Malignant colonic polyps – An update on pathology parameters

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Disclosure

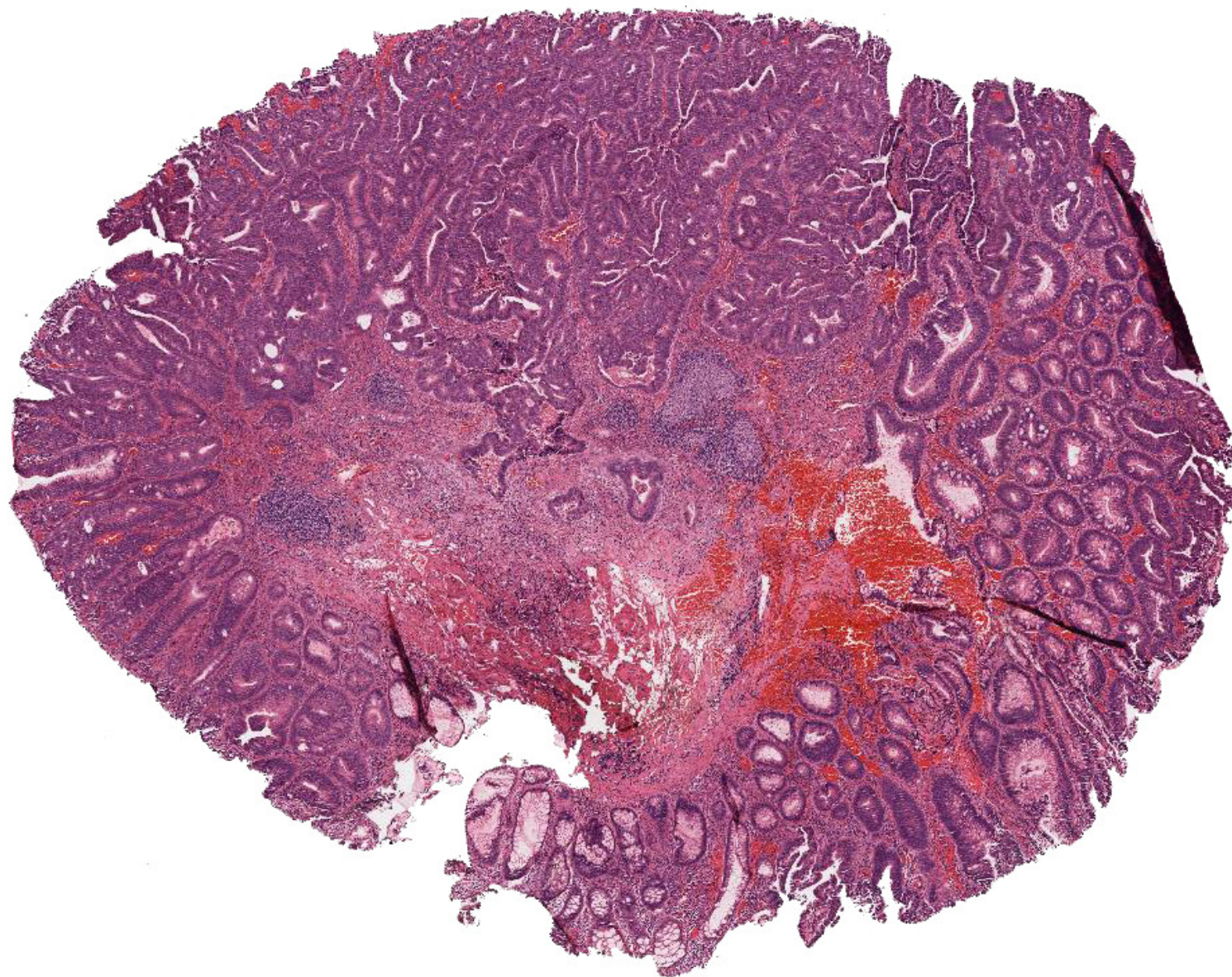No relevant financial relationship with commercial interest to disclose.

Outline

-Discuss the pathological hallmarks of malignant polyps

-Review 'high risk features' for regional lymph nodes metastasis

-Discuss tumour budding

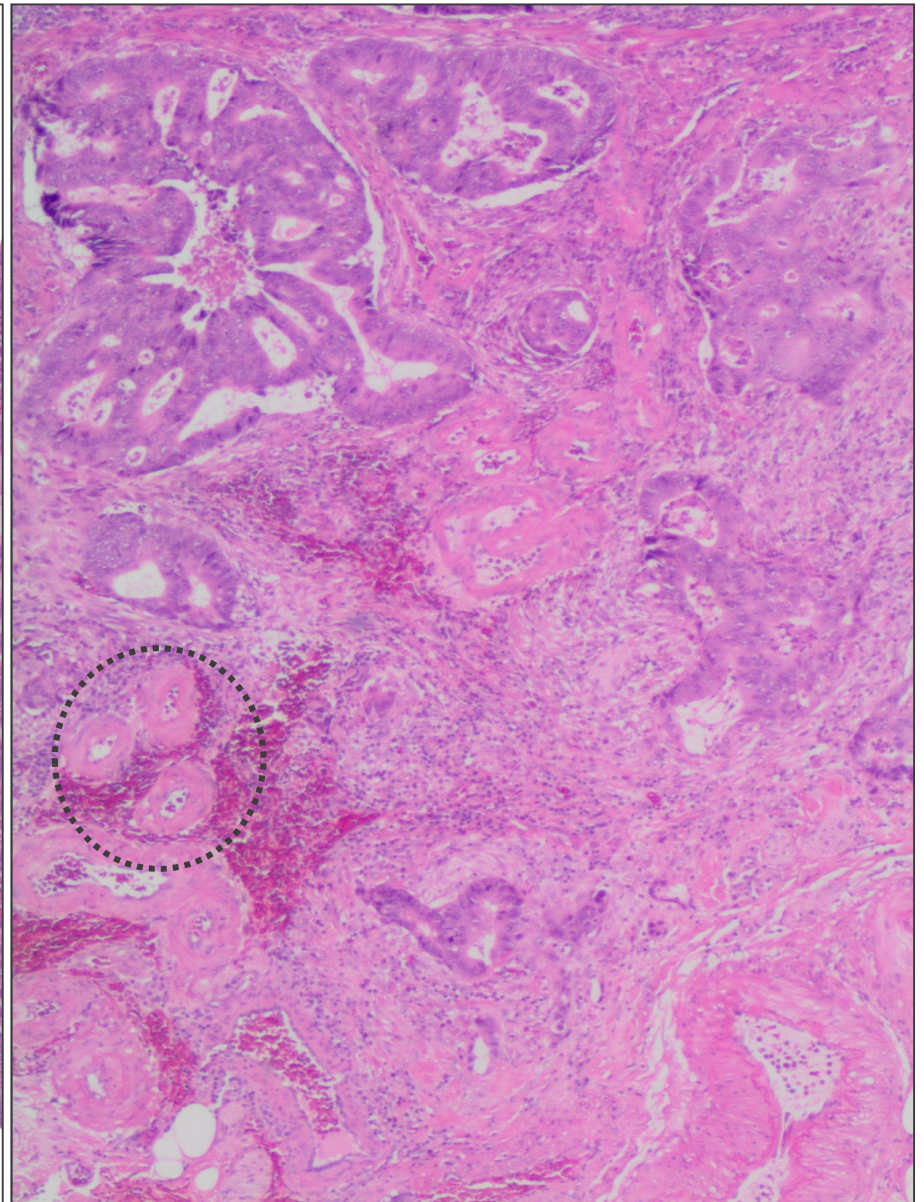-Review current state of pathology reporting for malignant polyps in BC
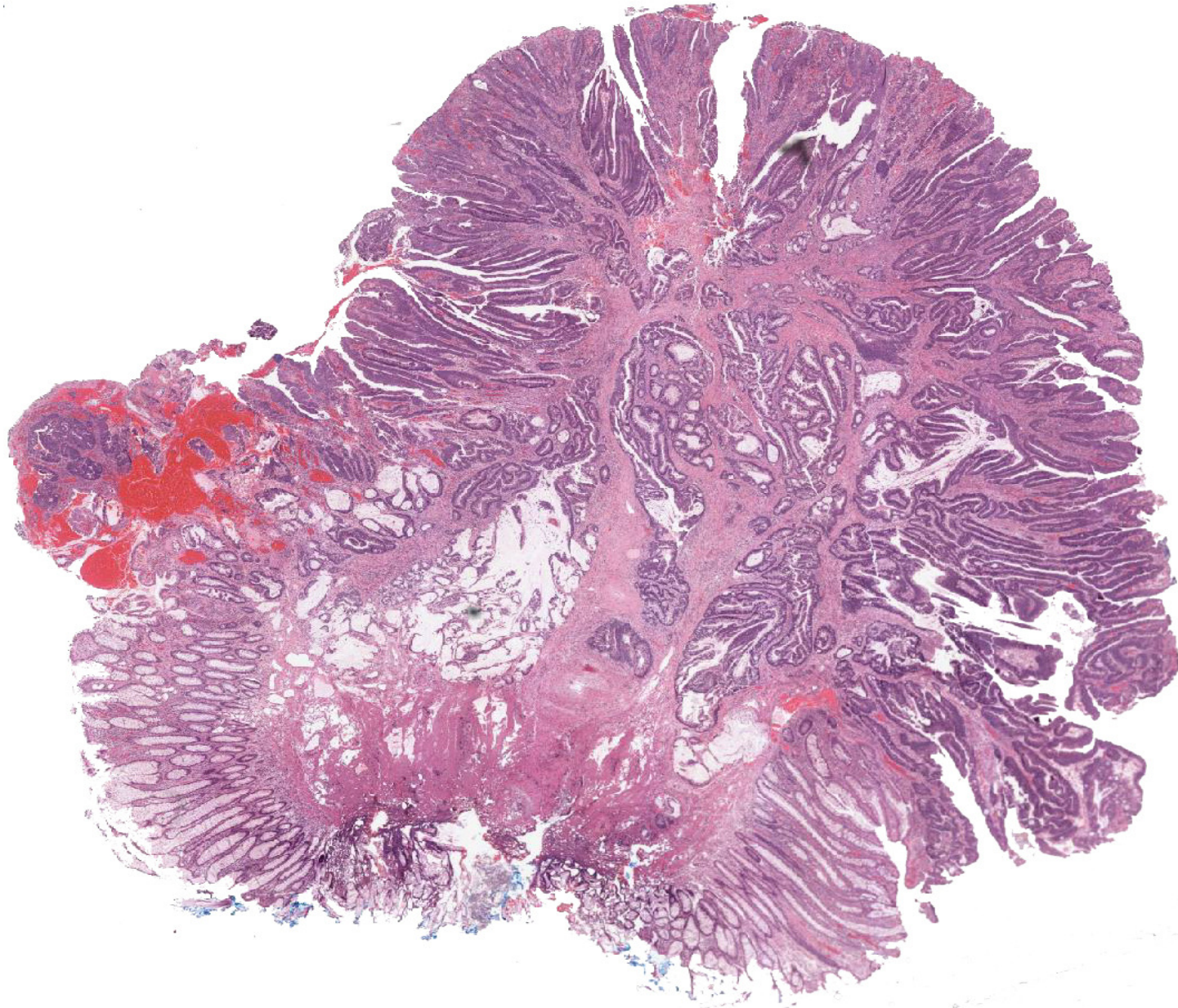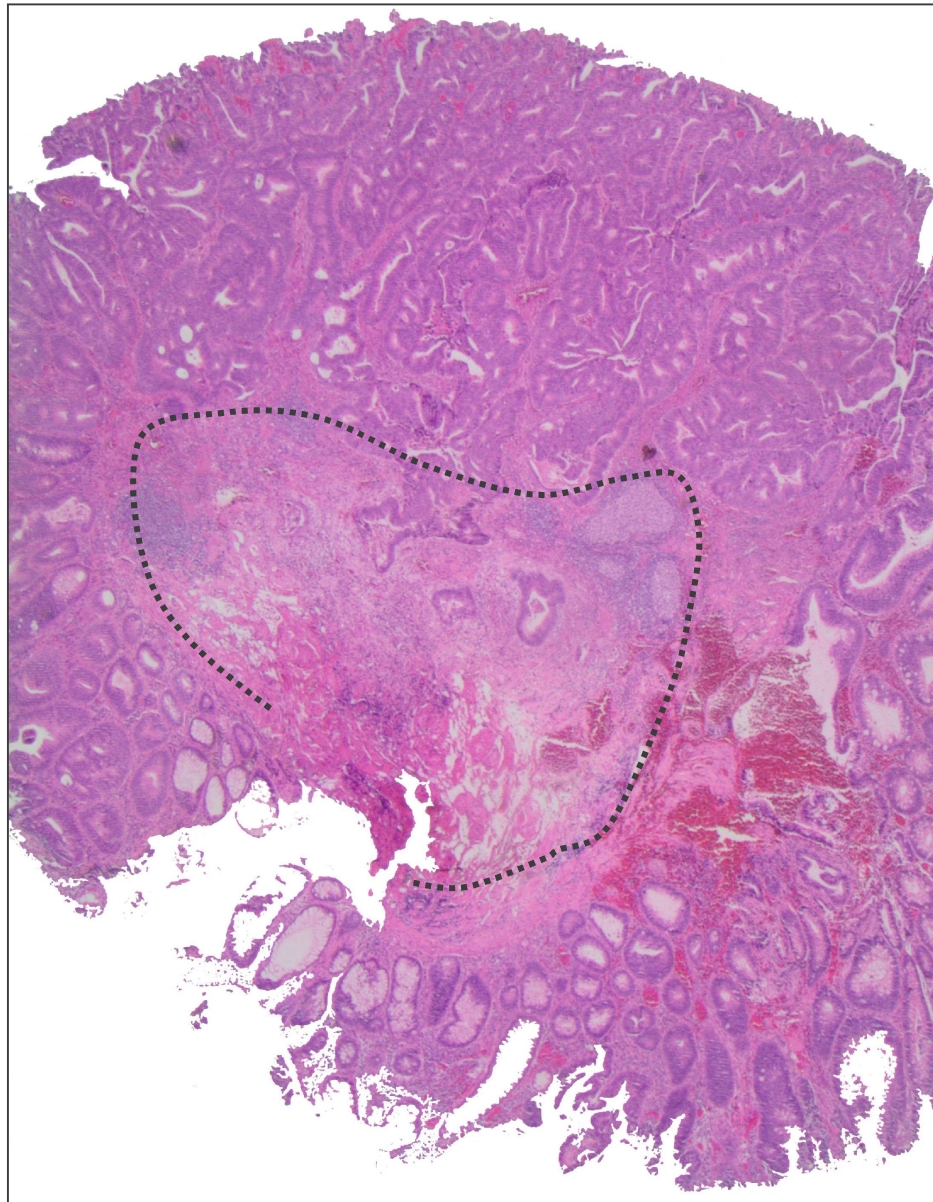
Follow the muscularis mucosae and check for infiltrative pattern of tumor adjacent to submucosal vessels and desmoplasia
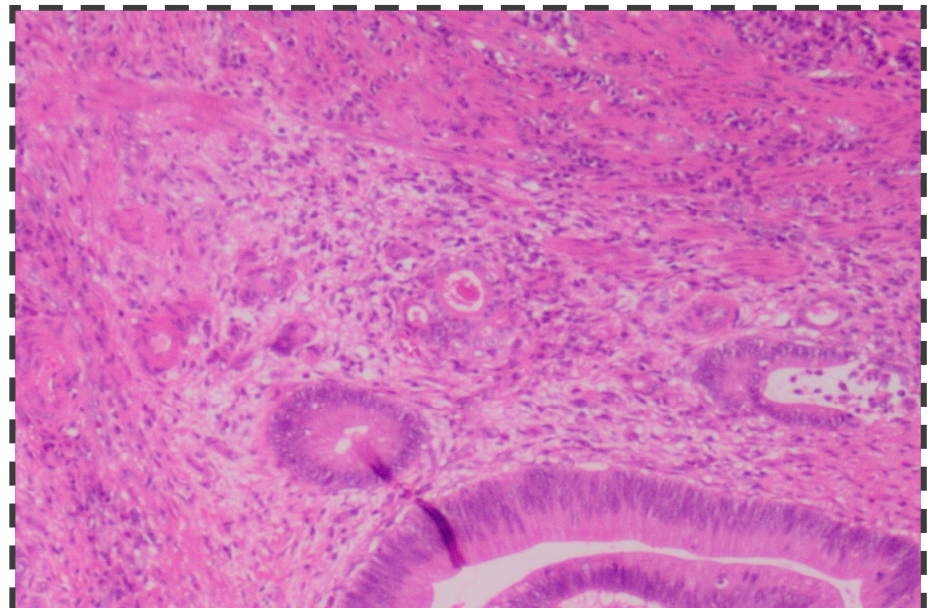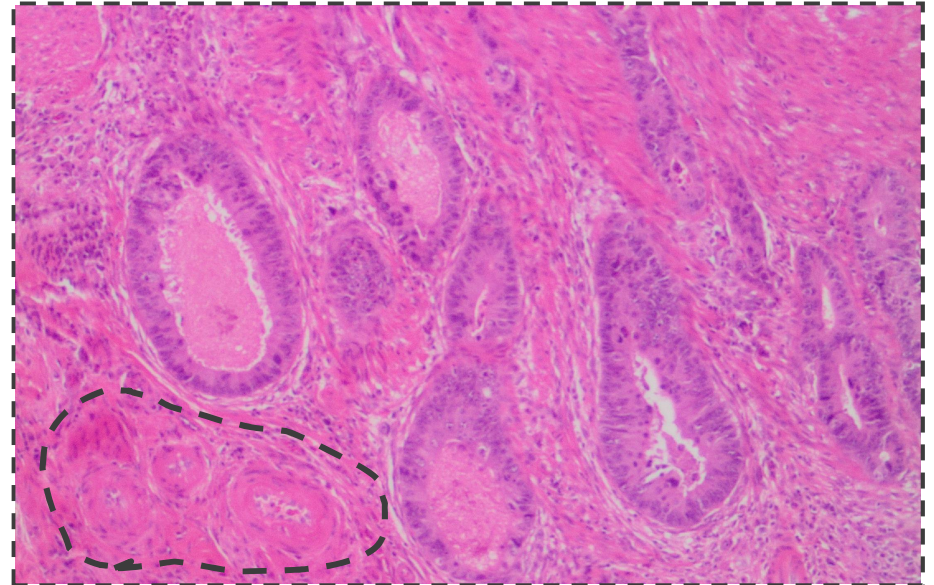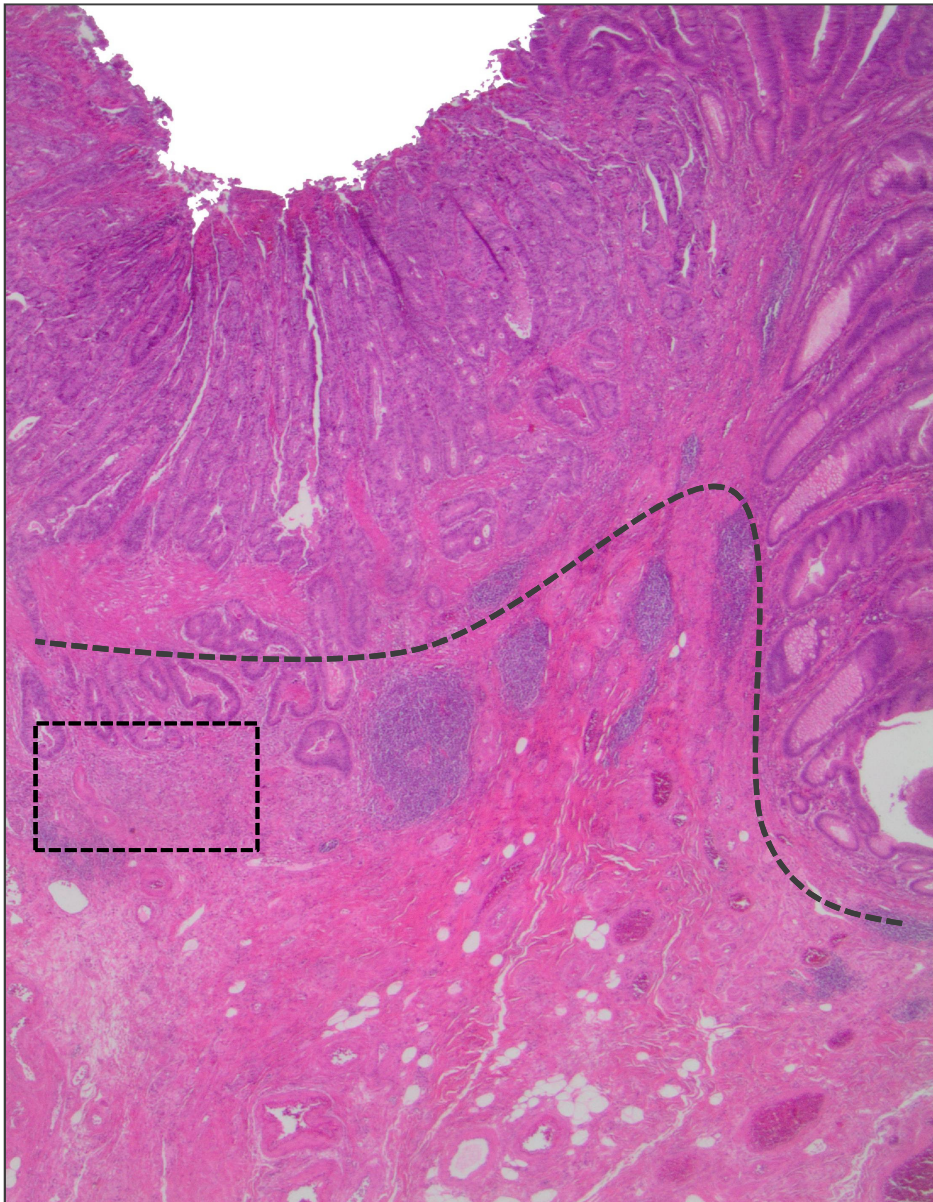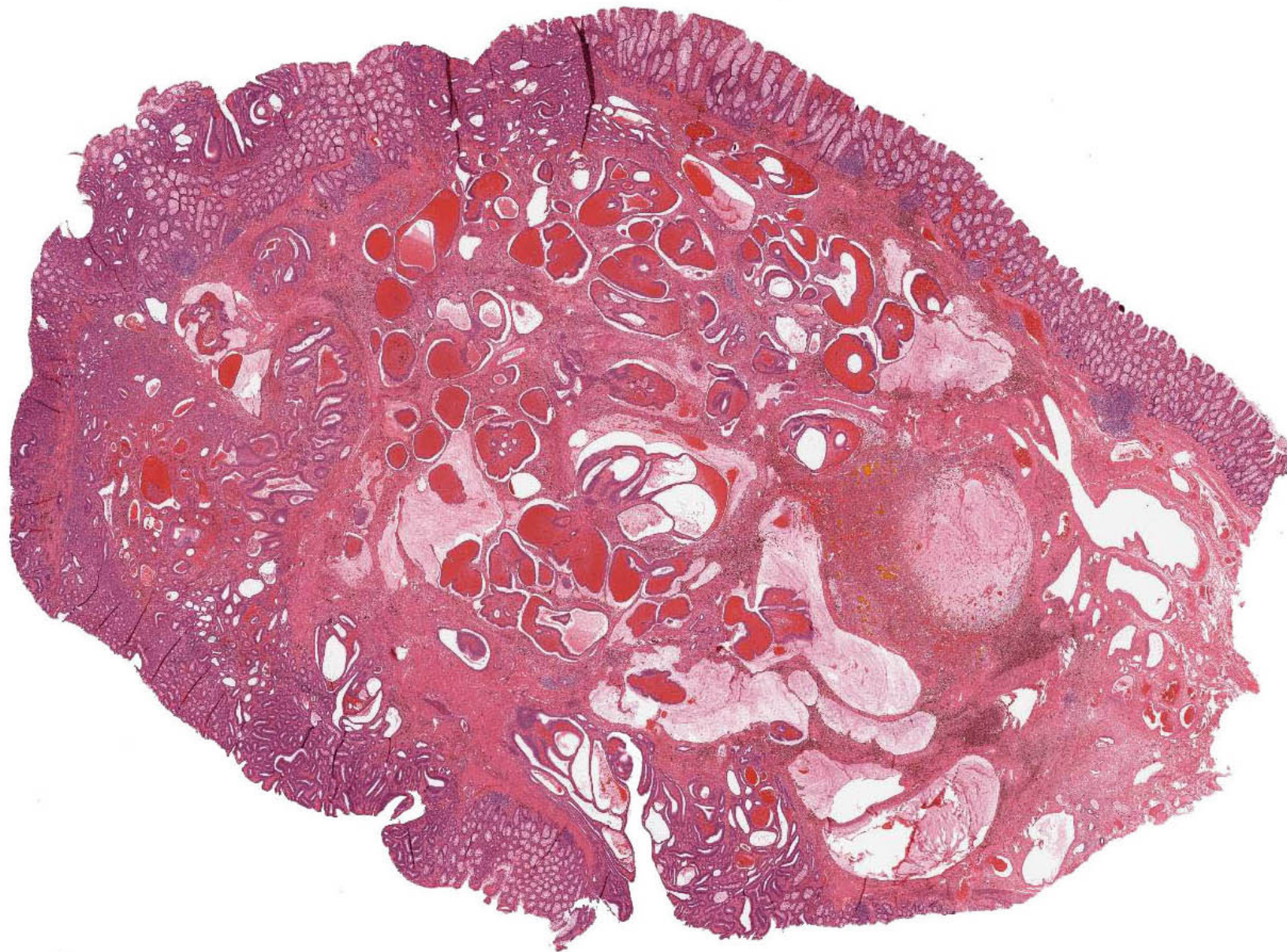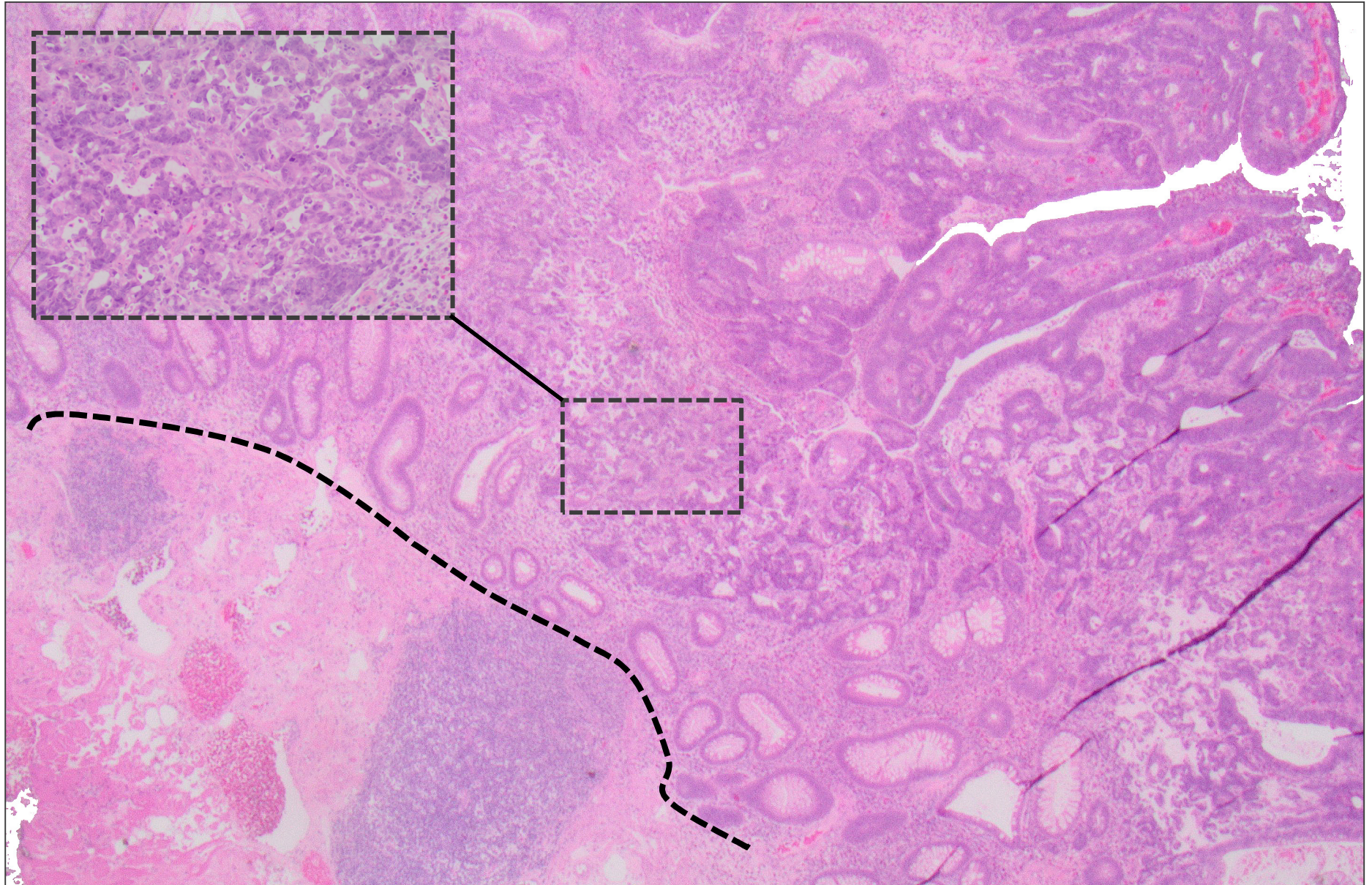
Challenging pathologic parameters in malignant colonic polyps – *and why you should care!*

Management of malignant polyps: *resect or not resect ?*
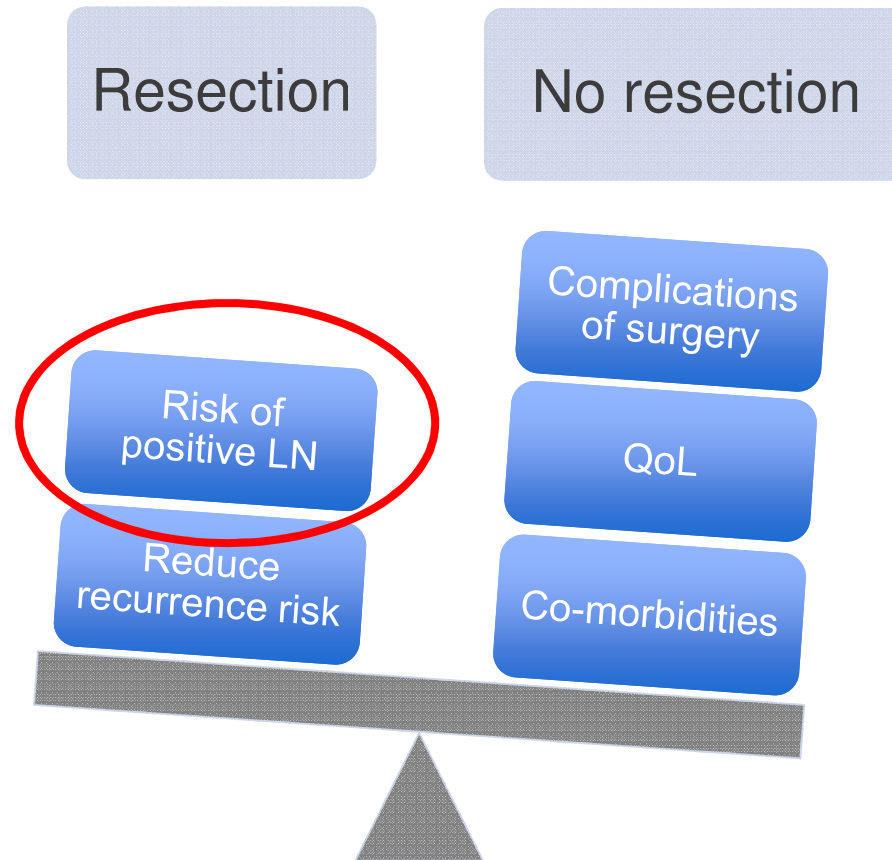
Does the risk of surgery outweigh the risk of metastatic disease?

Does one need to measure the depth of invasion?
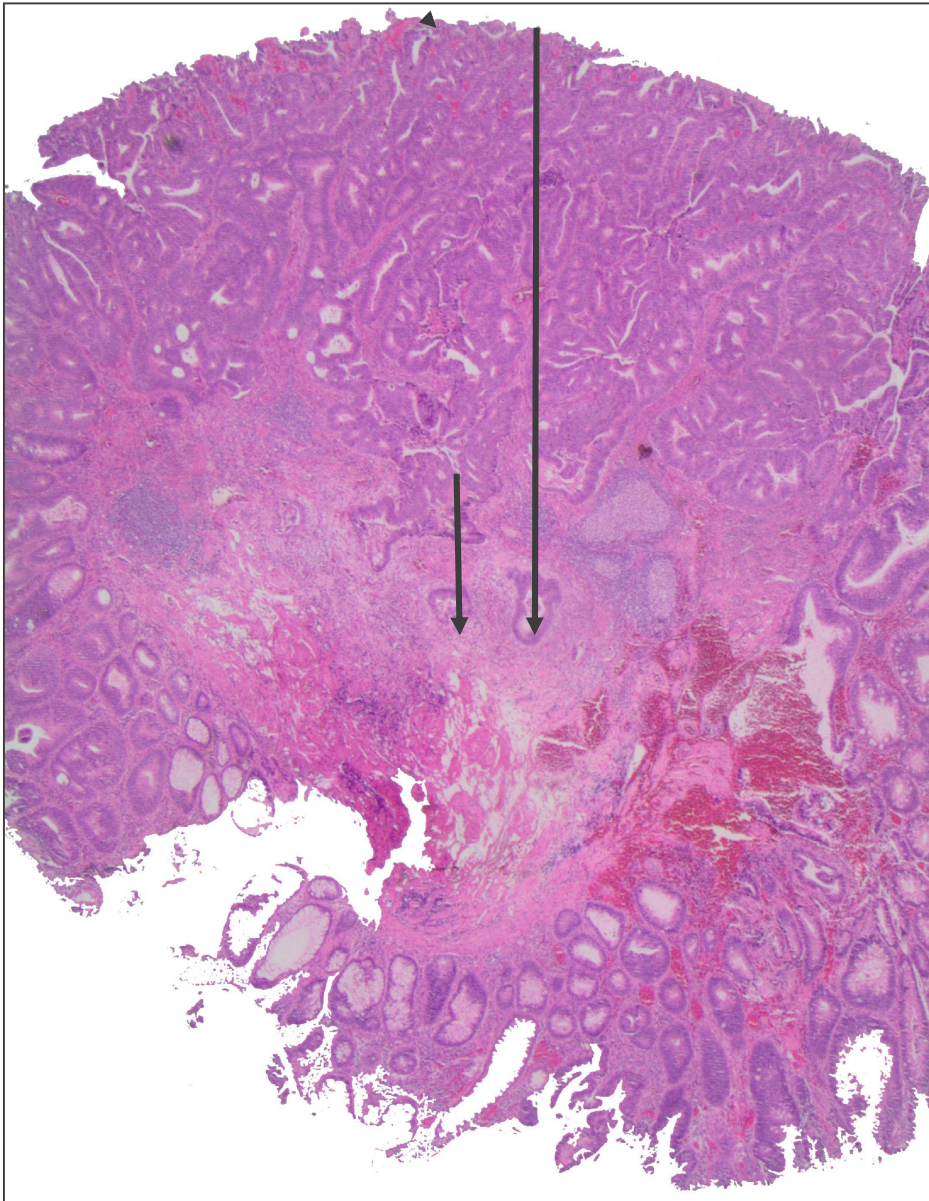
Mentioned in several European and Japanese guidelines:
- Is this criterion alone sufficient for subsequent resection?
- Where does one measure from?
- The tumour often obscures the MM as a starting point.
- Is deeper worse?

Depth of invasion and associated rLN involvement

Depth of submucosal invasion	# of cases	Nodal involvement
< 500 µm	23	0
500 – 1000 µm	15	1 (7%)
1000 – 2000 µm	38	2 (5%)
2000 – 3000 µm	61	11 (18%)
3000 – 4000 µm	45	5 (11%)
4000 – 5000 µm	31	6 (19%)
> 5000 µm	38	8 (21%)

The odds ratio of regional nodal involvement was 5.0 (range 1.5-17.0) at a threshold of 2 mm for tumour depth.

Ueno et al. Gastroenterology 2004 127:385-394

Width of invasive component

0.6 cm
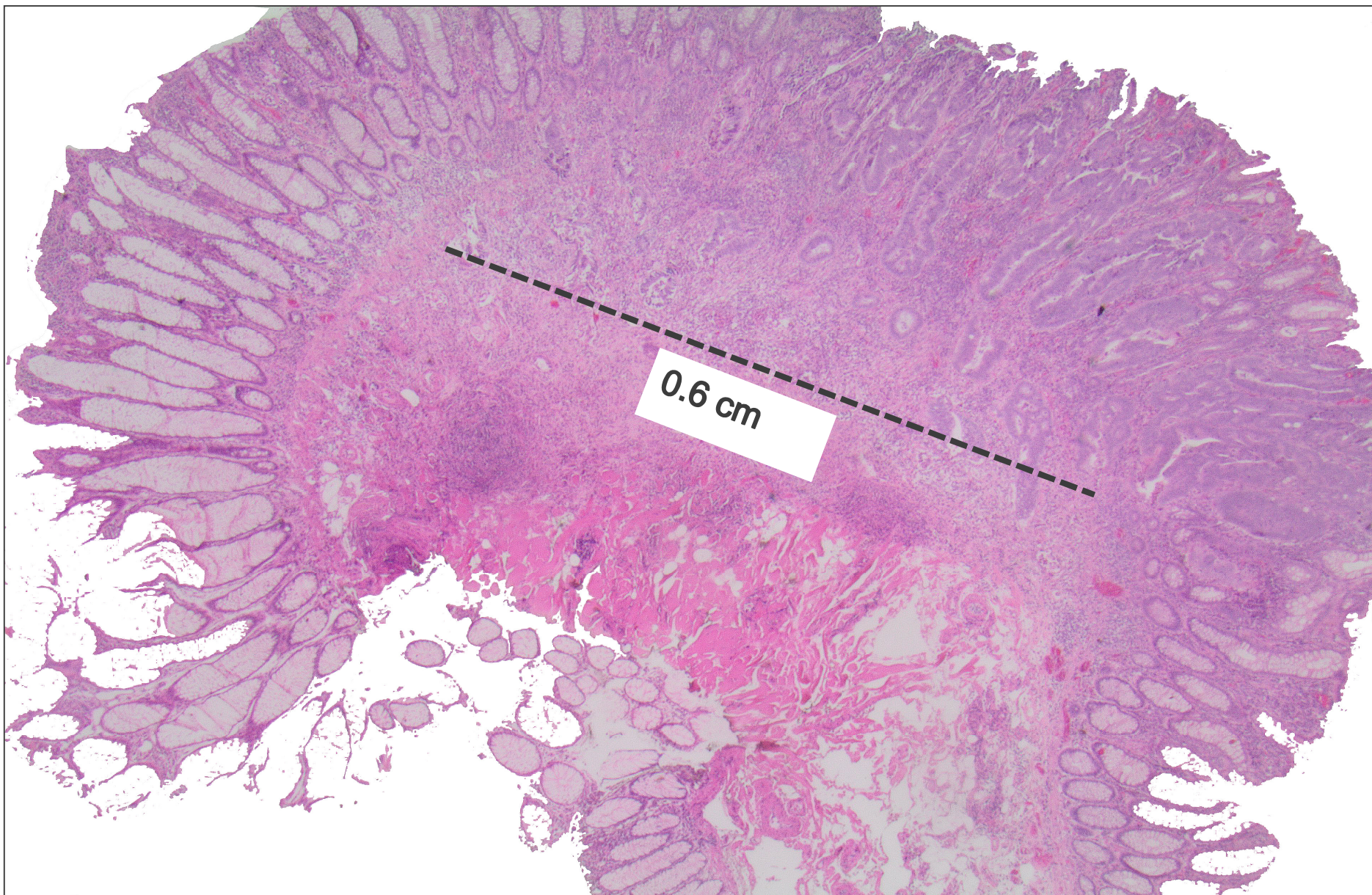
Width of invasion and associated rLN involvement

Width of submucosal invasion	# of cases	Nodal involvement
< 2000 µm	35	0
2000 ≤ X < 3000 µm	22	1 (4.5%)
3000 ≤ X < 4000 µm	24	1 (4.2%)
4000 ≤ X < 5000 µm	19	4 (21.1%)
5000 ≤ X < 6000 µm	23	4 (17.4%)
6000 ≤ X < 7000 µm	10	2 (20%)
7000 ≤ X < 8000 µm	26	4 (15.4%)
> 8000 µm	92	17 (18.5%)

The odds ratio of regional nodal involvement was 5.0 (range 4.5-21.1) at a threshold of 4 mm for tumour width.

Ueno et al. Gastroenterology 2004 127:385-394

Width of invasive component: *? interobserver variability*

The Ueno method for substaging pT1 colorectal adenocarcinoma by depth and width measurement: an interobserver study

L. M. Wang*, R. Guy†, E. Fryer*, C. Kartsonaki‡, P. Gill*, C. Hughes*, A. Szuts*, R. Perera*, R. Chetty* and N. Mortensen†

*Department of Cellular Pathology, John Radcliffe Hospital, University of Oxford, Headington, Oxford, UK, †Department of Colorectal Surgery, Churchill Hospital, University of Oxford, Headington, Oxford, UK and ‡CR-UK/MRC Oxford Institute for Radiation Oncology, Department of Oncology, John Radcliffe Hospital, University of Oxford, Headington, Oxford, UK

- 70 consecutive pT1 polyp CRCs assessed for depth and width of invasion.
- High risk if depth ≥ 2 mm or a width ≥ 4 mm
- The ICC for the 60-polyp CRCs was 0.67 for depth and 0.37 for width.

ORIGINAL CONTRIBUTION

Area of Submucosal Invasion and Width of Invasion Predicts Lymph Node Metastasis in pT1 Colorectal Cancers
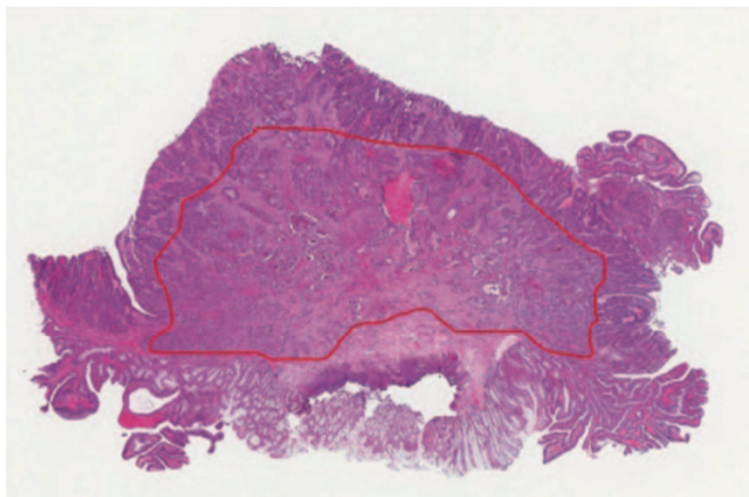

Figure 3. An example of measurement of the area of submucosal invasion within a lesion (contained within the red area). The estimated area of submucosal invasion is 41.42 mm². The site of the destroyed muscularis mucosae has been estimated.
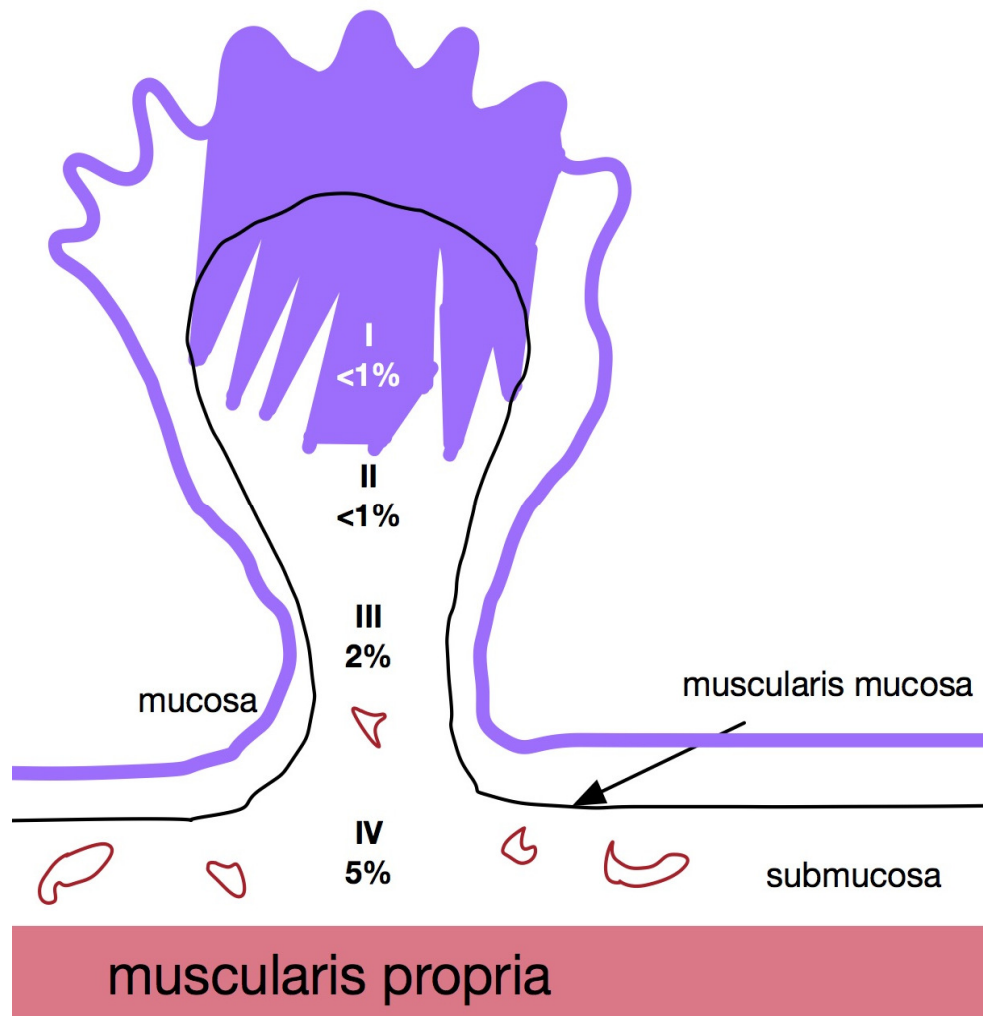
Table 2. Multivariate analysis of quantitative and qualitative factors for lymph node metastasis

Factor	LNM positive (n = 19), n (%)	Model 1				Model 2			
		OR	Lower 95% CI	Upper 95% CI	p	OR	Lower 95% CI	Upper 95% CI	p
Width of carcinoma									
<11.5 mm (n = 101)	2 (10.5)	12.12	2.19	67.23	0.004	***	***	***	***
≥11.5 mm (n = 106)	17 (89.5)								
Area of submucosal invasion of carcinoma									
<35 mm² (n = 102)	1 (5.3)	***	***	***	***	22.44	2.7	186.63	0.004
≥35 mm² (n = 105)	18 (94.7)								
Vascular invasion									
Yes (n = 9)	3 (15.8)	3.74	0.681	20.49	0.13	7.81	1.16	52.51	0.04
No (n = 198)	16 (84.2)								
Lymphatic invasion									
Yes (n = 7)	3 (15.8)	12.23	1.57	95.23	0.02	8.36	1.19	58.99	0.03
No (n = 200)	16 (84.2)								
Grade of differentiation									
Nonpoor (n = 198)	14 (73.7)	28.53	4.04	201.34	0.001	20.51	2.98	141.15	0.002
Poor (n = 9)	5 (26.3)								

Model 1 represents the analysis when the width of carcinoma ≥11.5 mm was tested with other qualitative factors. Model 2 represents the analysis when the area of submucosal invasion ≥35 mm² was tested with other qualitative factors. p values for this multivariate analysis were obtained by using logistic regression analysis.
LNM = lymph node metastasis.
***Denotes values that were not tested within the respective models.

Toh EW et al. Dis Colon Rectum 2015; 58: 393–400

I
<1%

II
<1%

III
2%

mucosa

muscularis mucosa

IV
5%

submucosa

muscularis propria

You need proper orientation!

Ueno et al. Gastroenterology 2004; 127:385-394
Haggitt et al. Gastroenterology 1985; 89(2):328-336
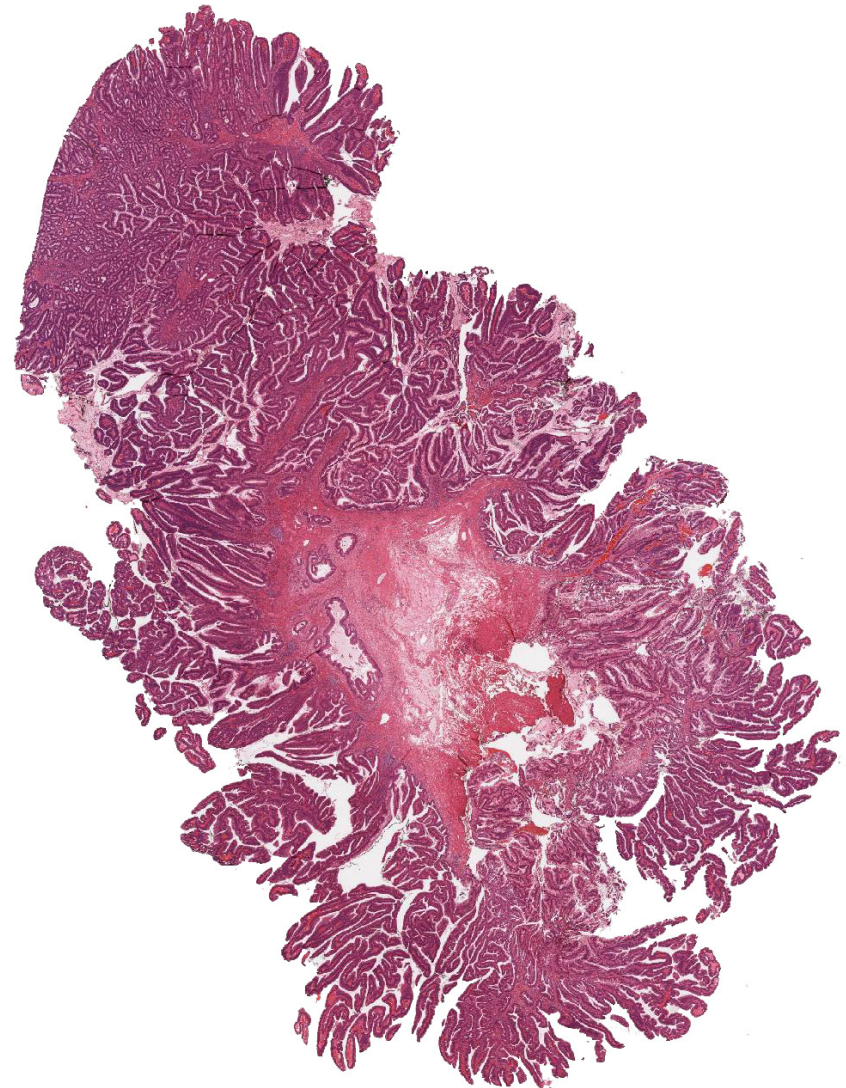
Substaging pT1 – Kikuchi levels for *non-polypoid* lesions

sm1   sm2   sm3

muscularis mucosae

mucosa

submucosa

muscularis propria
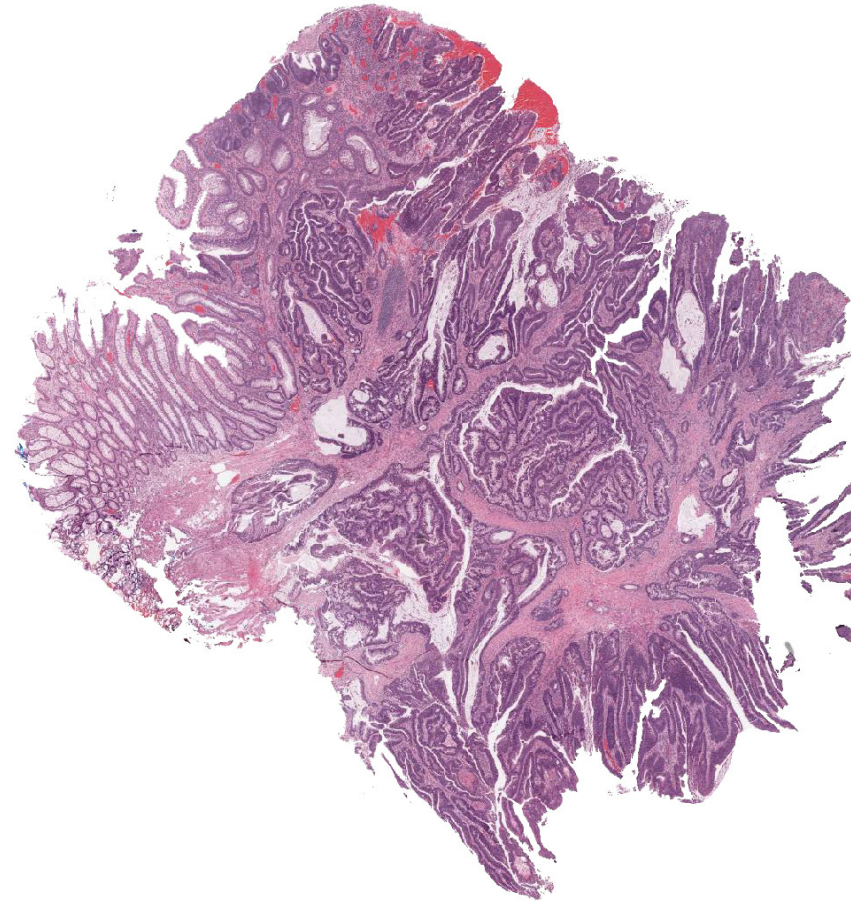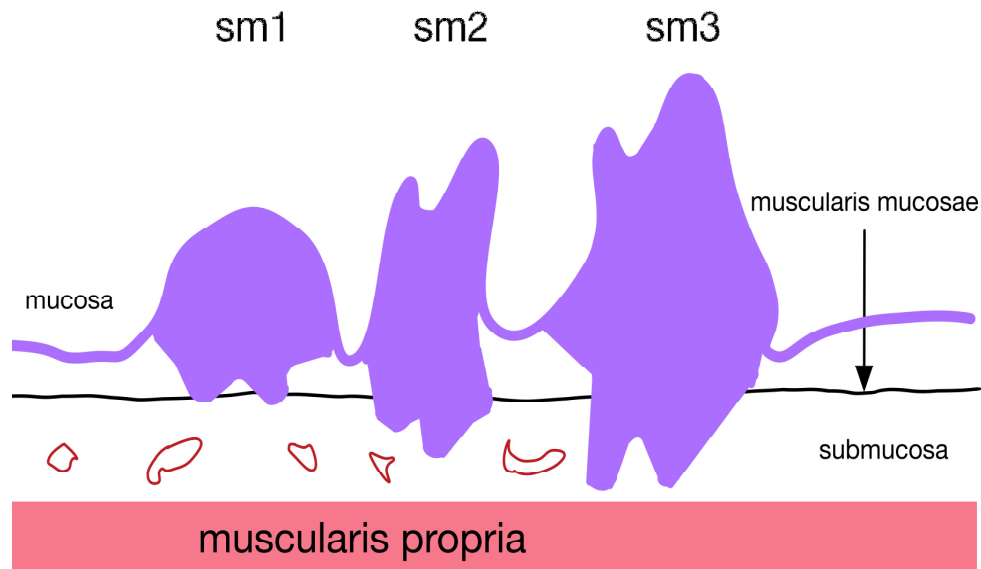
Proper staging requires knowing where the MP is.

Kikuchi et al. Dis Colon Rectum 1995 Dec;38(12):1286-95.

Lymphatic invasion
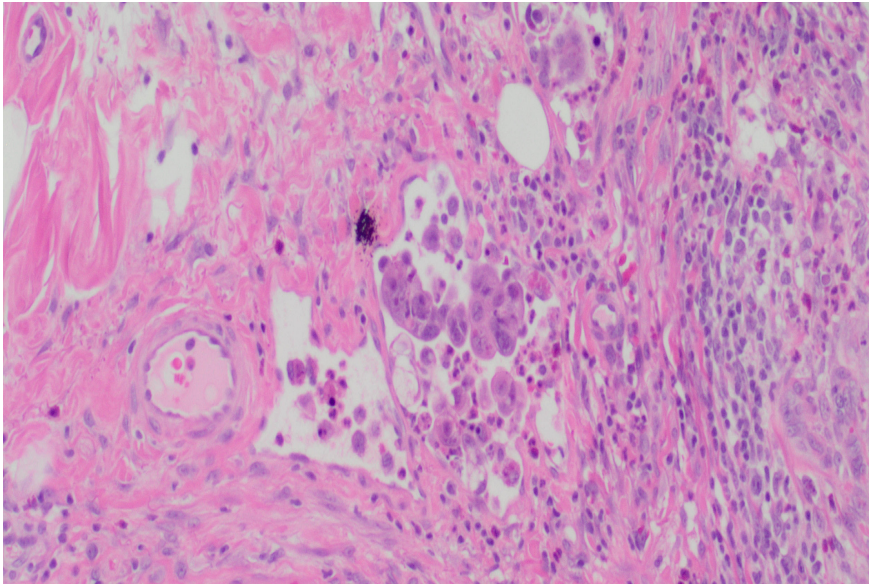
D2-40
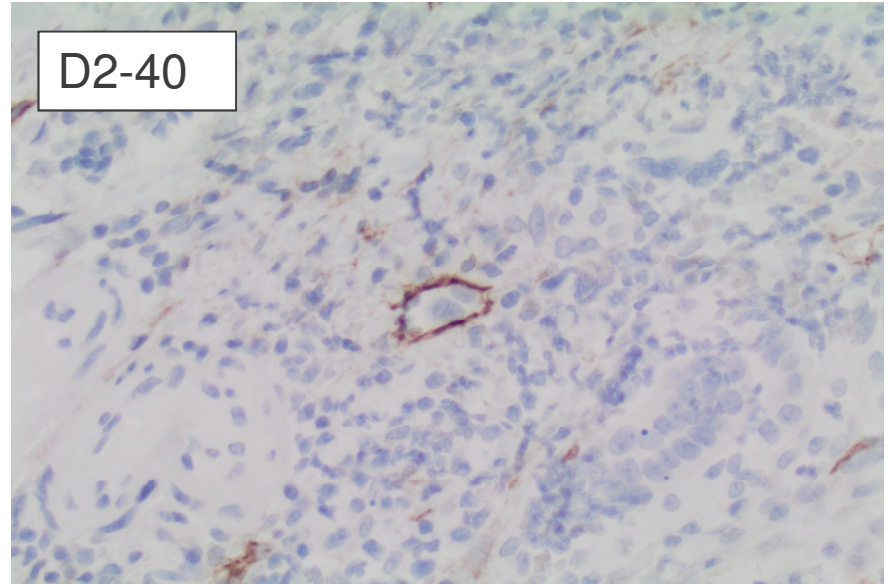
CD34
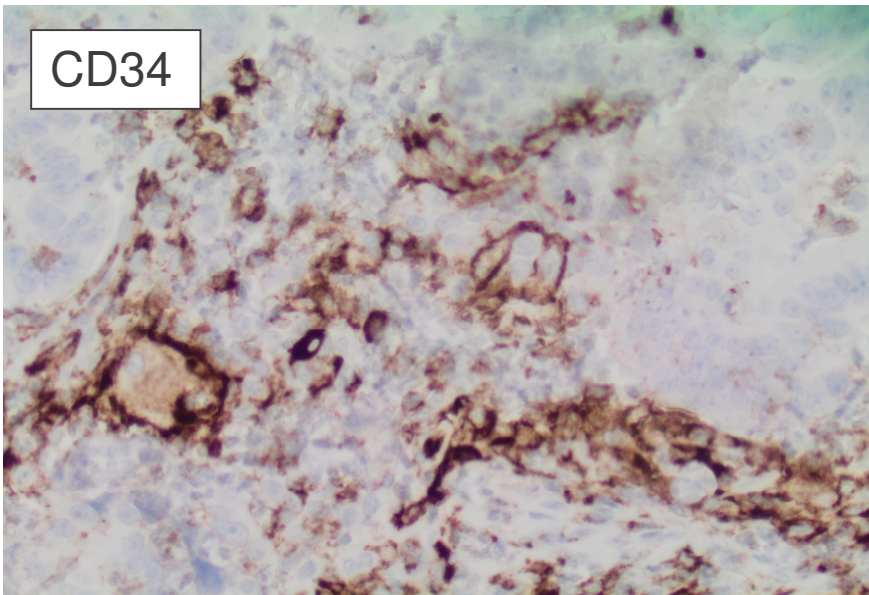
-Lesions called suspicious for vascular invasion tended to behave as though vascular invasion is present
-No routine staining, but will do it on a case by case basis
-Will report suspicious for vascular invasion with a comment.

Lymphatic or vascular invasion – *does the differentiation matter?*

Ishii et al. Int J Colorectal Dis 2009

	n	LN mets	No mets	p-value	Multivariate analysis
L1 (33%)	45	13 (29%)	32 (71%)	0.001	V1 no predictor of rLN
L0 (67%)	91	5 (5%)	86 (95%)		
V1 (25%)	34	3 (9%)	31 (91%)	0.38	
V0 (75%)	102	15 (15%)	87 (85%)		

Tateishi et al. Mod Path 2010

	n	LN mets	No mets	p-value	Multivariate analysis
L1 (24%)	76	25 (33%)	51 (67%)	<0.01	V1 no independent predictor of rLN
L0 (76%)	246	21 (9%)	225 (91%)		
V1 (14%)	45	13 (29%)	32 (71%)	<0.01	
V0 (86%)	277	33 (12%)	244 (88%)		

Lymphatic or vascular invasion – *does the differentiation matter?*
A real world problem !

Rectal polyp:
Invasive adenocarcinoma arising in tubular adenoma (malignant polyp), with unfavorable histology.

Comment:
[…] There is venous invasion by tumor. Venous invasion is predictive of long-term metastasis.

However, […] the case could be made for conservative follow-up with CEA and liver monitoring, as there is no evidence of lymphatic invasion.

2 mm
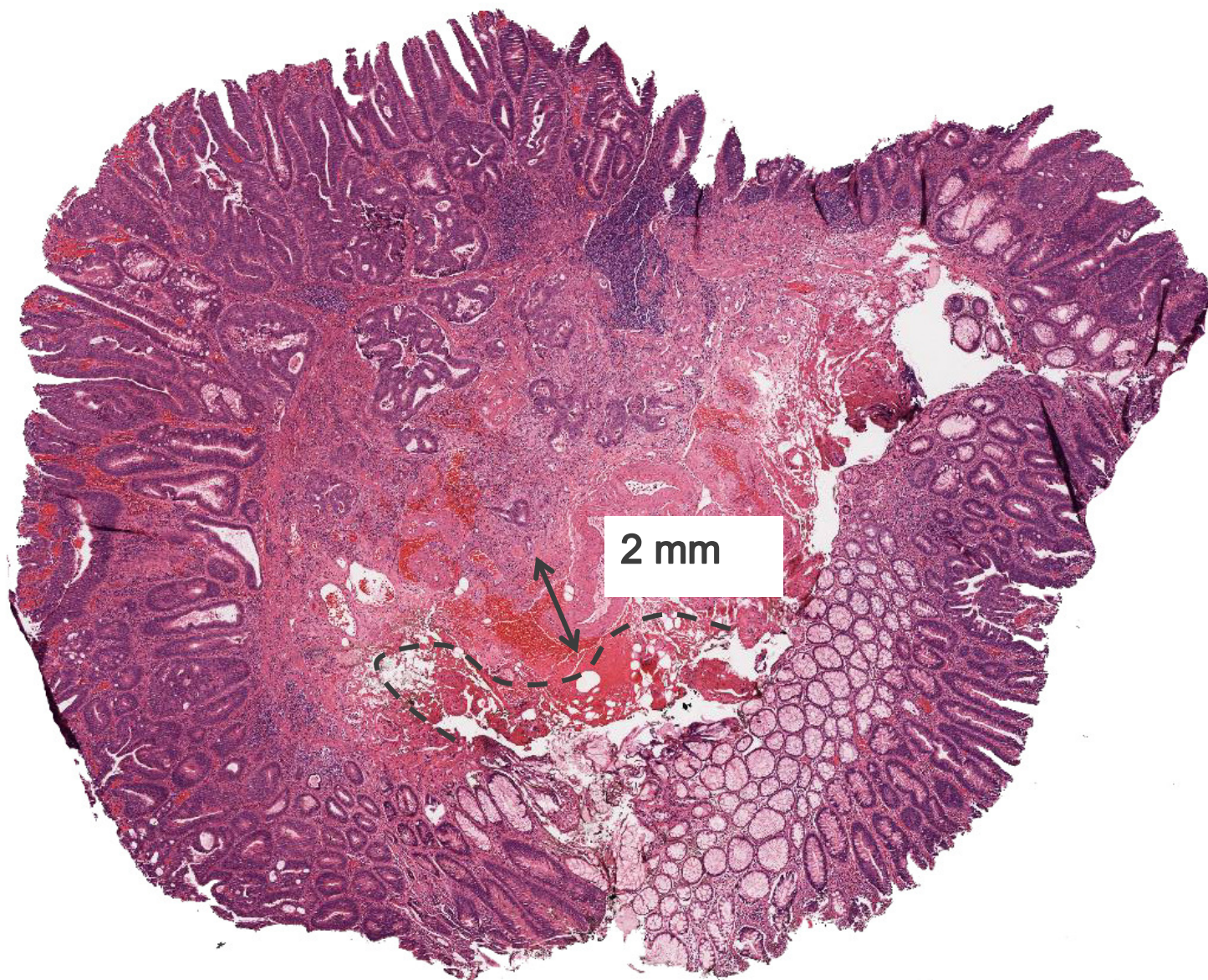
Margin assessment
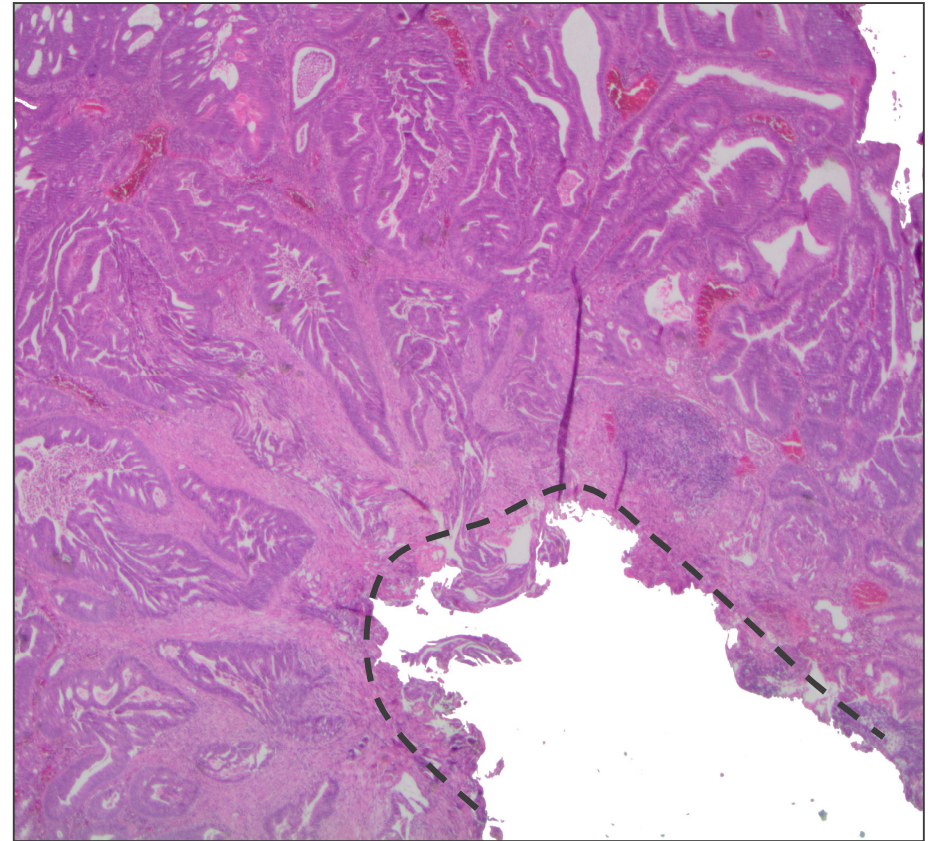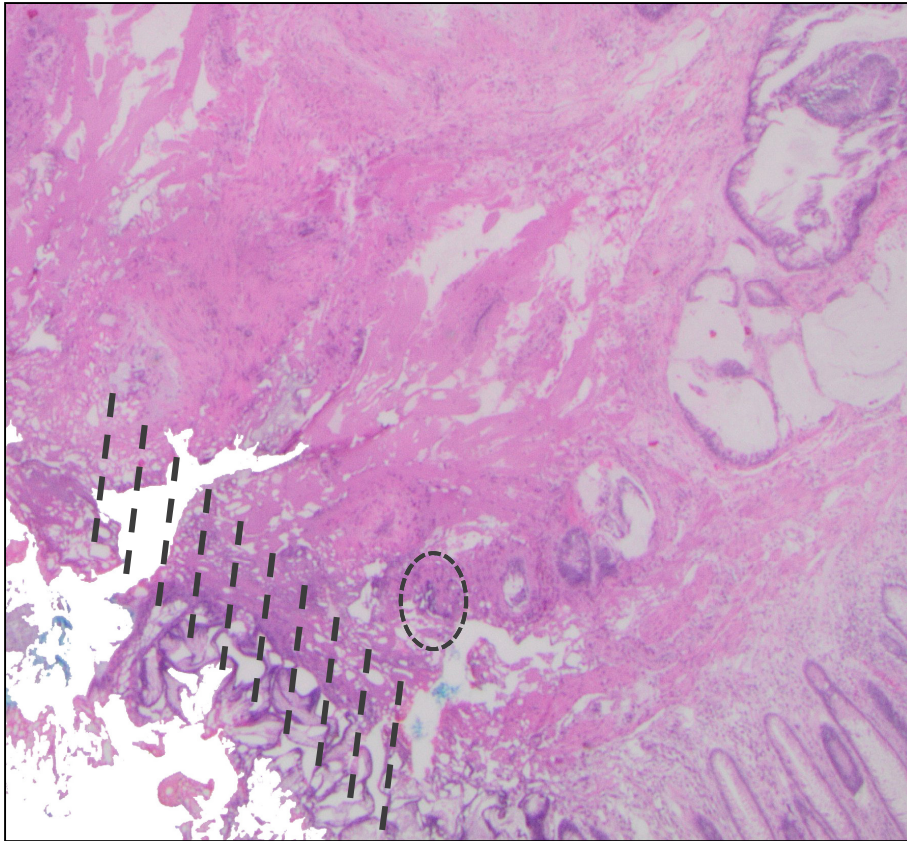
- 1 mm suggested as the cutoff point
- Tumor within cautery = positive margin
- Fragmentation precludes assessment of completeness of excision

Tumor budding at the invasive front

Tumor budding – *a histologic 'snapshot' of EMT*

Tumor center

Increased expression:
uPA (c), Maspin (n), pERK (n), TGF-beta (c), Matrilysin (n), p53 (n), uPAR (m/c)

Decreased expression:
CD8+ T-cells, pAKT (c), syndecan-1 (m)

Molecular factors

Frequent: APC gene mutation

Infrequent: microsatellite instability (MSI) and possibly CpG Isand Methylator Phenotype (CIMP-H)

Tumor centre → front

Increased expression:
EGFR (c/m), β-catenin (n), EphB2-/Bcl2- (c/m,c)

Decreased expression: E-cadherin (m), CD44 (m), CD44v6 (m), CD166 (m), EpCAM (m), APAF-1 (c)

Tumor buds

Increased expression:
MMP-2 (c), MMP-9 (c), CathB (c), CXCL12 (m/c), β-catenin (n), Beta-III-Tubulin (c), hMena (c) Laminin5γ2 (c), p16 (c and n), cyclinD1 (n), ABCG5 (c), CD133 (c)

Decreased expression:
Ki67 (n), E-cadherin (m)

Histological features

Frequent: infiltrating tumour margin, cytoplasmic podia

Infrequent: peritumoral lymphocytic inflammation, tumor infiltrating lymphocytes

Zlobec I, et al., Oncotarget 2010; 1: 651 - 661

Tumor budding – *clinical significance*

Paper	Patients	Results
Ueno 2004 (*Gastro*)	292 Stage I	Independent prognostic factor
Ueno 2004 (*Ann Surg*)	638 Stage II & III	Independent prognostic factor
Wang 2005 (*Dis Colon*)	159 Stage I	10.1% pt with LN-mets
Park 2004 (*Dis Colon*)	109 Stage II & III	(1) 61.5% had ITC (2) degree of TB correlated with ITC
Okuyama 2003 (*Dis Colon*)	196 Stage II	(1) 43.3% of tumors showed budding (2) Significantly associated with LN mets (3) Independent prognostic factor
Tanaka 2003 (*Dis Colon*)	138 Stage II	Only budding associated with recurrence
Okuyama 2003 (*J Surg Onc*)	83 pT3	Lower overall survival (51.8% vs. 85%, $P<0.002$)
Shinto 2006 (*Dis Colon*)	136 Stage II & III	(1) Lymph node mets ($P<0.0001$) (2) High recurrence rate ($P=0.0022$)
Kajiwara 2010 (*Dis Colon*)	244 Stage II	Significant LN met risk
Homma 2010 (*J Surg Oncol*)	65 Stage II	Significant LN mets ($P=0.002$)

Is this tumor budding stuff really going to stay around?

YES!

u^b

UNIVERSITÄT
BERN

April 27–29, 2016
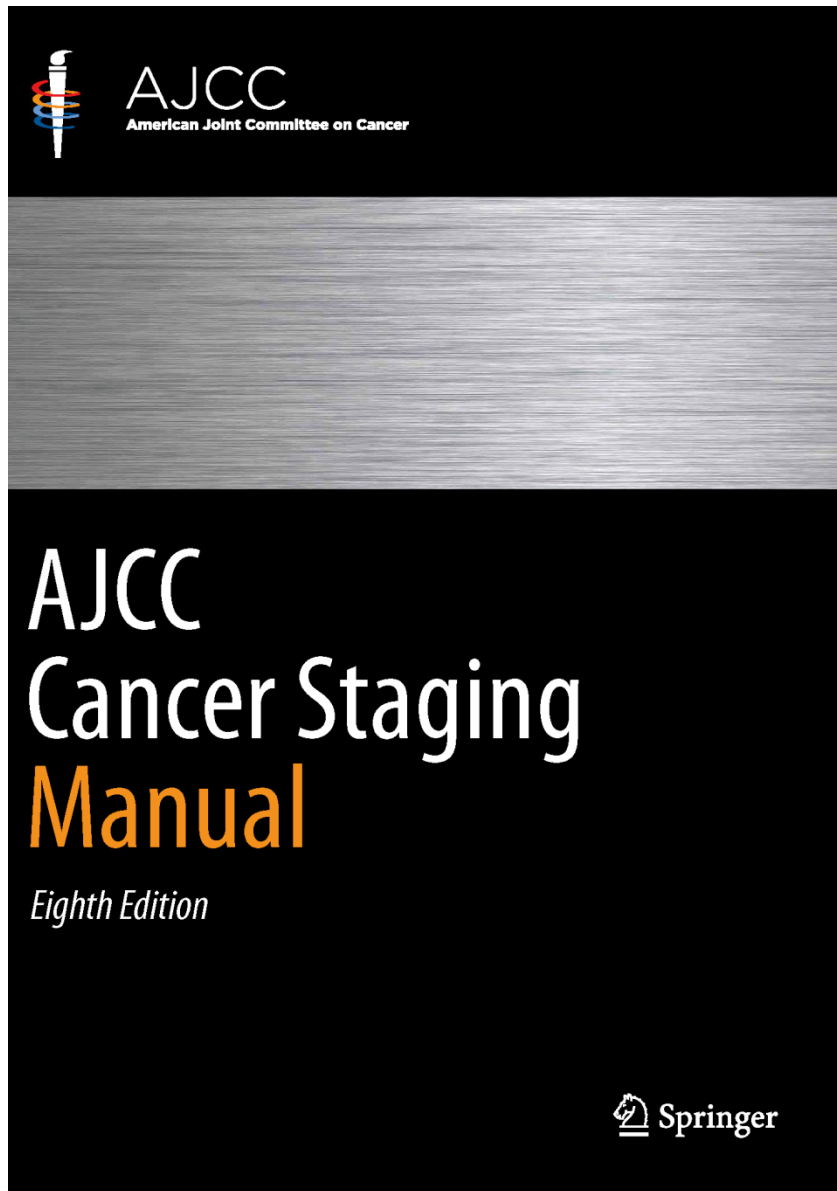Kursaal Bern, www.kursaal-bern.ch

International Tumor Budding
Consensus Conference
ITBCC 2016

Consensus Statements (*strong recommendation*):

-Tumor budding is an independent predictor of lymph node metastasis in pT1 colorectal cancer

-Tumor budding is counted on H&E.

-Tumor budding is assessed in the hotspot at the invasive front

Lugli A. et al. Mod Path Mod Pathol. 2017 Sep;30(9):1299-1311.

Is this tumor budding stuff really going to stay around?

AJCC
American Joint Committee on Cancer

AJCC Cancer Staging Manual

Eighth Edition

Springer

COLLEGE of AMERICAN PATHOLOGISTS

Protocol for the Examination of Specimens From Patients With Primary Carcinoma of the Colon and Rectum

Version: Colon Rectum 4.0.0.0   **Protocol Posting Date:** June 2017
Includes pTNM requirements from the 8th Edition, AJCC Staging Manual

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

Procedure	Description
Colectomy	Includes specimens designated total, partial, or segmental resection
Rectal Resection	Includes specimens designated low anterior resection or abdominoperineal resection
Tumor Type	**Description**
Carcinoma	Invasive carcinomas including small cell and large cell (poorly differentiated) neuroendocrine carcinoma

Lymphovascular Invasion (Notes D and E)
___ Not identified
___ Present
        + ___ Small vessel lymphovascular invasion
        + ___ Large vessel (venous) invasion
___ Cannot be determined

+ Tumor Budding (Note F)
+ ___ Number of tumor buds in 1 "hotspot" field (e specify total number in area=0.785 mm^2): _____
        + ___ Low score (0-4)
        + ___ Intermediate score (5-9)
        + ___ High score (10 or more)
+ ___ Cannot be determined

+   Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

5

Tumor budding – *scoring systems*

Paper	Patients	Stain	Scoring system
Morodomi 1998 (*Cancer*)	40 CRC	H&E	Count performed at four locations (1.25mm^2 field area) and average calculated
Hase 1993 (*Dis Colon*)	663 CRC	H&E	N/A: classified according to subjective impression
Ueno 2002 (*Histopath.*)	638 CRC	H&E	10 or more buds in 25X field (0.385mm^2)
Okuyama 2003 (*Dis Colon*)	196 CRC	H&E	N/A: classified according to subjective impression
Jass 2003 (*J Clin Path*)	95 CRC	H&E	5 buds in 40X field (area not specified)
Guzinska K 2005 (*Antican*)	24 CRC	H&E	Any budding considered positive
Ha 2005 (*Korean Can Ass*)	90 CRC	H&E	>7 buds in 20X field (area not specified)
Kanazawa 2008 (*Col Dis*)	159 CRC	H&E	0-1/3: mild; 1/3-2/3: moderate; >2/3: marked
Wang 2009 (*AJSP*)	128 CRC	H&E	5 fields (20X, 0.95mm^2); a median count of 1 or more buds considered positive

Tumor budding – *scoring system as per the International tumour budding consensus conference (ITBCC)*

Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016

Alessandro Lugli[1,22], Richard Kirsch[2,22], Yoichi Ajioka[3], Fred Bosman[4], Gieri Cathomas[5], Heather Dawson[1], Hala El Zimaity[6], Jean-François Fléjou[7], Tine Plato Hansen[8], Arndt Hartmann[9], Sanjay Kakar[10], Cord Langner[11], Iris Nagtegaal[12], Giacomo Puppa[13], Robert Riddell[2], Ari Ristimäki[14], Kieran Sheahan[15], Thomas Smyrk[16], Kenichi Sugihara[17], Benoît Terris[18], Hideki Ueno[19], Michael Vieth[20], Inti Zlobec[1] and Phil Quirke[21]

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

Figure 2 Conversion table to adjust and standardize the tumor bud count for different microscope types.

Recommendations on tumor budding in colorectal cancer
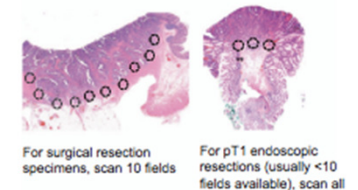
A Lugli et al

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

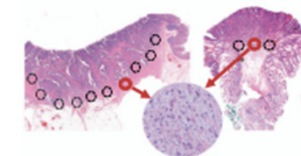| Objective magnification: 20		
Eyepiece FN Diameter (mm)	Specimen Area (mm2)	Normalization Factor
18	0.636	0.810
19	0.709	0.903
20	0.785	1.000
21	0.866	1.103
22	0.950	1.210
23	1.039	1.323
24	1.131	1.440
25	1.227	1.563
26	1.327	1.690

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)

5

$$\text{Tumor bud count per } 0.785 \text{ mm}^2 = \frac{\text{Bud count (20x objective)}}{\text{Normalization factor}^*}$$
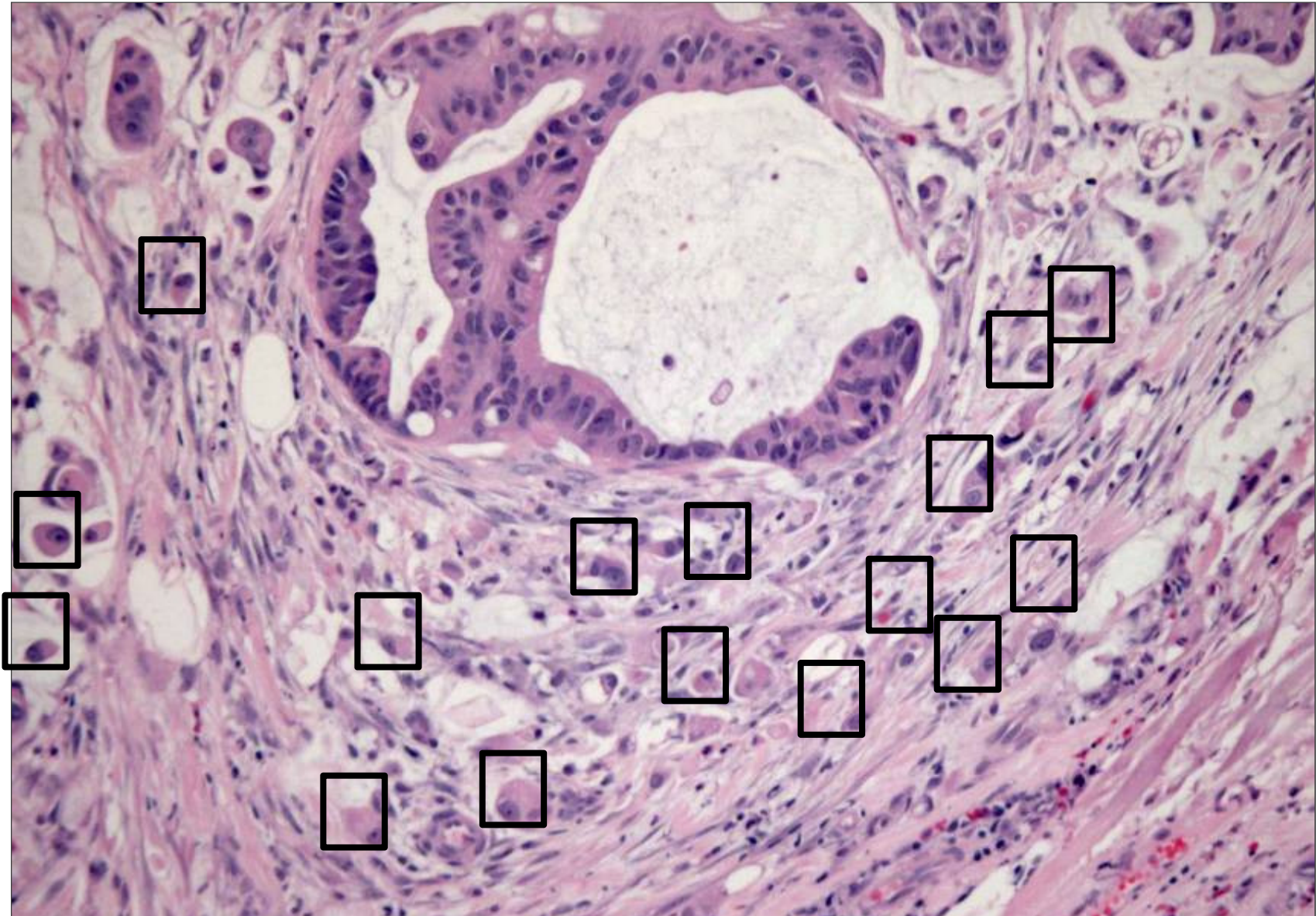
Bd1 (low):	0-4 buds	
Bd2 (intermediate):	5-9 buds	per 0.785 mm²
Bd3 (high):	≥10 buds	

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

Differential Prognostic Significance of Morphologic Invasive Markers in Colorectal Cancer: Tumor Budding and Cytoplasmic Podia

Eiji Shinto, M.D.,[1,3] Jeremy R. Jass, M.D.,[3] Hitoshi Tsuda, M.D.,[1] Taichi Sato, M.D.,[2]
Hideki Ueno, M.D.,[2] Kazuo Hase, M.D.,[4] Hidetaka Mochizuki, M.D.,[2]
Osamu Matsubara, M.D.[1]

Pseudofragmentation
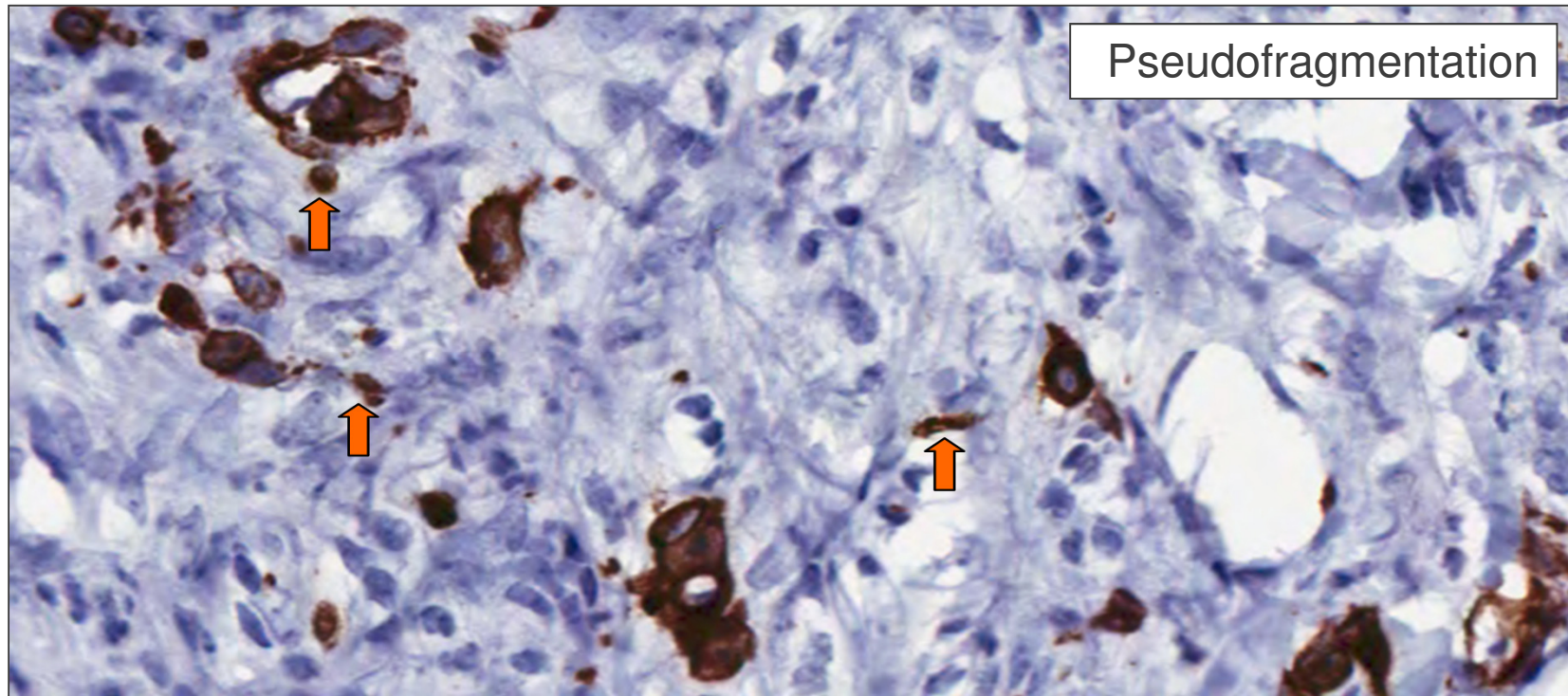
Tumor budding – *clinical implications in malignant polyps [as per 2016 JSCCR guidelines]*
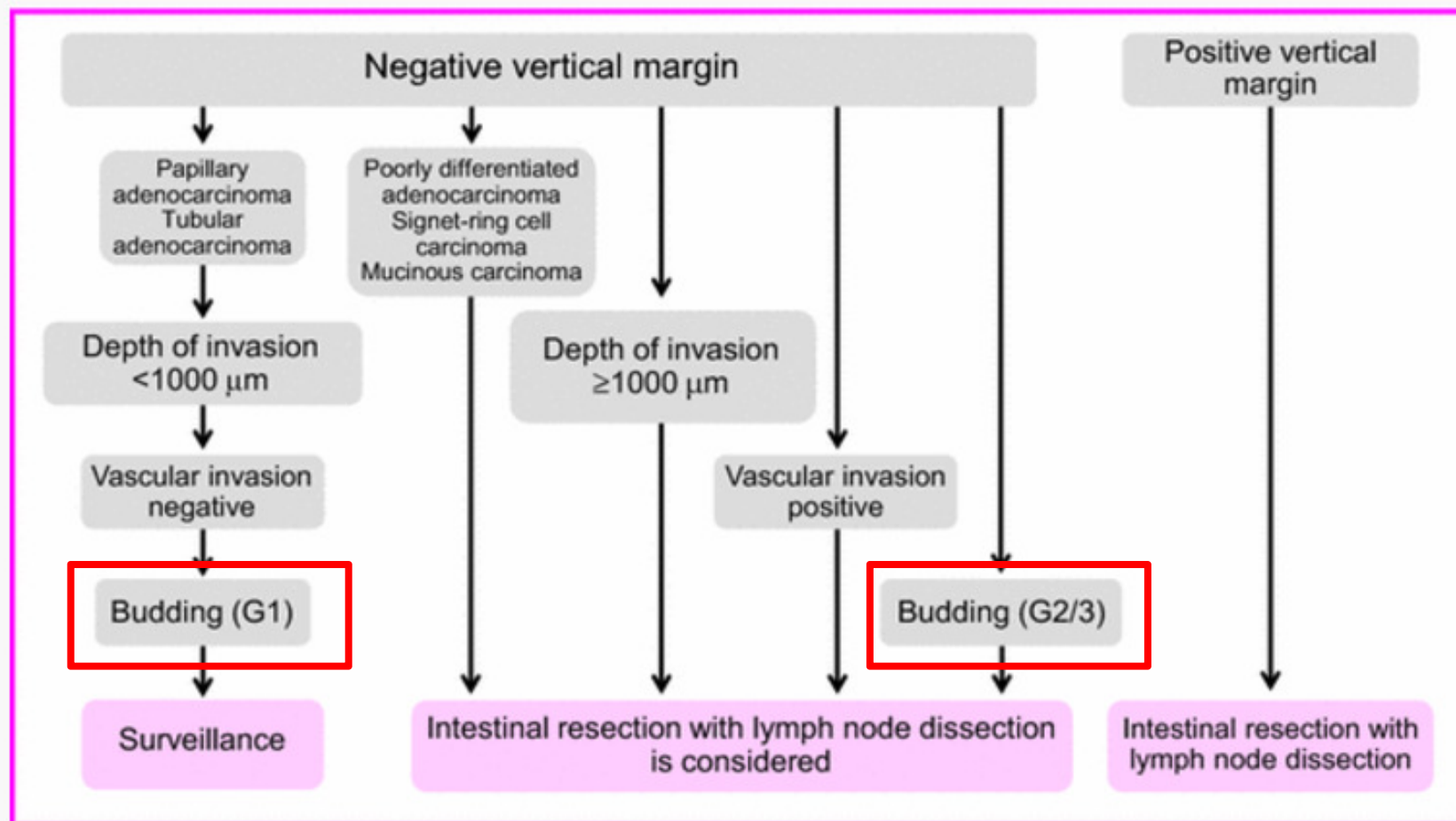
Fig. 10

Treatment strategies for pT1 (SM) cancer after endoscopic resection

Watanabe T. et al. Int J Clin Oncol. 2017 Mar 27. doi: 10.1007/s10147-017-1101-6.

What should be reported for malignant polyps?
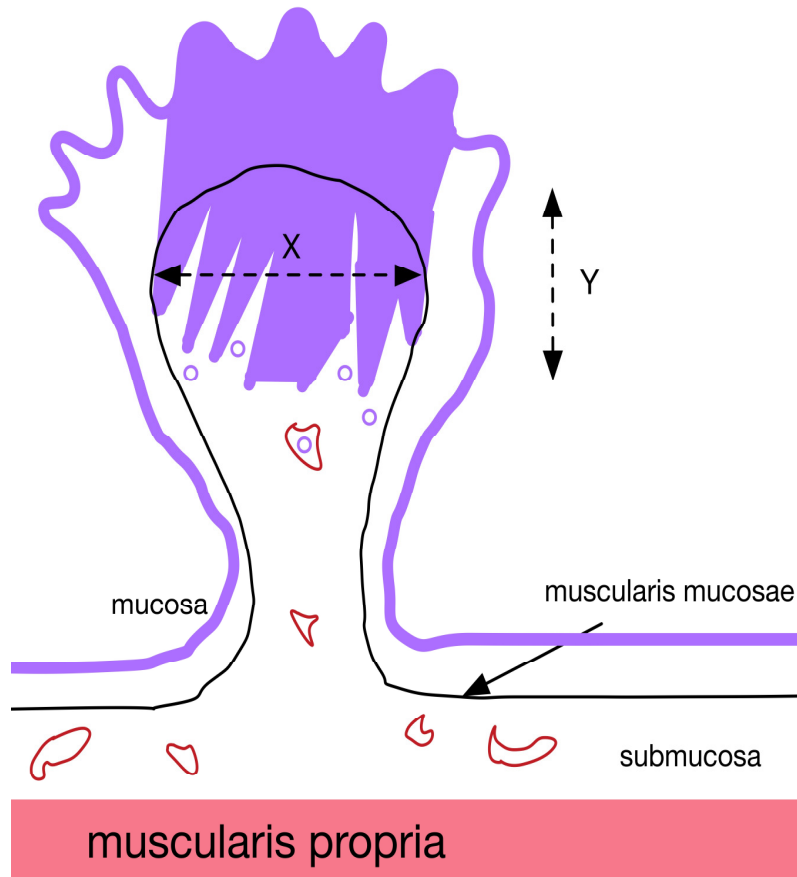
1. Presence/absence of poorly differentiated carcinoma (any amount)
2. Presence/absence of angiolymphatic invasion
3. Presence/absence of high-grade tumor budding
4. Distance of invasive component to margin
5. Depth of invasion (Haggitt/Kikuchi)
6. Width of invasion

Increased risk of rLN metastases	
One RF	20.7%
Two/Three RF	36.4%

Ueno H, *et al.*, A new prognostic staging system for rectal cancer. Annals of surgery 2004; 240(5): p. 832-9.

Thank you!