Right-sided cancer – is it down to a field effect?

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Disclosures

• Clinical Advisory Board:
  • Lumendi
  • Boston Scientific

• Speaker:
  • Olympus
  • Falk
Questions

- What do we mean by “field effect”?

- Are there likely candidates to mediate a field effect?

- Is there clinical (human) evidence to support a field effect?
Pathways to Colorectal cancer

Muto T, Bussey H, Morson B. Cancer 1975;36:2251-2270
## Colonoscopy outcomes

<table>
<thead>
<tr>
<th>Attempted colonoscopy</th>
<th>All Cancer</th>
<th>Right-Sided Cancer</th>
<th>Left-Sided Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Any</td>
<td>0.69 (0.63–0.74)</td>
<td>1.07 (0.94–1.21)</td>
<td>0.39 (0.34–0.45)</td>
</tr>
</tbody>
</table>

### Deaths from proximal colon cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Screening Lower Endoscopy</th>
<th>Screening Sigmoidoscopy</th>
<th>Screening Colonoscopy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths from proximal colon cancer‡</td>
<td>121</td>
<td>46</td>
<td>25</td>
</tr>
<tr>
<td>No. of deaths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>1.04 (0.73–1.47)</td>
<td>0.49 (0.31–0.79)</td>
</tr>
<tr>
<td>Multivariate hazard ratio (95% CI)†</td>
<td>1.00</td>
<td>1.04 (0.73–1.48)</td>
<td>0.47 (0.29–0.76)</td>
</tr>
</tbody>
</table>

### Deaths from distal colorectal cancer‡

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of deaths</th>
<th>Screening Sigmoidoscopy</th>
<th>Screening Colonoscopy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths from distal colorectal cancer‡</td>
<td>195</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>No. of deaths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>0.29 (0.19–0.46)</td>
<td>0.18 (0.10–0.30)</td>
</tr>
<tr>
<td>Multivariate hazard ratio (95% CI)†</td>
<td>1.00</td>
<td>0.31 (0.20–0.49)</td>
<td>0.18 (0.10–0.31)</td>
</tr>
</tbody>
</table>

“FIELD CANCERIZATION” IN ORAL STRATIFIED SQUAMOUS EPITHELIUM

Clinical Implications of Multicentric Origin

Daniel P. Slaughter, m.d., Harry W. Southwick, m.d.,
and Walter Smejkal, m.d.

...process of “field cancerization,” in which an area of epithelium has been preconditioned by an as-yet-unknown carcinogenic agent....
Field cancerisation in colitis

Leedham S et al, Gastroenterology, 2009
Widespread field cancerisation

<table>
<thead>
<tr>
<th>Year</th>
<th>Tissue sites and genotypes</th>
<th>Inferred clone growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td><img src="#" alt="Diagram 1" /></td>
<td><img src="#" alt="Diagram 2" /></td>
</tr>
<tr>
<td>1998</td>
<td><img src="#" alt="Diagram 3" /></td>
<td><img src="#" alt="Diagram 4" /></td>
</tr>
</tbody>
</table>

- **Normal/inflamed**
- **Hyperplasia**
- **Dysplasia**
- **Polyp**
- **Tumour**
- **Resection margin**

Genotypes:
- c.731G>A
- c.775G>T
- c.742C>T

Widespread field cancerisation

Widespread field cancerisation

Field cancerization in IBD – Clonal sweeps

Choi CR et al. Nat Rev Gastroenterol Hepatol 2017;14:218-229
**APC and FAP – genotype phenotype correlations**

- **20-amino acid repeats (β-catenin binding/degradation, GSK3-β phosphorylation)**
- **Heptad repeats (dimerisation)**
- **Armadillo repeats**
- **Basic domain (Microtubule binding, tubulin polymerisation)**

**Mutation cluster region**

- **Severe colonic disease**
  - Lamllum et al, Nat Med, 1999
  - Mutation cluster region: 1169 to 1495
- **Severe upper GI disease**
  - Groves et al, Am J Path, 2002
  - Mutation cluster region: 1169 to 1495

**AARs =** Beta-catenin binding = Wnt signalling in resultant polyp

**References:**
- Lamlum et al, Nat Med, 1999
- Groves et al, Am J Path, 2002
FAP APC mutation spectra (UGI vs LGI)

↑20 AARs = ↑Beta-catenin binding = ↓Wnt signalling in resultant polyp
FAP APC mutation spectra (UGI vs LGI)

% polyps

Number 20 AAR's

UGI vs LGI
p=0.000016
Simplified model

Excessive Wnt

Polyp initiation threshold

Basal Wnt signal/ stem cell number

Sporadic CRC. Right vs left colon

\[ P = 0.01 \]
Sporadic CRC

• Physiological gradient and mutation spectra determine CRC site
  – MSI tumours commonly result in mutations between codon 1450-1560 (2/3 AAR’s) because of presence of short repeats and are thus predominantly right sided
Methylation across the colon

Gradual change in cancer subtypes

Microbiome - biofilms

Dejea CM et al. PNAS 2014;111:18321-26
Fusobacterium load

CRC with Fusobacterium
### Serrated polyposis syndrome (SPS) Phenotype(s)

1. At least five serrated polyps proximal to the sigmoid colon, two of which are greater than 10 mm in diameter.

2. Any number of serrated polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis.

3. More than 20 serrated polyps of any size distributed throughout the colon.

*Serrated lesion refers to any combination of hyperplastic polyps and sessile serrated polyps.*
**PSC-IBD and bile acids**

- Tumour right colon 67% vs 36% PSC-IBD vs IBD alone
- OR 4.8 (95% CI 2.0-11.8)
- Altered bile acid composition
- Possible protective effect UDCA

Key messages

- What do we mean by “field effect”?
  - an area of epithelium has been preconditioned by an as-yet-unknown carcinogenic agent

- Are there likely candidates to mediate a field effect?
  - Wnt signaling
  - Methylation
  - Microbiome
  - Clonal sweeps

- Is there clinical evidence to support a field effect?
  - Serrated polyp distribution
  - PSC & UC
  - MSI-High CIMP +ve tumours
Acknowledgments

- Trevor Graham
  - Barts Cancer Institute

- Simon Leedham
  - Wellcome Trust Centre
  - Human Genetics