Serrated Lesions

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Serrated Lesions

Hyperplastic polyp
Serrated adenoma
Mixed polyp
Sessile serrated polyp
Serrated carcinoma
Hyperplastic Polyps

- Formerly metaplastic polyps
- Left > right, Male > female
- Infolded epithelial tufts, microvesicular cells, infrequent enlarged goblet cells in upper crypts
- May be prominent endocrine cells
- May be thickened subepithelial collagen plate
- No dysplasia
- Failure of anoikis (shedding of mature cells)
Hyperplastic Polyp

- Increase in frequency with age
- 17 times commoner in colons with carcinoma
- Similar dietary and lifestyle risk factors to CRC
- K-ras mutation common
- Clonal
- Monocryptal?
Serrated Adenoma

Dysplasia by definition, usually low grade
Eosinophilic cytoplasm
Pseudostratified, ‘pencillate’ nuclei
May be tubular, tubulovillous or villous
Invade to give serrated carcinoma

Longacre & Fenoglio-Preiser 1990
Traditional Serrated Adenoma

1-15% of all adenomas

Often left sided

Frequently pedunculated, villiform

Short, budding, ‘ectopic’ crypts

‘Filiform’ variants

Torlakovic et al 2003, 2008
Yantiss et al 2007
'Traditional' Serrated adenoma (TSA)
Filiform Serrated Adenoma
Mixed Polyps

Collision between hyperplastic polyp and adenoma

Dysplasia in Hyperplastic Polyp

Longacre & Fenoglio-Preiser 1990
Sessile Serrated Lesion (Polyp, Adenoma)

- Serrated polyps with unusual architectural features
  - Horizontal orientation of deep crypts
  - Serration down to crypt base
- No conventional dysplasia but may have ‘nuclear atypia’ or ‘hypermucinous’ change
- Right colon
- Females > males
- Large sessile, poorly defined

Torlakovic & Snover 1996
Sessile Serrated Lesion
(Polyp, Adenoma)

- Crypt dilatation
- Abnormal proliferation
- Normal subepithelial collagen plate
- Loss of MLH1
- Sometimes found in hyperplastic polyposis
- Often express MUC5AC or MUC6

Torlakovic et al 2003 AJSP 27: 65-81
Sessile serrated lesion
Serrated Adenocarcinoma

- 5-10% colorectal cancer
- Right colon and rectum
- Serrated, mucinous or trabecular growth pattern
- Abundant eosinophilic cytoplasm
- Chromatin condensation
- Preserved polarity
- No 'dirty' necrosis
Serrated Adenocarcinoma
Garcia-Solano J et al 2010 *Hum Pathol* 41: 1359-68
Serrated Adenocarcinoma

• Most arise in traditional serrated adenomas and are MSS
  - Distal tumours
  - Poor prognosis (30% 5-year survival)
• 20% arise in sessile serrated polyps and have MSI
  - Proximal tumours
  - Good prognosis (70% 5-year survival)

Right Sided Serrated Neoplasia

Microsatellite instability

$MLH1$ inactivation

DNA methylation (CIMP)

$BRAF$ mutation (80% in SSAs)

Baker K et al/ J Clin Pathol 2004; 57: 1089
**BRAF mutation**

- Typical adenomas: 0%
- Typical hyperplastic polyps: 19%
- Sessile serrated adenomas: 75-82%
- Traditional serrated adenomas: 20-30%
- Mixed Polyps: 57-89%
- HNPCC cancers: 0%
- All colorectal cancers: 15%
- MSI-high non-HNPCC cancers: 76%
Serrated Neoplasia Pathway

Proximal hyperplastic polyp

↓

Sessile serrated polyp

↓

Sessile serrated adenoma

↓

MSI-high, methylation-rich non-HNPCC “serrated” carcinoma

Left Sided Serrated Neoplasia

Microsatellite stable

*MLH1* expression retained

DNA methylation (CIMP)

No *BRAF* mutation

K-ras mutation (80% in TSAs)
Traditional Serrated Neoplasia Pathway

Hyperplastic polyp (Goblet cell type)

Traditional serrated adenoma

Distal MSS non-HNPCC serrated carcinoma

Sessile serrated pathway

Morphologic
Normal mucosa
Hyperplastic polyp
Sessile serrated adenoma

Molecular
Age-related methylation
BRAF mutation
Inhibition of apoptosis
Progressive methylation of additional genes
MLH1
MSI-H
Sessile serrated adenoma with dysplasia
Serrated adenocarcinoma

Traditional serrated pathway

Morphologic
Normal mucosa
Hyperplastic polyp
Sessile serrated adenoma

Molecular
KRA5 mutation
Other tumor-suppressor genes
MSI-L
MSS
Traditional serrated adenoma with dysplasia
Serrated adenocarcinoma

## 1250 Polyps at Colonoscopy

<table>
<thead>
<tr>
<th>Polyp</th>
<th>Dysplasia</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adenoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubular</td>
<td>+</td>
<td>55</td>
</tr>
<tr>
<td>Tubulovillous</td>
<td>+</td>
<td>15</td>
</tr>
<tr>
<td>Villous</td>
<td>+</td>
<td>1</td>
</tr>
<tr>
<td><strong>Serrated polyps</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperplastic</td>
<td>-</td>
<td>24.5</td>
</tr>
<tr>
<td>Sessile Serrated Polyp</td>
<td>-</td>
<td>2.5</td>
</tr>
<tr>
<td>Mixed Polyp</td>
<td>+</td>
<td>0.8</td>
</tr>
<tr>
<td>Serrated Adenoma (TSA)</td>
<td>+</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Frequency of SSPs reaches 7% in some series; observer reproducibility is an issue!
Risk of Malignancy in Sessile Serrated Lesions

- Unknown
- Up to 20% of cancers arise by the serrated pathways
- Microsatellite instability may speed up the evolution into carcinoma
- Patients with SSAs more likely to have additional serrated lesions and proximal hyperplastic polyps
- Case reports of rapid evolution of SSA to cancer
- Small series suggest further neoplasia occurs with similar (or greater) frequencies in SSA patients compared with adenoma patients
Natural History of Sessile Serrated Adenomas

- Asymptomatic population, 50-75 yrs, undergoing screening colonoscopy, N=3121
- 7.9% had Proximal large (>10mm) Non-dysplastic Serrated Polyps
- More likely than those without proximal NDSP to have advanced neoplasia (17.3% vs 10.0%) at baseline
- Large proximal NDSP and no neoplasia at baseline 3.14 times more likely to have subsequent neoplasia

Schreiner MA et al Gastroenterology 2010; 139: 1497-1502
Natural History of Sessile Serrated Adenomas

- 40 patients with SSAs and no history of colonic neoplasia
- 5 (12.5%) developed cancer, all in proximal colon
- 4/5 cancers had MSI

- 1.8% matched adenoma patients developed cancer

Lu FI et al AJSP 2010; 34: 927-34
Sessile Serrated Adenomas and 'Advanced' Histology

- Lieberman D et al
  Polyp Size and Advanced Histology in Patients Undergoing Colonoscopy Screening: Implications for CT Colonography
  Gastroenterology 2008; 135: 1100-5

- Van Dekken et al
  Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. Gut 2010; 59: 62-8
Management of Patients with Serrated Lesions

Typical Small Distal Hyperplastic Polyps
  No follow-up

Right sided Serrated Lesions
  Caution - depends on age, comorbidity, family history etc (but some recommend 3 yearly surveillance)

Sessile serrated polyps >1cm
  Excise and follow up for recurrence ~3 yearly

Dysplastic serrated lesions
  As adenomas
Reporting Serrated Lesions

Current requirements and proformas do not record serrated lesions per se (apart from hyperplastic polyps).

Serrated adenomas are recorded with conventional tubular, tubulovillous or villous adenomas – serration is not recognised.

SSPs are reported as right sided hyperplastic polyps – this may be harming people!
Reporting Serrated Lesions

Time for Change:

We need to agree a nomenclature for right sided sessile non dysplastic lesions - SSP or SSA (or SSA/P)

We must introduce categories for serrated adenomas and sessile serrated polyps in proformas, and modify diagnostic guidelines accordingly

We must review regularly the management implications for patients with serrated lesions.
• Serrated Lesions, once the Cinderellas of Colorectal Pathology, are assuming increased interest and clinical importance

• They probably contribute to the pathogenesis of up to 20% of Colorectal Cancers

• Serrated adenomas are biologically different in the left and right colons

• There is, as yet, insufficient data on which to make firm recommendations on surveillance of individuals with sessile serrated polyps without overt dysplasia

• We must modify our recording/reporting of serrated lesions within the BCSP
Acknowledgements

The late Jeremy Jass
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