Management of patients with serrated polyposis syndrome (SPS)

Evelien Dekker
Serrated polyposis syndrome
WHO 2010

1. ≥5 serrated polyps proximal to the sigmoid colon, of which 2 >10mm size, or
2. 1 serrated polyp proximal to recto-sigmoid in FDR of patient with SPS
3. >20 serrated polyps spread throughout the colon
Serrated polyposis syndrome
WHO 2019

1. ≥5 serrated polyps proximal to the rectum, all ≥5mm in size of which 2 ≥10mm, or
2. 1 serrated polyp proximal to recto-sigmoid in FDR of patient with SPS
3. >20 serrated polyps spread throughout the colon, of which at least 5 proximal to the rectum
Serrated polyposis syndrome
WHO 2019

• Clinical diagnosis!
Serrated polyposis syndrome

- Count *new* polyps on *subsequent* endoscopies: in colonoscopy screening populations prevalence 0.4-0.8%
- Most frequent type of polyposis, but diagnosis depends on endoscopist..

<table>
<thead>
<tr>
<th>Cohort name</th>
<th>UK</th>
<th>Spain</th>
<th>The Netherlands</th>
<th>Poland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort size, n</td>
<td>205.949</td>
<td>6.091</td>
<td>1.426</td>
<td>12.361</td>
</tr>
<tr>
<td>Diagnosed at initial colonoscopy, rate (95% CI)</td>
<td>0.03 (0.02 to 0.04)</td>
<td>0.5 (0.3 to 0.7)</td>
<td>0</td>
<td>0.1 (0 to 0.2)</td>
</tr>
<tr>
<td>Diagnosed during follow-up, rate (95% CI)</td>
<td>–</td>
<td>0.3 (0.2 to 0.5)</td>
<td>0.4 (0.1 to 0.9)</td>
<td>–</td>
</tr>
<tr>
<td>Diagnosed overall rate (95% CI) (at diagnosis-during follow-up)</td>
<td>0.8 (0.6 to 1.1)</td>
<td>0.4 (0.1 to 0.9)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

The information was not available for the Italian cohort.
Etiology:

- Mostly unclear..
- Many have FDRs with CRC
- High % smokers among SPS patients (56.9%), esp WHO 3
- Also patients with multiple serrated polyps not fulfilling WHO have an increased risk for CRC
- Germline RNF43.. but very infrequent

.. Is it one syndrome??
Serrated polyps: difficult to detect
Serrated polyps: difficult to detect
### Detection rates serrated polyps: variable!

<table>
<thead>
<tr>
<th>Endoscopist</th>
<th>Number of colonoscopies</th>
<th>Patient age(a)</th>
<th>Male</th>
<th>≥1 Adenoma</th>
<th>≥1≥1 Proximal serrated polyp</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3189</td>
<td>59.8 ± 8.0</td>
<td>52%</td>
<td>47%</td>
<td>18%</td>
</tr>
<tr>
<td>2</td>
<td>154</td>
<td>57.8 ± 8.0</td>
<td>45%</td>
<td>31%</td>
<td>10%</td>
</tr>
<tr>
<td>3</td>
<td>532</td>
<td>57.4 ± 7.3</td>
<td>45%</td>
<td>33%</td>
<td>6%</td>
</tr>
<tr>
<td>4</td>
<td>109</td>
<td>58.2 ± 7.0</td>
<td>46%</td>
<td>39%</td>
<td>11%</td>
</tr>
<tr>
<td>5</td>
<td>331</td>
<td>57.4 ± 6.9</td>
<td>48%</td>
<td>40%</td>
<td>13%</td>
</tr>
<tr>
<td>6</td>
<td>124</td>
<td>58.4 ± 6.9</td>
<td>44%</td>
<td>33%</td>
<td>8%</td>
</tr>
<tr>
<td>7</td>
<td>528</td>
<td>58.9 ± 7.7</td>
<td>41%</td>
<td>31%</td>
<td>11%</td>
</tr>
<tr>
<td>8</td>
<td>56</td>
<td>59.2 ± 7.6</td>
<td>50%</td>
<td>46%</td>
<td>13%</td>
</tr>
<tr>
<td>9</td>
<td>348</td>
<td>57.7 ± 7.5</td>
<td>37%</td>
<td>36%</td>
<td>12%</td>
</tr>
<tr>
<td>10</td>
<td>359</td>
<td>57.7 ± 7.3</td>
<td>53%</td>
<td>25%</td>
<td>3%</td>
</tr>
<tr>
<td>11</td>
<td>90</td>
<td>57.7 ± 6.7</td>
<td>52%</td>
<td>17%</td>
<td>1%</td>
</tr>
<tr>
<td>12</td>
<td>83</td>
<td>59.1 ± 8.3</td>
<td>52%</td>
<td>27%</td>
<td>2%</td>
</tr>
<tr>
<td>13</td>
<td>327</td>
<td>58.1 ± 7.8</td>
<td>60%</td>
<td>29%</td>
<td>11%</td>
</tr>
<tr>
<td>14</td>
<td>297</td>
<td>59.5 ± 8.2</td>
<td>50%</td>
<td>21%</td>
<td>4%</td>
</tr>
<tr>
<td>15</td>
<td>154</td>
<td>57.8 ± 8.0</td>
<td>45%</td>
<td>31%</td>
<td>10%</td>
</tr>
<tr>
<td>Combined</td>
<td>6681</td>
<td>58.9 ± 7.8</td>
<td>49%</td>
<td>38%</td>
<td>13%</td>
</tr>
</tbody>
</table>

\(a\) patient age in years.
Post-colonoscopy cancers (PCCRCs)

• **1-9%** of CRCs defined as PCCRC
• PCCRCs more CIMP (OR 2.19) & MSI (2.10)

<table>
<thead>
<tr>
<th>Table 2. Molecular characteristics of interval vs. non-interval cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td><strong>CIMP</strong></td>
</tr>
<tr>
<td>Positive</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td><strong>MSI</strong></td>
</tr>
<tr>
<td>MSI</td>
</tr>
<tr>
<td>MSS</td>
</tr>
</tbody>
</table>

• PCCRCs arise more often from (missed) serrated polyps!

Risk of CRC in SPS
Risk of CRC in SPS

- High: 15-70%
- Almost all CRCs at the time of or before of diagnosis SPS

Carballal Gut 2015; IJspeert Gut 2017; Rodriguez Endoscopy 2018; Boparai Gut 2010; Rubio Endoscopy 2006; Hyman 2006
Retrospective multicenter cohort UK & NL

N=480
Identified patients with SPS

Excluded N=19
- IBD (N=14)
- Hereditary CRC syndrome (N=5)

Excluded N=27
- Patients that fulfilled WHO criterion-2 only

N=434
Patients included for primary analysis

N=174
Patients that did not (yet) receive surveillance after initial clearing

N=260
Patients that received surveillance after initial clearing
## Baseline characteristics

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number</td>
<td>434</td>
</tr>
<tr>
<td>Age at diagnosis; median (IQR)</td>
<td>60.8 (51.7-67.0)</td>
</tr>
<tr>
<td>Male gender; n (%)</td>
<td>211 (48.6)</td>
</tr>
<tr>
<td>WHO subtype; n (%)</td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>117 (27.0)</td>
</tr>
<tr>
<td>Type 3</td>
<td>179 (41.2)</td>
</tr>
<tr>
<td>Type 1+3</td>
<td>138 (31.8)</td>
</tr>
<tr>
<td>History of smoking; n (%)</td>
<td>182 (56.9)*</td>
</tr>
<tr>
<td>First degree relative with CRC; n (%)</td>
<td>149 (38.4)*</td>
</tr>
<tr>
<td>Number of SPs; median (IQR)</td>
<td>29 (17-50)</td>
</tr>
<tr>
<td>Number of adenomas; median (IQR)</td>
<td>2 (0-5)</td>
</tr>
<tr>
<td>Number of SPs proximal to rectosigmoid; median (IQR)</td>
<td>14 (7-25)</td>
</tr>
<tr>
<td>Number of SPs ≥10mm; median (IQR)</td>
<td>3 (1-5)</td>
</tr>
<tr>
<td>At least 1 SP containing dysplasia; n (%)</td>
<td>114 (26.3)</td>
</tr>
<tr>
<td>At least 1 advanced adenoma; n (%)</td>
<td>153 (35.3)</td>
</tr>
</tbody>
</table>

* Referred to patients in which the variable was available
### Characteristics of patients with colorectal cancer

<table>
<thead>
<tr>
<th>Description</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with CRC; n (%)</td>
<td>127 (29.3)</td>
</tr>
<tr>
<td>Patients with two synchronous primary CRCs; n (%)</td>
<td>8 (1.8)</td>
</tr>
<tr>
<td>Patients with metachronous CRC; n (%)</td>
<td>9 (2.1)</td>
</tr>
<tr>
<td>Age at diagnosis first CRC; median (range)</td>
<td>60.8 (20.3-84.7)</td>
</tr>
<tr>
<td>Moment of diagnosis CRC; n (%)*</td>
<td></td>
</tr>
<tr>
<td>Before diagnosis SPS</td>
<td>74 (51.4)</td>
</tr>
<tr>
<td>At diagnosis SPS</td>
<td>68 (47.2)</td>
</tr>
<tr>
<td>During surveillance</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Location CRC (144 cancers); n (%)</td>
<td></td>
</tr>
<tr>
<td>Proximal colon</td>
<td>75 (52.1)</td>
</tr>
<tr>
<td>Distal colon</td>
<td>69 (47.9)</td>
</tr>
</tbody>
</table>
## Risk factors for CRC

<table>
<thead>
<tr>
<th>Risk factors for CRC (adjusted for age and gender)</th>
<th>Adjusted OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 SP containing dysplasia; n (%)</td>
<td>2.07 (1.28-3.33)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>At least 1 advanced adenoma; n (%)</td>
<td>2.30 (1.47-3.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fulfilling WHO criteria 1&amp;3; n (%)</td>
<td>1.60 (1.04-2.51)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>A history of smoking; n (%)</td>
<td>0.36 (0.23-0.56)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Management of patients with SPS

1) Awareness of importance serrated polyps
2) Awareness of diagnosis serrated polyposis syndrome
3) Improved detection of serrated polyps by endoscopists
   * High quality colonoscopy
   * Knowing what SPs look like
   * Role of advanced imaging techniques for detection??
4) Optimal polyp-removal techniques & prevention of CRC
Management of patients with SPS

1) Awareness of importance serrated polyps
2) Awareness of diagnosis serrated polyposis syndrome
3) Improved detection of serrated polyps by endoscopists
   * High quality colonoscopy
   * Knowing what SPs look like
   * Role of advanced imaging techniques for detection??
4) Optimal polyp-removal techniques & prevention of CRC
Evidence based!

Performance measures for lower gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy (ESGE) Quality Improvement Initiative

ABSTRACT
The European Society of Gastrointestinal Endoscopy and United European Gastroenterology present a short list of key performance measures for lower gastrointestinal endoscopy. We recommend that endoscopy services across Europe adopt the following seven key performance measures for lower gastrointestinal endoscopy for measurement and evaluation in daily practice at a center and endoscopist level:

1. Rate of adequate bowel preparation (minimum standard 90%);
2. Cecal intubation rate (minimum standard 90%);
3. Adenoma detection rate (minimum standard 25%);
4. Appropriate polypectomy technique (minimum standard 80%);
5. Complication rate (minimum standard not set);
6. Patient experience (minimum standard not set);
7. Appropriate post-polypectomy surveillance recommendations (minimum standard not set).

Other identified performance measures have been listed as less relevant based on an assessment of their importance, scientific acceptability, feasibility, usability, and comparison to competing measures.
Endoscopic diagnosis SSL: WASP-criteria

- Brown color? No
- Brown vessels? No
- Oval tubular or branched surface pattern? No

NICE type 1 polyp

- Clouded surface? Yes
- Indistinctive (vague) border? Yes
- Irregular shape? Yes
- Dark spots inside crypts? Yes

Sessile serrated adenoma/polyp
10 endoscopists were trained & improved!
Advanced endoscopic imaging?
Chromoendoscopy?

- FIT-positive screenees with proximal SPs ≥5mm
- Additional coloscopy with chromoendoscopy after 1 year
- 196/3444 FIT-positives with proximal SPs ≥5mm
  - 11 patients with SPS (0.32%)
  - 71 additional colo with chromo: 20 more SPS (0.90%)
- Remaining issues
  - Was it just second look with special eye for SPS?
  - Feasibility in daily practice?
  - Would NBI be comparable?

Rivero-Sanchez Endoscopy 2017
Polyp-resection
SPs difficult to delineate

CARE-study on incomplete resection of polyps:
• all: 10.1%
• SSLs vs adenomas: 31.0 vs 7.2% (RR 3.7)
Submucosal dye injection for demarcation

Piecemeal EMR
Submucosal dye injection

Cold snare piecemeal EMR
Be aware: SSL with dysplasia

Cytologic dysplasia (‘adenoma-like’)
SSL with dysplasia

“[dysplastic SSL] are mostly small polyps, only slightly larger than SSAs without dysplasia. They are uncommonly observed and occur in patients 17 years older than those with SSAs without dysplasia, suggesting a long dwell time with little change in size before rapid progression to malignancy”

(Bettington et al., Gut 2016)
SSL with dysplasia: resect whole lesion!
Optimal care for patients with SPS

Burden, risks, costs colonoscopy
Prevention CRC
Endoscopic resection of all polyps?

Clearing phase

• 24-27% requires surgery during clearing\(^1,2\)
  • Due to CRC (59-60%)\(^1,2\)
  • Due to high polyp burden (31-41%)\(^1,2\)
  • 44% of surgerical procedures is a (sub)total colectomy\(^2\)

\(^1\)IJspeert Gut 2017; \(^2\)Carballal Gut 2016
Surveillance intervals

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation surveillance interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Multi-society taskforce on CRC (US-MSTF)$^1$</td>
<td>1 year</td>
</tr>
<tr>
<td>National Dutch guideline$^2$</td>
<td>1-2 years</td>
</tr>
<tr>
<td>National Spanish guideline$^3$</td>
<td>1-2 years</td>
</tr>
<tr>
<td>Great Brittain expert consensus$^4$</td>
<td>1-2 years</td>
</tr>
</tbody>
</table>

Clinicians stay on safe side: median interval 1.1-1.3 years$^5,7,8$
-> Substantial colonoscopy burden
Cancer during surveillance: 5-year incidence rate 0-6.5%$^5-10$

Personalized surveillance protocol

Findings include at least one of the following:
- ≥1 advanced SP (TSA / ≥10mm / containing dysplasia)
- ≥1 advanced adenoma (≥10mm / high-grade dysplasia / ≥25% villous histology)
- ≥5 SSL (irrespective of size) / adenomas (irrespective of size) / HPs ≥ 5mm

- Yes: Surveillance after 1 year
- No: Surveillance after 2 years

Bleijenberg InSIGHT 2019
Personalized surveillance protocol: effective
Strong association WHO & risk AN

WHO I: 53% (95%CI 39-65%)

WHO I & III: 59% (95%CI 40-72%)

WHO III: 26% (95%CI 16-35%)

Log-rank p<0.001

Bleijenberg InSIGHT 2019
Risk AN after (sub) total colectomy

- 48 patients: 17% WHO I, 19% WHO III, 65% WHO I&III
- Median f.u. 4.7 years, mean 2 colonoscopies
- No CRC, in 13% AN, no difference between extent of surgery
**STEP 1: INITIAL CLEARING AFTER SERRATED POLYPOSIS SYNDROME DIAGNOSIS**

- **Serrated polyposis syndrome diagnosis**
- **Synchronous CRC?**
  - Yes → **Endoscopic treatment of CRC possible?** → No → High poly burden?
  - No → **Endoscopic removal of all polyps feasible?**
  - Yes → **Endoscopic clearing**
  - No → **Endoscopic clearing**
- **High poly burden?** → Yes → Consider (sub)total colectomy
- **Endoscopic clearing**
  - Remove all clinically relevant polyps

**Clinically relevant polyps:** All polyps ≥5mm in diameter, and all polyps <5mm with optical aspect of adenoma, sessile serrated lesion or traditional serrated adenoma.
Advanced polyps: Adenomas with high-grade dysplasia and/or villous component and/or diameter >10mm; Serrated polyps with dysplasia and/or diameter >10mm; Traditional serrated adenoma (TSA)

Clinically relevant polyps: All polyps ≥5mm in diameter, and all polyps <5mm with optical aspect of adenoma, sessile serrated lesion or traditional serrated adenoma.
Conclusions

Diagnosis and management of patients with SPS

- Diagnosis: still clinical, and might stay clinical..
- High quality colonoscopy is crucial
- Awareness, detection, characterization, treatment and surveillance of SPS should be optimized
- Surveillance schedules: not one size fits all -> personal risk-stratification in expert/trained centers!
Serrated polyposis: team work!