The pathology of bowel cancer screening

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Gloucester & Cheltenham, UK

Rodger C Haggitt Memorial Lecture
Rodger C Haggitt Gastrointestinal Society
USCAP, Vancouver, March 18, 2018
The pathology of bowel cancer screening

Even if you have never seen a specimen from bowel cancer screening, and never will, this lecture is still very relevant to you!!!
What gives me the right?

The UK, or more correctly England, in the vanguard?!?

The first (large) country to roll out full population screening for colorectal cancer in the world
<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Detection of Early Stage Cancer</th>
<th>Detection of Pre-Malignant Change</th>
<th>Detection of High Risk Patients</th>
<th>Screening Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical cancer</td>
<td></td>
<td></td>
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<td>Cervical smear</td>
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<td></td>
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<td>HPV testing</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>detection of early stage cancer</td>
<td>detection of pre-malignant change</td>
<td></td>
<td>Mammography</td>
</tr>
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<td></td>
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</tr>
<tr>
<td>Colorectal cancer</td>
<td>detection of early stage cancer</td>
<td>detection of pre-malignant change</td>
<td></td>
<td>FOB, FIT, endoscopy, etc</td>
</tr>
<tr>
<td>Test performance per screening test in asymptomatic, average-risk adults</td>
<td>gFOBT</td>
<td>FIT</td>
<td>FS</td>
<td>CTC</td>
</tr>
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<td>---</td>
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<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Sensitivity (%) for detecting advanced neoplasia</td>
<td>9 to 24&lt;sup&gt;43-48&lt;/sup&gt;</td>
<td>32 to 53&lt;sup&gt;43 44 47 49&lt;/sup&gt;</td>
<td>90 to 92&lt;sup&gt;*50&lt;/sup&gt;</td>
<td>88&lt;sup&gt;35&lt;/sup&gt; to 97&lt;sup&gt;43&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sensitivity (%) for detecting CRC</td>
<td>13 to 50&lt;sup&gt;44-46&lt;/sup&gt;</td>
<td>79&lt;sup&gt;52&lt;/sup&gt;</td>
<td>90 to 92&lt;sup&gt;*50&lt;/sup&gt;</td>
<td>100&lt;sup&gt;†53&lt;/sup&gt;</td>
</tr>
<tr>
<td>Reduction in CRC incidence (%) intention-to-screen</td>
<td>No&lt;sup&gt;‡19 54&lt;/sup&gt;</td>
<td>Unknown</td>
<td>18&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Unknown</td>
</tr>
<tr>
<td>Reduction in CRC mortality (%) intention-to-screen</td>
<td>14 to 16&lt;sup&gt;19&lt;/sup&gt;</td>
<td>22&lt;sup&gt;¶25&lt;/sup&gt;</td>
<td>28&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

* Sensitivity is given for the distal colon.
† No CRCs were missed by CTC in six screening trials.
‡ No reduction in incidence was found in three of four RCTs included in meta-analysis.
§ Meta-analysis of observational studies, more results expected.
¶ Ecological study.
CRC, colorectal cancer; CTC, CT colonography; FIT, faecal immunochemical test for haemoglobin; FS, flexible sigmoidoscopy; gFOBT, guaiac faecal occult blood test; RCT, randomised controlled trial.

Colorectal cancer screening: a global overview of existing programmes

Eline H Schreuders, Arlinda Ruco, Linda Rabeneck, Robert E Schoen, Joseph J Y Sung, Graeme P Young, Ernst J Kuipers

Gut 2015; 64: 1637-49.
Colorectal screening in North America

Canada
- National Colorectal Cancer Screening Network in place since 2007
- population-based screening organised by province
- FIT is the recommended test
- rapid roll-out
- seeing the same issues as UK

Thanks to David Driman, London, Ontario

USA
- too large a population to organise on national basis
- lots of opportunistic screening, by colonoscopy +/- FOB/FIT
- driven by American Cancer Society & 2008 AGA guidelines

Thanks to Kay Washington, Nashville, Tennessee
Colorectal Cancer Screening Fecal Testing Information - Highlights

Entry Level Test: Fecal Test Guaiac (FTg) Sampling Details (refer to slide #21)
• There are only two provinces (Manitoba and Ontario) which currently offer fecal test guaiac (FTg) as a screening test for colorectal cancer. FTg is offered to eligible individuals every two years. In Canada, the number of labs processing the results ranges from one lab (Manitoba) to six labs (Ontario). The FTg brands include Hemoccult II SENSA (Manitoba) and Hema-screen (Ontario).

Entry Level Test: Fecal Immunochemical Testing (FIT) Sampling Details (refer to slide #22-23)
• Eight provinces and two territories offer fecal immunochemical testing (FIT) up to every two years as a primary screening test for colorectal cancer. The most common brand for FIT in Canada is Alere (four provinces/one territory) and Polymedco (three provinces). Most provinces/territories require a single sample collection method for the FIT, whereas, one province and one territory collects two samples. The FIT cut-off value varies across Canada and ranges from 75 ng/ml (NWT) to ≥175 ng/ml (QC). The number of labs processing the FIT results ranges from one lab (six provinces/one territory) to five labs (one province).
In the UK, it’s not just England’s BCSP.....
Bowel cancer screening in England

• universal screening (60-70) by FOB first introduced in 2006

• then age extension to 75

• then one-off sigmoidoscopy screening at age 55 introduced independent of FOB screening and initiated in 2013

• now conversion from FOB to FIT
Faecal immunochemical test (FIT)

• due to be introduced in England in 2018
  – introduction in Scotland on 30.11.17

• single sample only

• kit is ‘more scientific-looking’ to participants

• only detects human (haemo)globin

• increased sensitivity e.g. for advanced adenomas
This is your test kit for NHS Bowel Cancer Screening. Using it takes only a few minutes. The test helps to detect bowel cancer early. The earlier bowel cancer is found, the easier it is to treat.

Instructions on using the kit are on the box (below) and on the additional information sheet enclosed.

Please make sure you have read the leaflet about bowel cancer screening that we sent to you. The leaflet tells you about screening, its benefits and risks. The information is to help you decide whether or not you want to have bowel cancer screening. You can use a copy of the leaflet and the test kit.

For more information about screening, or about using the test kit, call us on 0800 707 60 60. Calls are free from UK landlines. Or visit our website at http://www.cancerscreening.nhs.uk

**Instructions**

1. Write the date on this sample bottle.
2. Correctly sample kit.
3. Put back in bottle.
4. Seal the sample bottle back.

Freephone Helpline 0800 707 60 60
Calls are free from UK landlines. Or visit our website at http://www.cancerscreening.nhs.uk
Increased uptake and improved outcomes of bowel cancer screening with a faecal immunochemical test: results from a pilot study within the national screening programme in England

Sue Moss,¹ Christopher Mathews,¹ T J Day,² Steve Smith,³ Helen E Seaman,⁴ Julia Snowball,⁴ Stephen P Halloran⁴,⁵

ABSTRACT

Background The National Health Service Bowel Cancer Screening Programme (BCSP) in England uses a guaiac-based faecal occult blood test (gFOBT). A quantitative faecal immunochemical test (FIT) for haemoglobin (Hb) has many advantages, including being specific for human blood, detecting Hb at a much lower concentration with a single faecal sample and improved uptake.

Methods In 2014, a large comparative pilot study was performed within BCSP to establish the acceptability and

Significance of this study

What is already known on this subject?

- Guaiac-based faecal occult blood test (gFOBT) screening for bowel cancer reduces bowel cancer mortality in those screened by 25%.
- Uptake of gFOBt in the National Health Service (NHS) Bowel Cancer Screening Programme (BCSP) was 58.2% in the fiscal year 2014/2015.
FIT workload implications: the triple whammy for pathologists

- in England platform and cut-off for FIT not determined yet
- If ‘FIT 120’ chosen, potential increase in pathology workload could be:
  - increased uptake: 66% for FIT v 59% for FOB
  - increased positivity rate: 2.12 (‘FIT 120’) v 1.71 (2016 FOB positivity rate)
  - enhanced sensitivity for advanced adenomas: 2.0 for FIT v 1.5 for FOB

82% increase in pathology workload
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.....
The first 10,000 Northern Ireland BCSP specimens

- Adenocarcinoma: 2.8%
- Adenocarcinoma (in polyp): 0.8%
- Suspicion of malignancy: 0.4%
- Tubular adenoma: 48.7%
- Tubulovillous adenoma: 16.9%
- Hyperplastic polyp: 15.3%
- Sessile serrated lesion: 2.9%
- Traditional serrated adenoma: 0.3%
- Villous adenoma: 0.3%
- Inflammatory polyp: 0.7%
- Inflammation: 4.1%
- Other: 2.1%
- Normal: 4.8%
- Grand Total: 100%
Table 1. Frequencies of common histopathological diagnoses from 240,842 non-invasive lesions detected during screening colonoscopy since inception of the English Bowel Cancer Screening Programme

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubular adenoma</td>
<td>57%</td>
</tr>
<tr>
<td>Tubulovillous adenoma</td>
<td>18%</td>
</tr>
<tr>
<td>Villous adenoma</td>
<td>1%</td>
</tr>
<tr>
<td>Hyperplastic polyp</td>
<td>21%</td>
</tr>
<tr>
<td>Sessile serrated lesion</td>
<td>1%</td>
</tr>
<tr>
<td>Other</td>
<td>2%</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
</tr>
</tbody>
</table>
What colorectal cancer screening is all about….

- detecting early stage cancer

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

D
25%

A
8%

C
34%

B
33%

C
26%

D
1%

true A
26%

polyp cancers
22%
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathology Lost</td>
<td>No</td>
</tr>
<tr>
<td>Date of Receipt</td>
<td>21/09/2015</td>
</tr>
<tr>
<td>Date of Reporting</td>
<td>21/09/2015  (same day)</td>
</tr>
<tr>
<td>Pathology Provider</td>
<td>Cheltenham General Hospital - RTE01 (Gloucestershire Hospitals NHS Foundation Trust)</td>
</tr>
<tr>
<td>Pathologist</td>
<td>Shepherd, Neil (Consultant Pathologist - Gloucestershire Hospitals NHS Foundation Trust)</td>
</tr>
<tr>
<td>Polyp Type</td>
<td>Adenoma</td>
</tr>
<tr>
<td>Polyp Sub Type</td>
<td>Tubular adenoma</td>
</tr>
<tr>
<td>Polyp Excision Complete</td>
<td>Not Assessable</td>
</tr>
<tr>
<td>Polyp Size</td>
<td>2 mm</td>
</tr>
<tr>
<td>Polyp Dysplasia</td>
<td>Low grade dysplasia</td>
</tr>
<tr>
<td>Polyp Carcinoma</td>
<td>No</td>
</tr>
</tbody>
</table>
SURVEILLANCE FOLLOWING ADENOMA REMOVAL

Baseline colonoscopy

Low risk
1-2 adenomas
AND
both small (<1cm)

A
5 yr*

Findings at follow up
No adenomas → Cease follow-up
Low risk adenomas → A
Intermediate risk adenomas → B
High risk adenomas → C

Intermediate risk
3-4 small adenomas
OR
at least one ≥ 1cm

B
3 yr

Findings at follow up
1 negative exam → B
2 consecutive negative exams → Cease follow-up
Low or intermediate risk adenomas → B
High risk adenomas → C

High risk
≥5 small adenomas
OR
≥3 at least one ≥1cm

C
1 yr

Findings at follow up
Negative, low or intermediate risk adenomas → B
High risk adenomas → C

Other considerations
Age, comorbidity, family history, accuracy and completeness of examination

* No surveillance is an option for this group (see other considerations)

Reliability of pathological assessment of villosity and dysplasia grade

Interobserver variability in assessing dysplasia and architecture in colorectal adenomas: a multicentre Canadian study

Allison Osmond, Hector Li-Chang, Richard Kirsch, Dimitrios Divaris, Vincent Falck, Dong Feng Liu, Celia Marginean, Ken Newell, Jeremy Parfitt, Brian Rudrick, Heidi Sapp, Sharyn Smith, Joanna Walsh, Fasahat Wasty, David K Driman

Introduction
Although most colorectal carcinomas are thought to arise from colorectal adenomas (1–3), most adenomas, which are quite common, do not progress to invasive carcinoma (3, 4). Therefore, the study of advanced adenomas (those with severe dysplasia, CTS, and intramucosal carcinoma), which have a
# Reliability of pathological assessment of villosity and dysplasia grade

## TABLE 2. \( \kappa \) Indices for Interobserver Agreement

<table>
<thead>
<tr>
<th>Feature</th>
<th>( \kappa )</th>
<th>( P )</th>
<th>95% CI</th>
<th>Interobserver Agreement*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preconsensus diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-VC</td>
<td>0.21</td>
<td>&lt; 0.001</td>
<td>0.15-0.27</td>
<td>Poor</td>
</tr>
<tr>
<td>HGD</td>
<td>0.26</td>
<td>&lt; 0.001</td>
<td>0.20-0.32</td>
<td>Poor</td>
</tr>
<tr>
<td>AA</td>
<td>0.29</td>
<td>&lt; 0.001</td>
<td>0.23-0.35</td>
<td>Poor</td>
</tr>
<tr>
<td>Postconsensus diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-VC</td>
<td>0.37</td>
<td>&lt; 0.001</td>
<td>0.31-0.43</td>
<td>Poor</td>
</tr>
<tr>
<td>HGD</td>
<td>0.31</td>
<td>&lt; 0.001</td>
<td>0.25-0.37</td>
<td>Poor</td>
</tr>
<tr>
<td>AA</td>
<td>0.34</td>
<td>&lt; 0.001</td>
<td>0.28-0.40</td>
<td>Poor</td>
</tr>
</tbody>
</table>

*Improvement in \( \kappa \) (1-sided z-test): A-VC, \( P = 0.038 \); HGD, \( P = 0.11 \); AA, \( P = 0.14 \).

*Agreement beyond chance; poor: \( \kappa < 0.40 \); moderate: \( 0.40 \leq \kappa \leq 0.75 \); excellent: \( \kappa > 0.75 \).

CI indicates confidence interval.
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
Some polyp curios in BCSP....
Is this vascular invasion?
Is this vascular invasion?
A bit of Sunday in Vancouver 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’
Adenoma in a lympho-glandular complex: much commoner in the right colon
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
Four big issues in bowel cancer screening pathology (and all very relevant to routine colorectal pathology practice....)

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• the large adenomatous polyp of the sigmoid colon – expected but not the amount nor the diagnostic difficulties
The diagnosis of colorectal cancer on biopsy

- depends on definitions
- Japanese and Far East – cytological diagnosis
- North America and some of Europe – architectural features
- UK (and others) – definitive evidence of submucosal spread
Basil C Morson, doyen of GI pathologists, 1921-2016

“It’s your job to control surgeons”
The diagnosis of colorectal cancer on biopsy

- intramucosal carcinoma not allowed as a diagnosis in the UK
- those cases are called ‘high grade dysplasia’
- lymphatics in mucosa not capable of delivering metastatic disease
- you don’t want a large specimen by return of post

- biopsies may not show definite submucosal tissue
- provides considerable difficulties (certainly for UK pathologists)
The diagnosis of colorectal cancer on biopsy
The diagnosis of colorectal cancer on biopsy

- how to demonstrate submucosal involvement?
- juxtaposition to neural structures, fat and large arterioles and venules
- S100 immunohistochemistry?
Although not yet proven in definitive studies, we believe that juxtaposition of neoplastic glands to structures known to be in the submucosa, such as neural structures, fat and larger blood vessels, particularly arterioles and venules, are of considerable help in making a diagnosis of invasive adenocarcinoma. Indeed, some colleagues, in the UK at least, have advocated S100 immunohistochemistry to demonstrate juxtaposition of neoplastic glands to submucosal ganglia and nerve structures. This may be of some utility but requires rigorous observational studies to support this practice.

Loughrey MB, Quirke P, Shepherd NA. Royal College of Pathologists Dataset for colorectal cancer histopathology reports December 2017
The need for repeat biopsies?

• 64M

• 52mms mass lesion in the caecum

• biopsies show TVA with low grade dysplasia only

COMMENT: These biopsies do provide evidence of primary colorectal glandular neoplasia. Given the size of the lesion at colonoscopy, it is likely that endoscopic resection cannot be undertaken. In this situation, despite the lack of definitive evidence of invasive malignancy in these biopsies, there would appear to be a clear indication for right hemicolectomy. These facts should direct discussion in the Colorectal MDTM.
However, in about half of these (and mainly in the colon), the MDTM decided that further biopsies were not required because the original biopsies had confirmed primary glandular neoplasia and the clinical, endoscopic and imaging features demanded resection. It should be emphasised that these cases were mainly colonic and that rectal cancers, accounting for about 5% of the total number of cases in this audit, did more commonly require further biopsies. This was particularly important when an abdominoperineal resection would have been the proposed management strategy. So, particularly in the colon, there may not be a definitive argument for repeat biopsies, if clinical, endoscopic and imaging features demand resection, as long as the biopsies have confirmed primary colorectal glandular neoplasia.

Loughrey MB, Quirke P, Shepherd NA. Royal College of Pathologists Dataset for colorectal cancer; December 2017
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
What is serrated pathology?

- a distinctive morphological appearance in the large intestinal mucosa
- with specific molecular fingerprints
- but varied endoscopic and macroscopic features
- and a variable but highly significant neoplastic potential
- representing the most important advance in our understanding of colorectal cancer development in the last decade
25% of CRC develop arise via the serrated pathway
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
UK guidance for the pathological reporting of serrated lesions of the colorectum

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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 (HPSs), 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 HPSs. 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.

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
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
Histologic and Molecular Analyses of Colonic Perineurial-like Proliferations in Serrated Polyps: Perineurial-like Stromal Proliferations Are Seen in Sessile Serrated Adenomas

Reetesh K. Pai, MD,* Amirkaveh Mojtahed, MD,* Robert V. Rouse, MD,* Roy M. Soetikno, MD, MS,† Tonya Kaltenbach, MD, MS,† Lisa Ma, MS,* Daniel A. Arber, MD,* Thomas P. Plesiec, MD,‡ John R. Goldblum, MD,‡ and Rish K. Pai, MD, PhD‡

Benign Serrated Colorectal Fibroblastic Polyps/Intramucosal Perineuriomas Are True Mixed Epithelial-stromal Polyps (Hybrid Hyperplastic Polyp/Mucosal Perineurioma) With Frequent BRAF Mutations

Abbas Agaimy, MD,* Robert Stoehr, PhD,* Michael Vieth, MD,‡ and Arndt Hartmann, MD*
Traditional serrated adenoma

- usually distal colon/rectum
- up to 2% of all colorectal polyps
- villiform or filiform (tennis racket)
- unequivocal dysplasia
- eosinophilic cytoplasm
- pencillate nuclei
- ectopic crypt formation
- BRAF or KRAS mutation
Ectopic crypt formation in traditional serrated adenoma

- disruption of signalling pathways of stem cell control
- expansion of progenitor cell population in ectopic crypt foci/lateral buds
- these lateral bud cells proliferate and gain somatic mutations
- leading to dysplasia arising outside the stem cell niche
- and more rapid malignant transformation
Colorectal cancer molecular pathogenesis

**Conventional pathway**
- FAP
  - Germline APC
  - Chromosomal instability
  - KRAS
  - SMAD4
  - p53

- CIMP - CIN+

**Serrated pathway**
- Traditional serrated
  - APC or less commonly β-catenin, axin
  - KRAS/BRAF mutation
  - +/- Aberrant methylation

- CIMP - MSS

- CIMP+/- MSS

- CIMP + MSS

**Sessile serrated**
- BRAF mutation
- Aberrant methylation

- CIMP+ MSI-H

**Microsatellite instability**
- Lynch
  - Germline MSH2,6, MLH1,3, PMS1,2

- CIMP - MSI-H

**Ultramutated**
- PPAP
  - Germline POLE
  - POLED1

- Sporadic
  - POLE

- Diploid CIMP - MSS

- Ultramutated

**CIN**
- 1-2%

**CIMP**
- ~60%

**MSI**
- ?1-15%
  - 6-8%
  - 9-12%
  - 2-5%
  - <0.5%
  - ~4%
<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Prevalence Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>hyperplastic polyp</td>
<td>25 - 30% of all colorectal polyps</td>
</tr>
<tr>
<td>sessile serrated lesion</td>
<td>1.7 - 9% of all colorectal polyps</td>
</tr>
<tr>
<td>SSL with dysplasia</td>
<td>13% of SSLs</td>
</tr>
<tr>
<td>traditional serrated adenoma</td>
<td>0.6 - 1.9% of all colorectal polyps</td>
</tr>
<tr>
<td>serrated adenocarcinoma</td>
<td>10 - 25% of all colorectal cancers</td>
</tr>
</tbody>
</table>

Oxford audit

Total number SSLs diagnosed

Number of diagnosed SSAs
Endoscopic appearances of SSLs

• difficult to spot at endoscopy
• predilection for right side where the prep is usually worse
• flat and often draped over a fold
• adherent mucus often the only clue
Serrated lesions: pathological lesions

- small, mainly left sided, conventional hyperplastic polyp – common (30% of polyps in BCSP)

- mainly right-sided ‘sessile serrated lesion’ – easily missed but increasingly recognised

- more advanced right-sided sessile serrated lesion with dysplasia – ‘SSL with dysplasia’

- traditional serrated adenoma – left-sided (2% of adenomas)

- larger left-sided (rare) filiform serrated adenoma (less than 0.1% of adenomas)

- serration associated with stromal lesions, perineuriomas, lipomas, etc. Primary, secondary or divergent differentiation?!?

- inflammatory bowel disease, especially ulcerative colitis
British Society of Gastroenterology position statement on serrated polyps in the colon and rectum

James E East,1 Wendy S Atkin,2 Adrian C Bateman,3 Susan K Clark,4 Sunil Dolwani,5 Shara N Ket,1 Simon J Leedham,6 Perminder S Phull,7 Matt D Rutter,8,9 Neil A Shepherd,10 Ian Tomlinson,11 Colin J Rees9,12

Serrated surveillance flowchart

Detection

Patient with serrated polyp(s) resected (excluding diminutive hyperplastic lesions)

Polyps

All serrated polyps <10mm in size, no associated dysplasia and not meeting criteria for SPS

Serrated polyp either size ≥10mm, or with associated dysplasia, or TSA

Multiple serrated polyps meeting criteria for SPS

Surveillance Interval

No surveillance on the basis of serrated polyps

One off surveillance colonoscopy at 3 years

Surveillance colonoscopy every one to two years once colon cleared

There is no current data to suggest that risk for patients with adenomas and serrated polyps is cumulative and therefore each polyp group should be considered separately for surveillance. The shortest surveillance interval recommended should take precedence.

SPS, Serrated Polyposis Syndrome; TSA, traditional serrated adenoma

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
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......
What colorectal cancer screening is all about….

- detecting early stage cancer

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

- A: 8%
- B: 33%
- C: 26%
- D: 25%

Polyp cancers: 22%

True A: 26%
Management of polyp cancers

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

No resection
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 ?)

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
<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Number of tumours</th>
<th>Number of adverse outcomes</th>
<th>Features for adverse outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colacchio</td>
<td>1981</td>
<td>24</td>
<td>6</td>
<td>None</td>
</tr>
<tr>
<td>Lipper</td>
<td>1983</td>
<td>51</td>
<td>2</td>
<td>Margin</td>
</tr>
<tr>
<td>Haggitt</td>
<td>1985</td>
<td>64</td>
<td>8</td>
<td>Level</td>
</tr>
<tr>
<td>Cranley</td>
<td>1986</td>
<td>38</td>
<td>10</td>
<td>Grade, margin, lymphatic invasion</td>
</tr>
<tr>
<td>Vanneste</td>
<td>1986</td>
<td>44</td>
<td>3</td>
<td>Grade, margin, vascular invasion, level</td>
</tr>
<tr>
<td>Richards</td>
<td>1987</td>
<td>80</td>
<td>10</td>
<td>Grade, margin, stalk invasion, vascular invasion</td>
</tr>
<tr>
<td>Coverlizza</td>
<td>1989</td>
<td>31</td>
<td>6</td>
<td>Margin, grade, vascular invasion</td>
</tr>
<tr>
<td>Kyzer</td>
<td>1992</td>
<td>44</td>
<td>3</td>
<td>Level</td>
</tr>
<tr>
<td>Minamoto</td>
<td>1993</td>
<td>40</td>
<td>6</td>
<td>Grade, level, lymphatic invasion, growth pattern, adenomatous component</td>
</tr>
<tr>
<td>Kikuchi</td>
<td>1995</td>
<td>182</td>
<td>21</td>
<td>Level, tumour configuration, location</td>
</tr>
<tr>
<td>Hase</td>
<td>1995</td>
<td>79</td>
<td>11</td>
<td>Tumour budding, growth pattern grade, level, lymphatic invasion</td>
</tr>
<tr>
<td>Cooper</td>
<td>1995</td>
<td>140</td>
<td>16</td>
<td>Margin, grade, vascular invasion</td>
</tr>
<tr>
<td>Volk</td>
<td>1995</td>
<td>47</td>
<td>10</td>
<td>Grade, margin</td>
</tr>
<tr>
<td>Whitlow</td>
<td>1997</td>
<td>59</td>
<td>4</td>
<td>Level, margin, grade</td>
</tr>
<tr>
<td>Netzer</td>
<td>1998</td>
<td>70</td>
<td>16</td>
<td>Margin, vascular invasion, grade</td>
</tr>
<tr>
<td>Ueno</td>
<td>2004</td>
<td>292</td>
<td>50</td>
<td>Margin, vascular invasion, grade, tumour budding, depth/width of submucosal invasion</td>
</tr>
</tbody>
</table>
Histologic Risk Factors and Clinical Outcome in Colorectal Malignant Polyp: A Pooled-Data Analysis

Cesare Hassan, M.D.,\textsuperscript{1} Angelo Zullo, M.D.,\textsuperscript{1} Mauro Risio, M.D.,\textsuperscript{2} Francesco P. Rossini, M.D.,\textsuperscript{3} Sergio Morini, M.D.\textsuperscript{1}

Dis Colon Rectum 2005; 48: 1588–1596
Table 1.
Relationship Between Histologic Risk Factors and Clinical Outcomes

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

CI = confidence interval.
Data are numbers with percentages in parentheses unless otherwise indicated.

*aP < 0.05.
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/Tumour Board discussion
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
Classification of early colorectal cancer in polyps

Haggitt RC et al, 1985

Haggitt levels of invasion in pedunculated polyp cancers

**Level 1:** Invasion of the submucosa but limited to the head of the polyp

**Level 2:** Invasion extending into the neck of the polyp

**Level 3:** Invasion into any part of the stalk

**Level 4:** Invasion beyond the stalk but above the muscularis propria
Issues with pathological assessments

margin involvement

lacks logic: is evidence good enough? definitions

don't differentiate & 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

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%)

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

• now international standardisation on methodology

  Lugli et al, 2017

• not currently recommended for routine reporting but one for the future?
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.....
The most useful tool in BCSP?!?
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
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
Why the sigmoid colon?
Epithelial misplacement vs invasive carcinoma
Epithelial misplacement vs carcinoma: what to look for

- lamina propria accompaniment
- lack of desmoplastic reaction
- haemosiderin deposition
- muscular proliferation as in mucosal prolapse
- acute changes of infarction adjacent
- accompaniment by non-neoplastic epithelium (especially after previous intervention)
- continuity of epithelium (in 3D, at least) between superficial and deep components
Do you see epithelial continuity in cancer?
64M. 22mm sigmoid colonic polyp.
64M. 22mm sigmoid colonic polyp.
The importance of deeper levels
The importance of deeper levels:
67F. Sigmoid colonic polyp.
The importance of deeper levels: 67F. Sigmoid colonic polyp.
Accompaniment by non-neoplastic mucosa

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

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
MMP-1
p53
collagen IV
e-cadherin

Ki67/MIB1

Immunohistochemistry

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

Collagen IV

Immunohistochemistry: desmin and other SM markers are useful to demonstrate submucosal involvement.

Adenoma-like adenocarcinoma

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......
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
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
Expert Board:
double diagnosis (ie EM & carcinoma) in 3% of cases
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.
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 and FIT 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?
- has been seen in other screening programmes but seemingly preferentially in population screening programmes: Scotland, Wales, Northern Ireland, Republic of Ireland, Canada, France, Netherlands, Slovenia - some are establishing similar diagnostic boards for this extraordinary problem
Setting bowel cancer screening pathology standards

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

Phil Quirke • Mauro Risio • René Lambert • Lawrence von Karsa • Michael Vieth
CRC screening as a driver for enhanced overall colorectal pathology service quality

• adenoma pathology: classification and grading of dysplasia; villosity

• serrated pathology: sensible reclassification

• use of performance indicators and quality measures to drive up colorectal cancer reporting quality, especially through BCS QA

Loughrey MB, Quirke P, Shepherd NA. 
RCPPath guidelines for the reporting of colorectal cancer, 2014 & 2018
Aged 60 - 69? Do your FREE NHS bowel cancer screening test. It’s a lifesaver.

To find out more, call the FREE NHS Helpline on 0800 707 6060 or visit www.leedssouthandeastcgp.nhs.uk/bowelcancer
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

Dr Adrian Bateman
Professor David Driman
The late Professor Jeremy Jass
Professor Simon Leedham
Dr Maurice Loughrey
Professor Iris Nagtegaal
Professor Marco Novelli

Professor Phil Quirke
Professor Robert Riddell
Dr Scott Sanders
The late Professor Bryan Warren
Professor Kay Washington
Professor Geraint Williams
Rodger C Haggitt

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