Update on Colonic Serrated (and Conventional) Adenomatous Polyps

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Serrated Pathway of Colon Carcinogenesis

- Silencing of DNA mismatch repair genes by methylation of promoter region of genes
- MSI-High colorectal cancer
- Lack of APC, Kras and p53 mutations
- Serrated morphologic phenotype
Serrated Pathway of Colon Cancer: The Hypothesis

Normal → HP → SSP → MSI-H Invasive CRC

BRAF CIMP MSI
Classification of Serrated Colonic Polyps
(WHO 2010 Modified)

1. Non-Dysplastic Serrated Polyps
   Normal architecture, normal proliferation
   Microvesicular hyperplastic polyp
   Goblet cell hyperplastic polyp
   Mucin-poor hyperplastic polyp

   Abnormal Architecture, abnormal proliferation
   Sessile serrated adenoma/polyp

2. Dysplastic Serrated Polyps
   Sessile serrated polyp with dysplasia
   Serrated adenoma (traditional)
   Conventional adenoma with serrated architecture

3. Unclassifiable serrated polyp (either with or without dysplasia)

Microvesicular HP

- Sessile
- Microvesicular mucin
- Left > right colon
- Generally < 0.5 cm
Goblet Cell Rich HP

- Sessile
- Minimal serration
- Elongated crypts
- ↑ goblet cells
Mucin Poor HP

- Sessile
- No mucin
- ↑ serration
- Small cells with ↓ cytoplasm
- Dilated crypts
## Hyperplastic Polyps

<table>
<thead>
<tr>
<th>Molecular Features</th>
<th>Microvesicular</th>
<th>Goblet Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braf</td>
<td>80%</td>
<td>Rare</td>
</tr>
<tr>
<td>Kras</td>
<td>Rare</td>
<td>54%</td>
</tr>
<tr>
<td>CIMP-high</td>
<td>68%</td>
<td>Rare</td>
</tr>
<tr>
<td>P53</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Sessile Serrated Polyp

Synonyms

Sessile serrated Adenoma
Giant (large) hyperplastic polyp
HP with dysmaturation
HP with increased proliferation
HP with altered proliferation
Atypical HP
SSP Clinical Features

- More often located in the right colon
- Sessile, broad
- Usually $>0.5$ cm
- Up to 9% of all polyps (Spring et al, 2006)
  - Account for $\sim 1/3$ to $1/4$ of the serrated polyps
Sessile Serrated Polyp
Sessile Serrated Adenoma/Polyp

- Flat, broad, sessile
- Distorted crypts
- Aberrant diff/prolif
- Rt>left colon
- Generally >0.5 cm
- 9% of all colonic polyps
Sessile Serrated Polyp With Dysplasia
Left colon
0.3 cm

“Small” SSA/P
## Molecular Abnormalities of Colon Polyps and Cancer

<table>
<thead>
<tr>
<th>Polyp/cancer</th>
<th>CIMP high</th>
<th>MLH1 methylation</th>
<th>MSI</th>
<th>Braf</th>
<th>Kras</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional Ad</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Cancer CIN</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Cancer Lynch</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Cancer CIMP-high</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>HP</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>SSA/P</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>SSA/P with dys</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>TSA</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feature</th>
<th>HP Without Dysplasia</th>
<th>HP With Dysplasia</th>
<th>SSA/P Without Dysplasia</th>
<th>SSA/P With Dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right (N=21)</td>
<td>Left (N=23)</td>
<td>Right (N=13)</td>
<td>Left (N=7)</td>
</tr>
<tr>
<td>Mutations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS</td>
<td>14.3%</td>
<td>47.8%</td>
<td>0%</td>
<td>28.6%</td>
</tr>
<tr>
<td>BRAF</td>
<td>76.2%</td>
<td>17.4%</td>
<td>69.2%</td>
<td>14.3%</td>
</tr>
<tr>
<td>Methylation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MGMT</td>
<td>47.6%</td>
<td>34.8%</td>
<td>61.5%</td>
<td>57.1%</td>
</tr>
<tr>
<td>hMLH1*</td>
<td>81%</td>
<td>47.8%</td>
<td>92.3%</td>
<td>42.9%</td>
</tr>
<tr>
<td>hMLH1†</td>
<td>33.3%</td>
<td>13%</td>
<td>30.8%</td>
<td>14.3%</td>
</tr>
<tr>
<td>APC</td>
<td>28.6%</td>
<td>47.8%</td>
<td>30.8%</td>
<td>14.3%</td>
</tr>
<tr>
<td>p16</td>
<td>66.7%</td>
<td>52.2%</td>
<td>92.3%</td>
<td>42.9%</td>
</tr>
<tr>
<td>CIMP high</td>
<td>76.2%</td>
<td>43.5%</td>
<td>92.3%</td>
<td>42.9%</td>
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*Primers by Herman et al
†Primers by Park et al

SSP and Risk of Cancer

- SSP and MSI-H cancers have similar clinical features
  - Right sided, older female patients
- SSP precede MSI-H colorectal cancer
- Associated with hyperplastic polyposis syndrome
  - Heterogenous disorder
  - Familial clustering, underlying hereditary defect unknown
  - Some risk of colon cancer
Longitudinal Outcome Study of Sessile Serrated Adenomas of the Colorectum: An Increased Risk for Subsequent Right-sided Colorectal Carcinoma

<table>
<thead>
<tr>
<th>Subjects with High-grade Lesions</th>
<th>N</th>
<th>Subjects with subsequent AP with LGD</th>
<th>All High-grade Lesions</th>
<th>AP with HGD</th>
<th>CRC</th>
<th>Time from Diagnosis of Subsequent High-grade Lesions (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSA</td>
<td>40</td>
<td>18</td>
<td>6 (15%)</td>
<td>1</td>
<td>5 (13%)</td>
<td>8.3 (1-15)</td>
</tr>
<tr>
<td>HP</td>
<td>55</td>
<td>7</td>
<td>2 (4%)</td>
<td>1</td>
<td>1 (2%)</td>
<td>2.8 (2-3.6)</td>
</tr>
<tr>
<td>AP</td>
<td>55</td>
<td>26</td>
<td>3 (5%)</td>
<td>2</td>
<td>1 (2%)</td>
<td>3.2 (1.1-5.4)</td>
</tr>
</tbody>
</table>

AP indicates adenomatous polyp; CRC, colorectal carcinoma; HGD, high-grade dysplasia; HP, hyperplastic polyp; LGD, low-grade dysplasia; N, number of subjects without prior high-grade lesions; SSA, sessile serrated adenoma.

Longitudinal Outcome Study of Sessile Serrated Adenomas of the Colorectum: An Increased Risk for Subsequent Right-sided Colorectal Carcinoma

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<th>Subj w/ High-grade Lesions</th>
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Traditional Serrated Adenoma

- Pedunculated or sessile
- Eosinophilic cytoplasm (↓ mucin)
- Left > right colon
- Any size
TSA

Low-Grade  High-Grade  Adenocarcinoma
## Traditional Serrated Adenomas

### Molecular Features

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braf</td>
<td>30-60%</td>
</tr>
<tr>
<td>Kras</td>
<td>10-27%*</td>
</tr>
<tr>
<td>APC</td>
<td>5-28%</td>
</tr>
<tr>
<td>MGMT</td>
<td>17-26%</td>
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<tr>
<td>P53</td>
<td>10-20%</td>
</tr>
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</table>

*Associated with HGD & Carcinoma*
Adenoma with Serrated Architecture
# Serrated Polyps Management

<table>
<thead>
<tr>
<th>Hyperplastic Polyp</th>
<th><strong>Biopsy/Polypectomy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>SSA/P</td>
<td>- polypectomy (complete)</td>
</tr>
<tr>
<td></td>
<td>- adenoma-like surveillance?</td>
</tr>
<tr>
<td>SSA/P with Dysplasia</td>
<td>- polypectomy (complete)</td>
</tr>
<tr>
<td>Traditional SA</td>
<td>- advanced adenoma surveillance?</td>
</tr>
<tr>
<td></td>
<td>- colectomy for non-complete excisions?</td>
</tr>
</tbody>
</table>
Serrated Polyposis Syndrome*
(Formerly Hyperplastic Polyposis)

- $\geq 5$ serrated polyps proximal to sigmoid
  - $\geq 2$ at least 10 mm in size
- $\geq 1$ serrated polyp proximal to sigmoid
  - First degree relative with SPS
- $>20$ serrated polyps (any size) throughout colon

*No definitive gene mutation identified
Serrated Polyposis Syndrome

**Hallmarks of Genetic Disease**

- Phenotype diversity
- Multiple lesions (HP, SSP, Adenomas)
- Young age of onset
- Strong family history (50% have CRC)
- Restricted ethnicity
- 25-50% synchronous cancer in case series
- 7% risk at 5 years in surveillance
- “Methylator milieu” (Inherited? Acquired?)
Serrated Polyposis Syndrome

Treatment

- Screening at ≥40 years or 10 years younger than affected relative, 5 year intervals
- Surgery (extended Rt hemi or subtotal colectomy)
- Annual surveillance residual colon
- Endoscopic management is an option
  - Clear all proximal serrated polyps
  - Clear all >5 mm in size
Colonic Neoplastic Precursor Lesions

1. Benign conventional adenomas
   - Non-advanced (tubular, LGD, <1 cm)
   - Advanced (villous, HGD, >1 cm)

2. Malignant Colon Polyps
Advanced vs Non-Advanced Adenoma

- Criteria differ between studies
- No uniform/validated criteria for villi or HGD
- Can endoscopy discriminate 0.9 from 1.1 cm accurately?
Conventional Adenomas

Villous

Tubular
Tubular or Villous?
High-Grade Dysplasia?
“Advanced” Adenomas: Pathologists Don’t Agree

<table>
<thead>
<tr>
<th>21 Adenomas</th>
<th>Villous *2</th>
<th>HGD</th>
</tr>
</thead>
<tbody>
<tr>
<td>90% agreement</td>
<td>48%</td>
<td>62%</td>
</tr>
<tr>
<td>80% agreement</td>
<td>67%</td>
<td>71%</td>
</tr>
<tr>
<td>Kappa</td>
<td>0.49</td>
<td>0.43</td>
</tr>
</tbody>
</table>

*1GI pathologists agreed less than general pathologists

*2range of percent villosity; 2-100%

Golembeski et al, Mod Pathol 2007;120(S2):115A
<table>
<thead>
<tr>
<th>Adenomas</th>
<th>Villous</th>
<th>HGD</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI Pathologists</td>
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<td>62%</td>
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<td>67%</td>
<td>71%</td>
</tr>
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90% agreement
80% agreement
Kappa 0.49 0.43

*1 GI pathologists agreed less than general pathologists
*2 range of percent villosity; 2-100%

Golembeski et al, Mod Pathol 2007;120(S2):115A
Conventional Adenomas

Reporting Issues

- Status of margins
- Size
- Dysplasia (if <1 cm)
Malignant Colorectal Polyp Pathology

1. Definition/Terminology

2. Tissue Handling: Endoscopy/Pathology

3. Pathology Assessment
   - Prognostication
   - Reporting

4. Summary
Malignant Colorectal Polyp
Definition

Adenoma with *submucosal*
invasive adenocarcinoma

≠ *High grade dysplasia*

≠ *Intramucosal adenocarcinoma*
<table>
<thead>
<tr>
<th>Adenomas Terminology</th>
<th>WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysplasia/Intraepithelial neoplasia</td>
<td>pTis</td>
</tr>
<tr>
<td>- No BM invasion</td>
<td></td>
</tr>
<tr>
<td>Intramucosal adenocarcinoma</td>
<td>pTis</td>
</tr>
<tr>
<td>- LP or MM invasion</td>
<td></td>
</tr>
<tr>
<td>Submucosal adenocarcinoma</td>
<td>pT1</td>
</tr>
<tr>
<td>- Invasion beyond MM</td>
<td></td>
</tr>
</tbody>
</table>

"HGD" > "Invasive Adenoca"
Malignant Colon Polyp
Invasive Adenocarcinoma
Information Pathologists Need to Know

• Shape of Polyp (pedunculated, sessile)?

• Excised in total vs. piecemeal?

• Deepest (stalk) tissue margin

Do not pin, cut, or ink anything
Place in formalin ASAP!
Polypectomy vs. Colectomy

Factors

1. Patient factors
   - Age, co-morbidities, resectability, genetics (lynch), cancer phobia

1. Pathologic factors
   - Gross (sessile vs. pedunculated)
   - Microscopic
Unfavorable (High Risk) Features*

Summary

- Poor differentiation (high grade)
- LVI
- Positive margin (or <1 or 2 mm?)
- Tumor budding/ dedifferentiation
- Mucinous, cribriform morphology
- Sessile morphology (SM>1 cm) (Tumor depth and width)

* Indications for colectomy due to risk of LNM, recurrence, metastasis and mortality
Frequency of Carcinoma at colectomy or Followup Post Polypectomy for MCP

<table>
<thead>
<tr>
<th>Studies</th>
<th># Polyps</th>
<th>Unfavorable Outcome (Total)</th>
<th>Unfavorable Outcome (Low Risk* Polyps)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>1227</td>
<td>135 (11%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Low Risk= Margin>2 mm, low grade Tumor, no LVI

Seitz et al Dis Colon Rectm 2004;47: 1789-1797
Poor differentiation
Poor tumour differentiation

• 6-9% malignant polyps (should be <20%)
• Poor differentiation in any part of tumour but particularly at invasive edge (some studies required 50% of polyp)
• Patterns:
  o <50% gland lumina
  o mucinous
  o signet ring
  o tumour ‘buds’ with >5 cells
  o Gleeson pattern 4 like cribriform arrangements
  o Undifferentiated carcinoma
  o NOT true tumour budding (<5 cells)
Tumor Differentiation

– Risk:

<table>
<thead>
<tr>
<th></th>
<th>Residual disease</th>
<th>Metastasis</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>% (average)</td>
<td>18%</td>
<td>23%</td>
<td>15%</td>
</tr>
<tr>
<td>Odds ratio - Hassan</td>
<td>2</td>
<td>4</td>
<td>9**</td>
</tr>
<tr>
<td>%/Odds ratio - Ueno</td>
<td></td>
<td>29%/3 (multivariate)</td>
<td></td>
</tr>
</tbody>
</table>


– Problem = Interobserver agreement is not good
  - 0.14  Terris et al. Mod Path 2012;25(2)182A
Vascular invasion

<table>
<thead>
<tr>
<th>% (average)</th>
<th>Residual disease</th>
<th>Metastasis</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>18%</td>
<td></td>
<td>35% (LN)/5% (H)</td>
<td>3%</td>
</tr>
<tr>
<td>Odds ratio - Hassan</td>
<td>1</td>
<td>7/2**</td>
<td>1.5</td>
</tr>
<tr>
<td>%/Odds ratio - Ueno</td>
<td></td>
<td>31%/3 (multivariate)</td>
<td></td>
</tr>
</tbody>
</table>


• usually associated with another adverse prognostic factor
• Vascular invasion does not add to risk when other adverse factors are already present
• Interobserver agreement is poor/moderate – 37-77%
Tumor Margin

> 2mm - clear

POSITIVE
Margin of resection

- positive variously defined
  - In diathermy artefact
  - 1 HP field
  - <1mm
  - <2mm

- Ueno et al. *Gastroenterology* 2004; 127:385-94  ➔ only diathermy artefact involvement significant

- ≥1 mm clearance Butte et al. *Dis Colon Rectum* 2012; 55:122-127

- general agreement that ≥2mm is definitely clear

- positive margin -33% (using all definitions)
# Unfavorable Histology/Outcome

<table>
<thead>
<tr>
<th>Author</th>
<th># Cases</th>
<th>Margin</th>
<th>“Unfavorable” Histology</th>
<th>Adverse Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooper (1995)</td>
<td>140</td>
<td>&lt;1 mm</td>
<td>71 (50%)</td>
<td>20%</td>
</tr>
<tr>
<td>Volk (1995)</td>
<td>47</td>
<td>&lt;2 mm</td>
<td>30 (66%)</td>
<td>33%</td>
</tr>
<tr>
<td>Seitz (2004)</td>
<td>114</td>
<td>Clear</td>
<td>60 (52%)</td>
<td>27%</td>
</tr>
</tbody>
</table>

Poor diff, LVI, Margin <1 mm or <2 mm or clear
Tumour budding

- Identified as a significant prognostic factor in several papers
  - Ueno et al Gastroenterology 2004;127:385-94
  - Tateishi et al Mod Path 2010;1:1-5
  - Katajima et al J Gastroenterol 2004;39:534-43
- Uniform definition lacking – range from any budding to strict definition
  - Ueno paper = >5 buds (of <5 cells) in any one 20X field (FD = 0.785mm²);
  - Sohn paper = >10 buds
- Reproducibility?
Polyp morphology

- Pedunculated vs sessile
- Sessile - overall mortality 8x pedunculated polyps
- By definition all sessile polyps are Haggitt level IV (but this over estimates risk based on Haggitt data)
- Reason sessile is worse = increased adverse factors are usually present:
  - poor differentiation
  - vascular invasion
  - positive resection margin**
Polyp morphology

- Risk for sessile polyp Vs pedunculated polyp – pooled analysis*

<table>
<thead>
<tr>
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<th>Residual/recurrent disease</th>
<th>Metastasis</th>
<th>Mortality</th>
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<tbody>
<tr>
<td>% (average) - S</td>
<td>11%/6%</td>
<td>10%(LN)/4% (H)</td>
<td>5%</td>
</tr>
<tr>
<td>% (average) - P</td>
<td>3%/0.5%</td>
<td>10%(LN)/1% (H)</td>
<td>0.5%</td>
</tr>
<tr>
<td>Odds ratio - Hassan</td>
<td>4</td>
<td>1/4</td>
<td>10</td>
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*approximation (multivariate)

? not an independent risk factor for LN metastasis

However, most (85%) of sessile polyps had surgery
Pathologic Factors

Tumor size/depth of invasion
(Haggitt, Kichuki/Kudo)
Haggitt levels

Depth of invasion

Haggitt et al Gastroenterology 1985;89:328-36
Haggitt levels

- Haggitt paper Gastroenterology 1985;89:328-36

  - 8/64 (12.5%) submucosal invasive carcinoma had an adverse outcome (LN mets/tumour related death). These were:
    - Levels 0-2 = 0 cases (0%)
    - Level 3 = 1 case (12.5%)
    - Level 4 = 7 cases (87.5%)

  - Level 4 is the significant factor
  - 7/28 polyps were level 4 = PPV for adverse behaviour = 25%
Haggitt Levels

Limitations

1. Not clear # level 4 were pedunculated

2. 59 sessile polyps, by def’n level 4

3. Difficult to apply in practice
   - Poor orientation
   - Piecemeal specimens
   - Pedunculated vs sessile
   - Hard to distinguish levels
Kikuchi/Kudo levels

Sessile polyps

Lymph node metastasis risk

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>LN Metastasis Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>sm1: slight submucosal invasion from the muscularis mucosa.</td>
<td>3%</td>
</tr>
<tr>
<td>sm2: intermediate between sm1 and sm3.</td>
<td>8%</td>
</tr>
<tr>
<td>sm3: carcinoma invasion near the inner surface of the muscularis propria.</td>
<td>23%</td>
</tr>
</tbody>
</table>

Overall pT1 – 6-12%

Rectal location

- Rectal location, in particular, the distal 1/3 of rectum is an adverse factor for:
  1. LN metastases (up to 1/3)
  2. Recurrent/Residual disease (5-28%)

- Reason is not clear from the literature
- Surgical resection favoured for rectal site

Haggitt et al. Gastroenterology 1985;89:328-36
## Pathology Reporting

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<thead>
<tr>
<th>Mandatory</th>
<th>Highly recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasion vs. No invasion</td>
<td>Leading Edge characteristics</td>
</tr>
<tr>
<td></td>
<td>- Tumor budding</td>
</tr>
<tr>
<td></td>
<td>- Dedifferentiation</td>
</tr>
<tr>
<td>Type of Cancer</td>
<td>Desmoplasia</td>
</tr>
<tr>
<td>Tumor Differentiation</td>
<td>Mucinous or cribriform</td>
</tr>
<tr>
<td>LVI</td>
<td>Haggitt level (pedunculated)</td>
</tr>
<tr>
<td>Distance to deep margin (mm)</td>
<td>Kikuchi level (sessile)</td>
</tr>
<tr>
<td>Status of mucosal margins</td>
<td></td>
</tr>
</tbody>
</table>
Piecemeal Polypectomy

*Words of Caution*

- Invasion vs no invasion difficult to evaluate
  - Desmoplasia
  - MM breach ➔ Presume invasion
  - LVI

- Cannot assess: Deep margin (unless excised separately)
  - mucosal margins, leading edge, Haggitt or Kikuchi level

- Can assess: Type of tumor, differentiation, and status of cauterized tissue edges

Review with Pathologist at microscope!
## Surgical Resection Recommendations

<table>
<thead>
<tr>
<th>Site</th>
<th>Pedunculated</th>
<th>Sessile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>Unfavorable features</td>
<td>Unfavorable features</td>
</tr>
<tr>
<td></td>
<td>Haggitt 4</td>
<td>SM2, 3 (or &gt;1 mm)</td>
</tr>
<tr>
<td></td>
<td>Same</td>
<td>Piecemeal Excision</td>
</tr>
<tr>
<td>Rectum (Upper 2/3)</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td>Rectum (Lower 1/3)</td>
<td>Same</td>
<td>All</td>
</tr>
</tbody>
</table>

*N=70 cases  
Summary

1. Direct communication between endoscopist and pathologist is vital

2. Understand the terminology, staging and meaning of unfavorable features

3. Make sure polyps are evaluated in total (Don’t leave cancer in the tissue block!)

4. Don’t ever make false assumptions! Assume the worse