World Health Organization Classification  
– Colon Polyps

- Adenoma
  - Pathologic subtype
    - Tubular
    - Villous
    - Tubulovillous
  - With low-grade or high-grade dysplasia

- Hyperplastic Polyp
  - Microvesicular (MVHP)
  - Goblet-Cell Rich (GCHP)
  - Mucin-Poor (MPHP)

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

- Traditional Serrated Adenoma (TSA)

- Other: Hamartomas, Juvenile polyps, inflammatory pseudopolyps, etc.

World Health Organization Classification
– Serrated Polyps

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

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Why Should Gastroenterologists Care About Sessile Serrated Adenomas?

- They are:
  - Premalignant
  - Responsible for a significant fraction of interval colorectal cancers
  - Common
  - Easy to miss (by both colonoscopists and pathologists)
  - Difficult to resect completely

- Surveillance guidelines are evolving
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Basic Molecular Pathways in CRC

• Chromosomal Instability (CIN) Pathway-60%-70% of all CRC’s
  - Adenoma-carcinoma sequence (APC, K-RAS, p53)
• Mutator Pathway-5% of all CRC’s – frequently hereditary
  - Defective DNA mismatch repair (hMLH1, hMSH2, hMSH6, hPMS2)
  - Microsatellite instability (MSI)
  - Lynch syndrome
• Serrated/hypermethylator pathway-25%-30% of all CRC’s
  – Epigenetic DNA promoter hypermethylation leading to the CpG Island Methylator Phenotype (CIMP)
  – BRAF Mutation
  – Share molecular markers with SSA/P’s
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Serrated Pathway and Interval CRC: Overlap of Molecular Signatures

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

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

- Nurses’ Health Study and the Health Professionals Follow-up Study
  - 88,902 subjects, 22-year follow-up
  - Cancers diagnosed within 5 years of colonoscopy twice as likely to have CIMP and microsatellite instability


Quantifying CRC risk

- Population-based Danish study
  - 2045 CRC cases, 8105 cancer-free controls
  - Identified first polyp, hyperplastic polyps reviewed by expert pathologists

<table>
<thead>
<tr>
<th></th>
<th>Cases/controls</th>
<th>Adjusted OR (95% CI)</th>
<th>Estimated 10-year risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSA with synchronous</td>
<td>30/61</td>
<td>2.66 (1.70–4.16)</td>
<td>2.47%</td>
</tr>
<tr>
<td>conventional adenomas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSA without synchronous</td>
<td>49/81</td>
<td>3.40 (2.35–4.91)</td>
<td>3.16%</td>
</tr>
<tr>
<td>conventional adenomas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSA with cytologic</td>
<td>20/25</td>
<td>4.76 (2.59–8.73)</td>
<td>4.43%</td>
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<tr>
<td>dysplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSA without cytologic</td>
<td>59/117</td>
<td>2.75 (1.99–3.80)</td>
<td>2.56%</td>
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<tr>
<td>dysplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional adenomas</td>
<td>727/1631</td>
<td>2.50 (2.24–2.80)</td>
<td>2.33%</td>
</tr>
<tr>
<td>without SSA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSA overall</td>
<td>14/17</td>
<td>4.84 (2.36–9.93)</td>
<td>4.50%</td>
</tr>
<tr>
<td>Hyperplastic polyps</td>
<td>55/235</td>
<td>1.30 (0.96–1.77)</td>
<td>1.21%</td>
</tr>
</tbody>
</table>

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What is the Prevalence of SSA?

- Older studies reporting SSA prevalence rates generally reported aggregate data for groups of endoscopists with significant variability in individual detection rates (0-18%)
- Recent studies: Prevalence about 8-9%
  - Colonoscopy database of endoscopist with high polyp detection rate, combined with histological review by expert pathologist
    - 1910 average-risk patients
    - SSA prevalence = 8.1 % (0.6 % for SSA-CD)
      - *Abdeljawad et al. Gastrointest Endosc. 2015 Mar;81(3):517-24*
  - Colonoscopy database of 25 endoscopists with high ADR
    - 3364 patients, all indications
    - SSA prevalence = 9% (0.4% for SSA-CD)
      - *IJspeert et al. Endoscopy 2016 (in press).*
**Why Should Gastroenterologists Care About Sessile Serrated Adenomas?**

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**SSA: Most prevalent visual descriptors**

- Mucus cap (64%)
- Rim of debris or bubbles (52%)
- Alteration of the contour of a fold (37%)
- Interruption of underlying mucosal vascular pattern (32%)

*Tadepalli et al. Gastrointest Endosc 2011; 74: 1360-8*
After Washing

**SSA versus HP Predictors (NBI)**

Indistinct borders  
OR 2.38 (95% CI 1.14–4.96)

Cloud-like appearance  
OR 4.91 (95% CI 2.42–9.97)

Dark spots inside the crypts  
OR 2.05 (95% CI 1.02–4.11)

*Rex et al. Am J Gastroenterol 2012; 107:1315–1329*

Colonoscopy is best for SSA detection

- FIT has fairly low sensitivity for SSA’s.
  - 5% for FIT for serrated lesions ≥10 mm in the Cologuard study
  - Somewhat better in other studies, but still only 18.4%
- Fecal DNA seems to perform better
  - 42.4% sensitivity for serrated lesions ≥10 mm
- In RCT setting, colonoscopy detection of high-risk SSA much higher than CTC (OR 5.5)--especially for flat and proximal SSA, and SSA-CD
- Sigmoidoscopy is not a good option: Distal colorectal findings are not predictive of advanced serrated neoplasia in the proximal colon

Optimizing Detection of Serrated Polyps: Take your time and look again!

- Incident rate ratio for SP detection increases with each minute of WT above 6 minutes, with maximum benefit at 9 minutes
- Proximal colon retroflexion may modestly increase SSA yield, but could be “second pass” effect
- Bowel prep: Impact may be less than for adenoma detection, but recent studies show highest SSA yield if high-quality bowel prep
- Dye-based or electronic chromoendoscopy: No clear benefit to increase proximal SSA detection
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Problem of Interobserver Variability

• Often difficult to distinguish HP from SSA
• Considerable inter-observer variation, even among expert pathologists

• Review of 7215 screening colonoscopies at 32 centers 2008-2010:
  – Proximal serrated polyp detection rates varied from 0% to 9.8%
  – At 10 of 32 centers, the word “serrated” did not appear in pathology reports!

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Incomplete Resection: CARE study

- 346 polyps 5-20 mm, margins biopsied
- About 10% of polyps were incompletely resected
- Incomplete resection more common for:
  - Large vs. small neoplastic polyps
    (17.3% vs 6.8%; P=0.003)
  - SSA vs other neoplastic polyps
    (31.0% vs 7.2%; P<0.001)
- Nearly half (47.6%) of all large (10–20 mm) SSA incompletely removed.

Optimizing Resection of Serrated Polyps

- Identification of lesion margin is key to complete resection
  - Electronic or dye-based chromoendoscopy
  - Submucosal injection with contrast agent

- Cold snare for most serrated lesions <1 cm—AVOID FORCEPS

- Standard polypectomy techniques effective for most serrated polyps
  - Stiff snares may be better, although no comparative studies

EMR of large (≥2 cm) serrated lesions:
  - Indiana University experience:
    At follow up after 4-6 months, residual polyp rate not significantly different than adenomas of similar size (8.7% vs 11.1%, p=0.8)
    Rex et al. Gastrointest Endosc 2015; 82: 538-41

  - Australian multicenter study:
    Technical success of EMR for SSA better than for adenomas (99.1% vs. 94.5%, p< 0.001)
    Recurrence rate of SSP 20-25 mm lower than adenomas, similar for larger sizes
    Pellise et al. Gut 2016 (In press)
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<table>
<thead>
<tr>
<th>Polyp</th>
<th>Size (mm)</th>
<th>Number</th>
<th>Location</th>
<th>Surveillance Interval (y)</th>
</tr>
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<tbody>
<tr>
<td>Hyperplastic</td>
<td>&lt;10</td>
<td>&lt;20</td>
<td>Any</td>
<td>10 10</td>
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<tr>
<td>Hyperplastic</td>
<td>≤5</td>
<td>≤3</td>
<td>Proximal to Sigmoid</td>
<td>10 10</td>
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<tr>
<td>Hyperplastic</td>
<td>&lt;10</td>
<td>≥4</td>
<td>Proximal to Sigmoid</td>
<td>5 10</td>
</tr>
<tr>
<td>Hyperplastic</td>
<td>&gt;5</td>
<td>any</td>
<td>Proximal to Sigmoid</td>
<td>5 10</td>
</tr>
<tr>
<td>SSA</td>
<td>&lt;10</td>
<td>&lt;3</td>
<td>Any</td>
<td>5 5</td>
</tr>
<tr>
<td>TSA</td>
<td>&lt;10</td>
<td>&lt;3</td>
<td>Any</td>
<td>5 3</td>
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<tr>
<td>SSA or TSA</td>
<td>&lt;10</td>
<td>≥3</td>
<td>Any</td>
<td>3 3</td>
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<td>3 3</td>
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<td>SSA or TSA or HP</td>
<td>≥10</td>
<td>≥2</td>
<td>Any</td>
<td>1-3 3</td>
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<td>SSA with dysplasia</td>
<td>Any</td>
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<td>Any</td>
<td>1-3 3</td>
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<tr>
<td>Serrated Polyposis Syndrome</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Serrated Polyposis Syndrome: Recognize!

- Prevalence in colonoscopy-based programs about 1:2000
- Under-recognized in practice
- Associated with an increased risk of CRC
- May be associated with increased risk of extracolonic cancer, and increased risk of colonic and extracolonic cancers in family

SPS Criteria

- >20 serrated polyps throughout the colon
- At least 5 serrated polyps proximal to the sigmoid, of which 2 or more are >10 mm in size
- Serrated polyp in first-degree relative of patient with serrated polyposis.


Take Home Points: Why Should Gastroenterologists Care About Sessile Serrated Adenomas?

- They are:
  - Premalignant
  - Responsible for a significant fraction of interval colorectal cancers
  - Common (8-9%)
  - Easy to miss
    - Look hard, look twice on the right, know their morphology
    - Know your pathologists
  - Difficult to resect completely
    - No forceps!
    - Contrast agent or NBI to define borders
    - Take a rim of normal tissue
- Surveillance guidelines are evolving
  - Know them now, pay attention to updates!
Thank You!

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