Not so simple pathology: issues from the screening programme

Professor Neil A Shepherd
Gloucester & Cheltenham, UK

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

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

What colorectal cancer screening is all about....

A detecting early stage cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>True A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>Polyp Cancers</th>
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<tr>
<td>A</td>
<td>26%</td>
<td>8%</td>
<td>34%</td>
<td>25%</td>
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<td>B</td>
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Dukes staging for symptomatic CRC versus screen-detected CRC in the English BCSP

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

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

A. the diagnosis of colorectal cancer on biopsy

A. serrated pathology & what do we do about it – expected but not the amount nor the diagnostic difficulties

A. polyp cancers (pT1 disease) & what we do about it – expected but not the management difficulties

A. the large adenomatous polyp of the sigmoid colon – expected but not the amount nor the diagnostic difficulties
25% of CRC develop arise via the serrated pathway

Terminology of sessile serrated pathology

- Sessile serrated adenoma
  - Tatalovic and Snow, 1996
- Sessile serrated polyp/adenoma
  - WHO, 2010
- Sessile serrated polyp
- Sessile serrated lesion
  - UK & European colorectal screening guidelines

Increased Risk of Colorectal Cancer Development Among Patients With Serrated Polyps

“Some of the lecturer’s 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.”

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

- the diagnosis of colorectal cancer in biopsy
- serrated pathology: particularly do we want 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 adenoma/poly of the sigmoid colon – expected but not the amount nor the diagnostic difficulties

What colorectal cancer screening is all about....

- detecting early stage cancer

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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....
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 2mm?)


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, 1995; Lemo et al. 2006.
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

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’
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?

Loughrey & Shepherd, 2017

Is this 'vascular intrusion'?

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 MDT/Tumour Board discussion

Issues with pathological assessments

- margin involvement
  - lacks logic: is evidence good enough? definitions
  - less problems but still subjective
- poor differentiation & lymphovascular invasion
  - not Muscles mucosae & propria only for sessile lesions?
  - sessile polypoid subjective
- Kikuchi: differences in polyp type and influence on endoscopic resection
  - pedunculated, sub-pedunculated & sessile
- Haggitt: subjective, definitions
- budding, poorly differentiated clusters
  - subjective
- 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%)

The most useful tool in BCSP?!?

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

1. the diagnosis of colorectal cancer on biopsy
2. serrated pathology in cancer screening which – expected but not the amount and the diagnostic difficulties
3. polyp cancer (pT1 disease) & what we do about it – expected but not the management difficulties
4. 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 taeniae 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.
64M. 22mm sigmoid colonic polyp.

Pathological conundra in BCSP

- epithelial misplacement mimicking cancer
- 85% in sigmoid colon
- selected into BCSP 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...

The importance of deeper levels
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

Immunohistochemistry

- Works well in classic cases of pseudo-invasion and cancer
- Not so good in marginal cases

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

Expert Board assessments

- 249 cases: 20 cases in 2009; 72 in 2016
- Expert Board 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
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

A. bowel cancer screening and its QA continues to improve the overall quality of colorectal pathology
B. we really must make ourselves more useful for surveillance by ensuring good agreement levels with high grade dysplasia and villousity, in particular
C. our knowledge of serrated pathology is increasing exponentially but we still have a lot to learn
D. we have real management problems with polyp cancers: measurement +/- budding may be the answer in the future…
E. epithelial misplacement v cancer – the diagnostic conundrum of the century (in the UK at least…)…
F. 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………………

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