Helicobacter Pylori, Intestinal Metaplasia, and Gastric Cancer

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Disclosures: None
Gastric Cancer

I. Global & US Perspectives
II. Types of Gastric Cancer
III. Risk Factors
   • *Helicobacter pylori*
IV. Precursor Lesions
   • AGA Guidelines for Intestinal Metaplasia
V. Hereditary Gastric Cancers
VI. Treatment
Global Burden of Gastric Cancer

- Gastric cancer is the 5th most common cancer globally
  - Lifetime risk is ~1 in 54 men and ~1 in 126 women
  - Worldwide, there were 1,033,701 new cases in 2018 (representing 5.7% of all cancer cases diagnosed)

- Gastric cancer is the 3rd most common cause of cancer-related death, (after lung and colorectal cancers)
  - Responsible for 1 in every 12 deaths from cancer in 2018 (8.2% of all deaths)
  - Fatality rate of 75% throughout most of the world

Thrift et al CGH 2020
IARC: https://gco.iarc.fr/today/home
Global Burden of Gastric Cancer

There is **large global variability** in the incidence and mortality rates for gastric cancer

- **High incidence** in:
  - Eastern/South-Eastern Asia
  - Central/Eastern Europe
  - South America

- **Low incidence** in:
  - North America
  - Western Europe
  - Africa

Smyth et al Lancet 2020  
Thrift et al CGH 2020

IARC: https://gco.iarc.fr/today/home
Global Burden of Gastric Cancer

• Globally gastric cancer was the leading cause of cancer death until the 1980s, when taken over by lung cancer.

• Steady decrease in incidence and mortality in the 20th century, particularly in developed nations.

Gastric cancer was the leading cause of cancer death in the US until the late 1930s, and since then overall rates have declined.

In the US there are ~27,500 new cases of gastric cancer and ~11,000 deaths annually.
  • Early onset cases rising (1995-2003) - rates decreased by 2.6% per year among those age>50, but increased 1.3% in those age<50

5-year survival rates for patients with gastric cancer are among the lowest for all cancers in the US, at ~28%.

This is strongly related to stage of disease at diagnosis:
  • Locally diagnosed disease = 60%
  • Metastatic disease = <5%
  • 35% are diagnosed with distant-stage disease.
Gastric Cancer Subtypes

2 main topographic subtypes:

- **Cardia gastric cancer**
  - Area adjoining the esophagogastric junction

- **Non-cardia gastric cancer** (more common)
  - Arising from more distal stomach

Epidemiology and risk factor profiles for cardia gastric cancer and non-cardia gastric cancer are very different.

Gastric Cancer Subtypes

MOST COMMON: Adenocarcinoma (90-95%)
- Subtypes:
  - Intestinal (most common)
  - Diffuse (associated with hereditary cancer)

Other types include:
- Gastrointestinal stromal tumor (GIST)
- Neuroendocrine (carcinoid) tumors
- Primary gastric lymphoma
  - MALT: mucosal associated lymphoid tissue
- Very rare:
  - Squamous cell carcinomas
  - Small cell carcinomas
  - Leiomyosarcomas

Thrumurthy et al. BMJ 2013
Richman et al. Abd Rad 2017
Risk Factors for Gastric Cancer

**Older Age**
- Avg age 69 years, rising in younger groups

**Male sex**
- Lifetime risk of GC in the US is ~1 in 95 for men and ~1 in 154 for women

**Race/Ethnicity**
- 2-fold higher in Hispanics, non-Hispanic blacks, and Asians/Pacific Islanders than non-Hispanic whites

**Immigrants from high-risk countries**

**Family History / Hereditary syndromes**

**Epstein–Barr virus (8%)**

**Autoimmune gastritis**

**Diet**
- High in salt & nitroso compounds

**Environmental/Socio-demographic factors**
- Tobacco, heavy alcohol use, low SES, low level of physical activity, radiation exposure, obesity, GERD

**Helicobacter pylori**

Presence of precursor lesions

[Thrift et al CGH 2020](https://www.hopkinsmedicine.org/gastroenterology_hepatology/_pdfs/esophagus_stomach/gastric_cancer.pdf)

[Anderson et al JAMA 2010](https://www.hopkinsmedicine.org/gastroenterology_hepatology/_pdfs/esophagus_stomach/gastric_cancer.pdf)

Helicobacter Pylori

- In 1994, the WHO classified *H. pylori* as a group I carcinogen (reconfirmed 2009)
- Chronic infection with *H. pylori* is the main cause of gastric cancer
  - Accounts for 89% of distal gastric cancer cases worldwide
- Most *H. pylori* infections are acquired during childhood and persist for life unless treated
- Substantial regional variation in prevalence
  - Central/South America, Asia, Eastern Europe

Global Burden of Disease study, Lancet Gastroenterol Hepatol 2020
IARC Monogr Eval Carcinog Risks Hum 1994
Helicobacter Pylori

Types of Testing

• **Non-endoscopic**
  - Stool antigen test
    - Now with antibiotic sensitivity testing
  - Urea breath test
  - Serology testing

• **Endoscopic (biopsy-based)**
  - Histology
  - Rapid urease testing
  - PCR
  - Culture

Images: https://www.iaea.org/, https://www.aboutkidshealth.ca/
### Table 2. Recommended first-line therapies for *H pylori* infection

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drugs (doses)</th>
<th>Dosing frequency</th>
<th>Duration (days)</th>
<th>FDA approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin triple</td>
<td>PPI (standard or double dose)</td>
<td>BID</td>
<td>14</td>
<td>Yes*</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin (500mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amoxicillin (1gmr) or Metronidazole (500mg TID)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bismuth quadruple</td>
<td>PPI (standard dose)</td>
<td>BID</td>
<td>10–14</td>
<td>No*</td>
</tr>
<tr>
<td></td>
<td>Bismuth subcitrate (120–300mg) or subsalicylate (300mg)</td>
<td>QID</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tetracycline (500mg)</td>
<td>QID</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metronidazole (250–500mg)</td>
<td>QID (250)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant</td>
<td>PPI (standard dose)</td>
<td>BID</td>
<td>10–14</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin (500mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amoxicillin (1gmr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nitroimidazole (500mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequential</td>
<td>PPI (standard dose)+Amoxicillin (1gmr)</td>
<td>BID</td>
<td>5–7</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>PPI, Clarithromycin (500mg)+Nitroimidazole (500mg)</td>
<td>BID</td>
<td>5–7</td>
<td></td>
</tr>
<tr>
<td>Hybrid</td>
<td>PPI (standard dose)+Amoxicillin (1gmr)</td>
<td>BID</td>
<td>7</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>PPI, Amox, Clarithromycin (500mg), Nitroimidazole (500mg)</td>
<td>BID</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin triple</td>
<td>PPI (standard dose)</td>
<td>BID</td>
<td>10–14</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin (500mg)</td>
<td>QID</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amox (1gmr)</td>
<td>BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofloxacin sequential</td>
<td>PPI (standard or double dose)+Amox (1gmr)</td>
<td>BID</td>
<td>5–7</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>PPI, Amox, Levofloxacin (500mg QD), Nitroimidazole (500mg)</td>
<td>BID</td>
<td>5–7</td>
<td></td>
</tr>
<tr>
<td>LOAD</td>
<td>Levofloxacin (250mg)</td>
<td>QD</td>
<td>7–10</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>PPI (double dose)</td>
<td>QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nitazoxanide (500mg)</td>
<td>BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxycycline (100mg)</td>
<td>QD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BID, twice daily; FDA, Food and Drug Administration; PPI, proton pump inhibitor; TID, three times daily; QD, once daily; QID, four times daily.

*Several PPI, clarithromycin, and amoxicillin combinations have achieved FDA approval. PPI, clarithromycin and metronidazole is not an FDA-approved treatment regimen.

*PPI, bismuth, tetracycline, and metronidazole prescribed separately is not an FDA-approved treatment regimen. However, Pylera, a combination product containing bismuth subcitrate, tetracycline, and metronidazole combined with a PPI for 10 days is an FDA-approved treatment regimen.

*Metronidazole or tinidazole.
Confirm Eradication

- Any modality – ex. fecal antigen test, breath test, EGD
- 4+ weeks after completion of antibiotics
- PPI held for 1-2 weeks prior to testing
Utilized the national VHA pathology database (1994-2018)
371,813 subjects w/ H. pylori
2,024 (0.5%) developed GC
Risk factors for progression to gastric cancer:
• Age
• Male sex
• Hispanic Ethnicity
• Race: Black, Asian, or American Indian/Alaskan Native
• Smoking
Confirmation of Eradication Reduced GC Incidence
Non-cardia gastric adenocarcinoma progresses from normal mucosa to cancer through a well-defined pathway called the Correa cascade.

Opportunity to identify high-risk states (atrophy and intestinal metaplasia) and potentially treatable preneoplastic lesions (dysplasia) to prevent gastric cancer.
Prevalence of Precursor Lesions

Estimated prevalence in the US:
- **Atrophic Gastritis**: ~15%
- **Intestinal Metaplasia**: 4.8-11.7% (some suggest as high as 19%)
- **Dysplasia**: 0.24%

Greater in high-risk groups such as non-White racial/ethnic groups, immigrants from high-risk countries, and those with a family history of gastric cancer

Altayar et al Gastroenterology 2020
Huang et al GIE 2020
Nguyen et al CGH 2021
Shah et al Gastroenterology 2021
Swedish study - Data from national disease registers, using the general Swedish population as reference

- 405,172 with gastric biopsies (1979-2011)
- Linked to the national cancer register

Risk of Gastric Cancer within 20 years of EGD

- Normal mucosa → 1 in 256
- Gastritis → 1 in 85
- Atrophic Gastritis → 1 in 50
- Gastric Intestinal Metaplasia → 1 in 39
- Dysplasia → 1 in 19
US Data:
- 4,331 Kaiser Permanente Northern California members with GIM or dysplasia (1997-2006, followed to 2013)
  - Compared rates of GC with the general population
    - 4,146 with GIM → 17 GCs
      - RR 2.56; 95% CI 1.49-4.10
      - Median time to progression: 6.1 yrs
    - 141 with LGD → 6 GCs
      - RR 25.6, 95% CI 9.4–55.7
      - Median time to progression: 2.6 yrs
<table>
<thead>
<tr>
<th>Table 2. Follow-up of patients with gastric intestinal metaplasia and dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Total number at baseline endoscopy, n</td>
</tr>
<tr>
<td>Age at diagnosis of adenocarcinoma</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Interquartile range, years</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Female, n (%)</td>
</tr>
<tr>
<td>Male, n (%)</td>
</tr>
<tr>
<td>Follow-up time, years</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Interquartile range, years</td>
</tr>
<tr>
<td>Number of gastric adenocarcinoma during first year, n (%)</td>
</tr>
<tr>
<td>Number of gastric adenocarcinoma after first year, n (%)</td>
</tr>
<tr>
<td>Time to diagnosis of gastric adenocarcinoma (excluding cases during first year), years</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Interquartile range, years</td>
</tr>
</tbody>
</table>
Figure 2. Cumulative incidence of gastric adenocarcinoma in patients with premalignant gastric lesions. The Kaplan–Meier method was used to plot cumulative incidence of gastric adenocarcinoma. Individuals who developed gastric adenocarcinoma during the first year after the index endoscopy were excluded. Among patients with high-grade dysplasia who did not develop adenocarcinoma after 3 years of diagnosis, most patients had endoscopic or surgical resection (see text).
AGA Technical Review on Gastric Intestinal Metaplasia—Natural History and Clinical Outcomes

Andrew J. Gawron, Shailja C. Shah, Osama Altayar, Perica Davitkov, Douglas Morgan, Kevin Turner, and Reem A. Mustafa

Gastroenterology 2020;158:705–731

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>GIM</th>
<th>Follow-up</th>
<th>Person-years</th>
<th>GC</th>
<th>Events per 10,000 person-years</th>
<th>Events</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plummer, 2007</td>
<td>Venezuela</td>
<td>419</td>
<td>3</td>
<td>1342.3</td>
<td>0</td>
<td>0.0 [0.0; 12.8]</td>
<td>0.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correa, 1990</td>
<td>Colombia</td>
<td>298</td>
<td>5</td>
<td>1593.7</td>
<td>1</td>
<td>6.3 [0.0; 27.0]</td>
<td>1.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee, 2016</td>
<td>Taiwan</td>
<td>6778</td>
<td>5</td>
<td>40730.0</td>
<td>63</td>
<td>15.5 [11.9; 19.5]</td>
<td>25.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reddy, 2016</td>
<td>USA</td>
<td>906</td>
<td>5</td>
<td>4651.2</td>
<td>8</td>
<td>17.2 [7.0; 31.5]</td>
<td>2.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li, 2016</td>
<td>USA</td>
<td>4146</td>
<td>7</td>
<td>23658.0</td>
<td>17</td>
<td>7.2 [4.1; 11.1]</td>
<td>14.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Song, 2015</td>
<td>Sweden</td>
<td>11530</td>
<td>8</td>
<td>68122.0</td>
<td>76</td>
<td>11.2 [8.8; 13.8]</td>
<td>42.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim, 2008</td>
<td>Korea</td>
<td>249</td>
<td>9</td>
<td>2134.0</td>
<td>4</td>
<td>18.7 [4.0; 42.7]</td>
<td>1.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filipe, 1994</td>
<td>Slovenia</td>
<td>990</td>
<td>10</td>
<td>10738.1</td>
<td>26</td>
<td>24.2 [15.7; 34.5]</td>
<td>6.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sadjadi, 2014</td>
<td>Iran</td>
<td>129</td>
<td>10</td>
<td>1284.0</td>
<td>25</td>
<td>194.7 [125.1; 279.3]</td>
<td>0.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gonzalez, 2016</td>
<td>Spain</td>
<td>467</td>
<td>12</td>
<td>5502.7</td>
<td>23</td>
<td>41.8 [26.3; 60.8]</td>
<td>3.4%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fixed effect model: \( F=91\% , \tau^2=0.0002 , P<0.01 \)

Incidence rate of progression from GIM to gastric cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>GIM</th>
<th>Follow-up</th>
<th>Person-years</th>
<th>GC</th>
<th>Events per 10,000 person-years</th>
<th>Events</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reddy, 2016</td>
<td>906</td>
<td>5</td>
<td>4651.2</td>
<td>8</td>
<td>17.2 [7.0; 31.5]</td>
<td>16.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li, 2016</td>
<td>4146</td>
<td>7</td>
<td>23658.0</td>
<td>17</td>
<td>7.2 [4.1; 11.1]</td>
<td>83.6%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fixed effect model: \( F=73\% , \tau^2<0.0001 , P<0.05 \)

Incidence rate of progression from GIM to gastric cancer — USA studies only
CLINICAL PRACTICE GUIDELINES

AGA Clinical Practice Guidelines on Management of Gastric Intestinal Metaplasia

Samir Gupta,1,2 Dan Li,3,4 Hashem B. El Serag,5 Perica Davitkov,6,7 Osama Altayar,8 Shahnaz Sultan,9 Yngve Falck-Ytter,10,11 and Reem A. Mustafa1,2

Gastroenterology 2020;158:893–702

Table 4. AGA Recommendations for Management of Gastric Intestinal Metaplasia

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. In patients with GIM, the AGA recommends testing for H. pylori, followed by eradication over no testing and eradication</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>2. In patients with GIM, the AGA suggests against routine use of endoscopic surveillance Comments: Patients with GIM at higher risk for gastric cancer who put a high value on potential but uncertain reduction in gastric cancer mortality, and who put a low value on potential risks of surveillance endoscopies, may reasonably elect for surveillance. Patients with GIM specifically at higher risk of gastric cancer include those with: • Incomplete vs complete GIM • Extensive vs limited GIM • Family history of gastric cancerPatients at overall increased risk for gastric cancer include: • Racial/ethnic minorities • Immigrants from high incidence regions</td>
<td>Conditional</td>
<td>Very Low</td>
</tr>
<tr>
<td>3. In patients with GIM, the AGA suggests against routine repeat short-interval endoscopy with biopsies for the purpose of risk stratification Comments: Based on shared decision-making, patients with GIM and high-risk stigmata, concerns about completeness of baseline endoscopy, and/or who are at overall increased risk for gastric cancer (racial/ethnic minorities, immigrants from regions with high gastric cancer incidence, or individuals with family history of first-degree relative with gastric cancer) may reasonably elect for repeat endoscopy within 1 year for risk stratification.</td>
<td>Conditional</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

*aThere are insufficient data to guide optimal surveillance interval. Based on indirect evidence regarding cumulative gastric cancer incidence among patients with GIM, repeat upper endoscopy with careful mucosal visualization and gastric biopsies of the antrum and body and any concerning lesions may be considered in 3–5 years among patients with incidentally detected GIM, if shared decision-making favors surveillance.
In patients with intestinal metaplasia incidentally found on EGD:

1. Test and treat for *H. pylori*

2. No routine endoscopic surveillance, BUT surveillance should be considered in high-risk groups (3-5 year interval)
   - Patients with GIM specifically at higher risk of gastric cancer:
     - Incomplete GIM
     - Extensive GIM
     - Family history of gastric cancer
   - Patients at overall increased risk for gastric cancer:
     - Racial/ethnic groups (Hispanics, non-Hispanic blacks, Asians/Pacific Islanders)
     - Immigrants from high incidence regions

3. No routine short-interval EGD for risk stratification, but can consider at 1 year in high-risk individuals without a complete EGD

Note: No recommendations on screening for intestinal metaplasia.
Gastric Cancer Prevention

Globally, gastric cancer prevention has focused on:

- *H. pylori* screening and eradication
- Endoscopic screening and surveillance of gastric precancerous lesions

Several countries, including Korea, Japan, China, Venezuela, and Chile, have implemented screening programs.
- Ex. South Korea: biennial gastric cancer screening via EGD or upper GI series from age 40
- Screening programs led to higher rates of early gastric cancer detection and a 40% reduction in GC mortality

In the United States, there are no population-based screening programs, but targeted screening/surveillance in high-risk populations may help improve outcomes.
- Modeling studies suggest this may be effective and cost effective
- More research is needed on what populations this may benefit most

Zhang et al, Gastroenterology 2018
Choi et al. PloS One 2012
Who to evaluate?

Alarm Symptoms $\rightarrow$ refer for EGD!

** New onset of dyspepsia in patient $\geq 60$ years **

Abdominal pain
Unexplained weight loss
Anorexia/early satiety
Persistent vomiting
GI bleeding/Iron deficiency anemia
Dysphagia/Odynophagia

Hereditary Gastric Cancers

- **Family history** is a well-recognized risk factor for gastric cancer
  - Those with a first degree relative with GC have a **relative risk of 2.2** for developing the cancer themselves
  - Family history of GC also increases the likelihood of having **gastric intestinal metaplasia**

- While **10%** of the cases show familial aggregation, a specific hereditary cause is determined in only **1%–3% cases**
  - The most common is hereditary diffuse gastric cancer (**CDH1 mutation**)

Dhillon et al. 2001
Gomez et al. 2013
<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Genes</th>
<th>Cases associated with mutation, %</th>
<th>Inheritance</th>
<th>Gastric cancer risk, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary diffuse gastric cancer syndrome</td>
<td>CDH1</td>
<td>45</td>
<td>Autosomal dominant</td>
<td>56–70</td>
</tr>
<tr>
<td>Gastric adenocarcinoma and proximal polyposis syndrome</td>
<td>Implicated gene unknown</td>
<td>Not determined</td>
<td>Autosomal dominant</td>
<td>Not determined</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colon cancer</td>
<td>MLH1, MSH2, MSH6, PMS2</td>
<td>MSH2, ~60; MLH1, ~30; PMS2, MSH6, TGFBR2, and MLH3, ~10</td>
<td>Autosomal dominant</td>
<td>2–30</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>STK11</td>
<td>70</td>
<td>Autosomal dominant</td>
<td>29</td>
</tr>
<tr>
<td>Juvenile polyposis</td>
<td>SMAD4, BMPR1A</td>
<td>SMAD, 4–20; BMPR1A, 20–25</td>
<td>Autosomal dominant</td>
<td>21</td>
</tr>
<tr>
<td>Familial breast cancer</td>
<td>BRCA1, BRCA2</td>
<td>—</td>
<td>Autosomal dominant</td>
<td>5.5</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>TP53</td>
<td>70</td>
<td>Autosomal dominant</td>
<td>3.1–4.9</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>APC</td>
<td>≥90</td>
<td>Autosomal dominant</td>
<td>2.1–4.2</td>
</tr>
<tr>
<td>MYH-associated polyposis</td>
<td>MYH</td>
<td>~99</td>
<td>Autosomal recessive</td>
<td>Very low</td>
</tr>
</tbody>
</table>

The rare familial intestinal gastric cancer, ataxia telangiectasia, and xeroderma pigmentosum are not included in this table.
Hereditary Diffuse Gastric Cancer

• Autosomal dominant syndrome associated with signet ring cell carcinoma at a young age
  • 40% have a CDH1 mutation (also others - ex. CTNNA)
  • Consider referral to genetic counselor based on family history criteria

• Cumulative risk of HDGC by age 80:
  • Men 70%
  • Women 56%

• Average age of onset is 38 (cases as young as 14 documented)
• 60% present with Stage III and IV disease (5-year survival 4%)
• Also linked with increased risk of lobular breast cancer
• Association with H.pylori

Caldas et al. 1999
Cisco et al. 2008
Hansford et al. 2015
Hereditary Diffuse Gastric Cancer

GI & oncologic societies recommend individuals with pathogenic $CDH1$ gene mutations undergo prophylactic total gastrectomy (PTG) between ages 20 to 30

- All should undergo initial EGD assessment
- *Annual* endoscopic surveillance is reserved for those individuals who are not willing or able to undergo gastrectomy

EGD should be done with Cambridge Protocol
- 30-minute exam with repeated insufflation, extensive washing
- Targeted biopsies (pale patches, nodules, visible lesions)
- 30 random biopsies (5 biopsies each from 6 regions)
  - Pre-pylorus, antrum, transition zone, gastric body, fundus, cardia

Kumar et al. W J Gastro 2019
Gastric Cancer: Diagnosis and Treatment

Gastric cancer survival is strongly related to stage of disease at diagnosis.

Early Gastric Cancer

- **Endoscopic Mucosal Resection (EMR)** if size <10 mm
- **Endoscopic Submucosal Dissection (ESD)**
  - No LN involvement
  - Mucosal tumor without deep ulceration, size ≤20 mm in diameter (can consider in bigger lesions), differentiated histology

Locally Advanced Cancers

- **Gastrectomy**
- **Adjuvant therapy** is generally recommended for those patients with stage II or higher following gastrectomy

Unresectable Disease

- Requires systemic therapy
Summary

• There is significant **regional variability** in gastric cancer incidence globally (most common in East Asia, Central/Eastern Europe, Central/South America)

• Overall incidence continues to decline, though mortality remains high

• **H. pylori** is a group I carcinogen based on IARC/WHO classification – test and treat!

• Specific populations are considered **high risk** in the US, may warrant endoscopic surveillance:
  - Foreign born individuals from high incidence countries
  - Family history of gastric cancer
  - High risk race/ethnicity (Hispanics, Blacks, and Asians/Pacific Islanders)
  - Advanced intestinal metaplasia on EGD (incomplete, extensive)

• **Early diagnosis** is key!! → Outcomes improve when amenable to curative endoscopic or surgical resection
Questions?

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