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Dr. David Scaeffer declares he has no conflict(s) of interest to disclose.
Dr. Hector Li-Chang declares he has no conflicts of interest to disclose.
Dr. Risk Pai declares he has no conflicts of interest to disclose.
SC26: Colonic polyps

*Daily problems only pathologists understand*

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Associate Professor of Laboratory Medicine and Pathology
Increased number of colonoscopies – *have we seen the peak yet?*
Pathological classification of intestinal polyps

**Neoplastic**
- **Benign**
  - Hyperplastic
  - Lymphoid polyp
  - Ganglioneuroma
  - Leiomyoma
- **Dysplastic**
  - Adenoma
  - Serrated adenoma
  - DALM in IBD
  - Sessile serrated adenoma/polyp
- **Malignant**
  - 1°
    - Adenocarcinoma (malignant polyp)
    - Lymphomatous polyposis
    - GIST (occasionally)
    - NET
    - Metastatic (esp. melanoma, RCC)
    - Other (eg. leiomyosarcoma)
  - 2°

**Hamartomatous**
- Juvenile polyp
- Peutz-Jegher’s polyp
- PTEN (Cowden’s) disease
- Cronkhite-Canada syndrome

**Non-Neoplastic**
- **Inflammatory**
  - Pseudopolyp of IBD
  - Inflammatory polyp
  - Inflammatory fibroid polyp (mainly small bowel)
  - Inflammatory polyps secondary to mucosal prolapse
- **Other**
  - Endometriosis (occasionally)
  - Lymphangioma
  - AV Malformation
Endoscopic Classification of intestinal polyps

Paris classification:
- Type 0 – superficial polypoid, flat/depressed or excavated tumors
- Type 1 – polypoid carcinomas, usually attached on a wide base
- Type 2 – ulcerated with sharply demarcated and raised margins
- Type 3 – nonulcerated, diffusely infiltrating carcinomas
- Type 4 – unclassifiable advanced carcinomas

The Paris endoscopic classification of superficial neoplastic lesions. 2003 Gastrointestinal Endoscopy 58; 6
Paris Classification

Type 0-Ia

Type 0-IIa

Type 0-IIb

Photos courtesy of Dr. Fergal Donnellan, VGH
Clinical relevance of Paris Classification

<table>
<thead>
<tr>
<th>Paris Classification</th>
<th>Rate of submucosal invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 0 - III</td>
<td>Highest</td>
</tr>
<tr>
<td>Type 0 – I/IIc</td>
<td></td>
</tr>
<tr>
<td>Type 0 - IIa</td>
<td></td>
</tr>
<tr>
<td>Type 0 - IIb</td>
<td>Lowest</td>
</tr>
</tbody>
</table>

The Paris endoscopic classification of superficial neoplastic lesions. 2003 Gastrointestinal Endoscopy 58; 6
Kudo Classification – Pit Pattern Assessment

- **Pit Pattern I**: 0% Cancer, 0% Cancer, 28% Cancer
- **Pit Pattern II**: 0% Cancer, 72% Adenoma
- **Pit Pattern IIIL**: 13% Cancer, 87% Adenoma
- **Pit Pattern IIV**: 37% Cancer, 60% Adenoma
- **Pit Pattern V**: 63% Cancer

‘Poor man’s’ Pit Pattern assessment: granular or not granular

Photos courtesy of Dr. Fergal Donnellan, VGH
Multiple risk factors increase the risk of SMIC:
- 1% in 0–IIa granular lesion
- 46% in 0–IIac nongranular lesions
- 56% in 0–IIac nongranular lesions with tV pits

<table>
<thead>
<tr>
<th>Paris classification</th>
<th>n</th>
<th>% of total cohort</th>
<th>n (%) with SMI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is</td>
<td>146</td>
<td>30.5</td>
<td>11 (7.5)</td>
<td>.001</td>
</tr>
<tr>
<td>Ila</td>
<td>222</td>
<td>46.3</td>
<td>9 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Iib</td>
<td>9</td>
<td>1.9</td>
<td>1 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Ile or IIa+c</td>
<td>22</td>
<td>4.6</td>
<td>7 (31.8)</td>
<td></td>
</tr>
<tr>
<td>Ile + Ila</td>
<td>80</td>
<td>16.7</td>
<td>5 (6.3)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>0</td>
<td>0</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Surface morphology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granular</td>
<td>311</td>
<td>64.9</td>
<td>10 (3.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nongranular</td>
<td>98</td>
<td>20.5</td>
<td>15 (15.3)</td>
<td></td>
</tr>
<tr>
<td>Mixed granular and nongranular</td>
<td>30</td>
<td>6.3</td>
<td>3 (10)</td>
<td></td>
</tr>
<tr>
<td>Unable to classify</td>
<td>40</td>
<td>8.4</td>
<td>5 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Kudo pit pattern</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pit pattern I</td>
<td>7</td>
<td>1.5</td>
<td>0 (0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pit pattern II</td>
<td>41</td>
<td>8.6</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Pit pattern III</td>
<td>182</td>
<td>38.0</td>
<td>8 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Pit pattern IV</td>
<td>202</td>
<td>42.2</td>
<td>10 (5.0)</td>
<td></td>
</tr>
<tr>
<td>Pit pattern V</td>
<td>25</td>
<td>5.2</td>
<td>14 (56.0)</td>
<td></td>
</tr>
<tr>
<td>Unable to classify</td>
<td>22</td>
<td>4.6</td>
<td>1 (4.5)</td>
<td></td>
</tr>
</tbody>
</table>
Principals of colonic polypectomy

Probably not endoscopically resectable if:
• Involves more than one third circumference
• Involves appendix or terminal ileum
• Involves haustral folds

Polyps up to 5mm:
• Can use biopsy forceps (hot or cold)
• Can use cold snare

Polyps 5-10mm
• Can use snare (hot or cold)

Polyps >10mm
• Use hot snare
• Submucosal injection if hot snare

Types of resection:
• Single piece resection
• Endoscopic mucosal resection
• Piecemeal resection

Photos courtesy of Dr. Fergal Donnellan, VGH
### Types of snares

<table>
<thead>
<tr>
<th>Monofilament wire snares</th>
<th>Braided wire snares</th>
</tr>
</thead>
<tbody>
<tr>
<td>More cutting</td>
<td>More coagulation</td>
</tr>
<tr>
<td></td>
<td>Useful for flat polyps</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Standard snares</th>
<th>Mini snares</th>
</tr>
</thead>
<tbody>
<tr>
<td>5cm long x 2.5cm wide</td>
<td>3cm long x 1cm wide</td>
</tr>
<tr>
<td>Larger polyps</td>
<td>Tortuous colons</td>
</tr>
<tr>
<td>Straight colons</td>
<td>Diverticular disease</td>
</tr>
</tbody>
</table>

http://www.olympus.nl and www.bostonscientific.com
Injection for submucosal lift

- Methylene blue/indigo carmine with 10cc normal saline +/- epinephrine
- Injection placed either around edge of polyp or directly into the polyp
- ‘Non-lifting sign’:
  - Polyp may be fixed to the submucosa (? submucosal invasion)
  - Prior attempt at polypectomy with resultant scarring
- Minimal risk of tumour scarring

Photos courtesy of Dr. Fergal Donnellan, VGH
What should you expect to see in an endoscopy report for a colonic polypectomy:

- Polyp size
- Polyp location
- Polyp morphology (i.e. Paris/Kudo Classification)
- Method of removal
- Possible diagnosis based on endoscopic morphology

- Communicate with the gastroenterologist on an ongoing basis
- Advice them of missing/needed information on the requisition form
A. The malignant polyp:
   1. Differentiate misplaced epithelium from invasive adenocarcinoma.
   2. Interpret tumor budding as a high-risk feature.
   3. Recognize horizontal width of invasion as a high-risk feature.
   4. Interpret completeness of excision in a clinically meaningful way.

B. The serrated polyp:
   1. Classify serrated lesions.
   2. Understand the underlying molecular alterations.
   3. Discuss follow-up recommendations for serrated neoplasms.
   4. Understand dysplasia in serrated lesions.

C. The 'common' colonic polyp:
   1. Differentiate low-grade from high-grade dysplasia/IMC.
   2. Discuss polypoid dysplasia in IBD and appropriate terminology.
   3. Understand when to raise the possibility of a polyposis syndrome.
   4. Develop an approach to the 'subtle' polyp.
Case 1: Misplaced epithelium
Case 2: Malignant polyp
Case 3: SSA/P
Case 4: TSA
Case 5: HGD
Case 6: DALM/ALM
Case 7: Polyposis
Case 8: Subtle polyps
Case 1
Case History

• A 86 year old male with a positive FIT
• A 2.4 cm polyp is removed from the sigmoid colon
Questions – “Pseudoinvasion”? 

• Is there invasive carcinoma in these sections? 

• If yes, could the subsequent management be the same as that of a polyp without carcinoma?
Mucosal herniation, misplaced glands or “pseudo-invasion”

- Common (up to 2-10% of adenomas)

- Most commonly occurs in pedunculated sigmoid polyps (almost always left-sided)

- Caused by repeated torsion, ischemia and hemorrhage
  - May lead to increased screening/identification due to positive FIT tests
## Misplaced glands vs carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Misplaced glands</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>Almost all in left colon, most in sigmoid</td>
<td>Throughout colorectum</td>
</tr>
<tr>
<td><strong>Degree of dysplasia</strong></td>
<td>Similar to overlying adenoma</td>
<td>Usually more advanced, *can be similar (low-grade) rarely</td>
</tr>
<tr>
<td><strong>Gland shape</strong></td>
<td>Rounded or diamond-shaped</td>
<td>Irregular, infiltrative, *rarely regular/uniform</td>
</tr>
<tr>
<td><strong>Cystic dilatation</strong></td>
<td>Common</td>
<td>Rare</td>
</tr>
</tbody>
</table>
## Misplaced glands vs carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Misplaced glands</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjacent stroma</strong></td>
<td>With lamina propria, sometimes sclerotic, may have chronic inflammation/ granulation tissue</td>
<td>Desmoplastic, without lamina propria</td>
</tr>
<tr>
<td><strong>Hemosiderin</strong></td>
<td>Common</td>
<td>Rare/focal</td>
</tr>
<tr>
<td><strong>Mucin pools</strong></td>
<td>Rounded</td>
<td>Irregular</td>
</tr>
<tr>
<td><strong>Epithelium in mucin pools</strong></td>
<td>Single layer lines periphery or detached strips</td>
<td>Floating irregular fragments of epithelium</td>
</tr>
</tbody>
</table>
Particular problem areas

• High-grade dysplasia within misplaced glands
  — Note rounded nests and adjacent lamina propria

• Stromal fibrosis around misplaced glands
  — Note adjacent lamina propria around similar glands

• Well-differentiated carcinoma with lobular architecture
  — Absence of adjacent pseudoinvasion
Are ancillary stains useful?

• Yantiss et al. reported that MMP-1, p53, E-cadherin, and collagen IV were useful in distinguishing carcinoma from epithelial misplacement

• None of stains were 100% sensitive/specific
## Misplaced glands vs carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Misplaced glands</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagen type IV</td>
<td>Strong, continuous around nests</td>
<td>Weak, discontinuous</td>
</tr>
<tr>
<td>E-cadherin</td>
<td>Same intensity as adenoma</td>
<td>Decreased vs adenoma</td>
</tr>
<tr>
<td>p53</td>
<td>Wild-type</td>
<td>Mutated/increased</td>
</tr>
<tr>
<td>MMP-1</td>
<td>Negative</td>
<td>Increased</td>
</tr>
</tbody>
</table>

- No follow-up/confirmatory study
- These are not commonly used in practice, but worth a shot in truly challenging cases
Low-grade dysplasia giving rise to invasion

• Carcinoma may arise from low-grade dysplasia

• Rare, more frequently seen in IBD

• Carcinoma often well-differentiated in such cases, but shows definite infiltrative pattern
A brief comment

Diagnosis:
Sigmoid colon polyp:
- Tubulovillous adenoma with pseudo-invasion

• Is the term pseudo-invasion appropriate?
A brief comment

Diagnosis:
Sigmoid colon polyp:
-Tubulovillous adenoma with pseudo-invasion

• Is the term pseudo-invasion appropriate?

• Due to possibility of misunderstanding or oversight, consider using “misplaced glands/epithelium” or “mucosal herniation”
A brief comment

I asked a surgeon friend of mine what he understood by ‘pseudo-invasion’:

If I sign out a colonic adenoma as having pseudo-invasion, do you and most of your colleagues understand what I mean by that? There is concern that this term could lead to overly aggressive treatment, but not sure if that fear is well-founded.

Honestly I would call the pathologist. We still live in the likely outdated world of haggit classification. If I feel like a polyp has malignancy down in the neck or base I would recommend segmental resection. By the way you are wording
Sometimes VERY difficult to distinguish carcinoma from misplaced glands

• One recent study reviewed 32 cases with biopsy diagnosis of adenocarcinoma, and no residual carcinoma on resection (pT0)
  – 75% of time cancer correctly diagnosed on bx
  – 13% of time, false positive diagnosis of cancer (misplaced glands in 3 of the 4 misdiagnoses)
  – 13% of time, 2 pathologists couldn’t agree on presence of invasion
Sometimes VERY difficult to distinguish carcinoma from misplaced glands

• How would you sign this case out?
  – All pseudoinvasion?
  – Some invasive carcinoma?

• **NO** high-risk features for nodal metastases
  – No LVI, no budding, no poorly-differentiated carcinoma
Sometimes VERY difficult to distinguish carcinoma from misplaced glands

**Diagnosis:**

• *Tubular adenoma, with extensive mucosal herniation*
  
  – *Difficult to exclude focal low-grade adenocarcinoma, but please see Comment*

**Comment:**

  – “Even if there is focal invasive carcinoma, the risk of nodal metastases would be <1% given the present morphology, and polypectomy would suffice as treatment provided that local excision is complete.”
Summary

• Misplaced epithelium is common and can mimic carcinoma

• Some cases are more challenging than others

• Several features may aid in differentiating carcinoma from misplaced glands
  – IHC for **E-cadherin**, **p53**, MMP-1 and collagen IV has been suggested
Summary

• The term ‘misplaced epithelium’ is preferable to ‘pseudoinvasion’

• Distinguishing features may overlap or be difficult to characterize
  – Significant cause of resection lacking carcinoma
  – In most cases carcinoma will be low-grade without high-risk features for LN metastases, and good argument can be made for avoiding resection
Case 2 – The malignant polyp
Case 2 - Case history

A 52 year old male with a positive FIT. A 1.6 cm polyp is removed from the sigmoid colon.

- What is your diagnosis?
- What further management should be considered in this patient?
- Would you order any immunohistochemistry?
The ‘easy’ malignant polyp
Is this one invasive?
Another example.....
Follow the muscularis mucosae and check for tumor adjacent to submucosal vessels and desmoplasia
Mimics of invasion – *misplaced epithelium*
Mimics of invasion – (severe) high grade dysplasia
Management of malignant polyps: resect or not resect?

Does the risk of surgery outweigh the risk of metastatic disease?
Management of malignant polyps: *resect or not resect*?
30 day mortality rate of elective hemicolecotomy

1. Is the depth of invasion important?
2. What about the width of the tumor at the invasive front?
3. Shall I always stain for lymphovascular invasion?
4. How do I report completeness of excision?
5. Tumor budding – is that here to stay?
   • How many fields does one have to count?
   • What is the difference between budding and poorly differentiated carcinoma?
6. How do I write the report/comment?
Does one need to measure the depth of invasion?

Mentioned in several European and Japanese guidelines:
- Is this criterion alone sufficient for subsequent resection?
- Where does one measure from?
- The tumour often obscures the MM as a starting point.
- Is deeper worse?
The odds ratio of regional nodal involvement was 5.0 (range 1.5-17.0) at a threshold of 2000 μm for tumor depth.

<table>
<thead>
<tr>
<th>Depth of submucosal invasion</th>
<th># of cases</th>
<th>Nodal involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 500 μm</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>500 – 1000 μm</td>
<td>15</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>1000 – 2000 μm</td>
<td>38</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>2000 – 3000 μm</td>
<td>61</td>
<td>11 (18%)</td>
</tr>
<tr>
<td>3000 – 4000 μm</td>
<td>45</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>4000 – 5000 μm</td>
<td>31</td>
<td>6 (19%)</td>
</tr>
<tr>
<td>&gt; 5000 μm</td>
<td>38</td>
<td>8 (21%)</td>
</tr>
</tbody>
</table>
Width of invasive component

0.6 mm
The odds ratio of regional nodal involvement was 5.0 (range 4.5-21.1) at a threshold of 4000 µm for tumor width.

Width of invasive component: ? interobserver variability

The Ueno method for substaging pT1 colorectal adenocarcinoma by depth and width measurement: an interobserver study


*Department of Cellular Pathology, John Radcliffe Hospital, University of Oxford, Headington, Oxford, UK, †Department of Colorectal Surgery, Churchill Hospital, University of Oxford, Headington, Oxford, UK and ‡CR-UK/MRC Oxford Institute for Radiation Oncology, Department of Oncology, John Radcliffe Hospital, University of Oxford, Headington, Oxford, UK

Received 13 September 2013; accepted 25 October 2014; Accepted Article online 24 January 2015

• 70 consecutive pT1 polyp CRCs assessed for depth and width of invasion.
• High risk if depth ≥ 2000 µm or a width ≥ 4000 µm
• The ICC for the 60-polyp CRCs was 0.67 for depth and 0.37 for width.
Substaging pT1 – Haggitt levels for *polypoid* lesions

You need proper orientation!
Substaging pT1 – Kikuchi levels for non-polypoid lesions

Proper staging requires knowing where the MP is, so you need a resection specimen.

Kikuchi et al. Dis Colon Rectum 1995
Lymphatic invasion

Lesions called suspicious for vascular invasion tended to behave as though vascular invasion
- No routine staining, but will do it on a case by case basis
- Will report suspicious for vascular invasion with a comment.
Lymphatic or vascular invasion – *does the differentiation matter?*

**Ishii et al. Int J Colorectal Dis 2009**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>LN mets</th>
<th>No mets</th>
<th>p-value</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1 (33%)</td>
<td>45</td>
<td>13 (29%)</td>
<td>32 (71%)</td>
<td>0.001</td>
<td>V1 no predictor of rLN</td>
</tr>
<tr>
<td>L0 (67%)</td>
<td>91</td>
<td>5 (5%)</td>
<td>86 (95%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V1 (25%)</td>
<td>34</td>
<td>3 (9%)</td>
<td>31 (91%)</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>V0 (75%)</td>
<td>102</td>
<td>15 (15%)</td>
<td>87 (85%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Tateishi et al. Mod Path 2010**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>LN mets</th>
<th>No mets</th>
<th>p-value</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1 (24%)</td>
<td>76</td>
<td>25 (33%)</td>
<td>51 (67%)</td>
<td>&lt;0.01</td>
<td>V1 no independent predictor of rLN</td>
</tr>
<tr>
<td>L0 (76%)</td>
<td>246</td>
<td>21 (9%)</td>
<td>225 (91%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V1 (14%)</td>
<td>45</td>
<td>13 (29%)</td>
<td>32 (71%)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>V0 (86%)</td>
<td>277</td>
<td>33 (12%)</td>
<td>244 (88%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Margin assessment

1.8 mm
Margin assessment

- 1 mm suggested as the cutoff point
- Tumor within cautery = positive margin
- Fragmentation precludes assessment of completeness of excision
Tumor budding
Tumor budding – a histologic ‘snapshot’ of EMT

Zlobec I, et al., Oncotarget 2010; 1: 651 - 661
## Tumor budding – *clinical significance*

<table>
<thead>
<tr>
<th>Paper</th>
<th>Patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ueno 2004 (<em>Gastro</em>)</td>
<td>292 Stage I</td>
<td>Independent prognostic factor</td>
</tr>
<tr>
<td>Ueno 2004 (<em>Ann Surg</em>)</td>
<td>638 Stage II &amp; III</td>
<td>Independent prognostic factor</td>
</tr>
<tr>
<td>Wang 2005 (<em>Dis Colon</em>)</td>
<td>159 Stage I</td>
<td>10.1% pt with LN-mets</td>
</tr>
</tbody>
</table>
| Park 2004 (*Dis Colon*)     | 109 Stage II & III | (1) 61.5% had ITC  
<pre><code>                    |                      | (2) degree of TB correlated with ITC                                  |
</code></pre>
<p>| Okuyama 2003 (<em>Dis Colon</em>)  | 196 Stage II   | (1) 43.3% of tumors showed budding                                    |
|                            |                | (2) Significantly associated with LN mets                             |
|                            |                | (3) Independent prognostic factor                                     |
| Tanaka 2003 (<em>Dis Colon</em>)   | 138 Stage II   | Only budding associated with recurrence                                |
| Okuyama 2003 (<em>J Surg Onc</em>) | 83 pT3         | Lower overall survival (51.8% vs. 85%, P&lt;0.002)                        |
| Shinto 2006 (<em>Dis Colon</em>)   | 136 Stage II &amp; III | (1) Lymph node mets (P&lt;0.0001)                                     |
|                            |                | (2) High recurrence rate (P=0.0022)                                   |
| Kajiwara 2010 (<em>Dis Colon</em>) | 244 Stage II  | Significant LN met risk                                                |
| Homma 2010 (<em>J Surg Oncol</em>) | 65 Stage II    | Significant LN mets (P=0.002)                                         |</p>
<table>
<thead>
<tr>
<th>Paper</th>
<th>n</th>
<th>Stain</th>
<th>Scoring system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morodomi 1998 <em>(Cancer)</em></td>
<td>40</td>
<td>H&amp;E</td>
<td>Count performed at four locations (1.25mm² field area) and average calculated</td>
</tr>
<tr>
<td>Hase 1993 <em>(Dis Colon)</em></td>
<td>663</td>
<td>H&amp;E</td>
<td>N/A: classified according to subjective impression</td>
</tr>
<tr>
<td>Ueno 2002 <em>(Histopath.)</em></td>
<td>638</td>
<td>H&amp;E</td>
<td>10 or more buds in 25X field (0.385mm²)</td>
</tr>
<tr>
<td>Okuyama 2003 <em>(Dis Colon)</em></td>
<td>196</td>
<td>H&amp;E</td>
<td>N/A: classified according to subjective impression</td>
</tr>
<tr>
<td>Jass 2003 <em>(J Clin Path)</em></td>
<td>95</td>
<td>H&amp;E</td>
<td>5 buds in 40X field (area not specified)</td>
</tr>
<tr>
<td>Guzinska K 2005 <em>(Antican)</em></td>
<td>24</td>
<td>H&amp;E</td>
<td>Any budding considered positive</td>
</tr>
<tr>
<td>Ha 2005 <em>(Korean Can Ass)</em></td>
<td>90</td>
<td>H&amp;E</td>
<td>&gt;7 buds in 20X field (area not specified)</td>
</tr>
<tr>
<td>Kanazawa 2008 <em>(Col Dis)</em></td>
<td>159</td>
<td>H&amp;E</td>
<td>0-1/3: mild; 1/3-2/3: moderate; &gt;2/3: marked</td>
</tr>
<tr>
<td>Wang 2009 <em>(AJSP)</em></td>
<td>128</td>
<td>H&amp;E</td>
<td>5 fields (20X, 0.95mm²); a median count of 1 or more buds considered positive</td>
</tr>
</tbody>
</table>
Tumor budding – *scoring systems*

Ueno’s criteria:
- Tumour buds < 5 cells; 20x hpf ($\Theta = 0.385 \text{ mm}^2$)
- High grade budding: >10 buds of <5cells in a 20x hpf
  (Borderline budding: 5-9 buds of <5cells in a 20x hpf)
- No criteria for IHC (pCK) assessment

*Prognostic significance of tumor budding in rectal cancer biopsies before neoadjuvant therapy*

- Spot tumour buds at 4x power and confirm it at 10x
- Correlated with vascular invasion and LN metastases

Tumor budding – the ‘easy’ scenario
Tumor budding – *challenging scenarios*

- Fragmentation
- Mucinous Comp.
- Inflammation
- Stromal Cells
Tumor budding – *challenging scenarios*

- Fragmentation
- Mucinous Comp.
- Inflammation
- Stromal Cells
Differential Prognostic Significance of Morphologic Invasive Markers in Colorectal Cancer: Tumor Budding and Cytoplasmic Podia

Eiji Shinto, M.D.,1,3 Jeremy R. Jass, M.D.,3 Hitoshi Tsuda, M.D.,1 Taichi Sato, M.D.,2 Hideki Ueno, M.D.,2 Kazuo Hase, M.D.,4 Hidetaka Mochizuki, M.D.,2 Osamu Matsubara, M.D.1
Isn’t tumor budding just poorly differentiated carcinoma?

Poorly differentiated clusters (PDCs) as a novel histological predictor of nodal metastases in pT1 colorectal cancer

Valeria Barresi • Giovanni Branca • Antonio Ieni • Luca Reggiani Bonetti • Luigi Baron • Stefania Mondello • Giovanni Tuccari

- Poorly differentiated clusters (PDCs) ≥ 5 tumor cells with no gland formation.
- The presence of PDC, SM invasion depth ≥ 1000 µm and LVI was significantly associated with positive rLN (p<0.0001).
What should one report?

1. Presence/absence of poorly differentiated carcinoma (any amount)
2. Presence/absence of angiolymphatic invasion
3. Presence/absence of high-grade tumour budding
4. Distance of invasive AdenoCa to margin
5. Depth of invasion (Haggitt/Kikuchi)

Increased risk of rLN metastases

<table>
<thead>
<tr>
<th>RF Level</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>One RF</td>
<td>20.7%</td>
</tr>
<tr>
<td>Two/Three RF</td>
<td>36.4%</td>
</tr>
</tbody>
</table>

Sample report—*if no high risk features but fragmentation precludes margin assessment*

**Colon (sigmoid) polypectomy:**
Invasive colonic adenocarcinoma arising in a tubular adenoma:
- Negative for high grade tumor budding.
- Negative for lymphovascular invasion.
- Negative for poorly differentiated tumor component.
- Fragmentation and orientation preclude assessment of the resection margin.

**Comment:**
Due to the absence of high risk features for nodal metastasis (i.e. lymphovascular invasion, poorly differentiated component or tumor budding), no further surgical treatment is required for this polyp, provided it is fully excised. Given that the resection margin cannot be accurately assessed histologically, completeness of local excision needs to be ensured endoscopically.
Colon (sigmoid) polypectomy:
Invasive colonic adenocarcinoma arising in a tubular adenoma:
- POSITIVE for high grade tumor budding.
- Negative for lymphovascular invasion.
- Negative for poorly differentiated component.
- Completely excised; more than 3 mm from deep margin.

Comment:
While there is no evidence of lymphovascular invasion or a poorly differentiated component, the presence of tumor budding increases the risk of lymph node metastasis to approximately 15-25%.
In view of this, resection with regional lymphadenectomy should be considered in this patient, provided the risk of surgery does not outweigh the risk of metastatic disease.
Sample report – overt LVI and multiple polyps

Colon (sigmoid) polypectomy:
Invasive colonic adenocarcinoma arising in a tubular adenoma:
- POSITIVE for lymphovascular invasion.
- Negative for high grade tumor budding.
- Negative for poorly differentiated component.
- Completely excised; more than 2 mm from deep margin.

Comment:
In view of the overt angioinvasion, which is also used as a surrogate marker for an increased risk of nodal metastases, surgical resection with lymphadenectomy should be seriously considered in this patient. Given the patient’s age and the presence of multiple colonic adenomata we have requested the paraffin block to perform mismatch repair studies to exclude a germline mutation and will report these in an addendum. If present, this may influence the surgical management (local resection vs. subtotal colectomy).
Serrated Polyps

Dr. Rish K. Pai
Associate Professor
Mayo Clinic, Scottsdale, AZ
4mm cecal polyp
Diagnosis: A. SSA/P
B. HP
2mm splenic flexure polyp
Diagnosis: A. SSA/P
          B. HP
Questions that I will attempt to answer

• What is the evidence to support the serrated pathway?
• How are SSPs and HPs related?
• What are the features in serrated polyps that guide screening?
• What are the criteria to diagnose SSPs?
• What are the pitfalls in the diagnosis of SSPs?
Why should we care about serrated polyps?

- Microsatellite Stable CRC (MSS)
  - Serrated polyps
  - Adenomas
- Microsatellite Unstable CRC (MSI-high)
Evidence to support serrated pathway

- Patients with numerous serrated polyps are at increased risk of colorectal carcinoma (CRC).
- Large serrated polyps are associated with synchronous advanced polyps and CRC.
- Serrated polyps are present in areas that subsequently developed MSI-H CRC.
- Patients with MSI-H CRC often have serrated polyps elsewhere in the colon.
- Serrated polyps can develop dysplasia and are seen adjacent to some CRC.
- Serrated polyps have molecular features similar to MSI-H CRC.
Types of serrated polyps (40% of all polyps)

Related lesions but SSPs are further along in the serrated neoplasia pathway

- **65%**
  - Hyperplastic polyp (HP)
  - Microvesicular (MVHP)
  - Goblet cell rich (GCHP)

- **30%**
  - Sessile Serrated Polyp (SSP) [also known as SSA]

- **5%**
  - Traditional Serrated Adenoma (TSA)
• Important points:
  – SSPs probably develop from MVHPs: MVHPs aren’t completely innocuous but transformation to SSP is likely a rare event (occurs more commonly in the right colon).
  – Serrated pathway is characterized by hypermethylation of CpG islands (CIMP-high) and *BRAF* mutations.
Types of serrated polyps (40% of all polyps)

Related lesions but SSPs are further along in the serrated neoplasia pathway

Hyperplastic polyp (HP)
  - Microvesicular (MVHP)
  - Goblet cell rich (GCHP)

Sessile Serrated Polyp (SSP)

Traditional Serrated Adenoma (TSA)
Hyperplastic polyp (microvesicular)

**Clinical/Endoscopic features**
- 65% of serrated polyps
- Small
- Distal >> Proximal

**Pathologic features**
- Serrated crypts: serrations are limited to the upper 2/3 of crypts
- Crypts are elongated and straight
- Base of crypts are uniform
- No cytologic dysplasia
- Microvesicular mucin droplets
Microvesicular HP
Thickened subepithelial collagen layer
Sessile serrated polyp

**Clinical/Endoscopic features**
- 35% of all serrated polyps
- Larger than hyperplastic polyps
- Prominent mucosal fold with mucin cap
- Rim of debris/bubbles
- Proximal >> Distal

**Pathologic features**
- Resemble hyperplastic polyps
  - Serrated crypts
  - No cytologic dysplasia
  - Cells with microvesicular mucin
- **BUT Architectural differences:**
  - Serrations are present along the entire length of some crypts
  - The base of some crypts are dilated, irregular, and extend laterally.
Perineurial-like stromal proliferation
SSA/P and lipoma
SSP with cytologic dysplasia
“Serrated dysplasia” within SSP
## Sessile serrated polyps: follow-up

- Danish CRC study: 2,060 CRC cases, 8,237 controls
- Determined what polyps increase risk of CRC
- Reviewed all serrated polyps (4 GI pathologists)

<table>
<thead>
<tr>
<th>Polyp type</th>
<th>Cases %</th>
<th>Controls</th>
<th>Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No polyp</td>
<td>56.5</td>
<td>74.2</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>SSA/P with no cytologic dysplasia</td>
<td>2.9</td>
<td>1.4</td>
<td>2.75</td>
</tr>
<tr>
<td>SSA/P with cytologic dysplasia</td>
<td>1.0</td>
<td>0.3</td>
<td>4.76</td>
</tr>
<tr>
<td>Conventional adenoma</td>
<td>37</td>
<td>21</td>
<td>2.51</td>
</tr>
<tr>
<td>Hyperplastic polyp</td>
<td>5.1</td>
<td>4.4</td>
<td>1.69</td>
</tr>
</tbody>
</table>

### 2012 Recommendations for Surveillance and Screening Intervals in Individuals With Baseline Average Risk

<table>
<thead>
<tr>
<th>Baseline colonoscopy: most advanced finding(s)</th>
<th>Recommended surveillance interval (y)</th>
<th>Quality of evidence supporting the recommendation</th>
<th>New evidence stronger than 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serrated lesions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sessile serrated polyp(s) &lt;10 mm with no dysplasia</td>
<td>5</td>
<td>Low</td>
<td>NA</td>
</tr>
<tr>
<td>Sessile serrated polyp(s) ≥10 mm</td>
<td>3</td>
<td>Low</td>
<td>NA</td>
</tr>
<tr>
<td>Sessile serrated polyp with dysplasia</td>
<td>3</td>
<td>Low</td>
<td>NA</td>
</tr>
<tr>
<td>Traditional serrated adenoma</td>
<td>3</td>
<td>Low</td>
<td>NA</td>
</tr>
<tr>
<td>Serrated polyposis syndrome</td>
<td>1</td>
<td>Moderate</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Questions**

1. What about patients with multiple SSPs?
2. Is there any difference in proximal versus distal SSP?
3. What about HPs? Particularly proximal HPs?
Serrated polyps: Cancer risk

- HP
- Distal
- Few
- < 1 cm
- No dysplasia*

- SSP
- Proximal
- Many
- > 1 cm
- Dysplasia*

*For SSPs only
Serrated polyps: Cancer risk

- HP
- Distal
- Few
- < 1 cm
- No dysplasia*

SSP
- Proximal
- Many
- > 1 cm
- Dysplasia*

*For SSPs only
Serrated polyps: Cancer risk

- HP
- Distal
- Few
- < 1 cm
- No dysplasia*

Lower risk

- SSP
- Proximal
- Many
- > 1 cm
- Dysplasia*

Higher risk

*For SSPs only
## CCF Consensus Guidelines

### Recommendations based on Cleveland Clinic 2012 Consensus Meeting

<table>
<thead>
<tr>
<th>Polyp</th>
<th>Location</th>
<th>Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>HP &lt;10mm</td>
<td>Rectosigmoid</td>
<td>10</td>
</tr>
<tr>
<td>HP ≤5mm and ≤3 in number</td>
<td>Proximal to sigmoid</td>
<td>10</td>
</tr>
<tr>
<td>HP any size, ≥4 in number</td>
<td>Proximal to sigmoid</td>
<td>5</td>
</tr>
<tr>
<td>HP &gt;5mm, ≥1 in number</td>
<td>Proximal to sigmoid</td>
<td>5</td>
</tr>
<tr>
<td>SSP &lt;10mm, &lt;3 in number</td>
<td>Any</td>
<td>5</td>
</tr>
<tr>
<td>SSP ≥10mm, 1 in number</td>
<td>Any</td>
<td>3</td>
</tr>
<tr>
<td>SSP &lt;10 mm, ≥3 in number</td>
<td>Any</td>
<td>3</td>
</tr>
<tr>
<td>SSP ≥10 mm, ≥2 in number</td>
<td>Any</td>
<td>1 to 3</td>
</tr>
<tr>
<td>SSP with dysplasia, any size or number</td>
<td>Any</td>
<td>1 to 3</td>
</tr>
</tbody>
</table>

Making the diagnosis of SSP

• What are the criteria for a diagnosis of SSP?
  – Should we focus only on architecture?
    • How many crypts need to have abnormal architecture?
  – Should we consider size and location when we make the diagnosis?
## Serrated lesions: Diagnostic Issues

Histologic agreement among 7 GI pathologists on 109 serrated polyps

<table>
<thead>
<tr>
<th>Polyp</th>
<th>Overall Kappa</th>
<th>Individual Kappa</th>
<th>95% CI</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>All polyps</td>
<td>0.5</td>
<td></td>
<td>0.47-0.52</td>
<td>Moderate</td>
</tr>
<tr>
<td>HP</td>
<td>0.52</td>
<td></td>
<td>0.48-0.57</td>
<td>Moderate</td>
</tr>
<tr>
<td>SSP</td>
<td>0.56</td>
<td></td>
<td>0.51-0.60</td>
<td>Moderate</td>
</tr>
<tr>
<td>SSP with cytologic dysplasia</td>
<td>0.8</td>
<td></td>
<td>0.75-0.84</td>
<td>Excellent</td>
</tr>
</tbody>
</table>

Only moderate interobserver agreement

<table>
<thead>
<tr>
<th>Study</th>
<th>Polyp Category</th>
<th>Diagnostic criteria</th>
</tr>
</thead>
</table>
| Chung, et al  | SSP            | 1. >10 mm  
2. Proximal to hepatic flexure  
3. ≥4 of the following: exaggerated serration, crypt dilatation, increased crypt branching/horizontal growth, cytologic atypia, mitoses in upper half of crypt, increased cytoplasmic mucin, and epithelial stromal ratio >50% |
| Intermediate between HP and SSP |                | 1. <10 mm  
2. Any location in the bowel  
3. ≥4 of the criteria needed for SSP (above)                                                                                                                                 |
| HP            |                | Three or fewer of the above criteria                                                                                                                                 |
| Mohammadi et al. | SSP          | At least 2 of the following: basal crypt serration, crypt branching, and horizontal crypt growth                                                                                                                                 |
| Borderline SSP |                | Only 1 of the above criteria                                                                                                                                 |
| HP            |                | None of the above criteria                                                                                                                                 |
| WHO 2010      | SSP            | At least 2 adjacent crypts or 3 individual crypts with abnormal architecture                                                                                                                                 |
| HP            |                | Not meeting above criteria                                                                                                                                 |
| Aust et al    | SSP            | 1. Two of basal crypt serration, horizontal crypt growth, inverted crypts, and basal crypt dilatation  
2. The above features have to be in at least 2 crypts                                                                                                                                 |
| HP            |                | Not meeting above criteria                                                                                                                                 |
| Rex et al     | SSP            | At least one unequivocal architecturally distorted, dilated, and/or horizontally branched crypt                                                                                                                                 |
Minute splenic flexure polyp

Small SSP vs. HP, HP: 10 yr, SSP: 5 yr
How to make the diagnosis of SSP?

• Which criteria should we use?
    • WHO criteria: 12.1% were SSPs
    • Using Rex criteria: 14.7% were SSPs
    • Found that serrated polyps with any SSP-like crypts (Rex criteria) had clinical features more like SSPs than HPs (more proximal, larger, etc.)
  – They conclude that only 1 abnormal crypt is necessary for the diagnosis independent of size and location.

• Kolb et al found that using the Rex criteria resulted in improved interobserver agreement and a ~7% increase in the diagnosis of SSA/P compared to WHO criteria (J Clin Gastroenterol 2015, PMID: 26501882)
Pitfalls in the diagnosis of SSP

- **Mucosal Prolapse (left sided HPs)**
  - Pai et al (Histopathology 2010)
    - 276 serrated polyps, independent review by 2 pathologists
    - 30 polyps lacked consensus, 11/30 had features of mucosal prolapse.
  - Huang et al reanalyzed 78 rectal polyps diagnosed as SSP (Human Path 2013)
    - Mucosal prolapse was common in these “SSPs” and 31/78 were felt to be better classified as HPs with prolapse.
Mucosal Prolapse in serrated polyps

Prolapsed HP vs. SSP?
When there is mucosal prolapse, be very cautious in making a
Pitfalls in the diagnosis of SSP

- Poorly orientated biopsy fragments
  - As architecture is the most important determining feature of SSP, poorly oriented fragments are difficult to interpret.
  - Morales et al placed suspicious polyps in a paper envelope and flattened them before placing in formalin to help with embedding. (Endoscopy 2013 45(11):906)
  - This improved the interobserver agreement between pathologists and increased the % of polyps diagnosed as SSPs.
Hyperplastic polyp

Sessile serrated polyp

Poor orientation
Questions that I will attempt to answer

• What is the evidence to support the serrated pathway?
• How are SSPs and HPs related?
• What are the features in serrated polyps that guide screening?
• What are the criteria to diagnose SSPs?
• What are the pitfalls in the diagnosis of SSPs?
Traditional serrated adenoma

Dr. Rish K. Pai
Associate Professor
Mayo Clinic, Scottsdale, AZ
Diagnosis?

- A. Sessile serrated adenoma/polyp with cytologic dysplasia
- B. Traditional serrated adenoma
- C. Tubulovillous adenoma
- D. Mixed hyperplastic polyp/adenoma
Types of serrated polyps

- Hyperplastic polyp (HP)
  - Microvesicular (MVHP)
  - Goblet cell rich (GCHP)
- Sessile Serrated Polyp (SSP)
  (also known as SSA)
- Traditional Serrated Adenoma (TSA)

65%  
30%  
5%
Traditional serrated adenoma

- **Clinical/Endoscopic features**
  - 2-5% of serrated polyps
  - Large
  - Protuberant, exophytic
  - Distal>>Proximal

- **Pathologic features**
  - Villiform
  - Serrated crypts
  - Pseudostratified pencillate nuclei
  - Abundant eosinophilic cytoplasm
  - Ectopic crypts
Questions to be answered

• What is the relationship between TSAs, SSA/Ps and HPs?
• Is it important to recognize this polyp? Screening guidelines?
  – Is it an aggressive polyp?
• What are the defining pathologic features for this polyp?
  – Ectopic crypt foci?
• How do TSAs fit in the serrated pathway?
  – Molecular changes?
Around 30% of the time you can find a non-dysplastic serrated...
Questions to be answered

• What is the relationship between TSAs, SSA/Ps and HPs?
  – TSAs likely come from a non-dysplastic serrated polyp (either HP or SSA/P)
    • If this is true, why not call these SSA/Ps with cytologic dysplasia?
  – Calling these SSA/Ps with cytologic dysplasia doesn’t really tell the whole story – these are polyps with unique clinical, histologic, and molecular features.
  – Basically, TSAs are a specific form of serrated colorectal dysplasia
Questions to be answered

• What is the relationship between TSAs, SSA/Ps and HPs?

• Is it important to recognize this polyp? Screening guidelines?
  – Is it an aggressive polyp?

• What are the defining pathologic features for this polyp?
  – Ectopic crypt foci?

• How do TSAs fit in the serrated pathway?
  – Molecular changes?
From a prior study 717 polyps diagnosed as TSA
6 GI pathologists reclassified the serrated polyps according to WHO classification
- Only 420 of the original 717 were felt to be TSA
Of these, only 186 patients with TSAs had clinical, endoscopic, and follow-up data
Compared these 186 patients with TSAs to 372 age and sex-matched patients with only conventional adenomas
High-risk metachronous polyps are more frequent in patients with traditional serrated adenomas than in patients with conventional adenomas: a multicenter prospective study

Jin Young Yoon, MD, *1 Hyung Tae Kim, MD, *2 Sung Pil Hong, MD, PhD, 1 Hyun Gun Kim, MD, 3 Jin-Oh Kim, MD, 3 Dong-Hoon Yang, MD, 4 Dong Il Park, MD, 2 Seun Ja Park, MD, 5 Hyun-Soo Kim, MD, 6 Bora Keum, MD, 7 Cheol Hee Park, MD, 8 Chang Soo Eun, MD, 9 Suck-Ho Lee, MD, 3 Il Hyun Baek, MD, 8 Dong Kyung Chang, MD, PhD, 2 Tae Il Kim, MD, PhD 1
Seoul, Pusan, Wonju, Pyeongchon, Cheonan, Guri, Korea

(Gastrointest Endosc 2015;82:1087-93.)

| TABLE 3. Characteristics of polyps found in surveillance colonoscopies of traditional serrated adenoma and conventional adenoma patients |
|--------------------------------------------------|--------------------------------------------------|------------------|
| Polyp occurrence, yes/no                         | Traditional serrated adenomas (n = 186) | Conventional adenomas (n = 372) |
| No. of polyps                                     | 123/63 (66.1%/33.9%)                   | 162/210 (43.5%/56.5%)              |
| Range                                            | 1-40                                  | 1-30                              |
| Mean ± SD                                        | 4.5 ± 5.0                             | 3.2 ± 3.2                          |
| Size of the largest polyp, mm (range)            | 7.5 (2-30)                            | 5 (2-30)                           |
| Location of polyps                               |                                      |                                  |
| Right side of colon                              | 323 (51.0%)                           | 402 (51.4%)                       |
| Left side of colon                               | 211 (33.3%)                           | 283 (36.3%)                       |
| Rectum                                           | 99 (15.6%)                            | 95 (12.2%)                        |
| Type of adenomas                                 |                                      |                                  |
| Tubular adenoma                                  | 437 (84.7%)                           | 678 (86.9%)                       |
| Tubulovillous adenoma                            | 74 (14.3%)                            | 96 (12.3%)                        |
| Villous adenoma                                  | 5 (0.7%)                              | 6 (0.7%)                          |
| Conventional adenoma, yes/no                     | 102/84 (54.8%/45.2%)                 | 141/231 (37.9%/62.1%)             |
| Serrated adenoma, yes/no                         | 26/160 (14.0%/86.0%)                 | 3/369 (0.8%/99.2%)                |
| Hyperplastic polyp, yes/no                       | 62/124 (33.3%/66.7%)                 | 51/321 (13.7%/86.3%)              |

P value: .001
High-risk metachronous polyps are more frequent in patients with traditional serrated adenomas than in patients with conventional adenomas: a multicenter prospective study

Jin Young Yoon, MD, *1 Hyung Tae Kim, MD, *2 Sung Pil Hong, MD, PhD, 1 Hyun Gun Kim, MD, 3 Jin-Oh Kim, MD, 3 Dong-Hoon Yang, MD, 4 Dong Il Park, MD, 2 Seun Ja Park, MD, 5 Hyun-Soo Kim, MD, 6 Bora Keum, MD, 7 Cheol Hee Park, MD, 8 Chang Soo Eun, MD, 9 Suck-Ho Lee, MD, 3 Il Hyun Baek, MD, 8 Dong Kyung Chang, MD, PhD, 2 Tae Il Kim, MD, PhD 1

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<table>
<thead>
<tr>
<th>High-risk polyp</th>
<th>Traditional serrated adenomas (n = 186)</th>
<th>Conventional adenomas (n = 372)</th>
<th>High-risk conventional adenomas (n = 290)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>88 (47.3%)</td>
<td>119 (32.0%)</td>
<td>101 (32.0%)</td>
<td>&lt;.001,* .007†</td>
</tr>
<tr>
<td>No</td>
<td>98 (52.7%)</td>
<td>253 (68.0%)</td>
<td>189 (68.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Risk of developing an advanced adenoma:
Baseline TSA vs conventional adenoma:  **OR 2.37**
Baseline TSA vs advanced adenoma:  **OR 2.19**
### Table 1. 2012 Recommendations for Surveillance and Screening Intervals in Individuals With Baseline Average Risk

<table>
<thead>
<tr>
<th>Baseline colonoscopy: most advanced finding(s)</th>
<th>Recommended surveillance interval (y)</th>
<th>Quality of evidence supporting the recommendation</th>
<th>New evidence stronger than 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>No polyps</td>
<td>10</td>
<td>Moderate</td>
<td>Yes</td>
</tr>
<tr>
<td>Small (&lt;10 mm) hyperplastic polyps in rectum or sigmoid</td>
<td>10</td>
<td>Moderate</td>
<td>No</td>
</tr>
<tr>
<td>1-2 small (&lt;10 mm) tubular adenomas</td>
<td>5-10</td>
<td>Moderate</td>
<td>Yes</td>
</tr>
<tr>
<td>3-10 tubular adenomas</td>
<td>3</td>
<td>Moderate</td>
<td>Yes</td>
</tr>
<tr>
<td>&gt;10 adenomas</td>
<td>&lt;3</td>
<td>Moderate</td>
<td>No</td>
</tr>
<tr>
<td>One or more tubular adenomas ≥10 mm</td>
<td>3</td>
<td>High</td>
<td>Yes</td>
</tr>
<tr>
<td>One or more villous adenomas</td>
<td>3</td>
<td>Moderate</td>
<td>Yes</td>
</tr>
<tr>
<td>Adenoma with HGD</td>
<td>3</td>
<td>Moderate</td>
<td>No</td>
</tr>
<tr>
<td>Serrated lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sessile serrated polyp(s) &lt;10 mm with no dysplasia</td>
<td>5</td>
<td>Low</td>
<td>NA</td>
</tr>
<tr>
<td>Sessile serrated polyp(s) ≥10 mm</td>
<td>3</td>
<td>Low</td>
<td>NA</td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sessile serrated polyp with dysplasia</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Traditional serrated adenoma</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Serrated polyposis syndrome*</td>
<td>1</td>
<td>Moderate</td>
<td>NA</td>
</tr>
</tbody>
</table>

TSA: Screening guidelines

- Screening guidelines from Rex DK, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel.

<table>
<thead>
<tr>
<th>Polyp</th>
<th>Location</th>
<th>Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSA &lt;10mm, &lt;3 in number</td>
<td>Any</td>
<td>5</td>
</tr>
<tr>
<td>TSA ≥10mm, 1 in number</td>
<td>Any</td>
<td>3</td>
</tr>
<tr>
<td>TSA &lt;10 mm, ≥3 in number</td>
<td>Any</td>
<td>3</td>
</tr>
</tbody>
</table>

Potentially screening interval for a diagnosis of TSA should be minimum 3 years, potentially 1-3
Questions to be answered

• What is the relationship between TSAs, SSA/Ps and HPs?

• Is it important to recognize this polyp? Screening guidelines?
  – Is it an aggressive polyp?

• What are the defining pathologic features for this polyp?
  – Ectopic crypt foci?

• How do TSAs fit in the serrated pathway?
  – Molecular changes?
Sessile Serrated Adenoma (SSA) vs. Traditional Serrated Adenoma (TSA)

Emina Emilia Torlakovic, MD, PhD,* Jose D. Gomez, MD,†
David K. Driman, MBChB, FRCPC,‡ Jeremy R. Parfitt, MD,‡ Chang Wang, MD,*
Tama Benerjee, MD,* and Dale C. Snover, MD§

• Distinction between SSA and TSA difficult
• Evaluated 66 serrated polyps for shape, architectural features of crypts, eosinophilic cytoplasm, and distribution of proliferative zones
• Features of TSA
  • Ectopic crypt foci
  • Eosinophilic cytoplasm
  • Left sided location
Morphologic criteria

- Torlakovic and Snover proposed that ectopic crypt foci be a defining feature of TSA.
- However, ectopic crypt foci are not associated with any specific molecular alteration in TSAs.
TSAs can develop conventional dysplasia

- TSAs can develop conventional dysplasia that resembles a tubular or tubulovillous adenoma

- If it looks like conventional low-grade dysplasia, I don’t specifically mention it in my report

- If there is high-grade dysplasia mention in your report
Molecular features of TSAs

Analyzed 48 left-sided TSAs with a consensus diagnosis

<table>
<thead>
<tr>
<th>Variable analyzed</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF mutant</td>
<td>25 (47%)</td>
</tr>
<tr>
<td>KRAS mutant</td>
<td>23 (43%)</td>
</tr>
<tr>
<td>BRAF and KRAS wild-type</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>CpG island methylation (5-marker panel) (n = 31)</td>
<td></td>
</tr>
<tr>
<td>High (≥ 3)</td>
<td>7 (21%)</td>
</tr>
<tr>
<td>Low (1 to 2)</td>
<td>12 (39%)</td>
</tr>
<tr>
<td>Negative (0)</td>
<td>12 (39%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CACNA1G</th>
<th>IGF2</th>
<th>NEUROG1</th>
<th>RUNX3</th>
<th>SOCS1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAF</strong> mut TSAs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>KRAS</strong> mut TSAs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Serrated neoplasia

BRAF mut

Normal Mucosa

HP

SSP

SSP with cytologic dysplasia

MSI-High CRC

CpG DNA Methylation

VERY RARE

CpG Meth

KRAS mut

Normal Mucosa

BRAF mut

HP or "SSP"

TSA

TSA with conventional dysplasia

MSS CRC

?
TSA Take home points

- Distal location, protuberant/villiform
- Tall columnar cells with abundant eosinophilic cytoplasm, pseudostratified nuclei.
- Ectopic crypts are often present but are not required for the diagnosis.
- ~50% BRAF, ~40% KRAS, ~10% WT/WT
- ~25% may have a non-dysplastic serrated precursor
- Can develop conventional adenomatous dysplasia and give rise to colon cancer likely with low levels of CpG methylation.
Case 5
Case History

• A 52 year old man undergoes screening colonoscopy
• Two colonic polyps, each 0.5 cm
Questions – The conventional adenoma

• Is there high-grade dysplasia in these sections?
• Will a diagnosis of high-grade dysplasia alter clinical management?
Why do we bother characterizing adenomas?

• To exclude carcinoma, particularly one requiring further treatment

• To determine risk of subsequent advanced neoplasia
  – Determine interval for surveillance
# Usual surveillance intervals

<table>
<thead>
<tr>
<th>Baseline findings</th>
<th>Recommended Surveillance Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>No adenomas</td>
<td>10 years</td>
</tr>
<tr>
<td>1-2 adenomas</td>
<td>5-10 years</td>
</tr>
<tr>
<td>3-10 adenomas</td>
<td>3 years</td>
</tr>
<tr>
<td>&gt;10 adenomas</td>
<td>&lt;3 years</td>
</tr>
<tr>
<td>Adenoma &gt;1 cm</td>
<td>3 years</td>
</tr>
<tr>
<td>Adenoma with villous component</td>
<td>3 years</td>
</tr>
<tr>
<td>Adenoma with high-grade dysplasia</td>
<td>3 years</td>
</tr>
</tbody>
</table>

• Our job is to identify features that mandate getting a colonoscopy sooner
The advanced adenoma

- Size >1 cm

- Any villous component
  - i.e. tubulovillous adenoma or villous adenoma

- Any high-grade dysplasia
The Problem

• Definitions of high-grade dysplasia and villous architecture are not established and somewhat arbitrary...

• Even with uniform definitions, interobserver variability is significant
  – $K = 0.48$ for degree of dysplasia
  – $K = 0.54$ for architecture
Canadian Consensus Guidelines

• National Colorectal Cancer Screening Network: Classification of Benign Polyps
• Developed by panel of 29 pathologists with expertise in GI pathology
• To promote uniform reporting in Canada

High-grade dysplasia

• Whenever possible, diagnose at **low-power** using **architectural features**
  – Complex, appears blue and “dirty”
  – Crowding/back to back glands and cribiforming
  – Prominent intralumina tufting
  – Irregular budding
High-grade dysplasia

• Cytologic features *may* supplement architectural features:
  – loss of nuclear polarity
  – stratification through entire thickness
  – Open chromatin with prominent nucleoli
  – Atypical mitotic figures
  – Prominent apoptosis
High-grade dysplasia

• Caveats:
  – Can rely of cytology alone in limited biopsy
  – Features typically involve more than 1-2 crypts
  – If extensive/close to MM, can consider deeper sections to exclude superficial invasion
  – Some suggest comment: “NO metastatic potential” to dissuade over-treatment
Villous architecture

• Definition
  – Leaf-like projections lined by dysplastic glandular epithelium
  – Distinction of villous structures from elongated, separated tubules is sometimes problematic
  – Some define arbitrarily by the length of the glands exceeding twice the thickness of normal colorectal mucosa
“Foreshortened” Villi
• non-branching outgrowths protruding beyond the overall surface contour of an otherwise tubular lesion
Classical Villi
• Long, slender, upgrowths with thin stromal cores
• Little branching, usually parallel sides
• May have bulbous tips
Tubular vs Tubulovillous vs Villous

• Based on relative proportions of tubular and villous components:
  • <20-25% villous → classify as tubular
  • 20-25 - 75% villous → classify as tubulovillous
  • >75-80% villous → classify as villous
• small or fragmented biopsies from a known large polyp: presence of at least one villus merits classification as "at least tubulovillous"
Statement On Completeness of Excision?

• Optional for adenomas without HGD

• Required for:
  – Malignant polyps
  – Polyps with HGD:
    • state whether HGD present or absent at margin OR
    • state specifically if this is not assessable due to fragmentation
Should one report adenoma size?

• Most don’t, though some do...

• Discussion with endoscopists

• Studies based on size of *polyp*, not adenoma
  – Adenoma may be very minor part of polyp
  – Report size of polyp on gross exam, not size of adenoma on slide
"Intramucosal carcinoma" and "carcinoma in situ"

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Depth of Involvement</th>
<th>Finding</th>
<th>Usual Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGD</td>
<td>Mucosa (epithelium)</td>
<td>Low-grade dysplasia</td>
<td>Polypectomy* (No risk of mets)</td>
</tr>
<tr>
<td>HGD</td>
<td>Mucosa (epithelium)</td>
<td>High-grade dysplasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carcinoma in situ</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mucosa (lamina propria)</td>
<td>Intramucosal carcinoma</td>
<td></td>
</tr>
<tr>
<td>Invasive carcinoma</td>
<td>Submucosa</td>
<td>Invasive carcinoma (submucosal invasion)</td>
<td>Polypectomy or resection** (Met risk depends on histology)</td>
</tr>
</tbody>
</table>

* Depends on endoscopic resectability

**Depends on endoscopic resectability and presence of high-risk features for lymph node metastases
“Intramucosal carcinoma” and “carcinoma in situ”

• We avoid using “IMC” and “CIS” in the colorectum

• There is ~0 risk of lymph node metastases if invasion is confined to the mucosa

• We fall back on term “high-grade dysplasia” since they are the same clinically
  – Consider ensuring there is no SM invasion with deeper sections
Mismatch repair (MMR) immunohistochemistry in adenomas

- Sometimes requested by clinicians when only adenoma tissue available

- Performed, but Comment:
  - Sensitivity in patients with germline mutations (proven Lynch syndrome) is only 50-70%
  - If negative, further testing recommended
Summary: The Conventional Adenoma

• The main purpose of adenoma classification is to guide surveillance intervals

• Size >1 cm, number > 2, villous component >25% and HGD all decreased surveillance interval
Summary: The Conventional Adenoma

• Classification of HGD and villous architecture are imperfect
  – We still try our best!

• HGD is primarily a low-power diagnosis
  – Cytology alone may be used in limited biopsies
Summary: The Conventional Adenoma

• We recommend avoiding terms “carcinoma in situ” and “intramucosal carcinoma”

• Reporting size optional, may add value to some

• MMR testing is valid but sensitivity is low
Case 6 – The ‘IBD-Polyp’
A 43 year old woman with longstanding ulcerative colitis. Had recent flare-up despite treatment and undergoes colonoscopy for mucosal healing assessment. Two polyps are identified.

- What is your diagnosis of each polyp respectively?
- How would the management differ between the lesions?
Case 6 – polyp #1
Case 6 – polyp #2
Case 6 – endoscopic appearance

Photos courtesy of Dr. Fergal Donnellan, VGH
Case 6 – polyp #1
Case 6 – polyp #2
Case 6 – background mucosa for both polyps
**Terminology** | **Definition** | **Background mucosa**
--- | --- | ---
ALM | adenoma-like mass | colitic
DALM* (*aka* non-ALM) | Dysplasia-associated lesion or mass | colitic
non-ALM (*aka* DALM) | non-adenoma-like DALM | colitic
Sporadic adenoma | demarcated adenoma (can be tubular or sessile) | noncolitic

*Use with caution – know your audience! Patient may undergo colectomy irrespective of whether that is the correct treatment. For simplicity of separation ALM from non-adenoma-like dysplasia in this presentation the terminology of DALM is retained.*
Risk of CRC progression in IBD

Risk of progression to cancer is present in both UC and CDs.
-related to extent and duration of inflammation

Table 1
Risk of colorectal cancer in 3 population based Swedish cohorts (1954–1989) including 7607 patients with IBD (198,227 patient-years). 196 CRCs were found in 188 patients [19].

<table>
<thead>
<tr>
<th></th>
<th>10 years</th>
<th>20 years</th>
<th>30 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancolitis</td>
<td>1.5</td>
<td>3.8</td>
<td>7.6</td>
</tr>
<tr>
<td>UC</td>
<td>1</td>
<td>2.3</td>
<td>5.2</td>
</tr>
<tr>
<td>CD</td>
<td>0.5</td>
<td>1.4</td>
<td>2.2</td>
</tr>
</tbody>
</table>

- Patients with >10 years disease duration and pancolitis are at highest risk.
- Left-sided UC and those with proximal disease are also considered to be high risk.

IBD Dysplasia Molecular (Pathways of CRC formation in sporadic and chronic colitis associated cancer)

The scenario we all want to avoid.
The scenario we all want to avoid.
1. Can adenomas occur in colitic mucosa?
2. Is it possible to distinguish colitic dysplasia/DALMs from sporadic adenomas in colitic mucosa (ALMs)?
3. Does the distinction matter in terms of management?
### ALM vs. DALM – *histologic features*

<table>
<thead>
<tr>
<th></th>
<th>ALM</th>
<th>DALM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glandular structures</strong></td>
<td>• Round/oval</td>
<td>• Irregular</td>
</tr>
<tr>
<td></td>
<td>• Equal configuration</td>
<td>• Haphazard</td>
</tr>
<tr>
<td><strong>Proliferation zone</strong></td>
<td>• ‘Top-Down’ – morphology</td>
<td>• ‘Down-Top’ – morphology</td>
</tr>
<tr>
<td></td>
<td>• Neoplastic epithelium starts from the luminal side</td>
<td>• Neoplastic epithelium covers the entire length of the crypts finally reaching the luminal surface</td>
</tr>
<tr>
<td><strong>Mucin vacuoles</strong></td>
<td>• Even distribution</td>
<td>• Irregular (dystrophic)</td>
</tr>
<tr>
<td><strong>Nuclei</strong></td>
<td>• Palisading</td>
<td>• Oval/round</td>
</tr>
<tr>
<td></td>
<td>• Elongated</td>
<td>• Less densely packed</td>
</tr>
<tr>
<td></td>
<td>• Hyperchromatic</td>
<td>• Irregularly arranged</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Variation in chromatin</td>
</tr>
<tr>
<td><strong>Stroma</strong></td>
<td>• Loose</td>
<td>• Tightly packed</td>
</tr>
<tr>
<td></td>
<td>• Even arrangement</td>
<td>• Varying shape and thickness</td>
</tr>
<tr>
<td><strong>Delineation towards the adjacent mucosa</strong></td>
<td>• Sharp/abrupt</td>
<td>• Irregular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Less well defines</td>
</tr>
<tr>
<td><strong>ALM vs. DALM – clinical/endoscopic features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Endoscopic appearance ( cholmoendoscopy)</strong></td>
<td><strong>ALM</strong></td>
<td><strong>DALM</strong></td>
</tr>
<tr>
<td></td>
<td>• sharply demarcated</td>
<td>• irregular demarcated</td>
</tr>
<tr>
<td></td>
<td>• Kudo IIIS (small round)</td>
<td>• plaque-like</td>
</tr>
<tr>
<td></td>
<td>• Kudo IIIL (large round)</td>
<td>• elevated lesion</td>
</tr>
<tr>
<td></td>
<td>• Kudo IV (branch-like)</td>
<td>• verrucous</td>
</tr>
<tr>
<td><strong>Age of the patient</strong></td>
<td>&gt; 40 years</td>
<td>any age</td>
</tr>
<tr>
<td><strong>Onset age of colitis</strong></td>
<td>late onset</td>
<td>early onset</td>
</tr>
<tr>
<td><strong>Duration/extent of the underlying disease</strong></td>
<td>• &lt; 10 years</td>
<td>• &gt;10 years</td>
</tr>
<tr>
<td></td>
<td>• segmental</td>
<td>• pancolitis</td>
</tr>
<tr>
<td><strong>Localization within the affected segment colon</strong></td>
<td>noncolitic mucosa</td>
<td>colitic mucosa</td>
</tr>
<tr>
<td><strong>IHC</strong></td>
<td>Not helpful and shouldn’t be recommended at present</td>
<td></td>
</tr>
</tbody>
</table>
# ALM vs. DALM – Molecular analysis

<table>
<thead>
<tr>
<th></th>
<th>ALM</th>
<th>DALM</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC mutations</td>
<td>common</td>
<td>rare</td>
</tr>
<tr>
<td>β-catenin shift cyto -&gt; nuc</td>
<td>common</td>
<td>rare</td>
</tr>
<tr>
<td>p53 mutations</td>
<td>rare</td>
<td>very common</td>
</tr>
<tr>
<td>p16 mutations</td>
<td>rare</td>
<td>very common</td>
</tr>
<tr>
<td>Cyclin-D1</td>
<td>late upregulation</td>
<td>early upregulation</td>
</tr>
<tr>
<td>p21 (WAF/CIP1)</td>
<td>late upregulation</td>
<td>early downregulation</td>
</tr>
<tr>
<td>LOH – deletions on chromosome 3p within the vHPL gene locus</td>
<td>less frequent</td>
<td>frequent</td>
</tr>
</tbody>
</table>

DALM – management of polypoid dysplasia

- High-grade dysplasia
- Low-grade dysplasia
- Polyp
- Discrete polyp? Completely removed? No dysplasia elsewhere?
  - No
  - Yes
- Colonscopy in 3-6 months LGD confirmed?
  - Yes
  - No

Itzkowitz S et al. Gastroenterology 2004;126:1634
Colon (sigmoid) polypectomy:
(sporadic) Tubular adenoma, low grade dysplasia:
-Background chronic quiescent colitis.

Comment:
Although the histopathological features are those of a ‘sporadic adenoma’,
(assuming an endoscopic appearance in keeping with that), a lesion which
would be adequately treated with complete local endoscopic excision,
consideration to additional biopsies surrounding the base of the polyp should
be given to determine the status of the adjacent mucosa. If there is dysplasia
around the base, the elevated low grade dysplasia is better characterized as
low grade dysplasia arising in IBD with focal elevation with the attendant
increased risk of metachronous or synchronous malignancy. Additionally, a
dysplasia ‘run’ with segmental biopsies could be considered to exclude the
presence of concomitant flat dysplasia elsewhere.
An update on polyposis syndromes of the lower GI tract

Dr. Rish K. Pai
Associate Professor
Mayo Clinic, Scottsdale, AZ
Pathologists’ view of Lower GI Polyposis

• **Polyposis syndromes with predominately adenomas**
  – Familial adenomatous polyposis
  – Attenuated familial adenomatous polyposis
  – MUTYH-associated polyposis
  – Polymerase proofreading associated polyposis syndrome
  – Lynch syndrome (rarely)

• **Polyposis syndromes with both adenomas and serrated polyps**
  – Serrated polyposis syndrome
  – MUTYH-associated polyposis
  – Hereditary mixed polyposis syndrome
  – PTEN-hamartoma tumor syndrome

• **Polyposis with predominately hamartomatous polyps**
  – Juvenile polyposis
  – Peutz-Jeghers Polyposis
  – PTEN-hamartoma tumor syndrome
  – Hereditary mixed polyposis syndrome
  – Cronkhite-Canada syndrome
MUTYH-associated Polyposis (MAP)

- MUTYH protein functions to repair oxidative DNA damage
- Autosomal recessive polyposis
- >100 different mutations have been reported
  - Two mutations (Y179C & G396D) account for 70% of all mutant alleles
- Lead to G:C → T:A transversions
  - Somatic APC and KRAS mutations occur resulting in carcinogenesis
  - Characteristic c.34G>T (Gly12Cys) KRAS mutation

MUTYH-associated Polyposis (MAP)

- Often have >10-20 synchronous polyps
  - May be tubular adenomas, hyperplastic polyps, or sessile serrated polyps/adenomas (~40% have serrated polyps)

- Up to 1/3 of patients have CRC in the absence of multiple polyps

- Mean age of presentation 45 years

- No specific histologic phenotype for MUTYH-associated colorectal carcinoma
Extracolonic manifestations in MAP

• 20-25% have duodenal adenomas

• Fundic gland polyps are also seen

• CHRPE and osteomas reported

• Desmoid tumors are rare

• Increased incidence of extraintestinal malignancies (2x general population)\textsuperscript{1} – Ovarian, bladder, and skin

SSP from patient with MAP
## Spectrum of polyps in MAP

### Table 3. Clinical and pathologic characteristics of patients with MAP and non-MUTYH patients with multiple colonic polyps

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MAP patients (n = 27)</th>
<th>Non-MUTYH patients (n = 228)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis in years, mean (SD)</td>
<td>52.7 (11.02)</td>
<td>60.2 (11.97)</td>
<td>0.005</td>
</tr>
<tr>
<td>Total cases of colorectal cancer*, n (%)</td>
<td>16 (59.3%)</td>
<td>79 (35%)</td>
<td>0.014</td>
</tr>
<tr>
<td>New cases of colorectal cancer*, n (%)</td>
<td>7 (43.7%)</td>
<td>15 (19%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Personal history of any neoplasm, n (%)</td>
<td>4 (14.8%)</td>
<td>16 (7%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Familial history of colorectal cancer or colonic polyps, n (%)</td>
<td>14 (51.9%)</td>
<td>85 (37.3%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Polyp number, median (25–75 interquartile range)</td>
<td>35 (20–62)</td>
<td>15 (12–28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Polyps &gt;1 cm, median (25–75 interquartile range)</td>
<td>5 (0–9)</td>
<td>9 (0–21)</td>
<td>0.03</td>
</tr>
<tr>
<td>% Proximal polyps, mean (SD)</td>
<td>49 (26)</td>
<td>45 (28)</td>
<td>0.48</td>
</tr>
<tr>
<td>Presence of serrated polyps, n (%)</td>
<td>11 (40.75%)</td>
<td>148 (64.9%)</td>
<td>0.02</td>
</tr>
<tr>
<td>- Type (%)</td>
<td></td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>SSA</td>
<td>11</td>
<td>24.5</td>
<td></td>
</tr>
<tr>
<td>HP</td>
<td>69</td>
<td>75.5</td>
<td></td>
</tr>
<tr>
<td>- Location (%)</td>
<td></td>
<td></td>
<td>0.008</td>
</tr>
<tr>
<td>Proximal colon</td>
<td>83.3</td>
<td>31.6</td>
<td></td>
</tr>
<tr>
<td>Distal colon</td>
<td>16.7</td>
<td>68.4</td>
<td></td>
</tr>
<tr>
<td>Dysplasia in polyps (%)</td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>HG2 adenomas</td>
<td>7.4</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Serrated polyps</td>
<td>0</td>
<td>0.9</td>
<td>0.3</td>
</tr>
<tr>
<td>KRAS Gly12Cys mutation (%)</td>
<td>84.6</td>
<td>0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BRAF V600E mutation (%)</td>
<td>0</td>
<td>31.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Adenomas</td>
<td>0</td>
<td>0.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Serrated polyps</td>
<td>0</td>
<td>74.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NOTE: Bold values are statistically significant.
Abbreviations: HG2, high-grade dysplasia; SSA, sessile serrated adenoma; HP, hyperplastic polyps.
*Patients subjected to whole-gene analysis with no MUTYH biallelic mutation.
*Total cases of colorectal cancer refer to the total number of colorectal cancer cases before and after the first colonoscopy performed with diagnosis of colonic polyposis. New cases of colorectal cancer refer only to the colorectal cancer cases developed after this first colonoscopy.

• 229 microsatellite stable CRCs diagnosed in patients <50 yrs

• 4 patients (2%) had biallelic MUTYH mutations
  – 2/4 patients had multiple (3 & 12) synchronous tubular adenomas

• Offer MUTYH mutation analysis to patients with early-onset without MMR protein deficiency.
Prevalence and Phenotypes of *APC* and *MUTYH* Mutations in Patients With Multiple Colorectal Adenomas. *JAMA* 2012;308:485

Classic polyposis (≥100 adenomas, 1457 pts)
- 58% had an *APC* germline mutation
- 6.5% had biallelic *MUTYH* germline mutations

Attenuated polyposis (20-99 adenomas, 3253 pts)
- 10% had an *APC* germline mutation
- 7% had biallelic *MUTYH* germline mutations

10 to 19 adenomas (970 patients)
- 5% had an *APC* germline mutation
- 4% had biallelic *MUTYH* germline mutations

Earlier age at adenoma diagnosis and positive family history associated with increased likelihood of *APC* and/or *MUTYH* mutations.
Pathologists’ view of Lower GI Polyposis

• **Polyposis syndromes with predominately adenomas**
  – Familial adenomatous polyposis
  – Attenuated familial adenomatous polyposis
  – MUTYH-associated polyposis
  – **Polymerase proofreading associated polyposis syndrome**
  – Lynch syndrome (rarely)

• **Polyposis syndromes with both adenomas and serrated polyps**
  – Serrated polyposis syndrome
  – MUTYH-associated polyposis
  – Hereditary mixed polyposis syndrome
  – PTEN-hamartoma tumor syndrome

• **Polyposis with predominately hamartomatous polyps**
  – Juvenile polyposis
  – Peutz-Jeghers Polyposis
  – PTEN-hamartoma tumor syndrome
  – Hereditary mixed polyposis syndrome
  – Cronkhite-Canada syndrome
Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas *Nat Genetics* 2013;45:136.

- Whole genome sequencing performed on 15 patients with at least 10 adenomas diagnosed before 60 years of age and a family history of multiple adenomas/colorectal carcinoma (excluded *APC*, *MUTYH*, and Lynch syndrome).

- Identified 2 highly penetrant germline mutations in the proofreading domains of DNA polymerases, *POLE* and *POLD1*

- All carriers of the mutation developed colorectal carcinoma & adenomas and all family members lacking tumor or multiple adenomas were negative for the mutations.
Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas *Nat Genetics* 2013;45:136.

- Screening of 3805 colorectal carcinoma patients enriched for a family history of colorectal carcinoma, multiple adenomas, and early onset disease found 13 patients with germline POLE or POLD1 mutations.

- *POLE* and *POLD1* encode DNA polymerase proteins that important for proofreading and removal of corrected inserted nucleotides during DNA synthesis.
Polymerase Proofreading-associated Polyposis (PPAP)

• Variable phenotype in the colon/rectum
  – Most common: multiple (10-100) adenomas resembling attenuated polyposis with early onset colorectal carcinoma
  – Less common: <10 adenomas, some of which may be large, with later onset presentation similar to Lynch syndrome

• Increased risk of endometrial carcinoma & duodenal adenoma/carcinoma

• Rare cases of brain (oligodendroglioma) and breast (ductal) tumors

Polymerase Proofreading-associated Polyposis (PPAP)

- 4% of patients with HNPCC lacking germline MMR/EPCAM mutations (FCCTX) have POLE or POLD1 germline mutations.
- 7% of patients with polyposis lacking germline APC or MUTYH mutations have POLE or POLD1 germline mutations.

- Sporadic colorectal carcinoma with mutations in POLE have also been reported (~4% of CRC)

A germline homozygous mutation in the base-excision repair gene *NTHL1* causes adenomatous polyposis and colorectal cancer.

Robbert D A Weren¹, Marjolijn J L Lijtenberg¹,², C Marleen Kets¹, Richarda M de Voer¹, Eugène T P Verwiel¹, Liesbeth Spruijt¹, Wendy A G van Zelst-Stams¹, Marjolijn C Jongmans¹, Christian Gilissen¹, Jayne Y Hehir-Kwa¹, Alexander Hoischen¹, Jay Shendure³, Evan A Boyle³, Eveline J Kamping¹, Iris D Nagtegaal², Bastiaan B J Tops², Fokko M Nagengast⁴, Ad Geurts van Kessel¹, J Han J M van Krieken², Roland P Kuiper¹,⁵ & Nicoline Hoogerbrugge¹,⁵
Lynch Syndrome

- Accounts for 1 of every 35 patients with colorectal carcinoma
- Germline mutations or alterations in DNA mismatch repair (MMR) genes:
  - MLH1 (~35-40%)
  - MSH2 (~40%)
  - MSH6 (~10-15%)
  - PMS2 (~5-10%)
- Deletions in *EPCAM/TACSTD1* (~2%)
  - Result epigenetic silencing of the MSH2 gene by hypermethylation and loss of MSH2 and MSH6 expression.
Lynch Syndrome

- 11/83 had ≥ 10 adenomas (13%)
- Maximum synchronous polyps = 22
- Maximum metachronous polyps = 24

Inherited colorectal cancer caused by mutations in genes responsible for DNA replication errors:

- DNA mismatch repair: *MLH1, MSH2, MSH6, PMS2, EPCAM*

- DNA base excision repair: *MUTYH, NTHL1*

- DNA proofreading in replication: *POLE and POLD1*
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  - Cronkhite-Canada syndrome
Tumor #1
Tumor #1: PMS2
Tumor #2
Definition of SPS

• WHO definition
  (1) >20 serrated polyps anywhere in the colon (cumulative)
  (2) Any serrated polyp proximal to sigmoid in a patient with a first degree relative with SPS
  (3) ≥5 serrated polyps proximal to sigmoid with at least 2 greater than >10mm (cumulative)
Polyp landscape in SPS


<table>
<thead>
<tr>
<th>TABLE 1. Characteristics of 100 Patients With Serrated Polyposis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Recruitment sites</td>
</tr>
<tr>
<td>Australia</td>
</tr>
<tr>
<td>New Zealand</td>
</tr>
<tr>
<td>USA</td>
</tr>
<tr>
<td>Canada</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Age of diagnosis (y)</td>
</tr>
<tr>
<td>WHO criteria 2010</td>
</tr>
<tr>
<td>Criterion 1</td>
</tr>
<tr>
<td>Criterion 3</td>
</tr>
<tr>
<td>Criteria 1 and 3</td>
</tr>
<tr>
<td>Total polyp count</td>
</tr>
<tr>
<td>Polyp distribution</td>
</tr>
<tr>
<td>Pancolonic</td>
</tr>
<tr>
<td>Mostly proximal</td>
</tr>
<tr>
<td>Mostly distal</td>
</tr>
<tr>
<td>CRC present</td>
</tr>
<tr>
<td>Conventional adenoma present</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 2. Histologic Types of 406 Polyps Reviewed in Patients With Serrated Polyposis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyp</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Conventional adenoma—total</td>
</tr>
<tr>
<td>Tubular adenoma, low-grade dysplasia</td>
</tr>
<tr>
<td>Tubular adenoma, high-grade dysplasia</td>
</tr>
<tr>
<td>Tubulovillous adenoma, low-grade dysplasia</td>
</tr>
<tr>
<td>Tubulovillous adenoma, high-grade dysplasia</td>
</tr>
<tr>
<td>Serrated polyps—total</td>
</tr>
<tr>
<td>Microvesicular HP</td>
</tr>
<tr>
<td>Goblet cell HP</td>
</tr>
<tr>
<td>SSA/P</td>
</tr>
<tr>
<td>SSA/P, low-grade dysplasia</td>
</tr>
<tr>
<td>SSA/P, high-grade dysplasia</td>
</tr>
<tr>
<td>TSA</td>
</tr>
</tbody>
</table>

- Distributed throughout the colon
- ~40% BRAF mutated (arise through SSPs)
- ~40% BRAF/KRAS WT (possibly arise through conventional adenomas)

**TABLE 3.** Molecular Findings Stratified by MMR Deficiency Status and Colon Location in 38 CRCs for Which Information for all Features Was Available

<table>
<thead>
<tr>
<th></th>
<th>BRAF-mutated CRC</th>
<th>KRAS-mutated CRC</th>
<th>BRAF/KRAS Wild-type CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prox. Colon</td>
<td>Distal Colon</td>
<td>Total</td>
</tr>
<tr>
<td>MMRD</td>
<td>11</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>MMRP</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>1</td>
<td>18</td>
</tr>
</tbody>
</table>

MMRD indicates mismatch repair deficient; MMRP, mismatch repair proficient; Prox., proximal.
Pathologists’ view of Lower GI Polyposis

- Polyposis syndromes with predominately adenomas
  - Familial adenomatous polyposis
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  - MUTYH-associated polyposis
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  - Juvenile polyposis
  - Peutz-Jeghers Polyposis
  - PTEN-hamartoma tumor syndrome
  - Hereditary mixed polyposis syndrome
  - Cronkhite-Canada syndrome
Hamartomatous Polyps/Polyposis

• What the heck are these polyps?
  – Endoscopically-detected polypoid mixture of native epithelial and stromal elements or stroma alone (usually both)
  – At least partially non-neoplastic
  – Not better classified as another polyp
  – Includes Juvenile and Peutz-Jeghers polyps

• Pathology plays an important role in patients with multiple hamartomatous polyps
  – Particularly important is evaluation of the other polyps associated with the hamartomatous polyps and the background mucosa
Hamartomatous Polyps/Polyposis

• Terms that are have been used for hamartomatous polyps
  – Peutz-Jeghers polyp (most specific term: rarely used in the colon)
  – Juvenile polyp
  – Inflammatory polyp
• Individually Juvenile polyps are identical to sporadic inflammatory polyps
  – When there are multiple “inflammatory polyps” raising possibility of polyposis I simply say simply say “hamartomatous/inflammatory polyps” instead of juvenile polyp as these type of polyps can be seen in many polyposis syndromes
• Both Juvenile/inflammatory polyps and PJ-polyps can be confused with mucosal prolapse polyps

Hamartomatous polyps: Juvenile/Inflammatory type
Hamartomatous polyps: Juvenile/Inflammatory type
Hamartomatous polyps: Juvenile/Inflammatory type
Hamartomatous polyps: Juvenile/Inflammatory type
Prolapse polyp
Case

• 52 yo male with multiple polyps
• A few were tubular adenomas
Hamartomatous polyps: Juvenile/Inflammatory type
Lipoma
Diagnosis?

- Juvenile polyposis syndrome
- Hereditary mixed polyposis syndrome
- PTEN-hamartoma tumor syndrome
- Cronkite-Canada syndrome
**PTEN Hamartoma Tumor Syndrome**

- Has been referred to as Cowden syndrome (CS) and Bannayan-Riley-Ruvalcaba syndrome (BRRS)
- Autosomal dominant
- *PTEN (10q22-23)* tumor suppressor gene
  - Regulates cell cycle, apoptosis, and angiogenesis
PTEN Hamartoma Tumor Syndrome

- 1 in 200,000 individuals
- Mutation in PTEN gene
- Increased cancer risk
- Intestinal polyposis
  - Upper and lower GI tract

Table 3. Frequency of CS Features Observed in our PTEN Mutation–Positive Series

<table>
<thead>
<tr>
<th>CS feature</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrocephaly</td>
<td>95 (74.8)</td>
</tr>
<tr>
<td>GI polyps</td>
<td>64 (50.4)</td>
</tr>
<tr>
<td>Goiter/thyroid nodules</td>
<td>56 (44.1)</td>
</tr>
<tr>
<td>Benign breast disease&lt;sup&gt;a&lt;/sup&gt;</td>
<td>24 (37.5)</td>
</tr>
<tr>
<td>Breast cancer&lt;sup&gt;a&lt;/sup&gt;</td>
<td>24 (37.5)</td>
</tr>
<tr>
<td>Lipomas</td>
<td>44 (34.6)</td>
</tr>
<tr>
<td>Papillomatous papules</td>
<td>43 (33.9)</td>
</tr>
<tr>
<td>Endometrial fibroids&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17 (26.6)</td>
</tr>
<tr>
<td>Trichilemmomas</td>
<td>26 (20.5)</td>
</tr>
<tr>
<td>Penile freckling&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12 (19.0)</td>
</tr>
<tr>
<td>Acrual keratoses</td>
<td>21 (16.5)</td>
</tr>
<tr>
<td>Mental retardation/developmental delay</td>
<td>21 (16.5)</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>21 (16.5)</td>
</tr>
<tr>
<td>Endometrial cancer&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8 (12.5)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>9 (7.1)</td>
</tr>
<tr>
<td>Hermitte–Ducios disease</td>
<td>8 (6.3)</td>
</tr>
<tr>
<td>Autism</td>
<td>8 (6.3)</td>
</tr>
</tbody>
</table>

NOTE. GI polyps are the second most common feature.
<sup>a</sup>Female subjects only.
<sup>b</sup>Male subjects only.

Polyp types in PHTS

- Mixture of polyp types!
  - Glycogen acanthosis in esophagus
  - Hamartomatous/inflammatory polyps
  - Ganglioneuroma
  - Lipoma
  - Adenoma
  - Hyperplastic polyp
  - “funny polyps” that you can’t name
Ganglioneuromas of the GI tract

• 3 Types
  ‒ Polypoid ganglioneuroma: 65%
    • Never NF1
  ‒ Ganglioneuromatosis polyposis: 16%
    • Minority with PHTS
  ‒ Diffuse (mural) ganglioneuromatosis: 19%
    • Majority with NF1 or MEN 2b

Shekitka and Sobin.
AJSP. 1994
Hamartomatous polyposis

Hamartomatous Polyps

Sporadic

- CCS
- PJS

Hereditary

- JPS
- PHTS
- HMPS
Cronkhite-Canada Syndrome

- Polyps involve stomach, small bowel, and colorectum
- Polyps described as hamartomas BUT
  - Strikingly edematous lamina propria
  - Cystically dilated epithelial structures
  - May have abundant accompanying inflammation
- Atrophy and edema in non-polyp mucosa***
Hamartomatous polyps: Juvenile/Inflammatory type
Non-polyp colon
Ileum
Gastric polyp
Cronkhite-Canada Syndrome

- Dermatologic manifestations
  - Alopecia
  - Nail dystrophy (thinning, splitting, shedding)
  - Skin hyperpigmentation
- Variety of other clinical features
  - Cataracts
  - Thrombosis
  - Heart failure
  - Psychiatric disorders
CCS outcome

• Variable

• Historically - 50% five year survival
  
  – Death due to GI bleeding, sepsis, congestive heart failure
  
  – Mayo study found 90% remission on corticosteroids; azathioprine maintenance

  • ½ polyps have mild increase in IgG4 plasma cells

Hereditary mixed polyposis syndrome is caused by a 40-kb upstream duplication that leads to increased and ectopic expression of the BMP antagonist GREM1.

- Two kindreds of Ashkenazi Jewish descent with attenuated polyposis (10-100 polyps) with mixed morphologies:
  - Serrated polyps
  - Conventional adenomas that can progress to cancer
  - Hamartomatous-type polyps, resembling Peutz-Jeghers and juvenile polyps.

- Duplication of a region upstream of GREM1 leads increased GREM1 expression.
2nd Most common polyp after adenoma
“mixed HP/inflammatory polyp”

Photos courtesy of Dr. T. Plesec, CCF
Photos courtesy of Dr. T. Plesec, CCF
Photos courtesy of Dr. T. Plesec, CCF
Inflammatory/hamartomatous polyp

Hyperplastic polyp

Photos courtesy of Dr. T. Plesec. CCF
Inflammatory/hamartomatous polyp
Towards a More Complete Picture

• Inherited colorectal cancer caused by mutations in genes responsible for DNA replication errors:
  – DNA mismatch repair: \textit{MLH1, MSH2, MSH6, PMS2, EPCAM}
  – DNA base excision repair: \textit{MUTYH, NTHL1}
  – DNA proofreading in replication: \textit{POLE} and \textit{POLD1}

• Inherited colorectal cancer caused by mutations in genes in the mTOR/PI3K pathway:
Polyposis: Molecular pathways

Transcriptional effects, for example:
- mTOR: growth and proliferation, translation, increased VEGF-A expression
- β-catenin complexes with TCF/LEF, activating c-Myc and cyclinD1, leading to cell proliferation
- SMAD complex regulates cell growth and proliferation

GSK3β activates AP-1, leading to cell proliferation

MUTYH removes mispaired A
NTHL1 removes oxo-G

MLH1 > MSH6
PMS2

LS: MMR defect

Proofreading defect

POLE
PPAP
NGS Panel for Inherited CRC

- Lynch syndrome: *MLH1, MSH2, MSH6, PMS2, EPCAM*
- Autosomal dominant polyposis syndromes: *APC* (Familial adenomatous polyposis), *BMPR1A* and *SMAD4* (juvenile polyposis), *STK11* (Peutz-Jeghers syndrome), and *PTEN* (PTEN-hamartoma tumor syndrome)
- Autosomal recessive polyposis syndrome: *MUTYH*
- Recently discovered highly penetrant autosomal dominant polyposis syndromes
  - *GREM1*
  - Polymerase proofreading (*POLD1* and *POLE*)
  - *NTHL1*-associated polyposis
Polyposis at signout

- Mention in comment when you think about it!
  - Look up patient in medical record
    - Age? Family history? Have a diagnosis already?
  - Multiple polyps of distinctive type?
    - Peutz-Jeghers-type polyp – esp small bowel
    - Older pt with similar findings in non-polyps → CCS
    - Striking mixture of polyp types
      - PTEN-hamartoma tumor syndrome
      - Hereditary mixed polyposis → mixed HP/IP
    - Juvenile/inflammatory polyp – least specific individually
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Case 8
Case History

• A 34 year old woman
• Family history of colon cancer
• Single 0.3 cm polyp on colonoscopy
Questions – The hidden polyp

• Can you sign this out now?

• Or are additional levels necessary?
Causes for absence of epithelial polyp

• Sampling by endoscopist
  – Non-lesion (prominent mucosal fold/tag)
  – Lymphoid or mesenchymal lesion
  – Mucosa overlying submucosal lesion

• Lesion sampled but not sectioned (superficial or on opposite aspect of specimen)

• Subtle lesion histologically

• Error or artefact: In endoscopy suite, grossing, embedding/processing
You might consider signing this out now

• *Diagnosis:*
  
  *Submitted as “Colonic polyp”:*
  
  – *Prominent lymphoid aggregate*
  
  – *No epithelial lesion identified*

• What happens if we get deeper/step sections
Following 3 deeper levels...

• **Diagnosis:**

  *Colonic polyp:*
  – *Tubular adenoma*

• **What is the utility on ordering deeper levels in “negative” colonic biopsies?**
Factors that affect detection of submitted polyps

• Size of lesion relative to polyp

• Sectioning protocol used by laboratory
  – YLMV (Your lab may vary)

• Orientation of lesion within tissue fragment relative to microtome blade
How often do deeper levels detect a polyp?

• Among cases submitted as ‘polyp’ in which 3 original sections obtained

• Lesions on further sections in 4-30% (most studies 20-25%), usually adenomas

• Rotation of 180 degrees and re-embedding detects lesions in 30% of cases (adenoma in 20% and HPs in 10%)
How often do deeper levels detect a polyp?

- Most adenomas detected with deeper levels are small (<5 mm)
  - Some question their significance

- Hyperplastic polyps, leiomyomas, inflammatory polyps among other lesions

- Carcinoma is NOT detected, and high-grade dysplasia is likely exceptional
How many additional sections necessary

• Adenomas detected in first 2 levels in 83% of cases, and first 3 levels in 90% of cases

• Rare cases require 6+ additional levels
What is a lymphoid aggregate present?

- This *may* reduce the probability that an adenoma being identified, but the likelihood of identifying an adenoma is still significant (~10-24%)
Is it worth the extra cost?

- It costs approximately $90-110 to detect each additional adenoma (estimated technologist time, materials and pathologist time)
When does the diagnosis especially matter?

- Changes surveillance
  - i.e. interval for follow-up colonoscopy, method of surveillance
  - Influenced by
    - Findings at colonoscopy
    - Polyp diagnosis (number and type)
    - Family history
    - Physician/patient preferences
When does the diagnosis especially matter?

- It is useful to keep in mind what the thresholds are for your clinicians to alter their surveillance.

- American Cancer Society and American Gastroenterology Association have published guidelines.

- YEMV (your endoscopist may vary)
When does the diagnosis especially matter?

• Important thresholds:
  • 0 vs 1 adenoma
    – Surveillance @10 yrs vs colonoscopy @5-10 yrs
  • 2 vs 3+ adenomas
    – Colonoscopy @5-10 yrs vs colonoscopy at 3 yrs
  • >10 adenomas
    – Colonoscopy ≤ 3 yrs and polyposis syndrome considered
When does the diagnosis especially matter?

• *So surveillance interval will NOT be affected if considering 1 vs 2 adenomas,*

• *OR 3 vs >=4 adenomas*
When does the diagnosis especially matter?

- Hyperplastic polyposis syndrome
- Juvenile polyposis syndrome
- Peutz-Jeghers syndrome
- Cowden syndrome
Summary

• Deeper levels often detect lesions when initial sections are non-diagnostic (~20-25%)

• Size of lesion: tissue, sectioning protocol and orientation influence detection

• **Adenomas** are the lesions most frequently detected → may influence surveillance intervals (0 vs 1 and 2 vs 3 adenomas)
Summary

• High-grade dysplasia/carcinoma have **NOT** been described

• Lymphoid aggregates do **NOT** preclude presence of a true lesion

• 3 deeper levels detect 90% of adenomas

• Cost in most cases is worthwhile (≈$90)
Selected References


Schick BA, McLean CA and Driman DK. Negative colorectal polyp biopsies: the utility of cutting deeper levels. Virchows Arch. 2015;467:635-640.


