The Natural History of Right-Sided Lesions

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Disclosures

• None
Agenda

• Is there evidence that suggests a difference in natural history of right sided lesions?
  – Right-sided adenomas vs. left-sided adenomas
  – Right-sided serrated polyps vs. left-sided serrated polyps

• What do we know?

• Unanswereded questions
• Is there evidence that suggests a difference in natural history of right sided lesions?
  – Right-sided adenomas vs. left-sided adenomas
  – Right-sided serrated polyps vs. left-sided serrated polyps
• Unanswered questions
Evidence suggesting difference in natural history

- Colonoscopy with adenoma removal reduces mortality of CRC with ~50%\(^1\)

\(^1\)Zauber et al. NEJM 2012.
Evidence suggesting difference in natural history

- Magnitude of CRC mortality reduction is less in proximal colon than in distal colon\(^1\)

\(^1\)Nishihara et al. NEJM 2013
Evidence suggesting difference in natural history

- Difference in protective effect right-sided versus left-sided CRC mortality is corroborated by other studies\(^1,2\)

**Table 2.**

<table>
<thead>
<tr>
<th>Colonoscopy Status</th>
<th>All Cancers</th>
<th>Proximal Cancer</th>
<th>Distal Cancer</th>
<th>Unknown Site of Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>No colonoscopy</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Any colonoscopy</td>
<td>0.40</td>
<td>0.37 to 0.43</td>
<td>0.58</td>
<td>0.53 to 0.64</td>
</tr>
</tbody>
</table>

Abbreviations: CRC, colorectal cancer; OR, odds ratio.
*Conditional logistic regression, adjusted for comorbidities, socioeconomic status, and urban/rural status.

\(^1\)Baxter et al. J Clin Oncol 2011
\(^2\)Singh et al. Gastroenterology 2010
Evidence suggesting difference in natural history

- Post-colonoscopy CRCs are more often detected in the proximal colon\(^1\)-\(^4\)

\[ \text{OR} 2.4 \text{ (range 2.1-2.7)} \]

\(^1\) Stoffel et al. Gastroenterology 2016
\(^2\) Bressler et al. Gastroenterology 2007
\(^3\) Baxter et al. Ann Intern Med
\(^4\) Singh et al. Am J Gastroenterol 2014
Evidence suggesting difference in natural history

- Post-colonoscopy CRCs are mostly related to procedural factors\textsuperscript{1-4}

\textsuperscript{1}le Clercq et al. Gut 2014
\textsuperscript{2}Bressler et al. Gastroenterology 2007
\textsuperscript{3}Baxter et al. Ann Intern Med
\textsuperscript{4}Brenner et al. J Natl Cancer Inst 2010
Evidence suggesting difference in natural history

- Proximal CRCs\(^1\) and post-colonoscopy CRCs exhibit distinct molecular profile\(^2\)\(^-\)\(^5\)

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**Table 2. Molecular characteristics of interval vs. non-interval cancers**

<table>
<thead>
<tr>
<th></th>
<th>Interval</th>
<th>Non-interval</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIMP(^a)</td>
<td>31 (57%)</td>
<td>33 (33%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Negative</td>
<td>23 (43%)</td>
<td>75 (66%)</td>
<td></td>
</tr>
<tr>
<td>MSI(^b)</td>
<td>16 (29%)</td>
<td>12 (11%)</td>
<td>0.004</td>
</tr>
<tr>
<td>MSS</td>
<td>39 (71%)</td>
<td>95 (89%)</td>
<td></td>
</tr>
</tbody>
</table>

CIMP, CpG island methylator phenotype; MSI, microsatellite instability; MSS, microsatellite stable.

\(^a\)\(n=167\), \(^b\)\(n=162\).

All values expressed as number and % with respect to interval/non-interval status.

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\(^1\)Nishihara et al. Gut 2014
\(^2\)Arain et al. Am J Gastro 2009
\(^3\)Sawhney et al. Gastroenterology 2006
\(^4\)Shaukat et al. Dig Dis Sci 2010
Evidence suggesting difference in natural history

Colonoscopy is less effective against proximal CRC

Why?

Procedural factors (e.g. bowel preparation, cecal intubation, missed lesions)

Different natural history of proximal polyps! Suggested by:

• Distinct molecular characteristics
• Distinct histology
Agenda

• Is there evidence that suggests a difference in natural history of right sided lesions?
  
  – Right-sided adenomas vs. left-sided adenomas
  
  – Right-sided serrated polyps vs. left-sided serrated polyps

• Unanswered questions
Right-sided adenomas vs. Left-sided adenomas

What is known on the natural history of right sided adenomatous lesions?

- Clinical studies
- Modeling studies
Right-sided adenomas vs. Left-sided adenomas

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- Clinical studies
- Modeling studies
Right-sided adenomas vs. Left-sided adenomas

• Mizuno et al. observed >200 diminutive adenomas for a mean period of 7.8 years\(^1\)

• Adenomas grow slow in proximal colon

\(^1\)Mizuno et al. Dig Endosc 2010
Right-sided adenomas vs. Left-sided adenomas

- Tutein Nolthenius et al\textsuperscript{1}: more regression in proximal polyps
- Pickhardt et al\textsuperscript{2}: progression highest in cecum and rectum

\textsuperscript{1}Tutein Nolthenius et al. Am J Gastroenterol 2015
\textsuperscript{2}Pickhardt et al. Lancet Oncol 2013
Right-sided adenomas vs. Left-sided adenomas

- Right sided polyps with advanced neoplasia are smaller in size\textsuperscript{1}

\textsuperscript{1}Gupta et al. Clin Gastro Hep 2012
Right-sided adenomas vs. Left-sided adenomas

- Advanced adenomas in the proximal colon are more likely to be diminutive in size (OR 3.1) and non-polypoid (OR 4.7)\(^1\)

\[ \text{OR 8.5 (4.0-18.2)} \]

\(^1\) Rondagh et al. Endoscopy 2012
Right-sided adenomas vs. Left-sided adenomas

What is known on the natural history of right sided adenomatous lesions?

- Clinical studies
- Modeling studies
Right-sided adenomas vs. Left-sided adenomas

- Proximal adenoma prevalence increases with increasing age\(^1,2\)

\(^1\)Senore et al. Best Pract Res Gastro Hep
\(^2\)Meza et al. Cancer Res 2012
Right-sided adenomas vs. Left-sided adenomas

- Similarly, proximal CRC prevalence increases with increasing age\textsuperscript{1,2}

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\textsuperscript{1}Senore et al. Best Pract Res Gastro Hep
\textsuperscript{2}Meza et al. Cancer Res 2012
Summary

- Proximal adenomas seem to have a more aggressive behaviour
- Proximal adenoma and CRC prevalence increases with increasing age
• Is there evidence that suggests a difference in natural history of right sided lesions?
  – Right-sided adenomas vs. left-sided adenomas
  – Right-sided serrated polyps vs. left-sided serrated polyps

• Unanswered questions
Right-sided serrated polyps vs. Left-sided serrated polyps

<table>
<thead>
<tr>
<th>Shape</th>
<th>Mean size</th>
<th>Prevalence</th>
<th>Location</th>
<th>Precancerous</th>
</tr>
</thead>
<tbody>
<tr>
<td>HP</td>
<td>Flat, sessile</td>
<td>Small, often ≤5mm</td>
<td>Very common</td>
<td>Left colon</td>
</tr>
<tr>
<td>SSL</td>
<td>Flat, sessile</td>
<td>Larger than HP</td>
<td>Common</td>
<td>Right colon</td>
</tr>
<tr>
<td>TSA</td>
<td>Sessile, pedunculated</td>
<td>Larger than HP</td>
<td>Rare</td>
<td>Left colon</td>
</tr>
</tbody>
</table>
Right-sided serrated polyps vs. Left-sided serrated polyps

Pre-cancerous SPs are mostly *proximal*
Benign SPs are mostly *distal*

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\(^1\)IJspeert et al. Endoscopy 2016
Right-sided serrated polyps vs. Left-sided serrated polyps

- What is known on the natural history of right sided serrated lesions?
  - Translational studies
  - Clinical studies
Right-sided serrated polyps vs. Left-sided serrated polyps

Normal mucosa

BRAF V600E; CIMP

Non-dysplastic SSL

53-60%\(^1\)\(^2\)
Epi-genetic silencing MLH1

Dysplastic SSL MSI

Unknown

CRC MSI (not Lynch associated)
• 9-12% of all CRC\(^3\)
• Good prognosis \(^5\)

Dysplastic SSL MSS

40-47%\(^1\)\(^2\)
Unknown mechanism; Functional MLH1

CRC MSS
• 6-8% of all CRC\(^3\)
• Poor prognosis \(^4,5\)

\(^1\)Cancer Genome Atlas (cbioportal.org)
\(^2\)Jass et al. Histopathology 2007
\(^3\)Bettington et al. Histopathology 2013
\(^5\)Ribic et al, NEJM 2003
Right-sided serrated polyps vs. Left-sided serrated polyps

• What is known on the natural history of right sided serrated lesions?
  – Translational studies
  – Clinical studies
Right-sided serrated polyps vs. Left-sided serrated polyps

- HPs in rectum and sigmoid do not exhibit any growth$^{1-3}$

Fig. 2. Growth rate of polyps expressed in millimeters per year. Negative numbers indicate a decrease in polyp size over time. Larger numbers correspond to a faster rate of change in polyp size.

$^1$Bersentes et al. Am J Gastroenterol 1994
$^2$Hofstad et al. Gut 1994
$^3$Hoff et al. Scand J Gastroenterol 1986
Right-sided serrated polyps vs. Left-sided serrated polyps

- 3 SSLs had been observed by CT colonography\(^1,2\)
  - 1 progressed; 1 remained stable; 1 decreased in size before endoscopic removal with histopathology evaluation (none contained dysplasia)

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\(^1\)Tutein Nolthenius et al. Am J Gastroenterol 2015
\(^2\)Pickhardt et al. Lancet Oncol 2013
Right-sided serrated polyps vs. Left-sided serrated polyps

- Studies have documented foci of dysplasia and CRC developing within SSLs and TSAs\(^1,2\)

- SSLs with dysplasia make up 0.4% from all polyps.
- 78-87% located in the *proximal* colon\(^1-2\)

Right-sided serrated polyps vs. Left-sided serrated polyps

- Conflicting evidence on CRC dwell time of SSLs\textsuperscript{1,2}

> “[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”

\textsuperscript{(Bettington et al., Gut 2016)}

\textsuperscript{1}Lash et al. J Clin Pathol 2010
\textsuperscript{2}Bettington et al. Gut 2016
Right-sided serrated polyps vs. Left-sided serrated polyps

10-20 years?\textsuperscript{1,2}  
Months?\textsuperscript{1,2}

\textsuperscript{1}Bettington et al. Gut 2016  
\textsuperscript{2}East et al. Gut 2016
Right-sided serrated polyps vs. Left-sided serrated polyps

The natural course of serrated lesions: a difficult enigma to resolve

Editorial

Serrated route to colorectal cancer: back street or super highway?

• Studies are limited\(^1,2\)
  – SSLs were previously thought to be benign
  – SSLs difficult to detect on endoscopy\(^3,4\)
  – SSLs difficult to detect on histopathology\(^5,6\)

\(^1\)IJspeert et al. Gut 2016
\(^2\)Jass et al. Journal of Pathology 2001
\(^3\)Zorzi et al. Gut 2016
\(^4\)IJspeert et al. GIE 2015
\(^6\)Abdeljahwad et al. GIE 2015
Summary

• HPs in distal colon are innocent

• SSLs are precancerous are most often detected in the proximal colon

• Controversy exists on the dwell time of SSLs

• Data on natural history of serrated lesions are scarce and are limited

References:


Agenda

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• Unanswered questions
What do we know?

• Colonoscopy is less protective for proximal CRCs

• Natural behavior of left- and right sided lesions seems different

• Proximal adenomas seem to behave more aggressive

• Proximal serrated polyps seem to behave more aggressive
Questions to be answered

• Why do proximal lesions behave more aggressive?

• Why do proximal advanced lesions more often possess non-polypoid morphology?

• Why does the proximal adenoma and CRC prevalence increases with increasing age?

• What is the natural history of proximal serrated lesions?

• To what extent does this difference in natural history contributes to post-colonoscopy CRCs?
Future research

• Development of nationwide registries of postcolonoscopy CRC

• Molecular analysis of postcolonoscopy CRCs

• New studies leaving lesions in situ focusing on proximal lesions

• Molecular analysis of SSLs with and without dysplasia