Pathology of malignant colorectal polyps

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Gloucester & Cheltenham, UK

BSG/ACP Two-Day Liver & GI Pathology Symposium

Weetwood Hall, Leeds

Friday, 7th December 2012

A major influence on the workload of the GI pathologist……

NHS

Cancer Screening Programmes

Bowel Cancer Screening Programmes

In the UK, it's not just England's BCSP…..

NHS

Cancer Screening Programmes

Bowel Screening Wales

Sgrinio Coluddion Cymru

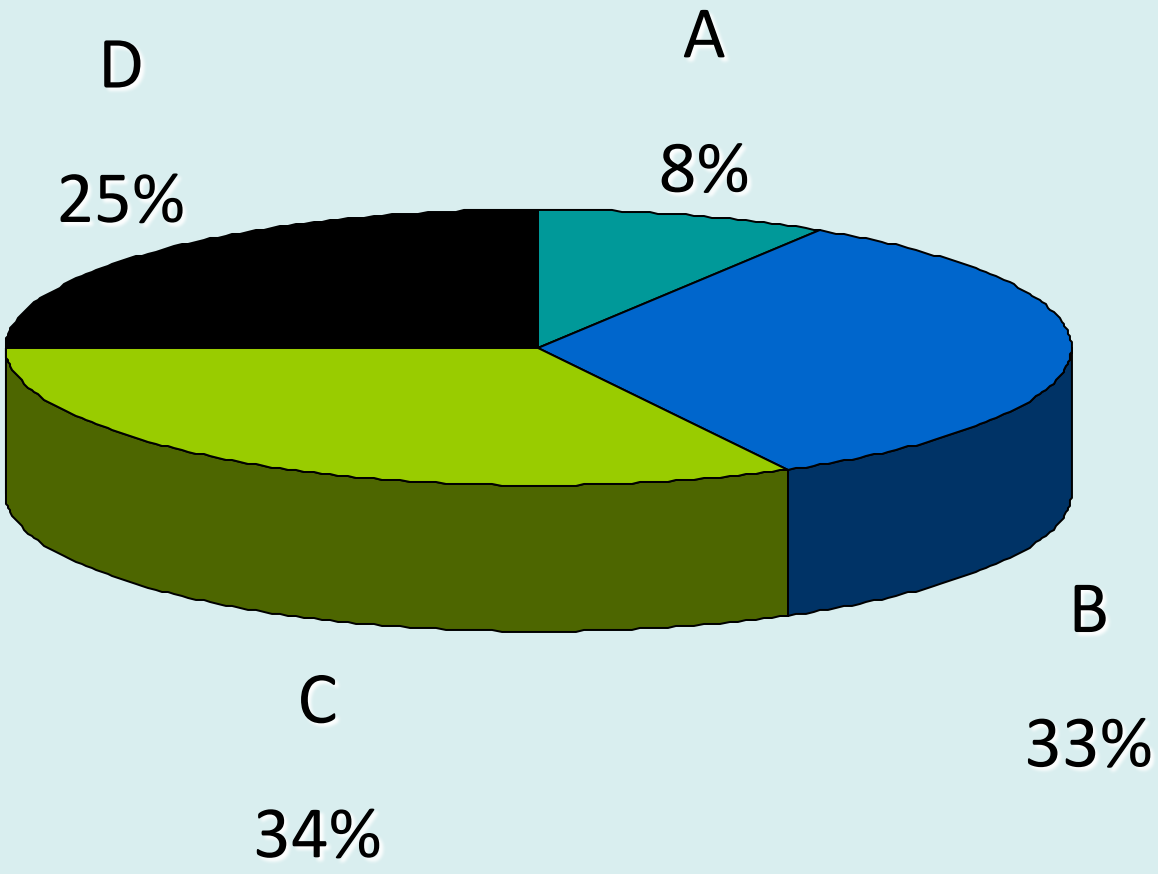
Bowel Screening:

Scottish Bowel Screening Programme

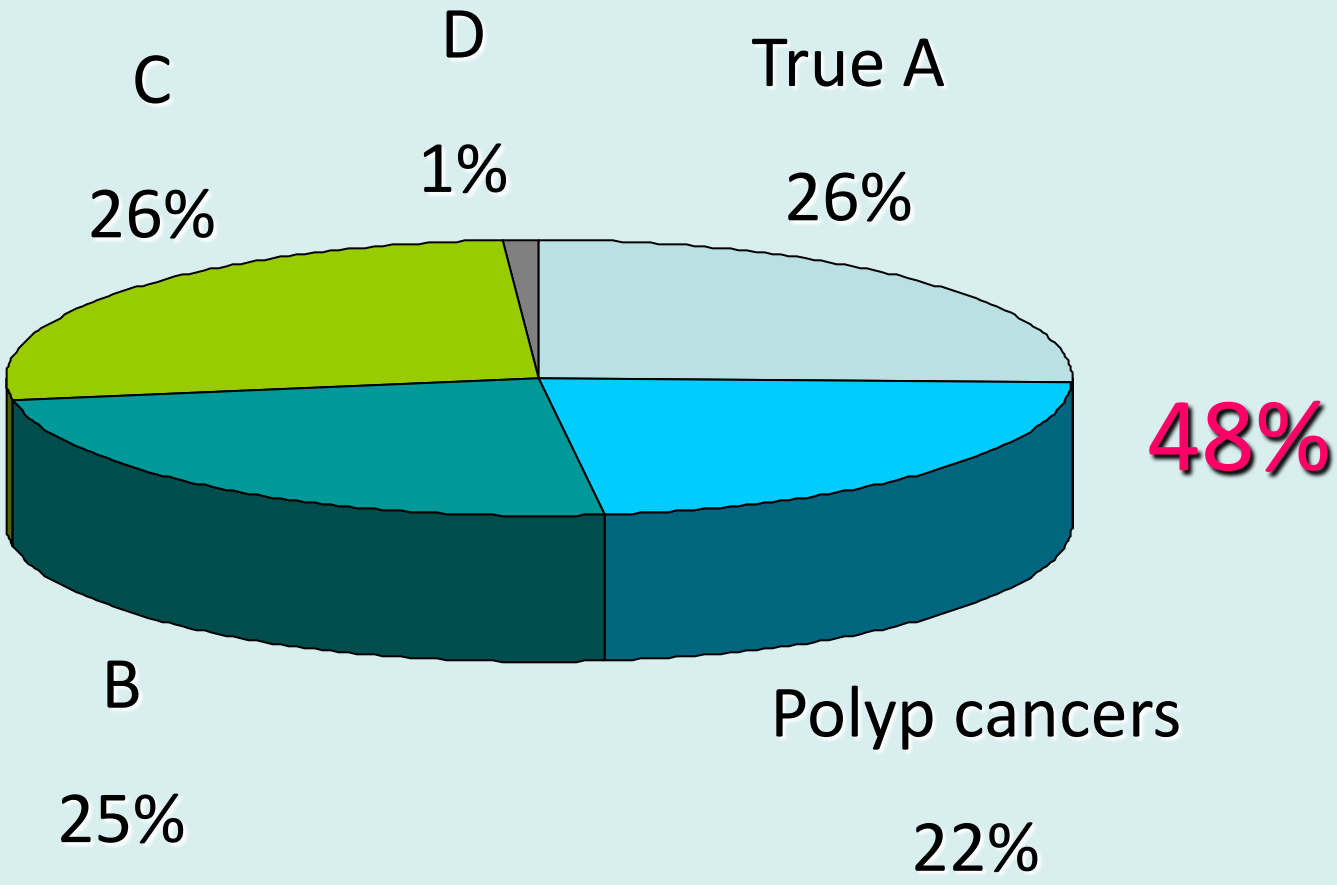
NICaN

Northern Ireland Cancer Network

Dukes stage distribution for symptomatic cancer



Dukes stage distribution for screen-detected cancers



pT1 cancers in BCSP

NORTH EAST SHA	8
NORTH WEST SHA	42
EAST MIDLANDS SHA	41
WEST MIDLANDS SHA	30
EAST OF ENGLAND SHA	32
YORKSHIRE & HUMBER SHA	31
LONDON SHA	23
SOUTH EAST COAST SHA	17
SOUTH CENTRAL SHA	17
SOUTH WEST SHA	40
TOTAL NUMBER CANCERS	1710
TOTAL NUMBER pT1	281
PERCENTAGE pT1	**16.4**

BCSP 10,000 cancers
1,700 pT1s
10-20 per year per Centre

The three big issues in BCSP pathology

- serrated pathology & what do we do about it – expected but not the amount nor the diagnostic difficulties
- polyp cancers (pT1 disease) & what we do about it – expected but not the management difficulties
- the large adenomatous polyp of the sigmoid colon – expected but not the amount nor the diagnostic difficulties

The three big issues in BCSP pathology

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The malignant polyp: pathological considerations

- is it really malignant?
- how common is this problem?
- when should we recommend resection after removal of a malignant polyp?

The malignant polyp: pathological considerations

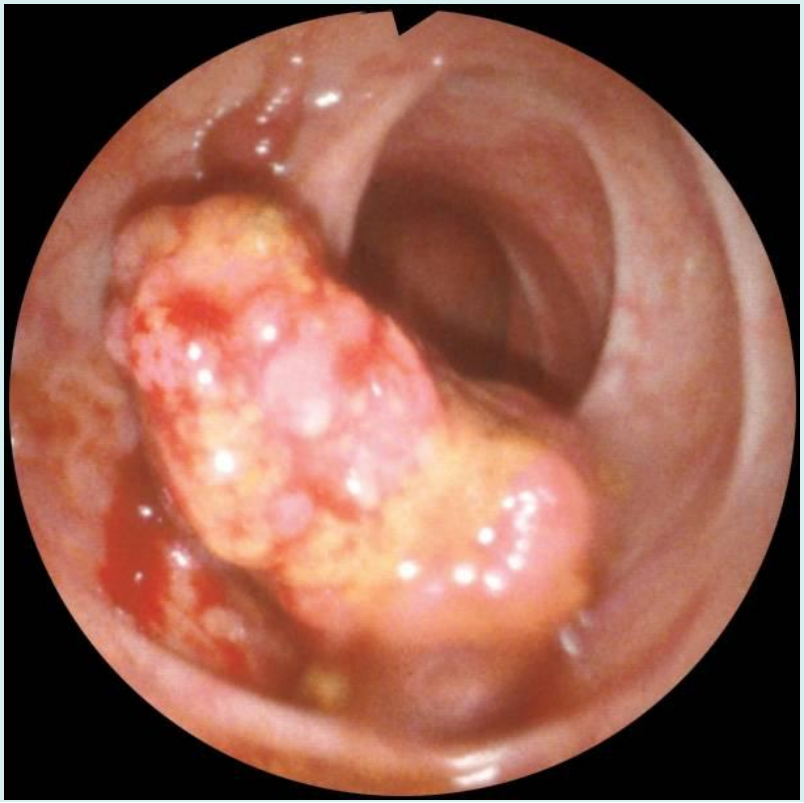
- is it really malignant?

  can the endoscopist tell?
  can the pathologist tell?

- how common is this problem?

- when should we recommend resection after removal of a malignant polyp?

The polyp harbouring malignancy….



The malignant polyp: pathological considerations

- is it really malignant?

  can the endoscopist tell?

  can the pathologist tell?

- BCSP QA experience

- BCSP pT1 polyp cancer audit

- BCSP polyp cancer double reporting recommendation

The three big issues in BCSP pathology

- serrated pathology & what do we do about it – expected but not the amount nor the diagnostic difficulties
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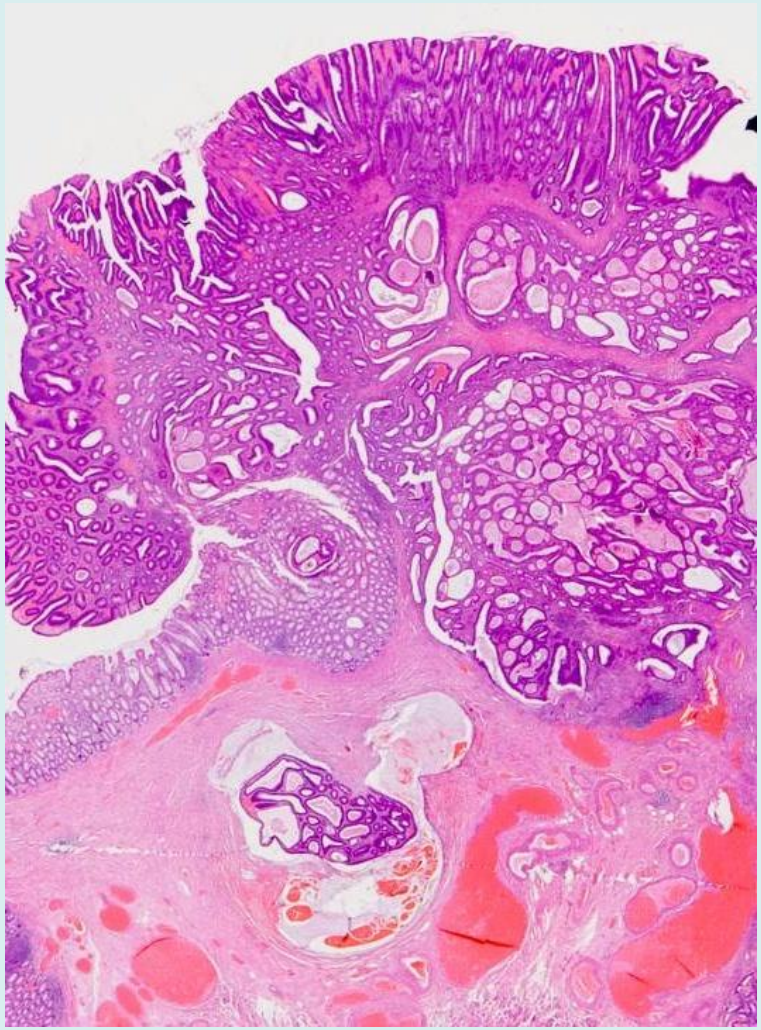
- the large adenomatous polyp of the sigmoid colon – expected but not the amount nor the diagnostic difficulties

The question

Is this cancer in the submucosa or is it the benign phenomenon of epithelial misplacement?

Epithelial misplacement in adenomas

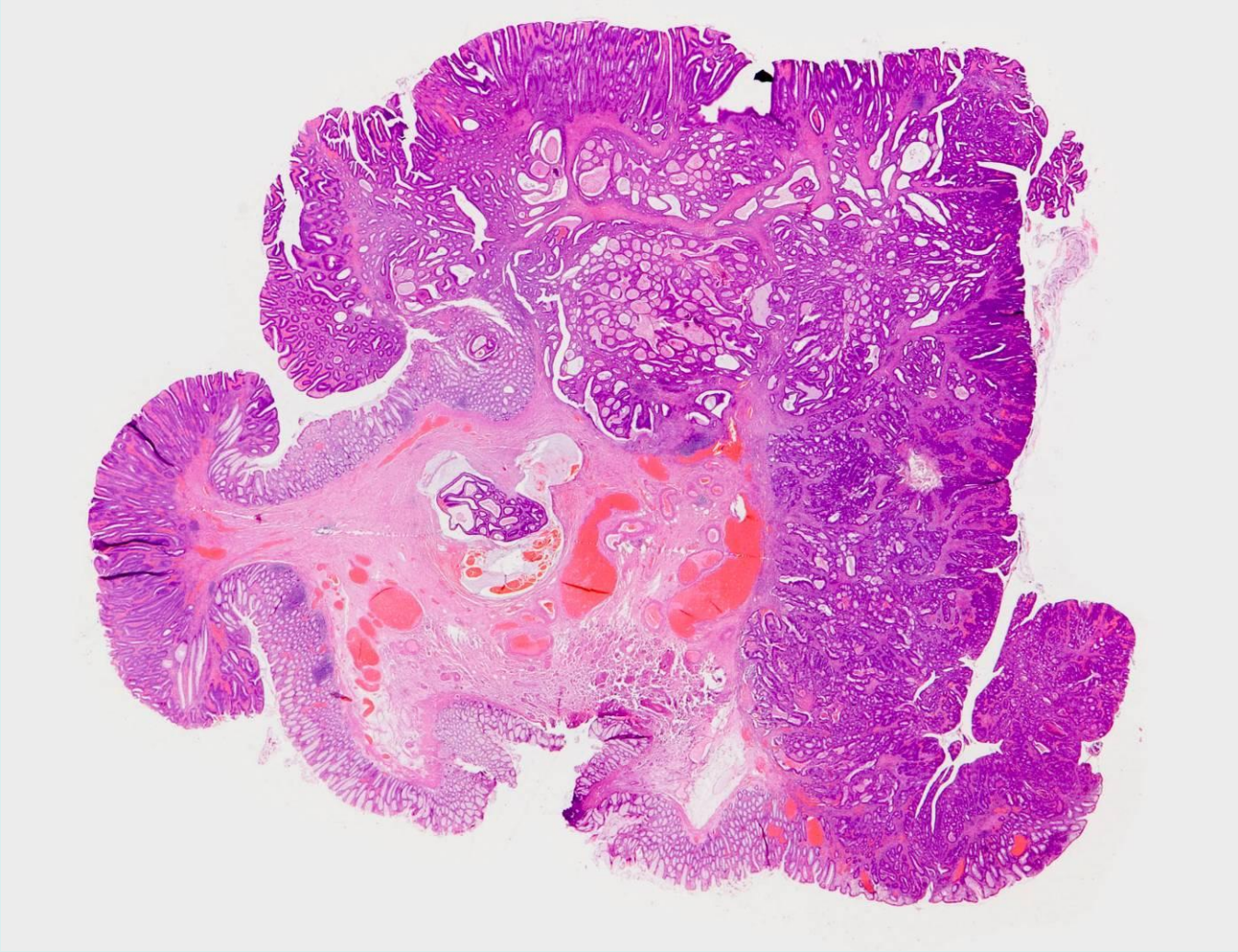
- 85% in sigmoid colon
- unusual in rectum (unless there has been previous meddling)
- same epithelium as surface, accompanied by lamina propria, haemosiderin deposition
- what about misplaced epithelium at the diathermy margin?
- intense pathological mimicry of invasive cancer



Epithelial misplacement vs invasive carcinoma

There is a very important adage in pathology:

why make two diagnoses when one will do?



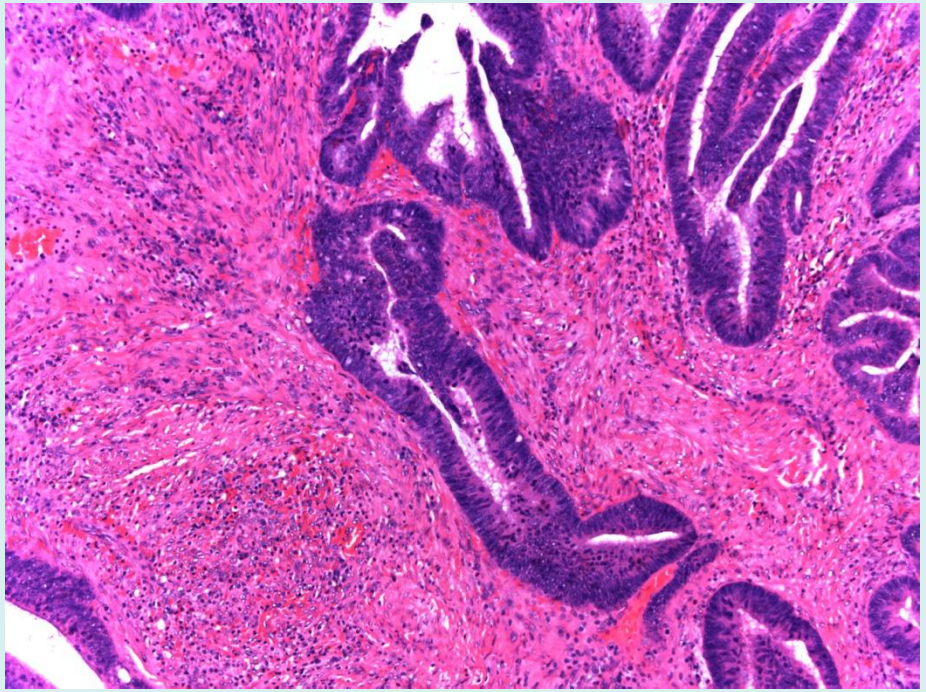
Differentiating epithelial misplacement from adenocarcinoma

- 87% in SC. Elsewhere if previous instrumentation/surgery. DC & other parts occasionally
- rectum rare unless previous meddling

- isolated glands
- budding
- vascular invasion and/or poor differentiation

- lamina propria accompaniment
- haemosiderin
- mucus lakes

- continuity of epithelium
- similar cytology and architecture
- muscular proliferation and mucosal prolapse changes
- evidence of acute necrosis



Pathological conundra in BCSP

- epithelial misplacement mimicking cancer
- 85% in sigmoid colon
- selected into BSCP as these are large prolapsing adenomatous polyps that bleed
- can be very difficult and some almost impossible
- require ‘Expert Board’ and BCSP-funded research
- but some are more straight forward and yet may be miscalled by pathologists….

BCSP Expert Board

- three pathologists – you need a majority for this highly subjective and difficult assessment
- N A Shepherd, D S A Sanders & M R Novelli
- funded (IT, postage, secretarial support) in England by BCSP (thanks, Julietta)
- opportunity for education and research into difficult EM v Ca cases

Original pathologist(s)	Expert Board Pathologist A	Expert Board Pathologist B	Expert Board Pathologist C
Mixed	Cancer	Cancer	Cancer
Benign	Benign	Benign	Benign
Cancer	Cancer	Cancer	Cancer
Equivocal	Cancer	Cancer	Cancer
Cancer	Benign	Benign	Benign
Equivocal	Cancer	Cancer	Cancer
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Equivocal	Cancer	Benign	Cancer
Benign	Benign	Benign	Benign
Cancer	Benign	Equivocal	Equivocal
Cancer	Benign	Benign	Benign
Equivocal	Benign	Benign	Benign
Equivocal	Benign	Equivocal	Benign
Cancer	Benign	Equivocal	Suspicious

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Equivocal	Cancer	Cancer	Cancer
Equivocal	Cancer	Cancer	Cancer
Equivocal	Cancer	Benign	Cancer
Benign	Benign	Benign	Benign
Cancer	Benign	Equivocal	Equivocal
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Equivocal	Benign	Benign	Benign
Equivocal	Benign	Equivocal	Benign
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BCSP Expert Board

Cases referred to Expert Board	177
Complete agreement between originating pathologist & EB	56
Original diagnosis equivocal but EB diagnosis certain	71
Diametrically opposite diagnosis: originating pathologist & EB	39
Both epithelial misplacement and cancer	7
Too difficult for EB (little or no agreement)	4

Epithelial misplacement vs carcinoma: a seedbed for research

- an almost unique phenomenon where pathologists get it badly wrong and experts can't agree as to whether it's cancer or not.....
- what to do?
- immunohistochemistry?

  Yantiss RK, Bosenberg MW, Antonioli DA, Odze RD. Utility of MMP-1, p53, e-cadherin and collagen IV immunohistochemical stains in the differential diagnosis of adenomas with misplaced epithelium versus adenomas with invasive adenocarcinoma. Am J Surg Pathol 2002; 26: 206-215.
- 3D reconstruction?
- clever spectroscopic analysis?
- optical coherence tomography analysis?

Epithelial misplacement vs carcinoma

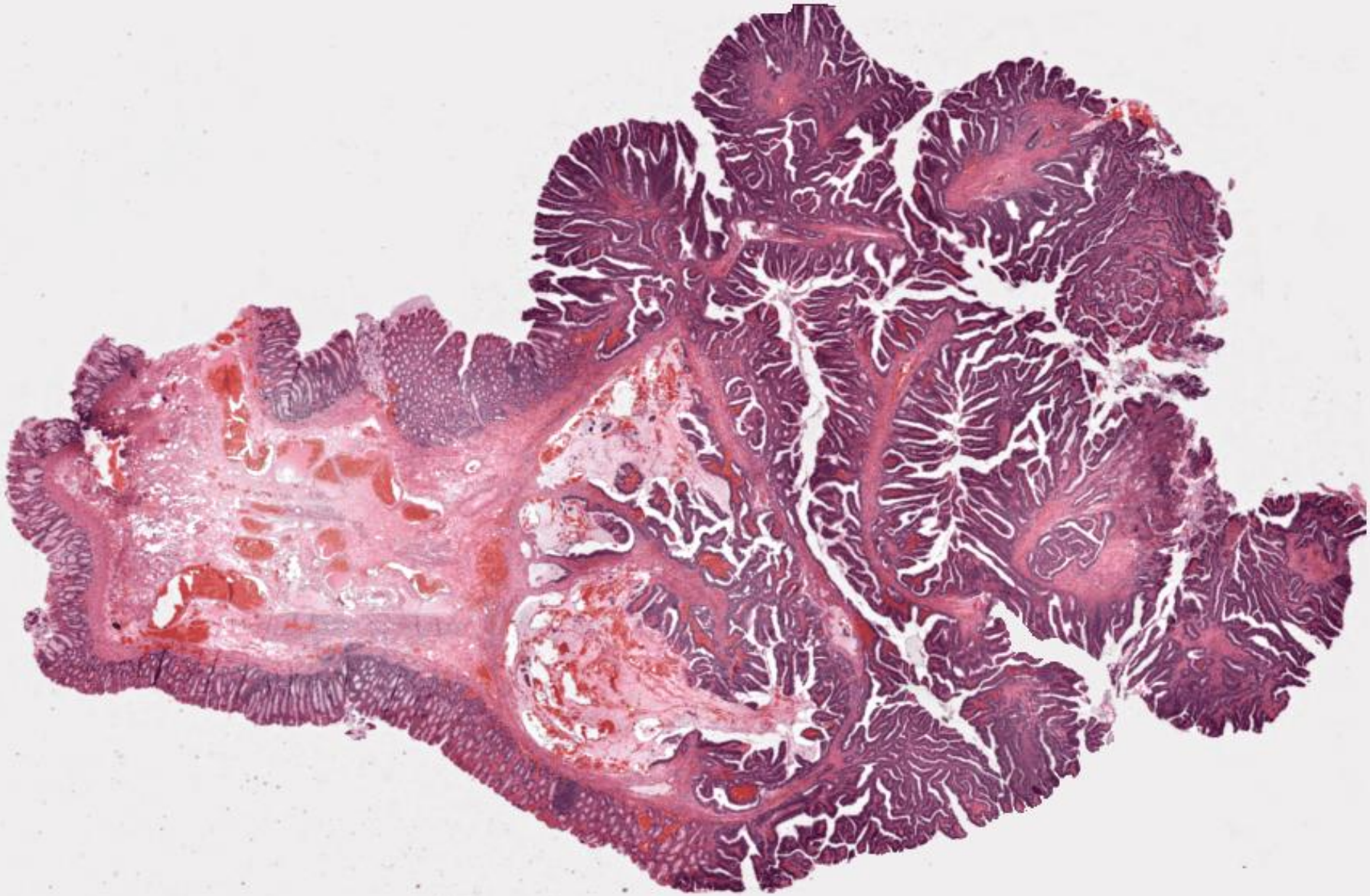
- immunohistochemistry
- 3D reconstruction
- infra-red spectroscopic analysis

Carey D, Kendall C, Stone N, Barr H, Shepherd NA.
Biophotonics Research Unit, Gloucestershire Royal Hospital, Gloucester, UK

With huge thanks to Phil Quirke, Darren Trainor and their colleagues

Epithelial misplacement

Epithelial misplacement



Epithelial misplacement vs carcinoma

- immunohistochemistry
- 3D reconstruction
- infra-red spectroscopic analysis

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Epithelial misplacement in sigmoid colonic polyps: a major conundrum in BCSP

- epithelial misplacement mimicking cancer: 85% in sigmoid colon
- selected into BSCP as these are large prolapsing adenomatous polyps that bleed – detected by FOB screening
- can be very difficult and some almost impossible, a phenomenon not really seen before in UK GI pathology
- require 'Expert Board' and BCSP-funded research
- a major source of diagnostic error, especially detected through rigid QA procedures – will it be as prevalent or as problematic in FIT screening?
- why has this phenomenon not been seen in other screening programmes?

The malignant polyp: pathological considerations

- is it really malignant?
- how common is this problem?
- when should we recommend resection after removal of a malignant polyp?

Polyp cancers: what is the size of the problem?

- adenocarcinoma found in 2.6 - 9.7% (mean 4.7%) of removed adenomatous polyps
- 1-2 per year per DGH in UK (they say!)

Haboubi NY, Scott NA.
Colorectal Disease 2000; 2: 2-7.

- In Gloucestershire, 10-20 per year

The malignant polyp: pathological considerations

- is it really malignant?
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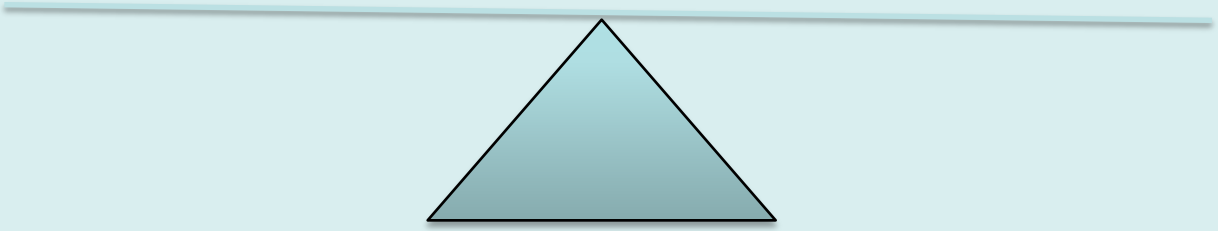
Management of polyp cancers

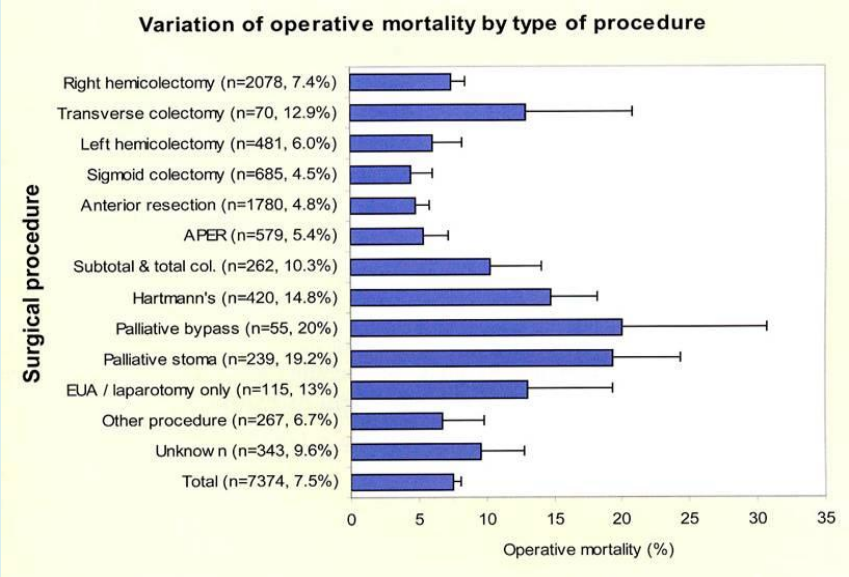
Resection **No resection**

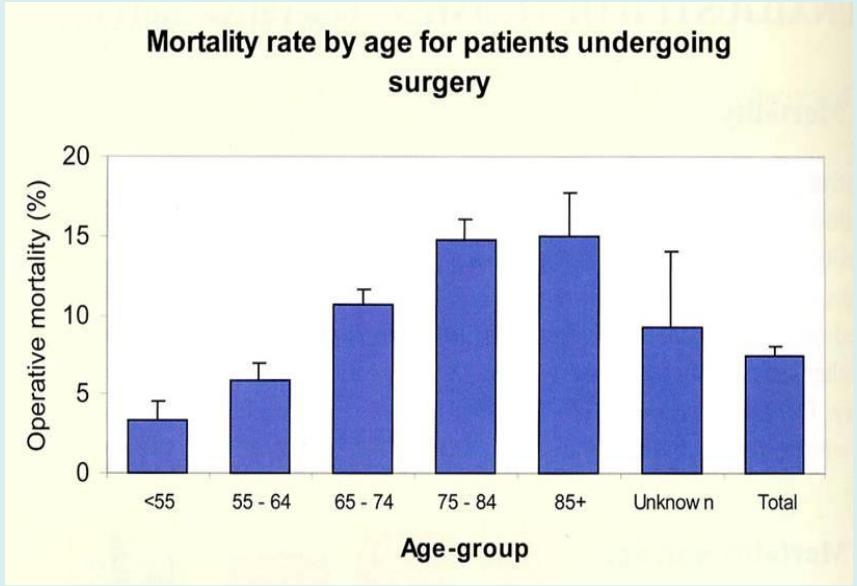


- reduce recurrence risk
  - risk of positive lymph nodes
  - sub stage pT1
  - site rectum > colon
- complications of surgery
  - mortality: surgical team, age, co-morbidity, country
  - morbidity
- quality of life
  - colostomy, anterior resection syndrome

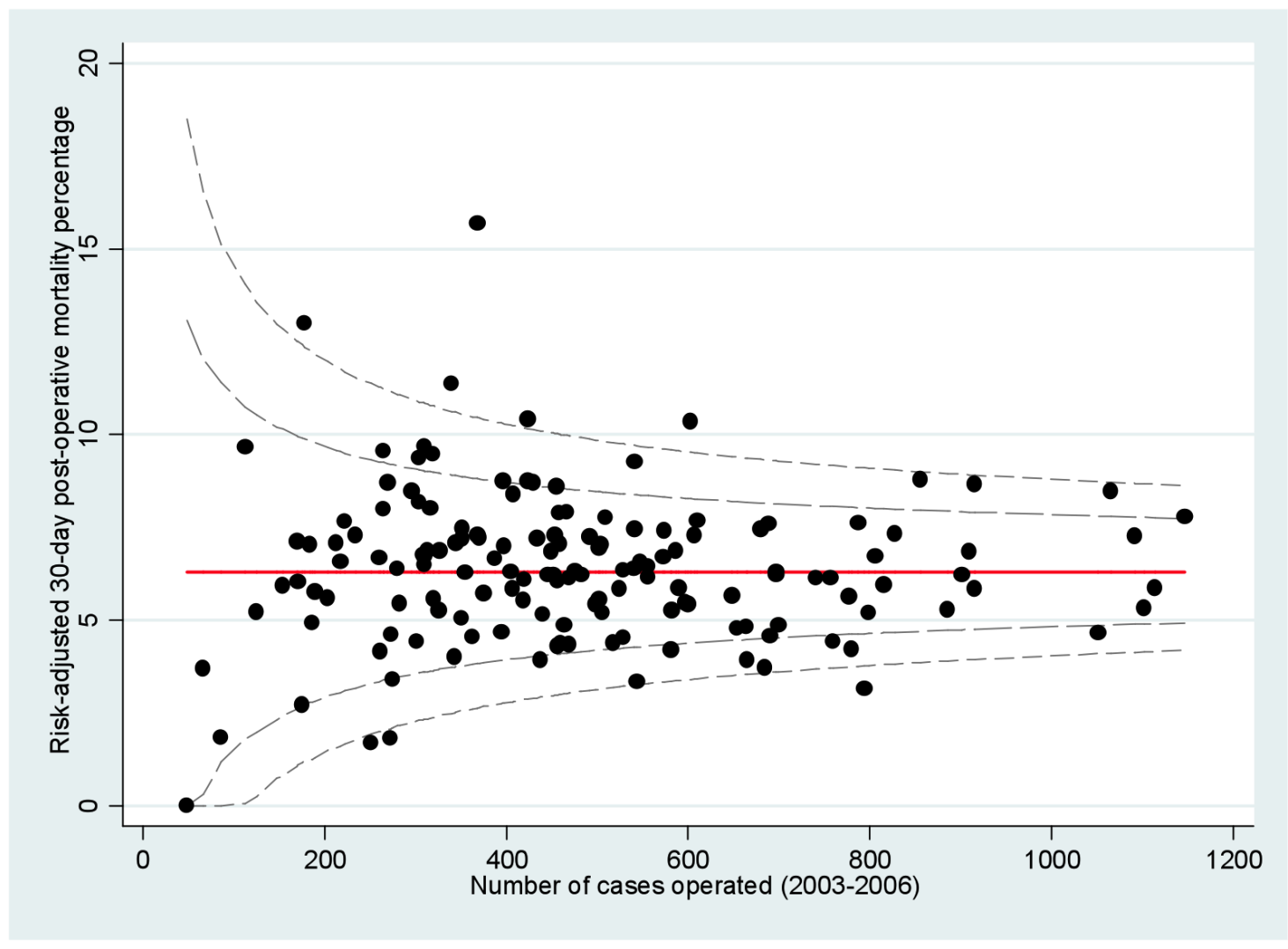
Carcinoma in polyps

MDTM assessment of the risk of LN metastasis against the risk of surgery





30 day post-operative mortality per UK centre adjusted for age, stage, deprivation etc…



Risk factors for adenomas undergoing malignant change

- size
- villosity
- high grade dysplasia
- site:

right colon	6.4%
left colon	8.0%
rectum	23.0%

Nusko G et al.
Int J Colorect Dis 1997; 12: 267-271.

The adenoma harbouring malignancy: the ‘big three’ criteria

- is it poorly differentiated?
- does it show vascular invasion?
- does it reach the margin? i.e. within 1 mm (or 2mms ?)

Cooper et al. Gastroenterology 1995; 108: 1657-65.

What do we do with the adenoma harbouring malignancy? The big three parameters

we can understand vascular invasion and poor differentiation

what about margin involvement?

many papers have attested (25 versus 5) that this is the most predictive parameter for ADVERSE PROGNOSIS, notwithstanding the lack of logic

Cooper et al, 1995;

Geraghty, Williams and Talbot, 1991

Table 2. Literature series of treatment indicators for early invasive colorectal cancers.

First author	Year	Number of tumours	Number of adverse outcomes	Features for adverse outcome
Colacchio	1981	24	6	None
Lipper	1983	51	2	Margin
Haggitt	1985	64	8	Level
Cranley	1986	38	10	Grade, margin, lymphatic invasion
Vanneste	1986	44	3	Grade, margin, vascular invasion, level
Richards	1987	80	10	Grade, margin, stalk invasion, vascular invasion
Coverlizza	1989	31	6	Margin, grade, vascular invasion
Kyzer	1992	44	3	Level
Minamoto	1993	40	6	Grade, level, lymphatic invasion, growth pattern, adenomatous component
Kikuchi	1995	182	21	Level, tumour configuration, location
Hase	1995	79	11	Tumour budding, growth pattern grade, level, lymphatic invasion
Cooper	1995	140	16	Margin, grade, vascular invasion
Volk	1995	47	10	Grade, margin
Whitlow	1997	59	4	Level, margin, grade
Netzer	1998	70	16	Margin, vascular invasion, grade
Ueno	2004	292	50	Margin, vascular invasion, grade, tumour budding, depth/width of submucosal invasion

Geboes K, Ectors N & Geboes KP, 2005

Diseases of the Colon & Rectum

Histologic Risk Factors and Clinical Outcome in Colorectal Malignant Polyp: A Pooled-Data Analysis

Cesare Hassan, M.D.,[1] Angelo Zullo, M.D.,[1] Mauro Risio, M.D.,[2]
Francesco P. Rossini, M.D.,[3] Sergio Morini, M.D.[1]

Dis Colon Rectum 2005; 48: 1588–1596

Gloucestershire Cellular Pathology Laboratory

Table 1.
Relationship Between Histologic Risk Factors and Clinical Outcomes

Risk Factor	Residual Disease	Recurrent Disease	Lymph Node Metastasis	Hematogenous Metastasis	Mortality
Margin of resection					
Positive	55/181 (30.4)[a]	13/77 (16.8)[a]	13/181 (7.2)	30/325 (9.2)[a]	26/325 (8)[a]
Negative	4/142 (2.8)	4/357 (1.12)	13/142 (9.2)	8/655 (1.2)	9/655 (1.4)
Odds ratio	15	17.9	0.8	8.2	6.2
95% CI	(5.3–42.7)	(5.7–56.7)	(0.3–1.7)	(3.7–18.2)	(2.9–13.5)
Poor differentiation					
Positive	10/56 (17.8%)	—	13/56 (23.2)[a]	11/14 (9.6)[a]	14/96 (14.6)[a]
Negative	29/324 (9%)	—	23/324 (7.1)	40/1,520 (2.6)	27/1,487 (1.8)
Odds ratio	2.2		3.9	3.9	9.2
95% CI	(1–4.8)		(1.9–8.4)	(2–7.9)	(4.7–18.3)
Vascular Invasion					
Positive	6/34 (17.6%)	—	12/34 (35.3)[a]	13/250 (5.2)	7/210 (3.3)
Negative	17/111 (15.3%)	—	8/111 (7.2)	38/1,279 (3)	28/1,194 (2.3)
Odds ratio	1.2		7	1.8	1.4
95% CI	(0.4–3.3)		(2.6–19.2)	(0.9–3.4)	(0.6–3.3)

CI = confidence interval.
Data are numbers with percentages in parentheses unless otherwise indicated.
[a]$P < 0.05$.

Vascular invasion in malignant polyps

significant predictor of metastasis

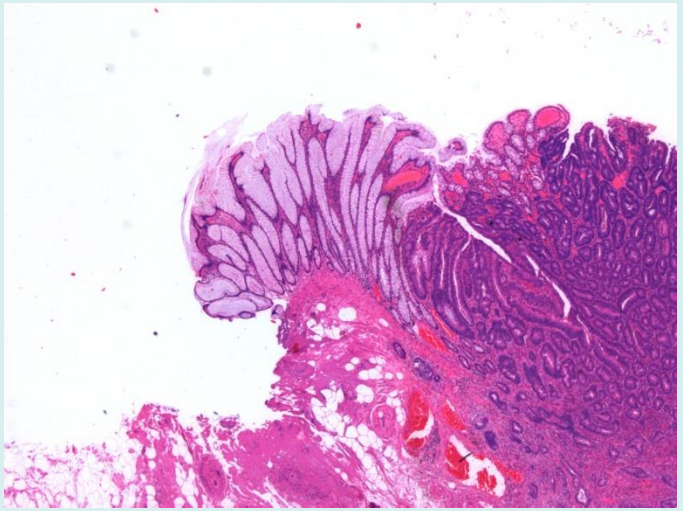
Muller et al. Gut 1989;30:1385-91

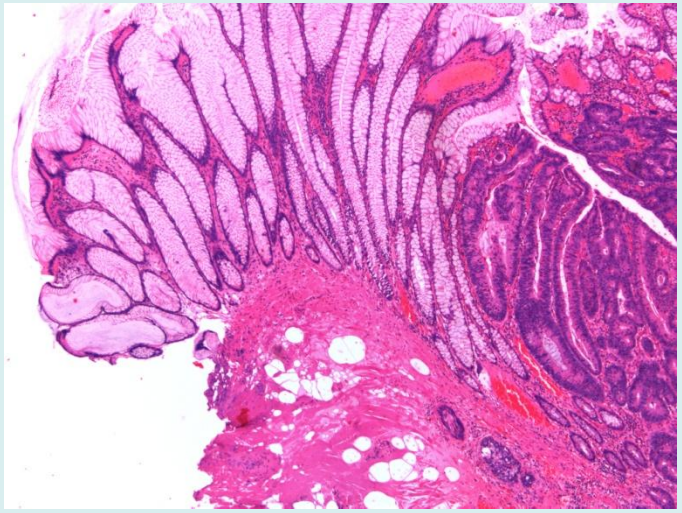
81 malignant polyps - 5 year follow up: no prognostic value

Geraghty, Williams & Talbot. Gut 1991;32:774-8

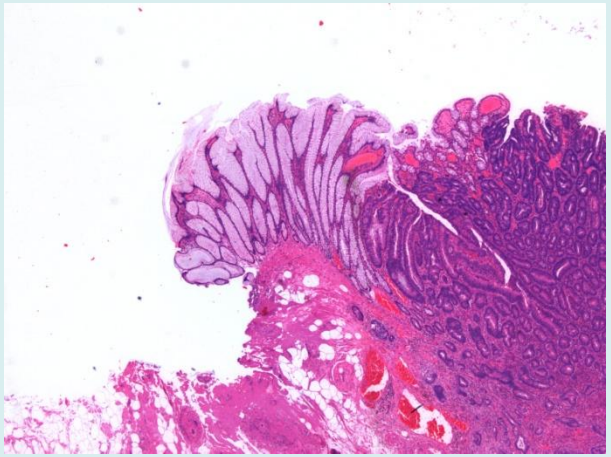
Margin involvement by cancer in malignant polyps

- commonest adverse prognostic parameter
- commonest isolated adverse prognostic parameter
- definition
- historically the single most important predictor of adverse prognosis but not, apparently, lymph node metastatic disease
- do we really believe that margin involvement should be an indicator for resection if it is not a good predictor of lymph node metastatic disease - in the current day practice of excellent polypectomy??

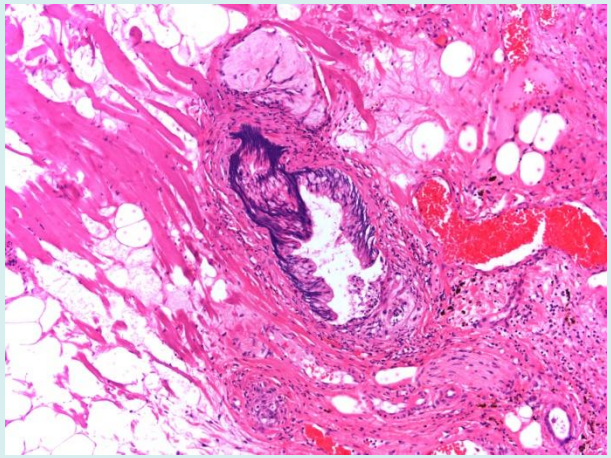


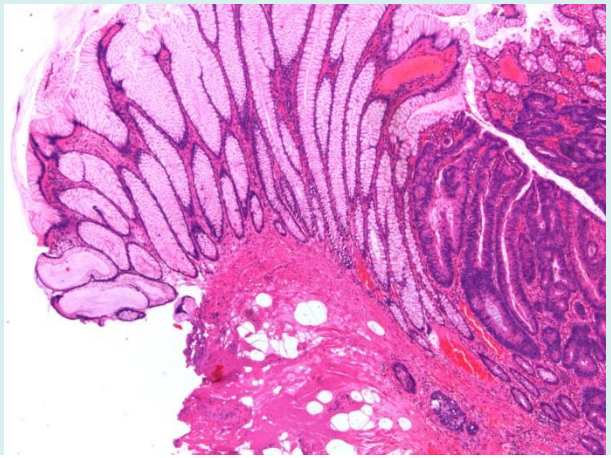


This week's case……..

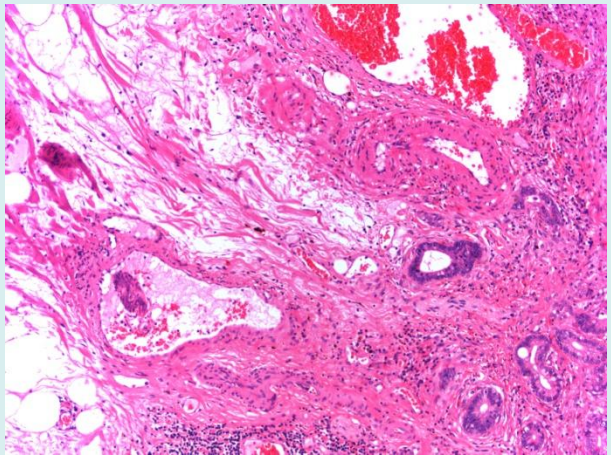


First level





Next level



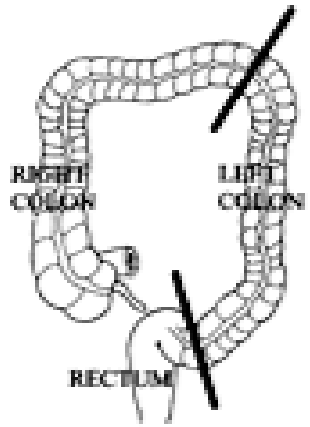
Selecting patients for resection

- a careful balance between risks of metastatic disease & risks of surgery
- happy about poorly differentiated and vascular invasion: difficulty is margin involvement……
- age and co-morbidity are important
- crucial MDTM discussion

Site is important for predicting lymph node metastatic disease in polyp/pT1 cancers

Lymph Node Metastasis in T1 Adenocarcinoma of the Colon and Rectum

Satoshi Okabe, M.D., Jinru Shia, M.D., Garrett Nash, M.D., W. Douglas Wong, M.D., José G. Guillem, M.D., M.P.H., Martin R. Weiser, M.D., Larissa Temple, M.D., Kenichi Sugibara, M.D., Philip B. Paty, M.D.



Location	TOKYO	NEW YORK	All Cases
Right Colon	1 /35 2.9%	2 /57 3.5%	3/92 3.0%*
Left Colon	3 /85 3.8%	10 /75 13%	13/160 8.0%**
Rectum	13/73 19%	14/103 14%	27/176 15%
Total	17/193 8.8%	26/235 11%	43/428 10%

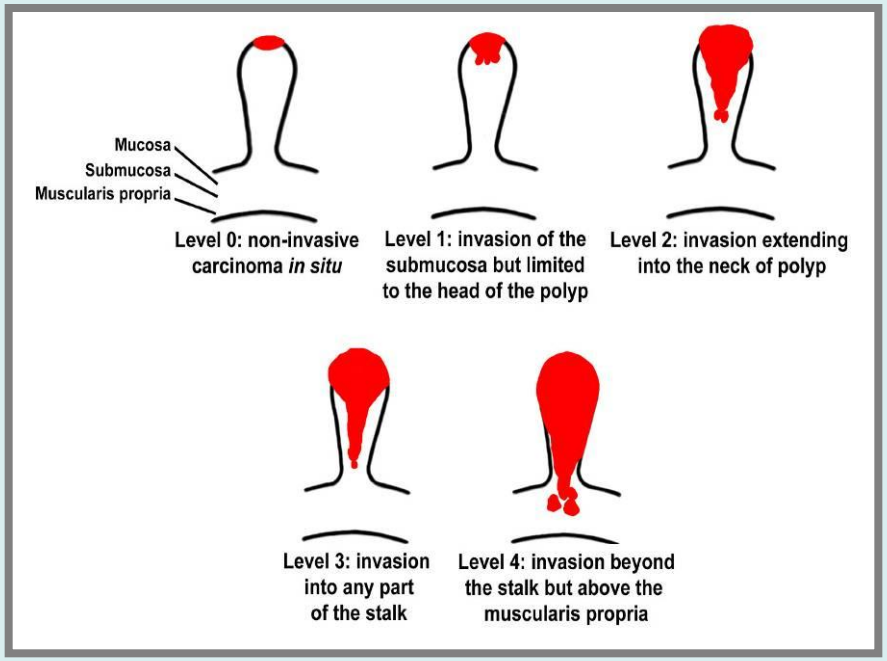
* P = .003 right colon versus rectum
** P = .04 left colon versus rectum

What are the high risk features?

- margin involvement
- poor differentiation
- lymphovascular invasion
- sm3 (Kikuchi)
- Haggitt 4
- sessile lesions: width > 30mm
- others
  - ? tumour budding
  - ? rectum
  - ? depth of spread

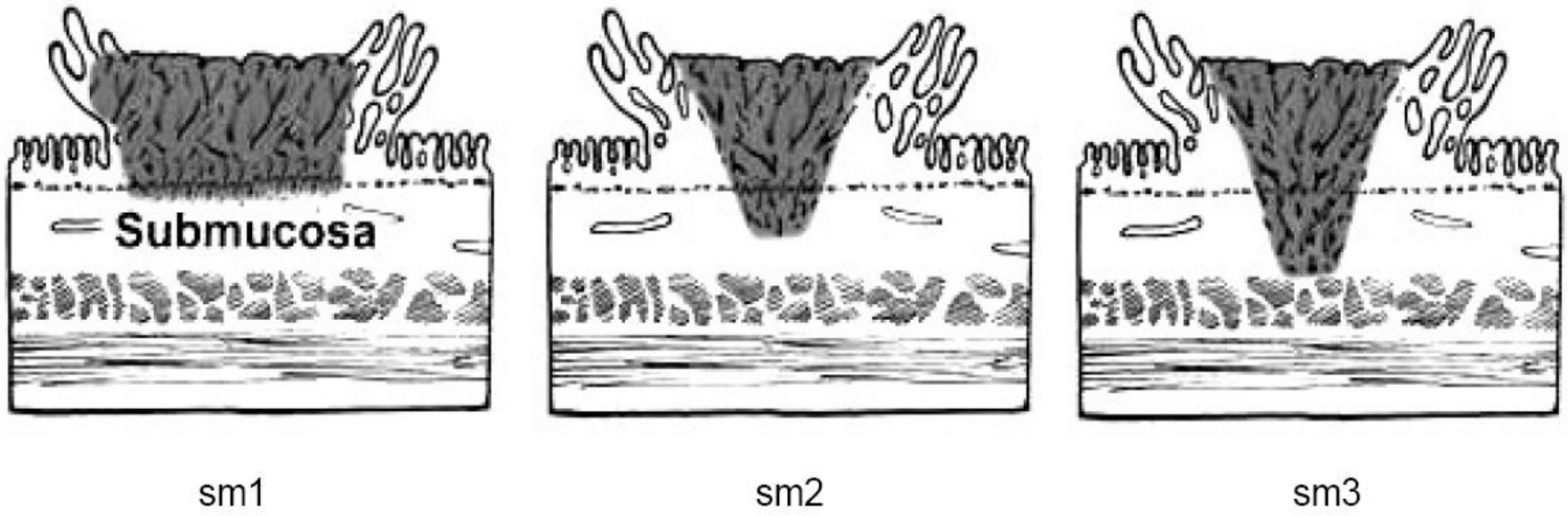
Classification of early colorectal cancer in polyps:

Haggitt et al, 1986



Kikuchi levels of submucosal infiltration

Kikuchi et al. Dis Colon Rectum 1995; 38: 1286-90.



risk of lymph node metastasis

sm1	sm2	sm3
0% (0/64)	5% (4/82)	22% (8/36)
0-4%	3-10%	10-25%

Measuring depth and width of invasion: Japanese methodology

Assessment of depth of invasion (*if completely excised*)

direct measurement from muscularis mucosae

depth > 2mm	20% node positive (vs. 5%)
width of invasive front > 4mm	20% node positive (vs 4%)

Ueno et al: Gastroenterology 2004; 127: 385-394.

Importance of depth of invasion

Cancer Science

The official journal of the Japanese Cancer Association

Risk of lymph node metastasis in patients with pedunculated type early invasive colorectal cancer: A retrospective multicenter study

Takahisa Matsuda,[1,11] Masakatsu Fukuzawa,[2] Toshio Uraoka,[3] Masataka Nishi,[2] Yuichiro Yamaguchi,[4] Nozomu Kobayashi,[5] Hiroaki Ikematsu,[6] Yutaka Saito,[1] Takeshi Nakajima,[1] Takahiro Fujii,[7] Yoshitaka Murakami,[8] Tadakazu Shimoda,[9] Ryoji Kushima[9] and Takahiro Fujimori[10]

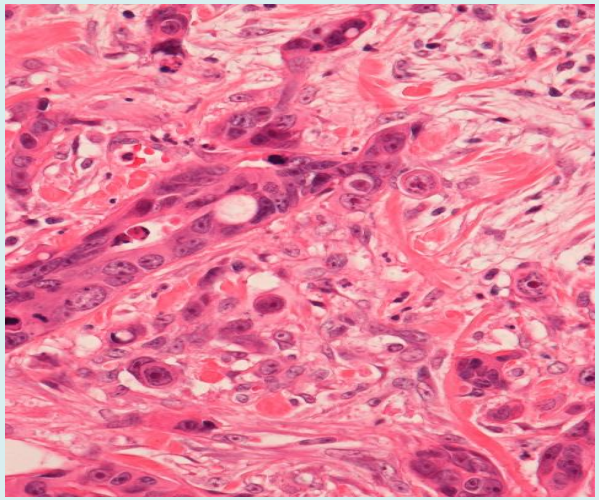
[1]Endoscopy Division, National Cancer Center Hospital, Tokyo; [2]Department of Gastroenterology and Hepatology, Tokyo Medical University Hospital, Tokyo; [3]Department of Endoscopy, Okayama University Hospital, Okayama; [4]Division of Endoscopy, Shizuoka Cancer Center, Shizuoka; [5]Department of Diagnostic Imaging, Tochigi Cancer Center, Tochigi; [6]Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa; [7]TF Clinic, Tokyo; [8]Department of Medical Statistics, Shiga University of Medical Science, Shiga; [9]Clinical Laboratory Division, National Cancer Center Hospital, Tokyo; [10]Department of Surgical and Molecular Pathology, Dokkyo University School of Medicine, Shimotsuga, Tochigi, Japan

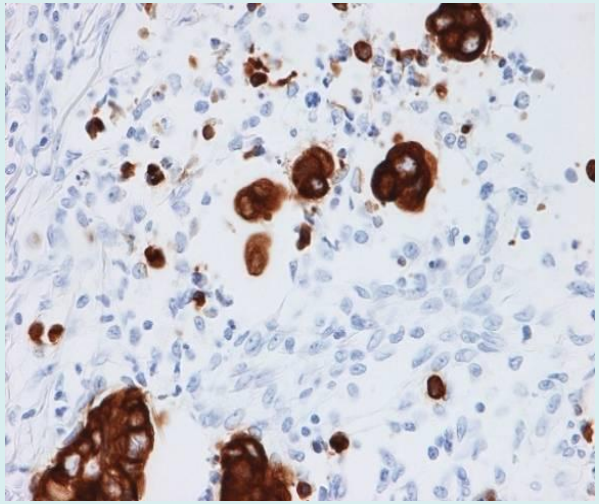
(Received November 11, 2010/Revised February 14, 2011; May 20, 2011/Accepted May 25, 2011/Accepted manuscript online May 31, 2011/Article first published online July 21, 2011)


CHAMPION BEER
of Gloucestershire
2006 & 2008
BUDDING
Stroud Brewery
Pale Ale
4.5%

What about tumour budding?

- detachment of single tumour cells or in small aggregates (< 5 cells) = dedifferentiation
- now known to be adverse prognostic marker
- abnormalities in EMT (epithelial-mesenchymal transition)





Budding in colorectal cancer

TABLE 3. Summary of the Published Literature Relating to Tumor Budding as a Prognostic Factor Including Information on: Number of Patients, Stage, and Methodology for Quantifying Tumor Budding

Author	No. Patients	Stages (UICC)	Location	End Point		Methodology of Tumor Budding Assessment
Hase et al[4]	663	I to III	Colorectal	5-y survival	H&E	Based on predominant pattern of tumor budding but methods not fully illustrated. BD-1: none/mild; BD-2: moderate/severe
Kanazawa et al[5]	159	II to IV	Colorectal	5-y cancer-related survival and recurrence-free survival	H&E	Similar to Hase et al.[4] Entire invasive margin assessed at 400 × magnification†
Nakamura et al[7]	200	II pT3 and T4	Colon	Cumulative 5 and 10-y survival	H&E	Similar to Hase et al.[4] Entire invasive margin of the largest cut section of whole tumor was assessed at 200 × and 400 × magnification.†High-grade budding: none/mild; low-grade budding: moderate/severe
Nakamura et al[8]	491	I to III	Colorectal	Occurrence of metachronous metastases	H&E	Similar to Hase et al.[4] Section with the largest diameter of colorectal lesion†
Okuyama et al[9]	179*	II and III	Colon	Cumulative 5-y survival	H&E	Methods not specified. Budding present or absent at invasive front
Okuyama et al[10]	83	II and III pT3	Rectal	Cumulative 5-y survival	H&E	Methods not specified. Budding present or absent at invasive front
Park et al[11]	174	I to IV pT2	Colon	5-y disease-free and overall survival	H&E	Tumor bud counting was performed at 20 × objective lens of 3 selected fields with highest budding intensity. Budding intensity was defined as the highest number of tumor buds among these 3 areas
Prall et al[14]	182*	I and II	Colorectal	Occurrence of metachronous metastases	IHC	Tumor bud counting (field of view 0.785 mm^2 at 250 × magnification). Budhigh: ≥ 25 buds; Budlow: < 25 buds
Tanaka et al[16]	138	II pT3	Colon	Cumulative disease-specific 5-y survival	H&E	Similar to Hase et al.[4] One H&E slide with the deepest portion of tumor penetration examined. BD-1: none/mild; BD-2: moderate/severe
Ueno et al[17]	638	I to III	Rectal	Cancer-specific survival	H&E	Tumor bud counting of 1 selected field with maximum budding intensity (field of view 0.385 mm^2 at 25 × objective lens). High-grade budding: ≥ 10; Low-grade budding: < 10

Where are we with tumour budding?

independent prognostic significance in polyp cancers

Ueno et al, 2004

independent significance in Dukes B/stage II colon cancers

Wang et al, 2009

less powerful in Dukes C/stage III

issues:

varying methods of assessment

heterogeneity

reproducibility

more data required

Issues with pathological assessment

margin involvement	lacks logic: is evidence good enough? definitions
poor differentiation & lymphovascular invasion	less problems but still subjective
sm3 (Kikuchi)	need muscularis mucosae & propria only for sessile lesions?
Haggitt 4	sessile v polypoid subjective
differences in polyp type	pedunculated sub-pedunculated sessile
budding	subjective; definitions
measuring: depth, width	inter-observer variation

RCPath dataset for colorectal cancer local excision

- please use, especially in BCSP
- currently undergoing revision
- 3rd edition available June 2013 (eds Loughrey MR, Quirke P, Shepherd NA)
- and we'll correct:

Complete resection at carcinoma at all margins

Lymphovascular invasion:

None

Possible

Definite

Local excisions on BCSS

Excision Details	
Pathology Provider lookup	
Date of Receipt	
Date of Reporting	
Authorising Pathologist lookup	
Specimen Type	
Maximum Tumour Diameter	0 mm
Tumour Type	
Differentiation	
Not Diagnostic of Cancer	
Local Invasion	
Maximum Thickness of Invasive Tumour from Muscularis Mucosae	mm
Level of Invasion	
Lymphatic or Vascular Invasion	
Background Adenoma	
Local Excision Margin Involvement	
Histological Measurement from Carcinoma to Nearest Deep Excision Margin	mm
Complete Resection of Margins	

The future and the answer

NHS

Cancer Screening Programmes

Bowel Cancer Screening Programmes

Take home messages

- the introduction of CRC screening drives up overall colorectal pathology reporting quality by introduction of standards, change of practice, external quality review and use of performance indicators and quality measures
- pT1 polyp cancers and their mimics (epithelial misplacement) provide huge consternation for pathologists, clinicians and patients
- bowel screening programmes will, hopefully, give us the answer…
- margin involvement in polyp cancers: definition and implication are the biggest controversies
- malignant polyps were made for MDTM discussion. It's a shame the patient isn't there as well……