But......

SSLs may occur on the left
and
TSAs may occur on the right
And some SSLs are pedunculated!

And some TSAs have *BRAF* mutations instead of *KRAS* mutations and arise in SSLs!

These lesions have no MSI or MLH1 loss

Normal mucosa

Microvesicular hyperplastic polyp

Sessile serrated lesion

Sessile serrated lesion with dysplasia / TSA

BRAF mutant, microsatellite-stable “serrated” carcinoma

M > F
Serrated tubulovillous adenoma of the large intestine

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Brisbane, QLD, Australia, and 8 Department of Chemical Pathology, Pathology Queensland, Brisbane, QLD, Australia
Serrated Tubulovillous Adenoma

<10% of all TVAs

Larger, more proximal location and more high grade dysplasia than conventional TVAs

More proximal than TSAs

No BRAF mutation, KRAS mutation in 67%

Microsatellite stable; MLH1 expression retained

CIMP-low or negative, MGMT inactivation

Nuclear β-catenin in 70%
## The Consensus Molecular Subtypes of Colorectal Cancer

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Percent</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMS1 - MSI immune</td>
<td>14%</td>
<td>MSI, CIMP high, hypermutation</td>
</tr>
<tr>
<td>CMS2 - Canonical</td>
<td>37%</td>
<td>SCNA high</td>
</tr>
<tr>
<td>CMS3 - Metabolic</td>
<td>13%</td>
<td>Mixed MSI status, SCNA low, CIMP low</td>
</tr>
<tr>
<td>CMS4 - Mesenchymal</td>
<td>23%</td>
<td>SCNA high</td>
</tr>
</tbody>
</table>

- **BRAF mutations**
  - Immune infiltration and activation
- **KRAS mutations**
  - WNT and MYC activation
  - Metabolic deregulation
  - Stromal infiltration, TGF-β activation, angiogenesis

<table>
<thead>
<tr>
<th>Feature</th>
<th>CMS1</th>
<th>CMS2</th>
<th>CMS3</th>
<th>CMS4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worse survival after relapse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worse relapse-free and overall survival</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Figure 5** Proposed taxonomy of colorectal cancer, reflecting significant biological differences in the gene expression-based molecular subtypes. CIMP, CpG island methylator phenotype; MSI, microsatellite instability; SCNA, somatic copy number alterations.

Serrated (Hyperplastic) Polyposis

- > 5 serrated polyps proximal to the sigmoid colon of which two are >10mm diameter

OR

- > 20 serrated polyps of any size distributed throughout the colon

OR

- Any number of serrated polyps proximal to the sigmoid colon with a 1st degree relative with serrated polyposis

WHO, 2010
Serrated Polyposis

- Hyperplastic polyps
- Sessile serrated lesions + dysplasia
  - Large
  - Villous
  - Complex architecture
  - May resemble atypical juvenile polyps
- Traditional serrated adenomas
- “Conventional” adenomas
Serrated (Hyperplastic) Polyposis

- 1:3000 population (but 1:300 in FOBT screening colonoscopies, including BCSP)
- 29-69% prevalence colorectal cancer
  - Earlier age, sometimes multiple
  - Often proximal with BRAF mutation & MSI
- 2-7% CRC risk at 5 years under surveillance
- 5x CRC risk in first degree relatives

- Familial clustering
  - Occasional patients have MUTYH-associated polyposis
- Restricted ethnicity
  - Caucasian of European descent
- Strong association with smoking (RR 8.3-12.7)

Prevalence

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic Polyp</td>
<td>25-30% of all colorectal polyps</td>
</tr>
<tr>
<td>Sessile Serrated Lesion</td>
<td>1.7-14% of all colorectal polyps</td>
</tr>
<tr>
<td>SSL with Dysplasia</td>
<td>13% of SSLs</td>
</tr>
<tr>
<td>Traditional Serrated Adenoma</td>
<td>0.6-1.9% of all colorectal polyps</td>
</tr>
</tbody>
</table>

Management of Serrated Polyps

- **Yes** Is Dysplasia Present? **No**

  - Traditional Serrated Adenoma
  - Sessile Serrated Lesion with Dysplasia
  - Hyperplastic Polyp
  - Sessile Serrated Lesion

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Complete removal and follow-up as conventional adenomas

Consider anatomic location and size of the polyp
Risk of Malignancy in Sessile Serrated Lesions

- Unknown
- Up to 20% of cancers have a ‘serrated’ phenotype/genotype
- Microsatellite instability (and other DNA repair defects) may speed up the evolution into carcinoma
- Case reports of rapid evolution of SSL to cancer

SSLs with Dysplasia or Carcinoma

- 137 cases
- Median size 9mm
- 85% proximal, 83% ‘flat’
- Cases with dysplasia similar age to cancer
- BRAF mutation 92.7%
- CIMP 94%
- MLH1 loss 74.5%
- “…suggests a rapid transition to malignancy following a long dwell time as an SSA without dysplasia.”

Bettington M et al. Gut 2016; in press
Natural History of Sessile Serrated ‘Adenomas’

- 40 patients with SSAs and no history of CRC or adenomas with high grade dysplasia
- Case notes, path records and cancer registry follow-up
- 5 (12.5%) developed cancer, all in proximal colon after 1-15 yrs, mean 8.3 yrs
- 4/5 cancers had MSI
- 1.8% matched conventional adenoma patients developed cancer

Nested Case-Control Study

- Danish Tumour Databases 1977-2009
- 272,342 individuals who underwent colonoscopy
- 2045 CRC and 8105 CRC-free
- First colorectal polyp during or after initial colonoscopy

<table>
<thead>
<tr>
<th>Type</th>
<th>Odds Ratio (CI)</th>
<th>10-yr risk of CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional adenomas</td>
<td>2.51 (2.25-2.80)</td>
<td>2.3%</td>
</tr>
<tr>
<td>Hyperplastic polyps</td>
<td>1.30 (0.96-1.77)</td>
<td>1.2%</td>
</tr>
<tr>
<td>SSL</td>
<td>3.07 (2.30-4.10)</td>
<td>2.6%</td>
</tr>
<tr>
<td>SSL with dysplasia</td>
<td>4.76 (2.59-8.73)</td>
<td>4.4%</td>
</tr>
<tr>
<td>SSL female</td>
<td>5.50 (3.05-8.37)</td>
<td></td>
</tr>
<tr>
<td>SSL proximal to splenic flexure</td>
<td>12.42 (4.88-31.58)</td>
<td></td>
</tr>
<tr>
<td>TSA</td>
<td>4.84 (2.36-9.93)</td>
<td>4.5%</td>
</tr>
</tbody>
</table>

Erichsen R et al. Gastroenterology 2016; 150: 895-902
Risk of Malignancy in Sessile Serrated Lesions

– Patients with SSLs are more likely to have synchronous serrated lesions, proximal hyperplastic polyps and (in some series) colorectal cancer

– Small series suggest further neoplasia occurs with similar (or greater) frequencies in SSL patients compared with adenoma patients

– Interval cancers in screening programmes are more often right-sided, CIMP-high, \textit{BRAF} mutant, or have MSI, possibly due to

  • Serrated lesions missed at colonoscopy that progress
  • Tumours arising \textit{de novo} and evolving more rapidly
‘Expert Panel’ Surveillance Recommendations

<table>
<thead>
<tr>
<th>HPs proximal to the sigmoid</th>
<th>&gt;4 or any &gt;5mm</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSL or TSA</td>
<td>&lt;3 and &lt;10mm</td>
<td>5 years</td>
</tr>
<tr>
<td>SSL or TSA</td>
<td>One &gt;10mm</td>
<td>3 years</td>
</tr>
<tr>
<td>SSL or TSA</td>
<td>&gt;3 and &lt;10mm</td>
<td>3 years</td>
</tr>
<tr>
<td>SSL</td>
<td>&gt;2 and &gt;10mm</td>
<td>1-3 years</td>
</tr>
<tr>
<td>SSL with Dysplasia</td>
<td></td>
<td>1-3 years</td>
</tr>
</tbody>
</table>

• Serrated lesions, once the Cinderellas of colorectal pathology, are assuming great interest and increasing clinical importance.

• They probably contribute to the pathogenesis of up to 20% of colorectal cancers that typically (but not exclusively) have widespread DNA methylation, \textit{BRAF} mutation and microsatellite instability.

• The spectrum of serrated lesions varies between the left and right colons.

• Serrated lesions with conventional dysplasia are managed in the same way as conventional adenomas.

• There are, as yet, insufficient data on which to make firm recommendations on surveillance of individuals with sessile serrated lesions without cytological dysplasia. Accordingly, current surveillance guidelines err on the side of caution.
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