General Session 7: Controversies in Screening and Surveillance in Colorectal Cancer

Complexities of Pathological Assessment: Serrated Polyps/Adenomas

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Learning Objectives

After reviewing this material, the participant should be able to:

• Describe the pathological, endoscopic and molecular differences among the three types of serrated polyps

• Compare the relative prevalence rates and cancer risks of the three types of serrated polyps

• Describe the differences in surveillance and treatment approaches for serrated polyps (sporadic and syndromic)
Outline

- Classification of serrated polyps
- Pathogenesis and molecular alterations
- Dysplastic potential and cancer risk
- Controversies in pathological interpretation
- Surveillance and treatment approaches
What Are Serrated Polyps?

• Category of colonic polyp redefined in the last 15 years on the basis of pathological, molecular and clinical features
  – Hyperplastic polyps formerly thought to have no malignant potential
  – Serrated polyps are now viewed as a family of lesions with varying histopathological features and malignant potential
  – 30-35% of colorectal cancer arises from serrated polyps in a dysplasia-carcinoma sequence via an alternate pathway
Why Are Serrated Polyps Important?

- High frequency in right colon: missed on colonoscopy
- Flat or sessile morphology: easily overlooked on colonoscopy
- Ill-defined borders: incomplete resection
- Pathological interpretation variable
  - Unfamiliarity with serrated pathway lesions and progression
  - Under-diagnosis of serrated lesions with cancer risk
- Under-diagnosis of syndromic disease
- Precursors of most CIMP* (either MSI or MSS) colorectal cancers
  - About a third of all CRC evolve through the serrated pathway
- Serrated morphology carcinoma is now a WHO subtype: frequent KRAS and BRAF mutations and poor prognosis

* CpG island methylator phenotype
What Are Serrated Polyps?

- Defined histopathologically by a single dominant feature: the tufted growth pattern of the epithelium that gives the polyp glands an appearance described as:
  - Stellate
  - Saw-toothed
  - Serrated

serrated washer
Architecture: Serrated Polyp vs. Adenomatous Polyp

Serrated vs. straight gland profiles

Serrrated polyp

Adenomatous polyp
## Classification of Serrated Polyps (WHO 2010)

<table>
<thead>
<tr>
<th>Serrate Subtype</th>
<th>Microscopic</th>
<th>Macroscopic</th>
<th>Dysplasia</th>
</tr>
</thead>
</table>
| Goblet cell hyperplastic polyp (GCHP) | Goblet cells  
Straight crypts  
Little serration | Flat  
Distal  
≤5 mm | No |
| Microvesicular hyperplastic polyp (MVHP) | Fine mucin droplets  
Straight crypts  
Serration in 1/3-2/3 of glands | Flat  
Proximal  
≤5 mm | No |
| Sessile serrated adenoma (SSA) | Dilated & distorted crypts  
L, J or anchor shaped crypts  
Serration throughout glands | Flat  
Mucinous “cap”  
Proximal  
Typically ≥1 cm | Yes |
| Traditional serrated adenoma (TSA) | Complex architecture  
Villous or filliform epithelial projections  
Eosinophilic cytoplasm | Pedunculated  
Distal  
≥1 cm, often large | Yes |
Serrated Polyp Types

- Goblet cell hyperplastic polyp
- Microvesicular hyperplastic polyp
- Sessile serrated adenoma
- Traditional serrated adenoma
## Prevalence

<table>
<thead>
<tr>
<th>Serrated polyp type</th>
<th>Prevalence</th>
<th>Commonality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic polyps</td>
<td>80-90% of all serrated polyps</td>
<td>Very common</td>
</tr>
<tr>
<td>Sessile serrated adenomas</td>
<td>10-25% of all serrated polyps</td>
<td>Fairly common</td>
</tr>
<tr>
<td>Traditional serrated adenomas</td>
<td>1-2% of all serrated polyps</td>
<td>Rare</td>
</tr>
</tbody>
</table>
Controversies: MVHP vs. SSA

- Moderate intra-observer agreement/disagreement ($\kappa = 0.56-0.63$)*
- Serrated polyps may have overlapping MVHP/SSA features
- Under-diagnosis of SSA (as a hyperplastic polyp) is common
- Minimum diagnostic criteria are controversial
  - If 2-3 adjacent crypts show SSA features, classified as an SSA (WHO)
  - Presence of one dilated crypt sufficient to classify as SSA (AGA)
- Cancer risk is related to dysplasia
  - Any SSA with conventional dysplasia is classified as “advanced” and should be considered equivalent to adenomatous polyp with high-grade dysplasia

*Perfect agreement: $K = 1$
Controversies: “Mixed” (Serrated/Adenomatous) Polyps

- Appearance: abrupt transition or side-by-side co-localization of glands typical of SSA (with or without dysplasia) and glands with confluent dysplasia typical of adenomatous polyp
- Some authorities classify these as “mixed” polyp
- Others regard these as SSAs with HGD
- Either way, cancer risk is related to the presence of dysplasia

HGD in serrated glands

HGD in straight glands
Serrated Polyposis Syndrome (SPS)

- Rare syndrome defined by Burt and Jass, 2000
  - Formerly known as hyperplastic polyposis syndrome
- Multiple and/or large serrated polyps
  - At least 5 serrated polyps proximal to sigmoid, 2 being > 10mm
  - Any number of serrated polyps and 1st degree relative with syndrome
  - >20 serrated polyps distributed throughout the colon
Serrated Polyposis Syndrome (SPS)

- Increased CRC risk but degree of risk unclear
  - Published series: 25-70% of patients had CRC at diagnosis or follow-up
  - Lifetime risk of 50%
  - Cumulative risk of cancer: 2-7% at 5 years (Carballal et al, Gut 2015)

- Surveillance: current recommendation = every year (WHO)

- Surgery warranted:
  - To prevent risk of progression
  - When carcinoma found
  - When endoscopic resection is unfeasible (lesions of large size or involving appendix or ileocecal valve)
Serrated Polyps: Molecular Profiles

Issues and implications:

- Hyperplastic polyps are true neoplasms with defined oncogene mutations
- MVHPs are precursors of SSAs
  - Association of MLH-1 hypermethylation and dysplasia suggests that MLH-1 hypermethylation is a late event with high risk of progression
- GCHPs are likely precursors of TSAs
  - Molecular characteristics and distal location suggest this
Pathogenesis: Serrated Pathway

CIMP = CpG island methylator phenotype
MSI = microsatellite instability
CIN = chromosomal instability

A-M Baket et al,
Scientific Reports, 2015; 5 : 8654 | DOI: 10.1038.
Molecular Progression:
MVHP → SSA → Dysplastic SSA → MSI CRC

Adenomatous vs. Serrated Pathway
Serrated Pathways

Serrated Neoplasia Pathway

- Proximal hyperplastic polyp
- Sessile serrated polyp
- Sessile serrated adenoma
- MSI-high, methylation-rich non-HNPCC “serrated” carcinoma

Higuchi T & Jass JR 2004 J Clin Pathol 57: 682

Traditional Serrated Neoplasia Pathway

- Hyperplastic polyp (Goblet cell type)
- Traditional serrated adenoma
- Distal MSS non-HNPCC serrated carcinoma

Higuchi T & Jass JR 2004 J Clin Pathol 57: 682

Geraint Williams, Pathology Department, Cardiff University
Surveillance for Serrated Polyps

- Recommendations related to:
  - Type
  - Size
  - Number
  - Location
# Serrated Polyps: Surveillance Recommendations

<table>
<thead>
<tr>
<th>Serrated polyp</th>
<th>USMSTF / ACA 2012 Recommended interval</th>
<th>Expert Panel 2012 Recommended interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goblet cell HP</td>
<td>None</td>
<td>5 years If proximal and &gt;5mm</td>
</tr>
<tr>
<td>Microvesicular HP</td>
<td>None</td>
<td>5 years If proximal and &gt;5mm</td>
</tr>
</tbody>
</table>
| Sessile SA/Polyp       | 5 years if < 10 mm 3 years if ≥ 10 mm   | • 5 years if <10 mm  
                          |                                        | • 3 years if ≥10 mm or any size and n≥3  
                          |                                        | • 1-3 years if ≥10 mm and n≥2 or dysplasia |
| Traditional SA         | 3 years                                | • 5 years if <10 mm  
<pre><code>                      |                                        | • 3 years if ≥ 10mm and n≥2              |
</code></pre>
<table>
<thead>
<tr>
<th>Lesion found</th>
<th>Surveillance interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serrated polyposis</td>
<td>1 year</td>
</tr>
<tr>
<td>Serrated polyp with any dysplasia</td>
<td>3 years</td>
</tr>
<tr>
<td>Serrated polyp proximal to the splenic flexure</td>
<td>3 years</td>
</tr>
<tr>
<td>Serrated polyp ≥10 mm</td>
<td>3 years</td>
</tr>
<tr>
<td>Serrated polyps &lt;10 mm and distal to splenic flexure</td>
<td>10 years</td>
</tr>
</tbody>
</table>
Summary

- Serrated polyps represent a spectrum of neoplasms with overlapping histopathological features that may create a challenge for interpretation and precise classification.
- Serrated adenomas may occur as sporadic or rarely syndromic lesions.
- Serrated polyps with dysplasia are classified as adenomas and carry a significant cancer risk that necessitates increased surveillance.
- Cancer risk is related to dysplasia as well as lesion location, size, and number.
- Molecular pathogenesis differs from that of adenomatous polyps.
- Resultant cancers have microsatellite instability rather than chromosomal instability.
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