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

Complexities of Pathological Assessment: Serrated Polyps/Adenomas

Carolyn Compton, MD, PhD
Professor of Life Sciences, ASU
Professor of Laboratory Medicine and Pathology, Mayo Clinic

PRESENTED AT: 2016 Gastrointestinal Cancers Symposium

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

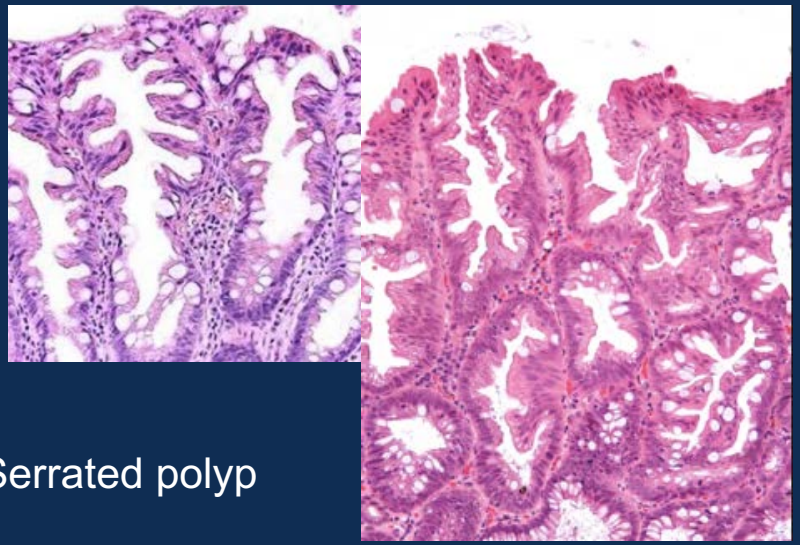
What Are Serrated Polyps?

- 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

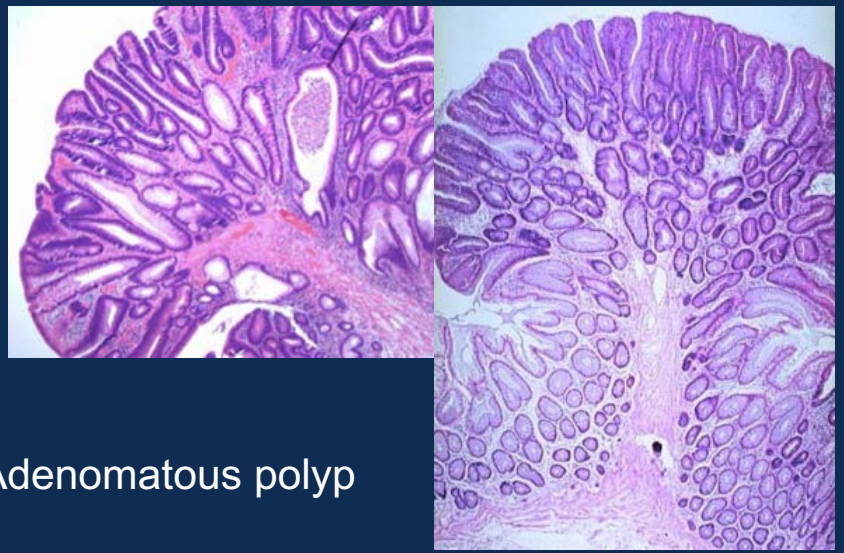
serrated washer

Architecture: Serrated Polyp vs. Adenomatous Polyp

Serrated vs. straight gland profiles



Serrated polyp



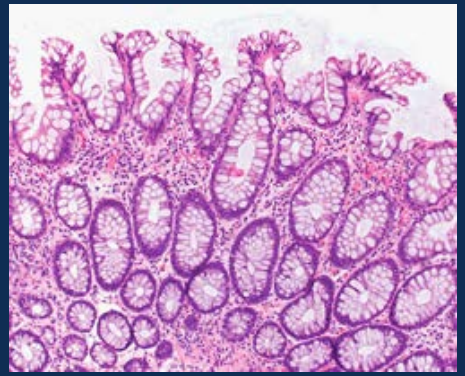
Adenomatous polyp

Classification of Serrated Polyps (WHO 2010)

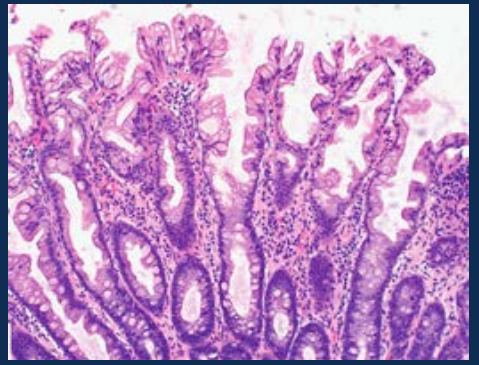
Serrate Subtype	Microscopic	Macroscopic	Dysplasia
Goblet cell hyperplastic polyp (GCHP)	Goblet cells Straight crypts Little serration	Flat Distal ≤5 mm	No
Microvesicular hyperplastic polyp (MVHP)	Fine mucin droplets Straight crypts Serration in 1/3-2/3 of glands	Flat Proximal ≤5 mm	No
Sessile serrated 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

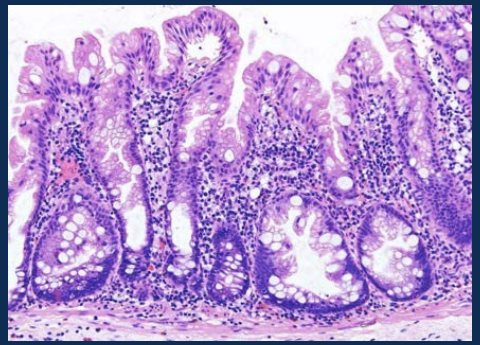
- Goblet cell hyperplastic polyp --------



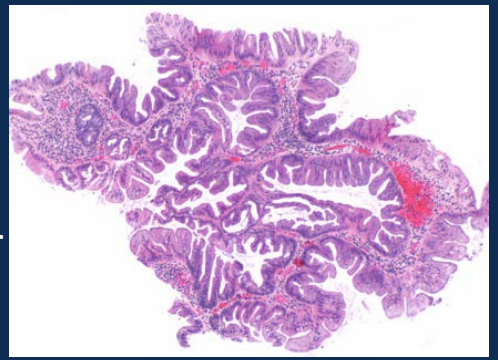
- Microvesicular hyperplastic polyp ----------



- Sessile serrated adenoma ----------



- Traditional serrated adenoma ----------



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Prevalence

Serrated polyp type	Prevalence	
Hyperplastic polyps	80-90% of all serrated polyps	Very common
Sessile serrated adenomas	10-25% of all serrated polyps	Fairly common
Traditional serrated adenomas	1-2% of all serrated polyps	Rare

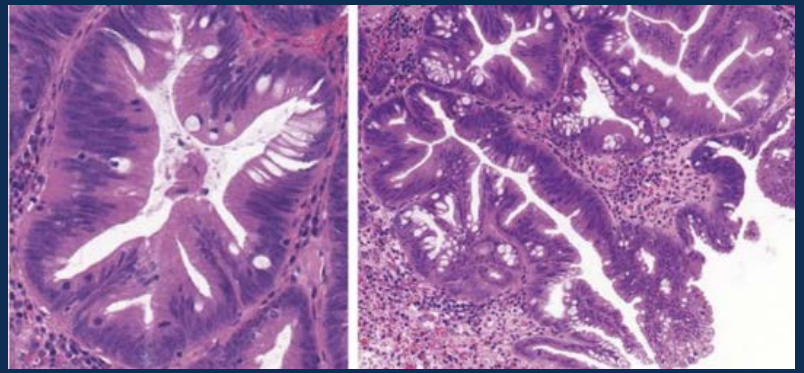
Controversies: MVHP vs. SSA

- Moderate intra-observer agreement/disagreement (κ = 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

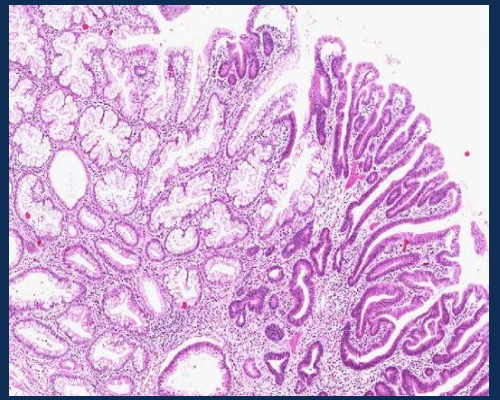
*Perfect agreement: K = 1

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



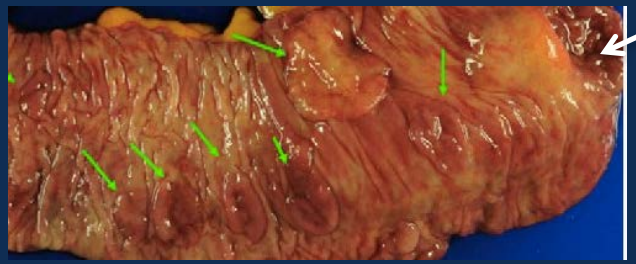
HGD in serrated glands



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)

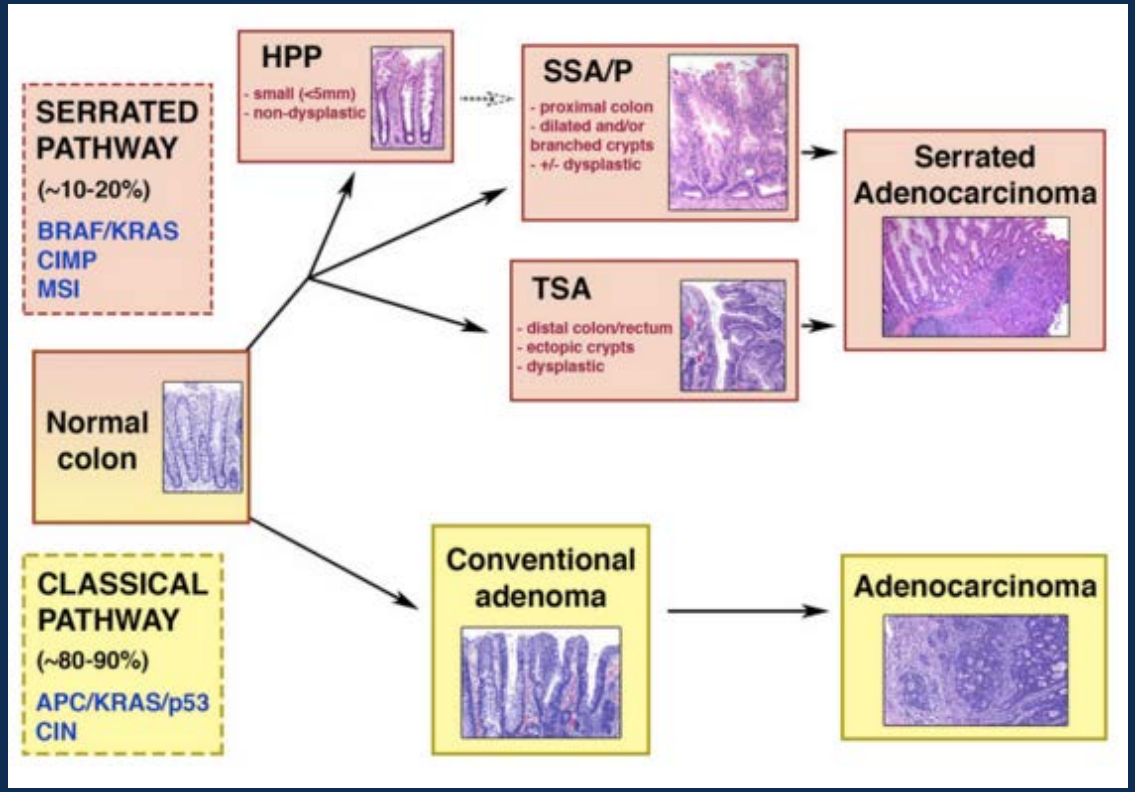
- Increased CRC risk but degree of risk unclear
  - Published series: 25-70% of patients had CRC at diagnosis or follow-up
  - Lifetime risk of 50%
  - Cumulative risk of cancer: 2 -7% at 5 years (Carballal et al, Gut 2015)
- Surveillance: current recommendation = every year (WHO)
- Surgery warranted:
  - 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.

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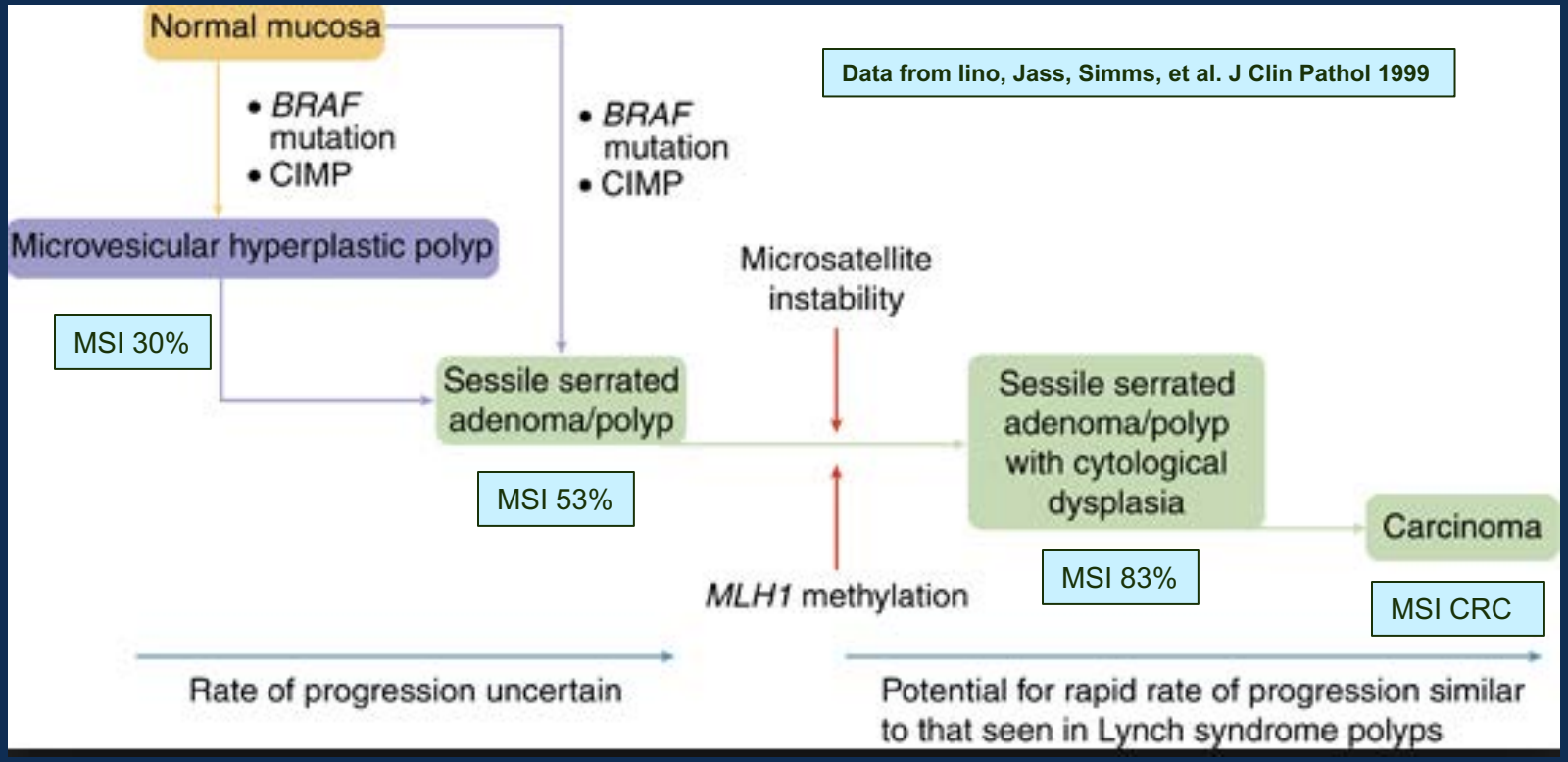
Molecular Progression:
MVHP ➔ SSA ➔ Dysplastic SSA ➔ MSI CRC



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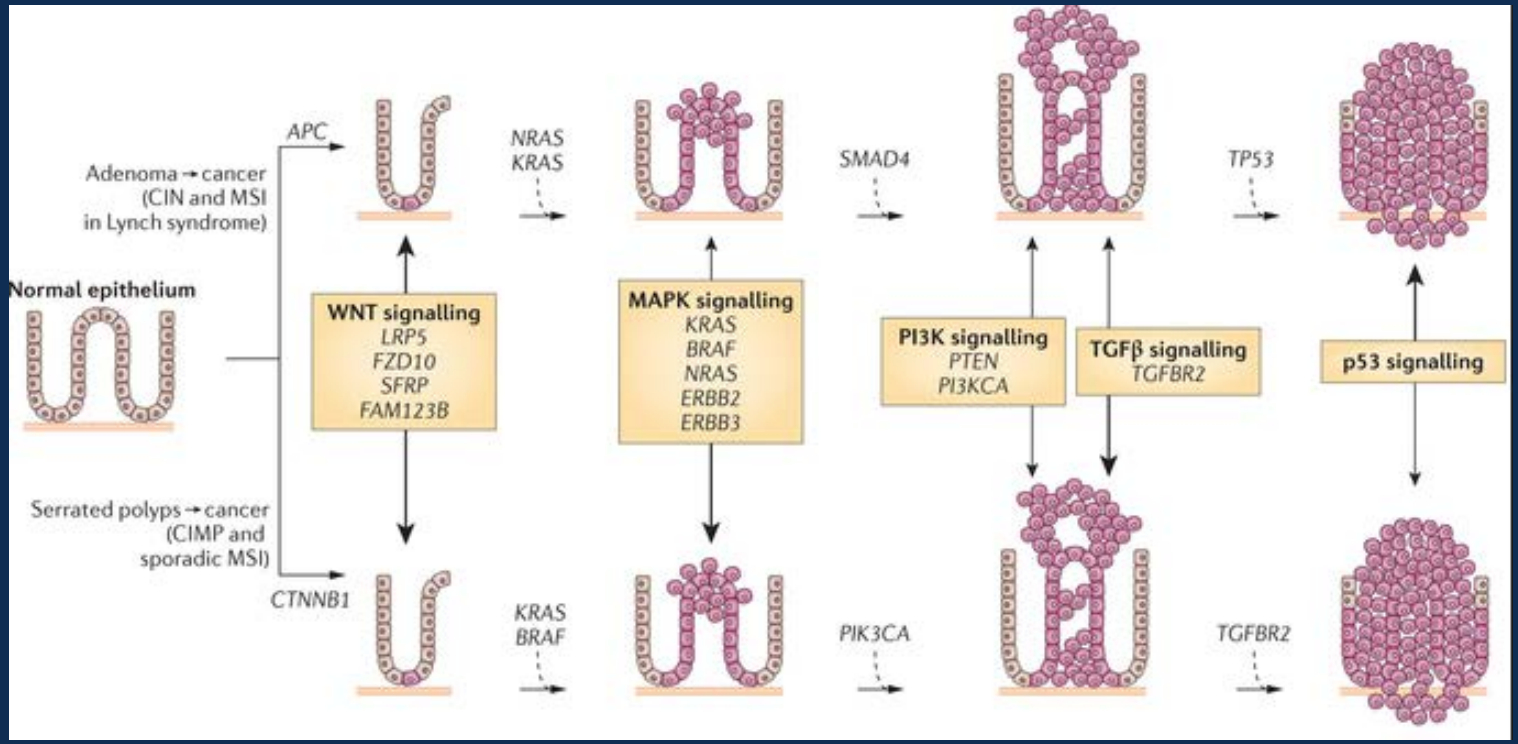
Adenomatous vs. Serrated Pathway



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Serrated Pathways

Serrated Neoplasia Pathway

Proximal hyperplastic polyp

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Sessile serrated polyp

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Sessile serrated adenoma

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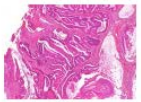
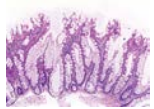
MSI-high, methylation-rich non-HNPCC "serrated" carcinoma



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

Traditional Serrated Neoplasia Pathway

Hyperplastic polyp (Goblet cell type)



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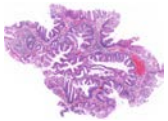
Traditional serrated adenoma



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Distal MSS non-HNPCC serrated carcinoma

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

Geraint Williams, Pathology Department, Cardiff University

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Surveillance for Serrated Polyps

- Recommendations related to:
  - Type
  - Size
  - Number
  - Location

Serrated Polyps: Surveillance Recommendations

Serrated polyp	USMSTF / ACA 2012 Recommended interval	Expert Panel 2012 Recommended interval
Goblet cell HP	None	5 years If proximal and >5mm
Microvesicular HP	None	5 years If proximal and >5mm
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 • 3 years if ≥ 10mm *and* n≥2

Serrated Polyps: Surveillance Recommendations

(Expert Opinion from Sweetser, Smyrk, Sugumar. Expert Rev Gastroenterol Hepatol 2011; 5: 627-35)

Lesion found	Surveillance interval
Serrated polyposis	1 year
Serrated polyp with any dysplasia	3 years
Serrated polyp proximal to the splenic flexure	3 years
Serrated polyp ≥10 mm	3 years
Serrated polyps <10 mm and distal to splenic flexure	10 years

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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