissue (adventitial) margin
 - ☒ Non-peritonealized surface
- ⌘ In colorectum, pertinent to:
 - ☒ Rectum
 - ☒ Right colon
 - ☒ Left colon

Margin Issues: CRM

Not all surface involvement is created equal

Non-serosal surface: + CRM

- ☒ Tumor classified as T3
- ☒ Resection considered incomplete (R1/R2)



Serosa with “perforation”

- ☒ Tumor classified as T4
- ☒ Resection considered complete

Margin Issues: CRM in Rectal Cancer



- ⌘ CRM is a critical factor in predicting local recurrence
- ⌘ Multivariate analyses in rectal cancer:
 - ☒ Chan et al, 1985
 - ☒ Quirke et al, 1986
 - ☒ Quirke & Scott, 1992
 - ☒ Adam et al, 1994
 - ☒ Stocchi et al, 2001
 - ☒ Nagtegaal et al, 2002
- ⌘ Colon cancer:
 - ☒ Petersen et al, 2002

Margin Issues: CRM in TME



- ⌘ Total mesorectal excision (TME): sharp dissection of mesorectal envelop
- ⌘ The surgeon as risk factor
 - ☒ Untrained in TME, local recurrence 25-45%
 - ☒ Trained in TME, local recurrence <7%

Margin Issues: CRM in TME

- ⌘ Even with TME, CRM predicts LR and OS
 - ⌘ Stage III disease: CRM and LR
 - ☒ Clearance 0-1 mm: LR risk 16% (“positive”)
 - ☒ Clearance >2 mm: LR risk 6%
 - ☒ Clearance of 1-2 mm: risk intermediate
 - ⌘ CRM and Survival
 - ☒ Relative risk 2.3 with CRM \leq 1 mm
 - ☒ Relative risk 1.0 with CRM >1 mm
 - ☒ Difference in RR is comparable to that of stage III vs. I/II
- Nagtegaal et al, Am J Surg Pathol 2002

Margin Issues: CRM



⌘ Despite overriding importance of CRM in rectal cancer, CRM was reported in **only 21%** of cases in NCCTG rectal cancer treatment trial conducted between 1979 and 1992.

- Stocchi et al, 2001

Margin Issues: CRM in TME



Complete/near complete TME vs incomplete TME
judged by **gross exam** predicts local recurrence,
distant metastasis, and (apparently thus far) survival.

- Nagtegaal et al, JCO 2002

The Quality of the TME Specimen



⌘ Incomplete

- ☒ Little bulk to mesorectum
- ☒ Defects in mesorectum down to muscle wall
- ☒ On transverse sectioning – very irregular CRM

⌘ Nearly Complete

- ☒ Moderate bulk to mesorectum
- ☒ Surface defects >5 mm but none to muscle
- ☒ No muscle visible except at insertion of levators

The Quality of the TME Specimen



⌘ Complete

- ☒ Intact bulky mesorectum with smooth surface
- ☒ Minor irregularities of mesorectal surface
- ☒ No surface defects > 5 mm in depth
- ☒ No coning towards distal margin
- ☒ On transverse sectioning – smooth CRM

The Quality of the TME Specimen



Poor surgery
little mesorectum



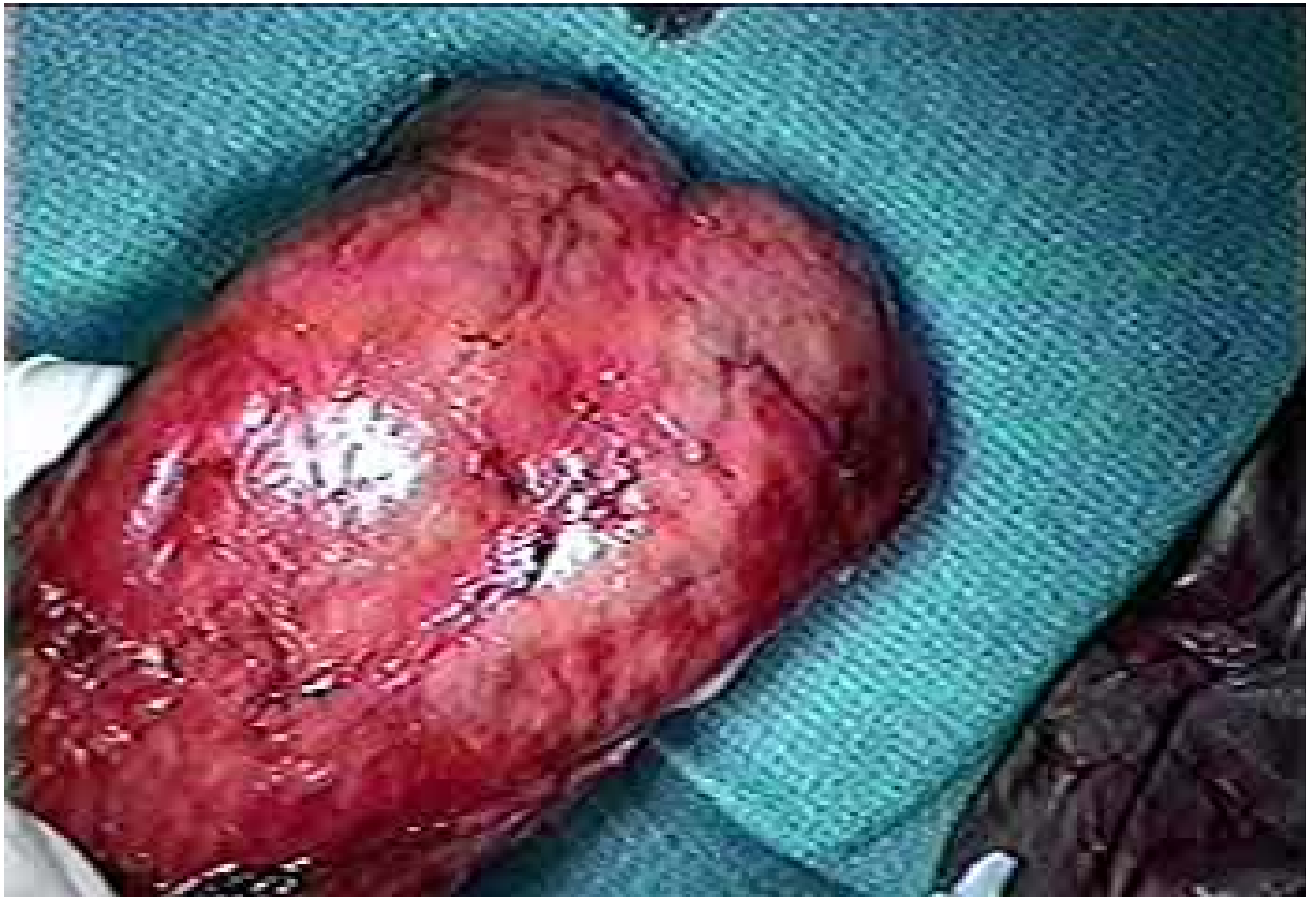
Average surgery with
incomplete removal of
mesorectum



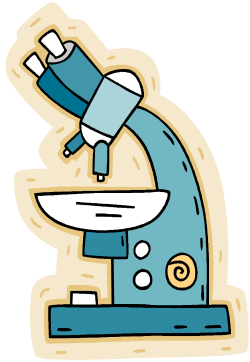
Excellent surgery with
complete mesorectal
excision

The Quality of the TME Specimen

⌘ Excellent surgery: Jose Guillem, MD, MSKCC



The Triumph of Low Tech



⌘ Needed infrastructure

☑ Microscope

☑ Eyeballs

☑ Ruler

☑ Brain

