SERRATED LESIONS OF THE COLON

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DISCLOSURE

Speaker Relationship with Industry, including
Consultant
Speaker
Ownership/Partnership
Principal Research
Institutional, Organizational or Other Financial Benefit:

NONE
PATHOLOGY: BASIC FEATURES

- Heterogeneous group of lesions
- Serrated (sawtooth) architecture of the epithelial compartment
- Subtypes defined by architectural features, and location/extent of the proliferative zone
- Evolving and controversial pathological definitions.

WHO Classification (2010)

- 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)

Serrated polyposis (formerly hyperplastic polyposis)

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


HYPERPLASTIC POLYPS

- All 3 subtypes characterized by crypt elongation
- Crypts are straight with narrow bases
- Proliferation in the lower third of the crypt, serration in the luminal aspect
- MVHP have microvesicular mucin
  - Mostly left colon, 15% right colon
- GCHP have mostly goblet cells, less serration
  - Nearly always left colon, small size
- Pathological and molecular differences between subtypes: No known clinical implications.
HYPERPLASTIC POLYP

- 15-25% of all serrated polyps
- Distorted architecture due to altered proliferative zone
- Proliferative zone often displaced from base to side
- Crypts are dilated and branched, L- or inverted T-shaped
- Crypts may be filled with mucin (endoscopic mucus cap)
- Crypts may herniate through muscularis mucosae (inverted growth pattern)
- SSA/P with cytologic dysplasia: Usually abrupt transition to area with dysplasia similar to conventional adenoma.
MVHP versus SSA/P

- Controversial issue
- Many serrated polyps have features of both MVHP and SSA/P, however minimum criteria needed to distinguish are unclear
- There is considerable inter-observer variation in differentiating MVHP from SSA/P, even among experts.

SSA/P with mucin-filled crypts

SSA/P: Inverted growth pattern
SSA/P with dysplasia

TSA

• Uncommon subtype of serrated polyps
• Usually located in the distal colon
• Complex and distorted architecture with villous elements (“filiform”)
• Recent studies suggest that best defining feature may be ectopic crypts due to loss of anchoring to muscularis mucosae
• Dysplasia may occur and progress to cancer, but molecular pathways are poorly defined.
Molecular Pathways in CRC

- Chromosomal instability (CIN)---60%-70%
  - Adenoma-carcinoma sequence

- Defective DNA mismatch repair, leading to microsatellite instability (MSI)---5%
  - Lynch syndrome

- Serrated pathway---25%-35%
  - BRAF oncogene mutations
  - Epigenetic DNA promoter hypermethylation leading to the CpG island methylator phenotype (CIMP).


The Serrated Pathway

- Leads to sporadic CRC with MSI, and some MSS CRCs with CIMP
- Activating mutation of BRAF (anti-apoptotic)
  - BRAF mutations present in SSA/P, and many MVHP
  - BRAF mutations are associated with CIMP+ CRCs
- Some CIMP+ CRCs have MSI, associated with hypermethylation of MLH1.

Clinical Implications

- Close links between serrated pathway and interval (post-colonoscopy) CRC:
  - Interval CRC 4 times more likely than non-interval CRC to have MSI
  - More likely to be located in the proximal colon
  - More likely to be associated with CIMP.

- Sawhney et al. Gastroenterology 2006; 131: 1700-5
Colonoscopy is less protective against right-sided CRC

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Outcome</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 (Adj OR)</td>
<td>0.33 (0.28-0.39)</td>
<td>0.99 (0.86-1.14)</td>
</tr>
<tr>
<td>Singh, 2010</td>
<td>CRC Mortality (SMR)</td>
<td>0.53 (0.42-0.67)</td>
<td>0.94 (0.77-1.17)</td>
</tr>
<tr>
<td>Brenner, 2010</td>
<td>Advanced Neoplasm Prevalence</td>
<td>0.33 (0.21-0.53)</td>
<td>1.05 (0.63-1.76)</td>
</tr>
<tr>
<td>Brenner, 2011</td>
<td>CRC Prevalence (OR)</td>
<td>0.16 (0.12-0.20)</td>
<td>0.44 (0.35-0.55)</td>
</tr>
</tbody>
</table>

Why is colonoscopy protection less in the right colon?

- **REVERSIBLE:**
  - Bowel prep
  - Operator Dependent
    - Cecal Intubation
    - Withdrawal time and technique
    - Adenoma detection
    - Detection of flat and depressed (non-polypoid) neoplasms
    - Detection of serrated polyps

- **IRREVERSIBLE:**
  - Tumor Biology

**HP: Endoscopic features**

- Usually sessile and 1-5 mm, rarely > 10 mm
- Typically distal (rectosigmoid), can be multiple
- Pearl-colored, pale, may disappear with insufflation

**SSA/P: Endoscopic features**

- Often flat, subtle appearance
- Larger than HP, 20%-50% > 10 mm
- Typically proximal colon
- Mucus cap
- Washing off the mucus cap: Polyp similar in color to surrounding mucosa, indistinct edges
- Surface similar to HP under NBI

- Vu et al. Dis Colon Rectum 2011; 54:1216-23
Large proximal colon serrated lesion

SSA/P with typical mucus cap

Courtesy Douglas Rex, MD
SSA/P: Beyond the mucus cap

- Retrospective analysis of high-resolution videos of 158 SSA/Ps
- 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%)


Colonoscopy 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.

- Colonoscopy performed by endoscopists with high completion and polypectomy rates more protective against proximal CRC


**VARIABLE DETECTION OF PROXIMAL SERRATED LESIONS**

   - 7192 average-risk screening colonoscopies by 13 endoscopists
   - Patients: Mean age 59, 44% male
   - 4535 polyps
   - Proximal serrated polyp detection range: 1.4%-7.6%
     (adenoma: 13.5%-36.4%)

   - 6681 average-risk screening colonoscopies by 15 endoscopists
   - Patients: Mean age 59, 49% male
   - 11,049 polyps
   - Proximal serrated polyp detection range: 1%-18%
     (adenoma: 17%-47%).

**CORRELATION BETWEEN ADENOMA AND PROXIMAL SERRATED POLYP DETECTION**

- Reanalysis of two colonoscopic databases
- Average-risk screening patients
- Significant correlation between ADR and proximal serrated polyp detection rate for men (R=0.71; P =0.003) and women (R=0.73; P=0.002).
- ADRs of 25% for men and 15% for women both corresponded to a proximal serrated polyp detection rate of 4.5%.

### Risk Stratification

<table>
<thead>
<tr>
<th></th>
<th>LOWER CRC RISK</th>
<th>HIGHER CRC RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>NUMBER</td>
<td>None/few</td>
<td>Many</td>
</tr>
<tr>
<td>SIZE</td>
<td>Small</td>
<td>Large</td>
</tr>
<tr>
<td>TYPE</td>
<td>HP</td>
<td>SSA/P or TSA, dysplasia</td>
</tr>
<tr>
<td>ANATOMIC LOCATION</td>
<td>Left colon</td>
<td>Right colon</td>
</tr>
</tbody>
</table>


### Surveillance intervals

<table>
<thead>
<tr>
<th>Finding</th>
<th>Interval (years)</th>
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<tbody>
<tr>
<td>HP &lt; 10 mm, rectosigmoid, any number</td>
<td>10</td>
</tr>
<tr>
<td>HP ≤ 5 mm, proximal to sigmoid, ≤ 3 in number</td>
<td>10</td>
</tr>
<tr>
<td>HP ≥ 4 in number, proximal to sigmoid</td>
<td>5</td>
</tr>
<tr>
<td>HP &gt; 5 mm proximal to sigmoid</td>
<td>5</td>
</tr>
<tr>
<td>SSA/P or TSA &lt; 10 mm</td>
<td>5</td>
</tr>
<tr>
<td>SSA/P or TSA ≥ 10 mm, or at least 3 SSA/P or TSA</td>
<td>3</td>
</tr>
<tr>
<td>SSA/P with dysplasia</td>
<td>1-3</td>
</tr>
<tr>
<td>Serrated polyposis</td>
<td>1</td>
</tr>
</tbody>
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Serrated lesions: take home points

- Important and clinically relevant
- High index of awareness for endoscopic appearance and clues, search deliberately especially in the right colon
- Remove all serrated lesions proximal to the sigmoid and all those > 5 mm in distal colon
- Communicate with your pathologist
- Shorten surveillance interval for SSA/P or TSA, larger size, higher number of proximal lesions.