DIMINUTIVE POLYPS: DISREGARD OR REMOVE?

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Case Presentation

- A 55-year-old male is referred for screening colonoscopy.
- He is in good health and takes no medications.
- He denies any family history of colorectal cancer or colon polyps.
- Colonoscopy demonstrates a single, 4 mm sessile ascending colon polyp, and was otherwise normal.
- Bowel preparation quality is adequate.

What would you do?
Decision Factors

• Polyp size
• Anticipated histology
• Polyp location
• Accuracy of pathologic assessment
• Natural history
• Cost-effectiveness
• Polypectomy risk.
Why even ask the question?

• Current standard: Resect everything
  - Exclude invasive cancer
  - Determine surveillance intervals

• Predict, Resect, Discard strategy
  - Select polyps would be characterized during colonoscopy,
  resected, but not sent for pathology
  - Histology predicted during colonoscopy
  - Potential for enormous cost savings

• Predict, Disregard strategy
  - Select polyps would be characterized during colonoscopy,
  not resected
  - Histology predicted during colonoscopy
  - Potential for enormous cost savings.
Cost-Effectiveness

- In resect and discard strategies for diminutive polyps the savings from avoiding pathology costs:
  - About $ 33 million in screening cases
  - About $ 1 billion USD for all colonoscopies

Hassan C, Pickhardt PJ, Rex DK. Clin Gastroenterol Hepatol 2010; 8: 865-9
# Cancer Prevalence by Polyp Size

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>≤ 5 mm</th>
<th>6-9 mm</th>
<th>≥ 10 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldridge (2001)</td>
<td>0%</td>
<td>1.5%</td>
<td>10.2%</td>
</tr>
<tr>
<td>Gschwantler (2002)</td>
<td>0%</td>
<td>0.9%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Pickhardt (2003)</td>
<td>0%</td>
<td>0%</td>
<td>2.4%</td>
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<tr>
<td>Church (2004)</td>
<td>0.05%</td>
<td>0.15%</td>
<td>3.1%</td>
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<tr>
<td>Odom (2005)</td>
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<td>0.65%</td>
<td>4%</td>
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<tr>
<td>Butterly (2006)</td>
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<td>0.4%</td>
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<tr>
<td>Kim (2007)</td>
<td>0%</td>
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<tr>
<td>Yoo (2007)</td>
<td>0%</td>
<td>0.5%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Lieberman (2008)</td>
<td>0%</td>
<td>0.17%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Graser (2009)</td>
<td>0%</td>
<td>0%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Rex (2009)</td>
<td>0.05%</td>
<td>0%</td>
<td></td>
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<tr>
<td>Gupta (2013)</td>
<td>0%</td>
<td>0%</td>
<td>0.3%</td>
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</tbody>
</table>
## Advanced Histology Prevalence by Polyp Size

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<tr>
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<tr>
<td>Aldridge (2001)</td>
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<td>6.8%</td>
<td>5.8%</td>
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<tr>
<td>Gschwantler (2002)</td>
<td>3.4%</td>
<td>12.5%</td>
<td>29.7%</td>
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<tr>
<td>Pickhardt (2003)</td>
<td>0.1%</td>
<td></td>
<td>16.3%</td>
</tr>
<tr>
<td>Church (2004)</td>
<td>2%</td>
<td>9.8%</td>
<td></td>
</tr>
<tr>
<td>Butterfly (2006)</td>
<td>2.6%</td>
<td>7.8%</td>
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<tr>
<td>Kim (2007)</td>
<td>0.2%</td>
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<tr>
<td>Yoo (2007)</td>
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<tr>
<td>Lieberman (2008)</td>
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<td>15.2%</td>
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<tr>
<td>Graser (2009)</td>
<td>1.7%</td>
<td>10.7%</td>
<td></td>
</tr>
<tr>
<td>Rex (2009)</td>
<td>0.9%</td>
<td>5.3%</td>
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<tr>
<td>Gupta (2013)</td>
<td>0.5%</td>
<td>1.5%</td>
<td>15.0%</td>
</tr>
</tbody>
</table>
A Changing Paradigm

Previous model (1990):
Almost all Colorectal cancers develop along the Vogelstein model (adenoma-carcinoma sequence)
Suppressor (chromosomal instability) pathway

Mutator (microsatellite instability) pathway

Serrated (CIMP+) pathway

Conventional adenoma-carcinoma sequence

MYH pathway

CIMP+MSS pathway

TSA pathway

Familial adenomatous polyposis

Lynch syndrome carcinoma

CIMP-MSS carcinoma – 60%

Sporadic CIMP-MSS carcinoma – 5%

CIMP+MSS carcinoma – 20%

Sporadic CIMP+MSS carcinoma – 13%

CIMP+MSS – 5%

TSA-associated carcinoma (?CIMP+MSI-L) – 1%

Adapted from Snover DC. Update on the serrated pathway to colorectal carcinoma. Hum Pathol (2010)
Basic Molecular Pathways in CRC

• Chromosomal Instability (CIN) Pathway---60%-70%
  - Adenoma-carcinoma sequence

• Mutator Pathway---5%
  - Defective DNA mismatch repair (*hMLH1, hMSH2, hMSH6, hPMS2*)
  - Microsatellite instability (MSI)
  - Example: HNPCC

• Serrated pathway---25%-35%
  - *BRAF* oncogene mutations
  - Epigenetic DNA promoter hypermethylation leading to the CpG island methylator phenotype (CIMP)
  - MSI +/−
World Health Organization Classification

- Hyperplastic Polyp
  - Microvesicular HP (MVHP)
  - Goblet-cell rich HP (GCHP)
  - Mucin-poor HP (MPHP)

- Sessile Serrated Adenoma/Polyp (SSA/P)
  - SSA/P without cytological dysplasia
  - SSA/P with cytological dysplasia

- Traditional Serrated Adenoma (TSA)

Normal Mucosa

Microvesicular Hyperplastic Polyp

BRAF mutation

Promoter hypermethylation

Sessile Serrated Adenoma/Polyp

MSI, MLH1 methylation

SSA/P with cytological dysplasia

Cancer

Variable progression

Rapid progression (HNPCC-like)

Snover D, et al. WHO classification of tumours. 2010
Serrated Pathway and Interval CRC

- Overlap in molecular signatures
- Compared to non-interval CRC, interval CRC is more likely to:
  - Demonstrate MSI
  - Be located in the proximal colon
  - Be associated with CIMP.

Sawhney et al. Gastroenterology 2006; 131: 1700-5
Arain et al. Am J Gastroenterol 2010; 105: 1189-95
Rectosigmoid Hyperplastic Polyps

- Usually sessile and 1-5 mm, rarely > 10 mm
- Can be multiple
- Pearl-colored, pale
- Distal HPs are not associated with increased risk of recurrent adenomas after baseline examination

Sessile Serrated Polyps

- Flat, subtle appearance
- Larger than hyperplastic polyps
- Typically proximal colon
- Mucus cap
- Similar in color to surrounding mucosa
- Surface grossly similar to HP

Vu et al. Dis Colon Rectum 2011; 54:1216-23
SSA/P versus HP: Can we distinguish based on endoscopic features?

- Modified Kudo pit (Type II-O) is specific but not sensitive for SSA/P and highly associated with BRAF mutation and CIMP
  → Requires Magnification


- Endoscopic predictors of SSA/P histology on NBI:
  - Cloud-like surface
  - Indistinct borders
  - Irregular shape
  - Dark spots inside the crypts
  → Image evaluation by experts

  *Hazewinkel et al. GIE 2013;77:916-24.*
Decreased protection in the right colon

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Outcome</th>
<th>Overall CRC (95% CI)</th>
<th>Left-sided CRC (95% CI)</th>
<th>Right-sided CRC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baxter, 2009</td>
<td>CRC Mortality (OR)</td>
<td>0.63 (0.57-0.69)</td>
<td>0.33 (0.28-0.39)</td>
<td>0.99 (0.86-1.14)</td>
</tr>
<tr>
<td>Ontario, Canada</td>
<td></td>
<td></td>
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<tr>
<td>Singh, 2010</td>
<td>CRC Mortality (SMR)</td>
<td>0.71 (0.61-0.82)</td>
<td>0.53 (0.42-0.67)</td>
<td>0.94 (0.77-1.17)</td>
</tr>
<tr>
<td>Manitoba, Canada</td>
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<tr>
<td>Brenner, 2011</td>
<td>CRC Incidence (OR)</td>
<td>0.23 (0.19-0.27)</td>
<td>0.16 (0.12-0.20)</td>
<td>0.44 (0.35-0.55)</td>
</tr>
<tr>
<td>Rhine-Neckar, Germany</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Baxter, 2012</td>
<td>CRC Mortality (OR)</td>
<td>0.40 (0.37-0.43)</td>
<td>0.24 (0.21-0.27)</td>
<td>0.58 (0.53-0.64)</td>
</tr>
<tr>
<td>SEER-Medicare</td>
<td></td>
<td></td>
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</tbody>
</table>

Singh et al. Gastroenterology 2010;139:1128–37
Colonoscopy Quality is Operator-Dependent

• Adenoma detection rate (ADR) is a validated predictor of CRC risk after screening colonoscopy
  → 10-fold increase risk of interval CRC if ADR <20%, compared to ≥ 20%

  *Kaminski et al. NEJM 2010; 362: 1795-1803*

• Many adenomas are missed during colonoscopy
  → 26% miss rate for diminutive adenomas

Polypectomy prevents Colorectal Cancer

Polypectomy protects against proximal cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>Proximal CRC OR (95% CI)</th>
<th>Distal CRC OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>% completeness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 80%</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>80-84%</td>
<td>1.16 (0.86–1.56)</td>
<td>0.90 (0.65–1.25)</td>
</tr>
<tr>
<td>85-89%</td>
<td>0.69 (0.51–0.93)</td>
<td>0.65 (0.47–0.89)</td>
</tr>
<tr>
<td>90-94%</td>
<td>0.66 (0.50–0.87)</td>
<td>0.71 (0.54–0.93)</td>
</tr>
<tr>
<td>&gt; 95%</td>
<td>0.72 (0.53–0.97)</td>
<td>0.73 (0.54–0.97)</td>
</tr>
<tr>
<td></td>
<td>P=0.002</td>
<td>P=0.03</td>
</tr>
<tr>
<td><strong>% polypectomy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10%</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>10-14%</td>
<td>1.11 (0.81–1.53)</td>
<td>0.99 (0.73–1.35)</td>
</tr>
<tr>
<td>15-19%</td>
<td>0.75 (0.54–1.04)</td>
<td>0.78 (0.57–1.06)</td>
</tr>
<tr>
<td>20-24%</td>
<td>0.75 (0.52–1.07)</td>
<td>0.82 (0.58–1.16)</td>
</tr>
<tr>
<td>25-29%</td>
<td>0.52 (0.35–0.79)</td>
<td>0.87 (0.61–1.24)</td>
</tr>
<tr>
<td>&gt;30%</td>
<td>0.61 (0.42–0.89)</td>
<td>0.79 (0.54–1.14)</td>
</tr>
<tr>
<td></td>
<td>P=0.0001</td>
<td>P=0.39</td>
</tr>
</tbody>
</table>

Accuracy of Pathologic Assessment

- Pathologists can reliably distinguish adenoma from non-adenoma, and whether there is cancer

- Inter-observer variability regarding:
  - Degree of dysplasia
  - Distinguishing hyperplastic polyp from SSP.

Natural History

• The great majority of diminutive polyps will not progress to cancer during a patient’s lifetime

• In most cases, diminutive polyps have been shown to remain stable or even regress with observation

  Hofstadt et al. Digestion 1998; 59: 148-56

• However, small and flat polyps are disproportionate contributors to interval CRC

Polyps with Advanced Neoplasia are Smaller in the Right than in the Left Colon

- Cross-sectional study of 233,414 polyps from 142,686 patients across the U.S.
  - Mean size of polyps with HGD or CRC smaller in the right colon (8.2 mm vs. 12.4 mm, p< 0.001)
  - Most (70%) right-sided advanced polyps were ≤ 9 mm
  - Most (63%) left-sided advanced polyps were > 9 mm
  - Right-sided advanced polyps were 5 times more likely to be < 6 mm and 3 times more likely to be 6-9 mm compared to left-sided lesions

Polypectomy Risk

• Risk of significant complications from cold resection techniques for diminutive polyps is very low

• However, a survey of gastroenterologists showed that 33% use hot biopsy forceps for polyps 1-3 mm


• Polypectomy risk in this setting due to inappropriate use of electrocautery to remove diminutive polyps

ASGE Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI)

1. In order for colorectal polyps ≤ 5 mm in size to be resected and discarded without pathologic assessment, endoscopic technology (when used with high confidence) used to determine histology of polyps ≤ 5 mm in size, when combined with the histopathologic assessment of polyps > 5 mm in size, should provide a ≥ 90% agreement in assignment of post-polypectomy surveillance intervals when compared to decisions based on pathology assessment of all identified polyps.

2. In order for a technology to be used to guide the decision to leave suspected rectosigmoid hyperplastic polyps ≤ 5 mm in size in place (without resection), the technology should provide ≥ 90% negative predictive value (when used with high confidence) for adenomatous histology.

ASGE PIVI on the real-time endoscopic assessment of the histology of diminutive colorectal polyps. GIE 2011; 73: 419-22.
# The NBI International Colorectal Endoscopic (NICE) Classification

<table>
<thead>
<tr>
<th>NICE Criterion</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td>Same or lighter than background</td>
<td>Browner relative to background (verify color arises from vessels)</td>
</tr>
<tr>
<td>Vessels</td>
<td>None, or isolated lacy vessels coursing across the lesion</td>
<td>Brown vessels surrounding white structures</td>
</tr>
<tr>
<td>Surface pattern</td>
<td>Dark or white spots of uniform size, or homogeneous absence of pattern</td>
<td>Oval, tubular, or branched white structures surrounded by brown vessels</td>
</tr>
<tr>
<td>Most likely pathology</td>
<td>Hyperplastic</td>
<td>Adenoma</td>
</tr>
</tbody>
</table>

Can the ASGE thresholds for real-time optical biopsy be met in clinical practice?

- Studies done by expert groups at referral centers: Narrow-band imaging can accurately predict polyp histology and colonoscopy surveillance intervals
  
  Gupta et al. GIE 2012; 75: 494-502  
  Paggi et al. Endoscopy 2012; 899-904  
  Ignjatovic et al. (DISCARD trial) Lancet Oncology 2009; 10: 1171-8

- Community-based gastroenterologists: Not quite there yet
  - Only 25% of MDs identified adenomas with ≥ 90% accuracy
  - Agreement between surveillance recommendations (high-confidence NBI versus pathology): 80%
  - NPV for diminutive rectosigmoid adenomas: 91%

DIMINUTIVE POLYPS: DISREGARD OR REMOVE?

• Polyp proximal to sigmoid colon: Remove!

• Rectosigmoid polyp:
  - High confidence hyperplastic histology: Disregard, or Resect and Discard
  - Low confidence hyperplastic histology: Remove.