Gastric Intestinal Metaplasia: Diagnosis, Endoscopic Management and Surveillance

Andrew Y. Wang, MD, FACG, FASGE

Associate Professor of Medicine
Co-Medical Director of Endoscopy
Director of Pancreatico-Biliary Endoscopy

Division of Gastroenterology and Hepatology
University of Virginia Health System

I have no conflicts of interest with respect to this presentation.

I disclose research funding from Cook Medical on the topic of metal biliary stents.
### Survey of ACG/VGS/SGNA attendees (Williamsburg, 2011)

<table>
<thead>
<tr>
<th>Gastric lesion</th>
<th>% considered premalignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic active gastritis without <em>H. pylori</em></td>
<td>26%</td>
</tr>
<tr>
<td>Chronic active gastritis with <em>H. pylori</em></td>
<td>39%</td>
</tr>
<tr>
<td>Atrophic gastritis</td>
<td>35%</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>68%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastric lesion</th>
<th>% considered premalignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune metaplastic gastritis</td>
<td>29%</td>
</tr>
<tr>
<td>Gastric adenoma</td>
<td>74%</td>
</tr>
<tr>
<td>Low-grade dysplasia</td>
<td>87%</td>
</tr>
<tr>
<td>High-grade dysplasia</td>
<td>100%</td>
</tr>
</tbody>
</table>

### Survey of ACG/VGS/SGNA attendees (Williamsburg, 2011)

**RE: Gastric intestinal metaplasia (IM)**

<table>
<thead>
<tr>
<th>Surveillance interval</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>No answer</td>
<td>45%</td>
</tr>
<tr>
<td>1-year follow-up</td>
<td>10%</td>
</tr>
<tr>
<td>2-year follow-up</td>
<td>16%</td>
</tr>
<tr>
<td>3-year follow-up</td>
<td>19%</td>
</tr>
<tr>
<td>5-year follow-up</td>
<td>10%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biopsy protocol</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>No answer</td>
<td>58%</td>
</tr>
<tr>
<td>Random</td>
<td>26%</td>
</tr>
<tr>
<td>Sydney protocol</td>
<td>3.2%</td>
</tr>
<tr>
<td>Antrum</td>
<td>3.2%</td>
</tr>
<tr>
<td>Proximal and distal stomach</td>
<td>3.2%</td>
</tr>
<tr>
<td>“Lesion” and abnormal appearing mucosa</td>
<td>3.2%</td>
</tr>
<tr>
<td>“Lesion” only</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

Frye JW...Wang AY. Am J Gastroenterol 2012;107;S43-44
### Gastric IM survey of ASGE members

<table>
<thead>
<tr>
<th>Consider gastric IM a premalignant lesion (response: yes)</th>
<th>All respondents</th>
<th>Academic clinicians</th>
<th>Private practice clinicians</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>56%</td>
<td>91</td>
<td>47%</td>
<td>30</td>
<td>56%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Screen for gastric IM (response: yes)</th>
<th>All respondents</th>
<th>Academic clinicians</th>
<th>Private practice clinicians</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>26%</td>
<td>42</td>
<td>23%</td>
<td>15</td>
<td>26%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Survey gastric IM (response: yes)</th>
<th>All respondents</th>
<th>Academic clinicians</th>
<th>Private practice clinicians</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>48%</td>
<td>75</td>
<td>42%</td>
<td>27</td>
<td>49%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time interval for those that survey patients with gastric IM</th>
<th>All respondents</th>
<th>Academic clinicians</th>
<th>Private practice clinicians</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>6 months</td>
<td>6.9%</td>
<td>5</td>
<td>3.8%</td>
<td>1</td>
</tr>
<tr>
<td>1 year</td>
<td>34.7%</td>
<td>25</td>
<td>34.6%</td>
<td>9</td>
</tr>
<tr>
<td>2 years</td>
<td>27.8%</td>
<td>20</td>
<td>30.8%</td>
<td>8</td>
</tr>
<tr>
<td>3 years</td>
<td>29.2%</td>
<td>21</td>
<td>34.6%</td>
<td>9</td>
</tr>
<tr>
<td>5 years</td>
<td>2.8%</td>
<td>2</td>
<td>0%</td>
<td>0</td>
</tr>
</tbody>
</table>

*162 physicians (87% men, from 32 states, 58% urban vs. 34% suburban)*

Frye JW,...Wang AY. Gastrointest Endosc 2013;77:AB261-2

### International rates of gastric cancer (2012)

![Map showing international rates of gastric cancer (2012)]

- Prevalence of gastric IM: 5-7%
- Progression to cancer: 0.5-1.8%

*Source: GLOBOCAN 2012 (IARC)*

Gomez JM, Wang AY. Gastroenterol Hepatol (NY) 2014;10
International rates of esophageal cancer (2012)

- Prevalence of esoph IM (BE) 6.8%
- Progression to cancer 0.12-0.5%

Cascade of premalignant gastric conditions

- Chronic gastritis
- Chronic atrophic gastritis
- Intestinal metaplasia
- Intraepithelial neoplasia (dysplasia)

Gastric cancer (intestinal type)

References:
- Correa P. Cancer Res 1992;52
- Areia M et al. (Gastrointest Endosc 2008;67
- Wang AY, Peura DA. Gastrointest Endoscopy Clin N Am 2011;21
- Gomez JM, Wang AY. Gastroenterol Hepatol (NY) 2014;10
Gastric intestinal metaplasia

- **Gastric IM** is defined by the loss of normal gastric epithelium and replacement with an intestinal phenotype containing goblet cells, Paneth cells, and absorptive cells
  - Complete vs. **incomplete** (H&E staining)
  - Focal vs. **multifocal**

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Photomicrographs of gastric intestinal metaplasia. (a) Complete type with well-defined goblet cells alternating with cosinophilic enterocytes displaying well-developed brush border (inset) and Paneth cells (arrow). (b) Incomplete type showing multiple intracytoplasmic mucin droplets of varying sizes and shapes, and absence of a brush border. (Hematoxylin and eosin; original magnification, ×400; inset, ×1,000.)

*Correa P et al. Am J Gastroenterol 2010; 105*
Risk factors for gastric cancer & IM

Gastric cancer
- Geographic
  - Eastern Asia
  - Eastern Europe
  - Andean Latin America
- U.S. ethnic populations
  - African Americans
  - Native Americans
  - Asian Americans
  - Latin Americans

Gastric IM
- Family history
- H. pylori infection
- High salt intake
- Smoking
- Alcohol
- Chronic bile reflux
- Atrophic gastritis

Correa P et al. Am J Gastroenterol 2010; 105

Incidence of gastric cancer among patients with gastric precancerous lesions: observational cohort study in a low risk Western population

Huan Song,1 Isabella Guncha Ekheden,1 Zongli Zheng,1 Jan Ericsson,2 Olof Nyren,1 Weimin Ye1

ABSTRACT

OBJECTIVE
To accurately measure the incidence of gastric cancer among patients with gastric precancerous lesions, and to quantify the excess incidence in comparison with people with normal mucosa on endoscopy and a general population.

DESIGN
Population based cohort study.

SETTING
Population of Sweden using data from its national disease registers.

PARTICIPANTS
405,172 patients who had gastric biopsy samples taken for non-malignant indications between 1979 and 2011.

Average follow-up of 10 years

Fig 2 | Cumulative incidence of gastric cancer among patients with different baseline diagnoses. First two years of follow-up excluded

Song H et al. BMJ 2015;351:h3867
Andrew Y. Wang, MD, FACG

Risk of gastric cancer within 20 years of EGD:
- Normal mucosa → 1 in 256
- Gastritis → 1 in 85
- Atrophic gastritis → 1 in 50
- Gastric IM → 1 in 39

Change on follow-up biopsies compared to the initial diagnosis (↑ or ↓ in the Correa's cascade) had **prognostic significance**

Song H et al. BMJ 2015;351:h3867

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**Table 3 | Hazard ratios and 95% confidence intervals for gastric cancer among patients with different lesions in the stomach compared with normal group**

<table>
<thead>
<tr>
<th>Mucosal status at baseline*</th>
<th>Hazard ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardia gastric cancer</td>
</tr>
<tr>
<td>Normal</td>
<td>Reference</td>
</tr>
<tr>
<td>Minor mucosal change</td>
<td>1.1 (0.4 to 2.9)</td>
</tr>
<tr>
<td>Gastritis</td>
<td>1.8 (1.2 to 2.9)</td>
</tr>
<tr>
<td>Atrophic gastritis</td>
<td>2.4 (1.1 to 4.8)</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>4.7 (2.3 to 9.5)</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>6.0 (2.3 to 15.9)</td>
</tr>
</tbody>
</table>

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**Not emphasized in U.S. GI training**

- **How to carefully examine the stomach on EGD**
- How to characterize GI neoplasia
  - Morphology
  - Advanced optical imaging/image-enhanced endoscopy
- Proper use of electrosurgical generators
- **When and how to perform EMR or ESD**
  - When is EMR insufficient?
  - When can ESD be done instead of surgery?
  - How to prepare a pathological specimen
- Principles of “surgical” oncology -- or “endosurgical” oncology
Endoscopic gastric examination

- Total interior surface area

**Stomach** – 800 cm²

**Colon** – 2,000 cm²

Sandle GI. Gut 1998;43
Helander HF, Fandriks L. Scand J Gastroenterol 2014;49
Marieb, E.N. Essentials of Human Anatomy and Physiology 2005

Sydney protocol for gastric biopsies

Gomez JM, Wang AY. Gastroenterol Hepatol (NY) 2014;10
Japanese method of gastric endoscopy

VIDEO FILE

Limitations of the Sydney protocol

- Detects *H. pylori* infection in virtually all infected patients
- *Intestinal metaplasia* may be missed in >50% of cases

Yantiss RK et al. Am J Gastroenterol 2009;104
Use of NBI and optical magnification to identify gastric intestinal metaplasia

Figure 1. a Bluish-white patchy areas were observed in narrow-band images of the antrum in patients with gastric intestinal metaplasia, and the light blue crest (LBC) appearance was frequently seen in those areas. b In the narrow-band imaging and magnifying endoscopy image, LBC appears as blue-white lines visible on the epithelial surface.

Light-blue crest sign as a marker of gastric intestinal metaplasia

Wang AY et al. Gastrointest Endosc 2010;71:AB362
Methylene blue magnification

- **Nonmetaplastic, nondysplastic mucosa:** no color change, regular pattern
- **Metaplastic mucosa:** blue color change, regular pattern
- **Dysplastic mucosa:** blue color change, irregular pattern

Whom should we biopsy?

- Patients with increased risk for gastric cancer
  - Systematic endoscopy with WL and IEE (NBI, etc.)
  - 5-station Sydney protocol (consider separating at least in to distal and proximal jars)
  - Even if the EGD is normal, might find *H. pylori*, eradication of which can be beneficial
- Patients with prior incomplete-type or multifocal gastric IM
- Patients with abnormal/concerning findings on EGD
- What about patients with no risk factors, only dyspepsia, and a normal EGD?
  - **No**
Frequency of gastric IM in Central Virginia

- 300 pts who had EGD and gastric biopsies at the University of Virginia (UVA) in 2011
  - *H. pylori* infection 2%
  - Chronic gastritis 20%
  - Gastric IM 5%

- **First-degree family history of gastric cancer was a risk factor for having gastric IM**
  - **OR 8.51** [95% CI: 1.52-40.22, *P*=0.018] on age-adjusted multivariate analysis

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### Associations among endoscopic findings and gastric IM

<table>
<thead>
<tr>
<th></th>
<th>Frequency in patients with gastric IM n=418</th>
<th>Frequency in patients without gastric IM n=171</th>
<th>Univariate analysis</th>
<th>Multivariate analysis (odds ratio, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastritis</td>
<td>100 (23.9%)</td>
<td>37 (21.6%)</td>
<td><em>P</em>=0.557</td>
<td>1.34 [0.84, 2.08], <em>P</em>=0.223</td>
</tr>
<tr>
<td>Atrophic gastritis</td>
<td>55 (13.2%)</td>
<td>9 (5.3%)</td>
<td><em>P</em>=0.004</td>
<td>2.05 [1.00, 4.58], <em>P</em>=0.051</td>
</tr>
<tr>
<td>Gastric mass</td>
<td>20 (4.8%)</td>
<td>0 (0%)</td>
<td><em>P</em>=0.001</td>
<td>8.84 [1.88, ∞], <em>P</em>=0.005</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>28 (6.7%)</td>
<td>23 (13.4%)</td>
<td><em>P</em>=0.011</td>
<td>0.49 [0.26, 0.91], <em>P</em>=0.023</td>
</tr>
<tr>
<td>Esophageal mass</td>
<td>2 (0.5%)</td>
<td>13 (7.6%)</td>
<td><em>P</em>&lt;0.001</td>
<td>0.04 [0.01-0.16], <em>P</em>&lt;0.001</td>
</tr>
<tr>
<td>Barrett’s esophagus</td>
<td>21 (5.0%)</td>
<td>13 (7.6%)</td>
<td><em>P</em>=0.235</td>
<td>0.56 [0.26, 1.21], <em>P</em>=0.134</td>
</tr>
</tbody>
</table>

Gomez JM…Wang AY. Journal of GHR 2013;2

Gomez JM…Wang AY. Gastrointest Endosc 2013;77-AB261
### Association among histopathological biopsy results and gastric IM

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency in patients with gastric IM n=468</th>
<th>Frequency in patients without gastric IM n=171</th>
<th>Univariate analysis</th>
<th>Multivariate analysis (odds ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic gastritis</td>
<td>265 (56.6%)</td>
<td>55 (32.2%)</td>
<td>P&lt;0.001</td>
<td>2.56 [1.75, 3.76], P&lt;0.001</td>
</tr>
<tr>
<td>H. pylori infection</td>
<td>46 (9.8%)</td>
<td>6 (3.5%)</td>
<td>P=0.007</td>
<td>3.07 [1.33, 8.20], P=0.007</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>18 (3.8%)</td>
<td>0 (0%)</td>
<td>P=0.003</td>
<td>6.97 [1.47, 31.6], P=0.015</td>
</tr>
<tr>
<td>Gastric dysplasia</td>
<td>19 (4.1%)</td>
<td>1 (0.6%)</td>
<td>P=0.017</td>
<td>6.11 [1.07, 31.5], P=0.038</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>21 (4.5%)</td>
<td>1 (0.6%)</td>
<td>P=0.010</td>
<td>6.53 [1.17, 39.4], P=0.027</td>
</tr>
<tr>
<td>AMAG</td>
<td>12 (2.6%)</td>
<td>0 (0%)</td>
<td>P=0.023</td>
<td>5.64 [1.35, 22.8], P=0.035</td>
</tr>
<tr>
<td>Barrett’s esophagus</td>
<td>14 (3.0%)</td>
<td>13 (7.6%)</td>
<td>P=0.016</td>
<td>0.28 [0.12, 0.63], P=0.003</td>
</tr>
<tr>
<td>EoE</td>
<td>1 (0.2%)</td>
<td>6 (3.5%)</td>
<td>P=0.002</td>
<td>0.10 [0.00, 0.74], P=0.020</td>
</tr>
<tr>
<td>Carcinoid tumor</td>
<td>10 (2.1%)</td>
<td>0 (0%)</td>
<td>P=0.043</td>
<td>5.13 [1.02, 25.7], P=0.047</td>
</tr>
<tr>
<td>Duodenitis</td>
<td>2 (0.4%)</td>
<td>6 (3.5%)</td>
<td>P=0.006</td>
<td>0.13 [0.02, 0.65], P=0.012</td>
</tr>
</tbody>
</table>

Gomez JM...Wang AY. Gastrointest Endosc 2013;77:A8261

### How to screen in the U.S.?

- Population-based screening would **not** be effective for gastric cancer in the U.S.
  - Overall, the risk remains low
- Consider screening adult patients with **family history of gastric cancer**
  - Particularly those who smoke
  - Test for and eradicate *H. pylori*
- If EGD done for any reason and gastric atrophy is found (or gastric IM suspected), consider 5-station Sydney protocol biopsies
  - Biopsies raised areas or those concerning for dysplasia and put specimens in separate jars
UVA Results – Gastric IM patients

2278 reported cases IM

1142 confirmed IM

1004

89 Preceding diagnosis of gastric CA

32 Gastric CA diagnosed within 6 months

78 with no clinical info in UVA EMR

868 < 6 months of follow up

675 enrolled

54 Gastric CA

661 no Gastric CA


UVA Results – Controls

6272 EGD with gastric Bx

1857 Normal gastric Bx

4415 Gastric abnormality on Bx

583 < 6 months of follow up

1 Gastric CA diagnosed within 6 months

1272 no Gastric CA

1275 enrolled

1 Gastric CA

## Results

<table>
<thead>
<tr>
<th></th>
<th>IM positive</th>
<th>IM negative</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>675</td>
<td>1,273</td>
<td>--</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.3 SD ± 13.9</td>
<td>44.5 SD ± 21.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male gender</td>
<td>48.6%</td>
<td>43.5%</td>
<td>0.5</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>67.3%</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>25.2%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>7.6%</td>
<td>6.9%</td>
<td>0.7</td>
</tr>
<tr>
<td>H. Pylori positive</td>
<td>17.5%</td>
<td>0%</td>
<td>0.001</td>
</tr>
<tr>
<td>Subsequent gastric CA</td>
<td>2.1%</td>
<td>0.1%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time interval to gastric CA (years)</td>
<td>4.0 SD ± 3.5</td>
<td>2.1 SD ± 0</td>
<td>0.61 (N.S.)</td>
</tr>
<tr>
<td>Follow-up time (years)</td>
<td>5.3, SD ± 4.1</td>
<td>3.1, SD ± 2.0</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### Gastric-cancer-free survival

**Actuarial risk of Gastric CA for pts with gastric IM:**
- 0.3% at 1 year
- 1.7% at 5 years
- 3.7% at 10 years
Management and surveillance of gastric intestinal metaplasia

- Pathology report with IM in a gastric mucosa biopsy sample
- Assess for H. pylori infection (test with serology if biopsy is negative) and treat
- Assess extension and type of IM in original biopsies

Extensive IM* or incomplete type

Yes

Endoscopic surveillance with mapping or serum PG levels at 1 year
Repeats every 3 years if extensive IM atrophy** or incomplete type IM persists

No

No surveillance required

Correa P et al. Am J Gastroenterol 2010;105

Management of precancerous conditions and lesions in the stomach (MAPS) guideline

- Patients with atrophic gastritis and/or intestinal metaplasia without dysplasia
- Patients with dysplasia
  - Endoscopy
  - Magnification chromoendoscopy and or narrow band imaging (NBI) may be offered
  - Biopsies: upper 3/4 of stomach and distal stomach (presumed nongastric conditions)
  - Spread of lesions
  - Grade of dysplasia
  - Undetermined atrophic gastritis or intestinal metaplasia only conditions
  - Anaplastic lesions in intestinal metaplasia
  - IM atrophy and high-grade dysplasia

(then stop)

H. pylori eradication

Follow-up

ESGE, EHSO, ESP, SPED

Dinis-Ribeiro M et al. Endoscopy. 2012;44
Where is the lesion?

Antral HGD

ESD and EMR for early gastric cancer

- 714 early gastric cancers (EGC) in 655 consecutive patients
  - Endoscopic submucosal dissection (ESD): 303
  - Endoscopic mucosal resection (EMR): 411
- Median follow-up of 3.2 years
- 3-year cumulative residual-free/recurrence-free rate was 94.4%
  - ESD 97.6% vs. EMR 92.5% (P=0.01)
- 3-year overall survival rate was 99.2%

Oda I et al. Gastric Cancer 2006;9
EMR of gastric LGD

Gomez JM, Wang AY. Gastroenterol Hepatol (NY) 2014;10

Piecemeal EMR vs. ESD

- 222 patients who had colorectal endoscopic piecemeal EMR (EPMR) and follow-up colonoscopy
  - 19% had local recurrence
  - EPMR with 5 or more specimens was associated with a 3-times greater likelihood of local recurrence (P=0.005)
- Local recurrence rate for early gastric cancer
  - EPMR 30%
  - En bloc ESD 0%
  - But neither group had EGC-related mortality over 10-year average follow-up

Sakamoto T et al. J Gastroenterol 2012;47
Horiki N et al. Surg Endosc 2012;26
Endoscopic submucosal dissection with electrosurgical knives in a patient on aspirin therapy (with video)

Andrew Y. Wang, MD, Fabian Emura, MD, PhD, Ichiro Oda, MD, Dawn G. Cox, RN, Hyun-soo Kim, MD, Paul Yeaton, MD

Charlottesville, Virginia, USA

Gastrointest Endosc 2010;72

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Dysplasia

Muscularis Mucosae

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Gastric ESD

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Mucosal gastric cancer – think ESD

Choi J et al. Gastrointest Endosc 2011;73

Submucosal cancer – think surgery

Irregular/nodular surface

A) Protrusion
B) Depression
C) Deep ulceration
D) Fusion of converging folds
E) Abrupt cutting of converging folds

Choi J et al. Gastrointest Endosc 2011;73
Take-home messages

• Gastric IM is a premalignant lesion associated with an increased risk of gastric cancer

• If you screen/survey for Barrett’s esophagus, then consider screening/surveillance for gastric IM

• We need to do a better job looking at the gastric mucosa when we do EGD

• If gastric dysplasia or early gastric cancer (Tis, T1a, or T1b/Sm1) is found, consider EMR (if the lesion is small) or refer for ESD