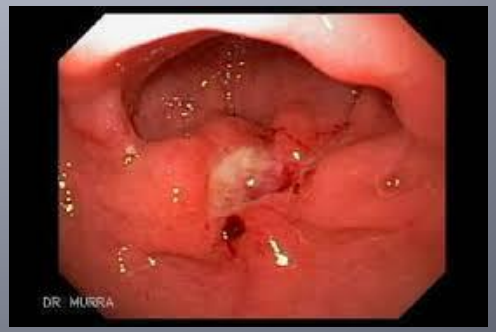
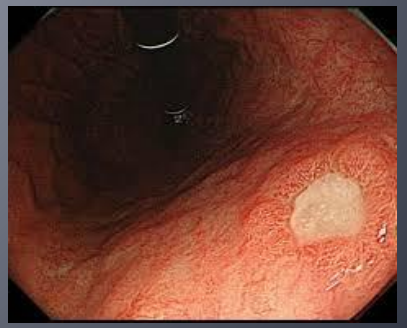
Helicobacter pylori infection and gastrointestinal malignancy

Mohammad Hussein, M.D.
Al-Assad University Hospital





The World Health Organization (WHO) has classified HP as a class I carcinogen since 1994

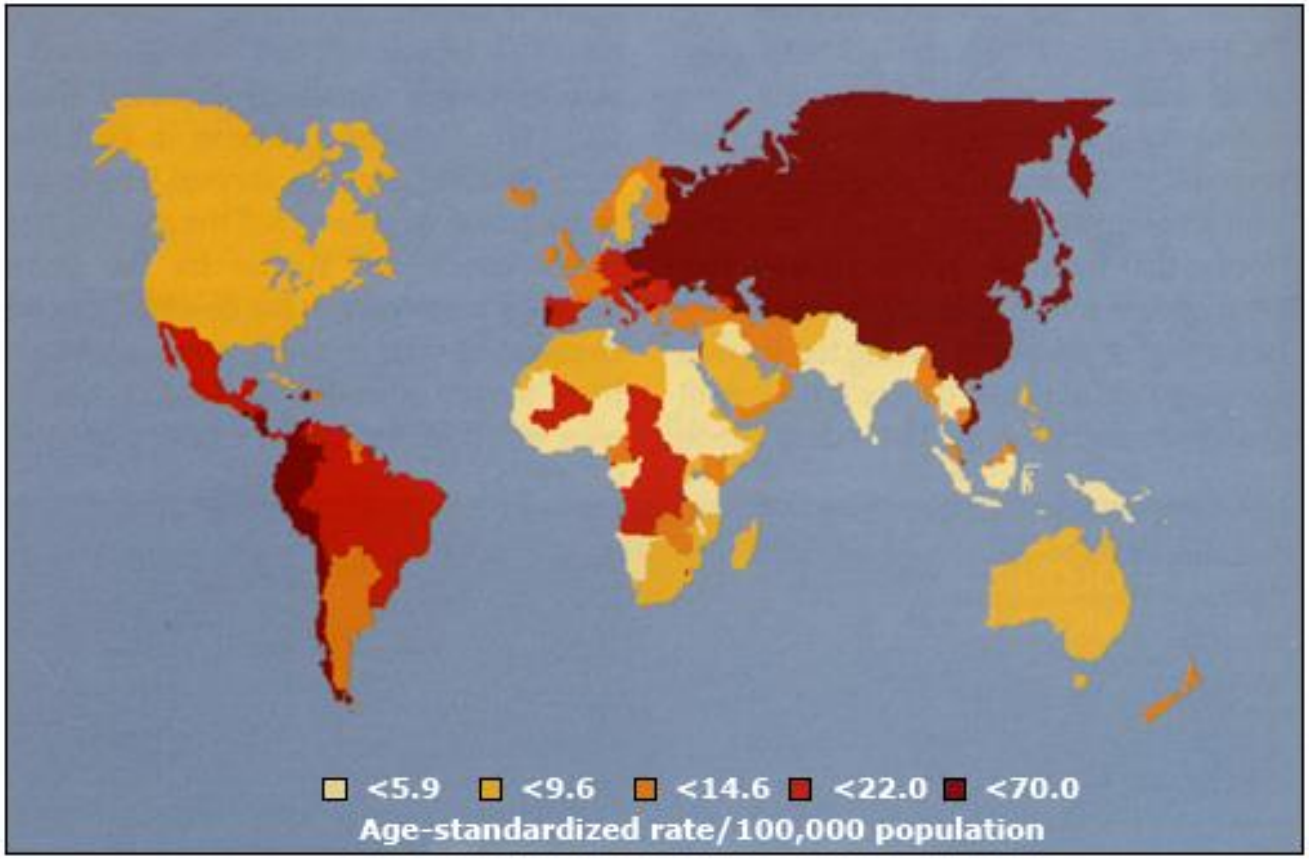
- Gastric adenocarcinoma
- Gastric lymphoma
- Colon cancer
- Pancreatic cancer
- Hepatobiliary cancer
- Esophageal cancer

Gastric adenocarcinoma

- One of the most common causes of cancer-related death in the world
- 90% of gastric tumors
- The incidence of gastric cancer varies with different geographic regions.

CA Cancer J Clin. 2011;61(2):69.

Global incidence of gastric cancer in men



The highest rates occur in Eastern Asia, South America, and Eastern Europe.

Stewart B, Keihues P. World Cancer Report, International Agency for Research on Cancer Press, Lyon France 2003. p.194.

2 Main sites of gastric adenocarcinoma

DISTAL (NON-CARDIA)

- Decreasing
- Risk factors
  - HP
  - low socioeconomic status
  - smoking
  - salty and smoked food intake
  - low consumption of fruits and vegetables
  - family history of GC

PROXIMAL (CARDIA)

- Increasing
- Risk factors
  - obesity
  - gastro-esophageal reflux disease
  - Barrett's esophagus

2 Main types (Lauren classification):

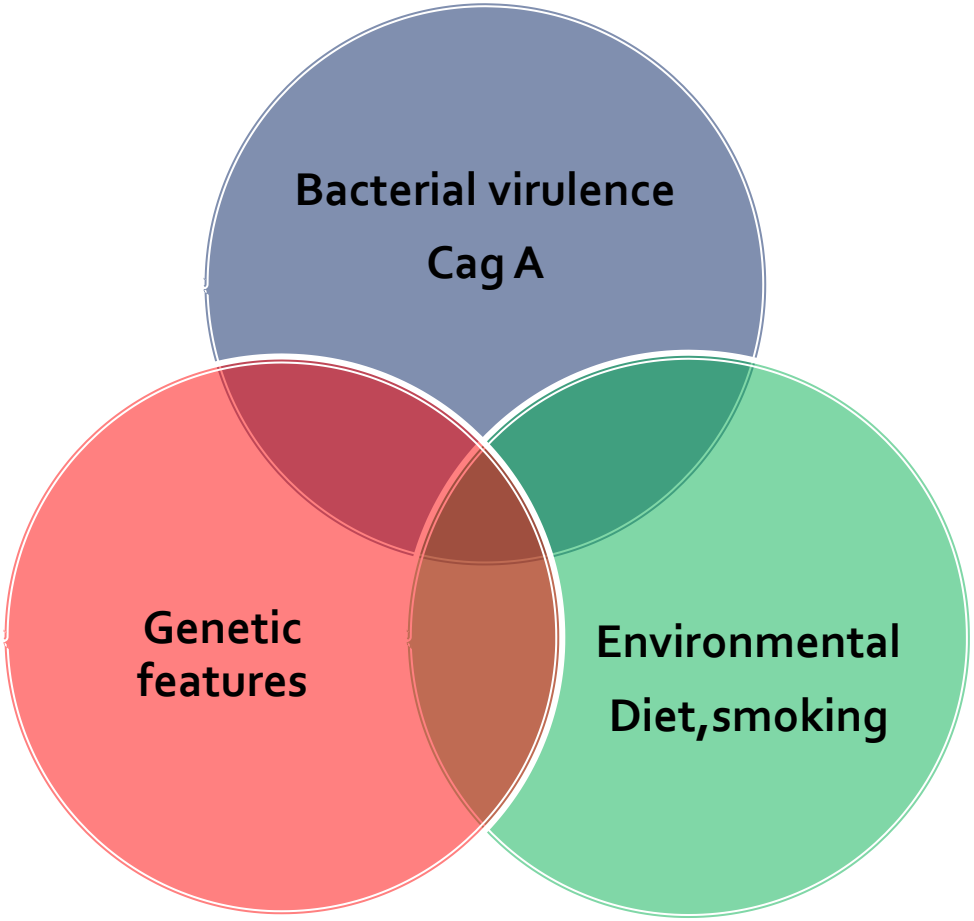
INTESTINAL TYPE

- corpus-dominant gastritis with intestinal metaplasia
- Older age groups

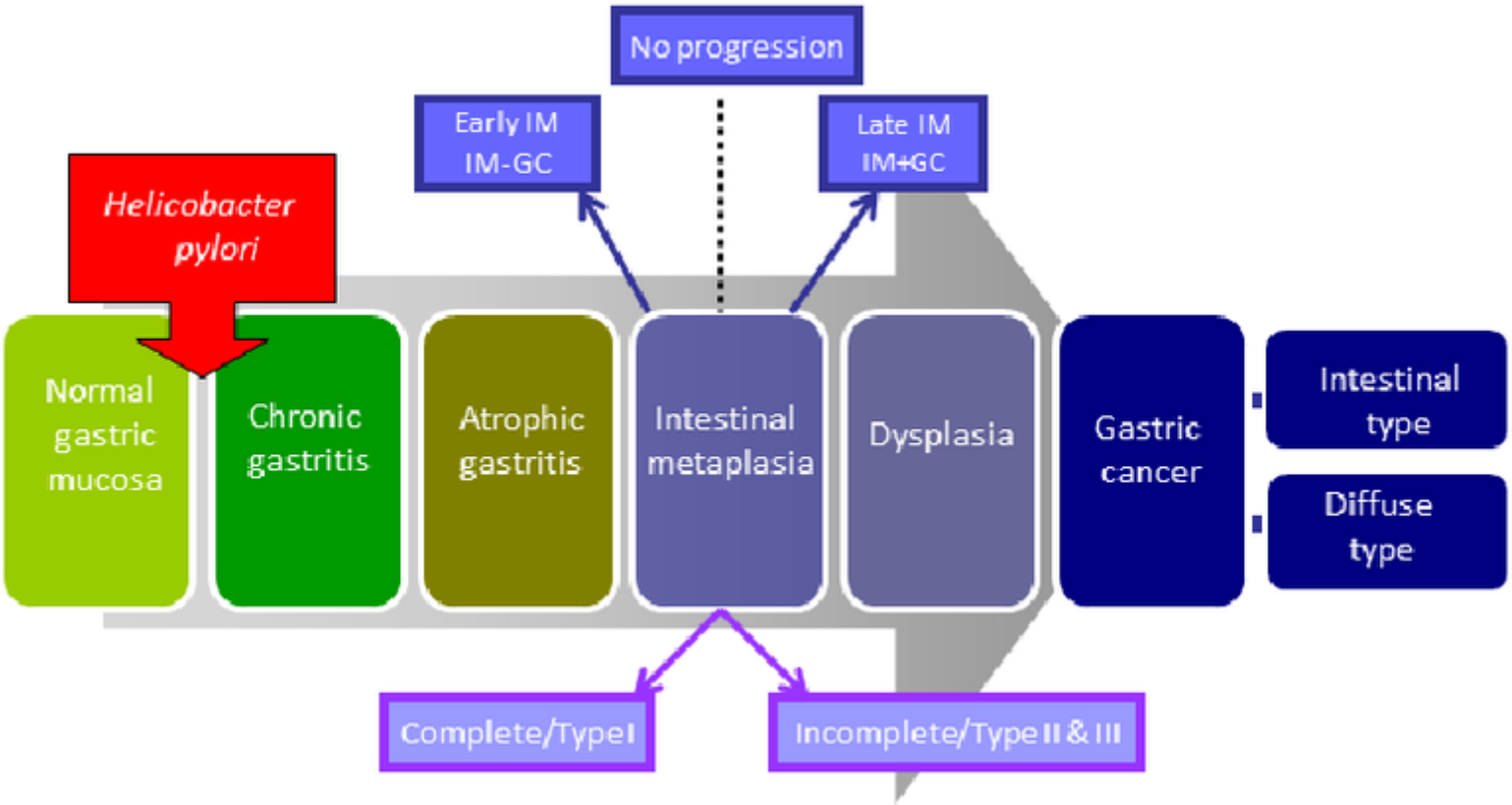
DIFFUSE TYPE

- superficial pangastritis without atrophy
- younger individuals

Etiology


Bacterial virulence
Cag A
Genetic features
Environmental
Diet,smoking

Gastric adenocarcinoma natural history



Gastric intestinal metaplasia

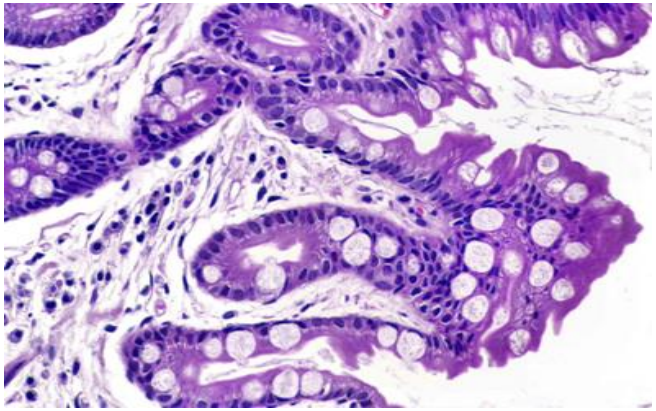
- **DEFINITIONS**
- Gastric intestinal metaplasia is defined as the replacement of the surface, foveolar, and glandular epithelium in the oxyntic or antral mucosa by intestinal epithelium
- Precancerous gastric lesion

Gastric intestinal metaplasia

- **Subtypes**
- **Limited intestinal metaplasia**: confined to one region of the stomach
- **Extensive intestinal metaplasia**: involves at least two areas of the stomach (the corpus and also either the antrum and/or incisura)

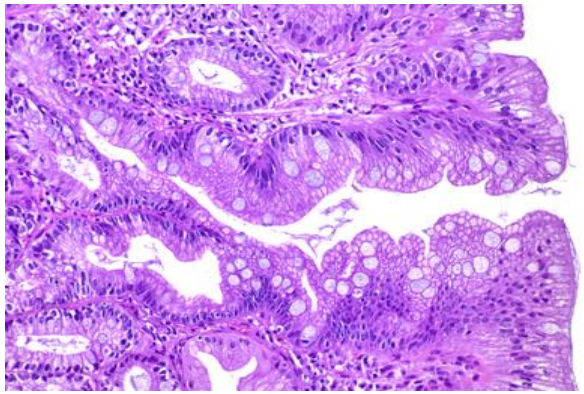
Gastric intestinal metaplasia

Complete gastric intestinal metaplasia



Small intestinal-type mucosa with goblet cells, a brush border, and eosinophilic enterocytes

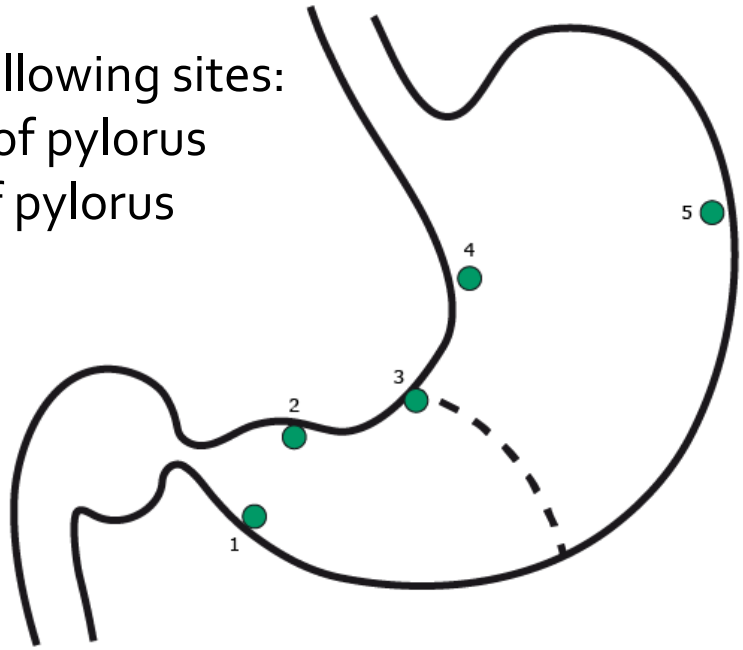
Incomplete gastric intestinal metaplasia



Colonic-type epithelium with multiple, irregular mucin droplets of variable size in the cytoplasm and absence of a brush border

Gastric biopsy mapping protocol

Gastric biopsies should be obtained from the following sites:
(1) Antrum, greater curvature, within 3 to 5 cm of pylorus
(2) Antrum, lesser curvature, within 3 to 5 cm of pylorus
(3) Incisura angularis
(4) Corpus, lesser curvature
(5) Corpus, greater curvature



Management

- The goal of management is to decrease the risk of gastric cancer
  - Screening and eradication of *H. Pylori* and
  - Endoscopic surveillance for gastric cancer

Management

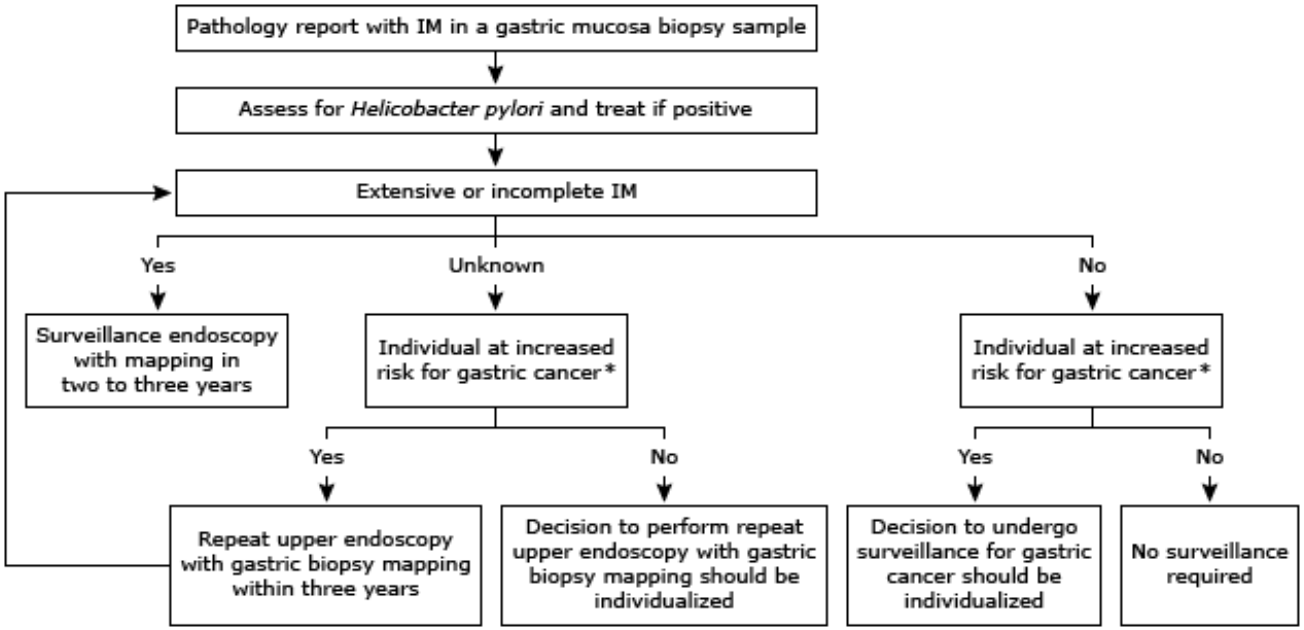
- Eradication of *H. pylori*
- Reverse the histologic changes in the majority of patients with chronic non atrophic gastritis and in many patients with multifocal atrophic gastritis
- Does not reverse intestinal metaplasia
- Slow the progression of intestinal metaplasia to gastric cancer

Management

- Progression of metaplasia and gastric dysplasia are associated with a decrease in the burden of *H. Pylori*.

- If the histology does not demonstrate evidence of *H. Pylori*, noninvasive testing (eg, stool antigen, urea breath test, serology) should be performed

Surveillance

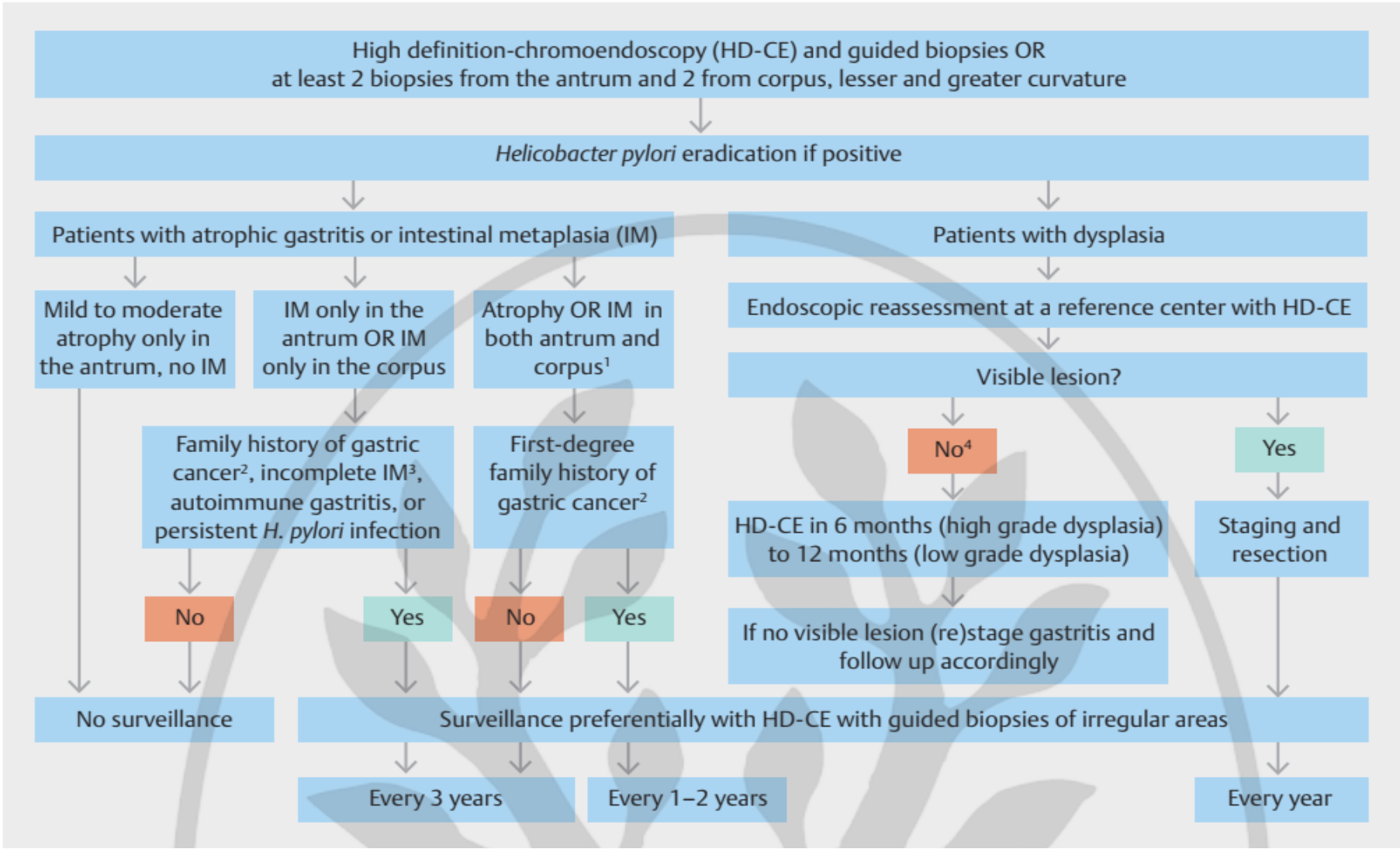


IM: intestinal metaplasia.

* Individuals at increased of gastric cancer include those with a family history of gastric cancer; non-Caucasian race/ethnicity, including African-Americans, Hispanics, and Asians; and first generation immigrants from high incidence regions (eg, Eastern Asia, mountainous Latin America).

Am J Gastroenterol 2010; 105:493.

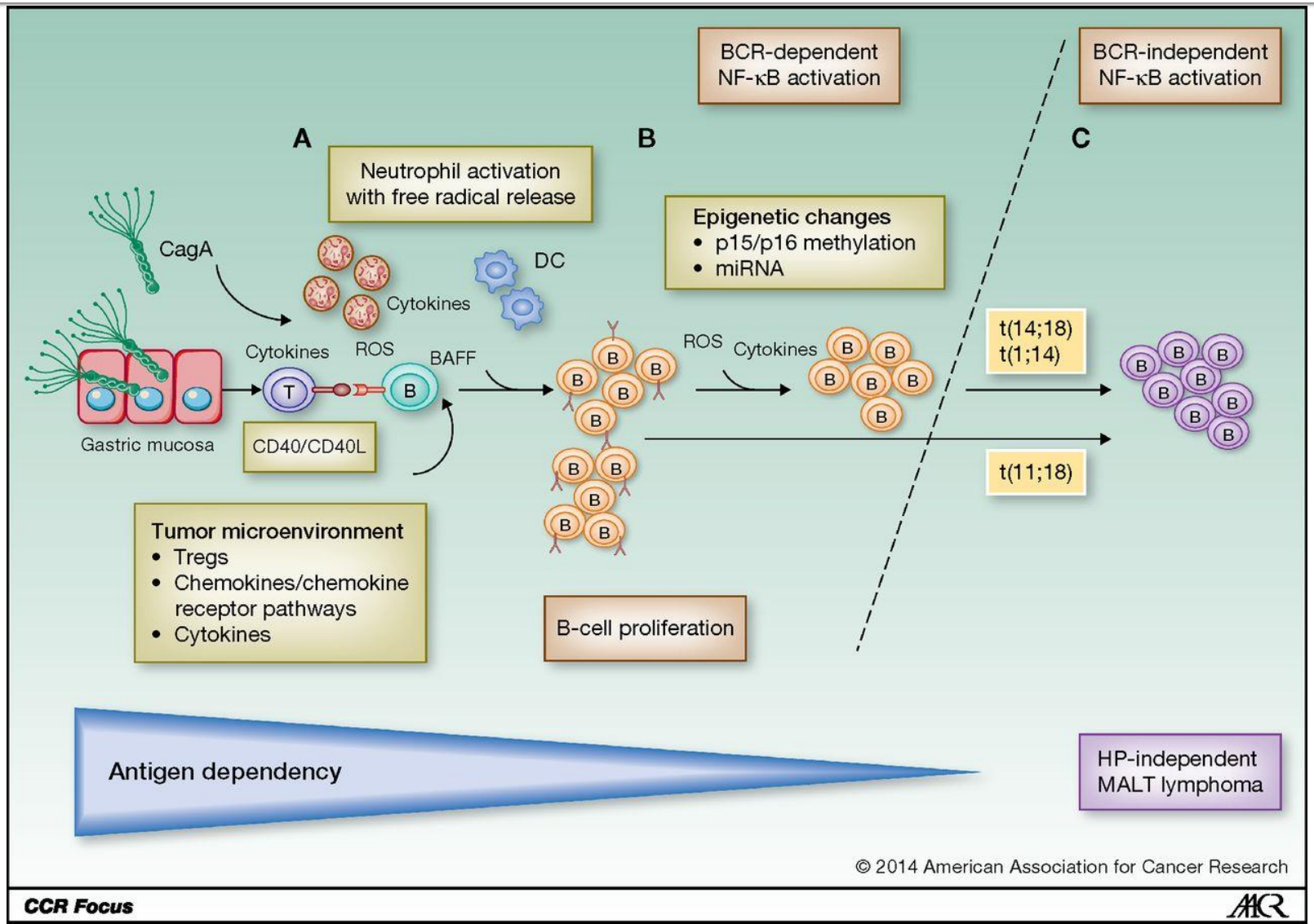
Surveillance, ESGE guidelines 2019



MALT lymphoma

- Extranodal marginal zone B-cell lymphoma
- Indolent non-hodgkin lymphoma
- Stomach is the most common site
- 3 percent of gastric neoplasms
- 10 percent of lymphomas

Etiology


BCR-dependent NF-κB activation
BCR-independent NF-κB activation
A
B
C
Neutrophil activation with free radical release
Epigenetic changes
• p15/p16 methylation
• miRNA
CagA
DC
Cytokines
Cytokines
ROS
BAFF
ROS
Cytokines
t(14;18)
t(1;14)
t(11;18)
T
B
Gastric mucosa
CD40/CD40L
Tumor microenvironment
• Tregs
• Chemokines/chemokine receptor pathways
• Cytokines
B-cell proliferation
Antigen dependency
HP-independent MALT lymphoma
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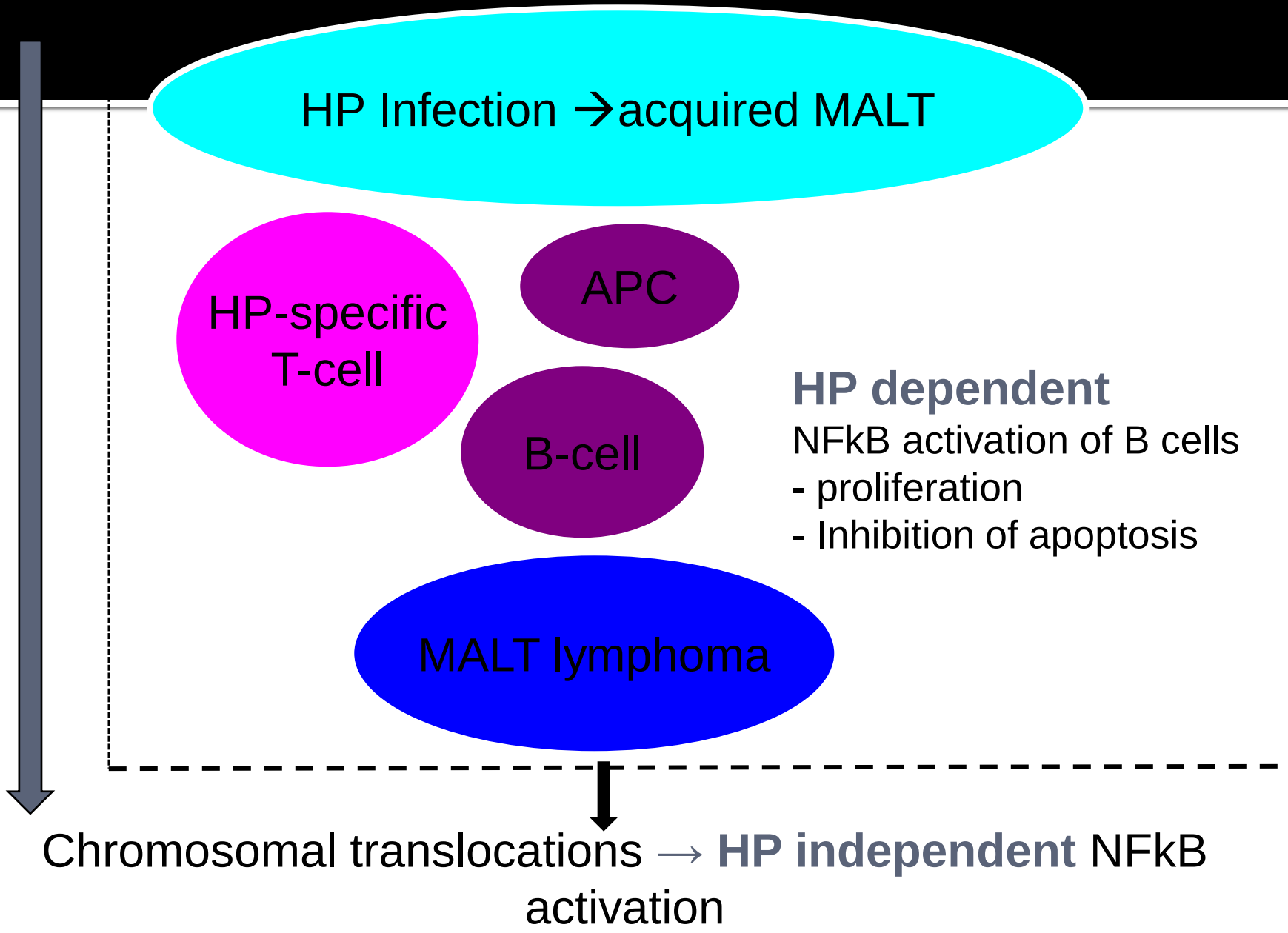
CCR Focus
AACR

Pathogenesis Gastric MALT Lymphoma:



Lugano staging system

Stage	Extent of lymphoma
I	Confined to GI tract (single primary, or multiple non-contiguous lesions)
II	Extending into abdomen from primary GI site
	II_1 = local nodal involvement
	II_2 = distant nodal involvement
IIE	Penetration of serosa to involve adjacent organ or tissues
	Specify site of involvement, e.g. IIE (pancreas)
	If both nodal involvement and involvement of adjacent organs, denote stage using both a subscript (1 or 2) and E, e.g. II_1 E (pancreas)
IV	Disseminated extra-nodal involvement or concomitant supra-diaphragmatic nodal involvement

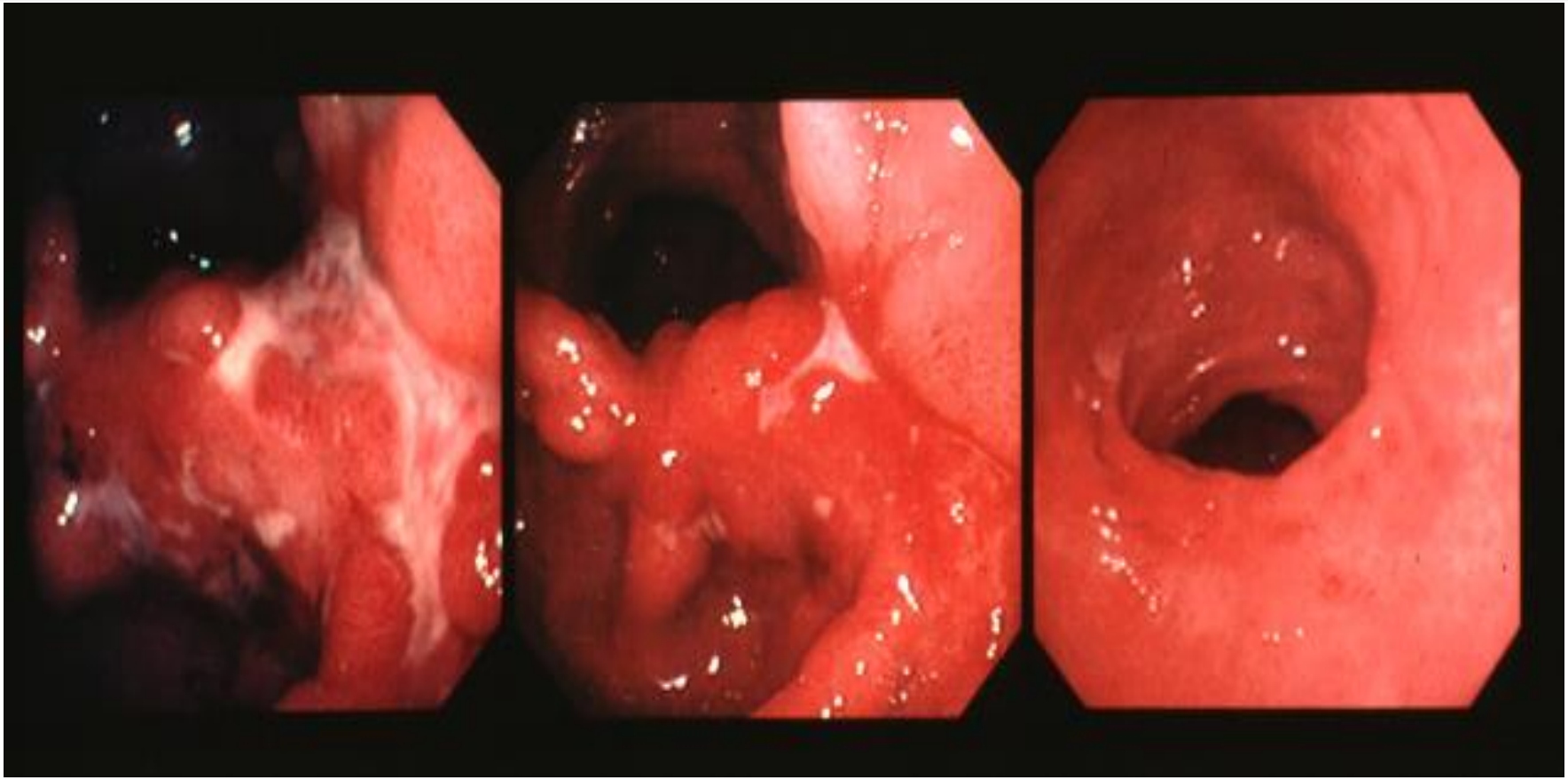
Treatment

- **Early stage H. pylori positive**
- initial *H. pylori* eradication therapy followed by surveillance
- Histologic CR was achieved in 50 to 83 percent of patients.
- The median time from *H. pylori* eradication to CR was 15 months

Treatment

- **Confirm eradication**
  - Four weeks after the completion of *H. pylori* eradication therapy
- **Assess tumor response**
  - periodic upper endoscopy with multiple biopsies to evaluate for tumor response and monitor for relapse
  - every three months until a histologic CR is attained

Effect of eradication of H.Pylori



Before Hp eradication

2 weeks post-eradication

10 months post-eradication

Dr Naomi Uemura, Hiroshima Japan

Treatment failures

- 20 to 30 %
- t(11;18) translocation
  - Radiation therapy
  - Single agent rituximab
  - Chemoimmunotherapy(Lugano stage IV disease)
  - Gastric resection is reserved for patients with complications such as perforation, bleeding, or obstruction

Early stage H. pylori negative

- Radiation therapy
- Single agent rituximab
- chemoimmunotherapy

- There have been case reports of tumor responses to *H. pylori* eradication in *H. pylori*-negative patients, presumably due to false negative results of *H. pylori* testing

Ann Oncol. 2013 May;24(5):1352-9. Epub 2013 Jan 24.

Colon Cancer

- An association between *H. pylori* infection and colorectal polyps and colorectal cancer has been described but remains controversial
- The biologic basis for such an association is uncertain
- One possibility is elevated serum gastrin levels in patients with *H. pylori* infection
- Gastrin receptors have been identified on a variety of colon cancer cell lines

Am J Epidemiol. 2012 Mar;175(5):441-50. Epub 2012 Jan 31.

Pancreatic Cancer

- An association between *H. pylori* infection and pancreatic cancer has been reported
- A possible mechanism proposed for the association of pancreatic cancer and *H. pylori* is the link between pancreatic cancer and chronic hyperacidity

J Natl Cancer Inst. 2001;93(12):937.
JOP. 2011 Jan;12(1):26-31.

Hepatobiliary Cancer

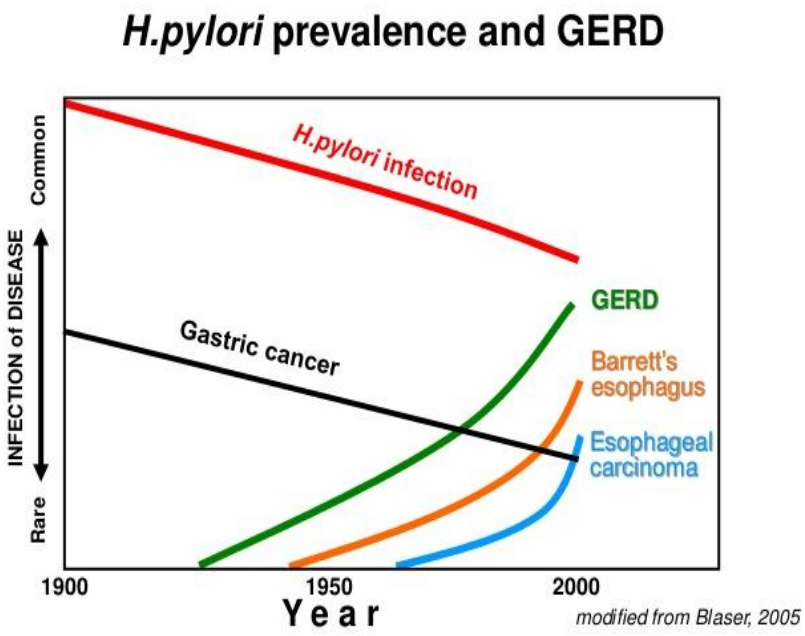
- identification of Helicobacter species in bile, gallstones, biliary, and hepatic tissues
- Several studies report an association between biliary tract carcinoma and infection with *H. pylori*

J Natl Cancer Inst. 2003;95(13):948.

Esophageal cancer

- In a meta-analysis of 28 selected studies confirmed a significant inverse association between H.pylori infection and esophageal adenocarcinoma

- The mechanisms underlying the protective role still need to be elucidated



Thank you