Gastric Intestinal Metaplasia – What to do?

David C. Metz, MD
Professor of Medicine, Division of Gastroenterology
Perelman School of Medicine at the University of Pennsylvania
Objectives

- Review incidence of intestinal metaplasia
- Discuss management with regard to associated disease states
- Review surveillance guidelines for patients after diagnosis
Intestinal Metaplasia

- Normal (intestinal) tissue in an abnormal location (stomach)
- May be complete (Type I with absorptive cells) or incomplete (Types II and III without absorptive cells)
- Consequence of gastric atrophy and achlorhydria
- Major causes: *H. pylori* infection and Autoimmune Atrophic Gastritis
- A step along the pathway to cancer (Correa)
- Incomplete type higher risk for cancer
Precursors and Consequences of Gastric Atrophy

Helicobacter pylori

Autoimmune gastritis

Gastric Atrophy

Gastric Cancer

Type 1 Carcinoids
**H. pylori Epidemiology**

Affects 50% of the world’s population!

After Marshall, 1995
Natural History of *H. pylori* infection

**H. pylori Infection and Gastric Cancer: the Correa Cascade**

- **H. pylori**
- **Possibly CagA**
- **tpr-met protooncogene**
- **Chronic gastritis**
- **Atrophic gastritis**
- **Intestinal metaplasia**
- **Dysplasia**
- **Gastric cancer**
- **k ras**
- **p53**
- **DCC (Deleted in Colorectal Cancer) Loss**
- **Microsatellite instability**
- **Host with specific IL-1β genotype**

**H. pylori and Risk of Gastric Cancer: Meta-analysis of Prospective Cohort Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases (n)</th>
<th>Median interval (yr)</th>
<th>Matched OR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>56</td>
<td>8.7</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>111</td>
<td>15.0</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>109</td>
<td>13.9</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>29</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>84</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>188</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>56</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>45</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td>208</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>Iceland</td>
<td>41</td>
<td>15.0</td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>120</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>181</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Summary</td>
<td>1228</td>
<td>6.0</td>
<td>2.36 (1.98–2.81)</td>
</tr>
</tbody>
</table>

## CagA *H. pylori* infection and Gastric Cancer Risk

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Cases infected (%)</th>
<th>Controls infected (%)</th>
<th>Odds Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CagA + vs uninfected</td>
<td>70/82 (85)</td>
<td>48/94 (51)</td>
<td>5.8 (2.6-13.0)</td>
</tr>
<tr>
<td>CagA – vs uninfected</td>
<td>20/32 (63)</td>
<td>41/87 (47)</td>
<td>2.2 (0.9-5.4)</td>
</tr>
</tbody>
</table>

# Interleukin Polymorphisms and Gastric Cancer

<table>
<thead>
<tr>
<th></th>
<th>Cancer (n=366)</th>
<th>Controls (n=479)</th>
<th>Atrophic relatives (n=33)</th>
<th>Normal relatives (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1B-31T</td>
<td>1.9 (1.5-2.6)</td>
<td>1</td>
<td>8.1 (1.8-37)</td>
<td>1</td>
</tr>
<tr>
<td>IL-1RN*2/*2</td>
<td>3.7 (2.4-5.7)</td>
<td>1</td>
<td>4.5 (1.5-14)</td>
<td>1</td>
</tr>
</tbody>
</table>

* Polish population (OR and 95% CI)

Proposed Gastric Carcinoma Sequence

*H. pylori* Gastritis

Pro-inflammatory phenotype (IL-1,10, TNFA phenotypes)

CagA infection

Corpus gastritis

? PPI Rx

Hypochlohydria and gastric atrophy

Intestinal Metaplasia

Nitroso compds

Dec Vitamin C

Smoking

Salt

Infection disappears

Dysplasia

Cancer

After El-Omar et al, Gastroenterology 2001;121:1002-4
Prospective Study of 1526 *H. pylori* Patients (mean f/u 7.8yrs 1-10.6)

Cancers During Follow Up

Cost-effectiveness of *H. pylori* Therapy to Prevent Gastric Cancer

Primary Prevention of Gastric Cancer (in a high risk region of China)

- 1,630 high-risk patients from Fujian province of China, all infected with *H. pylori*
  - 632 had pre-malignant lesions at baseline endoscopy (atrophy, intestinal metaplasia, dysplasia)
  - 998 had no premalignant lesions at baseline endoscopy
- Patients randomized to Hp Rx (Omep/Amox+clav/Metro) or to placebo Rx for 2 weeks
- Long term follow up (most for 7.5 years or more)

C-Y Wong et al. JAMA 291:187-194, 2005
Gastric Cancer in Fujian Province
(Wong et al)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=813)</th>
<th>Antibiotics (n=817)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANCERS</td>
<td>11</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>WITH PRE-MALIGNANT HISTOLOGY</td>
<td>5</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>NO PRE-MALIGNANT HISTOLOGY</td>
<td>6</td>
<td>0</td>
<td>0.02</td>
</tr>
</tbody>
</table>
H. pylori Therapy and Secondary Prevention of Early Gastric Cancer After Endoscopic Mucosal Resection

132 non-randomized Japanese pts after EMR for Early Cancer

Antibiotics N=65 (49%)
New cancers (0%)

No antibiotics N=67 (51%)
New cancers N=6 (9%)

2 yr follow up

Limitations of Test and Treat to Reduce Cancer Worldwide

- Testing is expensive
- Testing by antibody has limitations
- Treatment is not uniformly effective
- Treatment has side effects
- Resistance is an emerging problem
- Ideal timing of intervention is unclear
Risk Factors for Progression to Cancer

- Age >50 yrs
- Atrophic pangastritis (HP > PA)
- Severe (extensive) Intestinal metaplasia
- Incomplete IM
- First degree relatives of gastric cancer patients
- Smokers

Vannella et al. APT 2010;31:1042-50
Vannella et al. W J Gastro 2012;18:1279-85
Screening and Surveillance for Gastric Adenocarcinoma

- Low risk patients – possibly Q3Y (if at all)
- Higher risk patients - probably 1-3 yearly
  - Partial gastrectomy >20 yrs ago
  - Gastric intestinal metaplasia with dysplasia (especially incomplete)
  - Gastric ulcer
  - Family history of gastric cancer
  - Hereditary gastric cancer (Ecadherin mutation)
  - HNPCC, FAP
Detection of Early Gastric Cancer

• Endoscopy with biopsy/cytology
  - minimal number of biopsies from a GU to optimize cancer yield is 4-7
    – yield increased if brush cytology used adjunctively
    – up to 3-4% of endoscopically benign gastric ulcers are malignant

• Chromoendoscopy
  – Methylene blue identifies absorptive epithelia (intestinal metaplasia)
  – Congo red identifies acid secreting epithelia (bleaches in areas of neoplasia)
Accuracy of Methylene Blue Staining to Identify Gastric IM

Adapted from Fennerty et al Gastrointest Endosc 1992;38:696
Narrow Band Imaging to Detect Premalignant Lesions during EGD

<table>
<thead>
<tr>
<th></th>
<th>IM (n=68)</th>
<th>Dysplasia (n=9)</th>
<th>Neither (n=44)</th>
<th>Total (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both</td>
<td>47</td>
<td>8</td>
<td>31</td>
<td>86</td>
</tr>
<tr>
<td>NBI alone</td>
<td>21</td>
<td>1</td>
<td>11</td>
<td>33</td>
</tr>
<tr>
<td>White light alone</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Capelle et al. DDS 2010;55:3442-8
Updated ASGE Guideline: Management of premalignant and malignant gastric conditions

• Premalignant conditions
  – Polyps (FGPs, hyperplastic, adenomas)
  – Gastric Intestinal Metaplasia and
  – Pernicious anemia/atrophic gastritis
  – Gastric caerzinoids
  – Postgastrectomy syndromes
### Updated ASGE Guideline: Management of Gastric Polyps

<table>
<thead>
<tr>
<th>Association</th>
<th>Frequency</th>
<th>Malignancy Risk</th>
<th>Management</th>
<th>Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGPs</td>
<td>PPIs FAP</td>
<td>Common</td>
<td>Low *</td>
<td>Observe **</td>
</tr>
<tr>
<td>Hyperplastic</td>
<td><em>H. pylori</em> # Atrophy</td>
<td>Infrequent</td>
<td>Moderate ##</td>
<td>Remove &gt;1cm</td>
</tr>
<tr>
<td>Adenoma</td>
<td><em>H. Pylori</em> # Atrophy</td>
<td>Rare</td>
<td>High</td>
<td>Remove &gt;1cm</td>
</tr>
</tbody>
</table>

* Except for FAP
** Remove if >0.5-1cm
# Always treat and prove cure
## 5-19% with dysplasia

GIE 2015;82:1-8
Updated ASGE Guideline: Management of GIM, PA and postgastrectomy states

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cancer Risk</th>
<th>Surveillance</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal Metaplasia</td>
<td>11%</td>
<td>FH or Asian</td>
<td>Earlier detection</td>
</tr>
<tr>
<td>All</td>
<td>&gt;33% (25% @ 1yr) Intermediate</td>
<td>YES</td>
<td>Better outcome</td>
</tr>
<tr>
<td>HGD</td>
<td></td>
<td>YES</td>
<td>Unclear if cost effective</td>
</tr>
<tr>
<td>LGD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pernicious Anemia</td>
<td>1-3%</td>
<td>Unclear</td>
<td>Risk is early ?1yr</td>
</tr>
<tr>
<td>Postgastrectomy</td>
<td>0.8-8.9%</td>
<td>Unclear</td>
<td>Risk is late &gt;15yrs</td>
</tr>
</tbody>
</table>
Recommended Reading

• ASGE Guideline: The role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. GIE 2006;63:570-80

• Management of precancerous conditions and lesions in the stomach: guidelines from the ESGE, EHSG, ESP and SPED. Endoscopy 2012;44:74-94.

• Follow up of intestinal metaplasia in the stomach: When, how and why. WJ GI Onc 2012;15: 30-36

• ASGE Guideline: The role of endoscopy in the management of premalignant and malignant conditions of the stomach. GIE 2015;82:1-8
Conclusions

• Early detection of Gastric cancer is critical but
  – Who should undergo screening/surveillance still unclear
  – Benefit of population screening is unproven
  – Role of chromoendoscopy/NBI to detect IM unclear

• IM with dysplasia mandates intervention and surveillance

• Whether to survey US patients without dysplasia unclear

• Once identified, *H pylori* infection should be treated and follow up cure status confirmed