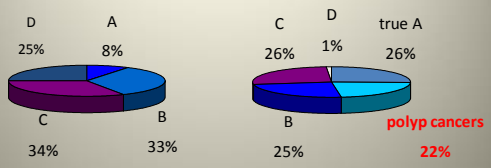
Not so simple pathology: issues from the screening programme

Professor Neil A Shepherd
Gloucester & Cheltenham, UK

Maastricht Pathology 2018
Maastricht, Netherlands
Tuesday, June 19, 2018

What colorectal cancer screening is all about….

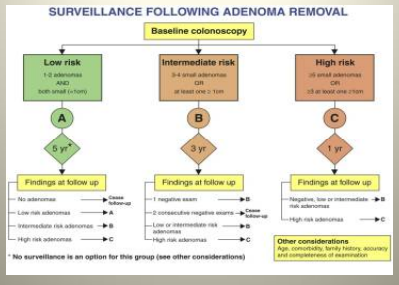
- **detecting early stage cancer**



Dukes staging for symptomatic CRC versus screen-detected CRC in the English BCSP

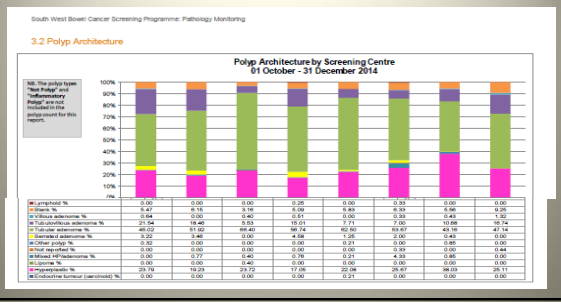
Bowel cancer screening: the subconscious musings of a Gloucestershire pathologist, circa 2006

- most of it will be a pathological doddle
- 130 extra polyps a year – mainly adenomas and HPs – piffle!
- a few more cancer resections but lots of easy Dukes A/stage 1
- and the BCSP Director is going to give us a whole wad of dosh to do it…..



Cairns SR, et al; BSG guidelines 2010 (after Atkin WS, Saunders BP; Gut 2002)

Variability in polyp type, BCSP South West



Four big issues in bowel cancer screening pathology (and all very relevant to routine colorectal pathology practice….)

- the diagnosis of colorectal cancer on biopsy
- 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

So, our only useful role in the pathological assessment of the most common colorectal polyp is…….

to confirm that it is an adenoma

we can't agree on villosity/villousness
low or high grade dysplasia

until we do, we won't be much use in determining further management in an important patient group

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25% of CRC develop arise via the serrated pathway

Gastroenterology 2016;150:895–902

Increased Risk of Colorectal Cancer Development Among Patients With Serrated Polyps

Rune Erichsen,[1] John A. Baron,[1,2] Stephen J. Hamilton-Dutoit,[3] Dale C. Snover,[4] Emina Emilia Torlakovic,[5] Lars Pedersen,[1] Trine Froslev,[1] Mogens Vyberg,[6] Stanley R. Hamilton,[7] and Henrik Toft Sorensen[1,2]

Table 4. Estimated 10-Year Risk of Colorectal Cancer for Each Polyp Type

	Cases/controls	Adjusted OR (95% CI)	Estimated 10-year risk[a]
SSA/P with synchronous conventional adenomas	30/61	2.66 (1.70–4.16)	2.47%
SSA/P without synchronous conventional adenomas	49/81	3.40 (2.35–4.91)	3.16%
SSA/P with cytologic dysplasia	20/25	4.76 (2.59–8.73)	4.43%
SSA/P without cytologic dysplasia	59/117	2.75 (1.99–3.80)	2.56%
Conventional adenomas without SSA/P	727/1631	2.50 (2.24–2.80)	2.33%
Traditional serrated adenomas overall	14/17	4.84 (2.36–9.93)	4.50%
Hyperplastic polyps only	55/235	1.30 (0.96–1.77)	1.21%

[a]The number of colorectal cancers among individuals without polyps (1155) divided by the total number of patients without polyps (209,744) and divided by the mean follow-up period (5.90 y) estimates the annual colorectal cancer risk (r). The 10-year risk for patients without polyps is estimated as $1-(1-r)^{10}$ and equals 0.93%. The 10-year risk of colorectal cancer for each polyp type then is estimated as the 10-year risk for patients without polyps times the OR for the relevant polyp type.

UK guidance for the pathological reporting of serrated lesions of the colorectum

Adrian C Bateman,[1] Neil A Shepherd[2]

ABSTRACT

Bowel cancer screening programmes have highlighted to endoscopists and clinicians the spectrum of serrated colorectal lesions. One of the most significant developments has been the recognition that sessile serrated lesions (SSLs), while bearing histological resemblance to hyperplastic polyps (HPs), may be associated with the enhanced development of epithelial dysplasia and colorectal adenocarcinoma. Different minimum criteria exist for the diagnosis of SSLs and their differentiation from HPs. Furthermore, the spectrum of terminology used to describe the entire range of serrated lesions is wide. This variability has impaired interobserver agreement during their histopathological assessment. Here, we provide guidance for the histopathological reporting of serrated lesions, including a simplified nomenclature system. Essentially, we recommend use of the following terms: HP, SSL, SSL with dysplasia, traditional serrated adenoma (TSA) and mixed polyp. It is hoped that this standardisation of nomenclature will facilitate studies of the biological significance of serrated lesions in terms of the relative risk of disease progression.

these lesions and the risk of disease progression associated with various histopathological factors.

This review provides guidance relating to a simplified nomenclature and classification system for serrated colorectal lesions.

NOMENCLATURE

The nomenclature of serrated lesions is complex, and there are differences of opinion between UK, European and US pathologists regarding the optimal terminology. We propose that serrated lesions should be given one of the following names according to their morphological features: HP, SSL, SSL with dysplasia, traditional serrated adenoma (TSA) and mixed polyp (box 1). The definitions of these lesions are given below.

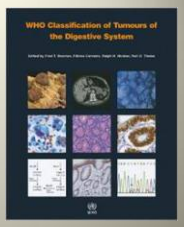
Hyperplastic polyp

These are small serrated lesions showing no features that would allow categorisation as an SSL and no evidence of dysplasia. *We use the term 'dysplasia' in this context to refer to the morphological appearances of epithelial neoplasia within the mucosa of the colon and rectum, for example, the epithelial*

Bateman AC, Shepherd NA. J Clin Pathol 2015: 68: 585-91.

Terminology of sessile serrated pathology

- sessile serrated adenoma
  Torlakovic and Snover, 1996
- sessile serrated polyp/adenoma
  WHO, 2010
- sessile serrated polyp
- sessile serrated lesion
  UK & European colorectal screening guidelines



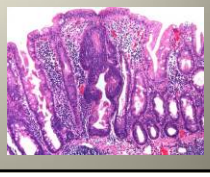
Quality assurance in pathology in colorectal cancer screening and diagnosis—European recommendations

Phil Quirke · Manuel Risio · René Lambert · Lawrence von Karsa · Michael Vieth

Box 1 Recommended terminology for (non-invasive) serrated lesions of the colon and rectum

- Hyperplastic polyp (HP)
- Sessile serrated lesion (SSL)
- SSL with dysplasia
- Traditional serrated adenoma (TSA)
- Mixed polyp

Approved by BSG Pathology Section, BCSP National Pathology Committee, RCPath, European CRC Screening Pathology Group & BSG Serrated Pathology Working Party



Rodger C. Haggitt Gastrointestinal Pathology Society
Sunday, March 18, 2018 1:30 PM-5:00 PM Session
Attendance: 600
Neil Shepherd (Rodger C. Haggitt Memorial Lecture: The Pathology of Bowel Cancer Screening)

"Some of the lecturers comments about serrated lesions, particularly regarding the term "sessile serrated lesion" was ill-founded and not mainstream and reflected a United Kingdom bias versus the rest of the world."

Polyp cancer issues

- is it cancer?
- double reporting recommendation in BCSP since 2012
- the phenomenon of epithelial misplacement/pseudoinvasion in BCS programmes
- other diagnostic issues and mimics
- what do we do about polyp cancer?
  measurement & budding may be king……

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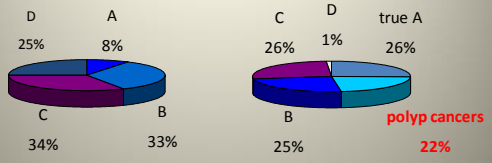


Dukes staging for symptomatic CRC versus screen-detected CRC in the English BCSP

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

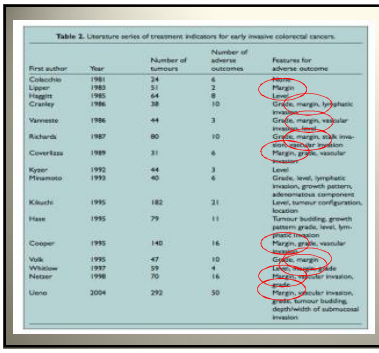


Table 2. Literature series of treatment indicators for early invasive colorectal cancers.

First author	Year	Number of tumours	Number of adverse outcomes	Features for adverse outcome
Colacchio	1981	24	6	Nerve
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
Whitelaw	1997	59	4	Level, invasion 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

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

we can understand vascular invasion & 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;
Ueno et al, 2004

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

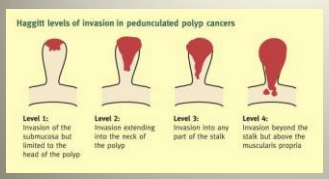
Table 1.
Relationship Between Histologic Risk Factors and Clinical Outcomes

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]$P < 0.05$.

Classification of early colorectal cancer in polyps

Haggitt RC et al, 1985



Margin involvement by cancer in malignant polyps

- commonest adverse prognostic parameter
- commonest isolated adverse prognostic parameter
- definition ?!?
- now at margin (we recommend…) and not within 1mm (for polyp cancers)
- margin is external border of diathermy mark
- ignore artefacts and cracks

Loughrey MB, Bateman AC, Shepherd NA, Quirke P. BCSP polyp reporting guidelines, 2018

Histologic factors associated with need for surgery in patients with pedunculated T1 colorectal cancer

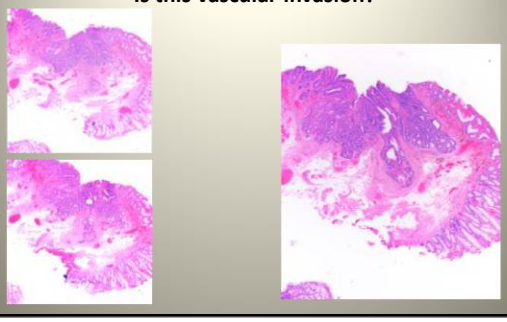
- cohort-nested matched case control study
- 78 patients from 13 Dutch hospitals
- model identified as significant factors:
  - lymphovascular invasion
  - Haggitt level 4
  - muscularis mucosae type B (incompletely or completely disrupted)
  - poorly differentiated clusters
  - tumour budding
- model 'might be used to identify patients likely to benefit from surgery'

Backes et al. Gastroenterology 2018

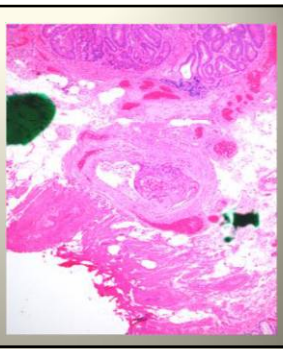
BCSP polyp cancer inter-observer study Leeds, February 2013

- poor levels of agreement with differentiation, lymphatic spread, vascular spread, margin positivity, even Haggitt…..
- good levels of agreement with margin positivity once definitions of margin had been established.
- best levels of agreement with MEASURING – depth of spread, width of cancer, distance from margin.
- measuring may be the future…..

Is this vascular invasion?



Is this vascular invasion?

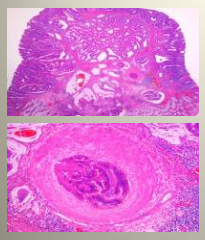


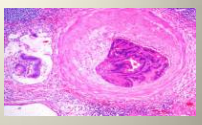
A bit of Tuesday in Maastricht philosophy……

You can have all the fancy immunohistochemistry and molecular biology you like, but what are the two most important adjunctive tests we do in Histopathology?

deeper levels
and the peer at the computer to get the patient's history…….

Is this vascular invasion?





'vascular intrusion'

Loughrey & Shepherd, 2017

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……
- uncertain value of 'newer' parameters
- age and co-morbidity are important
- crucial MDTM/Tumour Board discussion

Issues with pathological assessments

margin involvement	lacks logic: is evidence good enough? definitions
poor differentiation & lymphovascular invasion	less problems but still subjective
Kikuchi	needs muscularis mucosae & propria only for sessile lesions?
Haggitt	sessile v polypoid subjective
differences in polyp type and influence on endoscopic resection	pedunculated, sub-pedunculated & sessile
budding, poorly differentiated clusters	subjective; definitions
measuring: depth, width	inter-observer variation

Measuring depth and width of invasion: Japanese methodology

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

direct measurement from muscularis mucosae

depth > 2mm	20% nodal +ve (vs 5%)
width of invasive front > 4mm	20% nodal +ve (vs 4%)

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

The most useful tool in BCSP?!?

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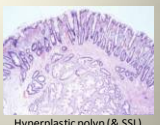
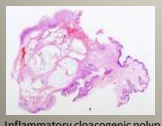
Epithelial misplacement (pseudo-invasion)

'Normal' colonic mucosa



Hyperplastic polyp (& SSL)

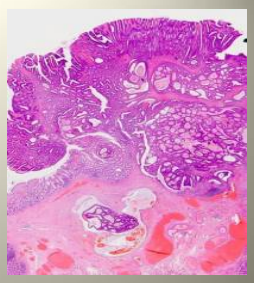


Inflammatory cloacogenic polyp

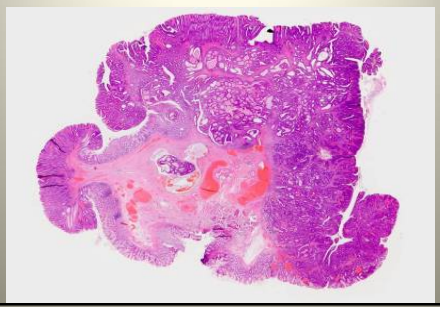
Peutz-Jeghers polyp

Epithelial misplacement in adenomas

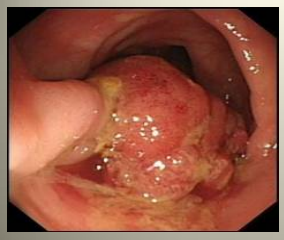
- 85% in sigmoid colon
- unusual in rectum (unless there has been previous intervention)
- same epithelium as surface, accompanied by lamina propria, haemosiderin deposition, continuity (in 3D)
- what about misplaced epithelium at the diathermy margin?
- intense pathological mimicry of invasive cancer

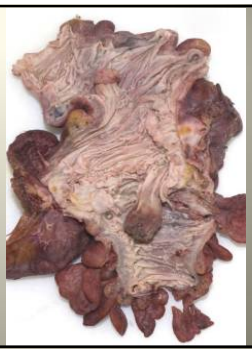


Epithelial misplacement vs invasive carcinoma

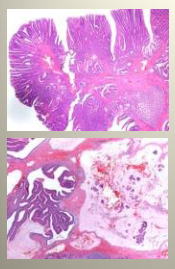


Why the sigmoid colon?





64M. 22mm sigmoid colonic polyp.



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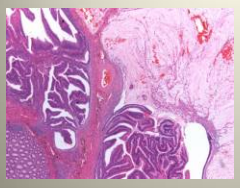
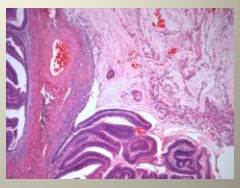
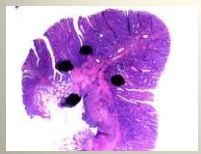


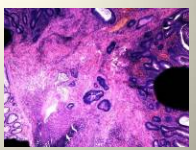


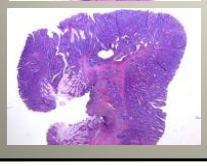
Pathological conundra in BCSP

- epithelial misplacement mimicking cancer
- 85% in sigmoid colon
- selected into BSCP as 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….

The importance of deeper levels







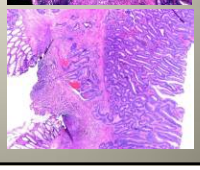


Table 2. A comparison of the pathological features that may be valuable in differentiating epithelial misplacement from invasive adenocarcinoma.

	Epithelial misplacement (EM)	Adenocarcinoma
Epithelial 'differentiation'	Usually similar to that of the surface adenomatous component	Variable and usually different to the surface adenomatous component
Lamina propria accompaniment	Characteristic but may be lacking when there is secondary inflammation and epithelial destruction	Usually absent. Can be present in rare, very well-differentiated carcinoma
Accompaniment by non-adenomatous epithelium	Characteristically seen when EM is due to previous intervention	Absent
Haemosiderin deposition	Characteristic and indicative of previous necrosis and/or haemorrhage	Usually absent
Mucosal prolapse changes	Often present	Usually absent
Mucus cysts	Characteristic. They probably represent epithelial misplacement that has become 'detached' from the more superficial components	Only present, usually, in mucinous tumours
Continuity with surface adenomatous component	Characteristic but often only appreciated in multiple levels and/or 3D reconstruction studies	Usually absent but some cases do show continuity, even in 3D reconstruction studies.
Involvement of muscularis propria (MP)	Usually absent. Can be seen very rarely, especially after previous intervention	Present if at least pT2
Budding	Usually absent but a similar phenomenon can be seen as a result of epithelial destruction and/or inflammation	Often present
Desmoplastic reaction to glands	Usually absent but fibromuscular stromal proliferation can accompany EM	Usually present
Lymphatic and/or vascular invasion	Absent	Diagnostic of cancer

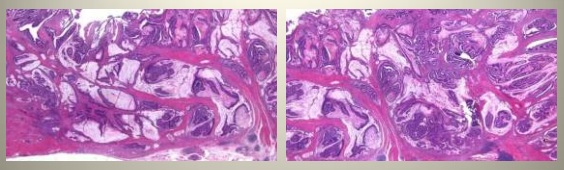
Loughrey & Shepherd. Histopathology ARI. January 2015

Adjunctive tests

If it's so difficult for us morphologists, do we have any reliable adjunctive tests?

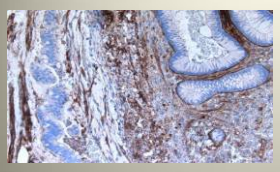
- immunohistochemistry
- three dimensional reconstruction
- in-situ molecular analysis

Adenoma-like adenocarcinoma



Gonzalez RS, Cates JMM, Washington MK, Beauchamp RD, Coffey RJ, Shi C. Adenoma-like adenocarcinoma: a subtype of colorectal carcinoma with good prognosis, deceptive appearance and frequent KRAS mutation. Histopathology 2016; 68: 183-190.

Immunohistochemistry

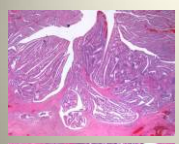


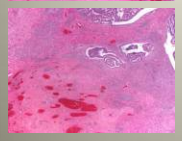
collagen IV

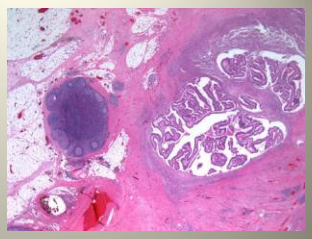
Yantiss RK, Bosenberg MW, Antonioli DA, Odze RD. Am J Surg Pathol 2002; 26: 206-215.

- works well in classic cases of pseudoinvasion and cancer
- not so good in marginal cases

57M. Caecal polyp.







Epithelial misplacement/cancer and difficult BCSP polyps

- the most extraordinary diagnostic conundrum I have seen (or, perhaps, recognised!) in my professional career
- low levels of inter-observer agreement amongst 'general' pathologists
- not perfect inter-observer agreement amongst 'experts'
- surely matched only by melanocytic lesions of the skin.....

Expert Board assessments

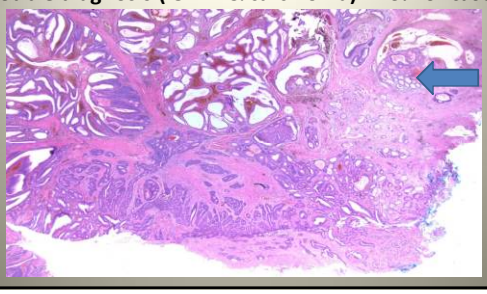
2009-16

- 249 cases: 20 cases in 2009; 72 in 2016
- EB three-way agreement of 80.3%: kappa score of 0.67 (substantial agreement)
- originating pathologist(s) v EB:
  benign diagnosis 30.6% v 80.2% (originator(s) v EB)
  diagnosis changed from originating pathologist(s) to EB in 50%
  mainly malignant to benign
- double diagnosis (ie EM and carcinoma) in 3% of cases

BCSP Expert Board

- three pathologists – you need a majority for this highly subjective and difficult assessment
- N A Shepherd, A C Bateman & M R Novelli
- funded (IT, postage, secretarial support) in England by BCSP
- opportunity for education and research into difficult EM v Ca cases
- similar expert boards established/being established in other countries – Scotland, Netherlands, Canada, etc

Expert Board: double diagnosis (ie EM & carcinoma) in 3% of cases



The UK 'Expert Board'

Griggs RKS, Novelli MR, Sanders DSA, Warren BF, Williams GT, Quirke P, Shepherd NA.
Challenging diagnostic issues in adenomatous polyps with epithelial misplacement in bowel cancer screening: five years' experience of the BCSP Expert Board.
Histopathology 2017; 70: 466–472.

Take home messages

- bowel cancer screening and its QA continues to improve the overall quality of colorectal pathology
- we really must make ourselves more useful for surveillance by ensuring good agreement levels with high grade dysplasia and villosity, in particular
- our knowledge of serrated pathology is increasing exponentially but we still have a lot to learn
- we have real management problems with polyp cancers: measurement +/- budding may be the answer in the future….
- epithelial misplacement v cancer – the diagnostic conundrum of the century (in the UK at least…)
- bowel cancer screening, with its quality induced by comprehensive quality assurance, quite massive numbers and comprehensive datasets, will ultimately give us the answers to many of these vexatious questions……..

Acknowledgements and appreciations

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