Gastric Intestinal Metaplasia and Carcinoids – What to do?

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Objectives

• Review incidence of intestinal metaplasia and carcinoids
• 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

**Gastric Carcinoids**

- Macroscopic neoplastic growth in the gastric mucosa
- Type 1 carcinoids also develop as a consequence of gastric atrophy and hypochlorhydria
- Final step along the NET gastric pathway (Solcia)
Precursors and Consequences of Gastric Atrophy

H. pylori

Gastric Atrophy

Autoimmune gastritis

Type 1 Carcinoids

Gastric Cancer

H. pylori Epidemiology

Affects 50% of the world’s population!
**Natural History of *H. pylori* infection**

- High level of acid production
  - Normal gastric mucosa
  - Acute *H. pylori* infection
  - Chronic *H. pylori* infection
  - Ante-predominant gastritis
  - Non-atrophic gastritis
  - Corpus-predominant atrophic gastritis
  - Intestinal metaplasia
  - Dysplasia
  - Gastric cancer

- Low level of acid production
  - Childhood
  - Advanced age


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

- *H. pylori* infection
  - Possibly CagA
  - *tpr-met* protooncogene

- Chronic gastritis

- Atrophic gastritis
  - *k ras*

- Intestinal metaplasia
  - *p53*

- Dysplasia

- *DCC (Deleted in Colorectal Cancer)* loss

- Gastric cancer

Host with specific *IL-1β* genotype

Microsatellite instability


**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>4.0</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>OR 1228</td>
<td>6.0</td>
<td>2.36 (1.98–2.81)</td>
</tr>
</tbody>
</table>


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**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 -> ? PPI Rx
Corpus gastritis
Hypochlohydria and gastric atrophy
Intestinal Metaplasia
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])

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NUD</td>
<td>4.7%</td>
</tr>
<tr>
<td>GU</td>
<td>3.4%</td>
</tr>
<tr>
<td>Hyp. Polyps</td>
<td>2.2%</td>
</tr>
<tr>
<td>DU (+ control)</td>
<td>0%</td>
</tr>
<tr>
<td>HP neg controls</td>
<td>0%</td>
</tr>
</tbody>
</table>

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>
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

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

Vannella et al APT 2010;31:1042-50
Vannella et al W J Gastro 2012;18:1279-85
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

Foregut - Gastric Carcinoids

- In recent studies 10-30% of all carcinoids are reported in the stomach
- There are **3 types** of Gastric Carcinoids
- Most gastric carcinoid tumors are diagnosed during endoscopy

Modlin IM. Gastroenterology 128:1717-51, 2005
**Gastric Carcinoids: Incidence**

- Cause: ? EGD vs Pathology vs PPI Rx


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**Gastric Carcinoids: Presentation**

<table>
<thead>
<tr>
<th>Carcinoid</th>
<th>% total</th>
<th>Multiplicity</th>
<th>Associations</th>
<th>Gastrin</th>
<th>Acid Secretion</th>
<th>Mets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>75</td>
<td>Yes</td>
<td>PA/atrophy</td>
<td>Increased</td>
<td>Low</td>
<td>V. rare</td>
</tr>
<tr>
<td>Type II</td>
<td>5-10</td>
<td>Yes</td>
<td>ZES/MEN-1</td>
<td>Increased</td>
<td>High</td>
<td>Rare</td>
</tr>
<tr>
<td>Type III</td>
<td>15-25</td>
<td>No</td>
<td>None</td>
<td>Normal</td>
<td>Normal</td>
<td>Common</td>
</tr>
</tbody>
</table>

Hypergastrinemia

- **Appropriate (with hypo- or achlorhydria)**
  - Drugs (H2RA's and PPI's)
  - Atrophic gastritis with/without PA
  - *H. pylori* pangastritis
  - Chronic renal failure
  - Vagotomy

- **Inappropriate (with hyperchlorhydria)**
  - ZES (sporadic or MEN-1)
  - Retained antrum syndrome
  - Antral predominant *H. pylori* infection (G-cell hyperplasia)
  - Massive intestinal resection (temporary)
  - Gastric outlet obstruction (reversible)
Type I Gastric Carcinoids: Pathophysiology

No Acid

LUMEN MUCOSA

ACh Gastrin Histamine Vagus Nerve

H+ K+ ATPase

cAMP Ca2+
Parietal Cell

ECLoma

No Feedback Inhibition

No Somatostatin

D Cell

g

Solcia’s Classification of ECL-Cell Hyperplasia

Classification of ECL Cell Proliferation

<table>
<thead>
<tr>
<th>Hyperplasia</th>
<th>Simple (diffuse)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Linear</td>
</tr>
<tr>
<td></td>
<td>Micronodular</td>
</tr>
<tr>
<td></td>
<td>Adenomatoid</td>
</tr>
<tr>
<td>Dysplasia (Pre-Neoplastic stage)</td>
<td>Enlarging micronodule</td>
</tr>
<tr>
<td></td>
<td>Fusing micronodule</td>
</tr>
<tr>
<td></td>
<td>Micrinvasive lesion</td>
</tr>
<tr>
<td></td>
<td>Nodule with newly formed strata</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>Intramucosal carcinoid</td>
</tr>
<tr>
<td></td>
<td>Invasive carcinoid</td>
</tr>
</tbody>
</table>

Type I Gastric Carcinoids

- Most prevalent (70-80% of all gastric carcinoids) 1,2
- Associated with hypergastrinemia and atrophic gastritis with or without pernicious anemia – predisposed to adenocarcinoma (<3%)
- Usually small, multiple lesions in the body and fundus
- Up to 20% infiltrate locally, up to 8% to lymph nodes 1,3
- In the absence of dysplasia, the standard of care for IM and atrophy is NOT to survey endoscopically (may change soon)
- Surveillance of Type 1 carcinoids is recommended but still controversial, frequency unclear (may change soon)1-3

1. Ruszniewski P. Neuroendocrinology 2006;84:158-164

Gastric Carcinoids in PA Vary
Type I Gastric Carcinoids: Treatment Should be Individualized

- Observation usually appropriate with survival similar to the general population 1-8
- Endoscopic polypectomy recommended for larger (>1cm) less numerous (<6) lesions 1-3,8
- EMR may be superior to snare polypectomy (submucosal) 7
- Local excision recommended for more numerous (>6), infiltrative lesions 1-3,8
- Antrectomy usually causes regression but has morbidity 1,2,3
- Somatostatin analog therapy induces regression 4-6

1. Ruszniewski P. Neuroendocrinology 2006;84:158-4
4. Campana D. Endocrine-related Cancer 2008;15:337-42
Gastric Carcinoids:
My Management Algorithm

Gastric Carcinoid

Gastric pH and Fasting Gastrin

pH and FSG high

Type I (atrophy)

Map stomach

Gastric Ca. None

O.R. Individualize *

* Options are:
1. Observation (favored)
2. Endoscopic surveillance (?? Cost effective)
3. Endoscopic resection (few large tumors)
4. Local excision (many large tumors)
5. Antrectomy (many large tumors)
6. Somatostatin Analogs (many large tumors)
7. Gastrin Antagonists (experimental) #

# Fossmark, R. APT 2012;36:1067
Gastric Carcinoids: My Management Algorithm

Gastric Carcinoid

Gastric pH and Fasting Gastrin

pH and FSG high

pH low, FSG high

Type I (atrophy)

Type II (MEN-1/ZES)

Map stomach

Octreoscan

Gastric Ca. None

Pit., PTH, enteropanc.

O.R. Individualize

Individualize

Gastric Carcinoids: My Management Algorithm

Gastric Carcinoid

Gastric pH and Fasting Gastrin

pH and FSG high

pH low, FSG high

pH and FSG normal

Type I (atrophy)

Type II (MEN-1/ZES)

Type III (sporadic)

Map stomach

Octreoscan

EUS

Gastric Ca. None

Pit., PTH, enteropanc.

Invasive

Not invasive

O.R. ? EMR (<3cm)

Individualize

Individualize

O.R.
Recommended Reading

- ASGE Guideline: The role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. GIE 2006;63:570-80
- Follow up of intestinal metaplasia in the stomach: When, how and why. WJ GI Onc 2012;15: 30-36

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
- Management of gastric carcinoids remains controversial
  - All lesions should be subtyped (FSG and gastric pH)
  - Management of type I carcinoids should be individualized according to various criteria
  - Role and timing of surveillance remains unclear