The malignant colorectal polyp

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Envoi Pathology

Envoi data reproduced from J Clin Path 2015 article

Definition

- Adenocarcinoma found in an endoscopically resected polypoidal tumour
    - Submucosal invasive tumour in a pre existing adenoma (conventional or serrated)
    - Polypoidal carcinoma
    - (‘intramucosal’ adenocarcinoma)

Importance

- Detection is increasing – **NBCSP**
- A **quality marker** for pathology practice standards
- Surgery versus conservative
  - Patient risk and economic benefit

What do we know?

1) RISK

- Resection specimens
  - **LN metastasis in 7-9%** (Envoi - 8.0%) * most important
  - Residual adenocarcinoma at polypectomy site ≤ 5%
  - Residual adenoma at polypectomy site ≤ 5-10%
  - **Overall rate of residual disease = 10-15%**

- All specimens
  - 50-60% of endoscopic MCP are followed by resection
  - Overall risk of **LN mets all MCP = 4%**
  - Overall risk of **residual disease all MCP = 7-10%** (Envoi =8.7%)

What do we know?

2) CLINICAL

- Males (55-60%)
- Mean age 60-65 years
- 3/4 are in rectum or sigmoid
- Sessile: pedunculated
  - 6:4 (Envoi) to 4:1 (Ueno) when assessed by pathologist
  - 1:2 when assessed by endoscopist
- MCP may be small
  - 25% ≤ 10mm
  - 1.7% ≤ 5mm

What do we know?

3) RISK FACTORS

- predict: LN mets, residual disease in wall, overall tumour specific survival
- 2 groups:

1) Qualitative
    - Differentiation, vascular invasion, margin status etc
2) Quantitative
    - Tumour size - Depth of invasion, tumour width, Haggitt, Kikuchi etc

- Tumour size is the most important risk factor

What are we trying to do?

Cost benefit analysis for surgery

- Costs
  - Risk of surgery – morbidity and mortality
  - Economic cost of unnecessary surgery
  - (‘sunk’ cost = tumour may already have metastasized beyond bowel wall or patient might die of another condition before the benefit of surgery accrues)
- Benefits
  - Remove residual disease that might latter directly cause morbidity or mortality

What are the issues?

1) Risk of residual disease for MCP is overstated

Risk criteria	Degree of Risk
Resection margin < 1mm	4
Resection margin 1-2mm	1
Pedunculated Haggitt level 4	4
Sessile: Kikuchi 2	2
Sessile: Kikuchi 3	4
Poor differentiation	3
Mucinous tumour	1
Tumour budding	1
Lymphovascular invasion	2

Total score	% risk of residual cancer
0	<3%
1	<5%
2	5-10%
3	8-15%
≥4	>20%

Williams JG, Pullan RD, Hill J et al. (2013). Management of the malignant colorectal polyp: ACPGBI position statement. Colorectal Dis Suppl. 2:1-38.

What are the issues?

1) Risk of residual disease for MCP is overstated

Number of risk factors	Nodal involvement	
	Ueno	Envoi
0	0.7%	2%
1	20.7%	8.2%
≥2	36.4%	12.2%

Risk factors = poor differentiation, lymphovascular invasion and tumour budding

Ueno et al Gastroenterology 2004;127:385-94 * half the MCP in this study were treated by primary surgical resection

What are the issues?

1) Risk of residual disease for MCP is overstated

T stage	N+ stage proportion (%)		
	Rectal cancer	Colon cancer	All untreated CRC Envoi
T1	10.2%	4.3%	6.3%
T2	22.3%	19.0%	15.0%
T3-4	51.2%	38.5%	46.2%

World J Gastroenterol. 2010 Nov 14; 16(42): 5375–5379

What are the issues?

2) Risk of surgical resection is overstated

- Quoted figures (overall)
  - mortality 2-5 %
  - morbidity 30 %
  - Anastomotic leak 1-4%
- Local colorectal surgeons are much better than this

What are the issues?

3) Risk for primary colonoscopic resection

Polyp size (cm)	Polyp location and morphology			
	Left colon		Right colon	
	Pedunculated (n = 987)	Sessile (n = 1577)	Pedunculated (n = 118)	Sessile (n = 1294)
< 1 cm	0 (250)	0.4 (950)	1.9 (54)	1.2 (729)
1.0–1.9 cm	0.6 (512)	0.9 (438)	3.9 (51)	3.5 (402)
≥ 2 cm	3.6 (225)	5.3 (189)	0 (13)	11.7 (163)

Munich polypectomy study (Endoscopy 2005;37:1116-1122) – Major complication rate = death, perforation, bleeding

BSG audit – perforation - 0.04%, bleeding - 0.26%, readmission – 0.14%

What are the issues?

4) The 5 year survival for stage III colorectal carcinoma is quite good and is getting better!

Stage	5-year Relative Survival Rate Colon vs Rectum
I	92% vs 87%
IIA	87% vs 80%
IIB	63% vs 49%
IIIA	89% vs 84%
IIIB	69% vs 78%
IIIC	53% vs 51%
IV	11% vs 12%

SEER data 2004 - 2010

Further treatment decision

1) Patient factors

   - Age
   - Co-morbidities
   - Genetic syndrome (eg Lynch, FAP)
   - Cancer phobia

Further treatment decision

2) Pathological factors

1) Qualitative
    - Differentiation, vascular invasion, margin status etc
2) Quantitative
    - Size of invasive tumour

Further treatment decision

3) Gastroenterologist/surgeon*

- Feeling on adequacy of endoscopic resection
- Personality
- Experience – EMR/ESD (gastroenterologist) vs laparoscopic resection (colorectal surgeon)
- Knowledge!!!

Recommendations for surgical resection: (from Nivatvongs S. Surg Clin N Am 2002;82:959–966)

A. Lesions in colon

a) Pedunculated Haggitt level 4 with invasion into distal third of submucosa, or pedunculated lesions with lymphovascular invasion

b) Sessile lesions removed with margin <2 mm

c) Sessile lesions removed piecemeal

d) Sessile lesions with depth of invasion into distal third of submucosa (Sm3)

e) Sessile lesions with lymphovascular invasion

B. Lesions in middle third and upper third rectum

Same as lesions in colon

C. Lesions in distal third rectum

a) Pedunculated Haggitt level 4 with invasion into distal third of submucosa, or pedunculated lesions with lymphovascular invasion

b) All sessile lesions

Bottom line

- Better pathological risk assessment
- Better endoscopic resection
- Better surgical outcomes
- Better oncological therapy if a LN met is missed
- ?? imaging techniques to detect LN met
- NBCSP = smaller malignant polyps

The risk benefit data is changing

All we can control is the pathology input

Pathological factors

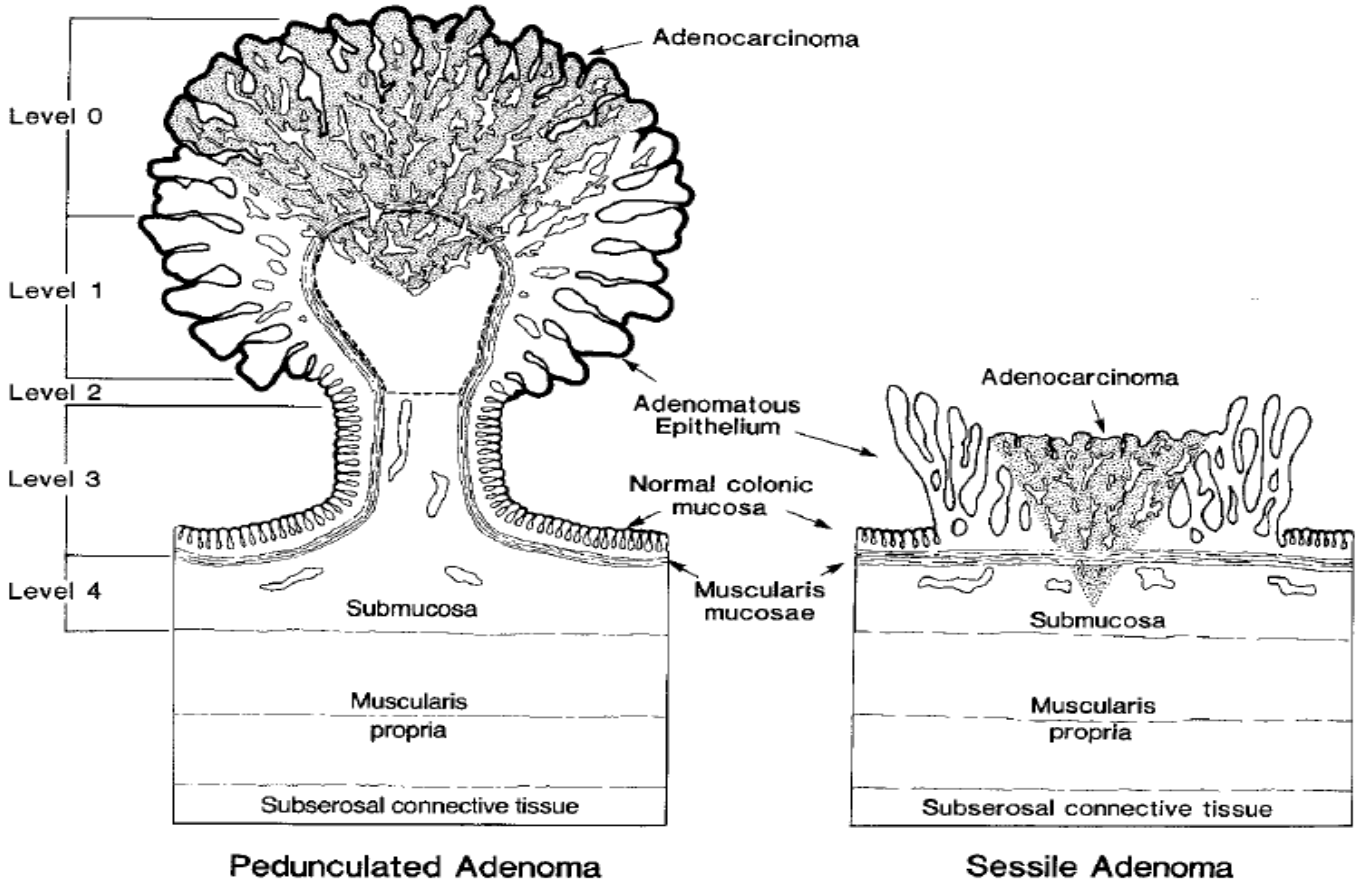
Quantitative factors

(Tumour size/depth of invasion)

1) Haggitt levels

- Depth of invasion

CIS or Intramucosal



Haggitt et al Gastroenterology 1985;89:328-36

1) Haggitt levels

- Haggitt paper Gastroenterology 1985;89:328-36
  - 129 cases (50% were level 0)
  - 70 (54%) pedunculated; 42 sessile, indeterminate 17
  - 51% underwent resection; 35% of all cases were primary resections
  - Lymphatic invasion - 2 cases
  - Venous invasion – 0 cases
  - 8 (6.2%) adverse outcome = LN mets in 4 (but not known in 3 cases who died); death from disease in 5

1) Haggitt levels

- 8/64 (12.5%) submucosal invasive carcinoma (levels 1-4) had an adverse outcome (LN mets/tumour related death). These were:
  - Levels 0-2 = 0 cases (0%)
  - Level 3 = 1 case (12.5%)
  - Level 4 = 7 cases (87.5%)** (2 were pedunculated, 6 were sessile)
- **Level 4 is the significant factor**
- 7/28 polyps were level 4 = PPV for adverse behaviour = 25%
- ?How many level 4 were pedunculated

1) Haggitt levels

- Problems:

1) 59 non pedunculated polyps were by definition level 4
   - (6 had adverse outcome = 10%)
2) 70 pedunculated polyps
   - ? how many level 4 invasion (2 adverse)
   - Data from paper suggests PPV of risk for pedunculated Level 4 > sessile level 4 (but data is incomplete)

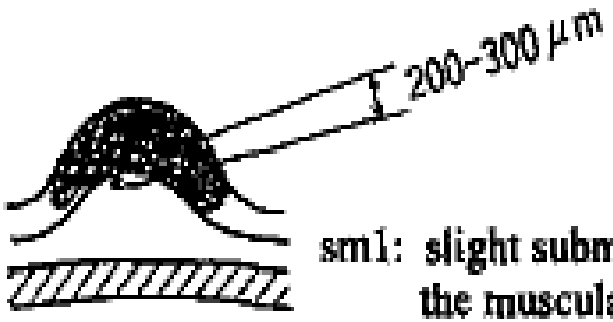
1) Haggitt levels

3) Difficult to apply in practice
   - poor orientation
   - Piecemeal specimen
   - Pedunculated vs sessile
   - Levels 1 vs 2 and 2 vs 3
4) Over interpretation by surgeons
5) Small series, not contemporary

- Envoi data
  - Less pedunculated polyps than reported in clinical series (43% vs 66%)
  - Pedunculated Haggitt level 4 = nil
  - Haggitt level 3 = 14%
    - 2 (12.5%) had LN mets (one was pT3 at resection)
    - 1 other case had residual adenocarcinoma in lymphatics
  - Haggitt level 2 = 19%
    - 1 (5.9%) had LN mets; large mucinous LVI
  - Haggitt level 1 = 10%
    - no LN mets

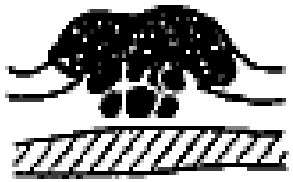
2) Kikuchi/Kudo levels

Sessile polyps



sm1: slight submucosal invasion from the muscularis mucosa.

sm2: intermediate between sm1 and sm3.



sm3: carcinoma invasion near the inner surface of the muscularis propria.

Kikuchi R et al Dis Colon Rectum 1995;38:1286-1295
Kudo S. Endoscopy 1993;25:455–61.

LN metastasis risk Nascimbeni R et al Dis Colon Rectum 2002;45:200–206.
3% (0% in contemporary studies)
8%
23%

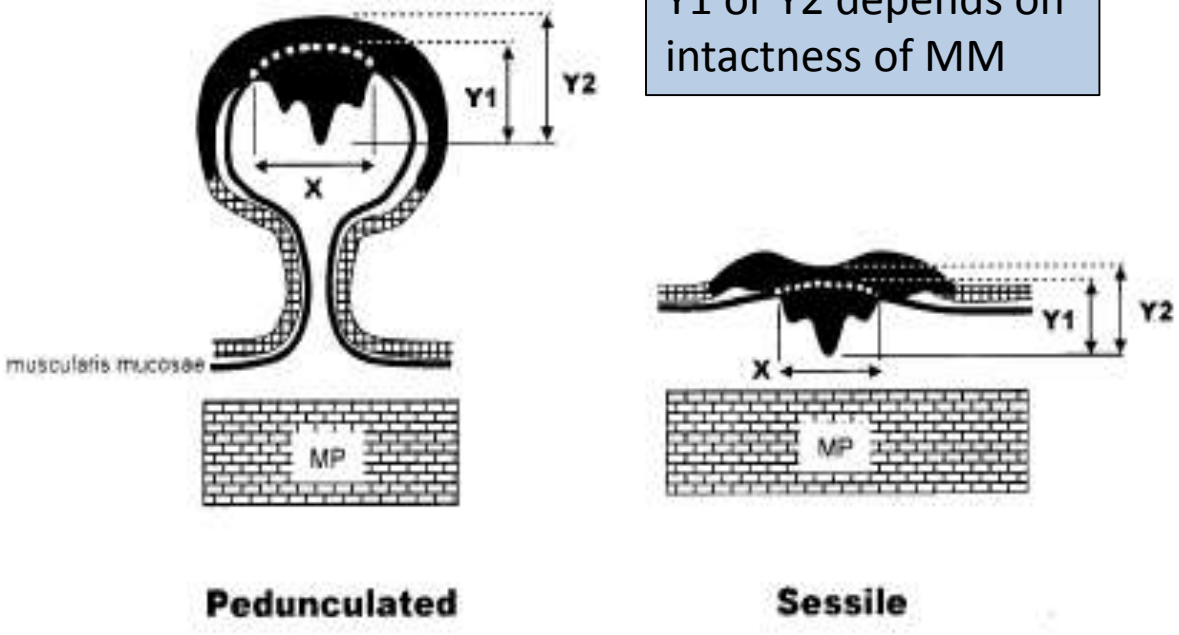
Overall pT1 – 6-12%

2) Kikuchi/Kudo levels

- Problems:
  1. Fragmented specimen
     - Invasion <0.3mm = Kikuchi sm1
     - Mid submucosal venous plexus is good surrogate for sm2
  2. Muscularis mucosae destroyed by tumour and/or extensive tumour ulceration
  3. Full thickness of submucosa is not included in standard endoscopic resection specimens (need ESD)
  4. Not applicable to pedunculated polyps

3) Tumour size - measured

- Width and Depth (surrogate of tumour volume) of invasive carcinoma
- **The most important prognostic feature – now confirmed in multiple studies**



Y1 or Y2 depends on intactness of MM

Ueno et al Gastroenterology 2004;127:385-94
292 pT1 adenocarcinoma (mostly in a pre-existing polyp)

LN metastasis risk

Width <2mm = 0%
Depth <0.5mm = 0%

Width <4mm = 2.5%
Depth <2mm = 3.9%

Width ≥ 4mm = 18.2%
Depth ≥ 2mm = 17.1%

Width ≥ 4mm and/or Depth ≥ 2mm predict LN metastasis

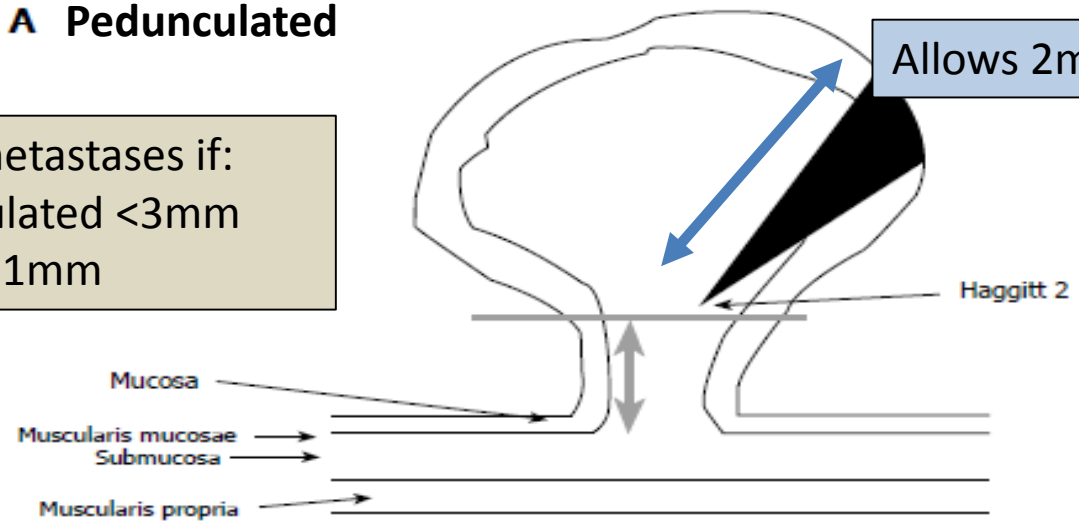
3) Katajima depth modification for pedunculated polyps

- Useful when sessile polyp is ulcerated or muscularis mucosae is destroyed
- Correlates tumour size in pedunculated polyps to sessile polyps

A Pedunculated

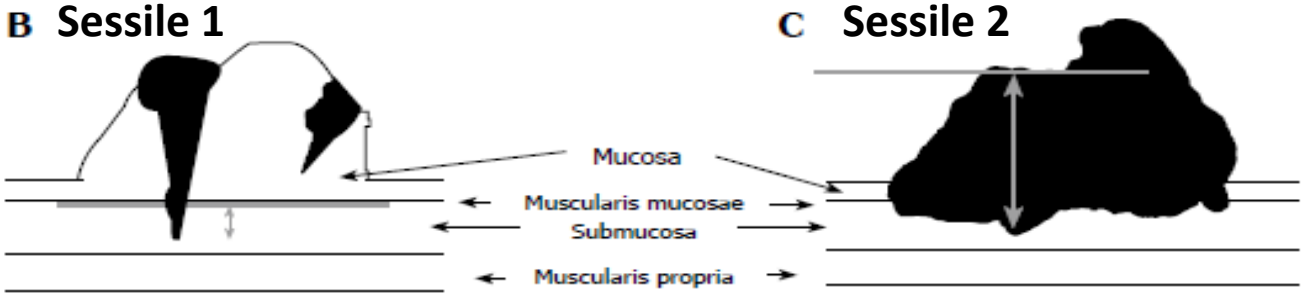
Allows 2mm for this distance

No lymph metastases if:
1) Pedunculated <3mm
2) Sessile <1mm



B Sessile 1

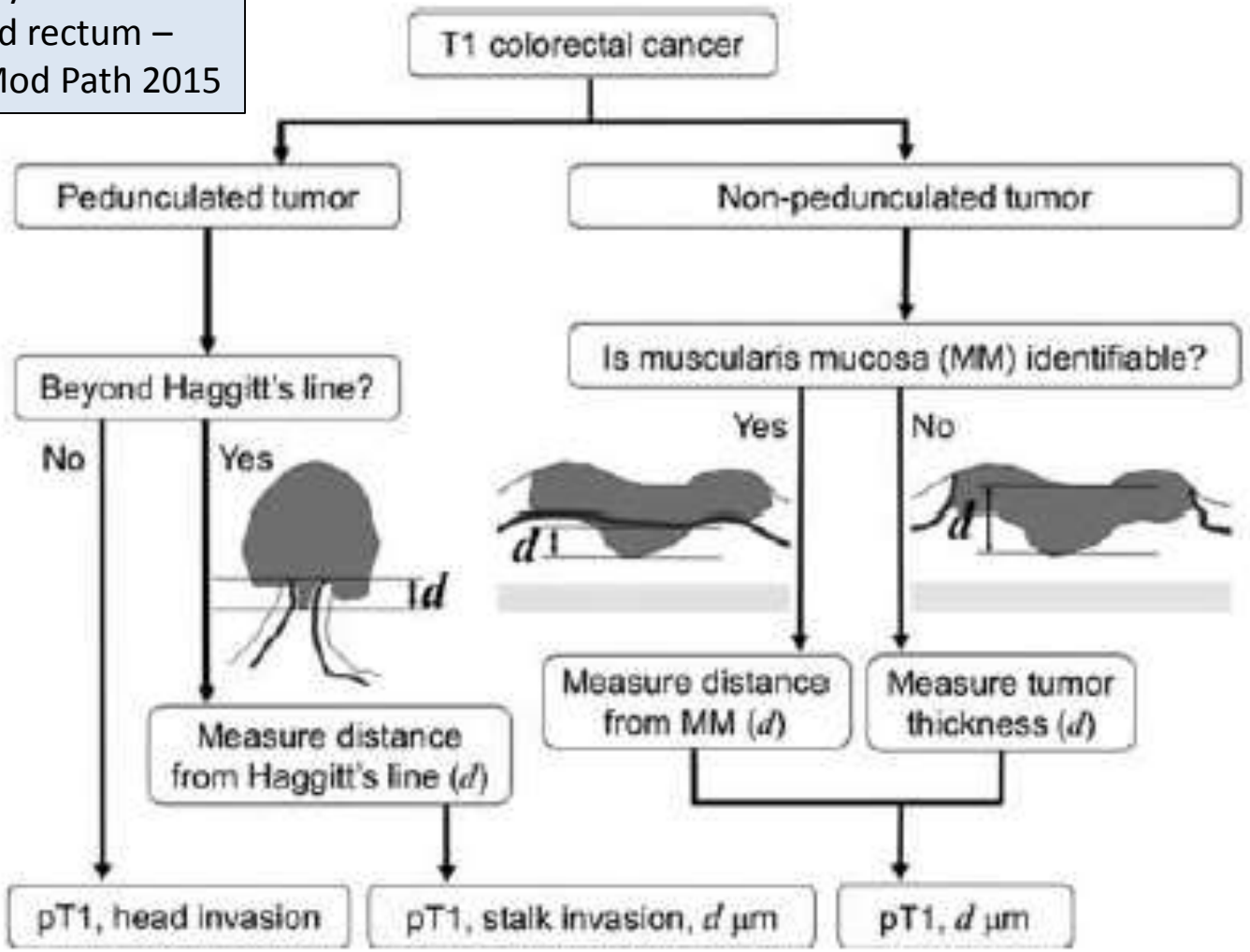
C Sessile 2



J Gastroenterol 2004;39(6):534-43; WJG 2010;16(25):3103-11

4) Current Japanese criteria*

Japanese society for cancer of the colon and rectum – Kawachi et al Mod Path 2015



Tumour size - measured

Problems:

1) Poor orientation (levels might help)

2) Fragmented specimen
   - Often one or two pieces contain the majority of the carcinoma
   - Can give a minimum size which often exceeds 2mm depth or 4mm width

3) Muscularis mucosae destroyed

   - Measure full thickness of adenocarcinoma

4) Sessile vs pedunculated

   - if no definite stalk – measure as per sessile polyp

Tumour size - measured

- Envoi data

Size	LN mets	No LN mets	Odds ratio	P value
Width of invasion >4mm	91.7%	51.5%	10.34 (1.31-81.43)	0.007
Depth of invasion >2mm	83.3%	48.0%	5.41 (1.16-25.26)	0.02

Size <1mm depth or <2mm width = 0% LN mets

Qualitative factors

1) Poor tumour differentiation

	Envoi (N=239)	Pooled analysis (Hassan et al N=1400)	Ueno et al (N = 292)	Butte (N=143)	Kawachi Mod path 2015 (N=805)
Poor differentiation	**18.4%** (all CRC = 20%)	**7.2%**	**26.7%**	**11.9%**	**32.2%**

- Wide variation in frequency
  - Poor interobserver agreement

    Kappa - 64-70% Cooper et al Gastroenterology. 1995;108:1657-65; 0.14 Terris et al Mod Path 2012;25(2)182A

- Studies are moving toward the concept of tumour grade rather than differentiation
- Requires MMR status

1) Poor tumour differentiation

	Residual disease	Metastasis	Mortality
% (average)	18%	23%	15%
Odds ratio - Hassan	2	4	9**
%/Odds ratio - Ueno		29%/3 (multivariate)	

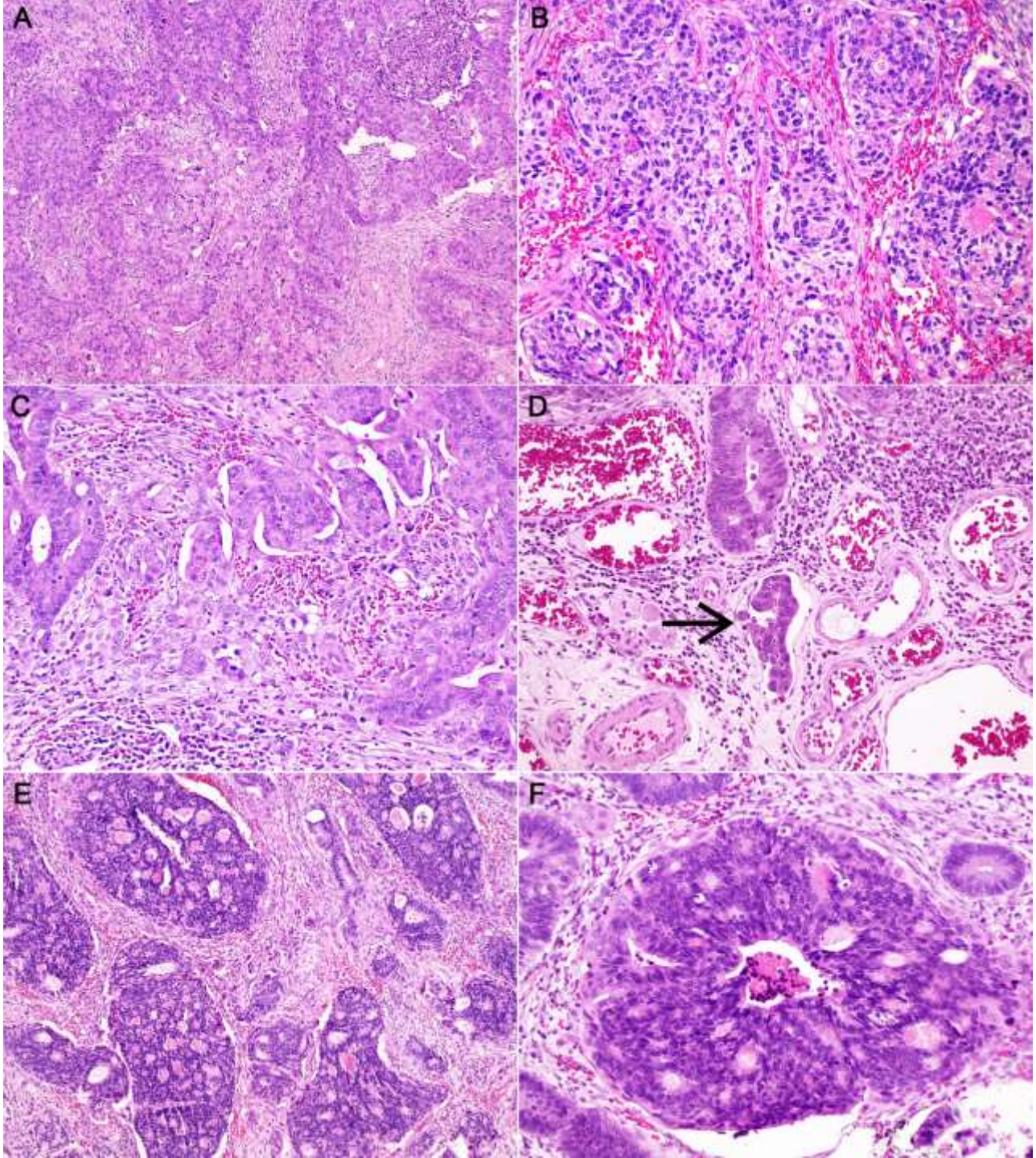
Hassan et al Dis Colon Rectum 2005;48:1588-96
Ueno et al Gastroenterology 2004;127:385-94

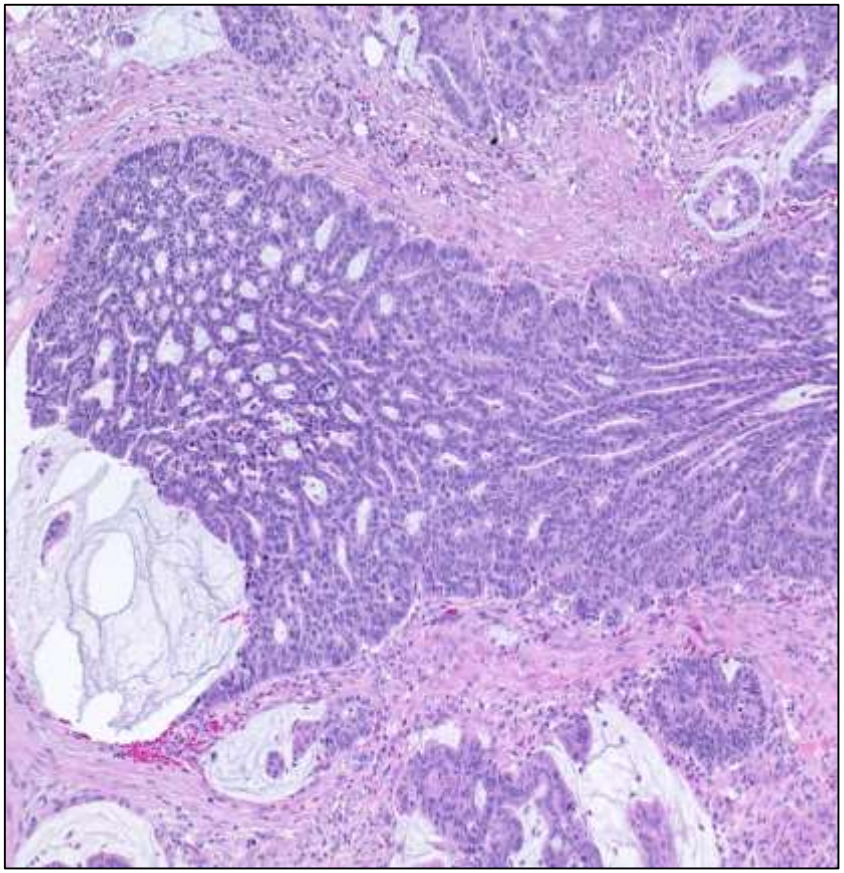
Consistently associated with adverse outcome in all studies

Probably because we all agree on the significant high grade lesions

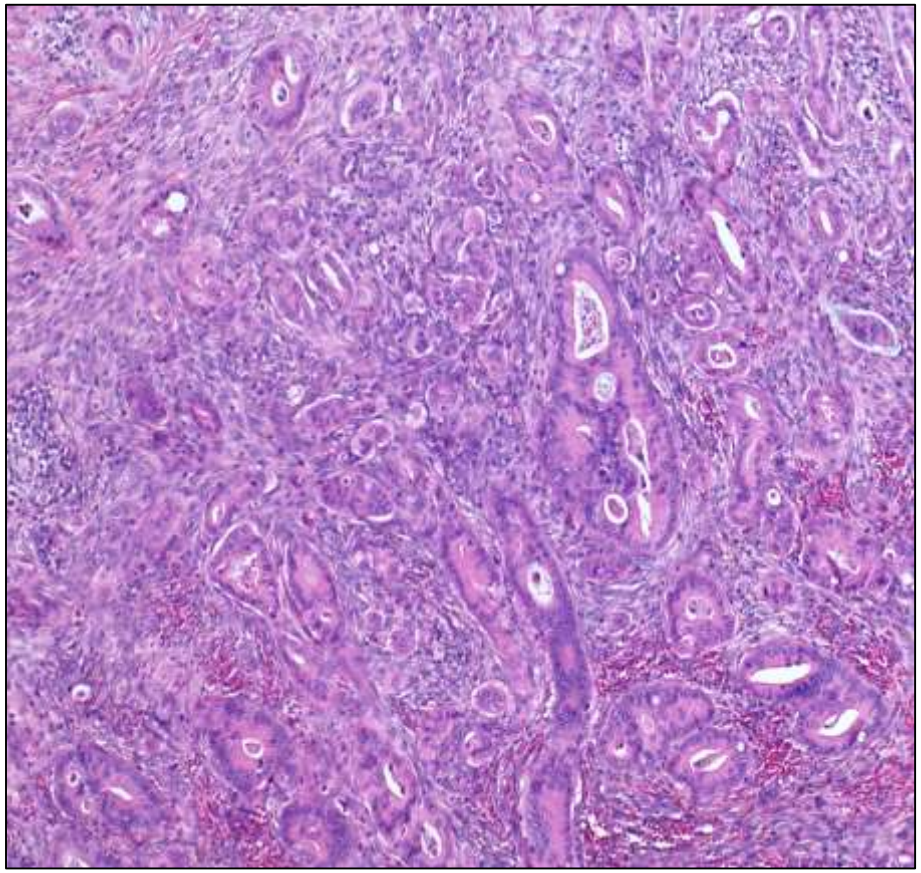
1) Poor tumour differentiation

- Poor differentiation in **any** part of tumour but particularly at invasive edge
- some studies require 50% of adenocarcinoma to be poorly differentiated
- Patterns:
  - <50% gland lumina
  - Mucinous (MLH-1 def)
  - Signet ring
  - Tumour ‘buds’ with >5 cells (poorly differentiated clusters)
  - Cribriform comedo
  - Undifferentiated carcinoma (?neuroendocrine)
  - **NOT** true tumour budding (<5 cells)

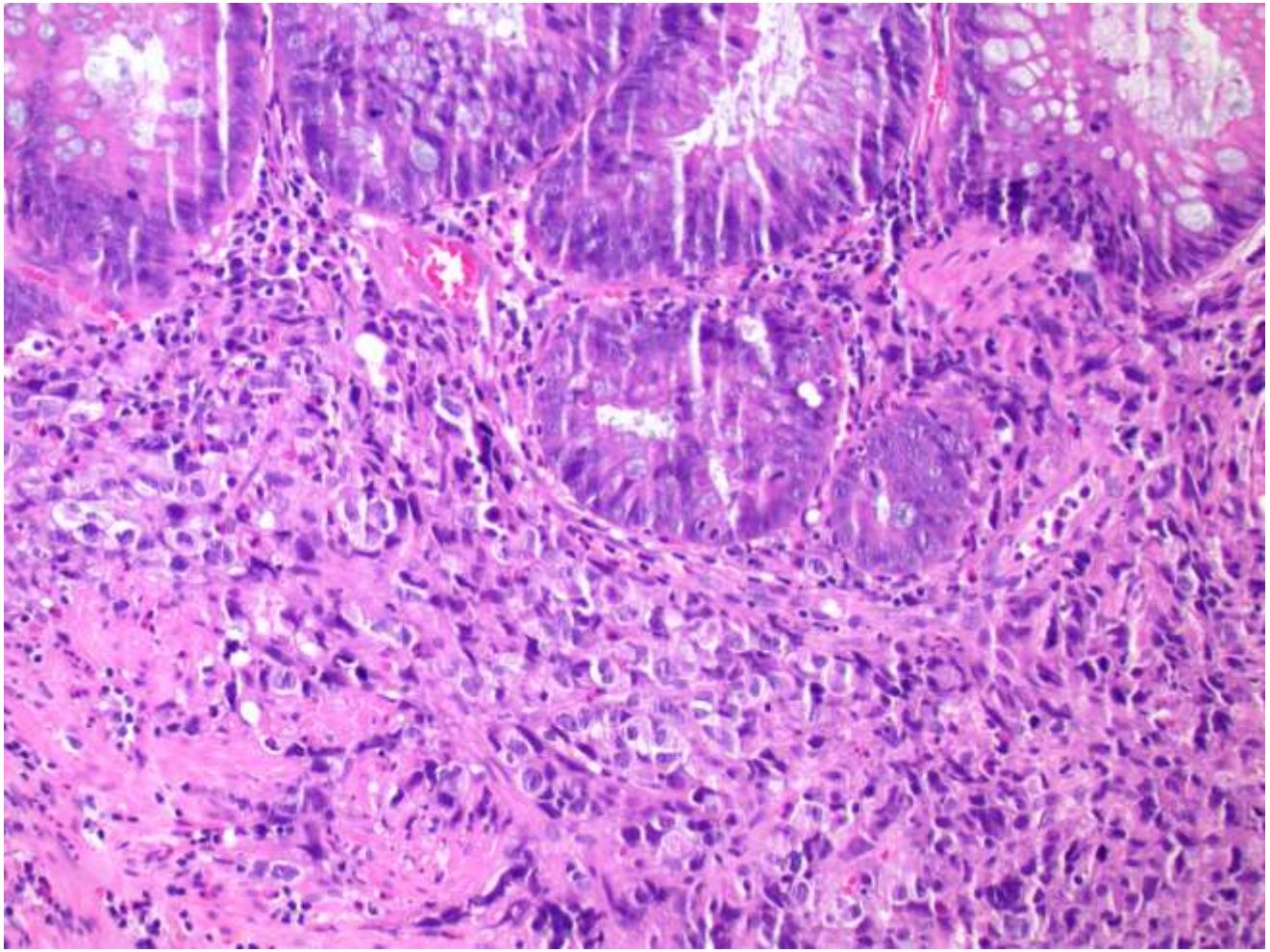

A
B
C
D
E
F



Cribriform and mucinous



Large buds – focal ‘dedifferentiation’
‘poorly differentiated clusters’



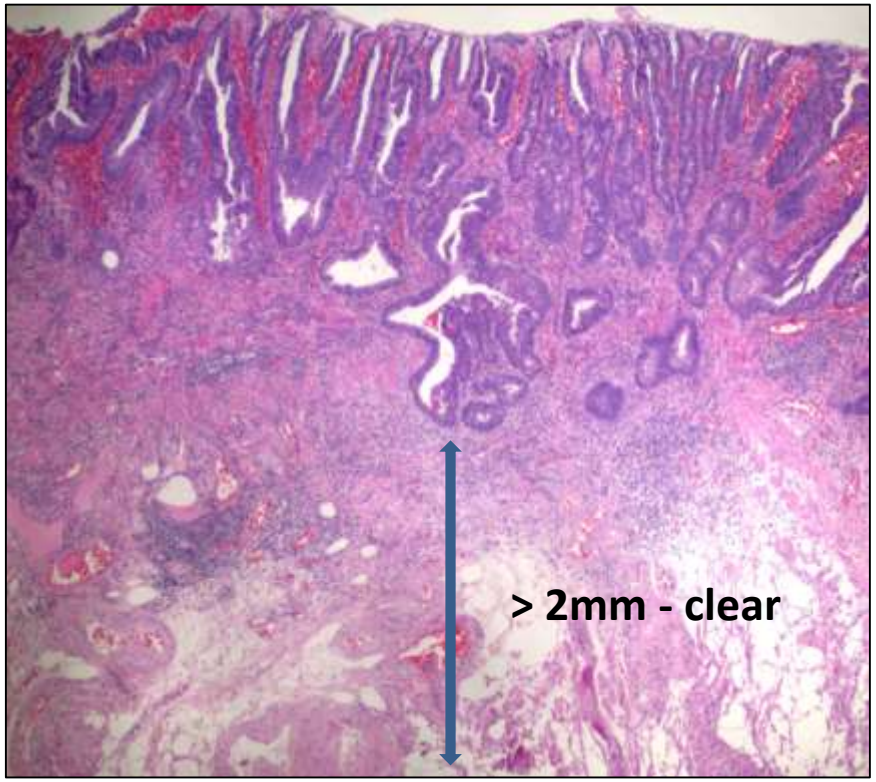
Beware!!! Neuroendocrine – very high risk of metastatic diseae

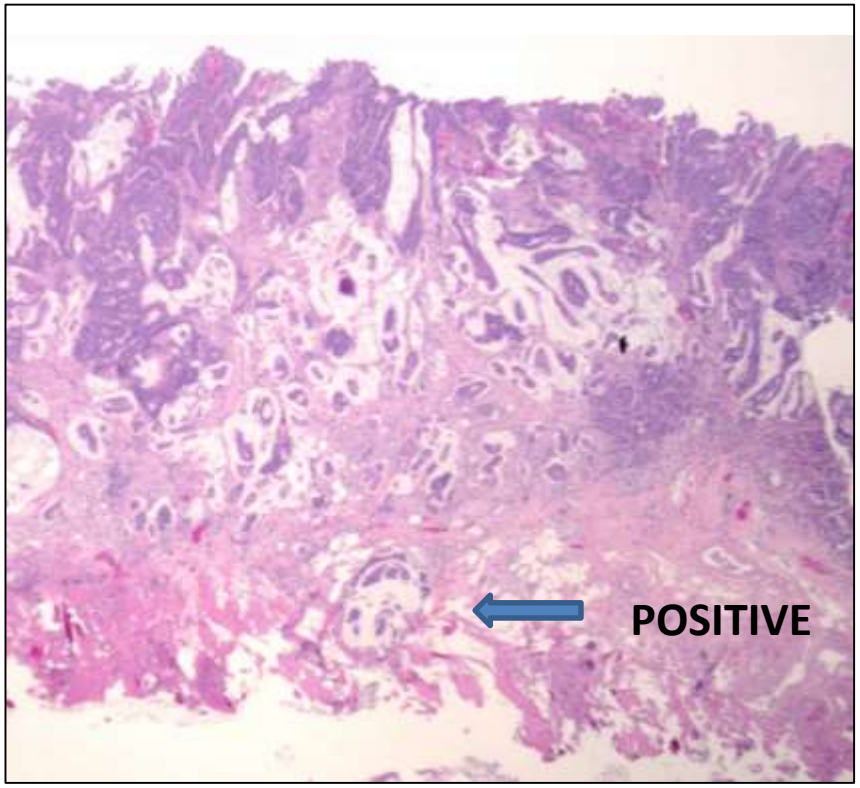
2) Margin of resection

- positive variously defined
  - In diathermy artefact
  - 1 HP field
  - <1mm
  - <2mm from margin

  } **deep margin**

- Ueno et al Gastroenterology 2004;127:385-94 → only involvement of diathermy artefact is significant
- ≥1 mm clearance Butte et al Dis Colon Rectum 2012;55:122-127
- **General agreement that ≥ 2mm is definitely clear**


> 2mm - clear


POSITIVE

2) Margin of resection

- Risk:

Too high – Ueno = 12.5%; Envoi 12%, Butte 11.2% (INTACT polyps)

	Residual disease	Metastasis	Mortality
% (average)	**30%**	**7%**	**8%**
Odds ratio	**15****	**1**	**6**

Hassan et al Dis Colon Rectum 2005;48:1588-96

- Interobserver agreement – good 86-93%
- positive margin = inadequate treatment **NOT** a risk for metastatic disease

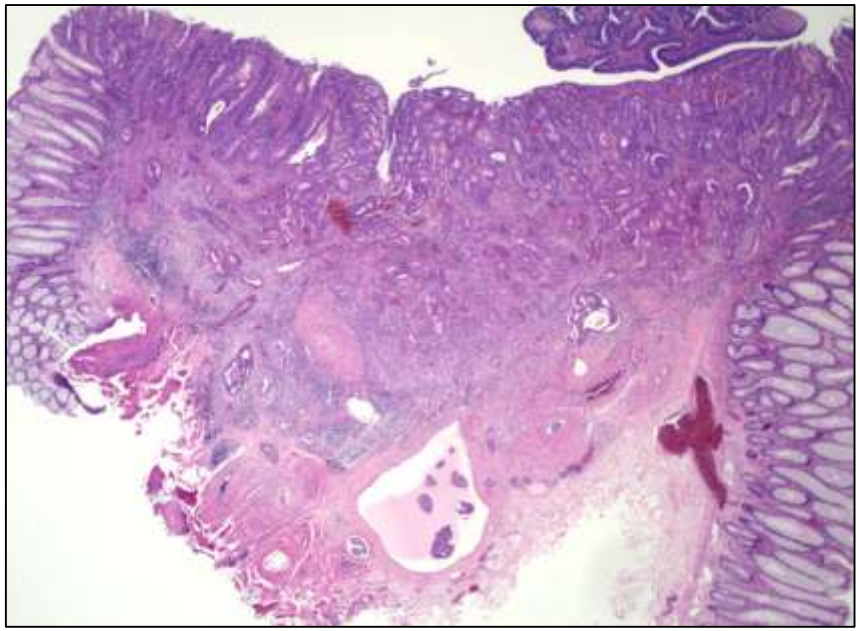
2) Margin of resection

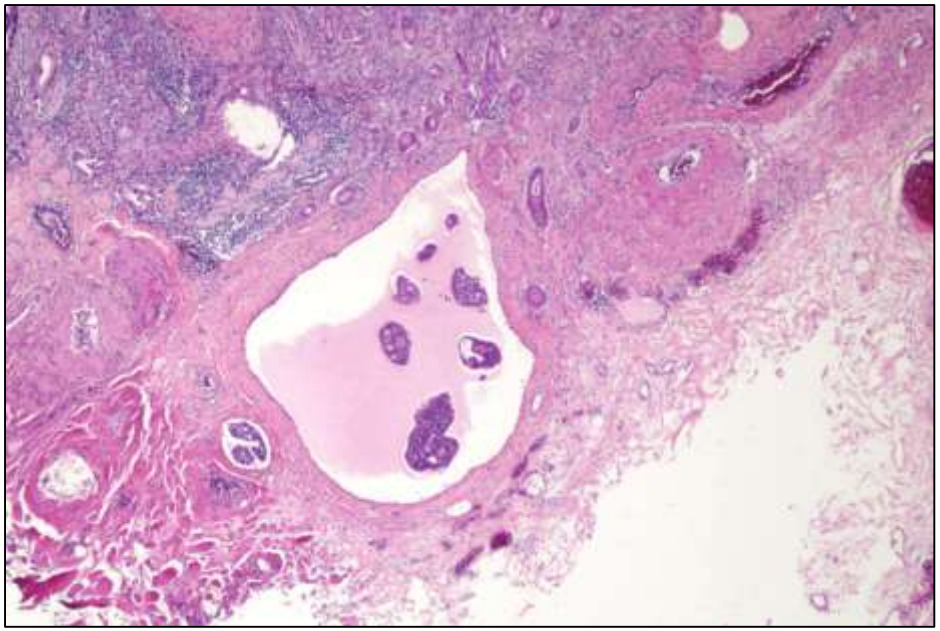
- Positive margin 33% (using all definitions)
- Envoi
  - Diathermy involvement 27.2%
  - no residual disease if clearance >0.1mm above diathermy artefact
- Positive margin = 12% risk of residual disease (adenoma or adenocarcinoma) at site of polypectomy

3) Vascular invasion

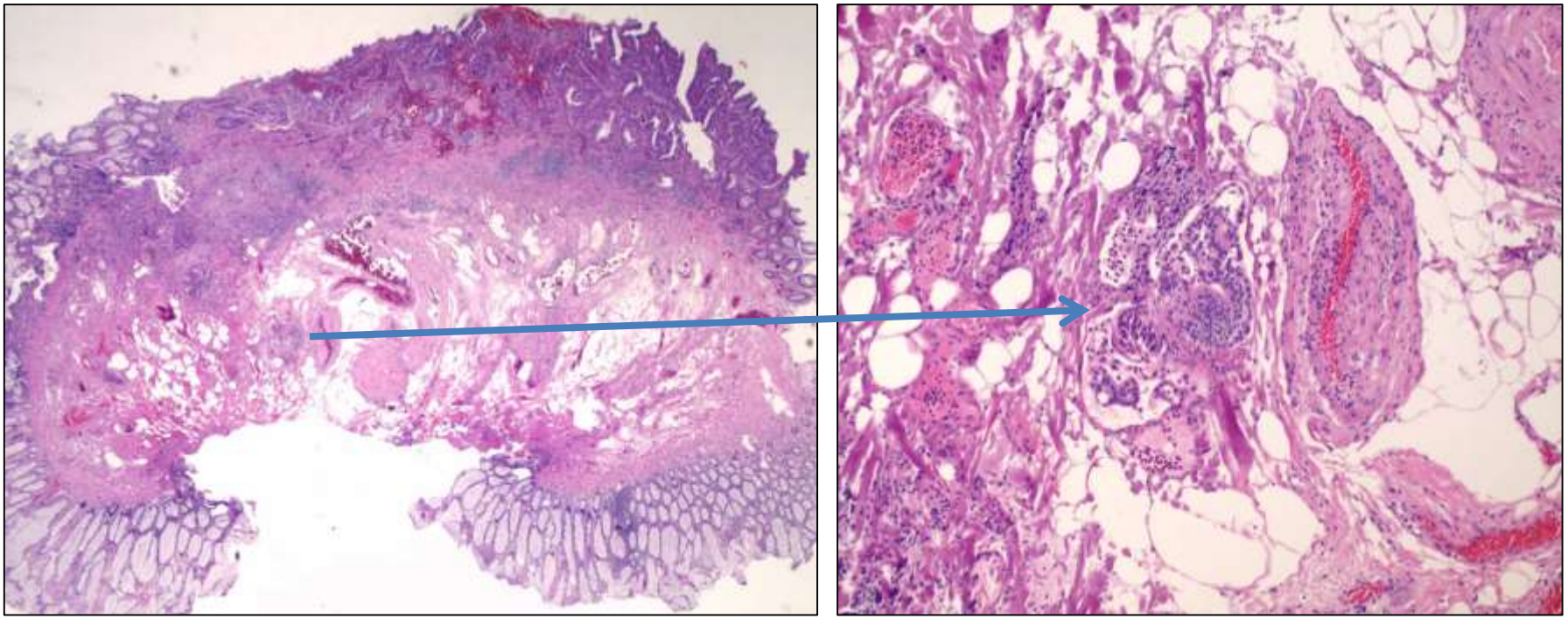
- Lymphatic or venous invasion
- Wide range of detection
  - 0-57% (average 18%)
    - Envoi LI = 23% VI = 9%, Butte = 18.2%, Ueno = 30%, Kawachi = 32%
  - PPV for LN mets is low (5-30%)
    - Only 7.3% of Envoi cases with LI had LN mets; 30% in Ueno, 19.2% in Butte
  - NPV for LN mets may also be poor
    - 50% in Butte; 67% at Envoi , 9% in Kawachi (resections) had LN mets despite no lymphatic invasion seen
- Has lead to inaccuracy/uncertainty in the significance of this prognostic factor

Sometimes easy!!

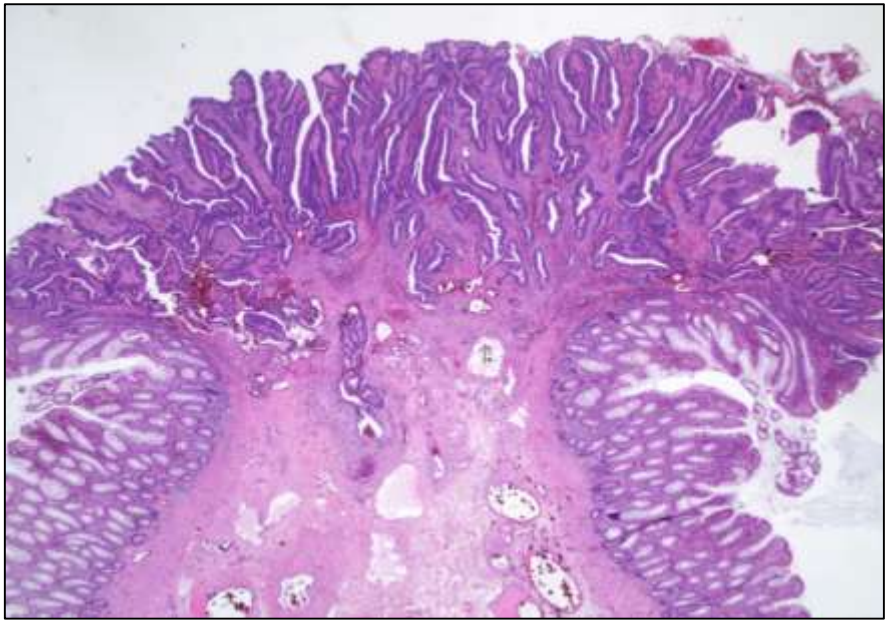


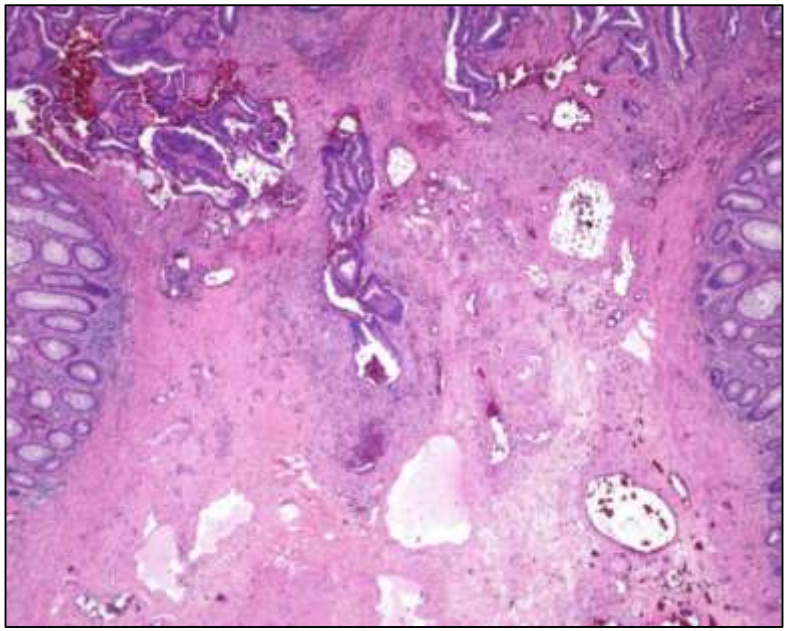


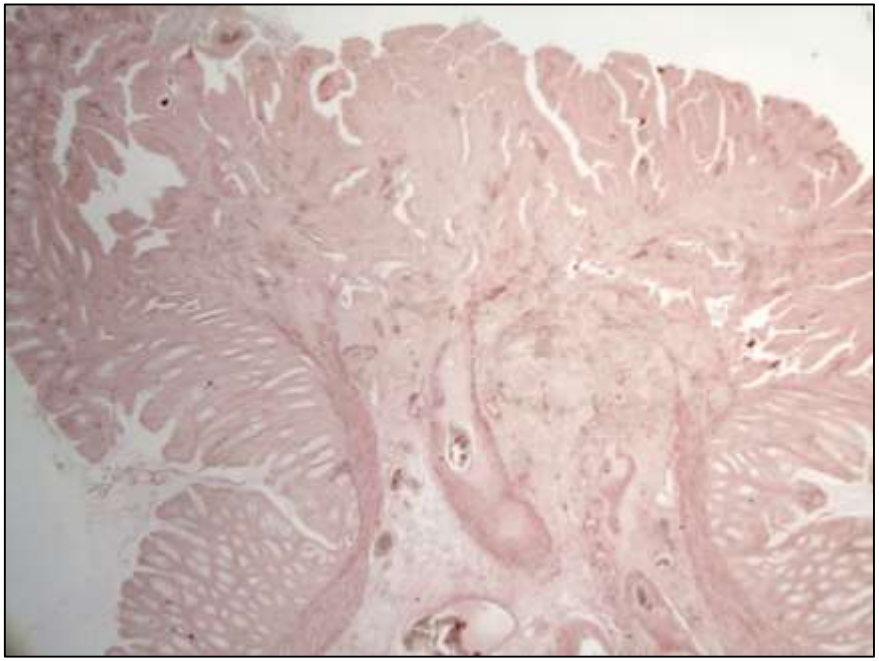
Often subtle – need to look carefully

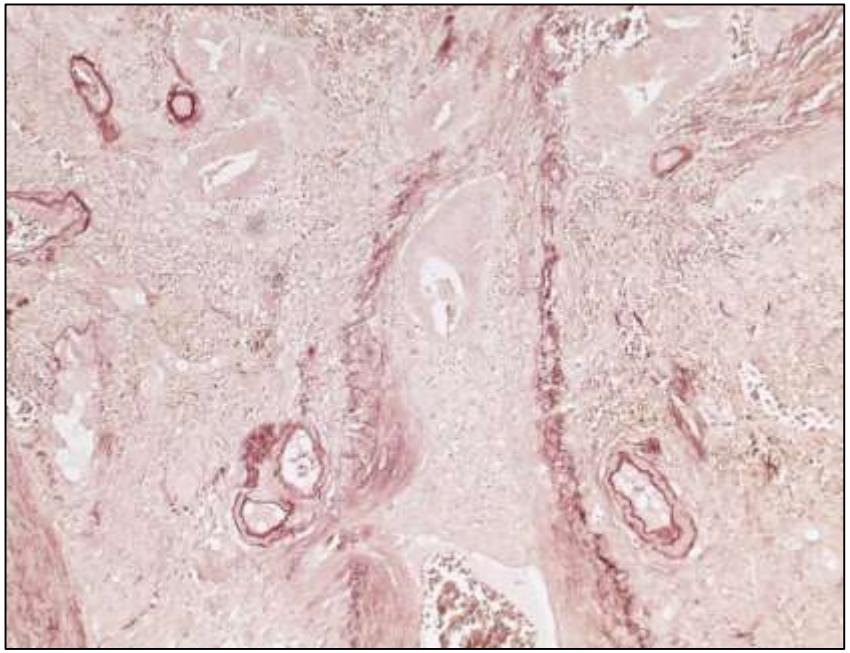


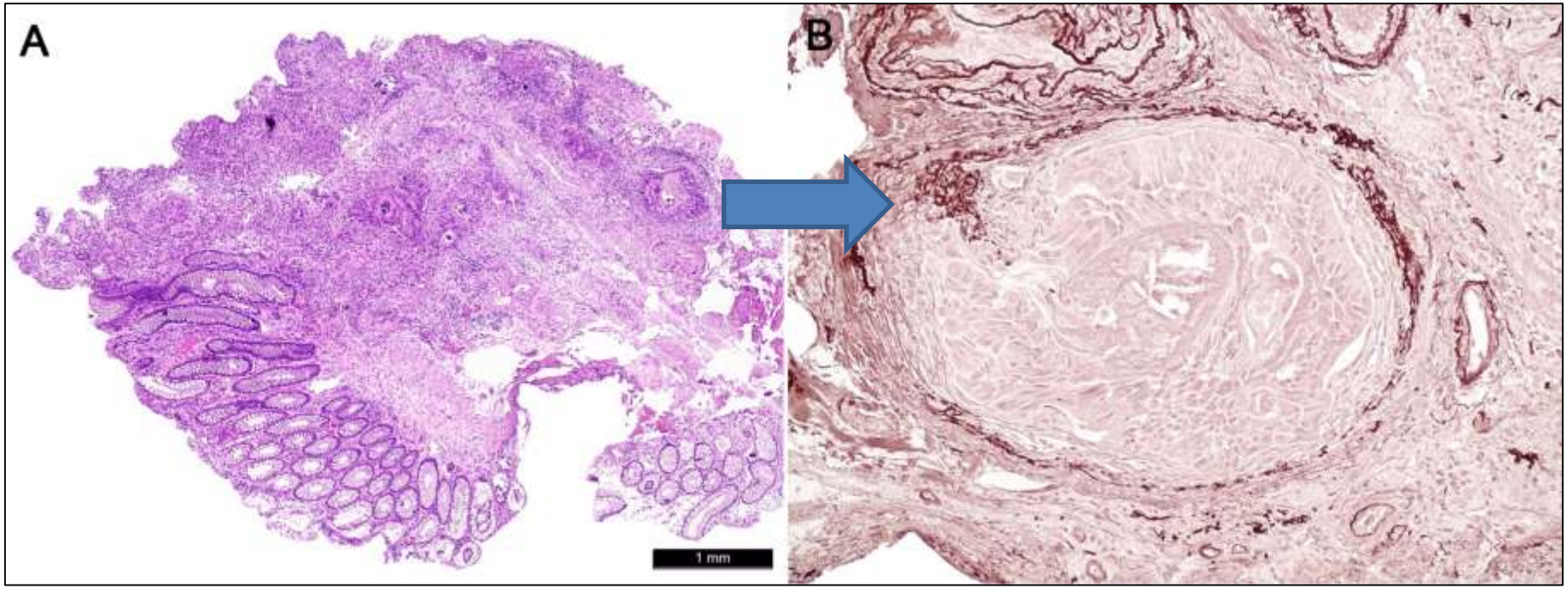
Orcein stain – excellent for venous invasion detection










A
B
1 mm

3) Vascular invasion

Too high!

	Residual disease	Metastasis	Mortality
% (average)	**18%**	**35%(LN)/5% (H)**	**3%**
Odds ratio - Hassan	**1**	**7/2****	**1.5**
%/Odds ratio - Ueno		**31%/3 (multivariate)**	

Hassan et al Dis Colon Rectum 2005;48:1588-96
Ueno et al Gastroenterology 2004;127:385-94

- usually associated with another adverse prognostic factor
- Vascular invasion does not add to risk when other adverse factors are already present
- Interobserver agreement is poor/moderate – 37-77%

4) Tumour budding

- Identified as a significant prognostic factor in several papers
  - Ueno et al Gastroenterology 2004;127:385-94
  - Tateishi et al Mod Path 2010;1:1-5
  - Sohn et al J Clin Pathol 2007;60:912-15
  - Katajima et al J Gastroenterol 2004;39:534-43
  - Yasuda et al Dis Colon Rectum 2007;50:1370-76
  - Choi et al Dis Colon Rectum 2009; 52: 438-445
  - Kawachi et al Mod Path 2015***
- Uniform definition lacking – range from any budding to strict definitions

Tumour budding

- Japanese criteria
  - Budding/sprouting was counted in a field measuring 0.95mm^2 using a 20 × objective lens and 10 × ocular lens and classified as grade 1 (0–4 foci in the field), grade 2 (5–9 foci), or grade 3 (≥10 foci)
  - Only grade 2/3 is significant “high grade”
  - Kawachi et al = no cases with high grade budding metastasized if invasive ca was <1mm deep
- US criteria
  - ≥ 10 buds = “high grade”

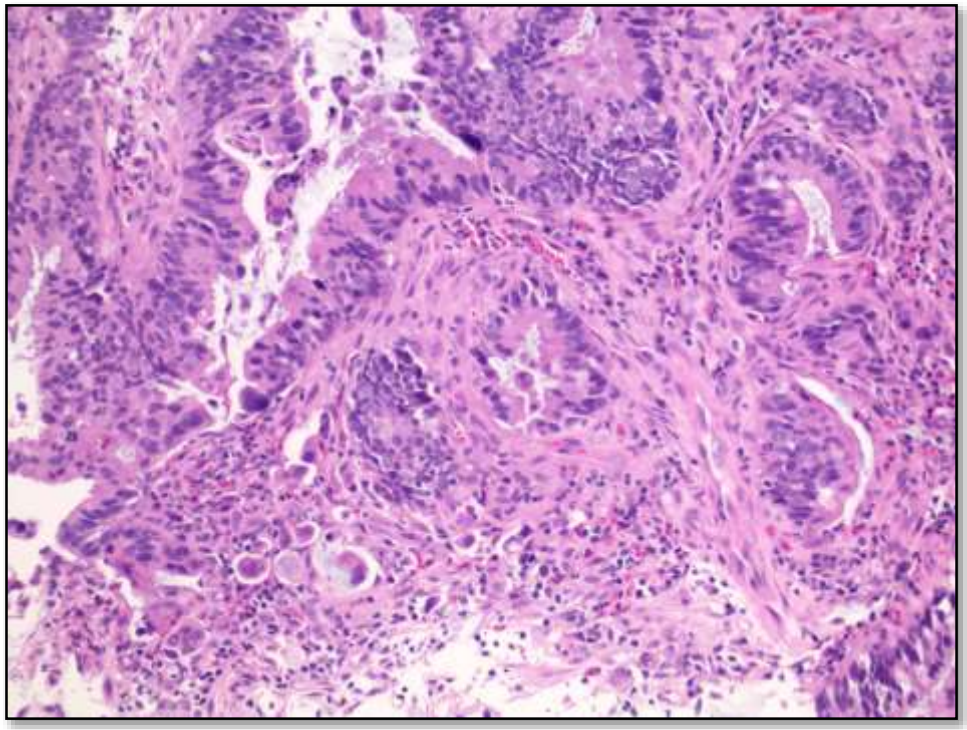
Tumour budding

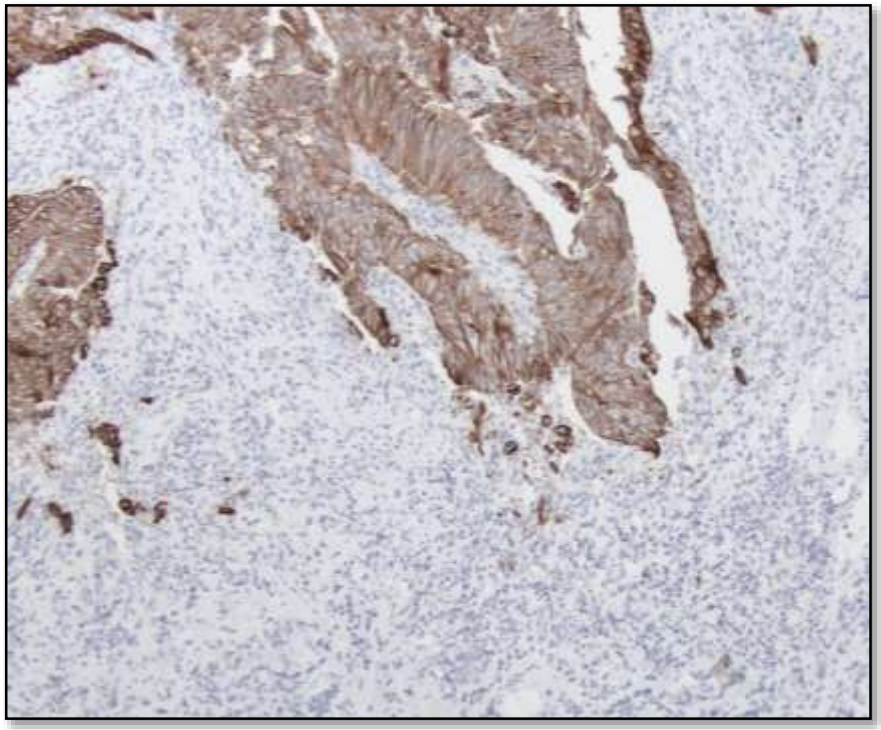
Problems:

1) Reproducibility

- Apparently high (AJSP 2015)
- But lots more buds if you use keratin

2) Field area of 0.95mm^2 = diameter 1.1mm so polyps <1mm are not reliably assessed and in the polyps reliably assessed it is probably not helpful to prognostication





4) Tumour budding

- Present in ~ 20-30% - however, bias to resection specimens in all studies (Envoi 29% - any)
- Risk
  - Kawachi – Odds ratio 3.14
- Prognostic relevance in malignant polyps treated only by endoscopy is still **not** established
- Perhaps tumour budding and poorly differentiated clusters should be merged into “high grade”

5) Polyp morphology

- Pedunculated vs sessile
- Sessile polyps have overall mortality 8 x that of pedunculated polyps
- Reason why sessile is worse = increased adverse factors are usually present:
    - poor differentiation
    - vascular invasion
    - **positive resection margin****

5) Polyp morphology

- Overall increased risk for sessile polyps

- Risk for sessile polyp Vs pedunculated polyp – pooled analysis*

	Residual/recurrent disease	Metastasis	Mortality
% (average) - S	**11%/6%**	**10%(LN)/4% (H)**	**5%**
% (average) - P	**3%/0.5%**	**10%(LN)/1% (H)**	**0.5%**
Odds ratio - Hassan	**4**	**1/4**	**10**

Hassan et al Dis Colon Rectum 2005;48:1588-96
*approximation (multivariate)

? not an *independent* risk for LN metastasis
However, most (85%) of sessile polyps had surgery

5) Polyp morphology

- Kawachi paper
  - slight increased risk for sessile polyps
  - but 80% of their polyps were sessile
- Envoi – no difference
- Problem
  - what is sessile and what is pedunculated?
    - Japanese series – 80% sessile
    - Western meta-analysis – 35% sessile
  - Pedunculated = presence of definite stalk

6) Rectal location

- Rectal location, in particular, the distal 1/3 of rectum is an adverse factor for:
  1. LN metastases (up to 1/3)
  2. Recurrent/Residual disease (5-28%)

Haggitt et al Gastroenterology 1985;89:328-36
Nascimbeni R et al Dis Colon Rectum 2002;45:200–206
Nivatvongs S. Surg Clin N Am 2002;82:959–966
Butte et al Dis Colon Rectum 2012;55:122-127

- Reason is not clear from the literature
- Problem = surgery is ULAR or APR

6) Others

- Cribriform pattern – adverse in Ueno paper
- Lymphatic density – Kaneko et al Dis Colon Rectum 2006;50:1-9
- Various IHC markers – Matrix metalloproteinase expression, p53, p27 Misaki et al Hirano et al
- Carcinomatous destruction of muscularis mucosae vs retained muscularis mucosae Tateishi et al Mod Path 2010;1:1-5
  - LN met rate
    - destroyed – 16%
    - preserved - 2%
- Polypoid carcinoma

Pathological risk assessment

Risk factors are additive

Ueno et al Gastroenterology 2004;127:385-94

Adverse Qualitative

1. Poor differentiation
2. Vascular invasion (L or V)
3. Tumour budding

(NOT margin involvement)

Nº Factors	LN met risk
0	0.7%*
1	20.7%
≥2	36.4%

* 7% micrometastasis rate

Adverse Quantitive

1. Width ≥ 4mm
2. Depth ≥ 2mm
3. Haggitt level 3/4

Adverse Quantitive

+

Adverse Qualitative

= did not change the LN metastasis risk

Risk factors are additive

Envoi data

Numbers of risk factors	Ueno's 3 risk factors	p value	Poor differentiation, cribriform pattern and invasive depth >2mm	p value	Poor differentiation, cribriform pattern and invasive width >4mm	p value
None	3/149 (2.0%)	0.016	0/97 (0%)	<0.0001	1/91 (1.1%)	<0.0001
1	4/49 (8.2%)		5/112 (4.5%)		3/116 (2.6%)	
2 or 3	5/41 (12.2%)		7/30 (23.3%)		8/32 (25.0%)	

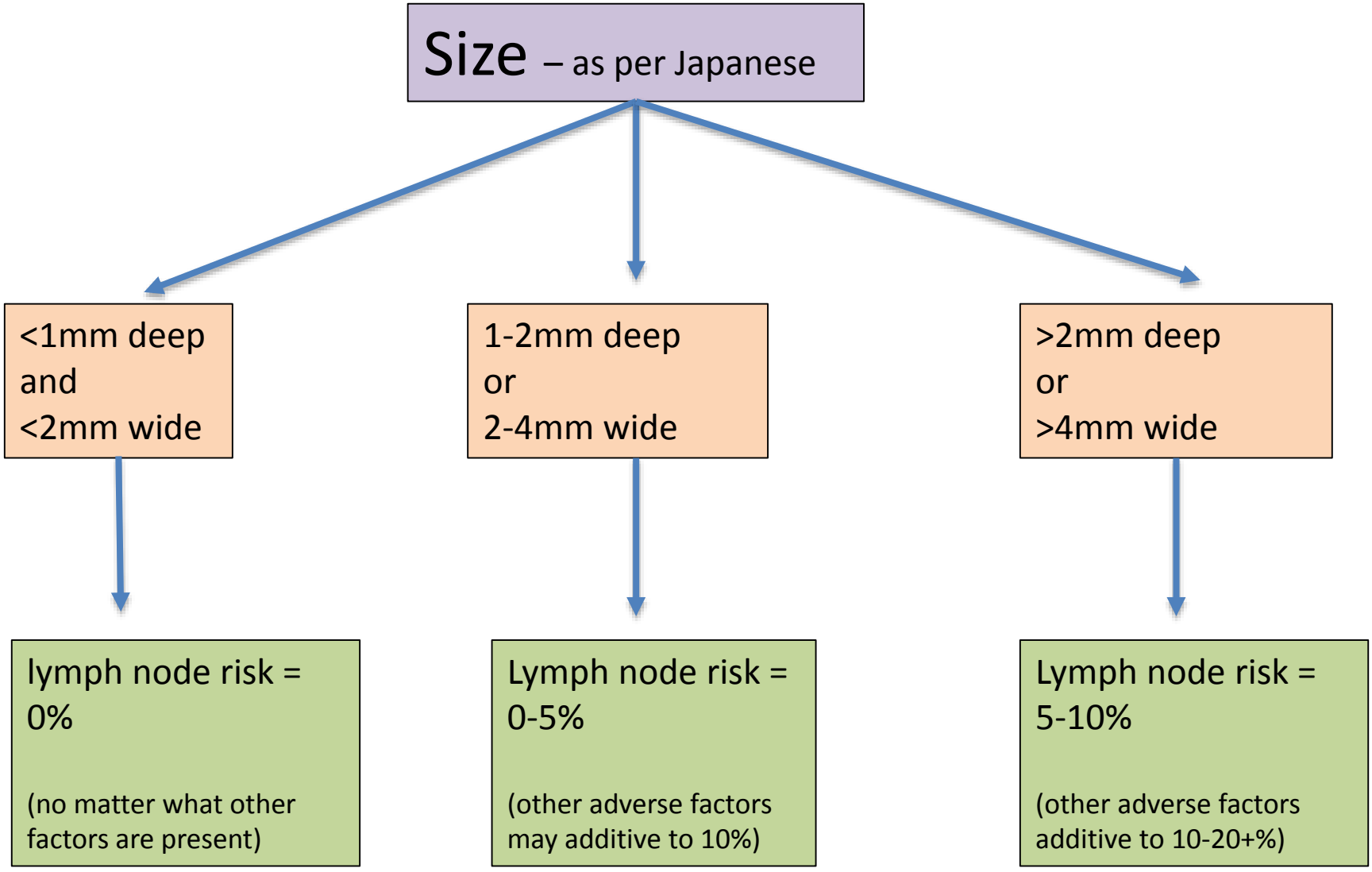
Risk factors are not equal

Table 2 Multivariate analysis of the six parameters for lymph node metastasis using a logistic regression model

Histologic parameters	*Odds ratio*	*(95% confidence interval)*	*P-value*
Depth of submucosal invasion ≥ 1000 μm	5.56	(2.14–19.10)	< 0.0001
High-grade budding/ sprouting (grade 2 or 3)	3.14	(1.91–5.21)	< 0.0001
High histologic grade	1.88	(0.63–5.09)	0.25
Positive lymphatic invasion	1.53	(0.94–2.50)	0.09
Nonpedunculated type	1.49	(0.64–4.11)	0.37
Positive venous invasion	1.08	(0.67–1.74)	0.75

Kawachi et al Mod Path 2015

How should we approach the MCP?



Adverse factor risk: Poor differentiation > tumour budding > LVI > rectal site
Margin involvement = 10-15% risk of residual adenoma or adenocarcinoma at polypectomy site
The haematogenous metastasis rate is <1-2% (with adverse risk factors)

Piecemeal specimen

- Measure size of largest piece of invasive adenocarcinoma
  - If >2mm deep and >4mm wide then adverse
  - Other factors add to the risk
  - If <1mm deep and <2mm wide and only in one piece → no risk
- Margin status requires endoscopic determination

Pathology report

Site

Size (as per Japanese)

- Depth of invasion (mm)
- Width of invasion (mm)
- Haggitt ± Kikuchi/Kudo level (optional)

Differentiation/grade (based on least differentiated area)

Tumour budding (high level)

Lymphatic invasion

Venous invasion

Margin status

- Clearance (carcinoma to margin - deep/circumferential):

Mismatch repair IHC:

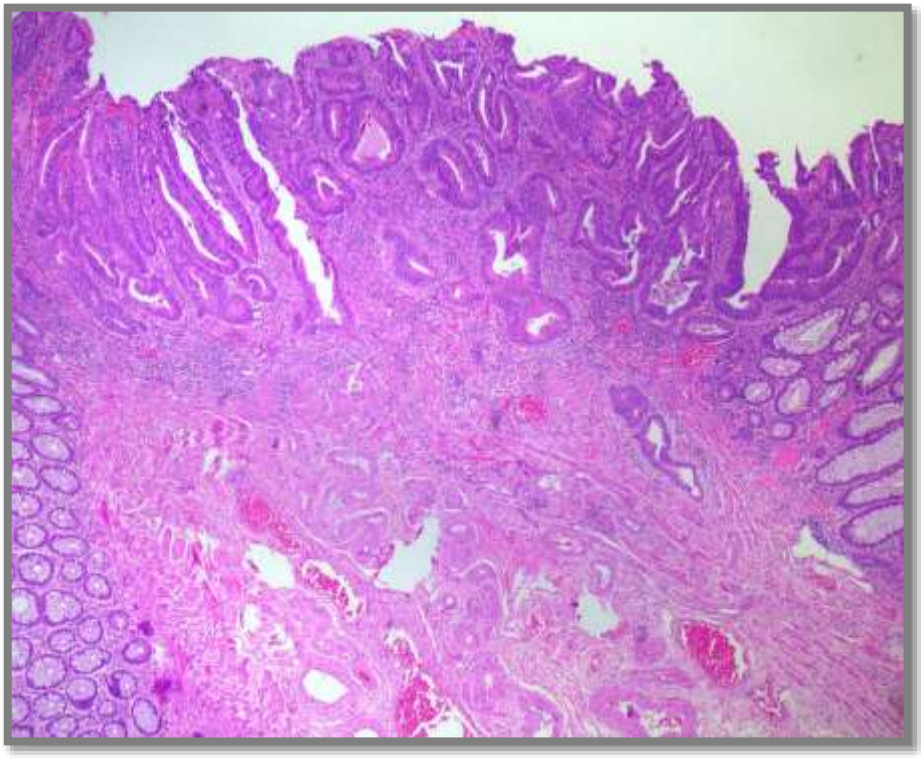
Adjacent adenoma type (if present):

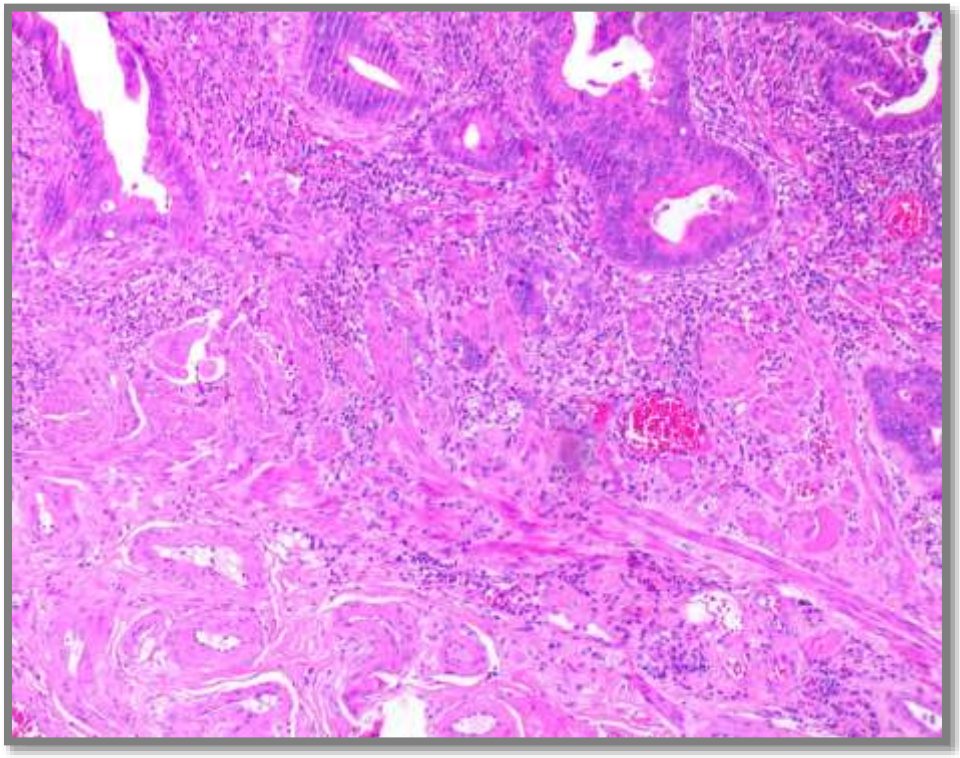
Comment …..

‘Intramucosal’ adenocarcinoma

- Tis in TNM
- Vienna classification (Japan/Europe)
- Just high grade dysplasia (HGD) in USA

- Increasingly encountering invasive adenocarcinoma with extension into a thickened reduplicated muscularis mucosae but not through this layer
- HGD does not seem appropriate but ?any metastatic risk





Pseudoinvasion

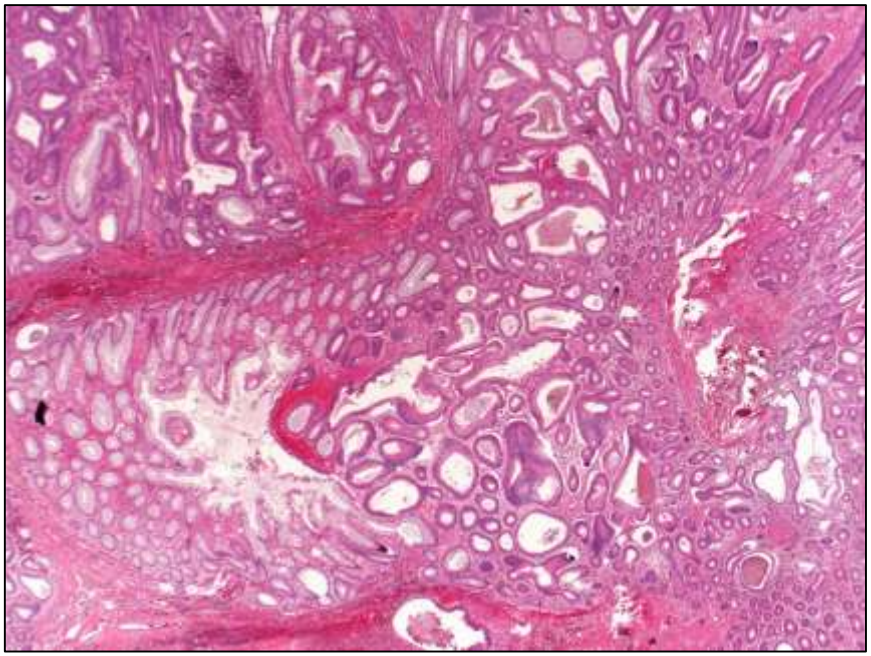
- 2-10% pedunculated polyps
- Left colon (sigmoid)
- Prolapse of dysplastic mucosa into submucosa following polyp torsion
- Note: can be associated with true invasive carcinoma
- Distinction from invasive carcinoma
  1. Architecture
  2. Stromal change
  3. Cytology

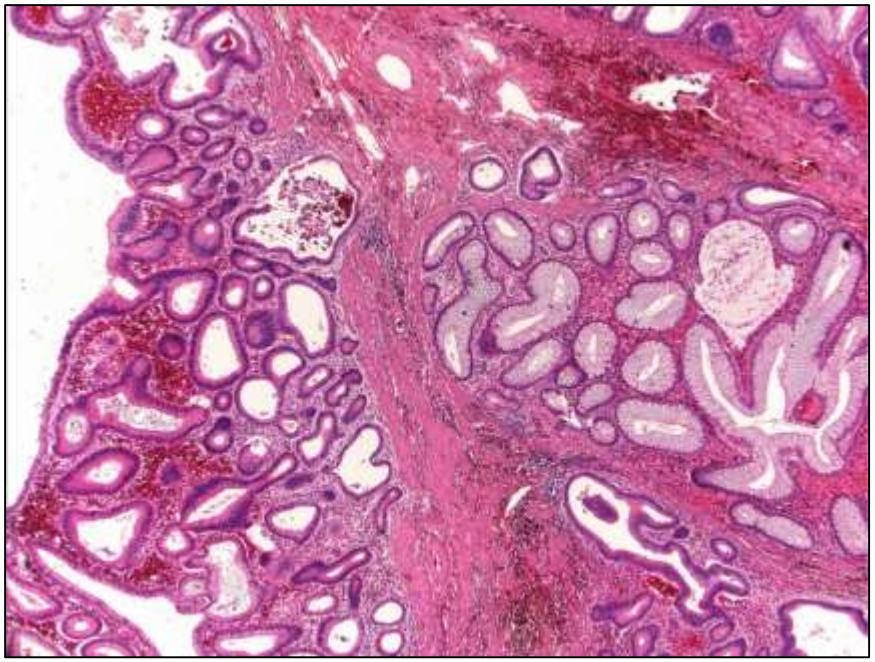
Pseudoinvasion - architecture

- Narrow gap in muscularis mucosae

  Tanazawa et al Pathology International. 2003;53: 584–590

- Rounded appearance to focus
- Rounded appearance of glands within focus

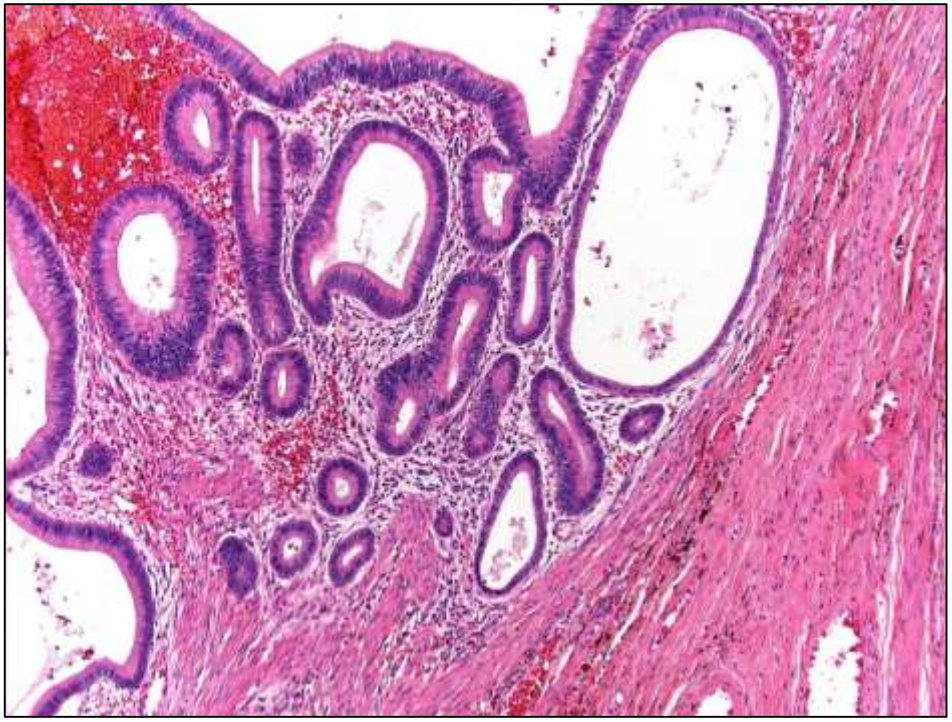


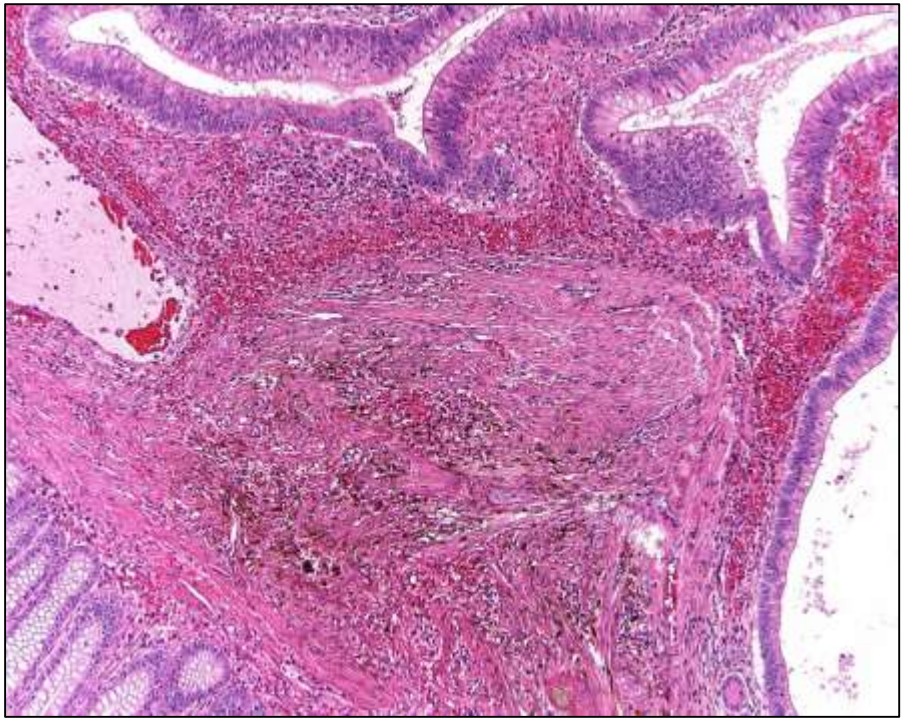


Pseudoinvasion - stroma

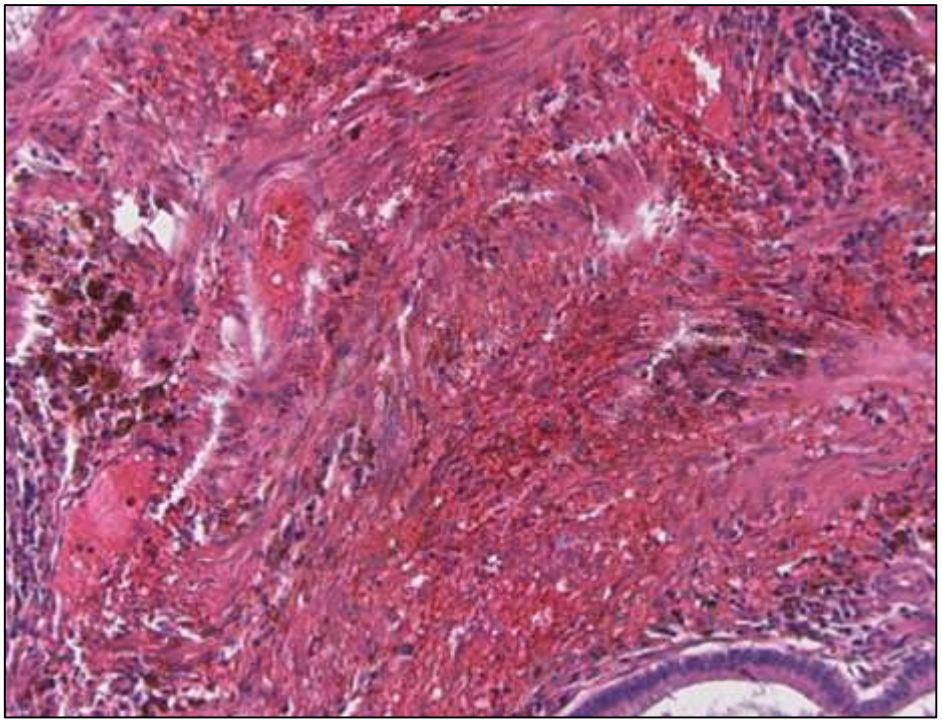
- Lamina propria surrounds glands
- Dense fibrosis (not desmoplasia)
- Smooth muscle hypertrophy (and 'fibromuscular')
- Haemosiderin
- Chronic inflamation
- Extravasated mucin
  - No epithelium or epithelium at edge – not epithelium floating in mucin pools

Pseudoinvasion

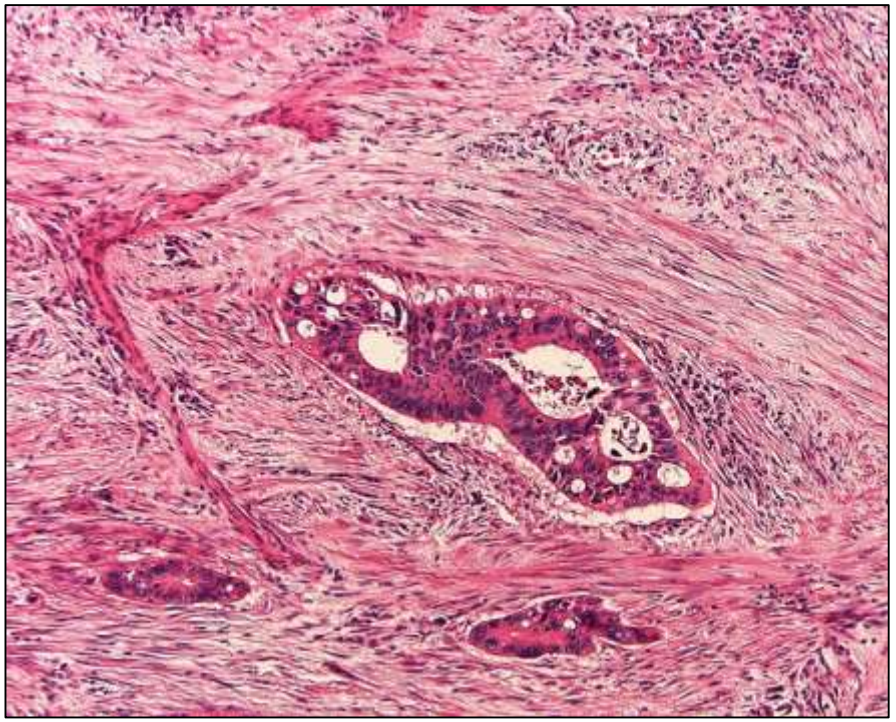


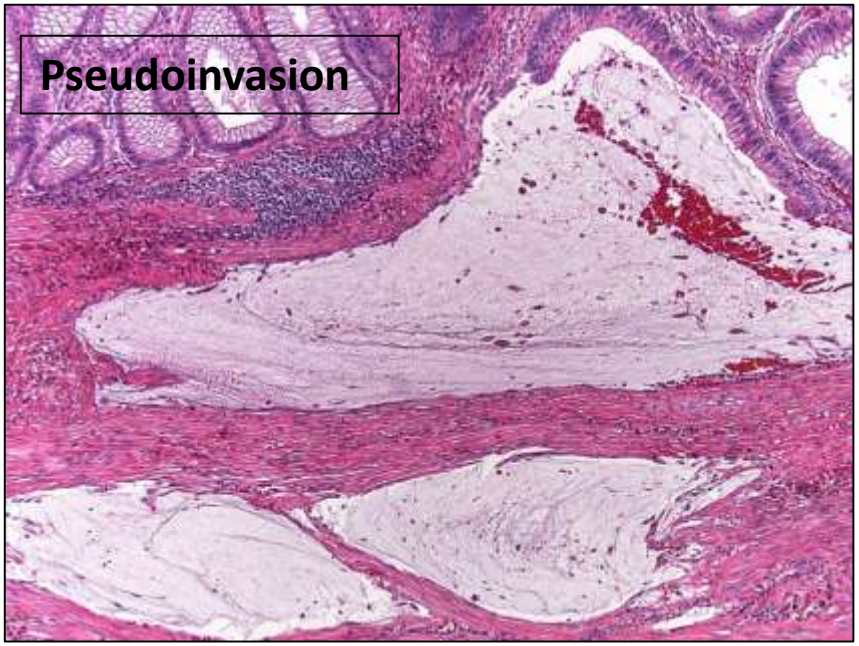


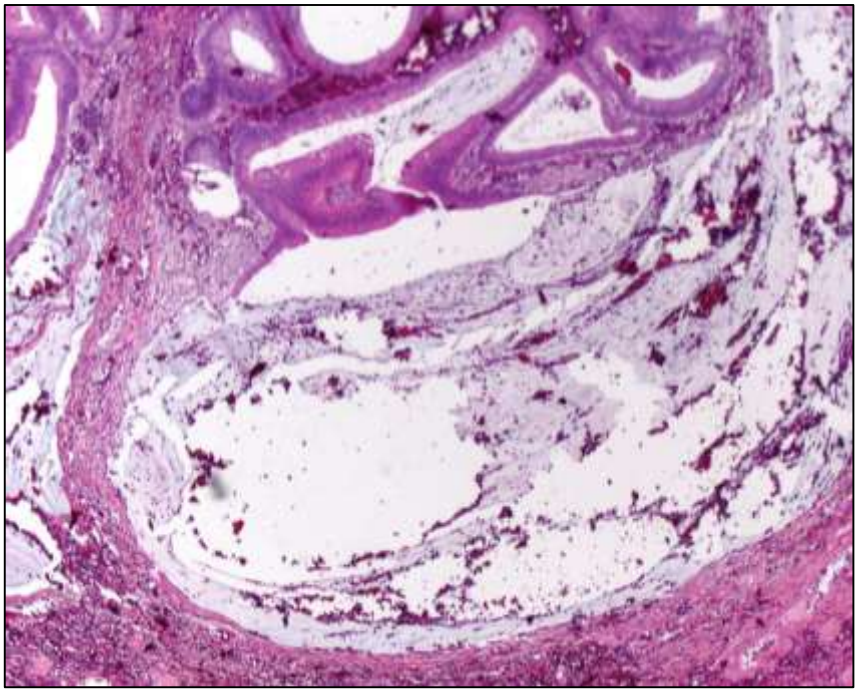
Pseudoinvasion



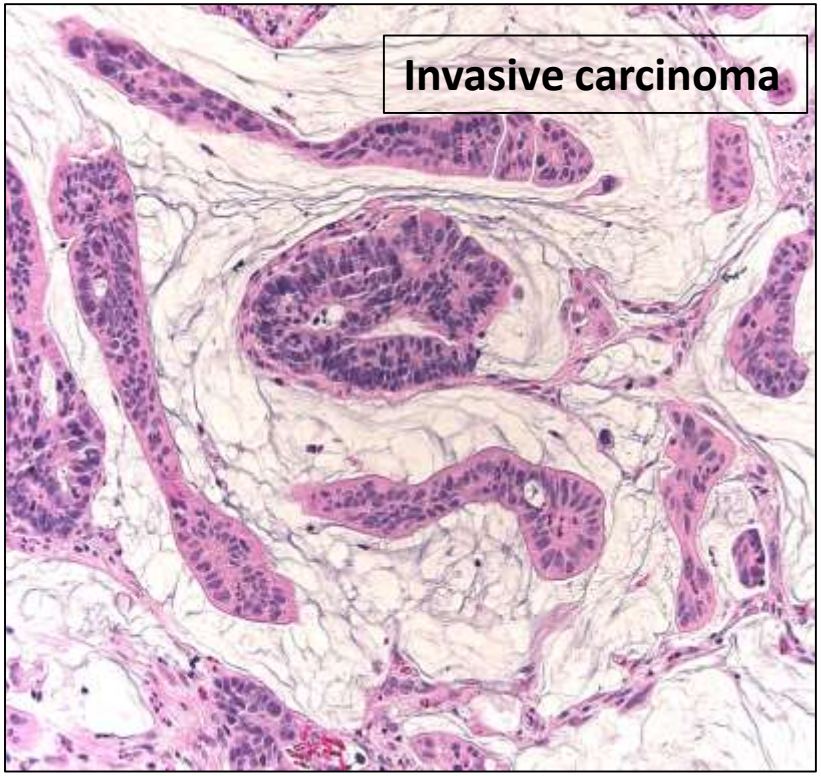
Invasive carcinoma





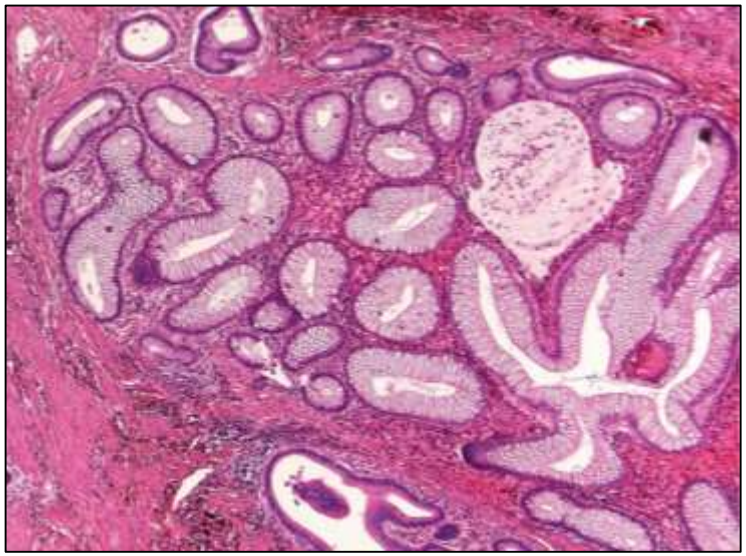


Vs



Pseudoinvasion - cytology

- Same as in overlying mucosa
- Pseudoinvasion of non dysplastic normal epithelium



- If it looks like invasive carcinoma – it probably is!

Pseudoinvasion - other

- p53 negative
- MMP-1 and Stromelysin-3 - negative

- Usually does not matter if we get it wrong since pseudoinvasive focus is clear of margin, vascular invasion negative and not poorly differentiated

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